

# Effects of the DNA state fluctuation on single-cell dynamics of self-regulating gene

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## Introduction

Coupling of heterogeneous reactions gives rise to complex cellular dynamics. In prokaryotic gene expression, for example, transcriptional activity of a gene is switched on/off when repressors unbind/bind to the operator region, while the number of repressors varies from  $10^0$  to  $10^3$  with burst production and degradation. When these different types of reactions are coupled, various phenomena are expected to emerge, depending on the difference or similarity of time scales of those reactions. Hitherto developed theoretical treatments, however, have assumed that the on/off switching of gene, or the DNA state alteration, is fast enough and missed the associated dynamical features of gene networks [1,2]. In this study, by explicitly describing the DNA state alteration, a systematic analytical method is developed to derive two-time correlation functions  $\langle \dots \rangle$  and response functions  $R$  of the single-cell dynamics of gene networks. As a first step toward understanding the dynamics of intricate gene networks, we apply this method to a circuit of a self-regulating gene and analyze the effects of the DNA state fluctuation. A possible physical meaning of the effective “temperature” defined as the ratio of  $C$  to  $R$  is also discussed.

## Method

We take a circuit of a self-regulating gene (Fig.1) as a simplest example. In this nonlinear circuit, proteins are synthesized from a single gene in a burst-like manner and a dimer of the expressed protein works as a repressor of its gene. The stochastic process in this system is described by a master equation with two variables, the number of proteins  $n$  ( $n=0,1,2, \dots$ ) and the DNA state  $\alpha$  ( $\alpha=1$  or  $0$ ). By using the analogy to quantum mechanics, the master equation can be transformed into the equivalent form of “wave equation” with a

non-Hermitian “Hamiltonian” [3].  $C$  and  $R$  can be calculated by taking variations of the generating function defined with this “Hamiltonian”. To derive the concrete form of the generating function, we use the path integral method, in which the classical path corresponds to the deterministic reaction equation and the semi-classical fluctuation around the classical path is taken into account.

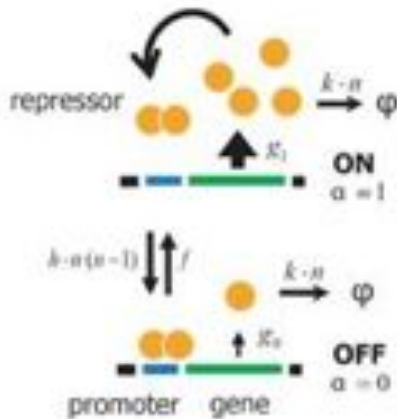


Fig.1. Model of a self-regulating gene. The dimer of the product protein works as a repressor, constituting a negative feedback loop.

## Results

$C$  and  $R$  were calculated for wide ranges of the protein synthesis rate ( $X^{\text{ad}}$ ) and the rate of the DNA state alteration ( $w^{\text{ad}}$ ). Examples of  $C$  and  $R$  for the number of proteins are shown in Fig.2 together with the results of the Monte Carlo (MC) simulation for comparison. In a wide parameter region,  $C$  and  $R$  can be fitted by a single exponential curve with a small time constant (B and D). When both  $X^{\text{ad}}$  and  $w^{\text{ad}}$  are small,  $C$  and  $R$  are fitted by a multiple-exponential function and the relaxation times of  $C$  and  $R$  grow very large in the region (C).

The effective temperature has a peak similar to the strength of fluctuation in the region of the single exponential decay of  $C$  and  $R$ . In the region of small  $X^{\text{ad}}$  and  $w^{\text{ad}}$ , on the other hand, the effective temperature shows a resonance of hyperbolic type. In this manner, the effective temperature is usable to detect dynamical anomalies of the gene circuit.

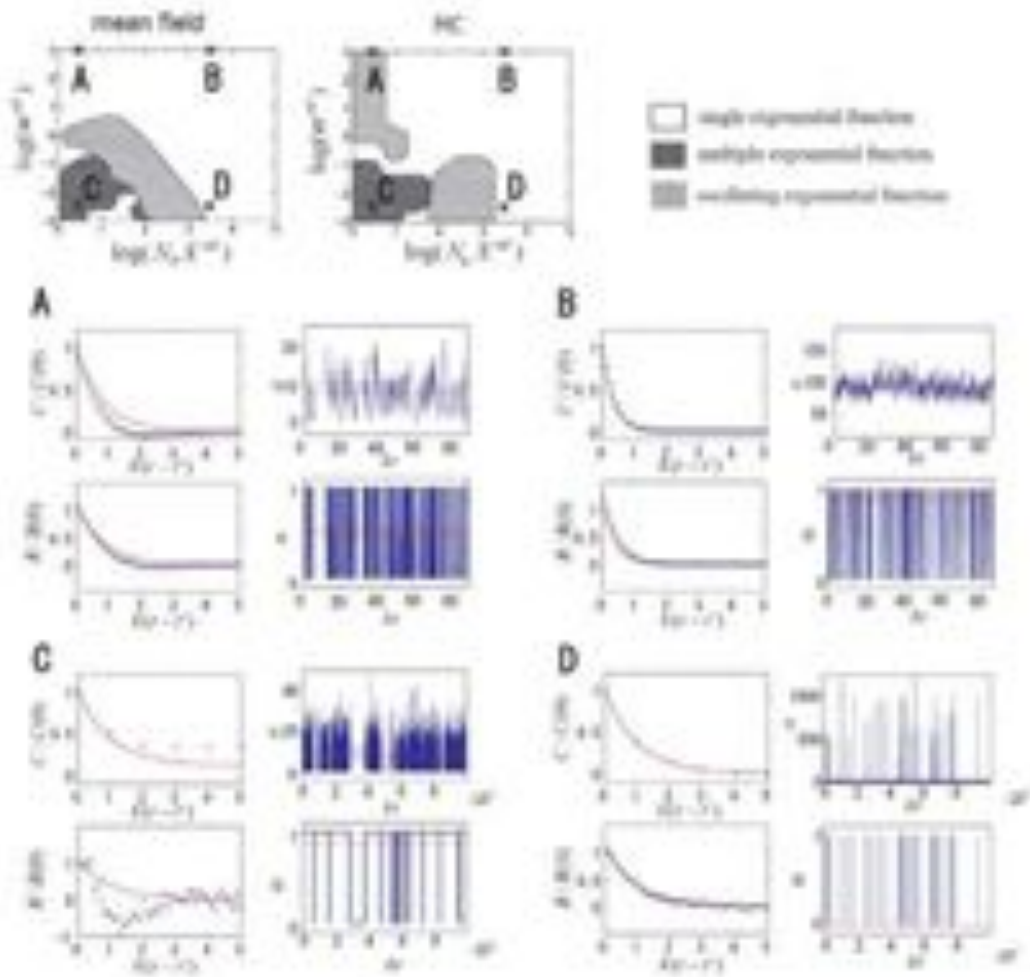


Fig.2. Functional form of  $C$  and examples of  $C$ ,  $R$  and MC trajectories. In top two figures, functional form of  $C(t-t')$  are shown on the plane of  $\log_{10} \omega^{ad}$  and  $\log_{10} N_b X^{ad}$ . For the points A, B, C, and D,  $C(t-t')/C(0)$  and  $R(t-t')/R(0)$  calculated by the mean-field theory (red lines) and those of the MC results (crosses) are compared. Also exemplified are MC trajectories of the protein number  $n$  and the DNA state  $\alpha$  shown as functions of time  $k(t-t')$ . The horizontal red lines in the figures of  $n$  and  $\alpha$  denote their averaged values.

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