Fighting change with change: adaptive variation in an uncertain world

Lauren Ancel Meyers and James J. Bull

Organisms live in an ever-changing world. Most of evolutionary theory considers one solution to this problem: population-level adaptation. In fact, empirical studies have revealed an enormous variety of mechanisms to cope with environmental fluctuations. Some organisms use behavioral or physiological modifications that leave no permanent trace in the genes of future generations. Others withstand environmental change through the regular production of diverse offspring, in which the diversity can be either genetic or nongenetic. Evolutionary theorists now have the opportunity to catch up with the empirical evolutionary biology, and to integrate the diverse forms of 'adaptive variation' into a single conceptual framework. Here, we propose a classification according to the level at which the adaptive variation occurs and discuss some of the mechanisms underlying the variation. This perspective unites independent lines of research in molecular biology, microbiology, macroevolution, ecology, immunology and neurobiology, and suggests directions for a more comprehensive theory of adaptive variation.

Published online: 14 October 2002

Lauren Ancel Meyers*
James J. Bull
Section of Integrative Biology and Institute for Cellular and Molecular Biology, University of Texas at Austin, 2401 Speedway, Patterson 141, Austin, TX 78712, USA.
*e-mail: ancel@mail.utexas.edu

Over 30 years ago, Levins wrote a seminal treatise on the theory of evolution in a fluctuating environment [1]. Introducing a simple graphical tool – the fitness set – he argued that the periodicity of environmental change determines whether a population will be polymorphic or monomorphic and, more generally, that environmental fluctuations preclude optimal adaptation to any single environment. This work marked the beginnings of a population genetic theory that acknowledges the complexities and fluidity of the external world.

Empirical studies of natural selection and of the molecular basis of phenotypic change have since shed new light on the evolution of populations in uncertain environments. They have shown, for example, that plants use phytochrome pigments to sense the red:far-red radiation ratio in the environment, and then modify their growth and morphology according to the perceived density of potential competitors [2–4]; that bacteria turn on the machinery for taking up iron from the environment, that is they synthesize siderophores – only when a lack of iron triggers the expression of over ten genes involved in the regulation of this system [5,6]; and that the flesh fly (*Sarcophaga crassipalpis*) enters facultative pupal diapause when short day length induces a hormonally controlled change in gene expression [7–9].

The ubiquitous challenge of environmental variability and the diversity of evolved strategies are, however, virtually ignored by the most widely used population genetics textbooks. Theoreticians are struggling to keep up with the rapid pace of the experimental discoveries. Pockets of population geneticists have built models of organisms evolving under variable conditions with the hope that they might explain some of the diverse modes of phenotypic variation that have been observed. But these models usually consider only one possible response to the problem of environmental heterogeneity; for example, only phenotypic plasticity or only polymorphism or only hypermutation. The science has now reached a point where an integration of these diverse empirical studies and disjoint theoretical approaches is not only possible, but also necessary for a comprehensive understanding of how evolution proceeds in natural settings.

Here, we make two arguments. First, populations always exist in dynamic environments. Thus, to understand the origins and diversity of life, we, as a community, must develop a theory for evolution under fluctuating conditions, one that will eventually be incorporated into the canon of evolutionary biology. Second, it is time to combine the diverse approaches to this problem into a unifying framework. Here, we propose a step toward this integrated perspective. This perspective is grounded in decades of empirical and theoretical research, of which we provide illustrative examples, but by no means a comprehensive literature review.

Scope of the problem

The topic of evolution in fluctuating environments encompasses a potentially wide range of phenomena. The basic problem is that the environment is heterogeneous in many dimensions, and that organisms themselves alter the world around them (Box 1). Although feedback from a population to its own environment will eventually be an important component of any comprehensive theory of adaptive variation, we begin with the simplest scenario, environmental fluctuations that are exogenous to the evolving population.

Adaptive variation

Rather than stand steadfast in the face of environmental change (Box 2), populations sometimes confront the fluctuations through phenotypic variation either: (1) within single individuals; (2) among individuals in the population at one time; or (3) in future generations. We extend this basic tripartite distinction into a hierarchy according to the biological units that manifest adaptive variation, and call it the 'levels of adaptive variation' (Table 1).

We illustrate each class of adaptive variation with a few empirically studied examples, although others no doubt exist. We emphasize, however, that it is nontrivial to demonstrate that a variable response to a fluctuating environment is indeed adaptive.

 0169-5347/02/$ – see front matter PII: S0169-5347(02)02633-2

Box 1. How the environment fluctuates

Temporal and spatial heterogeneity

Organisms inhabit environments that have many dimensions (temperature, precipitation, chemical concentrations, prey availability, etc.), each of which can vary temporally and/or spatially. The outcome of evolution under heterogeneous conditions depends, in a large part, on the nature of environmental variation. Spatial diversity can occur across large or small patches with respect to the life style of an organism (Levins's coarse- and fine-grained environments [a]), and, analogously, temporal fluctuations can occur over short or long timescales. Within these timescales, the variation can occur on a regular temporal scale, as with seasonal or diurnal patters of environmental change, or on an irregular or random scale. Spatial variation can also be very localized or occur on widespread geographical scales. In some respects, a stationary population experiencing temporal environmental fluctuations faces difficulties that are comparable to those experienced by mobile populations in a spatially heterogeneous environment.

