Can Population Genetics Adapt to Rapid Evolution?


Population genetics largely rests on a ‘standard model’ in which random genetic drift is the dominant force, selective sweeps occur infrequently, and deleterious mutations are purged from the population by purifying selection. Studies of phenotypic evolution in nature reveal a very different picture, with strong selection and rapid heritable trait changes being common. The time-rate scaling of phenotypic evolution suggests that selection on phenotypes is often fluctuating in direction, allowing phenotypes to respond rapidly to environmental fluctuations while remaining within relatively constant bounds over longer periods. Whether such rapid phenotypic evolution undermines the standard model will depend on how many genomic loci typically contribute to strongly selected traits and how phenotypic evolution impacts the dynamics of genetic variation in a population. Population-level sequencing will allow us to dissect the genetic basis of phenotypic evolution and study the evolutionary dynamics of genetic variation through direct measurement of polymorphism trajectories over time.

The Standard Model of Population Genetics

Charles Darwin thought of evolution as an innately slow process driven by small incremental changes that lead to noticeable differences between species only because they can accumulate over long periods of time. This view still runs deep in modern population genetics. We tend to assume that selective sweeps are rare in most natural populations and that most common genetic variation remains largely unaffected by such events. Catching a beneficial mutation on the fly should be extremely unlikely. Deleterious mutations can occur in individuals and some of them may have strong effects on fitness, yet purifying selection will prevent them from ever becoming prevalent in a population. The general conclusion in modern population genetics has been that the vast majority of common genetic variation should have only small effects on fitness, if any. Summarizing this view, John Gillespie wrote ‘the forces that alter the genetic structure of populations tend to be very weak, operating on time scales of thousands to millions of years’ [1].

The paradigm of slow evolution by small changes has convenient implications for both theory and practice. The few selective sweeps that occur should leave characteristic signatures in genomic data then allows us to identify recent adaptive events. Adaptation to environmental changes should proceed via well-separated successive fixations of new mutations in a process called an adaptive walk, which can be studied in theoretical models [2,3]. The dominant process in the evolution of common genetic polymorphisms should be random genetic drift, which we understand mathematically and can incorporate rather easily into our theoretical models and computational tools. Figure 1 provides an illustration of evolutionary dynamics under these assumptions, which we will hereafter refer to as the ‘standard model’ of population genetics.
The standard model’s drift-dominant view has enabled the development of a rapidly growing toolbox for inference of selection, demography, and population structure from genomic data [4,5]. It is also consistent with estimates of the molecular rate of adaptive evolution in large organisms, such as humans, as long as we assume that evolution generally occurs by random genetic drift and selection on consistently beneficial or deleterious mutations. For example, recent estimates suggest that on the order of 10,000 adaptive amino acid changes have occurred between humans and chimpanzees [6–8]—about one adaptive amino acid substitution every 50 generations. If those substitutions proceeded by selective sweeps with moderate fitness benefits of 1%, and using an average recombination rate of 1 cM/Mbp, each such event should have affected a surrounding genomic region of approximately 100 kbp. Assuming that sweeps occur uniformly across the genome, a random genomic position in the 3-Gbp human genome should therefore be affected only about once every 1,500,000 generations—much longer than the average lifespan of a neutral polymorphism.

Examples of Rapid Phenotypic Evolution in Nature and Experiment

Studies of ‘evolution in action’ paint a markedly different picture from the paradigm of slow molecular evolution commonly adopted in our population genetic models. These studies show that phenotypic traits can often change dramatically over the course of just a few generations. Peter and Rosemary Grant’s classic studies of rapid evolution in Darwin’s finches [9–11] are well known by both scientists and non-scientists, but many other studies have now demonstrated rapid change in heritable traits in other organisms. For example, Koskinen et al. observed that natural selection led to diversifying evolution in life-history traits in grayling over the course of only 10–20 generations after a small number of fish were introduced to a new lake [12]. Cichlid fish rapidly evolved the same elongated-body phenotype in isolated Nicaraguan crater lakes [13] and similarly high rates of phenotypic evolution have been observed in berry bug beak length [14,15], coloration and life-history traits in guppies [16,17], and rainbow trout [18]. One of the most rapid examples involves diapause date (a mechanism for avoiding fish predation) in the freshwater copepod...
Onychodiaptomus sanguineus, which changed at an average rate of roughly one standard deviation per selected generation following complete fish removal by drought \[19\]. Excellent reviews of the growing list of examples of rapid contemporary evolution are provided in \[20,21\].

