A two-step Bayesian approach for modeling a complex neurophysiological system

Ioannis I. Spyroglou and Alexandros G. Rigas

***Abstract*—**Our purpose in this paper is to model in a better way a complex neurophysiological system called muscle spindle. This system involves point processes as input and output. A two-step approach based on Bayesian logistic regression is used when a weakly informative and an informative prior is chosen. The parameters of the model which are of great interest are the threshold, the recovery, the summation and the carry-over effect function. The results show that the estimates derived from the Bayesian approach are similar to the ones obtained by the maximum likelihood method with the advantage of smaller confidence intervals. These results show the great importance of the two-step Bayesian approach which gives more representative models.

***Keywords*—**Muscle Spindle, Gamma motoneuron, Bayesian Logistic Regression, Prior distribution.

I. Introduction

The muscle spindle is a receptor that responds to the muscle changes and plays an important role in the initiation and reflex control of movement as well as in the maintenance of muscle posture [1,2]. The effects of the imposed stimuli on the muscle spindle are transmitted to the spinal cord by the axons of sensory nerves closely associated with the muscle spindle. In the absence of any input, the muscle spindle generates nerve action potentials at relatively constant rates. The output, which occurs under these conditions, is referred to as the spontaneous discharge of the muscle spindle. The discharge of the muscle spindle is also modified by action potentials carried by the axons of a group of cells whose bodies are located in the spine cord called gamma motoneurons [3,4].

The muscle spindle is considered as a stochastic system that involves point processes and can be modeled as in [5,6]. In addition a maximum likelihood approach can be proposed for identifying and modeling neuronal firing systems as described in [7,8]. In this work, a two – step Bayesian logistic regression is used to study the behavior of the muscle spindle. The parameters which are included in the models are the threshold, the recovery function, the summation function and the carry – over effect function [7,8,9]. The threshold is an unknown constant and can be estimated from the data. The system's own effect to the change of membrane's potential is described by the recovery function. The summation function describes how the input spikes that follow the last output spike affect the system and shows whether the behavior of the system is excitatory or inhibitory. Finally the carry – over effect function discussed in [9] describes the effect of the input spikes before the last output spike.

Bayesian methods have the advantage of requiring a single tool which is the Bayes theorem that makes their use simpler. An important advantage of the Bayesian logistic approach is that a prior information can be combined with the data in such a way that past information about a parameter can be included and form an informative prior distribution when new data are available [10,11]. A detailed discussion of the approach is given in the next section.

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II. Materials and Methods

A. Bayesian Logistic regression

We start with the creation of a probability model for the available data. Then it is necessary to select a prior distribution which reflects the prior knowledge someone may have about the model parameters. Afterwards, the likelihood function based on the probability model is obtained which is combined with the prior distribution to designate the posterior distribution. Finally as the posterior distribution is simulated, the estimates of the parameters become available [10]. In the case of the muscle spindle dataset, the dependent variable denoted by Y takes the value 1 when a spike occurs and 0 otherwise. Let p_t denote the probability that a spike occurs at time t. An appropriate probability model is a Bernoulli distribution model with probability p_t:

$$prob(y_t|\theta) = {p_t}^{y_t}(1-p_t)^{1-y_t} \quad (1)$$

The probabilities p_t are modeled by means of the logistic function in order to make them also dependent on the vectors of prognostic factors $x_t \in \mathbb{R}^p$ which are explained in the next subsections:

$$p_t = \frac{\exp(\theta^T \boldsymbol{x}_t)}{\{1+\exp(\theta^T \boldsymbol{x}_t)\}}.$$

The log – likelihood function is then given by:

$$l(y|\theta) = \sum_{t=1}^{n} y_t \log(p_t) + (1-y_t)\log(1-p_t), \quad (2)$$

which leads to the posterior distribution $p(\theta|y)$ by applying the Bayes' theorem as follows:

$$p(\theta|y) = \frac{p(\theta)p(y|\theta)}{\int p(\theta)p(y|\theta)d\theta} \propto p(\theta)l(y|\theta), \qquad (3)$$

where $p(\theta)$is the prior distribution.
Exact Bayesian inference for the parameter θ can only be achieved by appropriate standardization of the posterior. This can be done by means of integration. To achieve this task, we use the method of Markov-Chain-Monte-Carlo (MCMC). The MCMC algorithm implemented in this work is the Metropolis – Hastings algorithm with Gaussian Proposals [12,13].

B. Dataset

The data were collected by isolating a muscle spindle from a very thin muscle, located in the posterior leg of an anesthetized cat and separating the motoneurons from the spinal cord and the primary Ia axon to the spinal cord. The muscle was tightened with a muscle extruder, in order to keep the length under control during the recording of the data. The dataset for the spontaneous activity is a binary time series recorded for 15867 msec. The dataset with the presence of a gamma motoneuron as input to the system is also a binary time series recorded for 15866 msec.

