Bayesian Inference for Nonlinear Multivariate Diffusion Models Observed with Error

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Abstract

Diffusion processes governed by stochastic differential equations (SDEs) are a well established tool for modelling continuous time data from a wide range of areas. Consequently, techniques have been developed to estimate diffusion parameters from partial and discrete observations. Likelihood based inference can be problematic as closed form transition densities are rarely available. One widely used solution involves the introduction of latent data points between every pair of observations to allow an Euler-Maruyama approximation of the true transition densities to become accurate. In recent literature, Markov chain Monte Carlo (MCMC) methods have been used to sample the posterior distribution of latent data and model parameters; however, naive schemes suffer from a mixing problem that worsens with the degree of augmentation. In this paper, we explore an MCMC scheme whose performance is not adversely affected by the number of latent values. We illustrate the methodology by estimating parameters governing an auto-regulatory gene network, using partial and discrete data that is subject to measurement error.

Key words: Bayesian inference, particle filter, MCMC, nonlinear stochastic differential equation

1 Introduction

In the last twenty years, the desire to include unpredictable factors into modelling has encouraged much interest in diffusion models. As a consequence, the problem of how to efficiently estimate parameters governing stochastic

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differential equations (SDEs) has arisen. Some significant examples where this occurs include economics and finance (Black and Scholes, 1973; Cox et al., 1985) and, more recently, bioinformatics (Gillespie, 1992; Arkin et al., 1998; McAdams and Arkin, 1999).

Since transition densities of diffusions are unavailable in closed form for all but a few special cases, likelihood inference is not trivial. Attempts to overcome this problem can be categorised into three main areas; alternative estimators to the MLE include the use of estimating functions (Bibby and Sørensen, 1995) and the method of moments (Chan et al., 1992). Simulated maximum likelihood estimation (SMLE) approaches have been proposed by Pedersen (1995) and refined by Durham and Gallant (2002). Finally, Bayesian imputation methods have been proposed by Elerian et al. (2001), Roberts and Stramer (2001) and Eraker (2001). Most Bayesian and likelihood approaches approximate the underlying, true transition densities with a first order Euler discretisation. As inter-observation times are usually too large to be used as a time step with the Euler method, the observed low-frequency data are augmented with the introduction of $m - 1$ latent data points between every pair of observations. The Gibbs sampler or other Markov chain Monte Carlo (MCMC) schemes can then be used to sample the posterior of latent data and model parameters.

Unfortunately, the most natural Bayesian imputation approach can break down when the amount of augmentation is large. It is well documented (see for example Papaspiliopoulos et al. (2003)) that high dependence between unknown parameters in the diffusion (or volatility) coefficient and the missing data can result in arbitrarily slow rates of convergence of naive sampling strategies such as the single site Gibbs sampler employed by Eraker (2001) and Golightly and Wilkinson (2005a). Some attempts have been made to rectify this problem; Roberts and Stramer (2001) transform the SDE to give a constant diffusion coefficient and by so doing are able to overcome the dependence problem. Beskos et al. (2006) propose Monte Carlo methods which are both exact and computationally efficient, but also rely on a transformation to constant volatility. Such transformations can not be applied to many non-linear multivariate diffusions (such as those considered here) (Wilkinson, 2003) and work in this area remains of great interest.

In this paper we examine a Gibbs sampling algorithm that does not break down for large m (but in fact improves) and we compare it to the sequential MCMC scheme of Golightly and Wilkinson (2005b) and Golightly and Wilkinson (2006). Both algorithms are applied to noisy data generated from a simple auto-regulatory gene network; such networks are examined in Golightly and Wilkinson (2005a) and Golightly and Wilkinson (2006) and typically induce a diffusion that is high dimensional and nonlinear.

The remainder of this paper is organised as follows. In Section 2 we formulate the model and describe the estimation framework; convergence issues of naive sampling strategies are discussed in Section 2.1. We describe a novel MCMC scheme in Section 3 and outline filtering strategies in Section 4. The methodology is illustrated in Section 5 before conclusions are drawn in Section 6.

2 Diffusion Models

We consider inference for a d -dimensional Itô Diffusion that satisfies a stochastic differential equation of the form

$$dY(t) = \mu(Y(t), \Theta)dt + \beta^{\frac{1}{2}}(Y(t), \Theta)dW(t), \quad (1)$$

and assume that the conditions under which the SDE can be solved for $Y(t)$ are satisfied.

Often, we will have only partial data and therefore $Y(t)$ will consist of both observable and unobservable components. Hence we define $Y(t) = (X(t), Z(t))'$, where $X(t)$ defines the observable part and $Z(t)$ the unobservable part of the system. Note that $X(t)$ and $Z(t)$ have dimensions d_1 and d_2 respectively such that $Y(t)$ has dimension $d = d_1 + d_2$. We assume further that the process $X(t)$ is subject to measurement error such that we actually observe

$$V(t) = X(t) + \epsilon(t), \quad (2)$$

where $\epsilon(t) \sim N(0, \Sigma)$, $\Sigma = \text{diag}\{\sigma_i^2\}$ for $i = 1, \dots, d_1$, represents an independent noise process. Note that for unknown Σ , we have $\Theta = (\theta_1, \dots, \theta_p, \sigma_1, \dots, \sigma_{d_1})'$. The assumption of a diagonal Σ is in no way essential, but is adopted here in order to simplify the presentation. The process $V(t)$ will be observed at a finite number of times and the objective is to conduct inference for the (unknown) parameter vector Θ on the basis of these noisy, partial and discrete observations.

As already stated, we work with the discretized version of (1), given by the Euler approximation,

$$\Delta Y(t) = \mu(Y(t), \Theta)\Delta t + \beta^{\frac{1}{2}}(Y(t), \Theta)\Delta W(t), \quad (3)$$

where $\Delta W(t)$ is a d dimensional iid $N(0, I\Delta t)$ random vector. Now suppose we have measurements $v(\tau_i)$ at evenly spaced times $\tau_0, \tau_1, \dots, \tau_T$ with intervals of length $\Delta^* = \tau_{i+1} - \tau_i$. As Δ^* is often too large to be used as a time step in (3), we put $\Delta t = \Delta^*/m$ for some positive integer $m > 1$. By choosing m to be sufficiently large, we can ensure that the discretization bias is arbitrarily

small, but this also introduces the problem of $m - 1$ missing values in between every pair of observations.

We deal with these missing values by dividing the entire time interval $[\tau_0, \tau_T]$ into $mT + 1$ equidistant points $\tau_0 = t_0 < t_1 < \dots < t_n = \tau_T$ such that $V(t)$ is observed at times $t_0, t_m, \dots, t_n$. Altogether we have $d(Tm + 1)$ missing values which we substitute with simulations $Y(t_i)$. We refer to the collection of simulated data as the augmented data. Eraker (2001) denotes by $\hat{Y}$ the $d \times (n + 1)$ matrix obtained by stacking all elements of the augmented data, that is

$$\hat{Y} = \begin{pmatrix} X_1(t_0) & X_1(t_1) & \cdots & X_1(t_m) & X_1(t_{m+1}) & \cdots & X_1(t_n) \\ X_2(t_0) & X_2(t_1) & \cdots & X_2(t_m) & X_2(t_{m+1}) & \cdots & X_2(t_n) \\ \vdots & \vdots & & \vdots & \vdots & & \vdots \\ X_{d_1}(t_0) & X_{d_1}(t_1) & \cdots & X_{d_1}(t_m) & X_{d_1}(t_{m+1}) & \cdots & X_{d_1}(t_n) \\ Z_1(t_0) & Z_1(t_1) & \cdots & Z_1(t_m) & Z_1(t_{m+1}) & \cdots & Z_1(t_n) \\ \vdots & \vdots & & \vdots & \vdots & & \vdots \\ Z_{d_2}(t_0) & Z_{d_2}(t_1) & \cdots & Z_{d_2}(t_m) & Z_{d_2}(t_{m+1}) & \cdots & Z_{d_2}(t_n) \end{pmatrix}.$$

