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Bridging large-scale neuronal recordings and large-scale network models using dimensionality reduction

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A long-standing goal in neuroscience has been to bring together neuronal recordings and neural network modeling to understand brain function. Neuronal recordings can inform the development of network models, and network models can in turn provide predictions for subsequent experiments. Traditionally, neuronal recordings and network models have been related using single-neuron and pairwise spike train statistics. We review here recent studies that have begun to relate neuronal recordings and network models based on the multi-dimensional structure of neuronal population activity, as identified using dimensionality reduction. This approach has been used to study working memory, decision making, motor control, and more. Dimensionality reduction has provided common ground for incisive comparisons and tight interplay between neuronal recordings and network models.

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Introduction

For decades, the fields of experimental neuroscience and neural network modeling proceeded largely in parallel. Whereas experimental neuroscience focused on understanding how the activities of individual neurons relate to sensory stimuli and behavior, the modeling community sought to understand theoretically how neural networks can give rise to brain function. In recent years, developments in neuronal recording technology have enabled the simultaneous recording of hundreds of neurons or more [1]. Concurrently, increases in computational power have enabled the simulation of large neural networks [2]. Together, these developments should enable experimental data to more stringently constrain network model design and network models to better predict neuronal activity for subsequent experiments [3,4].

A key question is how to relate large-scale neuronal recordings with large-scale network models. Network models typically do not attempt to replicate the precise anatomical connectivity of the biological network from which the neurons are recorded, since the underlying anatomical connectivity is usually unknown (although technological developments are making this possible [5]). In such settings, there is not a one-to-one correspondence of each recorded neuron with a model neuron. To date, comparisons between recordings and models have primarily relied on aggregate spike train statistics based on single neurons (e.g., distribution of firing rates [6], distribution of tuning preferences [7], and Fano factor [8]) and pairs of neurons (e.g., spike time [9] and spike count correlations [10,11]), as well as single-neuron activity time courses [12•,13]. To go beyond single-neuron and pairwise statistics, recent studies have examined the multi-dimensional structure of neuronal population activity to uncover important insights into mechanisms underlying neuronal computation (e.g., [14,15,16,17•,18,19,20••,21,22,23,24]). This has motivated the inquiry of whether network models reproduce such population activity structure, in addition to single-neuron and pairwise statistics, raising the bar on what constitutes an agreement between a network model and neuronal recordings [3].

Population activity structure can be characterized using dimensionality reduction [25–27], which provides a concise summary (i.e., a low-dimensional representation) of how a population of neurons covaries and how their activities unfold over time. Several dimensionality reduction methods have been applied to neuronal population activity, including principal component analysis (e.g., [14,15,20••,

28,29]), demixed principal component analysis [30], factor analysis [16,19,31••], Gaussian-process factor analysis [32], latent factor analysis via dynamical systems [33], tensor component analysis [34], and more (see [25] for a review). The low-dimensional representation describes a neuronal process being carried out by the larger circuit from which the neurons were recorded [32,35]. The same dimensionality reduction method can be applied to the recorded activity and to the network model activity, resulting in population activity structures that can be directly compared (Figure 1). This benefit is also true of related methods for comparing neuronal recordings and network models involving neuronal decoding, population response similarity, and predicting the activity of one neuron from a population of other neurons [3].

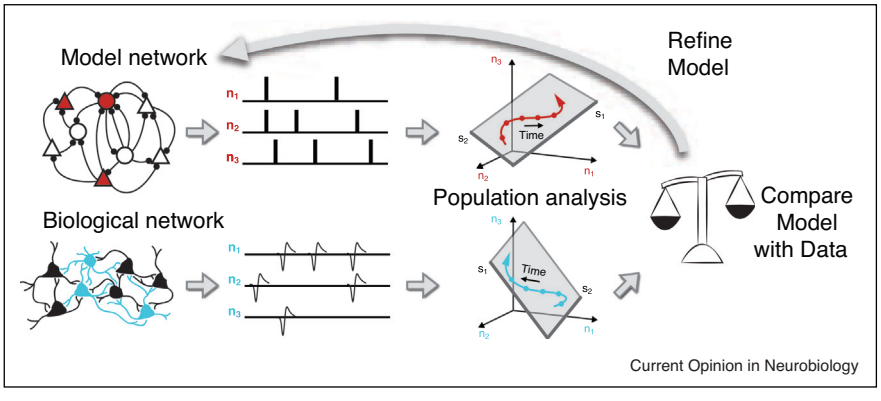
Dimensionality reduction has been adopted by recent studies to relate neuronal recordings and network models to study working memory, decision making, motor control, and more. Although many studies have separately employed large-scale neuronal recordings, large-scale network models, and dimensionality reduction, this review focuses on studies that incorporate all three components. Below we describe these studies, organized by the aspect of population activity structure used to relate neuronal recordings and network models: population activity time courses, functionally-defined neuronal subspaces, and population-wide neuronal variability. These were chosen first because they represent the key ways in which dimensionality reduction has been used in the literature to relate population recordings and network models. More importantly, these three categories represent fundamental aspects of population activity structure — how it unfolds over time, how different types of information can be encoded in different subspaces, and how it varies from trial to trial.

