Quasispecies evolution in general mean-field landscapes

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Abstract. – I consider a class of fitness landscapes, in which the fitness is a function of a finite number of phenotypic "traits", which are themselves linear functions of the genotype. I show that the stationary trait distribution in such a landscape can be explicitly evaluated in a suitably defined "thermodynamic limit", which is a combination of infinite-genome and strong selection limits. These considerations can be applied in particular to identify relevant features of the evolution of promoter binding sites, in spite of the shortness of the corresponding sequences.

The quasispecies (QS) model [1,2] is extremely useful to investigate the behavior of populations evolving in a given fitness landscape [3], although it is based on a rather unrealistic infinite-population approximation. It leads to the QS equation, which is a deterministic evolution equation for the fraction of individuals in the population carrying a given genotype. The dimensionality of the QS equation is in principle equal to the number of possible genotypes —an enormously large number even for the smallest organism. Most analytical treatments of the QS equation have therefore focused on situations where this number could be reduced by lumping together genotypes in a small number of classes. In some "master-sequence" landscapes, where fitness depends only on the Hamming distance from a given, optimal genotype [2,4], it is possible to treat together all genotypes whose Hamming distance from the master sequence is the same, forming what is called an error class. The QS equation can be projected on error classes, yielding a vast dimensionality reduction.

However, this simplification is not warranted in a number of interesting cases. Even in master sequence landscapes, the fitness can be a function not only of the number of mutations away from the peak, but also of *where* they appear: some sites in the sequence can be more important than others. On the other hand, there can be more than one fitness peak, quite unrelated to one another.

There have recently been a number of attempts to describe evolution in a low-dimensional space of quantitative traits, in a so-called *phenotypic* approach [5]. In this case the QS equation is low-dimensional from the outset, but the mutation model is more or less arbitrary.

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In particular, one loses the fact that different phenotypes can be expressed by greatly varying numbers of genotypes, and that equilibrium may be reached from a balance between fitness and mutational load.

In the present letter I show how the gap between the genotypic approach of the original QS model and the phenomenological phenotypic approach can be bridged for a class of fitness landscapes that I shall call the *general* mean-field landscapes. The main assumption is that the fitness is a function of a finite number of "phenotypical traits", which are themselves *linear* functions of the genotypical sequence. However, the dependence of the fitness on the traits is more or less arbitrary. Special cases of these landscapes are the single-peak landscape, the Hopfield [6,7] landscape considered by Leuthäusser [8], and the "mesa" landscape introduced by Gerland and Hwa [9] to model the evolution of DNA binding motifs. I shall describe the evolutionary dynamics in the "thermodynamic limit" introduced in refs. [10,11], which is close in spirit to the strong selection limit considered by Krug [12] to treat the transient in quasispecies evolution as a form of extremal dynamics.

I shall discuss my approach within a simple two-letter alphabet representation for the genotype. I defer to a further publication the generalization to the four-letter alphabet and a discussion of a number of more realistic fitness landscapes. I first define the QS equation and the general mean-field fitness landscapes. I then show how the solution of the QS equation can be reduced to an extremal problem within the thermodynamic limit and via an additional slow-change assumption. I then discuss the consequences of this approach in some interesting cases describing interesting evolutionary phenomena. The validity of my approximations is briefly discussed at the end.

I consider a very large population of individuals evolving according to a Darwinian (reproduction-mutation-selection) mechanism, with a one-parent (asexual) reproduction and with a simple point-mutation model of nucleotide substitution. I assume that the "genotype" is described by sequences of L binary units, $\sigma = (\sigma_i)$, $i = 1, \ldots, L$, $\sigma_i = \pm 1$. These sequences may describe, *e.g.*, a short segment of the genome, corresponding to a binding motif, as in [9]. I also assume non-overlapping generations, and define the fitness weight $W_\sigma \geq 0$ to be proportional to the expected number of offspring of an individual carrying the genotype σ. In the infinite-population limit, the fraction $x_\sigma(t)$ of individuals carrying the genotype σ at generation t obeys the QS equation

$$x_\sigma(t+1) = \frac{1}{\langle W \rangle_t} \sum_{\sigma'} Q_{\sigma\sigma'} W_{\sigma'} x_{\sigma'}(t), \tag{1}$$

