Impact of spike-train auto-structure on probability distribution of joint-spike events

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Abstract

The discussion whether temporally coordinated spiking activity really exists and whether it is relevant has been heated over the last few years. To investigate this issue, several approaches have been taken to determine whether synchronized events occur significantly above chance, \textit{i.e.} whether they occur more often than expected if the neurons fire independently. Most investigations ignore or destroy the auto-structure of the spiking activity of individual cells, or assume Poissonian spiking as a model. Such methods that ignore the auto-structure can significantly bias the coincidence statistics.

Here, we study the influence of the auto-structure on the probability distribution of coincident spiking events between tuples of mutually independent non-Poisson renewal processes. In particular, we consider two types of renewal processes that were suggested as appropriate models of experimental spike trains: a Gamma- and a log-normal- process. For a Gamma-process, we characterize the shape of the distribution analytically with the Fano factor ($FF_c$). In addition, we perform Monte-Carlo estimations to derive the full shape of the distribution and to derive the probability for false positives if a different process type is assumed as was actually present. We also determine how manipulations of such spike-trains, here dithering, used for the generation of surrogate data change the distribution of coincident events and influence the significance estimation.

We find, first, that the width of the coincidence count distribution and its $FF_c$ depend critically and in a non-trivial way on the detailed properties of the structure of the spike trains as characterized by the coefficient of variation $C_V$. Second, the dependency of the $FF_c$ on the $C_V$ is complex and mostly non-monotonic. Third, spike dithering, even if as small as a fraction of the inter-spike interval, can falsify the inference on coordinated firing.
**Key words and phrases:** spike synchrony, coincidence, joint-spike activity, renewal processes, gamma and log-normal process, spike train auto-structure, significance, dithering
1 Introduction

Synchronous spiking has been implicated in neural coding (e.g. Abeles et al., 1993; Gray et al., 1989; Riehle et al., 1997; Singer, 1999). It has been associated with cortical avalanches (e.g. Beggs & Plenz, 2003), or synfire chains (Abeles, 1991), and has also been used to constrain the mechanisms that give rise to cortical activity (Diesmann et al., 1999; Gutkin et al., 2001; Vicente et al., 2008; Sommer & Wennekers, 2001; Aoki & Aoyagi, 2007). Hence the determination of whether synchronized events occur above chance, i.e. whether they occur more often than expected if the neurons fire independently, has recently attracted considerable attention. Several approaches have been taken to investigate this issue (Amari et al., 2003; Aertsen et al., 1989; Brody, 1999; Brown et al., 2004; Truccolo et al., 2005; Gerstein & Perkel, 1972; Grün et al., 1999, 2002a,c; Grün, 2009; Ikegaya et al., 2004; Kass et al., 2005; König, 1994; Louis et al., 2010; Pipa & Grün, 2003; Pipa et al., 2007, 2008; Agmon, 2012; Ventura et al., 2005; Gerhard et al., 2011a,b; Pipa & Munk, 2011; Wu et al., 2011) ((e.g. Oram et al., 1999) performed a similar analysis, however, for patterns in single spike trains). Many of these approaches for the analysis of correlated spike trains imply more or less implicitly the assumption of Poisson spike trains, for example by simulating spike trains as Poisson processes with the same rate profiles as the neurons under investigation to determine the statistics of coincident events analytically. However, experimental inter-spike interval (ISI) distributions can show a substantial deviation from the exponential distribution, since the nature of experimental spike-trains can be dramatically different from Poisson processes (Burns & Webb, 1976; Levine, 1991; Teich et al., 1997; Iyengar & Liao, 1997; Nawrot et al., 2007; Smith, 1954a,b; Nawrot et al., 2008; Krahe & Gabbiani, 2004; Farkhooi et al., 2009). However, their effect on the occurrence of synchronous or spatio-temporal spike events has only rarely been investigated (Grün et al., 2002a; Pipa & Grün, 2003; Gerstein, 2004; Louis et al., 2010; Ventura et al., 2005). And in particular, which conclusions arise if such features of experimental spike trains are ignored. Figure 1 illustrates the influence of non-Poisson spike train structure (here modeled as renewal Gamma-processes) on the distribution of coin-
Figure 1: (A1-3) Raster plot for 50 trials of independent *Gamma*-processes with 3 different coefficient of variations of the inter-spike interval distribution (A1, B1: $C_V$=0.1; A2, B2: $C_V$=1, A3, B3: $C_V$=3). (B1-3) Distribution of coincidence counts shared by pairs of mutually independent *Gamma*-processes of the same kind as shown in A. Coincidence counts are derived as the sum of the binwise products of the spikes counts per bin. Dashed curves in (B1,B3) show the coincidence count distribution of $B_2$, that equals the case of Poisson processes ($\gamma = 1$), as a reference curve. $N_{\text{critical}}$ shown in $B_1, B_2, B_3$ indicates the critical number of coincidences that corresponds to a 1 % significance level under the assumption that the underlying spike trains are Poissonian. Hence any number of coincidences larger or equal $N_{\text{critical}}$ would be classified as significant. Coincidences were evaluated per trial based on a binned version (bin-length: $\Delta t = 4ms$) of the original renewal process. Each distribution in B represents sample from $T = 100000$ trials of each 5s length. The spike rate was chosen to be $R = 50Hz$. The false positive rate in B1 and B3 were increased in relation to the test level by 3 and 22 times (3 %, and 22 %), respectively.
cident spike events. The comparison of the distributions to the one of Poisson processes demonstrates that the shape of the coincidence distribution may be considerably affected by the spike-train structure. Thus, assuming Poisson in the presence of non-Poisson processes would lead to wrong estimations of the statistical significance of coincident spiking activity. This aspect will be rigourously evaluated in the first part of this contribution.

Two types of renewal processes (Gamma- and log-normal processes) considered as reasonable models for experimental spike trains (Burns & Webb, 1976; Levine, 1991; Teich et al., 1997) are used for the investigation. Their ISI characteristic can be parameterized by the coefficient of variation ($C_V$), and thus can be varied from bursty to regular spike-train structure. The influence of wrongly assumed spike-train structure onto the distribution used for significance estimation will be shown by analytical and numerical methods.

Another approach increasingly used for the creation of surrogate data for significance evaluation of correlated spike trains is dithering (Date et al., 1998; Davies et al., 2006; Gerstein, 2004; Hatsopoulos et al., 2003; Shmiel et al., 2006). This procedure is also often called jittering e.g. (Kuhn et al., 2003), but we prefer the reserve the term jitter for the temporal imprecision in the original data and use the term dithering for the manipulation of the data (Grün, 2009). The method intentionally destroys existing spike correlation by a small displacement of the timing of each individual spike by a random amount. Thereby the rate profiles stay almost unchanged. However, obviously this procedure interacts with the inter-spike intervals of the original spike-trains, and thus must lead to changes of the coincidence distribution. Although the efficiency of dithering was recently studied (Pazienti & Grün, 2007; Pazienti et al., 2008) there are no systematic investigations of the consequences of spike dithering on significance evaluation of correlation. Here we will show first, how the spike train structure interacts with dithering, and second, under which conditions the method may lead to occurrence of false positive results.

Finally we will discuss the results and also methods to avoid false positive results and wrong interpretation of data.
2 Spike-train models

Although it is well known that spike-trains are not Poissonian, this assumption is often used for simplicity for analytical and statistical purposes. There are three main facts that clearly indicate that biological spike-trains have an auto-structure which deviates from Poissonian processes. First, all neurons exhibit refractory periods after spike firing. This refractoriness makes short inter-spike intervals of the order of several milliseconds unlikely to happen and is therefore incompatible with the exponentially decaying inter-spike interval distribution of a Poisson process (Cox & Lewis, 1966). Second, biological neurons can fire with a certain temporal structure that can be described in a first approximation as regular or bursty firing. In the latter case neurons fire two or more spikes during short epochs, followed by longer episodes of silence. And third, neuronal firing might not be described by renewal processes but exhibit higher-order dependencies of spike times which lay further back in the past (Nawrot et al., 2007). In this paper we focus on the first two aspects and assume that the neuronal firing can be described by renewal processes. We study the impact of the refractoriness, the burstiness and the regularity of spike-trains on the probability distribution of coincident firing.

To this end we use two models of neuronal firing which are both renewal processes with two model parameters each: the Gamma-process and the log-normal-process. Both processes allow us to model burstiness, regularity, and refractoriness for different parameter combinations, and both have been proposed as models descriptions for neuronal spike-trains (Burns & Webb, 1976; Levine, 1991; Teich et al., 1997; Iyengar & Liao, 1997; Nawrot et al., 2007; Smith, 1954a,b; Nawrot et al., 2008).

2.1 Gamma-process

A Gamma-process occurs naturally when a integrate and fire model is driven by a Poisson input (Gerstein & Mandelbrot, 1964). The Gamma-process is a renewal process and is therefore only characterized by the inter-spike interval (’ISI’) distribution \( p(t) \). The ISI distribution for a Gamma-process with a given constant spike rate is described by:
\[ p_\gamma(t) = t^{\gamma-1} \frac{(\gamma R)^\gamma}{\Gamma(\gamma)} e^{-\gamma R t} \] for \( t > 0 \). \number{1}

This distribution is characterized by two variables, the spike rate, \( R \), and the shape-parameter, \( \gamma \). The Poisson-process is a special case of the Gamma-process for which \( \gamma = 1 \). Values of the shape-parameter \( \gamma \) smaller than 1 make the distribution become hyper-exponential and short intervals are more likely to occur than for a Poisson-process with the same rate. We use this parameter regime of a Gamma-process with a shape parameter smaller than 1 in order to model bursty spike-trains. In contrast, for very large values of the shape parameter \( \gamma \), the Gamma-distribution approaches a narrow normal distribution. Therefore, a Gamma-process with shape-parameter \( \gamma > 1 \) is used to model regular firing.