Population activity time courses

Dynamical structures, such as point attractors, line attractors, and limit cycles, arising from network models have long been hypothesized to underlie the computational ability of biological networks of neurons [36–38]. Such dynamical structures have been implicated in decision making [39,40], memory [41–43], oculomotor integration [44,45], motor control [46], olfaction [47], and more. A fundamental question in systems neuroscience is whether these dynamical structures are actually used by the brain. Although single-neuron and pairwise metrics can be informative [42,45], analyzing the activity of a population of neurons together has enabled deeper connections. In particular, the time course of the activity of a population of neurons can be summarized by low-dimensional neuronal trajectories [25], as identified by dimensionality reduction. These neuronal trajectories can provide a signature of a particular dynamical structure. For example, a point attractor shows convergent trajectories. The neuronal trajectories extracted from the recorded activity can then be compared with those extracted from the network model activity. Such a comparison does not require a one-to-one correspondence between each recorded neuron and a model neuron, but instead relies on a summary of the population activity time courses.

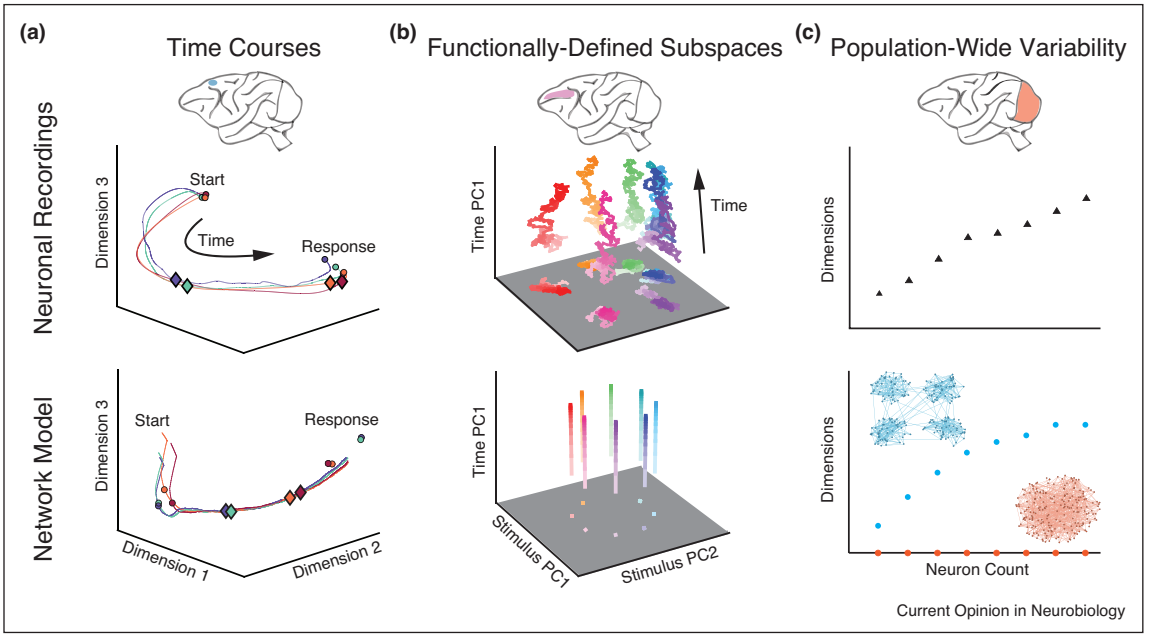
This approach was recently used to study how the brain flexibly controls the timing of behavior [48••,49]. By applying dimensionality reduction to neuronal activity recorded from medial frontal cortex, Wang et al. found that population activity time courses for different time intervals followed a stereotypical path, but traversed that path at different speeds (Figure 2a, top). To understand how a network of neurons can accomplish this, the authors trained a recurrent network model with 200 neurons to produce only the appropriate stimulus-behavior relationships.

Figure 1



Relating biological and model networks using population analyses: Because a model network typically does not attempt to replicate the precise anatomical connectivity of a biological network, there is not a one-to-one correspondence of each biological neuron with a model neuron. Dimensionality reduction can be used to obtain a concise summary of the population activity from each network. This provides common ground for incisive comparisons between biological and model networks. Discrepancies in the population activity structure between biological and model networks can then help to refine model networks.

