A Two-variable Model for Stochastic Modelling of Chemical Events with Multi-step Reactions

Qianqian Wu, Kate Smith-Miles and Tianhai Tian*
School of Mathematical Sciences
Monash University
Melbourne, Australia
Email:{qian-qian.wu, kate.smith-miles, tianhai.tian}@monash.edu

***Abstract*—The development of simple mathematical model for representing complicated real-life chemical reaction systems has been a fundamental issue in computational biology and bioinformatics. In particular, the accurate description of chemical events with multi-step chemical reactions has been regarded as an essential problem in chemistry and biophysics. To model chemical reaction systems in a manageable way, multi-step chemical reactions were normally simplified into a one-step reaction. In recent years, a number of modelling approaches have been attempted to use simplified model to describe multi-step chemical reactions accurately. In this work, we proposed a two-variable model to describe chemical events with multi-step chemical reactions. We introduced a new concept to represent the location of molecules in the multi-step reactions, and use it as the second indicator of the system dynamics. The accuracy of the proposed new model was evaluated via using a deterministic model. The proposed model has been applied to study the mRNA degradation process. Numerical simulations of the designed simplified models matched the simulations of multi-step chemical reactions very well.**

***Index Terms*—stochastic modelling, multi-step reactions, mRNA degradation**

I. Introduction

Recent advances in computational biology and bioinformatics have provided a variety of mathematical models to describe complex chemical reaction systems inside the cell. There has been amount of evidence showing that mathematical modelling is a powerful and predictive tool for exploring the dynamic properties of genetic regulatory networks, cell signalling transduction pathways and metabolic pathways [1] [2]. In spite of the substantial progress, there are still a number of fundamental issues that need to be addressed imperatively. Among them, the accurate description of chemical events with multi-step chemical reactions has been regarded as a central problem in chemistry and biophysics [3]. There are many biochemical events involving multi-step chemical reactions. One of the most well-known example is gene expression which usually involves a large number of steps including transcription, RNA processing, DNA translation and messenger RNA (mRNA) degradation which can all be considered as multi-step reaction systems. In particular, transcription is a multi-step process consisting of initiation, elongation and termination phases; and elongation is a sequence of reactions that occur at each elongation step for RNA polymerase passing through the DNA. The multi-step reaction processes also exist in other areas such as organic chemistry and biophysical chemistry [4]. For example, an ion channel may change its conformation through multistep allosteric transitions [5]. Therefore to accurately describe chemical events with multi-step reactions is a critical step in the development of mathematical models for characterizing complex biological systems.

To model chemical reaction systems in a manageable way, multi-step chemical reactions were traditionally simplified into a one-step reaction. For example, it was a widely used approach to use first order reactions to describe the degradation process of mRNA or protein. Since the simplified one-step reaction cannot provide concrete description of the dynamics of multi-step reactions, recently chemical reactions with time delay have been used to describe the multi-step chemical events or slow reactions more accurately [6]. To address the coupling of intrinsic noise in biochemical reactions with delays, a new methods called delay stochastic simulation algorithm (DSSA) was proposed by introducing time delay into the stochastic simulation algorithm (SSA) [7]. Unlike the classic SSA, which assumes instantaneously biochemical reaction systems was assumed to model, the DSSA was designed to characterize chemical systems with both fast and slow reactions. In fact the so-called slow reaction in most cases is a simplified version of the multi-step reactions. This delayed method has been applied for many physical and biological systems. For example, Barrio et al. applied the DSSA to mimick delays associated with transcription and translation and successfully explained the process for the regulation of Hes1 gene [7]. These simulation methods have also been used to successfully validate stochastic models of biological systems with slow reactions. Recently the work done by Mier-y-Teran-Romero et al. opened some new aspects for application of time delays in biological systems. They presented the developed time delay models for protein translation based on the partial differential equation (PDE) models and obtained a good agreement between the time delay model and mechanistic models, which allows us for further study of formulation of time delay models of coupled template polymerization process in modelling of genetic networks [8]. Other modelling techniques proposed recently include the slow-scale linear noise approximation and the stochastic quasi-steady-state assumption [9] [10].

