

## Causes of single position fitness landscape changes

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Amino acid propensities at an amino acid site change with time, leading to amino acid substitutions and to molecular evolution. However, the causes of these changes are unclear. They may arise due to environmental changes; alternatively, even in a constant environment, they may arise due to changes in interacting sites elsewhere in the genome under epistasis. To distinguish between these possibilities, we analyze the phylogenetic distribution of substitutions at amino acid sites in the course of evolution of vertebrates, insects and fungi. We show that in general the fitness of the amino acid currently occupying a given amino acid site increases with time. Using simulations, we show that this is consistent with epistatic changes. By contrast, in rapidly evolving sites, the fitness of the amino acid currently occupying a given amino acid site declines with time, consistently with environmental fluctuations uncorrelated with the current genome content.