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Abstract.   We consider the quasispecies description of a population evolving in both the 'master sequence' landscape (where a single sequence is evolutionarily preferred over all others) and the REM landscape (where the fitness of different sequences is an independent, identically distributed, random variable). We show that, in both cases, the error threshold is analogous to a *first-order* thermodynamical transition, where the overlap between the average genotype and the optimal one drops discontinuously to zero.

An equation describing the behaviour of populations of self-reproducing entities, subject to natural selection and to mutations, was introduced by Eigen [1]. The inheritable structure ('genotype') of these entities is described by a sequence of length L of symbols belonging to an alphabet of κ characters ($\kappa = 4$ in the case of nucleic acids). In the simple case, in which one such sequence is selectively preferred with respect to all others, Eigen was able to show that his equation (the *quasispecies equation*) implies a transition (called the *error threshold*) between two different behaviours.

- At a low mutation rate, the population is made up, at equilibrium, of sequences close to the preferred one (*master sequence*): it forms therefore a *quasispecies*.
- At a higher mutation rate, the distribution becomes uniform over sequence space.

This behaviour is reminiscent of a phase transition in statistical mechanics. Indeed, Leuthäusser [2] showed that the quasispecies equation is equivalent to a statistical mechanical model. The error threshold corresponds in this language to a thermodynamical transition of the statistical mechanical system.

Later, Tarazona [3] qualified this correspondence, by pointing out that the properties which described the behaviour of the evolving population corresponded to *surface* observables of the statistical mechanical model. In particular he argued that in the simple situation mentioned above, with a single master sequence, while the naive application of statistical mechanics predicted a first-order phase transition, the transition was continuous for the evolutionary model. The discrepancy between the two predictions was attributed to a surface phenomenon akin to wetting [4], where the disordered state is favoured on a surface layer whose thickness diverges as the phase transition is approached.

The statistical mechanics approach to the quasispecies equation was later used by Franz *et al* [5] to solve it in a 'rugged fitness landscape' (in which the selective value of each different sequence is an independent random variable) modelled by Derrida's random energy

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model (REM) [6]. In this case, a first-order transition between the quasispecies and the uniform behaviour was found. This result has been challenged by Higgs and Woodcock [7].

The aim of this paper is to point out that the discrepancy between predictions is due to the fact that one's attention is directed towards different observables in the different cases: a careful consideration of the 'infinite genome' $(L \to \infty)$ limit, necessary to obtain a sharp phase transition, shows that, in the 'master sequence' model, the error threshold is a first-order phase transition. This does not rule out the fact that, in the same limit, the fraction of individuals whose genotype is equal to the master sequence (or, for that matter, is at any finite Hamming distance away from it) goes smoothly to zero at the transition. In particular, the 'wetting phenomenon' described by Tarazona does not take place, at least in this case. Similar results hold for the rugged fitness landscape. We are aware that these considerations look rather academic, since the 'order parameter' which is more likely to be measured in actual field studies is rather the frequence of the wild type (probably corresponding to the frequence of the master sequence) than the overlap of the average genotype. Our contribution essentially aims at showing that the analogy between the error threshold and phase transition can be made sharper provided some confusing statements appearing in the literature are cleared out.

Let us consider the $\kappa=2$ 'master sequence' model, defined as follows. The genotype s is described by L units $s_i = \pm 1$, $i = 1, \ldots, L$. The quasispecies equation, which describe the evolution of the fraction $x_s(t)$ of individuals having the genotype s at generation t, takes the form

$$x_s(t + 1) = \frac{1}{Z(t)} \sum_{s'} Q_{ss'} w_{s'} x_{s'}(t) \tag{1}$$

where w_s is the fitness of sequence s and $\|Q_{ss'}\|$ is the mutation matrix. The normalization factor $Z(t)$ is given by

