Intrinsic Noise Induced State Transition in Coupled Positive and Negative Feedback Genetic Circuit

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***Abstract*—It is well known that gene regulatory circuits can be modeled by the deterministic or stochastic approach. In this paper, a three-component coupled positive and negative feedback genetic circuit is firstly modeled deterministically by Hill kinetics. Then, a corresponding stochastic model is also investigated by using Gellispie's stochastic simulation. Some typical dynamical behaviors of the genetic circuit are further discussed based on the bifurcation analysis of deterministic system, including monostability, bistability, excitability, and oscillation. This paper aims to further investigate the effect of intrinsic noise inherently in stochastic models on steady states transition. It includes: i) For the parameters in deterministically bistable region, intrinsic noise may induce bistable switch for the not too large system volume, which can be observed by the generation of a new stable steady state; ii) For the parameters in deterministically excitable region, intrinsic noise may induce periodic switch for the very large system volume, which can be observed by the stabilization of another unstable steady state and the switching between two stable states; iii) When time delays are introduced in these two models, similar phenomena can be observed. The above results will certainly increase the understanding of the inner relationships between different modeling for the genetic circuit. It sheds some light on the real- world engineering applications, such as the engineering design of synthetic circuits.**

I. Introduction

Over the last decades, genetic motifs with special dynamical behaviors have attracted an increasing attention from various disciplines. These motifs can demonstrate the bistable switch, oscillation, excitability, and the other special phenomenons[1]-[3], which can well explain some specific biological phenomenons and functions, such as circadian rhythms[4], biology memory[5], cell communication [6], cell differentiation [7], and so on.

It is well known that the negative feedback can generate oscillation[8], while the positive feedback can create multi-stability[5], [9], [10]. Recently, some coupled positive and negative feedback genetic motifs have been further investigated[11]-[19]. They found some interesting phenomena: i) Some negative feedback oscillators become more robust and tunable when coupled by a positive feedback loop[13]; ii) Some negative feedback oscillators have a widely tunable frequency and near-constant amplitude when coupled by a positive feedback loop [11].

As we know now, various models have been introduced to describe these coupled positive and negative feedback loops, such as Hill kinetics[12], [15]-[17], reaction rate equations[13], chemical master or Langevin equations [6], and so on. Note that the chemical master equations approach is an accurate modeling method at the expense of exhaustive computation time. Follow this line, various stochastic simulation algorithms are developed to accurately simulate the chemical master equations, such as Gillespie algorithm[20], τ leap method[21], hybrid method[22], and so on. Since time delay is ubiquitous in biological processes, some corresponding time delay stochastic simulation algorithms are also introduced[23]-[25]. Although these stochastic algorithms can well accurately describe some typical dynamical behaviors, the original deterministic ODEs or DDEs approaches are still widely used to analyze the dynamical behaviors. Therefore, an interesting question is what is the relationships between stochastic models and deterministic models. Moreover, what is the key role of intrinsic noises inherently in stochastic models?

According to the literature, Gonze et. al. firstly investigated the relationships between stochastic models and deterministic models of a circadian rhythms oscillator in Drosophila[26]. They found that the similar conclusions can be generally derived from the different models. Follow this line, Hao et. al. [17] further studied a minimal model of coupled positive and negative feedback loop, which is composed by transcriptional relations between two CREB proteins. In particular, the differences between different models aroused the special concern over the last decade[17], [26]. In [19], Turcotte et. al. discovered that the noise can stabilize the unstable state of an excitable genetic circuit. In this case, the noise can act as a genetic timer. Moreover, noise can induce bistable switch in bistable systems[27], [28]. Note that one of these two stable solutions is purely induced by noise which means that the noise can induce new steady state.

Inspired by the above question, this paper aims to investigate the effect of intrinsic noise inherently in stochastic models on steady states transition based on a three components coupled positive and negative feedback genetic loop. The main questions include: 1) How many different dynamical behaviors can

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the loop display? 2) What are the main differences between the deterministic model and its corresponding stochastic model for the different parameter regions? 3) Is the main function of intrinsic noise inherently in the stochastic model to maintain the stability of steady states or generate the new states?

The following paper is organized as follows. Section II introduces the deterministic model and its corresponding stochastic model. Bifurcation analysis of the ordinary differential equation (ODE) model and delay differential equation (DDE) model will be further explored in Section III. Section IV compares different models and investigates the proposed questions. Concluding remarks are given in Section V.

