CHINESE JOURNAL OF PHYSICS VOL. 53, NO. 5 October 2015

Exact Dynamics for a Mutator Gene Model

Tatiana Yakushkina,[1,2,*] David B. Saakian,[3,4,†] and Chin-Kun Hu[4,5,6,‡]

[1] *National Research University Higher School of Economics, Moscow 101000, Russia*
[2] *Faculty of Computational Mathematics and Cybernetics, Lomonosov Moscow State University, Moscow 119992, Russia*
[3] *Yerevan Physic Institute, Alikhanian Brothers St. 2, Yerevan 375036, Armenia*
[4] *Institute of Physics, Academia Sinica, Nankang, Taipei 11529, Taiwan*
[5] *National Center for Theoretical Sciences, National Tsing Hua University, Hsinchu 30013, Taiwan*
[6] *Business School, University of Shanghai for Science and Technology, Shanghai 200093, China*

(Received February 14, 2015; Revised September 10, 2015)

Complex systems in biology have attracted much attention in recent decades. We investigate the dynamics of a molecular evolution model related to the mutator gene phenomenon in biology. Here mutation in one gene drastically changes the properties of the whole genome. We investigated the Crow-Kimura version of the model, which can be mapped into a Hamilton-Jacobi equation. For the symmetric fitness landscape, we calculated the dynamics of the maximum of the total population distribution. We found two phases in the dynamics: a simple one when the maximum of the distribution moves along a characteristics, and a more involved one when the maximum jumps to another characteristic at some turnout point T.

DOI: 10.6122/CJP.20150910A PACS numbers: 87.23.Kg

I. INTRODUCTION

The objective of statistical physics developed by Boltzmann (20 February 1844 – 5 September 1906) [1] and Gibbs (11 February 1839 – 28 April 1903 [2] is to understand the properties of a macroscopic system from the interactions of the molecules or atoms of that system. In the development of statistical physics, it has often been found that simple model systems can be useful for understanding the collective or critical behavior [3, 4] of a complicated system consisting of a large number of atoms or molecules, and universality and scaling are important concepts in the study of phase transitions and critical phenomena [3, 4].

For example, in 1945 Guggenheim [5] reported that in the T/T_c versus $\rho/\ \rho_c$ plane (T, T_c, ρ, and ρ_c are the temperature, critical temperature, density, and critical density of the substance, respectively) the gas-liquid coexistence curves of N_e, A_r, K_r, X_e, N_2, O_2, CO, and CH_4 are very consistent with each other, and near the critical point the order

*Electronic address: tyakushkina@hse.ru
†Electronic address: saakian@yerphi.am
‡Electronic address: huck@phys.sinica.edu.tw

parameter [3] $|\rho - \rho_c| \sim |1 - (T/T_c)|^\beta$, with the critical exponent $\beta = 1/3$. In 1952, Yang and Lee proposed that the critical behavior of the gas-liquid system can be represented by a lattice-gas model [6], which is equivalent to the Ising model [7], in which each atom or molecule on a lattice site is assigned a variable which can be either $+1$ or -1. The Ising model has exact solutions when it is on one-dimensional, two-dimensional, and Bethe lattices [3, 7, 8, 9], and has attracted much attention.

In 1995–1996, Blöte and collaborators [10, 11] used Monte Carlo simulations to find that the critical exponent β of the spontaneous magnetization and ν of the correlation length [3] of a three-dimensional (3D) Ising model are 0.3269(6) [11] and 0.6301(8) [10], respectively. In 2009, Sengers and Shanks [12] reviewed the experimental data for gas-liquid critical systems and reported that the order parameter and the correlation length have critical exponents $\beta = 0.3245$ and $\nu = 0.629 \pm 0.003$, respectively. In 2012, Watanabe, Ito, and Hu [13] used molecular dynamics simulations to find that β and ν of a 3D Lennard-Jones (L-J) model system [14, 15, 16] are 0.3285(7) and 0.63(4), respectively. The values of β and ν obtained for simple model systems reported in [10, 11, 13] are highly consistent with the experimental data reported in [5, 12]. Using Monte Carlo methods [17, 18, 19, 20] and analytical methods [21, 22], it has been found that many critical systems have very nice universal and scaling behavior [23, 24, 25, 26, 27, 28, 29, 30, 31].

After the development of molecular biology, it is of interest to know whether one can use the ideas and methods of statistical physics to understand some interesting biological problems from the molecular level or to find some universal behavior in biological systems [32, 33]. It has been pointed out that slow relaxation of a spin glass model [34] at low temperatures can be slower than the critical slowing down of the Ising model [35]; such a result together with the glassy behavior of proteins [36] can be useful for understanding why biological systems, e.g., ancient seeds [37, 38], can be maintained in a non-equilibrium state for a very long time [39]. An all-atom protein model [40, 41] and an analytical method [42, 43] have been used to find universal volume to surface ratios for proteins in a Protein Data Bank (PDB) [44]. Statistical physics has been used to study molecular models of biological evolution [45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57], the origin of life [46, 47, 58, 59], and punctuated equilibrium [60], and some interesting results have been obtained. Following such developments, in this paper we use statistical physics to study the molecular evolution model with a mutator gene whose mutation is possibly related to cancer.