C. Prior Distribution

One of the most challenging tasks in Bayesian inference is the choice of the prior distribution because a wrong choice could lead to inadmissible results.
In the case of the muscle spindle we have no prior knowledge for the data. A commonly used prior distribution in these cases is a weakly informative Cauchy prior with location and scale parameters 0 and 2.5 respectively [14]. Main advantages of this prior distribution are the capability of dealing with complete separation and the application of more shrinkage to higher – order interactions. In this work we implemented the next steps for the choice of the prior distribution.
1) Apply a weakly informative Cauchy prior distribution with location and scale parameters 0 and 2.5 respectively on the data for the first 5000 msec. This is essential because initially, we do not have prior information about the Bayesian logistic regression coefficients.
2) Apply Bayesian logistic regression with this prior distribution and get a posterior distribution.
3) Use this posterior distribution as a prior for the rest of the sample.

D. Modeling the activity of Muscle Spindle

In this section the functions that describe the activity of the muscle spindle are analyzed. In the dataset with the spontaneous activity 416 spikes were observed as output in the Ia axon. Sampling with step of 1 msec we obtain a sequence of pulses consisting of 15867 points. This form of a binary time series can be presented as follows:

$$Y_t = \begin{cases} 1, & when\ a\ spike\ occures\ in\ (t, t+1] \\ 0, & otherwise' \end{cases}$$

where $t = 1,2, \dots, 15866\ msec$.

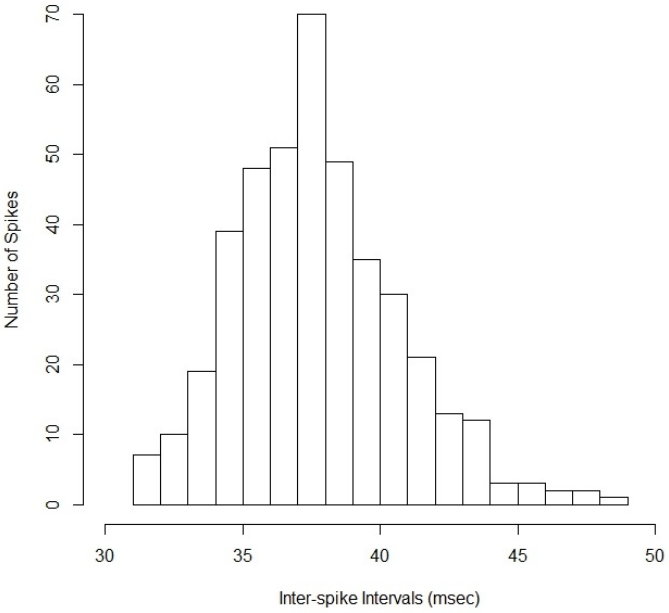


Fig. 1: Histogram of the inter–spike intervals for the output of the spontaneous activity.

The histogram in Fig. 1 shows that the smallest and the biggest interval between output spikes are 31 and 49 msec respectively. A possible choice for the threshold is an unknown constant, i.e.:

$$\theta_t^* = \theta_0.$$

The membrane's potential is denoted by U_t and in this case is equal to the recovery function which is denoted with V_t and is given by:

$$U_t = V_t = \begin{cases} \sum_{i=1}^{k} \theta_i(\gamma_t - min - 1)^i, \gamma_t \geq min + 1 \\ 0, \qquad otherwise \end{cases}, \quad (4)$$

where γ_t is the time elapsed since the previous output spike and min is the minimum interval between output spikes. The system fires spontaneously when the membrane's potential exceeds the threshold θ_0. Thus, the final form of the model in the case of the spontaneous activity is given by:

$$\log\left(\frac{p_t}{1-p_t}\right) = U_t - \theta_0, \qquad (5)$$

where p_t is the probability that the system fires.
Subsequently, the dataset when a gamma motoneuron is present consists of 538 spikes as output in the Ia axon and 1007 spikes as input. The histograms are presented in Figures 2 and 3. Additionally, the presence of the input affects the system by changing the membrane's potential of the sensory Ia axon as it is influenced both by internal and external processes. In this case the membrane's potential is given by:

$$U_t = \sum_{i=1}^{k} \theta_i \gamma_t^i + \sum_{u=0}^{\gamma_t - 1} a_u x_{t-u} + \sum_{w \geq \gamma_t} c_w x_{t-w}, \qquad (6)$$

where the second and the third term are the summation function and the carry – over effect function respectively. By γ_t we denote the time elapsed since the last output spike, u is the time interval between an input spike (occurring after the last output spike) and time t, and w is the time interval between an input spike (occurring before the last output spike) and time t. It has been shown in [9] that the addition of the carry – over effect function gives a better result in comparison with the model containing only the summation function. As a result, the final form of the model is the following:

$$\log\left(\frac{p_t}{1-p_t}\right) = \sum_{i=1}^{k} \theta_i \gamma_t^i + \sum_{u=0}^{\gamma_t - 1} a_u x_{t-u} + \sum_{w \geq \gamma_t} c_w x_{t-w} - \theta_0. \quad (7)$$

