Statistics of inverse interspike intervals: the instantaneous firing rate revisited

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The rate coding hypothesis is the oldest and still one of the most accepted and investigated scenarios in neuronal activity analyses. However, the actual neuronal firing rate, while informally understood, can be mathematically defined in several different ways. These definitions yield distinct results; even their average values may differ dramatically for the simplest neuronal models. Such an inconsistency, together with the importance of "firing rate", motivates us to revisit the classical concept of the instantaneous firing rate. We confirm that different notions of firing rate can in fact be compatible, at least in terms of their averages, by carefully discerning the time instant at which the neuronal activity is observed. Two general cases are distinguished: either the inspection time is synchronised with a reference time or with the neuronal spiking. The statistical properties of the instantaneous firing rate, including parameter estimation, are analyzed and compatibility with the intuitively understood concept is demonstrated.

Keywords: Instantaneous firing rate, Point process intensity, Firing rate estimation, Length-biased sampling

The electric discharge activity of neurons is composed of stereotyped events called action potentials or spikes. The exact timing of spikes under identical external conditions may vary from trial to trial. Since the early days of neuroscience it has been often assumed that neurons express information about their input by employing mainly the average *firing rate* (frequency) of spikes. However, reliable firing rate statistics can be difficult to obtain in certain experiments or even in mathematical models. The reciprocal value of the interval between consecutive spikes — known as the *instantaneous firing rate* — offers the traditionally employed alternative. Although the physical dimension of the instantaneous rate is compatible with the firing frequency, the averages of the two quantities differ. In this paper we reconcile this tension by pointing to the crucial role of the reference time at which we *inspect* the spike pattern. We describe two possible scenarios: the classical one, in which the inspection is aligned with spikes (yielding the mentioned incompatible averages), and the asynchronous one, in which the inspection time is fixed to an external reference time (and the mean instantaneous firing rate generally equals the mean firing frequency).

I. INTRODUCTION

Although it is universally accepted that neurons communicate using series of action potentials (spike trains) via chemical and electrical synapses, the exact structure of the neuronal code is not yet fully resolved. The classical rate coding paradigm states that the information sent along an axon is encoded in the number of spikes per observation time window[1]. In most sensory systems, the firing rate increases, generally non-linearly, with increasing stimulus intensity[2]. Characterization of these input-output properties of neurons, as well as of neuronal models, is commonly done by so-called transfer functions in which the firing rate is plotted against the input signal (e.g., the stimulus intensity). The transfer function is usually presented as a single curve, relating the mean (or the average of multiple experimental measurements) response to each stimulus level[3–6].

Instead of actual spike counts per time window, some researchers have considered the concept of the *instantaneous firing rate* in which is the reciprocal values of the interspike intervals (ISIs) are employed. Bessou, Laporte, and Pagés[7] proposed to display the inverse of ISIs and by superposition of records to construct a graph called the *frequencygram*. Knight[8] investigated the efficiency of the analogous method for a periodic signal. The list of papers where the method of reciprocal ISI was applied can be very extensive, so we add only a few examples. Sawczuk, Powers, and Binder[9], investigating spike frequency adaptation in hypoglossal motoneurons of the rat, used the reciprocal of the first ISI after stimulation as the magnitude of the initial adaptation. Martinez-Conde, Macknik, and Hubel[10], studying microsaccadic eye movements and firing of neurons in striate cortex of macaque monkey, also defined the instantaneous firing rate as the inverse of the ISI. Similarly, Lemon and Smith[11] used reciprocals of each ISI to estimate the instantaneous firing rate at the point of time at which the ISI under consideration terminated. The response to a stimulus was defined in the same way in Rospars *et al.*[12]. Not only experimental research uses reciprocal ISIs for deducing properties of neurons under investigation; theoretical research has also been based on this quantity[13]. For example, Pauluis and Baker[14] present a very detailed study of how to treat rapid changes in frequencygrams, whereas Harris and Waddington[15] investigated the inverse distributions of commonly applied models of ISIs.

The advantage of the instantaneous rate concept lies in the fact that ISI statistics are often more easily obtainable than

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count-based statistics. Nonetheless, the statistics of the classical "firing rate" and of the "instantaneous rate" differ in several key aspects. Probably the most important is that the mean instantaneous rate typically exceeds the (count-based) firing rate. In fact, for the simplest case of spike trains described by a homogeneous Poisson process, the mean instantaneous rate actually diverges[16].

The main message of this paper lies in revisiting the instantaneous firing rate concept and reconciling it with the count-based quantities. We carefully distinguish the statistical properties of observed ISIs under two sampling protocols, arguing in Section III A that fixing the inspection (observation) period with respect to external (laboratory or reference) time is essential. (Traditionally, although implicitly, the start of observation is the spike time.) We show that observing the instantaneous rate at a fixed reference time introduces sampling bias; however, the mean instantaneous rate then generally equals the firing intensity, as expected naturally. In Section III B we analyze, by means of the Cramér-Rao bound, how the bias-corrected instantaneous rate affects inferences about the firing intensity in several standard ISI renewal models. Finally, in Section III C we show how the data obtained in the spike-synchronized scenario may be converted to the reference-synchronized scenario without needing to repeat the experiment.

