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Modeling Gene Regulatory Networks Based on Nonlinear State-space Model

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Abstract: In the gene regulatory networks(GRNs), gene expression is usually regulated by some regulatory factors (or transcription factors), but the regulatory factors' activity is difficult to measure, and the regulatory effect among genes is typically nonlinear. This paper uses nonlinear Gaussian state-space model to construct gene regulatory networks. In the model, genes are considered as observation variables and regulatory factors are considered as internal state variables, it is more consistent with the actual biological systems. To identify the system, the unscented Kalman filter(UKF) algorithm is applied to estimate the states and parameters, Bayes information criterion (BIC) is applied to determine the dimension of the state variables. We model the regulatory networks of yeast genes' expression data with the method, the results show that the nonlinear state-space model can improve the accuracy of constructing regulation networks, and UKF algorithm can effectively estimate the parameters and states of nonlinear state-space model.

Key Words: Gene Regulatory Networks, Unscented Kalman Filter, Bayes Information Criterion, Nonlinear State-space Model

1 Introduction

As the rapid development of bioinformatics and various genome projects carried out, scientists have got a large number of initial data of molecular biology. Especially as the continuous advancement of DNA microarray technology and genome sequencing, the measurement of gene expression in genomic level has become possible. Although we can't accurately know much detail of the intracellular, gene expression data in genomic level has provided a lot of help to understand living cells thoroughly. And it has been widely applied in the aspect of medical diagnosis, treatment and drug design.

Until now, many models have been proposed to analysis and model gene expression data, such as Boolean network model[1], linear combination model, differential equation model[2], linear and nonlinear regression models, Bayesian network model[3], and so on. However, these models have some limitations, which can't well reflect the regulatory relationship between genes. For example, Boolean network model simply views a gene's expression state to be 'on' or 'off', which ignores those genes whose expression level is in a range; linear combination model's structure is relatively simple, but the accuracy is not high; differential equation model can describe the complex relationship of gene networks, but the parameters needed to learn are too much, the model is usually not sufficiently complete because of lacking data; Bayesian network model can deal with the data that have noise and missing, can estimate degree of confidence of network's different characteristics, but which can't describe the negative feedback and the time factor that universally existing in biological systems.

In some of existing models, genes are usually viewed as both internal state variables and observation variables. The viewpoint not only deviates from the actual biological systems, but also makes the system identification more difficult[4]. Actually, not all genes directly regulate gene expression in the cell, since only a part of genes are translated into regulatory and regulate gene expression, while others are translated into structure proteins, which do not participate gene regulation. C. Rangel[5] and Wu[6] et al. used a state-space model to construct the gene regulatory networks, in the model, genes are considered as observation variables which can be measuredand regulatory factors are considered as internal state variables which can't be observed, using state equations to describe the regulatory relationships between genes, it is in line with the actual biological systems. The model as follow:

$$\begin{cases} z(t+1) = A * z(t) + n_1(t) \\ x(t) = C * z(t) + n_2(t) \end{cases} \tag{1}$$

The vectors $x(t)$ and $z(t)$ consist of the observation variables and internal state variables of the system. The matrix A is the state transition matrix, C is the observation matrix. The vectors $n_1(t)$ and $n_2(t)$ stand for system noise and observation noise respectively.

Rui Yamaguchi[7] et al. modeled gene regulatory networks for yeast gene expression data based on state-space model showed in Eq.(1), the result is better, and it has a relatively high accuracy. However, cell is a complex and interrelated dynamic system, the metabolites, gene and protein in a cell constitute different biochemical reaction networks, such as metabolism system, signal transduction system, gene regulation system, and so on. And the interaction between genes in biological system is very complex, there may be a variety of regulatory relations. The linear model only captures main linear part of the system, usually does not accurately reflect the true regulatory relationships of biological system[8–10]. So this study improves the model showing in Eq.(1), and uses nonlinear state-space model to model gene regulatory networks.