Biotic and abiotic fluctuations

The fluctuating environment can be biotic or abiotic. Abiotic fluctuations are represented by changes in climate and other physical features of the environment; biotic fluctuations could occur as changes in food and/or prey abundance, predator and/or parasite abundance, interspecific competition, or even as changes in the demographics of the population itself. These biotic factors can perhaps be driven by changes in the abiotic environment. Whereas the distribution of abiotic fluctuations is easily imagined as having a fixed mean and variance, at least in the short term, biotic fluctuations could be cyclic or could involve a progressive change in the mean (as in an ever-escalating arms race). The former situation breaks down when abiotic fluctuations have biotic inputs and under catastrophic changes in exogenous conditions.

The endogenous environment

The fitness effects of a genetic element within an organism will be sensitive not only to exogenous factors such as weather, but also to phenomena that are endogenous to the population of the organism (such as allele frequencies) or even to the organism itself. For example, the genomic context of a single gene might impact the consequence of that gene to the fitness of the organism. Promoters, repressors and other epistatically interacting genes can affect the level to which the gene in question is expressed.

Reference

a Levins, R. (1968) *Evolution in Changing Environments*, Princeton University Press

The fact that environmental variation induces phenotypic variation does not constitute evidence of an evolutionary adaptation; it might just be that the developmental system is intrinsically labile.

Variation derived from a single genome

In the four models that follow, variation is favored only when it stems from a single genome. The variation occurs either within individuals bearing the genome (A and B), or among the immediate descendents of any such individual (C and D).

A. Within-individual, nongenetic variation

Physiological plasticity is the ability of organisms to change physically and behaviorally in response to changing conditions (e.g. a single bacterium turning on and off the machinery that metabolizes lactose, or human red blood cell concentrations responding to altitude). There are countless examples of such flexibility, as well as an extensive body of theory linking environmental variability with physiological plasticity [10,11].

Some organisms simply avoid unfavorable conditions. Mobility enables organisms to maintain relatively constant food resources, chemical concentrations, temperatures, habitats, and so on (e.g. birds, whales and some ungulates migrate as temperature and food availability change with the seasons, even flagellated bacteria can propel themselves to follow shifting concentrations of sugars).

B. Within-individual, genetic variation

This category refers to genetic changes in some cells of a multicellular organism within its lifetime. In some cases the modifications are transmitted to offspring. For example, nutrient deprivation induces mutations in the repetitive DNA that encodes rRNA of flax plants *Linum usitatissimum*. This leads to a phenotypic mosaic within a single plant, where the mutant cells either enter the seeds or cause modifications in size and branching pattern. These irreversible mutations are then stably transmitted to progeny [12,13].

In the case of the mammalian immune system, the environmental change is biotic. The organism experiences variable exposure to parasites and allergens throughout its life. Many cell types of the immune system undergo specialized, targeted genome rearrangements and experience elevated rates of point mutations, which ultimately creates a vast array of molecules for recognizing and destroying foreign antigens. Such somatic mutations are not heritable.

C. Between individual, nongenetic variation

Organisms will sometimes endure environmental change through the production of diverse offspring rather than through immediate physiological modification. Here we discuss several ways in which individual organisms might be sacrificed for the sake of the lineage in the face of ecological uncertainty.

Bet hedging. Many desert annual plants face a life-and-death situation each spring, the outcome of which depends on the timing of their germination. If an early rain is followed by more rain, prospects are good for the early germinant; if drought ensues, it will probably perish. As first suggested by Cohen, this situation favors a nongenetic probabilistic germination strategy, or bet hedging [14,15]. With seeds that germinate according to essentially a coin-flip strategy, a parent plant can be assured that at least some of its progeny will survive through any combination of wet and dry years.

Another form of bet hedging is possible with arthropod diapause, where some of the eggs or larval insects suspend development late in summer to avoid premature death from an early freeze. Likewise, the lysogeny of *Escherichia coli* by λ phage occurs stochastically – some infections will result in lysis (replication of the phage and destruction of the bacteria), whereas others will result in lysogeny (incorporation of the phage in to the bacterial genome). The maintenance of the lysogenic state requires that two phage proteins be cooperatively bound to an operator sequence within the bacteria genome. Stochastic factors in the cellular environment allow those proteins to become dissociated at a low frequency, which in turn triggers the cascade of phage genes involved in lysis [16]. Theory suggests that stochastic

Box 2. The ubiquitous alternative to adaptive variation: robustness

An organism facing a temporally variable environment can evolve a single phenotypic response regardless of external conditions. Many phenotypes do exhibit remarkable stability in spite of variable and sometimes unpredictable conditions. The insensitivity of most traits to most kinds of environmental fluctuations, also called robustness or homeostasis, is exhibited, for example, in the development of basic body plans in spite of variability in the embryonic environment and external fertilization, and in the ability of warm-blooded animals to thermoregulate in the face of fluctuating temperatures. Waddington was one of the first biologists to give an evolutionary explanation for the ubiquity of phenotypic stability [a]. Using the metaphor of an epigenetic landscape, he argued that developmental pathways evolve to be canalized, buffering the developing phenotype against environmental perturbations (Fig. I). For many traits, the advantage of robustness is that it enables the individual to develop a functional trait, independent of fluctuations in the embryonic environment. Debat and Patrice provide an excellent discussion and synthesis of the developments of the theory of canalization since the work of Waddington [b].