$$Z(t) = \sum_s w_s x_s(t).$$

The matrix element $Q_{ss'}$ is the conditional probability that a reproduction event of an individual with genotype s' produces one with genotype s. If one assumes pointwise mutations with uniform probability one has

$$Q_{ss'} = \mu^{d_H(s,s')} (1 - \mu)^{L - d_H(s,s')} \tag{2}$$

where

$$d_H(s, s') = \tfrac{1}{2} \sum_{i=1}^{L} (1 - s_i s_i') \tag{3}$$

is the Hamming distance between the sequences s and s', and μ is the mutation rate. The 'master sequence' is denoted by $s^0 = (s_i^0)$. The fitness w_s is then given by

$$w_s = \begin{cases} \exp(kL) & \text{if } s = s^0 \\ 1 & \text{otherwise.} \end{cases} \tag{4}$$

In this expression, $k > 0$ is a 'selective' inverse temperature. We have chosen to take $\ln w_{s^0} \propto L$ in order to obtain the infinite genome limit in close analogy with the thermodynamical limit. We shall discuss later the scaling considered by Eigen *et al* [1], in which $w_{S^0} \to$ constant.

As pointed out by Leuthäusser [2] and Tarazona [3], the solution of equation (1) can be expressed in terms of a statistical mechanical model. Let us consider a population evolving

for T generations from an initial condition in which $x_s = \delta_{ss^0}$. One has

$$x_s(T) = \frac{1}{\mathcal{Z}} \sum_{s(1),s(2),\ldots,s(T-1)} Q_{s(T)s(T-1)} w_{s(T-1)} \ldots Q_{s(1)s^0} w_{s^0}$$

$$= \frac{1}{\mathcal{Z}} \sum_{s(1),s(2),\ldots,s(T-1)} \exp\left[\sum_{t=1}^{T} (\ln Q_{s(t)s(t-1)} + \ln w_{s(t-1)}) \right]. \tag{5}$$

We have set $s(T) = s$, $s(0) = s^0$, and we have defined the normalization constant $\mathcal{Z}$ by

$$\mathcal{Z} = \sum_{s(1),s(2),\ldots,s(T-1),s(T)} \exp\left[\sum_{t=1}^{T} (\ln Q_{s(t)s(t-1)} + \ln w_{s(t-1)}) \right]$$

$$\equiv \sum_{s(1),s(2),\ldots,s(T-1),s(T)} \exp(-H\{s(t)\}).$$

The last line defines the symbol H. It now turns out that, for the 'master sequence' model,

$$-H\{s(t)\} \equiv \sum_{t=1}^{T} (\ln Q_{s(t)s(t-1)} + \ln w_{s(t-1)})$$

$$= TL \ln(1-\mu) + \sum_{t=1}^{T} \left(\beta \sum_{i=1}^{L} s_i(t)s_i(t-1) + k\delta_{s(t-1)s^0} \right) \tag{6}$$

where the 'mutation' inverse temperature β is defined by

$$\beta = \frac{1}{2} \ln \frac{1-\mu}{\mu}. \tag{7}$$

Expression (6) looks like the Hamiltonian (times the temperature) of an Ising system of TL spins, arranged in T layers of L spins each. The interlayer interactions, representing the correlation effects due to the heredity, are proportional to β, while the intralayer interactions, representing the selection, are proportional to k. Tarazona [3] pointed out that the intralayer interaction term corresponding to layer T is lacking in this expression: the system corresponds therefore to a statistical mechanical model with a free surface.

It is now easy to see that, in the limit $L \to \infty$ followed by $T \to \infty$, a phase transition separates an ordered ('frozen') regime in which one has $s(t) = s^0$ for all layers t except the last one, from a disordered ('free') one, in which all sequences s have the same probability, and the system behaves like a collection of L-independent one-dimensional Ising models at temperature β^{-1}. The transition line can be obtained by comparing the free energies F defined by $F = -\ln \mathcal{Z}$:

(1) for the ordered regime one has

$$F_1 = -TL(k+\beta) + \text{boundary terms} \tag{8}$$

(2) for the disordered regime one has

$$F_2 = -TL \ln(2\cosh\beta) + \text{boundary terms} \tag{9}$$

corresponding to the free energy per spin of a one-dimensional Ising model.

