Master Thesis

Bayesian Parameter Estimation of State-Space Models with Intractable Likelihood

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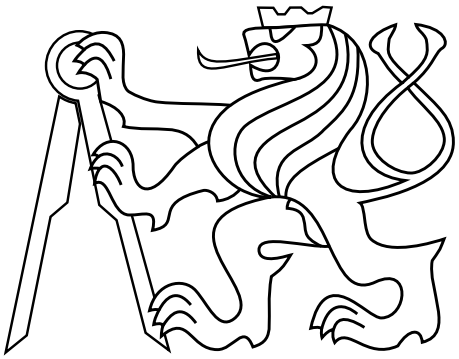

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ZADÁNÍ DIPLOMOVÉ PRÁCE

I. OSOBNÍ A STUDIJNÍ ÚDAJE

Příjmení: **Kala** Jméno: **Tomáš** Osobní číslo: **434690**

Fakulta/ústav: **Fakulta elektrotechnická**

Zadávající katedra/ústav: **Katedra počítačů**

Studijní program: **Otevřená informatika**

Studijní obor: **Bioinformatika**

II. ÚDAJE K DIPLOMOVÉ PRÁCI

Název diplomové práce:

Bayesovské odhadování parametrů stavových modelů při nedostupné věrohodnostní funkci

Název diplomové práce anglicky:

Bayesian parameter estimation of state-space models with intractable likelihood

Pokyny pro vypracování:

Stavové modely představují velmi populární formalismus vhodný pro popis celé řady různých náhodných procesů, od časových řad po aplikace v teorii řízení. Pokud tyto modely neobsahují statické parametry, lze pro jejich odhad použít např. Kalmanův filtr a jeho varianty, dále particle filtraci aj. Pokud ovšem statické parametry obsahují, tyto filtry zpravidla nekonvergují a nezbývá, než přikročit k optimalizačním technikám typu maximalizace věrohodnosti či particle Markov chain Monte Carlo. Další komplikace nastávají, pokud navíc není věrohodnostní funkce pro pozorovanou veličinu dostupná, nebo je nepřesná či příliš komplikovaná. Diplomová práce je specificky zaměřena poslední zmíněnou problematiku.
Specifické pokyny
1. Seznamte se s metodami pro odhadování stavových modelů pomocí kalmanovské filtrace a sekvenční Monte Carlo filtrace. Nastudujte problematiku statických parametrů a jejich odhadu.
2. Proveďte rešerši ohledně využití daných metod v oblasti bioinformatiky, například v modelování buněčných procesů.
3. Seznamte se s metodami ABC - Approximate Bayesian Computation a jejich využití ve filtraci stavových modelů.
4. Navrhněte vhodný způsob odhadování statických parametrů stavových modelů s využitím metod ABC.
5. Experimentálně (na vhodném problému z oblasti molekulární biologie) a případně teoreticky ověřte vlastnosti navržené metody, diskutujte její vlastnosti a navrhněte další možné směry výzkumu.

Seznam doporučené literatury:

1] C. C. Drovandi, A. N. Pettitt, and R. A. McCutchan, “Exact and approximate Bayesian inference for low integer-valued time series models with intractable likelihoods,” Bayesian Anal., vol. 11, no. 2, pp. 325–352, 2016.
[2] S. Martin, A. Jasra, S. S. Singh, N. Whiteley, P. Del Moral, and E. McCoy, “Approximate Bayesian Computation for Smoothing,” Stoch. Anal. Appl., vol. 32, no. 3, pp. 397–420, 2014.
[3] T. B. Schön, A. Svensson, L. Murray, and F. Lindsten, “Probabilistic learning of nonlinear dynamical systems using sequential Monte Carlo,” Mech. Syst. Signal Process., vol. 104, pp. 866–883, May 2018.
[4] C. Andrieu, A. Doucet, and R. Holenstein, “Particle Markov chain Monte Carlo methods,” J. R. Stat. Soc. Ser. B (Statistical Methodol., vol. 72, no. 3, pp. 269–342, Jun. 2010.
[5] K. Dedecius, “Adaptive kernels in approximate filtering of state-space models,” Int. J. Adapt. Control Signal Process., vol. 31, no. 6, pp. 938–952, Jun. 2017.

Jméno a pracoviště vedoucí(ho) diplomové práce:

Ing. Kamil Dedecius, Ph.D., ÚTIA AV ČR

Jméno a pracoviště druhé(ho) vedoucí(ho) nebo konzultanta(ky) diplomové práce:

Datum zadání diplomové práce: **04.02.2019** Termín odevzdání diplomové práce: **24.05.2019**

Platnost zadání diplomové práce: **20.09.2020**

Ing. Kamil Dedecius, Ph.D. podpis vedoucí(ho) práce	podpis vedoucí(ho) ústavu/katedry	prof. Ing. Pavel Ripka, CSc. podpis děkana(ky)

III. PŘEVZETÍ ZADÁNÍ

Diplomant bere na vědomí, že je povinen vypracovat diplomovou práci samostatně, bez cizí pomoci, s výjimkou poskytnutých konzultací. Seznam použité literatury, jiných pramenů a jmen konzultantů je třeba uvést v diplomové práci.

. | Datum převzetí zadání

Podpis studenta

Abstract

Abstract in English

Abstrakt

Abstract in Czech

Author statement for graduate thesis:

I declare that the presented work was developed independently and that I have listed all sources of information used within it in accordance with the methodical instructions for observing the ethical principles in the preparation of university theses.

Prague, date ....

signature

Acknowledgements

Contents

Chapter 1

Introduction

Probabilistic modelling arises in a wide variety of situations. Often, the measurements one uses to perform inference have been carried out with an unknown error. Frequently, one also does not have access to a correct model for the particular situation — the true model is either unknown, or even impossible to formulate.

In the former case, one naturally assumes a random error associated with the observations, and attempts to infer something from the data while accounting for this randomness.

In the latter case, one has no choice but to work with a given, although possibly simplified model, purely because of insufficient domain knowledge. Connected with such a model is some degree of uncertainty about its parameters. It is often beneficial to think of these parameters as random variables themselves, in accordance with the Bayesian methodology (Robert, 2007). Such formulation allows to formulate one's prior beliefs about the parameter values, and then updating them upon receiving new observations.

In this thesis, we work with state-space models (SSMs) consisting of a sequence of observed random variables y_t indexed by discrete time $t = 1, \ldots, T$, which have been generated by a latent random process $x_t,\ t = 1, \ldots, T$. The distribution of x_t and y_t is assumed to be parameterized by a static parameter θ. Our goal is to perform posterior inference about this parameter, given th observed sequence $\{y_t\}_{t=1}^{T}$. Furthermore, we assume that the likelihood function of the SSM is intractable and cannot be evaluated. This assumption is well-grounded, as the likelihood is only available in severely restricted cases to be discussed in Chapter 3, together with a formal definition of the SSM.

Our contribution is twofold. First, we show how to apply the Approximate Bayesian Computation (ABC) methodology (Rubin et al., 1984; Pritchard et al., 1999) to obtain an estimate of the likelihood even under a misspecified model for the observed variables y_t. Second, we use our results to model the genetic auto-regulation process in prokaryotes. Such a problem is suitable for a state-space model with a possibly misspecified observation model, as all attempts to describe such a complex system are necessarily simplified. The quote by the famous statistician George E. P. Box, *"all models are wrong, but some are useful"* (Box, 1979), comes to mind here.

