of many neurons of a particular class at a behaviorally relevant time frame [29,30]. Some day, these kinds of techniques might be able to test directly whether some of these circuit features underlie the capabilities that we consider peculiarly human. Cognitive capabilities — making judgments, formulating plans, making decisions — may use the same circuit features that are used for sensory processing, working on the abstracted information in the same way that sensory areas act upon primary sensory input. However, the important lessons of how to find function from form in neural circuits must be remembered or these new techniques won't give anything more than pretty pictures.

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Primer

Evolvability

Paul D. Sniegowski and Helen A. Murphy

Increasing numbers of biologists are invoking 'evolvability' to explain the general significance of genomic and developmental phenomena affecting genetic variation. What exactly is evolvability, and how important is it likely to be for our understanding of evolution? Definitions of evolvability are almost as numerous as the papers and books that have been written on the subject. All definitions agree that evolvability has to do with the capacity of populations to evolve — no surprise there. In actual use, however, evolvability can be a rather slippery concept with a variety of meanings and implications. The goals of this primer are to try to pin down some of the meanings of evolvability and to explain why evolvability is a controversial subject.

Evolvability and heritability

First, it is important to point out a basic way in which populations can vary in their capacities to evolve that is not controversial. A population with a large amount of heritable variation for fitness can certainly be considered more evolvable than one with very little heritable variation for fitness. Similarly, a population with a larger amount of heritable variation for a phenotypic character will respond more quickly to natural or artificial selection on that character than one with a smaller amount of such variation. Evolvability of this kind is central to our established quantitative genetic understanding of phenotypic evolution.

Evolvability and the generation of new variation

Most recent ideas about evolvability, however, focus on the capacity of populations to

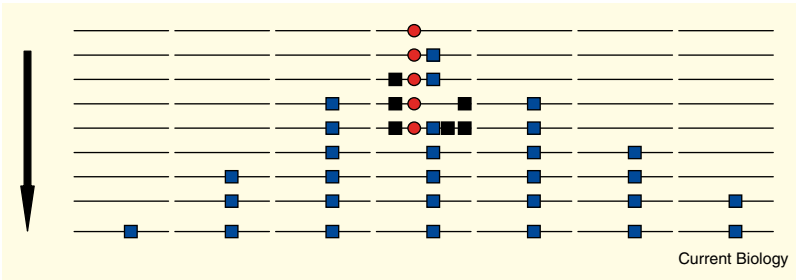

Figure 1. The population genetic problem with selection on evolvability.

A 'variability allele' (red circle) gives rise to a new beneficial allele (blue square) in the same genomic background. Because of recombination, the variability allele does not spread in the population along with the beneficial allele. Furthermore, because deleterious mutations (black squares) are far more common than beneficial ones, the variability allele occupies genomes that are more contaminated than average with deleterious mutations, and so it declines to very low frequency in the population.

produce new selectable variation, rather than on the amount of standing variation already present in populations. These recent ideas emphasise properties conferring intrinsic variability over static descriptors of variation. Implicit in this approach is a concern that the evolution of populations is limited by the rate at which new variation arises or by biases in the types of new variation that arise.

Researchers motivated by this concern argue that evolutionary theory has not adequately explained why populations possess sufficient intrinsic variability for long-term adaptation and phenotypic innovation. Accordingly, some have suggested that features such as elevated mutation rates, unusual mutational mechanisms and modular developmental programmes play major and previously unsuspected roles in facilitating evolution. It has even been proposed that the functional purpose of such features is to ensure an appropriate supply of variation for evolution: in the words of one recent author, that life has 'evolved to evolve'.

The problem of teleology

The idea that variability has been fine-tuned in order to maximize the evolutionary potential of populations is certainly controversial, although it is not new. The obvious reason to be suspicious of this idea is that it suggests a teleological view of evolution. Natural selection cannot adapt a population for future contingencies any more than an effect can precede its cause, so any future utility of the capacity to generate variation can have no influence on the maintenance of that capacity in the present. As Sydney Brenner supposedly remarked many years ago, it would make no sense for a population in an early geological period to retain a feature that was useless merely because it might "come in handy in the Cretaceous!"

Evolvability-as-adaptation?