The degradation process of mRNA illustrates a typical

* Corresponding author

978-1-4673-2560-8/12/$31.00 ©2012 IEEE

system with multi-step reactions and is also an important step in the regulation of gene expression [11]. Over the past decade, mRNA degradation has been studied deeply, but there still exist problems unsolved with respect to the enzymes, pathways and regulation of mRNA degradation including the role of P-bodies etc. [12] [13] [14]. Based on the detailed process including ploy(A) tail shortening, decapping and digestion, mathematical models have been designed for understanding the dynamics of mRNA degradation, including a linear multicomponent model which was designed to investigate the mRNA degradation problem as well as the nonsense-mediated decay of mRNA molecules in yeast [15] [16]. This model includes 23 first-order reactions that describes transcription, decapping, ploy(A) shortening, translocation and as well as digestion process. lt is the first detailed deterministic model that studies mRNA degradation. Simulation results suggested that the widely used mRNA half-life, obtained by using the first order reaction, underestimated the averaged life-span of mRNA molecules and also half-life is an important factor for determining the different steps in the degradation pathway. With robustness analysis, it showed that the change of deadenylation rate might lead to great variations in mRNA copy numbers. To interpret the complex reactions in this detailed mathematical model, a multi-step reaction model was proposed recently by using a chain of 11 chemical reactions [17]. Numerical simulations suggested that this simplified model gave very good approximation to the original detailed model with 23 chemical reactions .

To further simplify the degradation process of mRNA, another approach used time delay to represent the total time required in the multi-step reactions [17]. The simplified stochastic model with time delay was also adopted for studying the degradation process of mRNA molecules. Numerical results showed that the simple first-order reaction models could not approximate the detailed degradation process precisely [17]. And even with delay introduced, it still remains a challenge to represent the chemical events with multiple small step reactions accurately. Therefore, instead of using time delay to represent the missing intermediate reactions in the one-step reaction, we here introduce another modelling method by introducing a new concept, which is termed as the length of a molecule to represent the location of that molecule in the multi-step reactions, and use it as the second indicator of the system dynamics. The following sections are organized as follows. Section II will introduce the new modelling approach with two variables for describing chemical events with multi-step reactions. The accuracy of the proposed new model is evaluated with a deterministic model in section III. Section IV of this paper studies the mRNA degradation process using our new modelling approach.

II. New Modelling Method for Multi-step Reaction System

Let us consider the following chemical events with multi-step chemical reactions, which is adapted from the theoretical model studied by Y. Zhou et al [3]:

$$B_1 \xrightarrow{k_1} B_2 \xrightarrow{k_2} B_3 \xrightarrow{k_3} \cdots \xrightarrow{k_n} B_n \xrightarrow{k_n} P. \tag{1}$$

In this system, any molecule that starts from the "B_1" state has to experience $(n-1)$ intermediate state $B_2, \cdots, B_n$ before it is turned to a "P" state. The molecule P may be the product of this multi-step process. It may also represent the degradation process when $P = (\ )$.

We denote X as the total copy number of molecules B_i

$$X = \sum_{i=1}^{n} [B_i].$$

In addition, according to the distance to the final product, for each B_i molecule, we define a corresponding length of $n - i + 1$, therefore the total length of all molecules is given by

$$L = \sum_{i=1}^{n} (n - i + 1)[B_i].$$

The proposed new model was considered in the following way. When a reaction occurs, the total length will decrease by one while the total copy number of molecules may remain the same if the reaction is one of the first $(n-1)$ steps or decrease by one if the reaction is the last step. Therefore, the two-variable reaction model can be structured via two types of reactions:

$$(X, L) \to (X, L-1) \tag{2}$$

representing reactions for $B_i \xrightarrow{k_i} B_{i+1}$, and

$$(X, L) \to (X-1, L-1) \tag{3}$$

representing the reaction for $B_n \xrightarrow{k_n} P$.

