Identification of noisy response latency

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In many physical systems there is a time delay before an applied input (stimulation) has an impact on the output (response), and the quantification of this delay is of paramount interest. If the response can only be observed on top of an indistinguishable background signal, the estimation can be highly unreliable, unless the background signal is accounted for in the analysis. In fact, if the background signal is ignored, however small it is compared to the response and however large the delay is, the estimate of the time delay will go to zero for any reasonable estimator when increasing the number of observations. Here we propose a unified concept of response latency identification in event data corrupted by a background signal. It is done in the context of information transfer within a neural system, more specifically on spike trains from single neurons. The estimators are compared on simulated data and the most suitable for specific situations are recommended.

I. INTRODUCTION

The formal representation of series of uniform events appearing randomly in time as a stochastic point process is common in several branches of physics [1]. Here we investigate one specific problem related to this representation and discuss it in a common application of the theory, namely, studies on information transfer in neural systems. However, the methodology is applicable in any other field in which the following scenario can be found. Assume a series of primary events observable for a period of time. At a known time instant, either controlled by an experimenter or induced by an external event, an additional stream of indistinguishable events is added to the original one. The question is what the waiting time is to the first event coming from the new source. Obviously, taking the time to the first event after the defined time instant may give a very biased answer. The problem is common in computational neuroscience and we use its terminology and reasoning.

The only way a neuron can transmit information about rapidly varying signals is by a series of all or none events: the action potentials (spikes or firings). An action potential is taken in the limit as a Dirac delta function and thus a spike train may be considered as a realization of a stochastic point process [2,3]. A characteristic of neuronal units of different types is the existence of so-called spontaneous activity, i.e., the generation of spikes without any (controlled) stimulation, usually with a low firing rate. It can, as a first approximation, be described by a Poisson process with constant intensity [3]. It is not possible to analyze the transfer of information within the nervous system without investigating the effect of changing conditions [4]. A common experimental approach, especially for studying the sensory systems, is the presentation of a stimulus and checking if and how the neuron responds to it. The general reason is that the information about the stimulus is encoded in the reaction. It has been shown experimentally and theoretically that the spike latency (vaguely described as the time between stimulation and neuronal response) contains important information in auditory, visual, olfactory, and somatosensory modalities [5–16]. In Ref. [17] the latency is studied experimentally and described by a mathematical function. Therefore, the precise definition and determination of the response latency appear as important problems.

An often applied technique for the stimulated neuronal activity involves estimates of the firing rate profile. The estimated latency to a response is the first instant following the stimulus onset in which the firing rate changes significantly. In statistical terminology, this is a change-point estimation in the intensity (firing rate) function. Three alternative latency estimation methods were provided in Ref. [18], all based on detecting the time at which the firing rate increases from the baseline. In Ref. [19] formal statistical tests for latency effects were proposed and a detailed study of statistical properties of estimation and testing methods was conducted. Also Ref. [20] discussed whether the first-spike latency could be a candidate neural code and an algorithm for detecting the first-spike latency for a single neuron was presented. It was based on detecting a change in the spontaneous discharge Poisson process model caused by evoked spikes. All of these methods are based on finding the point where the firing rate of the underlying point process has changed [21–25]. However, many behavioral responses are completed so fast that the underlying sensory processes cannot rely on estimation of the neural firing rate over an extended time window. Then the approach has to be based on finding the first spike that appeared due to the stimulation. Of course, this implicitly assumes that the response is excitatory.

Another often applied approach is based on assuming that the first spike after the stimulus onset is caused by the stimulus. In Ref. [26] the first-spike latency is defined as the time from the onset of a stimulus to the time of occurrence of the first-response spike. In neurons without spontaneous activity, the response latency can be easily determined. However, in

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neurons possessing spontaneous spiking, the assessment of the response latency is more complicated. The first spike after the stimulus may be caused by the spontaneous activity rather than the stimulus itself. In Ref. [27] shifts in the first-spike latencies in inferior colliculus neurons produced by iontophoretically applied serotonin were demonstrated. Neurons that showed spontaneous activity higher than a fixed firing rate were excluded from that study. In this way, the bias caused by the possibility that the first spike after the stimulation is spontaneous rather than evoked was avoided. An alternative to an estimator of the latency could be a constant deduced from the physical properties of the system under consideration [28].

As shown, the terminology of response latency is rather broad. In the literature, with a few exceptions, the response latency is identified with the first-spike latency or it is defined as the delay between the stimulus onset and the evoked modulation in neural activity. Our aim is to present a unified concept of the response latency, which includes two types of response latencies, absolute and relative. Furthermore, statistical procedures to deduce the properties of these quantities are proposed and compared in simulated experiments, extending the methods in Refs. [29,30].

II. CHARACTER OF EXPERIMENTAL DATA

In a typical neuronal recording session, a stimulus is presented and the spike generation times from the stimulus onset are recorded. Unfortunately, also the spontaneous activity (firing prior to the stimulation) is inevitably included in the record. The trials are repeated after a period of time ensuring that the effect of stimulation has disappeared. The situation is illustrated in Fig. 1 together with definitions of quantities that
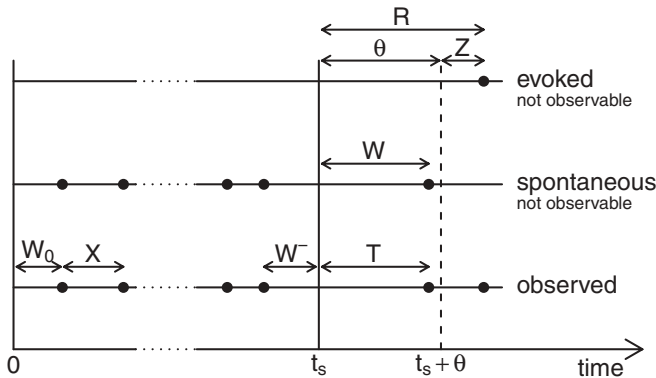

FIG. 1. Schematic description of the single experimental trial. Spikes are indicated with dots. At time 0 the measurements start and at time t_s a stimulus is applied. W (R) denotes the time to the first spontaneous (evoked) spike after t_s. For an observer, they cannot be distinguished. Here T represents the time to the first spike after the stimulus onset and is measured. In the presence of an *absolute response latency* θ, the response latency R is given by $\theta + Z$ and no evoked spikes can occur in $[t_s, t_s + \theta]$. In contrast, spontaneous spikes might occur in that time interval. The *relative response latency* Z denotes the time to the first evoked spike after $t_s + \theta$, the spontaneous ISIs are denoted by X, and the first spike after 0 is denoted by W_0. Finally, W^- corresponds to the backward recurrence time, defined as the time to the last spontaneous spike before t_s.

can be measured during the experiment and the ones we wish to deduce. The recorded spike train starts at time zero and is composed of spontaneously fired action potentials up to time t_s when the stimulation is presented. After that, the recorded spike train contains spontaneous spikes up to the moment of the first evoked spike. We assume that the spontaneous activity is not affected by the stimulus up to the first evoked spike. What happens after the first evoked spike is outside the scope of our study. The experiment is repeated n times and the recorded spike trains create n statistically indistinguishable trials.

In each trial we assume that there is at least a single spike prior to the stimulation, so there is an observable time interval W_0, defined as the time from 0 to the first spontaneous spike before t_s. Commonly, there is a set of complete interspike intervals (ISIs) between time 0 and t_s, denoted by X (see Fig. 1). In the theory of stochastic point processes, the quantity W_0 is called the forward recurrence time. The stimulation at time t_s divides the current interspike interval into two subintervals: the time from the last spontaneous spike to the instant of stimulation W^- (in the theory of stochastic point processes denoted as the backward recurrence time) and the time between the stimulation and the first spike after it, denoted by T. In most of the literature on stimulated neuronal activity, this time is called latency or response time or first-spike latency. However, imagine that the first spike after the stimulation onset is still not influenced or generated by the stimulation itself and would be there even in the absence of stimulation. Thus the spikes after the stimulation are either spontaneous or evoked, and for an observer these are indistinguishable. The situation is illustrated in Fig. 1. We denote the time to the evoked spike by R and call it *response latency*. We assume that the response latency is the sum of two components: *absolute* and *relative* response latency. The absolute response latency is denoted by θ and is defined as the time from the stimulation where no evoked spike can occur. The primary aim of the paper is to determine this delay. If the first spike after the stimulation is part of the prevailing spontaneous activity (which ends by the first evoked spike), this interval is denoted by W. Note that neither W nor R is observed, only their minimum T,

$$T = \min(R, W). \tag{1}$$

We assume that W and R are independent, i.e., the spontaneous and the stimulated activities are not related before the first evoked spike.

