Variational ansatz for quasispecies in the Eigen model

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We investigate the error threshold for the emergence of quasispecies in the Eigen model. By mapping to an effective Hamiltonian ruled by the "imaginary-time" Schrödinger equation, a variational ansatz is proposed and applied to calculate various properties associated with the quasispecies. The variational ansatz gives correct prediction for the survival population of the wild-type sequence and also reveals an unexpected universal scaling behavior near the error threshold. We compare the results from the variational ansatz with that from numerical methods and find excellent agreement. Though the emergence of the scaling behavior is not yet fully understood, it is remarkable that the universal scaling function reigns even for relatively short genome length such as \( L = 16 \). Further investigations may reveal the mechanism of the universal scaling and extract the essential ingredients for the emergence of the quasispecies in molecular evolution.

I. INTRODUCTION

Molecular perspective for biological evolution\cite{1–5} stired up interesting ideas and attracted much attention in recent decades. In 1971, Eigen proposed a simple but profound model to study the process of molecular replication and introduced the concept of quasispecies\cite{2} which turned out to be crucial in understanding the fundamental behavior of evolution. A quasispecies consists of a wild type with large fitness accompanied by a large number of mutant types in sequence space\cite{6}. The Eigen model refines our understanding of the evolutionary dynamics: Selection moves the population towards the better adapted mutants and explores for even better ones in the sequence space by random mutations. The Eigen model is particularly suitable for viral evolution\cite{4,5} and population genetics\cite{1,7,9} and is also widely applied to general evolutionary theories.

Error threshold\cite{10,11} appears as an upper bound on mutation rate, above which no effective selection can occur and the quasispecies becomes unstable. It places limits on how genetic information can be maintained and passed on from generations to generations and restricts possible theories for the origins of life. However, it is quite puzzling that some RNS viruses\cite{11–13} seem to have mutation rates close to the error threshold. The error threshold for the Eigen model was first derived by ignoring mutations of mutants back to the wild type, known as the assumption of no back mutation\cite{8}. Later, the model was extensively studied by mapping to equivalent statistical models\cite{14,18} and the existence of the error threshold can be viewed as a phase transition from the ordered phase (quasispecies) to the disordered phase (no effective selection). Exact solution of the model\cite{19–21} shows that the error threshold is identical to that derived under the assumption of no back mutation. In addition, the phase transition is shown to be first-order\cite{22}.

Though the exact solution\cite{19–21} is available for the Eigen model, due to technical complications, it is not yet clear why the error threshold derived within the assumption of no back mutation is identical to the exact solution. Meanwhile, it is desirable to devise a mean-field approach capturing the essence of the phase transition so that the order parameter can be computed (and understood) in the easiest way. Inspired by the fact that this is a first-order phase transition, it is possible for one to come up with a variational ansatz capturing the phase transition. In this article, we make a full use of the symmetry and propose a simple variational ansatz containing only two configurations in the sequence space. It is rather remarkable that the variational approach captures the essence of the phase transition including the error threshold and also the evolution of the wild-type population. It is quite surprising that error thresholds for different genome lengths, values of mutation rate and relative fitness collapse onto a universal curve, giving credit to the power of the variational ansatz. We also perform numerical calculations to verify the results obtained by the variational ansatz and find nice agreement between them.

This article is organized as follows. In Sec. [I] we briefly introduce the Eigen model and a gauge transformation to an equivalent Hamiltonian with imaginary-time dynamics. In Sec. [II] the Hamiltonian can be solved by the proposed variation ansatz, giving the error threshold and also the evolution of the wild-type population. In Sec. [III] we calculate the back-mutation rate to the wild type and confirm that the error threshold remains the same within the approximation of no back mutation. In Sec. [IV] we present a numerical approach to the Eigen model and compare the results with the variational approach.
II. EIGEN MODEL

Consider a DNA chain with genome length \( L \). The primary structure at each site of the chain takes on four different nucleotides (\( G, A, C \) and \( U \)). For simplicity, we choose to distinguish only among purines (\( R \)) and pyrimidines (\( Y \)). Thus, the total size of sequence space is reduced to \( 2^L \), yet still huge for numerical simulations. A viral genome with typical length \( L \sim 1000 \) will lead to a (reduced) sequence space of the size \( \sim 10^{3000} \). For more complex forms of life, the size of the sequence space increases tremendously and methods developed in statistical mechanics seem appropriate and powerful to address the dynamics of the genome evolution.

