



Reconstructing the functional connectivity of multiple spike trains using Hawkes models

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Paris, 8th September 2017

Dear Professor Crunelli,

Please find enclosed the manuscript "Reconstructing the functional connectivity of multiple spike trains using Hawkes models" which we would like to be considered for publication in the Journal of Neuroscience Methods.

I have read and have abided by the statement of ethical standards for manuscripts submitted to the Journal of Neuroscience Method.

Sincerely yours,

Prof. R.C. Lambert

Reconstructing the functional connectivity of multiple spike trains using Hawkes models

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Abstract

Background: Statistical models that predict neuron spike occurrence from the earlier spiking activity of the whole recorded network are promising tools to reconstruct functional connectivity graphs. Some of the previously used methods were in the general statistical framework of the multivariate Hawkes processes but they often required huge amount of data, prior knowledge about the recorded network, and may generate non stationary models that could not be directly used in simulation.

New Method: Here, we present a method, based on least-square estimators and LASSO penalty criteria, optimizing Hawkes models that can be used for simulation.

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Conclusions: The present method is robust, stable, applicable with an experimentally realistic amount of data, and does not require any prior knowledge of the studied network. Therefore, it can be used on a personal computer as a turn-key procedure to infer connectivity graphs and generate simulation models from simultaneous spike train recordings.

(193 words)

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1 Introduction

Ensemble spiking activities in neuron networks are the bases of information coding and processing within the brain. Thanks to the significant advances in electrophysiological techniques ([5]) and computational power over the last 20 years, simultaneous spike train recordings have been collected in many brain areas under various experimental conditions from anesthetized (see for example [27]) to fully awake animals performing complex behavioral tasks (see for example [28]). Consequently significant efforts are currently devoted to develop state of the art methods analyzing simultaneously recorded spike trains ([29, 26]). One of the main challenges faced by these methods is how to determine the potential interactions existing between the different neurons, i.e. to reconstruct the functional connectivity graph of the recorded network.

Commonly used approaches include several histogram-based methods to calculate the cross-correlation functions ([19]), the cross-intensity functions ([4]) or the joint peristimulus time histogram ([9]). These methods however only consider pairs of neurons and may easily lead to inaccurate functional connectivity graphs due, for example, to the presence of common inputs or connection chains within the recorded networks ([29]).

More recent methods are based on statistical models of all observed variables ([29, 26]). Among these methods, much attention has been paid to statistical models that aim to predict spike occurrence in a given neuron as a function of its earlier spikes, of the preceding activities of the other recorded neurons, and possibly of some other known external variables, such as stimuli or movement ([4, 8, 14, 16, 17, 18, 20, 21, 22, 23]). These models are in the general probabilistic framework of the multivariate Hawkes processes where the conditional intensity of point occurrence is a function $\Phi(\cdot)$ of a linear combination of the background point rate and of multiple temporal kernels. Each kernel materializes the potential impact of past neuron activities (both its own and those of other neurons). The model is fitted by determining the parameters of the kernels for which the actual recorded spike history has the highest probability. Hence, maximum likelihood optimization of Hawkes models with $\Phi(\cdot) = \exp(\cdot)$ to facilitate parameter optimization (known as General Linear Models (GLMs)) are popular methods used in a number of studies (see for example [22]). However since $\Phi(\cdot) = \exp(\cdot)$, GLMs are indeed non-linear Hawkes models that do not fulfilled the stationary criteria identified so far ([2, 15]) and may produce an increasing number of spikes along time during simulation. In addition, optimization of the many parameters of the GLMs is difficult and may lead to very noisy solutions that may be non-unique. Therefore these models require a prior knowledge of the network architecture or of the shape of the kernels ([7, 18, 22]). Here we show that a new method based on multivariate Hawkes processes, fulfilling stationary criteria, is robust, stable and practicable with an experimentally realistic amount of data. The method using least-square estimators and LASSO penalty criteria was successfully challenged to multiple Integrate and Fire (IF) models of neuron networks to demonstrate its efficiency and highlight its limits.

2 Method

2.1 Statistical Method

The n simultaneous spike trains were modeled using multivariate Hawkes processes that were characterized by their (conditional) intensity. The intensity $\lambda^i(t)$ of the i^{th} spike train N^i indicates the probability to see a new point around t for the spike train i given what already occurred on all the

spike trains strictly before time t . Intensities were of the following form

$$\lambda^i(t) = \left(\nu_i + \sum_{j=1}^n \sum_{T \in N^j, T < t} h_{j \rightarrow i}(t - T) \right)_+$$

The coefficient ν_i is the spontaneous firing rate and the functions $h_{j \rightarrow i}$ model the interaction of spike train j on spike train i . A large positive value of $h_{j \rightarrow i}(d)$ at a certain delay d indicates an excitation from the neuron generating the j^{th} spike train onto the neuron generating the i^{th} spike train. As a consequence, when a spike occurs on the j^{th} spike train, the apparition of a new spike on the i^{th} spike train is highly likely after a delay d . On the contrary if $h_{j \rightarrow i}(d)$ is very negative, the j^{th} spike train inhibits the apparition of new spikes on the i^{th} spike train after a delay d . By summing up all the possible interactions with all the possible delays, one obtain the current firing rate given the past events. It should be noted that the function $h_{i \rightarrow i}$ represents the auto-interaction of the spike train and therefore models some intrinsic properties of the neuron such as the spike refractory period (figure 1A). Since the inhibition might be strong enough to generate negative λ^i , the overall positive part $(.)_+$ is considered to avoid negative firing rate. However in the sequel and to make the method intelligible, we will assume that the case of too strong inhibition given the past events never occur so that λ^i remains linear in both ν_i and the $h_{j \rightarrow i}$'s.

The point measure dN_t^i , which counts 1 in a small interval if there is a spike for the i^{th} spike train in t and 0 otherwise, can therefore be seen as a noisy version of

$$\nu_i + \sum_{j=1}^n \sum_{T \in N^j, T < t} h_{j \rightarrow i}(t - T) \quad (1)$$

Therefore, modeling the n spike trains implies to estimate the ν_i 's and $h_{j \rightarrow i}$'s. To parametrize this problem, we assume the functions $h_{j \rightarrow i}$ to be piecewise constant on a partition of K bins of size δ (figure 1B)

$$h_{j \rightarrow i} = \sum_{k=1}^K a_{j \rightarrow i}^k \mathbf{1}_{((k-1)\delta, k\delta]}$$

with $a_{j \rightarrow i}^k$ and ν_i in Hz. The spontaneous part ν_i gives the average frequency of apparition of a new spike given that there is no past events. The coefficient $a_{j \rightarrow i}^k$ gives the average frequency gain, or loss, of the i^{th} spike train induced by the occurrence a spike on the j^{th} train in the preceding period between $(k-1)\delta$ and $k\delta$.

Note that in (1), we can rewrite

$$\sum_{T \in N^j, T < t} h_{j \rightarrow i}(t - T) = \sum_{k=1}^K a_{j \rightarrow i}^k N_{[t-k\delta, t-(k-1)\delta]}^j$$

where N_A^j denotes the number of spikes in interval A . Therefore organizing the unknown parameters (ν_i and $a_{j \rightarrow i}^k$) in the vector \mathbf{a}_i of size $1 + nK$, one can rewrite (1) as

$$\nu_i + \sum_{j=1}^n \sum_{T \in N^j, T < t} h_{j \rightarrow i}(t - T) = \mathbf{c}_t^\dagger \mathbf{a}_i$$

where † denotes the transposition and \mathbf{c}_t is an observable vector of size $1 + nK$ that depends on t , its first coordinate concerning ν_i is 1 and the others correspond to the number of spike occurrences in the past in the form of $N_{[t-k\delta, t-(k-1)\delta]}^j$.

