On Firing Rate Estimation for Dependent Interspike Intervals

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Abstract

A time dependent instantaneous firing rate may be related both to a time-varying behaviour of external inputs and to the lack of independency between ISIs. In this second case, the instantaneous firing rate does not enlighten the role of the ISIs dependencies and the conditional firing rate should be introduced. We propose a non parametric estimator for the conditional instantaneous firing rate for Markov, stationary and ergodic ISIs. An algorithm to check the reliability of the proposed estimator is introduced and its consistency properties are proved. The method is applied to data obtained from a stochastic two compartment model and to in vitro experimental data.

Keywords: Firing rate; Non parametric estimator; Markov ISIs.

1 Introduction

The firing rate characterizes the behaviour of spiking neurons and it is often used to evaluate the information encoded in neural responses. Its use dates back to

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Adrian (1928) who first assumed that information sent by a neuron is encoded in the number of spikes per observation time window. The frequency transfer function is then often studied to illustrate the relationship between input signal and firing rate, taken as constant for a fixed signal. Typically, the firing rate increases, generally non-linearly, with an increasing stimulus intensity (Kandel et al., 2000). The main objection to the use of the transfer function is that it ignores any information possibly encoded in the temporal structure of the spike train. Furthermore, different definitions of rate give rise to different shapes of the frequency transfer function. However, different definitions of rate are equivalent under specific conditions and differ in other instances (see Lansky et al. (2004)).

When the firing rate is not constant, i.e. when the firing is not a Poisson process, specific techniques are necessary to estimate the instantaneous firing rate avoiding artifacts (see Cunningham et al. (2009) for a review). An important tool in this framework is the kernel method. Optimizing the choice of kernels and of bins becomes necessary in the case of a time dependent input (see Shimazaki & Shinomoto (2010), Omi & Shinomoto (2011)). A method to estimate the firing rate in presence of non-stationary inputs was recently proposed in Iolov et al. (2013) for the case of slowly varying signals while Tamborrino et al. (2013) consider also the latency to improve the firing rate estimation.

A time dependent instantaneous firing rate is typically related with a time dependent input disregarding possible alternative causes that can determine this time dependencies. However, a time dependent instantaneous firing rate can also be determined by dependences between ISIs. Farkhooi et al. (2009) report experimental findings of negative serial correlation in ISIs observed in the sensory periphery as well as in central neurons in spontaneous activity. Generally dependences or correlations are studied between ISIs of different neurons of a group while are neglected those between successive ISIs of a single neuron such
as those observed in Farkhooi et al. (2009). These observations may not be related
with input features but may arise, for example, either assuming independent non
exponentially distributed ISIs or jointly dependent ISIs. In the case of dependent
ISIs, the instantaneous firing rate is not the correct tool to analyze data since it
confuses the actual cause of the observed time dependency. To enlighten the role
of the ISIs dependences on the firing rate, a conditional instantaneous firing rate
should be introduced. Indeed by using conditional distributions it is possible to
remove the classical renewal hypothesis (Cox 1970) supporting the analysis of
the instantaneous firing. Hence the past history of the spike train is considered in
instantaneous firing estimation. The instantaneous conditional firing is updated
after each ISI, thus accounting for the dependency between ISIs.

Estimators for the conditional spiking intensity exist in the literature in the
framework of maximum likelihood methods (Brown et al., 2001; Gerhard et al.,
2011). Advantages of such estimators include the possibility to perform tests of
hypotheses, to evaluate efficiency features or to compute standard error. However,
these advantages are based on the assumption that a specific model fits the data
and no result holds when the model is not true or is unknown. Unfortunately, the
model is known in a relative small number of cases and often its choice introduces
non controllable approximations.

Aim of this paper is to determine a conditional firing rate estimator for de-
pendent ISIs avoiding to introduce a model to describe their distribution. We
suggest a non parametric estimator for the instantaneous firing rate, conditioned
on the past history of the spike train. Under suitable hypotheses we prove the
consistency of the proposed estimator.

The paper is organized in the following way. In Section 2 we recall different
definitions of the firing rate taking care to enlighten their features if the ISIs are
dependent. In Section 3 we propose an estimator of the conditional instantaneous
firing rate of a neuron characterized by an ISI sequence that can be modelled as a Markov, ergodic and stationary process. The consistency of this estimator is proved in the Appendix. The direct check of Markov, ergodic and stationary hypotheses on the available data is not easy but it is necessary to make reliable the estimates. Hence in Section 4 we develop a statistical algorithm to validate \textit{a posteriori} our estimation by checking the underlying hypotheses by means of the obtained estimate. In Section 5 we apply the proposed method to estimate the conditional firing rate of simulated dependent ISIs. For this aim we resort to the stochastic two compartment model proposed in \cite{Lansky1999}. Indeed \cite{Benedetto2013} recently showed that suitable choices of the parameters of this simple model allow to generate sequences of ISIs that are statistically Markov, ergodic and stationary. Finally, in Section 6 we apply our results to in vitro experimental data.

2 Definitions of the firing rate

The firing rate can be defined in many different ways. Here we report the most usual definitions, their relationships and which spike train features best enlighten each of them. The ability of each definition to catch the nature of neural code strongly depends on the nature of the observed spike train. Specifically we distinguish the case of independent identically distributed ISIs from the case with dependent ISIs.