The time-dependent relative population of a particular sequence \( i \) is denoted as \( x_i(t) \). The selection is on the genotype level described by the fitness \( f_i \) for each sequence. In general, the fitness function can be rather complicated and evolves with time. Here it is assumed to take on its time-averaged value and treated as a constant. Eigen proposed a deterministic dynamics to describe the evolution of the quasispecies equation. The time evolution of the quasispecies equation is

\[
\frac{dx_i}{dt} = \sum_j (m_{ij} f_j - \phi \delta_{ij}) x_j
\]

(1)

where \( x_i \) and \( f_i \) are the relative population and the fitness of the sequence \( i \), while \( \phi = \sum_i x_i f_i \) is the average fitness for all sequences. The relative populations are normalized with \( \sum_i x_i = 1 \) initially and remain so under the time evolution of the quasispecies equation. The mutation matrix \( m_{ij} \) describes the probability to mutate from sequence \( j \) to sequence \( i \) in a generation and satisfies \( \sum_i m_{ij} = 1 \). If only point mutations are considered, it is straightforward to work out the mutation matrix

\[
m_{ij} = u^{d_{ij}} (1 - u)^{L-d_{ij}},
\]

(2)

where \( u \) is the probability for a single point mutation to occur within a generation and \( d_{ij} \) is the Hamming distance between the sequences. Since \( d_{ij} = d_{ji} \), it is clear that the mutation matrix \( m_{ij} \) is also symmetric.

The quasispecies equation can be transformed into an imaginary-time Schrödinger equation by the gauge transformation,

\[
\Psi_i(t) = \sqrt{f_i} x_i(t) e^{W(t)},
\]

(3)

where \( W(t) = \phi(t) \). Applying the gauge transformation to the quasispecies equation, the dynamics of \( \Psi_i(t) \) is captured by an effective Hamiltonian \( H_{ij} \),

\[
\frac{d\Psi_i}{dt} = -\sum_j H_{ij} \Psi_j, \ \text{with} \ H_{ij} = -\sqrt{f_i f_j} m_{ij}.
\]

(4)

One notices that the above equation can be obtained from the usual Schrödinger equation by replacing the time variable \( t \to it \) (and setting \( \hbar = 1 \)). Following the standard textbooks, the general solution for the “imaginary-time” Schrödinger equation is

\[
\Psi_i(t) = \sum_n c_n \Phi_i^0 e^{-E_n t},
\]

(5)

where \( E_n \) and \( \Phi_i^0 \) are the eigenvalues and eigenvectors of the effective Hamiltonian \( H_{ij} \). Note that the factor \( \sqrt{f_i} \) in the gauge transformation is crucial to make the Hamiltonian symmetric.

Unlike the intrinsic oscillatory nature of the usual Schrödinger equation, its imaginary-time version only keeps the ground state in the infinite-time limit,

\[
\lim_{t \to \infty} \Psi_i(t) \to c_0 \Phi_i^0 e^{-E_0 t},
\]

(6)

and greatly simplifies the calculations. Making use of the normalization condition, \( \sum_i x_i = 1 \), the exponential factor in the gauge transformation can be expressed as

\[
e^{W(t)} = \sum_i \frac{1}{\sqrt{f_i}} \Psi_i(t).
\]

(7)

