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Empirical Examination of the Threshold Model of Nerve Cell Firing

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Abstract

The aim of this paper is to apply a statistical technique; namely, the maximum likelihood estimation procedure to a simulated human nerve cell data. A generalized linear model with a Binomial distribution and logistic link function based on likelihood is set down for this purpose. This is an encouraging step to learn how the nerve cell is functioning to carry out a particular task. This conceptual model is basically consists of two main underlying processes, the Summation function(s) which represents a linear summation of the input effects on the output, the other is called a Threshold and Recovery function to present the spontaneous behavior of the cell and then reflects an intrinsic properties of the cell. The data consists of two inputs, X_{1i}, X_{2j}; $i = 1,2,...,n_1$; $j = 1,2,...,n_2$, representing the effect of any two neurons on a single neighboring neuron (output) in additional to that the time elapsed since the neuron last fired γ_t is also presented which then allow us to include a recovery process of the cell to the analysis. Since the traditional goodness of fit tests cannot be used for a generalized linear model with a Binomial distribution and logistic link function, we will not rely only on the deviance table in choosing among the models but also to test the selected model by introducing an empirical goodness of fit procedure based on theoretical and empirical probabilities obtained for given values of the linear predictor. The study is also aiming to compare the likelihood approach to other existing statistical techniques such as the point process technique. Simulated data set have been analyzed with the proposed procedures. The analysis showed that the likelihood, compared to the other approach, is more appropriate to describe the cell reactions and to reflect many of its main features.

Keywords: Maximum likelihood; Generalized linear model; Threshold and Recovery function; Logistic link function; Point process analysis.

1. Introduction

The analysis of Input–Output data of the nerve cell may provide a basis for understanding the operations that the central nervous system uses to carry out a particular task. Recently after the development of high speed computers, the investigation of the behavior of small network of nerve cells has become a very reach area of research which attracted many scientists worldwide. One used technique in analyzing the nerve behavior is the point process and more recently many generalized linear models based on maximum likelihood have been introduced and developed. This paper will investigate one such model. One target is to apply the likelihood procedure to fit a generalized linear model with Binomial distribution and logistic link function to a nerve cell data consisting of two inputs and a single output along with an additional input data allowing the inclusion of a recovery process which reflecting the intrinsic properties of the cell. The traditional square root of the cross-intensity function as time domain of point process technique is also obtained. The use of both maximum likelihood (via, the estimated summation function) and stochastic point process will allow us to compare results obtained by both approaches.

2.1 An Analytic Model:

Let us consider, the firings of a cluster of three neighboring neurons X_1, X_2 and Y which are described by the counting measures $X_1(t)$, $X_2(t)$ and $Y(t)$, respectively. Now, suppose we are interested in the firing of neuron Y and that the neurons X_1 and X_2 fired at times τ_1 and τ_2, respectively. Let $a_1(t-\tau_1)$ and $a_2(t-\tau_2)$ represent the effect of the neurons X_1 and X_2 on the potential at time t of the neuron Y, respectively. The quantities $\{a_1(.)\}$ and $\{a_2(.)\}$ will be called the summation functions, which represent the effects of the neurons X_1 and X_2 (two inputs) on the firing of a third neuron Y (an output), and describe the course that the potential would follow after a current impulse. The linearity assumption implies that the effects of current pulses at different times are additive, see Brillinger and Segundo (1979) and Brillinger (1988). Let $\gamma(t)$ denote the time elapsed at time t since the neuron Y last fired. At this point, let us assume that the only effect on the output is the effect of the inputs occurring after the previous output, and then the membrane potential $U(t)$ at its trigger zone may be represented as

$$U(t)=\int_0^{\gamma(t)} a_1(u)\, x_1(t-u)\, du + \int_0^{\gamma(t)} a_2(u)\, x_2(t-u)\, du \quad . \qquad (2.1.1)$$

The neuron Y tends to fire when the potential at its trigger zone exceeds an extant level called threshold. Now, let $\theta(t)$ denote the threshold potential level at the trigger zone at time t and assume that it has the form

$$\theta(t) = \theta^{*}(t) + \varepsilon(t) \tag{2.1.2}$$

with $\varepsilon(t)$ the noise, which includes contributions of unmeasured neurons that influence the firing of neuron, and $\theta^{*}(t)$ some function of t, representing the underlying form of the threshold at time t.

