Statistical modelling of neuron degeneration

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SUMMARY: Parkinson's disease, Huntington's disease, Amyotrophic lateral sclerosis (ALS) and Alzheimer's disease are all examples of neurodegenerative disorders that result from the premature death of nerve cells or neurons. In order to understand the mechanisms through which these diseases advance, a number of models have been put forward to describe the decline in the numbers of surviving neurons. Such work has been hampered by the poor quality of estimates of the numbers of surviving neurons and also by questionable model selection techniques. Recent work has favoured the adoption of the exponential model to explain neurodegenerative decline. We present in this paper a methodology for challenging this model, using data from patients with ALS. We use a two stage procedure to study motor unit numbers. The first stage involves determining the number of motor units in a muscle on several occasions over a period of time. The method of Ridall et al. (2007) is used which makes use of reversible jump Markov chain Monte Carlo (RJMCMC). The second stage involves the analysis of the RJMCMC output by using a hidden Markov process of decline. Two such processes of decline are compared. The first is the exponential where the rate parameter is constant. This is compared to a more general semi-parametric process where the rate parameter is allowed to vary over time. The rate is set to be piecewise constant between recordings where the magnitudes of the change in rate are weakly constrained by the length of the interval between recording occasions. Between model comparisons are based on electrophysiological data collected from a group of ALS patients where motor units (MUs) are gradually lost leading to progressive muscle weakness. By calculating marginal likelihoods, we find the Bayes factor in support of the exponential decline model against the more general alternative. This approach is illustrated with four ALS patients. Prediction of MU numbers lost, which incorporates both models, can also be made. Our methods, we therefore believe, have a role in formulating and evaluating biological models for neural degeneration of the motor system in ALS patients.

1. Introduction

Neurodegenerative diseases, such as Parkinson's disease, Huntington's disease, Alzheimer's disease and amyotrophic lateral sclerosis (ALS), involve the progressive death of populations of nerve cells. Our study is focused on the loss of functioning motor units of patients with ALS. This fatal disease of the motor system is enigmatic, with a spontaneous onset, lack of an obvious cause and lack of clinical markers to affirm diagnosis and measure the rates of progression of the disease. The reasons why the disease is difficult and problematic to study include the inaccessibility of the motor units and the inability of clinical examination to determine the number of remaining motor units (as we explain later in this section). A number of biologically plausible models have been suggested to describe the loss of motor units, (Kuether and Lipinski, 2007). A commonly used model is that of an exponential decline of the number of units where the rate of loss of units is assumed to be proportional to the number of remaining units. Travis (1998) and Li et al. (1996) find empirical support for this model and refer to it as the 'one hit model'. Others, for example Kuether and Lipinski (2007), refer to the same model as that of 'decelerated decline'.

In the present study we compare the exponential model of decline with plausible alternatives using a Bayesian approach. The aim of the present study is to develop a methodology for evaluating the evidence in favour of the constant rate, exponential decline model against a flexible semi-parametric model capable of incorporating the features of alternate models. To do this, we use data from subjects with ALS, where we have developed a means of obtaining an accurate estimate of the number of remaining motor neurons. We constructed a model of motor unit excitation using explicit assumptions that are based on knowledge of the physiology of motor nerves and muscles. We have refined this model and showed how estimates of the number of remaining motor neurons can be obtained using reversible jump Markov chain Monte Carlo (RJMCMC). With four patients in the present study, two of whom have typical ALS and two of whom have progressive lower

motor neurone weakness without the upper motor neurone features of ALS, the test procedure was carried out on a number of occasions and data collected over the progress of the disease.

Our overall approach involves two stages. Firstly, using data for each patient collected on different occasions, we perform RJMCMC motor unit number estimation using the method of Ridall et al. (2007) on each individual study. For the second stage, using the output of the RJMCMC, we construct a Markov process for the number of remaining motor units over the observation period. Using a Bayesian approach we demonstrate how to weigh the evidence in favour of the constant exponential decline model against that of a more complex time-varying rate process. We demonstrate our approach with the four patients with ALS and find that for one patient a constant exponential decline process is strongly supported and for two patients it is weakly supported whilst, for the last patient, there is strong evidence against.

In Section 2 we summarize the relevant literature for a description of the background of the problem. In Section 3 we describe how the RJMCMC analysis is summarized to give the first stage data of our approach. In Section 4 we describe the Markov process which represents the underlying mechanism by which units are lost and propose possible models for the evolution of the rate parameters. In Section 5 we describe the second stage of our approach, calculating Bayes factors for model selection, and in Section 6 we display both the results of our Markov chain Monte Carlo (MCMC) and our model selection procedure. In Section 7 we formulate our conclusions and discuss the neurological implications.

2. Background

In Section 2.1 we discuss some background to measuring the decline in the numbers of units while in Section 2.2 we review models for loss of nerve cells in neurodegenerative diseases. In Section 2.3 we consider approaches to statistical model choice in the neurological literature.

2.1 *The background of measuring decline of units*

Motor units (MU) are the functional units of the peripheral motor system. Each consists of an anterior horn cell, its axon and the muscle fibres that this neuron innervates (Sherrington, 1929).

