Closed Form Jitter Analysis of Neuronal Spike Trains

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Abstract

Interval jitter and spike resampling methods are used to analyze the time scale on which temporal correlations occur. They allow the computation of jitter corrected cross correlograms and the performance of an associated statistically robust hypothesis test to decide whether observed correlations at a given time scale are significant. Currently used Monte Carlo methods approximate the probability distribution of coincidences. They require generating $N_{MC}$ simulated spike trains of length $T$ and calculating their correlation with another spike train up to lag $\tau_{\text{max}}$. This is computationally costly $O(N_{MC} \times T \times \tau_{\text{max}})$ and it introduces errors in estimating the $p$ value. Instead, we propose to compute the distribution in closed form, with a complexity of $O(C_{\text{max}} \log(C_{\text{max}}) \tau_{\text{max}})$, where $C_{\text{max}}$ is the maximum possible number of coincidences. All results are then exact rather than approximate, and as a consequence, the $p$-values obtained are the theoretically best possible for the available data and test statistic. In addition, simulations with realistic parameters predict a speed increase over Monte Carlo methods of two orders of magnitude for hypothesis testing, and four orders of magnitude for computing the full jitter-corrected cross correlogram.
1 Introduction

Though there are many means by which neurons communicate, using both chemical and electrical mechanisms, most attention has been paid to series of action potentials (spikes). It is known that in some cases the detailed time structure of these spike trains is used for information transmission while in others, only the overall number of spikes in some interval seems to be important but not their position in the interval. Examples of the first type are various kinds of “temporal coding” schemes proposed for different neural system and for different functional roles, e.g. refs Abeles (1991); Singer and Gray (1995); Riehle et al. (1997); Niebur et al. (1993); Softky (1993); Steinmetz et al. (2000), while the latter is the well-known rate-code mechanism, e.g. refs. Adrian and Zotterman (1926); Shadlen and Newsome (1998). To distinguish between these two possibilities, it is necessary to find whether reproducible correlations at the relevant time scale are present in neuronal data. One common way to approach this problem is to use auto- or cross-correlation functions as test statistics. Then one can (a) search for non-trivial structure in the function, like deviations from uniformity, and (b) detect whether there are differences between these functions in different experimental (e.g. behavioral) conditions.

The situation is complicated by the influence of rate variations on the raw correlations. To increase the signal-to-noise ratio, correlations are typically computed as averages over many trials. Changes in the behavioral state of an animal, e.g. due to onset of sensory stimuli or motor responses that occur always at the same time during a trial, typically result in changes in neural firing rates which are common to many neurons. While these are genuine correlations, they are unrelated to the neuronal coding question. Different techniques have been developed to remove them, e.g. subtraction of a “shuffle predictor” Perkel et al. (1967), the average of cross correlations between spike trains from permuted trials. While this correction removes correlations that are time-locked to trial onset, it was later pointed out that peaks in the correlation function that may be taken as indicative of correlated firing (e.g. at zero lag) can also be caused by slow rate covariations Brody (1998, 1999). After finding a significant peak in the cross correlation function, this ambiguity can be addressed by analyzing the time scale at which the

\[ \text{A "shift predictor" is very similar but the correlation function is computed from trials that immediately follow each other, rather than from randomly selected trials.} \]
measured correlation arises.

It was pointed out more recently [Amarasingham et al., 2012] that the null hypothesis of spike trains being independent in earlier work [Perkel et al., 1967] is useless if their mean rates co-vary. Rate co-variation of means the spike trains are not independent which leads to its immediate rejection of the null without providing any further insight. Amarasingham and his colleagues instead proposed a more detailed null hypothesis, namely that within an interval of width \( \Delta \), the exact location of spikes does not matter. Then, under the null hypothesis, simulated spike trains can be generated by modifying the spike times of an original measured spike train within a range of \( \Delta \). The cross correlations obtained from these modified (“jittered”) spike trains are then compared to those obtained from the original. If significant differences are found, the null hypothesis is rejected and it is likely that non-random correlations at time scales \( \leq \Delta \) are present in the data. Additionally, this method gives rise to the computation of jitter-corrected cross correlograms, which have been used to compare changes in synchrony across experimental conditions [Hirabayashi et al., 2013a,b; Smith et al., 2013]. Because the method relies on repeated simulation of spike trains, it will be referred to as the Monte Carlo jitter method for the purposes of this paper.