The true vectors \mathbf{a}_i are unknown but since dN_t^i is a noisy version of $\mathbf{c}_t^\dagger \mathbf{a}_i$, one can therefore minimize the distance between dN_t^i 's and the $\mathbf{c}_t^\dagger \beta$ over all the possible vectors β of size $1 + nK$. If the spike trains were observed between 0 and T_{max} , one wants to minimize

$$\int_0^{T_{max}} (dN_t^i - \mathbf{c}_t^\dagger \beta dt)^2$$

Developing and keeping only the terms that depend on β , we end up with the following least-square criterion

$$LS^i(\beta) = -2 \int_0^{T_{max}} \mathbf{c}_t^\dagger \beta dN_t^i + \int_0^{T_{max}} \beta^\dagger \mathbf{c}_t \mathbf{c}_t^\dagger \beta dt = -2\mathbf{b}_i^\dagger \beta + \beta^\dagger \mathbf{G} \beta \quad (2)$$

where \mathbf{b}_i is an observable vector of size $1 + nK$: its first coordinate is the number of spikes between 0 and T_{max} for the i^{th} spike train and the other coordinates are given by $\int_0^{T_{max}} N_{[t-k\delta, t-(k-1)\delta)}^j dN_t^i$, for all j and k , that is in other words the cross-correlogram between the i^{th} spike train and the other j^{th} spike trains. The matrix \mathbf{G} is defined by

$$\mathbf{G} = \int_0^{T_{max}} \mathbf{c}_t \mathbf{c}_t^\dagger dt$$

Therefore, minimizing in β , the least-square estimate of the parameter \mathbf{a}_i is given by

$$\hat{\mathbf{a}}_i = \mathbf{G}^{-1} \mathbf{b}_i \quad (3)$$

It can be noted that the classical direct estimation of interactions between j and i as performed via cross-correlogram appears in \mathbf{b}_i . However, in many cases the simple cross-correlogram analysis can be misleading. For instance, a strong chain of excitation between 3 neurons as $1 \rightarrow 2 \rightarrow 3$ might result in cross-correlograms that suggest a non-existing direct excitation from 1 to 3. In equation (3), the matrix \mathbf{G} takes into account such potential complex relationships between the different recorded spike trains and its inversion untangles these links (see also the numerical experiment in [24]). However, as it is, the method is not optimal for two reasons:

- the number of parameters to estimate is huge. For example simultaneous recordings of $n = 10$ spike trains, considering $h_{j \rightarrow i}$ functions over 100ms divided in $K = 20$ bins of $\delta = 5$ ms, require estimation of 2010 parameters. Therefore, the observation duration T_{max} is usually not long enough to calculate a good estimation of such a huge number of parameters.
- many parameters are potentially irrelevant since a lot of the $h_{j \rightarrow i}$ are generally null. Therefore, one wants to estimate a sparse graph of interaction revealing the connections "really" used.

To stabilize the method as well as gain sparsity, we used a two-step Lasso method and first minimized the following criterion

$$LASSO^i(\beta) = -2\mathbf{b}_i^\dagger \beta + \beta^\dagger \mathbf{G} \beta + 2\mathbf{d}_i^\dagger |\beta|, \quad (4)$$

where $|\beta|$ is the vector whose coordinates are the absolute values of β and where \mathbf{d}_i is a vector of weights. The theory presented in [10] shows in a much more general framework that multivariate counting processes are highly heteroscedastic (i.e. the variance depends on the coefficient) and that therefore the weights need to be set accordingly to obtain a robust turn-key method. In particular [10] proposes data-dependent weights that are based on an estimation of the variance on the data

themselves. By simplifying the method fully detailed in [10], we end up with (the following equality should be understood coordinate by coordinate)

$$\mathbf{d}_i = \sqrt{2\gamma \log(n + n^2 K) \int_0^{T_{max}} \mathbf{c}_t^2 dN_t^i + \frac{\gamma \log(n + n^2 K)}{3}} \sup_{t \in [0, T_{max}]} |\mathbf{c}_t|.$$

The minimization of $LASSO^i(\beta)$ leads to an estimate $\hat{\mathbf{a}}_i^{BL}$ of the true parameters \mathbf{a}_i . "BL" stands for "Bernstein Lasso" since, the shape of the weights are derived by a Bernstein concentration inequality.

In particular, one can see that γ , which qualitatively controls the probability that the estimator is good, should be an absolute constant that do not depend on the problem at hand and can be calibrated in advance. Note that $\gamma = 0$ corresponds to the least-square estimate $\hat{\mathbf{a}}_i$ which is not sparse at all and that the sparsity (that is the number of null coefficients) increases with γ . As a consequence, small γ values should favor models with numerous interactions that probably do not exist in the network and large γ values, oversimplified models with missing interactions. As presented in the following part, the results obtained with spike-train simulations strongly suggest that $\gamma = 3$ is a reasonable choice.

The very powerful and theoretical results of [10] ensures that $\hat{\mathbf{a}}_i^{BL}$ provides the best "Hawkes" approximation of the intensity of the observed process. In particular, it does not assume that the underlying observed spike trains are obeying a Hawkes model, the method just fits the best possible (sparse) approximation in terms of $\mathbf{c}_t^\dagger \beta$.

Finally, to estimate the "strength" of the interaction of the j^{th} on the i^{th} spike trains, one may consider the integral of $h_{j \rightarrow i}$,

$$\int h_{j \rightarrow i}(x) dx = \sum_{k=1}^K a_{j \rightarrow i}^k \delta$$

that gives the overall average number of spikes gained (if positive) or lost (if negative) following the occurrence of a spike on the j^{th} train at any delay. However, since the occurrence of spikes in the j^{th} train may have complex effects combining both excitation and inhibition at different delays on the i^{th} spike train, the net modification in the number of spikes in the i^{th} train can be close to 0 in cases of strong combined excitatory and inhibitory interaction.

Therefore we introduce the overall *energy of an interaction* as the average number of spikes of the i^{th} spike train that have been modified (either *gain* or *loss*) by the presence of a spike on the j^{th} train at any delay, which is mathematically defined by

$$\int |h_{j \rightarrow i}(x)| dx = \sum_{k=1}^K |a_{j \rightarrow i}^k| \delta$$

Note that because Lasso estimates are known to be biased, we also performed a second step in the parameter estimation, where we calculate the Ordinary Least Square estimate on the support estimated by the Lasso estimator. This second estimator is denoted $\hat{\mathbf{a}}_i^{BOL}$. As long as one is only interested in determining whether the j^{th} spike train interacts with the i^{th} spike train, both estimators give exactly the same answer. However, to calculate the *energy of an interaction*, one should use the BOL estimate to avoid bias.

The toolbox required to run the present analysis method on simulated or recorded spike trains is available at <https://github.com/ybouret/neuro-stat>.