It follows from Eq. (1) and the independence of R and W that

$$\mathbb{P}(T > t) = \mathbb{P}[\min(R, W) > t] = \mathbb{P}(R > t)\mathbb{P}(W > t). \tag{2}$$

We are interested in understanding the role of the spontaneous activity in the response latency. In particular, we want to calculate the risk of failure when assuming $T = R$. This is the second aim of the paper. Consider therefore

$$p = \mathbb{P}(W < R) = \mathbb{P}(T = W), \tag{3}$$

i.e., the probability that the first observed spike after the stimulus onset is spontaneous. Obviously, $\mathbb{P}(T = R) = 1 - p$.

Throughout the paper, capital letters are used to stress that the quantities are random variables and lowercase

letters indicate their realizations. The cumulative distribution function (CDF) of a generic random variable Y is denoted by $F_Y(t) = P(Y \leqslant t)$, its survival function $1 - F_Y(t)$ by $\bar{F}_Y(t)$, its probability density function (PDF) by $f_Y(t)$, and the empirical CDF (ECDF) by $F_{Y;n}(t) = \frac{1}{n} \sum_{i=1}^{n} \mathbb{1}_{\{Y_i \leqslant t\}}$, where $\mathbb{1}_A$ is the indicator function of the set A. The average is denoted by $\bar{y} = \frac{1}{n} \sum_{i=1}^{n} y_i$. Finally, we use subindex i ($i = 1, \ldots, n$) for the serial number of the trial and subindex j ($j = 1, \ldots, m_i$) for the spontaneous ISIs in the time interval $[0, t_s]$ in the ith repetition.

III. MODEL

A. Spontaneous activity

If the spontaneous firing follows a renewal process model, the $X_{ij}(i = 1, \ldots, n; j = 1, \ldots, m_i)$ are independent and identically distributed random variables. Then the CDF of W is given by [31]

$$F_W(t) = \frac{\int_0^t [1 - F_X(x)]dx}{\mathbb{E}[X]} \qquad (4)$$

and it follows that the mean of W is

$$\mathbb{E}[W] = \frac{\mathbb{E}[X^2]}{2\mathbb{E}[X]}. \qquad (5)$$

In fact, Eq. (4) is also true under a less restrictive assumption. It is sufficient that the data are stationary, but when they are not independent, it can be difficult to estimate F_X. If the data are stationary, then the forward and the backward recurrence times W^- and W follow the same distribution [32]. Under this assumption, it is enough to know t_s and the involved pair of spikes in each trial. Even if the process is not stationary, it will be approximately true as long as the process is only slowly drifting.

Therefore, we consider two sampling strategies in the paper. Either all ISIs, i.e., the X_{ij}'s, prior to the stimulation enter in the statistical evaluation of the latency or only the time from the last spike prior to the stimulation, namely, W^-, can be used.

The simplest model to describe the spontaneous firing activity, often supported by experimental data [2,3], is a Poisson process and we will not consider other parametric models. Then X follows an exponential distribution with mean ISI equal to $1/\lambda > 0$ and PDF

$$f_X(t) = \lambda e^{-\lambda t}, \quad t > 0. \qquad (6)$$

In this case, as directly follows from Eq. (4), $f_{W_0}(\cdot) = f_{W^-}(\cdot) = f_W(\cdot) = f_X(\cdot)$.

To summarize, throughout the paper we consider separately the following three assumptions about the distribution of the ISIs before stimulation: (a) the renewal assumption, using all data prior to the stimulation in the analysis; (b) the stationarity assumption (or only slowly drifting), using only the backward recurrence time W^- in the analysis; and (c) the parametric assumption, i.e., independent and exponentially distributed ISIs, using all data prior to the stimulation in the analysis.

B. Neural response to a stimulus

Let the absolute response latency $\theta \geqslant 0$ be a constant and assume that no evoked spike can occur before time $t_s + \theta$. Under the approach employed here, the total time from stimulation to the first evoked spike can be rewritten as

$$R = \theta + Z,$$

where the relative response latency Z is a random variable accounting for the time between the end of the delay and the first evoked spike. The primary aim of this article is to determine the absolute response latency θ.

By definition, F_R is a shifted distribution with delay (or shift) θ, i.e.,

$$F_R(t) = 0 \quad \text{if } t \in [0,\theta], \quad F_R(t) > 0 \quad \text{if } t > \theta.$$

The presence of the absolute response latency implies $\mathbb{P}(T > t) = \mathbb{P}(Z > t - \theta)\mathbb{P}(W > t)$ and the CDF of R becomes

$$F_R(t) = F_Z(t - \theta) = \begin{cases} 0 & \text{if } t \in [0,\theta] \\ 1 - \frac{1 - F_T(t)}{1 - F_W(t)} & \text{if } t > \theta. \end{cases}$$

Therefore, R follows a shifted distribution with shift θ and distribution family F_Z. Likewise, the CDF of T is

$$\begin{aligned} F_T(t) &= 1 - [1 - F_Z(t - \theta)][1 - F_W(t)] \\ &= \begin{cases} F_W(t) & \text{if } t \in [0,\theta] \\ F_W(t) + F_Z(t - \theta)[1 - F_W(t)] & \text{if } t > \theta. \end{cases} \end{aligned} \qquad (7)$$

Thus θ satisfies

$$\theta = \inf\{t > 0 : F_T(t) \neq F_W(t)\}, \qquad (8)$$

which we will use to define a nonparametric estimator of θ. If it is reasonable to assume specific distributions, the following result will be useful to define parametric estimators of θ. For any (shifted or nonshifted) distribution family of R with $\theta \geqslant 0$, the nth moment of T is given by (see Appendix A)

$$\mathbb{E}[T^n] = \mathbb{E}[W^n]\left\{1 - e^{-\lambda\theta} \sum_{j=0}^{n-1} \frac{\lambda^j}{j!} \sum_{h=0}^{j} \binom{j-h}{h} \theta^h \mathcal{L}_Z^{(j-h)}(\lambda)\right\}. \qquad (9)$$

Here $\mathcal{L}_Z(s)$ denotes the Laplace transform of f_Z, i.e., $\mathcal{L}_Z(s) = \mathbb{E}[e^{-sZ}] = \int_0^\infty e^{-st} f_Z(t)dt$. The kth derivative is denoted by $\mathcal{L}_Z^{(k)}(\cdot)$. In particular, the first two moments are

$$\mathbb{E}[T] = \mathbb{E}[W][1 - e^{-\lambda\theta}\mathcal{L}_Z(\lambda)], \qquad (10)$$

$$\mathbb{E}[T^2] = \mathbb{E}[W^2]\{1 - e^{-\lambda\theta}[(1 + \lambda\theta)\mathcal{L}_Z(\lambda) + \lambda\mathcal{L}_Z^{(1)}(\lambda)]\}. \qquad (11)$$

The second aim of this paper is to estimate the probability p, given by Eq. (3). In Appendix B it is shown that

$$p = 1 - e^{-\lambda\theta}\mathcal{L}_Z(\lambda) = \frac{\mathbb{E}[T]}{\mathbb{E}[W]}, \qquad (12)$$

where the last equality follows from Eq. (10). Note that trivially $p \geqslant P(W \leqslant \theta) = 1 - e^{-\lambda\theta}$ and we therefore always have

$$\theta \leqslant -\frac{\ln(1 - p)}{\lambda} \qquad (13)$$

with equality if and only if $\mathbb{P}(R = \theta) = 1$. This can also be seen from Eq. (12) since the Laplace transform of a degenerate variable in 0 equals 1 and otherwise is strictly smaller than 1.

