Improvements to the Sensitivity of Gravitational Clustering for Multiple Neuron Recordings

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We outline two improvements to the technique of gravitational clustering for detection of neuronal synchrony, which are capable of improving the method’s detection of weak synchrony with limited data. The advantages of the enhancements are illustrated using data with known levels of synchrony and different interspike interval distributions. The novel simulation method described can easily generate such test data. An important dependence of the sensitivity of gravitational clustering to the interspike interval distribution of the analysed spike trains is described.

1 Introduction

There is an increasing realization among neuroscientists that neurons can code information by more complex means than just the mean firing rate of their discharge (Rieke, Warland, de Ruyter van Steveninck, & Bialek, 1997). One important additional neural code appears to be the simultaneous discharge of two or more cells. Such short-term synchrony has been proposed to underlie processing in a wide range of neural systems (Espinosa & Gerstein, 1988; Lindsey, Hernandez, Morris, & Shannon, 1992; Singer & Gray, 1995; Vaadia et al., 1995; Baker, Olivier, & Lemon, 1997). The detection of above-chance synchrony between cells from data limited in recording length and number of spikes is therefore an important and challenging analysis issue (Strangman, 1997).

Gravitational clustering (Gerstein, Perkel, & Dayhoff, 1985; Gerstein & Aertsen, 1985) has been proposed to permit rapid detection of synchronous cell assemblies in simultaneous recordings from large numbers of neurons. Each cell is represented as a particle in a higher-dimensional space. Action potentials produce transient “charges” on the particle corresponding to the cell that fired. The particles move according to forces caused by attraction or repulsion of the charges. Particles relating to cells that fire synchronously thereby aggregate together. Following a gravitational analysis, aggregated
groups of particles indicate the presence of synchronous cell assemblies. The dynamic nature of the method allows it to visualize changes in groupings of neural synchronization over the duration of the recording. The gravitational clustering approach has been successfully applied to a range of experimental data (Gochin, Gerstein, & Kaltenbach, 1990; Lindsey, Morris, Shannon, & Gerstein, 1997; Lindsey, Shannon, & Gerstein, 1989; Aertsen, Bonhoeffer, & Kruger, 1987; Aertsen et al., 1991).

When compared with conventional cross-correlation-based approaches, the principal advantage of gravitational clustering is that it scales simply with the number of neurons whose firing has been recorded and multiple pairwise interactions can be simultaneously detected. The sensitivity of gravitational clustering has been shown to be similar to cross-correlation approaches in detecting synchrony with limited data (Strangman, 1997). An important difference between the two methodologies is that while cross-correlation represents a model-free approach to synchrony detection, gravitational clustering is more restricted. In particular, the time course of charge increment on a given particle following a spike limits the detection of synchrony to that which has a comparable jitter in synchronization. A similar limitation is present in the unitary event method (Grün, 1996; Pauluis & Baker, 2000). Such constraints prevent detection of synchronies that do not conform to the implied template. However, in theory, focusing on only those events deemed of interest a priori could have the capability to improve the sensitivity of detection.

In this article we present several modifications to the gravitational clustering approach, which are designed to improve its sensitivity in detecting neural synchronization. The desired improvement is demonstrated for simulated data having a magnitude and time course of synchrony in accord with that seen in experimental data. In addition, an important dependence of the sensitivity of the gravitational approach on the interspike interval distribution of the analyzed units is described.

2 Simulation of Spike Trains with Different Interspike Interval Statistics and Fixed Synchrony Magnitude

In order to quantify our improvements, we require a means of producing simulated spike trains in which there is a prespecified level of synchronization above that expected by chance. This can be relatively straightforwardly achieved if the spikes are simulated as a Poisson process, which have an exponential distribution of interspike intervals (Aertsen & Gerstein, 1985; Strangman, 1997). However, real recordings of neurons in the central nervous system usually show a relative refractory period (Rodieck, Kiang, & Gerstein, 1962), and their interspike interval histograms can be better approximated by a gamma distribution (Kuffler, Fitzhugh, & Barlow, 1957; Stein, 1965). The following is a method by which specified synchrony in gamma distributions may be achieved.
Figure 1: Method of synchronous spike train simulation. (a) Poisson spike train $S$, which serves as the source of synchronous spikes. (b) These are copied with probability $p$ to the destination train $T$, which also has independent spikes (dotted lines). (c) Decimation produces a spike train with interspike intervals following a gamma distribution. (d, e) The process can be repeated to produce another such spike train. The spike trains of $c$ and $e$ will show synchronization above the chance level (boxed spikes), since in some instances spikes may result from the same $S$ spike. (f) Interspike interval histograms for simulated trains with Poisson and gamma-(order 4) distributed intervals. Firing rate in each case was 25 Hz. (g) Cross-correlation histograms for two pairs of spike trains. One pair had Poisson interval statistics, the other gamma statistics (fourth order). The shape and magnitude of the cross-correlation peak can be fixed independently of the interval statistics.