Let us describe the spike train through the ISIs and let $T$ be a random variable with the same distribution of the ISIs, shared by the entire spike train. The most used definitions (see amongst others \cite{Burkitt2000, VanRullen2001}) are the inverse of the average ISI

$$1/E(T),$$

(1)
which is commonly called firing rate, and the expectation of the inverse of an ISI
called the instantaneous mean firing rate. Values obtained with the second definition are always larger than those computed on the considered interval through $1/\mathbb{E}(T)$ (Lansky et al., 2004). Identical distribution of ISIs is required to give sense to these definitions.

A different description of spike train makes use of the number of spikes occurred up to time $t$, i.e. the counting process $N(t)$, $t \geq 0$ (see e.g. Cox & Isham, 1980). The quantity $N(t)/t$, is a measure of instantaneous firing rate accounting for the total number of spikes $N(t)$ up to time $t$. The firing rate (1) and the quantity $N(t)/t$ are connected through the well-known asymptotic formula

$$
\frac{1}{\mathbb{E}(T)} = \lim_{t \to \infty} \frac{\mathbb{E}(N(t))}{t}
$$

(Cox, 1970; Rudd & Brown, 1997). An alternative definition of the instantaneous firing rate is (e.g. Johnson, 1996)

$$
\lambda(t) = \lim_{\Delta t \to 0} \frac{\mathbb{E}[N(t+\Delta t) - N(t)]}{\Delta t}.
$$

(4)

This last expression does not consider the cumulative property of $N(t)/t$ that involves the whole history of the spike train. When the ISIs have a common distribution, it can be expressed in terms of the ISIs distribution through

$$
\lambda(t) = \frac{f(t)}{\mathbb{P}(T > t)}.
$$

(5)

where $f(t)$ is the probability density function of the random ISI $T$ (Cox & Lewis, 1966, Chapter 6).
Example 1 (Exponential ISIs with refractory period). To illustrate the use of these quantities let us consider a spike train with exponentially distributed ISIs, which cannot be shorter than a constant $\delta$. This constant $\delta$ models the refractory period of a neuron (Lansky et al., 2004). Then the ISI distribution is $F(t) = \mathbb{P}(T \leq t) = 1 - \exp(-(t - \delta))$, for every $t \geq \delta$. In this case the firing rate (1) and the mean instantaneous firing rate (2) are, respectively,

$$
\frac{1}{\mathbb{E}(T)} = \left(\int_{\delta}^{\infty} te^{-(t-\delta)} \, dt\right)^{-1} = \frac{1}{\delta + 1},
$$

$$
\mathbb{E}(1/T) = \int_{\delta}^{\infty} t^{-1}e^{-(t-\delta)} \, dt = e^{\delta}\Gamma(0,\delta) < \infty, \quad \forall \delta > 0,
$$

where $\Gamma(a,b)$ is the incomplete Gamma function. On the other hand if we compute the instantaneous firing rate by (4) or, equivalently, by (5), we get

$$
\lambda(t) = 1, \quad \forall t > 0.
$$

We explicitly remark that we would obtain the same firing rates in the case of dependent ISIs with the same common distribution, as (1), (2) and (5) do not consider any possible dependence on spike train history.

More realistic instances should consider either dependent and/or not identically distributed random variables. In particular, defining the firing rate as the instantaneous firing rate (4), conditioned on the spike train history,

$$
\lambda^*(t) = \lambda(t|N(s), 0 < s \leq t) = \lim_{\Delta t \to 0} \frac{\mathbb{E}[N(t + \Delta t) - N(t)|N(s), 0 < s \leq t]}{\Delta t},
$$

makes possible to account for ISIs dependencies. Mathematically, function (9) is known as the conditional intensity function of the underlying counting process $N(t)$. It measures the probability of a spike in $[t, t + \delta t)$ when the presence of a spike depends on the history of the spike train. If the process is an inhomogeneous
Poisson process, $\lambda^*(t)$ coincides with the rate of the process. It can also be defined in terms of the ISIs $T_i, i \geq 1$ given the past sequence of the ISIs $(T_j)_{j=1,\ldots,(i-1)}$. Consider a fixed time interval $[0,L]$, $0 < L < \infty$ and denote by $l_1, l_2, \ldots, l_{N(L)}$ the ordered set of the firing epochs until time $L$. Then the ISIs sequence can be expressed as $(T_i = l_i - l_{i-1}, i \geq 1, l_0 = 0)$ and the conditional probability density is

$$f_i(t|T_j, j = 1, \ldots, i-1) = \frac{d}{dt} P(T_i \leq t|T_j, j = 1, \ldots, i-1).$$

(10)

It is now possible to introduce the alternative definition [Daley & Vere-Jones 1988, Section 7.2],

$$\lambda^*(t) = \begin{cases} h(t), & 0 < t \leq l_1, \\ h_i(t - l_i-1|T_j, j = 1, \ldots, i-1), & l_{i-1} < t \leq l_i, i \geq 2. \end{cases}$$

(11)

This definition can be proven equivalent to (9). Here the functions

$$h(t) = -\frac{d}{dt} \ln[S(t)] = \frac{f(t)}{S(t)},$$

(12a)

$$h_i(t|T_j, j = 1, \ldots, i-1) = -\frac{d}{dt} \ln[S_i(t|T_j, j = 1, \ldots, i-1)]$$

$$= f_i(t|T_j, j = 1, \ldots, i-1)$$

$$S_i(t|T_j, j = 1, \ldots, i-1),$$

(12b)

are the ISI hazard rate function and the conditional ISI hazard rate function, respectively. Furthermore, $S(t) = 1 - \mathbb{P}(T \leq t) = 1 - \int_0^t f(s) ds$ and $S_i(t|T_j, j = 1, \ldots, i-1) = 1 - \mathbb{P}(T_i \leq t|T_j, j = 1, \ldots, i-1) = 1 - \int_0^t f_i(s|T_j, j = 1, \ldots, i-1) ds$ are the corresponding survival functions.

