Growth Rate Effects on Global Regulation of E. coli Oxygen Sensing

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Short Abstract — The long-term goal of this work is to characterize the relationship between cyclic regulation and the physiological constraints affecting the fumarate and nitrate reduction (FNR) network in Escherichia coli. In this report, we formulate a model of this system, fit its parameters to existing experimental data, and predict results that were not used in the fitting process. The results show excellent agreement between predicted and experimental data. Finally, we predict the effect altering the growth rate has on the dynamics of active FNR protein during the aerobic to anaerobic transition.

Keywords — Fumarate and Nitrate Reduction, FNR, Biochemical Systems Theory, Genetic Regulation.

I. INTRODUCTION

The FNR network of Escherichia coli regulates the shift between aerobic and anaerobic growth. Regulation of FNR involves a mechanism wherein FNR is produced and cycled through its active and inactive states. Dimeric 4Fe-FNR, a global transcription factor, adapts the cell to oxygen limiting conditions [1-3]. Aerobically, oxygen inactivates FNR, but the cell continues to produce and reactivate it [3]. This results in a constant cycling of FNR between its three states apoFNR, 4Fe-FNR, and 2Fe-FNR. Aerobic cycling is tuned so that the inactive apoFNR predominates [4]. Under anaerobic conditions, the absence of oxygen results in a rapid build up of 4Fe-FNR. The 4Fe-FNR form dimerizes to produce an active transcription factor that regulates hundreds of genes [1,2,5].

Between the synthesis, degradation, and construction of iron-sulfur clusters, E. coli pumps a constant stream of material through the FNR pathway and ties up valuable iron resources in the process. Paradoxically, the FNR cycle serves no apparent use under aerobic conditions [6]. Systems with this topology and apparent lack of physiological purpose have been termed futile cycles. There is reason to believe that futile cycles such as FNR, which have all their proteins at the ready, can respond quickly to an environmental signal. A cell that can transition rapidly between aerobiciosis and anaerobiosis has a potential growth advantage. The first step toward further understanding for the role of cycling in the FNR system is to develop a model we can analyze that accurately represents the real network.

II. MODEL CHARACTERISTICS

We formulate a model of the FNR system based on available literature and refine it to satisfy five experimental criteria and a set of pulse-chase data. By employing the technique of compartmental analysis to understand the intricacies of relating the model to a pulse-chase experiment, we are able to tease out a parameter set such that our model correctly mimics two wild-type pulse-chase assays.

We then introduce mutations into our model and predict the related mutant phenotypes. We test our model and its associated parameter set by checking its predictions against experimental data describing those mutant phenotypes. Specifically, we predict the pulse-chase curves of the mutants and show that the literature agrees with our predictions. We then predict the dynamics of the aerobic to anaerobic transition at different growth rates, which has never been experimentally examined.

III. CONCLUSION

We formulate a model of FNR regulation and fit its parameters to replicate wild-type behavior. We validate the model by correctly predicting known mutant behavior. We then proceed with predicting the dynamics of the FNR network at different growth rates.

REFERENCES


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