We begin by simulating two event trains, denoted $S$ and $T$, which are Poisson processes having rates $\lambda_S$ (see Figure 1a) and $\lambda_T$ (the dotted lines in Figure 1b). A randomly chosen fraction $p$ of the events from the first process are copied to the second, producing a Poisson process that has a rate of $p\lambda_S + \lambda_T$. This composite process is then decimated by selecting every $n$th event (see Figure 1c). A gamma process of order $n$ is defined as the waiting
time until the $n$th event of a Poisson process. The resultant simulated spike train $R_1$ of Figure 1c will therefore have an interspike interval distribution that follows a gamma distribution, order $n$, and a rate given by

$$\lambda_R = \frac{p \lambda_S + \lambda_T}{n}.$$  \hfill (2.1)

The process can then be repeated, using the same source spike train as used previously (see Figure 1a), but with a different seed for the random number generator used to generate $T$ and determine which spikes will be copied from $S$ (see Figure 1d). After decimation, this will result in a second spike train $R_2$, having the same rate and interspike interval statistics as $R_1$.

Because $R_1$ and $R_2$ were generated from the same spike train $S$, they will show an excess of synchronous discharges above the level expected by chance for two independent spike trains firing at a rate $\lambda_R$, since on occasion the same spike will be copied into each spike train from $S$ and also survive the $n$-fold decimation (boxed spikes in Figures 1c and 1e). This can be quantified as follows. Consider the central region of the cross-correlation histogram, with $R_2$ acting as the trigger and $R_1$ the target neuron. If a spike from $R_2$ occurs at a given time, we require the expected number of spikes from $R_1$, which will be observed in a time window $\Delta t$ wide around the time at which $R_2$ fired. This is given by:

$$E(R_1 \text{ within } \Delta t | R_2) = P(R_2 \text{ originated from } S) \times \begin{pmatrix} P(\text{same } S \text{ spike was copied to } R_1 \\
+ E(\text{other } S \text{ spikes occurred in } \Delta t, \text{ were copied to } R_1, \text{ and survived decimation}) \\
+ E(T_1 \text{ spikes occurred in } \Delta t \text{ and survived decimation}) \\
+ P(R_2 \text{ originated from } T_2) \\
\times \begin{pmatrix} E(S \text{ spikes occurred in } \Delta t, \text{ were copied to } R_1, \text{ and survived decimation}) \\
+ E(T_1 \text{ spikes occurred in } \Delta t \text{ and survived decimation}) \\
= P(R_2 \text{ originated from } S) \times P(\text{same } S \text{ spike was copied to } R_1 \\
\text{ and survived decimation}) \\
+ E(S \text{ spikes occurred in } \Delta t \text{ were copied to } R_1, \text{ and survived decimation}) \\
+ E(T_1 \text{ spikes occurred in } \Delta t \text{ and survived decimation}). \end{pmatrix} \end{pmatrix} \hfill (2.2)$$
Since

\[ P(R_2 \text{ originated from } S|R_2) + P(R_2 \text{ originated from } T_2|R_2) = 1. \] (2.3)

The sum of the last two terms of equation 2.2 is simply the expected number of spikes from neurone \( R_1 \) over a time \( \Delta t \). This is therefore the expected number of counts in the central part of the cross-correlation histogram that would be seen if \( R_1 \) and \( R_2 \) were independent. The first term is the excess counts in this part of the cross-correlation, due to the fact that \( R_1 \) and \( R_2 \) are synchronized together more than expected by chance. Both counts are normalized to the firing rate of \( R_2 \), the unit chosen to trigger the cross-correlation histogram. Denoting the strength of excess synchrony by \( s \) (Abeles, 1991):

\[
s = P(R_2 \text{ originated from } S)p(same \ S \ text{ spike was copied to } R_1 \ and \ survived \ decimation)
= \frac{\lambda_S p}{\lambda_S p + \lambda_T} \cdot \frac{p}{n}
= \frac{\lambda_S p^2}{n(\lambda_S p + \lambda_T)}. \] (2.4)

In general, we know the values of \( s \) and \( \lambda_R \), which are desired for the simulated spike trains. The three unknowns (\( p, \lambda_S, \) and \( \lambda_T \)) may then be adjusted to produce these in accordance with equations 2.1 and 2.4. Note that the solution to this problem is not unique. Varying \( p, \lambda_S, \) and \( \lambda_T \) over ranges that maintain the same \( s \) and \( \lambda_R \) will change the correlation of the resultant spike trains \( R \) with \( S \). This is of no interest, since \( S \) will not be used in any subsequent analysis, and hence any valid combination of parameters can be used.

Valid solutions to equations 2.1 and 2.4 will have \( 0 \leq p \leq 1 \), and all firing rates positive. This leads to a constraint on the maximum level of synchrony, which can be simulated for a particular gamma order \( n \):

\[
s < \frac{1}{n}. \] (2.5)

In practice when simulating realistic levels of physiological synchrony and interval distributions (typically \( s < 0.1, n < 10 \)), this constraint is not a serious limitation.

Excess synchrony between real neurons does not occur at exactly zero lag, but exhibits a jitter (typically some tens of milliseconds; Smith & Fetz, 1989). Such jitter can be easily incorporated into the simulation method described by jittering the spikes copied from \( S \) to \( R \) by a time distributed according to a given random distribution. This will not change the level of excess synchrony \( s \) produced, so long as it is quantified over a sufficiently long section of the cross-correlation histogram. The shape of the peak in
the cross-correlation histogram will be given by the autoconvolution of the jitter distribution function.

