Double-Chain Unscented Expectation Propagation for Inference in Stochastic Dynamical Models of Biological Processes
[Extended Abstract]

Hao Wu[1] and Stefan Bernhard[2]

[1] Department of Mathematics and Computer Science, Free University of Berlin, Arnimallee 6, 14195 Berlin, Germany
[2] Department of Medical Technology, Pforzheim University, Tiefenbronner Str. 65, 75175 Pforzheim, Germany

Abstract. In many fields of biology and medicine we are confronted with the task of analyzing and estimating a complex process based on partial observations. Many of these problems can be described by dynamical system models with unknown states and parameters. The Bayesian theory provides a statistical inference framework for such systems. But there is a fundamental and not satisfactorily solved problem in Bayesian inference of biological processes, that is how to approximate the posterior distributions fast and accurately in real world applications. Here we develop a new algorithm within the expectation propagation framework to solve this problem. The usefulness of the method will be demonstrated by applying it to two significantly different biomedically important problems: single-molecule fluorescence experiments and cardiovascular system measurements.

Keywords: stochastic dynamical model, Bayesian inference, single-molecule fluorescence experiment, cardiovascular system

1 Introduction

In many fields of biology and medicine, we can model a complex process by the following equation:

$$\begin{aligned} x_t &= f\left(x_{t-1}, \theta, v_t\right) \\ y_t &= g\left(x_t, \theta, w_t\right) \end{aligned} \tag{1}$$

where x_t is the system state at time $t = 0, \ldots, T$, y_t is the corresponding observation, v_t and w_t are system and observation noise with $v_t \sim \mathcal{N}\left(\mathbf{0}, \mathbf{Q}\right)$ and $w_t \sim \mathcal{N}\left(\mathbf{0}, \mathbf{R}\right)$, and θ denotes the vector of system parameters. A key problem of model (1) is how to estimate θ and $x_{0:T}$ from noisy observation $y_{1:T}$. Following the Bayes' Theorem, the estimates can be obtained from the posterior distribution

$$p\left(\theta, x_{0:T} | y_{1:T}\right) \propto \prod_{t=1}^{T} \Psi_t\left(x_{t-1}, x_t, \theta\right) \tag{2}$$

with

$$\Psi_t\left(x_{t-1}, x_t, \theta\right) = p\left(x_t | x_{t-1}, \theta\right) p\left(y_t | x_t, \theta\right) \tag{3}$$

Since the posterior is generally intractable, numerical computation is required. One widely used technique is Markov chain Monte Carlo (MCMC), which can achieve exact estimates through iterative sampling. But it is might be too much time consuming in many practical cases for the requirement of a large number of iterations. In order to improve the efficiency of Bayesian estimation, a lot of approximate Bayesian methods were developed to approximate the posteriors by tractable distributions, such as nonlinear Kalman smoother [1] and variational Bayesian method [2]. Minka [3] proposed an approximate inference algorithm called expectation propagation (EP), which can decompose the global Bayesian inference problem into a set of small-sized moment matching problems. In [4], Heskes and Zoeter applied EP to estimation problems of dynamical systems, and analyzed the advantages of EP over nonlinear Kalman smoother and variational Bayesian method. However, the accurate and fast moment matching is still a challenge for the EP framework of nonlinear dynamical system estimation. In this paper, we propose a new EP approach, which can be applied to model (1) with arbitrary f and g.

2 Expectation propagation framework

Generally, the approximate posterior distribution of (1) can be written as

$$\hat{p}\left(\theta, x_{0:T} | y_{1:T}\right) \propto \prod_{t=1}^{T} \hat{\Psi}_t\left(x_{t-1}, x_t, \theta | \gamma_t\right) \tag{4}$$

where $\hat{\Psi}_t$ is a parametric approximation model of Ψ_t with undetermined parameter γ_t, and the EP approach iteratively refines the values of $\gamma_{1:T}$ by:

$$\begin{aligned} \gamma_t \leftarrow \gamma_t^{\text{new}} = \arg\min_{\gamma_t} \mathrm{KL}\Big(& q_t\left(x_{t-1}, x_t, \theta\right) \,||\, \\ & \hat{\alpha}_{t-1}\left(x_{t-1}, \theta\right) \hat{\Psi}_t\left(x_{t-1}, x_t, \theta | \gamma_t\right) \hat{\beta}_t\left(x_t, \theta\right) \Big) \end{aligned} \tag{5}$$

where

$$q_t\left(x_{t-1}, x_t, \theta\right) \propto \hat{\alpha}_{t-1}\left(x_{t-1}, \theta\right) \Psi_t\left(x_{t-1}, x_t, \theta\right) \hat{\beta}_t\left(x_t, \theta\right) \tag{6}$$