The rest of the thesis is organized as follows. In Chapter 2, we review some of the related work. Discussed is the literature on Markov Chain Monte Carlo (MCMC) methods, and their use in estimating the parameters of an SSM. We state several results dealing with inference in SSMs with intractable likelihoods, as these are relevant to this thesis. Literature on ABC methods is reviewed as well, along with papers describing how these could be applied to SSMs. Finally, we discuss the application of SSMs to bioinformatics, focusing on molecular biology.

In Chapter 3, we define the assumed form of a state-space model. We show how one would implement a sampler to approximately infer the static parameters given a sequence of observations. We also show that in this basic form, such sampler is unusable, since it relies on the evaluation of the likelihood function, which is intractable (up to certain special cases). We then describe how this likelihood can be estimated using the particle filter (Doucet et al., 2001) without affecting the asymptotic properties of the sampler.

Chapter 4 provides a description of the ABC method, and also how it can be applied to estimate the likelihood even under a misspecified observation model. We discuss the pros and cons of such approach compared to the particle filter described in Chapter 3.

Chapter 5 provides numerical studies, where we apply the model developed in Chapter 4 to

several examples and compare it with the model utilizing the particle filter. This chapter also includes the prokaryotic auto-regulation study discussed earlier.

Finally, Chapter 6 concludes the thesis and discusses some possible directions to be investigated in the future.

Chapter 2

Related work

In this chapter, we provide a survey of literature relevant to our task. Addressed are works on the use of Markov Chain Monte Carlo methods for approximate inference, works on approximating the likelihood of state-space models by the particle filter, and on Approximate Bayesian Computation methods. We also give a section describing the use of the considered models in bioinformatics, focusing on molecular biology and genetics.

2.1 Markov Chain Monte Carlo methods

Monte Carlo methods can be described as a class of algorithms designed to simulate random samples from a distribution of interest, which itself is too complex to sample directly. Assuming that the probability density function of this distribution can be evaluated (at least up to a normalizing constant), Monte Carlo methods output a random sample approximately distributed according to the true distribution. *Markov Chain* Monte Carlo (MCMC) methods employ a Markov chain designed so that its stationary distribution is the target. At least asymptotically, the samples are indeed distributed according to the desired distribution.

An attractive property is that the transition distribution of such chain need not resemble the target distribution even closely, and that the problem is relatively unaffected by the dimensionality. The downside is a difficulty to determine convergence — for how long should a chain be ran in order to approximately reach the stationary distribution. In addition, one typically requires independent samples from the target distribution, which, however, the Markov chain samples are *not*. Typically, one needs to "thin" the Markov chain samples by keeping every nth one to ensure their approximate independence.

Perhaps the best known MCMC algorithm is the Metropolis algorithm (Metropolis et al., 1953), later improved by Hastings (1970). Random samples are iteratively generated from the Markov chain transition distribution, called the proposal distribution in this context. Each such sample is then compared with the previous one, and accepted with a certain probability which ensures that the stationary distribution is indeed the target. The go-to reference for Monte Carlo methods is Robert and Casella (2005). A particularly appealing treatment of MCMC methods with applications towards physics and machine learning can be found in MacKay (2002).

There are of course many more MCMC algorithms. For our task, the Metropolis-Hastings algorithm is sufficient, since the main problem is in the likelihood estimation, and not in designing the best sampler possible.

2.2 Parameter inference in state-space models

Assuming that the state-space model (SSM) takes the form informally stated in Chapter 1 and more formally given in Chapter 3, if all the parameters of interest are changing in time, that is, the inference is about x_t given $y_1, \ldots, y_t$, one arrives at the task of filtering.

If the transition distribution from state x_t to state x_{t+1} is linear in the states and corrupted by uncorrelated additive noise centered at 0, this task can be solved exactly by the Kalman filter (Kalman, 1960). The resulting filter is then optimal with respect to the mean squared error. An

especially nice overview of the Kalman filter connecting it with other linear statistical models is Roweis and Ghahramani (1999).

Once the state transition becomes non-linear, as is typically the case, one can use various generalizations of the Kalman filter, such as the extended Kalman filter (EKF), which locally linearizes the transition distribution, or the unscented Kalman filter (Julier and Uhlmann, 1997). These methods come without any optimality guarantees, though. The EKF additionally works best under a very mild non-linearity, due to its first-order approximation.

In recent years, the particle filter (Doucet et al., 2001) has become a popular alternative due to its particularly simple implementation, appealing asymptotic properties and the fact that it allows for the transition model to be arbitrarily non-linear. Since the particle filter is used later in Chapter 3, we postpone a more detailed description there.

If, on the other hand, some of the unknown parameters are static, the task becomes more complex. Blindly applying an MCMC algorithm or any other approximation is not possible, as the likelihood function, on which such algorithms typically depend, cannot be evaluated. The paper Andrieu et al. (2010) introduced the idea of using the particle filter to obtain an estimate of the likelihood, which has been shown in Del Moral (2004) to preserve the stationary distribution of the underlying Markov chain. The resulting algorithm is called *Marginal Metropolis-Hastings*. A more recent overview can be found in the tutorial by Schön et al. (2017).

2.3 Approximate Bayesian Computation

In its original formulation, the method of Approximate Bayesian Computation (ABC) provides a way to approximate the posterior distribution $p(\theta \mid y) \propto f(y \mid \theta)p(\theta)$, assuming that the prior $p(\cdot)$ is fully known, and that the likelihood $f(\cdot \mid \theta)$ can be sampled from, but not evaluated (Rubin et al., 1984; Pritchard et al., 1999). A more recent treatment of ABC methods can be found in Marin et al. (2012).

Briefly, ABC works by simulating a sample $\tilde{\theta}$ from the prior, substituting it to the likelihood, and generating pseudo-observations $\tilde{y}$. These are then compared to the real observations y, and if they are "similar enough", the sample $\tilde{\theta}$ is accepted. Otherwise, it is rejected. The posterior distribution of θ is then given in terms of these random samples $\tilde{\theta}$. This variant is referred to as the accept-reject ABC, for obvious reasons.

In this thesis, we apply the ABC method in place of the particle filter to allow for inference about the static parameter θ when the likelihood is not available. In addition, the use of ABC allows for a possibly misspecified observation model of the SSM, which is often the case, as one may not possess the necessary domain knowledge or computational power needed for the real model. Such a situation has been considered in Jasra (2015), although only through the use of the accept-reject variant given above.

Since accepting a sufficient number of samples may take a long time, an idea is to measure the distance between the true and pseudo-observations through a kernel function. This formulation would not reject any samples — instead, previously rejected samples would get assigned low weights. This has been investigated in Dedecius (2017), along with a proposed way to automatically tune the kernel width. How to exactly apply the ABC method to our problem is addressed in Chapter 4 in detail.

2.4 Applications to molecular biology

Finally, we review works describing how the framework of SSMs and their parameter inference can be applied in the context of bioinformatics, focusing on problems of molecular biology and genetics.

