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Mathematical Model of an Active Biological Continuous Medium with Account for the Deformations and Rearrangements of the Cells

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Abstract—A continuum model of the embryonic epithelial tissue with account for the active deformations and rearrangements of the cells is proposed. The stress tensor is represented as the sum of the stresses undergone by the cell directly and the tensor of active stresses that arise owing to contracting cellular protrusions anchored on the surface of neighboring cells and developing in response to cell reshaping (deformation). The strain rate tensor includes three components: elastic and two inelastic related to the active deformation of the cells and their rearrangement. The first of these components depends on the stresses in the cells and the reached cellular deformation level, whereas the second is determined by the active stresses. The problem of reaction of a thin sheet to a rapid stretching is solved and agreement with experimental data is obtained.

Keywords: cell systems, active media, biological morphogenesis, embryonic epithelium.

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The mechanical forces that arise during embryonic development can lead to the rearrangement of the cells and their directed motion [1, 2]. Numerous data testify that these forces are one of necessary factors of control of biological morphogenesis (see review [3]).

The process of cell rearrangement in cell sheets in response to the development of active tissue stresses plays an important part in embryonic development [4]. The cells of the embryonic tissue are able to change their neighbors in a result of active relative displacements. The embedding of cells between other cells (this process is called intercalation) may lead to changes in the proportions of the biological object even in the absence of cell divisions. The mechanisms of this shaping cannot be understood without investigating mathematical models that take into account the determining principles of motion organization in such a system.

The theoretical models of cell sheet deformation at the tissue level with account for the rearrangement and deformation of the cells, available from the literature, can be divided into several broad groups. In the cell mosaic models [5, 6] the deformations and rearrangements of the cells are treated as a stochastic process of permutation of cell-forming meshes, which is directed toward the minimization of the system energy. In another group of models [7, 8] the cells are represented by polygons whose vertices change their positions under the control of the balance of mechanical forces acting at the vertices (nodes) and corresponding to various types of interaction between them. The stresses in the medium are not considered: the stresses in the linear surface elements that connect the vertices are only taken into account. The temporal evolution of the configuration is also determined by the energy minimization condition. Currently, the finite element method is widely used [9, 10]. Continuum models that describe the mechanical behavior of cell sheets are sparse [11, 12].

An important weakness of the first two model types is the impossibility to formulate problems with boundary conditions for displacements and stresses because the force interactions are only taken into account through changes in the system energy. In the finite-element models formulated without continuum relations [9] the cell rearrangement is only related to surface tension and changes in the area of contact between neighboring cells. This type of cell interaction cannot always be associated with a physically clear mechanism, whereas obviously important mechanisms of cell interaction are not considered.The description of the observed phenomena within continuum models has so far not taken into account the interaction at the cellular level. As a result, it has been needed to postulate additional, without a clear physical meaning, hypotheses: about the existence of the homeostatic stress state described by a certain empirical equation [11] or the presence of a fixed, given in advance, direction of active stress development anisotropy [10, 12].

In the present study, we present a general continuum model that describes the active reactions of a plane embryonic epithelium cell layer with taking explicitly into account the deformations and rearrangements of the cells. The model is based on the general principles of modeling such tissues we formulated earlier [3, 13]. The model obtained is applied to describing the step loading of a tissue fragment. Within the framework of the model, without using any additional hypotheses, the experimentally observed phenomena are described, including the effect of hyper-restoration of the initial state, which manifests itself in cell elongation in the direction opposite to the tissue stretching axis.

1. GENERAL CONTINUUM MODEL

The cellular medium is treated as a two-dimensional continuum which remains plane during deformation. In the three-dimensional formulation this medium corresponds to a thin (in comparison with other two dimensions) layer unloaded in the direction normal to the layer. We will solve problems in which the layer is subjected to significant tangential loads. In combination with the condition of no loading over the wide surface this enables us to neglect the stresses acting in the direction perpendicular to the layer as compared with those acting in its plane. The possibility of practical realization of such loading will be discussed in what follows.

For describing strains and stresses we introduce the observer's coordinate system with coordinates x^i and the comoving coordinate system with coordinates ξ^s. Unbracketed Latin indices run through values 1, 2. For such upper and lower indices the summation convention applies. The law of medium motion has the form $x^i = x^i(t,\ \xi^s)$, where t is time. It is assumed that the deformation is determined by three mechanisms: elasticity, the active deformation of the cells, and their rearrangement.