Figure 2



Examples of comparing neuronal recordings and network models using dimensionality reduction. **(a)** (Top) Population activity time courses from medial frontal cortex during a time production task. Each trajectory represents a time course of neuronal activity during a different produced time interval. Circles represent the start and end of the time production interval and diamonds represent a fixed time interval after the start circle. Diamonds appear closer to the start of the trajectory on long-interval trials (blue) than short-interval trials (red), indicating that neuronal activity traverses the path at different speeds during the two intervals. (Bottom) Circles represent fixed points in the model network's dynamics and diamonds represent a fixed time interval after the start of the time production task. A similar difference in traversal speed is observed in the model network as was observed in the neural recordings. Adapted with permission from [48••]. **(b)** (Top) Delay period activity from prefrontal cortex during a delayed saccade task. Each trajectory represents a different stimulus condition. The trajectories for different stimuli remain well-separated in a stimulus subspace throughout the delay period. (Bottom) Network model activity demonstrating similar subspace stability. Adapted with permission from [20••]. **(c)** (Top) Dimensionality of population-wide neuronal variability in primary visual cortex increases with the number of neurons recorded. (Bottom) A similar dimensionality trend is observed for a spiking network model with clustered excitatory connections (blue), but not for a model with unstructured connectivity (red). Adapted with permission from [31••].

Wang et al. then applied dimensionality reduction to the activity from the network model. They surprisingly observed that the neuronal trajectories of the network model also followed a stereotypical path, even though the network model was not trained to reproduce the recorded activity (Figure 2a, bottom). This population-level correspondence enabled by dimensionality reduction laid the foundation for them to then dissect the network model to understand the core neuronal mechanisms [50]. They found that the input to the network drove the network activity from one fixed point to another, where the transition speed was determined by the depth of the energy basin created by the input (Figure 2a, bottom).

Other studies have also used this approach to understand how the time course of neuronal activity relates to computations underlying motor control [12•,51,52,53], decision making [17•,54,55•,56], and working memory [13,57]. In each of these studies, a network model was constructed without referencing the recorded activity. Dimensionality reduction was applied to extract neuronal trajectories to obtain a correspondence between the neuronal recordings and network models. To study the neuronal mechanisms underlying the observed time courses, the network models were then dissected to reveal dynamical structures, such as fixed points or point attractors [17•,54,55•], line attractors [17•], and oscillatory modes [12•,51,52,53]. Whether or not these dynamical structures are indeed at play in real neuronal networks is still an open question. Nevertheless, these studies are beginning to demonstrate that it is at least fruitful to interpret neuronal activity in terms of these dynamical structures, a process facilitated by dimensionality reduction.

Functionally-defined neuronal subspaces

Recent studies have investigated how distinct types of information encoded by the *same* neuronal population can be parsed by downstream brain circuits [58–60]. An enticing proposal is that different types of information are encoded in different subspaces within the population activity space, where the subspaces are identified using dimensionality reduction. For example, Kaufman et al.

[18] asked how it is possible for neurons in the motor cortex to be active during motor preparation, yet not generate an arm movement. They found that motor cortical activity during motor preparation resided outside of the activity subspace most related to muscle contractions. This allows the motor cortex to prepare arm movements without driving downstream circuits, a characteristic which can be implemented by a linear readout mechanism. This concept of functionally-defined neuronal subspaces has also been used in other studies of motor control [23,61–63], decision making [30,64], short-term memory [30,65], learning [19], and visual processing [24].

To understand how a neuronal circuit can implement and exploit such functionally-defined neuronal subspaces, one can construct a network model to see whether it reproduces the empirical observations. If so, one can then dissect the network to study the underlying mechanisms. Mante et al. [17•] applied dimensionality reduction to recordings in prefrontal cortex to find that motion and color of the visual stimulus were encoded in distinct subspaces. They then trained a recurrent network model with 100 neurons to produce only the appropriate stimulus-behavior relationships. When they applied the same dimensionality reduction method to the network model activity, they surprisingly found that the motion and color of the visual stimulus were also encoded in distinct subspaces, even though the network model was not trained to reproduce the recorded activity. This population-level correspondence between the network model and recordings was enabled by dimensionality reduction and went beyond comparisons based on individual neurons or pairs of neurons. Mante et al. then dissected the network model to uncover how the two types of information encoded in distinct subspaces can be selectively used to form a decision.

