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Variability in fitness effects can preclude selection of the fittest

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Abstract

Evolutionary biologists often predict the outcome of natural selection on an allele by measuring its effects on lifetime survival and reproduction of individual carriers. However, alleles affecting traits like sex, evolvability, and cooperation can cause fitness effects that depend heavily on differences in the environmental, social, and genetic context of individuals carrying the allele. This variability makes it difficult to summarize the evolutionary fate of an allele based solely on its effects on any one individual. Attempts to average over this variability can sometimes salvage the concept of fitness. In other cases evolutionary outcomes can only be predicted by considering the entire genealogy of an allele, thus limiting the utility of individual fitness altogether. We describe a number of intriguing new evolutionary phenomena that have emerged in studies that explicitly model long-term lineage dynamics and discuss implications for the evolution of infectious diseases.

Keywords

Natural selection; Fitness optimization; Varying environments; Group selection; Inclusive fitness; Mutation rate

I. Introduction

Evolutionary change is driven by the successive spread of alleles in a population. The outcome of natural selection can often be predicted by simply examining the effect of an allele on individual fitness: the lifetime reproductive success of individual bearers. However, the longterm outcome of natural selection on an allele also depends on its effects across an entire lineage defined here as the genealogy of an allele from its origination to its ultimate fixation or extinction in the population (Sidebar 1). When fitness effects are invariant across a lineage, the long-term fate of an allele can be deduced in a relatively straightforward manner from its recursive effects on survival and reproduction across descendent carriers. In other cases, the evolutionary success of an allele is not an obvious consequence of its effects on individuals. For example, variable environments can cause the same allele to have differing effects on fitness depending on an individuals' environmental context. Similarly, fitness effects may vary due to the presence of other alleles in the genome, which are themselves polymorphic in the population. In such cases, it is often presumed that traits will

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spread by natural selection so long as they increase the rate of spread of a lineage when averaged across all contexts (Eshel 1973, Nunney 1999b). This implies that natural selection favors traits that are beneficial not strictly to individuals, but to genetic lineages as a whole.

The concept that natural selection may optimize quantities related to the average success of an allele across its lineage has arisen in a wide range of problems, from varying environments to the evolution of sex and cooperation (Akçay and Van Cleve 2016, Eshel 1973, Kussell and Leibler 2005, Lehmann, et al. 2016, Nunney 1999a, Nunney 1999b). In general, this idea arises when the fitness effect of an allele varies between individual carriers, thereby limiting the ability to infer its long-term success based on measures of individual fitness alone. A large class of evolutionary problems fit this description and they can be classified by whether the variability across a lineage reflects environmental, social, or genetic factors. We outline examples of each in Table 1 and describe many of these in more detail in the main text. Each source of variation has largely been discussed within its own body of literature, where equivalent concepts are used to describe a distinct set of adaptations, often with distinct terminology.

Averaging the fitness effects of an allele across its lineage shifts the definition of fitness from a quantity related to individual reproduction to a measure of the success of allelic lineages. However, one must also acknowledge possible limitations in the ability of natural selection to favor traits that confer a long-term benefit to a lineage. Specifically, natural selection is myopic in nature-acting to increase the frequency of traits that confer an immediate advantage to individuals without regard to their future utility to a lineage. This shortsightedness can have dramatic consequences, particularly if it results in the permanent extinction of an allele prior to it realizing any average benefit in the long-term. Indeed, the notion that natural selection will act most strongly on alleles that confer a short-term advantage was championed by Maynard Smith (1964) and Williams (1966) in their now famous critique of group selection, and is still in use (Lynch 2007, Sniegowski and Murphy 2006). Is there a concept of fitness that can predict when natural selection favors traits that confer a long-term advantage across a lineage and when such traits are susceptible to shortsighted selection?

We begin by summarizing results from classical, lineage-invariant theory that successfully relates individual fitness to a lineage's eventual fate. We then discuss a diversity of examples of lineage-variable fitness, in which the fitness effects of an allele vary across its lineage of descendants. We next illustrate the shortcomings of averaging variability across the lineage in finite populations, in which alleles that are beneficial in the long-term are nevertheless vulnerable to extinction. Consequently, shortsighted selection in finite populations can limit the ability of natural selection to optimize even these measures of fitness. We then review cases in which the evolutionary fate of an allele is irreducible to any single measure of fitness, and can only be captured by explicitly tracking the fate of an allele in a model that considers lineage dynamics. We also draw attention to strikingly counterintuitive results that emerge in such models. For example, under some circumstances an allele that is on average selectively neutral can have fixation probabilities far above the neutral prediction, thus behaving like a beneficial mutation. Further, the tendency for an allele to spread or go extinct can vary with population size, an effect that does not exist when fitness effects are

invariant across a lineage. We conclude by highlighting implications for the evolution of infectious diseases and directions for future work.

II. Lineage-Invariant Fitness Effects

Before discussing cases in which the fitness effect of an allele varies among members of a lineage, we briefly consider the case where fitness effects are invariant across a lineage. Throughout, we will consider the evolutionary fate of a single mutant allele introduced to a population. We will place particular emphasis on the probability of fixation as a measure to quantify the evolutionary fate of an allele. Computing fixation probabilities requires integrating changes in the frequency of an allele across all possible configurations of an allelic lineage, and therefore summarizes its ultimate evolutionary success. While deriving fixation probabilities under scenarios of lineage-variable fitness effects can be analytically intractable, the concept is well defined and accessible computationally under a wide range of population genetic models. Finally, by summarizing the probability that an allele either fixes or goes extinct, this quantity provides a concise summary of the long-term evolutionary fate of an allele.

Consider an allele that influences the expected number of surviving offspring produced over the lifetime of its carriers. The most fundamental biological consideration regarding the fate of an allele by natural selection is how the allele influences this measure of fitness relative to that of the resident “wild type” in the population. This is most easily illustrated in the case of haploids, where the selection coefficient of an allele is defined as $s \equiv w_{mut}/w_{wt} - 1$. Here, w_{mut} and w_{wt} correspond to the reproductive success of the mutant and wildtype, respectively. The same quantity can be defined in diploids after additional assumptions regarding dominance, allelic segregation, and mating are made. Using an approximation of the Wright-Fisher model of population genetics, Kimura (1962) found the fixation probability of a mutation starting at frequency x_0 . In a haploid population of size N , Kimura’s formula reduces to:

$$P_{fix}(N, s, x_0) = \frac{1 - e^{-2Nsx_0}}{1 - e^{-2Ns}}. \quad (1)$$

We note that this result is quantitatively dependent on the assumptions of the Wright-Fisher model. In particular, this model assumes that each allelic lineage has a binomial distribution of offspring number. Other population genetic models, like that of Moran (1958), employ other distributions but all such models assume that carriers of an allele have a fixed distribution of offspring numbers. We designate such models as lineage-invariant, since they assume that an allele’s realized reproductive success follows a fixed distribution across its entire lineage. (Figure 1A). Critically, this assumption limits the applicability of results like Equation 1 in scenarios described below, where the offspring distribution is variable across an allele’s lineage.

III .Lineage-Variable Fitness Effects

Under the assumption that an allele exerts a constant, lineage-invariant effect on fitness, Equation 1 demonstrates that a mutant's effect on individual fitness is sufficient to predict the fate of its lineage. We now turn to cases where variability in the fitness effects of an allele can cause this result to fail. Examples of lineage-variable fitness effects emerge under many realistic biological scenarios, where alleles do not act alone to influence fitness but interact with different environmental, social, or genetic factors (Table 1, Figure 1). Consequently, the number of offspring produced by individuals in a lineage may not be drawn from any fixed distribution, violating the assumption of lineage invariance underlying Equation 1. We emphasize that such variability in offspring number is beyond that captured in classical models like Wright-Fisher, which allow variance but assume that the distribution of offspring number is fixed across the lineage. Our goal in this section is to highlight some of the relevant examples of variability in fitness of alleles represented by the three classes in Table 1 and to build some intuition for how they have been handled in the literature. We also seek to show that adaptations associated with each example depend uniquely on the effects of an allele on the fate of a lineage rather than on individual success.