At a certain time moment t, in processes rapid as compared with active cell reactions, the medium is considered as elastic. At each point, unloading can locally be realized, that is, in a small tissue particle the stresses be reduced to zero. Correspondingly, in the comoving coordinate system we can locally introduce at the actual moment the metric tensors of the actual state g'_{ij} and of the instantly unloaded state g'^*_{ij}. Here, the prime denotes the tensor components in the comoving coordinate system. Introduce the Green–Lagrange elastic strain tensor by the formula [14]

$$\varepsilon'^{(e)}_{ij} = \frac{1}{2}\left(g'_{ij} - g'^*_{ij}\right).$$

After the instantaneous elastic reaction to the removing of the load a further deformation occurs owing to active cell deformations. The state corresponding to the removing of this deformation as well is characterized by the metric g'^a_{ij}. Not all intermediate states introduced can be realized physically. The active cellular strain tensor is defined as

$$\varepsilon'^{(a)}_{ij} = \frac{1}{2}\left(g'^*_{ij} - g'^a_{ij}\right).$$

The medium deformation process is determined by the strain rate tensor e'_{ij} for which the following

formula is valid [14]:

$$e'_{ij} = \frac{1}{2}\left(\nabla_i u_j + \nabla_j u_i\right) = \frac{1}{2}\frac{dg'_{ij}}{dt} = \frac{d\varepsilon'^{(e)}_{ij}}{dt} + \frac{d\varepsilon'^{(a)}_{ij}}{dt} + \frac{1}{2}\frac{dg'^{a}_{ij}}{dt}, \tag{1.1}$$

where u_i are the medium velocity vector components.

The intercalational strain rate tensor (related to cell rearrangement) with components $e'^{(\mathrm{int})}_{ij}$ in the comoving coordinate system is defined by the formula

$$e'^{(\mathrm{int})}_{ij} = \frac{1}{2}\frac{dg'^{a}_{ij}}{dt}.$$

This tensor characterizes such active cell displacements at which the cells from a certain conventional, axially oriented row are built in between the cells of an adjacent row.

Relation (1.1) completely determines the law of deformation in the differential form for finite strains. It is now possible not to consider the total strain tensor which links the actual state with a certain state initial for the whole process [15].

Thus, the medium strain rate tensor is represented as the sum of three components: elastic, related to the elastic deformation of the cells, and two inelastic. One of these components is determined by the active deformations of the cells and is associated with changes in their shape and the other (e^{int}) occurs owing to cell rearrangement due to active cell motions.

Since the initial differentiation with respect to time is performed in the comoving coordinate system, for the strain rate tensor components in the observer's coordinate system the following expression can be obtained:

$$e_{ij} = \frac{D\varepsilon^{(e)}_{ij}}{Dt} + \frac{D\varepsilon^{(a)}_{ij}}{Dt} + e^{(\mathrm{int})}_{ij}. \tag{1.2}$$

Here (γ takes one of two values: a or e)

$$\frac{D\varepsilon^{(\gamma)}_{ij}}{Dt} = \frac{d\varepsilon^{(\gamma)}_{ij}}{dt} + \varepsilon^{(\gamma)}_{ik}\nabla_j u^k + \varepsilon^{(\gamma)}_{kj}\nabla_i u^k. \tag{1.3}$$

When writing down dynamic relations, we will consider the medium as a two-phase continuum that consists of the main and auxiliary phases. We will assume that the volume of the auxiliary phase can be neglected and all the above-formulated kinematic relations relate to the main phase. The auxiliary phase corresponds to the system of cell outgrowths (lamellipodia) that anchor at neighboring cells and provide the development of active contracting efforts which produce the compression of the main phase formed by the cell bodies. Characterizing the stress in the main phase by a tensor $\sigma^{(c)}$, in the auxiliary phase by a tensor τ, and in the medium as a whole by the tensor σ, we will assume the relation

$$\sigma = \sigma^{(c)} + \tau. \tag{1.4}$$

If there are no contractions in the auxiliary phase, the stress in the main phase corresponds to the stress in the medium. If in the medium as a whole there are no stresses, the phases may be stressed owing to intercellular interactions, in which case $\sigma^{(c)} = -\tau$.