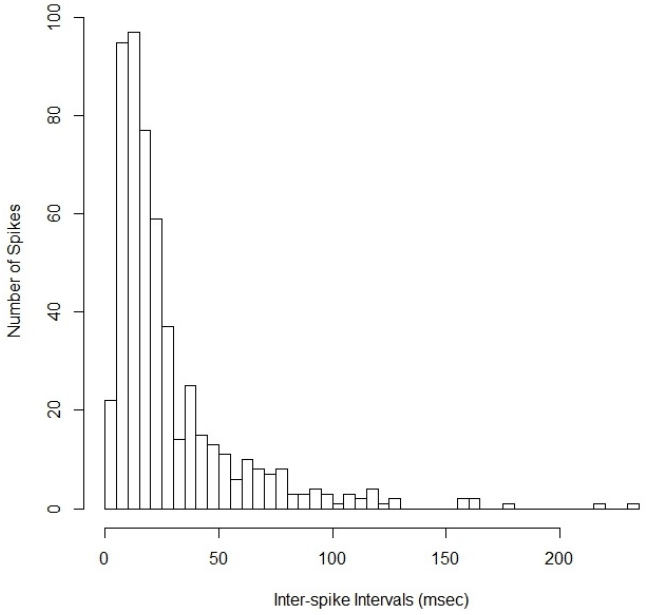


Fig. 2: Histogram of the output inter–spike intervals when a gamma motoneuron is present. Each Inter-spike interval is of 3 msec length.

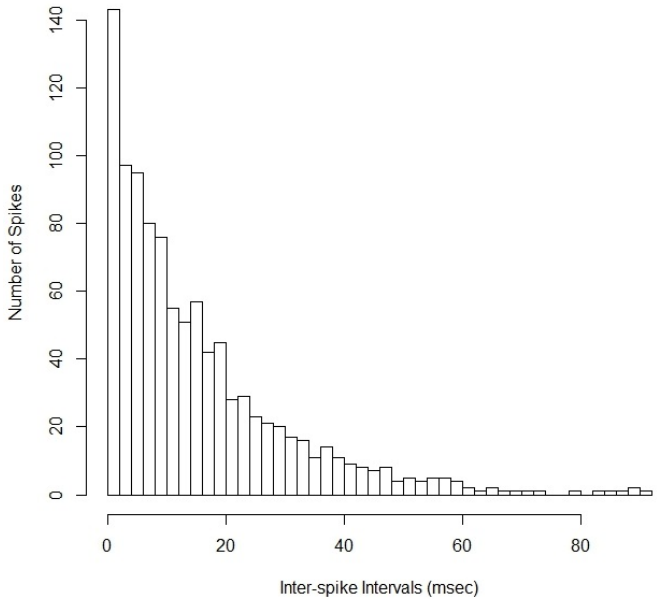


Fig. 3: Histogram of the input inter–spike intervals when a gamma motoneuron is present. Each Inter-spike interval is of 2 msec length.

E. Goodness of fit test with the use of Randomized Quantile Residuals

After fitting the model, it is always necessary to check the validity of the model. This can be done by means of the residuals, which are measurements of agreement between the observed and the estimated values.

A usual problem that occurs in logistic regression is that, the commonly used Pearson and Deviance residuals are far from normal. This means that they are not capable of giving any information about the validity of the model [15].

For this reason the randomized quantile residuals should be used, which are defined as follows [16]:

Let $F(y_t; p_t) = P(Y_t \leq y_t) = \sum_{m=0}^{\lfloor y_t \rfloor} p_t^m (1-p_t)^{1-m}$ be the cumulative binomial distribution of the t-th binary response, and $\lfloor y_t \rfloor$ is the greatest integer less than or equal to y_t, i.e. the 'floor' under y_t. Moreover,

$$a_t = \lim_{y \uparrow y_t} F(y; \widehat{p_t}) \text{ and } b_t = F(y; \widehat{p_t}).$$

Then the randomized quantile residuals for a logistic regression model are defined by

$$r_{rq,t} = \Phi^{-1}\{u\}, \quad (8)$$

where $\Phi(\cdot)$ is the cumulative distribution function of the standard normal, and u is a uniform random variable on the interval $(a_t, b_t]$.

These residuals can be used for any discrete distributed response. Thus, the validity of the model can now be tested by using goodness of fit tests for the normality of $r_{rq,t}$. A very commonly used method to test the null hypothesis that the randomized quantile residuals follow a standard normal distribution is the Anderson – Darling test [17].

The Q-Q plot of the randomized quantile residuals can also be a way of checking the validity of the model. A method for constructing pointwise a $\times 100\%$ rejection regions around the Q-Q plot of any random sample is proposed in [18] by using residual bootstrapping [19]. This method can help to inspect visually the deviations from the standard normal line in the Q-Q plot.