**Example 2** (Exponential ISIs with refractory period II). Let us reconsider the example with exponential ISIs in presence of a refractory period. It is obvious
that the conditional instantaneous firing rate coincides with the unconditional instantaneous firing rate \(^8\) when we have independent ISIs.

Then let us assume the presence of dependence between ISIs. Avoiding any attempt to give a biological significance to our example let us here hypothesize that

- the ISI sequence is Markov, i.e. in \((11)\), we have \(h_i(t-l_{i-1}|T_j, j=1, \ldots, i-1) = h_i(t-l_{i-1}|T_{i-1})\).

- the ISIs \(T_i\) and \(T_{i+1}, i \geq 1\), are dependent with joint distribution function

\[
P(T_i \leq \tau, T_{i+1} \leq \vartheta) = F(\tau)F(\vartheta)[1 + [1 - F(\tau)][1 - F(\vartheta)]],
\]

where \(\tau, \vartheta > 0\), \(F(t) = P(T \leq t)\).

If we compute the conditional instantaneous firing rate \(^9\), according to equation \((11)\), we get \(\lambda^*(t) = 1\) for \(\delta < t \leq l_1\), \(\lambda^*(t) = 0\), for \(0 < t \leq \delta\), and

\[
\lambda^*(t) = \begin{cases} 
0, & l_{i-1} < t \leq l_{i-1} + \delta, \\
\frac{1+(1-2e^{-\tau-l_{i-1}-\delta})[1-2e^{-\vartheta-(T_{i+1}-\delta)}]}{2-e^{-\tau-l_{i-1}-\delta}-2e^{-\vartheta-(T_{i+1}-\delta)}+2e^{-\tau-l_{i-1}-\delta}} & l_{i-1} + \delta < t \leq l_i,
\end{cases}
\]

with \(i \geq 2\). Despite the exponential distribution of the ISIs, we note that dependent ISIs determine a time dependent instantaneous firing rate (see Fig. 1 for an example; in blue, for comparison, the instantaneous firing rate \(^4\)).

With the aid of this example, we realize that time-depending instantaneous firing rates can be associated either to non stationarity of the increments of \(N(t)\) or to an underlying dependence structure of the ISIs.

The estimation of the firing rate makes use of the observed ISIs or of the observed counting process. Usually the estimators

\[
\frac{1}{\bar{T}} = \frac{n}{\sum_{i=1}^{n} T_i},
\]
Figure 1: A realization of the theoretical conditional instantaneous firing rate \((13)\) (black) together with the corresponding instantaneous firing rate \((4)\) (grey). Here the parameters are fixed at \((\lambda, \delta) = (1, 0.5)\) and the recorded ISIs are indicated by successive dashed vertical lines. Note that the conditional instantaneous firing rate is updated after each recorded spike. Except the initial period of time after each spike where the conditional instantaneous firing rate is zero (due to presence of refractoriness through the parameter \(\delta\)), in general it is not constant. In order to clarify the contribution of the dependence between consecutive ISIs to the behaviour of the conditional instantaneous firing rate, note that after a very short ISI (such as the one starting right after time \(t = 4\)) the conditional instantaneous firing rate becomes very high (after the time lapse \(\delta\) during which is zero). Viceversa, the ISI recorded around time \(t = 6\), which is quite long, implies a succeeding low conditional instantaneous firing rate. Furthermore notice how the conditional instantaneous firing rate exhibits a relaxation towards the instantaneous firing rate (grey) as time passes (see for instance the ISI starting around \(t = 1\)). This is connected to the fact that memory (dependence) is less and less important as time flows.
\[ \frac{1}{T} = \frac{1}{n} \sum_{i=1}^{n} \frac{1}{T_i}, \]  

(15)

are used for the inverse of the average ISI and for the instantaneous mean firing rate, respectively. The ratio between the number of spikes in \((0, t)\) and \(t\) can be used to estimate \(N(t)/t\). While the considered estimators have a very intuitive meaning if the ISIs are independent and identically distributed they lose their significance for dependent or not identically distributed ISIs.

Estimation techniques for equations (5) and (11) depend upon the knowledge of \(f(t)\) and \(f_i(t|T_j, j = 1, \ldots, i - 1), i = 2, 3, \ldots\), respectively. When these densities are given or hypothesized from data, classical parametric methods can be applied (Kalbfleish & Prentice, 2011). Hazard rate function estimators assuming the independence of the sample random variables have good convergence properties, but they are not applicable to dependent neural ISIs. A contribution to the study of the other cases is the subject of the present paper.

3 Firing rate estimation

The definition (11) of the conditional instantaneous firing rate depends on the hazard rate functions (12a) and (12b) of the underlying ISI process. Hence our firing rate estimation problem is strictly connected to the estimation of these hazard rate functions.

We model the ISIs as a Markov, ergodic and stationary process. Hence the ISIs are identically distributed random variables with shared unconditional probability density function \(f(t)\). Furthermore, due to the Markov hypothesis, the conditional probability density functions (10) become

\[ f_i(t|T_{i-1} = \tau, T_j = t_j, j = 1, \ldots, i - 2) = f_i(t|T_{i-1} = \tau) = f(t|\tau), \quad \forall i \geq 1. \]  

(16)
Therefore the hazard rate function (12b) simplifies to

\[ h(t|\tau) = \frac{f(t|\tau)}{S(t|\tau)}, \] (17)

where \( S(t|\tau) = 1 - \int_0^t f(s|\tau) \, ds \) is the associated conditional survival function.

