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WALLACE ARTHUR*

The evolutionary importance of developmental reprogramming and bias

Abstract - Evolutionary developmental biology has become recognized, over the last two decades, as a major source of new information, much of it at the molecular level, on the evolutionary process. However, it is only beginning to be recognized as a potential source of new concepts that may be relevant to evolutionary theory in general. I am referring in particular, here, to the idea that the dynamics of the developmental process may be just as important as the dynamics of gene frequencies in populations to the direction that evolution takes at the developmental, or phenotypic, level. In this paper, I approach this issue in three stages. First, I introduce the concept of developmental reprogramming, which is as fundamental to evolutionary changes at the organismic level as are mutation and selection at the genic and population levels. Second, I ask whether developmental reprogramming exhibits biases – that is, that it is somehow easier to change development in some ways than others. Finally, I examine whether such biases might interact with natural selection to determine the directions in which evolution proceeds. I formulate a logical argument that interactions between bias and selection may be widespread and important. But I also point out that there is now a great need for a research programme to produce both observational and experimental evidence that supports this argument.

Introduction

Evolution involves changes at the levels of the population, the organism and the gene. The foundations for understanding evolutionary processes at each of these levels were laid down, in the nineteenth century, by Darwin (1859), Haeckel (1866; building on the earlier work of von Baer and others), and Mendel (1866). Each of these foundations was built upon in the twentieth century; but these endeavours were far from synchronous. Population genetics, or mathematical Dar-

* Integrative Biology Group, The Darwin Building, University of Sunderland, Chester Road Campus, Sunderland SR1 3SD, United Kingdom - E-mail: wallace.arthur@sunderland.ac.uk

winism as we might call it, can be traced back as far as Fisher (1930), and indeed further. The modern study of genes exploded out of the seminal paper by Watson and Crick (1953). But comparative embryology was quiescent (if only in relative terms: Love and Raff, 2003) through much of the twentieth century, until it was reborn as evolutionary developmental biology (or evo-devo) in the 1980s, following (a) Gould's (1977a) re-kindling of interest in this area, and (b) the discovery of the homeobox (Scott and Weiner, 1984; McGinnis *et al*., 1984).

The result of this late start for evo-devo is that it has not yet made the contribution that it should to evolutionary theory, especially in terms of general concepts, where population genetics remains much more advanced. The aim of this paper is to contribute to the correction of this imbalance, by attempting to reveal some central concepts of evo-devo that are, in my view, as important for a full understanding of evolution as are those of population genetics. This paper is thus a continuation of the arguments that I have developed in a series of recent papers (Arthur, 2000, 2001, 2002) and a book (Arthur, 2004b). Other authors who have made or are making similar attempts include Gould and Lewontin (1979), Alberch (1980), Raff (2000) and Yampolsky and Stoltzfus (2001).

Conceptual evo-devo could be referred to as neo-Haeckelism, because Haeckel was the leading figure in the attempt to formulate general evolutionary theories based on comparative embryological evidence in the era immediately following publication of *The Origin*. (In contrast, von Baer never accepted evolution in general or natural selection in particular [Raikov, 1968]). The reason why I would not particularly advocate the use of 'neo-Haeckelism' is only that we already have 'evo-devo' and there is never much sense in introducing redundant terms. It is certainly *not* because of the various criticisms of Haeckel that have been made by recent authors, including Gould (1977a) and Richardson *et al*. (1997). In particular, it is worth pointing out that Haeckel did not, at least in later life, believe that the ontogenies of descendants went through developmental stages that resembled the *adults* of their ancestors, as is abundantly clear from his referring (Haeckel 1896; p. 18) to the human embryo as going through stages that resemble "the undeveloped embryo form" of apes, dogs and rabbits. Nor was Haeckel opposed to the main thrusts of von Baer's (1828) work; indeed he frequently praises von Baer. The recent defence of Haeckel by Sander (2002) is timely.