II. Mathematical Models

A. Deterministic Modeling

As we know now, the coupled positive and negative feedback loops widely exist in biological systems[11], [14]-[17], such as the MAPK/PKC system, the CREB system, the yeast galactose utilization network, just to name a few. Fig. 1 shows a typical coupled positive and negative feedback genetic loop, where gene G_x, G_y, G_z dominate the production of transcription factors or protein X, Y, Z, the transcription factor X activates the expression of gene G_y, G_z, Y, Z activates and represses the expression of gene G_x. Here, the regulation relationships between gene G_x, G_y constitute of the positive feedback loop and G_x, G_z comprise of the negative feedback loop. Tian et. al. investigated some dynamical behaviors of the deterministic model of this circuit[15]. Hereafter, for simplicity, suppose that the transcription factors Y, Z are competitively binding to the promoter site of gene G_x. Similarly, the other binding manners, such as exclusive binding, independent binding, cooperative binding, can also be investigated.

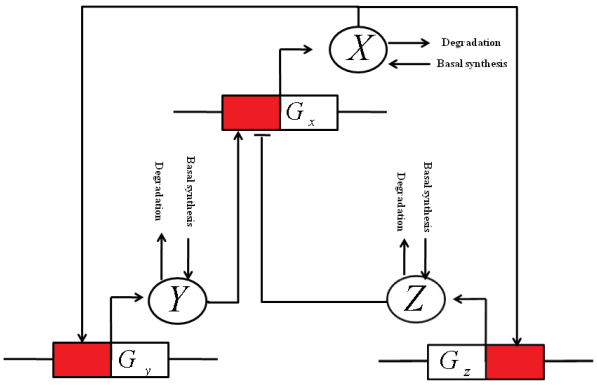

Fig. 1. The coupled positive and negative feedback genetic loop, where the transcription factor X activates the expression of gene G_y, G_z, Y, Z activates and represses the expression of gene G_x. Regulation relationships between gene G_x, G_y form the positive feedback loop and G_x, G_z consist of the negative feedback loop, where $\rightarrow$: activation, $\dashv$: repression. Here, there exists a degradation and basal synthesis processes for each kind of proteins.

Let the concentrations of protein X, Y, Z be x, y, z. The dimensionless model of concentration evolutions of X, Y, Z can be rewritten as follows:

$$\begin{cases} \dot{x} = \frac{\alpha_1 y^2}{1+y^2+z^2} - d_1 x + r_1, \\ \dot{y} = \frac{\alpha_2 x^2}{1+x^2} - d_2 y + r_2, \\ \dot{z} = \frac{\alpha_3 x^2}{1+x^2} - d_3 z + r_3, \end{cases} \quad (1)$$

where α_i is dimensionless maximal transcription rate, d_i is degradation rate, r_i denotes basal synthesis rate, and $i = i = 1, 2, 3$.

Since time delays are ubiquitous in nature, gene regulation processes can also be treated as a time delayed system. Over the last decade, there are numerous results reported on the time delays in protein degradation, transcription process, or translation process[23], [24]. For simplicity, only the time delay in protein degradation will be considered in this paper. The corresponding time delayed model of (1) is described by

$$\begin{cases} \dot{x} = \alpha_1 \frac{y^2}{1+y^2+z^2} - d_1 x(t-\tau_1) + r_1, \\ \dot{y} = \alpha_2 \frac{x^2}{1+x^2} - d_2 y(t-\tau_2) + r_2, \\ \dot{z} = \alpha_3 \frac{x^2}{1+x^2} - d_3 z(t-\tau_3) + r_3, \end{cases} \quad (2)$$

where $\tau_i\,(i = 1, 2, 3)$ are time delays of degradation in each protein.

In the following, let $\tau = (4, 2, 4)$, $\alpha_1 = 1, d_1 = 0.3, d_2 = 0.2, d_3 = 0.025, r_1 = 0.03, r_3 = 0.05$. The above parameters are selected from [15], [18], [30].

B. Stochastic Modeling

In general, there are two typical kinds of stochastic models[26]. One model is directly derived from the deterministic system (1), called birth-death process[17], [26], [29]. And the other model considers the detailed processes of gene transcription, translation, degradation, basal synthesis, polymerization, complex formation, and so on, called developed process. Hereafter, the stochastic model directly derived from the deterministic system will be further discussed. And the developed model will be explored in the future journal paper. Tab. 1 shows the simplified reactions and their corresponding propensity functions, where Ω is system volume, $N_i(i = x, y, z)$ are the molecular numbers of protein X, Y, Z, respectively.