After suggesting two-variable reaction model, the SSA method which is the basic approach for various forms of modelling chemical systems will be applied to simulate the new model. It is described by the following algorithm.

Algorithm I

1) Based on the total molecule number X and total length L, we can calculate the propensity function

$$a_0 = kX,$$

where k is the harmonic mean of the rate constants

$$k = \frac{n}{\frac{1}{k_1} + \cdots + \frac{1}{k_n}}. \tag{4}$$

2) Determine the stepsize for the next reaction

$$\tau = \frac{1}{a_0} ln \frac{1}{r_1},$$

where $r_1 \sim U(0,1)$.

3) Generate a sample $r_2 \sim U(0,1)$ to determine which reaction from reactions (2) and (3) will occur,

$$(X, L) = \begin{cases} (X, L-1) & \text{if } r_2 > f, \\ (X-1, L-1) & \text{if } r_2 < f, \end{cases}$$

where f is the probability of the firing of the last reaction and then the system is updated.

4) Go back to step 1.

The key question remaining in the proposed model is to define a proper probability function f to describe the firing of the last reaction. It is clear that this probability should depend on the values of total molecule number X, total length L and the number of reactions n. Our initial attempt suggested that it could be difficult to find an analytical expression of the probability function $f(X, L, n)$.

In this work, we proposed to use the following expression, given by

$$\text{Type I:} \qquad f(X, L, n, q) = 1 - \left(\frac{L - X}{X(n-1)}\right)^q, \quad (5)$$

and an alternative expression is

$$\text{Type II:} \qquad f(X, L, n, q) = \left(1 - \frac{L - X}{X(n-1)}\right)^q. \quad (6)$$

The aim for this work is to test the feasibility of the two proposed functions f, find for the optimal q value under various simulation methods and apply the new modelling method to biological systems such as the process of mRNA degradation, which will be introduced in the following sections III and IV.

III. Ordinary Differential Equation Model

After we find the linear relation between the optimal value of q and the number of reactions n through the probability simulations, we next studied the corresponding ordinary differential equation (ODE) model to test the feasibility of the approximation probability function. Solving a set of ODEs numerically is another common way for describing the system with a set of chemical reactions. From multi-step chemical reaction system (1), the ODE model is formed as follows:

$$\begin{aligned} \frac{dB_1}{dt} &= -k_1 B_1, \\ \frac{dB_2}{dt} &= k_1 B_1 - k_2 B_2, \\ &\vdots \\ \frac{dB_n}{dt} &= k_{n-1} B_{n-1} - k_n B_n, \\ \frac{dP}{dt} &= k_n B_n. \end{aligned} \quad (7)$$

We can calculate the total molecule number X as

$$X = B_1 + \cdots + B_n,$$

and the total length of the molecules L is

$$L = B_n + 2B_{n-1} + \cdots + nB_1.$$

By adding up all the ODEs, then we have a new set of ODEs for the total molecule number X and total length L , given by

$$\begin{aligned} \frac{dX}{dt} &= -kB_n, \\ \frac{dL}{dt} &= -kX, \end{aligned} \quad (8)$$

