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Parameter estimation and Stability of equilibrium of Gene Regulatory Network by Piecewise Multi-affine approach

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Abstract In this paper, we developed a new method to estimate parameter area and analyze the stability of equilibrium for gene regulatory network by piecewise multi-affine (PMA) approach. For the PMA function, it is continuous and the thresholds of its partition the phase space into many subspace. In every subspace, the model can be transformed into linear model, so the stable and unstable manifolds of equilibrium points can be determined analytically and stability and bifurcation can be obtained easily and the corresponding parameter areas can be obtained. This method allows us to estimate and tune parameter for a kind of high dimensional gene network and analyze the dynamical behaviors of its. In the end, Repressilator model, as an example, illustrates the validity of the method in this paper.

Keywords Stability;Gene Regulatory Network;Piecewise Multi-affine approach.

1 Introduction

The current explosive growth in genomic data and the advancement of new experimental tool has led to a rapidly growing interest, and how to understand the gene function becomes one of the main challenges, so we face to how to model frameworks and method for analyzing gene regulation and the interplay of genes and proteins. Gene and proteins interact to form a complex network that performs complex biological function. Gene regulatory network (GRN) is viewed as a biochemically dynamical system which provides a powerful tool for studying gene regulation process in living organisms. Generally, there are two types of gene network models, i.e., continue model and discrete model. The Boolean model is the most important discrete model when the activity of each gene is expressed in the state ON or OFF and the state of a gene is determined by Boolean function, The continuous model, primarily coupled differential equation model [14-17] and more particularly by system of piecewise affine differential equation [2], these approaches are based on a class of piecewise-linear (PL) differential equation model originally proposed

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by Leon Glass [7].The state variable in the PL model corresponding to the concentrations of proteins encoded by genes in the network, while the differential equations represent the interaction arising from the regulatory influence of some proteins on the synthesis and degradation of others. The regulatory interactions are modeled by means of step functions, which gives rise to the PL structure of differential equation and the gene regulatory equations were simplified to piecewise linear and uncoupled equation. The flaw of this approach is that the new equation is not defined in the threshold hyperplane. In [5] Plahte improved this defect by using graded sigmoid function with different steepness, but this method consider the limit solution only when the steep sigmoid approach step function. In this paper, we reconstruct the model from the character of the regulatory function by using a new piecewise multi-affine approach, and study the dynamics dynamical behavior in high- dimensional gene regulatory network. It is well known that the dynamical behaviors of high dimensional gene networks are very complex and the valuable results are very exiguous. Mestl et al.[3], consider the chaos and other dynamical behaviors in high- dimensional gene network with PL model. In this paper, we consider a class of models of regulatory network with piecewise multi-affine differential equation model. Regulation function is Hill function, which present S type and is nonlinear, customarily. To simplify the Hill function, we replace it with piecewise multi-affine function which possesses the character of Hill function and also takes on S type. Due to the linearity of piecewise multi-affine, the new model can be studied easily. Moreover, we can also estimate the bound of parameter involved the deferential equation model and analyze the gene regulatory network qualitatively, so as to test experimental data.

The paper is organized as follows. In section 2, we present our generalized framework for modeling gene regulatory network. In section 3, we discuss the parameter estimation based on PMA approach. In section 4, we will study the dynamical behavior of GRN. In section 5, The Repressilator model illustrate the validity to biological system. Section 6 contains the final discussion and conclusion.

2 The gene regulatory network model

From biology we can know that the activity of a gene is regulated by other genes through the concentrations of their gene production, i.e., the transcription factors (TF) regulation, can be quantified by the "response characteristics", i.e, the level of gene expression as a function of concentration of TF, see Fig.1.

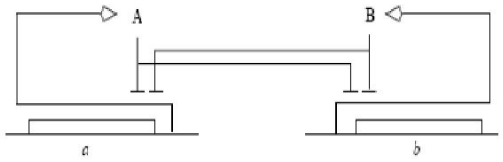

Figure 1: a,b represent genes, which transcribed from separate promoters and encode the protein A and B, each of which control the express of both genes.

From biology we can know that the activity of a gene is regulated by other genes through the concentrations of their gene production, i.e., the transcription factors (TF) regulation, can be quantified by the "response characteristics", i.e, the level of gene expression as a function of concentration of TF, see Fig.1.

