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Speed of evolution in large asexual populations with diminishing returns

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HIGHLIGHTS

- Experiments with large asexual populations show a sublinear increase of fitness.
- We describe the phenomenon using a minimal model with diminishing returns.
- We propose a procedure to compare the model with data.
- We apply the procedure to data from two different experiments with bacteria.

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ABSTRACT

The adaptive evolution of large asexual populations is generally characterized by competition between clones carrying different beneficial mutations. Interference slows down the adaptation speed and makes the theoretical description of the dynamics more complex with respect to the successional occurrence and fixation of beneficial mutations typical of small populations. A simplified modeling framework considering multiple beneficial mutations with equal and constant fitness advantage is known to capture some of the essential features of laboratory evolution experiments. However, in these experiments the relative advantage of a beneficial mutation is generally dependent on the genetic background. In particular, the general pattern is that, as mutations in different loci accumulate, the relative advantage of new mutations decreases, a trend often referred to as "diminishing return" epistasis. Here, we propose a phenomenological model that generalizes the fixed-advantage framework to include this negative epistasis in a simple way. We evaluate analytically as well as with direct simulations the quantitative consequences of diminishing returns on the evolutionary dynamics. The speed of adaptation decreases in time and reaches a limit value corresponding to neutral evolution in the long time limit. This corresponds to an increase of the diversity in terms of "classes of mutation" in the population. Finally, we show how the model can be compared with dynamic data on fitness and number of beneficial mutations from laboratory evolution experiments.

1. Introduction

Thanks to contemporary technologies such as phenotypic characterization and high-throughput sequencing, previously unachievable quantitative measurements of the results of controlled laboratory evolution experiments are now possible. This is guiding theoretical investigations and could make the validation and falsification of phenomenological theories feasible (Hindré et al., 2012; Barrick et al., 2009; Tenaillon et al., 2012), with notable consequences in a wide range of bio-technological and ecological investigations.

In the specific case of large asexual (or rarely recombining) populations of microorganisms, a high number of beneficial mutations emerge in different clones, and cannot be mixed because of slow or

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absent recombination. These beneficial mutations appearing in parallel coexist and compete to drive adaptation. This phenomenon of concurrent beneficial mutations (sometimes generically termed "clonal interference"), is related to the Fisher-Muller hypothesis (or Hill-Robertson effect) for the advantage of recombination (Felsenstein, 1974).

In general, different mutations can bring different fitness advantages. The distribution of these advantages is not known precisely. It has been shown to be species-specific, dependent on the genomic region where the mutation occurs (e.g., coding or non-coding), and differently skewed for beneficial and deleterious mutations. However, it is often approximated by an exponential distribution for modeling simplicity (Gerrish and Lenski, 1998; Orr, 2003; Keightley and Eyre-Walker, 2007; Eyre-Walker and Keightley, 2007).

Recent models have generally dealt with the competition between mutations of different strengths and the competition between mutations that arise on different fitness backgrounds separately. The first effect, the role of a distribution of fitness changes, called "clonal interference",[1] is analyzed by several models (Gerrish and Lenski, 1998; Wilke, 2004; Park et al., 2010). In these models any individual is either the wild type or a mutant derived directly from the wild type. Thus, multiple mutations arising in the extant mutants are neglected. Conversely, models that explicitly deal with multiple mutations typically assume that all mutations have the same (positive or negative) effect (Park et al., 2010; Tsimring et al., 1996; Desai and Fisher, 2007; Brunet et al., 2008; Desai et al., 2012) (recent work incorporating both effects (Good et al., 2012) has shown that for peaked distribution of advantage this is the correct effective theory). The latter kind of model has the advantage of being simpler to treat and accessible analytically. It is characterized by a Gaussian-like traveling wave for the histogram of log-fitness throughout the population. In absence of epistasis, this wave moves toward higher log-fitness with a constant speed and shape (Park et al., 2010; Tsimring et al., 1996; Rouzine et al., 2003, 2008; Hallatschek and Korolev, 2009). New mutations are fixed in the population if they occur in the high-fitness edge (or "nose") of the distribution (Desai and Fisher, 2007; Brunet et al., 2008). Consequently, a quantitative law relates the width of the log-fitness histogram and the adaptation speed.