The inverse gauge transformation can thus be found,

\[
x_i(t) = \frac{1}{\sqrt{f_i}} \Psi_i(t) e^{-W(t)}
\]

(8)

In the infinite-time limit, only the ground-state wave function survives and the relative populations are

\[
x_i^* = \lim_{t \to \infty} x_i(t) = \left( \frac{1}{\sum_i \Phi_i^0 / \sqrt{f_i}} \right) \frac{1}{\sqrt{f_i}} \Phi_i^0.
\]

(9)

Note that the constant \( c_0 \) cancels itself out and does not appear in \( x_i^* \). To find the survival populations \( x_i^* \), one only needs to find the ground state \( \Phi_i^0 \) of the effective Hamiltonian.

III. VARIATIONAL ANSATZ

In Eigen’s original proposal, the wild-type sequence, say, \( 0 \) has maximum fitness \( f_0 = f_M \) and all other sequences \( i \neq 0 \) have a common background fitness \( f_i = f < f_M \). Even though the single-peak fitness landscape is simple, the size of the sequence space is still huge \( N_s = 2^L \). Since the fitness landscape is obviously symmetric around the wild-type peak, it is convenient to introduce the representation for arbitrary configurations,

\[
\Psi = (\psi^0, \psi^1, ..., \psi^L),
\]

(10)

where \( \psi^d \) is a row vector representing states with Hamming distance \( d \) to the peak and thus has the dimension of \( C^L_d = L! / d! (L - d)! \).
and numerically diagonalize the Hamiltonian to obtain the ground state. The s-wave symmetry helps tremendously and reduces the size of the relevant sequence space from $N_s = 2^L$ to just $(L + 1)$. The comparison between the s-wave decomposition and the exact solution will be discussed in Section VI.

Though the s-wave decomposition largely reduces the effective dimension of the sequence space, it is still too complicated for analytic manipulations. Here we choose two symmetric base functions,

$$\Psi^0 = (1, 0, ..., 0), \quad \Psi^1 = \frac{1}{\sqrt{N_s}} (0, 1, 1, ..., 1),$$

and use variational approach to estimate the error threshold for the Eigen model. Construct the variational wave function for the ground state

$$\Psi_i = c_0 \Psi^0 + c_1 \Psi^1,$$

so that the variational energy takes the form

$$E(c_1, c_2, \lambda) = \sum_{n,m=0,1} c_n H^v_{nm} c_m + \lambda (c_0^2 + c_1^2),$$

where the Lagrange multiplier arises from the normalization constraint $c_0^2 + c_1^2 = 1$ and the variational Hamiltonian $H^v_{nm} = \sum_{ij} \Psi_i^* H_{ij} \Psi_j$ is a $2 \times 2$ real symmetric matrix,

$$H^v_{00} = -f_M (1 - u)^L,$$

$$H^v_{11} = -\frac{f}{N_s - 1} \sum_{i,j \neq 0} u^{d_{ij}} (1 - u)^L - d_{ij}$$

$$= -\frac{f}{N_s - 1} \left( \sum_{i \neq 0, j} - \sum_{i \neq 0, j = 0} \right) u^{d_{ij}} (1 - u)^L - d_{ij}$$

$$= -f + \frac{f}{N_s - 1} [1 - (1 - u)^L],$$

$$H^v_{01} = H^v_{10} = -\sqrt{\frac{f_M f}{N_s - 1}} [1 - (1 - u)^L].$$

Minimizing the variational energy $E(c_1, c_2, \lambda)$ is equivalent to diagonalizing the $2 \times 2$ variational Hamiltonian $H^v_{nm}$, which can be rewritten as

$$H^v_{nm} = C \mathbf{1} + f \begin{pmatrix} -\epsilon & -\Delta \\ -\Delta & \epsilon \end{pmatrix},$$

where the constant term does not affect the frequencies $x_i(t)$ after the inverse gauge transformation,