The starting point: developmental reprogramming

To discuss the developmental/organismic level of evolutionary change in a satisfactory way, it is necessary to have a term to describe all changes at that level, comparable to the umbrella-terms mutation (gene level) and selection (population level). I introduced the term developmental reprogramming for this purpose (Arthur 2000). The rationale underlying this choice was based on the fact that a mutant gene will only end up affecting the phenotype (and so fitness) if it repro-

grams development in some way. Some authors dislike the use of 'program' in this context because they regard it as philosophically loaded and giving the impression that the 'genetic program' is supreme, with epigenetic factors being merely passive (Minelli, 2003). However, in using 'reprogramming' I do not mean to imply such genetic supremacy. Rather, I think that what happens in ontogeny is that there is an interplay between two approximately equal partners – the genetic and epigenetic programmes – and that this interplay is itself influenced in many, perhaps most, cases by environmental factors.

Of course, it is the concept, rather than the term, that matters. If anyone can think of a better term, fine. When I first started to think about this issue I toyed with the term 'heterorhesis', meaning 'different flow'. This derives from the work of Waddington (1957), who used 'homeorhesis' (same flow) to refer to the ability of many developmental pathways to maintain the same route despite various mutational or environmental perturbations. Waddington's point was that this property that he called homeorhesis had some similarities with the more familiar physiological term homeostasis; but it also had an important difference, namely that what was adhered to or returned to following a perturbation was an equilibrial flow rather than a static equilibrium point. In the end, I decided that the potential misinterpretation of 'reprogramming' was a lesser evil than the obscurity (and lack of euphony) of 'heterorhesis'. But again, it is the concept that counts.

The importance of the concept can be seen by reference to Figure 1. Some of the subdivisions of reprogramming, in particular heterochrony, are familiar to evolutionary biologists. But the Figure reveals what a gaping hole in our terminology there was before the introduction of reprogramming. The previous lack of an

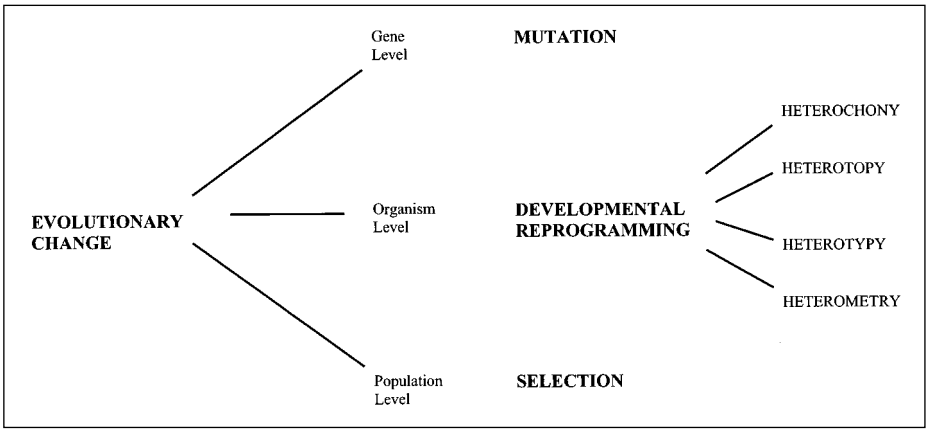

Fig. 1. Three levels of evolutionary change, with overall descriptors of the nature of change at each level. That for the organismic level – developmental programming – is divided into its four sub-types – changes in time, space, type and amount.

umbrella term at the organismic level led many authors to overstate the importance of heterochrony (e.g. Gould, 1977a; McKinney and McNamara, 1991; McNamara 1997). Of course, I agree with them that heterochrony is an important type of reprogramming. But that falls far short of implying that heterochrony is the *only* type of reprogramming, as the title and subtitle of McKinney and McNamara's book conspire to do – *Heterochrony: The Evolution of Ontogeny.*