Figure 1f shows the interspike interval histograms for two such simulated spike trains, having $n = 1$ (Poisson process) and $n = 4$. The rate $\lambda_R$ was 25 Hz for both simulations, and $s = 0.07$. The higher-order gamma process produced an interspike interval histogram with a realistic relative refractory period and therefore more closely approximated real neuron spiking. Figure 1g shows the correlation between pairs of simulated neurons for these two cases. The copying process included a jitter that was gaussian distributed with a standard deviation of 5 ms. The overlaid cross-correlation histograms are identical to within estimation noise. It was verified that the shape of the peak was equal to the autoconvolution of the gaussian jitter function. The peak area above baseline divided by the number of trigger spikes was very close to 0.07.

The above method thereby allows the simulation of any number of spike trains with preset synchronization and interspike interval characteristics, using methods that are highly computationally efficient to implement. While the description above has assumed that the parameters of the spike trains (firing rate and synchrony strength) are stationary throughout the simulation, the method is not restricted to this case. Using equations 2.1 and 2.4, the firing rates $\lambda_S$ and $\lambda_T$ may be computed as a function of time once the desired rate $\lambda_R(t)$ and synchrony strength $s(t)$ are known. Spike trains $S$ and $T$ can then be simulated as inhomogeneous Poisson processes, and mixed and decimated as described above to produce nonstationary simulated spike trains $R$.

3 Improvements to the Sensitivity of Gravitational Clustering

3.1 Formalism of Gravitational Technique. $N$ neurons are assumed to be simultaneously recorded. Following previous work on gravitational clustering (Gerstein et al., 1985; Aertsen & Gerstein, 1985), we represent these cells as $N$ particles in $N$-dimensional space. The initial coordinate along the $j$th axis of the $i$th particle is given by:

$$x_{ij} = \begin{cases} 1 & i = j \\ 0 & i \neq j. \end{cases}$$

(3.1)

The charge on particle $i$ at time $t$ is given by:

$$q_i(t) = \sum_k K(t - T_k) - \lambda_{ci},$$

(3.2)

where $T_k$ are the times of the spikes fired by this cell and $K(t)$ is a kernel function that is convolved with the spike train. The kernel function is assumed to have unit area. The firing rate of the $i$th neuron is given by $\lambda_{ci}$; this
is subtracted to ensure that the mean charge on a given particle is zero. In this article, only data with stationary firing rates are considered. However, it is possible to extend the method to nonstationary rates, in which case a time-varying rate \( \lambda_i(t) \) is subtracted in equation 3.2. The rate is normally estimated over a short window of data (Gerstein & Aertsen, 1985). Enhancements to the gravity method here proposed should also be usable when neurons change their firing rates by making this modification.

In the usual gravitational clustering analysis, particle positions are adjusted according to the pairwise attractions between particles. Thus, using a discrete time step of \( \delta t \), the position update rule is:

\[
x_i(t + \delta t) = x_i(t) + \kappa \delta t \sum_{j \neq i} Q_{i,j} \frac{x_j - x_i}{|x_j - x_i|},
\]

where

\[
Q_{i,j} = \tau_i \tau_j,
\]

The constant \( \kappa \) controls the rate of aggregation of synchronized neurons. The time step \( \delta t \) was fixed at 1 ms throughout this article. The denominator term within the summation prevents a dependence on the current separation of particles; an alternative version, where this is omitted, has been previously described (Dayhoff, 1994).

3.2 Effect of Moving-Window Smoothing on Charge Product. As a first potential improvement to the method of gravitational clustering, we propose increasing the sensitivity of the method to repeated instances of synchrony between the same two cells within a particular observation window. The inspiration for this approach comes from the intuitive consideration that whereas two neurons may fire once in synchrony simply by chance, two such occurrences within a short space of time are considerably less likely unless both are firing in bursts. Such an extension may be straightforwardly generated by calculating \( Q_{i,j} \) as a moving average of the charge product over a window extending back in time for a duration \( w \):

\[
Q_{i,j}(t) = \frac{1}{w} \int_{t-w}^{t} \tau_i(u) \tau_j(u) du.
\]

Figure 2a shows the effect such a moving-window smoothing approach has on the distribution of \( Q_{i,j} \) computed between two independently firing neurons. The two spike trains were simulated to have a firing rate of 25 Hz and interspike intervals that followed a gamma distribution, order 4. The kernel function \( K(t) \) was an exponential:

\[
K(t) = \begin{cases} 
\exp(-t/\tau) & t > 0 \\
0 & t \leq 0
\end{cases}
\]

(3.6)
Calculation of $Q_{i,j}$ on single points as equation 3.4 led to a distribution that was sharply peaked. By contrast, using a window length $w = 1$ s long, the distribution was approximately gaussian. The distribution histograms of Figure 2a have been plotted with the $x$-axis scaled by the standard deviation of the distributions. In addition to changing the form of the charge product distribution function, the standard deviation was reduced by a factor of 12.7 using the 1 s window. The conventional gravity analysis method achieves smoothing and the consequent noise reduction implicitly through the development of the particle trajectory. However, as will be shown below, it can be advantageous to perform this explicitly according to equation 3.5.
3.3 Detection of Synchrony Using Charge Products. Figure 2b shows the effect of different firing rates on the variability of the charge products. The lines show a linear regression relating the standard deviation of the $Q_{ij}$ calculated with a 1 s window to the cell firing rate; each line is calculated for runs using different values of the time constant $\tau$ in the kernel function $K(t)$. The variability of the charge product increases with the increasing firing rate of the cells, as more transient increases in the individual charges occur each second. The slope of this relationship is much steeper when small values of $\tau$ are used. Small $\tau$ leads to a single charge being flat except just after a spike, when a high-amplitude sharp transient occurs (the kernel amplitude will be large, since it is brief but constrained to have unit area). Large $\tau$ results in a much more even, and hence less variable, charge profile. These changes in single charge variabilities are reflected in the variance of the charge product $Q_{ij}$ as shown in Figure 2b.