It is natural to relate the elastic strain to the stress in the main phase $\sigma^{(c)}$. In what follows, generally, the elastic strains are not assumed to be small. However, since our calculations are of qualitative and estimative nature, we will use for simplicity the linear dependence

$$\sigma^{(c)} = E\varepsilon^{(e)}, \tag{1.5}$$

where E is the tensor of elastic coefficients. Here and in what follows, all material tensors and tensor functions are assumed to depend on the medium anisotropy parameters.

Assume that the active cellular strain rate tensor $\varepsilon^{(a)}$ depends on the stress experienced by the cells $\sigma^{(c)}$ and the actual level of the active strain so that the cellular active strain tends to a certain value determined by this stress. After the external load is removed, in the absence of active stresses in the medium, the active deformation of the cells disappears and the cell shape returns to the initial one.

As a maximally simple variant of such dependence, we will assume the linear relation

$$\frac{D\varepsilon_{ij}^{(a)}}{Dt} = K_{ijkl}\sigma^{kl(c)} - L_{ij}^{\ kl}\varepsilon_{kl}^{(a)}, \tag{1.6}$$

where K_{ijkl} and $L_{ij}^{\ kl}$ are tensor coefficients in the observer's coordinate system. On the left side of the equality the derivative with respect to time is the lower Oldroyd derivative and can be calculated by formula (1.3) [16]. The use of this derivative provides the invariance of the relations considered.

Nowadays, there is no unambiguous reply to the question: what precisely, stresses or strains, does trigger the development of active stresses leading to cell rearrangement? There are data in favor of each of these mechanisms [3]. In any case, the cells react to a disturbance of their normal mechanical state. Assume that the development of active stresses in the auxiliary phase (and hence the subsequent rearrangement) is determined by the deviation of the cell shape from the normal one, i.e., by the cellular deformation of the main phase.

Using this hypothesis, we will take as the constitutive equation for τ in the comoving coordinate system the following dependence for the contravariant components of the tensor of relative derivatives of the active stress tensor with respect to time:

$$\left.\frac{d\tau'^{ij}}{dt}\right|_{\xi_i=\text{const}} = F'^{ij}(\varepsilon'^{(c)}) - N'^{ij}_{\ \ kl}\tau'^{kl}. \tag{1.7}$$

Here, F' is a tensor function and N' a tensor coefficient. The first term describes the development of active stresses in reply to a change in the cell shape: its determining argument is the total cellular strain tensor $\varepsilon'^{(c)} = \varepsilon'^{(e)} + \varepsilon'^{(a)}$. The second term takes into account the relaxation of active stresses.

Then, in the Eulerian coordinate system the last equation can be rewritten in the form

$$\frac{D_U\tau^{ij}}{Dt} = F^{ij} - N^{ij}_{\ \ kl}\tau^{kl}. \tag{1.8}$$

Here, on the left side of the equality, the upper Oldroyd derivative can be calculated by the formula [16]

$$\frac{D_U\tau^{ij}}{Dt} = \frac{d\tau^{ij}}{dt} - \tau^{kj}\nabla_k u^i - \tau^{ik}\nabla_k u^j.$$

It is convenient to describe the properties of the tensor function F in the local orthogonal coordinate system with axes directed along the principal directions of the cellular strain tensor. In this coordinate system the relative (with respect to the initial state) lengths of a medium element along the principal axes can be found at finite strains by formulas [14] $l_i/l_{0i} = 1/\sqrt{1-2\varepsilon'^{(c)}_i}$, where l_i is the length of the element after deformation in the i-direction, l_{0i} its initial length, and $\varepsilon'^{(c)}_i$ are the principal values of the tensor $\varepsilon'^{(c)i}_{\ \ j}$. The principal values of the tensor $\varepsilon'^{(c)i}_{\ \ j}$ can be found by solving the equation $\det(\lambda\delta^i_j - \varepsilon'^{(c)i}_{\ \ j}) = 0$. Take into account that the more elongated the cell in a certain direction (and correspondingly narrower) the easier the development of cell outgrowths in the perpendicular direction and the seizure by them of not only cells with which there is a direct contact. Assume that the initial cell shape is in average isotropic: $l_{01} = l_{02}$. The effect of the cell deviation from the isotropic shape on the development of active stresses can then be taken in the maximally simple form into account by setting in the principal coordinate system $F'^1_{\ 1} = M\, l_2/l_1$