Rapid phenotypic evolution is also commonly observed in evolution experiments. Conover and Munch documented changes in body mass in a marine fish of both a 45% increase (high selection) and a 25% decrease (low selection) over the course of only four generations of artificial selection \[22\]. Anolis lizards repeatedly evolved larger toe pads over just 20 generations (Figure 2A), allowing them to reach higher perch heights in response to invasion by a congener \[23\]. In laboratory microcosms of rotifer–algal dynamics, the alga Chlamydomonas evolved coloniality as a defense trait within a single population cycle of high rotifer density \[24,25\]. In soil mites, a 76% increase in age to maturity was observed over a few generations after a wild

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Figure 2. Rapid Evolution of Phenotypes and Genotypes. (A) Anolis carolinensis lizards on small islands in Florida repeatedly moved to higher perches within just a few generations after invasion by their competitor Anolis sagrei \[23\]. These adaptations were associated with rapid, heritable changes in toe pad area that occurred at a rate of roughly 0.1 standard deviations per generation. (B) Evolutionary dynamics observed in an initially clonal Saccharomyces cerevisiae population growing in rich medium for 1000 generations \[42\]. Different colors specify the six main ‘cohorts’ observed in the population over the course of the experiment. Even beneficial driver mutations must often hitchhike with functionally unrelated co-drivers in their cohort because of clonal interference. The numbers in parentheses indicate how often mutations were observed in the specific gene across 40 replicate evolution experiments.

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population was transferred into a novel laboratory environment [26]. Similarly dramatic changes in life-history strategies were observed in seed beetles after a host-shift [27].

These abundant examples of rapid phenotypic evolution are not automatically inconsistent with the paradigm that molecular evolution in nature should generally remain slow. For instance, there is probably ascertainment bias towards reporting examples of rapid phenotypic evolution in the literature, compared with studies of populations in which nothing happened [28]. Another issue is knowing the extent to which contemporary evolution is driven by environments changing much faster than ‘natural’ due to human activities. Classic examples of such human-induced adaptations include the rapid evolution of industrial melanism in the peppered moth [29] and the increased rates of phenotypic change in human-harvested organisms [30].

Even if rapid phenotypic evolution is common in nature, evolutionary dynamics on the molecular level could remain practically indistinguishable from random genetic drift if rapidly evolving traits tend to be highly polygenic [31,32]. In that case, their selective responses could be due to subtle frequency changes of genetic polymorphisms at a large number of loci. This so-called infinitesimal model of adaptation [3] has a long tradition in population genetics and is widely used for analyzing and predicting how quantitative traits respond both to natural selection and to artificial selection in applied animal and plant breeding experiments [33].

However, it is also possible that molecular adaptation could be abundant despite a slow rate of phenotypic changes if molecular changes occur to maintain a relatively constant phenotype in the face of frequent environmental change [34–36]. Thus, without better knowledge about the actual rates of phenotypic change and how this affects the trajectories of genetic variation in a population, it is difficult to say whether the standard model is still appropriate.

Examples of Rapid Molecular Evolution at Individual Loci

Important additional clues are provided by sequencing studies that increasingly allow us to dissect the genomic basis of phenotypic evolution. Such studies have revealed many examples of rapid phenotypic adaptation that were associated with extensive allele-frequency changes at individual genetic loci. One prominent example is the adaptation of marine sticklebacks to freshwater environments, which is driven by only a small set of genomic loci [37] yet has occurred repeatedly over just 50 generations after an earthquake created multiple freshwater ponds [38]. Similarly, wild crickets have rapidly evolved a specific wing phenotype that, while lowering the potential of males to attract females, protects them from a parasitoid fly, and this single-locus Mendelian trait has evolve repeatedly on neighboring Hawaiian islands [39].

Extensive frequency changes of molecular variants are also commonly observed in laboratory evolution. A particularly striking example was provided by Levy et al., who evolved an initially clonal population of 10^8 asexual yeast cells under glucose-limited conditions for 168 generations [40]. Using a clever barcoding technology that allowed them to track mutations at extremely low population frequencies, they detected thousands of de novo beneficial mutations that competed with each other such that only a few eventually became prevalent in the population. This type of adaptive dynamics is commonly referred to as clonal interference (Figure 2B) and has been observed in other evolution experiments [41–43]. It is very different from the adaptive walk model of successive selective sweeps assumed by the standard model. These experiments also showcase the ample adaptive potential of microbial populations even when they are initially clonal, providing an explanation for why such populations can often respond so surprisingly quickly to environmental challenges [44].