In contrast to the spontaneous activity, we have no experimental evidence about the distribution of R. A commonly applied model to describe spike data is the gamma distribution [33,34] and we apply it to describe the relative response latency. Thus $Z \sim \Gamma(\alpha,\beta)$ and therefore R follows a shifted gamma distribution $R \sim \Gamma_{sh}(\theta,\alpha,\beta)$. The gamma distribution has the PDF

$$f_{Z;\Gamma}(t) = \frac{1}{\alpha^\beta \Gamma(\beta)} t^{\beta-1} e^{-t/\alpha}, \quad t > 0 \tag{14}$$

and mean $\mathbb{E}[Z] = \alpha\beta$, implying $\mathbb{E}[R] = \theta + \alpha\beta$. Here $\beta > 0$ and $\alpha > 0$ denote the shape and the scale parameters, respectively, and $\Gamma(\beta)$ denotes the gamma function. In particular, the exponential distribution $R \sim \exp_{sh}(\theta,\omega)$ can be obtained as a special case if in Eq. (14) $\beta = 1$ and $\omega = 1/\alpha$. Then ω reflects the firing frequency. Other distributions, such as the inverse Gaussian, Weibull, or log-normal, can also be employed. For many distributions, $\mathcal{L}_Z^{(1)}(\cdot) = g_Z(\cdot)\mathcal{L}_Z(\cdot)$ for a function g_Z. In particular, for the gamma distribution

$$\mathcal{L}_Z(\lambda) = (1 + \lambda\alpha)^{-\beta}, \quad g_Z(\lambda) = \frac{\alpha\beta}{1 + \lambda\alpha}. \tag{15}$$

IV. PARAMETER IDENTIFICATION

The aim of this paper is the estimation of θ and p. Note that whereas θ is a parameter of the model, p is not. Indeed, p is a probability characterizing the properties of the model, in particular, giving information about the risk of failure when assuming $T = R$.

A. Estimation of the probability that the first spike after stimulus onset is spontaneous

To estimate p expressed by Eq. (12) we need estimators of $\mathbb{E}[T]$ and $\mathbb{E}[W]$. Since T is observed, we simply estimate $\mathbb{E}[T]$ by $\bar{t}$. Under the stationarity assumption when the spontaneous ISIs cannot be used for the statistical evaluation, $\mathbb{E}[W]$ can be estimated by the empirical mean of W^-, $\overline{w^-}$. Under the renewal assumption the X_{ij}'s can be used, but first we make no assumptions about the parametric form of F_X. Using Eq. (5), the mean of W might be estimated from the empirical moments of X, namely, $\bar{x}$ and $\overline{x^2}$. However, due to the predefined finite sampling interval $[0,t_s]$, $\bar{x}$ underestimates $\mathbb{E}[X]$, since only ISIs shorter than t_s can be observed, and the density function

is proportional to the observation length t_s. The bias can be very large if t_s is not large compared to the mean of X, as can be confirmed by simulations (results not shown; see Ref. [33]). The density of the distribution of the sampled ISIs is $\eta^{-1}(t_s - t)f_X(t)$ for $t \in [0,t_s]$ and 0 otherwise, where $\eta = \int_0^{t_s}(t_s - t)f_X(t)dt = \int_0^{t_s} F_X(t)dt$ is the normalizing constant [33]. Therefore, the following sample averages have approximate means $\mathbb{E}[\bar{X}] \approx \eta^{-1}(t_s\mathbb{E}[X] - \mathbb{E}[X^2])$ and $\mathbb{E}[\overline{X^2/(t_s - X)}] \approx \eta^{-1}\mathbb{E}[X^2]$, where we have assumed t_s large enough to use the approximation $\int_0^{t_s} tf_X(t)dt \approx \int_0^\infty tf_X(t)dt = \mathbb{E}[X]$. Isolating $\mathbb{E}[X^2]$ and $\mathbb{E}[X]$ we obtain the estimators

$$\tilde{x^2} = \eta \frac{1}{\sum_{i=1}^n m_i} \sum_{i=1}^n \sum_{j=1}^{m_i} \frac{x_{ij}^2}{t_s - x_{ij}}, \quad \tilde{x} = \eta \frac{\bar{x} + \tilde{x^2}}{t_s}$$

and $\mathbb{E}[W]$ can be estimated by $\tilde{x^2}/2\tilde{x}$. Note that the normalizing constant η cancels out. When $t_s \to \infty$, the estimator converges to the usual empirical estimator. If the parametric approach is applied, i.e., X follows Eq. (6), then the likelihood estimator of λ is [35]

$$\hat{\lambda} = \frac{\sum_{i=1}^n (m_i + 1)}{n t_s}. \tag{16}$$

To summarize, we have the following estimators of p:

$$\hat{p}_a = \frac{2\tilde{x}\bar{t}}{\tilde{x^2}}, \quad \hat{p}_b = \frac{\bar{t}}{w^-}, \quad \hat{p}_c = \bar{t}\hat{\lambda}, \tag{17}$$

under the renewal, the stationarity, and the parametric assumptions, respectively.

B. Estimation of the absolute response latency

We propose several estimators for the absolute response latency θ. The first group makes no assumptions about the distribution of the time to the first evoked spike. One estimator is based on the identification of θ with one of the measured times to the first spike after stimulation. Taking the shortest of them indirectly assumes that there is no spontaneous spike after stimulation. Those that are larger takes into account that there are also some spontaneous spikes mixed with the evoked activity and should depend on n, as will be shown. Another employs Eq. (8) for a nonparametric identification of θ. The other group of estimators assumes that the parametric forms of the distributions of W and R are known, i.e., the method of moments and maximum likelihood inference. The proposed estimators and their assumptions are summarized in Table I.

TABLE I. Proposed estimators of the absolute response latency θ under different assumptions for the spontaneous and evoked activities.

Estimator	Method	Assumption on W	Assumption on R
$\hat{\theta}_1$	$\hat{\theta}_1 = \min\{t_1,\ldots,t_n\}$	model free	model free
$\hat{\theta}_2$	$\hat{\theta}_2 = t^{(k)}, k = \lfloor n\hat{p} \rfloor + 1$	$\hat{\theta}_{2a}$, renewal; $\hat{\theta}_{2b}$, stationary; $\hat{\theta}_{2c}$, F_W known	model free
$\hat{\theta}_3$	based on CDFs	$\hat{\theta}_{3a}$, renewal; $\hat{\theta}_{3b}$, stationary; $\hat{\theta}_{3c}$, F_W known	model free
$\hat{\theta}_4$	maximum likelihood	F_W known	F_R known
$\hat{\theta}_5$	moment estimation	F_W known	F_R known
$\hat{\theta}_6$	maximum likelihood	F_W known	$R \sim \exp_{sh}(\theta,\omega)$

1. Naive estimator of θ

The first estimator $\hat{\theta}_1$ is defined as

$$\hat{\theta}_1 = \min\{t_1, \ldots, t_n\}.$$

It represents a simple estimator that can be used in a preliminary analysis, ignoring the presence of spontaneous activity, i.e., assuming $T = R$. Any other estimator should improve the performance by including the spontaneous activity in the analysis.

Note that any estimator that is defined as the kth-order statistic of $(t_1, \ldots, t_n)$, denoted by $t^{(k)}$ (e.g., $\hat{\theta}_1 = t^{(1)}$), will necessarily go to zero for any fixed k when the sample size increases since the number of spontaneous spikes before time $t_s + \theta$ in the sample will increase with n. In particular, if $Z \sim \exp(\omega)$ the mean of $\hat{\theta}_1$ is given by

$$\mathbb{E}[\hat{\theta}_1] = -\theta e^{-n\lambda\theta} + \frac{1}{n}(1 - e^{-n\lambda\theta}) + \frac{n}{n+1}\theta e^{-(n+1)\lambda\theta - \omega\theta}$$
$$+ \frac{n}{(n+1)(n+2)(\lambda+\omega)}e^{-(n+2)\lambda\theta - 2\omega\theta} \quad (18)$$

(see Appendix C). Note that it goes to zero as $n \to \infty$ independently of the value of θ and therefore it is not consistent. Thus any estimator based on an order statistic should depend on n.