The anterior horn cells are located within the ventral horn of the spinal column. In ALS there is progressive loss of MUs. Loss of MUs may be compensated by collateral sprouting of other intact motor axons to re innervate the denervated muscle fibres, (Wohlfart, 1958). This compensatory process results in an increased MU size, with an increased number of muscle fibres per MU and a fairly well maintained force output of affected muscles. Consequently, muscle weakness is not apparent until the rate of new sprouting is insufficient or until there are few remaining MUs. By that time up to 80% of a patient's MUs in a muscle may be lost, (Sica and McComas, 2003). This also means that muscle strength is an inaccurate marker of the number of MUs and, hence, of the progression of ALS. To measure numbers of MUs, Ridall et al. (2007) develop a stochastic model using the underlying biology to explain the data from electrophysiological studies. RJMCMC is used to provide an estimate of the number of surviving motor units.

2.2 *Models of decline of neurons in neurodegenerative diseases*

We first describe some models for the loss of nerve cells in neurodegenerative diseases. The death rate of a particular neuron at time t is denoted by λ_t. When N is large we can model decline by the differential equation: $\frac{dN_t}{dt} = -\lambda_t N_t$ where N_t denotes the number of functioning neurons at time t. However, we model the process of decline as discrete and stochastic, taking only positive integer values, giving the Markov process with transition probabilities

$$P\left(N_{t+d} = j | N_t = i, \lambda_t\right) = \begin{cases} 1 - \lambda_t id + o(d); & j = i \\ \lambda_t id + o(d); & j = i - 1, \end{cases} \tag{1}$$

where the remaining transition probabilities are $o(d)$ for a small time increment d. We now describe some models of the decline of the numbers of neurons found in the literature.

(i) Constant rate or exponential decline.

The exponential model is widely favoured by Clarke et al. (2001) and Clarke et al. (2000). The model is consistent with an assumption that the death of neurons is preceded by a single, independent and cataclysmic biochemical event. The death rate parameter λ_t is fixed with respect to time and assumed independent of other units. Decline can be modeled deterministically by $\frac{dN_t}{dt} = -\lambda N_t$, giving $N_t = N_0 e^{-\lambda t}$, where N_0 is the initial number of units at the beginning of the disease process. The adoption of this model has important clinical implications because it suggests that the remaining neurons are healthy and still functioning and can somehow be rescued from the disease process (Clarke et al., 2001). In evaluating whether this model applies to ALS, a broad range of alternatives needs to be considered. These alternative models are described below.

(ii) Linear decline.

Armon (2003) concludes that the decline or the number of surviving units is linear in time in ALS patients. This implies that the rate of decline is not related to the initial number of neurons. Such a decline could be explained by a damaging agent which captures neurons one by one. Andres et al. (1988) also finds that the decline is linear but uses a score based on muscle strength which, as we have explained, is not directly related to motor unit numbers because of collateral sprouting. In the linear decline model, the rate of decline is not proportional to the number of functioning units, (Kuether and Lipinski, 2007).

(iii) Sigmoidal decline.

The assumption that the rate of decline of a unit is proportional to the number of dead units, giving $\frac{dN_t}{dt} = -\lambda N_t (N_0 - N_t)$, leads to the logistic or sigmoidal model. In the event that the process was accelerated by dying rather than dead motor units a departure from the logistic decline would be likely and a bivariate representation of the decline process would be more appropriate.

(iv) Accelerated aging and the cumulative damage model.

This type of cell death can be found in the process of aging in biological systems (Kuether and Lipinski, 2007). This behaviour can be described by the Gompertz equation, $N_t = N_0 \exp\{(-a \exp(bt)\}$ where a and b are constants. Here decline is not governed by the behaviour of other units but by alterations within the cell through some intrinsic defect. For example,this could be related to the inability to maintain essential cellular proteins with aging or alternatively through exposure to exogenous agents. This is consistent with a model of cumulative damage where cell death is more likely later in the disease. In ALS, examples of cumulative damage include oxygen toxicity and the subsequent damage to macromolecules (Aggarwai and Neilson, 2001) (Swash and Ingram, 1988), the accumulation or mislocalisation of mutant proteins in the cell (Li et al., 1996), and an accelerating process such as abnormal protein aggregation promoting the formation of further abnormal protein. The implication is that the cell death rate, λ_t, increases with time.

(vi) The heterogeneous model.

Here not all motor units have the same death rate. For instance, in a given muscle there could be two or more types of motor unit, each with different properties. Clarke and Lumsden (2005) represents the decline process of each component i by use of a distinct rate constant $\lambda^{(i)}$: $N_t^{(i)} = N_0^{(i)} e^{-\lambda^{(i)} t}$. With some ALS patients we have observed that the rate of decline slows down in the final stage of disease when the number of motor units is less than 20. Such behaviour could be explained by survival of more resilient motor neurons. Proschan (1963) shows that any any non-null mixture of exponential distributions will always result in an exponentially decreasing hazard rate.

(vii) The multi-hit model.