Environmental interactions

Natural environments are inherently variable and therefore present an obvious challenge to the assumption that an allele will have the same effect on fitness for all carriers. Variation in the environment over time will cause contemporary members of a lineage to experience the same distribution of offspring number, but this distribution now depends on time (Figure 1B). Contrastingly, under spatial variation in the environment, contemporary members will experience fitness effects that depend on the interaction between their shared allele and the local environment they encounter. This again implies that no single distribution in offspring number will be generally applicable. In either case, if environmental change is so rapid that individuals encounter a succession of different environments in their lifetime, then fitness can be described as a lifetime average of total survival and reproduction (Levins 1968). We will therefore focus on the more interesting case where environments vary on a timescale greater than the generation time of the organism; here averaging can often be misleading.

The greatest progress has been made in models of temporally varying environments, in which case the selection coefficient s is no longer a constant, but a time-dependent quantity, $s(t)$. Formal analysis typically requires specifying a particular form of $s(t)$ at the expense of generality. It is commonly assumed that environments are randomly drawn from a fixed distribution or that the population size is infinite (Dempster 1955, Gillespie 1973, Kussell and Leibler 2005, Lewontin and Cohen 1969). Under these assumptions, a diverse set of models can be integrated based on how variation in fitness correlates within and between members of two competing lineages (Frank and Slatkin 1990). We note, however, that such an approach is limited to deriving the instantaneous change in allele frequency rather than explicitly modeling lineage dynamics. Another consequence of assuming random environmental change and infinite populations is that natural selection will favor alleles that increase the long-term growth rate of a lineage, averaged over all environments (Dempster 1955, Gillespie 1973, Kussell and Leibler 2005, Lewontin and Cohen 1969, Stearns 2000).

Formally, this corresponds to an increase in the geometric mean fitness, or equivalently, the arithmetic mean of intrinsic growth rate (Sidebar 2), and is generalizable to other forms of $s(t)$ (Cvijovic, et al. 2015). Importantly, even arbitrarily large but finite populations experience genetic drift, which can limit the ability to maximize the long-term growth rate of lineages in certain environmental scenarios. We discuss these limitations in more detail below.

Despite its limitations in finite populations, the principle that natural selection in variable environments acts to increase geometric mean fitness is a key theoretical insight, and it is presumed to underlie numerous adaptations. These include strategies like developmental and phenotypic plasticity that allow organisms to alter their phenotype and development in direct response to local environmental conditions (Meyers and Bull 2002, Via, et al. 1995). Under more unpredictable environmental scenarios, selection can favor the evolution of bet-hedging traits in which an allele causes the undirected exaggeration of phenotypic noise among members of a lineage, thereby allowing a single genotype to spread environmental risk among different phenotypes that are suited to different environments (Fraser and Kaern 2009, Gillespie 1974, Kussell and Leibler 2005, Philippi and Seger 1989). Such a strategy is inherently dependent on selection favoring traits that confer a long-term benefit across a lineage, since individuals will experience differing fitness values depending on their phenotype and the environment they encounter. By spreading the risk of fitness losses under future environmental uncertainty across members of a lineage, bet-hedging helps to ensure survival and reproduction across the lineage as a whole, regardless of the environment. Examples of adaptive bet-hedging strategies have been noted in plants (Childs, et al. 2010, Clauss and Venable 2000, Gremer and Venable 2014), insects (Hopper 1999, Menu, et al. 2000), and microbes (Balaban, et al. 2004, Jones and Lennon 2010, Levy, et al. 2012).

Social interactions

Fitness can also be influenced by interactions with other conspecifics. These interactions can create a type of lineage-variable fitness known as frequency dependent selection, where the fitness effects of an allele are dependent on the frequency of the allele in the population. In other scenarios, the fitness effect of an allele might depend on the population size, called density dependence. Frequency and density dependence are conveniently analyzed in the context of evolutionary game theory (Sidebar 3), which allows one to consider the ability of an initially rare allele to invade a population fixed for a wild-type allele (Maynard Smith 1982, Maynard Smith and Price 1973). This approach provides a generalization of the concept of a selection coefficient to instances where fitness cannot be wholly represented by a constant value. A classic example of frequency-dependent selection arises when considering cooperative traits. Here, cooperative acts incur a cost to individuals and are therefore susceptible to invasion by selfish “cheater” strategies that avoid the cost of cooperating while still reaping the benefit. Cheater strategies are typically favored by selection when rare, since their fitness advantage requires interactions with cooperators. Despite the inherent susceptibility to cheaters, cooperation is common in nature and is presumed to underlie major transitions in evolutionary history, such as the evolution of multicellularity (Szathmary and Maynard Smith 1995). The mechanisms promoting the

evolution and maintenance of cooperation are therefore of long-standing interest to biologists.

Significant theoretical progress on the evolution of cooperation arose with the formulation of inclusive fitness theory. Hamilton (1964) showed that alleles controlling cooperation may be beneficial on average so long as the beneficiary of cooperative actions share a copy of the allele. The key realization of this theory is that cooperative acts need not directly increase the reproductive success of individual bearers, but instead must increase the rate of spread of an allelic lineage (Akçay and Van Cleve 2016). Cooperation can also be stable under cases of multilevel selection (Luo 2014, Simon, et al. 2013, Traulsen and Nowak 2006). The formation and dissolution of new groups is itself a reproductive process, and the long-term fate of a lineage is therefore sensitive to the influence of an allele on group-level reproduction (Figure 1C). A well-known example is infectious disease, discussed below, in which individual cells or viral particles must replicate within hosts and also spread among hosts to establish new infections.

There is ample empirical evidence for the stability of cooperative traits in nature if selection favors traits that increase the long-term growth rate of a lineage at the expense of individual fitness. For example, a large number of studies have shown how cooperation, which appears costly to individuals, can prevail through the action of group selection and kin selection (Gore, et al. 2009, Koschwanez, et al. 2013, Rainey and Rainey 2003, Turner and Chao 1999, Velicer, et al. 2000). Perhaps more intriguing is the evolution of “policing” phenotypes that function to reduce the short-term benefits of selfish cheater phenotypes and thereby stabilize cooperation (Frank 1995, Nunney 1999b, Travisano and Velicer 2004). For example, in social insects, reproduction by the worker caste constitutes a selfish trait that can undermine colony reproductive interests. To prevent selfish reproduction among workers, social insects have evolved anti-cheater strategies, where colony members will systematically destroy eggs laid by workers (Ratnieks and Visscher 1989). Tumor suppressor genes of multi-cellular organisms perform a similar function by recognizing and destroying cells that violate normal growth regulation and thereby preventing outgrowths of genetically selfish cancer cells (Nunney 1999a).