III. Results

A. Bayesian Logistic regression models

In this section the results of the two – step Bayesian logistic regression are presented. Using the Metropolis – Hastings algorithm mentioned in the previous section with 100000 MCMC samples with a burn - in period of 25000 samples, the results are shown in the models described by Tables I and II of the Appendix. It must be mentioned that a thinning interval equal to 10 was used to remove dependencies between successive simulations as well. The posterior distributions derived with the use of a Cauchy weakly informative prior for the spontaneous case are presented in Fig. A1 (see Appendix). Then, these posteriors which are almost Gaussian are used as priors to the rest of the sample to obtain the final model. The results from this procedure produce better results than the maximum likelihood method as far as the confidence intervals are concerned. The Bayesian procedure gives smaller standard

errors for all the coefficients which make the Bayesian models more representative for modeling the system of the muscle spindle. At the same time, the mean squared error is almost identical to the one obtained by the maximum likelihood method.

As it is shown in Table I (see Appendix) for the spontaneous activity we use a fifth order polynomial since the 95% credible intervals of $\hat{\theta}_i$ for $i \geq 6$ contain zero. The threshold and the recovery function for both maximum likelihood method and the two – step Bayesian logistic regression are shown in Fig. A2 (see Appendix).

It can be seen that the confidence intervals are smaller in the two – step Bayesian approach.

The same applies to the other cases as well as described in Figures A3-A5.

Despite the fact that this method gives smaller confidence intervals it is obvious that the functions of the system are almost identical and as a result the conclusions are the same.

The estimates show in both cases (maximum likelihood and Bayesian approach) that the system does not fire spontaneously through the Ia axon when a gamma motoneuron is present. This can be seen in Fig. A3 (see Appendix) where the estimate of the recovery function is below the estimated threshold. In addition in Fig. A4 (see Appendix) we can see from the summation function that there is a significant effect on the response of the system when the distance between the input and the output spikes is between 11-26 msec. Finally in Fig. A5 (see Appendix) it appears that the input spikes between 11 and 24 msec before the last output spike have the most significant effect on the response of the system. This can also be seen in Table II (see Appendix) as the corresponding coefficients do not contain zero in the 95% credible interval which implies that these coefficients are statistically significant. The whole implementation was conducted in RGui 3.3.3 with the use of "MCMCpack" package [20].

B. Goodness of fit test

Fig. 4 shows the Q-Q plot of the randomized quantile residuals of the models. The 5% rejection regions were computed after 1000 Bootstrap simulations. Only 0.15% of the 10867 residuals lie outside of the 5% rejection regions and generally it seems that there are no serious deviations from normality. In addition the Anderson – Darling statistic is 0.2481 with a p – value of 0.7508 which indicates that the null hypothesis that the residuals follow an approximate standard normal cannot be rejected.

Furthermore, Fig. 5 shows the Q-Q plot of the randomized quantile residuals for the model when a gamma motoneuron is present. Here only 0.34 % of the 10866 residuals lie outside the 5% rejection regions. Also, the Anderson – Darling statistic is 0.22584 with a p – value of 0.8191 which also indicates that the null hypothesis that the residuals follow an approximate standard normal cannot be rejected.

IV. Conclusion

In this paper we examined the behavior of the muscle spindle using a two-step Bayesian Logistic regression model. Initially due to absence of prior knowledge for the distribution of the coefficients, a weakly informative Cauchy prior was applied in the first 5000 msec. Then the posterior distributions obtained by this procedure were used as informative prior distributions for the rest of the sample. The results showed that this method exhibits better results than the maximum likelihood in terms of confidence intervals and in the same time keeping almost an identical mean squared error. This means that this method gives more representative results. For future research, it will be interesting to examine how this method performs in larger datasets and when the length of the muscle spindle is changed. Also it is important to examine what happens in the secondary output of the system (II axon).

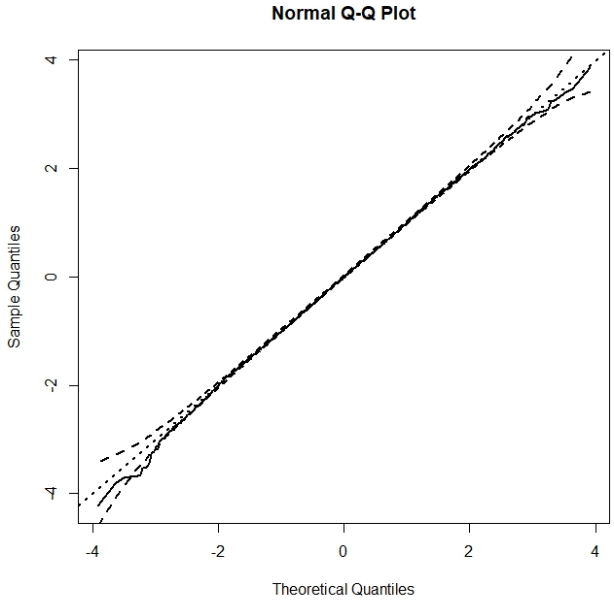


Fig. 4: The Q-Q plot of the randomized residuals of the fitted model in the case of the spontaneous activity. The dashed lines represent the 5% rejection regions.