The mutator gene phenomenon [61] (the change of one gene type creates strong instability in the whole genome) plays an important role in the evolution of cancer [62, 63, 64]. The mutation rate of healthy cells is too low to explain the large number of mutations present in cancer cells, and it has been proposed that there is a special mechanism of genome instability to create a large number of mutations. Technically this can be accomplished via the mutation of genes responsible for the genome stability, and as a result there is substantial increase in a mutation rate of the genome. The cancer can be described as a clonal (asexual) evolution of the cells citeno76,pe06. The phenomenon has been investigated using the methods of statistical physics, and several approximate results [67, 68] have been derived, as well some aspects of the model with linear fitness have been solved [69]. In [70] we give

the general solution of the statics, mapping the model into the Hamilton-Jacobi equation (HJE) [71, 72, 73, 74, 75]. For biological applications the dynamics of the phenomenon is especially important [76, 77], and it has been investigated approximately in [67, 68]. In the current article we solve exactly the dynamics for the model presented in [70].

II. MODEL SYSTEM AND CALCULATED RESULTS

We consider the evolutionary process on the symmetric fitness landscape. The genome consists of $(N+1)$ genes with 2 alleles each, represented by $s_\tau = \pm 1, \quad \tau = 0, \ldots, N$. The first gene s_0 defines the mutation rate for the genome: it is either a normal allele ($s_0 = 1$) or a mutator ($s_0 = -1$). Thus we have 2^{N+1} different genotypes $S_i = (s_0, s_1, \ldots, s_N), i = 1, \ldots, 2^{N+1}$. We can use the Hamming distance $l \equiv d_{1i} = (N - \Sigma_{\tau=1}^{N} s_\tau)/2$ to denote the number of mutations of $S_i = (\pm 1, s_1, \ldots, s_N)$ from the reference sequence, which can be taken to be $(\pm 1, 1, \ldots, 1)$ without loss of generality. For symmetric fitness landscapes, we consider N Hamming classes, labeled by $l = 1, \ldots, N$; all sequences in the same class have the same Hamming distance from the reference sequence, and the replicators (viruses or cells) with the genomes from the same Hamming class have the same fitness. We use the notation $x = \sum_{\tau=1}^{N} s_\tau / N$ by analogy with magnetization of the spin system, and it leads to the equality $x = 1 - 2l/N$. We denote the relative frequencies of the replicators in the l-th Hamming class with normal genotype as P_l, and for the mutator types as Q_l.

The relative frequencies P_l and Q_l correspond to the state of the system. We can write the evolutionary dynamics as a kinetic process with the system state defined at nodes of two chains, and there are transitions both within the same chain as well as transitions between chains, as shown in Fig. 1 [78].

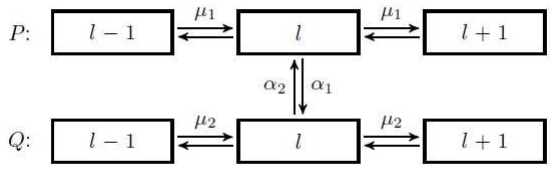

FIG. 1: The scheme of available transitions for the system states (arrows denote transitions). The upper chain corresponds to the genome without a mutator allele; the lower chain corresponds to the genome with a mutator allele.

The $\sqsubset$ **...** $\sqsupset$ denotes the possible system state. The upper chain corresponds to the genome without a mutator allele; the lower chain corresponds to the genome with a mutator allele. A similar scheme has been used to study evolutionary games with randomly changing

payoff matrices [78]. We have the following system of equations:

$$\begin{aligned}\frac{dP_l(t)}{dt} &= P_l(Nf(x) - N(\mu_1+\alpha_1)) + \mu_1(P_{l-1}(N-l+1) + P_{l+1}(l+1)) + \alpha_2 Q_l N,\\ \frac{dQ_l(t)}{dt} &= Q_l(Ng(x) - N(\mu_2+\alpha_2)) + \mu_2(Q_{l-1}(N-l+1) + Q_{l+1}(l+1)) + \alpha_1 P_l N.\end{aligned} \tag{1}$$

Here μ_1 and μ_2 are the mutation rates for the genome configuration of the upper and the lower chains, respectively. Transition rates from the upper chain to the lower chain, and from the lower chain to the upper chain are given by α_1 and α_2, respectively. The functions $f(x)$ and $g(x)$ are the fitness functions for the genomes of the upper and the lower chains, respectively.

When $\alpha_1 = 0$ and $\alpha_2 = 0$, Eq. (1) describes the system of two decoupled Crow-Kimura models, the first one with the fitness function $f(x)$ and mutation rate μ_1, the second one with the fitness function $g(x)$ and mutation rate μ_2. The term $P_{l-1}(N-l+1)$ describes the mutation from the $(l-1)$-th Hamming class to the l-th Hammimg class, and $P_{l+1}(l+1)$ describes the mutation process from the $(l+1)$-th Hamming class to the l-th class. We have these non-trivial coefficients because we formulated the evolutionary dynamics for the Hammimg class probabilities [49].

We consider a simple generalization of the Crow-Kimura model [45, 49, 51, 74]. To obtain Eq. (1), we have used a standard transformation to remove the nonlinear term proportional to the mean fitness in the original Crow-Kimura model [49, 51, 74].

Our goal is to calculate the dynamics of the model. The investigation of evolutionary dynamics attracted a lot of interest recently. Two main methods here are the specific mean-field approach in case of single-peak fitness [51, 79, 80, 81, 82, 82] and the HJE method [71, 72, 73, 74, 75]. The HJE result has been confirmed via an alternative approach by the methods of quantum field theory in [83].