The variability in the charge product $Q_{ij}$ shown in Figure 2a when two neurons fire independently means that detection of a mean increase in $Q_{ij}$ due to slight excess synchrony between the neurons is not trivial. The extent to which the synchronous and independent cases are separated can be measured by the statistic $d'$ (Green & Swets, 1966). This is illustrated by Figure 2c, and calculated according to

$$d' = \frac{Q_{ij}^{SYNC} - Q_{ij}^{INDEP}}{\text{stdev}(Q_{ij}^{INDEP})}. \quad (3.7)$$

The mean charge for an individual neuron is fixed to zero by equation 3.2; hence for independent neurons, the charge product will have zero mean, and the term $Q_{ij}^{INDEP}$ can be ignored. Figure 2d plots $d'$ versus the amount
of synchrony between the neurons, quantified by the measure $s$ defined above. This is shown for simulated spike trains with Poisson distributed interspike intervals. Different superimposed symbols show the results for spike trains with firing rates varying from 5 to 100 Hz. The points appear to lie approximately on the same line, indicating that the detectability of synchrony depends only weakly on the unit firing rates in this case. This is in agreement with previous observations (Strangman, 1997).

The rate of occurrence of excess coincidences will be directly proportional to the neuron firing rate (where the constant of proportionality is $s$ as defined above). Hence, the numerator of equation 3.7 must show firing-rate dependence. The finding that the $d'$ measure is essentially independent of firing rate indicates that the changes in the denominator (the standard deviation; see Figure 2b) balance those in the numerator when working with spikes having Poisson distributed interspike intervals.

Figure 2e shows a similar plot of $d'$ versus $s$, but now calculated using spike trains simulated to have interspike intervals distributed according to a fourth-order gamma process. The difference from Figure 2d is readily apparent. Firing rate now has a profound effect on the slope of the relationship between $d'$ and $s$, as shown by the fitted regression lines for each tested frequency. The changes in the numerator of equation 3.7 are independent of the interval statistics of the spike trains (not shown). However, gamma-distributed intervals have lower variance than a Poisson train of the same firing rate (Shadlen & Newsome, 1998); the standard deviation of $Q_{ij}$ in the denominator of equation 3.7 thus rises less steeply with firing rate than the increase in the mean of $Q_{ij}$ in the presence of excess synchrony. If the neurons have a refractory period with a gamma-like interval distribution, synchrony of a given strength is more easily detected when the cells fire at higher rates.

Figure 2f shows in more detail the effect of changing $n$, the order of the gamma process underlying the simulated spike trains, on the slope of $d'$ versus $s$. The simulations displayed in this example had a constant firing rate of 25 Hz. There is a sharp increase in the slope as the order is increased above $n = 1$; thereafter, the slope rises only slowly. For an order of $n = 4$, the fitted regression line is indistinguishable from $n = 8$. It can be seen that detection of synchrony is improved by more than twofold if neurons show a relative refractory period in their interspike intervals histograms, compared with the detectability obtained from Poisson spike trains with the same-size cross-correlation peak. A similar result was obtained using spike trains constructed as Poisson processes with a dead time to model the refractory period (data not shown). The effect of interspike interval distribution on the detection of correlation has also been noted by Davey, Ellaway, and Stein (1986) in a different context.

### 3.4 Use of a Nonlinearity to Improve Detection.

At high noise levels, when the measure $d'$ is small, detection of synchrony (i.e., a nonzero mean
Gravitational Clustering

$Q_{i,j}$ can occur only by averaging over sufficient data to overcome the noise. However, at higher levels of $d'$, it is possible to enhance detection by making the forces between particles depend nonlinearly on $Q_{i,j}$, yielding the following update rule:

$$x_i(t + \Delta t) = x_i(t) + \kappa \Delta t \sum_{j \neq i} f(Q_{i,j}) \frac{x_j - x_i}{|x_j - x_i|},$$

(3.8)

where $f(u)$ is a nonlinear function with a slope that increases its magnitude with increasing distance from $u = 0$. This will have the effect of suppressing small, noisy fluctuations and enhancing the large excursions in $Q_{i,j}$, which are unlikely to have been caused by chance. The simplest suitable form of nonlinearity is:

$$f(u) = A|u|^m \text{sign}(u),$$

(3.9)

where the power $m$ can be varied to change the functional form; use of this form permits even and nonintegral $m$ while ensuring that the sign of $f(u)$ always equals the sign of $u$. The constant $A$ permits scaling of the function. For practical application of the algorithm, we have found it convenient first to scale $Q_{i,j}$ by its standard deviation:

$$Q'_{i,j}(t) = \frac{Q_{i,j}(t)}{\text{stdev}(Q_{i,j})}.$$  

(3.10)

Such a scaling makes the variability of all charge products the same, regardless of cell firing rate or interspike interval statistics. By normalizing for this first, the choices of constant $\kappa$ in equation 3.8 can be standardized, and the same value used across different data sets. This avoids the need to tune performance of the algorithm by testing multiple values of $\kappa$. The standard deviation of the charge product can be calculated over the entire length of the data if the firing rate of the neurones is stationary or by using a moving window if not (compare with the calculation of mean charge using a moving window in nonstationary data; Gerstein & Aertsen, 1985). Normalization by standard deviation as a means to correct for nonstationarity has also been used by Aertsen et al. (1987; Aertsen, Gerstein, Habib, & Palm, 1989).

