Variability in fitness effects and the limitations of lineage selection

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Abstract

Natural selection is sensitive not only to the effect of a trait on total number of offspring produced but also to how a trait affects an individual's entire lineage of descendants. Here we show how a large number of seemingly disparate evolutionary problems, including sex, evolvability, and cooperation, all share the property that fitness varies among members of a lineage. This feature makes it difficult to summarize the evolutionary fate of an allele based solely on its effects on individual reproduction. We show that attempts to average over this variability are often justified, but can sometimes cause misleading results. We then describe a number of intriguing new evolutionary phenomena that have emerged in studies that explicitly model the fate of alleles that influence long-term lineage dynamics. We conclude with prospects for generalizations of population genetics theory and discuss how this theory might be applied to the evolution of infectious diseases.

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I. Introduction

Evolution by natural selection is driven by heritable differences in the reproductive success of individuals. However, the long-term outcome of natural selection depends not only on the effects of an allele on individual bearers but also on its effects across its entire lineage of descendants (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 members of the lineage. 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 a population. In such cases, it is often presumed that natural selection will favor traits providing a net increase in fitness averaged across a lineage via the process of lineage selection (Eshel, 1973, Nunney, 1999b). In other words, natural selection is predicted to favor traits that are beneficial not strictly to individuals, but to genetic lineages.

The notion of lineage selection has arisen independently in a variety of evolutionary problems (Kussell and Leibler, 2005, Nunney, 1999a, Akçay and Van Cleve, 2016, Lehmann et al., 2016, Eshel, 1973, Nunney, 1999b). In general, lineage selection applies to cases where the fitness effects of an allele are variable across a genetic lineage, thereby limiting the ability to infer the long-term success of an allele based on individual fitness. A large class of evolutionary problems fit this description and they can be classified based on whether the variability across a lineage

arises due to environmental, genetic, or social factors. We outline examples of each in Table 1 and describe them in more detail in the main text. Each source of variation has largely been discussed within its own body of literature, where lineage selection or equivalent concepts are used to describe a distinct set of adaptations, often with distinct terminology. Despite some obvious similarities, there have been few attempts at synthesizing what is known in each of these cases into a formal quantitative theory of lineage selection.

A common feature of lineage selection is the notion that variability in fitness across a lineage can be averaged to define a quantity representing an "effective" fitness. We discuss the equivalence of different approaches to averaging across a lineage below – which include familiar notions such as geometric mean fitness and inclusive fitness. Generally, such averages shift the focus from individuals to lineages and suggest that natural selection will favor traits that increase the long-term average growth of a genetic lineage. However, natural selection is myopic in nature-acting to increase the frequency of traits that confer an immediate advantage without regard to their future utility. This shortsightedness can have dramatic consequences, particularly if it results in the permanent extinction of an allele prior to it realizing any long-term benefit. 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 (Sniegowski and Murphy, 2006, Lynch, 2007). When does natural selection favor traits that confer a long-term benefit to a lineage and when does shortsighted evolution limit this ability?

After briefly summarizing results from classical, lineage-invariant theory that successfully relates individual fitness to a lineage's eventual fate, we discuss a diversity of examples of lineage selection and emphasize the shared theme of variability in fitness across a lineage. We illustrate the shortcomings of averaging variability across a lineage in the context of finite populations, in which alleles that are beneficial in the long-term are nevertheless vulnerable to extinction. Consequently, shortsighted evolution in finite populations can limit the ability of natural selection to optimize even these measures of fitness. Finally, we discuss other counterintuitive results that emerge in examples where lineage variability is modeled explicitly, which provide more general insights into underappreciated features the evolutionary process. We conclude by highlighting implications for the evolution of infectious diseases and directions for future work.

II. Lineage Invariant Selection

Evolutionary biologists are fundamentally concerned with understanding the outcome of natural selection on traits that influence the fate of an individuals' descendent lineage. Before discussing the realm of lineage selection – where fitness varies among members of a lineage – we will first consider the case where fitness effects are invariant across a lineage. Our emphasis throughout will be on the field of population genetics, which has a rich tradition of analyzing dynamical models that combine various evolutionary forces including natural selection, genetic drift, and mutation. This emphasis reflects not only our own expertise but also the fact that such dynamical treatments of evolution provide a comprehensive analysis of a lineage – starting from its origination in the population and ending with its ultimate fixation or extinction. We will

therefore be decidedly brief in our overview of other aspects of evolutionary theory, which include techniques such as game theory and quantitative genetics that capture effects over shorter intervals of the evolutionary process.

Consider an allele that influences the expected number of surviving offspring produced over the lifetime of its carriers. Formally, we allow the precise number of offspring produced by any particular individual in this lineage to be a Poisson random variable drawn independently from an identical distribution, with mean defined as the Wrightian fitness, w. This concept of fitness articulates well with the Darwinian notion of fitness as lifetime reproductive success. The most fundamental consideration regarding the fate of an allele by natural selection is to consider whether the allele influences this measure of fitness relative to the resident "wild type" in the population. In population genetics, this fitness effect is most often denoted with the selection coefficient, s, defined as the proportional change in expected number of offspring relative to the wild-type: $s \equiv w_{\mathrm{mut}}/w_{\mathrm{wt}} - 1$.

Now consider a population with constant size, N. Since the number of surviving offspring born to an individual is a random variable, we allow for random fluctuations in the number of individuals carrying an allele as the basis for genetic drift. Assuming that generations are discrete and non-overlapping we can approximate the allele frequency dynamics using the Wright-Fisher model. We emphasize that the Wright-Fisher process and related models capture the interplay between natural selection and genetic drift in finite populations by incorporating stochasticity in the number of surviving offspring born to each individual. However, they assume that the

distribution in that number remains constant across a lineage, and we refer to this assumption as lineage invariant selection (Figure 1A).

Given this framework, we can obtain solutions for a number of quantities pertaining to the fate of a mutant allele based on its selection coefficient, s. Of particular interest given our concern with the ultimate fate of a lineage is the ultimate probability that an allele displaces all alternatives in the population, known as the probability of fixation, P_{fix}. Kimura (1962) found this quantity for a mutation starting at frequency x_0, in a haploid, randomly mating population of size N, using a continuous diffusion approximation of the Wright-Fisher process:

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

This result highlights many of the key features of classical population genetics theory. Focusing on the case where an allele starts from a single mutation in the population, we will assume that $x_0 = 1/N$. Solving for the limit as s approaches zero leads to $P_{\text{fix}} = 1/N$. This defines the neutral expectation that the probability of fixation of an allele is simply equal to its starting frequency. Now consider a beneficial mutation, $s > 0$. Here, $P_{\text{fix}} > 1/N$, but only asymptotically approaches 1.0 as s grows, even as population size N tends to infinity (Haldane, 1927). In other words, fixation of even a strongly beneficial is not assured due to the fact genetic drift dominates allele frequency dynamics until there are roughly $1/s$ copies in the population. This effect is worsened in small populations since $1/s$ copies may be an appreciable fraction of the population. Thus as s or N get small, $1/s$ approaches N and genetic drift comes to dominate selection. This result – known as the drift barrier – implies that mutations are effectively neutral from the standpoint of natural selection, unless $s > 1/N$. Finally, and somewhat less intuitively, Kimura's formula also shows that even deleterious mutations ($s < 0$), can have a nonzero fixation probability. Here

again, genetic drift can overwhelm natural selection in populations roughly no larger than $1/|s|$ individuals.

