Ranking proposed yeast feedback networks through Approximate Bayesian Computation parameter estimation and model selection.

Patrick McCarter[1,3], Justin English[2], Henrik Dohlman[1,2,3], Tim Elston[1,2].

Stress-Activated Protein Kinase (SAPK) pathways utilize specialized Mitogen-Activated Protein Kinases (MAPK) to protect cells against environmental stressors. However dysregulated SAPK pathways are also found in several pathologies. In this work we apply a multi-disciplinary research strategy that combines mathematical modeling, model selection, biochemical and genetic experimentation in the *S. cerevisiae* (yeast) High-Osmolarity Glycerol (HOG) pathway to better understand how MAPKs coordinate responses to environmental stress.

I. Purpose

Mitogen-Activated Protein Kinases (MAPK) protect cells against ischemia[1], hyper-osmolarity, uv-irradiation[1], [2] and other stressors. However dysregulated MAPK pathways are also found in Alzheimer's Disease[5], Amyotrophic Lateral Sclerosis[3] and cancer[4]. In this work we detail a multi-disciplinary research effort that combines mathematical modeling, biochemical and genetic experimentation in the *S. cerevisiae* (yeast) High-Osmolarity Glycerol (HOG) pathway to better understand how MAPKs coordinate responses to environmental stress. The HOG pathway is a prototypical Stress-Activated Protein Kinase pathway that transmits osmostress to the Hog1 MAPK via two distinct signaling branches (Sho1, Sln1). Hog1, which is homologous to the mammalian p38 and JNK kinases, translocates to the nucleus upon activation, where it induces activation of stress response genes.

Using Phos-Tag polyacrylamide western blot analysis[5], we have shown that Hog1 activation is encoded via positive feedback and that deactivation is encoded via negative feedback[6]. We use mathematical modeling to identify the most likely feedback network that dynamically regulates Hog1 in response to sustained hyper-osmotic stress. We have thus far been successful in identifying models that agree with our preliminary experimental data. We now extend our modeling process to objectively rank the models using Approximate Bayesian Computation (ABC) techniques to perform model selection[7].

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Curriculum in Bioinformatics and Computational Biology[1], Department of Pharmacology[2], Department of Biochemistry and Biophysics[3], University of North Carolina School of Medicine, Chapel Hill, NC, USA

II. Conclusion

Many signaling mechanisms discovered in yeast are conserved in human cells. Understanding how MAPKs are regulated during stress and how MAPK dysregulation contributes to pathology is critical for human health.

III. References

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