

# **The evolution of protein sequences – (nearly) every mutation counts**

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Protein sequences constantly change in the course of evolution, or drift, while structure and function remain largely unchanged. We do not, however, fully understand what governs these changes. Some proteins evolve very fast whilst others barely change, and different rates of evolution do not relate to how essential a protein is.

I will describe experimental and computational approaches aimed at understanding how protein sequences diverge. These include directed evolution experiments, and systematic mappings of the effects of protein mutations using deep sequencing.

Overall, it appears that almost no mutation is neutral. Even sequence exchanges that appeared initially at neutral, have, once other positions have drifted, an effect on the protein's stability and/or function. Overall, the divergence of protein sequences is highly correlated, or epistatic - given the right sequence context, even utterly conserved and functionally essential residues may change.