

# Statistical Physics of Biological Evolution

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**Abstract.** This is an extended abstract of lectures delivered at the 4th Warsaw Summer School on Statistical Physics in Kazimierz Dolny, June 25-July 2, 2011.

The mathematical theory of evolution is concerned with the changes in the genetic composition of populations that occur under the influence of the evolutionary forces of selection, mutation and demographic noise. In its focus on noisy, collective behavior in large ensembles of (relatively) simple constituents it displays many conceptual similarities to statistical physics, which have given rise to a fruitful interaction between the two fields in recent years. The aim of the lectures delivered at Kazimierz Dolny was to introduce the basic concepts of the theory and to describe some recent work, with particular emphasis on results that are relevant to evolution experiments with microbial populations. These brief notes summarize the main issues that were presented and provide a fairly extensive list of references.

## 1. Basic concepts and evolutionary regimes

The basics of mathematical population genetics were developed in the 1930's by Fisher, Haldane and Wright [19, 24, 25, 51, 52]. These three names are generally associated with the 'modern synthesis' of evolutionary biology, which unified the discrete nature of Mendelian heredity with the Darwinian picture of adaptation by small changes accumulated over long periods of time. Their key insight was that evolution should be viewed as a stochastic phenomenon, where discrete, random mutational changes in single individuals give rise to a seemingly deterministic adaptive process on the population level. In this perspective, evolutionary theory is the statistical mechanics of genes.

The standard model of adaptation on the population level is the Wright-Fisher model, which describes the evolution of a population of fixed size  $N$  in discrete, non-overlapping generations. Mutations occur randomly at rate  $U$  per generation, and selection is incorporated as a bias in the choice of offspring. Mathematically, the Wright-Fisher model can be defined as a branching process conditioned on a fixed population size [41].

An important elementary process is the *fixation* of a new mutation which initially arises in a single individual. The probability of fixation can be computed exactly for the

branching process [24] as well as for the Moran model [38], a continuous time process where individuals replicate and die one at a time. The most commonly used expression for the fixation probability was derived by Kimura [29] in a continuum approximation based on a Langevin equation for the mutant frequency. A new mutation is most likely to go extinct during the early stage of the fixation process, and mutations that survive this initial stochastic regime are called *established* [9, 37].

Depending on the population parameters  $N$ ,  $U$  and the typical selection coefficient  $s$  describing the fitness advantage of the mutant, different evolutionary regimes emerge [23, 41]. Selection is strong if  $Ns \gg 1$  and weak if  $Ns \ll 1$ . Moreover, when the time to fixation  $t_{\text{fix}} \sim s^{-1} \ln N$  is short compared to the time  $t_{\text{mut}} \sim (sUN)^{-1}$  between subsequent establishment events, mutations fix independently, whereas for  $t_{\text{fix}} > t_{\text{mut}}$  they interfere (see Lecture 4 for further discussion of this regime).

## 2. Sequence space and fitness landscapes

The genetic information is encoded in linear sequences of symbols drawn from a finite alphabet. On the microscopic level the symbols stand for nucleotides forming DNA or RNA molecules, or for amino acids forming proteins; on the coarse grained level of classical population genetics, they stand for different variants (*alleles*) of a gene. For many purposes it is sufficient to consider binary sequences, where the symbols merely indicate the presence or absence of a mutation at a given genetic locus. The space of binary sequences of length  $L$  is the  $L$ -dimensional *hypercube* endowed with the *Hamming distance* as the natural metric; the Hamming distance between two sequences is simply the number of letters in which they differ.

Assuming that the fitness of an individual is completely determined by its genotype, fitness can be viewed as a function on sequence space. This idea was first introduced by Haldane [25] and Wright [52], who also pointed out that the existence of multiple peaks in the fitness landscape was a likely scenario that could obstruct the evolutionary process. Later Maynard Smith envisioned evolutionary trajectories as pathways in the space of amino acid sequences that are constrained to move from one viable protein to another [36]. Recent years have seen a surge of renewed interest in the concept, triggered primarily by the availability of empirical data where fitness (or some proxy thereof, such as antibiotic resistance) is measured for all  $2^L$  combinations of  $L$  mutations (typically  $L = 4 - 8$ ), see [5, 6, 10, 14, 33, 44, 50].

