Mathematical description
of heat transfer in living tissue

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Preface

How living organisms function and organize themselves is a very attractive and challenging problem. This problem is extremely complex because living organisms involve a great number of hierarchy levels from biomacromolecules up to total organisms functioning as a whole which are related to each other by energy and mass flow. Nevertheless, one of the possible ways to solve this problem is to divide the whole hierarchical structure into different levels that can be considered individually in the framework of a single branch of science. Living tissue forms a basic level of this hierarchy which in turn contains own complex hierarchical substructure and, from the stand point of heat and mass transfer, can be treated as a certain medium.

Traditionally theoretical and mathematical physics deals with continuous media for investigation of which a large number of various methods have been developed. It is natural to apply the methods of theoretical and mathematical physics to analysis of transport phenomena, in particular, heat and mass transfer in living tissues. In this way one can obtain not only particular results important for specific problems in biology, medicine and biophysics, but also penetrate deeply into the main principles of functioning and organization of living organism as a whole because these principles are likely to be similar for each of the hierarchy levels.

For the theory of heat and mass transfer in living tissue one of the central issues is how to create good models that describe these transport phenomena, at least on the mesoscopic level, in terms of certain physical fields and the corresponding governing equations accounting for interaction between different levels of the living tissue hierarchy. In this way it is quite possible to meet new problems that can be of significant interest from the stand point of other natural hierarchical systems. The present book states the bioheat transfer problem, which from our point of view describes the main properties of transport phenomena peculiar to such media.

Let us make clear the subtitle of the present book which contains three key characteristics of living tissue, mainly, "hierarchically organized", "active" and "heterogeneous" medium.

Roughly speaking, living tissue consists of two subsystems: the cellular tissue treated as a uniform medium and a highly branching hierarchical vascular network involving arterial and venous beds. Blood flow through the arterial bed supplies the cellular tissue with oxygen, nutritious products, etc. and controls heat balance in the system. Through the venous bed blood flow withdraws products resulting from a life activity of the cellular tissue.

The vascular network is embedded into the cellular tissue and in spite of its small relative volume the vascular network mainly determines heat and mass propagation. This is the case due to the fast convective transport with blood flow in vessels. Such a characteristic feature makes living tissue as highly heterogeneous media where low - dimension heterogeneities form fast transport paths

controlling bioheat transfer in living tissue.

Such significant effect of low - dimensional heterogeneities on transport phenomena is also met in diffusion processes in polycrystals and crystals with dislocations where grain boundaries or dislocations form the fast diffusion paths. However, living tissue differs significantly from such media in that vessels make up a highly branching network of unique architectonics and blood flow in vessels of one level are directly related to blood flow in all other vessels. Therefore, in order to describe influence of blood flow on heat and mass propagation the vascular network should be taken into account as a whole rather than in terms of individual vessels. This characteristic feature of living tissue is reflected in the term "hierarchically organized media".

Living tissue is not only a highly heterogeneous but also an active medium. The fact is that the cellular tissue under various conditions requires different amount of oxygen, nutritious products, etc. Therefore, the vascular network must respond to variations in the cellular tissue state in the proper way. Due to expansion of a single vessel leading, in principle, to blood flow redistribution over the whole vascular actually all vessels should take part in the vascular networks response to local variations of the tissue state parameters. In other words, the vascular network response is the cooperative action of all the vessels. Variations in vessel parameters lead to alterations of heterogeneity characteristics. Therefore, for example, oxygen and heat propagation affect the state of living tissue, leading to blood flow redistribution over the vascular network due to its response, which in turn alter heterogeneity properties and affects oxygen and heat propagation. Thus, such transport phenomena should exhibit nonlinear behavior, and living tissue is an active distributed system with self-regulation.

The three inalienable characteristics of living tissue are the essence of the bioheat transfer problem in its own right.

In this monograph we do not claim the complete solution of the bioheat transfer problem that could be used in comparing with particular experimental data. In fact, in the present monograph we formulate a simple model for heat transfer in living tissue with self-regulation. The initial point of the model is the governing equations describing heat transfer in living tissue at the mesoscopic level, i.e. considering different vessels individually. Then, basing on the well known equivalence of the diffusion type process and random walks, we develop a certain regular procedure that enables us to average these mesoscopic equations practically over all scales of the hierarchical vascular network. The microscopic governing equations obtained in this way describe living tissue in terms of an active medium with continuously distributed self-regulation.

One of the interesting results obtained in the present monograph is that there can be the phenomena of ideal self-regulation in large active hierarchical systems. Large hierarchical systems are characterized by such a great information flow that none of its elements can possess whole information required of governing the system behavior. Nevertheless, there exists a cooperative mechanism of regulation which involves individual response of each element to the corresponding hierarchical piece of information and leads to ideal system response due to self - processing of information. The particular results are obtained for

bioheat transfer. However, self-regulation in other natural hierarchical systems seems to be organized in a similar way.

The characteristics of large hierarchical systems occurring in nature are discussed from the stand point of regulation problems. By way of example, some ecological and economic systems are considered. An cooperative mechanism of self-regulation which enables the system to function ideally is proposed.

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Part I

The basis of the bioheat transfer theory

Chapter 1

INTRODUCTION: Essentials of the description of transport phenomena in highly heterogeneous media. What the bioheat transfer problem is

Transport phenomena such as diffusion and heat propagation in solids, liquids as well as in condensed materials of complex structure can be usually described in the framework of the phenomenological approach where, for example, gradients in concentrations of diffusing species and temperature give rise to local mass and heat flow in the medium. In the simplest case diffusion of a scalar field c is characterized by its flux $\mathbf{J}_c$ proportional to the gradient $\boldsymbol{\nabla}c$. When the medium itself can move in space, at least locally, the flux $\mathbf{J}_c$ contains the term proportional also to the local velocity $\mathbf{v}$ of the medium motion. In other words,

$$\mathbf{J}_c = -D\boldsymbol{\nabla}c + \mathbf{v}c \qquad (1.1)$$

and the governing equation of evolution of the field c follows from the conservation law

$$\frac{\partial c}{\partial t} = -\boldsymbol{\nabla}\mathbf{J}_c + q. \qquad (1.2)$$

Here D is the diffusion coefficient and q is the net density of sources and sinks.

There is a large number of various media where kinetic coefficients (for example, the diffusion coefficient D) or the local velocity $\mathbf{v}$ vary in space dramatically.

From a mathematical point of view the consideration of heat and mass transfer in these media is closely connected with bioheat transfer in living tissue. For this reason we direct our attention to the discussion of characteristic features of these media. In particular, in polycrystals and crystals with dislocation diffusion coefficients in the regular crystal lattice and in the vicinity of the grain boundaries and dislocations differ in magnitude by a factor of $10^5 - 10^8$. In the system formed by materials of different structures and composition (composite materials) the heat conductivity also vary in space considerably. In porous media transport phenomena are controlled by convective flow of gas or liquid through channels of complex branched form. Therefore, in such media the local velocity $\mathbf{v}(\mathbf{r}, t)$ of convective flux governing mass and heat propagation depends on the spatial coordinates $\mathbf{r}$ and, may be, the time t significantly. Turbulent fluid is also a highly heterogeneous medium from the standpoint of mass and heat transfer. Indeed, due to laminar flow instability the velocity $\mathbf{v}(\mathbf{r}, t)$ is actually a random vector whose space-time distribution is characterized by a large number of scales.

It should be noted that transport phenomena in a biological and natural environment system can be also treated in such terms, at least qualitatively. For example, contaminant propagation controlled by rivers, winds blowing in a forest, and mountains, as well as epidemic propagation over regions of non-uniform population can be described in this approach.

For such media the substantial spatial (and may be temporal) dependence of kinetic coefficients and the velocity $\mathbf{v}$ on small scales ℓ is actually the essence of their highly inhomogeneity. Indeed, equations similar to (1.2) which govern transport phenomena form practically microscopic description of these processes because they explicitly contain spatial inhomogeneities of scales ℓ. In particular, for the scalar field c we get

$$\frac{\partial c}{\partial t} = \boldsymbol{\nabla}\left[D(\mathbf{r}, t, \ell)\boldsymbol{\nabla}c - \mathbf{v}(\mathbf{r}, t, \ell)c\right] + q(\mathbf{r}, t). \tag{1.3}$$

The solution $c(\mathbf{r}, t, \ell)$ of this equation contains all the details of the field c distribution on small scales of order ℓ as well as on large scales $\mathcal{L}$ characterizing the medium as a whole. However, evolution of such systems and transport phenomena in them usually are of importance only on spatial scales much greater than ℓ. So, the theory of mass and heat transfer in these highly heterogeneous media can be based on the corresponding diffusing field averaged on scales ℓ. In other words, we should find the field

$$c_a(\mathbf{r}, t) = \langle c(\mathbf{r}, t, \ell) \rangle_\ell$$

where the symbol $\langle \ldots \rangle$ stands for averaging on scales ℓ. In addition, directly finding the solution of equation (1.3) is a stubborn mathematical problem. Therefore, for such heterogeneous media the main aim of the transport problem is to reduce the microscopic equations similar to (1.3) to certain macroscopic equations describing the system evolution in terms of the averaged diffusing

fields (c_a). The generality of this problem for different branches of the theoretical and mathematical physics, applied mathematics makes the development of the corresponding averaging technique an interesting mathematical problem in its own right.

Obviously that an adequate averaging technique cannot be constructed for entire system in the general case. When all the microscopic spatial scales as well as the corresponding temporal scales can be treated as small parameters such technique has practically been developed and there is a great number of works devoted to this problem for different systems(for a review see, e.g., [8, 71, 98, 79, 89, 47] and references therein). In this case for media such as composite materials, polycrystals, porous media, etc. the obtained macroscopic governing equations usually retain their initial form similar to (1.3) and contain certain smoothed effective kinetic coefficients and the mean local velocity.

When the conditions of the microscopic scales are small they are violated and the problem becomes more complicated. For example, the macroscopic equation of grain boundary diffusion will contain the partial derivative of fractal order with respect to the time when certain temporal microscopic scales are not small [58].

For turbulent fluids the velocity field $\mathbf{v}(\mathbf{r}, t, \{\ell, \tau_\ell\})$ is a result of cooperative interaction between a huge number of vortexes characterized by a wide range of spatial scales $\{\ell\}$ from a characteristic dimension $\mathcal{L}$ of the system as a whole up to an extremely small scale $\ell_{\min} \ll \mathcal{L}$. The corresponding temporal scales $\{\tau_\ell\}$ of the velocity nonuniformities also vary over a wide range [55, 97]. Therefore, although transport phenomena in turbulent fluids have been considered for many years. The theory of these processes is far from being completed [44, 109, 100, 49]. The basic difficulty is that one should take into account the simultaneous effect of a large number of different vortexes in diffusion processes and it is impossible to single out beforehand a vortex controlling transport phenomena. Moreover, diffusing field, for example, temperature can affect liquid motion. In this case the macroscopic governing equations of heat transfer should allow for the nonlinear interaction of liquid motion and heat propagation.

Such a problem of multiscale averaging the microscopic equations of turbulent transport is also met in describing transport phenomena in other systems. Contaminant diffusion in a river flowing through a brush of reeds and the wind blowing in a forest are two typical examples of these processes [80].

Heat transfer along with mass transport in living tissue comprises all the characteristic features inherent in the aforementioned systems. In fact, living tissue (Fig. 1.1) is a heterogeneous medium involving blood vessels embedded into cellular tissue and heat propagation in cellular tissue and inside vessels with blood flow differs significantly in properties. So, like composite materials, polycrystals and crystals with dislocations living tissue contains certain regions with various kinetic coefficients and heat transfer is governed by an equation similar to (1.3). The main difference between heat propagation in the cellular tissue and vessels is that heat slowly diffuses inside the former region and blood flow in vessels forms paths of its fast convective transport [43].

However, in contrast to such physical systems the heterogeneities of living

Figure 1.1: Vascular network of real living tissue.

tissue due to vascular network are characterized by hierarchical architectonics: the vascular network involves vessels of different lengths, from large arteries and veins of length $\mathcal{L}$ up to small capillaries of length ℓ_{cap}. Since smaller vessels and larger ones are connected through the branching points the velocity field $\mathbf{v}(\mathbf{r}, t)$ of blood in vessels of one hierarchy level is correlated with that of other levels rather than independent of each other. From this point of view the problem of heat and mass transfer in living tissue is closely connected with the turbulent transport problem in hydrodynamics because heat and mass propagation in living tissue is also governed by cooperative influence of blood velocity field $\mathbf{v}(\mathbf{r}, t, \ell)$ in vessels of all the lengths from $\mathcal{L}$ to ℓ_{cap}.

Living tissue also possesses a peculiarity that makes it distinct from physical and mechanical media. This difference is that the vascular network is active and responds to variations in the cellular tissue state. In cellular tissue the temperature, oxygen concentration, etc. vary in time the vessels will expand or contract, increasing or decreasing blood flow in order to supply cellular tissue with blood amount required. Therefore, in development of the theory of transport phenomena in living tissue one should also take into account the physical parameters of vessels belonging to all the hierarchy levels vary in such a self–consistent way it enables the vascular network to respond properly and, so, living tissue to adapt to new conditions.

Thus, any theory that claims to describe adequately real transport phenomena in living tissue should account for these basic properties. One of the first steps in this direction is the development of an averaging technique converting the microscopic equations similar to (1.3) into macroscopic governing equations describing evolution of certain smoothed fields. Obtaining such macroscopic governing equations for heat propagation in living tissue is the essence of the bioheat transfer problem. It should be noted that, in fact, this problem involves basic parts, the former is constructing the averaging technique in its own right, the latter is the description of the living tissue active behavior. Correspondingly, the present book considers these questions successively.

The book is organized as follows. The theory developed previously treats heat transfer in living tissue actually at the phenomenological level, based

mainly on the conservation of blood and energy and practically does not account details of heat interaction between vessels of different levels. These models and their background are briefly reviewed in Chapter 2. Here we also represent the well known rough classification of all blood vessels according to their influence on heat propagation which is the first physiological background for any model of living tissue. Besides, we discuss what macroscopic physical variables (continuous fields) bioheat transfer theory should deal with. In particular, in addition to the smoothed temperature the blood flow rate $j(\mathbf{r}, t)$ is such a state variable.

Real living tissues are extremely complex systems and there is a large number of processes where heat transfer occurs. So, the model proposed in this book is certain not to be able to describe real processes of bioheat transfer in full measure. It solely takes into account the main characteristic features of living tissue and can be the basis for analysis of temperature distribution under extreme conditions (e.g., during hyperthermia treatment) when the temperature is a leading parameter the state. Certain physiological properties of real living tissues, including architectonics of vascular networks, what determines a region of living tissue that can be treated as a distributed medium, mechanisms of tissue response to temperature variations are considered in Chapter 3. In no case this Chapter can be regarded as an introduction to physiology of living tissues in its own right. We understand that a large number of important physiological problems is beyond the scope of our discussion. We consider only those forming the starting point of the proposed model and motivating the properties to be ascribed to blood vessels.

In Chapter 4 we specify microscopic equations, governing temperature distribution in cellular tissue and vessels individually, as well as the vascular network architectonics. A particular form of vascular network, on one hand, must meet certain conditions (Chapter 3) and, on the other hand, may be chosen for convenience. The latter is possible because, as will be shown in Chapters 6 and 7, the heat propagation exhibits the self - averaging properties and solely characteristic properties of vessel branching have remarkable effect on heat transfer. In this Chapter we also formulate the specific model for the vessel response to temperature variations in cellular tissue.

Then, in Chapters 5–7 instead of solving the microscopic temperature evolution equations directly we describe bioheat transfer in terms of random walks in living tissue. This is possible due to the well known equivalence of diffusive type processes and random motion of certain Brownian particles. The characteristic path of walker motion in living tissue involves an alternating sequence of walker motion inside the vessels with blood flow and in the cellular tissue. Finding the mean displacement of a typical walker at a given time we gain capability to trace the typical way of walker motion through the hierarchical vessel system and to propose the desired averaging procedure. In this way we will be able to obtain specific form of the macroscopic bioheat equation under various conditions. The developed procedure enables us to classify all the vessels of the given vascular network according to their influence on heat transfer. The latter forms the basis of thermoregulation theory dealing with temperature response of individual vessels.

The result of averaging the microscopic description of the hierarchical model is presented in Chapter 8 by the generalized bioheat equation. This equation, first, contains terms, treating living tissue as an effective homogeneous medium. This medium, however, has additional effective heat sinks caused by blood flow. In other words, averaging initial microscopic equations of the divergence form leads to the appearance of sinks whose density is proportional to the blood flow rate. The fact is that large vessels form traps of the Brownian particles rather than paths of their fast transport from the standpoint of their motion in cellular tissue. In addition, it turns out that under certain conditions the renormalization coefficient of the temperature diffusivity practically does not depend on the physical parameters of the system. This is a direct consequence of the vascular network being hierarchically organized. The generalized bioheat equation contains other terms whose appearance is caused by the discrete distribution of small vessels in the space and which are regarded as random spatial inhomogeneities. The corresponding characteristic properties of random spatial nonuniformities and fluctuations of the tissue temperature are analyzed in detail in Chapters 14, 15.

When blood flow distribution over the vascular network becomes substantially non-uniform the bioheat equation should be modified which is the subject of Chapters 9–10. In this case not only the temperature, but also the rate must be smoothed and the contains two equations: averaged temperature and the averaged blood flow rate equations.

By Chapter 10 we complete, the development of the averaging technique. Then, we consider the active behavior of living tissue, namely, the vascular network response to variations of temperature in cellular tissue. At this point we meet a certain fundamental problem that can be stated in the general case and is typical not only for living tissues but also for a large number of hierarchically organized living systems in nature. All of them need permanent supply of external products for life activities and inside these systems the products are delivered to different elements through supplying networks organized hierarchically. Their peculiar property is the capacity for responding and adapting to changes in the environment. The latter requires redistribution of the product flow inside a system over the supplying network. Since, as a rule, the products for life activity enter a living system centrally there must be a certain mechanism that governs the proper response of the supplying network at all the hierarchy levels. Such control of the supplying network dynamics requires processing a great amount of information characterizing the system behavior at the all hierarchy levels. However, none of its elements can possess all the information required of the governing system. Therefore, how a natural large hierarchically organized systems can respond properly to changes in the environment is a challenging problem. In the present book we deal with the bioheat transfer problem by showing that there can be a cooperative mechanism of self-regulation which involves individual response of each element to the corresponding hierarchical piece of information and leads to the ideal system functioning due to self-processing of information. It is believed that such a cooperative mechanism of self-regulation is inherent practically to all natural large hierarchical systems.

In living tissue blood flows through the vascular network involving arterial and venous beds supplies cellular tissue with oxygen, nutritious products, etc. At the same time blood withdraws carbon dioxide and products resulting from life activities of the cellular tissue. Both the arterial and venous beds are of the tree form contain a large number of hierarchy levels and are similar in structure. The living tissue responses to disturbances in life activity, for instance, through vessel response to variations of the blood temperature, the carbon dioxide concentration, which gives rise to expansion or contraction of arteries. These aspects form the base of the model for vascular network response developed in Chapters 11–12. The general equations governing the active living tissue behavior are reduced to the local relation of the blood flow rate $j(\mathbf{r}, t)$ and the tissue temperature $T(\mathbf{r}, t)$ in the spatial case which we call the ideal self–regulation. The existence of the local relationship between $j(\mathbf{r}, t)$ and $T(\mathbf{r}, t)$ is a surprise because it is the consequence of a complicated mutual compensation between blood flows at all the hierarchy levels.

In Chapter 13 we apply the developed theory to analysis of heat transfer in living tissue containing a tumor. We do not pretend to total description of temperature distribution in this case, we only try to grasp the main rough characteristics of temperature distribution near small tumors which can occur in hyperthermia treatment. The same concerns the problems of cryosurgery treatment.

As it has been mentioned above the cooperative mechanism of self–regulation is inherent not only in biological organisms, but also in large ecological and economic systems. So, in Appendix we, firstly, generalize the model for ideal self–regulation proposed for living tissue. Then, we show that the market with perfect competition can possess ideal self–regulation too. From this point of view we also consider some problems that occur in ecological models of the Lotka–Volterra type.

Chapter 2

Mean field approach to the bioheat transfer problem

2.1 Modern models for heat transfer in living tissue

The theory of heat transfer in living tissue that has been developed in the last years is mainly aimed at promoting a better understanding of real processes that take place in living tissue during its strong heating or cooling.

Mathematical analysis of temperature distribution in living tissue on scales of a single organ is, on one hand, of considerable interest for understanding fundamental problems of human physiology as well as for treatment of specific diseases. In fact, for example, in hyperthermia treatment of a small tumor a tissue region containing the tumor is locally heated to high temperature by external power sources. In this case mathematical modelling of temperature distribution is required to optimize the treatment (for a review see e.g. [3, 43, 83, 96] and references therein).

On the other hand, description of transport phenomena, in particular, heat transfer in living tissues, is a challenging problem of mathematical biophysics in its own right. The matter is that blood flow in vessels forms a branching network of fast heat transport and, from the standpoint of heat transfer, living tissue is a highly inhomogeneous and hierarchically organized medium. Besides, due to vessel response to temperature variations this medium is characterized by nonlinear phenomena responsible for thermoregulation.

By now a number of models for heat transfer in living tissue have been proposed. Reviews on bioheat transfer in living tissue can be found in [6, 15, 22, 54, 85]. Below we shall outline some of these models and their physical background.

The simplest approach to description of bioheat transfer is to consider living tissue in terms of an effective homogeneous continuum where thermal interac-

tion between cellular tissue and blood is treated as a distributed heat sink. In physical sense, the heat sink is caused, for example, by heating of blood in its passage through the tissue. Within the framework of this approach we may write the following equation for the tissue temperature

$$c_t\rho_t\frac{\partial T}{\partial t} = \boldsymbol{\nabla}(\kappa\boldsymbol{\nabla}T) - c_b\rho_b j(T - T_a) + q_h, \qquad (2.1)$$

where c_t, ρ_t are the density and heat capacity of the tissue, c_b, ρ_b are the same values for blood, κ is the tissue thermal conductivity, q_h is the heat generation rate caused by metabolic processes and external power sources, T_a is the temperature of blood in large arteries of a systemic circulation, and j is the blood flow rate, i.e. the volume of blood flowing through unit tissue volume per unit time.

   This equation has been firstly introduced by Pennes [81] and now is widely known as the conventional bioheat transfer equation. He assumes that arterial blood enters capillaries of a tissue domain under consideration without heat exchange with the surrounding cellular tissue, then attains thermal equilibrium practically instantaneously , and leaves this tissue domain through a venous bed without heat exchange again.

   Since blood flow in vessels gives rise to convective heat transport it has been proposed a model [107] where living tissue is treated as a continuum with effective convective flux $\mathbf{v}_{\text{eff}}(r)$, and the governing bioheat equation is of the form

$$c_t\rho_t\frac{\partial T}{\partial t} = \boldsymbol{\nabla}(\kappa\boldsymbol{\nabla}T) - c_b\rho_b\mathbf{v}_{\text{eff}}\boldsymbol{\nabla}T + q_h. \qquad (2.2)$$

   Chen and Holmes [17] have considered heat transfer in living tissue containing hierarchical system of vessels and analyzed the main properties of heat exchange between blood in different vessels and the surrounding cellular tissue. This allowed them to justify adequately the continuum approach to bioheat description and to propose more adequate equation for the tissue temperature evolution in small-scale living tissue domain [17, 18]

$$c_t\rho_t\frac{\partial T}{\partial t} = \boldsymbol{\nabla}(\kappa_{\text{eff}}\boldsymbol{\nabla}T) - c_b\rho_b j_v^*(T - T_a^*) - c_b\rho_b\mathbf{v}_{\text{eff}}\boldsymbol{\nabla}T + q_h. \qquad (2.3)$$

Here κ_{eff} is the effective thermal conductivity, j_v^* – the blood flow rate determined by arteries where blood practically attains thermal equilibrium with the cellular tissue for the first time and T_a^* – the initial blood temperature in these arteries.

   In real living tissues the arterial bed is typically located in the immediate vicinity of the corresponding venous bed. The blood temperature in arteries can differ significantly from the blood temperature in veins, so, in principle, there must be an essential heat exchange between an artery and the nearest

vein of the same level. This effect is phenomenologically taken into account in the effective conductivity model [51, 52, 101]

$$c_t \rho_t \frac{\partial T}{\partial t} = \boldsymbol{\nabla}(\kappa_{\text{eff}} \boldsymbol{\nabla} T) + q_h \qquad (2.4)$$

and in [101] the particular relationship between the effective and intrinsic thermal conductivity κ_{eff} and the blood flow parameters has been found. It should be noted that effective conductivity model has both the strong and weak sides (for more details see [6, 7, 13, 14, 102, 104, 107].

All these models allow for various features of the bioheat transfer process. So, each of them may be valid, at least at the qualitative level, under certain conditions. Therefore, taking into account the present state of the bioheat transfer theory it has been suggested to use for application the following generalized bioheat equation which combines the main models mentioned above [23]:

$$c_t \rho_t \frac{\partial T}{\partial t} = \boldsymbol{\nabla}(\kappa_{\text{eff}} \boldsymbol{\nabla} T) - f c_b \rho_b j (T - T_a) + q_h. \qquad (2.5)$$

Here the effective thermal conductivity κ_{eff} and the factor f ranging from 0 to 1 are phenomenological parameters.

Concluding this section we would like to point out that in order to find the valid limits of the given collection of bioheat equations, including the generalized equation (2.5), as well as to obtain the specific expressions for the corresponding kinetic coefficients one needs a successive procedure that would enable to get a macroscopic equation by averaging directly the corresponding microscopic governing equations. This procedure should take into account the hierarchical structure of vascular network, correlations in mutual arrangement of vessels belonging to different levels, vessel response to temperature variations, etc. In the present work we intend to develop such a procedure.

2.2   Rough classification of blood vessels according to their influence on heat propagation

From the standpoint of heat transfer living tissue may be represented as a homogeneous continuum (cellular tissue) in which a hierarchical vascular network is embedded. Heat propagation in the cellular tissue and in blood flowing through the vessels is different in properties, viz., in the cellular tissue heat propagation is controlled by thermal conduction and inside vessels the convective heat transport can play a main role. The number of vessel levels in the vascular network is typically large $N \approx 10 - 20$ [73, 94], so blood flow in vessels of different hierarchy levels affects variously heat transfer.

In order to characterize the effect of blood flow in a single vessel on heat propagation it is usually used the quantity $l_\parallel$ defined as the length after which the blood temperature in the vessel has practically approached the temperature

of the surrounding tissue in the corresponding tissue cylinder, i.e. the tissue domain falling on one vessel of the given level. If for a given vessel the value $l_\parallel$ is much larger than the vessel length l ($l_\parallel \gg l$) blood flow in it will affect heat transfer significantly. Otherwise, $l_\parallel \ll l$, the blood flow effect is ignorable [16, 17]. In order to imagine the extent to which blood flow in vessels of different levels can affect heat transfer we represent Table 1 where characteristic properties of blood flow in various vessels as

Table 1

vessel type	diameter	length l	flow	number	$l_\parallel$	$l_\parallel/l$
	(mm)	(cm)	(cm/s)		(cm)	
aorta	10	40	50	1	12500	310
large arteries	3	20	13	40	290	15
main branches	1	10	8	600	20	2.0
secondary branches	0.6	4	8	1800	7.2	1.8
tertiary branches	0.14	1.4	3.4	$7.6 \cdot 10^4$	0.17	0.1
terminal branches	0.05	0.1	2	10^6	0.013	0.1
terminal arteries	0.03	0.15	0.4	$1.3 \cdot 10^7$	0.0009	0.006
arterioles	0.02	0.2	0.3	$4 \cdot 10^7$	0.0003	0.002
capillaries	0.008	0.1	0.07	$1.2 \cdot 10^9$	0.00001	0.0001
venules	0.03	0.2	0.07	$8 \cdot 10^7$	0.00016	0.001
terminal branches	0.07	0.15	0.07	$1.3 \cdot 10^7$	0.0009	0.006
terminal vein	0.13	0.1	0.3	10^6	0.013	0.1
tertiary veins	0.28	1.4	0.8	$7.6 \cdot 10^4$	0.16	0.1
secondary veins	1.5	4	1.3	1800	7.3	1.8
main veins	2.4	10	1.5	600	22	2.2
large veins	6	20	3.6	40	320	16
vena cava	12.5	40	33	1	12900	320

well as vessels themselves are introduced [6, 17, 22, 103].

As it follows from Table 1 the vessels where arterial blood attains thermal equilibrium with the surrounding cellular tissue for the first time are approximately of the length $l_\parallel \sim 2\,\text{cm}$. Typically a regional vascular network contains vessels whose length is much larger and much smaller than $l_\parallel$. Thus, the bioheat transfer models should take into account that the vascular network can contain vessels significantly different in effect on heat transfer. In particular, blood flow in vessels of length $l > l_\parallel$ forms a complex system of fast heat transport paths, leading to high heterogeneity of living tissue.

2.3   Mean field approach

In the first section of this chapter we represented various forms of the macroscopic bioheat equation proposed by different authors. All these models are actually based on the mean field approach, firstly used in the simplest form by Pennes [81]. This approach principally grasps the essence of heat transfer in living tissue so we discuss it in more detail.

Let us consider a certain living tissue domain $\mathcal{Q}$ of size ℓ that, on one hand,

Figure 2.1: A schematic representation of artery and vein trees in living tissue domain $\mathcal{Q}$.

is not too small and vessels in which blood is in thermal equilibrium with the surrounding cellular tissue are entirely located in this domain (Fig. 2.1). The maximal length of such vessels is about $l_\parallel$, so $\ell > l_\parallel$. The averaged temperature T of the cellular tissue is considered to be approximately constant over the domain $\mathcal{Q}$. Besides, we assume that only one large artery and vein of length $l > l_\parallel$ go into the region $\mathcal{Q}$ where they join branching into small vessels.

For the points of the domain $\mathcal{Q}$ not belonging to a small neighborhood of large vessels the true tissue temperature T_{tr} obeys the equation

$$\frac{\partial T_{tr}}{\partial t} = D\boldsymbol{\nabla}^2 T_{tr} - \mathbf{v}(\mathbf{r})\boldsymbol{\nabla} T_{tr} + \frac{q_h}{c_t \rho_t}, \tag{2.6}$$

where $D = \kappa/(c_t \rho_t)$ is the temperature diffusivity and for the sake of simplicity we have ignored the difference between physical parameters of the cellular tissue and blood. The value of $\mathbf{v}(\mathbf{r})$ is determined by blood flow in small vessels randomly oriented in space, thus, the velocity $\mathbf{v}(\mathbf{r})$ is also treated as random field $\mathbf{v}(\mathbf{r}) = \{v_1(\mathbf{r}), v_2(\mathbf{r}), v_3(\mathbf{r})\}$ with a small correlation length $l_{\mathrm{cor}} \ll l_\parallel$. In other words, we set

$$\langle \mathbf{v}(\mathbf{r})\rangle = 0 \tag{2.7}$$

and

$$\langle v_i(\mathbf{r}) v_j(\mathbf{r}')\rangle = v_f^2 g_{ij}\left(\frac{\mathbf{r} - \mathbf{r}'}{l_{\mathrm{cor}}}\right), \tag{2.8}$$

where the symbol $\langle \ldots \rangle$ stands for averaging over the small scales, v_f is the mean amplitude of the velocity $\mathbf{v}(\mathbf{r})$, and $g_{ij}(\mathbf{r})$ is a certain function of order unity for $|\mathbf{r}| \sim 1$ which tends to zero as $|\mathbf{r}| \to \infty$. In addition, due to blood incompressibility the field $\mathbf{v}(\mathbf{r})$ must obey the equation

$$\boldsymbol{\nabla}\mathbf{v}(\mathbf{r}) = 0 \tag{2.9}$$

which allows us to write

$$\mathbf{v}(\mathbf{r}) = \mathbf{\nabla} \times \mathbf{a}(\mathbf{r}), \tag{2.10}$$

where $\mathbf{a}(\mathbf{r}) = [a_1(\mathbf{r}), a_2(\mathbf{r}), a_3(\mathbf{r})]$ is a certain random field determined practically by the concentration of the small vessels and the mean velocity of blood flow in them. The latter allows us to set

$$\langle \mathbf{a}(\mathbf{r}) \rangle = 0 \tag{2.11}$$

and

$$\langle a_i(\mathbf{r}) a_j(\mathbf{r}') \rangle = a_f^2 \delta_{ij} g_a \left(\frac{|\mathbf{r} - \mathbf{r}'|}{l_{\mathrm{cor}}} \right). \tag{2.12}$$

Here $a_f = v_f l_{\mathrm{cor}}$ is the mean amplitude of the value $\mathbf{a}(\mathbf{r})$, δ_{ij} is the Kronecker delta, and the function $g_a(r)$ is such that $g_a(r) > 0$, for $r \sim 1$ the value of $g_a(r) \sim 1$, and $g_a(r) \to 0$ as $r \to \infty$. In these terms the expression (2.8) may be rewritten as

$$\langle v_i(\mathbf{r}) v_j(\mathbf{r}') \rangle = -(v_f l_{\mathrm{cor}})^2 \left[\delta_{ij} \mathbf{\nabla}^2 - \mathbf{\nabla}_i \mathbf{\nabla}_j \right] g_a \left(\frac{|\mathbf{r} - \mathbf{r}'|}{l_{\mathrm{cor}}} \right). \tag{2.13}$$

The true tissue temperature T_{tr} involves two parts: one is the averaged temperature T, the other, $\tilde{T}$, characterizes random nonuniformities in temperature distribution caused by the field $\mathbf{v}(\mathbf{r})$. The value of $\tilde{T}$ is considered to be small and the averaged temperature distribution $T(\mathbf{r}, t)$ is regarded as a smooth field varying slowly in time. This allows us to separate equation (2.6) into the following two equations governing the fields $\tilde{T}$, T individually

$$\frac{\partial T}{\partial t} = D \mathbf{\nabla}^2 T - \mathbf{\nabla} \left\langle \mathbf{v}(\mathbf{r}) \tilde{T} \right\rangle + \frac{q_h}{c_t \rho_t}, \tag{2.14}$$

$$D \mathbf{\nabla}^2 \tilde{T} - \mathbf{v}(\mathbf{r}) \mathbf{\nabla} T = 0. \tag{2.15}$$

The solution of equation (2.15) is of the form

$$\tilde{T}(\mathbf{r}) = -\frac{1}{4\pi D} \int d\mathbf{r}' \frac{1}{|\mathbf{r} - \mathbf{r}'|} \mathbf{v}(\mathbf{r}') \mathbf{\nabla} T(\mathbf{r}'). \tag{2.16}$$

Substituting (2.16) into (2.14) we get

$$\frac{\partial T}{\partial t} = D \mathbf{\nabla}^2 T + \frac{1}{4\pi D} \sum_{i,j=1}^{3} \left[\int d\mathbf{r}' \frac{1}{|\mathbf{r} - \mathbf{r}'|} \langle v_i(\mathbf{r}) v_j(\mathbf{r}') \rangle \right] \mathbf{\nabla}_i T \mathbf{\nabla}_j T + \frac{q_h}{c_t \rho_t}, \tag{2.17}$$

where we have also taken into account that the value $\mathbf{\nabla} T$ is practically constant on the scale l_{cor}. Substituting (2.13) into (2.17) we find that evolution of the

averaged temperature at such points of living tissue can be described in terms of the effective medium model, namely

$$\frac{\partial T}{\partial t} = D_{\text{eff}}\boldsymbol{\nabla}^2 T + \frac{q_h}{c_t\rho_t}, \qquad (2.18)$$

where the effective temperature diffusivity is

$$D_{\text{eff}} = D\left[1 + g_a(0)\left(\frac{v_f l_{\text{cor}}}{D}\right)^2\right]. \qquad (2.19)$$

In the vicinity of large vessels equation (2.18) does not hold which is due to heat interaction between the cellular tissue and blood in such arteries and veins. In order to allow for this interaction let us write the heat conservation equation for the domain $\mathcal{Q}$ as a whole

$$\frac{d}{dt}\int_{\mathcal{Q}} d\mathbf{r}\, T = D_{\text{eff}}\oint_{\partial\mathcal{Q}} ds\,\boldsymbol{\nabla}_n T + J(T_a - T_v) + \frac{1}{c_t\rho_t}\int_{\mathcal{Q}} d\mathbf{r}\, q_h. \qquad (2.20)$$

Here the first term on the left–hand side of equation (2.20) describes heat flow through the boundary $\partial\mathcal{Q}$ of the domain $\mathcal{Q}$, the second one is caused by heat flow going into and out of the domain $\mathcal{Q}$ with blood through large artery and vein, T_a and T_v are the temperatures of blood in these vessels at the boundary $\partial\mathcal{Q}$, and J is the total blood flow going through the given domain. For the value of J we may write

$$J = \int_{\mathcal{Q}} d\mathbf{r}\, j(\mathbf{r}). \qquad (2.21)$$

Depending on the vessel architectonics, the temperature T_v of blood in the large vein going out of the domain $\mathcal{Q}$ is approximately equal to the averaged tissue temperature T or there can be a substantial difference between these temperatures. If the venous and arterial beds are not located in a closed vicinity of each other then any vein is far enough from the arteries of the same length and thereby $T_v \approx T$ because blood in small vessels is in thermal equilibrium with the surrounding cellular tissue. When the vascular network is organized in such way that arteries and veins are located in the vicinity of one another there is a strong heat exchange between blood flows in a vein and in the corresponding artery (counter current vessels). So, in this case $|T_v - T_a| < |T - T_a|$. In order to allow for the given heat interaction we may introduce a cofactor $f < 1$ into the relation

$$(T_v - T_a) = (T - T_a)f. \qquad (2.22)$$

Then assuming the fields $T(\mathbf{r})$ and $j(\mathbf{r})$ to be approximately constant over the domain $\mathcal{Q}$ and taking into account expressions (2.21) and (2.22) we can convert equation (2.20) into the following partial differential equation

$$\frac{\partial T}{\partial t} = D_{\text{eff}}\boldsymbol{\nabla}^2 T - fj(T - T_a) + \frac{q_h}{c_t\rho_t}, \qquad (2.23)$$

which practically exactly coincides with the generalized bioheat equation (2.5).

Equation (2.23) actually is phenomenological rather than the reliable result of averaging the microscopic bioheat equations. It contains at least two parameters, the effective diffusivity D_{eff} and the cofactor f which cannot be found in the framework of the mean field approach. In addition, the question of whether the averaged tissue temperature can be practically constant on spatial scales of order $l_{\parallel}$ is beyond the mean field theory of bioheat transfer. The same concerns the form of the microscopic bioheat equation when the blood flow rate is extremely non-uniform distributed over living tissue.

Due to the vessel system being hierarchically organized blood flow distribution over the vascular network as well as over the tissue domain has to be characterized by strong correlations between different hierarchy levels and also by spatial correlations. Therefore, in order to describe the blood flow effect on heat transfer one should take into account the vascular network as a whole rather than consider vessels of different levels individually. The vascular network models (see, e.g., [6, 7, 106]) dealing with living tissue phantoms containing infinitely long vessels or models where the effect of blood flow in different vessels on heat transfer are treated in the same terms [45, 101, 103] cannot form the basis of the successive procedure of averaging the microscopic equations. The next characteristic property of living tissue is its active response to temperature variations. Living tissue tries to remain it temperature within a certain vital interval $[T_-, T_+]$. Therefore, if a certain tissue domain is, for example, heated, the vessels supplying this domain with blood will expand and the blood flow rate will increase. In order to find specific relationship between the blood flow rate $j(\mathbf{r})$ and the tissue temperature field $T(\mathbf{r})$ one should, in principle, account for the temperature response of the vascular network as a whole. Thus, the bioheat equations discussed in section 2.1 can use only phenomenological models for the relation $j(T)$ (see, e.g., [17, 43]). It should be noted that blood flow rate can increase locally by tenfold [95].

In order to go out of the framework of the mean field approach we will describe bioheat transfer in terms of random walks in living tissue, instead of solving the microscopic temperature evolution equations directly. This is possible due to the well known equivalence of diffusive type processes and random motion of certain Brownian particles. For example, in the theory of grain boundary diffusion and diffusion in crystals with dislocations such an approach has enabled to obtain rigorous equations for anomalous diffusion [1, 63, 56, 57, 58].

Chapter 3

Physiological background

3.1 Microcirculatory region as a basic fundamental domain of bioheat transfer theory

In the theory of bioheat transfer living tissue is regarded as a certain part of a living organism. The models mentioned in Introduction treat living tissue as a continuum containing vessels where blood flow is predetermined. So, these models consider vessels of different levels practically independently of each other [6]. In the same time blood flow distribution over vessels belonging to different levels must be self - consistent due to the hierarchical organization of vascular networks. Therefore, on one hand, in order to develop the desired successive averaging procedure we need to take into account blood flow distribution over all hierarchy levels that can affect the blood flow rate at a point under consideration. On the other hand, it is impossible to describe heat transfer in a living organism as a whole, including blood flow distribution over its systemic circulation, in the context of continuous theory. The latter also is of a little consequence when the tissue region affected directly, for example, heated by external power sources is not sufficiently large.

Therefore, first of all, we should specify a minimal region of a living organism for which a complete theory of heat transfer can be developed. In other words, such a theory has to describe in the self-consistent way the distribution of the tissue temperature as well as the blood flow rate over the tissue domain under consideration. This minimal region of living organism will be called the basic fundamental domain of living tissue.

In living organisms a microcirculatory bed region can be treated as a basic fundamental domain. In fact, the main aim of systemic circulation is to maintain the arterial-venous pressure drop P at a given constant. A regional circulation, i.e. the vascular network of a single organ, varying its resistance to blood flow supplies different points of the organ with such amount of blood that is needed for the organ activities [73, 74, 72]. For a relatively simple organ its whole regional circulation is a microcirculatory bed. In other organs a microcirculatory

bed is a certain part of the organ regional circulation, for example, brain pial arterial network forms a single microcirculatory bed. In this case blood flow in different microcirculatory beds, in principle, can be analyzed independently of each other [73].

In the present work we consider heat transfer in a living tissue domain that contains a complete vessel system forming a single microcirculatory bed.

We would like to point out that analysis of temperature distribution in living tissue under strong local heating touches one of the fundamental problems in mathematical biophysics, viz. mathematical description of heat and mass transfer, and associated self-regulation processes in living organisms on scales of a single microcirculatory bed.

The matter is that, on one hand, a tissue domain containing a single microcirculatory bed is ordinarily large enough so, that first, transport of oxygen, possibly other nutrients as well as heat over the domain is mainly caused by blood flow in the vascular bed. Second, due to self-regulations processes the distribution of O_2, CO_2, etc. as well as the temperature field in their turn control blood flow redistribution over the vascular network. Thus, already on such scales mass and heat transfer possesses properties peculiar to living organisms. On the other hand, different parts of the same microcirculatory bed seem to be similar in physiological function and structure. So, in the context of field theory there can be a suitable mathematical model for heat and mass transfer in living tissue on scales of a single microcirculatory bed. In addition, due to the relative volume of vascular network being typically small, from the viewpoint of mass and heat transfer living tissue is an active extremely heterogeneous medium which is characterized by a peculiar geometry of fast transport paths whose properties depend on the temperature field and concentrations of diffusing elements. Therefore, description of mass and heat transfer also forms a mathematical problem in its own right.

Let us now discuss some fundamental properties of real microcirculatory beds and heat transfer in living tissue that form the ground for the following constructions.

When a living tissue domain containing a microcirculatory bed is in the normal state, i.e. the temperature as well as the concentration of O_2, CO_2, etc. are constant over the domain, the blood flow rate is uniformly distributed over this domain too. If the latter takes place, every small part of the domain (in comparison with the domain itself) is bound to contain, on the average, an equal number of vessels, whose lengths are smaller than the size of this part. In addition, in the normal state the parameters describing blood flow in vessels of the same level must be equal for these vessels because, otherwise, it would give rise to nonuniform distribution of the blood flow rate $j(\mathbf{r})$. Therefore, architectonics of such a microcirculatory bed have to satisfy the condition that any path along the vascular network from the host artery to a small arteriole and then from the corresponding venule to the host vein (or, at least, along the arteries and veins determining the resistance of the vascular network to blood flow) must be of an equal length.

Typically, a vascular network involves arterial and venous parts in the tree

form as well as the system of artery-artery, vein-vein and artery-vein anastomoses [73, 92]. However, there are organs containing a few number of anastomoses or practically no one at all. Moreover, it seems that the basic role of anastomoses is to compensate, for the blood flow redistribution over the vascular network when self-regulation processes cause, for example, substantial expansion of some vessels [73] and this subject deserves an individual investigation. Therefore, in the present work we shall ignore anastomoses and assume that arteries and veins make up the arterial and venous bed of the tree form.

The real capillary system connecting arterioles and venules with each other involves host and minor capillaries [73]. As a rule, the former join arterioles to the nearest venules, whereas, the latter are transformed into a capillary network by a large number of capillary anastomoses [73]. This capillary network can connect not only the nearest venules and arterioles but also distant ones. It should be noted that such a capillary bed has been previously considered in terms of a porous medium in modelling heat transfer [91, 107]. Under certain conditions rheological properties of blood give rise to switching on or switching off the minor capillary bed [73]. Therefore, as it follows from the percolation theory, (see. e.g., [4, 5, 25]) connection between distant arterioles and venules can play a significant role in heat transport, at least in the vicinity of the switching points. In addition, in accordance with the results obtained below (see Section 6.5), capillary influence on heat transport is collective, i.e. only the mean properties of the capillary system geometry are the factor. We may use any model for a capillary system which is equivalent to the real one with respect to the main characteristic details.

From the standpoint of heat transfer the specific geometry of vascular network is not a factor (see Chapters 5-7); thus, solely the characteristic details of vessel branching (for example, the mean number of arteries formed by branching of one artery whose length is twice as large) should be taken into account. The latter allows us to choose the specific vascular network architectonics for convenience. Typically the resistance of a microcirculatory bed to blood flow is mainly determined by an artery collection involving vessels of different lengths. Therefore, we may assume that, at least in normal living tissue venules, capillaries, and arterioles have no significant direct effect on the blood flow redistribution. For real microcirculatory beds the resistance to blood flow in venous parts is not a factor. Arterial and venous parts of the same microcirculatory bed, on the average, are approximately similar in geometry [73, 92, 74, 72]. Veins have wider diameters than arteries of the same length, thus, the blood pressure drop across a microcirculatory bed is mainly caused by the resistance of its arterial bed. However, as it follows from the results obtained in Chapter 5, heat transfer in living tissue actually depends on blood currents in vessels rather than on the velocity field of blood flow in the vessels and their radii individually. So, due to the arterial and venous beds being of the tree form the blood current patterns on the arterial and venous parts of the same vascular network are approximately identical. There is a certain self-averaging property of heat transfer in living tissue (see Chapter 5) owing to which specific features of the arterial and venous beds are not the factor. So, for simplicity we may consider the sym-

metrical model for the vascular network where the arterial and venous parts are the mirror images of each other and the total pressure drop is twice as large.

3.2 Characteristics of temperature distribution in living tissue

Temperature distribution in living tissue is characterized by a number of spatial scales. One of them is the distance l_D on which the tissue temperature variations are directly controlled by heat conduction in the cellular tissue. According to the conventional bioheat equation (2.1)

$$l_D \sim \left(\frac{D}{j} \right)^{1/2} \qquad (3.1)$$

where $D = \kappa/(c_t \rho_t)$ is the tissue thermal diffusivity and we have taken into account that $\rho_b \sim \rho_t \, ; c_b \sim c_t$. It will be shown below in the present work, the estimate (3.1) holds also true for living tissue with countercurrent vascular networks. The spatial scale l_D is associated with the temporal scale $\tau_D \sim l_D^2/D \sim 1/j$. There is another characteristic spatial scale l_v that is the mean length of a single vessel where arterial blood attains thermal equilibrium with the surrounding cellular tissue for the first time in its motion through the vessel system from large arteries to arterioles. The value of l_v practically coincides with the thermal equilibrium length $l_\parallel$ after which the blood temperature in a vessel has approached the temperature of the surrounding tissue: $l_v \sim l_\parallel$. According to [16, 103]

$$l_\parallel \sim \frac{a^2 v}{D} \ln \left(\frac{d}{a} \right) \qquad (3.2)$$

where a is the radius of a vessel under consideration, d is the mean distance between vessels of the same length l and v is the blood velocity averaged over the vessel cross section. Typically $l \sim d$ [105], then from the condition $l_v \sim l_\parallel$, and expression (3.2) we get

$$l_v \sim \left(\frac{D}{j} \frac{1}{\ln(d/a)} \right) \qquad (3.3)$$

where we have also taken into account the relation $j \sim (a^2 v)/l^3$ because $\pi^2 a^2 v$ is the total blood current flowing through the tissue domain falling on one vessel of this type whose volume is about $d^2 l_v \sim l_v^3$.

The quantity l_v classifies vessels by their influence on heat transfer. For typical values of the tissue thermal diffusivity $D \sim 2 \cdot 10^{-3} (cm^2/s)$, the blood

flow rate $j \sim 6 \cdot 10^{-3} \cdot s^{-1}$, and the ratio $d/a \sim 40$ we get $l_D \sim 0,6cm$; $l_v \sim 0,3cm$ and $\tau_D \sim 3\,\mathrm{min}$. For real microcirculatory beds ordinarily the mean length of the shortest vessels (capillaries, venules, arterioles) is well below l_v , whereas that of host arteries and veins is substantially larger that l_v . In this case, as it will be shown in Chapter 6, the value l_v divides all vessels of a microcirculatory bed into two classes according to length. The first class involves the vessels whose length is larger than l_v , and the second class consists of the vessels whose length is smaller than l_v.

Blood flowing through the first class vessels has actually no time to attain thermodynamic equilibrium with the surrounding cellular tissue and, thereby, may be considered to take no part, on the average, in heat exchange with the cellular tissue [17, 18]. The latter allows us to suppose that at branching points of the first class vessels not only the conservation law of blood current but also the conservation law of heat current are true. For this reason in the first class arteries the blood temperature is practically equal to the temperature T_a of blood in large arteries of systemic circulation, which is assumed to be a predetermined quantity. In the first class veins blood must be characterized by its own temperature T^*. Indeed, into a given vein of the first class through smaller veins, also belonging to the first class, blood comes without loss in heat from different point of a tissue domain whose size is about the vein length. So, when, for example, the tissue temperature $T(\mathbf{r}, t)$ is nonuniform on scales of order $l > l_v$ the temperature of blood in a vein, whose length is larger than l, will not coincide with the mean tissue temperature in the vein neighborhood of radius l.

In the second class vessels blood is in thermodynamic equilibrium with the cellular tissue and has no significant direct effect on heat transfer in living tissue. Below the vessels of the first and second classes will be also called heat conservation (or thermoimpermeable) and heat dissipation (or thermopermeable), respectively.

Keeping in mind microcirculatory beds such as those of kidney, muscles etc. [48] we consider a three-dimensional vascular network embedded in a tissue domain Q_0 three spatial sizes of which (L_x, L_y, L_z) are of the same order. Moreover, the given domain Q_0 may be assumed to be of the cube form because in this case its specific geometry practically is not a factor. When one of the spatial sizes, e.g. L_x, is substantially smaller than the others but well above l_D (i.e. $l_D \ll L_x \ll L_y, L_z$) the resistance to blood flow in vessels that are responsible for blood redistribution over the domain Q_0 on scales being larger than L_x seems to be ignorable. Thus, in this case we may divide the domain Q_0 into cubes of the volume L_x^3 and consider heat transfer in the obtained subdomains individually. When $L_x \ll l_D$ heat transfer in such a domain should be analyzed within the framework of a two-dimensional model which is the subject of an individual investigation. Besides, for real living tissues it is quite natural to assume that if both the tissue temperature T and the concentration of O_2, CO_2, etc. are constant over a domain, which contains a single microcirculatory bed, then the blood flow rate j will be also constant over this domain. Within the framework of the model under consideration such an assumption gives rise to the

requirement that the vascular network is uniformly distributed over the domain Q_0. The term "uniformly" means that each subdomain of diameter l contains approximately an equal number of vessels, whose lengths are smaller than l , as it is observed in real living tissues [73, 92].

3.3   The main properties of temperature self-regulation in living tissue

The main objective of the thermoregulation theory is to obtain the equation governing evolution of the blood flow rate $j(r)$ at every point of the microcirculatory bed domain as the tissue temperature varies in this domain. Previously, in mathematical analysis of the tissue temperature distribution the blood flow rate $j(\mathbf{r}, t)$ is usually taken into consideration in terms of a predetermined function of the coordinates $\mathbf{r}$ and the time t. However, when the tissue temperature T attains values about $42 - 44^0 C$ self-regulation processes in the living organ lead to a strong dependence of the blood flow rate j on the temperature field $T(\mathbf{r}, t)$. According to the available experimental data [94] self-regulation processes can locally increase the blood flow rate by tenfold. It should be pointed out that in the general case the relation $j = j\{T\}$ is of a functional form. In other words a value of j at a point $\mathbf{r}$ must depend on characteristics of temperature distribution over a certain domain rather than on the temperature $T(\mathbf{r})$ at the given point $\mathbf{r}$ only. Indeed, let a certain artery directly supplies a domain Q' with blood. Then, for example, increase in its diameter induced by temperature variation at some point causes increase in the blood flow rate j at least in the whole domain Q'. Therefore, the proposed local models for the $j\{T\}$ dependence, based on experimental data, i.e. the models where the functional $j\{T\}$ is given in terms of a local function $j(T)$, seems to be justified for relatively uniform temperature distribution only.

Now let us discuss some characteristics of the real vascular network response to temperature variations. In principle, strong heating of a living tissue domain can cause a response in the organism as a whole system. However, when the domain affected directly is small enough increase in blood flow inside the given tissue domain will be mainly controlled by the corresponding microcirculatory bed. In this case large vessels of systemic circulation, which supply different organs with blood, can be treated as an infinitely large blood reservoir where the pressure drop is maintained at a constant value P [73]. Due to the conservation law of heat current in the first class veins the temperature T^* of blood in these veins is a natural parameter for control of the temperature field $T(\mathbf{r}, t)$ in the cellular tissue. Indeed, since heat exchange between blood in the first class veins and the cellular tissue is ignorable., the temperature T_i^* of blood, for example, in a vein i of the first class should be approximately equal to the mean tissue temperature T_i in the subdomain Q_i from which blood is carried away through the given vein. So, the value of T_i^* can immediately specify the response of

the corresponding artery directly supplying the given tissue subdomain Q_i with blood.

The precise details of temperature self-regulation processes in living tissue, in particular, the position of temperature receptors and the mechanism of their response are still the subject of investigations. So, let us discuss some speculations on this problem. It is quite natural to assume that such temperature receptors should be located in veins. Indeed, in this case their "readings" immediately enable the organism to get information on the temperature distribution over the tissue on all scales. If they were uniformly distributed in the cellular tissue, then to respond to temperature variations in the proper way, for each artery the individual transformation of their "readings" would be required. This would make the system of the organism response to temperature variations more complicated and, therefore, less reliable. Nowadays such receptors are usually assumed to be located in veins, in arteries as well as in the cellular tissue [73]. However, the position of temperature receptors is practically a factor only for sufficiently large vessels of a microcirculatory bed, viz., for the first class vessels. So, in the sequel we shall assume that all temperature receptors are in the veins. As to the mechanism of the vascular network response to temperature variations, the available experimental date indicate that there are certain receptors located in veins which by means of the nervous system determine response of the corresponding arteries [73]. These receptors are sensitive to the concentration of such components as H^+, K^+, CO_2 etc. However, variations in the tissue temperature give rise to change in the metabolic process and vice versa. So, there must be a local relation between the temperature field $T(\mathbf{r}, t)$ and the concentration of such components because their diffusion coefficients are much less than the thermal diffusivity. Besides, for the first class veins propagation of these components and heat propagation possess the same properties. Therefore, it is quite justified to assume that there is a similar local relation between the blood temperature T^* and the concentration of these components in blood. So, such receptors can be regarded as ones responding to the blood temperature T^*. Taking into account the aforementioned characteristics of tissue thermoregulation we, first, assume that the response of an artery i is directly controlled by the temperature T_i^* of blood in the corresponding vein i and, second, describe the temperature self-regulation process in terms of time variations in vessel resistances to blood flow, which are caused by variations in the blood temperature.

