

The scale independence of evolution

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SUMMARY In this paper, I argue that the ultimate causes of morphological, and hence developmental, evolution are scale independent. In other words, micro- and macroevolutionary patterns show fundamental similarities and therefore are most simply explained as being caused by the same kinds of evolutionary forces. I begin by examining the evolution of single lineages and argue that dynamics of adaptive evolution are the same for bacteria in test-tube evolution experiments and fossil lineages. Similarly, I argue that the essential features of adaptive radiations large and small can be

attributed to conventional forces such as mutation and diversifying natural selection due to competition. I then address recent claims that the molecular features of metazoan development are the result of clade-level selection for evolvability, and suggest that these features can be more easily explained by conventional individual-level selection for the suppression of deleterious pleiotropic effects. Finally, I ask what must be known if we are to understand the ultimate causes of molecular and developmental diversity.

INTRODUCTION

Douglas Erwin and I have been given the unenviable task of revisiting a debate that has exercised the finest minds in evolutionary biology generation upon generation since the *Origin*, namely, the debate over whether or not the grand sweep of evolution visible to the comparative anatomist and paleontologist can be explained by the minute evolutionary effects visible to the naturalist and experimentalist. There are at least three reasons for revisiting this debate. First, our understanding of macroevolutionary patterns has altered considerably in recent years. We now know, for example, much more about the evolution of morphological disparity than we did even a few years ago, and what we know demands explanation. Second, comparative cellular and developmental biology has shown new classes of phenomena that equally require explanation (e.g., the deep homologies of signalling pathways), indeed, which have suggested the importance of new evolutionary forces (evolvability). Finally, our understanding of microevolutionary forces has shifted as a result of both technical advances (e.g., quantitative trait locus mapping, test-tube evolution) and conceptual ones (adaptive models, the role of clade selection).

The last is of particular importance. I shall not claim here that the array of traditional microevolutionary phenomena (mutations of small effect, individual-level selection) which were codified by the Neo-Darwinian synthesis of the 1940s are adequate to explain large-scale evolutionary patterns. Rather, I shall argue that our view of the forces that influence the evolution of populations is different now from what it

was even 20 years ago, to the extent of incorporating some aspects of what is traditionally macroevolutionary theory. However, I shall also argue that the forces that influence the evolution of populations, species, and higher taxa are fundamentally the same. In other words, evolutionary forces are scale independent. I shall also suggest that scale independence obtains in the adaptive evolution of single lineages, in cases of evolutionary radiations, and also perhaps in the evolution of developmental mechanisms. To do this, I shall draw upon recent results in population and developmental genetics and, most importantly, the relatively new discipline of experimental evolution.

HYPERBOLIC WALKS AND THE MUTATIONAL THIRD WAY

Twenty or so years ago, in the wake of Eldredge and Gould's controversial 1972 paper on punctuated equilibria, much ink was spilled debating the ability of standard microevolutionary (or Neo-Darwinian) mechanisms to explain the way in which individual lineages or populations appeared to evolve in the fossil record. At the heart of the controversy lay such questions as: What are the causes of rapid evolution? Can the substitution of individual mutations account for jumps in the fossil record? and Why are some lineages static for so long? (Eldredge and Gould 1972; Stanley 1979; Gould 1982; Charlesworth et al. 1982; Maynard Smith 1983; Turner 1983; Wallace 1985). Here I ask what we have learned about the evolutionary genetics of adaptation (and hence morphologi-

cal evolution) since the debate over these questions flared and died away.

I shall take it for granted that we now have good examples of gradual and rapid—sometimes punctuated—evolution over series of fossils with resolutions of 10^3 – 10^4 years, as well as stasis (Williamson 1981; Malmgren et al. 1984; Sheldon 1987; Gould and Eldredge 1993; Futuyma 1997)—though I shall offer no opinion as to the relative frequency of these modes. Of the various mechanisms that have, at various times, proposed to explain rapid evolution in the fossil or phylogenetic record, none has been so consistently controversial as the claim that they are caused by the fixation of alleles of large effect—macromutations (e.g., Goldschmidt 1940; Stanley 1979). In general, population geneticists have argued that, a few cases such as mimicry in butterflies and warfarin resistance in rats aside, alleles—many alleles—of small effect are the stuff of phenotypic evolution (e.g., Charlesworth et al. 1982; Wallace 1985). This is for two reasons. First, the abundance of variation segregating natural populations, and the ability of mutation to keep this topped up even as it is exhausted by natural selection, means that there is simply no need to invoke a special class of large mutations to explain morphological evolution. Second, alleles of large effect are more likely to be deleterious than those of small effect, thus making the former poor candidates for major evolutionary roles.

While the abundance of genetic variation in natural populations cannot be doubted, recent theoretical and empirical work suggests that a more nuanced view of the genetics of morphological, and adaptive, evolution is required than given by either the macromutationists or their critics. To begin with, the claim that alleles of large effect were unlikely to have a role in adaptation was based upon R. A. Fisher's demonstration that if an organism was envisioned (rather abstractly) as a collection of orthogonal traits, then very small random changes in those characters would tend to be advantageous 50% of the time, while large mutations would be very rarely so (Fisher 1958; see Orr 1998 for an especially clear explanation of this). This result was widely interpreted as demonstrating that mutations of large effect would, therefore, have a low probability of fixation. But, as Kimura (1983) pointed out, this is not so since when favorable mutations of large effect do occur—however rare they might be—they should tend to be fixed more often than small ones. In an important study, Orr (1998) has recently gone beyond Fisher's and Kimura's model to show that the distribution of alleles that are fixed in an adaptive walk to an optimum is actually a negative exponential. To be sure, many alleles of small effect are fixed, but so, quite often, are large ones. What is more, as a population evolves, selection often tends to pick out and fix alleles of large effect first and smaller ones later, so that the rate of evolution is at first fast, but then slows down. There is a hyperbolic walk to the optimum.