Assuming that $Q'_{i,j}$ is normally distributed (a reasonable approximation if a moving-window smoothing process is used, due to the central limit theorem; see Figure 2a), the variance of $f(Q'_{i,j})$ will then be

$$\sigma^2 = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{\infty} A^2 u^{2m} e^{-u^2/2} du.$$  

(3.11)

The parameter $A$ can be adjusted to make $\sigma^2 = 1$ for the chosen value of $m$. This permits experimentation with different $m$ without causing the severe
changes to the excursions of the random walks undergone by particles that relate to independent spikes.

A measure of the improvement of discrimination achieved by using $f(Q'_{i,j})$ rather than $Q'_{i,j}$ is given by

$$
\frac{f(Q'_{i,j})}{Q_{i,j}} = \frac{\int_{-\infty}^{\infty} f(u) e^{-\frac{(u-d)^2}{2}} du}{\int_{-\infty}^{\infty} u e^{-\frac{(u-d)^2}{2}} du}.
$$

(3.12)

Figure 3a shows the behavior of this measure for different values of $d'$, using various powers $m$ of nonlinearity. It can be seen that for $d'$ as low as 0.5, the ratio of equation 3.12 is below one for all powers higher than unity. This indicates that for such a low signal-to-noise ratio, no improvement in discriminability can be obtained above and beyond the linear case. Use of a nonlinearity simply enhances noise fluctuations and degrades discrimination. However, for larger $d'$, the curves rise above one, indicating that a nonlinearity can enhance performance. The peak in these curves, indicating the optimal power to use, occurs at greater powers the larger $d'$.

Figure 3b shows this best power as a function of $d'$ (solid line). It can be seen that even for quite modest values of $d'$ (corresponding to a mean $Q_{i,j}$ just over one standard deviation away from zero), use of a nonlinearity is expected to improve the performance of the gravitational clustering algorithm. The dotted line in Figure 3b indicates the point at which curves similar to those of Figure 3a recross an ordinate value of one. This indicates the highest power that can be safely used to yield performance that is no worse than the usual gravity algorithm with $f(u) = u$. From this perspective, use of a low power function (e.g., cubic, $m = 3$) will enhance, or at least not degrade, the performance of gravitational clustering for all but the very weakest correlations.

Moving-window smoothing of the charge product $q_iq_j$ as described by equation 3.5 is an essential prerequisite for application of a nonlinearity as described above. Without it, the standard deviation of the charge product will be so great that $d'$ will never exceed the region of Figure 3b where no better performance than a linear $f(u)$ can be achieved. Conversely, window smoothing cannot achieve any performance gains without a nonlinear $f$. This can readily be understood upon reexamination of equations 3.3 through 3.5. With a linear $f$, the position of a particle at a given time after starting the analysis will depend on the integral of the products between its charge and its neighbors up to that time. This will be the same whether the integration is performed entirely implicitly by the movement of the particles themselves (equations 3.3 and 3.4), or effectively in two stages by equation 3.5 followed by particle movements.

3.5 Performance Improvement by Triple Pair Enhancement. An important feature of the gravity technique is its ability to detect multiple cells
Figure 3: (a) Effect of the power used in the nonlinearity of equations 3.8 and 3.9 on discriminability, relative to the discriminability with a power of one (linearity). Lines are shown for $d' = 0.5, 1, 1.5, 1.7, 2$. (b) Optimal power of nonlinearity to use for the best discrimination as a function of $d'$ (solid line) and the highest power that will be no worse than linearity (dotted line).

that are members of the same synchronous assembly; such assembly membership is indicated by the clusters into which particles coalesce. This feature of the method suggests a further possible enhancement. Suppose three neurons, $i$, $j$, and $k$, are members of the same assembly. The pairwise synchronous firings $(i, j)$, $(i, k)$, and $(j, k)$ will each occur at above-chance rates, and this will lead the particles to move toward each other in the ordinary gravity computation. However, since all three neurons are part of the same
assembly, we might expect an excess temporal clustering of the several pair coincidences within a moving window of length $w$. Such counts of multiple pair coincidences are highly unlikely to occur by chance. The occurrence of triple pairs will be a much more robust indicator of assembly membership than any one of the individual pairwise synchronies alone.