Microbial populations tend to be large and adaptive genetic variants can therefore arise readily by de novo mutation. Yet even in experiments with much smaller populations, artificial selection
often produces extensive allele-frequency changes at many genetic loci. For example, Burke et al. exposed a laboratory population of *Drosophila melanogaster* to artificial selection for accelerated development and observed dozens of genomic regions that showed strong allele-frequency differentiation over the course of the experiment [45]. Similar dynamics have been observed in selection experiments for other traits, including body size [46], temperature response [47,48], and pathogen resistance [49,50].

The adaptive dynamics observed in these experiments were, again, very different from the classic selective sweep model, while also differing from the clonal interference dynamics observed in microbial experiments. Because of the typically small population sizes, adaptation was likely to have proceeded from standing genetic variation already present in the population. Under such circumstances, adaptation is expected to produce so-called soft selective sweeps, where multiple alleles at the same locus rise in frequency simultaneously [51]. Interestingly, fixation of a selected allele was rarely observed in these experiments [45], suggesting that many of the responding alleles may not be unconditionally beneficial.

**Are Short-Term and Long-Term Evolutionary Rates Different?**

If rapid phenotypic evolution is indeed common in nature and often associated with extensive frequency changes of molecular variants at many loci, why do we not observe higher levels of molecular divergence between extant species? A possible explanation is that selection may not always be as static as assumed by the standard model. If a considerable fraction of genetic variants has selection coefficients that vary in sign over space and time, being advantageous at some times and locations and disadvantageous at others, these variants could enable rapid evolutionary responses without being driven towards fixation or loss in the population. Molecular evolution would therefore appear slow over the timescales of extant species despite pervasive adaptive changes at any point in time.

In the ecological literature, temporally fluctuating selection on phenotypic traits is generally assumed to be common and has been invoked to explain the discrepancy between long-term and short-term rates of phenotypic evolution [52–57]. Figure 3 summarizes empirical estimates of rates of phenotypic evolution for studies spanning a few generations to the macroevolutionary scale of extant species lifetimes, where trait changes can be estimated over scales of tens of millions of years. In both cases, rates of phenotypic evolution are inversely proportional to the timescale of measurement. That is, they tend to be fast when estimated over short timescales...
but become increasingly slower as the time intervals expand. This scaling arises naturally if phenotypic traits can change rapidly in response to environmental fluctuations but remain within relatively constant bounds over longer periods [28,44,52,53].

All natural environments fluctuate, often dramatically, with frequent changes in intensity and reversals of direction. Day–night cycles of light and temperature lead to changes in microbial populations. Seasonality is a ubiquitous driver of fluctuating selection in organisms with generation times of a month or less. At longer timescales, many populations cycle in abundance every few generations, often as a result of interactions with other species [58,59]. Changes due to climate variation can be extreme, with warm years and cold years, wet years and dry years, and periods of high fire frequency and years of low all affecting local populations, although often driven by global processes such as the El Nino Southern Oscillation, the Pacific Decadal Oscillation, and the North Atlantic Oscillation. Recruitment variation between years is frequently on the order of 100-fold to 10,000-fold for a variety of organisms, including plants, invertebrates, and vertebrates from diverse habitats [60]. Birth and death rates in plankton populations can vary as much as tenfold or more within a season [61]. Biotic factors such as resource quality [9], predation intensity [62], and rapid evolution of interacting species [35] are also potential sources of temporally fluctuating selection. While some populations evolve adaptations to tolerate or even take advantage of such changes in the conditions they experience, such as bet-hedging strategies and adaptive phenotypic plasticity [63], others track these fluctuations with heritable trait changes [9,62].

Population Genetics Might Be Underestimating the Role of Temporally Fluctuating Selection

While it is widely acknowledged that spatially varying selection can play an important role in the dynamics and maintenance of molecular variation [64], population genetics has remained rather skeptical regarding the significance of temporally fluctuating selection. This view traces back to theoretical arguments showing that, in standard models with non-overlapping generations, temporally fluctuating selection cannot maintain a polymorphism unless the heterozygote has higher geometric mean fitness than either homozygote [1,65,66]. As a result, temporally fluctuating selection—and any other forms of balancing selection—are seldom incorporated in our population genetic models. Importantly, this theoretical argument does not preclude that fluctuating selection could strongly impact the frequency dynamics and persistence time of genetic polymorphisms; it says only that temporally fluctuating selection on its own will not maintain these polymorphisms for very long.

