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Functional network stability and average minimal distance – A framework to rapidly assess dynamics of functional network representations

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HIGHLIGHTS

- A framework to rapidly detect dynamics of functional network states.
- It captures functional connectivity patterns more effectively than other methods.
- Functional similarity metric measures global network response to local changes.
- It bridges the gap between time scales of neural activity and behavioral states.

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ABSTRACT

Background: Recent advances in neurophysiological recording techniques have increased both the spatial and temporal resolution of data. New methodologies are required that can handle large data sets in an efficient manner as well as to make quantifiable, and realistic, predictions about the global modality of the brain from under-sampled recordings.
New method: To rectify both problems, we first propose an analytical modification to an existing functional connectivity algorithm, Average Minimal Distance (AMD), to rapidly capture functional network connectivity. We then complement this algorithm by introducing Functional Network Stability (FuNS), a metric that can be used to quickly assess the global network dynamic changes over time, without being constrained by the activities of a specific set of neurons.
Results: We systematically test the performance of AMD and FuNS (1) on artificial spiking data with different statistical characteristics, (2) from spiking data generated using a neural network model, and (3) using in vivo data recorded from mouse hippocampus during fear learning. Our results show that AMD and FuNS are able to monitor the change in network dynamics during memory consolidation.
Comparison with other methods: AMD outperforms traditional bootstrapping and cross-correlation (CC) methods in both significance and computation time. Simultaneously, FuNS provides a reliable way to establish a link between local structural network changes, global dynamics of network-wide representations activity, and behavior.
Conclusions: The AMD-FuNS framework should be universally useful in linking long time-scale, global network dynamics and cognitive behavior.

1. Introduction

New multisite recording techniques have generated a wealth of data on neuronal activity patterns in various brain modalities (Buzsaki, 2004; Lichtman et al., 2008; Luo et al., 2008; Chorev et al., 2009). An unresolved question is how, using such data sets, one can

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correctly identify large-scale network dynamics from populations of neurons which either may, or may not, include neurons involved in a particular cognitive process of interest. This is due in part to the fact that even high-density recordings sample only a sparse subset of the neural system responsible for the modality in question. It is also complicated by the inherent separation of temporal scales over which neural vs. behavioral measurements occur.

In response to this question, multiple linear and non-linear techniques have been developed over the years to assess functional connectivity between neurons, and to possibly infer from it structural connectivity (see for example: Friston et al., 2013; Bastos and Schoffelen, 2016; Cimenser et al., 2011; Cestnik and Rosenblum, 2017; Zaytsev et al., 2015; Poli et al., 2016; Shen et al., 2015; Wang et al., 2014). More recent approaches utilize network theory to establish links between recorded data and the underlying connectivity (see for example: Newman, 2004, 2006, 2010; Ponten et al., 2010; Rubinov and Sporns, 2010; Sporns et al., 2000; De Vico Fallani et al., 2014; Supekar et al., 2008; Boccaletti et al., 2006; Stafford et al., 2014; Petersen and Sporns, 2015; Misic and Sporns, 2016; Park and Friston, 2013; Bassett et al., 2010; Feldt et al., 2011; Gu et al., 2015; Medaglia et al., 2017; Davison et al., 2015; Hermundstad et al., 2011; Bassett et al., 2011; Shimono and Beggs, 2015; Nigam et al., 2016; Nakhnikian et al., 2014; Pajevic and Plenz, 2009). The idea is that, by estimating networks based on functional interactions, one can potentially gain insight into global dynamics, which reflect the general property of the whole network, instead of a specific subset of neurons. While all these approaches can provide insightful information, they share some the same problems. These methods are often limited by undersampling (and potentially unrepresentative sampling) of neuronal recordings, and are not optimized for monitoring changes in network structure across extended time periods (i.e., those associated with behaviors of interest, such as memory formation).

Here we propose a novel technique that rapidly estimates functional connectivity between recorded neurons. Then, rather than characterizing details of the recovered network, the metric measures changes in the network dynamical stability over time. The technique is based on an estimation of Average Minimal Distance (AMD) between spike trains of recorded neurons, a metric which has previously been compared to other clustering algorithms (Feldt et al., 2009). Here, we expand on this work and show that the analytic estimation of AMD for the null case, when the two cells are independent, allows for rapid estimation of the significance of pairwise connections between the spike trains, without need for time-expensive bootstrapping.

Further, Functional Network Stability (FuNS) is introduced and is monitored over timescales relevant for behavior. We show that FuNS measures global change in network dynamics in response to localized changes within the network. This, in part, alleviates the problem of sparse sampling so prevalent in neuroscience.

