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PARAMETER ESTIMATION AND STABILITY ANALYSIS OF GENE-REGULATION NETWORK OF BACTERIOPHAGE

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Abstract. This essay considers an ordinary differential equation on the phage λ regulatory network model, which has one and only one steady internal equilibrium by simplifying the calculation. Meanwhile, we use Ensemble Kalman Filter (EnKF) approach to compute the ratio of chemical reaction rate constant in the phage gene regulation network and combine the regulatory mechanism of the network to infer the amount of protein or DNA to avoid the high cost of protein-DNA detection. By changing the size of the initial ensemble of parameters, we get estimates with different precision. Numerical results clarify that the Ensemble Kalman Filter have an effect on parameter estimation of the phage regulatory network compared with the least square method. It perhaps is a relatively effective method to calculate unknown parameters in the biochemical network model by parameter estimation to lower the cost of biological experiments.

Keywords: gene-regulation; equilibrium; EnKF.

2010 AMS Subject Classification: 92C45, 93E25, 97K70.

1. INTRODUCTION

The process of cell is regulated by the genetic program which takes advantage of the interaction between protein-DNA in regulating function [1]. CI and Cro, as products of gene

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expression in λ bacteriophage, play a distinct role in determining its mode of growth[2]. In an infected host cell, the phage λ pours its chromosome into the host and leaves the shell of protein outside the host. Subsequently, phage selects one of two survival modes including lysogenic and bacteriolytic states. That is, it may produce new phage particles in the host cell by causing cell lysis, or it may build a dormant state lysogenic, nucleic acid is integrated into the host bacterial chromosome, where the reconstituted genome is called as a prophage[3]. Numerous positive regulatory factors and negative regulatory factors have been found in this model to regulate gene expression after transcriptional regulation[4].

Comprehending the physiological properties of interactions between regulatory factors of the gene regulation networks is significant. Here, the networks are simulated as a biochemical reaction model and the synergistic effect of biochemical reactants is considered in the model. Until now, there are four main types of models used to control network simulation, i.e., boolean networks, ordinary differential equation, stochastic model and hybrid model. Boolean networks are the first model to be discussed, the state is determined by a boolean function of the genes state(ON and OFF)[5, 6]. Chao established the stochastic model of gene expression regulation based on the two-state model and studied its performance[7]. The work covered in the article involves in analyzing the stability of the equilibrium of the ordinary differential equation in phage λ regulatory network model. In addition to measuring technical deficiencies, computing protein concentration is difficult and more expensive, it also takes more time to distinguish between different translations of the same protein in some biological experiments[8]. Therefore, it is significant to use parameter estimation to computer the unknown parameters in the biochemical network.

Our article is structured as follows. In section 2, we introduce the Genetic-Regulatory networks model and study the existence and stability of system equilibrium. Section 3 outlines the estimated approach to model parameters, i.e., the magnitude of proteins Y and dimer Y_2 with the ratio of the rate constants of chemical reactions in a gene regulatory network are estimated by Ensemble Kalman Filter(EnKF). In section 4 we simulate the stability of the genetic regulatory networks and parameter estimation. Finally, the conclusion is drawn in section 5.

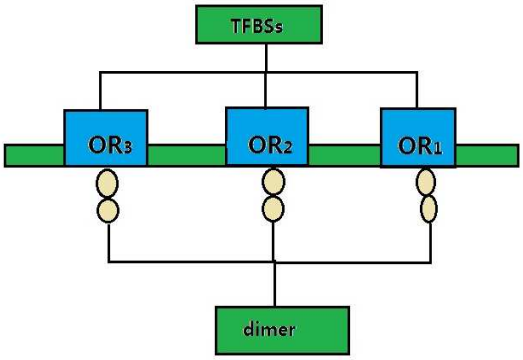


FIGURE 1. The regulatory region of λ phage P_{RM} promoter.

