Systematic bifurcation analysis of feedback-regulated bacterial two-component systems

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***Short Abstract* — Bistability is an important phenomenon in biological regulatory networks that can serve as a mechanism for memory formation and to generate phenotypical heterogeneity. Bistable behavior was described in some bacterial two-component signaling systems, however the explanations often remain somewhat *ad hoc*, with different biochemical mechanisms arbitrarily included and omitted, sometimes implying that bistability is impossible or, alternatively, ubiquitous. By analyzing a number of biochemically plausible topologies and performing large-scale parameter sampling we identify the post-translational and transcriptional processes conducive to bistable behavior, quantifying the bistability range for different topologies.**

***Keywords* — two-component systems, hysteresis, bistability, bifurcation analysis, variable elimination, feedback regulation, numerical continuation, parameter sampling**

I. INTRODUCTION AND OBJECTIVES

BACTERIAL two-component systems are the main information channels that bacteria use to monitor their environment and make metabolic and developmental decisions. Most two-component systems are auto-inducing, that is, one of the outputs of the pathway are the components of the pathway itself, ie. sensor kinases and response regulators. This positive transcriptional feedback loop operating on the post-translational species raises the possibility of hysteretic behavior, which would seem logical especially for pathways controlling developmental decisions. A number of theoretical models showing the possibility of bistable (and usually hysteretic [9] as well) behavior were published in recent years, where bistability arises due to the transcriptional feedback loop [1][2][4] or is inherent in the post-translational module itself [3]. However these models often assume different biochemical (post-translational) mechanisms and are difficult to compare. Moreover, sensitivity of bistable behavior to parameters and also to minor changes in the model topology is often neglected. To systematically explore the biochemical mechanisms conducive to bistable behavior and its robustness to variations in rate constants we perform comprehensive bifurcation analysis on a number of topologies.

II. METHODS

We first perform systematic bifurcation analysis [5][6] for different post-translational topologies, using recently developed analytical techniques [7][8] to reduce the number of variables first and then solve the resulting nonlinear algebraic equations numerically. Then the analysis is extended to transcriptional feedback regulation as well. To be able to handle bifurcation points we wrote a pseudoarclength continuation algorithm [5] that can obtain all solutions (including unstable ones) within the specified input range. The frequency of bistable behavior for different topologies and its correlation with the relative strength of different biochemical processes (such as exogenous (de)phosphorylation, dimerization etc.) is quantified and discussed.

III. RESULTS AND CONCLUSION

By performing bifurcation analysis that combines large-scale parameter scanning and systematic exploration of a number of biochemically plausible topologies we quantify the overall likelihood of bistable behavior in feedback-regulated two-component systems and identify the requirements of robust bistable behavior both in terms of reaction network structure and parameter values.

REFERENCES

[1] Tiwari A, et al. (2010) The interplay of multiple feedback loops with post-translational kinetics results in bistability of mycobacterial stress response, *J Phys Biol* **7(3)**:036005-036019

[2] Ghosh S, et al. (2011) Phenotypic heterogeneity in mycobacterial stringent response, *BMC Systems Biology***5:18**

[3] Igoshin, OA, Alves, R and Savageau, MA (2007), Hysteretic and graded responses in bacterial two-component signal transduction, *Molecular Microbiology*, **68**: 1196–1215

[4] Veening JW et al (2008) Transient heterogeneity in extracellular protease production by Bacillus subtilis, *MolSyst Biol*.**4**:184

[5] Qiao L et al (2007) Bistability and oscillations in the Huang-Ferrell model of MAPK signaling, *PLoS Comp Biol***3(9)**:1819-26.

[6] Zumsande M, Gross T (2010) Bifurcations and chaos in the MAPK signaling cascade, *J Theor Biol*.**7;265(3)**:481-91

[7] Thomson M, Gunawardena (2009) Unlimited multistability in multisite phosphorylation systems, *Nature* **460(7252)**:274-7

[8] Feliu E, Wiuf C (2013) Variable elimination in post-translational modification reaction networks with mass-action kinetics **66(1-2)**:281-310

[9] Guidi GM, Goldbeter A. (1997) Bistability without hysteresis in chemical reaction systems: A theoretical analysis of irreversible transitions between multiple steady states. *J Phys Chem A*. **101**:9367–9376

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