In this paper, deterministic ODE is solved by Runger-Kutta method in Matlab; DDE will be solved by dde23 in Matlab; Bifurcation analysis is performed by Oscill8[31] and DDE-BIFTOOL[32]; Stability analysis as well as some bifurcation diagrams are performed in XPPAUT[33]. Stochastic simulations of stochastic models are performed in Matlab. For undelayed stochastic models, direct Gillespie algorithm [20] is used, while for delayed case, the rejection method introduced in [24] will be used, which has been proved to be an accurate method to simulate systems with delays [25].

III. Bifurcation Of Deterministic Models

A. One Parameter Bifurcation

Firstly, we perform bifurcation analysis for the deterministic ODE system (1), where α_2, α_3 are chosen as bifurcation

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TABLE I
STOCHASTIC MODEL DIRECTLY DERIVED FROM THE DETERMINISTIC SYSTEM.

Reaction	propensity function	Increment of molecular numbers
$\emptyset \xrightarrow{a_1} X$	$a_1 = \frac{\alpha_1 \Omega N_y^2}{\Omega^2 + N_y^2 + N_z^2}$	$(1,0,0)^T$
$X \xrightarrow{a_2} \emptyset$	$a_2 = d_1 N_x$	$(-1,0,0)^T$
$\emptyset \xrightarrow{a_3} X$	$a_3 = r_1 \Omega$	$(1,0,0)^T$
$\emptyset \xrightarrow{a_4} Y$	$a_4 = \frac{\alpha_2 \Omega N_x^2}{\Omega^2 + N_x^2}$	$(0,1,0)^T$
$Y \xrightarrow{a_5} \emptyset$	$a_5 = d_2 N_y$	$(0,-1,0)^T$
$\emptyset \xrightarrow{a_6} Y$	$a_6 = r_2 \Omega$	$(0,1,0)^T$
$\emptyset \xrightarrow{a_7} Z$	$a_7 = \frac{\alpha_3 \Omega N_x^2}{\Omega^2 + N_x^2}$	$(0,0,1)^T$
$Z \xrightarrow{a_8} \emptyset$	$a_8 = d_3 N_z$	$(0,0,-1)^T$
$\emptyset \xrightarrow{a_9} Z$	$a_9 = r_3 \Omega$	$(0,0,1)^T$

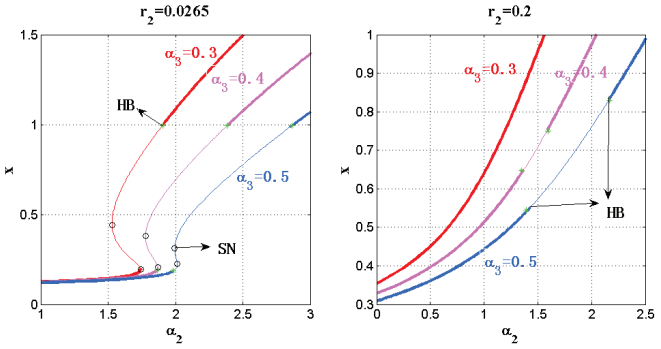

Fig. 2. One parameter bifurcation diagrams for system (1). Left: $r_2 = 0.0265$; Right: $r_2 = 0.2$; For both cases, bifurcation diagrams for $\alpha_3 = 0.3, 0.4, 0.5$ are plotted. SN: Saddle-Node point, HB: Hopf Bifurcation point. Thin lines represent unstable steady states, thick lines represent stable ones.

parameters in this section. From Fig.2, when $r_2 = 0.0265$, one parameter bifurcation diagrams of x with respect to α_2 reveal that there are two Saddle-Node (SN) points between two Hopf Bifurcation (HB) points, which reveals that for certain α_2, the system has three steady states, but further by XPPAUT, only one is stable. In fact, this region between two SN nodes are excitable ones, which can also be seen from two parameters bifurcation diagrams in subsection B; while for $r_2 = 0.2$, there are only two HB points for $\alpha_3 = 0.4, 0.5$, which means that only monostable and oscillation behaviors can be observed for certain α_3.