The genetic architectures that underlie such robustness are diverse, as are the evolutionary conditions that favor such structures. In bacteriophage, for example, the ability to infect two strains of bacteria in an environment where the availability of bacteria is constantly shifting can be achieved through two different mechanisms: multiple copies of slightly divergent tail-fiber genes (the tail-fiber is responsible for recognition of and attachment to viable bacterial hosts) that are simultaneously expressed mature phage particles [c], or a single copy of a 'generalist' tail-fiber gene [d]. On a more molecular scale, the diversity of architectures is also evident with the more complex patterns of interactions that underlie, for example, the stability of individual biopolymers – where thermodynamic stability in RNA is achieved partly through stable G–C (guanine and cytosine) bonds in helical regions – and the stability of transcriptional networks – where functional redundancy seems to play an important role [e,f]. Not only are the mechanisms of robustness diverse, but the robustness of a phenotype often also entails optimal variation on a smaller scale. Consider thermoregulation in homeothermic animals. Constancy of body temperature (one phenotype) in a varying environment depends on the regulation of shivering, panting and sweating (other phenotypes). Since Levins' introduction of fitness sets, there have been several theoretical characterizations of the population genetic conditions that favor such robustness [g–j].

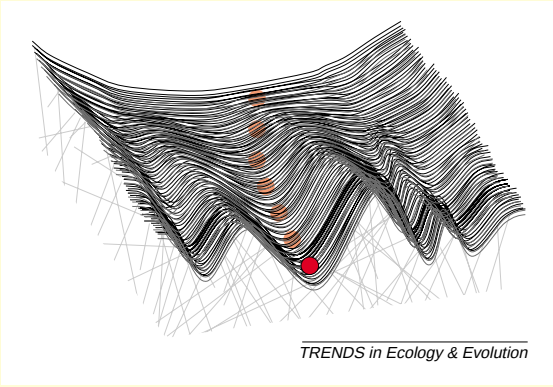

Fig. I. Waddington's epigenetic landscape [k]. This caricature of organismal development shows a ball rolling down a hilly plane towards the eventual phenotype. The hills and valleys of the plane are buttressed by the interactions of the underlying genes. Environmental perturbations move the ball along the surface whereas genetic perturbations alter the topography. A canalized developmental pathway is a steep one, in which the ball is very likely to reach a single (or a few) endpoints, even when the environment pushes the ball slightly off course. Reproduced from [k].

References

a Waddington, C. (1957) *The Strategy of the Genes*, MacMillan
b Debat, V. and Patrice, D. (2001) Mapping phenotypes: canalization, plasticity and developmental stability. *Trends Ecol. Evol.* 16, 555–561
c Scholl, D. *et al.* (2001) Bacteriophage K1-5 encodes two different tail fiber proteins, allowing it to infect and replicate on both K1 and K5 strains of *Escherichia coli*. *J. Virol.* 75, 2509–2515
d Morona, R. and Henning, U. (1984) Host range mutants of bacteriophage Ox2 can use two different outer membrane proteins of *Escherichia coli* K-12 as receptors. *J. Bacteriol.* 159, 579–582
e Ancel, L. and Fontana, W. (2000) Plasticity, evolvability, and modularity in RNA. *J. Exp. Zool.* 288, 242–283
f Tavazoie, S. *et al.* (1999) Systematic determination of genetic network architecture. *Nat. Genet.* 22, 281–285
g Hartl, D.L. *et al.* (1985) Limits of adaptation: the evolution of selective neutrality. *Genetics* 111, 655–674
h Wagner, G.P. *et al.* (1997) A population genetic theory of canalization. *Evolution* 51, 329–347
i Wagner, A. and Stadler, P.F. (1999) Viral RNA and evolved mutational robustness. *J. Exp. Zool.* 285, 119–127
j Lenski, R.E. *et al.* (1999) Genome complexity, robustness, and genetic interactions in digital organisms. *Nature* 400, 661–664
k Waddington, C.H. (1975) *The Evolution of an Evolutionist*, Cornell University Press

lysogeny might have evolved as an adaptive solution to fluctuations in availability of bacterial hosts [17,18].

Finally, bet hedging can also be achieved through offspring dispersal across a spatially heterogeneous environment. When an environment consists of niches that become available for colonization stochastically, then the optimal genotype produces a mix of dispersing and nondispersing progeny [19].

Developmental plasticity. Some organisms follow distinct, irreversible developmental pathways in response to local conditions, as opposed to adopting different 'random' phenotypes before experiencing the environment (as in bet hedging). Developmental plasticity is favored when the state of the environment experienced by the developing organism is a good predictor of future environmental conditions, and can thus serve as a cue for an appropriate phenotype.

