4bw Regulatory Networks in Escherichia Coli: Chemogenomic-Based Identification of the Nitrogen Oxide Response and Stochastic Modeling of Pap Operon Regulation

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Two representative regulatory networks in E. coli were investigated using complementary approaches. For one network, expression data was used to identify network elements; for the other, existing network data was used to generate a model that predicts expression. In the first network, nitric oxide response elements were identified using a chemogenomic-based analysis of expression. This approach has thus far identified both previously known and new RNOS response elements. In the second network, a mathematical model of pap operon regulation was formulated based on existing mechanistic data. The model predicts expression data in a variety of conditions and in regulatory mutants and demonstrates the applicability of mathematical modeling to investigation of regulatory networks.

Reactive nitrogen oxide species (RNOS) are produced by the human immune system in response to bacterial infection and thus the bacterial response to RNOS is relevant to the understanding of pathogenesis. In order to identify RNOS transcriptional response regulators and the underlying network structure in E. coli, we have used Network Component Analysis (NCA) to decompose transcriptome measurements into transcription factor activity (TFA) and partial network structure. We have employed an iterative investigation between NCA and transcriptomic experiments in order to include non-traditional transcriptional response elements, such as the stringent response, in the data analysis. In this manner, we have identified the ArcAB two-component system, iron-sulfur cluster repair regulator IscR, known RNOS-response regulator NorR, and the stringent response as RNOS response elements in E. coli. Additionally, we have identified new potential regulatory connections within the response network.

As described in (Jarboe et al 2004), we have generated a mathematical model of pap operon regulation based on existing mechanistic data. This model was used to investigate the role of individual regulatory components in overall system behavior and to demonstrate the contribution of regulatory models to understanding systems biology. The pap operon encodes the P-pili, which are often associated with pyelonephritis and thus the results are applicable to both pathogenesis and public health. Generation of this model included description of 140 regulatory states and estimation of 21 independent parameters. The model was verified using reported data and then used to investigate the sensitivity of the system to regulator levels and growth rate as well as the behavior of two in silico regulatory mutants. We have used two mathematical approaches, the Gillespie method (Jarboe et al 2004) and Markov Chain modeling (Zhou et al 2005).