III. Lineage Selection

Under the assumption that an allele exerts a constant, lineage invariant, effect on fitness, Equation 1 demonstrates that a mutant's fitness effect is sufficient predict the fate of its lineage. We now turn to cases of lineage selection, where variability in the fitness effects of an allele can cause this result to fail. Lineage selection emerges under more realistic biological scenarios, where alleles do not act alone to influence fitness but interact with different environmental, genetic, or social 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 models like Wright-Fisher, which require the distribution of offspring number to be fixed. Our goal in this section is to highlight some of the relevant examples of variability in fitness of an allele 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 members of a lineage.

Variation in the environment over time will cause contemporary members of a lineage to experience the same distribution of fitness values, 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 implies that no single distribution in offspring number will be generally applicable (e.g., Gillespie, 1974). 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.

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 across all types of variation. It is commonly assumed that environments are randomly drawn from a fixed distribution (Lewontin and Cohen, 1969, Dempster, 1955, Gillespie, 1973, Kussell and Leibler, 2005). 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 average direction of change in allele frequency rather than explicitly modeling lineage dynamics. Another consequence of assuming random environmental change is that natural selection will favor alleles that increase the long-term growth rate of a lineage, averaged over all environments (Lewontin and Cohen, 1969, Gillespie, 1973, Stearns, 2000, Kussell and Leibler, 2005,

204 Dempster, 1955). Formally, this corresponds to an increase in the geometric mean fitness, or
205 equivalently, the mean intrinsic growth rate (Sidebar 2), and is generalizable to other forms of
206 $s(t)$ (Cvijović et al., 2015).
207
208 The principle that natural selection in variable environments acts to increase geometric mean
209 fitness is one of the key theoretical results on variable environments and it is presumed to
210 underlie numerous adaptations. These include strategies like developmental and phenotypic
211 plasticity that allow adaptive phenotypic responses to environmental conditions that may not be
212 encountered by all individuals (Meyers and Bull, 2002, Via et al., 1995). More notable is the
213 evolution of bet-hedging traits in which an allele causes the exaggeration of phenotypic noise
214 among members of a lineage, thereby allowing a single genotype to spread environmental risk
215 among different phenotypes that are suited to different environments (Philippi and Seger, 1989,
216 Fraser and Kaern, 2009, Gillespie, 1974, Kussell and Leibler, 2005). Such a strategy is inherently
217 dependent on lineage selection, since individuals will experience differing fitness values
218 depending on their phenotype and the environment they encounter. By spreading the risk of
219 fitness losses under future environmental uncertainty across members of a lineage, bet-hedging
220 helps to ensure survival and reproduction across the lineage as a whole, regardless of the
221 environment. Examples of adaptive bet-hedging strategies have been noted in plants (Gremer
222 and Venable, 2014, Clauss and Venable, 2000, Childs et al., 2010), insects (Hopper, 1999, Menu
223 et al., 2000), and microbes (Balaban et al., 2004, Jones and Lennon, 2010, Levy et al., 2012).
224
225 *Genetic interactions*
226

227 Alleles don't influence fitness alone but do so as part of an integrated genome. The genetic
228 background of an allele is therefore another important source of variability in fitness across a
229 lineage. Perhaps the most obvious example is that of epistasis (Phillips, 1998), in which the
230 fitness effect of a mutation depends on its genetic context. Empirical evidence suggests that
231 epistasis among alleles is widespread (Costanzo et al., 2016, Wang et al., 2014, Weinreich et al.,
232 2013, Kryazhimskiy et al., 2014, Mossman et al., 2016) and therefore provides an important
233 source of variability in the fitness effects of an allele, particularly in sexual populations. Similar
234 variation in fitness can occur in asexual populations due to secondary mutations that arise on the
235 genetic background of an allele as it spreads. This effect is most important in large populations
236 or under high mutation rates. Such conditions lead more generally to a condition of clonal
237 interference (Gerrish and Lenski, 1998), in which multiple asexual lineages carry competing
238 beneficial mutations, thereby interfering with one another's fixation. The fate of a lineage under
239 clonal interference cannot be decided by the selection coefficient of a single allele, but instead
240 depends on the process of successive mutations accumulating along a series of competing
241 asexual lineages (Lang et al., 2013, Desai and Fisher, 2007). Indeed, this presents a major hurdle
242 to adapting populations, since the lack of recombination implies strict genetic linkage among
243 mutations that occur on the same background. This lack of recombination can also lead to
244 Muller's ratchet (Haigh, 1978, Muller, 1964), in which the serial fixation of deleterious
245 mutations by genetic drift can cause fitness to erode along an asexual lineage.
246
247 The constraints on asexual adaptation due to clonal interference and Muller's ratchet provide
248 strong arguments for why so many organismal life cycles include periods of recombination or
249 sexual reproduction. Indeed, numerous theories for the evolution of sex have been put forth,

250 mostly relying on arguments for why sex is beneficial in terms of the long-term evolutionary
251 success of a lineage (Nunney, 1999b). This is because sex is inherently costly to individuals, who
252 must invest time and energy in mating and further invest resources into the production of males,
253 which are not capable of independent reproduction (Maynard Smith, 1978). These costs could,
254 however, be balanced by the fact that sex appears to increase the long-term adaptive potential of
255 lineages (Nunney, 1989, Nunney, 1999b). For example, under certain conditions of epistasis,
256 recombination can accelerate both the pace of adaptation (Eshel and Feldman, 1970) and the
257 ability of populations to purge deleterious mutations and fend off Muller's ratchet (Kondrashov,
258 1988). Furthermore, sexual reproduction can increase rates of adaptation by allowing beneficial
259 mutations that arise on different backgrounds to be combined into a single genotype, thereby
260 limiting the constraints imposed by clonal interference (McDonald et al., 2016, Cooper, 2007).
261 Finally, the red-queen hypothesis (Van Valen, 1973, Hamilton et al., 1990), asserts that the
262 constant creation of new genotypes under recombination can be a strategy allowing organisms to
263 more readily compete in a co-evolutionary arms race with parasites. Indeed, sex is likely to have
264 evolved for a combination of reasons and empirical observations support many of the hypotheses
265 that have been put forth (Colegrave, 2002, Goddard et al., 2005, Cooper, 2007, McDonald et al.,
266 2016, Morran et al., 2011).
267
268 Sex and recombination are not the only processes that increase rates of adaptation. There has
269 been substantial recent attention on whether natural selection can act more generally on the
270 ability of populations to adapt, or its evolvability. Selection for evolvability is contentious, since
271 the ability to evolve is a feature of populations and would therefore appear to require a form of
272 group selection operating on biological populations (Sniegowski and Murphy, 2006, Lynch,

