Objective Procedure for Reconstructing Couplings in Complex Systems

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Inferring directional connectivity from point process data of multiple elements is desired in various scientific fields such as neuroscience, geography, economics, etc. Here, we propose an inference procedure for this goal based on the kinetic Ising model. The procedure is composed of two steps: (1) determination of the time-bin size for transforming the point-process data to discrete time binary data and (2) screening of relevant couplings from the estimated networks. For these, we develop simple methods based on information theory and computational statistics. Applications to data from artificial and in vitro neuronal networks show that the proposed procedure performs fairly well when identifying relevant couplings, including the discrimination of their signs, with low computational cost. These results highlight the potential utility of the kinetic Ising model to analyze real interacting systems with event occurrences.

Introduction.— Event occurrence sequences consisting of multiple elements are ubiquitously observed in nature and society, including in neuronal spikes \cite{1,3}, earthquakes \cite{4}, economics \cite{5}, etc. \cite{6,7}. Recent technological advances in experiments enable us to measure multi-point signals simultaneously, which is expected to reveal many features of such complex systems. For example, in the nervous system, neuronal activities can be recorded at multi-points by multielectrode arrays \cite{8,9} or calcium imaging \cite{10,11}. These types of observations provide rich data and help us understand mechanisms of information processing in large coupled systems beyond the single-neuron level \cite{12,15}.

Statistical mechanics has offered powerful tools to carry out the inference of intrinsic structure from such measurements. In the equilibrium case with undirectional (symmetric) couplings, the mean-field formulae for the statistical inference have been developed previously \cite{16,19} and successfully applied to biological data \cite{20,24}. Recently, not only undirectional but also directionational (asymmetric) connectivity structures behind such data have been revealed by improved systematic techniques \cite{25,30,31,32}, which pushes on their applications for real data.

While the statistical mechanical approaches have succeeded in revealing the nontrivial natures of biological systems, there still remain unsatisfactory points in those earlier studies. Two crucial points are the lack of objective criteria to determine the bin size for discretizing signals in time and to effectively screen relevant couplings obtained by inference techniques. In this Letter, we propose an objective procedure to resolve these defects based on the methods of information theory (Method I in Fig.1) and computational statistics (Method II in Fig.1), respectively. Our methods can be applied to a wide variety of dynamical systems exhibiting event sequences irrespective of the directionality of connectivities. As motivating examples, we applied our methods to a mathematical model of neuronal networks called the Izhikevich model \cite{33,34} and to in vitro neuronal networks of rats cortical cells.

Theory.— In this study, we use the kinetic Ising model which consists of $N$ elements with possible $2$ discrete state values $s_i(t) = \pm 1$. The state with $s_i(t) = 1$ corresponds to the firing of the neuron $i$ while $s_i(t) = -1$ means no firing at time $t$. This model is supposed to obey the Galuber dynamics:

\begin{equation}
P\left( s(t+1) | s(t) \right) = \prod_{i=1}^{N} \frac{\exp \left[ s_i(t+1) H_i(t) \right]}{\exp \left[ H_i(t) \right] + \exp \left[ -H_i(t) \right]},
\end{equation}

where $H_i(t)$ is the effective field defined as $H_i(t) = h_i(t) + \sum_{j=1}^{N} J_{ij} s_j(t)$, $h_i(t)$ is the external force, and $J_{ij}$ is the

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coupling strength from \( j \) to \( i \). This model corresponds to the generalized McCulloch-Pitts model \([36]\) in theoretical neuroscience and also logistic regression \([37]\) in statistics.

As a starting point, here, we employ the simplest mean-field inverse formula \( J^{\text{est}} = A^{-1}DC^{-1} \), where \( A_{ij} = (1 - m_i^2) \delta_{ij} \), \([23, 26]\), although other more sophisticated formulae can be used in combination with our proposed methods. We denoted the mean and covariances as \( m_i = \langle s_i(t) \rangle \), \( C_{ij} = \langle s_i(t)s_j(t) \rangle - m_im_j \) and \( D_{ij} = \langle s_i(t+1)s_j(t) \rangle - m_im_j \), where the bracket represents the time average \([38, 39]\), which is expected to accord with the ensemble average of the stochastic dynamics under the ergodic assumption. The formula gives us the estimated coupling matrix from these statistical quantities evaluated from observed times series.