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2 The Nonlinear State-space Model of Gene Regulatory Networks

Gene regulatory networks mainly consist of the interaction of gene fragments in the cells and other regulatory substances, it reflects the regulation of relations between cells, guides the expression process of gene to mRNA, which is a continuous complex dynamic systems in fact[11].

2.1 The Definition of The Model

This study extends the model showed in Eq.(1), adds the sigmoid excitation function in the state equation to reflect the nonlinear relationship between genes, observation equation remains the same, so we get a nonlinear state-space model, the model as follow:

$$\begin{cases} x_{k+1} = \mathrm{A} * x_k + B * \mathrm{S}(\mathrm{x_k}) + \omega_k \\ y_k = \mathrm{C} * x_k + \nu_k \end{cases} \tag{2}$$

In the Eq.(2), the vector y_k consists of the observation variables, the vector x_k consists of the internal state variables. The matrixes $A = [a_{ij}]_{p\times p}$ and $B = [b_{ij}]_{p\times p}$ are the linear part and nonlinear part state transition matrixes of internal state variables respectively, they provide the key information for internal variables affect each other, where p is the number of the internal state variables. The matrix $C = [a_{ik}]_{n\times p}$ is the translation matrix from internal state variables to observed variables, which shows the effect of internal regulatory factors on gene expression. The vectors $\nu_k \sim N(0_p, Q)$ and $w_k \sim N(0_n, R)$ stand for system noise and observation noise respectively, We assume that they are mutually independent gaussian noise. $S(x_k)$ is a sigmoid function based on independent variable x_k .sigmoid function, referred to as the S function, is a nonlinear function of neuron, whose expression is:

$$S(x) = \frac{1}{1+e^{-x}} \tag{3}$$

S function is a good threshold function, which is continuous, smooth, completely monotonic, and central symmetry in point(0, 0.5). The function curve can be divided into three parts: slowly increases at first, then increases rapidly, and gradually stabilized finally, it can reflect the general rule of things' occurrence, development and maturity, so it also known as growth curve. The function is often applied to compound and generate different functions, to represent the effect of complex system, which has been widely applied in biology, environmental science, ecology, demography, economic forecasting and many other fields. This study uses the function to represent the nonlinear relationship between genes in the cell.

When the model is defined, we need to address the following questions:

- How to determine the dimension of the internal state variables;
- How to estimate the internal state variables x_k;
- How to identify the system parameters A, B and C.

2.2 The Selection of Data

The study found that many genes related to hereditary diseases had a very high homology with the yeast genes. To research the physiological function of these genes encoding proteins and their interactions with other proteins will help us to understand these genetic diseases[12]. At the same time, the yeast is a unicellular organism, the number of whose genes is relatively small, and the research about yeast gene is more mature, the expression data can get in many public genome databases.

The dataset used in this study is available at web site of Computational Genomics. The original dataset contains more than 6000 genes for 24 equally spaced time points, and whose profiles have missing data. we select 309 genes' complete expression data to construct the regulatory networks.

2.3 Determining The Number of Internal State Variables

The state variables are the internal factors of the state-space model, which determine the output of the system. And the dimensions of the state variables determine the complexity of the system and the accuracy of system description. Akaike information criterion(AIC) and Bayesian information criterions(BIC) can be applied to determine the dimension of the state variables[13], their expression as follows. Akaike information criterion:

$$AIC(k) = -2\ln L(Y_N|\hat{\theta}_k) + 2k \tag{4}$$

Bayesian (Schwarz) information criterion:

$$BIC(k) = -2\ln L(Y_N|\hat{\theta}_k) + k\ln n \tag{5}$$

In the Eq.(4) and Eq.(5), $L(Y_N|\hat{\theta}_k)$ is log-likelihood function of Y_N ,$\hat{\theta}_k$ is maximum likelihood estimate of parameters, k is the number of estimated parameters, n is the number of sampling points. The dimension when BIC or AIC has the minimum value is identified as the optimal dimension of state vectors, that is $k = \arg\min_k BIC(k)$ or $k = \arg\min_k AIC(k)$.