The above observation inspires the following modification to the particle movement rule of equation 3.8:

$$x_i(t + \delta t) = x_i(t) + \kappa \delta t \sum_{j \neq i} f(Q_{i,j}) g \left( \sum_{k \neq i, j} Q'_{i,k} Q_{j,k} \right) \frac{x_j - x_i}{|x_j - x_i|}.$$  (3.13)

The function $g(u)$ is intended to scale the force experienced by the particle. The following are desirable features of this function. When the argument of $g$ is zero, no augmentation or diminution of the force should occur; hence $g(0) = 1$. We have found that a sigmoid function is not suitable, since the maximal slope around $u = 0$ enhances small chance fluctuations in $u$. The slope of the function $g$ should instead be zero at $u = 0$ but increase in magnitude to either side. A suitable function among the many that are possible, and which we have found effective, is:

$$g(u) = \begin{cases} 0 & u < -2 \\ 1 + \frac{u^3}{8} & -1 \leq u < 2\sqrt[3]{3} \\ 4 & u \geq 2\sqrt[3]{3}. \end{cases}$$  (3.14)

This function is thresholded at $g = 0$; it can thus never become negative, so that force directions cannot be reversed. It is likewise thresholded at $g = 4$; this prevents extreme outliers of the summed charge products from excessively disrupting the gravity condensation.

If no other neuron fires synchronously with cells $i$ and $j$ during the window period $w$, the summation over $k$ in equation 3.13 will be close to zero; $g$ will be nearly one, and the algorithm will be unaffected. However, if another cell $k$ does participate in the assembly in the period $w$, the summation will on average be above zero, since both $Q'_{i,k}$ and $Q_{j,k}$ will have nonzero, positive mean. The force causing aggregation between $i$ and $j$ will therefore be enhanced. By symmetry, a similar effect will occur for the force between particle pairs $(i, k)$ and $(j, k)$, and all three particles will therefore condense together more rapidly than had the term in $g(u)$ not been included. The practical success of this modification is demonstrated in the next section.

It would be possible to extend this approach to groups larger than three neurons; however, this would increase the number of combinations that need to be examined and is expected to be helpful only if large assemblies are present. Use of groups of three is expected to cause assemblies with larger numbers of members to aggregate considerably faster, since such populations have several subgroups of size three. We therefore have not investigated further than the triple pair approach outlined.
Figure 4 illustrates the results of gravitational analysis using the modifications described above. This was performed on simulated data. Ten neurons were used, all with a constant firing rate of 25 Hz. Three of these cells were synchronized together, with a synchrony strength $s = 0.1$; the copying process used to produce the synchronized spikes incorporated a temporal jitter that was normally distributed, with 5 ms standard deviation (as in Figure 1g). Figures 4a through 4c present the results when the simulated...
spike trains were Poisson processes (order $n = 1$); Figures 4c, 4d, and 4f are the results for a different data set, simulated so that the interspike intervals were gamma distributed, order $n = 4$. The figures are plots of the pairwise distances between particles as a function of time, for the 50 s duration of the simulation. A smoothing window $w = 1$ s was used, and the kernel time constant was $\tau = 10$ ms.

Figures 4a and 4d show the results for a conventional gravity analysis, as defined by equations 3.3 and 3.4. Three of the distance traces, corresponding to the distances between the particles representing the three cells synchronized together, condensed and became clearly separated from the other lines. (The crossed line to the right of each graph indicates the mean and standard deviation of distance trajectories for pairs where neither neuron is part of the synchronized assembly.) The separation occurs earlier and is somewhat more pronounced at the end of the run, for the data with gamma order 4 interspike intervals (see Figure 4d) compared with the Poisson case (see Figure 4a); this agrees with the results of Figure 2, which suggested that synchrony is more easily detected in a gamma spike train.

Figures 4b and 4e show the performance of the algorithm modified to use a cubic nonlinearity ($m = 3$ in equation 3.9). Particle condensation is considerably impaired for the Poisson spike trains, such that only two traces appear clearly separated from the noise excursions by the end of the analysis. Separation is adequate for the gamma distributed spike train.

Figures 4c and 4f show the performance when using the further modification described by equations 3.13 and 3.14. Once again, separation of the three distance traces relating to synchronized pairs is poorly achieved for the Poisson simulations (see Figure 4c), but good separation occurs for the spikes with gamma intervals (see Figure 4f).

Figure 4: Facing page. Results of gravitational analysis using different algorithms. (a–c) Pairwise distances between particles as a function of time, using Poisson distributed spike trains. (d–f) Using spike trains having a gamma distribution of interspike intervals (fourth order). (a,d) Conventional linear gravity method; (b,e) with cubic nonlinearity; (c,f) cubic nonlinearity and triple pair enhancement. The cross on the right of each plot shows the mean plus or minus standard deviation of the interpair distance at $t = 50$ s for all pairs where neither neuron was part of the synchronized assembly. The ordinate scales have been chosen such that the height of this marker is the same in a–c and d–f, permitting visual comparison of the magnitude of the particle aggregation relative to the aggregation noise. (g,h) Relative performance of the linear, cubic, and cubic plus triple enhancement algorithms, shown by solid, dotted, and dashed lines respectively. The lines show the mean of 20 runs using different simulated data in each case. The bars to the right indicate the standard error of the mean computed over the 20 runs at time 50 s. Spike trains were Poisson in g and had fourth-order gamma interval statistics in h.
While some differences between the performance of the different algorithms can be assessed by eye, it is desirable to develop a quantitative measurement of the degree to which particles representing synchronized neurons aggregate. We have chosen to use the following measure for this purpose:

\[ Z = \frac{\bar{d}_{i,j \in I} - \bar{d}_{i,j \in S}}{\text{std dev}(d_{i,j \in I})} \]

(4.1)

where \( d_{i,j} \) is the distance between the \( i \)th and \( j \)th particle, \( S \) represents the set of synchronized neurons, and \( I \) is the set of independently firing neurons in the same simulation. This measure \( Z \) has analogies with \( d' \) as defined in equation 3.7; it is the difference between the mean separation of the particles representing synchronous and independently firing neurons, expressed in terms of the variability seen in the independently firing interparticle distances. A similar measure would be appropriate for real, nonsimulated data where neuron synchrony properties are not known a priori. Here we would identify the synchronized neurons in terms of condensing trajectories.