Orr's model also suggests an explanation for the results of quantitative trait locus studies on the adaptive differences (be they morphological, physiological, or behavioral) between species, which tends to suggest that the alleles that are fixed between species have surprisingly large effects (Bradshaw et al. 1995, 1998; Laurie et al. 1997; True et al. 1997; Voss and Shaffer 1997; Jones 1998; Stern 1998) and that these effects are larger than those found segregating within species (Laurie et al. 1997). One of the most striking of these results is the Voss and Shaffer (1997) confirmation that the difference in life-cycle between the paedomorphic Mexican axolotl and its metamorphic relative is largely controlled by a single quantitative trait locus. Having said that, several caveats surround the interpretation of such results. First, when evolutionary geneticists speak of mutations of large effect, they generally do not mean systemic macromutations of any description (see Stanley 1979), but rather mutations with an easily detectable effect which account for a sizeable fraction of the total phenotypic variance (see Laurie et al. 1997). Second, most of these studies have not yet identified causal loci, but rather quantitative trait loci: not only are large quantitative trait loci easier to detect than small ones, but a given quantitative trait locus may conceal the effects of more than one locus. A third, more subtle issue, is that even if we could, as perhaps with *Ambystoma*, attribute a difference between species to a single allele of large effect, we do not know whether this allele is not merely the latest in a succession of weaker alleles at the same locus (Voss and Shaffer 1997; Carroll 1995). In other words, the evolution of a trait can erase its own genetic past. Fourth, it remains true that there are few studies on the genetic basis of species differences (there are more on differences among cultivars). But we can say that the genes responsible for differences among species show a wide range of effects, and that the distribution of their effects is often roughly a negative exponential, not, as Fisher supposed, uniformly, vanishingly small (Orr and Coyne 1992; Orr 1998).

Can, then, the substitution of a single allele in the course of a lineage's evolution give rise to morphological punctuation? Perhaps. Laurie et al. (1997) showed that several quantitative trait loci on the third chromosome could each account for 10–15% of the difference in genital morphology between *Drosophila simulans* and *Drosophila mauritiana*. They calculate that the substitution of any one of these alleles might be sufficient, by itself, to give a population whose phenotypic distribution barely overlapped that of its ancestor. Bearing all the earlier caveats in mind, this is comparable to the kinds of differences seen in punctuated events in fossil lineages. At the height of the punctuated equilibrium controversy, Maynard Smith (1983) and Turner (1983) made much the same point; it can be now made with greater force. Of course, whether a given punctuation is attributable to the substitution of one or many alleles (or merely phenotypic plasticity) is a moot point, but these results do confirm the hope that the molecular basis of species differences can be identified.

Quantitative trait locus studies aside, the other major empirical advance in the genetics of adaptation comes from test-tube evolution experiments in which populations are followed for thousands of generations and in which many of the phenomena of macroevolution can be studied. In what is now the most famous (and certainly the lengthiest) of all microbial selection experiments, Lenski et al. (1991) established 12 replicate populations of *Escherichia coli* from a single clone and permitted them to adapt to a novel laboratory regime. Each population underwent about six generations of binary fission per day; by 1994, they had undergone 10,000 generations of evolution in their novel environment—and the experiment continues. These populations have allowed the detailed study of the roles of adaptation, contingency, and history in determining evolutionary trajectories (Travisano et al. 1995); they have also allowed a good look at stasis.

Lenski et al. (1991) studied the evolution of fitness itself. They did this by competing the evolving strains against their ancestors (which were stored deep frozen) at regular intervals. In the first 2000 generations of evolution, these populations improved their fitness in their new environment by 30%. Between generations 2000 and 5000 they gained another 10%; in the next 5000 generations they gained only 2%—not quite stasis, but getting there (Lenski et al. 1991; Lenski and Travisano 1994). In fact, the pattern of evolution shown by these populations is the hyperbolic adaptive walk predicted by Orr's (1998) model, the assumptions of which (a haploid creature forced to adapt to a novel environment by means of novel mutations) are met closely by Lenski's experiment. What is more, a morphological trait, cell size, shows a very similar pattern (Fig. 1) (Elena et al. 1996). So why does evolution slow down in the *E. coli* populations? The most obvious explanation, that they simply run out of genetic variation per se, cannot be true. Although the experiment began with a single clone, the huge population sizes ($\sim 5 \times 10^8$) ensured that each population contained about 10^6 new mutations each day. Their ability to still produce useful mutations was proved when, at generation 2000, subclones were placed in yet another (high temperature) environment, to which they promptly adapted with great speed (Bennett et al. 1990). But in their own environment, it seems that evolution was grinding to a halt because they were simply approaching an optimum: nearly all the single mutations that would confer substantial fitness advantages had been already used up; what was left was either deleterious, neutral, or only very weakly beneficial.