Using DDE-BIFTOOL, bifurcation diagrams for DDE system (2) are shown in Fig.3. The left panel shows the case for $r_2 = 0.0265$, while the right panel shows the case for $r_2 = 0.2$. Similar cases like ODE model can be observed in Fig.3.

B. Two Parameters Bifurcation Diagrams for ODE and DDE

From Fig.4 of two parameters bifurcation diagrams of ODE and DDE systems, when $r_2 = 0.0265$,, the parameter space (α_2, α_3) are divided into six regions, which are marked with $I, II, ..., VI$, among which, I denotes bistable region; II represents excitable region; III and IV are monostable regions; VI can display oscillation with three unstable steady states

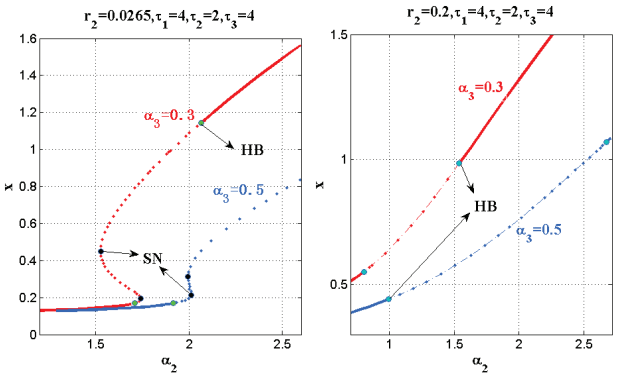

Fig. 3. One parameter bifurcation diagrams for system (2). The left panel shows steady states x versus α_2 for $r_2 = 0.0265, \alpha_3 = 0.3, 0.5, \tau_1 = 4, \tau_2 = 2, \tau_3 = 4$,, while the right panel shows the case for $r_2 = 0.2$. Dotted lines are unstable, while thick lines represent stable steady states.

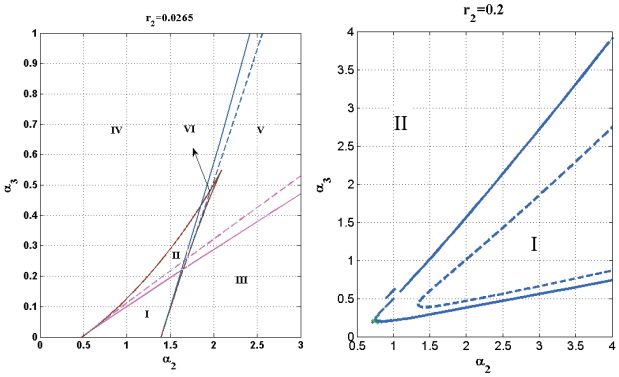

Fig. 4. Two parameter bifurcation diagrams and comparison between ODE and DDE systems. Dotted lines show bifurcations of ODE system, while solid lines show the cases for the corresponding DDE system. Here, parameters for the left panel are taken as $r_2 = 0.0265$, $r_2 = 0.2$ for the right panel, time delays are $\tau = (4,2,4)^T$. For the left panel, I: Bistable region; II: Excitable region; III and IV: Monostable; VI: Oscillation with three unstable steady states and V: Oscillation region with one unstable steady state. While for the right panel, I: Oscillation region; II: Monostable.

and V is Oscillation region with one unstable steady state. Whereas, for $r_2 = 0.2$, the parameter space are partitioned into two regions by two kinds of dynamical behaviors. Compared between bifurcation diagrams of ODE and DDE system, one can easily find that time delays can expand oscillation regions, when time delays are introduced, original monostable system can become oscillation ones, which verifies the existing conclusion that delay can induce oscillation[23].

IV. DETERMINISTIC MODEL VERSUS STOCHASTIC MODEL

A. Effect of Molecular Noise

System size Ω governs the size of fluctuations in reaction systems[34], which has been discussed in many books [34] and references therein, to get the Fokker-Planck approximation from Kammers-Moyal expansion of the corresponding chemical master equations. Fig.5 and 6 show deterministic as well as stochastic simulations both without delays and with delays under different system volumes. Fig.5 shows stochastic simula-

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tion results for models without delays listed in Table.1, where system volume is taken as $\Omega = 1000, 100, 10$, and initial molecular numbers are $N_x(0) = 500, N_y(0) = 0, N_z(0) = 0$. While, Fig.6 only shows stochastic simulation with $\Omega = 10$. From Fig.5 and 6, we find that for small system volumes, noise in the reaction systems make the evolution of protein concentrations fluctuate abruptly. We can also conclude that molecular numbers under stochastic regimes are roughly equal to concentrations of deterministic regimes scaled by Ω. For parameters locating in monostable region, stochastic results are also roughly equal to deterministic concentrations scaled by Ω, we omit these figures due to space limitations.

