Spatial Localization of Chaperone BiP in the Endoplasmic Reticulum of Yeast

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***Abstract* — We have developed a spatial model of protein interactions in the endoplasmic reticulum (ER) of yeast (*Saccharomyces cerevisiae*) to study the impact of spatial heterogeneity on the functionality of these proteins. At the ER membrane, chaperone BiP interacts with the membrane-bound Sec63 in assisting protein translocation. Our computational simulations suggest that Sec63's localization at the ER membrane enables a heterogeneous distribution of BiP in the ER, and may facilitate BiP's role in translocation.**

In eukaryotes, the endoplasmic reticulum (ER) serves as the first membrane-enclosed organelle in the secretory pathway, with functions including protein folding, translocation of nascent peptides, protein degradation, and karyogamy. [1] Molecular chaperones, of the Hsp70 family of proteins, participate in assisting these processes through co-chaperone interactions and are essential to cellular function and survival. Some of these processes occur near the membrane, while others occur in the ER lumen (interior) leading to the hypothesis that spatial localization impacts protein function. Our focus is in investigating how BiP, an ER resident chaperone of yeast, interacts with the membrane-bound co-chaperone Sec63 in translocation, a process in which BiP assists in guiding a nascent protein through a membrane pore into the ER lumen.

In vitro experiments [2] suggest that Sec63 acts as an anchor, localizing BiP within the proximity to the translocation channel, and accelerates the transit of a peptide through the membrane by regulating ATP hydrolysis of the chaperone. This work combines the experimental evidence of co-chaperone mediated interactions with a spatial component describing ER sub-compartments of the membrane and lumen. Our goal is to use modeling to better understand the role of Sec63 in the distribution of BiP within the ER.

Our partial differential equation (PDE) model (Figure 1) incorporates: (1) chemical reactions taking place in both the membrane-associated zone and the lumen, and (2) diffusion from the membrane into the ER lumen. Kinetic constants were obtained from the literature from yeast and mammalian data. The irregular geometry of the ER was simplified to an annular sphere and assumed to be symmetric. The system was then modeled in one spatial dimension.

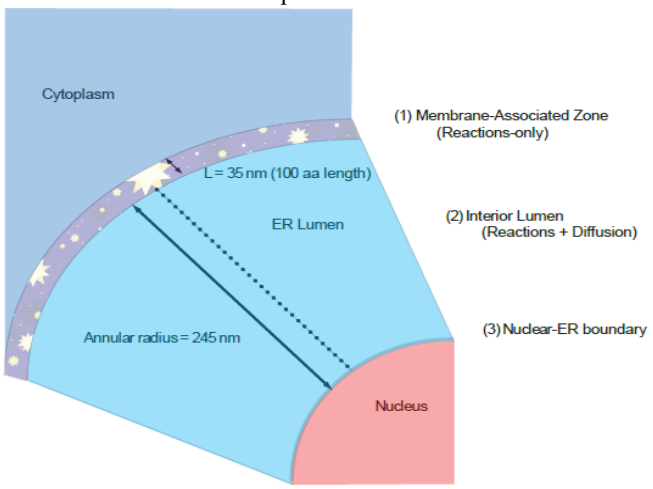

Figure 1: Schematic of the PDE model consisting of a membrane-associated zone and lumen.

Computational scenarios were constructed to mimic wild-type (membrane-bound) and variant forms of Sec63 in relation to the interaction with BiP in translocation. We found that when Sec63 participates in translocation through localization at the membrane, the spatial distribution of BiP is heterogeneous, with more BiP at the surface. When translocation is inhibited by removing Sec63's membrane tether, the distribution of BiP in the ER becomes homogeneous. Our computational simulations suggest that Sec63's localization and the resulting binding to BiP near the ER membrane surface enable a heterogeneous distribution of BiP in the ER, and may facilitate BiP's role in translocation.

In creating this model, we have taken a step in making predictions to determine the relative importance of BiP in its interactions in the ER. Next we intend to investigate the impact of low BiP concentrations on system behavior and whether the irregularity of the ER geometry affects localization or BiP function.

Acknowledgements: This work was funded by NSF IGERT DGE02-21715, and NIH GM07529.

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References

[1] Fewell SW, Travers K, Weissman JS, Brodsky JL (2001). The action of molecular chaperones in the early secretory pathway. *Ann. Rev. Genetics* 35(1), 149-191.

[2] Corsi AK, Schekman R (1997). The luminal domain of Sec63 stimulates the ATPase activity of BiP and mediates BiP recruitment to the translocon in *Saccharomyces cerevisiae*. *J. Cell Biol*. 137(7), 1483-1493.