In order to estimate the instantaneous conditional firing rate (11) we propose the following non-parametric estimator for the ISI conditional hazard rate function (17):

\[ \hat{h}_n(t|\tau) = \frac{\hat{f}_n(t|\tau)}{\hat{S}_n(t|\tau)}, \] (18)

where \( \hat{S}_n(t|\tau) = 1 - \int_0^t \hat{f}_n(s|\tau) \, ds \) and (Arfi, 1998; Ould-Said, 1997)

\[ \hat{f}_n(t|\tau) = \frac{\hat{f}_n(\tau, t)}{\hat{f}_n(\tau)}, \] (19)

with

\[ \hat{f}_n(\tau, t) = \frac{1}{n c_n^2} \sum_{i=1}^{n} K_1 \left( \frac{t - T_i}{c_n} \right) K_2 \left( \frac{t - T_{i+1}}{c_n} \right), \] (20)

\[ \hat{f}_n(t) = \frac{1}{n c_n} \sum_{i=1}^{n} K_1 \left( \frac{t - T_i}{c_n} \right). \] (21)

The estimator (19) is a uniform strong consistent estimator for the ISI conditional probability density function (10) on any compact interval \([0, J] \subseteq \mathbb{R}_+\). Here \( \{c_n\} \) is a sequence of positive real numbers satisfying

\[ \lim_{n \to \infty} c_n = 0, \quad \lim_{n \to \infty} n c_n = \infty, \] (22)
and $K_j$, $j = 1, 2$, are symmetric and real-valued kernel functions verifying

$$K_j(t) \geq 0, \quad \int_{-\infty}^{\infty} K_j(t) \, dt = 1, \quad \lim_{|t| \to \infty} |t| K_j(t) = 0. \quad (23)$$

Moreover, we assume that the kernels have bounded variation and that $K_1$ is strictly positive.

We do not consider the value of the instantaneous firing rate on the first ISI because of the lack of knowledge on the preceding ISI. However, it is possible to estimate the unconditional firing rate through

$$\hat{h}_n(t) = \frac{\hat{f}_n(t)}{\hat{S}_n(t)}, \quad (24)$$

where $\hat{S}_n(t) = 1 - \int_0^t \hat{f}_n(s) \, ds$. In Figure 2 we reconsider Example 2 for which we compare the theoretical conditional instantaneous firing rate (13) with its conditional estimator (18). Note furthermore that the use of (24) to estimate (12a) in (11) is an approximation because the sampling does not start at time zero of the theoretical model.

We have the following theorem.

**Theorem 1.** Let us consider a simple point process $N(t)$ (i.e. a point process admitting at most one single event at any time), with Markov, ergodic and stationary inter-event intervals $T_i$, $i \geq 1$. Under some regularity conditions on the ISI probability density functions and the kernels $K_1$ and $K_2$, for all sequences $\{b_n\}$ satisfying

$$\lim_{n \to +\infty} nb_n^4 \ln n = \infty, \quad (25)$$

(see Appendix C for complete details) the estimators (24) and (18) are uniform strong consistent estimators of the hazard rate functions (12a) and (17) on $[0, M]$. 


Figure 2: Two different realizations of the theoretical conditional instantaneous firing rate (13) (black line) together with its estimate (18) (red line). The parameters are \((\lambda, \delta) = (1, 0.5)\).
$0 < M \leq L$, i.e.

$$\lim_{n \to +\infty} \sup_{t \in [0, M]} |\hat{h}_n(t) - h(t)| = 0 \quad \text{a.s.} \quad (26)$$

$$\lim_{n \to +\infty} \sup_{(r,t) \in [0, M]^2} |\hat{h}_n(t|r) - h(t|r)| = 0 \quad \text{a.s.} \quad (27)$$

First, note that since on each observed bin it is impossible to record more than a single spike, it is reasonable to model the spike train through a simple point process. Second, an estimator for $\lambda^*(t)$ can be given as

$$\hat{\lambda}_n^*(t) = \hat{h}_n(t - l_{i-1}|T_{i-1} = t_{i-1}), \quad l_{i-1} < t \leq l_i. \quad (28)$$

Formula (28) holds for $i = 2, \ldots, n$, because for an ergodic and stationary process, the estimation of $\lambda^*$ in the first ISI cannot be performed in the lack of knowledge on the preceding ISI.

### 4 An a posteriori validation algorithm

The firing rate estimator (28) has good asymptotic properties when ISIs can be modelled through stationary ergodic processes. Having a sample of ISIs, specific tests of stationarity can be performed, checking the behaviour of their mean or of higher moments or even using ad-hoc techniques as in Sacerdote & Zucca (2007). These checks cannot guarantee strong stationarity of ISIs but can help to detect time dependences. More difficult is the check of ergodicity. This is a model feature that cannot be tested from a single time record of ISIs. Wishing to analyzing the reliability of the proposed estimator, we present here an a posteriori validation algorithm. The idea of such procedure is the following. We know that, due to the time-rescaling theorem, any simple point process with an integrable conditional intensity function $\lambda^*(t)$ may be transformed into a unit-rate Poisson process, by the random time transformation $t \to \Lambda^*(t) = \int_0^t \lambda^*(u) du$ (see Appendix A for the
complete statement of the theorem). Hence, we perform such transformation and we check whether the obtained point process is a unit-rate Poisson process. If we cannot reject the Poisson characterization of the transformed process, we conclude that our estimator is reliable, having correctly acted as a firing rate.