To investigate the system (1) using the HJE method, we introduce the following ansatz [84] considering the notation $x = 1 - 2l/N$ mentioned above:

$$P_l(t) \equiv P(x,t) = v_1 \exp[Nu(x,t)]; \quad Q_l(t) \equiv Q(x,t) = v_2 \exp[Nu(x,t)]. \tag{2}$$

We get:

$$\begin{aligned}\frac{\partial u(x,t)}{\partial t} &= f(x) - \alpha_1 + \mu_1\left(\frac{1+x}{2}e^{2p} + \frac{1-x}{2}e^{-2p} - 1\right) + \frac{v_2}{v_1}\alpha_2,\\ \frac{\partial u(x,t)}{\partial t} &= g(x) - \alpha_2 + \mu_2\left(\frac{1+x}{2}e^{2p} + \frac{1-x}{2}e^{-2p} - 1\right) + \frac{v_1}{v_2}\alpha_1.\end{aligned} \tag{3}$$

Here p is the derivative of $u(x,t)$ with respect to x: $\frac{\partial u(x,t)}{\partial x} \equiv p$. The derivative of $u(x,t)$ with respect to the time variable is denoted by $q \equiv \frac{\partial u(x,t)}{\partial t}$.

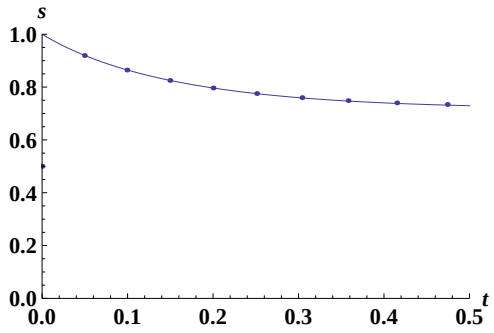

FIG. 2: The dynamics of maximum $s \equiv x^*$ versus the time t, for the case of identical mutation rates $\mu_1 = \mu_2 = \mu = 1$, and different fitness functions $f(x) = 3x^2/2$ and $g(x) = 2x^2$ for two chains with $N = 100$ and $s(0) = 1$. We have $x_c \approx 0.96$. The direct solution (smooth line) versus the analytical results (points) by Eq. (10). The effect of the variance to the dynamics is stronger than the effect of fitness steepness and s decreases monotonically with time, see Eq. (7).

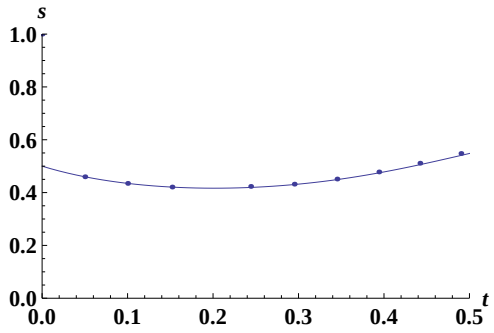

FIG. 3: The dynamics of the maximum $s \equiv x^*$ versus the time t, for the case of identical mutation rates $\mu_1 = \mu_2 = \mu = 1$ and different fitness functions $f(x) = 3x^2/2$ and $g(x) = 2x^2$ for two chains with $N = 100$ and $s(0) = 0.5$. The direct solution (smooth line) versus the analytical results (points) by Eqs. (10) and (12). We have $T \approx 0.2$ and $s(T) \approx 0.417154$, corresponding to the minimum of the curve. The mean fitness $R(t)$ equals $f(s(t))$. The effect of the variance on the dynamics is not always stronger than the effect of fitness steepness, and thus s is not a monotonic function of time t, see Eq. (7).

II-1. Chains with the same mutation rate

Let us suppose that $\mu_1 = \mu_2 = 1$, $\alpha_1 = \alpha_2 = \alpha$. Removing the variables v_1, v_2 from the system of equations in (3), we derive the Hamilton-Jacobi equation (HJE) with an expression for the Hamiltonian $H_\pm$:

$$\frac{\partial u(x,t)}{\partial t} + H_\pm(x,p) = 0,$$
$$-H_\pm = F_\pm(x) + \frac{1+x}{2}e^{2p} + \frac{1-x}{2}e^{-2p} - 1, \tag{4}$$

where

$$F_{\pm}(x) = \frac{f(x)+g(x)}{2} - \alpha \pm \frac{\sqrt{(f(x)-g(x))^2+4\alpha^2}}{2}. \tag{5}$$

$F_{\pm}(x)$ is the effective fitness function. When $f(x) = g(x)$, $F_{+}(x) = f(x) = g(x)$.

Consider now the dynamics of the maximum of the distribution. Let as assume the following ansatz in the vicinity of the maximum $x^*(t)$:

$$\begin{aligned} u &= -K(t)\frac{(x-x^*(t))^2}{2}, \\ K(t) &\equiv \frac{\partial^2 u(t,x^*(t))}{\partial x^2}, \end{aligned} \tag{6}$$

where $1/(K(t)N)$ is the variance of the distribution. We get from Eq. (4) the following equation:

$$\frac{dx^*(t)}{dt} = \frac{-2xK(t)+F'_{\pm}(x)}{K(t)}. \tag{7}$$

We take $f(x)$ as a monotonic function in the region $0 < x < 1$. The first term $-2xK(t)$ is related to the variance. When the variance is small ($K(t)$ is large), the $x^*(t)$ decreases monotonically (the same with the mean fitness). After some critical value of variance, related to the steepness of the fitness, $F'_{\pm}(x)$, the mean fitness and average magnetization $x^*(t)$ begin to rise.

To solve the partial differential equation (4), we can use ordinary differential equations: the Hamilton equations [85, 86]. The lines described by these equations are the characteristics of Eq. (4).