We now let $Y^i = (X^i, Z^i)$ denote the i^{th} column of $\hat{Y}$. By adopting a fully Bayesian approach, we summarise our *a priori* beliefs about Θ and Y^0 via the prior distributions $\pi(\Theta)$ and $\pi(Y^0)$ respectively. Then the joint posterior density for parameters and augmented data is given by

$$\pi(\hat{Y}, \Theta | D_n) \propto \pi(\Theta) \pi(Y^0) \left[\prod_{i=0}^{n-1} \pi(Y^{i+1} | Y^i, \Theta) \right] \left[\prod_{i \in \{0, m, \dots, n\}} \pi(v^i | X^i, \Theta) \right], \quad (4)$$

where v^i denotes $v(t_i)$, $D_n = (v^0, v^m, \dots, v^n)$,

$$\pi(Y^{i+1} | Y^i, \Theta) = \phi(Y^{i+1}; Y^i + \mu_i \Delta t, \beta_i \Delta t) \quad (5)$$

and

$$\pi(v^i | X^i, \Theta) = \phi(v^i; X^i, \Sigma). \quad (6)$$

Here, $\mu_i = \mu(Y^i, \Theta)$, $\beta_i = \beta(Y^i, \Theta)$ and $\phi(\cdot; \psi, \gamma)$ denotes the Gaussian density with mean ψ and variance matrix γ . Note that $\pi(Y^{i+1} | Y^i, \Theta)$ is the one step ahead transition density obtained from the Euler discretization.

2.1 Gibbs Sampling (Convergence Issues)

As discussed in Tanner and Wong (1987), inference may proceed by alternating between simulation of parameters conditional on augmented data, and

simulation of the missing data given the observed data and the current state of the model parameters. As the joint posterior, (4) is usually high dimensional, a Gibbs sampler is a particularly convenient way of sampling from it. For nonlinear diffusions, direct sampling of the full conditional distributions is not possible and a Metropolis within Gibbs move can be implemented. Various sampling strategies have been proposed; Eraker (2001) and Golightly and Wilkinson (2005a) update one column of $\hat{Y}$ at a time whilst Shephard and Pitt (1997) update $\hat{Y}$ in random blocks. The former method of updating one column (which we refer to as the “single site Gibbs sampler”) leads to an algorithm with a rate of convergence that worsens linearly with m . In fact, as m increases, one can make very precise inference about the diffusion coefficient of the process via the quadratic variation (see Roberts and Stramer (2001)). It is this dependence (between the quadratic variation and diffusion coefficient) that results in slow mixing of MCMC algorithms such as the single site Gibbs sampler. Though the block updating method of Shephard and Pitt (1997) is able to help overcome the dependence within the latent process, dependence between the parameters and latent process remains high and convergence will still become arbitrarily slow as either m or the number of observations increases. Roberts and Stramer (2001) overcome this dependence in the context of univariate diffusions by transforming the missing data, giving a partially non-centered parameterisation which leads to an irreducible algorithm even in the limit $m \rightarrow \infty$. However, for a d -dimensional diffusion satisfying (1), finding such a transformation requires an invertible function, $g : \mathbf{R}^d \rightarrow \mathbf{R}^d$ such that

$$\nabla g(\nabla g)' = \beta^{-1}.$$

As discussed by Papaspiliopoulos et al. (2003), this equation is almost always impossible to solve in practice for general non-linear multivariate diffusions such as those considered here. Sequential filtering algorithms have been suggested in Golightly and Wilkinson (2005b) among others and rely on a joint update of Θ and the latent data. Whilst such schemes overcome the dependence issue, they are known to suffer from degeneracy problems as the amount of data increases (see Liu and West (2001) for a discussion).

Here, we develop and illustrate an MCMC strategy which can be easily implemented for any nonlinear multivariate diffusion and does not suffer from the convergence problems of the single site Gibbs sampler; in essence, by alternatively sampling from the posterior of parameters and the driving Brownian motion process (rather than the latent data), we can overcome the dependence between Θ and the latent data. The idea is motivated by the “innovation” scheme of Chib et al. (2004); however, our details and strategy are different; the algorithm we consider can be applied to any partially observed diffusion process (that may be subject to measurement error) and doesn’t rely on being able to untangle the diffusion — that is for our method, the unobserved component, $Z(t)$ can depend on $X(t)$ in a nonlinear way (and vice-versa). We also compare the algorithm to the simulation filter of Golightly and Wilkinson

(2006) — see Section 4 for a brief outline.

3 The Innovation Scheme

Consider data $D_n = (v^0, v^m, \dots, v^n)$ and a Gibbs sampler which samples from the distribution $(\Theta, \hat{Y}|D_n)$ by alternating between draws of Θ conditional on $\hat{Y}$ (and D_n) and the latent data, $\hat{Y}$, conditional on Θ (and D_n). Naturally, for large m such a strategy will result in a chain with arbitrarily slow convergence times. The innovation scheme, however, is subtly different.

Corresponding to the sample path of $Y(t)$, given by $\hat{Y} = (Y^0, Y^1, \dots, Y^n)$, is a skeleton of $W(t)$, the driving Brownian process. We denote this skeleton by $\hat{W} = (W^0, W^1, \dots, W^n)$ and note that under the Euler approximation, (3) (or any discrete approximation of (1)), there is a one-to-one relationship between $\hat{W}$ and $\hat{Y}$, conditional on Θ . Therefore, rather than sample the distribution $(\Theta, \hat{Y}|D_n)$, the innovation scheme samples $(\Theta, \hat{W}|D_n)$ by alternating between draws of Θ conditional on the data and $\hat{W}$, and $\hat{W}$ conditional on Θ and the data.

Algorithmically:-

- (1) Initialise all unknowns. Set the iteration counter to $s = 1$.
- (2) Sample $\hat{W}$ conditional on parameters and the data by updating the latent data, using $(\hat{Y}|\Theta, D_n)$.
- (3) Update parameters by drawing from $(\Theta|\hat{W}, D_n)$.
- (4) Increment s and return to 2.

Step 2 can be performed using a series of Metropolis-Hastings (M-H) moves (see Section 3.1). By updating the latent data, $\hat{W}$ is obtained deterministically, conditional on the current value of Θ . We use a M-H step in 3 to obtain a new Θ (see Section 3.2). Our new value of Θ can then be combined with the skeleton, $\hat{W}$ to give a new sample path $\hat{Y}$, ready to be used in step 2. Hence at every iteration of the algorithm, the volatility of the sample path will be consistent with the current parameter value — this is crucial in order to overcome the dependence issue highlighted by Roberts and Stramer (2001). We now detail each step individually.

3.1 Updating the latent data points

Whilst Chib et al. (2004) update $\hat{Y}$ using random block sizes, our algorithm requires updating in blocks of size $2m + 1$. Note that in the case of complete observation and the absence of measurement error, there is a much simpler

version of this algorithm using blocks of size m , but we do not present that here.