The go-to reference for stochastic modelling in biology is Wilkinson (2011). It contains a broad overview of applications of various probabilistic models to examples from molecular biology and chemistry. Included is a description of the Gillespie algorithm Gillespie (1976, 1977) used to simulate chemical reactions, which we use in Chapter 5.

A recent application of SSMs to molecular biology can be found in Golightly and J Wilkinson (2011), where the authors use the particle filter to approximate the unknown likelihoods of various biological models. We implement these examples in Chapter 5 and compare them with the ABC approximation.

The paper d'Alché Buc et al. (2007) models biological networks, such as gene regulatory networks or signalling pathways, by SSMs, and estimates their parameters. The static parameters of the model are viewed as dynamic states which, however, do not change in time. The unscented Kalman filter is then applied to estimate these "dynamic" parameters. Such approach is simple, as it does not require the use of MCMC algorithms, but comes without the appealing asymptotic properties of MCMC inference.

Wang et al. (2009), Sun et al. (2008) and Zeng et al. (2011) proceed in a similar fashion when estimating the parameters of various biochemical networks. The used models are only mildly nonlinear, and so the extended Kalman filter is sufficient, again without any asymptotic guarantees of identifying the true parameters.

An interesting approach to learning the structure of a gene regulatory network from a gene expression time series can be found in Noor et al. (2012). First, the particle filter is applied to learn the hidden states of the network. Once these hidden states are known, the LASSO regression is applied to learn a sparse representation of the regulatory network, since each gene is assumed to interact only with a small number of other genes.

Chapter 3

Learning the parameters of a state-space model

This chapter describes the state-space model (SSM) formulation we are working with. In Section 3.1, we state our assumptions about the individual probability distributions. Then in Section 3.2, we calculate the posterior distribution of the parameters of interest, and show that straightforward inference is not possible. Further on, we derive a sampler to approximate this distribution. By itself, this sampler is unusable, as it requires the evaluation of the model likelihood. To circumvent this, we introduce the particle filter in Section 3.3. This section gives the definition and some of the properties of the filter. Later in Section 3.4 we show how to use the particle filter to estimate the likelihood, and argue that it does not affect the asymptotic properties of the sampler.

Most of this chapter is based on Andrieu et al. (2010) and Schön et al. (2017).

3.1 State-Space Model definition

The state-space model, often also called the hidden Markov model (HMM) assumes a sequence of latent states $\{\boldsymbol{x}_t\}_{t=0}^{\infty} \subseteq \mathbb{R}^{d_x}$ following a Markov chain, and a sequence of observed variables $\{\boldsymbol{y}_t\}_{t=1}^{\infty} \subseteq \mathbb{R}^{d_y}$. All involved distributions are parameterized by an unknown static parameter $\boldsymbol{\theta} \in \Theta \subset \mathbb{R}^d$.

For a fixed time $T \geq 1$, we use the shorthands $\boldsymbol{x}_{0:T} = \{\boldsymbol{x}_t\}_{t=0}^{T}$ and $\boldsymbol{y}_{1:T} = \{\boldsymbol{y}_t\}_{t=1}^{T}$.

The HMM formulation means that the joint distribution of $\boldsymbol{x}_{0:T}$ and $\boldsymbol{y}_{1:T}$ factorizes, for any $T \geq 1$, into

$$p(\boldsymbol{x}_{0:T}, \boldsymbol{y}_{1:T} \mid \boldsymbol{\theta}) = p(\boldsymbol{x}_0 \mid \boldsymbol{\theta}) \prod_{t=1}^{T} f_t(\boldsymbol{x}_t \mid \boldsymbol{x}_{t-1}, \boldsymbol{\theta}) g_t(\boldsymbol{y}_t \mid \boldsymbol{x}_t, \boldsymbol{\theta}), \tag{3.1}$$

where p is the prior distribution over the initial state, f_t is the transition distribution at time t and g_t is the observation model at time t.

The factorization (3.1) can be written more clearly as

$$\begin{aligned} \boldsymbol{x}_0 \mid \boldsymbol{\theta} &\sim p(\cdot \mid \boldsymbol{\theta}), \\ \boldsymbol{x}_t \mid \boldsymbol{x}_{t-1}, \boldsymbol{\theta} &\sim f_t(\cdot \mid \boldsymbol{x}_{t-1}, \boldsymbol{\theta}), \quad t = 1, \ldots, T, \\ \boldsymbol{y}_t \mid \boldsymbol{x}_t, \boldsymbol{\theta} &\sim g_t(\cdot \mid \boldsymbol{x}_t, \boldsymbol{\theta}), \quad t = 1, \ldots, T. \end{aligned}$$

Finally, in accordance with the Bayesian approach (Robert, 2007), we introduce a prior distribution π over the unknown parameters $\boldsymbol{\theta}$ quantifying our knowledge about $\boldsymbol{\theta}$ before observing any data. This allows us to state the full joint distribution

$$p(\boldsymbol{x}_{0:T}, \boldsymbol{y}_{1:T}, \boldsymbol{\theta}) = p(\boldsymbol{x}_{0:T}, \boldsymbol{y}_{1:T} \mid \boldsymbol{\theta}) \pi(\boldsymbol{\theta}). \tag{3.2}$$

The corresponding graphical model is depicted in Figure 3.1.

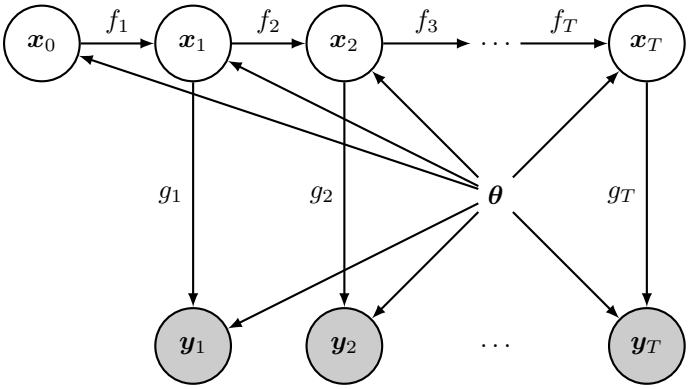

Figure 3.1: Graphical model describing the full joint distribution (3.2). The shaded nodes denote the observed variables, white nodes represent the latent variables.

3.2 Parameter inference

Given an observed sequence $\boldsymbol{y}_{1:T}$, Bayesian inference relies on the joint posterior density

$$p(\boldsymbol{\theta}, \boldsymbol{x}_{0:T} \mid \boldsymbol{y}_{1:T}) = \underbrace{p(\boldsymbol{x}_{0:T} \mid \boldsymbol{\theta}, \boldsymbol{y}_{1:T})}_{\text{State inference}} \underbrace{p(\boldsymbol{\theta} \mid \boldsymbol{y}_{1:T})}_{\text{Parameter inference}}. \tag{3.3}$$

Our primary interest is to perform inference about the static parameter $\boldsymbol{\theta}$. From (3.3), it is clear that to infer about the hidden states $\boldsymbol{x}_{0:T}$, one needs knowledge about $\boldsymbol{\theta}$, so even if the hidden states are of interest, inference about $\boldsymbol{\theta}$ is necessary. Section 3.4 actually shows how to estimate $\boldsymbol{x}_{0:T}$ as a by-product.