Is this kind of evolutionary dynamic found in natural populations? For some paleontologists (Eldredge and Gould 1972; Jablonski 1999), the long periods in which fossil lineages showed no evolution is due to genetic homeostasis or developmental buffering. The nature of such mechanisms is usually left rather mysterious, and there does not seem to be

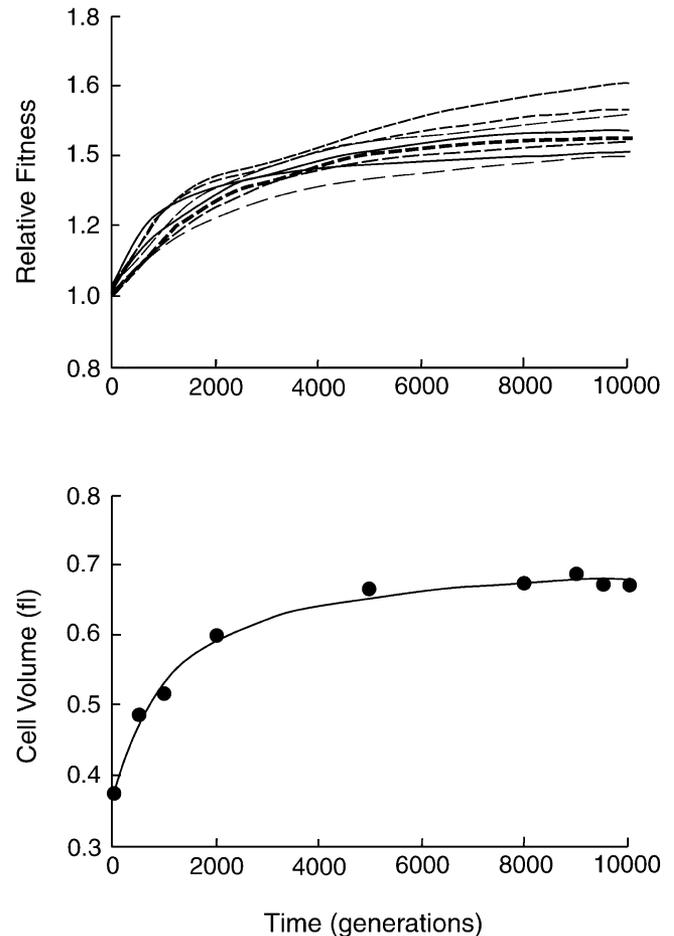


Fig 1. Hyperbolic adaptive walks in bacterial evolution. (A) Competitive fitness of 12 evolved strains relative to their single common ancestor over the course of 10,000 generations of evolution in a novel environment. (B) Cell size of one of these strains over the same time period. After Lenski and Travisano (1994).

any evidence for them. On the contrary, there is abundant evidence that natural populations can respond very rapidly to selection when presented with new selective challenges (Charlesworth et al. 1982; Endler 1986; Williams 1992). In what is, perhaps, the best of such studies, Reznick et al. (1997) transplanted two natural populations of guppies to pools where they experienced novel predation regimes. The guppies responded to their new homes by evolving at rates that varied between 3700 and 45,000 darwins (depending on the trait and population), rates comparable to those seen in artificial selection experiments, and many orders of magnitude faster than those seen in the fossil record. Strikingly, even this short period of time was enough to show convergence to an evolutionary optimum, at least in males which, in one population, ceased to evolve after about 4 years. Hyperbolic adaptive walks are also the simplest (but not the only) explanation for Gingerich's (1983) observation that

rates of evolution are related to the time interval over which they are measured by a negative exponential function.

The gap between the time scales of even the lengthiest studies on living populations and even the most finely resolved of studies on fossil populations is such that we shall never be able to extrapolate from one to the other with perfect confidence. Even so, it is now difficult to avoid the conclusion that the effects of natural selection acting on a single lineage are sufficient to account for variation in evolutionary rates seen in the fossil record, and that other mechanisms such as genetic homeostasis, speciation or species selection are not required.

RADIATIONS OLD AND NEW

Here I wish to consider some of the causes of organic diversity, and the evidence for their action. I am especially interested in evolutionary radiations: those occasions when we see an especially remarkable flourishing of organic forms within a relatively short period of time. It is only recently that rigorous phylogenetic methods have been used to identify such radiations (Sanderson and Donoghue 1996), but even so there are enough striking cases to convince us that bursts of diversification have been a constant feature of life throughout the Phanerozoic. Some radiations have given rise merely to species flocks and genera (e.g., Mbuna cichlids; Albertson et al. 1999); others have given rise to new families and orders (e.g., Cenozoic Mammals; Hunter and Jernvall 1995), and then there is the most interesting putative radiation of all: the one that gave rise to the 30-odd extant phyla. Some (Gould 1989; Arthur 1997; Gerhart and Kirschner 1997) have argued that this last radiation must have been somehow different from other radiations that succeeded it. Three reasons have traditionally been given for this: that as far as a literal interpretation of the fossil record goes, the metazoan radiation occurred in a very short period of time, 5–30 million years, depending on whether or not you count certain Ediacaran creatures in (Fortey et al. 1996; Conway Morris 1998a, 1998b); that it gave rise to an enormous diversity in form, that is, highly disparate taxa (sensu. Gould 1989) which we now recognize as phyla and classes; that this flourishing of disparate taxa was at first associated with low diversity (numbers of families, genera, species), but then followed by an Ordovician burst of diversity, as for the most part, it has ever since (Conway Morris 1998b). I consider each of these arguments in turn.