2. GENETIC-REGULATORY NETWORKS MODEL AND PROPERTIES

Specific consequences from the dynamics of genetic-regulatory networks are instrumental. it not only instrumental to comprehend the properties of the inherent stochasticity quantitatively but also to parameter estimating[9]. Therefore, let us turn to the introduction to the regulation process of the gene regulation network system that λ phage infects escherichia coli. The P_{RM} region of the λ bacteriophage involving the transcription factor binding sites(TFBS) are OR_1, OR_2, and OR_3 in the promoter region, respectively, as shown in Fig.1. The CI repressor which expressed by CI gene is the most dynamic protein in the lysogen state. The binding sites of transcription factors are OR_1 and OR_2, and the CRo gene is inhibited in the lysogen state, whereas the CI gene is transcribed. When λ phage is in the bacteriolytic state, the CRo repressor (CRo gene product) is integrated and occupies sites OR_2 and OR_3.

According to the magnitude of the reaction rate constant, we divide the biochemical reactions from the process of gene regulation into two types: fast reaction and slow reaction[10, 11]. Supposing the fast reactions for dimerization and the slow reactions for binding with sites are in equilibrium[9]. Then, satisfying the equilibrium reactions of genetic-regulatory network reactions are given by

$$Y + Y \underset{k2}{\overset{k1}{\longleftrightarrow}} Y_2 \qquad D + P \xrightarrow{k_t} D + P + nY$$

$$D + Y_2 \underset{k4}{\overset{k3}{\longleftrightarrow}} D_1 \qquad D_1 + Y \xrightarrow{k_t} D_1 + P + nY$$

$$D_1 + Y_2 \underset{k6}{\overset{k5}{\longleftrightarrow}} D_2 \qquad D_2 + Y \xrightarrow{ak_t} D_2 + P + nY$$

$$D_2 + Y_2 \underset{k8}{\overset{k7}{\leftrightarrow}} D_3 \qquad\qquad Y \xrightarrow{k_d} \phi$$

where Y, Y_2, and D specified as the repressor, repressor dimer, and DNA promoter site, and D_i denotes the dimer binding to the OR_i site for $i = 1,2,3,4$, with $k_j (j = 1,2,\cdots)$ the constants of reaction rate. k_t and k_d are transcription and degradation constants, respectively. P represents the concentration of RNA polymerase, n signifies the count of proteins per mRNA transcripts, and constraint $a > 1$ is the extent of transcription is strengthened by protein dimer binding to OR_2. We discern that the reactants involved in biochemical reactions include:Y, Y_2, D, D_1, D_2, D_3, P. For the concentration of reactant P may be permanent as catalysis, therefore, we concern the concentration variation of other reactants:Y, Y_2, D, D_1, D_2, D_3. Meanwhile, the time evolution of the fast and slow reaction system concentrations is described by the system of ordinary differential equations as follows

$$\begin{cases} \dfrac{dY}{dt} = \dfrac{-k_1 Y(Y-1)}{2} - kdY + k_2 Y_2 + nktDP + nktD_1 P + anktD_2 P, \\ \dfrac{dY_2}{dt} = \dfrac{k_1 Y(Y-1)}{2} - (k_2 + k_3 D + k_5 D_1 + k_7 D_2) Y_2 + k_4 D_1 + k_6 D_2 + k_8 D_3, \\ \dfrac{dD}{dt} = k_4 D_1 - k_3 D Y_2, \\ \dfrac{dD_1}{dt} = k_3 D Y_2 - k_4 D_1 - k_5 D_1 Y_2 + k_6 D_2, \\ \dfrac{dD_2}{dt} = k_5 D_1 Y_2 - k_6 D_2 - k_7 D_2 Y_2 + k_8 D_3, \\ \dfrac{dD_3}{dt} = k_7 D_2 Y_2 - k_8 D_3. \end{cases} \tag{2.1}$$

We suppose that the total concentration of DNA promoter sites $H = D + D_1 + D_2 + D_3$ is constant. Even when the set of ODEs is analytically awkward, it is possible to discuss an "equilibrium" solution of the system by analytic means. An equilibrium solution is a set of concentrations which will not vary over time, hence that is discovered by setting the RHS(Right Hand Side) of simultaneous equations to zero. the equilibriums of gene regulation network system are obtained by the calculation: $E_0 = (0,0,0,0,0,0)$; $E_1 = (1,0,\frac{kd}{nktP},0,0,0)$. However, when $Y_2 \neq 0, D = 0, D_1 \neq 0, D_2 \neq 0, D_3 \neq 0, Y \neq 0$, there may be two equilibria by computation. On the basis of supposing condition: $H = D + D_1 + D_2 + D_3$(i.e. $\frac{dD}{dt} + \frac{dD_1}{dt} + \frac{dD_2}{dt} + \frac{dD_3}{dt} = 0$), the

