Effects of Molecular Noise on the Multistability in a Synthetic Genetic Oscillator

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Abstract. We used 3-genes genetic oscillator as a model of oscillators coupled with quorum sensing, implemented as the production of a diffusive molecule, autoinducer. The autoinducer stimulates expression of the target gene within the oscillator's core, providing a positive feedback. Previous studies suggest that there is a hysteresis in the system between oscillatory (OS) and stationary (SS) dynamical solutions. We question the robustness of these attractors in presence of molecular noise, existing due to small number of molecules in the characteristic processes of gene expression. We showed distributions of return times of OS near and within the hysteresis region. The SS is revealed by the return times duration increase as the system approaches hysteresis. Moreover, the amplitude of stochastic oscillations is larger because of sensitivity of the system to the steady state even outside of the hysteresis. The sensitivity is caused by the stochastic drift in the parameter space.

Keywords: multistability, hysteresis, genetic oscillator.

1 Introduction

Oscillators are common in all contexts of life. For example, genes interact with each other constituting a network [1] which, for a certain structure, may lead to temporal oscillations in protein numbers and, thus, in a whole biochemical regulatory network which is governed by these genes [1].

The ability of living organisms to maintain the period and amplitude of temporal oscillations in presence of molecular noise and environmental fluctuations can be crucial for viability and evolutionary fitness of a single individual as well as a population [2].

We use a model of a synthetic 3-genes oscillator, repressilator [1], with quorum sensing (QS) [3], a mechanism for inter-cellular communication. Each gene in the network inhibits production of a gene next to it, thus, a cyclic structure is formed (Fig. 1). In addition to a ring of three genes, the scheme contains a coupling module implemented as a production of a small diffusive molecule — autoinducer (AI), which is a common agent for QS [3].

The recent study has shown new properties of the model: coexistence (hysteresis) of regular limit cycle (LC) and stable steady state (SSS) in a single cell oscillator [4]. The hysteresis between the LC and the SSS confers a cell the possibility to choose

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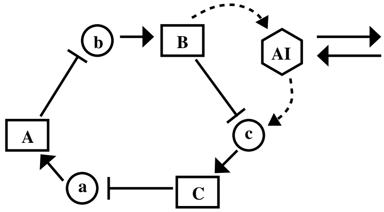

Fig. 1. Scheme of the repressilator with QS. Lowercase and uppercase letters are mRNA and proteins, respectively.

between different responses to external stimuli, for example, additional AI influx. Here we consider effects of noise, occurring due to small number of molecules, on a hysteresis properties of the circuit, since noise may lead to completely new dynamical regimes in a multistable system or destroy existing ones. We show how the dynamical properties of the stochastic system, like period distributions and amplitude of oscillations, change as the system approaches the hysteresis region.

2 Methods

We will use a dimension version (see in [5]) of the dimensionless model presented in [6] to study the stochastic effects on the dynamics of the single cell oscillator [4].

To account for noise due to small numbers of molecules constituting the system we use a standard approach, simulations using Stochastic Simulation Algorithm (SSA) [7]. Linear chemical interactions are modeled as unimolecular reactions. The propensities for the nonlinear reactions are represented by the corresponding nonlinear deterministic functions and computed at each step of the algorithm. We use this model technique due to unknown complex interactions taking place during these reactions.

For each parameter set we perform 100/400 simulations, each 10^5 s long, sampled every second. For the time series we compute the distribution of return times (periods) by taking a Poincaré section in the discrete state space and computing time intervals between moments when trajectory passes the section in one direction. The section is taken so that it is equidistant from maximum and minimum of the deterministic oscillations. If there are fast oscillations in the time series we choose 5000 s to be a minimal possible period: the algorithm sums computed periods until the sum reaches the threshold of 5000 s, then a period value is stored. We found 5000 s to be enough to cut off the fast fluctuations from the time series and not large enough to skew the true period distribution. This analysis is performed on the most abundant in numbers variable B.

3 Results

The dynamics of the deterministic model of the repressilator with QS is characterized by the limit cycle (LC) attractor that corresponds to the temporal oscillations of the system. This stable attractor emerges at the Hopf bifurcation for sufficiently large transcriptional rate [4].