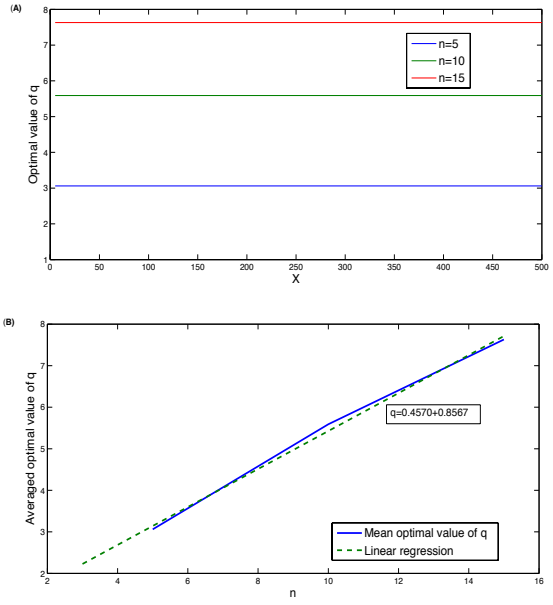

Fig. 1: Simulation results from the ODE model: (A) for the optimal q value against different X, (B) averaged optimal values for q against n.

where k is the harmonic mean of the rate constants (4). Note that in the (8), kB_n can be approximated with the probability function f as they all act as the probability for the occurrence of last step reaction. Thus in this work we proposed the following ODE model to represent the chemical events with multi-step chemical reactions

$$\begin{aligned} \frac{dL}{dt} &= -kX, \\ \frac{dX}{dt} &= -kX\left(1 - \frac{L - X}{X(n-1)}\right)^q. \end{aligned} \quad (9)$$

From the original ODEs (7), we can find the exact solutions for B_i with the given initial conditions $B_i(0)$ and rate constants k_i under a certain long enough time frame. The approximated ODEs (9) will be solved numerically for various q values under the same conditions.

Simulations were operated with conditions of $n = 5, 10, 15$ and $X = [5\ 10\ 50\ 100\ 200\ 500]$ respectively, i.e. for each n value we use the function ode23s in MATLAB to solve the system (9) for different cases with various initial X values.With the simulation results, Fig. 1 (A) was plotted which show some patterns such that optimal q increases when number of chemical reactions n increases and it does not fluctuate significantly with various initial X values.

A linear regression for the averaged optimal q versus n can be revealed from Fig.1 (B), the equation is described in the following form

$$\bar{q} = 0.4570n + 0.8567. \quad (10)$$

One of the important findings is that the value of q is dependent on the number of reactions n, but independent on the total copy number X. In addition, when q is close to the optimal q value, the difference between the error of optimal approximation and that using q is quite small. As a general rule, the value of q can be approximated with $n/2$.

With these findings of linear relationship between q and n, we can rewrite the probability function f in terms of L, X, and n such as

$$f(L, X, n) = (1 - \frac{L - X}{X(n-1)})^{0.4570n+0.8567}. \quad (11)$$

IV. Application to mRNA degradation

Based on the linear multi-component model studied by D. Cao and R. Parker [15], a simplified mathematical model to represent the mRNA decay was proposed, which is presented by the following Table 1 [17]. It is assumed that the gene transcription is a zeroth-order process which is given by reaction S_1 under a rate constant of 1. And then the mRNA molecules species A in the nucleus will translocate into the cytosol as species B via reaction S_2 under a rate constant of 0.2. Different from the original model, it was suggested that species B would start the poly(A) shortening process through reactions $S_3, \cdots, S_9$ with various rate instead of undergoing decapping reaction, $5'$-to-$3'$ / $3'$-to-$5'$ exonucleolytic degradation or digestion processes. Reaction S_{10} is a further exonucleolytic degradation to trim the mRNA with a poly(A) tail length of zero to produce species FG, which will be degraded in the end by reaction S_{11}. Since the fragment product (FG) is not a functional mRNA, we excluded reaction S_{11} for our consideration.

TABLE I: Reactions and kinetic rates of the simplified stochastic model. The rate constants s_i are in the unit of 1/sec.