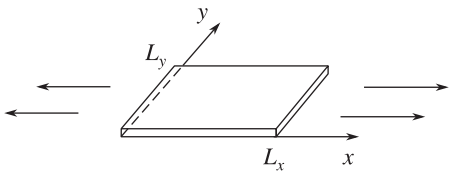

Fig. 1. Diagram of the experiment: the arrows show the direction of the initial stretching.

and $F_2^2 = M\, l_1/l_2$, where M is a coefficient, and assuming the other components to be equal to zero. In the invariant tensor form we obtain for the essentially nonlinear function F the expression

$$F'^{ij} = \frac{g'^{ij} - 2\varepsilon'^{(c)ij}}{\sqrt{\det(\delta^i_j - 2\varepsilon'^{(c)i}{}_j)}}.$$

Then, in the Eulerian coordinate system Eq. (1.8) can be rewritten in the form

$$\frac{D_U \tau^{ij}}{Dt} = M\frac{g^{ij} - 2\varepsilon^{(c)ij}}{\sqrt{\det(\delta^i_j - \varepsilon^{(c)i}{}_j)}} - N^{ij}{}_{kl}\tau^{kl}. \tag{1.9}$$

The equations obtained describes the gradual transition of the active stresses to a level determined by the cell deformation.

We will define the intercalational deformation of the cells by the relation $e^{(\mathrm{int})} = e^{(\mathrm{int})}(\tau,\ \sigma^{(c)})$. Treating the intercalation as a result of the action of only the active stresses in the auxiliary medium and restricting consideration to the linear case, assume the corresponding dependence in the form

$$e^{(\mathrm{int})} = G\tau. \tag{1.10}$$

We will assume the deformation process to be quasi-static. Then, for obtaining the complete system of equations, which would enable us to find the unknowns e, $\varepsilon^{(e)}$, $\varepsilon^{(a)}$, $e^{(\mathrm{int})}$, σ, $\sigma^{(c)}$, τ, and u, we should supplement Eqs. (1.2), (1.4)–(1.6), (1.9), and (1.10) with the equilibrium and compatibility equations

$$\begin{aligned} &\nabla\cdot\sigma = 0,\\ &e_{ij} = \frac{1}{2}\left(\nabla_i u_j + \nabla_j u_i\right). \end{aligned} \tag{1.11}$$

2. FORMULATION OF THE PROBLEM OF UNIAXIAL CELL LAYER EXTENSION

We will apply the above-formulated general equations to solving the problem of uniaxial stretching of a layer that initially, in the observer's coordinate system, occupies the region $[0;\ L_x]\times[0;\ L_y]$ (Fig. 1). Assume that in the layer plane the material characteristics of the two-dimensional medium considered are isotropic.

The extension occurs under the action of surface forces applied at the moment $t = 0$ to the lateral surfaces $x = 0$ and $x = L_x$ parallel to the Ox axis. At the ends, the resultant forces are equal in magnitude and opposite in direction. The other boundaries remain unloaded. We will assume that at the strip ends the surface forces are independent of the y coordinate, i.e., at $x = 0$ and $x = L_x$ the only nonzero stress tensor component $\sigma_{11} = \sigma(t)$ is given. We assume that at $t < 0$ there have been no stresses and strains.

With account for the boundary conditions, the equilibrium equations admit a solution which yields the stress distribution within the layer in the form $\sigma_{11} = \sigma(t)$, $\sigma_{12} = \sigma_{22} = 0$.

Thus, σ_{11} is a function of time alone, that is, the stress distribution is spatially uniform, the axial stress being determined by the boundary conditions. As a result, in the equations that will be presented below all unknowns (except for velocities) are also spatially uniform and the compatibility equations for strain rates are thus satisfied.