There is some experimental evidence validating the Gaussian assumption for $\varepsilon(t)$ given in Holden (1976). One simple form for $\theta^{*}(t)$ is the constant form,

$$\theta^{*}(t) = \theta_0 \tag{2.1.3}.$$

This leads to the assumption of an absolute constant threshold level. Furthermore, let $\Omega(t)$ represent the history of a particular process, i.e., those variables determined up to and including time t that are necessary to describe the evolution of the process. For the processes $X_1(t-u)$ and $X_2(t-u)$, we may write

$$\Omega(t) = \{X_1(t-u),\ X_2(t-u);\ u \le t\}. \tag{2.1.4}$$

It will be convenient for computational purposes, specifically in determining the maximum likelihood estimates via standard statistical packages, to record the values of the point processes only at discrete times $t\ (t = 0, \pm h, \pm 2h, ...)$. If a small sampling interval of length h is selected, then the process will take only the values 0 or 1. Thus, for a sampling interval of length h, with h suitably small the point process $Y(t)$ can be replaced by a discrete 0-1 valued series Y_t, such that

$$Y_t = \begin{cases} 1 & ;\text{if there is an event in } (t, t+h] \\ 0 & ;\text{otherwise.} \end{cases}$$

Discrete approximation of equation (4.1.1) may be written as

$$U_t = \sum_{u=0}^{\gamma_t - 1} (a_1)_u (X_1)_{t-u} + \sum_{u=0}^{\gamma_t - 1} (a_2)_u (X_2)_{t-u} \tag{2.1.5}$$

Similarly, equations (2.1.2 and 2.1.3) may appear in their discrete approximation form as,

$$\theta_t = \theta_t^{*} + \varepsilon_t \tag{2.1.6}$$

$$\theta_t^{*} = \theta_0 \tag{2.1.7}$$

Let P_t be the conditional probability of the neuron Y firing, given the history of the process, then we may have

$$\begin{aligned} P_t &= \Pr\{ Y_t = 1 \mid \Omega_t \} \\ &= \Pr\{ U_r \text{ crosses } \theta_r \text{ for some r in } (t, t+h] \mid \Omega_t \} \\ &\cong \Pr\{ U_t \geq \theta_t \mid \Omega_t \} = \Pr\{ U_t \geq \theta_t^* + \varepsilon_t \mid \Omega_t \} \\ &= \Pr\{ \varepsilon_t \leq U_t - \theta_t^* \mid \Omega_t \} = F\{ U_t - \theta_t^* \mid \Omega_t \} \end{aligned} \tag{2.1.8}$$

where $F(.)$ denotes the cumulative distribution function of the random error ε_t. Now, we may write

$$\Pr(Y_t = 1 \mid \Omega_t) = P_t \text{ and } \Pr(Y_t = 0 \mid \Omega_t) = 1 - P_t \tag{2.1.9}$$

for the probabilities of "success" (or firing) and "failure" (or not firing), respectively. Therefore the response variable Y_t will follow the Bernoulli distribution with parameter P_t, i.e.,

$$\Pr(Y_t = y_t) = P_t^{y_t} (1 - P_t)^{1 - y_t} \quad ; y_t = 0, 1. \tag{2.1.10}$$

The likelihood function that need to be maximized is given by

$$l_0 = \prod_t P_t^{y_t} (1 - P_t)^{1 - y_t} \tag{2.1.11}$$

It is more convenient to add a recovery term, V_t, to U_t, to allow for spontaneous firings of the neuron and to describe the intrinsic membrane properties of the cell. We shall see later that, V_t plays a further role in our model. It seems natural to see if a polynomial form for V_t is adequate.