Bayesian inference To perform Bayesian inference about $\boldsymbol{\theta}$, we express the posterior of $\boldsymbol{\theta}$ by applying the Bayes theorem:

$$p(\boldsymbol{\theta} \mid \boldsymbol{y}_{1:T}) = \frac{p(\boldsymbol{y}_{1:T} \mid \boldsymbol{\theta})\pi(\boldsymbol{\theta})}{\int p(\boldsymbol{y}_{1:T} \mid \boldsymbol{\theta})\pi(\boldsymbol{\theta}) \,\mathrm{d}\boldsymbol{\theta}}. \tag{3.4}$$

Evaluating the likelihood $p(\boldsymbol{y}_{1:T} \mid \boldsymbol{\theta})$ requires marginalizing over $\boldsymbol{x}_{0:T}$:

$$p(\boldsymbol{y}_{1:T} \mid \boldsymbol{\theta}) = \int p(\boldsymbol{x}_{0:T}, \boldsymbol{y}_{1:T} \mid \boldsymbol{\theta}) \,\mathrm{d}\boldsymbol{x}_{0:T},$$

where $p(\boldsymbol{x}_{0:T}, \boldsymbol{y}_{1:T} \mid \boldsymbol{\theta})$ is given in (3.1). Unless the SSM is linear and Gaussian, such $d_x(T+1)$-dimensional integral is intractable (Andrieu et al., 2010).

Inference under tractable likelihood assumption For the time being, we proceed as if the likelihood was tractable. We derive a sampler for $\boldsymbol{\theta}$ and note which component cannot be evaluated due to the likelihood being present. Section 3.4 then describes the necessary changes to allow circumventing the likelihood evaluation.

Often, the interest is not in the posterior $p(\boldsymbol{\theta} \mid \boldsymbol{y}_{1:T})$ itself, but on the expectation of some function ϕ w.r.t. this distribution, i.e. on

$$\mathbb{E}_{p(\boldsymbol{\theta}|\boldsymbol{y}_{1:T})}[\phi(\boldsymbol{\theta})] = \int \phi(\boldsymbol{\theta}) p(\boldsymbol{\theta} \mid \boldsymbol{y}_{1:T}) \,\mathrm{d}\boldsymbol{\theta}. \tag{3.5}$$

We use the Metropolis-Hastings algorithm (Metropolis et al., 1953; Hastings, 1970) to obtain M samples from $p(\boldsymbol{\theta} \mid \boldsymbol{y}_{1:T})$, denoted as $\boldsymbol{\theta}^{(m)}$, $m = 1, \ldots, M$. The integral (3.5) is then approximated as the arithmetic mean

$$\frac{1}{M} \sum_{m=1}^{M} \phi(\boldsymbol{\theta}^{(m)}).$$

An appealing property of the Metropolis-Hastings algorithm is that such arithmetic mean converges to (3.5) almost surely (Robert and Casella, 2005), i.e.

$$\frac{1}{M} \sum_{m=1}^{M} \phi(\boldsymbol{\theta}^{(m)}) \xrightarrow{a.s} \int \phi(\boldsymbol{\theta}) p(\boldsymbol{\theta} \mid \boldsymbol{y}_{1:T}) \,\mathrm{d}\boldsymbol{\theta},$$

where $\xrightarrow{a.s.}$ denotes almost sure convergence.

Finally, we note that if one is indeed interested in the distribution $p(\boldsymbol{\theta} \mid \boldsymbol{y}_{1:T})$ itself, it can be recovered by the empirical distribution

$$\widehat{p}(\boldsymbol{\theta} \mid \boldsymbol{y}_{1:T}) = \frac{1}{M} \sum_{m=1}^{M} \delta_{\boldsymbol{\theta}^{(m)}}(\boldsymbol{\theta}),$$

where δ denotes the Dirac distribution. This estimate can be additionally smoothed using kernel methods (Wand and Jones, 1994).

Metropolis-Hastings algorithm The Metropolis-Hastings algorithm is described in Algorithm 1. Although well-known, it is included for comparison with the variant introduced in Section 3.4.

The target distribution is the parameter posterior $p(\boldsymbol{\theta} \mid \boldsymbol{y}_{1:T}) \propto p(\boldsymbol{y}_{1:T} \mid \boldsymbol{\theta})\pi(\boldsymbol{\theta})$. In this case, it is not necessary to evaluate the normalizing constant, since it gets cancelled out.

The algorithm further requires a proposal distribution q. Similarly to the prior π, it is problem-dependent, and must be selected carefully.

Algorithm 1 Metropolis-Hastings

Input: Number of samples M, $\{\boldsymbol{y}_1, \ldots, \boldsymbol{y}_T\}$

1: Initialize $\boldsymbol{\theta}^{(0)}$.
2: **for** $m = 1$ **to** M **do**
3: Sample $\boldsymbol{\theta}' \sim q(\cdot \mid \boldsymbol{\theta}^{(m-1)})$.
4: Calculate the aceptance probability

$$\alpha = \min\left\{1, \frac{p(\boldsymbol{y}_{1:T} \mid \boldsymbol{\theta}')\pi(\boldsymbol{\theta}')}{p(\boldsymbol{y}_{1:T} \mid \boldsymbol{\theta}^{(m-1)})\pi(\boldsymbol{\theta}^{(m-1)})} \frac{q(\boldsymbol{\theta}^{(m-1)} \mid \boldsymbol{\theta}')}{q(\boldsymbol{\theta}' \mid \boldsymbol{\theta}^{(m-1)})}\right\}. \tag{3.6}$$

5: Sample $u \sim \mathcal{U}(0, 1)$.
6: **if** $u \leq \alpha$ **then**
7: $\boldsymbol{\theta}^{(m)} \leftarrow \boldsymbol{\theta}'$ ▷ With probability α, accept the proposed sample.
8: **else**
9: $\boldsymbol{\theta}^{(m)} \leftarrow \boldsymbol{\theta}^{(m-1)}$ ▷ With probability $1 - \alpha$, reject the proposed sample.
10: **end if**
11: **end for**

Output: $\left\{\boldsymbol{\theta}^{(1)}, \ldots, \boldsymbol{\theta}^{(M)}\right\}$

We see that the acceptance probability (3.6) cannot be calculated, as it depends on the intractable likelihood $p(\boldsymbol{y}_{1:T} \mid \boldsymbol{\theta})$. In Section 3.4, we give a modified variant of the Metropolis-Hastings algorithm, where the likelihood is approximated using the particle filter. The derivation of this filter is the content of the next section.

3.3 The particle filter

The particle filter (Doucet et al., 2001) is a method for approximating the filtering distribution $p(\boldsymbol{x}_t \mid \boldsymbol{y}_{1:t}, \boldsymbol{\theta})$ using a finite number of samples called particles. The algorithm is also known as sequential Monte Carlo or sequential importance sampling. The latter name sheds some light on how the method works, and it is exactly through importance sampling that the particle filter is derived.

Importance sampling Here we briefly review the basic idea behind importance sampling. For a more thorough treatment, the reader is referred to MacKay (2002) or Robert and Casella (2005).

