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Statistical Mechanics of Eigen's Evolution Model

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The correspondence between Eigen's model of macromolecular evolution and the equilibrium statistical mechanics of an inhomogeneous Ising system is developed. The free energy landscape of random Ising systems with the Hopfield Hamiltonian as a special example is applied to the replication rate coefficient landscape. The coupling constants are scaled with $1/l$, since the maxima of any landscape must not increase with the length of the macromolecules. The calculated error threshold relation then agrees with Eigen's expression, which was derived in a different way. It gives an explicit expression for the superiority parameter in terms of the parameters of the landscape. The dynamics of selection and evolution is discussed.

KEY WORDS: Macromolecular evolution; inhomogeneous, random Ising systems; replication number landscape; error threshold; quasispecies.

1. INTRODUCTION

Selection of species is an example from biology for a phase transition far from thermal equilibrium. Here we are interested in Eigen's evolution model,[1] which is governed by a set of nonlinear chemical rate equations. It was shown[2] that one can describe the dynamics of this system by the equilibrium thermodynamics of a 2-dim inhomogeneous spin system. This is analogous to the correspondence between d-dim dynamic systems (e.g., quantum mechanical spin systems[3] or cellular automata[4]) and the equilibrium statistical mechanics of $(d+1)$-dim Ising models. Here the macromolecules are described by 1-dim Ising or λ-state Potts spin chains. The full time development is represented as a 2-dim spin configuration, where one boundary row is fixed according to the initial condition of the dynamic system. The spin system becomes homogeneous only far away from that boundary, which then describes the stationary state. In this work

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the correspondence between the two fields, evolution dynamics and statistical mechanics, is established and applied to concrete models of the replication rate coefficient landscape.

Eigen's equations give a quantitative description of the evolutionary behavior of macromolecules like RNA and DNA under well-defined experimental conditions. If the imposed selection pressure consists in a high rate of replications, the macroscopic equations for the normalized concentration variables $x_i(t)$ are[1]

$$\dot{x}_i = A(i)x_i - \sum_{k \neq i} W(k, i)x_i + \sum_{k \neq i} W(i, k)x_k - x_i \sum_k A(k)x_k \tag{1.1}$$

The positive replication rate coefficients (rrc) $A(i)$ are assumed to be independent of time. For the case of point mutations only, which keep the length l of the molecules fixed, the mutation rate coefficients $W(k, i)$ are given by

$$W(k, i) = A(i)q^{l-d_{ik}}\left(\frac{1-q}{\lambda-1}\right)^{d_{ik}} \tag{1.2}$$

q is an average probability of exact replication of a base, λ is the number of different nucleotides that build up the macromolecules (four for RNA and DNA), and d_{ik} is the Hamming distance between sequence i and k.

Equation (1.1) becomes identical to a Master equation only for an rrc landscape $A(i)$ that does not vary with i. In this case the nonlinear flux term $-x_i \sum_k A(k)x_k$ cancels with the replication term $A(i)x_i$. The dynamics of the λ^l possible realizations of macromolecules can be viewed as a random walk on an l-dim hypercube, where more than nearest neighbor jumps are allowed, or expressed in another way, as a spin dynamics with multiple spin flips per unit time. However, no selection of species occurs, because of the degeneracy of $A(i)$. For nontrivial rrc landscapes one can still linearize Eq. (1.1) by the transformation[5]

$$y_i(t) = x_i(t) \exp\left[\int_0^t dt' \sum_k A(k)\, x_k(t')\right] \tag{1.3}$$

The resulting linear differential equation system

$$\dot{y}_i = A(i)\, y_i - \sum_{k \neq i} W(k, i)\, y_i + \sum_{k \neq i} W(i, k)\, y_k \tag{1.4}$$

is not a Master equation, because the transition rate matrix W does not satisfy the condition $\sum_k W(k, i) = 0$ for all i, which results in unnormalized variables $y_i(t)$. The dynamics of (1.1) and (1.4) is characterized by the

behavior of the eigenvalues and eigenvectors of the replication-mutation matrix W, where in the long-time limit only the largest eigenvalues and eigenvectors become important. With the equivalence of W to a transfer matrix T of a two-dimensional Potts model (Ising model in the case $\lambda = 2$),[2] one can discuss the dynamical equations by treating an inhomogeneous spin system in thermodynamic equilibrium with the correct cost function $H(\beta)$.

In Section 2 we develop the full correspondence between the quantities that characterize the evolution equations and the Ising system. Section 3 discusses the nature of the rrc landscape $A(i)$ and the meaning of random spin systems in this context. The Mattis model and the Hopfield Hamiltonian serve as special examples where Eigen's error threshold relation is calculated. The dynamics in these landscapes is qualitatively discussed. Section 4 summarizes the results.

2. STATISTICAL MECHANICS OF THE EVOLUTION EQUATION

In the following, Eigen's evolution equation will be treated in a discrete version[6]:

$$\mathbf{y}(n) = W^n \mathbf{y}(0) \tag{2.1}$$

The normalized concentration variables are given by

$$x_i(n) = \frac{y_i(n)}{\sum_k y_k(n)}$$

The elements of W are the same as in Eq. (1.2), but with $A(i)$ denoting now the number of copies of sequence i produced within a given generation time.