Rai and Van Ryzin (1981) explains the model of cell death as a mechanism involving a multi-step biochemical cascade consisting of a sequence of necessary events. The overall death rate

is determined by rate constants for the transitions within this cascade and would lead to a

multiphase version of equation 1.

(viii) The delayed onset model.

In this model the process of decline does not start until some time after disease onset.

A special case, proposed by Kuether and Lipinski (2007), is that the decline is given by the

quadratic form $N_t = N_0 - c(t - t_O)^2$ for $t > t_O$ for onset at t_O but N_t is constant, equal to N_0

prior to onset, so that the rate of decline is linear in the time since onset.

2.3 *A coherent Bayesian approach for model choice for neurological decline*

Various attempts to select the best mathematical model to describe the loss of neurons can be found

in the literature. Clarke et al. (2001) consider the sigmoidal decline model as an alternative to the

exponential decline model and select the best model as the one with the lowest p-value. Clarke

et al. (2001) consider an exponentially decreasing death rate model as an alternative to the constant

death rate model and compare models on the basis of R^2 values and associated p-values for the

null hypothesis of no linear correlation. Here, the exponentially decreasing death rate model can

be arbitrarily close to the constant death rate model. On a more general basis the method of Clarke

et al. (2001) is flawed. P-values derived from goodness-of-fit tests were not intended for comparing

different models but rather intended as a way of obtaining a measure of evidence against specific

null hypotheses. For a series of putative models, a series of p-values derived from a likelihood ratio

test of one model as the null against another as the alternative fails because of the incoherence, non-

transitive and non-reflexive nature of the resulting p-values.

We approach the problem of model comparison using a coherent Bayesian method. We con-

struct a flexible alternative model encompassing a range of models for neurodegeneration. This is

achieved by allowing the death rate parameter to vary from one short period of time to the next.

The model constrains the rate parameter to vary weakly but we have made some simplifications to

make computations feasible. We compare the constant death rate model against the flexible model

using the Bayesian method of computing a Bayes factor. This involves computing the marginal likelihood by integrating out all of the parameters from the full probability model, which can be a computationally challenging exercise; see Friel and Pettitt (2008) for a review of methods. We also use the power posterior method of Friel and Pettitt (2008) to compute the marginal likelihood.

3. From first stage posterior to second stage likelihood

Instead of using a full probability model that combines both a model to infer the number of remaining units in a given muscle on various occasions with a choice of models of decline over time, we take a computationally less complex approach. The first stage of our approach involves using the technique of Ridall et al. (2007) to estimate the posterior distributions of the number of remaining units in a given muscle on various occasions. The posterior distribution of the number of remaining units, $p(N|y)$, at various instances of time can be summarised by a discrete distribution for N which we describe as a histogram. We denote each of these histograms at time τ_t, by $\underset{\sim}{h}_t$ where $t = 0, 1, 2, \ldots, T$. Histograms from an ALS patient recorded on multiple occasions over a period of time are shown in the nine panels of Figure 1. In the second stage of our analysis we interpret these histograms as data.

[Figure 1 about here.]

4. The hidden stochastic process of decline

We assume that the true number of units N_τ at time τ is non-increasing and subject to a process of decline where the probability of neuron death is constant between the tth and $t + 1^{th}$ recordings taken at times τ_t and time τ_{t+1}. This process of decline is observed indirectly at times τ_t, where $t = 0, 1, 2, \ldots, T$. Information is provided by the estimated posterior summaries $\underset{\sim}{h}_t$, that is the output of, say, 1000 thinned values from the RJMCMC expressed as relative frequencies over

integers. We denote this by a 'likelihood' $p(\underset{\sim}{h}_t \mid N_{\tau_t})$. These data are combined together to give the

likelihood

$$p(\underline{\mathbf{h}} \mid \mathbf{N}) = \prod_{t=0}^{T} p(\underset{\sim}{h}_t \mid N_{\tau_t}), \tag{2}$$

Then the true number of units has a distribution $p(\mathbf{N} \mid \boldsymbol{\lambda})$ with $\boldsymbol{\lambda}$ the rate parameter of the Markov

process describing the decline in the number of units.

Between any two observations, ie for times $\tau \in [\tau_t, \tau_{t+1})$, we assume the rate parameter is fixed

at λ_t and the nonzero transition probabilities for the number of remaining units N satisfy

$$P\left(N_{\tau+d} = j | N_\tau = i, \lambda_t\right) = \begin{cases} 1 - \lambda_t i d + o(d); & j = i \\ \\ \lambda_t i d + o(d); & j = i - 1, \end{cases}$$

where d is a small time interval. Elements of the probability transition matrix, $P\left(N_{\tau_{t+1}} = j \mid N_{\tau_t} = i\right)$,

for this interval of time, can be calculated from the infinitesimal generator matrix $\mathbf{G}^{(\lambda_t)}$, using the

matrix exponential $e^{\mathbf{G}^{(\lambda_t)}(\tau_{t+1} - \tau_t)}$, where

$$G_{i,j}^{(\lambda_t)} = \begin{cases} -\lambda_t i; & j = i \\ \\ \lambda_t i; & j = i - 1 \end{cases}.$$