The LC persists in a wide range of the transcriptional rate, but with its increase LC undergoes the infinite period bifurcation (IPB), i.e. the rotation of the representation point at the limit cycle is stopped due to the falling into a fixed point attractor in the phase space and the period of the oscillation goes to infinity. This fixed point attractor corresponds to the stable steady state dynamics of the system and is not related to the emergence of HB. The latter stable steady state (SSS) appears because of the AI influence on the system [4] and in some range of the transcriptional rates there are two stable dynamical behaviors of the system: the oscillations (LC) and the stationary dynamics (SSS). This leads the system to the hysteresis [4]. The study of the hysteresis deserves a special attention because of the new regulatory possibilities of the repressilators with quorum sensing.

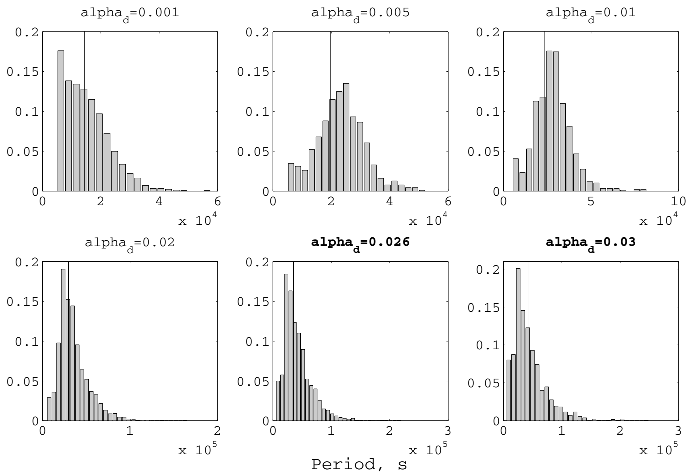

Fig. 2. The period distributions for different values of transcription rate (alpha$_{\mathrm{d}}$). Two last values are within hysteresis region (shown in bold). Vertical line denotes deterministic period. 100 and 400 simulations were performed for the distributions of the first and second row, respectively.

We perform stochastic simulations of the system to determine to what extent molecular noise affects the hysteresis properties of the system. We use the period distribution analysis (see the Methods) of the stochastic system in the conditions where the hysteresis occurs [4]. We choose 6 values of the transcription rate (here denoted as alpha$_{\mathrm{d}}$) and compute the distributions of periods for each of them. Results are shown in Fig. 2.

For the smallest value of the transcription rate (alpha$_{\mathrm{d}}$ = 0.001) the peak of the period distribution corresponds to the lowest values of found periods (Fig. 2). This occurs because of the highly intensive intrinsic noise due to small alpha$_{\mathrm{d}}$. Thus, the LC is smashed by the noise and the dominating fluctuations are mostly captured by the period distribution analysis. As alpha$_{\mathrm{d}}$ approaches the IPB the LC grows in amplitude and the oscillations become more pronounced, and, additionally, the system becomes increasingly perturbed by the SSS. Namely, the stochasticity causes the drift in the parameter space that in practice creates the hysteresis where there is no hysteresis in the deterministic system. Thus, before the deterministic hysteresis region the peak of the period distribution passes to smaller values as compared to the deterministic period (Fig. 2), which appears because of the fast transitions between two attractors as the SSS becomes stronger in perturbing the system. These fast transitions do not allow the stochastic system to have the same period as that of the deterministic system, which can be clearly seen for much larger period values (data not shown). Namely, due to the high fluctuations' level the system's life time in either of the attractors is significantly shortened.

The amplitude of the stochastic oscillations before the hysteresis region becomes larger as compared to the deterministic case due to the perturbation caused by SSS. This also causes the appearance of the larger periods, which can be seen from the distribution peaks shifted rightwards from the corresponding deterministic periods for some moderate values of $\mathrm{alpha_d} = \{0.005, 0.01\}$ (Fig. 2), where the LC is not either smashed by the noise or in the hysteresis region determined by the stochastic effects.

4 Conclusions

In this work we questioned the robustness of the multistability of the repressilator with quorum sensing in presence of molecular noise. We have shown that noise highly affects the oscillatory behavior of the repressilator by increasing the amplitude of the oscillations with moderate fluctuations in the period. The stochastic system has been shown to reveal the stable steady state even for the parameters outside of the hysteresis region. We have shown that the straightforward application of the Gillespie algorithm (standard approach in modeling gene expression [2]) to the model indicates that the system is weakly anchored in either of attractors present in the hysteresis region.

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