Protein-protein interactions stabilize constituent proteins and act as evolutionary capacitors

Purushottam D. Dixit[1] and Sergei Maslov[1]

***Short Abstract* — Interacting proteins present a lower monomer concentration in the intracellular medium. Effectively, the concentration of the unfolded state of the monomer is also lowered. For cytoplasmic proteins of baker's yeast, we estimate that, in energetic terms, protein-protein interactions can account for ~2-4 kT of stabilization of the folded state of the monomer. We confirm our hypothesis that this stabilization interferes with the evolution of stable protein sequences: interaction network allows proteins to explore metastable regions of the sequence space, i.e. proteins receiving significant energetic help from their binding partners are more likely to misfold/unfold on their own.**

***Keywords* — Protein-protein interaction, protein stability, evolutionary capacitance**

I. Extended abstract

Protein-protein interactions prevent protein aggregation as aggregation prone surface regions usually overlap with interaction interfaces [1]. Also, proteins in multi-protein complexes effectively present a lower monomer concentration inside the cell. Since free monomers are susceptible to misfolding/unfolding, interacting proteins may face a reduced risk of aggregation compared to free monomeric proteins. We interpret this reduced risk as an additional interaction induced stabilization of an otherwise monomeric protein and quantify its magnitude. The stability is a function of the strength of protein-protein interaction, the number of interaction partners, and the concetration of interacting proteins. We propose that proteins in the interaction network may act as evolutionary capacitors for their binding partners: the interaction partners may contribute to the effective stability of proteins which are allowed to explore the less stable regions of the sequence space. Inversely, unstable proteins are expected to receive significant additional stability from the interaction network.

We test our idea on the interaction network of baker's yeast. We estimate that the interactions can account for 2-4 kT of stabilization and can be as high as 5-6 kT. Thus, interactions may interfere with the evolution of stable protein sequences. In fact, the interaction induced stability is correlated with predicted protein aggregation propensity. Moreover, the aggregation propensity is correlated with not only the total abundance of the protein [2,3,4] but also the total free monomer concentration. We employ a simplified model for the evolution of a hypothetical proteome wherein the fitness of the organism depends only on the total amount of unfolded proteins in the cytosol. The model is able to explain the observed relation between protein stability and interaction induced stability as a function of the effective population size. The model suggests that under high selection pressure, induced stability acts as as a secondary mechanism for proteins stability by supporting selectively the proteins which cannot evolve stability. The the genetic drift regime, interaction in duced stability plays the dominant role in the overall stability of proteins by stabilizing all proteins regardless of their inherent stability. We conclude by outlining biophysical and evolutionary experiments to test our hypothesis.

Acknowledgements: This work was funded by the DOE pilot project "Tools and models for integrating multiple cellular networks"

[1]Department of Biology, Brookhaven National Lab, Upton NY 11973. E-mail:pdixit@bnl.gov

[1]Department of Biology, Brookhaven National Lab, Upton NY 11973. E-mail:maslov@bnl.gov

References

[1] Pechemann, S. et al. PNAS, 106:10159, 2009
[2] Drummand D. A. et al. PNAS 102:14338, 2005
[3] Tartaglia G. G. et al. JMB, 380:245, 2008
[4] Drummond D. A. and Wilke C. O., Cell 134:341, 2008