We have assumed a stochastic process of decline with the Markov property (see for example Cox

and Miller (1965)), so that

$$p(\mathbf{N} \mid \boldsymbol{\lambda}) = p(N_{\tau_0}) \prod_{t=1}^{T} p(N_{\tau_t} \mid N_{\tau_{t-1}}, \lambda_t) \quad \mathbf{1}(N_{\tau_t} \leq N_{\tau_{t-1}}), \tag{3}$$

where $\Delta \tau_t = \tau_t - \tau_{t-1}$ are the time increments and the non-increasing constraint is imposed on the

N_{τ_t} with $\mathbf{1}$ being the indicator function. We assume that λ_t is constant in $[\tau_t, \ \tau_{t+1})$, and the motor

unit reductions over an interval are therefore binomial and

$$N_{\tau_t} | N_{\tau_{t-1}}, \lambda_t \sim \text{Binomial}\left(N_{\tau_{t-1}}, e^{-\lambda_t \Delta \tau_t}\right) \qquad t = 1, 2, \dots, T.$$

We assume a distribution for N_{τ_0}, the initial number of units at time τ_0. Without assuming specific

knowledge we assume that N_{τ_0} is uniformly distributed over the integers $\{1, 2, \ldots, N_{\max}\}$ where $N_{\max}$ is set to 300.

The probability model can be written as the product of the RJMCMC output, expressed as a likelihood, $p(\underline{\mathbf{h}} \mid \mathbf{N})$, a stochastic process, $p(\mathbf{N} \mid \boldsymbol{\lambda})$, the rate parameters, $p(\boldsymbol{\lambda} \mid \boldsymbol{\Phi})$, which describe the process of neuron death, and the priors for the rate parameters, $p(\boldsymbol{\Phi})$.

$$p(\underline{\mathbf{h}} \mid \mathbf{N})p(\mathbf{N} \mid \boldsymbol{\lambda})p(\boldsymbol{\lambda} \mid \boldsymbol{\Phi})p(\boldsymbol{\Phi}).$$

4.1 *Models for the evolution of the rate parameters*

To understand the disease process better, we now present two models which differ in how the rate parameter $\boldsymbol{\lambda}$ is parameterized.

$\mathcal{M}_1$: A piecewise constant rate $\boldsymbol{\lambda}$.

To allow the rate parameters to vary smoothly and multiplicatively from interval to interval, we allocate each rate parameter a mean of the previous rate parameter, λ_{t-1}, and a variance proportional to the length of the interval of time, $\Delta \tau_t$, and equal to $\Delta \tau_t / \kappa$.

$$\lambda_t \mid \lambda_{t-1}, \kappa \quad \sim \quad \text{Gamma}\left(\frac{\kappa \lambda_{t-1}^2}{\Delta_{\tau_t}}, \frac{\kappa \lambda_{t-1}}{\Delta_{\tau_t}}\right) \quad t = 1, 2, \ldots, T$$

$$\lambda_0 \quad \sim \quad \text{Gamma}\left(\epsilon, \epsilon\right).$$

In the above, Gamma $(\cdot, \cdot)$ denotes the Gamma distribution so that λ_t has conditional mean equal to λ_{t-1}. We chose $\epsilon = .01$ which corresponds to a non-informative prior for λ_0. The precision parameter κ is also given a non-informative gamma prior, $p(\kappa)$, where $\kappa \sim \text{Gamma}\left(\epsilon_1, \epsilon_1\right)$ where ϵ_1 was set at $\epsilon_1 = .1$ The probability model for this model can be depicted using a directed acyclic graph (DAG) which is shown in Figure 2.

$\mathcal{M}_2$: Constant death rate.

In this model we assume that the rate is unchanged over time, ie $\lambda_t = \lambda$.

Model $\mathcal{M}_2$ provides a simple model for MU decline so that the expected number of units at time τ_1 given N_0 units at time τ_0 is $N_0 e^{-\lambda(\tau_1 - \tau_0)}$. Model $\mathcal{M}_1$ allows the rate parameter λ_t to vary from time interval to time interval while incorporating the simpler model. We discuss neurological implications of these two models later.

[Figure 2 about here.]

5. Model comparison

We compare the two models $\mathcal{M}_i, \quad i = 1, 2$ by calculating a Bayes factor from the logs of their marginal likelihoods using thermodynamic integration of the expected log likelihood obtained by sampling from the power posterior as shown in Friel and Pettitt (2008) and shown below in Equation 4 .

$$p(\boldsymbol{\theta}|\underline{\mathbf{h}}, \phi, \mathcal{M}_i) \propto \left[p(\underline{\mathbf{h}} \mid \boldsymbol{\theta}, \mathcal{M}_i) \right]^{\phi} p(\boldsymbol{\theta} \mid \mathcal{M}_i), \quad \phi \in [0, 1]. \tag{4}$$

where $p(\boldsymbol{\theta} \mid \mathcal{M}_i) = p(\mathbf{N} \mid \boldsymbol{\lambda})p(\boldsymbol{\lambda} \mid \boldsymbol{\Phi}, \mathcal{M}_i)p(\boldsymbol{\Phi} \mid \mathcal{M}_i)$ represents all the unknowns and the components have already been defined in Section 4. The log of the marginal likelihood can be calculated using path sampling, and the identity shown below.