AIC and BIC can ensure good fitting for data and avoid overfitting, so they are widely applied in the determination of model order. However, the BIC has more stringent penalty term than AIC, which pay more attention to the conciseness of modelit is more suitable for large sample[6, 14]. The data that gene expression regulatory networks often contain thousands of genes' expression data, the scale of data is very large, so we choose BIC to determine the number of internal state variables in the model. From the comparison results of table 1, we can see the number of state variables determined by the BIC is significantly less than the AIC, and with the expansion of the scale of the selected genes, the difference is more obvious. Figure 1 shows the curve of the BIC for

Table 1: The number of state variables using BIC and AIC respectively when we selected different number of genes

The number of genes	The minimum value for the BIC	The minimum value for the AIC
20	4	5
30	5	7
50	5	7
100	5	8
150	6	9
200	6	10
250	7	10
309	7	11

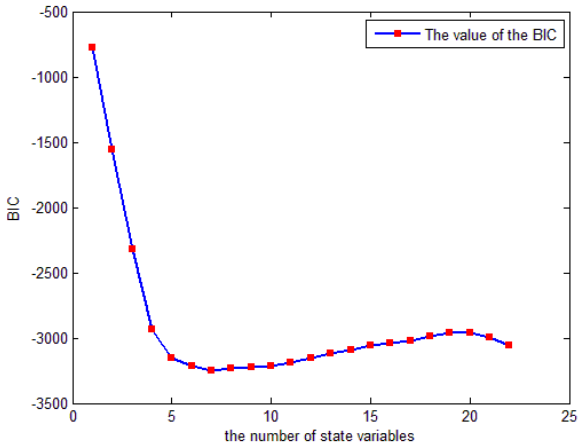

Fig. 1: The BIC curve of selected genes in study

the 309 yeast genes selected in this study. From the curve we can see that BIC has a minimum value when the number of internal state variables is 7, so we obtain the optimal dimension of state variables is 7.

2.4 The Identification of the Model

The identification of model means according to a criterion to choose a best model fitting with the actual data from a set of model classes. The dynamic characteristics of the identification object are bound to the performance of its changing input and output data, so the essence of identification is to extract the mathematical model of the object from the measured data using mathematical methods[15]. Figure 2 shows the general flow chart of the model identification. There are

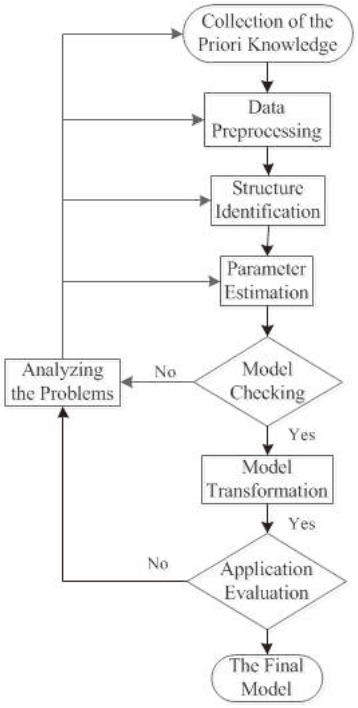

Fig. 2: The flow diagram of model identification

some typical methods for state-space model parameters' identification, such as generalized least squares(GLS), expectation maximization(EM) algorithm, Kalman filter(KF) algorithm, and so on. To use GLS, we must know the state variables, however the state variables can't be observed in the gene regulatory networks. EM algorithm can estimate parameters and noise through maximized the logarithm likelihood function, and can estimate the states' expectations with Kalman filter and Kalman smoothing algorithm. Rui Yamaguchi[7] and Kojima[16] et al. constructed gene regulatory networks with state-space model, and apply EM algorithm to identify the system, which had a good results. But EM algorithm only limits to the linear state-space model.

Extended Kalman filter (EKF) algorithm widely applied in the state estimation of nonlinear system, and has been generally recognized by the academia[17, 18]. However, this approach has two shortcomings: firstly, when the system has stronger non-linearity, it has a relatively high error rate because of neglected the higher order terms in the linearization, the algorithm may not completely converge; secondly, the EKF requires to calculate the Jacobi matrixes in the linearization process, the complexity of the algorithm is higher. To overcome these drawbacks, we use UKF to identify the nonlinear system.