where $\langle W \rangle_t = \sum_\sigma W_\sigma x_\sigma(t)$ is the average fitness weight and $\mathsf{Q} = (Q_{\sigma\sigma'})$ is the mutation matrix. Within a simple independent mutation model with mutation probability per generation equal to μ_i at unit i one has [8]

$$Q_{\sigma\sigma'} = \prod_i \left(\mu_i^{\delta_{\sigma_i\sigma_i'}} (1-\mu_i)^{1-\delta_{\sigma_i\sigma_i'}} \right) \propto \exp\left[\sum_{i=1}^L \beta_i \sigma_i \sigma_i' \right], \tag{2}$$

where $\beta_i = \frac{1}{2} \log\left(\mu_i^{-1} - 1 \right)$.

In a general mean-field landscape, the fitness weight W_σ depends on the genotype σ only via a finite number of linear "traits" m^α, $\alpha = 1, \ldots, p$, defined by

$$m_\sigma^\alpha = \frac{1}{L} \sum_{i=1}^L \xi_i^\alpha \sigma_i, \tag{3}$$

as a function of the vectors $\xi^\alpha = (\xi_i^\alpha)$. One can assume in the following either that these vectors are known, or that their components are independent random variables. Our results will be expressed as averages over the distribution of the components of the ξ^α in both cases.

The fitness weight W_σ then assumes the form

$$W_\sigma \propto \exp\left[L\,\kappa\phi(\vec{m}_\sigma)\right], \tag{4}$$

where κ is a selection coefficient, $\vec{m}_\sigma = (m_\sigma^\alpha)$ and $\phi(\,\cdot\,)$ is a rather arbitrary function of its argument. Special cases include:

The master-sequence landscape. Here $p = 1$ (m is a scalar) and $\phi(m)$ is, say, a monotonically increasing function of m. The master sequence corresponds to $\sigma_i = \operatorname{sign}\xi_i^1$. The usual sharp-peak landscape corresponds to $\xi_i^\alpha = \pm 1$ and $\phi(m)$ equal to 1 if $m = 1$ and to 0 otherwise. One can consider in general $\phi(m) = m^\lambda$, where λ is an epistasis parameter (no epistasis for $\lambda = 1$, positive epistasis for $\lambda > 1$, etc.). The "mesa" landscape [9] corresponds to $\phi(m) = (1 + \exp\left[-\lambda(m - m_0)\right])^{-1}$ [13, 14], where λ can be taken to infinity.

The Hopfield landscape. Here $p > 1$ (but finite), and $\phi(\vec{m})$ is a function of the p-dimensional vector $\vec{m} = (m^\alpha)$. In the original Hopfield model one has $\phi(\vec{m}) = \frac{1}{2}\sum_\alpha (m^\alpha)^2$, but ϕ can be more general. However, even if $\phi(\vec{m}) = \sum_\alpha \phi_\alpha(m^\alpha)$, the different components of $\vec{m}$ are not independent, since adaptation in one component may disrupt adaptation in the other. For example, one may consider a sequence which should exhibit an affinity larger than some threshold for a given factor, and *lower* than another threshold for another one, as in the "molecular ecology" experiments of Ordoukhanian and Joyce [15], in which a Class I Ligase ribozyme is made to evolve in the presence of a 10–23 DNA enzyme which binds to the same subsequence as the substrate.

The Royal Road landscape. This landscape is rather popular in the theory of Genetic Algorithms, because it embodies neutrality and adaptation in a simple way [16]. The genotype of length $L = BK$ is divided into K blocks of length B each. For each block α, m^α is defined by $m^\alpha = B^{-1}\sum_{i\in B_\alpha} \xi_i^\alpha \sigma_i$, where B_α is the set of units which belong to block α. The difference with the Hopfield landscapes is that the blocks do not overlap. If ϕ is additive with respect to the blocks, the evolution of each block is independent of the other in the quasispecies model. The most interesting results are therefore obtained when there is epistatic interaction between the different blocks.

