Network architectures compatible with the nonmonotonic dynamics of central metabolism genes under hypoxic stress in *M. tuberculosis*

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Short Abstract — Mycobacterium tuberculosis **responds to stress encountered during infection by arresting multiplication and undergoing major metabolic remodeling leading to dormancy. The metabolic genes *gltA1* and *icl1* are controlled by the sigma factor E (σ^E) and they are induced in response to adaptive immunity in the lungs of infected mice. We investigate the relationships between the network architecture and underlying dynamics for σ^E network to explain nonmonotonic kinetics of induction of these central metabolism genes under hypoxic stress.**

Keywords — M. Tuberculosis**, Sigma Factor E, Feed-Forward Loops, hypoxic stress response.**

I. Background

THE tuberculosis is a major infectious disease of humans. One-third of the world population is infected with M. tuberculosis, and 1.7 million people died from it in 2009 (http://www.who.int/tb/). Systems biology approaches provide the tools crucial to understand the stress response of the tubercle bacillus and control the disease.

One of the best characterized mycobacterial sigma factors, σ^E, controls expression of genes that down-modulate the macrophage inflammatory response, and other target genes critical to central metabolism, such as *icl1* (glyoxylate shunt) and *gltA1* (methylcitrate cycle), and their local regulators (*lrpI* and *lrpG*). Our goal is to understand σ^E regulatory network dynamics in *M. tuberculosis*.

Datta *et al.* showed non-monotonic induction of these local regulators (LR) and target genes in the σ^E network [1]. However, it is not clear how this dynamics is achieved.

II. Results

Using the theory of monotone systems with inputs and outputs [2], we conclude that the network proposed in [1] is inconsistent with the non-monotonic behavior, as it is not possible to get non-monotonic kinetics without a negative loop in the network. Therefore, potential network solutions for non-monotonic gene expression dynamics must include either a negative feedback or an incoherent feed-forward loop. We generated several network topologies based on known and hypothetical biochemical interactions. For each network, we built mathematical models to predict time-course data of mRNA and proteins. Then, we used numerical optimization methods to determine parameter sets that best fit available experimental data. Based on goodness of fit, we either accept or reject candidate network architectures.

Because of the sigmoidal response of σ^E to hypoxic stress, the network should also include a positive feedback. This is found between σ^E and MprA [3]. Effective cooperativity in LR induction indicates either ultrasensitive regulation of σ^E activity postranslationally by antisigma factor or positive feedback of LR on itself. The model predicts a negative regulator which may be either a transcription factor or a protease. In case this negative regulator is a protease, the model requires positive autoregulation of LR. By examining the σ^E and MprA regulons, we found several candidate genes such as proteases *pepD, rv2460c,* and transcription factors *clgR, rv3855* that might be responsible for the negative loop.

III. Conclusion

Protease PepD is a good candidate for the proposed negative regulator [4]. More dense time series data would help distinguish among possible networks. New experiments are designed to distinguish among possible networks and to verify some of the model predictions including the predicted negative regulator in the network.

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