Formalizing, we first compute the conditional firing rate estimator \( \hat{\lambda}_n^\ast \), defined by equation (28). Then, we perform the following time transformation

\[
t \rightarrow \hat{\Lambda}_n^\ast(t) = \int_0^t \hat{\lambda}_n^\ast(u) \, du.
\]  

(29)

Under this time-change, the ISIs \( T_i = l_i - l_{i-1}, i \geq 1 \) and \( l_0 = 0 \), become

\[
\tilde{T}_i = \hat{\Lambda}_n^\ast(l_i) - \hat{\Lambda}_n^\ast(l_{i-1}) = \int_{l_{i-1}}^{l_i} \hat{\lambda}_n^\ast(u) \, du, \quad i = 1, \ldots, n.
\]  

(30)

If the firing rate estimator (28) is reliable, i.e. if the hypotheses supporting its computation are verified, the transformed ISIs (30) should be independent and identically distributed (i.i.d.) exponential random variables with mean 1, according to the time-rescaling theorem. Hence a way to validate our estimator on sample data is to check the independence and exponential distribution of the transformed ISIs.

We can perform a goodness-of-fit test to verify if the sequence \( \{\tilde{T}_i, i = 1, \ldots, n\} \) follows the exponential distribution with mean 1. Then we can compute any dependence index, like the correlation coefficient \( \rho \) (Spearman, 1910) or the Kendall’s tau (Kendall, 1938), of the couples \( (\tilde{T}_i, \tilde{T}_{i+1}), i = 1, \ldots, n-1 \), to check whether the successive transformed ISIs are independent.

Here we propose also another alternative test of the hypotheses on the transformed ISIs, based on the concept of independent copula. Intuitively the independent copula is the joint probability distribution of two independent uniform random variables. It is able to fit the relationship of independence between any
group of independent random variables (for more details on the independent copula, see Appendix B). If the transformed ISIs are i.i.d. exponential random variables with mean 1, the copula of two subsequent transformed ISIs should be the independent copula, with exponential marginals of mean 1. To verify this, we consider the further ISI transformation, based on the exponential distribution assumption,

\[ Z_i = 1 - e^{-\bar{T}_i}. \]  

(31)

When \( T_i \sim \exp(1), \{Z_i, i \geq 1\} \) is a collection of i.i.d. uniform random variables on \([0, 1]\). Therefore, the copula of \( Z_i \) and \( Z_{i+1}, i = 1, 2, \ldots, n \), should be the independent copula with uniform marginals. Hence, another way to verify the reliability of (28) on the transformed ISIs is to perform a uniformity test (goodness-of-fit test for the uniform distribution on \([0, 1]\)) and a goodness-of-fit test for the independent copula on the collection \( \{Z_i, i \geq 1\} \). In particular, we apply the goodness-of-fit test for copulas proposed in Genest et al. (2009).

Summarizing, an \textit{a posteriori} validation test for the proposed firing rate estimator (28) follows this algorithm.

\textbf{Algorithm 1. (Validation algorithm)}

1. \textit{Estimate the firing rate through} (28).

2. \textit{Compute the transformed ISIs}

\[ \bar{T}_i = \int_{l_{i-1}}^{l_i} \hat{\lambda}_n^*(u) \, du, \quad i = 1, 2, \ldots, n. \]

3. \textit{Test the hypothesis that} \( \bar{T}_i \) \textit{are i.i.d. exponential random variables of mean 1:}

   a. \textit{Apply the transformation} \( Z_i = 1 - e^{-\bar{T}_i}, i = 1, 2, \ldots, n \), \textit{and test that these transformed random variables are uniform on} \([0, 1]\).
b. Perform a goodness-of-fit test for the independent copula on the couples 
\((Z_i, Z_{i+1}), i = 1, 2, \ldots, n - 1\).

Note that testing that \(Z_i, i = 1, 2, \ldots, n\), are i.i.d. uniform random variables on \([0, 1]\) is equivalent to test that \(T_i, i = 1, 2, \ldots, n\), are i.i.d. exponential random variables with mean 1, i.e. that the transformed process is a unit-rate Poisson process.

**Remark 1.** In Algorithm 1 we perform a goodness-of-fit test for copulas to verify the independence between \(Z_i\) and \(Z_{i+1}\). However any other test of independence can be applied, like a classical chi-squared test.

## 5 The stochastic two-compartment neural model

We consider here the stochastic two-compartment model proposed in [Lansky & Rodriguez (1999)](#). It is a two-dimensional Leaky Integrate and Fire type model that generalizes the one-dimensional Ornstein–Uhlenbeck model ([Ricciardi & Sacerdote, 1979](#)). The introduction of the second component allows us to relax the resetting rule of the membrane potential. In a recent paper we showed that spike trains generated by this model exhibit dependent ISIs for suitable ranges of the paramenters ([Benedetto & Sacerdote, 2013](#)). Here we use ISIs generated by this model to estimate the conditional firing rate through the estimator proposed in this paper.

In the stochastic two compartment model the neuron is described by two interconnected compartments, modelling the membrane potential dynamics of the dendritic tree and the soma, respectively. The dendritic component is responsible for receiving external inputs, while the somatic component emits outputs. Hence, external inputs reach indirectly the soma by the interconnection between the two compartments.
The model is then described by a bivariate diffusion process \( \{X(t), t \geq 0\} \), whose components \( X_1(t) \) and \( X_2(t) \) model the membrane potential evolution in the dendritic and somatic compartment, respectively. Assuming that external inputs have intensity \( \mu \) and variance \( \sigma^2 \), the process obeys to the system of stochastic differential equations

\[
\begin{align*}
\frac{dX_1(t)}{dt} &= (-\alpha X_1(t) + \alpha_r [X_2(t) - X_1(t)] + \mu) dt + \sigma dB(t), \\
\frac{dX_2(t)}{dt} &= (-\alpha X_2(t) + \alpha_r [X_1(t) - X_2(t)]) dt.
\end{align*}
\]

Here \( \alpha_r \) accounts for the strength of the interconnection between the two compartments, while \( \alpha \) is the leakage constant that models the spontaneous membrane potential decay in absence of inputs.