2. Estimator of θ based on the proportion of spontaneous spikes in the sample

To improve $\hat{\theta}_1$, we propose an order statistic estimator depending on n and taking into account the presence of spontaneous activity. The probability that the first spike after the stimulus onset is spontaneous, $\mathbb{P}(T = W) = p$, is the expected proportion of spontaneous spikes. We therefore expect np spontaneous spikes and $n(1 - p)$ evoked spikes in a sample of size n. Thus we propose to estimate θ as the kth-order statistic given by

$$\hat{\theta}_2 = t^{(k)}, \quad k = \lfloor n\hat{p} \rfloor + 1, \quad (19)$$

where $\lfloor x \rfloor$ denotes the integer part of x and $\hat{p}$ is any of the estimators of p. This corresponds to assuming that all the observations $t_i < t^{(k)}$ are spontaneous and all $t_i \geqslant t^{(k)}$ are evoked, while in fact the two distributions overlap, especially if θ is small. Consequently, we expect θ to be overestimated with decreasing bias as θ increases and also not consistent.

3. Estimator of θ based on cumulative distribution functions

A different approach to the estimation of the absolute response latency is to use Eq. (8). Obviously, the estimated distributions are different and we need to define a criterion to distinguish between statistical fluctuation and systematic difference. We propose to use the standard deviation of the difference between $\hat{F}_T(t)$ and $\hat{F}_W(t)$ when $t \leqslant \theta$, denoted by $\sigma(t)$, as a measure of the statistical fluctuation. On $[0, \theta]$, no evoked activity is present and therefore $\sigma(t)$ does not depend on R. Then we estimate θ as the maximum time such that the difference between the two distributions is smaller than the statistical fluctuation $\sigma(t)$, i.e., $\hat{F}_T(t)$ and $\hat{F}_W(t)$ cannot be statistically distinguished. Thus $\hat{\theta}_3$ is defined as

$$\hat{\theta}_3 = \max\{t \in [0, \tilde{t}] : [\hat{F}_T(t) - \hat{F}_W(t)] \leqslant \hat{\sigma}(t)\}, \quad (20)$$

where $\tilde{t}$ is chosen as the time that maximizes the distance between $\hat{F}_T(t)$ and $\hat{F}_W(t)$, i.e.,

$$\tilde{t} = \arg\max_{t \in [0, t^{(n)}]} [\hat{F}_T(t) - \hat{F}_W(t)],$$

and $t^{(n)} = \max(t_1, \ldots, t_n)$. We estimate F_T by the ECDF $F_{T;n}(t)$. The choice of $\hat{F}_W(t)$ depends on the underlying assumptions and determines $\sigma(t)$. To obtain closed and manageable expressions for the level $\sigma(t)$, we will assume that W is exponential and then under this assumption find the distribution of $\sigma(t)$ for the different estimators of λ. In Appendix D it is shown that $\sigma(t)$ is estimated by

$$\sigma_b(t) = \sqrt{\frac{2}{n}e^{-t/\overline{w^-}}(1 - e^{-t/\overline{w^-}})}, \quad (21)$$

$$\sigma_c(t) = \sqrt{\frac{1}{n}e^{-\hat{\lambda}t}(1 - e^{-\hat{\lambda}t}) + e^{\hat{\lambda}nt_s(e^{-2t/nt_s}-1)} - e^{2\hat{\lambda}nt_s(e^{-t/nt_s}-1)}} \quad (22)$$

under the stationarity and parametric assumptions, respectively. Under the renewal assumption, the calculation of $\sigma(t)$ becomes more complicated. We therefore approximate $\sigma(t)$ by $\sigma_c(t)$, estimating λ by $2\tilde{x}/\tilde{x^2}$. We expect $\hat{\theta}_3$ to be consistent, as observed from simulations, since $\hat{F}_{T;n}$ and $\hat{F}_W$ converge to the true distributions F_T and F_W and σ_b and σ_c go to zero as $n \to \infty$.

4. Parametric approach: Maximum likelihood estimation of θ

The density of the distribution of T derived from Eq. (7) assuming $F_W(t) = 1 - e^{-\lambda t}$ is

$$f_T(t) = e^{-\lambda t}f_Z(t - \theta)\mathbb{1}_{\{t>\theta\}} + \lambda e^{-\lambda t}[1 - F_Z(t - \theta)\mathbb{1}_{\{t>\theta\}}], \quad (23)$$

where we have introduced the indicator function in the expression to emphasize the allowed values of t, which will be useful when evaluating the log-likelihood function $\sum_{i=1}^{n} \ln f_T(t_i)$ at the sampled values. The presence of θ complicates the inference because the likelihood function is not differentiable with respect to θ. Therefore, we should maximize directly the log-likelihood function to obtain an estimator of θ. We denote by $\hat{\theta}_4$ the maximum likelihood estimator (MLE) of θ.

Assume $R \sim \exp_{sh}(\theta, \omega)$ and thus $Z \sim \exp(\omega)$. The likelihood equation for ω is

$$0 = \sum_{i=1}^{n} \frac{1 - (\lambda+\omega)(t_i-\theta)}{\lambda+\omega}\mathbb{1}_{\{t_i>\theta\}}. \quad (24)$$

Note that from Eq. (24), only the sum $\lambda + \omega$ can be estimated. Estimate λ by Eq. (16) and obtain $\hat{\omega}$ as the solution of Eq. (24) for fixed θ as

$$\widehat{\omega + \lambda} = \frac{\sum_{i=1}^{n} \mathbb{1}_{\{t_i>\theta\}}}{\sum_{i=1}^{n}(t_i-\theta)\mathbb{1}_{\{t_i>\theta\}}}, \quad \hat{\omega} = \widehat{\omega + \lambda} - \hat{\lambda}.$$

The profile likelihood becomes

$$\tilde{l}_t(\theta) = -\hat{\lambda}\sum_{i=1}^n t_i + \sum_{i=1}^n [\hat{\lambda}(t_i - \theta) - 1]\mathbb{1}_{\{t_i > \theta\}}$$
$$+ \sum_{i=1}^n \ln(\widehat{\omega}\mathbb{1}_{\{t_i > \theta\}} + \hat{\lambda}).$$

Since $\tilde{l}_t(\theta)$ is strictly increasing for $\theta \in (t_i, t_{i+1})$, with $i = 1, \ldots, n-1$, it follows that θ can be estimated as the time $t_i - \epsilon$ maximizing $l_t(\theta)$, with $\epsilon > 0$ small enough, which can be maximized numerically to obtain $\hat{\theta}$.

Now assume $R \sim \Gamma_{\text{sh}}(\theta, \alpha, \beta)$ and thus $Z \sim \Gamma(\alpha, \beta)$. The log-likelihood function becomes

$$l_t(\theta, \alpha, \beta) = -\hat{\lambda}\sum_{i=1}^n t_i + \sum_{i=1}^n \ln\{f_{Z;\Gamma}(t_i - \theta)\mathbb{1}_{\{t_i > \theta\}}$$
$$+ \hat{\lambda}[1 - F_{Z;\Gamma}(t_i - \theta)\mathbb{1}_{\{t_i > \theta\}}]\},$$

which can be maximized numerically to obtain the unknown parameters θ, α, and β. Here $F_{Z;\Gamma}(t) = \gamma(\beta, t/\alpha)/\Gamma(\beta)$, where $\gamma(\beta, t/\alpha)$ is the lower incomplete gamma function. Even if the likelihood function is not differentiable with respect to θ, we expect that the MLE is consistent, as observed from simulations.

5. Parametric approach: Moment estimator of θ

A different approach when $X \sim \exp(\lambda)$ and the distribution family of R is given consists in equating the theoretical moments of T given by Eq. (9) with the empirical moments. In particular, we solve a system of equations given by the first two or three moments in the two or three unknown parameters, namely, (θ, ω) when $Z \sim \exp(\omega)$ or (θ, α, β) when $Z \sim \Gamma(\alpha, \beta)$. We denote by $\hat{\theta}_5$ the moment estimator (ME) of θ.

