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Motor unit number estimation, a Bayesian approach

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SUMMARY. All muscle contractions are dependent on the functioning of motor units. In diseases such as amyotrophic lateral sclerosis (ALS), progressive loss of motor units leads to gradual paralysis. A major difficulty in the search for a treatment for these diseases has been the lack of a reliable measure of disease progression. One possible measure would be an estimate of the number of surviving motor units. Despite over 30 years of motor unit number estimation (MUNE), all proposed methods have been met with practical and theoretical objections. Our aim is to develop a method of MUNE that overcomes these objections. We record the compound muscle action potential (CMAP) from a selected muscle in response to a graded electrical stimulation applied to the nerve. As the stimulus increases, the threshold of each motor unit is exceeded, and the size of the CMAP increases until a maximum response is obtained. However, the threshold potential required to excite an axon is not a precise value but fluctuates over a small range leading to probabilistic activation of motor units in response to a given stimulus. When the threshold ranges of motor units overlap, there may be alternation where the number of motor units that fire in response to the stimulus is variable. This means that increments in the value of the CMAP correspond to the firing of different combinations of motor

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units. At a fixed stimulus, variability in the CMAP, measured as variance, can be used to conduct MUNE using the ‘statistical’ or the ‘Poisson’ method. However, this method relies on the assumptions that the numbers of motor units that are firing probabilistically have the Poisson distribution and that all single motor units action potentials (MUAP) have a fixed and identical size. These assumptions are not necessarily correct. We propose to develop a Bayesian statistical methodology to analyse electrophysiological data to provide an estimate of motor unit numbers. Our method of MUNE incorporates the variability of the threshold, the variability between and within single MUAPs and baseline variability. Our model not only gives the most probable number of motor units but also provides information about both the population of units and individual units. We use Markov chain Monte Carlo to obtain information about the characteristics of individual motor units and about the population of motor units and the BIC for MUNE. We test our method of MUNE on three subjects. Our method provides a reproducible estimate for a patient with stable but severe ALS. In a serial study, we demonstrate a decline in the number of motor unit numbers with a patient with rapidly advancing disease. Finally, with our last patient, we show that our method has the capacity to estimate a larger numbers of motor units.

Keywords: amyotrophic lateral sclerosis (ALS); compound muscle action potential (CMAP); mixture model; motor unit action potential (MUAP); motor unit number estimation (MUNE).

1. Introduction

The motor system is responsible for the coordination of the action of joints, muscles and bones with external sensory information. The fundamental unit on which movement is dependent is the motor unit which is the individual motor nerve fibre together with the muscle fibres it activates (Sherrington, 1929). The aim of this study is to develop a Bayesian statistical methodology to analyse electrophysiological data to provide an estimate of motor unit numbers. Because motor unit firing is probabilistic (Stein and Yang, 1990), statistical methods are applicable to determine the number of motor units that supply a muscle.

Amyotrophic lateral sclerosis (ALS) and poliomyelitis are examples of diseases that involve the progressive loss of motor units that make muscles contract. In such diseases an existing reserve and collateral sprouting of axons (Bjornskov et al., 1984) from healthy motor units compensate for loss of motor units. Weakness is noticed if the rate of new sprouting is insufficient when there are too few remaining motor units to maintain muscle strength (Hansen and Ballantyne, 1978). At present, there is no reliable means of quantifying and detecting change in the number of motor units. This means that assessment of progression of diseases such as ALS is largely limited to clinical assessment of muscular strength and that it is not possible to detect the early stages of the disease when motor units are lost but strength is preserved. Thus having a successful means of estimating the number of motor units should assist in the early diagnosis of disease and the monitoring of disease progression. The history of attempts to estimate motor unit numbers has spanned over 30 years. A number of different methods of motor unit number estimation (MUNE) have been developed since the original incremental method of McComas et al. (1971). Most have been based on the calculation of the mean size of motor unit potentials. These include multiple point stimulation (Doherty and Brown, 1993) and spike triggered averaging (Bromberg, 1993). Recent methods have used statistical techniques based on the probabilistic nature of the firing of a motor unit in response to a stimulus. This variability means that firing of different combinations of motor units leads to variability in the size of the CMAP responses (Daube, 1995) (Slawnych et al., 1996). Common criticisms of current MUNE methods include the presence of subjectivity in the estimation process, the failure to obtain a representative sample of units and the failure to incorporate all potential causes of uncertainty. Our aim is to construct a model that meets these criticisms by accounting for several important sources of variability and avoiding subjectivity.

In Section 2 we describe the biological mechanisms involved in motor unit response and show how this leads to our statistical modelling assumptions. In Section 3 we present details of the data collection whilst, in Section 4, a critical view of two previous methods of MUNE is given. In Section

5 we then present our Bayesian model for estimating the number of units, N . In Section 6 we present the results of our analysis and in Section 7 we present a conclusion and discussion.

2. Background to our model and statement of assumptions

We use Benarroch et al. (1999) to present an account of the biological properties of motor units in order to provide a rationale for three broad assumptions. We point out the physiological sources of variability and systematic effects that must be kept in mind when modelling the motor unit response to an electrical stimulation at the nerve.

[Figure 1 about here.]

[Figure 2 about here.]

Figure (1) shows the principal components of the motor unit, which is comprised of a ventral or anterior horn cell in the spinal cord, a motor axon and the muscle fibres that it activates. The membrane of the axon has a resting potential that is governed by the exchange of ions principally at the nodes of Ranvier (see Figure (1)). In its resting state, the sodium and potassium ions are in equilibrium and a potential difference is maintained by adenosine triphosphatase (ATP), an energy dependent pump. After electrical stimulation, in an all or nothing response, and only if the stimulus exceeds a threshold for activation, there is a sudden increase in the permeability of the membrane to sodium ions which enter the axon reversing the polarity of the membrane. This is followed by a slower and less extreme increase in permeability of potassium in the reverse direction. These two actions are responsible for the initial change in potential, the spike of action potential, and the smaller after-potential of the opposite sign, as shown in Figure (2). During the refractory period the unit cannot be stimulated. These are the concepts first developed by Hodgkin and Huxley (1952). The membrane potential returns to normal after about 150 msec (Kuwabara et al., 2001). We collect data from trains of stimuli separated by intervals of either 500 msec or 1000 msec and assume that excitability has returned to normal by the time of the next stimulus.

Propagation of the impulse along the axon occurs because the action potential is sufficient to exceed the threshold of the node in the immediately adjacent membrane and triggers a similar response. In this way the impulse is transmitted along the axon.

Motor units have excitability properties. In general, excitability is regarded as the strength of the stimulus required to excite the axon. Modern concepts of excitability arise from the work of Bostock et al. (1998) who used threshold tracking and other experimental techniques to measure excitability of peripheral nerves (Burke et al., 2001). The threshold of a single axon is not a precise value, but fluctuates over a range. Verveen (1960) suggested that the probability of response is the same with each stimulus and is independent of the preceding responses, when the interval between stimuli is larger than the recovery period.

One measure of excitability is the level of stimulus for which an axon has a 50% probability of firing (Bruce et al., 1999). Another measure of excitability is the *threshold precision* also known as relative spread.

It is now known that the variability in threshold is due to ion channel fluctuations. Hales et al. (2004) followed the method of Chow and White (1996) and modelled eight gating states in transient sodium channels and four gating states in persistent sodium ion channels (of which one is conducting) to describe excitability. Hales et al. (2004) found that the each threshold distribution is very well described by a Gaussian distribution. Slawnych et al. (1996) and Brown and Milner-Brown (1976) regard the way the motor units respond to varying stimuli as a series of sigmoidal activation curves, one for each unit. These above considerations lead to our first set of assumptions which concern the axon and its response to electrical stimulation. This assumption deals with the firing of axons and the variability of the threshold.

Assumption 1 *Motor units fire independently of each other in an all or nothing response and the response to each stimulus is independent of the response to previous stimuli. Motor unit firing only occurs if the stimulus intensity exceeds a variable threshold. The threshold for each unit*

is distributed as a Gaussian variable with its own mean threshold and precision parameter. The mean threshold is defined as the stimulus at which a unit has a 50% probability of firing. The precision parameter defines the range over which the unit exhibits probabilistic firing. The probability of a unit firing as a function of the stimulus can therefore be represented by a sigmoidal curve known as an ‘excitability curve’ (Brown and Milner-Brown, 1976).

The terminal branches of the axon terminate at the neuromuscular junction where acetyl choline is released depolarising the muscle membrane and generating an action potential that spreads through the muscle causing muscle contraction. We refer to the action potential arising from a single motor unit as a single motor unit action potential (single MUAP). In diseases such as ALS, as anterior horn cells die the denervated muscles produce signals that attract branches from axons of healthy units in a process called ‘collateral sprouting’ (Bjornskov et al., 1984). In this way, surviving motor axons are able to activate muscle fibres previously supplied by the axon that has been lost. The muscle action potential generated by one motor unit depends on the number of muscle fibres that the unit supplies. This varies between muscles and motor units (Feinstein et al., 1955) and there is likely to be additional variability in patients with collateral sprouting. This source of variability of single MUAP size is not accounted for in other MUNE methods. For this reason, in our statistical model, we allocate a separate parameter for the mean area of each single MUAP. In addition, there is variability within motor units, particularly in ALS, where the MUAPs may show observable variability of shape on electromyographic examination (Stålberg and Sonoo, 1994). The above considerations lead us to our second assumption which deals with the within and between unit variability of the CMAP area.