	Reaction	Rate constant s_i	Comment
S_1	$DNA \to A$	1	transcription
S_2	$A \to B$	0.2	transport
S_3	$B \to BC1$	0.011	full-length 70A-60A
S_4	$BC1 \to BC2$	0.022	full-length 60A-50A
S_5	$BC2 \to BC3$	0.022	full-length 50A-40A
S_6	$BC3 \to BC4$	0.022	full-length 40A-30A
S_7	$BC4 \to BC5$	0.022	full-length 30A-20A
S_8	$BC5 \to BC6$	0.023	full-length 20A-10A
S_9	$BC6 \to BC7$	0.0099	full-length 10A-0A
S_{10}	$BC7 \to FG$	0.5006	fragment production
S_{11}	$FG \to ()$	0.00066	fragment degradation

To apply our proposed two-variable model to this mRNA degradation process, the following reaction model is built by constructing realization of $\mathbf{X} = (A, B, BC1, \cdots, BC7)$. Each reaction has its corresponding propensity function shown as below:

$$\begin{array}{ll} \text{Reaction} & \text{Propensity function} \\ DNA \xrightarrow{s_1} A & a_1 = 1, \\ A \xrightarrow{s_2} B & a_2 = 0.2 \cdot A, \\ B \xrightarrow{s_2} BC1 & a_3 = 0.011 \cdot B, \\ BC1 \xrightarrow{s_3} BC2 & a_4 = 0.022 \cdot BC1, \\ \vdots & \vdots \\ BC7 \xrightarrow{s_{10}} FG & a_{10} = 0.5006 \cdot BC7. \end{array} \quad (12)$$

The total mRNA molecule number X and total length L can be calculated as

$$\begin{aligned} X &= A + B + BC1 + \cdots + BC7, \\ L &= 9A + 8B + 7BC1 + \cdots + BC7. \end{aligned}$$

The SSA that generates a trajectory of the system step by step instead of following the time evolution of the probabilities is used here for the simulation. In each step, the SSA starts from its current system state $\mathbf{x}(t) = \mathbf{x}$ and examine itself two questions: When will the next reaction occur and which reaction will it be? Gillespie derived the formula for answering these two questions by studying the joint probability density function $p(\tau, j|\mathbf{x}; t)$, where τ is the time interval for next reaction to occur. And for each reaction R_j, the propensity function $a_j(\mathbf{x})$ is defined by a given state $\mathbf{x}(t) = \mathbf{x}$ and the value of $a_j(\mathbf{x})dt$ that represents the probability of one reaction will occur somewhere during the infinitesimal time interval $[t, t + dt)$ [18]. The SSA is an exact procedure for generating the time and index of the next occurring reaction according its current state and the propensity functions, which are defined as

$$a_0(\mathbf{x}) = \sum_{j=1}^{M} a_j(\mathbf{x}).$$

Also the time interval τ can be obtained with

$$\tau = \frac{1}{a_0(\mathbf{x})} ln \frac{1}{r_1},$$

where $r_1 \sim U(0, 1)$.

With the SSA simulations for above model (12), we will have the exact solutions for this mRNA degradation problem. On the other hand, using the proposed two variable chemical reaction systems and the approximated function (11) we finalized, we can set up a simpler model for the same mRNA degradation problem through constructing realization $\mathbf{X} = (L, X)$. With $n = 9$, each chemical reactions with its corresponding propensity function are described as

$$\begin{array}{ll} \text{Reaction} & \text{Propensity function} \\ DNA \xrightarrow{k_1} (9L, X) & a_1 = k_1, \\ (X, L) \xrightarrow{k} (X, L-1) & a_2 = k \cdot X \cdot (1 - f(L, X, 9)), \\ (X, L) \xrightarrow{k} (X-1, L-1) & a_3 = k \cdot X \cdot f(L, X, 9). \end{array}$$

Note that here $k_1 = s_1 = 1$ as it's the rate for producing mRNA species. The rate constant k can be calculated from (4) with $(S_2, \cdots, S_{10})$, given as

$$k = \frac{9}{\sum_{i=2}^{10} \frac{1}{s_i}} = 0.0212 \tag{13}$$

Initial conditions we took here are $\mathbf{X} = [10\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0]$ for the exact SSA and $\mathbf{X} = [90\ 10]$ for the approximated SSA. We carried out two numerical tests.