2.2 Neuron network simulations

The accuracy and limits of the present method to model interacting spike trains were studied using simulated networks of n ($n \leq 10$) Integrate and Fire neurons (IF). Simulations were performed with the IntFire4 class of IF in the Neuron 7.4 environment ([13]). Briefly, each artificial neuron integrates fast monoexponentially decaying ($\tau_e = 3\text{ms}$) excitatory and slower alpha function like biexponential ($\tau_{i1} = 5\text{ms}$, $\tau_{i2} = 10\text{ms}$) inhibitory inputs with a membrane time constant τ_m (30ms) and fires when the membrane state variable reaches the threshold 1. After firing the membrane state is set to 0. Excitatory events are scaled such that an isolated event of weight 1 will produce a maximum membrane potential of 1 (threshold) and an isolated inhibitory event of weight -1 will produce a minimum membrane potential of -1 (see details in [6]). Each IF were driven by a Poisson excitatory input to induce spontaneous firing activity. Except when otherwise stated the resulting spontaneous firing rates were set to 11Hz.

3 Results

Hawkes-model based detection of excitatory and inhibitory connections. To evaluate the efficiency of the present method in detecting spike train interactions, artificial networks of 10 spontaneously active IF were constructed with a single excitatory or inhibitory connection inserted between 2 of the neurons (figure 2A). The efficiency of any detection methods should obviously depend on both the strength of the excitatory or inhibitory input and the amount of available data. Therefore, simulations were run with increasing connection weights (from 0.1 to 1.25 and 0.4 to 1.4 for excitatory and inhibitory connections, respectively) and analysis were conducted on various observation duration (from 20s to 360s). Practically, 100min of simulated spike trains were generated in each case that were further subdivided in samples of the required duration. In each conditions the analysis was therefore performed on multiple data sets in order to assess the reproducibility of the results (for analysis conducted with short duration data sets, only the first 100 samples were considered). In all analysis, the $h_{j \rightarrow i}$ functions were evaluated with $K = 10$ bins of $\delta = 5\text{ms}$. Note that for the same value of γ , one can either double K or decrease δ without modifying the overall shape of the interaction functions (data not shown). However, the choice of γ is crucial for the accuracy of the detection of the existing interactions within the network and we have therefore performed multiple analysis systematically increasing γ from 0.02 to 6 (non-regular grid). As presented in the *Statistical Method*, if γ is too small, the estimation procedure should create Hawkes models with non-null interaction functions that do not correspond to existing connections in the neuronal network. We therefore calculated in each condition the False Positive Rate (FPR) as the percentage of data sets where an additional interaction (i.e. a non zero interaction function $h_{j \rightarrow i}$ that does not correspond to an existing interaction between the simulated neurons) was found. As presented in the figure 2B showing for each condition the smallest value of γ (noted γ_{lim}) that guarantees a FPR inferior to 5%, γ values greater than 2.15 for excitatory interactions and 2.45 for inhibitory interactions should be selected in order to avoid Hawkes models suggesting non-existing connections. However, since larger γ values may favor Hawkes models with missing connection, we calculated in a second step the True Detection Rate (TDR) as the percentage of data sets where the functional connectivity graph was perfectly estimated for $\gamma = 3, 3.5$ and 4 (figure 2C). For both excitatory and inhibitory connection, the TDR curves were similar for the three γ values, with slightly better performance for $\gamma = 3$. As shown in figure 2C1, although the TDR is larger for stronger excitatory connection since a high connection weight increases the proportion of spikes due to the excitatory inputs in the analysed data, detection of excitatory interaction appears highly efficient in every conditions. Hence, with approximately 1350 spikes spontaneously generated in

each IF during 120s long data sets, network reconstructions were already perfect in every trials with a connection weight of 0.15 that only added about 230 supplementary spikes to the target IF, corresponding to a 17% increase in firing rate. However, as for any statistical methods, detection efficiency drops dramatically with shorter data sets such that, for 20s long duration where about 230 spontaneously generated spikes / IF were available to perform the analysis, the excitatory connection had to increase the firing frequency by at least 63% for accurate detection in every trials.

For obvious statistical reasons, inhibitory input are trickier to detect than excitatory ones. Indeed, in analysis based on extracellular recordings, the presence of an inhibitory connection is revealed by missing spikes and such events may be rare if the intrinsic firing rate of the target neuron is low or the inhibitory input weak. Therefore, accurate detection of inhibitory inputs requires large amount of data and strong probability of spike suppression. Accordingly, although perfect detection was already achieved in every trials with data set of 160s (about 1800 spontaneously generated spikes / IF), this required strong inhibitory connection weight of 0.6 that decreased the firing frequency of the target neurons by 61% (figure 2C2). An additional difficulty to detect inhibitory connection is illustrated by the shape of the TDR curves that are not monotone functions of the inhibitory input weight. Indeed strong inhibition can paradoxically make the target neuron almost silent and therefore invisible in the data set, inducing a drastic decrease in the detection efficiency.

Nevertheless, we conclude from these first series of simulations that setting $\gamma = 3$ minimizes the probability to construct models with non-existing or missing connection.

”Energy” of the $h_{j \rightarrow i}$ functions help to discard non-existing connection. Since Hawkes models seemed highly efficient to infer excitatory relationships from spike trains, we further investigated the success rate of the method when it was challenged with classical difficulties in spike correlation analysis such as large differences in firing frequencies or the presence of common inputs in the network.

So far, the intrinsic firing rates of every IF in our simulated networks were similar and fixed around 11Hz. However, two independent neurons recorded simultaneously and displaying very different firing rates may present apparent spike correlation if the firing probability of the fastest neuron is high enough to ensure its firing closely around every spikes occurring in the slowest neuron. In such case, the most favorable Hawkes model that fit to the data may include a false excitatory connection linking the two neurons. Therefore, simulating non-connected IFs among which one neuron presented an up to 20 time faster firing rate than the other ones, we evaluated in each case the γ_{lim} value that guaranteed a FPR inferior to 5%. As shown in figure 3A, $\gamma = 3$ could not assure a FPR inferior to 5% in every cases, in particular for long data sets that contained many spike correlation occurring by chance. From a mathematical point of view, it may seem counter-intuitive that error occurrences increased with data set duration. However, IF and neuron firings are not true Hawkes processes and reducing the data variance effect with long data sets makes the bias of the model more apparent. Nevertheless, the method was surprisingly robust since for every data set duration tested, FPR inferior to 5% was still achieved with $\gamma \leq 3$ for simulations where one of the IFs was firing almost ten time faster than the other ones.

Another classical difficulty in spike train analysis arises when recorded neurons are serially connected with strong excitatory links since correlation may exist between the spikes of the first and last neurons of the chain although no direct connection is present. Similar problem is met when neurons share a strong common excitatory input that creates spike correlation in the absence of direct connection between the target neurons. Therefore we systematically investigated, as a function of the data set duration and connection weight, the ability of our model-based method to infer connection diagram without false additional link in networks comprising serial connections (figure

3B) or shared inputs (figure 3C). As expected, in both cases, the best Hawkes approximation contained false connection in more than 5% of the analysis when the weight of the connection increased. However, looking more closely at the $h_{j \rightarrow i}$ functions, it clearly appeared that, when reported, the additional interaction displayed a very low "energy" compared to existing connection (figure 4). Therefore, systematically discarding connections with "energy" inferior to an arbitrary threshold, allowed to almost perfectly suppress additional false connection in Hawkes model fitted with $\gamma \leq 3$ (figure 3B and C, middle graphs). However, although discarding low "energy" functions always improved reconstruction of the true connection graph, optimizing the choice of the discarded connection would require to adapt the threshold value in each case. Different rules can be designed to fix such threshold value and we report here one method that produced good results in the relatively simple simulations used in the present paper as an example. The $E_{j \rightarrow i} = \int h_{j \rightarrow i}$, which represent the number of additional points that are created in average in the spike train i thanks to the presence of one spike on the j^{th} spike train, were computed and sorted in increasing order. The first large "jump" in the ordered sequence of $E_{j \rightarrow i}$ can then be used to set the threshold value. In practice, the successive differences in the sorted sequence of $E_{j \rightarrow i}$ were calculated and the first difference superior to 15% of the largest one designed the first large "jump". Accordingly the $h_{j \rightarrow i}$ functions corresponding to $E_{j \rightarrow i}$ smallest than this first large "jump" were discarded (figure 5). When applied to the Hawkes models fitted to the previous simulations (figure 3B and C, bottom graphs), this method allowed to perfectly reconstruct the simulated network in every cases.

