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Fluctuations and the limit of predictability in protein evolution

Protein evolution involves mutations occurring across a wide range of time scales. In analogy with other disordered systems, this dynamical heterogeneity suggests strong correlations between mutations happening at distinct sites and times. To quantify these correlations, we examine the role of various fluctuation sources in protein evolution, simulated using a data-driven epistatic landscape. By applying spatio-temporal correlation functions inspired by statistical physics, we disentangle fluctuations originating from the ancestral protein sequence from those driven by stochastic mutations along independent evolutionary paths. Our analysis shows that, in diverse protein families, fluctuations from the ancestral sequence predominate at shorter time scales. This allows us to identify a time scale over which ancestral sequence information persists, enabling its reconstruction. We link this persistence to the strength of epistatic interactions: ancestral sequences with stronger epistatic signatures impact evolutionary trajectories over extended periods. At longer time scales, however, ancestral influence fades as epistatically constrained sites evolve collectively. To confirm this idea, we apply a standard ancestral sequence reconstruction algorithm and verify that the time-dependent recovery error is influenced by the properties of the ancestor itself.

Role

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