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A new method for detecting
neural interconnectivity

by

Klaus J. Utikal *)

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Abstract

We propose a class of counting process models for analysing firing times of an ensemble of neurons. We allow the counting process intensities to be unspecified, unknown functions of the times passed since the most recent firings.

Under this assumption we derive a class of statistics with their respective thresholds as well as graphical methods for detecting neural connectivity.

We introduce a model under which detection is shown to be certain for long series of observations and suggest ways to estimate strength and classify the interactions as inhibition or excitation.

The power of the proposed methods is compared by simulating observations from artificial networks.

By analysing empirically obtained series we obtain results which are consistent with those obtained from cross correlation based methods but in addition obtain new insights on further aspects of the interactions.

Key words: neural firing times, inhibition, excitation, spiketrain series, stochastic dynamical system, counting processes, Markovian interval process, intensities, martingale dynamics.

JEL C12, C13, C14

1 Introduction and summary

The firing activities of a neural ensemble are naturally described in terms of a multivariate counting process. Using counting process intensities to characterize the probability of a jump in the near future given the past of the process the following stochastic model was proposed in Utikal (1994a): The intensity of any component is a general, unknown, nonrandom function of the time since the last jump of the component, i.e. its backwards recurrence time (BRT) as well as of the BRTs of some or all of the other components of the system. It has turned out that this model, called Markovian interval process, which was introduced by Cox and Lewis for the analysis of component failure times in the context of reliability theory, is also suitable for the analysis of firing times of connected neurons. It has been shown by Utikal (1994b) that a nonparametric estimate of the firing intensity will display geometric properties characteristical for neural interactions. Inhibition of a target is manifested as a sudden drop of the intensity a certain time after a trigger firing to a lower level for a certain duration whereafter it rebounces to its previous level as suddenly as it had dropped. This is easily recognized in the geometric display of the target's intensity estimate as a surface which at a certain BRT of the trigger is cut by a sharp valley, independent within certain limits of the BRT of the target.

This has lead to the suggestion of a new method of graphically detecting inhibition and estimating its maximal strength, duration, and change over time, which can be superior to cross correlation methods for small as well as large samples as is illustrated in Utikal(1995a).

In this article we propose now a quantitative method of detecting neural interactions which will be shown to lead to consistent inference within the framework of Markovian interval processes.

Moreover, a special class of processes is introduced under which the proposed method is easily motivated and most naturally interpreted. For these models which we call proportional hazard Markovian interval processes (PhMips) the intensity of any component is an unknown, general function of its own BRT which is modulated by step functions of the BRTs of the other components. These step functions have a value equal to one except on some unknown intervals where they may take other constant, unknown values reflecting strengths of delayed effects which extend for certain durations.

The method of detecting those effects is based on a diagram which may be considered a modification of the cross correlation histogram (CCH) of Perkel et al. (1967) for pairs of neurons but which is also straightforwardly generalized to e.g. triplets of two triggers and a target. Nonstationary controlled or uncontrolled effects within the system can be incorporated and its significance tested for. Moreover can it be used to test for significance of cumulative effects of successive trigger firings or aftereffects of a trigger firing beyond a target firing.

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We assess the validity and power of the proposed method in a simulation study using networks from Utikal (1995a) and MacGregor (1987). This leads to recommendations on the sample sizes required to produce reliable results. Using empirically obtained data our analyses are shown to be consistent with results previously obtained by other authors using cross correlation methods but moreover previously hidden effects are found to play a significant role. The results are interpreted in terms of a PhMip and the problem of superposition of effects from different triggers is addressed.

Other related work on modeling statistical aspects of neural firing times using intensity based counting process theory has been done in the past. Chornoboy et al. (1986) assume additivity of the trigger effects i.e. the targets firing intensity is decomposed into a sum over all observed triggers of arbitrary univariate functions of the BRTs of each trigger. Nonparametric functional estimation of the component functions has been carried out in a computationally efficient way but no numerical tests for significance of the observed effects was given. As their model is a special case of the Markovian interval process described here, our test applies to their model as well.

A model introduced by Borisyuk et al. (1985) can be seen as a forerunner to the PhMip introduced here. Being more general, our model avoids the shortcomings their model encounters in certain situations as further explained below.

The remainder of this paper is organized as follows. In Section 2 we introduce Mips and PhMips and relate them to intensity based counting process models proposed by other authors.

The main result is contained in Section 3. The simulation study is contained in Section 4 and applications to empirically obtained data are given in Section 5. The proofs of the theorems are appended in the Section 6.

2   Model

The method of detecting neural interactions discussed in Section 3 is shown to be a consistent procedure under the following model. The firing activities of an ensemble of $p + 1$ neurons is conveniently described by a $(p + 1)$variate counting process $\mathbf{N} = (N, N^{(1)}, ..., N^{(p)})$ whose components jump at their respective firing times $\{\tau_1, \tau_2, ...\}$, $\{\tau_1^{(1)}, \tau_2^{(1)}, ...\}$, ..., $\{\tau_1^{(p)}, \tau_2^{(p)}, ...\}$. We model the firing intensity of a neuron as a certain jump intensity of the corresponding counting process. It is well known that, given the past history of the process $\mathbf{N}$, denoted by $\mathcal{F}_t$, the components of $\mathbf{N}(t)$ can be decomposed into a sum of its dual predictable projection or intensity process λ_t and an $\mathcal{F}_t$-martingale $M(t)$

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$$N(t) \quad = \quad \int_0^t \lambda_s \, ds + M(t) \tag{2.1a}$$

$$N^{(r)}(t) \quad = \quad \int_0^t \lambda_s^{(r)} \, ds + M^{(r)}(t) \tag{2.1b}$$

for $r = 1, \cdots, p$ where $(\mathcal{F}_t)$ is a filtration satisfying the "usual conditions", see Andersen et al (1992) p.60. As an alternative notation for (2.1) we also use

$$dN(t) \quad = \quad \lambda_t \, dt + dM(t)$$
$$dN^{(r)}(t) \quad = \quad \lambda_t^{(r)} \, dt + dM^{(r)}(t) \, .$$

The proposed models specify the intensity as some unknown or partially known function of the times passed since the last jump of the components of $\mathbf{N}$ i.e. its backwards recurrence times (BRTs). Denote the BRT of $N^{(p)}$ at t, by $t - \tau_{N^{(p)}}^{(p)}$, see Figure (2.1).
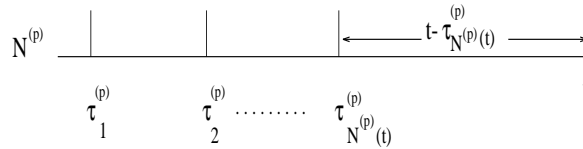

Figure 2.1. Backwards recurrence times of $N^{(p)}$

All models discussed here are special cases of the following model in which the intensities of the components are functions of the BRTs of the components of $\mathbf{N}$. These functions are arbitrary, unknown, assumed to be continuous and positively bounded away from zero on every compact domain, i.e.

$$dN(t) = \alpha \quad \left(t - \tau_{N(t-)}, t - \tau_{N^{(1)}(t-)}^{(1)}, ..., t - \tau_{N^{(p)}(t-)}^{(p)} \right) + dM(t) \tag{2.2a}$$

$$dN^{(r)}(t) = \alpha^{(r)} \quad \left(t - \tau_{N(t-)}, t - \tau_{N^{(1)}(t-)}^{(1)}, ..., t - \tau_{N^{(p)}(t-)}^{(p)} \right) + dM(t) \tag{2.2b}$$

for $r = 1, \ldots, p$.

These processes, called Markovian interval process by Cox & Lewis (1972) who in the context of reliability theory assume a dependence of the probabilities of a components breakdown in the very near future on the ages of some or all components in the system. The ergodic properties of the stochastic system described by (2.2) were studied by Slud (1984).

As there is no further assumption on the functional form of $\alpha, \alpha^{(1)}, \ldots, \alpha^{(r)}$ these models are very general. It has been shown in Utikal (1994a, 1994b, 1994c,

1995a) that they are useful tools for analysing the firing activities of small networks. Neural interactions are characterized through geometric properties of the function α which are also clearly reflected in their functional estimates and give a much clearer picture and impression than is usually obtained by the crosscorrelogram.

The following derivatives of model (2.2) will be considered, obtained by restricting the domain of definition or by further specifying the functions involved.