3 Parameter Identification Based on UKF

UKF is an algorithm combining unscented transform and Kalman filter, it is effective to overcome the low accuracy and poor stability of EKF.

3.1 Unscented Transformation

The unscented transformation (UT) is a method for calculating the statistics of a random variable which undergoes a nonlinear transformation. The basic idea is that selecting some kind of weighted points $\mathrm{S_i} = \{\mathrm{W_i}, \mathrm{X_i}\}$ according to the mean and variance of the original variables to approximate distribution of the original variables by a rule. $\mathrm{X_i}$ is called σ point. Calculating the γ_i that the σ points' spread through the function $f(\cdot)$, then calculating the mean $\bar{Y}$ and the variance $\mathrm{P_Y}$ through γ_i.

The key of unscented transform algorithm is the selection of σ sampling points, including the number of selected, the range, and the weights for the σ points. Not only the σ points can represent the distribution characteristics of the original variables, but also make the criterion function for evaluating the degree of approximation obtain a minimum value. Assuming the n-dimensional random variable X, whose mean is $\overline{X}$ and Variance is P_X, using symmetrical sampling method, generating 2n+1 weighted sampling points:

$$\begin{cases} X_0 = \overline{X} \\ X_i = \overline{X} + (\sqrt{(n+\lambda)P_X})_i, i = 1, ..., n \\ X_i = \overline{X} - (\sqrt{(n+\lambda)P_X})_i, i = n+1, ..., 2n \end{cases} \tag{6}$$

$$\begin{cases} W_0^{(m)} = \lambda/(n+\lambda) \\ W_0^{(c)} = \lambda/(n+\lambda) + (1-\alpha^2+\beta) \\ W_i^m = W_i^c = 1/(2(n+\lambda)), i = 1, ..., 2n \end{cases} \tag{7}$$

$$\lambda = \alpha^2(n+k) - n \tag{8}$$

Where $W_i^{(m)}$ is the estimated weights of the mean, $W_i^{(c)}$ is the estimated weights of covariance, $\alpha > 0$ is the scale factor, which controls the distribution of σ points, choosing a

smaller positive value generally; $\beta \geq 0$ is the weighted item, which reflects the high order moment information, controls the peak of the estimated state. $(\sqrt{(n+\lambda)P_X})_i$ is the i-th row(column) of the matrix $(n+\lambda)P_X$'s mean square root.

Taking these σ points into the output function, that is $Y_i = f(X_i)$, here the mean $\overline{Y}$ and covariance P_Y of random vector can be calculated as:

$$\begin{cases} \overline{Y} = \sum_{i=0}^{2n} W_i^{(m)} Y_i \\ P_Y = \sum_{i=0}^{2n} W_i^{(c)} (Y_i - \overline{Y})(Y_i - \overline{Y})^T \end{cases} \tag{9}$$

The process of unscented transformation as follows:

1) Select the value of parameters k, α and β .
2) Use the Eq.(6) and Eq.(7) to calculate the σ points and their weights.
3) Do nonlinear transformation for each σ points. The points are taken into the nonlinear function $Y_i = f(X_i), i = 0, 1, 2, \cdots, 2n$, to generate the set of points γ.
4) Use the Eq.(9) to calculate the mean $\overline{X}$ and variance $\mathrm{P_Y}$ of γ .

3.2 The Unscented Kalman Filter(UKF)

Julier[19] et al. proposed the unscented Kalman filter algorithm based on unscented transformation. The algorithm does not need to calculate the derivative, and with high precision, so it has been wildly concerned[20]. Assuming the state-space model of the system is a nonlinear gaussian model, like the Eq.(2), the UKF algorithm is as follows:

1) Initialization.

$$\hat{X}_0 = E[X_0] \tag{10}$$

$$P_0 = E[(X_0 - \hat{X}_0)(X_0 - \hat{X}_0)^T] \tag{11}$$

$\hat{X}_0$ and P_0 are the mean and covariance matrix of the initial state.

