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Potential connectomics complements the endeavour of 'no synapse left behind' in the cortex

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Does understanding brain function require characterizing every last synapse? The answer depends on the meaning of 'understanding'. Mapping the full connectome of a whole mammalian brain with electron or super-resolution light microscopy is surely a daunting challenge (Lu, 2011). The paper in this issue of *The Journal of Physiology* by Ramaswamy *et al.* (2011) shows that simple stochastic selection of contacts among axo-dendritic spatial proximities captures the statistics of somatically recorded physiological signals. Digital reconstructions of neuronal morphology were randomly distributed in a simulated 3D cortical volume. Virtual synapses were then assigned to incidental axo-dendritic overlaps, modelling kinetics and amplitudes based on experimental measures. The resulting somatic EPSPs recorded *in silico* reproduced the distributions observed *in vitro*. It is too early to say how this finding will generalize across cortical regions, layers, and pre- and postsynaptic cell types. Most importantly, it remains unknown if neuronal morphology is sufficient to specify all other essential aspects of synaptic computation, such as efficacy (Komendantov & Ascoli, 2009), but also integration, homeostasis, plasticity and metabotropic cascades. This new report nevertheless lends support to the notion that detailed circuitry may reflect individual experience rather than general coding principles (Kalisman *et al.* 2005).

Though experience may significantly shape circuitry, the adult cortex is not a genuine 'blank slate'. It cannot adapt its wiring to *any* arbitrary pattern, because its axonal and dendritic arbours do constrain the formation of synapses, powerfully gating what can be learned. The contribution of this paper lies in showing that the postsynaptic potentials reaching the soma are statistically determined by the morphology of identified neuronal classes rather than by the specific synapse locations. Thus, comprehensive knowledge of every single synapse (what Americans might call 'no synapse left behind') may not be strictly necessary to reverse-engineer the brain. Instead, an anatomically realistic virtual network might be simulated by generating spatial distributions of appropriately shaped, packed and oriented neuronal forests re-sampled from large amounts of three-dimensional digital reconstructions at the light microscopy level (Kozloski, 2011).

A new perspective emerges from the evidence accumulating in this and several other studies. Two distinct levels of connectomics can be recognized. One is that of actual synapses, with vesicle release, neurotransmitter receptors, etc. The other is that of potential contacts, consisting of spatial proximities of axonal and dendritic branches (Stepanyants & Chklovskii, 2005). It would be too reductive, and often incorrect, to consider synapses simply as a random subset of axo-dendritic proximities or to view axo-dendritic proximities as synaptic predictors (Peter's rule: Braitenberg and Schüz, 1998). *Actual and potential connectivity represent two different physical entities, each with a separate and unique function.* Their exact cognitive correlates are yet to be discovered, but it is tempting to speculate. Actual circuits might reflect knowledge, while potential circuits might relate to the capability to acquire new knowledge (given the right experience). The full specification of both actual and potential connectivity may characterize an individual and that individual's specific history, while the overall population statistics of those measures may quantify an attribute of the species. Scaling out further, the modular building blocks or repeating motifs of neural networks at both the actual and potential levels of description could reflect underlying computing mechanisms.

The general patterns of dendritic and axonal morphology in each neuron class take shape during development. Different brain regions mature asynchronously and display critical windows for rewiring at dramatically disparate ages. Certain parts of the brain, such as the prefrontal cortex and especially the hippocampus, maintain high structural plasticity throughout adulthood. In these regions, spines twitch in and out of dendrites in a matter of minutes, boutons crawl up and down their axons in an activity- and experience-dependent manner, and newborn neurons are continuously embedded in the functional blueprint. These dynamics continuously rewire the actual connectome within the more stable potential connectivity map. Thus, in hippocampal and similarly plastic cortices, potential connections might constitute more relevant neural correlates of information processing than actual synapses.

It is also intriguing that synaptic invariance results particularly from the morphological *diversity* of neuronal arbours. Although the general branching patterns (Sholl distributions, etc.) are considered revealing signatures of a given neuronal class, no two neurons are ever exactly alike. The actual meandering and locations of axons and dendrites constitute the real constraints of (and potential for) synaptic connectivity. These specific tree configurations also change, although at a slower time scale than synapses, possibly corresponding to long-term learning processes, such as the progressive adaptation to new contexts or environments. By providing fixed links, actual synapses delimit the extent of this branch-level plasticity, perhaps reflecting the common experience that old knowledge sometimes hampers the acquisition of new knowledge.

The article also illustrates important methodological considerations that are taken for granted in physics, but are still too often underappreciated in neuroscience. Modelling is an essential element in the process of discovery, along with experiments and theory. Whereas experiments can disprove theoretical assumptions by falsifying hypotheses, computer simulations enable the demonstration that a theoretical explanation is *complete*, by showing that the postulated mechanism is *sufficient* to reproduce the observed phenomenon. Agile theoretical developments are frequently better aided by flexible and extensive exploration of models than by slow, costly, invasive and technologically limited experiments. Theory indicates how experimental measures should constrain

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and validate computer simulations, and how those simulations can help interpret empirical results, integrate knowledge and design new experiments. Neuroanatomy is particularly needy in these regards, because the complexity of human brain connectivity is so massive that data collection alone will not suffice to explain its function. Although only a few years old, computational neuroanatomy has rapidly advanced into a powerful approach with mature resources (e.g. NeuroMorpho.Org) and a thriving research community.

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