1. If we are not sure how to model the cumulative effects of several trigger firings after a target firing, this can be avoided by stopping the observations at a consecutive trigger firing and restrict the model to hold at times t while at most one firing of any trigger component has been observed, i.e.

$$\tau_n \le t < \tau^{(r)}_{N^{(r)}(\tau_n)+2} \wedge \tau_{n+1} \tag{2.3}$$

for $n = 1, \ldots$ and $r = 1, \ldots, p$.

2. A simplification of the model is obtained under the hypothesis that after a firing of N and before the next firing of $\mathbf{N}$ the function α depends on the BRT of N only, i.e.

$$\alpha = \alpha(t - \tau_{N(t-)}) \text{ if } \tau_n < t < \tau^{(r)}_{N^{(r)}(\tau_n)+1} \text{ for all } r = 1, \ldots, p \ . \tag{2.4}$$

In other words we assume in (2.4) that the aftereffect of a trigger after a target firing is negligible. This hypothesis has been tested for a related model in Utikal (1994c) and, for the data considered in Example 1 of the present work, cannot be rejected ($\text{p} - \text{value} > .10$).

Model (2.2) under (2.3), (2.4) is used in the analyses presented in Section 5.

3. On the other hand one can investigate if there is an aftereffect of the jth trigger after a target firing took place by considering sequences specified by

$$\tau^{(i)}_{N^{(i)}_{(\tau_n)}} \le \tau^{(j)}_{N^{(j)}_{(\tau_n)}} \le \tau_n < t \le \tau_{n+1} \wedge \tau^{(i)}_{N^{(i)}(\tau_n)+1}$$

for all $i = 1, \ldots, p$.

4. More general models are obtained by incorporating dependence on the last several trigger events after a target firing. This leads to models of the form (2.1), (2.2) where dependence of α is extended to

$$t - \tau^{(1)}_{N^{(1)}(t-)}, \ldots, t - \tau^{(1)}_{N^{(1)}(t-)-k_1}, \ldots, t - \tau^{(p)}_{N^{(p)}(t-)}, \ldots, t - \tau^{(p)}_{N^{(p)}(t-)-k_p} \ .$$

An important special case of this is given by for $p = 1$, $k_p = 1$. A more general model for this case is obtained by requiring the above to hold only while

$$\tau_n < t \le \tau_{n+1} \wedge \tau^{(1)}_{N^{(1)}(\tau_n)+3} \ .$$

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This is a useful generalization e.g. for infering on cumulative effects of two sucessive trigger firings. However, in order not to overburden the notation, we will only consider the case $k = k_1 = \cdots = k_p = 0$ and leave straightforward generalizations to the reader.

Further observed variables describing factors thought to influence the firing activities of the ensemble can be incorporated into the model. These may be controlled or uncontrolled by the experimenter e.g. indicating presence or absence of "treatments" or outside stimuli.

As a special case of (2.2) we assume that the effects of the BRTs multiply. This leads to the multiplicative or proportional hazards Mip (PhMip)

$$dN(t) = \lambda_0 \left(t - \tau_{N(t-)} \right) \alpha \left(t - \tau^{(1)}_{N^{(1)}(t-)}, \ldots, t - \tau^{(p)}_{N^{(p)}(t-)} \right) \quad +dM(t) \quad \text{(2.5a)}$$

$$dN^{(r)}(t) = \alpha^{(r)} \left(t - \tau_{N(t-)}, t - \tau^{(1)}_{N^{(1)}(t-)}, \ldots, t - \tau^{(p)}_{N^{(p)}(t-)} \right) \quad +dM(t) \quad \text{(2.5b)}$$

for $r = 1, \ldots, p$.

To model the dependence observed in Utikal (1995c) and briefly described in the introduction we propose a semiparametric model whose parametric part is specified as

$$\alpha(s_1, \ldots, s_p) = 1 + \sum_{B \in \mathcal{A}} \mathtt{hi}_B \, \mathrm{I}\left\{ (s_1, \ldots, s_p) \in B \right\} \quad \text{(2.6)}$$

where $\mathcal{A}$ is a given fixed partition of the space of backward recurrence times and $\mathtt{hi}_B$ are unknown parameters such that $\mathtt{hi}_B > -1$. The function λ_0 is arbitrary, unknown, positive, continuous. In the special case $p = 1$, i.e. for a pair of neurons, (2.6) is reduced to

$$\lambda_t = \lambda_0(t - \tau_{N(t-)})(1 + \mathtt{hi}) \, \mathrm{I}\{\mathtt{del} < t - \tau^{(1)}_{N^{(1)}_{(t-)}} < \mathtt{del} + \mathtt{dur}\} \quad \text{(2.7)}$$

where $\mathtt{del}$ and $\mathtt{del} + \mathtt{dur}$ are unknown parameters from a given finite set.

This model stipulates an intensity of N which varies as a (smooth) function of the time since the last jump of N and which is interrupted by sudden rise or fall for a short period of $\mathtt{dur}$, starting at a time $\mathtt{del}$ after a jump of $N^{(1)}$ and which disappears thereafter as suddenly as it arose. This way $N^{(1)}$ transmits its effect on N which may be exciting $(\mathtt{hi} > 0)$ or inhibiting $(-1 < \mathtt{hi} < 0)$.

An obvious specialization of (2.6) is given by

$$\alpha_B(s_1, \ldots, s_p) = \prod_{r=1}^{p} \left(1 + \mathtt{hi}_r \mathrm{I}\{s_r \in B_r\} \right)$$

where $B = \times_{r=1}^{p} B_r$. It is seen in Example 2 of Section 5 however that this might quickly become too severe of a restriction.

We note that other attempts of describing neural firing activities have been made using models that are special cases of (2.2). The model proposed by Borisyuk et al (1985) is closely related to ours. It is specified by an intensity of the form (2.5) with

$$\alpha(s) = \exp\left\{\beta \exp\{s/12\}\right\}. \tag{2.8}$$

This function has been proposed earlier as a model for transient phenomena by Cox & Oakes (1984). As is shown in Borisyuk et al. (1985) and Utikal (1994c), this model can describe adequately certain networks; for undelayed excitations of a certain duration the model reconstructs correctly the structure of simulated network of known wiring. A generalization of (2.8) to possibly delayed effects of unknown duration leads to a model for which inference can be studied by methods similar to ours. However, we believe that sudden jumps of an intensity, as those observed in Utikal (1994b) should not be modeled by using continuously decreasing functions α_k as in (2.8). This has been attempted in Utikal (1994c) with unsatisfying outcome; estimators and inference are becoming increasingly numerically unstable the more disruptive and visible the simulated effects become.

Note that instead of giving the model (2.2) a multiplicative structure as we do in (2.5) additivity is another possibility. This was done in Chornoboy et al (1986) who proposed the model

$$\lambda_t = \alpha\left(t - \tau_{N(t-)}\right) + \sum_{k=1}^{p} \alpha_k\left(t - \tau_{N^{(k)}(t-)}^{(k)}\right). \tag{2.9}$$

However, we have found (2.5) convenient for modeling certain two-component-networks like the one analysed nonparametrically in Utikal (1995c); a sudden drop to zero of the intensity may be simpler to explain by a factor dropping to zero in a product than by a sum of hazards. The important question of discriminating between additive and multiplicative models needs further investigation.

3 Inference

In this section we construct tests for the independence of N from the backwards recurrence times (BRT) of $N^{(1)}, \ldots, N^{(p)}$ assuming model (2.2).

From observing one single trajectory of the processes we derive the BRT process

$$\mathbf{X}(t) = (t - \tau_{N(t)^{(1)}}^{(1)}, \ldots, t - \tau_{N(t)^{(p)}}^{(p)})$$

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as indicated in Figure 3.1.
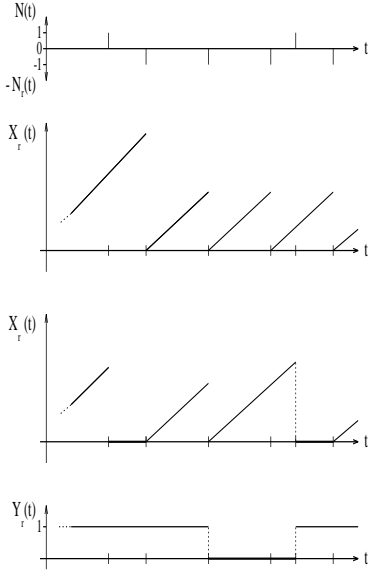
If the model is assumed to hold only at times during which a certain pattern of counts is repeated e.g. as in (2.3), we introduce an auxiliary process $\mathbf{Y}(t) = \{Y_r(t), r = 1, \ldots p\}$. During times at which (2.3) is violated, the process $Y_r(t)$ is set to zero and otherwise we set $Y_r(t) = 1$. Denote $Y = \min\{Y_1, \ldots, Y_p\}$. In the absence of any restrictions, $Y(t)$ equals one for all times. If other restrictions on the times during which the model is to hold are imposed, this is incorporated accordingly.