Consider times t_j , t_M and t_{M+} where j is an integer multiple of m , $M = j + m$ and $M^+ = M + m$. Note that these times correspond to the noisy and partial observations, v^j , v^M and v^{M^+} . Treating Y^j and Y^{M^+} as fixed, the full conditional for $Y^{j+1}, \dots, Y^{j+2m-1}$ is

$$\pi(Y^{j+1}, \dots, Y^{j+2m-1} | Y^j, Y^{M^+}, v^M, \Theta) \propto \pi(v^M | X^M, \Theta) \prod_{i=j}^{j+2m-1} \pi(Y^{i+1} | Y^i, \Theta). \quad (7)$$

By sampling this distribution for $j = 0, m, \dots, n - 2m$, the use of overlapping blocks with a free mid-point ensures that we have an irreducible algorithm. Hence at iteration s of the innovation scheme, we would like to draw

$$Y^{j+1}, \dots, Y^{j+2m-1} \sim \pi(Y^{j+1}, \dots, Y^{j+2m-1} | Y^j, Y^{M^+}, v^M, \Theta)$$

where Y^j is obtained at iteration (s) and Y^{M^+} at iteration $(s - 1)$. Naturally, the end-points of the process, Y^0 and Y^n must also be updated. For every sweep of the sampler we fix Y^m and draw from

$$\pi(Y^0, \dots, Y^{m-1} | Y^m, v^0, \Theta) \propto \pi(v^0 | X^0, \Theta) \prod_{i=0}^{m-1} \pi(Y^{i+1} | Y^i, \Theta) \quad (8)$$

and fix Y^{n-m} and draw from

$$\pi(Y^{n-m+1}, \dots, Y^n | Y^{n-m}, v^n, \Theta) \propto \pi(v^n | X^n, \Theta) \prod_{i=n-m}^{n-1} \pi(Y^{i+1} | Y^i, \Theta), \quad (9)$$

thus ensuring that Y^0 and Y^n are updated.

Note that simulating $Y^{j+1}, \dots, Y^{j+2m-1}$ is not trivial. The Euler scheme allows handling of the likelihood between two consecutive values of the process (since we have a linear Gaussian structure in this case). However, obtaining the conditional density of missing values between two given observations that are $2m$ steps apart, under the non-linear structure of the underlying diffusion process, is complicated. As discussed in Chib et al. (2004), a similar process (which we denote by Y_*) can be considered as a proposal in an MCMC step — one that starts at $Y_*(t_j) = Y^j$, ends at $Y_*(t_{M+}) = Y^{M^+}$ and has the same diffusion function as the Y process. Here, we consider the diffusion bridge of Durham and Gallant (2002) and Chib et al. (2004),

$$\begin{aligned} dY_*(t) &= \mu_*(Y_*, \Theta) dt + \beta^{\frac{1}{2}}(Y_*, \Theta) dW(t) \\ &= \frac{Y_*(t_{M+}) - Y_*(t)}{t_{M+} - t} dt + \beta^{\frac{1}{2}}(Y_*, \Theta) dW(t), \end{aligned} \quad (10)$$

and suppress the dependence of μ_* on t to simplify the notation. Note that (10) can be easily sampled using the Euler approximation and numerical simulation is discussed in Section 3.1.1. We now let $P_{Y|\Theta}$ denote the law of the process given by (1) and $Q_{Y|\Theta}$ denote the law of the process, (10). Since $dY(t)$ and $dY_*(t)$ have common diffusion functions, $P_{Y|\Theta}$ and $Q_{Y|\Theta}$ are locally equivalent and the resulting likelihood ratio for the path $\{Y(t) : t \in [t_j, t_{M^+}]\}$ is given by Girsanov's formula (Øksendal, 1995, p. 162). Ignoring dependence on Θ , we obtain

$$\log \left\{ \frac{dP}{dQ}(Y(t)) \right\} = \text{const} + \int_{t_j}^{t_{M^+}} [\mu(Y) - \mu_*(Y)]' \beta^{-1}(Y) dY(t) - \frac{1}{2} \int_{t_j}^{t_{M^+}} [\mu(Y) - \mu_*(Y)]' \beta^{-1}(Y) [\mu(Y) - \mu_*(Y)] dt. \quad (11)$$

Hence, at iteration s of the innovation scheme we can propose the path $Y_*^{j+1}, \dots, Y_*^{M^+-1}$ by sampling from (10) and accept it with probability

$$\min \left\{ 1, \frac{\frac{dP}{dQ}(Y_*(t)) \pi(v^M | X_*^M)}{\frac{dP}{dQ}(Y(t)) \pi(v^M | X^M)} \right\}.$$

3.1.1 Numerical Simulation

The proposal process, (10) can easily be sampled by utilising the Euler approximation. Hence, treating Y^j and Y^{M^+} as fixed, we may propose Y_*^{i+1} , for $i = j, \dots, M^+ - 2$ using

$$Y_*^{i+1} | Y_*, Y^{M^+}, \Theta \sim N \left(Y_*^i + \frac{Y^{M^+} - Y_*^i}{M^+ - i}, \beta(Y_*^i, \Theta) \Delta t \right). \quad (12)$$

Such a proposal however, suffers two major drawbacks. Firstly, for a “small” measurement error variance, not conditioning on the data point v^M will lead to a low acceptance rate. Secondly, the variance of (12) is non-anticipating. We therefore use a slightly different two step discrete time approximation of (10) by utilising the modified bridge construct of Durham and Gallant (2002).

Consider first the task of proposing $Y_*^{j+1}, \dots, Y_*^M$. An efficient method would be to draw Y_*^{i+1} , for $i = j, \dots, M - 1$ from a Gaussian approximation to $\pi(Y_*^{i+1} | Y_*^i, v^M, Y^{M^+}, \Theta)$, denoted by $\tilde{\pi}(Y_*^{i+1} | Y_*^i, v^M, Y^{M^+}, \Theta)$ which we derive in Appendix A.3. We find however that the simpler Gaussian approximation, $\tilde{\pi}(Y_*^{i+1} | Y_*^i, v^M, \Theta)$ given by (A.8) works sufficiently well for the model considered in Section 5.

Finally, we draw Y_*^{i+1} , for $i = M, \dots, M^+ - 2$ from the Gaussian approx-

imation, $\tilde{\pi}(Y_*^{i+1}|Y_*^i, Y^{M^+}, \Theta)$ given by (A.5). This density was first used in the context of fully observed diffusions with no error by Durham and Gallant (2002) and the path produced by the density is often referred to as the modified bridge. See Appendix (A.1) for a derivation.

If at the end of iteration $s - 1$ we have $Y^{j+1}, \dots, Y^{M^+-1}$, then at iteration s we accept a move to $Y_*^{j+1}, \dots, Y_*^{M^+-1}$ with probability $\min\{1, \alpha\}$ where α is given by

$$\frac{\left[\pi(v^M | X_*^M) \prod_{i=j}^{M^+-1} \pi(Y_*^{i+1} | Y_*^i) \right] \left[\prod_{i=j}^{M-1} \tilde{\pi}(Y^{i+1} | Y^i, v^M) \prod_{i=M}^{M^+-2} \tilde{\pi}(Y^{i+1} | Y^i, Y^{M^+}) \right]}{\left[\pi(v^M | X^M) \prod_{i=j}^{M^+-1} \pi(Y^{i+1} | Y^i) \right] \left[\prod_{i=j}^{M-1} \tilde{\pi}(Y_*^{i+1} | Y_*^i, v^M) \prod_{i=M}^{M^+-2} \tilde{\pi}(Y_*^{i+1} | Y_*^i, Y^{M^+}) \right]}$$

after suppressing dependence on Θ . Note that we bracket the target and proposal densities for transparency. We repeat this step for $j = 0, m, \dots, n - 2m$ leaving the task of updating Y^0 and Y^n . We achieve this by drawing from the densities (8) and (9) using a M-H step. We start by drawing Y_*^0 using a Gaussian random walk type move. We then propose $Y_*^1, \dots, Y_*^{m-1}$ from (A.5) with M^+ replaced by m . Finally, we treat Y^{n-m} as fixed and draw Y_*^{i+1} for $i = n - m, \dots, n - 1$, from $\tilde{\pi}(Y_*^{i+1} | Y_*^i, v^n, \Theta)$ (see Appendix (A.2)). Acceptance probabilities for these moves can be computed in the usual way.