The Hamiltonian does not depend on time, therefore the $q \equiv \frac{\partial u(x,t)}{\partial t}$ is a constant along the characteristics, defined via the Hamilton equations. We write the Hamiltonian equation for x and determine the equations for the characteristics [85, 86]:

$$\dot{x} = -\frac{dH}{dp} = (1+x)e^{2p} - (1-x)e^{-2p}. \tag{8}$$

Then using an equation $q = -H$, we rewrite Eq. (8) as:

$$\dot{x} = \pm 2\sqrt{(q-F_{\pm}+1)^2-(1-x^2)}; \tag{9}$$

Taking into account all possible combinations of signs in Eq. (9), we obtain 4 different characteristics. The solution of the characteristics allows us to calculate the whole distribution analytically, which is a rather complicated task and lies beyond the scope of this investigation. Since in this paper we are interested only in the position of the maximum, we can solve an easier problem.

At the maximum point (x^*, t^*) we have $p = 0$. Therefore, while calculating the dynamics of the maximum, we take $q = F_{+}$ according to Eq. (4). Integrating Eq. (9), we

obtain the time required for the maximum to reach the point x^* starting from the initial point x_0

$$t = \left| \frac{1}{2} \int_{x_0}^{x^*} \frac{1}{\sqrt{(F_+(x^*) - F_+(\xi) + 1)^2 - (1-\xi^2)}} d\xi \right|. \tag{10}$$

The solution of Eq. (10) gives $s \equiv x^*$ as a function of t. The calculated results are shown in Fig. 2 as dots, which are consistent very well with the solid line obtained from direct numerical simulation of Eq. (1).

The alternative solution can take place as well. While integrating Eq. (9) along the characteristic we can arrive at some point x_1 where $dx/dt = 0$. In this case we use the "$-$" sign in the right hand part of Eq. (9) after the turning point x_1. Hence we denote by x_1 the solution of the equation

$$(F_+(x^*) - F_+(x_1) + 1 + \alpha)^2 - (1 - x_1^2) = 0. \tag{11}$$

Concerning the possibility of this sign change, we rewrite (10) as

$$\begin{aligned} t \;=\; & \left| \frac{1}{2} \int_{x_0}^{x_1} \frac{1}{\sqrt{(F_+(x^*) - F_+(\xi) + 1)^2 - (1-\xi^2)}} d\xi \right| \\ & + \left| \frac{1}{2} \int_{x_1}^{x^*} \frac{1}{\sqrt{(F_+(x^*) - F_+(\xi) + 1)^2 - (1-\xi^2)}} d\xi \right|. \end{aligned} \tag{12}$$

The solution of Eq. (10) is valid for $t < T$. Here T is given by Eq. (10) on the assumption that the turning point $x_1 \equiv x_0$

$$(F_+(x^*) - F_+(x_0) + 1)^2 - (1 - x_0^2) = 0. \tag{13}$$

The transition between two solutions takes place at the point $x_0 = x_c$, where the latter is the argument value that maximizes the following expression

$$\max_x [F_+(x) + \sqrt{(1-x^2)} - 1] = F_+(x_c) + \sqrt{(1-(x_c)^2)} - 1. \tag{14}$$

Thus for $x > x_c$ we should take the solution (10), while for $x < x_c$ the solutions (10) and (12). In Fig. 3 we provide an example of the latter case.

II-2. Chains with different mutation rates

In this subsection we investigate the system with the same fitness functions $f(x) = g(x)$ and transition rates α, but different mutation rates. Let us take $\mu_1 = 1$ and $\mu_2 = \mu$.

The Hamiltonian has the form

$$\begin{aligned} -H_\pm \;=\; & f(x) - \alpha + \frac{1+\mu}{2}\Big(-1 + \frac{1+x}{2}e^{2p} + \frac{1-x}{2}e^{-2p}\Big) \\ & \pm \frac{1}{2}\sqrt{(1-\mu)^2\Big(-1 + \frac{1+x}{2}e^{2p} + \frac{1-x}{2}e^{-2p}\Big)^2 + 4\alpha^2}. \end{aligned} \tag{15}$$

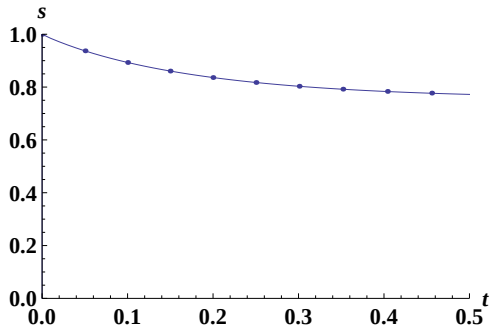

FIG. 4: The dynamics of the maximum s versus time t, for the case $\mu_1 = 1$, $f(x) = g(x) = 3x^2/2$, $\mu_2 = 0.5$ with $N = 200$ and $s(0) = 1$. The analytical results (points) by Eq. (25) are very well consistent with the direct numerical solution of Eq. (1). The effect of the variance on the dynamics is stronger than the effect of fitness steepness, and thus s decreases monotonically with the time t.

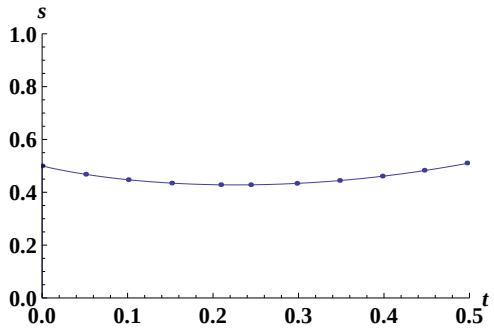

FIG. 5: The dynamics of the maximum s versus time t, for the case $\mu_1 = 1$, $f(x) = g(x) = 3x^2/2$, $\mu_2 = 0.5$ with $N = 200$ and $s(0) = 1$. The analytical results (points) by Eqs. (25) and (28) are very well consistent with the direct numerical solution of Eq. (1). The effect of the variance on the dynamics is not always stronger than the effect of fitness steepness, and thus x is not a monotonic function of the time t.