II. DEFINITIONS OF NEURONAL FIRING RATE

Spike times $0 < S_1 < S_2 < \dots$ are often modeled as realizations of a *stochastic point process*[17]. See Cox and Lewis [18] for more details on the key concepts of point process terminology briefly summarised below. Assume, for convenience, that the time $t = 0$ is not related to the actual spike times, i.e., it is fixed with respect to some *reference* time before the point process realization. The *interspike intervals* (ISIs), X_i, are defined as $X_i = S_{i+1} - S_i, i = 1, 2, \dots$ (Fig. 1A). The associated *counting process*, $N(t_1, t_2)$, for any $t_2 > t_1$, is a random variable describing the number of spikes in some interval $(t_1, t_2]$. The spike times S_i and the process $N(0, t)$ are then related by $\{S_i \le t\} = \{N(0, t) \ge i\}$, for $i = 1, 2, \dots$. The mean (expected) spike count in $(t_1, t_2]$ is denoted as $\mathbb{E}[N(t_1, t_2)]$. The *firing intensity* $\lambda(t)$ of the spiking process at some time t is

$$\lambda(t) = \lim_{\varepsilon \downarrow 0} \frac{\mathbb{E}[N(t, t+\varepsilon)]}{\varepsilon}. \tag{1}$$

The probability distribution of $N(t, t+\varepsilon)$ generally depends on the history (the spike times) of the process up to time t, hence $\lambda(t)$ is frequently called *conditional intensity* of the point process. The history dependence can be reduced considerably for simple (e.g., renewal) ISI models.

Often, especially in the experimental setup, the limit in Eq. (1) is not available, and the firing rate is defined as the actual number of spikes in a sufficiently long time window of duration w (set by the experimenter). The *mean firing rate* ν is typically of interest[1,19],

$$\nu(t, w) = \frac{\mathbb{E}[N(t, t+w)]}{w} \tag{2}$$

Little can be said about the relationship between $\lambda(t)$ and $\nu(t, w)$ without knowing the exact probabilistic description of the underlying point process. Still, certain rather general statements are possible under the following assumptions.

First, assume that the ISI sequence, $\{X_1, X_2, \dots\}$, forms a *renewal process*, i.e., a sequence of independent and identically distributed (i.i.d) random variables (rv) with probability density function (pdf) $p_X(x)$ and mean ISI denoted as $\mathbb{E}(X)$. The "elementary renewal theorem" then states that

$$\frac{1}{\mathbb{E}(X)} = \lim_{w \to \infty} \nu(t, w). \tag{3}$$

Note that Eq. (3) holds independently of t. In particular, it may be that $t = S_i$ or t is chosen randomly, without any reference to the point process realization. Moreover, Eq. (3) relates the mean firing rate to the mean ISI, and hence justifies the interpretation of $1/\mathbb{E}(X)$ as the mean *firing rate in the steady state*[20,21].

Second, assume that the time t is chosen without any reference to S_i, i.e., randomly with respect to the point process realization. Then t most likely falls within some ISI, say X_k, and hence the time to first spike after t, $S_k - t$, generally does not follow the renewal pdf p_X. The sequence of rvs $\{S_k - t, X_{k+1}, X_{k+2}, \dots\}$ is thus not stationary; however, the corresponding stochastic process is often denoted as a "steady state" or "equilibrium renewal" process, since $\lambda = \lambda(t)$ and $\nu(w) = \nu(t, w)$ do not depend on t anymore. The "firing rate/intensity" definitions above coincide and for all $w > 0$ it holds

$$\lambda = \frac{1}{\mathbb{E}(X)} = \nu(w). \tag{4}$$

Essentially, Eqs. (3) and (4) show how the count-based and the ISI-based definitions of 'firing rate' are related to each other. Due to this fact, the list of studies on the mean ISI in neuronal models of very different complexities is almost endless, see[22–26] for a few recent examples.

A. Instantaneous firing rate

The subject of this paper is the classical concept of *instantaneous firing rate*, which, as described in the Introduction, is defined as the inverse of the ISI. Under the renewal model, the instantaneous firing rate F is a rv obtained from the ISI rv X by the one-to-one transformation $F = 1/X$. Of particular interest is the mean value, $\mathbb{E}(F) = \mathbb{E}(1/X)$. It holds that

$$\mathbb{E}\left(\frac{1}{X}\right) \ge \frac{1}{\mathbb{E}(X)}, \tag{5}$$

with equality if and only if the distribution of X is concentrated at a single point, i.e., all ISIs are of equal length. Hence, for any neuronal model, the mean instantaneous firing rate is higher than the steady-state firing rate[16]. The "traditional" approach to the instantaneous firing rate thus is to separate $\mathbb{E}(F)$ from the definitions in Eqs. (1)–(3), and employ the quantity as a measure of its own kind.

