Relaxation dynamics in Dyson's model for the origin of metabolism

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This paper discusses some aspects of the dynamical evolution of the system described by Dyson's model for the origin of metabolism. First, the mean number of mutation events required to observe the origin of metabolism in the model is calculated. This number can span a large range depending upon the values of some critical parameters. Second, the dynamics of the relaxation to equilibrium is investigated by computing the correlation function of an on-off random function that defines the instantaneous state of the system. It was found that the dynamics of the system is well described by a double or a stretched exponential relaxation. [S1063-651X(96)10207-5]

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I. INTRODUCTION

In an earlier paper [1] we discussed a model for the origin of metabolism that was introduced by Dyson [2]. One of the hypotheses for the elaboration of the model is that cells came first, enzymes second, and genes much later [2,3]. The primitive cell is envisaged as an inert droplet containing a population of polymer molecules composed of bound monomer units analogous to the amino acids that make up modern proteins. There is no Darwinian selection. Changes in the polymer populations within the cell proceed by random discrete steps of mutation, each mutation being a replacement of one monomer by another at one of the sites in a polymer. In a given population of polymers, the bound monomers are either in active or in inactive states, the active monomers being in sites where they contribute to the ability of a polymer to act as a catalyst. The probability that a monomer inserted by a fresh mutation is active is described by the autocatalytic function $\phi(x)$, which only depends upon the fraction x of active monomers already present in the population. The monomers are assumed to belong to $1+\nu=1/\phi(0)$ equally abundant species and so the active state is unique, whereas there are ν possibilities for the inactive states. Modeled in this way, the essential feature for the origin of metabolism lies in the transition that occurs for the total population of the droplet from the disorganized or *dead* state to the organized or *alive* state [1,2]. In this context, the terms alive and dead mean the presence and absence of metabolic organization.

We showed in Ref. [1] that the concept of a spin glass as a model for the transition to biological order is applicable to Dyson's model for the origin of metabolism. Because the theoretical framework provided by the random energy model [4] can be employed to study the problem, the equilibrium properties for the model can be completely determined. For instance, the droplet cell, as described above, was characterized in terms of the features of a rugged potential energy landscape in which the monomers strongly interact with each other. It was shown that the law of inheritance from parent to daughter given by the autocatalytic function $\phi(x)$ is completely governed by the nature of interactions between monomers. As a consequence, the diversity of the population of monomers and the precision of the polymerizing catalysts were found to be intimately related.

Our main interest in this paper is to study the dynamical evolution of the droplet population with respect to mutation events. To do this, we consider that the droplet contains N monomers and assume that its configuration is solely specified by the number $i=0,1,\ldots,N$ of monomers active after t mutations. In what follows, for convenience, the number t of mutation events will often be called the time t. The variation of $i(t)$ corresponds to a discrete one-step Markov process $i\rightarrow i+1, i\rightarrow i-1$; i.e., the population in the droplet does a biased one-dimensional random walk. It follows that the daughter population and its ancestors are not correlated. The probability of finding i active monomers in the population after t mutation events is denoted by $P(i,t)$, and the time evolution of the population is descibed by the master equation

$$\frac{\partial P(i,t)}{\partial t}=\sum_{j=0}^{N}\omega_{ij}P(j,t), \tag{1}$$

where ω_{ij} are the matrix elements of the $(N+1)\times(N+1)$ nonsymmetric matrix of transition probabilities per unit of mutation. They obey detailed balance:

$$\omega_{i,j}P_{\mathrm{eq}}(i)=\omega_{j,i}P_{\mathrm{eq}}(j), \tag{2}$$

where $P_{\mathrm{eq}}(i)$ is the equilibrium probability of finding i monomers active in the system. The transition probabilities are defined as [2]

$$\begin{aligned} &i\rightarrow i+1: \quad \omega_{i,i+1}=(N-i)\phi(i/N), \ \ \omega_{-1,0}=0,\\ &i-1\leftarrow i\rightarrow i+1: \quad \omega_{i,i}=-\omega_{i,i+1}-\omega_{i,i-1}, \end{aligned} \tag{3}$$

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$$i \to i-1: \quad \omega_{i,i-1} = i[1-\phi(i/N)], \quad \omega_{0,-1} = 0.$$

$\phi(x)$ is the autocatalytic probability that the mutated unit is active in a droplet that already contains i active monomers and is defined, as before [1], as being of Glauber type:

$$\phi(x) = \frac{1}{1+\exp[E_a(x)/k_BT]} = \frac{1}{1+\exp(A-Bx)} \tag{4}$$

with $x = i/N$ being the fraction of active monomers, $E_a(x)$ the activation energy for the transition between two configurations $i \to i+1$, and k_BT the thermal energy. The constants A and B are given by [1]

$$A = \frac{4zJ-2\varepsilon}{k_BT} \text{ and } B = \frac{8zJ}{k_BT}, \tag{5}$$

where ε is the energy gained (lost) for a monomer to be active (inactive), zJ is the interaction energy between monomers, and z is the average coordination number.

The outline of the paper is as follows. In Sec. II, the characteristics for systems dead, symmetric, and alive are defined from the equilibrium distribution. In Sec. III a first passage time formalism is used to determine how long it takes for a population to switch spontaneously from the disorganized to the organized state for each of the systems. Section IV is devoted to a study of the relaxation dynamics in the three systems defined in Sec. II. This is done by numerically solving the master equation that describes the time evolution of the population and by computing the autocorrelation function of an arbitrary random physical quantity. The paper ends with concluding remarks in Sec. V.

II. EQUILIBRIUM DISTRIBUTION

The stationary solution of Eq. (1) with the transition rates (3) is given by

$$P_{\rm eq}(i) = \frac{1}{Z}\exp\left\{-\sum_{j=1}^{i}\ln\left(\frac{\omega_{j,j-1}}{\omega_{j,j+1}}\right)\right\}, \tag{6}$$

where Z is the partition function defined as

$$Z = \sum_{i=1}^{N}\exp\left\{-\sum_{j=1}^{i}\ln\left(\frac{\omega_{j,j-1}}{\omega_{j,j+1}}\right)\right\}. \tag{7}$$

The equilibrium distribution is the Boltzmann distribution:

$$P_{\rm eq}(x) \sim e^{-NU(x)} \tag{8}$$

where $U(x)$ is the potential of the free energy of the droplet containing N interacting monomers. It has been shown [1] (see also Appendix B) that the potential $U(x)$ can be written as

$$U(x) = x\ln(x) + (1-x)\ln(1-x) + Ax - \frac{B}{2}x^2. \tag{9}$$

The equilibrium distribution, calculated from Eq. (6), and the potential $U(x)$ are displayed in Figs. 1(a) and 1(b) for some selected systems. It was shown in Ref. [1] that for