$$V_t = \begin{cases} \sum_{i=1}^{k} \theta_i (\gamma_t - \zeta_1 - 1)^i ; & \gamma_t \geq \zeta_1 + 1 \\ 0 ; & \gamma_t \leq \zeta_1 + 1 \end{cases} \tag{2.1.12}$$

where γ_t denotes the time elapsed since the time of the last output spike and ζ_1 denotes the minimum of the output inter-spike intervals. The recovery function is forced to be zero for $\gamma_t \leq \zeta_1 + 1$ since there will be no data for smaller values of γ_t. The potential at the trigger zone is reset immediately after the neuron fires and then may rise steadily again on its own without any influence by other neurons. This behavior suggests adding the recovery function term, V_t. The idea of introducing a recovery function to the likelihood model was first suggested by Brillinger and Segundo (1979), which then developed by Yousef (1995). One way to investigate the relationship between the input and the output is through the linear combination,

$$\eta_t = \sum_{j=1}^{k}(X_1)_{tj}\beta_j + \sum_{i=1}^{k}(X_2)_{ti}\alpha_i \; ; \quad -\infty < \eta_t < \infty \tag{2.1.13}$$

where $\beta_j, \alpha_j \; (j = 1, 2, 3, ..., k)$ are the unknown parameters to be estimated. To consider P_t as a linear combination of the form given in equation (2.1.13) above would inevitably contradict probability laws, which require $0 \le P_t \le 1$ and therefore a convenient transformation that maps the unit interval into the whole real line $(-\infty, \infty)$ is then needed. This leads to the idea of a link function, see McCullagh and Nelder (1992) for more details. Two particular link functions for the binomial models are the Probit and Logit link functions, the Probit link function is given by,

$$P_t = \Phi(\eta_t) = \Phi\left(\sum_{j=1}^{k}(X_1)_{tj}\beta_j + \sum_{i=1}^{k}(X_2)_{ti}\alpha_i\right) \tag{2.1.14}$$

The $\Phi(.)$ is the normal cumulative distribution function. The other possible link functions is the logistic function,

$$P_t = \exp(\eta_t)/(1+\exp(\eta_t))$$
$$= \exp\left(\sum_{j=1}^{k}(X_1)_{tj}\beta_j + \sum_{i=1}^{k}(X_2)_{ti}\alpha_i\right)/\left(1+\exp\left(\sum_{j=1}^{k}(X_1)_{tj}\beta_j + \sum_{i=1}^{k}(X_2)_{ti}\alpha_i\right)\right) \tag{2.1.15}$$

2.2 The Bernoulli Log Likelihood

The log likelihood function of the response variable, Y_t may be written as,

$$l(\underline{P}; \underline{y}) = \log_e \prod_t P_t^{y_t}(1-P_t)^{1-y_t}$$
$$= \sum_t \left[y_t \log_e P_t + (1-y_t)\log_e (1-P_t) \right]$$
$$= \sum_t \left[y_t \log_e \left(\frac{P_t}{1-P_t}\right) + \log_e (1-P_t) \right] \tag{2.2.1}$$

In order to express this form of the log-likelihood as a function of the unknown parameters β_j and $\alpha_j (j = 1,2,...,k)$, we have,

$$l(\underline{\beta}; \underline{y}) = \sum_t \sum_j y_t \left(\sum_{j=1}^{k}(X_1)_{tj}\beta_j + \sum_{i=1}^{k}(X_2)_{ti}\alpha_i \right)$$
$$- \sum_t \log \left[1+\exp\left(\sum_{j=1}^{k}(X_1)_{tj}\beta_j + \sum_{i=1}^{k}(X_2)_{ti}\alpha_i \right) \right] \tag{2.2.2}$$

This could be differentiated with respect to the $\beta's$ and $\alpha's$ to obtain the required estimates of the unknown parameters.