III. RESULTS AND DISCUSSION

A. Statistics of the instantaneous firing rate depends on the inspection time

We denote the time t at which we determine the instantaneous firing rate as the *inspection time* t_0. If the inspection time t_0 is synchronized with spikes then we essentially observe the spike train properties (over trials) at *random* time instants with respect to the laboratory (reference) time (Fig. 1B). Such an observation protocol is arguably inconsistent if we expect that the firing intensity λ is modulated by external events (stimulus) that occur naturally independently of exact spike times. In order to infer λ properly, the observation time must be *fixed* with respect to the external time, i.e, *random* with respect to spike times (Fig. 1C). However, even under completely steady-state conditions, with ISIs following a renewal process, and with just a single trial (spike train) available, the inference based on the observed instantaneous firing rate differs *significantly*, as argued below. We distinguish the two situations by denoting:

(i) rv F with pdf $p_F(f)$, denoted as the *synchronous instantaneous firing rate (SIFR)*, which describes the reciprocal ISI in the *spike-synchronized* setup (Fig. 1B),

(ii) rv R with pdf $p_R(r)$, denoted as the *asynchronous instantaneous firing rate (AIFR)*, describing the reciprocal ISI in the *fixed reference time* situation (Fig. 1C).

We compare the pdfs of the instantaneous firing rates F and R. Under the assumption that the neuronal firing is described by a renewal ISI model, $X \sim p_X(x)$ and $\mathbb{E}(X) = 1/\lambda$, it follows from $F = 1/X$ and from the rules for the rv transformation that the SIFR F is distributed according to the pdf

$$p_F(f) = \frac{p_X(1/f)}{f^2}. \tag{6}$$

The properties of p_F, its moments, and especially the consequences of Eq. (5), were analyzed in detail for different statistical and biophysical models of neuronal activity by Lansky, Rodriguez, and Sacerdote[16].

Next, we reconcile the statistical properties of the instantaneous rate concept with Eq. (4); namely, we justify its label as the "rate", by reconsidering the derivation of Eq. (6). The interpretation of the pdf p_F is that it describes the relative frequencies of occurrence of different possible values of the reciprocal ISI. However, it *does not* account for the relative *weight* of $F = f$, i.e., the duration of the time segment each value occupies (Fig. 1). If one aims to interpret $\mathbb{E}(F)$ in the light of Eq. (4), then the "time course" of the instantaneous firing rate, i.e., the frequencygram[7], becomes important. Or, equivalently, we realize that the probability of observing a particular ISI at a random inspection time is proportional to the ISI duration. The rv $\tilde{X}$ describing such ISIs is *length-biased* with respect to rv X[18] and $\tilde{X} \sim \lambda \tilde{x} p_X(\tilde{x})$ (Fig. 1C). The AIFR, $R = 1/\tilde{X}$, is therefore described by the pdf

$$p_R(r) = \frac{\lambda p_X(1/r)}{r^3}. \tag{7}$$

The immediate consequence of Eq. (7) is that (*cf.* Eq. 5)

$$\mathbb{E}(R) = \frac{1}{\mathbb{E}(X)} = \lambda, \tag{8}$$

which follows by applying the expectation operator to Eq. (7). Therefore, the sampling bias "corrects" the distribution of the SIFR so that $\mathbb{E}(R) = \lambda$ holds for the AIFR, as desired. The relationship for the variance is derived similarly,

$$\mathrm{Var}(R) = \lambda\, \mathbb{E}(F) - \lambda^2. \tag{9}$$

The behavior of $\mathrm{Var}(R)$ thus critically depends on the value of $\mathbb{E}(F) = \mathbb{E}(1/X)$.

B. Firing intensity estimation from the instantaneous rate

Since the mean AIFR, $\mathbb{E}(R)$, *equals* the firing intensity, λ, of the renewal process, it is natural to ask how "well" one may *estimate* the true value of λ from the observed AIFR. The problem of estimation precision is generally non-trivial. It is often more practical to evaluate the Cramér-Rao bound on the mean square error (MSE) instead. Assuming unbiased estimation, together with certain mild regularity conditions[27], the Cramér-Rao bound states that the MSE for any given λ satisfies $\mathrm{MSE}(\lambda) \geq 1/J(\lambda)$, where $J(\lambda)$ is the *Fisher information*,

$$J(\lambda) = J(\lambda|R) = \int \left(\frac{\partial \log p_R(r;\lambda)}{\partial \lambda} \right)^2 p_R(r;\lambda)\, \mathrm{d}r. \tag{10}$$

We explicitly denote the dependence of the pdf of R on the intensity, λ, $p_R(r;\lambda) = p_R(r)$, and we indicate that the estimate of λ is based on observations of a particular rv, e.g., $J(\lambda|R)$, $J(\lambda|X)$, etc.