For example, the cichlid *Astatoreochromis alluaudi* exhibits remarkable developmental plasticity of jaw morphology, which might have evolved for coping with heterogeneity of food sources. When groups of genetically indistinguishable fish were fed either snails or insects, the former group developed significantly larger jaw muscles and bones, and a different distribution of tooth types than did the latter group [20,21]. Spadefoot toad tadpoles *Spea bombifrons* and *S. multiplicata* similarly follow one of two alternative developmental trajectories. If a tadpole has the opportunity to eat fairy shrimp or a fellow tadpole, then it will probably become a large-headed carnivore, otherwise it becomes a small-headed omnivore [22].

Note that some forms of developmental variability could simply be nonadaptive biophysical responses to environment inputs. For example, Waddington showed that wild-type *Drosophila melanogaster* embryos develop a second thorax region when exposed to ether. The induction of this aberrant phenotype is presumably a nonadaptive developmental response to certain environmental stimuli [23].

D. Between-individual, genetic variation

An organism can also produce variable offspring via a high mutation rate, so that not only will its own offspring be diverse, but also its offspring's offspring*.

Table 1. Adaptive variation maintained in response to fluctuating environments

Level at which beneficial variation is generated	Level of variation[a]	Evolutionary phenomenon	Signal[b]	Response[c]	Examples	Refs
Single genome	Within individual nongenetic	Physiological plasticity	Yes and no	Random and directed	Environmental induction of gene expression, physiological adaptation, learning, seasonal migration	[11]
	Within individual, genetic	Somatic evolution	No	Random	Immune system; Loss of repetitive DNA in flax	[12]
	Between individual, nongenetic	Bet hedging	No	Random	Seed dormancy; diapause; λ lysogeny; dispersal	[14,17]
		Developmental plasiticity	Yes	Directed	Cichlid jaw morphology; grasshopper aposematism	[20,50]
	Between individual, genetic	Hypermutation	Yes and no	Random	Mutator strains; phase shifting	[24,27]
Population	Between lineage	Polymorphism	No	Random	Color morphs in *Linanthus*	[38]

[a]The distinction between genetic and nongenetic refers to whether the phenotypic variation requires changes in the DNA sequence, that is, mutation. In all cases of genetic and nongenetic variation discussed here, however, genes play an important role in determining the phenotype.
[b]This category denotes whether the production of phenotypic variants is triggered by cues in the environment.
[c]This category denotes whether specific variants are appropriate for the current environment or they are produced at random with respect to the current environment. Note that directed responses can only occur when the organism is able to detect an environmental signal.

This mechanism of adaptive variation has been observed in several bacteria species, in which it is thought that the rapid production of variants enables survival in fluctuating conditions [24,25].

Several molecular mechanisms have been characterized for elevated mutation rates. Some bacteria have deficiencies in DNA repair enzymes, which prevent the correction of replication mistakes or of chemical alterations of DNA that lead to mutations. Such mutator strains experience a genome-wide elevated mutation rate, and have evolved in both laboratory and natural environments [26–28]. Other laboratory mutator strains exhibit high mutation rates that result from transposable elements that jump randomly, interrupting genes throughout the chromosome [29].

With mutator strains, the adaptive mutations are rarely (if ever) in the same genes as those that cause the elevated mutation rate. Thus, recombination can uncouple the mutators from the resulting beneficial mutations, and thereby prevent their evolutionary longevity [30]. An elevated mutation rate is maintained in a variable environment only when the mutator mechanism remains within the evolving genome. Adaptive genetic variation therefore has a direct parallel to bet hedging – it will evolve when the mechanism for producing variation remains within a single lineage.

Organisms also evolve localized elevated mutation rates. Phase shifting in bacteria is a mutational and/or recombinational process that mediates frequent transitions between different patterns of gene expression. There are several well-known examples of phase variation. In *Salmonella typhimurium*, recombination inverts a segment containing a promoter to orient it toward or away from important structural and regulatory genes. The orientation of the segment determines which of two slightly divergent flagellin genes is expressed [31,32]. Shifting between the two types occurs stochastically once every 10^3–10^5 generations.

A second mechanism for phase variation is mutation at microsatellites (stretches of repeated nucleotide motifs) embedded within genes. Certain repeat sequences lower the replication fidelity of polymerase, so that frameshift mutations arise frequently. Such mutation can disrupt the reading frame so that translation is terminated prematurely or results in nonfunctional amino acid sequences, or, alternatively, can restore a previously disrupted reading frame. These kinds of mutation hotspots occur in the genes encoding surface proteins in several pathogenic bacteria, including *Neiserria meningitidis*, *N. gonorrhoeae*, *Haemophilus influenzae* and *E. coli*, and are thought to mediate the turning on and off of antigens as a lineage of bacteria colonizes a host [24].

Under conditions where no single genome can meet the multiplicity of environmental challenges, these between-individual mechanisms enable lineages of cells to produce sufficient diversity to persist. These examples describe 'random' phenotypic variation, as opposed to 'directed' phenotypic variation. Whereas some forms of phenotypic plasticity and developmental plasticity involve appropriate phenotypic responses to environmental cues, bet hedging and hypermutation produce a range of variants without measuring the environment, only some of which will be appropriate for the current conditions. The SOS response of bacteria is a form of hypermutation that is both 'direct' and 'random' simultaneously. Certain environmental stimuli, including heat shock, radiation and chemical stress, cause the rate of spontaneous mutation to increase. The resulting variation arises in direct response to environmental stresses, yet the nature of that variation is random, and often not appropriate for the environment. Furthermore, the increased mutation rate is temporary and ceases when conditions improve [33].

