Correlated pseudo-marginal schemes for time-discretised stochastic kinetic models

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Abstract

The challenging problem of conducting fully Bayesian inference for the reaction rate constants governing stochastic kinetic models (SKMs) is considered. Given the challenges underlying this problem, the Markov jump process representation is routinely replaced by an approximation based on a suitable time-discretisation of the system of interest. Improving the accuracy of these schemes amounts to using an ever finer discretisation level, which in the context of the inference problem, requires integrating over the uncertainty in the process at a predetermined number of intermediate times between observations. Pseudo-marginal Metropolis-Hastings schemes are increasingly used, since for a given discretisation level, the observed data likelihood can be unbiasedly estimated using a particle filter. When observations are particularly informative, an auxiliary particle filter can be implemented, by propagating particles conditional on the next observation. Recent work in state-space settings has shown how the pseudo-marginal approach can be made much more efficient by correlating the underlying pseudo-random numbers used to form the estimate of likelihood at the current and proposed values of the unknown parameters. This approach is extended to the time discretised SKM framework by correlating the innovations that drive the auxiliary particle filter. The resulting approach is found to offer substantial gains in efficiency over a standard implementation.

Keywords: auxiliary particle filter (APF); Bayesian inference; Markov jump process (MJP); Poisson leap; chemical Langevin equation; particle MCMC.

1 Introduction

A stochastic kinetic model (SKM) typically refers to a reaction network, an associated rate law and a probabilistic description of the reaction dynamics. Reactions occur continuously in time with a reaction occurrence resulting in a discrete change to the system state. A Markov jump process (MJP) therefore provides a natural description of the time-course behaviour of the species involved in the reaction network. The resulting modelling framework is fairly flexible and consequently, has been used ubiquitously in areas such as epidemiology (Lin and Ludkovski, 2013; McKinley et al., 2014; O'Neill and Roberts, 1999), population ecology (Ferm et al., 2008; Boys et al., 2008; Gillespie and Golightly, 2010) and systems biology (Wilkinson, 2009; Golightly and Wilkinson, 2015; Koblents and Miguez, 2015; Hey et al., 2015). A concise introduction to SKMs can be found in Wilkinson (2012).

Whilst exact simulation of the MJP is straightforward (using for example the direct method of Gillespie (1976)), performing exact fully Bayesian inference is made problematic by the intractability of the observed data likelihood. Consequently, several approaches have been developed that make use of computationally intensive methods. These include the use of data augmentation (Boys and Giles, 2007; Boys et al., 2008) together with Markov chain Monte Carlo

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(MCMC), reversible jump MCMC (Boys et al., 2008; Wang et al., 2010), population Monte Carlo (Koblents and Miguez, 2015) and particle MCMC (Andrieu et al., 2010; Golightly and Wilkinson, 2011; Owen et al., 2015). Such methods typically require many simulations of the jump process, prohibiting their use for SKMs with many reactions and species. Consequently, there has been much interest in the development of exact (simulation-based) inference schemes for cheap approximations of the MJP. In particular, approximations based on time-discretisation do not require simulation of every reaction event, but rather update the state of the system in one go, after a particular time-step (typically chosen by the practitioner). In this paper, we focus on two such approximations, the Poisson leap (Gillespie, 2001; Anderson, 2008) and chemical Langevin equation, also known as the diffusion approximation (Gillespie, 1992, 2000; Golightly and Wilkinson, 2005). Our umbrella aim is the development of fully Bayesian inference schemes that are both computationally and statistically efficient.

When working with the time-discretised process, inference is still far from straightforward. Ensuring a desired level of accuracy requires the introduction of a pre-specified number of intermediate time-points between observations. Since the latent process at these time-points cannot be integrated out analytically, the observed data likelihood under the approximate model remains intractable. We therefore develop a particle MCMC scheme for performing fully Bayesian inference for either the Poisson leap or CLE and improve computational efficiency over a vanilla implementation in two ways. First, an auxiliary particle filter (Pitt and Shephard, 1999) is used to (unbiasedly) estimate the observed data likelihood. As shown by Golightly and Wilkinson (2015), this is crucial in avoiding highly variable likelihood estimates in scenarios where intrinsic stochasticity outweighs the error in the observation process. Essentially, particles are propagated conditional on future observations by using a suitable bridge construct. When using the Poisson leap, we propose to use the conditioned reaction hazard of Golightly and Wilkinson (2015). For the CLE, we use the modified diffusion bridge (MDB) of Durham and Gallant (2002) (or the appropriate extension to incomplete observation described in Whitaker et al. (2017b)). Finally, we make use of the recently proposed correlated pseudo-marginal algorithm (Deligiannidis et al., 2017; Dahlin et al., 2015), which introduces positive correlation between successive likelihood estimates in order to reduce the variance of the acceptance ratio.

Our approach is to introduce correlation between the bridges generated by the auxiliary particle filter at iteration i and those generated at iteration i+1. When using the CLE, this can be achieved by correlating the Gaussian innovations that drive the MDB. When using the Poisson leap, the numbers of reaction events conditional on the next observation can be used. A similar approach is described in Tran et al. (2016) for a univariate diffusion process. Choppala et al. (2016) consider a Lotka–Volterra reaction network and calculate the observed data likelihood by averaging G 'blocks' of unbiased estimates (which can be computed in parallel). Correlation is introduced by only updating the likelihood in a randomly chosen block. This is the so-called blockwise pseudo-marginal method. Our contribution is a unified framework for applying a correlated pseudo-marginal algorithm to a general class of time-discretised stochastic kinetic models, that additionally allows a flexible observation regime. In particular, we consider incomplete observation of the model components as well as Gaussian measurement error. We apply the resulting methodology to four examples arising in systems biology and epidemiology, using both real and synthetic data.

The remainder of this paper is organised as follows. Section 2 gives a brief introduction to SKMs with particular attention to the derivation of the Poisson leap and CLE approximations. The inference algorithm is described in detail in Section 3 and applied to several examples in Section 4. Conclusions are drawn in Section 5.

2 Stochastic kinetic models

Consider a reaction network involving s species $\mathcal{X}_1, \ldots, \mathcal{X}_s$ and v reactions $\mathcal{R}_1, \ldots, \mathcal{R}_v$ such that

$$\sum_{j=1}^{s} p_{ij} \mathcal{X}_j \longrightarrow \sum_{j=1}^{s} q_{ij} \mathcal{X}_j, \quad i = 1, \dots, v$$

where p_{ij} and q_{ij} are non-negative integers known as stoichiometric coefficients. Let $X_{j,t}$ denote the (discrete) number of species \mathcal{X}_j at time t, and let X_t be the s-vector $X_t = (X_{1,t}, \dots, X_{s,t})^T$. The time evolution of X_t is most naturally described by a Markov jump process (MJP), so that for an infinitesimal time increment dt and an instantaneous hazard $h_i(X_t, c_i)$, the probability of a type i reaction occurring in the time interval (t, t + dt] is $h_i(X_t, c_i)dt$. Under the standard assumption of mass action kinetics, h_i is proportional to a product of binomial coefficients. Specifically

$$h_i(X_t, c_i) = c_i \prod_{j=1}^s {X_{j,t} \choose p_{ij}}.$$

Values for $c = (c_1, \ldots, c_v)^T$, the initial system state $X_0 = x_0$ and the $s \times v$ stoichiometry matrix S whose (i, j)th element is given by $q_{ji} - p_{ji}$, complete specification of the Markov process. Despite the intractability of the probability mass function governing the state of the system at any time t, generating exact realisations of the MJP is straightforward via a technique known in this context as Gillespie's direct method (Gillespie, 1977). In brief, if the current time and state of the system are t and X_t respectively, then the time to the next event will be exponentially distributed with rate parameter

$$h_0(X_t, c) = \sum_{i=1}^{v} h_i(X_t, c_i),$$

and the event will be a reaction of type \mathcal{R}_i with probability $h_i(X_t, c_i)/h_0(X_t, c)$ independently of the inter-event time.

2.1 Time-discretisation

Whilst generating simulations of the MJP description of the SKM is straightforward, capturing every occurrence of a reaction time and type can be computationally expensive, and this may preclude use of the MJP as an inferential model. We therefore consider two approximations to the MJP, the Poisson leap method and the chemical Langevin equation, and give a brief, informal derivation of both approaches.

Consider an infinitesimal time interval, (t, t + dt], over which the reaction hazards will remain constant almost surely. The occurrence of reaction events can therefore be regarded as the occurrence of events of a Poisson process with independent realisations for each reaction type. Hence, for an interval $(t, t + \Delta t]$ of finite length, Δt , and the current system state X_t , the number of reaction events of type i, r_i , is Poisson distributed with rate $h_i(X_t, c)\Delta t$. Let $r = (r_1, \ldots, r_v)^T$. It should then be clear that the system state can be updated approximately, according to

$$X_{t+\Delta t} = X_t + Sr. (1)$$

Further extensions to this approach (although not pursued here) involve stepping ahead a variable amount of time τ , based on the rate constants and the current state of the system. This gives the so called τ -leap algorithm (Gillespie, 2001).