By definition, the vessel resistance R to blood flow is the quantity appearing in the relationship $\Delta P = RJ$ between the pressure drop ΔP across a given vessel and the blood current J in it. Due to blood being complex in structure, nonlinear effects in its rheology give rise, in particular, to dependence of the vessel resistance on the mean blood velocity. In other words, in the general case the resistance R is a function of J. However, under normal conditions such nonlinear effects exert appreciable influence on blood flow only in vessels whose radius a is less than $50 \div 100\mu m$ [73]. For real microcirculatory beds a typical value of the ratio between the length l and radius a of a given artery is about $(l/a) \sim 30 - 40$. Therefore, the possible dependence $R(J)$ has to be

Figure 3.1: The vessels resistance R as a function of the blood temperature T^* (a) and the corresponding quasistationary dependence of the tissue temperature T on the uniform heat generation rate q (b) (thecurves r and i display the real and ideal dependencies).

taken into account only for vessels whose length is smaller than $0.15 \div 0.3 cm$. As it has been obtained above, the value $l_v \sim 0.3 cm$, thus, the nonlinear effects in blood rheology can play an important role in blood redistribution over the second class vessels only, at least when the blood flow rate is not extremely high. For this reason in the present manuscript we shall ignore the blood current dependence of the vessel resistances. The influence of these nonlinear effects on thermoregulation and heat transfer in living tissue may be the subject of individual investigations. In addition, in the quasistationary case the resistance R_i of the artery i as well as the vein i is supposed to be a given explicit function of the temperature T_i^* of blood in the vein i : $R_i = R_n(T_i^*)$ where n is the level number of this vessel pair.

Finally, we discuss the properties that the function $R_n(T^*)$ must possess. Let T_{nor} be the temperature required for the normal functioning of the organ and q_n be the corresponding value of the heat generation rate. For $T_{\mathrm{nor}} > T_a$ increase or decrease in q gives rise to increase or decrease in the tissue temperature T_a respectively. To compensate these temperature variations the response of the arteries should cause an increase or appropriate decrease in the blood flow rate, because for $T_{\mathrm{nor}} > T_a$ arterial blood can be regarded as a cooling source. This effect takes place when $R_n(T^*)$ is a decreasing function in the region $T^* > T_a$. If $T_{\mathrm{nor}} < T_a$, then, as it can be shown similarly, $R_n(T^*)$ must be an increasing function for $T^* < T_a$. Such a behavior of the function $R_n(T^*)$ in the general form is displayed in Fig. 3.1a by the line "r", and Fig. 3.1b shows the corresponding quasistationary dependence of the tissue temperature T^* on the heat generation rate q for heat sources uniformly distributed over the tissue. When the heat generation rate becomes large enough and the vessels exhaust their possibility of responding the temperature self-regulation process is depressed. In this case the resistance $R_n = R_{\mathrm{min}}$ ceases to depend on T^* and, as the value of the heat generation rate q increases, the temperature T goes beyond the interval $[T_-, T_+]$ where the organ tissue can survive. For $T > T_+$ or $T < T_-$ after a certain time the organ capacity for functioning is irreversibly

depressed. However, description of the latter process is an individual problem and is not considered here.

In the present work special attention will be focused on a certain idealized model for the $R_n(T^*)$ dependence that is shown in Fig. 3.1a by the line "i" and can be represented as

$$R_n^{id}(T^*) = \begin{cases} R_n^0 \left[1 - \frac{|T^* - T_a|}{\Delta}\right] & ; \quad \text{if} \quad |T^* - T_a| \leqslant \Delta \\ 0 & ; \quad \text{if} \quad |T^* - T_a| > \Delta \end{cases} \quad , \qquad (3.4)$$

where R_n^0 is a certain constant for a given vessel pair, Δ is the half width of the vital temperature interval, and for simplicity we have set $T_+ = T_a + \Delta$ and $T_- = T_a - \Delta$. The corresponding ideal dependence of T on q is displayed in Fig. 3.1b by the curve 'i'. It should be pointed out that within the framework of the given model the resistance $R_n^{id}(T_i^*)$ goes to zero at the same temperature $T_i^* = T_+$ or $T_i^* = T_-$ for each vessel pair and, thus, in the quasistationary case the tissue temperature $T(\mathbf{r}, t)$ cannot go beyond the interval $[T_-; T_+]$. For this reason, when the vessel response can be described by the function $R_n^{id}(T^*)$ the temperature self-regulation process will be also referred to as ideal.

Characteristics of heat transfer and the temperature self-regulation process that we have discussed above are the main ground essentials for the following model proposed in the present work.

Chapter 4

Hierarchical model for living tissue and the governing equations

4.1 Evolution equations for the temperature of cellular tissue and blood in vessels

Due to heat conduction of living tissue practically all spatial scales of the temperature field $T(\mathbf{r}, t)$ are well above the single cell size. This allows us to consider the cellular tissue in terms of an isotropic continuum in which the temperature obeys the equation:

$$\rho_t c_t \frac{\partial T}{\partial t} = \kappa \boldsymbol{\nabla}^2 T + q_h. \tag{4.1}$$

Here as well as in the Introduction q_h is the heat generation rate caused by metabolic processes and electromagnetic or ultrasonic radiation absorption, ρ_t, c_t, κ are the density, specific heat capacity, and thermal conductivity of the tissue which are regarded as constant quantities.

Let us describe each vessel as a pipe of length l and radius a. The temperature field T^* of blood inside vessels satisfies the equation:

$$\rho_t c_t \left(\frac{\partial T^*}{\partial t} + \mathbf{v}(\mathbf{r}) \boldsymbol{\nabla} T^* \right) = \kappa \boldsymbol{\nabla}^2 T^* + q_h \tag{4.2}$$

subject to the boundary conditions at the vessel interface σ

$$T|_\sigma = T^*|_\sigma, \tag{4.3}$$

$$\boldsymbol{\nabla}_n T \,|_\sigma = \boldsymbol{\nabla}_n T^* \,|_\sigma \;. \tag{4.4}$$

Here for the sake of simplicity the density, heat capacity and thermal conductivity of blood are assumed to be the same as for the cellular tissue, $\mathbf{v}(\mathbf{r})$ is the velocity field of blood flow inside the vessel system. The velocity $\mathbf{v}(\mathbf{r})$ substantially varies over the cross section of any vessel and, in particular, attains its maximum at the center of a vessel and is equal to zero at its boundary. However, as it follows from the results obtained below (see Chapter 5), to describe the influence of blood flow in a given vessel on heat transfer we may take into account only the blood flow velocity v averaged over its cross section. Boundary conditions (4.3), (4.4) represent equality of the blood and tissue temperature T, T^* and continuity of the normal component of the heat flux at the vessel interface. In addition, the total relative volume of the vessels in the tissue domain under consideration is assumed to be small, which allows us to ignore the term q_h in equation (4.2).

4.2 Hierarchical model for the vascular network

The vascular network involves vessels of all lengths from capillaries to the host artery and vein, however, as it will be shown in Part.2, just only vessels of a certain length l_v directly control the tissue temperature. Moreover, the effect of the latter vessels on heat transfer depends solely on the characteristic properties of their spatial distribution. This results from the fact that the tissue temperature at a given point $\mathbf{r}$ is practically determined by the mean heat generation rate in the neighborhood Q of the point $\mathbf{r}$, whose size is above l_D, and by the collective influence of l_v length vessels which are within this neighborhood.

In heat transfer the role of vessels whose lengths are substantially larger than l_v is to transport blood practically without heat exchange with the cellular tissue. Arteries and veins whose lengths are smaller than l_v have practically no effect on heat transfer at all. Since the mean distance between capillaries can be much less than their characteristic lengths the capillary network is able, in principle, to influence on heat transport, however, their effect is also collective.

Thus, heat transfer actually depends only on characteristic properties of the vascular network architectonics and blood flow distribution over the vascular network. This means, for example, that the tissue temperature at the point $\mathbf{r}$ depends on the total number of l_v length vessels be inside Q rather than on details of their interconnections. This characteristic of heat transfer in living tissue, which will be called the self-averaging property of heat transfer, allows us to choose the following model for the microcirculatory bed.

In accordance with Chapter 3 we assume that the vascular network (the microcirculatory bed) under consideration is embedded in a cube Q_0 of the volume $(2l_0/\sqrt{3})^3$. The host artery and the host vein of length l_0 and radius a_0 go into and out of the cube Q_0 through one of its corners (Fig.4.1). They form the initial (zeros) level of the vascular network. The host artery reaches the cube center O_0 where it branches out into eight arteries of the first level.

Figure 4.1:   Fragment of the vascular network architectonics under consideration including interconnection between vessels of different levels. (the solid and point lines represent arteries and veins respectively).

Figure 4.2: Dichotomously branching vascular network model.

Each artery of the first level reaches a center O_1 of one of the eight cubes $\{Q_1\}$ (called the fundamental domains of the first level) which compose together the cube Q_0 . In the centers $\{O_1\}$ each of the first level arteries in its turn branches out into eight second level arteries. Then the artery branching is continued in a similar way up to level $N \gg 1$. The geometry of the venous bed is identical to the arterial one at all the levels.

There is an alternative to the proposed model for the vascular network architectonics that is based on the dichotomously branching tree. The characteristic fragment of this vascular network is shown in Fig. 4.2. As for the first model the dichotomously branching vascular network is uniformly distributed over the basic fundamental domain Q_0, i.e. each of the fundamental domain of level n contains identical collection of vessels whose lengths are smaller than its size and the path on the vascular network from any of the smallest arteries (or veins) to the tree stem is the same.

Figure 4.3: Representation of a real fragment of vascular network (a) as the eightfold branching point (b).

Therefore, from the stand point of heat transfer these two models for vascular network are practically equivalent because the particular form of vessel branching points is of little consequence. The similarity between the two vascular network models as well as a real vascular network can be established by identifying vascular network fragments that connect the center points $\{O_n, O_{n+1}\}$ of fundamental domains of neighboring hierarchy levels. This identification for a real vascular network and the model represented in Fig. 4.1 is illustrated in Fig. 4.3. In Fig. 4.2 the arterial bed of the dichotomously branching vascular network is represented by the thick solid line and venous one is shown by the pointed line. We assume that the arteries and veins whose level number n is less or equal to $n_{cc}(n \leqslant n_{cc})$ are located in the immediate vicinity of each other whereas the arteries and veins of higher levels, $n > n_{cc}$, do not correlate in orientation. The possibility of such behavior is demonstrated in Fig. 4.2 and stems from the fact that the vessels can go out of branching points in different directions. The value n_{cc} is a parameter of the vascular network model and may be equal to any number of the collection $\{0, 1, ..., N\}$. If $n_{cc} = 0$ there is no counter current vessels pair, whereas when $n_{cc} = N$ all the arteries and the corresponding veins are parallel to each other.

In the eight - fold branching point model (Fig. 4.1) we also introduce the parameter n_{cc} which divides all vessels into two groups. The arteries and veins of the first group whose level number $n \leqslant n_{cc}$ form countercurrent pairs and the arteries and veins of the second group for which $n > n_{cc}$ are formally not considered to correlate in orientation.

The main attention in the present work will be focused on the first vascular network model because dealing with this model we avoid awkward mathematical calculations.

When the blood temperature is equal to the arterial temperature of systemic circulation T_a, all vessels of one level (for example of level n) and blood flows in them are assumed to be equivalent and are described by the same set of parameters, such as their length l_n, radius a_n and the mean velocity v_n of blood

in these vessels, i.e.

$$\{l_n = l_0 2^{-n};\ a_n;\ v_n\}. \tag{4.5}$$

Due to the blood current conservation law at the branching points for the given vascular network architectonics these parameters satisfy the relation:

$$\pi a_n^2 v_n M_n = J_0, \tag{4.6}$$

where n is the level number, $M_n = 2^{3n}$ is the total number of arteries or veins belonging to level n, and J_0 is the total blood current going into the cube Q_0 or, what is the same, is the blood current in the host artery or vein. For real vascular networks the ratio of the length to radius of a single vessel weakly depends on its length and is about $30 - 40$ [73]. Therefore, in addition, we assume that

$$\frac{l_n}{a_n} = w(n)\frac{l_0}{a_0}, \tag{4.7}$$

where $w(n)$ is such a smooth function of the level number n that $w(0) = 1$ and $w(n)$ is of order unity. In the following numerical estimations we also shall set $l_n/a_n \sim 30 - 40$. Each countercurrent pair, for example, that of level n is also characterized by the distance b_n between its vessels. In the given model we assume that the ratio b_n/a_n is a constant

$$\frac{b_n}{a_n} = \mu \tag{4.8}$$

and $\mu \geqslant 2$.

The last level vessels of the arterial and venous beds (called below arterioles and venules, respectively) are interconnected by the capillary system in the following way. Each arteriole branches out into m $(m \gg 1)$ capillaries forming a "chimney brush" structure (CB structure) (Fig. 4.4). Then without branching capillaries connect with venules in a similar way. Each capillary is described by the set of the parameters l_c, a_c, v_c obeying a relation similar to (4.6), viz

$$\pi a_c^2 v_c m = \pi a_N^2 v_N = \frac{1}{M} J_0 \tag{4.9}$$

where $M_N = M = 2^{3N}$ is the total number of arterioles or venules in the microcirculatory bed, l_c and a_c are the length and radius of capillary and v_c is the mean velocity of blood in it.

Below we shall consider individually two different structures of the capillary system that correspond to one of the following two inequalities $l_c \geq l_N$ and $l_c \gg l_N$.

Figure 4.4: Geometry of capillary system.

In the former case each arteriole can be connected with the first nearest neighbor venule only and capillaries are practically straight pipes. In the latter case we assume that each arteriole is joined to every venule being inside its neighborhood of size of order $\mathcal{R}$ by an approximately equal number of capillaries. In addition, we also assume that each capillary keeps its spatial direction within the scale $\lambda \geq l_N$. So, λ is also the mean curvature radius of a capillary regarded as a line, and on scales above λ different parts of a capillary are oriented independently from one another. Therefore, in this case we may represent each capillary as a set of randomly oriented in space rectilinear portions of length λ and assume that every arteriole and venule spaced at distance r are joined to each other, on the average, by $m(r)$ capillaries where

$$m(r) = \frac{V_N m}{(2\pi \mathcal{R}^2)^{3/2}} \exp\left\{-\frac{r^2}{2\mathcal{R}^2}\right\},\qquad(4.10)$$

$V_N = (2l_N/\sqrt{3})^3$ is the volume of fundamental domain of the last level, and

$$\mathcal{R}^2 = \frac{1}{3}(l_c\lambda) \qquad (4.11)$$

Expressions (4.10) and (4.11) result from the fact that the terminal point of a broken line made up of $\mathcal{N} = l_c/\lambda$ such randomly oriented portions, is characterized by the spatial distribution $P_{bl}(r)$ of the form [39]

$$P_{bl}(r) = \frac{1}{\left(\frac{2}{3}\pi\mathcal{N}\lambda^2\right)^{3/2}} \exp\left(-\frac{r^2}{\frac{2}{3}\mathcal{N}\lambda^2}\right), \qquad (4.12)$$

where $\mathcal{N}\lambda^2 = \lambda l_c = 3\mathcal{R}^2$ can be treated as the mean squared distance between the initial and terminal points of this broken line. Therefore, the probability for a capillary generated by an arteriole to reach a venule located at a distance r is $P_{bl}(r)V_N$ because all the capillaries terminating inside an elementary domain must go into the venule in this domain. Multiplying the last value by m we obtain the mean number of capillaries joining an arteriole and a venule spaced at the distance r. Immediately follows expression (4.10).

Equations (4.1),(4.2) and boundary conditions (4.3),(4.4) with the vascular network model described above are the mathematical formulation of the heat transfer problem. It should be mentioned that the temperature T_a of blood going into the tissue domain Q_0 through the host artery is the given parameter of the system.

For the purpose of the following investigations we also estimate the mean distance between vessels of certain types. By definition, the mean distance d between vessels of a given type is a quantity appearing in the expression $V = d^2l$ for the mean volume V falling on each vessel of this type. Due to every fundamental domain of level n containing just one artery of level n the mean distance between these arteries is

$$d_n = \left(\frac{2}{\sqrt{3}}\right)^{3/2} l_n. \qquad (4.13)$$

Obviously, d_n is also the mean distance between the veins of level n. The tissue domain Q_0 contains $(l_0/l_N)^3$ arterioles (because $M = 2^{3N} = (l_0/l_N)^3$) and, thus, $m(l_c/\lambda)(l_0/l_N)^3$ a practically rectilinear portions of the capillaries. Therefore, the quantity $d_c^2\lambda m(l_c/\lambda)(l_0/l_N)^3$, where $(d_c^2\lambda)$ is the mean volume falling on one capillary rectilinear portion, must be equal to the volume $V_0 = (2l_0/\sqrt{3})^3$ of the domain Q_0. We obtain the desired expression for the mean distance between the capillary rectilinear portions or, what is the same, for the mean distance d_c between the capillaries themselves

$$d_c = \left(\frac{2}{\sqrt{3}}\right)^{3/2} \left(\frac{l_N^3}{ml_c}\right)^{1/2}. \qquad (4.14)$$

Another quantity required for the further analysis is the blood flow rate $j(\mathbf{r})$ regarded as a continuous field defined at every point of the tissue domain Q_0. In the general case, including also nonuniform blood flow distribution over a vascular network, this quantity can be defined in the following way. Let us divide the total tissue domain into domains $\{Q_i\}$ of volume V and consider solely the arterial part of the vascular network. Then, for each domain Q_i we can find the total blood current J_i going into this domain through the arterial bed. By definition, the blood flow rate averaged over the domain Q_i is

$$\langle j \rangle_{Q_i} = \frac{J_i}{V}. \tag{4.15}$$

In this way we obtain the system of quantities $\{\langle j \rangle_{Q_i}\}$ associated with the given partition $\{Q_i\}$ of the total tissue domain. Let there exist such a partition $\{Q_i\}$ that, on one hand, each domain Q_i contains a large number of arteries, thereby, the quantities $\{J_i\}$ cannot change significantly at least for the nearest domains and, on the other hand, their characteristic spatial size $(V)^{1/3}$ is small enough. The latter means that all physical processes under consideration are controlled by collective influence of blood flow in arteries which belong to different domains rather than to the same. In this case we may interpolate the system $\{\langle j \rangle_{Q_i}\}$ by a certain smooth field $j(\mathbf{r})$ called the blood flow rate field or the blood flow rate. In particular, when for each branch of the arterial bed after a certain level blood flow is practically uniformly distributed over it, the obtained field $j(\mathbf{r})$ obviously does not depend on a partition of the total tissue domain provided its domains are small enough. So, at least in the latter case, the definition of the blood flow rate is worthwhile.

For the model of the living tissue described in this section it is natural to consider a partition of the total tissue domain Q_0 into fundamental domains $\{Q_n\}$ of level n. Since each of these fundamental domains is supplied with blood by an artery of level n, which is contained in it, the total blood current J_i going into a given domain Q_i coincides with the blood current in the corresponding artery of level n. When blood flow is uniformly distributed over the vascular network, thus, according to (4.6) the blood current in each artery of level n is equal to $J_i = J_0 2^{-3n}$ where J_0 can be regarded as the total blood current going into the tissue domain Q_0. Expression (4.5) enables us to represent the volume V_n of a fundamental domain belonging to level n in terms of $V_n = (2l_n/\sqrt{3})^3 = V_0 2^{-3n}$, where V_0 is the volume of the domain Q_0. Thereby, from (4.15) we find that the quantities $\langle j \rangle_{Q_n}$ are equal to the same value

$$j_c = \frac{J_0}{V_0} \equiv \left(\frac{\sqrt{3}}{2} \right)^3 \frac{J_0}{l_0^3} \tag{4.16}$$

but independent of the level number. Therefore, in the given case the blood flow rate is the uniform field $j(\mathbf{r}) = j_0$.

4.3   Governing equations for blood flow distribution over the vascular network

Now we formulate the governing equations for blood flow distribution over the vascular network.

Due to the self-averaging property the effect of blood flow on heat transfer is mainly governed by the blood current pattern on the vascular network rather than by particular details of vessel geometry and the blood velocity field $\mathbf{v}$ in the vessels individually. Therefore, in order to describe the vessel response to temperature variations we may deal with the vascular network considering every vessel as a whole, i.e. we need not to take into account particular details of the blood flux inside a given vessel and may allow for the mean properties of the blood flux in this vessel. So, in accordance with Chapters 3,4, each vessel is characterized by the resistance R to blood current J in it, which is assumed to be independent of J and governed by the blood temperature T^* in the corresponding vein.

The blood current distribution $\{J_i\}$ over the vascular network, obeys the conservation law of blood at branching points. In particular, for a given branching point B_a of the arterial bed we have

$$\sum_{B_a} J_{\text{out}} = J_{\text{in}}, \tag{4.17}$$

where J_{in} and J_{out} are the blood currents in the arteries going in and out of the branching point B_a and the sum runs over all the arteries going out of the branching point B_a. For a branching point B_v of the venous bed we get a similar expression, viz.:

$$\sum_{B_v} J_{\text{in}} = J_{\text{out}}, \tag{4.18}$$

where J_{in} and J_{out} are the same quantities for the veins forming the branching point B_v, but the sum runs over all the veins going in the branching point B_v. Secondly, the blood current pattern $\{J_i\}$ is related with the pressure distribution $\{P_i\}$ over the branching points of the vascular network by the expression

$$J_i R_i = \Delta P_i \ , \tag{4.19}$$

where ΔP_i is the pressure drop across the vessel i and R_i – the resistance of the vessel i. The additional condition, that the total pressure drop across the vascular network is equal to $2P$, and the collection of equations (4.17),(4.18) and (4.19) for different branching points and vessels, respectively, forms the complete system of Kirchhoff's equations governing the blood current pattern on the vascular network. It should be noted that within the framework of

the symmetrical model for the microcirculatory bed (see Chapters 3,4) we may confine ourselves to analysis of the blood current pattern on the venous part only.

In the framework of the classical approach to description of heat transfer in living tissue blood flow is conventionally characterized by the blood flow rate distribution $j(\mathbf{r}, t)$ determined at every point of the tissue domain. So, for the purpose of the following analysis we need to specify the relationship between the blood current pattern $\{J_i\}$ and the blood flow rate $j(\mathbf{r}, t)$. Since the last level number $N \gg 1$ and, thus, the length $l_N = l_0 2^{-N}$ of the last level arteries and veins may be treated as a small spatial scale, it is natural to assume that the blood flow distribution over the vascular network is uniform on scales of order l_N. In this case, according to the definition of blood flow rate, we can write

$$J_{i_\mathbf{r}} = V_N j(\mathbf{r}, t), \tag{4.20}$$

where $J_{i_\mathbf{r}}$ is the blood current in the last level artery (arteriole) $i_\mathbf{r}$ (or, what is the same, in the last level vein (venule) $i_\mathbf{r}$ that is located in the elementary domain $Q_{N\mathbf{r}}$ containing the point $\mathbf{r}$. By virtue of expressions (4.18),(4.19) and the adopted model for the vascular network embedding from (4.20) it immediately follows that the blood current J_i in the artery i or vein i contained in the fundamental domain Q_i of the same level n and the blood flow rate $j(\mathbf{r}, t)$ are related as

$$J_i = \int_{Q_i} d\mathbf{r}\, j(\mathbf{r}, t), \tag{4.21}$$

because the artery i directly supplies the whole domain Q_i with blood and the vein i drains it. Expression (4.21) is the desired relationship between the blood current pattern and the blood flow rate distribution.

4.4   Model for vessel response to temperature variations. Mechanism of temperature self-regulation

Thermoregulation in living tissue gives rise to vessel temperature variations which are described as variations in the vessel resistances $\{R_i\}$ to blood flow. Therefore, in order to complete the bioheat transfer theory we need to specify the equations governing the vessel resistance evolution.

When the tissue temperature is constant over the domain Q_0 and coincides with the systemic arterial blood temperature T_a ($T = T_a$), the temperature T^* of blood in all the vessels will coincide with T_a too ($T^* = T_a$). In this case all vessels of the same level are assumed to be equivalent and are characterized by the resistance

$$R_n^0 = R_0 2^{3n} \rho(n), \tag{4.22}$$

where n is the number of the given level and $\rho(n)$ is a smooth function of n such as $\rho(0) = 1$ and $\rho(n) \to 0$ as $n \to \infty$. It should be pointed out that from (4.22) of the R_n^0 dependence follows from the requirement of the blood flow redistribution over the vascular network controlled by an artery group comprising vessels of different lengths. This property is typical for real microcirculatory beds and its relation with form (4.22) of the R_n dependence can be illustrated as follows.

When the resistances of vessels belonging to one level are equal at each branching point the blood current splits into eight equal parts. Therefore, for any path on the vascular network leading from the arterial bed stem to the capillaries and then to the venous bed stem we can write

$$2P = 2 \left\{ J_0 R_0 + \frac{1}{8} J_0 R_1 + \frac{1}{8^2} J_0 R_2 + \ldots \right\} = 2 J_0 \sum_{n=0}^{N} 2^{-3n} R_n^0, \tag{4.23}$$

where we have ignored the capillary bed resistance. From the latter expression and formula (4.22) we find the total resistance R^* of the vascular network

$$R^* = R_0 \sum_{n=0}^{N} \rho(n). \tag{4.24}$$

It follows that the total resistance of the microcirculatory bed is determined by an artery group comprising vessels of different levels if $\rho(n)$ is a smooth function of n. Otherwise, the bed resistance and, consequently, the blood flow rate redistribution due to thermoregulation will be controlled by vessels practically of one level.

Besides, form (4.22) of the R_n dependence can be partly justified in physical terms. It is natural to assume that the vessel radius a_n changes in the same way as the length $l_n = l_0 2^{-n}$ during vessel branching. In other words, we may suppose that $a_n \simeq a_0 2^{-\gamma n}$ where a_0 is the host vessel radius and the constant $\gamma \approx 1$. Characterizing rheological properties of blood by the effective coefficient μ_{eff} of viscosity the vessel resistance R to blood flow is given by the formula [55]

$$R = \frac{8}{\pi} \mu_{\text{eff}} \frac{l}{a^4}. \tag{4.25}$$

Thus, when, for example, $\mu_{\text{eff}}(a) \sim a^\alpha$, where α is a constant [73], this expression leads to formula (4.22) for

$$\gamma = \frac{4}{4 - \alpha}. \tag{4.26}$$

In particular, for $\alpha \leqslant 1$ [73] the value $\gamma \approx 1$.

When the tissue temperature is nonuniform distributed over the domain Q_0 the blood temperature is also nonuniform and due to self-regulation processes the resistances of all the vessels can become different. In this case, in accordance with the remarks on the temperature self-regulation discussed in Section 3.3, the response of any artery to temperature variations is assumed to coincide with that of the corresponding vein and to be governed by the temperature of blood in this vein. The term "corresponding" means that the given artery and vein belong to the same level and are connected with each other through vessels of the higher levels. In mathematical terms we specify the response of such two vessels, for instance, of an artery i or vein i by the following model.

According to Section 3.3 the response of a vessel to temperature variations can be described in terms of the dependence of the vessel radius a on the temperature T^* of blood in this vessel if it is a vein or in the corresponding vein for an artery. The vessel response is assumed to be specified by the following simple phenomenological equation

$$\tau^*(a)\frac{da}{dt} + a_0 f^*\left(\frac{a}{a_0}\right) = a_0 \frac{|T^* - T_a|}{\Delta}. \tag{4.27}$$

Here the first term on the left-hand side describes delay of the vessel response to the dimensionless "signal" $|T^* - T_a|/\Delta$ generated by "temperature" receptors, $\tau^*(a)$ is the characteristic time delay of this process, a_0 is the vessel radius for $T^* = T_a$, and the second term represents the vessel counteraction to its expansion. The qualitative behavior of the function $f^*(a/a_0)$ is shown in Fig. 4.5. Let the resistance R of the given vessel depend on its radius a as:

Figure 4.5: The qualitative shape of the function $f^*(a/a_0)$

$$R = \frac{\text{constant}}{a^\beta}, \tag{4.28}$$

where the constant $\beta > 0$. Then taking into account (4.27) and (4.28) we find

$$\tau\frac{dR}{dt} + (R - R^0)f\left(\frac{R}{R_0}\right) = -R_0\frac{|T^* - T_a|}{\Delta} \ . \tag{4.29}$$

Here we have introduced the quantities

$$R^0 = R\mid_{a=a_0}; \tau = \tau^*(a)\frac{1}{\beta}\left(\frac{a}{a_0}\right)^{\beta+1} \tag{4.30}$$

and the function

$$f(x) = \frac{1}{(1-x)}f^*\left[\left(\frac{1}{x}\right)^{1/\beta}\right] \ . \tag{4.31}$$

Within the framework of the proposed model in equation (4.29) the value of τ is determined by the time delay in the response of both the vessel muscles and the nervous system. There are also other additional mechanisms of the time delay. One of them is associated with the time required for an appropriate heated portion of blood to reach a given vein. Another can be realized when the response of vessels to temperature variations occurs through their response to variations in the concentrations of K^+, H^+, etc. (see Introduction and Chapter 3). Indeed, in this case in order to cause variations in the K^+, H^+, etc. concentrations a certain time τ is required for change in the metabolic process is due to the tissue temperature alteration. At least within the framework of a qualitative analysis we may combine all the mechanisms of the time delay in one mathematical term $\tau\frac{\partial R}{\partial t}$ and describe dynamics of the vessel response by equation (4.29). Setting for simplicity $\tau =$ constant, where τ is a certain phenomenological time delay, we immediately obtain the desired equation for the resistance R_i:

$$\tau_n\frac{dR_i}{dt} + (R_i - R_n^0)f\left(\frac{R_i}{R_n^0}\right) = -R_n^0\frac{|T_i^* - T_a|}{\Delta} \ , \tag{4.32}$$

where n is the level number of the given vessel pair, τ_n is the characteristic time of the n-th level vessel response; Δ is the halfwidth of the temperature vital interval, and the function $f(x)$ describes the vessel capacity for responding. In addition, following Section 3.3 we assume that in the quasistationary case the resistance R_i^q of the vein i or the artery i is an explicit function of T_i^*, viz.

$$R_i^q = R_n^0\varphi\left(\frac{|T_i^* - T_a|}{\Delta}\right) \ , \tag{4.33}$$

where $\varphi(x)$ is a certain given function universal for all the vessels. The properties of this function have been actually discussed in Section 3.3. Besides, as it follows from (4.32) and (4.33) the functions $f(x)$ and $\varphi(x)$ are related by the expression

$$[1 - \varphi(x)] \cdot f[\varphi(x)] = x \; . \tag{4.34}$$

In particular, according to the definition given in Section 3.3 for the ideal temperature self-regulation process

$$\varphi^{id}(x) = \left\{ \begin{array}{cl} 1 - x & , \quad \text{if} \quad 0 \leqslant x \leqslant 1, \\ 0 & , \quad \text{if} \quad 1 < x \end{array} \right. \tag{4.35}$$

and, by virtue of (4.34), $f^{id}(x) = 1$ for $0 < x \leqslant 1$ and $f^{id}(x)$ is undefined at $x = 0$. The behavior of the functions $f(x)$ and $\varphi(x)$ for the real and ideal thermoregulation is displayed in Fig. 4.6. The blood temperature T_i^* appearing

Figure 4.6: Behavior of the function $\varphi(x)$ (a) and the function $f(x)$ (b) for the real (curves r) and ideal (curves i) thermoregulation.

in equation (4.32) and expression (4.33) is actually the mean temperature of blood in the vessel i. However, due to the blood temperature field $T^*(\mathbf{r}, t)$ being practically constant over a single vessel we may not distinguish between the quantity T_i^* and the true temperature of blood in the given vessel.

Chapter 5

Random walk description of heat transfer

5.1 The Fokker-Planck equation and random walk description of heat propagation

The bioheat transfer problem stated in Sections 4.1, 4.2 describes the tissue temperature evolution at the microscopic level, i.e. considers each vessel individually. In order to develop an averaging procedure of these microscopic equations and to obtain a macroscopic model for bioheat transfer we shall make use of the random walk description of heat transfer. For this purpose we should write equations (4.1),(4.2) in the form of the Fokker - Planck equation. Its solution can be represented in terms of a path integral, which immediately leads to the desired random walk description.

Due to blood being an incompressible liquid and, thus, $\boldsymbol{\nabla}\mathbf{v} = 0$, the system of equations (4.1), (4.2) subject to boundary conditions (4.3), (4.4) can be rewritten in the form of the Fokker - Planck equation with sources, i.e.

$$\frac{\partial C}{\partial t} = \boldsymbol{\nabla}^2(DC) - \boldsymbol{\nabla}(\mathbf{v}(\mathbf{r})C) + q. \qquad (5.1)$$

Here $C = (T - T_a)/(T_a V_N)$ and $C = (T^* - T_a)/(T_a V_N)$ in the cellular tissue and inside the vessels, respectively, $q = q_h/(\rho_t c_t T_a V_N)$, $D = \kappa/(\rho_t c_t)$ is the thermal diffusivity of the tissue, and V_N is the volume of fundamental domain of the last level. We note that in the cellular tissue $\mathbf{v}(\mathbf{r}) = 0$ and the value C has the dimension of concentration, and its variation from zero can be caused by heat generation only when the size of the tissue domain Q_0 is large enough, viz, $l_0 \gg l_D$.

If we ignore effect of the domain Q_0 boundaries on heat transfer, then the

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solution of equation (5.1) can be written as

$$C(\mathbf{r}, t) = \int\limits_{-\infty}^{t} dt' \int\limits_{Q_0} d\mathbf{r}' G(\mathbf{r}, t \mid \mathbf{r}', t') q(\mathbf{r}', t'). \qquad (5.2)$$

where the Green function $G(\mathbf{r}, t \mid \mathbf{r}', t')$ admits the path integral representation

$$G(\mathbf{r}, t \mid \mathbf{r}', t') = \int \mathcal{D}\{r[t'']\} \exp\left\{ -\frac{1}{4D} \int\limits_{t'}^{t} dt'' [\mathbf{r}(t'') - \mathbf{v}(\mathbf{r}[t''], t'')]^2 \right\}, \quad (5.3)$$

where $\mathcal{D}\{r[t'']\}$ is the Wiener integral measure of the paths and $\{\mathbf{r}[t'']\}$ is a given realization of paths connecting the initial and terminal points: $\mathbf{r}(t') = \mathbf{r}', \mathbf{r}(t) = \mathbf{r}$. The well known relationship between the Fokker - Planck equation and random motion of certain Brownian particles enables us to mimic heat transfer in living tissue described by equation (5.1) or path integral (5.3) as random motion of certain walkers governed by the stochastic equation

$$\mathbf{r} = \mathbf{v}(r, t) + \mathbf{f}(t), \qquad (5.4)$$

where $\mathbf{f}(t) = \{f_x(t), f_y(t), f_z(t)\}$ is a random force such that

$$\langle \mathbf{f}(t) \rangle = 0, \qquad (5.5)$$

$$\langle \mathbf{f}_\alpha(t) \mathbf{f}_{\alpha'}(t') \rangle = 2D\delta(t - t')\delta_{\alpha\alpha'}. \qquad (5.6)$$

Here $\langle (\dots) \rangle$ is the mean value of $(\dots)$, $\alpha, \alpha' = x, y, z; \delta_{\alpha\alpha'}$ is the Kronecker delta and $\delta(t)$ is the Dirac delta function.

Equation (5.4) determines the path of a walker in living tissue. The walker created in the cellular tissue randomly moves in the cellular tissue until it reaches the vessel boundary which is permeable for it due to conditions (4.3) and (4.4). Then, the walker is transported with blood flow until it either goes out of the vessels into the cellular tissue again or leaves the domain Q_0, containing the microcirculatory bed, through the host vein with blood. Therefore, each path of a walker involves a sequence of portions associated with its migration either inside the cellular tissue or in the vessels.

In this description of heat transfer q is the generation rate of the walks, C is the walker concentration in the tissue and in blood, and D is their diffusion coefficient.

It should be noted that the value of q can be negative. So, to describe heat transfer in terms of random walker we have to introduce two types of walkers: "positive" and "negative" ones. However, due to equations (4.1), (4.2) and boundary conditions (4.3),(4.4) being linear, the motion of a walker can be

Figure 5.1: System of parallel vessels. The directed wavy line represents characteristics path of the walker motion in the cellular tissue and in vessels.

considered without regard to the arrangement of other walkers. Since from the walker motion standpoint the two types of the walkers are identical we may not distinguish them.

To simplify the following analysis, in this Chapter let us, first, consider characteristic properties of random walks in the tissue phantom containing the vessel system in the form of hexagonal array of straight identical pipes parallel, for example, to the z-axis (Fig. 5.1). We assume that the array spacing d_p is well above the pipe radius $a(d_p \gg a)$ and blood currents in different pipes are randomly oriented in space, with the probability of blood flow in the positive z-direction being equal to $1/2(1 + \xi)$ and that of the opposite direction being equal to $1/2(1 - \xi)$ where $\mid \xi \mid < 1$.

Second, we shall analyse characteristic properties of walker random motion in the tissue phantom containing the system of counter current pipes pairs

arranged in a similar way.

5.2 Random walks in the tissue phantom containing the hexagonal array of straight parallel pipes

Here we consider random walks in the tissue phantom that contains the vessel system involving straight identical pipes parallel to the z-axis (Fig. 5.1). We assume that the pipes make up a hexagonal array of spacing d_p, which is well above the pipe radius a $(d_p \gg a)$, and in the xy-plane normal to the pipes this array forms a hexagonal lattice of discs centered at points $\{\boldsymbol{\rho}_i\}$ (Fig. 5.1). The velocity field $\mathbf{v}(\mathbf{r}) = \{0, 0, v(\boldsymbol{\rho})\}$ of blood flow in the given vessel system will be described in terms of

$$v(\boldsymbol{\rho}) = \pi a^2 v \sum_i \xi_i U(\boldsymbol{\rho} - \boldsymbol{\rho}_i) \qquad (5.7)$$

Here v is the mean velocity of blood in the pipes taken individually, the sum runs over all the pipes, the quantity ξ_i specifying the direction of blood flow in the pipe i takes the values $+1$ and -1 for the positive and negative z-directions, respectively, $\boldsymbol{\rho}$ is the projection of the vector $\mathbf{r}$ into the xy-plane (S_{xy}). The function $U(\boldsymbol{\rho})$ normalized to unity describes the blood velocity distribution over the pipe cross section satisfies the equality, by definition,

$$\int\limits_{S_{xy}} d\boldsymbol{\rho}\, U(\boldsymbol{\rho} - \boldsymbol{\rho}_i) \equiv \int\limits_{S_{xy}} d\boldsymbol{\rho}_i U(\boldsymbol{\rho} - \boldsymbol{\rho}_i) = 1. \qquad (5.8)$$

The quantities $\{\xi_i\}$ are regarded as pairwise independent random variables obeying the conditions

$$\langle \xi_i \rangle = \xi, \qquad (5.9)$$

$$\langle \xi_i \xi_{i'} \rangle = \delta_{ii'} + \xi^2(1 - \delta_{ii'}), \qquad (5.10)$$

where ξ is a constant such that $\mid \xi \mid < 1$, $\delta_{ii'}$ is the Kronecker delta. For the given tissue phantom the velocity $\mathbf{v}(\mathbf{r}, t)$ of blood flux solely depends on the vector $\boldsymbol{\rho}$ rather than on the coordinate z and the time t. Therefore, according to equation (5.4) random walks in the given medium can be described in terms of two-dimensional random walks $\{\boldsymbol{\rho}[t]\}$ in the xy-plane
and one-dimensional random walks $\{z[t]\}$ along the z-axis, with the former being independent of the latter.

Firstly, we shall analyse the characteristic properties of the distance $l_\parallel(t, \boldsymbol{\rho}_0)$ that walkers starting from the point $\mathbf{r}_0 = \{\boldsymbol{\rho}_0, 0\}$ travel along the z-axis during the time t. By virtue of (5.4) for a given realization $\mathbf{r}[t] = \{\boldsymbol{\rho}[t], z[t]\}$ of walker paths we may write

$$l_\parallel(t, \boldsymbol{\rho}_0) = \int_0^t dt' \left\{ f_z(t') + \int_{S_{xy}} d\boldsymbol{\rho}' v(\boldsymbol{\rho}') \delta(\boldsymbol{\rho}' - \boldsymbol{\rho}[t']) \right\}, \qquad (5.11)$$

where $f_z(t')$ is the random force causing the walker chaotic motion along the z-axis and satisfying conditions (5.5),(5.6), and $\delta(\boldsymbol{\rho})$ are the spatial δ- functions.

Below in this Section we shall consider two different limits that practically describe characteristic properties of the walker motion in the vicinity of a single pipe and the collective pipe influence.

5.2.1   A single pipe

When $t \ll d_p^2/(2D)$ we confine ourselves to the case where the initial point $\mathbf{r}_0$ of the walker paths is in the vicinity of a certain pipe, for example, of the pipe i_0, i.e. $\left| \boldsymbol{\rho}_{i_0} - \boldsymbol{\rho}_0 \right| \sim a$. In this case blood flow in all the pipes except for the pipe i_0 has practically no effect on the walker motion and expression (5.6) can be rewritten in the form

$$l_\parallel(t, \boldsymbol{\rho}_0) = \int_0^t dt' \left\{ f_z(t') + \pi a^2 v \xi_{i_0} \int_{S_{xy}} d\boldsymbol{\rho}' U(\boldsymbol{\rho}' - \boldsymbol{\rho}_{i_0}) \delta(\boldsymbol{\rho}' - \boldsymbol{\rho}[t']) \right\}. \quad (5.12)$$

Substituting (5.2) into (5.6) we may take into account the term i_0 only. Let us calculate the mathematical expectations of $l_\parallel(t, \boldsymbol{\rho}_0)$ and $l_\parallel^2(t, \boldsymbol{\rho}_0)$ regarded as functionals of $\mathbf{r}[t]$. To do this we make use of the following relations:

$$\langle \delta(\boldsymbol{\rho} - \boldsymbol{\rho}[t]) \rangle_w = G(\boldsymbol{\rho}, \boldsymbol{\rho}_0, t), \qquad (5.13)$$

$$\langle \delta(\boldsymbol{\rho} - \boldsymbol{\rho}[t]) \delta(\boldsymbol{\rho}' - \boldsymbol{\rho}[t']) \rangle_w =$$

$$= \begin{cases} G(\boldsymbol{\rho}, \boldsymbol{\rho}', t - t') G(\boldsymbol{\rho}', \boldsymbol{\rho}_0, t'), & \text{if} \quad t' < t, \\ G(\boldsymbol{\rho}', \boldsymbol{\rho}, t' - t) G(\boldsymbol{\rho}, \boldsymbol{\rho}_0, t), & \text{if} \quad t' > t, \end{cases} \qquad (5.14)$$

where the symbol $\langle (\dots) \rangle_w$ designates the value of $(\dots)$ averaged over all the possible walker paths under consideration and $G(\boldsymbol{\rho}, \boldsymbol{\rho}_0, t)$ is the probability for the two-dimensional random walker starting at the point $\boldsymbol{\rho}_0$ to reach the point $\boldsymbol{\rho}$ in the time t. We note that formula (5.9) directly results from the definition of the averaging procedure. Indeed, for an arbitrary function $\mathcal{F}(\boldsymbol{\rho})$

$$\langle \mathcal{F}(\boldsymbol{\rho}\,[t]) \rangle_w = \int_{S_{xy}} d\boldsymbol{\rho}'\mathcal{F}(\boldsymbol{\rho}')G(\boldsymbol{\rho}',\boldsymbol{\rho}_0,t), \tag{5.15}$$

it immediately follows expression (5.9). Formula (5.10) can be proved in a similar way by representation of the probability for walkers starting at the point $\boldsymbol{\rho}_0$ to reach the point $\boldsymbol{\rho}$ in the time t provided they have visited the point $\boldsymbol{\rho}'$ at time t' in terms of

$$G(\boldsymbol{\rho},\boldsymbol{\rho}',t-t')G(\boldsymbol{\rho}',\boldsymbol{\rho}_0,t'). \tag{5.16}$$

The possibility of such a representation follows from the fact that the given two - dimensional random walks are the Markov process [48]. The function $G(\boldsymbol{\rho},\boldsymbol{\rho}_0,t)$ obeys the diffusion equation [26]

$$\frac{\partial G}{\partial t} = D\boldsymbol{\nabla}^2 G \tag{5.17}$$

and meets the initial condition

$$G|_{t=0} = \delta(\boldsymbol{\rho}-\boldsymbol{\rho}_0). \tag{5.18}$$

For the two-dimensional random walks subject to no additional constraints from (5.17) and (5.18) we find

$$G(\boldsymbol{\rho},\boldsymbol{\rho}_0,t) = \frac{1}{4\pi Dt}\exp\left[-\frac{(\boldsymbol{\rho}-\boldsymbol{\rho}_0)^2}{4Dt}\right]. \tag{5.19}$$

Now let us obtain the specific expressions for the desired quantities $\langle l_\parallel(t,\boldsymbol{\rho}_0) \rangle_w$ and $\left\langle l_\parallel^2(t,\boldsymbol{\rho}_0) \right\rangle_w$. Averaging formula (5.12)

$$\langle l_\parallel(t,\boldsymbol{\rho}_0) \rangle_w = \pi a^2 v\xi_{i_0}\int_0^t dt'\int_{S_{xy}} d\boldsymbol{\rho}'U(\boldsymbol{\rho}'-\boldsymbol{\rho}_{i_0}) < \delta(\boldsymbol{\rho}'-\boldsymbol{\rho}\,[t']) >_w \tag{5.20}$$

Substituting (5.13) into (5.20) we get

$$\langle l_\parallel(t,\boldsymbol{\rho}_0) \rangle_w = \pi a^2 v\xi_{i_0}\int_0^t dt'\int_{S_{xy}} d\boldsymbol{\rho}'U(\boldsymbol{\rho}'-\boldsymbol{\rho}_{i_0})G(\boldsymbol{\rho}'-\boldsymbol{\rho}_0,t'), \tag{5.21}$$

Squaring expression (5.12) and taking into account that the random force $f_z(t)$ and the random walkers in the xy - plane are independent of each other, thus, $\langle f_z(t')\delta(\boldsymbol{\rho}'-\boldsymbol{\rho}\,[t'']) \rangle_w = 0$ we obtain

$$\left\langle l_\parallel^2(t, \boldsymbol{\rho}_0) \right\rangle_w = \int\limits_0^t \int\limits_0^t dt' dt'' \left\langle f_z(t') f_z(t'') \right\rangle_w +$$

$$+ (\pi a^2 v)^2 \xi_{i_0}^2 \int\limits_{S_{xy}} \int\limits_{S_{xy}} d\boldsymbol{\rho}' d\boldsymbol{\rho}'' U(\boldsymbol{\rho}' - \boldsymbol{\rho}_{i_0}) U(\boldsymbol{\rho}'' - \boldsymbol{\rho}_{i_0}) \cdot$$

$$\cdot \left\langle \delta(\boldsymbol{\rho}' - \boldsymbol{\rho}\,[t']) \delta(\boldsymbol{\rho}'' - \boldsymbol{\rho}\,[t'']) \right\rangle_w . \tag{5.22}$$

According to (5.6) the first term on the right-hand side of expression (5.22) is equal to $2Dt$. In order to transform the second term we make use of the identity

$$\int\limits_0^t \int\limits_0^t dt' dt'' (\dots) = \int\limits_0^t dt' \int\limits_0^{t'} dt'' (\dots) + \int\limits_0^t dt'' \int\limits_0^{t''} dt' (\dots) . \tag{5.23}$$

Then the symmetry of the second term of expression (5.22) with respect to the replacement $\boldsymbol{\rho}' \to \boldsymbol{\rho}''$ and $\boldsymbol{\rho}'' \to \boldsymbol{\rho}'$ enables us to represent it as

$$2(\pi a^2 v)^2 \int\limits_0^t dt' \int\limits_0^{t'} dt'' \int\limits_{S_{xy}} \int\limits_{S_{xy}} d\boldsymbol{\rho}' d\boldsymbol{\rho}'' U(\boldsymbol{\rho}' - \boldsymbol{\rho}_{i_0}) U(\boldsymbol{\rho}'' - \boldsymbol{\rho}_{i_0}) \cdot$$

$$\cdot \left\langle \delta(\boldsymbol{\rho}' - \boldsymbol{\rho}\,[t']) \delta(\boldsymbol{\rho}'' - \boldsymbol{\rho}\,[t'']) \right\rangle_w .$$

where we have taken into account that $\xi_{i_0}^2 \equiv 1$. Substituting (5.14) into the last term we obtain the following expression for quantity $\left\langle l_\parallel^2(t, \boldsymbol{\rho}_0) \right\rangle_w$:

$$\left\langle (l_\parallel(t, \boldsymbol{\rho}_0))^2 \right\rangle_w = 2Dt + (\pi a^2 v)^2 2 \int\limits_0^t dt' \int\limits_0^{t'} dt'' \int\limits_{S_{xy}} d\boldsymbol{\rho}' \int\limits_{S_{xy}} d\boldsymbol{\rho}'' \cdot$$

$$\cdot U(\boldsymbol{\rho}' - \boldsymbol{\rho}_{i_0}) U(\boldsymbol{\rho}'' - \boldsymbol{\rho}_{i_0}) G(\boldsymbol{\rho}', \boldsymbol{\rho}'', t' - t'') G(\boldsymbol{\rho}'', \boldsymbol{\rho}_0, t''). \tag{5.24}$$

The function $U(\boldsymbol{\rho})$ differs from zero in the domain $| \boldsymbol{\rho} | < a$ only, whereas, for $t' \gg \tau_a = a^2/(2D)$ on scales of order a variations of the function $G(\boldsymbol{\rho}', \boldsymbol{\rho}_0, t')$ are ignorable. The latter, together with (5.8), (5.19) and the condition $| \boldsymbol{\rho}_0 - \boldsymbol{\rho}_{i_0} | \sim a$ allow us to set

$$\int\limits_{S_{xy}} d\boldsymbol{\rho}'U(\boldsymbol{\rho}' - \boldsymbol{\rho}_{i_0})G(\boldsymbol{\rho}',\boldsymbol{\rho}_0,t') \simeq \frac{1}{4\pi Dt'}. \tag{5.25}$$

If we formally substitute (5.25) into (5.21) then the integral over t' becomes divergent one with a logarithmic singularity at $t' = +0$. We meet a similar situation when dealing with expression (5.24). Thus, for $t \gg \tau_a$ particular details of the function $U(\boldsymbol{\rho})$ are of little consequence and in this case we may choose, for example, the following form of the given function

$$U(\boldsymbol{\rho}) = \frac{1}{\pi a^2} \exp\left[-\frac{(\boldsymbol{\rho})^2}{a^2}\right]. \tag{5.26}$$

The choice of function (5.26) is connected with the useful identity that will be widely used in the following calculations:

$$\int\limits_{S_{xy}} d\boldsymbol{\rho}''\mathcal{G}(\boldsymbol{\rho} - \boldsymbol{\rho}''; A_1)\mathcal{G}(\boldsymbol{\rho}'' - \boldsymbol{\rho}'; A_2) = \mathcal{G}(\boldsymbol{\rho} - \boldsymbol{\rho}'; A_1 + A_2), \tag{5.27}$$

where $A_1, A_2 > 0$ and

$$\mathcal{G}(\boldsymbol{\rho}, A) = \frac{1}{\pi A} \exp\left\{-\frac{\rho^2}{A}\right\}. \tag{5.28}$$

Then, substituting (5.19) and (5.26) into (5.21) and (5.24) using (5.27), and directly integrating with respect to $\boldsymbol{\rho}', \boldsymbol{\rho}''$ and t', t'' for $t \gg \tau_a$ and $| \boldsymbol{\rho}_{i_0} - \boldsymbol{\rho}_0 | \sim a$ we obtain

$$\langle l_{\parallel}(t, \boldsymbol{\rho}_0)\rangle_w \approx \frac{a^2 v}{2D} \xi_{i_0} \ln\left(\frac{(2Dt)^{1/2}}{a}\right), \tag{5.29}$$

$$\langle (l_{\parallel}(t, \boldsymbol{\rho}_0))^2\rangle_w \approx 2Dt + 2\langle l_{\parallel}(t, \boldsymbol{\rho}_0)\rangle^2. \tag{5.30}$$

In particular, comparing (5.29), (5.30) with one another we find that the mean distance $\langle l_{\parallel}(t)\rangle$ travelled by a walker along a pipe with blood flow in it for the time t such that $\tau_a \ll t \ll d_p^2/(2D)$ can be estimated as

$$\langle l_{\parallel}(t)\rangle \approx \frac{a^2 v}{2D} \ln\left(\frac{(2Dt)^{1/2}}{a}\right). \tag{5.31}$$

It should be pointed out that expression (5.31) can be also obtained in the following way. Clearly, $\langle l_{\parallel}(t)\rangle \approx v \langle t_p \rangle$, where $\langle t_p \rangle$ is the mean total time during

which a walker being initially near a certain pipe, for example, the pipe i_0, is inside this pipe. For a given realization $\boldsymbol{\rho}\,[t]$ of the two-dimensional random walks the total residence time of walkers inside the pipe i_0 is

$$t_p = \int\limits_0^t dt' \Theta_{i_0}(\boldsymbol{\rho}\,[t']), \qquad (5.32)$$

where $\Theta_{i_0}(\boldsymbol{\rho}\,)$ is the characteristic function of the pipe i_0, i.e.

$$\Theta_{i_0}(\boldsymbol{\rho}) = \left\{ \begin{array}{lll} 1 & , & \text{if} \quad |\,\boldsymbol{\rho} - \boldsymbol{\rho}_{i_0}\,| < a \\ 0 & , & \text{if} \quad |\,\boldsymbol{\rho} - \boldsymbol{\rho}_{i_0}\,| > a \end{array} \right. . \qquad (5.33)$$

The identity

$$\Theta_{i_0}(\boldsymbol{\rho}) = \int\limits_{|\boldsymbol{\rho}\,' - \boldsymbol{\rho}_{i_0}| < a} d\boldsymbol{\rho}\,' \delta(\boldsymbol{\rho}\,' - \boldsymbol{\rho}\,) \qquad (5.34)$$

enables us to rewrite (5.32) as

$$t_p = \int\limits_0^t dt' \int\limits_{|\boldsymbol{\rho}\,' - \boldsymbol{\rho}_{i_0}| < a} d\boldsymbol{\rho}\,\delta(\boldsymbol{\rho} - \boldsymbol{\rho}\,[t']). \qquad (5.35)$$

By virtue of (5.13) and (5.19) from (5.35) we get

$$\langle t_p \rangle \approx \frac{a^2}{2D} \ln\left(\frac{(2Dt)^{1/2}}{a} \right) \qquad (5.36)$$

and the estimate $\langle l_{\|}(t) \rangle \approx v \langle t_p \rangle$ leads to expression (5.31).

