Global Tolerance of Biochemical Systems and the Design of Moiety-Transfer Cycles

Pedro M. B. M. Coelho[1,2], Armindo Salvador[3], and Michael A. Savageau[2]

***Short Abstract* — A central "dogma" emerging in systems biology is that biological systems are selected for robustness to perturbations. However, the lack of effective approaches for quantifying the tolerance of biological systems to potentially large perturbations has hitherto hampered understanding of the molecular underpinnings of biological robustness. Here we introduce a generic approach to identifying and characterizing the boundaries where the performance of a biological system deteriorates abruptly. This conceptual framework allows us to precisely define and quantify "global tolerance" as the ratio between the normal value of a parameter and the value at such a boundary.**

***Keywords* — Moiety-transfer cycles, design space, local robustness, global tolerance, piecewise power-law representation, Bode analysis.**

I. Introduction

ROBUSTNESS of organisms is widely observed although difficult to precisely characterize. Performance can remain nearly constant within some neighborhood of the normal operating regime, leading to homeostasis, but then abruptly break down with pathological consequences beyond this neighborhood [1,2]. Currently, there is no generic approach to identifying boundaries where local performance deteriorates abruptly, and this has hindered understanding of the molecular basis of biological robustness. Here we introduce a generic approach for characterizing boundaries between operational regimes based on the piecewise power-law representation of the system's components [3]. This conceptual framework allows us to define "global tolerance" as the ratio between the normal value of a parameter and the value at such a boundary [3]. We illustrate the utility of this concept for a class of moiety-transfer cycles, which is a widespread module in biology.

Acknowledgements: This work was supported in part by fellowships to PC (SFRH/BD/8304/2002) and AS (SFRH/BPD/9457/2002) from Fundacao para a Ciencia e Tecnologia, Portugal, and by grants to AS (PTDC/QUI/70523/2006) from Fundacao para a Ciencia e a Tecnologia, Portugal, and to MAS (RO1-GM30054) from the US Public Health Service.

[1]Chemistry Department, University of Coimbra, Portugal. E-mail: pbcoelho@ucdavis.edu

[2]Biomedical Engineering Department, University of California, Davis, CA, USA. E-mail: masavageau@ucdavis.edu

[3]Center for Neurosciences and Cell Biology, University of Coimbra, Portugal. E-mail: salvador@cnc.uc.pt

II. Methods

The strategy for our analysis involves (i) decomposition of the system's design space into unique regions with boundaries precisely defined by the "cross-overs" or "breakpoints" in the piecewise power-law representation [4], (ii) determination of the system behavior in each region [5], (iii) evaluation of system behavior according to a set of quantitative criteria based on the function of the system, and (iv) determination of the global tolerance to changes in the values for the parameters and concentrations of the system.

III. Conclusion

Our results show a region of "best" local performance surrounded by "poor" regions; also, selection for improved local performance often pushes the operating values away from regime boundaries, thus increasing global tolerance. This is a desirable property that facilitates the evolutionary adaptation of the moiety-transfer cycle to changing environmental demands. These predictions agree with experimental data from the reduced nicotinamide adenine dinucleotide phosphate (NADPH) redox cycle of human erythrocytes.

References

[1] Salvador A and Savageau MA. (2003) Quantitative evolutionary design of glucose 6-phosphate dehydrogenase expression in human erythrocytes. *Proc Natl Acad Sci U S A*, **100**, 14463-14468.

[2] Salvador A and Savageau MA. (2006) Evolution of enzymes in a series is driven by dissimilar functional demands. *Proc Natl Acad Sci U S A*, **103**, 2226-2231.

[3] Coelho PM, Salvador A and Savageau MA. (2009) Quantifying global tolerance of biochemical systems: design implications for moiety-transfer cycles. *PLoS Comput Biol*, **5**, e1000319.

[4] Savageau MA. (2001) Design principles for elementary gene circuits: Elements, methods, and examples. *Chaos*, **11**, 142-159.

[5] Savageau MA. (1971) Concepts relating the behavior of biochemical systems to their underlying molecular properties. *Arch Biochem Biophys*, **145**, 612-621.