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Mean instantaneous firing frequency is always higher than the firing rate

Petr Lánský[1], Roger Rodriguez[2], Laura Sacerdote[3]

[1] Institute of Physiology, Academy of Sciences of the Czech Republic, Videnská 1083,
142 20 Prague 4, Czech Republic
[2] Centre de Physique Théorique, CNRS and Faculté des Sciences de Luminy, Université de la Méditerranée, Luminy-Case 907, F-13288 Marseille Cedex 09, France
[3] Department of Mathematics, University of Torino, via Carlo Alberto 10, 10 123 Torino, Italy

Corresponding author:
Petr Lánský
Institute of Physiology
Academy of Sciences of Czech Republic
Videnská 1083,
142 20 Prague 4
Czech Republic
e-mail : lansky@biomed.cas.cz
phone +420 241 062 585
fax +420 241 062 488

Abstract Frequency coding is considered as one of the most common coding strategies employed by the neural systems. This fact leads, in experiments as well as in theoretical studies, to construction of so called transfer functions where the output firing frequency is plotted against the input intensity. However, the term "firing frequency" can be understood differently in different context. Basically, it means that the number of spikes over an interval of preselected length is counted and then divided by the length of the interval, but due to the obvious limitations, the length of observation cannot be arbitrary long. Then firing frequency is defined as reciprocal to the mean interspike interval. In parallel, an instantaneous firing frequency can be defined as reciprocal to the length of current interspike interval and by taking a mean of these, the definition can be extended to introduce the mean instantaneous firing frequency. All these definitions of firing frequency are compared in aim to contribute to a better understanding of the input-output properties of a neuron.

1 Introduction

For a constant signal or under the steady-state conditions, characterization of the input-output properties of neurons, as well as of the neuronal models, is commonly done via so called frequency (input-output) transfer functions in which the output frequency of firing is plotted against the strength (again often frequency) of the input signal. By constructing the transfer functions, it is implicitly presumed, that the information in the investigated neuron is coded by the frequency of the action potentials which is the classical coding schema in neural systems (Adrian, 1928). Characterization of the input signals by the frequency of evoked action potentials requires to give a proper definition of the firing frequency and to extend it for the transient signals. Up to now various definitions of the term "spiking frequency" have been adopted (Awiszus, 1988; Ermentrout, 1998; Gerstner and van Hemmen, 1992) and the concept of the rate coding is carefully treated by Gerstner and Kistler (2002).

In the laboratory situation, the crucial question in identification of the *"firing rate"* (frequency, intensity) is stationarity of the counting process of spikes and without this stationarity speaking about the firing rate loses its sense. The most common and intuitive understanding of the firing frequency is based on counting events (spikes) appearing in an interval of prescribed duration and dividing this number by the length of this interval. An argument against the use of this method is that the duration of observation interval can be limited for several reasons; either the required stationarity disappears outside the interval or its length is out of control of an experimentalist. The conditions are often very variable during experiments. For example, in studies on hippocampal place cells, the dwell time of a freely moving animal in the given part of the arena always changes (Fenton and Muller, 1998). Similarly, in experiments with neurons in sensory systems the observation periods have to be reduced to the time when the stimuli acts upon the neuron (Rieke et al., 1997). In other cases, an applied pharmaceutical treatment has a limited duration and neuron must be recorded only within this time. As we will mention later, for a short observation period the sensitive point is not only the limited length of the observation, but also the time origin in which the counting of spikes starts (if identified with an action potential or not). Gerstner and

Kistler (2002) discuss how to average over time (repetitions of experiments) or over different neurons to improve the estimates of the firing rate.

A related method used for determination of the firing frequency is based on calculation of inverse of the average interspike interval (ISI). We will see that this method and the previously mentioned one (based on counting process) are under specific conditions identical and thus in the theoretical studies reciprocal of the mean ISI is usually declared as the firing rate (Burkitt and Clark, 2000; Van Rullen and Thorpe, 2001 and many others). Of course, for small samples both methods are influenced by the selection of the beginning and the end of the observation period (see Fig. 1), but the aim of this paper is not to study the effect of small sample size. In the extremal situation with only one spike available during the observation period, calculation of the mean ISI fails to provide any information. With two spikes speaking about "mean" ISI is possible and probably less influenced by other factors than the number of spikes in a vaguely determined period.