Functional connectivity graphs The ability of the present method to reconstruct functional connectivity graphs was finally tested using randomly generated small networks of IFs ($n = 7$). Each IF presented a spontaneous firing rate selected at random in $[10, 40]$ Hz. Connection from the j^{th} to the i^{th} IF had a $1/n$ probability in order to ensure a sparse graph according to Erdős-Renyi random graphs properties. Each existing connection was determined as excitatory or inhibitory with a probability taken at random on $[0, 1]$ and fixed for each graph. Excitatory and inhibitory weights $w_{j \rightarrow i}$ were set uniformly at random in $[0.2, 0.5]$ and $[-0.9, -0.6]$, respectively. Among the 100 randomly designed networks that were simulated, 11 networks generated less than 8 spikes in 7 minutes due to strong global inhibition and were thereafter discarded. We then observed the number of errors, either additional or missing excitatory/inhibitory connections, in the 89 remaining functional connectivity graphs that were reconstructed (figure 6A). Additional non-existing inhibition was never observed and increasing the data set duration improved the detection of inhibitory connections, as expected from the difficulties in detecting inhibition mentioned above. As a consequence the proportion of networks in which inhibition was perfectly inferred drastically increased with the data set duration from 30 to 75% (figure 6B, left graph). However, although long data set duration similarly improved the detection of existing excitatory connection, it also favored Hawkes approximations with non-existing excitatory connections (figure 6A). Therefore, the improved detection of existing excitatory connection being counterbalanced by the appearance of non-existing ones (see green line in the left graph of figure 6B), the proportion of networks with perfectly detected excitation remained almost stable above 60%. Hence, refining the functional excitatory connectivity graphs ($h_{j \rightarrow i}$ functions with $E_{j \rightarrow i} = \int h_{j \rightarrow i} > 0$) by discarding low "energy" functions using the first large "jump" method significantly increased the proportion of perfectly detected excitatory networks up to 80% (figure 6B, right graph). As shown in figure 7, Hawkes models optimization from data sets up to 400s long were achieved in less than 1.5s on a personal computer.

4 Discussion

We will briefly discuss below the rationale to design the present method modeling spike trains with multivariate Hawkes processes.

General formulation of the intensity of Hawkes processes is

$$\lambda^i(t) = \Phi \left(\nu_i + \sum_{j=1}^n \sum_{T \in N^j, T < t} h_{j \rightarrow i}(t - T) \right),$$

where Φ is a fixed function. For linear Hawkes processes initially introduced by Hawkes in the 70's to model earthquakes and their aftershocks [11], $\Phi(.) = .$ (the identity) but from a probabilistic point of view, such processes can only be used when every $h_{j \rightarrow i}$ function corresponds to excitation to preclude the possibility of negative intensity. To solve this problem when modeling networks with both excitatory and inhibitory connections, we chose $\Phi(.) = (.)_+$, the positive part.

One can prove that linear Hawkes processes can be in a stationary regime if and only if the largest eigenvalue of the matrix $(\int h_{j \rightarrow i})$ is smaller than 1 [12]. If this condition is not fulfilled, these processes generate an exponentially increasing number of spikes with t , which obviously precludes the use of such Hawkes processes to simulate neuronal activity. For more general Hawkes processes, Brémaud and Massoulié ([2]) showed that if Φ is k -Lipschitz (i.e. the slope of every segment linking 2 points of the function Φ is less than k) with $k \leq 1$, and if the largest eigenvalue of the energy matrix $(\int |h_{j \rightarrow i}|)$ is strictly smaller than 1, then such Hawkes processes can be in a stationary regime. These conditions are easily fulfilled in our model using $\Phi(.) = (.)_+$. This ensures that our method generates stationary models that can be used not only to reconstruct the functional connectivity graph from spike trains but also to simulate data sets without producing exponentially growing number of spikes during simulation.

In counting processes, parameter estimation is generally performed using maximum likelihood method since, under some regularity conditions, maximum likelihood estimators produce the smallest asymptotic variance [31]. However they are generally difficult to compute. Therefore to efficiently optimize linear Hawkes models with experimentally manageable data sets, we rather used least-square estimators that are consistent and much easier to derive than maximum likelihood estimators. Because of the presence of log function in the maximum likelihood equation, some authors made a different choice and still used Hawkes models with maximum likelihood estimators and $\Phi(.) = \exp(.)$ (see [22, 18, 7]) to facilitate parameter optimization. However, as explained above, such Hawkes models do not fulfill the stationary conditions identified so far and therefore may produce an exponentially growing number of spikes during simulation. Despite the computational difficulty, maximum likelihood estimators of linear Hawkes processes have nevertheless been previously used on spike trains [8]. However, good performances were only obtained with more than thousands of points per spike train precluding the use of this approach in practice. An alternative method especially designed to optimize linear Hawkes process relies on the inversion of an empirical version of the Wiener Hopf system that couples the matrix of interaction functions to the infinitesimal covariance matrix ([1]). Although such method also requires that the data set is huge to make the empirical version of the Wiener Hopf system close enough to the expected one, similar approaches have been previously used in neurosciences ([20, 21, 14, 16]).

Due to experimental constraints, the number of unknown parameters in the model is large with respect to the size of the data set and the output variability of the optimization procedure is high. To reduce this variability, we applied a penalization criteria by looking for a sparse parameter vector, assuming that many of the unknown coefficients should be null. In the classical " ℓ_0 penalty" approach, the final contrast (either the maximum likelihood or the least square contrast) of a given

parameter vector is penalized by a function of the number of non zero coefficients. It is commonly accepted that this method efficiently approximates the right non zero coefficients as long as the number of parameters is relatively small and fixed with respect to the number of observation. In [25], we demonstrated that up to a small modification of the " ℓ_0 penalty", this criterion penalizing least-square contrast can also be used for a large number of parameters and applied even if this number is large with respect to the size of the available data. However, this criterion is numerically very long to minimize in this case. Therefore, to facilitate the numerical implementation, we favored a " ℓ_1 penalty" that penalizes the contrast by the ℓ_1 -norm of the coefficients rather than the number of non zero coefficients (see also [22] for other ℓ_1 -type penalties). This criteria, known as a LASSO criteria, was first introduced by Tibshirani in regression [30], and we previously proved ([10]) that one should use a weighted " ℓ_1 penalty", as the one described in (4), to derive a turn-key procedure that adapts to the problem heteroscedasticity, i.e. the potential large differences in the variance of the estimated parameters.

