Type of noise determines cell decision

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***Short Abstract* — The aim of this study is to demonstrate that in molecular dynamical systems with underlying bistability, type of noise determines the most stable attractor. We consider two examples of simple stochastic models of gene expression with a nonlinear feedback: the model of self-regulating gene and the toggle switch model. We demonstrate that the dominating type of noise dictates in which state the stationary probability density is concentrated. Although the steady-state attractors are defined by the deterministic approximation of the stochastic system, their relative stability is controlled by the type of noise.**

***Keywords* — stochastic gene expression, bistability**

I. Motivation

The bistable regulatory elements enhance heterogeneity and may allow cells in multicellular organism to specialize and specify their fate. The simplest regulatory element exhibiting bistability is the self-regulating gene controlled by a nonlinear positive feedback. Second analyzed example is the toggle switch model.

II. Self-regulating gene model

We consider stochastic model of gene expression with the nonlinear positive feedback. It is assumed that the gene may be in one of the two states: active or inactive. We focus on the case in which in the deterministic approximation the system has two stable steady state solutions. Two types of noise are considered: transcriptional (characteristic for bacteria) — due to the limited number of protein molecules and gene switching noise (important in Eukaryotes) — due to gene activation and inactivation transitions. We explore the correspondence between the stochastic system and its deterministic approximation in the limit of low noise. When noise decreases to zero the stationary probability distribution (SPD) converges to Dirac delta in one of two stable steady states. We investigate analytically two approximations of the original system: *adiabatic* in which the transitions between active and inactive gene states are infinitely frequent, and *continuous* in which the discrete number of molecules is replaced by continuous concentration. The first approximation is justified for bacteria, while the second one can be applied for higher eukaryotes. We found that in a broad range of parameters the SPD of the system in the adiabatic approximation converges to Dirac delta in a different steady state than the SPD of the system in the continuous approximation. This suggests that the ratio of the transcriptional to the gene-switching noise dictates which state becomes a global attractor. We verified this hypothesis by Monte Carlo simulations of the exact model, see Fig. 1.

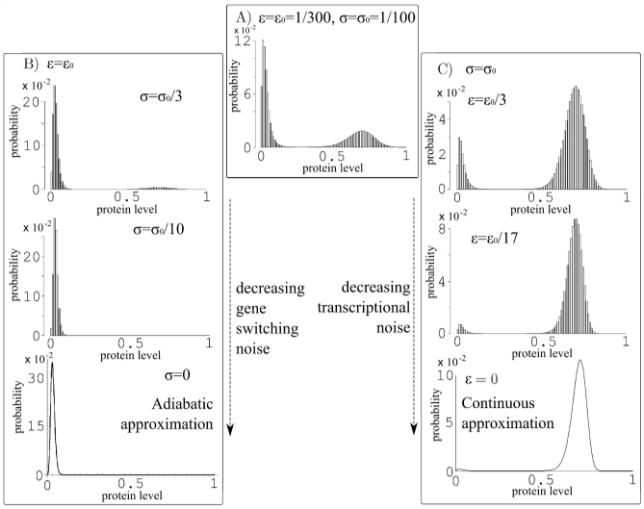

Fig. 1. The system converges to inactive steady state when the value of gene switching noise σ (inverse of gene inactivation rate) decreases to zero, and to active steady state when value of transcriptional noise ε (inverse of mRNA production rate)

III. Toggle switch model

In the toggle switch model we consider three types of noise: gene switching noise, transcriptional noise and dimerization noise. We numerically calculated impact of each noise parameter on the SPD variance in each basin of attraction of the two stable steady states. We found that the change of noise parameters for each gene alters the protein SPD, influencing probability mass fraction in each of two basins of attraction. The increase of probability mass fraction in a given basin of attraction correlates with the decrease of variance of SPD in this attraction basin. Interestingly, decrease of the gene switching noise or the transcriptional noise promotes the gene activation, whereas decrease of dimerization noise promotes activation of the competing gene.

IV. Conclusion

Our study demonstrates that in systems with underlying bistability, like genetic switches, the noise characteristic controls in which of the epigenetic attractors cell population will settle.

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