To model Gamma spike-trains given a certain coefficient of variation \( C_V \) of the inter-spike interval distribution (\( C_V = \sigma_t/\langle t \rangle \)), we use the expected value of the inter-spike interval \( \langle t \rangle = 1/R \) and the variance \( \sigma_t^2 = 1/(\gamma R^2) \) to express the shape parameter \( \gamma \) by the coefficient of variation \( C_V \):

\[ \gamma = \frac{1}{C_V^2} \] \number{2}

### 2.2 log-normal-process

The log-normal-process is a renewal process with log-normal-distributed inter-spike intervals. Its inter-spike interval distribution (\( p(t)_{log-normal} \)) is defined by:

\[ p(t)_{log-normal} = \frac{1}{k\sqrt{2\pi}} \exp\left(\frac{-(\ln(t) - a)^2}{2k^2}\right) \] \number{3}

Compared to the ISI distribution of a Gamma-process, the log-normal ISI distribution is, first, more heavy tailed for the same \( C_V \), and second, very short intervals are, even for high \( C_V \), unlikely to happen. The moments of the log-normal-distribution are given by:

\[ \langle t^n \rangle = \int_0^{+\infty} t^n p(t) \, dt = e^{na + a^2k^2} \] \number{4}
To model spike-trains given an expected spike rate, $R$, and coefficient of variation, $C_V$, we can express the parameters $a$ and $k$ as

$$a = -\ln R - \frac{1}{2} \ln (C_V^2 + 1)$$  \hspace{1cm} (5)$$

and

$$k = \sqrt{\ln (C_V^2 + 1)} \hspace{1cm} (6)$$

### 3 Coincidence Count Distribution

In this section we derive and discuss the impact of the inter-spike interval distribution on the shape of coincidence count distributions. To stress the importance of this interplay we first give a few examples in order to demonstrate that the impact of the detailed inter-spike interval distribution on the coincidence count distribution can be rather important.

The first example we look at is the comparison of different renewal processes that look identical concerning two features that are frequently used to characterize biological spike-trains: the $C_V$ of the inter-spike interval distribution and the Fano factor $FF_s$ of the spike count distributions. As a second example we show that dithering of individual spikes can alter the coincidence count distribution for different renewal processes characterized by the same $C_V$ in very different ways.

Following these examples we present analytical expressions and a rigorous discussion of the mean and the variance of the coincidence count distribution for a frequently used model of biological spike trains, the *Gamma*-process in case of integer shape parameters. We then complement this analytical derivation by numerical estimations of the mean and the variance for *Gamma*-processes with non-integer shape parameters as well as with a second kind of renewal process with *log-normal*-distributed inter-spike intervals.

#### 3.1 Coincidences

Given two parallel spike-train processes we define a coincidence based on binned versions of the original processes. The binned spike trains are obtained by segmenting the time axis into exclusive bins, each of length $\Delta t$, and counting the exact number of spikes $n_k$
Figure 2: (A1-4) Inter-spike interval distribution of Gamma-processes. The solid distribution is the ISI distribution of the original Gamma-process, while the dashed curve indicates the ISI distribution after individual spikes of the original Gamma-process were dithered by a random displacement normally distributed with zero mean and a standard deviation of $\sigma_d = 5\text{ms}$. (B1-4) Count distribution $p(\Delta t)$ of coincidences between two mutually independent Gamma-processes of the same kind as shown in A1 - 4. Coincidences were evaluated per trial based on a binned version (bin-length: $\Delta t = 4\text{ms}$) of the original renewal processes. The coincidence count distribution is shown for two variations: for a binned version of the original Gamma-processes (gray filled), and for a second process, where spikes of the original Gamma-processes have been dithered first and then binned (dashed). Each distribution in A and B represents sample from $T = 100000$ trials, each of $5\text{s}$ length. The spike rate was chosen to be $R = 50\text{Hz}$. Different rows indicate different model $C_V$s (A1, B1: $C_V = 0.1$; A2, B2: $C_V = 0.5$; A3, B3: $C_V = 1$; A4, B4: $C_V = 1.5$).
Figure 3: Same as shown in Figure 2, but for a log-normal- inter-spike interval distributed renewal process. (A1-4) ISI distribution of log-normal-processes (solid: ISI distribution of the original log-normal-process; dashed: after dithering). (B1-4) Count distribution $p(\Delta t)$ of coincidences between two mutually independent log-normal-processes of the same kind as shown in A1 – 4. The coincidence count distribution for the original log-normal-processes (binned) is shown in gray (filled), and for dithered spikes before binning was applied (dashed). Same parameters as in figure 2.

per bin $k$ (no clipping; clipping reduces any number of spikes larger than 1 to 1, see (Grün et al., 2002b)). The number of coincidences in bin $k$ shared by the two corresponding simultaneous bins of neuron 1 and neuron 2 is then defined by $N^k_c = n^k_1 n^k_2$.

3.1.1 Examples of coincidence count distributions for Gamma- and log-normal-processes

As a first example of the importance of the inter-spike interval distribution on the coincidence count distribution we show in figure 2 and 3 the coincidence count distributions for Gamma- and log-normal-processes for the case of four different $C_V$s but equal spike rate $R$ and bin widths $\Delta t$. Figure 2:B1 and 3:B1 show the coincidence count distribution for a Gamma- and log-normal-process, respectively, in case of very regular spiking activity
yielding an $C_V$ of 0.1. In contrast, panel B4 in both figures shows the coincidence count distribution for a $C_V$ of 1.5. Please note that the nature of the log-normal- distribution makes very short intervals very unlikely, even for $C_V$ values larger than 1, while short intervals are very likely for the same $C_V$ in the case of a Gamma-process.

That difference in the likelihood of short ISIs makes the distribution of the coincidence counts much broader in case of the Gamma-process than for the log-normal-process (see figure 4A, 5A3, 5B3 for quantification of the broadening in terms of fano factor). This emphasizes that the detailed structure, namely the stronger burstiness for Gamma- compared to log-normal- processes, is responsible for making the coincidence distribution different even though the $C_V$ and the $FF_s$ of the spike counts are identical.

### 3.1.2 Example for the effect of dithering on the coincidence count distribution

Another peculiarity occurs when individual spikes are dithered (Date et al., 1998; Davies et al., 2006; Gerstein, 2004; Hatsopoulos et al., 2003; Shmiel et al., 2006). This technique is often used for statistical purposes to derive surrogate data, e.g. to derive the probability of coincidence firing under the assumption that neurons fire independently. Dithering is defined by a random variation of the spike timing of individual spikes by a random offset, e.g. drawn i.i.d from a gaussian distribution with zero mean and variance $\sigma^2_d$ e.g. (Jones et al., 2004). Since the Gamma-process with $C_V=1$ is actually a Poisson process, dithering does neither effect the ISI distribution nor the coincidence count distribution as shown in figure 2:B3.

However, even though the $C_V$ and the Fano factor of the spike count distribution are identical for both the Poisson- and the log-normal-distribution, dithering changes the shape of the coincidence count distribution for the log-normal-process (fig. 3:B3) but not for the Poisson processes (fig 2:B3). In contrast, we see the opposite effect for a $C_V = 1.5$. Dithering changes the coincidence distribution in case of the Gamma-process, but it stays nearly unchanged for of the log-normal-process. These examples show that dithering changes the shape of the coincidence count distribution in a rather unpredictable way when the nature of the underlying process is unknown.
3.2 Fano factor ($FF_C$) of coincidence count distribution for renewal processes

After having presented examples that emphasize the necessity of a deeper understanding of the interplay between the nature of a renewal process and the coincidence count distribution, we will now give a rigorous analytical description of the mean and the variance of the coincidence count distribution of a $Gamma$-process with integer shape parameter $\gamma \in \mathbb{N}$.

To this end, we first derive the expected number of coincidences. If $n_i^k$ is the number of spikes from neuron $i$ in bin $k$, the number of coincidences, $N_c$, counting over bins $k = 0$ to $K - 1$ is

$$N_c = \sum_{k=0}^{K-1} n_i^1 n_i^2.$$  \hfill (7)

The average number of coincidences, $\langle N_c \rangle$, is given by

$$\langle N_c \rangle = \left\langle \sum_{k=0}^{K-1} n_i^1 n_i^2 \right\rangle = \sum_{k=0}^{K-1} \langle n_i^1 n_i^2 \rangle = K \langle n_i^1 \rangle \langle n_i^2 \rangle.$$  \hfill (8)

If the spike times of the two neurons are generated by independent stationary renewal processes (in equilibrium), this is equal to

$$\langle N_c \rangle = K \langle n_i^1 \rangle \langle n_i^2 \rangle = K R_1 R_2 (\Delta t)^2,$$  \hfill (9)

where $\Delta t$ is the bin width and $R_i$ the rate of neuron $i$. This result demonstrates that the expected number of coincidences is independent of the nature of the renewal process.

Next, we are going to derive the variance of the coincidence count distribution, and use it to calculate the Fano-factor $FF_C$. The mean square of the spike count, $\langle N_c^2 \rangle$, satisfies

$$\langle N_c^2 \rangle = \left\langle \left( \sum_{k=0}^{K-1} n_i^1 n_i^2 \right)^2 \right\rangle = \sum_{k=0}^{K-1} \sum_{l=0}^{K-1} \langle n_i^1 n_i^2 \rangle \langle n_k^1 n_k^2 \rangle.$$  \hfill (10)
Here we have used the independence of the renewal processes to write \( \langle n_k^1 n_k^1 n_k^2 n_k^2 \rangle = \langle n_k^1 n_k^1 \rangle \langle n_k^2 n_k^2 \rangle \) and \( A^i_k \) is the auto-correlation for the binned spike-train of neuron \( i \), \( A^i_k = \langle n_i^1 n_{i+k}^1 \rangle \). The variance in the number of coincidences, \( \sigma^2(N_c) \), is

\[
\sigma^2(N_c) = \sum_{k=0}^{K-1} \sum_{l=0}^{K-1} [A^i_{k-l} A^i_{k-l} - (R_1 R_2)^2 (\Delta t)^4] .
\]  

(11)

Using \( k_+ = k + l \) and \( k_- = k - l \) this can be written as

\[
\sigma^2(N_c) = \sum_{k_-=-K+1}^{K-1} \sum_{k_+ = |k_-|}^{2K-2-|k_-|} [A^i_{k_-} A^2_{k_-} - (R_1 R_2)^2 (\Delta t)^4] ,
\]

(12)

where we have used \( \sum_{k_+ = |k_-|}^{2K-2-|k_-|} \) to denote that in the sum over \( k_+ \) only every second term should be taken. The reason for that restriction is that the combination of \( k_+ + k_- = 2k \) and \( k_+ - k_- = 2l \), makes \( k_+ \) take only even values if \( k_- \) is even, and \( k_+ \) take only odd values if \( k_- \) is odd.