*Although genetic mutations alter the genome *per se*, mutators often produce a cloud of genotypes focused around a wild type. We therefore classify hypermutability as a form of within-genome variation, where 'genome' refers loosely to a set of closely related genotypes.

Population-level variation

In population-level responses to a fluctuating environment, adaptive variation is achieved through long-term maintenance of multiple lineages [34–36]. In 1955, Dempster demonstrated that the persistence of a genotype in a fluctuating environment requires high geometric mean fitness [37]. Haldane and Jayakar also argued mathematically that polymorphism for a recessive allele is maintained when the arithmetic mean fitness of the recessive allele is >1 but its geometric mean fitness is <1 (assuming a dominant fitness of 1) [38]. These conditions might hold, for example, if the recessive phenotype is usually more fit than is the dominant, except in rare catastrophic years that dramatically lower the fitness of the recessive.

A recent version of this model that incorporates seed banks can explain the maintenance of the striking blue-white flower polymorphism in the desert annual *Linanthus parryae* [39]. The white-flowered plants fare better in wet years, whereas the blue-flowered plants fare better in dry years because of the drought-resistant properties of the blue pigment, anthocyanin. Interestingly, flower color *per se* appears to be irrelevant to fitness. This model differs from the strict Haldane-Jayakar model because it involves two levels of (presumably) adaptive variation: a Haldane–Jayakar adaptive polymorphism for anthocyanin plus bet hedging for seed germination (the seed bank).

Populations can also achieve polymorphism under conditions of spatial diversity. In 1953, Levene introduced a now widely cited model of a diploid species evolving in the presence of two ecological niches [40]. He demonstrated that polymorphism is stable when the different genotypes have sufficiently divergent abilities to exploit the two different resources.

Gillespie extended the theory of polymorphism as the product of both spatial and temporal environmental heterogeneity. Among many interesting results, his models demonstrate that both the abundance and spatial independence of ecological resources increases the likelihood of polymorphism [35]; and that the frequency of ecological change – the environmental grain – is inversely correlated with the likelihood of polymorphism [41]. More recently, Frank and Slatkin introduced a mathematical framework in which to synthesize these diverse models, and to compare generally the evolutionary implications of spatial and temporal diversity [42].

When populations are their own changing environment

Our discussion considers primarily variation that is maintained in the presence of environmental fluctuations that are exogenous to the population. In fact, the environmental perturbations that organisms confront are often much more complex. As a population evolves, the frequency of phenotypes in the population changes. When those phenotypes are themselves selective forces acting on the population, or when they feedback to such selective forces, then evolution necessarily occurs in a fluctuating environment. Such dynamics have been studied in the guise of density-dependent selection, frequency-dependent selection, and niche construction. Models have shown multiple outcomes for such scenarios: stable polymorphism, stable and unstable cycling of genotypes, and the absence of phenotypic variation. Kerr *et al.* have shown that flammability in plants that resprout after fires – a phenotype whose frequency obviously affects the local fitness of all organisms – can lead to all three outcomes [43].

No universal solution

One organism, multiple mechanisms

A single organism can display multiple strategies, each coping with fluctuations in a different facet of the environment. For example, on the within-individual level, *E. coli* has multiple systems for transcription regulation in response to environmental stimuli. They can sense and respond to changes in temperature, osmolarity, pH, noxious chemicals, DNA-damaging agents, mineral abundance, energy sources, electron acceptors, metabolites, chemical signals from other bacteria, and parasites. Also, on the within-individual, nongenetic level, flagellar filaments propel both tumbling and smooth motility, which enable bacteria to sample their environment randomly and follow gradients toward or away from (un)desirable chemical concentrations.

Escherichia coli also adopts between-individual genetic strategies. Laboratory strains of *E. coli* have evolved to be global mutators, presumably in response to the challenges of adapting to changing conditions. *Escherichia coli* are also local mutators in that their pili undergo phase variation. This is thought to enable populations of *E. coli* to face the fluctuating requirements of infection: early in infection pili are necessary for binding to epithelial cells; whereas later pili become a burdensome target for immunity.

Toward a unified framework for adaptive variation

Why does *E. coli* have a physiological switch for lactose metabolism but a genetic switch for pili expression? Why do some plants employ polymorphism to fend off a diversity of invading parasites, but use within-individual developmental plasticity to respond to water and light availability? The classification of adaptive variation according to the level (lineage or population, within individual or between individual) and mechanism (genetic or nongenetic variation) conceptually unites seemingly diverse phenomena from very different biological fields, and, thus leads to these kinds of interesting question.