Figures 4g and 4h show how \( Z \) varies during the gravity analysis for the different situations illustrated in the earlier part of the figure. The lines represent the mean of \( Z \) calculated over 20 data sets simulated with different random number seeds. The variability is indicated by the bars to the right of each graph, which represent one standard error either side of the mean, assessed from the 20 separate analyses at time 50 s. The solid lines show the behavior of \( Z \) using conventional gravity analysis (see Figures 4a and 4d), the dotted line using a cubic nonlinearity (see Figures 4b and 4e), and the dashed line using the triple pair enhancement (see Figures 4c and 4f). Figure 4g presents the results for analysis of Poisson spike trains. Conventional gravity analysis without modification here clearly gives the best result, with a discriminability some 50% higher than either of the two more complex algorithms. By contrast, Figure 4h shows the opposite effect when gamma-distributed spike trains are analyzed. All three lines are consistently above their corresponding plots in Figure 4g, confirming the increased detectability of synchrony for a spike train with gamma compared with Poisson interinterval statistics. A modest but worthwhile improvement over the conventional algorithm is achieved by using the cubic nonlinearity. A considerable improvement (almost a twofold rise in \( Z \)) can be achieved by combining the nonlinear and triple pair enhancement approaches. Since experimentally recorded spike trains will usually have interspike intervals closer to a gamma than a Poisson distribution, a similar improvement should be seen in experimental data.

Figure 5 presents data showing the robustness of this result. Figure 5a plots the final value of \( Z \) after a 50 s analysis, similar to that in Figure 4, for the three algorithms, as a function of the order of the gamma distribution of interspike intervals of the simulated spike trains. The same line style
Figure 5: (a) Efficiency of gravitational algorithms (measured by $Z$ at the end of a 50 s analysis run) depending on the order of the gamma distribution that their interspike intervals follow ($n$). Results with conventional linear gravity, a cubic nonlinearity, and the nonlinearity combined with triple pair enhancement are shown by solid, dotted, and dashed lines, respectively. Each point marks the mean from the analysis of 20 runs; error bars mark the standard error calculated over the same sample. (b) Variation of algorithm efficiency with the number of neurons in the synchronized assembly. Display conventions as in Figure 5.

Conventions as in Figures 4g and 4h have been used to denote the three algorithm variants under investigation. The usual gravitational method is superior only for Poisson spike trains ($n = 1$). Performance of the three techniques is the same for $n = 2$; at all higher orders, there is a clear advantage in using the modifications detailed in this article.
The triple pair enhancement algorithm was specifically designed to enhance assemblies with three members; it is important to be certain that its performance in other situations is adequate. Figure 5b accordingly indicates the effect of the size of the assembly on the relative performance of the three methods. Use of a cubic nonlinearity provided a fairly consistent increment over the usual, linear algorithm at all assembly sizes tested. Values of $Z$ using triple pair enhancement overlap those produced without it when only two cells are synchronized, indicating that this method introduces no appreciable extra noise in the small assembly case. However, the benefits of triple pair enhancement grow rapidly with larger assemblies, presumably due to the combinatorial rise in the number of triple pairs that can be formed.

5 Gravitational Clustering Averaged Relative to an External Event

The techniques described allow detection of synchronous cell assemblies when analysis can be performed over a relatively long period of time. The enhancements described rely on moving-window smoothing. The width of this window must be sufficient to produce a reasonable probability of more than one excess coincidence between a given pair of cells within it. At the firing rate (25 Hz) and strength of synchrony ($s = 0.1$) considered above, there is a probability of 0.71 of two excess synchronous events occurring within a 1 s window (computed from the Poisson counting distribution). Reducing the window duration would decrease the probability of more than one excess synchronous event falling within the window. The improvements in performance described above would thus be considerably degraded, due to the reduction in $d'$.

However, in many experiments, the aim is to investigate the modulation of synchronous firing over much shorter timescales (typically tens to hundreds of milliseconds). The small number of spikes in such short sections means that reliable conclusions cannot be reached on the basis of a single trial. The usual solution is to average the time course of synchrony over multiple trials with reference to an external event such as a stimulus occurrence or behavioral marker (Aertsen et al., 1989; Grün, 1996; Pauluis & Baker, 2000). The increased amount of data then available permits increased statistical power.

The gravitational clustering approach is also amenable to such across-trial averaging. In order to use the enhancements described above, this averaging is performed as follows. The pairwise, smoothed charge products $Q_{i,j}(t)$ are found for each available trial using equation 3.5. These are then averaged across trials, to obtain a set of mean charge product time courses $\overline{Q_{i,j}(t)}$. The standard error of the mean, computed across trials, can then be used to scale the charge product time courses according to equation 3.10, obtaining $\overline{Q_{i,j}(t)}$. The gravitational analysis is carried out by using these values in equations 3.3, 3.8, or 3.13. By averaging over multiple trials, the
noise level of $Q'_{i,j}$ is reduced, increasing $d'$ and permitting the use of a nonlinearity and triple pair enhancement.

