Local and Global Dynamics in Protein Networks

Boris Y. Rubinstein[1], Jay R. Unruh[1], Brian D. Slaughter[1], Arupratan Das[1], Juntao Gao[1], Inês M. Pinto[1], and Rong Li[1]

***Short Abstract* — We report a development of an interactive hybrid *Mathematica*-ImageJ based software for analysis of Cdc42 membrane protein spatial distribution and dynamics in the polarized yeast cells. We also discuss a novel approach to describe the dynamic characteristics of proteins localized to the polar cortical domain (PCD) in the budding yeast. The approach is based on the analysis of the protein's physical interaction network modularity, local connectivity and set of kinetic constants describing the modules.**

***Keywords* — network modularization, Cdc42 protein, yeast cell, *Mathematica*, Image J, interactive tool.**

Description of dynamics and membrane spatial distribution of the Cdc42 protein, which is key regulator of polarized morphogenesis in budding yeast cells, is important for understanding of cellular polarization maintenance. A simple mathematical model suggested in [2] describes Cdc42 membrane dynamics depending on surface diffusion, internalization to cytosol and return flow from the cytosolic pool to PCD. Membrane internalization rates inside and outside of PCD are assumed to be different.

We extend [1] this model to the case when the Cdc42 dynamics is governed by two independent processes characterized possibly by different geometric domains. We obtain an analytical solution for the steady state membrane protein distribution that should be fitted to the experimental data to obtain the model parameter values. The fitting procedure requires both analysis of FRAP image data and comparison to the analytic distribution characteristics.

We develop interactive software that uses ImageJ, open source Java-based image processing software, and commercial computer algebra package *Mathematica*. The *Mathematica* user selects the FRAP image stack, performs simple operations (selection of background area, region of interest, etc.) in ImageJ to collect required information. The control is transferred back to *Mathematica* to finish computation and obtain the model parameter values. This software can be useful for detailed analysis of sertain proteins playing key roles in cell life cycle.

A global view on protein dynamics is represented by the analysis of physical (or genetic) interactions network. One of the popular approaches consists in establishment of modular structure of the network where each module can be associated with some biological function. There exist several modularization algorithms including the one described in [3] which we use for the modularization of the protein network localized to PCD and identify 5 modules that have distinct functions.

The protein dynamics characterized by the residence time a protein spends at PCD we measure using an iFRAP method for proteins from two modules. We cannot find any significant correlation between certain protein residence time and its network nodal properties. On the other hand, assigning a characteristic kinetic constant τ to each module, we find that the residence time can be estimated by the weighted average link time with various modules as determined by the τ values and number of links of this protein with various modules in the network.

To validate this model we select a set of 10 proteins with their links most widely distributed to various modules (therefore providing information on other interacting modules) and use an exhaustive search algorithm to find minimal "training" set and obtain τ values for all modules. We check this prediction by measuring the residence time for several proteins from the third module and these values are close to the predicted ones.

We hypothesize that protein dynamics in the PCD are globally determined by the protein interaction network properties and kinetic constants that characterize functional modules of the PCD.

References

[1] Slaughter B.D., et al. (2009) Dual modes of Cdc42 recycling fine-tune polarized morphogenesis. *Developmental Cell* **17**, 823-835.

[2] Marco E., et al. (2007) Endocytosis optimizes the dynamic localization of membrane proteins that regulate cortical polarity. *Cell* **129**, 411-422.

[3] Guimerà R., Amaral L.A.N. (2005) Functional cartography of complex metabolic networks. *Nature* **433**, 895-900.

Acknowledgements: This work was funded by NIH grant GM057063.

[1]Stowers Institute for Medical Research, Kansas City, MO, 64110. E-mail: bru@stowers-institute.org