It should now be clear from (1) that the expectation and variance of the infinitesimal dX_t are

$$E(dX_t) = S h(X_t, c)dt, \quad Var(dX_t) = S \operatorname{diag}\{h(X_t, c)\}S^T dt,$$

where $h(X_t, c) = (h_1(X_t, c_1), \dots, h_v(X_t, c_v))^T$. Hence, a further approximation can be obtained by constructing the Itô stochastic differential equation (SDE) that has the same infinitesimal mean and variance as the true MJP. That is

$$dX_t = S h(X_t, c)dt + \sqrt{S \operatorname{diag}\{h(X_t, c)\}S^T} dW_t,$$
(2)

where W_t is an s-vector of standard Brownian motion and $\sqrt{S \operatorname{diag}\{h(X_t,c)\}S^T}$ is an $s \times s$ matrix B such that $BB^T = S \operatorname{diag}\{h(X_t,c)\}S^T$. Equation (2) is the SDE most commonly referred to as the chemical Langevin equation (CLE), and can be shown to approximate the SKM increasingly well in high concentration scenarios (Gillespie, 2000). The CLE can rarely be solved analytically, and it is common to work with a discretisation such as the Euler-Maruyama discretisation which gives

$$X_{t+\Delta t} = X_t + S h(X_t, c) \Delta t + \sqrt{S \operatorname{diag}\{h(X_t, c)\}S^T \Delta t} Z$$

where Z is a standard multivariate Gaussian random variable.

3 Bayesian inference

3.1 Setup

Suppose that the Markov jump process is not observed directly, but observations y_t (on a regular grid) are available and assumed conditionally independent (given the latent jump process) with conditional probability distribution obtained via the observation equation,

$$Y_t = P^T X_t + \varepsilon_t, \qquad \varepsilon_t \sim \mathcal{N}(0, \Sigma), \qquad t = 1, \dots, n.$$
 (3)

Here, Y_t is a length-p vector, P is a constant matrix of dimension $s \times p$ and ε_t is a length-p Gaussian random vector. The density linking the observed and latent process is denoted by $p(y_t|x_t)$. For simplicity we assume that Σ is known.

In what follows, we replace the expensive MJP with either the Poisson leap approximation or chemical Langevin equation, and perform exact (simulation-based) Bayesian inference using the approximate model. We anticipate that the time between observations is too large for these approximations to be directly applied and therefore introduce intermediate times between observations. Hence, without loss of generality, consider an equally spaced partition of the time interval [t-1,t] as

$$t - 1 = \tau_{t-1,0} < \tau_{t-1,1} < \dots < \tau_{t-1,m-1} < \tau_{t-1,m} = t \tag{4}$$

where $\tau_{t-1,i+1} - \tau_{t-1,i} = \Delta \tau = 1/m$. Hence, the approximation is applied recursively over each sub-interval $[\tau_{t-1,i}, \tau_{t-1,i+1}]$ rather than in a single instance over [t-1,t]. Note that the value m is pre-specified by the practitioner and controls both the accuracy and computational cost of the approximation.

Suppose now that the main objective is inference for the rate constants c given data $y = (y_1, \ldots, y_n)^T$. To this end, consider the marginal posterior

$$\pi(c) \propto \pi_0(c)p(y|c)$$
 (5)

where $\pi_0(c)$ is the prior density ascribed to c. Unfortunately, (5) is complicated by the observed data likelihood p(y|c). For the CLE, this satisfies

$$p(y|c) = \int p(x|c)p(y|x)dx$$

where $x = (x_{\tau_{1,0}}, \dots, x_{\tau_{1,m}}, x_{\tau_{2,0}}, x_{\tau_{2,1}}, \dots, x_{\tau_{n-1,m}})$. Additionally,

$$p(x|c) = p(x_1) \prod_{t=1}^{n-1} \prod_{i=0}^{m-1} N\left(x_{\tau_{t,i+1}}; x_{\tau_{t,i}} + Sh(x_{\tau_{t,i}}, c)\Delta\tau, S\operatorname{diag}\{h(x_{\tau_{t,i}}, c)\}S^T\Delta\tau\right)$$
(6)

and

$$p(y|x) = \prod_{t=1}^{n} N\left(y_t; P^T x_t, \Sigma\right)$$
(7)

where $N(\cdot; a, B)$ denotes the pdf of a Gaussian random variable with mean a and variance B. For the Poisson leap approximation we have that

$$p(y|c) = \sum_{x_1,r} p(x_1)p(r|x_1,c)p(y|r,x_1)$$

where $r = (r_{\tau_{1,1}}, \dots, r_{\tau_{1,m}}, r_{\tau_{2,1}}, r_{\tau_{2,2}}, \dots, r_{\tau_{n-1,m}})$ and for example, $r_{\tau_{t,i}} = (r_{\tau_{t,i,1}}, \dots, r_{\tau_{t,i,v}})^T$ is the length-v vector containing the number of reactions of each type in the interval $[\tau_{t,i-1}, \tau_{t,i}]$. It should be clear that given x_1 and r, x can be obtained deterministically through recursive application of (1). Hence $p(y|r,x_1)$ coincides with p(y|x) above and

$$p(r|x_1, c) = \prod_{t=1}^{n-1} \prod_{i=0}^{m-1} \prod_{j=1}^{v} \text{Po}\left(r_{\tau_{t,i+1,j}}; h_j(x_{\tau_{t,i}}, c_j) \Delta \tau\right)$$

where $Po(\cdot; h)$ denotes the mass function of a Poisson random variable with mean h.

Owing to the intractability of p(y|c), the posterior in (5) is sampled via Markov chain Monte Carlo (MCMC). In particular, a suitably constructed pseudo-marginal Metropolis–Hastings scheme (PMMH) (Beaumont, 2003; Andrieu and Roberts, 2009; Andrieu et al., 2010) provides an effective way of performing this task. We briefly describe this approach in the next section alongside an adaptation of a recently proposed modification (the so-called correlated PMMH method) that gives a significant improvement in efficiency over the basic scheme.

3.2 Correlated pseudo-marginal Metropolis-Hastings

Suppose that auxiliary variables $U \sim g(u)$ can be used to generate a non-negative unbiased estimator $\hat{p}_U(y|c)$ of p(y|c). Therefore, an unbiased (up to a constant) estimator of the posterior is

$$\hat{\pi}_U(c) = \pi_0(c)\hat{p}_U(y|c).$$

The PMMH scheme is an MH scheme targeting

$$\tilde{\pi}(c, u) = \pi_0(c)g(u)\hat{p}_u(y|c)$$

which has marginal distribution

$$\int \pi_0(c)g(u)\hat{p}_u(y|c)\,du \propto \pi(c).$$

For a proposal kernel of the form q(c'|c)g(u'), the MH acceptance probability is

$$\alpha \left\{ (c', u') | (c, u) \right\} = \min \left\{ 1, \frac{\tilde{\pi}(c', u')}{\tilde{\pi}(c, u)} \times \frac{q(c|c')g(u)}{q(c'|c)g(u')} \right\}$$

$$= \min \left\{ 1, \frac{\pi_0(c')\hat{p}_{u'}(y|c')}{\pi_0(c)\hat{p}_{u}(y|c)} \times \frac{q(c|c')}{q(c'|c)} \right\}$$
(8)

and therefore the density associated with the auxiliary variables need not be evaluated.

Note that the proposal kernel need not be restricted to the use of g(u'). The correlated PMMH scheme (Deligiannidis et al., 2017; Dahlin et al., 2015) generalises the PMMH scheme by using a proposal kernel of the form g(c'|c)K(u'|u) where $K(\cdot|\cdot)$ satisfies the detailed balance equation

$$g(u)K(u'|u) = g(u')K(u|u').$$
 (9)

It is straightforward to show that a MH scheme with proposal kernel q(c'|c)K(u'|u) and acceptance probability (8) satisfies detailed balance with respect to the target $\tilde{\pi}(c, u)$. Upon negating the trivial scenario that the chain does not move, we have that

$$\begin{split} \tilde{\pi}(c,u)q(c'|c)K(u'|u)\alpha \left\{ (c',u')|(c,u) \right\} \\ &= \min \left\{ \pi_0(c)g(u)\hat{p}_u(y|c)q(c'|c)K(u'|u) \,,\, \pi_0(c')g(u)\hat{p}_{u'}(y|c')q(c|c')K(u'|u) \right\} \\ &= \min \left\{ \pi_0(c)g(u)\hat{p}_u(y|c)q(c'|c)K(u'|u) \,,\, \pi_0(c')g(u')\hat{p}_{u'}(y|c')q(c|c')K(u|u') \right\} \\ &= \tilde{\pi}(c',u')q(c|c')K(u|u')\alpha \left\{ (c,u)|(c',u') \right\} \end{split}$$

where (9) is used to deduce the third line.

In practice, g(u) is a standard Gaussian density and K(u'|u) is taken to be the kernel associated with a Crank–Nicolson proposal. That is

$$g(u) = N(u; 0, I_d)$$
 and $K(u'|u) = N(u'; \rho u, (1 - \rho^2) I_d)$

where I_d is the identity matrix whose dimension d is determined by the number of elements in u and ρ is chosen to be close to 1, to induce positive correlation between $\hat{p}_U(y|c)$ and $\hat{p}_{U'}(y|c')$. Taking $\rho = 0$ gives the special case that K(u'|u) = g(u'), which corresponds to the PMMH scheme. The motivation for taking $\rho \approx 1$ is to reduce the variance of the acceptance probability in (8). Consequently, significant gains in statistical efficiency (relative to the standard PMMH scheme) may be expected. In scenarios where U is not normally distributed (as is the case for the Poisson leap approximation) it is straightforward to generate uniform random variates via $\Phi(U)$ (where $\Phi(\cdot)$ is the cdf of a standard normal random variable). These uniform draws can then be transformed e.g. to give Poisson draws, via the inversion method.