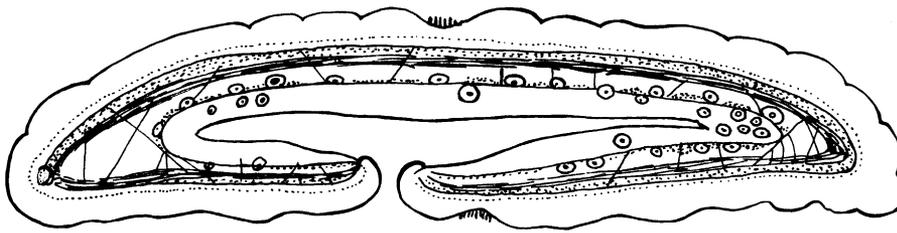
Of these three arguments, the first—rapidity—appears increasingly weak; several lines of evidence, molecular and paleontological, suggest that the Cambrian explosion was preceded by a long period of cladogenesis in which the modern phyla diversified as microscopic creatures, as yet lost to the fossil record (Fortey et al. 1996, 1997; Knoll and

Carroll 1999; Valentine et al. 1999). Wray et al. (1996) claimed a 1.2 bya date for the triploblast radiation on the basis of molecular clock data; more recent studies tend to support a younger date of about 630 mya (Lynch 1999), but even that leaves another 100 million years of potential cladogenic time before the radiation is fully seen in the fossil record.

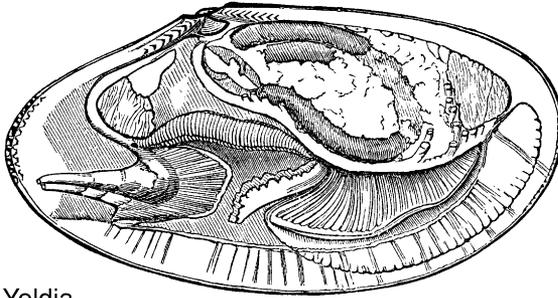
The empirical core of the second argument—great disparity—is certainly true. Were someone to quantify metazoan disparity, either in adult body form (Baupläne) or at particular developmental stages (Phylotypes) we would certainly find that greater numbers of highly disparate taxa appeared in the mid-Cambrian than have since (e.g., Wills et al. 1994 for arthropods). But does this mean that no highly disparate taxa have been produced since? Are all Baupläne and Phylotypes ancient? Clearly not. As Richard Strathmann sardonically observed some years ago, were the cyprid larva of the Rhizocephalans not known, they would, for their bizarre adult body forms, be surely placed in a phylum of their own, yet they are derived from the prosaic barnacle (Hoeg 1992). Perhaps an even better example is provided by that mysterious worm *Xenoturbella*, which has been variously placed among the platyhelminthes, the holothuroids, the enteropneusts, or simply by itself (Nielsen 1995; Ax 1996). Recent molecular, developmental, and ultrastructural evidence suggests that it is a Nuculid clam (Fig. 2): just sans shell, sans gills, sans foot, in fact, sans just about anything that make it recognizably a mollusc (Norén and Jondelius 1997; Israelsen 1999). Examples like these suggest to me that the claim that the Cambrian (or Vendian) was uniquely capable of producing very disparate taxa is simply wrong; it just happens to be where most of them first cropped up.

The third line of evidence for the uniqueness of the Metazoan radiation—the initial lack, but subsequent expansion, of diversity—seems also to be a robust pattern (Conway Morris 1998b). But in this the Metazoan radiation differs from other radiations only in magnitude, not in kind. Recent studies have shown that an early flourishing of disparity, followed by a filling in of many, more similar forms, is a very common feature of radiations as diverse as Cambrian arthropods and Cenozoic ungulates (Foote 1997 for a review). It is probably true for Mbuna cichlids as well. A recent molecular phylogeny shows that the disparity in jaw and tooth morphology upon which Mbuna genera are based antedates the enormous diversity of coloration which distinguishes species (Albertson et al. 1999).

To sum up, the radiation that gave rise to the Metazoa is remarkable only for its magnitude and subsequent global impact upon the history of life; however, its essential features do not differ from more modest and recent radiations. If so, then we have no reason to believe that the general causes of the Metazoan radiation differ from those of others. This brings us to the vexed question of just what the necessary and sufficient causes of adaptive radiations—whatever their



Xenoturbella



Yoldia

Fig. 2. Evolution of a new clam Bauplan. *Xenoturbella* (mid sagittal top), an obscure free-living marine worm, has a simple organization strongly reminiscent of a flatworm. Yet it appears to be closely related the nuculid clams such as *Yoldia* (lateral view below)—clear evidence that post-Vendian metazoa have not lost their capacity to generate radically new morphologies. After Ax 1996 and Woodward 1890, respectively.

scale—are. To circumscribe this immense topic is impossible, so I shall consider just three causal factors: the genetic basis of radiations, the role of competition, and, in the next section, the role of evolvability.