$\hat{\alpha}_{t-1}\left(x_{t-1}, \theta\right)$ and $\hat{\beta}_t\left(x_t, \theta\right)$ denote approximations of $p\left(x_{t-1}, \theta | y_{1:t-1}\right)$ and $p\left(x_t, \theta | y_{t+1:T}\right)$ obtained by $\left\{\hat{\Psi}_k | k \neq t\right\}$. It can be proved that if $\hat{\Psi}_{1:T}$ are exponential family densities, then (5) can be solved by matching moments of $q_t\left(x_{t-1}, x_t, \theta\right)$ (see [4] for details). In this paper, we only consider the case that $\hat{\Psi}_t$ is a multivariate normal distribution, then γ_t can be obtained by the first two moments of $q_t\left(x_{t-1}, x_t, \theta\right)$,

and $q_t(x_{t-1}, x_t, \theta)$ can be equivalently described by the following submodel

$$\begin{aligned} x_{t-1}, \theta &\sim \hat{\alpha}_{t-1}(x_{t-1}, \theta) \\ v_t &\sim \mathcal{N}(\mathbf{0}, \mathbf{Q}) \\ w_t &\sim \mathcal{N}(\mathbf{0}, \mathbf{R}) \\ x'_t, \theta' &\sim \hat{\beta}_t(x_t, \theta) \\ x_t &= f(x_{t-1}, \theta, v_t) \\ y_t &= g(x_t, \theta, w_t) \end{aligned} \tag{7}$$

with $q_t(x_{t-1}, x_t, \theta) = p_{\text{sub}}(x_{t-1}, x_t, \theta | x_t = x'_t, \theta = \theta', y_t)$, where $p_{\text{sub}}(\cdot)$ denotes the density under the submodel (7). Note that $\hat{\alpha}_{t-1}(x_{t-1}, \theta)$ and $\hat{\beta}_t(x_t, \theta)$ are both multivariate normal distribution, then we can get the first two moments of $q_t(x_{t-1}, x_t, \theta)$ by the unscented Kalman filter [1]. However, it is easy to prove that this method is equivalent to an unscented Kalman smoother (UKS) [5], and γ_t keeps fixed after the first iteration because the sigma point positions of (x_{t-1}, x_t, θ) in the unscented transformation only depends on $\hat{\alpha}_{t-1}(x_{t-1}, \theta)$, which means the approximate posterior distribution cannot be further refined by multiple iterations.

3 Double-chain unscented expectation propagation

Here we propose a new unscented EP algorithm based on the double chain structure of Bayesian networks, which approximates the square of posterior instead of the posterior itself with

$$\begin{aligned} p^2(x_{0:T}, \theta | y_{1:T}) &\propto \prod_{t=1}^{T} \Psi_t^2(x_{t-1}, x_t, \theta) \\ &\approx \prod_{t=1}^{T} \hat{\Psi}_{t,1}(x_{t-1}, x_t, \theta | \gamma_{t,1}) \hat{\Psi}_{t,2}(x_{t-1}, x_t, \theta | \gamma_{t,2}) \end{aligned}$$

where $\hat{\Psi}_{t,1}$ and $\hat{\Psi}_{t,2}$ are both approximations of Ψ_t, and the corresponding update of $\gamma_{t,i}$ can be written as

$$\begin{aligned} \gamma_{t,i} \leftarrow \gamma_{t,i}^{\text{new}} = \arg\min_{\gamma_{t,i}} \text{KL}\Big(& q_{t,i}(x_{t-1}, x_t, \theta) \,||\, \hat{\Psi}_{t,3-i}(x_{t-1}, x_t, \theta | \gamma_{t,3-i}) \\ & \cdot \hat{\alpha}_{t-1}^2(x_{t-1}, \theta) \, \hat{\Psi}_{t,i}(x_{t-1}, x_t, \theta | \gamma_{t,i}) \, \hat{\beta}_t^2(x_t, \theta) \Big) \end{aligned} \tag{8}$$

where

$$\begin{aligned} q_{t,i}(x_{t-1}, x_t, \theta) \propto & \, \hat{\alpha}_{t-1}^2(x_{t-1}, \theta) \, \hat{\Psi}_{t,3-i}(x_{t-1}, x_t, \theta | \gamma_{t,3-i}) \\ & \Psi_t(x_{t-1}, x_t, \theta) \, \hat{\beta}_t^2(x_t, \theta) \end{aligned} \tag{9}$$