5.2.2 The cooperative effect of the pipe system on walker motion

When $t \gg d_p^2/(2D)$ and, thus, practically each walker in its motion visits a large number of pipes we determine the mathematical expectations of $l_{\|}(t, \boldsymbol{\rho}_0)$ and $(l_{\|}(t, \boldsymbol{\rho}_0))^2$ regarded as functions of the independent random variables $\mathbf{r}\,[t], \{\xi_i\}$ and $\boldsymbol{\rho}_0$, with the latter being characterized by uniform distribution over the xy-plane.

Substituting (5.7) into (5.11) and averaging the latter over these random variables we get

$$\left\langle l_{\parallel}(t, \boldsymbol{\rho}_0)\right\rangle_{w, \rho_0, \xi} = \pi a^2 v < \xi_i > \sum_i \int\limits_0^t dt' \int\limits_{S_{xy}} d\boldsymbol{\rho}' \cdot$$

$$\cdot U(\boldsymbol{\rho}' - \boldsymbol{\rho}_i) \left\langle\left\langle\delta(\boldsymbol{\rho}' - \boldsymbol{\rho}\,[t'])\right\rangle_w\right\rangle_{\rho_0} . \tag{5.37}$$

Here the sum runs over all the pipes and $\langle(\dots)\rangle_{\rho_0}$ stands for the value of $(\dots)$ averaged over the random variable $\boldsymbol{\rho}_0$ and determined by the formal expression

$$\langle(\dots)\rangle_{\rho_0} = \frac{1}{S_{xy}} \int\limits_{S_{xy}} d\boldsymbol{\rho}_0(\dots) \tag{5.38}$$

where S_{xy} denotes the area of the xy-plane treated as some large value and $1/S_{xy}$ is the probability density of the variable ρ_0 distribution. Formulas (5.9), (5.13) and (5.38) allow us to represent expression (4.34) in the form

$$\left\langle l_{\parallel}(t, \boldsymbol{\rho}_0)\right\rangle_{w, \rho_0, \xi} =$$

$$\pi a^2 v \xi \frac{1}{S_{xy}} \sum_i \int\limits_0^t dt' \int\limits_{S_{xy}} d\boldsymbol{\rho}_0 \int\limits_{S_{xy}} d\boldsymbol{\rho}' U(\boldsymbol{\rho}' - \boldsymbol{\rho}_i) G(\boldsymbol{\rho}', \boldsymbol{\rho}_0, t'). \tag{5.39}$$

By virtue of (5.19)

$$\int\limits_{S_{xy}} d\boldsymbol{\rho}_0 G(\boldsymbol{\rho}'', \boldsymbol{\rho}_0, t'') = 1. \tag{5.40}$$

The latter identity and the chosen form (5.26) of the function $U(\boldsymbol{\rho})$ enable us to integrate over $\boldsymbol{\rho}'$ and in expressions (5.39)

$$\left\langle (l_{\parallel}(t, \boldsymbol{\rho}_0))^2\right\rangle_{w, \rho_0, \xi} = \pi a^2 v \xi + \frac{1}{S_{xy}} \sum_i l_i, \tag{5.41}$$

where $l_i \equiv 1$ for each site of the lattice $\{\boldsymbol{\rho}_2\}$. Following the definition of mean distance between vessels (see Section 4.2) we may set

$$\frac{1}{S_{xy}} \sum_i l_i = \frac{1}{d^2}, \tag{5.42}$$

where d is the mean distance between the pipes or, what is the same, between the discs of the lattice $\{\boldsymbol{\rho}_i\}$ in the xy - plane. Thus, from (5.41) we find

$$\langle l_\parallel(t,\boldsymbol{\rho}_0)\rangle_{w,\rho_0,\xi} = \frac{\pi a^2 v}{d^2}\xi t. \tag{5.43}$$

In order to find the relationship between d and d_p we note that, by definition, d^2 is the mean area of the xy-plane per each disk and for the given disk lattice the value of d^2 coincides with the area of the Wigner - Seitz cell [42, 50, 83, 108] shown in Fig. 5.1. Thus,

$$d^2 = \frac{\sqrt{3}}{2}d_p^2. \tag{5.44}$$

Now let us calculate the averaged value of $l_\parallel^2(t,\boldsymbol{\rho}_0)$. Substituting (5.7) into (5.12), squaring the obtained result we find

$$\left\langle l_\parallel^2(t,\boldsymbol{\rho}_0)\right\rangle_{w,\rho_0,\xi} = \int\limits_0^t\int\limits_0^t dt'dt'' \left\{\langle f_z(t')f_z(t'')\rangle +\right.$$

$$+(\pi a^2 v)^2 \sum_{i',i''} \langle \xi_{i'}\xi_{i''}\rangle_\xi \int\limits_{S_{xy}}\int\limits_{S_{xy}} d\boldsymbol{\rho}'d\boldsymbol{\rho}''U(\boldsymbol{\rho}'-\boldsymbol{\rho}_{i'})U(\boldsymbol{\rho}''-\boldsymbol{\rho}'_{i''}) \cdot$$

$$\left. \cdot\langle\langle\delta(\boldsymbol{\rho}'-\boldsymbol{\rho}\,[t'])\delta(\boldsymbol{\rho}''-\boldsymbol{\rho}\,[t''])\rangle_w\rangle_{\rho_0}\right\}. \tag{5.45}$$

By virtue of (5.6), (5.10), (5.14), (5.38) and identity (5.23) formula (5.45) can be rewritten in the form

$$\langle(l_\parallel(t,\boldsymbol{\rho}_0))^2\rangle_{w,\rho_0,\xi} = 2Dt + 2(\pi a^2 v)^2\frac{1}{S_{xy}}\sum_{i',i''}[(1-\xi^2)\delta_{i',i''}+\xi^2]\cdot$$

$$\cdot\int\limits_0^t dt'\int\limits_0^{t'} dt''\int\limits_{S_{xy}} d\boldsymbol{\rho}'\int\limits_{S_{xy}} d\boldsymbol{\rho}''\int\limits_{S_{xy}} d\boldsymbol{\rho}_0 U(\boldsymbol{\rho}'-\boldsymbol{\rho}'_i)U(\boldsymbol{\rho}''-\boldsymbol{\rho}'_{i''})\cdot$$

$$\cdot G(\boldsymbol{\rho}',\boldsymbol{\rho}'',t'-t'')G(\boldsymbol{\rho}'',\boldsymbol{\rho}_0,t''). \tag{5.46}$$

Taking into account identity (5.27) and (5.40) from (5.46) we find

$$\langle (l_\parallel(t, \boldsymbol{\rho}_0))^2 \rangle_{w, \rho_0, \xi} = 2Dt + 2(\pi a^2 v)^2 \frac{1}{S_{xy}} \sum_{i', i''} [(1 - \xi^2) \delta_{i', i''} + \xi^2] \cdot$$

$$\cdot \int_0^t dt' \int_0^{t'} dt'' \frac{1}{4\pi D(t' - t'' + \tau_a)} \exp\left\{ -\frac{(\boldsymbol{\rho}_{i'} - \boldsymbol{\rho}_{i''})^2}{4D(t' - t'' + \tau_a)} \right\}, \tag{5.47}$$

where as before

$$\tau_a = \frac{a^2}{2D}. \tag{5.48}$$

Replacing the variable t'' by the new variable $t' - t''$ under integral (5.47), introducing the new vector $\boldsymbol{\rho}_i = \boldsymbol{\rho}_{i'} - \boldsymbol{\rho}_{i''}$ of the lattice $\{\rho_i\}$ and using (5.42) from (5.47) we have

$$\langle (l_\parallel(t, \boldsymbol{\rho}_0))^2 \rangle = 2Dt + 2\frac{(\pi a^2 v)^2}{d^2} \int_0^t dt' \int_0^{t'} dt'' \frac{1}{4\pi D(t'' + \tau_a)} \cdot$$

$$\cdot \left\{ (1 - \xi^2) + \xi^2 \sum_i \exp\left[-\frac{(\boldsymbol{\rho}_i)^2}{4D(t'' + \tau_a)} \right] \right\}. \tag{5.49}$$

In order to calculate the sum in formula (5.49) let us consider the lattice $\{\mathbf{g}_i\}$ reciprocal to the lattice $\{\boldsymbol{\rho}_i\}$. Drawing on the definition of reciprocal lattice[42, 50, 108]we can show that the lattice $\{\mathbf{g}_i\}$ is also hexagonal one, its spacing

$$d_p^* = \frac{4\pi}{\sqrt{3}} \frac{1}{d_p}, \tag{5.50}$$

and all the vectors $\{\mathbf{g}_i\}$ can be represented in terms of

$$\mathbf{g}_i = n_i d_p^* \left\{ \frac{\sqrt{3}}{2}; -\frac{1}{2} \right\} + m_i d_p^* \{0, 1\}, \tag{5.51}$$

where n_i, m_i are integers (Fig. 5.2). Expanding the delta function $\delta(\boldsymbol{\rho})$ into the Fourier series in the Wigner-Seitz cell of the lattice $\{\boldsymbol{\rho}_i\}$ we get the well known formula [50, 108] to be used in the following analysis

Figure 5.2: The lattice $\rho(a)$ and its reciprocal lattice g_i (Q_w, Q_w^* are the Wigner-Seitz cells).

$$\sum_i \delta(\boldsymbol{\rho} - \boldsymbol{\rho}_i) = \frac{1}{d^2} \sum_i \exp[i\boldsymbol{\rho}\,\mathbf{g}_i]. \qquad (5.52)$$

because d^2 coincides with the area of the Wigner - Seitz cell. Identity (5.52) allows us to rewrite the last term on the ring-hand side of (5.49) in the form

$$\sum_i \frac{1}{4\pi D(t'' + \tau_a)} \exp\left[-\frac{(\boldsymbol{\rho}_i)^2}{4\pi D(t'' + \tau_a)}\right] = \int_{S_{xy}} d\boldsymbol{\rho} \frac{1}{4\pi D(t'' + \tau_a)} \cdot$$

$$\cdot \exp\left[-\frac{(\boldsymbol{\rho})^2}{4\pi D(t'' + \tau_a)}\right] \sum_i \delta(\boldsymbol{\rho} - \boldsymbol{\rho}_i) = \frac{1}{d^2} \sum_i \int_{S_{xy}} d\boldsymbol{\rho} \frac{1}{4\pi D(t'' + \tau_a)} \cdot$$

$$\cdot \exp\left[i\boldsymbol{\rho}\mathbf{g}_i - \frac{(\boldsymbol{\rho})^2}{4\pi D(t'' + \tau_a)}\right] = \frac{1}{d^2} \sum_i \exp\left[-(\mathbf{g}_i)^2 D(t'' + \tau_a)\right].$$

Substituting (5.52) into (5.49) and integrating with respect to t' and t'' for $t \gg d_p^2/(2D)$ we find

$$\langle (l_\parallel(t, \boldsymbol{\rho}_0))^2 \rangle \approx \langle l_\parallel(t, \boldsymbol{\rho}_0) \rangle^2 + 2Dt \left\{ 1 + \frac{\pi}{4} \left(\frac{a^2 v}{Dd}\right)^2 ((1 - \right.$$

$$\left. -\xi^2) \ln\left(\frac{t}{\tau_a e}\right) + \xi^2 \frac{4\pi}{d^2} \sum_i' \frac{1}{(\mathbf{g}_i)^2} \exp[-(\mathbf{g}_i)^2 D\tau_a] \right\}, \qquad (5.53)$$

where e is the base of the natural logarithm and the prime on the sum over i indicates that the term corresponding to $\mathbf{g}_i = 0$ is omitted. Due to $a \ll d_p$ the

main contribution to the sum in (5.53) is determined by a large number of sites of lattice $\{\mathbf{g}_i\}$. Therefore, the value of this sum can be found from the following approximate equality

$$\sum_i' \frac{1}{(\mathbf{g}_i)^2} \exp[-(\mathbf{g}_i)^2 D\tau_a] \approx \frac{2}{\sqrt{3}(d_p^*)^2} 2\pi \int\limits_{d_p^*}^{\infty} dg \frac{1}{g} \exp[-g^2 D\tau_a], \qquad (5.54)$$

where $(\sqrt{3}/2)(d_p^*)^2$ is the area of the Wigner-Seitz cell of the reciprocal lattice $\{\mathbf{g}_i\}$ and the cut-off parameter d_p^* for the logarithmic divergence at small values of g arises from the absence of g_i^2 less than $(d_p^*)^2$ in (5.54). Expressions (5.44), (5.47) and (5.54) enable us to represent (5.53) in the form

$$\langle (l_\parallel(t, \boldsymbol{\rho}_0))^2 \rangle \approx \langle l_\parallel(t, \boldsymbol{\rho}_0) \rangle^2 + 2Dt \Bigg\{ 1 +$$

$$+ \frac{\pi}{4} \left(\frac{a^2 v}{Dd} \right)^2 \left[(1 - \xi^2) \ln \left(\frac{t}{\tau_a e} \right) + \xi^2 \ln \left(\frac{\sqrt{3}d^2}{8\gamma\pi^2 D\tau_a} \right) \right] \Bigg\}, \qquad (5.55)$$

where γ is the Euler constant. Expressions (5.43) and (5.55) are the desired results of the given Section.

It should be pointed out that in the case under consideration the walker random motion along the pipes does not obey the regular diffusion law because, as it follows from (5.55), for $|\xi| < 1$, the dispersion of the random variable $l_\parallel(t, \boldsymbol{\rho}_0)$ depends on the time t as $t\ln(t/\tau_a)$ rather than t. Thus, from the standpoint of random walks the tissue phantom containing straight parallel pipes cannot be described in terms of a medium with an effective diffusion coefficient . However, in the general case, i.e. for the tissue that contains vessels variously oriented in space, this conclusion does not hold true. This question is the subject of the next Subsection.

5.2.3   The effective medium description of the tissue phantom with pipes differently oriented in space

In real living tissues vessels are variously oriented in space. In the present Section we analyse characteristic properties of random walks in a tissue phantom similar to one considered before, which, however contains, in addition, pipes parallel to the xy - plane. In particular, we shall show that the influence of pipes parallel to the xy - plane allows one to introduce the effective diffusion coefficient and estimate its value, based on the results obtained in the previous Subsection.

The tissue phantom is assumed to contain the pipe system specified in Subsection 5.2.1 and pipes oriented randomly in the xy - plane, with the mean distance between these pipes being equal to d.

In the previous Subsections we represented three - dimensional random walks $\mathbf{r}\,[t] = (\rho[t], z[t])$ as two - dimensional random walks $\boldsymbol{\rho}\,[t]$ and random walks $z[t]$ along the z - axis. In the tissue phantom containing solely pipes parallel to the z - axis the two - dimensional random walks are independent of the one - dimensional ones. When the tissue phantom contains pipes variously oriented in space random walks in the xy - plane depend on the walker motion along the z - axis because during motion along the z - axis the walker can meet a pipe parallel to the xy - plane, which gives rise to its fast transport along the xy - plane with blood in these pipes.

Since, the characteristics of walker motion in the xy - plane determine properties of their motion along the z - axis walker motion in the tissue phantom with undirected pipes and pipes variously oriented in space can differ in properties.

Therefore, keeping in mind walker motion in the z-direction, first we, analyse the effect of blood flow on the two - dimensional random walks in the xy-plane. When the time t of the walker motion satisfies the condition $t \ll d^2/(2D)$ we may ignore the influence of blood flow in vessels on the two-dimensional random walks. This is justified because walkers at initial time near a vessel parallel to z - axis, practically cannot reach other vessels during this time. When $t \gg d^2/(2D)$ actually each walker in its motion visits a large number of vessels including the vessels parallel to the xy-plane. In this case we can, at least roughly, describe the walker motion along the xy-plane in terms of two - dimensional random walks in a medium with an effective diffusion coefficient D_{eff}. We note that the effect of blood flow on the walker motion should be taken into account only when $D_{\mathrm{eff}} \gg D$. Therefore, for the sake of simplicity, the latter inequality is assumed to be true beforehand. Within the framework of the adopted assumptions expression (5.46) holds true provided the function $G(\boldsymbol{\rho}, \boldsymbol{\rho}', t)$ is specified by formula (5.19) for $t \ll d^2/(2D)$ only, whereas for $t \gg d^2/(2D)$ it is given by the formula

$$G(\boldsymbol{\rho}, \boldsymbol{\rho}', t) \approx \frac{1}{4\pi D_{\mathrm{eff}} t} \exp\left[-\frac{(\boldsymbol{\rho} - \boldsymbol{\rho}')^2}{4 D_{\mathrm{eff}} t}\right]. \qquad (5.56)$$

According to (5.46) and (5.49) the time dependence $t \ln(t/\tau_a)$ practically arises from the term

$$\int\limits_0^t dt' \int\limits_{\tau_a}^{t'} dt'' G(0, 0, t' - t''). \qquad (5.57)$$

Here the function $G(0, 0, t' - t'')$ determines the probability for the two-dimensional random walks originating at the point $\boldsymbol{\rho} = 0$ at time t'' to return to the initial point at time t'. As it follows from (5.19) and (5.56) for $t \gg \tau_a = t^2/(2D)$ term (5.57) is approximately equal to

$$\frac{1}{4\pi}\left[\frac{1}{D}\ln\frac{\tau_d}{\tau_a}+\frac{1}{D_{\text{eff}}}\ln\frac{t}{\tau_d}\right]. \tag{5.58}$$

When the value of the time t is not extremely large, i.e.

$$\frac{d^2}{2D}\ll t\ll\frac{d^2}{2D}\left(\frac{d^2}{a^2}\right)^{\frac{D_{\text{eff}}}{D}} \tag{5.59}$$

this term can be estimated as

$$\frac{t}{4\pi D}\ln\left(\frac{d^2}{2D\tau_a}\right). \tag{5.60}$$

Expression (5.60) shows that on temporal scales (5.59) the effect which blood flow in vessels parallel to the xy-plane has on the two-dimensional random walks is actually reduced to inhibiting these random walks from returning to their initial point on temporal scales $t\gg d^2/(2D)$. So, in the general case the time dependence of $\left\langle(l_\parallel(t,\boldsymbol{\rho}_0))^2\right\rangle$ obeys the regular diffusion law, viz., according to (5.43), (5.53), (5.55) and (5.60)

$$\left\langle(l_\parallel(t,\boldsymbol{\rho}_0))^2\right\rangle\approx\left\langle l_\parallel(t,\boldsymbol{\rho}_0)\right\rangle^2+2Dt\left\{1+\frac{\pi}{4}\left(\frac{a^2v}{Dd}\right)^2\ln\left(\frac{d^2}{2D\tau_a}\right)\right\}. \tag{5.61}$$

Therefore, by virtue of (5.43) and (5.61), in the tissue phantom containing straight parallel pipes where, however, pipes of other directions are also present walker during a time $t\gg d^2/(2D)$ travels a distance $l_\parallel(t)$ along the pipes which is characterized by the mean values

$$\left\langle l_\parallel(t)\right\rangle=v_{\text{eff}}t,\quad\left\langle(l_\parallel(t))^2\right\rangle=\left\langle l_\parallel(t)\right\rangle^2+D_{\text{eff}}t, \tag{5.62}$$

where the coefficients

$$v_{\text{eff}}=\frac{\pi a^2v}{d^2}\xi \tag{5.63}$$

and

$$D_{\text{eff}}\simeq D\left[1+\frac{\pi}{2}\left(\frac{a^2v}{Dd}\right)^2\ln\left(\frac{d}{(2D\tau_a)^{1/2}}\right)\right]. \tag{5.64}$$

In considering walker motion in the z-direction on a time scale $t\gg d^2/(2D)$ we can choose such a time scale τ that $d/(2D)\ll\tau\ll t$ and represent the

probability $\mathcal{P}(z, z' \mid t, t')$ for the walker to reach the point z at time t provided it has been at the point z' at time t' in the form

$$\mathcal{P}(z, z' \mid t, t') = \int\limits_{-\infty}^{+\infty} \cdots \int\limits_{-\infty}^{+\infty} dz_1 \ldots dz_N \mathcal{P}(z, z_N \mid t, t - \tau) \ldots$$

$$\mathcal{P}(z_N, z_N - 1 \quad \mid \quad t - \tau, t - 2\tau) \tag{5.65}$$
$$\ldots \mathcal{P}(z_2, z_1 \mid t' + 2\tau, t' + \tau) \mathcal{P}(z_1, z' \mid t' + \tau, t'),$$

where $t = t' + (N+1)\tau$. For $N \gg 1$ the specific form of the function $\mathcal{P}(z, z' \mid t + \tau, t)$ is not a factor and only must lead to relations (5.62) (see, e.g., [38]). The latter allows us to write

$$\mathcal{P}(z_1, z' \mid t + \tau, t) = \frac{1}{4(\pi D_{\text{eff}}\tau)^{1/2}} \exp\left\{ -\frac{(z - z' - v_{\text{eff}}\tau)^2}{4 D_{\text{eff}}\tau} \right\}. \tag{5.66}$$

Substituting (5.66) into (5.65) and going to continuum description we get

$$\mathcal{P}(z, z' \mid t, t') = \int \mathcal{D}z[t''] \exp\left\{ -\frac{1}{4} \int\limits_{t'}^{t} dt'' \frac{(\dot{z} - v_{\text{eff}})^2}{D_{\text{eff}}} \right\}. \tag{5.67}$$

Therefore, distribution of walkers in such a tissue phantom evolves according to the equation

$$\frac{\partial C}{\partial t} = \boldsymbol{\nabla}[D_{\text{eff}} \boldsymbol{\nabla} C - v_{\text{eff}} C]. \tag{5.68}$$

In other words, from the standpoint of walker motion this tissue phantom can be described in term of a medium with the effective diffusion coefficient D_{eff} for the direction parallel to the pipes and with convective flux whose velocity

$$\mathbf{v}_{\text{eff}} = v_{\text{eff}} \mathbf{n}_z, \tag{5.69}$$

where $\mathbf{n}_z$ is the unit vector in the positive z-direction.

5.3 Random walks in the tissue phantom without touching the pipes

As will be shown below in the following Chapter large veins can be treated as walker traps because if a walker reaches such a vessel it will leave the fundamental tissue domain with blood for a short time. Therefore, another characteristic

parameter of heat transfer in living tissue is the mean time during which a walker goes in the cellular tissue without touching the vessels.

In the present Section we consider this problem for the tissue phantom described in Section 5.2.

Let us calculate the mean time τ_l during which walkers created in the tissue containing the straight parallel pipes (Fig. 5.1) travel in it without touching the pipes. For the given geometry of the pipe system this time can be regarded as the mean time during which walkers created in the xy-plane travel in this plane without touching the disk system shown in Fig. 5.1.

To calculate the value of τ_l we need to find the probability $F(\boldsymbol{\rho}_0, t)$ for a walker initially created at point $\boldsymbol{\rho}_0$ to reach for the first time the boundary $\sigma = \cup_i\{|\ \boldsymbol{\rho} - \boldsymbol{\rho}_i\ | = a\}$ of the disk system in the time t. Then, the mean time $\tau_l(\boldsymbol{\rho}_0)$ during which the walker travels in the xy - plane without touching the boundary σ is

$$\tau_l(\boldsymbol{\rho}_0) = \int\limits_0^\infty dt\, t\, F(\boldsymbol{\rho}_0, t) \tag{5.70}$$

and

$$\tau_l = \left\langle \tau_l(\boldsymbol{\rho}_0) \right\rangle_{\boldsymbol{\rho}_0}. \tag{5.71}$$

The function $F(\boldsymbol{\rho}_0, t)$ is directly related to the probability $G(\boldsymbol{\rho}, \boldsymbol{\rho}_0, t)$ for such a walker starting from the point $\boldsymbol{\rho}_0$ at initial time to reach the point $\boldsymbol{\rho}$ in the time t without touching the disks. This probability as a function of $\boldsymbol{\rho}$ obeys equation (5.17) at points external to the disks, meets initial condition (5.18) and the boundary condition

$$G\big|_{\boldsymbol{\rho} \in \sigma} = 0. \tag{5.72}$$

It is well known (see, e.g., [38]), $G(\boldsymbol{\rho}, \boldsymbol{\rho}_0, t)$ as a function of $\boldsymbol{\rho}_0$ must also satisfy the inverse Fokker - Planck equation

$$\frac{\partial G}{\partial t} = D\boldsymbol{\nabla}_{\rho_0}^2 G. \tag{5.73}$$

The probability of finding the walker in the tissue at time t can be equivalently represented as

$$\int\limits_{S_{xy}\backslash\cup_i|\boldsymbol{\rho}-\boldsymbol{\rho}_i|\leqslant a} d\boldsymbol{\rho}\, G(\boldsymbol{\rho}, \boldsymbol{\rho}_0, t) = \int\limits_t^\infty dt'\, F(\boldsymbol{\rho}_0, t'), \tag{5.74}$$

Taking into account expression (5.74), integrating equation (5.73) over ρ in the region external to the disk system and finding the derivatives of both the parts of the obtained equation we get

$$\frac{\partial F}{\partial t} = D\boldsymbol{\nabla}^2_{\rho_0} F. \tag{5.75}$$

Obviously, for $\rho_0 \notin \sigma$

$$F\mid_{t=0} = 0 \tag{5.76}$$

because a certain time is needed for the walker to reach the disk boundary. From (5.75) and (5.76) we obtain that the Laplace transform $F_L(\boldsymbol{\rho}_0, s)$ of the function $F(\boldsymbol{\rho}_0, t)$:

$$F_L(\boldsymbol{\rho}_0, s) = \int\limits_0^\infty dt e^{-st} F(\boldsymbol{\rho}_0, t) \tag{5.77}$$

satisfies the equation

$$sF_L = D\boldsymbol{\nabla}^2_{\boldsymbol{\rho}_0} F_L \tag{5.78}$$

subject to the boundary condition

$$F_L\big|_{\boldsymbol{\rho} \in \sigma} = 1. \tag{5.79}$$

Boundary condition (5.79) implies that a walker created in the immediate vicinity of the boundary σ reaches this boundary in no time.

Obviously, $F_L(\boldsymbol{\rho}_0, s)$ is a periodic function, thus, the normal gradient of $F_L(\boldsymbol{\rho}_0, s)$ at the boundary σ_w of any Wigner-Seitz cell of the lattice $\{\boldsymbol{\rho}_i\}$ (Fig. 5.1) must be equal to zero. Thus, in order to find the function $F_L(\boldsymbol{\rho}_0, s)$ we may consider the solution of equation (5.78) subject to the boundary conditions

$$F_L\big|_{|\boldsymbol{\rho}_0|=a} = 1, \tag{5.80}$$

$$\boldsymbol{\nabla}_n F_L\big|_{\boldsymbol{\rho} \in \sigma_w^0} = 0, \tag{5.81}$$

where σ_w^0 is the boundary of the Wigner-Seitz cell centered at the point $\boldsymbol{\rho}_i = 0$. To a good approximation we may replace this Wigner-Seitz cell by a disk of the same area, whose radius $r = (\sqrt{3}/(2\pi))^{1/2} d_p$ (Fig. 5.1), and require that the function $F_L(\boldsymbol{\rho}_0, s)$ satisfies the condition

$$\boldsymbol{\nabla}_n F_L\big|_{|\boldsymbol{\rho}_0|=r} = 0. \tag{5.82}$$

The solution of (5.78) meeting conditions (5.80) and (5.82) is of the form

$$F_L(\boldsymbol{\rho}_0, s) = A I_0\left[\rho_0 \left(\frac{s}{D}\right)^{1/2}\right] + B K_0\left[\rho_0 \left(\frac{s}{D}\right)^{1/2}\right], \tag{5.83}$$

where

$$A = K_1\left[r\left(\frac{s}{D}\right)^{1/2}\right]\left\{I_0\left[a\left(\frac{s}{D}\right)^{1/2}\right]K_1\left[r\left(\frac{s}{D}\right)^{1/2}\right] + \right.$$

$$\left. + K_0\left[a\left(\frac{s}{D}\right)^{1/2}\right]I_1\left[r\left(\frac{s}{D}\right)^{1/2}\right]\right\}^{-1} \tag{5.84}$$

and

$$B = I_1\left[r\left(\frac{s}{D}\right)^{1/2}\right]\left\{I_0\left[a\left(\frac{s}{D}\right)^{1/2}\right]K_1\left[r\left(\frac{s}{D}\right)^{1/2}\right] + \right.$$

$$\left. + K_0\left[a\left(\frac{s}{D}\right)^{1/2}\right]I_1\left[r\left(\frac{s}{D}\right)^{1/2}\right]\right\}^{-1}. \tag{5.85}$$

Here I_0, I_1, K_0, K_1 are the modified Bessel functions of order zero and one, of the first and second kind, respectively. Averaging the function (5.83) over the domain $a \leqslant |\boldsymbol{\rho}_0| \leqslant r$ we get

$$< F_L(\boldsymbol{\rho}_0, s) >= \frac{2a}{(r^2 - a^2)}\left(\frac{D}{s}\right)^{1/2}\left\{K_1\left[a\left(\frac{s}{D}\right)^{1/2}\right]I_1\left[r\left(\frac{s}{D}\right)^{1/2}\right] - \right.$$

$$\left. - I_1\left[a\left(\frac{s}{D}\right)^{1/2}\right]K_1\left[r\left(\frac{s}{D}\right)^{1/2}\right]\right\}\left\{I_0\left[a\left(\frac{s}{D}\right)^{1/2}\right]K_1\left[r\left(\frac{s}{D}\right)^{1/2}\right] + \right.$$

$$\left. + K_0\left[a\left(\frac{s}{D}\right)^{1/2}\right]I_1\left[r\left(\frac{s}{D}\right)^{1/2}\right]\right\}^{-1}. \tag{5.86}$$

Let us consider the function $\langle F_L(\boldsymbol{\rho}_0, s)\rangle$ for $s \ll D/r^2$. Expanding each function appearing in (5.86) into a power series of s and a/d_p from (5.86) we get

$$\langle F_L(\boldsymbol{\rho}_0, s)\rangle \approx \frac{1}{1 + s\frac{r^2}{2D}\ln\left(\frac{r}{a}\right)}. \tag{5.87}$$

If $D/r^2 \ll s \ll D/a^2$, then, according to (5.86) the function $\langle F_L(\boldsymbol{\rho}_0, s) \rangle \ll 1$. Therefore, by virtue of (5.87) we may represent the inverse transform of (5.87) in the form

$$\langle F(\boldsymbol{\rho}_0, s) \rangle = \frac{1}{\tau_l} \exp\left[-\frac{t}{\tau_l}\right],\tag{5.88}$$

where

$$\tau_l = \frac{r^2}{2D} \ln\left(\frac{r}{a}\right).\tag{5.89}$$

Therefore, according to definition (5.70), (5.71) we obtain that τ_l is the desired mean time of walker motion without touching the pipes.

Since $d_p \gg a$ and, as follows from the definition of the mean distance between the pipes, $\pi r^2 = d^2$, we may rewrite formula (5.89) in the form

$$\tau_l \approx \frac{d^2}{2\pi D} \ln\left(\frac{d}{a}\right),\tag{5.90}$$

where we have ignored the term $1/2 \ln \pi$ in the cofactor $\ln(r/a) = \ln(d/a) - 1/2 \ln \pi$. In addition, it should be pointed out that for $\rho_0 \sim a$ and $D/d^2 \ll s \ll d/a^2$ according to (5.83)

$$F_L(\boldsymbol{\rho}_0, s) \simeq \frac{K_0\left[\rho_0 \left(\frac{s}{D}\right)^{1/2}\right]}{K_0\left[a \left(\frac{s}{D}\right)^{1/2}\right]}.\tag{5.91}$$

Thereby, for the time $t \leqslant d^2/(2D)$ practically each walker created near a pipe (i.e. for which $\rho_0 \sim a$) inevitably crosses this pipe at least one time.

5.4 Random walks in the tissue phantom containing the hexagonal array of countercurrent pairs

In the present Section we analyse characteristic properties of random walks in the tissue phantom that contains the vessel system involving straight identical pipes of radius a parallel to the z-axis and grouped in pairs where blood currents flow in the opposite directions (Fig. 5.3). We assume that the pipes pairs make up a hexagonal array of spacing $d_p \gg a$. In other words, all the countercurrent pairs are assumed to be located in the vicinity of certain straight lines crossing the xy-plane at points $\{\boldsymbol{\rho}_i\}$ forming the hexagonal array.

Blood flow in this vessel system is characterized by the following blood velocity field $v(\boldsymbol{\rho})$ in the z-direction:

Figure 5.3: The xy crossection of the hexagonal array of counter current pipes

$$v(\boldsymbol{\rho}) = \pi a^2 v \sum_i [U(\boldsymbol{\rho} - \boldsymbol{\rho}_i^+) - U(\boldsymbol{\rho} - \boldsymbol{\rho}_i^-)], \tag{5.92}$$

where as in Section 5.2 v is the mean velocity of blood in single pipes, the sum runs over all the pairs and $\boldsymbol{\rho}_i^+, \boldsymbol{\rho}_i^-$ are the points at which the centre lines of pipes with blood flow in the positive and negative directions cross the xy-plane. The function $U(\boldsymbol{\rho})$ normalized to unity describes the blood flow distribution inside a pipe and, for the sake of simplicity, will be given in the form (5.26). The pipe center line coordinates $\{\boldsymbol{\rho}_i^+, \boldsymbol{\rho}_i^-\}$ are considered to be pairwise independent random variables characterized by the distribution functions

$$\Phi_i(\boldsymbol{\rho}) = \frac{1}{\pi b^2} \exp\left\{ -\frac{(\boldsymbol{\rho} - \boldsymbol{\rho}_i)^2}{b^2} \right\}. \tag{5.93}$$

Here $b = \mu a$ is the mean distance between pipes of a single pair and $\mu \geq 2$ is a system parameter.

Following Section 5.2 in order to analyse characteristic properties of random walks in this tissue phantom we calculate the mean values of distance

$$l_\parallel(\vec{t}, \boldsymbol{\rho}_0) = \int_0^t dt' \left\{ f_z(t') + \int_{S_{xy}} d\boldsymbol{\rho}' v(\boldsymbol{\rho}') \delta(\boldsymbol{\rho}' - \boldsymbol{\rho}[t']) \right\} \tag{5.94}$$

which a walker created at the point $\{\boldsymbol{\rho}_0, t\}$ travel in the z-direction during the time t providing it moves along the path $\mathbf{r}[t'] = \{\boldsymbol{\rho}[t'], z[t']\}$.

Below we shall consider two different limits that characterize influence of a single counter current pair on walker motion and their cooperative effect.

5.4.1 A single counter current pair

In this Subsection we assume that the time t meets the condition

$$\tau_a = \frac{a^2}{2D} \ll t \ll \frac{d_p^2}{2D} \qquad (5.95)$$

and the walker has been created near the pair i_0 at the point $\boldsymbol{\rho}_0 \approx \boldsymbol{\rho}_{i_0}$, i.e. $|\boldsymbol{\rho}_{i_0} - \boldsymbol{\rho}_0| \sim a$. In this case we may take into account only the pipe pair i_0.

Replicating practically one-to-one calculations of Section 5.2 we get

$$\langle l_\parallel(t, \boldsymbol{\rho}_0) \rangle_w = \pi a^2 v \int\limits_0^t dt' \int\limits_{S_{xy}} d\boldsymbol{\rho}' U_{i_0}^p(\boldsymbol{\rho}') G(\boldsymbol{\rho}' - \boldsymbol{\rho}_0, t') \qquad (5.96)$$

and

$$\langle (l_\parallel(t, \boldsymbol{\rho}_0))^2 \rangle_w = 2Dt + (\pi a^2 v)^2 2 \int\limits_0^t dt' \int\limits_0^{t'} dt'' \int\limits_{S_{xy}} \int\limits_{S_{xy}} d\boldsymbol{\rho}' d\boldsymbol{\rho}'' \cdot$$

$$\cdot U_{i_0}^p(\boldsymbol{\rho}') U_{i_0}^p(\boldsymbol{\rho}'') G(\boldsymbol{\rho}' - \boldsymbol{\rho}'', t' - t') G(\boldsymbol{\rho}'' - \boldsymbol{\rho}_0, t''). \qquad (5.97)$$

Here $G(\boldsymbol{\rho}, t)$ is the probability for a walker created at the point $\boldsymbol{\rho}_0 = 0$ in the xy - plane to reach the point $\boldsymbol{\rho}$ in the time t and is determined by expression (5.19), and

$$U_i^p(\boldsymbol{\rho}) = U_i(\boldsymbol{\rho} - \boldsymbol{\rho}_i{}^+) - U(\boldsymbol{\rho} - \boldsymbol{\rho}_i{}^-). \qquad (5.98)$$

Let us, first, estimate integral (5.96). Formulas (5.19), (5.26) and identity (5.27) allow us to integrate directly over $\boldsymbol{\rho}''$ in expression (5.96). In this way we get

$$< l_\parallel(t, \boldsymbol{\rho}_0) >_w = \pi a^2 v 2 \int\limits_0^t dt' \frac{1}{\pi[4Dt' + a^2]} \cdot$$

$$\cdot \left\{ \exp\left[-\frac{(\boldsymbol{\rho}_0 - \boldsymbol{\rho}_{i_0}^+)^2}{4Dt' + a^2} \right] - \exp\left[-\frac{(\boldsymbol{\rho}_0 - \boldsymbol{\rho}_{i_0}^-)^2}{4Dt' + a^2} \right] \right\} \qquad (5.99)$$

For $\left|\boldsymbol{\rho}_0 - \boldsymbol{\rho}_{i_0}{}^+\right| \sim a$; $\left|\boldsymbol{\rho}_0 - \boldsymbol{\rho}_{i_0}{}^-\right| \sim a$ and $t \gg a^2/(2D)$ the integral (5.99) is about

$$\frac{a^2}{\pi[4Dt]^2}. \tag{5.100}$$

Since the integral

$$\int\limits_{T}^{\infty} \frac{dt}{t^2} \tag{5.101}$$

converges at the upper limits, the main contribution to integral (5.99) is associated with values of the time t' being about a^2/D. The latter enables us to estimate the mean value $\langle l_{\parallel}(t, \boldsymbol{\rho}_0)\rangle$ as

$$\left|\langle l_{\parallel}(t, \boldsymbol{\rho}_0)\rangle\right| \sim \frac{a^2 v}{2D} = v\tau_a. \tag{5.102}$$

For the sake of simplicity we calculate the value $\langle (l_{\parallel}(t, \boldsymbol{\rho}_0))^2 \rangle$ averaged over all the possible arrangement of the pipe centre lines $\{\boldsymbol{\rho}_{i_0}{}^+, \boldsymbol{\rho}_{i_0}{}^-\}$. By definition

$$\langle U_{i_0}^p(\boldsymbol{\rho}\,')U_{i_0}^p(\boldsymbol{\rho}\,'')\rangle_{\pm} =$$

$$= \int\limits_{S_{xy}} \int\limits_{S_{xy}} d\boldsymbol{\rho}_{i_0}{}^+ d\boldsymbol{\rho}_{i_0}{}^- \Phi_{i_0}(\boldsymbol{\rho}_{i_0}{}^+)\Phi_{i_0}(\boldsymbol{\rho}_{i_0}{}^-)U_{i_0}^p(\boldsymbol{\rho}\,')U_{i_0}^p(\boldsymbol{\rho}\,''). \tag{5.103}$$

Substituting (5.98) into (5.97), then, averaging according to rule (5.103) and taking into account that the superscripts "+" and "−" become the dummy indexes, we get

$$\langle (l_{\parallel}(t, \boldsymbol{\rho}_0))^2 \rangle_{w,\pm} = 2Dt + 4(\pi a^2 v)^2 \int\limits_0^t dt' \int\limits_0^{t'} dt'' \iint\limits_{S_{xy}} d\boldsymbol{\rho}\,' d\boldsymbol{\rho}\,'' \cdot$$

$$\cdot \left\{ \int\limits_{S_{xy}} d\boldsymbol{\rho}^+ \Phi_{i_0}(\boldsymbol{\rho}_{i_0}{}^+)U(\boldsymbol{\rho}\,' - \boldsymbol{\rho}^+)U(\boldsymbol{\rho}\,'' - \boldsymbol{\rho}^+) \cdot \right.$$

$$\cdot G(\boldsymbol{\rho}\,' - \boldsymbol{\rho}\,'', t' - t'')G(\boldsymbol{\rho}\,'' - \boldsymbol{\rho}_0, t'') -$$

$$- \iint\limits_{S_{xy}} d\boldsymbol{\rho}^+ d\boldsymbol{\rho}^- \Phi_{i_0}(\boldsymbol{\rho}^+)\Phi_{i_0}(\boldsymbol{\rho}^-)U(\boldsymbol{\rho}\,' - \boldsymbol{\rho}^+)U(\boldsymbol{\rho}\,'' - \boldsymbol{\rho}^-) \cdot$$

$$\left. \cdot G(\boldsymbol{\rho}\,' - \boldsymbol{\rho}\,'', t' - t'')G(\boldsymbol{\rho}\,'' - \boldsymbol{\rho}_0, t'') \right\}, \tag{5.104}$$

where we also have integrated over ρ^- in the first term in the braces.

All the cofactors of the integrals in (5.104) are of the form given by formula (5.28). So, it is convenient to represent the integral term of (5.104) as the diagram shown in Fig. 5.4. The line between two points (Fig. 5.4a) represents the function $\mathcal{G}(\boldsymbol{\rho}_0 - \boldsymbol{\rho}', A)$ given by (5.28), the solid circuits show the fixed coordinates and the empty circuits correspond to variables of integration. Some of the rules of diagram transformation to be used are given in Fig. 5.4b. Following these rules we reduce formula (5.104) whose integral term is shown in Fig. 5.4c to the expression

$$\langle (l_\parallel(t, \boldsymbol{\rho}_0))^2 \rangle_{w,\pm} = 2Dt + \frac{4}{\pi^2}(\pi a^2 v)^2 \int\limits_0^t dt' \int\limits_0^{t'} dt'' \cdot$$

$$\cdot \left\{ \frac{1}{4D(t'-t'') + 2a^2} \frac{1}{(4Dt'' + b^2 + \sum_-)} \exp\left[-\frac{(\boldsymbol{\rho}_0 - \boldsymbol{\rho}_{i_0})^2}{4Dt'' + b^2 + \sum_+} \right] - \right.$$

$$\left. - \frac{1}{4D(t'-t'') + 2(a^2 + b^2)} \frac{1}{(4Dt'' + \sum_-)} \exp\left[-\frac{(\boldsymbol{\rho}_0 - \boldsymbol{\rho}_{i_0})^2}{4Dt'' + \sum_-} \right] \right\}, \qquad (5.105)$$

where

$$\sum_+ = \frac{a^2[4D(t'-t'') + a^2]}{4D(t'-t'') + 2a^2}, \qquad (5.106)$$

$$\sum_- = \frac{a^2[4D(t'-t'') + (a^2 + b^2)]}{4D(t'-t'') + 2(a^2 + b^2)}. \qquad (5.107)$$

For $t' - t'' \gg \tau_a \sim a^2/D$; b^2/D according to (5.106), (5.107) $\sum_+ \simeq a^2$; $\sum_- \simeq a^2 + b^2$. Therefore, as seen from (5.105) the main contribution to the integral (5.105) is associated with the region $t' - t'' \sim \tau_a$. For $|\boldsymbol{\rho}_0 - \boldsymbol{\rho}_{i_0}| \sim a$ and $t'' \gg a^2/D$ we may rewrite the term in the braces as

$$\frac{1}{4Dt''} \frac{2b^2}{[4D(t'-t'') + 2a^2][4D(t'-t'') + 2(a^2 + b^2)]}. \qquad (5.108)$$

If we substitute this term into integral (5.105) then, it will diverge logarithmically, which may be cut-off at $t'' \sim \tau_a$. In this way integrating over t' and t'' we obtain

$$\langle (l_\parallel(t, \boldsymbol{\rho}_0))^2 \rangle_{w,\pm} = 2Dt + \left(\frac{a^2 v}{2D} \right)^2 \ln(1 + \mu^2) \ln \frac{t}{\tau_a}. \qquad (5.109)$$

Figure 5.4: Diagrams representation of integral terms.

Formulas (5.102) and (5.109) give the desired mean values of the distance travelled by a walker along the pipes during the time t. Concluding the present Subsection we note that blood flow in a single pipe and a single countercurrent pair affects walker motion in different way. Indeed, according to (5.43), (5.55) for a single pipe the blood flow effect may be treated in terms of convective transport and the mean displacement $l_\parallel$ along the pipe with blood flow is $l_\parallel \approx vt_p$, where t_p is the mean residence time of walkers inside the pipe (see Subsection 5.2.1). For a single counter current pair, according to (5.102) and (5.109) the blood flow effect is diffusive in nature. The matter is that a walker during its motion visits alternately vessels with the opposite blood flow directions. During each visit of a pipe the walker with blood flow travels, on the average, a disk line $v\tau_a$. The mean number of such visits can be estimated as t_p/τ_a. Due to the walker visiting each of the pair pipes randomly the mean squared distance $l_\parallel$ travelled by the walker along the pipes is about

$$l_\parallel^2 \sim (v\tau_a)^2 \frac{t_p}{\tau_a} \qquad (5.110)$$

and substituting (5.36) into this expression we immediately get formula (5.109).

5.4.2   The cooperative effect of countercurrent pairs

When $t \gg d_p^2/(2D)$ walkers during their motion visit a large number of counter current pairs. Therefore, in this case the total effect of blood flow in the counter current pairs must be cooperative and the tissue phantom containing this pipe pairs can be described in terms of an effective medium.

In the present Subsection we calculate the mean squared distance $l_\parallel(t, \boldsymbol{\rho}_0)$ travelled by a worker during the time t along the z - axis (see (5.94)). We note that for the tissue phantom under consideration $\langle l_\parallel(t, \boldsymbol{\rho}_0)\rangle_{w,\pm} = 0$. Replicating practically one - to - one the calculations of Subsection 5.2.2 from (5.92), (5.94) we obtain an expression similar to (5.46)

$$\left\langle (l_\parallel(t, \boldsymbol{\rho}_0))^2 \right\rangle_{\boldsymbol{\rho}_0, w, \pm} = 2Dt + 2(\pi a^2 v)^2 \frac{1}{S_{xy}} \sum_{i', i''} \int\limits_0^t dt' \int\limits_0^{t'} dt'' \cdot$$

$$\cdot \int \int\limits_{S_{xy}} \int d\boldsymbol{\rho}' d\boldsymbol{\rho}'' d\boldsymbol{\rho}_0 < U_{i'}^p(\boldsymbol{\rho}') U_{i''}^p(\boldsymbol{\rho}'') >_\pm \cdot$$

$$\cdot G(\boldsymbol{\rho}' - \boldsymbol{\rho}'', t' - t'') G(\boldsymbol{\rho}'' - \boldsymbol{\rho}_0, t''). \tag{5.111}$$

Noting that according to (5.98) and (5.103)

$$\langle U_i^p(\boldsymbol{\rho})\rangle_\pm = 0 \tag{5.112}$$

and the arrangement of pipe center lines for different countercurrent pairs are pairwise independent we may write

$$\langle U_{i'}^p(\boldsymbol{\rho}') U_{i''}^p(\boldsymbol{\rho}'')\rangle = \delta_{i'i''} \langle U_{i'}^p(\boldsymbol{\rho}') U_{i'}^p(\boldsymbol{\rho}'')\rangle . \tag{5.113}$$

The substitution of (5.113) into (5.111), formula (5.40) and (5.42) yield

$$\left\langle (l_\parallel(t, \boldsymbol{\rho}_0))^2 \right\rangle_{\boldsymbol{\rho}_0, w, \pm} = 2Dt + 4\frac{(\pi a^2 v)^2}{d^2} \int\limits_0^t dt' \int\limits_0^{t'} dt'' \int\limits_{S_{xy}} \int\limits_{S_{xy}} d\boldsymbol{\rho}' d\boldsymbol{\rho}'' \cdot$$

$$\cdot \left\{ \int\limits_{S_{xy}} d\boldsymbol{\rho}^+ \Phi_i(\boldsymbol{\rho}^+) U(\boldsymbol{\rho}' - \boldsymbol{\rho}^+) U(\boldsymbol{\rho}'' - \boldsymbol{\rho}^+) G(\boldsymbol{\rho}' - \boldsymbol{\rho}'', t' - t'') - \right.$$

Figure 5.5: Diagram representation of integral term in $< (l_\parallel(t, \boldsymbol{\rho}_0))^2 >_{\boldsymbol{\rho}_0, w, \pm}$.

$$
\left. \int\limits_{S_{xy}} \int d\boldsymbol{\rho}^+ d\boldsymbol{\rho}^- \Phi_i(\boldsymbol{\rho}^+) \Phi_i(\boldsymbol{\rho}^-) U(\boldsymbol{\rho}' - \boldsymbol{\rho}^+) U(\boldsymbol{\rho}' - \boldsymbol{\rho}^-) G(\boldsymbol{\rho}' - \boldsymbol{\rho}'', t' - t'') \right\}
$$

$$(5.114)$$

where d is the mean distance between the counter current pair given by expression (5.44) and i denotes any fixed pair, for example, the pair with $\boldsymbol{\rho}_i = 0$. The diagram representing the integral term in (5.114) is shown in Fig. 5.5. Following the rules indicated in Fig. 5.4b, we get

$$
\left\langle (l_\parallel(t, \boldsymbol{\rho}_0))^2 \right\rangle_{\boldsymbol{\rho}_0, w, \pm} = 2Dt + 4 \frac{(\pi a^2 v)^2}{d^2} \frac{1}{\pi} \int\limits_0^t dt' \int\limits_0^{t'} dt'' \cdot
$$

$$
\cdot \left[\frac{1}{4D(t' - t'') + 2a^2} - \frac{1}{4D(t' - t'') + 2(a^2 + b^2)} \right]
$$

$$(5.115)$$

It immediately follows that

$$
\left\langle (l_\parallel(t, \boldsymbol{\rho}_0))^2 \right\rangle_{\boldsymbol{\rho}_0, w, \pm} = 2Dt \left\{ 1 + \frac{\pi}{2} \left(\frac{a^2 v}{Dd} \right) \ln(1 + \mu^2) \right\}.
$$

$$(5.116)$$

Since the mean distance $\left\langle (l_\parallel(t, \boldsymbol{\rho}_0))^2 \right\rangle$ travelled by a walker along the pipes during the time t is directly proportional to the time t, this tissue phantom may be described in terms of an effective medium with the diffusion coefficient

$$D_{\text{eff}} = \left\{ 1 + \frac{\pi}{2} \left(\frac{a^2 v}{Dd} \right)^2 \ln(1 + \mu^2) \right\} D. \qquad (5.117)$$

Concluding the present Subsection we point out that for the given tissue phantom in contrast to the tissue phantom considered in Section 5.2 formula (5.116) does not contain a term proportional to $t \ln t$. This is the case because a walker returning to the same countercurrent pair for the next time it is travelled with blood flow in arbitrary direction.

5.5 Main characteristics of walker motion in living tissue with nonhierarchical vascular network

In previous Sections we have considered heat transfer in living tissue phantom containing vessels of the same parameters. This model does not account for the hierarchical nature of vascular networks in real living tissue. However, the results obtained in the framework of this model form the base for the following analysis of heat transfer in living tissue with hierarchical network. Therefore, in the present Section to gain a better comprehension we outline the main characteristics of random walkers in these tissue phantoms and discuss their physical meaning.

Random walks in living tissue can be characterized by two time scales playing important roles in analysis of bioheat transfer.

One of them is the mean residence time $\langle t_p \rangle$ of a walker inside a given pipe during its motion for the time $t \gg a^2/(2D)$ provided it was initially near this pipe. According to (5.36)

$$\langle t_p \rangle \simeq \frac{a^2}{2D} \ln \left[\frac{(2Dt)^{1/2}}{a} \right]. \qquad (5.118)$$

Obviously, the total mean time $\langle t_p \rangle$ during which a walker created near a counter current pair is inside the pipes of this pair is also given by expression (5.118). The other is the mean time τ_l during which a walker goes in the tissue without touching the pipes. This time scale is the same for both of the tissue phantoms considered above where individual pipes or countercurrent pairs form hexagonal areas are of equal spacing. Therefore, according to (5.92)

$$\tau_l \simeq \frac{d^2}{2\pi D} \ln \left(\frac{d}{a} \right), \qquad (5.119)$$

where $d = (\sqrt{3}/2)^{1/2} d_p$ is the mean distance between the pipes or the counter current pairs (see (5.44)). However, if the walker is initially near a certain pipe it practically inevitably will cross the boundary of the pipe within a time $t \ll \tau_l$.

Depending on the value of $2Dt/d^2$ the walker motion in the direction along the pipes differs in properties. In particular, for tissue with unit pipes when $a^2/(2D) \ll t \ll d^2/(2D)$ a walker, which is initially near a certain pipe, travels with blood flow in this pipe, the mean distance (see (5.29) and (5.31))

$$\langle l_{\parallel}(t) \rangle \simeq \frac{a^2 v}{2D} \ln \left[\frac{(2Dt)^{1/2}}{a} \right], \tag{5.120}$$

where v is the mean velocity of blood in the given pipe. In this case the mean square of a distance $l_{\parallel}(t)$ travelled by the walker during the time t, including its motion in the cellular tissue as well as in the blood stream, is (see (5.30))

$$\langle (l_{\parallel}(t))^2 \rangle \simeq 2Dt + 2 \langle l_{\parallel}(t) \rangle^2. \tag{5.121}$$

We note that expression (5.120) can be also rewritten in the form $\langle l_{\parallel}(t) \rangle = v \langle t_p \rangle$. Therefore, in this case blood flow effect may be treated in terms of convective transport.

For the tissue with counter current pairs the characteristic distance $l_{\parallel}(t)$ travelled by a walker created near a pipe pair with blood along these pipes is about (see (5.109)).

$$l_{\parallel}(t) \approx \frac{a^2 v}{2D} \left[2 \ln(1 + \mu^2) \ln \frac{(2Dt)^{1/2}}{a} \right]^{1/2} \tag{5.122}$$

where μ is the mean ration of the distance between pipes to the pipes radius of a single pair. In this case direction of the walker displacement is random and

$$l_{\parallel}(t) \sim v[\tau_a \langle t_p \rangle]^{1/2} \tag{5.123}$$

where $\tau_a = a^2/(2D)$.

When $t \gg d^2/(2D)$, or, more precisely, $t \gg \tau_l$, practically each walker in its motion visits a large number of pipes and we may describe the walker motion along the pipes in terms of random walks in homogeneous medium with the effective diffusion coefficient (see (5.64) and (5.117))

$$D_{\text{eff}} \approx D \left\{ 1 + \frac{\pi}{2} \left(\frac{a^2 v}{Dd} \right)^2 \left[\ln \left(\frac{d}{a} \right) \right]^\beta \right\} \tag{5.124}$$

under an uniform convective flux with the velocity (see (5.63))

$$\mathbf{v}_{\text{eff}} \approx \frac{\pi a^2 v}{d^2} \xi \mathbf{n}_Z, \tag{5.125}$$

where $\mathbf{n}_z$ is the unit vector in the positive z - direction and $\beta = 1$ for tissue with unit vessels and $\beta = 0$ for tissue with counter current pairs.

In the framework of qualitative analysis expressions (5.124) and (5.125) can be also obtained in the following way. First, we consider tissue with unit vessels. Let us assume that at a certain time a walker is near a given pipe. During a time $t < d^2/(2D)$ blood flow in the other pipes has practically no effect on its motion. Thereby, according to (5.120) and (5.122), the mean value of the distance $l_\parallel$ travelled by the walker along the pipe with blood flow during the time $t \sim d^2/(2D)$ can be estimated as

$$\langle l_\parallel \rangle \approx \frac{a^2 v}{2D} \ln \left(\frac{d}{a} \right) \tag{5.126}$$

and, in addition,

$$\left\langle l_\parallel^2 \right\rangle \approx 2 \left\langle l_\parallel \right\rangle^2. \tag{5.127}$$

then, we shall assume that in the time $t \sim d^2/(2D)$ the walker escapes from the neighborhood of this pipe whose radius is $d_p/2$ and in the time τ_l it reaches one of the pipes again. Due to $d \gg a$ the time τ_l can be considered to be substantially greater than $d^2/(2D)$ and, thus, we may assume that the walker reaches another pipe.