$$\log p(\underline{\mathbf{h}} \mid \mathcal{M}) = \int_0^1 \mathbf{E}_{\boldsymbol{\theta}|\underline{\mathbf{h}}, \phi, \mathcal{M}} \log p(\underline{\mathbf{h}} \mid \boldsymbol{\theta}, \mathcal{M}) \, d\phi. \tag{5}$$

The expectation in the integrand can be approximated by calculating a simulation average:

$$\mathbf{E}_{\boldsymbol{\theta}|\underline{\mathbf{h}}, \phi, \mathcal{M}} \log p(\underline{\mathbf{h}} \mid \boldsymbol{\theta}, \mathcal{M}) \approx \frac{\sum^J \log p(\underline{\mathbf{h}} \mid \boldsymbol{\theta}, \mathcal{M})}{J} \tag{6}$$

where $\boldsymbol{\theta}$ is taken from the MCMC output simulated from the powered posterior given by Equation 4 once convergence is attained. The integral can be approximated by allocating ϕ values from the range $[0, 1]$. Simpson's rule can be used to approximate the integral given in Equation 5. The Bayes factor for two models $\mathcal{M}_1$ and $\mathcal{M}_2$ is given by $B_{12} = \frac{p(\underline{h}_1|\mathcal{M}_1)}{p(\underline{h}_2|\mathcal{M}_2)}$.

We used a fifth order power sequence, used 5,000 iterations per power and repeated the marginal likelihood calculation three times with three different smoothing priors.

6. Results of our analysis

The progress of the patients (a) to (d) is shown in Figure 3 in four panels labelled patient (a) to patient(d). Within each of these frames, the upper right hand sub-panels shows the output of the first stage of our model, the RJMCMC. The modes of the marginal posterior distribtions of the number of units are marked with error bars displaying the posterior standard deviations. Repetitions are represented by a slight horizontal movement of each bar. Below these on the lower right of each panel show the MCMC output which are derived from the RJMCMC output smoothed by application of the second stage of our model. These are the outputs of N_t from the two models for the stochastic death process, models $\mathcal{M}_1$ and $\mathcal{M}_2$.

[Figure 3 about here.]

Figure 4 shows the results of our model comparisons. Bayes factors are shown in the second, third and fourth columns, respectively. The repetitions are used to show the lack of sensitivity of the values of the Bayes factor to the prior for the parameter κ. The three priors used are $\epsilon_1 \in \{0.001, 0.01, 0.1\}$ giving a wide range of uninformative Gamma distribution priors. Weak evidence in favour of a changing rate parameter is shown by Patients (a) and (c) with Bayes factors equal to 2.3 and 1.4, respectively. Strong evidence for the same model is shown for patient (b) with Bayes factor equal to 12.3. The constant rate process is strongly favoured for patient (d) with Bayes factor equal to 0.13. For patients (a), (c), and (d), the progress of the disease can be represented by a single rate parameter or alternately a half life, τ.

95% credible intervals for the half life of patient (a) is $\tau_c \in [280 \quad 547]$ days, for patient (c) is $\tau_c \in [206 \quad 447]$ days and that of patient (d) is $\tau_d \in [242 \quad 671]$ days.

[Figure 4 about here.]

The serial studies given in Figure 3 show the evolution of the parameters for the piecewise constant rate model in each bottom left hand side panel. Note that for patient (a) the rate is

increasing whereas for patient (c) the rate is decreasing and the rate appears to decrease throughout the disease. However there is a drop in rate for the last 20 units.

7. Discussion and Conclusion

7.1 *Statistical Aspects*

Using data collected from a quick and painless automated electrophysiological scan, we have developed a computationally efficient and statistically sound method for monitoring the number of motor units on repeated occasions in muscles of patients with ALS, an incurable neurological disease, that advances with time. To determine the rate at which motor units are lost, we regard the output of the RJMCMC analyses as data and then employ a hidden stochastic process of decline, to construct a method of both smoothing the output from the RJMCMC and obtaining estimates of the evolving neuron death rate parameter when it changes. By comparing Bayes factors of models containing an evolving rate parameter with models with a fixed death rate parameter, we have found a means of categorizing the dynamics of the disease progress.

By taking our two stage approach to the analysis of the serial data we have smoothed the process of neuron decline and provided evidence for or against the constant rate, exponential decline model. In order to estimate the number of remaining units at each time point and to choose between the two models for the death rate, we could have employed RJMCMC twice. This would have been a computationally challenging task, and we chose to avoid this. Our approach also provides a predictive distribution for motor unit decline at some future time. The predictive distribution can be found by averaging over the two possible models using the marginal likelihood values to find posterior model probabilities and so automatically weighting each model appropriately without the need to choose between them. Such a predictive distribution could be used to measure the effect of some intervention.