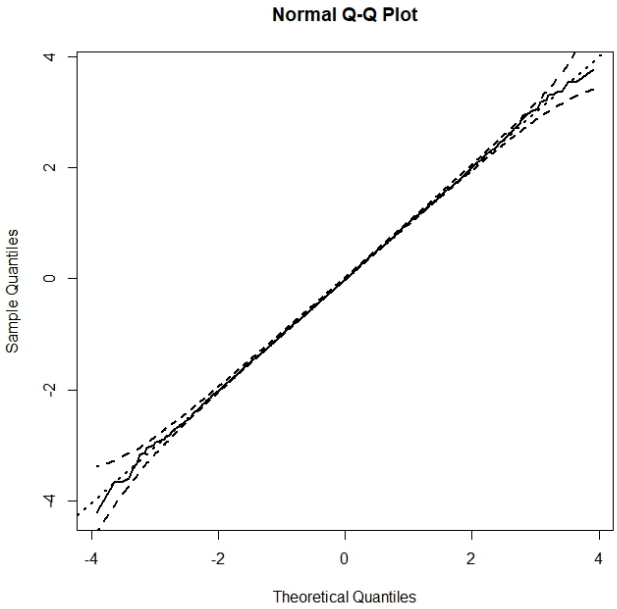


Fig. 5: The Q-Q plot of the randomized residuals of the fitted model when a gamma motoneuron is present. The dashed lines represent the 5% rejection regions.