Equation (2.1) can be viewed as a path integral formulation for evolution. The distribution of macromolecules in the nth generation depends on all possible trajectories between the initial state $\mathbf{y}(0)$ and the final state $\mathbf{y}(n)$. Let $\{|s^i\rangle\}$ denote a complete orthonormal set of all possible sequences in the ith generation. For macromolecules of length l built up by λ bases, there are λ^l possible states. With the initial condition $\mathbf{y}(0) = |s^0\rangle$, Eq. (2.1) can then be written as

$$\mathbf{y}(n) = \sum_{\{|s^{n-1}\rangle\}} \cdots \sum_{\{|s^1\rangle\}} W|s^{n-1}\rangle\langle s^{n-1}|\, W|s^{n-2}\rangle \cdots \langle s^1|\, W|s^0\rangle \tag{2.1'}$$

The elements of the vector $W|s^{i-1}\rangle$ give the number of all possible macromolecules in generation i that were produced by macromolecule

$|s^{i-1}\rangle$. Each evolutionary path can be characterized by a 2-dim spin configuration Σ with rows representing macromolecules at a certain time.

In the following, only binary sequences are considered, which are characterized by Ising spin variables $s_j^i = \pm 1$ denoting a purine or pyrimidine at site j of a macromolecule in generation i. With these variables the elements of W can be written in the form of Boltzmann weights[2]:

$$W(i+1, i) = h(q) \exp[\ln A(i)] \exp\left(\beta J_y \sum_j s_j^{i+1} s_j^i\right) \tag{2.2}$$

with $\beta = |\ln[(1-q)/q]|$, $J_y = \pm\frac{1}{2}$ for $\frac{1}{2} \leqslant q \leqslant 1$ and $0 \leqslant q \leqslant \frac{1}{2}$, respectively, and the spin-configuration-independent function $h(q) = [q(1-q)]^{l/2}$. In this form W has the structure of a transfer matrix of an Ising system with nearest neighbor interaction in the y direction, which represents the time axis in the evolutionary process. The probability for a special realization Σ of an evolutionary path is given by

$$p(\Sigma) = e^{-\beta H(\beta)}/Z \tag{2.3}$$

with the β-dependent cost function $H(\beta)$:

$$H(\beta) = -\sum_{i=0}^{n-1} \sum_{j=1}^{l} \left[J_y s_j^{i+1} s_j^i + \frac{1}{\beta} \ln A(i) \right] - \frac{nl}{2\beta} \ln[q(1-q)] \tag{2.4}$$

The partition function Z is the sum over all possible trajectories weighted with $e^{-\beta H(\beta)}$. By treating the cost function $H(\beta)$ as a Hamiltonian of an Ising system, all relevant equilibrium quantities have their counterpart in quantities characteristic for the evolution dynamics far from equilibrium. The central notions of the latter are selection, quasispecies, error threshold, growth rate, and relaxation times,[1] which correspond to equilibrium phase transition, surface magnetization, critical temperature, free energy per row, and correlation length as well as interfacial energy. In deriving these relations, let us go back to Eq. (2.1) and write its formal solution in terms of eigenvalues λ_i and eigenvectors $\boldsymbol{\varphi}_i$ of the matrix W:

$$\mathbf{y}(n) = a_1 \boldsymbol{\varphi}_1 \lambda_1^n + a_2 \boldsymbol{\varphi}_2 \lambda_2^n + \cdots$$

$$\mathbf{x}(n) = \frac{\boldsymbol{\varphi}_1 + (a_2/a_1)(\lambda_2/\lambda_1)^n \boldsymbol{\varphi}_2 + \cdots}{\sum_k \varphi_{1k} + (a_2/a_1)(\lambda_2/\lambda_1)^n \varphi_{2k} + \cdots}$$

The growth rate is defined as the logarithm of the largest eigenvalue λ_1. The relaxation into the stationary state is determined by the ratio a_2/a_1,

which depends on the overlap of the initial state with φ_1, as well as by the ratio of the largest to the second largest eigenvalue λ_2:

$$g = \ln \lambda_1 \tag{2.5}$$

$$\tau^{-1} = \ln(\lambda_1/\lambda_2) \tag{2.6}$$

As long as W is an irreducible matrix, which is the case for macromolecules of finite length and replication numbers (rn) $A(i) > 0$, λ_1 is not degenerate and the relaxation time does not diverge. In the stationary state all maxima of $A(i)$ are occupied according to their height and the height of their surroundings. τ measures the relaxation time into this state, which can exceed any observation time. In practical experiments, however, one is interested in the fast relaxation into metastable states each of them characterized by its individual growth rate. In addition, there exists for reasonable models of $A(i)$ a slow time scale for transitions between metastable states.