Before illustrating the firing intensity estimation precision on several classic ISI models, we introduce general remarks that simplify or even avoid the evaluation of the integral in Eq. (10). In general, the Fisher information is *invariant* with respect to any information-preserving (one-to-one) transformation of the rv R[27]. Therefore, since $F = 1/X$,

$$J(\lambda|X) = J(\lambda|F). \tag{11}$$

In the following we henceforth examine only $J(\lambda|X)$ and $J(\lambda|R)$. The ISI pdf $p_X(x;\lambda)$ belongs to the *scale* (more precisely rate) family of distributions if it satisfies

$$p_X(x;\lambda) = \lambda p_X(\lambda x; 1). \tag{12}$$

By substituting Eq. (12) into Eq. (10) it is easy to verify that the Fisher information satisfies the proportionality relation[28]

$$J(\lambda|X) = \frac{\alpha_X}{\lambda^2}, \tag{13}$$

where α_X does not depend on λ, and under mild continuity conditions on p_X,

$$\alpha_X = 1 - \int x^2 \frac{\partial^2 \log p_X(x;1)}{\partial x^2} p_X(x;1)\, \mathrm{d}x. \tag{14}$$

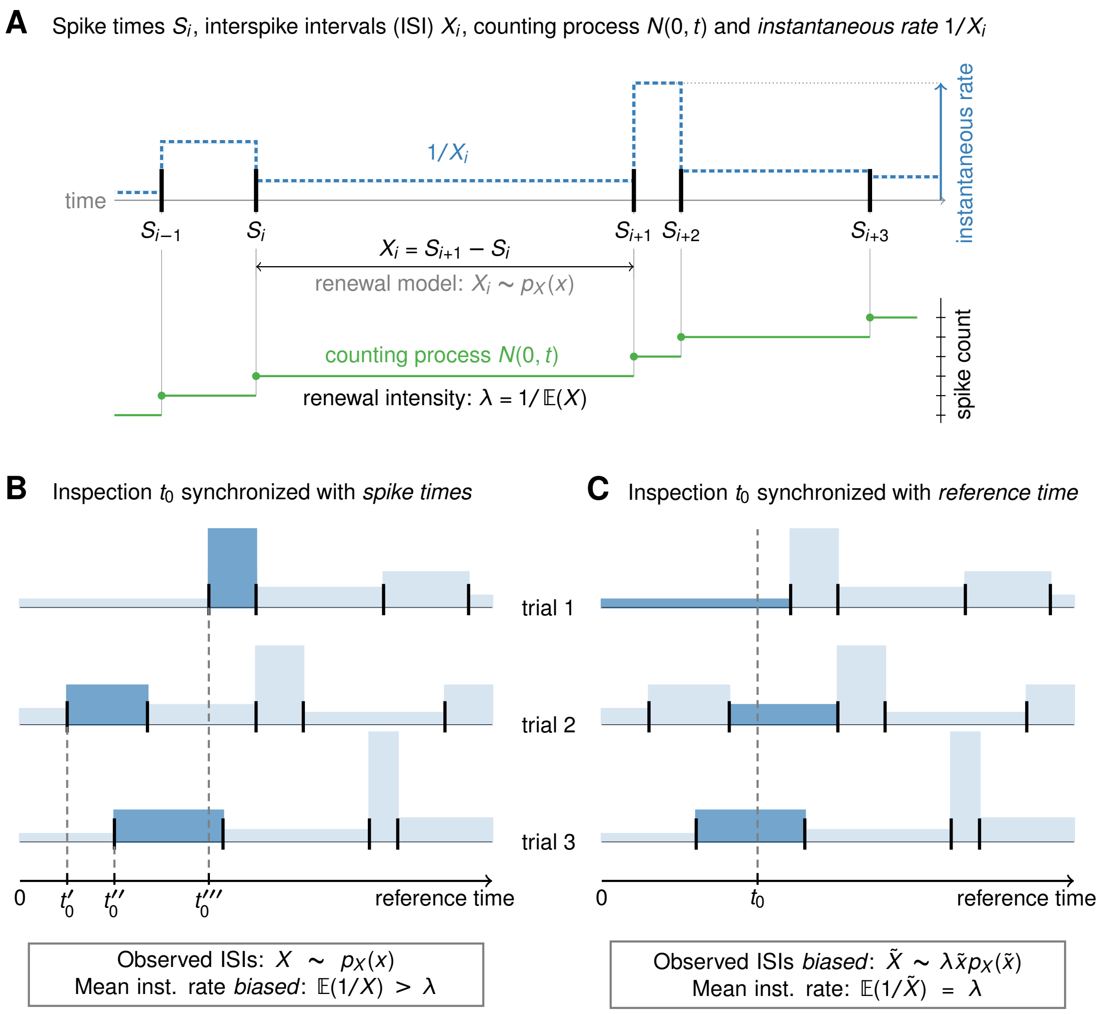

FIG. 1. Neuronal spiking activity and the instantaneous firing rate. (**A**) Spikes arrive at times S_i; the corresponding interspike intervals (ISI) are denoted as X_i and the instantaneous firing rate is the inverse ISI (dashed). The associated counting process $N(t)$ is needed for the general definition of the firing intensity λ (Eq. 1). Under steady-state conditions, ISIs are assumed to be independent and identically distributed with probability density function (p.d.f) p_X (renewal ISI model); the firing intensity λ is the inverse of the mean ISI. The pdf of possible values of the instantaneous firing rate depends critically on the inspection time t_0 (start of observation). (**B**) The inspection always starts at a spike, i.e., the spike train is observed at random instants (over trials) with respect to the reference time ($t_0', t_0'', \dots$), which is problematic if λ varies with external influences. Furthermore, the mean instantaneous rate exceeds the value of λ even for renewal