APPENDIX

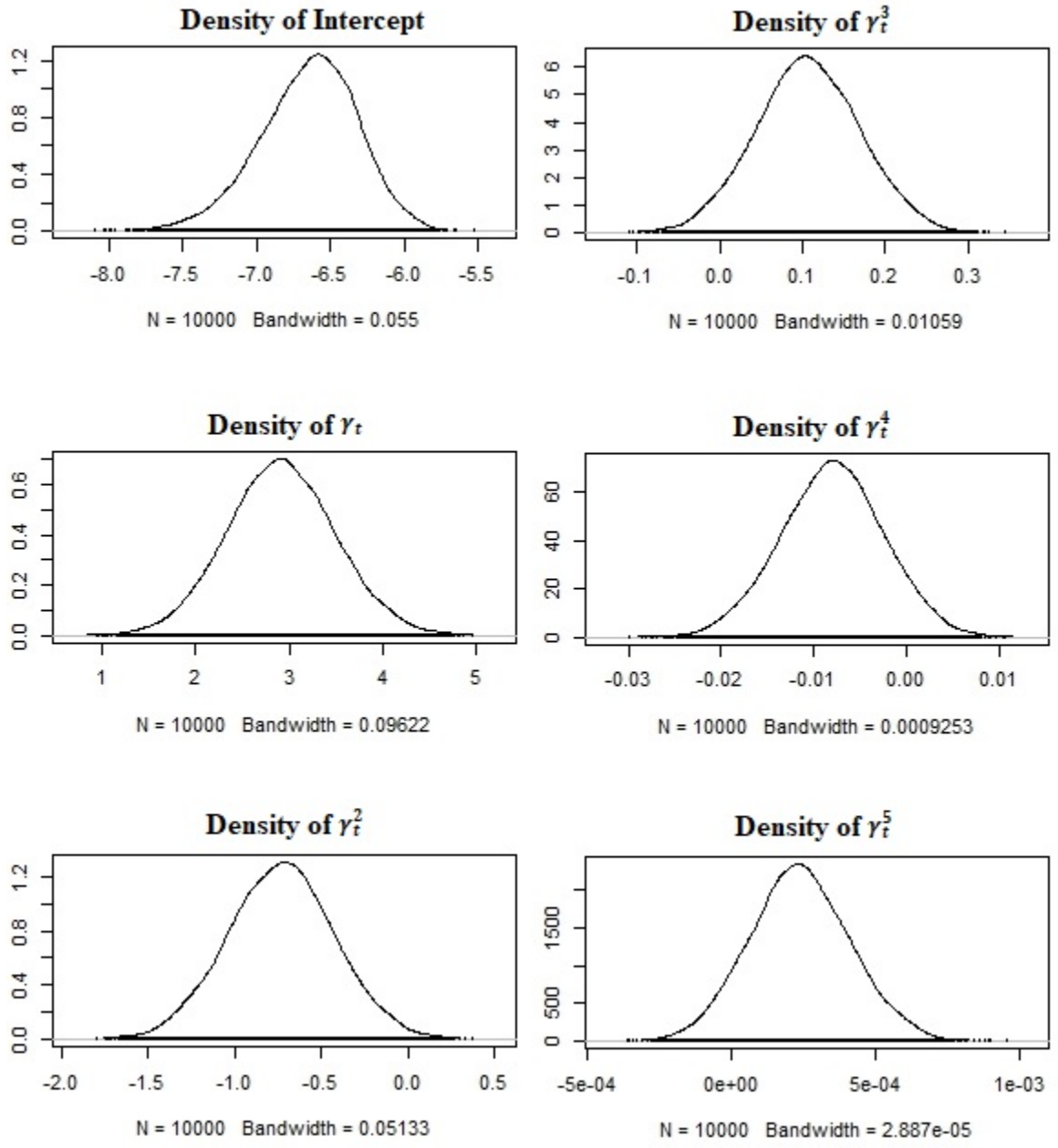
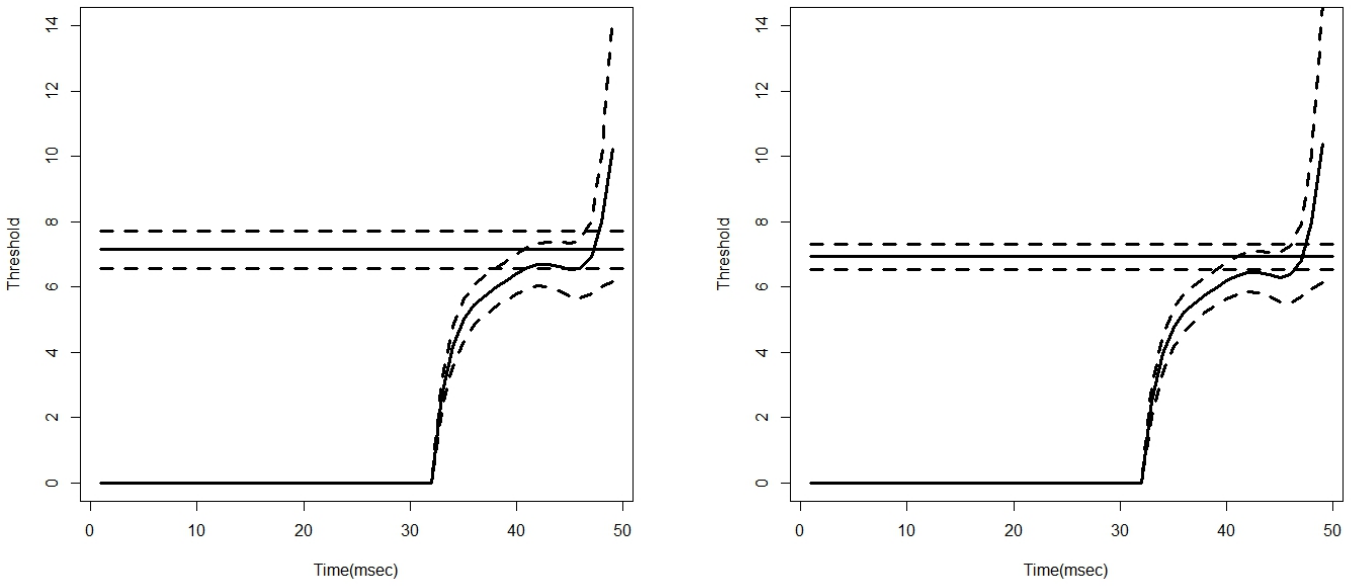
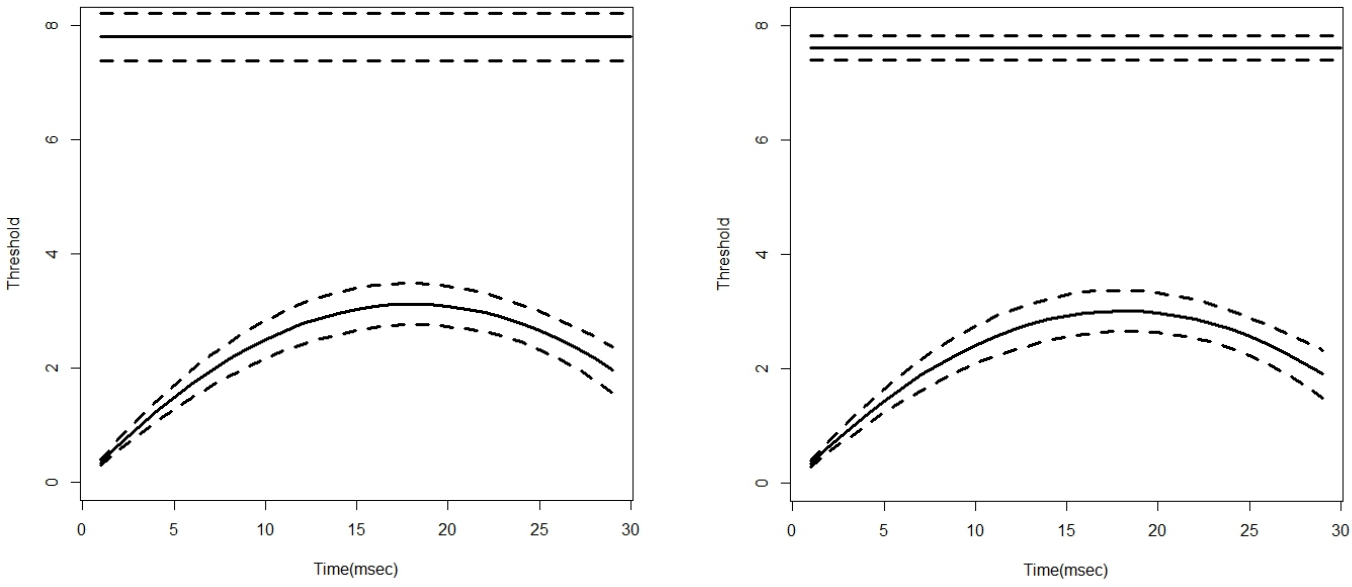