In ecology, the allegation that temporal fluctuations cannot promote diversity is widely contested, growing from the discovery of the storage effect mechanism for coexistence of competing species in fluctuating environments [67]. The storage effect is driven by density-dependent changes in covariance between environment quality and competition. When a species is common, it cannot take full advantage of a year when conditions are good for reproduction because high offspring production will lead to intense competition, limiting population growth. A rare species, by contrast, may not have this problem because high reproduction by a few individuals may have little effect on the overall level of crowding in the population. In a year that is good for the rare species but bad for others, it can have high per capita reproductive success. However, these gains by the rare come to nothing if they are wiped out in bad years. The storage effect can therefore maintain coexistence only if species are buffered against sudden rapid declines. One natural way for this to occur is if generations overlap and established individuals are immune to the causes of temporal variation (e.g., viability selection on offspring, no selection on adults).

The population genetic analog to the storage effect is that an allele close to fixation cannot increase in frequency by much regardless of how strongly it is favored by selection at the time. A
rare allele, by contrast, has the potential for rapid increase when it is favored by selection. Once the assumption of non-overlapping generations is dropped, this mechanism can already maintain a genetic polymorphism in a model of stabilizing selection with a randomly fluctuating trait optimum [68,69]. Precisely this kind of dynamic was observed in a population of freshwater copepods subject to interannual fluctuations in selection for a life-history trait and in which only a fraction of the diapausing eggs produced each year hatched the following year [62,70]. Yi and Dean demonstrated a similar outcome in a chemostat model of microbial competition where overall population abundance was bounded [71].

Another type of genomic storage effect can promote genetic polymorphism in fluctuating environments through recombination [72,73]. The way this mechanism works is that a target allele could have its deleterious effects buffered in detrimental environments if it becomes genetically linked to a modifier allele. Once the environment changes and the target allele becomes advantageous without the modifier, it can escape the modifier background through recombination and enjoy full selective advantage [73]. Importantly, this mechanism does not require any form of age-specific or spatial heterogeneity in selection.

Heterozygote advantage itself could play a more prominent role in adaptive dynamics and maintenance of genetic diversity than previously recognized. Sellis et al. showed that adaptive walks in diploids should often proceed via successive balanced states (Figure 4A), where invading alleles are beneficial in heterozygotes but overshoot the fitness optimum in homozygotes [74]. The resulting short-lived balanced states allow diploid populations to adapt more rapidly to fluctuating environments by maintaining phenotypically consequential variation in a population, although these ephemeral balanced polymorphisms will remain mostly invisible to current scans for long-term balancing selection.

In addition to these theoretical arguments, there is accumulating experimental evidence that balancing and fluctuating selection on the molecular level may be more widespread than currently accommodated in our population genomic models [75–83]. A particularly striking

Figure 4. Evolutionary Dynamics Beyond the Standard Model. (A) Allele-frequency trajectories at a single locus in a diploid population during simulated adaptive walks in Fisher’s geometric model of adaptation [74]. Different colors indicate the different alleles that were observed in the population. Most beneficial alleles do not reach 100% frequency but are maintained for some time at intermediate frequencies due to heterozygote advantage. They are then displaced by new beneficial alleles that themselves are often balanced. (B) Allele-frequency trajectories at 1750 SNPs in the Drosophila melanogaster genome that were observed to fluctuate between seasons in a North American orchard [81]. Allele frequencies are polarized such that they are higher in the spring than in the fall.
example of pervasive fluctuating selection has recently been provided by Bergland et al., who studied fruit fly samples collected in a temperate orchard in Pennsylvania and identified hundreds of polymorphisms that showed dramatic and repeatable oscillations in allele frequencies between seasons (Figure 4B) [81].

**Population Genetics Beyond the Standard Model**

In the standard model we tend to assume that the selection coefficients of mutations remain constant over time and space. If instead selection coefficients often vary, evolutionary dynamics could be quite different. In this case, selection could play a much more important role among the processes that cause alleles to change in frequency over time. Classic selective sweeps, however, would remain rare, as alleles would usually not be driven all the way to fixation or loss. Instead, we should more often observe incomplete sweeps, soft sweeps, and alleles that rapidly change in frequency but in an inconsistent manner. Identifying selection from patterns of genetic diversity would be much more difficult in this case and scans for selective sweeps would provide us with only a very limited picture of the overall contribution of selection to evolutionary dynamics.

It would also no longer hold that functional genetic variants should necessarily have small effects on fitness if they are common in a population. Some of those common variants could be quite consequential, just not consistently good or bad. Indeed, these variants would be the very ones most likely to play a key role in providing the potential for the rapid evolutionary responses to environmental change. An extreme example of this is mutations conferring resistance to drugs or pesticides, which can provide tremendous fitness benefits in the exposed parts of a population where they would sweep rapidly but typically carry high costs in untreated populations where they hence remain rare.