The same situation occurs in the statistical mechanics of Ising systems. The elements of the (asymmetric) transfer matrix of a 2-dim square-lattice Ising system with Hamiltonian

$$H = \sum_{i=0}^{n-1} \left[E(i) - \sum_{j=1}^{l} J_y s_j^{i+1} s_j^i \right]$$

are[7]

$$T(i+1, i) = \exp[-\beta E(i)] \exp\left(\beta J_y \sum_j s_j^{i+1} s_j^i \right) \tag{2.7}$$

$E(i)$ is the energy of spins within one row and $\beta = 1/kT$. The free energy per row in the limit $n \to \infty$ is determined by the largest eigenvalue $\lambda_1^{(T)}$ of T, which can become degenerate only in the thermodynamic limit for $T \leqslant T_c$. The correlation length in the y direction is given by the ratio of the two largest eigenvalues:

$$-\beta f = \lim_{n \to \infty} \frac{1}{n} \ln Z = \ln \lambda_1^{(T)} \tag{2.8}$$

$$\xi^{-1} = \ln \frac{\lambda_1^{(T)}}{\lambda_2^{(T)}} \tag{2.9}$$

In a state with broken ergodicity the phase space is divided into several components where each component has its own free energy and correlation length. ξ corresponds therefore to the fast relaxation time around one

maximum of the rn landscape. For finite l there is only one largest eigenvalue $\lambda_1^{(T)}$, which is asymptotically degenerate. The ratio of the largest two eigenvalues for a system with only two symmetric phases is of the order of the exponential of the interfacial energy lf^{int},[8]

$$\ln \frac{\lambda_1^{(T)}}{\lambda_{1'}^{(T)}} = O[\exp(-\beta l f^{\text{int}})] \tag{2.10}$$

The relaxation time into a state where both maxima are equally populated is therefore determined by the probability of establishing an interface of energy lf^{int}.

Breaking of ergodicity in the Ising system is related to the appearance of an order parameter below T_c, which can be a homogeneous magnetization for easy-type interactions as in a ferromagnet or a function of local magnetizations such as the EA order parameter in spin glasses.[9] In dealing with the evolution equations one needs a criterion for selection, i.e., localization of macromolecules in a subregion of the l-dim configuration space. In order to get a macroscopic occupation of only a few sequences, the single-digit copying accuracy q must exceed a threshold value.[1] With the relation

$$\beta = \left| \ln \frac{1-q}{q} \right| \tag{2.11}$$

the error threshold q^{cr} is determined by the critical temperature T_c of the corresponding Ising system. Since macromolecules are information carriers, their sequence of nucleotides must not have a simple periodic arrangement. Hence, a local order parameter has to be used, which will be the local surface magnetization of the Ising system with one free boundary and no interactions within that row. Let us treat a matrix W that allows for the existence of metastable states of a lifetime longer than the observation time. Then the largest eigenvector $\boldsymbol{\varphi}_1$ of such a metastable state has components proportional to the occupation number of the sequences. Eigen's concept of the quasispecies[1] refers to this distribution of macromolecules:

$$\mathbf{x}(n) = \frac{\boldsymbol{\varphi}_1}{\sum_k \varphi_{1k}} = \frac{1}{Z} \sum_{\{|s^{n-1}\rangle\}} \cdots \sum_{\{|s^1\rangle\}} W|s^{n-1}\rangle \cdots \langle s^1| W|s^0\rangle \qquad \text{for large } n \tag{2.12}$$

Because of the equivalent structure of the elements of W and T and the asymmetric writing of T, where the interaction energy $E(i)$ appears only in the lower row, a criterion for characterizing the width of the quasispecies is the local surface magnetization:

$$\langle s_j^{sf} \rangle = \sum_{\{\Sigma\}} s_j^n \, p(\Sigma) = \sum_i s_j^n x_i(n) \qquad \text{for large } n \tag{2.13}$$

The index i stands for the spin configurations of the last row. The missing interaction to the spin row of the "future" and the absence of the rn in the last row (no interactions in the x direction) lead to a decrease of the surface magnetization relative to the bulk value. A decrease of the ordering temperature T_c^{sf} relative to T_c of the bulk is related to the question of "dead layers" at magnetic surfaces of Ising systems.[10] For simple short-range ferromagnetic interactions in the x direction it can be shown[10] that dead layers cannot exist, i.e., $\langle s_j^{\mathrm{sf}} \rangle$ vanishes at the same temperature as $\langle s_j \rangle$ of the bulk. However, one can find a different behavior for other models, as in the case of a mean-field ferromagnetic interaction in the x direction[11] or a λ-state Potts model,[10] where $T_c^{\mathrm{sf}} < T_c$. It is T_c^{sf} that characterizes the onset of localization of the quasispecies in sequence space.

The introduction of a cost function $H(\beta)$ in Eq. (2.4) for each evolutionary path also allows an alternate optimization strategy to find the quasispecies and the deterministic path leading to it from a given starting sequence. The optimization procedure used so far[12] consists in producing mutants from the starting sequence and keeping those with higher replication number, while those with lower rn are killed with a certain probability. The sequences in this survival set are then the new starting sequences. The quasispecies is found when the sequence spectrum no longer changes. With the cost function $H(\beta)$, this step-by-step search is replaced by a strategy that already sees the whole time development from $t=0$ to $t=n$. By fixing the spin row at $i=0$ (starting sequence) and choosing n large enough, the quasispecies distribution is characterized by a local surface magnetization of the inhomogeneous 2-dim spin system under the condition of minimal free energy. To obtain the full (deterministic) time development of the macromolecular distribution between $t=0$ and $t=n$, one needs n different spin systems. In each generation i the thermodynamic system consists of i rows, where only the last row determines the macromolecular distribution of that generation.