So called "instantaneous" firing frequency can be defined for a single ISI as inverse of its length (see Pauluis and Baker (2000) for historical notes on this method). This implicitly assumes that the current ISI is the "mean" over a short period of time. Then, in an analogous manner to the firing frequency over an interval of some fixed length, the mean of these instantaneous firing frequencies can define *"mean instantaneous firing rate"*. Similarly, (Knight, 1972; Barbi et al., 1975) define instantaneous rate as reciprocal to the period from the last spike and thus both definitions coincide at the moments of spike generation. These two methods, inverse of the mean ISI and the mean of inverse ISI, are equally suitable for experimental and simulated (modeled) data. Formally, it means that if available ISIs are denoted $\{t_1, ..., t_n\}$, which are independent realizations of a random variable T, then either $1/\bar{t} = 1/\frac{1}{n}\sum_{i=1}^{n} t_i$ or $\overline{(1/t)} = \frac{1}{n}\sum_{i=1}^{n}\frac{1}{t_i}$ are calculated. This corresponds to situation in which it is assumed that ISIs are realization of a random variable T and either $1/E(T)$ or $E(1/T)$, where symbol E is used for mean throughout this paper, are evaluated. One can see the differences in definition of firing frequency on a simple numerical example (Fig. 1).

In this article we are going to compare the above introduced methods of firing rate quantification for the common neuronal models and to point out the possible differences and implications for inference on real data. The paper does not deal with the time-variable and stochastic rates.

2 Basic results

Standard definition of the rate function of discharge (firing) is (Johnson, 1996)

$$f(t) = \lim_{\Delta t \to 0} \frac{E(N(t + \Delta t) - N(t))}{\Delta t}, \tag{2.1}$$

where N is the counting process of spikes. If this function is independent of t and thus constant, which is the presumption considered in this article, it is called the firing rate. As already mentioned, a natural way to calculate the firing rate of a neuron is to divide the number of elicited spikes, $N(t)$, by the length of observation period, t. The mean of ISIs, $E(T)$, is connected to the mean of the counting process, $E(N(t))$, by the asymptotic formula

$$\frac{1}{E(T)} = \lim_{t \to \infty} \frac{E(N(t))}{t}, \tag{2.2}$$

(see e.g., Cox and Lewis, 1966; Rudd and Brown, 1997). Formula (2.2) holds true for finite t only under the condition that $N(t)$ is a stationary point process. Cox and Lewis (1966) show details how $E(N(t))$ is related to the inverse of the mean ISI. The necessary condition for stationarity of the counting process is that it starts in an arbitrary time and this implies that the sequence of ISIs cannot be stationary. However, for a renewal process disregarding the time before the first spike (i.e., starting the sequence of ISIs with the first spike) solves the problem and non-renewal models are outside the scope of this paper. Nevertheless, as illustrated in Fig. 1, equation (2.2) does not hold if the mean ISI is replaced by the sample average and the mean of the counting process by its sample value. The theoretical result given by equation (2.2) can be used if the observation period is sufficiently long. This usually is not the case in estimating the firing rates as the observation period contains rather few spikes. Gerstner and Kistler (2002) give 100-500 ms as a usual length of the observation period and this obviously permits only a few spikes. To overwhelm this difficulty, the averaging over time appearing in equation (2.2) is replaced by averaging over different neurons or over repetition of experiment on the same neuron. In this case, the inference has to be based on realization of the random variable T. Hence, we focus on the estimate and the comparison of the firing frequency, $1/E(T)$ and the mean instantaneous frequency, $E(1/T)$.

In theoretical inference, we can use the fact that the function $1/t$ is convex and by using *Jensen's inequality* (e.g., Rao (1965), p.120) we can prove that for any positive random variable T,

$$E\big(1/T\big) \geq 1/E(T), \tag{2.3}$$

which permits us to conclude: *The mean instantaneous frequency is always higher or at least equal to the firing frequency.* This result will be in sequel illustrated and quantified on several common stochastic models of membrane depolarization and also on several generic statistical descriptors often used for characterization of experimental data.

3 Generic models of spike trains

3.1 Gamma distribution of ISIs

The Gamma distribution is often and successfully fitted to experimentally observed histograms of ISIs and is often taken as a theoretical model for which further conclusions are derived (e.g., Baker and Gerstein, 2001). The probability density function of T is

$$g(t) = \frac{\lambda^v\, e^{-\lambda t} t^{v-1}}{\Gamma(v)} \tag{3.1}$$

where Γ is the Gamma function and $v > 0$ and $\lambda > 0$ are the parameters. (Below probability density will be denoted by $g(.)$.) The statistical moments are well known for this distribution and thus we can directly write

$$1/E(T) = \frac{\lambda}{v}\,. \tag{3.2}$$

For $X = 1/T$, we have

$$g(x) = \frac{1}{x\Gamma(v)}\, e^{-\lambda/x} (\lambda/x)^v \tag{3.3}$$

and the mean for distribution (3.3) can be calculated which yields for $v > 1$

$$E(1/T) = \frac{\lambda}{v-1} \,. \tag{3.4}$$

Compared with equation (3.2) we can see that the difference between two rates is decreasing for increasing v. This is expected since for increasing v, the interval distribution becomes more sharply peaked, i.e., approaches the deterministic case, and in the deterministic case the two measures become identical.