Assumption 2 *Each motor unit upon firing emits an action potential in the muscle characterised by an area or amplitude which is independent of the stimulus and normally distributed about a mean particular to that unit with a variance common to all units. (These means can then be allocated a suitable distribution to describe their between unit variability.)*

Although there is a procedure for taking recordings from individual motor units, this is time consuming and invasive since it involves the insertion of a recording electrode beneath the skin. Our method of MUNE involves a relatively non-invasive electrophysiological technique which uses the application of a stimulating electrode to a nerve and the taping of a recording electrode to the muscle supplied by that nerve. The compound muscle action potential (CMAP) recorded is the summation of the single MUAPs of those units that fire. For low stimulus intensities only a few motor units are activated. As the strength of the stimulus increases more axon fibers are activated which stimulate single MUAPs which contribute to the CMAP. When all the motor units are excited the CMAP is at its maximum irrespective of any additional stimulus that is applied. The CMAP responses generated at the surface of the muscle are recorded by electrodes. As with all such systems, there is background noise and background variability that are due to the nature of the recording device. We now present our final assumption which deals with the additivity of the muscle action potentials.

Assumption 3 *The measured CMAP area is the superposition of the muscle action potentials (described by Assumption 2) of those units that respond to a stimulus (as described in Assumption 1) together with a component from the baseline noise which itself is normally distributed with its own mean and variance.*

3. Electrophysiological protocol and data collection

This section gives a discussion of our data collection protocol followed by a summary of some of the technical problems with our method of data collection. The studies were performed at The Royal Brisbane and Women's Hospital using a Nicolet Viking IV system. This equipment has the software program for the generation of stimuli of a given intensity and a given rate, monitors the CMAPs and displays them as shown in Figure (3). The area and the amplitude of the waveform are calculated and these measurements as well as the magnitude of the stimulus are recorded for subsequent analysis. Variation along the segment AB, the baseline, on Figure (3) is known as baseline noise.

[Figure 3 about here.]

Our protocol resembles that of McComas et al. (1971) by using a graded increase in stimulus intensity but differs by using stimulus levels that cover the whole range. This approach is critical to our technique, as it enables the collection of data from all the motor units supplying the muscle. However, because the firing threshold is not precise, motor unit firing in response to a stimulus is probabilistic, determined by whether the threshold of the motor unit is, at that moment, above or below the stimulus intensity. This leads to the phenomenon of ‘alternation’ where increments in the amplitude or the area of the CMAP are due to the firing of different combinations of motor units. Thus the addition of single MUAPs to the CMAP as the stimulus is increased is stochastic or probabilistic rather than deterministic.

Recordings can be impaired by a variety of factors, and two of the more important are the following. The first is to do with electrode placement. If muscles other than the target are stimulated then recordings may contain responses from these additional muscles. This can be seen as a positive deflection in the CMAP recording. This effect can be minimised by careful placement of the electrodes. The second is the problem of movement of the patient. Patient movement can cause faulty recording and can be reduced by immobilising the limb with a Velcro strap.

4. Previous methods of MUNE

We now describe two influential methods in the history of MUNE, stating their implicit assumptions and some of the practical and theoretical objections that others have raised in response to them (Shefner, 2001). The first is the original incremental method (McComas et al., 1971) and the second is the statistical or Poisson method (Daube, 1995).

4.1 The incremental technique

McComas et al. (1971) describe a technique where recordings of CMAP were taken from the *extensor digitorum brevis*, gradually increasing the stimuli until up to 10 jumps in CMAP amplitude

had been observed. In this approach, each discrete increment of potential was assumed to correspond to the excitation of a new motor unit. The mean size of individual motor units was taken to be the average of these increments and the MUNE was calculated by dividing the maximum CMAP size by the mean of the increments. The first objection to this method is the subjectivity involved in the identification of jumps. The second is the failure to account for alternation which will usually lead to an overestimate of the number of motor units. Note that if there are n units firing probabilistically then there are up to $2^n - 1$ increments in the CMAP. As the stimulus is increased, an increment in the CMAP may be the result of motor units that were firing alternately at lower stimuli are now firing together, rather than a new motor unit firing. A third objection, raised by Shefner (2001) is that the amplitudes of area of units excited at low stimulus may not be representative of the complete range. Galea et al. (1991) gave an ad-hoc algorithm to compensate for the alternation effect.

4.2 *The Poisson or statistical method*

This method was proposed by Daube (1995) to address the problem of alternation. In contrast to the incremental technique, MUNE using the Poisson method is carried out with the stimulus fixed. At three separate fixed stimuli, the mean, minimum, and variance of the CMAP area are calculated.

The number of units that fire, n_t , at a given stimulus, S , and time, t , is the sum of those units that fire with near certainty, n_a , and those units that fire probabilistically (some of the time). The ones that fire some of the time, $n_t - n_a$, are assumed to be from the Poisson distribution and independent. The so-called Poisson estimate can be derived by assuming that:

$$(n_t | S) \sim n_a + Po(\lambda), \quad t = 1, 2, \dots, T. \quad (1)$$

Let μ be the single MUAP, which is assumed to be identical for all units. Then the area of the CMAP at any time, y_t , is given by $y_t = n_t\mu$. It can be seen that $\text{var}(y_t) = \lambda\mu^2$, $E(y_t) = (n_a + \lambda)\mu$ leading to $E(y_t) - \min(y_t) = \lambda\mu$. From this follows the *statistical* estimate of the CMAP area of one unit, $\hat{\mu}$,

$$\hat{\mu} = \frac{\text{var}(y_t)}{\text{mean}(y_t) - \min(y_t)}. \quad (2)$$

The MUNE is found by dividing the range of CMAP area by $\hat{\mu}$. This method uses the probabilistic firing of units but does not take into account other sources of variation such as variability of single MUAP size, which is likely to be important in ALS. A large number of modifications improve the reproducibility of the Poisson method (Shefner et al., 1999) (Lomen-Hoerth and Olney, 1999). A consensus of how this should be carried out is presented in Bromberg (2003). Nevertheless, as we show in Section 6.3, these additions still produce upwardly biased estimates. Recently Blok et al. (2005) have suggested a modification to the Poisson method, keeping the the assumption about the lack of variability of the single MUAPs but replacing the Poisson assumption by a binomial assumption. In Section 6.5, in light of estimates from our own model, we also show how the two assumptions necessary for the validity of both the Poisson method and the method of Blok et al. (2005) are inappropriate.

5. Our proposed stochastic model for MUNE for a variable stimulus

We have adopted a Bayesian approach to inference for our model, however there are at least two other means of estimating the parameters. The first is direct maximisation of the marginal likelihood using numerical methods. This is not feasible because of the time required to integrate out the missing variables in the proposed model. A more feasible solution is to use the EM algorithm which iteratively maximises the complete likelihood using the expected values of the missing variables. We have avoided this approach because of the extra effort and uncertainty that is involved in finding the standard errors of the parameters. In using a Bayesian approach using Markov chain Monte Carlo we are able to estimate posterior distributions and, in this way we generally obtain better measures of the uncertainty of our parameters. With good estimates of the uncertainty of the parameters we are able to make statistical comparisons both of individual units and the populations of units.

Let N be the number of motor units and let k depict a given unit where $k = 1, 2, \dots, N$. Let y_t be the measurement of CMAP area recorded at stimulus S_t , for $t = 1, 2, \dots, T$, where T is the number of measurements taken. We denote all the observations by $\mathbf{y} = \{y_1, y_2, \dots, y_T\}$ and all the stimulus

values by $\mathbf{S} = \{S_1, S_2, \dots, S_T\}$. We now develop, in detail, the assumptions given earlier.

Assumption 1

Let the threshold of motor unit k at time t be $\tau_{k,t}$. We assume that the thresholds of each unit, $k = 1, \dots, N$, vary randomly and independently according to the normal distribution:

$$\tau_{k,t} \sim N\left(m_k, \frac{1}{\delta_k^2}\right), \quad (3)$$

where for a particular unit, m_k is the mean threshold and δ_k^2 is the precision of the threshold of that unit. If the threshold is exceeded by the stimulus, i.e. if $S_t > \tau_{k,t}$, then unit k fires at time t . We now standardise the latent variable $\tau_{k,t}$ by making the transformation:

$$z_{k,t} = \delta_k(S_t - \tau_{k,t}).$$

The sign of $z_{k,t}$ determines whether a unit will fire or not and define

$$\begin{aligned} I(z_{k,t}) &= 0, & z_{k,t} < 0, \\ &= 1, & z_{k,t} \geq 0. \end{aligned}$$

Thus $z_t = \{z_{1,t}, z_{2,t}, \dots, z_{N,t}\}$ is a multivariate normal random value with mean parameter $\Phi_t = \delta_k(S_t - m_k)$, $k = 1, 2, \dots, N$ and variance parameter \mathbf{I}_N , which is the identity matrix of order N .

Hence

$$(\mathbf{z}_t \mid S_t, \boldsymbol{\delta}, \mathbf{m}) \sim N(\Phi_t, \mathbf{I}_N), \quad (4)$$

where $\mathbf{m} = \{m_1, m_2, \dots, m_N\}$ and $\boldsymbol{\delta} = \{\delta_1, \delta_2, \dots, \delta_N\}$. The parameters \mathbf{m} and $\boldsymbol{\delta}$ are considered random effects described by hyper-priors as shown in Section 5.1. Next we express (4) as a standard linear model so that efficient block updates can be carried out in the MCMC process. We let $\Phi_t = \mathbf{X}_t \boldsymbol{\beta}$

where

$$\boldsymbol{\beta} = (\delta_1, m_1\delta_1, \delta_2, m_2\delta_2, \dots, \delta_N, m_N\delta_N)^T \quad (5)$$

$$\mathbf{X}_t = I_N \otimes (S_t, -1) = \begin{pmatrix} S_t & -1 & 0 & 0 & \dots & 0 & 0 \\ 0 & 0 & S_t & -1 & \dots & 0 & 0 \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & 0 & 0 & \dots & S_t & -1 \end{pmatrix}. \quad (6)$$

Because the latent states, $\mathbf{z} = \{\mathbf{z}_1, \mathbf{z}_2, \dots, \mathbf{z}_T\}$, are assumed conditionally independent, the probability density of \mathbf{z} is given by

$$p(\mathbf{z} | S, \boldsymbol{\delta}, \mathbf{m}) = \frac{e^{-\frac{1}{2} \sum_{t=1}^T \{(z_t - X_t \boldsymbol{\beta})^T (z_t - X_t \boldsymbol{\beta})\}}}{(2\pi)^{\frac{NT}{2}}}. \quad (7)$$

Assumption 2

Single MUAPs are assumed normally distributed around the mean for that unit, μ_k , with a common variance σ^2 . The parameters, μ_k , can be modelled as fixed or random effects.