One important long-term goal of this enterprise is summarized by the following challenge: for each strategy, identify the set of conditions under which it can evolve. Where do we begin? What we know so far is a mix of results from very system-specific or mechanism-specific theoretical studies. Previous models suggest that there is some correlation between the nature of the environmental fluctuations and the

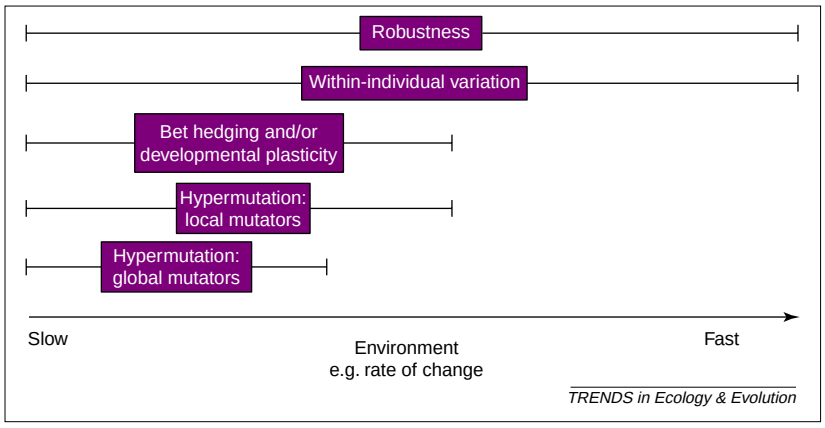

Fig. 1. Environmental heterogeneity and adaptive variation. This depicts the ranges of environmental volatility for which each level of adaptive variation is appropriate. As the rate of environmental fluctuation increases, the between-individual strategies will be too slow to keep pace with the changes.

level at which adaptive variation evolves [44–46]. In particular, fine-grained fluctuations tend to favor within-individual strategies (models A and B) because the environment changes too often to benefit any strategy that fixes phenotypes for life. Other models predict that bet hedging is a favorable response to a severely fluctuating environment, but genetic polymorphism is not, because a genome that produces only one phenotype eventually encounters an environment that wipes that phenotype out [15].

To illustrate the intuition gleaned from such models, Fig. 1 considers the viability of different strategies as a function of the volatility of the environment. Robustness enables an organism to produce the optimal phenotype regardless of the frequency of environmental perturbations. Physiological plasticity might enable an immediate beneficial physiological modification, whenever a new challenge arises. With developmental plasticity, however, individual organisms are stuck, and only in the next generation might their offspring, by chance, be optimal for the new environment. This strategy will, therefore, work only when the changes in environment are sufficiently rare to allow lineages to keep up. Similarly, hypermutation produces variants only during cell division. Local mutators will have a higher probability of realizing the appropriate mutation during each cell division than will global mutators, and will therefore keep up with more rapidly shifting conditions.

One might be tempted to ask why between-individual strategies evolve at all when they are less broadly applicable than within-individual strategies. The answer is that the frequency of environmental change is only one small piece of the puzzle. The evolution of any mode of adaptive variation (or robustness) will depend first on whether the mechanisms to produce such variation are available through mutation in the first place. Then, if they do arise, we must consider the consequences of such mechanisms on the viability and fecundity of the organisms that possess them. One can imagine a scenario in which within-individual mechanisms for variation are not easily produced through mutations or, if they are, then they are energetically costly and entail reduced fecundity.

This leads to two further questions: which phenotypes can be produced by mutations? And what are the implications of such phenotypes for the fitness of an organism? Only recently have population geneticists begun to turn from very simple and abstract genotype-to-phenotype maps to more complex and biologically realistic models that address the nature of the phenotypic variation produced by mutations. For example, the evolution of robustness and plasticity is being examined using explicit models of the segment polarity gene network in *Drosophila* [47] and of the folding of RNA molecules into their secondary structure [48,49]. In general, we do not yet understand enough about the molecular genetics of all phenotypes to predict which mechanisms of adaptive variation might evolve, but we are headed that way.

If our goal is to develop a comprehensive theory of adaptive variation, we must turn from the kinds of intuitive speculation and piecemeal analysis presented above, to a more holistic strategy. Figure 2 illustrates one possible route towards this objective. The first challenge is to identify empirically all potentially relevant parameters, which might relate to the environment, life history, genetics, demographics, and so on. The second challenge is then to determine the range of values for each of these parameters that favors any particular strategy. In the hypothetical case illustrated in Fig. 2, we consider three relevant parameters – environmental predictability, fecundity (or growth potential of a

