Simulation based sequential Monte Carlo methods for discretely observed Markov processes

Peter Neal

April 17, 2014

Abstract

Parameter estimation for discretely observed Markov processes is a challenging problem. However, simulation of Markov processes is straightforward using the Gillespie algorithm. We exploit this ease of simulation to develop an effective sequential Monte Carlo (SMC) algorithm for obtaining samples from the posterior distribution of the parameters. In particular, we introduce two key innovations, coupled simulations, which allow us to study multiple parameter values on the basis of a single simulation, and a simple, yet effective, importance sampling scheme for steering simulations towards the observed data. These innovations substantially improve the efficiency of the SMC algorithm with minimal effect on the speed of the simulation process. The SMC algorithm is successfully applied to two examples, a Lotka-Volterra model and a Repressilator model.

Keywords: Markov process; sequential Monte Carlo; coupling; importance sampling; simulation.

1 Introduction

Markov processes are used to model a wide range of biological systems, for example, epidemic models (Bailey (1975)), predator-prey models (Boys et al. (2008)) and gene regulatory systems (Toni et al. (2009)). The above are examples of individual-based compartmental models, where the system spends an exponentially distributed length of time in the current state before making a transition to a new state. Both the mean length of stay in the current state and the probability of transition to a particular new state are only dependent upon the current state of the system and the model parameters.

Parameter estimation for Markov processes is straightforward if the entire continuous time process is observed. However, this is rarely the case with the system often observed at a discrete collection of points with either complete or partial observations of the system occurring at the observation points. Observation of the process at a discrete set of points does not yield a tractable likelihood for parameter estimation. One solution in a Bayesian context is to use data augmentation MCMC (Markov chain Monte
Carlo), see for example Boys et al. (2008). However, the data augmentation MCMC algorithm will often require large scale data imputation since typically many events, possibly running into the hundreds or thousands, will have taken place between each pair of observations. This can often result in poor mixing of the MCMC algorithm given the strong correlation between the model parameters and the imputed data.

It is necessary to consider alternatives to data augmentation MCMC. Assuming that the number of individuals in each of the compartments is relatively large, the Markov process can be approximated by a system of ordinary differential equations (ode), with a diffusive limit about the ode solution, Kurtz (1971). This has been exploited to create diffusion and linear noise approximation algorithms, see for example Golightly and Wilkinson (2011) and Fearnhead et al. (2014). However, there are many biological systems, including the gene regulatory system considered in Section 6, where the total number in a component can often be very small, even 0 and the above approximations are often not appropriate.

An alternative to MCMC which has been applied to Markov processes is Approximate Bayesian Computation (ABC), see Tavaré et al. (1997) and Beaumont et al. (2002). ABC is a simulation based method where in its simplest form data, $x$, is simulated using the model for a given set of parameters $\theta$ chosen from the prior distribution on $\theta$. If $x$ is sufficiently close to the observed data, $x^*$, then the parameters $\theta$ are accepted from the (approximate) posterior distribution of $\theta|x^*$. (If sufficiently close to is replaced by equal to the accepted values are independent and identically distributed observations from the posterior distribution of $\theta$.) Using ABC for Markov processes is straightforward given the ease with which Markov processes can be simulated using the Gillespie algorithm Gillespie (1976). However, as noted in White et al. (2014), the probability of simulating the entire Markov process and getting $x$ close to $x^*$ is (extremely) small. The solution proposed in White et al. (2014) is, in the case where the Markov process is completely observed at each observation point, to exploit the Markov structure of the process and consider each interval (between observation points) separately. In particular, White et al. (2014) factorise the likelihood and estimate the posterior distribution of the parameters based upon each interval (component in the factorised likelihood) before combining the estimates to gain an overall estimate of the posterior distribution.

In this paper, we take the approach of White et al. (2014) piecewise simulation of the Markov process as our starting point. More precisely, we outline a sequential Monte Carlo (SMC) algorithm which is applicable in the case where the Markov process is only partially observed at each observation time point.
The SMC algorithm updates the posterior distribution of the parameters $\theta$ after each time point and uses simulation between successive observation points with parameters drawn from the current posterior distribution to update the posterior distribution. The sequential evaluation of the posterior distribution, improves upon simply choosing parameters from the prior, which is the case in White et al. (2014). The basic SMC algorithm is described in Section 3 but we propose two innovations which substantially improve the efficiency of the SMC algorithm in Section 4. The first innovation is to use coupled simulations of the Markov process allowing us to consider a set of parameter values from the posterior distribution using a single simulation. Coupled simulations for ABC were proposed and successfully applied to household epidemic models in Neal (2012) and we develop their usefulness for Markov processes below. The second innovation is a simple, yet effective, importance sampling procedure to direct the simulation process towards the observed data. A similar idea, but very different in its details, is the diffusion bridge used in Golightly and Wilkinson (2011). A key element behind both innovations is to not significantly slow down the simulation of the Markov process using the Gillespie algorithm which is successfully achieved. Moreover, we show that the two innovations substantially improve the efficiency of the SMC algorithm on their own but that the real benefits are seen when they are combined. In Section 5 it is shown that using the coupled simulations and importance sampling reduces the computational cost of the algorithm by at least a factor of 30.

The paper is structured as follows. In Section 2 we give an introduction to Markov processes and a useful reparameterisation of the Markov process which is exploited in developing the coupled simulations. We also outline the two examples used to illustrate the methodology, the Lotka-Volterra (predator-prey) model (Boys et al. 2008, White et al. 2014) and the Repressilator model for gene regularity systems (Elowitz and Leibler 2000, Toni et al. 2009). In Section 3 we outline the SMC algorithm before introducing our two innovations coupled simulations and importance sampling in Section 4. In Sections 5 and 6 we apply the SMC algorithm to the Lotka-Volterra and Repressilator models, respectively. Parameter estimation for the Lotka-Volterra model has proved to be challenging, see Boys et al. 2008, and it therefore gives a useful testing ground for our methodology. The SMC algorithm works very effectively even in the case where only the prey levels are observed. Analysing the Repressilator model is substantially more challenging than the Lotka-Volterra model due to the large number of events (between 1000 and 7000) which occur between observation points. However, the SMC algorithm is successfully applied to this model. Finally, in Section 7 we give a brief summary of our findings and outline possible extensions of the current work.
2 Markov Processes and Examples

In this Section we introduce Markov processes along with a simple reparameterisation that will be exploited in developing coupled simulations of the Markov process in Section 4. We also describe the two examples studied later in the paper the stochastic Lotka-Volterra model (Wilkinson (2011), Toni et al. (2009), White et al. (2014)) and the Repressilator model (Elowitz and Leibler (2000), Toni et al. (2009)). These examples illustrate the chosen parameterisation framework.

Consider a Markov process \( \mathcal{X} \) and let \( \mathbf{X}(t) \) denote the state of the process at time \( t \). Suppose that the evolution of the Markov process is governed by the parameters \( \theta_\alpha = (\alpha, \omega) \) and that there are \( K \) possible types of transitions. For \( k = 1, 2, \ldots, K \), let \( \varrho_k(\mathbf{X}(t), \theta_\alpha) = \alpha_k \rho_k(\mathbf{X}(t), \omega) \) denote the transition rate for a transition of type \( k \), given that the current state of the process is \( \mathbf{X}(t) \) and the parameters are \( \theta_\alpha \). For the generic description we assume that the \( \alpha_k \)'s are distinct but this is not necessary as demonstrated in the Repressilator example below. In many situations \( \omega \) will be empty and then the parameters, \( \theta_\alpha = \alpha \), simply govern how fast events are taking place. It will be useful later on to reparameterise the transition rates by setting \( \theta = (\beta, \omega, \phi) \), where \( \phi = \alpha_K \) and for \( k = 1, 2, \ldots, K \), \( \beta_k = \alpha_k / \phi \). (Note that \( \beta_K = 1 \).)

Then at time \( t \), given that the current state of the Markov process is \( \mathbf{X}(t) \), the time until the next event is \( \text{Exp}(\sum_{k=1}^K \varrho_k(\mathbf{X}(t), \theta_\alpha)) = \text{Exp}(\sum_{k=1}^K \beta_k \rho_k(\mathbf{X}(t), \omega))/\phi \), where \( \text{Exp}(\lambda) \) denotes an exponential distribution with mean \( 1/\lambda \). The probability that the transition is of type \( k \) is

\[
\frac{\varrho_k(\mathbf{X}(t), \theta_\alpha)}{\sum_{l=1}^K \varrho_l(\mathbf{X}(t), \theta_\alpha)} = \frac{\beta_k \rho_k(\mathbf{X}(t), \omega)}{\sum_{l=1}^K \beta_l \rho_l(\mathbf{X}(t), \omega)}. \tag{2.1}
\]

The key observation is that \( \text{Exp}(\sum_{k=1}^K \beta_k \rho_k(\mathbf{X}(t), \omega)) \) and (2.1) are independent of \( \phi \). Thus \( \phi \) denotes the speed measure of the Markov process; a fact that we will exploit later in the paper.