The solution of the QS equation can be expressed as a "functional integral". One defines $x_\sigma(t) = y_\sigma(t)/\sum_{\sigma'} y_{\sigma'}(t)$, where the y_σ's follow the *linear* QS equation

$$y_\sigma(t + 1) = \sum_{\sigma'} Q_{\sigma\sigma'}\, W_{\sigma'}\, y_{\sigma'}(t). \tag{5}$$

One can then write

$$y_\sigma(t + 1) \equiv y_{\sigma(t+1)} = \sum_{\sigma(t)}\cdots\sum_{\sigma(0)} \exp\left[\sum_{\tau=0}^t \left(\sum_{i=1}^N \beta_i\sigma_i(\tau + 1)\sigma_i(\tau) + L\kappa\phi(\vec{m}_{\sigma(\tau)})\right)\right] y_{\sigma(0)}. \tag{6}$$

By using the Fourier representation of the delta-function, this expression can be written as

$$y_{\sigma(t+1)} \propto \int \prod_{\tau=0}^{t} \left(\mathrm{d}\vec{m}(\tau) \frac{\mathrm{d}\vec{\lambda}(\tau)}{2\pi i} \right) \exp\left[\sum_{\tau=0}^{t} L \left(\kappa\phi(\vec{m}(\tau)) - \vec{\lambda}(\tau) \cdot \vec{m}(\tau) \right) \right] \times$$

$$\times \prod_{i=1}^{L} \left\{ \sum_{\sigma_i(t)} \cdots \sum_{\sigma_i(0)} \exp\left[\sum_{\tau=0}^{t} \sum_{i=1}^{L} \left(\beta_i \sigma_i(\tau+1)\sigma_i(\tau) + \vec{\lambda}(\tau) \cdot \vec{\xi_i}\sigma_i(\tau) \right) \right] \right\} y_{\sigma(0)}. \quad (7)$$

Here we have set, *e.g.*, $\vec{\lambda} \cdot \vec{\xi_i} = \sum_\alpha \lambda^\alpha \xi_i^\alpha$. If we neglect multiple-spin correlation in the initial condition, the second line can be written as

$$\mathcal{J}_{\sigma(t+1)} = \prod_{i=1}^{L} \sum_{\sigma_i(0)} \left\{ \prod_{\tau=0}^{t} \left[\mathsf{K}(\beta_I, \vec{\lambda}(\tau) \cdot \vec{\xi_i}) \right]_{\sigma_i(t+1)\sigma_i(0)} y_{\sigma_i(0)} \right\}, \quad (8)$$

where $\mathsf{K}(\beta, h) = (\exp[\beta\sigma\sigma' + h\sigma'])$ is the transfer matrix of a 1D Ising model.

If $\lambda(\tau)$ and $m(\tau)$ are "slowly varying" one has

$$\prod_{\tau=t'}^{t} \mathsf{K}(\beta_i, \vec{\lambda}(\tau) \cdot \vec{\xi_i}) \simeq \mathsf{K}^{t-t'}(\beta_i, \vec{\lambda}(\tau) \cdot \vec{\xi_i}) \simeq K_{\max}^{t-t'}(\beta, \vec{\lambda}(\tau) \cdot \vec{\xi_i}) \mathsf{P}_{\max}(\beta_i, \vec{\lambda}(\tau) \cdot \vec{\xi_i}), \quad (9)$$

where $K_{\max}(\beta_i, h)$ is the larger eigenvalue of $\mathsf{K}(\beta, h)$, and $\mathsf{P}_{\max}(\beta, h)$ the projector on the corresponding eigenvector.

Define

$$\sum_{\sigma} \delta\left(L\vec{m} - L\vec{m}_\sigma \right) y_\sigma(t) = \exp\left[LF(\vec{m}, t) \right]. \quad (10)$$

Then, if in the initial condition y_σ depends on σ only via $\vec{m}$, and within the slow-change approximation,

$$\exp\left[LF(\vec{m}, t+1) \right] \propto \int \prod_{\tau=0}^{t} \mathrm{d}\vec{m}(\tau) \int \prod_{\tau=0}^{t+1} \frac{\mathrm{d}\vec{\lambda}(\tau)}{2\pi i} \exp\left[\sum_{\tau=0}^{t+1} L \left(\kappa\phi(\vec{m}(\tau)) - \vec{\lambda}(\tau) \cdot \vec{m}(\tau) \right) \right] \times$$

$$\times \exp\left[L \sum_{\tau=0}^{t} \overline{\ln K_{\max}(\beta, \vec{\lambda}(\tau) \cdot \vec{\xi})} + LF(\vec{m}(0), 0) \right]. \quad (11)$$