Assume $R \sim \exp_{\text{sh}}(\theta, \omega)$ and estimate λ by Eq. (16). From Eqs. (10), (11), (15), and (E3) for $\beta = 1$ and $\alpha = 1/\omega$ we obtain

$$\theta = \frac{p - \frac{\mathbb{E}[T^2]}{\mathbb{E}[W^2]}}{\lambda(1-p)} - \frac{1}{\lambda + \omega}, \quad 1 - p - e^{-\lambda\theta}\frac{\omega}{\omega + \lambda} = 0.$$

Replacing $p, \mathbb{E}[T^2], \lambda$, and $\mathbb{E}[W^2]$ by $\hat{p}, \overline{t^2}, \hat{\lambda}$, and $2/\hat{\lambda}^2$ we can solve the system with respect to ω and θ.

Now assume $R \sim \Gamma_{\text{sh}}(\theta, \alpha, \beta)$. From Eqs. (10) and (15) we get

$$\beta = -\frac{\ln(1-p) + \lambda\theta}{\ln(1+\lambda\alpha)}.$$

Plugging β into Eq. (11) we get

$$\theta = \frac{\left(p - \frac{\mathbb{E}[T^2]}{\mathbb{E}[W^2]}\right)(1+\lambda\alpha)\ln(1+\lambda\alpha) + \lambda\alpha(1-p)\ln(1-p)}{\lambda(1-p)[(1+\lambda\alpha)\ln(1+\lambda\alpha) - \lambda\alpha]}.$$

Substituting β and θ into Eq. (9) for $n = 3$, we obtain an equation in α that can be solved numerically.

Unfortunately, the moment equations do not always have a solution with positive parameters for a given sample. This is

due to the following inequality, which is shown in Appendix E:

$$\frac{\mathbb{E}[T^2]}{\mathbb{E}[W^2]} > p + (1-p)\ln(1-p). \quad (25)$$

It is always fulfilled from a theoretical point of view, but, as we will see later, the empirical counterpart might not be satisfied in a particular sample, especially if n is small or θ is large, in which case the moment estimator is not well defined. From the law of large numbers, the ME is consistent since it is expressed as a differentiable function of averages.

V. SIMULATION STUDY

A. Setup

We simulated a spontaneous spike train following a Poisson process with firing rate $\lambda = 1\text{s}^{-1}$ for a time period up to the first spike after 10s and thus $\mathbb{E}[W] = 1\text{s}$. At time $t_s = 10\text{s}$, the evoked activity was simulated by shifted exponentially ($\omega = 10\text{s}^{-1}$) or gamma distributed ($\alpha = 0.05\text{s}$ and $\beta = 2$) random variables R such that $\mathbb{E}[Z] = 0.1\text{s}$. Then we obtained a realization of T using Eq. (1). The empirical data end with the first spike after stimulus and therefore the recording of spikes ended at T. This was repeated to obtain samples of size n, where n varied between 10 and 150 in steps of 10, and each sample was repeated for different values of θ between 0.05 and 0.4 in steps of 0.025. For these values of θ, p was varying from 0.14 to 0.39. Finally, for each value of n and θ, we repeated this procedure 10 000 times, obtaining 10 000 statistically indistinguishable and independent trials.

We denote by $\hat{\theta}_a, \hat{\theta}_b$, and $\hat{\theta}_c$ the estimators of θ under the renewal, the stationarity, and the parametric assumptions and likewise for p. It is also of interest to evaluate how a misspecification of the model influences the statistical inference. We denote by $\hat{\theta}_6$ the misspecified estimator of θ, computed as $\hat{\theta}_4$ under the wrong assumption $Z \sim \exp(\omega)$, when in fact it is gamma distributed, $Z \sim \Gamma(\alpha, \beta)$.

To compare different estimators, we use the relative mean error R_{ME} to evaluate the bias and the relative mean square error R_{MSE}, which incorporates both the variance and the bias. They are defined as the average over the 10 000 repetitions of the quantities

$$E_{\text{rel}}(\hat{\theta}) = \frac{\hat{\theta} - \theta}{\theta}, \qquad E_{\text{rel sq}}(\hat{\theta}) = \frac{(\hat{\theta} - \theta)^2}{\theta^2}$$

and likewise for p.

B. Results for p

In Fig. 2 we report the $R_{\text{ME}}(\hat{p})$ and $R_{\text{MSE}}(\hat{p})$ when R is shifted exponential or gamma distributed with $\mathbb{E}[Z] = 0.1\text{s}$ for different values of n and θ. As expected, all $R_{\text{ME}}(\hat{p})$ and $R_{\text{MSE}}(\hat{p})$ decrease as n increases. For fixed n, $R_{\text{ME}}(\hat{p})$ is approximately constant, i.e., the performance of $\hat{p}$ does not depend on θ. This is expected because the bias is primarily due to the estimator of λ, which does not depend on θ. Also the $R_{\text{MSE}}(\hat{p})$ is approximately constant for fixed n, which is explained by the mean of T that is changing with θ, and estimated by a simple average and thus unbiased. The variance is primarily determined by the sample size and is only slowly varying with θ. The parametric estimator $\hat{p}_c$ largely
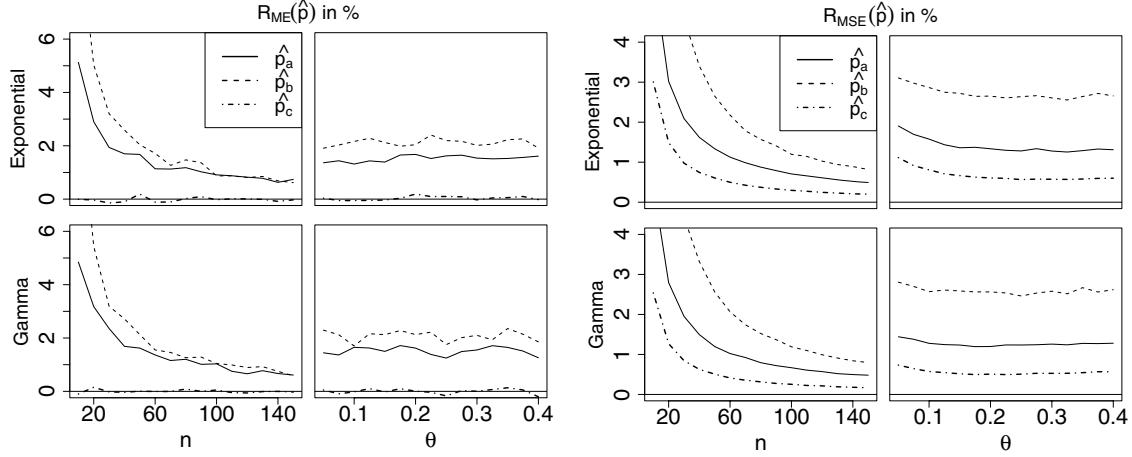
FIG. 2. Dependence of $R_{\mathrm{ME}}(\hat{p})$ and $R_{\mathrm{MSE}}(\hat{p})$ (average over 10 000 simulations) on the number of observations and the absolute response latency when W is exponential with rate $\lambda = 1\mathrm{s}^{-1}$. Top panels: Z is exponential with rate $\omega = 10\mathrm{s}^{-1}$. Bottom panels: Z is gamma with $\alpha = 0.05\mathrm{s}$ and $\beta = 2$. In both cases $\mathbb{E}[Z] = 0.1\mathrm{s}$. Left panels: Different values of n for fixed $\theta = 0.2\mathrm{s}$, with $p \approx 0.26$. Right panels: Different values of θ for fixed $n = 50$. Here p varies between 0.14 and 0.39. Also shown are the estimators of p under the renewal assumption $\hat{p}_a$ (solid line), the stationarity assumption $\hat{p}_b$ (dashed line), and the parametric assumption $\hat{p}_c$ (dot-dashed line), given by Eq. (17).

outperforms the other two, it has no bias, and R_{MSE} is less than 1%, even for a sample size as small as $n = 30$. The other two overestimate p, which is also expected, since they are ratios of positive estimators, which tend to have heavy right tails. Furthermore, $\hat{p}_a$ performs better than $\hat{p}_b$ with respect to both R_{ME} and R_{MSE}. This happens because $\hat{p}_a$ and $\hat{p}_c$ use all ISIs sampled before the stimulation, whereas $\hat{p}_b$ uses only the time from the last spike before stimulation, W^-. Thus $\hat{p}_a$ and $\hat{p}_c$ are based on a larger sample size, reducing the estimation error, compared to $\hat{p}_b$. To conclude, with only a sample size of $n = 50$ the error is less than 3% and p appears to be well estimated by any of the proposed estimators, even for small sample sizes.