In this paper, based on the structure of gene regulation network presented in [7], we generalized it and consider the n-dimensional differential equation model described as follows

$$\frac{dx_i}{dt} = \sum_{j=1}^{n} k_{ij} f_{ij}(x_j) - \gamma_i x_i + k_{i,0} \tag{1}$$

$k_{i,0}$ represents leakages form, k_{ij} are the production rate parameter, $f_{ij}(x_j)$ are regulation function which represents that gene j regulates gene i. Here we introduce an adjacency matrix $M = (m_{ij})$, $m_{ij} = 1$ if gene j regulates gene i, $m_{ij} = 0$ if gene j does not regulate gene i. So we can know the regulation of different genes from adjacency matrix M. So (1) can be modified as follows

$$\frac{dx_i}{dt} = \sum_{j=1}^{n} k_{ij} m_{ij} f_{ij}(x_j) - \gamma_i x_i + k_{i,0} \tag{2}$$

In compact matrix form (2) can be written as

$$\frac{dX}{dt} = F(X,\mu) = f(X) - \Gamma X + K_0 \tag{3}$$

Where $X = (x_1, x_2 \ldots\ldots x_n)$, $\Gamma = \begin{pmatrix} \gamma_1 & 0 & \ldots & 0 \\ 0 & \gamma_2 & \ldots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \ldots & \gamma_n \end{pmatrix}$, $K_0 = \begin{pmatrix} k_{1,0} & 0 & \ldots & 0 \\ 0 & k_{2,0} & \ldots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \ldots & k_{n,0} \end{pmatrix}$,

$f(X) = \begin{pmatrix} f_1 & 0 & \ldots & 0 \\ 0 & f_2 & \ldots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \ldots & f_n \end{pmatrix}$, $f_i = \sum_{j=1}^{n} k_{ij} m_{ij} f_{ij}(x_j)$, μ can be seen as one of parameter.

Customarily, regulation function $f_{ij}x_j$ is Hill function as follows

$$f_{ij}(x_i) = \begin{cases} \frac{x_j^n}{x_j^n + \theta_{ij}^n}, & if\ TF\ is\ an\ activator\ of\ gene, \\ \frac{\theta_j^n}{x_j^n + \theta_{ij}^n}, & if\ TF\ is\ an\ repressor\ of\ gene. \end{cases} \tag{4}$$

Where TF represents transcription factor. Denote

$$f_{ij}^{+} = \frac{x_j^n}{x_j^n + \theta_{ij}^n} \quad and \quad f_{ij}^{-} = 1 - f_{ij}^{+} \tag{5}$$

In [14], Jong and his co-worker make use of step function (Heaviside step function) as regulation function, but step function is not continuous. In [5], Plahte et al., utilized steep sigmoid function which approaches its limit case (i.e., Step function). In the above case, they all touch upon the case when solution lies in the threshold hyperplane. In this paper, we replace (2) with a new continuous function, i.e., piecewise multi-affine function as follows

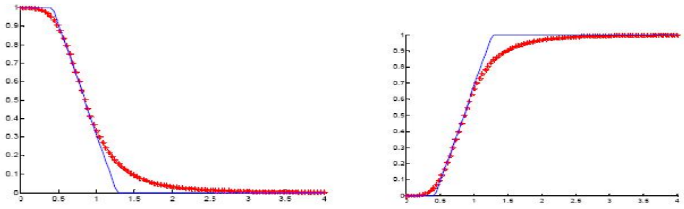

Figure 2: shows the approximation of hill function by piecewise multi-affine function, Better approximations can be obtained by using more breakpoints.

$$f_{ij}^{-}(x_i)=\begin{cases}1 & x_j<\lambda_{ij}^1\\ \frac{1}{2}-\frac{p(x_j-\theta_{ij})}{4\theta_{ij}} & \lambda_{ij}^1<x_j<\lambda_{ij}^2\\ 0 & x_j>\lambda_{ij}^2\end{cases} \tag{6}$$

$f_{ij}^{-}=1-f_{ij}^{+}$,where $\lambda_{ij}^1=\theta_{ij}-\frac{2\theta_{ij}}{n}$, $\lambda_{ij}^2=\theta_{ij}+\frac{2\theta_{ij}}{n}$.

Function (6) has the property as follows

(i) The slope of (6) is same to the slope of (4) at point $(\theta_{ij},\frac{1}{2})$.

(ii) Function (6) takes on S type which is similar to function (4).

3 Parameter estimation based on PMA approach.

For the system (2), there are many parameters, but we can not determine the certain value of the total parameter by the experimental data. So we need to develop method to tune the parameter. In this section, we tune the parameter of gene regulatory network by PMA approach.