2) To calculate the σ points.

$$X_{k-1} = [\hat{X}_{k-1}\,,\ \hat{X}_{k-1} + (\sqrt{(n+\lambda)P_{k-1}})\,,\ \hat{X}_{k-1} + (\sqrt{(n+\lambda)P_{k-1}})] \tag{12}$$

3) The UKF forecast.

$$X_{k|k-1} = F[X_{k-1}, U_{k-1}] \tag{13}$$

$$X_k^- = \sum_{i=0}^{2n} W_i^{(m)} X_{i,k|k-1} \tag{14}$$

$$P_k^- = \sum_{i=0}^{2n} W_i^{(c)} (X_{i,k|k-1} - \hat{X}_k^-)(X_{i,k|k-1} - \hat{X}_k^-)^T + Q \tag{15}$$

$$Y_{k|k-1} = H(X_{k|k-1}) \tag{16}$$

$$Y_k^- = \sum_{i=0}^{2n} W_i^{(m)} Y_{i,k|k-1} \tag{17}$$

4) The UKF updata.

$$P_{Y_k Y_K} = \sum_{i=0}^{2n} W_i^{(c)} (Y_{i,k|k-1} - \hat{Y}_k^-)(Y_{i,k|k-1} - \hat{Y}_k^-)^T + R \tag{18}$$

$$P_{X_k Y_K} = \sum_{i=0}^{2n} W_i^{(c)} (X_{i,k|k-1} - \hat{X}_k^-)(Y_{i,k|k-1} - \hat{Y}_k^-)^T \tag{19}$$

$$K_k = P_{X_k Y_K} P_{X_k Y_K}^{-1} \tag{20}$$

$$\hat{X}_k = X_k^- + K_k(Y_k - \hat{Y}_k^-) \tag{21}$$

$$P_k = P_k^- - K_k P_{Y_k Y_K} K_k^T \tag{22}$$

Where n is the dimension of the state variables, K_k is Kalman gain matrix, Q is the covariance of process noise , R is the covariance of measurement noise ,W_i is the weight.

The UKF can be accurate to second-order moment of the true posterior distribution for calculating the mean and covariance, but EKF is only a first-order approximation of the linear function. therefore, the UKF algorithm has higher accuracy.

3.3 UKF Applys to The Nonlinear State-space Model

In the Eq.(2), the state variables and parameters are all unknown. Not only we need to identify the parameters, but also need to estimate the states of the system. We can regard the parameter and state variables as a new state variables, that is,

$$X_k = \begin{bmatrix} x_k \\ \theta_k \end{bmatrix} \tag{23}$$

Then Eq.(2) can be expressed as

$$\begin{cases} X_{k+1} = f(X_k) + \varepsilon_k \\ Y_k = h(X_k) + \nu_k \end{cases} \tag{24}$$

Where

$$f(X_k) = \begin{bmatrix} x_{k+1} \\ \theta_{k+1} \end{bmatrix} = \begin{bmatrix} Ax_k \\ \theta_k \end{bmatrix} + \begin{bmatrix} \omega_k \\ 0 \end{bmatrix} \tag{25}$$

$$h(X_k) = Cx_k \tag{26}$$

$$\varepsilon_k = [\omega_k^T, 0]^T \tag{27}$$

The parameters need to identify in the Eq.(24) are $A = (a_{ij})_{p\times p}$, $B = (b_{ij})_{p\times p}$ and $C = (c_{ij})_{n\times p}$, where p is the number of internal state variables, n is the number of observed variables. In order to be able to use the UKF, we need to do some transformations for A, B and C, remove the each column of the matrix in turn and arrange in a new column vector as follow:

$$A_{uk} = [a_{11}, a_{21}, \cdots, a_{p1}, \cdots, a_{1p}, a_{2p}, \cdots, a_{pp}]^T \tag{28}$$

$$B_{uk} = [b_{11}, b_{21}, \cdots, b_{n1}, \cdots, b_{1p}, b_{2p}, \cdots, b_{np}]^T \tag{29}$$

$$C_{uk} = [c_{11}, c_{21}, \cdots, c_{n1}, \cdots, c_{1p}, c_{2p}, \cdots, c_{np}]^T \tag{30}$$

Then

$$\theta_k = \begin{bmatrix} A_{uk} \\ C_{uk} \end{bmatrix}, X_k = \begin{bmatrix} x_k \\ \theta_k \end{bmatrix} \tag{31}$$

Where A_{uk}, B_{uk} and C_{uk} represent the value of recombination parameters in time k. After doing the transformations above, then we can use the UKF to identify the model.