The correlated PMMH scheme is summarised in Algorithm 1. After initialisation, each iteration requires computation of $\hat{p}_{u'}(y|c')$. This is achieved by executing an auxiliary particle filter (for each proposed value (c', u')), which we describe in the next section.

3.3 Auxiliary particle filter

The observed data likelihood p(y|c) can be factorised as

$$p(y|c) = p(y_1|c) \prod_{t=2}^{n} p(y_t|y_{1:t-1}, c)$$
(10)

where $y_{1:t-1} = (y_1, \ldots, y_{t-1})$. Although the constituent terms in (10) will typically be intractable, a particle filter provides an efficient mechanism for their estimation. Moreover, the particle filter that we consider here gives an unbiased estimator of p(y|c) (Del Moral, 2004; Pitt et al., 2012) and hence can be used in steps 1(b) and 2(b) of the CPMMH scheme; see Algorithm 1. For a concise introduction to particle filters, we refer the reader to Künsch (2013) and the references therein.

The basic idea behind the particle filter is to recursively approximate the sequence of filtering densities $p(x_t|y_{1:t},c)$ using a sequence of importance sampling and resampling steps. Let $u=(u_1,\ldots,u_n)$ denote a realisation of the random variables required by the particle filter. We further adopt the partition $u_t=(\tilde{u}_t,\bar{u}_t)^T$ to distinguish between the variables used to propagate state particles and those used in the resampling step, respectively. Note that $\tilde{u}_t=(\tilde{u}_t^1,\ldots,\tilde{u}_t^N)$

Algorithm 1 Correlated PMMH scheme (CPMMH)

Input: correlation parameter ρ and the number of CPMMH iterations n_{iters} . **Output:** $c^{(1)}, \ldots, c^{(n_{\text{iters}})}$.

- 1. For iteration i = 0:
 - (a) Set $c^{(0)}$ in the support of $\pi(c)$ and draw $u^{(0)} \sim N(0, I_d)$.
 - (b) Compute $\hat{p}_{u^{(0)}}(y|c^{(0)})$ by running Algorithm 2 with $(c,u) = (c^{(0)}, u^{(0)})$.
- 2. For iteration $i = 1, ..., n_{\text{iters}}$:
 - (a) Draw $c' \sim q(\cdot | c^{(i-1)})$ and $\omega \sim N(0, I_d)$. Put $u' = \rho u^{(i-1)} + \sqrt{1 \rho^2} \omega$.
 - (b) Compute $\hat{p}_{u'}(y|c')$ by running Algorithm 2 with (c,u)=(c',u').
 - (c) With probability $\alpha\{(c', u')|(c^{(i-1)}, u^{(i-1)})\}$ given by (8), put $(c^{(i)}, u^{(i)}) = (c', u')$ otherwise store the current values $(c^{(i)}, u^{(i)}) = (c^{(i-1)}, u^{(i-1)})$.

corresponding to a filter with N particles and $\tilde{u}_t^i = (\tilde{u}_{t,1}^i, \dots, \tilde{u}_{t,m}^i)$ for t > 1, corresponding to the discretisation introduced in Section 3.1.

Given a weighted sample of 'particles' $\{x_{t-1}^i, w(u_{t-1}^i)\}_{i=1}^N$ approximately distributed according to $p(x_{t-1}|y_{1:t-1},c)$, the particle filter uses the approximation

$$\hat{p}(x_{(t-1,t]}|y_{1:t},c) \propto p(y_t|x_t,c) \sum_{i=1}^{N} p(x_{(t-1,t]}|x_{t-1}^i,c)w(u_{t-1}^i)$$
(11)

where, in the case of the CLE, $x_{(t-1,t]} = (x_{\tau_{t-1,1}}, \dots, x_{\tau_{t-1,m}})$. We focus here on the CLE for reasons of brevity but note that in the case of the Poisson leap approximation, $x_{(t-1,t]}$ is replaced by $r_{(t-1,t]} = (r_{\tau_{t-1,1}}, \dots, r_{\tau_{t-1,m}})$ since x_t can be obtained deterministically using the state x_{t-1} and the number of reactions of each type in the interval (t-1,t].

The form of (11) suggests a simple importance sampling/resampling strategy where particles are resampled (with replacement) in proportion to their weights, propagated via $x_{(t-1,t]}^i = f_t(\tilde{u}_t^i) \sim p(\cdot|x_{t-1}^i,c)$ and reweighted by $p(y_t|x_t^i,c)$. Here, $f_t(\cdot)$ is a deterministic function of \tilde{u}_t^i (and the parameters c) that gives an explicit connection between the particles and auxiliary variables. Repeating this procedure at each time point gives the bootstrap particle filter (BPF) of Gordon et al. (1993). As discussed in Del Moral and Murray (2015) and Golightly and Wilkinson (2015) however, this scheme is likely to perform poorly when observations are informative. In this case very few particles will have reasonable weight, leading to an estimator of observed data likelihood with high variance. This problem can be alleviated through the use of an auxiliary particle filter (APF) (Pitt and Shephard, 1999; Pitt et al., 2012) which propagates particles via $x_{(t-1,t]}^i = f_t(\tilde{u}_t^i) \sim g(\cdot|x_{t-1}^i,y_t,c)$, with the special case of $g(\cdot|x_{t-1}^i,y_t,c) = p(\cdot|x_{t-1}^i,c)$ giving the BPF.

The APF is described generically in Algorithm 2. The output of the APF can be used to estimate the constituent terms in (10) by simply taking the average unnormalised weight; see steps 1(c) and 2(e). A discussion of the sorting and resampling steps 2(a) and 2(b) is provided in Section 3.3.1. Suitable propagation densities $g(x_{(t-1,t]}|x_{t-1},y_t,c)$ and $g(r_{(t-1,t]}|x_{t-1},y_t,c)$ (as necessary for the Poisson leap) are given in Section 3.3.2.

3.3.1 Resampling

For the resampling step we follow Deligiannidis et al. (2017) and use systematic resampling, which only requires simulating a single uniform random variable at each time point. These can be con-

Algorithm 2 Auxiliary particle filter

Input: parameters c, auxiliary variables u and the number of particles N.

Output: estimate $\hat{p}_u(y|c)$ of the observed data likelihood.

- 1. Initialisation (t = 1).
 - (a) **Sample** the prior. Draw $\tilde{u}_1^i \sim N(0,1)$ and put $x_1^i = f_1(\tilde{u}_1^i) \sim p(\cdot), i = 1, \dots, N$.
 - (b) Compute the weights. For i = 1, ..., N set

$$\tilde{w}(u_1^i) = p(y_1|x_1^i, c), \qquad w(u_1^i) = \frac{\tilde{w}(u_1^i)}{\sum_{j=1}^N \tilde{w}(u_1^j)}.$$

- (c) **Update** observed data likelihood estimate. Compute $\hat{p}_{u_1}(y_1|c) = \sum_{i=1}^{N} \tilde{w}(u_1^i)/N$.
- 2. For times t = 2, 3, ..., n:
 - (a) **Sort.** Obtain the sorted index s(i) and put $\{x_{t-1}^i, w(u_{t-1}^i)\} := \{x_{t-1}^{s(i)}, w(u_{t-1}^{s(i)})\}, i = 1, \ldots, N.$
 - (b) **Resample.** Obtain ancestor indices a_{t-1}^i , $i=1,\ldots,N$ using systematic resampling on the collection of weights $\{w(u_{t-1}^1),\ldots,w(u_{t-1}^N)\}$.
 - (c) **Propagate.** Draw $\tilde{u}_t^i \sim N(0_m, I_m)$ and put $x_{(t-1,t]}^i = f_t(\tilde{u}_t^i) \sim g(\cdot | x_{t-1}^{a_{t-1}^i}, y_t, c), i = 1, \ldots, N.$
 - (d) Compute the weights. For i = 1, ..., N set

$$\tilde{w}(u_t^i) = \frac{p(y_t|x_t^i, c)p(x_{(t-1,t]}^i|x_{t-1}^{a_{t-1}^i, c})}{g(x_{(t-1,t]}^i|x_{t-1}^{a_{t-1}^i, y_t, c})}, \qquad w(u_t^i) = \frac{\tilde{w}(u_t^i)}{\sum_{j=1}^N \tilde{w}(u_t^j)}.$$

(e) **Update** observed data likelihood estimate. Compute

$$\hat{p}_{u_{1:t}}(y_{1:t}|c) = \hat{p}_{u_{1:t-1}}(y_{1:t-1}|c)\hat{p}_{u_t}(y_t|y_{1:t-1},c)$$

where $\hat{p}_{u_t}(y_t|y_{1:t-1},c) = \frac{1}{N} \sum_{i=1}^{N} \tilde{w}(u_t^i)$.

structed from $\bar{u}_t \sim \mathrm{N}(0,1)$ via $\Phi(\bar{u}_t)$. Sorted uniforms can then be found via $\bar{u}_{Rt}^i = (i-1)/N + \Phi(\bar{u}_t)/N, i = 1, \ldots, N$ which are in turn used to choose indices a_{t-1}^i that (marginally) satisfy $\Pr(a_{t-1}^i = k) = w(u_{t-1}^k)$. Note that upon changing c and u the effect of the resampling step is likely to prune out different particles, thus breaking the correlation between successive estimates of observed data likelihood. To alleviate this problem, Deligiannidis et al. (2017) sort the particles before resampling via the Hilbert sort procedure of Gerber and Chopin (2015). We follow Choppala et al. (2016) by using a simple Euclidean sorting procedure. At observation time t (immediately after propagation), we sort the particle trajectories $x_{(t-1,t]}^i$ as follows. The first sorted particle corresponds to that with the smallest value of the first component of the set $\{x_t^1, \ldots, x_t^N\}$. The remaining particles are chosen by minimising the Euclidean distance between the currently selected particle and the set of all other particles.