The stochastic Lotka-Volterra model is a model for predator-prey dynamics, see, for example, Wilkinson (2011). There are two species with for \( t \geq 0 \), \( X_1(t) \) and \( X_2(t) \) denoting the total number of prey and predators at time \( t \), respectively. There are three types of transition; a birth of a prey \( ((X_1(t), X_2(t)) \rightarrow (X_1(t) + 1, X_2(t))) \), a predator eats a prey, resulting in the death of a prey and the birth of a predator \( ((X_1(t), X_2(t)) \rightarrow (X_1(t) - 1, X_2(t) + 1)) \) and the death of a predator \( ((X_1(t), X_2(t)) \rightarrow (X_1(t), X_2(t) - 1)) \).

Let \( \theta_\alpha = \alpha = (\alpha_1, \alpha_2, \alpha_3) \) and \( \theta = (\beta_1, \beta_2, \phi) \), where \( \phi = \alpha_3 \) and \( \beta_i = \alpha_i / \alpha_3 \) \( (i = 1, 2) \). Then the infinitesimal transition rates at time \( t \) for the three types of transitions are \( \alpha_1 X_1(t) = \beta_1 \phi X_1(t) \) (birth of a prey), \( \alpha_2 X_1(t) X_2(t) = \beta_2 \phi X_1(t) X_2(t) \) (predator eats prey) and \( \alpha_3 X_2(t) = \phi X_2(t) \) (death of a predator).
The Repressilator model is a popular toy model for gene regulatory systems (Elowitz and Leibler (2000), Toni et al. (2009)). The model consists of three genes which produce messenger RNA (mRNA), and where each gene’s mRNA transcribes a repressor protein for the next gene in the loop. For \( i = 1, 2, 3 \), let \( Y_i(t) \) and \( Z_i(t) \) denote the total abundance of mRNA and protein, respectively, of gene \( i \) at time \( t \). The model has 12 types of transitions. For each gene there is production (birth) and decay (death) of mRNA and translation (birth) and decay (death) of proteins. Let \( \theta = (\alpha_1, \alpha_2, \alpha_3, \alpha_4, \omega) \), or alternatively, \( \theta = (\beta_1, \beta_2, \beta_3, \omega, \phi) \). Given \( X(t) = (Y_1(t), Y_2(t), Y_3(t), Z_1(t), Z_2(t), Z_3(t)) \), the transition rates for gene \( i \) \((i = 1, 2, 3) \) with correspondingly \( j = 3, 1, 2 \), are,

- \( \alpha_1 \frac{Z_i(t)}{1+Z_i(t)} + \alpha_2 \left( = \phi \left( \frac{\beta_1}{1+Z_i(t)} + \beta_2 \right) \right) \) production of mRNA \( (Y_i(t) \rightarrow Y_i(t) + 1) \),
- \( \alpha_3 Y_i(t) (= \phi Y_i(t)) \) decay of mRNA \( (Y_i(t) \rightarrow Y_i(t) - 1) \),
- \( \alpha_3 Y_i(t) (= \phi \beta_3 Y_i(t)) \) protein translation \( (Z_i(t) \rightarrow Z_i(t) + 1) \),
- \( \alpha_3 Z_i(t) (= \phi \beta_3 Z_i(t)) \) protein decay \( (Z_i(t) \rightarrow Z_i(t) - 1) \).

Note that \( \omega \) is non-empty in this model with \( \omega \) governing the effect of the repressor protein on the next gene in the loop.

Throughout this paper we assume that the Markov process is observed at discrete time points \( t_0(= 0), t_1, \ldots, t_n \). Typically, we take the observation points to be equally spaced and at unit time intervals so that \( t_i = i \), although there is nothing to restrict us to this case. Let \( x_i = X(t_i) \) denote the state of the system at time point \( t_i \) and \( x = (x_0, \ldots, x_n) \) with \( x_{a:b} = (x_a, \ldots, x_b) \). We assume that the process might be only partially observed at any time point, that is, \( X(t_i) = (Y(t_i), Z(t_i)) \), where \( Y(t_i) \) is observed and \( Z(t_i) \) is unobserved. For example, for the analysis of the Repressilator model in Section 6, we follow Toni et al. (2009), Section 3.2.1 in assuming that the abundance of mRNA is observed at each time point but that the protein levels are unobserved. Therefore, we write \( x_i = (y_i, z_i) \) to distinguish between the observed and unobserved data at time point \( i \), and we have that \( y = (y_0, \ldots, y_n) \) denotes the observed data. We are interested in \( \pi(\theta|y) \), the posterior distribution of the parameters given the observed data. Note that the approach we take allows, in principle, for different information to be available at different time points. For example, in the Lotka-Volterra model we could know both predator and prey numbers at some time points and only prey numbers at other time points. However, for ease of exposition, we shall restrict ourselves to assuming that the same information about the Markov process is observed at each time point with the possible exception of knowing the full initial conditions of the Markov process.
3 Sequential Monte Carlo

In this Section we outline a sequential Monte Carlo algorithm for obtaining samples from $\pi(\theta|y)$ or $\pi(\theta, z_0|y)$ with the latter being useful for predictive purposes. The approach we take is based upon the Liu and West filter, see, for example, Fearnhead and Taylor (2013). Thus an alternative is needed by adding a small random disturbance. For example, replacing $\theta_i$ for generating $\theta_i$, the parameter space, $\Theta$, see, for example, Fearnhead and Taylor (2013). Thus an alternative is needed by adding a small random disturbance. For example, replacing $\theta_i$ by $\theta_i + \zeta_i$, where $\zeta_i \sim N(0, S_i)$ for some appropriately chosen variance matrix $S_i$. As pointed out in Liu and West (2001), this approach leads to a loss of information between time points, as artificial noise has been added to the model parameters, which leads to increasingly diffuse estimates of the posterior distribution. The solution proposed in Liu and West (2001), Section 3.2, which we follow in this paper is as follows. Let $\mu_{t-1}$ and $V_{t-1}$ denote the estimated...
An alternative approach for updating \( \theta \) (Monte Carlo) posterior mean and variance of \( \pi(\theta | y_{0:t-1}) \). Let \( h > 0 \) be a smoothing parameter and \( a = \sqrt{1-h^2} \). Simulate \( \zeta_t^j \sim N(0, h^2 V_{t-1}) \) and replace \( \theta_t^j \) by

\[
a\theta_t^j + (1-a)\mu_{t-1} + \zeta_t^j,
\]

where \( \theta_t^j = \theta_{t-1}^i \) with probability \( \omega_{t-1}^i / \sum_k \omega_{t-1}^k \). This ensures that the proposed parameters have mean \( \mu_{t-1} \) and variance \( V_{t-1} \). It is recommended in Liu and West (2001), Section 3 to choose \( \delta \) around 0.99, where \( h^2 = 1 - ((3\delta - 1)/2\delta)^2 \). This gives \( h = 0.1004 \).

An alternative approach for updating \( \theta \) (\( \theta_\alpha \)) is to use MCMC moves for the particles, see for example, Storvik (2002) and Fearnhead (2002). Let \( a_{0:t} \) denote the trajectory of the Markov process up to time \( t \). For the case \( \omega = \emptyset \) and with independent gamma distributed priors on the components of \( \alpha \), \( \pi(\theta_\alpha | a_{0:t}, x_{0:t}) \) is the product of \( K \) independent Gamma densities with

\[
\alpha_k | a_{0:t}, x_{0:t} \sim \text{Gamma} \left( E_k(t) + A_k, \int_0^t \rho_k(a_k(s)) ds + B_k \right),
\]

where \( E_k(t) \) denotes the total number of type \( k \) transitions in the interval \([0, t]\) and \( \text{Gamma}(A_k, B_k) \) is the prior on \( \alpha_k \). Therefore it is sufficient to keep track of \((E_k(t), \int_0^t \rho_k(a_k(s)) ds) \) \((k = 1, 2, \ldots, K)\) rather than the full trajectory \( a_{0:t} \), see Fearnhead (2002). The main reasons for focussing on the Liu and West (2001) approach is the ease with which it can be implemented with the coupled simulations introduced in Section 4 using \( \theta \) rather than \( \theta_\alpha \) and that its efficiency is not compromised by \( \omega \neq \emptyset \), where no low-dimensional sufficient statistics exist.