While the Monte Carlo jitter method (described fully in Section 2.1) is useful and easily generalized to complex statistical tests and hypotheses, its practical utility is limited by the inherent trade-off between accuracy and computation time in all Monte Carlo methods. As we will show in Section 3.2, the computation time may be prohibitively long, and even at this cost, it will only be a numerical approximation of the true solution. In the case where the test statistic is the cross-correlation value at a single lag, the \( p \) value can be computed exactly, as was shown by [Harrison, 2013]. In the present study, we therefore explore the benefits of computing in closed form the distribution which is only approximated by the Monte Carlo simulations. Accordingly we refer to this method, described in Section 2.2, as the closed form jitter method. In addition to computing the \( p \) value for rejecting the null hypothesis exactly we show that the computation of the jitter-corrected cross correlogram follows readily from that derivation. The computational performance of the closed form jitter and Monte Carlo jitter methods are compared theoretically (as computational complexity) in Section 3.1 and practically (as computational time) in Section 3.2.
Closed Form Jitter Analysis

$T$ Length of binned spike trains
$X, Y$ Two spike trains
$\tau$ Correlation Lag
$C(\tau)$ Correlation of $X$ and $Y$
$\Delta$ Jitter interval width
$i$ Index over Monte Carlo simulated signals
$j$ Index over jitter intervals
$N(X, j)$ Number of spikes in $X$ in interval $j$
$X_{i}^{MC}$ $i$th Monte Carlo simulated signal
$N_{MC}$ Number of Monte Carlo simulated signals
$C_{i}^{MC}$ Correlation of $X_{i}^{MC}$ and $Y$
$R_{\tau}$ Number of cases where $C_{i}^{MC}(\tau) > C(\tau)$
$p_{\tau}$ $p$ Value for correlation at lag $\tau$
$\text{JCCG}(\tau)$ Jitter-corrected Cross Correlogram
$P_{\tau}(C_{i}^{MC})$ Monte Carlo estimate of the distribution of correlations at lag $\tau$
$C_{j}^{int}$ Number of coincidences in the $j$th interval
$P_{\tau}(C(\tau))$ True distribution of correlations at lag $\tau$
$\tau_{\max}$ Maximum $\tau$ value processed
$N_{\max}$ Maximum value of $N(X, j)$ or $N(Y, j)$
$C_{\max}$ Maximum possible number of coincidences

Table 1: **Glossary.** Variables are listed in the order in which they are introduced.
2 Materials and Methods

2.1 The Monte Carlo Jitter Method

Utilizing the Monte Carlo jitter method (Amarasingham et al., 2012), it is possible to determine whether correlations arise from fine temporal structure or larger scale variations, sometimes referred to as rate covariations. This determination is made by comparing a test statistic (in this case cross correlations) of an original pair of spike trains against those computed from a set of jittered spike trains as described below. The jitter method, like cross correlation, operates on binned spike trains which we take as binary signals with values 0 and 1 and integer arguments 0 to \( T - 1 \), where \( T \) is the number of bins in the spike train. The binary assumption implies that the bin size is small enough (typically 1ms or so) such that two spikes cannot be recorded in a single time bin. A sufficiently small bin size can always be chosen since there are limits on the minimal inter-spike interval time due to the refractory period of the neurons in question.

Let \( X(t) \) and \( Y(t) \) be two such binned spike trains. The processing then consists of the following steps:

1. Compute the cross correlation \( C(\tau) \) between the original \( X \) and \( Y \),

\[
C(\tau) = \sum_t X(t - \tau)Y(t)
\]

where the sum runs from 0 to \( T - 1 \) and \( X \) is assumed to be 0 if its argument is outside that range.

2. Subdivide one of the signals, say \( X \), into intervals of width \( \Delta \).

3. Count the number of spikes in each interval of \( X \). In interval \( j \) this is,

\[
N(X, j) = \sum_{k=j\Delta}^{(j+1)\Delta-1} X(k)
\]

4. For \( X \) generate \( N_{MC} \) Monte Carlo simulated signals \( \{X_{iMC}\}_i \), in which the spike counts for each interval are the same as in the corresponding interval in \( X \), such that \( N(X_{iMC}, j) = N(X, j) \) for all \( i, j \). However, now spike times within the interval are all equally likely. Spike times should be sampled without replacement to ensure that the spike count stays constant without putting multiple spikes in a single bin.
5. Compute the cross correlation $C_{i}^{MC}(\tau)$ for lag time $\tau$ between each $X_{i}^{MC}$ and the second spike train $Y$ to get an estimate of the distribution $P_{\tau}(C^{MC})$ of cross correlation values for each time lag $\tau$.