Using this relation we obtain \( \sum_{k_+ = |k_-|}^{2K-2-|k_-|} \) to be \( K - |k_-| \), so that the variance can be written as

\[
\sigma^2(N_c) = \sum_{k_-=-K+1}^{K-1} (K - |k_-|) [A^i_{k_-} A^2_{k_-} - (R_1 R_2)^2 (\Delta t)^4] .
\]

(13)

Using this and Eqn. 9, the Fano-factor of the coincidence count distribution, \( FF_c \), can be written as

\[
FF_c = \frac{\sigma^2(N_c)}{\langle N_c \rangle} = \frac{1}{R_1 R_2 (\Delta t)^2} \sum_{k=-K+1}^{K-1} \left( 1 - \frac{|k|}{K} \right) [A^i_k A^2_k - (R_1 R_2)^2 (\Delta t)^4] .
\]

(14)

Next we take the limit \( K \to \infty \), and use the fact that as \( |k| \) approaches infinity (\( |k| \to \infty \)), \( A^i_k \) approaches \( (R_1 \Delta t)^2 \) exponentially. Therefore \( A^i_k A^2_k - (R_1 R_2)^2 (\Delta t)^4 \) approaches 0 exponentially as \( |k| \) increases.

As a result, the term which involves \( |k|/K \) becomes negligible as \( K \) becomes large. In consequence, as \( K \) increases, the Fano factor approaches:

\[
FF_c = \frac{1}{R_1 R_2 (\Delta t)^2} \sum_{k=-\infty}^{\infty} [A^i_k A^2_k - (R_1 R_2)^2 (\Delta t)^4] .
\]

(15)

Using the symmetry of the auto-correlation this can also be written as

\[
FF_c = \frac{A^i_0 A^2_0 - (R_1 R_2)^2 (\Delta t)^4}{R_1 R_2 (\Delta t)^2} + 2 \sum_{\ell=1}^{\infty} \frac{A^i_{\ell} A^2_{\ell} - (R_1 R_2)^2 (\Delta t)^4}{R_1 R_2 (\Delta t)^2} .
\]

(16)
Note that the so far derived analytical expression for the Fano factor (Eqn. 16) holds for any renewal process as well as any stationary non-renewal point process for which the auto-correlation approaches $R^2(\Delta t)^2$ sufficiently fast.

### 3.3 Analytical derivation of $FF_c$ for *Poisson*-processes

In general there is no way to arrive to an analytical expression for Eqn. 16 from the inter-spike interval distribution of a given spike-train $i$, $p_i(t)$. However, for the simplest case of a renewal process, namely the *Poisson*-process ($p_i(t) = R_i \exp(-R_i t)$), the Fano factor becomes a very simple expression. To derive the auto-correlation of the *Poisson*-process we use $A_k = R_i \Delta t \delta_k + (R_i \Delta t)^2$, where $\delta_k$ is the Kronecker delta. $\delta_k$ takes the value of 1 for $k = 0$ and the value of 0 otherwise. This simplifies Eqn. 16 to:

$$FF_c = 1 + (R_1 + R_2) \Delta t.$$  \hspace{1cm} (17)

Please note that $FF_c$ is larger than 1 and grows with increasing spike rates and bin width. The reason for that is, that we counted the number of coincidences as the product of the number of spikes of simultaneous bins (Eqn. 7).

Mostly for the reason of simplification, an alternative way of counting coincidences has been proposed that requires for the spike trains to be binary sequences. In this case the number of coincidences per bin can be either 0 or 1 (clipping). Please note that also in this case the Fano factor $FF_{c^{\text{clip}}}$ does not equal 1. In fact, $FF_{c^{\text{clip}}}$ is smaller than 1 in case of underlying *Poisson*-processes.

### 3.4 Analytical derivation of $FF_c$ for *Gamma*-Processes

After having derived the Fano factor $FF_c$ for *Poisson*-processes, we will now derive a closed analytical expression of $FF_c$ for *Gamma*-processes.

In appendix B we show that for a $\gamma$-th order *Gamma*-process with integer $\gamma$ and rate $R$ the auto-correlation $A_k$ satisfies

$$A_0 = \frac{R \Delta t}{\gamma} + (R \Delta t)^2 - 2 \sum_{l=1}^{\gamma-1} B_l \quad \text{with} \quad \gamma \in \mathbb{N}$$  \hspace{1cm} (18)
Figure 4: Analytically determined Fano Factor $FF_c$. (A) $FF_c$ as a function of the $C_V$ for four different products $R\Delta t$. (B) As in A $FF_c$ as a function of the $C_V$, but for for two neurons with different rate $R_1 = R + \Delta R$ and $R_2 = R - \Delta R$, and a bin-width $\Delta t$ so that $R\Delta t = 0.2$. (C) $FF_{C}$ as a function of $\Delta R/R$ for the order $\gamma = 2, 4, 8, 16, 32$ for the same bin width. (D) $FF_{C}$ plotted against the product $R\Delta t$ for gamma processes with $\gamma = 1, 2, 4, 16, 32$. 
and, for $k \neq 0$,

$$A_k = (R \Delta t)^2 + \sum_{l=1}^{\gamma-1} B_l (1 - Z_l) |Z_l|^{k-1}$$  \hspace{1cm} (19)$$

where, using $x_l^i = \exp(2 \pi R \Delta t)$, $Z_l$ satisfies

$$Z_l = \exp[-(1 - x_l^i) \gamma R \Delta t],$$  \hspace{1cm} (20)$$

while

$$B_l = \frac{x_l^i}{\gamma^2(1 - x_l^i)^2} (1 - Z_l).$$  \hspace{1cm} (21)$$

Inserting this into Eqn. 16 and using $\sum_{k=1}^{\infty} z^k = z/(1 - z)$ for $|z| < 1$, we obtain, after some algebra, the following value for the Fano factor of the number of coincidences for two independent spike-trains generated by Gamma-processes with rates $R_i$ and of shape parameter $\gamma_i$:

$$FF_c = \frac{1}{\gamma_1 \gamma_2} + \frac{R_1 \Delta t}{\gamma_2} + \frac{R_2 \Delta t}{\gamma_1} - \frac{2}{\gamma_1 R_2 \Delta t} \sum_{l=1}^{\gamma_2 - 1} B_l^2 - \frac{2}{\gamma_2 R_1 \Delta t} \sum_{k=1}^{\gamma_1 - 1} B_k^1 + \frac{4}{R_1 R_2 (\Delta t)^2} \sum_{k=1}^{\gamma_1 - 1} \sum_{l=1}^{\gamma_2 - 1} B_k^1 B_l^2 \left( 1 + \frac{1}{2} \frac{(1 - Z_k^1)(1 - Z_l^2)}{1 - Z_k^1 Z_l^2} \right),$$  \hspace{1cm} (22)$$

where $Z_l^i$ and $B_l^i$ are determined by Eqns. 20 and 21 using the parameters $R_i$ and $\gamma_i$.

Hence, Eqn. 22 is a closed analytical expression for the Fano factor $FF_c$ of the coincidence count distribution of two mutually independent Gamma-processes with integer shape factors in case coincidences are counted by the product of spike counts per bin as defined in Eqn. 7.

Using Eqn. 22 we then studied the functional dependencies of $FF_c$ as a function of, first, the shape parameter, second, different rates for the two spike-trains considered simultaneously, and third, the product of the bin width and the spike rate $R \Delta t$ (see figure 4).

In figure 4A we plot $FF_c$ as a function of the $C_V$ for 4 variations of the product of the spike rate and the bin width $R \Delta t$ for two processes with identical rate $R = R_1 = R_2$ and identical shape factors $\gamma = \gamma_1 = \gamma_2$. It demonstrates that the value of $FF_c$ changes non-monotonically with increasing values of $C_V$. For low order of $\gamma$, $FF_c$ decreases
with increasing shape parameter, while $FF_c$ increases with $\gamma$ for larger values of the shape parameter. Moreover, while $FF_c$ is below 1 for all four variations of $R\Delta t$ for an intermediate range of the $C_V$, it is larger than 1 for low and high values of the $C_V$.

As a second variation (Fig. 4B), we used Eqn. 22 to study changes of the Fano factor $FF_c$ as function of the $C_V$ for the case that the rates of process one and two are differing but have same shape factors $\gamma = \gamma_1 = \gamma_2$. The bin width is chosen such that $R\Delta t = 0.2$. We quantify the difference in rate by $\Delta R/R$ with $R_1 = R + \Delta R$ and $R_2 = R - \Delta R$. For $\gamma = 1$ the Fano factor is $FF_c = 1 + (R_1 + R_2)\Delta t = 1.4$ and does not depend on $\Delta R$, such that we reproduce the results from figure 4A. For small values of $\gamma$ the dependence on $\Delta R$ is weak, but for large $\gamma$ there is a strong dependence. However, this dependence is not monotonic either.

For small differences of $\Delta R/R$ that are larger than $\Delta R/R = 0.1$ the qualitative behavior for small values of $C_V$ are quite different and stay below one, while the difference across differences of $\Delta R/R$ for larger values of the $C_V$ disappears.

In figure 4C we study $FF_c$ as a function of the difference in rate $\Delta R/R$ for five different shape parameters and $R\Delta t = 0.2$. Again the plot demonstrates that the behavior is not linear nor trivial. With increasing shape parameter the mapping becomes more complex. While it is monotonic as a function of the absolute value of $\Delta R/R$ for shape factors $\gamma = 2, 4, 8, 16$, the relation becomes non-monotonic for shape parameter $\gamma = 32$. For larger $\gamma$ the $FF_c$ has a maximum for $\Delta R = 0$ and drops more rapidly with $|\Delta R|$ as $\gamma$ is increased. However, for very large $\gamma$ there is a secondary peak for $\Delta R \approx 1/3$ for this value of $\Delta R$, $R_1 = 2R_2$. Presumably for even larger $\gamma$ there is another peak when $R_1 = 3R_2$. This illustrates that the Fano factor of the coincidence counts can change quite unexpectedly and strongly even for very small differences in the spike rates of two independent processes if the Gamma-processes becomes very regular.