It would be of interest to investigate a Bayesian approach to the modelling which we have

presented and which would replace the two stage approach by merging both the MUNE RJMCMC and the stochastic model choice, having a large RJMCMC. We have made various approximations in our analysis here and this gold standard could be used to investigate the accuracy of our approximations. For example, it would also be possible to extend the model with the evolving rate parameter so that a finer grid of time intervals could be used which are not dependent on the times of the study. Another approximation which we have used is the discrete normal approximation for the RJMCMC output which could be replaced by a set of thinned values from the MCMC output.

7.2 *Neurological Aspects*

As described in section 2.2, different mechanisms for neuron death lead to different mathematical models of decline. Conversely, from the mathematical model that best describes the data, we may be able to infer the mechanism of cell death .

   The models in Section 4.1, apart from the constant rate model, lead to models with non-exponential decline. Each of the non-exponential decline models can be approximated by a more general model where the rate parameter is allowed to vary over time, the type proposed in Section 4.1. In this study, two patients had typical ALS and two patients had a variant of ALS, and the patients with typical ALS could be distinguished from the others by our analysis. This bodes well for the possiblilty of anaysis of the rates of loss of units as a tool to identify different types of degeneration.

   We can envisage three models for the death rate of motor units in ALS, each with a resulting biological mechanism to explain it.

(1) The death rate of a motor unit is fixed and independent of all other units. The neuron death mechanism is due to some internal process similar to aging but the process of decline is initiated by some initial cataclysmic biochemical event.

(2) The death rate of a motor unit changes with time. An increasing rate could be explained by an accelerating aging process or to a deceasing rate or due to differences between types of motor units.

(3) The death rate of a neuron is dependent upon the structural and spatial properties of the surrounding afflicted units. This implies transmission by some damaging agent.

The methodology presented in this paper offers a way of weighing the evidence for whether the death rate of a neuron is constant over time or whether it changes over time. A fixed death rate would imply that neurodegeneration is of type (1) above. On the other hand if the rate was found to be changing over time then the reason for this change could either be type (2), that is, due to some transmission process or alternately due to an accelerating aging process, or of type (3), dependent upon the structural and spatial properties of the surrounding afflicted units.

There is little firm evidence to be found for each of these types of loss in the literature. A major reason for this is that the symptoms such as strength are masked because of the process of collateral sprouting. We have not attempted to differentiate between (2) and (3) but have developed a methodology for distinguishing these from (1), the motor unit death process with a fixed rate. Our methods, we therefore believe, have a role in formulating and evaluating biological models for neural degeneration of the motor system in ALS patients.

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Appendix: Monte Carlo Markov Chain

$\lambda_t \mid \ldots$

The full conditionals of λ_t for $t = 0, 1, 2, \ldots, T$ are

$$p(\lambda_t \mid \ldots) = \begin{cases} p(\lambda_t)p(\lambda_{t+1} \mid \lambda_t, \kappa) & t = 0 \\ p(\lambda_t \mid \lambda_{t-1}, \kappa)p(\lambda_{t+1} \mid \lambda_t, \kappa)p(N_{\tau_t}|N_{\tau_{t-1}}, \lambda_t, \Delta\tau_t) & t = 1, \ldots, T-1. \\ p(\lambda_t \mid \lambda_{t-1}, \kappa)p(N_{\tau_t}|N_{\tau_{t-1}}, \lambda_t) & t = T. \end{cases}$$

We sample from $p(\lambda_i \mid \ldots)$ using random walk Metropolis on the log scale.

$N_{\tau_t} \mid \ldots$

N_{τ_t} is updated using Gibbs sampling from $N_{\tau_t} \in \{N_{\tau_{t-1}}, N_{\tau_{t-1}} + 1, \ldots, N_{\tau_{t+1}}\}$ using probabilities

$$p(N_{\tau_t} \mid \ldots) \sim p(\underset{\sim}{h}_t \mid N_{\tau_t})p(N_{\tau_{t+1}}|N_{\tau_t}, \lambda_{t+1}, \Delta\tau_{t+1})p(N_{\tau_t}|N_{\tau_{t-1}}, \lambda_t, \Delta\tau_t).$$