system (2.1) is simplified as follows

$$\begin{aligned} \frac{dY}{dt} &= \frac{-k_1 Y(Y-1)}{2} - kdY + k_2 Y_2 + A, \\ \frac{dY_2}{dt} &= \frac{k_1 Y(Y-1)}{2} - k_2 Y_2 - CY_2 + B, \end{aligned} \tag{2.2}$$

where $A = (a+2)nktPD > \frac{kd}{2}, B = (k_4+k_6+k_8)D, C = (k_3+k_5+k_7)D$. Next, we explore the stability of the equilibrium signified by $E^*(Y^*, Y_2^*)$ with $Y^* > 0$ and $Y_2^* > 0$. A straightforward observation from the equation (2.2), which is never exists three boundary equilibria $O(0,0)$, $E_1(Y^*,0)$, $E_2(0,Y_2^*)$, while the interior equilibrium of system (2.2) meet the characteristic equation at E^* satisfies

$$\lambda^2 + P\lambda + Q = 0, \tag{2.3}$$

where

$$P = \frac{k_1(2Y^*-1)}{2} + kd + k_2 + C,\ Q = \frac{Ck_1(2Y^*-1)}{2} + kd(k_2+C),$$

as a consequence, the interior equilibrium $E^* = (Y^*, Y_2^*)$ is stabilized with $P > 0$ and $Q > 0$. When you put it all together, there is only a stable internal equilibrium in the system (2.2).

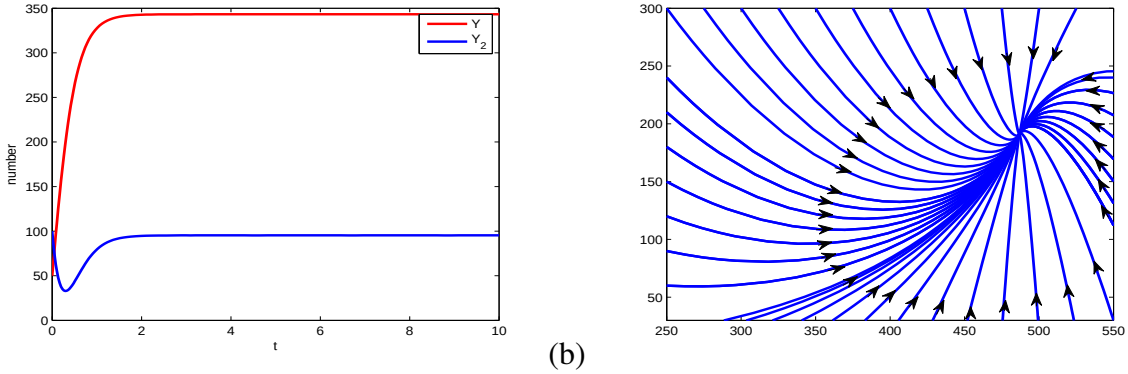


FIGURE 2. (a) shows that the evolution of gene regulation system with time. (b) displays that the interior equilibria E^* is stable, when parameters Y and Y_2 take different initial values, differentially.

3. METHOD

Mathematical modeling is instrumental in estimating the parameters of the model reliably and accurately[12]. We may be hampered by the unknown parameters such as rate constant

Algorithm 1 : EnKF Algorithm pseudocode.