To apply the inverse kinetic Ising scheme to spike train data, we firstly determine the length \( \Delta \tau \) of the time bin as in Fig. 11 from a view point of the information theory \([40]\). We begin with the spike series which is obtained from the spike series which is obtained from the estimated coupling matrix \( J^{\text{est}} \) of the kinetic Ising system. The formula gives

\[
\prod_{i \neq j} P \left( n_{ij}^{++}, n_{ij}^{-+}, n_{ij}^{+-}, n_{ij}^{--} \mid p_{ij}^+, p_{ij}^- \right) = \prod_{i \neq j} \frac{(M - 1)!}{n_{ij}^{++}!n_{ij}^{-+}!n_{ij}^{+-}!n_{ij}^{--}!} \left( p_{ij}^+ p_{ij}^- \right)^{n_{ij}^{++}} \left( (1 - p_{ij}^+) p_{ij}^- \right)^{n_{ij}^{-+}} \left( p_{ij}^+ (1 - p_{ij}^-) \right)^{n_{ij}^{+-}} \left( (1 - p_{ij}^+) (1 - p_{ij}^-) \right)^{n_{ij}^{--}},
\]

where the last expression \([2]\) is derived by the Stirling’s formula and

\[
I_{\Delta \tau} (s_i(t+1); s_j(t)) = \sum_{(\alpha, \beta) \in \{++, -\}} \frac{n_{ij}^{\alpha \beta}}{M - 1} \log \frac{n_{ij}^{\alpha \beta}}{p_{ij}^+ p_{ij}^-}
\]

represents the mutual information of neurons \( i \) and \( j \) between successive time bins. Notation \( \{++, -\} \) denotes the direct product \( \{+,-\} \times \{+,-\} \). In Eq. \([2]\), contributions from self-interactions are omitted to focus on interactions between different neurons. Our aim is to determine the bin size \( \Delta \tau \) such that the likelihood \([2]\) is minimized as

\[
\Delta \tau_{\text{opt}} = \arg \max_{\Delta \tau} \left( T \sum_{i \neq j} I_{\Delta \tau} (s_i(t+1); s_j(t)) \right)
\]

where \( |n_{ij}^{\alpha \beta}/M - 1 - p_{ij}^+ p_{ij}^-| \ll 1 \) holds, the gross mutual information \((M - 1)I_{\Delta \tau} (s_i(t+1); s_j(t))\) is approximated as

\[
(M - 1)I_{\Delta \tau} (s_i(t+1); s_j(t)) \approx \frac{1}{2} \sum_{(\alpha, \beta) \in \{++, -\}} \left( n_{ij}^{\alpha \beta} - (M - 1)p_{ij}^+ p_{ij}^- \right)^2 \frac{1}{(M - 1)p_{ij}^+ p_{ij}^-}
\]

which is nothing but the half of Pearson’s chi-squared test statistic with 1 degree of freedom. This method chooses the value of \( \Delta \tau \) with which the null hypothesis is rejected with the most restrict criterion by the chi-square test or g-test \([41]\). In the following, given the spike sequences, we use this value of \( \Delta \tau_{\text{opt}} \).

Once the optimal time bin size has been decided, it is straightforward to apply the inverse Ising formula to the coarse-grained binary sequence. Calculating the estimated coupling matrix \( J^{\text{est}} \) by the mean-field formula,
for each pair \((i, j)\), provides us with continuous-valued \(J_{ij}^{\text{est}}\). This continuity often makes results unclear in that it is not easy to distinguish statistically significant couplings from the others. Therefore, we introduce an additional computational-statistical step \([12, 43]\) to extract the relevant couplings from \(J_{ij}^{\text{est}}\). As a preparation we generate \(L\) randomized time series, each of which is obtained by shuffling the original coarse-grained sequence with \(\Delta t_{\text{opt}}\) in the time direction individually for each element. For all the series, we calculate the coupling matrices \(\{(J_{ij}^{\text{ran}}(\tau))\}_{\tau = 1}^{L}\). Then, for each pair \((i, j)\), we have \(L\) reference values \(\{(J_{ij}^{\text{ran}}(\tau)_{ij})\}_{\tau = 1}^{L}\) against the value for the non-randomized data, \(J_{ij}^{\text{est}}\). If this non-randomized value is relevant, its absolute value is considered to be sufficiently larger than those of the \(L\) reference values. According to this idea, we accept \(J_{ij}^{\text{est}}\) as a relevant coupling only if its absolute value is larger than the \(p_{\text{th}}L\) largest value among \(\{(J_{ij}^{\text{ran}}(\tau)_{ij})\}_{\tau = 1}^{L}\). The value \(p_{\text{th}}\) is a parameter controlling the tightness of this criterion and should be small enough.