In this case from the Hamilton equation we obtain

$$\dot{x} = -\frac{dH}{dp} = \left(\frac{1+x}{2}e^{2p} - \frac{1-x}{2}e^{-2p}\right) \times \left((\mu+1) \pm \frac{(\mu-1)^2(-2+(1+x)e^{2p}+(1-x)e^{-2p})}{\sqrt{(1-\mu)^2(-2+(1+x)e^{2p}+(1-x)e^{-2p})^2+16\alpha^2}}\right). \quad (16)$$

We introduce two functions:

$$K_+(q,x) = \frac{1+x}{2}e^{2p} + \frac{1-x}{2}e^{-2p}; \quad (17)$$
$$K_-(q,x) = \frac{1+x}{2}e^{2p} - \frac{1-x}{2}e^{-2p}.$$

With these notations Eq. (16) transforms into

$$\dot{x} = K_-(q,x) \times \left((\mu+1) \pm \frac{(\mu-1)^2 (K_+(q,x)-1)}{\sqrt{(\mu-1)^2 (K_+(q,x)-1)^2 + 4\alpha^2}} \right). \tag{18}$$

From (17) we can derive

$$K_-(q,x) = \pm \sqrt{K_+^2(q,x) - (1-x^2)}. \tag{19}$$

Substituting the above in Eq. (15) we get the following equation for K_+:

$$q = f(x) - \alpha + \frac{1+\mu}{2}(K_+(q,x)-1) \pm \frac{1}{2}\sqrt{(1-\mu)^2 (K_+(q,x)-1)^2 + 4\alpha^2}. \tag{20}$$

It leads to a quadratic equation for $(K_+(q,x)-1)$:

$$\mu (K_+(q,x)-1)^2 + (q - f(x) - \alpha)^2 - \alpha^2 - (q - f(x) + \alpha)(1+\mu)(K_+(q,x)-1) = 0. \tag{21}$$

We get the solution

$$K_+(q,x) = 1 + \frac{1}{2\mu}((q + \alpha - f(x))(1+\mu) \pm \sqrt{D}); \tag{22}$$

here D is a discriminant of Eq. (21):

$$D = (q + \alpha - f(x))^2 (1-\mu)^2 + 4\mu\alpha^2. \tag{23}$$

We obtain two different expressions for the dynamics of the maximum. We can associate q with the maximum point x^*:

$$q = f(x^*). \tag{24}$$

For the simple case when the maximum trajectory is along the single characteristics, see Fig. 4, we use Eq. (24) and derive

$$t = \int_{x_0}^{x^*} \frac{dy}{K_-(f(x^*),y)\left(\mu + 1 + \frac{M^2 (K_+(f(x^*),x)-1)}{\sqrt{M^2 (K_+(f(x^*),x)-1)^2 + 4\alpha^2}}\right)}, \tag{25}$$

where we denoted $M \equiv \mu - 1$.

This solution is valid for $x_0 > x_c$, where x_c is defined as a maximum point of

$$\max \left[f(x) - \alpha + \frac{1+\mu}{2}(-1 + \sqrt{1-x^2}) + \frac{1}{2}\sqrt{(1-\mu)^2 (-1+\sqrt{1-x^2})^2 + 4\alpha^2} \right]. \tag{26}$$

For $x_0 < x_c$, see Fig. 5, we should use the latter expression for $t < T$, where T is given by Eq. (25) with x^* given by

$$K_-(f(x^*), x_0) = 0. \tag{27}$$

For $t > T$ we should use

$$t = \left| \int_{x_0}^{x_1} \frac{dy}{K_-(f(x^*),y)\left(\mu+1+\frac{M^2(K_+(f(x^*),y)-1)}{\sqrt{M^2(K_+(f(x^*),y)-1)^2+4\alpha^2}}\right)} \right| + \left| \int_{x_1}^{x^*} \frac{dy}{K_-(f(x^*),y)\left(\mu+1+\frac{M^2(K_+(f(x^*),y)-1)}{\sqrt{M^2(K_+(f(x^*),y)-1)^2+4\alpha^2}}\right)} \right|. \quad (28)$$

Here x_1 is the solution of the following equation:

$$K_-(f(x^*),x_1) = 0. \quad (29)$$

We obtain the turnout time t looking at the solution of $dx^*/dt = 0$, where $x^*(t)$ is given by Eq. (28).

III. DISCUSSION

In this paper, we investigated the dynamics of a mutator model. The dynamics of evolution models is a rather hot subject [51, 71, 72, 74, 75, 79, 80, 81, 82]. We solved the exact dynamics of the mutator model [70].

We solved the model of evolving population for the symmetric fitness case; the model is equivalent to two chains of equations with vertical connections between them. Such models were intensively investigated recently [84, 87]. They are related to cross diffusion models, applied in molecular ratchets. We used the Hamilton-Jacobi equation to study the dynamics of the maximum. Our Hamiltonian has two branches and there are 4 classes of characteristics. In this work we considered the case when there are back and forward transitions between chains of equations, and we worked with one branch of the Hamiltonian and two classes of characteristics. We performed numerics, confirming well our analytical results. It will be interesting to look for the situations when all the branches of the Hamiltonian and classes of the characteristics are involved in the dynamics. Perhaps this is the situation when $\alpha_2 = 0$ and $\alpha_1 > 0$.

