What governs the rate of amino acid substitutions?

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Researchers from various backgrounds have developed different conceptual models for how proteins evolve. Evolutionary biologists have emphasized how conservative mutations would be more likely to be accepted than more radical changes, just as how adjusting the fine focus of a microscope is more likely to yield an improvement than adjusting the course focus. Scientists with more of a structural biology background describe the match between location in the protein and the suitability of any amino acid for such a location - mutations to more suitable amino acids, including radical changes, should be accepted at a higher rate. There has been a growing understanding that a protein is an integrated system so that many of the selective constraints are properties of the entire protein such as structure, stability, solubility, and resistance to aggregation. In this perspective, the selection acting on one site is always in the context of the amino acids found in other sites. And as with the tangled bank described by Darwin, there will be a complex network of feedback loops; substitutions at one focal position will affect the selection acting on other sites; the corresponding substitutions at these other sites will, in turn, influence the selection acting on the focal position. These contrasting perspectives suggest different approaches to understanding and interpreting molecular evolution. We can simulate protein evolution in-silico over long periods of evolutionary time, and use these simulations to develop our ideas about what substitution models need to capture, the types of errors that might result from an inappropriate model, and how these approaches - with the help of concepts drawn from the chemical and physical sciences - can be reconciled.