3.2 Sampling Θ conditional on the Brownian process

The final step in the innovation scheme is to sample a new Θ conditional on the Brownian process; since we cannot update Θ directly, we use a M-H step. We first combine the current sample path, $\hat{Y}$ with the current parameter value, Θ to obtain a skeleton path of the Brownian process, $\hat{W}$. This is valid since, conditional on Θ there is a one-to-one relationship between $\hat{Y}$ and $\hat{W}$ over $t \in [0, T]$ (Chib et al., 2004). Hence we can obtain $\hat{W}$ (corresponding to the current sample path, $\hat{Y}$), for example, by re-arranging the Euler approximation to give the *Brownian increments*, $\Delta W^i = W^{i+1} - W^i$ for $i = 0, \dots, n - 1$, as a function of the latent data points Y^i, Y^{i+1} and Θ . That is

$$\Delta W^i = (\beta_i)^{-\frac{1}{2}} (\Delta Y^i - \mu_i \Delta t) \quad (13)$$

where $\Delta Y^i = Y^{i+1} - Y^i$ and we use the shorthand notation of Section 2 for $\mu(Y^i, \Theta)$ and $\beta(Y^i, \Theta)$. Note that in this step, Y^0 and W^0 are treated as fixed so that $\hat{W}$ is entirely determined from the increments.

We then propose a new Θ_* using a suitable proposal density $g(\cdot)$ which may depend on $Y(t)$, $W(t)$ and the current Θ . We find that the Gaussian random

walk update of Golightly and Wilkinson (2005a) works well. Then, by combining Θ_* with $\{\Delta W^i, i = 0, \dots, n-1\}$ and using the Euler approximation, (3), we can propose a new sample path $Y^0, Y_*^1, \dots, Y_*^n$ deterministically. The resulting acceptance probability is analogous to that when performing a joint update of Θ and the latent data, $\hat{Y}$. Since the new path has been proposed, all be it deterministically, from (3) and $g(\cdot)$ is symmetric in Θ and Θ_* for the random walk update, the acceptance probability for the move reduces to

$$\min \left\{ 1, \frac{\pi(\Theta_*) \prod_{i=1}^T \pi(v^{im} | X_*^{im}, \Theta_*)}{\pi(\Theta) \prod_{i=1}^T \pi(v^{im} | X^{im}, \Theta)} \right\}.$$

Note that conditional on Θ , ΔW^i can be obtained from ΔY^i under any discrete time approximation of the underlying SDE since there is a one-to-one relationship between $\hat{W}$ and $\hat{Y}$. Choice of this approximation is important as it is then used to propose a new sample path, $Y^0, Y_*^1, \dots, Y_*^n$. In this context, use of the first order Euler discretisation as a proposal density is somewhat inefficient, since using it ignores the data, $v^0, v^m, \dots, v^n$. We therefore use a slightly different approach by utilising the modified bridge of (A.2).

Consider times t_j and t_M – recall that j is an integer multiple of m and $M = j + m$. Fixing Y^j and for $i = j, j+1, \dots, M-1$, the density $\tilde{\pi}(Y^{i+1} | Y^i, v^M, \Theta)$ can be thought of as the transition density of the discrete time process of the form

$$Y^{i+1} = Y^i + \psi_i \Delta t + (\gamma_i)^{\frac{1}{2}} \Delta W^i, \quad \Delta W^i \sim N_d(0, I \Delta t), \quad (14)$$

where ψ_i and γ_i are given by (A.9) and (A.10) respectively. Note that in the case of complete data and no error, simulating from (14) will give a diffusion bridge conditioned to start at Y^j and finish at Y^M . Our goal then is to use (14) to propose a new path $Y^0, Y_*^1, \dots, Y_*^n$ conditional on the proposed new Θ_* and $\hat{W}$. To achieve this, we first calculate the Brownian increments, corresponding to the skeleton path, by re-arranging (14) to give ΔW^i as a function of $\hat{Y}$ and Θ . This gives the one-to-one relationship,

$$\Delta W^i = (\gamma_i)^{-\frac{1}{2}} (\Delta Y^i - \psi_i \Delta t). \quad (15)$$

Now, since Y^0 and W^0 are assumed to be fixed, (15) is easily applied for each $j = 0, m, \dots, n-m$ and $i = j, \dots, M-1$ to give $\{\Delta W^i, i = 0, \dots, n-1\}$. We then propose a new Θ_* using a Gaussian random walk move and obtain the proposed new sample path deterministically using Θ_* , $\{\Delta W^i, i = 0, \dots, n-1\}$ and (14). Note that in the case of full observation with no error, the increments $\Delta W^i, i = m-1, 2m-1, \dots, n-1$, corresponding to the end-points of each subinterval are not stored, as in this case, the latent path is conditioned to hit each data point exactly.

We accept Θ_* (and therefore $Y_*^0, Y_*^1, \dots, Y_*^n$) with probability $\min\{1, \alpha\}$ where α is given by

$$\frac{\left[\pi(\Theta_*) \prod_{i=1}^T \pi(v^{im} | X_*^{im}, \Theta_*) \prod_{i=0}^{n-1} \pi(Y_*^{i+1} | Y_*^i, \Theta_*) \right] \left[\prod_{i=0}^{n-1} \tilde{\pi}(Y_*^{i+1} | Y_*^i, v^{(\lfloor i/m+1 \rfloor)m}, \Theta) \right]}{\left[\pi(\Theta) \prod_{i=1}^T \pi(v^{im} | X^{im}, \Theta) \prod_{i=0}^{n-1} \pi(Y^{i+1} | Y^i, \Theta) \right] \left[\prod_{i=0}^{n-1} \tilde{\pi}(Y_*^{i+1} | Y_*^i, v^{(\lfloor i/m+1 \rfloor)m}, \Theta_*) \right]},$$

where $\lfloor x \rfloor$ denotes the integer part of x .

After every iteration of the innovation scheme, each new Θ is entirely consistent with the sample path $\hat{Y}$, and the dependence between them is overcome. For further discussion see Chib et al. (2004).

4 Sequential Filtering for Parameters and State — the Simulation Filter

In this section we briefly summarise the the sequential MCMC scheme of Golightly and Wilkinson (2005b) and Golightly and Wilkinson (2006) which we refer to as the simulation filter.

In the context of discrete time series with unobserved state variables, Bayesian sequential filtering has been discussed extensively, e.g., Berzuini et al. (1997), Pitt and Shephard (1999) and Doucet et al. (2000) and Del Moral et al. (2002). Filtering for both parameters and state has been discussed by Liu and West (2001), Stroud et al. (2004) and Johannes et al. (2006). We consider data $D_j = (v^0, v^m, \dots, v^j)$, (where j is an integer multiple of m) arriving at times $t_0, t_m, \dots, t_j$. Recall that at time t_M (putting $M = j + m$), new data v^M are accompanied by m missing columns, $Y^{j+1}, \dots, Y^M$. As each observation becomes available we are interested in the on-line estimation of the unknown parameter vector, Θ .