C. Results for θ

It follows from Eq. (18) that $\hat{\theta}_1$ has an R_{ME} between -70% and -100% when R belongs to a shifted exponential distribution family with $\theta \in (0, 0.4]$ and n between 10 and 150. This is confirmed in simulations (results not shown) and emphasizes the importance of not ignoring the spontaneous activity in the analysis. Since the other estimators take the spontaneous activity into account, we expect that $|R_{\mathrm{ME}}(\hat{\theta})| \leqslant |R_{\mathrm{ME}}(\hat{\theta}_1)|$ and we do not consider $\hat{\theta}_1$ further.

Figure 3 shows $R_{\mathrm{ME}}(\hat{\theta})$ and Fig. 4 shows $R_{\mathrm{MSE}}(\hat{\theta})$, focusing only on those estimators, which have errors less than 10%. For this reason, the ME of the gamma distribution is not shown. Indeed, it performs better than $\hat{\theta}_1$, but is still unacceptable, probably due to the large number of samples where the estimator is not well defined (see below). Considerable improvement is observed with $\hat{\theta}_2$, which is the best nonparametric estimator when n is small or θ is large and always has a smaller variance than $\hat{\theta}_3$. When n increases, $R_{\mathrm{ME}}(\hat{\theta}_2)$ reaches an asymptotic level away from 0 that depends on how much the distributions F_W and F_R overlap. This is due to the assumption that all the spontaneous spikes come before the evoked spikes. A good feature of $\hat{\theta}_2$ is that it does not seem to depend on the underlying assumption for F_W since the R_{ME} and R_{MSE} of

$\hat{\theta}_{2;a}$, $\hat{\theta}_{2;b}$, and $\hat{\theta}_{2;c}$ are almost identical. When n is large or θ is small $\hat{\theta}_3$ is the best nonparametric estimator. Simulations show that it depends only slightly on the underlying assumptions for
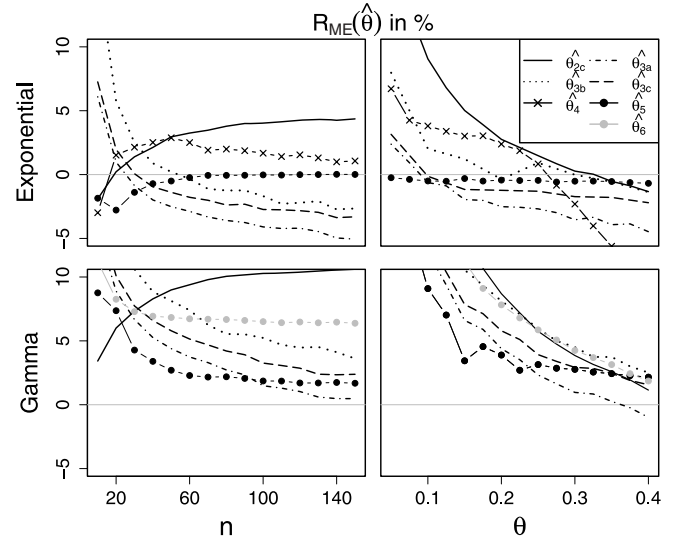

FIG. 3. Dependence of $R_{\mathrm{ME}}(\hat{\theta})$ (average over 10 000 simulations) on the number of observations and the absolute response latency when W is exponential with rate $\lambda = 1\mathrm{s}^{-1}$ for estimators with errors less than 10%. Top panels: Z is exponential with rate $\omega = 10\mathrm{s}^{-1}$. Bottom panels: Z is gamma with $\alpha = 0.05\mathrm{s}$ and $\beta = 2$. In both cases $\mathbb{E}[Z] = 0.1\mathrm{s}$. Left panels: Different values of n and $\theta = 0.2\mathrm{s}$. Right panels: Different values of θ and $n = 50$. The following estimators are shown: the p estimator $\hat{\theta}_{2;c}$ under the parametric assumption (solid line); the CDF estimators $\hat{\theta}_3$ under the renewal assumption (dot-dashed line), the stationarity assumption (dotted line), or the parametric assumption (long-dashed line); the MLE $\hat{\theta}_4$ (circles); the ME $\hat{\theta}_5$ (crosses) (only in the top panels); and the misspecified estimator $\hat{\theta}_6$ (gray circles) (only in the bottom panels). The estimators $\hat{\theta}_2$ under the renewal and stationarity assumptions $\hat{\theta}_{2;a}$ and $\hat{\theta}_{2;b}$ are not reported since they are almost identical to $\hat{\theta}_{2;c}$.
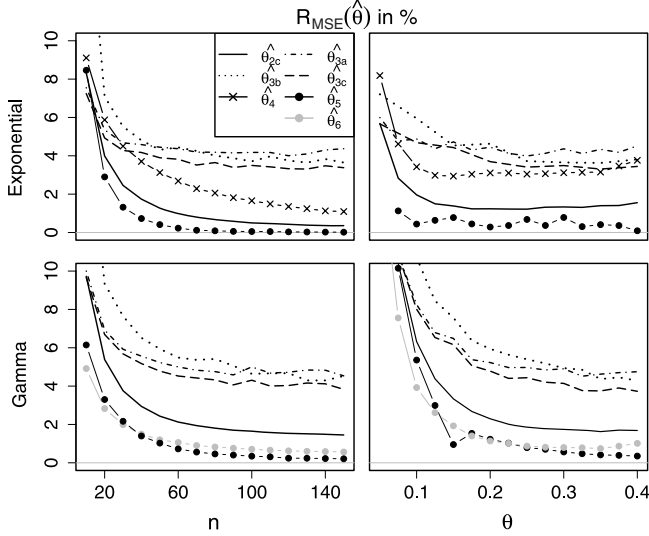
FIG. 4. Dependence of $R_{\mathrm{MSE}}(\hat{\theta})$ (average over 10 000 simulations) on the number of observations and the absolute response latency when W is exponential with rate $\lambda = 1\mathrm{s}^{-1}$ for estimators with errors less than 10%. Top panels: Z is exponential with rate $\omega = 10\mathrm{s}^{-1}$. Bottom panels: Z is gamma with $\alpha = 0.05\mathrm{s}$ and $\beta = 2$. Left panels: Different values of n and $\theta = 0.2\mathrm{s}$. Right panels: Different values of θ and $n = 50$. The following estimators are shown: the p estimator $\hat{\theta}_{2;c}$ under the parametric assumption (solid line); the CDF estimators $\hat{\theta}_3$ under the renewal assumption (dot-dashed line), the stationarity assumption (dotted line), or the parametric assumption (long-dashed line); the MLE $\hat{\theta}_4$ (circles); the ME $\hat{\theta}_5$ (crosses) (only in the top panels); and the misspecified estimator $\hat{\theta}_6$ (gray circles) (only in the bottom panels). The estimators $\hat{\theta}_2$ under the renewal and stationarity assumptions $\hat{\theta}_{2;a}$ and $\hat{\theta}_{2;b}$ are not reported since they are almost identical to $\hat{\theta}_{2;c}$.

F_W. The error is in all cases small even for moderate sample sizes.

As expected, the MLE provides the best estimates of θ. The ME is acceptable only when Z follows an exponential distribution. The MLE is more reliable than the ME approach, as is usually observed comparing MEs and MLEs. In particular, for $n = 50$ fixed the $R_{\mathrm{ME}}(\hat{\theta}_5)$ gets worse for large θ. This is probably due to the fact that the estimator is defined only if the parameter condition (25) is satisfied, which is often not the case, especially for large θ or small n. The percentages of the simulated samples where the estimator is undefined are reported in Fig. 5. Note that the right-hand side of Eq. (25) is increasing in p. Therefore an estimate $\hat{p}$ much larger than the true p tends to violate condition (25) and the ME is not defined.