In estimating the parameters for discretely observed Markov processes, we start with a slight adaption of the SIR algorithm with the Liu-West (Liu and West (2001)) filter before developing improvements of the algorithm to make it more efficient in Section 4. First, note that \( \pi(y_t, z_t | \theta, y_{t-1}, z_{t-1}) \) is unknown. Therefore we simulate a realisation of the Markov process with parameters \( \theta \) and starting at \( X(t-1) = (Y(t-1), Z(t-1)) = (y_{t-1}, z_{t-1}) \) between times \( t-1 \) and \( t \). If \( Y(t) = y_t \), we set \( \omega = 1 \), the simulation is consistent with the observed data, otherwise we set \( \omega = 0 \). That is, we have an unbiased, indicator estimate for \( \pi(y_t | \theta, y_{t-1}, z_{t-1}) \) with \( z_t \), in the case \( \omega_t = 1 \), being an unbiased draw from \( \pi(z_t | y_t, \theta, y_{t-1}, z_{t-1}) \). Secondly, if we run a fixed number of particles \( N \) it is possible that no simulation will be accepted. Thus at each \( t \) we sample particles until a fixed number of simulations, \( M \), are accepted. These ideas are developed further in Section 4 where the weights \( \omega \) are no longer indicator variables and the simulations are run until a given effective sample size, \( M \), is reached.

The above developments give rise to the following sequential Monte Carlo (SMC) algorithm.
SMC algorithm

1. Set \( l = 0 \).

2. While \( l < M \):
   
   (a) Sample \( \theta \) and \( z_0 \) from \( \pi(\theta, z_0) \).
   
   (b) Simulate the Markov process \( X \) with parameters \( \theta \) and starting point \( X(t_0) = (y_0, z_0) \) from time \( t_0 \) to time \( t_1 \), and let \( x'_1 = (y'_1, z'_1) \) denote \( X(t_1) \).
   
   (c) If \( y'_1 = y_1 \), accept the simulation by setting \( l = l + 1 \) and \( (\theta^l, z^l) = (\theta, z'_1) \). Otherwise the simulation is rejected.

Fix \( h > 0 \) and \( a = \sqrt{1 - h^2} \). For \( t = 2, 3, \ldots, n \):

1. Compute \( \mu_{i-1} \) and \( V_{i-1} \), the mean and variance of \( \{\theta^1_{i-1}, \theta^2_{i-1}, \ldots, \theta^M_{i-1}\} \).

2. Set \( l = 0 \).

3. While \( l < M \):
   
   (a) Sample \( (\tilde{\theta}, z) \), uniformly at random from \( \{(\theta^1_{i-1}, z^1_{i-1}), (\theta^2_{i-1}, z^2_{i-1}), \ldots, (\theta^M_{i-1}, z^M_{i-1})\} \).
   
   (b) Sample \( \zeta \sim \mathcal{N}(0, h^2 V_{i-1}) \) and set \( \theta^* = a \theta + (1 - a) \mu_{i-1} + \zeta \).
   
   (c) Simulate the Markov process \( X \) with parameters \( \theta^* \) and starting point \( X(t_{i-1}) = (y_{i-1}, z) \) from time \( t_{i-1} \) to time \( t_i \), and let \( x'_i = (y'_i, z'_i) \) denote \( X(t_i) \).
   
   (d) If \( y'_i = y_i \), accept the simulation by setting \( l = l + 1 \) and \( (\theta^l_i, z^l_i) = (\theta^*, z'_i) \). Otherwise the simulation is rejected.

In the terminology of [White et al. (2014)](https://www.jstatsoft.org/v06/i01/paper), this is a sequential exact Bayesian computation (EBC) algorithm. The term EBC refers to employing an ABC simulation procedure without approximation, i.e., an exact match is observed. It is straightforward to adapt the above algorithm to form a sequential ABC algorithm, where an exact match is replaced by comparing summary statistics of the simulated and observed data, accepting simulations where these are sufficiently close, or to the case where the Markov process is observed with observational error. In the sequel, we focus on perfect, but partial, observation of the Markov process.
4 Coupled simulations and Importance sampling

The key limitation of the SMC algorithm described at the end of Section 3 is that the probability that a simulation, with parameters $\theta$ and starting from $X(t_{i-1}) = x_{i-1}$, will result in $Y(t_i) = y_i$ is often prohibitively small. Therefore we look for ways to improve the rejection sampling scheme in the SMC algorithm. Two approaches are proposed, coupled simulation and importance sampling, these can be used either in isolation or as in this paper combined. However, for clarity of exposition we describe the two approaches separately.

4.1 Coupled simulation

For the coupled simulations we explicitly use the reparameterised $\theta = (\beta, \omega, \phi)$ for simulating the Markov process $X$. Let $W$ denote the Markov process $X$ with parameters $\vartheta = (\beta, \omega, 1)$, that is, fixing $\phi = 1$. Thus $W$ is a special case of $X$ but it suffices to study $W$, since $X$ can be viewed as a speeded up ($\phi > 1$) or slowed down ($\phi < 1$) version of $W$. Let $W(t) = (W^y(t), W^z(t))$ denote the state of $W$ at time $t$, where $W^y(t)$ and $W^z(t)$ correspond to the observed and unobserved components, respectively, of the Markov process. Then at time $t$, the transition rate for a transition of type $k$ is $\beta_k \rho_k (W(t), \omega)$ ($k = 1, 2, \ldots, K$). Now suppose that $W(0) = x_{i-1}$. Then a realization of $X(t_i)$ given $X(t_{i-1}) = x_{i-1}$ and $\theta = (\beta, \omega, \phi)$ can be obtained by setting $X(t_i) = W(\phi(t_i - t_{i-1}))$. Now if $W$ is simulated on the interval $[0, S]$ using $\vartheta = (\beta, \omega, 1)$, then realizations of $X(t_i)$ can be generated for $\{(\beta, \omega, \phi); 0 \leq \phi \leq S/(t_i - t_{i-1})\}$. Therefore we can construct simulations from $X(t_i)$ for a whole set of parameters from a single simulation of $W$. In particular, for any $0 \leq \tau \leq S$, where $W^y(\tau) = y_i$, we have a simulated realisation with parameters $(\beta, \omega, \phi = \tau/(t_i - t_{i-1}))$ and starting at $X(t_{i-1}) = x_{i-1}$ which results in $X(t_i)$ with $Y(t_i) = y_i$.

Throughout this paper $t_i - t_{i-1} = 1$, so $\phi = \tau$ but this need not be the case.

We use the term coupled simulations for the above construction since we are coupling together a sequence of parameter values in one simulation. This is similar to the coupled ABC idea introduced by Neal (2012). The main difference is that here we only consider varying one parameter, $\phi$, rather than the whole set of parameters, $\theta$ in the coupling. Since $W(t)$ is piecewise constant, it is straightforward to obtain $A_\phi = \{\phi; W^y(\phi(t_i - t_{i-1})) = y_i\}$. We discuss how to exploit $A_\phi$ in Section 4.3 below.
4.2 Importance sampling

A key problem with simulation-based statistical inference is that typically the probability that a simulated data set coincides with the observed data set is extremely small. One natural solution is to use importance sampling, Ripley (1987), to steer the simulation towards the observed data, see Neal and Huang (2013). The aim is to do this in a fast, efficient manner, so that the speed with which the process is simulated is not severely compromised. The simple solution we offer is to simulate from an alternative, time inhomogeneous Markov process \( R \). Let \( a = \{ a_i; t_{i-1} \leq s \leq t_i \} \) denote a realisation of a Markov process between times \( t_{i-1} \) and \( t_i \) with \( f_X(a; \theta, x_{i-1}) \) and \( f_R(a; \theta, x_{i-1}) \) denoting the probability density function for \( a \) under \( X \) and \( R \), respectively, with parameters \( \theta \) and starting at \( x_{i-1} \). We have that

\[
\pi(Y(t_i) = y_i | \theta, X(t_{i-1}) = x_{i-1}) = \int \pi(X(t_i) = x_i | \theta, X(t_{i-1}) = x_{i-1}, X = a) \frac{f_X(a; \theta, x_{i-1})}{f_R(a; \theta, x_{i-1})} f_R(a; \theta, x_{i-1}) \, da
\]

\[
= \int 1\{a^\gamma_i = y_i\} \frac{f_X(a; \theta, x_{i-1})}{f_R(a; \theta, x_{i-1})} f_R(a; \theta, x_{i-1}) \, da,
\]