Denote $\max\{x_i\}$,$i=1,2,\cdots n$,is the maximum of concentration x_i.The phase space $(x_1,x_2,\cdots x_n)\in R^n$ can be partitioned into many subspace R_i which the number of it can be determined by the threshold λ_{ij} of the above piecewise affine function. In every subspace R_i, system (2) has different form, but every subsystem is linear in R_i. For the subspace R_i, we consider the equilibrium point $X_i^*=(x_{i1}^*,x_{i2}^*),\cdots x_{in}^*$,$X_i^*$ can be computed easily.

For the parametric expression of X_i^*, which the bound of parameters must belong to R_i, we can tune the parameter. If X_i^* does not belong to R_i,we can search another subspace. In section 5, we give a example to illustrate the validity of the above method.

4 Stability and bifurcations in the GRN

In this section, we will analyze the stability and bifurcation of gene network (1).

In subspace R_i, denote A is the coefficient matrix of linear system, we have the following conclusion.

Theorem 3.1 Suppose that $F(X,\mu), X \in R^n, \mu \in R^!$ satisfies the condition as follows

(1) In the subspace R_i, the equilibrium $X^*(\mu)$ of system (3) lies in the R_i.

(2) For $X = X^*(\mu), F(X^*.\mu) \equiv 0$.

(3) In the neighborhood of $(X^*.\mu)$, F is analytic for X and μ.

(4) where the real part of eigenvalues of $B : R^2 \to R^2$ are zeros and the real part of eigenvalues of $C : R^{n-2} \to R^{n-2}$ are negative. In the meantime, the projection of the trajectory of system (4) in the plane $x_1 - x_2$ tend spirally to origin (when $t \to +\infty$ or $t \to -\infty$).

Such that,for system (3), when $\mu = \mu_c$,if $X = X^*(\mu)$ is asymptotically stable (or asymptotically unstable) and $\mu > \mu_c(\mu < \mu_c)$ corresponds to the state which is asymptotically stable (or asymptotically unstable), then in the neighborhood of $X = X^*(\mu_c)$ when $\mu > \mu_c(\mu < \mu_c)$ and $|\mu - \mu_c|$ is sufficiently small, system (3) has asymptotically stable (unstable) closed orbit.

Theorem 3.1 If $X^* \in R_i$, there is at least one positive eigenvalue, then the solution is not stable .

The proof of theorem 3.3 is obvious, because the trajectory in the direction with positive eigenvalue is dispersive, so the orbit is unstable.

Remark 2. (1) In the case of theorem 3.3, we should investigate another R_j as above.

(2) If $X^* \in R_i$, we should investigate another R_j until $X^* \in R_j$.

Remark 3. the above conclusions are obtained in subspace R_i , but for the system (3), the equilibrium lies in the neighborhood of equilibrium of subsystem. From global structure, sum of every subsystem with PMA function is similar to original system with Hill function, so we study the original system by above theorem.

5 Example

In this section, we present example to show the effectiveness and the correctness of our theoretical results by using the above method.

In [19], Elowiz, et al., consider the GRN as follows

$$\begin{cases} \frac{dm_i}{dt} = -m_i + \frac{\alpha}{1+p_j^n} + \alpha_0 \\ \frac{dp_i}{dt} = -\beta(p_i - m_i) \end{cases} \tag{7}$$

where $i = lacI, tetR, cI$, $j = cI, lacI, tetR$. α, α_0, β and n represent promoter rate without repressor, leakiness term in saturating repressor, ratio of protein decay rate to mRNA decay rates and Hill coefficient of the repressor, respectively.$m_i(t) = [mRNA], p_i(t) = [repressor]$. For simplification, lacI denotes 1, tetR denotes 2, cI denotes 3. From the above discussion, we replace $\frac{1}{1+p_j^n}$ with the piecewise-affine function as follows

$$f_{ij}^-(p_i) = \begin{cases} 1 & x_j < 1 - \frac{2}{n} \\ \frac{1}{2} - \frac{n(p_j-1)}{4} & 1 - \frac{2}{n} < x_j < 1 + \frac{2}{n} \\ 0 & x_j > 1 + \frac{2}{n} \end{cases} \tag{8}$$

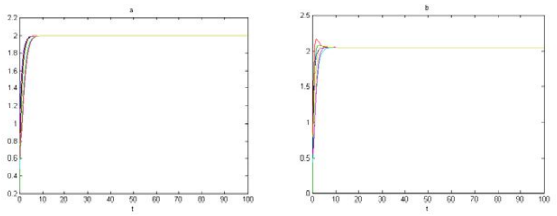

Figure 3: (a) the temporal evolution of system (9) (b) the temporal evolution of system (7), the parameter $\alpha = 1, \alpha_0 = 2, \beta = 1$ in the subspace $(0,0,0)$.