## 3. Evolutionary accessibility of fitness landscapes

In population genetic terminology, the notion of *epistasis* refers to interactions between different mutations in their effect on fitness. Of particular importance is *sign epistasis*, which implies that a given mutation may be beneficial (increasing fitness) or deleterious (decreasing fitness) depending on the presence of mutations at other loci. Fitness landscapes without sign epistasis are simple, in the sense that they possess a unique

fitness maximum, and fitness increases monotonically along any path approaching the maximum [49]. In the presence of sign epistasis at least some of the paths become inaccessible, in the sense that they include steps of decreasing fitness, but the existence of multiple fitness maxima requires a specific, stronger form of *reciprocal* sign epistasis [45].

The empirical studies described above in Lecture 2 show that sign epistasis is prevalent in nature, and it is therefore important to devise fitness landscape models that allow to quantify this feature. From the point of view of statistical physics, a natural approach is to consider random ensembles of fitness landscapes with prescribed statistics. In the simplest case random fitness values are assigned independently to the genotypes, resulting in the House of Cards (HoC) model first introduced by Kingman [30] and Kauffman and Levin [27] in the genetic context; in the statistical physics of spin glasses this is known as Derrida's Random Energy Model (REM) [8].

It is easy to see that the probability for a given genotype to be a local fitness maximum is simply  $1/(L+1)$  in the HoC model, and it can be shown that the distribution of the number of fitness maxima is asymptotically normal [3, 34]. A simple combinatorial argument can also be applied to the question of evolutionary accessibility, showing that the expected number of fitness-monotonic paths to the global fitness optimum is equal to 1 irrespective of  $L$  and of the initial distance to the peak [21]. However, the full distribution of the number of accessible paths can only be explored by numerical simulations. It is found to display large sample-to-sample fluctuations, with the majority of realizations (approaching unity for large  $L$ ) having no accessible path spanning the entire landscape.

Real fitness landscapes are not likely to be entirely uncorrelated, and different models with a tunable degree of fitness correlations have been proposed. A classic example is the LK-model introduced by Kauffman and Weinberger [28], in which each of  $L$  loci interacts randomly with  $K$  other loci. For  $K = 0$  the landscape is non-epistatic, while for  $K = L - 1$  it becomes equivalent to the HoC model. The statistics of local maxima in the LK-model has been addressed analytically by probabilists [15, 32], but the properties of accessible mutational pathways has only been studied by simulations so far [21]. In marked contrast to the HoC model, one finds an increase of evolutionary accessibility with increasing  $L$  (in the sense that the likelihood to find at least one spanning accessible path to the global fitness maximum increases) when the number of interacting loci  $K$  is taken to be proportional to (but smaller than)  $L$ .

A second example of a tunably rugged fitness landscape is the Rough Mt. Fuji (RMF) model originally introduced in the context of protein evolution [1]. In this model random fitness values (as in the HoC model) are superimposed on an overall fitness gradient of tunable strength  $\theta$ ; in spin glass language, the model is equivalent to the REM in an external field. The problem of evolutionary accessibility in the RMF is closely related to the theory of records in sets of independent random variables with a linear drift [20], and by exploiting this connection analytic results for the expected number of accessible paths can be derived. One finds an increase of accessibility with

increasing  $L$  for any  $\theta > 0$ , reflecting the fact that the factorial growth in the number of possible pathways overwhelms the exponential decrease in the probability of any given pathway to be accessible [21].