As a last variation (see Fig. 4D), we study $FF_c$ as a function of the $R\Delta t$ for 5 variations of the shape factor $\gamma$. Again the complexity of the behavior increases with increasing shape factor. For a Poisson-process $FF_c$ grows linearly with the rate difference $R\Delta t$, while it is also non-monotonic for shape factors $\gamma = 2, 4, 16, 32$. 

15
This set of results demonstrates that the Fano Factor $FF_c$ of the coincidence count distribution depends in a complex and non-intuitive way on all three parameters: 1. the shape factor $\gamma$ and the $CV$, 2. the product of the spike rate and the bin width $R\Delta t$, and 3. the difference between the spike rates of two independent Gamma-processes.

The fact that even small changes of single parameters that are each in a biological plausible range can alter the Fano factor quite heavily and emphasize that a statistical inference on coincident firing may fail in case that it is based on the assumption that neuronal firing can be approximated by Poissonian processes. We find that if the $CV$ of the processes is approximately smaller than 0.2 or larger than 0.7, the significance would be overestimated, and for values in between it would be underestimated (figure 4A). The picture changes if the firing rates of the two considered processes differ. Then the significance tends also to be underestimated for small CVs (figure 4B,C). The underestimation is stronger if rate differences are larger (figure 4D).

3.5 Numerical estimation of the coincidence count distribution

Next, we will complement the analytical results from the last section with numerical estimations for the Gamma-processes with non-integer order parameter, and use log-normal-processes as a second kind of renewal processes. As for the analytical derivation of the Fano Factor $FF_c$ for the coincidence count distribution, we choose the coefficient of variation ($CV$) of the ISI distribution for the parametrization of both processes (see Eqn. 2 and Eqn. 6). We first checked the correspondence between the analytically predicted model $CV$ and the numerical estimation for the Gamma- and log-normal-process (see Figure 5 A1 and B1). For all tested parameter combinations the numerical estimations of $CV$ corresponded to the analytically predicted values.

In a further step, we study the effect of dithering of individual spikes (i.i.d, Gaussian, zero mean and 5ms standard deviation) of Gamma- and log-normal-processes on the $CV$ of the resulting processes (figure 5A2 and B2). Dither widths as small as 5ms change the $CV$ of the original process quite strongly and increase the $CV$. This is because processes with small values of $CV$ have many pairs of spikes that occur in short intervals and can be
Figure 5: Two different renewal processes are underlying results in A and B. (A): Gamma-process with an inter-spike interval distribution following a Gamma-distribution, (B): log-normal-process following a log-normal distribution. (A1,B1) Estimated CV on the y-axis as a function of the analytically predicted CV. (A2,B2) Same as in (A1,B1) but individual spikes were dithered by an random delay normally distributed with zero mean and a standard deviation of 5ms. (A3,B3) Fano factor of the coincidence count distribution as a function of the model CV. Coincidences were evaluated based on a binned version (bin-length for black solid: $\Delta t = 1\text{ms}$, black dashed: $\Delta t = 2\text{ms}$, grey solid: $\Delta t = 3\text{ms}$, grey dashed: $\Delta t = 4\text{ms}$) of the original renewal process used in A1-2,B1-2. Both process types (Gamma-and log-normal) were parameterized by the product of the bin-length $\Delta t$ in units of [s] and the firing rate $R$ in units of [Hz] (see legend). Each estimation of the CV or Fano factor was based on $T = 2000$ trials of each 5s length. The spike rate were chosen to $R = 50$ Hz. Error bars indicate one standard deviation.
characterized as bursty. Exactly this bursty activity is destroyed for even small amounts of dithering, since the short timescale of the dithering is comparable to the timescale of the bursts. For an original $C_V$ of about 1, there is no obvious change, but for original $C_V$ larger than 1, there is a tendency for resulting $C_V$'s to be smaller than 1. Intuitively that can be explained by the fact that dithering makes the inter-spike interval distribution of any kind of spiking activity more Poisson alike.

To estimate $FF_C$ for non-integer $Gamma$-processes with shape factors $\gamma$ ranging from 0.4 to 100 ($C_V$ from 0.1 to 1.5), as well as renewal processes with $log-normal$-distributed ISIs for values of $C_V$ between 0.1 to 1.5 we used Monte-Carlo estimations (figure 5A3, B3; for details regarding the numerical procedure we refer to Appendix C). The numerical results of the $Gamma$-process correspond to the analytically predicted values (cmp. figure 4A). For shape parameters smaller than 1, for which we do not have analytical predictions, the value $FF_C$ grows with increasing $C_V$ and increases of the product $R\Delta t$. The qualitative behavior of changes of $FF_C$ for a $log-normal$-process as a function of the $C_V$ are comparable to the changes in the case of a $Gamma$-process. Both processes exhibit non-linear and non-monotonic changes of $FF_C$ as function of $C_V$. Moreover, both processes exhibit a low $FF_C$ for intermediate values of $C_V$, while values of $FF_C$ are large for very low and high values of $C_V$.

In general, changes of $FF_C$ are more pronounced for larger values of the product $R\Delta t$. This is true for both kinds of processes. However, despite the qualitatively identical behavior, changes for larger values $C_V$ are up to 2 times stronger for $log-normal$-processes than for $Gamma$-processes.

### 3.6 Comparison of the full distributions

To compare the full shape of the distribution of coincidence counts we use quantile-quantile plots ('QQ-plots'). We first compare the distribution for $Gamma$- (Fig. 6 A1-3) and $log-normal$-processes (Fig. 6 B1-3) with the distribution for Poisson processes, for the case that all three types of processes have identical spike rate ($R=50Hz$). Differences between distributions resulting from $Gamma$- and $log-normal$-processes as compared to
Figure 6: Quantile-Quantile (QQ) plots describing the relation between two coincidence count distributions based on two different kinds of renewal processes. Each distribution represents sample from $T = 10000$ trials of each 5s length. Each QQ-plot shows the variation of 4 different model $C_V$ values ($C_V=0.1$, $C_V=0.45$, $C_V=0.85$, $C_V=1.5$). (A1-3) Y-axis shows the quantile of the coincidence count distribution $Q$ (Gamma-process) based on two mutually independent Gamma-processes, while the x-axis shows the quantile $Q$ (Poisson-process) for two mutually independent Poisson-processes. For both, the $Q$ (Gamma-process) and the $Q$ (Poisson-process), the spike rate was chosen to be $R = 50$ Hz. Coincidences were evaluated per trial based on a binned version (bin-length $\Delta t$) of both original renewal processes. (B1-3) The same as shown in A1 – 3 but based on log-normal- processes instead of Gamma-processes. Parameters for B1 – 3 are the same parameters as in A1 – 3. Different rows indicate different bin-length $\Delta t$ (A1, B1: $\Delta t=1ms$; A2, B2: $\Delta t=2ms$; A3, B3: $\Delta t=4ms$)
Poisson-processes are particularly obvious in the tails of the distributions. Because the average coincidence count is unaffected by the shape of the ISI distribution, the medians of the distributions are almost the same (QQ-plots cut the diagonal close to 0.5). Large and small values of $C_V$, i.e. deviating from $C_V = 1$, make the coincidence count distributions of the Gamma- and log-normal-processes more heavily tailed than the distribution resulting from Poisson-processes, whereas for intermediate values of the $C_V$, their tails are less pronounced. The fact that these differences are especially pronounced in the tails imply strong consequences for hypothesis testing. To illustrate that we added two insets for each QQ-plot showing the first 10% from 0 to 0.1 corresponding of the left tail of the distribution (insets above the diagonal in figure 6A1-3 and 6 B1-3) and the last 10% from 0.9 to 1 corresponding to the right tail of the distribution (insets below the diagonal in figures 6).

For the left tail of the distribution, any curve above the diagonal is indicating an increased false positive level if the test statistics is based on the assumption that spike-trains follow Poissonian firing. In contrast, any curve below the diagonal indicates a reduced amount of false positives and therefore a conservative hypothesis test. The actual amount of false positives in comparison to the given the test-level (values along the x-axis) is equal to the value of the QQ-curve (y-axis) at the given test-level (x-axis). In case of the right tail of the distribution (insets on below the diagonal showing values ranging from 0.9 to 1), this relation is the opposite. Here, any curve below the diagonal is indicating an increased level of false positives. For this case the actual amount of false positives, given the assumption of Poissonian firing, is equal to 1 minus the value at which the curve intersects a given value of the x-axis that equals the assumed test-level. Note that the interpretation of false positives occurring at the different tails of the distribution would be interpreted differently. While false positives in the left tail of the distribution would be interpreted as an overestimation of lacking coincidences, they would be interpreted as an overestimation of excess synchrony at the right tail. Typically of interest are tests showing the existence of excess synchrony.

Differences between the distributions can be quite dramatic, such that the amount
of false positives can be considerably increased (see figure 6A3,B3) for large bin width, as well as for large values of the $C_V$. Qualitatively changes for both types of processes, the \textit{Gamma-} and \textit{log-normal-}processes, compared to Poisson are very similar. Quantitative differences are most pronounced in the tails where differences in comparison to distributions generated by \textit{Poisson-}processes are generally strong.

4 Influence of dithering on coincidence distribution

4.1 Analytical approach for \textit{Gamma-}processes

As we have shown above, the Fano factor for the number of coincidences $FF_c$ depends on the auto-correlations of the spikes trains of the two neurons, $A^{(i)}_k$. The auto-correlation of the spike-trains after dithering is applied will be different from the auto-correlation of the undithered spike-trains. Hence dithering will change the shape of the distribution and thus the Fano factor of the coincidence count.

In general, it is not possible to analytically derive the Fano factor of the coincidences after dithering. However, it is instructive to consider the extreme with an extremely large width of the dithering kernel. In this case the auto-correlation becomes flat, except for the peak at zero delay. Nevertheless, the process is not Poissonian, since dithering does not change the spike count distribution for the two processes.