When $s_1 = k_1 = 1$, we notice that the rate of last-step degradation is $s_{10} = 0.5006$ and the synthesis rate for mRNA species A is $s_1 = k_1 = 1$ which is greater than s_{10}. Fig. 2 shows that both X and L will become steady in the long run as the equilibrium achieves. Fig. $2(A)$ and (C) represent an example of three simulations of X and L over a time period of $1,300$ seconds from the exact results derived from the detailed multi-step reaction model, while Fig.$2(B)$ and (D) show the three approximated simulation results for X and L over the same amount of time. By taking the average over the $10,000$ simulations, the averaged values for X and L can be compared for both models shown by Fig. $2(E)$ and (F) respectively. They reveal that the approximated solutions approach the exact simulations very well.

Instead of having non-zero rate of reaction S_1, we also simulated the two models with the zero rate of mRNA synthesis, which means that there will be having no more further production of new mRNA species A molecules adding into the reaction system. Therefore, unlike the previous case, L and X will both decrease and tend to 0 eventually, which can be revealed from Fig. 3. And with this numerical test, it also shows that the approximated solutions are close to the exact results. Hence with this application, we found that the approximated SSA using the proposed two-variable model indeed creates a good approximation for the exact model. It further confirms that the form of q achieved before is a good approximation. In addition, we found that the computing time taken for generating simulation results using approximated two-variable model is much shorter than the ones using the detailed multi-step reaction method.

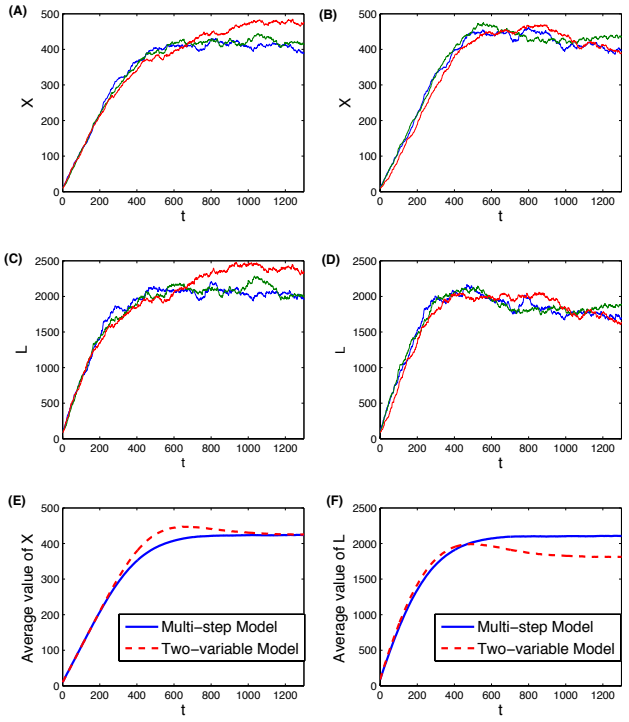

Fig. 2: The SSA simulation results with $s_1 = k_1 = 1$: (A, C) three simulations of X and L values over t for the detailed multi-step reaction model, (B, D) three simulations of X and L values over t for approximated model with two variables, (E) the mean value of X with $10,000$ simulations for both models, (F) the mean value of L with $10,000$ simulations for both models.

V. Conclusion

In this work, we have proposed a new model to describe chemical events with multi-step chemical reactions. This represents a major step in designing simplified mathematical model to represent complex chemical reactions systems, which is a fundamental issue in computational biology and bioinformatics. In addition to the total molecule number, we proposed to use the length of a molecule to represent its location in the multi-step chemical reactions. We used the ODE model to find the optimal value in the non-linear function via comparison of the simulations derived from detailed multi-step chemical reaction model and our proposed two-variable model. Our designed model has been successfully applied for the stochastic simulations of the mRNA degradation process. Numerical simulations of the designed simplified models match the simulations of the stochastic model with multi-step chemical reactions very well.