Whenever \( X_2(t) \) reaches a characteristic threshold \( S \) the neuron emits an action potential. Then \( X_2(t) \) restarts from a resetting potential value that we assume equal to zero (a shift makes always possible this choice) while \( X_1(t) \) continues its evolution. The absence of dendritic resetting makes the ISIs dependent on the past evolution of the neuron dynamics. Sensitivity analysis was applied in \[\text{Benedetto \& Sacerdote (2013)}\] to determine the model values of parameters that make its ISIs stationary but dependent. Here we simulate samples of 1000 ISIs from this model for different choices of the parameters, we determine the conditional firing rate \[\text{(11)}\] corresponding to each choice and we check the reliability of the obtained results by means of the algorithm proposed in the previous section. According to the hypotheses of Theorem \[\text{1}\] (see Appendix \[\text{C}\]) for our study we use:

1. Gaussian kernels \( K_1 \) and \( K_2 \) with mean zero and standard deviation equal to 0.2;

2. Kernel weights \( b_n = n^{-\beta} \) where \( n \) is the sample size and \( \beta = 0.2 \).

We report the results of the algorithm in Table \[\text{1}\]. The first three cases in Table \[\text{1}\]
Figure 3: An example of the estimated conditional instantaneous firing rate for the two-compartment model described in Section 5. In the upper and middle figures, the membrane potential respectively in the dendritic and somatic compartment is depicted. The lower figure shows the corresponding estimated conditional instantaneous firing rate $\hat{\lambda}^*(t)$. Here the parameters are set to $(a, a_r, \mu, \sigma, S) = (0.05, 0.5, 3.5, 1, 10)$. The estimation is performed by means of Gaussian kernels with standard deviation set at 1.5. The ISIs here are rather short and the instantaneous firing rate rather high (but unknown). This can be understood by noticing that the conditional instantaneous firing rate is still growing when a new spike (and therefore a new conditioning event) occurs. The faster the instantaneous firing rate is, the sooner a conditioning event happens but still the presence of dependence between consecutive ISIs can be appreciated by considering the fact that after each recorded ISI the conditional instantaneous firing rate grows differently.
correspond to Markov dependent ISIs as shown in Benedetto & Sacerdote (2013). The proposed estimator cannot be safely applied in the fourth case of Table 1. Indeed the use of algorithm of Section 4 shows that the hypotheses for its use are not verified. In this case, successive ISIs exhibit longer memory, as suggested in Benedetto & Sacerdote (2013). A variant of the proposed estimator can be easily developed to account for this longer memory. For example one should consider a rate intensity conditioned on the two previous ISIs.

Table 1: Results of the uniformity test and the copula goodness-of-fit test of Algorithm 1 applied on ISIs simulated by the two-compartment model (32). In the last case the copula goodness-of-fit test fails, as the ISI process is statistically a Markov process of order 2. Indeed for values of \( \mu \) close to the threshold \( S \), the ISIs become very short and the evolution of the two-compartment model is more dependent on its past history (see Benedetto & Sacerdote (2013) for details).

| Parameters                                      | Uniformity test p-value | Copula goodness-of-fit test p-value |
|-------------------------------------------------|--------------------------|-------------------------------------|
| \( \alpha = 0.05, \alpha_r = 0.5, \mu = 4, \sigma = 1, S = 10 \) | 0.88                     | 0.97                                |
| \( \alpha = 0.05, \alpha_r = 0.25, \mu = 4, \sigma = 1, S = 10 \) | 0.84                     | 0.62                                |
| \( \alpha = 0.05, \alpha_r = 0.5, \mu = 3.5, \sigma = 1, S = 10 \) | 0.69                     | 0.87                                |
| \( \alpha = 0.05, \alpha_r = 0.5, \mu = 8, \sigma = 1, S = 10 \) | 0.21                     | 0.01                                |

6 Application to experimental data

We analyze here experimental data taken from the Internet\(^1\). This data were recorded and discussed by Rauch et al. (2003) and correspond to single electrode in vitro recordings from rat neocortical pyramidal cells under random in vivo-

\(^1\)http://lcn.epfl.ch/~gerstner/QuantNeuronMod2007/
Figure 4: An example of the estimated conditional instantaneous firing rate for real data as described in Section 6. The estimation is performed with Gaussian kernels with standard deviation set at 1.5. Time is measured in milliseconds.

like current injection. We limit our discussion to the analysis of the dataset file 07-1.spiketimes. The injected colored noise current (Ornstein–Uhlenbeck process) determines dependencies between ISIs. For the analyzed dataset, the colored noise has a mean of 320 pA and a standard deviation of 41 pA. According to Rauch et al. (2003), cells responded with an action potential activity with stationary statistics that could be sustained throughout long stimulation intervals. The Kendall’s Tau test on adjacent ISIs reveals a negative dependence; indeed \( \tau = -0.118 \) and the independence test furnishes us with a p-value equal to 0.0001. Note that the lack of independence may be due both to the colored noise and to causes internal to the neuron’s dynamics. Due to this fact it becomes interesting to estimate the conditional instantaneous firing rate (see Fig. 4). The a posteriori test for ergodicity (see Algorithm 1) confirms the reliability of our estimation. Indeed the uniformity test on the transformed ISIs gives a p-value equal to 0.92 and the independence of the time-changed ISIs is confirmed by a test on the Kendall’s Tau \( (\tau = -0.0219, \ p-value = 0.47) \). Furthermore, the goodness-of-fit copula test for independence copula gives a p-value equal to 0.99.
7 Conclusions