ISI models. (**C**) The inspection is a fixed event in the reference time (t_0), hence random with respect to spike times, resulting in the probability of observed ISIs being proportional to their duration. The ISI pdf becomes length-biased ($\tilde{X}$), however, the mean instantaneous firing rate always equals λ.

If $p_X(x;\lambda)$ is a scale family in λ, then $p_F(f;\lambda)$ in Eq. (6) is a scale family in $1/\lambda$ (since $F = 1/X$), and due to Eq. (7) it also holds for $p_R(r;\lambda)$,

$$p_R(r;\lambda) = \frac{p_R(r/\lambda;1)}{\lambda}. \tag{15}$$

Generally, for any rv which is a scale family in some parameter θ such that $\theta = \varphi(\lambda) = 1/\lambda$, it follows from Eq. (13) and from the re-parameterization of the Fisher information[27],

$$J(\lambda) \propto \frac{\varphi'(\lambda)^2}{\varphi(\lambda)^2} \propto \frac{1}{\lambda^2}. \tag{16}$$

For more general considerations see Kostal[29]. Therefore,

$$J(\lambda|R) = \frac{\alpha_R}{\lambda^2}, \tag{17}$$

where the constant α_R is given analogously to Eq. (14) with $p_R(r;1)$ appearing on the right-hand side. In general $\alpha_X \neq \alpha_R$ unless certain "symmetry" between the p.d.f's p_X and p_R exists (see examples *(iv, v)* below).

(i) The *Poisson process* is one of the most frequently used models of neuronal firing[17,19]. The pdf of ISIs is

$$p_X(x;\lambda) = \lambda e^{-\lambda x}, \tag{18}$$

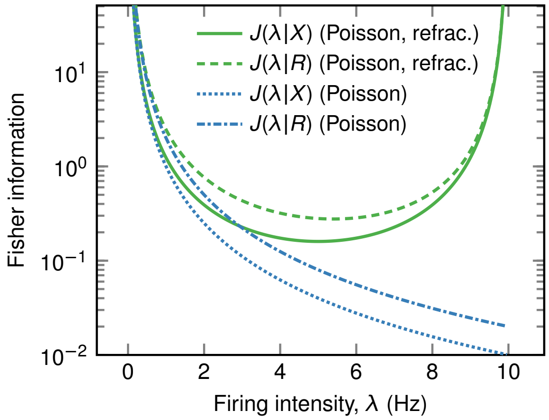

FIG. 2. Fisher information about firing intensity λ for the Poisson model (Eq. 18, dash-dotted, dotted) and Poisson with refractory period (Eq. 21, $\tau = 0.1$ s, solid, dashed). The two situations for each case correspond to the information obtained either directly from the ISIs, $J(\lambda|X)$ (Fig. 1B), or from the asynchronous instantaneous firing rate (AIFR), $J(\lambda|R)$ (Fig. 1C). For both models, it holds that $J(\lambda|R) > J(\lambda|X)$. The refractory period improves the decoding precision, i.e., $J(\lambda|\cdot)$ increases, as λ tends to $1/\tau$ and spiking activity becomes perfectly regular.

