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Type of noise defines global attractors in bistable molecular regulatory systems

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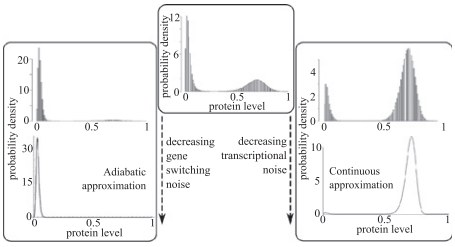
HIGHLIGHTS

- We analyze stochastic bistable model of single autoregulatory gene.
- Gene switching, transcriptional and translational noises are considered.
- We show that the most stable attractor is determined by the type of noise.
- The noise characteristics changes during cell cycle and development.
- Noise type changes modify the relative occupancy of epigenetic attractors.

GRAPHICAL ABSTRACT

Influence of noise on the stationary probability distribution for a single autoregulatory gene with bistability. For low gene switching noise (fast gene switching) the system settles in the inactive steady state (low protein level). For low transcriptional noise (high transcription rate) the system settles in the active steady state (high protein level).



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ABSTRACT

The aim of this study is to demonstrate that in molecular dynamical systems with the underlying bi- or multistability, the type of noise determines the most strongly attracting steady state or stochastic attractor. As an example we consider a simple stochastic model of autoregulatory gene with a nonlinear positive feedback, which in the deterministic approximation has two stable steady state solutions. Three types of noise are considered: transcriptional and translational – due to the small number of gene product molecules and the gene switching noise – due to gene activation and inactivation transitions. We demonstrate that the type of noise in addition to the noise magnitude dictates the allocation of probability mass between the two stable steady states. In particular, we found that when the gene switching noise dominates over the transcriptional and translational noise (which is characteristic of eukaryotes), the gene preferentially activates, while in the opposite case, when the transcriptional noise dominates (which is characteristic of prokaryotes) the gene preferentially remains inactive. Moreover, even in the zero-noise limit, when the probability mass generically concentrates in the vicinity of one of two steady states, the choice of the most strongly attracting steady state is noise type-dependent. Although the epigenetic attractors are defined with the aid of the deterministic approximation of the stochastic regulatory process, their relative attractivity is controlled by the type of noise, in addition to noise magnitude. Since noise characteristics vary during the cell cycle and development, such mode of regulation can be potentially employed by cells to switch between alternative epigenetic attractors.

1. Introduction

From the mathematical perspective intracellular regulatory processes can be considered as stochastic dynamical systems.

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Stochasticity arises due to the limited number of reacting molecules such as gene copies, mRNA or proteins. In systems with underlying bistability, even for low noise, the stochastic trajectories exhibit stochastic jumps between basins of attraction and thus diverge qualitatively from the deterministic solutions. The relative stability of steady states depends on the system volume (or noise strength) (Vellela and Qian, 2009). In this study, we analyze the bistable stochastic system with three different types of noise and demonstrate that the dominating type of noise determines the most strongly attracting steady state (global stochastic attractor). That is, two systems with the same deterministic approximation may have qualitatively different stationary probability distributions (SPD) depending on the noise characteristic, even in the zero noise limit.

We consider two models of gene expression with autoregulation. We will assume that the gene is positively regulated by its own product in a cooperative manner, which leads to the nonlinear positive feedback and bistability. Single-cell experiments suggest that gene expression can be described by a three-stage model (Blake et al., 2003; Raser and O'Shea, 2004). The gene promoter can switch between two states (Ko, 1991; Raj et al., 2006; Chubb et al., 2006), one active and one inactive. Such transitions could be associated with binding and unbinding of repressors or transcription factors or with changes in chromatin structure. Transcription can only occur if the promoter is active. The next two stages are mRNA transcription and protein translation. In certain cases when mRNA is very unstable and quickly translated, transcription and translation processes can be lumped together (Kepler and Elston, 2001; Hornos et al., 2005). The resulting model has thus two stages: gene regulation and protein synthesis. Such simplification allows for analytical treatment of the problem, however, lumping of transcription and translation processes may influence the impact of feedback on noise strength (Marquez-Lago and Stelling, 2010). Therefore, in addition to the simplified two-stage model we analyze numerically a more detailed three-stage model in which processes of gene regulation, mRNA transcription and protein translation are explicitly included. The considered models have three types of noise: *transcriptional and translational* – due to the limited number of product molecules, and *gene switching* noise – due to gene state transitions.