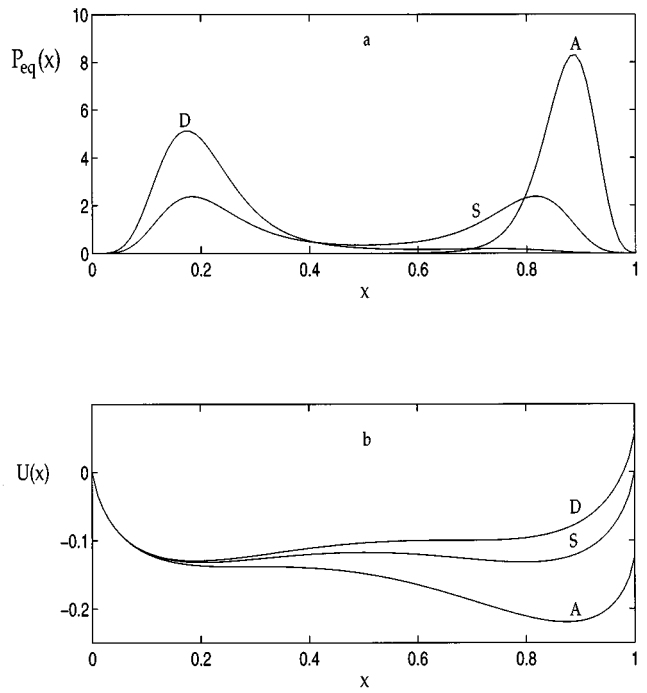

FIG. 1. (a) Equilibrium distribution $P_{\rm eq}(x)$ calculated from Eq. (6) with $\nu = 10$ and $N = 100$ for the three systems symmetric (S), dead (D), and alive (A). The corresponding values for the pair of parameters (A,B) are (2.3,4.6), (2.3,4.49), and (2.3,4.85), respectively. (b) The shapes of the potential $U(x)$ corresponding to the above systems.

$A > A_c = 2$ and $B > B_c = 4$ the potential $U(x)$ is bistable and exhibits two stable minima at $x = \alpha$ (disorganized state) and at $x = \gamma$ (organized state), and an unstable maximum at $x = \beta$ with $\alpha < \beta < \gamma$ (see Tables I and II). The organized state is called ''alive'' because most monomers are active, and together they maintain the catalytic processes which keep them active. The disorganized state is called ''dead'' since most monomers are inactive and do not work in the same collaborative fashion. Accordingly, it is possible to consider three special cases for systems with respect to the occurrence of the order-disorder transition

(i) *Dead system*. In this system, $U(x)$ has only a stable minimum in the disorganized state and the potential barrier coincides with the organized state such that $\alpha < \beta = \gamma$. Because of the absence of the stable organized state this situation is called a dead system. Numerical analysis shows that the variation of the height of the potential barrier, $\Delta = U(\beta) - U(\alpha)$, with the diversity ν can be written as

$$\Delta \simeq 0.0174\nu_e, \quad \nu_e \geqslant 0, \tag{10}$$

where $\nu_e = |\nu - \nu_c|$ plays the role of an effective diversity in the system. The critical diversity ν_c is related to A_c by $\nu_c = \exp\{A_c\}$.

(ii) *Alive system*. This case is the opposite of the dead system. The unique minimum of $U(x)$ is actually in the organized state and the unstable barrier top coincides with the disorganized state such that $\alpha = \beta < \gamma$. As above, this situation is called an alive system because of the absence of a

TABLE I. Some selected values for A and B in the three systems alive, symmetric, and dead. A is related to the number $\nu+1$ of monomer species (or the degeneracy of a given monomer) by the relation $A=\ln(\nu)$. α and γ are the locations of the disorganized and organized states, respectively, and β is the barrier position. For the symmetric system, $B=2A$ and $\beta=0.5$.

Diversity		Alive			Symmetric		Dead	
ν	B	$\alpha=\beta$	γ	α	γ	B	α	$\beta=\gamma$
7.389	4	0.5	0.5	0.5	0.5	4	0.5	0.5
8	4.1851	0.3947	0.7047	0.3333	0.6667	4.1414	0.3190	0.5924
10	4.8524	0.2904	0.8744	0.2029	0.7971	4.4936	0.1906	0.6657
12	5.5516	0.2358	0.9385	0.1483	0.8517	4.7603	0.1391	0.6998
14	6.2639	0.1994	0.9686	0.1169	0.8831	4.9771	0.1098	0.7215
16	6.9831	0.1732	0.9836	0.0964	0.9036	5.1601	0.0908	0.7371
18	7.7066	0.1532	0.9914	0.0819	0.9181	5.3186	0.0773	0.7490
19	8.0693	0.1400	0.9938	0.0761	0.9239	5.3904	0.0720	0.7500
20	8.4329	0.1375	0.9955	0.0711	0.9289	5.4584	0.0674	0.7585

stable disorganized state. The ν dependence for the barrier height, $\Delta'=U(\beta)-U(\gamma)$, reads

$$\Delta' \simeq 0.0123 \nu_e^{1.8}, \quad \nu_e \geqslant 0. \tag{11}$$

(iii) *Symmetric system*. Between the two extreme situations described above there is a third case called a symmetric system, characterized by a double-well structure for $U(x)$ with the top of the barrier at $\beta=1/2$ and two equal wells at α and γ such that $\alpha=1-\gamma$ and $B=2A$. The ν dependence for the barriers, $\Delta'=\Delta$, is given by

$$\Delta \simeq 0.0097 \nu_e, \quad \nu_e \geqslant 0. \tag{12}$$

The phase diagram in the space $\{\epsilon, zJ\}$ representing the composition of the population shows a typical cusp for which the points inside the cusp at $(0,\frac{1}{2})$ correspond to the transition region (see Fig. 1 of Ref. [1]). For all systems the barrier heights Δ and Δ' cancel at the cusp $\nu_e=0$, where the bistability of $U(x)$ vanishes. Beyond the cusp, both Δ and Δ' increase with the diversity and are, by definition, equal to zero in the alive and dead systems, respectively. Apart from the symmetric system, the organized and disorganized states are not mirror images of each other and so there are differences between Δ and Δ'. This also indicates that any dynamical evolution will be intrinsically biased in these systems. The bias, controlled by either the energy ε or the difference $\Delta'-\Delta$, is negative, zero, and positive for the dead, symmetric, and alive systems, respectively.

TABLE II. Values of potential barriers as a function of ν, with $\Delta=U(\beta)-U(\alpha)$ and $\Delta'=U(\beta)-U(\gamma)$.

Diversity	Alive	Symmetric	Dead
ν	Δ'	Δ	Δ
7.389	0.0	0.0	0.0
8.0	0.45618×10^{-2}	0.11293×10^{-2}	0.26955×10^{-2}
10.0	0.81130×10^{-1}	0.14495×10^{-1}	0.29808×10^{-1}
12.0	0.22926	0.33967×10^{-1}	0.66028×10^{-1}
14.0	0.42384	0.54878×10^{-1}	0.10344
16.0	0.64906	0.75588×10^{-1}	0.13972
18.0	0.89541	0.95497×10^{-1}	0.17417
19.0	0.10245×10	0.10508	0.19069
20.0	0.11569×10	0.11441	0.20663

III. MEAN NUMBER OF MUTATION EVENTS

We want to determine the mean number τ of mutation events after which a system starting out in the disordered dead state reaches an ordered state for the first time. In general, the population of monomers will spend a long time in either the dead or alive states, making small random fluctuations around the stable equilibrium. There may, however, be fluctuations which take the whole population of the droplet over the top of the barrier from one stable equilibrium to the other. Thus the origin of metabolism comes about when a system in a dead state makes such a transition to the alive state. τ is the mean number of mutation events required to observe this transtion and is exactly the mean first passage (nondimensional) time for a system starting out at $i=\alpha N$ to reach the point $i=\gamma N$.

