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LETTER TO THE EDITOR

From adaptation to molecular evolution

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There have been an increasing number of calls in recent years for a 'post-modern' synthesis of evolutionary biology, extending the modern synthesis of the 40–50's by including molecular aspects of development (evo–devo), phenotypic plasticity driving genetic evolution, or epigenetic inheritance (for example, Pigliucci, 2007). This illustrates an infusion of evolutionary thinking into all aspects of modern biology, creating a need for integrative approaches and increased exchange between complementary fields. These calls often go along with a healthy questioning of orthodoxy in the light of current empirical evidence. However, alternatives should be scrutinized with as much skepticism as the mainstream theory they aim to replace or improve. We need to ask whether each theory—Neo-Darwinism or the proposed alternative—is sufficient to explain observed patterns, not whether it is necessary. That some observed patterns could be due to another process does not argue against Neo-Darwinism, if this other process is not a sufficient explanation in other situations. As an analogy, relativity theory is not always necessary to explain the motion of particles, but it is sufficient to account for all known mechanics, whereas Newton's theory is not.

Interpreting the enormous amount of emerging molecular data requires such an integrative approach. To use these data to infer population processes behind patterns of adaptation, we need models that describe how natural selection operates on traits, how this translates into changes in nucleotide sequences, and whether unique molecular signatures can be detected under alternative, plausible scenarios. In a recent paper in this journal, Hughes (2011) argues that, because current statistical approaches fail to reliably detect strong evidence of positive selection at the molecular level (while they reveal substantial evidence of purifying selection), we need to explain the origin of adaptation at the phenotypic level by a process other than the Neo-Darwinian one, that is, cumulative substitutions of beneficial mutations. Specifically, he proposes that adaptation may arise when ancestral phenotypic plasticity in a variable environment is lost in a more homogeneous environment by the accumulation of deleterious mutations under relaxed selection (the plasticity–relaxation–mutation hypothesis, or PRM). He suggests that most evolutionists have overlooked this alternative explanation, because it does not fit their Neo-Darwinian understanding of adaptation.

We hold that the PRM hypothesis is neither a more parsimonious hypothesis, nor one more consistent with data, than the Neo-Darwinian mode of adaptation. Patterns of molecular evolution can agree well with predictions from the Neo-Darwinian view of adaptation, provided we use more explicit models for phenotypic selection in a new environment and for the genetic architecture of adaptive traits.

IS PRM A MORE CONVINCING MECHANISM OF ADAPTATION?

Several conceptual and empirical arguments can be raised against PRM as 'a major mechanism for the origin of evolved adaptations, and perhaps, more common than the Neo-Darwinian mechanism' (Hughes, 2011).

Conceptual problems

The PRM hypothesis relies on ancestral plasticity. However, it does not explain why the ancestral state should be phenotypically plastic, or why this plasticity should be adaptive in the first place. Plasticity of a particular trait (defined broadly as a change in this trait with its environment of expression) need not always be adaptive, as nicely exemplified by cases of countergradient variation (Grether, 2005). It could even be argued that producing consistent phenotypes in the face of various influences from the environment is one of the greatest challenges of ontogeny (West-Eberhard, 2003). However, whenever there is sufficient genetic variance in plasticity, plasticity may evolve by natural selection to become adaptive (Via and Lande, 1985). In contrast, the PRM hypothesis appears to assume that plasticity is initially adaptive, but not as a result of natural selection. Hughes (2011) argues that this should be common because of exaptation, whereby a given trait becomes selected for a different function from the one it had in the evolutionary history of the species (Gould and Vrba, 1982). However, exaptation is fortuitous, as noted by Hughes (2001), and as such, it can hardly be invoked as a general mechanism for adaptation. Exaptation also does not necessarily imply plasticity, as 'the use of the pre-existing trait in a new context' (Hughes, 2011) can occur without any plastic change in the trait itself.

In support of his argument, Hughes (2011) suggests that phenotypic plasticity in random directions should allow the PRM mechanism to operate one-third of the time. This overly optimistic prediction is an artifact of considering the simple scenario of two possible phenotypic values and two optima for a single trait. Actual living organisms are complex and their ecological niches are multidimensional, such that most random phenotypic changes (either plastic or genetic) are likely to be detrimental (Fisher, 1930, pp 38–41).