Genetic interactions

Alleles don’t influence fitness alone but do so as part of an integrated genome. Genetic interactions between loci are therefore a fundamental source of lineage-variable fitness effects, requiring multi-locus models of population genetics that are distinct from the single-locus models considered previously. The fitness effects of an allele can greatly depend on the genotype at other loci, leading to the phenomenon of epistasis (Phillips 1998). Epistasis quantifies the deviation in fitness effects of multiple alleles in combination compared with expectations based on their effects in isolation. Empirical evidence suggests that epistasis among alleles is widespread (Costanzo, et al. 2016, Kryazhimskiy, et al. 2014, Weinreich, et al. 2013) and is therefore likely to be an important source of variability in the fitness effects of an allele. These effects are particularly important in sexual populations, where recombination will cause alleles to continually move across different genetic backgrounds, thereby causing lineages to exhibit variation in fitness. For example, Neher and Shraiman

(2009) have demonstrated that, comparing organisms with increasing levels of recombination, selection with epistasis first shifts from operating on whole genomes to haplotypic blocks and then to individual alleles. Even without epistasis, alleles may experience variability in their effects on fitness if they are nonrandomly associated with other loci in the genome. For example, a beneficial mutation that happens to arise on a chromosome also bearing a deleterious mutation will spread much more slowly than expected until recombination breaks them apart. Such associations can greatly impact the fixation probability of the mutation (Barton 1995a).

In some cases, alleles change how organisms live and reproduce in such a way that they alter the genetic associations that their lineage experiences. The evolution of such alleles is best handled using the framework of modifier theory (Otto 2013; Sidebar 4). Sexual reproduction is a well-studied example, where consideration of an allele influencing the rates of sex and genetic recombination can help to resolve the conflict between short-term costs of sex to individuals and the long-term advantages of sex to lineages (Barton 1995b). This conflict in selective pressures arises because sex is inherently costly to individuals, who must invest time and energy in mating and further invest resources into the production of males, which are not capable of independent reproduction (Maynard Smith 1978). Nevertheless, these costs can be balanced by the many long-term evolutionary advantages that sex confers to lineages (Nunney 1989, Nunney 1999b). For example, under certain conditions of epistasis, recombination can accelerate both the pace of adaptation (Eshel and Feldman 1970) and the ability of populations to purge deleterious mutations (Kondrashov 1988), associating modifiers of sex with higher fitness lineages. Furthermore, even in the absence of epistasis sexual reproduction can increase rates of adaptation by allowing beneficial mutations that arise on different backgrounds to be combined into a single genotype, thereby limiting the constraints imposed by clonal interference (Cooper 2007, McDonald, et al. 2016). Finally, the red-queen hypothesis (Hamilton, et al. 1990, Van Valen, asserts that the constant creation of new genotypes under recombination can allow organisms to more readily compete in a co-evolutionary arms race with parasites. Indeed, sex is likely to have evolved for a combination of reasons and empirical observations support many of the hypotheses that have been put forth (Colegrave 2002, Cooper 2007, Goddard, et al. 2005, McDonald, et al. 2016, Morran, et al. 2011).

Sex and recombination are not the only genetic processes that increase rates of adaptation. There has been substantial recent attention on whether natural selection can act more generally on the ability of populations to adapt, or its evolvability. Selection for evolvability is contentious, since the ability to adapt to future contingencies is a feature of populations and would therefore appear to require evolutionary foresight and group selection operating on biological populations (Lynch 2007, Pigliucci 2008, Sniegowski and Murphy 2006, but see Watson and Szathmáry 2016). However, traits that increase evolvability could also arise by the process of natural selection favoring traits that are beneficial on average, with lineages being more likely to persist over longer evolutionary periods if they are able to adapt to future conditions (Eshel 1973). While numerous traits could increase evolvability (Wagner and Altenberg 1996), there has been a great deal of attention paid to the evolution of alleles which influence the mutation rate (Denamur and Matic 2006, Sniegowski, et al. 2000). Here again, modifier theory can help to resolve the conflict between short-term

selection, which may favor lower mutation rates to reduce genetic load, and long-term selection favoring lineages that are able to adapt to environmental challenges. Mutation rate modifiers have been observed in microbial populations both in the lab (Sniegowski, et al. 1997) and in nature (LeClerc, et al. 1996, Matic, et al. 1997). “Mutator” alleles spread due to linkage disequilibrium with mutations they produce (Sidebar 4) and can thereby influence the statistical properties and long-term fate of lineages (Chao and Cox 1983, Sniegowski, et al. 1997) (Figure 1D). In such scenarios, evolvability arises as a by-product of indirect selection and genetic hitchhiking of mutators (Sniegowski and Murphy 2006), though there are also notable examples in which histories of repeated environmental change could directly favor the evolution of traits that increase evolvability (Graves, et al. 2013, Moxon, et al. 1994).

IV .Limitations of fitness averages

Limitations due to short-sighted selection

A central theme in many of the treatments of lineage-variable fitness effects is that fitness differences can be averaged across a lineage using concepts like geometric mean fitness and inclusive fitness. These extended fitness averages provide a convenient way to determine if an allele has a positive or negative effect on a lineage-by instead determining whether it increases the long-term rate of spread of a lineage as a whole. We also note the equivalency between these concepts and several related averages that depict long-term growth rates. For example, pathogens are widely assumed to maximize their long-term transmission success, R_0 (Alizon, et al. 2009, Anderson and May 1982). Similarly, other mathematical concepts equivalent to the long-term growth rate are sometimes used as a measure fitness in variable environments (Kussell and Leibler 2005) and the concept of invasion fitness (Sidebar 3) indicates whether natural selection tends to favor the spread of a trait across the backgrounds experienced (Lehmann, et al. 2016).

Similar averages have been used to deal with variation in an allele’s genetic background on the premise of free recombination (Falconer 1994, Livnat and Papadimitriou 2016). In general, averages across variability in reproductive success are meant to allow one to directly define an “effective” selection coefficient in order to identify which allele increases fitness. An even more ambitious goal would be to salvage Equation 1, which is possible under scenarios of rapid environmental change but not in general (Cvijovic, et al. 2015, Uecker and Hermisson 2011).

Unfortunately, there are fundamental problems with the use of these averages. Specifically, shortsighted selection can drive alleles to extinction, regardless of their long-term benefit to a lineage. This is most readily seen in the case of a changing environment (Figure 2), where it has been noted in several contexts (Cvijovic, et al. 2015, Gerland and Hwa 2009, King and Masel 2007, Lande and Goodnight 2007, Masel, et al. 2007). For example, consider a mutation with a lower long-term mean fitness than the resident allele. If the mutation happens to arise during a temporary shift in the environment in which the allele is favorable, then provided it survives genetic drift, the allele will increase in frequency following a logistic function and reach a frequency of one in approximately $2\ln(Ns)/s$ generations (Desai and Fisher 2007). Thus, if the time frame of the environmental shift, τ , is longer than

the fixation time ($\tau \gg 2 \ln(Ns)/s$), then the allele will fix regardless of its long-term disadvantage. This reasoning provides a straightforward threshold for the time scale of environmental shifts, beyond which natural selection is blind to the allele's long-term costs and benefits (Cvijovič, et al. 2015). Of course, this result is derived under the assumption of a well-mixed population of constant size, and other factors such as demographic changes and population subdivision could substantially extend this upper bound. Still, these considerations demonstrate an inherent time-constraint imposed by evolution in finite populations, which only disappear as a mathematical artifact in infinite populations (Figure 2C).

Similar limitations can be seen whenever the timescale of change in the fitness effects of an allele are greater than the time needed for natural selection to fix alleles conferring a short-term advantage. For example, models of multi-level selection become dominated by shortsighted selection of selfish phenotypes whenever group-level reproductive events are rare (Luo 2014). This breakdown in favor of shortsighted selection is analogous to that in variable environments (compare to Figure 2) and can be understood by considering the relative effects of individual and group selection on changes to allele frequency. Natural selection takes about s generations to double the frequency of a selfish trait within groups, where s denotes the within-group benefit of a selfish trait. On the other hand, increased rates of group reproduction in groups of non-selfish individuals will double the frequency of a cooperative trait after approximately wr generations, where r is the group-level selection coefficient and w is the number of individual generations between group reproductive events. This heuristic reasoning implies that shortsighted selection in favor of a selfish trait will dominate allele frequency changes and preclude the evolution of cooperation whenever $s \gg wr$, which very closely matches results derived by formal analysis (Luo 2014).