It is sometimes suggested that the genetic basis of the Metazoan radiation was, in some fashion, qualitatively different from those of others. Arthur (1997) argues that early metazoan lineages tended to produce or at least fix mutations that were different in magnitude and kind from those that were fixed in lineages that arose later, being larger in effect, and acting earlier in development. After the Cambrian explosion, animals were more integrated, early mutations of large effect were more likely to be deleterious, and so it is that we no longer see the evolution of radically disparate forms. This argument has several components, and I confess that I find myself more sympathetic to at least some of them than previously (Leroi 1998).

Were mutations of large effect fixed early in the Metazoan radiation? Perhaps. Orr's (1998) results on the distribution of mutational effects fixed in the course of an adaptive walk, suggest that this might be a general property of the early phases of adaptive radiations. The decline in the size of the mutations fixed seen in his model is not, however, due to the increasing integration of the evolving taxa (that is, resistance to mutation per se) but rather simply arises from the dynamics of selection as an optimum is approached. Indeed, as I shall discuss below, there seems to be very little evidence that any organ or developmental stage of any modern organism cannot readily respond to selection as it might have in the Vendian. I would ask those who doubt this to reflect upon *Xenoturbella*.

Were mutations with an early effect upon development

more commonly fixed at the start of the metazoan radiation? This seems plausible if, as is commonly asserted, adult disparity is the result of changes in early (or mid) development and if that is when metazoan disparity indeed evolved. The picture is, however, blurred by the clear evidence that early ontogeny has continued to evolve, in various taxa, throughout the Phanerozoic (Raff 1996; McHugh and Rouse 1998). Thus if any developmental stage was uniquely vulnerable to mutations at the start of the metazoan radiation, it can only be the phylotypic stage. The empirical existence of phylotypic stages seems, however, uncertain. While fairly conserved stages do exist in vertebrates and arthropods (the pharyngula and the germ-band stages, respectively), a uniquely conserved stage has not been demonstrated for most phyla and probably does not exist for many (e.g., the Mollusca whose early and larval development—clams to cephalopods—seem to show no universal themes.) Even the vertebrate pharyngula is, at best, only a weakly conserved stage (Richardson 1999). But all these arguments are merely anecdotal. There is great need for studies that rigorously quantify embryonic, larval, and adult disparity throughout the span and depth of metazoan history; only when such studies have been done will we be able to infer, however tenuously, that particular kinds of mutations were especially important at one point in metazoan history but not another.

At the heart of the classical theory of adaptive radiations is the idea that competition among newly evolved species is responsible for diversifying natural selection and so the rapid evolution that is the hallmark of such radiations (see Schluter 1996 for a review). The role of competition in accounting for morphological disparity has long been controversial, the evidence for it indirect (Grant 1994), and for some radiations,

such as the metazoan, probably unobtainable. However, two recent experimental studies have demonstrated directly how competition can very quickly bring about rapid morphological divergence. The first of these concerns the three-spine sticklebacks (*Gasterosteus aculeatus* complex), which inhabit a series of small Canadian lakes. Each lake has a pair of stickleback species which differ in habitat (benthic vs. limnetic), diet (littoral invertebrates vs. plankton) and morphology (large bodies with big mouths and few gill rakers versus small bodies with small mouths and many gill rakers) (Schluter 1996). Much indirect evidence suggests that these species pairs have evolved independently and that the differences between them are due to competition. For example, in the occasional lake which contains only one stickleback species, the form and habits of the fish are intermediate to the benthic/limnetic species of other lakes—classical evidence for competitive displacement. But now there is direct evidence for the role of competition in driving this radiation. In an elegant experiment, Schluter (1994) raised a solitary species in experimental ponds and showed that its growth was strongly reduced in the presence of a limnetic competitor. Critically, he also showed that those fish with phenotypes most similar to the competitor suffered most; in other words, the competitor caused diversifying selection of the type predicted by classical theory.

Although this experiment clearly demonstrated selection, it took place over only one generation and so did not show evolution. To see adaptive radiations form before our eyes, we have once again to turn to microbes. The 10,000 generation experiment of Lenski et al. (1991) demonstrated how rapidly fitness can increase when bacteria are exposed to a new environment, but did not show much evidence of adaptive divergence between genotypes within a population. This was certainly because the environment in question had no spatial structure: it was a liquid culture kept homogenous by shaking. In such an environment there may be only one optimal genotype at any given time which will sweep to fixation. What happens if, as in the real world, there is spatial structure? Rainey and Travisano (1998) introduced a single genotype of another bacterium, *Pseudomonas fluorescens*, to liquid cultures that were either still or shaken. As in *E. coli*, the shaken cultures did not evolve any diversity (as detectable by colony morphology when plated on agar). The still cultures, however, invariably evolved at least three different forms within 10 days which then persisted. What is more, each of these different forms occupied, and adapted to, a different part of their little biosphere (a 25 ml beaker): one was a bottom dweller, another formed a mat at the surface, another was somewhere in between. This sort of niche partitioning suggested to Rainey and Travisano that diversifying natural selection maintained the existence of these morphs. Uniquely, they did a series of competition experiments which directly demonstrated frequency-dependent selection

between the morphs of the sort that can maintain their stable existence.