Ironically, it is easiest to find examples of re-programming caused by particular mutations in cases where the mutations concerned are probably not involved in evolutionary change. The many mutations that alter the development and morphology of *Drosophila melanogaster*, including such familiar ones as *vestigial*, have been catalogued in considerable detail by Lindsley and Zimm (1992). But because these are mostly large-effect mutations, while evolutionary changes are usually based on mutations of much smaller individual effects, their relevance is in a sense indirect. However, occasionally evolution does incorporate mutations of reasonably large effect where the kind of developmental reprogramming can be described. A classic example is the mutation involved in switching dextrality to sinistrality (and vice versa) in gastropod evolution, where the reprogramming starts right back at the beginning of cleavage (Murray and Clarke, 1966; Verdonk and van den Biggelaar, 1983).

I do not intend, here, to discuss the relative commonness, or importance, of the four types of reprogramming listed in Figure 1. This is because I suspect that they often occur in combination. Rather, the central question that I want to address is whether developmental reprogramming, whichever form it takes, tends to be 'biased', and if so then whether such biases might play a role in determining the directions of evolutionary change. I will argue that they do indeed play such a role. This point of view is controversial, especially from a neo-Darwinian perspective.

Developmental Bias

Defining bias is not a simple task. The basic idea is that developmental pathways are more 'easily' reprogrammed in some directions than others. In order to picture such a state of affairs, we need to have (a) some framework for depicting directionality; (b) a sort of 'null model' of zero-bias situations; and (c) more than a vague notion of what is meant by 'ease' of reprogramming. I will take these three things in turn.

One way to picture directionality is shown in Figure 2. Here, the course of development is shown as an arrow through 3-dimensional space. Let us suppose that the vertical dimension is 'cell number'. The other two dimensions can be any two characters, or even combinations of characters, for example of the type that would arise from a principal compnent analysis. What we see in the Figure is an egg-to-adult trajectory in which the developing organism increases in cell number while at the same time shifting in the values of other characters.

This general type of picture will be sufficient for our purposes here, but it is

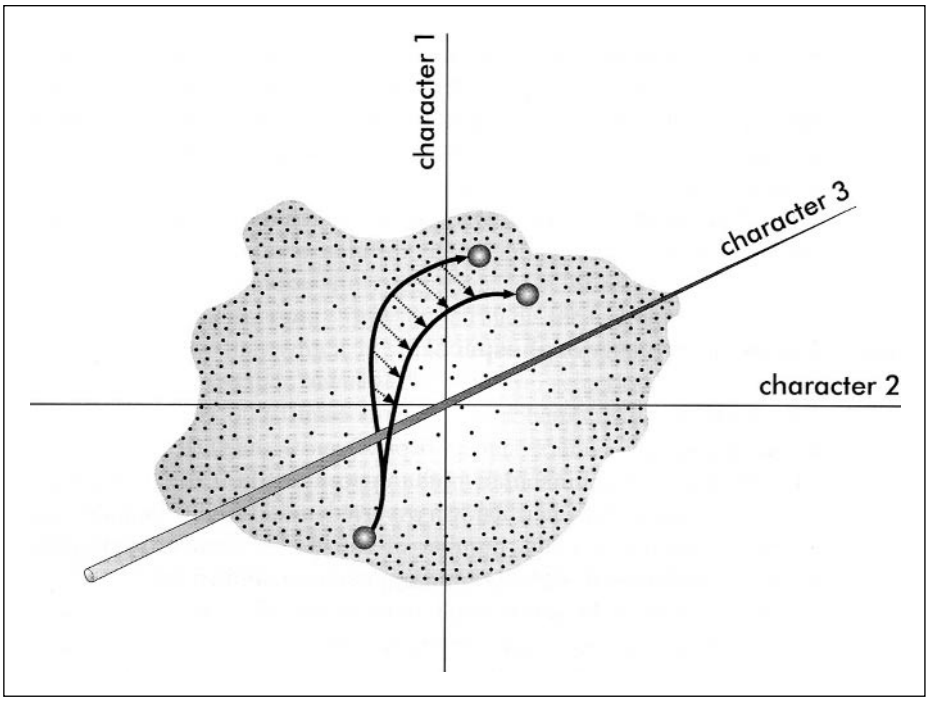

Fig. 2. Representation of developmental pathways (solid arrows) from egg to adult in 3-dimensional morphospace. Reprogramming (dotted arrows) alters an original (LH) pathway to a new one.