273 2007, Pigliucci, 2008). However, traits that increase evolvability could also arise by the process
274 of lineage selection, with lineages being more likely to persist over longer evolutionary periods if
275 they are able to adapt to future conditions (Eshel, 1973). Since mutation is the raw material
276 required for adaptation, there has been a great deal of attention paid to the evolution of alleles
277 which influence the mutation rate – known as mutation rate modifiers (Sniegowski et al., 2000,
278 Denamur and Matic, 2006). Mutation rate modifiers have been observed in microbial populations
279 both in the lab (Sniegowski et al., 1997) and in nature (LeClerc et al., 1996, Matic et al., 1997).
280 The fate of such "mutator" alleles is intriguing, since they often arise without a direct effect on
281 fitness themselves (Chao and Cox, 1983, Sniegowski et al., 1997). In asexual populations,
282 mutators are still physically linked to the mutations they produce and can thereby influence the
283 statistical properties and long-term fate of lineages (Figure 1C). In such scenarios, evolvability
284 arises as a by-product of indirect selection and genetic hitchhiking of mutators (Sniegowski and
285 Murphy, 2006). However, there are notable exceptions in which selection on evolvability may be
286 more direct. This appears to be the case in pathogens, where lineage selection has favored
287 elevated mutation rates in antigens to increase the capacity to adapt to a dynamic vertebrate
288 immune response (Moxon et al., 1994, Graves et al., 2013).
289
290 *Social interactions*
291
292 Fitness can be influenced not only by environmental and genetic factors but also by interactions
293 with other conspecifics. These interactions can create a type of variability across a lineage
294 known as frequency dependent selection, where the fitness effects of an allele are dependent on
295 the frequency of the allele in the population. Frequency dependence is 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. Cheaters are typically beneficial when rare, since their fitness advantage requires interactions with other cooperators. Despite the inherent susceptibility to cheaters, cooperation is common in nature and is presumed to underlie underlying 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 genes controlling cooperation may be beneficial on average so long as the beneficiary of cooperative actions are kin, which are likely to share the genes controlling cooperation by common descent. 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 average effect of a gene across the lineage of cooperators (Akçay and Van Cleve, 2016). Cooperation can also be stable under cases of multi-level selection (Traulsen and Nowak, 2006, Luo, 2014, Simon et al., 2013). The formation and dissolution of new groups is itself a reproductive process and the long-term fate of a lineage is therefore

319 sensitive to the influence of an allele on group-level reproduction (Figure 1D). A well-known
320 example is infectious diseases, discussed below, in which individual cells or viral particles
321 replicate within hosts but also spread among hosts to establish new infections.
322
323 There is ample empirical evidence for the stability of cooperative traits in nature due to lineage
324 selection. For example, a large number of studies have shown how cooperation can prevail
325 through the action of group selection and kin selection (Velicer et al., 2000, Koschwanez et al.,
326 2013, Gore et al., 2009, Turner and Chao, 1999, Rainey and Rainey, 2003). Perhaps a more
327 intriguing result of lineage selection is the evolution of "policing" phenotypes that function to
328 reduce the potential benefits to cheaters (Frank, 1995, Nunney, 1999b, Travisano and Velicer,
329 2004). For example, in social insects, reproduction by the worker caste constitutes a selfish trait
330 that can undermine colony reproductive interests. To prevent selfish reproduction among
331 workers, social insects have evolved anti-cheater strategies, where colony members will
332 systematically destroy eggs laid by workers (Ratnieks and Visscher, 1989). Tumor suppressor
333 genes of multi-cellular organisms perform a similar function by recognizing and destroying cells
334 that violate normal growth regulation and thereby preventing outgrowths of genetically selfish
335 cancer cells (Nunney, 1999a). Finally, group selection dynamics can even result in Simpson's
336 paradox (Blyth, 1972) in which the overall frequency of cooperators increases despite their
337 systematic tendency to decrease within groups (Chuang et al., 2009). The fact that a trait can
338 spread even as it selects against in every individual carrier shows the potential for lineage
339 selection to prevail over selection on individuals.
340
341 **IV. Limitations to lineage selection**

342

343 *Limitations of fitness averages*

344

345 A central theme in many of the treatments of lineage selection described above is that fitness
346 differences can be averaged across a lineage using concepts like geometric mean fitness and
347 inclusive fitness. These extended fitness averages provide a convenient way to determine if an
348 allele has a positive or negative affect on a lineage. We also note the equivalency between these
349 concepts and several related averages. For example, pathogens are widely assumed to maximize
350 their long-term transmission success, R_0 (Anderson and May, 1982, Alizon et al., 2009).
351 Similarly, Lyapunov exponents are sometimes used to derive long-term growth rates in variable
352 environments (Kussell and Leibler, 2005) and the concept of invasion fitness in evolutionary
353 game theory (Sidebar 3) indicates whether natural selection tends to favor a trait under frequency
354 dependence (Lehmann et al., 2016). Similar averages have been used to deal with variation in an
355 allele's genetic background (Livnat and Papadimitriou, 2016, Falconer, 1994). In general,
356 averages across the variability in reproductive success are meant to allow one to directly define a
357 selection coefficient in order to identify which allele increases fitness. An even more ambitious
358 goal would be if Equation 1 could be salvaged altogether, as is the case under scenarios of rapid
359 environmental change (Cvijović et al., 2015).

360

361 Unfortunately, there are fundamental problems with the use of these averages that can preclude
362 natural selection from maximizing fitness averages. Specifically, shortsighted evolution can
363 drive alleles permanently extinct, regardless of their long-term benefit to a lineage. This is most
364 readily seen in the case of a changing environment (Figure 2), where it has been noted in several

contexts (Masel et al., 2007, King and Masel, 2007, Gerland and Hwa, 2009, Cvijović et al., 2015). Assume that a mutation arises in an environment in which it is beneficial and that the environment is constant for τ generations. Provided it survives genetic drift, the allele will increase in frequency following a logistic function and reach a frequency of one in approximately $2 \cdot \ln(Ns)/s$ generations (Desai and Fisher, 2007). Thus, if $\tau \gg 2 \cdot \ln(Ns)/s$, then alleles will arise and fix all in the same environment (Cvijović et al., 2015). This provides a straightforward threshold, beyond which natural selection is blind to the allele's long-term benefit. Of course, this threshold 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 short-sighted evolution of selfish phenotypes whenever group-level reproductive events are rare (Luo 2014, Doebeli). This breakdown in favor of shortsighted evolution is analogous to that in variable environments (Figure 2B) 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 $w \cdot r$ 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 short-sighted evolution in favor of a selfish trait will dominate allele frequency changes and preclude the evolution of cooperation whenever $s \gg w \cdot r$, 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 variability across a lineage have yielded a number of results that are not readily captured by Equation 1. Recently, Cvijović 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. 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 drift barrier is substantially greater compared to that in a constant environment, which implies that natural selection also becomes

less efficient at distinguishing beneficial and deleterious mutations. Finally, as populations become smaller or swings in frequency more dramatic, fixation becomes independent of the average selection coefficient, creating conditions where the fixation probability is not even a monotonically increasing function of long-term fitness.

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 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. A 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 same sort of dependence on population size arises in a model of fluctuating environments (Takahata et al., 1975), as well as in mutators (Wylie et al., 2009, André and Godelle, 2006, Raynes et al., 2014). 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 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 the relationship in Equation 1.