Fig. A1: Posterior distribution of the regression coefficients with the use of the first 5000 msec and a Cauchy weakly informative prior in the case of the spontaneous discharge.



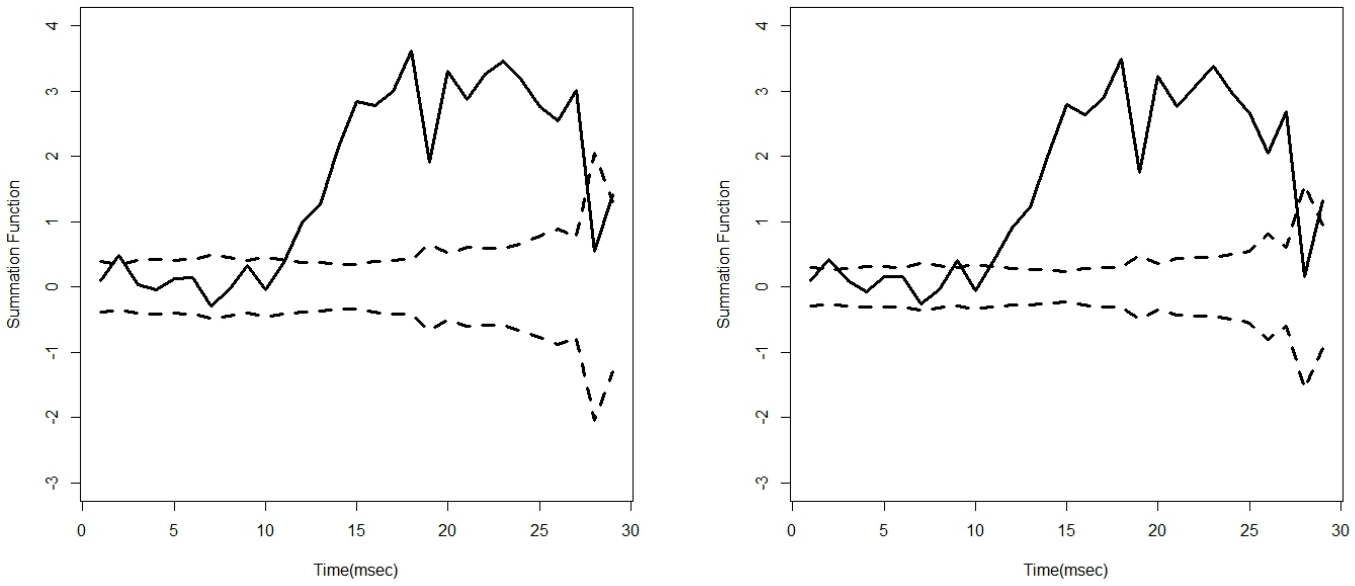
(a) (b)

Fig. A2: Estimates of the threshold and recovery function in the case of the spontaneous discharge. The dashed lines represent the 95% confidence limits. Fig. A2a is the recovery function estimated with the maximum likelihood approach and A2b with the Bayesian Approach