where \( a^\gamma_i \) corresponds to the observed components of the Markov process. Thus using importance sampling we can simulate a realisation \( a \) from \( R \), with

\[
1\{a^\gamma_i = y_i\} \frac{f_X(a; \theta, x_{i-1})}{f_R(a; \theta, x_{i-1})}
\]

giving an unbiased estimate of \( \pi(Y(t_i) = y_i | \theta, X(t_{i-1}) = x_{i-1}) \). Whilst, any choice of \( R \) could be used, for practical purposes we want to be able to compute the ratio in (4.2) rapidly. Therefore we use the following Markov process \( R \) with \( R(s) \) denoting the state of the process at time \( s \). Start with \( R(t_{i-1}) = x_{i-1} \) and \( P = 1 \). For \( s \geq t_{i-1} \), suppose that \( R(s) = r \), then the waiting time until the next event is exponentially distributed with rate \( \phi \sum_{k=1}^{K} \beta_k \rho_k(r, \omega) \) and we simulate the time to the next event from this distribution. Let \( p_k = \beta_k \rho_k(r, \omega) / \sum_{i=1}^{K} \beta_i \rho_i(r, \omega) \), the probability that a type \( k \) transition takes place in \( X \), if \( X(s) = r \). Now instead of choosing the transition type according to \( p = (p_1, \ldots, p_K) \), we choose according to \( q = (q_1, \ldots, q_K) \), where \( q \) can depend upon the current state \( R(s) = r \), the time \( s \), the model parameters \( \theta \) and the target \( y_i \). If a transition of type \( k \) is chosen, we update \( R(s) \) accordingly and set \( P = P \times p_k / q_k \). The process stops at time \( t \) with \( P \) equal \( f_X(a; \theta, x_{i-1}) / f_R(a; \theta, x_{i-1}) \). Thus the importance sampler is extremely easy to implement and can offer significant gains in terms of efficiency of the simulation algorithm. The choice of \( q \) is problem specific and we discuss this in relation to the Lotka-Volterra and Repressilator examples in Sections 5 and 6 respectively.
4.3 Sequential Monte Carlo algorithm

We outline how the SMC algorithm introduced in Section 3 can be modified to make use of coupled simulations and importance sampling. We begin by describing how to modify the sequential step for $i > 1$ before considering $i = 1$.

Suppose that we have a sample of $N_{i-1}$ particles from $\pi(\theta, z_{i-1}|y_{0:i-1})$. That is, we have $(\theta^1_{i-1}, z^1_{i-1}, \omega^1_{i-1}), \ldots, (\theta^{N_{i-1}}_{i-1}, z^{N_{i-1}}_{i-1}, \omega^{N_{i-1}}_{i-1})$, where $\omega^j_{i-1}$ is the relative weight attached to $(\theta^j_{i-1}, z^j_{i-1})$ and the computation of $\omega^j_{i-1}$ will be discussed below. As before we can compute $\mu_{i-1}$ and $V_{i-1}$, although we will primarily use $\mu_{i-1}$ and $\tilde{V}_{i-1}$, the estimated mean and variance of $\theta^*$. For notational convenience we denote $\theta^*$ by $\tilde{\theta}$. It is useful to write $\theta = (\beta, \omega, \phi)(= (\tilde{\theta}, \phi))$ with $V_{i-1}$ written as

$$V_{i-1} = \left( \begin{array}{c} \tilde{V}_{i-1} \\ \tilde{C}_{i-1} \end{array} \right).$$

(4.3)

Let $\sigma^2_\phi = V^\phi_{i-1} - \tilde{C}^T_{i-1} \tilde{V}_{i-1}^{-1} \tilde{C}_{i-1}$, the conditional variance of $\phi$ given the other parameters, $\tilde{\theta}$. This will be important in exploiting the coupled simulations.

Set $l = 0$, $L = 0$ and while $L < M$, we perform the following steps in place of those in Step 3 of the SMC algorithm.

(a) Sample $(\theta, z)$ from $(\theta^1_{i-1}, z^1_{i-1}), \ldots, (\theta^{N_{i-1}}_{i-1}, z^{N_{i-1}}_{i-1})$ with probability $\omega^j_{i-1}/ \sum_{k=1}^{N_{i-1}} \omega^k_{i-1}$ of choosing $(\theta^j_{i-1}, z^j_{i-1})$.

(b) Sample $\tilde{\zeta} \sim N(0, h^2 \tilde{V}_{i-1})$ and set $\theta^* = a\tilde{\theta} + (1-a)\tilde{\mu}_{i-1} + \tilde{\zeta}$.

(c) The conditional distribution of $\phi^*$ given $\theta^*$ is

$$N(a \phi + (1-a) \mu^\phi + \tilde{C}^T_{i-1} \tilde{V}_{i-1}^{-1} \tilde{C}_{i-1} \tilde{\zeta}, \sigma^2_\phi) = N(\tilde{\phi}, \sigma^2_\phi),$$

(4.4)

Simulate $U \sim U(0,1)$ and set $B = \{r; g(r; \tilde{\phi}, \sigma^2_\phi) \geq U g(\tilde{\phi}; \tilde{\phi}, \sigma^2_\phi)\}$, where $g(r; \mu, \sigma^2)$ denotes the probability density function of a $N(\mu, \sigma^2)$ evaluated at $r$.

(d) Set $P = 1$ and $b_M = \sup\{x; x \in B\}$.

Simulate a Markov process $\mathcal{W}$ with parameters $\varrho = (\theta^*, 1)$ and $W(0) = x_{i-1}$ from time 0 to time $b_M$ incorporating importance sampling. That is, if currently $W(t) = w$, we simulate $\tau$ from an exponential distribution with rate $\sum_{k=1}^{K} \beta^*_k p_k(w, \omega^*)$. Then for $t \leq s < t + \tau$, $W(s) = w$. At time $t + \tau$, a transition takes place with the transition chosen according to $q$. If a transition of type $k$ is chosen, we update $W(t+\tau)$ accordingly and set $P = P \times p_k/q_k$, where $p_k = \beta^*_k p_k(w, \omega^*)/ \sum_{l=1}^{K} \beta^*_l p_l(w, \omega^*)$. 

11
For \( s \in \mathcal{B} \), if \( \mathbf{W}^y(s) = \mathbf{y}_i \), set \( k_s \) equal to the current value of \( P \), otherwise set \( k_s = 0. \) Then set 
\[
\varpi = \int_{s \in \mathcal{B}} k_s \, ds,
\]
the relative weight of the simulation.

(e) If \( \varpi > 0 \), sample \( \phi^+ \) from \( \mathcal{B} \) with probability density function proportional to \( k_s \). Set \( l = l + 1 \) and 
\[
(\tilde{\theta}^i_l, \phi^i_l, \mathbf{z}^i_l, \mathcal{w}^i_l) = (\theta^*, \phi^+, \mathbf{W}^z(\phi^+), \varpi).
\]
Set \( L = \{ \sum_{k=1}^{l} \mathcal{w}^k_i \}^2 / \{ \sum_{j=1}^{l} (\mathcal{w}^j_i)^2 \} \), the effective sample size.

We discuss the implications of the above procedure. Step (a) simply draws a particle according to its relative weight from \( \pi(\theta, \mathbf{z}_{i-1} | \mathbf{y}_{0:i-1}) \) and step (b) applies the Liu-West correction to all the parameters except \( \phi \). Step (c) produces a random set of values \( \mathcal{B} \) of the form \( \mathcal{B} = \{ r \in [\tilde{\phi} - T, \tilde{\phi} + T] \} \), where \( T \) is a random variable determined by \( U \) and \( \sigma^2_\phi \). For any \( r \in \mathbb{R} \), the probability that \( r \in \mathcal{B} \) is proportional to \( g(r; \tilde{\phi}, \sigma^2_\phi) \). The set \( \mathcal{D} = \{ (\tilde{\theta}, r, \mathbf{z}) ; r \in \mathcal{B} \} \) is a set of parameters from the distribution generated from \( (\theta^i_{1-1}, \mathbf{z}^i_{1-1}, \mathcal{w}^i_{1-1}), \ldots, (\theta^i_{N_i-1}, \mathbf{z}^i_{N_i-1}, \mathcal{w}^i_{N_i-1}) \) with the Liu-West Gaussian kernel smoothing. This mimics the posterior sets generated in Neal (2012) with more details on the construction of sets for a random variable given in the Appendix. In particular, \( \mathcal{D} \) is an (approximate) sample of parameter values from \( \pi(\theta, \mathbf{z}_{i-1} | \mathbf{y}_{0:i-1}) \) with the approximation given by the Liu-West smoothing and is no different to that generated by the SMC algorithm. Returning to (3.2), we have a sample from \( \pi(\tilde{\theta}, \mathbf{z}_{i-1} | \mathbf{y}_{0:i-1}) \) and have constructed a set \( \mathcal{B} \) from \( \pi(\phi \theta, \mathbf{z}_{i-1}, \mathbf{y}_{0:i-1}) \). Therefore we need to estimate \( \pi(\mathbf{y}_i, \mathbf{z}_i | \tilde{\theta}, \mathbf{x}_{i-1}) \) in order to get a sample from \( \pi(\mathbf{y}_i, \mathbf{z}_i | \mathbf{y}_{0:i}) \). In step (d), we simulate the process \( \mathcal{W} \) and consider \( \phi \) values lying in \( \mathcal{B} \).