If the coupling matrix is symmetric, systems are described by an equilibrium distribution in the static manner, and hence we use the mutual information between equal-time states \(I_{\Delta \tau}(s_i(t); s_j(t))\) instead of \(I_{\Delta \tau}(s_i(t + 1); s_j(t))\) in Eq. (4). The mean-field inverse formula is replaced as \(J_{ij}^{\text{est}} = A^{-1} - C^{-1}\) \([16, 17]\).

The Izhikevich model (Numerical Simulation).—To confirm the effectiveness of our methods, we employ, as a first example, the Izhikevich model. This model is a standard neuronal model and generates neurobiologically plausible spike sequences \([33, 34]\). We first set 100 neurons (90 excitatory and 10 inhibitory) on an asymmetric cyclic chain, where each neuron projects synaptic connections to up to 3 clockwise neighboring neurons and sends signals. The coupling strengths were drawn from uniform distributions between 5 and 10 for the excitatory neurons and between \(-20\) and \(-10\) for the inhibitory neurons, respectively. The other parameters were set as in \([33, 34]\). The spike trains generated by this model are plotted in Fig. 2(a) while the coupling matrix is exhibited in (b), where the minimal time step is \(\Delta t = 1\) ms and the time length used for the inference is \(T = 10^6\) ms. The means of the gross mutual information \((M - 1)I_{\Delta \tau}(s_i(t + 1); s_j(t))\) in Eq. (4) over all pairs are shown versus \(\Delta \tau\) in (c). The curve produces a nearly unimodal feature with a sharp peak at \(\Delta \tau = 5\) ms, which indicates the unique optimal \(\Delta \tau\). Then, we created the binned spike time raster with \(\Delta \tau = 5\) ms; thereby applying the inverse formula and adopting only \(J_{ij}\) whose absolute value exceeds the threshold namely the largest values among the estimates for the \(L = 100\) randomized time series, which corresponds to the criterion \(p_{\text{th}} = 0.01\), yielded the relevant couplings shown in Fig. 2(d). The original asymmetric structure with the excitatory and inhibitory couplings was recovered sufficiently, while the models used for the generation and inference are different. As a comparison, we applied the symmetric inference procedure to the same data, the results of which are shown in Fig. 2(e) and (f). In (e) the gross mutual information is exhibited, which yields larger optimal \(\Delta \tau\). To express the regularity observed for the asymmetric model using the symmetric model, it is necessary to merge successive bins for describing events in neighboring time steps as simultaneous events. This may be the reason why the optimal bin size for the symmetric model is considerably larger than that for the asymmetric model. The estimated couplings with \(\Delta \tau = 15\) ms, which is shown in (f), are localized around the diagonal line but distributed in
the both sides, while the true couplings used for the simulation are unidirectional. In (g) the ratios of true/false positive/negative are shown. Both models succeeded in identifying the connections with their signs, although the symmetric inference has larger false positive rates. We also show the conditional ratios of the correctness under the conditions of the existence, absence, excitatory and inhibitory couplings in (f). The conditions of the existence and absence are calculated as \( \frac{TP}{(TP + FN)} \) and \( \frac{TN}{(TN + FP)} \), which are known as the sensitivity and specificity, respectively.

![Image](image_url)

**FIG. 3.** (Color online) Application to the Izhikevich model on the asymmetric random network, where \( q \) denotes the connection probability. (a) True/False positive/negative ratios and (b) the conditional ratios of the correctness in the asymmetric and symmetric inferences. The bars represent the standard deviations over 5 simulations.