Transcriptional and translational noises are characteristic for prokaryotes in which the mRNA and protein numbers are very small (McAdams and Arkin, 1997; Kierzek et al., 2001; Ozbudak et al., 2002). Recently, Taniguchi et al. (2010) quantified the mean expression of more than 1000 *Escherichia coli* genes and found that the most frequent average protein number is of order of 10, while the most frequent average mRNA number is smaller than one. The gene switching in prokaryotes is thought to be very fast and thus gene regulation is frequently considered in the so called adiabatic approximation (Hornos et al., 2005), as a process that includes only mRNA transcription and protein translation (Thattai and Oudenaarden, 2001; Swain et al., 2002; Shahrezaei and Swain, 2008).

Gene switching noise is important in eukaryotes (Blake et al., 2003; Ko, 1991; Chubb et al., 2006; Raj and Oudenaarden, 2009) in which the transitions between the *on* and *off* states are much less frequent. Analysis of gene expression in mammalian cells showed that mRNA is synthesized in bursts, during periods of time when the gene is transcriptionally active (Raj et al., 2006). Slow gene switching can result in bimodal mRNA and protein probability distributions even in systems without underlying bistability (Hornos et al., 2005; Shahrezaei and Swain, 2008). Bimodality may arise also without bistability in two-stage cascades in which the regulatory gene produces transcription factors that have a nonlinear effect on the activity of the target gene (Ochab-Marcinek and Tabaka, 2010). In contrast to prokaryotes, in eukaryotes the characteristic mRNA and protein numbers are much larger. Therefore the transcriptional and translational noises in many cases may be neglected (Lipniacki et al., 2006, 2007; Bobrowski et al., 2007) or considered in the diffusion approximation (van Kampen, 2007; Kepler and Elston, 2001). Cell cycle transcriptional regulator gene SWI6 in yeast is an example of a gene with expression noise originating almost only from gene switching noise, while transcriptional noise is negligible (Becksei et al., 2005).

The bistable regulatory elements received a lot of attention in the last decade as they enhance heterogeneity and may allow cells in multicellular organism to specialize and specify their fate. Decisions between cell death, survival, proliferation and senescence are associated with bistability and stochasticity, magnitude of which controls transition rates between the particular attractors (Hasty et al., 2000; Puszynski et al., 2008; Lipniacki et al., 2008). In prokaryotes the bistability is regarded as an optimal strategy for coping with infrequent changes in the environment (Kussell and Leibler, 2005).

The simplest regulatory element exhibiting bistability is the self-regulating gene controlled by a nonlinear positive feedback (Hornos et al., 2005; Walczak et al., 2005; Karmakar and Bose, 2007; Hat et al., 2007; Schultz et al., 2007; Siegal-Gaskins et al., 2009). While not often found as an isolated entity, the self-regulating gene is a common element of biological networks; for example, 40% of *E. coli* transcription factors negatively regulate their own transcription (Rosenfeld et al., 2002). van Sinderen and Vemnema (1994) demonstrated that transcription factor comK acts as an autoregulatory switch in *Bacillus subtilis*. The synthetic auto-regulatory eukaryotic gene switch was studied in Saccharomyces cerevisiae (Becskei et al., 2001). The other intensively studied regulatory element exhibiting bistability is the toggle switch – a pair of mutual repressors (Lipshtat et al., 2006; Chatterjee et al., 2008). A classical example is the double-negative regulatory circuit governing alternative lysogenic and lytic states of phage lambda (Ptashne, 2004), lactose utilization network (Ozbudak et al., 2004) or Delta–Notch regulation (Sprinzak et al., 2010).

Despite the low copy number of proteins and mRNAs genetic switches may exhibit very low transition rates, resulting in stable epigenetic properties that persist in simplest organisms for many generations (Ptashne, 2004; Acar et al., 2005), reviewed by Chatterjee et al. (2008). The attractors of genetic networks can be associated with distinct cell types achieved during cell differentiation (Acar et al., 2005; Chang et al., 2006). In a single cell, in the long time scale the relative occupancy of steady states is determined by their relative stability. The same, however, may not be true for cell population when the two steady states are associated with different growth rates. As demonstrated, by Nevozhay et al. (2012) using synthetic bistable gene circuit, the fraction of cells in the most strongly attracting steady state may be low, if these cells have lower growth rate than cells in the less stable steady state. Thus, in the context of cell population the relative occupancy of a given state is defined by rates of state to state transitions (or memory) and fitness associated with particular steady states.

The paper is organized as follows: in the following section we consider the two-stage gene autoregulation model and its three approximations:

- the deterministic approximation,
- the continuous approximation with the gene switching noise only,
- and the adiabatic approximation with the transcriptional and translational noise only.