179. A Regulated odel for *Clostridium acetobutylicum* ased on Response to utanol and utyrate tress

Satyakam Dash[1]* (sid5219@engr.psu.edu), Thomas J. Mueller[1]* (tjm5293@psu.edu), Keerthi P. Venkataramanan[2], **Eleftherios T. Papoutsais**[2], and **Costas D. Aranas**[1]

[1]Department of Chemical Engineering, The Pennsylvania State University, University Park, PA;
[2]Department of Chemical Engineering and Delaware Biotechnology Institute, University of Delaware, Newark, DE.

http://maranas.che.psu.edu

Project Goals: This project aims to understand and model the stress response of *Clostridium acetobutylicum* ATCC 2 to two important toxic metabolites: butanol and butyrate, using a regulated genome scale model.

Clostridia are anaerobic Gram-positive Firmicutes containing broad and flexible systems for substrate utilization, which have been used successfully to produce a range of industrial compounds. In particular, *Clostridium acetobutylicum* has been used to produce butanol on an industrial-scale through acetone–butanol–ethanol (ABE) fermentation. A genome-scale model is a powerful tool for understanding the metabolic capacity of an organism. The inclusion of regulatory information to a genome-scale model provides additional reliability for phenotype predictions. This work describes the construction of a genome-scale metabolic model of *C. acetobutylicum* ATCC 824, *i*CAC802, and its integration with experimental gene transcription data. *i*CAC802 spans 802 genes and includes 1137 metabolites and 1470 reactions along with gene-protein-reaction associations.

Both ^{13}C-MFA and gene deletion data in the ABE fermentation pathway were used to test the predicted allowable flux ranges by the model. Transcription data measured in response to two stressors, butanol and butyrate, were used to impose 1071 regulatory constraints in the form of flux bound constraints for the *i*CAC802 model using the E-Flux method. These bounds affected the flux of tens of reactions in core metabolism. This regulated metabolic model was tested through comparisons with experimental fermentation data under the same stressed conditions. The regulated model showed down-regulation of glucose uptake as observed experimentally under stress conditions. The model including the regulatory restrictions under stress exhibited an approximately 50% reduction in biomass yield which is in broad agreement with experimental data. The experimental fermentation data for acetate and butyrate also lie within the flux ranges predicted by the model.

Our ultimate goal in developing a regulated model is to achieve precise, condition-specific metabolic predictions to aid redesign in pursue of a desired overproduction phenotype.

The work was supported by the genomic science grant from Department of Energy, USA (grant # DE-SC0007092).