To scrutinize the conditions where our inference procedure operates well, the systems on random networks are also studied. For each pair \((i, j)\), except for the self pairs, a connection from \( j \) to \( i \) was generated with a probability \( q \). The coupling strengths were drawn from uniform distributions between 2 and 3 for the excitatory neurons and between \(-6\) and \(-4\) for the inhibitory neurons, where 90 and 10 neurons are excitatory and inhibitory, respectively. The other conditions were the same as those in the chain model. The obtained optimal bin sizes were not so different from the ones on the chain model, and we adopted the same values. The ratios of true/false positive/negative in the asymmetric and symmetric inferences are shown in Fig. 3(a) while the conditional ratios of the correctness in (b). The asymmetric model has higher expressive power and hence higher performance here. These results highlight the broad applicability of the proposed inference procedure.

**Cultured neuronal networks (Experimental data).**—We also study cultured neuronal systems introduced in [44] to demonstrate the applicability of our methods to real systems. Rat cortical neurons were cultured in a micro well so that they were likely to connect asymmetrically to clockwise neighboring cells, which provides a similar condition to that of the Izhikevich model in Fig. 2. Spontaneous spiking activities of neurons were recorded from 64 electrodes of a multi-electrode array, where the measurement time is \( \Delta t = 40 \mu s \) and the whole time length used here is 120 s. Spike sorting [45] was subsequently applied to the recording data and 100 neurons were identified.

The spike raster plot during 1 second is exhibited in Fig. 4(a). The means of the gross mutual information over the all pairs are plotted in (b). In this case, an almost unimodal shape is also observed. Setting \( \Delta \tau = 4 ms \) by the asymmetric inference, where the excitatory and inhibitory couplings are displayed by the red and blue elements, respectively. (d) The estimated ratios of coupling types except for the absence. (e-g) Corresponding panels by the symmetric inference method using the same data. In (f) the network is inferred with a time window size \( \Delta \tau = 10 ms \).
We also show the counterpart results by the symmetric inference methods in (e-g). A similar chain-like network structure is inferred, although the coupling plot (f) tends to be noisier and finer structures in couplings are missed.

Conclusion.— In this Letter, we proposed objective and systematic methods for processing spike time series data in the inverse problem using the kinetic Ising model. The first method is for appropriately discretizing the time bin and the second is for effectively screening couplings obtained as the solution of the inverse problem. We showed that they work well, both in simulated and in vitro neuronal networks. These results highlight that the kinetic asymmetric Ising model is quite effective to study the dynamics on complex networks.

We stress that it is straightforward to generalize the present methods to other systems, such as cases with multi-component or continuous variables, than the Ising variable. Implementation in those cases will facilitate a deeper comprehension of complex systems.