3.2 Poisson process and its modification

The spikes are generated in accordance with a Poisson process if $v = 1$ in model (3.1). Then from equation (3.2) follows that $1/E(T) = \lambda$ and equation (3.4) implies that $E(1/T) = \infty$. This striking difference is caused by existence of very short ISIs and was already noted in Johnson (1996). Let us thus assume that the model is the dead-time Poisson process (modeling a refractory period) in which intervals between events are exponentially distributed but cannot be shorter than a constant δ. Then ISI distribution is $\lambda exp(-\lambda(t-\delta))$ and $1/E(T) = \lambda/(\lambda\delta + 1)$. The mean instantaneous frequency is

$$E(1/T) = \int_0^\infty \frac{\lambda exp(-\lambda z)}{(z+\delta)} dz \tag{3.5}$$

which is finite. In Fig. 2a we show the firing rate and mean instantaneous firing rate in dependency on the inverse of the length of the refractory period δ. We can see that both definitions tend to give the same result with increasing the refractory period. This is expected since the process becomes almost deterministic when the refractory period dominates T.

4 Simple stochastic models

4.1 Perfect integrate-and-fire (Gerstein-Mandelbrot model)

This simple model is closer to the statistical descriptors like those in the previous Section than to the models aiming on realistic description of neurons considered below. It means that even if the data fit the model perfectly, it can be used for their characterization, but hardly any biophysical conclusions can be deduced from this fact. The probability density function of T is known as the Inverse Gaussian distribution,

$$g(t) = \frac{S}{\sigma\sqrt{2\pi t^3}} exp\left\{ -\frac{(S-\mu t)^2}{2\sigma^2 t} \right\} \tag{4.1}$$

where μ, σ^2, S are constants characterizing the neuron and its input (Tuckwell, 1988). Its statistical moments are well known and thus we can directly write

$$1/E(T) = \frac{\mu}{S} \, . \tag{4.2}$$

For $X = 1/T$, we have

$$g(x) = \frac{S}{\sigma\sqrt{2\pi x}} exp\left\{ -\frac{(Sx-\mu)^2}{2x\sigma^2} \right\} \tag{4.3}$$

and the mean for distribution (4.3) can be calculated which yields

$$E(1/T) = \frac{\mu}{S} + \frac{\sigma^2}{S^2} \, . \tag{4.4}$$

Comparing equations (4.2) and (4.4) we can see that the difference between mean instantaneous frequency and the firing frequency increases with increasing σ which characterizes the noise and decreases with decreasing S which is the firing threshold of the model.

4.2 Leaky integrate-and-fire (Ornstein-Uhlenbeck model)

The Ornstein-Uhlenbeck stochastic process restricted by a threshold, called leaky integrate-and-fire (LIF) model, is the most common compromise between tractability and realism in neuronal modeling (Tuckwell, 1988; Gerstner and Kistler, 2002). In this model, the behavior of the depolarization V of the membrane is described by the stochastic differential equation

$$dV = (-\frac{V}{\tau} + \mu)dt + \sigma dW \, , \; V(0) = 0, \tag{4.5}$$

where, $\tau > 0$ is the time constant of the neuron, W is a standard Wiener process (Gaussian noise with unity-sized delta function), μ and σ^2 are constants characterizing the input and $t = 0$ is time of the last spike generation. The possibility to identify the time of the previous spike with time zero is due to the fact that the process of intervals generated by the first passages of process (4.5) across the threshold S is a renewal one.

The solution of the first-passage-time problem is not a simple task for model (4.5) and numerical and simulation techniques have been widely used (Ricciardi and Sacerdote, 1979; Ricciardi and Sato, 1990). The Laplace transform of the first-passage-time probability density function is available (see Tuckwell, 1988 for historical references) and from it its mean can be derived. The firing rate, $f = 1/E(T)$, can be approximated by the following linear function

$$F = \frac{1}{\pi \tau S}\left(\sigma\sqrt{\pi\tau} + 2\tau\mu - S\right), \tag{4.6}$$

(Lansky and Sacerdote, 2001). The ranges in which this approximation is valid is restricted to the values of parameters for which the quantities $(\mu\sqrt{\tau})/\sigma$ and $(\mu\sqrt{\tau} - (S/\sqrt{\tau}))/\sigma$ are small. This means that, first of all, for sufficiently large amplitudes of noise the response function is linear. Linearization (4.6) is quite robust and valid in wide ranges of parameters.