In this way we represent the walker path as a sequence of steps on the pipe array which practically does not contain returning to pipes that have been visited before. When $t \gg \tau_l$ such a sequence involves t/τ_l pairwise independent steps, with the length of one step obeying conditions (5.126) and (5.127). Taking into account that blood flow in a vessel is oriented in the positive z - direction with probability $1/2(1 + \xi)$ and in the opposite one with probability $1/2(1 - \xi)$ we find the following expressions for the total length $\tilde{l}_\parallel(t)$ of this step sequence along the pipes (cf. e.g., of. [26])

$$\left\langle \tilde{l}_\parallel(t) \right\rangle \approx \xi \left\langle l_\parallel \right\rangle \frac{t}{\tau_l} = \frac{\pi a^2 v}{d^2} \xi t \tag{5.128}$$

and

$$\left\langle (\tilde{l}_\parallel(t))^2 \right\rangle = \left(\left\langle l_\parallel^2 \right\rangle - \xi^2 \left\langle l_\parallel \right\rangle^2 \right) \frac{t}{\tau_l} + \left(\xi \left\langle l_\parallel \right\rangle \frac{t}{\tau_l} \right)^2 =$$

$$= 2D \left[\frac{(2 - \xi^2)\pi}{4} \left(\frac{a^2 v}{Dd} \right)^2 \ln \left(\frac{d}{a} \right) \right] t + \left\langle \tilde{l}_\parallel(t) \right\rangle^2. \tag{5.129}$$

Expression (5.125) immediately results from (5.128) and expression (5.129) leads to formula (5.124) if, in addition, we allow for a random motion of walkers in the tissue itself and do not distinguish between $(2 - \xi^2)/4$ and $1/2$.

Besides, we note that for $\xi = \pm 1$, i.e. for the system of pipes with blood flow in the same direction, we may consider the blood flow effect on walker motion in terms of convective transport only. Indeed, for example, according to (5.128) and (5.129) for $|\xi| \sim 1$ and $t \gg \tau_l$ we get $[\left\langle (\tilde{l}_\parallel(t))^2 \right\rangle - \left\langle \tilde{l}_\parallel(t) \right\rangle^2]/\left\langle \tilde{l}_\parallel(t) \right\rangle^2 \sim (t/\tau_l)^{-1}$ and, thereby, in this case the random component of the walker displacement is not a factor.

For tissue with counter current pairs these speculations also hold true. Indeed, within replacement the term pipe by the term countercurrent pair, the random walk representation will be the same. Here, however, we should set $\xi = 0$ and for $\left\langle l_\parallel^2 \right\rangle$ use formula (5.121) with $(2Dt)^2 \sim d^2$. then, formula (5.129) immediately leads to expression (5.124) with $\beta = 0$.

5.6   Vessel classification

In the present Section we classify vessels of various lengths and different levels according to their "individual" influence on walker motion. The term "individual" implies that we take into account at the same time only vessels of one level. In other words, we do not allow for collective effect of vessels belonging to different levels on walker motion in living tissue. Dealing with living tissue containing unit vessels we consider vessels individually. For living tissue with countercurrent vascular network a single pair of countercurrent vessels should be regarded as a unit basic structure of the vascular network architectonics.

Description of individual influence of a single unit vessel and a single countercurrent pair is practically the same. Therefore, we will (in this Section) focus the main attention on unit vessels. For counter current pair solely the final results are formulated.

Let at a certain time a walker reaches a vessel of level n. then, within the time $t_n \approx d_n^2/(2D)$ (where d_n is the mean distance between the n-th level vessels) the walker is practically located inside the fundamental domain Q_n containing this vessel. Since there are practically no other vessels of level n in the domain Q_n the individual effect of blood flow in the given vessel on the walker motion in the domain Q_n can be measured in terms of the mean distance $l_{\parallel n}$ which the walker would travel along the vessel with blood flow in it during the time t_n, if the vessel were infinitely long. In accordance with (5.120)

$$l_{\parallel i} = \frac{a_i^2 v_i}{2D} \ln\left(\frac{d_n}{a_i}\right). \tag{5.130}$$

where a_i and v_i are the radius of the given vessel and v is the mean velocity of blood in it.

Due to walker random motion in the cellular tissue itself, the walker passes, in addition, a distance of order $(2Dt_n)^{1/2} \sim d_n \sim l_n$ during this time. Thus, blood flow in the given vessel will have a substantial individual effect on the walker motion if $l_{\parallel n} \gg l_n$. Otherwise, such an effect will be ignorable.

For each vessel of the vascular network let us introduce the parameter

$$\zeta_i = \frac{a_i^2 v_i}{2Dl_n} \ln\left(\frac{d_n}{a_i}\right),$$
(5.131)

which, by virtue of (5.130), is the ratio $l_{\parallel n}/l_n$. For a counter current pair, for example, pair i of level n

$$l_{\parallel i} = \frac{a_i^2 v_i}{2D} \left[\ln\left(\frac{d_n}{a_i}\right)\right]^{1/2}$$
(5.132)

and

$$\zeta_i = \frac{a_i^2 v_i}{2Dl_n} \left[\ln\left(\frac{d_n}{a_i}\right)\right]^{1/2}$$
(5.133)

These parameters enable us to divide all the vessels in two classes according to the value of ζ_i. By definition, the first class (Class 1) consists of vessels (counter current pairs) corresponding to the value $\zeta_i > 1$ and the second class (Class 2) involves vessels (counter current pairs) for which $\zeta_i < 1$. If a given vessel of level n meets the condition $\zeta_i \ll 1$, i.e. $l_{\parallel i} \ll l_n$, and there is no one vessel of the first class in the fundamental domain Q_n containing this vessel, then,in the time t_n walkers which are near the given vessel will be distributed practically uniformly over the whole domain Q_n. In terms of heat transfer this means that blood flowing through the given vessel has enough time to attain thermal equilibrium with the tissue in the domain Q_n. In other words, the temperature of blood portion during its motion through this vessel will coincide with the tissue temperature averaged over the domain Q_n. Therefore, vessels of Class 2 will be called heat - dissipation vessels. If walkers are initially near a vessel of level n corresponding to the value $\zeta_i \gg 1$, i.e. for which $l_{\parallel i} \gg l_n$, they will go out of the domain Q_n, that contains this vessel, remaining inside a neighborhood of this vessel whose radius is much smaller than d_n. In other words, due to high velocity of blood in the given vessel its temperature has practically no time to become equal to the mean tissue temperature in the domain Q_n. Therefore, vessels of Class 1 will be called heat conservation vessels, because, as it will be shown in Section 6.1, we may ignore heat exchange between blood in these vessels and the surrounding cellular tissue.

Vessels, for which $\zeta_i \sim 1$, exhibit the properties of both heat - dissipation and heat - conservation vessels and to describe in detail their influence on heat transfer more complicated analysis is required. Nevertheless, as it will be shown in Section 6.1, we may divide all the vessels of the vascular network in two classes according to their influence on heat transfer by the rigorous inequalities $\zeta_i < 1$ and $\zeta_i > 1$.

The same comments regarding the vessel classification refer equally to the counter current pairs.

In a similar way we can consider the capillary system and introduce the corresponding parameter

$$\zeta_c = \frac{a_c^2 v_c}{2Dl_c} \ln\left(\frac{d_c}{a_c}\right),\qquad(5.134)$$

which classifies capillaries as heat-conservation or heat-dissipation vessels.

Part II

Transport phenomena caused by blood flow through hierarchical vascular network

Chapter 6

The effect of different group vessels on heat transfer in living tissue

In the previous Chapter we analyzed characteristics of heat transfer in living tissue that are caused by individual effect of vessels belonging to different levels. The present Chapter deals with the main properties that bioheat transfer exhibits due to blood flow distribution over the whole vessel tree. Therefore, we shall confine our consideration to uniform blood flow distribution over vascular network.

6.1 Dependence of the vessel classification parameter on hierarchy level

Since the vessel classification parameter ζ_i plays an important role in description of the blood flow effect on heat transfer in this Section we analyse in detail the classification parameter as a function of the level number n and the total blood current J_0 through the vascular network. In the case under consideration blood current $\pi a_n^2 v_n$ in each vessel of one level is the same and depends on the level number n only. Thus, by virtue of (4.5), (4.6) and (5.130), (5.131) the classification parameter ζ_n for unit vessels and countercurrent pairs can be represented as

$$\zeta_n = G 2^{-2n} \left(\ln \frac{l_0}{a_0} \right)^{-\frac{1}{2}[1-\beta(n)]} \tag{6.1}$$

where the function

$$\beta(n) = \left\{ \begin{array}{ll} 0 & ; \quad n \leqslant n_{cc} \\ 1 & ; \quad n > n_{cc} \end{array} \right. , \tag{6.2}$$

the dimensionless total blood current

$$G = \frac{J_0}{2\pi D l_0} \ln\left(\frac{l_0}{a_0}\right) \equiv \frac{4jl_0^2}{3\sqrt{3}\pi D} \ln\left(\frac{l_0}{a_0}\right) \tag{6.3}$$

and we have ignored the difference between $\ln(d_n/a_n)$ and $\ln(l_0/a_0)$. The latter is justified because l_n/a_n is a large parameter whereas l_n/d_n and $w(n)$ (see (4.7)) are of order unity. The function $\beta(n)$ reflects the fact that the vascular network contains the countercurrent pairs up to level n_{cc}.

Let us analyse the solution $n = n_t$ of the equation

$$\zeta_n|_{n=n_t} = 1. \tag{6.4}$$

for various values of G. The classification parameter ζ_n as a function of n for different values of G is shown in Fig. 6.1 where n is treated as a continuous variable. As seen in Fig. 6.1 there can exist one n_t or two roots n_t, n_t^* of equation (6.4) depending on the value of G. The jump on the curve $\zeta(n)$ is due to countercurrent pairs vanishing at level n_{cc}. The dependence of the roots on the total blood current (G) is shown in Fig. 6.1b and in the region $G_1 < G < G_2$ involves two single-valued branches. However, as it will become clear from the following analysis and is discussed in detail in Chapter 9 we should choose the lower root n_t of equation (6.4) because it is a connected part of the vascular network involving the first class vessels among with the tree stem that determine the collective effect of vessels of different levels on heat transfer. The solid line in Fig. 6.1b shows the dependence of this root n_t on the dimensionless total blood current G which can be specified in terms of

$$n_t = \left\{ \begin{array}{ll} \frac{1}{2\ln 2} \ln \frac{G}{G_0}, & \text{for} \quad G_0 \leqslant G \leqslant G_{cc}, \\ \frac{1}{2\ln 2} \ln G, & \text{for} \quad G_{cc} \leqslant G, \end{array} \right. \tag{6.5}$$

where $G_0 = (\ln(l_0/a_0))^{1/2}$ and $G_{cc} = 2^{2n_{cc}}(\ln(l_0/a_0))^{1/2}$.

As it will be shown below, heat exchange between blood and the cellular tissue is directly controlled by vessels of level n_t. Therefore, when $G < G_0$ blood flow has practically no effect on heat transfer and for this reason we shall examine only the case

$$G \gg G_0. \tag{6.6}$$

In particular , for typical values of $l_0 \sim 5cm$, $c_t \sim 3.5 J/g \cdot K$, $\rho_t \sim g/cm^3$, $\kappa \sim 7 \cdot 10^{-3} J/s \cdot cm \cdot K$, the mean blood flow rate $j \sim 10^{-3} s^{-1}$, and setting $l_0/a_0 \sim 40$

Figure 6.1: The classification parameter ζ_n as a function of n for different values $G_1 < G_2 < G_3$ (a) and the solution n_t as a function of the dimensionless total blood current G (b).($n_{st} = n_{cc} + \frac{1}{2}\ln\ln\frac{l_0}{a_0}$; $G_0 = \left(\ln\frac{l_0}{a_0}\right)^{1/2}$; $G_{cc}^* = 2^{2n_{cc}}$; $G_{cc} = 2^{2n_{cc}}(\ln(l_0/a_0))^{1/2}$);.$G_0 = \left(\ln\frac{l_0}{a_0}\right)^{1/2}$; $G_{cc}^* = 2^{2n_{cc}}$; $G_{cc} = 2^{2n_{cc}}(\ln(l_0/a_0))^{1/2}$)..

from (6.3) we find $G \sim 10$. For kidney, where blood flow is of the highest level [76] setting $j \sim 10^{-2}s^{-1}$ we get $G \sim 100$.

In this Chapter we shall show that the vessels of the vascular network described in Chapter 3 can be divided, in principle, into four possible groups in accordance with their influence on heat transfer. These groups are the countercurrent pairs of Class 1 and the veins of Class 1 for which level number $n \leqslant n_t$ and countercurrent pairs of Class 2 and, may be, the first class veins for which $n_{cc} \leqslant n < n_t$; the arteries of Class 1; the arteries,veins; and the capillary system. Below their influence on heat transfer will be considered individually.

6.2 The effect of the heat conservation countercurrent pairs and veins on heat transfer

Let us, first, consider the characteristic properties of the walker motion that are caused by the first class veins. If at a certain time a walker reaches a vein of level n for which $\zeta_n \gg 1$ then,it will be transported by blood flow in this vein into a small (in comparison with Q_n) neighborhood of a vein belonging to level $(n-1)$ and connected with the given one through the corresponding branching point. This is the case because the mean time τ_{b_n} of this process satisfies the inequality $\tau_{b_n} \ll d_n^2/(2D)$. Indeed, when $1 \ll \zeta_n \ll \ln(d_n/a_n)$ and, thereby, the time $\tau_{b_n} \gg d_n^2/(2D)$ (see (6.7)) its value can be estimated by setting $t = \tau_{b_n}$

and $< l_\parallel(t) >= l_n$ in expression (5.120). In this way taking into account (5.131) we obtain

$$\tau_{bn} \sim \frac{a_n^2}{2D} \exp\left\{\frac{2\ln(d_n/a_n)}{\zeta_n}\right\} \equiv \frac{d_n^2}{2D} \exp\left\{-\frac{(\zeta_n - 1)}{\zeta_n} 2\ln\left(\frac{d_n}{a_n}\right)\right\}. \qquad (6.7)$$

For $\zeta_n \gg \ln(d_n/a_n)$ there are two possible cases differing in way by which the walker goes into the given vein for the first time. When the walker goes into this vein with blood flow from a vein of level $(n + 1)$ through the corresponding branching point it immediately arrives at central points of the given vein. Clearly, in this case the value of τ_{bn} can be estimated as

$$\tau_{bn} \sim \frac{l_n}{v_n} \equiv \frac{a_n^2}{2D\zeta_n} \ln\left(\frac{d_n}{a_n}\right) \qquad (6.8)$$

because during the time $\tau_{bn} \ll a_n^2/(2D)$ the walker practically cannot reach the boundary of this vein. If the walker goes into the vein through its boundary, the walker during its motion along this vein will be located inside the boundary neighborhood whose thickness is about $(2D\tau_{bn})^{1/2} \ll a_n$, alternately going inside the vein and in the cellular tissue. Assuming that at vessel boundaries the blood velocity is equal to zero and inside vein and arteries of microcirculatory beds the velocity field of blood flow is approximately specified by parabolic distribution over the vessel cross section, we can estimate the blood velocity averaged over the given vein boundary neighborhood as $< v >= v_n(2D\tau_{bn})^{1/2}/a_n$. Thus, in this case

$$\tau_{bn} \sim \frac{l_n}{< v >} = \frac{a_n^2}{2D}\left[\frac{1}{\zeta_n}\ln\left(\frac{d_n}{a_n}\right)\right]^{2/3} \qquad (6.9)$$

So, in the three cases the time $\tau_{bn} \ll d_n^2/(2D)$.

By virtue of (6.1) for $n > n_{cc}$ the value $(\ln(d_n/a_n))/\zeta_n = (2\pi Dl_0/J_0)2^{2n}$. Thereby, according to (6.7) - (6.9), the ratio $a_n^2/(2D\tau_{bn})$ increases as n decreases. Thus, for all the first class veins of the given group $\tau_{bn} \ll a_n^2/(2D)$ except the veins whose level number n satisfies the inequality $n_* < n < n_t$ for which $\tau_{bn} \gg a_n^2/(2D)$. Here the value n_* is specified by the condition $(2D\tau_{bn})/a_n^2 \sim 1$ or, what is practically the same according to (6.7) - (6.9), by the equality $\zeta_{n_*} = \ln(d_{n_*}/a_{n_*})$. From the latter equality and expressions (6.1), (6.5) we get

$$n_* \approx n_t - \frac{1}{2\ln 2} \ln\left[\ln\left(\frac{l_0}{a_0}\right)\right] \qquad (6.10)$$

In particular, for $l_0/a_0 \sim 40$ the value $(n_t - n_*) \sim 1$.

Figure 6.2: Schematic representation of walker trapping by the first class veins. On intersecting the dashed region a walker gets the central points of the next level veins and never returns to the cellular tissue.

Let us show that a walker, being initially near a first class vein of level n for which $\zeta_n \gg 1$, can be found in the cellular tissue only within a time of order τ_{bn}. To do this we consider the two following possible cases.

A walker, being initially close to the boundary of a vein whose level number $n < n_*$ is bound to arrive at central points of the vein system including several nearest levels $(n-1), (n-2)$, etc. To justify this statement we consider the walker motion in living tissue with a real vessel system made of two-fold branching points (Fig. 6.2). For the eight - fold branching point model of the vascular network this statement is borne out to greater accuracy. In this case $\tau_{bn} \ll a_n^2/(2D)$, therefore, if the walker starts in the vicinity of the dashed region of the vein boundary, then,the walker will remain in it during its motion along this vein and after passing through the branching point it will get the central points. The probability of this event is about $1/2$. If the walker starts near the other side of the vein boundary, then,it will get in the neighborhood of the dashed side of the $(n-1)$-th level vein with probability $1/2$. In this case after passing through the corresponding branching point the walker gets the central points again. The total probability for the walker to reach the central points after passing through these two branching points is approximately $3/4$. It is obvious that after passing m' branching points the probability of getting the central points is about $(1 - (2)^{-m'})$.

So, within the framework of the eight-fold branching point model for the vascular network it is natural to assume that the walker after passing m' branching points arrives at the central points with probability $(1 - (2)^{-3m'})$ because the eight-fold branching points represent practically the fragment of real vascular network containing three two-fold branching points. Therefore, the walker practically gets the central points after passing several branching points. Besides,

due to ζ_n and a_n depending on n approximately as 2^{2n} and 2^{-n}, respectively, according to (6.9) in this case τ_{bn} varies with n as $2^{-(2n)/3}$ and the mean total time of reaching the central points by the walker is about τ_{bn}. By virtue of (6.7) for walkers moving inside veins the ratio $a_n^2/(2D\tau_{bn})$ varies with n practically as 2^{-2n}. Therefore, after getting the central points the walker never returns to the cellular tissue again and leaves the microcirculatory bed domain Q_0 through the host vein with blood flow, because it has practically no time to reach vein boundaries during its motion with blood flow through the vein system.

As will be seen from the results obtained below in this Section, vessels of other types have no significant effect on the walker motion in the vicinity of a vein whose level number $n^* < n < n_t$. For example, according to (5.120) and (5.122), on temporal scales $t \gg a_n^2/(2D)$ the effect of blood flow in such a vein on the walker motion is practically determined by the blood current $\pi a_n^2 v_n$ in it rather than the mean blood velocity v_n and the vessel radius a_n individually. Indeed, by virtue of (5.39), in this case the mean distance $< l_\|(t) >$ travelled by a walker along the vein depends on n through the term $a_n^2 v_n$ as 2^{-3n}, whereas the logarithmic cofactor leads to a linear dependence only. Therefore, to show that a walker, which is initially near a vein whose level number $n_* < n < n_t$, reaches a vein of level n_* in a time τ'_{bn} of order τ_{bn} we may consider its motion in the vicinity of the following inhomogeneous pipe. We assume that this imaginary pipe of radius a_n involves different parts of lengths $l_n, l_{n-1}, l_{n-2}, \ldots, l_0$, where the mean blood velocity is equal to $u_n = v_n$, $u_{n-1} = v_{n-1}(a_{n-1}/a_n)^2$, $u_{n-2} = v_{n-2}(a_{n-2}/a_n)^2, \ldots$ The time required for the walker to pass the whole length of this pipe in its motion with blood in the pipe is about

$$\sum_{n'=0}^{n} \frac{l_{n'}}{u_{n'}} = a_n^2 \sum_{n'=0}^{n} \frac{l_{n'}}{v_{n'} a_{n'}^2} \sim \frac{l_n}{v_n}, \qquad (6.11)$$

where we have taken into account (4.5) and (4.6). According to (5.118) the mean residence time $\langle t_p \rangle$ of the walker inside the pipe during its motion in the vicinity of this pipe for the time $t \gg a_n^2/(2D)$ can be estimated as $a_n^2/(2D) \ln[(2Dt)^{1/2}/a_n]$. In addition, as it follows from comparison between (5.120) and (5.122) the dispersion of the walker residence time t_p is about the square of its mean value. Therefore, by virtue of (6.11), the desired time τ'_{bn} in which the walker reaches a vein of level n_* can be found from the expression

$$\frac{l_n}{v_n} \sim \frac{a_n^2}{2D} \ln \left[\frac{(2D\tau'_{bn})^{1/2}}{a_n} \right]. \qquad (6.12)$$

We get formula (6.7) again, and, thus, $\tau'_{bn} \sim \tau_{bn}$.

After reaching a vein of level n_* the walker will arrive at central points of veins whose level number $n < n_*$ in a time of order τ_{bn_*}, which, by virtue of (6.9), is well below the time $\tau_{bn} : \tau_{bn_*} \ll \tau_{bn}$. So, in the given case the time required for the walker to get central points of the vessel system involving veins

of levels $n < n_*$, where upon it hardly ever returns to the cellular tissue, is about $\tau'_{bn} + \tau_{bn^*} \sim \tau_{bn}$.

Another time scale characterizing the influence of blood flow in the first class veins on the walker motion is the mean time τ_{ln} during which a walker can go in the cellular tissue without touching the veins of level n provided all other vessels have no effect on its motion. From the viewpoint of walker motion in the cellular tissue near a vein of level n, this vein can be regarded as an infinitely long pipe. In addition, every fundamental domain Q_n of level n contains just one vein of the same level, with its characteristic spatial size being about the vein length. Therefore, to estimate the value of the time τ_{l_n} we may conceive the veins of level n as a collection of pipes forming a hexagonal array for which the mean distance between the pipes coincides with the mean distance d_n between these veins. So, according to (5.119), we get

$$\tau_{l_n} \sim \frac{d_n^2}{2\pi D} \ln\left(\frac{d_n}{a_n}\right). \tag{6.13}$$

If we had taken into account veins of Class 2 and arteries then, their influence on such walker motion could not significantly modify expression (6.13) (see the next Section).

The results obtained above allow us to regard the first class veins for which $\zeta \gg 1$ as walker traps. Indeed, on one hand, if wandering through the cellular tissue a walker crosses one of these veins, for example, a vein of a level n then, practically after the time τ_{bn} it will arrive at central points of veins whose level number $n' < n_*$ whereupon the walker hardly ever returns to the cellular tissue. According to (6.7)-(6.9) the time $\tau_{bn} \ll d_n^2/(2D)$. On the other hand, as it follows from (6.13), the mean time, after which a walker created in the cellular tissue can reach a vein of a level n, satisfies the inequality $\tau_{l_n} > d_n^2/(2D)$. Therefore, a walker may be thought of as arriving at the central points in no time (in comparison with $d_n^2/(2D)$) after crossing one of the first class veins. In other words, these veins may be considered to be walker traps.

Capillaries can exert some effect on the walker motion in the tissue. However, when their effect is significant and thereby expression (6.13) should be modified, capillaries themselves transport walkers practically inside veins for which $n < n_*$. Thus, also in this case the first class veins may be regarded as walker traps.

In accordance with (6.7) veins of level $n \sim n_t$, i.e. for which $\zeta_n > 1$, meet the inequality $\tau_{bn} < d_n^2/(2D)$. However, owing to expression (6.13) containing the logarithmic cofactor $\ln(d_n/a_n)$ treated in the given model as a large value, we may assume that $\tau_{bn} \ll \tau_{l_n}$ for such veins too. Therefore, veins of levels $n \sim n_t$ also can be regarded as walker traps. The latter allows us to treat all the veins for which $\zeta_n > 1$ as walker traps and to divide all the veins of the venous bed in Class 1 and Class 2 by the rigorous inequalities $\zeta_n > 1$ and $\zeta_n < 1$ respectively.

Below in this Section we shall ignore the effect of blood flow in the second class countercurrent pair veins, arteries and capillaries on the walker motion in the tissue. Due to the relative volume of the vascular network being small

value the mean time during which a walker can go in the cellular tissue without touching the first class veins is determined by the expression

$$\frac{1}{\tau} \sim \sum_{n=0}^{n_t} \frac{1}{\tau_{l_n}} \tag{6.14}$$

where n_t is regarded as a cutoff parameter. The value d_n depends on n as 2^{-n} whereas $\ln(d_n/a_n)$ is a smooth function of n. So, by virtue of (6.13), the main contribution to sum (6.14) is associated with the last term, i.e. $\tau \sim \tau_{ln_t}$. Therefore, although the walker can be trapped by any vein of Class 1 the veins of the smallest length in this group, i.e. that of level n_t play the main role in walker trapping. The role of the larger veins is practically to transport trapped walkers with blood flow to the host vein. The n_t-th level veins possess the properties of traps as well as fast migration paths in the cellular tissue with the latter being the characteristic property of the second class vessels. Nevertheless, the veins of level n_t trap only and assuming that walker trapping is controlled by these veins set $\tau = \tau_{ln_t}$.

Keeping in mind these assumptions and the definition of the blood flow rate j described in Chapter 4, from (6.13) we get

$$\tau = \frac{d_{n_t}^2}{2\pi D} \ln \frac{d_{n_t}}{a_{n_t}} = \frac{1}{j}, \tag{6.15}$$

where we have also taken into account the relationship $V_{n_t} = l_{n_t} d_{n_t}^2$ and represented the blood flow rate, i.e. the volume of blood flowing through the unit tissue volume per unit time, in terms of $j = \pi a_{n_t}^2 v_{n_t}/V_{n_t}$.

In a similar way we can analyse influence of the first class countercurrent pairs. In particular, we find that these countercurrent pairs may be treated as walker traps and the life time of walker migration in the cellular tissue is

$$\tau_l = \frac{d_{n_t}^2}{2\pi D} \ln \frac{d_{n_t}}{a_{n_t}} = \frac{1}{j} \sqrt{\ln \frac{l_0}{a_0}} \tag{6.16}$$

where we have taken into account formula (6.1). Depending on the relation between the values of n_t and n_{cc} either expression (6.15) or expression (6.16) describes the total effect of blood flow in these first class vessels on heat transfer.

In conclusion of this Section we point out that according to (6.15),(6.16) during the lifetime τ a walker can pass in the tissue a distance of order $\sqrt{6D\tau} \sim d_{n_t}\sqrt{\ln(d_{n_t}/a_{n_t})}$. Since in the given model $\ln(d_n/a_n)$ is treated as a large parameter this distance is considered to be well about the mean distance between the veins of level n_t which control walker trapping. So, a walker in its motion in the cellular tissue has possibility of crossing not only the first nearest veins but any vein in the tissue domain whose radius is about $(6D\tau)^{1/2}$. Due to $\ln(d_{n_t}/a_{n_t})$ being a large parameter such a domain contains a large number of

veins belonging to level n_t. Thereby, specific details of their spatial arrangement in the given domain are of little consequence and solely the mean properties of their distribution in this domain, in particular, the mean distance between the n_t-th level veins, have the main effect on heat transfer in living tissue. The given characteristics of the walker motion is the ground of the self-averaging property conservation vessels. The effect of the specific details of the vein arrangement on heat transfer can be described in terms of random spatial nonuniformities of the tissue temperature, which is the subject of Chapter 15.

It is also should be noted that according to Chapter 5 all the first class vessels are called heat conservation vessels, although this is rigorously justified in reference, for example, to veins whose level number $n < n_*$. Indeed, for such veins $2D\tau_{bn} \ll a_n^2$ and, thereby, a trapped walker cannot return to the cellular tissue during its motion with blood through these veins. In terms of heat transfer blood flowing through such a vein has no time to attain thermal equilibrium with cellular tissue surrounding it. In this case we may ignore heat exchange between blood and the surrounding cellular tissue when analyzing distribution of heat currents over the vessel system involving such a first class vein. For a vein whose level number $n_* < n < n_t$ the value $2D\tau_{bn} \gg a_n^2$ and blood flowing through it has enough time to attain thermal equilibrium with the cellular tissue in a small neighborhood of this vein. Nevertheless, along the vein transport of walkers located in this neighborhood is mainly caused by blood flow in the given vein rather than by random motion of walkers in the tissue. Thus, for such veins the total current of the walkers along a given vein, i.e. the total heat current associated with this vein, can be estimated as $\pi a_n^2 v_n C_n$ (or $\pi a_n^2 v_n \rho_t c_t (T_n^* - T_a)$), where $C_n(T_n^*)$ is the mean walker concentration (the mean blood temperature) in the given vein. Therefore, distribution of heat flow over such veins is also controlled by blood flow in the vessels. The latter allows us to refer to these veins as heat conservation vessels too.

These comments with respect to the heat conservation countercurrent pair also hold true.

It should be pointed out that from the standpoint of heat transport with blood through vessels the division of vessels into the countercurrent pairs and unit arteries and veins is justified solely by vessels whose level number $n \sim n_t$. Indeed, when $\zeta_n > \ln(l_0/a_0)$ and, thus, $a_n^2 v_n/(2D) > l_n$ a walker inside this vessel has no time to reach the vessel boundary during its motion with blood through this vessel. In other words, blood flow through this vessel practically does not lose its energy due to heat exchange with the surrounding cellular tissue. Solving the equation $\zeta_n \mid_{n^*} = 1$ we find that $n_t - n_* \sim 1$ (see 6.10).

Therefore, the countercurrent pairs whose level number $n < n_*$ practically consist of arteries and veins for which heat exchange is not essential.

Figure 6.3: Geometry of a possible walker path (directed line) in the system of the first class arteries.

6.3   The effect of heat conservation arteries on the walker motion

The next group which we shall consider is the arteries of Class 1. In the given model due to both the arterial and venous beds of the same geometry, this group involves all the arteries, whose level number $n < n_t$. As in the case analyzed in Section 6.2, if a walker crosses a boundary of one of these arteries, for example, an artery of level n, it will be transported by blood flow to an artery of the next level within the time $\tau_{bn} \ll d_n^2/(2D)$. However, because of the opposite direction of blood flow in the arterial system in comparison with the venous one, the walker will be transported to arteries whose level numbers are $(n+1), (n+2), (n+3), \ldots$ until it reaches an artery of level n_t.

After reaching such an artery the walker leaves the first class arteries and begins to migrate randomly in the tissue again because arteries whose level number $n > n_t$ cannot substantially affect heat transfer.

Therefore, if the walker crosses a boundary of an n-th level artery, then, for a time of order $\tau_{bn} \ll \tau$ it will be transported by blood flow over a distance being approximately equal to l_n. Indeed, as it can be seen from Fig. 6.3 travelling along a possible path in blood stream (the directed line) from the given artery to arteries of level n_t the walker can merely arrive at points which are inside the fundamental domain Q_n of volume $(2l_n/\sqrt{3})^3$ that contains the given n-th level artery. In addition, due to the geometric structure of the given vascular network, walkers initially crossing this artery will be uniformly distributed over the domain Q_n in a time of order τ_{bn}.

When the capillary system has no substantial effect on heat transfer, we may assume that after reaching the n_t -th level arteries the walker randomly

goes in the cellular tissue until it crosses a boundary of an artery or a vein whose level number $n \sim n_t$. In this case the walker meets an artery of level n_t as well as a vein of the same level with the probability about $1/2$. The latter follows from the fact that, on one hand, the probability for a walker to meet larger arteries or veins is small enough because the mean distances between the arteries whose level number $n \ll n_t$ are well above d_{n_t} and, on the other hand, the influence of the second class vessels on the random walker is not significant. A possible effect of the capillary system on the random walker can solely decrease the probability of meeting arteries (see Section 6.5). So, after reaching an artery of level $n < n_t$ for the first time and before being trapped by one of the n_t -th level veins and then,being carried away by blood flow from the microcirculatory bed domain, the walker has the possibility of meeting a few arteries whose level number is about n_t. Each meeting with such an artery gives rise to walker displacement with blood flow over the distance of order l_{n_t}. Thus, after meeting a vein of level $n < n_t$ and before being trapped in a time of order τ the walker can pass in the tissue a distance of order $(l_n^2 + \tilde{g}l_{n_t}^2 + 6D\tau)^{1/2}$, where the constant $\tilde{g} \sim 1$. Therefore, the first class arteries merely cause fast migration of walkers, and their influence on the walker motion can be described in terms of an effective diffusion coefficient D_{eff}. Indeed, on the average, the probability for a walker to meet an artery of level $n < n_t$ before being trapped by the first class veins is small enough because for such arteries $d_n \gg d_{n_t}$. So, when describing the effect of the first class arteries on the walker motion solely arteries whose level number $n \sim n_t$ should be taken into account within the framework of the countercurrent model. In this case the effective diffusion coefficient can be estimated as $D_{\text{eff}} \sim (\tilde{g}l_{n_t}^2 + 6D\tau)/6\tau \sim D[1 + \tilde{g}/\ln(d_{n_t}/a_{n_t})]$, where the constant $\tilde{g}$ is also about one and expressions (6.15), (6.16) have been taken into account. The renormalization coefficient $(1 + \tilde{g}/\ln(d_{n_t}/a_{n_t}))$ is of order unity, therefore, on the average, the first class arteries have no substantial direct effect on heat transfer. However, on scales smaller than l_{n_t} these arteries can give rise to appearance of marked variations in the temperature field.

Effect of blood flow in large vessels on bioheat transfer requires an individual investigation and cannot be rigorously described within the framework of the continuum model. Large vessels should be taken into account separately as much as possible [20, 22, 75].

6.4 Influence of the heat dissipation vessels on the walker motion

The following group, which we shall consider, is the vessels of Class 2. By virtue of (6.3) and (6.5) this group involves all vessels whose level number $n > n_t$. To investigate the influence of this vessel group on heat transfer we analyse random walks in the vicinity of these vessels, for example, in the vicinity of a vessel belonging to level n.

If a walker is near this vessel at initial time, it will be inside its neighborhood

of radius d_n within the time $d_n^2/(2D)$. During this time (as it has been discussed in Section 6.3) the walker can be transported by blood flow over the distance $l_{\parallel n}$ (see formula (5.77)) which is substantially smaller than the vessel length $l_n : l_{\parallel n} \ll l_n$. The latter allows us to ignore the influence of such a vessel on the random walks in its neighborhood because the distance $l_{\parallel n}$ which the walker passes inside the vessel is small in comparison with the distance that it passes in the tissue for the time $d_n^2/(2D)$.

In a time of order $d_n^2/(2D)$ the walker reaches points being at a distance of order l_n from the vessel and practically never comes back to this vessel. Therefore, the main amount of the second class vessels has no significant effect on heat transfer.

The exception is the arteries, veins, and may be the countercurrent pairs whose level number $n \approx n_t$ for which $l_{\parallel n} \leqslant l_{n_t}$. Such vessels may have the cooperative effect on heat transfer only, which may be described in terms of a continuum medium with the effective diffusion coefficient D_{eff}. Due to vessels being oriented randomly in space on scale of order l_{n_t} the mean blood velocity $\langle \mathbf{v}(\mathbf{r}, t) \rangle$ is equal to zero: $\langle \mathbf{v}(\mathbf{r}, t) \rangle = 0$.

In order to estimate the value of D_{eff} we can make use of the results obtained in Sections 5.2 and 5.3, because $l_{\parallel n} \leqslant l_n$ and the mean distance between vessels of one level is about their length. Expressing $a_n^2 v_n/(2D)$ as a function of ζ_n from (5.131) and (5.133) substituting into (5.124), and summing up influence of all the vessels whose level number $n \geq n_t$, we get

$$D_{\text{eff}} = D \left\{ 1 + \frac{\pi 3\sqrt{3}}{4} \frac{1}{\ln(l_0/a_0)} \sum_{n \geq n_t}^{N} \zeta_n^2 \right\}. \qquad (6.17)$$

where expression (4.13) has been also taken into account. Assuming that $(N - n_t \gg 1)$ and accounting for number (6.1) we obtain

$$D_{\text{eff}} = D \left\{ 1 + \pi\sqrt{3} \frac{1}{\ln(l_0/a_0)} \right\} \qquad (6.18)$$

It should be pointed out that this value of D_{eff} is independent of the total blood current through the vascular network which is actually determined by its architectonics only due to the self - similarity of the vascular network at various levels. However, there is an exception to the latter conclusion when the dimensionless total blood current G belongs to the interval $[G_{cc}^*, G_{cc}]$ where $G_{cc}^* = 2^{2n_{cc}}$ and $G_{cc} = 2^{2n_{cc}}(\ln l_0/a_0)^{1/2}$ (see Fig. 6.1). For these values of G Class 2 contains heat - conservation veins and arteries whose level number n meets the condition $n_{cc} \leqslant n \leqslant n_t^*$ where n_t^* is the second root of equation (6.4). These vessels are separated from the tree stem by heat dissipation countercurrent pairs, so, their influence on heat transfer is reduced to renormalization of the diffusion coefficient only. Then, replicating practically one-to-one the latter calculations we obtain

$$D_{\text{eff}} = D \left\{ 1 + \pi\sqrt{3} \frac{1}{\ln(l_0/a_0)} \left(\frac{G}{G_{cc}^*} \right)^2 \right\} \tag{6.19}$$

for $G_{cc}^* \leqslant G \leqslant G_{cc} = G_{cc}^* [\ln(l_0/a_0)]^{1/2}$.

6.5 Influence of the capillary on the walker motion

Finally, let us analyse the effect of the capillary system on heat transfer. By virtue of (4.9), (5.131), and (5.134), the classification parameters ζ_N and ζ_c for the last level vessels and capillaries are related as

$$\zeta_c = \frac{l_N}{ml_c} \frac{\ln(d_c/a_c)}{\ln(d_N/a_N)} \zeta_N. \tag{6.20}$$

In the adopted model for the vascular network $l_N < l_c$ and $m \gg 1$, thus, according to the latter expression we may assume that $\zeta_c < \zeta_N$. So, if capillaries belonged to Class 1, i.e. $\zeta_c > 1$, then,all the vessels would be heat-impermeable, because in this case the inequalities $\{\zeta_n > 1\}$ would be true for all the levels. In other words, in this case blood flowing through the given microcirculatory bed could not attain thermal equilibrium with the cellular tissue and from the standpoint of thermoregulation such a high blood flow rate would not be justified. For this reason we shall only examine the case $\zeta_c \ll 1$, i.e. due to (4.9) and (5.134)

$$\zeta_c = \frac{J_0}{2\pi m M D l_c} \ln \left(\frac{d_c}{a_c} \right) \ll 1. \tag{6.21}$$

Thereby, the capillaries are assumed to belong to Class 2. However, their effect on heat transfer can be significantly in contrast to the arteries and veins of Class 2. Indeed, the mean distance d_c between the capillaries is well below their length l_c. Therefore, the characteristic distance $l_{\|n}$, over which a walker is transported along a capillary by blood flow before going out of its neighborhood of radius d_c, can be substantially larger than $d_c (l_{\|c} \gg d_c)$ although $l_{\|c} \ll l_c$.

First, we shall estimate $l_{\|c}$. Taking into account expressions (4.9), (5.120), (5.131) and setting $t \sim d_c^2/(2D)$ we get the desired value

$$l_{\|c} \sim \frac{a_c^2 v_c}{2D} \ln \left(\frac{d_c}{a_c} \right) = l_N \frac{\zeta_N}{m} \frac{\ln(d_c/a_c)}{\ln(d_N/a_N)}. \tag{6.22}$$

Now let us consider a certain vessel of level N, for example, a venule i and its neighborhood $Q_i(d_N)$ whose diameter is about d_N. The system of capillaries,

or more correctly, of their portions being in this neighborhood can be divided into two subgroups.

The first subgroup consists of all capillary portions connected directly with the given venule, the second subgroup involves the rest. Blood currents in the first subgroup capillaries is believed to be directed along the radius $\mathbf{r}$ to the center of the neighborhood, i.e. to the venule. Blood currents in the second subgroup capillaries as well as the orientations of these capillaries in space are assumed to be random. Therefore, the effects of the two subgroups on heat transfer are different and we shall analyse them individually. In particular the influence of the second subgroup capillaries can be described in terms of the effective diffusion coefficient D_{eff}.

Since each capillary keeps its spatial direction within the scale $\lambda > l_N$ (see Chapter 3) the first subgroup comprises m rectilinear capillary portions of the length d_N and is of the CB structure form (Fig. 4.4).

The quantity to be used in the following analysis is the mean distance $d_I(r)$ between the first subgroup capillaries at distance r from the venule i. The value $d_I(r)$ is defined as follows. Let us consider a cylindrical neighborhood $Q_i(r)$ of the given venule whose radius is $r < d_N$. The first subgroup capillaries must intersect its boundary at m points. By definition, $d_I^2(r)$ is the mean area of the neighborhood boundary that falls on one intersection point. Therefore, the mean distance $d_I(r)$ satisfies the relation $2\pi r l_N \sim m[d_I(r)]^2$, where $2\pi r l_N$ is the boundary area of the given venule neighborhood. Whence, we find

$$d_I(r) \sim \left(\frac{2\pi r l_N}{m} \right)^{1/2} . \tag{6.23}$$

The first subgroup of capillaries and the system of corresponding pipes with equally directed blood currents (considered in Chapter 5) have approximately the same effect on heat transfer. Therefore, the effect of the first capillary subgroup on the random walks in the neighborhood $Q_i(d_N)$ of the venule i can be described in terms of walker motion in an effective convective stream whose velocity field, by virtue of (5.125), is specified by the expression

$$\mathbf{v}_{\text{eff}}^{\vee}(\mathbf{r}) \sim \frac{\pi a_c^2}{d_I^2(r)} \mathbf{v}_c \tag{6.24}$$

and is directed to the neighborhood center, i.e. to the venule. Substituting (6.23) into (6.24) we get

$$\mathbf{v}_{\text{eff}}^{\vee}(\mathbf{r}) \sim -\frac{1}{2\pi} \frac{\pi a_c^2 v_c m}{l_N} \frac{\mathbf{r}}{r^2} . \tag{6.25}$$

In addition, taking into account (4.9) and the definition of the blood flow rate, according to which we may set $j = \pi a_N^2 v_N / (l_N d_N^2)$, the (6.25) can be rewritten as

$$\mathbf{v}_{\text{eff}}^{\vee}(\mathbf{r}) \sim -\frac{1}{2\pi} j \frac{d_N^2}{r} \frac{\mathbf{r}}{r}. \tag{6.26}$$

Expressions (6.25) and (6.26) hold true until the radius r becomes less than the distance $l_{\parallel c}$ over which a walker is transported by the blood flow in a capillary during its location in the vicinity of this capillary: $r > l_{\parallel c}$. Otherwise ($r < l_{\parallel c}$), the walker will go into the venule actually with blood flow in a single capillary and the representation of the walker motion in terms of random walks in a homogeneous medium does not hold.

Description of the first subgroup effect on random walks in the neighborhood $Q_i(d_N)$ containing an arteriole in its center is the same but the direction of velocity field (6.26) must be changed to the opposite one, i.e.

$$\mathbf{v}_{\text{eff}}^{a}(\mathbf{r}) \sim \frac{1}{2\pi} j \frac{d_N^2}{r} \frac{\mathbf{r}}{r}. \tag{6.27}$$

In particular, expression (6.26) allows us to find the time τ_v required for a walker to reach a venule, provided at initial time it was at a distance r of order d_N from the venule and its motion towards the venule is mainly caused by blood flow in capillaries of the first subgroup. In this case the characteristic time required for the walker to go from one of the nearest arterioles to the given venule is also about τ_v. Solving the equation

$$\frac{d\mathbf{r}}{dt} = \mathbf{v}_{\text{eff}}^{\vee}(\mathbf{r}) \tag{6.28}$$

under the initial condition $r|_{t=0} = r_N = d_N/\sqrt{\pi}$ we get $r(t) = d_N/[\sqrt{\pi}(1 - jt)]$ and, therefore, the desired time is

$$\tau_v \sim \frac{1}{j}, \tag{6.29}$$

We point out that the given initial condition corresponds to the estimate of the volume of the venule neighborhood, $Q_i(d_N)$ as the mean tissue volume per one venule, i.e. $\pi r_N^2 l_N = d_N^2 l_N$.

Resulting walker motion in the domain $Q_i(r_N)$ is affected not only by the blood flow in the capillaries of the first subgroup but also by the blood flow in the second subgroup capillaries as well as walker motion in the cellular tissue itself. Thus, in addition, we shall obtain the condition when the influence of the first subgroup capillaries on walker motion in the neighborhood $Q_i(r_N)$ should be taken into account. In the general case stationary distribution $C_{\text{st}}(r)$ of the walkers in $Q_i(r_N)$ obeys the equation.

$$D_{\text{eff}} \boldsymbol{\nabla} C_{\text{st}} - \mathbf{v}_{\text{eff}}^{\vee} C_{\text{st}} = 0 \tag{6.30}$$

Whence, taking into account that expression (6.26) can be rewritten in the form

$$\mathbf{v}_{\text{eff}}^{\vee} = -\boldsymbol{\nabla}\left[\frac{1}{2\pi}jd_N^2 l_n r\right],\tag{6.31}$$

we find

$$C_{\text{st}}(r_N) \approx C_{\text{st}}(a_N)\exp\left\{-\frac{d_N^2 j}{2\pi D_{\text{eff}}}\ln\left(\frac{r_N}{a_N}\right)\right\},\tag{6.32}$$

where $C_{\text{st}}(a_N)$ and $C_{\text{st}}(r_N)$ are the walker concentrations near the venule i and at the boundary of $Q_i(r_N)$.

The capillaries of the first subgroup have a significant effect on the walker motion when $C_{\text{st}}(r_N) \gg C_{\text{st}}(a_N)$. Then, representing the blood flow rate as $j = \pi a_N^2 v_N/(l_N d_N^2)$ from (5.131) and (6.32), we obtain the desired condition

$$\frac{d_N^2 j}{2\pi D_{\text{eff}}}\ln\left(\frac{d_N}{a_N}\right) \equiv \frac{D}{D_{\text{eff}}}\zeta_N \gg 1,\tag{6.33}$$

where we have ignored $\ln\sqrt{\pi}$ in comparison with $\ln(d_N/a_N)$ which plays an important role in heat transfer.

The second subgroup of capillaries plays an important role in heat transfer in the case $l_c \gg l_N$ only, when the number of the capillary portions which belong to this subgroup is substantially larger than that of the first subgroup. Due to both spatial orientation of the capillary portions and the direction of the blood currents in them being random, the second group affects the random walks in a similar way as does the system of the corresponding pipes considered in Section 5.2 for which $\zeta = 0$. Therefore, according to (5.124), on scales well above $l_{\parallel c}$ we can describe the effect of blood flow in the second subgroup capillaries on heat transfer in terms of an effective isotropic medium with the diffusion coefficient

$$D_{\text{eff}} \sim D\left[1 + \frac{\pi}{2}\left(\frac{a_c^2 v_c}{Dd_c}\right)^2\ln\left(\frac{d_c}{a_c}\right)\right].\tag{6.34}$$

Taking into account (4.9), (4.14), (5.131) we rewrite (6.34) in the form

$$D_{\text{eff}} \sim D\left[1 + \frac{3\sqrt{3}\pi}{4}\frac{\ln(d_c/a_c)}{[\ln(d_N/a_N)]^2}\frac{l_c}{l_N m}\zeta_N^2\right].\tag{6.35}$$

On scales smaller than $l_{\parallel c}$ the motion of a walker in capillaries with blood flow and its migration in the cellular tissue should be considered individually.

As it follows from expression (6.35) it is convenient to characterize the renormalization of the diffusion coefficient due to blood flow in the capillaries by the parameter

$$\gamma = \frac{3\sqrt{3}\pi}{4} \frac{\ln(d_c/a_c)}{[\ln(d_N/a_N)]^2} \frac{l_c}{ml_N} \qquad (6.36)$$

If $\gamma \gg 1$, i.e. the capillary length l_c is large enough, the influence of the capillary system can become essential at not-too-high blood flow rates when $n_t < N$. When $\gamma \ll 1$ the blood flow rate must attain large values for the capillary system to be able to change the diffusion coefficient. Therefore, capillaries forming the network with $\gamma \ll 1$ will be called short, and other wise, $\gamma \gg 1$ will be referred to as long.

Concluding Chapter 6 we would like to outline which vessels contribute to what kind of heat transport. The countercurrent pairs of Class 1 and the first class veins whose level number $n \leqslant n_t$ form the walker traps with the smallest vessels of this class playing a dominant role in walker trapping. With blood flow through the large first class veins walkers go out of the tissue domain without returning into the cellular tissue.

The arteries of Class 1 also form paths of the fast walker migration in tissue, however, due to the opposite direction of blood flow in them in comparison with that of veins the role of the first class arteries in the walker propagation is not significant. From the heat transfer standpoint the large first class veins and arteries form the vessel system through which blood goes into and out of the tissue practically without heat exchange with the cellular tissue. Large vessels, however, are responsible for spatial nonuniformities in the tissue temperature and should be analyzed individually.

The effect of the arteries, veins, and countercurrent pairs of Class 2 is reduced to the renormalization of the diffusion coefficient. Capillaries, which are assumed to belong to Class 2, can affect the walker motion in tissue because of $d_c \ll l_c$. However, their influence causes more fast migration of walkers in tissue rather than gives rise to the walker escape from the tissue domain. The effect of the first subgroup capillaries in the walker motion may be described in terms of the walker motion in an effective convective stream and the effect of the second subgroup capillaries is also reduced to renormalization of the diffusion coefficient.

Chapter 7

Form of the bioheat equation in different limits, depending on the blood flow rate

In the previous Chapter we have described bioheat transfer in terms of random walks in living tissue containing the hierarchical vascular network and analyzed characteristic properties of walker motion. In the present Chapter based on the obtained results we develop a continuum description of heat transfer in such living tissue.

7.1   Continuum model for walker trapping

When a walker during its motion reaches one of the countercurrent pairs of Class 1 or a first class vein it will be transported with blood flow to large veins for a short time. Whereupon it never returns to the cellular tissue and leaves the microcirculatory bed domain Q_0 with blood through the host vein. From the standpoint of the cellular tissue this event can be treated as walker disappearance and such a vessel plays the role of a region where walkers die at a certain rate. In this way the total rate $\Gamma_i\{C\}$ at which walkers are destroyed in the region of first class vessels, for example, the vessel of level n may be written as

$$\Gamma_i\{C\} = \Gamma_n \int\limits_{Q_n} d\mathbf{r} \int\limits_0^{l_n} ds\, \delta[\mathbf{r} - \boldsymbol{\xi}_i(s)] C(\mathbf{r}) \qquad (7.1)$$

where Q_n is the fundamental domain containing this vessel, $\boldsymbol{\xi}_i(s)$ specifies the position of vein or countercurrent pair treated as a line, s is its natural parameter and Γ_n is a certain constant. At the same time the total walker dissipation rate in the domain Q_n, according to Chapter 6 must be equal to

$$\Gamma_n\{C\} = \int\limits_{Q_n} d\mathbf{r}\, C(\mathbf{r})\frac{1}{\tau_l}. \tag{7.2}$$

For vessels of level n_t, which are the smallest vessels capable of trapping walkers, $l_{\|n} \sim l_{n_t}$, so the walker concentration is approximately uniform on scales of order l_{n_t}. The latter allows us to regard the concentration C in expressions (7.1) and (7.2) as a constant. The equating the two expressions we find

$$\Gamma_{n_t} = d_{n_t}^2 \frac{1}{\tau_l}. \tag{7.3}$$

Taking into account (6.15), (6.16) from (7.3) we obtain

$$\Gamma_{n_t} = j \left(\ln \frac{l_0}{a_0} \right)^{(\beta(n_t)-1)/2} d_{n_t}^2. \tag{7.4}$$

The vessels of level n_t practically control the walker trapping because the number of the first class vessels per unit volume is practically determined by vessels of this level. The latter enables us to take into account solely the vessels $\{i_t\}$ of level n_t in description of walker disappearance. In this way the living tissue is represented as a medium with distributed traps where the rate of walker disappearance is given by the expression

$$\Gamma\{C\} = j \left(\ln \frac{l_0}{a_0} \right)^{(\beta(n_t)-1)/2} \int\limits_{Q_0} d\mathbf{r}\, C(\mathbf{r})\chi(\mathbf{r}) \tag{7.5}$$

where

$$\chi(\mathbf{r}) = d_{n_t}^2 \sum_{i_t} \int\limits_0^{l_{n_t}} ds\,\delta[\mathbf{r} - \boldsymbol{\xi}_{i_t}(s)] \tag{7.6}$$

is the dimensionless density of traps and the sum runs over all the vessels of level n_t.

In what follows the trap density $\chi(\mathbf{r})$ will be treated as a field with random nonuniformities. This approach enables us to describe both the mean characteristics of the tissue temperature and nonuniformities in the tissue temperature due to the discreteness of the n_t - th level distribution.

The mean value of $\chi(\mathbf{r})$ is equal to one because every fundamental domain of level n_t contains just one vein or countercurrent pair of the same level. Therefore, bearing in mind values averaged on scales of order l_{n_t}, we may replace quantity (7.65) by a certain nonuniform field characterized by spatial scales larger than l_{n_t} or of the same order, viz

$$d_{n_t}^2 \sum_{i_t} \int_0^{l_{n_t}} ds\delta[\mathbf{r} - \boldsymbol{\xi}_{i_t}(s)] = 1 + \chi_t(\mathbf{r}),\qquad(7.7)$$

where $\chi_t(\mathbf{r})$ is a nonuniform field whose mean value is equal to zero.