Finally, it is worth mentioning that few models, close to Hawkes processes, were previously used to asses functional connectivity. One of the initial work was performed by Brillinger and coauthors ([3, 4]) who successfully identified interactions between pairs and triplets of neurons in non recurrent Aplysia networks. However, it appears difficult to apply this method to numerous simultaneously recorded spike trains without a prior knowledge on the network connectivity. More recently, Cox model with classical Cox estimations, pseudolikelihood and corresponding tests were used to asses the existence of neuron connectivity ([17]). Such model may be considered as ($\Phi = \exp$) Hawkes models where the influence of only the first preceding spikes, and not the whole history of the neuron spiking, is considered to determine the intensity functions. Furthermore, the optimization procedure implied to limit the number of estimated parameters, a strong parametric assumption that may involve prior knowledge of the studied neuron networks. Pouzat and Chaffiol ([23]) developed similar approaches (Wold model) considering the distances to the two preceding spikes and estimated the "interaction" functions using log-likelihood criterion penalized by Wahba regularization. However, the method is computationally intensive and should be difficult to apply to numerous simultaneous recorded spike trains.

5 Conclusion

In conclusion, when challenge to IF models of neuron networks, our method based on multivariate Hawkes processes efficiently retrieve the hidden functional connectivity. The method is robust, stable and does not require huge amount of data. Therefore, we propose that it can be used as a turn-key procedure to infer potential connectivity graph and generate simulation models from simultaneous spike train recordings.

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Legends

Figure 1 : Spike train model using multivariate Hawkes processes. **A.** For the 3 trains ($N^{1,2,3}$) presented, each vertical line indicates the time of occurrence (T, T', \dots) of a spike. The probability that a new spike occurs at time t on the spike train N^1 is given by the conditional intensity $\lambda^1(t)$. The autointeraction function $h_{1 \rightarrow 1}$ indicating the spike refractory period, the interaction function $h_{2 \rightarrow 1}$, materializing the successive excitation/inhibition actions of neuron 2 on neuron 1, and the interaction function $h_{3 \rightarrow 1}$, presenting the simple excitation of neuron 3 on neuron 1, are illustrated for the 2 spikes preceding t in each spike trains. Note that in this example only the last spike occurring in each spike train have a significant effect on the spike probability of N^1 a time t . **B.** Example of a functions $h_{j \rightarrow i}$ considered as piecewise constant on a partition of $K = 10$ bins of size δ .

Figure 2 : Detection of a single connection within a small network. **A.** Connection diagram of the simulated networks. Each IF received a Poisson excitatory input (not shown) generating intrinsic firing rate around 11Hz. Simulations were run while systematically increasing the weight of the excitatory (w_e) or inhibitory (w_i) connection between the IF 5 and 8. **B.** Color coded graphs presenting the minimal γ values (γ_{lim}) that guaranteed an additional false interaction in less than 5% of the data sets as a function of the excitatory (left graph) or inhibitory (right graph) weight and the duration of the data sets. **C.** Graphs presenting the % of data sets, for which the network connectivity with the single excitatory (**1** : top graphs) or inhibitory (**2** : bottom graphs) input from IF 5 to 8 was perfectly estimated (TDR), as a function of both the data set duration and the connectivity weight.

Figure 3 : Robustness of excitatory connection detection. **A.** Left diagram : each of the 4 unconnected IF received Poisson excitatory inputs (not shown) to induce spontaneous firing. Simulations were run with various intrinsic firing rates for the 1st IF (ν_1 from 11 to 234Hz, non-regular grid) while the 3 other IF were kept at a constant firing rate of 11Hz. Right graph : Color coded graphs presenting the minimal γ values (γ_{lim}) that guaranteed an additional false interaction in less than 5% of the data sets as a function of the 1st IF firing rate and the duration of the data sets. In simulations where none of the tested γ values could fulfilled the required condition the corresponding squares were left white. **B.** Top connection diagram : Each IF received a Poisson excitatory input (not shown) generating intrinsic firing rate around 11Hz. Simulations were run while systematically increasing the weight of the excitatory (w_e) connections between the IF $1 \rightarrow 2$ and $2 \rightarrow 3$. Top graph : Color coded graphs presenting the minimal γ values (γ_{lim}) that guaranteed an additional false interaction in less than 5% of the data sets as a function of the excitatory weight and the duration of the data sets. In simulations where none of the tested γ values could fulfilled the required condition the corresponding squares were left white. Middle graph : same graph constructed from models where connections with *energy* inferior to 0.13 were discarded (see *Statistical Method*). Bottom graph : same graph constructed from models where connections were discarded according to the "first large jump method" (see *Results*). **C.** Same legends as in **B** for 4 IF networks where IF 2 and 3 shared a common input (top connection diagram).

Figure 4 : Small network implementing common excitatory inputs. **A.** Connection diagram of the simulated networks. Each IF received a Poisson excitatory input (not shown) generating intrinsic firing rate around 11Hz. IF 2 and 4 shared a common input of weight w_e from IF 1. **B.** Color coded graphs presenting the % of 60s long data sets where the presence of a connection from IF_j to IF_i (non null $h_{j \rightarrow i}$) was indicated by Hawk models fitted with a γ value of 3. For $w_e=0.25$ (top graph) only the auto-interaction functions, $h_{i \rightarrow i}$, and the 2 functions $h_{1 \rightarrow 2}$ and $h_{1 \rightarrow 4}$,

corresponding to existing connections within the network were reported. However, when increasing w_e to 0.60 (bottom graph), Hawkes models suggested the presence of a non-existing bidirectional connection between IF 2 and 4 in less than 10% of the data sets. **C.** Color coded graphs of the "energy" of the $h_{j \rightarrow i}$ functions for simulations with $w_e=0.25$ (top graph) and 0.60 (bottom graph). Note that the average values of the "energy" were calculated from data sets reporting non-null $h_{j \rightarrow i}$ functions.

Figure 5 : Discarding low "energy" functions using the first large "jump" method.