3. RANDOM ISING SYSTEMS FOR EVOLUTION PROCESSES

3.1. The Replication Number Landscape $A(i)$

There is still insufficient knowledge about the nature of the rn landscape, especially how the interactions between the nucleotides determine the $A(i)$. Many of the experiments are done with the RNA of coliphages, with a chain length of 4000–5000 nucleotides.[13] The information about the kinetics that is relevant in our context is as follows:

1. *In vitro* experiments show that for adapted sequences the rn of the

plus strand is almost equal to that of the complementary minus strand.

2. To a first approximation the rns of the macromolecules are independent of l within a wide range of length.
3. The rns depend strongly on the secondary and tertiary structure of the macromolecules. Long-range interactions between the nucleotides appear because nucleotides that are far apart in the linear arrangement become close neighbors after the folding of the RNA.

From site-directed mutagenesis experiments and studies of phylogenetic trees one gets additional information about the ruggedness and connectivity of the rn landscape[14]:

4. In general, sequences differing by only a small Hamming distance have similar functional fitness, here rns.
5. There exist relatively unrelated sequences with the same functional destination and efficiency, i.e., the rn landscape must have several global maxima at unrelated configurations and there are ridges connecting them.
6. The ratio of purines to pyrimidines in stable sequences is about 1:1.

To account for these points and the above-mentioned "random" arrangement of nucleotides, the concepts developed in the statistical mechanics of random Ising systems seem to be a good starting point to model the rn landscape. Here the term "random" is used in contrast to periodic, which would contain no information for RNA molecules. While a purely random sequence does not contain information either, an RNA molecule looks "random" to somebody unable to read the genetic code. The rn landscape will be modeled by a function consisting of long-range pair spin interactions only (points 3 and 4), which includes no interactions with a magnetic field (point 1), shows frustration (point 5), and has local maxima at sequences containing up and down spins in equal amounts (point 6). To account for point 2, one has to scale the coupling constants adequately.

Anderson[15] used the extremely rugged free energy landscape of the SK spin-glass Hamiltonian[16] in his model of prebiotic evolution. In our case another Hamiltonian seems to be better suited to model the rn landscape for actual experiments. This is Hopfield's Hamiltonian[17] applied to neural networks:

$$E = = -\frac{1}{2} \sum_{j \neq j'} J_{jj'} s_j s_{j'} \tag{3.1}$$

with

$$J_{jj'} = \frac{J_x}{N} \sum_{\mu=1}^{p} \xi_j^\mu \xi_{j'}^\mu \tag{3.2}$$

The p sets of $\{\xi^\mu\}$ are certain patterns learnt by the neural network, which consists of N spins s_j. The ξ_j^μ are taken to be independent quenched variables with probability distribution

$$p(\xi_j^\mu) = \frac{1}{2}\delta(\xi_j^\mu - 1) + \frac{1}{2}\delta(\xi_j^\mu + 1) \tag{3.3}$$

The free energy landscape of (3.1), (3.2) was studied in detail by Amit *et al.*[18,19] In the limit $\alpha = p/N \to 0$ for $N \to \infty$ there are $2p$ degenerate global minima fully correlated with the $2p$ patterns $\{\xi^\mu\}$ and $\{-\xi^\mu\}$. In addition, one gets a number of local minima and saddle points growing exponentially with p. In this limit of low storage the global minima (Mattis states) do not disturb each other and show the same thermodynamic properties (correlation length, etc.) as a simple two-phase ferromagnet. By increasing the parameter α, the free energy landscape at $T=0$ becomes more and more similar to the SK spin glass.[19]

In applying the Hopfield Hamiltonian to the rn landscape with the relation $A(i) = e^{-E(i)}$, one has more flexibility for its construction by varying the number of input configurations $\{\xi^\mu\}$, which are now the mastersequences [= sequences belonging to global maxima of $A(i)$]. In contrast to a pure spin-glass Hamiltonian, this landscape has fewer peaks and more extended flat areas and seems to fit better the experimental results.[13] Note that the spin symmetric states $\{-\xi^\mu\}$ are the complementary sequences, which usually do not encode proteins.

3.2. Error Threshold and Quasispecies Distribution for a Mattis Model

Before we continue to apply the Hopfield Hamiltonian to the evolution equation, let us discuss the main features, such as error threshold and relaxation times for the simplest case $p = 1$. The results gained from this case are directly applicable to the behavior of the dynamic system near the global maxima of the Hopfield rn landscape. For $p = 1$, Eqs. (3.1) and (3.2) model a landscape with two global maxima at configurations $\{\xi^1\}$ and $\{-\xi^1\}$. Since E is an extensive quantity, the maxima of the rns $A(i) = e^{-E(i)}$ increase exponentially with the length l of the macromolecules, which is in contrast to experimental observations (point

2), The easiest way to get the proper behavior is by scaling the interaction constant J_x with $1/l$:

$$A(i) = \exp\left[\frac{1}{2}\frac{J_x}{l^2}\sum_{j\neq j'}\xi_j^1\xi_{j'}^1 s_j^i s_{j'}^i\right] \tag{3.4}$$