Following the first passage time approach and by imposing reflecting and absorbing boundary conditions at $i=0$ and $i=\gamma N$, respectively, one can show that the mean number of mutation events can be obtained from the relation

$$\tau = \sum_{i=\alpha N}^{\gamma N-1} \frac{1}{\omega_{i,i+1} P_{\mathrm{eq}}(i)} \sum_{j=1}^{i} P_{\mathrm{eq}}(j). \tag{13}$$

The nonfactorization of transition rates $\omega_{i,j}$ precludes an analytical expression for τ. However, more information can be gained from the asymptotic approximation for τ obtained in the continuum limit of Eq. (13). This has been done in Appendix C and the numerical results can be summarized as ($\nu_e>0$)

$$\tau \simeq \begin{cases} 8.16 N^{1/6} \exp(N\Delta), & \text{dead} \\ 24.34 \exp(N\Delta), & \text{symmetric} \\ 13.79 \nu_e^{-0.265} N^{1/4}, & \text{alive.} \end{cases} \tag{14}$$

According to this, the behavior of τ versus the diversity is expected to be dramatically different between the alive system and the two others.

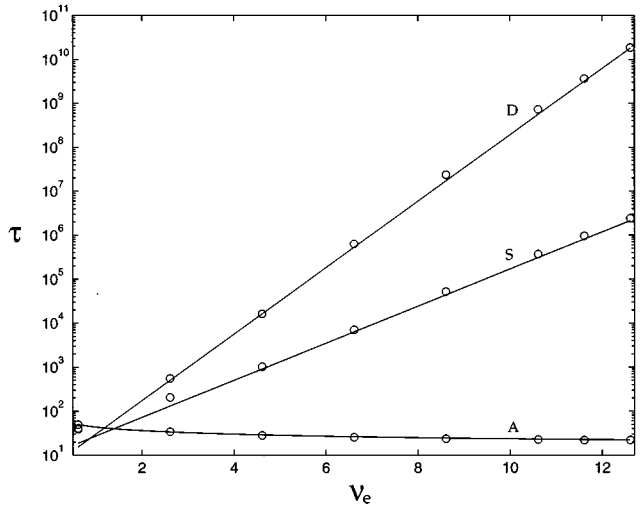

FIG. 2. Mean number of mutation events τ as a function of the effective diversity ν_e for the symmetric (S), dead (D), and alive (A) systems. The data (circles) are obtained from the computation of the formula in Eq. (13) for a population of size $N=100$. The solid lines through the data correspond to the asymptotic expressions of Eq. (14).

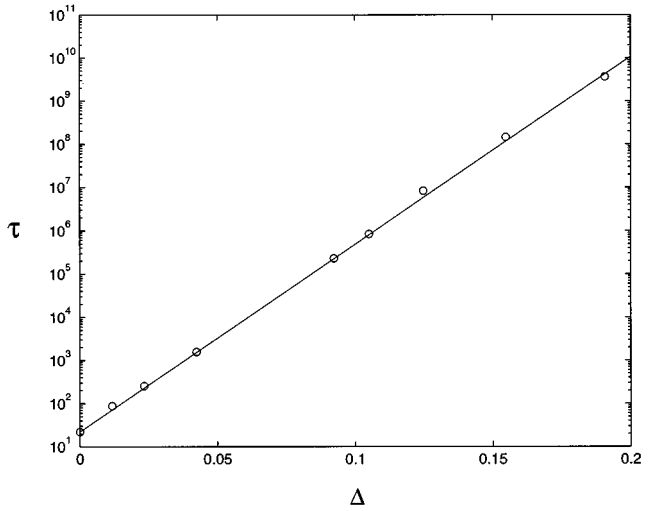

FIG. 3. Mean number of mutation events τ as a function of barrier height Δ for $\nu=19$ and $N=100$. The solid line through the data (circles) corresponds to Eq. (15).

For dead and symmetric systems, τ grows exponentially with the effective diversity and the size of the population. Numerical analysis confirms these facts, as shown in Fig. 2, which displays a semilogarithmic plot of τ versus ν_e. The plot for $N=100$ was obtained using the exact formula in Eq. (13) and the lines through the data correspond to the approximation of Eq. (14). This exponential growth for τ is very similar to the period of a Poincaré cycle and corresponds to the so-called Levinthal time for protein folding [5]. On proceeding by random search among all possible configurations, the system finds the metabolic organized state with difficulty, so that the mean number of mutations required to observe that transition is immense. It follows that the origin of metabolism is exponentially improbable in such systems.

For the alive system, on the other hand, τ slowly decreases with ν_e, as depicted in Fig. 2, since the probability of choosing an active monomer among the others goes down with the chemical diversity as $1/\nu_e$. The number of mutations required to find the organized state is dramatically reduced and the origin of metabolism is now a quite frequent event. The system explores a very small number of possible configurations in order to find the alive state. At first sight, it seems that the effective diversity or the total number of possible configurations is exponentially reduced, so making the search more efficient and less long. This stems essentially from the barrierless downhill structure of the potential $U(x)$, which admits a unique stable minimum in the alive state. It is to be noted that the $N^{1/4}$ dependence of τ for the alive system suggests that τ keeps comparable values for population sizes ranging over about three order of magnitude. For instance,

$$\frac{\tau(\nu_e,N)}{\tau(\nu_e,N=10^2)}=1,\ 1.78, 3.16 \quad \text{for} \quad N=10^2,\ 10^3,\ 10^4.$$

The variation of both the diversity and the size of the population of monomers has little effect on the origin of metabolism for the alive system. This robustness of the process against variation or fluctuations of ν_e and N is not seen in the symmetric and dead systems because of the finite values of Δ.