We assume that we have an equally weighted sample of size S , $\{(\Theta_{(s)}, Y_{(s)}^j), s = 1, \dots, S\}$ (with weights $w_{(s)}^j = 1/S$), from the distribution $\pi(\Theta, Y^j | D_j)$, which we will denote by $\pi_j(\Theta, Y^j)$. At time t_M , we observe v^M and assimilation of the information contained in v^M consists of generating a sample, $\{(\Theta_{(s)}, Y_{(s)}^M), s = 1, \dots, S\}$ from the posterior $\pi_M(\Theta, Y^M)$ which can be found by formulating the posterior for parameters and augmented data, then integrating out the

latent data. Using (4) we have

$$\pi_M(\Theta, Y^M) \propto \int_{\hat{Y}_M} \pi(\Theta) \pi(Y^0) \prod_{i=0}^{M-1} \pi(Y^{i+1}|Y^i, \Theta) \prod_{i \in \{0, m, \dots, M\}} \pi(v^i|X^i, \Theta) \quad (16)$$

where we define $\hat{Y}_M = (Y^0, Y^1, \dots, Y^{M-1})$ and is simply the vector of latent values up to time t_M . Hence our target is

$$\pi_M(\Theta, Y^M) \propto \pi_j(\Theta, Y^j) \pi(v^M|X^M, \Theta) \prod_{i=j}^{M-1} \pi(Y^{i+1}|Y^i, \Theta) \quad (17)$$

with $Y^j, \dots, Y^{M-1}$ integrated out. As $\pi_j(\Theta, Y^j)$ has no analytic form, we recursively approximate $\Theta, Y^j|D_j$ by the “particles” $\{(\Theta_{(s)}, Y_{(s)}^j), s = 1, \dots, S\}$ with each $\Theta_{(s)}, Y_{(s)}^j$ having a discrete probability mass of $w_{(s)}^j = 1/S$. We assume that as $S \rightarrow \infty$, the particles approximate the filtering density, $\pi_j(\Theta, Y^j)$ increasingly well. Filters which treat the discrete support generated by the particles as the true (filtering) distribution are known as particle filters. Various implementations of particle filters have been proposed in the literature including sampling/importance resampling (Doucet et al., 2000) and MCMC (Pitt and Shephard, 1999). Here we focus on an MCMC approach.

In the first step of our MCMC scheme, propose (Θ_*, Y_*^j) from $\pi_j(\Theta, Y^j)$ using the kernel density estimate of $\pi_j(\cdot, \cdot)$. First select an integer, u , uniformly from the set $\{1, \dots, S\}$ and then put

$$(\Theta_*, Y_*^j)' \sim N\{(\Theta_{(u)}, Y_{(u)}^j)', \omega^2 B\} \quad (18)$$

where B is the Monte Carlo posterior variance and the overall scale of the kernel is a function of the smoothing parameter ω^2 , usually around 0.02. Note that the kernel density estimate is necessary to avoid sample impoverishment which occurs when the number of distinct particles become arbitrarily small (Golightly and Wilkinson, 2005b). For large datasets however, Liu and West (2001) suggest that the random disturbances add up to give “information loss” over time (as the kernel density function is always over-dispersed relative to the posterior sample by a factor $1 + \omega^2$). A kernel shrinkage method can be used to correct this (see Liu and West (2001) for a discussion).

We then draw Y_*^{i+1} for $i = j, \dots, M-1$ recursively from $\tilde{\pi}(Y_*^{i+1}|Y_*^i, v^M, \Theta_*)$ and accept the move with probability $\min\{1, \alpha\}$ where

$$\alpha = \frac{\left[\pi(v^M|X_*^M, \Theta_*) \prod_{i=j}^{M-1} \pi(Y_*^{i+1}|Y_*^i, \Theta_*) \right] \left[\prod_{i=j}^{M-1} \tilde{\pi}(Y_*^{i+1}|Y_*^i, v^M, \Theta_*) \right]}{\left[\pi(v^M|X^M, \Theta) \prod_{i=j}^{M-1} \pi(Y^{i+1}|Y^i, \Theta) \right] \left[\prod_{i=j}^{M-1} \tilde{\pi}(Y_*^{i+1}|Y_*^i, v^M, \Theta_*) \right]}.$$

We repeat this step for S iterations (after a burn-in period) and discard all draws except Θ and Y^M to obtain the desired sample, $\{(\Theta_{(s)}, Y_{(s)}^M), s = 1, \dots, S\}$ from $\pi_M(\Theta, Y^M)$. Note that variations on the sampling strategy are possible; in Golightly and Wilkinson (2006), X_*^M is drawn from $\pi(X_*^M | v^M, \Theta_*)$ and then $Y_*^{j+1}, \dots, Y_*^{M-1}$ are simulated using the modified bridge density, (A.5), further conditioned on X_*^M . Finally Z_*^M is drawn from the Euler transition density conditioned on X_*^M , $\pi(Z_*^M | Y_*^{M-1}, X_*^M, \Theta_*)$.

5 Simulation Study: Auto-regulatory Gene Network

Transcriptional regulation has been studied extensively in both prokaryotic and eukaryotic organisms (see, for example McAdams and Arkin (1999) and Latchman (2002)). In a simple model of prokaryotic auto regulation, a protein (l) coded for by a gene (i) represses its own transcription and also the transcription of another gene, (g) by binding to a regulatory region upstream of the gene. We simplify the repression mechanisms with the reactions,

We represent the transcription of i, the binding of a ribosome to mRNA, the translation of mRNA and the folding of the resulting polypeptide chain into a folding protein, l, by

Similarly, we represent the transcription of g and translation mechanism by

Finally, the model is completed by mRNA degradation,

and protein degradation,

For a detailed discussion of gene regulation see Ptashne (1992) and Latchman (2002).

We illustrate the methodology of Section 3 by estimating the rate constants governing the diffusion approximation of the network given by the above reactions. We start by assuming a rate constant, c_i , for each reaction, R_i and consider the time evolution of the system as a Markov process with state

$$Y = (Y_1, Y_2, \dots, Y_8)' = (\text{l}, \text{G}, \text{l} \cdot \text{i}, \text{l} \cdot \text{g}, \text{i}, \text{g}, \text{r}_\text{i}, \text{r}_\text{g})'$$

denoting the number of molecules of each respective species at time t . With the species ordered by the preceding equation, we can represent our network by the 12×8 net effect reaction matrix $A = (a_{ij})$ where a_{ij} denotes the net gain in the number of molecules of species j after reaction R_i has occurred. We obtain

$$A' = \begin{pmatrix} -1 & 1 & -1 & 1 & 0 & 1 & 0 & 0 & 0 & 0 & -1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & -1 \\ 1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ -1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & -1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & -1 & 0 & 0 \end{pmatrix}. \quad (24)$$

We now calculate the diffusion approximation by applying the Fokker-Planck equation to the chemical master equation associated with the process. See Golightly and Wilkinson (2005a) and Wilkinson (2006) for further details. It is easily seen that drift and diffusion coefficients are given by

$$\mu(Y, \Theta) = A' h(Y, \Theta), \quad \beta(Y, \Theta) = A' \text{diag}\{h(Y, \Theta)\} A, \quad (25)$$

where $h(Y, \Theta)$ is the column vector of hazards $h_i(Y, c_i)$. Before application of the above equation, it should be noted that the net effect matrix A is not of full rank (as the number of molecules of $\text{l} \cdot \text{i}$ and $\text{l} \cdot \text{g}$ are related to the number of molecules of i and g respectively) and this will yield a rank degenerate diffusion matrix. Inspection of (24) reveals that adding row 3 of A' to row 5 implies

$$\text{l} \cdot \text{i} + \text{i} = K_1 \quad (26)$$

and similarly, adding row 4 to row 6 yields

$$\text{l} \cdot \text{g} + \text{g} = K_2 \quad (27)$$

where K_1 and K_2 are known as conservation constants. As this rank degeneracy will complicate the inference methods of Sections 3 and 4, we remove

rows 3 and 4 from A' to obtain A of full rank. We then use (26) and (27) to substitute $K_1 - i$ and $K_2 - g$ for $l \cdot i$ and $l \cdot g$ respectively to reduce our model to one involving just 6 chemical species, $Y = (l, G, i, g, r_i, r_g)'$. The full diffusion approximation can then be computed using (25), for example,

$$\mu(Y, \Theta) = \begin{pmatrix} c_2(K_1 - i) + c_4(K_2 - g) + c_6r_i - c_1li - c_3lg - c_{11}l \\ c_8r_g - c_{12}G \\ c_2(K_1 - i) - c_1li \\ c_4(K_2 - g) - c_3lg \\ c_5i - c_9r_i \\ c_7g - c_{10}r_g \end{pmatrix}.$$

Though we work with the reduced system in Sections 5.1 and 5.2, both sampling schemes can be implemented for the full model by working with the Moore-Penrose generalised inverse of the diffusion matrix.

5.1 Results: Fully Observed Model

We repeat the sampling experiments of Golightly and Wilkinson (2006) by implementing the innovation scheme and the simulation filter for the fully observed case. We assume that we observe $Y(t) = (l(t), G(t), i(t), g(t), r_i(t), r_g(t))'$ at all times t and consider data, $\mathcal{D}_1$, consisting of 30 observations on $[0, 29]$ with each data point subject to Gaussian error with zero mean and variance $\sigma^2 = 3$ (so that $\Sigma = \sigma^2 I$ in (2)), which we assume to be unknown. Note that all data (including the datasets considered in Section 5.2) were simulated from the true discrete stochastic kinetic model using the Gillespie algorithm, and not from the diffusion approximation. Values for $(c_1, \dots, c_{12})$ that produced the data are 0.08, 0.82, 0.09, 0.9, 0.25, 0.1, 0.35, 0.3, 0.1, 0.1, 0.12, 0.1 and we place Uniform $U(-5, 1)$ priors on each $\log(c_i)$, for $i = 1, \dots, 12$ and σ . Note that K_1 and K_2 (the number of copies of each gene) are set to be 10 and are assumed to be known.

We run the innovation scheme and the simulation filter for each $m = 2, 8, 20$; the innovation scheme is run for 4 million iterations with a thin of 200, yielding a sample of 20,000 to be used as the main monitoring run. We run the simulation filter for 4.5 million iterations with a thin of 150, giving $S = 30,000$ particles at each time point. Posterior means and standard deviations for Θ based on the output of the innovation scheme and the simulation filter are reported in Tables A.1 and A.2 respectively. Fig. A.1 gives trace and posterior density plots obtained from the output of each sampler and $m = 2$. Autocorrelation plots for a selection of parameters can be found in Fig. A.2.

[Figure 1 about here.]

[Figure 2 about here.]

[Table 1 about here.]

[Table 2 about here.]

Tables A.1 and A.2 reveal that both sampling strategies produce estimates that are close to the true values that produced the sample data. Inspection of Fig. A.1 reveals that both the innovation scheme and the simulation filter produce estimates that are consistent with one another. The advantage of including latent variables in the estimation is abundantly clear; for example, running the innovation scheme with $m = 2$ ($\Delta t = 0.5$) yields posterior means of c_8 and c_{12} as 0.212 and 0.074 whilst true values are 0.3 and 0.1 respectively. Increasing m to 20 ($\Delta t = 0.05$) gives a marked increase in accuracy with posterior means of 0.241 and 0.086. Note that whilst posterior means for c_1 , c_2 , c_3 and c_4 are fairly inaccurate for all choices of m , the posterior means of c_1/c_2 and c_3/c_4 , corresponding to the overall propensities for the reversible reactions, R_1 and R_2 , R_3 and R_4 , are very close to the true values that produced the data.

We assess the relative performance of each scheme by studying the sample autocorrelation functions for each parameter; Fig. A.2 shows that as we increase m , autocorrelations still die down very quickly for both schemes. In fact, at lag 100, parameter draws are no more autocorrelated for $m = 20$ than for $m = 2$.

5.2 Results: Partially Observed Model

We now turn our attention to the application of the innovation scheme to the partially observed model. Again, we repeat the experiments of Golightly and Wilkinson (2006) by considering 3 datasets; $\mathcal{D}_2$, $\mathcal{D}_3$ and $\mathcal{D}_4$, each independently simulated with stochastic rate constants, $c_1, \dots, c_{12}$ as in Section 5.1. $\mathcal{D}_2$ consists of 30 observations on $X(t) = (\mathbf{l}(t), \mathbf{G}(t), \mathbf{r}_i(t), \mathbf{r}_g(t))'$ with each data point subject to measurement error with variance $\sigma^2 = 3.0$. $\mathcal{D}_3$ contains 40 observations on protein levels only; $X(t) = (\mathbf{l}(t), \mathbf{G}(t))'$ and the variance of the measurement error is $\sigma^2 = 3.0$. Finally, $\mathcal{D}_4$ contains 20 observations on RNA levels; $X(t) = (\mathbf{r}_i(t), \mathbf{r}_g(t))'$ with $\sigma^2 = 2.0$. For each dataset, we assume that the variance of the measurement error is known and that the number of copies of each gene is known to be $K_1 = K_2 = 10$. As in Section 5.1, we place uniform priors on each $\log(c_i)$ and also on $\log(Z^0)$. We run the innovation scheme and the simulation filter for each dataset with $m = 20$; 4 million iterations with a thin of 200 are performed, leaving 20,000 iterations for the

main monitoring run. Figs. A.3-A.4 and Tables A.3 and A.4 summarise the posterior distribution based on the MCMC output of each scheme.

[Figure 3 about here.]

[Figure 4 about here.]

[Table 3 about here.]

[Table 4 about here.]

Inspection of Fig. A.3 reveals that both samplers produce estimates that are close to the true values that generated the sample data and running scheme until convergence gives estimates that are consistent with each other. As shown in Fig. A.4, autocorrelations obtained from each scheme die down very quickly, though the simulation filter yields sample values which are generally much less autocorrelated than those of the innovation scheme.

As found in Golightly and Wilkinson (2006), when observing a subset of species, estimates are in general more accurate for rate constants governing reactions involving those species. For example c_{11} and c_{12} (pertaining to protein degradation reactions given by (23) with true values of 0.12 and 0.1 are estimated to be 0.126 and 0.157 using the innovation scheme with 20 observations on RNA levels ($\mathcal{D}_4$). However, when using 40 observations on protein levels ($\mathcal{D}_3$), we see an increase in accuracy with estimates of 0.108 and 0.086 respectively.

Note that both the innovation scheme and simulation filter are coded in C and executed on a Pentium IV 1.8 GHz processor. Computational times for the innovation scheme and simulation filter for a dataset of length 20 (simulated from the model), with $m = 20$ and 20,000 iterations are approximately 4 and 20 minutes respectively.

6 Discussion

By considering the analysis of a partially and discretely observed SDE as a missing data problem, Bayesian inference is usually undertaken by adopting a Gibbs sampler or MCMC approach. Whilst naive schemes (such as those of Eraker (2001) and Golightly and Wilkinson (2005a)) can be satisfactory for small amounts of augmentation ($m \leq 5$), they can break down as m increases due to high dependence between the latent data and parameters governing the volatility coefficient (Roberts and Stramer, 2001). In this paper, by employing a reparameterisation similar to that of Chib et al. (2004), we have provided an MCMC scheme to sample diffusion parameters, that is not afflicted by this

dependence issue. By applying the methodology to the estimation of parameters governing the diffusion approximation of a regulatory gene network, we have shown that the scheme works well for high dimensional diffusions that are observed with error.

The sequential simulation filter of Golightly and Wilkinson (2005b) and Golightly and Wilkinson (2006) was also considered. Whilst the simulation filter does not break down for large m , posterior samples do ultimately degenerate when large datasets are used. Although this is not a significant practical problem in the context of stochastic biochemical rate constant estimation (where datasets are typically relatively small), it does limit the utility of the algorithm. The innovation scheme, on the other hand, does not suffer from this problem.

A Calculating the Modified Diffusion Bridge

A.1 Fixed end points

Consider times t_j and t_M (where j is an integer multiple of m and $M = j + m$) such that the corresponding states are Y^j and Y^M which we will assume to be fixed. The modified diffusion bridge is constructed by sampling Y^{i+1} for $i = 0, \dots, M-2$ from a Gaussian approximation to $\pi(Y^{i+1}|Y^i, Y^M)$ for which we denote the approximate density by $\tilde{\pi}(Y^{i+1}|Y^i, Y^M)$. Note that we suppress the dependence of this density on Θ for simplicity.