To calculate the Fano factor of the coincidence count distribution consider a case in which the neurons fire $N_1$ and $N_2$ spikes respectively. With this extreme dithering each spike has an equal probability to occur in any of the bins, and the bin in which it occurs is independent from that of the other spikes. Therefore the joint probability of having $\tilde{n}^{(i)}_k$ spike in bin $k$ is

$$P_i(\tilde{n}^{(1)}_0, \tilde{n}^{(1)}_1, \ldots, \tilde{n}^{(1)}_{K-1}) = \frac{N_1!}{\tilde{n}^{(1)}_0! \tilde{n}^{(1)}_1! \ldots \tilde{n}^{(1)}_{K-1}!} \prod_{j=0}^{K-1} \left( \frac{1}{K} \right)^{\tilde{n}^{(i)}_j} .$$

(23)

The average number of coincidences in these dithered spike-trains is

$$\langle N_c | N_1, N_2 \rangle = \sum_{k=0}^{K-1} \langle \tilde{n}^{(1)}_k \rangle \langle \tilde{n}^{(2)}_k \rangle$$

$$= K \langle \tilde{n}^{(1)}_k \rangle \langle \tilde{n}^{(2)}_k \rangle .$$

(24)
Where \( \langle \tilde{n}_k^{(i)} \rangle \), the average number of spikes in a bin is just the total number of spikes, \( N_i \), divided by the total number of bins, \( K \). Thus

\[
\langle N_c | N_1, N_2 \rangle = \frac{N_1 N_2}{K} .
\] (25)

The expected value of the square of the number of coincidences, given \( N_1 \) and \( N_2 \) satisfies

\[
\langle N_c^2 | N_1, N_2 \rangle = \sum_{k=0}^{K-1} \sum_{l=0}^{K-1} \langle \tilde{n}_k^{(1)} \tilde{n}_l^{(1)} \rangle \langle \tilde{n}_k^{(2)} \tilde{n}_l^{(2)} \rangle + K \langle (\tilde{n}_k^{(1)})^2 \rangle \langle (\tilde{n}_k^{(2)})^2 \rangle .
\] (26)

Here \( \langle \tilde{n}_k^{(i)} \tilde{n}_l^{(i)} \rangle \) is the expected value of the product of the number of spikes in two different bins, while \( \langle (\tilde{n}_k^{(i)})^2 \rangle \) is the expected value of the square of the number of spikes in a bin. Using Eqn. 23 for the probability distribution for the binned spike-train it is straightforward to show that

\[
\langle \tilde{n}_k^{(i)} \tilde{n}_l^{(i)} \rangle = \frac{N_i (N_i - 1)}{K^2}
\] (27)

and

\[
\langle (\tilde{n}_k^{(i)})^2 \rangle = \frac{N_i (N_i - 1)}{K^2} + \frac{N_i}{K} .
\] (28)

Using this we obtain, after some algebra, for \( \langle N_c^2 | N_1, N_2 \rangle \)

\[
\langle N_c^2 | N_1, N_2 \rangle = \frac{N_1^2 N_2^2}{K^2} + \frac{N_1 N_2}{K} \left( 1 - \frac{1}{K} \right) .
\] (29)

To obtain the expected average \( \langle N_c \rangle \) and mean square \( \langle N_c^2 \rangle \) of the coincidences we have to average these values over the distributions of the spike counts, \( N_1 \) and \( N_2 \).

\[
\langle N_c \rangle = \langle \frac{N_1 N_2}{K} \rangle_{N_1, N_2} = \frac{\langle N_1 \rangle \langle N_2 \rangle}{K}
\] (30)

and

\[
\langle N_c^2 \rangle = \langle \frac{N_1^2 N_2^2}{K^2} + \frac{N_1 N_2}{K} \left( 1 - \frac{1}{K} \right) \rangle_{N_1, N_2}
\]

\[
= \left( \frac{\langle N_1 \rangle^2 + \sigma^2(N_1) (\langle N_2 \rangle^2 + \sigma^2(N_2))}{K^2} + \frac{\langle N_1 \rangle \langle N_2 \rangle}{K} \left( 1 - \frac{1}{K} \right) \right) .
\] (31)
Figure 7: Analytically derived Fano factor of the coincidence count distribution for pairs of mutually independent Gamma processes as a function of applied dither $\sigma_d$. To dither the spike time of each individual spike time is changed by a random amount, that was i.i.d. gaussian distributed with zero mean and a standard deviation $\sigma_d$. To achieve simplicity and uniformity $\sigma_d$ is expressed in units of the expected inter-spike interval $1/R$. The range of a typical jitter, ranging form $0.1 R\Delta t$ to $R\Delta t$ is indicated by a shadowed area. Individual lines represent Gamma-processes with different shape factors $\gamma$ ( $\gamma=1 : C_V=1 / \gamma=2 : C_V=0.7 / \gamma=4 : C_V=0.5 / \gamma=8 : C_V=0.35 / \gamma=16 : C_V=0.25 / \gamma=32 : C_V=0.18$).
Using this we obtain for the Fano factor

\[
FF_c \equiv \frac{\langle N^2_c \rangle - \langle N_c \rangle^2}{\langle N_c \rangle} = 1 + \frac{\langle N_1 \rangle \sigma(N_2)}{K \langle N_2 \rangle} + \frac{\langle N_2 \rangle \sigma(N_1)}{K \langle N_1 \rangle} + \frac{1}{K} \left( \frac{\sigma(N_1) \sigma(N_2)}{\langle N_1 \rangle \langle N_2 \rangle} - 1 \right) .
\]

The expected value for the spike counts \( \langle N_i \rangle \) is given by \( \langle N_i \rangle = R_i K \Delta t \), while \( \sigma(N_i) \langle N_i \rangle \) is just \( FF^i \), the Fano factor for the spike count for neuron \( i \). Thus for large \( K \) we obtain for the \( FF_c \) of extremely dithered spike-trains in the large \( K \) limit

\[
FF_c = 1 + (R_1 \times FF^{(2)}_s + R_2 \times FF^{(1)}_s) \Delta t .
\]

(33)

Note that in this derivation we have not used the fact that spike trains are renewal processes. This result holds for any stationary process.

If the spikes are generated by a renewal process \( FF^i_s(i) \) satisfies, for large \( K \), \( FF^i_s = [C^{(i)}_V]^2 \), where \( C^{(i)}_V \) is the coefficient of variation for neuron \( i \). Thus in the large \( K \) limit the Fano factor after extreme dithering approaches

\[
FF_c = 1 + (R_1 [C^{(2)}_V]^2 + R_2 [C^{(1)}_V]^2) \Delta t
\]

(34)

for renewal processes. For smaller amounts of dithering we cannot easily obtain the auto-correlation after dithering analytically, but it can be obtained numerically from the auto-correlation of the undithered spike-train.

To do this we write the auto-correlation \( A(t) \) as

\[
A(t) = R \delta(t) + \tilde{A}(t) ,
\]

(35)

where \( R \delta(t) \) describes the part of the auto-correlation due to the same spike, while \( \tilde{A}(t) \) describes the probability density for having two different spikes a time \( t \) apart. Similarly we can write the auto-correlation \( A_d(t) \) of the dithered spike train as

\[
A_d(t) = R_d \delta(t) + \tilde{A}_d(t) ,
\]

(36)

where \( R_d \) is the firing rate of the dithered spike-train, and \( \tilde{A}_d(t) \) the probability density of two spikes in the dithered spike-train being \( t \) apart. Since dithering does not change
the firing rate, \( R_d = R \), while the probability of two different dithered spikes being a time \( t \) apart is just the probability that in the original spike-train the spikes where \( t - t_1 + t_2 \), averaged over the probability that the first of these is displaced by an amount \( t_1 \) and the second by \( t_2 \). Thus \( \tilde{A}_d \) satisfies

\[
\tilde{A}_d(t) = \int \int \tilde{A}(t + t_2 - t_1) \kappa(t_1) \kappa(t_2) \, dt_2 \, dt_1,
\]

where \( \kappa(t) \) is the probability that a spike is dithered by an amount \( t \). If the kernel \( \kappa \) is a Gaussian with standard deviation this can be simplified to

\[
\tilde{A}_d(t) = \int \tilde{A}(t + t_1) \exp \left( -\frac{t_1^2}{4\sigma_d^2} \right) \frac{dt_1}{2\sqrt{\pi}\sigma_d}.
\]

It is straightforward to calculate this numerically, after which it is easy to obtain the auto-correlation for the binned spike-trains using the approach outlined in the Appendix.

The impact of dither on the Fano factor \( FF_c \) is very non-intuitive. Changes of \( FF_c \) are monotonic for small shape factors of the Gamma-process and non-monotonic for large shape factors and can amount on up to 40\% of relative changes. Strongest changes occur for dithering that is of the order of 0.1 to 1 times the average inter-spike interval (figure 7).

This is exactly the range that is used for significance estimations, since any smaller amount of dithering does not destroy coincidences and any larger dithering could change the profile of rate changes. This emphasizes that the actual p-value describing the likelihood that coincidence events are due to chance might depend on the amount of dithering, whereas the relation can be non-monotonic.