It is interesting to determine the effect of a variation of the potential on τ. Specifically, how is the mean number τ (or the mean time) modified when the potential $U(x)$ is *adiabatically* changed from a dead to an alive state? For an adiabatic change, we require that the time scale $1/\Omega$ for the variation of the shape of $U(x)$ is much larger than the characteristic time $\tau_{\rm rx}$ for the relaxation to equilibrium for the system; i.e., $\Omega\tau_{\rm rx}\ll 1$. Such changes can take place due either to the influence of other catalysts as in the enzymatic reaction or to certain external influences that could occur during long periods of the evolution. The effect of switching the potential shape from that for a dead system to that for an alive one is to increase both the energy ε gained for making a monomer active and the interaction energy zJ between monomers. Thus the system goes from a state of low stress to a more constrained one. To work out how such changes modify τ, we have computed the mean number τ as a function of the barrier height Δ for a fixed diversity $\nu=19$ and a population $N=100$. To maintain the value of ν [$=\exp(A)$] constant when changing the potential, it is necessary to adjust the values of the control energies ε and zJ. The value of Δ allows us to characterize the variation of the potential and it takes the values of $\Delta=0,\ 0.114,$ and 0.207 in the alive, symmetric, and dead systems, respectively. The results are illustrated in Fig. 3, from which it can be seen that there is an exponential drop in the value of τ when the potential barrier goes down to zero in the alive configuration. The solid line through the numerical data is obtained from Eq. (13) and is

$$\tau=\tau_a\exp(N\Delta), \tag{15}$$

where $\tau_a=22.1$ and is the mean number of mutations in the alive system. In connection with the folding time for a protein, Zwanzig *et al.* [6], using a similar approach, have shown that the Levinthal time can be considerably reduced if

there is an energy penalty for making an incorrect bond, the correct bond meaning the native state of the amino acid. Here, $-\Delta$ plays the role of that energy penalty and τ can be regarded as the dimensionless folding time. The real time is obtained by multiplying τ by the characteristic rate constant to interconvert one state of the amino acid to another.

It is also possible to ask the real time that it takes for a population originally in the dead state to switch spontaneously to an alive state. To answer this we need to determine the average time interval between mutation events at each site. Unfortunately, it is difficult to obtain a reasonable estimate of a value for this time, which has certainly changed in the course of evolution.

IV. RELAXATION TO EQUILIBRIUM

For the purpose of the relaxation dynamics we need to calculate the Green's function $G(i,t|j)$ of Eq. (1), subject to the conditions

$$G(i,t|j)=\delta_{i,j} \text{ at } t=0, \lim_{t\to\infty} G(i,t|j)=P_{\rm eq}(i),\forall j. \tag{16}$$

The master equation in Eq. (1) can be symmetrized by making the transformation [7,8]

$$f(i,t)=[P_{\rm eq}(i)]^{-1/2}P(i,t) \tag{17}$$

to give

$$\frac{\partial f(i,t)}{\partial t}=\sum_{j=0}^{N} H_{ij}f(j,t), \qquad H_{ij}=\sqrt{\omega_{ij}\omega_{ji}}, \tag{18}$$

where $\mathbf{H}$ is an $(N+1)\times(N+1)$ symmetric matrix. The problem is now reduced to computing the eigenvalues λ_n and eigenvectors ψ_n of $\mathbf{H}$ such that

$$\mathbf{H}\psi_n=-\lambda_n\psi_n \quad (n=0,\ldots,N), \tag{19}$$

where ψ_n is the normalized column vector with elements $(\psi_n(0),\psi_n(1),\ldots,\psi_n(N))$. The equilibrium condition requires that the spectrum of $\mathbf{H}$ contains at least a zero eigenvalue, $\lambda_0=0$, and the corresponding eigenvector ψ_0 is related to the equilibrium distribution by

$$P_{\rm eq}(i)=|\psi_0(i)|^2. \tag{20}$$

By using the inverse tranformation of Eq. (17), it is possible to deduce that the Green's function, or the conditional probability, for Eq. (1) is given by

$$G(i,t|j)=\frac{\psi_0(i)}{\psi_0(j)}\sum_{n=0}^{N}\psi_n(i)\psi_n(j)e^{-\lambda_n t}. \tag{21}$$

Therefore the time correlation function for any observable O can be computed in terms of the Green's function from the relation

$$\langle O(t)O(0)\rangle=\sum_{i,j=0}^{N} O_i G(i,t|j)O_j P_{\rm eq}(j)$$

$$=\sum_{n=0}^{N}\left(\sum_{i=0}^{N} O_i\psi_0(i)\psi_n(i)\right)^2 e^{-\lambda_n t}. \tag{22}$$

The correlation function is no longer normalized since from Eq. (16)

$$\lim_{t\to 0}\langle O(t)O(0)\rangle=\langle O^2\rangle \text{ and } \lim_{t\to\infty}\langle O(t)O(0)\rangle=\langle O\rangle^2, \tag{23}$$

where the average is defined as $\langle g\rangle=\Sigma_i g(i)P_{\rm eq}(i)$, and $P_{\rm eq}(i)$ is the equilibrium distribution defined above. We define the normalized correlation function $C(t)$ by

$$C(t)=\frac{\langle O(t)O(0)\rangle-\langle O\rangle^2}{\langle O^2\rangle-\langle O\rangle^2} \tag{24}$$

and the corresponding relaxation time $\tau_{\rm rx}$ by

$$\tau_{\rm rx}=\int_0^\infty C(t)dt. \tag{25}$$

Following Szabo *et al.* [9], the relaxation time associated with the observable O can be written in the continuum limit as

$$\tau_{\rm rx}=\frac{1}{\langle\delta O^2\rangle}\int_0^1\frac{dx}{D(x)P_{\rm eq}(x)}\left[\int_x^1\delta O(y)P_{\rm eq}(y)dy\right]^2, \tag{26}$$

where $D(x)$ is the x-dependent diffusion coefficient and $\delta O=O-\langle O\rangle$ describes the fluctuations around the mean value of O.

In Appendix B it is shown how in the continuum limit for the master equation a Smoluchowski equation is obtained. It is instructive to consider the qualitative properties of this equation to gain insight into the correlation function. The structure of the diffusion equation suggests a double exponential relaxation, since the time evolution of the probability distribution consists of two terms, a drift term $\partial_x[DP(\partial_x V)]$, which causes the distribution function to move toward the nearest local minimum with its width controlled by the thermal energy, and a diffusion term $\partial_x D(\partial_x P)$, which describes the probability for the whole system to jump from a metastable minimum to a distant global minimum. Roughly speaking, relaxation times τ_s and τ_l can be associated with the drift and the diffusion terms, respectively, in such a way that the total correlation function reads

$$C(t)=(1-c)\exp\left\{-\frac{t}{\tau_s}\right\}+c\exp\left\{-\frac{t}{\tau_l}\right\}$$

$$\text{with } \tau_{\rm rx}=(1-c)\tau_s+c\tau_l, \tag{27}$$

where τ_s and τ_l are the short and long relaxation times, respectively, and the constant c quantifies the importance of τ_l to the total relaxation.

Such a relaxation dynamics can be understood as follows. When the system is perturbed such that the initial distribution is centered in the neighborhood of one local minimum,

the drift term will cause the distribution function to relax on the time scale τ_s to the time-dependent distribution centered around that minimum. On the time scale τ_l (generally, $\tau_l > \tau_s$) the diffusion will asymptotically move the distribution to its final time-independent form given by $P_{\rm eq}(x)$. Accordingly, one generally expects a nonexponential relaxation dynamics for a diffusion process on a potential surface. It is shown in Appendix A how to calculate τ_s, τ_l, and c for the double exponential approximation. In particular, it is found that $\tau_l = 1/\lambda_1$, with λ_1 being the smallest nonzero eigenvalue of the matrix **H**. The single exponential relaxation appears as an extremum limit when $\tau_s \ll \tau_l$. Nevertheless, it is to be noted that a description in terms of two relaxation times for $C(t)$ is valid only when the drift term is simple enough to be described by a single time scale. For more complex potential surfaces that generate a distribution of time scales, the relaxation dynamics is multiexponential and can be represented by a stretched exponential of the form

$$C(t) = \exp\left\{ -\left(\frac{t}{\tau_0} \right)^{\mu} \right\} \quad \text{with} \quad \tau_{\rm rx} = \Gamma\left(\frac{1}{\mu} + 1 \right) \tau_0, \quad (28)$$

where $\tau_{\rm rx}$ is the number of mutation events needed to observe the relaxation of the system to equilibrium.