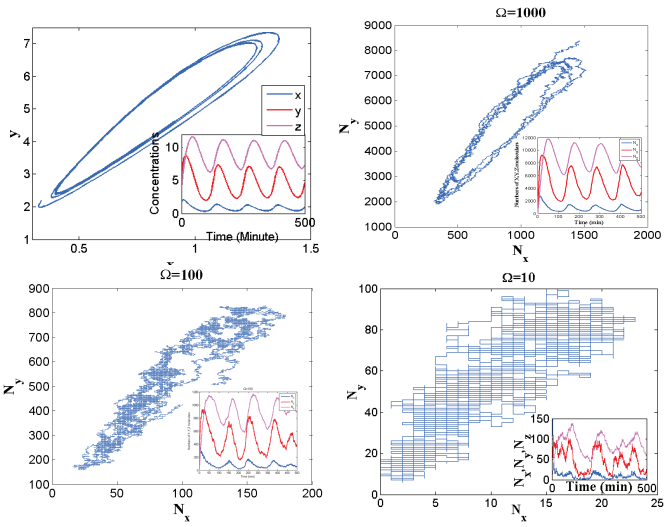

Fig. 5. Deterministic and stochastic simulation results without delays for parameters locating in oscillation region. The second to fourth panels show time evolutions as well as phase portraits in the x-y plane for protein numbers under stochastic regime with reactions in Table.1. Where system volumes are taken as $\Omega = 1000, 100, 10$, respectively, and $\alpha_2 = 2, \alpha_3 = 0.5, r_2 = 0.2$.

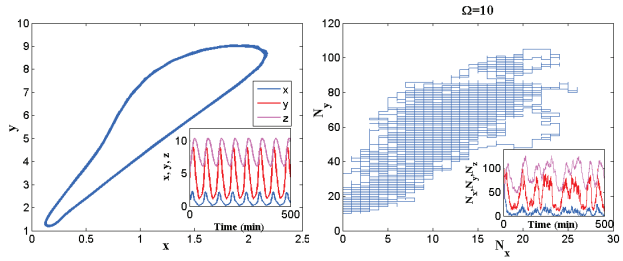

Fig. 6. Deterministic and stochastic simulation results with delays for parameters locating in oscillation region. The second panel shows time evolutions as well as phase portraits in the x-y plane for protein numbers under stochastic regime with reactions listed in Table.1. System volume is taken as $\Omega = 10$ and $\alpha_2 = 2, \alpha_3 = 0.5, r_2 = 0.2$.

Summing up, we can conclude that when system parameters locate in deterministically monostable and oscillation regions, similar results can be derived from deterministic and its corresponding stochastic models.

B. Steady State Transition From Unstable To Stable

Excitability has been observed in a wide range of natural systems, such as lasers, chemical reactions, ion channels, neural systems, cardiovascular tissues and climate dynamics[35], [36], as well as gene regulatory circuits[19], [37], [38]. Common features to all of these excitable systems are that there are three steady states, one is a "rest" state or vegetative growth state, which is stable; the other two are unstable, and called "excited" state and "refractory" state (correspondingly, saddle and competence state in [19], [37]).

From Fig.4, for $r_2 = 0.0265$, there is an excitable region labeled by region II. When $\alpha_2 = 1.7, \alpha_3 = 0.3$, system (1) is excitable, there are just three steady states for the system, one is stable, the other two are unstable. To further investigate this case, we investigate system (1) analytically. Let the right hand side of system (1) to be zero and we consider its steady states:

$$\begin{cases} \frac{\alpha_1 y^2}{1+y^2+z^2} - d_1 x + r_1 = 0, \\ \frac{\alpha_2 x^2}{1+x^2} - d_2 y + r_2 = 0, \\ \frac{\alpha_3 x^2}{1+x^2} - d_3 z + r_3 = 0. \end{cases} \quad (3)$$