Interestingly, the misspecified $\hat{\theta}_6$ that wrongly assumes Z exponentially distributed when $R \sim \Gamma_{\mathrm{sh}}(\theta, \alpha, \beta)$ gives acceptable estimates of θ, even if more biased, but with approximately the same R_{MSE} as the correct MLE. This would of course not be the case for the other parameters α and β.

The results might depend on the particular choice of the distribution for Z and its parameter values. Simulations were also conducted for the inverse Gaussian distribution and for $\beta = 0.8$ and 10 in the gamma distribution (results not shown). The results for the estimation of θ are similar, though a larger sample size is needed when $\beta = 10$.
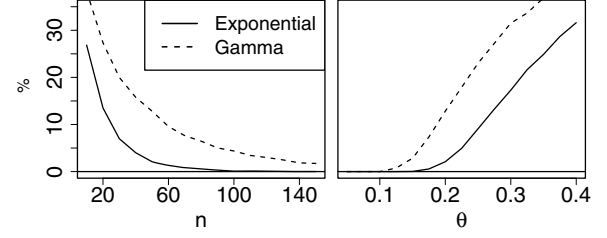

FIG. 5. Percentage of repetitions out of 10 000 that do not fulfill condition (25). For these data sets, the ME $\hat{\theta}_5$ cannot be evaluated. Here W is exponential with rate $\lambda = 1\mathrm{s}^{-1}$; Z is exponential with rate $\omega = 10\mathrm{s}^{-1}$ (solid line) or Z is gamma with $\alpha = 0.05\mathrm{s}$ and $\beta = 2$ (dashed line). Left panels: Different values of n for fixed $\theta = 0.2\mathrm{s}$. Right panels: Different values of θ for fixed $n = 50$.

VI. CONCLUSION

It can be discussed if the model in this paper reflects the biology correctly, more specifically, whether the spontaneous and the evoked activity can be distinguished once the stimulus is applied, since both are being produced by the same neuron. First, during the absolute latency no spike is influenced by the stimulus and the activity is thus well described by the spontaneous spikes. Second, during the response latency, our aim is simply to estimate how the time dynamics of spikes is changed by the stimulus. Further, the model can be considered a more general model. Assume that the observed output comes from a cluster of processing units, e.g., neurons, and some of these are changed by the stimulus and others are not, but they cannot be distinguished. This scenario would originate an observed response as described by our model.

A shortcoming of the analysis is the limitation of using only the first spike after the stimulus onset, ignoring the possible information carried by the entire spike train. The approach pursued here of first-spike coding is an alternative to the frequency coding principle. It would be interesting to extend the methods developed in this paper over the entire spike train after stimulus onset.

To conclude, numerical simulations emphasize the importance of taking into account the spontaneous activity W when estimating θ in order to avoid a serious bias. We suggest choosing the MLE if it is reasonable to assume that the evoked activity follows an exponential or gamma distribution, leading to a parametric estimation of θ. If no information about the distribution of R is available, we suggest applying the p estimator $\hat{\theta}_2$, which always estimates θ reasonably well, is easy to compute, and gives the same performance for any of the underlying assumptions for F_W. For simplicity, or from lack of knowledge of R, we also suggest using the misspecified estimator $\hat{\theta}_6$, assuming an evoked activity exponential, which does not appear to introduce a large error in the estimation of θ.

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APPENDIX A: MOMENTS OF *T*

</div>

Assume that $X \sim \exp(\lambda)$ and R belongs to a shifted distribution family. Then the nth moment of T can be calculated using Eq. (23) as follows:

$$\mathbb{E}[T^n] = \int_0^\infty t^n f_T(t)dt = \int_0^\theta t^n f_W(t)dt + \int_\theta^\infty t^n \{f_Z(t-\theta)[1-F_W(t)] + f_W(t)[1-F_Z(t-\theta)]\}dt\, dt$$

$$= \int_0^\infty t^n f_W(t)dt - \int_0^\infty (y+\theta)^n f_W(y+\theta)F_Z(y)dy + \int_0^\infty (y+\theta)^n f_Z(y)[1-F_W(y+\theta)]dt$$

$$= \mathbb{E}[W^n] - \int_0^\infty (y+\theta)^n \lambda e^{-\lambda(y+\theta)}F_Z(y)dy + \int_0^\infty (y+\theta)^n f_Z(y)e^{-\lambda(y+\theta)}. \tag{A1}$$

The second term can be solved by integration by parts:

$$\int_0^\infty (y+\theta)^n \lambda e^{-\lambda(y+\theta)}F_Z(y)dy$$

$$= \sum_{k=0}^n \frac{n!}{(n-k)!}\frac{1}{\lambda^k}\int_0^\infty (y+\theta)^{n-k}f_Z(y)e^{-\lambda(y+\theta)}dy. \tag{A2}$$

Using the binomial theorem, the $(n-k)$th power of $(y+\theta)$ can be expanded as

$$(y+\theta)^{n-k} = \sum_{h=0}^{n-k}\binom{n-k}{h}y^{n-k-h}\theta^h.$$

Therefore, the integral in Eq. (A2) becomes

$$\int_0^\infty (y+\theta)^{n-k}f_Z(y)e^{-\lambda(y+\theta)}$$

$$= e^{-\lambda\theta}\sum_{h=0}^{n-k}\binom{n-k}{h}\theta^h\int_0^\infty y^{n-k-h}e^{-\lambda y}f_Z(y)dy$$

$$= e^{-\lambda\theta}\sum_{h=0}^{n-k}\binom{n-k}{h}\theta^h \mathcal{L}_Z^{(n-k-h)}(\lambda), \tag{A3}$$

where $\mathcal{L}_Z^{(j)}(\lambda)$ is the jth derivative of the Laplace transform of Z evaluated in λ. By plugging Eq. (A3) into Eq. (A2) and then into Eq. (A1), noting that the term for $k=0$ cancels out with the last integral in Eq. (A1), we finally obtain

$$\mathbb{E}[T^n] = \mathbb{E}[W^n]\bigg\{1 - e^{-\lambda\theta}\sum_{k=1}^n \frac{\lambda^{n-k}}{(n-k)!}\sum_{h=0}^{n-k}\binom{n-k}{h}$$

$$\times \theta^h \mathcal{L}_Z^{(n-k-h)}(\lambda)\bigg\},$$

where we have used that $\mathbb{E}[W^n] = n!/\lambda^n$. The final expression (9) is obtained by the change of index $j = n - k$.

<div align="center">

APPENDIX B: CALCULATION OF *p*

</div>

Assume that X follows Eq. (6) and R belongs to a shifted distribution family. To compute the probability p that the first spike after the stimulus onset is spontaneous, we proceed as follows. Define $U = R + (-W)$. Then

$$p = \mathbb{P}(W < R) = \mathbb{P}(U > 0) = \int_0^\infty f_U(t)dt,$$

where f_U is the convolution of f_R and $f_{(-W)}$. Here $f_{(-W)}$ is defined by

$$f_{(-W)}(s) = f_W(-s)\mathbb{1}_{\{s\leqslant 0\}} = \lambda e^{\lambda s}\mathbb{1}_{\{s\leqslant 0\}}$$

and $f_R(t) = f_Z(t-\theta)\mathbb{1}_{\{t\geqslant 0\}}$. Then the density f_U is given by

$$f_U(t) = \int_{-\infty}^\infty f_R(u)f_{(-W)}(t-u)du$$

$$= \int_t^\infty f_Z(u-\theta)\mathbb{1}_{\{u>\theta\}}\lambda e^{\lambda(t-u)}du$$

$$= \lambda e^{\lambda t - \lambda\theta}\left[\mathcal{L}_Z(\lambda)\mathbb{1}_{\{0\leqslant t\leqslant\theta\}} + \mathbb{1}_{\{t>\theta\}}\int_{t-\theta}^\infty f_Z(x)e^{-\lambda x}dx\right]$$

and therefore p becomes

$$p = \lambda e^{-\lambda\theta}\mathcal{L}_Z(\lambda)\int_0^\theta e^{\lambda t}dt + \lambda e^{-\lambda\theta}\int_\theta^\infty\int_{t-\theta}^\infty e^{\lambda(t-u)}f_Z(u)du\, dt$$

$$= (1-e^{-\lambda\theta})\mathcal{L}_Z(\lambda) + e^{-\lambda\theta}\int_0^\infty\left(\int_\theta^{u+\theta}\lambda e^{\lambda t}dt\right)e^{-\lambda u}f_Z(u)du$$

$$= (1-e^{-\lambda\theta})\mathcal{L}_Z(\lambda) + \int_0^\infty(1-e^{-\lambda u})f_Z(u)du,$$

which implies Eq. (12).