We will retain notations e, $\varepsilon^{(e)}$, $\varepsilon^{(a)}$, and $e^{(\mathrm{int})}$ for the axial strains and strain rates. For the axial components of other tensors the previous notations will also be retained, whereas their normal components will be denoted by the subscript "y". In view of isotropy, Eqs. (1.2), (1.4)–(1.6), and (1.9)–(1.11) can be rewritten in the following form:

$$
\begin{gathered}
e = \frac{D\varepsilon^{(e)}}{Dt} + \frac{D\varepsilon^{(a)}}{Dt} + e^{(\mathrm{int})}, \qquad e_y = \frac{D\varepsilon_y^{(e)}}{Dt} + \frac{D\varepsilon_y^{(a)}}{Dt} + e_y^{(\mathrm{int})}, \\
\sigma = \sigma^{(c)} + \tau, \qquad \sigma_y^{(c)} + \tau_y = 0, \\
\varepsilon^{(e)} = \frac{1}{E}\bigl(\sigma^{(c)} - \nu\sigma_y^{(c)}\bigr), \qquad \varepsilon_y^{(e)} = \frac{1}{E}\bigl(\sigma_y^{(c)} - \nu\sigma^{(c)}\bigr), \\
\frac{D\varepsilon^{(a)}}{Dt} = \frac{1}{T_1}\bigl(k(\sigma^{(c)} - \nu_1\sigma_y^{(c)}) - \varepsilon^{(a)}\bigr), \\
\frac{D\varepsilon_y^{(a)}}{Dt} = \frac{1}{T_1}\bigl(k(\sigma_y^{(c)} - \nu_1\sigma^{(c)}) - \varepsilon_y^{(a)}\bigr), \\
\varepsilon^{(c)} = \varepsilon^{(e)} + \varepsilon^{(a)}, \qquad \varepsilon_y^{(c)} = \varepsilon_y^{(e)} + \varepsilon_y^{(a)}, \\
\frac{D_U\tau}{Dt} = m\frac{1 - 2\varepsilon^{(c)}}{\sqrt{(1 - 2\varepsilon^{(c)})(1 - 2\varepsilon_y^{(c)})}} - \frac{1}{T_2}\tau, \\
\frac{D_U\tau_y}{Dt} = m\frac{1 - 2\varepsilon_y^{(c)}}{\sqrt{(1 - 2\varepsilon^{(c)})(1 - 2\varepsilon_y^{(c)})}} - \frac{1}{T_2}\tau_y, \\
e^{(\mathrm{int})} = -G(\tau - \nu_2\tau_y), \qquad e_y^{(\mathrm{int})} = -G(\tau_y - \nu_2\tau), \\
\frac{\partial\sigma}{\partial x} = 0, \qquad e = \frac{\partial u}{\partial x}, \qquad e_y = \frac{\partial u_y}{\partial y}.
\end{gathered}
\tag{2.1}
$$

System (2.1) contains 9 model constants, including two elastic moduli: tensile modulus E and Poisson's ratio ν. The constants T_1 and T_2 have the meaning of characteristic times of the active cellular deformation and active stress development, respectively.

Since the action of the active stresses directed perpendicular to the stretching axis τ_y favors the wedging-in of the cells between one another and the growth of the axial strain rate, on the right sides of the equations for intercalational strain rates, before the bracket, a minus sign is taken ($G > 0$).

As observations show, the cell area remains almost unchanged during deformation. In order to ensure the realization of this condition separately for the cellular and intercalational deformations, we will set $\nu = \nu_1 = \nu_2 = 1$. As immediately follows from the expressions for $e^{(\mathrm{int})}$ and $e_{(y)}^{(\mathrm{int})}$ in (2.1), equality $\nu_2 = 1$ guarantees the two-dimensional incompressibility during intercalational deformations. On the other hand, the equalities $\nu = \nu_1 = 1$ guarantee, as can be shown using the expressions for the cellular strain components, the incompressibility during cellular deformations but not separately for the elastic and active components. Naturally, the incompressibility of the entire two-dimensional medium is also ensured: $e + e_y = 0$.

3. SOLUTION OF THE PROBLEM OF AN INSTANTANEOUSLY STRETCHED LAYER

Consider a model problem, most elementary mechanically, whose solution allows us to adequately describe the phenomena observed experimentally.

Let the tissue fragment be instantaneously stretched along the Ox axis by a quantity $\Delta L = \text{const}$ and its length then be fixed, which leads to the appearance of an axial elastic tensile stress $\sigma_0 = E\varepsilon_0$, where $\varepsilon_0 = 0.5(1 - 1/(1 + \Delta L/L_x)^2)$. As initial conditions at $t = 0$, we will take $\sigma = \sigma_0$, $\tau = \tau_y = 0$, and $\varepsilon^{(a)} = \varepsilon_y^{(a)} = 0$. Boundary conditions are assigned at the specimen ends: $u = u_y = 0$ at $x = 0$ and $x = L_x + \Delta L$.