The PRM also assumes a direct connection between relaxed selection and reduced plasticity. In an environment where selection is relaxed, phenotypes evolve under the sole influence of random genetic drift. The theory of random genetic drift was extended to phenotypes several decades ago (Lande, 1976), but whether genetic drift should result in reduced or increased phenotypic plasticity is far from obvious. It depends on the phenotypic effects of mutation, on how the environment affected phenotypic selection before relaxation of the latter, and on whether the genetic basis of phenotypic plasticity *per se* is different from that of the corresponding traits measured in a common environment.

We also note that PRM is a theory for specialization rather than for adaptation. It aims to explain how the breadth of an ecological niche evolves to be reduced, rather than how the mean phenotype in a population evolves to allow good performance in a given

environment. As a consequence, the PRM hypothesis assumes that adaptation only occurs after homogenization of the environment, allowing relaxed purifying selection to operate. This seems like a rather restrictive condition; why should homogenization of the environment occur more often than the reverse? In fact, previous theory has shown that even in a spatially heterogeneous environment, the accumulation of mutations that are deleterious in rare marginal habitats (that contribute little to the overall reproduction of a species), but neutral in the main habitat, can cause the evolution of specialization (Kawecki *et al.*, 1997). This process is similar to, but more general than, the proposed PRM, because it allows for partial relaxation of selection (when an environment is present at low frequency), and makes no assumption about plasticity.

Consistency with data

Although Hughes (2011) presents a mechanism for adaptation at both the phenotypic and molecular level, he paradoxically refers little to the vast amount of empirical data on microevolution observed 'live', which is the most direct evidence we have about the process behind adaptation patterns. There is considerable evidence that the mean heritable component of phenotypes in a population can change in response to selection. These data come from artificial selection (reviewed in, for example, Falconer and Mackay, 1996), experimental evolution in the laboratory (Lenski *et al.*, 1991) or in the wild (Barrett *et al.*, 2008), and monitoring of natural populations (reviewed in Kruuk *et al.*, 2008). In some cases, the molecular mechanisms involved are well characterized (see Stapley *et al.*, 2010 for a recent review). Positive selection at underlying genes, as predicted under the Neo-Darwinian mechanism, has even been observed in real time for traits with relatively simple genetic determinism (Imhof and Schlotterer, 2001; Barrett *et al.*, 2008).

Other mechanisms of phenotypic change can also operate in the wild, including phenotypic plasticity (Charmantier *et al.*, 2008). There is a sizeable empirical literature (reviewed in, for example, Schlichting and Pigliucci, 1998) on genetic assimilation of initially plastic phenotypic responses, notably in response to strong stresses such as extreme temperatures, which bears a resemblance with the proposed PRM mechanism. Recent theory (Lande, 2009) highlights how these results can be interpreted within the Neo-Darwinian framework. However, there is little empirical evidence for a prevalent role in adaptation of reduced plasticity due to mutation accumulation under relaxed selection in a homogeneous environment.

Despite Hughes' arguments, evidence from modern molecular data do not appear to favor PRM over Neo-Darwinian adaptation either. Hughes (2007) and others (McDonald and Kreitman, 1991; Eyre-Walker, 2002) have emphasized that relaxed purifying selection during a bottleneck can produce a molecular signal similar to that of positive selection with the popular M-K test. This would seem to imply that PRM, which involves relaxed purifying selection, could also cause excesses of non-synonymous divergence/polymorphism (D/P), as commonly detected in molecular data, and most often attributed to positive selection. However, a bottleneck reduces the efficiency of purifying selection only transiently, such that divergence of nearly neutral deleterious mutations at non-synonymous sites is temporarily increased, whereas their polymorphism (which depends on more recent values of the effective population size) is more constrained, thus inflating D/P. In contrast, the PRM hypothesis relies on permanently relaxed selection, causing both divergence and polymorphism to be consistent with neutrality at non-synonymous sites. This cannot account for observed excesses of D/P at non-synonymous relative to synonymous sites. PRM also does not predict the characteristic pattern of neutral polymorphism left along a recombining chromosome by the rapid selective sweep of a single beneficial mutation (Kim and Stephan, 2002), even though this pattern can be mimicked to some extent by bottlenecks of intermediate severity (Jensen *et al.*, 2005).