3. Likelihood Applications to Simulated Multiple Input and Single Output Data

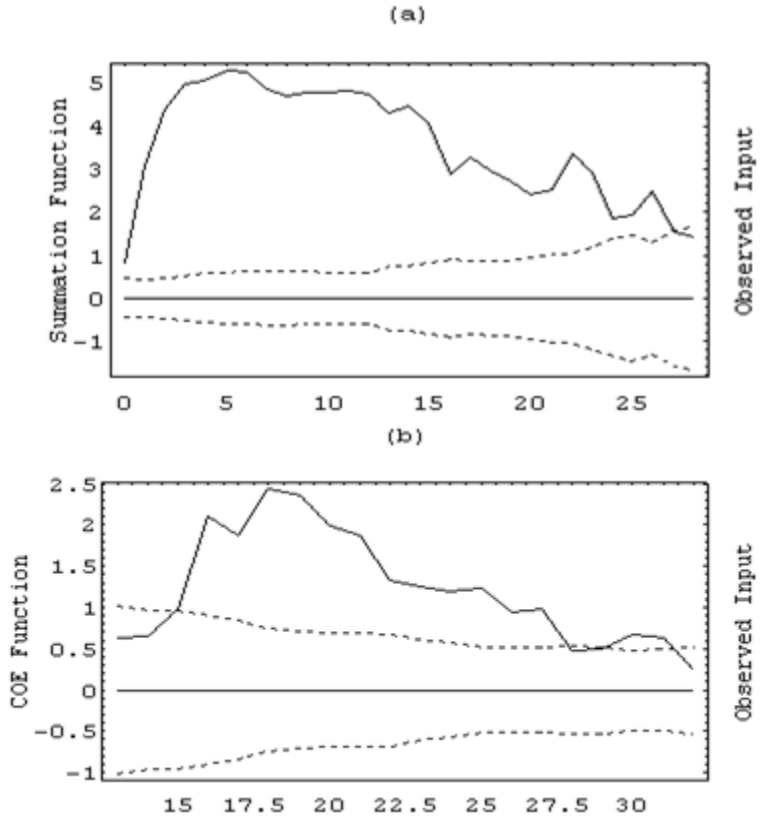
We demonstrate the application of the maximum likelihood approach with a simulated set of data where we have one observed (spike train) input and one "unobservable" input, and one observed output, where the observed spike trains are replace by zero one valued series taking a sampling interval h of 1msec. The simulation was done by using a conductance based neuronal model using an excitatory input. To increase the output firing rate in order to match comparable experimental data, a continuous input representing a population of "unobservable" inputs has been used to stimulate the cell (Halliday, 1994). These "unobservable" inputs are used as a stimulus to the cell to increase its firing rate as well as to mimic the behavior of real cells. For more details see Halliday (1994). Thus the likelihood approach can be used to analyze a set of simulated data which contains along with the observed input and output spike train data, a continuous input z_t which is discretized over small intervals of length 1 msec. This has been scaled such that z_t takes on values between 0 and 1 and represents the "unobservable" inputs (Halliday, 1994).

The simulated data set demonstrated here consisted of a 0-1 valued series of approximately 60000 points for each of the observed input and output, along with 60000 points for the "unobservable" inputs. The membrane potential on the trigger zone of the cell at any given time t may be given in its approximate discrete form by

$$U_t = V_t + \sum_{u=0}^{\gamma_t - 1} a_u x_{t-u} + \sum_{w \geq \gamma_t} c_w x_{t-w} + \sum_{u=0}^{\gamma_t - 1} b_u z_{t-u} + \sum_{w \geq \gamma_t} d_w z_{t-w} \qquad (3.1.1)$$

where γ_t is the time elapsed at time t since the time of the last output spike, the two sets of coefficients $\{a_u\}$, $\{c_w\}$ represent the summation and carry-over effect functions for the observed input, respectively, whereas the two sets of coefficients $\{b_u\}$, $\{d_w\}$ represent the summation and carry-over effect functions for the "unobservable" input, respectively. The numbers of spikes observed were 2398 and 2991 for the observed input and output, respectively. Fig.3.1.1a and Fig.3.1.2a represent the two estimated summation functions, $\{\hat{a}_u\}$ and $\{\hat{b}_u\}$ for the observed and "unobservable" inputs respectively, and suggest that, while the summation function for the observed inputs reveals an excitatory effect lasting about 26 msec. The summation function for the "unobservable" inputs shows longer excitatory effects lasting about 34 msec. The "unobservable" inputs also seem to have larger effects than the observed inputs as can be seen both from the reduction in deviance (Table 3.1.1) when the two summation functions are fitted separately, and from the fact that the estimated coefficients, $\{\hat{b}_u\}$ for the "unobservable" summation function are much

more statistically significant at any given lag than the estimated coefficients, $\{\hat{a}_u\}$ for the observed summation function. Carry-over effects for the observed as well as for the "unobservable" inputs are present. Fig.3.1.1b represents the estimated carry-over effect function for the observed inputs and suggests excitatory effects lasting from about 16 to 27 msec. The estimated carry-over effect function for the "unobservable" inputs as given in Fig.3.1.2b suggests excitatory effects lasting from about 18 to 25 msec. But each of the two carry-over effect functions has a relatively small effect compared to their corresponding summation functions, as can be seen both from the comparatively small reduction in deviance from models with only summation functions to models with both summation and carry-over effect functions, and from the fact that the parameters of the two summation functions tend to be much more statistically significant than those of the corresponding carry-over effect functions. The threshold and recovery functions are well-estimated up to about 42 msec as shown in Fig.3.1.1c and suggest that the probability of an output spike is small up to about 20 msec, but it then increases rapidly and the chance of an output spike becomes quite large after about 30 msec.



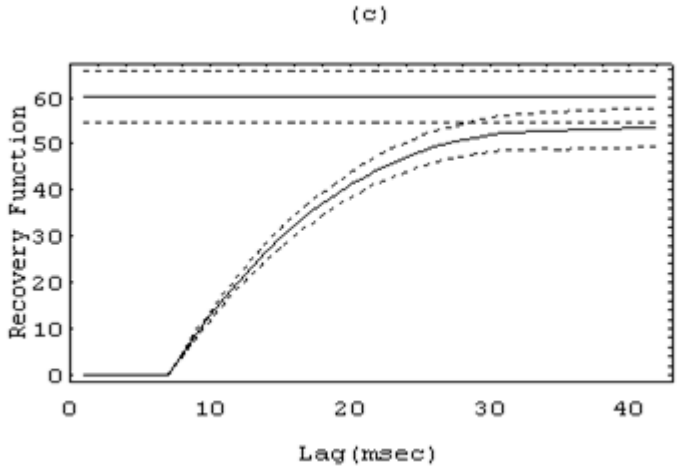
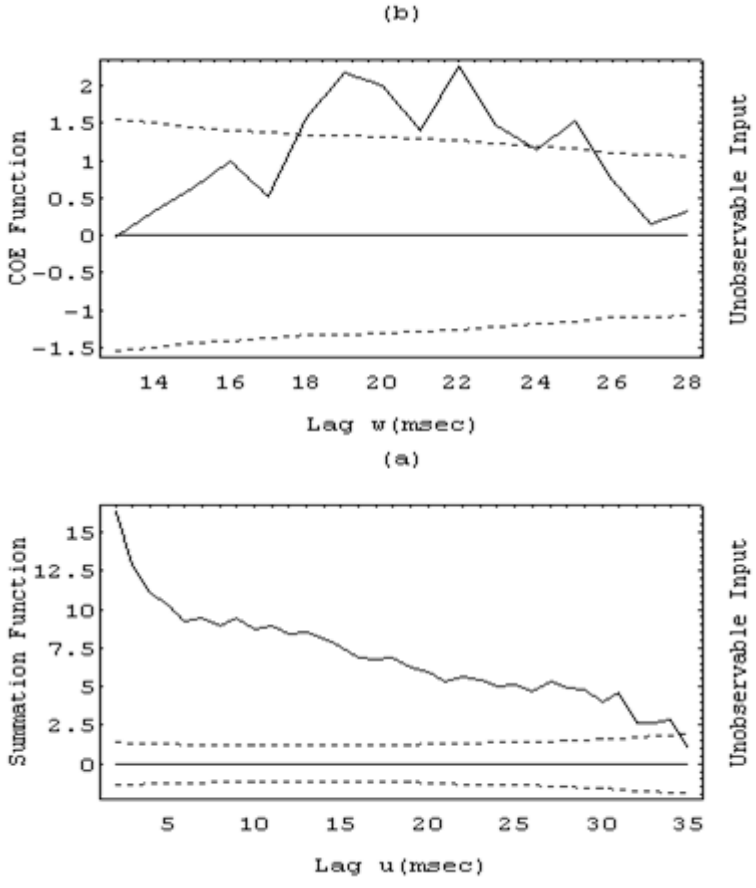


Fig.3.1.1 a) Estimated summation function. b) Estimated carry-over effect function.c) Estimated recovery (lower curve) and threshold (upper solid line) functions.