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3.3.2 Propagation

We require a suitable importance proposal $g(x_{(t-1,t]}|x_{t-1},y_t,c)$ (or $g(r_{(t-1,t]}|x_{t-1},y_t,c)$ in the case of the Poisson leap method) that takes into account the information in y_t . Consider a time interval [t-1,t] and recall the partition in (4) which we will write as

$$t-1 = \tau_0 < \tau_1 < \ldots < \tau_{m-1} < \tau_m = t$$

for notational simplicity. We adopt the following factorisations,

$$g(x_{(t-1,t]}|x_{t-1},y_t,c) = \prod_{k=0}^{m-1} g(x_{\tau_{k+1}}|x_{\tau_k},y_t,c), \qquad g(r_{(t-1,t]}|x_{t-1},y_t,c) = \prod_{k=0}^{m-1} g(r_{\tau_{k+1}}|x_{\tau_k},y_t,c)$$

and seek suitable expressions for the constituent terms in each product. In the case of the CLE, we use the modified diffusion bridge construct of Durham and Gallant (2002) (see also Whitaker et al. (2017b) for a recent discussion) which effectively uses a linear Gaussian approximation of $X_{\tau_{k+1}}|x_{\tau_k}, y_t, c$. We obtain

$$g(x_{\tau_{k+1}}|x_{\tau_k}, y_t, c) = N\left(x_{\tau_{k+1}}; x_{\tau_k} + \mu(x_{\tau_k}, c)\Delta\tau, \Psi(x_{\tau_k}, c)\Delta\tau\right)$$
(12)

where

$$\mu(x_{\tau_k}, c) = \alpha_k + \beta_k P \left(P^T \beta_k P \Delta_k + \Sigma \right)^{-1} \left\{ y_t - P^T (x_{\tau_k} + \alpha_k \Delta_k) \right\}$$

and

$$\Psi(x_{\tau_k}, c) = \beta_k - \beta_k P \left(P^T \beta_k P \Delta_k + \Sigma \right)^{-1} P^T \beta_k \Delta \tau.$$

Here $\alpha_k = S h(x_{\tau_k}, c)$, $\beta_k = S \operatorname{diag}\{h(x_{\tau_k}, c)\}S^T$ and $\Delta_k = t - \tau_k$. Given that the importance density in (12) is Gaussian, it is straightforward to perform the propagation step in Algorithm 2. We draw $\tilde{u}_{t,k+1}^i \sim \mathrm{N}(0, I_s)$ and set

$$x_{\tau_{k+1}} = x_{\tau_k} + \mu(x_{\tau_k}, c)\Delta\tau + \sqrt{\Psi(x_{\tau_k}, c)\Delta\tau} \,\tilde{u}_{t,k+1}^i, \qquad k = 0, \dots, m-1.$$

For the Poisson leap approximation, we take $g(r_{\tau_{k+1}}|x_{\tau_k}, y_t, c)$ to be a Poisson probability with rate given by an approximation to the expected number of reaction events in $[\tau_k, \tau_{k+1}]$ given the current state of the system and, crucially, the observation y_t . The derivation of this approximate rate can be found in Golightly and Wilkinson (2015) and is given by

$$h^*(x_{\tau_k}, c | y_t) = h(x_{\tau_k}, c) + \operatorname{diag}\{h(x_{\tau_k}, c)\}S^T P \left(P^T \beta_k P \Delta_k + \Sigma\right)^{-1} \left\{y_t - P^T (x_{\tau_k} + \alpha_k \Delta_k)\right\}.$$

Hence, we obtain

$$g(r_{\tau_{k+1}}|x_{\tau_k}, y_t, c) = \prod_{j=1}^{v} \text{Po}\left(r_{\tau_{k+1,j}}; h_j^*(x_{\tau_k}, c|y_t) \Delta \tau\right).$$
(13)

The propagation step in Algorithm 2 can be performed by first drawing $\tilde{u}_{t,k+1}^i \sim N(0, I_v)$ and then applying the inverse Poisson CDF to each component of $\Phi(\tilde{u}_{t,k+1}^i)$ to give $r_{\tau_{k+1}}$, for $k = 0, \ldots, m-1$. We then set

$$x_{\tau_{k+1}} = x_{\tau_k} + Sr_{\tau_{k+1}}, \qquad k = 0, \dots, m-1.$$

3.4 Computational considerations

A single iteration of the CPMMH scheme described in Algorithm 1 requires $n - 1 \times m \times N$ draws of the bridge construct with density (12) when using the CLE, and mass function (13) when using the Poisson leap. Recall that n is the number of observations, m is the number of latent process values per observation interval and N is the number of particles in the auxiliary particle filter. The

cost of drawing from (12) and (13) will be dictated by the number of observed components p, since the inversion of a $p \times p$ matrix is required. Nevertheless, for many systems of interest, it is unlikely that all components will be observed (Golightly and Wilkinson, 2015), and we therefore anticipate that for systems with many species, $p \ll s$ where s is the number of species. It remains for the practitioner to choose m and N to balance posterior accuracy and computational cost.

We follow Stramer and Bognar (2011) and Golightly and Wilkinson (2011) among others, by performing short pilot runs of the inference scheme (for a fixed, conservative value of N) with increasing values of m, until no discernible difference in the posterior output is detected (e.g. by visual inspection of kernel density estimates of the marginal parameter posteriors). For the examples in Section 4, we find that $m \leq 10$ is sufficient.

The number of particles N controls the variance of the estimator of observed data likelihood $\hat{p}_U(y|c)$. As the variances increases, the acceptance probability of the pseudo-marginal MH scheme rapidly decreases to 0 (Pitt et al., 2012), resulting in 'sticky' behaviour of the parameter chains. Practical advice for choosing N to balance mixing performance and computational cost can found in Doucet et al. (2015) and Sherlock et al. (2015). The variance of the log-posterior (denoted σ_N^2 , computed with N particles) at a central value of c (e.g. the estimated posterior median) should be around 2. For the CPMMH scheme, Tran et al. (2016) suggests choosing N so that $\sigma_N^2 = 2.16/1 - \rho_l^2$ where ρ_l is the estimated correlation between $\hat{p}_u(y|c)$ and $\hat{p}_{u'}(y|c')$. Note that for $\rho_l = 0$ corresponding to the vanilla PMMH case, the aforementioned tuning advice is broadly consistent with Doucet et al. (2015) and Sherlock et al. (2015).

4 Applications

To illustrate the proposed approach we consider four applications of increasing complexity. A simple immigration—death model is considered in Section 4.1. We fit the CLE to synthetic data and compare CPMMH with PMMH and additionally, the state-of-the-art MCMC scheme, that is, the modified innovation scheme (MIS) of Golightly and Wilkinson (2008), described briefly in the appendix. In Section 4.2, we fit the CLE associated with a Lotka–Volterra model to synthetic data. We also investigate the effect of increasing observation noise on the performance of the CPMMH scheme. The autoregulatory network of Sherlock et al. (2014) is considered in Section 4.3. We generate synthetic data that is inherently discrete, precluding the use of the CLE as an inferential model. We therefore perform inference using the Poisson leap, and additionally explore the effect of using a bootstrap particle filter on the performance of the CPMMH scheme. Finally, the CLE approximation of a Susceptible–Infected–Removed (SIR) epidemic model is fitted using data on an influenza outbreak in a boys' boarding school in Great Britain (BMJ News and Notes, 1978). It is assumed that the infection rate is a mean reverting diffusion process giving a model with two unobserved components.