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[1] F. Rieke, D. Warland, R. d. Ruyter van Steveninck, and W. Bialek, Spikes: Exploring the Neural Code (MIT press, Cambridge, 1997).
[2] P. Dayan and L. F. Abbott, Theoretical neuroscience, Vol. 806 (MIT Press, Cambridge, 2001).
[3] W. Gerstner and W. M. Kistler, Spiking neuron models: Single neurons, populations, plasticity (Cambridge University Press, Cambridge, 2002).
[4] Y. Ogata, Ann. Inst. Stat. Math. 50, 379 (1998).
[5] C. G. Bowsher, J. Econometr. 141, 876 (2007).
[6] A. Barrat, M. Barthelemy, and A. Vespignani, Dynamical processes on complex networks (Cambridge University Press, Cambridge, 2008).
[7] A.-L. Barabási, Network science (Cambridge University Press, Cambridge, 2016).
[8] G. Buzsáki, Nat. Neurosci. 7, 446 (2004).
[9] E. N. Brown, R. E. Kass, and P. P. Mitra, Nat. Neurosci. 7, 456 (2004).
[10] Y. Ikegaya, G. Aaron, R. Cossart, D. Aronov, I. Lampi, D. Ferster, and R. Yuste, Science 304, 559 (2004).
[11] A. Cheng, J. T. Gonçalves, P. Golshani, K. Arisaka, and C. Porter-Cailliau, Nat. Methods 8, 139 (2011).
[12] R. Yuste, Nat. Rev. Neurosci. 16, 487 (2015).
[13] Y. Roudi, B. Dunn, and J. Hertz, Curr. Opin. Neurobiol. 32, 38 (2015).
[14] A. D. Grosmark and G. Buzsáki, Science 351, 1440 (2016).
[15] W. Maass, Curr. Opin. Behav. Sci. 11, 81 (2016).
[16] H. J. Kappen and F. d. B. Rodriguez, Neural Comput. 10, 1137 (1998).
[17] T. Tanaka, Phys. Rev. E 58, 2302 (1998).
[18] V. Sassak and R. Monasson, J. Phys. A 42, 055001 (2009).
[19] Y. Roudi, J. Tyrcha, and J. Hertz, Phys. Rev. E 79, 051915 (2009).
[20] E. Schneidman, M. J. Berry, R. Segev, and W. Bialek, Nature 440, 1007 (2006).
[21] J. Shlens, G. D. Field, J. L. Gauthier, M. I. Grivich, D. Petrusca, A. Sher, A. M. Litke, and E. Chichilnisky, J. Neurosci. 26, 8254 (2006).
[22] S. Cocco, S. Leibler, and R. Monasson, Proc. Nat. Acad. Sci. 106, 14058 (2009).
[23] A. Tang, D. Jackson, J. Hobbs, W. Chen, J. L. Smith, H. Patel, A. Prieto, D. Petrusca, M. I. Grivich, A. Sher, et al., J. Neurosci. 28, 505 (2008).
[24] I. E. Ohiorhenuan, F. Mechler, K. P. Purpura, A. M. Schmid, Q. Hu, and J. D. Victor, Nature 466, 617 (2010).
[25] Y. Roudi and J. Hertz, Phys. Rev. Lett. 106, 048702 (2011).
[26] M. Mézard and J. Sakellariou, J. Stat. Mech. , L07001 (2011).
[27] H.-L. Zeng, E. Aurell, M. Alava, and H. Mahmoudi, Phys. Rev. E 83, 041135 (2011).
[28] J. Sakellariou, Y. Roudi, M. Mezard, and J. Hertz, Philos. Mag. 92, 272 (2012).
[29] E. Aurell and M. Ekeberg, Phys. Rev. Lett. 108, 090201 (2012).
[30] H.-L. Zeng, M. Alava, E. Aurell, J. Hertz, and Y. Roudi, Phys. Rev. Lett. 110, 210601 (2013).
[31] J. Tyrcha, Y. Roudi, M. Marsili, and J. Hertz, J. Stat. Mech. , P03005 (2013).
[32] B. Dunn, M. Morreaunet, and Y. Roudi, PLOS Comput. Biol. 11, e1004052 (2015).
[33] E. M. Izhikevich, IEEE Trans. Neural Netw. 14, 1569 (2003).
[34] E. M. Izhikevich, IEEE Trans. Neural Netw. 15, 1063 (2004).
[35] E. M. Izhikevich and G. M. Edelman, Proc. Natl. Acad. Sci. 105, 3593 (2008).
[36] W. S. McCulloch and W. Pitts, Bull. Math. Biophys. 5, 115 (1943).
[37] D. R. Cox, J. Roy. Stat. Soc. B , 215 (1958).
[38] M. M. Churchland, B. M. Yu, M. Sahani, and K. V. Shenoy, Curr. Opin. Neurobiol. 17, 609 (2007).
[39] J. P. Cunningham and B. M. Yu, Nat. Neurosci. 17, 1500 (2014).
[40] S. Kullback, Information theory and statistics (Dover, New York, 1997).
[41] R. Sokalr and F. Rohlf, Biometry: The principles and practice of statistics in biological research (W.H. Freeman and Company, San Francisco, 2011).
[42] J. Aru, J. Aru, V. Priesemann, M. Wibral, L. Lana, G. Pipa, W. Singer, and R. Vicente, Curr. Opin. Neurobiol. 31, 51 (2015).
[43] Y. Xu, E. Aurell, J. Corander, and Y. Kabashima, arXiv:1704.01459 (2017).
[44] T. Isomura, K. Shimba, Y. Takayama, A. Takeuchi, K. Kotani, and Y. Jimbo, J. Neural Eng. 12, 066023 (2015).
[45] T. Takekawa, Y. Isomura, and T. Fukai, Eur. J. Neurosci. 31, 263 (2010).