Beyond fitness averages

In addition to the role of extinction in tipping the outcome of selection toward shortsighted traits, studies explicitly modeling fitness variability across a lineage have yielded a number of additional results that are not readily captured by Equation 1. Recently, Cvijovič, et al. (2015) examined the case of a periodic environment that alternates between two states. An allele that is favored in one environment but disfavored in the next can follow unintuitive dynamics, particularly when large changes in allele frequency occur within environmental epochs. In the classic, lineage-invariant scenario discussed above, fixation of a neutral allele from a single starting copy requires traversing from a starting frequency of $1/N$ to a frequency of 1 by the action of genetic drift alone. In contrast, mutations in a fluctuating environment experience selective pressures continually, albeit of varying signs and intensities. This means that alleles can be driven to very high or very low frequencies by natural selection and then achieve fixation or loss due to genetic drift with far greater probability than predicted by Equation 1 (Figure 2D). Cvijović et al. (2015) show that this effect can cause the fixation probability of an allele to increase well beyond the neutral expectation of $1/N$, even when alleles are neutral or deleterious on average. Furthermore, the same study finds that natural selection can become less efficient at recognizing long-term fitness effects-causing mutations to behave as though they were effectively neutral, even when they are beneficial or deleterious on average. Finally, as populations become smaller

or swings in frequency more dramatic, fixation can become independent of the average selection coefficient, creating conditions where the fixation probability is not even a monotonically increasing function of long-term fitness (Cvijović, et al. 2015).

Another intriguing result emerges when the mean reproductive success across a lineage is held constant but its variance is altered. For example, Gillespie (1974) considered a model meant to capture spatial variation in the environment by relaxing the assumption of a Poisson-distributed number of offspring. Gillespie found that here the natural way to quantify fitness is $w = \mu - \frac{1}{N}\sigma^2$ where μ is the mean number of offspring, σ^2 is its variance, and N is the population size (compare this case with spatial variation to Sidebar 2 with temporal variation). The dependence on both the mean and variance in offspring number reflects the fact that small values of offspring number cause a disproportionate reduction in long-term geometric mean fitness (Sidebar 2). Another striking feature of this model is the appearance of population size in the definition of fitness, which suggests that the same allele can be favored or disfavored depending solely on the population size. This occurs because fluctuations in fitness in smaller populations can have a greater propensity to drive an entire lineage to very low values of realized fitness, thereby exacerbating the effects of fluctuations in reproductive number on long-term growth rates. This same sort of dependence on population size arises in a model of fluctuating environments (Takahata, et al. 1975), mutators (André and Godelle 2006, Raynes, et al. 2014, Wylie, et al. 2009) and cooperators (Nowak, et al. 2004). We emphasize that the population size dependence in the above examples is distinct from that of Equation 1, where population size influences the efficiency of natural selection but does not affect its sign. Instead, variability in fitness across a lineage makes it possible that a subset of individuals will experience strong selective pressures that are not dominated by drift, even in small populations. This implies that genetic drift and natural selection do not, in general, scale according to the relationship in Equation 1.

The most intriguing feature of lineage variability is the possibility that the fate of an allele may not always be reducible to a selection coefficient at all. This is certainly the case for the evolution of modifiers, where associations between modifiers and other loci cause temporal autocorrelation in this distribution among sub-lineages in the genealogy (Figure 1D).

Consequently, the offspring distribution is not only changing through time, but is also inherently linked to the underlying lineage dynamics. For example, in the case of mutators, one is unable to define any selection coefficient that predicts P_{fix} , but must instead derive P_{fix} directly under models that explicitly capture the dynamics of secondary mutations and clonal interference (Good and Desai 2016). Although one could then use P_{fix} to retrospectively define an effective coefficient for any given population size using Equation 1 (Wylie, et al. 2009), it seems that one cannot generally define such a selection coefficient *a priori*. Moreover, even given such an effective selection coefficient, true P_{fix} doesn't scale with N in the manner predicted by Equation 1 (Good and Desai 2016). This inability to reduce the fate of an allele to a single fitness quantity without directly computing its fate highlights an inherent irreducibility of the evolutionary process-sometimes there is no concept of fitness suitable to predict the fate of an allele without explicitly modeling the process and computing it directly.

V .Implications for infectious disease evolution

One of the most promising applications of models considering lineage-variable fitness effects is in predicting and controlling the evolution of infectious diseases. Medically important traits such as pathogen virulence and drug resistance evolve rapidly and there has been considerable interest in the development of evolution-proof vaccines and antibiotics (Allen, et al. 2014, Day and Read 2016, Huijben, et al. 2013, Read, et al. 2011). Pathogen lineages experience a variety of extrinsic environmental changes including a dynamic immune response, a diverse set of tissues and hosts, and varying exposure to drugs. Additionally, since reproduction occurs both within and between hosts, multi-level selection can create conflicting selective pressures operating over different timescales (Kawashima, et al. 2009, Levin and Bull 1994). Finally, the dynamic immune response targeting antigenic epitopes has resulted in the selective pressures favoring mutator genes capable of immune evasion and antigenic evolvability (Deitsch, et al. 2009, Graves, et al. 2013, Moxon, et al. 1994). Variability across lineages therefore appears to be the rule rather than the exception in infectious disease evolution.

Predicting pathogen evolution and designing evolution-proof drugs will be greatly aided by models that combine the various selective pressures operating at different levels and timescales during the pathogen life-cycle. Traditional models have generally assumed that natural selection will favor traits that increase the long-term epidemiological success. For example, virulence is widely regarded as an adaptation to balance the increased rate of transmission by more aggressive diseases with the reduced duration of infection caused by host mortality or immune selection (Alizon, et al. 2009, Alizon and Michalakakis 2015, Anderson and May 1982, Bull and Llaurens 2014). However, the assumption that natural selection will maximize transmission success is analogous to selection maximizing other long-term measures of lineage success, like geometric mean fitness, and is therefore sensitive to the limitations discussed above (Figure 2). Specifically, shortsighted selection occurring within-hosts may act as a barrier for traits that could increase long-term transmission success (Levin and Bull 1994; Sidebar 2). Indeed, models that include mutation or competition between strains within hosts, or other ecological dynamics have demonstrated the inability of selection to maximize transmission success (Alizon, et al. 2013, Bonhoeffer and Nowak 1994, Day 2003).

There is broad support for the prediction that shortsighted selection and selection acting to increase traits that are beneficial on average can interact to shape infectious disease traits. For example, empirical studies in HIV (Alizon and Fraser 2013) and enteric bacteria (Giraud, et al. 2001) show how short-sighted selection can dominate patterns of evolution and lead to reductions in long-term transmission success. In *Salmonella enterica*, the need to maintain costly virulence factors that are susceptible to short-sighted selection for cheaters appears to have favored a strategy of cheater prevention that helps to stabilize long-term infectivity (Diard, et al. 2013, Frank 2013, Mulder and Coombs 2013). Theoretical progress on the role of interaction between the differing timescales of selection in pathogens is being made using models that explicitly combine mechanistic within-host processes with long-term epidemiological dynamics (Coombs, et al. 2007, Day and Gandon 2007, Gilchrist and Coombs 2006, Mideo, et al. 2008). In addition, new experimental technologies such as

lineage tracking of pathogens using barcode deep-sequencing (Blundell and Levy 2014, Levy, et al. 2015) offer exciting opportunities to measure selective pressures occurring within hosts and integrate them with more traditional epidemiological data.