Assumption 3

The baseline noise is normally distributed around its mean, μ_b , with variance σ_b^2 . Using the assumption of additivity, the expected CMAP will be the sum of expected single MUAPs and the expected level of baseline noise. Similarly, the variance of the CMAP area will be the sum of the variances of those units that fire and the baseline variance. Because the observations of CMAP area are assumed conditionally independent, y_t will be distributed normally as:

$$(y_t | \mathbf{z}_t, \boldsymbol{\mu}, \mu_b, \sigma_b, \sigma) \sim N\left(\mu_b + \sum_{k=1}^N \mu_k I(z_{k,t}), \sigma_b^2 + \sigma^2 \sum_{k=1}^N I(z_{k,t})\right). \quad (8)$$

For notational simplicity we let

$$\mu_t^T = \mu_b + \sum_{k=1}^N I(z_{k,t}) \mu_k \quad (9)$$

$$V_t = \sigma^2 n_t + \sigma_b^2, \quad n_t = \sum_{k=1}^N I(z_{k,t}). \quad (10)$$

The probability of the observations, \mathbf{y} , in terms of the latent variable \mathbf{z} is therefore:

$$p(\mathbf{y} \mid \mathbf{z}, \mu_b, \sigma_b, \boldsymbol{\mu}, \sigma) = \frac{e^{-\sum_{t=1}^T \frac{(y_t - \mu_t^T)^2}{2V_t}}}{\prod_{t=1}^N \sqrt{2\pi V_t}}. \quad (11)$$

5.1 Priors

For the Bayesian analysis we need to define priors for various parameters.

1. The mean of the baseline noise, μ_b , is allocated a gamma distribution:

$$\mu_b \sim \text{Gam}(\alpha_2, \beta_2),$$

where $\alpha_2 = \beta_2 = .001$. Thus the probability density function of μ_b is $f(\mu_b \mid \alpha_2, \beta_2)$ where

$$f(x \mid \alpha, \beta) = \frac{\beta^\alpha x^{\alpha-1} e^{-\beta x}}{\Gamma(\alpha)}.$$

2. For each k , the single MUAPs μ_k , are allocated left truncated gamma distributions:

$$\mu_k \sim \text{Gam}_T(\alpha_\mu, \beta_\mu, \mu_{\min}),$$

where μ_{\min} is a minimum possible value. This prior is the only informative prior of the model.

For the data analysed here the smallest expected single MUAP was set at $\mu_{\min} = 100\mu Vms$.

Thus the probability density function, $g(\mu_k \mid \alpha_\mu, \beta_\mu, \mu_{\min})$, of μ_k is

$$g(x \mid \alpha, \beta, \mu_{\min}) = \begin{cases} \frac{f(x \mid \alpha, \beta)}{1 - \int_{x=\mu_{\min}}^{\infty} f(x \mid \alpha, \beta) dx} & x \geq \mu_{\min} \\ 0 & x < \mu_{\min} \end{cases}$$

Our procedure in our data analysis was to initially allocate μ_k fixed effects and then, if appropriate, to allow μ_k to be modelled as random effects by allowing α_μ and β_μ to vary as hyper-parameters with priors given later in this section.

3. The variance, σ^2 , is allocated a non-informative inverse gamma distribution:

$$\sigma^2 \sim \text{IGam}(\alpha_3, \beta_3),$$

where $\alpha_3 = \beta_3 = .001$. Thus the probability density function, $f(\sigma^2 \mid \alpha_3, \beta_3)$, of σ^2 is $f(x \mid$

$$\alpha, \beta) = \frac{\beta^\alpha x^{-(\alpha+1)} e^{-\frac{\beta}{x}}}{\Gamma(\alpha)}.$$

4. The variance, σ_b^2 , is allocated a non-informative inverse gamma distribution:

$$\sigma_b^2 \sim IGam(\alpha_4, \beta_4),$$

where $\alpha_4 = \beta_4 = .001$.

5. The threshold precision parameters, δ_k^2 , are assumed to be gamma random effects: $\delta_k^2 \sim Gam(\alpha_\delta, \beta_\delta)$. The mean threshold parameters, m_k , are assumed to be normal random effects: $m_k \sim N(\mu_m, \sigma_m^2)$. The parameter β is expressed in terms of the threshold precision parameters, δ , and the mean threshold parameters, \mathbf{m} , using (5). The prior for β is given by:

$$p(\beta) = p(\mathbf{m})p(\delta^2)|\mathbf{J}|, \quad (12)$$

where $|\mathbf{J}| = 2^N$.

6. The hyper-parameters, α_μ , β_μ , α_δ , and β_δ are given non-informative improper priors:

$$p(\alpha_\mu, \beta_\mu, \alpha_\delta, \beta_\delta) \propto 1$$

7. The hyper-parameter, μ_m , is given a normal non-informative prior:

$$\mu_m \sim N(0, 1/\tau_\epsilon)$$

where $\tau_\epsilon = 1/\sigma_\epsilon^2 = .001$.

8. The hyper-parameter, σ_m^2 , is given a non-informative inverse Gamma prior:

$$\sigma_m^2 \sim IGam(\alpha_1, \beta_1),$$

where $\alpha_1 = \beta_1 = .001$.

5.2 The probability model

The probability model can be depicted in the directed acyclic graph (DAG), shown in Figure (4). The full probability model can be written in the form below. We have suppressed the dependence of the model on N for notational simplicity.

[Figure 4 about here.]

$$\begin{aligned} p(\mathbf{z}, \mathbf{y}, \Theta \mid \mathbf{S}) &= p(\mathbf{z}, \mathbf{y} \mid \Theta, \mathbf{S})p(\Theta) \\ &= p(\mathbf{y} \mid \mathbf{z}, \Theta_y)p(\mathbf{z} \mid \Theta_z, \mathbf{S})p(\Theta), \end{aligned} \quad (13)$$

where $\Theta = \{\Theta_z, \Theta_y\}$ where $\Theta_z = \{\mathbf{m}, \boldsymbol{\delta}, \mu_m, \sigma_m, \alpha_\delta, \beta_\delta\}$, $\Theta_y = \{\boldsymbol{\mu}, \mu_b, \sigma, \sigma_b, \alpha_\mu, \beta_\mu\}$.

5.3 Some MCMC considerations

Markov chain Monte Carlo (MCMC) is used to estimate the posterior distributions, $p(\Theta \mid \mathbf{S}, \mathbf{y})$, of these parameters. The full conditionals and sampling schemes necessary for this approach are given in the appendix.

A problem with using random walk Metropolis-Hastings updates is that each parameter using this scheme requires a separate tuning parameter. To avoid the necessity of optimising these parameters when updating the variability parameters σ^2 and σ_b^2 we instead simulate from a gamma approximation to the full conditionals. The parameters for this gamma distribution are chosen so that they have the same mode and variance as the full conditional.

5.4 The marginal likelihood

We define the *marginal likelihood* as joint probability density function of the data and the unobserved states, integrated over the states:

$$\begin{aligned} L^m(\Theta) &= p(\mathbf{y} \mid N, \Theta) \\ &= \int p(\mathbf{y} \mid \mathbf{z}, \Theta_y, N)p(\mathbf{z} \mid \Theta_z, \mathbf{S}, N)d\mathbf{z}. \end{aligned} \quad (14)$$

where we have explicitly introduced the number of units, N , as a parameter. For our study, the integral expressed in (14) is intractable but can be approximated using the following method. We make R draws for each observation from the distribution of the latent variable: $z_t^{(r)} \sim N(\Phi_t, \mathbf{I}_N)$, $r = 1, 2, \dots, R$ and then calculate

$$\hat{L}_t = \frac{\sum_{r=1}^R N(y_t; \mu_b + \sum_{k=1}^N \mu_k I(z_{k,t}^{(r)}), \sigma_b^2 + \sigma^2 \sum_{k=1}^N I(z_{k,t}^{(r)}))}{R}. \quad (15)$$

Having done this for each data point, the likelihood for all the data can be approximated as: $\hat{L}^m(\Theta) = \prod_{t=1}^T \hat{L}_t$. Below we evaluate $\hat{L}^m(\Theta)$ at $\Theta = \hat{\Theta}$, the posterior mode.

5.5 Model selection to infer N

We approach the problem of estimating the value of N by extending the probability model to include N explicitly rather than considering the problem as one of model choice. See, for example, the Deviance Information Criterion (DIC) (Spiegelhalter et al., 2002), Akaike's Information Criterion (AIC), (Akaike, 1978) and the Bayesian information criterion (BIC) (Schwarz, 1978), (Hastie et al., 2001).

We require the posterior probability, $p(N | \mathbf{y})$, where $p(N | \mathbf{y}) \propto p(N)p(\mathbf{y} | N)$. We have assumed an uninformative uniform prior for N . The marginal probability, $p(\mathbf{y} | N)$, can be obtained by integrating out all the parameters, Θ , giving

$$p(\mathbf{y} | N) = \int p(\mathbf{y} | N, \Theta)p(\Theta | N)d\Theta,$$

where $p(\mathbf{y} | N, \Theta)$ has been found by using (14).