Below, the statistical underpinnings of AMD and FuNS are detailed. We compare AMD and cross-correlation (CC) on both surrogate data and model simulation data. Model results show the applicability of AMD and FuNS on excitatory-only networks, as well as on mixed networks of excitatory and inhibitory neurons poised near a balance between excitation and inhibition, a regime thought to be a universal dynamical state achieved by brain networks, resulting in enhanced information processing properties (Froemke, 2015; Barral and Reyes, 2016; Poil et al., 2012; Berg et al., 2007; Rubin et al., 2017). We end by analyzing experimental data recorded from the mouse hippocampus during contextual fear memory formation. Our results indicate that AMD yields results comparable to that of the gold-standard CC, but, importantly, it is orders of magnitude faster and reports statistically significant increases in FuNS due to behavioral-based network topological changes compared to CC FuNS (please see Table 1 for all the abbreviations).

Table 1
List of Common Abbreviations.

Abbreviation	Full Name
AMD	Average Minimal Distance
CA1	Cornu Ammonis 1
CC	Cross-correlation
CFC	Contextual Fear Conditioning
E/I	Excitatory/Inhibitory Ratio
FC	Functional Connectivity
FCM	Functional Connectivity Matrix
FSM	Functional Stability Matrix
FuNS	Functional Network Stability
IAF	Integrate and fire
ISI	Interspike interval

2. Methods

2.1. Statistical methods

2.1.1. Average minimal distance (AMD) and its significance estimation

Pairwise functional connectivity is estimated using average minimal distance (AMD) (Feldt et al., 2009) (Fig. 1) separating the relative spike times between neurons. AMD is calculated as follows: given the full spike trains $\{S_1, S_2, \ldots, S_n\}$ for n neurons within a network, the pairwise functional relationship, FC_{ij}, of the i^{th} and j^{th} neurons is evaluated by comparing the average temporal closeness of spike trains S_i and S_j to the expected sampling distance of train S_j (Fig. 1a). That is,

$\boldsymbol{AMD_{ij}} = \frac{1}{\boldsymbol{N_i}}\sum_{\boldsymbol{k}} \Delta \boldsymbol{t_k^i}$, where N_i is the number of events in S_i and $\Delta \boldsymbol{t_k^i}$ is the temporal distance between an event k in S_i to the nearest event in S_j. With AMD measured, the functional connectivity (FC) is calculated as $\boldsymbol{FC_{ij}} = \sqrt{\boldsymbol{N_i}} * \left(\boldsymbol{AMD_{ij}} - \boldsymbol{\mu_j}\right)/\boldsymbol{\sigma_j}$, which is expressed in terms of probabilistic significance of connectivity between pair ij. The mean and standard deviation, μ_j and σ_j, of the expected sampling distance, assuming that the spike trains are independent, can be calculated from either: 1) boot-strapping (i.e. randomizing the spike trains multiple times and reassessing the AMD for the null hypothesis being statistically independent of the two spike trains), or 2) numerical estimation of expected values given the distribution of inter-spike intervals (ISIs) on S_j. Hereafter, the analytical method is referred to as “fast AMD” and the bootstrapping method as “bootstrapped AMD”. For a system with n neurons, the functional connectivity value between each pair of spike trains is calculated, generating an n-by-n Functional Connectivity Matrix (FCM).

In the fast AMD approach, the maximal distance between an input spike and any spike in the spike train to be analyzed is $\frac{\boldsymbol{ISI_i}}{2}$. Then, the expected mean distance between spikes in the independent spike trains is $\boldsymbol{\mu_i} = \frac{\boldsymbol{ISI_i}}{4}$, where ISI_i is the corresponding interspike interval of spike train i (Fig. 1b). Calculating the first and second raw moments from the maximal distance then yields $\boldsymbol{\mu_1^L} = \frac{1}{4}\boldsymbol{L}$ and $\boldsymbol{\mu_2^L} = \frac{1}{12}\boldsymbol{L}^2$ for a specific ISI with length L. Taking into account the probability of observing an ISI with length L over the recording interval T, $\boldsymbol{p}(\boldsymbol{L}) = \frac{\boldsymbol{L}}{\boldsymbol{T}}$, the first and second moment for sampling the whole spike train randomly are then $\boldsymbol{\mu}_1 = \sum_{\boldsymbol{L}} \frac{\boldsymbol{L}}{\boldsymbol{T}}\boldsymbol{\mu_1^L} = \frac{1}{4\boldsymbol{T}}\sum_{\boldsymbol{L}}\boldsymbol{L}^2$ and $\boldsymbol{\mu}_2 = \sum_{\boldsymbol{L}} \frac{\boldsymbol{L}}{\boldsymbol{T}}\boldsymbol{\mu_2^L} = \frac{1}{12\boldsymbol{T}}\sum_{\boldsymbol{L}}\boldsymbol{L}^3$, respectively. The expected mean and standard deviation of a random spike train are then calculated as $\boldsymbol{\mu} = \boldsymbol{\mu}_1$ and $\boldsymbol{\sigma} = \sqrt{\boldsymbol{\mu}_2 - \boldsymbol{\mu}_1^2}$.