Input: Input: the initial value of state vector, $\alpha_0 = [Y, Y_2]^T$;the true value of parameter $\beta_0 = [A, B]$;thus,generating the initial ensemble $\psi = [\beta, \alpha]$;

Output: Output:the Assimilation value of ensemble ψ_t^a;

initial: tspan,$Z_t, Y_0, Y_{20}, A_0, B_0$;
for each $t \in [0, tspan]$ **do**
    get the prediction value ψ_t^f=prediction(t,Y_0,Y_{20},A_i,B_i); ▷ $using(3.5)$
    get the measurement value with perturbationZ_t; ▷ $using(3.7)$
    caculate the kalman gain K; ▷ $using(3.9)$
    update:get the Assimilation value X_t^a; ▷ $using(3.10)$
    caculate the covariance matrix of the Assimilation value P_t^a; ▷ $using(3.12)$
end for
return X_t^a, P_t^a.

with analyzing the main idea of systems biology. Meanwhile, estimating parameters in partially observed noise data is a challenging problem[13]. Here, parameter estimation was performed using the Ensemble Kalman Filter(EnKF), which is capable of dealing with high-dimensional nonlinear systems simultaneously[14]. The basic idea is to initialize the state and parameter vectors and update each individual in the initial data set with observation information through Kalman filtering to obtain the assimilation set. It is noteworthy that the sealed parameter vector $\theta = (\theta_1, \theta_2, \dots \theta_k)^T$ that we undertake to estimate is constants. It is possible to view them as plus state variables with a rate of variation equal to zero. With these settings, we regard them as constant functions of time instead of constant numbers. This approach is usually referred to as state extension[8, 12]. Our system (2.2) is given

$$\begin{cases} \frac{dX}{dt} = G(Y, Y_2; \theta), \\ \frac{d\theta}{dt} = 0, \\ \eta = h(X_0), \end{cases} \tag{3.1}$$

where the state vector $X = (Y, Y_2; \theta)^T$, $\theta = (A, B)^T$, G is satisfied with the nonlinear system (2.2). The output function h is used to yield the measurement value, X_0 represents the original

value of the state. To put it more precisely, we estimate the continuous time process of the model by using the discrete measurement value of the output function y. As to the parameters θ, since $\dot{\theta} = 0$ it is visible that $\theta(t) = \theta_0$ for all $t \geq t_0$. Primarily, we demand some initial definition to prepare for proceeding the filter. Ideally, X_0 should be the initial conditions of the process, but this is obviously impossible. Since we do not have any measurements available to estimate X_0, it might make senses to take our initial value of X_0 equal to the average given by $G(t;X)$. Therefore, we write

$$X_t^f \triangleq (X_t^{f(1)}, X_t^{f(2)}, \cdots, X_t^{f(q)}),\ X_t^{f(i)} \triangleq (Y_t, Y_{2t}, A_t, B_t)^T,\ i = 1,2,\cdots,n. \tag{3.2}$$

where $X_t^f \in R^{n\times q}$, which is the predicting samples ensemble of state X at time t. n and p denote the dimension of state and the number of samples, respectively. Meanwhile, mean of state prediction $\overline{X^f}$ as well as the matrix of state prediction error covariance P_t^f are defined by

$$\overline{X_t^f} = \frac{1}{q}\sum_{i=1}^{q} X_t^{f(i)},\ i = 1,2,\cdots,n,\ P_t^f = \frac{1}{q-1}\widetilde{e_t^{xx}}(\widetilde{e_t^{xx}})^T. \tag{3.3}$$

Where $\widetilde{e_t^{xx}}$ is the residual of state prediction

$$\widetilde{e_t^{xx}} \triangleq (X_t^{f(1)} - \overline{X_t^f}, X_t^{f(2)} - \overline{X_t^f}, \cdots, X_t^{f(q)} - \overline{X_t^f}). \tag{3.4}$$