The difference in height between the maximum and the minimum of $A(i)$ now has the fixed value $(e^{J_x/2}-1)$. However, as the configuration space increases exponentially with l, the maxima become increasingly flatter, leading to longer relaxation times around them. There is no true phase transition with breaking of ergodicity in the sense that after infinitely many generations only one maximum of $A(i)$ is populated. In the infinite time limit both maxima will be equally occupied. As to the question of selection, one is interested in whether the distribution of macromolecules around these maxima is localized or not. By focusing on only one maximum, the macromolecular spectrum can be characterized by an order parameter that vanishes at a critical copying accuracy q^{cr}. Depending on the range of q, this value approaches 1 or 0 in the limit $l\to\infty$, because then the spins decouple in the x direction, which leads to 1-dim spin chains with the critical temperature at $T_c\to 0$.

The cost function for the landscape (3.4) is, according to Eq. (2.4),

$$H(\beta) = -\sum_{i=0}^{n-1}\sum_{j=1}^{l}\left[J_y s_j^{i+1}s_j^i + \frac{J_x}{2\beta l^2}\sum_{j'=1,j'\neq j}^{l}\xi_j^1\xi_{j'}^1 s_j^i s_{j'}^i\right] \tag{3.5}$$

Here the spin-independent part has been omitted, which would modify only the growth rate by an additional term $\ln h(q)$. The interaction constant J_y can be ferromagnetic or antiferromagnetic, depending on the range of q. In nature only the antiferromagnetic case is represented because of the complementary base-pairing principle. The order parameter then would have to be a local sublattice magnetization. Since we have assumed a spin symmetric rn landscape, the ferromagnetic and antiferromagnetic interactions lead to identical results for all of the thermodynamic quantities of interest. In case of the correlation function one has to consider each sublattice separately, in order to avoid the oscillations. For simplicity, we will therefore treat the case $J_y = +\frac{1}{2}$.

To evaluate the partition function Z for the cost function (3.5), one can follow closely the steps used for the corresponding statistical mechanics system, where $J_x/\beta l$ is replaced by J'_x.[20] With the new Ising spin variables $\eta_j^i = \xi_j^1 s_j^i$ the expression for Z is

$$Z = \exp\left(-\frac{nJ_x}{2l}\right)\sum_{\text{all}\,\eta_j^i=\pm 1}\exp\left\{\sum_{i=0}^{n-1}\left[\frac{J_x}{2l^2}\left(\sum_j \eta_j^i\right)^2 + \beta J_y\sum_j \eta_j^i\eta_j^{i+1}\right]\right\} \tag{3.6}$$

Using the familiar Gauss identity

$$\exp\left(\frac{a^{i2}}{2}\right)=\frac{1}{(2\pi)^{1/2}}\int_{-\infty}^{\infty} dx^i \exp\left(-\frac{x^{i2}}{2}+a^i x^i\right) \tag{3.7}$$

where $a^i=[(J_x)^{1/2}/l]\sum_j \eta_j^i$ and with the substitution $x^i=lJ_x^{1/2}m^i$, one gets for (3.6)

$$Z=\exp\left(-\frac{nJ_x}{2l}\right)\left(\frac{J_x}{2\pi}\right)^{n/2} l^n \int_{-\infty}^{\infty}\cdots\int_{-\infty}^{\infty} dm^1\cdots dm^n$$
$$\times\exp\left(-\frac{1}{2}l^2J_x\sum_{i=0}^{n-1} m^{i2}+l\ln Z_1\right)$$

with

$$Z_1=\sum_{\text{all }\eta^i=\pm 1}\exp\left[\sum_i(\beta J_y\eta^i\eta^{i+1}+J_x m^i\eta^i)\right] \tag{3.8}$$

Z_1 is the partition function of a 1-dim Ising chain with row-dependent effective field $J_x m^i$. For large but finite l ($l\sim 10^3$–10^4) one can use saddle-point method to evaluate the integral. For a homogeneous system one has $m^i=m\ \forall i$, which finally leads to the expression

$$\lim_{n\to\infty}\frac{1}{n}\ln Z=-\frac{1}{2}l^2J_x m^2+l\ln\lambda_1(m)+O\left(\frac{J_x}{l}\right) \tag{3.9}$$

$\lambda_1(m)$ is the largest eigenvalue of a 1-dim Ising chain in the effective field $J_x m$:

$$\lambda_1(m)=e^{\beta J_y}\cosh J_x m+(e^{-2\beta J_y}+e^{2\beta J_y}\sinh^2 J_x m)^{1/2} \tag{3.10}$$

m is determined by taking the maximum of Eq. (3.9), which leads to the self-consistent equation

$$lm=\frac{e^{\beta J_y}\sinh J_x m}{(e^{-2\beta J_y}+e^{2\beta J_y}+e^{2\beta J_y}\sinh^2 J_x m)^{1/2}} \tag{3.11}$$