The field $\chi_t(\mathbf{r})$ is specified by particular details of the vessel arrangement in space on the scale l_{n_t}. However, when we consider solely characteristic features of the walker concentration $C(\mathbf{r}, t)$ on these scales, the particular details of the vessel arrangement is of little consequence. Thereby, to analyse the characteristic properties of spatial nonuniformities in the temperature distribution, i.e. in the walker concentration, the vessel arrangement may be described as a system of n_t-th level vessels randomly distributed in the cellular tissue. For real microcirculatory beds small arteries and veins must be uniformly distributed in the tissue because, other wise, for example, lack of the tissue oxygen supply can occur. So, in the given analysis we assume that the arrangement of the n_t-th level veins is random on the scale l_{n_t} only and does not exhibit spatial random nonuniformities of scales larger than l_{n_t}. Under such conditions the field $\chi_t(\mathbf{r})$ can be considered to be random one obeying the conditions

$$\langle \chi_t(\mathbf{r}) \rangle = 0 \qquad(7.8)$$

and

$$\langle \chi_t(\mathbf{r})\chi_t(\mathbf{r}') \rangle = g\left(\frac{|\mathbf{r} - \mathbf{r}'|}{l_{n_t}}\right) \qquad(7.9)$$

where

$$g(x) = \frac{1}{2^{3/2}} \exp\left[-\frac{3\pi}{8}x^2\right] - \frac{1}{2^{3/2}} \exp\left[-\frac{\pi}{4}x^2\right]. \qquad(7.10)$$

In order to derive the form (7.10) of the correlation function (7.9) let us consider properties of spatial nonuniformities in the vessel distribution. For this purpose we transform the quantity

$$d_n^2 \sum_i \int_0^{l_n} ds\delta[\mathbf{r} - \boldsymbol{\xi}_i(s)]. \qquad(7.11)$$

Let $\mathbf{r}_i$ be the middle point of the curve $\boldsymbol{\xi}_i(s)$. Then at a fixed value of s we define the smoothing ($\langle ... \rangle_{d_n}$) of the function $\delta[\mathbf{r} - \boldsymbol{\xi}_i(s)]$ on the scale d_n as follows,

$$\langle \delta[\mathbf{r} - \boldsymbol{\xi}_i(s)] \rangle_{d_n} = \int d\boldsymbol{\xi}\, \delta[\mathbf{r} - \boldsymbol{\xi}] \mathcal{P}_i(\boldsymbol{\xi}) \tag{7.12}$$

where the function

$$\mathcal{P}_i(\boldsymbol{\xi}) = \frac{1}{V_n} \exp\left\{ -\frac{(\boldsymbol{\xi} - \mathbf{r}_i)^2}{2\tilde{l}^2} \right\} \tag{7.13}$$

where $V_n = d_n^2 l_n$ is the volume of a domain Q_n and the length $\tilde{l}$ is determined by the relation $(2\pi\tilde{l}^2)^{3/2} = V_n$, i.e. $\tilde{l} = V_n^{1/3}(2\pi)^{-1/2}$, characterizes the disposition of the given vessel treated as a random curve. Whence, it follows that

$$\langle \delta[\mathbf{r} - \boldsymbol{\xi}_i(s)] \rangle_{d_n} =$$

$$= \frac{1}{V_n} \int\limits_{Q_0} d\boldsymbol{\xi}\, \delta[\mathbf{r} - \boldsymbol{\xi}] \exp\left[-\frac{(\boldsymbol{\xi} - \mathbf{r}_i)^2}{2\tilde{l}^2} \right] = \frac{1}{V_n} \exp\left[-\frac{(\mathbf{r} - \mathbf{r}_i)^2}{2\tilde{l}^2} \right]. \tag{7.14}$$

Following (7.7) for level n we represent quantity (7.11) as then smoothing quantity (7.14) we get

$$d_n^2 \sum_i \int\limits_0^{l_n} ds\, \langle \delta[\mathbf{r} - \boldsymbol{\xi}_i(s)] \rangle_{d_n} = 1 + \chi_n(\mathbf{r}), \tag{7.15}$$

where the random field $\chi_n(\mathbf{r})$ is specified by the expression

$$\chi_n(\mathbf{r}) = \sum_i \exp\left[-\frac{(\mathbf{r} - \mathbf{r}_i)^2}{2\tilde{l}^2} \right] - 1. \tag{7.16}$$

Distribution of the points $\{\mathbf{r}_i\}$ is assumed to be random on scales of order l_n only. In other words we shall suppose that each vessel of level n is randomly and practically uniformly distributed in a domain whose volume is about V_n and intersection of such domains containing different vessels of level n is not considerable. These conditions can be described in terms of the following one- and two-point distribution functions. The one-point distribution function $g_1(r)$, i.e. the probability density of finding a given point i at the point $\mathbf{r}$ averaged over all possible realizations of the other point arrangement, is supposed to be equal to $1/V_0$:

$$\langle \delta[\mathbf{r} - \mathbf{r}_i] \rangle = g_1(\mathbf{r}) = \frac{1}{V_0}, \qquad (7.17)$$

where $\delta(\mathbf{r})$ is the spatial δ-function, the symbol $\langle ... \rangle$ means averaging over arrangement of all the points $\{r_i\}$ and V_0 is the volume of the domain Q_0. The two-point distribution function $g(\mathbf{r}, \mathbf{r}')$, i.e. the probability density of finding a given pair of the points i, i' at $\mathbf{r}$ and $\mathbf{r}'$, respectively, averaged over all possible realizations of the other point arrangement, is specified, for simplicity, in the form

$$\langle \delta[\mathbf{r} - \mathbf{r}_i] \delta[\mathbf{r}' - \mathbf{r}_{i'}] \rangle = g_2(\mathbf{r}, \mathbf{r}') = \frac{1}{V_0^2} \left\{ 1 - \exp\left[-\frac{(\mathbf{r} - \mathbf{r}')^2}{2\tilde{l}^2} \right] \right\}. \qquad (7.18)$$

Formula (7.18) means that, on one hand, two points i and i' are practically independent of each other when the distance $|\mathbf{r} - \mathbf{r}'|$ between them substantial large than $\tilde{l}$. On the other hand, point pairs characterized by small distance $|\mathbf{r} - \mathbf{r}'| \ll \tilde{l}$ are absent. We note that function $g_2(\mathbf{r}, \mathbf{r}')$ satisfies the condition $\langle \tilde{N}^2 \rangle = \langle \tilde{N} \rangle^2$, where $\tilde{N}$ is the total number of points $\{\mathbf{r}_i\}$ contained in arbitrary domain Q whose volume V_Q is well above $V_n = l_n d_n^2$. This condition implies that on scales larger than l_n the arrangement of the points $\{\mathbf{r}_i\}$ exhibits no spatial random nonuniformities. Indeed

$$\tilde{N} = \sum_i \int_Q d\mathbf{r} \delta[\mathbf{r} - \mathbf{r}_i] \qquad (7.19)$$

and taking into account (7.17) and (7.18) we get

$$\langle \tilde{N} \rangle = \sum_i \frac{V_Q}{V_0} = \frac{V_Q}{V_n}, \qquad (7.20)$$

because V_n is equal to the mean volume of the domain Q_0 which falls on one vein or one countercurrent pair of level n, i.e. falls on one point of the collection $\{\mathbf{r}_i\}$. Then

$$\langle \tilde{N}^2 \rangle = \sum_i \frac{V_Q}{V_0} \cdot$$
$$\left\{ 1 + \sideset{}{'}\sum_{i'} \frac{1}{V_0} \left[V_Q - \iint_Q d\mathbf{r} d\mathbf{r}' \exp\left(-\frac{(\mathbf{r} - \mathbf{r}')^2}{2\tilde{l}^2} \right) \right] \right\}, \qquad (7.21)$$

where the prime on the sum over i' indicates that summation is carried out over all $i' \neq i$ and we also have used the relation

$$\langle \delta[\mathbf{r} - \mathbf{r}_i]\delta[\mathbf{r}' - \mathbf{r}_i]\rangle = \int\limits_{Q_0} d\mathbf{r}' g_1(\mathbf{r}'')\delta[\mathbf{r} - \mathbf{r}'']\delta[\mathbf{r}' - \mathbf{r}''] = \frac{1}{V_0}\delta[\mathbf{r} - \mathbf{r}']. \quad (7.22)$$

For $V_Q \gg V_n$ in the limit $V_0 \to \infty$ from (7.20) and (7.21) we obtain

$$\left\langle \tilde{N}^2 \right\rangle \simeq \left\langle \tilde{N} \right\rangle^2 + \frac{V_Q}{V_n}\left[1 - \frac{(2\pi\tilde{l}^2)^{3/2}}{V_n}\right] = \left\langle \tilde{N} \right\rangle^2 \qquad (7.23)$$

due to, by definition, $(2\pi\tilde{l}^2)^{3/2} = V_n$.

Within the framework of the adopted assumptions from (7.16) we get

$$\langle \chi_n(\mathbf{r})\rangle = \sum_i \int\limits_{Q_0} d\mathbf{r}_i g_1(\mathbf{r}_i) \exp\left[-\frac{(\mathbf{r} - \mathbf{r}_i)^2}{2\tilde{l}^2}\right] - 1 \qquad (7.24)$$

and due to (7.17)

$$\langle \chi_n(\mathbf{r})\rangle = \sum_i \frac{1}{V_0}(2\pi\tilde{l}^2)^{3/2} - 1 = \frac{(2\pi\tilde{l}^2)^{3/2}}{V_n} - 1 = 0. \qquad (7.25)$$

Then taken into account (7.18), we find, by definition

$$g\left(\frac{|\mathbf{r} - \mathbf{r}'|}{l_n}\right) = <\chi_n(\mathbf{r})\chi_n(\mathbf{r}')>=$$

$$= \sideset{}{'}\sum_{i,i'} \int\limits_{Q_0}\int\limits_{Q_0} d\mathbf{r}_i d\mathbf{r}_{i'} g_2(\mathbf{r}_i, \mathbf{r}_{i'}) \exp\left[-\frac{(\mathbf{r} - \mathbf{r}_i)^2}{2\tilde{l}^2}\right] \cdot$$

$$\cdot \exp\left[-\frac{(\mathbf{r} - \mathbf{r}_{i'})^2}{2\tilde{l}^2}\right] + \sum_i \int\limits_{Q_0} d\mathbf{r}_i g_1(\mathbf{r}_i) \exp\left[-\frac{(\mathbf{r} - \mathbf{r}_i)^2}{2\tilde{l}^2}\right] \cdot$$

$$\cdot \exp\left[-\frac{(\mathbf{r}' - \mathbf{r}_i)^2}{2\tilde{l}^2}\right] - 2\sum_i \int\limits_{Q_0} d\mathbf{r}_i g_1(\mathbf{r}_i) \exp\left[-\frac{(\mathbf{r} - \mathbf{r}_i)^2}{2\tilde{l}^2}\right] + 1. \qquad (7.26)$$

Then substituting (7.17), (7.18) into (7.26) and passing to the limit $V_0 \to \infty$, we can rewrite the latter expression in the form

$$g\left(\frac{|\,\mathbf{r} - \mathbf{r}'\,|}{l_n}\right) = \frac{1}{V_N} \int\limits_{\mathcal{R}^3} d\mathbf{r}\,'' \exp\left[-\frac{(\mathbf{r} - \mathbf{r}\,'')^2}{2\tilde{l}^2} - \frac{(\mathbf{r}' - \mathbf{r}\,'')^2}{2\tilde{l}^2}\right] -$$

$$-\frac{1}{V_N^2} \int\limits_{\mathcal{R}^3}\int d\mathbf{r}\,''d\mathbf{r}\,''' \exp\left[-\frac{(\mathbf{r} - \mathbf{r}\,'')^2}{2\tilde{l}^2} - \frac{(\mathbf{r}\,'' - \mathbf{r}\,''')^2}{2\tilde{l}^2} - \frac{(\mathbf{r}\,''' - \mathbf{r}')^2}{2\tilde{l}^2}\right]. \quad (7.27)$$

Here, in addition, we have taken into account that the last integral term in expression (7.26) is equal to two, i is a dummy index, and

$$\frac{1}{V_0}\sum_i = \frac{\mathcal{N}}{V_0} = \frac{1}{V_n}$$

$$\frac{1}{V_0^2}{\sum_{i,i'}}' = \frac{\mathcal{N}(\mathcal{N} - 1)}{V_0^2} \to \frac{1}{V_n^2}$$

where $\mathcal{N}$ is the total number of the points in the collection $\{\mathbf{r}_i\}$. Using the transformation rules shown in Fig. 5.4b from (7.27) we obtain

$$g\left(\frac{|\,\mathbf{r} - \mathbf{r}'\,|}{l_n}\right) = \frac{1}{2^{3/2}}\exp\left[-\frac{(\mathbf{r} - \mathbf{r}')^2}{4\tilde{l}^2}\right] -$$

$$-\frac{1}{3^{3/2}}\exp\left[-\frac{(\mathbf{r} - \mathbf{r}')^2}{8\tilde{l}^2}\right].$$

Whence it immediately follows expression (7.10) where $n = n_t$.

7.2　Parameters determining the form of bioheat transfer equation. The case of no influence of capillary system

The specific form of bioheat equation depends on the characteristic parameters of the vascular network architectonics and the total blood current flowing through the microcirculatory bed. In order to classify the form of bioheat equation it is convenient to specify different possible limits by the parameters γ (see (6.36)) and G. The former characterizes the way in which the capillary system can affect heat transfer and the latter determines the level number n_t of the vessels directly controlling heat exchange between blood and the cellular tissue.

The final result of the present Chapter is illustrated in Fig. 7.1 which shows how the form of bioheat equation changes as the dimensionless total blood

current G increases for vascular network with short ($\gamma \ll 1$) and long ($\gamma \gg 1$) capillaries. Below in this Section we shall consider heat transfer in living tissue with short capillaries when $n_t < N$ e.i. there are both heat - conservation and heat - dissipation vessels viz:

$$\gamma \ll 1; \quad G_0 \ll G \ll M^{2/3}, \qquad (7.28)$$

where $G_0 = \left(\ln \frac{l_0}{a_0}\right)^{1/2}$ and $M = 2^{3N}$ is the total number of the venules or arterioles (see Chapter 4). It should be noted that the first inequality is the condition on geometry of the vascular network whereas the last two are actually the condition on the value of the total blood current J_0, with the former ($G \gg G_0$) being the overall restriction assumed in the present work (see (6.6)) and the latter, according to (6.1),(6.3), implying that $\zeta_N \ll 1$. In this case the capillary system practically has no effect on heat transfer. In fact, the renormalization of the diffusion coefficient caused by the effect of the second subgroup capillaries (see expression (6.35)) is not appreciable. Thus solely the venous and arterial trees should be taken into account.

Such situation has been practically considered in Section 6.2 and Section 6.4 where the effect of blood flow on heat transfer has been treated in terms of walker trapping and renormalization of the diffusion coefficient. Therefore, taking into account continuum description of walker trapping stated in Section 7.1 we can write the following bioheat equation

$$\frac{\partial C}{\partial t} = \boldsymbol{\nabla}(D_{\text{eff}}\boldsymbol{\nabla}C) - j[1 + \chi_t(\mathbf{r})]C \left[\ln\left(\frac{l_0}{a_0}\right)\right]^{(\beta(n_t)-1)/2} + q. \qquad (7.29)$$

Here D_{eff} is given by formula (6.18) or (6.19), $\chi_t(\mathbf{r})$ is the random field obeying conditions (7.8), (7.9) and the value of n_t as function of G is specified by expression (6.5) and shown in Fig. 6.1b.

In particular, if we ignore the spatial nonuniformities in the vessel distribution (the field $\xi_t(\mathbf{r})$) and consider $G > G_{cc}$, then equation (7.29) will become.

$$\frac{\partial C}{\partial t} = \boldsymbol{\nabla}(D_{\text{eff}}\boldsymbol{\nabla}C) - jC + q. \qquad (7.30)$$

The latter equation practically coincides with the conventional bioheat equation with the replacement $C \to (T - T_a)/(T_a V_N)$. For $G > G_{cc}$ in a similar way we get

$$\frac{\partial C}{\partial t} = \boldsymbol{\nabla}(D_{\text{eff}}\boldsymbol{\nabla}C) - j\frac{1}{[\ln(l_0/a_0)]^{1/2}}C + q. \qquad (7.31)$$

Concluding this Section we discuss the properties of heat exchange between blood and the cellular tissue. Let in a fundamental domain Q_n of level $n <$

Figure 7.1: Characteristic types of heat transfer in living tissue depending on the total blood current (in units of G) in the microcirculatory bed. Figures "a" and "b" correspond to the vascular network with short ($\gamma \ll 1$) and long ($\gamma \gg 1$) capillaries, respectively. (M is the total number of the arterioles).

n_t whose size $l_n \gg l_{n_t}$ the tissue temperature T be approximately uniform. Then, when the blood - tissue heat exchange is directly controlled by unit veins of level n_t, i.e. $G > G_{cc}$, the temperature T^* of blood in the large vein i_n of level n drawing this domain must be equal to the tissue temperature T. The latter is the case because blood in veins of level n_t is approximately in thermodynamic equilibrium with the surrounding cellular tissue and arteries of level n_t are, at, on the average, the distance $d_{n_t} \sim l_{n_t}$. This future of bioheat transfer is reflected in the form of the second term (jC) on the right - hand side of equations (7.30), (7.31). If the blood - tissue heat exchange is controlled by the countercurrent pairs of level n_t, i.e. if $G < G_{cc}$, then heat exchange between arterial and venous blood in the countercurrent vessels of this pairs is significant. So, venous blood initially flowing through small vessels where it was in thermodynamic equilibrium with the cellular tissue and until it reaches large veins of level $n < n_*$, where heat conduction does not play a significant role, inevitably loses a certain portion of heat. Therefore, in this case the temperature T^* of blood in the vein i_n is not equal to the tissue temperature. The relationship between T^*, T and T_a, in general, may be written as $T^* = T_a + (T - T_a)\sigma_{av}$ where σ_{av} is a certain coefficient. In the given case the volumetric dissipation rate of heat in living tissue can be represented in terms of $jc_t\rho_t(T^* - T_a) = jc_t\rho_t\sigma_{av}(T - T_a)$. Comparing the latter with the second term of (7.31) we find that $\sigma_{av} = [\ln(l_0/a_0)]^{-1/2}$. Therefore, in the given situation the relationship between the temperatures T^*, T_a and T is of the form

$$T^* = T_a + \frac{1}{[\ln(l_0/a_0)]^{1/2}}(T - T_a). \tag{7.32}$$

Expression (7.32) will be used in the theory of thermoregulation (see Part 4).

$$\frac{\partial C}{\partial t} = D_{\mathrm{eff}}\boldsymbol{\nabla}^2 C - j[1 + \chi_t(\mathbf{r})]C + q.$$

It should be pointed out that (7.16) will practically coincide with bioheat equation (2.1) within the replacement $C \to (T - T_a)/(T_a V_N)$, if we ignore the term $\chi_t(\mathbf{r})$.

7.3   Bioheat equation for living tissue with short capillaries

As the blood flow rate increases, the value of n_t decreases and at certain G it becomes equal to N. For greater values of the blood flow rate the capillary network affect significantly heat transfer. In this case there are two limits differ in properties of heat transfer which will be analyzed individually in the present Section.

7.3.1 Convective type heat transport. The porous medium model

Let us consider the limit

$$\gamma \ll 1; \quad M^{2/3} \ll G \ll \frac{1}{\gamma} M^{2/3}. \tag{7.33}$$

The last two inequalities can be also represented as $1 \ll \zeta_N \ll 1/\gamma$, therefore, in this case there are no arteries and veins of Class 2, and Class 1 involves all the arteries and veins of the vascular network with the vessels of the shortest length belonging to level N but not to level n_t.

According to Section 6.2 we can describe the effect of such a vessel system on heat transfer in terms of the walker motion in a medium containing walker traps in the form of the venules distributed in the tissue at the mean distance d_N from each other. However, in this case the walker motion in the neighborhood $Q_i(d_N)$ of a given venule or arteriole is mainly controlled by blood flow in capillaries of the first subgroup. Indeed, the influence of the second subgroup capillaries on the walker motion gives rise to renormalization of the diffusion coefficient (see (6.35)). Thereby, as it follows from (6.33) and (6.35), the first subgroup capillaries mainly control the walker motion in $Q_i(d_N)$ if

$$\frac{1}{\zeta_N} + \gamma\zeta_N \ll 1. \tag{7.34}$$

The first term is associated with diffusion in the cellular tissue and the second one describes the effect of the second subgroup capillaries. Due to (7.33) both these terms are small. Therefore, we may account for solely convective type transport of the walkers.

Thus, in a cylindrical neighborhood $Q_i(r_N)$ of the radius $r_N = d_N/\sqrt{\pi}$ containing a venule i in its center, the walker distribution is practically of two-dimensional form and can be described by the two-dimensional equation

$$\frac{\partial C}{\partial t} = -\boldsymbol{\nabla}[\mathbf{v}_{\text{eff}}^{\vee}(\mathbf{r})C] - jd_N^2 C\big|_{r=0}\,\delta(\mathbf{r}) + q(\mathbf{r}, t). \tag{7.35}$$

Here following Section 7.1 we have represented the venule as a trap of the two - dimensional δ - function form whose parameters satisfy the condition that the rate of the walker escape from $Q_i(r_N)$ is determined by blood flow through the venule as it must be if the venules belong to Class 1. Indeed, in the given case the total rate of the walker escape with blood flow through the venule is equal to $\pi a_N^2 v_N C|_{r=0}$ where $C|_{r=0}$ is the walker concentration in the venule. According to the definition of the blood flow rate (see Chapter 4) we may set $j = \pi a_N^2 v_N/(l_N d_N^2)$. Thereby, the walker escape rate per unit length of the venule is $jd_N^2 C|_{r=0}$ which is exactly the coefficient of the δ-function in (7.35).

As it follows from (4.13), (6.22), (6.36), and (7.33), in this case the mean distance $l_{\|c}$ which a walker passes with blood in a capillary before going out of its neighborhood of radius $d_N/\sqrt{\pi}$, satisfies the condition $l_{\|c} \ll \frac{\ln(d_N/a_N)}{2\pi}d_N^2/l_c < d_N$ because, at least $l_c > d_N$ according to the adopted model for the capillary system (see Chapter 4). Thus, on one hand, expression (6.26) is true for all values of $r < d_N$ except for a small neighborhood of the point $\mathbf{r} = 0$ whose radius is about $l_{\|c}$. On the other hand, when $q(\mathbf{r}, t)$ is approximately constant on the scale d_N, the formal stationary solution of equation (7.35) with $\mathbf{v}_{\text{eff}}^{\vee}$ specified by expression (6.26) for all $r < d_N$ cannot vary substantially on scales of order $l_{\|c}$. Therefore, we may assume that in the given case expression (6.26) holds true for all $r < d_N$, and , thereby, represent it in the form

$$\mathbf{v}_{\text{eff}}^{\vee}(\mathbf{r}) = \boldsymbol{\nabla}\mathcal{P}^{\vee}(\mathbf{r}), \tag{7.36}$$

where $\mathcal{P}^{\vee}(\mathbf{r})$ is the velocity potential satisfying the equation

$$\boldsymbol{\nabla}^2\mathcal{P}^{\vee}(\mathbf{r}) = -jd_N^2\delta(\mathbf{r}). \tag{7.37}$$

Taking into account (7.37) we also may rewrite equation (7.35) as

$$\frac{\partial C}{\partial t} = -\mathbf{v}_{\text{eff}}^{\vee}(\mathbf{r})\boldsymbol{\nabla}C + q. \tag{7.38}$$

It should be pointed out that although when obtaining equation (7.38) we have used only approximate values of the corresponding coefficients, for example, the cofactor jd_N^2 in the second term on the right-hand side of equation (7.35), its form complies with the general laws of blood and heat conservation.

For a similar neighborhood $Q_i(r_N)$ containing an arteriole in its center, practically in the same way we obtain the following equation for the walker distribution

$$\frac{\partial C}{\partial t} = -\boldsymbol{\nabla}[\mathbf{v}_{\text{eff}}^{a}(\mathbf{r})C] + q(\mathbf{r}, t) \tag{7.39}$$

where

$$\mathbf{v}_{\text{eff}}^{a}(\mathbf{r}) = \boldsymbol{\nabla}\mathcal{P}^{a}(\mathbf{r}) \tag{7.40}$$

and

$$\boldsymbol{\nabla}^2\mathcal{P}^{a} = jd_N^2\delta(\mathbf{r}). \tag{7.41}$$

We point out that equation (7.39) contains no terms like $jd_N^2C|_{r=0}\delta(\mathbf{r})$ because the effect of the arterioles on the walker motion is not significant (see Section 6.2,6.3).

Generalizing these results on the whose microcirculatory bed domain in the case under consideration we can describe the walker distribution in the tissue by the equation

$$\frac{\partial C}{\partial t} + \mathbf{v}_{\text{eff}}^{\vee} \boldsymbol{\nabla} C + \boldsymbol{\nabla}[\mathbf{v}_{\text{eff}}^{a} C] = q. \tag{7.42}$$

Here,

$$\mathbf{v}_{\text{eff}}^{\vee} = \boldsymbol{\nabla} \mathcal{P}^{\vee}; \quad \mathbf{v}_{\text{eff}}^{a} = \boldsymbol{\nabla} \mathcal{P}^{a}, \tag{7.43}$$

where

$$\boldsymbol{\nabla}^2 \mathcal{P}^{\vee} = -jd_N^2 \sum_{i_N} \int_0^{l_N} ds \delta[\mathbf{r} - \boldsymbol{\xi}_{i_N}^{\vee}(s)] \tag{7.44}$$

$$\boldsymbol{\nabla}^2 \mathcal{P}^{a} = jd_N^2 \sum_{i_N} \int_0^{l_N} ds \delta[\mathbf{r} - \boldsymbol{\xi}_{i_N}^{a}(s)], \tag{7.45}$$

the functions $\boldsymbol{\xi}_{i_N}^{\vee}(s)$ and $\boldsymbol{\xi}_{i_N}^{a}(s)$ specify the spatial position of the center lines of the arterioles and venules, and s is their natural parameter. We note that the given model considers the collection of the arterioles and venules as rectilinear paths $\{\boldsymbol{\xi}_{i_N}^{a}(s), \boldsymbol{\xi}_{i_N}^{\vee}(s)\}$, respectively, and deals with the capillary system in terms of a porous medium.

As it follows from the solution of equations (7.35) and (7.39), the walker concentration (i.e. the temperature field) practically exhibits no nonuniformities on scales much smaller than d_N. Therefore, we may average the right-hand side of equations (7.44) and (7.45) over the coordinates $\{\boldsymbol{\xi}_{i_N}^{a}(s), \boldsymbol{\xi}_{i_N}^{\vee}(s)\}$ on scales smaller that d_N. Besides, just as in the previous case, we regard the venules and arterioles as vessels randomly distributed in the tissue and their arrangement can exhibit random spatial fluctuations of scale l_N only. In addition, due to the arterioles and venules being separated from each other by capillaries, fluctuations in their distribution are assumed to be opposite on scales of order l_N. Then, as it is shown in Section 7.1, we may replace the following quantities on the right-hand side of equations (7.44), (7.45) by some random field

$$d_N^2 \sum_{i_N} \int_0^{l_N} ds \delta[\mathbf{r} - \boldsymbol{\xi}_{i_N}^{\vee}(s)] \rightarrow 1 + \chi_v(\mathbf{r}), \tag{7.46}$$

$$d_N^2 \sum_{i_N} \int_0^{l_N} ds \delta[\mathbf{r} - \boldsymbol{\xi}_{i_N}^{a}(s)] \rightarrow 1 - \chi_v(\mathbf{r}), \tag{7.47}$$

where the second replacement results from the latter assumption. In (7.46), (7.47) $\chi_v(\mathbf{r})$ is a random function of $\mathbf{r}$ satisfying the conditions

$$\langle \chi_v(\mathbf{r}) \rangle = 0, \tag{7.48}$$

$$\langle \chi_v(\mathbf{r}) \chi_v(\mathbf{r}') \rangle = g\left(\frac{|\mathbf{r} - \mathbf{r}'|}{l_N} \right). \tag{7.49}$$

The function $g(x)$ is specified by expression (7.10).

The identity

$$\mathbf{v}_{\text{eff}}^{\vee} \boldsymbol{\nabla} C \equiv \boldsymbol{\nabla}[\mathbf{v}_{\text{eff}}^{\vee} C] - C \boldsymbol{\nabla} \mathbf{v}_{\text{eff}}^{\vee}, \tag{7.50}$$

expressions (7.43), and also transformations (7.46),(7.47) allow us to rewrite equation (7.42) in the form

$$\frac{\partial C}{\partial t} + \boldsymbol{\nabla}[\mathbf{v}_{\text{eff}} C] + j[1 + \chi_v(\mathbf{r})]C = q. \tag{7.51}$$

Here, $\mathbf{v}_{\text{eff}}(\mathbf{r})$ is the velocity of effective potential blood flow defined by the formula

$$\mathbf{v}_{\text{eff}} = \boldsymbol{\nabla} \mathcal{P}, \tag{7.52}$$

where $\mathcal{P} = \mathcal{P}^a + \mathcal{P}^{\vee}$ is the velocity potential which satisfies the equation

$$\boldsymbol{\nabla}^2 \mathcal{P} = -2j\chi_v(\mathbf{r}). \tag{7.53}$$

7.3.2 The diffusive type heat transport

Here we analyse heat transfer in the limit

$$\gamma \ll 1; \quad l_N \ll l_c; \quad \frac{M^{2/3}}{\gamma} \ll G \ll M^{2/3} \frac{ml_c}{l_N} \frac{\ln(d_N/a_N)}{\ln(d_c/a_c)}. \tag{7.54}$$

Under these conditions, as in the previous case, venules can be regarded as walker traps. However, here, until a walker reaches one of the venules, i.e. until it is trapped, its motion in the tissue is mainly controlled by capillaries of the second subgroup. Indeed, $\zeta_N \approx GM^{-2/3}$ (see (6.2), (6.3)) and, thereby, first, according to (6.35), (6.36), (7.54), the value of the effective diffusion coefficient D_{eff} is determined by the effect of blood flow in capillaries. Second, the influence of blood flow in the first subgroup capillaries on the walker motion in the vicinity

of a given venule or arteriole is ignorable, as it follows from (7.34) and (7.54). We also point out that the last inequality of (7.54) due to (6.18), (6.19) practically coincides with the assumed overall restriction (6.21) implying that capillaries are heat-permeable vessels.

There is a certain small neighborhood of a given venule or arteriole where the first subgroup capillaries are dominant in number. At the boundary of this neighborhood the mean distance $d_I(r_c)$ between the capillaries of the first subgroup must be equal to the mean distance between the capillaries of the second subgroup which is about d_c due to $l_c \gg l_N$. Whence, using (4.14), (6.23) and (6.36) we find that the radius of this neighborhood is

$$r_c \sim \frac{l_N}{m} \frac{1}{\gamma} \frac{\ln(d_c/a_c)}{[\ln(d_N/a_N)]^2}. \qquad (7.55)$$

However, the mean distance $l_{\|c}$ over which a walker is transported along a capillary by blood flow during its location in the capillary is substantially larger than r_c. Indeed, taking into account (6.22),(7.55) and the third inequality of (7.54) we get

$$\frac{r_c}{l_{\|c}} \sim \frac{1}{\gamma \zeta_N} \frac{1}{\ln(d_N/a_N)} \ll 1. \qquad (7.56)$$

Therefore, to describe the manner in which a walker can arrive at a given venule we have to consider in more detail its motion in the vicinity of this venule.

When $l_{\|c} \ll l_N$ for a walker that has come into a neighborhood $Q_i(l_{\|c})$ of a given venule i whose radius is about $l_{\|c}$, there are practically two ways of going into the venule. In one way the walker may get into one of the capillaries leading to the venule, i.e. belonging to the first subgroup, and with blood flow arrive at the venule. In the other way, the walker, first, gets into a capillary of the second subgroup, that passes near this venule, then leaves this capillary in the vicinity of the venule and going through the cellular tissue reaches the venule. On scales larger than $l_{\|c}$ we may describe the walker motion in terms of random walks in an effective homogeneous medium with the diffusion coefficient $D_{\text{eff}} \gg D$.

Let us find, first, the probabilities of the walker reaching the venule in the two ways. By virtue of (7.56) in the neighborhood $Q_i(l_{\|c})$ the second subgroup capillaries are dominant in number and, thus, the mean distance between these capillaries is about d_c. The distance $d_I(r)$ between the first subgroup capillaries depends on the distance r from the venule i (see (6.23)). However, due to (7.56) its value averaged over the neighborhood $Q_i(l_{\|c})$ is well above d_c and can be estimated as $d_I(l_{\|c}) \gg d_c$. So, in the neighborhood $Q_i(l_{\|c})$ approximately $d_I(l_{\|c})/d_c^2$ capillaries of the second subgroup fall at one capillary of the first subgroup. The latter allows us to estimate the probability that the walker wandering throughout the cellular tissue in $Q_i(l_{\|c})$ meets a capillary of the first rather than the second subgroup, i.e. actually the probability of the walker arriving at the venule in the first way, as

$$p_1 \sim \frac{d_c^2}{d_I^2(l_{\|c})} \sim \left[\gamma \zeta_N \ln \left(\frac{d_N}{a_N} \right) \right]^{-1} \ll 1. \tag{7.57}$$

When obtaining (7.57) expressions (4.14), (6.22),(6.23) and (6.36) have been also taken into account.

As it follows from (5.119) and Section 6.4 the mean time during which a walker can go in the cellular tissue without touching the capillaries is about $\tau_{lc} \sim d_c^2/(2\pi D) \ln(d_c/a_c)$. During this time the walker passes a distance of order $(D\tau_{lc})^{1/2} \sim d_c[\frac{1}{(2\pi)} \ln(d_c/a_c)]^{1/2}$. So, in cases where the walker motion in the neighborhood $Q_i(l_{\|c})$ on the scale $l_{\|c}$ is determined by blood flow in the second subgroup capillaries only, the walker can arrive at the venule, if it leaves the capillaries near the venule at a distance smaller than $d_c[\frac{1}{(2\pi)} \ln(d_c/a_c)]^{1/2}$.

As it is shown in Chapter 5 the motion of the walker in tissue with capillaries can be represented in terms of sequential parts of its motion near one of the capillaries and in the cellular tissue without touching the capillaries. In motion near a capillary before going out of its nearest neighborhood the walker passes, on the average, the distance $l_{\|c}$. So, when moving near a capillary passing through the neighborhood $Q_i(l_{\|c})$ the walker leaves the capillary inside $Q_i(l_{\|c})$ and the probability of leaving the capillary in the vicinity of a given point is approximately the same for all the points of $Q_i(l_{\|c})$. If, then, the walker meets another capillary it will go out of the neighborhood $Q_i(l_{\|c})$ with blood flow in this capillary.

Thus, for the walker to arrive at the venule it is necessary that (i) the capillary, blood flow wherein has transported the walker into $Q_i(l_{\|c})$, pass near the venule at a distance of order $d_c[\frac{1}{(2\pi)} \ln(d_c/a_c)]^{1/2}$ (ii) the walker leave the capillary near the venule at a distance of the same order and (iii) reach the venule within the time $\tau_{lc} \sim d_c^2/(2\pi D) \ln(d_c/a_c)$. Taking into account the aforesaid the probability of the first event as well as the second one can be estimated as $d_c/l_{\|c}[\frac{1}{(2\pi)} \ln(d_c/a_c)]^{1/2}$. In Chapter 5 we have obtained expression (5.91) practically for the Laplace transform of the probability for a walker going in the cellular tissue to reach for the first time the boundary of a pipe of radius a at time t provided the walker has been at a distance ρ_0 from the pipe centerline at initial time. Setting in this expression $\rho_0 \sim (2D\tau_{lc})^{1/2}$ and the Laplace transform variable $s = 1/\tau_{lc}$ we may estimate the probability of the third event. In this way by virtue of (5.91) and the obtained expressions for the probability of the first and second events, the probability of the walker arriving at the venule in the second way can be represented as

$$p_2 \sim \frac{d_c^2}{2\pi l_{\|c}^2} \ln \left(\frac{d_c}{a_c} \right) \left[\ln \left(\frac{(2D\tau_{lc})^{1/2}}{a_N} \right) \right]^{-1} \sim$$

$$\sim \left[\gamma \zeta_N^2 \ln \left(\frac{(2D\tau_{lc})^{1/2}}{a_N} \right) \right]^{-1} \ll 1. \tag{7.58}$$

When obtaining (7.58) we have assumed that $2D\tau_{lc} \gg a_N^2$, used the asymptotic formula for the Bessel function $k_0(x)$ for $x \ll 1$, supposed that $k_0(x) \sim 1$ for $x \sim 1$, and also taken into account (4.14),(6.22), and (6.36).

Now let us analyse the walker motion on scales larger than $l_{\parallel c}$. If for each venule we specify the neighborhood $Q_i(l_{\parallel c})$ of radius $l_{\parallel c}$ then, we may assert that a walker, during its motion in the tissue before being trapped by the venules, visits a large number of such venule neighborhoods. Indeed, on one hand, as it follows from the results obtained below (see (7.64)) and, in addition, as one could expect on the basis of the general laws of heat transfer, the mean time τ during which a walker is inside the tissue before being trapped by the venules, is about $1/j(\tau \sim 1/j)$. On the other hand, according to (6.13) the mean time in which a walker reaches one of the given venules neighborhoods for the first time can be estimated as

$$\frac{d_N^2}{2\pi D_{\text{eff}}} \ln\left(\frac{d_N}{l_{\parallel c}}\right) \sim \frac{1}{j\gamma\zeta_N} \frac{\ln(d_N/l_{\parallel c})}{\ln(d_N/a_N)}, \qquad (7.59)$$

where also (5.131), (6.35), (6.36) and the relation $j = \pi a_N^2 v_N/(l_N d_N^2)$ have been taken into account. Therefore, a walker, during its motion in tissue for the time τ, visits, on the average, N_d different venule neighborhoods where due to (6.35), (7.54), (7.59), and the relation $M = 2^{3N}$

$$N_d \sim \frac{2\pi D_{\text{eff}}\tau}{d_N^2} \left[\ln\left(\frac{d_N}{l_{\parallel c}}\right)\right]^{-1} \sim \tau j\gamma\zeta_N \frac{\ln\left(\frac{d_N}{a_N}\right)}{\ln\left(\frac{d_N}{l_{\parallel c}}\right)} > \gamma G M^{-2/3} \gg 1, \qquad (7.60)$$

provided $\tau j \sim 1$.

For a walker that at initial time is inside a given neighborhood $Q_i(l_{\parallel c})$ of a venule i the total time $< t_Q >$, during which the walker resides in this neighborhood until it goes out of the fundamental domain Q_N containing the venule i, can be estimated by setting in (4.109) $t \sim d_N^2/(2D_{\text{eff}})$ and replacing D by D_{eff} and a by $l_{\parallel c}(D \to D_{\text{eff}}, a \to l_{\parallel c})$. In this way we get

$$\langle t_Q \rangle \sim \frac{l_{\parallel c}^2}{2D_{\text{eff}}} \ln\left(\frac{d_N}{l_{\parallel c}}\right). \qquad (7.61)$$

According to the description of the walker motion in tissue with capillaries which has been developed in Chapter 5, a walker can go inside the cellular tissue without touching the capillaries, on the average, during the time $\tau_{lc} \sim d_c^2/(2\pi D)\ln(d_c/a_c)$ (cf.(4.110)). Then, the walker gets into a capillary and with blood flow travels a distance of order $l_{\parallel c}$ along the capillary until it leaves the nearest neighborhood $Q_i(d_c)$ of this capillary in a time of order $d_c^2/(2D)$. The sequence of the two types of the walker motion, i.e. its motion solely in the cellular tissue for a time of order τ_{lc} and its subsequent motion in $Q_i(d_c)$, can be

regarded as one complex step of the walker on the capillary network. The latter allows us to consider the walker motion in the tissue, until the walker is trapped by the venules, in terms of random walker on the capillary network which are made up of such steps. In limit (7.54) $l_{\|c} \gg d_c(\ln(d_c/a_c))^{1/2}$, i.e. $D_{\text{eff}} \gg D$, thereby, the mean duration of one step is about $l_{\|c}^2/(2D_{\text{eff}})$ because in this case the total length of one step is practically equal to $l_{\|c}$. We note that the mean step duration is bound to be of order $\tau_{lc} \sim d_c^2/(2\pi D) \ln(d_c/a_c)$ due to in the given model $\ln(d_c/a_c)$ being regarded as a large parameter. By virtue of (6.22) and (6.34) the two estimates of the same quantity are in agreement with one other. So for random walks originating in the vicinity of the venule i and corresponding to the walker motion inside the fundamental domain Q_N expression (7.61) and the former estimate of the step duration allow us to represent the mean total number N_i of the steps inside the neighborhood $Q_i(l_{\|c})$ in the form

$$N_i \sim \ln\left(\frac{d_N}{l_{\|c}}\right). \tag{7.62}$$

Thus, if a walker during its motion in tissue during the time τ visits N_d such venule neighborhoods, then for the corresponding random walk the total number of its steps inside these neighborhoods can be estimated as $N_t \sim N_i N_d$. Then, from (7.60) and (7.62) we obtain

$$N_t \sim \frac{2\pi D_{\text{eff}}\tau}{d_N^2} \sim \tau j \gamma \zeta_N \ln\left(\frac{d_N}{a_N}\right). \tag{7.63}$$

One step of such random walks actually describes the walker motion on scales of order $l_{\|c}$. So, the walker trapping, for example, by a venule i, can be treated in terms of interruption of the corresponding random walk when its steps reach the neighborhood $Q_i(l_{\|c})$ of the given venule. The probability of such interruption is determined by the probability of the walker arriving at the venule after coming into $Q_i(l_{\|c})$. Thereby, it is equal to $p_1 + p_2$.

The results obtained above allow us to estimate the mean time τ during which walkers are inside the tissue before being trapped by the venules, i.e. their lifetime in the tissue. Indeed, if for the time τ a random walk, representing the walker motion in the tissue, visits the system of the neighborhoods $\{Q_i(l_{\|c})\}$ N_t times, the probability of its interruption will be about $\exp\{-N_t(p_1 + p_2)\}$ due to p_1 and p_2 being much less than one. Therefore, the random walk will be practically interrupted, i.e. the walker will be trapped by the venules, when $N_t(p_1 + p_2) \sim 1$. Whence, also taking into account (7.57),(7.58), and (7.63), we get

$$\tau j \left[1 + \frac{1}{\zeta_N} \frac{\ln(d_N/a_N)}{\ln((2D\tau_{lc})^{1/2}/a_N)}\right] \sim 1. \tag{7.64}$$

By virtue of (7.54), $\zeta_N \sim GM^{-2/3} \gg 1/\gamma$ and $\gamma \ll 1$, thereby, the second term on the left-hand side of (7.64) may be ignored. Keeping the latter in mind from

(7.64) we obtain expressions (6.15), (6.16) for τ again. It should be pointed out that in the given case according to (7.64) the walker trapping mainly comes about in the first way.

When $l_{\parallel c} \gg l_N$ the points of successive intersections of different capillaries by a walker is believed to be randomly distributed on the scale l_N. Therefore, in this case, to reach the venules a walker is bound to go into any capillary at any point being along the capillary at a distance smaller than $l_{\parallel c}$ from a point where it connects with a venule. The probability p_c of this event can be estimated as

$$p_c \sim \frac{l_{\parallel c}}{l_c}.$$ (7.65)

The mean time of walker migration in tissue between sequential intersections of different capillaries is $\tau_{lc} \sim d_c^2/(2\pi D) \ln(d_c/a_c)$. Thus, in this case the lifetime τ satisfies the relation

$$p_c \frac{\tau}{\tau_{lc}} \sim \tau \frac{l_{\parallel c}}{l_c} \frac{2\pi D}{d_c^2 \ln(d_c/a_c)} \sim 1.$$ (7.66)

Whence, taking into account (4.13), (4.14), (5.131) , (6.22) and the relation $j = \pi a_N^2 v_N/(l_N d_N^2)$ we get expressions (6.15), (6.16) again.

As it has been mentioned above in limit (7.54) the walker motion in tissue on scales larger than $l_{\parallel c}$ can be treated in terms of random motion of the walkers in a homogeneous medium with the effective diffusion coefficient D_{eff}.

So, in this limit the walker concentration C obeys the equation:

$$\frac{\partial C}{\partial t} = \boldsymbol{\nabla}(D_{\text{eff}} \boldsymbol{\nabla} C) - jC + q.$$ (7.67)

It should be pointed out that in (7.67) we have ignored possible spatial nonuniformities in the walker distribution that are caused by features of the venule arrangement on scales of order l_N. The latter is justified because in the given case for a walker to be trapped it has to visit a large number of the venule neighborhoods $\{Q_i(l_{\parallel c})\}$ due to $p_1 + p_2 \ll 1$.

The three limits considered below and the corresponding main properties of heat transfer are displayed in Fig. 7.1a.

7.4   Influence of long capillaries on heat transfer

In this Section we shall show that the effect of long capillaries ($\gamma \gg 1$) on heat transfer reduces solely to renormalization of the diffusion coefficient D and the desired form of bioheat equation coincides with (7.67). For these purposes we analyse individually each of the possible limits.

The limit:

$$\gamma \gg 1; \quad \frac{M^{2/3}}{\gamma^{1/2}} \ll G \ll M^{2/3}. \tag{7.68}$$

For this geometry of the capillary network there is no range of the parameter G corresponding to the convective type transport because for any value of G the capillaries of the first subgroup have no significant effect on the walker motion. Indeed, the first subgroup capillaries can affect the walker motion if inequality (7.34) is true. However ,$1/\zeta_N + \gamma\zeta_N \geq 2\gamma^{1/2}$, thus, in limit (7.68) inequality (7.34) cannot be true for any ζ_N, i.e. any G.

When $\gamma\zeta_N^2 \sim \gamma[GM^{-2/3}]^2 \ll 1$ the influence of the second subgroup capillaries is also ignorable as it follows from (6.35). So, in this case and in limit (7.23) the properties of heat transfer are identical. When $\zeta_N \sim GM^{-2/3} \gg 1$ the venules and arterioles are the smallest vessels of the first class, the second class veins do not exist at all, and the walker transport in the tissue is controlled by capillaries of the second group. This case has been practically considered in limit (7.54). For this reason when $\gamma > 1$ we shall examine limit (7.68) only when $1/\gamma^{1/2} \ll \zeta_N \ll 1$.

In this case the walker transport in the tissue on scales larger than $l_{\|c}$ is controlled by blood flow in the capillaries and can be described by random motion of the walkers in a medium with the effective diffusion coefficient $D_{\text{eff}} \gg D$. The venules and arterioles, however, are heat-permeable vessels, thus, the walkers can be trapped only by veins whose level number $n \leqslant n_t < N$. None of the capillaries is connected with the veins directly (except for the venules). So in this case, as it has been discussed in limit (7.54) regarding to the walker trapping in the second way, to get into a vein of level n a walker should, first, reach the vein neighborhood of radius $d_c[1/(2\pi)\ln(d_c/a_c)]^{1/2}$ with blood flow in a capillary passing near the vein and then leave this capillary and travelling through the cellular tissue go into the vein.

Keeping the latter in mind and replicating one-to-one the analysis leading to formulas (7.58) and (7.63) we obtain the following. First, for a walker that has come into a neighborhood $Q_i(l_{\|c})$ of such a vein, whose radius is about $l_{\|c}$, the probability of getting into the vein before leaving this neighborhood is approximately equal to

$$p_2' \sim \left[\gamma_N^2 \ln\left(\frac{(2D\tau_{lc})^{1/2}}{a_n}\right)\right]^{-1} \tag{7.69}$$

and due to (7.68) $p_2' \ll 1$. Second, on scales larger than $l_{\|c}$ we may represent a path of the walker motion in the tissue during time $t \gg \tau_{lc} \sim d_c^2/(2\pi D)\ln(d_c/a_c)$ as a random walk formed by a sequence of steps, the mean length of which is about $l_{\|c}$. In these terms during a time $t \gg d_n^2/(2\pi D)\ln(d_c/a_c)$ the random walk can visit such neighborhoods of the n-th level veins N_t' times where, on the average,

$$N'_t \sim \frac{d_N^2}{d_n^2}(tj)\gamma\zeta_N \ln\left(\frac{d_N}{a_N}\right) \tag{7.70}$$

provided the random walk has not been interrupted, i.e. the walker has not been trapped.

Expressions (7.69),(7.70) enable us to find the mean time τ'_{ln} during which a walker traveling through the tissue will get into one of the n-th level veins. Indeed, this time is bound to satisfy the relation

$$p'_2 N'_t|_{t=\tau'_{ln}} \sim 1. \tag{7.71}$$

Substituting (7.69),(7.70) into (7.71) we obtain

$$\tau'_{ln} \sim \frac{1}{j}\zeta_n \frac{\ln((2D\tau_{lc})^{1/2}/a_n)}{\ln(d_N/a_N)}, \tag{7.72}$$

where we also have taken into account the identity

$$\zeta_n\left[d_n^2 \ln\left(\frac{d_n}{a_n}\right)\right]^{-1} \equiv \zeta_n\left[d_N^2 \ln\left(\frac{d_N}{a_N}\right)\right]^{-1} \tag{7.73}$$

resulting from (4.6),(4.13), and (5.131).

In the case under consideration not all veins of the first class can trap walkers but only those whose parameter ζ_n meets the condition

$$\zeta_n \geq \frac{\ln(d_n/a_n)}{\ln((2D\tau_{lc})^{1/2}/a_n)}. \tag{7.74}$$

In fact, if a walker arrives at central points of a vein whose level number $n < n_*$, i.e. for which $\zeta_n \geq \ln(d_n/a_n)$ the walker will be trapped because in this case it has no time to return to the cellular tissue. If a walker reaches a vein whose level number $n > n_*$ it will be in the vicinity of this vein within the time τ_{lc} only. In a time of order τ_{lc} the walker gets into one of the capillaries blood flow wherein carries the walker away from the vein. So, practically replicating the analysis of Section 6.2 and taking into account (4.4) we find that the walker will be trapped by this vein if

$$l_n < \frac{a_n^2 v_n}{2D} \ln\left(\frac{(2D\tau_{lc})^{1/2}}{a_n}\right). \tag{7.75}$$

The latter condition and expression (4.15) directly lead us to condition (7.74). The walker trapping is practically controlled by the shortest veins whose parameter ζ_n meets condition (7.74), i.e. by the veins whose level number n'_t obeys the equation

$$\zeta_{n'_t} \approx \frac{\ln(d_{n'_t}/a_{n'_t})}{\ln((2D\tau_{lc})^{1/2}/a_{n'_t})}. \tag{7.76}$$

Thus, the mean time τ during which a walker will be trapped, may be found from (7.72) setting $t = \tau$ and $n = n'_t$. By virtue of (7.76), in this way we obtain the estimate $\tau \sim 1/j$ again.

Therefore, also in the case under consideration the walker distribution in tissue is governed by equation (7.67). Besides, it should be pointed out that in limit (7.68) the class of the heat-impermeable vessels contains the veins whose level number $n < n'_t$ rather than $n < n_t$, where $n_* < n'_t < n_t$. However, due to $l_n/a_n \sim 30 - 40$ (see the comments just below expression (4.7)) and according to (6.10) the value $n_t - n_* \sim 1$. For this reason we have ignored the latter characteristics in the general analysis of heat transfer in the previous sections.

The possible types of heat transfer in living tissue where capillaries are sufficiently long ($\gamma \gg 1$) are displayed in Fig. 7.1b.

In conclusion of this Chapter we note that when the characteristic total length of capillaries joining a given arteriole to venules is not too long (i.e. when $\gamma \ll 1$ within the framework of the present model), depending on the value of G the effect of the capillary system on heat transfer can be of different types. In particular, in limit (7.23) the capillary system influence is ignorable and in this case the temperature distribution (in terms of the walker concentration) is described by equation (7.29).

In limit (7.33) the capillary system causes convectional type transport of heat in the tissue and the tissue temperature obeys equation (7.51). In this case the capillary system may be considered in terms of a porous medium.

In limit (7.54) heat transport is controlled again by diffusive type process in a certain effective medium but with the effective diffusion coefficient D_{eff} being a function of the blood flow rate.

When the capillary length is long enough (i.e. when $\gamma \gg 1$) the range of convectional type transport is absent. In this case heat transfer is controlled by diffusive type transport. In limit (7.68) the cellular tissue containing the capillary system can be treated as an effective uniform medium with the diffusion coefficient D_{eff}.

Chapter 8

Generalized bioheat equation

In Chapter 7 in the possible limits we have obtained the different forms of the equation governing evolution of the temperature field $T(\mathbf{r}, t)$ in tissue (in terms of the walker concentration $C(\mathbf{r}, t)$). Comparing these equations with each other we can propose a generalized bioheat equation which describes heat transfer in living tissue. It should be pointed out that such a model is bound to comprise equations (7.29), (7.51), and (7.67) as particular cases. The present analysis also holds true for the nonuniform blood flow rate $j(\mathbf{r})$ providing all spatial scales of its nonuniformities are well above l_{n_t} if $\zeta_N < 1$ and l_N for $\zeta_N > 1$. Due to (4.11) when $l_c \gg l_N$ the value $\mathcal{R} \gg l_N$ and, thus, there are cases where the influence of such nonuniformities in $j(r)$ on heat transfer should be taken into account in the generalized model.

We note that equations (7.29) and (7.67) are practically of the same form because for $D_{\text{eff}} \gg D$ the influence of the random field $\chi_t(\mathbf{r})$ on heat transfer is suppressed. To combine these equations with equation (7.51) we may represent the mean walker flux $\mathbf{J}_w$ as the sum of the diffusive type flux and the convective one:

$$\mathbf{J}_w = -\boldsymbol{\nabla}[D_{\text{eff}} C] + \mathbf{v}_{\text{eff}} C, \tag{8.1}$$

where D_{eff} and $\mathbf{v}_{\text{eff}}$ are determined by expressions (6.18), (6.19), (6.31) (or (6.32)) and (7.40), respectively. In all the limits considered in Chapter 7 expression (8.1) yields the correct results. Also we point out that on scales larger than $l_{\|c}$ heat transport, i.e. the walker motion, in the tissue seems to be described by stochastic processes of the Ito type. So in expression (8.1) we have to put the effective diffusion coefficient D_{eff} after the operator $\boldsymbol{\nabla}$ [38]. Besides it is possible to generalize the bioheat equations (7.29) and (7.51) in such a way that the generalized equation allows for nonuniformities in the trap distribution and the convective treat transport due to blood flow in the capillary system.

8.1 Effective diffusion coefficient

Due to the effective diffusion coefficient D_{eff} being the result of cooperative influence of all the vessels the total value of D_{eff} can be represented as the sum of particular values of effective diffusion coefficients induced by blood flow in vessels of various groups. In other words we may write

$$D_{\text{eff}} = D[1 + F_v(G) + F_c(G)], \tag{8.2}$$

where $G = \frac{4jl_0^2}{3\sqrt{3}\pi D} \ln\left(\frac{l_0}{a_0}\right)$, the term $F_v(G)$ is caused by blood flow in the second class vessels and the capillary system is responsible for the term $F_c(G)$. According to (6.18) and (6.19) for $G_0 < G < G_{cc}^*$ or $G_{cc} < G < M^{2/3}$

$$F_v(G) = \pi\sqrt{3}\frac{1}{\ln(l_0/a_0)}, \tag{8.3}$$

for $G_{cc}^* < G < G_{cc}$

$$F_v(G) = \pi\sqrt{3}\frac{1}{\ln(l_0/a_0)}\left(\frac{G}{G_{cc}^*}\right)^2, \tag{8.4}$$

and for $G > M^{2/3}$

$$F_v(G) = 0, \tag{8.5}$$

because for $G > M^{2/3}$ vessels of Class 2 do not exist. By virtue of (6.32) and (6.3)

$$F_c(G) = \gamma M^{4/3} G^2. \tag{8.6}$$

8.2 Effective convective flux

The results obtained in Section 7.3 actually describes the general convective type effect of blood flow in capillaries of the first subgroup. Beyond limit (7.33) the influence of these capillaries on heat transfer is practically ignorable. Thus, the corresponding expressions can be considered to blood for all values of G. Therefore, we may assume that in living tissue there is an effective potential convective flux whose velocity field $\mathbf{v}_{\text{eff}}(\mathbf{r})$ is specified by expressions

$$\mathbf{v}_{\text{eff}}(\mathbf{r}) = \boldsymbol{\nabla}\mathcal{P}. \tag{8.7}$$

Here the velocity potential $\mathcal{P}$ obeys the equation

$$\nabla^2 \mathcal{P} = -2j(\mathbf{r})\chi_v(\mathbf{r}) \tag{8.8}$$

and the random field $\chi_v(\mathbf{r})$ satisfies the conditions

$$< \chi_v(\mathbf{r}) >= 0, \tag{8.9}$$

$$< \chi_v(\mathbf{r})\chi_v(\mathbf{r}') >= g\left(\frac{|\mathbf{r} - \mathbf{r}'|}{l_N}\right), \tag{8.10}$$

where the function $g(x)$ is given by expression (7.10).

