183. Determining the control circuitry of redox metabolism at the genome-scale

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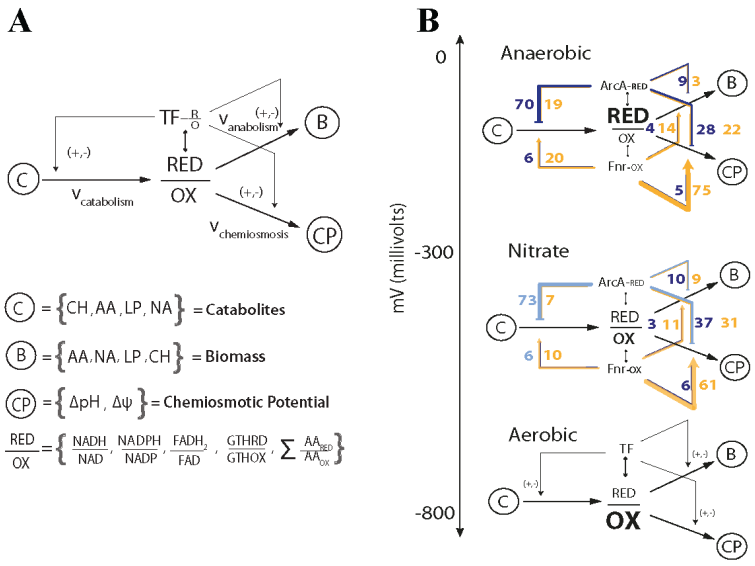
Project Goals:
This project aims to: (1) create a fully curated, bottom up reconstruction of the transcriptional regulatory network in *Escherichia Coli*, (2) determine fundamental constraints on the regulatory response via network and sequence level features, (3) develop a non-Boolean constraints based modeling approach for regulation, (4) integrate the transcriptional regulatory network with metabolic and macromolecular synthesis models, and (5) provide a platform for genome scale metabolic engineering and synthetic design.

Project Description:
Determining how facultative anaerobic organisms sense and direct cellular responses to oxygen availability has been the subject of intense study. However, even in the model organism Escherichia coli, existing mechanisms only explain a small fraction of the hundreds of genes that are regulated. Here we propose a model that accounts for the full breadth of regulated genes by detailing how two global transcription factors (TFs), ArcA and Fnr of Escherichia coli, sense redox ratios and act on a genome-wide basis to coordinately balance anabolic, catabolic, and energy generation pathways. We first addressed gaps in the regulatory network by carrying out ChIP-chip and gene expression experiments to identify 463 regulatory events. We then interfaced this reconstructed regulatory network with a highly curated genome-scale metabolic model and show that ArcA and Fnr control > 80% of total metabolic flux. Finally, we provide evidence for a proposed feedforward with feedback trim model by calculating a 0.71($p < 1e-6$) correlation between changes in metabolic flux and changes in regulatory activity across fermentative and nitrate respiratory conditions. We also are able to relate the proposed model to a wealth of previously generated data.


A
TF
R
O
RED
OX
C
B
CP
(+,-)
$v_{catabolism}$
$v_{anabolism}$
$v_{chemiosmosis}$
C = {CH, AA, LP, NA} = Catabolites
B = {AA, NA, LP, CH} = Biomass
CP = {ΔpH, Δψ} = Chemiosmotic Potential
RED/OX = {NADH/NAD, NADPH/NADP, FADH2/FAD, GTHRD/GTHOX, Σ AA_RED/AA_OX}
B
0
-300
-800
mV (millivolts)
Anaerobic
ArcA-RED
RED
OX
Fnr-OX
70 19
6 20
9 3
4 14
28 22
5 75
Nitrate
73 7
6 10
10 9
3 11
37 31
6 61
Aerobic
TF