The quantitative measures of evolutionary accessibility developed in the model studies can be applied to empirical fitness landscapes, with the aim of testing the models and estimating epistasis parameters like  $K$  and  $\theta$ . For this purpose it is useful to decompose the landscape into subgraphs spanned by subsets of the total set of  $L$  mutations under consideration, and to study the behavior of the accessibility measures as a function of subgraph size. Applying this approach to a fitness data set containing combinations of 8 individually deleterious mutations in the filamentous fungus *Aspergillus niger* [10], it was found that the data are well described by an LK-model with  $K/L \approx 1/2$ , or by an RMF-model with an intermediate value of  $\theta$  [21].

#### 4. Clonal interference and the benefits of sex

The reason for the emergence and maintenance of sexual reproduction is a long-standing puzzle in evolutionary biology, and a number of genetic mechanisms that could explain the ubiquity of sex in higher organisms have been proposed over the past century. A classic example is the Muller-Fisher mechanism [19, 39], which is based on the observation that beneficial mutations arising in different individuals in an asexual population compete for fixation and therefore obstruct each other's incorporation into the population; in contrast, in sexuals two individuals carrying different beneficial mutations can mate, thus combining the mutations into a single genome. This phenomenon of *clonal interference* sets in when the time scale  $t_{\text{fix}}$  of fixation exceeds the time  $t_{\text{mut}}$  between subsequent beneficial mutations, see Lecture 1, and it is predicted to dramatically slow down the speed of adaptation in large asexual populations.

Early attempts to quantify the Muller-Fisher mechanism arrived at the conclusion that the speed of adaptation reaches a finite limit for  $N \rightarrow \infty$  [7, 18, 37], but recent work has uncovered a more complex scenario [41]. The standard model used in these studies assumes an unlimited supply of beneficial mutations with independent fitness effects (no epistatic interactions) and selection coefficients  $s$  drawn from a probability density  $f(s)$ .

Since beneficial mutations typically constitute a small fraction of all possible mutations, there is little empirical information on the shape of  $f(s)$  [17], but theoretical arguments favor an exponential form [40]; alternatively, for theoretical convenience it is often assumed that all mutations have the same effect and  $f(s) = \delta(s - s_0)$  [9]. In the latter case a systematic calculation of the speed of adaptation is possible, based on the idea that the fitness distribution of the population can be described as a traveling wave of constant shape moving towards higher fitness [4, 46, 47, 48]. A key result is that the speed of adaptation is proportional to the logarithm of population size, in stark contrast to the behavior for small populations where mutations fix independently and

the dependence is linear in  $N$ .

An approximate treatment applicable to the case of continuous distributions of selection coefficients has been proposed by Gerrish and Lenski [22]. This theory assumes that only the mutation with largest selection coefficient among those appearing during a typical fixation time survives. As a consequence, the speed of adaptation depends on the tail shape of  $f(s)$  and is proportional to  $\ln N$  for the exponential distribution.

Effects of clonal interference on the speed of adaptation have been observed, at least qualitatively, in evolution experiments with bacterial populations [11, 12, 13, 16]. By detecting and analyzing individual beneficial mutations, such experiments can also be used to determine the parameters of the model, primarily the beneficial mutation rate and the mean selection coefficient [43]; however these estimates depend strongly on the assumption made regarding the distribution  $f(s)$  [26].

As was noted long ago by Maynard Smith [35], the advantage of recombination due to the Muller-Fisher effect disappears in infinite populations. In that limit recombination affects the speed of adaptation only if mutations interact epistatically. To be precise, recombination aids adaptation if the effect of an mutation decreases as the number of mutations increases (*negative epistasis*) [31] but slows it down in the opposite case. In the presence of *sign epistasis* (as introduced in Lecture 3) recombination can be strongly detrimental, leading to a complete localization of the population at suboptimal fitness peaks for infinite  $N$  [14, 42] and an exponential growth of the escape time with  $N$  when the population size is finite [2]. Thus in general recombination can be beneficial or deleterious depending on the structure of the fitness landscape.

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