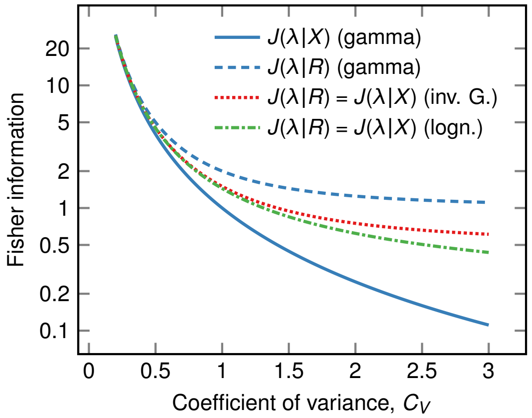

FIG. 3. Dependence on the ISI coefficient of variation (C_V) of Fisher information about the firing intensity $\lambda = 1$ for several renewal ISI models. Information obtained from ISIs, $J(\lambda|X)$ may differ from the information obtained from the asynchronous instantaneous firing rate (AIFR), $J(\lambda|R)$ (Fig. 1C), e.g., for the gamma model of ISIs (Eq. 24). For the inverse Gaussian (dashed) and lognormal (dash-dotted) ISI models, the Fisher information about λ is the same, whether the ISIs or the AIFR is observed. Note that, for $C_V = 1$, the gamma model corresponds to the Poissonian firing.

and the Fisher information is well known[27]

$$J(\lambda|X) = \frac{1}{\lambda^2}. \tag{19}$$

By employing Eq. (7) and directly integrating Eq. (10) we find that the Fisher information about λ obtained from the AIFR is twice as large as that from SIFR (Fig. 2),

$$J(\lambda|R) = \frac{2}{\lambda^2}. \tag{20}$$

(ii) Poisson-like neuron with absolute refractory period. The absolute refractory phase is a state of a neuron, coming immediately after spike generation, during which it is impossible for another spike to be emitted[30]. The exponential pdf in Eq. (18) can be modified to account for the refractory period $\tau > 0$ as

$$p_X(x;\lambda) = \begin{cases} a(\lambda)e^{-a(\lambda)(x-\tau)}, & \text{if } x > \tau, \\ 0, & \text{elsewhere,} \end{cases} \tag{21}$$

$$a(\lambda) = \frac{\lambda}{1-\lambda\tau}, \quad \lambda < 1/\tau,$$

to keep $\mathbb{E}(X) = 1/\lambda$. Unlike in the examples *(i)* and *(iii-vi)* (below), the p_X in Eq. (21) is not a scale family in λ; hence Eqs. (13) and (17) do not apply. The Fisher information is

$$J(\lambda|X) = \frac{1}{(\lambda\tau - 1)^2\lambda^2}, \tag{22}$$

$$J(\lambda|R) = (2 - \lambda^2\tau^2)J(\lambda|X), \tag{23}$$

and $J(\lambda|R) > J(\lambda|X)$. The function $J(\lambda|\cdot)$ is non-monotonic in λ (Fig. 2), approaching infinity both as $\lambda \to 0$ (small value of λ generally implies small MSE as well since $\lambda > 0$) and as $\lambda \to 1/\tau$ (the firing is described by a perfect pacemaker).

(iii) The *Gamma distribution* is one of the most frequent statistical descriptors of ISIs employed in experimental data analysis[31,32]. The pdf p_X, parameterized by the intensity λ and coefficient of variation of ISIs, $C_V = \lambda\sqrt{\mathrm{Var}(X)}$, is

$$p_X(x;\lambda) = \left(\frac{\lambda}{C_V^2}\right)^{1/C_V^2} \Gamma(1/C_V^2)\, x^{1/C_V^2 - 1} \exp\left(-\frac{\lambda x}{C_V^2}\right), \tag{24}$$

where $\Gamma(z) = \int_0^\infty t^{z-1}\exp(-t)\,\mathrm{d}t$ is the gamma function[33]. For this model we have

$$J(\lambda|X) = \frac{1}{C_V^2\lambda^2}, \tag{25}$$

$$J(\lambda|R) = \frac{1 + C_V^{-2}}{\lambda^2}. \tag{26}$$

Note that for $C_V = 1$ the ISI pdf in Eq. (24) equals the exponential pdf in Eq. (18), and that for all values of C_V it holds $J(\lambda|R) > J(\lambda|X)$ (Fig. 3).

(iv) The *inverse Gaussian distribution*[34] is often used to describe neural activity and fitted to experimentally observed ISIs[35,36]. This pdf p_X describes the spiking activity of a stochastic variant of the perfect integrator, the non-leaky integrate and fire stochastic neuronal model. The pdf of the inverse Gaussian distribution can be expressed as

$$p_X(x;\lambda) = \sqrt{\frac{1}{2\pi\lambda C_V^2 x^3}} \exp\left[-\frac{\lambda}{2C_V^2}\frac{(x-1/\lambda)^2}{x}\right]. \tag{27}$$

The Fisher information is

$$J(\lambda|X) = \frac{2 + C_V^2}{2C_V^2\lambda^2}. \tag{28}$$

By inspecting Eq. (27), we find that p_X satisfies a curious "symmetric" relation (*cf.* Eq. 7),

$$p_R(r;\lambda) = p_X(r;1/\lambda), \tag{29}$$

e.g., the "profiles" (or "shapes") of p_X and p_R are exactly the same for $\lambda = 1$. Therefore, due to the Fisher information re-parameterization[29], it holds that $J(\lambda|R) = J(\lambda|X)$ (Fig. 3).