We simultaneously consider realisations of \( \mathcal{X} \) for all parameters \( \{ (\theta^*, \phi); \phi \in \mathcal{B} \} \) and it thus suffices to simulate \( \mathcal{W} \) on the interval \([0, b_M]\). Note that \( \varpi \) is given by
\[
\int_{\phi \in \mathcal{B}} 1(\mathbf{W}^y_s \mathbf{y}_i) \frac{f_{\mathcal{W}}(\mathbf{a}; \tilde{\theta}^*, \phi, \mathbf{x}_{i-1})}{f_{\mathcal{R}}(\mathbf{a}; \tilde{\theta}^*, \phi, \mathbf{x}_{i-1})} \, d\phi = \int_{\phi \in \mathcal{B}} k_\phi \, d\phi. \tag{4.5}
\]

Now \( \varpi / (\sqrt{2\pi} \sigma_\phi) \) is an unbiased estimate of \( \pi(\mathbf{Y}(t_i) = \mathbf{y}_i | \tilde{\theta}^*, \mathbf{X}(t_{i-1}) = \mathbf{x}_{i-1}) \), where
\[
\pi(\mathbf{Y}(t_i) = \mathbf{y}_i | \tilde{\theta}^*, \mathbf{X}(t_{i-1}) = \mathbf{x}_{i-1}) = \int \int \pi(\mathbf{Y}(t_i) = \mathbf{y}_i | \tilde{\theta}^*, \mathbf{X}(t_{i-1}) = \mathbf{x}_{i-1}, \phi, \mathcal{W} = \mathbf{a}) \frac{f_{\mathcal{W}}(\mathbf{a}; \tilde{\theta}^*, \phi, \mathbf{x}_{i-1})}{f_{\mathcal{R}}(\mathbf{a}; \tilde{\theta}^*, \phi, \mathbf{x}_{i-1})} \\
\times f_{\mathcal{R}}(\mathbf{a}; \tilde{\theta}^*, \phi, \mathbf{x}_{i-1}) \pi(\phi \tilde{\theta}^*, \mathbf{X}(t_{i-1}) = \mathbf{x}_{i-1}) \, d\mathbf{a} \, d\phi = \int k_\phi f_{\mathcal{R}}(\mathbf{a}; (\tilde{\theta}^*, \phi), \mathbf{x}_{i-1}) \pi(\phi \tilde{\theta}^*, \mathbf{X}(t_{i-1}) = \mathbf{x}_{i-1}) \, d\mathbf{a} \, d\phi. \tag{4.6}
\]
The details are given in the Appendix. The computation and storage of \( k_s \) \( s \in \mathcal{B} \) is straightforward as \( k_s \) is piecewise-constant. Then \( \varpi / (\sqrt{2\pi} \sigma_\phi) \) is an estimate of \( \pi(\tilde{\theta}, \mathbf{z}_{i-1} | \mathbf{y}_{0:i}) \), with the computation of \( \varpi \) based on the simulation taking into account both the importance sampling weights (steering of the
simulation) and the time spent $W^y(s) = y_i$ for $s \in B$. Finally, in step (e), we obtain a sample $(\phi, z_i)$ from $\pi(\phi, z_i| \theta, z_{i-1}, y_{0:i})$. This is done on the basis of the simulated $W$ by sampling $\phi^+$ from the set $B$, proportional to $k_s$, and then setting $z_i = W^z(\phi^+)$, the corresponding value of the process for the unobserved components of the Markov process.

For the case $i = 1$, the choice of $(\tilde{\theta}, z)$ and $B$ changes to take into account the prior distribution but steps (d) and (e) remain unchanged. If we have that $\pi(\theta, z) = \pi(\tilde{\theta}, z)\pi(\phi)$, then we simply simulate $(\tilde{\theta}, z)$ from its prior and set $B = \{r; \pi(\phi = r) \geq U \max_x \pi(\phi = x)\}$, where $U \sim U(0,1)$, and proceed as above. However, a prior may naturally be specified in terms of $\theta_\alpha$ and the above prior independence between $\tilde{\theta}$ and $\phi$ will then not be the case in general. In this paper we consider the case where the prior on $\theta_\alpha$ is uniform on $D_\alpha \subset \mathbb{R}^d$ with $D_\alpha$ being a $d$-dimensional cube. This results in the prior on $\theta$ being uniform on a set $D \subset \mathbb{R}^d$ and it is then easy to simulate $\tilde{\theta}$ and choose the appropriate $B$. We discuss the details in relation to specific examples in Sections 5 and 6.

A key question is how much more computationally intensive is the sequential Monte Carlo algorithm with coupled simulations and importance sampling compared with the SMC algorithm. The computationally intensive part of both algorithms is running the simulations with the computations of means, variances and other quantities between time points being minimal. Therefore we compare mean time required per simulation. For $i > 1$, the mean period length for which the SMC algorithm is run is $\tilde{\phi}$ and for the sequential Monte Carlo algorithm with coupled simulations the mean period length is $\tilde{\phi} + 1.254h\sigma_\phi$. Typically, $\sigma_\phi$ is relatively small compared with $\tilde{\phi}$, so the additional time required per simulation is small. Furthermore, if $\sigma_\phi$ is relatively large, then so typically will $B$, and the use of coupled simulations will be particularly useful. The computation of importance sampling probabilities depends upon how these are computed but for the examples in this paper, the computation of $q$ is similar in complexity to the computation of $p$. Therefore incorporating coupled simulations and importance sampling will at most double the time required per simulation. For the examples studied in Sections 5 and 6 it was found that the additional time was approximately only 20% longer per simulation.

A secondary question is the choice of $h$. For Liu and West (2001), the choice of $h$ depends upon kernel smoothing considerations, a compromise between under and over smoothing with the ideal $h \approx 0.1$. For the sequential Monte Carlo algorithm, additionally $h$ determines the size of the set $B$ in the coupled simulations, and increasing $h$ will increase the acceptance rate. Thus alongside increasing $h$, we can increase $M$, the effective sample size without increasing the mean number of simulations at each time.
point. Consequently, we typically take $h$ in the range 0.15 to 0.20, which still results in $\delta$ between 0.95 – 0.99, the range advocated in Liu and West (2001). We briefly discuss varying $h$ at the end of Section 5.2.

5 Lotka-Volterra model

5.1 Introduction

The stochastic Lotka-Volterra model has proved a useful testing ground for statistical inference techniques for Markov processes. For example, reversible jump MCMC (Boys et al. (2008)), SMC-ABC (Toni et al. (2009)), particle MCMC (Golightly and Wilkinson (2011)) and piecewise ABC (White et al. (2014)). In all of the above papers the methodology is tested on simulated data and it is assumed that the Lotka-Volterra process is observed at a discrete number of points with either both predator and prey numbers being observed or only prey numbers are observed. The observations are assumed to be exact in Boys et al. (2008) and White et al. (2014), to have observation error in Golightly and Wilkinson (2011) and are averaged over replicates in Toni et al. (2009). The reversible jump MCMC algorithm of Boys et al. (2008) is computationally intensive and experiences poor mixing due to the large amount of data augmentation involved. The SMC-ABC algorithm of Toni et al. (2009) appears to work reasonably with multiple data replicates with the true parameter values lying in the support of the reported posterior distribution. However, it is not possible to assess the level of approximation of the posterior distribution. The particle MCMC of Golightly and Wilkinson (2011), which uses an SDE approximation and diffusion bridges (importance sampling), works well when the data is observed with error. However, the performance of the particle MCMC severely worsens as the noise term becomes smaller, see White et al. (2014). The piecewise ABC of White et al. (2014) requires that both predator and prey numbers are observed and its performance is highly sensitive to the choice of prior.