To study the relaxation dynamics further, we simplify the problem by dividing every configuration of the droplet cell described by the potential $U(i/N)$ into two subspaces, dead (D) and alive (A). For any configuration having i active monomers the droplet will be seen to be in the state D for $i < \beta N$ and in the state A for $i > \beta N$, where β is the position of the potential barrier. Each state of the droplet has an associated observable $m(t)$, which is defined by the step function

$$m(t) = \theta[\beta N - i(t)] = \begin{cases} 1, & i(t) < \beta N \\ 0, & i(t) > \beta N. \end{cases} \quad (29)$$

$m(t)$, which defines the instantaneous state of the droplet, could correspond to a physical quantity such as, for instance, the polarization, magnetization, or reactivity of the system, or its ability to perform certain functions. It is also similar to the simple output functions used in neural networks. From that viewpoint it would be interesting to consider other forms for $m(t)$, such as $m(t) = \phi(x(t))$. Such questions will be addressed in future work. Here we focus on the simple version of the response function $m(t)$.

By substituting O by m in Eq. (22), we obtain the number correlation function:

$$\langle m(t) m(0) \rangle = \sum_{i,j=0}^{\beta N} G(i,t|j) P_{\rm eq}(j). \quad (30)$$

The quantity characteristic of the relaxation to equilibrium is then the normalized autocorrelation function $C(t)$ given by

$$C(t) = \frac{\sum_{i,j=0}^{\beta N} \{ G(i,t|j) - G(i,\infty|j) \} P_{\rm eq}(j)}{\sum_{i,j=0}^{\beta N} \{ G(i,0|j) - G(i,\infty|j) \} P_{\rm eq}(j)}. \quad (31)$$

By using δm in Eq. (26), the relaxation time for the observable m can be written as

$$\tau_{\rm rx} = \frac{K}{1+K} \int_0^{\beta} \frac{e^{V(x)} dx}{Z_D D(x)} \left[\int_0^x e^{-V(y)} dy \right]^2 + \frac{1}{1+K} \int_{\beta}^1 \frac{e^{V(x)} dx}{Z_A D(x)} \left[\int_x^1 e^{-V(y)} dy \right]^2 \quad (32)$$

as previously given by Schulten *et al.* [10], with $V(x)$ and $D(x)$ defined in Eqs. (B5) and (B9), respectively. To obtain Eq. (32) we have introduced the equilibrium constant $K = Z_A / Z_D$, where

$$Z_D = \int_0^{\beta} e^{-V(x)} dx \quad \text{and} \quad Z_A = \int_{\beta}^1 e^{-V(x)} dx. \quad (33)$$

The simplest case to consider is the symmetric system for which $K = 1$. For $\Delta = 0$ the numerical computation of integrals in Eq. (32) leads to $\tau_{\rm rx} \simeq 1.02 N^{1/2}$ for the relaxation time at the cusp. In proceeding as in Appendix C it can be shown that when $N\Delta \gtrsim 1$ the relaxation time for the symmetric system reduces to

$$\tau_{\rm rx} = \int_0^{\beta} \frac{e^{V(x)} dx}{Z_D D(x)} \left[\int_0^x e^{-V(y)} dy \right]^2 \simeq \frac{1}{2} \tau, \quad (34)$$

where τ is the mean first passage time as calculated in the previous section. For the dead and alive systems the equilibrium constant is, respectively, $K \propto e^{-N\Delta}$ and $K \propto e^{N\Delta'}$, and the approximation procedure outlined in Appendix C can also be used to estimate the relaxation time. We report below the numerical analysis results obtained from Eq. (32) in the limit of large N and above the cusp. We have for $\nu_e \gtrsim 0.61$

$$\tau_{\rm rx} \simeq \begin{cases} 14.7 \nu_e^{-0.37} \exp\{ -\nu_e^{-0.75} \} N^{0.28}, & \text{dead} \\ 12.3 \exp(N\Delta), & \text{symmetric} \\ 16.9 \nu_e^{-0.48} \exp\{ -\nu_e^{-0.75} \} N^{0.26}, & \text{alive.} \end{cases} \quad (35)$$

These expressions provide most of the information we need to know about the relaxation time regardless of the nature of the relaxation dynamics. To go further, the correlation functions defined by Eq. (31) were computed for the three systems (dead, alive, and symmetric) with a population size of monomers of $N = 100$. For all the functions $C(t)$, the fits obtained using the double exponential form of Eq. (27) were essentially exact with $\tau_l \simeq \lambda_1$ for all systems.

At the cusp $\nu_e = 0$ the potential has a unique global minimum at $x = 1/2$ and τ_l as defined above does not exist. However, the potential is quite flat around this minimum point since all derivatives of $U(x)$ of order smaller than 4 are equal to zero at $x = 1/2$. The potential can be roughly subdivided into a central region, in which there is a quasifree diffusion, separating two regions at the edges where the drift term dominates the dynamics. In this respect, τ_l can be reinterpreted as the equilibration time of the probability distribution within the flat region of the potential. The relaxation time $\tau_{\rm rx} \simeq 11.55$, obtained for this case, is very close to the theoretical value $\tau_{\rm rx} = 11.592$.

TABLE III. Values of λ_1 as a function of ν. The long relaxation time is given as $\tau_l = 1/\lambda_1$.

Diversity	Alive	Symmetric	Dead
7.389	0.069182	0.069182	0.069182
8.0	0.048387	0.049006	0.053181
10.0	0.037772	0.011979	0.033084
12.0	0.045251	0.002132	0.036190
14.0	0.050414	0.000307	0.039366
16.0	0.054348	0.000042	0.041658
18.0	0.057490	0.000006	0.043307
20.0	0.060010	0.000001	0.044643

Out of the cusp, the major effect of the double well structure of the potential is to increase τ_l. In the symmetric system, the relaxation time grows exponentially with ν_e slowing down the relaxation. This is exhibited in Fig. 2 and in Table III since $\tau_{rx} \simeq \tau/2 = 1/\lambda_1$. For $\nu_e < 2.6$ the relaxation is still double exponential since the barrier height is $N\Delta \lesssim 1$ and the potential is little modified from its form at the cusp. For $\nu_e \geqslant 2.6$ the relaxation dynamics is reduced to a single exponential with $\tau_{rx} = 1/\lambda_1$ because the ratio $\tau_s/\tau_l \propto \exp(-N\Delta)$ tends to zero when ν_e gets larger, i.e., for $N\Delta \gg 1$. In this limit the dynamics of the system can be approximated by a phenomenological first order kinetic rate equation that leads to an exponential relaxation to equilibrium [10].

