SHELL SEMINAR SERIES
CHEMICAL & BIOLOGICAL ENGINEERING

Metabolite Valves: Dynamic Control of Metabolic Flux for Pathway Engineering

Kristala L. J. Prather

Arthur D. Little Professor of Chemical Engineering
MacVicar Faculty Fellow
Massachusetts Institute of Technology, Cambridge, MA

Friday, February 1st, 2019 • 10 a.m. • CTLM, Room 102

ABSTRACT Microbial strains have been successfully engineered to produce a wide variety of chemical compounds, several of which have been commercialized. As new products are targeted for biological synthesis, yield is frequently considered a primary driver towards determining feasibility. Theoretical yields can be calculated, establishing an upper limit on the potential conversion of starting substrates to target compounds. Such yields typically ignore loss of substrate to byproducts, with the assumption that competing reactions can be eliminated, usually by deleting the genes encoding the corresponding enzymes. However, when an enzyme encodes an essential gene, especially one involved in primary metabolism, deletion is not a viable option. Reducing gene expression in a static fashion is possible, but this solution ignores the metabolic demand needed for synthesis of the enzymes required for the desired pathway.

We have developed “metabolite valves” to address this challenge. The valves are designed to allow high flux through the essential enzyme during an initial period where growth is favored. Following an external perturbation, enzyme activity is then reduced, enabling a higher precursor pool to be diverted towards the pathway of interest. We have designed valves with control at both the transcriptional and post-translational levels. In both cases, key enzymes in glucose metabolism are regulated, and two different compounds are targeted for heterologous production. We have measured increased concentrations of intracellular metabolites once the valve is closed, and have demonstrated that these increased pools lead to increased product yields. We have also incorporated quorum-sensing circuits into the valve design, enabling fully autonomous triggering of flux regulation. These metabolite valves should prove broadly useful for dynamic control of metabolic flux, resulting in improvements in product yields.

BIO **Dr. Kristala Jones Prather** is the Arthur D. Little Professor of Chemical Engineering at MIT. She received an S.B. degree from MIT in 1994 and Ph.D. from the University of California, Berkeley (1999), and worked 4 years in BioProcess Research and Development at the Merck Research Labs prior to joining the faculty of MIT. Her research interests are centered on the design and assembly of recombinant microorganisms for the production of small molecules, with additional efforts in novel bioprocess design approaches. A particular focus is the elucidation of design principles for the production of unnatural organic compounds with engineered control of metabolic flux within the framework of the burgeoning field of synthetic biology. Prather is the recipient of an Office of Naval Research Young Investigator Award (2005), a Technology Review “TR35” Young Innovator Award (2007), a National Science Foundation CAREER Award (2010), the Biochemical Engineering Journal Young Investigator Award (2011), and the Charles Thom Award of the Society for Industrial Microbiology and Biotechnology (2017). Additional honors include selection as the Van Ness Lecturer at Rensselaer Polytechnic Institute (2012), and as a Fellow of the Radcliffe Institute for Advanced Study (2014-2015). Prather has been recognized for excellence in teaching with the C. Michael Mohr Outstanding Faculty Award for Undergraduate Teaching in the Dept. of Chemical Engineering (2006, 2016), the MIT School of Engineering Junior Bose Award for Excellence in Teaching (2010), and through appointment as a MacVicar Faculty Fellow (2014), the highest honor given for undergraduate teaching at MIT.

COLORADOSCHOOLOFMINES
EARTH • ENERGY • ENVIRONMENT