Perhaps 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

434 the evolution of mutation rate modifiers, where the succession of *de novo* beneficial and
435 deleterious mutations results not only in variability in the distribution of offspring numbers
436 across a lineage, but also in temporal autocorrelation in this distribution among the resulting sub-
437 lineages (Figure 2C). Consequently, the offspring distribution is not only changing through time,
438 but is also inherently linked to the underlying lineage dynamics. This implies that one is unable
439 to define any selection coefficient for a mutator that predicts $P_{\text{fix.}}$, but must instead derive P_{fix}
440 directly under models that explicitly capture the dynamics of secondary mutations and clonal
441 interference (Good and Desai, 2016). Although one could then use P_{fix} to retrospectively define
442 an effective coefficient using Equation 1 (Wylie et al., 2009), it seems that one cannot generally
443 define such a selection coefficient *a priori*. It is conceivable that similar properties might emerge
444 in the context of variable environments and other examples of lineage selection, though such
445 results have not been described to our knowledge.
446
447 **V. Implications for infectious disease evolution**
448
449 One of the most promising applications for theoretical developments related to variability in
450 fitness across a lineage is in predicting and controlling the evolution of infectious diseases.
451 Medically important traits such as pathogen virulence and drug resistance evolve rapidly and
452 there has been considerable interest in the development of evolution-proof vaccines and
453 antibiotics (Day and Read, 2016, Huijben et al., 2013, Read et al., 2011, Allen et al., 2014).
454 Pathogen lineages experience a variety of extrinsic environmental changes including a dynamic
455 immune response, a diverse set of tissues and hosts, and varying exposure to drugs. Additionally,
456 since reproduction occurs both within and between hosts, multi-level selection can create

457 conflicting selective pressures operating over different timescales (Levin and Bull, 1994,
458 Kawashima et al., 2009). Finally, the dynamic immune response targeting antigenic epitopes has
459 resulted in the selective pressures favoring mutator genes capable of immune evasion and
460 antigenic evolvability (Deitsch et al., 2009, Graves et al., 2013, Moxon et al., 1994). Variability
461 across lineages therefore appears to be the rule rather than the exception in infectious disease
462 evolution.
463
464 Predicting pathogen evolution and designing evolution-proof drugs will be greatly aided by
465 models that combine the various selective pressures operating at different levels and timescales
466 during the pathogen life-cycle. Traditional models have generally assumed that natural selection
467 will favor traits that increase the long-term epidemiological success. For example, virulence is
468 widely regarded as an adaptation to balance the increased rate of transmission by more
469 aggressive diseases with the reduced duration of infection caused by host mortality or immune
470 selection (Anderson and May, 1982, Alizon et al., 2009, Alizon and Michalakis, 2015, Bull and
471 Lauring, 2014). However, the assumption that natural selection will maximize transmission
472 success is analogous to selection maximizing other long-term measures of lineage success, like
473 geometric mean fitness, and is therefore sensitive to the limitations discussed above (Figure 2).
474 Specifically, shortsighted evolutionary processes occurring within-hosts may act as a barrier for
475 traits that could increase long-term transmission success (Levin and Bull, 1994; Sidebar 2).
476 Indeed, models that include mutation or competition between strains within-hosts or other
477 ecological dynamics have demonstrated the inability of selection to maximize transmission
478 success (Bonhoeffer and Nowak, 1994, Day, 2003, Alizon et al., 2013).
479

480 There is broad support for the prediction that shortsighted evolution and lineage selection can
481 influence the evolution of infectious diseases. For example, empirical studies in HIV (Alizon and
482 Fraser, 2013) and enteric bacteria (Giraud et al., 2001) show how short-sighted evolution can
483 dominate patterns of evolution and lead to reductions in long-term transmission success. In
484 *Salmonella enterica*, lineage selection appears to have favored a strategy to preclude shortsighted
485 evolution and stabilize long-term infectivity (Diard et al., 2013, Frank, 2013, Mulder and
486 Coombes, 2013). Further theoretical progress on the role of lineage selection in pathogens could
487 come from models that explicitly combine mechanistic within-host processes with long-term
488 epidemiological dynamics (Coombs et al., 2007, Gilchrist and Coombs, 2006, Day and Gandon,
489 2007, Mideo et al., 2008). In addition, new experimental technologies such as lineage tracking of
490 pathogens using barcode deep-sequencing (Blundell and Levy, 2014, Levy et al., 2015) offer
491 exciting opportunities to measure selective pressures occurring within-hosts and integrate them
492 with more traditional epidemiological data.
493
494 **VI. Conclusions**
495
496 Evolutionary biologists have traditionally assumed that natural selection acts to favor traits that
497 increase individual survival and reproductive success. However, individual fitness cannot always
498 capture the long-term evolutionary fate of an allele when variability in fitness effects arise due to
499 environmental, genetic or social interactions (Table 1, Figure 1). Lineage selection seeks to
500 address this variability by averaging fitness across the various environmental, genetic, and social
501 contexts an allele encounters. However, this approach can fail in finite populations where an
502 allele's predicted fate can be interrupted by fixation or extinction due to shortsighted evolution

503 (Figure 2B). Furthermore, genetic drift and natural selection interact in unexpected ways when
504 variability in fitness effects occurs over a comparable timescale to allele frequency (Cvijović et
505 al. 2015, Figure 2D). More strikingly, examples from studies of mutation rate modifiers indicate
506 that there may be no way to summarize the direction of natural selection on an allele without
507 simply modeling its long-term lineage dynamics. Taken together, these findings may have
508 particular relevance for the study of infectious pathogens, where alleles are likely to experience
509 variability due to a combination of environmental, genetic, and social interactions.
510
511 Variability in the fitness effects of an allele challenge the conventional premise of population
512 genetics which assumes that individual offspring number can be drawn from a fixed distribution
513 for all members of a lineage (Figure 1). Cases where the typical assumption of a Poisson
514 offspring distribution have been relaxed (Gillespie, 1974) have yielded intriguing new
515 evolutionary properties such as dependence on both the mean and variance in fitness effects and
516 a critical effect of population size in determining whether an allele is beneficial. Other examples
517 allow properties of the offspring distribution to vary in time, but still assume that the form of the
518 distribution is fixed (Cvijović et al., 2015). In other cases, it appears that allele frequency
519 dynamics cannot always be reduced to one of independent draws from any offspring distribution,
520 time-dependent or not. This effect is most recognizable in mutators, where the offspring
521 distribution changes in a manner that is inseparable from the underlying lineage dynamics caused
522 by secondary mutations and selection on sub-lineages (Figure 1C). Thus, while theoretical
523 progress has been in understanding processes where the offspring distribution takes on more
524 general forms (Cannings, 1974, Der et al., 2012, 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 selection.

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 appear sufficiently general to account for all cases of lineages selection. 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 evolution (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.

540 **Literature cited**

541

542

543 Akçay, E. & Van Cleve, J. 2016. There is no fitness but fitness, and the lineage is its bearer.
544 *Philos. Trans. R. Soc. Lond., B, Biol. Sci.,* 371**:**20150085.

545

546 Alizon, S., De Roode, J. C. & Michalakis, Y. 2013. Multiple infections and the evolution of
547 virulence. *Ecol. Lett.,* 16**:**556-567.

548

549 Alizon, S. & Fraser, C. 2013. Within-host and between-host evolutionary rates across the HIV-1
550 genome. *Retrovirology,* 10**:**49.

551

552 Alizon, S., Hurford, A., Mideo, N. & Van Baalen, M. 2009. Virulence evolution and the trade-
553 off hypothesis: History, current state of affairs and the future. *J. Evol. Biol.,* 22**:**245-59.

554

555 Alizon, S. & Michalakis, Y. 2015. Adaptive virulence evolution: The good old fitness-based
556 approach. *Trends Ecol. Evol.,* 30**:**248-54.

557

558 Allen, R. C., Popat, R., Diggle, S. P. & Brown, S. P. 2014. Targeting virulence: Can we make
559 evolution-proof drugs? *Nature Rev. Microbiol.,* 12**:**300-308.

560

561 Anderson, R. M. & May, R. M. 1982. Coevolution of hosts and parasites. *Parasitology,* 85 (Pt
562 2)**:**411-26.

André, J.-B. & Godelle, B. 2006. The evolution of mutation rate in finite asexual populations. *Genetics,* 172**:**611-626.

Balaban, N. Q., Merrin, J., Chait, R., Kowalik, L. & Leibler, S. 2004. Bacterial persistence as a phenotypic switch. *Science,* 305**:**1622-5.