Despite advances in theory and technology, the computation of the marginal probabilities for complex models remains a formidable challenge. Three approaches to this are analytical approximation (DiCiccio et al., 1997), numerical integration and Monte Carlo simulation (Evans and Swartz, 2000). We use the first of these. Raftery (1996) uses a version of the Laplacian approximation and a further asymptotic approximation to derive an expression for the log of the marginal likelihood,

$$\log p(\mathbf{y} | N) \approx \log p(\mathbf{y} | \hat{\Theta}, N) - \frac{p_N}{2} \log(T), \quad (16)$$

where $\hat{\Theta}$ is the posterior mode and for our applications $p_N = 3N + 9$ is the number of parameters used in the N unit model. We follow Raftery (1996) and use the multivariate median as an approximation to the mode. Let $\Theta^{(r)}$, $r = 1, 2, \dots, R$ be successive draws from the posterior distribution taken from the MCMC output. The multivariate median is defined as the value of $\Theta^{(r)}$ that minimises $\sum_s |\Theta^{(s)} - \Theta^{(r)}|$ where $|\cdot|$ defines the $L1$ median as defined by Small (1990).

Assuming an uninformative prior for N then

$$\begin{aligned} \log p(N | y) &= \text{const} + \log p(\mathbf{y} | N) \\ &\approx \text{const} - \frac{1}{2} \text{BIC}, \end{aligned} \tag{17}$$

using (16) and substituting for the BIC. Generally, the BIC would give an overprecise approximation to the posterior $p(N | y)$.

6. Results of our analysis

In this section we give clinical descriptions of our patients, show the results of our method of MUNE, compare our results with previous methods and, show that our method also yields estimates of the characteristics of individual units, use our model to present a critique of two of the assumptions of the Poisson method and finally we report on our diagnostic plots performed on the residuals of our model.

6.1 Patients

The first patient is a 50 year old male with ALS, who has lost almost all strength of the left hand, but was clinically stable. He was studied on four occasions, over a period of several months. His left ulnar nerve was stimulated and recordings taken from the surface of the *abductor digiti minimi*. This patient was studied to assess whether the results of our analysis were stable over time in a patient who was clinically weak, but not deteriorating. The second patient, a 75 year old male, had a bulbar presentation of ALS but has rapidly advancing disease in both his hands. The data was also collected from the *abductor digiti minimi* muscle upon stimulation of the right ulnar nerve at intervals over a

period of four months. We use this data set to illustrate that we are able to measure rate of loss of units. The third patient was 64 year old female with previous poliomyelitis as child. The data was collected from the *extensor digitorum brevis* in the leg upon stimulation of the peroneal nerve. We use this data set to illustrate that MUNE, using our method, can be made with subjects with a larger number of units. We also use data from this patient to compare our method of MUNE with previous methods. The fourth subject was normal and used as a control. No rigorous model selection was performed on the data from this patient.

[Figure 5 about here.]

Figure (5) shows recordings of percentage CMAP area plotted against the level of stimulus taken from three patients. Note the appearance of discrete jumps with increasing stimulus intensity as the stimulus exceeds the thresholds of increasing numbers of units.

6.2 MUNE

All simulations were performed using MCMC using the full conditionals given in the appendix and performed using the language Matlab. An initial 10,000 iterations were used to ensure convergence which was tested for using the CODA software (Best et al., 1995). The BIC was independently calculated, 25 times for each value of N , which gave sufficient accuracy for our purposes as shown below.

For our first patient, studied at intervals over several months, the stimulus response curve Figure (5) (1A)-(1D) showed different appearances. However, our MUNE calculations showed that the value of the BIC was lowest for $N = 5$. See Figure (6) (1A)-(1D). These results suggest that our estimate appears to be reproducible and that there is strong evidence that there are five surviving units.

In our second study we are able to measure the rate of loss of units over a three month period with a patient with rapidly progressive ALS. In Figure (5) (2A)-(2C), the data are plotted and in Figure (6) (2A)-(2C) the values of the BIC are plotted. The estimated most likely number of units is $N = 14$ in

May 2004, $N = 13$ in June 2004 and $N = 11$ in July 2004. These estimates are consistent with the clinical course of the patient, who showed increasing weakness.

The third study was conducted with a patient with poliomyelitis as a child. In Figure (5) (3A), the data are plotted, and in Figure (6) (3A) the values of the BIC are plotted. Our method indicated the most likely estimate of the number of units using our technique was $N = 24$.

[Figure 6 about here.]

6.3 Comparison with other methods

For the third patient, we compared our results to MUNE with the incremental method and the Poisson method. For the incremental method, we look at Figure (5) (3A) at a stimulus of 29mA and count 10 steps with a percentage CMAP area of 24%. This leads to an average single MUAP of $\hat{\mu} = 2.4\%$ which leads to an estimate of about $N_{\text{inc}} = \frac{94}{2.4} \approx 39$. (In all datasets the maximum CMAP is seldom 100%. This is because the initial sweep that the hardware uses to estimate this is inaccurate). This estimate is likely to be upwardly biased because of alternation as are all methods based on the counting of levels. This is because each step does not necessarily correspond to the recruitment of an additional unit.

For the Poisson method, we changed the data collection protocol and collected about 300 observations at three fixed stimulus values. The application of equation (2) yields averages of $\hat{\mu}_1 = 0.74\%$, $\hat{\mu}_2 = 2.34\%$, and $\hat{\mu}_3 = 1.43\%$. The weighted average of these (according to the number estimated to be firing probabilistically for that stimulus) is $\hat{\mu} = 1.53\%$ giving the Poisson estimate of approximately $N_{\text{Pois}} = \frac{79}{1.26} \approx 63$. Note the CMAP range in the calculation is 79% after gaps $> 10\%$ in the CMAP have been excluded. If the modifications suggested by Shefner et al. (1999) and Lomen-Hoerth and Olney (1999) as well as others summarised in Bromberg (2003) are applied this falls to about $N \approx 40$. The Poisson or statistical method does not account for the considerable variation in mean single MUAPs that exists for patients with ALS. For the $N = 24$ unit model we have estimated a 95% credible interval for the standard deviation, $\text{sd}(\mu_k)$ of (1.32, 2.22), where the 95% credible

interval for the mean of the expected single MUAPs is (3.85, 3.91). The credible interval for $\text{sd}(\mu_k)$ does not include zero, contradicting an assumption of the Poisson method. In Section (6.5), from a model that uses data from a normal patient, we look critically at two of the assumptions of the Poisson method.

6.4 *Estimates of individual motor units*

In this section, we look at the excitability curves and expected single MUAPs for patient one's data sets for the preferred five unit models calculated at the posterior mode. In Figure (7) we have used configurations 1-4, taken from the first patient, to plot the excitability curves and the expected components of the CMAP area for several points from each of the data sets.

[Figure 7 about here.]

The second column displays the excitability curves, plotted using the modal values of β taken from the posterior distribution. The third column shows vertical bars denoting the expected CMAP, μ_t^T (given by 9), showing its components, the expected single MUAPs, μ_k , of those units that are firing at instances, t , and for each of the points highlighted by asterisks in the first column. The same points are denoted in the third column by the '+' symbol to show the fit which is good. Note from the plots that there appears to be one small unit and perhaps one large unit but their respective sizes vary from session to session. Also note that the units are not activated in a fixed order as the stimulus is increased. The order of activation is different on each occasion, presumably because of the variation of the position of the stimulating and recording electrodes. This variability in apparent excitability could be due to changes in the locations of the electrode because of the need for the stimulus to be transmitted through the volume conductor.

6.5 *Illumination of the Poisson method in terms of the new model*

We now examine, using the data taken from patient four, a normal patient, the two assumptions of the Poisson method. In Figure (8), we have plotted the excitability curves of a population of $N = 80$ motor units estimated from modal values of the posterior distributions of the excitability parameters.

[Figure 8 about here.]

There is no convincing argument to suggest that the Poisson assumption, (1), will hold. Rather than being Poisson, the distribution of $n_t - n_a$, assuming the Bernoulli distributions are fixed, will be most of the time under-dispersed relative to a binomial where n_t is the number of units firing at time t . The binomial assumption as made by Blok et al. (2005) will only be appropriate in the rare case when the Bernoulli probabilities are identical. In Figure (8) (A) we show data collected from a normal subject. In Figure (8)(B), the excitability curves are calculated from the posterior distribution of a $N = 80$ unit model (which is not necessarily the best model but gave a good fit). The probabilities of each unit firing for a fixed stimulus, $S = 9mA$, are given by the intercepts on the bold vertical line and are all different. The Poisson approximation would only hold if the firing probabilities were similar and small in magnitude.

Next we show that the second assumption of the Poisson method, that the single MUAPs are identical, would appear to be incorrect and, as an approximation, gets poorer as ALS progresses. By looking at the modal posterior estimates of the hyper-parameters, we are able to estimate trends in the distribution of the population of units. Figure (9) illustrates how we are able to monitor the evolution of the distributions of single MUAPs recorded from patient two who has a deteriorating condition. We include the estimate of the corresponding distribution of the single MUAP areas from data taken from a healthy patient, patient four, for comparison.

[Figure 9 about here.]

Firstly, we note the increase in both the spread and mean of single MUAP areas over time for patient two. This is consistent with the development of collateral sprouting. Secondly, we note that corresponding distribution of single MUAP areas from a healthy patient is more concentrated. However the variance is not zero so there is between unit variability in the size of the single MUAP areas. Thus, in our view, the Poisson method will not work even with patients with large numbers of units.