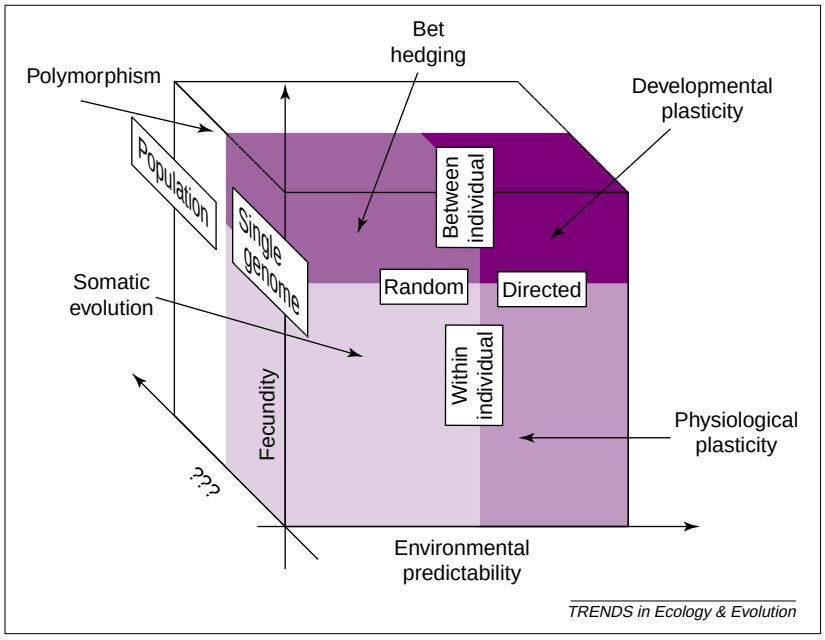

Fig. 2. The evolutionary basis of different strategies. We expect that different mechanisms of adaptive variation will evolve under different conditions. Different levels of environmental predictability and fecundity (taken as a loose measure of how quickly the population grows relative to the rate of environmental change) are likely to have different impacts on whether between- or within-individual, and random or directed responses evolve. We also consider that there might be factors enhancing the evolution of singe-genome versus population responses, but do not venture a guess as to what such factors might be (as represented by "???"). The extent to which this figure – or one similar in kind – captures reality is a topic for future work.

population), and a third unspecified parameter. Using intuition, we speculate that certain strategies will be limited to certain quadrants of this space. The different shadings represent different classes of adaptive variation, and in particular, the form that is most favored at any given set of coordinates.

For the first axis – environmental predictability – we reason that populations can only evolve directed forms of adaptive variation if there exist sufficiently reliable cues in the environment. Environmental unpredictability will limit a population to evolving only random strategies. The fecundity axis refers to the growth potential of a population. Organisms that can afford to produce only a few offspring or that have long generation times relative to the changing environment, will be more likely to evolve within-individual strategies than between-individual strategies that come at the expense of nonviable offspring. The remaining axis is unspecified because we know little about the evolutionary conditions that favor polymorphism over single genome strategies. Most theory juxtaposes polymorphism with the null model of no form of adaptive variation whatsoever. We can speculate that polymorphism might be favored when it is costly for a single genome to harbor the ability to produce multiple phenotypes.

The levels of variation classification system highlights regularities among seemingly diverse phenomena, and is a first step toward a conceptual unification of diverse systems for confronting environmental heterogeneity. Figure 2 is merely a low-dimensional caricature of what one might find for a real population in a real environment. There might be many more relevant parameters, much more overlap in the kinds of strategies that might succeed given any set of parameter values, or partitioning along nonorthogonal lines. Both steps of the enterprise – empirically assessing the relevant factors and theoretically predicting the evolutionary consequences of these factors – require more rigorous formulations, and offer many interesting challenges for the future.

Acknowledgements
We thank Curt Lively, Michael Turelli, Michael Lachmann, Ben Kerr, Mark Tanaka and David Pfennig for their insightful comments. This work was supported, in part, by a National Science Foundation Postdoctoral Fellowship in Biological Informatics to L.A.M. and the Miescher Regents Professorship and NIH grant GM 57756 to J.J.B.