We derive $\tilde{\pi}(Y^{i+1}|Y^i, Y^M)$ by formulating the approximate joint density of Y^{i+1} and Y^M (conditional on Y^i) and using MVN theory to condition on Y^M . We therefore start with the density of Y^M conditional on Y^{i+1} which we obtain using a very crude Euler approximation,

$$\tilde{\pi}(Y^M|Y^{i+1}) = \phi(Y^M; Y^{i+1} + \mu_{i+1}\Delta^+, \beta_{i+1}\Delta^+) \quad (\text{A.1})$$

where $\Delta^+ = (M - i - 1)\Delta t$ and we use the short-hand notation of Chapter 3, writing μ_{i+1} and β_{i+1} for $\mu(Y^{i+1})$ and $\beta(Y^{i+1})$. To give a linear Gaussian structure, we approximate (A.1) further by noting that μ and β are locally constant (by assumption). Estimating μ_{i+1} and β_{i+1} by μ_i and β_i respectively, we obtain

$$\tilde{\pi}(Y^M|Y^{i+1}) = \phi(Y^M; Y^{i+1} + \mu_i\Delta^+, \beta_i\Delta^+). \quad (\text{A.2})$$

The density $\pi(Y^{i+1}|Y^i)$ is the one step ahead Euler transition density given by

$$\pi(Y^{i+1}|Y^i) = \phi(Y^{i+1}; Y^i + \mu_i\Delta t, \beta_i\Delta t) \quad (\text{A.3})$$

and we can therefore construct the approximate joint density of Y^{i+1} and Y^M (conditional on Y^i) using MVN conditioning results which yield

$$\begin{pmatrix} Y^{i+1} \\ Y^M \end{pmatrix} \sim N_{2d} \left\{ \begin{pmatrix} Y^i + \mu_i\Delta t \\ Y^i + \mu_i\Delta^- \end{pmatrix}, \begin{pmatrix} \beta_i\Delta t & \beta_i\Delta t \\ \beta_i\Delta t & \beta_i\Delta^- \end{pmatrix} \right\}, \quad (\text{A.4})$$

where $\Delta^- = (M - i)\Delta t$. We now condition (A.4) on Y^M to give

$$\tilde{\pi}(Y^{i+1}|Y^i, Y^M) = \phi \left(Y^{i+1}; Y^i + \frac{Y^M - Y^i}{M - i}, \frac{M - i - 1}{M - i} \beta_i \Delta t \right). \quad (\text{A.5})$$

This is the form of the modified bridge given in Durham and Gallant (2002). We now consider two extensions of the diffusion bridge construct.

A.2 Conditioning on v^M

It may be the case that we only have one fixed end-point, Y^j and we wish to draw $Y^{j+1}, \dots, Y^M$ conditional on Y^j and the (noisy) observation v^M . We achieve this by sampling Y^{i+1} for $i = j, \dots, M-1$ from a Gaussian approximation to $\pi(Y^{i+1}|Y^i, v^M)$ which we denote by $\tilde{\pi}(Y^{i+1}|Y^i, v^M)$. We start by approximating the density of v^M conditional on Y^{i+1} as

$$\tilde{\pi}(v^M|Y^{i+1}) = \phi(v^M; X^{i+1} + \mu_i^{xx}\Delta^+, \beta_i^{xx}\Delta^+) \quad (\text{A.6})$$

using a partition of μ_i and β_i of the form

$$\mu_i = \begin{pmatrix} \mu_i^x \\ \mu_i^z \end{pmatrix}, \quad \beta_i = \begin{pmatrix} \beta_i^{xx} & \beta_i^{xz} \\ \beta_i^{zx} & \beta_i^{zz} \end{pmatrix}.$$

Recall also that Σ is the variance of the measurement error density, (6). Combining (A.6) with the one step ahead Euler transition, (A.3), we obtain the approximate joint density of Y^{i+1} and v^M (conditional on Y^i) as

$$\begin{pmatrix} Y^{i+1} \\ v^M \end{pmatrix} \sim N_{d+d_1} \left\{ \begin{pmatrix} Y^i + \mu_i \Delta t \\ X^i + \mu_i^x \Delta^- \end{pmatrix}, \begin{pmatrix} \beta_i \Delta t & C_i \Delta t \\ C_i' \Delta t & \beta_i^{xx} \Delta^- + \Sigma \end{pmatrix} \right\}, \quad (\text{A.7})$$

where $C_i' = (\beta_i^{xx}, \beta_i^{xz})$. Conditioning (A.7) on v^M yields

$$\tilde{\pi}(Y^{i+1}|Y^i, v^M) = \phi(Y^{i+1}; Y^i + \psi_i \Delta t, \gamma_i \Delta t), \quad (\text{A.8})$$

where

$$\psi_i = \mu_i + C_i (\beta_i^{xx} \Delta^- + \Sigma)^{-1} (v^M - [X^i + \mu_i^{xx} \Delta^-]) \quad (\text{A.9})$$

and

$$\gamma_i = \beta_i - C_i (\beta_i^{xx} \Delta^- + \Sigma)^{-1} C_i' \Delta t. \quad (\text{A.10})$$

A.3 Fixed end points with mid-point conditioning

Consider the block updating scheme of Section 3.1 and the task of sampling $Y^{j+1}, \dots, Y^M$ conditional on the end points Y^j, Y^{M^+} and also the noisy mid-point, v^M (recall that j is a multiple of m , $M = j+m$ and $M^+ = M+m$). This is achieved by sampling Y^{i+1} for $i = j, \dots, M-1$ from a Gaussian approximation to $\pi(Y^{i+1}|Y^i, v^M, Y^{M^+})$ which we denote by $\tilde{\pi}(Y^{i+1}|Y^i, v^M, Y^{M^+})$. We start by approximating the density of Y^{M^+} conditional on Y^{i+1} (and v^M) as

$$\tilde{\pi}(Y^{M^+}|Y^{i+1}) = \phi(Y^{M^+}; Y^{i+1} + \mu_i \Delta^{++}, \beta_i \Delta^{++}), \quad (\text{A.11})$$

where $\Delta^{++} = (M^+ - j - 1)\Delta t$. This ensures that we have a linear Gaussian system. Then, combining (A.11) with approximate joint density of Y^{i+1} and v^M , (A.7), we obtain the approximate joint density of Y^{i+1} and Y^{M^+} and v^M (conditional on Y^i) as

$$\begin{pmatrix} Y^{i+1} \\ Y^{M^+} \\ v^M \end{pmatrix} \sim N_{2d+d_1} \left\{ \begin{pmatrix} Y^i + \mu_i \Delta t \\ Y^i + \mu_i \Delta^\sim \\ X^i + \mu_i^x \Delta^- \end{pmatrix}, \begin{pmatrix} \beta_i \Delta t & \beta_i \Delta t & C_i \Delta t \\ \beta_i \Delta t & \beta_i \Delta^\sim & C_i \Delta t \\ C'_i \Delta t & C'_i \Delta t & \beta_i^{xx} \Delta^- + \Sigma \end{pmatrix} \right\}, \quad (\text{A.12})$$

where $\Delta^\sim = (M^+ - i)\Delta t$. Conditioning (A.12) on v^M and Y^{M^+} yields

$$\tilde{\pi}(Y^{i+1} | Y^i, v^M) = \phi(Y^{i+1}; Y^i + \psi'_i \Delta t, \gamma'_i \Delta t), \quad (\text{A.13})$$

where

$$\psi'_i = \mu_i + (\beta_i, C_i) \begin{pmatrix} \beta_i \Delta^\sim & C_i \Delta t \\ C'_i \Delta t & \beta_i^{xx} \Delta^- + \Sigma \end{pmatrix}^{-1} \begin{pmatrix} Y^{M^+} - [Y^i + \mu_i^x \Delta^\sim] \\ v^M - [X^i + \mu_i^x \Delta^-] \end{pmatrix}$$

and

$$\gamma'_i = \beta_i - (\beta_i, C_i) \begin{pmatrix} \beta_i \Delta^\sim & C_i \Delta t \\ C'_i \Delta t & \beta_i^{xx} \Delta^- + \Sigma \end{pmatrix}^{-1} \begin{pmatrix} \beta_i \Delta t \\ C'_i \Delta t \end{pmatrix}.$$