From Eq(3), one has:

$$y = \frac{1}{d_2}(\frac{\alpha_2 x^2}{1+x^2} + r_2); z = \frac{1}{d_3}(\frac{\alpha_3 x^2}{1+x^2} + r_3).$$

Substitute y, z into $f(x) = \frac{\alpha_1 y^2}{1+y^2+z^2} - d_1 x + r_1$, we have: $f(x) = r_1 - d_1 x +$

$$\frac{\alpha_1 d_3^2[(\alpha_2 + r_2)x^2 + r_2]^2}{d_2^2 d_3^2 (1+x^2)^2 + d_3^2[(\alpha_2 + r_2)x^2 + r_2]^2 + d_2^2[(\alpha_3 + r_3)x^2 + r_3]^2}.$$

The roots of function $f(x)$ are steady states x values. For $\alpha_2 = 1.7, \alpha_3 = 0.3$, Fig.7 shows deterministic as well as stochastic simulation results, the inset figure of the first panel shows that $f(x)$ crosses the straight line $g(x) = 0$ for three times, at 0.168, 0.23589 and 0.77928, respectively, therefore, there are three steady states in system (1). One can easily judge that among these three steady states, one is stable, the other two are unstable, as noted by black dot and hollow circles.

By using software package XPPAUT, one can easily analysis kinds of these singular points. For stable steady states $(0.168, 0.36583, 2.3294)$, linearized system (1) at this point shows that, there are two complex eigenvalues with negative real part and one negative real eigenvalue for Jacobian matrix. For unstable steady state $(0.23589, 0.58055, 2.6325)$, there are one positive real eigenvalue and two negative ones, therefore, it is a saddle node. For the second unstable steady state $(0.77928, 3.344, 6.5339)$, there are two complex eigenvalues with positive real part and one negative real eigenvalue, which indicates that it is a saddle focus node.

From Fig.7, we see that for system volume from 10 to 1000, stochastic periodic switch can always be observed under stochastic simulations, where the system can switch between its stable "rest" state and saddle focus state. Further, protein number distributions under different system volumes show some bimodal distributions, this demonstrates that the behavior in this excitable region has switchable feature[39], which is

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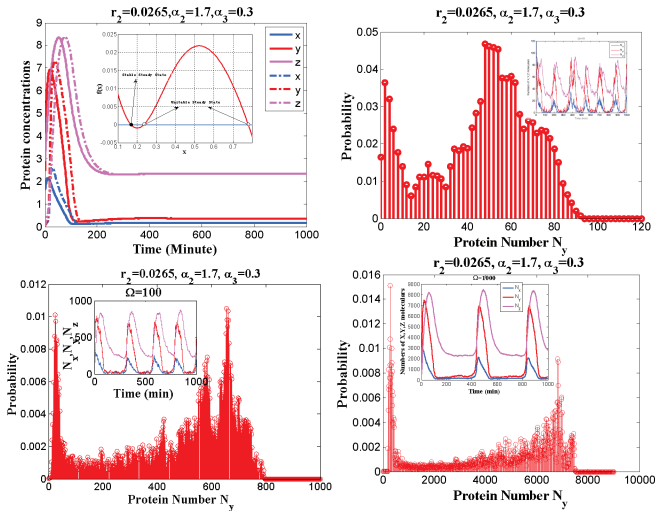

Fig. 7. Deterministic versus stochastic simulations for parameters locating in excitable region. Where $\alpha_2 = 1.7, \alpha_3 = 0.3$ and $r_2 = 0.0265$. The first panel shows deterministic time evolutions, the last three panels show probability distribution of protein number N_y as well as time evolutions under stochastic simulations for $\Omega = 10, 100, 1000$, respectively. Where periodic switch behaviors can always be observed.

very similar to the so called periodic switch phenomenon in [40].

Similar to Ref.[19], this periodic switch in stochastic regime can be explained as intrinsic noise induced stabilization of the unstable saddle focus node and induced switch between these two states. For detailed discussion, one can refer to [19] or our future journal paper. In a word, when parameters locate in deterministically excitable region, intrinsic noise inherently in stochastic models can induce the unstable saddle focus point into stable one and also induce transitions between them. Moreover, this stochastic periodic switch behavior can happen even with very large system volumes.