References

1 Levins, R. (1968) *Evolution in Changing Environments*, Princeton University Press
2 Ballare, C.L. *et al.* (1990) Far-red radiation reflected from adjacent leaves: an early signal of competition in plant canopies. *Science* 247, 329–332
3 Gibson, D. *et al.* (1992) The effects of plant density on shoot and leaf lamina angles in *Lolium multiflorum* and *Paspalum dilatatum*. *Ann. Bot.* 70, 69–73
4 Schmitt, J. *et al.* (1999) Manipulative approaches to testing adaptive plasticity: phytochrome-mediated shade-avoidance responses in plants. *Am. Nat.* 1, 154
5 Neilands, J.B. (1981) Iron absorption and transport in microorganisms. *Annu. Rev. Nutr.* 1, 27–46
6 Crosa, J.H. (1997) Signal transduction and transcriptional and posttranscriptional control of iron-regulated genes in bacteria. *Microbiol. Mol. Biol. Rev.* 61, 319–336
7 Denlinger, D.L. (1971) Embryonic determination of pupal diapause induction in the flesh fly *Sarcophaga crassipalpis*. *Macquart. J. Insect Physiol.* 17, 1815–1822
8 Chippendale, G.M. (1983) Larval and Pupal Diapause. In *Endocrinology of Insects* (Downer, R.G.H. and Laufer, H., eds), pp. 343–356, Alan R Liss
9 Denlinger, D.L. (1985) Hormonal Control of Diapause. In *Comprehensive Insect Physiology, Biochemistry and Pharmacology* (Kerkut, G.A. and Gilbert, L.I., eds), pp. 353–412, Pergamon Press
10 Schmalhausen, I.I. (1949) *Factors of Evolution*, Blakiston
11 Schlicting, C.D. and Pigliucci, M. (1998) *Phenotypic Evolution: A Reaction Norm Perspective*, Sinauer Associates
12 Marx, J.L. (1984) Instability in plants and the ghost of Lamarck. *Science* 224, 1415–1416
13 Cullis, C.A. (1988) Control of Variation in Higher Plants. In *Evolutionary Processes and Metaphors* (Ho, M-W. and Fox, S.W., eds), pp. 49–62, John Wiley & Sons
14 Cohen, D. (1966) Optimizing reproduction in a randomly varying environment. *J. Theor. Biol.* 12, 119–129
15 Bull, J.J. (1987) Evolution of phenotypic variance. *Evolution* 41, 303–315
16 Ptashne, M. (1992) *A Genetic Switch Phage λ and Higher Organisms*, Cell Press and Blackwell Science
17 Stewart, F.M. and Levin, B.R. (1984) The population biology of bacterial viruses: why be temperate. *Theor. Popul. Biol.* 26, 93–117
18 Mittler, J. (1996) Evolution of the genetic switch in temperate bacteriophage. I. Basic Theory. *J. Theor. Biol.* 179, 161–172
19 Hamilton, W.D. and May, R.M. (1977) Dispersal in stable habitats. *Nature* 269, 578–581
20 Smits, J.D. *et al.* (1996) Functional changes in the anatomy of the pharyngeal jaw apparatus of *Astoreochromis alluaudi* (Pisces, Cichlidae), and their effects on adjacent structures. *Biol. J. Linn. Soc.* 59, 389–409
21 Smits, J.D. *et al.* (1996) Differences between inter- and intraspecific architectonic adaptations to pharyngeal mollusc crushing in cichlid fishes. *Biol. J. Linn. Soc.* 59, 367–387
22 Pfennig, D.W. and Murphy, P.J. (2000) Character displacement in polyphenic tadpoles. *Evolution* 54, 1738–1749
23 Waddington, C.H. (1953) Genetic assimilation of an acquired character. *Evolution* 7, 118–126
24 Moxon, E.R. *et al.* (1994) Adaptive evolution of highly mutable loci in pathogenic bacteria. *Curr. Biol.* 4, 24–33
25 Frank, S. (2002) *Immunology and Evolution of Infectious Disease*, Princeton University Press.
26 Oliver, A. *et al.* (2000) Height frequency of hypermutable *Pseudomonas aeruginosa* in cystic fibrosis lung infection. *Science* 288, 1251–1253
27 Tenaillon, O. *et al.* (1999) Mutators, population size, adaptive landscape and the adaptation of asexual populations of bacteria. *Genetics* 152, 485–493
28 Miller, J.H. (1998) Mutators in *Escherichia coli*. *Mutat. Res.* 409, 99–106
29 Chao, L. *et al.* (1983) Transposable elements as mutator genes in evolution. *Nature* 303, 633–635
30 Matic, L. *et al.* (1996) Genetic barriers among bacteria. *Trends Microbiol.* 4, 69–73
31 Lederberg, J. and Iino, T. (1956) Phase variation in salmonella. *Genetics* 41, 743–757
32 Zieg, J. *et al.* (1977) Recombinational switch for gene expression. *Science* 196, 170–172
33 McKenzie, G.J. and Rosenberg, S.M. (2001) Adaptive mutations, mutator DNA polymerases and genetic change strategies of pathogens. *Curr. Opin. Microbiol.* 4, 586–594
34 Gillespie, J.H. (1972) The effects of stochastic environments on allele frequencies in natural populations. *Theor. Popul. Biol.* 3, 241–248
35 Gillespie, J.H. (1974) Polymorphism in patchy environments. *Am. Nat.* 108, 145–151
36 Gillespie, J.H. (1985) The interaction of genetic drift and mutation with selection in a fluctuating environment. *Theor. Popul. Biol.* 27, 222–237
37 Dempster, E.R. (1955) Maintenance of genetic heterogeneity. *Cold Spring Harb. Symp. Quant. Biol.* 20, 25–32
38 Haldane, J.B.S. and Jayakar, S.D. (1963) Polymorphism due to selection of varying direction. *J. Genet.* 58, 237–242
39 Turelli, M. *et al.* (2001) Stable two-allele polymorphisms maintained by fluctuating fitnesses and seed banks: Protecting the blues in *Linanthus parryae*. *Evolution* 55, 1283–1298
40 Levene, H. (1953) Genetic equilibrium when more than one ecological niche is available. *Am. Nat.* 87, 331–333
41 Gillespie, J.H. (1974) The role of environmental grain in the maintenance of genetic variation. *Am. Nat.* 108, 831–836
42 Frank, S.A. and Slatkin, M. (1990) Evolution in a variable environment. *Am. Nat.* 136, 244–260
43 Kerr, B. *et al.* (1999) Rekindling an old flame: a haploid model for the evolution and impact of flammability in resprouting plants. *Evol. Ecol. Res.* 1, 807–833
44 Jablonka, E. *et al.* (1995) The adaptive advantage of phenotypic memory in changing environments. *Philos. Trans. R. Soc. Lond. B* 350, 133–141
45 Lachmann, M. and Jablonka, E. (1996) The inheritance of phenotypes: an adaptation to fluctuating environments. *J. Theor. Biol.* 181, 1–9
46 Pfennig, K.S. (2001) Evolution of pathogen virulence: the role of variation in host phenotype. *Proc. R. Soc. Lond. Ser. B* 268, 755–760
47 von Dassow, G. *et al.* (2000) The segment polarity network is a robust developmental module. *Nature* 406, 188–192
48 Fontana, W. and Schuster, P. (1998) Continuity in evolution: on the nature of transitions. *Science* 280, 1451–1455
49 Ancel, L. and Fontana, W. (2000) Plasticity, evolvability and modularity in RNA. *J. Exp. Zool.* 288, 242–283