8.3 Nonuniformities in heat sink due to the vessel discreteness

In Chapter 7 we also have considered the influence of random nonuniformities in vessel positions on the walker trapping. In limits (7.28) and (7.33) where this influence is the strongest, it can be described by the terms of the same form, viz. $jC\chi_t$ and $jC\chi_v$, respectively. In limits (7.54) and (7.68) this effect is suppressed due to $D_{\text{eff}} \gg D$. Therefore, in both these cases we may describe the walker trapping (heat disappearance) by the term $j(\mathbf{r})[1 + \chi_t(\mathbf{r})]C$, where $\chi_t(\mathbf{r})$ is a random field (denoted by the same symbol) that meets the conditions

$$\langle \chi_t(\mathbf{r}) \rangle = 0, \tag{8.11}$$

$$\langle \chi_t(\mathbf{r})\chi_t(\mathbf{r}') \rangle = g\left(\frac{|\mathbf{r} - \mathbf{r}'|}{l_t}\right), \tag{8.12}$$

where $g(x)$ is specified by expression (7.10) again and

$$l_t = l_n \mid_{n=n_t} = l_0 2^{-n_t(G)} \tag{8.13}$$

or by virtue of (6.4), for $G \leqslant G_{cc}$ when the vessel tree contains countercurrent pairs at level n_t

$$l_t \simeq \left[\frac{3\sqrt{3}\pi}{4} \frac{D}{j[\ln(d_0/a_0)]^{1/2}}\right]^{1/2}, \tag{8.14}$$

and for $G_{cc} < G < M^{2/3}$ when unit veins and arteries belong to level n_t.

$$l_t = \left[\frac{3\sqrt{3}\pi}{4} \frac{D}{j \ln(d_0/a_0)} \right]^{1/2}. \tag{8.15}$$

For $G > M^{2/3}$ there is no artery or vein of Class 2 and in this case

$$l_t = l_N. \tag{8.16}$$

When $G > M^{2/3}$ the random fields $\chi_t(r)$ and $\chi_v(r)$ must be identical, otherwise, $G < M^{2/3}$ they are independent of each other. Such conditions we may represent in the following form

$$\langle \chi_t(\mathbf{r})\chi_v(\mathbf{r}') \rangle = g\left(\frac{\mid \mathbf{r} - \mathbf{r}' \mid}{l_N} \right) \theta(l_N - l_{n_t}) \tag{8.17}$$

where $\Theta(x) = 0$ for $x < 0$ and $\Theta(x) = 1$ when $x > 0$ and l_{n_t} is formally given by expressions (8.15) for $G > M^{2/3}$.

8.4 Generalized bioheat transfer equation

Comparing equations (7.29), (7.51) and (7.67), (6.35) with each other, taking into account expressions obtained above in this Section and returning to the variable T (see Chapter 4) we may write the generalized bioheat equation in the following form

$$c_t\rho_t \frac{\partial T}{\partial t} = \kappa[1 + F_v(G) + F_c(G)]\boldsymbol{\nabla}^2 T - c_t\rho_t \boldsymbol{\nabla}[\mathbf{v}_{\text{eff}}(T - T_a)] -$$

$$-c_t\rho_t j \left(\ln \frac{l_0}{a_0} \right)^{(\beta(n_t)-1)/2} [1 + \chi_t(\mathbf{r})](T - T_a) + q_h. \tag{8.18}$$

The system of equation (8.18) and expressions (8.3), (8.4), (8.5), (8.6) forms the proposed generalized model for heat transfer.

It should be pointed out once again that the proposed model is justified only when all spatial scales of nonuniformities in the blood flow rate j are well above l_t. The opposite case can take place, for example, in hyperthermia of a small tumor, and to investigate the corresponding influence of the blood flow rate on heat transfer individual analysis is required.

Concluding the present Chapter we compare the derived equation (8.18) with bioheat equations proposed by other authors.

When $G \ll M^{2/3}$ the value $n_t \ll N$ and blood flow in capillaries practically has no significant effect on heat transfer. In this case, if we, in addition, ignore

random temperature nonuniformities, equation (8.18) practically coincides with equation (2.5) where the unknown phenomenological parameter

$$f = \frac{1}{[\ln(l_0/a_0)]^{1/2}}$$

for $G < G_{cc}$. When $G > G_{cc}$ the parameter $f = 1$ and equation (8.18) goes over into the equation similar to equation (2.3). We note once again that it is the countercurrent effect responsible for small values of the coefficient f, and the effective conductivity model (2.4) is justified for temperature distribution nonuniform on spatial scales of order $[\kappa \ln(l_0/a_0)/(c_t \rho_t j)]^{1/2}$. For extremely high blood flow rates, when $G < M^{2/3}$ the effective convective heat transport can be dominant, which justifies, at least qualitatively, equation (2.2).

Part III

Heat transfer in living tissue with extremely nonuniform blood flow distribution

Equation (8.18) as well as (2.1) - (2.5) has been obtained practically by averaging the microscopic equations governing heat transfer in living tissue on scales of individual vessels. In other words, the mathematical approach to the heat transfer description associated with equation (8.18) actually considers living tissue in terms of a uniform (may be anisotropic) continuum. The latter is justified as long as the tissue temperature and the blood flow distribution over the vascular network are practically uniform on the scale l_v, characterizing inhomogeneity of the living tissue from the heat transfer standpoint. The magnitude of l_v is approximately equal to the length of vessels, that directly control heat exchange between the cellular tissue and blood, and for typical values of $j \sim 3 \cdot 10^{-3} s^{-1}$ can be estimated as $l_v \sim 0.5 cm$ (see Chapter 3). When heating or cooling the living tissue is sufficiently strong the thermoregulation gives rise to substantial local dependence of the blood flow rate on the tissue temperature [95]. Therefore, if the size of the tissue domain affected directly is less than l_v (which typically is the case, at least, in cryosurgery the blood flow distribution and, consequently, the blood flow rate can became nonuniform already on scales of order l_v. In this case to describe heat transfer in living tissue correctly the bioheat equation should be modified.

In the present part we propose a possible alternative to such a modified bioheat equation which governs heat transfer in living tissue with extremely nonuniform blood flow distribution over the vascular network.

Chapter 9

The bioheat equation and the averaged blood flow rate

9.1 Should the bioheat equation contain the true blood flow rate?

Equation (8.18) has been justified in the previous part for uniform blood flow distribution over the microcirculatory bed domain. This raises the question of whether the obtained bioheat equation holds for substantially nonuniform blood flow distribution and the relative question how to modify it in order to describe adequately heat transfer in living tissue with nonuniform blood flow rate.

For this purpose we consider the physical effects that are reflected in the conventional bioheat equation

$$c_t \rho_t \frac{\partial T}{\partial t} = D \boldsymbol{\nabla}^2 T - j(T - T_a) + q_T. \tag{9.1}$$

The second term on the right-hand side of this equation describes heat exchange between blood and the cellular tissue as volumetric heat dissipation. The heat sink term is rigorously justified solely for uniform blood flow distribution over the vascular network. The matter is that in the strict sense in tissue there is no local heat dissipation. Blood upon attaining thermal equilibrium with the surrounding tissue during its motion in small vessels is withdrawn through large veins practically without heat loss. The latter is due to the velocity of heat convective transport with blood flow increasing more quickly than the vessel length as the level number decreases during the blood motion towards the vein stem. Thus, for cellular tissue such blood - tissue exchange is local in nature. If blood flow is substantially nonuniform distributed over the vascular network,

then there can be such a path on the vein tree that the main amount of blood flows through the veins forming this path. The blood current along this path may not vary significantly. So, for a blood portion flowing along such a path to words the stem its balk velocity will increase more slowly than the vessel length. Therefore, in this case there is a possibility that blood will lose heat energy during the motion through large veins. The latter gives rise actually to heat exchange between various tissue regions which differ significantly in size and such heat exchange can be described either in terms of the local blood flow rate or by effective heat conductivity.

To demonstrate the validity of such speculations let us consider stationary solution of equation (9.1) where the heat generation rate $q_T(\mathbf{r})$ differs from zero only inside a certain fundamental domain Q^* of size l^* and the true blood flow rate $j(\mathbf{r})$ takes the value j^* inside the domain Q^* and j at the exterior points. The value of j^* is assumed to be large enough so that $(l^*)^2 \gg D/j^*$ and, thus, the formal stationary solution of equation (9.1) must be located in the domain Q^*.

However, the microscopic theory of bioheat transfer can lead to another result. To show this let us consider blood current J along the path $\mathcal{P}_{on}$ the vein tree that originates at the vein i^* which directly drains the domain Q^* and terminates at the tree stem. Due to the conservation of blood at the branching points the blood current $J(l)$ in a vein of length l belonging to this path is about

$$J(l) \sim \left[j + j^* \left(\frac{l^*}{l} \right)^3 \right] l^3. \tag{9.2}$$

Then, according to $\left(\zeta_n = \frac{a^2 v}{2} \right)$ for the vessels of the path $\mathcal{P}$ the classification parameter $\zeta(l)$ treated as a function of l can be represented in the form

$$\zeta(l) \sim \frac{l^2 \ln \left(\frac{l_0}{a_0} \right)}{D} \left[j + j^* \left(\frac{l^*}{l} \right)^3 \right]. \tag{9.3}$$

The minimum ζ_{in} of the function $\zeta(l)$ is about

$$\zeta_{\text{in}} \sim \frac{(l^*)^2}{D} \ln \left(\frac{l_0}{a_0} \right) [(j^*)^2 j]^{1/3}, \tag{9.4}$$

and is attained at

$$l_{\text{in}} \sim \left(\frac{j^*}{j} \right)^{1/3} l^*. \tag{9.5}$$

Thus, as follows from (9.4), for

$$j \ll j^* \left[\frac{1}{(l^*)^2 j^*} \right]^3 \frac{1}{\left(\ln \frac{l_0}{a_0} \right)^3} \tag{9.6}$$

the minimum value of the vessel classification parameter $\zeta_{min} \ll 1$. Besides, $\zeta(l^+) \gg 1$. Therefore under condition (9.6) the path contains heat-conservation veins separated by a collection of heat-dissipation veins. Thereby, heat energy withdrawn by blood flow through veins of length l^* from the domain Q^+ is lost inevitably at veins of the length $l_{min} \gg l^*$ and distributed practically uniformly over a tissue domain of size l_{min}. This conclusion is in contradiction with the formal solution of equation (9.1).

Obviously, these speculations hold true for heat transfer in living tissue with countercurrent pairs.

Summarizing the aforesaid we can assert that the bioheat transfer equation should not contain the true blood flow rate. We also note that Chen and Holmes [17] were the first who proposed an alternative to bioheat equation which deals with a certain averaged blood flow rate rather than the true one.

In the following Section we develop certain procedure that enables us to modify the bioheat equation and conceptually coincides the analyses of heat transfer in living tissue with the nonuniform blood flow rate formulated above.

9.2   The heat conservation vein tree

The blood flow rate is typically uniform on scales of capillary length. Therefore when analyzing properties of heat transfer in living tissue with the nonuniform blood flow rate we may focus main attention on cases where the capillary system does not affect significantly heat propagation. Under such conditions solely a blood flow in the venous bed substantially affects the walker motion. Therefore we may confine our consideration to the venous bed and the corresponding blood current pattern $\{J_i\}$. The effect of a blood flow through the arterial bed is practically reduced to renormalization of diffusion coefficient, which also will be taken into account in the present Part. Besides, for the sake of simplicity we consider the case when the vascular network is entirely made up of either unit vessels ($n_{cc} = 0$) or countercurrent pairs ($n_{cc} = N$).

When blood flow is nonuniform distributed over the microcirculatory bed, to classify a given vein i according to its effect on walker motion we should take into account the whole blood current pattern $\{J_i\}$ rather than the blood current J_i in this vessel only. In order to construct the desired classification, let us specify for each point $\mathbf{r}$ of the domain Q_0 a sequence of fundamental domains $\{Q_{nr}\} = \{Q_0, Q_{1r}, ..., Q_{Nr}\}$ where the n-th term Q_{nr} is the fundamental domain of level n which contains the given point $\mathbf{r}$. Besides, by the symbol i_{nr} we denote the vein corresponding to the domain Q_{nr}, i.e. the vein of level n that is contained in the domain Q_{nr}. On the venous part of the vascular network the vein collection $\{i_{nr}\} = \{i_0, i_{1r}, ..., i_{Nr}\}$ forms a path leading from the host

vein $i_0 \equiv i_{0r}$ to the vein i_{Nr} corresponding to the elementary domain Q_{Nr}. In addition, formulae (5.131), (5.133) enables us to match up the number sequence $\{\zeta_{nr}\} = \{\zeta_0, \zeta_{1r}, ..., \zeta_{Nr}\}$ for the vein collection $\{i_{nr}\}$. In what follows we shall assume that the number sequence $\{\zeta_{nr}\}$ can be interpolated by a function $\zeta(n, r)$ of the continuous variable n being smooth on scales of order unity.

When the blood flow distribution is uniform, according to (4.5) and (4.18) the blood current in a vein of level n is $J_n = J_0/M_n = J_0 2^{-3n}$, where J_0 is the blood current in the host vein or, what is the same, the total blood current flowing through the microcirculatory bed. Whence, taking into account (4.5), (5.131), and (5.133) we get $\zeta_{nr} = \zeta_0 2^{-2n}$ for every point r. So, in this case the function $\zeta(n, r)$ is decreasing with respect to the variable n.

When blood flow is nonuniform distributed over the microcirculatory bed the function $\zeta(n, r)$ for a fixed value of r does not have to be monotone. Indeed, let, for example, the resistance to blood flow along a certain path $\{i_{nr'}\}$ be extremely small in comparison with other possible paths. In this case the blood currents in all the veins $\{i_{nr'}\}$ are approximately the same and due to $l_n = l_0 2^{-n}$ and (5.131) and (5.133) we get $\zeta_n \approx \zeta_0 2^{-n}$.

In the framework of the adopted assumptions the host vein corresponds to the parameter $\zeta_0 \gg 1$, whereas the last level veins $\{i_N\}$ are associated with $\{\zeta_{i_N} \ll 1\}$. The former inequality follows from the assumption $l_0 \gg l_v$ because, by virtue of (5.131), (5.133), and (3.3) and the estimate $\tilde{j} \sim J_0/l_0^3$, we obtain $\zeta_0 \sim (l_0/l_v)^2 \gg 1$. The latter inequalities are justified by that in the given Section effect of blood flow in capillaries on heat transfer is assumed to be ignorable. Under these conditions a possible characteristic behavior of the function $\zeta(n, r)$ for a fixed value of r is displayed in Fig. 9.1 by the solid and dashed lines for nonuniform and uniform blood flow distributions, respectively. Due to $\zeta_0 \gg 1$ and $\{\zeta_{i_N} \ll 1\}$ the equation $\zeta(n, r) = 1$ has, at least, one root for every point r and any root is substantially greater than one. The integer nearest to the first, i.e. to the least root of the equation $\zeta(n, r) = 1$ will be designated as n_r (Fig. 9.1). In other words, n_r is such an integer that

$$\zeta(n_r, r) \approx 1 \tag{9.7}$$

and for all $n < n_r$

$$\zeta(n_r, r) > 1. \tag{9.8}$$

Let $\{i_{nr}\}^*$ be a part of the vein collection $\{i_{nr}\}$ that involves all the veins whose level number $0 \leqslant n \leqslant n_r$, i.e. $\{i_{nr}\}^* = \{i_0, i_{1r}, ..., i_{n_r r}\}$. In this way the collection of integers $\{n_r\}$ allows us to specify the vein system $\mathcal{V}$ consisting of the veins belonging, at least, to one of the possible vein collections $\{i_{nr}\}^*$. In other words, the system $\mathcal{V}$ is the greatest connected part of the venous bed that is entirely made up of the veins for which $\zeta_i \geq 1$. The vein collection $\{i\}_v$ comprising all the veins whose level number $n = n_r$ for some point r may be regarded as a certain "boundary" of the tree $\mathcal{V}$.

Figure 9.1: Possible characteristic behaviour of the function $\zeta(n, r)$ for a fixed value of **r** when the blood flow distribution is nonuniform (the solid line) and unoform (the thin line).

Due to $\zeta_i > 1$ for all the veins of the tree $\mathcal{V}$ (except the veins $\{i\}_v$ for which $\zeta \simeq 1$) the blood flow in each of these veins substantially affects the walker motion. Therefore, once a walker has crossed the boundary of one of these veins, for example, of a vein belonging to level n, in a short time it will be transported by blood flow into a small neighborhood of a vein belonging to level $(n-1)$ or it will arrive at the central points of the this vein. The following motion of the walker will proceed in a similar manner. Thus, as it can be shown directly replicating practically one-to-one the analysis presented in Chapter 6, if a walker crosses the boundary of the vein system $\mathcal{V}$, then in a short time it will arrive at central points of these veins and leave the tissue domain Q_0 with blood flow through the host vein actually without returning into the cellular tissue. This event may be regarded as walker trapping, thus, we can consider the vein tree $\mathcal{V}$ in terms of walker traps.

Since the mean distance between the vessels of the tree $\mathcal{V}$ is mainly determined by the shortest veins, i.e. by the veins belonging to the "boundary" of the tree $\mathcal{V}$, the walker trapping is actually controlled by the veins $\{i\}_v$. The more larger vessels of the tree $\mathcal{V}$ form the paths of walker fast transport from the veins $\{i\}_v$ to the host vein. It also should be noted that there can be veins with the corresponding parameters $\zeta_i > 1$ which do not belong to the vessel system $\mathcal{V}$, if blood flow is distributed over the vascular network extremely nonuniform. The blood flow in these veins may have a substantial local effect on walker motion. However, once a walker has crossed the boundary of one of these veins it is rapidly transported by blood flow only until it reaches a vein for which $\zeta_i < 1$. Thereafter, the walker inevitably will leave the latter vein and travel a distance in the cellular tissue much larger than its length. Thus, blood flow in veins not belonging to the vessel system $\mathcal{V}$ does not practically affect walker motion,

although the inequality $\zeta_i > 1$ can hold for some of these veins (Fig. 9.1). Returning to the terms of heat transfer the aforesaid allows us to treat the vessel system $\mathcal{V}$ as a part of the venous bed where blood moves so fast that, first, heat transport in these vessels is mainly governed by blood convective stream, and, second, blood has no time to attain thermal equilibrium with the surrounding cellular tissue.

Since , as it has been mentioned before the walker trapping is mainly controlled the veins $\{i\}_v$ the local life time $\tau(\mathbf{r})$ of walkers being in a small neighborhood of the point $\mathbf{r}$ can be estimated as (see (5.15a,b))

$$\tau(\mathbf{r}) \approx \frac{d_{n_r}^2}{2\pi D} \ln \frac{d_{n_r}}{a_{n_r}} \tag{9.9}$$

where d_{n_r} is the mean distance between veins of level n_r and in the given model for the vascular network (4.13)

$$d_{n_r} = \left[\frac{V_{n_r}}{l_{n_r}} \right]^{1/2} = \left(\frac{2}{\sqrt{3}} \right)^{3/2} l_{n_r}. \tag{9.10}$$

9.3 The basic cover of microcirculatory bed domain. The bioheat equation

In order to find the relationship between the characteristics of the vessel system $\mathcal{V}$ and, consequently, of the walker trapping and the blood flow distribution described in terms of the blood flow rate $j(\mathbf{r})$ we need the following collections of fundamental domains. Let Q_v be the fundamental domain corresponding to a given vein i_{vr}, i.e. the fundamental domain of the same level as the vein i_{vr} that contains the given vein as well as the point $\mathbf{r}$ specifying the vein collection $\{i_{nr}\}$ which the vein i_{vr} belongs to. In this way considering all the veins of the collection $\{i_{vr}\}$ we can specify the collection of fundamental domains $\{Q_v\}$ called the basic cover of the tissue domain Q_0. Different domains of $\{Q_v\}$ are disjoint and every point $\mathbf{r}$ of the domain Q_0 belongs to one of them and each domain of $\{Q_v\}$ contains just one vein of the collection $\{i_v\}$.

In accordance with the results obtained below on temporal scales about $\tau(r)$ the walker spreads over a distance of order l_{n_r} practically uniformly. So, considering walker motion in the cellular tissue on spatial scales of order l_{n_r} we can characterize the effect of blood flow in the vein i_{vr} by the mean rate $r_w(\mathbf{r})$ of walker disappearance in the domain Q_{vr} which is equal to

$$r_w(\mathbf{r}) = \frac{1}{\tau(\mathbf{r})} C(\mathbf{r}). \tag{9.11}$$

The basic cover $\{Q_{vr}\}$ allows us to define a new quantity $j_v(r)$ called the averaged blood flow rate according to the formula

$$j_v(\mathbf{r}) = \frac{1}{V_{nr}} \int\limits_{Q_{vr}} d\mathbf{r} j(\mathbf{r}) \tag{9.12}$$

where V_r is the volume of the domain $Q_{vr} \in \{Q_v\}$ containing the given point $\mathbf{r}$. Taking into account (4.7) we also may set

$$j_v(\mathbf{r}) = \frac{1}{V_{nr}} J i_{vr}. \tag{9.13}$$

Expressions (5.131), (5.133), (9.7), (9.9) - (9.11), and (9.13) lead to the following formula for the walker disappearance rate

$$r_w(\mathbf{r}) = j_v(\mathbf{r}) \left(\ln \frac{l_0}{a_0} \right)^{(\beta_{cc}-1)/2} C_w(\mathbf{r}), \tag{9.14}$$

where $\beta_{cc} = 0$ for the countercurrent vascular network and $\beta_{cc} = 1$ for the unit vessel network (cf. formula (6.2)). In addition, the expressions mentioned above enable us to represent the relationship between the averaged blood flow rate $j_v(r)$ and the length l_{n_r} of the corresponding vein i_{vr} of the system $\{i\}_v$ in the form

$$l_{n_r}^2 \approx \frac{3\sqrt{3}\pi}{4} \frac{D}{j_v(r)} \frac{1}{L}, \tag{9.15}$$

where $L = \left[\ln \left(\frac{l_0}{a_0} \right) \right]^{(\beta_{cc}-1)/2}$.

Since, for the veins of the system $\{i\}_v$ the classification parameter $\zeta(n_r, \mathbf{r})$ = 1 they are not only walker traps but also some exhibit properties heat - dissipation vessels. In particular vessels with $\zeta_i \leqslant 1$ give rise to renormalization of the diffusion coefficient $D \rightarrow D_{\text{eff}} = D(1 + F_v)$. In the case under consideration the renormalization coefficient F_v is constant as it has been shown in Section 6.4. Therefore, the effect of the blood flow rate in the veins (or countercurrent pars) of the system $\{i\}_v$ is actually reduced to walker trapping and renormalization of the diffusion coefficient. Therefore, taking into account expression (9.4) we may write the equation governing evolution of walker distribution in living tissue in terms of

$$\frac{\partial C}{\partial t} = D_{\text{eff}} \boldsymbol{\nabla}^2 C - j_v \left(\ln \frac{l_0}{a_0} \right)^{(\beta_{cc}-1)/2} C + q \tag{9.16}$$

where the effective diffusion coefficient $D_{\text{eff}} = D[1 + F_v]$ where F_v is given by expression (8.3).

Equation (9.16) is actually the result of averaging microscopic equations (4.1), (4.2) over the basic cover $\{Q_{vr}\}$. Returning to terms of heat transfer, equation (9.16) may be rewritten as

$$c_t \rho_t \frac{\partial T}{\partial t} = \kappa_{\text{eff}} \boldsymbol{\nabla}^2 T - c_t \rho_t j_v \left[\ln \left(\frac{l_0}{a_0} \right) \right]^{(\beta_{cc}-1)/2} (T - T_a) + q_h \qquad (9.17)$$

with $\kappa_{\text{eff}} = \kappa[1 + F_v]$. This equation is the desired bioheat equation governing evolution of the tissue temperature. It should be noted that in small regions containing vessels with $\zeta_i > 1$, which, however, do not belong to the vessel system $\mathcal{V}$, the effective diffusion coefficient can exceed the value $D[1 + F_v]$. This is the case for a region containing vessels of the sequence $\{i_{nr}\}$ whose level number is within the interval $[n_r^*, n_r^{**}]$ shown in Fig. 9.1. However influence of this regions on heat transfer is not significant due to small relative volume of such regions.

Concluding the present Section we would like to point out that according to equation (9.16) or (9.17), the characteristic spatial scale l_D of the tissue temperature variations is about

$$l_D = \left[D_{\text{eff}} / \left(\ln \frac{l_0}{a_0} \right)^{(\beta_{cc}-1)/2} j_v \right]^{1/2}$$

whereas the length of the veins directly controlling heat exchange between blood and the cellular tissue is $l_{n_r} \sim (D/(j_v L))^{1/2}$ (see formula (9.15)). Thus,

$$\frac{l_{n_r}}{l_D} \sim \left[\frac{D}{D_{\text{eff}} \ln(l_0/a_0)} \right]^{1/2}.$$

In the given approach the value $\ln(l_0/a_0)$ is treated as a large parameter, which allows us to suppose that $l_{n_r} \ll l_D$. In particular, this inequality justifies the adopted basic assumption of uniformity of the tissue temperature on spatial scales of order l_{n_r}.

Chapter 10

Relationship between the averaged and true blood flow rates

In order to complete bioheat equation (9.17) we need an expression or equation specifying the relationship between the averaged (j_v) and true (j) blood flow rates. In the present Chapter we propose an alternative to this relation.

10.1 The integral form of the relationship between the averaged and true blood flow rates

According to the definition of the averaged blood flow rate proposed in the previous Section, we can write the following formula for the relationship between the true ($j(\mathbf{r})$) and averaged ($j_v(\mathbf{r})$) blood flow rates

$$j_v(\mathbf{r}) = \int_{Q_0} d\mathbf{r}' G(\mathbf{r}, \mathbf{r}') j(\mathbf{r}'). \tag{10.1}$$

Here the kernel of the linear operator G is given by the expression

$$G(\mathbf{r}, \mathbf{r}') = \sum_{i \in \{i_{vr}\}} \frac{1}{V_i} \Theta_i(\mathbf{r}) \Theta_i(\mathbf{r}'), \tag{10.2}$$

where $\Theta_i(\mathbf{r})$ is the characteristic function of the fundamental domain Θ_i of volume V_i corresponding to the vein i i.e.

$$\Theta_i(\mathbf{r}) = \left\{ \begin{array}{ll} 1 & \text{if} \quad \mathbf{r} \in \Theta_i \\ 0 & \text{if} \quad \mathbf{r} \notin \Theta_i \end{array} \right. \tag{10.3}$$

and the sum runs over all the veins of the system $\{i_{vr}\}$. Expression (10.1) may be regarded as a linear transformation of the field $j(\mathbf{r}')$. In these terms G is a linear operator which, by virtue of (10.2), is self-adjoint, i.e.

$$G(\mathbf{r}, \mathbf{r}') = G(\mathbf{r}', \mathbf{r}) \tag{10.4}$$

and meets the condition

$$\int_{Q_0} d\mathbf{r} G(\mathbf{r}, \mathbf{r}') = 1 \tag{10.5}$$

as it must be due to the conservation of fluid mass.

We note that the averaged blood flow rate j_v determined by formula (10.1) is a piecewise constant field with steps at the boundaries of the domains $\{Q_{vr}\}$. Besides, transformation (10.1) leads to some loss of information due to the existence of the eigenfunctions with the zero eigenvalue.

The partition of the domain Q_0 into domains of the basic cover is directly associated with the averaged blood flow rate, (see, e.g. expression (9.12)). Therefore, although formula (10.1) may be, in principle, regarded as the desired relationship between the averaged and true blood flow rate, it is actually unfeasible to use it because the kernel $G(\mathbf{r}, \mathbf{r}')$ depends on the averaged blood flow rate rather than the true one. In this case it would be worthwhile to invert transformation (10.1), however, to do it directly is impossible due to operator (10.2) possessing the zero eigenvalue. Since the particular details in the behavior of the averaged blood flow rate on spatial scales of order l_{n_r} are of little consequence for heat transfer, we may modify the kernel $G(\mathbf{r}, \mathbf{r}')$ in order to invert transformation (10.1). This is the subject of the next Section.

10.2 The smoothing procedure for the integral operator and the inverse operator

The smoothing procedure is actually specified by the replacement of kernel (10.2) by a certain kernel $\tilde{G}(\mathbf{r}, \mathbf{r}')$ smooth on scales of the basic cover for which there exists an operator $\tilde{G}^{-1}$ inverse to the operator $\tilde{G}$. In addition the kernel $\tilde{G}(\mathbf{r}, \mathbf{r}')$ also must satisfy conditions (10.4), (10.5) because of these expressions stem from the general properties of the averaging procedure.

The inverse operator $\tilde{G}^{-1}$ enables us to write the true blood flow rate $j(\mathbf{r})$ as an explicit functional of $j_v(\mathbf{r})$.

$$j(\mathbf{r}) = \int_{Q_0} d\mathbf{r}' \tilde{G}^{-1}(\mathbf{r}, \mathbf{r}') j_v(\mathbf{r}') \tag{10.6}$$

where the kernel $\tilde{G}^{-1}(\mathbf{r}, \mathbf{r}')$ also meets conditions (10.4), (10.5). Indeed, from definition,

$$\int_{Q_0} d\mathbf{r}'' \tilde{G}^{-1}(\mathbf{r}, \mathbf{r}'') \tilde{G}(\mathbf{r}'', \mathbf{r}') = \int_{Q_0} d\mathbf{r}'' \tilde{G}(\mathbf{r}, \mathbf{r}'') \tilde{G}^{-1}(\mathbf{r}'', \mathbf{r}') = \delta(\mathbf{r} - \mathbf{r}'). \quad (10.7)$$

Then, first, writing expression (10.7) for the pairs $(\mathbf{r}, \mathbf{r}')$ and $(\mathbf{r}', \mathbf{r})$, subtracting from one other, and taking into account (10.4) we get

$$\tilde{G}^{-1}(\mathbf{r}, \mathbf{r}') = \tilde{G}^{-1}(\mathbf{r}', \mathbf{r}). \quad (10.8)$$

Second, integration of (10.7) with respect to $\mathbf{r}'$ over Q_0 and equality (10.8) yields

$$\int_{Q_0} d\mathbf{r}' \tilde{G}^{-1}(\mathbf{r}, \mathbf{r}'). \quad (10.9)$$

The linear transformation (10.6) can be also represented in terms of the Fourier transforms $j_F(\mathbf{k}), j_{Fv}(\mathbf{k})$ of the fields $j(\mathbf{r}), j_v(\mathbf{r})$ and the Fourier transform $\tilde{G}_F^{-1}(\mathbf{k}, \mathbf{k}')$ of the kernel $\tilde{G}^{-1}(\mathbf{r}, \mathbf{r}')$, viz.:

$$j_F(\mathbf{k}) = \sum_{\mathbf{k}'} \tilde{G}_F^{-1}(\mathbf{k}, \mathbf{k}') j_{Fv}(\mathbf{k}') \quad (10.10)$$

where

$$\tilde{G}_F^{-1}(\mathbf{k}, \mathbf{k}') = \frac{1}{V_0} \int_{Q_0} \int d\mathbf{r} d\mathbf{r}' \tilde{G}^{-1}(\mathbf{r}, \mathbf{r}') \exp[i(\mathbf{k}\mathbf{r} - \mathbf{k}'\mathbf{r}')]. \quad (10.11)$$

$V_0 = \Lambda_0^3$ is the volume of the microcirculatory bed domain Q_0, and the sum runs over all the vectors $\mathbf{k} = \frac{2\pi}{\Lambda_0}(n_x, n_y, n_z)$, for $n_x, n_y, n_z = 0, \pm 1, \pm 2 \ldots$

Setting $\mathbf{k}'$ or $\mathbf{k}$ be equal to zero and taking into account (10.8), (10.9) we obtain that the function $\tilde{G}_F^{-1}(\mathbf{k}, \mathbf{k}')$ must obey the following general properties

$$\tilde{G}_F^{-1}(\mathbf{k}, 0) = \tilde{G}_F^{-1}(0, \mathbf{k}) = \delta_{\mathbf{k},0}. \quad (10.12)$$

As it follows from the definition of $j_v(\mathbf{r})$ the averaged blood flow rate $j_v(\mathbf{r})$ has to be a smooth function on scales of the basic cover. Therefore, the function $j_v(\mathbf{r})$ cannot vary significantly inside any domain Q_{i_v} of the basic cover. In terms of smoothed fields the averaging procedure (10.6) is no longer averaging over the collection of discrete cubes but is specified by a certain field $l(r)$ whose value at each point $\mathbf{r}$ determines the characteristic size of neighborhood centered

at the point $\mathbf{r}$ over which the true blood flow rate $j(\mathbf{r})$ should be averaged. Keeping in mind the Gauss type averaging procedure it is natural to suppose that $[2\pi l^2(r)]^{3/2}$ is equal to the volume $V_{\Gamma_v} = (d_{n_r}^2 l_{n_r})$ of the fundamental domain Q_{n_r} belonging to the basic cover. Then, from (9.16) we obtain

$$l^2(r) = \frac{\sqrt{3}}{2} \frac{D}{j_v(r)L} \tag{10.13}$$

where $j_v(r)$ is the smoothed averaged blood flow rate. Due to the field $j_v(r)$ being smooth on scales $j(r)$ the value $l(r)\nabla j_v(r)$ cannot substantially exceed $j_v(r)$. Therefore, we may seek the particular expression for the operator $\tilde{G}^{-1}$ in the form of a certain truncation of the operator $\tilde{G}^{-1}$ expansion into a power series of ∇. In order to analyse characteristic features of such a representation we consider the averaging procedure the value $l(\mathbf{r})$ is formally constant, $l(\mathbf{r}) = l$. In this case it is natural to specify the kernel $\tilde{G}_h(\mathbf{r}, \mathbf{r}')$ as

$$\tilde{G}_h(\mathbf{r}, \mathbf{r}') = \frac{1}{(2\pi l^2)^{3/2}} \exp\left[-\frac{(\mathbf{r} - \mathbf{r}')}{2l^2}\right]. \tag{10.14}$$

The integral transformation (10.1) with kernel (10.14) becomes the convolution, thus, the Fourier transforms $j_v(\mathbf{k}), j_{Fv}(\mathbf{k})$ of the fields $j(\mathbf{r})$ and $j_v(\mathbf{r})$ are related by the expression for $l \ll \Lambda_0$

$$j_F(\mathbf{k}) = G_{hF}(\mathbf{k})j_{Fv}(\mathbf{k}) \tag{10.15}$$

where

$$G_{hF}(\mathbf{k}) = \frac{1}{(2\pi l^2)^{3/2}} \int_{\mathcal{R}^3} d\mathbf{r} \exp\left(-\frac{\mathbf{r}\,2}{2l^2} + i\mathbf{k}\mathbf{r}\right) = \exp\left(-\frac{1}{2}l^2k^2\right). \tag{10.16}$$

Comparing (10.10) and (10.15) we find the following expression for the inverse operator $\tilde{G}^{-1}$:

$$\tilde{G}_F^{-1}(\mathbf{k}, \mathbf{k}') = \delta_{\mathbf{k}, \mathbf{k}'} \exp\left(\frac{1}{2}l^2k^2\right). \tag{10.17}$$

Since, we may confine our consideration to the region $kl \leqslant 1$ and the function $\exp(\frac{1}{2}l^2k^2)$ is increasing it is possible to expand this function in a power series of k^2l^2 and to truncate the power series at the second term. In this way we get

$$\tilde{G}_F^{-1}(\mathbf{k}, \mathbf{k}') = \delta_{\mathbf{k}, \mathbf{k}'}\left(1 + \frac{1}{2}l^2k^2\right). \tag{10.18}$$

Transformation (10.10) with kernel (10.18) can be rewritten in the form

$$j(\mathbf{r}) = j_v(\mathbf{r}) - \frac{1}{2}l^2\boldsymbol{\nabla}^2 j_v(\mathbf{r}).$$ (10.19)

We point out that such approximation of the function $G_{hF}(\mathbf{k})$ is impossible due to $\exp\left\{\frac{1}{2}l^2k^2\right\}$ being a decreasing function and its truncation similar to (10.18) leading to a wrong result for $lk \sim 1$.

In the general case, i.e. when the field $l^2(r$ is nonuniform we may specify this operator G^{-1} to the second order $\boldsymbol{\nabla}$ by the formula for its action on an arbitrary function Ψ

$$\tilde{G}^{-1}\Psi = \{1 - A_1(r)\boldsymbol{\nabla}^2 - \boldsymbol{\nabla}A_2(r)\boldsymbol{\nabla} - \boldsymbol{\nabla}^2 A_3(r)\}\Psi$$ (10.20)

where $A_1(r)$, $A_2(r)$ and $A_3(r)$ are proportional to $l^2(r)$. It should be noted that form (10.20) is the unique expression containing two vector objects ($\boldsymbol{\nabla}$) and a scalar field (l^2). For the operator G^{-1} determined by expression (10.20) the Fourier transform of its kernel is of the form

$$\tilde{G}_F^{-1}(\mathbf{k},\mathbf{k}') = \delta_{\mathbf{k},\mathbf{k}'} + A_{1F}(\mathbf{k}-\mathbf{k}')\mathbf{k}'^2 + \mathbf{k}A_{2F}(\mathbf{k}-\mathbf{k}')\mathbf{k}' + \mathbf{k}^2 A_3(\mathbf{k}-\mathbf{k}').$$ (10.21)

Here A_{iF} is the Fourier transform of the function $A_i(\mathbf{r})$ $i = 1, 2, 3)$. Condition (10.12) immediately gives $A_1 = A_2 = 0$. Thereby under the adopted assumptions the general form of the transformation (10.6) is

$$\tilde{G}^{-1}j_v = j_v - C\boldsymbol{\nabla}(l^2(\mathbf{r})\boldsymbol{\nabla}j_v)$$ (10.22)

comparing (9.19) and (9.22) we find $C = \frac{1}{2}$.

Expression (10.22) is the desired formula for the smoothed inverse operator $\tilde{G}^{-1}$.

10.3 Differential form of the relationship between the true and averaged blood flow rates

Formula (10.22) actually specifies the procedure of inverting relationship (10.1). In this way using the identity $\tilde{G}^{-1}\tilde{G} = 1$ we obtain the expression

$$j = \tilde{G}^{-1}j_v$$ (10.23)

whose right-hand side contains only the averaged blood flow rate due to the field $l^2(\mathbf{r})$ being directly determined by $j_v(\mathbf{r})$. The substitution of (10.13) into

(10.22) leads equation (10.23) to the equation determining the desired relationship between the true and averaged blood flow rates:

$$j_v - D_v \boldsymbol{\nabla}^2 \ln j_v = j \qquad (10.24)$$

where

$$D_v = \frac{\sqrt{3}}{4} \frac{\kappa}{c_t \rho_t} \frac{1}{L}. \qquad (10.25)$$

Dealing with a tissue domain bounded by a real physical interface σ we need to complete equation (10.24) by a certain condition at the interface σ. In order to determine this boundary condition let us consider a domain Q' which is practically made up from fundamental cubes of the basic cover. Then for the averaged blood flow rate j_v defined by formula (10.1) with kernel (10.2) we have

$$\int_{Q'} d\mathbf{r} j_v(\mathbf{r}) = \int_{Q'} d\mathbf{r} j(\mathbf{r}). \qquad (10.26)$$

In terms of smoothed fields relation (10.26) leads to the condition

$$\oint_{\partial Q'} ds \frac{D_v}{j_v} \boldsymbol{\nabla}_n j_v = 0 \qquad (10.27)$$

the boundary $\partial Q'$ of such a region Q'. According to (10.27) the term $D_v \boldsymbol{\nabla} \ln j_v$ is the seeming blood flow across the boundary $\partial Q'$ due averaging the blood flow rate in the vicinity of the domain boundary over exterior points. Since, the averaging procedure never runs over exterior points to the real interface σ we may set

$$\boldsymbol{\nabla}_n j_v |_\sigma = 0. \qquad (10.28)$$

This expression is the desired boundary condition for equation (10.24).

Part IV

Theory of heat transfer in living tissue with temperature self-regulation

When the tissue temperature T becomes high enough, $T \sim 42 \div 44^o C$ thermoregulation in living tissue causes significant increase in the blood flow rate. In particular, under local heating the blood flow rate can increase by ten-fold. Therefore, to complete bioheat transfer equation governing evolution of the tissue temperature a theory of living tissue response to temperature variation in terms of the blood flow rate dependence on the temperature distribution should be developed. The present Part is mainly devoted to this subject.

Chapter 11

Theory of self-regulation under local heating of living tissue

The microscopic description of vessel response to temperature variations has been stated in Sections 3.3 and 4.4. There we have specified the model where the flow resistance R_i of vein i is directly controlled by the mean temperature of blood in this vein and the flow resistance R_i of an artery i' is governed by the mean blood temperature in the corresponding vein i'. The flow resistance $\{R_i\}$ of all vessels given, we can find the blood distribution over the vascular network and, thus, the blood flow rate distribution over the microcirculatory bed domain Q_0, as depending on the blood temperature pattern $\{T_i^*\}$ on the vein tree. So, relating the blood temperature pattern $\{T_i^*\}$ to the tissue temperature distribution $T(\mathbf{r})$ and, may be, the blood flow rate distribution $j(\mathbf{r})$ we solve, in principle, the temperature regulation problem.

11.1 Governing equations for blood temperature distribution over the vein tree

In this Section we obtain the explicit relationship between the patterns of blood currents $\{J_i\}$ and the blood temperature $\{T_i^*\}$ on the vascular network on one hand, the blood flow rate j and the tissue temperature, on the other hand.

As in Part 3 for the sake of simplicity we consider the case when the effect of blood flow in capillaries on heat transfer is ignorable and the vascular network either is entirely made up of countercurrent pairs ($n_{cc} = N$) or involves unit vessels only ($n_{cc} = 0$). By virtue of the adopted assumptions, the length l_N of the last level vessels is the smallest spatial scale, thus, in particular, $l_N \ll l_v, l_D$ and, thereby, the blood flow rate $j(\mathbf{r}, t)$ can be regarded as a field practically uniform on the scale l_N. In this case the relationship between the blood flow

rate $j(r)$ and the blood currents $\{J_i\}_N$ in the last level vessels may be given in terms of

$$J_{ir} = V_N j(r),$$

where J_{ir} is, for example, the blood current in the last level vein i_r that together with the point $\mathbf{r}$ is contained in the same elementary domain Q_{Nr} of volume V_N. Then for the adopted vascular network embedding in the cube Q_0 from the last expression and equations (4.18) representing the conservation law of blood flow at branching points we immediately find the following expression for the blood current J_i in the vein i:

$$J_i = \int_{Q_0} dr \Theta_i(r) j(r) \, , \tag{11.1}$$

where $\Theta_i(r)$ as in Section 10.1 is the characteristic function of the fundamental domain Q_i being of the same level as the vein i and containing this vein inside itself, viz.:

$$\Theta_i(r) = \left\{ \begin{array}{lll} 1 & , & \text{if} \quad r \in Q_i \\ 0 & , & \text{if} \quad r \notin Q_i. \end{array} \right. \, .$$

To describe heat exchange between the cellular tissue and blood, and, thus, to find the relationship between and the blood temperature pattern $\{T_i\}$ the temperature field $T(\mathbf{r}, t)$ we make use the results obtained in Section 9.2. According to these results on the vein tree we can single out a certain connected part (the vessel system $\mathcal{V}$) which invols vessels for which the classification parameter $\zeta_i > 1$. The "boundary" of the vessel system $\mathcal{V}$ is made up of veins $\{i_v\}$ for which $\zeta_{i_v} = 1$. The system of fundamental domains corresponding the veins $\{i_v\}$ forms the basic cover $\{Q_v\}$. In veins belonging to the vessel system $\mathcal{V}$ except for the vein $\{i_v\}$ blood moves so fast that heat transport in these vessels is mainly controlled by blood convective stream and blood has no time to attain thermal equilibrium with the surrounding cellular tissue as well as for the countercurrent vascular network with blood in the nearest artery. Therefore, first, blood in the veins of the system $\mathcal{V}$ should be characterized by its own temperature T^*. Second, the conservation of energy at the branching points of the vessel system $\mathcal{V}$, for example, at a branching point B_v can be represented in the form

$$\sum_{B_v} T^*_{\text{in}} J_{\text{in}} = T_{\text{out}} J_{\text{out}} \tag{11.2}$$

where $J_{\text{in}}, J_{\text{out}}, T^*_{\text{in}}, T_{\text{out}}$ are the blood currents and the mean temperatures of blood in the veins going into this branching point.

The blood flow in veins for which $\zeta_i < 1$ is in thermodynamic equilibrium with the cellular tissue and its temperature coincides locally with the tissue temperature T: $T_i^* \simeq T$. The latter condition is also true for separated veins of Class 1; the veins of the system $\{i_v\}$ exhibit properties of both the heat - conservation and heat - dissipation veins. The tissue temperature cannot vary significantly on scales of the basic cover $\{Q_v\}$. Therefore, the way how the temperature of a blood portion varies during the motion from the veins of level $n > n_{t_r}$ to veins of level $n < n_{t_r}$ (n_{t_r} is the number level of the vein i_{vr}) can be characterized considering the local tissue temperature T constant. This question has been discussed in Chapter 7 where we have shown that the relationship between the temperature T^* of blood in veins with $n < n_t$ and the tissue temperature T is different for the unit vein network and the countercurrent pair network. Since, the effect of blood flow in arteries with $n \simeq n_t$ is not significant for the unit vein network the temperature of blood does not practically vary during its motion from veins of level $n > n_t$ to veins of level $n < n_t$ (see formula (7.30), (7.31)) for the unit vessel network we may set

$$T_{i_v}^* = T_i \qquad (11.3)$$

where T_i is the tissue temperature in the fundamental domain belonging to the basic cover $\{Q_v\}$ and containing the vein i_v. Heat exchange between venous and arterial blood in a countercurrent pair whose level number $n \approx n_t$ is significant. Therefore, venous blood loses heat energy during its motion from heat - dissipation vein $n > n_{t_r}$ to heat - conservation veins $n < n_{t_r}$ at the instant it passes the veins whose level $n \approx n_t$. Formula (7.32) allows us to write the following relationship between $T_{i_v}^*$ and T_i for the countercurrent vascular network:

$$T_{i_v}^* - T_a = \frac{1}{[\ln(l_0/a_0)]^{1/2}}(T_i - T_a) \qquad (11.4)$$

Expressions (11.3) and (11.4) are actually the "boundary" conditions for the system of equations (11.2).

Since, the tissue temperature cannot vary significantly on scales of the basic cover $\{Q_v\}$ we may rewrite formulae (11.3), (11.4) as

$$(T_{i_v}^* - T_a)J_{i_v} = \beta_v \int\limits_{Q_v} d\mathbf{r}\, \Theta_i(\mathbf{r})(T - T_a)j \qquad (11.5)$$

where $\beta_v = 1$ for unit veins and $\beta = \frac{1}{\ln(l_0/a_0)}$ for countercurrent pairs. Q_{iv} is the domain of the collection $\{Q_v\}$ that contains the vein i_v and expression (11.1) has been taken into account.

The vascular network embedding allows us to write the following formula for each branching point, for example, branching point B

$$\Theta_{\text{out}}(\mathbf{r}) = \sum_B \Theta_{\text{in}}(\mathbf{r})$$

where the sum runs over all the veins going into the branching point B. Then, taken into account (4.18) and substituting (11.5) into (11.2) for, first, for the branching points of the vessel system $\mathcal{V}$ that contain the veins $\{i_v\}$ and then, successively performing the summation for any vein i of the vessel system $\mathcal{V}$, we find

$$(T_i^* - T_a)J_i = \beta_v \int\limits_{Q_0} d\mathbf{r}\, \Theta_i(\mathbf{r})(T - T_a)j \tag{11.6}$$

For small veins, for example vein i, with $n_i > n_{t_r}$ blood is in thermodynamic equilibrium with the cellular tissue and the tissue temperature in the fundamental domain Q_i is practically constant. Therefore, formula (11.1) enables us to write an expression similar to (11.6), viz.

$$(T_i^* - T_a)J_i = \int\limits_{Q_0} d\mathbf{r}\, \Theta_i(\mathbf{r})(T - T_a)j \tag{11.7}$$

For $\beta_v = 1$ expressions (11.6) , (11.7) are of the same form. The latter enables us to regard formula (11.11) as the general relationship between the temperature T_i^* of blood in a vein i, the blood current J_i in this vein, the tissue temperature T and the blood flow rate j for the unit vessel network.

For the countercurrent vascular network formula (11.10) can be regarded as the general relationship between these quantities if the cofactor β_v is treated as a function taking the value $\beta_v = 1/\sqrt{\ln(l_0/a_0)}$ for the veins of the vessel system $\mathcal{V}$ and $\beta_v = 1$ for small veins. In order to complete the given relationship between T_i^*, J_i, T and j we need to find the explicit form of the dependence of β_v on the tissue temperature $T(\mathbf{r})$ and the blood flow rate $j(\mathbf{r})$ (or may be the averaged blood flow rate $j_v(\mathbf{r})$). For each of the large veins belonging to the vessel system $\mathcal{V}$ the corresponding fundamental domain can be represented as the union of domains belonging to the basic cover $\{Q_v\}$. Therefore, so, using the definition (10.1) of the averaged blood flow rate $j_v(\mathbf{r})$, we rewrite the definition (5.133) of the classification parameter for countercurrent pairs whose veins belong to the vessel system $\mathcal{V}$ in the form

$$\zeta_i = \zeta_{v_i} = \frac{[\ln(l_0/a_0)]^{1/2}}{2\pi Dl_i} \int\limits_{Q_i} d\mathbf{r} j_v(\mathbf{r}). \tag{11.8}$$

For the veins of the system $\mathcal{V}$ the value $\zeta_{v_i} > 1$ and $\zeta_{v_i} \approx 1$ for the "boundary" $\{i_v\}$ of the system $\mathcal{V}$. Since, the field $j_v(\mathbf{r})$ is the blood flow rate averaged over

the basic cover $\{Q_v\}$ for a vein i not belonging to the vessel system $\mathcal{V}$ the formal value

$$\int\limits_{Q_i} j_v(\mathbf{r})d\mathbf{r}$$

is equal to the blood current in the vein i providing blood flowing through the vein i_v supplying the domain Q_i is uniformly distributed over the corresponding domain Q_{i_v}. By constitution for the vein i_v the value $\zeta_{v_i} = 1$. Thus, for every vein not belonging to the vessel system $\mathcal{V}$ the formal value of ζ_{v_i} given by expression (11.8) must be less than unity; $\zeta_{v_i} < 1$ if $i \notin \mathcal{V}$. These properties of the quantity ζ_{v_i} enable us to use ζ_{v_i} as the classification parameter of belonging to the vessel system $\mathcal{V}$. Therefore, the dependence of the value β_v on the vein position on the vessel tree can be written in the form

$$\beta_v = \left\{ \begin{array}{lll} [\ln(l_0/a_0)]^{-1/2} & ; \quad \text{if} \quad \zeta_v > 1, \\ 1 & ; \quad \text{if} \quad \zeta_v < 1. \end{array} \right. \tag{11.9}$$

So, the system of expressions (11.1), (11.7), or the system of expressions (11.1), (11.6), (11.8), (11.9) specifies the desired relationship between the patterns of the blood currents $\{J_i\}$ and the blood temperature $\{T_i^*\}$ on one hand, and the blood flow rates $j(\mathbf{r}), j_v(\mathbf{r})$ and the tissue temperature $T(\mathbf{r})$ on the other hand for the unit vessel network and the countercurrent vascular network, respectively.

The obtained results actually specify the vessel flow resistances $\{R_i\}$ as functions of the blood flow rate and the tissue temperature. So, in order to find the blood flow rate distribution over the microcirculatory bed domain Q_0 as a functional of the tissue temperature, which is the subject of the thermoregulation theory, we need to obtain expressions that describe the blood current pattern $\{J_i\}$ and, thus, the blood flow rate $j(\mathbf{r})$ in living tissue for given values of the vessel resistances. The following two Sections are devoted to this problem.

11.2 Additional effective pressure sources. The Green matrix for the Kirchhoff equations of blood flow redistribution over the vascular network

To find the relation between the tissue temperature $T(\mathbf{r}, t)$ and the blood flow rate $j(\mathbf{r}, t)$ we should solve the system of Kirchhoff's equations (4.18), (4.19). However, when the tissue temperature is nonuniform in the domain Q_0, resistances of all the veins (and the arteries) can be different in magnitude because of the vascular network response to temperature variations. In this case solving

Kirchhoff's equations directly is troublesome. In order to avoid this problem let us introduce quantities $\{\varepsilon\}$ called additional effective pressure sources (EPSs) which are ascribed to all the vessels. For the i-th artery and vein of level n_i the additional EPS ε is defined by the expression

$$\varepsilon = -J_i(R_i - R_{n_i}^0).$$ (11.10)

Formula (11.10) allows us to rewrite the second Kirchhoff's equation (4.19) in terms of:

$$J_i R_{n_i}^0 = \Delta P_i + \varepsilon.$$ (11.11)

The collection of equations (4.18) and (11.11) for different branching points and vessels forms the system of Kirchhoff's equations describing the blood current pattern on a vascular network of the same geometry where vessels, however, are not sensitive to variations in the blood temperature and thermoregulation gives rise to the additional EPSs. The latter vascular network will be referred to below as homogeneous one. In this way, when EPSs have the known values the analysis of the blood current redistribution over the microcirculatory bed with vessels sensitive to the blood temperature is reduced to solving Kirchhoff's equations for the corresponding homogeneous vascular network.

Differentiating relation (11.10) with respect to the time t and taking into account equation (4.32) we find the following evolution equation for the quantity ε:

$$\tau_{n_i} \frac{d\varepsilon}{dt} + \varepsilon \left[f \left(1 - \frac{\varepsilon}{J_i R_{n_i}^\circ} \right) - \tau_{n_i} \frac{d}{dt} \ln J_i \right] = R_{n_i}^\circ \frac{1}{\Delta} \left| (T_i^* - T_a) J_i \right|.$$ (11.12)

In obtaining (11.12) we also have assumed that the current J_i cannot change its direction.

The system of equations (11.12) and relations (11.1), (11.6) or (11.7) specifies the dependence of EPSs on the tissue temperature $T(\mathbf{r}, t)$ and the blood flow rate $j(\mathbf{r}, t)$. If, however, we find the solution of the system of Kirchhoff's equations (4.18) and (11.11) and, thereby, obtain the blood flow rate as a function of EPSs, then, we shall be able to get an equation that directly specifies the relationship between j and T. Such a relation with equations (9.4) and (10.26) forms the desired complete description of heat transfer in living tissue.

For the venous bed of the corresponding homogeneous vascular network containing EPSs the solution of the system of Kirchhoff's equations (4.18), (11.11) can be written in the form

$$J_i\{\varepsilon\} = \sum_{i'} \Lambda_{ii'} \left[\varepsilon_{i'} + P \delta_{n_{i'} 0} \right].$$ (11.13)

Here Λ_{ij} is the Green matrix, i.e. the solution of these equations when $P = 0$ and all $\varepsilon_{i'} = 0$ except for $\varepsilon|_{i'=j} = 1$, $\delta_{n_{i'} 0}$ is the Kronecker symbol and n_j is the level number of the vein j. We note the possibility of representation (11.13)

Figure 11.1: Schematic representation of the homogeneous venous bed containing EPSs.

the results from the linearity of equations (4.18) and (11.11) with respect to the blood currents $\{J_i\}$.