In this paper we solved exactly the dynamics of a rather involved evolution model with a mutator gene. The dynamics of simpler evolution models [88, 89] had been applied to the mathematical modeling of cancer progression and tumor growth. As we have chosen our model just from cancer biology, we hope that our results also can be applied to the modeling of cancer.

Acknowledgements

We would like to thank the referee for carefully reading the paper and giving useful comments. This work was supported by Grants MOST 101-2923-M-001 -003 -MY3, MOST

103-2112-M-001-016, and MOST 103-2811-M-001-171. TY was partly supported by joint grant between Russian Foundation for Basic Research (RFBR) and Taiwan Ministry of Science and Technology (MOST) with Grant No. 12-01-92004HHC-a.

References

[1] L. Boltzmann, *Lectures on gas theory* (1896, 1898), translated by S. G. Brush (University of California Press, Berkeley, 1964), reprinted (Dover, New York, 1995).
[2] J. W. Gibbs, *Elementary Principles in Statistical Mechanics* (New York, 1902), reprinted (Ox Bow Press, Woodbridge, CT, 1981).
[3] H. E. Stanley, *Introduction to Phase Transitions and Critical Phenomena* (Oxford Univ. Press, New York, 1971).
[4] C. K. Hu, Chinese J. Phys. **52**, 1 (2014).
[5] E. A. Guggenheim, J. Chem. Phys. **13**, 253 (1945). doi: 10.1063/1.1724033
[6] C. N. Yang and T. D. Lee, Phys. Rev. **87**, 404 (1952); doi: 10.1103/PhysRev.87.404
T. D. Lee and C. N. Yang, Phys. Rev. **87**, 410 (1952). doi: 10.1103/PhysRev.87.404
[7] E. Ising, Zeitschrift fur Physik **31**, 253 (1925). doi: 10.1007/BF02980577
[8] L. Onsager, Phys. Rev. **65**, 117 (1944); doi: 10.1103/PhysRev.65.117.
B. Kaufman, Phys. Rev. **76**, 1232 (1949); doi: 10.1103/PhysRev.76.1232.
C. N. Yang, Phys. Rev. **85**, 808 (1952); doi: 10.1103/PhysRev.85.808.
M. C. Wu and C. K. Hu, J Phys. A: Math. Gen. **35**, 5189 (2002). doi: 10.1088/0305-4470/35/25/304
[9] N. S. Izmailian and C. K. Hu, Physica A **254**, 198-206 (1998);
doi: 10.1016/S0378-4371(98)00193-9.
C. K. Hu and N. S. Izmailian, Phys. Rev. E **58**, 1644 (1998). doi: 10.1103/PhysRevE.58.1644
[10] H. W. J. Blöte, E. Luijten, and J. R. Heringa, J. Phys. A: Math. Gen. **28**, 6289 (1995). doi: 10.1088/0305-4470/28/22/007
[11] A. L. Talapov and H. W. J. Blöte, J. Phys. A: Math. Gen. **29**, 5727 (1996). doi: 10.1088/0305-4470/29/17/042
[12] J. V. Sengers and J. G. Shanks, J. Stat. Phys. **137**, 857 (2009). doi: 10.1007/s10955-009-9840-z
[13] H. Watanabe, N. Ito, and C. K. Hu, J. Chem. Phys. **136**, 204102 (2012). doi: 10.1063/1.4720089
[14] J. E. Jones, Proc. R. Soc. London A **106**, 463 (1924). doi: 10.1098/rspa.1924.0082
[15] J. E. Lennard-Jones, Proc. Phys. Soc. **43**, 461 (1931). doi: 10.1088/0959-5309/43/5/301
[16] J. E. Jones married Mrs. Lennard in 1925 and used the family name Lennard-Jones in his papers after marriage.
[17] N. Metropolis and S. Ulam, J. Amer. Stat. Assoc. **44**, 335 (1949). doi: 10.2307/2280232
[18] N. Metropolis, A. W. Rosenbluth, M. N. Rosenbluth, A. H. Teller, and E. Teller, J. Chem. Phys. **21**, 1087 (1953).
[19] C. K. Hu, Phys. Rev. B **46**, 6592 (1992). doi: 10.1103/PhysRevB.46.6592
[20] C. K. Hu, Phys. Rev. Lett. **69**, 2739 (1992). doi: 10.1103/PhysRevLett.69.2739
[21] M. C. Wu and C. K. Hu, J. Phys. A. **35**, 5189 (2002). doi: 10.1088/0305-4470/35/25/304
[22] E. V. Ivashkevich, N. S. Izmailian, and C. K. Hu, J. Phys. A. **35**, 5543 (2002).
doi: 10.1088/0305-4470/35/27/302
[23] C. K. Hu, J. Phys. A **27**, L813-L820 (1994).
[24] C. K. Hu, C. Y. Lin, and J. A. Chen, Phys. Rev. Lett. **75**, 193 (1995).
[25] C. K. Hu and C. Y. Lin, Phys. Rev. Lett. **77**, 8-11 (1996).