However, there are still a number of challenging issues that require further research to address. The core of the proposed new model is a non-linear function that is designed to approximate the probability of the firing of the last chemical reaction. On top of that, more accurate information regarding the probability will clearly lead to more sophisticated stochastic models to describe chemical events with multi-step reactions. In addition, the derived relationship between the optimal value in the non-linear function and the key parameters of the multi-step reactions should be further validated by stochastic simulations that is a more appropriate approach to describe biological systems with small copy numbers of molecules. Finally we discussed the mRNA degradation process in this work by adding the synthesis of mRNA molecules into the multi-step reaction system. It is expected that the proposed two-variable model will be incorporated into more complex biological systems including genetic regulatory networks, telomere length regulation as well as cell differentiation and death.

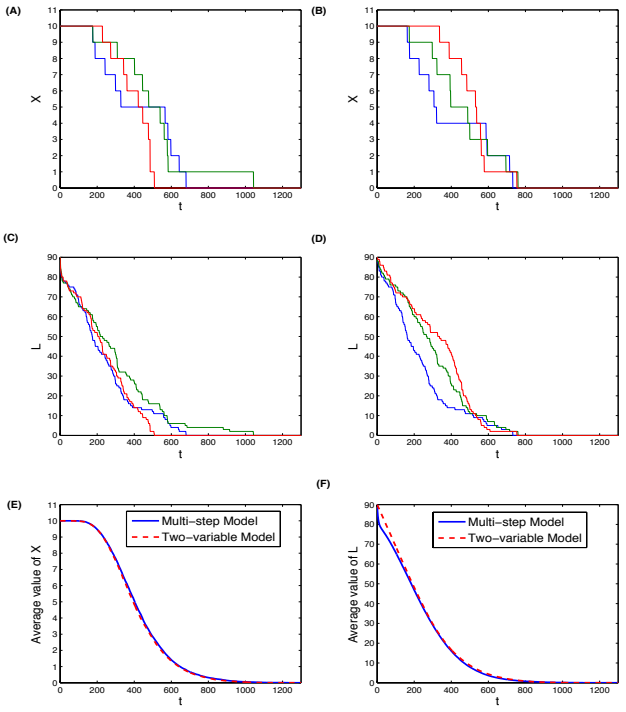

Fig. 3: The SSA simulation results with $s_1 = k_1 = 0$: (A, C) three simulations of X and L values over t for the detailed multi-step reaction model, (B, D) three simulations of X and L values over t for approximated model with two variables, (E) the mean value of X with $10,000$ simulations for both models, (F) the mean value of L with $10,000$ simulations for both models.

REFERENCES

[1] J. Lewis, "From signals to patterns: Space, time, and mathematics in developmental biology," *Science*, vol. 322, no. 5900, pp. 399–403, 2008. [Online]. Available: http://www.sciencemag.org/content/322/5900/399.abstract

[2] C. J. Tomlin and J. D. Axelrod, "Biology by numbers: mathematical modelling in developmental biology," *Nat. Rev. Genet*, vol. 8, no. 5, pp. 331–340, May 2007. [Online]. Available: http://dx.doi.org/10.1038/nrg2098

[3] Y. Zhou and X. Zhuang, "Kinetic analysis of sequential multistep reactions," *The Journal of Physical Chemistry B*, vol. 111, no. 48, pp. 13 600–13 610, 2007. [Online]. Available: http://pubs.acs.org/doi/abs/10.1021/jp073708%2B

[4] S. E. Branz, "A primer to mechanism in organic chemistry (sykes, peter)," *Journal of Chemical Education*, vol. 73, no. 12, p. A313, 1996. [Online]. Available: http://pubs.acs.org/doi/abs/10.1021/ed073pA313.2

[5] F. Qin and L. Li, "Model-based fitting of single-channel dwell-time distributions," *Biophysical Journal*, vol. 87, no. 3, pp. 1657 – 1671, 2004. [Online]. Available: http://www.sciencedirect.com/science/article/pii/S0006349504736474

