Dynamics of Repressilator: From Noise to Coherent Oscillation

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1 Introduction

Gene expression unavoidably bears noise because of the single molecular nature of DNA and the small number of each kind of proteins in the cell [1, 3]. Thus, systematic analyses of the stochastic dynamics are most desired to understand the design principle of the gene network and to interpret experimental expression data quantitatively. Here, we theoretically examine a simple genetic oscillator composed of three genes [2] to examine how the noise affects the oscillatory behavior of the circuit.

2 Methods and Results

2.1 The Network Motif and the Model

The repressilator is a network composed of three genes in which proteins synthesized by one gene repress the expression of the other gene (Fig. 1a). We model the expression process at each gene as in fig1b. Proteins which will act on the other gene as repressors are synthesized with the rate g when the gene is active ($S = 1$) but with a negligibly small rate when inactive ($S = 0$). The repressor synthesized by the other gene binds in a dimer form to the promoter region with the rate $h(n) = h_0 n^2$ and detaches with the rate f, where n is the number of this specific repressors in the cell. Each repressor protein is degraded with the rate k without regard to the gene state. When the gene switch fluctuates on and off, the representative value of the number of proteins is $X = g/2k$. The ratio between time scales, $\omega = f/k$ measures the "adiabaticity" of the gene switching. The master equation is derived to represent the stochastic dynamics of the network of Fig. 1a.

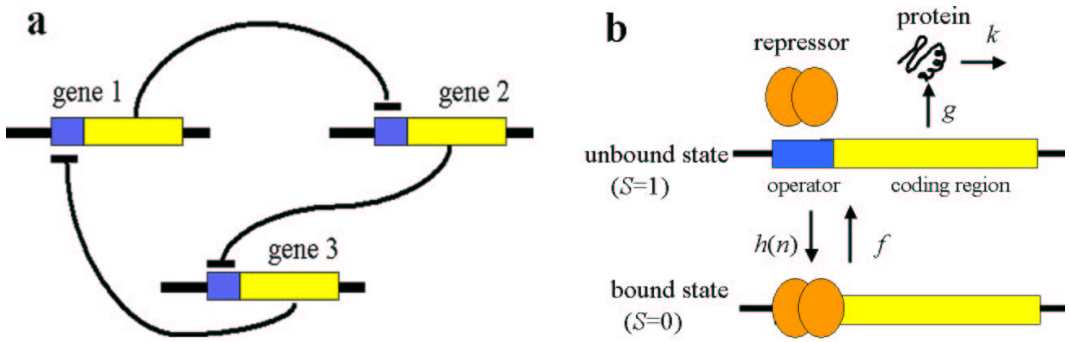

Figure 1: **a**, Repressilator network. Lines connecting each gene to the other show the negative regulatory relation. **b**, Each gene has two states, the active state that repressor is unbound ($S = 1$) and the inactive state with the repressor bound ($S = 0$).

2.2 The Mean Field Approximation and Computer Simulation

One of the systematic approach to solve the master equation is to use the analogy of quantum mechanics to the stochastic process. A mathematical formalism was developed by representing proteins as "bosons" and the gene state as a "spin" [4]. With this analogy the mean-field equation of the stochastic process is derived in a straightforward way with the Hartree-like variational approximation for bosons. The Monte Carlo (MC) simulation with the Gillespie algorithm was carried out and compared with the mean-field results.

2.3 Results

The mean-field solution shows the Hopf bifurcation from the stationary state to the limit cycle by varying X and ω (Fig. 2 left). The corresponding MC results are shown in Fig. 2 A∼C. At the point A with small X and small ω, the number of proteins fluctuates in a confined area. At the point B with intermediate X and ω, the MC trajectory mostly stays in one of narrow stable areas and intermittently makes transitions between areas. At the point C with large X and ω, the trajectory is attracted to a closed orbit and fluctuates around it.

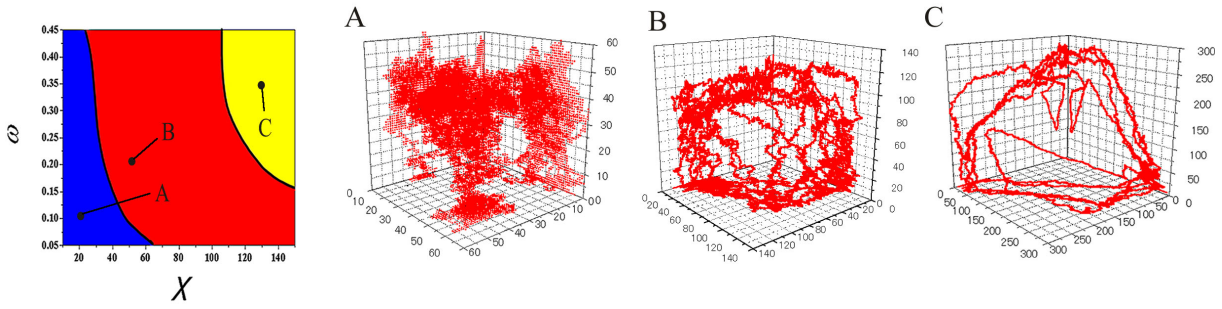

Figure 2: The left figure is the phase diagram in the mean field approximation. The mean-field solution shows the Hopf bifurcation from the stable node (blue region) through the stable spiral (red) to the limit cycle (yellow). Right figures (A∼C) are MC trajectories with parameters A, B and C in the left figure, showing the dynamical change of the number of proteins synthesized by gene1, gene2, and gene3.

3 Discussion

We showed how the coherent oscillation emerges from the noisy fluctuating dynamics. The limit cycle collapses to the transient dynamics when X or ω is decreased. It would be interesting to examine the possibility that the living cell uses this mechanism to reset the oscillatory phase in the biological rhythm. A similar phase diagram was found for a two-gene toggle switch circuit. In the mean-field approximation, a single stationary state at small X and ω bifurcates into two stationary states at larger X and ω [4]. The rapid change of the statistic features of MC trajectories is observed by changing X and ω. Also in this case, noisy fluctuations turn into the coherent switching transitions as X and ω increase.

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