$$C_{i}^{MC}(\tau) = \sum_{t} X_{i}^{MC}(t - \tau) Y(t)$$

6. Let $R_{\tau}$ be the number of simulations where $C_{i}^{MC}(\tau) \geq C(\tau)$. Then the p value for a given lag $\tau$ is computed as

$$p_{\tau} = \frac{R_{\tau} + 1}{N_{MC} + 1}$$

7. If desired, a jitter-corrected cross correlogram (JCCG), defined using the expectation operator $E[\cdot]$, can be computed as

$$JCCG(\tau) = C(\tau) - E[C^{MC}(\tau)] \approx C(\tau) - \frac{1}{N_{MC}} \sum_{i} C_{i}^{MC}(\tau) \quad (2)$$

where the approximation approaches equality with $N_{MC} \to \infty$.

Jittering the spikes within an interval of size $\Delta$ destroys all correlations at time scales within this interval. The cross correlations computed from the jittered spike trains therefore are not correlated on time scales $\Delta$ or smaller, and $P_{\tau}(C^{MC})$ is the distribution of correlations at time lag $\tau$ obtained under the null hypothesis that correlations at time scales $\leq \Delta$ are indistinguishable from random correlations. If the measured cross correlation $C(\tau)$ is significantly outside this distribution, we have to reject the null hypothesis and we conclude that nonrandom correlations at lag $\tau$ with time scales $\leq \Delta$ are found in the observed spike trains. If, on the other hand, the observed correlation is consistent with what is seen in the distribution of jittered spike trains, then we cannot reject the null hypothesis. This means we cannot exclude that the observed synchrony is caused by correlations on time scales outside the jittered range, in other words that the observed correlation at lag time $\tau$ is caused by rate variations on time scales greater than $\Delta$.

In practice, $X(t)$ and $Y(t)$ do not have to be gathered from a continuous block of time. In the case of multiple trials of the same experimental condition, it may be useful to concatenate the recorded spike trains (possibly
at removing sections of them, like those recorded during stimulus onsets). In doing so, a period of no spiking of width \( \tau_{\text{max}} \) (the largest correlation lag of interest) should be added between the trials so that correlations between trials don’t affect the outcome of the jitter procedure.

As mentioned in Section 1, the practical utility of the Monte Carlo method is limited by the trade-off between accuracy and computation time inherent in all Monte Carlo algorithms. Furthermore, in practice a single set of Monte Carlo simulations is often generated for many hypothesis tests (i.e. tests at multiple lags), introducing potential dependencies between the different tests when they should be treated independently. In order to avoid both of these issues, the probability distribution \( P_\tau(C^{MC}) \) can be computed exactly and independently for each time lag as described in the following.

### 2.2 Closed Form Computation

#### 2.2.1 Probability Distribution For One Interval

First, let us consider a single interval consisting of \( \Delta \) time bins. For example, if spike times have been binned to 2 ms, for an interval of width 20 ms we have \( \Delta = 10 \). Since time has been discretized, it is still possible to discuss this unitless value as a length of time, a time scale, or an interval width for a given bin size. As before, we assume that the sequence is binary, so each bin has either zero or one spike. This is true even when the spike times are jittered because spike times are sampled without replacement. For this single interval, the probability of a given number of coincidences occurring is determined by three values: \( \Delta, N(X,j) \) the number of spikes in interval \( j \) of spike train \( X \), and \( N(Y,j) \) the number of spikes in interval \( j \) of spike train \( Y \).

As a first step, we count the number of perfect coincidences, in which one spike occurs in both \( X \) and \( Y \) within the same time bin, meaning \( \tau = 0 \). Using the standard notation of \( \binom{a}{b} \) for the combinatorial operation \( a \) choose \( b \), we find that there are \( \binom{\Delta}{N(X,j)} \) ways to distribute \( N(X,j) \) spikes in \( \Delta \) available bins. The number of empty (spike-less) bins in spike train \( Y \) is \([\Delta - N(Y,j)]\). The number of ways to distribute \( N(X,j) \) spikes such that each of them falls into one of these empty bins is \( \binom{\Delta-N(Y,j)}{N(X,j)} \). These are all

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\(^2\)The procedure of generating one set of spike trains for multiple lags is appropriate inappropriate only if each lag is being tested independently. If the test statistic is the sum of \( C(\tau) \) over a range of lag values, a single set of simulated spike trains is appropriate.
possible cases in which a coincidence is avoided. The probability that zero coincidences occur in the \( j \)-th interval is therefore

\[
P(C_{j}^{\text{int}} = 0 | \Delta, N(X, j), N(Y, j)) = \frac{(\Delta - N(Y, j))}{N(X, j)}
\]

where \( C_{j}^{\text{int}} \) is the number of coincidences in this interval.