VI. Conclusions

Evolutionary biologists have often emphasized individual fitness effects when modeling the outcome of natural selection on an allele. However, such a measure of fitness cannot always capture long-term evolutionary behavior when variability in fitness effects arise due to environmental, social or genetic interactions (Table 1, Figure 1). In some cases, averaging lineage-variable fitness across the various environmental, social and genetic contexts an allele encounters allows for the application of classical population genetics results based on traditional notions of fitness. However, this approach can fail in finite populations where an allele's predicted fate can be interrupted by fixation or extinction due to shortsighted selection (Figure 2B). Furthermore, genetic drift and natural selection interact in unexpected ways when variability in fitness effects occurs over a comparable timescale to selection (Cvijovi et al. 2015, Figure 2D). More strikingly, studies of modifiers indicate that there may be no way to summarize the direction of natural selection on an allele without simply modeling its long-term lineage dynamics (e.g., Good and Desai 2016). Taken together, these results clearly illustrate inadequacies in the concept of individual fitness for predicting evolutionary outcomes, and motivate the ongoing development of more general frameworks for modeling lineage-variable fitness effects. Such models may have particular relevance for the study of infectious pathogens, where alleles are likely to experience variability due to a combination of environmental, genetic, and social interactions.

Variability in the fitness effects of an allele challenge the assumption that offspring number can be drawn from a fixed distribution for all members of a lineage (Figure 1). Cases where the typical assumption of a lineage-invariant offspring distribution have been relaxed (Gillespie 1974) have yielded intriguing new evolutionary properties such as dependence on both the mean and variance in fitness effects and a critical effect of population size in determining whether an allele is beneficial. Other examples allow properties of the offspring distribution to vary in time, but still assume that the form of the distribution is fixed (Cvijovi et al. 2015). In yet other cases, it appears that allele frequency dynamics cannot be reduced to one of independent draws from any offspring distribution, time-dependent or not. This effect is most recognizable in mutators and other modifiers, where the offspring distribution changes in a manner that is inseparable from the underlying lineage dynamics caused by secondary mutations and selection on sub-lineages (Figure 1D). Thus, while theoretical progress has been made in understanding processes where the offspring distribution takes on more general forms (Cannings 1974, Der, et al. 2011), we are still far from a population genetics theory with which to predict the fate of an allele in general scenarios of lineage-variable fitness effects.

Lineage variability also highlights the need for caution when interpreting the adaptive significance of biological traits in nature. Emphasis has often been placed on individual fitness effects at the expense of neglecting the ability of selection to favor traits that have longer term consequences on the fate of an allele (Williams 1966). Indeed, there are a

plurality of definitions of fitness (Orr 2009) with each generalizing the concept of fitness under a particular source of lineage variability but none that are sufficiently general to account for all examples. Caution is warranted when considering traits in the context of their long-term effects on a lineage, since such traits are inherently susceptible to shortsighted selection (Figure 2). Thus, while it is often safe to assume that selection will favor traits on the basis of extended fitness metrics, it is also important to consider the inherent limitations in the ability of natural selection to optimize any measure of fitness.

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Glossary of terms (To appear adjacent to first use of each term or phrase)

Selection coefficient:

A quantity summarizing the fitness effect of an allele relative to an alternative wild-type allele

Lineage-variable fitness effects:

Differing fitness effects of an allele between individuals due to genetic, social, or environmental interactions

Offspring distribution:

A discrete probability distribution that captures the stochasticity in an individual organism's reproductive success

Cheater:

An individual that benefits from cooperative interactions of other individuals without itself contributing to the cost of cooperating

Frequency dependent selection:

A model in which the fitness of an allele depends on its frequency in the population as a consequence of interactions between organisms

Epistasis:

The phenotypic effect of a mutation varies with genetic context

Modifier loci:

Loci that modify the fitness effects of alleles at other loci in the genome, thereby influencing fitness indirectly

Indirect selection:

Selection acting on a modifier locus mediated by statistical associations with fitness effects at other loci in the genome

Clonal interference:

Competition between mutational independent asexual lineages, each carrying one or more beneficial mutations

Genetic drift:

Stochastic variation in allele frequency as a consequence of stochasticity in reproduction inherent in finite populations

Literature cited

- Akçay E, Van Cleve J. 2016 There is no fitness but fitness, and the lineage is its bearer. *Philos. Trans. R. Soc. Lond., B, Biol. Sci.* 371: 20150085
- Alizon S, de Roode JC, Michalakakis Y. 2013 Multiple infections and the evolution of virulence. *Ecol. Lett.* 16: 556–67 [PubMed: 23347009]
- Alizon S, Fraser C. 2013 Within-host and between-host evolutionary rates across the HIV-1 genome. *Retrovirology* 10: 49 [PubMed: 23639104]
- Alizon S, Hurford A, Mideo N, Van Baalen M. 2009 Virulence evolution and the trade-off hypothesis: history, current state of affairs and the future. *J. Evol. Biol.* 22: 245–59 [PubMed: 19196383]
- Alizon S, Michalakakis Y. 2015 Adaptive virulence evolution: the good old fitness-based approach. *Trends Ecol. Evol.* 30: 248–54 [PubMed: 25837917]
- Allen RC, Popat R, Diggle SP, Brown SP. 2014 Targeting virulence: can we make evolution-proof drugs? *Nature Rev. Microbiol.* 12: 300–08 [PubMed: 24625893]
- Anderson RM, May RM. 1982 Coevolution of hosts and parasites. *Parasitology* 85 (Pt 2): 411–26 [PubMed: 6755367]
- André J-B, Godelle B. 2006 The Evolution of Mutation Rate in Finite Asexual Populations. *Genetics* 172: 611–26 [PubMed: 16157667]
- Balaban NQ, Merrin J, Chait R, Kowalik L, Leibler S. 2004 Bacterial persistence as a phenotypic switch. *Science* 305: 1622–5 [PubMed: 15308767]
- Barton NH. 1995a Linkage and the Limits to Natural Selection. *Genetics* 140:821–41 [PubMed: 7498757]
- Barton NH. 1995b A general model for the evolution of recombination. *Genetical Research* 65: 123–44 [PubMed: 7605514]
- Blundell JR, Levy SF. 2014 Beyond genome sequencing: Lineage tracking with barcodes to study the dynamics of evolution, infection, and cancer. *Genomics* 104: 417–30 [PubMed: 25260907]
- Bonhoeffer S, Nowak MA. 1994 Mutation and the Evolution of Virulence. *Proc. R. Soc. B* 258: 133–40
- Bull JJ, Llaurens AS. 2014 Theory and empiricism in virulence evolution. *PLoS Pathog.* 10: e1004387 [PubMed: 25340792]
- Cannings C 1974 The latent roots of certain Markov chains arising in genetics: a new approach, I. Haploid models. *Adv. Appl. Probab.* 6: 260–90
- Chao L, Cox EC. 1983 Competition between high and low mutating strains of *Escherichia coli*. *Evolution* 37: 125–34 [PubMed: 28568016]
- Childs DZ, Metcalf C, Rees M. 2010 Evolutionary bet-hedging in the real world: empirical evidence and challenges revealed by plants. *Proc. R. Soc. B* 277: 3055–64
- Clauss M, Venable D. 2000 Seed germination in desert annuals: an empirical test of adaptive bet hedging. *Am. Nat.* 155: 168–86 [PubMed: 10686159]
- Colegrave N 2002 Sex releases the speed limit on evolution. *Nature* 420: 664–66 [PubMed: 12478292]
- Coombs D, Gilchrist MA, Ball CL. 2007 Evaluating the importance of within-and between-host selection pressures on the evolution of chronic pathogens. *Theor. Popul. Biol.* 72: 576–91 [PubMed: 17900643]
- Cooper TF. 2007 Recombination speeds adaptation by reducing competition between beneficial mutations in populations of *Escherichia coli*. *PLoS biology* 5: e225 [PubMed: 17713986]

