Noisy Nonlinear Gene Regulatory Networks Analysis Using Ensemble Kalman Filter Based Particle Filter without a Model

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ABSTRACT

In this paper, we propose a novel ensemble Kalman filter based particle filter for gene regulatory networks (GRNs) analysis, which incorporates ensemble Kalman filter into particle filter. New particles generated by particle filter are sampled by ensemble Kalman filter, which can take current measurements into account to predict the system states. This will alleviate the sample degeneracy problem in particle filter. The proposed method is model-free algorithm. Both particle filter and ensemble Kalman filter can be applied when the model is unknown, noisy, and nonlinear. This combination of approaches results in comparable accuracy, efficiency, and robustness. In the GRNs analysis, simulation results show that the proposed ensemble Kalman filter based particle filter performs better than particle filter in identifying dynamics relations among genes.

CCS Concepts

•Applied computing → Systems biology;

Keywords

gene regulatory networks;noise analysis;ensemble Kalman filter;particle filter

1. INTRODUCTION

The analysis of GRNs is one necessary step to discover drugs for gene related disease. With more time series data available, it becomes possible to find GRNs. GRNs are inherently noisy and nonlinear. Generally, GRNs can be par-

tioned into two categories: linear models and nonlinear models.

1.1 Linear GRNs

The regulators in linear GRNs contribute to the inputs of regulate functions in additive manner [1]. The linear models are efficient to infer large GRNs with high level abstraction. In [1] and [4], the authors demonstrated the linear model in numero and real expression data sets. Another benefit for linear model is to process noise using many available linear filters. A system of ordinary differential equations(ODEs) is transformed into a linear additive regulation model with noise. The expression level of a gene at a certain point can be calculated by the weighted sum of the expression levels of all genes in the network at a previous time point [3]. It may be represented by ODEs

$$\frac{de_i}{dt} = \sum_{j=1}^N w_{ij}e_j + \sum_{k=1}^K \nu_{ik}u_k + \beta_i \quad (1)$$

where e_i is the gene expression level of the i^{th} gene. N is the number of genes in the GRNs. w_{ij} represents the effect of the j^{th} gene on the i^{th} gene. Negative w_{ij} means inhibition while positive w_{ij} represents activation. u_k is the k^{th} external (control) variable. ν_{ik} represents the effect of the k^{th} external variable on the i^{th} gene. K is the number of external variable. β is a bias term. In [2], the noise in the input data is considered in the linear additive regulation model. For each new input data, there is small amount of Gaussian noise with the same standard deviation added. In those models, steady states are obtained by solving linear programming problems.

1.2 Nonlinear GRNs

Compared with linear models, nonlinear models are computationally intensive and require more data. However, nonlinear models can reveal complex dynamic relations among genes in more details, which approach reality.

Nonlinear models involving ODEs are examples of nonlinear continuous models. Assuming there are N genes of interest and x_i denotes the state (such as the microarray

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reading) of the i^{th} gene, then the dynamics of the GRN may be modeled as

$$\frac{dx_i}{dt} = f_i(x_1, x_2, \dots, x_N) + \nu_i \quad i = 1, 2, \dots, N. \quad (2)$$

where ν_i is external noise.

Functions $(f_i, \forall i)$ are nonlinear functions to be estimated.

If each f_i is a polynomial, the model is a polynomial model [9]. In [9], genetic programming is applied to infer the terms of polynomial equations. The constants are estimated by linear filters. The complexity is $\Omega(N^2)$. Therefore, it is hard to apply this model to higher dimensional system.

In [12], sigmoidal function is applied. The functions $(f_i, \forall i)$ are in the form

$$\frac{dx_i}{dt} = \frac{C_{i,1}}{1 + e^{-\{\sum_{j=1}^n [(w_{ij} + \mu_{ij})x_j] + \beta_i\}}} - C_{i,2}x_i \quad i = 1, 2, \dots, N. \quad (3)$$

where $C_{i,1}$ and $C_{i,2} > 0$ are two parameters. β_i is an input and w_{ij} is the weight value for input j on gene i . μ_{ij} and ν_i are intrinsic noise and external noise, respectively. However, this model is limited. It can be applied to certain GRNs only.