The local bulk magnetization $\langle s_j\rangle$ is given by

$$\langle s_j\rangle=\xi_j^1 lm \tag{3.12}$$

which shows that lm is the average overlap between $\langle s_j\rangle$ and the random variable ξ_j^1, which becomes 1 in the limit of exact replication, i.e., for $\beta\to\infty$. In a first approximation the surface magnetization (2.13), which

characterizes the quasispecies, can be obtained by using a surface sheet model[10,21] where the spins of the surface row are assumed to interact with the mean bulk spins $\langle s_j \rangle$. With the cost function (3.5) this leads to

$$\langle s_j^{\mathrm{sf}} \rangle = \tanh(\beta J_y \langle s_j \rangle) \tag{3.13}$$

Note that in this approximation $\langle s_j^{\mathrm{sf}} \rangle$ vanishes at the same temperature as $\langle s_j \rangle$. In an exact treatment of $\langle s_j^{\mathrm{sf}} \rangle$, however, it can be shown[11] that T_c^{sf} is smaller than T_c, which is derived from (3.11), but shows the same characteristic relation between $l^{\max}$ and $1-q^{\mathrm{cr}}$. Expanding Eq. (3.11) for small m and finite length l yields the critical line

$$J_x/l = e^{-2\beta^c J_y} \tag{3.14}$$

Note that this is valid only in the limit $J_x/l \ll 1$, where the corrections in the saddle-point approximation can be neglected. In this limit the critical copying accuracy is always larger than 1/2, i.e., $\beta^c > 0$. Below β^c the average overlap lm vanishes, which means an extended quasispecies distribution in sequence space. By using the relation (2.11) between β^c and q^{cr} the error threshold relation for the surface sheet model is

$$l^{\max} = J_x q^{\mathrm{cr}}/(1-q^{\mathrm{cr}}) \tag{3.15}$$

Macromolecules longer than $l^{\max}$ will localize around $\{\pm\xi^1\}$, thus being able to keep information only if the copying accuracy is larger than q^{cr}. Equation (3.15) is in agreement with Eigen's error threshold,[1] which is derived by the requirement that in the stationary state the occupation of the mastersequence must be nonzero. This is equivalent to the statement that the production number of correct copies of the mastersequence must be higher than the average production number (including correct and incorrect copies) of all other molecules:[1,6]

$$A^{\max} q^l > \frac{\sum_{i \neq \max} A(i)\, x_i(n)}{\sum_{i \neq \max} x_i(n)} \qquad \text{for} \quad n \to \infty$$

For q close to 1 this leads to

$$l^{\max} = \ln \sigma/(1-q^{\mathrm{cr}})$$

with

$$\sigma = \frac{A^{\max}}{\sum_{i \neq \max} A(i)\, x_i(n) / \sum_{i \neq \max} x_i(n)} \qquad \text{for} \quad n \to \infty \tag{3.16}$$

Here the superiority parameter σ of the dominant species still contains the occupation numbers $x_i(n)$, which depend on $A(i)$ and q^{cr}. In our model

(3.4), where the mastersequence $\{\xi^1\}$ has the rn $e^{J_x/2}$, the superiority parameter is $e^{J_x q^{cr}}$ in the surface sheet approximation, which shows the dependence on the height of the rn landscape. An exact treatment of the boundary condition yields the value $e^{J_x/2}$ for σ.[11]

The biologically important relation between l^{max} and $1-q^{cr}$ is characteristic for rn landscapes with length-independent height of the maxima. Evolutionary processes, however, must occur above q^{cr} (below T_c), for three reasons. First, a quasispecies distribution contains the mastersequence in macroscopic amounts of typically 4%. Then there would be neither selection of a quasispecies within observational times nor the slow evolutionary search for better adapted species, because of the critical slowing down (divergence of ξ) and the vanishing of the interfacial energy near T_c. To give an estimate for the time scales of the dynamics in a rn landscape where the two mastersequences differ in all positions, let us use the exact expressions for ξ and lf^{int} of the topologically related Onsager model.[8] With interaction parameters $J_x/\beta l$ and $J_y=\frac{1}{2}$ one can express the ratio $\tau^{slow}/\tau^{fast}=e^{\beta l f^{int}}/\xi$ in terms of the deviation $\Delta\beta$ from β^c: $\tau^{slow}/\tau^{fast}\simeq \Delta\beta^{\exp(l\Delta\beta)}$. For macromolecules of length $l\sim 10^3$ one gets unrealistic high values for this ratio if one tries to keep the quasispecies distribution narrow. This is due to the fact that l spins have to be flipped in a transition from one maximum to the other. A landscape with local maxima at sequences differing in only a fraction of spin positions has lower interfacial energies at error probabilities where the quasispecies is well localized. The expression τ^{slow}/τ^{fast} of the Onsager model with the total length l replaced by an effective length determined by the Hamming distance between two mastersequences could give a first estimate of the dynamic time scales for selection and evolution at an error probability that deviates from β^c by $\Delta\beta$. Spin-glass Hamiltonians offer the possibility to generate the multitude of local maxima at sequences with nonvanishing overlap and thus allow transitions between metastable states within reasonable times.