4.2 Appropriateness of dithering to realize the null-hypothesis of independence

So far we have analytically described the impact of dithering on the Fano factor \( FF_c \) of Gamma-processes with integer shape factor. Next, we again supplement the analytical expressions of \( FF_c \) by Monte-Carlo based estimations of the full shape of the distribution of coincidence counts of undithered and dithered Gamma- and log-normal-processes. In addition, we explore in how far the use of dithering is appropriate as an implementation of the null-hypothesis of independence in a significance test of spike coincidences.
Figure 8: Probability of false positives (test level: 1%) for coincidences shared by a pair of mutually independent a \textit{Gamma}-processes (A1-4) or \textit{log-normal}-processes. The statistical significance of a coincidence count of the original pair of processes was evaluated based on dithered versions of the original spike-trains. The dithering for each individual spike of the spike-trains was randomly distributed following a normal distribution with standard deviation $\sigma_d$ in milliseconds. The amount of dithering $\sigma_d$ was varied ($\sigma_d=5\text{ms}$, $\sigma_d=10\text{ms}$, $\sigma_d=20\text{ms}$, $\sigma_d=40\text{ms}$). In addition the bin-width was varied (different rows: A1,B1 $\Delta t=1\text{ms}$, A1,B1 $\Delta t=2\text{ms}$, A1,B1 $\Delta t=3\text{ms}$, A1,B1 $\Delta t=4\text{ms}$). The firing rate of the processes was 50 Hz in all the cases.
Thus we use the distribution of coincidence counts derived from mutually independent and dithered Gamma- and log-normal-processes as respective reference distributions and estimate the probability for significant outcomes of the 'original', undithered spike trains. By comparing the distributions from the undithered to the dithered coincidence count distributions we derive an estimate for the probability of false positive outcomes. This is done in the following way: we first determine the critical number of coincidences \( N_{\text{critical}} \) from the coincidence count distribution of the dithered processes as the minimal count just becoming significant given the test level \( \alpha \) such that \( p(N \geq N_{\text{critical}}) = \text{test-level} \). Then we compute the probability of false positives of the corresponding undithered processes as \( p(N_{\text{undith}} \geq N_{\text{critical}}) \). Since these three numbers \( N \), \( N_{\text{undith}} \), and \( N_{\text{critical}} \) are integer numbers, we use a linear interpolation on the cumulative distribution of the reference distribution to derive an interpolated \( N_{\text{critical}} \) to overcome variations in the effective significance level \( \alpha \) occurring due to the discretness of the coincidence count distribution. We use four different amounts of dithering (\( \sigma_d = 5\text{ms}, 10\text{ms}, 20\text{ms}, \text{and} 40\text{ms} \)) that are Gaussian distributed with zero mean and a standard deviation of \( \sigma_d \). The spike rate was 50 Hz, and inter-spike intervals were Gamma-distributed in figure 8A1-A4 and log-normal-distributed in figure 8B1-B4.

For low and intermediate values of the \( CV \) the qualitative and quantitative behavior of both process types is quite similar. Small values of the \( CV \) lead to increases of the amount of false positives up to 7 times compared to the test level. Intermediate values of the \( CV \) yield for both process types a level of false positives that is comparable to the test-level. Only for high values of the \( CV \) the false positives behave differently for Gamma- and log-normal-processes. While for Gamma-processes the false positives are increased, its probability is comparable to the test-level in case of log-normal-processes. The reason is that the probability for small inter-spike intervals for log-normal-processes and Gamma-processes are very different for larger \( CV \). In case of Gamma-processes the distribution is hyper-exponential, and short intervals are very likely, whereas for log-normal-processes the probability for very short intervals is zero and very low for small ISIs. Since dithering destroys more effectively very short intervals than larger ones, the
coincidence count distributions are in particular affected by this procedure.

This illustrates that the influence of dithering cannot be predicted by the $C_V$ of the underlying spike-trains alone. Changes of the coincidence count distribution due to dithering depend on the very detailed structure of the inter-spike interval distribution. For testing if coincidences are occurring by chance, dithering was introduced to destroy eventually existing excess coincidences between neurons to derive the distribution of coincident events occurring by chance. However, since dithering destroys not only coincident events of coupled neurons, but also the shape of the coincidence distribution due to changes on the auto-structure, it is not possible to tell the one effect apart from the other. Therefore, significant deviations of the number of coincidences could be due to either changes on the auto-structure or due to coupling of neurons. This illustrates that dithering, even if very small compared to the expected inter-spike interval, or other methods that manipulate the auto-structure of the original spike-trains may lead to false conclusions whether or not excess synchronous activity occurs.

Please note that the procedure we have taken here provides us an average estimate of the effect of manipulation by dithering. However, in the case of aiming to estimate the significance of a found number of coincidences in a data set, dithering is applied many times to the original data set. Based on the coincidences counted in each dithered version of the original data the coincidence distribution is generated that then serves for significance estimation of the number of coincidences found in the original data set (see for details (Louis et al., 2010; Louis & Grün, 2010)).

5 Discussion

Coordinated neuronal activity across many neurons has been discussed to be a major component of neuronal activity and to be involved in neuronal coding. However, the discussion whether coordinated activity really exists and if it is used for coding (e.g., Hebb, 1949; Barlow, 1972; Rieke et al., 1997; Shadlen & Movshon, 1999; Singer, 1999; Eggermont, 1990; deCharms & Zador, 2000) remains heated and controversial. While on the one hand a large and still growing number of studies confirmed that coordinated
neuronal activity like coincidences, spatio-temporal patterns or avalanches occur more often than expected by chance, other studies reported the opposite (e.g., Baker & Lemon, 2000). A major uncertainty is that it is unknown to what degree statistical features of the individual processes are involuntarily neglected, and thus change the likelihood that experimentally observed instances of coordinated neuronal activity can be explained just by chance (see for a review on these issues Grün, 2009).

The existence of auto-structure within spike-trains is undoubted, since, first, neurons have a refractory period after they fired a spike, second, neurons fire often with a temporal structure that is for example bursty, regular or periodic. Third, neuronal firing might not be described by renewal processes but exhibit higher-order dependencies of spike times further in the past (Nawrot et al., 2007). In this paper we studied the influence of the auto-structure of renewal processes on the shape of the coincidence count distribution of pairs of mutually independent point processes. To this end we derived an analytical expression for the expected mean coincidence count value, and also the Fano factor of the coincidence counts via the auto-correlation of the coincidences, in particular for Gamma-renewal processes with integer shape parameters. We supplemented these results with Monte-Carlo estimations of the full shape of the coincidence counts distributions for Gamma-renewal processes with non-integer and integer shape parameters, as well as for a renewal processes with log-normal-distributed inter-spike intervals.

Our first major finding is that the width of the coincidence count distribution depends critically and in a non-trivial way on detailed properties of the inter-spike interval distribution. This is best illustrated by the complex and non-monotonic dependency of the Fano factor $FF_c$ on the $CV$ of the inter-spike intervals for both the Gamma-and log-normal-process (see figures 4 and 5). The complexity of the $FF_c$ becomes even more apparent when differences in the individual spike rates $\Delta R$, changes in the bin-length $\Delta t$ or changes in the shape parameter $\gamma$ are considered. All of these affect the $FF_c$ non-linearly and non-monotonically for shape parameters larger than 1.

The second major finding is that the width of the coincidence count distribution characterized by $FF_c$ depends on the detailed properties of the individual point processes.
This is demonstrated by differences in the Fano Factor for Gamma- and log-normal-processes with identical $C_V$ of the inter-spike interval distributions (figure 5). Still, for both types of processes we found that $C_V$ values indicative of strong regularity or burstiness lead to a larger Fano factor than for intermediate $C_V$'s when the firing rates of the processes are identical. Note, the complex and mostly non-monotonic behavior of the Fano factor for Gamma-processes as a function of the rate difference $\Delta R$ and the order parameter $\gamma$ requires a precise knowledge of these parameters to allow for a prediction of $FF_c$. This suggests that predictions of the $FF_c$ based on estimated model parameters without knowing the underlying distributions is not be trustworthy.

5.1 Interaction of spike count variability and spike-train regularity

The Fano factor of the coincidences is mainly determined by two factors. One is variability in the number of spikes for each of the spike-trains, the other is the sharpness of the ISI distribution. If the ISI distribution for both spike-trains is very narrow, and both processes have the same rate, the following is true: if there is a coincidence at a time $t = t_0$ the probability that there is a second coincidence at a time $t \approx t_0 + \langle t \rangle$ is high, while this probability is low if there is no coincidence at time $t = t_0$. This leads to an increase in the variability of the number of coincidences. On the other hand, a higher variability in the number of spikes of the individual neurons also leads to a larger Fano factor of the coincidences. These effects can be separated by dithering the spike-trains by an amount large compared to the average ISI. This dithering destroys the fine temporal structure in the spike times but maintains the number of spikes and thus their count variability. Indeed we observed in this case that the $FF_c$ only depends on the Fano factor of the spikes counts $FF_s$ of the two neurons (see Eqn. 34).

Since the Fano factor of the spike count is equal to $C_V^2$ for renewal processes, this allows for a qualitative understanding of the width of the distribution of coincident events as a function of the coefficient of variation. As the $C_V$ is decreased from a high value, the effect of lowering the Fano factor of the spike counts $FF_s$ dominates, and the Fano factor
of the coincidences $FF_c$ decreases. For small $C_V$ the effect of the fine temporal structure becomes increasingly important. In the latter case $FF_c$ increases as $C_V$ is lowered even more. The point where this transition occurs, however, depends strongly on the details of the renewal processes. Note also that the higher likelihood of having a coincidence at time $t \approx t_0 + \langle t \rangle$ given a coincidence at time $t = t_0$ only applies when the two spike-trains have almost the same rate. This is true to a lesser extent when the ratio of the rates is around 1:2, or in general $n : m$ (with $n, m \in \mathbb{N}$).

5.1.1 Interaction of higher complexity of more than two neurons

So far we discussed the impact of the inter-spike interval distribution on the distribution of coincidence counts across pairs of neurons. We extended the analytical calculation for integer Gamma-processes to higher complexities, i.e. triplet, quadruplet, quintuplet, or in general $\xi$-tuplet coincidences. For triplets, the expected number of coincidences $\langle N_C \rangle$ is given by

$$\langle N_c \rangle = KR_1R_2R_3(\Delta t)^3,$$

while their Fano factor, $FF_c$, satisfies

$$FF_c = \frac{1}{R_1R_2R_3(\Delta t)^3} \sum_k \left[ A_k^1A_k^2A_k^3 - (R_1R_2R_3)^2(\Delta t)^6 \right].$$

Analogous expressions apply for $\xi$-tuplets of higher complexities, where the change of the Fano factor is becoming even stronger. Moreover, the direction of the change, whether $FF_c$ increases or decreases, does not stay the same with increasing complexities (data not shown).

5.2 Statistical inference from dithering

In order to statistically evaluate the existence of coordinated firing, one needs to define a model that predicts the number of coincidences occurring by chance for mutually independent processes. Different approaches have been taken to derive an approximate model for independent processes from recorded biological spike-trains. The approaches can be classified into two classes: first, approaches that consider the full auto-structure of the spiking activity of each individual neuron (Pipa et al., 2007, 2008; Harrison & Geman, 2009), and
second, approaches that ignore - at least partly - the auto-structure. Here we explored
the approach of dithering (e.g. Date et al., 1998; Abeles & Gat, 2001; Hatsopoulos et al.,
2003; Shmiel et al., 2006) that belongs in the latter class.