Blundell, J. R. & Levy, S. F. 2014. Beyond genome sequencing: Lineage tracking with barcodes to study the dynamics of evolution, infection, and cancer. *Genomics,* 104**:**417-430.

Blyth, C. R. 1972. On Simpson's paradox and the sure-thing principle. *J. Amer. Statist. Assoc.,* 67**:**364-366.

Bonhoeffer, S. & Nowak, M. A. 1994. Mutation and the evolution of virulence. *Proc. R. Soc. B,* 258**:**133-140.

Bull, J. J. & Lauring, A. S. 2014. Theory and empiricism in virulence evolution. *PLoS Pathog.,* 10**:**e1004387.

Cannings, C. 1974. The latent roots of certain markov chains arising in genetics: A new approach, i. Haploid models. *Adv. Appl. Probab.,* 6**:**260-290.

585 Chao, L. & Cox, E. C. 1983. Competition between high and low mutating strains of *Escherichia*
586 *coli*. *Evolution,* 37**:**125-134.
587
588 Childs, D. Z., Metcalf, C. & Rees, M. 2010. Evolutionary bet-hedging in the real world:
589 Empirical evidence and challenges revealed by plants. *Proc. R. Soc. B,* 277**:**3055-64.
590
591 Chuang, J. S., Rivoire, O. & Leibler, S. 2009. Simpson's paradox in a synthetic microbial system.
592 *Science,* 323**:**272-275.
593
594 Clauss, M. & Venable, D. 2000. Seed germination in desert annuals: An empirical test of
595 adaptive bet hedging. *Am. Nat.,* 155**:**168-186.
596
597 Colegrave, N. 2002. Sex releases the speed limit on evolution. *Nature,* 420**:**664-666.
598
599 Coombs, D., Gilchrist, M. A. & Ball, C. L. 2007. Evaluating the importance of within- and
600 between-host selection pressures on the evolution of chronic pathogens. *Theor. Popul.*
601 *Biol.,* 72**:**576-91.
602
603 Cooper, T. F. 2007. Recombination speeds adaptation by reducing competition between
604 beneficial mutations in populations of *Escherichia coli*. *PLoS Biology,* 5**:**e225.
605

606 Costanzo, M., Vandersluis, B., Koch, E. N., Baryshnikova, A., Pons, C., Tan, G., Wang, W., et
607 al. 2016. A global genetic interaction network maps a wiring diagram of cellular function.
608 *Science,* 353:aaf1420.
609
610 Cvijović, I., Good, B. H., Jerison, E. R. & Desai, M. M. 2015. Fate of a mutation in a fluctuating
611 environment. *Proc. Natl. Acad. Sci. USA,* 112:E5021-E5028.
612
613 Day, T. 2003. Virulence evolution and the timing of disease life-history events. *Trends Ecol.*
614 *Evol.,* 18:113-118.
615
616 Day, T. & Gandon, S. 2007. Applying population-genetic models in theoretical evolutionary
617 epidemiology. *Ecol. Lett.,* 10:876-888.
618
619 Day, T. & Read, A. F. 2016. Does high-dose antimicrobial chemotherapy prevent the evolution
620 of resistance? *PLoS Comput. Biol.,* 12:e1004689.
621
622 Deitsch, K. W., Lukehart, S. A. & Stringer, J. R. 2009. Common strategies for antigenic
623 variation by bacterial, fungal and protozoan pathogens. *Nature Rev. Microbiol.,* 7:493-
624 503.
625
626 Dempster, E. R. 1955. Maintenance of genetic heterogeneity. *Cold Spring Harb. Symp. Quant.*
627 *Biol. ,* 20:25-31.
628

Denamur, E. & Matic, I. 2006. Evolution of mutation rates in bacteria. *Mol. Microbiol.,* 60**:**820-827.

Der, R., Epstein, C. & Plotkin, J. B. 2012. Dynamics of neutral and selected alleles when the offspring distribution is skewed. *Genetics,* 191**:**1331-1344.

Der, R., Epstein, C. L. & Plotkin, J. B. 2011. Generalized population models and the nature of genetic drift. *Theor. Popul. Biol.,* 80**:**80-99.

Desai, M. M. & Fisher, D. S. 2007. Beneficial mutation selection balance and the effect of linkage on positive selection. *Genetics,* 176**:**1759-98.

Diard, M., Garcia, V., Maier, L., Remus-Emsermann, M. N. P., Regoes, R. R., Ackermann, M. & Hardt, W.-D. 2013. Stabilization of cooperative virulence by the expression of an avirulent phenotype. *Nature,* 494**:**353-356.

Eshel, I. 1973. Clone-selection and optimal rates of mutation. *J Appl. Probab.,* 10**:**728-738.

Eshel, I. & Feldman, M. W. 1970. On the evolutionary effect of recombination. *Theor. Popul. Biol.,* 1**:**88-100.

Falconer, D. S. 1994. *Introduction to quantitative genetics,* Essex, England, Longman Scientific and Technical.

652

653 Frank, S. A. 1995. Mutual policing and repression of competition in the evolution of cooperative
654 groups. *Nature,* 377**:**520-522.

655

656 Frank, Steven a. 2013. Microbial evolution: Regulatory design prevents cancer-like overgrowths.
657 *Curr. Biol.,* 23**:**R343-R346.

658

659 Frank, S. A. & Slatkin, M. 1990. Evolution in a variable environment. *Am. Nat.,* 136**:**244-260.

660

661 Fraser, D. & Kaern, M. 2009. A chance at survival: Gene expression noise and phenotypic
662 diversification strategies. *Mol. Microbiol.,* 71**:**1333-40.

663

664 Gerland, U. & Hwa, T. 2009. Evolutionary selection between alternative modes of gene
665 regulation. *Proc. Natl. Acad. Sci. USA,* 106**:**8841-8846.

666

667 Gerrish, P. J. & Lenski, R. E. 1998. The fate of competing beneficial mutations in an asexual
668 population. *Genetica,* 102**:**127.

669

670 Gilchrist, M. A. & Coombs, D. 2006. Evolution of virulence: Interdependence, constraints, and
671 selection using nested models. *Theor. Popul. Biol.,* 69**:**145-53.

672

673 Gillespie, J. H. 1973. Natural selection with varying selection coefficients–a haploid model.
674 *Genet. Res.,* 21**:**115-120.

675

676 Gillespie, J. H. 1974. Natural selection for within-generation variance in offspring number.
677 *Genetics,* 76**:**601-606.

678

679 Giraud, A., Matic, I., Tenaillon, O., Clara, A., Radman, M., Fons, M. & Taddei, F. 2001. Costs
680 and benefits of high mutation rates: Adaptive evolution of bacteria in the mouse gut.
681 *Science,* 291**:**2606-8.

682

683 Goddard, M. R., Godfray, H. C. J. & Burt, A. 2005. Sex increases the efficacy of natural
684 selection in experimental yeast populations. *Nature,* 434**:**636-640.

685

686 Good, B. H. & Desai, M. M. 2016. Evolution of mutation rates in rapidly adapting asexual
687 populations. *Genetics,* 204**:**1249-66.

688

689 Gore, J., Youk, H. & Van Oudenaarden, A. 2009. Snowdrift game dynamics and facultative
690 cheating in yeast. *Nature,* 459**:**253-6.

691

692 Graves, C. J., Ros, V. I., Stevenson, B., Sniegowski, P. D. & Brisson, D. 2013. Natural selection
693 promotes antigenic evolvability. *PLoS Pathog.,* 9**:**e1003766.