Teleology need not be invoked to support evolvability arguments, however. A history of environmental uncertainty could favor a population with increased variability over others because such a population was more successful at adapting. One might call this the evolvability-as-adaptation hypothesis. This hypothesis is intuitively appealing, but it has its own set of problems. For one thing, it assumes that variability — the capacity to generate new variation — is generally limiting to population persistence and success in nature. This assumption lacks empirical support. Most natural populations have large amounts of standing genetic variation and do not necessarily depend on *de novo* variation in order to adapt to environmental change. Directly observed rates of short-term evolution in natural populations often far exceed those inferred from the fossil record, and this too implies that there is ample capacity for adaptation in response to selection in most populations. In short, there are grounds for doubting that the selective conditions necessary to favor increased variability are generally important in nature.

But even when conditions might favor increased variability, evolvability-as-adaptation is problematic. Because populations, not individuals, evolve and adapt, it follows that evolvability-as-adaptation must be the consequence of selection among populations rather than selection among individuals. Selection among populations is possible, in principle, but it is a very weak force compared with individual-level selection. Individual selection, in turn, is likely to oppose genome-wide increases in variability: an allele that increases the generation of new variation will not be selectively favored on its own merits within a population (barring any fortuitous pleiotropic effect it may have on individual fitness); instead, selection will affect its frequency as a consequence of its association with fitness mutations at other gene loci. A 'variability allele' may well cause more new beneficial variants to arise, but recombination — a nearly ubiquitous feature of living populations — will dissociate it from these variants and keep it from spreading in a population (Figure 1). Indeed, because most new variation affecting fitness is harmful, a variability allele will tend to occupy genomic backgrounds of lower-than-average fitness and will therefore be disfavored by natural selection.

Two fundamental population genetic factors thus oppose increases in variability: recombination, and the prevalence of deleterious mutations over beneficial mutations. Where these factors are weakened, the evolution of increased variability is more likely. Experimental and theoretical studies, for example, have shown that high genomic mutation rates

tend to evolve in strictly asexual populations, where 'mutator' alleles defective in genomic replication and repair processes can hitchhike to high frequency with beneficial mutations. It remains unclear, though, whether mutator hitchhiking represents evolvability-as-adaptation or is merely a byproduct of asexuality; in the long run, an elevated genomic mutation rate must be harmful because of the extra deleterious mutations it engenders.

A more convincing example of selection for evolvability is found in the so-called 'contingency loci' of microbial pathogens, where the effects of both recombination and deleterious mutation are mitigated. The immune system of a host can generate a relentless, dynamically specific, and lethal selective regime that favors rapid production of antigenic (as opposed to functional) novelty in a pathogen, and this has the effect of increasing the ratio of beneficial to deleterious mutations at antigen-encoding loci. Interestingly, unstable sequence features such as tandem repeats tend to be found disproportionately near and within such loci in pathogens, where they enhance variability and remain linked to new beneficial mutations. Contingency loci provide our best example of evolvability-as-adaptation, but their relevance to the general question of whether evolvability-as-adaptation is a major missing component of evolutionary theory seems rather limited.

In general, evolvability-as-adaptation has the same kinds of logical problems that G.C. Williams noted decades ago when questioning group-level selective explanations of animal behavior in his book *Adaptation and Natural Selection* (1966). Williams's injunction at the time to search for evolutionary explanations at no higher a level of biological organization than is necessary still makes sense, as does his memorable observation that "adaptation is a special and onerous concept that should be used only where it is really necessary".

Evolvability-as-byproduct?

If selection for evolvability is unlikely in most circumstances, does this necessarily mean that variability differences can have no effect on the evolution of populations? No: populations can differ in variability for reasons unrelated to selection on their capacities to adapt and evolve, and such differences could still have incidental effects on evolvability. One might call this the evolvability-as-byproduct hypothesis.

The distinction between the evolvability-as-adaptation and evolvability-as-byproduct hypotheses is well illustrated by contrasting interpretations of the biological significance of transposable genetic elements. Transposable elements are ubiquitous and have been discovered in almost all well-characterised genomes. Their replication, insertion, and recombinational activities produce mutations that can be quite different in their effects from those produced by simple errors in base incorporation during genome replication, and mutations induced by transposable elements contribute substantially to the genomic spontaneous mutation rate in some organisms. Barbara McClintock, the discoverer of transposable elements, argued that their biological purpose was to mediate the responses of genomes to stress and evolutionary challenge: this is an example of the evolvability-as-adaptation hypothesis. A more parsimonious alternative view — and one that has been well supported by studies of the population biology of transposable elements — is that these elements are parasitic DNA entities that are maintained, like all parasites, by virtue of their ability to replicate faster than selection can eliminate them from the host population. Populations with and without these elements might differ in their evolvability because of the distinct types of mutation they cause (evolvability-as-byproduct), but evolvability-as-adaptation need not be invoked to explain why populations harbour transposable elements.

