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Dynamics of small genetic circuits subject to stochastic partitioning in cell division

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HIGHLIGHTS

- We study effects of partitioning errors on the dynamics of genetic circuits.
- Effects of partitioning errors differ widely with network topology and behavior.
- In switches, errors reduce the phenotype distribution's variance across generations.
- The synchrony of a population with clocks is robust to the majority of errors.
- Errors produce qualitatively different effects than noise in gene expression.

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ABSTRACT

In prokaryotes, partitioning errors during cell division are expected to be a non-negligible source of cell-to-cell diversity in protein numbers. Here, we make use of stochastic simulations to investigate how different degrees of partitioning errors in division affect the cell-to-cell diversity of the dynamics of two genetic circuits, a bistable switch and a clock. First, we find that on average, the stability of the switch decreases with increasing partitioning errors. Despite this, anti-correlations between sister cells, introduced by the partitioning errors, enhance the chances that one of them will remain in the mother cell's state in the next generation, even if the switch is unstable. This reduces the variance of the proportion of phenotypes across generations. In the genetic clock, we find that the robustness of the period decreases with increasing partitioning errors. Nevertheless, the population synchrony is remarkably robust to most errors, only significantly decreasing for the most extreme degree of errors. We conclude that errors in partitioning affect the dynamics of genetic circuits, but the effects are network-dependent and qualitatively different from noise in gene expression.

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1. Introduction

Phenotypic diversity is a feature of all cell populations, including monoclonal ones, that significantly affects their survival chances, particularly in fluctuating environments (Kussell and Leibler, 2005; Samoilov et al., 2006). The stochastic nature of the biochemical reactions involved in the dynamics of gene regulatory networks is one well-known contributing source of phenotypic diversity (Kaern et al., 2005; McAdams and Arkin, 1999).

Recently, it has been recognized that the partitioning of plasmids, RNAs, proteins and other macromolecules during cell division can also be a non-negligible source of phenotypic diversity (Huh and Paulsson, 2011a, 2011b; Lloyd-Price et al., 2012). Similar to noise in gene expression, this source generates diversity that can propagate through reaction networks to high-copy number components, even in organisms with a morphologically symmetric division process, such as *Escherichia coli* (Huh and Paulsson, 2011a). After establishing a mathematical framework with which to characterize this source of noise (Huh and Paulsson, 2011b), it was shown that the random errors in partitioning result in cell-to-cell diversity in RNA and protein numbers that is difficult to distinguish from the diversity arising from gene expression noise, when observing cell populations at a single time moment (Huh and Paulsson, 2011a). Nevertheless, while noise in gene expression continuously generates diversity, noise from partitioning only occurs sparsely, when cells divide. Thus, the effects of these two sources should be readily distinguishable from a temporal perspective (Lloyd-Price et al., 2012). So far, it is unknown how these two sources of noise differ in regards to their effects on the dynamics of genetic circuits.

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Most cellular processes are regulated by small genetic networks, named motifs (Wolf and Arkin, 2003; Alon, 2007). It is conceivable that the noise in the process of partitioning of the products of gene expression affects the cell-to-cell diversity of behaviors of these motifs. Here, we study the effects of errors in partitioning on the behavior of two such motifs, the Toggle Switch (Gardner et al., 2000) and the Repressilator (Elowitz and Leibler, 2000). These two circuits differ widely in behavior. While the former is able to switch between two noisy attractors (Ribeiro et al., 2006; Ribeiro and Kauffman, 2007; Zhu et al., 2007), the latter only has one noisy attractor, a limit cycle (Elowitz and Leibler, 2000; Zhu et al., 2007; Loinger and Biham, 2007). Due to their dynamic properties, these circuits are likely candidates to serve as master regulators of future synthetic genetic circuits. Also, similar circuits have evolved in natural cells to perform similar tasks (Wolf and Arkin, 2002; Arkin et al., 1998; Lahav et al., 2004; Nelson et al., 2004). Thus, understanding the effects of random partitioning of RNA and proteins in cell division on the dynamics of these two circuits may aid in understanding how cells maintain robust phenotypes across generations.

