NEWS AND COMMENTARY

Molecular clocks

The heavy, the cold, and the slow

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The best answer to the long-standing debate over the key determinates of the rate of molecular evolution might lie in a combination of two previously separate explanations, a new study reveals.

In the early 1960s, evolutionary biologists were engaged in a debate over whether there existed any regular patterns in the rate of evolution of genetic sequences. In response to this debate, Zuckerkandl and Pauling (1965) wrote a landmark paper in which they demonstrated that indeed in mammalian globin genes substitutions accumulated as a linear function of time. Zuckerkandl and Pauling termed their discovery the molecular clock.

A couple of years later, Kimura constructed a solid population-genetic basis for the molecular clock, under the assumption that most mutations are neutral or nearly neutral (Kimura, 1968, Kimura, 1983): neutral mutations appear at a rate proportional to the product of population size N and neutral mutation rate μ , and go to fixation with probability $1/N$. Thus, the rate of neutral evolution is given simply by $N\mu/N = \mu$. The neutral mutation rate μ is itself a product of the organism's overall mutation rate and the fraction of mutations that are neutral. The latter quantity can vary from gene to gene or from species to species. Therefore, according to Kimura's theory, the speed of the molecular clock can vary across species. This theoretical possibility appears to be borne out by empirical evidence. For example, rates of the molecular clock change with generation time (eg Wu and Li, 1985), temperature (eg Bleiweiss, 1998), or body size (eg Martin and Palumbi, 1993).

In a recent article, Gillooly *et al* (2005) raise an interesting hypothesis: the factors that speed up or slow down the overall rate of evolution of different species can be combined into a single scaling law that takes into account temperature and body size. Thus, at a

given temperature, the molecular clock slows down with increasing body mass, whereas at a given body mass, it speeds up with increasing temperature.

Gillooly *et al* make a convincing case that their combined scaling law provides a much better fit for molecular clock data than scaling laws that consider only one of the two factors. Their data set includes a fairly diverse set of species such as mammals, fish, birds, reptiles, and invertebrates, but excludes any microbial life forms. The data set spans 10 orders of magnitude in body size (from over 10^7 g in a whale to 10^{-3} g in a spider), and it spans a temperature range from 0°C (in an arctic fish) to 40°C (in various bird species).

Gillooly *et al* then use their scaling law to recalculate the molecular clocks of two species pairs for which the divergence time estimated from fossil data differs substantially from the divergence time previously estimated with molecular clock methods. They show that if they correct the molecular clock in these species for both body mass and temperature, the divergence time derived from the molecular clock is in agreement with the one derived from fossil data.

Is there an underlying theory that can explain Gillooly *et al*'s observation? Gillooly *et al* argue that the underlying principle responsible for the observed scaling is that the molecular clock ticks at a constant rate per unit of mass-specific metabolic energy rather than at a constant rate per unit time. The mass-specific metabolic rate, in turn, scales with body mass and temperature. For the scaling with body mass, Gillooly *et al* employ the West-Brown-Enquist (WBE) model, which correlates mass-specific metabolic rate with body size raised to the negative quarter power (West *et al*, 1997). This model is based on the fractal geometry of distribution networks within organisms.

The WBE model has recently received substantial criticism. For example,

some opponents argue that the WBE model is mathematically inconsistent (Kozłowski and Konarzewski, 2004), while others argue that in plants and warm-blooded animals, the flow of energy through the body surface puts tighter constraints on the mass-specific metabolic rate than do distribution networks (Makarieva *et al*, 2003). The latter argument predicts that the mass-specific metabolic rate scales with body size raised to the negative one-third, rather than one-fourth, and that there should be deviations from this scaling law for very massive organisms. Owing to these criticisms, the theoretical arguments for the particular scaling law used by Gillooly *et al* appear to be on shaky grounds.

However, regardless of how the discussion about the WBE model will play out in the future, the value of Gillooly *et al*'s contribution is the discovery of the empirical scaling law. Future work will have to show how well this scaling law holds up in more extensive data sets, and whether a similar scaling law extends to or exists also in the microbial world. Finally, it will be interesting to see whether theoreticians can come up with a generally accepted explanation for how and why the mass-specific metabolic rate should scale with body size and temperature, and by what mechanism an organism's metabolic rate affects its mutation rate.

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