694

695 Gremer, J. R. & Venable, D. L. 2014. Bet hedging in desert winter annual plants: Optimal
696 germination strategies in a variable environment. *Ecol. Lett.,* 17**:**380-7.

697

Haigh, J. 1978. The accumulation of deleterious genes in a population—Muller's ratchet. *Theor. Popul. Biol.,* 14:251-267.

Haldane, J. B. S. 1927. A mathematical theory of natural and artificial selection. Part V: Selection and mutation. *Proc. Camb. Phil. Soc,* 23:838-844.

Hamilton, W. D. 1964. The genetical evolution of social behaviour. I. *Theor. Popul. Biol.,* 7:1-16.

Hamilton, W. D., Axelrod, R. & Tanese, R. 1990. Sexual reproduction as an adaptation to resist parasites (a review). *Proc. Natl. Acad. Sci. USA,* 87:3566-3573.

Hopper, K. R. 1999. Risk-spreading and bet-hedging in insect population biology. *Annu. Rev. Entomol.,* 44:535-560.

Huijben, S., Bell, A. S., Sim, D. G., Tomasello, D., Mideo, N., Day, T. & Read, A. F. 2013. Aggressive chemotherapy and the selection of drug resistant pathogens. *PLoS Pathog.,* 9:e1003578.

Jones, S. E. & Lennon, J. T. 2010. Dormancy contributes to the maintenance of microbial diversity. *Proc. Natl. Acad. Sci. USA,* 107:5881-6.

720 Kawashima, Y., Pfafferott, K., Frater, J., Matthews, P., Payne, R., Addo, M., Gatanaga, H., et al.
721 2009. Adaptation of HIV-1 to human leukocyte antigen class I. *Nature,* 458**:**641-645.
722
723 Kimura, M. 1962. On the probability of fixation of mutant genes in a population. *Genetics,*
724 47**:**713-719.
725
726 King, O. D. & Masel, J. 2007. The evolution of bet-hedging adaptations to rare scenarios. *Theor.*
727 *Popul. Biol.,* 72**:**560-575.
728
729 Kondrashov, A. S. 1988. Deleterious mutations and the evolution of sex. *Nature,* 336**:**435-440.
730
731 Koschwanez, J. H., Foster, K. R. & Murray, A. W. 2013. Improved use of a public good selects
732 for the evolution of undifferentiated multicellularity. *eLife,* 2**:**e00367.
733
734 Kryazhimskiy, S., Rice, D. P., Jerison, E. R. & Desai, M. M. 2014. Global epistasis makes
735 adaptation predictable despite sequence-level stochasticity. *Science,* 344**:**1519-1522.
736
737 Kussell, E. & Leibler, S. 2005. Phenotypic diversity, population growth, and information in
738 fluctuating environments. *Science,* 309**:**2075-2078.
739
740 Lang, G. I., Rice, D. P., Hickman, M. J., Sodergren, E., Weinstock, G. M., Botstein, D. & Desai,
741 M. M. 2013. Pervasive genetic hitchhiking and clonal interference in forty evolving yeast
742 populations. *Nature,* 500**:**571-4.

743

744 Leclerc, J. E., Li, B., Payne, W. L. & Cebula, T. A. 1996. High mutation frequencies among
745 *Escherichia coli* and *Salmonella* pathogens. *Science,* 274**:**1208-11.
746

747 Lehmann, L., Mullon, C., Akçay, E. & Van Cleve, J. 2016. Invasion fitness, inclusive fitness,
748 and reproductive numbers in heterogeneous populations. *Evolution,* 70**:**1689-1702.
749

750 Levin, B. R. & Bull, J. J. 1994. Short-sighted evolution and the virulence of pathogenic
751 microorganisms. *Trends Microbiol.,* 2**:**76-81.
752

753 Levins, R. 1968. *Evolution in changing environments: Some theoretical explorations,* Princeton,
754 NJ, Princeton University Press.
755

756 Levy, S. F., Blundell, J. R., Venkataram, S., Petrov, D. A., Fisher, D. S. & Sherlock, G. 2015.
757 Quantitative evolutionary dynamics using high-resolution lineage tracking. *Nature,*
758 519**:**181-6.
759

760 Levy, S. F., Ziv, N. & Siegal, M. L. 2012. Bet hedging in yeast by heterogeneous, age-correlated
761 expression of a stress protectant. *PLoS Biol.,* 10**:**e1001325.
762

763 Lewontin, R. C. & Cohen, D. 1969. On population growth in a randomly varying environment.
764 *Proc. Natl. Acad. Sci. USA,* 62**:**1056-1060.
765

Livnat, A. & Papadimitriou, C. H. 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**:**8597-8604.

Masel, J., King, Oliver d. & Maughan, H. 2007. The loss of adaptive plasticity during long periods of environmental stasis. *Am. Nat.,* 169**:**38-46.

Matic, I., Radman, M., Taddei, F., Picard, B., Doit, C., Bingen, E., Denamur, E., et al. 1997. Highly variable mutation rates in commensal and pathogenic *Escherichia coli*. *Science,* 277**:**1833-1834.

Maynard Smith, J. 1964. Group selection and kin selection. *Nature,* 201**:**1145-1147.

Maynard Smith, J. 1978. *The evolution of sex*, Cambridge Univ Press.

Maynard Smith, J. 1982. *Evolution and the theory of games*, Cambridge University Press.

Maynard Smith, J. & Price, G. 1973. The logic of animal conflict. *Nature,* 246**:**15.

789

790 McDonald, M. J., Rice, D. P. & Desai, M. M. 2016. Sex speeds adaptation by altering the
791 dynamics of molecular evolution. *Nature,* 531**:**233-236.

792

793 Menu, F., Roebuck, J.-P. & Viala, M. 2000. Bet-hedging diapause strategies in stochastic
794 environments. *Am. Nat.,* 155**:**724-734.

795

796 Meyers, L. A. & Bull, J. J. 2002. Fighting change with change: Adaptive variation in an
797 uncertain world. *Trends Ecol. Evol.,* 17**:**551-557.

798

799 Mideo, N., Alizon, S. & Day, T. 2008. Linking within- and between-host dynamics in the
800 evolutionary epidemiology of infectious diseases. *Trends Ecol .Evol.,* 23**:**511-7.

801

802 Morran, L. T., Schmidt, O. G., Gelarden, I. A., Parrish, R. C. & Lively, C. M. 2011. Running
803 with the red queen: Host-parasite coevolution selects for biparental sex. *Science,*
804 333**:**216-218.

805

806 Mossman, J. A., Biancani, L. M., Zhu, C.-T. & Rand, D. M. 2016. Mitonuclear epistasis for
807 development time and its modification by diet in *Drosophila*. *Genetics,* 203**:**463-84.

808

809 Moxon, E. R., Rainey, P. B., Nowak, M. A. & Lenski, R. E. 1994. Adaptive evolution of highly
810 mutable loci in pathogenic bacteria. *Curr. Biol.,* 4**:**24-33.

811

Mulder, D. T. & Coombes, B. K. 2013. Infection biology: Cheats never prosper. *Nature,* 494**:**321-322.

Muller, H. J. 1964. The relation of recombination to mutational advance. *Mutat. Res.,* 106**:**2-9.

Nunney, L. 1989. The maintenance of sex by group selection. *Evolution,* 43**:**245-257.

Nunney, L. 1999a. Lineage selection and the evolution of multistage carcinogenesis. *Proc. R. Soc. B,* 266**:**493-498.

Nunney, L. 1999b. Lineage selection: Natural selection for long-term benefit. *In:* Keller, L. (ed.) *Levels of selection in evolution.* Princeton, NJ: Princeton University Press.

