Recently it was indicated that fitness costs due to misfolded proteins are a determinant of evolutionary rate and selection originating in protein stability is a driving force of protein evolution. Here we examine protein evolution under the selection maintaining protein stability.

Protein fitness studied is a generic form of fitness costs due to misfolded proteins; $s = \kappa \exp(\Delta G / kT) (1 - \exp(\Delta \Delta G / kT))$, where s and $\Delta \Delta G$ are selective advantage and stability change of a mutant protein, ΔG is the folding free energy of the wild-type protein, and κ is a parameter representing protein abundance and indispensability. The distribution of $\Delta \Delta G$ is approximated to be a bi-Gaussian distribution, which represents structurally slightly- or highly-constrained sites. Also, the mean of the distribution is negatively proportional to ΔG.

The evolution of this gene has an equilibrium point ΔG_e, the range of which is consistent with observed values in the ProTherm database. The probability distribution of K_a/K_s, the ratio of nonsynonymous to synonymous substitution rate per site, over fixed mutants in the vicinity of the equilibrium shows that nearly neutral selection is predominant only in low-abundant, non-essential proteins of $\Delta G_e > -2.5$ kcal/mol. In the other proteins, positive selection on stabilizing mutations is significant to maintain protein stability at equilibrium as well as random drift on slightly negative mutations, although the average $<K_a/K_s>$ is less than 1. Slow evolutionary rates can be caused by high protein abundance/indispensability and large effective population size, which produce positive shifts of $\Delta \Delta G$ through decreasing ΔG_e, and by strong structural constraints, which directly make $\Delta \Delta G$ more positive. Protein abundance/indispensability more affect evolutionary rate for less constrained proteins, and structural constraint for less abundant, less essential proteins.
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