Consider a situation where the expectation of some function ϕ w.r.t. the distribution with density p,

$$\Phi \coloneqq \mathbb{E}_p[\phi(\boldsymbol{X})] = \int \phi(\boldsymbol{x})p(\boldsymbol{x}) \, \mathrm{d}\boldsymbol{x}, \tag{3.7}$$

is of interest. Assume that the integral is analytically intractable, and that one cannot generate samples from p to approximate this expectation. Assume further that the density p can be

evaluated, at least up to a multiplicative constant, i.e. that it takes the form

$$p(\boldsymbol{x}) = \frac{p^*(\boldsymbol{x})}{Z},$$

where Z is an unknown normalizing constant, and p^* can be evaluated. Such situation frequently arises in Bayesian statistics, where a posterior distribution of interest $p(\boldsymbol{\theta} \mid \boldsymbol{x}) = \frac{p(\boldsymbol{x}|\boldsymbol{\theta})p(\boldsymbol{\theta})}{\int p(\boldsymbol{x}|\boldsymbol{\theta})p(\boldsymbol{\theta})\,\mathrm{d}\boldsymbol{\theta}}$ is given in terms of the Bayes theorem. The normalizing constant in the denominator is often unavailable in analytic form. However, the numerator can be evaluated.

Next, we introduce a (typically simpler) distribution with probability density $q(\boldsymbol{x}) = \frac{q^*(\boldsymbol{x})}{Z_Q}$ such that

1. One can sample from q;
2. One can evaluate q^*;
3. $p(\boldsymbol{x}) > 0$ implies $q(\boldsymbol{x}) > 0$.

The expectation (3.7) can then be written as

$$\Phi = \int \phi(\boldsymbol{x}) \frac{q(\boldsymbol{x})}{q(\boldsymbol{x})} p(\boldsymbol{x})\,\mathrm{d}\boldsymbol{x} = \int \phi(\boldsymbol{x}) \underbrace{\frac{p(\boldsymbol{x})}{q(\boldsymbol{x})}}_{w^*(\boldsymbol{x})} q(\boldsymbol{x})\,\mathrm{d}\boldsymbol{x} = \mathbb{E}_q[\phi(\boldsymbol{X}) w^*(\boldsymbol{X})],$$

where $w^*(\boldsymbol{x})$ are called the importance weights. By defining $w(\boldsymbol{x}) = \frac{p^*(\boldsymbol{x})}{q^*(\boldsymbol{x})}$, Φ can be approximated by

$$\Phi \approx \widehat{\Phi} \coloneqq \frac{\sum_{i=1}^N \phi(\boldsymbol{x}^{(i)}) w(\boldsymbol{x}^{(i)})}{\sum_{i=1}^N w(\boldsymbol{x}^{(i)})}, \quad \boldsymbol{x}^{(1)}, \ldots, \boldsymbol{x}^{(N)} \overset{iid}{\sim} q.$$

We note that by using w instead of w^* and normalizing by the weights sum instead of the sample size N, we bypass the evaluation of Z and Z_Q, since they cancel out. The importance weights here account for correcting the discrepancy between the distribution q and the true distribution p.

The estimator $\widehat{\Phi}$ converges to the true expectation Φ as $N \to \infty$. However, it is not necessarily unbiased (MacKay, 2002).

Sequential importance sampling (SIS) The SIS algorithm uses a weighted set of particles $\left\{\left(\boldsymbol{x}_t^{(i)}, w_t^{(i)}\right) : i = 1, \ldots, N\right\}$, to represent the filtering distribution $p(\boldsymbol{x}_t \mid \boldsymbol{y}_{1:t}, \boldsymbol{\theta})$. To simplify notation, we write $w_t^{(i)}$ instead of $w_t(\boldsymbol{x}^{(i)})$ from now on. The empirical approximation to $p(\boldsymbol{x}_t \mid \boldsymbol{y}_{1:t}, \boldsymbol{\theta})$ is then

$$\widehat{p}(\boldsymbol{x}_t \mid \boldsymbol{y}_{1:t}, \boldsymbol{\theta}) = \frac{\sum_{i=1}^N w_t^{(i)} \delta_{\boldsymbol{x}_t^{(i)}}(\boldsymbol{x}_t)}{\sum_{i=1}^N w_t^{(i)}}.$$

As the name suggests, the algorithm involves a sequential application of the importance sampling procedure with increasing time t.

Returning to the SSM (3.1), we consider the posterior distribution of a sequence of states $\boldsymbol{x}_{0:t}$ given a sequence of observations $\boldsymbol{y}_{1:t}$. By application of the Bayes theorem, we obtain the following recursive formula:

$$\begin{aligned} p(\boldsymbol{x}_{0:t} \mid \boldsymbol{y}_{1:t}) &\propto p(\boldsymbol{y}_t \mid \boldsymbol{x}_{0:t}, \boldsymbol{y}_{1:t-1}) p(\boldsymbol{x}_{0:t} \mid \boldsymbol{y}_{1:t-1}) \\ &= g_t(\boldsymbol{y}_t \mid \boldsymbol{x}_t) p(\boldsymbol{x}_t \mid \boldsymbol{x}_{0:t-1}, \boldsymbol{y}_{1:t-1}) p(\boldsymbol{x}_{0:t-1} \mid \boldsymbol{y}_{1:t-1}) \\ &= g_t(\boldsymbol{y}_t \mid \boldsymbol{x}_t) f_t(\boldsymbol{x}_t \mid \boldsymbol{x}_{t-1}) p(\boldsymbol{x}_{0:t-1} \mid \boldsymbol{y}_{1:t-1}), \end{aligned}$$

where the equalities follow from the hidden Markov model independence assumptions. For better clarity, we suppress the static parameter $\boldsymbol{\theta}$ from the conditioning.

For the target $p(\boldsymbol{x}_{0:t} \mid \boldsymbol{y}_{1:t})$, we introduce the importance sampling distribution $q(\boldsymbol{x}_{0:t} \mid \boldsymbol{y}_{1:t})$ and sample $\boldsymbol{x}_{0:t}^{(i)}$ from it. The importance weights are (up to normalization) given by

$$\begin{aligned} w_t^{(i)} &\propto \frac{p(\boldsymbol{x}_{0:t}(i) \mid \boldsymbol{y}_{1:t})}{q(\boldsymbol{x}_{0:t}^{(i)} \mid \boldsymbol{y}_{1:t})} \\ &\propto \frac{g_t(\boldsymbol{y}_t \mid \boldsymbol{x}_t^{(i)}) f_t(\boldsymbol{x}_t^{(i)} \mid \boldsymbol{x}_{t-1}^{(i)}) p(\boldsymbol{x}_{0:t-1}^{(i)} \mid \boldsymbol{y}_{1:t-1})}{q(\boldsymbol{x}_{0:t}^{(i)} \mid \boldsymbol{y}_{1:t})}. \end{aligned} \tag{3.8}$$

By definition of the conditional probability and the hidden Markov model assumptions, we can write the importance sampling distribution as

$$q(\boldsymbol{x}_{0:t} \mid \boldsymbol{y}_{1:t}) = q(\boldsymbol{x}_t \mid \boldsymbol{x}_{0:t-1}, \boldsymbol{y}_{1:t}) q(\boldsymbol{x}_{0:t-1} \mid \boldsymbol{y}_{1:t-1}).$$