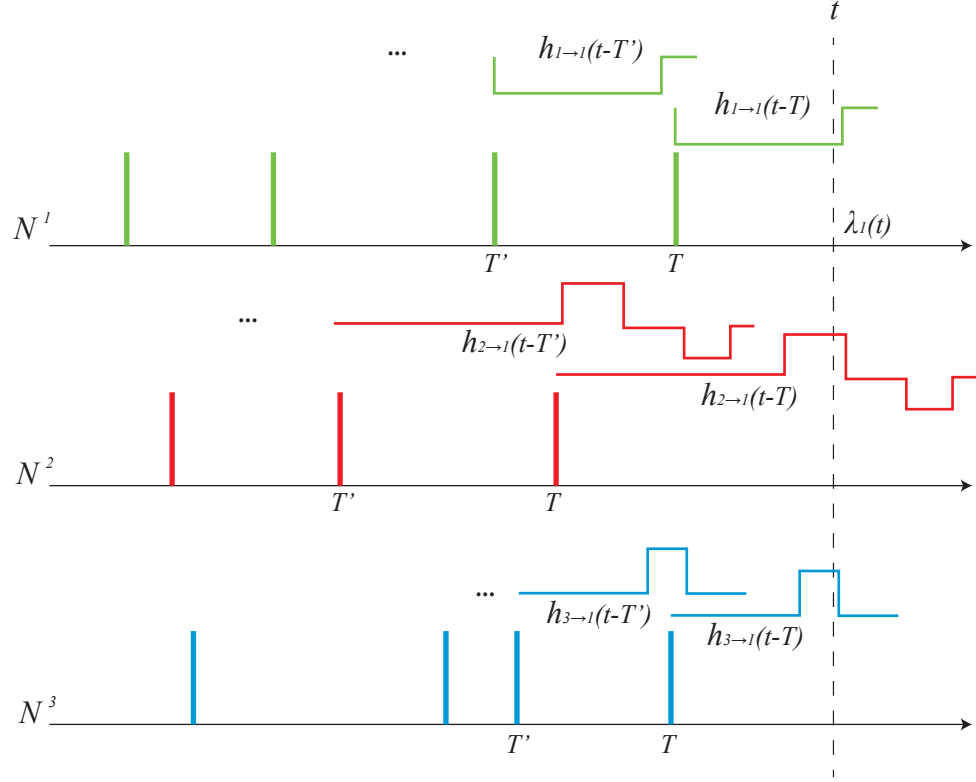
A. Connection diagram of the simulated network. The strong excitatory connection of weight $w_e = 0.60$ are materialized with black arrows. Each IF received a Poisson excitatory input (not shown) generating intrinsic firing rate around 11Hz. The presence of multiple common inputs in this strongly connected network increases the probability that some non-existing connections (red dotted arrows) maybe added in the reconstructed networks. **B.** Color coded graph presenting the % of 60s long data sets where the presence of a connection from IF_j to IF_i (non null $h_{j \rightarrow i}$) was indicated by Hawkes models fitted with a γ value of 3. As expected, non-existing connections were suggested in a small number of cases. **C.** Plots showing the $E_{j \rightarrow i} = \int h_{j \rightarrow i}$ sorted in increasing order for 3 data sets of 40s (graph 1.), 60s (graph 2.) and 300s (graph 3.). In each plot, black arrow indicates the largest "jump" in the ordered sequence of $E_{j \rightarrow i}$ and red arrows materialize 15% of this largest "jump". Discarding the $h_{j \rightarrow i}$ functions corresponding to $E_{j \rightarrow i}$ smaller than the first "jump" larger than the 15% arrow removed the non-existing connections (highlighted in grey) but did not discard any existing connections.

Figure 6 : Inferring functional connectivity graphs with Hawkes model-based method.

A. Number of additional and missing excitation/inhibition connections (median and 0.1 quantile values) in the reconstructed functional connectivity graphs of 89 randomly generated IF networks (see *Results*) as a function of data set duration. Hawkes models were fitted using a γ value of 3. **B.** Left graph : Percentage as a function of the data set duration of 89 randomly generated IF networks in which the excitatory (red line) or inhibitory (blue line) connections were perfectly inferred with the Hawkes model-based method. The green line shows the % of non-existing excitation added in the Hawkes models. The dashed line materializes the 5% limit. Right graph : same graph constructed from models where connections were discarded according to the "first large jump method" (see *Results*).

Figure 7 : Computational cost of the Hawkes model-based method. Graph presenting the median (black line) and 0.1 quantile values (dotted lines) of the required computational time to reconstruct functional connectivity graphs of 89 randomly generated IF networks (see figure 6) as a function of data set duration. Parallel computation using 4 threads were performed on a MacBook Pro 2.7GHz with 8GB of RAM.

A.



B.

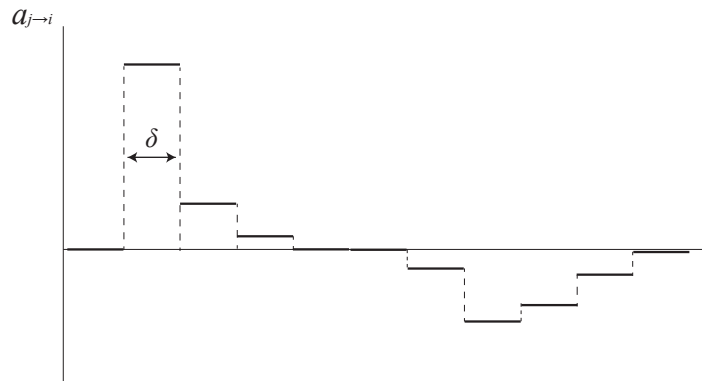


Figure 1:

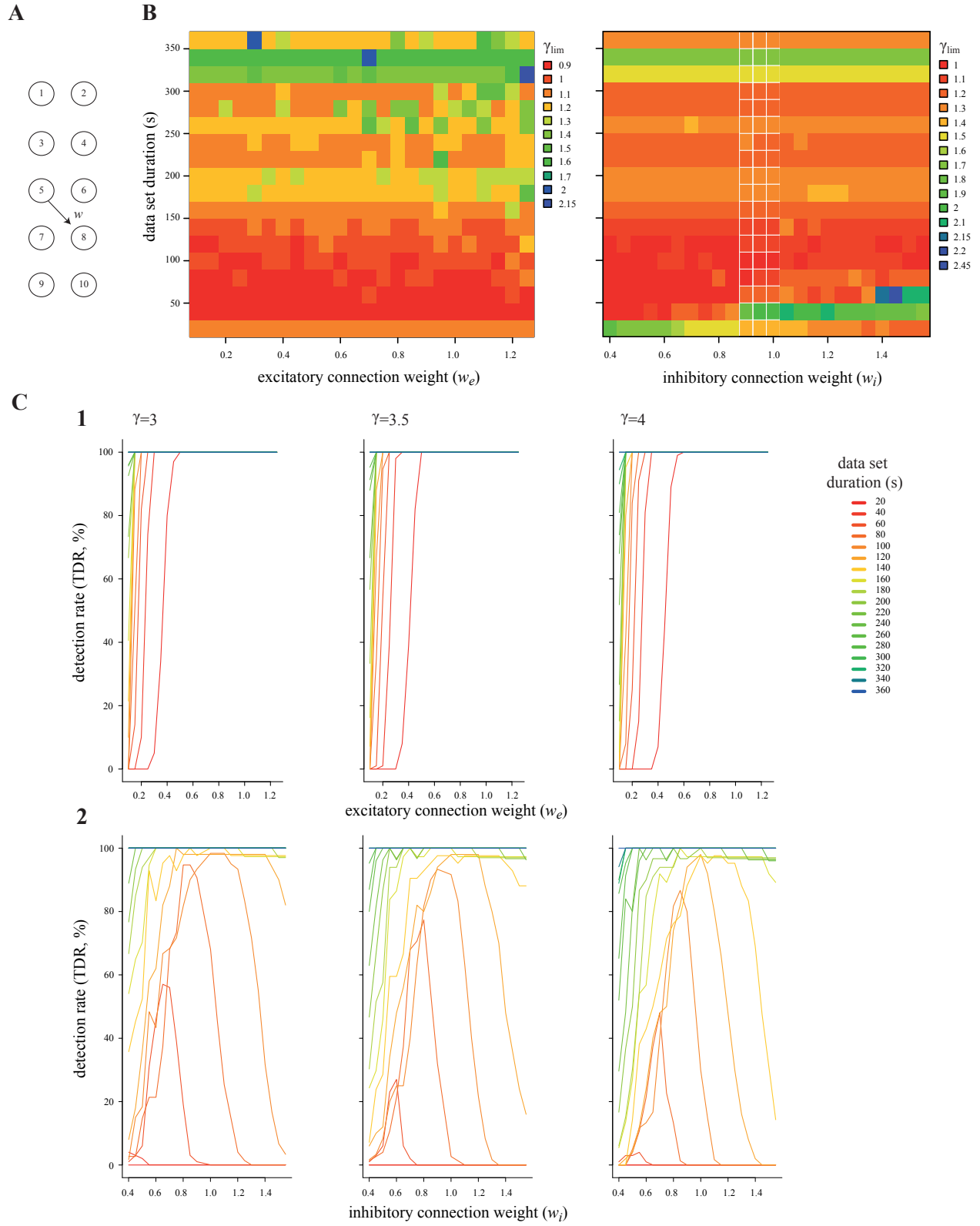


Figure 2:

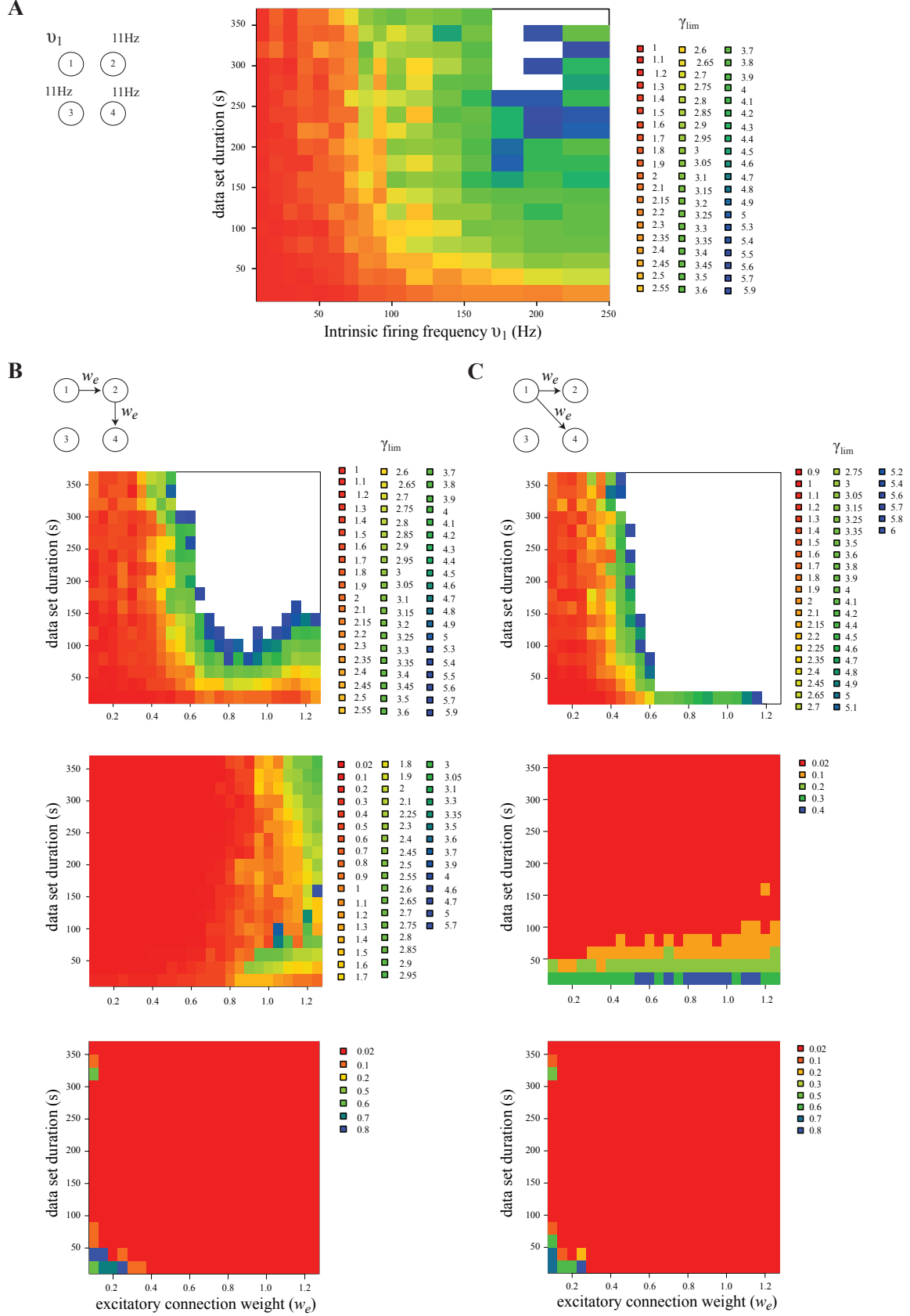


Figure 3:

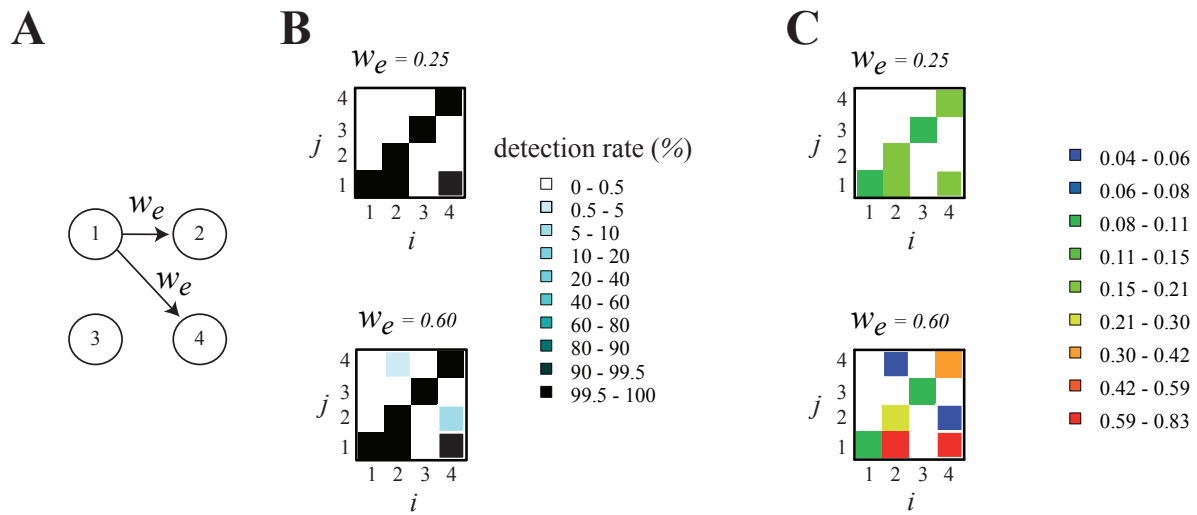


Figure 4:

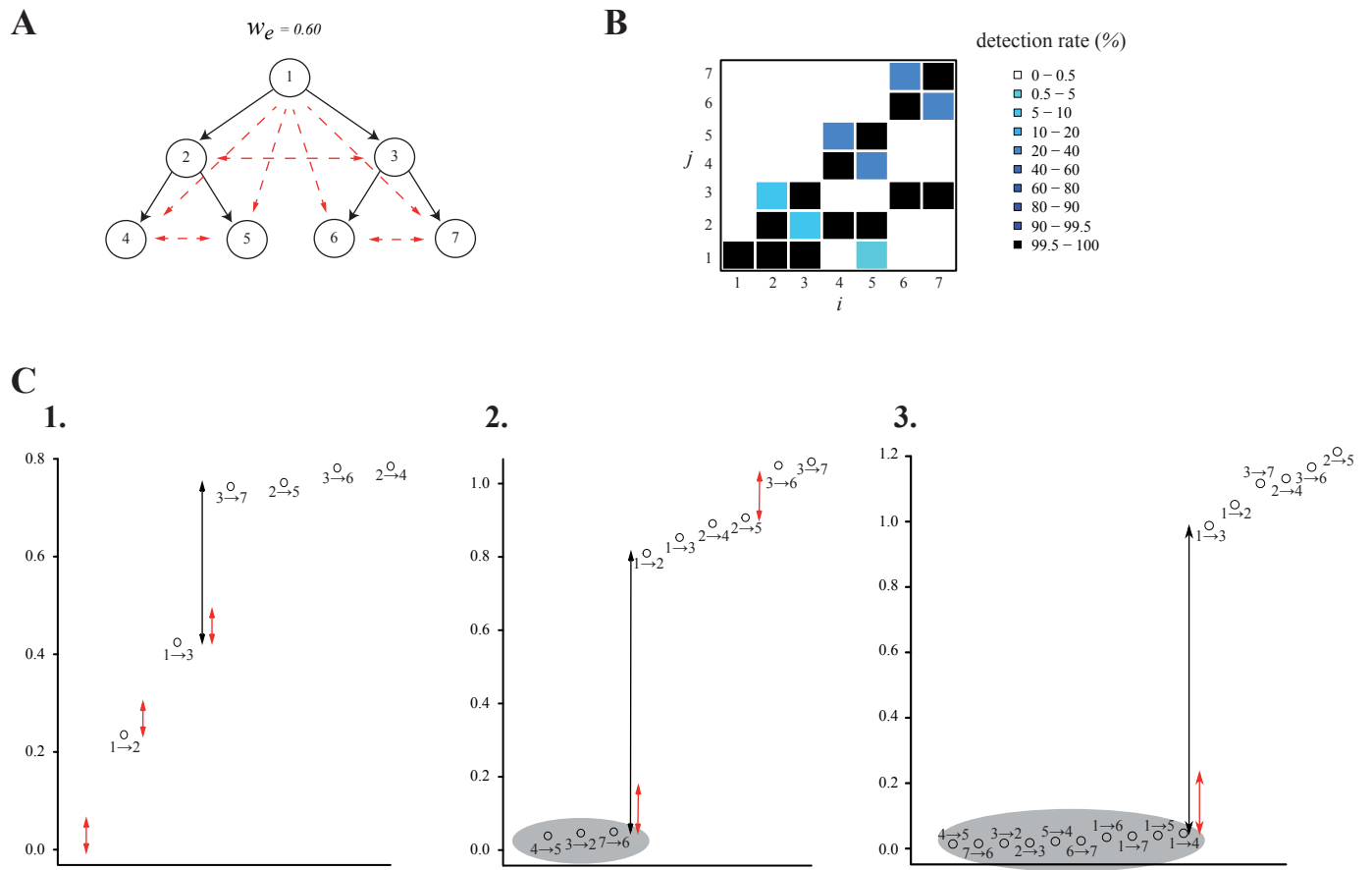
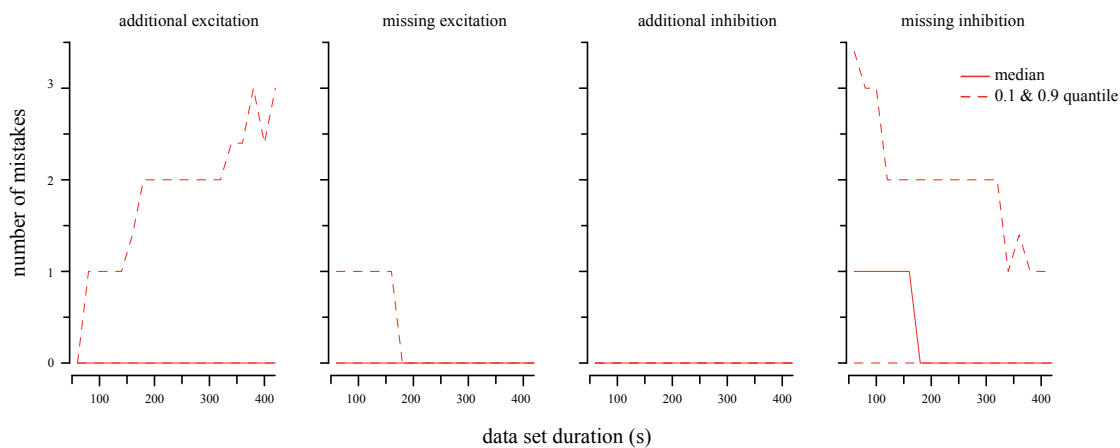


Figure 5:

A



B

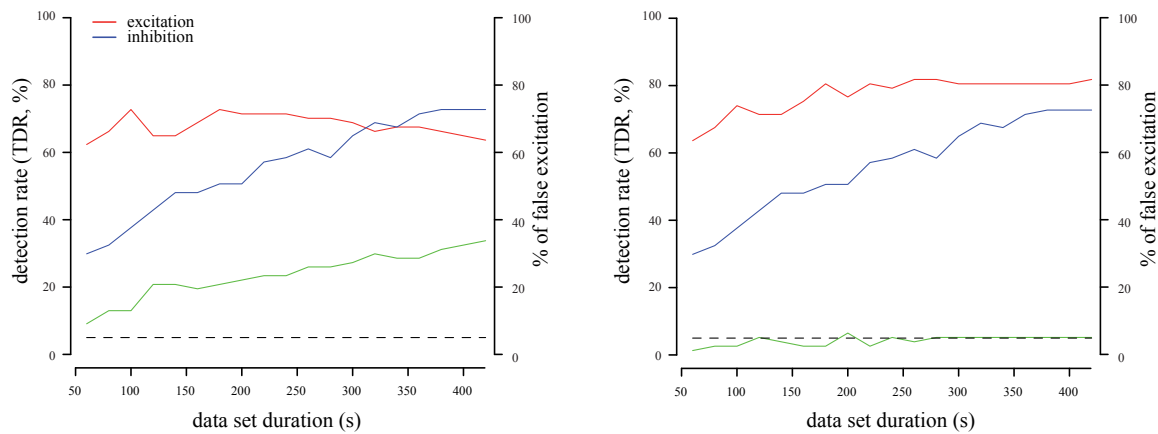


Figure 6:

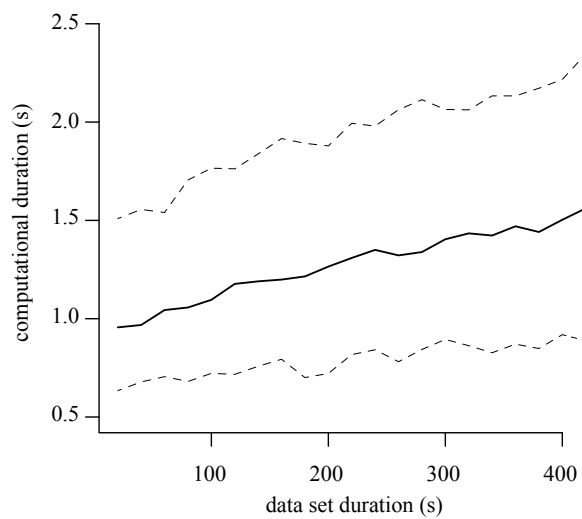


Figure 7: