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FANO FACTOR ESTIMATION

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Abstract. Fano factor is one of the most widely used measures of variability of spike trains. Its standard estimator is the ratio of sample variance to sample mean of spike counts observed in a time window and the quality of the estimator strongly depends on the length of the window. We investigate this dependence under the assumption that the spike train behaves as an equilibrium renewal process. It is shown what characteristics of the spike train have large effect on the estimator bias. Namely, the effect of refractory period is analytically evaluated. Next, we create an approximate asymptotic formula for the mean square error of the estimator, which can also be used to find minimum of the error in estimation from single spike trains. The accuracy of the Fano factor estimator is compared with the accuracy of the estimator based on the squared coefficient of variation. All the results are illustrated for spike trains with gamma and inverse Gaussian probability distributions of interspike intervals. Finally, we discuss possibilities of how to select a suitable observation window for the Fano factor estimation.

1. Introduction.

One of the most important open questions in neuroscience is how neurons code transfered information into spike trains. The basic and frequently considered concept is rate coding [11]. It assumes that the information is coded by the spike rate, which is mostly calculated as a spike count average. The spike rate, however, does not fully depend on exact spike times, different spike sequences can yield the same spike rate. So there is the possibility that there is more information in a spike train than what can be coded using the spike rate. A natural extension of the rate coding, which better reflects the specific spike timing, is variability coding [20]. In that case, it is assumed that the variability in spike trains also carries information. The question whether the variability coding is used in real neurons or the variability is caused just by a noise without useful information is still unanswered. However, this issue increases the importance of suitable variance measurement and estimation.

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The spike train variability is usually examined based on one of two following neuronal data types - a single (long) spike train or multiple (short) spike trains. By a single spike train we understand a relatively long record of spike activity, often spontaneous, of one neuron. On the other hand, multiple spike trains often arise from repeated measurements (repeated trials) of the immediate reaction to a stimulus. The reaction is usually of limited duration therefore there is the demand on a short observation window.

There are many possibilities how to measure the variability in spike trains. Often it is assumed that the spike trains satisfy the definition of renewal process and so a measure of variability of continuous positive random variables, which represent the length of interspike intervals (ISIs), can be used [14]. Such a typical and basic measure is coefficient of variation (CV), which is the ratio of the square root of the variance of the length of the ISIs to their mean. Alternatively, the variability of numbers of spikes occurred in an observation window is measured. In that case, mainly the Fano factor (FF), the ratio of the variance of the number of spikes to the mean, is used. Although CV and FF, as defined, represent different types of variability, they are closely related for renewal processes - with increasing length of the observation window FF converges to CV^2 [18]. Thus to measure their common value it is possible to use CV as well as FF.

Modeling of spike trains using renewal processes assumes independent and identically distributed lengths of ISIs which certainly not always apply to real spike trains, often the spike rate changes in time or the ISIs are correlated [10]. However, there are situations when such a description of ISIs can be appropriate. For instance, when we observe the spike train in a short time window then, even if the character of the spike train changes in time, the observed part can be approximately stationary. The second situation where the spike train often seems to be well described by a renewal process is during spontaneous activity. Moreover, it is possible to eliminate rate changes before variability estimation using a time transformation [18]. Let us notice that also some local measures [22, 24], which are less sensitive to spike rate changes, and methods for extracting the firing variability and the firing rate simultaneously [15, 23] were proposed.

Estimation of both CV and FF is not always trivial. For short spike trains (short observation window) the probability of observation of large ISIs is reduced and therefore the standard estimator of CV (square root of sample variance of ISIs divided by sample mean) is biased. In this case, there is a bias also in the standard estimator of the limit value of FF (sample variance of spike counts divided by sample mean). It is caused by the fact that we estimate FF for infinite intervals based on finite, short observation window. In estimation from single spike train, these issues are usually minor, but there is another complication in FF estimation. To be able to use the estimator, we need data in form of spike counts. They are naturally obtained by segmentation of the spike train into intervals of the same length and the accuracy of the estimator surely depends on this length. However, it is not clear how to choose the most suitable one.

In this article, we explore some problematic aspects of estimation of the limit value of FF from repeated trials and from a single spike train and show that there are situations when the estimator of FF is more suitable for estimation of CV (squared) than its commonly used estimator. Firstly, we describe and illustrate the dependency of FF on the length of the observation window and investigate the effect of refractory period on this dependence. In [25], a decrease of FF for short observation window caused by refractory period is shown, in [7] it is analytically explained for a Poisson process with absolute refractory period. We show this effect analytically also for equilibrium renewal processes with absolute or relative refractory period. Next, an approximate asymptotic formula for the mean square error (MSE) of the estimator is derived and its accuracy verified using simulated spike trains. This formula can be used, among others, to approximate the MSE in estimation from single spike trains and thus also to choose the suitable length of intervals into which the spike train is segmented. Finally, we compare the accuracy of CV and FF estimators based on simulated spike trains and discuss the suitable choice of the observation window for the FF estimator. For numerical illustrations, we use gamma and inverse Gaussian probability distributions of ISIs.

2. **Theory.**

Neural spike trains are often described as a renewal process, where it is assumed that the lengths of ISIs are independent and identically distributed continuous positive random variables. We denote this random variable by T, its probability density function (pdf) by $f(t)$ and cumulative distribution function (cdf) by $F(t)$. The process can also be described as a counting process $\{N_t,\, t \geq 0\}$, which represents the number of spikes occurred from time zero to a time t. For the complete description of a spike train, it is also necessary to specify the position of time zero. Commonly, the observation begins either at the moment of a spike (ordinary renewal process) or in a random moment, unrelated to the spike train (equilibrium renewal process).

The coefficient of variation (CV) and the Fano Factor (FF) are defined as

$$\mathrm{CV} = \frac{\sqrt{\mathrm{Var}(T)}}{\mathrm{E}(T)}, \tag{1}$$

$$\mathrm{FF} = \lim_{t\to\infty} \mathrm{FF}_t, \tag{2}$$

where

$$\mathrm{FF}_t = \frac{\mathrm{Var}(N_t)}{\mathrm{E}(N_t)}, \tag{3}$$

$\mathrm{E}(T)$ and $\mathrm{E}(N_t)$ denote means of random variables T, and N_t and $\mathrm{Var}(T)$ and $\mathrm{Var}(N_t)$ denote their variances. While CV describes directly the variability of the random variable T, FF aims at the variability of N_t. Since T represents only ISIs, not the time up to the first spike, in formula (1), and since t tends to infinity in definition (2), it is not necessary to specify the condition for selection of time zero (in other words, the values of CV and FF do not depend on whether the corresponding renewal process is ordinary or equilibrium).

The estimation of CV is straightforward, its standard estimator is the ratio of the square root of the sample variance to the sample mean of ISIs, thus

$$\widehat{\mathrm{CV}} = \frac{\sqrt{s_T^2}}{\overline{T}} = \frac{\sqrt{\frac{1}{n-1}\sum_{i=1}^{n}(T_i - \frac{1}{n}\sum_{i=1}^{n} T_i)^2}}{\frac{1}{n}\sum_{i=1}^{n} T_i}, \tag{4}$$

where $T_1, T_2, \ldots, T_n$ denote the lengths of ISIs. This estimator is biased, however, the problem has been dealt with in [8, 14].

Estimate of FF is commonly calculated based on numbers of spikes occurred in time intervals (in an observation window) of length t. We denote these numbers by

$N_t^1, N_t^2, \dots, N_t^n$. Then the usual estimator of FF is

$$\widehat{\mathrm{FF}} = \frac{s^2_{N_t}}{\overline{N}_t} = \frac{\frac{1}{n-1}\sum_{i=1}^n (N_t^i - \frac{1}{n}\sum_{i=1}^n N_t^i)^2}{\frac{1}{n}\sum_{i=1}^n N_t^i}. \tag{5}$$

The counts N_t^i, $i = 1, \dots, n$, are mostly obtained from n trials, but also, not so frequently, by segmentation of a single spike train (of a length τ) into n parts (see Figure 1). However, even if we assume that both the trials and the single spike train correspond to the same equilibrium renewal process, these situations are not completely equivalent from the point of view of properties of N_t^i. Later, this issue will be discussed in more detail.

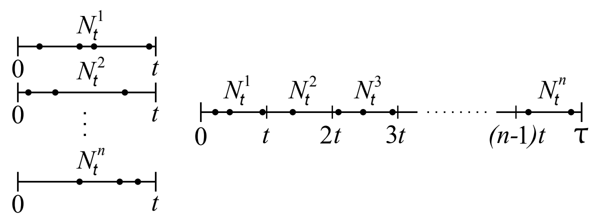

Figure 1. Two types of neuronal data for FF estimation, n trials (left) and segmented single spike train of length τ (right).

There is a clear discrepancy between definition (2) and estimator (5). The value of t tends to infinity in the definition of FF, but it is finite and often relatively short in a specific data set. Therefore, formula (5) is more likely an estimator of FF_t. The difference between FF_t and FF causes, for short t, relatively strong bias of $\widehat{\mathrm{FF}}$ [17]. Thus the behavior of FF_t, as a function of t, highly affects the quality of $\widehat{\mathrm{FF}}$. Above all, the rate of convergence to its limit is important. Basic and well known, [5, 13, 17, 19], properties of FF_t which hold for renewal processes are

$$\lim_{t\to 0^+} \mathrm{FF}_t = 1, \tag{6}$$

$$\lim_{t\to\infty} \mathrm{FF}_t = \frac{\mathrm{Var}(T)}{\mathrm{E}(T)^2} = \mathrm{CV}^2, \tag{7}$$

the latter also yields the relationship

$$\mathrm{FF} = \mathrm{CV}^2. \tag{8}$$

Formula (6) can be understood using the fact that the probability distribution of N_t converges, independently of the probability distribution of T, to a Bernoulli distribution as $t \to 0$ (just zero or one spike can occur in $[0, t]$). On the other hand, the probability distribution of N_t is normal for $t \to \infty$ [5], which can be used to justify formula (7).

It follows from relationships (6) and (7) that FF_t goes from one to CV^2 (= FF) as t goes from zero to infinity, but the behavior of FF_t between these two values is not obvious. The simplest situation is for the exponential distribution of T (N_t is the Poisson process), in this case $\mathrm{FF}_t = 1$ for all $t > 0$. For more complex probability distributions of T (e.g., gamma, inverse Gaussian or log-normal) it is possible to approximate FF_t for large t, [5],

$$\mathrm{FF}_t \approx \mathrm{CV}^2 + \frac{1}{t}\left[\frac{\mathrm{E}(T)}{2}\left(1 + \frac{\mathrm{Var}(T)}{\mathrm{E}^2(T)}\right)^2 - \frac{1}{3}\frac{\mathrm{E}(T^3)}{\mathrm{E}^2(T)}\right], \quad \text{for } t \to \infty, \tag{9}$$

however, FF_t itself cannot be exactly expressed in a closed form.

Relationship (8) is an important property of renewal processes, which may be used in various ways. One possibility is estimation of CV^2 instead of FF. However, it is not obvious which estimator is more accurate. Later, we examine this issue using simulated spike trains. Another way how to apply equation (8) is joint analysis of CV^2 and FF estimates, as in [18]. Using this method we can for example test whether the spike train corresponds to a renewal process.

Let us notice that the function FF_t can behave significantly different for non-renewal processes. Mainly, it can diverge for $t \to \infty$. In [25] there is shown a situation when FF_t increases as a power-law function. One of the reasons which can cause such a behavior is ISIs correlation. For example, for equilibrium point processes with correlated ISIs it holds, [17],

$$\lim_{t\to\infty} \mathrm{FF}_t = \mathrm{CV}^2 \left(1 + 2\sum_{i=1}^{\infty} \xi_i\right), \tag{10}$$

where ξ_i is the linear correlation coefficient of ith order of the ISIs. Thus FF is not in general equal to CV^2, however, these situations are out of the scope of this article.

3. Results.

In this section, we present some new properties of FF_t and $\widehat{\mathrm{FF}}$ under the condition that N_t is an equilibrium renewal process.

3.1. Properties of FF_t.

Firstly, we derive a formula which can be used for numerical calculation of FF_t. Let us rewrite definition (3), using the formula, [5],

$$\mathrm{E}(N_t) = \frac{t}{\mathrm{E}(T)}, \tag{11}$$

into the form

$$\mathrm{FF}_t = \frac{\mathrm{E}(T)}{t}\mathrm{E}(N_t^2) - \frac{t}{\mathrm{E}(T)}. \tag{12}$$

There is not a formula similar to equation (11) for $\mathrm{E}(N_t^2)$ so we use its Laplace transform, [13],

$$\mathcal{L}\{\mathrm{E}(N_t^2)\}(s) = \frac{1 + \tilde{f}(s)}{\mathrm{E}(T)s^2[1 - \tilde{f}(s)]}, \tag{13}$$

where $\tilde{f}(s)$ is the Laplace transform of pdf $f(t)$. Then from equations (12) and (13) we get

$$\mathrm{FF}_t = \frac{1}{t}\mathcal{L}^{-1}\left\{\frac{1 + \tilde{f}(s)}{s^2[1 - \tilde{f}(s)]}\right\}(t) - \frac{t}{\mathrm{E}(T)}, \tag{14}$$

where $\mathcal{L}^{-1}$ denotes the inverse Laplace transform. Formula (14) allows us to calculate FF_t for any t and any probability distribution of T.

Next, we will specify the behavior of FF_t near zero for a certain situation. Namely, if for pdf $f(t)$ it holds that

$$f(t) \approx at,\ a \geq 0,\ \text{for } t \to 0^+, \tag{15}$$

then (see Appendix A)

$$\lim_{t\to 0^+} \frac{\mathrm{dFF}_t}{\mathrm{d}t} = -\frac{1}{\mathrm{E}(T)}. \tag{16}$$

Condition (15) corresponds to the concept of relative refractory period (very low probability of short ISIs), thus this result can be formulated so that the relative refractory period causes an initial decrease of FF_t independently of the value of FF.

The presence of an absolute refractory period leads to a similar effect. Instead of ISIs of length T we now assume ISIs of length $T+r$, where $r>0$ represents the length of the absolute refractory period. Then (see Appendix A)

$$\mathrm{FF}_t = 1 - \frac{t}{\mathrm{E}(T)+r}, \quad \text{for } 0 < t \le r. \tag{17}$$

Thus FF_t is just a line with slope $-1/(\mathrm{E}(T)+r)$ in $(0,r]$. Further, it follows from equation (7) that

$$\mathrm{FF} = \frac{\mathrm{Var}(T)}{(\mathrm{E}(T)+r)^2}, \tag{18}$$

so the value of FF is lower than in the situation without a refractory period (because the mean of ISIs is now larger and the variance does not change).

3.2. Mean square error of $\widehat{\mathrm{FF}}$.

A suitable and often used measure of accuracy of an estimator is the mean square error (MSE). It includes both bias and variance so it is useful in situations when we deal with bias-variance tradeoff. Here we present an approximate asymptotic formula for the MSE of $\widehat{\mathrm{FF}}$ under the assumption that the random variables N_t^i, $i=1,\dots,n$, describe independent and identical equilibrium renewal processes.

MSE of $\widehat{\mathrm{FF}}$ is defined as

$$\mathrm{MSE}(\widehat{\mathrm{FF}}) = \mathrm{E}(\widehat{\mathrm{FF}} - \mathrm{FF})^2 \tag{19}$$

and it can be rewritten into the form

$$\begin{aligned}\mathrm{MSE}(\widehat{\mathrm{FF}}) &= [\mathrm{E}(\widehat{\mathrm{FF}}) - \mathrm{FF}]^2 + \mathrm{E}[\widehat{\mathrm{FF}} - \mathrm{E}(\widehat{\mathrm{FF}})]^2 \\ &= \mathrm{Bias}^2(\widehat{\mathrm{FF}}) + \mathrm{Var}(\widehat{\mathrm{FF}}).\end{aligned} \tag{20}$$

For large t and n it is possible to approximate $\mathrm{MSE}(\widehat{\mathrm{FF}})$ using formula (see Appendix B)

$$\begin{aligned}\mathrm{MSE}(\widehat{\mathrm{FF}}) \approx &\left[\frac{1}{t}\mathrm{E}(T)\mathrm{G}(T)\right]^2 \\ &+ \frac{\mathrm{E}^2(T)}{t^2}\left[\frac{2}{n-1} + \frac{\mathrm{E}^2(T)}{nt^2}\left(\mathrm{G}(T) + \frac{\mathrm{FF}}{\mathrm{E}(T)}t\right)\right] \\ &\cdot \left[\mathrm{G}(T) + \frac{\mathrm{FF}}{\mathrm{E}(T)}t\right]^2, \text{ for } t\to\infty,\ n\to\infty,\end{aligned} \tag{21}$$

where

$$\mathrm{G}(T) = \frac{1}{2}(1+\mathrm{FF})^2 - \frac{1}{3}\frac{\mathrm{E}(T^3)}{\mathrm{E}^3(T)}. \tag{22}$$

The first summand in formula (21) represents the squared bias and the second one corresponds to the variance of $\mathrm{MSE}(\widehat{\mathrm{FF}})$.

4. **Examples.** In this section we aim to illustrate properties of FF_t and $\widehat{\mathrm{FF}}$ in some specific situations by using numerical calculations and simulations. As probability distributions of T, we use gamma and inverse Gaussian (IG) distributions. They are probably the most widely used distributions for modeling of lengths of ISIs [8, 17, 19].

The pdf of the gamma distribution is

$$f_G(t;\lambda,k)=\frac{\lambda^k t^{k-1}e^{-\lambda t}}{\Gamma(k)},\quad t\geq 0,\, \lambda>0,\, k>0, \tag{23}$$

where Γ denotes the Gamma function, and the pdf of the IG distribution is

$$f_I(t;\mu,\nu)=\sqrt{\frac{\nu}{2\pi t^3}}\exp\left\{-\frac{\nu(t-\mu)^2}{2\mu^2 t}\right\},\quad t\geq 0,\, \mu>0,\, \nu>0. \tag{24}$$

An advantage of these pdfs is that it is possible to calculate analytically their Laplace transforms, which are necessary for application of formula (14). Note that the pdf (23) with $k=1$ is the exponential distribution and the corresponding counting process N_t is a Poisson process.

Both of these probability distributions (gamma and IG) have two parameters, and their values can be uniquely related to $\mathrm{E}(T)$ and FF. It holds that

$$\lambda=\frac{1}{\mathrm{E}(T)\mathrm{FF}},\; k=\frac{1}{\mathrm{FF}} \tag{25}$$

for the gamma distribution and

$$\mu=\mathrm{E}(T),\; \nu=\frac{\mathrm{E}(T)}{\mathrm{FF}} \tag{26}$$

for the IG distribution.

4.1. **Behavior of** FF_t**.** Here we illustrate the dependency of FF_t on t, calculating (approximating) their values using formula (14).

In Fig. 2, there are displayed the graphs of FF_t and corresponding probability densities for various values of FF. We see that FF_t goes from one to CV^2 and also its initial behavior corresponds to relationship (16), FF_t starts with a decrease at zero if pdf of T satisfies condition (15). This causes relatively large difference between FF_t curves for gamma and IG probability distributions even with the same FF and $\mathrm{E}(T)$ - for IG probability distribution, they can be nonmonotonic and, for $\mathrm{FF}>1$, the convergence to FF is evidently slower than for gamma distribution. It is caused by the presence of relative refractory period for all values of FF. On the other hand, there is no refractory period for gamma distribution with $\mathrm{FF}>1$ so FF_t is, in this case, always monotonic.

Next, we illustrate the effect of the absolute refractory period. We calculate FF_t for the same situations as in Fig. 2 with the difference that we add a refractory period of length $r=0.1$ to T (see Fig. 3). The graph of FF_t is now initially a line, which slope does not depend on the value of FF. Evident consequence is also slower convergence of FF_t to its limit value for $\mathrm{FF}>1$.

Finally, in Fig. 4, there is shown the accuracy of the approximation (9). We see that it is always better for low values of FF and, if $\mathrm{FF}>1$, it is also substantially better for gamma probability distribution of T than for IG distribution.

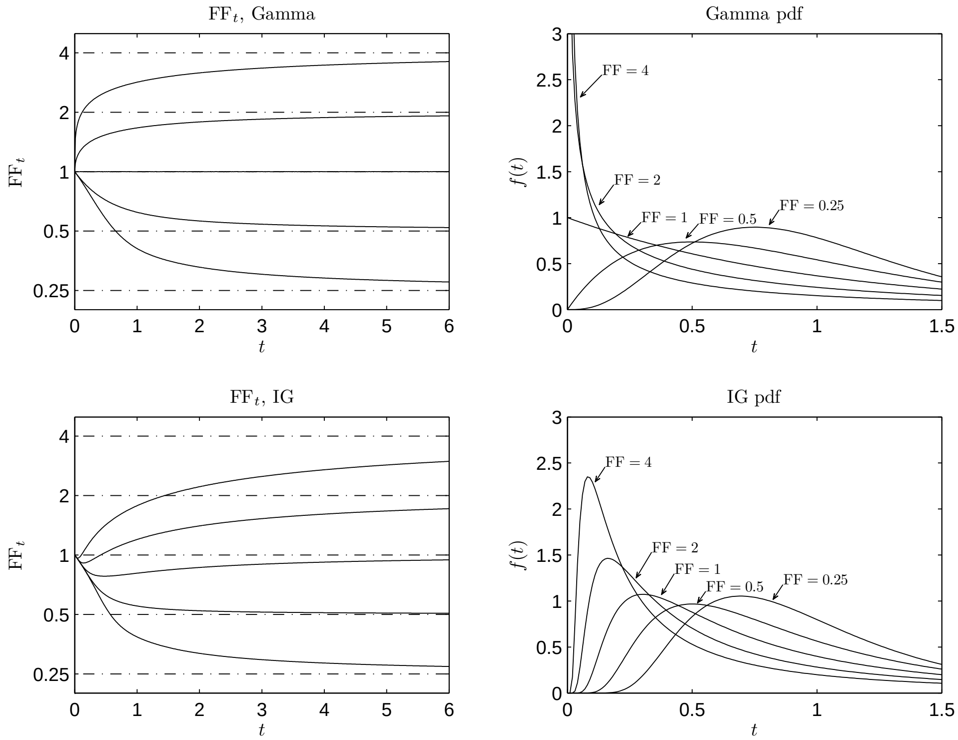

FIGURE 2. Left: Graphs of FF_t for gamma and IG probability distributions of T. Mean of T is always one, values of FF are 0.25, 0.5, 1, 2, 4 (from bottom to top). FF_t-axis is logarithmically scaled. Values of FF_t are calculated numerically using formula (14). Right: Probability density functions of gamma and IG distributions corresponding to the curves on the left.

4.2. **Numerical experiments.** There are some questions we are not able to answer using the analytical results. For example, we do not know the accuracy of asymptotic the approximation (21) or which estimator, (4) or (5), is more suitable to estimate FF. Therefore, these and some other issues are examined here using simulated spike trains.

For measuring the error of the estimators we use sample mean square error which is given by

$$\widehat{\mathrm{MSE}}(\hat{\theta}) = \frac{1}{m}\sum_{i=1}^{m}(\hat{\theta}_i - \theta)^2, \tag{27}$$

where $\hat{\theta}$ is an estimator of θ and $\hat{\theta}_1, \hat{\theta}_2, \ldots, \hat{\theta}_m$ are calculated realizations of $\hat{\theta}$. Definition (27) is a sample analogy (estimator) of formula (19), if it is not confusing we refer to both as MSE only. Their relative square roots in percents are shown in figures.

4.2.1. $\mathrm{MSE}(\widehat{\mathrm{FF}})$ *in estimation from independent trials.* Here we wish to clarify the question for what t and n it is possible to use relationship (21) as a reliable approximation of $\mathrm{MSE}(\widehat{\mathrm{FF}})$ in estimation from repeated trials. To that end, we calculate

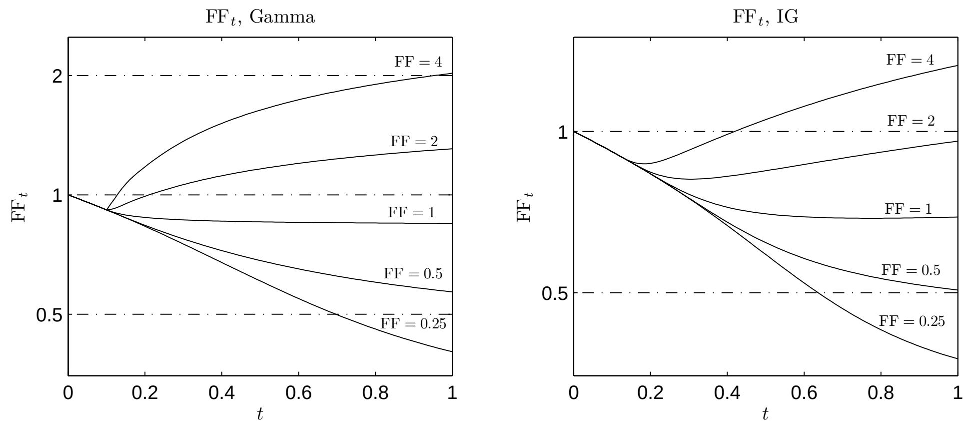

FIGURE 3. Graphs of FF_t for gamma (left) and IG (right) probability distributions of T with absolute refractory period. Mean of T is always 1.1 (of which 0.1 is the absolute refractory period), values of FF are 0.25, 0.5, 1, 2, 4 (from bottom to top). FF_t-axis is logarithmically scaled. Values of FF_t are calculated numerically using formula (14).

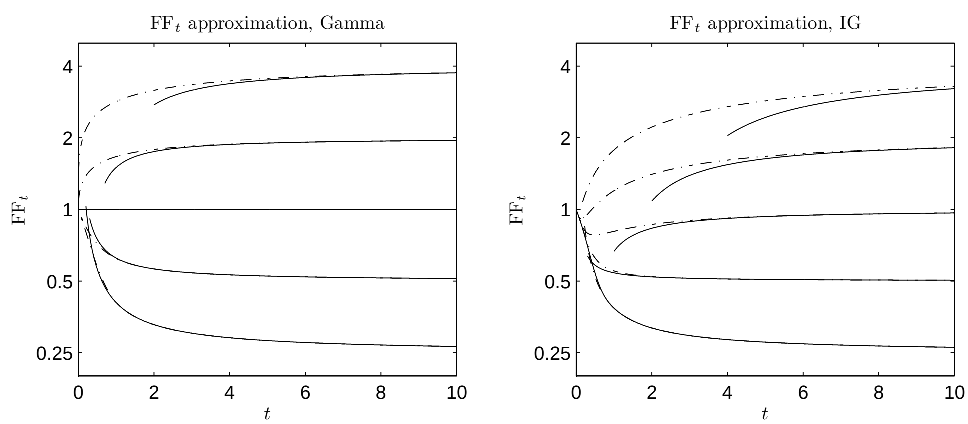

FIGURE 4. Graphs of FF_t (dash-dotted line) and their approximations calculated using formula (9) (solid line) for gamma (left) and IG (right) probability distributions of T. Mean of T is always one, values of FF are 0.25, 0.5, 1, 2, 4 (from bottom to top). FF_t-axis is logarithmically scaled.

MSE based on estimates from simulated spike trains and compare it with values of MSE obtained using approximation (21). This comparison is shown in Fig. 5. We see that the differences between approximated and simulated values of MSE are in considered situations relatively small. It seems that if $\mathrm{FF} < 2$ then formula (21) is a sufficiently accurate approximation of MSE for t about four means of ISIs and n about 25. Moreover, the accuracy quickly improves with decreasing value of FF.

4.2.2. $\mathrm{MSE}(\widehat{\mathrm{FF}})$ *in estimation from single spike train.* In FF estimation from a single spike train it is necessary to segment the spike train into n parts (intervals) of

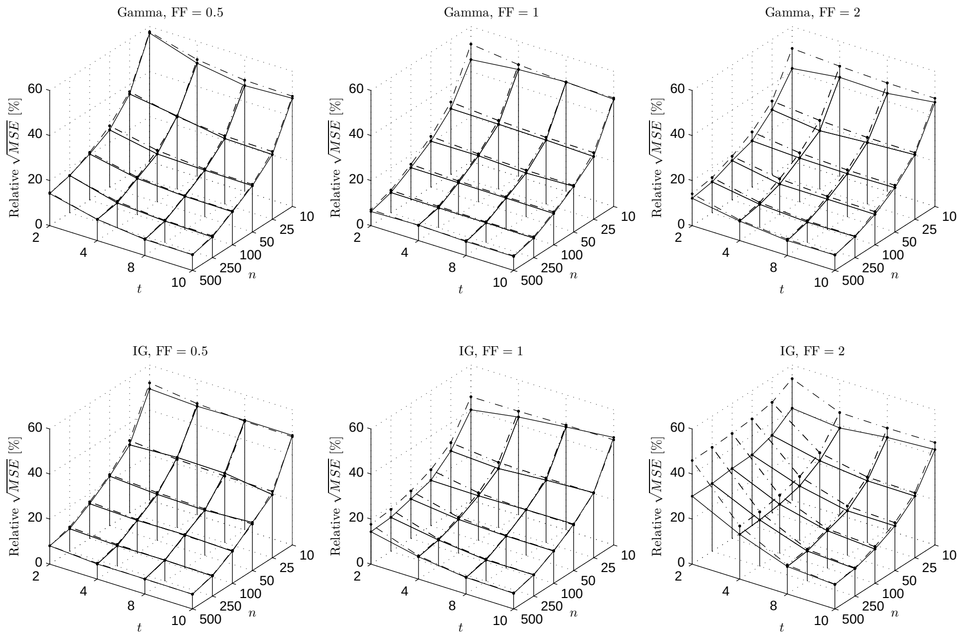

FIGURE 5. Relative $\sqrt{\mathrm{MSE}}$ of $\widehat{\mathrm{FF}}$ in percents obtained using simulations (solid line) and using formula (21) (dashed line). ISIs have gamma (upper panels) and IG (lower panels) probability distributions with mean one and FF $= 0.5, 1, 2$. Simulated values are calculated based on 1000 estimates of FF.