The situation is somewhat different in the dead and alive systems, where the barrier coalesces with one of the wells in the potential. For the two systems, the ratio τ_l/τ_s of relaxation times slightly increases with ν_e, falling between 14.47 and 27 for the alive system and between 14.76 and 18.8 for the dead one. The typical value for the constant c is close to $c \simeq 0.83$ ($c \simeq 0.785$) for the alive (dead) system, indicating that about 83% (78.5%) of the overall relaxation is dominated by the long time relaxation which originates from the diffusion. Therefore the dynamics of the system are still

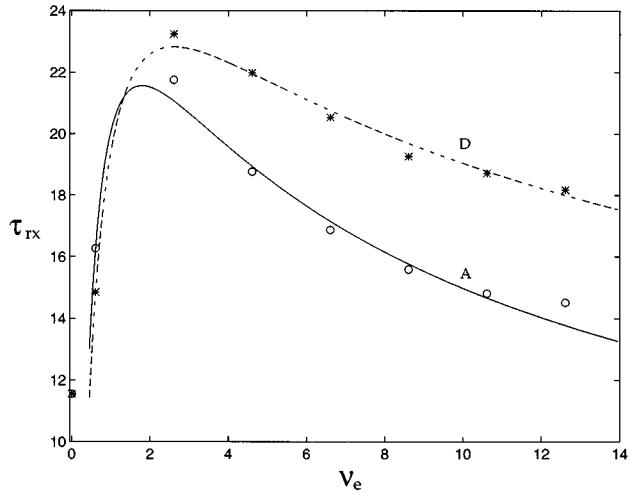

FIG. 4. The relaxation time τ_{rx} versus ν_e for the alive (circles and solid line) and dead (asterisks and dashed line) systems. The points are obtained from the double exponential fits to the correlation function (see text), and the lines represent the approximations in Eq. (35).

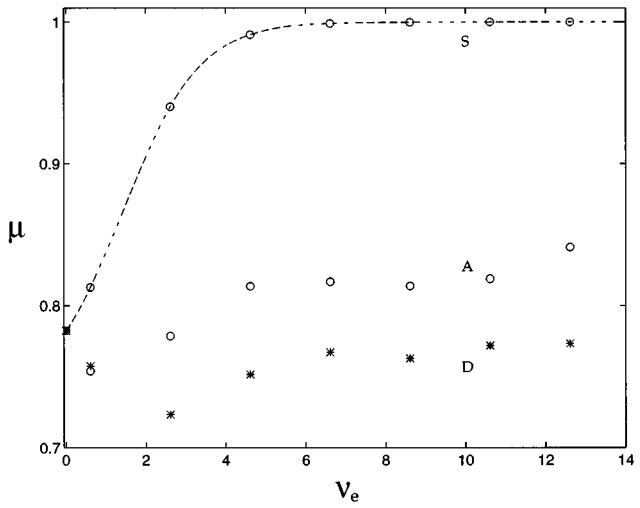

FIG. 5. The exponent μ versus ν_e for the systems symmetric (circles and dashed line), dead (asterisks), and alive (circles).

well described by the double exponential relaxation. This is illustrated in Fig. 4, which shows the variation of τ_{rx} versus ν_e obtained by using a double exponential form for the relaxation and the forms of Eq. (35). In contrast to the symmetric system, τ_{rx} initially increases with ν_e and then shows a power law falloff. For $\nu_e < 1$ the potential is little modified from its form at the cusp, and all additional perturbative features cause an increase of the relaxation time. For $\nu_e \gg 1$ the potential is completely different and there is a rapid relaxation to the unique and deep stable minimum of the system. The relaxation is speeded up with ν_e because the overall gradient toward the bottom of the potential well increases with ν_e. The difference in the relaxation time between the two systems, alive and dead, is due to the different ν dependence of the potential gradient in each system.

For illustrative purposes, the stretched exponential of Eq. (28) was also used as a fitting function for the relaxation. Good fits were obtained for all curves of $C(t)$. As depicted in Fig. 5, the exponent μ is comprised between 0.75 and 0.84 for both dead and alive systems while it goes from $\mu \simeq 0.8$ to $\mu \simeq 1$ in the symmetric system. Note that the values of μ in the alive system are greater than in the dead system indicating that the relaxation is more rapid in the alive system than in the dead one.

V. CONCLUDING REMARKS

In this paper we have computed the mean number of mutation events τ required to observe the origin of metabolism, which is characterized as the transition from the dead state to the alive state in Dyson's model. The mean number was found to be very similar to the Levinthal time for protein folding. In particular, for a given population of monomers, τ grows exponentially with the effective diversity in the dead and symmetric systems while it decreases for the alive system. In the latter case, it appears as if most of the degrees of freedom of the system are ''frozen,'' allowing a very few of them to control the fate of the whole system. This is illustrated by the exponential falloff to a nonzero constant of τ when, at fixed ν and N, the system is modified from the dead

configuration to the alive one by adiabatically tuning the control parameters of the potential for the system. This operation removes the system from the dead state of low stress into the more constrained alive state by simultaneously enhancing the energy gained for activating a monomer and the interaction energy between monomers. It is to be noted that these features are very reminiscent of a number of other problems, including the folding problem, for example, in which the analogues of the dead and alive states are the unfolded and folded states, respectively. Bryngelson and Wolynes have used the same type of potential of free energy $U(x)$ for studying protein folding within the framework of the random energy model [11]. More generally, this analogy can apply to any problem of a phase transition that admits a two-states description.

We have also examined the relaxation dynamics of the system by computing the correlation function of a random and binary response function that defines the instantaneous state of the system. It was found that the relaxation to equilibrium is well described by either a double exponential or a stretched exponential. Such dynamical studies of the random energy model [12,13] have already been perfomed in other contexts by, for example, Shakhnovich and Gutin [14] and Fernandez [15]. In these studies the transition rates were factorizable and analytic solutions to the master equation were obtained. The equilibrium correlation functions displayed various forms, including power law and stretched exponential relaxation. In our problem the transition rates are no longer factorizable and the master equation was solved numerically. Even for a simple two-state response function the relaxation dynamics for the balance of the populations is not necessarily exponential but depends on the system considered. Roughly speaking, the scenario for the relaxation proceeds in two steps. First, there is a rapid relaxation that drives the system to a metastable state of low (high) metabolic activity for the alive (dead) system. It is followed by a second step of slow relaxation, essentially controlled by diffusion, that takes the system from the unstable state and slides it down the slope into the global minimum. The ratio of the slow to the fast relaxation times is about 17.2 and 21.2 for the dead and alive systems, respectively. That ratio of relaxation times becomes so large in the symmetric system that the slowing down relaxation is reduced to a single exponential, since it is dominated by the time of jumping from one minimum to the other. A similar image for the relaxation dynamics was pointed out by Perico *et al.* [16], who also noted the robustness of the double exponential approximation to describe the correlation function. Finally, it would be useful and instructive to study the relaxation dynamics through an intrinsic function of the system, the autocatalytic probability, for example. Such work will be reported elsewhere.