[26] F. G. Wang and C. K. Hu, Phys. Rev. E **56**, 2310-2313 (1997). doi: 10.1103/PhysRevE.56.2310
[27] Y. Okabe, K. Kaneda, M. Kikuchi, and C. K. Hu, Phys. Rev. E **59**, 1585-1588 (1999).
[28] Y. Tomita, Y. Okabe, and C. K. Hu, Phys. Rev. E **60**, 2716-2720 (1999). doi: 10.1103/PhysRevE.60.2716
[29] N. S. Izmailian and C. K. Hu, Phys. Rev. Lett. **86**, 5160-5163 (2001). doi: 10.1103/PhysRevLett.86.5160
[30] M. C. Wu, C. K. Hu, and N. S. Izmailian, Phys. Rev. E **67**, 065103 (2003). doi: 10.1103/PhysRevE.67.065103
[31] N. Sh. Izmailian, K. B. Oganesyan, M. C. Wu, and C. K. Hu, Phys. Rev. E **73**, 016128 (2006). doi: 10.1103/PhysRevE.73.016128
[32] H. Li, R. Helling, C. Tang, and N. Wingreen, Science **273**, 666-669 (1996); M. S. Li *et al.*, Phys. Rev. lett. **105**, 218101 (2010); doi: 10.1103/PhysRevLett.105.218101N. T. Co, C.-K. Hu, and M. S. Li, J. Chem. Phys. **138**, 185101 (2013); doi: 10.1063/1.4804299. C. N. Chen, Y. H. Hsieh, and C. K. Hu, EPL **104**, 20005 (2013). doi: 10.1209/0295-5075/104/20005
[33] W. J. Ma and C. K. Hu, J. Phys. Soc. Japan **79**, 024005 (2010); doi: 10.1143/JPSJ.79.024005
W. J. Ma and C. K. Hu, J. Phys. Soc. Japan **79**, 024006 (2010); doi: 10.1143/JPSJ.79.024006
W. J. Ma and C. K. Hu, J. Phys. Soc. Japan **79**, 054001 (2010); doi: 10.1143/JPSJ.79.054001
W. J. Ma and C. K. Hu, J. Phys. Soc. Japan **79**, 104002 (2010); doi: 10.1143/JPSJ.79.104002
C. K. Hu and W.-J. Ma, Prog. Theor. Phys. Supp. **184**, 369 (2010); doi: 10.1143/PTPS.184.369
C. K. Hu, J. Phys.: Conf. Ser. **604**, 012009 (2015). doi: 10.1088/1742-6596/604/1/012009
[34] C. Dasgupta, S. K. Ma, and C.-K. Hu, Phys. Rev. B **20**, 3837 (1979). doi: 10.1103/PhysRevB.20.3837
[35] F. G. Wang and C.-K. Hu, Phys. Rev. E **56**, 2310 (1997). doi: 10.1103/PhysRevE.56.2310
[36] S. G. Gevorkian, A. E. Allahverdyan, D. S. Gevorgyan, and C.-K. Hu, EPL **95**, 23001 (2011); doi: 10.1209/0295-5075/95/23001
S. G. Gevorkian, A. E. Allahverdyan, D. S. Gevorgyan, A. L. Simonian, and C.-K. Hu, Plos One **8**, e78526 (2013); doi: 10.1371/journal.pone.0078526
S. G. Gevorkian, A.E. Allahverdyan, D. S. Gevorgyan, and C.-K. Hu, Scienific Reports **5**, 13064 (2015). doi: 10.1038/srep13064
[37] S. Sallon *et al.*, Science **320**, 1464 (2008). doi: 10.1126/science.1153600
[38] S. Yashina *et al.*, Proc. Nat. Acad. SCi. USA **109**, 4008 (2012). doi: 10.1073/pnas.1118386109
[39] C.-K. Hu, AIP Conference Proceedings **1518**, 541 (2013).
[40] F. Eisenmenger, U. H. E. Hansmann, S. Hayryan, and C.-K. Hu, Comput. Phys. Commun. **138**, 192 (2001). doi: 10.1016/S0010-4655(01)00197-7
[41] F. Eisenmenger, U. H. E. Hansmann, S. Hayryan, and C.-K. Hu, Comput. Phys. Commun. **174**, 422 (2006). doi: 10.1016/j.cpc.2005.10.013
[42] S. Hayryan, C.-K. Hu, J. Skrivanek, E. Hayryan, and I. Pokorny, J. Comp. Chem. **26**, 334 (2005). doi: 10.1002/jcc.20125
[43] J. Busa *et al.*, Comp. Phys. Commun. **165**, 59 (2005); J. Busa Jr. S. Hayryan, M. C. Wu, J. Busa, and C.-K. Hu, Comp. Phys. Commun. **183**, 2494 (2012).
[44] M. C. Wu, M. S. Li, W. J. Ma, M. Kouza, and C. K. Hu, EPL **96**, 68005 (2011). doi: 10.1209/0295-5075/96/68005
[45] J. F. Crow and M. Kimura, *An Introduction to Population Genetics Theory* (Harper Row, New York, 1970).
[46] M. Eigen, Naturwissenschaften **58**, 465 (1971). doi: 10.1007/BF00623322
[47] M. Eigen, J. S. McCaskill, and P. Schuster, Adv. Chem. Phys. **75**, 149 (1989).
[48] E. Baake, M. Baake, and H. Wagner, Phys. Rev. Lett. **78**, 559 (1997). doi: 10.1103/PhysRevLett.78.559