Figure 6 shows an example of the application of such trial-averaged gravitational clustering. One hundred trials, each 3 s long, were simulated in which 10 neurons discharged at 25 Hz with interspike intervals following a fourth-order gamma process. For the first 1.5 s of each trial, neurons 1, 2, and 3 were synchronized together; for the last 1.5 s of each trial, these cells ceased to show excess correlation, and cells 4, 5, and 6 became synchronized instead ($s = 0.1$ in all cases). Figures 6a, 6b, and 6c show the results of gravitational clustering using the linear, nonlinear (quintic, $m = 5$ in equation 3.9), and triple-pair enhancement algorithms, respectively. A considerably shorter smoothing window, $w = 100$ ms, was used in comparison to previous analyses to retain temporal resolution. The higher power of nonlinearity compared with that used earlier (quintic compared with cubic) takes advantage of the improved signal-to-noise ratio available by averaging across trials (see Figure 3b). The pairwise distances plotted here have been adjusted by subtracting from each distance its value at $t = 1.5$ s. This renders the changes that occur on either side of this point more easily seen.

In each case, the three pairs relating to the synchronized cells show clear separation from the remaining pairs. It should be noted that while the plots appear symmetrical, this is in fact not the case, since a different set of pairs condenses before and after the normalization point in the middle of the analysis. In addition to a clustering of the distances between particles representing the three synchronized neurons, a second group can be seen to separate from the remaining distances to a lesser extent. These are distance pairs that include one of the synchronized cells and one of the independently firing ones. This small condensation of distance is expected from the geometry of the situation, as illustrated schematically in Figures 6d and 6e. If the two filled particles condense together, but there are no net attractive forces between them and the white particle, this will still result in a narrowing of the distance between the white and black particles. Such a small apparent condensation of pairs including only one synchronized neuron is often not noticeable in gravity analysis due to a high noise level (e.g., see Figure 4).

The improved algorithms described in this article clearly provide for a reduced level of noise in the distance plots of Figures 6b and 6c compared with Figure 6a. This is quantified in Figures 6f and 6g using the measure $Z$ defined in equation 4.1. Figure 6f presents the $Z$ calculation for the (1,2,3) assembly, and Figure 6g for the (4,5,6) one. The calculation of $Z$ has again been carried out over 20 separate simulations (each of 100 trials); the thin lines show the mean, plus or minus one standard error. The same line styles have been used as in Figures 4 and 5 to code the different analysis types. The order of relative efficiency of the three versions of the algorithm is as expected from the previous analysis (linear worse than nonlinear, which is
Figure 6: Results using trial-averaged gravitational analysis. (a–c) The results using conventional linear gravity, a quintic (fifth power) nonlinearity, and the nonlinearity combined with triple pair enhancement, respectively. Traces are the interpair distances as a function of time relative to the trial onset. Distances have been normalized by subtraction of their value at time 1.5 s for clarity of display. Distance plots have been labeled in b according to whether they relate to pairs in which both neurons were part of the synchronized assembly (S-S), only one was in the assembly (S-S) or neither were (S-S). Note that the two different assemblies $S_1$ and $S_2$, which were active before and after time 1.5 s, respectively, are separated before and after this time. (d) Schematic showing how apparent condensation can occur simply due to the geometry of the system. The black particles attract each other due to excess synchronization; the white particle, by contrast, represents an independently firing cell and experiences no net forces. After the black particles have condensed together (e), the distance between them and the white particle is nevertheless reduced. This explains the apparent condensation of the S-S pairs in a–c. (f) Efficiency of the three algorithms computed for assembly (1,2,3), which was synchronized for the first half of each trial. Line-style conventions are as in Figures 4g and 4h. (g) The same for assembly (4,5,6), which was active in the second half of each trial. Traces show the mean and standard deviation of $Z$ computed over 20 simulation runs.

worse than nonlinear with triple pair enhancement); the magnitude of the performance enhancement (greater than a 17-fold increase in $Z$) is, however, considerably greater than in the previous examples, which did not use trial averaging.
The two enhancements to the gravitational clustering algorithm presented in this article are capable of a considerable improvement in its sensitivity for detecting synchronous cell assemblies. While not universally applicable, the range of parameters over which it becomes worthwhile to use the two adjustments is wide and encompasses much of that seen physiologically. Implementation of the improvements to the gravity analysis will carry with it the cost of somewhat lengthened computation time. While this was of some concern only a few years ago (Dayhoff, 1994), rapid advances in computer power have rendered this of less consequence.

An interesting observation made in the course of the work presented here is that a given level of synchrony is harder to detect (i.e., requires more data before reaching significance) for a Poisson event train compared with events having a relative refractory period, as simulated by the gamma distribution. Detection of synchrony by neurons has some analogues to the gravity method (e.g., compare exponentially decaying kernels with cortical excitatory postsynaptic potentials), suggesting that this result may also hold for synchrony detection by neurons. If true, it would imply that the relative refractory period can be viewed as an important adaptation to permit accurate synchrony detection. This hypothesis, currently speculative, clearly requires further work.

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References


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