The analysis of the features exhibited by recorded ISIs often ground on the study of their statistics. The most used quantities in this framework are the firing rate and the instantaneous firing rate. Typically its estimation is performed assuming that ISIs are independent despite experimental evidence on dependences between successive ISIs. This choice may influence analysis results. Here we stressed consequences of ignoring dependences on the instantaneous rate estimation and we propose a non parametric estimator for the case of ergodic stationary ISIs with successive ISIs characterized by the Markov property. Use of such estimator could improve data analysis. For example, in the case of in vitro recording, the comparison of data obtained with white or colored noise could differentiate dependences determined by the external inputs from those determined by the internal dynamics of the neuron.

We illustrated the use of the proposed estimator on simulated and on in vitro recorded data. Furthermore we proved its consistency property and we gave an algorithm to check the Markov ergodic stationary hypothesis on data.

A natural extension of the proposed approach refers to data exhibiting memory also between non contiguos ISIs. Furthermore we plan to apply the method to non stationary data introducing their preliminary cleaning from possible periodicity or presence of trends.

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A The time-rescaling theorem

For the sake of completeness we recall here the time-rescaling theorem that is a well-known result in probability theory. In neuroscience it is applied for example in [Brown et al. (2001) and Gerhard et al. (2011)] to develop goodness-of-fit tests for parametric point process models of neuronal spike trains.

**Theorem 2** (Time-rescaling theorem). Let $N(t)$ be a point process admitting only unitary jumps, with integrable conditional intensity function $\lambda^*(t)$, modelling a spike train with interspike intervals $T_i = l_i - l_{i-1}$, $i \geq 1$, where $l_0 = 0$ and $l_i$, $i \geq 1$, are the spiking epochs. We define

$$\Lambda^*(t) = \int_0^t \lambda^*(u) \, du. \quad (33)$$

Then, under the random time transformation $t \rightarrow \Lambda^*(t)$, the transformed process $\tilde{N}(t) = N(\Lambda^*^{-1}(t))$ is a unit-rate Poisson process.

Moreover the transformed ISIs

$$\tilde{T}_i = \Lambda^*(l_i) - \Lambda^*(l_{i-1}) = \int_{l_{i-1}}^{l_i} \lambda^*(u) \, du,$$

are i.i.d. exponential random variables with mean 1, as they are waiting times of a unit-rate Poisson process.

B Bivariate copulas

Let us consider two uniform random variables $U$ and $V$ on $[0, 1]$. Assume that they are not necessary independent. They are related by their joint distribution function

$$C(u, v) = \mathbb{P}(U \leq u, V \leq v). \quad (34)$$
The function $C : [0, 1] \times [0, 1] \rightarrow [0, 1]$ is called bivariate copula.

Consider now the marginal cumulative distribution functions $F_X(x) = \mathbb{P}(X \leq x)$ and $F_Y(y) = \mathbb{P}(Y \leq y)$ of two random variables $X$ and $Y$. It is easy to check that

$$C(F_X(x), F_Y(y))$$

defines a bivariate distribution with marginals $F_X(x)$ and $F_Y(y)$.

A celebrated theorem by Sklar (1959) establishes that any bivariate distribution can be written as in (35). Furthermore, if the marginals are continuous then the copula representation is unique (Nelsen, 1999).

Copulas contain all the information related to the dependence between the random variables and do not involve marginal distributions. Hence, by means of copulas we can separate the study of bivariate distributions into two parts: the marginal behaviour and the dependency structure between the random variables. The simplest bivariate copula is the independent copula. It is defined as

$$C(u, v) = uv, \quad (u, v) \in [0, 1]^2,$$

and it represents the joint distribution of two independent uniform random variables on $[0, 1]$.

### C Complete hypotheses and proof of Theorem 1

Here we write

$$f_i(\tau, t|T_j, j = 1, \ldots, i - 1) = \frac{d^2}{d\tau dt} \mathbb{P}(T_{i+1} \leq \tau, T_i \leq t|T_j, j = 1, \ldots, i - 1)$$

for the joint conditional density function of the couple $(T_i, T_{i+1})$ given the joint past history of an ISI and its subsequent until the couple $(T_{i-1}, T_i)$. The convergence
properties of the estimator (18) depend on the following hypotheses.

h1. The joint densities \(f(\tau, t)\) and \(f_i(\tau, t|T_j, j = 1, \ldots, i - 1)\) belong to the space \(C_0(\mathbb{R}^2)\) of real-valued continuous functions on \(\mathbb{R}^2\) approaching zero at infinity.

h2. The marginal densities \(f(t)\) and \(f_i(t|T_j, j = 1, \ldots, i - 1)\) belong to the space \(C_0(\mathbb{R})\) of real-valued continuous functions on \(\mathbb{R}\) approaching zero at infinity.