There are many features of populations that may have incidental effects on evolvability. For example, it has been proposed that modularity in gene regulatory networks may have contributed evolutionary flexibility to development and facilitated the diversification of animal body plans. This idea was inspired in part by the previous observations of computer scientists that modularly structured evolutionary algorithm programs are more evolvable than nonmodular ones. Although the coding structures of evolutionary algorithms can be manipulated by programmers to ensure evolvability, genetic control over development is more likely to have been shaped and constrained by individual fitness effects than by its long-term consequences for taxonomic and adaptive divergence. Nonetheless, it is a reasonable hypothesis that modularity of developmental control has had important side consequences for the variability of animal populations. In another example, it has recently been proposed that prion activity in yeast, which can allow translational read-through of stop codons and hence the expression of novel variation, may enhance evolvability. Again, it is questionable whether prion activity represents evolvability-as-adaptation for the kinds of reasons discussed above, but it is plausible that prion activity has incidental effects on evolvability.

The problem of testability

In fact, it is rather easy to pile up examples of genomic and developmental features that may affect evolvability, and this is a bit troubling: How do we know when it is necessary — rather than just appealing — to invoke evolvability differences in order to explain evolutionary histories? The problem here is that the evolvability-as-byproduct hypothesis is probably correct in a very broad sense that tells us little we did not already know:

because newly arising variation modifies existing organismal blueprints, large differences between taxa imply differences in the kinds and amounts of new variation that can arise. The new variation immediately available to a metazoan population, for example, is obviously different from that immediately available to a single-celled eukaryote population. It follows that the evolvabilities of metazoans and single-celled eukaryotes are probably different at present, at least in the short term. It would be far more interesting, though, to know whether differences in evolvability explain in the first place why some single-celled lineages became metazoans whereas others remained single-celled, and this is a much more difficult problem.

Invoking variability as a retrospective explanation for why one clade has diversified or changed more than another does not rule out the possibility that the clades evolved differently for reasons unrelated to variability. And finding isolated examples of evolutionary novelties related to distinctive variability mechanisms — for example, mutations of major phenotypic effect caused by transposable elements — provides only anecdotal evidence for the importance of such variability mechanisms in evolution. As other commentators on evolvability have noted, there is a need for quantitative, testable predictions concerning evolvability rather than retrospective and anecdotal arguments. Approaches such as computer simulation and long-term experimental evolution may yield some progress in this direction because they allow direct manipulation and assessment of the effects of variability differences on evolution, but even these kinds of approaches may not provide dependable insights into whether and how variability differences have actually affected the evolution of natural populations.

Conclusion

Our knowledge of molecular mechanisms that affect the origin of variation in populations has grown very rapidly in recent decades; in contrast, our fundamental genetic understanding of natural selection developed before 1950 and has not changed in major ways since then. To some, this historical disjunction suggests that evolutionary theory cannot account for the origin and maintenance of mechanisms affecting variability and is overdue for major revision. It is indeed attractive to suppose that the most important evolutionary feature of organisms — their very capacity to evolve and adapt — is itself an adaptation, but this is probably only true in highly restricted circumstances. Instead, variability is probably most often a byproduct of the messy and intricate ways in which genomes have evolved. And the possibility that incidental differences in variability between populations have caused differences in evolvability with profound consequences for evolutionary history remains an interesting — but largely untested — hypothesis.

Further reading

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Neural basis of time changes during saccades

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Normal vision consists of periods of fixation (around 300 ms) interspersed with rapid eye movements called saccades. Saccades create special problems for the visual system, such as rapid, whole field motion across the retina and changes in the relationship between object positions in space and image positions on the retina [1]. Changes to visual processing occur around the time of saccades to cope with these problems. Two time-related phenomena resulting from this altered processing are perceptual time compression during a saccade and slight post-saccadic time expansion [2]. We show that neurons in visual areas of primate parietal cortex have reduced latencies to visual stimulation at the time of a saccade [3,4]. This observation provides a neural explanation for the time related perceptual changes.

Morrone *et al.* [2] demonstrated time compression of visually presented stimuli (but not of audible clicks) during saccades. They presented successive flashed visual stimuli to people and found that the inter-stimulus interval was underestimated if the flashes were presented slightly before or during a saccade. Observers underestimated a 110 ms interval by up to 60 ms. Interestingly, the precision of time estimations was increased during saccades, and for critical time intervals there was an inversion of time. The inversion was observed by asking subjects to report the temporal order of the flashed bars: observers consistently reported the second flash as