6.6 *Model diagnostics*

[Figure 10 about here.]

In this section we briefly report on an examination of some of our statistical assumptions. Figure (10) shows a selection of diagnostic plots performed on the Pearson residuals from the analysis of the third data set shown in Figure (5), (3A). Plots (A) and (B) of Figure (10) indicate that the assumption that the observations are normally distributed around their expected values would appear to be justified. Plot (C) indicates no discernable relationship between the stimulus and the residuals. The plots (D)-(E), indicate that the residuals show a small amount of autocorrelation. In fact there is a small amount of autocorrelation in several of our models and we comment on it in the discussion; plot (F) indicates a good fit.

7. **Conclusions and discussion**

There is a need to develop a method of following the clinical course of patients with diseases that result in loss of motor units. The most important reason for this is that measurements of muscle power do not reflect the number of remaining motor units because of collateral sprouting, where healthy axons take on the role of axons that are lost.

Although the statistical (Poisson) method has been used to measure MUNE, including in a recent clinical trial (Shefner et al., 2004), there are considerable problems with the use of the technique to estimate the loss of units over time (Armon, 2003). The Poisson method has the advantage of recognising the problem of alternation, which is a phenomenon resulting from the probabilistic nature of motor unit firing in response to a stimulus which leads to a variability of the response. However, we question the two assumptions that the Poisson method relies on. Firstly, that the single MUAPs have the same size and secondly, that the units firing probabilistically, for a given stimulus, have the Poisson distribution.

Instead, we have proposed a model that avoids these assumptions and used a data collection pro-

tocol resembling that used in the incremental method of McComas et al. (1971) over the whole range of stimuli. We overcome the problems of the Poisson method by modelling alternation and removing subjectivity from our method of MUNE. In our approach, we believe we have fulfilled the need for research outlined by Enoka (2002), who expressed the view that “the field would benefit from an experimental study that unambiguously determined the significance of alternation in the identification of single motor units with the application of graded stimulation to the peripheral nerve”.

Our method has provided consistent estimates for a patient with stable but severe ALS. In a serial study, we have been able to monitor the loss of units with a patient with rapidly advancing disease. Finally, we have shown that our method is capable of estimating motor unit numbers for a patient with a moderate number of remaining units. In all patients we have been able to estimate the variance of the mean single MUAPs. We have also been able to estimate the distribution of the two excitability parameters: the mean threshold and the threshold precision. Such estimates may provide useful measures in understanding the disease.

The validity of our method of MUNE depends on the appropriateness of our assumptions. We have chosen carefully assumptions that are sufficiently complex to capture the important biological mechanisms involved and use simple enough approximations to allow estimation which is computationally feasible. Three broad biological assumptions have been made, the first relating to the stimulation of the peripheral nerves and the other two relating to the electrical response of the muscles fibres and the recording of the CMAP. We comment on each below.

Assumption 1: The biological basis of the variability of the threshold of each unit is well-established and relies on an understanding of the probabilistic nature of the response of axons to electrical stimulation. In essence, because of ion-channel fluctuation, the threshold for firing is not precise, but varies across a narrow range (Hales et al., 2004). We also assume that the effect of each stimulus is independent of the other stimuli. The autocorrelation, in the residuals noted in Section

6.6, is very small but nevertheless surprising. This is because the rate of stimulation that we are using is such that the interval between stimuli is much longer than the refractory period of the action potential shown in Figure (2). However we note that there have been examples in the literature where activity has been shown to cause alterations in the polarisation of axons. For instance, Vagg et al. (1998) show that maximal voluntary contraction can cause hyperpolarisation thought to be due to metabolic changes. We hope to study further the relationship between autocorrelation and rate of progression of disease for a range of patients. We also plan to construct a model where the assumption of independence between observations can be relaxed and simple autocorrelation modelled.

Assumption 2: This assumption incorporates (i) the between unit variability in the expected single MUAP sizes, μ_k , and (ii) a common within unit variation with variance σ^2 . For (i), estimation of the distribution of the single MUAPs indicates that the between unit variation was highly significant in all data sets with $N > 10$ and well described by a Gamma distribution. The basis for this assumption is speculative, but could include variability at the pre-synaptic and post-synaptic sites of the neuromuscular junction. For $N \leq 10$, a fixed effects model appears more appropriate and this is reflected in the large posterior variances for μ_k . For (ii), the assumption of constant within unit variability may not always be true and needs to be checked. For instance, an intermittent failure of conduction in terminal branches or at the neuromuscular junctions of some of the units would lead to extra variation in those units. Residual diagnostics of the data sets that we have analysed, Figure (10) (B), do not give evidence of a failure of this assumption for the patients we have studied.

We also assume that the single MUAPs are independent of the stimulus. Figure (10) shows little evidence of a relationship between the stimulus and CMAP area of individual units. However dependence on stimulus cannot be wholly discounted as for some parts of the plots are smooth and contain no discernable gaps (eg the low stimulus values of Figure (5), (2A)).

In Section (5.1) we assumed a lower bound on μ_{\min} , for μ_k , the expected single MUAP of a

unit if it fires. Some authors have suggested that the minimum size is $25\mu Vms$ (Bromberg, 2003) but, having experimented with repeated studies where recordings are made on the same muscle with different configurations of the electrodes, we found that our higher value of $\mu_{\min} = 100\mu Vms$ gave better reproducibility for these kinds of studies. We aim to further research an appropriate setting of this parameter.

Assumption 3: We have assumed that the areas from each unit contribute strictly additively to the CMAP area. This assumption is dependent on the strict negativity of the waveform of each unit contributing to the CMAP enclosed by the two markers BC shown in Figure (3). If there is any variation in the duration of the action potential of individual motor units then phase cancellation may occur. Thus this assumption can only hold as a close approximation and will be improved by the optimally setting of the markers.

In terms of the statistical methods used, it is clear to us that the approximation leading to (16) may not always be good enough for our purposes particularly with patients with large N . We are currently developing a model where the number of units N can be treated as a stochastic variable, with a prior, and sampled from a posterior using MCMC in a similar manner to that which we have demonstrated in this article. To do this we need to use and develop the theory of trans-dimensional MCMC (Green, 2003).

There are uncommon examples of data collected from ALS patients where our assumptions are violated to such an extent that our model, in its current form, will not work. Such an example is with a patient exhibiting decremental responses (Wang et al., 2001) in their CMAP response. Here, if a unit has just fired then subsequent action potentials are reduced violating assumptions 1 and 2. In future models we hope to have a means of detecting and correcting for this effect.

Finally, and most importantly, we propose to increase computational efficiency so that this model can be used for conducting MUNE with patients with a large number of units. When this is done we

believe we will have a means of making an early detection of disease.

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Appendix

The full conditionals for MCMC

We use the notation from Equations 9 and 10.

$\mathbf{z}_t \mid \dots$

Since $p(\mathbf{z}_t \mid \dots) \propto p(\mathbf{z}_t \mid \Theta_z)p(y_t \mid \mathbf{z}_t, \Theta_y)$

at each time instance, t , a proposal $\mathbf{z}_t \rightarrow \tilde{\mathbf{z}}_t$ is made from the prior distribution:

$$(\tilde{\mathbf{z}}_t \mid \dots) \sim N(\Phi_t, \Sigma).$$

$\mu_b \mid \dots$

Since

$$p(\mu_b \mid \dots) \propto p(\mu_b)N\left(\mu_b; \frac{\sum_{t=1}^T \frac{y_t - \sum_{k=1}^N \mu_k I(z_{k,t})}{V_t}}{\sum_{t=1}^T \frac{1}{V_t}}, \frac{1}{\sum_{t=1}^T \frac{1}{V_t}}\right),$$

a proposal $\mu_b \rightarrow \tilde{\mu}_b$ is made from the second term above.

$\mu_k \mid \dots$

Similar comments to μ_b above hold for μ_k since if $\check{\mu}_{k,t} = \mu_t^T - I(z_{k,t})\mu_k$ then

$$p(\mu_k \mid \dots) \propto p(\mu_k)N\left(\mu_k; \frac{\sum_{t=1:z_{k,t}>0}^T \frac{y_t - \check{\mu}_{k,t}}{V_t}}{\sum_{t=1:z_{k,t}>0}^T \frac{1}{V_t}}, \frac{1}{\sum_{t=1:z_{k,t}>0}^T \frac{1}{V_t}}\right).$$

$\sigma^2 \mid \dots$

The mode, $\hat{\sigma}^2$, is found by numerically solving for σ^2 in the equation

$$\frac{\partial \log p(\sigma^2 \mid \dots)}{\partial \sigma^2} = -\frac{1}{2} \sum_{t=1}^T \frac{n_t}{\sigma^2 n_t + \sigma_b^2} + \frac{1}{2} \sum_{t=1}^T \frac{n_t (y_t - \mu_t^T)^2}{(\sigma^2 n_t + \sigma_b^2)^2} + \frac{\beta_3}{\sigma^4} - \frac{\alpha_3 + 1}{\sigma^2} = 0,$$

and approximating the variance by $\hat{V}(\hat{\sigma}^2) = (-H(\hat{\sigma}^2))^{-1}$ at that mode where

$$H(\hat{\sigma}^2) = \frac{1}{2} \sum_{t=1}^T \frac{n_t^2}{V_t^2} - \sum_{t=1}^T \frac{n_t^2 (y_t - \mu_t^T)^2}{V_t^3} - \frac{2\beta_3}{\sigma^6} + \frac{\alpha_3 + 1}{\sigma^4} \Bigg|_{\hat{\sigma}^2}.$$

We make a proposal from the gamma distribution $\text{Gamma}(\alpha, \beta)$, which we denote by $q(\tilde{\sigma}^2)$, with the same mode and variance as the full conditional where the parameters α and β can be found by solving the simultaneous equations $\frac{\alpha-1}{\beta} = \hat{\sigma}^2$ and $\frac{\alpha}{\beta^2} = (-H(\hat{\sigma}^2))^{-1}$. A proposal $q : \sigma^2 \rightarrow \tilde{\sigma}^2$ is made from the $\text{Gamma}(\alpha, \beta)$ distribution.