- Costanzo M, VanderSluis B, Koch EN, Baryshnikova A, Pons C, et al. 2016 A global genetic interaction network maps a wiring diagram of cellular function. *Science* 353: aaf1420 [PubMed: 27708008]
- Cvijovi I, Good BH, Jerison ER, Desai MM. 2015 Fate of a mutation in a fluctuating environment. *Proc. Natl. Acad. Sci. USA* 112: E5021–E28 [PubMed: 26305937]
- Day T 2003 Virulence evolution and the timing of disease life-history events. *Trends Ecol. Evol.* 18: 113–18
- Day T, Gandon S. 2007 Applying population-genetic models in theoretical evolutionary epidemiology. *Ecol. Lett.* 10: 876–88 [PubMed: 17845288]
- Day T, Read AF. 2016 Does high-dose antimicrobial chemotherapy prevent the evolution of resistance? *PLoS Comput. Biol.* 12: e1004689 [PubMed: 26820986]
- Deitsch KW, Lukehart SA, Stringer JR. 2009 Common strategies for antigenic variation by bacterial, fungal and protozoan pathogens. *Nature Rev. Microbiol.* 7: 493–503 [PubMed: 19503065]
- Dempster ER. 1955 Maintenance of genetic heterogeneity. *Cold Spring Harb. Symp. Quant. Biol.* 20: 25–31 [PubMed: 13433552]
- Denamur E, Matic I. 2006 Evolution of mutation rates in bacteria. *Mol. Microbiol.* 60: 820–27 [PubMed: 16677295]
- Der R, Epstein CL, Plotkin JB. 2011 Generalized population models and the nature of genetic drift. *Theor. Popul. Biol.* 80: 80–99 [PubMed: 21718713]
- Desai MM, Fisher DS. 2007 Beneficial mutation selection balance and the effect of linkage on positive selection. *Genetics* 176: 1759–98 [PubMed: 17483432]
- Diard M, Garcia V, Maier L, Remus-Emsermann MNP, Regoes RR, et al. 2013 Stabilization of cooperative virulence by the expression of an avirulent phenotype. *Nature* 494: 353–56 [PubMed: 23426324]
- Eshel I 1973 Clone-Selection and Optimal Rates of Mutation. *JAppl. Probab.* 10: 728–38
- Eshel I, Feldman MW. 1970 On the evolutionary effect of recombination. *Theor. Popul. Biol.* 1: 88–100 [PubMed: 5527627]
- Eshel I, Feldman MW, Bergman A. 1998 Long-term Evolution, Short-term Evolution, and Population Genetic Theory. *Journal of Theoretical Biology* 191: 391–96
- Falconer DS. 1994 *Introduction to Quantitative Genetics*. Essex, England: Longman Scientific and Technical. 438 pp.
- Frank SA. 1995 Mutual policing and repression of competition in the evolution of cooperative groups. *Nature* 377: 520–22 [PubMed: 7566147]
- Frank SA. 2013 Microbial Evolution: Regulatory Design Prevents Cancer-like Overgrowths. *Curr. Biol.* 23: R343–R46 [PubMed: 23660352]
- Frank SA, Slatkin M. 1990 Evolution in a variable environment. *Am. Nat.* 136: 244–60
- Fraser D, Kaern M. 2009 A chance at survival: gene expression noise and phenotypic diversification strategies. *MolMicrobiol* 71: 1333–40
- Gerland U, Hwa T. 2009 Evolutionary selection between alternative modes of gene regulation. *Proc. Natl. Acad. Sci. USA* 106: 8841–46 [PubMed: 19470486]
- Gilchrist MA, Coombs D. 2006 Evolution of virulence: interdependence, constraints, and selection using nested models. *Theor. Popul. Biol.* 69: 145–53 [PubMed: 16198387]
- Gillespie JH. 1973 Natural selection with varying selection coefficients—a haploid model. *Genet. Res.* 21: 115–20
- Gillespie JH. 1974 Natural selection for within-generation variance in offspring number. *Genetics* 76: 601–06 [PubMed: 4833578]
- Giraud A, Matic I, Tenaillon O, Clara A, Radman M, et al. 2001 Costs and benefits of high mutation rates: adaptive evolution of bacteria in the mouse gut. *Science* 291: 2606–8 [PubMed: 11283373]
- Goddard MR, Godfray HCJ, Burt A. 2005 Sex increases the efficacy of natural selection in experimental yeast populations. *Nature* 434: 636–40 [PubMed: 15800622]
- Good BH, Desai MM. 2016 Evolution of Mutation Rates in Rapidly Adapting Asexual Populations. *Genetics* 204: 1249–66 [PubMed: 27646140]

- Gore J, Youk H, Van Oudenaarden A. 2009 Snowdrift game dynamics and facultative cheating in yeast. *Nature* 459: 253–56 [PubMed: 19349960]
- Graves CJ, Ros VI, Stevenson B, Sniegowski PD, Brisson D. 2013 Natural selection promotes antigenic evolvability. *PLoS Pathog.* 9: e1003766
- Gremer JR, Venable DL. 2014 Bet hedging in desert winter annual plants: optimal germination strategies in a variable environment. *Ecol. Lett.* 17: 380–7 [PubMed: 24393387]
- Haldane JBS. 1927 A mathematical theory of natural and artificial selection. Part V: Selection and mutation. *Proc. Camb. Phil. Soc* 23: 838–44
- Hamilton WD. 1964 The genetical evolution of social behaviour. I. *Theor. Popul. Biol.* 7: 1–16
- Hamilton WD, Axelrod R, Tanese R. 1990 Sexual reproduction as an adaptation to resist parasites (a review). *Proc. Natl. Acad. Sci. USA* 87: 3566–73 [PubMed: 2185476]
- Hopper KR. 1999 Risk-spreading and bet-hedging in insect population biology 1. *Annu. Rev. Entomol.* 44: 535–60 [PubMed: 15012381]
- Huijben S, Bell AS, Sim DG, Tomasello D, Mideo N, et al. 2013 Aggressive chemotherapy and the selection of drug resistant pathogens. *PLoS Pathog* 9: e1003578 [PubMed: 24068922]
- Jones SE, Lennon JT. 2010 Dormancy contributes to the maintenance of microbial diversity. *Proc Natl Acad Sci U S A* 107: 5881–6 [PubMed: 20231463]
- Kawashima Y, Pfafferoth K, Frater J, Matthews P, Payne R, et al. 2009 Adaptation of HIV-1 to human leukocyte antigen class I. *Nature* 458: 641–45 [PubMed: 19242411]
- Kimura M 1962 On the probability of fixation of mutant genes in a population. *Genetics* 47: 713–19 [PubMed: 14456043]
- King OD, Masel J. 2007 The evolution of bet-hedging adaptations to rare scenarios. *Theor. Popul. Biol.* 72: 560–75 [PubMed: 17915273]
- Kondrashov AS. 1988 Deleterious mutations and the evolution of sex. *Nature* 336: 435–40 [PubMed: 3057385]
- Koschwanez JH, Foster KR, Murray AW. 2013 Improved use of a public good selects for the evolution of undifferentiated multicellularity. *eLife* 2: e00367 [PubMed: 23577233]
- Kryazhimskiy S, Rice DP, Jerison ER, Desai MM. 2014 Global epistasis makes adaptation predictable despite sequence-level stochasticity. *Science* 344: 1519–22 [PubMed: 24970088]
- Kussell E, Leibler S. 2005 Phenotypic Diversity, Population Growth, and Information in Fluctuating Environments. *Science* 309: 2075–78 [PubMed: 16123265]
- Lande R, Goodnight C. 2007 Expected relative fitness and the adaptive topography of fluctuating selection. *Evolution* 61: 1835–46 [PubMed: 17683427]
- LeClerc JE, Li B, Payne WL, Cebula TA. 1996 High mutation frequencies among *Escherichia coli* and *Salmonella* pathogens. *Science* 274: 1208 [PubMed: 8895473]
- Lehmann L, Mullon C, Akçay E, Van Cleve J. 2016 Invasion fitness, inclusive fitness, and reproductive numbers in heterogeneous populations. *Evolution* 70: 1689–702 [PubMed: 27282317]
- Levin BR, Bull JJ. 1994 Short-sighted evolution and the virulence of pathogenic microorganisms. *Trends in Microbiology* 2: 76–81 [PubMed: 8156275]
- Levins R 1968 *Evolution in changing environments: Some theoretical explorations*. Princeton, NJ: Princeton University Press 120 pp.
- Levy SF, Blundell JR, Venkataram S, Petrov DA, Fisher DS, Sherlock G. 2015 Quantitative evolutionary dynamics using high-resolution lineage tracking. *Nature* 519: 181–+ [PubMed: 25731169]
- Levy SF, Ziv N, Siegal ML. 2012 Bet hedging in yeast by heterogeneous, age-correlated expression of a stress protectant. *PLoS Biol.* 10: e1001325 [PubMed: 22589700]
- Lewontin RC, Cohen D. 1969 On population growth in a randomly varying environment. *Proc. Natl. Acad. Sci. USA* 62: 1056–60 [PubMed: 5256406]
- Livnat A, Papadimitriou CH. 2016 Sex as an Algorithm: The Theory of Evolution Under the Lens of Computation. *Commun. ACM* 59: 84–93
- Luo S 2014 A unifying framework reveals key properties of multilevel selection. *Theor. Popul. Biol.* 341: 41–52