$$C = -\frac{1}{2} \left[ f_M m_{00} + f - \frac{f}{N_s - 1} (1 - m_{00}) \right]$$

with $m_{00} = (1 - u)^L$ and will be dropped in the following calculations. The dimensionless parameters $\epsilon$ and $\Delta$ in the variational Hamiltonian are

$$\epsilon(u, L, r) = \frac{1}{2} \left[ r m_{00} - 1 \right] + \frac{1 - m_{00}}{2(N_s - 1)},$$

$$\Delta(u, L, r) = \sqrt{\frac{r}{N_s - 1}} [1 - m_{00}],$$

and

Since we are interested in the low-energy sector of the effective Hamiltonian, it is sufficient to keep the so-called “s-wave” sector only. That is to say, out of the many states with the same Hamming distance to the wild-type sequence, one only needs to keep the totally symmetric state with the same Hamming distance to the wild-type sequence, one only needs to keep the totally symmetric state for each Hamming distance,

$$\Psi^0_s = (\psi^0_0, 0, ..., 0) = (1, 0, 0, ..., 0),$$

$$\Psi^1_s = (0, \psi^1_0, 0, ..., 0) = \sqrt{\frac{1}{L}} (0, 1, 1, ..., 1, 0, 0, 0),$$

and other $\Psi^s$ can be constructed in a similar way. Writing down the effective Hamiltonian explicitly,

$$H_{ij} = -\sqrt{f_i f_j} u^{d_{ij}} (1 - u)^L - d_{ij},$$

one can construct the reduced $(L + 1) \times (L + 1)$ Hamiltonian in the s-wave sector

$$H_{nm} = \sum_{ij} \Psi_i^s H_{ij} \Psi_j^m,$$
where \( r = f_M / f \) is the relative fitness of the dominant sequence and \( N_s = 2^L \) is the size of the sequence space. The eigenvalues of the variational Hamiltonian are

\[
E_{\pm} = \pm \sqrt{\epsilon^2 + \Delta^2}.
\]

Therefore, the ground-state energy within the variational approximation corresponds to the negative eigenvalue \( E = E_- \) with the eigenvector

\[
c_0 = \frac{\Delta}{\sqrt{\epsilon^2 + \Delta^2} - \epsilon} = \frac{\sqrt{\epsilon^2 + \Delta^2 + \epsilon}}{\Delta}. \tag{26}
\]

With the coefficients \( c_0 \) and \( c_1 \) at hand, the ground state within the variational approximation is

\[
\Phi^{00} = \left( c_0, \frac{c_1}{\sqrt{N_s - 1}}, \frac{c_1}{\sqrt{N_s - 1}}, \ldots, \frac{c_1}{\sqrt{N_s - 1}} \right). \tag{27}
\]

The relative population of the wild-type sequence in the infinite-time limit can be computed from the variational ground state,

\[
x_0^*(u, L, r) = \frac{1}{\sum_j \Phi_{00}^j / \sqrt{f_j}} \frac{1}{\sqrt{f_0}} \Phi_0^{00} = \frac{\sqrt{\epsilon^2 + \Delta^2 + \epsilon}}{\sqrt{\epsilon^2 + \Delta^2 + \epsilon + \sqrt{r(2^L - 1)} \Delta}}. \tag{28}
\]

As shown in Fig. 1, the survival population of the wild-type sequence \( x_0^* \) is plotted against the probability of point mutation \( u \) for different genome lengths ranging from \( L = 10 \) to \( L = 22 \) for the relative fitness \( r \equiv f_M / f = 2 \).