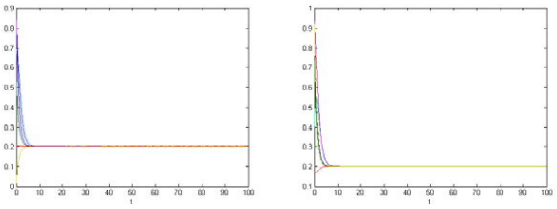

Figure 4: (a) the temporal evolution of system (9) (b) the temporal evolution of system (7), the parameter $\alpha = 0.1, \alpha_0 = 0.1, \beta = 1$ in the subspace $(1,1,1)$.

So the subspace $p_1 \times p_2 \times p_3 \in R^3$ can be partitioned into 27 subspaces as follows $(0,0,0),(0,0,1),(0,0,m),(0,m,0),(0,m,1),(0,m,m),(0,1,0),(0,1,1),(0,1,m)$, $(m,0,0),(m,0,1),(m,0,m),(m,1,0),(m,1,1),(m,1,m),(m,m,0),(m,m,1),(m,m,m)$, $(1,0,0),(1,0,m),(1,0,1),(1,1,0),(1,1,1),(1,1,m),(1,m,0),(1,m,1),(1,m,m)$, where 0, m and 1 represent the value of $f_{ij}^{-}(p_j)$, respectively. In the following, we will study the system (11) in above subspace, Assumed that n=4, obviously, there are subspace (0,0,0) and (1,1,1) which satisfied that the equilibrium points lies in the above subspace. Now we investigate the subspace (0,0,0) and (1,1,1),respectively. In subspace (0,0,0), when n=4, the system (7) can be reduced to the following equation

$$\begin{cases} \frac{dm_i}{dt} = -m_i + \alpha_0 \\ \frac{dp_i}{dt} = -\beta(p_i - m_i) \end{cases} \tag{9}$$

From system (9), we can know that $X^* = (\alpha_0, \alpha_0, \alpha_0, \alpha_0, \alpha_0, \alpha_0)$ is the equilibrium point of system (9) and the eigenvalues of coefficient matrix are $(-1, -\beta, -1, -\beta, -1, \beta)$. Obviously, only when $\beta > 0$ and $\alpha_0 > \frac{3}{2}$, the X^* lies in the subspace (0,0,0). According to theorem 3.2, we can know that the trajectory of (9) tend stably to the equilibrium point X^* . So under the approach of (8), the trajectories of (11) have the same behavior under the neighborhood of equilibrium point. By using the simulation for system (9) and (7), the Fig.4 shows the above conclusion. **So we should tune the parameter under $\beta > 0$ and $\alpha_0 > \frac{3}{2}$.**

In the subspace (1,1,1), the discussion is similar to the above case. From the above

discussion, original system is structural stable, so stability of the approximate system (9) is same to that of system (7) in the near equilibrium point (See fig.4).

6 Discussion and conclusion

In this paper, we developed a new method for qualitative simulation of genetic regulatory networks by a class of piecewise multi-affine differential equation that has been well studied in bioinformatics. The models involved in this paper are based on piecewise multi-affine function approximation of regulatory interactions involved in the synthesis and degradation of proteins. Experimental evidence shows the activation of a gene, as a function of the concentration of a regulatory protein, often follows a sigmoid curve presented by Hill function. When the sigmoid curve is very steep, some people replace Hill function with step function, but when the slope of Hill function is not very steep, the step function is disabled. So we developed the piecewise multi-affine function (PMA) which is continuous to replace the Hill function. Therefore, the phase space can be partitioned into many subspace by the threshold of PMA function, in many subspace, the model becomes linear model which be treated easily. Moreover, duo to the continuity of PMA, we can study well the case when the model equation lies in the threshold hyperplane. The above method help to tune GRN and analyze the robustness of GRN. To describe the validity of our method, we studied the Repressilator model [19].The results of numerical simulation shows the stability of equilibrium is uniform between original system and approximate system with PMA function. In the future, we hope to design a software by using this method and apply this method to gene network existing to tune its parameter so as to open out the phenomena of life and model complex gene network.

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