5.2.1 Dithering as implementation of the null-hypothesis for coincidences

Dithering of individual spikes was proposed to test whether coincidences occur by chance.
The basic idea is that dithering destroys existing coincident events caused by neuronal
coupling. In order to test if in the original data set coincidences occur more often than ex-
pected by chance, their number is compared with the distribution of coincidences derived
by dithering. Since, small amounts of dithering do not alter the rate profile significantly,
it was advertised for the detection of synchronized neuronal activity during the presence
of rate variation. However, as shown here, dithering destroys not only coincident events
induced by coupling, but also changes the shape of the coincidence distribution due to
changes of the auto-structure. Therefore, significant deviations from the number of co-
incidences expected by chance can be either due to changes of auto-structure or due to
coupling of neurons. To judge whether changes of the auto-structure are of practical rele-
vance for significance estimation based on dithering, we investigated to what degree $FF_c$
and the shape of the coincidence count distribution changes as a function of the amount
of dither and the nature of the auto-structure of the spike-trains.

The amount of dither is constrained by two time-scales. The lower bound is given
by the bin-length $\Delta t$. Any change smaller or of the order of $\Delta t$ has hardly a chance to
destroy potentially existing coordinated events (Pazienti et al., 2008). The upper bound
is given by the fastest timescale of rate changes present in the data. Therefore dithering
should be chosen of a particular width, e.g. from a Gaussian distribution with zero mean
and variance $\sigma_d^2$.

We derived analytically the effect of dithering on the Fano factor of the coincident
count distribution $FF_c$. The main result is that changes of $FF_c$ for changes of $\sigma_d$ are
non-monotonic and can either decrease or increase the variance of the coincidence count
distribution for Gamma-processes with a shape factor larger or equal than two. Strongest
changes of $FF_c$ occur exactly for the domain $(0.1(t) < \sigma_d < \langle t \rangle)$ that is often used to manipulate recorded biological spike-trains to get a model for independent firing. To understand the impact of this procedure on the estimation of the statistical significance of coordinated firing, we estimated the probability for false positives. To this end we estimated the probability for significant coincidence counts of simulated mutually independent Gamma- or log-normal-processes given the coincidence count distributions derived from dithered versions of the spike-trains.

We found that false positives were considerably increased for small values of the $C_V$, both for Gamma- and log-normal-processes. For larger values of the $C_V > 1$, only the Gamma-process expressed an increased level of false positives. Thus even very small amounts of dithers of less than the expected ISI interval, can influence the occurrence of false positives quite strongly. Hence, even alternative dither approaches (Davies et al., 2006) that aim to minimize the amount of changes on the spiking data by adapting the amount of jitter by preceding and subsequent ISIs may lead to false conclusions whether synchronous activity occurs by chance or not.

5.2.2 Dithering as implementation of null-hypothesis for complex patterns

So far we discussed the impact of dithering on distributions of coincidences between two neurons. Since dithering had also been applied to derive the statistical significance of higher complexity $\xi$-tuplets as well as for spatio-temporal patterns (Abeles & Gat, 2001) that can involve many neurons and more than one spike from the same neuron, we also studied the impact of dithering on changes of $FF_c$ for higher complexities $\xi$. We found (data not shown here) for the case of synchronous firing of $\xi$ spikes within $n$ neurons for integer Gamma-processes that the effect of dithering on the width of the coincidence distribution gets more pronounced with increasing complexity. However, the direction of the change of $FF_c$, i.e. whether dithering broadens or narrows the distribution, can be different for different complexities even for the same $\sigma_d$, and cannot predicted from the effect of dithering on doublets. However, for most values of $C_V$ dithering decreases the Fano factor of the coincidence count distribution $FF_c$ for complexities $\xi > 2$. This means
that for most values of \( C_V \) dithering leads to an increased level of false positives.

In case of coincident firing which involves maximally one spike per neuron, the expected value of coincident events stays unchanged for different types of auto-structures, while the variability of the coincident count distribution changes. In case of spatio-temporal patterns, that can include more than a single spike from each neuron, the situation is different. Here, the auto-correlation influences the probability of occurrences of a certain spike sequence of the same neuron directly. Hence, any auto-structure that deviates from Poissonian firing leads not only to a change of the variance but also to a change of the expected value of the number of spatio-temporal patterns. Whether the expected number is larger or smaller than in case of Poissonian firing depends on the auto-correlation. If the auto-correlation exhibits a bump which corresponds to the interval between spikes of the same neuron in the spatio-temporal pattern, the expected number will be larger than in case of a Poisson processes.

Hence, in case of spatio-temporal patterns, dithering cannot only alter the variance of the count distribution of spatio-temporal patterns, but also the expected number. This makes a prediction of changes on the distribution of spatio-temporal pattern due to dithering difficult. However, our results suggest that spike-trains that are very regular or bursty, have a higher number of chance patterns as compared to Poisson processes. Thus dithering may trivially reduce the expected number and involves the danger of generating false positives. Unfortunately, up to now such an investigation is missing. However, it was shown that assuming a wrong shape factor for surrogate Gamma-processes, e.g. too low, would also yield a lower expectation that for the correct shape factor (Gerstein, 2004). Vice versa, assuming a shape factor for surrogate data higher than in real data would lead to the opposite conclusion (Baker & Lemon, 2000).

5.2.3 Relation to other spike correlation analysis approaches

This present study directly relates to other correlation analysis approaches, which base their significance evaluation on certain assumptions. For example the Unitary Events (UE) analysis (Grün et al., 2002a,c) in its original form assumes Poisson statistics to an-
analyze the significance of coincident spike events (see Grün (2009) for surrogate based UE analysis). This assumption enables to calculate the coincidences distribution analytically. Thus, given the results in this paper, one would expect that assuming Poisson processes in the presence of e.g. bursty processes would lead to false positive outcomes in the UE analysis (cf. figure 5). However, this is not the case (Grün, 2009). The reason is two-fold. First, the UE analysis operates on binned and clipped spike trains, which considerably reduces the burstiness. Second, the UE analysis adjusts the mean of the coincidence distribution (Poisson) used for the significance evaluation according to the spike counts in the data under evaluation. The comparison of coincidence counts resulting from Poisson and non-Poisson processes shown in this present study was based on distributions derived from many realizations parameterized by the firing rate of the processes. As a consequence, spike count variations of the various realizations also contribute to the width of the distributions which UE avoids (see for details the companion paper Pipa et al., 2010). Further, the UE analysis leads for intermediate $C_V$s to less false positives as the applied test level, which explains the enhanced significance of excess spike synchrony found in a comparative analysis of the same data by NeuroXidence and UE (Pipa et al., 2007).

Louis et al. (2010) compared extensively various surrogate approaches for the significance estimation of excess spike synchrony in the framework of the Unitary Event analysis (Grüne et al., 2002c). Pairs of spike trains were modeled as Gamma processes in non-stationary settings and significance of empirically found coincidences was evaluated using surrogate data. Different flavours of spike dithering, i.e. mere dither, square root dither, joint-ISI-dither and dithering in operational time were studied, despite shift procedures as e.g. used in (Pipa et al., 2007). The false positive level decreased for the methods that increasingly include more features of the original spike trains, but still showed an increased FP level for small $C_V$s. Thus the results agree with the findings in this current study for $C_V < 1$, but differ for $C_V > 1$. In that range FPs were at the expected level (significance level) due to the reasons discussed above for the Unitary Events analysis.
5.3 Conclusion

These results demonstrate that dithering with a dither width much smaller than the average inter-spike interval can falsify the statistical inference on the existence of coordinated neuronal activity. This holds not only for coincidence patterns of two neurons, but also for patterns composed of more neurons or for spatio-temporal patterns. The amount of over- or underestimation of the statistical significance depends on details of the auto-structure of the original spike-trains and cannot be predicted on the basis of the $C_V$ alone.
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Appendix A  List of symbols used

\[ t \]  Inter-spike-interval ('ISI')
\[ p(t) \]  ISI distribution
\[ \langle t \rangle \]  Expected value inter-spike interval \( t \)
\[ \sigma^2_t \]  Variance of the ISI distribution
\[ R \]  Spike rate \( R = \frac{1}{\langle t \rangle} \) in units of spikes per sec
\[ C_V \]  Coefficient of variation of the ISI distribution
\[ FF_c \]  Fano factor of the coincidence count distribution
\[ \gamma \]  Shape parameter of the Gamma distribution
\[ a, k \]  Parameter of the log-normal distribution
\[ T \]  Number of trials (realizations) with \( t = 1 \ldots T \)
\[ \Delta t \]  Bin-width for binning the spike-trains, in units of sec
\[ T_w \]  Duration of the spike-trains in units of sec
\[ n_i \]  Spike count in bin \( i \) (\( n_i \in \mathbb{N}_0 \))
\[ N_c \]  Total number of coincidences in interval of \( T_w = \Delta t \times I \), corresponding to \( I \) bins
\[ N_{critical} \]  Minimal number of coincidences required for significant excess
\[ \sigma^2_d \]  Variance of dither distribution
\[ FF_s \]  Fano Factor of the spike count distribution

Appendix B  Auto-correlation of the Gamma-process

Appendix B.1  Continuous time

In an \( \gamma \)-th order Gamma-process with rate \( R \) the inter-spike intervals are drawn from the distribution

\[
p(t) = \gamma R \left( \frac{(\gamma R t)^{\gamma-1}}{\gamma - 1} \right) e^{-\gamma R t}.
\]  (41)

This means that the probability density \( p_k(t) \) for the \( k \)-th spike to occur at time \( t \), given that the zeroth spike occurred at time 0, satisfies

\[
p_k(t) = \gamma R \left( \frac{(\gamma R t)^{\gamma k-1}}{(\gamma k - 1)!} \right) e^{-\gamma R t}.
\]  (42)

This can be shown by induction: \( p_1(t) = p(t) \) and if \( p_k \) satisfies Eqn. (42), \( p_{k+1} \) is given
by

\[ p_{k+1}(t) = \int_0^t p_k(t-t')p(t')dt' \]

\[ = \frac{(\gamma R)^{(k+1)}}{(k\gamma - 1)!} e^{-\gamma R t} \int_0^t (t-t')^{(k-1)}(t')^{\gamma-1}dt' \]

\[ = \frac{(\gamma R)^{(k+1)}}{(k\gamma - 1)!} e^{-\gamma R t} \gamma^{(k+1)-1} \int_0^1 (1-x)^{(k-1)}x^{\gamma-1}dx \]

\[ = \frac{\gamma R (\gamma R t)^{(k+1)-1}}{[\gamma(k+1)-1]!} e^{-\gamma R t}, \quad (43) \]

where we have used \( \int_0^1 (1-x)^m x^n dx = m!n!/(n+m)! \).