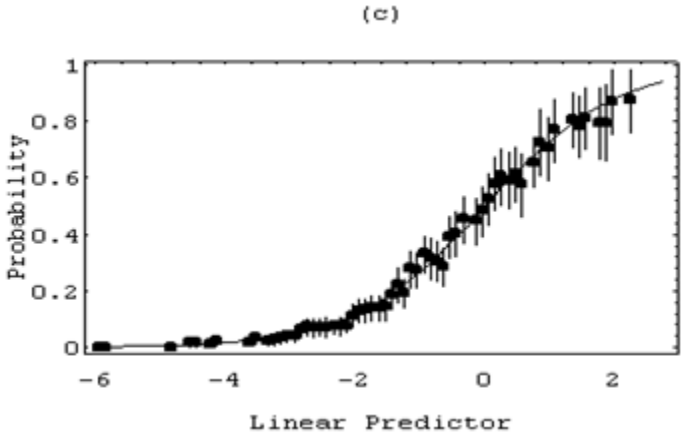


Fig.3.1.2 a) Estimated summation function for the "unobservable" input. b) Estimated carry-over effect function for the "unobservable" input. c) The goodness of fit plot for the full model.

The deviance table given in Table.3.1.1 illustrates the sequential fitting of a set of successively more complex models in the most complete situation available to us; namely one where "unobservable" inputs can be taken into consideration. The unobservable inputs explain more of the variability than either the summation function or the recovery function when fitted alone; although each of them is sufficiently informative to be worth fitting. This is a feature of the way in which the data have been simulated.

The second is that fitting all five components reduces the deviance from 20111 (the initial model) to 6708; a reduction of about 67% and the best we have so far been able to achieve. The goodness of fit test (Fig.3.1.2c) corresponding to the final model reveals that the fit of the model is very satisfactory. It is possible to use values of the linear predictor much larger than we have been able to in previous data sets because more input information was available to us in this case. This leads to circumstances where the probability of an output spike is very large. The third is to note some of the various effects of adding the recovery function to a previous model. Adding it to the null model reduces the deviance by 4581. Adding it to the "unobservable" inputs reduces the deviance by only 176. Adding it to the summation function reduces the deviance by 4103. This requires careful interpretation. Evidently the information contained in the recovery function is largely orthogonal to that contained in the summation function because the two reductions in deviance, 4581 and 4103, are quite similar. However the recovery function contains almost no extra information to that contained in the "unobservable" inputs, as the additional reduction in deviance is very small. Evidently the recovery function "explains" part of the effects of the "unobservable" inputs if these latter are not (or cannot be) modeled. We shall need to be very careful therefore not to give the recovery function a physiological interpretation which may not be meaningful. It seems therefore in general that, unless all inputs are modeled, the recovery function will contain some input information. The

square root of the estimated cross-intensity function given in Fig.3.1.3b indicates an excitatory effect of an input lasting about 5 msec only. This duration is very short compared with the 26 msec duration of an excitatory effect suggested by the summation function for the observed inputs given in Fig.3.1.2a. The square root of the cross-intensity function seems to underestimate the underlying excitatory effects of a synaptic input and provides little of the information available in the full likelihood model. Fig.3.1.3a gives the estimated cross-intensity function. The residual deviance for this model is 19720; a reduction of only 391 from the null model, providing still further evidence that the cross-intensity function in general has very poor explanatory power. The goodness of fit plot for a model containing only the cross-intensity function (shown in Fig.3.1.3c) indicates that the fit is a very poor one compared with that for the five components model shown in Fig.3.1.2c. This can be seen both from the relatively small values of the predicted probabilities ($\hat{P}(\eta) \leq 0.2$).

Table.3.1.1 Deviance of all considered models.

Model	Deviance
Recovery Function	15530
$(\text{Summation Function})_1$ Observed Inputs	17669
$(\text{Summation Function})_2$ Unobserved Inputs	12875
$(\text{Summation Fun.})_1 + (\text{COE})_1$	17223
$(\text{Summation Fun.})_1$ + Recovery Fun.	13566
$(\text{Summation Fun.})_2$ + Recovery Fun.	12699
$(\text{Summation Fun.})_2 + (\text{COE})_2$	12704
$(\text{Summation Fun.})_1 + (\text{Summation Fun.})_2$	8897
$(\text{Summation Fun.})_1$ + Recovery Fun. + $(\text{COE})_1$	17223
$(\text{Summation Fun.})_2 + (\text{COE})_2$ + Recovery Fun.	12632
$(\text{Summation Fun.})_1 + (\text{COE})_1 +$ $(\text{Summation Fun.}) + (\text{COE})_2$	7331
$(\text{Summation Function})_1 + (\text{COE})_1 +$ $(\text{Summation Function})_2 + (\text{COE})_2 +$ Recovery Function	6708

4. Conclusion

The approach shows great flexibility. The recovery (and threshold) functions, when all inputs can be measured, represent intrinsic properties of the neurone and no analogous measure is available using the traditional stochastic point process techniques. The linear summation of the effects of the input spike train on the membrane potential have been further separated into the effects of input spikes occurring at times after the time of the last output spike and the effects of input spikes occurring at times prior to the time of the previous output spike. These two types of

input effect are measured by the summation function and its corresponding carry-over effect function respectively.