S-system is a promising model to capture the rich dynamics of GRNs [7, 8, 13]. The S-system model is given by:

$$\frac{dx_i}{dt} = \alpha_i \prod_{j=1}^N x_j^{g_{i,j}} - \beta_i \prod_{j=1}^N x_j^{h_{i,j}}, \quad (i = 1, \dots, N) \quad (4)$$

where x_i are state variables. α_i and β_i are positive rate constants. $g_{i,j}$ and $h_{i,j}$ are exponential parameters called kinetic orders. If $g_{i,j} > 0$, gene j will induce the expression of gene i . On the contrary, gene j will inhibit the expression of gene i if $g_{i,j} < 0$. $h_{i,j}$ will have the opposite effects on controlling gene expressions compared with $g_{i,j}$. The S-system is a quantitative model, which is characterized by power laws of exponential functions. It has a rich structure capability of capturing various dynamics in many biochemical systems. In addition, the S-system model has been proven to be successful in modeling GRNs [13, 7, 8]. However, the complexity is intensive. The structure is fixed. The time complexity of exponent estimation is high. These limit the application of S-system in GRNs.

In this paper, GRNs are analyzed without parametric prediction using ensemble filter based particle filter. The contribution of paper is to overcome the overfitting problem introduced by deterministic and stochastic models. If the model overfits data, it will sacrifice the predictive accuracy. In the proposed method, there is no model involved. It is not necessary to balance between the minimization of error and actual GRNs like deterministic and stochastic models. The paper includes four sections. In section two, the particle filter and ensemble Kalman filter are formulated, and the proposed ensemble Kalman filter based particle filter algorithm is given in detail. In section three, models are simulated using synthetic and real microarray data with discussions. Section four is for the conclusion of the research.

2. ENSEMBLE KALMAN FILTER BASED PARTICLE FILTER

2.1 Particle filter

Particle filter is also called Sequential Monte Carlo (SMC) methods. Particle filter is a set of genetic-type particle Monte Carlo methodologies to solve the filtering problem [10]. It is a probability-based filter. The key idea is to generate a given number M state vectors based on the probability density function(pdf) [10].

In particle filter, the microarray data is represented in terms of the variables y_i , which are also a set of noisy observations.

A state space model is given below.

$$\begin{aligned} x_i &= f(x_{i-1}, t_{i-1}) + \nu_i \\ y_i &= h(x_i, t_i) + \mu_i \end{aligned} \quad (5)$$

$f(\cdot)$ is the system dynamic function. $h(\cdot)$ is the system observation function. They are nonlinear and noisy. x_i is the state vector. y_i is the observation vector. ν_i is system noise vector with covariance Q . μ_i is the observation noise vector with covariance R .

The general procedure of particle filter in GRNs analysis is given by Algorithm 1 [10].

Algorithm 1 Particle filter algorithm in GRNs analysis

Input: Nonlinear and noisy unknown function f , $\mu_{i,j}$, ν_i , the initial state $pdf(x_0)$, state vector x_i , and observation vector y_i .

- 1: Generate M initial posteriori particles on the basis of the $pdf(x_0)$: $x_{0,j}^+(j = 1, \dots, M)$. M is the number of particles.
- 2: **for** $i = 1 \rightarrow K$ **do**
- 3: Perform the time propagation step to obtain a priori particles $x_{i,j}^-$

$$x_{i,j}^- = f_{i-1}(x_{i-1,j}^+, w_{i-1}^j) \quad (j = 1, \dots, M) \quad (6)$$

where w_{i-1}^j is generated on the basis of pdf of w_{k-1} .

- 4: Compute the relative likelihood q_j of each particle $x_{i,j}^-$ conditioned on the measurement of y_i on the basis of nonlinear measurement equation and the pdf of the measurement noise

$$q_j = \frac{1}{(2\pi)^{L/2} |R|} \exp\left(\frac{-[y^* - h(x_{i,j}^-)]^T R^{-1} [y^* - h(x_{i,j}^-)]}{2}\right) \quad (7)$$

where y^* is a specific measurement, and L is the number of elements.

- 5: Scale the relative likelihoods

$$q_j = \frac{q_j}{\sum_{m=1}^M q_m} \quad (8)$$

- 6: Resampling step: generate posteriori particles $x_{i,j}^+$ on the basis of the relative likelihoods q_i
- 7: Accept those higher importance weights particles with cumulative probabilities bigger than a given threshold.
- 8: Compute the mean and covariance on the basis of $x_{i,j}^+$ which are distributed according to the $pdf(x_i|y_i)$.
- 9: **end for**
- 10: Estimate the RMS error

$$RMS = \left(\frac{1}{N^2} \sum_{i=1}^N |X_i^* - X_i|\right)^{1/2}$$

where X_i^* is one given measurement.

2.2 Ensemble Kalman filter

The ensemble Kalman filter is one optimal estimator with error statistics predicted using ensemble integration to solve the Fokker-Planck equation [5]. Ensemble Kalman filter without a model is proposed in [6]. The proposed method can analyze time series data without access to a model. For GRNs, dynamic relations among genes are inferred from noisy training data set. Since particle filter can also analyze data without a model, modified ensemble Kalman filter in [6] is adopted. The system and state equations are the same as equations (5) in particle filter.

The modified ensemble Kalman filter is given by Algorithm 2 [10, 6].

Algorithm 2 Modified ensemble Kalman filter algorithm in GRNs analysis

Input: Nonlinear and noisy unknown function f , $\mu_{i,j}$, ν_i , the initial state $pdf(x_0)$, state vector x_i , and observation vector y_i .

- 1: Generate M initial posteriori particles on the basis of the $pdf(x_0)$: $x_{0,j}^+(j = 1, \dots, M)$. M is the number of particles.
- 2: **for** $i = 1 \rightarrow K$ **do**
- 3: A priori particles $x_{i,j}^-$ is given by the mean of the resulting state ensemble
- 4: The covariance matrices P_i^- , the covariance of the resulting state and observed states P_i^{xy} , and the cross-covariance matrix P_i^{xy} are given below. Perform the time-update equations

$$\begin{aligned} P_i^- &= \sum_{i=1}^E (x_{i,j}^- - x_i^-)(x_{i,j}^- - x_i^-)^T + Q \\ P_i^{xy} &= \sum_{i=1}^E (y_{i,j}^- - y_i^-)(y_{i,j}^- - y_i^-)^T + R \\ P_i^{xy} &= \sum_{i=1}^E (x_{i,j}^- - x_i^-)(y_{i,j}^- - y_i^-)^T \end{aligned} \quad (9)$$

where x_i^- and y_i^- are the mean of the resulting state ensemble and the mean of the observed ensemble, respectively.

- 5: State and covariance are estimated with observation using following equations.

$$\begin{aligned} K_i^- &= P_i^{xy}(P_i^y)^{-1} \\ P_i^+ &= P_i^- - P_i^{xy}(P_i^y)^{-1}P_i^{xy} \\ x_i^+ &= x_i^- + K_i^-(y_i - y_i^-) \end{aligned} \quad (10)$$

6: **end for**

2.3 Proposed ensemble Kalman filter based particle filter

The proposed ensemble Kalman filter based particle filter is shown in Algorithm 3. Ensemble Kalman filter is applied to predict new particles based on the state estimation in the last step of particle filter. Thus, the proposed algorithm can alleviate the sample degeneracy problem in particle filter

algorithm. The proposed algorithm can also adjust gain imbalance factor by adjusting attenuation factor, which can compromise between accuracy and robustness.

Algorithm 3 Ensemble Kalman filter based particle filter in GRNs analysis

- Input:** Nonlinear and noisy function f , $\mu_{i,j}$, ν_i , the initial state $pdf(x_0)$, state vector x_i , and observation vector y_i .
- 1: Generate M initial posteriori particles on the basis of the $pdf(x_0)$: $x_{0,j}^+(j = 1, \dots, M)$. M is the number of particles.
 - 2: **for** $i = 1 \rightarrow K$ **do**
 - 3: Perform ensemble Kalman Filter prediction
 - 4: **for** $k = 1 \rightarrow M$ **do**
 - 5: A priori particles $x_{k,j}^-$ is given by the mean of the resulting state ensemble
 - 6: The covariance matrices P_k^- , the covariance of the resulting state and observed states P_k^y , and the cross-covariance matrix P_k^{xy} are given by performing the time-update equations in (9)
 - 7: State and covariance are estimated with observation using equations in (10).
 - 8: **end for**
 - 9: Compute the relative likelihood q_j of each particle $x_{i,j}^-$ conditioned on the measurement of y_i on the basis of nonlinear measurement equation and the pdf of the measurement noise using equation(7)
 - 10: Scale the relative likelihoods using equation(8)
 - 11: Resampling step: generate posteriori particles $x_{i,j}^+$ on the basis of the relative likelihoods q_i
 - 12: Accept those higher importance weights particles with cumulative probabilities bigger than a given threshold.
 - 13: Compute the mean and covariance on the basis of $x_{i,j}^+$ which are distributed according to the $pdf(x_i|y_i)$.
 - 14: **end for**
 - 15: Estimate the RMS error using equation(9)
-

2.4 Complexity analysis of the proposed algorithm

The efficiency of the proposed algorithm is compared with the standard particle filter.