We consider the case where the observations are assumed to be exact with either both predator and prey numbers or only prey numbers observed. It is relatively straightforward to adapt the methods to the case with observational error. We present analysis from one simulated data set although similar findings were observed with other data sets across a range of parameter values. The data consists of observations at time points $t = 0, 1, \ldots, 40$, of a simulation of the Lotka-Volterra model with with $\theta_\alpha = (1, 0.005, 0.6)$ ($\theta = (\beta_1, \beta_2, \phi) = (5/3, 5/600, 3/5)$) and $x_0 = (71, 79)$. The observed data are plotted in Figure 1. The parameter values chosen correspond to those used in White et al. (2014) and are double the parameters
values used in Boys et al. (2008). Thus our observations are further apart than Boys et al. (2008), with White et al. (2014) not reporting the observation times. The total number of events in the simulation between time 0 and time 40 is over 14000, which highlights the degree of data augmentation that would be required if a data-augmentation MCMC algorithm were to be used. A vague prior was placed on $\theta$ with $U(-4,2)$ and $U(-8,-3)$ chosen for $\log(\beta_1)$ and $\log(\beta_2)$, respectively, and a $U(0,2)$ prior for $\phi$.

5.2 Predator and prey numbers observed

The implementation of the SMC algorithm is as detailed in Section 4.3, with only details of the importance sampling, given below, needing to be specified. In particular, we use a local linearisation of the Markov process to devise the importance sampling distribution $q$.

For interval $i$, the target (observed) data is $x_i$. In particular, given parameters $\theta^*$ and $\phi|\theta^* \sim N(\tilde{\phi}, \sigma^2_{\phi})$, we aim for $W(\tilde{\phi}) = x_i$, where $W(0) = x_{i-1}$. Given an event occurs at time $0 < s < \tilde{\phi}$ and $W(s) = w$, we choose $q$ as follows, with $q = p$ for $s \geq \tilde{\phi}$. Let $L_1 = x_{i,1} - W_1(s)$ and $L_2 = x_{i,2} - W_2(s)$, the differences between the target and the current prey and predator numbers, respectively. Let $R = (\tilde{\phi} - s) \times \sum_{k=1}^{K} \beta_k \rho_k(W(s))$, the expected number of events in $W$ on the interval $(s, \tilde{\phi}]$, if the current transition
rates are maintained. Then we set

\[
\begin{align*}
Q_1 &= \max \left\{ 0, \frac{R + 2L_1 + L_2}{3R} \right\} \\
Q_2 &= \max \left\{ 0, \frac{R - L_1 + L_2}{3R} \right\} \\
Q_3 &= \max \left\{ 0, \frac{R - L_1 - 2L_2}{3R} \right\}, \tag{5.1}
\end{align*}
\]

and then normalise, if necessary, by setting \( Q_i \) equal to

\[
Q_i = \frac{Q_i}{\sum_{j=1}^{3} Q_j}.
\]

Assuming that \( Q_1, Q_2 \) and \( Q_3 \) in (5.1) are positive then the average effect over the interval \((s, \tilde{\phi}]\) with \( R \) transitions is for the number of prey and predator to increase by \( L_1 \) and \( L_2 \) (decrease if \( L_1/L_2 \) are negative), respectively. Thus naively we could set \( q_i = Q_i \) \((i = 1, 2, 3)\). However, this leads to a very poorly performing importance sampler. We found it best to put more weight on \( Q = (Q_1, Q_2, Q_3) \) as \( s \) approached \( \tilde{\phi} \) with

\[
q_i = \left(1 - \epsilon \left(\frac{s}{\tilde{\phi}}\right)^\kappa\right)p_i + \epsilon \left(\frac{s}{\tilde{\phi}}\right)^\kappa Q_i \quad (i = 1, 2, 3), \tag{5.2}
\]

for some \( 0 \leq \epsilon \leq 1 \) and \( \kappa \geq 0 \). We found that \( \epsilon = 0.3 \) and \( \kappa = 2 \) performed well across a range of data sets as a compromise between the transition probability, \( p \), and the steering probability \( Q \).

We set \( M = 1000 \) and \( h = 0.15 \). We ran the code with no importance sampling for \( i = 1 \) and the above importance sampling regime with \( \epsilon = 0.3 \) and \( \kappa = 2 \) for \( i > 1 \). It was observed that it was beneficial not to have importance sampling at the first time point. The total number of simulations across the 40 time points was 14,100,811, a mean of just over 350,000 simulations per time point. There is considerable variation in the number of simulations per time point ranging from 54,447 for time point 8 to 2,516,218 for time point 4. In Figure 2, the estimated posterior mean plus and minus two times the estimated posterior standard deviation of \( \alpha_i (= \beta_i \phi) \) \((i = 1, 2, 3)\), evaluated after each time point. We note a significant change at time point 4 and also notable changes at time points 21 and 31 which are the other two time points that required over a million simulations. However, it is not obvious from the data in Figure 1 that we should expect a notable change in the parameters at these time points. Finally, the estimated posterior means and standard deviations for \( \theta_{a|x_{0:40}} \) are given in Table 5.2. The posterior means are close to the chosen parameter values. The standard deviations are similar to those reported in Boys et al. (2008), Table 1, using reversible jump MCMC, admittedly for a different data set, and this is observed across different data sets. Thus the Liu-West procedure is not only providing good estimates of the mean of the parameters but also the uncertainty in the posterior distribution of the parameters.

It is informative to compare the performance of the SMC algorithm with coupled simulations and importance sampling with the SMC algorithm with only one or neither of these modifications. The coupled
Figure 2: Plots of mean of $\theta_\alpha$ parameters plus/minus two standard deviations.

| Parameter | $\alpha_1$ | $\alpha_2$ | $\alpha_3$ |
|-----------|------------|------------|------------|
| Mean      | 0.970      | 0.00503    | 0.609      |
| St. Dev.  | $1.64 \times 10^{-2}$ | $9.78 \times 10^{-5}$ | $1.03 \times 10^{-2}$ |
simulations required on average twice as long to run at the first time point. However for subsequent time points the additional computational cost was substantially smaller following the discussion at the end of Section 4. The importance sampling slowed down the speed of the simulations by at most 20%. It was found that for \( M = 1000 \), the SMC algorithm with neither modification required approximately 920 million simulations in total, whereas the SMC algorithm with only coupled simulations or importance sampling required approximately 90 million simulations in total in both cases. Thus the modifications to the SMC algorithm make it at least 30 times faster (allowing for twice as long per simulation).

Finally, we comment briefly on varying \( h \). We found that increasing \( h \) to 0.20 or reducing \( h \) to 0.10, for fixed \( M \) resulted in approximately 28% fewer and 22% more simulations, respectively. Consistent estimation of the posterior means was observed across the different values of \( h \) with the estimated posterior standard deviation increasing slightly with increasing \( h \).

5.3 Only prey levels observed

A more challenging statistical problem is where only the prey numbers are observed at each time point, \cite{Boys2008}. The reversible jump MCMC algorithm of \cite{Boys2008} incurs additional mixing problems with this case but is still able to recover parameter values consistent with those used for simulation, see \cite{Boys2008}, Table 2. The piecewise ABC algorithm of \cite{White2014} is unable to deal with this case as complete observation of the Markov process at each time point is required.

Implementation of the SMC algorithm is similar to in Section 5.2 with a few minor modifications. The same prior is used for \( \theta \) but now a prior is required for \( X_2(0) \), for which we use a discrete uniform on the range 10 to 300, inclusive. Given that we only require the simulations to match on prey levels, we increased \( M \) to 10000 and reduced \( h \) to 0.1. This resulted in a total of 8,991,017 simulations over the 40 time points. Finally, the importance sampling is modified to take into account that only the prey numbers need to match. Specifically, for \( 0 < s < \hat{\phi} \), we let \( L_1 = x_{i,1} - W_1(s) \) and \( R = (\hat{\phi} - s) \times \sum_{k=1}^{K} \beta_k \rho_k(W(s)) \) as before. Then we set,

\[
\begin{align*}
Q_1 &= \frac{R(p_1 + p_2) + L_1}{2R} \\
Q_2 &= \frac{R(p_1 + p_2) - L_1}{2R},
\end{align*}
\tag{5.3}
\]

restricted to \( 0 \leq Q_1, Q_2 \leq p_1 + p_2 \). That is, if \( Q_1 < 0 \) (\( Q_2 < 0 \)), we set \( Q_1 = 0 \) (\( Q_1 = p_1 + p_2 \)) and
Table 2: Estimated posterior means and standard deviations for $\theta_\alpha|y_{0:40}$.

| Parameter | $\alpha_1$ | $\alpha_2$ | $\alpha_3$ |
|-----------|------------|------------|------------|
| Mean      | 0.951      | 0.00537    | 0.642      |
| St. Dev.  | $1.05 \times 10^{-1}$ | $6.08 \times 10^{-4}$ | $7.46 \times 10^{-2}$ |

$Q_2 = p_1 + p_2$ ($Q_2 = 0$). Thus letting $Q_3 = p_3$, we set

$$q_i = \left(1 - \epsilon \left(\frac{\alpha}{\phi}\right)^\kappa\right)p_i + \epsilon \left(\frac{\alpha}{\phi}\right)^\kappa Q_i \quad (i = 1, 2, 3), \quad (5.4)$$

with $\epsilon = 0.3$ and $\kappa = 2$ as before. Note that $q_3 = p_3$.