probably sensible, nevertheless, to point out some of its limitations before proceeding to examine it further. These are as follows: first, the picture has too few dimensions; second, it suggests a passage through morphospace whose dimensionality is constant, whereas in fact new dimensions come into being as development proceeds; third, it shows development as a 'smooth' process, whereas in some cases, such as metamorphosis of holometabolous insects, this is far from being true. For now, I will proceed with the assumption that these simplifications inherent in the picture shown in Figure 2 will not affect the argument.

So, we move on to the question of how to picture zero-bias situations. In Figure 2, one particular form of reprogramming is shown, as a deflection of the ontogenetic trajectory (small arrows). Other forms of reprogramming can easily be imagined as different deflections. In fact, 'deflection' is too restrictive a word, because in some cases we might find that an instance of reprogramming causes initial deflection from the original trajectory, but then partial convergence to it in later developmental stages. There is an effectively infinite possible number of altered trajectories.

The zero-bias situation can now be simply described: there is no developmental bias when, considering all the kinds of reprogramming that can occur as a result

of diverse mutations in all those genes that affect the developmental process, every possible direction of change in the overall ontogenetic trajectory is equally probable. Since there is only one equiprobable scenario in contrast to billions of biased (i.e. non-equiprobable) ones, the ubiquity of bias becomes apparent.

But we have still to examine that concept of 'ease' of reprogramming. This is one of those deceptively simple ideas, like Kirschner and Gerhart's (1998) 'evolvability', that is worth probing into in detail rather than accepting at face value. So, what *exactly* do we mean by 'ease' in the present context? In order to answer this question, it is helpful to formalize the argument somewhat, as follows. Let us call the original developmental trajectory, prior to any reprogramming that we want to consider, T_0. There is an infinite number of possible altered trajectories following mutation and reprogramming; we can call these T_1, T_2, T_3, … etc. Each of these has a certain probability of being produced. The best way to think of these probabilities is in the context of a natural population of the organism concerned, that is, the context in which evolutionary changes take place.

Over a long period of a population's history, say several thousand generations, mutations will occur in many of the genes that affect the developmental trajectory. I will simply call these 'developmental genes' from here on. Some such genes may be more prone to mutation than others; some may be characterized by mutations that have bigger effects than others, or have a greater diversity of effects than others, and so on. A particular new trajectory may be able to be produced by more than one type of mutation of a particular developmental gene, or even by mutations of different developmental genes. Summing across all mutations (of all developmental genes) that occur in the period of time under consideration, we could in theory determine the probabilities of each form of reprogramming; that is, the probability of producing each new trajectory. We can call these probabilities $p(T_1)$, $p(T_2)$, $p(T_3)$, etc.

We can now define 'ease' in probabilistic terms. The ease of reprogramming towards any new trajectory T_i is simply $p(T_i)$. The extent to which these 'eases', or probabilities, vary depends on the dynamics of the developmental process. It could be that one trajectory, say T_{45}, is a sort of 'attractor' in that many forms of mutationally-induced reprogramming lead in that direction. Alternatively, it may be that the variation in p values across different i values is much less pronounced. But in any event, we end up with the same conclusion as before: some form of variation is inevitable; therefore we should expect developmental bias to be ubiquitous, even if it is difficult (or impossible) to predict exactly what form it will take.

It is important to note that the above argument makes no reference to natural selection. That is, it takes no account of the relative fitnesses of the various new trajectories that reprogramming can produce. This omission is not an oversight; rather it is deliberate. If my aim is to consider the relative importance of developmental bias and natural selection as determinants of evolutionary direction, and to examine how the two processes might interact, it is important to ensure that they are not conflated at the outset.