Since the rate constants must be strictly positive we update $\log c$ using a random walk proposal with Gaussian innovations. We took the innovation variance to be the posterior variance of $\log c$ (estimated from a pilot run) scaled by a factor of $2.56^2/v$ for CPMMH and $2.38^2/v$ for MIS, where v is the number of rate constants. We chose the number of particles N by following the practical advice described in Section 3.4. To ensure reasonable mixing of the auxiliary variables U, we adopted the conservative choice of $\rho = 0.99$. In each example we use effective sample size (ESS) as a comparator. That is

$$ESS = \frac{n_{\text{iters}}}{1 + 2\sum_{k=1}^{\infty} \alpha_k}$$

where α_k is the autocorrelation function for the series at lag k and n_{iters} is the number of iterations in the main monitoring run. The ESS can be computed using the R package CODA (Plummer et al., 2006). We report the minimum effective sample size over all components, denoted by ESS_{min}. All algorithms are coded in R and were run on a desktop computer with an Intel Core i7-4770 processor

at 3.40GHz. An R implementation of PMMH, CPMMH and MIS for generic (univariate) diffusion processes is available at https://github.com/csgillespie/cor-pseudo-marginal

4.1 Immigration—death model

The immigration—death reaction network takes the form

$$\mathcal{R}_1: \emptyset \xrightarrow{c_1} \mathcal{X}_1 \qquad \mathcal{R}_2: \mathcal{X}_1 \xrightarrow{c_2} \emptyset$$

with immigration and death reactions shown respectively. The stoichiometry matrix is

$$S = \begin{pmatrix} 1 & -1 \end{pmatrix}$$

and the associated hazard function is

$$h(X_t, c) = (c_1, c_2 X_t)^T$$

where X_t denotes the state of the system at time t. Applying (2) directly gives the CLE as

$$dX_t = (c_1 - c_2 X_t) dt + \sqrt{(c_1 + c_2 X_t)} dW_t.$$

We generated a synthetic data set consisting of 101 observations by simulating from the Markov jump process via Gillespie's direct method and retaining the system state at integer times. To provide a challenging scenario for the CLE, we took $c_1 = 4$ and $c_2 = 0.8$ giving inherently discrete trajectories that 'mean revert' around the value 5. Moreover, we took $X_0 = 500$ so that typical trajectories exhibit nonlinear dynamics over the time interval [0, 10]. We assume error-free observation of X_t so that the latent path between observation times, which is propagated according to equation (12), becomes

$$g(x_{\tau_{k+1}}|x_{\tau_k}, x_t, c) = N\left(x_{\tau_{k+1}}; x_{\tau_k} + \frac{x_t - x_{\tau_k}}{t - \tau_k} \Delta \tau, \frac{t - \tau_{k+1}}{t - \tau_k} \beta(x_{\tau_k}, c) \Delta \tau\right),$$

which can be sampled for k = 0, 1, ..., m - 2. We also note in the case of error-free observation of all components of X_t (as is considered in this application), the auxiliary particle filter can be seen as a simple importance sampler. Consequently, the sorting and resampling steps of Algorithm 2 are not required here.

We took independent $N(0, 10^2)$ priors for $\log c_1$ and $\log c_2$, and determined an appropriate discretisation level by performing short runs of MIS with $\Delta \tau \in \{0.05, 0.1, 0.2, 0.5\}$. Since there was very little difference in posteriors beyond $\Delta \tau = 0.2$, we used this value in the main monitoring runs which consisted of 2×10^4 iterations of MIS, CPMMH and PMMH. The results are summarised by Figures 1–2 and Table 1.

Table 1 shows a comparison of each competing inference scheme. Practical advice (as described above) suggests that CPMMH can tolerate much smaller values of N, with the scheme only requiring a value of N around 2 (and we report results for N=1,2) when $\rho=0.99$ compared to N=50 for PMMH. Moreover, we found that the PMMH scheme often exhibited 'sticky' behaviour, resulting in relatively low effective sample sizes. Consequently, in terms of minimum ESS per second, CPMMH (with $\rho=0.99,\ N=1$) outperforms PMMH by a factor of 210, reducing to 150 when N=2.

As noted by Deligiannidis et al. (2017), values of ρ close to 1 can result in slow mixing of the auxiliary variables U, in turn giving parameter correlograms that exhibit long range dependence. This does not appear to be the case for $\rho=0.99$ (see middle panel of Figure 2). Nevertheless, we note that reducing ρ to 0.9 still gives an increase in overall efficiency of almost two orders of magnitude over PMMH. When comparing CPMMH to the modified innovation scheme we obtain similar ESS values. However, the relatively low computational cost of CPMMH (with $\rho=0.99$, N=1) results in an improvement in overall efficiency (with an mESS/s of 42 vs 18).

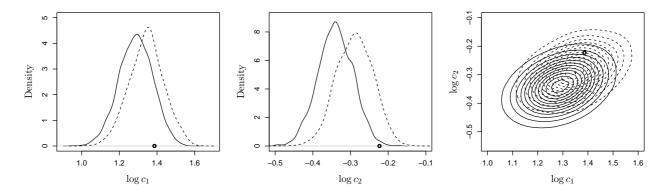


Figure 1: Immigration—death model. Left and middle panels: marginal posterior distributions based on the CLE (solid lines) and MJP (dashed lines). Right panel: Contour plot of the joint posterior based on the CLE (solid line) and MJP (dashed line). The true values of $\log c_1$ and $\log c_2$ are indicated.

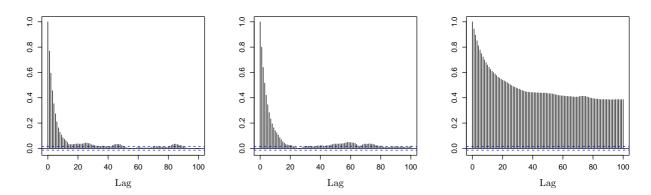


Figure 2: Immigration-death model. Correlogram based on $\log c_2$ samples from the output of MIS (left panel), CPMMH with $\rho = 0.99$ (middle panel) and PMMH (right panel).

The effect of the CLE as an inferential model can be seen in Figure 1. Marginal posteriors based on the CLE exhibit small discrepancies when compared to those obtained under the MJP (obtained using the PMMH method described in Golightly and Wilkinson (2015)). This is unsurprising given the discrete nature of the synthetic data. Nevertheless, posterior samples under the CLE are consistent with the true values that produced the data. Moreover, the inference scheme for the MJP gave a minimum ESS per second of 0.0062. Hence, for this example, sacrificing a small amount of posterior accuracy by using the CLE as an inferential model gives an increase in overall efficiency of a factor of over 3 orders of magnitude. Given the additional computational complexity of the remaining applications, in what follows we focus on either the CLE or Poisson leap as the inferential model.

4.2 Lotka-Volterra model

The Lotka–Volterra system comprises two biochemical species (prey and predator) and three reaction channels (prey reproduction, prey death and predator reproduction, predator death). The reaction list is

$$\mathcal{R}_1: \mathcal{X}_1 \xrightarrow{c_1} 2\mathcal{X}_1, \quad \mathcal{R}_2: \mathcal{X}_1 + \mathcal{X}_2 \xrightarrow{c_2} 2\mathcal{X}_2 \quad \text{and} \quad \mathcal{R}_3: \mathcal{X}_2 \xrightarrow{c_3} \emptyset.$$

Algorithm	ρ	N	CPU (s)	mESS	mESS/s	Rel.
MIS	_	_	121	2190	18	90
CPMMH	0.99	1	45	1910	42	210
	0.99	2	78	2370	30	150
	0.90	1	45	820	18	90
PMMH	0	50	1740	380	0.2	1

Table 1: Immigration–death model. Correlation parameter ρ , number of particles N, CPU time (in seconds s), minimum ESS, minimum ESS per second and relative (to PMMH) minimum ESS per second. All results are based on 2×10^4 iterations of each scheme.

Let $X_t = (X_{1,t}, X_{2,t})^T$ denote the system state at time t. The stoichiometry matrix associated with the system is

$$S = \left(\begin{array}{ccc} 1 & -1 & 0 \\ 0 & 1 & -1 \end{array}\right)$$

and the associated hazard function is

$$h(X_t, c) = (c_1 X_{1,t}, c_2 X_{1,t} X_{2,t}, c_3 X_{2,t})^T.$$

The CLE for this model is given by

$$d\begin{pmatrix} X_{1,t} \\ X_{2,t} \end{pmatrix} = \begin{pmatrix} c_1 X_{1,t} - c_2 X_{1,t} X_{2,t} \\ c_2 X_{1,t} X_{2,t} - c_3 X_{2,t} \end{pmatrix} dt + \begin{pmatrix} c_1 X_{1,t} + c_2 X_{1,t} X_{2,t} & -c_2 X_{1,t} X_{2,t} \\ -c_2 X_{1,t} X_{2,t} & c_2 X_{1,t} X_{2,t} + c_3 X_{2,t} \end{pmatrix}^{\frac{1}{2}} d\begin{pmatrix} W_{1,t} \\ W_{2,t} \end{pmatrix},$$

where $W_{1,t}$ and $W_{2,t}$ are independent standard Brownian motion processes.

We generated a single realisation of the jump process at 51 integer times via Gillespie's direct method with rate constants as in Boys et al. (2008), that is, $c = (0.5, 0.0025, 0.3)^T$ and an initial condition of $X_0 = (100, 100)^T$. We then obtained three data sets by corrupting the system state according to

$$Y_t \sim N(X_t, \sigma^2 I_2)$$

where I_2 is the 2×2 identity matrix and $\sigma \in \{1, 5, 10\}$ giving data sets designated as \mathcal{D}_1 , \mathcal{D}_2 and \mathcal{D}_3 respectively. We took independent $N(0, 10^2)$ priors for each $\log c_i$, i = 1, 2, 3, and followed Golightly and Wilkinson (2011) by setting $\Delta \tau = 0.2$. The main monitoring runs consisted of 10^5 iterations of MIS, CPMMH (with $\rho = 0.99$) and PMMH. The results are summarised in Figure 3 and Table 2.