$\kappa \mid \ldots$

The full conditional for the precision parameter is given by $p(\kappa \mid \ldots) \propto p(\kappa)\prod_{t=1}^{T}p(\lambda_t \mid \lambda_{t-1}, \kappa)$. We sample from $p(\kappa \mid \ldots)$ using random walk Metropolis on the log scale.
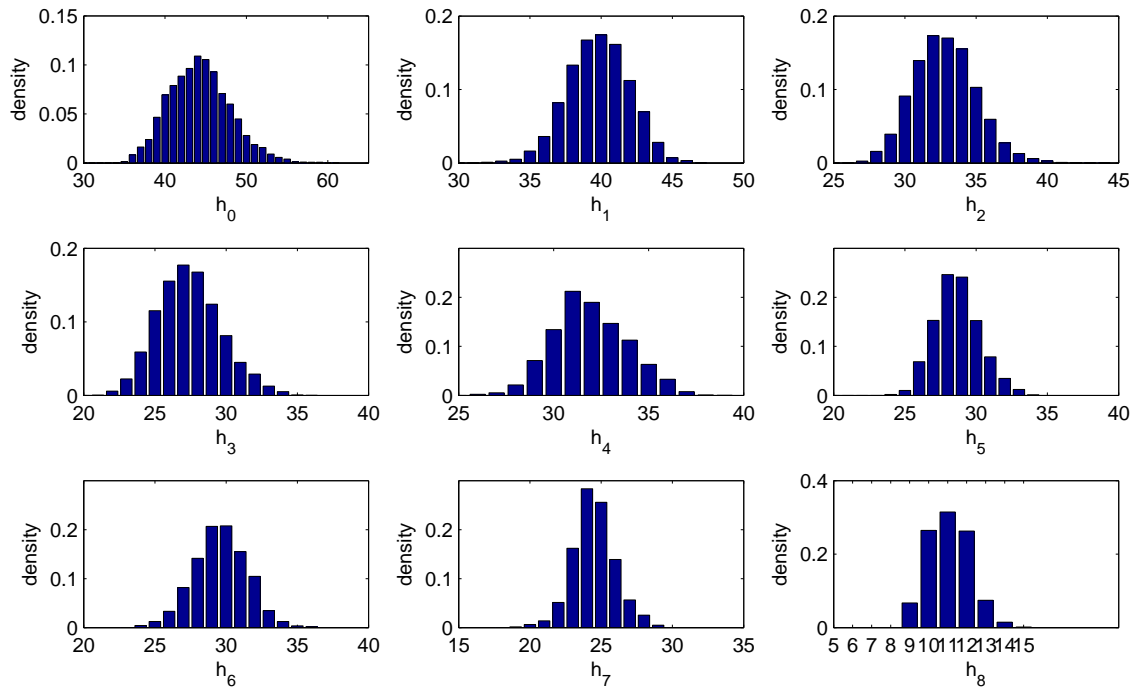
Figure 1. The plots show the output of the first stage RJMCMC for one patient on nine occasions where the histograms, $h_0, \ldots h_8$ give the marginal posterior probabilities of the number of remaining motor neurons, N.
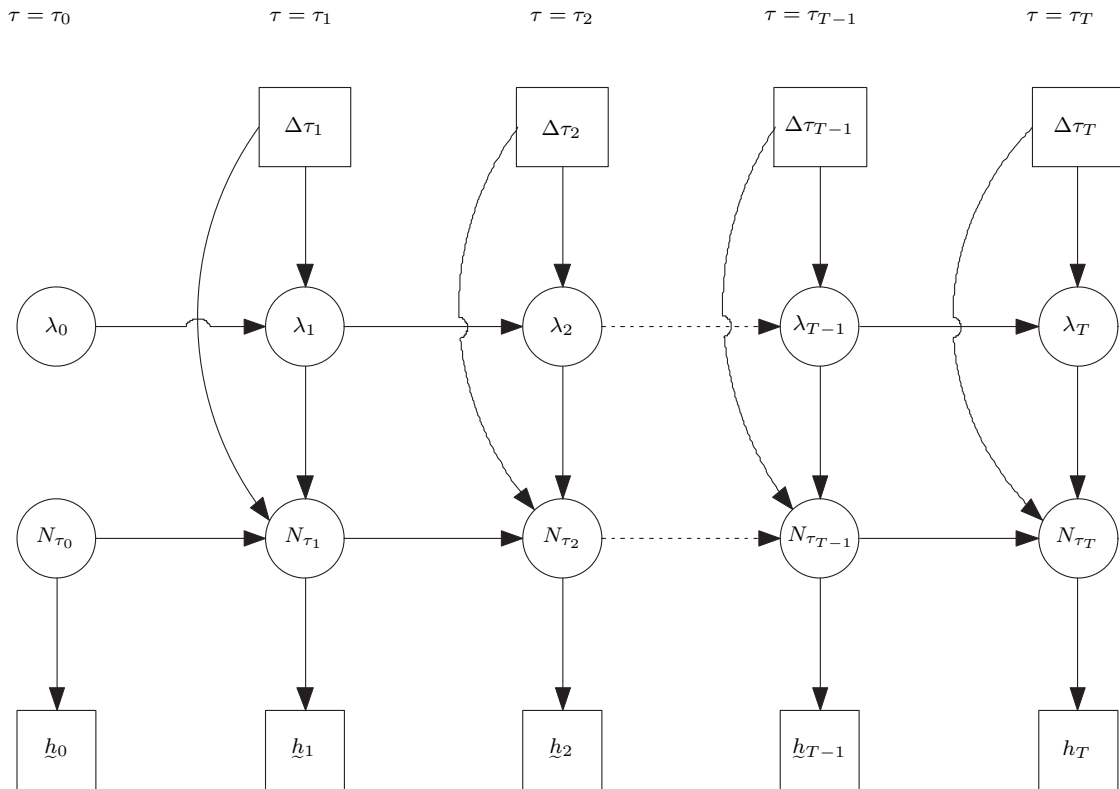
Figure 2. The Directed Acyclic Graph shows the probability model for $\mathcal{M}_1$. The $h_0, \ldots, h_T$ refer to the stage one estimation of the posterior distribution of the number of remaining neurons at time τ_t where the first study starts at t_{τ_0}. N_{τ_t} refers to the underlying process of decline, the λ_t are the rate parameters and the τ_t are the measurement times.
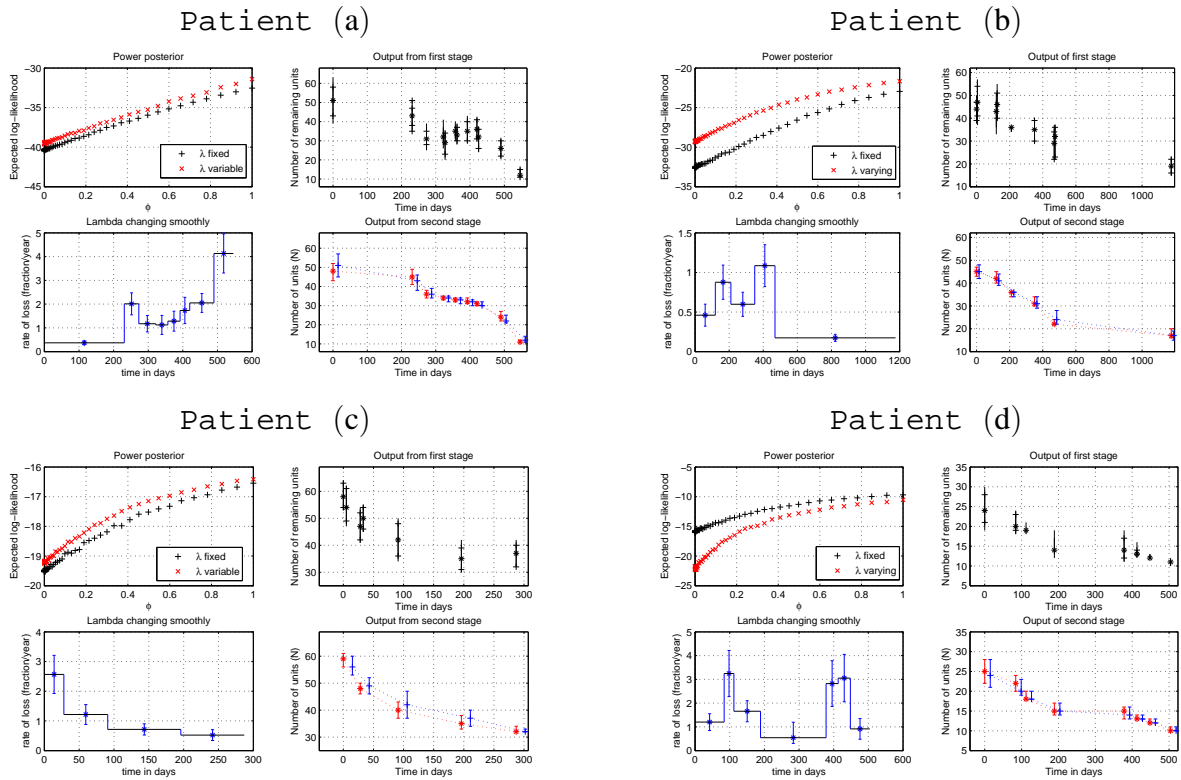
Figure 3. The MCMC output for each of the Patients (a) to (d) is shown above as four sub-panels within four frames representing each patient. We describe each of these sub-panels starting on the right and going from top to bottom. The top right hand panels show the output of the first stage. The modal estimates from the posterior output of the RJMCMC are enclosed by vertical error bars showing posterior standard deviations. Note that some of these error bars have have been