The error threshold, where the quasispecies disappears, marks the phase transition and, in theory, is only well defined in the thermal dynamic limit with infinite genome length. Although there is no extra numerical cost to choose a longer genome length \( L \) within the variational approach, we intentionally choose relatively short \( Ls \) to highlight the sharpness of the phase transition at finite genome lengths. Furthermore, for chosen relative fitness \( r \), the survival populations \( x_0^*(u, L) \) for different \( u \) and \( L \) can be collapsed onto a universal curve when plotted with the rescaled variable

\[
g = \frac{uL}{\ln r}. \tag{29}
\]

As is evident in Fig. 1, the collapse is almost perfect even for such short genome lengths. The error threshold occurs at \( g_c = 1 \), i.e., \( u_L = \ln(f_M / f) \) which agrees with the exact solution.

The universal curves for the survival population \( x_0^*(g, r) \) can be derived by taking the genome length \( L \) to infinity. Taking \( L \to \infty \) but keeping \( g \) and \( r \) finite, the stay-on probability is \( m_{00} = (1 - u)^L \to r^{-g} \). Since the off-diagonal term \( \Delta \) is negligibly small in this limit, the survival population of the wild-type sequence is greatly simplified,

\[
x_0^*(g, r) = \lim_{L \to \infty} x_0^*(u, r, L) = \frac{1}{r^g} \frac{1}{\frac{1}{2} \left| \gamma^{1-g} - 1 \right| + \frac{1}{2} \left| r^{1-g} - 1 \right|} + (1 - r^{-g}). \tag{30}
\]

Since the relative fitness \( r \) is greater than unity, the numerator is zero for \( g > 1 \) and the scaling function takes the simple form,

\[
x_0^*(g, r) = \Theta(1 - g) \frac{r^{1-g} - 1}{r - 1}. \tag{31}
\]

Magically, this form is identical to that derived under the assumption of no back mutations to the wild-type sequence. The universal scaling behavior within the variational approach is robust, hinting that the simple variational ansatz captures the essence of the phase transition.

**IV. NO BACK MUTATION?**

The variational ansatz also provides a helping hand to checking how good the assumption of no back mutations is. A good indicator is the ratio between the back-mutating rate and the rate to stay on the wild-type sequence,

\[
\chi(u, L, r) = \frac{\sum_{j \neq 0} m_{0j} f_j x_j^*}{m_{00} f_0 x_0^*}. \tag{32}
\]

Within the variational approximation, all \( x_j^* = x_1^* \) for \( j \neq 0 \) and the summation in the numerator can be carried out without difficulty,

\[
\chi(u, L, r) = \frac{x_1^* f(1 - m_{00})}{x_0^* f_M m_{00}} = \sqrt{\frac{f}{f_M} \frac{1 - m_{00}}{m_{00}} \frac{c_1}{\sqrt{(N_s - 1) c_0}}}. \tag{33}
\]
Thus, the scaling function for the back-mutation indicator in the infinite genome length is
\[ \chi(g, r) = \Theta(g - 1) \left( r^{g-1} - 1 \right). \] (35)

The universal function \( \chi(g, r) \) is zero in the presence of the quasispecies, i.e., ignoring the back mutations to the wild-type sequence is justified.

V. NUMERICAL VERIFICATION

To check the validity of the variational ansatz, we also solve the Eigen model numerically. We start with Eigen’s proposal and study the evolution of populations \( X_i(t) \) (not relative populations) in discrete generations,
\[ X_i(t+1) = \sum_j m_{ij} f_j X_j(t), \] (36)
where the mutation matrix \( m_{ij} \) and the fitness function \( f_i \) are defined previously. It is convenient to introduce the growth matrix \( G \) defined as
\[ G_{ij} = m_{ij} f_j - \delta_{ij}. \] (37)

Positive eigenvalues of the growth matrix imply population growth and negative ones mean diminishing populations. The stationary state then corresponds to the eigenstate of \( G \) with the largest eigenvalue.

