**A multiscale model of metabolism and protein expression predicts the response of *E.* coli to oxidative stress**

Laurence Yang1, James T. Yurkovich1,2, Colton J. Lloyd1, Ali Ebrahim1, Michael A. Saunders3, Bernhard O. Palsson1,2,4

1Department of Bioengineering, University of California, San Diego, La Jolla, California, USA. 2Bioinformatics and Systems Biology Program, University of California, San Diego, La Jolla, California, USA. 3Department of Management Science and Engineering, Stanford University, Stanford, California, USA. 4Novo Nordisk Foundation Center for Biosustainability, The Technical University of Denmark, Hørsholm, Denmark

Genome-scale models (GEMs) are mathematical optimization-based models that predict fluxes through biochemical reaction networks comprising metabolism. Since 2012, GEMs have been extended to include protein expression, resulting in multiscale models of Metabolism and macromolecular Expression (ME models). The computational challenges associated with these multiscale models were recently addressed. Subsequently, we have investigated how ME models can be further developed to expand the biological scope of their predictions.

First, we investigated discrepancies between predicted versus measured proteome allocation of the generalist microbe *Escherichia coli* under 15 growth conditions. To do so, we estimated from proteomics data the fraction of proteome allocated toward functions of no immediate benefit for growth in that condition. These functions were enriched for the general stress response sigma factor σS and could thus be considered as “hedging” functions. From these estimates, we constrained the ME model at the levels of transcription and translation to express these proteins. Our predictions of metabolism and growth rate improved markedly.

Second, we reconstructed the pathways of protein damage by the reactive oxygen species (ROS) hydrogen peroxide and superoxide, and the repair processes. Specifically, we modeled the inactivation and repair of Fe-S-dependent enzymes. We also modeled the loss of mononuclear Fe(II) from metalloenzymes and their subsequent mismetallation by alternate divalent metal ions including Zn(II) and Mg(II). This “stressME” model quantitatively reproduced the inactivation of Fe(II)- and iron-sulfur cluster-dependent enzymes under varying oxidative stress. We could also predict the system-wide effect of oxidative stress, including shifts in proteome allocation (validated using high-throughput omics data) and fitness under varying ROS concentrations. The stressME model thus provides a mechanistic framework for studying microbial response to oxidative stress. StressME is expected to be useful for investigating the tolerance of pathogens against immune responses and certain antibiotics.

Presenter: Laurence Yang, Ph.D.

Funded by the National Institute of General Medical Sciences of the National Institutes of Health (award U01GM102098)