Heredity (2005) 94, 1–2

www.nature.com/hdy

NEWS AND COMMENTARY

Evolutionary genetics

The evolution of evolution

G Bell

Heredity (2005) **94,** 1–2. doi:10.1038/sj.hdy.6800608
Published online 3 November 2004

A recent claim, that the ability of genetic systems to evolve will itself evolve in a predictable fashion, brings a new challenge to our studies of evolution. It is commonly accepted that environmental change leads to adaptation through natural selection, within the constraints set by a particular genetic system. It is much less straightforward to enquire whether a genetic system itself can evolve, and, if so, what the consequences would be. Earl and Deem (2004) have recently claimed just this: that a fundamental feature of genetic systems – their 'evolvability' – will itself evolve predictably in response to environmental perturbation.

At a low level of genetic organization, this is a familiar phenomenon whose mechanism is well understood. In asexual populations, severe environmental stress creates intense selection that causes an increase of fitness in the new conditions of growth relative to the ancestor. An indirect effect of intense selection is the occasional fixation of mutator genes, which usually encode defective versions of DNA polymerases, and thereby elevate rates of point mutation by factors of 10–1000. They spread, despite the fact that almost all the mutations they cause are deleterious, because the mutator gene is completely linked to all the mutations it causes. Among the large number of mutations that the mutator causes will occasionally occur a mutation that confers increased fitness in the new environment; as this beneficial mutation spreads through the population, it will carry the mutator with it. Conventional population genetics theory can describe this process and it has also been demonstrated in the laboratory (eg Sniegowski *et al*, 1997).

It is now clear, however, that evolutionary change does not always proceed smoothly through base substitution at single loci. The mosaic nature of bacterial genomes, the mobility of plasmids and other genetic elements, the idiosyncratic nature of mating-type genes in sexual microbes and the genetic regulation of development in multicellular organisms all show that variation at higher levels of genetic organization is also important in evolution. (For a set of papers describing such phenomena, see *Genetica*, Vol 118, 2003). Such higher-level sources of variation are hard to incorporate in theoretical evolutionary modelling, which usually relies on defining a restricted range of genotypes and then finding out which remain after selection. Individual-based computer simulation is one promising alternative to the standard approach. In this alternative approach, types or combinations of types with unexpected properties may appear and spread during the course of the simulation. Systems of this sort are now being used to investigate the fundamental features of evolutionary change that are inaccessible to equation-driven methods (eg Yedid and Bell, 2002; Lenski *et al*, 2003).

Earl and Deem (2004) present one such model of protein evolution, in which a population of molecules undergoes selection based on the energy state inferred from their structure. The authors modelled molecules comprised of 100 amino acids, arranged as 10 non-overlapping subdomains of 10 amino acids each. The molecule's energy state is determined partly by the chemical properties of individual amino acids and partly by the conformation of each subdomain – there are five permissible conformations, such as loops and helices. In each cycle of selection, only 20% of molecules with lowest energy were allowed to replicate. The descendant sequences may differ from their parents through small-scale genetic changes corresponding to point mutations – an alteration in the chemical properties of individual amino acids – or through large-scale changes corresponding to the replacement of large sections of a gene – replacement of an entire subdomain with a sequence of the same kind, drawn randomly from a general pool. Either change occurs with a probability that is specific to a particular sequence, as though the genes responsible for regulating the level of error were completely linked to the gene that encodes the structure of the protein exposed to selection. The descendant sequence inherits these probabilities, with a slight adjustment up or down. Thus, as sequences evolve towards minimal energy levels, their propensity to vary may evolve too – Earl and Deem call this property the 'evolvability' of the system.

Under constant directional selection, mutation rates at equilibrium will approach zero, for small-scale and large-scale effects. This is because any change will be deleterious once the optimal sequence has evolved, and selection will therefore favour linked genes that minimize the mutation rate. If the environment changes from time to time, this argument fails. The periodic renewal of directional selection favours sequences whose descendants vary, because these sequences will tend to converge more rapidly on the new optimum. To model environmental change, Earl and Deem altered the identities of amino acids and subdomains after a given number of cycles of replication. This shifted the sequences relative to the optimum, and generated a new episode of directional selection.

The main finding of the simulations was that frequent severe disturbance (the re-allocation of types of subdomain) leads to greater evolvability (a higher rate of replacement of subdomains from the pool). Perhaps this is not very surprising, at least with hindsight: when the type of each subdomain is changed, modifying the high-level organization of the molecule, the only effective response may be through structural change at the same level. Earl and Deem draw the broader conclusion that severe disturbance selects for genetic systems that facilitate rapid adaptation through large-scale genetic changes. So evolvability itself evolves, and is always greater in more highly disturbed environments.

The replacement of an entire subdomain with a random alternative from the pool is analogous to bacterial transformation, and has a more distant resemblance to meiotic recombination. A large fraction of many, if not most, bacterial genomes has been recently acquired from other lineages by horizontal transfer (Ochman *et al*, 2000). Some of the sequences involved are gene cassettes, which are inserted into specific sites and immediately confer antibiotic resistance or new metabolic capabilities (Michael *et al*, 2004). Evolution does not require macromutations: laboratory experiments have shown that bacterial populations readily adapt to novel conditions of growth when their

ancestor is isogenic and free of plasmids (reviewed by Elena and Lenski, 2003). Evolution in natural bacterial communities, however, may often be driven by the acquisition of plug-and-play modules from a 'metagenome' of thousands of locally available sequences. The crucial issue is whether the propensity to do this is itself selected. DNA can be taken up by bacterial cells, despite its high molecular weight, and bacteria that live in environments rich in DNA may even use it as a food source. Other things being equal, however, the incorporation of foreign DNA sequences into the genome is severely discouraged by selection, because of the risk of infection by viruses and other parasitic elements. Less effective defences would increase the rates of horizontal transfer, just as less accurate polymerases increase the rates of point mutation, albeit at a cost. Earl and Deem's simulations thus seem to capture an important aspect of evolution in natural communities of bacteria.

The parallel with recombination is perhaps less persuasive, because of two features of sexual genetics: meiotic recombination destroys epistatic combinations just as readily as it creates them, and modifiers of recombination are not linked to the genes whose recombination they facilitate. Although we now have laboratory demonstrations that sex increases the rate of adaptation (Kaltz and Bell, 2002), the prevalence of sex in natural populations may require a genetic feedback between co-evolving systems, which is absent from Earl and Deem's model.

Carroll (2002) has recently emphasized that the most important features of organisms, such as the proliferation of body plans among multicellular organisms, are difficult to explain in terms of the gradualistic selection of point mutations in structural genes. Instead they seem to involve the rearrangement, duplication and insertion of genetic material at a higher level of genome organization. By revealing these unexpected features of evolution, molecular genetics has created the need for theoretical tools to explain them. Earl and Deem's models are an interesting advance in the development of this new kind of population genetics.

G Bell is at the Biology Department, McGill University, 1205 ave Docteur Penfield, Montreal, Quebec, Canada H3A 1B1.

e-mail: Graham.bell@mcgill.ca

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