System (2.1) admits the solution $u = u_y = 0$, which corresponds to the absence of total strains. In this case, the relative time derivatives D/Dt and D_U/Dt go over into partial derivatives and (2.1) can be transformed into the system of three equations with three unknowns σ, $\Delta\tau = \tau_y - \tau$, and $\varepsilon^{(c)}$.

Introduce the dimensionless quantities

$$\sigma^* = \frac{\sigma}{mT_2}, \quad \Delta\tau^* = \frac{\Delta\tau}{mT_2}, \quad t^* = \frac{t}{T_2}, \quad T^* = \frac{T_1}{T_2}, \quad k^* = kE, \quad G^* = GmT_2^2, \quad E^* = \frac{E}{mT_2}.$$

After some transformations, system (2.1) takes the following form:

$$\frac{\partial\sigma^*}{\partial t^*} = -\frac{1}{T^*}(k^* + 1)\sigma^* + \left(\frac{E^*}{T^*} - \frac{4}{\sqrt{1 - 4(\varepsilon^{(c)})^2}}\right)\varepsilon^{(c)} - \left(\frac{k^* + 1}{T^*} + G^*E^* - 1\right)\Delta\tau^*,$$

$$\frac{\partial\Delta\tau^*}{\partial t^*} = \frac{4\varepsilon^{(c)}}{\sqrt{1 - 4(\varepsilon^{(c)})^2}} - \Delta\tau^*, \tag{3.1}$$

$$\frac{\partial\varepsilon^{(c)}}{\partial t^*} = -G^*\Delta\tau^*.$$

For this system the initial conditions at $t = t_0$ are $\sigma^* = \sigma_0^* = E^*\varepsilon_0$, $\Delta\tau^* = 0$, and $\varepsilon^{(c)} = \varepsilon_0$.

In the problem considered, the last two equations of system (3.1) can be separated from the first equation and determine the evolution of the active stress and the total cellular strain as functions of time. The total cellular strain is determined by two dimensionless parameters ε_0 and G^*: $\varepsilon^{(c)} = \varepsilon^{(c)}(t^*;\ \varepsilon_0,\ G^*)$. Substituting in the first equation the functions $\varepsilon^{(c)} = \varepsilon^{(c)}(t^*)$ and $\Delta\tau^*(t^*)$, we obtain the stress evolution which is determined by the entire set of dimensionless parameters: $\sigma^*(t^*;\ \varepsilon_0,\ G^*,\ T^*,\ k^*,\ E^*)$.

Basing on estimations [17], as characteristic times for the development of the active cellular deformations (related to the reconstruction of the internal structures and membranes of the cells) and the active stresses (with the formation, anchoring and contraction of lamellipodia), we will take the following values: $T_1 = 10$ min and $T_2 = 1$ h. In calculation we will assume that the fragment is stretched by 80%, which corresponds to $\varepsilon_0 = 0.35$.

The mechanical properties of the embryonic epithelium are strongly inhomogeneous over the layer thickness, its strength characteristics being provided almost completely by a narrow region adjacent to its external surface where the cortical filaments and tight junctions are concentrated [3, 18]. More correctly, we could speak of the surface elastic modulus of a two-dimensional medium, which was estimated in [18] by a value $E_s \sim 90$ kPa μm. Basing on this estimate, we will assume for the layer of thickness 30 μm the average elastic modulus $E = 3$ kPa.

The parameters m, G, and k cannot be estimated directly basing on the available experimental data. In calculations, we used as basic values $m = 0.5$ kPa h^{-1}, $G = 1$ kPa^{-1} h^{-1}, and $k = 0.6$ kPa^{-1}. As will be shown below, at values of this order we managed to obtain qualitative agreement with the effects observed experimentally.

Numerical simulation was carried out using the fourth-order Runge–Kutta method.

4. RESULTS AND DISCUSSION

The results of solution of the model problem demonstrate active cellular reactions of the embryonic tissue to its mechanical stretching (Figs. 2–4). The restructuring of the internal parameters of the medium occurs with the total strain conserved over the entire time of the experiment. After the fragment is fixed in the stretched state characterized by the presence of tensile stresses, there starts the process of replacing the elastic (passive) strain by the active cellular strain, which gradually leads to stress relaxation. Most boldly, this can be seen in Fig. 2, where on the same time scale the evolution of the strain components $\varepsilon^{(c)}$ and $\varepsilon^{(e)}$ and the total tissue stress σ^* is shown for the basic set of parameters. In the first short stage, the elastic strain component $\varepsilon^{(e)}$ and the tensile stress σ^* fall rapidly, while the total cellular strain component $\varepsilon^{(c)}$ remains on this time interval almost unchanged.