A further use of the indicator Y is for screening out extraordinary long times between successive firings of the target. As is illustrated in Utikal (1995b) it is recommendable to limit these times to some physiologically meaningful region, less than some value T, say (e.g. 275 ms) in Example 1 of Section 5. This is achieved by setting $Y(t) = 0$ while

Figure 3.1: $k^{\underline{th}}$ BRT process

$$t - \tau_N(t) > \text{T}. \tag{3.1}$$

This condition will be assumed throughout. We base inference on the following statistics. We denote the indicator function of a set B by I_B. Define

$$\mu_t(B) = \sum_{\substack{\tau_{j+1} < t \\ Y(\tau_{j+1}) > 0}} \left\{ \mathrm{I}_B\{\mathbf{X}(\tau_{j+1})\} - \frac{\sum_{R_t(\tau_{j+1})} \mathrm{I}_B\{\mathbf{X}(\tau_k + \tau_{j+1} - \tau_j)\}}{\sum_{R_t(\tau_{j+1})} 1} \right\} \tag{3.2}$$

and similarly

$$\sigma_t^2(B) = \sum_{\substack{\tau_{j+1} < t \\ Y(\tau_{j+1}) > 0}} \left\{ \mathrm{I}_B\{\mathbf{X}(\tau_{j+1})\} - \frac{\sum_{R_t(\tau_{j+1})} \mathrm{I}_B\{\mathbf{X}(\tau_k + \tau_{j+1} - \tau_j)\}}{\sum_{R_t(\tau_{j+1})} 1} \right\}^2 \tag{3.3}$$

where $R_t(\tau_{j+1}) = \{\tau_k : \ t > \tau_{k+1} > \tau_k + \tau_{j+1} - \tau_j, \ Y(\tau_k) > 0\}$.

The introduction of these statistics is motivated as follows. Each time the target fires we compute from the total number of cases in which a target has not

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fired for more than the observed time the percentage for which their respective BRTs fall within limits set by B. This percentage is then related to the event wether that the target fired with a respective trigger's BRT lying inside the range set by B. If a trigger is inhibiting after a time and for a duration within the limits set by B we would expect this difference to be significantly negative, and in the opposite case of excitation significantly positive.

We consider the following test statistics. Denote by $\mathcal{C}$ a finite collection of hypercubes in the covariate space of $\mathbb{R}^p$. For each hypercube in $\mathcal{C}$ there must be another member of $\mathcal{C}$ which is adjacent in the sense that they share a face. The collection of all unions of adjacent cubes in $\mathcal{C}$ is denoted by $\mathcal{B}(\mathcal{C})$. Denoting the square root of σ^2 by σ we define

$$
\begin{aligned}
\xi_1 &= \max_{B \in \mathcal{B}(\mathcal{C})} \frac{|\mu(B)|}{\sigma(B)} \\
\xi_2 &= \max_{B \in \mathcal{C}} \frac{|\mu(B)|}{\sigma(B)} \\
\xi_3 &= \max_{B \in \mathcal{B}(\mathcal{C})} \left\{ \sum_C \frac{|\mu(C)|}{\sigma(C)}, \text{ where } C \in \mathcal{C} \text{ such that } B = \cup C \right\} \\
\xi_4 &= \max_{B \in \mathcal{B}(\mathcal{C})} \left\{ \sum_C \frac{\mu(C)^2}{\sigma^2(c)}, \text{ where } C \in \mathcal{C} \text{ such that } B = \cup C \right\}.
\end{aligned}
$$

For further motivation we also note that $\mu(B)/\sigma(B)$ approximates the standardized partial likelihood score in model (2.5)-(2.6) under the hypothesis $H_0 : \mathtt{hi}_B = 0$ against the alternative that $\mathtt{hi}_B \neq 0$ for some fixed known B. More precisely, Cox's partial likelihood of observing $\{(\tau_{j+1} - \tau_j, X_1(\tau_j + s), \ldots, X_p(\tau_j + s)), \ s \leq \tau_{j+1} - \tau_j, \ j = 1, 2, \ldots\}$ for one single, known set B can be approximated by

$$
L(\mathtt{hi}) = \prod_{\substack{0 < \tau_{j+1} < t \\ Y(\tau_{j+1}) \neq 0}} \frac{1 + \mathtt{hi}\, \mathrm{I}_B(X(\tau_{j+1}))}{\sum_{R_t(\tau_{j+1})}(1 + \mathtt{hi}\, \mathrm{I}_B(X(\tau_k + \tau_{j+1} - \tau_j)))} . \tag{3.4}
$$

Evaluating $(\partial/\partial\mathtt{hi}) \log(L)$ in zero one obtains $\mu(B)$ as defined in (3.1). From this point of view ξ_1 can be expected to be the most powerful of all four tests considered. This is confirmed by the simulations in the following section.

Moreover, for this reason one can choose from a variety of existing software to compute $\mu(B)/\sigma(B)$ for any fixed B. Any program that computes "score test statistic" in the Cox model may be used, provided the model allows for time dependent covariates to be included, e.g. PHREG of SAS. It is then possible to use the indicator that the trigger's BRTs at a target firing fall within the range of B as covariates while the target's BRT plays the role of the response variable.

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Maximizing (3.3) with respect to the unknown parameters of (2.6), one would expect to obtain reasonable estimators for these. Maximization is facilitated by using differentiability in `hi` of (3.3) while plotting $\mu(B)/\sigma(B)$, as further explained below, one gets starting values for the maximization in `del` and `dur` as in (2.7).

The following theorem will be useful in computing the distribution of the test statistics defined below. We assume that the components of $\mathbf{N}$ have intensities of the form (2.2) and N has an intensity of the form (2.6) with $\alpha \equiv 1$. We have the following theorem.

THEOREM 3.1: Under the null hypothesis $H_0 : \quad N \quad$ is an independent renewal process we have for $t \to \infty$

(i) $(\mu/\sigma)(B)$ is asymptotically standard normal.

(ii) $\mu(B^{(1)})$ and $\mu(B^{(2)})$ are asymptotically independent if $B^{(1)} \cap B^{(2)} = \emptyset$.

(iii) $\mu(B^{(1)}) + \mu(B^{(2)}) = \mu(B^{(1)} \cup B^{(2)})$ if $B^{(1)} \cap B^{(2)} = \emptyset$.

It follows from this theorem that the distribution of ξ_2 can be computed approximately as that of a maximum deviation of independent standard Gaussian random variables.

Likewise the distribution of ξ_3 is approximately equal to that of a maximum over sums of absolute values of independent standard Gaussian random variables and that of ξ_4 can be approximately computed as that of a maximum over simulated sums of independent chi-square random variables with one degree of freedom each.

While the distribution of ξ_1 depends on parameters of the data generating process, i.e. has to be computed anew for each new series of observations, this is not the case for ξ_2, ξ_3, ξ_4.

The distribution of ξ_1 can be determined as follows. Denote by $\overset{\mathcal{D}}{=}$ equality in distribution.

COROLLARY 3.2: As $t \to \infty$

$$\left(\frac{\mu}{\sigma}\right)\left(\bigcup_{j=j_1}^{j_2} B_j\right) \overset{\mathcal{D}}{=} \frac{\sum_{j=1}^{j_2-j_1+1} X_j \sigma(B_j)}{\sqrt{\sum_{j=1}^{j_2-j_1+1} \sigma^2(B_j)}} + o(1)$$

where $B_{j_1} \cap B_{j_2} = \emptyset$ if $j_1 \neq j_2$ and $X_1, X_2, \ldots$ are independent standard normal random variables.

The test statistic ξ_2 has the additional advantage that it leads to a simple graphic method of detecting inhibition or excitation. Partitioning the region

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of interest into disjoint intervals B, the random variables $\mu(B) / \sigma(B)$ are independent standard Gaussian processes. If their maximum exceeds a critical threshold value, the corresponding interval is likely to contain the time at which the effect of a trigger on the target manifests. The sign of this maximal deviation indicates the inhibiting or exciting natures of the effect. The threshold value can be approximately chosen according to the following corollary.

COROLLARY 3.3: As $t \rightarrow \infty$

$$P(\xi_2 > x) \rightarrow (2(1 - \Phi(x)))^n \tag{3.5}$$

where n is the number of disjoint equally sized hypercubes in the collection $\mathcal{C}$ and where $\Phi(x)$ is the standard normal distribution.

For computationally simple approximations to this distribution we refer to Leadbetter et al. (1982).

As another corollary to the proof of Theorem 3.1 we show that tests based on $\xi_1, \ldots, \xi_4$ are consistent in detecting neural effects if these are present.

COROLLARY 3.4: Assume model (2.5), (2.6) with $\text{hi}_B \neq 0$ for some B. Then $|\mu|/\sigma \rightarrow \infty$ as $t \rightarrow \infty$.

Using the same principles we can easily adjust the proposed tests to account for the effects of other observed covariates or to test for the significance of their effects. Suppose for instance that a covariate $\psi(t)$ is binary, indicating presence or absence of a certain condition at time t. One way to test the significance of ψ is to compute ξ_i separately over times corresponding to different values of ψ, say $\xi_i(\psi = 0)$ and $\xi_i(\psi = 1)$. Under the assumption that these statistics are independent the asymptotic distribution of their difference can be found from Theorem 3.1. Another way is to model the effect of ψ explicitly in (2.5), (2.6) and then derive a test statistic from maximizing the functional corresponding to (3.3).

The bivariate case ($p = 1$) will receive special attention in the next section. It is shown in Utikal (1995a) by graphical means, that models (2.2)-(2.7) can lead to correct inference even where the CCH gives a misleading picture. Moreover, it will be seen that the power of the test based on ξ_2 is surprisingly high when compared to ξ_1.

4   Simulations

Two simulation studies are carried out to assess the goodness of the methods proposed in Section 3. In Simulation 1 an extremely simple network of two neurons is used to estimate the power of detecting independence, excitation, and inhibition where strength, location, and duration of the effects are varied

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systematically. The power of $\xi_1, \ldots, \xi_4$ is compared and recommendations concerning the required number of firings are drawn. In Simulation 2 we analyse data generated by a neuronal generator which models the underlying physiological processes more realistically. It is shown that the method recovers correctly the wirings of a network of five neurons even when the numbers of observed firings lie below those recommended in Simulation 1.

A comparison of the power of detection for the proposed method relative to cross correlation based methods is not intended in the present article. However, it can be conjectured from the results in Utikal (1995a) that for certain values of the parameters in the model considered in Simulation 1 our method compares favorably.

Simulation 1: We simulate firing times from a pair of neurons such that

(i) the firing intensity is constant before a trigger firing

(ii) For `del` units of time after a trigger firing the targets intensity remains unchanged. Provided no other firing of trigger or target have occurred, after `del` units the targets intensity jumps to a new level `hi` where it remains for `dur` units and whereafter it falls back to its previous level.

(iii) Whenever a new trigger firing occurs, the targets firing intensity is regenerated at (ii), whenever a new target firing occurs, it regenerates at (i).

For an algorithmic descriptions and further applications of this network see Utikal (1995a). In mathematical terms this means we simulate a trajectory of the bivariate counting process (2.5), (2.7) with $r = 1$ and $\lambda_0 = 1$. As trigger process we choose a homogenous Poisson process, hence we obtain the system

$$
dN(t) = (1 + \text{hi})\, I \left\{ \text{del} < t < t - \tau^{(1)}_{N^{(1)}_{(t-)}}(1) < \text{del} + \text{dur} \right\} dt + dM(t)
$$
$$
dN^{(1)}(t) = dt + dM^{(1)}(t)
$$

with side conditions (2.3) and (2.4).

The programs used in the simulations are written in C and Splus and are available from the author. The random number generator `ran2` of Press et al. (1988) was used.

The CCH for a pair of typical replications of the simulation corresponding to different alternatives specified in Table 4.2 is shown in Figure 4.1.
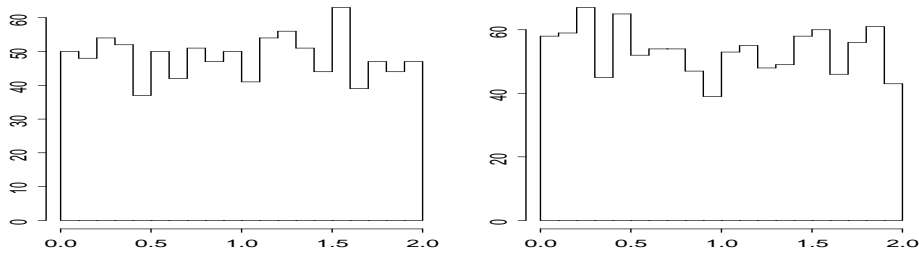
Figure 4.1. CCH for different alternatives.

Figure 3.2	model			p-value		
	hi	del	dur	mpl	numint	triggers
[left]	0.882	0.40	0.10	0.04	10	2000
[right]	1.600	0.40	0.10	0.07	10	2000

Table 4.1: Tests from samples with CCH dislayed in Figure 3.2.

It is seen from Figure 4.2 that for moderate sample sizes the simulated Poisson counts frequently tend to accumulate and build up spurious but remarkable singular features in the cross correlogram which the test statistic records as abnormal as much as the human eye does. It has been confirmed by our simulations that for these cases the test statistics indicate highly significant interactions consistent with perceived patterns. More precisely, score functions and the derived statistics are maximized for durations that correspond to towering hights or steep valleys of the CCH. Therefore it is not surprising that rather large sample sizes are needed to assure the specified α-level of the test.
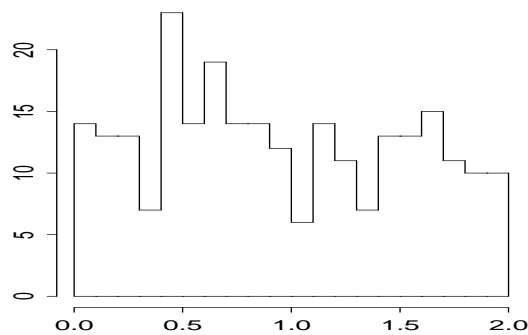

Figure 4.2 Small sample CCH for a pair of independent Poisson processes.

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The following table gives the power of the four tests proposed above for H_0 : $\mathtt{hi}_A = 0$ for all $A \in \mathcal{A}$ against the alternative H_a : $\mathtt{hi}_A \neq 0$ for some A. We consider different levels of significance and different sample sizes (i.e. number of triggers). The relevant time interval of the BRT is partitional into either five or ten intervals of equal width. The power calculations for each test are based on 1000 replications.

It can be concluded that under the null hypothesis the tests based on ξ_2, ξ_3, ξ_4 are more volatile than ξ_1. Under the alternative the power of ξ_2 is quite good when compared with ξ_1 for impulses of short duration but is overtaken by ξ_3 and ξ_4 for larger values of $\mathtt{dur}$.