h3. The conditional density functions \(f_i(\tau, t|T_j, j = 1, \ldots, i - 1)\) and \(f_i(t|T_j, j = 1, \ldots, i - 1)\) are Lipschitz with ratio 1,

\[
|f_i(\tau, t|T_j, j = 1, \ldots, i - 1) - f_i(\tau', t'|T_j, j = 1, \ldots, i - 1)| \leq |\tau - \tau'| + |t - t'|,
\]

\[
|f_i(t|T_j, j = 1, \ldots, i - 1) - f_i(t'|T_j, j = 1, \ldots, i - 1)| \leq |t - t'|.
\]

h4. Let \([0, M] \subseteq \mathbb{R}_+\) be a compact interval. We assume that for all \(t\) in an \(\epsilon\)-neighbourhood \([0, M]_\epsilon\) of \([0, M]\) there exists \(\gamma_\epsilon > 0\) such that \(f(t) > \gamma_\epsilon\).

h5. The kernels \(K_j, j = 1, 2\), are Hölder with ratio \(L < \infty\) and order \(\gamma \in [0, 1]\),

\[
|K_1(\tau) - K_1(\tau')| \leq L|\tau - \tau'|^\gamma, \quad (\tau, \tau') \in \mathbb{R}^2,
\]

\[
|K_2(t) - K_2(t')| \leq L|t - t'|^\gamma, \quad (t, t') \in \mathbb{R}^2.
\]

**Remark 2.** These assumptions are satisfied by any ergodic process with sufficiently smooth probability density functions (see Delecroix (1987)).

To prove Theorem 1 we first recall that the estimator (21) is a uniform strong consistent estimator for \(f(t)\) on any compact interval \([0, J] \subseteq \mathbb{R}_+\) (Parzen 1962; Rosenblatt 1956) (see also Delecroix et al. 1992), and then we need the following auxiliary lemma.
Lemma 1. Under the hypotheses and notations of Theorem 1,

\[ \hat{S}_n(t) = 1 - \int_0^t \hat{f}_n(s) \, ds, \]

\[ \hat{S}_n(t|\tau) = 1 - \int_0^t \hat{f}_n(s|\tau) \, ds, \]

are uniform strong consistent estimator on \([0,M]\) of the survival functions

\[ S(t) = 1 - \int_0^t f(s) \, ds \]

and \( S(t|\tau) = 1 - \int_0^t f(s|\tau) \, ds \), i.e.

\[ \lim_{n \to \infty} \sup_{t \in [0,M]} |S(t) - \hat{S}_n(t)| = 0, \quad \text{a.s.} \]

\[ \lim_{n \to \infty} \sup_{t \in [0,M]} |S(t|\tau) - \hat{S}_n(t|\tau)| = 0, \quad \text{a.s.} \]

Proof. We report only the proof for \( \hat{S}_n(t) \), as the proof for \( \hat{S}_n(t|\tau) \) is analogous.

\[
\begin{align*}
\sup_{t \in [0,M]} |S(t) - \hat{S}_n(t)| &= \sup_{t \in [0,M]} \left| \int_0^t \hat{f}_n(s) \, ds - \int_0^t f(s) \, ds \right| \\
&\leq \sup_{t \in [0,M]} \int_0^t |\hat{f}_n(s) - f(s)| \, ds \\
&\leq \sup_{t \in [0,M]} \int_0^t \sup_{s' \in [0,M]} |\hat{f}_n(s') - f(s')| \, ds' \\
&= \sup_{s' \in [0,M]} |\hat{f}_n(s') - f(s')| \quad \sup_{t \in [0,M]} \int_0^t \, ds \\
&= T \sup_{s' \in [0,M]} |\hat{f}_n(s') - f(s')|.
\end{align*}
\]

Finally, by applying the convergence properties of the estimator (21) (or of the estimator (19) if we are concerned with \( \hat{S}_n(t|\tau) \)), we obtain the thesis. \( \square \)

Remark 3. Observe that \( S(t) \), \( S(t|\tau) \), \( \hat{S}_n(t) \) and \( \hat{S}_n(t|\tau) \) are bounded and strictly positive functions on \([0,M]\), as they are survival functions or sums of survival functions associated to strictly positive kernel functions.

Now we have all the tools to prove Theorem 1.
Proof of Theorem: We report only the proof for the estimator \( \hat{h}_n(t) \), as the proof for \( \hat{h}_n(t|t) \) is analogous. Under the hypotheses h1–h5, we get

\[
\sup_{t \in [0,M]} \left| \hat{h}_n(t) - h(t) \right| = \sup_{t \in [0,M]} \left| \frac{\hat{f}_n(t)S(t) - f(t)\hat{S}_n(t)}{\hat{S}_n(t)S(t)} \right|
\]

\[
= \sup_{t \in [0,M]} \left| \hat{f}_n(t)S(t) - f(t)\hat{S}_n(t) + f(t)S(t) - f(t)\hat{S}_n(t) \right|
\]

\[
\leq \sup_{t \in [0,M]} \left| \frac{\hat{f}_n(t) - f(t)}{\hat{S}_n(t)S(t)} \right| \sup_{t \in [0,M]} |S(t)| + \sup_{t \in [0,M]} \left| \frac{S(t) - \hat{S}_n(t)}{\hat{S}_n(t)S(t)} \right| |f(t)|
\]

\[
\leq \frac{\sup_{t \in [0,M]} |\hat{f}_n(t) - f(t)|}{\inf_{t \in [0,M]} |\hat{S}_n(t)S(t)|} \sup_{t \in [0,M]} |S(t)| + \frac{\sup_{t \in [0,M]} |S(t) - \hat{S}_n(t)|}{\inf_{t \in [0,M]} |\hat{S}_n(t)S(t)|} \sup_{t \in [0,M]} |f(t)|
\]

Applying the convergence properties of the estimator (21) and Lemma 1 we get the thesis, as \( S(t) \) and \( \hat{S}_n(t) \) are bounded and strictly positive functions and \( f(x) \in C_0(\mathbb{R}) \).

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