

A model of protein evolution within local fitness landscape changing with time

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Each amino acid in protein interacts with others. Thus fitness contribution of specific amino acid in particular site depends on the whole genetic background. This background changes over time resulting in change of allele fitness. In other words selection acting against particular alleles is not constant. We developed methods of analysis of long-term protein evolution which allow us to observe patterns of this altering selection. Then we formulate a covarion-like model of protein evolution, which describes this process mathematically. The model tracks not only the evolution of sequence but also the evolution of its local fitness landscape. In more details we allow fitness contribution of specific amino acid in particular site switch from being acceptable to being deleterious and *vice versa*. We calculated the rate of this switches for approximately 100 bacterial genes and 10000 vertebrates' genes. It appears that fitness landscape changes very fast: on average 5 switches between allowed and blocked states occur on the same timeframe as a single amino acid substitution.