

# Molecular Rate Variation (Molecular Clocks)

## Molecular Rate Variation

The rate of molecular evolution is the rate at which substitutions accumulate in an organism's genome. Rates of molecular evolution can vary dramatically, for example, the rate of molecular evolution in some viruses is around one substitution per base pair per 1,000 years (Pagán et al. 2010), while in mammals the rate is around one substitution per base pair per 1,000 million years (Nabholz et al. 2008). Even closely related plants and animals can have rates of molecular evolution that vary by more than an order of magnitude (Thomas et al. 2006; Smith and Donoghue 2008; Welch et al. 2008; Lanfear et al. 2013). Accounting for molecular rate variation is important in methods that use molecular sequence data to date the divergences between species (molecular dating).

There has been a great deal of research into the causes of variation in rates of molecular evolution. This research has identified a range of factors which may cause variation in the rate of molecular evolution (Bromham 2011), and these factors can be broken up into those that affect the mutation rate and those that affect the rate at which new mutations are fixed in a population (the fixation rate). An increase in either the mutation rate or the fixation rate can potentially increase the overall rate of molecular evolution, although there are some situations in which these increases will leave the rate of molecular evolution unchanged (de Visser et al. 1999).

Many factors have been suggested to increase mutation rates in DNA sequences, including temperature, UV radiation, oxygen radicals, recombination, genome copying, and natural selection (Martin and Palumbi 1993; Davies et al. 2004; Wright et al. 2006; Lanfear et al. 2007; Thomas et al. 2010; Hodgkinson and Eyre-Walker 2011; Wright et al. 2011; Lourenço et al. 2013; Lanfear et al. 2013). In principle, variation in any of these factors could cause variation in the rates of molecular evolution between species, although the evidence for this is weak for UV radiation and oxygen radicals in particular (Davies et al. 2004; Lanfear et al. 2007; Joyner-Matos et al. 2011; Lanfear et al. 2013). However, there is good evidence that the many mutations occur during genome-copying events (meiosis and mitosis) and that variation in long-term rates of genome copying may explain much of the variation in the rates of molecular evolution between species (Smith and Donoghue 2008; Welch et al. 2008; Thomas et al. 2010; Lanfear et al. 2013). Intriguingly, it has also been suggested that natural selection may play a role in determining mutation rates and rates of molecular evolution, either through selection for increased longevity (Nabholz et al. 2008; Welch et al. 2008; Galtier et al. 2009) or through the reduced efficacy of natural selection in small populations (Lynch 2010, 2011).

Anything that increases the fixation rate of new mutations can also increase the substitution rate. Two factors combine to determine the fixation rate of a new mutation: the effect of that mutation on the carrier's fitness and the effective population size of the host population. As fitness effects become more beneficial and effective population sizes get larger, fixation rates increase (Woolfit 2009). This is because a population's effective population size determines the balance of power between natural selection and genetic drift. The larger the effective population size, the stronger natural selection is relative to genetic drift, and the faster beneficial mutations are fixed in the population, and deleterious mutations removed. Because we expect most mutations to be deleterious, it is generally thought that organisms with smaller effective population size should have faster rates of molecular evolution. Some studies have supported this idea and have shown that organisms with smaller effective population sizes tend to evolve more quickly, at least by some measure of the rate of molecular evolution (Moran 1996; Woolfit and Bromham 2003, 2005). However, other results suggest that the relationship between population size and the rate of molecular evolution can be much more complex than this simple model suggests (Charlesworth and Eyre-Walker 2007; Wright et al. 2009).

We have a fairly good understanding of the most important causes of variation in rates of molecular evolution. But despite this, we can often explain less than half of the variation that we can measure, suggesting that we still have a lot to learn. A better understanding of molecular rate variation is important because it can help improve molecular dating methods. Perhaps the best example of this is the development of new methods which leverage what we know about the causes and correlates of molecular rates to directly improve our estimates of divergence dates from DNA sequence data (Lartillot and Poujol 2011; Lartillot and Delsuc 2012). As our understanding of molecular rate variation continues to increase, we will be able to continue to improve the accuracy of molecular dating methods.

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