Figure 3 shows that posterior samples are consistent with the true values that produced the data, despite using an approximate inferential model (the CLE). Table 2 shows a comparison of each competing inference scheme. When using data set \mathcal{D}_1 ($\sigma=1$), CPMMH outperforms PMMH by an order of magnitude (in terms of overall efficiency) and compares favourably with MIS. However, it is clear that as the measurement error standard deviation (σ) increases, PMMH and CPMMH require more particles, in order to effectively integrate over increasing uncertainty in the observation process. Consequently, MIS outperforms PMMH and CPMMH when using \mathcal{D}_2 ($\sigma=5$) and \mathcal{D}_3 ($\sigma=10$), although the relative difference is less than an order of magnitude for MIS vs CPMMH. It is worth noting that the rate of increase in N is greater for CPMMH than for PMMH. Increasing σ appears to break down the correlation between successive estimates of the log-posterior. Fixing the parameter values at the posterior mean and estimating the correlation, denoted by ρ_l , between $\hat{p}_u(y|c)$ and $\hat{p}_{u'}(y|c)$ gave $\rho_l=0.97$ for \mathcal{D}_1 , $\rho_l=0.91$ for \mathcal{D}_2 and $\rho_l=0.57$ for \mathcal{D}_3 . Nevertheless, we still observe a worthwhile increase in overall efficiency of a factor of 2 for CPMMH vs PMMH, when using data set \mathcal{D}_3 corresponding to the relatively extreme $\sigma=10$.

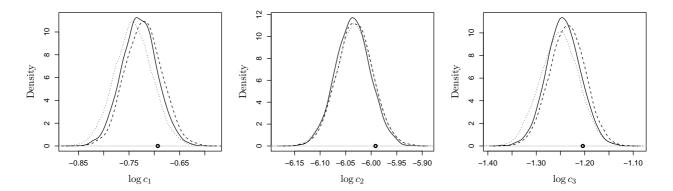


Figure 3: Lotka–Volterra model. Marginal posterior distributions based on the output of CPMMH ($\rho = 0.99$) using data sets \mathcal{D}_1 (solid lines), \mathcal{D}_2 (dashed lines) and \mathcal{D}_3 (dotted lines). The true values of $\log c_1$, $\log c_2$ and $\log c_3$ are indicated.

Data set	Algorithm	N	CPU(s)	mESS	$\mathrm{mESS/s}$	Rel.
•						
$\mathcal{D}_1 \ (\sigma = 1)$	MIS	_	14700	9218	0.627	13.5
	CPMMH	3	11280	8023	0.711	16.3
	PMMH	16	59730	2771	0.046	1.0
$\mathcal{D}_2 \ (\sigma = 5)$	MIS	_	14600	8139	0.558	14.3
	CPMMH	8	29780	3681	0.124	3.2
	PMMH	20	75930	2959	0.039	1.0
$\mathcal{D}_3 \ (\sigma = 10)$	MIS	_	14690	6436	0.438	15.3
	CPMMH	19	71520	3516	0.049	1.7
	PMMH	28	105770	3031	0.029	1.0

Table 2: Lotka–Volterra model. Number of particles N, CPU time (in seconds s), minimum ESS, minimum ESS per second and relative (to PMMH) minimum ESS per second. All results are based on 10^5 iterations of each scheme.

4.3 Autoregulatory network

In this section, we consider a simple autoregulatory network with two species, \mathcal{X}_1 and \mathcal{X}_2 whose time-course behaviour evolves according to the set of coupled reactions

$$\mathcal{R}_{1}: \emptyset \xrightarrow{c_{1}} \mathcal{X}_{1},$$

$$\mathcal{R}_{2}: \emptyset \xrightarrow{c_{2}} \mathcal{X}_{2},$$

$$\mathcal{R}_{3}: \mathcal{X}_{1} \xrightarrow{c_{3}} \emptyset,$$

$$\mathcal{R}_{4}: \mathcal{X}_{2} \xrightarrow{c_{4}} \emptyset,$$

$$\mathcal{R}_{5}: \mathcal{X}_{1} + \mathcal{X}_{2} \xrightarrow{c_{5}} 2\mathcal{X}_{2}.$$

Essentially, reactions R_1 and R_2 represent immigration and reactions R_3 and R_4 represent death. The species interact via R_5 . Let $X_t = (X_{1,t}, X_{2,t})^T$ denote the system state at time t. The stoichiometry matrix associated with the system is

$$S = \left(\begin{array}{cccc} 1 & 0 & -1 & 0 & -1 \\ 0 & 1 & 0 & -1 & 1 \end{array}\right)$$

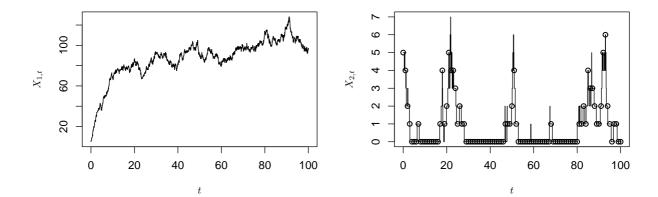


Figure 4: Autoregulatory network. A single realisation of the jump process with $c = (10, 0.1, 0.7, 0.008)^T$ and $X_0 = (5, 5)^T$. Observations are indicated by circles.

Algorithm	N	CPU(s)	mESS	$\mathrm{mESS/s}$	Rel.
CPMMH (APF) PMMH (APF) PMMH (BPF)	20	15580	1272	0.082	6.2
	55	42010	1302	0.031	2.4
	200	95800	1263	0.013	1

Table 3: Autoregulatory network. Number of particles N, CPU time (in seconds s), minimum ESS, minimum ESS per second and relative (to bootstrap filter driven PMMH) minimum ESS per second. All results are based on 10^5 iterations of each scheme.

and the associated hazard function is

$$h(X_t, c) = (c_1, c_2, c_3 X_{1,t}, c_4 X_{2,t}, c_5 X_{1,t} X_{2,t})^T.$$

We simulated a single realisation of the jump process at 101 integer times via Gillespie's direct method with rate constants $c = (10, 0.1, 0.1, 0.7, 0.008)^T$ and an initial condition of $X_0 = (5, 5)^T$. We then discarded the values of $X_{1,t}$ to leave observations of $X_{2,t}$ only. The full data trace used to generate the data set is given in Figure 4. The inherently discrete nature of the data set coupled with long time periods where $X_{2,t} = 0$ make applying the CLE impractical. We therefore use the Poisson leap approximation as the inferential model. To provide a challenging scenario, we assume error-free observation of $X_{2,t}$ so that step 2(d) of Algorithm 2 assigns a weight of 0 to the particle x_t^i unless $x_{2,t}^i$ coincides with the observation at time t. We took a weakly informative Gamma(10, 1) prior for c_1 and Gamma(0.1,0.1) priors for the remaining rate constants. We found little difference in sampled posterior values for a value of $\Delta \tau$ beyond 0.2 and therefore used this value in our main monitoring runs which consisted of 10^5 iterations of CPMMH (with $\rho = 0.996$, which we found to work well for the partial observation scenario) and PMMH. We report results based on both the auxiliary and bootstrap particle filter driven pseudo-marginal schemes. The results are summarised in Table 3 and Figure 5.

Again, we chose the number of particles N by following the practical advice of Tran et al. (2016) for CPMMH and Sherlock et al. (2015) for PMMH. Inspection of Table 3 reveals that the bootstrap particle filter (BPF) driven PMMH scheme required N=200 particles. This reduces to N=55 when using the auxiliary particle filter (APF), and reduces further still to N=20 when strong and positive correlation is introduced between successive values of the random variables that drive the APF. Despite the APF driven scheme requiring many fewer particles than the BPF, overall efficiency (as measured by minimum ESS per second) is only increased by a factor of 2.4 due to

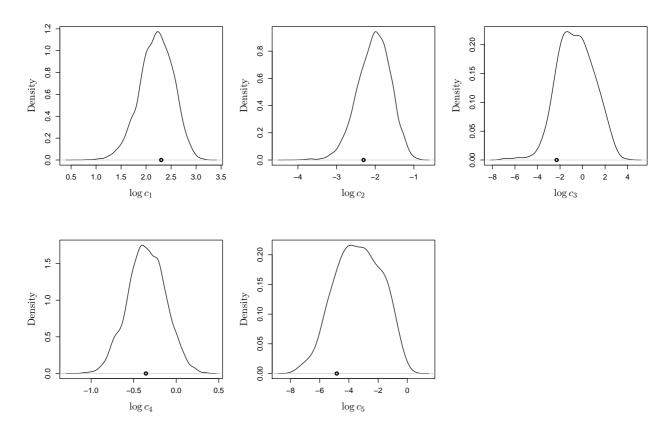


Figure 5: Autoregulatory network. Marginal posterior distributions based on the output of CP-MMH ($\rho = 0.996$). The true values of $\log c_i$, i = 1, ..., 5, are indicated.

the computational complexity of the conditioned hazard, which is used to propagate state particles within the APF. The correlated implementation gives a further increase of a factor of 2.6, giving a 6-fold increase in overall efficiency over the most basic PMMH scheme.

4.4 Epidemic model

The Susceptible–Infected–Removed (SIR) epidemic model (see Andersson and Britton, 2000) describes the evolution of two species (susceptibles \mathcal{X}_1 and infectives \mathcal{X}_2) via two reaction channels which correspond to an infection of a susceptible individual and a removal of an infective individual. The reaction equations are

$$\mathcal{R}_1: \mathcal{X}_1 + \mathcal{X}_2 \xrightarrow{c_1} 2\mathcal{X}_2$$

 $\mathcal{R}_2: \mathcal{X}_2 \xrightarrow{c_2} \emptyset.$

The stoichiometry matrix is

$$S = \left(\begin{array}{cc} -1 & 0\\ 1 & -1 \end{array}\right)$$

and the associated hazard function is

$$h(X_t, c) = (c_1 X_{1,t} X_{2,t}, c_2 X_{2,t})^T.$$

We consider a data set consisting of the daily number of pupils confined to bed (out of a total of 763) during an influenza outbreak in a boys' boarding school in Great Britain, instigated by a

Day	1	2	3	4	5	6	7	8	9	10
No. of infectives	1	3	6	25	73	221	294	257	236	189
Day	11	12	13	14	15					

Table 4: Boarding school data.