a length t to obtain the spike counts for application of $\widehat{\mathrm{FF}}$ and it is not obvious what t to use. For short intervals, the estimator is strongly biased, but with increasing t the number of intervals decreases (because of fixed length of the spike train) and that leads to an increase of variance of $\widehat{\mathrm{FF}}$. Therefore, here we examine the dependency of $\mathrm{MSE}(\widehat{\mathrm{FF}})$ on t and try to applicate formula (21) to its approximation. However, this formula was derived under the assumption that the spike counts are obtained from independent identical equilibrium renewal processes, which is different situation from one equilibrium renewal process segmented into n parts. For example, the spike counts are not completely independent (except for the Poisson process). However, following simulations indicate that violation of these assumptions does not play any role.

We obtain every estimate of FF based on one simulated spike train, which is segmented into intervals of length t. The length of the whole spike train is always $\tau = 1000$ (mean of ISIs is one), thus $n = [1000/t]$ (integer part of $1000/t$). In this way, we obtain the dependency of MSE of $\widehat{\mathrm{FF}}$ on t and compare it with values obtained using approximation (21) (see Fig. 6). We can conclude that there is a minimum of MSE for a certain value of t. However, if $\mathrm{FF} = 1$, this minimum occurs for $t = 0$ (more precisely, $\mathrm{MSE} \to 0$ for $t \to 0$). This is obvious because $\mathrm{FF}_t \to 1$ for $t \to 0$. Moreover, for the IG distribution with $\mathrm{FF} = 1$, there is another (local) minimum, which is caused by the nonmonocity of FF_t. We also see that the values of MSE and especially their minima are in all situations relatively

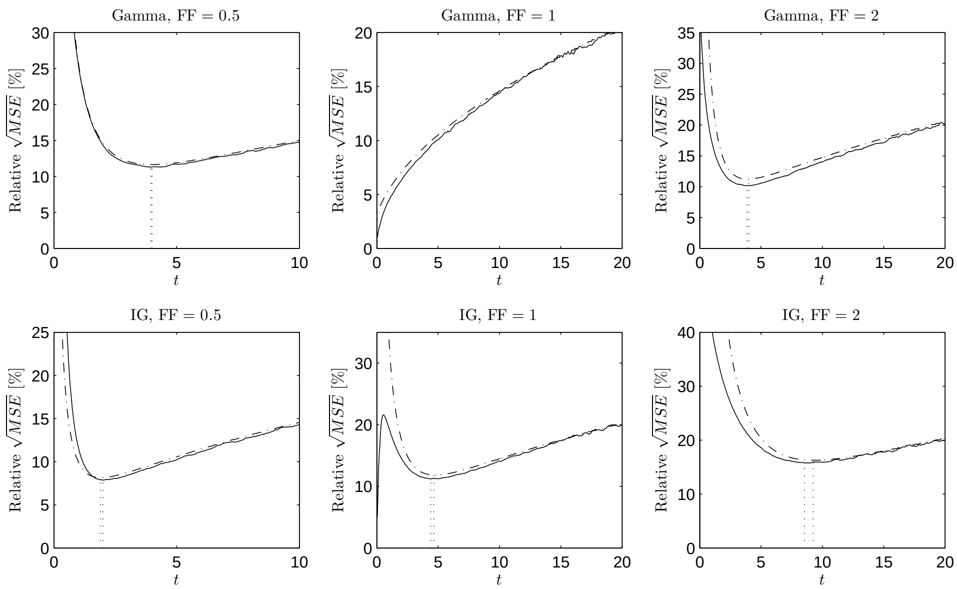

FIGURE 6. Relative $\sqrt{\text{MSE}}$ of $\widehat{\text{FF}}$ in percents in dependence on window size t calculated using formula (21) (dash-dotted line) and using simulations (solid line) in estimation from single spike train. ISIs follow gamma (upper panels) and IG (lower panels) distributions with mean one and FF $= 0.5, 1, 2$. The length of the spike trains is always $\tau = 1000$. Simulated values are calculated based on 1000 estimates of FF, corresponding curves are smoothed using moving average method.

well approximated by formula (21). One exception is the situation with for the IG distribution with FF $= 1$, where only the local minimum is approximated.

4.2.3. *Comparison of* $\widehat{\text{FF}}$ *and* $\widehat{\text{CV}}^2$. Due to relationship (8), there is the possibility of estimating FF using estimator of CV and vice versa, therefore, the question which of them is more precise arises. To clarify this issue we calculate and compare their MSE based on simulated spike trains in various situations, short repeated trials and single spike train are distinguished. In the first case, estimation using both estimators is problematic. Mainly, $\widehat{\text{CV}}$ is, as well as $\widehat{\text{FF}}$, strongly biased. We cannot observe ISIs longer than the length of the observation window and thus the variability in ISIs seems to be lower than it is. This problem almost vanishes in estimation from a single spike train, but on the other hand, there is the problem with the spike train segmentation for $\widehat{\text{FF}}$. As was shown, its MSE depends on used length of intervals t and therefore, to obtain "the best possible estimate", we use t which minimizes formula (21). However, it is necessary to avoid situations when this minimum is very low for FF near one (see Fig. 6), thus the minimal t we use is 3 (in mean ISI units). The results of these simulations are in Fig. 7.

Although there are some exceptions, it can be concluded the FF estimator is more suitable for estimation from short repeated trials and CV estimator for estimation from single spike trains. The exception in the first case is for spike trains with low