The direction of evolutionary change

The argument so far is hardly controversial. That is, my claim of the existence, and indeed the ubiquity, of developmental bias is unlikely to provoke a counter-claim from any particular school of evolutionary theory. But things are about to change. That is because we are now approaching the most important, and also the most controversial, part of the argument, namely that bias not only exists but also is an important determinant of the directions that evolution takes.

Statements that evolution's direction is largely, or even entirely, determined by natural selection can be found in the literature from Wallace (1870) to the present day (e.g. Rieseberg *et al*., 2002). Although not all population geneticists agree with such a statement (especially when made in the stronger 'entirely' form), it has been regarded by many as the mainstream view. Some of those who have argued against it have taken what is, in a sense, the opposite view – that developmental bias is more important than selection (Gould and Lewontin, 1979; Goodwin, 1994). However, I agree with neither the 'mainstream' nor the 'alternative' view. Rather, I believe that both bias and selection are important, and that it is *their interaction* that is the most crucial thing. If this is so, then neither is more important than the other; rather both are essential components of a general theory of evolutionary directionality.

The argument for the interaction between bias and selection being crucial is based on Figure 3. Here, the morphological dimensions of Figure 2 have been condensed from three to two, but an extra dimension – fitness – has been added in the form of a series of contours that define fitness peaks. This is the old idea of an adaptive landscape (Wright, 1932), but used in a rather different, and explicitly developmental, way that requires some explanation.

First, we need to note that the axes are unspecified (and possibly compound) developmental variables, as befits a general argument. Second, we need to picture the 'old' and 'new' ontogenetic trajectories in relation to these axes. The old one (i.e. prior to reprogramming) is represented as a solid line; various possible post-reprogramming trajectories are shown as dashed lines. Third, we need to represent bias. This is done by showing a greater spread of new trajectories 'under' the original one than 'over' it.

We are now in a position to consider the possible effects of selection. To simplify matters, let us consider selection acting at just one particular stage in the developmental process, marked with a square in the Figure. Hypothetical fitness contours are shown, for that stage, as circles. There are two fitness peaks, and these are equidistant from the original trajectory. Peak 1 is 'higher' than peak 2 – that is, it has greater fitness. However, because of the developmental bias, there is no overlap between the available developmental variation and the slope leading to peak 1, while there is such an overlap with peak 2. So the combination of bias and selection takes the population to peak 2 – that is, in a direction that is fitter but suboptimal.

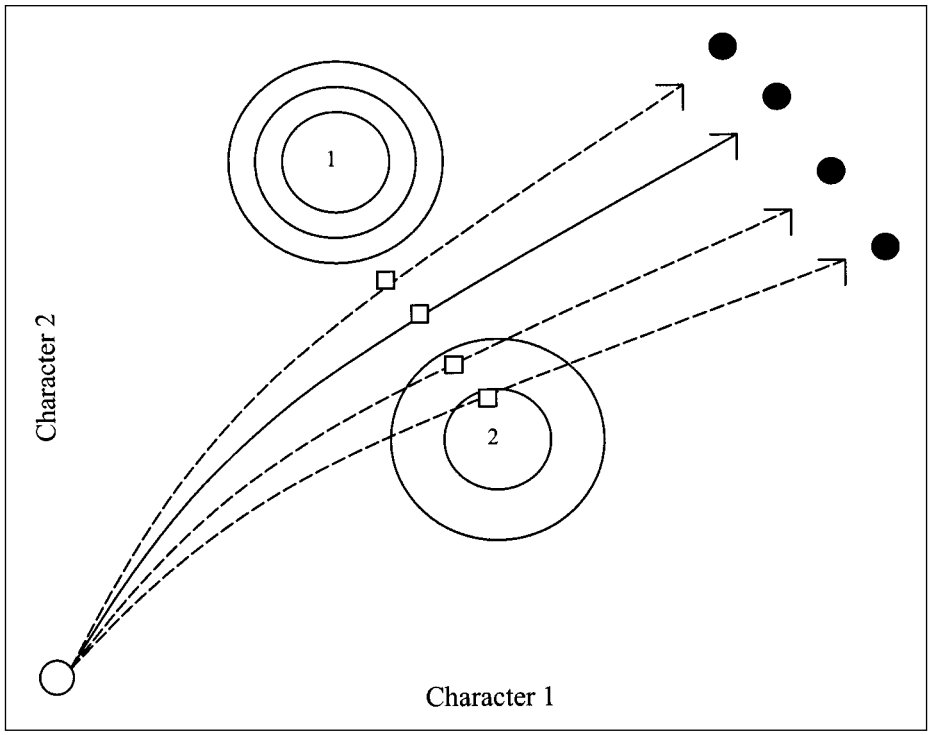

Fig. 3. Developmental trajectories in 2-dimensional space, both original (solid arrow) and reprogrammed following mutations in developmental genes (dashed arrows). Fitness contours (circles) related to one particular stage of development (open squares). Although fitness peak 1 is higher than peak 2, the population will evolve towards peak 2 because of the biased nature of the variation.

This very simple point has enormous implications, because the process described is only a snapshot of evolutionary change. In fact, since evolution is a continuous process, with each change using as a starting point the result of the previous one, the effect of the bias/selection interaction in choosing one peak rather than another over one period of time may lead, over the much longer term, to a very different evolutionary outcome than that which would have prevailed if the alternative choice had been made.

Discussion

There are many distinct approaches within the field that has become known to its practitioners as evo-devo. This is because the questions that are central to this field of endeavour are complex, and require many different sorts of inputs if we are to have any hope of answering them. Some of the most important questions are: How does development evolve at the molecular level? How do we reconcile the

accumulating body of data on comparative developmental genetics with old ideas like homology? And to what extent is development itself an active rather than a passive player in the evolutionary process? Although I have been entirely concerned with the last of these questions here, I suspect that in the near future one of the most interesting challenges will be to connect up the work that is being done to answer these different questions; that is, to connect up conceptual, molecular, palaeontological, and other, strands of evo-devo.

In particular, unravelling the molecular and cellular processes that underlie the idea of developmental bias, which I have dealt with largely in abstract terms here, represents a major challenge. Many have argued that changes in the way that developmental genes are regulated, for example by transcription factors, are responsible for much of morphological evolution (Carroll *et al.*, 2001, Levine and Tjian, 2003). This seems likely to be true, but we need to go beyond such generalizations if the molecular work is to be usefully connected with its conceptual equivalent. For my purposes here, for example, it would be interesting to know if certain kinds of changes in the regulation of gene expression are 'easier' to achieve than others.

But it is not just molecular and conceptual approaches that need to be tied together. One other major input to evo-devo, which I have so far ignored in the present paper, is the role of the environment in determining how development proceeds. The study of this, which has recently been referred to by some authors as 'eco-devo', is of considerable importance. What is reprogrammed, and evolves, in many cases is not a fixed developmental trajectory, but rather a spectrum of possible trajectories, with the precise environmental conditions determining which of these prevails – the 'developmental reaction norm' (Schlichting and Pigliucci 1998).

It is important to recognize that evo-devo needs to be able to encompass 'population thinking'. For simplicity, I adopted the approach above of talking about an original (pre-reprogramming) and an altered (post-reprogramming) developmental trajectory. But in reality, at any moment in time a population could more accurately be described as a 'bundle' of trajectories, because of the continuous variation in development/morphology that is always found. And in many cases, there is discontinuous variation too. The commonest form of this is of course sexual dimorphism, but castes, ecotypes etc are important too, so long as their heritabilities (or the heritabilities of variation in the relevant reaction norms) are non-zero.