By substituting into (3.8), we obtain the following recursion:

$$\begin{aligned} w_t^{(i)} &\propto \frac{g_t(\boldsymbol{y}_t \mid \boldsymbol{x}_t^{(i)}) f_t(\boldsymbol{x}_t^{(i)} \mid \boldsymbol{x}_{t-1}^{(i)})}{q(\boldsymbol{x}_t^{(i)} \mid \boldsymbol{x}_{0:t-1}^{(i)}, \boldsymbol{y}_{1:t})} \frac{p(\boldsymbol{x}_{0:t-1}^{(i)} \mid \boldsymbol{y}_{1:t-1})}{q(\boldsymbol{x}_{0:t-1}^{(i)} \mid \boldsymbol{y}_{1:t-1})} \\ &\propto \frac{g_t(\boldsymbol{y}_t \mid \boldsymbol{x}_t^{(i)}) f_t(\boldsymbol{x}_t^{(i)} \mid \boldsymbol{x}_{t-1}^{(i)})}{q(\boldsymbol{x}_t^{(i)} \mid \boldsymbol{x}_{0:t-1}^{(i)}, \boldsymbol{y}_{1:t})} w_{t-1}^{(i)}. \end{aligned} \tag{3.9}$$

So updating the ith weight when transitioning from time $t-1$ to t is a relatively simple task involving only multiplication by the first fraction in (3.9).

The sequential importance sampling algorithm is summarized in Algorithm 2. This by itself is

Algorithm 2 Sequential Importance Sampling

Input: Number of particles N, current parameter value $\boldsymbol{\theta}$, $\{\boldsymbol{y}_1, \ldots, \boldsymbol{y}_T\}$

1: Sample $\boldsymbol{x}_0^{(i)} \sim p(\cdot \mid \boldsymbol{\theta}), \quad i = 1, \ldots, N.$ ▷ Initialize N particles.
2: $w_0^{(i)} \leftarrow \frac{1}{N}, \quad i = 1, \ldots, N.$ ▷ Initialize uniform weights.
3: **for** $t = 1$ **to** T **do**
4: Sample $\boldsymbol{x}_t^{(i)} \sim q(\cdot \mid \boldsymbol{x}_{0:t-1}^{(i)}, \boldsymbol{y}_{1:t}, \boldsymbol{\theta}), \quad i = 1, \ldots, N.$ ▷ Sample N new particles.
5: Set $w_t^{(i)} \propto \frac{g_t(\boldsymbol{y}_t \mid \boldsymbol{x}_t^{(i)}, \boldsymbol{\theta}) f_t(\boldsymbol{x}_t^{(i)} \mid \boldsymbol{x}_{t-1}^{(i)}, \boldsymbol{\theta})}{q(\boldsymbol{x}_t^{(i)} \mid \boldsymbol{x}_{0:t-1}^{(i)}, \boldsymbol{y}_{1:t}, \boldsymbol{\theta})} w_{t-1}^{(i)}, \quad i = 1, \ldots, N.$ ▷ Update the weights as per (3.9).
6: **end for**

almost the particle filter. There are still two issues to be addressed, though. First, the problem of weight degeneracy discussed in the next paragraph. Second, the choice of the importance sampling distribution q addressed later.

Resampling A serious problem preventing the use of the SIS algorithm is that the weights degenerate over time. In each time step, the variance of the weights reduces (Doucet et al., 2001). This means that the (normalized) weights always converge to a situation where a single weight is 1 and the others are 0.

To alleviate this, the following resampling step is introduced.

Algorithm 3 Multinomial resampling

Input: Importance weights $w_t^{(1)}, \ldots, w_t^{(N)}$, particles $\boldsymbol{x}_t^{(1)}, \ldots, \boldsymbol{x}_t^{(N)}$.

1: $\widetilde{w}_t^{(i)} \leftarrow \frac{w_t^{(i)}}{\sum_{j=1}^N w_t^{(j)}}, \quad i = 1, \ldots, N.$ ▷ Normalize the weights.
2: Sample a_i s.t. $\mathbb{P}(a_i = j) = \widetilde{w}_t^{(j)}, \quad i, j = 1, \ldots, N.$ ▷ Sample indices with replacement.
3: $w_t^{(a_i)} \leftarrow \frac{1}{N}, \quad i = 1, \ldots, N.$ ▷ Reset weights.

Output: Resampled particles $\boldsymbol{x}_t^{(a_1)}, \ldots, \boldsymbol{x}_t^{(a_N)}$ and weights $w_t^{(a_1)}, \ldots, w_t^{(a_N)}$.

The normalized importance weights are interpreted as a probability vector of a categorical distribution. The particles are then resampled (sampled with replacement) according to this distribution. This effectively selects a population of "strong individuals" for the next time step.

The above described procedure is known as multinomial resampling. There are other, more complex, approaches, such as stratified resampling (Douc and Cappe, 2005) which further reduce the variance of the weights, at the cost of added computational complexity.

The particle filter The remaining step is the choice of the importance sampling distribution q. Obviously, the more similar this distribution is to the target, the closer approximation we obtain.

The particle filter arises when the transition distribution f_t is chosen as the importance distribution, that is, when

$$q(\boldsymbol{x}_t \mid \boldsymbol{x}_{0:t-1}, \boldsymbol{y}_{1:t}, \boldsymbol{\theta}) = f_t(\boldsymbol{x}_t \mid \boldsymbol{x}_{t-1}, \boldsymbol{\theta}).$$

The importance weights (3.9) then simplify into

$$w_t^{(i)} \propto g_t(\boldsymbol{y}_t \mid \boldsymbol{x}_t^{(i)}) w_{t-1}^{(i)}. \tag{3.10}$$

This form of q is not optimal (the target) distribution. It is however "close" to it. The optimal distribution would be $q(\boldsymbol{x}_t \mid \boldsymbol{x}_{0:t-1}, \boldsymbol{y}_{1:t}, \boldsymbol{\theta}) = p(\boldsymbol{x}_t \mid \boldsymbol{x}_{t-1}, \boldsymbol{y}_t, \boldsymbol{\theta})$, due to factorization assumptions of the SSM (3.1). Calculating it would involve marginalization over $\boldsymbol{x}_t$,

$$p(\boldsymbol{x}_t \mid \boldsymbol{x}_{t-1}, \boldsymbol{y}_t, \boldsymbol{\theta}) = \frac{p(\boldsymbol{x}_t, \boldsymbol{y}_t \mid \boldsymbol{x}_{t-1}, \boldsymbol{\theta})}{\int p(\boldsymbol{x}_t, \boldsymbol{y}_t \mid \boldsymbol{x}_{t-1}, \boldsymbol{\theta}) \, \mathrm{d}\boldsymbol{x}_t} = \frac{f_t(\boldsymbol{x}_t \mid \boldsymbol{x}_{t-1}, \boldsymbol{\theta}) g_t(\boldsymbol{y}_t \mid \boldsymbol{x}_t, \boldsymbol{\theta})}{\int f_t(\boldsymbol{x}_t \mid \boldsymbol{x}_{t-1}, \boldsymbol{\theta}) g_t(\boldsymbol{y}_t \mid \boldsymbol{x}_t, \boldsymbol{\theta}) \, \mathrm{d}\boldsymbol{x}_t},$$

which is generally not possible.