We can generalize equation (3) to a non-zero number \( c \) of coincidences by breaking the numerator up into the number of ways that \( c \) spikes can coincide with the spikes in \( Y \), and \( N(X, j) - c \) spikes coincide with the gaps (or non-spikes) in \( Y \). We can thus compute a probability distribution for each interval \( j \),

\[
P(C_{j}^{\text{int}} = c | \Delta, N(X, j), N(Y, j)) = \frac{(\Delta - N(Y, j))}{N(X, j)} \binom{N(Y, j)}{c} \frac{1}{(N(X, j))}
\]

where we follow the customary convention of setting the value of a “choose” operation to zero if either of its arguments is negative, or if its upper argument is less than the lower. If this happens in the numerator of eq. (4), the probability on the left hand side becomes zero. Of course, the denominator is always positive since \( N(X, j) \leq \Delta \). This is a hypergeometric distribution.

Equation (4) is easily generalized to nonzero values of \( \tau \) by applying the analysis leading to it to a shifted version of \( Y \). For the computation of \( N(Y, j) \), this implies adding \( \tau \) to the summation limits in eq. (1) As with other correlation algorithms, the boundaries of finite spike trains (beginning and end) result in fewer intervals to analyze as \( \tau \) gets further away from zero. Thus generalizing eq. (4) to non-zero \( \tau \), we denote the resulting number of coincidences as \( C_{j}^{\text{int}}(\tau) \) and the associated probability distributions as \( P_{\tau}^{\text{int}} \).

### 2.2.2 Jitter-Corrected Cross Correlation

Once we have the analytical probability distribution for the correlations, we can obtain all relevant quantities to characterize the pairwise correlations between two spike trains. It is straightforward to compute the commonly used jitter-corrected cross correlogram (e.g., Hirabayashi et al., 2013a,b; Smith et al., 2013) which shows the correlation function after all correlations on time scales longer than \( \Delta \) have been removed. It is defined in analogy to equation (2) where the expectation value of the stochastic solution, \( \mathbb{E}[C^{\text{MC}}(\tau)] \), was used.
We can replace this approximation by the exact solution $E[C^\text{int}(\tau)]$. Furthermore, by the null hypothesis each interval is conditionally independent based on the spike counts. Therefore, the JCCG can be computed without approximation by

$$\text{JCCG}(\tau) = C(\tau) - E\left[\sum_j C^\text{int}_j(\tau)\right] = C(\tau) - \sum_j E[C^\text{int}_j(\tau)]$$

(5)

which, as should be remembered, is computed for a specific jitter interval width $\Delta$. The expectation on the right can either be calculated for each window as $N(x, j) \times N(y, j)/\Delta$.

The jitter-corrected cross correlogram is used, for instance, when the scientific question of interest is whether there are significant changes in synchrony between conditions, rather than a test of the presence or absence of synchrony. It is then used as part of a bootstrap statistical test in which the observed pairwise correlation is compared with the distribution obtained from eq. 5.

2.2.3 Probability Distribution For Spike Train

One can also obtain the probability distribution for the entire signal $P_\tau(C(\tau))$ as the convolution of the individual probability distributions for all intervals, $P^\text{int}_\tau$. This is identical to computing $P_\tau(C^{\text{MC}})$ from Section 2.1 with an infinite number of Monte Carlo simulations for each value of $\tau$. One can then evaluate how likely it is that the observed cross correlation $C(\tau)$ is explained by this probability distribution. The likelihood $p$ that this is the case is obtained as the integral of the probability density function exceeding $C(\tau)$, as in

$$p_\tau = \sum_{c=C(\tau)}^{\infty} P_\tau(c)$$

(6)

3 Results

3.1 Computational Complexity

In many situations, the statistical distributions underlying the phenomena under study are complicated or unknown and performing Monte Carlo simulations are the only way to make progress, even though it may be costly and
it introduces additional randomness in the processing. In the case considered here (binary spike trains, null hypothesis of uniform spike time distribution in fixed interval, cross correlation test statistic), the distribution $P_r(C)$ can be computed directly, using the closed form jitter method described above, without the need for repeated simulations. This section will compare the computational complexity of using the Monte Carlo jitter method against the direct computation using the closed form jitter method.