(v) The *lognormal distribution* of interspike intervals, with some exceptions[37], is rarely presented as a result of a neuronal model. However, it represents quite a common descriptor in experimental data analysis[36]. The pdf is

$$p_X(x;\lambda) = \frac{1}{x\sqrt{2\pi\beta}} \exp\left\{-\frac{1}{8}\frac{[\beta + 2\log(x\lambda)]^2}{\beta}\right\}, \tag{30}$$

$$\beta = \log(1 + C_V^2), \tag{31}$$

which also satisfies Eq. (29); hence the Fisher information can be written as[38]

$$J(\lambda|X) = J(\lambda|R) = \frac{1}{\lambda^2\beta}. \tag{32}$$

(vi) The *inverted gamma distribution*[39] does not appear to have ever been used as a renewal ISI model. We use it just to illustrate that, at least in theory, it may be that $J(\lambda|R) < J(\lambda|X)$. A particular instance of the inverted gamma pdf is the AIFR pdf p_R resulting from the exponential ISI distribution in Eq. (18), which makes the following analysis straightforward. Let

$$p_X(x;\lambda) = x^{-3}\lambda^{-2}e^{-1/(\lambda x)}, \tag{33}$$

then $p_R(r;\lambda) = e^{-r/\lambda}/\lambda$, and therefore

$$J(\lambda|R) = \frac{1}{\lambda^2}, \tag{34}$$

$$J(\lambda|X) = \frac{2}{\lambda^2}, \tag{35}$$

symmetrically to Eqs. (19) and (20).

The dependence on C_V of values of Fisher information for the ISI models above are shown in Fig. 3. Whether $J(\lambda|R)$ is going to be equal to, smaller, or greater than $J(\lambda|X)$, for some pdf p_X, cannot be apparently deduced from any conveniently simple statistical characteristics of p_X (such as its moments), and rather depends on the complete analytic form of p_X.

C. Instantaneous firing rate distribution from observations

In the preceding sections, we investigated the impact of the choice of inspection time (Fig. 1B, C) on the properties of the instantaneous rate pdf and its consequences for process intensity estimation. In practice, however, the analytic form of the ISI pdf is often unknown and inference is based on observations only. In the following we demonstrate a simple approach, under the renewal assumption, that relates the observations at fixed inspection times (Fig. 1C) to the observations synchronized with spiking (Fig. 1B).

Let $\{f_1, f_2, \ldots, f_n\}$ be n observations of the SIFR F (Fig. 1B). If the renewal assumption is justified, the data may be conveniently collected from consecutive ISIs within a single trial. Typically, the pdf is estimated either by kernel-based methods or histograms[40,41]. Since the pdf p_R is obtained by adjusting the relative weight of each observation f_i in proportion to the ISI duration, as argued in Section III A, the standard kernel density estimation may be modified as

$$\widehat{p}_R(r) = \sum_{i=1}^{n} w(f_i)K(r - f_i), \tag{36}$$

where K is a suitable kernel function and

$$w(f_i) = \frac{1}{f_i}\left(\sum_{k=1}^{n}\frac{1}{f_k}\right)^{-1}, \tag{37}$$

is the corresponding "weight" of each observation f_i. If $w(f_i) = 1/n$ then Eq. (36) becomes the kernel estimator of p_F.

Similarly, one may modify the histogram estimate of p_F to estimate p_R instead. The value (height) of the histogram of $\widehat{p}_F$ in each bin equals n_B/n, where n_B is the number of observations f_i within the bin. To obtain the corresponding histogram of $\widehat{p}_R$ it is sufficient to multiply the height in each bin by the factor $n/n_B \sum_{i\in B} w(f_i)$, where B is the subset of indices of observations within the bin and $w(f_i)$ is given by Eq. (37). Fig. 4A illustrates both kernel and histogram methods on a sample of $n = 100$ values of the SIFR observations obtained from the gamma ISI model (Eq. 24) with $\lambda = 1$ Hz and $C_V = 0.7$ under the spike-synchronized setup (Fig. 1B). By employing Eq. (36) and the described histogram modification, the same sample, $\{f_i\}_{i=1}^{100}$, also provides the estimate of the pdf p_R (Fig. 4B) under the fixed inspection time setup (Fig. 1C). The kernel function K is Gaussian with standard deviation equal to 0.2.