Dimensionality reduction has also revealed that, in some cases, standard network models do not reproduce the functionally-defined subspaces identified from neuronal recordings. For example, Murray et al. [20••] applied dimensionality reduction to recordings in prefrontal cortex during a working memory task to find that, even though firing rates of individual neurons changed over time, there was a subspace in which the activity stably encoded the memorized target location (Figure 2b, top). They then applied the same analyses to activity from several prominent network models and found that none of them reproduced both the time-varying activity of individual neurons and the subspace in which the memory was stably encoded. This provided the impetus to develop a new network model that did reproduce these features of the recorded activity (Figure 2b, bottom) (see also [66]). As another example, Elsayed et al. [67•] found that standard network models do not reproduce the empirical observation described above that neuronal activity during movement preparation and movement execution lie in orthogonal subspaces. Such insights obtained using dimensionality reduction can guide the development of more sophisticated network models.

Population-wide neuronal variability

The previous sections focus largely on neuronal activity that is averaged across trials and on firing rate-based network models. This naturally obscures the trial-to-trial variability that is a fundamental feature of neuronal responses across the cortex [68], both at the level of single neuron responses [69] as well as variability shared by the population [11,70]. Theoretical and experimental studies have focused on how the structure of that variability places limits on information coding [71–74], and in turn influences our behavior. At the same time, a growing body of work has demonstrated that variability can be thought of not only as noise to be removed, but also as a signature of ongoing decision processes and cognitive variables (e.g., [75–77]). To move beyond single-neuron and pairwise measurements of neuronal variability, recent studies have begun to consider population-wide measures of neuronal variability [78–82], as enabled by dimensionality reduction. Such measures allow one to (i) assess whether the large number of single-neuron and pairwise variability measurements can be succinctly summarized by a small number of variables (e.g., the entire population increasing and decreasing its activity together can be described by a single scalar variable), and (ii) relate the population activity on individual experimental trials to behavior [22,32–34,83–85].

In parallel with the growing interest in neuronal variability, there have been attempts to create network models that exhibit variability matching recorded neurons. In particular, a class of models has used the balance between excitation and inhibition as a way to generate variability as an emergent property of network structure, rather than via an external variable source [71,86,87]. In these models, the particular structure of the network has a large impact on the population-wide variability that emerges. Using the lens of factor analysis, Williamson et al. [31••] found that the dimensionality of spontaneous activity fluctuations in V1 neurons increases with the number of recorded neurons (Figure 2c, top). This was more consistent with activity generated by networks with clustered excitatory connections [8] than networks with unstructured connectivity [86] (Figure 2c, bottom). The combination of population-wide measures of variability (in this case, dimensionality) and the ability to manipulate model network structures facilitated an understanding of how features of variability observed in biological networks relate to network structure.

The approach of using dimensionality reduction to compare the population-wide variability of neuronal recordings and network models has also been applied to study spontaneous versus evoked activity [88•,89], the activity of different classes of neurons [90], and the activity during

different behavioral conditions, such as attention [81,82]. Dimensionality reduction has also been used to analyze population activity from balanced network models to help identify the crucial network architecture and synaptic timescales required to produce the low-dimensional shared variability that is widely reported in neuronal recordings [82,87]. Together these studies demonstrate the power of combining dimensionality reduction and network models to understand the mechanisms and effects of neuronal variability.

Conclusion

Dimensionality reduction has enabled incisive comparisons between biological and model networks in terms of population activity time courses, functionally-defined neuronal subspaces, and population-wide neuronal variability. Such comparisons result in either (i) a correspondence between the neuronal recordings and the network model, in which case the model can be dissected to understand underlying network mechanisms, or (ii) discrepancies between the neuronal recordings and standard network models, leading to the development of improved models. This approach (cf. Figure 1) has already provided insight into the neuronal mechanisms underlying brain functions such as working memory, decision making, and motor control, and is likely to become even more important as the scale of neuronal recordings and network models grows.

A key consideration in network modeling is what aspects of neuronal recordings the model should reproduce. We posit that the population activity structure (including population activity time courses, functionally-defined neuronal subspaces, and population-wide neuronal variability) will provide key signatures of how neurons work together to give rise to brain function. Thus, if a network model is to provide a systems-level account of brain function, we should require it to reproduce the population activity structure of neuronal recordings, in addition to existing population metrics [3] and standard spike train statistics based on individual and pairs of neurons.

Most studies described here have used neuronal recordings to inform network models via dimensionality reduction. An important future direction is to use network models and dimensionality reduction to design new experiments and form predictions. For example, if one day we can experimentally perturb neuronal activity in specified directions in the population activity space [91], we can test whether driving the population activity in particular directions leads to particular decisions or movements predicted by the network model. The hope is to establish a virtuous cycle, where neuronal recordings and network models closely inform each other through the common ground provided by dimensionality reduction.

Conflicts of interest statement

Nothing declared.

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