The Toggle Switch is a two-gene motif, where each gene expresses a transcription factor that represses the expression of the other gene. As this circuit has two noisy attractors (Gardner et al., 2000; Arkin et al., 1998), it can store one bit of information. It can thus be used to make decisions (Arkin et al., 1998), or to store the results of one (Wolf and Arkin, 2003). The level of gene expression noise determines the frequency at which the Toggle Switch changes between its noisy attractors (Loinger et al., 2007; Potapov et al., 2011). A well-studied Toggle Switch is the "λ-switch", a decision circuit of the λ phage (Arkin et al., 1998), which determines whether an infecting phage will lyse the cell or, instead, integrate itself into the bacterial genome, forming a lysogen. The lytic cycle can be activated in lysogens either stochastically (Neubauer and Calef, 1970), or due to environmental cues such as irradiation by UV light (Baluch and Sussman, 1978). Meanwhile, the Repressilator is a synthetic three-gene motif which exhibits oscillatory behavior (Elowitz and Leibler, 2000), as each gene represses the next gene in the loop. In the Repressilator, gene expression noise determines the robustness of the period of oscillation (Häkkinen et al., 2013).

We study the effects of errors in partitioning on the behavior of these two circuits, focusing on their ability to 'hold state' (i.e. on the stability of their noisy attractors) across cell lineages, when subject to different partitioning schemes. Namely, we explore a wide range of magnitudes of partitioning errors, since in *E. coli* the process of partitioning of gene expression products ranges from highly symmetric (Di Ventura and Sourjik, 2011) to heavily asymmetric, e.g. due to spatially organized protein production (Montero Llopis et al., 2010). For this, we first examine the switching dynamics of the Toggle Switch in cell lineages. In this context, we further consider two biologically motivated scenarios: the phenotypic diversity in a continuous cell culture, and the population dynamics when one state of the switch is lethal to the cells, as in the case of λ lysogens. We then study the effects of errors in partitioning on the behavior of the Repressilator. Specifically, we study the robustness of the period of oscillations, and the rate of desynchronization across cell lineages of an initially synchronous population.

2. Methods

The models used here contain three main components. The first is the genetic circuit within each cell. The second is cell growth and division, and the last is the partitioning scheme of the proteins and RNA molecules in division. For simulations, we used the SGNS2 stochastic simulator (Lloyd-Price et al., 2012), which utilizes the Stochastic Simulation Algorithm (Gillespie, 1977).

2.1. Stochastic model of gene expression

The model of gene expression, illustrated in Fig. 1A, consists of the following set of reactions (Häkkinen et al., 2013):

$$\mathrm{Pr} \xrightarrow{k_c \times f(R,V)} \mathrm{Pr}_c \tag{1}$$

$$\mathrm{Pr}_c \xrightarrow{k_o} \mathrm{Pr} + \mathrm{M} \tag{2}$$

$$\mathrm{M} \xrightarrow{k_P} \mathrm{M} + \mathrm{P} \tag{3}$$

$$\mathrm{M} \xrightarrow{d_M} \varnothing \tag{4}$$

$$\mathrm{P} \xrightarrow{d_P} \varnothing \tag{5}$$

The model includes transcription (Reactions (1) and (2)), translation (reaction (3)), and degradation of mRNA (M, Reaction (4)) and proteins (P, reaction (5)). Transcription initiation is a two-step process, consisting of the closed and open complex formations (Buc and McClure, 1985; Ribeiro et al., 2010). The free promoter is represented by Pr and the promoter-RNAP complex is represented by Pr_c. Here, the closed complex formation can be repressed by a transcription factor produced by another gene by blocking access to the transcription start site. The repression function is a hill function with hill coefficient 2, as in (Zhu et al., 2007). Specifically, it is

$$f(R,V) = \frac{K_d^2}{\left(\frac{R}{V}\right)^2 + K_d^2} \tag{6}$$

where R is the number of repressor molecules, V is the normalized volume of the cell ranging from 0.5 to 1 over the cell cycle, and K_d is the dissociation constant. This repression function arises when the promoter has two operator sites, and there is strongly cooperative binding between the two repressors which bind there.

2.2. Cell growth and division

Cell division in *E. coli* is remarkably stable, with little variance in division time of sister cells when under optimal growth conditions (squared coefficient of variation of division times ≈ 0.02 (Hoffman and Frank, 1965)). We therefore divide cells according to a fixed doubling time T_D, implying that the population doubles in size synchronously. Cell growth is modeled by increasing V linearly from 0.5 to 1 over the lifetime of the cell.

Each cell division is modeled as an instantaneous process which occurs at regular intervals, wherein the DNA (i.e. the promoter region, Pr) is replicated, and the M and P molecules are randomly partitioned into the daughter cells (see next section). After division, we assume that the promoters in the daughter cells are in the initial state (Pr), since any bound molecules are assumed to have been removed from the DNA by the DNA polymerase during replication (Guptasarma, 1995).

To illustrate the dynamics of the single-gene expression model from the previous section with the growth and division model here, we show several time traces in Fig. 1C, as well as the average behavior. Note that the subtle oscillatory behavior observed in the average behavior is due to the effects of linear cell growth and exponential protein degradation.

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