$\hat{\alpha}_{t-1}^2(x_{t-1},\theta)$ and $\hat{\beta}_t^2(x_t,\theta)$ denote approximations of $p^2(x_{t-1},\theta|y_{1:t-1})$ and $p^2(x_t,\theta|y_{t+1:T})$ obtained by $\left\{\hat{\Psi}_{k,l}|k\neq t,l=1,2\right\}$. Then we can calculate $\gamma_{t,i}^{\text{new}}$ in (8) by applying the unscented Kalman filter to the following submodel

$$\begin{aligned} x_{t-1},x_t',\theta &\sim \hat{\alpha}_{t-1}^2(x_{t-1},\theta)\,\hat{\Psi}_{t,3-i}(x_{t-1},x_t,\theta|\gamma_{t,3-i})\,\hat{\beta}_t^2(x_t,\theta) \\ v_t &\sim \mathcal{N}(\mathbf{0},\mathbf{Q}) \\ w_t &\sim \mathcal{N}(\mathbf{0},\mathbf{R}) \\ x_t &= f(x_{t-1},\theta,v_t) \\ y_t &= g(x_t,\theta,w_t) \end{aligned} \tag{10}$$

with $q_{t,i}(x_{t-1},x_t,\theta)=p_{\text{sub-dc}}(x_{t-1},x_t,\theta|x_t=x_t',y_t)$, where $p_{\text{sub-dc}}(\cdot)$ denotes the density under the submodel (10). We call this method the double-chain unscented expectation propagation (DC-UEP). It can be observed that in the DC-UEP, the information contained in $\hat{\Psi}_{t,3-i}$ is used to modify the corresponding sigma point positions such that $\gamma_{t,i}$ can be iteratively refined and estimated with more accuracy than in the UKS.

4 Applications

In this section, we apply the proposed method to two estimation problems which arise from real world problems concerning single-molecule fluorescence experiment and measurement of cardiovascular system.

4.1 Single-molecule fluorescence experiment

Fluorescence resonance energy transfer (FRET) is a powerful technique that is commonly used to track binding or folding processes in macromolecules as a spectroscopic ruler [6]. In a FRET experiment, two chemical groups, one donor and one acceptor dye, are attached at defined positions to the molecule(s). After excitation of the donor, the donor emits a donor photon (usually green), or the energy is transfered to the nearby acceptor dye which then emits an acceptor photon (usually red). The transfer efficiency (probability of an emitted photon being an acceptor photon) can be calculated by the Förster law:

$$E=\frac{1}{1+(r/R_0)^6} \tag{11}$$

where E is the transfer efficiency, r is the interdye distance, and R_0 is the dye-specific effective Förster radius which depends on the composition of the dyes. Recently, the single-molecule FRET (smFRET) technique have been matured, which allows one to record arrival times of individual photons from single molecules, and provides information of single molecular conformational changes. [7] proposed that the trajectory of interdye distance of an smFRET can be described by a Brownian dynamics:

$$\dot{x}=-\frac{\partial V(x)}{\partial x}+\sqrt{Q}w \tag{12}$$

where $x = r/R_0$, $V(x)$ is the potential function of x, Q is the diffusion constant, and w is a Gaussian white noise with deviation 1. From the estimation of $V(x)$, we can also get the estimation of stationary distribution of x since

$$\pi(x) \propto \exp\left(-\frac{2V(x)}{Q}\right) \tag{13}$$

Here we apply the DC-UEP, UKS and the conventional time window (TW) method to the estimation of interdye distance trajectory and its stationary distribution of smFRET based on the Euler discrete-time model of (12). (The FRET data are generated by the simulation model in Section V.D of [7].) Table 1 displays the means and variances of the estimation errors over 30 independent simulations. Not surprisingly, the Brownian dynamics based approximate Bayesian methods perform significantly better than TW. Comparison of the DC-UEP and UKS shows that the iterative modification in the DC-UEP approach can effectively the estimation accuracy of the parameters.

