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Brain structure and dynamics across scales: in search of rules

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Louis Henry Sullivan, the father of skyscrapers, famously stated 'Form ever follows function'. In this short review, we will focus on the relationship between form (structure) and function (dynamics) in the brain. We summarize recent advances on the quantification of directed- and weighted-mesoscopic connectivity of mammalian cortex, the exponential distance rule for mesoscopic and microscopic circuit wiring, a spatially embedded random model of inter-areal cortical networks, and a large-scale dynamical circuit model of money's cortex that gives rise to a hierarchy of timescales. These findings demonstrate that inter-areal cortical networks are dense (hence such concepts as 'small-world' need to be refined when applied to the brain), spatially dependent (therefore purely topological approach of graph theory has limited applicability) and heterogeneous (consequently cortical areas cannot be treated as identical 'nodes').

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Introduction

Recent years have witnessed a sea-change in our knowledge of the microscopic local cortical circuits and mesoscopic long-distance connectivity between cortical areas. Kennedy's group recently published a series of papers reporting a new dataset of quantitative- and weighted-inter-areal connectivity in the macaque monkey cortex [1••,2,3••]. Moreover, two separate teams reported datasets on the mouse whole-brain connectome [4••,5••]. The findings revealed that the inter-areal connectivity at the mesoscopic level are dense (more than 50% of all possible connections are present) and dependent on spatial distances between cortical areas. These findings have highlighted limitations of theoretical analysis of brain circuits in terms of purely topological networks with sparse connectivity, and have led to the proposal of an alternative class of spatially embedded random networks which could be more fruitful in Neuroscience [3••,6••,7]. In this review, we summarize recent advances and discuss to what extent those findings are valid across scales from microscopic to mesoscopic cortical circuits, and between primate and rodent.

Whereas structural connectivity is essential for understanding the constraints of brain function, it alone is insufficient to predict the dynamical behavior of neural circuits. Consider two identical neurons interconnected by mutually inhibition. Given this connectome, can one predict the network's behavior? It turns out that experimentation and theory have uncovered multiple possibilities. First, both neurons may simply remain silent. Second, in response to inputs, the system may behave as a switch, with only one neuron to be active at any one time. Third, if the neurons are endowed with a slow adaptation, each could take turns to be active leading to a 'half-center' oscillator, which is the core of rhythmic central pattern generators. Finally, under certain conditions, the two neurons can be perfectly synchronized, spike by spike: the two neurons fire at the same time, leading to mutual inhibition after a brief delay, and when this inhibition has decayed they can fire again together [8]. This simple example illustrates that dynamical behavior often cannot be deduced from anatomy in a straightforward fashion; physiology and modeling are important for discovering the dynamical operations of neural circuits.

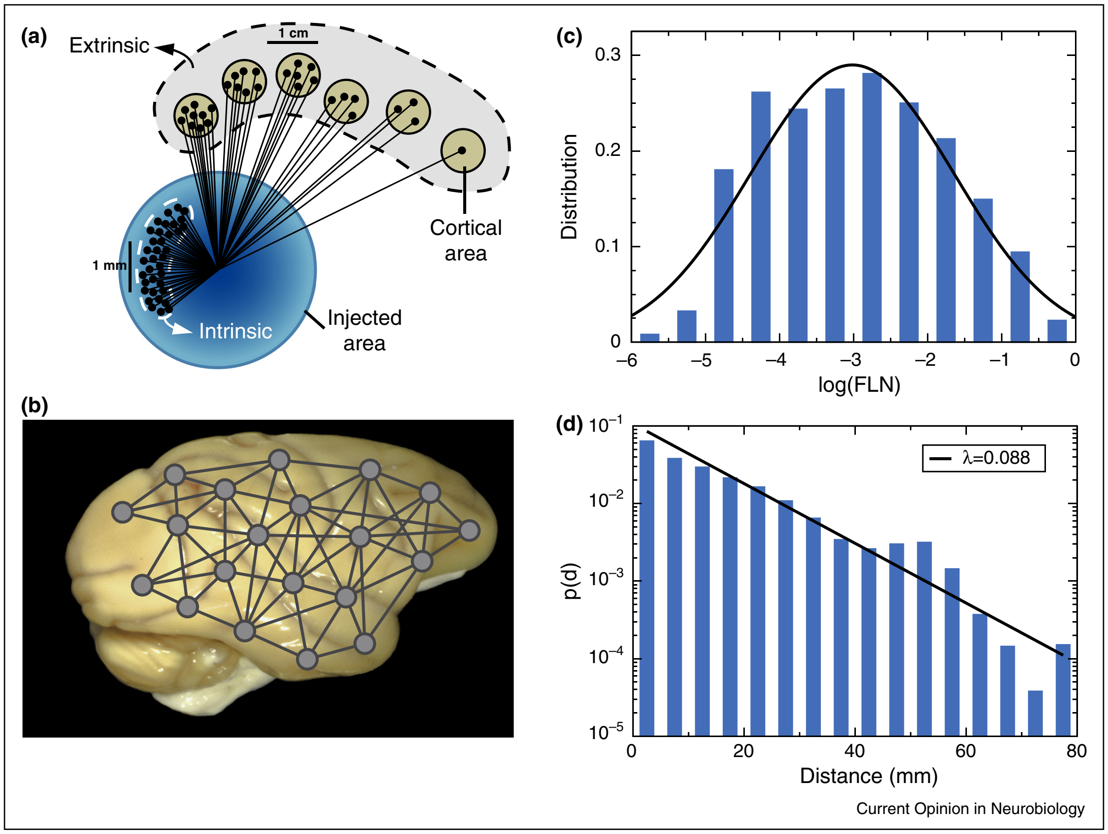
To tackle the brain-wide complex dynamics, which give rise to neuronal function and behavior, several groups have developed large-scale dynamical models [9••,10,11••]. In particular, combining monkey interareal connectivity with data on the areal differences in the number of spine counts per pyramidal neuron [12], our model naturally exhibits a hierarchy of timescales [11••]. These findings exemplify a fruitful interplay between theory and experimentation in discovering general principles of how large-scale brain systems work. This progress has opened the door to tackle complex brain dynamical phenomena including neural avalanches [13] and lognormal distribution of firing rates [14••] in future research.

Spatially embedded microscopic and mesoscopic cortical connectivity

Local neuronal networks in the cortex exhibit non-random configurations with a wide range of synaptic strengths [15]. Because the connections within local areas account for about 80% of the total connections of the cortex [1••], the local circuits constitute a large part of the cortical machine. A recent investigation described the functional organization of synaptic strength in the local circuit thereby making a major contribution to our understanding of the cortex [16••]. These authors used natural images *in vivo* to look at the correlation of activity in neighboring neurons in the supragranular layers of the mouse visual cortex, before completing whole cell recordings of the same neurons in a slice preparation. These technically challenging experiments revealed the functional organization of the local circuit; the strong reciprocal connections are mostly found between pairs of neurons with high correlated responses and similar stimulus selectivity whereas neurons with uncorrelated response are infrequently and weakly connected. These findings, extended to showing that cells with similar receptive fields were preferentially connected, are highly significant because they go some way to explaining how recurrent excitation of the supragranular layer neurons amplifies and sharpens weak thalamic inputs [17], or produces self-sustained persistent activity in a number of cortical areas [18]. These results suggest that local circuit neurons may form subnetworks [19–22], that could provide an important infrastructure supporting global and local integration.

One interpretation of the strongly interconnected neighboring neurons in the supragranular layers is that they constitute cell assemblies. In a sensory area, these cell assemblies not only encode sensory input but also could integrate contextual information such as reward, attention and expectation [21]. These contextual interactions are derived largely from the network of long-range inter-areal connections (see Figure 1). The inter-areal graph in macaque has a density of 67%, with individual target areas receiving inputs from between 30 and 80 source areas suggesting high levels of global interactions [2]. The specificity of the inter-areal

Figure 1



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Inter-areal connections of macaque monkey cortex. **(A)** A retrograde tracer is injected in a (target) area, and relative weight of connection between a source area and the target area is quantified by the fraction of labelled neurons (FLN), which is the number of labelled neurons in the source area divided by the total number of labelled neurons. **(B)** The analysis is carried out with a number of cortical areas, leading to a weighted- and directed-inter-areal network connectivity. **(C)** FLNs span five order of magnitudes and are fit by a lognormal distribution. (D) FLN between a pair of cortical areas is an exponential function of their distance, with the characteristic distance length of ~11 mm. Adapted with permission from [1••].