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APPENDIX A: DOUBLE EXPONENTIAL APPROXIMATION

From Eq. (22) the normalized correlation function can be written as

$$C(t)=\frac{\sum_{n=0}^{N}\left(\sum_{i=0}^{N}O_i\psi_0(i)\psi_n(i)\right)^2 e^{-\lambda_n t}-\langle O\rangle^2}{\langle O^2\rangle-\langle O\rangle^2}$$

$$=\sum_{n=1}^{N}c_n e^{-\lambda_n t}, \tag{A1}$$

where the weight c_n associated with the eigenvalue λ_n is defined as

$$c_n=\frac{1}{\langle O^2\rangle-\langle O\rangle^2}\left(\sum_{i=0}^{N}O_i\psi_0(i)\psi_n(i)\right)^2, \quad \sum_{n=1}^{N}c_n=1. \tag{A2}$$

When the eigenvalues of the matrix **H** are ordered as $\lambda_0=0<\lambda_1<\lambda_2<\cdots$, Eq. (A1) can be seen as a perturbation expansion for the correlation function. The zeroth order of perturbation consists in keeping only the first term of the summation. This gives a single exponential with decay $1/\lambda_1$ that legitimately describes the long time relaxation of $C(t)$. The remaining higher orders of the expansion contribute with different weights c_n to the short time relaxation, which is essentially multiexponential. In the first order of perturbation, the short time relaxation can also be approximated by a single exponential with a rescaled decay time. This leads to the double exponential approximation for $C(t)$ as follows:

$$C(t)\simeq(1-c_1)e^{-\lambda_s t}+c_1 e^{-\lambda_1 t}. \tag{A3}$$

To derive Eq. (A3) we have used $C(0)=1$. The short time eigenvalue λ_s ($\geq\lambda_2$) is obtained by requiring that the relaxation time calculated from Eq. (A3) be exact, i.e.,

$$\tau_{\rm rx}=\frac{1-c_1}{\lambda_s}+\frac{c_1}{\lambda_1}=\sum_{n=1}^{N}\frac{c_n}{\lambda_n}, \tag{A4}$$

to give

$$\frac{1}{\lambda_s}=\sum_{n=2}^{N}\frac{1}{\lambda_n}g(n)=\left\langle\frac{1}{\lambda_n}\right\rangle \tag{A5}$$

with the distribution $g(n)$ defined as

$$g(n)=\frac{c_n}{1-c_1}, \quad n\geq 2. \tag{A6}$$

It follows that the double exponential approximation will be more accurate when the ratio $g(n)/\lambda_n$ falls off rapidly with n. Thus, the summation in Eq. (A5) can be truncated to a certain order. In the first order approximation, for instance, this gives

$$\lambda_s\simeq\frac{1-c_1}{c_2}\lambda_2>\lambda_2. \tag{A7}$$

APPENDIX B: CONTINUOUS LIMIT FOR THE MASTER EQUATION

The master equation Eq. (1) can be rewritten as

$$\frac{\partial P(x,t)}{\partial t}=\omega^{+}(x-\epsilon)P(x-\epsilon,t)+\omega^{-}(x+\epsilon)P(x+\epsilon,t)$$
$$-[\omega^{+}(x)+\omega^{-}(x)]P(x,t), \tag{B1}$$

where $\omega^{\pm}(x)$ [corresponding to $\omega_{i,i\pm1}$ of Eq. (3)] denotes the transition rates for $x\to x\pm\epsilon$, respectively, with x being the fraction of the active monomer and $\epsilon=1/N$. We define the diffusion coefficient $D(x)$ and the force $f(x)$ for the mutation events such that

$$\omega^{+}(x)=\frac{D(x)}{\epsilon^{2}}\exp\{-\tfrac{1}{2}\epsilon f(x)\},$$
$$\omega^{-}(x)=\frac{D(x)}{\epsilon^{2}}\exp\{+\tfrac{1}{2}\epsilon f(x)\}. \tag{B2}$$

The first order Taylor expansion in Eq. (B2) leads to

$$\frac{\partial P(x,t)}{\partial t}=\frac{1}{2\epsilon}[D(x+\epsilon)f(x+\epsilon)P(x+\epsilon,t)-D(x-\epsilon)$$
$$\times f(x-\epsilon)P(x-\epsilon,t)]+\frac{1}{\epsilon^{2}}[D(x+\epsilon)P(x+\epsilon,t)$$
$$-2D(x)P(x,t)+D(x-\epsilon)P(x-\epsilon,t)]. \tag{B3}$$

In the limit of small ϵ, Eq. (B1) becomes

$$\frac{\partial P(x,t)}{\partial t}=\frac{\partial}{\partial x}[D(x)f(x)P(x,t)]+\frac{\partial^{2}}{\partial x^{2}}[D(x)P(x,t)]$$
$$=\frac{\partial}{\partial x}\left\{D(x)\frac{\partial V(x)}{\partial x}+D(x)\frac{\partial}{\partial x}\right\}P(x,t). \tag{B4}$$

Defining the potential $V(x)$ by

$$V(x)=NU(x)+\ln[D(x)], \tag{B5}$$

we obtain the Smoluchowski equation:

$$\frac{\partial P(x,t)}{\partial t}=\frac{\partial}{\partial x}\left\{D(x)e^{-V(x)}\frac{\partial}{\partial x}[e^{V(x)}P(x,t)]\right\} \tag{B6}$$

with

$$D(x)=\epsilon^{2}\sqrt{\omega^{-}(x)\omega^{+}(x)} \tag{B7}$$

and

$$U(x)=\epsilon\int^{x}f(y)dy=\int^{x}\ln\left(\frac{\omega^{-}(y)}{\omega^{+}(y)}\right)dy. \tag{B8}$$

Thus, for the rates given by Eq. (3), the expression for the diffusion coefficient is

$$D(x)=\frac{\{x(1-x)\phi(x)[1-\phi(x)]\}^{1/2}}{N}, \tag{B9}$$

and for the potential,

$$U(x)=x\ln(x)+(1-x)\ln(1-x)+Ax-\frac{B}{2}x^{2}. \tag{B10}$$

APPENDIX C: MEAN FIRST PASSAGE TIME

The continuous version of Eq. (13) can be written as

$$\tau=\int_{\alpha}^{\gamma}\frac{dx}{D(x)e^{-V(x)}}\int_{0}^{x}e^{-V(y)}dy=\int_{\alpha}^{\gamma}e^{NU(x)}dx\int_{0}^{x}e^{-V(y)}dy, \tag{C1}$$

where the potential $V(x)$ is defined by Eq. (B5) and $D(x)$ and $U(x)$ are given by Eq. (B9) and Eq. (B10), respectively. Since we are concerned only by values of $D(x)$ and its derivatives calculated at points where $U'(x)=0$ (the prime denoting the derivative with respect to x) so that $\phi(x)=x$, the expression for $D(x)$ then simplifies to

$$D(x)=\frac{x(1-x)}{N}. \tag{C2}$$

To estimate the mean first passage time we use the well known procedure that approximates $U(x)$ and $V(x)$ around the local minimum and maximum. The asymptotic approximations we derive are valid only in the limit of large N and beyond the cusp, $\nu_{e}>1$. We consider three situations depending upon the shape of $U(x)$.