The particle filter is summarized in Algorithm 4. The algorithm is called *bootstrap* particle

Algorithm 4 Bootstrap particle filter

Input: Number of particles N, current parameter value $\boldsymbol{\theta}$, $\{\boldsymbol{y}_1, \ldots, \boldsymbol{y}_T\}$

1: Sample $\boldsymbol{x}_0^{(i)} \sim p(\cdot \mid \boldsymbol{\theta}), \quad i = 1, \ldots, N.$ ▷ Initialize N particles.
2: $w_0^{(i)} \leftarrow \frac{1}{N}, \quad i = 1, \ldots, N.$ ▷ Initialize uniform weights.
3: **for** $t = 1$ **to** T **do**
4: Sample $\boldsymbol{x}_t^{(i)} \sim f_t(\boldsymbol{x}_t \mid \boldsymbol{x}_{t-1}, \boldsymbol{\theta}), \quad i = 1, \ldots, N.$ ▷ Sample N new particles.
5: Set $w_t^{(i)} \propto g_t(\boldsymbol{y}_t \mid \boldsymbol{x}_t^{(i)}, \boldsymbol{\theta}) w_{t-1}^{(i)}, \quad i = 1, \ldots, N.$ ▷ Update the weights as per (3.10).
6: Resample $\boldsymbol{x}_t^{(i)}$ and reset $w_t^{(i)}$ using Algorithm 3, $\quad i = 1, \ldots, N.$
7: **end for**

filter, due to resemblance of the resampling step to the non-parametric bootstrap (Efron, 1979).

3.4 Using the particle filter to estimate the likelihood

As mentioned in Section 3.3 is typically used to approximate the filtering distribution $p(\boldsymbol{x}_t \mid \boldsymbol{y}_{1:t}, \boldsymbol{\theta})$. However, we use it to provide a tractable approximation to the likelihood $p(\boldsymbol{y}_{1:T} \mid \boldsymbol{\theta})$ such that it does not affect the limiting distribution of the Markov chain used in the Metropolis-Hastings algorithm. This section describes how it is done, and gives the resulting variant of the Metropolis-Hastings algorithm.

Suppose that we are in possession of an estimator $\widehat{z}$ of the likelihood $p(\boldsymbol{y}_{1:T} \mid \boldsymbol{\theta})$. As such, it necessarily depends on $\boldsymbol{y}_{1:T}$ and $\boldsymbol{\theta}$. Since we aim to use the particle filter to calculate $\widehat{z}$, the estimator also depends on the importance weights. This makes the estimator a random variable with some distribution denoted $\psi(z \mid \boldsymbol{\theta}, \boldsymbol{y}_{1:T})$.

We now return to our model (3.4) and introduce $\widehat{z}$ as an auxiliary variable, along with our variable of interest $\boldsymbol{\theta}$. This changes the target distribution from $p(\boldsymbol{\theta} \mid \boldsymbol{y}_{1:T})$ to

$$\psi(\boldsymbol{\theta}, z \mid \boldsymbol{y}_{1:T}) = p(\boldsymbol{\theta} \mid \boldsymbol{y}_{1:T}) \psi(z \mid \boldsymbol{\theta}, \boldsymbol{y}_{1:T}) = \frac{p(\boldsymbol{y}_{1:T} \mid \boldsymbol{\theta}) p(\boldsymbol{\theta})}{p(\boldsymbol{y}_{1:T})} \psi(z \mid \boldsymbol{\theta}, \boldsymbol{y}_{1:T}). \tag{3.11}$$

In theory, we could now construct a Metropolis-Hastings algorithm with $\psi(\boldsymbol{\theta}, z \mid \boldsymbol{y}_{1:T})$ as the target, instead of $p(\boldsymbol{\theta} \mid \boldsymbol{y}_{1:T})$ as was the case in Algorithm 1. However, this would not solve our problem, since calculating the acceptance ratio still requires the calculation of the likelihood $p(\boldsymbol{y}_{1:T} \mid \boldsymbol{\theta})$, as (3.11) makes clear.

Instead, we define a new target distribution over $(\boldsymbol{\theta}, \widehat{z})$ by replacing the likelihood in (3.11) by its estimate $\widehat{z}$:

$$\pi(\boldsymbol{\theta}, z \mid \boldsymbol{y}_{1:T}) \coloneqq \frac{z p(\boldsymbol{\theta})}{p(\boldsymbol{y}_{1:T})} \psi(z \mid \boldsymbol{\theta}, \boldsymbol{y}_{1:T}). \tag{3.12}$$

There are of course some conditions imposed on $\pi(\boldsymbol{\theta}, z \mid \boldsymbol{y}_{1:T})$ for it to be useful:

1. $\pi(\boldsymbol{\theta}, z \mid \boldsymbol{y}_{1:T})$ must be non-negative for all $(\boldsymbol{\theta}, z)$;
2. $\pi(\boldsymbol{\theta}, z \mid \boldsymbol{y}_{1:T})$ must integrate to 1;
3. the marginal distribution of $\pi(\boldsymbol{\theta}, z \mid \boldsymbol{y}_{1:T})$ for $\boldsymbol{\theta}$ must be the original target $p(\boldsymbol{\theta} \mid \boldsymbol{y}_{1:T})$.

The first two conditions simply state that π is a valid probability distribution. The third condition ensures that by constructing a Metropolis-Hastings algorithm with π as the target, the original target distribution is preserved once the auxiliary variables are marginalized out. All three conditions are satisfied is $\widehat{z}$ is a non-negative unbiased estimator of the likelihood $p(\boldsymbol{y}_{1:T} \mid \boldsymbol{\theta})$. This is shown as follows.

1. Non-negativity of π follows from the assumed non-negativity of the estimator $\widehat{z}$ and validity of the distributions in (3.12).

2, 3. Assume that $\widehat{z}$ is an unbiased estimate of $p(\boldsymbol{y}_{1:T} \mid \boldsymbol{\theta})$, i.e. that $\mathbb{E}_\psi[\widehat{z}] = p(\boldsymbol{y}_{1:T} \mid \boldsymbol{\theta})$. Consider now the marginal of π for $\boldsymbol{\theta}$:

$$\begin{aligned}\int \pi(\boldsymbol{\theta}, z \mid \boldsymbol{y}_{1:T}) \,\mathrm{d}z &= \frac{p(\boldsymbol{\theta})}{p(\boldsymbol{y}_{1:T})} \int z\psi(z \mid \boldsymbol{\theta}, \boldsymbol{y}_{1:T}) \,\mathrm{d}z \\ &= \frac{p(\boldsymbol{\theta})}{p(\boldsymbol{y}_{1:T})} \mathbb{E}_\psi[\widehat{z}] \\ &= \frac{p(\boldsymbol{\theta})}{p(\boldsymbol{y}_{1:T})} p(\boldsymbol{y}_{1:T} \mid \boldsymbol{\theta}) \\ &= p(\boldsymbol{\theta} \mid \boldsymbol{y}_{1:T}),\end{aligned} \tag{3.13}$$

the original target distribution. This satisfies condition 3. For condition 2, we simply integrate (3.13) w.r.t. $\boldsymbol{\theta}$, which results in 1 due to $p(\boldsymbol{\theta} \mid \boldsymbol{y}_{1:T})$ being a valid probability distribution.