Table 1. Quantitative comparison of errors of the estimating interdye distance trajectories and the stationary distribution. The error of stationary distribution is defined as $\mathrm{KL}(\pi(x)||\hat{\pi}(x)) = \int \pi(x) \log(\pi(x)/\hat{\pi}(x))\, dx$.

Method	RRMSE of x		$\mathrm{KL}(\pi(x)\|\|\hat{\pi}(x))$	
	mean	var $[\times 10^{-3}]$	mean	var
DC-UEP	0.0833	0.0635	0.0746	0.0011
UKS	0.0917	0.0775	0.1266	0.0047
TW	0.1201	0.2326	0.5130	0.0497

4.2 Cardiovascular system: Hidden signal and parameter estimation

The research in computational cardiovascular physiology has focused on the development of forward models that describe the dynamics of the cardiovascular system [8,9,10]. In previous studies it was shown that lumped parameter models are reasonable approximations to describe the fluid flow in most regions of the cardiovascular system. Typically these models predict blood pressure and flow by ordinary differential equations (ODEs) in analogy to an equivalent electrical RCL-circuit [8,9,10].

Fig. 1 is an example of lumped model of the cardiovascular system consisting of 6 arterial segments, where each segment i is represented by an electrical RCL-circuit, and the electrical current and voltage is related to arterial blood flow q_i and pressure p_i, respectively. The electrical resistances R_i correspond to the viscos flow resistance, the inductances L_i account for the blood inertia forces and the arterial compliances, i.e. the elasticity of the vessel walls, are described by electrical capacitors C_i. Note that the evolution of the lumped model can be described by an SDE (see [11] for details), and the parameters of the electric

analogue circuit are determined by the structural and physiological parameters with [8]

$$R_i = \frac{8\nu l_i}{\pi r_i^4}, \qquad L_i = \frac{\rho l_i}{\pi r_i^2}, \qquad C_i = \frac{2\pi r_i^3 l_i}{E_i h_i}. \tag{14}$$

where l_i, r_i, h_i and E_i denote the length, radius, wall thickness and Youngs modulus of the i-th segment. Therefore, we can use the Bayesian method to estimate the structural and physiological parameters from some q_i and p_i. (This kind of problems usually appear in the non-invasive measurement.)

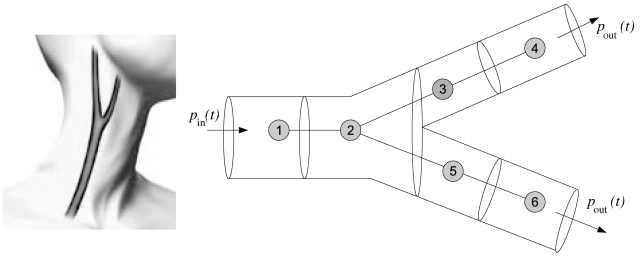

Fig. 1. Human carotis bifurcation and the corresponding simplified network structure with 6 segments.

Here we apply the DC-UEP and UKS to a simulation model of the cardiovascular system shown in Fig. 1 with (q_3, p_3, q_5, p_5) given. (The detailed description of the simulation model is given in [11].) The estimation results are given in Table 2. It can be seen that the proposed DC-UEP significantly outperforms the UKS.

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Table 2. Quantitative comparison of errors of parameter and state estimates using different methods. The estimates are defined by expectations of the approximate posterior distributions, and the mean and variance of the RRMSE calculated over 30 independent runs.

Methods	RRMSE of flows		RRMSE of pressures		RRMSE of $\{r_i\}$	
	mean	var $[\times 10^{-3}]$	mean	var $[\times 10^{-3}]$	mean	var $[\times 10^{-3}]$
UEP	0.1186	0.0565	0.0137	0.0008	0.0348	0.3200
UKS	2.7089	277.1	0.5200	110.0	0.5382	132.5

Methods	RRMSE of $\{l_i\}$		RRMSE of Eh	
	mean	var $[\times 10^{-3}]$	mean	var $[\times 10^{-3}]$
UEP	0.0833	3.1767	0.0401	0.5822
UKS	0.7494	389.8	0.3853	9.8

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