The assumption that each mutation can be assigned a fixed selection coefficient lies at the foundation of many key concepts in population genetics, including mutation–selection balance and the Poisson random field [84]. These concepts, in turn, form the basis for approaches widely used to infer evolutionary parameters from population genomic data, such as McDonald–Kreitman-type tests for estimating rates of adaptive substitution [85–87] and inference of the distribution of fitness effects of new mutations [6,88–90]. It is unclear to what extent these approaches would be affected by frequent fluctuating selection, except that they would almost certainly underestimate the prevalence and strength of selection.

Finally, if fluctuating selection is common, even neutral genetic variation might not be subject to random genetic drift alone. Linked selection could strongly affect the dynamics of neutral polymorphisms similarly to so-called genetic draft, which describes the effects of linked selection on neutral polymorphisms under frequent classic selective sweeps [91,92]. However, while genetic draft is expected to leave characteristic signatures in the frequency spectra of neutral diversity, such as an excess of high- and low-frequency polymorphisms [93–95], incomplete and soft sweeps can leave these spectra relatively undisturbed [91]. Thus, the stochastic dynamics of neutral polymorphisms could be fundamentally different from random genetic drift, with most of their frequency changes over time being driven by linked selection, but it would be difficult to discern these dynamics from drift-dominated evolution based on patterns of neutral genetic diversity in a single population sample.

If linked selection plays an important role in the dynamics of neutral polymorphism, this could have profound implications on population genetic inferences, given that basically all of our methods for inferring demography and population structure from population genomic data are based on the drift-dominant paradigm. We already know that genetic draft can severely mislead these approaches [7,96] and it is reasonable to assume that linked selection from incomplete and soft sweeps will cause similar problems.
Population Genetics Should Embrace Rapid Evolution

The appeal of modern population genetics stems in no small part from the elegance and simplicity of its underlying theoretical models. These models were largely devised in times when data were limited to measurements of molecular divergences between species and rough estimates of the genetic diversity within populations. Kimura’s neutral theory of molecular evolution [97] provided a convincing explanation for the patterns in these data that did not require processes more complicated than random genetic drift, purifying selection, and the occasional selective sweep.

Yet as we have presented in this review, there is accumulating evidence that the standard model is insufficient to describe the rapid phenotypic evolution often observed in nature and experiments. The time-rate scaling of phenotypic evolution strongly suggests that the selection driving these phenotypic changes is fluctuating, so that rapid short-term changes do not accumulate into large long-term changes. The genes underlying these changes then do not fit into any of the categories in the standard model (Figure 1), unless we are truly in the limiting situation of the infinitesimal model, where substantial, ecologically important changes in traits occur without substantial frequency changes at any polymorphic site in the genome.

Whether most rapidly evolving traits truly are polygenic, so that the infinitesimal model applies, is an open question. We have described examples where the answer is ‘no’—a few genes of large effect are responsible, but these may be unrepresentative. There are very few such traits for which we know much about the phenotype-genotype map, and understanding phenotype-genotype maps is a difficult and longstanding problem unlikely to see a quick resolution.

Concluding Remarks

With genome sequencing becoming easier and cheaper, we have the opportunity to directly observe the essence of evolution: how allele frequencies change over time within a population, as in Figure 4B. With such data we can finally test the key assumptions of our population genetic models and study the processes that govern the patterns and dynamics of genetic variation in populations (see Outstanding Questions).

Key to achieving this goal will be extensive population sampling across time and space, along with measurements of environmental factors, abiotic and biotic, that are potential sources of fluctuating selection. These samples need to be taken frequently enough to observe short-term genetic changes before they are reversed when selection changes in direction. Identifying the relevant timescale of genetic change must come from an ecological understanding of the selective forces acting on the population and the timescales of variation in the factors that give rise to directional selection and rapid evolutionary responses. The first computational approaches that will allow us to test directly for variable selection, given temporally high-resolution population genomic data, are already being developed [33,98,99]. We are about to enter exciting times for population genetics.

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Outstanding Questions

How common is rapid evolution in nature and how does this impact the dynamics of genetic variation in a population?

Is rapid evolution typically underlain by subtle frequency changes of many polymorphisms or do large-effect loci play an important role as well?

How realistic are the assumptions that we can assign a fixed selection coefficient to each mutation that remains constant across time and that potential epistatic interactions can be ignored?

What roles do fluctuating and balancing selection play in the evolutionary dynamics of genetic polymorphisms?

Is random genetic drift truly the dominant process in the evolution of common genetic variation or could linked selection play an important role as well?

If drift is not the dominant process, how will this affect our population genetic machinery for inference of selection, demography, and population structure from population genomic data?

How can we leverage the new population-level datasets to answer these questions by studying directly how polymorphisms change in frequency over time?

References


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