Orr, H. A. 2009. Fitness and its role in evolutionary genetics. *Nature Rev. Genet.,* 10**:**531-9.

Philippi, T. & Seger, J. 1989. Hedging one's evolutionary bets, revisited. *Trends Ecol. Evol.,* 4**:**41-4.

Phillips, P. C. 1998. The language of gene interaction. *Genetics,* 149**:**1167-1171.

Pigliucci, M. 2008. Is evolvability evolvable? *Nature Rev. Genet.,* 9**:**75-82.

Rainey, P. B. & Rainey, K. 2003. Evolution of cooperation and conflict in experimental bacterial populations. *Nature,* 425**:**72-74.

Ratnieks, F. L. & Visscher, P. K. 1989. Worker policing in the honeybee. *Nature,* 342**:**796-797.

Raynes, Y., Halstead, A. L. & Sniegowski, P. D. 2014. The effect of population bottlenecks on mutation rate evolution in asexual populations. *J. Evol. Biol.,* 27**:**161-169.

Read, A. F., Day, T. & Huijben, S. 2011. The evolution of drug resistance and the curious orthodoxy of aggressive chemotherapy. *Proc. Natl. Acad. Sci. USA,* 108**:**10871-10877.

Simon, B., Fletcher, J. A. & Doebeli, M. 2013. Towards a general theory of group selection. *Evolution,* 67**:**1561-1572.

Sniegowski, P. D., Gerrish, P. J., Johnson, T. & Shaver, A. 2000. The evolution of mutation rates: Separating causes from consequences. *Bioessays,* 22**:**1057-1066.

Sniegowski, P. D., Gerrish, P. J. & Lenski, R. E. 1997. Evolution of high mutation rates in experimental populations of *E. coli*. *Nature,* 387**:**703-705.

Sniegowski, P. D. & Murphy, H. A. 2006. Evolvability. *Curr. Biol.,* 16**:**R831-R834.

Stearns, S. C. 2000. Daniel Bernoulli (1738): Evolution and economics under risk. *J. Biosci.,* 25:221-8.

Szathmary, E. & Maynard Smith, J. 1995. The major evolutionary transitions. *Nature,* 374:227-232.

Takahata, N., Ishii, K. & Matsuda, H. 1975. Effect of temporal fluctuation of selection coefficient on gene frequency in a population. *Proc. Natl. Acad. Sci. USA,* 72:4541-4545.

Traulsen, A. & Hauert, C. 2009. Stochastic evolutionary game dynamics. *In:* Schuster, H. G. (ed.) *Reviews of nonlinear dynamics and complexity.* Weinheim, Germany: Wiley-VCH Verlag GmbH & Co.

Traulsen, A. & Nowak, M. A. 2006. Evolution of cooperation by multilevel selection. *Proc. Natl. Acad. Sci. USA,* 103:10952-10955.

Travisano, M. & Velicer, G. J. 2004. Strategies of microbial cheater control. *Trends Microbiol.,* 12:72-78.

Turner, P. E. & Chao, L. 1999. Prisoner's dilemma in an RNA virus. *Nature,* 398:441-443.

Van Valen, L. 1973. A new evolutionary law. *Evolutionary theory,* 1:1-30.

879 Velicer, G. J., Kroos, L. & Lenski, R. E. 2000. Developmental cheating in the social bacterium
880 *Myxococcus xanthus*. *Nature,* 404:598-601.
881
882 Via, S., Gomulkiewicz, R., De Jong, G., Scheiner, S. M., Schlichting, C. D. & Van Tienderen, P.
883 H. 1995. Adaptive phenotypic plasticity: Consensus and controversy. *Trends Ecol. Evol.,*
884 10:212-7.
885
886 Wang, X., Fu, A. Q., Mcnerney, M. E. & White, K. P. 2014. Widespread genetic epistasis among
887 cancer genes. *Nature communications,* 5.
888
889 Weinreich, D. M., Lan, Y., Wylie, C. S. & Heckendorn, R. B. 2013. Should evolutionary
890 geneticists worry about high order epistasis? *Current Opinion in Development and*
891 *Genetics,* 23:700-707.
892
893 Williams, G. C. 1966. *Adaptation and natural selection: A critique of some current evolutionary*
894 *thought*, Princeton university press.
895
896 Wylie, C. S., Ghim, C. M., Kessler, D. A. & Levine, H. 2009. The fixation probability of rare
897 mutators in finite asexual populations. *Genetics,* 181:1595-1602.
898

Sidebar 1 – What is a lineage? (Typeset near 'Introduction')

We define a lineage as the full genealogy of descendent copies of an allele starting from the original copy and ending at its long-term fate: extinction, fixation, or maintenance as a stable polymorphism in the population. A traditional approach in population genetics has been to describe the long-term evolutionary fate of a mutant allele influencing some biological trait under the combined influence of evolutionary processes like mutation, genetic drift, migration, and natural selection. Using analytical approaches from stochastic process theory, this work seeks to calculate the probability that such an allele ultimately reaches a frequency of one, or achieves fixation, in the population. This approach places emphasis not solely on the individual reproductive process but also on the long-term fate of a genetic lineage carrying the mutation. It therefore captures a much larger class of phenomena where fitness may not be directly affected among individual carriers of an allele but the allele instead influences the statistical properties of a lineage (Wylie et al., 2009). Our focus will be primarily on lineage of asexual haploid lineages, which are easier to analyze and depict. However, the approach and definition of a lineage given here extends naturally to sexual diploid organisms.

Sidebar 2 – Geometric mean fitness (Typeset near beginning of 'Lineage selection')

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 = $(\prod_{t=1}^{n} w_t)^{1/n}$, where w_t is the Wrightian fitness of a trait in generation t. The same quantity can be expressed as a linear average over the natural log of this fitness value, GMF = $\exp(\frac{1}{n}\sum_{t=1}^{n} \log(w_t))$. In practice, approximations are used such as GMF ≈ $\mu - \sigma^2/\mu$, 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 end of 'Lineage selection' 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 (Lehmann et al., 2016). While there are notable exceptions (Traulsen and Nowak, 2006, Traulsen and Hauert, 2009), game theoretic models are typically deterministic and describe the tendency for allele frequency change but not the statistical properties of lineages in finite populations.

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

Lineage selection: Competition between two or more lineages in population.

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

Cheater: An organism that produces little or no public good but utilizes those goods produced by other organisms.

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 responsible for genetic properties of a genome, such as mutation rate, recombination rate and mutational robustness.

Indirect selection: Selection acting on a modifier locus mediated by its effect on the fitness at other loci in the genome. Indirect selection models commonly assume that the modifier is intrinsically selectively neutral, and require that recombination rates are low.