3.1.1 Monte Carlo Method

In the Monte Carlo algorithm, the data generation step requires a permutation of $\Delta$ data points for each interval and simulation. Since a single permutation operation has a computational complexity $O(\Delta)$, and $\Delta$ times the number of intervals is the length of the signal $T$, generating the set of Monte Carlo simulations $\{X_{MC}^i\}$ is $O(N_{MC} \times T)$. The complexity of cross correlation or convolution of two signals with lengths $T$ is $O(T \times \log T)$, assuming an FFT-based method (Cooley and Tukey, 1965) is used. So computing the full Monte Carlo probability distribution for all values of $\tau$ is $O(N_{MC} \times T \times \log T)$. In many cases, not all values of $\tau$ are needed. If the correlation is computed only for the subset of delay values from 0 to $\tau_{\text{max}}$, the complexity for the Monte Carlo jitter method is

$$O(N_{MC} \times T \times \tau_{\text{max}})$$

Computing the jitter-corrected cross correlogram by this method only requires one additional sum, with complexity $O(N_{MC} \times \tau_{\text{max}})$ so the total complexity remains unchanged.

3.1.2 Closed Form Probability Distribution

To compute the exact probability distribution with the closed form jitter method, note that the values of the distribution can be precomputed based on the maximum values of $N(X, j)$ and $N(Y, j)$ over all $j$; call this maximum $N_{\text{max}}$. Also, $n \choose k$ operations can be as fast as $O(\min(k, n - k))$ (Manolopoulos, 2002). Therefore, a three dimensional table of all possible values of $P(C^\text{int}_j | N(X, j), N(Y, j))$ can be precomputed and then looked up for each interval. Generating this table requires up to $N_{\text{max}}$ different values of $C$, $N_{\text{max}}$ values of $N(X, j)$, and $N_{\text{max}}$ values of $N(Y, j)$. Computing each value requires three $n \choose k$ operations, which are on the order of $O(N_{\text{max}})$,
so the total computation of the probability table is \( O(N_{\text{max}}^4) \). While the exponent is high, the expression does not have any dependence on the length of the signal and, furthermore, \( N_{\text{max}} \leq \Delta \) is a small number in essentially all cases of interest. In practice, for analyzing neurophysiological data it is rare that a time resolution finer than 1 ms is needed, or controlling for cross correlations at time scales larger than approximately 100 ms (i.e. \( \Delta \approx 100 \)). The full lookup table is therefore maximally a \( 100 \times 100 \times 100 \) matrix, which requires negligible resources to compute and store.

To compute the combined probability distribution \( P_{\tau}(C) \) over all intervals, all interval probability distributions \( P_{\tau}(C_{\text{int}}^j) \) must be convolved, and the computational complexity of the problem is dominated by these convolution operations. As will be shown, we can improve performance by taking advantage of the structure of the problem at hand, since many of the convolution operations are identical. As a result, the convolutions can be grouped together based on \( N(X, j) \) and \( N(Y, j) \) and quickly combined so that \( O(T) \) convolutions will turn into \( O(N_{\text{max}}^2) \) convolutions. This can be done by the following procedure:

1. Take the Fast Fourier Transform (FFT) of \( P_{\tau}(C_{\text{int}}^j | N(X, j), N(Y, j)) \) for each encountered value of \( N(X, j) \) and \( N(Y, j) \).

2. Raise each complex frequency spectrum value to a power equal to the number of times that the \( (N(X, j), N(Y, j)) \) pair appears.

3. Multiply these frequency spectra.

4. Take the inverse FFT of the result to get the final probability distribution \( P_{\tau}(C) \) and compute \( p_{\tau} \) as in equation 6.