The forces demonstrated by this experiment are precisely those which have been classically thought to be responsible for adaptive radiations. There is even some evidence that this experiment replicates, in miniature, one of the most striking features of adaptive radiations in the wild: the tendency of disparity to evolve early in the radiation, and high diversity later on. In the still cultures, other morphs similar, but not identical, to one of the three that evolved first, start popping up after 10 days of evolution—possible evidence of yet further niche subdivision (Rainey and Travisano, 1998; Rainey personal communication). This experiment fails to mimic real radiations in only one respect: since the bacteria are clonal, evolutionary divergence does not require speciation. I now turn to roles of speciation, clade selection, and evolvability in adaptive radiations in general, and the metazoan radiation in particular.

FLEXIBLE, BUT NOT SO ROBUST

Like the processes that bring about adaptation in single lineages, and the form of adaptive radiations, clade selection is scale independent. That is, we may speak of the differential birth and death of the most ephemeral of local populations, species, phyla, or even kingdoms (Williams 1992). Clade selection may work in several ways. Most simply, a trait (breeding system, habitat) may directly influence the probability that a clade will give rise to a new clade or else go extinct. There are at least a few reasonably well supported examples of both, for clades of various degrees of antiquity and taxonomic level (see examples in Williams 1992; Hunter 1998). The best cases give a simple way in which the trait in question influences clade topology. For example, up until very recently, Lake Victoria contained about 300 species of Haplochromine cichlid possessed of enormous diversity in morphology, appetites, habitat, and color. But there were other fish as well, including one species of catfish, one sardine, and one lungfish. All these fish have been in the lake since it last dried up, about 12,400 years ago (Martens 1997); the cichlid flock, being monophyletic, is thought to have evolved since then. Why have the cichlids radiated where the sardine, catfish, and lungfish have not? Several explanations have been offered for this, but the most promising seems to be that it has something to do with their breeding habits: Haplochromine cichlids have elaborate courtship behaviors which might well diverge rapidly in allopatry (when lake levels are low and populations cut off) and, then, they mouthbrood their young, which tends to promote philopatry (Dorit 1990; Goldschmidt 1998). These habits seem to be a recipe for easy speciation which the sardine, at least, lacks, having no courting habits and planktonic young. It's notable

that the best case we have of sympatric speciation comes from another cichlid species flock in West African crater lakes (Schliewen et al. 1994).

A rather more subtle, and indirect, form of clade selection is that which is thought to be due to key innovations. Here, a trait does not directly influence the proliferation and extinction rate of branches in a clade, rather it influences the rate of (typically) morphological evolution by unlocking previously hidden potential, and this in turn promotes the evolutionary success of the clade by permitting specialization, the invasion of new habitats and the like. This is a much weaker kind of clade selection since it relies on repeated bouts of individual-level selection to promote disparity which may eventually bring about differential birth or death of clades. The most convincing case is probably Hunter and Jernvall's (1995) claim that the hypocone, a kind of mammalian tooth cusp, permitted the evolution of various specialized teeth in mammals, and so the many radiations of herbivores in the Eocene. Unlike virtually all previous attempts to identify key innovations (e.g., Liem 1974), this study has the virtue of showing how a trait that evolved repeatedly (20 times), repeatedly permitted further morphological evolution, and was then repeatedly associated with high diversity; its ability to persuade lies in the numbers.

This example is worth a closer look. To begin with, the hypocone (like mouthbrooding in cichlids) must have been fixed in various lineages by individual-level selection. This structure then influences the distribution of mutational effects, such that some kinds of tooth mutations are either possible, or else advantageous, in these lineages, where they are either impossible, or else disadvantageous, in lineages which lack hypocones. In genetic terms, hypocone genes interact epistatically with other novel tooth mutations altering either their gross phenotypes or fitness. These novel mutations are then the basis for further evolution, again, by individual level selection, and are the basis of teeth not possible in hypoconeless lineages, a variety which then promotes increased rates of speciation (perhaps by permitting the invasion of new habitats—grasslands in this case) or else immunity from extinction. That this process can, and probably has, worked seems clear. But it's a long road from hypocones to the evolutionary success of Eocene grazers.

The hypocone, in current jargon, is a structure that confers evolvability. Note, that it did not evolve for its future influence on clade success; it evolved for the immediate benefits that it conferred. Kirschner and Gerhart (1998) seem to have something similar in mind when they suggest that certain properties of metazoan development were responsible for the evolutionary success of the metazoa, or the relative success of particular phyla. But they go further and argue that evolvability itself has evolved. The traits that they propose confer evolvability are nothing so concrete as the possession of a hypocone, but are instead rather general: a development

that has flexibility, robustness, redundancy, compartmentation, and a host of other abstract nouns.

To see what Kirschner and Gerhardt mean by these terms, I shall give just one of their examples. Sensory Organ Precursor (SOP) cells in *Drosophila* form bristles; the location of SOPs is exquisitely controlled, first by a host of positional signals dependent on the familiar signalling molecules such as Dpp, Hh, Wg, as well as intracellular Hox levels, and, second by a Notch-Delta-dependent lateral inhibition system; the actual differentiation of the bristle from SOPs involve yet other genes. This system is said to show compartmentation of two types: the multiple controls ensure that SOP formation in one part of the body is spatially compartmentalized from SOP formation elsewhere; SOP formation is also temporally compartmentalized from bristle formation. Now, Kirschner and Gerhardt clearly recognize that bristles are under individual level selection (they are, after all, sensory organs). But it is the way that they are made that is important. For them, "a system with such great flexibility of use in one individual would seem exquisitely suited to generate, by modest mutation, different patterns in different individuals in evolution" (Kirschner and Gerhart, 1998). That is, the particular specification mechanisms of bristles is not just the result of evolutionary change, but exists in order to facilitate it. This same reasoning is then applied to just about any feature of metazoan cell and developmental biology (eucaryote transcription, regulation by calmodulin, the existence of gene clusters, etc). At all levels of organization, those clades which were the most flexible, robust, etc. were the most successful; those that were less so, lost out.