$\sigma_b^2 \mid \dots$

The parameter σ_b^2 is dealt in a similar manner to σ^2 above. The mode, $\hat{\sigma}_b^2$, is found by numerically solving for σ_b^2 in the equation

$$\frac{\partial \log(p(\boldsymbol{\mu}, \mu_b, \sigma_b, \sigma \mid \mathbf{y}))}{\partial \sigma_b^2} = -\frac{1}{2} \sum_{t=1}^T \frac{n_t}{V_t} + \frac{1}{2} \sum_{t=1}^T \frac{n_t (y_t - \mu_t^T)^2}{V_t^2} + \frac{\beta_4}{\sigma_b^4} - \frac{\alpha_4 + 1}{\sigma_b^2} = 0$$

and approximating the variance by $\hat{V}(\hat{\sigma}_b^2) = (-H(\hat{\sigma}_b^2))^{-1}$ at that mode where

$$H(\hat{\sigma}_b^2) = \left(\frac{1}{2} \sum_{t=1}^T \frac{1}{V_t^2} - \sum_{t=1}^T \frac{(y_t - \mu_t^T)^2}{V_t^3} - \frac{2\beta_4}{\sigma_b^6} + \frac{\alpha_4 + 1}{\sigma_b^4} \right) \Bigg|_{\hat{\sigma}_b^2}.$$

$\boldsymbol{\beta} \mid \dots$

A block proposal $\tilde{\boldsymbol{\beta}}$ is made from the multivariate normal distribution, (the likelihood component):

$$(\tilde{\boldsymbol{\beta}} \mid \mathbf{z}, \boldsymbol{\Theta}_z, \mathbf{S}) \sim N(\hat{\boldsymbol{\beta}}, \hat{V})$$

where $\hat{\boldsymbol{\beta}} = \left(\sum_{t=1}^T \mathbf{X}_t^T \mathbf{X}_t \right)^{-1} \sum_{t=1}^T \mathbf{X}_t^T \mathbf{z}_t$, $\hat{V} = \left(\sum_{t=1}^T \mathbf{X}_t^T \mathbf{X}_t \right)^{-1}$ and \mathbf{X}_t is defined by (6).

$\alpha_\delta, \beta_\delta \mid \dots$

The derivative of $\mathbf{L} = \log p(\boldsymbol{\delta} \mid \alpha_\delta, \beta_\delta)$ with respect to α_δ and β_δ gives

$$\mathbf{S} = \begin{pmatrix} N \log \beta_\delta + \sum_{k=1}^N \delta_k - N \Psi_2(\alpha_\delta) \\ \frac{N \alpha_\delta}{\beta_\delta} - \sum_{k=1}^N \delta_k \end{pmatrix}. \text{ The modal values of } \alpha_\delta \text{ and } \beta_\delta \text{ can be found by solving}$$

$$\mathbf{S} = 0 \text{ using Newton's method using the Hessian which is } \mathbf{H} = \begin{pmatrix} -N \Psi_3(\alpha_\delta) & \frac{N}{\beta_\delta} \\ \frac{N}{\beta_\delta} & -\frac{N \alpha_\delta}{\beta_\delta^2} \end{pmatrix}, \text{ where } \Psi_2 \text{ is}$$

the digamma function and Ψ_3 is the trigamma function. If $\begin{pmatrix} \hat{\alpha}_\delta \\ \hat{\beta}_\delta \end{pmatrix}$ is the solution to this then a proposal

$q : \begin{pmatrix} \alpha_\delta \\ \beta_\delta \end{pmatrix} \rightarrow \begin{pmatrix} \tilde{\alpha}_\delta \\ \tilde{\beta}_\delta \end{pmatrix}$ is made from the bivariate normal distribution:

$$\begin{pmatrix} \tilde{\alpha}_\delta \\ \tilde{\beta}_\delta \end{pmatrix} \sim N \left[\begin{pmatrix} \hat{\alpha}_\delta \\ \hat{\beta}_\delta \end{pmatrix}, \begin{pmatrix} N \Psi_3(\alpha_\delta) & -\frac{N}{\beta_\delta} \\ -\frac{N}{\beta_\delta} & \frac{N \alpha_\delta}{\beta_\delta^2} \end{pmatrix}^{-1} \right].$$

$\alpha_\mu, \beta_\mu \mid \dots$

The parameters α_μ and β_μ are dealt in a similar way to α_δ and β_δ above.

To get a proposal we assume that the random effects, $\boldsymbol{\mu}$, are approximately gamma. The derivative of $\mathbf{L} = \log p(\boldsymbol{\mu} \mid \alpha_\mu, \beta_\mu)$ with respect to α_μ and β_μ gives

$\mathbf{S} = \begin{pmatrix} N \log \beta_\mu + \sum_{k=1}^N \mu_k - N \Psi_2(\alpha_\mu) \\ \frac{N \alpha_\mu}{\beta_\mu} - \sum_{k=1}^N \mu_k \end{pmatrix}$. The modal values of α_μ and β_μ can be found by solving

$\mathbf{S} = 0$ using Newton's method using the Hessian which is $\mathbf{H} = \begin{pmatrix} -N \Psi_3(\alpha_\mu) & \frac{N}{\beta_\mu} \\ \frac{N}{\beta_\mu} & -\frac{N \alpha_\mu}{\beta_\mu^2} \end{pmatrix}$.

$\mu_m \mid \dots$

We sample μ_m from its full conditional:

$$(\mu_m \mid \dots) \sim N \left(\frac{\tau_m \sum_{i=1}^N m_i}{\tau_\epsilon + N \tau_m}, \frac{1}{\tau_\epsilon + N \tau_m} \right),$$

where $\tau_m = 1/\sigma_m^2$ and $\tau_\epsilon = 1/\sigma_\epsilon^2$.

$\tau_m \mid \dots$

We sample τ_m from its full conditional:

$$(\tau_m \mid \dots) \sim \text{Gamma} \left(\frac{N}{2} + \alpha_1, \frac{\sum_{i=1}^N (m_i - \mu_m)^2}{2} + \beta_1 \right).$$

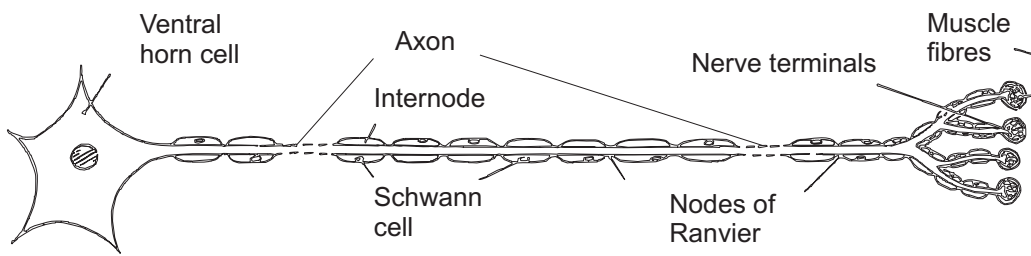


Figure 1.

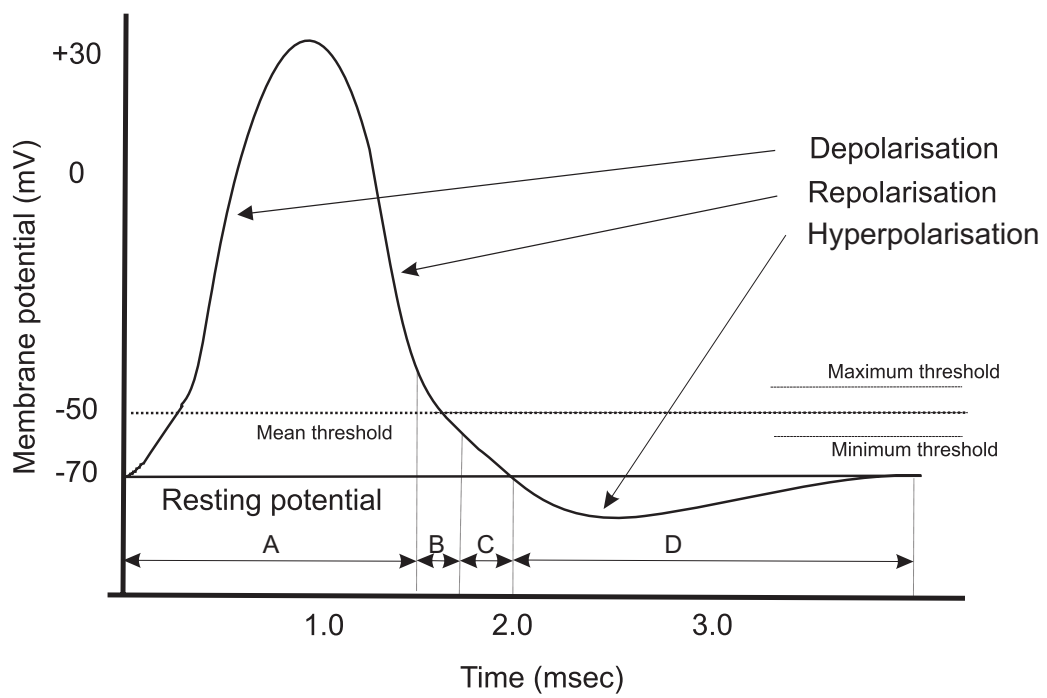


Figure 2.

