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Review

# Connectivity inference from neural recording data: Challenges, mathematical bases and research directions

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A B S T R A C T

This article presents a review of computational methods for connectivity inference from neural activity data derived from multi-electrode recordings or fluorescence imaging. We first identify biophysical and technical challenges in connectivity inference along the data processing pipeline. We then review connectivity inference methods based on two major mathematical foundations, namely, descriptive model-free approaches and generative model-based approaches. We investigate representative studies in both categories and clarify which challenges have been addressed by which method. We further identify critical open issues and possible research directions.



**Contents**



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## 1. Introduction

Understanding operational principles of neural circuits is a major goal of recent international brain science programs, such as the BRAIN Initiative in the U.S. (Insel, Landis, & Collins, 2013; Martin & Chun, 2016), the Human Brain Project in the E.U. (Amunts et al., 2016; Markram 2012), and the Brain/MINDS program in Japan (Okano & Mitra, 2015; Okano et al., 2016). A common emphasis in these programs is utilization of high-throughput, systematic data acquisition and advanced computational technologies. The aim of this paper is to present a systematic review of computational methods for inferring neural connectivity from high-dimensional neural activity recording data, such as multiple electrode arrays and calcium fluorescence imaging.

Why do we need to infer neural connectivity? High-dimensional neural recording data tell us a lot about information representation in the brain through correlation or decoding analyses with relevant sensory, motor, or cognitive signals. However, in order to understand operational principles of the brain, it is important to identify the circuit mechanisms that encode and transform information, such as extraction of sensory features and production of motor action patterns (Churchland & Sejnowski, 1992). Knowing the wiring diagram of neuronal circuits is critical to explain how such representations are produced, predicting how the network would behave in a novel situation, and extracting the brain's algorithms for technical applications (Sporns, Tononi, & Kötter, 2005).

The network of the brain can be analyzed at various spatial scales (Gerstner, Kistler, Naud, & Paninski, 2014). At the macroscopic level, there are more than a hundred anatomical brain areas and connection structure across those areas give us an understanding of the overall processing architecture of the brain. At the mesoscopic level, connections of neurons within each local area, as well as their projections to other areas, are characterized in order to understand computational mechanisms of neural circuits. At the microscopic level, locations and features of synapses on dendritic arbors of each neuron are analyzed to understand operational mechanisms of single neurons.

This review focuses on the mesoscopic level, inferring connections between neurons in local circuits on the basis of neural activity recording data from multi-electrode recordings or fluorescence imaging. Connectivity inference from anatomical data, such as diffusion MRI at the macroscopic level, tracer injection at the mesoscopic level, and serial electron microscopy data at the microscopic data, are beyond the scope of this review. Some methods, especially those of model-free approaches, may also be applicable to connectivity inference from functional MRI data at the macroscopic level.

This paper presents an overview of challenges in network inference and different mathematical approaches to address those challenges. We first review the data processing pipeline of connectivity analysis and identify both biophysical and computational difficulties. From mathematical viewpoint, we classify connectivity inference methods broadly into descriptive, model-free approaches and generative, model-based approaches and explain representative methods in each category. We then examine which