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Parameter	True Value	Mean (Standard Deviation)		
		$m = 2$	$m = 8$	$m = 20$
c_1	0.08	0.018 (0.011)	0.030 (0.030)	0.036 (0.039)
c_2	0.82	0.172 (0.118)	0.295 (0.303)	0.346 (0.377)
c_1/c_2	0.096	0.118 (0.057)	0.122 (0.076)	0.119 (0.068)
c_3	0.09	0.015 (0.010)	0.035 (0.043)	0.046 (0.061)
c_4	0.9	0.118 (0.091)	0.283 (0.371)	0.379 (0.507)
c_3/c_4	0.1	0.157 (0.104)	0.164 (0.124)	0.157 (0.111)
c_5	0.25	0.398 (0.219)	0.447 (0.256)	0.476 (0.270)
c_6	0.1	0.264 (0.146)	0.328 (0.270)	0.362 (0.317)
c_7	0.35	0.361 (0.218)	0.353 (0.294)	0.377 (0.297)
c_8	0.3	0.212 (0.108)	0.235 (0.124)	0.241 (0.126)
c_9	0.1	0.158 (0.087)	0.176 (0.101)	0.187 (0.106)
c_{10}	0.1	0.098 (0.069)	0.127 (0.093)	0.135 (0.093)
c_{11}	0.12	0.411 (0.238)	0.436 (0.536)	0.419 (0.591)
c_{12}	0.1	0.074 (0.043)	0.084 (0.047)	0.086 (0.050)
σ	1.732	1.677 (0.231)	1.622 (0.256)	1.604 (0.250)

Table A.1

Posterior means and standard deviations for Θ estimated on 30 observations ($\mathcal{D}_1$) from the fully observed model. Estimation results are based on a final sample of size 20,000, thinned from 4,000,000 iterations of the innovation scheme.

Parameter	True Value	Mean (Standard Deviation)		
		$m = 2$	$m = 8$	$m = 20$
c_1	0.08	0.021 (0.017)	0.025 (0.016)	0.042 (0.038)
c_2	0.82	0.279 (0.249)	0.263 (0.237)	0.498 (0.553)
c_1/c_2	0.096	0.097 (0.058)	0.111 (0.078)	0.102 (0.075)
c_3	0.09	0.012 (0.010)	0.036 (0.048)	0.052 (0.042)
c_4	0.9	0.100 (0.113)	0.310 (0.547)	0.509 (0.521)
c_3/c_4	0.1	0.118 (0.106)	0.138 (0.156)	0.122 (0.125)
c_5	0.25	0.418 (0.276)	0.407 (0.479)	0.435 (0.321)
c_6	0.1	0.138 (0.101)	0.385 (0.373)	0.369 (0.243)
c_7	0.35	0.359 (0.101)	0.392 (0.447)	0.301 (0.201)
c_8	0.3	0.210 (0.140)	0.246 (0.189)	0.202 (0.089)
c_9	0.1	0.114 (0.086)	0.108 (0.148)	0.127 (0.105)
c_{10}	0.1	0.119 (0.121)	0.159 (0.142)	0.105 (0.074)
c_{11}	0.12	0.275 (0.144)	0.372 (0.503)	0.389 (0.299)
c_{12}	0.1	0.093 (0.060)	0.111 (0.080)	0.094 (0.042)
σ	1.732	1.672 (0.310)	1.660 (0.254)	1.672 (0.268)

Table A.2

Posterior means and standard deviations for Θ estimated on 30 observations ($\mathcal{D}_1$) from the fully observed model. Estimation results are based on a final sample of size 30,000, thinned from 4,500,000 iterations of the simulation filter.

Parameter	True Value	Mean (Standard Deviation)		
		$\mathcal{D}_2$	$\mathcal{D}_3$	$\mathcal{D}_4$
c_1	0.08	0.033 (0.034)	0.039 (0.035)	0.034 (0.046)
c_2	0.82	0.243 (0.254)	0.374 (0.362)	0.247 (0.250)
c_1/c_2	0.096	0.225 (0.251)	0.183 (0.200)	0.273 (0.356)
c_3	0.09	0.031 (0.033)	0.025 (0.024)	0.038 (0.048)
c_4	0.9	0.208 (0.251)	0.226 (0.261)	0.208 (0.256)
c_3/c_4	0.1	0.341 (0.367)	0.214 (0.211)	0.450 (0.670)
c_5	0.25	0.328 (0.226)	0.345 (0.371)	0.363 (0.204)
c_6	0.1	0.225 (0.173)	0.137 (0.212)	0.076 (0.142)
c_7	0.35	0.408 (0.206)	0.212 (0.344)	0.089 (0.118)
c_8	0.3	0.345 (0.101)	0.629 (0.299)	0.293 (0.338)
c_9	0.1	0.123 (0.100)	0.131 (0.150)	0.073 (0.064)
c_{10}	0.1	0.050 (0.030)	0.157 (0.182)	0.029 (0.029)
c_{11}	0.12	0.310 (0.240)	0.108 (0.142)	0.126 (0.196)
c_{12}	0.1	0.124 (0.048)	0.086 (0.030)	0.157 (0.233)

Table A.3

Posterior means and standard deviations for parameters estimated using datasets $\mathcal{D}_2$, $\mathcal{D}_3$ and $\mathcal{D}_4$ from the partially observed model. Discretization is set at $m = 20$ and the estimation results are based on a final sample of size 20,000, thinned from 4,000,000 iterations of the innovation scheme.

Parameter	True Value	Mean (Standard Deviation)		
		$\mathcal{D}_2$	$\mathcal{D}_3$	$\mathcal{D}_4$
c_1	0.08	0.020 (0.014)	0.037 (0.031)	0.036 (0.058)
c_2	0.82	0.250 (0.225)	0.341 (0.325)	0.210 (0.267)
c_1/c_2	0.096	0.204 (0.354)	0.248 (0.341)	0.326 (0.432)
c_3	0.09	0.035 (0.042)	0.033 (0.041)	0.036 (0.051)
c_4	0.9	0.228 (0.323)	0.321 (0.342)	0.184 (0.237)
c_3/c_4	0.1	0.417 (0.473)	0.268 (0.344)	0.462 (0.691)
c_5	0.25	0.348 (0.272)	0.326 (0.355)	0.396 (0.263)
c_6	0.1	0.179 (0.074)	0.061 (0.107)	0.071 (0.112)
c_7	0.35	0.393 (0.194)	0.174 (0.225)	0.120 (0.183)
c_8	0.3	0.241 (0.072)	0.556 (0.270)	0.373 (0.389)
c_9	0.1	0.103 (0.064)	0.162 (0.241)	0.076 (0.066)
c_{10}	0.1	0.054 (0.037)	0.156 (0.207)	0.031 (0.032)
c_{11}	0.12	0.198 (0.189)	0.077 (0.062)	0.151 (0.176)
c_{12}	0.1	0.098 (0.052)	0.092 (0.034)	0.159 (0.258)

Table A.4

Posterior means and standard deviations for parameters estimated using datasets $\mathcal{D}_2$, $\mathcal{D}_3$ and $\mathcal{D}_4$ from the partially observed model. Discretization is set at $m = 20$ and the estimation results are based on a final sample of size 20,000, thinned from 4,000,000 iterations of the simulation filter.