Due to the homogeneity of the given vascular network shown schematically in Fig. 11.1 when the vein j is the host one, the values of Λ_{ij} are equal for all veins i of the same level. So, from (4.18) we get $2^3\Lambda_{ij} = \Lambda_{i'j}$ if $n_j = 0$ and $n_i = n_{i'} + 1$ because exactly eight veins go in each branching point. Whence, it follows that

$$\Lambda_{ij}\big|_{n_j=0} = 2^{-3n_i}\Lambda_{ij}\big|_{\substack{n_i=0 \\ n_j=0}} \quad . \tag{11.14}$$

Let us set the total pressure drop across the venous bed $P = 1$, all EPSs $\varepsilon = 0$ and then, sum up equation (11.11) along any path $\mathcal{P}$ from the host vein to a

vein of the last level. In this way taking into account (4.22),(11.13) we obtain

$$P = \sum_{i \in \mathcal{P}} J_i R_{n_i}^0 = \sum_{n_i=0}^{N} \Lambda_{ij}\big|_{n_j=0} \, 2^{3n_i} \rho(n_i) R_0$$

and

$$\Lambda_{ij}\big|_{\substack{n_i=0 \\ n_j=0}} \cdot R_0 \sum_{n=0}^{N} \rho(n) = 1. \tag{11.15}$$

Then, introducing quantities $\{Z(n)\}$ defined as

$$Z(n) = \sum_{n'=n}^{N} \rho(n') \tag{11.16}$$

from (11.14) and (11.15) we get

$$\Lambda_{ij}\big|_{n_j=0} = 2^{-3n_i} \frac{1}{R_0 Z(0)}. \tag{11.17}$$

To find Λ_{ij} for a vein j whose level number $n_j \geq 1$ we consider a path $O_j O_0$ on the vascular network, shown in Fig. 11.1 by the dashed line which joins the given vein j to the host vein and directed from higher to lower levels. This path divides the whole venous bed into the path $O_j O_0$ and disconnected with each other branches whose initial veins go into branching points on the path $O_j O_0$. For $P = 0$ and $\varepsilon = 0$ except for $\varepsilon|_{i'=j} = 1$ in all veins belonging both to the same level and to the same branch the corresponding blood currents must be identical. This allows us to transform the graph shown in Fig. 11.1 into the one shown in Fig. 11.2, where the given path $O_j O_0$ is represented by the sequence of veins designated by $\{n_j, n_j-1, n_j-2, \ldots, 1, 0\}$ having of resistances $\{R_{n_j}^0; R_{n_j-1}^0; R_{n_j-2}^0; R_1^0; R_0^0\}$. Each vein of this sequence at its terminal points is connected with a block of identical branches labeled by the level number of the corresponding vein (Fig. 11.2).

Let $\tilde{J}_n$ be the blood current in vein n and I_n be the total blood current in branch block n which are caused by the action of EPS $\varepsilon_j = 1$. The total resistance of block n for $1 \leqslant n \leqslant n_j$ is

$$r_n = \frac{1}{7} R_n^0 + \frac{1}{7 \cdot 8} R_{n+1}^0 + \frac{1}{7 \cdot 8 \cdot 8} R_{n+2}^0 + \ldots$$

i.e.

$$r_n = \frac{1}{(2^3 - 1)} \sum_{p=n}^{N} 2^{-3(p-n)} R_p^0, \tag{11.18}$$

Figure 11.2: The block form of the homogeneous venous bed for $P = 0$, $\varepsilon_{i'} = 0$ except $\varepsilon_{i'}|_{i'=j} = 1$ (a) and the structure of a subblock (b).

thereby, from (4.22) and (11.16) we get for $1 \leqslant n \leqslant n_j$

$$r_n = \frac{1}{(2^3 - 1)} 2^{3n} R_0 Z(n) . \tag{11.19}$$

In a similar way we obtain the expression for the resistance of the last (n_j+1)-th block:

$$r_{n_j+1} = \frac{1}{2^3} 2^{3(n_j+1)} R_0 Z(n_j + 1). \tag{11.20}$$

The introduced quantities, i.e. $\tilde{J}_n, I_n$, and r_n enable us to transform the system of equations (4.18), (11.11) for $P = 0$ and $\varepsilon_{i'} = 0$ except $\varepsilon_{i'}|_{i'=j} = 1$ into the Kirchhoff's equations associated with the network shown in Fig. 11.2 viz. to the following equations for $1 \leqslant n \leqslant n_j$:

$$I_n = \tilde{J}_n - \tilde{J}_{n-1} , \tag{11.21}$$

for $2 \leqslant n \leqslant n_j$

$$I_n r_n = \tilde{J}_{n-1} R_{n-1}^0 + I_{n-1} r_{n-1} , \tag{11.22}$$

and into two equations that are bound up with the first and the last elements of the given network:

$$I_1 r_1 = \tilde{J}_0 R_0 , \tag{11.23}$$

$$\tilde{J}_{n_j}[r_{n_j+1} + R_{n_j}^0] + I_{n_j} r_{n_j} = 1 . \tag{11.24}$$

It should be noted that the last two equations can be regarded as certain boundary conditions for the system of equations (11.21), (11.22). Due to $\rho(n)$ being a smooth function of n the ratio $\rho(n)/Z(n)$ may be treated as a small value for $N - n \gg 1$. The latter allows us to find directly the solution of equations (11.21) - (11.24) which is matter of the next Subsection.

11.2.1 Continuous solution of the Kirchhoff equations

Taking into account (4.22), (11.16), (11.19), and (11.20) we can rewrite equation (11.22)-(11.24) in terms of

$$2^3 I_n Z(n) = (2^3 - 1)\tilde{J}_{n-1}\rho(n - 1) + I_{n-1} Z(n - 1) \tag{11.25}$$

for $2 \leqslant n \leqslant n_j$ and

$$2^3 I_1 Z(1) = (2^3 - 1)\tilde{J}_0, \tag{11.26}$$

$$\tilde{J}_{n_j} + \frac{1}{(2^3 - 1)} I_{n_j} = \frac{1}{R_0 Z(n_j)} 2^{-3n_j}. \tag{11.27}$$

where, in addition, we have taken into account the identity $z(n+1)+\rho(n) = z(n)$

First, let us analyse the solution of equations (11.25) and (11.26) when $n \sim 1$. Due to smoothness of the function $\rho(n)$ for such values of n the function $\rho(n)$ as well as $Z(n)$ is supposed to be constant: $\rho(n) \simeq \rho(0) = 1$ and $Z(n) \simeq Z(0) \gg 1$. Then, from (10.23) and (10.24) we get

$$2^3 I_n - I_{n-1} = (2^3 - 1)\frac{1}{Z(0)}\tilde{J}_{n-1} \tag{11.28}$$

and

$$2^3 I_1 = (2^3 - 1)\frac{1}{Z(0)}\tilde{J}_0. \tag{11.29}$$

We shall seek the solution of (11.21), (11.28), and (11.29) in the form

$$\tilde{J}_n = A_+\zeta_+^n + A_-\zeta_-^n \ , \tag{11.30}$$

where $A_{+,-}; \zeta_{+,-}$ are some constants. Substituting (11.30) into (11.21) we get

$$I_n = A_+\zeta_+^{(n-1)}(\zeta_+ - 1) + a_-\zeta_-^{(n-1)}(\zeta_- - 1).$$

Then, the substitution of this expression into (11.28) shows us that the constants ζ_+, ζ_- are the roots of the following equation:

$$(\zeta - 1)(2^3\zeta - 1) = \frac{2^3 - 1}{Z(0)}\zeta . \tag{11.31}$$

Whence, it follows that to the first order in the small parameter $1/Z(0)$:

$$\zeta_+ = 1 + \frac{1}{Z(0)}; \qquad \zeta_- = 2^{-3}\left(1 - \frac{1}{Z(0)}\right). \tag{11.32}$$

To the same order in $1/Z(0)$ from (11.21) and (11.29) we find that the constants A_+, A_- are related by the expression

$$\frac{A_-}{A_+} = \frac{1}{(2^3 - 1)Z(0)} \ll 1. \tag{11.33}$$

According to (11.32) the first term on the right-hand side of (11.30) is an increasing function of n, whereas the second one is a decreasing function. Therefore, by virtue of (11.33) the former is substantially larger than the latter for all $n \sim 1$. So, we may ignore the second term and regard the first one as a function of the continuous variable n. This allows us to set

$$\tilde{J}_n - \tilde{J}_{n-1} = \frac{\partial \tilde{J}_n}{\partial n} \tag{11.34}$$

in equation (11.21), to assume that $I_{n-1} \approx I_n$ in (11.28), and also to rewrite (11.30) in terms of

$$\tilde{J}_n \simeq A_+ \exp\left\{\frac{1}{Z(0)}n\right\} . \tag{11.35}$$

In this case the system of equations (11.21) and (11.28) is reduced to the equation

$$\frac{\partial \tilde{J}_n}{\partial n} = \frac{1}{Z(0)}\tilde{J}_n \tag{11.36}$$

and function (11.35) is the general solution of the latter equation. So, "boundary condition" (11.29) is responsible only for the existence of the second term in (11.30) and, therefore, can be ignored.

As it follows from the form of equations (11.21), (11.22), their general solution contains two arbitrary constants, for example, $\tilde{J}_0, \tilde{J}_1$, as it takes place for the constants A_+, A_- in expression (11.30). Indeed, all the other values of $\tilde{I}_n$ and $\tilde{J}_n$ can be determined by iteration. So, there is no solution of equations (11.21), (11.22) different from (11.30) in the region $n \sim 1$. Thereby, the influence of "boundary condition" (11.23) on the solution of equations (11.21) and (11.22) is ignorable and we may seek this solution in the class of smooth functions of the continuous variable n. In particular, in this case the general solution of equations (11.21), (11.22) contains only one arbitrary constant that can be found from "boundary condition" (11.24).

Within the framework of the assumptions adopted above due to (11.16), and (11.21) the quantities $\tilde{J}_n$ and I_n as well as $\rho(n)$ and $Z(n)$ are related by the expressions

$$I_n = \frac{\partial \tilde{J}_n}{\partial n} , \tag{11.37}$$

$$\rho_n = -\frac{\partial Z(n)}{\partial n} , \tag{11.38}$$

and the system of equations (11.21), (11.25), (11.27) reduces to the following equation

$$\frac{\partial \tilde{J}_n}{\partial n}Z(n) + \tilde{J}_n\frac{\partial Z(n)}{\partial n} = 0 \tag{11.39}$$

subject to the boundary condition

$$\tilde{J}_n \mid_{n=n_j} = 2^{-3n_j}\frac{1}{R_0 Z(n_j)} . \tag{11.40}$$

In obtaining these expressions, we have also taken into account relation (11.34), supposing that $\mid I_{n+1} - I_n \mid \ll I_n$ and $\mid Z(n+1) - Z(n) \mid \ll Z(n)$. Besides,

we have ignored the second term on the left-hand side of (11.27) because $I_{n_j} = \tilde{J}_{n_j-1} - \tilde{J}_{n_j} \ll \tilde{J}_{n_j}$.

The solution of equation (11.39) meeting boundary condition (11.40) is of the form

$$\tilde{J}_n = 2^{-3n_j} \frac{1}{R_0 Z(n)} \tag{11.41}$$

and, thus, from (11.21) and (11.34) we obtain

$$I_n = 2^{-3n_j} \frac{\rho(n)}{R_0 [Z(n)]^2} \; . \tag{11.42}$$

In order to obtain the relation between Λ_{ij} and the quantities $\tilde{J}_n, I_n$ we, first, classify all possible pairs of veins $\{i, i'\}$ into two groups. The first group of the pairs designated by $\{i, i'\}_+$ comprises all pairs of veins that can be joined by a path on the vascular network directed either from higher to lower levels or vice versa, i.e. by a path with a constant direction. Such a path is depicted in Fig. 11.1 by line $O_j O_{i_+}$. The second group involves such pairs of veins $\{i, i'\}_-$ that can be connected by a path on the venous bed whose direction is changed at a certain branching point B as shown in Fig. 11.1 by the curve $O_j O_{i_-}$. In other words, such a path initially goes, for example, from the vein i towards the host vein until it reaches a certain branching point $B_{ii'}$ and then, the path runs towards the vein i going in the opposite direction. In this case we also ascribe to this branching point the level number n_B of the veins going into it and specify the pair $\{i, i'\}_-$ also in terms of $\{i, i', B_{ii'}\}_-$.

If for a vein i whose level number $n_i \leqslant n_j$ the pair $\{ij\}$ belongs to the first group, then, the vein i is one of the veins of the sequence $\{n_j, n_{j-1}, \ldots, 1, 0\}$, viz. vein n_i. In this case as it follows from the definition of the Green matrix $\Lambda_{ij} = \tilde{J}_{n_i}$. Thereby, according to (11.41), for a pair $\{ij\}_+$ where $n_i \leqslant n_j$

$$\Lambda_{ij} = 2^{-3n_j} \frac{1}{R_0 Z(n_i)}. \tag{11.43}$$

A vein i will belong to the last $(n_j + 1)$-th block of branches, if its level number $n_i > n_j$ and this vein along with the vein j forms a pair $\{i, j\}_+$ of the first group. The total number of such veins for a fixed value of n_i is $2^{3(n_i-n_j)}$, and the total blood current in this block is $\tilde{J}_{n_j}$. Since, the blood current $\tilde{J}_{n_j}$ is uniformly distributed among these veins, in anyone of them the blood current is $2^{-3(n_i-n_j)} \tilde{J}_{n_j}$. Therefore, according to the definition of Λ_{ij} and by virtue of (11.41) we obtain the following expression for a pair $\{i, j\}_+$ where $n_i > n_j$:

$$\Lambda_{ij} = 2^{-3n_i} \frac{1}{R_0 Z(n_j)} \; . \tag{11.44}$$

Now let us consider a pair $\{i, j, B_{ij}\}_-$. The given vein i is located in branch block n_B where the total number of veins belonging to the same level n_i is, obviously, $(2^3 - 1)2^{3(n_i - n_B)}$. So, in this case a blood current in the vein i is $(2^3 - 1)^{-1}2^{-3(n_i - n_B)}I_{n_B}$. Whence, by virtue of (11.19) for the pair $\{i, j, B_{ij}\}_-$ we get

$$\Lambda_{ij} = -\frac{1}{2^3 - 1}2^{-3(n_i + n_j - n_B)}\frac{\rho(n_B)}{R_0[Z(n_B)]^2} \ . \tag{11.45}$$

In formula (11.45) the sign '-' means that in the given vein i the blood current Λ_{ij} caused by the additional EPS $\varepsilon_j = 1$ associated with the vein j is directed from lower to higher levels. In other words, this blood current and the total blood current in the vein i, which is induced by the collective action of all the EPSs and the real pressure drop P have opposite directions.

We note that expression (11.17) is actually contained in formula (11.44) as a special case. So, formulae (11.43)-(11.45) specify the desired Green matrix $\parallel \Lambda_{ij} \parallel$ completely. Thereby, these expressions along with definition (11.10), equation (11.12), and relation (11.13) reduce the model for temperature self-regulation developed in Section 4.4 to one dealing with the tissue temperature $T(\mathbf{r}, t)$, the blood flow rate $j(\mathbf{r}, t)$ and the collection of quantities whose evolution is determined by these fields directly. In order to facilitate perception of the proposed model in the following Section we shall briefly review its basic grounds, assumption and relations.

11.3 Governing equations of vascular network response

Within the framework of the proposed model the blood current J_i and the temperature T_i^* of blood in a vessel i, the true and averaged blood flow rate j, j_v and the temperature field T are related by expressions (11.1) and (11.6), (11.7) viz.

$$J_i = \int_{Q_0} d\mathbf{r}\Theta_i(\mathbf{r})j(\mathbf{r}) \ , \tag{11.46}$$

$$(T_i^* - T_a)J_i = \int_{Q_0} d\mathbf{r}\Theta_i(\mathbf{r})(T - T_a)j \tag{11.47}$$

for the unit vessel network, and for the countercurrent vascular network

$$(T_i^* - T_a)J_i = \beta_v(\zeta_v)\int_{Q_0} d\mathbf{r}\Theta_i(\mathbf{r})(T - T_a)j. \tag{11.48}$$

Here $\Theta_i(\mathbf{r})$ is the characteristic function of the domain Q_i, the function $\beta_v(\zeta_v)$ as well the value ζ_v are given by expressions (11.8), (11.9).

The response of the vessels to temperature variations is described in terms of the additional effective pressure sources (EPSs) specified by (11.10), viz.:

$$\varepsilon = -J_i(R_i - R_n^0) \,, \tag{11.49}$$

which evolve according to equation (11.12);

$$\tau_n \frac{d\varepsilon}{dt} + \varepsilon \left[f\left(1 - \frac{\varepsilon}{J_i R_n^0}\right) - \tau_n \frac{d}{dt} \ln J_i \right] = R_n^0 \frac{1}{\Delta} |(T_i^* - T_a)J_i| \,. \tag{11.50}$$

Here τ_n is the characteristic time of the n-th level vessel response, the function $f(x)$ is determined by the quasistationary dependence of the vessel resistances on the blood temperature, (see formula (4.33)), $R_n^0 = R_i|_{T_i^*=T_a}$ as a function of n is described by (4.22).

The given system of equations is completed by relation (11.13) between EPSs and the blood current pattern $\{J_i\}$ on the vascular network

$$J_i = \sum_{i'} \Lambda_{ii'} [\varepsilon_{i'} + P\delta_{n_{i'}0}] \,, \tag{11.51}$$

where P is the true pressure drop across the venous bed and the Green matrix $\Lambda_{ii'}$ is specified by formulae (11.43)-(11.45).

In the following Chapter on the basis of the developed model we shall consider heat transfer in living tissue characterized by ideal temperature self-regulation.

Chapter 12

Theory of ideal
temperature self-regulation

12.1 Ideal response of the vascular network variation

In the present Section we consider heat transfer in a certain idealized living tissue where the vascular network response to temperature variations can control whatever strong heating. By definition (Chapter 3) the thermoregulation process is called ideal when temperature of living tissue under quasistationary heating cannot go out of the vital temperature interval $[T_-, T_+]$. This situation will take place if for each vein i (and artery i) the quasistationary dependence of its resistance R_i^q on the blood temperature T_i^* is of the form $R_i^q(T_i^*) = R_{n_i}^0 \cdot \varphi^{id}((T_i^* - T_a)/\Delta)$ where the function $\varphi^{id}(x)$ is given by formula (4.35). Indeed, in this case, if in a certain domain the tissue temperature were higher than T_+, the temperature of blood in veins through which blood is carried away from the given tissue domain should be higher than T_+ too. Therefore, on the vascular network there would exist a path of zero resistance. The latter would give rise to an infinitely high blood flow rate playing the cooling role, owing to which the tissue temperature in the given domain should drop up to the arterial blood temperature T_a. We note that the countercurrent effect leads to a certain renormalization of the values T_+ and T_- only.

We shall confine ourselves to the following additional assumptions. First, we assume that the heat generation rate $q(\mathbf{r}, t) \geq 0$ at all the points of the tissue domain Q_0 and at its boundary ∂Q_0 the temperature $T \mid_{\partial Q}$ is maintained at the value $T_a (T \mid_{\partial Q_0} = T_a)$ Chapter 4. In this case we may suppose beforehand that the inequalities $T(r, t) \geq T_a$ and $T_i^* \geq T_a$ hold at all the points of the domain Q_0 and for all the vessels. Second, the characteristic time τ_n of the vessel response is assumed to be the same for all the vessels, i.e. $\tau_n = \tau$. Third, we shall ignore the term $\tau_n \frac{d}{dt} \ln(J_i)$ in equation (11.50). This term actually

describes dynamic interaction between EPSs and has no substantial effect on blood flow redistributions over the vascular network at least in the following two possible limit cases. When $\tau \ll \tau_T$, where τ_T is the characteristic time of tissue temperature variations, the vascular network response will be quasistationary, and the term along with the first transient term in (11.50) will be ignorable. When $\tau \gg \tau_T$ and, in addition, the stationary heating of living tissue is not high the value of $\tau_n \frac{d}{dt} \ln(J_i)$ should be negligibly small in comparison with $\tau_n \frac{d}{dt} ln(\varepsilon)$. Indeed, in this case the derivative $\frac{d}{dt} ln(J_i)$ can be estimated as $(\frac{d}{dt} ln(\varepsilon)) \frac{\varepsilon}{P}$ and the stationary value of ε_i/P is a small parameter. Besides, the inequalities $\varepsilon < J_i R_{n_i}^0$ for all the veins are considered to be true in advance because in the given case these assumptions cannot lead to wrong results as it follows from the discussions of equation (12.12). Dealing with the countercurrent vascular network we also assume that the vascular network resistance to blood flow is mainly controlled by large vessels whose level number $n < n_t$ for any values of the blood flow rate.

According to (4.34) and (4.35) for the ideal temperature self-regulation process $f^{\mathrm{id}}(x) = 1$, when $x < 1$. Owing to the adopted assumptions and taking into account expressions (11.46), (11.48) we may rewrite equation (11.50) in the form

$$\tau \frac{d\varepsilon}{dt} + \varepsilon = R_n^0 \frac{1}{\Delta} \beta_{cc} \int_{Q_0} d\mathbf{r} \Theta_i(\mathbf{r})[T(\mathbf{r}) - T_a] j(\mathbf{r}) . \tag{12.1}$$

where $\beta_{cc} = 1$ for the unit vessel network and $\beta_{cc} = [\ln(l_0/a_0)]^{-1/2}$ for the countercurrent vascular network. The latter is justified because dealing with the blood flow redistribution over the countercurrent vascular network may allows for large vessels with $n < n_t$ only.

Expression (11.51) and equation (12.1) enable us to represent J_i in a vein i of level n_i in terms of

$$J_i = J_{ni}^0 + J_i^a , \tag{12.2}$$

where J_{ni}^0 is the blood current when the tissue temperature $T = T_a$ and, thus, $T_i^* = T_a$ for all the veins and the additional blood current J_i^a caused by the self-regulation process obey the equation

$$\tau \frac{dJ_i^a}{dt} + J_i^a = \frac{\beta_{cc}}{\Delta} \int_{Q_0} d\mathbf{r} j(\mathbf{r})[T(\mathbf{r}) - T_a] \sum_{i'} \Lambda_{ii'} R_{n_{i'}}^0 \Theta_{i'}(\mathbf{r}) . \tag{12.3}$$

Expression (12.3) can be significantly simplified. For this purpose in the following subsection we prove a certain identity playing an important role in the theory of thermoregulation.

12.1.1 The ideal thermoregulation identity

Let us show that for a vein i whose level number $1 \ll n_i \ll N$ of lower order in the small parameter $\rho(n_i)/Z(n_i)$

$$\sum_{i'} \Lambda_{ii'} R^0_{n_{i'}} \Theta_{i'}(\mathbf{r}) = \Theta_i(\mathbf{r}) \ . \tag{12.4}$$

Every point $\mathbf{r}$ of the tissue domain Q_0, except points belonging to a set of zero measure, is located inside just one fundamental domain Q_{nr} for each level n. Thereby, practically for any point $\mathbf{r}$ we can specify the collection $\{Q_{nr}\}$ of all the fundamental domains containing the point $\mathbf{r}$. The domain collection $\{Q_{nr}\}$ in its turn specifies the sequence $\{i_{nr}\}$ of connected veins $\{i_o, i_{1r}, i_{2r}, ..., i_{Nr}\}$ whose n-th term is the vein i_{nr} of level n contained in the domain Q_{nr}. The veins $\{i_{nr}\}$ form a continuous path $\mathcal{P}_r$ on the venous bed which leads from the host vein i_0 to the vein i_{Nr} of the last level.

In formula (12.4) the functions $\{\Theta_{i'}(r)\}$ are different from zero for the veins $\{i_{nr}\}$ only, thus,

$$\tilde{\Lambda}_i(\mathbf{r}) \equiv \sum_{i'} \Lambda_{ii'} R^0_{n_{i'}} \Theta_{i'}(\mathbf{r}) = \sum_{i' \in \{i_{nr}\}} \Lambda_{ii'} R^0_{n_{i'}} \ . \tag{12.5}$$

First, let the domain Q_i corresponding to the vein i belong to the domain system $\{Q_{nr}\}$ and, thereby, the vein i of level n_i be one of the veins $\{i_{nr}\}$. Then, for this vein, taking into account expressions (4.22), (11.16), and (11.43)-(11.44) from (12.5) at lower order in $\rho(n_i)/Z(n_i)$ we obtain

$$\tilde{\Lambda}_i(\mathbf{r}) = \sum_{n_{i'}=0}^{n_i-1} \Lambda_{ii'} R^0_{n_{i'}} + \sum_{n_{i'}=n_i}^{N} \Lambda_{ii'} R^0_{n_{i'}} =$$

$$\sum_{n'_i=0}^{n_i-1} 2^{-3(n_i-n_{i'})} \frac{\rho(n_{i'})}{Z(n_{i'})} + \sum_{n'_i=n_i}^{N} \frac{\rho(n_{i'})}{Z(n_i)}$$

thus,

$$\tilde{\Lambda}_i(\mathbf{r}) = 1 + \sum_{p=1}^{n_i} 2^{-3p} \frac{\rho(n_i-p)}{Z(n_i-p)} \simeq 1 \ , \tag{12.6}$$

because of $\rho(n)$ and $Z(n)$ being smooth functions of n.

Now, let the domain Q_i not belong to the collection $\{Q_{nr}\}$ and, thus, the corresponding vein i be none of the veins $\{i_{nr}\}$. In this case on the path $\mathcal{P}_r$ there exists a branching point B of level n_B at which the branch containing the vein i is connected with the path $\mathcal{P}_r$. The branching point B divides the vein sequence $\{i_{nr}\}$ into two parts according to level number. The veins whose level number $n_{ir} < n_B$ form with the vein i pairs $\{i_{nr}, i\}_+$ of the first group, whereas for the veins whose level number $n_{ir} \geq n_B$ the pairs $\{i_{nr}, i\}_-$ belong to the

second group and are of type $\{i_{nr}, i, B\}_-$. Thus, for such a vein i substituting (4.22), (11.44), and (11.45) into (12.5) and, in addition, taking into account (11.16) we obtain

$$\tilde{\Lambda}_i(\mathbf{r}) = \sum_{n_{i'}=0}^{n_B-1} \Lambda_{ii'} R^0_{n_{i'}} + \sum_{n_{i'}=n_B}^{N} \Lambda_{ii'} R^0_{n_{i'}} =$$

$$\sum_{n_{i'}=0}^{n_B-1} 2^{-3(n_i-n_{i'})} \frac{\rho(n_{i'})}{Z(n_{i'})} - \sum_{n_{i'}=n_B}^{N} 2^{-3(n_i-n_B)} \frac{\rho(n_B)\rho(n_{i'})}{Z^2(n_B)}$$

thus,

$$\tilde{\Lambda}_i(\mathbf{r}) = 2^{-3(n_i-n_B)} \left[\sum_{p=1}^{n_B} 2^{-3p} \frac{\rho(n_B - p)}{Z(n_B - p)} - \frac{1}{(2^3 - 1)} \frac{\rho(n_B)}{Z(n_B)} \right] . \qquad (12.7)$$

Due to $\rho(n)$ and $Z(n)$ being smooth functions of n the main contribution to the first term in (12.7) is associated with $p \sim 1$, which allows us to expand the function $\rho(n - p)/Z(n - p)$ in a power series of p. In this way accounting for the two first terms from (12.7) we find

$$\tilde{\Lambda}_i(\mathbf{r}) = \left\{ 2^{-3n_i} \frac{1}{7} \frac{\rho(n_B)}{Z(n_B)} + 2^{-3(n_i-n_B)} . \right.$$

$$\left. \cdot \frac{8}{49} \left[1 - 2^{-3n_B}(n_B + 1) + n_B 2^{-3(n_B+1)} \right] \frac{d}{dn} \frac{\rho(n)}{Z(n)} \bigg|_{n=n_B} \right\} . \qquad (12.8)$$

By virtue of the adopted assumptions for the vein i $n_i \geq n_B$, and $n_i \gg 1$. So, the vein i in the value $\tilde{\Lambda}_i(r)$ differ from zero no more than at the second order in the small parameter $\rho(n)/Z(n)$. Therefore, if the point $\mathbf{r}$ is located inside the domain Q_i corresponding to the vein i, then, the domain Q_i belongs to the collection $\{Q_{n_r}\}$ and, thus, $\tilde{\Lambda}_i(\mathbf{r}) = 1$. When the domain Q_i does not contain the point $\mathbf{r}$ it does not belong to $\{Q_{n_r}\}$, and, at first order in the parameter $\rho(n)/Z(n)$ the value $\tilde{\Lambda}_i(\mathbf{r}) = 0$; whence, we immediately obtain formula (12.4).

12.1.2   Quasilocal equation for the temperature dependence of the blood flow rate

In what follows we shall confine ourselves to lower order in the small parameter $\rho(n)/Z(n)$. Then, identity (12.4) reduces equation (12.3) to the equation

$$\tau \frac{dJ_i^a}{dt} + J_i^a = \frac{\beta_{cc}}{\Delta} \int\limits_{Q_0} d\mathbf{r}\, \Theta_i(\mathbf{r}) j(\mathbf{r})[T(\mathbf{r}) - T_a] \,. \tag{12.9}$$

Let us choose such a small fundamental domain Q_i that its size l_i is well below all the characteristic spatial scales of the fields $j(\mathbf{r})$ and $T(\mathbf{r})$ (however, as before $l_i \gg l_N$). In this case by virtue of (11.46) we may set

$$J_i^a = \int\limits_{Q_0} d\mathbf{r}\, \Theta_i(\mathbf{r})[j(\mathbf{r}) - j_0] = V_i[j(\mathbf{r}) - j_0] \,, \tag{12.10}$$

and

$$\int\limits_{Q_0} d\mathbf{r}\, \Theta_i(\mathbf{r}) j(\mathbf{r})[T(\mathbf{r}) - T_a] = V_i j(\mathbf{r})[T(\mathbf{r}) - T_a] \,, \tag{12.11}$$

where $\mathbf{r}$ is an arbitrary point of the domain Q_i, V_i is its volume, and j_0 is the blood flow rate when the tissue temperature $T(r,t) = T_a$. Expression (12.10) and (12.11) allow us to rewrite equation (12.9) in terms of

$$\tau \frac{\partial j}{\partial t} + j \left[1 - \beta_{cc} \frac{T - T_a}{\Delta} \right] = j_0 \,. \tag{12.12}$$

Equation (12.12) specifies the vascular network response to temperature variations and along with the bioheat equation for the temperature evolution and the relationship between the true and averaged blood flow rates forms the desired description of heat transfer in living tissue with ideal thermoregulation which is called the quasi-local model for .

When deriving equation (12.12) we have assumed a priori that within the framework of the adopted approximations the inequalities $\varepsilon_i < J_i R_{n_i}^0$ are true. The validity of this assumption directly results from (12.12). Indeed, otherwise, according to (11.10) the resistance to blood flow at least in one of the veins would be negative and in this vein the blood current should flow in the opposite direction and at the corresponding points of the tissue domain the blood flow rate would be negative. However, as it follows from (12.12) the blood flow rate j is positive for any value of T if at the initial time $j\mid_{t=t_0} \geq 0$ for all the points of Q_0.

12.2 Mathematical modelling of temperature distribution in living tissue under local strong heating

In the present section we study some characteristic properties of heat transfer in living tissue when the size of the region affected directly can be small or

the tissue heating is significantly nonstationary. We show that under local heating there can be remarkable difference between the averaged and true blood flow rates. So, for bioheat transfer in real living tissues the dependence of the temperature evolution on the averaged blood flow rate rather than the true one can play a significant role. Besides, evolution of the tissue temperature in living tissue due to thermoregulation under strong heating and a similar process in nonbiological media differ markedly in properties. In particular, delay in vessel response can give rise to anomalous behavior of a transient process in living tissue.

The properties of the given model has been analyzed numerically. We have considered the solution of equations (11.46), (11.47) and (12.12) which in the dimensionless form can be rewritten as [62]:

$$\frac{\partial \theta}{\partial t} = \boldsymbol{\nabla}^2 \theta - \eta_v \theta + q_\theta \ , \tag{12.13}$$

$$\eta_v - \frac{1}{L} \boldsymbol{\nabla}^2 \ln \eta_v = \eta \ , \tag{12.14}$$

$$\alpha \frac{\partial \eta}{\partial t} + \eta(1 - \theta) = 1 \ . \tag{12.15}$$

Here, for the unit vessel network $\theta = \beta_{cc}(T - T_a)/\Delta$ is the dimensionless tissue temperature, $\eta = j/j_0$ and $\eta_v = j_v/j_0$ are the dimensionless true and averaged blood flow rates, all the lengths and the time t are measured in units of $[\kappa/(c_t \rho_t j_0)]^{1/2}$ and $1/j_0$ respectively; the constants $\alpha = \tau j_0$; $L \sim (\kappa_{\text{eff}}/\kappa) \ln(l_0/a_0)$; and $q_\theta = q/(c_t \rho_t \Delta)$ are the dimensionless temperature generation rate.

For the countercurrent vascular network $\theta = \frac{(T - T_a)}{\Delta} [\ln(l_0/a_0)]^{1/2}$; $\eta = j/j_0$; $\eta_v = j_v/j_v$, the unit length and the unit time are $\left\{ \kappa_{\text{eff}} \frac{[\ln(l_0/a_0)]^{1/2}}{c_t \rho_t j_v} \right\}^{1/2}$, $[\ln(l_0/a_0)^{1/2}]/j_0$, respectively, $\alpha = \frac{j_0 \tau}{[\ln(l_0/a_0)]^{1/2}}$ and $L = (\kappa_{\text{eff}}/\kappa) \ln(l_0/a_0)$. In numerical calculations we have set $L \sim 4$ because the value l_0/a_0 is typically equal to $30 - 40$ for real microcirculatory beds; $\alpha = 0.5; 3.0$ and obtained the solution of equations (12.13)-(12.15) in unbound one-, two-, and three-dimensional spaces for the following form of the temperature generation rate

$$q_\theta(\mathbf{r}) = q_0 \exp\{-\frac{r}{\lambda_q}\} \ , \tag{12.16}$$

where $\lambda_q = 0.3; 1.0; 3.0$.

Fig. 12.1a,b shows the stationary temperature distribution as well as the stationary distributions of the true and averaged blood flow rates in the three-dimensional space for $\lambda_q = 0.3$. As seen from Fig. 12.1b there is a significant difference between the true blood flow rate and the averaged one when the

Figure 12.1: The stationary tissue temperature θ (a), the true and averaged blood flow rates η, η_v (b) as functions of the radius r in the three-dimensional space ($\lambda_q = 0.3$; $L = 4$, lines 1 and 2 correspond to $q_0 = 0.5; 50$; respectively).

Figure 12.2: The stationary tissue temperature θ_{max} and the blood flow rate η_{max} at $r = 0$ as functions of q_0 (the three - dimentional space, $\lambda_q = 0.3$, $L = 4$, the thin line corresponds to $\eta_{max}(r)$ for $L = \infty$).

temperature field is nonuniform enough and the temperature maximum attains the boundary $T_+(\theta_+ = 1)$ of the vital interval. Therefore, in this case the nonlocality in the dependence of the averaged blood flow rate on the tissue temperature is a factor. To collaborate the last conclusion, Fig. 12.2 shows the maxima of the tissue temperature $\theta_{max} = \theta \mid_{r=0}$ and the
true blood flow rate $\eta_{max} = \eta \mid_{r=0}$ as functions of the value q_0 for the three-dimensional space and $\lambda_q = 0.3$. The solid lines display θ_{max} vs. q_0 and η_{max} vs. q_0 in the given model and the dashed line shows the $\eta_{max}(q_0)$ dependencies in the case where the averaged blood flow rate has been formally replaced by the true one in equation (12.14), i.e., where the nonlocality of the $\eta_v(\theta)$ dependence has been ignored. In Fig. 12.3 we have plotted θ_{max}, η_{max}, and η_{vmax} versus q_0 for the different values of the characteristic size $\lambda_q = 0.3; 1.0$ of the directly heated three-dimensional region. The same dependencies for two- and one-dimensional regions and $\lambda_q = 0.3$ are displayed in Fig. 12.4. As seen from Fig. 12.3 and Fig. 12.4 not only increase in the characteristic size λ_q but also decrease in the dimensionality of the heated region weaken the nonlocality effect of the relation $j_v(T)$.

Characteristics of the transient process for the system being at the state $\{\theta = 0, \eta = 1\}$ at the initial time are shown in Fig. 12.5a,b,c,d for $\alpha = 0.5; 3.0$, and $\lambda_q = 0.3; 3.0$. As it should be expected, when $\lambda_q \gg 1$ and q_0 is not large enough, such as $\theta_{max} \ll 1$ and $\eta \approx 1$, the time increase in the tissue temperature is monotone (Fig. 12.5a). However, if the quantity q_0 is sufficiently large and the tissue temperature θ_{max} attains values of order one during a time less than the delay time of vessel response, then the tissue temperature can go out of the vital interval for a certain time and in the given case the time increase in the tissue temperature is nonmonotone (Fig. 12.5a). Fig. 12.5c,d show that the transient process also possesses, in principle, the same characteristics when the

Figure 12.3: The stationary tissue temperature θ_{max}, the true and averaged blood flow rates η_{max}, η_{vmax} at $r = 0$ as functions of q_0 in the three-dimensional space for $\lambda_q = 0.3$ and 1.0. (parts (a) and (b), respectively).

tissue temperature distribution over living tissue is substantially nonuniform. As it should be expected, nonmonotony of the transient process becomes more pronounced as the characteristic time τ of the vessel response and the size of the region affected directly increase.

Figure 12.4: The stationary tissue temperature θ_{max}, the true and averaged blood flow rates η_{max}, η_{vmax} at $r = 0$ as functions of q_0 in the two- and one-dimensional spaces for $\lambda_q = 0.3$. (parts (a) and (b), respectively).

Figure 12.5: The maximum tissue temperature θ_{max} (a,c) and the maximum blood flow rates η_{max}, η_{vmax} (b,d) vs. the time for the system being initially at the state $\{\theta = 0, \eta = 1\}$. (The three-dimensional space, in the parts (a,b) $\lambda_q = 3.0, \alpha = 3.0$, curves 1,2 correspond to $q_0 = 1.0; 5.0$, respectively; in the parts (c,d) $\lambda_q = 0.3$, curves 1,2,3 correspond to $(q_0 = 5.0, \alpha = 3.0); (q_0 = 15.0, \alpha = 3.0)$ and $(q_0 = 15.0, \alpha = 0.5)$, respectively.

Chapter 13

Heat transfer in living tissue containing a tumor

In the present Chapter we develop a model for heat transfer in living tissue containing a tumor whose diameter is substantially less than the characteristic size of a single microcirculatory bed. Real vascular networks in normal tissues and in tumors differ in architectonics. However, if a given idealized vascular network and the real one give rise to the same pattern of the blood flow rate, then, they will be mathematically equivalent from the heat transfer standpoint. The latter allows us to make use of the model developed in the previous Section for a normal microcirculatory bed after a certain modification of this model.

Typically, for a real tumor response of its vessels to temperature variations as well as variations in concentration of O_2, CO_2, etc. is depressed. So, under a strong heating in normal tissue the blood flow rate can increase by tenfold, whereas in tumors it remains practically at the same level. Under ordinary conditions the blood flow rates in normal tissue and in a tumor can differ little in magnitude (see e.g.,[95]).

13.1 Black spot model of tumor

Keeping the aforementioned in mind we consider the following model for living tissue with a tumor [1, 35]. The vascular network contained in the tissue domain Q_0 is assumed to be of the same geometry as one described in the previous Chapters. The tumor will be treated in terms of a certain fundamental domain Q_t inside which the vessels are distinguished from other normal vessels by their temperature responses. We suppose that the temperature response of the normal vessels is ideal whereas the vessels contained in the tumor domain Q_t do not respond to blood temperature at all. In addition, the resistances of the latter vessels are assumed to have such values that the distribution of the blood flow rate $j_t(\mathbf{r})$ over the tumor domain Q_t is of a given form when the tissue temperature coincides with the arterial blood temperature T_a. Besides, in what

follows for simplicity we shall study only the case $j_t(\mathbf{r}) \geq j_0$. In addition, due to description of heat transfer in living tissue containing the unit vessel network and in tissue with the countercurrent vascular network being the same within the renormalization of the blood flow rate in this Chapter we consider the unit vessel network only.

Let us introduce a new quantity T_s called the seeming temperature that is specified by the expression

$$T_s(\mathbf{r}) = T(\mathbf{r})[1 - \Theta_t(\mathbf{r})] + \left[T_a + \Delta\frac{j_t(\mathbf{r}) - j_0}{j_t(\mathbf{r})}\right]\Theta_t(\mathbf{r}), \qquad (13.1)$$

where $\Theta_t(\mathbf{r})$ is the characteristic function of the tumor domain Q_t. As seen from (13.1) the seeming temperature T_s coincides with the tissue temperature outside the domain Q_t and is independent of time inside this domain. The seeming temperature T_s enables us to specify another system of effective quantities called the effective temperature of blood. We ascribe to each vein i a value $T^*_{\text{eff}\,i}$ that, by definition, is related with the seeming temperature $T_s(\mathbf{r})$ by expression similar to (11.47), viz.,

$$J_i T^*_{\text{eff}\,i} = \int\limits_{Q_0} d\mathbf{r}\,\Theta_i(\mathbf{r})j(\mathbf{r})T_s(\mathbf{r}). \qquad (13.2)$$

In other words, the pattern $\{T^*_{\text{eff}\,i}\}$ of the effective blood temperature, the blood current pattern $\{J_i\}$, and the seeming temperature $T_s(\mathbf{r})$ are related with each other in the same way as do the true blood temperature pattern $\{T^*_i\}$, the blood current pattern $\{J_i\}$, and the true tissue temperature.

Now let us compare the temperature response of the vascular network embedded in the tissue domain containing the tumor with the response of the corresponding normal vascular network whose vessels, however, are sensitive to the effective rather than true blood temperature. First, a small vein contained inside Q_t, carries blood away from a certain part of the domain Q_t. Therefore, according to (13.2), effective temperature of blood in this vein is totally determined by the seeming temperature $T_s(r)$ in the tumor domain Q_t. Thus, for such a small vein sensitive to the effective blood temperature its resistance will keep a constant value regardless of variations in the true temperature. Second, it is possible to ignore the contribution of the tumor domain Q_t to the blood current in a vein whose length l is, at least, twice as large as the mean size l_t of the domain Q_t. Indeed, the total volume of the domain, from which this large vein carries blood away, is about $V \sim (l/l_t)^3 V_t$ where V_t is the volume of Q_t. So, for $l \geq 2l_t$ we may suppose that $V \gg V_t$. Besides, a self-regulation process has a considerable effect on heat transfer only when the tissue temperature approaches near the boundary of the vital temperature interval. In this case blood flow in vessels being in the normal tissue increases essentially, whereas blood flow in vessels located in the tumor can vary sufficiently weaker. The latter also reduces the contribution of the domain Q_t to blood flow in such large veins.

Due to the seeming and true tissue temperature being distinguished in the tumor domain Q_t only, the response of these large veins will be similar for the

two vascular networks. In addition, setting $T(\mathbf{r}) = T_a$ and substituting (13.1) into (12.12) we find that the response of the normal vascular network to the seeming temperature $T_s \mid_{T=T_a}$ leads to the required value of the blood flow rate in the domain Q_t.

Therefore, we may describe the response of the vascular network embedded in the domain containing the tumor in terms of the response of the corresponding normal vascular network to the effective blood temperature. The given approach will be called the black spot model. It should be pointed out that the black spot model can, in principle, give rise to a wrong result when in the tumor $T - T_a \gg T_+ - T_a$. However, such a high heating of the living tissue is not so interesting. We also note that the black spot model can describe the vessel response of the microcirculatory bed when the self-regulation process is not ideal.

Within the framework of the black spot model for the ideal self-regulation process equation (12.12) should be replaced by the equation

$$\tau \frac{\partial j}{\partial t} + j \left[1 - \frac{T_s - T_a}{\Delta} \right] = j_0 \qquad (13.3)$$

or, in agreement with definition (13.1), for $\mathbf{r} \notin Q_t$ by the equation

$$\tau \frac{\partial j}{\partial t} + j \left[1 - \frac{T - T_a}{\Delta} \right] = j_0 \qquad (13.4)$$

and for $\mathbf{r} \in Q_t$ by the expression

$$j = j_t(\mathbf{r}). \qquad (13.5)$$

The system of equations (9.17), (10.24), (13.3) or (13.4), (13.5) forms the desired description of heat transfer in living tissue with a tumor.

13.2 Mathematical modelling of temperature distribution in tissue domain containing a tumour during hyperthermia treatment

Within the framework of the given description the characteristics of the tissue temperature field $T(\mathbf{r}, t)$ and the blood flow rate distribution $j(\mathbf{r}, t)$ have been studied numerically for a tumor of spherical form embedded in the unbound three-dimensional space in which $j_t = j_0$. The model under consideration involves dimensionless equations corresponding to (13.4) and (13.5): for $r < \lambda_t$

$$\eta = 1 \qquad (13.6)$$

and for $r > \lambda_t$

$$\alpha \frac{\partial \eta}{\partial t} + \eta[1 - \theta] = 1, \qquad (13.7)$$

where λ_t (in units of $[\kappa_{\text{eff}}/(c_t\rho_t j_0)]^{1/2}$) is the radius of the tumor. For the sake of simplicity, we have considered uniform stationary heating, i. e., in expression (12.16) set $\lambda_q = \infty$.

Since, the tissue temperature can vary substantially only on spatial scales larger than $\sqrt{(D/j_v)}$ ($\eta_v^{-1/2}$ in the dimensionless units) in heating the tumor whose radius $l_t \gg \sqrt{(D/j_0)}$ (i. e. $\lambda_t \gg 1$) the temperature field will become essentially nonuniform in the vicinity of the tumor already when the tissue temperature attains the middle points of the vital temperature interval. If $l_t \ll \sqrt{(D/j_0)}$ (i. e. $\lambda_t \ll 1$), then, for the nonuniform temperature distribution to occur in the vicinity of such a tumor much stronger heating of the tissue is required. Indeed in this case the blood flow rate j in the normal tissue must first increase substantially and become larger than (D/l_t^2). Therefore, we have analyzed the dependence of the tissue temperature field on the heating power for a small ($\lambda_t < 1$) and ($\lambda_t > 1$) large tumor individually.

Fig. 13.1 shows obtained distributions of the dimensionless tissue temperature $\theta(\mathbf{r})$, the true and averaged blood flow rates $\eta(\mathbf{r}), \eta_v(\mathbf{r})$ for the small tumor whose radius $\lambda_t = 0.3$. The similar results for the sufficiently large tumor of radius $\lambda_t = 3$ are presented in Fig. 13.2. As it should be expected, under ideal thermoregulation the tissue temperature can go out of the vital interval in the tumor only, whereas in the normal tissue the increase in the blood flow rate keeps tissue temperature within this interval. According to Fig. 13.2 the temperature in the large tumor becomes already noticeably different from the normal tissue temperature when the latter attains the value $\theta \sim 0.5$ and in the normal tissue the blood flow rate increases twice. For the small tumor (see Fig. 13.1) the similar difference takes place as the normal tissue temperature comes near to the boundary of the vital interval ($\theta_+ = 1$) and in the normal tissue the blood flow rate increases by tenfold.

We note that once the temperature in the normal tissue has practically attained the upper boundary of the vital interval $T_+ = T_a + \Delta$ ($\theta_+ = 1$) and the temperature in the tumor has become noticeably higher than T_+, the stationary temperature distribution in the tumor domain Q_t can be approximately described by the formal equation

$$\kappa_{\text{eff}}\boldsymbol{\nabla}^2 T - c_t\rho_t j_t(r)(T - T_a) + q = 0 \qquad (13.8)$$

under the boundary condition

$$T\,|_{\mathbf{r}\in\partial Q_t} = T_+ \,, \qquad (13.9)$$

where ∂Q_t is the boundary of the tumor domain Q_t. It also should be pointed out that equation (13.8) contains the true blood flow rate $j_t(\mathbf{r})$ rather than the averaged one $j_v(\mathbf{r})$.

For a large tumor (whose radius $\lambda_t \gg 1$) such replacement is obviously justified. For a small tumor, ($\lambda_t \ll 1$) it also does not lead to wrong results. To validate the latter statement with regard to a small tumor, we analyse the one-dimensional solution of equations (12.13) and (12.14) when $\eta = 1$ for $x > 0$ and $\eta = \eta_n$ for $x < 0$ where $\eta_n \gg 1$ is a constant. By this example we can

Figure 13.1: The distributions of the tissue temperature θ (a), the true (thick line) and averaged (dashed line) blood flow rates η, η_v (b) in the vicinity of the tumour whose radius $\lambda_t = 0.3$ (curves 1,2 correspond to different values of the heat generation rate: $q_0 = 5.0; 15.0$; respectively).

demonstrate qualitatively the main properties of the temperature distribution in the vicinity of an interface separating living tissue regions where the blood flow rates differ significantly in magnitude. Solving equation (12.14) for the given $\eta(x)$ dependence directly we found that in the region $(\eta_n L)^{-1/2} \ll x \ll L^{-1/2}$ the averaged blood flow rate $\eta_v(x) \approx 2(Lx^2)^{-1}$ and $\eta_v(x) \approx 1$ for $x \geq L^{-1/2}$. Thus, on one hand, for $x \gg (\eta_n L)^{-1/2}$ the averaged blood flow rate practically differs from the true one in the region $x \leqslant L^{-1/2}$. On the other hand, according to (12.13) the averaged blood flow rate of value η_v has a considerable effect on the temperature distribution solely on scale larger than $L_\eta \sim \eta_v^{-1/2}$. So, for $\eta_v(x) \sim 2(Lx^2)^{-1}$ the ratio $x/L_\eta \sim (2/L)^{1/2}$ can be regarded as a small parameter when $L \gg 1$ and, thereby, at lower order in $1/L$ we can ignore the term $\eta_v \theta$ in equation (12.13) for $0 < x \leqslant L^{-1/2}$. Therefore, when in the normal tissue the blood flow rate $j \gg (D/l_t^2)$ in order to describe temperature distribution in a small tumor (as well as in a large tumor) we mayreplace in equation (12.13) the averaged blood flow rate by the true one.

Figure 13.2: The distributions of the tissue temperature θ (a), and the true and averaged (dashed line) blood flow rates η, η_v (b) in the vicinity of the tumor whose radius $\lambda_t = 3$ (curves 1,2 correspond to different values of the heat generation rate: $q_0 = 1.0; 15.0$, respectively). Fig.a,b show the distribution along the radius, and Fig.c,d represent the distribution in the plane crossing the tumor domain through the center.

13.3   Two boundary model for freezing of living tissue during cryosurgery treatment

Mathematical analysis of temperature distribution in living tissue during freezing is useful in the study and optimization of cryosurgical treatment. For the last few years a number of different approaches to describing a heat transfer process in living tissue during freezing have been proposed (for a review see [2, 9, 19, 21, 37, 91, 93]). Within the framework of these approaches the obtained bioheat equation is of the form (2.1) Propagation of the freezing front Γ is conventionally described in terms of the free boundary problem of the Stefan-type:

$$v_n \rho_t \mathcal{L} = -(\kappa \boldsymbol{\nabla}_n T) \mid_{\Gamma_+} + (\kappa \boldsymbol{\nabla}_n T) \mid_{\Gamma_-}, \qquad (13.10)$$

$$T \mid_{\Gamma_+} = T \mid_{\Gamma_-} = T_f, \qquad (13.11)$$

where $\mathcal{L}$ is the latent heat of fusion, Γ_+ and Γ_- denote the boundaries of the freezing front on the living and frozen sides of the tissue, respectively, and T_f is the freezing temperature.

A more accurate description of a heat transfer process in living tissue is obtained if one takes into account the fact that living tissue form an active, highly heterogeneous medium. Also, when the size of the frozen region of the tissue is small in comparison with the characteristic length of the blood vessels that directly control heat exchange between the cellular tissue and blood, the heterogeneity of living tissue has a substantial effect on the heat transfer process. Therefore, equation (2.1) which models the blood flow rate in terms of a continuous field $j(\mathbf{r})$ has to be modified [2].

The response of the living tissue to the effects of strong cooling or strong heating can cause the blood flow rate to vary by an order of magnitude. In general, if the temperature distribution in the tissue is substantially nonuniform as, for example, in cryosurgery, then, the temperature dependence of the blood flow rate is nonlocal and the blood flow rate at a given point depends on certain characteristics of the temperature distribution rate other than the tissue temperature at the point only.

In this Section on the developed background we shall formulate a model for the thermal response in living tissue during the freezing process that will include the effects of the aforementioned factors [2].

As it has been shown in Section 13.1 heat transfer in living tissue containing regions where tissue is anomalous in properties can be treated, at least qualitatively, in terms of heat transfer in living tissue where the vascular network responds to an effective (seeming) tissue temperature rather than the real one. Keeping in mind the black spot model we shall describe living tissue freezing as follows. The frozen region is regarded to be a certain fundamental domain Q_f where resistances of the vessels are infinitely great, thereby, the blood flow rate

Figure 13.3: Two boundary model for tissue freezing processes: a - the vessel resistance as a function of the blood temperature, b - characteristic region of living tissue.

in this region is equal to zero; $j_f(\mathbf{r}) = 0$ if $\mathbf{r} \in Q_f$. The frozen domain Q_f is assumed to be small in comparison with the microcirculatory bed domain Q_0. It is natural to treat the freezing temperature T_f as the lower boundary of the vital temperature interval $[T_-, T_+]$, i.e. $T_f = T_-$. Any model for the freezing process should be able to describe propagation of the freezing front Γ where the temperature T_f is attained. Therefore the theory of ideal thermoregulation developed in Chapter 12 in this case cannot be directly used because it leads to infinitely large value of the blood flow rate at $T = T_f$.

The matter is that in this model the flow resistance R_i of a vessel becomes zero at $T = T_f$. For real vascular network vessels reach the limit of expanding as temperature decreases and the vessel resistance attains a certain minimum. This causes the blood flow rate to attain certain large but finite values in the living tissue domain where the temperature $T \gg T_f$. Such behavior of the temperature vessel response will be described in terms of the developed theory of thermoregulation where the blood temperature dependence $R_i(T) = R_n^0 \varphi\left(\frac{T^* - T_a}{\Delta}\right)$ of the vessel resistance is shown in Fig. 13.3a. In the region $T_{vr} < T < T_a$ as for the model of ideal thermoregulation the resistance R_i of a vessel i decreases linearly with the blood temperature T_f^* until its value attains the temperature T_{vr} near the lower boundary T_f of the vital interval. In the region $T_f < T^* < T_{vr}$ the vessel does not respond to temperature variations and its flow resistance R_i is constant and equal to $R_{min} = R_n^0\left(\frac{T_{vr} - T_f}{\Delta}\right)$. In the frozen tissue region, $T < T_f$, the vessel resistance formally becomes infinitely large.

The black spot model developed in Section 13.1 enables us to describe freezing process of living tissue with vessels responding to temperature variations as it has been stated above within in the framework of the following model.

In the frozen region Q_f the tissue temperature evolves according to the

conventional heat conduction equation for solids:

$$c_t\rho_t\frac{\partial T}{\partial t} = \kappa\boldsymbol{\nabla}^2 T - q_f, \tag{13.12}$$

where κ is the intrinsic tissue conductivity and q_f is the rate of tissue cooling.