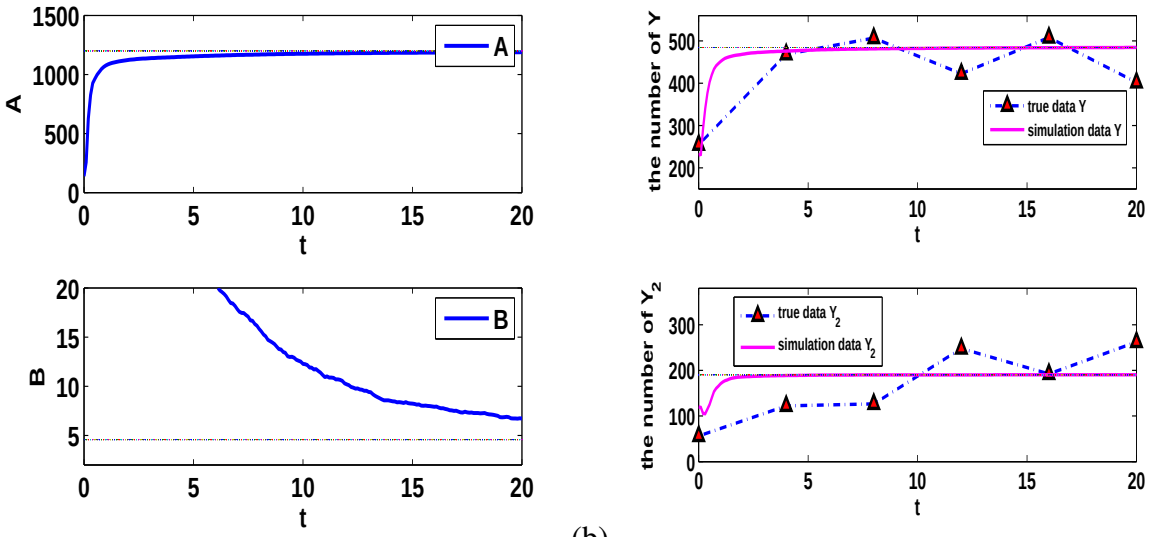
Upon the above definition, we employ the prediction equation and the update equation to estimate the state X in the phage model.

1. Initialization: $Y_0, Y_{20}, A_0, B_0, tspan$.

2. Prediction: Input the i-th $(i = 1,2,\cdots,n)$ data into the model (2.2) with the parameter A and B. We would obtain the prediction state of the next observation moment t, then the prediction state and model parameters are integrated into a joint state vector X_t^f. The EnKF prediction equation is written as follow

$$\begin{pmatrix} Y_{(t)}^f \\ Y_{2(t)}^f \\ A_{(t)}^f \\ B_{(t)}^f \end{pmatrix} = \begin{pmatrix} \frac{-k_1 Y_{(t-1)}(Y_{(t-1)}-1)}{2} - kdY_{(t-1)} + k_2 Y_{2(t-1)} + A \\ \frac{k_1 Y_{(t-1)}(Y_{(t-1)}-1)}{2} - k_2 Y_{2(t-1)} - CY_{2(t-1)} + B \\ 0 \\ 0 \end{pmatrix} + \begin{pmatrix} \varepsilon_1^j \\ \varepsilon_2^j \\ \varepsilon_3^j \\ \varepsilon_4^j \end{pmatrix}. \tag{3.5}$$

Superscript t and f denote as the time and prediction of state separately. Variable ε assigned the process noise generally, which is referred to as a Gaussian random variable with zero mean



(a) (b)

FIGURE 3. At the ensemble size is 20, (a) illuminates that the estimated parameter set $\{A,B\}$ (blue line) and the real values(broken line) become $\{A = 1189.2, B = 6.48\}$ and $\{A = 1200, B = 4.58\}$, respectively. (b) shows that the amount of state collection $\{Y, Y_2\}$ is $\{Y = 484.1, Y_2 = 189.1\}$ by EnKF(full line), while the red solid triangle dotted line denotes the measured values, which is $\{Y = 486.8, Y_2 = 191.1\}$.

and covariance R, dimensions are consistent with model members,i.e.,$j = 1,2,\cdots,q$[15]. To simplify the calculation, we would write it as

$$X_t^f = G(X_{t-1}) + \varepsilon. \tag{3.6}$$

3. Measurement: generating the assemble of measurement

$$\begin{pmatrix} Y_{(t)}^l \\ Y_{2(t)}^l \end{pmatrix} = \begin{pmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \end{pmatrix} \begin{pmatrix} Y_{(t)}^l \\ Y_{2(t)}^l \\ A_{(t)}^l \\ B_{(t)}^l \end{pmatrix} + \begin{pmatrix} \varepsilon_1^l \\ \varepsilon_2^l \end{pmatrix}, \ l = 1,2,\cdots q. \tag{3.7}$$