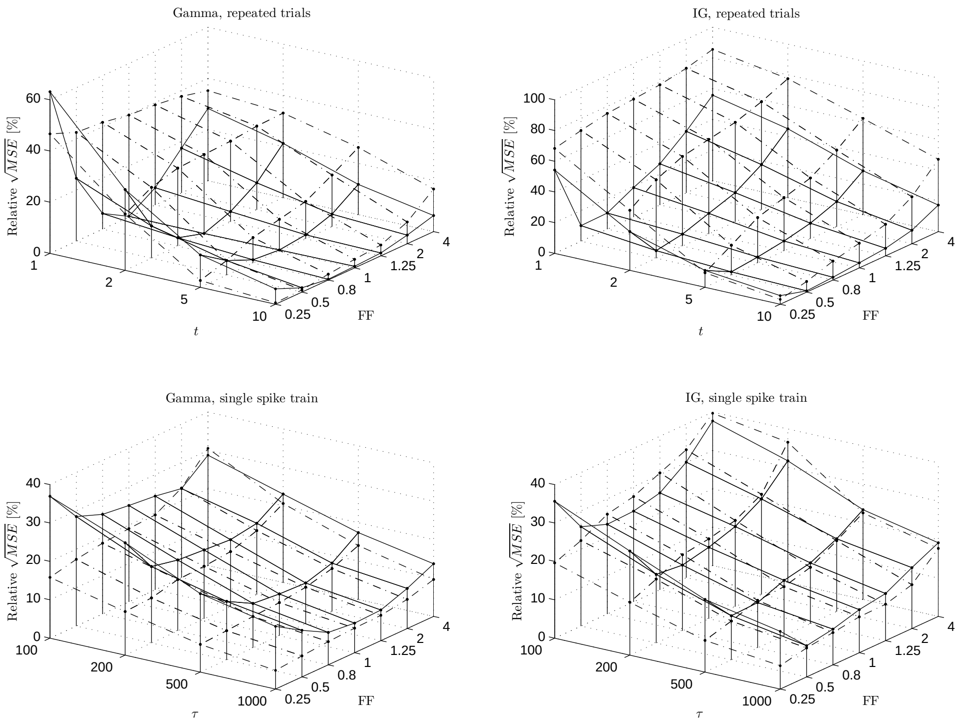

FIGURE 7. Relative $\sqrt{\mathrm{MSE}}$ of $\widehat{\mathrm{FF}}$ (solid line) and of $\widehat{\mathrm{CV}}^2$ (dash-dotted line) in percents in estimating from repeated trials (upper panels) and in estimating from single spike train (lower panels). ISIs follow gamma (left) and IG (right) distributions with mean one and with various values of FF. In estimation from repeated trials, every error is calculated based on 1000 estimates, obtained from 1000 trials. In estimation from a single spike train, the values of the errors are calculated based on 1000 estimates.

variability (approximately for FF < 0.25), when $\widehat{\mathrm{CV}}^2$ seems to be more accurate than $\widehat{\mathrm{FF}}$. In the second case, MSE of $\widehat{\mathrm{FF}}$ is rarely lower than MSE of $\widehat{\mathrm{CV}}^2$. However, this occurs mainly for small τ and FF around one, when the used lower limit for t (3 means of ISIs, which in practice is still too low) is applied.

4.2.4. *Influence of refractory period on* $\widehat{\mathrm{FF}}$. We have shown that both relative and absolute refractory periods have strong influence on the behavior of the function FF_t. Here we explore the practical consequence in FF estimation. We compare MSE of $\widehat{\mathrm{FF}}$ for gamma distribution of T and for IG distribution of T with added absolute refractory period in dependence on the length of the observation window t. These probability distributions are very different from the point of view of refractory period - the first one has no absolute refractory period and, for FF > 1, also no relative refractory period and the second one has always both types of refractory periods. However, their mean and FF (including the refractory period in the case of IG distribution) are set to be the same. The MSE comparison is in Fig. 8. The error is lower for T with "larger" refractory period for FF $= 0.5$ and vice versa

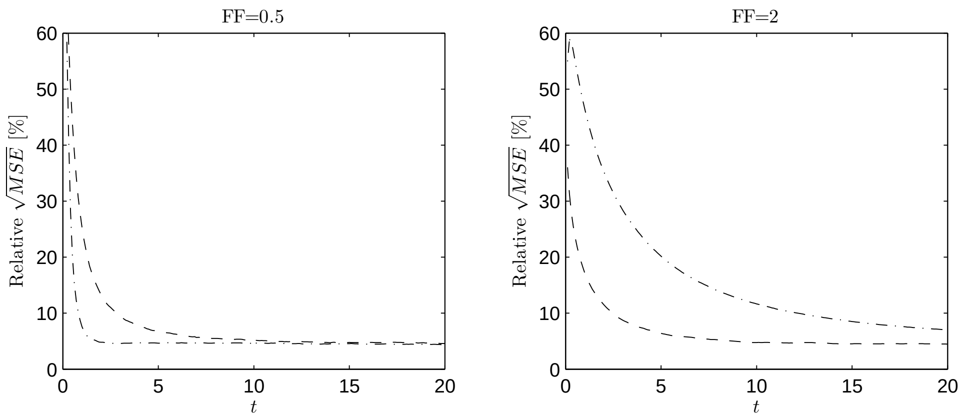

FIGURE 8. Relative $\sqrt{\text{MSE}}$ of $\widehat{\text{FF}}$ in percents for gamma distribution of T without absolute refractory period (dashed) and for IG distribution of T with absolute refractory period (dash-dotted) in dependence on the length of the observation window t. Mean of T is always one and the value of FF is 0.5 (left) and 2 (right) (all including the refractory period of length 0.1 in the case of IG distribution). The errors are calculated based on 1000 values of $\widehat{\text{FF}}$, each estimated from 1000 generated spike trains of relevant length.

for FF = 2. Moreover, in the latter situation, the difference in error is very large. This can be easily understood, refractory period causes an initial decrease of FF_t, thus the convergence to FF is accelerated if FF < 1 (approximately, for FF slightly below one the decrease may be too large) and reduced if FF > 1.

5. Choice of the observation window.

5.1. Estimation from independent trials.

Repeated trials are used mainly in measuring the response to a stimulus. The stimulus causes a change of the character of the spike train, including its variability, which we want to measure. However, this change lasts only for a short time so there is the demand of short observation windows. It of course contradicts with the demand of sufficiently large observation window which is important from the point of view of the accuracy of the FF estimator. Thus, we aim mainly to answer the question how short the observation window can be so that the estimator is still sufficiently accurate.

In this situation, the problem of the estimator is its strong bias for short window length t. It may be approximately expressed as the difference $\text{FF}_t - \text{FF}$, therefore the behavior of the function FF_t is crucial. A theoretical possibility how to measure the bias and select a suitable t is to use the bias approximation from formula (21). However, in practice we do not have the necessary information about the spike trains (e.g., $\text{E}(T^3)$ and of course FF) and thus the observation window must be chosen only heuristically based on general knowledge of FF_t.

From presented illustrations of FF_t, it is obvious that very short trials (e.g., shorter than the mean of the ISIs) are clearly almost always inappropriate. However, this problem complicates in the presence of a refractory period. As was shown, both relative and absolute refractory periods causes the FF_t to be initially lower than one independently of FF. Moreover, if FF > 1 then, even for relatively large observation

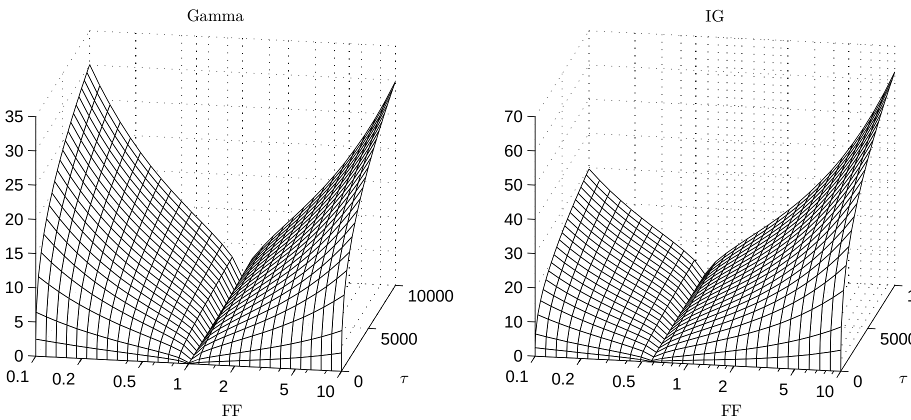

FIGURE 9. Values of t which minimize formula (21) in dependence on FF and length of the spike train τ. ISIs follow gamma (left) and IG (right) distributions with mean one. The FF-axis is logarithmically scaled.

windows, presence of the refractory period, while preserving the value of FF, causes a very large increase of the error of $\widehat{\mathrm{FF}}$ (see Fig. 8). Thus, in selection of window size, absence or presence of the refractory period should be taken into account.

