Master Thesis

Bayesian Parameter Estimation of State-Space Models with Intractable Likelihood

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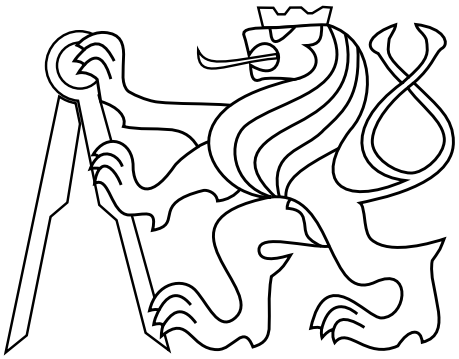

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ZADÁNÍ DIPLOMOVÉ PRÁCE

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:

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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.

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

$$\boldsymbol{x}_0 \mid \boldsymbol{\theta} \sim p(\cdot \mid \boldsymbol{\theta}), \tag{3.2}$$

$$\boldsymbol{x}_t \mid \boldsymbol{x}_{t-1}, \boldsymbol{\theta} \sim f_t(\cdot \mid \boldsymbol{x}_{t-1}, \boldsymbol{\theta}), \quad t = 1, \ldots, T, \tag{3.3}$$

$$\boldsymbol{y}_t \mid \boldsymbol{x}_t, \boldsymbol{\theta} \sim g_t(\cdot \mid \boldsymbol{x}_t, \boldsymbol{\theta}), \quad t = 1, \ldots, T. \tag{3.4}$$

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

$$p(\boldsymbol{x}_{0:T}, \boldsymbol{y}_{1:T}, \boldsymbol{\theta}) = p(\boldsymbol{x}_{0:T}, \boldsymbol{y}_{1:T} \mid \boldsymbol{\theta}) \pi(\boldsymbol{\theta}). \tag{3.5}$$

The corresponding graphical model is depicted in Figure 3.1.

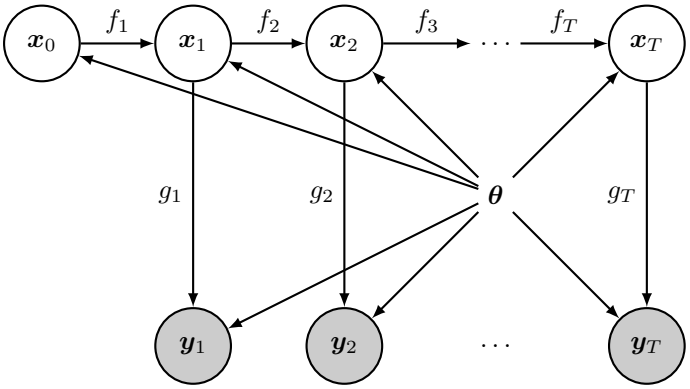

Figure 3.1: Graphical model describing the full joint distribution (3.5). The shaded nodes denote the observed variables, white nodes represent the latent variables.

3.2 Parameter inference

3.3 The particle filter

3.4 Using the particle filter to estimate likelihood

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

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