Later, the slower process of development of active stresses in the auxiliary phase, which arise in response to the cell deformation, becomes discernable. This process triggers the intercalational deformation determined by the relative displacements of the cells and finally leading to the restoration of their initial shape. In Fig. 2, we can see a slow decrease in the cellular strain $\varepsilon^{(c)}$ accompanied by further (now slow) decrease in the elastic strain component and the tissue stress. Visually, decrease in $\varepsilon^{(c)}$ corresponds to decrease in the number of cell rows in the direction perpendicular to the direction of stretching. Since the characteristic times are substantially different, the intercalation process becomes important when the elastic strains and the cellular and tissue stresses are mainly relaxed.

Note that the characteristic times of the two stages considered coincide with T_1 and T_2 (in the dimensionless form T^* and 1) for the basic set of parameters but with deviating from the basic values this is, generally, not so. The thing is that the duration of each stage of the process is not determined by a single quantity. The dynamics of the intercalational stage are determined by the dimensionless parameter $G^* = GmT_2^2$ which depends on not the active stress rate with the characteristic time T_2 alone but also their level m and the intensity of mutual penetration of the cells in response to these stresses G. As can be seen from Fig. 3, with decrease in G^* the dimensionless characteristic time of the process increases and may become much greater than unity. The "cellular" stage (before the intercalations start) depends on all dimensionless parameters, not only the active strain rate (with the characteristic time T^*). It turns out that of importance is (Fig. 4) the dimensionless parameter $k^* = kE$ which takes into account the effect of the stressed state of the cell on its elastic (E) and active (k) deformation: with decrease in k^* the duration of the first stage increases and finally the frontier between the stages diffuses.

The restoration of the initial cell shape (that is the vanishing of the cellular strain $\varepsilon^{(c)}$) and decrease in stress are nonmonotonic (Fig. 2): in a certain stage there arise cells oriented perpendicular to the stretching axis ($\varepsilon^{(c)} < 0$) and negative stresses. The degree of this non-monotonicity is strongly affected by the intercalational parameter G^* (Fig. 3). The greater this parameter, the higher the absolute value of the negative cellular strain and the earlier the cellular deformation develops. After the first splash of the negative cellular deformation we can observe damped oscillations which can hardly be recorded experimentally in view of the roughness of measurements.

From Fig. 2 it can be seen that both strain components shown change synchronously (change sign simultaneously), whereas the total stress changes sign each time with a significant advance ("leads in phase"). In particular, this means that the medium as a whole begins to undergo compression ($\sigma < 0$) when the cells are still stretched, which is possible owing to the presence of active stresses in the auxiliary medium τ.

On time intervals where $\sigma < 0$ the specimen released at the boundaries does not contract but elongates. This can be seen from the second and third strings of system (2.1). The release at the boundaries corresponds to an instantaneous change in the boundary conditions: the no-displacement condition is replaced by the condition of equality to zero for the stress σ. The stresses in the auxiliary medium τ and τ_y cannot change instantaneously by virtue of the equations that determine them. Therefore, increase in σ from a negative value to zero leads to an instantaneous increase in the axial cellular stress $\sigma^{(c)}$ (at $\sigma_y^{(c)}$ unchanged) and the elastic strain $\varepsilon^{(e)}$, i.e., to stretching.

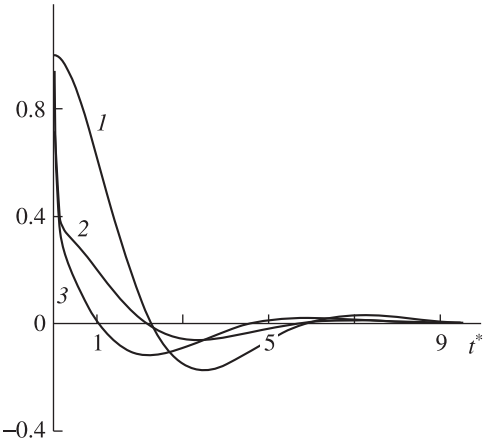

Fig. 2. Evolution of the total cellular strain $\varepsilon^{(c)}/\varepsilon_0$ (*1*), the elastic strain $\varepsilon^{(e)}/\varepsilon_0$ (*2*), and the total medium stress σ^*/σ_0^* (*3*) at basic parameter values; the quantities are divided by their initial values, so that all the three curves start from unity.