To check the validity of the \( s \)-wave decomposition, we compute the eigenvalues of \( G \) in the projected sequence space and compare the results to the exact diagonalization in the full space. As shown in Fig. 4, the \( s \)-wave decomposition works rather well. Near the error threshold \( g_c = 1 \), there are only two symmetric states coming close...
to each other. A detail check reveals that these are just the variational wave functions we chose before. Therefore, the numerical results lend hands to the support of our variational ansatz. Although the numerical results presented here are for evolution in discrete time steps, one can prove (not shown here) that the stationary state of the quasispecies equation gives identical configuration.

It is interesting to go beyond the Eigen model and see whether the variational ansatz still works. It is known in the literature, by taking the evolutionary time step to the continuous limit, the relations between \( f_i, u \) (Eigen) and \( G_i, \Gamma \) (Crow-Kimura) are

\[
f_i = 1 + G_i \Delta t, \quad u = \Gamma \Delta t,
\]

where \( \Delta t \) is the microscopic time step before taking continuous limit. The rescaled variable \( g \) thus takes a slightly different form,

\[
g = \frac{uL}{\ln(\dot{f}_M/\dot{f})} = \lim_{\Delta t \to 0} \frac{\Gamma L \Delta t}{\ln(1 + G M \Delta t) - \ln(1 + G \Delta t)} = \frac{\Gamma L}{G M - G}.
\]

Plotted against the rescaled variable \( g \), the survival populations of the wild-type sequence for discrete Eigen model and the continuous Crow-Kimura model are shown in Fig. 5. For discrete Eigen model with genome length \( L = 16 \), the survival population \( x_0 \) is very close to the universal scaling function in Fig. 2. As the relative fitness \( r = f_M/f \) approaches unity, the curve moves closer to that obtained from the Crow-Kimura model. The results from the Crow-Kimura model at shorter genome lengths are also plotted for later comparison.

To compare the stationary states in the quasispecies equation and the Crow-Kimura model, we need to take \( r \to 1 \) in the variational ansatz,

\[
\epsilon_e(g, L) = \lim_{r \to 1} \frac{\epsilon}{r - 1} = \frac{1}{2} \left[ 1 - g + \frac{g}{2^L - 1} \right],
\]

\[
\Delta_e(g, L) = \lim_{r \to 1} \frac{\Delta}{r - 1} = \frac{1}{\sqrt{2^L - 1}} g.
\]

After some algebra, the survival frequency of the dominant sequence \( x_0^*(g, L) \) in the continuous limit is

\[
x_0^*(g, L) = \frac{\sqrt{\epsilon_e^2 + \Delta_e^2} + \epsilon_e + g}{\sqrt{\epsilon_e^2 + \Delta_e^2} + \epsilon_e + g}.
\]

These curves for finite genome length \( L \) are plotted in Fig. 6 and agree rather well with those obtained from Crow-Kimura model in Fig. 5. Furthermore, the above expression becomes extremely simple when the genome length goes to infinity,

\[
\lim_{r \to 1} x_0^*(g, r) = \Theta(1 - g) \lim_{r \to 1} \frac{r^{1 - g} - 1}{r - 1} = \Theta(1 - g) \times (1 - g).
\]

It is quite remarkable that the universal scaling function with infinite genome length in the continuous limit is just a straight line.

The numerical results from the discrete Eigen model and the Crow-Kimura model agree very well with the
variational ansatz we proposed for the quasispecies equation. The success of the variational approach relies on the fact that there are only two active states near the phase transition (error threshold), verified by the exact diagonalization. Although the exact solution for the Eigen model has been obtained in the literature, our variational ansatz provides a simpler approach at the cost of negligible errors. The no-back-mutation assumption is examined and only remains justified in the presence of the quasispecies. The universal scaling behavior near the error threshold was unexpected and further confirmed the validity of the variational approach. Though the emergence of the scaling behavior is not yet fully understood, it is remarkable that the universal scaling function reigns even for relatively short genome length such as $L = 16$. Further investigations may reveal the mechanism of the universal scaling and extract the essential ingredients for the emergence of the quasispecies in molecular evolution.

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