[49] E. Baake and H. Wagner, Genet. Res. **78**, 93 (2001). doi: 10.1017/S0016672301005110
[50] D. B. Saakian and C. K. Hu, Phys. Rev. E **69**, 021913 (2004). doi: 10.1103/PhysRevE.69.021913
[51] D. B. Saakian and C. K. Hu, Phys. Rev. E **69**, 046121 (2004). doi: 10.1103/PhysRevE.69.046121
[52] D. B. Saakian, C.-K. Hu, and H. Khachatryan, Phys. Rev. E **70**, 041908 (2004). doi: 10.1103/PhysRevE.70.041908
[53] D. B. Saakian and C.-K. Hu, Proc. Natl. Acad. Sci. USA **103**, 4935 (2006). doi: 10.1073/pnas.0504924103
[54] D. B. Saakian, E. Munoz, C.-K. Hu, and M. W. Deem, Phys. Rev. E **73**, 041913 (2006). doi: 10.1103/PhysRevE.73.041913
[55] D. B. Saakian, M. W. Deem, and C.-K. Hu, EPL **98**, 18001 (2012). doi: 10.1209/0295-5075/98/18001
[56] Z. Kirakosyan, Chinese J. Phys. **50**, 101 (2012); M. Ghazaryan and D. B. Saakian, Chinese J. Phys. **53**, 060901 (2015).
[57] D. B. Saakian and C.-K. Hu, Phys. Rev. E **88**, 052717 (2013). doi: 10.1103/PhysRevE.88.052717
[58] D. B. Saakian, C. K. Biebricher, and C. K. Hu, PLoS One **6**, e21904 (2011). doi: 10.1371/journal.pone.0021904
[59] Z. Kirakosyan, D. B. Saakian, and C.-K. Hu, J. Phys. Soc. Jpn. **81**, 114801 (2012). doi: 10.1143/JPSJ.81.114801
[60] D. B. Saakian, M. Ghazaryan, and C.-K. Hu, Phys. Rev. E **90**, 022712 (2014). doi: 0.1103/PhysRevE.90.022712
[61] L. A. Loeb, C. F. Springgate, N. Battula, Cancer Res. **34**, 2311 (1974).
[62] L. A. Loeb, K. R. Loeb, and J. P. Anderson, Proc. Natl. Acad. Sci. USA **100**, 776 (2003). doi: 10.1073/pnas.0334858100
[63] E. J. Fox and L. A. Loeb, Seminars in Cancer Biology **20**, 353 (2010). doi: 10.1016/j.semcancer.2010.10.005
[64] L. A. Loeb, Nature Review Cancers **11**, 450 (2011). doi: 10.1038/nrc3063
[65] P. C. Nowell, Science **194**, 23 (1976). doi: 10.1126/science.959840
[66] L. M. F. Merlo, J. W. Pepper, B. J. Reid, and C. C. Maley, Nature Review Cancers **6**, 924 (2006).
[67] D. Kessler and H. Levine, Phys. Rev. Lett. **80**, 2012 (1998). doi: 10.1103/PhysRevLett.80.2012
[68] P. Gorodetsky and E. Tannenbaum, Phys. Rev. E **77**, 042901 (2008). doi: 10.1103/PhysRevE.77.042901
[69] A. Nagar and K. Jain, Phys. Rev. Lett. **102**, 038101 (2009). doi: 10.1103/PhysRevLett.102.038101
[70] D. B. Saakian, T. Yakushkina, and C.-K. Hu, preprint.
[71] D. B. Saakian, J. Stat. Phys. **128**, 781 (2007). doi: 10.1007/s10955-007-9334-9
[72] K. Sato and K. Kaneko, Phys. Rev. E **75**, 061909 (2007). doi: 10.1103/PhysRevE.75.061909
[73] D. B. Saakian, Z. Kirakosan, and C.-K. Hu, Phys. Rev. E **77**, 061907 (2008). doi: 10.1103/PhysRevE.77.061907
[74] D. B. Saakian, O. Rozanova, and A. Akmetzhanov, Phys. Rev. E **78**, 041908 (2008). doi: 10.1103/PhysRevE.78.041908
[75] N. N. Subbotina and L. G. Shagalova, The Proceedings of Steklov Institute of Mathematics **277**, 234 (2012). doi: 10.1134/S0081543812040177
[76] L. Chao and E. C. Cox, Evolution **37**, 125 (1983). doi: 10.2307/2408181
[77] P. D. Sniegowski, P. J. Gerrish, and R. E. Lenski, Nature **387**, 703 (1997). doi: 10.1038/42701
[78] T. Yakushkina, D. B. Saakian, A. Bratus, and C. K. Hu, J. Phys. Soc. Japan **84**, 064802 (2015). doi: 10.7566/JPSJ.84.064802

[79] D. B. Saakian and J. F. Fontanari, Phys. Rev. E **80**, 041903 (2009). doi: 10.1103/PhysRevE.80.041903
[80] A. G. M. Neves, Phys. Rev. E **82**, 031915 (2010). doi: 10.1103/PhysRevE.82.031915
[81] M. Ancliff and J. M. Park, Phys. Rev. E **82**, 021904 (2010). doi: 10.1103/PhysRevE.82.021904
[82] G. Wonpyang, J. of Korean Phys. Soc. **57**, 287 (2010).
[83] M. Ancliff and J. M. Park, J. Korean Phys. Soc. **61**, 1898 (2012). doi: 10.3938/jkps.61.1898
[84] V. Galstyan and D. B. Saakian, Phys. Rev. E **86**, 011125 (2012). doi: 10.1103/PhysRevE.86.011125
[85] A. Melikyan *Generalized Characteristics of First Order PDEs*, (Birkhäuser, Boston, 1998). doi: 10.1007/978-1-4612-1758-9
[86] L. C. Evans, *Partial Differential Equations, second edition*, (American Math. Society, 2010).
[87] M. Assaf, E. Roberts, and Z. Luthey-Schulten, Phys. Rev. Lett. **106**, 248102 (2011). doi: 10.1103/PhysRevLett.106.248102
[88] I. Bozica *et al.*, Proc. Natl. Acad. Sci. USA **107**, 18545-18550 (2010).
[89] C. D. Mc *et al.*, Proc. Natl. Acad. Sci. USA **110**, 2910-2915 (2013).