Dynamics of Stress Response in Bacteria

Satyajit D. Rao[1], Pratik Dutta[2], Maria Laura Gennaro[2] and Oleg Igoshin[1]

***Short Abstract* — In order to successfully colonize a host, bacterial pathogens must sense and adapt to stress conditions such as damage to cell membrane. In human pathogen *Mycobacterium tuberculosis*, the disease causing agent of Tuberculosis, response to cell membrane damage is regulated by MprA/B two-component signaling system, and the alternative sigma factor σ^E. The stress regulatory network features multiple layers of regulation including transcriptional feedback and post-translational regulation. Using time-course qRT-PCR data for *sigE* and *mprA* genes following exposure to membrane damaging stress, we aim to uncover how network architecture shapes the observed dynamic response.**

***Keywords* — dynamical properties, feedback, networks.**

I. Introduction

THE pathogen *Mycobacterium tuberculosis* (Mtb) can cause a latent tuberculosis (TB) infection by reprogramming its metabolism and gene expression to a persistent, non-replicating state. To successfully colonize human hosts, Mtb must sense and adapt to stresses generated by the host immune system [1]. One such stress, damage to cell membrane, is regulated by transcriptional master regulators – MprA/B two-component system (TCS) and alternative sigma factor σ^E [2].

Exposure of Mtb cells to membrane damaging stress leads to activation of the MprA/B TCS. MprA is autoregulatory, and upregulates the *mprA-mprB* operon. In addition, it activates transcription of *sigE*, whose gene product σ^E in turn upregulates *mprA-mprB* [4]. This sets up a network with two transcriptional positive feedback loops – direct (autoregulation) and indirect. Further complexity is added to the network by post-translational sequestration of σ^E by its cognate anti-sigma factor RseA, preventing downstream gene activation [3].

II. Results

Previous theoretical work from our lab has suggested that the MprA/B- σ^E network described above can be bistable [3]. Specifically, the positive feedback loops combined with ultrasensitivity generated by strong σ^E-RseA interaction give rise to bistability in some parameter ranges. However, a step change from unstressed to stressed conditions with this bistable model results in a large activation delay. To verify this experimentally, we quantified transcript abundance of *mprA*, *sigE* and *sigB* (reporter for σ^E activity) in Mtb cells exposed to surfactant SDS. Time course of the transcripts was collected along with dose-response measurements at increasing and decreasing SDS doses. While time-course measurements reveal surprisingly rapid accumulation given the positive feedback circuit, dose-response measurements reveal hysteresis in *sigE*, *mprA* transcript levels between previously unstressed and previously stressed Mtb cells.

Utilizing this data, we have succeeded in constructing a model that explains the dynamical properties of MprA/B-σ^E stress response pathway. We report that a chaperone, DnaK, known to suppress MprB autokinase activity plays a role in generating bistability. In absence of this chaperone mechanism, our models display a trade-off between short transcript accumulation time and hysteresis in transcript levels. Short transcript accumulation time is observed in absolute concentration robustness (ACR) regime of MprA/B TCS wherein, the level of phosphorylated MprA depends only on the signal level, provided enough MprA protein is present [4]. In this regime, bistability is ruled out and simulations do not display dose-response hysteresis. On the other hand, outside this regime in bistable conditions, dose-response hysteresis is observed but the models display high transcript accumulation times. We report that the network model including DnaK-MprB interaction does not possess ACR. The model is bistable at intermediate SDS concentrations, giving rise to hysteresis in transcript levels. Interestingly, we can still maintain short transcript accumulation times, avoiding the previous models' trade-off.

III. Conclusion

We find that a trade-off exists between short accumulation time and hysteresis in transcript levels in the classical two-component system model. In contrast, using a DnaK-dependent activation mechanism of MprA/B, we can explain the hysteresis in dose-response while avoiding the previous trade-off. Stress-independent, constitutive production of DnaK, along with positive feedback to MprA/B are critical for hysteretic bistability.

References

[1] Wayne and Sohaskey (2001), Nonreplicating Persistence of Mycobacterium Tuberculosis, *Annu. Rev. Microbiol.* **55** 139-163.

[2] H. He, et al. (2006) MprAB Is a Stress-Responsive Two-Component System That Directly Regulates Expression of Sigma Factors SigB and SigE in Mycobacterium tuberculosis, *J. Bacteriol.*, **188** (6)

[3] Tiwari A, Balázsi G, Gennaro ML, and Igoshin OA, (2010) The interplay of multiple feedback loops with post-translational kinetics results in bistability of mycobacterial stress response, *Phys. Biol.*, **7**(3)

[4] G. Shinar and M. Feinberg, (2010) Structural sources of robustness in biochemical reaction networks. *Science* **327** (5971)

[1]Department of Bioengineering, Rice University, E-mail: satyajit@rice.edu

[2]Public Health Research Institute, New Jersey Medical School, Rutgers University, Newark, NJ, USA.