CONNECTING MOLECULAR EVOLUTION TO ADAPTATION THEORY

Hughes' (2011) main justification for the PRM as an alternative mechanisms for adaptation is that molecular signatures of purifying (negative) selection overwhelm those of positive selection, a pattern he considers to be inconsistent with the Neo-Darwinian process of adaptation. In contrast, the PRM mechanism only involves purifying selection or its relaxation. This leads Hughes (2011) to assert that purifying selection at the molecular level should be taken as the best available evidence for adaptation, and support of the PRM hypothesis. However purifying selection may act (at least in theory) on unconditionally deleterious mutations with fitness effects independent of the environment (for example, lethal mutations that disrupt major 'housekeeping' genes), whereas Hughes' (2011) definition of adaptation involves relative fitness with respect to a given environment. Therefore, molecular signatures of purifying selection are not by themselves evidence of adaptation, and do not lend particular support to the PRM hypothesis.

Prevalent molecular signatures of purifying selection need not be a challenge for the Neo-Darwinian view of adaptation. In an enlightening review, also published in *Heredity*, Hughes (2007) argued that methods that search for signatures of positive selection using interspecific divergence data (notably the above-mentioned MK test) are based on assumptions about the genetics of adaptation that are often not met in nature. In particular, they assume repeated independent substitutions of beneficial mutations in the same gene, which is not necessarily likely apart from cases of coevolving genes with highly specific molecular targets (Hughes 2007). However, the lack of effective statistics does not warrant new theories of adaptation such as PRM. It warrants a redoubled effort to develop statistics linked to more realistic models of the genetics of adaptation.

The hallmark of the genetics of adaptation is the environment dependence of fitness effects of mutation. Genes involved in adaptation to a particular axis of environmental variation have an input of beneficial mutations that depends on this environment. If there is an optimum phenotype set by the environment, the proportion of beneficial mutations and rate of adaptive evolution will increase with maladaptation of the 'wild-type' genotype, measured as its (log)fitness difference with the optimum phenotype (Martin and Lenormand, 2006).

Such a view of adaptation, which has proven to be fairly consistent with mutant analysis across taxa and environments (Martin and Lenormand, 2006; Wang *et al.*, 2009), has several implications for molecular evolution. First, the relative amount of positive versus negative selection at any gene depends on the genetic and environmental context. Second, observed rates of adaptive substitutions should be set by rates of phenotypic evolution, which themselves depend on rates of environmental change, to the extent that those cause natural selection on phenotypes.

Recent analysis across many traits and taxa suggests that rates of phenotypic evolution are highly heterogeneous in time, mostly consistent with 'sudden' adaptation (on ecological time scales) to a new optimum followed by long stasis due to stabilizing selection (Estes and Arnold, 2007). Genetically, this mode of adaptation would involve a few early beneficial substitutions driven by positive selection, followed by many generations of purifying (negative) selection against mutants

that deviate from the constant optimum. This is clearly consistent with patterns at the molecular level.

Third, beneficial mutations are distributed across genes, as many adaptive traits have a broad and complex genetic basis. This is most obvious for continuously distributed quantitative traits, but genetical analysis of some seemingly simple adaptations such as insecticide resistance also reflect complex genetics, with several duplications, gene rearrangements and sequence polymorphisms segregating within a population (Labbé *et al.*, 2007). It is also well documented that genetic response to strong selection pressures often implies major genes at first, and later many genes of smaller effects (Lande, 1983; Orr, 1998), which affects the molecular signature of selection (Chevin and Hospital, 2008). Cases of parallel genetic evolution involving the same genes in several populations have also been characterized (Mundy *et al.*, 2004; Colosimo *et al.*, 2005), and studied theoretically by modeling the heterogeneity across loci of mutation effects on adaptive traits across environments (Chevin *et al.*, 2010). However, it is doubtful that factors causing parallel evolution also cause recurrent substitution at the same gene within a population.

To sum up, realistic models for the genetics of adaptation, consistent with current evidence from both distributions of fitness effects of mutations, and micro-evolution at the phenotypic and genetic level, should yield patterns of molecular evolution that are at least qualitatively consistent with observations, without the need to invoke alternatives such as PRM. The next challenge is to move from qualitative agreement to quantitative predictions and statistical tests. This effort was initiated by a few recent studies (Orr, 2002; Gu, 2007; Chevin *et al.*, 2010), but more work is doubtless needed before statistical approaches in molecular evolution can be reconciled with current knowledge about the genetics of adaptation.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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