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Marginal reversible jump Markov chain Monte Carlo with application to motor unit number estimation

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ABSTRACT

Motor unit number estimation (MUNE) is a method which aims to provide a quantitative indicator of progression of diseases that lead to a loss of motor units, such as motor neurone disease. However the development of a reliable, repeatable and fast real-time MUNE method has proved elusive hitherto. Previously, a reversible jump Markov chain Monte Carlo (RJMCMC) algorithm has been implemented to produce a posterior distribution for the number of motor units using a Bayesian hierarchical model that takes into account biological information about motor unit activation. However this approach can be unreliable for some datasets since it can suffer from poor cross-dimensional mixing. The focus is on improved inference by marginalising over latent variables to create the likelihood. More specifically, the emphasis is on how this marginalisation can improve the RJMCMC mixing and that alternative approaches that utilise the likelihood (e.g. DIC) can be investigated. For this model the marginalisation is over latent variables which, for a larger number of motor units, is an intractable summation over all combinations of a set of latent binary variables whose joint sample space increases exponentially with the number of motor units. A tractable and accurate approximation for this quantity is provided and also other approximations based on Monte Carlo estimates that can be incorporated into RJMCMC are investigated.

1. Introduction

1.1. Background

Measuring the progress of diseases of the motor units, such as amyotrophic lateral sclerosis (ALS) and post-polio syndrome, is a challenge for clinical neurologists. As Shefner (2009) states, any outcome measure that assesses the patient's function, including survival, is a reflection of both the underlying disease process and the body's physiological attempts at compensation. Motor unit number estimation (MUNE) is an attempt to estimate the number of motor units (MUs) that remain and serial studies can show the progression of the disease. Bromberg (2007) provides a recent account of progress in the area.

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In addition to assessing disease progression, MUNE can be used to monitor attempts at therapy. For example one aspect of the Miami project to cure paralysis involves attempting to enhance motor neuron survival, axon regeneration and muscle re-innervation from patients who have experienced a spinal cord injury (Casella et al., 2010). MUNE can be utilised to investigate how many MUs re-innervate the muscles following cell transplantation treatment.

An aim of our MUNE project is to develop a reliable and repeatable method for estimating the number of MUs, N, in a given muscle so that the method can be incorporated into the electromyography system (e.g. Viking Select EMG machine, Nicolet Biomedical, Madison, WI, USA) used in hospital neurology clinics around the world. A reliable MUNE method would be able to handle a wide variety of clinical datasets without user intervention while a repeatable MUNE method would give comparable results under two different data collections on the same patient under the same conditions. Typically, data collection in the clinic takes 10–15 min.

Ridall et al. (2006, 2007) present a Bayesian MUNE method based on data obtained from a stimulus response curve (Henderson et al., 2006) which is the graph of the compound muscle action potential (CMAP) obtained using surface electrodes from repeated stimulation of a nerve at stimulus intensities ranging from threshold (where no MUs respond) to supramaximal (where all MUs respond giving the maximum response). See Fig. 1(d) for an example of a real dataset collected from a patient severely affected by ALS. Motor units fire probabilistically over a range of stimulus values (Pecher, 1939).

The Bayesian hierarchical model developed by Ridall et al. (2006) overcomes some of the simplifying assumptions used in other statistical approaches, such as the Poisson method (Daube, 1995; Lomen-Hoerth and Slawnych, 2003) and the binomial method (Blok et al., 2005), and accommodates data from both diseased and normal patients. Ridall et al. (2006) compare varying N models using the Bayesian information criterion (BIC) (Raftery, 1996), but this approach has two difficulties, the first that the number of unknown parameters has to be specified and, the second, that the posterior median has to be found. The first is difficult as the model of Ridall et al. (2006) involves random effects and latent variables and the second is problematic as the fixed N model posterior displays multimodality, as pointed out by Glasbey (2007) in the discussion of Ridall et al. (2007). Use of the deviance information criterion (DIC) (Spiegelhalter et al., 2002) also has difficulties as the MUNE model involves hidden variables and the deviance is ambiguously defined in such cases. Such difficulties are illustrated, for example, for the mixture model in Celeux et al. (2006).

The approach of Ridall et al. (2007) estimates the number of MUs, N, by using reversible jump Markov chain Monte Carlo (RJMCMC) (see Liu et al. (2011) for a recent application of RJMCMC) on the joint model space of N and MU parameters. Extensive use of the algorithm with clinical data has shown that it sometimes suffers from poor mixing, with between N jumps occurring at extremely low frequencies. The challenge in designing a successful and reliable RJMCMC algorithm is therefore to overcome the within fixed N model posterior multimodality and have moves between varying N models with reasonably large probabilities. If the within-model posterior MCMC paths become trapped within local modes with low probability this can result in misleading between varying N model comparisons. Therefore we seek an approach that has thorough within fixed N model exploration of the posterior and between varying N model posterior comparisons. Our main focus is on improving the latter, between varying N model mixing of the chain with the aim of increasing the reliability of the method. However, an advantageous by-product of the RJMCMC approach is that it encourages more global exploration of the parameter space, which can lead to better within-model mixing (Green, 2003).

1.2. Approach and outline

The model relies upon latent binary indicator variables that specify which MUs are firing at each observation. The RJMCMC approach of Ridall et al. (2007) involves proposals for these indicators when proposing a model dimension change (i.e. a change in N) and reduces the probability of acceptance. The main objective of this paper is to demonstrate that the use of the likelihood (with the latent variables marginalised over) and various approximations to it substantially improves mixing. Integrating out the firing indicators dramatically reduces the dimension between adjacent models, which facilitates the increase in acceptance rates of between-model moves.

This paper is not the first demonstration of applying marginalisation within RJMCMC to improve mixing. For example, Vermaak et al. (2004) analytically integrates out various parameters and samples from the resulting marginal space in a time series example. Andrieu and Roberts (2009) approximately integrates out a set of continuous latent variables via an importance sampling approximation. However, our application is unique as we require marginalising over a multivariate binary distribution whose dimension grows exponentially with an increase in the number of MUs. For even small N exact computation is not possible. We compare and contrast two approaches to improving the RJMCMC, one based on a deterministic approximation and one based on simulation to marginalise over the binary latent variables using an MCMC algorithm presented in Andrieu and Roberts (2009) and which has good theoretical properties. A by-product of the availability of the deterministic approximation to the likelihood is that model choice criteria (as opposed to posterior model probabilities) such as DIC (Spiegelhalter et al., 2002) can be calculated more easily since the number of parameters is known explicitly. However, the DIC relies on the posterior distribution being approximately multivariate normal, whereas our experience suggests that the (marginal) posterior distributions of the parameters of the MUNE model can be highly irregular and multi-modal. It appears that, for our model and data, within-model based criteria such as DIC cannot be converted to cross model posterior probabilities and we empirically confirm this so emphasising the need for a good RJMCMC algorithm.

We also give details of the modification of the statistical model of Ridall et al. (2006, 2007) as suggested by recent data analysis and consultation with neurologists. More specifically, we make some simplifications to the model so that fewer