In Figure 3, the estimated posterior mean plus and minus two times the estimated posterior standard deviation of $\alpha_i (= \beta_i \phi)$ ($i = 1, 2, 3$), evaluated after each time point. We again note a significant change in the parameters at time points 21 and 31. The estimation of $\alpha_1$ is more erratic than the other two parameters but appears to be settling down towards the end of the observation period. The estimated posterior means and standard deviations for $\theta_\alpha|y_{0:40}$ are given in Table 5.3. Whilst the estimated posterior means are similar to those obtained in Table 5.2 with predator and prey numbers observed, there is substantially greater uncertainty in the posterior distribution of the parameters. This is consistent with Boys et al. (2008), Table 2.

6 Repressilator model

We follow Toni et al. (2009) in analysing data simulated from the Repressilator model with $\theta_\alpha = (\alpha_1, \alpha_2, \alpha_3, \alpha_4, \omega) = (1000, 1, 5, 1, 2)$, initial mRNA levels $Y(0) = (0, 0, 0)$ and protein levels $Z(0) = (2, 1, 3)$. The data was simulated for 50 time units with over 140,000 events taking place. The mRNA levels of the three genes were observed at times 1, 2, ..., 50, shown in Figure 4 below, whilst the protein levels, apart from the initial numbers, were unobserved.

The key difference from Toni et al. (2009) is that we assume that $\alpha_4$ is unknown. Uniform priors are chosen for $\theta_\alpha$: $\pi(\alpha_1) \sim U(500, 2500)$, $\pi(\alpha_2) \sim U(0, 10)$, $\pi(\alpha_3) \sim U(0, 10)$, $\pi(\alpha_4) \sim U(0.5, 2)$ and $\pi(\omega) \sim U(0, 10)$. Transforming this into a prior for $\theta$ is straightforward, by drawing $\beta_1 \sim U[250, 5000]$, $\beta_2 \sim U[0, 10]$, $\beta_3 \sim U[0, 20]$ and $\omega \sim U[0, 10]$. Then set $B \subseteq [0.5, 2]$ such that for $\phi \in B$, $\alpha_k = \beta_k \phi$ ($k = 1, 2, 3$) is within the appropriate prior range.

Employing the SMC algorithm for the Repressilator model is more computationally challenging than for the Lotka-Volterra data set. Firstly, the simulated data has on average over 2800 events between
Figure 3: Plots of mean of $\theta_{\alpha}$ parameters plus/minus two standard deviations.
observations. Secondly, the observed data is 3 dimensional rather than 1 or 2 dimensional as in the Lotka-Volterra case. Thirdly, there are 12 rather than 3 transition types. Consequently, we found taking $M = 1000$ and $h = 0.2$ ($a = 0.9798$) offered a good compromise between precision of estimates and efficient running of the SMC algorithm.

In Section 5 for the Lotka-Volterra model, a locally linear importance sampling scheme was found to be useful. Given the non-linear behaviour of the growth and decline of the mRNA gene levels, an alternative approach is used here. Suppose that the target for time $t_i$ is $y_i = (y_{i,1}, y_{i,2}, y_{i,3})$ with correspondingly $z_i = (z_{i,1}, z_{i,2}, z_{i,3})$ unobserved and that the process is currently at $W(s) = (w^y_s, w^z_s)$ with a transition occurring at time $s$. Let $p^p_k$, $p^D_k$, $p^T_k$ and $p^C_k$ denote the transition probabilities of mRNA production, mRNA decay, protein translation and protein decay, respectively, of gene $k$. Set $q^T_k = p^T_k$ and $q^C_k = p^C_k$. That is, we focus the importance sampling on mRNA production and decay where we have a target leaving the protein probabilities unchanged. Let

$$D_k = \left\{ \frac{\beta_1}{1 + y_{i,j}^y} + \beta_2 + y_{i,k} \right\}^{\frac{1}{2}} \times \left\{ \frac{\beta_1}{1 + (w_{s,j}^y)^y} + \beta_2 + w_{s,k}^y \right\}^{\frac{1}{2}},$$

(6.1)

where $j = 3, 1, 2$ corresponds to $k = 1, 2, 3$. Then $D_k$ is geometric mean of the rate of change (production and decay) of gene $k$ mRNA at times $s$ (current) and $t$ (target). Note that since $z_{i,j}$ is unobserved $y_{i,j}$ represents a best guess for $z_{i,j}$. Let $L_k = y_{i,k} - w_{s,k}^y$, the difference between the target and current levels
Table 3: Estimated posterior means and standard deviations for $\theta_\alpha | y_{0:50}, z_0$.

| Parameter | $\alpha_1$ | $\alpha_2$ | $\alpha_3$ | $\alpha_4$ | $\omega$ |
|-----------|------------|------------|------------|------------|---------|
| Mean      | 1030       | 1.036      | 6.363      | 0.9807     | 2.079   |
| St. Dev.  | 59.49      | 0.2912     | 1.012      | 0.0173     | 0.0745  |

of gene $k$ mRNA. Let $\delta = \hat{\phi} - s$, then we set $b_k = (\delta D_k + L_k)/(2\delta D_k)$ and $d_k = (\delta D_k - L_k)/(2\delta D_k)$. Note that $b_k + d_k = 1$ and if $b_k$ and $d_k$ lie outside 0 and 1, we reset the minimum value to 0 and the maximum value to 1. Let $Q^P_k = b_k(p^P_k + p^D_k)$ and $Q^D_k = d_k(p^P_k + p^D_k)$, then we take the importance sampling weights to be

$$q^P_k = \left(1 - \epsilon \left(\frac{s}{\hat{\phi}}\right)^\kappa\right)p^P_k + \epsilon \left(\frac{s}{\hat{\phi}}\right)^\kappa Q^P_k$$

(6.2)

$$q^D_k = \left(1 - \epsilon \left(\frac{s}{\hat{\phi}}\right)^\kappa\right)p^D_k + \epsilon \left(\frac{s}{\hat{\phi}}\right)^\kappa Q^D_k.$$  

(6.3)

This results in increasing/decreasing the production and decay rates of the mRNA of gene $k$ to push the $W^y(s)$ towards $y_i$. As in the Lotka-Volterra model there is an increased push as $s$ approaches $\hat{\phi}$. We found that $\epsilon = 0.2$ and $\kappa = 4$ worked well with typically between 1.3 and 2.0 times as many simulations typically required if importance sampling was not used.

The total number of simulations across the 50 time points was 583,272,179. There is considerable variation in the number of simulations per time point ranging from just over a million for time points 3, 9 and 13 to over 118 million (20.3% of all simulations) for time point 41. Time point 41 stood out with no other time point requiring more than 33 million simulations. In Figure 5, the estimated posterior means of the $\alpha$ parameters are given along with lines denoting the mean plus and minus two standard deviations for every fifth time point from time point 5 to 50. A similar plot is observed for $\omega$. In all cases the estimated posterior mean after 50 time points are close to the true simulated parameters with good estimation of the parameters being apparent from as few as 10 time points for some parameters. This suggests that the mRNA levels are very informative about the parameters of the model. However, there is greater uncertainty in $\alpha_3$, which governs the protein production and decay rates, than the other parameters. This is not surprising as the estimation of $\alpha_3$ depends exclusively on the unobserved protein levels. Similar observations concerning parameter estimates were seen with other simulated data sets. Finally, the estimated posterior means and standard deviations for $\theta_\alpha | y_{0:50}, z_0$ are given in Table 6.
Figure 5: Plots of mean of $\alpha$ parameters plus/minus two standard deviations.
7 Conclusions

This paper has introduced a sequential Monte Carlo (SMC) algorithm for discretely observed Markov processes which can successfully and efficiently obtain samples from the posterior distribution of the parameters. The two key innovations of coupled simulations and a simple, yet effective, importance sampler have been central to this success and are complementary to each other. Both innovations offer improvements throughout the SMC algorithm, however, the coupled simulations are particularly effective in the early stages where there is greater uncertainty about the parameters with larger sets $B$. The importance sampling on the other hand is particularly useful when the outcome $Y(t_i)$ is unusual given $X(t_{i-1})$ and $\theta$. The coupled simulations are straightforward to implement given the reparameterisation, whereas the importance sampling is problem specific but the importance sampling approaches taken in this paper, especially the local linearisation in Section 5, should be generally applicable.