For \( t > 0 \), the autocorrelation of a spike-train, \( A(t) \), is given by

\[ A(t) = R \sum_{k=1}^{\infty} p_k(t). \quad (44) \]

For a \( \gamma \)-th order \textit{Gamma}-process this is given by

\[ A(t) = \gamma R^2 \sum_{k=1}^{\infty} \frac{(\gamma R t)^{(k-1)}}{(\gamma k - 1)!} e^{-\gamma R t} \]

\[ = \gamma R^2 \sum_{k=1}^{\infty} a_{\gamma,k} \frac{(\gamma R t)^{(k-1)}}{(k - 1)!} e^{-\gamma R t}, \quad (45) \]

where \( a_{\gamma,k} = 1 \) if \( k \) is a multiple of \( \gamma \) and \( a_{\gamma,k} = 0 \) otherwise.

We can write for \( a_{\gamma,k} \), \( a_{\gamma,k} = \frac{1}{\gamma} \sum_{l=0}^{\gamma-1} x_{\gamma l} \), where \( x_{\gamma} = \exp(2\pi i/\gamma) \). That this choice has the right properties can be seen as follows: If \( k \) is a multiple of \( \gamma \), \( x_{\gamma l} = 1 \) for all \( l \), so that \( a_{\gamma,k} = 1 \), while if \( k \) is not a multiple of \( \gamma \), \( x_{\gamma k} \neq 1 \), but \( \gamma(1-x_{\gamma})a_{\gamma,k} = \sum_{l=0}^{\gamma-1} x_{\gamma l} - \sum_{l=1}^{\gamma} x_{\gamma l} = 1 - x_{\gamma k} = 0 \), so that \( a_{\gamma,k} = 0 \).

Using this parametrization of \( a_{\gamma,k} \) one obtains

\[ A(t) = R^2 \sum_{k=1}^{\infty} \sum_{l=0}^{\gamma-1} x_{\gamma l} \frac{(\gamma R t)^{(k-1)}}{(k - 1)!} e^{-\gamma R t} \]

\[ = R^2 \sum_{l=0}^{\gamma-1} x_{\gamma l} \sum_{k=1}^{\infty} \frac{(x_{\gamma l}^\gamma R t)^{(k-1)}}{(k - 1)!} e^{-\gamma R t} \]

\[ = R^2 \left( 1 + \sum_{l=1}^{\gamma-1} x_{\gamma l} e^{-(1-x_{\gamma l}^\gamma)\alpha R t} \right) . \quad (46) \]
Using $A(-t) = A(t)$ and the contribution of the correlation of each spike with itself we obtain for the full auto-correlation

$$A(t) = R\delta(t) + R^2 \left( 1 + \sum_{l=1}^{\gamma-1} x^l_\gamma e^{-(1-x^l_\gamma)R|t|} \right).$$  \hfill (47)

**Appendix B.2  Binning**

We now bin the spikes in bins of width $\Delta t$ and denote by $A_k$ the average of the product of the number of spikes in bins $l$ and $l + k$.

$$A_k = \int_0^{\Delta t} \int_0^{\Delta t} A(k\Delta t + t_2 - t_1) \, dt_2 \, dt_1.$$  \hfill (48)

For $k = 0$ we have

$$A_0 = \int_0^{\Delta t} \int_0^{\Delta t} R\delta(t_2 - t_1) + R^2 \left( 1 + \sum_{l=1}^{\gamma-1} x^l_\gamma e^{-(1-x^l_\gamma)R|t_2 - t_1|} \right) \, dt_2 \, dt_1$$

$$= R\Delta t + (R\Delta t)^2 + 2R^2 \sum_{l=1}^{\gamma-1} x^l_\gamma \int_0^{\Delta t} e^{-(1-x^l_\gamma)Rt} \, dt_1$$

$$= R\Delta t + (R\Delta t)^2 2R^2 \sum_{l=1}^{\gamma-1} x^l_\gamma \int_0^{\Delta t} \left( 1 - e^{-(1-x^l_\gamma)Rt} \right) \, dt_1$$

$$= R\Delta t \left( 1 + \frac{2}{\gamma} \sum_{l=1}^{\gamma-1} \frac{x^l_\gamma}{1 - x^l_\gamma} \right) + (R\Delta t)^2 - 2 \sum_{l=1}^{\gamma-1} \frac{x^l_\gamma}{\gamma^2} \left[ 1 - e^{-(1-x^l_\gamma)R\Delta t} \right].$$  \hfill (49)

Using $\frac{x^l_\gamma}{1 - x^l_\gamma} = \frac{1}{x^l_{\gamma-1}}$ we can write

$$\sum_{l=1}^{\gamma-1} \frac{x^l_\gamma}{1 - x^l_\gamma} = \sum_{l=1}^{\gamma-1} \frac{1}{x^l_{\gamma-1} - 1} = -\sum_{l=1}^{\gamma-1} \frac{1}{1 - x^l_\gamma},$$  \hfill (50)

which can be used to write

$$\sum_{l=1}^{\gamma-1} \frac{x^l_\gamma}{1 - x^l_\gamma} = \frac{1}{2} \left[ \sum_{l=1}^{\gamma-1} \frac{x^l_\gamma}{1 - x^l_\gamma} - \sum_{l=1}^{\gamma-1} \frac{1}{1 - x^l_\gamma} \right] = \frac{1}{2} \sum_{l=1}^{\gamma-1} \frac{x^l_\gamma - 1}{1 - x^l_\gamma} = -\frac{\gamma - 1}{2}$$  \hfill (51)

Thus $A_0$ can be written as

$$A_0 = \frac{R\Delta t}{\gamma} + (R\Delta t)^2 - 2 \sum_{l=1}^{\gamma-1} B_l,$$  \hfill (52)

with

$$B_l = \frac{x^l_\gamma}{\gamma^2(1 - x^l_\gamma)^2} \left( 1 - e^{-(1-x^l_\gamma)R\Delta t} \right).$$  \hfill (53)
For $k > 0$ one obtains

$$A_k = \int_0^{\Delta t} R^2 \left( 1 + \sum_{l=1}^{\gamma-1} x_l e^{-\left(1-x_l\right)\gamma R(k\Delta t+t_2-t_1)} \right) dt_2 dt_1$$

$$= (R\Delta t)^2 + R^2 \sum_{l=1}^{\gamma-1} x_l e^{-\left(1-x_l\right)\gamma Rk\Delta t} \int_0^{\Delta t} e^{(1-x_l)\gamma R t_1} dt_1 \int_0^{\Delta t} e^{-\left(1-x_l\right)\gamma R t_2} dt_2$$

$$= (R\Delta t)^2 + \sum_{l=1}^{\gamma-1} R^2 x_l e^{-\left(1-x_l\right)\gamma Rk\Delta t} \gamma^2 (1-x_l^2) \left[ e^{(1-x_l)\gamma R \Delta t} + e^{-\left(1-x_l\right)\gamma R \Delta t} - 2 \right]. \quad (54)$$

For $k < 0$ we can use $A_k = A_{-k}$ so that for $k \neq 0$ $A_k$ is given by

$$A_k = (R\Delta t)^2 + \sum_{l=1}^{\gamma-1} B_l (1 - Z_l) [Z_l]^{\left|k\right|} \quad (55)$$

with

$$Z_l^t = e^{-\left(1-x_l\right)\gamma R \Delta t}. \quad (56)$$

### Appendix C  Estimation of the Coincidence Count distribution

To estimate the coincidence count distribution we used the following procedure:

1. We generate mutually independent pairs of spike-trains of length $T_w$ as stochastic realizations of the same underlying process. To this end we draw iteratively as many inter-spike-intervals $t_i$ from the same underlying ISI distribution $p(\Delta t)$ as needed to cover a period of $T_w + 2\rho$. Hence, two periods of each length $\rho$, one preceding $T_w$ and one afterwards, are used to randomize the starting conditions (‘warm up’). $\rho$ was selected to be 500s. That gives on average 25000 spikes in the warm up period for a spike rate of 50Hz. In addition the first initial interval was drawn form a exponential distribution with the same expected ISI.

2. Binning of the sequence of inter-spike intervals. We partitioned $T_w$ into $i = 1 \ldots I$ exclusive bins each of length $\Delta t$, and counted the number of spikes $n_i$ falling into each individual bin ($n_i \in N_0$).

3. Next, the number of coincidences were derived. To this end, we derived the coincidence count for each individual bin as the product of the spike counts of correspond-
ing bins $i$ of the first $n^1_i$ and the second spike-train $n^2_i$. In a last step we computed the sum of coincidences $N_c = \sum_{i=1}^{I} n^a_i n^b_i$ across all $i$ bins in the interval of $T_w$.

4. Step 1 to 4 was iterated $T$ times ('trials') to estimate the probability distribution of $p(N_c)$ by $\hat{p}(N_c)$.

References


A1

$C_V = 0.1$

B1

$N_{\text{critical}}$

Poisson ($\gamma = 1$)

A2

$C_V = 1$

B2

$N_{\text{critical}}$

Poisson ($\gamma = 1$)

A3

$C_V = 3$

B3

$N_{\text{critical}}$

Poisson ($\gamma = 1$)
$C_V = 0.1$

$C_V = 0.5$

$C_V = 1$

$C_V = 1.5$
Legend

- $C_V = 0.1$
- $C_V = 0.45$
- $C_V = 0.85$
- $C_V = 1.5$
Fano factor (\( FF_c \))

dither-width \( \sigma_d \) in units of \( 1/R \)

\( \gamma = 1 \)
\( \gamma = 2 \)
\( \gamma = 4 \)
\( \gamma = 8 \)
\( \gamma = 16 \)
\( \gamma = 32 \)