The second characteristic of the spike trains which has large influence on FF_t is the value of FF itself. For $\mathrm{FF} \leq 1$, the length of the observation window about $5 - 10$ means of ISIs, as suggested in [18], can be mostly appropriate. The same value of t seems to be sufficient for $\mathrm{FF} > 1$, if there is no refractory period (as for the gamma distribution, see Fig. 2). The most problematic situation is for $\mathrm{FF} > 1$ in presence of a refractory period. The observation window should be larger than in the previous cases. However, its length cannot be specified more precisely.

5.2. **Estimation from single spike train.** In this situation, the selection of a suitable t for spike train segmentation is the compromise between larger bias and larger variance of $\widehat{\mathrm{FF}}$. We have shown that there is some t which minimizes $\mathrm{MSE}(\widehat{\mathrm{FF}})$ (we denote it by t_o) and this minimum can be approximated using formula (21). For illustration, we approximate t_o for spike trains with various length τ and various values of FF (see Fig. 9).

Again, we see that some values of t_o are too small for practical use. It is caused by the fact that MSE is minimized just for a specific value of FF. In practice, we do not know, of course, the value of FF and thus it is not possible to use direct minimization of relationship (21). However, we can find such a window that $\mathrm{MSE}(\widehat{\mathrm{FF}})$ is acceptable for a range of possible values of FF. This range may be deduced from a preliminary estimate of FF obtained using estimator (5) with a heuristically chosen value of t. We also do not know the values of $\mathrm{E}(T)$ and $\mathrm{E}(T^3)$ for formula (21), but it is now possible to estimate them.

Let us illustrate the described procedure on an example. Suppose that we have a spike train with the following estimates: $\widehat{\mathrm{E}}(T) = 1$, $\widehat{\mathrm{E}}(T^3) = 6$ and $\widehat{\mathrm{FF}} = 1$ and we want to find t which would provide more precise estimate of FF (more precise estimator). It should hold that $\mathrm{MSE}(\widehat{\mathrm{FF}})$ is low for $\mathrm{FF} = 1$ and also for sufficiently wide range of values around one (e.g. for interval $[0.5, 2]$). We plot this situation

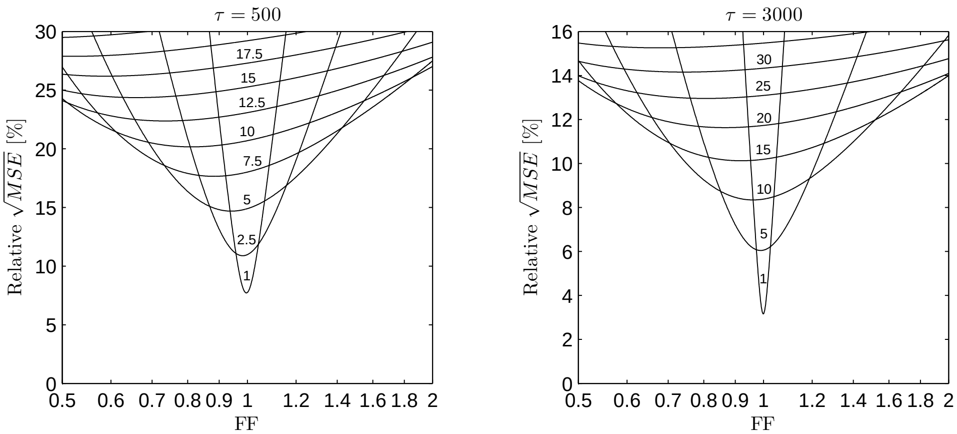

FIGURE 10. Relative $\sqrt{\text{MSE}}$ of $\widehat{\text{FF}}$ in percents in dependence on FF in estimation from single spike train with fixed length τ for various window length t, calculated using (21) ($\text{E}(T) = 1$, $\text{E}(T^3) = 6$, $\tau = 500$ (left) and 3000 (right)). Every curve corresponds to a value of t, these values are displayed in the figures. FF-axis is logarithmically scaled.

for two values of τ, and various values of t (see Fig. 10). The choice of a suitable t now depends on what properties of the estimator $\widehat{\text{FF}}$ we expect. For example, for $\tau = 500$ and $t < 5$, MSE is for many values of FF too large. On the other hand, MSE is unnecessarily large for most likely values of FF (around one) when $t > 10$. Thus, t about 7.5 seems to be a suitable compromise. Analogously, a good choice for $\tau = 3000$ could be $t = 15$.

6. **Conclusions.** We have focused on Fano factor estimation using the standard estimator under the assumption that the spike train satisfies the definition of equilibrium renewal process. Two usual types of neuronal data, repeated trials and single spike train, were considered. In both situations, the accuracy of the estimator strongly depends on the length of the observation window t and so its right choice is important.

In estimating from independent trials, the main problem is the bias of the estimator for short t. We have shown that, beside the value of FF, also refractory period has crucial effect on its value. To be able to avoid the bias, it is important to know the behavior of the function FF_t. However, this information is in practice limited, so it is necessary at least to assume a range of possible values of FF and whether or not the refractory period plays a role. In estimating from a single spike train, we have to take into account also the variance, thus there is a window size t which is optimal from the point of view of the mean square error. This optimal t can be approximated using derived MSE formula.

Because of the property $\text{CV}^2 = \text{FF}$, which holds for renewal processes, we have also compared the accuracy of the estimator of FF with the standard estimator of CV^2. There is no systematic preference, however, in estimation from repeated trials, $\widehat{\text{FF}}$ is mostly more precise than $\widehat{\text{CV}}^2$ and vice versa in estimation from single spike trains.

There is still a possibility to extend this work using different models of spike train, more general or realistic than a renewal process. For example, correlation of ISIs, which is not included in renewal processes, is often observed in experiments [10] and, as was shown in [1, 2], it has a large effect on the dependency of the FF estimate on the length of the observation window.

Appendix A. Proof of properties (16) and (17).

Proof. Here we prove properties (16) and (17). To that end, we modify formula (12), using (11), into the form

$$\begin{aligned}\mathrm{FF}_t &= 1 + \frac{\mathrm{E}(T)}{t}\mathrm{E}[N_t(N_t-1)] - \frac{t}{\mathrm{E}(T)} \\ &= 1 + \frac{\mathrm{E}(T)}{t}\sum_{n=2}^{\infty} n(n-1)P_n(t) - \frac{t}{\mathrm{E}(T)}, \qquad (28)\end{aligned}$$

where $P_n(t)$ denotes the probability that n spikes occur in an interval of length t. Then

$$\begin{aligned}\frac{\mathrm{dFF}_t}{\mathrm{d}t} &= -\frac{\mathrm{E}(T)}{t^2}\sum_{n=2}^{\infty} n(n-1)P_n(t) \\ &\quad + \frac{\mathrm{E}(T)}{t}\sum_{n=2}^{\infty} n(n-1)\frac{\mathrm{d}P_n(t)}{\mathrm{d}t} - \frac{1}{\mathrm{E}(T)} \qquad (29) \\ &= \frac{\mathrm{E}(T)}{t}\sum_{n=2}^{\infty} n(n-1)\left(\frac{\mathrm{d}P_n(t)}{\mathrm{d}t} - \frac{P_n(t)}{t}\right) - \frac{1}{\mathrm{E}(T)}. \qquad (30)\end{aligned}$$

Next we use the Laplace transform. It holds, [13],

$$\mathcal{L}\{P_n\}(s) = \frac{(1-\tilde{f}(s))^2(\tilde{f}(s))^{n-1}}{s^2\mathrm{E}(T)} \qquad (31)$$

and

$$\mathcal{L}\left\{\frac{\mathrm{d}P_n(t)}{\mathrm{d}t}\right\}(s) = s\mathcal{L}\{P_n\}(s), \qquad (32)$$

where equation (32) can be directly derived from the definition of the Laplace transform.