There are a few concluding remarks to make about the SMC algorithm. Firstly, it is trivial to parallelise as at any given time point simulations can be run independently. Thus as the simulations are the time consuming part of the SMC algorithm efficient use of available computing power can be made. Secondly, we have assumed that the observations from the Markov process are exact, if only sometimes partial. It is however straightforward to extend the SMC algorithm to data with observation error.

The SMC algorithm has its origins in the ABC algorithm (Tavaré et al. (1997), Beaumont et al. (2002)) and the ideas developed in this paper could be more widely applied to refining ABC algorithms. The sequential approach of building up the simulation of a stochastic process with refinement of the posterior distribution could be widely used. Also as noted in White et al. (2014), simulating a stochastic processes in stages allows for greater precision to be used in the agreement between the simulated and observed data without severely compromising the acceptance probability. Moreover, coupled simulations and in particular, importance sampling within simulations are worth considering in the implementation of ABC algorithms. Whilst, considerable attention in the ABC literature has been devoted to choice of $\theta$ (for example, MCMC-ABC, Marjoram et al. (2003) and SMC-ABC, Sisson et al. (2007)) and the choice and evaluation of summary statistics (for example, local-linear regression, Beaumont et al. (2002) and semi-automatic ABC, Fearnhead and Prangle (2012)), there has been little research into improvement of the simulation process to make the ABC algorithm more efficient. As illustrated in this paper it is possible to improve on the simulation process without significantly compromising the efficiency of the simulation process.
Acknowledgements

The author was supported by the Engineering and Physical Sciences Research Council under grant EP/J008443/1.

Appendix: Random variable sets

We outline how sets of values can be drawn from a random variable and how these can be exploited to give unbiased estimates of key quantities of interest. In particular, we show how this relates to the construction and use of $B$ in Section 4.3.

Let a random variable $X$ have probability density function $f(x)$ and let $\kappa = \sup_x \{ f(x) \}$. Then if $U \sim U[0,1]$, let $A_U = \{ x : f(x) \geq U \kappa \}$ be a set drawn from $X$. For any function $g(\cdot)$,

$$\hat{\theta} = \kappa \int_{x \in A_U} g(x) \, dx$$

is an unbiased estimate of $\theta = E[g(X)]$, since

$$E[\hat{\theta}] = \int_0^1 \kappa \int_{x \in A_u} g(x) \, dx \, du$$

$$= \kappa \int_{-\infty}^{\infty} g(x) \int_0^1 1_{\{x \in A_u\}} \, du \, dx$$

$$= \kappa \int_{-\infty}^{\infty} g(x) \frac{f(x)}{\kappa} \, dx = \theta.$$ 

(2)

Let $B_u$ denote the set $B$ constructed in Section 4.3 step (c), with explicit dependence on $u$. Note that the maximum of the probability density function of $N(\tilde{\phi}, \sigma_\phi)$ is $\kappa = 1/(\sqrt{2\pi}\sigma_\phi)$, independent of $\tilde{\phi}$. It then follows from (2) that $\varpi/\sqrt{2\pi}\sigma_\phi$, given by (4.5) satisfies

$$E \left[ \frac{\varpi}{\sqrt{2\pi}\sigma_\phi} \right] = \int \int \frac{1}{\sqrt{2\pi}\sigma_\phi} \int_{\Phi} k_\phi \, d\phi \, du \int_{\Theta} \{ \int_{\theta \in B_u} f_R(a; (\tilde{\theta}^*, \phi), x_{i-1}) \, da \} \, d\phi$$

$$= \int \int k_\phi \pi(\phi \tilde{\theta}^*, X(t_{i-1}) = x_{i-1}) f_R(a; (\tilde{\theta}^*, \phi), x_{i-1}) \, da \, d\phi$$

$$= \pi(Y(t_i) = y_i | \tilde{\theta}^*, X(t_{i-1}) = x_{i-1})$$

(3)

as required.
References

Beaumont, M., Zhang, W. and Balding, D. (2002) Approximate Bayesian computation in population genetics. *Genetics* **162**, 2025–2035.

Bailey, N.T.J. (1975). *The Mathematical Theory of Infectious Diseases and its Applications. Second edition*. Griffin, London

Boys, R.J., Wilkinson, D.J. and Kirkwood, T.B.L. (2008) Bayesian inference for a discretely observed stochastic kinetic model. *Stat. Comput.*, **18**, 125–135.

Elowitz, M. B. and Leibler, S. (2000) A synthetic oscillatory network of transcriptional regulators. *Nature* **403**, 335–338.

Fearnhead, P. (2002) MCMC, sufficient statistics and particle filters. *Journal of Computational and Graphical Statistics* **11**, 848–862.

Fearnhead, P., Giagos, V. and Sherlock, C. (2014) Inference for reaction networks using the Linear Noise Approximation. *To appear in Biometrics*

Fearnhead, P. and Prangle, D. (2012) Constructing summary statistics for approximate Bayesian computation: semi-automatic approximate Bayesian computation (with discussion). *J. R. Stat. Soc. Ser. B* **74**, 419–474

Fearnhead, P. and Tayler, B. (2013) An adaptive sequential Monte Carlo Sampler. *Bayesian Analysis* **8**, 411–438.

Gillespie, D. T. (1976) A general method for numerically simulating the stochastic time evolution of coupled chemical reactions. *J. Comp. Phys.* **22**, 403–434.

Golightly, A. and Wilkinson, D.J. (2011) Bayesian parameter inference for stochastic biochemical network models using particle Markov chain Monte Carlo. *Interface Focus* **1**, 807–820.

Gordon, N.J., Salmond, D.J. and Smith, A.F.M. (1993) Novel approach to non-linear/non-Gaussian Bayesian state estimation. *IEEE Proceedings-F* **140**, 107–113.

Kurtz, T. (1970). Solutions of ordinary differential equations as limits of pure jump Markov processes. *J. Appl. Prob.* **7** 49–58.
Kurtz, T. (1971). Limit theorems for sequences of jump Markov processes approximating ordinary differential processes. *J. Appl. Prob.* **8** 344–356.

Liu, J. and West, M. (2001). Combined parameter and state estimation in simulation-based filtering. In Doucet, A., de Freitas, N., and Gordon, N. J., editors, *Sequential Monte Carlo Methods in Practice*, pages 197–223. Springer-Verlag.

Marjoram, P., Molitor, J., Plagnol, V. and Tavaré, S. (2003) Markov chain Monte Carlo without likelihoods. *Proc. Natl. Acad. Sci. USA*, **100**, 15324–15328.

Neal, P. (2012) Efficient likelihood-free Bayesian computation for household epidemic. *Stats and Computing*, **22**, 1239–1256.

Neal, P. and Huang, C.L.T. (2013) Forward simulation MCMC with applications to stochastic epidemic models. *Under revision. Submitted to Scand. J. Stats.*

Ripley, B.D. (1987) *Stochastic Simulation*. Wiley & Sons.

Sisson, S. A., Fan, Y. and Tanaka, M. M. (2007) Sequential Monte Carlo without likelihoods. *Proc. Natl. Acad. Sci. USA*, **104**, 1760–1765.

Storvik, G. (2002) Particle filters for state-space models with the presence of unknown static parameters. *IEEE Transactions on Signal Processing*, **50** 281-289.

Tavaré, S., Balding, D.J., Griffiths, R.C. and Donnelly, P. (1997) Inferring coalescence times from DNA sequence data. *Genetics*, **145**, 505–518.

Toni, T., Welch, D., Strelkowa, N., Ipsen, A. and Stumpf, M. (2009) Approximate Bayesian computation scheme for parameter inference and model selection in dynamical systems. *J. Roy. Soc. Interface* **6**, 187–202.

White, S., Kypraios, T. and Preston, S. (2013) Fast Approximate Bayesian Computation for discretely observed Markov models using a factorised posterior distribution. *To appear in Stats. and Computing*

Wilkinson, D. (2011) *Stochastic modelling for systems biology*. Chapman & Hall/CRC.