968 **Clonal interference**: Competition between mutational independent lineages, each carrying one
969 or more beneficial mutations. Clonal interference is common in asexual populations in which the
970 beneficial mutation rate is larger than approximately the reciprocal of the population size.
971
972 **Genetic drift**: stochastic variation in allele frequency as a consequence of stochasticity in
973 reproduction inherent in finite populations.
974
975 **Drift barrier**: the limit on the efficiency of natural selection imposed by genetic drift.
976

977 **Figure Captions**

978

979 **Figure 1. Variability in fitness across a lineage in diverse models.** The defining feature of
980 lineage selection is the presence of variability across a lineage either among contemporary
981 individuals (vertical axis) or between individuals in time (horizontal axis). Genealogies are
982 shown for two competing allelic lineages indicated by circles. The focal lineage is shaded yellow
983 and the wild-type lineage is shaded black. **A.** Lineage carrying a beneficial allele (yellow) rising
984 to fixation under the classical scenario of lineage invariance. **B.** Lineage carrying an allele that
985 alternates from beneficial to deleterious in a variable environment. Contemporary individuals
986 share an identical fitness, and hence an identical selection coefficient, but this quantity changes
987 between generations. **C.** Evolution of a mutator lineage that experiences increased rates of both
988 deleterious (red dots) and beneficial (grey background) mutations. Fitness in the lineage varies
989 both among contemporary individuals and between generations. **D.** A cooperative lineage under
990 a group selection model. Within-group selective pressures cause the allele to be disfavored over
991 short timescales. Groups with more cooperative alleles tend to displace other groups over longer
992 timescales (shown with solid grey lines).

993

Figure 2. Limitations of fitness averages in finite populations. Evolution in a periodic environment results in four distinct regimes characterized by the relative timescale of natural selection ($1/s$) and environmental change (τ). Simulation results of the model described by Cvijović et al. (2015) are shown in blue and the expected change of an allele with the same average fitness effect in a constant environment is shown in red. Unless otherwise noted, simulations are conducted with an average selection coefficient of 0.05 and a population size of 100,000. Selection coefficients are held constant at ± 0.06 within each environment while the timescale of environmental change is varied (beneficial environmental epochs are shaded grey while deleterious epochs are unshaded). **A.** When the environment changes fast relative to changes in allele frequency (small $s\tau$), the average change in allele frequency is well approximated by a fitness average like geometric mean fitness. **B.** When the environment changes slower 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, averages like the geometric mean fitness 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 become arbitrarily close to zero or one but never permanently achieve fixation or extinction. **D.** Average fitness breaks down when large fluctuations in allele frequency occur on a similar timescale to environmental change (intermediate $s\tau$). This is due to the amplification of fluctuations by genetic drift whenever alleles reach very high or very low frequencies (Cvijović et al. 2015). Note that genetic drift occurring as the frequency of the allele approaches 1 causes it to respond only modestly to the second deleterious epoch. The allele subsequently achieved fixation much sooner than would be expected on the basis of its average fitness effect.

1017 **Table 1.** Sources of variability across a lineage and associated adaptations (*Typeset near*

1018 *'Introduction'*)

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

1019

1020 **Figure 1**

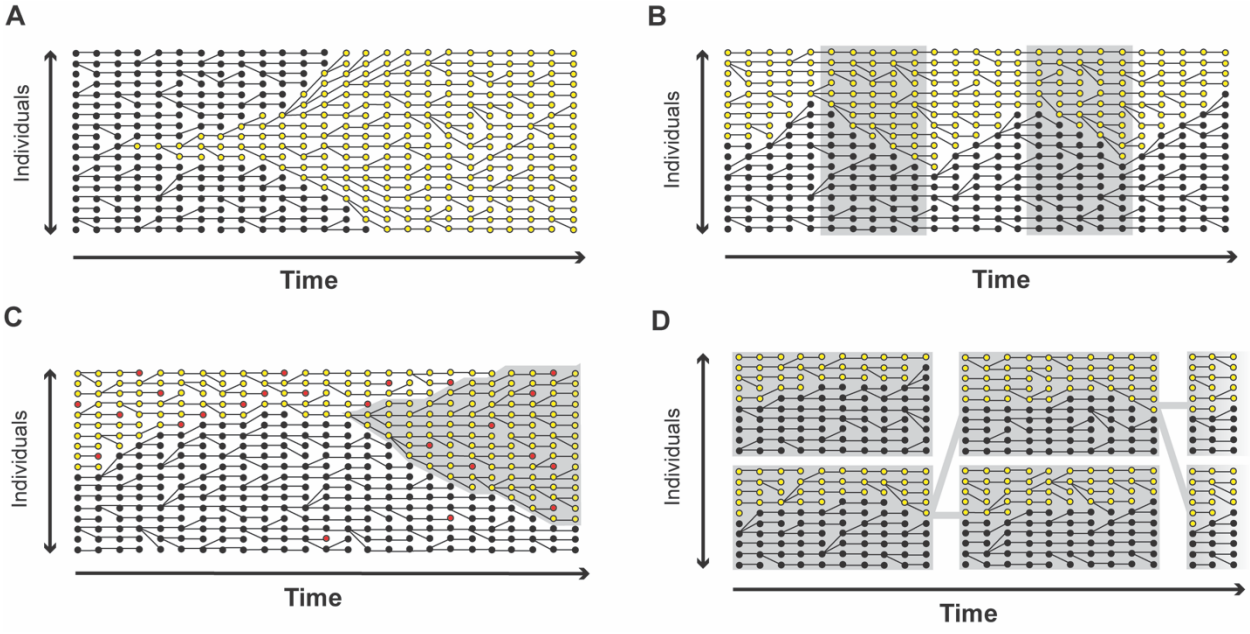

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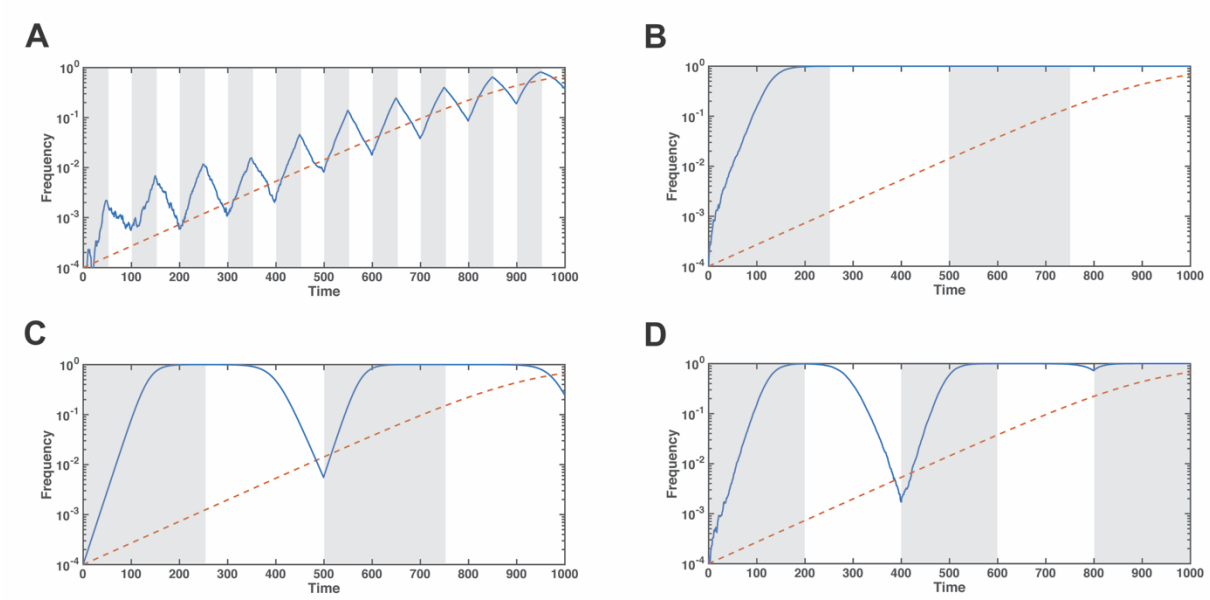
Figure 2


A
B
C
D
Frequency
Time
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10^{-1}
10^{-2}
10^{-3}
10^{-4}
0
100
200
300
400
500
600
700
800
900
1000