Here $\overline{\ln K_{\max}(\beta, \vec{\lambda} \cdot \vec{\xi})} = \mathcal{F}(\vec{\lambda}(\tau))$ is the average of $\ln K_{\max}(\beta, \vec{\lambda} \cdot \vec{\xi})$ with respect to the distribution of the β's and of the $\vec{\xi}$'s. This can be either the average over the actual, known distribution of these quantities, if one is lucky enough to know it; or over some reasonable *a priori* distribution otherwise.

If L is large enough, this expression can be evaluated by the saddle point method. In particular, the error threshold can be identified at stationarity, by looking at the extremum of the function $\kappa\phi(\vec{m}) - \vec{\lambda} \cdot \vec{m} + \mathcal{F}(\vec{\lambda})$ with respect to $(\vec{m}, \vec{\lambda})$. This corresponds to the extremum $\vec{m}^*$ of $\kappa\phi(\vec{m}) + \Gamma(\vec{m})$, where $\Gamma(\vec{m})$ is the Legendre transform of $\mathcal{F}(\vec{\lambda})$ with respect to $\vec{\lambda}$[1]. If the distribution of the ξ's is symmetrical, the maximum of $\Gamma(m)$ is located at the origin. As β increases (*i.e.*, as the mutation rate gets smaller), $\Gamma(m)$ becomes flatter and flatter. As β becomes larger than a threshold value β_{th}, m^* moves away from the origin: this is

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[1] This value is not equal to the *actual* average value of m in the stationary population [4], but is close enough to it if the mutation rate is small.
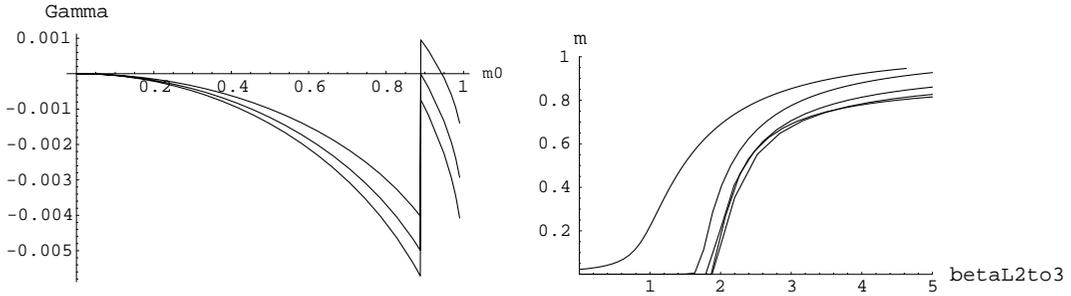
Fig. 1 – Left: the error threshold for the $p = 1$ case in the mesa landscape $\phi(m) = \theta(m - m_0)$. The function $\kappa\phi(m) + \Gamma(m)$ is plotted *vs.* m for (from bottom up) $\beta = 2.25, 2.3425, 2.45$. We have set $\kappa = 0.005$ and $m_0 = 8/9$. One observes that the maximum moves from the origin to m_0 for $\beta = \beta_{\text{th}} = 2.3425$. Right: finite-size scaling $m = m(\beta, L)$ for $\kappa = 0.005$ and $m_0 = 8/9$. X-axis: $(\beta - \beta_{\text{th}})L^{2/3}$ with $\beta_{\text{th}} = 2.3425$. From left to right: $L = 8, 16, 32, 64, 128$.

the error threshold: see fig. 1 (left). Within a simple "mesa" landscape, the error threshold is approximately located at the point in which $\kappa\phi(m_0) + \Gamma(m_0)$ becomes larger than $\Gamma(0)$. For $\beta > \beta_{\text{th}}$, the optimum m^* remains close to m_0, except (for finite λ) at extremely small mutation rates, in agreement with the results of refs. [9, 17].