Let $H = \begin{pmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \end{pmatrix}$, $\eta_t = (Y_{(t)}^l, Y_{2(t)}^l, A_{(t)}^l, B_{(t)}^l)^T$, $Z_t^l = (Y_{(t)}^l, Y_{2(t)}^l)^T$, $\varepsilon = (\varepsilon_1^l, \varepsilon_2^l)^T$. Variable ε is assumed to be the measurement noise and represents the reliability of the measurements. The measurement noise is also assumed to be Gaussian with zero mean and the covariance

matrix would be denoted by ω. Once more. We combine the output function h in the system (2.2) with the measured value at time t as the measurement of state η_t, so this is simplified

$$Z_t^l = H\eta_t + \varepsilon^l,\ l = 1,2,\cdots q. \tag{3.8}$$

4. Update: the Kalman gain:

$$K_t = P_t^f H^T (HP_t^f H^T + \omega)^{-1}. \tag{3.9}$$

Usually in actual computation, we could calculate $P_t^f H^T$ and $HP_t^f H^T$ directly. The objective is to obtain the filter to update status

$$X_t^a = X_t^f + K_t(Z_t^l - HX_t^f),\ l = 1,2,\cdots q. \tag{3.10}$$

Where $Z_t^l - HX_t^f$ is residuals between measured and predicted values, K_t could be used to adjust X_t^f. In addition to weigh the covariance of the prediction state P_t^f and the magnitude of the measurement error covariance ω.

5. The mean of the assimilation values and the covariance matrix of assimilation data P_t^a are following

$$E(X_t^a) = E(X_t^f) + K(E(Z_t^l) - HE(X_t^f)), \tag{3.11}$$

$$\begin{aligned} P_t^a =& E[(X_t^a - E(X_t^a))(X_t^a - E(X_t^a))^T] \\ =& [(I - K_t H)(X_t^f - \overline{X_t^f}) + K_t(Z_t - E(Z_t))][(I - K_t H)(X_T^f - \overline{X_t^f}) + K_t(Z_t - E(Z_t))]^T \\ =& (I - K_t H)P_t^f (I - K_t H)^T + \omega. \end{aligned} \tag{3.12}$$

4. RESULT

The primarily kinetic behavior of the regulatory system of phage has been discussed. We know the model steady positive solution is existent and only one. From Fig.1, it is clear that the progress of gene regulation system up to a certain state. Meanwhile, we select $n, a, kt, kd, k_i (i = 1,2,\ldots,8)$ as the parameters to produce some numerical modelings. For instance, let $n = 2, a = 2, kt = 0.3, kd = 0.04, k_1 = 0.01, k_2 = 0.01, k_3 = 0.4, k_4 = 0.008, k_5 = 0.12, k_6 = 0.25, k_7 = 0.1, k_8 = 0.2$. (it assumes the reaction rate in the process of gene regulation to be a positive number less than 1.) By direct numerical calculation, the initial concentration of protein Y and dimer

Y_2 take different initial conditions separately, while the effect of gene expression is changeless, which tends to equilibrium $E^* = (486.8, 191.1)$. Because of the stochasticity should be inherent in gene regulation from transcription to protein synthesis, there are many uncertainties in gene regulatory. We may not pay more attention to the quantity of protein and dimer change in the gene expression process. While we are concerned with the quantity of protein and dimer, which would be in a stable state after approximately 10 minutes. The real value of the parameter col-