Inside the unfrozen living tissue its temperature is governed by the equation

$$c_t\rho_t\frac{\partial T}{\partial t} = \kappa_{\text{eff}}\boldsymbol{\nabla}^2 T - j_v c_t\rho_t(T - T_a). \tag{13.13}$$

Here the effective heat conductivity κ_{eff} is related with the intrinsic conductivity κ by the expression $\kappa_{\text{eff}} = \kappa[1 + F_v(G) + F_c(G)]$ (see (8.18)) and, in addition, we have ignored the metabolic heat generation rate and the difference between the densities and heat capacities of the cellular tissue and blood. Following (13.10), (13.11) we assume that propagation of the freezing front $\Gamma = \partial Q_f$ is controlled, in mathematical terms, by conditions

$$v_n\rho_t\mathcal{L} = -\left.(\kappa_{\text{eff}}\boldsymbol{\nabla}_n T)\right|_{\Gamma_+} + \left.(\kappa\boldsymbol{\nabla}_n T)\right|_{\Gamma_-} \tag{13.14}$$

and

$$\left.T\right|_{\Gamma_+} = \left.T\right|_{\Gamma_-} = T_f. \tag{13.15}$$

Inside the unfrozen living tissue there are two regions that are different in thermoregulation properties. In the first one, Q_{vr} (Fig. 13.3), adjacent to the frozen domain Q_f the tissue temperature varies from T_f to T_{vr}, and the blood flow rate is constant and equal to

$$j = j_0\frac{T_a - T_+}{T_{vr} - T_f}. \tag{13.16}$$

In the second region, where $T < T_{vr}$ the blood flow rate is related to the local value of the tissue temperature by the equation

$$\tau\frac{\partial j}{\partial t} + j\frac{T - T_f}{T_a - T_f} = j_0. \tag{13.17}$$

At the interface Γ_{vr} of these two domains

$$\left.T\right|_{\Gamma_{vr}^+} = \left.T\right|_{\Gamma_{vr}^-} \tag{13.18}$$

and

$$\left.\boldsymbol{\nabla}_n T\right|_{\Gamma_{vr}^+} = \left.\boldsymbol{\nabla}_n T\right|_{\Gamma_{vr}^-} \tag{13.19}$$

due to the interface Γ_{vr} containing no heat sink. The averaged and true blood flow rates are related, as before, by the equation

$$j_v - \frac{\kappa}{c_t \rho_t L} \boldsymbol{\nabla}^2 \ln j_v = j. \tag{13.20}$$

At the interface Γ_{vr} the averaged blood flow rate as well as its spatial derivatives is continuous, and at the freezing front Γ, according to (10.28)

$$\boldsymbol{\nabla}_n j_v|_{\Gamma^+} = 0. \tag{13.21}$$

This model allows not only for the phenomena caused by phase transition during freezing living tissue, but also characteristics of living tissue response to substantial cooling as well as nonlocality in heat exchange between the cellular tissue and blood. It should be noted that in spite of this two boundary model containing the collection of equations (13.12) - (13.21) within the framework of this model the temperature distribution can be analyzed not only numerically but also by analytical methods. The variational principles developed for the Stefan type problems, (see., e.g., [27, 28, 29, 30, 31]) allow one to reduce the system of equations (13.12) - (13.21) to interface dynamics of the two regions in living tissue.

It should be noted that not only cryosurgery problem in living tissue can be described by free boundary problem. The similar situation we can meet in the description of the dynamics of local thermal coagulation leading to the necrosis growth limited by heat diffusion into the surrounding live tissue. Dealing with this problem we keep in mind the following process. Absorption of laser light delivered into a small internal region of living tissue causes the temperature to attain such high values (about $70^o C$) that lead to immediate coagulation in this region. Heat diffusion into the surrounding live tissue causes its further thermal coagulation, giving rise to the growth of the necrosis domain. Different mathematical models of the description of the dynamics of local thermal coagulation in live tissue has been considered in [64]-[69] and is outside the problems considered in this manuscript.

Part V

Fluctuations and small scale nonuniformities of the tissue temperature

In the previous Chapters we have actually reduced the bioheat transfer problem to description of heat propagation in a certain homogeneous continuum with complex properties. However, as for any heterogeneous medium, the temperature distribution in living tissue can exhibit spatial nonuniformities and spatiotemporal fluctuations due to the discreteness of vessel arrangement and random time variations of vessel characteristics leading to fluctuations in a blood flow. In this Part we study mean characteristics of spatiotemporal fluctuations and nonuniformities in the tissue temperature treated as random fields [58]. Such parameters as the mean amplitude and the correlation length of the temperature nonuniformities can be used in interpretation of the available experimental data.

Chapter 14

Characteristics of spatial-temporal fluctuations of the tissue temperature

14.1 Fluctuations in the tissue temperature due to time variations of the blood flow rate

In living tissue blood flow in vessels of a vascular network forms branched paths of fast heat transfer as well as fast transport of O_2 and some other components. Owing to this, heat and mass transfer in living tissue possesses specific properties, and the blood flow rate treated in terms of a continuous field $j(\mathbf{r}, t)$ is one of the fundamental characteristics of these processes.

Typically, blood flow in a vessel of length l directly controls the mean blood flow rate in a tissue domain Q whose size is about l, whereas smaller vessels are responsible for blood flow redistribution over different parts of this domain. Therefore, fluctuations in vessel resistance to blood flow in it caused, for example, by time variations in its radius are bound to give rise to spatiotemporal fluctuations in the blood flow rate $j(\mathbf{r}, t)$ in the tissue domain Q which are correlated on spatial scales of order l and on temporal scales determined by the vessel characteristics. These fluctuations in $j(\mathbf{r}, t)$, in their turn, cause spatiotemporal fluctuations in the tissue temperature. Since, the vascular network involves vessels of different lengths, both the tissue temperature and distribution of these components can exhibit fluctuations characterized by a wide range of spatial and temporal scales.

The purpose of this present Chapter is to investigate the characteristics of these fluctuations and their dependence on the vascular network architectonics.

Fluctuations in distribution of O_2, CO_2 etc. are expected to have the same properties.

For the sake of simplicity we assume that the heat capacities as well as the thermal conductivities of the cellular tissue and blood are the same and independent of temperature, the vascular network involves unit vessels only ($n_{cc} = 0$) and consider temperature fluctuations characterized by spatial scales much larger than the length l_{n_t} of vessels directly controlling heat exchange between blood and the cellular tissue. In this case the bioheat equation obtained in Chapters 7, 8 can be rewritten in the form:

$$\frac{\partial}{\partial t}T = D_{\text{eff}}\boldsymbol{\nabla}^2 T - j(T - T_a) + q_h, \tag{14.1}$$

where $j_v \approx j$ under the adopted assumptions. The heat generation rate q_h that is considered to be constant leads to a uniform distribution of the tissue temperature with the mean value $T_0 = T_a + q_h/j_0$ where j_0 is the mean value of the blood flow rate.

We shall account for temperature fluctuations δT caused only by inherent fluctuations in vessel resistances to blood flow. Therefore, linearizing equation (14.1) with respect to δT near T_0 we get

$$\frac{\partial}{\partial t}\delta T = D_{\text{eff}}\boldsymbol{\nabla}^2 \delta T - \left[j_0 + \frac{\partial j}{\partial T}\bigg|_{T=T_0}(T_0 - T_a)\right]\delta T - \delta j(T_0 - T_a), \tag{14.2}$$

where the derivative $\partial j/\partial T$ is associated with the temperature dependence of the blood flow rate and δj is the blood flow rate fluctuations inherent to living tissue. In the general case the derivative $\partial j/\partial T$ is an operator. However, first, when the difference $(T_0 - T_a)$ is substantially less than the width of the vital temperature interval of living tissue, this term is likely to be small enough in comparison with j_0. Second, when the $j(T)$ dependence is a local function it leads to the renormalization of j only. Therefore, the term $\frac{\partial j}{\partial T}(T_0 - T_a)$ in (14.2) will be ignored.

To analyze the characteristics of temperature fluctuations, first, we shall find the correlation function

$$G_{\mathbf{r},t} = \langle\!\langle \delta T_{\mathbf{r}'+\mathbf{r},t'+t}\delta T_{\mathbf{r}',t'}\rangle\!\rangle, \tag{14.3}$$

where symbol $\ll ... \gg$ denotes averaging over both the time t' and the tissue points $\mathbf{r}'$ under the conditions $t =$constant and $|\mathbf{r}|=$constant.

Let us introduce the correlation function of the blood flow rate fluctuations

$$\Omega_{\mathbf{r},t} = \langle\!\langle \delta j_{\mathbf{r}'+\mathbf{r},t'+t}\delta j_{\mathbf{r}',t'}\rangle\!\rangle. \tag{14.4}$$

Then taking into account adopted assumptions from (14.2) we obtain the following relationship between the Fourier transforms of the above two correlation

functions (14.3) and (14.4) with respect to both the time t and the coordinates **r**:

$$G(\mathbf{k}, w) = (T_0 - T_a)^2 \frac{\Omega(\mathbf{k}, w)}{w^2 + (D_{\text{eff}} k^2 + j_0)^2}. \tag{14.5}$$

Here w and $\mathbf{k}$ are the variables conjugate to t and $\mathbf{r}$, respectively. It should be pointed out that when averaging the product $(\delta j \delta j)$ in (14.4) over the time t' only we get the function

$$\Omega_{\mathbf{r'r},t} = \langle \delta j_{\mathbf{r'},t'+t} \delta j_{\mathbf{r'},t} \rangle, \tag{14.6}$$

which depends on both the variables $\mathbf{r'}, \mathbf{r}$. This nonuniformity will be discussed below.

Since, in the case under consideration the mean tissue temperature is constant in the domain Q_0 the blood temperature in all the veins is practically the same. Therefore, implying the mean values all veins and arteries of one level, for example, level n must be characterized by the same flow resistance (see (4.22))

$$R(n) = R_0 \varphi \left(\frac{T_0 - T_a}{\Delta} \right) 2^{3n} \rho(n). \tag{14.7}$$

Within the framework of the adopted model we may confine our consideration to the venous bed only the pressure drop P across which is assumed to be constant.

Random time variations of the blood flow are caused by fluctuations of the vessel parameters, in particular, vessel radius, biochemical blood composition, etc. All these factors eventually give rise to random time variations of the vessel resistances. So, in the present Section time variations of blood flow rate are considered to occur because of fluctuations in the vessel resistances. In addition, for the sake of simplicity, fluctuations in the flow resistance of a vessel are characterized by a single correlation time.

For a given vein, for example vein i, fluctuations $\delta R_i(t)$ in their resistance are described by a correlation time $1/w(n)$ which can depend on the vein level number n. In other words, we represent the correlation function of these fluctuations in the form

$$\langle \delta R_i(t + t') \delta R_i(t') \rangle = R^2(n_i) \epsilon \Delta(n_i) \exp(-w(n_i) |t|), \tag{14.8}$$

where ϵ is a small constant ($\epsilon \ll 1$), the function $\Delta(n)$ accounts for specific details of the correlation function dependence on n and $\Delta(0) = 1$. In particular, $\Delta(n)$ is a smooth function of n providing that the resistance $R(n)$ is a power function of a, and the ratio $\langle (\delta a_n)^2 \rangle / a_n^2$ depends smoothly on n. Therefore, in the following for the sake of simplicity we shall regard both $\Delta(n)$ and $w(n)$ as smooth functions of n. For different vessels fluctuations in their resistances are assumed to be uncorrelated.

14.2 Correlation function of the blood flow rate fluctuations

In order to find blood flow redistribution over the vascular network caused by time variations of the vessels resistances and, thereby, to obtain time variations in the blood flow rate distribution over living tissue, we should solve the system of the Kirchhoff equations (4.18), (4.19) to the first approximation in ε due to $\varepsilon \ll 1$.

At lower order in ε, i.e. when fluctuations in the resistances $\delta R_i(t)$ are not accounted for, the solution of the equations (4.18), (4.19) describes the uniform distribution of blood flow over the vascular network and is of the form

$$J_i = J_0(n_i) = 2^{-3n_i} J_0, \tag{14.9}$$

where n_i is the level number of the vein i and J_0 is the total blood current in the tree stem. Then, actually following the procedure proposed in Section 11.2. Due to $\varepsilon \ll 1$ to the first order in $\delta R_i(t)$ equation (4.19) can be replaced by the equation

$$J_i R(n_i) = \Delta P_i - J_0(n_i)\delta R_i(t). \tag{14.10}$$

Equations (14.9) and (14.10) may be regarded as the system of the Kirchhoff equations describing blood flow distribution over a certain vascular network of the same architectonics where, however, the vessel resistances $R(n_i)$ are constant values and there are some random effective pressure sources

$$\varepsilon_i = -J_0(n_i)\delta R_i(t) \tag{14.11}$$

associated with these vessels. Being pairwise independent and random quantities these effective pressure sources $\{\varepsilon_i\}$ cause fluctuations in the blood currents. As shown in Section 11.2 and Section 11.3 linearity of equations (14.10), (14.11) with respect to the blood currents allows us to represent the solution of these equations in terms of

$$J_i = J_0(n_i) + \sum_{i'} \Lambda_{ii'}\varepsilon_{i'}, \tag{14.12}$$

where the sum runs over all the arteries, and the elements of the matrix $\|\Lambda_{ii'}\|$ are specified in the following way (see Section 11.3 expressions (11.43) - (11.45)). Let us denote by $\{ii'\}_+$ such a pair of veins i and i' that can be joined by a path of constant direction on the vascular network. This path may be directed either from higher to lower levels or vice versa (the vein pair $\{i_1, i_2\}_+$ in Fig. 14.1a). Then, for a vein pair $\{ii'\}_+$ where $n_i < n_{i'}$

Figure 14.1: Schematic representation of the vein tree.

$$\Lambda_{ii'} = \frac{1}{R_* Z(n_i)} 2^{-3n_i'} \tag{14.13}$$

and for $n_i > n_i'$

$$\Lambda_{ii'} = \frac{1}{R_* Z(n_i')} 2^{-3n_i}. \tag{14.14}$$

Here $R_* = R_0 \varphi \left(\frac{T^* - T_a}{\Delta} \right)$, $Z(n)$ is the function defined by formula (11.16). The other pairs of veins $\{ii'\}_-$ are characterized by paths with variable directions, i.e. for a pair $\{ii'\}_-$ the veins i, i' can be joined by a path whose direction becomes opposite at a certain branching point $B_{ii'}$ (the vein pair $\{i_2, i_3\}$ in Fig. 14.1a). Let us ascribe to a branching point B the level n of a vein, that goes in it. Then,

$$\Lambda_{ii'} = -\frac{\rho(n_{B_{ii'}})}{7 R_* Z^2(n_{B_{ii'}})} 2^{3(n_{B_{ii'}} - n_i - n_j)}. \tag{14.15}$$

It should be pointed out that because of $Z(n)$ being a smooth function the ratio $\rho(n)/Z(n)$ can be treated as a small parameter.

According to (4.20) the relationship between the blood current pattern $\{J_i\}$ and the blood flow rate $j(\mathbf{r})$ is determined by the formula $J_{i_r} = V_N j(\mathbf{r})$ where i_r is the last level vein contained among with the point $\mathbf{r}$ in the same fundamental domain Q_{Nr} of volume V_N. This formula and expression (14.12) enable us to represent the correlation function (14.6) in the form:

$$\Omega_{r,r',t} = \frac{1}{V_N^2} \sum_i \sum_{i'} \Lambda_{i_r i} \Lambda_{i_{r'} i'} \langle \varepsilon_i \varepsilon_{i'} \rangle. \tag{14.16}$$

Then, substituting formula (14.11) into (14.16) and taking into account expression (14.8) and pair wise independence of the vessel resistance fluctuations of each other we can rewrite (14.16) as

$$\Omega_{\mathbf{r},\mathbf{r}',t} = \frac{\epsilon}{V_N^2} \sum_i \Lambda_{i_\mathbf{r} i} \Lambda_{i_{\mathbf{r}'} i} J_0^2(n_i) R^2(n_i) \exp\{-w(n_i)t\} \Delta(n_i). \tag{14.17}$$

In order to calculate sum (14.17) we divide all the veins into four groups and consider their contribution into sum (14.17) individually. The first group involves veins that form the first type pairs with both the venules, i.e. all the veins $\{i\}$ for which $\{i_r, i\} = \{i_r, i\}_+$ and $\{i_r, i\} = \{i_{r'}, i\}_+$. These veins make up a path on the vein tree that originates at the branching point $B_{rr'}$ (Fig. 14.1a) where blood streams in the venules i_r and $i_{r'}$ merge into one stream and terminates at the tree stem. In Fig. 14.1b the given path is displayed by the

solid line. For each of this group, for example, vein i the value $\Lambda_{i_r i}$ is determined by expression (14.14), i.e.

$$\Lambda_{i_r i} = 2^{-3N} \frac{1}{R_*} \frac{1}{Z(n_i)} \tag{14.18}$$

because $n_{i_r} = N$. The same expression gives the value $\Lambda_{i_{r'} i}$. Then, the contribution $\Omega^{(1)}_{r,r',t}$ to expression (14.17) is of the form

$$\Omega^{(1)}_{r,r',t} = \frac{\epsilon}{V_N^2} 2^{-6N} J_0^2 \sum_{n_i=0}^{n_{rr'}-1} \left[\frac{\rho(n_i)}{Z(n_i)} \right]^2 \Delta(n_i) \exp(-w(n_i)\,|t|), \tag{14.19}$$

where $n_{rr'}$ is the level number of the branching point $B_{rr'}$ and we have taken into account the identity

$$\frac{1}{R_*^2} J_0^2(n_i) R^2(n_i) = J_0^2 [\rho(n_i)]^2. \tag{14.20}$$

The second group consists of the veins that belong to one of the two paths on the vein tree which join the venule i_r and venule i_r with the branching point $B_{rr'}$. All these veins $\{i\}$ form either the pairs $\{i_r, i\}_+$ and $\{i_{r'}, iB_{rr'}\}_-$ or the pairs $\{i_{r'}, iB_{rr'}\}_-$ and $\{i_{r'}, i\}_+$, which is illustrated in Fig. 14.1c. For this part of the vein tree formula (14.18) gives the values $\Lambda_{i_r i}$ and $\Lambda_{i_{r'} i}$ for $\{i_r, i\}_+$ and $\{i_{r'}, i\}_+$ and formula (14.18) becomes

$$\Lambda_{i_r i} = -\frac{1}{7R_*} 2^{-3N} \frac{\rho(n_{rr'})}{[Z(n_{rr'})]^2} 2^{-3(n_i - n_{rr'})} \tag{14.21}$$

or $\{i_r, i, B_{rr'}\}_-$ and the same expression for $\{i_{r'}, i, B_{rr'}\}$. The two paths determine an equal contribution to the sum (14.17), thus, the summand in (14.17) associated with these veins is

$$\Omega^{(2)}_{r,r',t} = -\frac{2\epsilon}{V_N^2} 2^{-6N} J_0^2 \sum_{n_i=n_{rr'}}^{N} \frac{1}{7} \frac{[\rho(n_i)]^2 \rho(n_{rr'})}{Z(n_i)[Z(n_{rr'})]^2} 2^{-3(n_i - n_{rr})} .$$

$$\cdot \Delta(n_i) \exp(-w(n_i)\,|t|) \tag{14.22}$$

Due to $\rho(n), Z(n), \Delta(n)$ and $w(n)$ being smooth functions of n the value $\Omega^{(2)}_{r,r',t}$ can be estimated as

$$\Omega^{(2)}_{r,r',t} \sim -\frac{2}{7} \frac{2\epsilon}{V_N^2} 2^{-6N} J_0^2 \left[\frac{\rho(n_{rr'})}{Z(n_{rr'})} \right]^3 \Delta(n_{rr'}) \exp(-w(n_{rr'})t) \tag{14.23}$$

because in (14.22) the terms with $n_i \approx n_{rr'}$ determine the main contribution. The third group involves all the veins belonging to the branch with the node at the branching point $B_{rr'}$ except for the veins of the second group. (Fig. 14.1d). Each vein of the third group, for example, vein i with venules i_r and $i_{r'}$ forms either pairs $\{i_r, i, B\}_-$ and $\{i_{r'}, i, B_{rr'}\}_-$ or $\{i_r, i, B_{rr'}\}$ and $\{i_{r'}, i, B\}$ where B is a certain branching point belonging to one of the paths made up of the second group veins. For pairs similar to $\{i_r, i, B_{rr'}\}$ the values $\Lambda_{i_r i}$ and $\Lambda_{i_{r'} i}$ are given by formula (14.21) According to (4.17) such pairs as $\{i_r, i, B\}$ correspond to

$$\Lambda_{i_r i} = -\frac{1}{7R_*} 2^{-3N} \frac{\rho(n_B)}{[Z(n_B)]^2} 2^{-3(n_i - n_B)}. \tag{14.24}$$

For fixed level numbers n_B and $n_i \geq n_B$ the total number of veins is $2(2^3 - 1)2^{3(n_i - n_B)}$. Therefore, the corresponding summand in (14.17) is equal to

$$\Omega^{(3)}_{r,r',t} = -\frac{\epsilon}{V_N^2} 2^{-6N} J_0^2 \sum_{n_B = n_{rr'}}^{N} \sum_{n_i = n_B}^{N} \frac{2}{7} 2^{3(n_i - n_B)} \cdot$$

$$\cdot \frac{[\rho(n_{rr'})]^2 \rho(n_B)[\rho(n_i)]^2}{[Z(n_{rr'})]^2 [Z(n_B)]^2} 2^{-3(2n_i - n_{rr} - n_B)} \Delta(n_i) \exp(-w(n_i)|t|). \tag{14.25}$$

As before, the terms with $n_i \sim n_B \sim n_{rr'}$ give the main contribution to (14.25). So,

$$\Omega^{(3)}_{r,r',t} \sim \frac{2}{7} \frac{\epsilon}{V_N^2} 2^{-6N} J_0^2 \left[\frac{\rho(n_{rr'})}{Z(n_{rr'})}\right]^4 \Delta(n_{rr'}) \exp(-w(n_{rr'})t). \tag{14.26}$$

The forth group of veins consists of the remaining veins. All these veins form with venules $i_r, i_{r'}$ the pairs of the type $\{i_r, i, B\}_-, \{i_{r'}, i, B\}_+$ where B is a certain branching point on the path made up of the first group veins (Fig. 14.1e). In this case the values $\Lambda_{i_r i}$ and $\Lambda_{i_{r'} i}$ are of the form (14.24) for the fixed number of n_B and n_i the total number of the veins is $(2^3 - 1)2^{3(n_i - n_B)}$. Whence we get the following expression for the corresponding summand

$$\Omega^{(4)}_{r,r',t} = \frac{\epsilon}{V_N^2} 2^{-6N} J_0^2 \sum_{n_B = 0}^{n_{rr'} - 1} \sum_{n_i = n_B}^{N} \frac{1}{7} 2^{3(n_i - n_B)} \cdot$$

$$\cdot \frac{[\rho(n_B)]^2 [\rho(n_i)]^2}{[Z(n_B)]^4} 2^{-6(n_i - n_B)} \Delta(n_i) \exp(-w(n_i)|t|). \tag{14.27}$$

Since, $\rho(n_i)$ is a smooth function of n, when summing over n_i in (4.32) we may set $\rho(n_i) = \rho(n_B)$. In this way from (4.32) we get

$$\Omega^{(4)}_{r,r',t} = \frac{\epsilon}{V_N^2} 2^{-6N} J_0^2 \frac{8}{49} \sum_{n_B=0}^{n_{rr'}-1} \left[\frac{\rho(n_B)}{Z(n_B)} \right]^4 \Delta(n_B) \exp(-w(n_B)\,|t|). \qquad (14.28)$$

Due to $\rho(n)$ being a smooth function of n for $N-n \gg 1$ the ratio $\rho(n)/Z(n) \ll 1$ is a small parameter. Therefore, comparing $\Omega^{(i)}_{r,r',t}$ with each other we find that the main contribution to the value $\Omega_{r,r',t}$ is given by the first group veins. So, formula (14.19) enables us to the represent (14.17) as

$$\Omega_{r,r',t} = \epsilon j_0^2 \int_0^{n_{rr'}} dn \left[\frac{\rho(n)}{z(n)} \right]^2 \Delta(n) \exp(-w(n_B)\,|t|) \qquad (14.29)$$

Here we have taken into account that the mean total blood current flowing through the vein tree and the mean value j_0 of the blood flow rate are related by the expression $J_0 = 2^{3N} V_N j_0$ and have converted the sum with respect to n into the integral over the continuous variable n.

Formula (4.34) is the desired expression for the correlation function of blood flow rate fluctuations. The spectral density of these fluctuations is the Fourier transform of the correlation function with respect to the time

$$\Omega_{\mathbf{r},\mathbf{r}'}(w) = 2\epsilon j_0^2 \int_0^{n_{\mathbf{r},\mathbf{r}'}} dn \left[\frac{\rho(n)}{Z(n)} \right]^2 \Delta(n) \frac{w(n)}{w^2(n) + w^2}. \qquad (14.30)$$

The mean distance r between the arteries $i_{\mathbf{r}}, i_{\mathbf{r}'}$ of the pairs $\{ii'\}$ corresponding to the same branching point $B_{\mathbf{rr}'}$ can be estimated as $r \sim l_{n_{\mathbf{rr}'}} = l_0 2^{-n_{\mathbf{rr}'}}$, thereby $n_{\mathbf{rr}'} \sim log_2(l_0/r)$. Due to the latter estimate and $\Omega_{\mathbf{r},\mathbf{r}'}(w)$ being a smooth function of $n_{\mathbf{rr}'}$ on averaging (14.30) over the cube Q_0 for $r \ll l_0$ we may set.

$$\Omega_{\mathbf{r}}(w) \approx \Omega_{\mathbf{r}',\mathbf{r}}(w)\big|_{n_{\mathbf{rr}'}=\log_2(l_0/r)}. \qquad (14.31)$$

In the next Section based on the obtained results we shall discuss some characteristic properties of spatia - temporal fluctuations in the tissue temperature which are caused by random time variations of the vessel parameters.

14.3 Characteristics of the tissue temperature fluctuations on different scales

It is natural to assume that the characteristic time $1/w(n)$ of the vessel resistance fluctuations decreases with vessel length. So, the value $w(n)$ is likely to be an

increasing function of n. Typically the resistance of the vascular network to blood flow is mainly determined by large vessels rather than small venules and arterioles. Thus, in the given model we must assume that the function $j(n)$ is an decreasing function of n such that the formal integral

$$\int_0^\infty \rho(n)dn$$

is convergent. The aforementioned allows us to consider in more detail the special case where $\Delta(n) = 1, w(n) = w_0 \exp(n\nu_w)$ and $\rho(n) = \rho(0) \exp(-n\nu_\rho)$, when ν_w and ν_ρ are small positive constants but $\nu_w N$, $\nu_\rho N \gg 1$. In this case as it follows from (14.30),(14.31) within the frequency interval $w(0) \ll w \ll w(N)$

$$\Omega_{\mathbf{r}}(w) \approx 2\epsilon j_0^2 \frac{\nu_\rho^2}{\nu_w} \frac{1}{w} \tan^{-1}\left[\frac{w_0}{w}\left(\frac{l_0}{r}\right)^{\nu_w/\ln 2}\right]. \tag{14.32}$$

In particular, if $w \ll w_r = w_0(l_0/r)^{(\nu_w/\ln 2)}$

$$\Omega_{\mathbf{r}}(w) \approx \pi\epsilon j_0^2 \frac{\nu_\rho^2}{\nu_w} \frac{1}{w} \tag{14.33}$$

and for $w \gg w_r$

$$\Omega_{\mathbf{r}}(w) \approx 2\epsilon j_0^2 \frac{\nu_\rho^2}{\nu_w} \frac{w}{w^2} \left(\frac{l_0}{r}\right)^{\nu_w/\ln 2}. \tag{14.34}$$

According to (14.5) on spatial scales r where $Dr^{-2} \ll j_0$ or $Dr^{-2} \ll w$ the Fourier transform $G_{\mathbf{r}}(w)$ of the correlation function $G_{\mathbf{r},t}$ is directly specified by the function $\Omega_{\mathbf{r}}(w)$, viz.

$$G_{\mathbf{r}}(w) \simeq \frac{(T_0 - T_a)^2}{w^2 + j_0^2}\Omega_{\mathbf{r}}(w). \tag{14.35}$$

In particular, as it follows from (14.33) and (14.35) if $w(0) \ll j_0$ then, there is a frequency interval $w(0) \ll w \ll w_r, j_0$ where

$$G_{\mathbf{r}}(w) \sim 1/w, \tag{14.36}$$

i.e. in this case fluctuations in the living tissue temperature can exhibit $1/f$ behavior.

Concluding the present Section we would like to point out that there is a certain spatial nonuniformity of the correlation function caused by the vascular

network architectonics. Indeed, in neighborhoods of the points A and A' being at a small distance from each other heat transfer can be controlled by different branches of the arterial bed. Owing to this, in one direction fluctuations in the blood flow rate and, correspondent, in the tissue temperature could be correlated, whereas in the opposite direction such correlations are practically absent. In addition we note, that because the typical values of the blood flow rate are about $j \sim 10^{-2} \div 10^{-3} s^{-1}$ according to (14.35) the fluctuations of the tissue temperature can exhibit $1/f$ behavior for sufficiently low frequencies. However, fluctuations in the blood flow rate can exhibit $1/f$ behavior in substantially wider frequency interval (see formula (14.33)) and can cause similar fluctuations in other physical quantities in living tissues.

Chapter 15

Small scale nonuniformities of the tissue temperature

From the standpoint of heat transfer living tissue is a highly heterogeneous medium. So, the tissue temperature will exhibit spatial nonuniformities even though a living tissue domain that contains a single microcirculatory bed of a simple structure is uniformly heated. In this case spatial nonuniformities of the tissue temperature are determined by intrinsic properties of living tissue as a heterogeneous medium and may be considered in terms of random fields.

There are two different type nonuniformities in the temperature. The first type nonuniformities occur due to influence of blood flow in large vessels and occur in certain regions whose relative volume is not large. So, description of these nonuniformities cannot be reduced to continuum approximation and should be considered individually [53, 75, 85]. The second type nonuniformities of the tissue temperature are caused by relatively small vessels of level n_t which directly control heat exchange between the tissue and blood. The nature of these temperature nonuniformities is the discreteness of vessel arrangement. We note that a similar formulation of this problem has been stated in [7].

In the present Chapter we shall examine the main properties of such random temperature nonuniformities, in particular, their mean amplitude and correlation length, which are fundamental characteristics of heat transfer in living tissue.

15.1 The tissue temperature nonuniformities due to random vessel arrangement

For the sake of simplicity we confine ourselves to limit (7.28) where the capillary system has no significant effect on heat transfer, the length l_N of the last level vessels (arterioles and venules) is well below l_{n_t} and spatial nonuniformities in the tissue temperature distribution are mainly caused by arrangement of the

n_t-th level arteries and veins. It should be pointed out that these assumptions are justified for real microcirculatory beds because for typical values of $j \sim 10^{-3}s^{-1}$; $\kappa \sim 7 \cdot 10^{-3}J/cm \cdot s \cdot K$, $\rho_t \sim 1g/cm$, $c_t \sim 3.5J/g \cdot K$ and setting $l_0/a_0 \sim 40$ from (8.14), (8.15) we get $l_{n_t} \sim 0.5cm$, which is well above the characteristic length of real capillaries. In this case, as it follows from (8.18), the stationary tissue temperature obeys the equation

$$\kappa_{\mathrm{eff}}\boldsymbol{\nabla}^2 T - c_t\rho_t jf[1 + \chi_t(\mathbf{r})](T - T_a) + q_h = 0, \tag{15.1}$$

where

$$f = \left[\ln\frac{l_0}{a_0}\right]^{(\beta(n_t)-1)/2},$$

i.e. $f = 1$ for the unit vessel network and $f = [\ln(l_0/a_0)]^{-1/2}$ for the counter-current vascular network, the blood flow rate j and the heat generation rate q_h are assumed to be constant over the domain Q_0, the random field $\chi_t(\mathbf{r})$ satisfies relations (8.11), (8.12) and according to (8.14), (8.15) its characteristic correlation length

$$l_t = \left[\frac{3\sqrt{3}\pi}{4}\frac{\kappa}{f\rho_t c_t \ln(l_0/a_0)j}\right]^{1/2}. \tag{15.2}$$

By virtue of (7.10) the maximum of the correlation function $g(x)$ is $g(0) \sim 0.16$. Therefore, in equation (15.1) the random field $\chi_t(\mathbf{r})$ as well as the nonuniform component $T^{\sim}(\mathbf{r})$ of the tissue temperature associated with this field can be treated as small quantities. Then, linearizing equation (15.1) with respect to $\chi_t(\mathbf{r})$ and $T^{\sim}(\mathbf{r})$ we get

$$\kappa_{\mathrm{eff}}\boldsymbol{\nabla}^2 T^{\sim} - c_t\rho_t jf T^{\sim} = c_t\rho_t jf(T^{(0)} - T_a)\chi_t(\mathbf{r}), \tag{15.3}$$

where the uniform component of the tissue temperature

$$T^{(0)} = \frac{q_h}{f\rho_t c_t j} + T_a. \tag{15.4}$$

For the Fourier transforms of the functions $T^{\sim}(\mathbf{r})$ and $\chi_t(\mathbf{r})$:

$$T_F(\mathbf{k}) = \frac{1}{(2\pi)^{3/2}}\int\limits_{Q_0} d\mathbf{r}e^{-i\mathbf{k}\mathbf{r}}T^{\sim}(\mathbf{r}) \tag{15.5}$$

and

$$\chi_F(\mathbf{k}) = \frac{1}{(2\pi)^{3/2}} \int\limits_{Q_0} d\mathbf{r} e^{-i\mathbf{k}\mathbf{r}} \chi_t(\mathbf{r}) \tag{15.6}$$

equation (15.3) takes the form

$$(k^2 \kappa_{\text{eff}} + c_t \rho_t j f) T_F(\mathbf{k}) = -\rho_t c_t j f (T^{(0)} - T_a) \chi_F(\mathbf{k}). \tag{15.7}$$

Here the domain Q_0 may be regarded as the unbounded three - dimensional space $\mathcal{R}^3$, and $\mathbf{k}$ is a point of the wave vector space $\mathcal{R}_F^3$. Besides, by virtue of (7.10), (8.11) and (8.12) the random field $\chi_F(\mathbf{k})$ obeys the conditions

$$\langle \chi_F(\mathbf{k}) \rangle = 0 \tag{15.8}$$

and

$$\langle \chi_F(\mathbf{k}) \chi_F(\mathbf{k}') \rangle = \delta(\mathbf{k} + \mathbf{k}') \int d\mathbf{r} e^{-i\mathbf{k}\mathbf{r}} g\left(\frac{|\mathbf{r}|}{l_t}\right) =$$

$$= \delta(\mathbf{k} + \mathbf{k}') \left(\frac{4}{3} l_t^2\right)^{3/2} \left\{ \exp\left[-\frac{2}{3\pi} l_t^2 k^2\right] - \exp\left[-\frac{1}{\pi} l_t^2 k^2\right] \right\}, \tag{15.9}$$

where $\delta(\mathbf{k})$ is the δ - function in the space $\mathcal{R}_F^3$, and also we have taken into account the identity

$$\int\limits_{\mathcal{R}^3} d\mathbf{r} \exp(i\mathbf{k}\mathbf{r}) = (2\pi)^3 \delta(\mathbf{k}). \tag{15.10}$$

For (15.5) the inverse transform is

$$T^\sim(\mathbf{r}) = \frac{1}{(2\pi)^{3/2}} \int\limits_{\mathcal{R}_F^3} d\mathbf{k} \exp(i\mathbf{k}\mathbf{r}) T_F(\mathbf{k}). \tag{15.11}$$

Thereby, due to (15.2) and (15.7) - (15.9) random nonuniform component $T^\sim(\mathbf{r})$ of the tissue temperature obeys the conditions

$$\langle T^\sim(\mathbf{r}) \rangle = 0 \tag{15.12}$$

and

$$\langle T^\sim(\mathbf{r}) T^\sim(\mathbf{r}') \rangle = (T^{(0)} - T_a)^2 g_T\left(\frac{|\mathbf{r} - \mathbf{r}'|}{l_t}\right), \tag{15.13}$$

where the correlation function g_T of the temperature random nonuniformities is specified by the expression

$$g_T\left(\frac{|\mathbf{r}|}{l_t}\right) = \frac{1}{(2\pi)^3}\int\limits_{\mathcal{R}_F^3} d\mathbf{k}\left(\frac{4}{3}l_t^2\right)^{3/2}\exp\left[il_t\mathbf{k}\left(\frac{\mathbf{r}}{l_t}\right)\right]\left\{\exp\left[-\frac{2}{3\pi}l_t^2k^2\right]-\right.$$

$$\left.-\exp\left[-\frac{1}{\pi}l_t^2k^2\right]\right\}\left[1+\frac{4}{3\sqrt{3}\pi}L_nl_t^2k^2\right]^{-2}. \tag{15.14}$$

where $L_n = (\kappa_{\text{eff}}/\kappa)\ln(l_0/a_0)$.

Expressions (15.13) and (15.14) specify the desired correlation function of the random nonuniformities in the tissue temperature. In the given model the value L_n is regarded as a large parameter. The latter enables us to simplify formula (15.14) and, thus, to analyse in more detail characteristic properties of these temperature fluctuations.

15.2   Correlation function of temperature nonuniformities and their characteristic properties

Converting from the variable $\mathbf{k}$ to the new variable $\mathbf{p} = (1/\sqrt{\pi})l_t\mathbf{k}$ integral (15.14) can be rewritten as

$$g\left(\frac{|\mathbf{r}|}{l_t}\right) = \frac{1}{(3\pi)^{3/2}}\int\limits_{\Re^3} d\mathbf{p}\exp\left[i\sqrt{\pi}\mathbf{p}\frac{\mathbf{r}}{l_t}\right]\left(\exp\left[-\frac{2}{3}p^2\right]-\right.$$

$$\left.-\exp[-p^2]\right)\left[1+\frac{4}{3\sqrt{3}}L_np^2\right]^{-2}. \tag{15.15}$$

By passing to spherical coordinates and integrating over the angles we get

$$g(x) = \frac{3\sqrt{3}}{4\pi L_n^2}\frac{1}{x}\int\limits_0^\infty dp\,p\sin(\sqrt{\pi}px)\left(\exp\left[-\frac{2}{3}p^2\right]-\right.$$

$$\left.-\exp[-p^2]\right)\left[p^2+\frac{3\sqrt{3}}{4L_n}\right]^{-2}, \tag{15.16}$$

where $x =| \mathbf{r} | /l_t$. If in (15.16) we replace $(p^2 + \frac{3\sqrt{3}}{4}/L_n)$ by p^2, the obtained integral will converge. So at lower order in the small parameter L_n^{-1} expression (15.16) can be represented in terms of

$$g(x) \simeq \frac{3\sqrt{3}}{4\pi L_n^2} \frac{1}{x} \int\limits_0^\infty \frac{dp}{p^3} \sin(\sqrt{\pi}xp) \left[e^{-\frac{2}{3}p^2} - e^{-p^2} \right]. \qquad (15.17)$$

Noting that

$$\frac{1}{p^2} \left[e^{-\frac{2}{3}p^2} - e^{-p^2} \right] = \int\limits_{2/3}^1 dy e^{-yp^2} \qquad (15.18)$$

we rewrite (15.17) as

$$g(x) \simeq \frac{3\sqrt{3}}{4\pi L_n^2} \frac{1}{x} \int\limits_{2/3}^1 dy \int\limits_0^\infty dp \frac{1}{p} \sin(\sqrt{\pi}xp) e^{-yp^2} \qquad (15.19)$$

The formula

$$\int\limits_0^\infty dp \frac{1}{p} \sin(\sqrt{\pi}xp) e^{-yp^2} = \frac{\pi}{2} erf\left(\frac{\sqrt{\pi}x}{2\sqrt{y}} \right) \qquad (15.20)$$

enables us to transform expression (15.19) as

$$g(x) = \frac{3\sqrt{3}}{8L_n^2} \frac{1}{x} \int\limits_{2/3}^1 dy \, erf\left(\frac{\sqrt{\pi}x}{2\sqrt{y}} \right). \qquad (15.21)$$

Since, for $x \leqslant 1$ in formula (15.21) the integrand is approximately constant, this expression can also be rewritten in the form

$$g_T(x) \approx \frac{\sqrt{3}}{8} \frac{1}{L_n^2} \frac{1}{x} erf\left(\frac{\sqrt{\pi}}{2}x \right). \qquad (15.22)$$

Therefore, in the case under consideration the characteristic correlation length of random nonuniformities of the tissue temperature is about l_t and, according to (15.13) and (15.22) their mean amplitude δT is

$$\delta T \sim [g_T(0)]^{1/2} \mid T^{(0)} - T_a \mid \sim \frac{1}{L_n} \mid T^{(0)} - T_a \mid \qquad (15.23)$$

Thus, the ratio $\delta T / \left| T^{(0)} - T_a \right|$ is determined solely by the characteristic features of the vascular network architectonics and is independent of such physical parameters of the cellular tissue as ρ_t, c_t, κ and the blood flow rate j. In particular, for $l_0/a_0 \sim 30$ and $D_{\text{eff}} \sim 2D$ from (15.23) we obtain $\delta T / \left| T^{(0)} - T_a \right| \sim 10\%$. In addition, we would like to point out that these characteristics of heat transfer, among other possible phenomena mentioned in [2], can be responsible for freezing of living tissues within the finite temperature interval rather than at a fixed value of temperature.

Chapter 16

Some comments on the bioheat transfer problem and the obtained results

16.1 What the book is about from the standpoint of biophysics and medicine

Scientists studying mass and heat propagation in real living tissues as transport phenomena in certain distributed media, that is at the macroscopic level, deal with such quantities as the tissue temperature, the concentration of oxygen or dioxide carbon, etc. averaged on the microscopic scales. So, they need reliable mathematical models that could be able, first, to describe adequately experimental data and, second, to predict the tissue behavior under various conditions. It is especially of great importance for hyperthermia treatment or cryosurgery when living tissue is brought closely to boundaries of vital conditions.

However real functioning of living tissues is mainly investigated at the microscopic level considering tissue elements, including cells and blood vessels, individually. Therefore, there is a wide gap between macroscopic modelling and the knowledge obtained by detail analysis of microscopic processes in living tissues. To build up a bridge between the two levels is a difficult problem because of complex hierarchical structure of living tissues and strong interaction of hierarchy levels with each other.

One of the possible ways mostly used at present is the phenomenological mechanical approach in the framework of which transport phenomena are described by equations based on certain analogies between living tissue and various systems of condensed matter. Thus, such equations have to contain a set of parameters that can be found by the experimental way only. Since, in this approach specific microscopic properties of living tissue functioning are not the factor, the results obtained by solving the corresponding macroscopic equations with their

parameters taking certain chosen values can fit the experimental data formally only. In other words, values of these parameters chosen in order to explain and predict the tissue behavior under one conditions can lead to nothing under others. Besides, making such a theory fit the particular experimental data one pays no attention to the various specific features of microscopic tissue behavior. So, in this approach it is very difficult to distinct what microscopic processes are responsible for the variations in the tissue state as a whole or, moreover, whether these variations are due to quantitative changes in the intensities of the present microscopic processes or new ones have come into being.

Another way to build the desired bridge between the microscopic and macroscopic levels is to develop, as it is usually done in theoretical physics, a certain relatively rigorous technique converting a microscopic description of transport phenomena in living tissues into macroscopic one. The theory of mass and heat transfer developed in this way aggregates all the characteristic features of the living tissue structure and, so, it is possible to estimate beforehand values of the corresponding parameters and to control their variations under different conditions. In this case the results obtained in modelling enable one to establish the identity of what processes in living tissue play the main role. In addition, the model parameters falling beyond the expected intervals indicate that a principally new process has come into play. It is this problem that has been the main subject of the present book.

The next Section formally summarizes the main physical results of this book. Here we go through the book from the beginning schematically singling out the essence of the adopted model and the clues to understanding what the main results obtained mean for scientists who do not specialize in the applied mathematics and theoretical physics.

The proposed model for bioheat transfer actually allows for the main two fundamental characteristics of transport phenomena in living tissue, heat diffusion in cellular tissue and its convective transport with blood flow. Heat propagation involves the two components on scales of living tissue structure, however, their relative contribution is different on various scales.

In contrast to the condensed matter systems heat transfer in living tissue should be considered simultaneously at all the scales up to the dimensions of the microcirculation bed region. The matter is that the vascular network response to local variations in the tissue temperature can cause blood flow redistribution in all the points of the given microcirculatory bed, whereas different microcirculatory beds function practically independently of each other, at least, until the regulation system of the whole organism comes into play.

On spatial scales l from the capillary length up to lengths of small blood vessels, $l < 0.5\,\mathrm{cm}$, the cooperative effect of heat conductivity in cellular tissue and convective transport with blood flow is the diffusion type transport with the effective diffusivity D_{eff}. The value of the effective diffusivity $D_{\mathrm{eff}} = FD$ is determined by the contribution of all the small vessels which is reflected by the cofactor F relating the diffusivity D of the cellular tissue to the effective diffusivity D_{eff}. In the general case the coefficient F depends on the mean blood velocity in these small vessels, their characteristic length, radius, etc.,

including the maximal length of a vessel that may be regarded as small. The latter value in turn depends on the mean blood velocity in these vessels. Due to the microcirculation bed being organized hierarchically all these values vary with the total blood flow through the given vascular network and it turns out, as shown in the present book, the coefficient F becomes constant because variations of the quantities mentioned above compensate each other. The coefficient F is actually determined by $\ln(l/a)$, where l/a is the mean ratio between the length and radius of blood vessels. For real microcirculatory beds $l/a \sim 40$ and the value of F is estimated as $F \sim 1 \div 3$. Experimental analysis of heat propagation can only define more exactly this value. If an experimental value of F is found to be much larger than one it will means that a certain large artery goes near a heated tissue region and blood flow in this artery passing a sequence of branching points transports heat over large distances. The latter process, however, cannot be characterized by an effective diffusivity, moreover, it is not at all described by the diffusion type equations and requires an individual analysis which can be performed using the random walk approach developed in the present book.

Blood in large vessels of lengths $l > 1$ cm moves so fast that it has practically no time to attain thermal equilibrium with the surrounding cellular tissue and, thereby, the blood flow in them carry heat away from the microcirculatory bed. From the standpoint of heat transfer this effect is treated as heat dissipation whose intensity is proportional to the product of the blood flow rate j and the coefficient f of the sink efficiency. The coefficient f takes into account the heat exchange between blood flows in large arteries and veins going in the closed vicinity of each other (counter current vessels). The value of f varies in the interval from $f \approx 0.5$ for the counter current vascular network and $f = 1$ for vascular networks where the venous and arterial beds are not correlated in spatial arrangement. In the present book we have shown that the value of f is determined by the microcirculation bed architectonics only for the same reason as the ratio D_{eff}/D. In no case the heat dissipation effect can be ignored, that is the coefficient f can be set equal zero. Experimentally the value of f can be found as the ratio $(T_v - T_a)/(T - T_a)$ where T_v, T_a, T are the blood temperature in large veins, arteries and the tissue temperature.

Besides, in experimental analysis of temperature distribution in living tissue one should account for that in addition to temperature nonuniformities due to large vessels there also must be spatial random nonuniformities in the tissue temperature which are intrinsic in living tissue and occur at every point of living tissue.

Concerning with bioheat transfer one inevitably meets thermoregulation problem. In particular, local strong heating can give rise to increase in the blood flow rate by tenfold due to living tissue response. By now the thermoregulation problem is far from been well studied even at the physiological level. In the phenomenological approach this effect is ordinary described by a local relationship $j(T)$ between the blood flow rate and the tissue temperature, which is obtained from experimental data of a heating large living tissue regions. What this relation does describe when the size of heated tissue region is about or less than $1 \div 2$ cm and the blood flow rate becomes extremely nonuniform is

a question, in particular, whether the relationship $j(T)$ changes its form or it ceases to exist at all and the relation between the blood flow rate and the tissue temperature becomes nonlocal. Especially, variations of blood flow at one point caused by the temperature increase at another point is a well known effect in living organisms.

In the present book we tried to develop such a model for thermoregulation that allows one to attain small scales. We made use of the notion concept of the effective temperature receptors which take into account the main characteristics of possible humoral and neurogenic mechanisms of microcirculation bed self–regulation. It turns out that there are some conditions under which the local $j(T)$ dependence holds also when the size of a heated region becomes small. In the general case this relation is certain to be nonlocal because of a nonlinear response of blood vessels to temperature variations as well as difference in the delay times of vessels belonging to various levels of the vascular network. Nevertheless, the local $j(T)$ relation may be used as the first rough approximation.

Concerning modelling hyperthermia treatment of tumors, we did not pose the problem of describing all the processes occurring in tumors under strong heating. We singled out only that the substantial tumor property from the standpoint of bioheat transfer which enables the blood flow rate in tumor to remain at the same level at the same time when the blood flow rate in the normal tissue surrounding the tumor increases by tenfold. This is one of the main reasons why the temperature in tumors can remarkably exceed the temperature in the normal tissue, leading to tumor destruction only.

16.2   Brief view on the results obtained for the bioheat transfer problem

Recapitulating the results obtained above we would like to draw the following conclusions.

– Vessels whose level number $n \approx n_t$ mainly control heat exchange between blood and the cellular tissue. These vessels exhibit properties of both the heat conservation and heat dissipation vessels. Influence of blood flow in these vessels on heat transfer is actually reduced, first, to renormalization of the tissue heat conductivity with the renormalization coefficient actually depending on the characteristic details of the vascular network only. Second, the vessels of level $n \approx n_t$ determine relationship between the tissue temperature and the temperature of blood in the "heat - conservation" veins. In particular, in the case of a uniform tissue temperature distribution when level n_t consists of unit vessels the blood temperature in veins of Class 1 coincides with the tissue temperature. When level n_t involves countercurrent pairs the blood temperature in heat - conservation veins is lower that the tissue temperature. In this case the difference between the venous and arterial blood temperatures in large vessels is proportional to the difference between the tissue temperature and the arterial temperature T_a with the constant of proportionality depending on the

characteristic details of the vascular network architectonics.

– When the blood flow rate is not too high such that the influence of the capillary system is ignorable and the blood flow rate in practically uniform on scales of order l_{n_t} temperature distribution can be described by the bioheat transfer equation with the effective diffusion coefficient and the heat sink. The countercurrent effect is responsible for the renormalization of the heat sink term only.

– Temperature distribution in living tissue is practically independent of specific details of vessel branching and depends only on characteristic features of the vascular network architectonics. In particular, it can depend on the mean distance between vessels of a given level or the mean number of arteries of the same length which are generated by branching of one artery whose length is two times as large. These characteristics called the self-averaging property of heat transfer in living tissue allow one to consider a model for the vascular network chosen for convenience.

– The characteristic features of vascular network architectonics, at least, of microcirculatory beds, can be directly determined by general requirements on the blood flow rate. For example, equality of the blood flow rate at different points of the same microcirculatory bed domain (when other quantities such as the tissue temperature, the concentration of O_2, CO_2, etc. are constant over the given domain) can specify the main characteristic details of vessel branching as well as the vascular network embedding in the corresponding domain.

– The peculiar properties of heat exchange between blood and the cellular tissue are the existence of the hierarchical system of branching points where venous blood streams merge with each other.

– Depending on the value $G = J_0/(2\pi D l_0)\ln(l_0/a_0)$ all arteries and veins of the vascular network can be divided into two classes. Class 1 involves the vessels called "heat - conservation" vessels whose level number $n < n_t(G)$ and the vessels of levels $n > n_t$ called "heat - dissipation" vessels forming Class 2. In description of heat transfer in living tissue the arteries of Class 1 may be considered in terms of the sources of blood with the temperature T_a. The basic role of the veins belonging to Class 1 is reduced to carrying away blood from the tissue without heat exchange with it. The influence of the vessels, belonging to Class 2, on heat transfer is ignorable. Blood in these vessels is in thermal equilibrium with the cellular tissue.

– When the characteristic total length of capillaries joining given arterioles to venules is not too long (i.e. when $\gamma \ll 1$ within the framework of the present model), depending on the value of G, the effect of the capillary system on heat transfer can be of different types.

– As the blood flow rate increases the capillary system causes convective heat transport in the tissue and in this case the capillary system may be considered in terms of porous medium.

– On further blood flow rate increasing heat transport is controlled again by diffusive type process in a certain effective medium but with the effective diffusion coefficient D_{eff} being a function of the blood flow rate.

– When the capillary length is long enough (i.e. when $\gamma \gg 1$) the range of

convectional type transport is absent. In this case heat transfer is controlled by diffusive type transport and the cellular tissue containing the capillary system can be treated as an effective uniform medium with the diffusion coefficient D_{eff}.

– Temperature distribution, in principle, can be characterized by a wide range of spatial scales from the length of the smallest vessels (the arterioles and venules) up to the length of the host artery or vein. However, the basic scale which should be taken into account is of order l_{n_t} for the diffusive type transport and l_N (the venules length) for the convective type.

– In the case when heat transfer is controlled by heat conservative vessels which can be regarded as a typical case for real living tissue, the ratio between the mean amplitude of temperature random nonuniformities and the mean value of $(T - T_a)$ is mainly determined by the characteristic features of the vascular network architectonics and is about 10%.

– Spatial temporal fluctuations in the tissue temperature and the blood flow rate caused by random time variations in the parameters of vessels forming a hierarchical vascular network can exhibit $1/f$ behavior.

– When the blood flow rate becomes substantially nonuniform on spatial scales of order l_{n_t} the tissue temperature evolution is controlled by the averaged blood flow rate rather than true one. The relationship between the true and averaged blood flow rates can be written in the differential form.

– The vascular network response to temperature variations in living tissue is represented in terms of variations in vessel resistances to blood flow with the total resistance of vascular network being determined by a large number of vessels belonging to different hierarchy levels. The flow resistance of each artery - vein pairs is considered to be governed by the temperature of blood in the corresponding vein. This blood temperature dependence of vessel resistance forms a cooperative mechanism of living tissue self-regulation which is based on individual response of each vessel to the corresponding hierarchical piece of information and leads to thermoregulation due to self - processing of information. With blood flow resistance being a linear function of blood temperature this temperature self-regulation becomes ideal, i.e. local variations in the tissue temperature give rise to variations in the blood flow rate at the same points only. Within the framework of ideal self-regulation time variations of the true blood flow rate are locally governed by the tissue temperature.

– Nonideality of the vessel response not only alters the form of local relationship between the true blood flow rate and the tissue temperature but also gives rise to a nonlocal dependence of the blood flow rate on the tissue temperature distribution over living tissue. Inequality of the delay times for vessels belonging to different levels can cause a nonlocal relationship between the blood flow rate and the tissue temperature during transient processes.

– When the capillary system has no significant effect on heat transfer and thermoregulation can be treated as ideal, bioheat transfer is governed by the system of three equations, namely: the parabolic equation for the tissue temperature evolutions with the heat sink term proportional to the averaged blood flow rate; the elliptic equation determining the relationship between the averaged and true blood flow rate; and the ordinary differential equation which

relates time variations in the true blood flow rate to local values of the tissue temperature.

– When the living tissue region affected directly is small, the difference between the true and averaged blood flow rates can become substantial which has a remarkable effect on the temperature distribution in living tissue.

– Time delay in vessel response can give rise to nonmonotone growth of the tissue temperature under rapid heating of living tissue. As a result, the tissue temperature can go beyond the vital temperature interval for a time of the same order as the time delay.

– Due to depression of temperature response of tumor vessels the temperature in a tumor exceeds significantly the mean tissue temperature under to uniform sufficiently strong heating of living tissue. The value of heat generation rate needed for such heating depends on the tumor size.

– Freezing processes in living tissue can be described by the two boundary model which deals with propagation of freezing front separating the frozen and living regions of the tissue and the boundary of a certain living tissue domain where the blood flow rate has attained it maximum.

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