- Lynch M 2007 The frailty of adaptive hypotheses for the origins of organismal complexity. *Proc. Natl. Acad. Sci. USA* 104: 8597–604 [PubMed: 17494740]
- Masel J, King Oliver D, Maughan H. 2007 The Loss of Adaptive Plasticity during Long Periods of Environmental Stasis. *Am. Nat.* 169: 38–46 [PubMed: 17206583]
- Matic I, Radman M, Taddei F, Picard B, Doit C, et al. 1997 Highly variable mutation rates in commensal and pathogenic *Escherichia coli*. *Science* 277: 1833–34 [PubMed: 9324769]
- Maynard Smith J 1964 Group Selection and Kin Selection. *Nature* 201: 1145–47
- Maynard Smith J 1978 *The evolution of sex*: Cambridge Univ Press
- Maynard Smith J 1982 *Evolution and the Theory of Games*: Cambridge Univ Press
- Maynard Smith J, Price G. 1973 The logic of animal conflict. *Nature* 246: 15
- McDonald MJ, Rice DP, Desai MM. 2016 Sex speeds adaptation by altering the dynamics of molecular evolution. *Nature* 531: 233–36 [PubMed: 26909573]
- Menu F, Roebuck J-P, Viala M. 2000 Bet-hedging diapause strategies in stochastic environments. *Am. Nat.* 155: 724–34 [PubMed: 10805640]
- Meyers LA, Bull JJ. 2002 Fighting change with change: adaptive variation in an uncertain world. *Trends Ecol. Evol.* 17: 551–57
- Mideo N, Alizon S, Day T. 2008 Linking within- and between-host dynamics in the evolutionary epidemiology of infectious diseases. *Trends Ecol. Evol.* 23: 511–7 [PubMed: 18657880]
- Moran PAP 1958 *Random Processes in Genetics*. *Math. Proc. Cambridge* 54: 60–71
- Morran LT, Schmidt OG, Gelarden IA, Parrish RC, Lively CM. 2011 Running with the Red Queen: host-parasite coevolution selects for biparental sex. *Science* 333: 216–18 [PubMed: 21737739]
- Moxon ER, Rainey PB, Nowak MA, Lenski RE. 1994 Adaptive evolution of highly mutable loci in pathogenic bacteria. *Curr. Biol.* 4: 24–33 [PubMed: 7922307]
- Mulder DT, Coombes BK. 2013 Infection biology: Cheats never prosper. *Nature* 494: 321–22 [PubMed: 23426321]
- Neher RA, Shraiman BI. 2009 Competition between recombination and epistasis can cause a transition from allele to genotype selection. *Proc. Natl. Acad. Sci. USA* 106: 6866–71 [PubMed: 19366665]
- Nowak MA, Sasaki A, Taylor C, Fudenberg D. 2004 Emergence of cooperation and evolutionary stability in finite populations. *Nature* 428: 646–50 [PubMed: 15071593]
- Nunney L 1989 The Maintenance of Sex by Group Selection. *Evolution* 43: 245–57 [PubMed: 28568559]
- Nunney L 1999a Lineage selection and the evolution of multistage carcinogenesis. *Proc. R. Soc. B* 266: 493–98
- Nunney L 1999b Lineage selection: natural selection for long-term benefit In *Levels of selection in evolution*, ed. Keller L, pp. 238–52. Princeton, NJ: Princeton University Press
- Orr HA. 2009 Fitness and its role in evolutionary genetics. *Nature Rev. Genet.* 10: 531–9 [PubMed: 19546856]
- Otto SP. 2013 *Evolution of Modifier Genes and Biological Systems* In *Princeton Guide to Evolution*, ed. Baum DA, Futuyma DJ, pp. 253–60. Princeton, NJ: Princeton University Press
- Philippi T, Seger J. 1989 Hedging one's evolutionary bets, revisited. *Trends Ecol. Evol.* 4: 41–4 [PubMed: 21227310]
- Phillips PC. 1998 The language of gene interaction. *Genetics* 149: 1167–71 [PubMed: 9649511]
- Pigliucci M 2008 Is evolvability evolvable? *Nature Rev. Genet.* 9: 75–82 [PubMed: 18059367]
- Rainey PB, Rainey K. 2003 Evolution of cooperation and conflict in experimental bacterial populations. *Nature* 425: 72–74 [PubMed: 12955142]
- Ratnieks FL, Visscher PK. 1989 Worker policing in the honeybee. *Nature* 342: 796–97
- Raynes Y, Halstead AL, Sniegowski PD. 2014 The effect of population bottlenecks on mutation rate evolution in asexual populations. *J. Evol. Biol.* 27: 161–69 [PubMed: 24330404]
- Read AF, Day T, Huijben S. 2011 The evolution of drug resistance and the curious orthodoxy of aggressive chemotherapy. *Proc. Natl. Acad. Sci. USA* 108: 10871–77 [PubMed: 21690376]
- Simon B, Fletcher JA, Doebeli M. 2013 Towards a general theory of group selection. *Evolution* 67: 1561–72 [PubMed: 23730751]

Sidebar 1 – What is a lineage? (Typeset 903 near ‘Introduction’)

We define a lineage as the full genealogy of descendent copies of an allele of interest starting from the original copy and ending at its long-term fate: extinction, fixation, or maintenance as a stable polymorphism in the population. The concept of a lineage is most intuitive in the case of a single locus, haploid population that reproduces asexually (Figure 1). Here it corresponds directly to the genealogy of individuals carrying the allele. The concept of a lineage also extends naturally to sexual diploid organisms and multi-locus scenarios. Here, other features such as dominance, epistasis, mutation at other loci, and linkage and recombination can create variability in reproduction among individuals carrying an allele and create new opportunities for variability across an allelic lineage. Such scenarios decouple the allelic genealogy and the genealogy of individual organisms. Nevertheless, our focus on examining evolution as a process related to the ultimate success of allelic lineages rather than individuals applies equally to such scenarios.