1. Symmetric system

The potential $U(x)$ has a double well structure with two equal minima at $x=\alpha$ and $x=\gamma$ and a barrier at $x=\beta=1/2$. Consider first the integral

$$I(x)=\int_{0}^{x}e^{-V(y)}dy. \tag{C3}$$

Since $I(x)$ is small for $x<\alpha$ and $\alpha<x<\gamma$, it can be well approximated by its value around $x=\alpha$. Using a quadratic approximation around $x=\alpha$ for $V(x)$,

$$V(x)\simeq V(\alpha)+V'(\alpha)(x-\alpha)+\tfrac{1}{2}V''(\alpha)(x-\alpha)^{2}, \tag{C4}$$

with

$$V'(\alpha)=\frac{1-2\alpha}{\alpha(1-\alpha)}>0 \tag{C5}$$

and

$$V''(\alpha)=NU''(\alpha)\left\{1-\frac{1-2\alpha(1-\alpha)}{N\alpha(1-\alpha)[1-B\alpha(1-\alpha)]}\right\}, \tag{C6}$$

we can estimate $I(x)$ as

$$I(x)\simeq\theta(x-\alpha)e^{-V(\alpha)}\int_{-\infty}^{\infty}e^{-V'(\alpha)y-V''(\alpha)y^{2}/2}dy$$
$$=\left(\frac{2\pi}{V''(\alpha)}\right)^{1/2}e^{-V(\alpha)+[V'^{2}(\alpha)/2V''(\alpha)]}\theta(x-\alpha), \tag{C7}$$

where $\theta()$ is the Heaviside function. To calculate the remaining integral in Eq. (C1) we expand $U(x)$ around $x=\beta$ in the same way as above:

$$U(x)\simeq U(\beta)-\frac{1}{2}|U''(\beta)|(x-\beta)^2. \tag{C8}$$

In the limit $N\gg 1$, the mean first passage time is given by

$$\tau\simeq \frac{2\pi\exp\{(1-2\alpha)^2/2N\alpha(1-\alpha)[1-B\alpha(1-\alpha)]\}}{\sqrt{[1-B\alpha(1-\alpha)][B\beta(1-\beta)-1]}} \times\left[\frac{\beta(1-\beta)}{\alpha(1-\alpha)}\right]^{1/2} e^{N\Delta}. \tag{C9}$$

2. Dead system

The top of the barrier coincides with the potential well at $x=\beta=\gamma>1/2$. Equation (C7) is still a good approximation for $I(x)$ while $V(x)$ is now expanded locally around $x=\gamma$ by a cubic potential:

$$U(x)\simeq U(\gamma)+\frac{1}{3!}U'''(\gamma)(x-\gamma)^3 \tag{C10}$$

with

$$U'''(\gamma)=\frac{2\gamma-1}{\gamma^2(1-\gamma)^2}>0. \tag{C11}$$

The remaining integral in Eq. (C1) can be estimated as

$$\int_\alpha^\gamma e^{NU(x)}dx\simeq e^{NU(\gamma)}\int_0^\infty e^{-NU'''(\gamma)y^3/3!}dy =\Gamma\left(\frac{4}{3}\right)\left(\frac{6}{NU'''(\gamma)}\right)^{1/3}e^{NU(\gamma)}. \tag{C12}$$

After calculation, we find

$$\tau\simeq\Gamma\left(\frac{4}{3}\right) \times\left\{\frac{2\pi\exp\{(1-2\alpha)^2/N\alpha(1-\alpha)[1-B\alpha(1-\alpha)]\}}{\alpha(1-\alpha)[1-B\alpha(1-\alpha)]}\right\}^{1/2} \times\left\{\frac{6\gamma^2(1-\gamma^2)}{2\gamma-1}\right\}^{1/3}N^{1/6}e^{N\Delta}. \tag{C13}$$

3. Alive system

In this case, the top of the barrier coincides with the well at $x=\alpha=\beta<1/2$ where both $U'(x)=U''(x)=0$. Then Eq. (C7) is no longer valid. However, $V(x)$ can be approximated around $x=\alpha$ as

$$V(x)\simeq V(\alpha)+V'(\alpha)(x-\alpha)+\frac{1}{2!}V''(\alpha)(x-\alpha)^2 +\frac{1}{3!}V'''(\alpha)(x-\alpha)^3. \tag{C14}$$

The integral $I(x)$ can then be written as

$$I(x)\simeq e^{-V(\alpha)}\int_0^x dy e^{-V'(\alpha)(y-\alpha)-(1/2!)V''(\alpha)(y-\alpha)^2-(1/3!)V'''(\alpha)(y-\alpha)^3}, \tag{C15}$$

which satisfies the equation

$$\frac{d^2I(x)}{dx^2}+\frac{dV}{dx}\frac{dI(x)}{dx}=0 \tag{C16}$$

with

$$\frac{dV}{dx}=V'(\alpha)+V''(\alpha)(x-\alpha)+\tfrac{1}{2}V'''(\alpha)(x-\alpha)^2. \tag{C17}$$

On changing the variable by

$$z=\left(\frac{V'''(\alpha)}{2}\right)^{1/3}\left[x-\alpha+\frac{V''(\alpha)}{V'''(\alpha)}\right] \tag{C18}$$

and letting

$$a=\left(\frac{2}{V'''(\alpha)}\right)^{1/3}\left[\frac{[V''(\alpha)]^2}{2V'''(\alpha)}-V'(\alpha)\right] \tag{C19}$$

we obtain the equation

$$\frac{d^2I(z)}{dz^2}+(z^2-a)\frac{dI(z)}{dz}=0 \tag{C20}$$

for which the solution is the incomplete Airy integral [17] defined as

$$\mathrm{Ai}(z,a)=\int_0^z e^{-y^3/3+ay}dy. \tag{C21}$$

The integral $I(x)$ is then given as

$$I(x)=\mathrm{Ai}(z,a)e^{-V(\alpha)}. \tag{C22}$$

As above, we expand $U(x)$ up to third order:

$$U(x)\simeq U(\alpha)+\frac{1}{3!}U'''(\alpha)(x-\alpha)^3, \tag{C23}$$

where

$$U'''(\alpha) = -\frac{1-2\alpha}{\alpha^2(1-\alpha)^2} < 0 \tag{C24}$$

$$\tau \simeq \frac{N}{\alpha(1-\alpha)} \int_{\alpha}^{\gamma} \mathrm{Ai}(z,a)\, e^{-(1/3!)N|U'''(\alpha)|(x-\alpha)^3} dx. \tag{C25}$$

to obtain

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