5. Repeat steps 2 through 4 for each value of \( \tau \) to be tested.

The FFT operations in step 1 must be zero-padded up to the maximum number of coincident spikes \( C_{\text{max}} \) to account for the highest possible number of synchronous spikes in the combined probability distribution. Therefore the FFT operation in step 1 is \( O(C_{\text{max}} \times \log(C_{\text{max}})) \). In step 2 exponentiation is \( O(1) \). However there are \( O(T \times N_{\text{max}}^2) \) exponents to be taken, repeated \( \tau_{\text{max}} \) times in step 5. Step 3 requires \( O(T \times N_{\text{max}}^2) \) multiplications, again repeated \( \tau_{\text{max}} \) times. In step 4 the length of the spectral signal (to be inverted by FFT) is \( C_{\text{max}} \), so the operation is \( O(C_{\text{max}} \times \log(C_{\text{max}})) \) repeated \( \tau_{\text{max}} \) times. When
combining these steps, note that $C_{\text{max}}$ is proportional to $T$. However $C_{\text{max}}$ will be used when relevant because it captures the frequency dependence of the computation time. Therefore the total computational complexity is

\[ O(C_{\text{max}} \times \log(C_{\text{max}}) \times \tau_{\text{max}}) \]

Note that because the zero-frequency component of a probability distribution is always exactly unity, the inverse FFT computation will have accuracy limited by the precision of the numerical system. In practice this implies that $p$ values less than $10^{-13}$ will not be estimated accurately.

### 3.1.3 Jitter-Corrected Cross Correlation

Both the complexity analysis and the actual computation of the jitter-corrected cross correlogram is much simpler than that of the probability distribution. We generate a lookup table of possible $E[C_{\text{int}}]$ values and, from equation 5, the jitter-corrected correlogram can be computed at a speed of

\[ O(T \times \tau_{\text{max}}) \]

### 3.2 Computational Execution Time

For practical applications, consumption of resources is an important limitation for any computational method. For the size of problems encountered in typical neurophysiological experiments, the only limiting resource is execution time. To compare the performance of the Monte Carlo jitter and the closed form method, the two algorithms were run side by side in the MATLAB environment (Mathworks, Natick MA). Synthetic spike trains were generated that varied in both frequency of spiking (5 to 500 Hz) and length (1 to 91 seconds). For each (time, frequency) condition, 50 spike trains were generated, binned to 1 ms, and the average processing time was computed. Processing was performed with $\tau_{\text{max}} = 100\text{ms}$ and $\Delta = 20$. All computations were performed on an Intel i7 920 processor with 12 GB of RAM running Linux Ubuntu 12.04.

For the Monte-Carlo method, $N_{\text{MC}}$ was set to 1000. This selection of $N_{\text{MC}}$ is unrealistically low for two reasons. First, it can at best result in a
Bonferroni corrected $p$ value of 0.201 due to the 201 $p$ values being tested in the range of $-\tau_{\text{max}}$ to $\tau_{\text{max}}$. As the execution for $N_{MC} = 1000$ already takes 5.7 days to run, increasing $N_{MC}$ is impractical. Second, only a single set of Monte-Carlo trials were generated for all lag values computed, inducing potential correlations between the $p$ values. These correlations should decrease as more trials are generated. Therefore results are extrapolated to $N_{MC} = 20,000$ (resulting in a minimum $p \approx 0.01$) under the assumption that the processing for 20 times as many simulations would take 20 times as long. Though the bonferroni correction used here is conservative, it is less conservative (by an order of magnitude) than simulating a whole new set of spike trains for each $p$ value as would be required to entirely eliminate any correlations between the $p$ values.

For the closed form jitter method, all lookup tables were computed de novo for each spike train. This is a conservative approach (favoring the Monte Carlo technique) since performance of the closed form jitter method could be improved by computing the tables only once and using them for all spike trains. This is certainly advised in a “production environment.”

The results of this simulation, shown in Figure 1, illustrate a number of features about the speed of the two algorithms. Plotted is the performance gain, defined as the ratio of the computation time between the Monte Carlo jitter method and the closed form jitter method. The first observation is that the closed form method is substantially faster than the Monte Carlo method in all cases considered. Second, while the performance gain depends only weakly on spike train length, it does decrease with increasing firing rate. This is because the computation time of the closed form jitter method increases with firing rate. In practice, however, it is rare to observe firing at sustained frequencies exceeding 100 Hz in physiological recordings. In the physiological range, the closed form jitter algorithm is faster by a factor of approximately 180 to 7200.

Harrison (2013) uses importance sampling to accelerate the Monte Carlo hypothesis testing process which requires drawing fewer samples. In that work the number of samples needed, even for a low Bonferroni corrected $p$ value, is reduced to 100. However, each sample is reported to take 18 times as long to generate and process as before, effectively resulting in a simulation about 11 times faster than the Monte Carlo simulation with $N_{MC} = 20,000$. Therefore, under physiological conditions the closed form computation has an expected speed-up of 16 to 650 times compared to the importance sampling method. It should be noted that in cases where even lower $p$ values are needed
because of multiple hypothesis constraints, importance sampling will provide larger gains in estimating very small $p$ values. In these cases, increasing the $p$ value requirements has no effect on the computation speed of the closed form method, so the closed form method can be expected to be faster in all cases.