By using the fact that the Laplace transform $\tilde{g}(s)$ of the first-passage-time probability density function is available, the mean of $1/T$ can be calculated by using the primitive function of this Laplace transform,

$$E(1/T) = \left[-\int^{s} \tilde{g}(w)dw\right]_{s=0}. \tag{4.7}$$

The input-output frequency curves using the firing rate and the mean instantaneous rate are compared in Fig. 2b. To improve a possibility of comparison with other models, model (4.5) was transformed into dimensionless variables. It means that the time is in units of time constant τ and voltage in units the firing threshold S. We can see that only for large amplitude of noise, almost half of the threshold value, the difference becomes substantial.

4.3 Diffusion model with inhibitory reversal potential (Feller model)

To include some other features of real neurons in LIF model, the reversal potentials can be introduced into model (4.5). In one of the variants of this model, introduced by Lansky and

Lanska (1987), the behavior of the depolarization V of the membrane is described by the stochastic differential equation

$$dV = (-\frac{V}{\tau} + \mu)dt + \sigma\sqrt{V - V_I}dW\ ,\ V(0) = 0, \tag{4.8}$$

where the parameters have the same interpretation as in equation (4.5) and $V_I < 0$ is the inhibitory reversal potential (Lansky et al., 1995). As for the LIF model, the Laplace transform of the ISI can be written in a closed form

$$g(s) = \frac{1}{\phi\left(s\tau,\ (\mu + 1)\frac{\sqrt{-V_I}}{2\sigma};\ \frac{S\sqrt{-V_I}}{2\tau\sigma}\right)}\ , \tag{4.9}$$

where $\phi(a,\ b; x)$ is the Kummer function (Abramowitz and Stegun, 1965). Equation (4.9) was used for numerical evaluation of the mean instantaneous frequency via equation (4.7) and the mean ISI was calculated by using the Siegert formula (Siegert, 1951). To see the difference between the LIF model and model (4.8) we attempted to have the same set of parameters used in both models. The problem arises for fixing the noise amplitude as in model (4.8) it depends on the actual level of the membrane depolarization V. The amplitude of noise was made equal at the resting level, which is one of the methods applied in Lansky et al. (1995). The input-output frequency curves for firing rate and mean instantaneous rate are compared in Fig. 2c. Again, as for the LIF model, the dimensionless variant of equation (4.8) was used. We can see that the difference between two definitions of firing frequency is less remarkable here than it is for the LIF model.

5 Biophysical model with noise.

To illustrate the achieved results on a realistic model of a neuron we investigated the Morris-Lecar model which is a simplification of the original Hodgkin-Huxley system. Two kinds of channels, voltage gated Ca^{++} channels and voltage gated delayed rectifier K^{+} channels, are present in this model of excitable cell membrane, (Morris and Lecar, 1981; Rinzel and Ermentrout, 1989). When a noisy external input is applied, the system of equations for the normalized membrane depolarization $V(t)$ and for $X(t)$ representing the fraction of open

K^+ channels can be written in the form

$$\frac{dV}{dt} = \overline{g_{Ca}}\,\overline{m}(V_{Ca} - V) + \overline{g_K}\,X(V_K - V) + \overline{g_L}(V_L - V) + I^{ext} + \eta(t), \qquad (5.1)$$

and

$$\frac{dX}{dt} = k_X(V)(\overline{X}(V) - X)\,, \qquad (5.2)$$

where the time is also normalized. The calcium current plays the role of sodium current in the original Hodgkin-Huxley system. However, the calcium channels respond to voltage so rapidly that instantaneous activation is assumed for them with the associated ionic conductance $\overline{g_{Ca}}\;\overline{m}(V)$. I^{ext} is an applied external normalized current and $\eta(t)$ is a white noise perturbation such that $<\eta(s)\eta(t)> \; = \sigma\delta(s-t)$, where σ is a constant. The functions $\overline{m}(V)$, $\overline{X}(V)$ and $k_X(V)$ are of the form

$$\overline{m}(V) = \frac{1}{2}(1 + tanh(\frac{V - V_1}{V_2})),$$

$$\overline{X}(V) = \frac{1}{2}(1 + tanh(\frac{V - V_3}{V_4}))\,, \qquad (5.3)$$

$$k_X(V) = \varphi cosh(\frac{V - V_3}{2V_4}))\,.$$

In these equations, $k_X(V(t))$ is a relaxation constant for a given $V(t)$, further, $\overline{g_{Ca}}$, $\overline{g_K}$ and $\overline{g_L}$ are constants representing normalized conductances, V_{Ca}, V_K and V_L are normalized resting potentials for the two different kinds of ions and for leakage current, finally V_1,V_2,V_3,V_4 and φ are constants. The values of all constants were taken from Rinzel and Ermentrout (1989).

