Engineering Regulatory Protein Complex through Interface Design: a Dynamic Simulation Study

Yi Mao[1]

Short Abstract — **Dynamic protein interactions underlie much of the signal transduction networks that regulate biological processes. Here we use elastic network modeling of proteins to study how the information transmission in signal transduction is facilitated by the functional architecture of proteins. A designed chimeric protein, PAS-DHFR, which exhibited light-dependent catalytic activity that depended on the site of connection and on known signaling mechanisms in both proteins, was chosen as a model system. Protein dynamic simulations characterize the signal transduction pathways involved in this protein complex, and the results support the concept of engineering regulatory activities into proteins through interface design.**

Keywords **— elastic network model, correlation analysis, pathway.**

I. Purpose

Cells process information about the external world through networks of proteins and small molecules that constitute the signal transduction machinery. The goal of our study is to understand the molecular basis of these information processing systems. Recent experiments have explored the possibility of constructing a synthetic regulatory protein complex by joining two proteins across the surface sites, such that the activity of one protein might control the activity of the other. PAS-DHFR, a designed chimeric protein that connects a light-sensing signaling PAS domain with Escherichia coli dihydrofolate reductase (DHFR), possessed catalytic activity regulated by light [1]. One of the major challenge in designing such a system is to find the right interface of linking these two proteins, which permits the information transmission from one protein to the other. The search was accomplished by utilizing a statistical coupling analysis (SCA) of sequence data in the reported study. The SCA method is based on identifying coevolving amino acid residues involved in enzyme catalysis. It requires a sufficient amount of sequence data with high accuracy, and is unable to provide structural insights.

Acknowledgements: This work was funded by NSF Award #EF-0832858IH.

[1]National Institute for Mathematical and Biological Synthesis, University of Tennessee, Knoxville, TN 37996 E-mail: maoyi0@gmail.com

Here we employ a coarse-grained protein model (elastic network model) to identify possible pathways of communications in PAS-DHFR. The correlation matrix computed from elastic network modeling [2] is subject to clustering analysis, which then yields signal transduction pathways initiated at the ligand binding sites. In order to generate coupled activities in designed chimeric proteins, an interface that links signal transduction pathways in both proteins is sought after.

II. Results

A. Identification of signal pathways based on correlation matrix and clustering analysis

The correlation matrix contains the energetic correlations between all interacting residue–residue pairs generated by the elastic network modeling. To extract information about protein domain-domain interactions, a clustering algorithm (Markov cluster algorithm) was performed on the correlation matrix. The residues clustered with the binding site constitute a pathway that extends to the distal regions on the surface.

B. Interface design

For PAS domain, the signal pathway from the ligand binding site consists of the α3 helix and β4-β5 linker on the surface; while in DHFR the clustering analysis reveals βF-βG loop as the most distant surface-exposed site with the strong coupling with the enzyme active site. The interface is then identified as the region connecting both surface sites.

III. Conclusion

The structural based protein dynamic modeling is a robust approach in identifying pathways of intramolecular signal transduction.

References

[1] Lee, J., M. Natarajan, V. C. Nashine, M. Socolich, T. Vo, W. P. Russ, S. J. Benkovic, and R. Ranganathan (2008) Surface Sites for Engineering Allosteric Control in Proteins. *Science*. 322,438-442.

[2] Chennubhotla, C, Rader, AJ., Yang, LW, and Bahar, I. (2005) *Phys. Biol.* 2,S173-S180.

[3] Mao Y, "Engineering regulatory protein complex through interface design: a dynamical simulation study" in preparation.