Another improvement mentioned in Section 2.2.2 is the ability of the closed form jitter method to compute the jitter corrected correlogram very rapidly, without computing the null hypothesis distribution of correlation values. To show the magnitude of the improvement, the simulation was repeated with only the mean of the null hypothesis distribution computed under the closed form jitter method since this is all that is needed for the corrected correlation function, eq. 5. We also restricted firing frequencies to the range 5–200 Hz. Figure 2 shows the ratio of the time it takes to compute equation 2 vs. equation 5. In these cases, the closed form jitter calculation is substantially faster (480x–13,000x), with increasing benefits for increasing spike train lengths. As discussed previously, the spike train length is typically not that of individual trials but of the concatenation of many trials.

4 Discussion

The importance, or absence of it, of precise timing of neural spikes has been discussed for the last half-century. Several techniques have been developed to characterize neuronal responses at fine time scales and it is clear that statistical methods have to be developed with much care to avoid wrong conclusions (e.g. Gawne and Richmond, 1993; Roy et al., 2000). One important difficulty is that firing rates can co-vary in the neurons under study. It is well-known that such co-variations are observable in quantities like pairwise cross correlation functions but they are typically considered as irrelevant from the point of view of neuronal coding or of determining the connectivity in the underlying circuitry. For instance, the onset of a stimulus will typically generate a temporary increase in firing rates in sensory cortex but the resulting increase in cross correlation is usually not considered of importance for neural coding (for an exception see Chase and Young, 2007, who showed that spike timing relative to onset-related population activity is informative). One common way to subtract such stimulus-locked effects is by subtracting a “shuffle predictor” (Perkel et al., 1967), obtained by computing cross correlations between spike trains from permuted trials. It has been pointed out
repeatedly (see references in the Introduction) that this does not eliminate spurious correlations, including close to $\tau = 0$ (synchrony). Brody (1998, 1999) and Amarasingham et al. (2012) proved that adopting the null hypothesis of independent neurons cannot solve the problem. Observation of such correlations is, indeed, evidence against the null hypothesis of independence between the two observed spike trains. Rejection of this null hypothesis can, however, occur either because spikes in the two spike trains are correlated “one-by-one” (synchrony), or because of slow firing rate covariations common to both spike trains. The fact that this null hypothesis can be rejected does not tell us why it is rejected. If the question is whether synchrony exists at less than a given time scale (only), this is the wrong null hypothesis. Instead, the time scale needs to be specified explicitly. The null hypothesis chosen by Amarasingham et al. (2012) is that changes of spike times within a time interval of size $\Delta$ have no effect on the computed statistic, in this case the correlation function. It is this null hypothesis that is tested by computer simulation in the Amarasingham et al. (2012) study and analytically in this report.

A key element of the methods discussed here is that the jitter intervals are defined without reference to the original spike trains. This ensures that if the null hypothesis is true, there is no way to distinguish the original spike trains from the Monte Carlo simulated spike trains. This characteristic (called exchangeability) ensures that the obtained $p$ values are from a well formulated hypothesis test. If, on the other hand, the resampling method was changed so that each spike was jittered about its original spike time, then even under the null hypothesis the original spike train would stand out from the rest because all of its spikes would be at the center of the jitter intervals. Therefore the resulting test would not be a proper statistical test and should be avoided (Amarasingham et al., 2012).

We have discussed two ways one can choose to characterize the correlations between two spike trains. One is a strict hypothesis testing approach. A null hypothesis is formulated, namely that the observed correlations are indistinguishable from correlations between spike trains whose spikes have been distributed randomly within intervals of length $\Delta$, without changing the number of spikes in each interval. By comparing the observed correlation with those in the distribution generated under the null hypothesis, it is then decided for a given $\alpha$ whether the null hypothesis can be rejected.

The alternative is to compute the time-resolved correlation function and “correct” for the correlations as observed under the null hypothesis, by sub-
tracting the expectation value of the latter. This is the more commonly cho-

sen approach, perhaps because the time-resolved correlation function is both
intuitive and familiar. The distribution of JCCG values can be compared
between experimental conditions (indicating a change in 'excess synchrony')
using a bootstrap test to test for significance. Also, its shape (e.g. the
location of peaks) may provide insight that goes beyond the yes-no answer
whether the null hypothesis can be rejected or not.