Sidebar 2 – Geometric mean fitness (Typeset near beginning of 916 ‘Lineage-Variable Fitness Effects’)

A widely appreciated result regarding adaptations to varying environments is the principle that natural selection will favor traits based on their geometric mean fitness. When reproductive success changes between generations, natural selection favors traits that increase the long-term geometric mean fitness (GMF). Reflecting the multiplicative nature of reproduction, GMF is the product of fitness in each generation, raised to the reciprocal of the number of generations. Algebraically, $GMF = \left(\prod_{t=1}^n w_t \right)^{1/n}$, where w_t is the expected number of offspring produced in generation t . The same quantity can be expressed as a linear average of the population growth rate (equivalent to the natural logarithm of expected offspring number), written $GMF = \exp\left[\frac{1}{n} \sum_{t=1}^n \ln(w_t)\right]$. In practice, approximations are used such as $GMF \approx \mu - \sigma^2/\mu$, where μ is the arithmetic mean fitness and σ^2 is the variance in fitness. This formula explicates the fact that natural selection favors increases in mean fitness, but also decreases in the variance of fitness. This implies that natural selection can be risk averse, favoring alleles with lower variance in fitness even at the expense of decreasing fitness on average.

Sidebar 3 – Evolutionary game theory (Typeset near middle of 932 ‘Lineage-Variable Fitness Effects’ or beginning of ‘Limitations of Fitness averages’)

Evolutionary game theory (Maynard Smith 1982) analyzes an interaction among a set of competing alleles or “strategies” and summarizes their effect in a matrix representing the fitness payoff of all pairwise competitions among competitors. Such a framework is most useful in the context of frequency dependent selection, where the fitness effects of an allele are not easily summarized by a constant selection coefficient. Such a framework provides a natural way to determine whether a new allele starting from a single copy will tend to increase in frequency or “invade” a population that is fixed for an alternative allele. This leads to the concept of an evolutionarily stable strategy or ESS, which is defined as a strategy or allele that cannot be invaded by any alternative strategy starting at

an initially small frequency. The ability of an allele to invade, or invasion fitness, is a generalization of the notion of a selection coefficient to the case of frequency dependent selection and describes the long-term stability of a mutation against other competing mutations (Eshel, et al. 1998, Lehmann, et al. 2016). While there are notable exceptions (Traulsen and Hauert 2009, Traulsen and Nowak 2006), game theoretic models are typically deterministic and describe the central tendency for allele frequency change but not the statistical properties of lineages in finite populations.

Sidebar 4 – Modifier theory (typeset near end of ‘Lineage Variable Fitness Effects’)

Modifier theory refers to a class of multi-locus population genetic models that track the fate of a gene that alters a biological phenomenon of interest (e.g., recombination rate, mutation rate, dominance, mode of reproduction). Modifier alleles may have direct fitness effects, but they are also subject to indirect selection, where their influence on fitness is mediated by their co-occurrence with alleles at other loci (Otto 2013). For example, an allele that alters the mutation rate may not directly affect fitness, but by changing the rate at which deleterious and beneficial mutations at other loci arise and spread, the lineage of the mutation modifier can experience important indirect fitness effects (Sniegowski, et al. 2000). Since the evolutionary fate of modifiers can be influenced by their effects across an entire allelic genealogy, modifier theory is an inherently lineage-centered framework. One of the most general findings in modifier theory is that the balance between maximizing short-and long-term fitness depends on recombination rate. This follows because recombination disrupts linkage disequilibrium, thereby weakening the association of a modifier with fitness affecting loci and hampering indirect selection.

Figure 1. Variability in fitness across a lineage in diverse models.

A large number of realistic biological scenarios can result in the presence of variation in fitness across a lineage either among contemporary individuals (vertical axis) or between individuals in time (horizontal axis). Genealogies are shown for two competing allelic lineages indicated by circles. The focal lineage is shaded yellow and the wild-type lineage is shaded black. Curves on the bottom of each panel depict changes to the mean (blue) and variance (orange) of fitness across the focal lineage. **A.** Lineage carrying a beneficial allele (yellow) rising to fixation under the classical scenario of lineage invariance. **B.** Lineage carrying an allele that alternates from beneficial to deleterious in a variable environment. Contemporary individuals share an identical fitness, and hence an identical selection coefficient, but this quantity changes over time. **C.** A cooperative lineage under a group selection model. Within-group selective pressures cause the allele to be disfavored over short timescales. Groups with more cooperative alleles tend to displace other groups over longer timescales (shown with solid grey lines). Group extinction and recolonization events are indicated by breaks in the shaded grey background. Variance in fitness increases during these events since some members of the lineage experience a lower within group fitness while others experience an increase in fitness due to group reproduction. **D.** Evolution of an asexual mutator lineage that experiences increased rates of both deleterious (red dots) and beneficial (grey background) mutations. In both **C** and **D**, fitness in the lineage varies both among contemporary individuals and over time.

Figure 2. Limitations of fitness averages in finite populations.

Evolution in a periodically changing environment results in four distinct regimes characterized by the relative timescale of natural selection ($1/s$) and environmental change (τ). Stochastic simulation results of the model described by Cvijović et al. (2015) are shown in blue, and the expected frequency of an allele with the same average selection coefficient in a constant environment is shown in red. In this model, selection coefficients are defined based on the growth rate relative to the wildtype, and thus averaged using an arithmetic mean (Sidebar 2). Unless otherwise noted, simulations were conducted with a population size of 100,000 and selection coefficients alternated between 0.05 ± 0.06 . The timescale of environmental change is varied between panels; in each, beneficial environmental periods are shaded grey and deleterious periods are unshaded. **A.** When the environment changes quickly relative to changes in allele frequency (small $s\tau$), the average change in allele frequency is well approximated by its average fitness effect. **B.** When the environment changes more slowly than the time of fixation of an allele (large $s\tau$), mutations tend to arise and fix all in the same environment, regardless of their average fitness effect. **C.** In infinite populations, fitness averages are accurate regardless of the timescale of environmental change. This is an artifact of the fact that, in the absence of genetic drift, allele frequencies can become arbitrarily close to zero or one but never permanently achieve fixation or extinction. **D.** Average selection coefficients cannot predict the evolutionary dynamics of an allele when large fluctuations in allele frequency occur on a similar timescale to environmental change (intermediate $s\tau$). This breakdown is due to the inability of fitness averages to capture the effects of genetic drift whenever alleles reach very high or very low frequencies (Cvijović et al. 2015). In the simulation shown, natural selection nearly brought the allele to fixation during the second beneficial environment. Strong genetic drift at allele frequencies close to one then caused a weak response to selection in the second deleterious environment. The allele subsequently fixed in the third beneficial environment, far sooner than would be expected based on its average fitness effect. This premature fixation and

extinction of alleles by genetic drift is not captured by their average fitness effect and illustrates how fixation probabilities can diverge substantially from those predicted solely on the average selection coefficient of an allele.

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Table 1.

Sources of variability across a lineage and associated adaptations (*Typeset near ‘Introduction’*)

	Basis of variability in fitness		
	Environmental	Social	Genetic
Specific examples	Spatial variation	Kin selection	Genetic associations
	Temporal variation	Multi-level selection	Mutation
			Epistasis
Adaptations	Bet-hedging	Cooperation	Sex/recombination
	Phenotypic plasticity	Policing	Mutation rate modifiers
			Evolvability

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