The transition line is given by the condition $F_1 = F_2$ (where the boundary terms are neglected) and reads

$$k_t(\beta) = \ln(2\cosh\beta) - \beta. \tag{10}$$

In terms of the mutation rate μ, this corresponds to $k_t = |\ln(1-\mu)|$, as originally obtained by Eigen [1].

We now show in more detail that all layers but the last one (corresponding to $t = T$) are 'frozen' for $k > k_t(\beta)$, in the sense that the only configurations which contribute in the infinite genome limit are those for which $s(t) = s^0$ for $t < T$. Let us consider the last-but-one layer ($t = T - 1$), and let us momentarily assume that the preceding layer is frozen. The last layer is free, because there are no contributions from the intralayer interactions at $t = T$ [3]. There are two possibilities for $s(T - 1)$.

(1) 'Frozen': $s(T - 1) = s^0$: this yields a contribution $\exp[L(k + \beta)] \times (2 \cosh \beta)^L$ to the partition sum; the second factor comes from the sum over the configurations of the last layer.

(2) 'Free': summing also over the configurations of the last-but-one layer, one obtains the contribution $(2 \cosh \beta)^{2L}$.

Because one has, by hypothesis, $k > k_t(\beta) = \ln(2 \cosh \beta) - \beta$, the first contribution dominates for $L \to \infty$. By induction, one can show in the same way that it is not possible for a label $t_0 < T$ to separate 'frozen' layers (for $t < t_0$) from 'free' ones (for $t \geqslant t_0$).

Let us now define, following Tarazona [3], the order parameter m as the overlap of the average sequence ($\langle s_i \rangle$) with the master sequence s^0:

$$m = \frac{1}{L} \sum_{i=1}^{L} \langle s_i \rangle s_i^0 = 1 - 2\langle d_H(s, s^0) \rangle / L. \tag{11}$$

The angular brackets denote the population average:

$$\langle A(s) \rangle = \sum_s x_s A(s) \tag{12}$$

where we have taken into account the fact that $\sum_s x_x = 1$.

In the ordered phase, all layers but the last one are frozen to the master sequence. It is then a simple matter to show that

$$m = \tanh \beta = 1 - 2\mu. \tag{13}$$

On the other hand, $m = 0$, obviously, in the disordered phase. We have thus obtained the result that the phase transition is of *first order*, and that m drops discontinuously from $1 - 2\mu$ to 0 as k falls below the transition value k_t. Let us also remark that equation (13) predicts that $m = 0$ for $\beta = 0$, even for $k > k_t(0) = \ln 2$, as it is reasonable to expect on intuitive grounds.

This analysis is supported by the numerical solution of the quasispecies equation for finite L. We show in figure 1 the order parameter as a function of μ for different values of L. The value of k is such that the error threshold takes place for $\mu = \mu_t = 0.25$. One clearly sees that the curve approaches a discontinuous behaviour as L increases, in contrast to the statements contained in [3]. Let us remark that, properly speaking, the weight $x_{s^0}(T)$ in the population approaches zero in the thermodynamical limit ($L \to \infty$, k, β = constant). Nevertheless, the population forms a *bona fide* quasispecies, in the sense of [1].

Eigen [1], Leuthäusser [2], and Tarazona [3] have considered a situation in which the fitness ratio w_{s^0}/w_s is kept constant as L increases. In this case, if the mutation rate μ (and hence β) is kept constant, one eventually crosses over smoothly to a 'disordered' regime, independently of the value of this ratio. This is the point that Eigen wanted to make when he introduced the quasispecies equation, back in 1971: that the error threshold prevented biological information to be maintained, if genome length exceeded a certain value.