C. Intrinsic Noise Induced New Steady State And Transition

From Fig.4, for the case that $r_2 = 0.0265$, when parameters α_2, α_3 locate in region I, bistable behavior can be observed. We take $\alpha_2 = 1.2, \alpha_3 = 0.1$, then system (1) is bistable, Fig.8 shows deterministic as well as stochastic simulation results. Where, nullcline for x is drawn in the first panel, and the second panel shows time evolutions of protein concentrations, which is drawn under two different sets of initial state values; The third panel shows probability distribution for protein numbers of Y, as well as time evolutions when system volume is 10, and the fourth panel shows the case for $\Omega = 100$, where molecular numbers mainly fluctuate around one of its stable steady states. From deterministic result, for two different sets of initial state values, the system converges to two different steady states, while under the observation of stochastic simulation with small system volume, switch between the two deterministic stable steady states is presented. We note that in this observation, the appearance of one of the states is purely induced by intrinsic noise, thus, intrinsic noise can induce new state. We also note that, when system volume is small, molecular noise becomes important in evolution, this noise can drive the system switch between its two steady states, while for large system volume, molecular noise is comparatively low, and is not high enough to overcome double wells potential, therefore, switch can not happen.

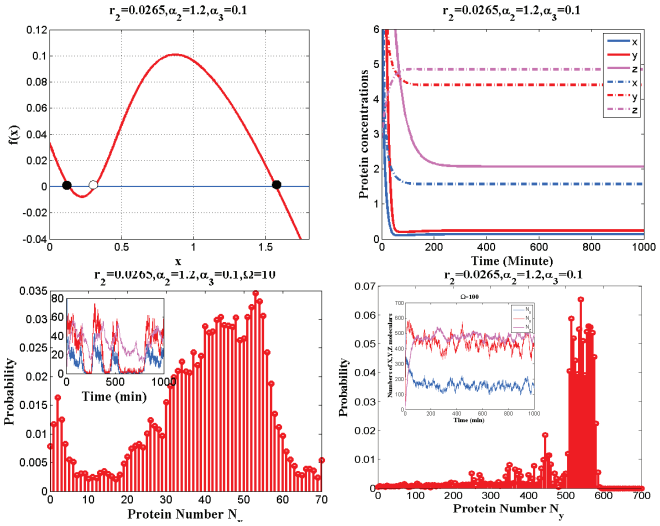

Fig. 8. Deterministic versus stochastic simulations for parameters locating in bistable region. Where $\alpha_2 = 1.2, \alpha_3 = 0.1$ and $r_2 = 0.0265$. The first panel shows nullcline for x, the second panel shows deterministic time evolutions under two different sets of initial values, and stochastic simulation results and probability distributions of protein number N_y with system volume $\Omega = 10, 100$ are shown in last two panels. For $\Omega = 100$, bistable switch can not be observed due to relatively low molecular noise.

For delayed case, there is also a bistable region for $r_2 = 0.0265$, we note that similar conclusions can be derived as undelayed case, figures and detailed discussions are omitted due to space limitation. We demonstrate that the switch behaviors observed in this subsection can be understood from the perspective of noise induced new steady state and transition between them. At some time, the system fluctuates around one of its stable steady states, but with the accumulation of potential due to noise, the system jumps to its second stable steady state, and this transition can happen only when intrinsic noise is relatively large enough.

V. Conclusion

This paper has further investigated the deterministic model and its corresponding stochastic model for a three components coupled positive and negative feedback genetic circuit. Bifurcation diagrams of the deterministic system show that the circuit can display monostable, bistable, excitable as well as oscillation behaviors. From the perspective of steady states transition, we discover that the unstable steady state can transit to attractive point under the stochastic regimes for the parameters in the deterministically excitable regions. Furthermore, for the parameters in bistable region, the intrinsic noise can promote to generate the new stable state and drive it to jump between these two stable states for the large enough noise strength to overcome double well potential.

In particular, for system (1) with $r_2 = 0.0265$, two parameters bifurcation diagram indicates us that there exist two oscillation regions. Here, the main difference lies in that one region (VI) has three unstable steady states, however, the other region (V) has only one unstable steady state. This issue will be further explored in our future journal paper since this conference paper only focuses on the steady states transition in stochastic regimes.

It should be pointed out that the differences between deterministic model and its corresponding stochastic model are obvious for the coupled positive and negative feedback genetic circuit with time delays and without time delays. The above results guide us how to select the suitable model to describe the specific biological circuits. It sheds some lights on the potential engineering applications in synthetic circuits.

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