Interaction of transcriptional feedbacks and post-translational kinetics leads to bistability in genetic circuits with multiple feedback loops

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Short Abstract — **Mycobacterial persistence has been recently linked to its stress-response network comprising MprA/MprB two-component system, alternative sigma factor σ^E and its anti-sigma factor RseA. This network contains multiple positive transcriptional feedbacks which may give rise to bistability, making it a good candidate for controlling the mycobacterial persistence switch. To analyze the possibility of bistability in this network, we develop a new method that involves network decoupling into transcriptional and posttranslational interaction modules. We formulate a general necessary condition for bistability based on the logarithmic gains of the two modules and predict that over-expression or deletion of RseA can eliminate bistability.**

***Keywords* — Transcriptional Regulation, Post-translational Kinetics, Bistability, Stress-response, Mycobacteria**

I. BACKGROUND

Bacterial persistence is a phenomenon in which a genetically identical fraction of a population can survive exposure to stress [1]. It has been linked to the inherent phenotypic heterogeneity in microbial populations [2] with persister cells in *Escherichia coli* shown to display either reduced growth rates or a non-growing phenotype [3]. Recently mycobacterial persistence has been associated to the stress-response network containing the MprA/MprB two-component system (TCS) along with the alternative sigma factor σ^E and its anti-sigma factor RseA. In this network, the first feedback arises due to the transcriptional autoregulation of the *mprAB* operon, while the second feedback arises from the transcriptional regulation of the *sigE* operon by phosphorylated MprA and the subsequent upregulation of the *mprAB* operon from a σ^E-dependent promoter. A study of *relA* transcription dynamics from a σ^E-dependent promoter in single *Mycobacterium smegmatis* cells revealed bimodal distribution of gene expression in the population [4]. This bimodality was hypothesized to be associated with bistability in the upstream MprA/MprB network originating from its transcriptional autoregulation. Thus, we analyze this stress-response network for presence of bistability. Additionally, we apply the method developed here to examine bistability in genetic circuits comprising two transcription factors and all possible feedback interactions. We investigate how different couplings of autoregulation and cross-regulation affect network bistability.

II. RESULTS

To analyze the mycobacterial stress-response network we construct a mathematical model and develop a novel approach which involves decoupling the network into transcriptional and posttranslational interaction modules. As a result we reduce the dimensionality of the dynamical system and independently analyze input-output relations in the two modules to formulate a necessary condition for bistability in terms of their logarithmic gains. The necessary condition was used to systematically examine the dynamics of different reduced versions of the full network and to understand the role of each component in generating bistability. We first analyze the autoregulated MprA/MprB TCS and find that the TCS is not bistable in a biochemically relevant parameter range. Subsequently, we introduce the second feedback to find that it weakens the overall positive feedback and is unable to induce bistability. Finally, we include the post-translational regulation of σ^E by the anti-sigma factor RseA. This interaction significantly increases the effective cooperativity and leads the system to bistability, which is robust to parameter variation.

III. CONCLUSION

We predict over-expression or deletion of RseA, the key element controlling the ultrasensitive response, can eliminate bistability. We also observe that coupling of multiple transcriptional feedback loops with an OR gate makes bistability less likely as compared to the AND gate.

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