displaced slightly on the horizontal axis to show repetitions on the same day. The panels below these show the smoothed output, N_t, from the application of the second stage of the model, the stochastic death process. The output from models $\mathcal{M}_1$ and $\mathcal{M}_2$ is shown as modal estimates with error bars showing the posterior standard deviations. The bottom left panel displays the modal estimates of the time varying and piecewise constant rate parameter λ_t obtained from model $\mathcal{M}_1$. The posterior standard deviations are shown as error bars. The top left hand panels are used to show the result of model selection between models $\mathcal{M}_1$ and $\mathcal{M}_2$. The horizontal axis shows ϕ and the vertical axis shows the expected log likelihood approximated using equation 6. The Bayes factors of the two models is the signed exponent of the areas between the two curves and are presented in Figure 4.

	BF_1	BF_2	BF_3	λ	std
(a)	2.3351	2.3346	2.3395	0.0018	0.0003
(b)	12.2680	12.2711	12.3269		
(c)	1.3827	1.3662	1.3811	0.0024	0.0005
(d)	0.1258	0.1277	0.1289	0.0018	0.0005

Figure 4. The table gives: column 1, the patient identity, (a), …, (d); columns 2, 3 and 4, the Bayes factors (BF_1,BF_2 and BF_3) of model $\mathcal{M}_1$ with respect to $\mathcal{M}_2$ using the three different priors: $\epsilon_1 \in \{0.001, 0.01, 0.1\}$, Columns 5 and 6 show the posterior mean and standard deviations for λ, the rate parameter of $\mathcal{M}_2$.