Chapter 4

Approximate Bayesian Computation

Chapter 5

Applications

5.1 Preliminary: the Gillespie algorithm

5.2 Lotka-Volterra model

5.3 Prokaryotic auto-regulation model

Chapter 6

Conclusion and future work

Bibliography

C. Andrieu, A. Doucet, and R. Holenstein. Particle markov chain monte carlo methods (with discussion). *Journal of the Royal Statistical Society, Series B*, 72:1–33, 01 2010.

G. E. Box. Robustness in the strategy of scientific model building. In *Robustness in statistics*, pages 201–236. Elsevier, 1979.

F. d'Alché Buc, M. Quach, and N. Brunel. Estimating parameters and hidden variables in non-linear state-space models based on ODEs for biological networks inference. *Bioinformatics*, 23 (23):3209–3216, 12 2007. ISSN 1367-4803. doi: 10.1093/bioinformatics/btm510. URL `https://doi.org/10.1093/bioinformatics/btm510`.

K. Dedecius. Adaptive kernels in approximate filtering of state-space models. *International Journal of Adaptive Control and Signal Processing*, 31(6):938–952, 2017. doi: 10.1002/acs.2739. URL `https://onlinelibrary.wiley.com/doi/abs/10.1002/acs.2739`.

P. Del Moral. *Feynman-Kac Formulae: Genealogical and Interacting Particle Systems With Applications*, volume 100. 05 2004. ISBN 0387202684. doi: 10.1007/978-1-4684-9393-1.

R. Douc and O. Cappe. Comparison of resampling schemes for particle filtering. pages 64 – 69, 10 2005. ISBN 953-184-089-X. doi: 10.1109/ISPA.2005.195385.

A. Doucet, A. Smith, N. de Freitas, and N. Gordon. *Sequential Monte Carlo Methods in Practice*. Information Science and Statistics. Springer New York, 2001. ISBN 9780387951461. URL `https://books.google.cz/books?id=uxX-koqKtMMC`.

B. Efron. Bootstrap methods: Another look at the jackknife. *The Annals of Statistics*, 7(1):1–26, 1979.

D. T. Gillespie. A General Method for Numerically Simulating the Stochastic Time Evolution of Coupled Chemical Reactions. *Journal of Computational Physics*, 22:403–434, Dec. 1976. doi: 10.1016/0021-9991(76)90041-3.

D. T. Gillespie. Exact stochastic simulation of coupled chemical reactions. *The Journal of Physical Chemistry*, 81(25):2340–2361, 1977. doi: 10.1021/j100540a008. URL `https://doi.org/10.1021/j100540a008`.

A. Golightly and D. J Wilkinson. Bayesian parameter inference for stochastic biochemical network models using particle markov chain monte carlo. *Interface focus*, 1:807–20, 12 2011. doi: 10.1098/rsfs.2011.0047.

W. K. Hastings. Monte carlo sampling methods using markov chains and their applications. *Biometrika*, 57(1):97–109, 1970. doi: 10.1093/biomet/57.1.97. URL `http://biomet.oxfordjournals.org/cgi/content/abstract/57/1/97`.

A. Jasra. Approximate bayesian computation for a class of time series models. *International Statistical Review*, 83(3):405–435, 2015. doi: 10.1111/insr.12089. URL `https://onlinelibrary.wiley.com/doi/abs/10.1111/insr.12089`.

S. J. Julier and J. K. Uhlmann. A new extension of the kalman filter to nonlinear systems. pages 182–193, 1997.

R. Kalman. A new approach to linear filtering and prediction problems. *Journal of Basic Engineering (ASME)*, 82D:35–45, 01 1960. doi: 10.1115/1.3662552.

D. J. C. MacKay. *Information Theory, Inference & Learning Algorithms*. Cambridge University Press, New York, NY, USA, 2002. ISBN 0521642981.

J.-M. Marin, P. Pudlo, C. P. Robert, and R. J. Ryder. Approximate bayesian computational methods. *Statistics and Computing*, 22(6):1167–1180, 2012.

N. Metropolis, A. W. Rosenbluth, M. N. Rosenbluth, A. H. Teller, and E. Teller. Equation of state calculations by fast computing machines. *The journal of chemical physics*, 21(6):1087–1092, 1953.

A. Noor, E. Serpedin, M. N. Nounou, and H. N. Nounou. Inferring gene regulatory networks via nonlinear state-space models and exploiting sparsity. *IEEE/ACM Transactions on Computational Biology and Bioinformatics*, 9:1203–1211, 2012.

J. K. Pritchard, M. T. Seielstad, A. Perez-Lezaun, and M. W. Feldman. Population growth of human y chromosomes: a study of y chromosome microsatellites. *Molecular biology and evolution*, 16(12):1791–1798, 1999.

C. Robert. *The Bayesian choice: from decision-theoretic foundations to computational implementation*. Springer Science & Business Media, 2007.

C. P. Robert and G. Casella. *Monte Carlo Statistical Methods (Springer Texts in Statistics)*. Springer-Verlag, Berlin, Heidelberg, 2005. ISBN 0387212396.

S. Roweis and Z. Ghahramani. A unifying review of linear gaussian models. *Neural Comput.*, 11(2):305–345, Feb. 1999. ISSN 0899-7667. doi: 10.1162/089976699300016674. URL `http://dx.doi.org/10.1162/089976699300016674`.

D. B. Rubin et al. Bayesianly justifiable and relevant frequency calculations for the applied statistician. *The Annals of Statistics*, 12(4):1151–1172, 1984.

T. Schön, A. Lindholm, L. Murray, and F. Lindsten. Probabilistic learning of nonlinear dynamical systems using sequential monte carlo. *Mechanical Systems and Signal Processing*, 03 2017. doi: 10.1016/j.ymssp.2017.10.033.

X. Sun, L. X. Jin, and M. Xiong. Extended kalman filter for estimation of parameters in nonlinear state-space models of biochemical networks. *PLoS ONE*, 3:1220 – 4, 2008.

M. Wand and M. Jones. *Kernel Smoothing*. Chapman & Hall/CRC Monographs on Statistics & Applied Probability. Taylor & Francis, 1994. ISBN 9780412552700. URL `https://books.google.cz/books?id=GTOOi5yE008C`.

Z. Wang, X. Liu, Y. Liu, J. Liang, and V. Vinciotti. An extended kalman filtering approach to modeling nonlinear dynamic gene regulatory networks via short gene expression time series. *IEEE/ACM transactions on computational biology and bioinformatics / IEEE, ACM*, 6:410–9, 07 2009. doi: 10.1109/TCBB.2009.5.

D. Wilkinson. *Stochastic Modelling for Systems Biology, Second Edition*. Chapman & Hall/CRC Mathematical and Computational Biology. Taylor & Francis, 2011. ISBN 9781439837726. URL `https://books.google.cz/books?id=G3BaHtBrW68C`.

N. Zeng, Z. Wang, Y. Li, M. Du, and X. Liu. Inference of nonlinear state-space models for sandwich-type lateral flow immunoassay using extended kalman filtering. *IEEE Transactions on Biomedical Engineering*, 58:1959–1966, 2011.