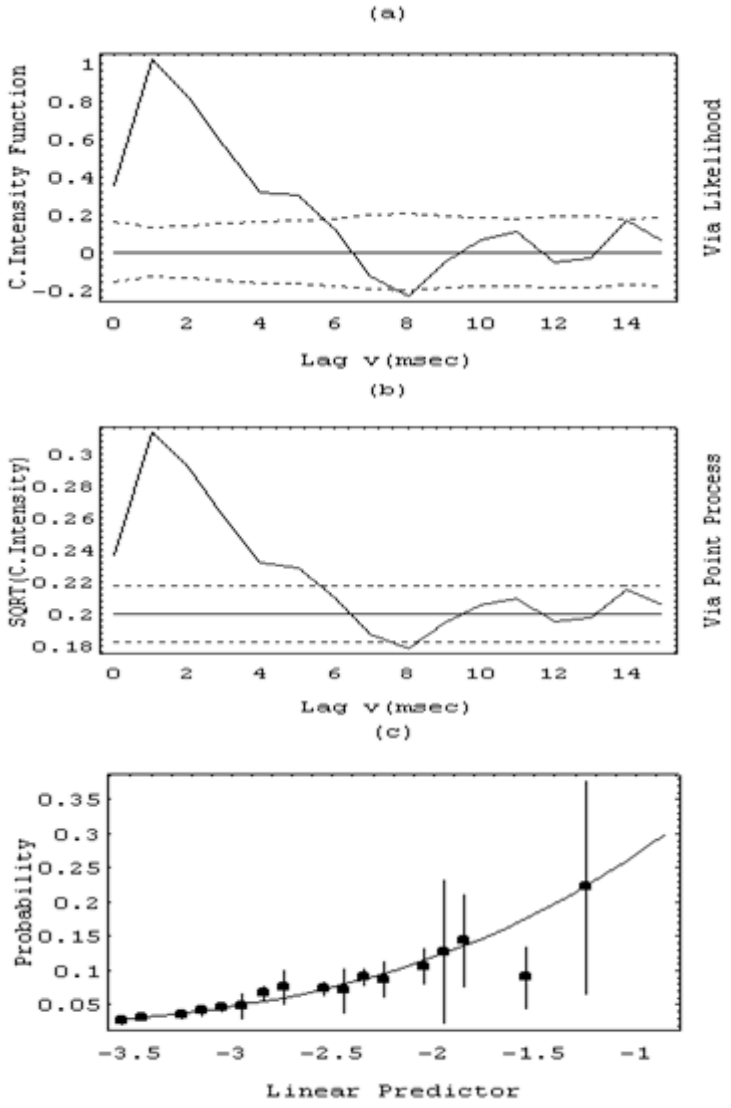


Fig.3.1.3 a) The cross-intensity function estimated via likelihood. b) The square root of the cross-intensity function estimated via the point process approach. The dotted lines in a) and b) give $\pm$ two standard error limits for the cross-intensity functions plotted about zero in (a) and about the square root of estimated output mean rate in (b). c) The goodness of fit plot corresponds to the model given in a).

The analysis suggests that the square root of the cross intensity function as a time domain measure of the degree of associations between two processes usually underestimates the underlying effects of a synaptic input and it may further produce results that contradict the way in which the data have been simulated. The summation

function, by contrast, provides an alternative measure which seems to be more informative and reliable in terms of reduction in deviance. Also it seems to be more consistent with the way in which the data are simulated. Unlike the cross-intensity approach, the likelihood procedure also allows for continuous “unobservable” inputs to be involved in the analyses, and both summation and carry-over effect functions for the “unobservable” inputs can be estimated.

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