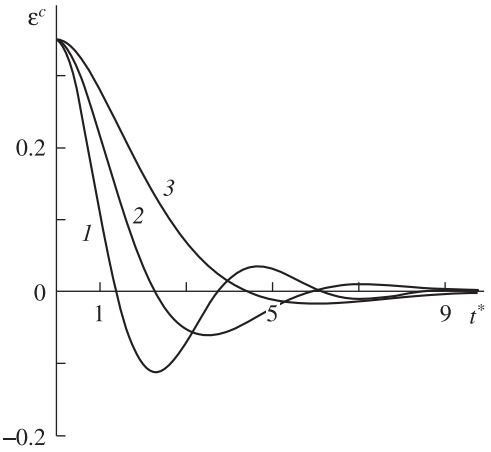

Fig. 3. Evolution of the total cellular strain $\varepsilon^{(c)}$ at $\varepsilon_0 = 0.35$ and $G^* = 1$ (*1*), 0.5 (*2*), 0.25 (*3*).

This fact can be treated as a manifestation of the hyper-restoration principle known in developmental biology [19], which can be formulated as follows: If a cell or tissue fragment is deviated by an external force from the initial equilibrium state, it responds by the generation of mechanical forces directed to the restoration of the initial state but, as this state is reached, the process, as a rule, continues, which leads to a deviation in the opposite direction.

All above-mentioned effects have been observed experimentally [3, 17]. The experimental situation is always somewhat different from the idealized formulation considered, which demonstrates the properties of the model most vividly. In reality, the embryonic epithelium is attached to the layer of a mechanically weak and easily extensible tissue several cell layers thick. The above formulation is most close to experiments with the so-called "sandwich" which consists of two such composite layers so pushed together that properly epithelial layers are directed outward and stuck together are the lining tissues. In another group of experiments a single composite layer is spread over a compliant latex substrate. In this case, at each point of the layer the total strain is determined by the substrate strains, which corresponds to another formulation of the mechanical problem. However, the qualitative conclusions remain valid.

In the present study, we have first managed to describe mathematically the mechanical effects related to the cell deformations and intercalations and to quantitatively adjust the results with the experimentally observed characteristic times of constituent processes. In the previous version of the model [3, 13] we did not manage to do this in full measure although in general the process was described correctly. The key step has turned out to be the introduction of the auxiliary phase related to lamellipodia.

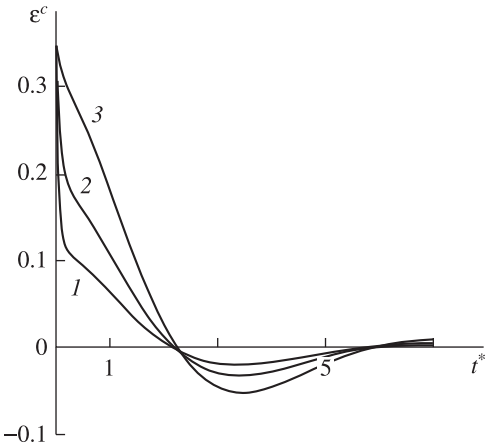

Fig. 4. Evolution of the elastic strain $\varepsilon^{(e)}$ at $k^* = 2.1$ (*1*), 0.9 (*2*), 0.18 (*3*); for other parameters the basic values are taken.

The model considered is developed to describe a specific group of experiments. However, it can be generalized for analyzing various processes in which the same mechanisms, active mechanical cell reactions and intercalations, are important. Such generalizations are necessary for modelling the active polarization of cells in the processes of biological shaping, bending of cell sheets, etc.

Summary. A continuum model which describes the active reactions of a plane embryonic epithelium cell layer and takes into account the active deformations and intercalations of the cells is formulated. The characteristic feature of the model is the explicit introduction of average parameters responsible for the reshaping and stressed state of the cells, as well as for the force interaction between them. The problem of mechanical reaction of a tissue fragment to an initial rapid extension is solved. Agreement with experimentally observed phenomena is obtained.

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