GGSB PRELIM QUESTION # 4

Molecular features constrain molecular evolution. Because evolutionary changes in protein sequences reflect pressures and constraints on protein function, and function often arises from a protein's folded structure, evolution depends strongly on how mutations alter the stability with which a sequence folds into its native structure. Proteins tend to be marginally stable, a consistent observation which has inspired longstanding controversy.

1) Discuss how natural selection constrains protein stability. What other evolutionary forces constrain stability? Describe competing explanations for why proteins are marginally stable.

2) Suppose you wish to test the hypothesis that, for a specific protein, a particular function depends on marginal stability. How would you experimentally test this hypothesis? Describe conclusions you could draw from, and limitations of, your experimental approach. Gong et al. studied the evolution of influenza nucleoprotein.

3) Describe the system employed by the authors. What surprising discovery do they make about the L259S mutation? Why is the concept of epistasis important in understanding this finding?

4) How do the authors conclude that mutational effects are mediated by protein stability? What is their model for the interplay between mutational effects on function and stability in the evolution of influenza nucleoprotein?

5) Discuss the relationship between the observed marginal stability of evolved proteins and the evolution of nucleoprotein as conceptualized by Gong et al.

Reference

Stability-mediated epistasis constrains the evolution of an influenza protein," Gong LI, Suchard MA, Bloom JD, eLife 2013;2:e00631