In the Amarasingham et al. (2012) study, the Monte Carlo procedure is
further developed to account for more potential causes of fine timing effects
besides synchrony such as ramping spike rates within an interval or inter-
spike interval distribution effects. These methods are straightforward and
statistically well-defined. Like any Monte Carlo method, however, they only
generate an approximation to the underlying distribution whose quality de-
dpends on the number of surrogate spike trains. In practice what is more prob-
lematic is that the method can be computationally very costly. For instance,
as discussed in section 3.2 our example problem using the simplest of the
null hypotheses discussed (50 spike trains of a few seconds long each, mean
rates between 1 and 100 Hz, maximal time lag of 100 ms, $\alpha = 0.01$ with Bon-
ferroni correction applied) would have required a simulation several months
long on a reasonably fast machine. We therefore only simulated $N_{MC} = 1000$
trials and extrapolated to the execution time needed for $N_{MC} = 20,000$ but
even that abbreviated Monte Carlo run took nearly six days. Some progress
can be made by using much faster machines or many machines (the problem
parallelizes easily) but execution time is clearly a problem.

In contrast, the closed form jitter methods this report focuses on are ex-
act, rather than approximate. More important for practical applications may
be that they are extremely efficient, with a speed-up of at least two orders of
magnitude for the hypothesis testing approach, and four orders of magnitude
for the full correlation functions. Even over importance sampling methods
(Harrison, 2013), they have been shown to provide a substantial increase in
speed. For the hypothesis testing examples used in our study (whose scope is
quite comparable to that of typical neurophysiological experiments, assum-
ing a proper Bonferroni correction is applied), computation time is reduced
from more than 100 days under the original Monte Carlo method to about
one night. Computational time required for the full correlation function is
reduced from over 100 days to a few minutes. An increase in performance on
this scale is more than merely a quantitative improvement. For instance, it is
essentially impossible to explore variations in the analyses (like the influence
of the jitter time scale $\Delta$) if each computational run takes a few months, but it is easy to do if it takes minutes.

So far we were only concerned with correlations between two spike trains. Modern recording techniques are already increasing the number of simultaneously recorded spike trains to tens or hundreds. Unfortunately, the closed-form jitter method is limited in the ability to analyze large ensembles. This is because the correlation functions of some pairs in an ensemble will restrict the possible correlation values of other pairs. For example, if there are three neurons $X$, $Y$, and $Z$, and the pairs $XY$ and $YZ$ have perfect correlation, then the pair $XZ$ must also have perfect correlation. A Monte-Carlo jitter analysis that jitters an entire ensemble of neurons and then performs a hypothesis test on the ensemble can be performed relatively simply, but no such closed-form method exists yet. In order to avoid the constraints of the type described above, only $N - 1$ pairs of neurons can be analyzed with closed form methods when $N$ neurons are recorded.

Additionally, the nature of the exact solutions provides an opportunity for further exact analysis. Having a closed form solution allows questions about the effects of spike sorting errors, the value of $\Delta$, or the structure of $JCCG(\tau)$ to be addressed rigorously and more precisely than is possible with any numerical method.

In conclusion, we study a statistical framework for quantifying correlations between spike trains at given time scales. It can be applied both for hypothesis testing and for correcting observed correlation functions for correlations at these time scales. Results are exact, and both computational complexity and computational time for realistic examples are several orders of magnitude lower than related approaches based on Monte Carlo simulations.

Matlab code will be made available by the authors upon request.

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Figure 1: Performance gain in implementing the closed form jitter method for \( p \) value computations. Gain is defined as the ratio in computation time between the Monte Carlo Jitter method and the closed form jitter method. Processing parameters used are \( \tau_{\text{max}} = 100\,ms \), \( \Delta = 20 \), and \( N_{\text{MC}} = 20,000 \) (see text for details).
Figure 2: Performance gain in implementing the closed form jitter method for Jitter Corrected Correlogram computations. Gain is defined as the ratio in computation time between the Monte Carlo Jitter method and the closed form jitter method. Processing parameters used are $\tau_{\text{max}} = 100 ms$, $\Delta = 20$, and $N_{MC} = 20,000$ (see text for details). The lowered performance gain at signal length of 1 second is due to the overhead of computing the probability table de novo for each spike train.