The evolvability hypothesis attempts to explain the major features of metazoan development by repeated clade selection, a mechanism that is logically possible, but also far weaker than individual-level selection. It also seems untestable. This is for two reasons. First, because the properties in question are so all encompassing and ill defined there is no way of assessing whether one clade has more of them or fewer, or possibly none at all. The fungi are, perhaps, the sister group to the Metazoa, but there are only 50,000 nominal species of them, against the more than 1,000,000 animals. Is this because the development of *Aspergillus* is less flexible-robust than that of *Drosophila*? It is difficult to know how to begin to answer such a question. Worse, many of the properties identified by Kirschner and Gerhart are held by them to be unique to Metazoa, and so their evolutionary roles cannot be tested by the comparative method. You may as easily assert, without fear of contradiction, that the success of the animals is due to their having hydroxyproline (a more old fashioned hypothesis reviewed by Erwin 1993, who makes a similar point).

Of course it is possible to make testable hypotheses about the contribution of some genomic or developmental property

to the relative success of particular clades. For example, Gerhart and Kirschner (1997, p. 605) propose (in the absence of data) that the evolutionary conservatism of the priapulids is due to their possessing an inadequate number of Hox genes. We now know this is not so. In fact, priapulids seem to have more Hox genes than their close relatives, the superbly speciose nematodes (de Rosa et al. 1999). Since earlier studies have also shown no relation between Hox-cluster size and morphological complexity or species diversity (Meyer 1998), this should come as no surprise. Although the importance of Hox genes in nematode, arthropod, and vertebrate development is undisputed, they seem rather remote from the factors that immediately influence clade diversity and disparity: ecological opportunity, breeding system, mass extinctions, and the like. For this reason, I suspect that searches for associations between any genomic feature (except perhaps ploidy) and clade diversity and disparity are likely to be futile.

If the features of Metazoan development that impress Kirschner and Gerhart as being selected for evolvability can be explained by individual level selection, then their elaborate and weak mechanism should be discarded. In the next section, I shall outline why this is so.

THE ROAD FROM SERFDOM

That Metazoan development is compartmentalized at various levels has long been recognized by the term modularity (Raff 1996; Wagner and Altenberg 1996 for history). Gerhardt and Kirschner are not the first to propose that modularity might be due to clade selection for evolvability (see Dawkins 1996; Wagner and Altenberg 1996) but there are no formal models which might demonstrate the efficacy of the process. Another kind of explanation, also invoked by Kirschner and Gerhart, is that modularity reduces the rate at which deleterious mutations arise. This is a variant of an old idea: the evolution of genetic canalization to mitigate the effects of deleterious mutations. But this is also likely to be a very weak force since purifying selection tends to eliminate deleterious mutations anyway (Wagner et al. 1997). To explain modularity, however, we would like a vigorous and general type of selection pressure.

One of the features of genetic systems is that they are despotic. That is, as they evolve, they frequently assert control over parts of an organism which, had it the choice, it would far prefer were left alone. Trade-offs are an example of this: selection for increased longevity in *Drosophila* occurs at the expense of another fitness component, early fecundity (Leroi et al. 1994a); there are innumerable other examples (Stearns 1992). The despotic nature of genetic systems is usually the result of pleiotropy; and when pleiotropic effects upon fitness are opposed (antagonistic pleiotropy), then the response

to selection is determined by the balance of the antagonistic effects—the net fitness of an allele is what matters, regardless of the contribution of particular pathways, organs, fitness components, etc. As in the above example, trade-offs are generally identified by their contrary effects upon fitness components, but one may equally speak of a trade-off between, say, running speed and endurance in lizards. It might be said that trade-offs due to antagonistic pleiotropic effects are a manifestation of an insufficiency of modularity, or, to use Kirschner and Gerhart's term, strong linkage between pathways, organs, and fitness components, when weak linkage would be desirable. And while trade-offs (or antagonistic pleiotropy) are often thought to be immutable, a genetic or developmental constraint, over the long evolutionary run this obviously cannot be true. I propose, then (with surely no great originality) that modularity arises from the breaking of the genomic despotism of antagonistic pleiotropy by means of epistatic suppressors.

Here is a simple example. Pseudocentipedes, a fictitious taxon, have many identical pairs of appendages that run the length of their bodies, and no positional information system by which one pair may be differentiated from another. There is selection upon appendage length, but it is in opposite directions in different parts of the body. Anteriorly, short appendages are desirable (to feed with), while posteriorly, long appendages are wanted (for locomotion), but since all appendages are controlled by a common despotic mechanism, the evolution of appendage length will depend on the balance of these conflicting selection pressures. That is, any allele that influences appendage length will have antagonistic pleiotropic effects upon fitness. We can see that any mutation which breaks the genetic association between anterior and posterior appendages, that is, which suppresses the deleterious pleiotropic effect, would be strongly selected. Such a mutation would be, in effect, the beginnings of an anterior–posterior positional information system, and a modular organization where there was none before.