[6] N. A. Monk, "Oscillatory expression of Hes1, p53, and NF-kappaB driven by transcriptional time delays." *Current Biology*, vol. 13, no. 16, pp. 1409–1413, Aug. 2003. [Online]. Available: http://view.ncbi.nlm.nih.gov/pubmed/12932324

[7] M. Barrio, K. Burrage, A. Leier, and T. Tian, "Oscillatory regulation of hes1: Discrete stochastic delay modelling and simulation." *PLoS Computational Biology*, vol. 2, no. 9, 2006. [Online]. Available: http://dblp.uni-trier.de/db/journals/ploscb/ploscb2.html#BarrioBLT06

[8] L. M. y Teran-Romero, M. Silber, and V. Hatzimanikatis, "The origins of time-delay in template biopolymerization processes." *PLoS Computational Biology*, vol. 6, no. 4, 2010. [Online]. Available: http://dblp.uni-trier.de/db/journals/ploscb/ploscb6.html#Mier-y-Teran-RomeroSH10

[9] P. Thomas, A. Straube, and R. Grima, "The slow-scale linear noise approximation: an accurate, reduced stochastic description of biochemical networks under timescale separation conditions." *BMC Syst Biol*, vol. 6, no. 1, p. 39, 2012.

[10] R. Srivastava, E. L. Haseltine, E. Mastny, and J. B. Rawlings, "The stochastic quasi-steady-state assumption: reducing the model but not the noise." *J Chem Phys*, vol. 134, no. 15, p. 154109, 2011. [Online]. Available: http://www.biomedsearch.com/nih/stochastic-quasi-steady-state-assumption/21513377.html

[11] P. Mitchell and D. Tollervey, "mrna turnover," *Current Opinion in Cell Biology*, vol. 13, no. 3, pp. 320 – 325, 2001. [Online]. Available: http://www.sciencedirect.com/science/article/pii/S0955067400002143

[12] N. L. Garneau, J. Wilusz, and C. J. Wilusz, "The highways and byways of mRNA decay," *Nat Rev Mol Cell Biol*, vol. 8, no. 2, pp. 113–126, Feb. 2007. [Online]. Available: http://dx.doi.org/10.1038/nrm2104

[13] A.-B. Shyu, M. F. Wilkinson, and A. van Hoof, "Messenger RNA regulation: to translate or to degrade," *EMBO J*, vol. 2, no. 3, pp. 471–478, 2008. [Online]. Available: http://dx.doi.org/10.1038/sj.emboj.76019774

[14] A. van Hoof and R. Parker, "Messenger rna degradation: Beginning at the end," *Current Biology*, vol. 12, no. 8, pp. R285 – R287, 2002. [Online]. Available: http://www.sciencedirect.com/science/article/pii/S0960982202008023

[15] D. Cao and R. Parker, "Computational modeling of eukaryotic mRNA turnover." *RNA*, vol. 7, no. 9, pp. 1192–1212, Sep. 2001. [Online]. Available: http://rnajournal.cshlp.org/content/7/9/1192.abstract

[16] ——, "Computational modeling and experimental analysis of nonsense-mediated decay in yeast," *Cell*, vol. 113, no. 4, pp. 533 – 545, 2003. [Online]. Available: http://www.sciencedirect.com/science/article/pii/S0092867403003532

[17] T. Tian, "Simplified stochastic models with time delay for studying the degradation process of mRNA molecules," *International Journal of Data Mining and Bioinformatics*, 2012 (in press).

[18] D. T. Gillespie, "Exact stochastic simulation of coupled chemical reactions," *J. Phys. Chem.*, vol. 81, no. 25, pp. 2340–2361, 1977. [Online]. Available: http://pubs3.acs.org/acs/journals/doilookup?in_doi=10.1021/j100540a008