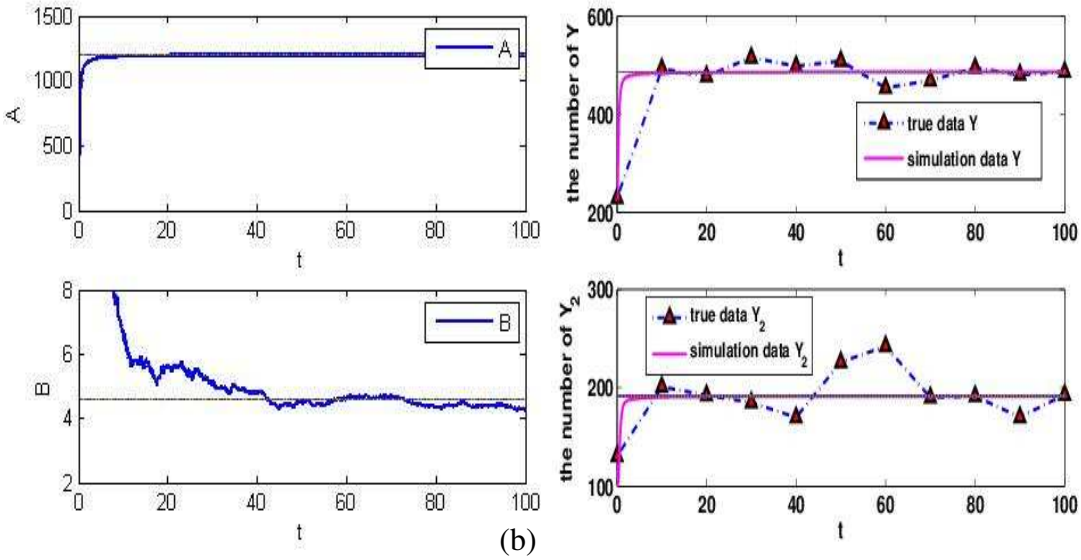


FIGURE 4. The estimated parameter(full line) and the real values(dash) become $\{Y = 483.9, Y_2 = 189.1, A = 1198.9, B = 4.75\}$ and $\{Y = 486.8, Y_2 = 191.1, A = 1200, B = 4.58\}$ at the ensemble size is 100.

lection is equivalent to $\{Y = 486.8, Y_2 = 191.1, A = 1200, B = 4.58\}$. Fig.3 briefly illustrates that the values of estimated parameters are equivalent to $\{Y = 484.1, Y_2 = 189.1, A = 1189.2, B = 6.48\}$ in case of the ensemble size is 20. Nevertheless, Fig.4 makes clear that the magnitude of the ensemble is 100, the parameters are equal to $\{Y = 483.9, Y_2 = 189.1, A = 1198.9, B = 4.75\}$, it may be noted that the initial estimates are the same as above. Next, a comparison of the different ensemble size indicates that modest-sized ensemble can track the evolution of the state with high accuracy.

Least-squares method center around finding the collection of parameters that minimize some distance measure between the simulated data and the observed data[16]. The state parameters Y and Y_2 estimated by the Least Square method are shown in Figure 5. The filled triangles

and circles are the true value of Y and Y_2, respectively. The blue and green line represent the simulation data of Y and Y_2, separately. While the parameters A and B are estimated by least square method act as 1217 and 2.75. Consequently, the set of parameters that meet the minimum distance between the simulated data and the real data is discontented.

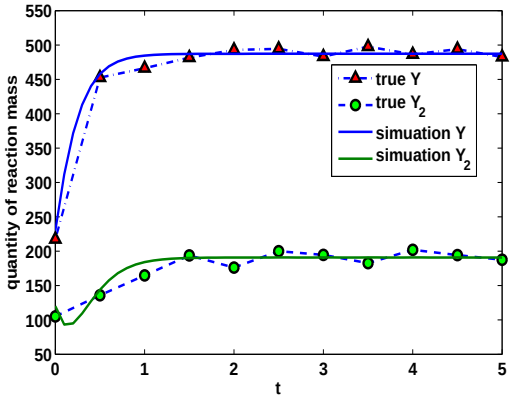


FIGURE 5. The filled Triangles and circles are the true value of Y and Y_2. the blue and green line represent the simulation data of Y and Y_2, respectively.

5. DISCUSSION AND PROSPECT

This essay takes the regulation network of bacteriophage gene with ODE in the model into account and analyzes the existence and stability of the equilibrium of the model. Our conclusion is that the rate of reaction of the chemical reaction equation satisfies the condition of $(a+2)nktPD > \frac{kd}{2}$ and just only one steady equilibrium $E^*(Y^*, Y_2^*)$. While assuming that we possess limited information about the regulation network model and the experiment is too expensive and time-consuming. It makes sense to apply the Ensemble Kalman Filter to estimate the parameters of interest based on limited library information. Furthermore, this essay considered that the size of the estimated ensemble is bigger the cost of some related experiments is higher. Therefore, the better parameter ensemble size in the future work needed to be computed.

Conflict of Interests

The authors declare that there is no conflict of interests.

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