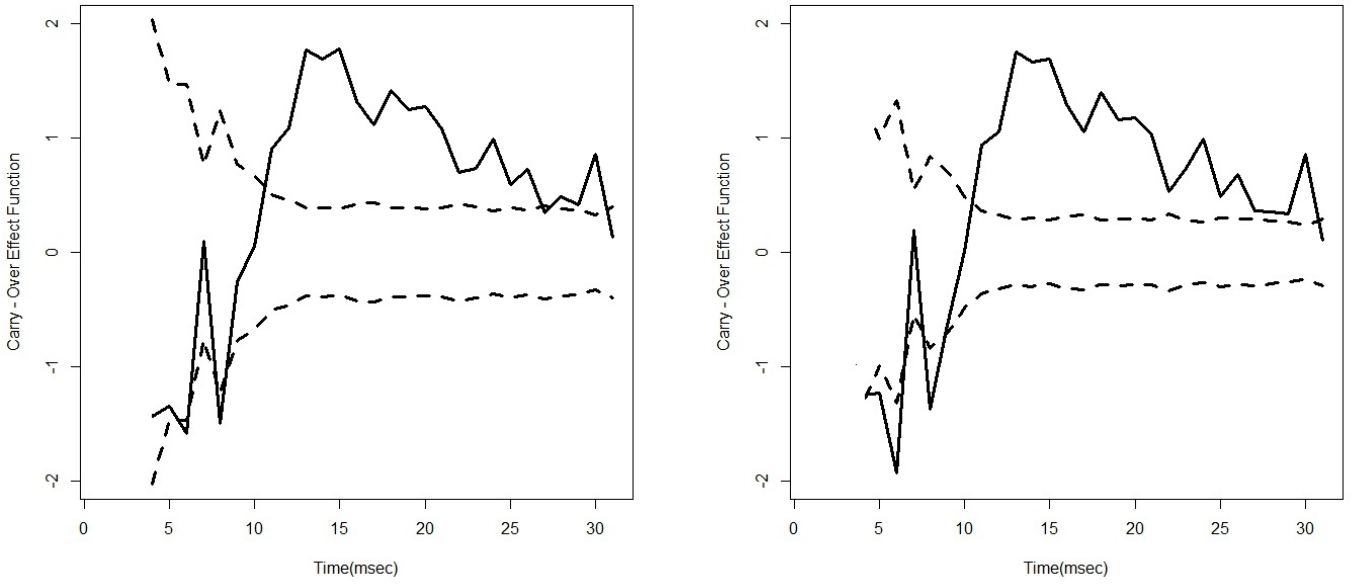
(a) (b)

Fig. A3: Estimates of the threshold and recovery function when a gamma motoneuron is present. The dashed lines represent the 95% confidence limits. Fig. A3a is the recovery function estimated by the maximum likelihood method and A3b with the Bayesian Approach.



(a) (b)

Fig. A4: Estimates of the summation function when a gamma motoneuron is present. The dashed lines represent the 95% confidence limits. Fig. A4a is the summation function estimated by the maximum likelihood method and A4b with the Bayesian Approach.



(a) (b)

Fig. A5: Estimates of the carry-over effect function when a gamma motoneuron is present. The dashed lines represent the 95% confidence limits. Fig. A5a is the carry-over effect function estimated by the maximum likelihood method and A5b with the Bayesian Approach.

Table I: Estimated coefficients (Posterior Mean) and standard errors in the case of the spontaneous discharge.

Coefficient	Posterior mean	Posterior SD
Constant (θ_0)	-6.923	0.1977
θ_1	3.2089	0.2333
θ_2	-0.8028	0.1058
θ_3	0.10616	0.01928
θ_4	-0.0068035	0.001504
θ_5	0.0001652	0.00004172

Table II: Estimated coefficients (Posterior Mean) and standard errors when a gamma motoneuron is present.

Coefficients	Posterior mean	Posterior SD
Constant (θ_0)	-7.618907	0.108858
θ_1	0.333184	0.01436
θ_2	-0.009232	0.000561
a_0	0.090420	0.152474
a_1	0.417394	0.137391
a_2	0.092297	0.145588
a_3	-0.079783	0.160363
a_4	0.151592	0.156771
a_5	0.163096	0.154844
a_6	-0.265992	0.184475
a_7	-0.050035	0.167762
a_8	0.406696	0.148034
a_9	-0.057672	0.173045
a_{10}	0.403084	0.155638
a_{11}	0.904310	0.145005
a_{12}	1.234174	0.139036
a_{13}	2.029581	0.132973
a_{14}	2.794553	0.116689
a_{15}	2.645543	0.144025
a_{16}	2.891222	0.154222
a_{17}	3.488673	0.154343
a_{18}	1.754975	0.249089
a_{19}	3.225401	0.184409
a_{20}	2.770269	0.223597
a_{21}	3.070738	0.226795
a_{22}	3.375994	0.226955
a_{23}	2.983989	0.253456
a_{24}	2.659327	0.281284
a_{25}	2.052024	0.409523
a_{26}	2.693054	0.31129
a_{27}	0.163596	0.801225
a_{28}	1.320236	0.474857
c_4	-1.247532	0.685394
c_5	-1.234037	0.507991
c_6	-1.930154	0.6765
c_7	0.190744	0.277347
c_8	-1.372749	0.43018
c_9	-0.636757	0.361041
c_{10}	0.005051	0.24809
c_{11}	0.940712	0.186162
c_{12}	1.057297	0.165226
c_{13}	1.751495	0.144835
c_{14}	1.662515	0.153424
c_{15}	1.695869	0.142771
c_{16}	1.291875	0.161367
c_{17}	1.049825	0.167638
c_{18}	1.401288	0.145025
c_{19}	1.159556	0.147859
c_{20}	1.178059	0.146732
c_{21}	1.025652	0.146153
c_{22}	0.529577	0.171938
c_{23}	0.737469	0.146148
c_{24}	0.996309	0.137052
c_{25}	0.487847	0.153795
c_{26}	0.682556	0.14704
c_{27}	0.359692	0.148814
c_{28}	0.357239	0.140875
c_{29}	0.338669	0.133709
c_{30}	0.861967	0.120433
c_{31}	0.106188	0.148163

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