When constant and Gaussian white noise inputs are applied, the random variable T is calculated. In the Fig. 1d, inverse of mean $E(T)$ and mean $E(1/T)$ are shown in dependency on the amplitude of noise for different values of the constant input. The same effect as for the simple neuronal models is observed.

7 Discussion and Conclusions

The calculation of number of spikes per long time window is rather unrealistic from point of view of neural system. Thus, it is assumed that the time averaging is in real systems replaced by population averaging giving the same result (counting spikes emitted by a neuron during period of one minute is the same as counting spikes of 600 neurons emitting spikes within 100 milliseconds). This possibility of replacing time averaging by population averaging would be especially important for evaluation of firing rates in transient situations like in the evoked activity.

The terminology when speaking about the firing rates is not always clear. Sometimes constant firing rate is called mean rate, while at other occasions the function $f(t)$ given by equation (2.1) and really averaged over some interval of time is called mean firing rate. Also the instantaneous rate is understood in different ways. In some cases it is the firing probability in an infinitesimally short interval (Johnson, 1996; Fourcard and Brunel, 2002). In other cases the reciprocal of the ISIs or their smoothed version is used; Pauluis and Baker (2000) and Johnson (1996) compare these two approaches. The difference is well illustrated on the extremal case (deterministic firing - constant ISIs) in which σ in LIF given by equation (4.5) tends to zero. From one point of view, the firing rate is a sequence of delta functions of time with peaks located at the moments of spikes and instantaneous firing rate is either zero or 1/ISI. From the other point of view, adopted here, the rate and instantaneous rate coincide and are equal to reciprocal of the ISI. While the first approach may be seen as more informative, we have to remind that we a priori presume that the rate is constant over the whole period of observation.

Van Rullen and Thorpe (2001) compared the counting method to calculate the firing rate with the ISI method and declared the latter one as potentially more accurate then the first one. However, under the conditions valid in their paper, the authors preferred the latency to the first spike as the neuronal code. It is actually again closely related to the ISI distribution but not based on the counting process.

We compared two methods for evaluation of the firing rate in this article. Despite that one of them gives systematically larger value, the difference between them is not so enormous, at least in the conditions investigated here. The only exception is the Poissonian firing which anyway can be rarely considered as a realistic description of neuronal firing. For other models only strong noise makes the methods substantially different. One advantage of the mean instantaneous firing rate is that statistical properties of the random variable $1/T$ can be derived and thus confidence intervals found and testing procedures for comparison of the rates under different experimental situations can be applied. This is not so easy for the firing rate calculated as $1/E(T)$. The only way to overcome this defect of the reciprocal of the mean ISI is to use known properties of spike counts (Treves et al., 1999; Settanni and Treves, 2000).

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Figure legends:

Fig. 1 A schematical example of experimental data. Observation starts at time zero and lasts for 0.2s with three spikes or four spikes if there is spike at time origin. The firing frequency calculated in three different ways are $f_1 = 1/\bar{t} = 20\,(25)\mathrm{s}^{-1}$, $f_2 =$ #spikes/period $= 15\,(20)$ s^{-1}, $f_3 = \overline{(1/t)} = 23.81\,(32.54)\,\mathrm{s}^{-1}$, where the numbers in parentheses hold if the observation starts with a spike.

Fig. 2 Comparison of the input-output curves in dependency on the parameters of the models. (a) The firing rate (lower curve) and the mean instantaneous firing rate (upper curve) in dependency on the inverse value of the length of refractory period $1/\delta$ for Poissonian firing with rate $\lambda = 20s^{-1}$; the frequencies and $1/\delta$ are given in s^{-1}. (b) - (d) The firing rates (full lines) and the mean instantaneous firing rates (dashed lines) are plotted as function of the amplitude of the noise for different levels of the input. (b) LIF neuronal model, from top to the bottom $\mu =$ 1.5, 1, 0.5 and 0.1, the firing threshold $S = 1$, $\tau = 1$. (c) Feller neuronal model, the same levels of the input μ and the same parameters as for the LIF, $V_I = -1$, (d) Morris-Lecar neuronal model, from top to the bottom $I^{ext} =$ 0.145, 0.125, 0.105 and 0.085.