Equilibrium correlations in a model for multidimensional epistasis

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We investigate a statistical model for multidimensional epistasis. The genotype is devided into subsequences, and within each subsequence mutations which occur in a prescribed order are beneficial. The bit-string model used to represent the genotype, may be cast in the form of a ferromagnetic Ising model with a staggered field. We obtain the actual correlations between mutations at different sites, within an equilibrium population at a given tolerance, which we define to be the temperature of the statistical ensemble.

I. INTRODUCTION

Although evolution takes place via a combination of random mutations and natural selection, it seems to proceed rather rapidly along directed paths in the space of all possible genetic states. It is a challenging problem to try to understand the mechanisms which lead to this phenomenon [1].

Eigen has pointed out that each “species” actually consists of a more or less narrow distribution in the phase space of all possible genetic states, and this distribution may shift, in response to environmental pressure [4]. Natural selection in response to environmental factors is usually modelled in terms of a “fitness function” which is a measure of the survival probability and/or reproductive capability of the individual.

Those mutations which have a salutary effect on the fitness persist in the population and lead to new variants; other, neutral mutations may simply be carried along since they do not affect the well being of the individual. Deleterious mutations usually affect the organism adversely, and the accumulation of too many will reduce the fitness drastically.

The simplest hypothesis biologists have adopted regarding how the number of mutations affect the fitness, is that each deleterious mutation reduces the fitness by an identical factor, say 1/a, a > 1. This is equivalent to assuming that the effect of each deleterious mutation is independent of the others, or that there is no “epistasis” between the mutations, and leads to a fitness function which decays exponentially with m, the number of mutations, as \( f \sim \exp(-\alpha m) \), where \( \alpha = \ln a \). A different type of assumption can be made, to take f to depend on m in a step-wise fashion, so that the value of f is unaffected for m less than a threshold, after which it is reduced drastically.

It is clear, however, that there can be epistatic interactions between mutations at different points on the genetic string and that the expression of unmutated genes may be affected by the presence of mutations at certain loci, and so on. Therefore f may depend not only on the total number of mutations, but also on their location, and may also increase as the result of mutations at certain loci. It has recently been pointed out that the fitness may depend strongly on the order in which certain mutations may occur [2]. As a case in point, for a mutation leading to a certain modification to be beneficial, one must already have had a mutation leading to the emergence of a feature which will benefit from this modification.

This type of epistasis actually lends itself to a treatment in terms of statistical equilibria, with the appropriate choice of a fitness function.

In this paper we will represent a complete genomic sequence with epistatic interactions by a one dimensional ferromagnetic Ising model. We will subdivide the total genotype into subsequences (here taken to be of length 2, without any loss of generality), and stipulate that mutations can lead to salutory effects only if they occur in a certain order within these subsequences. We will further introduce a new quantity, the “tolerance” of the environment, which will have to be taken into account to determine how strongly epistasis interactions affect the overall fitness. Our aim will be to compute, within this model, the effective correlations between mutations at different sites, at fixed tolerance, within a population at equilibrium.

II. THE MODEL

Since Eigen first introduced the quasi-species model [4] bitstring models of genetic evolution have been extensively studied numerically [5, 10, 11, 12]. In this approach, the genotype of an individual is represented by a string of Boolean variables \( s_i \), \( i = 1, \ldots N \), which can obviously be identified with a one dimensional system of Ising spins [9]. If one takes the wild type, or the initial genotype, to consist of a string of 0’s, each point mutation is indicated by flipping the bit representing a given gene, from 0 to 1.

We would like to avail ourselves of the analytically known results on the exactly solvable Ising model in equilibrium, to be able to make definite predictions regarding the correlation of mutated genes on a given genotype, under assumptions similar to those of Kondrashov and Kondrashov [2].

We devide the one dimensional string of spins repre-
senting the state of the genome, into dimers. We demand that the fitness is only increased relative to the wild type (all zeroes) if the bits that flip to 1 occur sequentially. Thus, within each dimer, \((0,0), (1,0), (1,1)\) are in increasing order of fitness while \((0,1)\) is less fit than \((0,0)\).

Let us first construct a cost function by defining the Ising Hamiltonian,

\[
\mathcal{H} = -J/2 \sum_i s_i s_{i+1} - K \sum_{\text{odd}} s_i - H \sum_{\text{seven}} s_i ,
\]

where for greater convenince in manipulation, we have defined the variables \(s_i = 2(\sigma_i - 1/2)\). The value of \(\mathcal{H}\) for each given sequence of \(\{s_i\}\) will serve as a cost function, in terms of which we may define the fitness. Notice that in the first term, we have a coupling between nearest neighbors, which tends to reduce the “cost” for those configurations in which the adjacent “spins” are in the same state. If the constants, \(K\) and \(H\), which correspond to a staggered external field in an Ising model, are here chosen as \(K = 3J/4\) and \(H = -J/4\), then we obtain a situation in which the dimer configurations \((-1,1), (-1,-1), (1,-1)\) and \((1,1)\) have decreasing cost.

Then \(f\) is defined as

\[
f = \frac{1}{Z}e^{-\beta H}
\]

where \(\beta\) is a measure of how effective the cost function is in affecting the fitness, and \(Z\) is a normalization factor so that \(f \in (0,1)\). Note that \(f\{\{s_i\}\}\) can be identified as the Boltzmann factor in an equilibrium statistical model with the Hamiltonian \(H\), at constant inverse “temperature” \(\beta^{-1}\), and corresponds to the probability of observing, within an equilibrium population, the particular genotype \(\{s_i\}\). Temperature may be seen as the amount of randomness, or disorder in the system, competing with the cost function in determining the fitness. The higher the temperature, or randomness, the weaker will be the effect of the cost function in determining the state of the system. Therefore we define

\[
T \equiv \beta^{-1}
\]

as the tolerance in the system. Here \(J\) is a measure of the strength of the interaction between the states of each of the sites (alleles), \(\sigma_i\). Clearly, \(\beta\) and \(J\) will always occur together in this model, in the product \(\beta J\), and we may simply absorb \(J\) into the definition of \(\beta\).

