Asymmetric Stochastic Switching Driven by Intrinsic Noise

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***Short Abstract* – Low-copy-number molecules are involved in many functions in cells. The intrinsic fluctuations of these numbers can enable stochastic switching between multiple steady states, inducing phenotypic variability. Herein we present a theoretical and computational study based on Master Equations and Fokker-Planck and Langevin descriptions of stochastic switching for a genetic circuit of autoactivation. We show that in this circuit the intrinsic fluctuations arising from low-copy numbers, which are inherently state-dependent, drive asymmetric switching. Our study unravels that intrinsic fluctuations, while not required to describe bistability, are fundamental to understand stochastic switching and the dynamical relative stability of multiple states.**

***Keywords* – Bistability, Positive Feedback Loop, Stochastic, Switching**

I. INTRODUCTION

Genetic networks are dynamic biochemical systems which frequently involve low copy numbers of reactants, making them inherently stochastic. This stochasticity has been known to affect their behaviour in relevant ways, either in benefit or in detriment [1]. For instance, when these systems are bistable, fluctuations can enable stochastic switching from one state to another. This switching has been shown to enhance the fitness of populations of unicellular organisms in changing environments and its dynamics have been characterized [2,3]. Genetic or biochemical bistability showing a high concentration (ON) and a low concentration (OFF) states commonly arises from nonlinear dynamics involving a positive feedback loop in which a molecular species upregulates, directly or indirectly, its own production. Herein we adress the issue of how intrinsic noise controls stochastic switching in bistable systems.

II. METHODS

We used a well-known model for the simplest positive feedback loop possible: a self activating loop in which the molecule promotes its own production according to a Hill function [4,5]. In order to characterize stochastic switching we derive the corresponding Master Equation and Fokker-Planck Equation [5]. The resulting Langevin Equation reads:

$$\dot{x} = A(x) + \sqrt{B(x)}\,\xi(t)$$

$$A(x) = \frac{ax^2}{x^2+1} - x + R, \quad B(x) = \frac{ax^2}{x^2+1} + x + R$$

$$\langle \xi(t) \rangle = 0, \quad \langle \xi(t)\xi(t') \rangle = \frac{1}{V}\delta(t-t')$$

where a is the maximal production rate, R is a basal production rate and V is the cell volume. The noise obtained from the proper derivation of the Langevin equation is a multiplicative noise of intensity $B(x)/V$. We did a theoretical and simulated analysis of the bifurcation diagram, stochastic potential and Mean First Passage Time from each of the states for this model [5].

In order to pinpoint the features introduced by intrinsic noise, we also studied these properties for a system with the same deterministic dynamics as the previous one but is subjected to an additive noise of constant intensity B_0.

III. RESULTS AND CONCLUSIONS

Our results [6] show that multiplicative noise does not produce great differences in stable states or bistability range. Dynamically though, intrinsic noise produces asymmetry in switching rates (relative to the energy barrier), effectively stabilizing the OFF state, whereas additive noise does not. Interestingly, this asymmetric switching exists and has been experimentally measured by Acar et al in the bistable gallactose signalling network in yeast [3]. This shows that intrinsic fluctuations are fundamental to understand stochastic switching in nonlinear biological systems, and a simplistic approach in which one considers additive noise as a correction can leave out key features of such a system.

REFERENCES

[1] Eldar A, Elowitz MB (2010) Functional roles of noise in genetic circuits. *Nature* **467**, 167-173

[2] Acar M, Mettetal JT, van Oudenaarden A (2008) Stochastic switching as a survival strategy in fluctuating environments. *Nature Genetics* **40**, 471-475

[3] Acar M, Becksei A, van Oudenaarden A (2005) Enhancement of cellular memory by reducing stochastic transitions. *Nature* **435**, 228-232.

[4] Becksei A, Seraphin B, Serrano L (2001) Positive feedback in eukaryotic gene networks: cell differentiation by graded to binary response. *The EMBO Journal* **20**, 2528-2535.

[5] Cheng Z, et al (2008) Robustness analysis of cellular memory in an autoactivating positive feedback system. *FEBS Letters* **528**, 3776-3782.

[6] Frigola D, et al (2012) Asymmetric stochastic switching driven by intrinsic molecular noise. *PloS ONE* **7(2)**, e31407

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