In this situation, there is no sharp phase transition, and the question of whether it is of first or second order is pointless. However, even in this case, one can obtain a phase transition in the limit $L \to \infty$, if one keeps the average number μL of mutations constant.
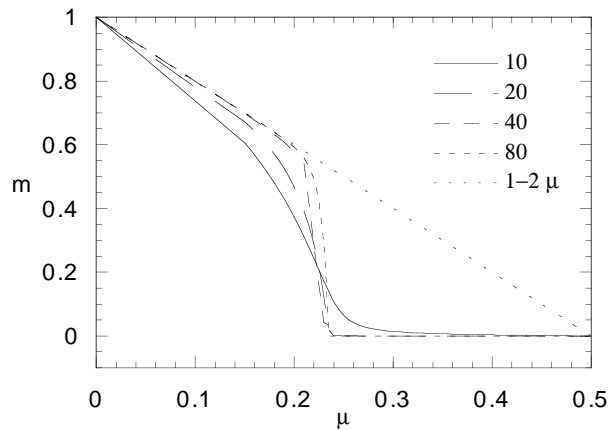
Figure 1. Order parameter m in the 'master sequence' model as a function of the mutation rate μ for $L = 10, 20, 40, 80$. The selective temperature k equals $\ln \frac{4}{3}$. Also plotted is the prediction of equation (13).
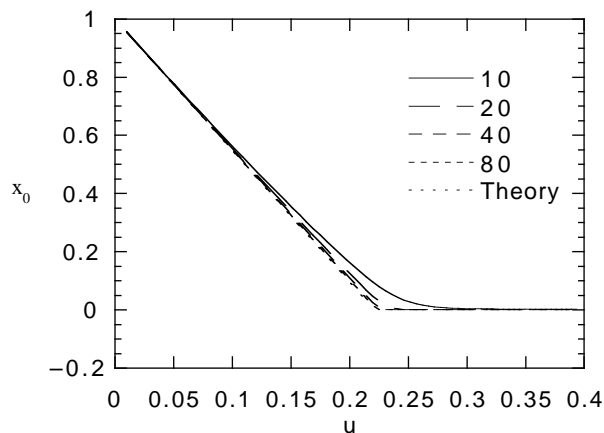

Figure 2. Weight $x_{s^0} = x_0$ of the master sequence as a function of the total mutation rate $u = 1 - \exp(-\mu L)$ for $L = 10, 20, 40, 80$. We have chosen $kL = \frac{1}{4}$ so that $\mu_t L = \frac{1}{4}$. Also plotted is the prediction [8] $x_{s^0} = 1 - u/u_t$, where u_t is the value of u at the transition.

This corresponds to taking $\ln \beta \propto L$. It is possible to solve the problem in this limit, and the results coincide with what one obtains by taking the same limit in the equations we have written above. In particular, the transition is still of first order, but now the order parameter m jumps from 1 to 0: just above the transition, the *whole* population lies a finite Hamming distance away from the master sequence (even though the weight of the master sequence goes smoothly to zero).

On the other hand, this behaviour does contradict the fact that the weight $x_{s^0}(T)$ of the master sequence (which does not vanish if μ is small enough) approaches zero *continuously* at the error threshold, as exhibited in figure 2. The limit behaviour is indeed given by [8]

$$
x_{s^0} = \begin{cases} 1 - u/u_t & \text{for } u < u_t \\ 0 & \text{otherwise} \end{cases} \tag{14}
$$

where $u = 1 - \exp(-\mu L)$ is the total mutation probability, and u_t is the corresponding transition value. However, even in the infinite genome limit, the whole population is the offspring of master sequence individuals at each generation, and has therefore a finite overlap with the master sequence, as soon as one is above the transition.