From relationships (15), (31), (32) and using one of Abel and Tauber theorems, which expresses the similarity of behavior of

$$\frac{h(t)}{t^m}, \text{ for } t \to 0^+$$

and

$$\frac{s^{m+1}\mathcal{L}\{h\}(s)}{m!}, \text{ for } s \to \infty, \; m \in \mathbb{N}_0,$$

[13, 21], where as the function $h(t)$ we use $P_n(t)$ and $f(t)$, we further obtain

$$\lim_{t\to 0^+}\frac{\mathrm{E}(T)}{t}\sum_{n=2}^{\infty} n(n-1)\left(\frac{\mathrm{d}P_n(t)}{\mathrm{d}t} - \frac{P_n(t)}{t}\right) = 0,$$

which with formula (30) yields (16).

Finally, in presence of a refractory period of length $r > 0$, it holds $P_n(t) = 0$ for $t \le r$, $n \ge 2$, thus using (28) we get (17). □

Appendix B. Proof of relationship (21).

Proof. In this appendix we derive relationship (21). We use formula (20) and derive firstly formulas for the bias and the variance. We start with bias, thus we need a formula for $\mathrm{E}(\widehat{\mathrm{FF}})$. Estimators $s^2_{N_t}$ and $\overline{N}_t$ in definition (5) are unbiased estimators of $\mathrm{Var}(N_t)$ and $\mathrm{E}(N_t)$, thus

$$\mathrm{E}(s^2_{N_t}) = \mathrm{Var}(N_t),\ \mathrm{E}(\overline{N}_t) = \mathrm{E}(N_t) \tag{33}$$

and using the law of large numbers

$$s^2_{N_t} \to \mathrm{Var}(N_t),\ \overline{N}_t \to \mathrm{E}(N_t),\ \text{for } n \to \infty. \tag{34}$$

That implies

$$\mathrm{E}(\widehat{\mathrm{FF}}) \approx \mathrm{FF}_t,\ \text{for } n \to \infty. \tag{35}$$

Then from formulas (9) and (35) we get

$$\mathrm{Bias}(\widehat{\mathrm{FF}}) \approx \frac{1}{t}\left[\frac{\mathrm{E}(T)}{2}\left(1+\frac{\mathrm{Var}(T)}{\mathrm{E}^2(T)}\right)^2 - \frac{1}{3}\frac{\mathrm{E}(T^3)}{\mathrm{E}^2(T)}\right], \quad \text{for } t \to \infty,\ n \to \infty. \tag{36}$$

Formula for the variance of $\widehat{\mathrm{FF}}$ we find assuming normality of N_t, which holds for $t \to \infty$. Then, [16],

$$\frac{n-1}{\mathrm{Var}(N_t)} s^2_{N_t} \sim \chi^2(n-1), \quad \overline{N}_t \sim N\left(\mathrm{E}(N_t), \frac{\mathrm{Var}(N_t)}{n}\right),$$

where $N(\mathrm{E}(N_t), \mathrm{Var}(N_t)/n)$ denotes the Gaussian (normal) distribution with mean $\mathrm{E}(N_t)$ and variance $\mathrm{Var}(N_t)/n$ and $\chi^2(n-1)$ denotes the Chi-squared distribution with $n-1$ degrees of freedom. Therefore

$$\mathrm{Var}(\overline{N}_t) = \frac{\mathrm{Var}(N_t)}{n},\ \mathrm{Var}(s^2_{N_t}) = \frac{2\mathrm{Var}^2(N_t)}{n-1}. \tag{37}$$

Next, from relationships (33), (37) and from independence of $s^2_{N_t}$ and $\overline{N_t}$ (from normality of N_t) we get

$$\mathrm{Var}(\widehat{\mathrm{FF}}) = \mathrm{Var}\left(\frac{s^2_{N_t}}{\overline{N}_t}\right) \approx \frac{\mathrm{E}^2(s^2_{N_t})}{\mathrm{E}^2(\overline{N_t})}\left[\frac{\mathrm{Var}(s^2_{N_t})}{\mathrm{E}^2(s^2_{N_t})} + \frac{\mathrm{Var}(\overline{N}_t)}{\mathrm{E}^2(\overline{N}_t)}\right] =$$
$$= \frac{\mathrm{Var}^2(N_t)}{\mathrm{E}^2(N_t)}\left[\frac{2}{n-1} + \frac{\mathrm{Var}(N_t)}{n\mathrm{E}^2(N_t)}\right], \quad \text{for } t \to \infty, n \to \infty, \tag{38}$$

where we used approximation (first order Taylor expansion)

$$\mathrm{Var}\left(\frac{R}{S}\right) \approx \frac{\mathrm{E}^2(R)}{\mathrm{E}^2(S)}\left[\frac{\mathrm{Var}(R)}{\mathrm{E}^2(R)} - \frac{2(\mathrm{Cov}(R,S))}{\mathrm{E}(R)\mathrm{E}(S)} + \frac{\mathrm{Var}(S)}{E^2(S)}\right], \tag{39}$$

where S and R are arbitrary positive continuous random variables.

Now we have formulas for both bias (36) and variance (38) and thus we can put them into relationship (20),

$$\mathrm{MSE}(\widehat{\mathrm{FF}}) \approx \frac{1}{t^2}\left[\frac{\mathrm{E}(T)}{2}\left(1+\frac{\mathrm{Var}(T)}{\mathrm{E}^2(T)}\right)^2 - \frac{1}{3}\frac{\mathrm{E}(T^3)}{\mathrm{E}^2(T)}\right]^2$$
$$+ \frac{\mathrm{Var}^2(N_t)}{\mathrm{E}^2(N_t)}\left[\frac{2}{n-1} + \frac{\mathrm{Var}(N_t)}{n\mathrm{E}^2(N_t)}\right], \quad \text{for } t \to \infty,\ n \to \infty. \tag{40}$$

Further, $\mathrm{E}(N_t)$ we replace with (11) and for $\mathrm{Var}(N_t)$ we use another asymptotic relationship, [5],

$$\mathrm{Var}(N_t) \approx \frac{\mathrm{Var}(T)}{\mathrm{E}^3(T)}t + \frac{1}{2}\left(1 + \frac{\mathrm{Var}(T)}{\mathrm{E}^2(T)}\right)^2 - \frac{1}{3}\frac{\mathrm{E}(T^3)}{\mathrm{E}^3(T)}, \quad \text{for } t \to \infty. \tag{41}$$

So we obtain the final formula (instead of $\mathrm{Var}(T)/\mathrm{E}^2(T) = \mathrm{CV}^2$ we write FF)

$$\begin{aligned}\mathrm{MSE}(\widehat{\mathrm{FF}}) \approx &\left[\frac{1}{t}\mathrm{E}(T)\mathrm{G}(T)\right]^2 \\ &+ \frac{\mathrm{E}^2(T)}{t^2}\left[\frac{2}{n-1} + \frac{\mathrm{E}^2(T)}{nt^2}\left(\mathrm{G}(T) + \frac{\mathrm{FF}}{\mathrm{E}(T)}t\right)\right] \\ &\cdot \left[\mathrm{G}(T) + \frac{\mathrm{FF}}{\mathrm{E}(T)}t\right]^2, \text{ for } t \to \infty,\ n \to \infty,\end{aligned} \tag{42}$$

where

$$\mathrm{G}(T) = \frac{1}{2}(1 + \mathrm{FF})^2 - \frac{1}{3}\frac{\mathrm{E}(T^3)}{\mathrm{E}^3(T)}. \tag{43}$$

□

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