3.3. $A(i)$ from Hopfield's Model for Neural Networks

The steps used to treat the cost function (3.5) can be easily generalized to the more complicated landscape $A(i)$ constructed from the Hopfield Hamiltonian (3.1), (3.2). The cost function is now

$$H(\beta)=-\sum_{i=0}^{n-1}\left[\sum_{j=1}^{l} J_y s_j^i s_j^{i+1}+\frac{1}{2}\frac{J_x}{\beta l^2}\sum_{\mu=1}^{p}\left(\sum_{j=1}^{l}\xi_j^\mu s_j^i\right)^2\right]+\frac{1}{2}\frac{J_x}{\beta l}pn \tag{3.17}$$

The number of mastersequences p is assumed to be so small that even for finite l the spin-glass solutions[19] can be neglected and only one order parameter, namely the macroscopic overlap with the sequences $\{\xi^\mu\}$, has

to be considered. Hence, one has to be well below $p/l = 0.051$,[19] where the Mattis states become the absolute maxima of the rn landscape. Instead of using the Gauss identity (3.7) for the single-indexed variable a^i, one now has double-indexed variables $a^{\mu i} = [(J_x)^{1/2}/l] \sum_{j=1}^{l} \xi_j^\mu s_j^i$ and $m^{\mu i}$, where i specifies the row and μ one of the p mastersequences. The partition function Z is then given by

$$Z = \exp\left(-\frac{J_x np}{2l}\right)\left(\frac{J_x}{2\pi}\right)^{np/2} l^{np} \int_{-\infty}^{\infty} \left(\prod_{i,\mu} dm^{\mu i}\right)$$
$$\times \exp\left[-\frac{1}{2} l^2 J_x \sum_i \mathbf{m}^{i^2} + \sum_{j=1}^{l} \ln Z_1(j)\right]$$

with

$$Z_1(j) = \sum_{\text{all } s_j^i = \pm 1} \exp\left[\sum_i (\beta J_y s_j^i s_j^{i+1} + J_x \mathbf{m}^i \xi_j s_j^i)\right] \tag{3.18}$$

For homogeneous systems one can again argue that the p-component vector $\mathbf{m}^i$ is independent of i. In analogy to the treatment of the pure Hopfield Hamiltonian, one finds in the limit of large but finite l

$$\frac{1}{l} \lim_{n \to \infty} \frac{1}{n} \ln Z = -\frac{1}{2} l J_x \mathbf{m}^2 + \frac{1}{l} \sum_{j=1}^{l} \ln \lambda_1(\mathbf{m}\xi_j) \tag{3.19}$$

with $\lambda_1(\mathbf{m}\xi_j)$ given by Eq. (3.10). The $\mathbf{m}$ is determined by the saddle point equations $\partial f/\partial m^\mu = 0$, which lead, together with the self-averaging property of $\ln Z$, to the self-consistent equations

$$l\mathbf{m} = \left\langle\!\!\left\langle \xi \frac{e^{\beta J_y} \sinh J_x \mathbf{m}\xi}{(e^{-2\beta J_y} + e^{2\beta J_y} \sinh^2 J_x \mathbf{m}\xi)^{1/2}} \right\rangle\!\!\right\rangle \tag{3.20}$$

$$\langle s_j \rangle = \frac{e^{\beta J_y} \sinh J_x \mathbf{m}\xi_j}{(e^{-2\beta J_y} + e^{2\beta J_y} \sinh^2 J_x \mathbf{m}\xi_j)^{1/2}} \tag{3.21}$$

The average $\langle\!\langle \cdots \rangle\!\rangle$ in (3.20) is carried out with the distribution $P(\{\xi^\mu\}) = \prod_\mu p(\xi^\mu)$, with $p(\xi^\mu)$ from Eq. (3.3), and replaces the sum $(1/l) \sum_{j=1}^{l}$. The discussion of the solutions of Eqs. (3.19) and (3.20) follows closely the steps for the pure Hopfield Hamiltonian.[18] The additional ferromagnetic nearest neighbor interaction in the y direction increases the critical temperature, but does not change the nature and the stability behavior of the solutions. Let us start with the Mattis type of solution of Eq. (3.20), which one gets for the case $\mathbf{m} = m_1(1, 0, \ldots, 0)$. These states describe the stationary solutions of the evolution equation around one of the global maxima $\{\xi^\mu\}$ of the rn landscape. After averaging Eq. (3.20) with the distribution $p(\xi^1)$, one finds

the same self-consistent equation for m_1 as in the case of the Mattis model [Eq. (3.11)], which leads to the same error threshold relation (3.14), (3.15). After infinitely many replication steps ($n \to \infty$) all of the $2p$ Mattis states will be equally populated.