Model			Test						
hi	del	dur	ξ_1	ξ_2	ξ_3	ξ_4	alpha	int	triggers
0.00			0.153	0.167	0.151	0.216	0.10	5	500
0.00			0.091	0.109	0.098	0.132	0.05	5	500
0.00			0.127	0.128	0.125	0.189	0.10	5	750
0.00			0.070	0.075	0.078	0.104	0.05	5	750
0.00			0.107	0.127	0.109	0.164	0.10	5	1000
0.00			0.074	0.075	0.078	0.092	0.05	5	1000
0.00			0.188	0.195	0.191	0.213	0.10	10	750
0.00			0.138	0.145	0.147	0.155	0.05	10	750
0.00			0.165	0.179	0.170	0.188	0.10	10	1000
0.00			0.113	0.127	0.130	0.133	0.05	10	1000
0.00			0.130	0.150	0.145	0.157	0.10	10	1500
0.00			0.080	0.106	0.088	0.102	0.05	10	1500
0.00			0.102	0.122	0.112	0.130	0.10	10	2000
0.00			0.049	0.076	0.05	0.076	0.05	10	2000
0.50	0.40	0.10	0.376	0.457	0.366	0.536	0.10	10	1500
0.50	0.40	0.10	0.245	0.324	0.267	0.417	0.05	10	1500
0.50	0.40	0.20	0.603	0.499	0.586	0.617	0.10	10	1500
0.50	0.40	0.20	0.457	0.359	0.468	0.514	0.05	10	1500
-0.30	0.40	0.10	0.459	0.490	0.468	0.554	0.10	10	1500
-0.30	0.40	0.10	0.358	0.388	0.378	0.426	0.05	10	1500
-0.30	0.40	0.20	0.529	0.495	0.541	0.536	0.10	10	1500
-0.30	0.40	0.20	0.429	0.398	0.456	0.443	0.50	10	1500
-0.30	0.40	0.30	0.674	0.577	0.693	0.671	0.10	10	1500
-0.30	0.40	0.30	0.569	0.478	0.607	0.570	0.05	10	1500

Table 4.2: Power of the tests $\xi_1, \ldots, \xi_4$

Simulation 2: The firing times of five neurons $N_1, \ldots, N_5$ were generated by Lindsey (1993) using the neural generator SYSTM11 of MacGregor (1987).

Three of the neurons are serially connected $N_2 \longrightarrow N_3 \longrightarrow N_4$, i.e. N_2

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excites N_3 and N_4 is excited by N_3 while N_1, N_5 fire independently. This data was previously analysed by Utikal (1994c) using model (2.8). Using model (2.2)–(2.4) now and testing for the independence of N_i from N_j we obtain the following p-values of the test based on ξ_1 displayed in Table 4.3.

An effect of N_2 on N_3 as well as of N_3 on N_4 can be clearly perceived from the table. The sample sizes used are given in Table 4.4, where numbers in parenthesis indicate censored events, i.e. $Y(\tau_j) = 0$, see the beginning of Section 3. We also note from Table 4.3 a borderline significance of an effect of N_4 on N_2. This effect is to be attributed to the relative smallness of the sample. By changing the partition of the backwards recurrence time range from 10 intervals to 8 intervals a second test was run on the subgroup of N_2, N_3, N_4. From the p-values displayed in Table 4.5 it can be seen that the effect of N_4 on N_2 was spurious while the effects of N_2 on N_3 and of N_3 on N_4 are confirmed.

p-values		target				
		1	2	3	4	5
	1		0.30	0.17	0.21	0.36
	2	0.89		0.00	0.45	0.68
trigger	3	0.69	0.72		0.02	0.71
	4	0.64	0.10	0.20		0.84
	5	0.46	0.65	0.24	0.64	

Table 4.3: full group (p-values)

trigger events	target				
	1	2	3	4	5
1		1216(85)	1273(82)	1260(76)	1172(85)
2	554(285)		1273(263)	1260(285)	1171(290)
trigger 3	554(306)	1216(299)		1260(306)	1172(319)
4	554(318)	1216(311)	1273(287)		1172(302)
5	554(285)	1217(270)	1273(268)	1260(248)	

Table 4.4: full group (trigger events), number of censored observations in parenthesis

p-values	target		
	2	3	4
2		0.00	0.28
trigger 3	0.74		0.01
4	0.31	0.66	

Table 4.5: reduced group (p-values)

5 Application

In this section two sets of neurophysiological data, describing the firing activities of groups of neurons recorded in form of a multivariate spike train series, are reanalysed. We apply the methods of automatic detection of neural interactions introduced in Section 3. In addition we present a simple graphical device illustrating significance, nature, delay, and location of the detected effects. In the first example we show the robustness of the method towards variation in the number of unaffected target firings. In the second example we study the interaction of two triggers on a target. The results obtained are in accordance with those obtained by previous analysts using cross-correlation analysis, however new and additional insights into the firing activities are gained from the data.

Example 1: Lindsey et al. (1992) recorded the firing times of a pair of neurons located in the midline brain stem of a cat. From an inspection of the CCH it is suggested that the target is affected by an inhibiting trigger firing at a time later than 50 ms. This data was reanalysed by Utikal (1994b), (1995a) using Markovian interval processes which suggest a time to maximal inhibition of approximately 60 ms after a trigger firing.
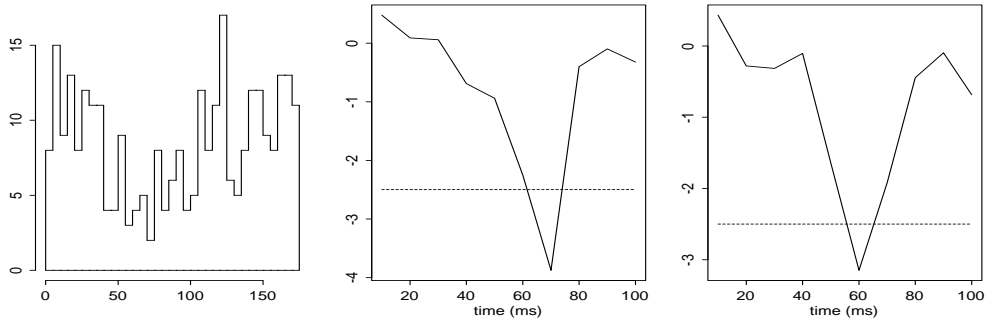
Figure 5.1: CCH and scoreplots restricted time range 175 ms [center] and 350 ms [right]

By dividing up the range of the backwards recurrence time of the trigger of 100 ms into 10 intervals $B_1, \ldots, B_n$ and graphing the values of $\mu(B)/\sigma(B)$ as defined in (3.1),(3.2), we obtain Figures (5.2)[center] and (5.2)[right]. These two figures were produced to illustrate the robustness of the method from variations in the range of times between target and the following trigger firings as explained next. 90% thresholds were computed from (3.5) and represented in the picture by a straight horizontal line.

It was shown in Utikal (1994b) that the perceived strength of the effect may crucially depend on the backwards recurrence time of the target at the time of the trigger firing. For the data analysed in this example, the effect was strongly present only for times up to 175 ms and completely disappeared on targets with a backwards recurrence time of more than 350 ms at a trigger firing. This way the effect is "drowned" in the presence of a large number of targets with abnormally high backwards recurrence times. The tests considered here are remarkably invariant against this peril. While the center graph was produced after filtering out all observations with backwards recurrence times exceeding 175 ms at the time of a target firing, this range was increased to 350 ms in the plot of Figure (5.2) [right] with little effect.

Example 2: The firing times of a group of five neurons were measured and analysed by Lindsey et al (1994). A total of 61,247 firings were counted, a segment of the observed series is displayed in Figure 5.2.
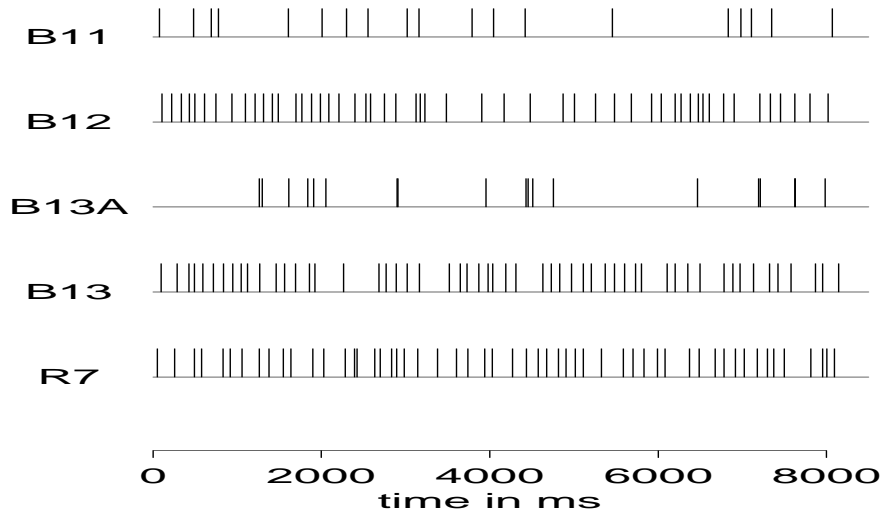
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Figure 5.2: Data MR90.ADT.

	p-value
R7 → B11	0.00
R7 → B12	0.00
R7 → B13A	0.06
B13A → B11	0.00
B13A → B12	0.00
B11 → B12	0.00
B11 → B13	0.03
B12 → B13	0.02

Table 5.1: p-values for ξ_1-test for reduced sample (10,000 firings) indicate significant interactions beyond those detected graphically in Figure 5.3 [right]

Detection tests and estimates of connectivity effects, their strength, and duration were obtained by the above authors using cross correlation based methods. More precisely, based on the CCH a detectability index of Aertsen and Gerstein (1985) was used, defined as "the ratio of the maximum amplitude of departure from the background, d, to the background, divided by the standard deviation of the correlogram noise". This simple ad hoc method requires compution and inspection of a CCH of up to 475 ms to obtain their results.
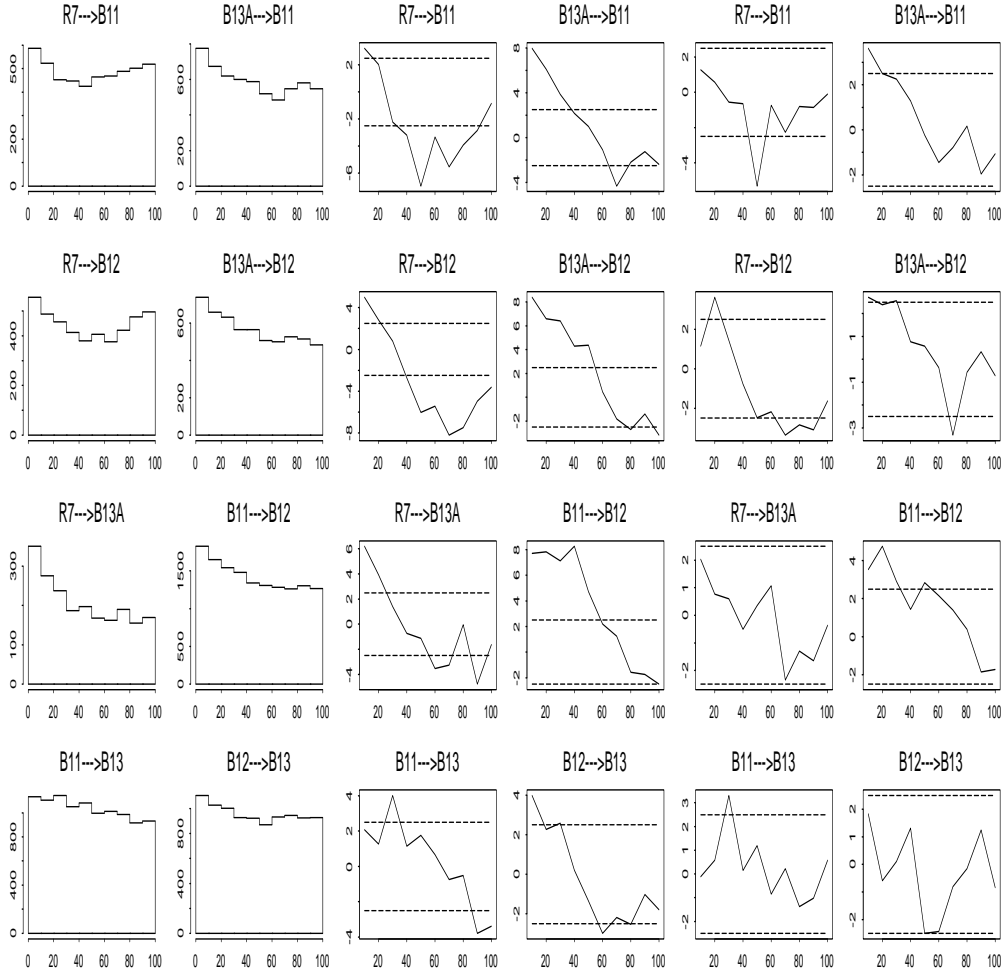
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Figure 5.3: CCH and scores with joint 90% confidence bands; total series
length: 61247 counts [center], 10000 counts [right].

As can be seen from Figure 5.3[center], the one dimensional score plots
$\mu(B)/\sigma(B)$ as defined in (3.1), (3.2) lead to similar conclusions on the connect-
edness of pairs of neurons as those of Lindsey et al (1994) in Figure 5.3[left]. In
order to study dependence of our methods on the sample size, we reduce the
number of observed firings from 61247 to 10000. It comes as no surprise that
the graphical indicators reflect the connectivity relations now in a weaker form,
see Figure 5.3 [right]. However, as is shown in Table 5.1, the test based on ξ_1
still indicates connectivity among *all* pairs considered, even for those for which
the scores remain within the chosen 90% confidence bands in Figure 5.3 [right]
as computed from (3.5).

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We now take the step to extend the analysis from pairs to triplets of neurons, i.e. trigger1, trigger2, target. We use a partition of the square with sides 0 to 100 ms into 36 subsquares {B}. These are formed by considering different ranges for the duration of time since trigger firings. Also included is the region of particular importance in which one trigger has already fired but the other trigger has not yet fired since the last target firing. This region is represented by the bands of 6 squares each limited by the horizontal axes in the plots of Figure 5.4. It can be seen from those plots that in all three cases of triplets considered a clear distinction emerges in the firing patterns of the target after a firing of trigger1, depending if trigger2 has fired already or still has not done so: If trigger2 (i.e. B11, respectively B13A) has not fired, trigger1 (i.e. R7) inhibits the target as consistent with the one dimensional scoreplots and the CCH of Figure 5.3. But the exciting effects of trigger1 can only be detected (in case one) *after* a firing of trigger2. The excitatory effects of trigger1 are consistent with those displayed in Figure 5.3 but can only be recognized with clarity during the first 40 ms after a firing of trigger2. Inhibition by trigger1 is independent of trigger2 in the third case. Given that both triggers have fired, their effects on the target seem manifest only if the firings take place consecutively within a short amount of time (i.e. 20-40ms). Using (3.5), we determine an approximate 90% region between two planes intersecting the vertical axes at ± 3.
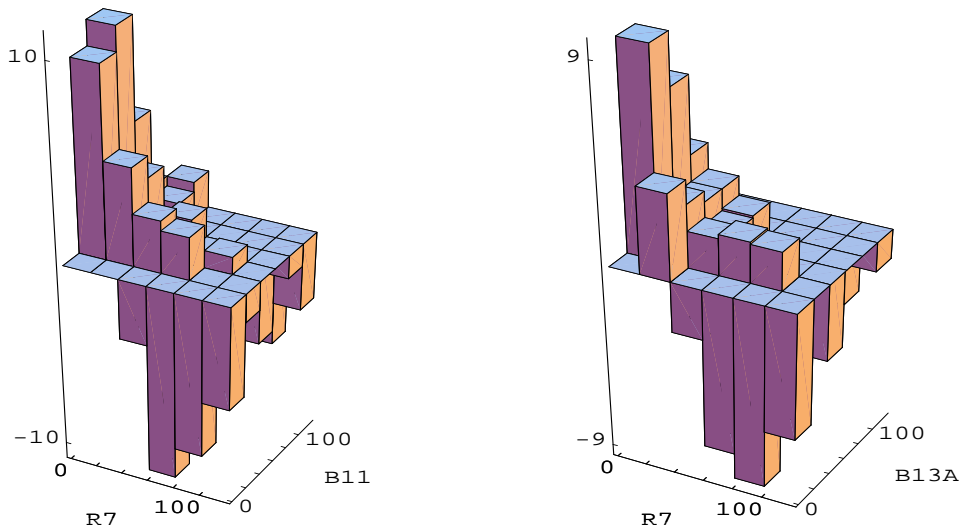

Figure 5.4 a, b. Both scoreplots show inhibition of B12 by R7 *only before* a firing of B11 [left] resp. B13A [right]. Excitation can be detected *only after* a firing of B11[left] but independent of B13A[right].
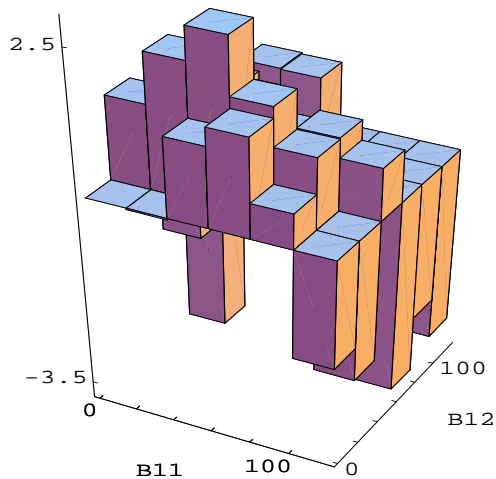
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Figure 5.4 c. Scoreplot shows that inhibition of B13 by B11 independent of B12.

6 Proofs

The proofs use standard techniques from intensity based counting process and martingale theory as exposed e.g. in Karr (1986) combined with facts from the theory of Markov processes.

Repeated applications of the central limit theorem for martingales and the weak law of large numbers for Markov chains are left indicated and details of the proofs are omitted.

For ease of exposition we restrict attention to the case of two neurons, i.e. model (2.2) with $r = 1$. The proof of Theorem 3.1 exploits the Markov property of the backwards recurrence process

$$\mathbf{Z}(t) = (t - \tau_{N(t-)}, t - \tau^{(1)}_{N^{(1)}(t-)}).$$

Denote by $\mathcal{F}_t$ the sigma-field generated by the internal history of $\mathbf{Z}$, i.e.

$$\mathcal{F}_t = \sigma(\{\mathbf{Z}(v), \quad 0 \leq v < t\}) \tag{6.1}$$

and $\{\tau_1^*, \tau_2^*, \ldots\}$ as the jump times of $N(t) + N^{(1)}(t)$. As is further explained in Utikal (1995b), the processes $\{\mathbf{Z}(\tau_n^*)\}$ and $\{\mathbf{Z}(\tau_n)\}$ are $\mathcal{F}_{\tau_n^*}$- respectively $\mathcal{F}_{\tau_n}$- Markov chains with a one-dimensional state space and transition densities determined by $\alpha, \alpha^{(1)}$. Under the conditions that $\alpha, \alpha^{(1)}$ are continuous and

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strictly positive, Doeblin's condition (condition "D" on p. 192 of Doob (1953)) is satisfied which implies the existence of a limiting density f to which the transition densities converge exponentially fast. In what follows all (unconditional) expected values are taken with respect to this limiting distribution. More precisely, suppose that $f(x|x_1)$ is the transition density of $\{\mathbf{Z}(\tau_n^*)\}$. Then

$$|f^{(n)}(x|x_1) - f(x)| \leq C\rho^n \tag{6.2}$$

uniformly in x, x_1 for some generic constants $C > 0, \rho \in (0,1)$. Similarly, if $A_n(x|x_1)$ is the hazard of the transition distribution, i.e.

$$\int_0^x f^{(n)}(v|x_1)dv = 1 - e^{-A_n(x|x_1)}$$

then

$$|dA_n(x|x_1) - dA_n(x)| \leq C\rho^n dx. \tag{6.3}$$

In what follows we will describe the transitions using counting process intensities. For given τ_n define the one-step jump processes

$$\begin{aligned}
N_n(s) &= I\{\tau_{n+1} \leq \tau_n + s\} \\
Y_n(s) &= I\{\tau_n + s \leq \tau_{n+1}\}
\end{aligned}$$

and the filtration

$$\mathcal{F}_n(s) = \mathcal{F}(\tau_n + s) = \sigma\{\mathbf{Z}(v), 0 \leq v < \tau_n + s\}. \tag{6.4}$$

Then with respect to $\mathcal{F}_n(s)$ the following semi-martingale decomposition of $N_n(s)$ holds:

$$dN_n(s) = Y_n(s)\,\alpha(\mathbf{Z}(\tau_n + s))\,ds + dM_n(s) \tag{6.5}$$

where the quadratic variation process of M is given by

$$d < M_n > (s) = Y_n(s)\,\alpha(\mathbf{Z}(\tau_n + s))\,ds \tag{6.6}$$

where α is defined in (2.2a).

Under H_0 formulas (6.5), (6.6) simplify to

$$\begin{aligned}
dN_n(s) &= Y_n(s)\,\alpha(s)\,ds + dM_n(s) \\
d < M_n > (s) &= Y_n(s)\,\alpha(s)\,ds.
\end{aligned}$$

We now come to the description of the process $\mu_t(B), \sigma_t^2(B)$ defined in (3.1), (3.2). Define

$$\begin{aligned}
\chi_n(s) &= I\{\tau_n + s - \tau_{N^{(1)}(\tau_n+s-)}^{(1)} \in B\}\,, \\
S1_n(s) &= \sum_{i=1}^n \chi_i(s)Y_i(s)\,, & \overline{N}_n(s) &= \sum_{i=1}^n N_i(s) \\
S0_n(s) &= \sum_{i=1}^n Y_i(s)\,, & \overline{M}_n(s) &= \sum_{i=1}^n M_i(s)\,.
\end{aligned}$$

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In this notation we have

$$\mu_B^{(n)} = \sum_{i=1}^{n} \int_0^{\mathbf{T}} \chi_i(v)\, dN_i(v) - \int_0^{\mathbf{T}} \frac{S1(v)}{S0(v)}\, d\overline{N}(v)$$

and $\sigma_B^{2(n)}$ similarly.

To proof Theorem 3.1 we observe that

$$\sum_{i=1}^{n} \int_0^s \chi_i\, dN_i - \int_0^s \frac{S1}{S0}\, d\overline{N} = \sum_{i=1}^{n} \int_0^s \chi_i\, (dN_i - Y_i d\Lambda) - \int_0^s \frac{S1}{S0} \left(d\overline{N} - S0\, d\Lambda\right) \quad (6.7)$$

where Λ is any function of bounded variation. Now, under H_0 we choose $d\Lambda = \alpha(s)\, ds$ and write

$$\mu_B^{(n)} = I_1^{(n)} - I_2^{(n)} + I_3^{(n)} \tag{6.8}$$

where

$$I_1^{(n)} = \sum_{i=1}^{n} \int_0^{\mathbf{T}} (\chi_i - \frac{\mathbf{E}\,\chi}{\mathbf{E}\,Y})dM_i$$

$$I_2^{(n)} = \int_0^{\mathbf{T}} \frac{S1 - n\mathbf{E}\,\chi}{n\mathbf{E}\,Y} d\overline{M}$$

$$I_3^{(n)} = \int_0^{\mathbf{T}} \frac{S1}{S0} \frac{S0 - n\mathbf{E}\,Y}{n\mathbf{E}\,Y} d\overline{M}$$

where the expectation is taken with respect to the limiting distribution.

To show convergence of $(1/\sqrt{n})I_1^{(n)}$, we introduce the processes

$$I_1^{(n+1)}(s) = I_1^{(n)} + \int_0^s (\chi_{n+1} - \frac{\mathbf{E}\,\chi}{\mathbf{E}\,Y})dM_{n+1}.$$

Note that $I_1^{(n+1)}(s)$ is an $\mathcal{F}_n(s)$-martingale (see (6.4)) with quadratic variation

$$d < I_1^{(n)} > (s) = \left(\chi_{n+1}(s) - \frac{\mathbf{E}\,\chi(s)}{\mathbf{E}\,Y(s)}\right)^2 Y_{n+1}\alpha(\mathbf{Z}(\tau_{n+1} + s))ds \quad .$$

It now follows from application of a martingale central limit theorem for compensated counting integrals using the weak law of large numbers for Markov chains that $1/\sqrt{n}\ \ I_1^{(n)}$ converges to a Gaussian random variable with mean zero and variance σ^2 equal to the limit in probability of $< I_1^{(n)} > (\infty)/n$. It remains to show that $I_2^{(n)}/\sqrt{n}$ and $I_3^{(n)}/\sqrt{n}$ are negligible. We start with the following lemma.

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Lemma 1:

$$\mathbf{E}_0(\int_0^{\mathbf{T}} (\mathrm{S}1 - n\mathbf{E}\ \chi)d\overline{M})^2 = O(n^2)$$

as $n \to \infty$, where $\mathbf{E}_0$ is the expectation with respect to the initial distribution of the process.

Proof: Introduce the notation $\hat{\chi}_i = \chi_i - \mathbf{E}\chi$. Then

$$\mathbf{E}_0(\int_0^{\mathbf{T}} (\mathrm{S}1 - n\mathbf{E}\ \chi)\ d\overline{M})^2 = \mathbf{E}_0(\sum_{i_1,i_2} \int_0^{\mathbf{T}} \hat{\chi}_{i_1}\ dM_{i_2})^2$$

$$= \sum_{i_1,i_2,i_3,i_4} \mathbf{E}_0 \int_0^{\mathbf{T}} \hat{\chi}_{i_1}\ dM_{i_2} \int_0^{\mathbf{T}} \hat{\chi}_{i_3}\ dM_{i_4}\ . \tag{6.9}$$

For all four indices different we consider the following two cases.

First case: $\quad i_4 > \max\{i_1, i_2, i_3\}$.

Using the martingale property we conclude

$$\mathbf{E}_0 \int_0^{\mathbf{T}} \hat{\chi}_{i_1}\ dM_{i_2} \int_0^{\mathbf{T}} \hat{\chi}_{i_3}\ dM_{i_4} = \mathbf{E}_0 \left(\int_0^{\mathbf{T}} \hat{\chi}_{i_1}\ dM_{i_2} \mathbf{E}_0 \left(\int_0^{\mathbf{T}} \hat{\chi}_{i_3}\ dM_{i_4} | \mathcal{F}_{i_4}(0) \right) \right) = 0$$

Second case: $\quad i_3 > \max\{i_1, i_2, i_4\} = i$.

$$\left| \mathbf{E}_0 \int_0^{\mathbf{T}} \hat{\chi}_{i_1}\ dM_{i_2} \int_0^{\mathbf{T}} \hat{\chi}_{i_3}\ dM_{i_4} \right| \le \mathbf{E}_0 \left| \int_0^{\mathbf{T}} \hat{\chi}_{i_1}\ dM_{i_2} \int_0^{\mathbf{T}} \mathbf{E}_0(\hat{\chi}_{i_3} | \mathcal{F}_i(0))\ dM_{i_4} \right|$$

But $|\mathbf{E}_0(\hat{\chi}_{i_3} | \mathcal{F}_i)| \le C\rho^{-(i_3-i)}$ by exponential convergence of the transition densities (6.1). This and the uniform boundedness of the first integral imply that

$$\sum_i \sum_{i_3 > i} \mathbf{E}_0 | \int_0^{\mathbf{T}} \hat{\chi}_{i_1} dM_{i_2} \int_0^{\mathbf{T}} \hat{\chi}_{i_3} dM_{i_4} |$$

is uniformly bounded.

We next have to consider the possibility that any two of $\{i_1, i_2, i_3, i_4\}$ are equal. Hence we consider the additional case.

Third case: $\quad i_2 = i_4$.

If $\max\{i_1, i_3\} > i_4$ we can argue as in the previous case. On the other hand, if $i_4 > \max\{i_1, i_3\} = i$ we use the martingale property to conclude that

$$\begin{aligned}
\mathbf{E}_0 \int_0^{\mathbf{T}} \hat{\chi}_{i_1}\ dM_{i_2} \int_0^{\mathbf{T}} \hat{\chi}_{i_3}\ dM_{i_4} &= \mathbf{E}_0 \int_0^{\mathbf{T}} \hat{\chi}_{i_1} \hat{\chi}_{i_3}\ d < M_{i_4} > \\
&= \mathbf{E}_0 \int_0^{\mathbf{T}} \hat{\chi}_{i_1} \hat{\chi}_{i_3} \mathbf{E}_0(d < M_{i_4} > | \mathcal{F}_i(0)) \\
&= \left(\mathbf{E}_0 \int_0^{\mathbf{T}} \hat{\chi}_{i_1} \hat{\chi}_{i_3} \mathbf{E}_0 Y_{i_4}\ dA \right) \left(1 + O(\rho^{-(i_4-i)}) \right)
\end{aligned}$$

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where the last equation follows from exponential convergence of the hazards of the transition densities (6.2). Now by arguing as in the second case, we obtain for the first summand on the right hand side above

$$|\mathbf{E}_0 \int_0^{\mathbf{T}} \hat{\chi}_{i_1} \hat{\chi}_{i_3} \mathbf{E}_0 Y_{i_4} \, dA| \le C\rho^{-|i_1 - i_3|}.$$

The cases that three or four of the indices are equal needs no further consideration since the summands of (6.9) are uniformly bounded. $\square$

To apply this result we observe that $\mathbf{E} \text{ S0}(v) \ge \mathbf{E} \text{ S0}(\mathbf{T}) > n\varepsilon$ for some $\varepsilon > 0$ because of the strict positivity and continuity of $\alpha, \alpha^{(1)}$. Hence the lemma implies that $I_2^{(n)} = O_p(1)$ as $n \to \infty$. To show that the third term on the right-hand side of (6.7) is negligible, a similar argument to that of Lemma 1 is applied using that $|\text{S1}/\text{S0}| \le 1$. The proof is lengthy but straightforward and will be omitted. This concludes the proof of part (i).

Parts (ii) and (iii) of Theorem 3.1 are proved using similar arguments. Define

$$\xi_n(B,s) = I\{\tau_n + s - \tau^{(1)}_{N^{(1)}(\tau_n+s-)} \in B\}$$

$$\text{S1}_n(B,s) = \sum_{i=1}^n \xi_i(B,s).$$

We observe that with

$$\mathcal{M}_n(B,s) = \sum_{i=1}^n \int_0^s \left(\xi_i(B) - \frac{\mathbf{E}\xi(B)}{\mathbf{E} \, Y} \right) \, dM_i$$

the martingales $\mathcal{M}_n(B_{r_1}, \cdot), \mathcal{M}_n(B_{r_2}, \cdot)$ are orthogonal for $B_{r_1} \cap B_{r_2} = \emptyset$. Their joint convergence is then shown using the Cramer Wold device and the martingale central limit theorem. $\square$

To prove consistency of the test, i.e. Corollary 3.4, we assume the model (2.5), (2.6) i.e. $d\Lambda_i = \lambda_0(s) \, Y_i(s) \, (1 + \texttt{hi} \, \chi_i(s))$ and obtain a partition similar to (6.3)

$$\sum_{i=1}^n \int \chi_i \, dN_i - \int \frac{\text{S1}}{\text{S0}} \, d\overline{N} = \sum_{i=1}^n \int \chi(dN_i - Y_i d\Lambda_i) - \int \frac{\text{S1}}{\text{S0}}(d\overline{N} - \sum_{i=1}^n Y_i \, d\Lambda_i) + I_4^{(n)} + I_5^{(n)}$$

where

$$I_4^{(n)} = \sum_{i=1}^n \int \chi_i Y_i \, d\Lambda_i$$

$$I_5^{(n)} = -\sum_{i=1}^n \int \frac{\text{S1}}{\text{S0}} Y_i \, d\Lambda_i.$$

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It follows by the same arguments as before that the first two terms on the right hand side above are $O(n^{-\frac{1}{2}})$. Now, by the law of large numbers

$$\frac{1}{n}I_4^{(n)} \longrightarrow \int_0^{\mathbf{T}} \mathbf{E}\chi Y(1+ \texttt{hi}\ \chi)\lambda_0\, ds$$

$$-\frac{1}{n}I_5^{(n)} \longrightarrow \int_0^{\mathbf{T}} \frac{\mathbf{E}\ \chi}{\mathbf{E}\ Y}\mathbf{E}Y(1+ \texttt{hi}\ \chi)\lambda_0\, ds = \int_0^{\mathbf{T}} \frac{\mathbf{E}\chi Y}{\mathbf{E}Y}\mathbf{E}Y(1+ \texttt{hi}\ \chi)\lambda_0\, ds$$

such that under the condition of the model $(1/n)(I_4^{(n)} + I_5^{(n)}) \longrightarrow 0$ if and only if $\texttt{hi} = 0$. This can be seen as follows. Denote the above limits by I_4 and I_5. By elementary probability calculus it can be seen that

$$\mathbf{E}\ \chi\ Y(1+\texttt{hi}\ \chi) \geq \frac{\mathbf{E}\ \chi\ Y}{\mathbf{E}\ Y}\mathbf{E}\ Y(1+\texttt{hi}\ \chi). \tag{6.10}$$

If $\texttt{hi}\neq 0$ equality can hold only if $\mathbf{E}\chi Y = \mathbf{E}Y$, i.e. $\mathbf{E}(X|Y) = 1$ or $\mathbf{E}(Y|X = 0) = 0$. This is in contradiction to the hypothesis of strict positivity of α in model (2.2). Therefore the inequality in (6.10) is strict. Because of continuity of $\mathbf{E}\chi, \mathbf{E}Y, \mathbf{E}\chi Y$ and positivity of λ_0 this implies strict inequality of I_4 and I_5. $\qquad\square$

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