A report that a switch of a yeast protein to a ‘prion’ state triggers diverse phenotypic changes has prompted re-examination of the processes of evolution. To what extent should processes of gene expression and control be interpreted in terms of their capacity to allow future evolution as well as present adaptation?

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The recent tragic cases of ‘variant’ Creutzfeldt–Jakob disease that are thought to be related to the United Kingdom’s epidemic of bovine spongiform encephalitis have raised the profile of genes encoding proteins capable of forming the self-perpetuating protein configurations known as ‘prions’. While the dangerous effects of prions are becoming increasingly known, less well understood are some proteins’ capacities to adopt such conformations. In the yeast Saccharomyces cerevisiae, the translation termination protein Sup35 will, in its prion form, allow translational readthrough past some stop codons [1]. The ability to form the prion requires the amino-terminal and middle portions of the protein — the ‘NM’ part — and cells bearing only the carboxy-terminal part of Sup35 seem capable of normal translation. The state lacking the prion, [psi–], switches spontaneously to the prion state [psi+], at a frequency of between 10–7 and 10–5. Now, True and Lindquist [2] have detected many phenotypic differences between [psi+], [psi–] strains and isogenic strains that lacked the NM parts of the Sup35 gene, implying that the effects of the NM region cannot arise solely from this region’s capacity to trigger prion formation. Lindquist’s view [4] is that the presence of the prion, and its effect of creating novel phenotypes, is of evolutionary importance, even if the creation of evolutionary change has not been causally linked to the evolution of the prion itself.

The significance of the results is, in fact, hard to assess. It is not intrinsically surprising that the [psi+] state changes phenotypes, nor that environmental conditions can be found in which these altered phenotypes can enhance fitness. One important issue is therefore whether mutations, or epigenetically created abnormal patterns of gene expression, are a priori so likely to be deleterious, even in laboratory environments, that it is interesting if changes of this kind can often increase growth rate. Some might say that the yeast would be expected to be so poorly adapted to some of the test environments that it is unsurprising that random changes have a positive effect.

Two types of adaptive effect are hypothesised by True and Lindquist [2]. One is the possibility that there are
environmental cycles, and that the random change between the $[\psi^+]$ and $[\psi^-]$ states will act as a switch allowing occasional cells to arise, and spread by selection, that now show the patterns of gene expression best adapted to the alternative environment. The other possibility is that, in the times when the prion is off, random and neutral changes occur in sequences $3'$ to stop codons which, when the prion is recreated, are expressed simultaneously, creating a suite of changes in many genes, which might, by chance, be advantageous, as long as the $[\psi^-]$ state persists.

For True and Lindquist [2], the simultaneous activation of genetic changes at many loci is relevant to the evolutionary 'enigma' that new functions may require several independent genetic changes. The view that 'conventional' neo-Darwinian evolution cannot explain such events is, however, largely a creationist myth. The ideal experiment conceptually would be to carry out an interspecific comparison of those amino-acid sequences that are expressed only when the prion allows readthrough into the synonymous differences which do not. A low interspecific $K_a/K_s$ ratio — the ratio of the normally untranslated $3'$ regions of mRNAs, to see if there is a low interspecific $K_a/K_s$ ratio — the ratio of sequence differences that change the encoded protein sequence to the synonymous differences which do not. A low interspecific $K_a/K_s$ ratio would indicate that there are selective constraints on these DNA sequences that operate in the phases when they are translated into protein sequences. This is not possible in practice, as the relevant genes have not been identified, but the finding of selective constraints, acting in $[\psi^-]$ phases, on sequences beyond the stop codon would favour the cycling hypothesis.

For each of the two hypotheses put forward by True and Lindquist [2], explicit population genetics models can be devised, which show that each situation could be capable of maintaining the prion-generating sequences, at least if clonality is assumed, if the environmental changes are of the right kinds (for example, see [5]). Experimental evolution of Escherichia coli in a new environment has been shown to favour mutations that raise mutation rates elsewhere in the genome [6]. But if switches to and from the prion state facilitate adaptation to cycling environments, an obvious concern is that the shift to the prion state is random, and not triggered by the environment in which the readthrough elongated proteins are advantageous. If the switch between proteins could be made deterministically and adaptively, this would give an advantage, as there would no longer be selection operating against individual cells that failed to make the epigenetic switch. Moreover, environment-induced changes in gene expression maintained by positive feedback are quite common, and this would seem to be a much better strategy for yeast to reach the same endpoint that the prion is hypothesised to be controlling.

The title of Partridge and Barton’s commentary [3] reminds us that the issue here is 'evolvability', and this mirrors recent speculations that genes create phenotypes in such a way that options for future evolution are enhanced [7–9]. One can imagine a genotype, which, while optimally adapted to current environments, might be incapable of future adaptive change — it might lack evolvability. It is obvious that organisms ancestral to the very different organisms alive today possessed evolvability and an inductive argument implies that today's organisms must do so also. What then are the features of the ways in which the genes make the phenotype that allow such evolvability, and is there an evolutionary argument that says that evolvability would itself evolve?

These two questions are intimately related. Evolvability obviously exists, and Kirshner and Gerhart [7,8] identify various features of the control of cellular processes in metazoans, in particular, as ones which create evolvability. The problem is that evolvability is intrinsically quantitative not qualitative. We might wish to think of it as the proportion of radically different designs created by mutation that are viable and fertile. They do not have to have a fitness greater than pre-existing designs, as evolvability implies environmental change, which might reverse selective differentials. But once we think of evolvability as a quantitative trait, merely documenting examples of evolvability is inadequate. We may say that organisms are evolvable, but compared to what? The danger of evolvability becoming a platitude is obvious, unless we have a theory predicting that it will itself evolve.

We can, of course, imagine different lineages with equally optimal phenotypes in present environments, but differing in their ability to adapt to changed environments in the future. Following environmental change, the more evolvable clade survives and diversifies and replaces the one whose members could not adapt. Unfortunately, while plausible, the above is a clade-selection model, which evolutionary theory has traditionally found difficult to deal with. A mutation which increases evolvability would — if evolvability comes with a cost — be expected to be eliminated over the microevolutionary population genetics timescale. Short-term evolution will fix the genotype with the highest fitness. Only in the rare cases when the genotype with the highest fitness also has high evolvability will the lineage acquire the evolvability which would give it an advantage in the longer-term process of clade selection.

We should also remember that, while it is circular that a clade that evolves diversity must have been capable of finding the genotypes to do so, it does not follow from this that the accessibility or inaccessibility of such genotypes is necessarily the explanation for the difference between successful and unsuccessful clades. An unsuccessful clade might have been just as evolvable as a successful one, but
the genotypes that it could produce might not have matched the particular demands made by the changing environments. Thus again, if evolvability is looked on as quantitative and prospective, rather than absolute and retrospective, it is hard to predict the quantitative relationship between evolvability and clade survival, and with it produce a quantitative model for the evolution of evolvability.

References