The symmetric solutions of the Hopfield Hamiltonian[18] belong to local maxima and ridges connecting local as well as global maxima of the rn landscape. In the evolutionary dynamics metastable localization around the local maxima will occur during the search for the global maxima. Since their height is lower than those of the Mattis states,[18] a more exact copying accuracy is needed to maintain a metastable state. With the same Ansatz $\mathbf{m} = m_n(1, 1,..., 1, 0,..., 0)$ as used in the Hopfield model for these solutions, one gets identical expressions for the overlap lm_n and the ordering of the growth rates near $q = 1$: $g_1 > g_3 > g_5 > \cdots g_6 > g_2$. The even-$n$ solutions remain unstable at all temperatures as in the pure Hopfield Hamiltonian. This can be seen from Eq. (3.20), where the $\sinh J_x \mathbf{m}\xi$ can take on the value zero, which means that a finite fraction of spins remains disordered, or, in the language of evolution dynamics, no metastable localization of a quasispecies is possible at mountain ridges. The odd-n solutions become metastable above copying accuracies q_n^{cr}, which decrease with increasing height of the local maxima: $q_1^{\mathrm{cr}} < q_3^{\mathrm{cr}} < q_5^{\mathrm{cr}} < \cdots$. During evolution the width of the quasispecies distribution would thus become increasingly narrow if the length l of the macromolecules and the copying accuracy q is kept fixed. If nature chooses the way of an invariant width of the quasispecies distribution, the macromolecules are able to increase their information content by increasing l.

Because of the multitude of local maxima provided by the Hopfield rn landscape, the macroscopic evolution equations still contain a random element. While the relaxation around one local maximum is purely deterministic once macromolecules appear in its neighborhood, the search for the global maxima can proceed via many different paths where individual steps cannot be predicted with certainty. The evolutionary hopping,[1,22] i.e., the transition between metastable states, is always connected with the establishment of an interface between any two states. The characteristic transition time is determined by the probability to provide the extra energy of the interface: $\tau \sim e^{\beta l f^{\mathrm{int}}}$. Between states with large mutual overlap lf^{int} will be low, which makes transitions more likely than to states with little overlap.

4. SUMMARY AND OUTLOOK

For Eigen's evolution model the connection between physics and biology was established. The macroscopic chemical rate equations, which

show a nonequilibrium phase transition, namely the selection of macromolecules, can be solved by treating an inhomogeneous Ising model with one fixed boundary row under thermal equilibrium conditions. A cost function $H(\beta)$ for every realization of an evolutionary path was derived [Eq. (2.4)]. With $H(\beta)$ as a Hamiltonian of statistical mechanics all relevant quantities of the dynamic system were expressed in terms of the Ising system [Eqs. (2.5)–(2.13)]. For the central input in the evolution equations, the replication number landscape, the experimental knowledge is still insufficient. This leads to a certain arbitrariness in the construction of $A(i)$ and therefore only global features were tried to be modeled correctly. Of special importance is the free energy landscape of random Ising systems, where Hopfield's model for neural networks is one example. Because of the phenomenon of frustration, they provide the necessary multitude of local and global maxima in the rn landscape, which allows for the appearance of a large diversity of species and a complicated dynamics.

The $A(i)$ is constructed from the relation $A(i) = e^{-E(i)}$. If $E(i)$ had the property of an energy function, the rns would increase exponentially with the length l of the macromolecules. Since this is in contrast to experiments, which to a first approximation show length-independent rns, one has to scale the interaction constants with $1/l$. It was shown that this rescaling is crucial for the reproduction of Eigen's error threshold, which restricts the maximally possible length of selected macromolecules to a finite value for copying accuracies smaller than one. For the case of localization around the global maxima of a Hopfield-type rn landscape the error threshold derived from the vanishing of the order parameter satisfies the relation $l^{\max} = J_x q^{\mathrm{cr}}/(1 - q^{\mathrm{cr}})$. This corresponds to a superiority parameter $\sigma = \exp(J_x q^{\mathrm{cr}})$, which shows the dependence on the height of the rn maximum. It was argued that evolutionary dynamics must occur below this error threshold because of the critical slowing down near q^{cr}, which makes selection of a quasispecies impossible within observational times. In addition, no slow evolutionary search for better adapted species would be possible, because of the disappearance of the interfacial energy. It was shown that one needs a rn landscape with local maxima at sequences differing in only a fraction of spin positions. Only then do the interfacial energies become low enough to allow well-localized quasispecies and transitions between metastable states within realistic times. The rn landscapes constructed from spin-glass Hamiltonians, where Hopfield's Hamiltonian is one example, generate the necessary multitude of local maxima at sequences with nonvanishing overlap. They also bring a random element into the macroscopic evolution equations in the sense that many different paths lead to the stable stationary state of equal occupation of all global maxima.

In this work several restrictions have been imposed on the evolution

dynamics. First, only binary sequences, i.e., Ising spin chains, have been treated instead of four-state Potts spin chains. Experiments show[13] that in the base-pairing mechanism copying errors of the type C–U and G–A occur preferably. In addition, there are special sites in a sequence where copying errors do not matter in the function of the encoded protein and therefore are more likely to occur than at other sites. These two facts make a site- and nucleotide-dependent copying accuracy necessary. The replication numbers of the plus and minus strands can differ substantially for sequences that are not well adapted,[13] in contrast to sequences that belong to maxima of the rn landscape, where this difference is small, but observable. Adding a small uniform magnetic field in the cost function $H(\beta)$ does not substantially alter the rn of the mastersequences, which are composed of about equal amounts of purines and pyrimidines, but leads to a big difference in rn for the plus and minus strands of the other intermediate sequences. Finally, the biologically most important and efficient mutations consist of insertions and deletions of nucleotide clusters, which change the total length of the sequences. Within the statistical mechanics approach a row-dependent chemical potential would have to be introduced in addition to a specification of the mutation rate coefficients.

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