The time cost function of particle filter is $T(K, M) = \sum_{i=1}^K \sum_{j=1}^M C1 = C1KM \in \Omega(KM)$, where K is the total number of time steps. M is the total number of particle in each loop. $C1$ is the time cost for each loop of particle filter.

The time cost function of proposed algorithm is $T(K, M) = \sum_{i=1}^K \sum_{j=1}^M (C1 + C2) = (C1 + C2)KM \in \Omega(KM)$, where $C2$ is the time cost for each loop of the ensemble Kalman filter. Usually, if $k \ll m$, we have $T(K, M) \in \Omega(M)$. The proposed algorithm has the same level of time efficiency as the particle filter algorithm.

3. SIMULATION RESULTS

In order to test the proposed ensemble Kalman filter based particle filter, data from both synthetic models and real microarray experiments are used.

3.1 Synthetic model simulation

The GRNs model analysis using ensemble Kalman filter based particle filter is tested by synthetic data generated

from the model in [11]. For the proposed algorithm, it is not necessary to have the exact model of $f(\cdot)$. Noisy time series data is the main input for the model. The model has three inputs: gene $X1$, gene $X2$, and gene $X3$. The simulation results from standard particle filter and the proposed algorithm are compared.

Fig. 1, Fig. 2, and Fig. 3 show the simulation results with noise covariance $Q = 10$ and $R = 0.08$. It is obvious that both standard particle filter and ensemble Kalman filter based particle filter can estimate the gene state throughout the entire simulation procedure. Ensemble Kalman filter based particle filter can estimate better results compared with the standard particle filter.

Figure 1: Synthetic simulation data for $X1$ with Noise

Figure 2: Synthetic simulation data for $X2$ with Noise

Fig. 4, Fig. 5, and Fig. 6 show the estimation error based on time using the standard particle filter and the proposed algorithm. Table 1 shows the accumulative error using $RMS = (\frac{1}{N^2} \sum_{i=1}^N |X_i^* - X_i|)^{1/2}$. We can see that the proposed ensemble Kalman based particle filter can guarantee the estimation accuracy and performs better than the stan-

Figure 3: Synthetic simulation data for $X3$ with Noise

dard particle filter. The reason is that the proposed method can employ current measurements. However, standard particle filter does not think over current measurements. From Fig. 4, Fig. 5, Fig. 6, and table 1, we can conclude that the proposed method is much more robust than standard particle filter and comes with satisfactory results in the whole process.

Table 1: The RMS error from standard particle filter and ensemble Kalman filter based particle filter

Method	X1	X2	X3
Standard particle filter	18.1174	9.89067	6.86664
Proposed method	16.5263	9.22541	6.61891

Figure 4: Estimation error of $X1$

Figure 5: Estimation error of X_2

Figure 7: Microarray data simulation for HAP1

Figure 6: Estimation error of X_3

Figure 8: Microarray data simulation for CYB2

Figure 9: Microarray data simulation for CYC7

3.2 Microarray data simulation

In this part of the simulation, time-series gene-expression data corresponding to yeast protein synthesis [11] are considered. Five genes (HAP1(X_1), CYB2(X_2), CYC7(X_3), CYT1(X_4), COX5A(X_5)) are selected because the relations among them have been revealed by biological experiments.

Ensemble Kalman filter based particle filter is applied to analyze the real microarray data with noise. Results are shown in Fig. 7, Fig. 8, Fig. 9, Fig. 10, and Fig. 11 for genes HAP1, CYB2, CYC7, CYT1, and COX5A. We can see that the proposed method performs well on the real nonlinear noisy microarray data.

Figure 10: Microarray data simulation for CYT1

Figure 11: Microarray data simulation for COX5A

4. CONCLUSION

In this paper, a novel ensemble Kalman filter based particle filter is proposed. The proposed method overcomes the overfitting problem in deterministic and stochastic models. There is no sacrifice of predictive accuracy. The simulation results show that the proposed method has better accuracy, robustness, and efficiency in GRNs analysis. The proposed method takes current measures into account, which makes particle distribution more approach to the station posterior distribution. Furthermore, the proposed method can be applied to nonlinear and nonparametric forecasting models. GRNs are one of those models. Finally, both synthetic and real microarray experiment data are applied to the proposed method. Results show that the proposed algorithm is effective and practicable in GRNs analysis. The future work is to apply the proposed algorithm in gene control networks with high dimensional data.

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