In Figure 4, I give an outline picture of the various different components of the evolution of development that we need to understand. There is a long way to go before we will have a satisfactory comprehension of all the processes involved. But at least we have come far enough to know that the scientific journey that evo-devo represents is, and will continue to be, an exciting one.

Finally, returning to my core argument, the view that I am putting forward can be seen as a 'compromise' view in relation to one of Gould's (1977b) famous 'eternal metaphors' – the internal/external one. Neo-Darwinism, especially in some of its more populist forms (Dawkins, 1986), comes close to being a pan-externalist

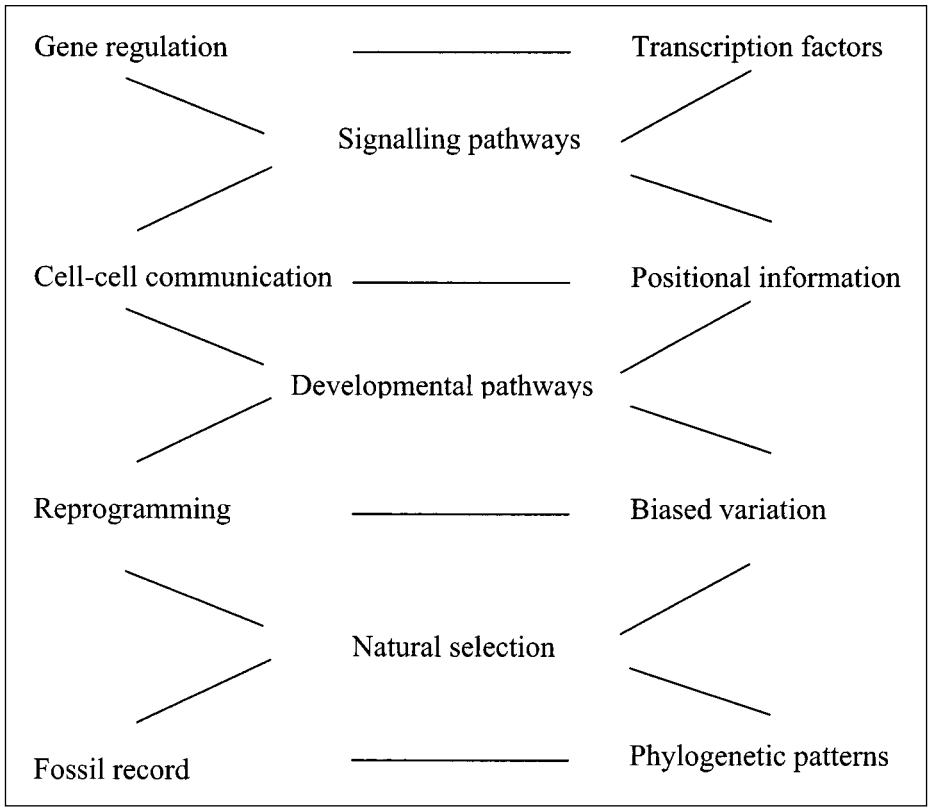

Fig. 4. The enormous scope of evo-devo: from molecular processes taking seconds to phylogenetic processes taking aeons. Some of the main linkages are shown; but many others are not (simply in order to avoid a very cluttered diagram).

view of how the direction of evolution is determined. The followers of some other schools of evolutionary thinking have taken an almost pan-internalist view. This is true both of the early orthogeneticists (see Bowler, 1983, chapter 7, for an account) and of some recent stucturalist approaches such as that of Goodwin (1994). Here, I have argued that the reason why evolution takes the courses that it does, and not others, is the result of the interplay between internal and external agencies. No doubt many biologists will remain unpersuaded of the truth of this hypothesis until there is some concrete evidence to back it up. So for those of us who are interested in this issue, the next step is to find such evidence. This is quite a challenge, because it is not merely evidence of bias that we need but, in addition, evidence that bias can have a directional evolutionary effect. Deciding which kinds of observations and experiments might provide such evidence is the task at hand, followed closely by conducting them and acquiring the relevant data.

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