It is also possible, at least in certain cases, to find the differentiable one-to-one transformation function φ that maps the rv F to the rv R. That is, if the observations $\{f_1, f_2, \ldots, f_n\}$ are i.i.d. according to the pdf p_F then $\{\varphi(f_1), \varphi(f_2), \ldots, \varphi(f_n)\}$ are i.i.d. according to p_R. Assume that the increasing function $f = \xi(r)$ is the inverse of φ. It follows from Eqs. (6), (7), and from the transformation rule, that ξ satisfies the implicit differential equation

$$\frac{\lambda p_F(r)}{r} = \xi'(r)\, p_F\big(\xi(r)\big). \tag{38}$$

The practical usability of this transformation-based approach is apparently limited since the knowledge of p_F is assumed. For the purpose of illustration we find ξ for the exponential distribution of ISIs (Poisson neuron) from Eq. (18). Due to the

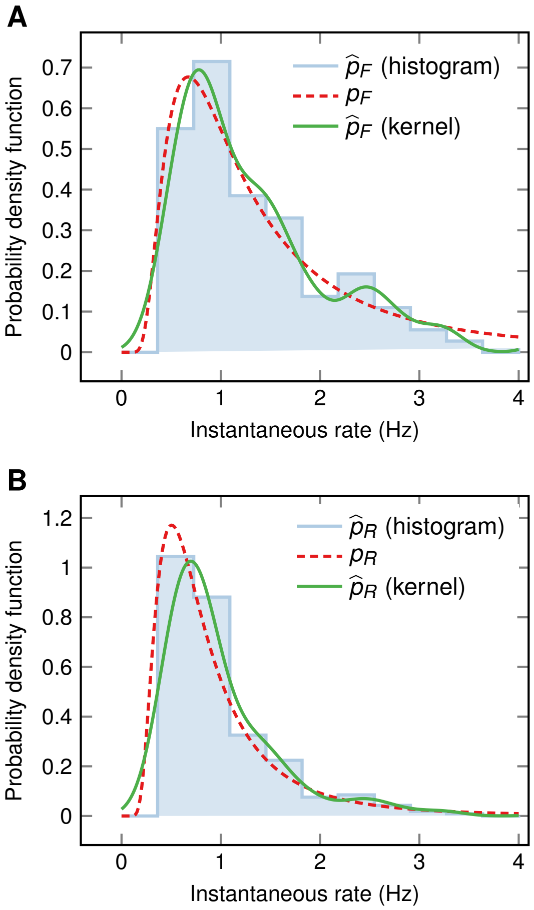

FIG. 4. Estimation of the instantaneous firing rate pdf from observations. A sample of 100 ISIs was generated by the gamma pdf (Eq. 24) with $\lambda = 1\,\text{Hz}$, $C_V = 0.7$. (**A**) Histogram and kernel (Gaussian, std. dev. set to 0.2) estimates of the (classical) synchronous instantaneous firing rate (SIFR) pdf p_F of the generated ISI reciprocal values (Fig. 1B) compared against the true pdf (dashed). (**B**) The same data sample was used to estimate the asynchronous instantaneous firing rate (AIFR) pdf p_R (Eq. 36) that would be observed if the inspection time was unrelated to the actual spike times and fixed to the reference (laboratory) time (Fig. 1C). Hence it is possible to change between the two scenarios, described by p_F resp. p_R, without needing to repeat the experiment.

simple form of p_X, it is more tractable to solve Eq. (38) in an analogous form, adapted to the exponential ISI p.d.f,

$$\lambda^2 x e^{-\lambda x} = \lambda \eta'(x)\, e^{-\lambda \eta(x)}, \tag{39}$$

with the natural initial condition $\eta(0) = 0$. Then it must be that

$$\xi(r) = \frac{1}{\eta(1/r)}, \tag{40}$$

as follows from the inverse relationship between the ISI and the instantaneous firing rate. The solution to Eq. (39) is found to be

$$\eta(x) = x - \frac{\log(1 + \lambda x)}{\lambda}. \tag{41}$$

Substituting $\xi(r)$ from Eq. (40) into Eq. (38) for $p_F(f) = \lambda e^{-\lambda/f}/f^2$ (due to Eq. 6) reveals that it is indeed the correct solution. The inverse, $r = \xi^{-1}(f) = \varphi(f)$, although uniquely determined by Eqs. (40) and (41), cannot be expressed in terms of elementary functions. (It is also possible to obtain a closed-form expression for ξ in the case of gamma and lognormal pdfs of ISIs; however, additional substitutions are necessary and the results are rather cumbersome.)

IV. CONCLUSIONS

We demonstrated that, depending on how a spike train is observed, the statistical properties of the instantaneous firing rate critically differ. We showed that, by synchronizing the inspection time with the external (reference) time, the statistics of the instantaneous firing rate changes. The mean of the asynchronous firing rate equals the inverse of the mean ISI, unlike in the classical (synchronous) case. Taken together, our findings can be summarised by the following main points. First, we reinterpreted the instantaneous firing rate so that it is consistent with firing intensity of the point process, as "expected" (desired) naturally. Second, due to the key differences in the statistics between the synchronous and asynchronous instantaneous rates, parameter estimation precision also differs between the two cases. In particular, the Fisher information about the firing rate in the Poisson model is greater when observing the asynchronous instantaneous rate than when observing ISIs directly. Third, we showed that it is possible to "convert" observed data between the asynchronous and synchronous scenarios, without needing to repeat experimental measurements

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