4 The Experiments and Results

The nonlinear state-space model is applied to the selected 309 yeast genes' expression data, to construct the gene expression regulatory networks, then using the UKF algorithm to identify the system parameters. the identification results are shown in Figure 3 and Figure 4. Figure 3 shows the state transition matrix A's part components, Figure 4 shows the nonlinear state transition matrixes B's part components.

Using the model parameters A, B, C and the state variables $\hat{x}_k$ obtained from the identification, we can get the appropriate output $\hat{y}_k$ with equation(2). Choosing the genes 'YBR202W', 'YBR255W', 'YBR262C' and 'YBR301W', Comparing with the real gene expression data, as shown in figure 5, we can see that our model's output result is better fitting to the actual data. UKF algorithm and EKF algorithm all belong to the kalman filter algorithm, are widely applied in the state estimation of nonlinear gaussian system, but these two algorithms' principle and the basic starting point are different. For weak nonlinear system, the identification accuracy of the both algorithms is almost similar, but when the system is of strong nonlinear, there will have a big deviation with EKF algorithm.

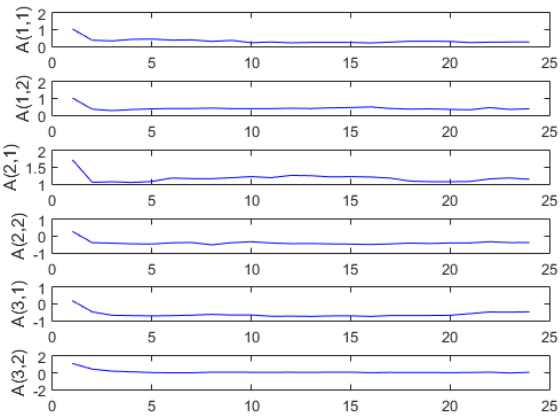

Fig. 3: The result of matrix A's part components.

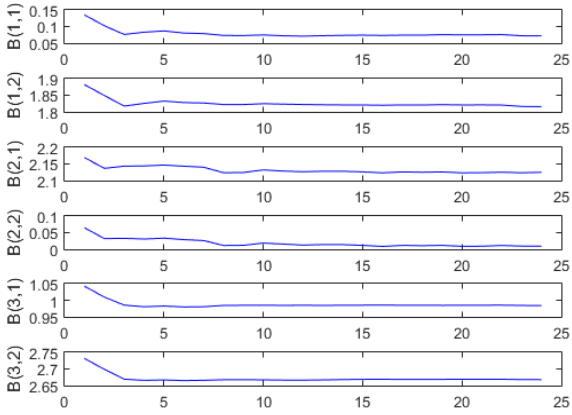

Fig. 4: The result of matrix B's part components.

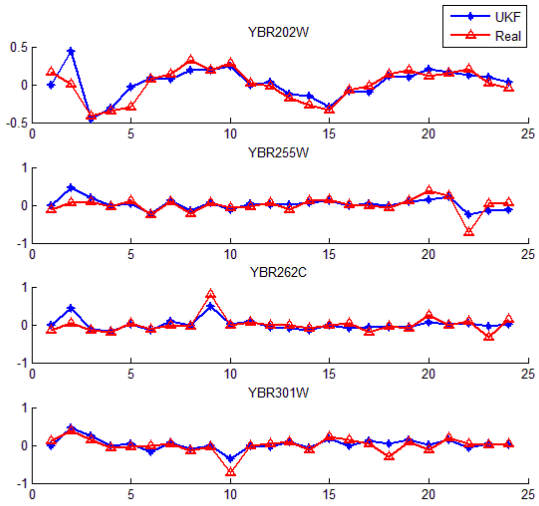

Fig. 5: The comparison between estimation value and real value of 4 genes expression data.