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APPENDIX C: MEAN OF $\hat{\theta}_1$

</div>

Assume that X follows Eq. (6) and R belongs to a shifted exponential family. We have

$$\mathbb{P}(\hat{\theta}_1 > t) = \mathbb{P}(t_1 > t, \ldots, t_n > t)$$

$$= \prod_{i=1}^n[1-F_T(t)] = [1-F_T(t)]^n$$

and therefore $\mathbb{P}(\hat{\theta}_1 \leqslant t) = 1 - [1-F_T(t)]^n$ with density $n[1-F_T(t)]^{n-1}f_T(t)$. From Eq. (7) we obtain

$$\mathbb{E}[\hat{\theta}_1] = \int_0^\theta nt[1-F_W(t)]^{n-1}(t)f_W(t)dt$$

$$+ \int_\theta^\infty nt[1-F_W(t)]^n[1-F_Z(t-\theta)]^{n-1}f_Z(t-\theta)dt$$

$$+ \int_\theta^\infty nt[1-F_W(t)]^{n-1}[1-F_Z(t-\theta)]^n f_W(t)dt,$$

which implies Eq. (18).

APPENDIX D: STATISTICAL FLUCTUATION OF $\hat{F}_T(t) - \hat{F}_W(t)$

Assume $t \in [0, \theta]$. The variance of the difference between $\hat{F}_T(t)$ and $\hat{F}_W(t)$, denoted by $\sigma^2(t)$, is defined as

$$\sigma^2(t) = \text{Var}[\hat{F}_T(t) - \hat{F}_W(t)]$$
$$= \text{Var}[\hat{F}_T(t)] + \text{Var}[\hat{F}_W(t)] - 2\,\text{Cov}[\hat{F}_T(t), \hat{F}_W(t)].$$
$$(D1)$$

Define $A_{n;t} = \sum_{i=1}^{n} \mathbb{1}_{\{t_i \leqslant t\}}$; then $\hat{F}_{T;n} = A_{n;t}/n$. Here $A_{n;t}$ counts the number of observations $t_i \leqslant t$. Under the stationarity assumption $\hat{F}_W(t) = \hat{F}_{W^-;n}(t) = B_{n;t}/n$, where $B_{n;t} = \mathbb{1}_{\{w_i^- \leqslant t\}}$. Since $F_T(t) = F_{W^-}(t)$ for all $t \in [0, \theta]$, it follows that $A_{n;t}$ and $B_{n;t}$ are identically distributed random variables with covariance given by

$$\text{Cov}(A_{n;t}, B_{n;t}) = \sum_{i=1}^{n} \sum_{j=1}^{n} \text{Cov}\big(\mathbb{1}_{\{t_i \leqslant t\}}, \mathbb{1}_{\{w_j^- \leqslant t\}}\big)$$
$$= n\,\text{Cov}\big(\mathbb{1}_{\{t_j \leqslant t\}}, \mathbb{1}_{\{w_j^- \leqslant t\}}\big)$$
$$= n[\mathbb{P}(W \leqslant t, W^- \leqslant t) - F_W(t)^2]. \quad (D2)$$

In the second equality we have used that t_i and w_j^- are independent for $i \neq j$. If X follows Eq. (6), then the joint PDF of W and W^- at time (r, s), denoted by $f_{W^-;W}(r, s)$, is given by $\lambda^2 e^{-\lambda(r+s)}$ [36]. Therefore,

$$\mathbb{P}(W^- \leqslant t, W \leqslant t) = \int_0^t \int_0^t f_{W^-;W}(r, s)\,dr\,ds$$
$$= \int_0^t \lambda e^{-\lambda r}\,dr \int_0^t \lambda e^{-\lambda s}\,ds = F_W(t)^2.$$

Thus, by Eq. (D2), $\text{Cov}(A_{n;t}, B_{n;t}) = 0$. Note that this is not generally true; it is due to the memoryless property of the exponential distribution. In general, the backward and the forward recurrence times are negatively correlated. Plugging $F_{T;n}(t)$ and $F_{W^-;n}(t)$ into Eq. (D1), we obtain

$$\sigma_b^2(t) = \text{Var}[F_{T;n}(t) - F_{W^-;n}(t)] = \frac{2}{n^2}\text{Var}(A_{n;t})$$
$$= \frac{2}{n} F_W(t)[1 - F_W(t)].$$

Then the standard deviation $\sigma_b(t)$ equals Eq. (21).

Under the parametric assumption $\hat{F}_W = 1 - e^{-\hat{\lambda}t}$. Then Eq. (D1) becomes

$$\sigma_c^2(t) = \frac{1}{n} F_W(t)[1 - F_W(t)] + \text{Var}(e^{-\hat{\lambda}t}) + \frac{2}{n}\text{Cov}(A_{n;t}, e^{-\hat{\lambda}t})$$
$$= \frac{1}{n}(1 - e^{-\lambda t})e^{-\lambda t} + \text{Var}(e^{-\hat{\lambda}t}), \quad (D3)$$

where the covariance is null because of the same reasons as above. Rewrite Eq. (16) as

$$\hat{\lambda} = \frac{\sum_{i=1}^{n} N_i(t_s)}{n t_s} = \frac{N(t_s)}{n t_s},$$

where $N_i(t_s)$ is the random variable counting the number of spontaneous spikes in $[0, t_s]$ in the ith trial. By assumption $N(t_s)$ follows a Poisson distribution with rate $\lambda n t_s$. Therefore,

$$\text{Var}(e^{-\hat{\lambda}t}) = \mathbb{E}[e^{-N(t_s)(2t/n t_s)}] - \mathbb{E}[e^{-N(t_s)(t/n t_s)}]^2$$
$$= \mathcal{L}_{N(t_s)}\left(\frac{2t}{n t_s}\right) - \mathcal{L}_{N(t_s)}^2\left(\frac{t}{n t_s}\right)$$
$$= e^{\lambda n t_s(e^{-2t/n t_s} - 1)} - e^{2\lambda n t_s(e^{-t/n t_s} - 1)}, \quad (D4)$$

where $\mathcal{L}_{N(t_s)}$ denotes the Laplace transform of $f_{N(t_s)}$. Plugging Eq. (D4) into Eq. (D3) and taking the square root, we finally obtain Eq. (22).

APPENDIX E: CONDITIONS ON THE PARAMETERS OF R

From Eq. (12) we have that

$$e^{-\lambda\theta} \mathcal{L}_Z(\lambda) = 1 - p \quad (E1)$$

and it follows

$$\theta = -\frac{\ln(1-p)}{\lambda} + \frac{\ln\mathcal{L}_Z(\lambda)}{\lambda}. \quad (E2)$$

Assume $Z \sim \Gamma(\alpha, \beta)$ and write $\mathcal{L}_Z^{(1)}(\lambda) = g_Z(\lambda)\mathcal{L}_Z(\lambda)$ given by Eq. (15). Using Eq. (E1), rewrite Eq. (11) as

$$\frac{\mathbb{E}[T^2]}{\mathbb{E}[W^2]} = p - (1-p)\lambda[\theta + g_Z(\lambda)]. \quad (E3)$$

Plugging Eq. (E2) into Eq. (E3), we get

$$\frac{\mathbb{E}[T^2]}{\mathbb{E}[W^2]} = p + (1-p)\ln(1-p)$$
$$+ \frac{\beta(1-p)}{1+\lambda\alpha}[\ln(1+\lambda\alpha)(1+\lambda\alpha) - \lambda\alpha].$$

Condition (25) follows by noting that the expression in square brackets on the right-hand side is larger than 0.

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