There appears to be one important discrepancy between the models described so far and the behavior of bacteria evolved in the laboratory for longer times (roughly, >1000 generations). This discrepancy is well represented by the experimental sub-linear increase on long time-scales of the average population log-fitness (or fitness advantage) (Kryazhimskiy et al., 2009). This is in contrast with the linear increase predicted theoretically by many models even if they have been compared successfully with the diversity and adaptation speed of short-time laboratory evolution experiments (Desai et al., 2007). Therefore, the core issue is to understand the evolutionary mechanisms at the basis of the experimental slowing down of the adaptation process.

Furthermore, two recent experimental studies (Khan et al., 2011; Chou et al., 2011) have shown a common trend in the advantage of combined beneficial mutations occurring in different genes. In most of the cases analyzed, the combined advantage is lower than the sum of that of individual mutations. In other words, when mutations of loci in different genes accumulate, the effective advantage of each of them is lower. This was shown by combinatorial genetics techniques, by constructing all the possible configurations of a small set of mutations, and evaluating their advantage through competition experiments. This decrease of the advantage carried by a mutation as the background fitness increases provides a possible mechanism at the basis of the observed sub-linear increase of the average fitness in long-term evolutionary experiments (Khan et al., 2011).

This trend, referred to as "diminishing returns" epistasis, had been previously suggested theoretically on the basis of the general pattern of adaptation observed in long-term microbial experiments (Kryazhimskiy et al., 2009), using a modeling framework that neglected concurrent or multiple mutations. Another study predicts the same principle on the basis of a simple fitness landscape model combined with the distribution of single mutation effects measured experimentally (Martin et al., 2007). The actual pattern in the fitness advantage associated to the same mutation in different backgrounds observed by the two studies is complex, as, on top of the diminishing return effect, the advantage appears to depend on the mutation identity. Even more recent systematic experiments (Tenaillon et al., 2012) are unveiling a complex scenario where different mechanisms coexist for the interactions of mutations between and within functional "blocks", which can span multiple genes along the genome. However, the full experimental complexity is difficult to incorporate in a treatable model, and experimental data on linked mutations and interference between them are difficult to obtain. Thus, simplified descriptions, as the multiple-mutations model, are useful to model evolving populations using a minimal quantity of information on mutations and fitness advantage.

Here, we take a simplified approach to study the diversity and speed of adaptation in presence of diminishing returns. We define a framework that can account for multiple mutations, and incorporates the effect of diminishing return epistasis. Namely, the fitness of a mutation depends only on its order of appearance in a clone, and decreases with it. This generalizes the non-epistatic multiple-mutations model (Desai and Fisher, 2007; Brunet et al., 2008) (recovered in case the advantage decrease with the number of acquired mutations is zero). We preserve the model assumption that evolution is driven by beneficial mutations which appear with constant rate (see the Discussion for an evaluation of these assumptions in light of the results). We study the infinite-N behavior of this model using standard techniques, and the diversity of the finite-population behavior across realizations. At finite population sizes, we show that the analytical quantitative estimates of the speed of adaptation of the constant advantage multiple-mutations model can be applied with appropriate modifications.

2. Basic features of the model

2.1. Model definition

We build a minimal population-genetics model (Park et al., 2010; Wright et al., 1931; Fisher, 1930) including diminishing return epistasis in presence of competition between beneficial mutations. The model describes a population of N haploid individuals, or sequences, in which each individual of type i produces a random number of offsprings with average equal to its fitness w_i. Inheritance is introduced by assigning the fitness of the parent to the offspring. Mutations change the mean fitness of the offspring w_i' relative to the parental one w_i according to the relation $w_i' = w_i(1+s) \simeq w_i e^s$. While the fitness advantage associated to new mutations is a complex issue (Eyre-Walker and Keightley, 2007), in presence of abundant beneficial mutations, deleterious mutations (negative effect on fitness, $s<0$) do not typically contribute to the adaptation of large populations and can be neglected (Park et al., 2010; Brunet et al., 2008; Desai and Fisher, 2007).

[1] Note that the term has a strict sense in this case. In the following we will reserve the term clonal interference to this stricter meaning of competition between mutations of different strength, and talk of interference between beneficial mutations in the generic case.