Algorithm	N	CPU (m)	mESS	$\mathrm{mESS/m}$	Rel.
СРММН	90	2765	226	0.08	7.2
PMMH	600	26338	299	0.01	1

Table 5: Epidemic model. Number of particles N, CPU time (in minutes m), minimum ESS, minimum ESS per minute and relative minimum ESS per minute. All results are based on 2×10^5 iterations of each scheme.

single pupil. Hence, $X_0 = (762, 1)^T$. The data are displayed graphically in BMJ News and Notes (1978) and converted into counts in Fuchs (2013). For completeness, we give the data in Table 4. We work with the CLE which has the form

$$d\begin{pmatrix} X_{1,t} \\ X_{2,t} \end{pmatrix} = \begin{pmatrix} -c_1 X_{1,t} X_{2,t} \\ c_1 X_{1,t} X_{2,t} - c_2 X_{2,t} \end{pmatrix} dt + \begin{pmatrix} c_1 X_{1,t} X_{2,t} & -c_1 X_{1,t} X_{2,t} \\ -c_1 X_{1,t} X_{2,t} & c_1 X_{1,t} X_{2,t} + c_2 X_{2,t} \end{pmatrix}^{1/2} d\begin{pmatrix} W_{1,t} \\ W_{2,t} \end{pmatrix}.$$
(14)

We further assume that the infection rate is a mean reverting diffusion process governed by the SDE

$$d\log c_{1,t} = c_3(c_4 - \log c_{1,t})dt + c_5 dW_{3,t}.$$
 (15)

Hence, the inferential model is specified by (14) and (15), where c_1 is replaced by $c_{1,t}$ in (14). We wish to infer $c = (c_2, c_3, c_4, c_5)^T$ based on measurements of $X_{2,t}$ only, giving a partially observed system. We took a normal N(0, 10²) prior on the reversion level c_4 of log $c_{1,t}$, and exponential Exp(1) priors for the remaining parameters. For simplicity, we fixed the initial unobserved infection rate by taking $\log c_{1,0} = -6$. The discretisation level was fixed by taking $\Delta \tau = 0.1$. The main monitoring runs consisted of 2×10^5 iterations of CPMMH and PMMH. The results are summarised in Figure 6 and Table 5. It is evident that CPMMH outperforms PMMH in terms of overall efficiency (as measured here by minimum ESS per minute) by a factor of 7.

5 Discussion

Exact (simulation-based) Bayesian inference for Markov jump processes (MJPs) is often rendered impracticable due to the requirement of many (millions of) exact simulations of the jump process. This computational cost can be controlled by replacing the inferential model with an approximation based on time-discretisation. Two such approximations that are routinely applied within the SKM literature are the (discretised) chemical Langevin equation (CLE) and Poisson leap. When using either approximation, the accuracy can be improved by introducing additional intermediate time-points between observation instances and integrating over the uncertainty associated with the induced latent process. As is the case for the MJP, the observed data likelihood under this implementation of time-discretisation remains intractable, requiring the use of PMMH. The key difference however, is that the number of intermediate time-points at which the latent process must be simulated can be pre-specified by the practitioner, with fewer time-points giving reduced computational cost, at the expense of accuracy of the inferential model.

Taking either the (discretised) CLE or Poisson leap as the inferential model to be fitted, we increased the efficiency of PMMH by adapting the recently proposed correlated pseudo-marginal Metropolis–Hastings (CPMMH) algorithm (Deligiannidis et al., 2017; Dahlin et al., 2015) to our

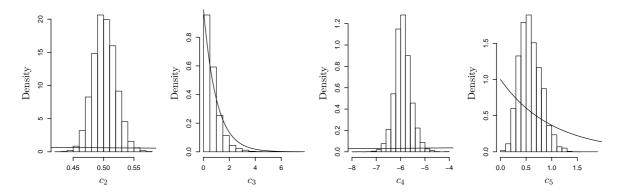


Figure 6: Epidemic model. Marginal posterior distributions based on the output of CPMMH (histograms). Prior densities are given by the solid lines.

setting. Positive correlation between successive observed data likelihood estimates was introduced by correlating the innovations that drive the proposal mechanism in the auxiliary particle filter. Essentially, the innovations are drawn from a kernel that satisfies detailed balance with respect to the innovation density. For a Gaussian innovation density (as is the case when using the CLE), a Crank–Nicolson proposal can be used. In the case of the Poisson leap, it is straightforward to map between Gaussian draws from a Crank–Nicolson proposal and the required Poisson variates. Whilst the degree of correlation present in the generation of the Gaussian innovations may be close to one, this does not necessarily directly translate into high correlations in the observed data likelihood. Nevertheless, in our experiments we see an improvement in performance relative to the standard PMMH scheme.

For a fully observed, error-free immigration-death model, we found that it was possible to obtain an increase in overall efficiency (as measured by minimum effective sample size per second) of CPMMH over PMMH of around two orders of magnitude, whilst giving comparable performance to the modified innovation scheme of Golightly and Wilkinson (2008). To investigate the effect of measurement error, we applied each competing scheme to synthetic data generated from a Lotka-Volterra system and further corrupted with additive Gaussian noise. Not surprisingly, the performance of CPMMH worsens as the measurement error is increased, although we note that even in a relatively extreme scenario where the measurement error variance and average species values are of a similar order of magnitude, CPMMH outperforms PMMH by a factor of 2. We further applied CPMMH to a Poisson leap approximation of an autoregulatory network and to an SDE model of an influenza outbreak in a boys' boarding school. Despite only observing a subset of model components in both examples, we found that CPMMH outperforms PMMH by a factor of around 3 for the autoregulatory network and by a factor of 7 for the epidemic model. We note that bigger efficiency gains can be potentially achieved for extremely long data sets. For univariate models, it may be possible to scale the number of particles N at rate $n^{1/2}$ (where n is the number of observations) rather than at rate n, as is necessary for PMMH (Bérard et al., 2014). For bivariate models, it may be possible to scale N at rate $n^{2/3}$. See Deligiannidis et al. (2017) for further discussion.

The CPMMH algorithm can be improved upon in a number of ways. When using a particle filter to estimate the observed data likelihood, it may be beneficial to resample less often, thus preserving correlation between successive estimates of the observed data likelihood. Whether or not this is practically feasible will depend on the accuracy of the driving bridge proposal process. In scenarios with relatively few observations and when the proposal process is particularly effective, it may even be possible to avoid the resampling step altogether so that the particle filter is replaced by an

importance sampler. The algorithm would also benefit from the availability of parallel computing architectures. In this case, the block pseudo-marginal method of Choppala et al. (2016) could be used. A comparison of this approach with the methods described in this paper remains an area of active research.

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References

- Anderson, D. F. (2008). Incorporating postleap checks in tau-leaping. *The Journal of Chemical Physics*, 128:054103.
- Andersson, H. k. and Britton, T. (2000). Stochastic epidemic models and their statistical analysis, volume 151 of Lecture Notes in Statistics. Springer-Verlag, New York.
- Andrieu, C., Doucet, A., and Holenstein, R. (2010). Particle Markov chain Monte Carlo methods (with discussion). *Journal of the Royal Statistical Society, Series B*, 72(3):1–269.
- Andrieu, C. and Roberts, G. O. (2009). The pseudo-marginal approach for efficient computation.

 Annals of Statistics, 37:697–725.
- Beaumont, M. A. (2003). Estimation of population growth or decline in genetically monitored populations. *Genetics*, 164:1139–1160.
- Bérard, J., Del Moral, P., and Doucet, A. (2014). A lognormal central limit theorem for particle approximations of normalizing constants. *Electronic Journal of Probability*, 19:1–28.
- BMJ News and Notes (1978). Influenza in a boarding school. British Medical Journal, page 587.
- Boys, R. J. and Giles, P. R. (2007). Bayesian inference for stochastic epidemic models with time-inhomogeneous removal rates. *Journal of Mathematical Biology*, 55:223–247.
- Boys, R. J., Wilkinson, D. J., and Kirkwood, T. B. L. (2008). Bayesian inference for a discretely observed stochastic kinetic model. *Statistics and Computing*, 18:125–135.
- Choppala, P., Gunawan, D., Chen, J., Tran, M.-N., and Kohn, R. (2016). Bayesian inference for state space models using block and correlated pseudo marginal methods. Available from http://arxiv.org/abs/1612.07072.
- Dahlin, J., Lindsten, F., Kronander, J., and Schon, T. B. (2015). Accelerating pseudo-marginal Metropolis-Hastings by correlating auxiliary variables. Available from https://arxiv.1511.05483v1.
- Del Moral, P. (2004). Feynman-Kac Formulae: Genealogical and Interacting Particle Systems with Applications. Springer, New York.
- Del Moral, P. and Murray, L. M. (2015). Sequential Monte Carlo with highly informative observations. SIAM/ASA Journal on Uncertainty Quantification, 3(1):969–997.
- Deligiannidis, G., Doucet, A., and Pitt, M. K. (2017). The correlated pseudo-marginal method. Available from https://arxiv.1511.04992v4.
- Doucet, A., Pitt, M. K., and Kohn, R. (2015). Efficient implementation of Markov chain Monte Carlo when using an unbiased likelihood estimator. *Biometrika*, 102:295–313.