The fitness \(f\) is normalized to take values between \((0,1)\), by defining

\[
Z \equiv \sum_{\{s_i\}} e^{-\beta H[\{s_i\}]} .
\]

Using the transfer matrix method, this sum may be computed exactly. We may then compute the expectation values \(m_i = \langle s_i \rangle\). Note that the quantity \((m_i + 1)/2\) corresponds to the probability of finding a mutation on either of the sublattices, \(i\) odd, or \(i\) even. The results are shown in Fig. 1, as a function of \(T/J\), which is the (inverse) ratio of the strength of the epistasis to the tolerance in the system. The “staggered magnetization,” \(m_s \equiv \langle s_i(\text{odd}) - s_i(\text{even}) \rangle\) is shown in Fig. 2, and is twice the difference between the probabilities of encountering a mutation on either of the two sublattices (the first or the second sites belonging to a dimer). It is seen to peak sharply at small values of the tolerance, and then the difference decays to zero, as the tolerance becomes very large, at which point the fitness function becomes essentially flat.

In Fig. 3a, b and c, we display the correlation functions, \(C_2 = \langle s_i s_{i+2} \rangle\) and \(C_1 = \langle s_i s_{i+1} \rangle\), as well as the subtracted correlation function \(C_s \langle s_i s_{i+2} \rangle - \langle s_i \rangle \langle s_{i+2} \rangle\), as a function of \(T/J\). It can clearly be seen here as well, that the effect of epistatic interactions in building up correlations between mutated sites on the gene string, is felt strongly within a given range of tolerances, in units of the strength of interaction. At \(T = 0\), since the genes are in the ordered state with all \(s_i = 1\), the excess correlation \(C_s\) due to the interactions, is nil. In the other extreme of very large tolerances, the system is completely disordered, correlations vanish, so that the two terms in \(C_s\) tend to each other, and both tend to zero.

To further elucidate the meaning of tolerance, we may compute the relative variances \(v_m\), where

\[
v_m^2 \equiv \langle (s_i - m_i)^2 \rangle .
\]

It is easy to see, that within a mean field approximation, where all the spins interact pairwise with each other, i.e.,

\[
\mathcal{H} = -J/N \sum_{\langle ij \rangle} s_i s_j ,
\]

\(v_m^2 = T/2J\); thus the ratio \(T/J\) is a measure of the size of the fluctuations about the mean. In genome space, this means \(\sqrt{T/J}\) is a measure of the radius of the distribution of genotypes about the most frequently encountered one, in equilibrium.

### III. CONCLUSIONS

In summary, we have cast an epistatic quasispecies model in terms of a one dimensional Ising model with staggered magnetic field, to give greater advantage to certain subsequences of genes that may be mutated. We defined a “tolerance” of the system, to introduce an equilibrium statistical ensemble, namely one whose statistical properties do not change in time. Correlations induced on the genetic sequence of individuals in this equilibrium population have been computed as a function of the tolerance and the strength of the epistatic interaction, using exact solutions of the Ising model in one dimension. It has been shown that non-trivial correlations between mutated sites on the gene string may arise only in a finite range of the tolerance for a given interaction strength.

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[1] J. Maynard Smith, *Evolutionary Genetics* (Oxford University Press, Oxford, 1998).
[2] F. Kondrashov and A.S. Kondrashov, Proc. Natl. Acad. Sci. USA 98, 12089 (2001), and references therein.
[3] S. Özçelik and A. Erzan, “Hamiltonian model for multidimensional epistasis,” [physics/0207079](http://arxiv.org/abs/physics/0207079) and Int. J. Mod. Phys. C, to appear.
[4] M. Eigen, Naturwissenschaften 58, 465 (1971).
[5] see P.M.C. de Oliveira, *Computing Boolean Statistical Models* (World Scientific, Singapore, 1991).
[6] A. Kondrashov, Nature (London) 336, 435 (1988).
[7] J. Thoms, P. Donahue, and N. Jan, J. Physique I 5, 935 (1995); C. Amitrano, L. Peliti and M. Saber, “Molecular evolution on sugared landscapes,” in *Proteins, RNA and the Immune System*, A.S. Perelson and S.A. Kauffmann, eds., (Addison and Wesley, Redwood City, 1991).
[8] A. C. Pai, *Foundations of Genetics* (McGraw-Hill International Editions, 1985), pp.93.
[9] E. Ising, Z. Phys. 31, 253 (1925).
[10] B. Orcal, E. Tuzel, V. Sevim, N. Jan, A. Erzan, Int. J. Mod. Phys. C 11, 973 (2000)
[11] E. Tuzel, V. Sevim, A. Erzan, Phys. Rev. E 64, 061908 (2001).
[12] E. Tuzel, V. Sevim, A. Erzn, Proc. Nat. Acad. Sci. (USA) 98, 13774 (2001).

**Figure captions**

1. The magnetization at a) odd, b) even sites, of the one dimensional Ising model on these respective sublattices, as a function of the “tolerance.” The probability of encountering mutations at these respective sites is given by \((m_i + 1)/2\).

2. The “staggered magnetization” is twice the difference between the probabilities of encountering mutated genes at the first or the second site of the dimers into which the genome has been decomposed.

3. The correlations function between mutated sites on a) analogous sites on neighboring dimers, b) odd-even sites c) the subtracted correlation function between analogous sites.