In order to analyze the finite-length behavior of the system, it is useful to apply the Schrödinger equation approach to the quasispecies equation [9, 18]. The role of the quantum constant $\hbar$ is played by the inverse of the genome length L. In the simple mesa landscape, the quasispecies equation can be transformed into a Schrödinger equation in a potential which is the superposition of a harmonic-oscillator potential near $m = 0$ and a linear potential with a barrier near the threshold. The finite-length threshold $\beta_{\text{th}}(L)$ can be identified by the condition that the ground-state energies near the two classical minima are equal. One thus obtains the result that $\beta_{\text{th}}(L)$ reaches its asymptotic value as $\beta_{\text{th}}(L) = \beta_{\text{th}}(\infty) + \text{O}(L^{-2/3})$, rather than $\text{O}(L^{-1})$, which holds for the sharp-peak landscape (cf. ref. [4]) or for smoother ones. The width of the distribution in m above the threshold also behaves like $L^{-2/3}$. The transition is however quite sharp even for moderate values of L, as can be seen by the finite-scaling analysis shown in fig. 1 (right).

I discuss the Hopfield landscape in the didactically simple case of $p = 2$, $\xi_i^\alpha = \pm 1$. One can easily evaluate $\Gamma(\vec{m})$ numerically: it exhibits a maximum at $\vec{m} = 0$, and is higher on the
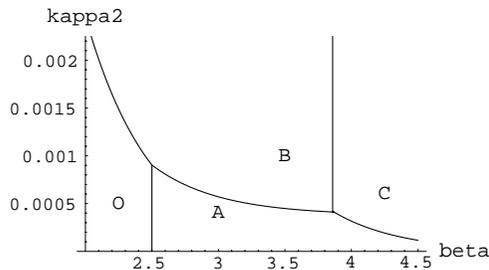

Fig. 2 – The phase diagram in the (β, κ_2)-plane for the $p = 2$ Hopfield landscape, with $\kappa\phi(\vec{m}) = \kappa_1\theta(m^1 - 0.33) + \kappa_2\theta(m^2 - 0.5)$, and $\kappa_1 = 0.377417 \cdot 10^{-4}$. The letters denote the stability regions for the points O: $\vec{m}^* = (0, 0)$, A: $\vec{m}^* = (0.33, 0)$, B: $\vec{m}^* = (0, 0.5)$, and C: $\vec{m}^* = (0.33, 0.5)$.

axes. Again, it becomes flatter and flatter as β increases. Let us consider the case in which $\kappa\phi(\vec{m}) = \kappa_1\theta(m^1 - m_0^1) + \kappa_2\theta(m^2 - m_0^2)$. One can identify the error thresholds $(\beta_{\text{th}}^1, \beta_{\text{th}}^2)$ on the two axes, and the actual threshold will take place at the smaller β_{th}. However, there might be a second threshold at a larger value of β, where $\vec{m}^*$ moves from one axis to another, and even a third one, where $\vec{m}^*$ acquires two nonzero components. See fig. 2.

In the Royal Road case, each block will have its own $\Gamma(m)$ function. If the fitness function $\phi(\vec{m})$ is a sum of contributions, one for each block, the stationary point will be determined independently for each component as the optimum of $\kappa_\alpha\phi_\alpha(m^\alpha) + \Gamma(m^\alpha)$. On the other hand, if there is epistatic interaction among blocks, appearing in $\phi(\vec{m})$, one can find a more complex phase diagram.

Summarizing, I have shown how it is possible to solve for the stationary behavior of the quasispecies equation in a number of nontrivial fitness landscapes, provided the "thermodynamic" and the slow-change limits are taken. The thermodynamic limit seems far-fetched if one is considering, as in [9], the evolution of binding motifs. Nevertheless, the error threshold is well identified by the present approach, and the basic conclusion that m^* is close to the threshold follows directly. The transition appears to be first-order in our language, since it corresponds to the "bulk" transition, while in [9] it is described as the corresponding wetting transition near a wall (cf. [4]). The slow-change limit applies in the stationary regime, and can also be valid in the transient regime if the mutation rates are not too small: the condition is that the number of generations needed to equilibrate with a given value of λ should be smaller than the number of generations in which λ itself varies significantly. This is true if the selective pressures are not too large, and the mutation rates not too small. The application of the present approach to the dynamics is a problem worth further investigation.

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