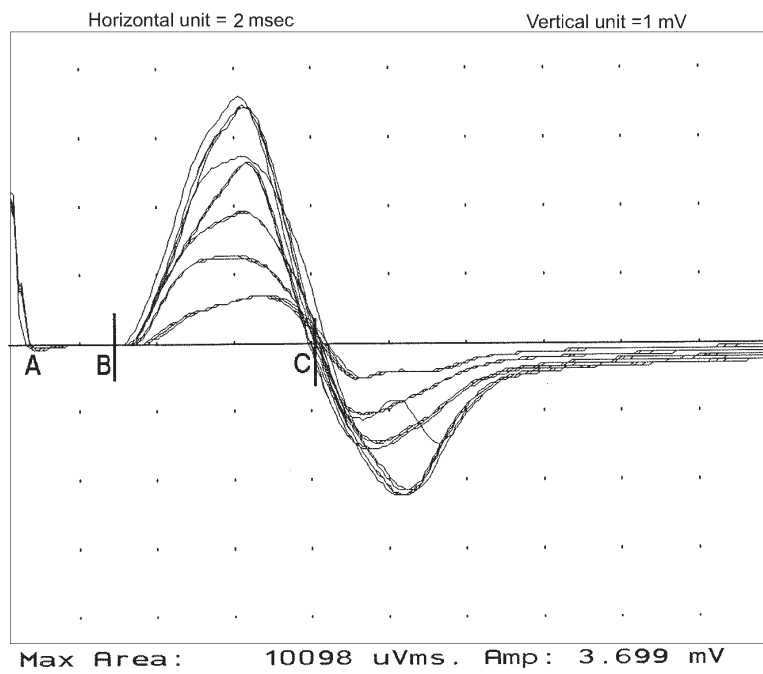


Figure 3.

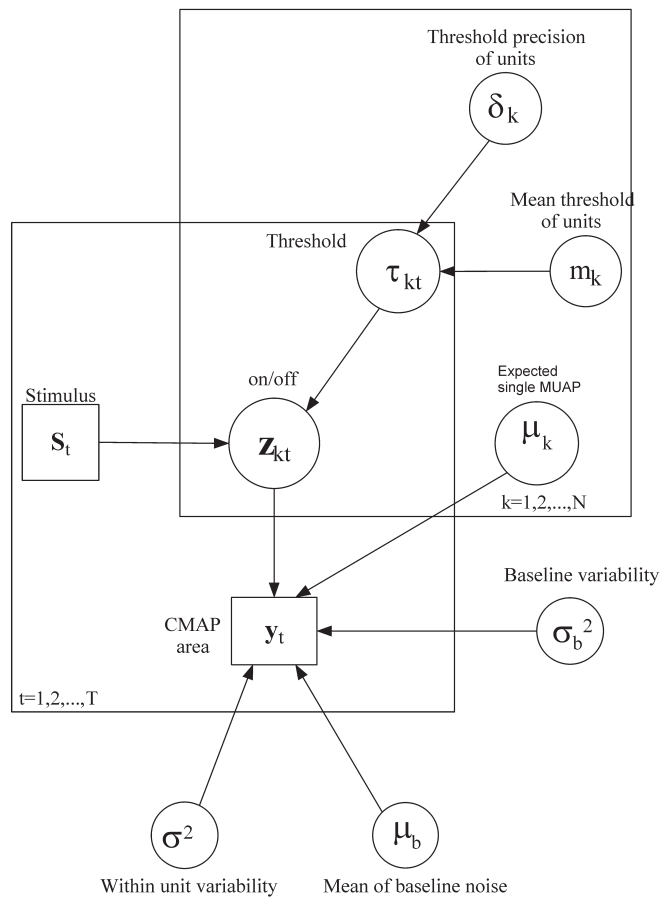


Figure 4.

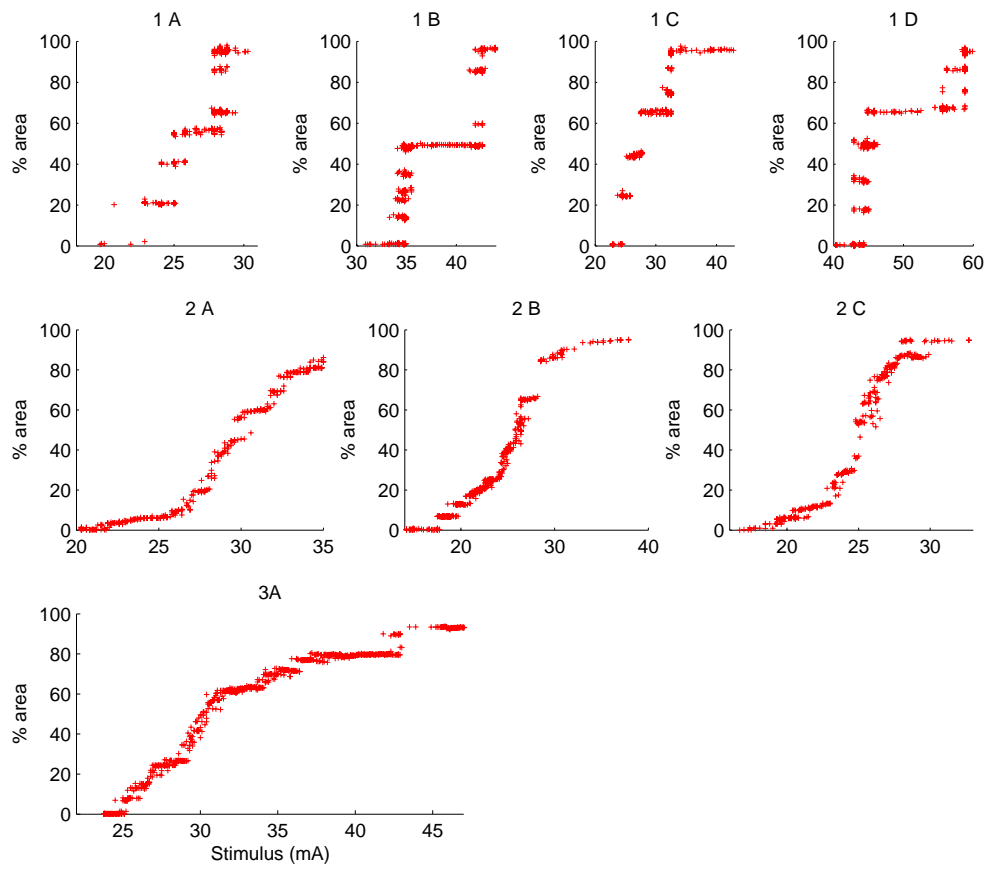


Figure 5.

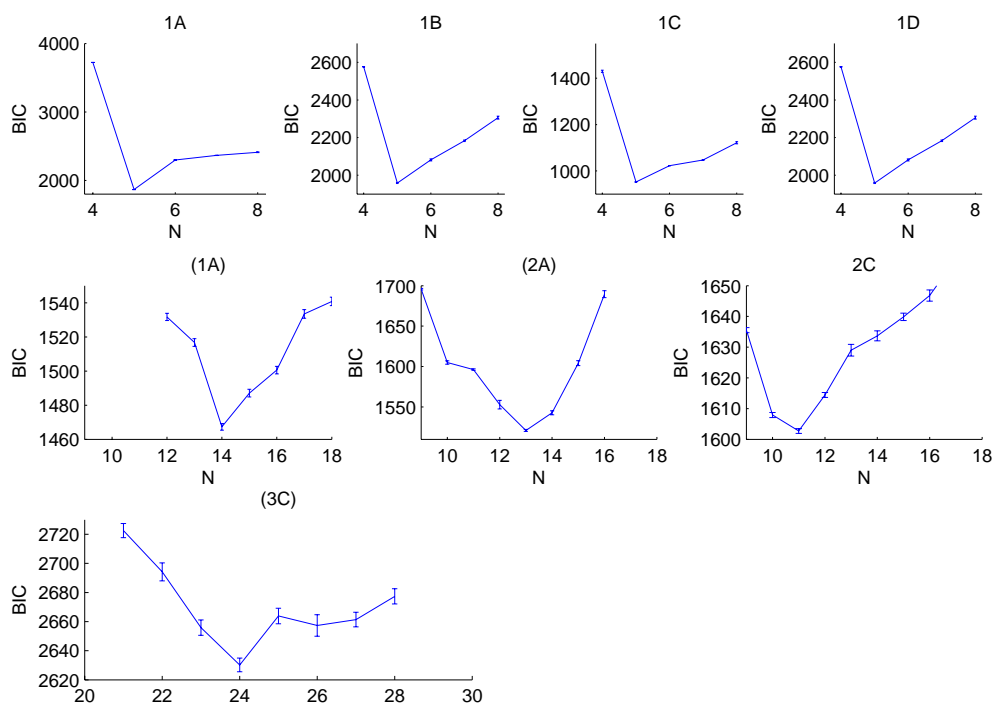


Figure 6.