- Durham, G. B. and Gallant, R. A. (2002). Numerical techniques for maximum likelihood estimation of continuous time diffusion processes. *Journal of Business and Economic Statistics*, 20:279–316.
- Ferm, L., Lötstedt, P., and Hellander, A. (2008). A hierarchy of approximations of the master equation scaled by a size parameter. *Journal of Scientific Computating*, 34(2):127–151.
- Fuchs, C. (2013). Inference for diffusion processes with applications in Life Sciences. Springer, Heidelberg.
- Gerber, M. and Chopin, N. (2015). Sequential quasi Monte Carlo (with discussion). *Journal of the Royal Statistical Society, Series B*, 77:509–579.
- Gillespie, C. S. and Golightly, A. (2010). Bayesian inference for generalized stochastic population growth models with application to aphids. *Journal of the Royal Statistical Society, Series C*, 52:341–357.
- Gillespie, D. T. (1976). A general method for numerically simulating the stochastic time evolution of coupled chemical reactions. *Journal of Computational Physics*, 22(4):403–434.
- Gillespie, D. T. (1977). Exact stochastic simulation of coupled chemical reactions. *Journal of Physical Chemistry*, 81:2340–2361.
- Gillespie, D. T. (1992). A rigorous derivation of the chemical master equation. *Physica A*, 188:404–425.
- Gillespie, D. T. (2000). The chemical Langevin equation. *Journal of Chemical Physics*, 113(1):297–306.
- Gillespie, D. T. (2001). Approximate accelerated stochastic simulation of chemically reacting systems. *Journal of Chemical Physics*, 115(4):1716–1732.
- Golightly, A. and Wilkinson, D. J. (2005). Bayesian inference for stochastic kinetic models using a diffusion approximation. *Biometrics*, 61(3):781–788.
- Golightly, A. and Wilkinson, D. J. (2008). Bayesian inference for nonlinear multivariate diffusion models observed with error. *Computational Statistics and Data Analysis*, 52(3):1674–1693.
- Golightly, A. and Wilkinson, D. J. (2011). Bayesian parameter inference for stochastic biochemical network models using particle Markov chain Monte Carlo. *Interface Focus*, 1(6):807–820.
- Golightly, A. and Wilkinson, D. J. (2015). Bayesian inference for Markov jump processes with informative observations. *Statistical Applications in Genetics and Molecular Biology*, 14(2):169–188.
- Gordon, N. J., Salmond, D. J., and Smith, A. F. M. (1993). Novel approach to nonlinear/non-Gaussian Bayesian state estimation. *IEE Proceedings-F*, 140:107–113.
- Hey, K. L., Momiji, H., Featherstone, K., Davis, J. R. E., White, M. R. H., Rand, D. A., and Finkenstädt, B. (2015). A stochastic transcriptional switch model for single cell imaging data. *Biostatistics*, 16:655–669.
- Koblents, E. and Miguez, J. (2015). A population Monte Carlo scheme with transformed weights and its application to stochastic kinetic models. *Statistics and Computing*, 25:407–425.
- Künsch, H. R. (2013). Partile filters. Bernoulli, 19:1391–1403.

- Lin, J. and Ludkovski, M. (2013). Sequential Bayesian inference in hidden Markov stochastic kinetic models with application to detection and response to seasonal epidemics. *Statistics and Computing*, 24:1047–1062.
- McKinley, T. J., Ross, J. V., Deardon, R., and Cook, A. R. (2014). Simulation-based Bayesian inference for epidemic models. *Computational Statistics and Data Analysis*, 71:434–447.
- O'Neill, P. D. and Roberts, G. O. (1999). Bayesian inference for partially observed stochastic epidemics. *Journal of the Royal Statistical Society, Series A*, 162:121–129.
- Owen, J., Wilkinson, D. J., and Gillespie, C. S. (2015). Likelihood free inference for Markov processes: a comparison. *Statistical Applications in Genetics and Molecular Biology*, 14(2):189–209.
- Pitt, M. K., dos Santos Silva, R., Giordani, P., and Kohn, R. (2012). On some properties of Markov chain Monte Carlo simulation methods based on the particle filter. *Journal of Econometrics*, 171(2):134–151.
- Pitt, M. K. and Shephard, N. (1999). Filtering via simulation: Auxiliary particle filters. *Journal* of the American Statistical Association, 446:590–599.
- Plummer, M., Best, N., Cowles, K., and Vines, K. (2006). CODA: convergence diagnosis and output analysis for MCMC. *R News*, 6(1):7–11.
- Roberts, G. O. and Stramer, O. (2001). On inference for non-linear diffusion models using Metropolis-Hastings algorithms. *Biometrika*, 88(3):603–621.
- Sherlock, C., Golightly, A., and Gillespie, C. S. (2014). Bayesian inference for hybrid discrete-continuous systems biology models. *Inverse Problems*, 30:114005.
- Sherlock, C., Thiery, A., Roberts, G. O., and Rosenthal, J. S. (2015). On the effciency of pseudo-marginal random walk Metropolis algorithms. *The Annals of Statistics*, 43(1):238–275.
- Stramer, O. and Bognar, M. (2011). Bayesian inference for irreducible diffusion processes using the pseudo-marginal approach. *Bayesian Analysis*, 6:231–258.
- Tran, M.-N., Kohn, R., Quiroz, M., and Villani, M. (2016). Block-wise pseudo-marginal Metropolis-Hastings. Available from http://arxiv.org/abs/1603.02485.
- Wang, Y., Christley, S., Mjolsness, E., and Xie, X. (2010). Parameter inference for discretely observed stochastic kinetic models using stochastic gradient descent. *BMC Systems Biology*, 4:99.
- Whitaker, G. A., Golightly, A., Boys, R. J., and Sherlock, C. (2017a). Bayesian inference for diffusion driven mixed-effects models. *Bayesian Analysis*, 12:435–463.
- Whitaker, G. A., Golightly, A., Boys, R. J., and Sherlock, C. (2017b). Improved bridge constructs for stochastic differential equations. *Statistics and Computing*, 27:885–900.
- Wilkinson, D. J. (2009). Stochastic modelling for quantitative description of heterogeneous biological systems. *Nature Reviews Genetics*, 10:122–133.
- Wilkinson, D. J. (2012). Stochastic Modelling for Systems Biology. Chapman & Hall/CRC Press, Boca Raton, Florida, 2nd edition.

A Modified innovation scheme

We give a brief description of the modified innovation scheme (MIS) and refer the reader to Whitaker et al. (2017a) and the references therein for further details.

Consider the joint posterior of c and the latent process x under the CLE given by

$$\pi(c,x) \propto \pi_0(c)p(x|c)p(y|x)$$

where p(x|c) and p(y|x) can be found in (6) and (7). A Gibbs sampler can be used to generate draws from $\pi(c,x)$ by alternately sampling from the full conditionals

- 1. p(x|c,y),
- 2. p(c|x).

It is straightforward to sample p(x|c,y) using Metropolis within Gibbs coupled with a suitable blocking approach. For example, the latent process can be updated over each interval [t-1,t+1], $t=1,2,\ldots,n-1$ with the modified diffusion bridge construct in (12) used as the proposal mechanism. The use of overlapping blocks in this way ensures that latent process is updated at the observation times (as well as at all other intermediate times). The full conditional p(c|x) can be sampled via Metropolis within Gibbs however for small values of $\Delta \tau$, dependence between the parameters and latent process can render this approach impractical. This well known problem is discussed at length in Roberts and Stramer (2001). The issue is circumvented by the MIS via a reparameterisation. The basic idea is to draw parameter values conditional on a process whose quadratic variation does not determine c. For example, for a time interval [0,T], conditioning on the innovations that drive the modified diffusion bridge construct leads to the continuous-time innovation process

$$dZ_{t} = \beta(X_{t}, c)^{-1/2} \left(dX_{t} - \frac{x_{T} - X_{t}}{T - t} dt \right)$$

$$= \beta(X_{t}, c)^{-1/2} \left\{ \alpha(X_{t}, c) - \frac{x_{T} - X_{t}}{T - t} \right\} dt + dW_{t}$$
(16)

where $\alpha(X_t, c) = S h(X_t, c)$ and $\beta(X_t, c) = S \operatorname{diag}\{h(X_t, c)\}S^T$. A justification for conditioning on realisations of this process in a Gibbs sampler can be found in Fuchs (2013). In practice, we work with a discretisation of (16), that is, the modified diffusion bridge construct. For the induced invertible mapping x = f(z) (where we have suppressed dependence of $f(\cdot)$ on c and the values of the latent process at the observation times), the full conditional density required in step 2 is easily shown to be

$$p(c|z) \propto \pi_0(c)p\{f(z)|c\}J\{f(z)|c\}$$
 (17)

where $p\{f(z)|c\}$ is given by (6) and

$$J\{f(z)|c\} \propto \prod_{t=1}^{n-1} \prod_{k=1}^{m-1} |\beta(x_{\tau_{t,k-1}},c)|^{-1/2}$$

is the Jacobian determinant of f. Naturally, the full conditional in (17) will typically be intractable, requiring the use of Metropolis-within-Gibbs updates. We propose to update $\log c$ using random walk Metropolis with Gaussian innovations.