The evolutionary process that I have described for Pseudocentipedes is a common one. There are at least two, perhaps three, examples of how antagonistic pleiotropic effects—which are ubiquitous—have become suppressed in the course of evolution. The first comes, again, from microbes. Lenski (1988a) isolated a series of mutations in *E. coli* that conferred complete resistance to T4 phage. In the absence of T4, all had low competitive fitness compared with their T4-sensitive ancestor; thus there was an antagonistic pleiotropic effect between fitness with and without the phage, though for some mutants this effect was severe, in others less so. Lenski (1988b) then showed that if these T4-resistant strains were evolved for 400 generations in the absence of the phage, they swiftly regained the fitness that they had lost in becoming resistant, what is more, they did so without losing phage resistance itself. Thus the elimination of the antagonistic pleiotro-

pic effects of phage resistance was accomplished not by reversion, but by the evolution of epistatic modifiers—partial suppressors. The second example is a very similar case involving the evolution (in the wild) of modifiers of the deleterious pleiotropic effects of diazonin resistance in blowflies. Here, a resistance allele appears to have the pleiotropic consequence of increasing fluctuating asymmetry in the wings, a deleterious trait which seems to have resulted in the evolution of a modifier allele at another locus which decreases asymmetry without reducing resistance (McKenzie and Batterham 1994). Perhaps a third example comes from the evolution of mimicry in butterflies. In the Müllerian mimicry ring formed by *Heliconius*, it is clear that selection first acts to fix mutations of large effect that cause the mimics to have wing color patterns that generally resemble each other, and that these are then followed by a series of further substitutions that refine the pattern (Turner 1983). As in the other examples, further evolution suppresses part of the phenotypic effect of the initial adaptation. It is just that in this case there is no evidence that the suppressed effect is antagonistic (it need not be, it could be weakly advantageous, but the modifier even more so).

Even though we know little about the molecular basis of the main adaptations (T4 resistance, diazonin resistance, or wing pattern), much less their modifiers, in each case it is clear that these organisms have become more modular: one part of the phenotype has become disassociated from some other part. Were we able to see the molecular causes of this disassociation, we would see some level of regulation that was not there before, or not utilized to such an extent. Perhaps this will soon be possible. The main blowfly resistance gene (*Rdl-1*) has been identified as a GABA receptor/chloride channel gene and the modifier is thought to be *Scalloped Wings*, a *Notch* homolog. How these particular alleles interact to partition diazonin resistance from wing shape is still, however, unknown (McKenzie and Batterham 1994).

The search for freedom from despotic genomic control should occur just about everywhere. The cumulative effect of that search, over much time and at many levels, would be to give organisms flexibility, robustness, weak-linkage, compartmentation, etc., in short, all the features that Kirschner and Gerhart assert have been selected for their evolvability. Nevertheless, I make no claim that some critical liberating step was responsible for the rise of the Metazoa or any other taxon. Nor, I think, is it possible to say whether we should expect complexity or versatility or modularity to generally increase in evolution (see Vermeij 1974; Bonner 1988; McShea 1998) for there are certainly other selective forces that favor integration and simplification (Arthur 1997). Even if such trends could be demonstrated, they would be consistent with many different selective forces (e.g., evolvability or selection for efficiency by the division of labor; see Bell and Mooers 1997).

THE SCALE OF DEVELOPMENTAL EVOLUTION

In this paper, I have argued that the adaptive walks which *E. coli*, guppies, and lineages of fossil snails show in response to new environmental challenges are fundamentally alike. I have also argued that the adaptive radiation of *Pseudomonas* in a beaker, Cichlids in Lake Malawi, and the Metazoa in the Precambrian seas share important features and causes. Finally, I have argued that the features of developmental systems—especially modularity and all that it entails—can also be seen to have diverged at taxonomic levels both high and low, and have done so as the result of conventional individual-level selection, albeit with the twist of being dependent on particular kinds of pleiotropy and epistasis. Since the case for the homogeneity of the forces that give rise to micro- and macroevolutionary diversity—what I have called the scale-independence of evolution—must nearly always rest upon analogy between well understood microevolutionary patterns and those of larger scale whose causes are obscure, none of these arguments is very strong. But of the three, the most tentative is surely the last which, following Gerhardt and Kirschner, seeks to explain why animals are put together in the way that they are. The reason for this weakness is simple. While we know something about the mechanisms by which diverse model organisms construct their bodies, and even something about the conservatism and lability of those mechanisms among more obscure phyla, classes, and orders, we know as yet very little about such things at a finer scale: that of populations, species, and genera (Arthur 1999). Studies on closely related fruitflies (Stern 1998), butterflies (Monteiro et al. 1997), and nematodes (Sommer 1997; Cunha et al. 1999) promise to fill this gap, but they are not enough. For by now it should be clear that any one pattern of developmental evolution visible among species or higher taxa can probably be explained in a number of mutually irreconcilable ways, and that the reasons for preferring one explanation over another are not strong. This is a generic weakness of the comparative method (Leroi et al. 1994b); to overcome it, the tools of evolutionary analysis—sequence analysis, field studies, quantitative genetics, experimental evolution—will have to be applied to development as they have to metabolic biochemistry and bird songs. Once this has been done, perhaps then we shall be able to speak more convincingly about the antiquity, generality, indeed, scale independence of the causes of developmental evolution.

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