Let us now consider the REM fitness landscape. In this case the fitness w_s is given by

$$w_s = \exp(-kE(s)) \tag{15}$$

where the 'energies' $E(s)$ of different sequences are independent normally distributed random variables, with zero average and a variance equal to $L/2$. We have correspondingly

$$\mathcal{Z} = \sum_{s(1),\dots,s(T)} \exp\left[\sum_{t=1}^{T-1}\left(\beta \sum_{i=1}^{L} s_i(t)s_i(t+1) - kE(s(t))\right)\right] \tag{16}$$

where, as before, we assume that $s(0)$ corresponds to an energy minimum. The bulk properties of this model have been studied in [5] with the replica method. We briefly illustrate here the results, using the argument originally developed by Derrida [6] to solve the REM. Consider two neighbouring layers, t and $t+1$, whose overlap q, defined by

$$q = \frac{1}{L}\sum_{i=1}^{L} s_i(t)s_i(t+1)$$

has a fixed value. The average number of these configurations with energy equal to E is given by

$$\mathcal{N}(E, q) \sim \exp(LS(q) - E^2/L) \tag{17}$$

where $S(q) = \ln 2 - \frac{1}{2}[(1+q)\ln(1+q) + (1-q)\ln(1-q)]$. The typical value is equal to the average value if the latter is exponentially large, and vanishes otherwise. We can thus write for a typical sample:

$$\mathcal{Z} = \int_{(LS(q)-E^2/L)>0} dE\, dq\, \mathcal{N}(E, q) \exp[T(-kE + L\beta q)]. \tag{18}$$

This expression is dominated by the saddle point in the free phase, and by the smallest value of the energy (and $q = 1$) in the frozen phase. The typical value can be obtained by equation (17), by setting $\mathcal{N}(E, 0) \sim O(1)$, and is equal to $-L\sqrt{\ln 2}$. The free energy is thus

$$F = \begin{cases} -TL[\ln(2\cosh\beta) + k^2/4] & \text{in the free phase} \\ -TL\left(k\sqrt{\ln 2} + \beta\right) & \text{in the frozen phase.} \end{cases} \tag{19}$$

By a comparison of the free energies, the transition line is located at [5]

$$k_t(\beta) = 2\left(\sqrt{\ln 2} - \sqrt{\beta - \ln(\cosh\beta)}\right). \tag{20}$$

We remark *en passant* that, in contrast to the REM and other systems with discontinuous glass transitions [9], here the transition is thermodynamically of first order, with a latent heat that can easily be computed from equation (19).

The surface (evolutionary) properties can be worked out as in the 'master sequence' case. Let us consider the frozen phase, and let us assume that layer $T-2$ is frozen into one of the REM ground states. We focus on layer $T-1$ and assume that layer T is free. Layer T then has no influence on layer $T-1$, whose contribution to the free energy is given by

$$\mathcal{Z}_{T-1} = \sum_{s(T-1)} \exp\left(-kE(s(T-1)) + \beta\sum_i s_i(T-2)s_i(T-1)\right). \tag{21}$$

Analysing equation (21) as above, we find a freezing transition into the ground state, with the same conditions as for the bulk. Therefore, as long as $k > k_t$, all layers but the last one are frozen in the energy ground state. It is clear at this point that all along the frozen phase $m = (1/L) \sum_i \langle s_i(0) s_i(t) \rangle$ is independent of t for $t > 0$, and is given by $m = \tanh \beta$. In the same way, the weight of the optimal sequence behaves as in the 'master sequence' model.

Summarizing, we have shown that in the 'master sequence' and in the REM landscapes for the quasispecies equation, in the limit in which one can speak of sharp phase transitions, surface phenomena do not appear. Indeed the surface passively follows the behaviour of the bulk. This is due to the pathology of the model, that is one-dimensional in the time direction, but mean field as in the sequence direction. The analysis also shows that 'master sequence' and REM landscapes, apart from details, have very similar evolutive properties.

Acknowledgments

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