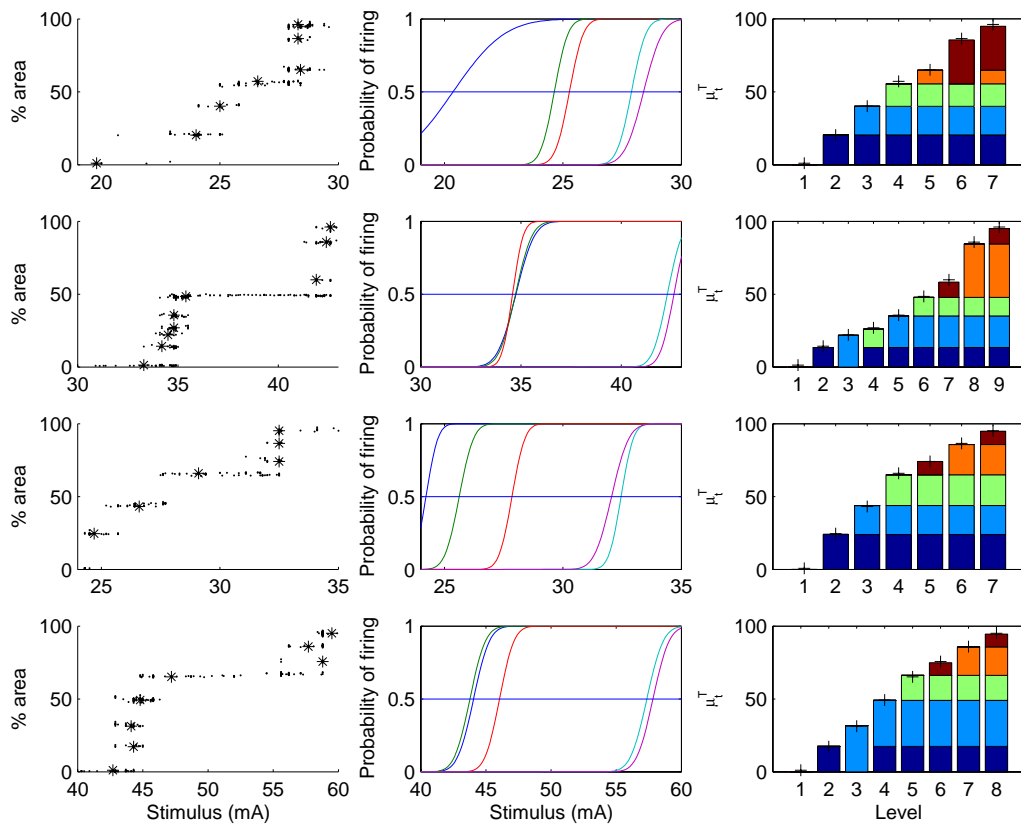


Figure 7.

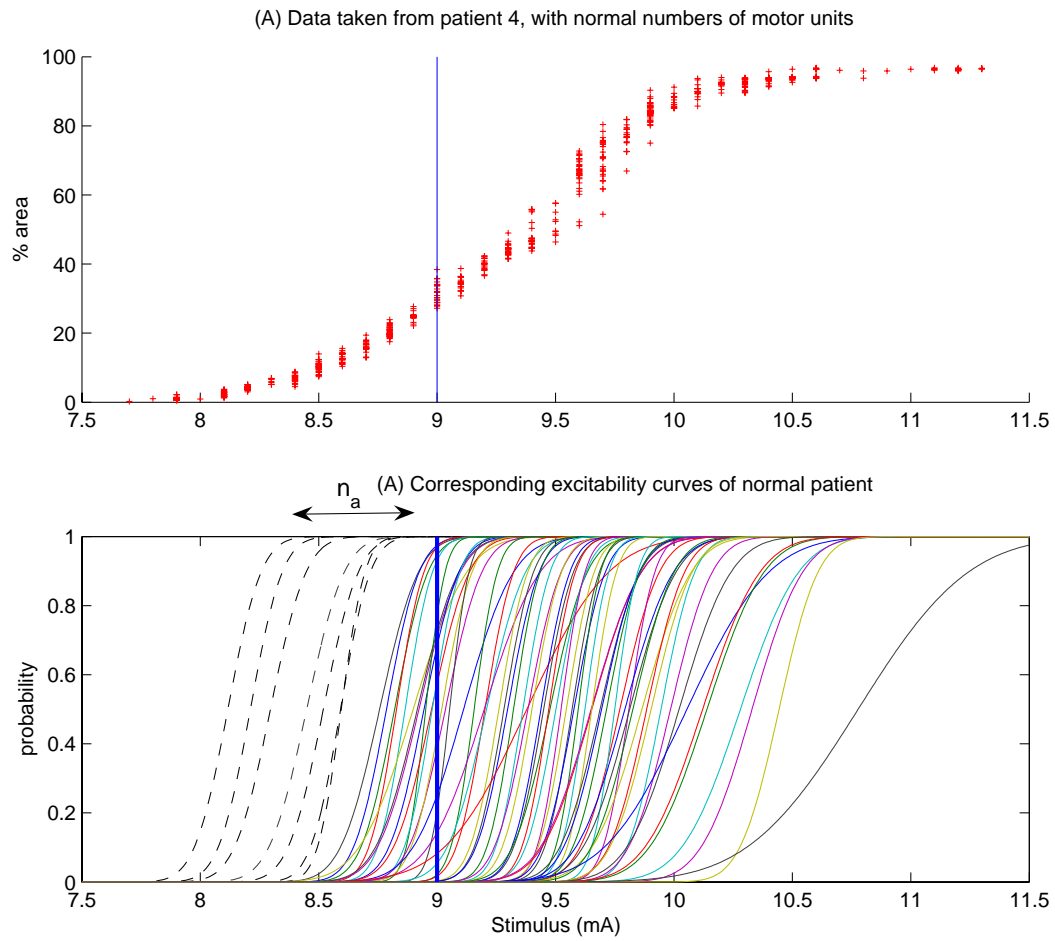


Figure 8.

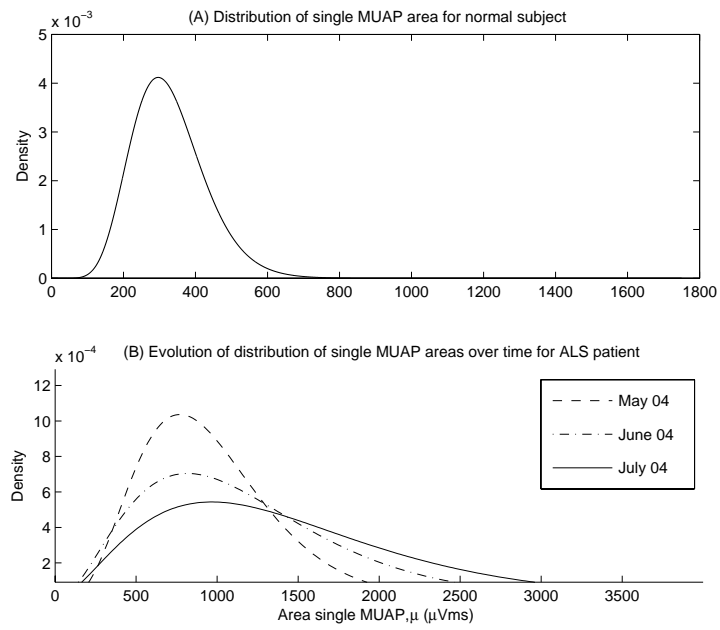


Figure 9.

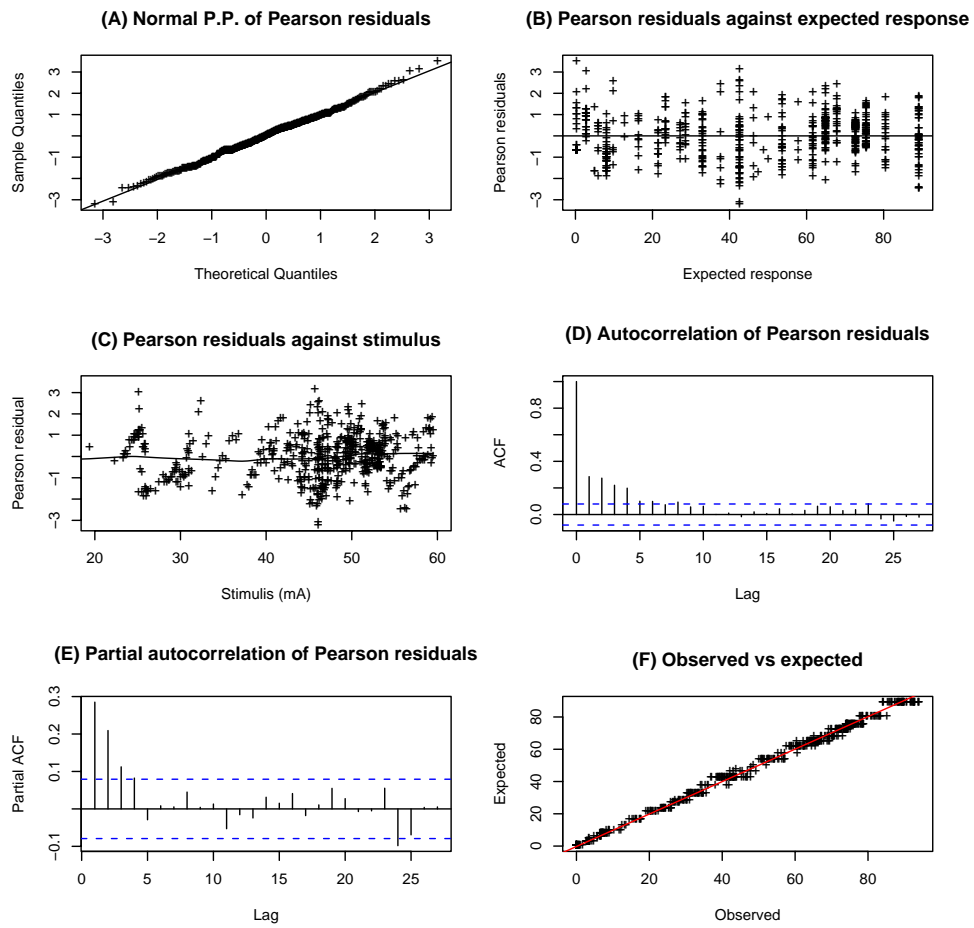


Figure 10.