Comparing the identification and Fitting effect of UKF and EKF, as shown in figure 6, we can see the UKF is slightly better than EKF. Because the model used in this study just added a weak nonlinear sigmoid function to the state equation, it doesn't fully shows the advantage of the UKF. Both the two algorithms need to set initial value when the recursive calculation, The initial value can affect the recognition results. Especially, the gene regulatory networks is a complex multiple output system, which is more sensitive to initial value. we need to set different initial values, to identify many times, and get the optimal parameters to fit the actual data better.

figure 7 shows the comparison between linear state-space model and nonlinear state-space model, we can see that the accuracy of nonlinear state-space model is better, which can be better fitting of the actual data.

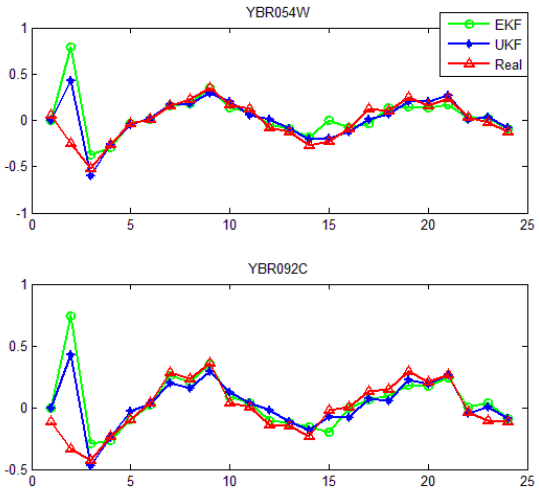

Fig. 6: The comparison between UKF and EKF.

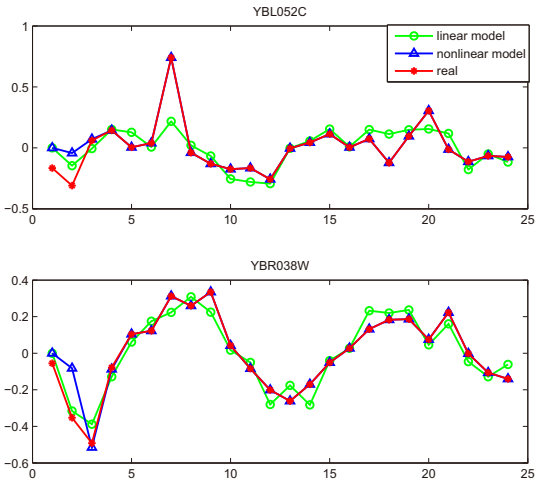

Fig. 7: The comparison between linear state-space model and nonlinear state-space model.

5 Conclusion

This paper uses nonlinear Gaussian state-space model to construct the gene expression regulatory networks, the UKF algorithm has been applied to model the gene regulatory network from yeast genes time series data, the result is better, which can be better fitting of gene expression data. Compared to previous models, our model has the following characteristics. First we use nonlinear Gaussian state-space model, that can capture the typically nonlinear regulatory relationship among genes. Second, genes are considered as observation variables and regulatory factors are considered as internal state variables in the model, that can reflect the fact that genes may be regulated by some internal regulatory. Finally, We use BIC criterion to determine the number of state variables, it effectively reduces the difficulty of system identification, at the same time, we use the UKF algorithm to identify the parameters of the nonlinear state-space model, improved the accuracy of the model.

Of course, our model and method also have some shortcomings. first, the model that we confined is a gaussian model, we assumes the noise is gaussian distribution, in fact true noise distribution maybe many forms, the late study will be extended to non-Gaussian model; second, we don't consider the time delay of biological systems in the study of gene regulatory networks, For example, it takes time in the process of transcription, transmitting, and translation, we need to consider this aspect in the later research.

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