The central nervous system (CNS) is composed of multiple layers of networks, physical, chemical, electrical, and molecular. The physical network, dubbed the 'connectome', describes the spatial organisation of billions of neurons, their interconnections, and their development and plasticity. The chemical network represents the subsets of the physical network that provide, amongst other things, positive and negative feedback systems of excitatory and inhibitory neurons. The electrical network describes the signal processing performed by collections of neurons over very short timescales and is ultimately regarded as the output or the activity of the brain. Finally, molecular networks are defined by the production and interaction of nucleic and amino acids within each of the cells of the CNS; complex pathways of often large numbers of interacting proteins define the state and function of each neuron and whose dysfunction underly almost all neuropathological conditions.

TABLE, FIGURE? Time vs. space

physical network: mostly spatial, some temporal (more at the beginning) but slower over long periods into adulthood
chemical network: mostly spatial (neurotransmitters/receptors), changes occur fast for electrical transmission, and fairly slowly (30mins?) for adaptation
electrical network: spatial and temporal (very fast!)
molecular network: spatial, temporal limited by transcription and translation (fairly slow, mins-hours)

At the finest level of resolution, these four layers of network all involve, in some way or another, the direct physical interaction of cells, chemicals, molecules, or electrons. However, due to the immense complexity of all of these component interactions, to make sense of it all we must generalise and abstract these. The most common method for achieving this is to construct networks of associations. For example, changes in blood flow measured by fMRI are associated with changes in brain activity, and two or more brain regions with similar patterns of blood flow can be thought of as having an association with each other. Similarly, measuring the expression/abundance of many thousands of RNA transcripts can reveal multiple correlated RNAs that we can then suppose are similar regulated by the cell, despite there being little or no evidence of a direct interaction between these molecules. Just as the fMRI signal can be correlated over regions of the brain, so too can the expression of RNA in order to try to identify larger regions of the brain (or collections of neurons) that are molecularly similar or that respond similarly to perturbation.

TABLE, FIGURE? Abstraction

physical: broad connections, connectome, brain regions/tissues
chemical: ?
electrical: proxy blood flow (fMRI) for activity, else activity measured electrically but both have poor resolution
molecular: co-expression, use the proxy of abundance for interaction/association

Mathematical networks are attractive representations for these abstract associations, in which the edges between nodes (which can represent individual genes, clusters of

genes, or groups of neurons) are a simple means of summarising an association that may in all likelihood actually involve multiple sets of physical interactions. Integration of multiple levels of measurement of cellular regulation of gene expression has been facilitated by the flexibility and generalisability that the network framework provides.

Organisation by connectivity

Brain imaging methods such as in-vivo tract tracing [ref] have begun to elucidate the physical connectivity of the primate brain at the single-neuron level and have paved the way for network models that facilitate deeper understanding of cortical anatomy and hierarchical organisation. The cortical neuronal network can be subdivided into more than 100 distinct areas [ref], which are defined by a characteristic profile of internal and inter-area connectivity [ref]. In fact, it appears that this neuronal connectivity is highly modular, in that it is dominated by connections internal to each area, with only ~20% of all connections being between neurons in different areas [ref]. Each area is considered to have a primary feature, for example in processing sensory or cognitive signals, and is an excellent analogue of the modular characteristics of intra-cellular molecular networks in which proteins in tightly controlled functional groups coordinate as part of larger pathways to achieve well defined cellular functions.

Small-world network models have performed particularly well in describing both molecular networks and this cortical architecture as they reflect the high degree of clustering and small path-length found in these densely modular systems [ref]. For example, the physical interactions of proteins located in complexes at the synapse conform to this small-world network model as each protein is only about three-steps away from all other proteins. However, unlike metabolic networks [ref], the neuronal network is probably not scale-free, instead exhibiting an exponential degree-distribution [ref].

Organisation by spatial arrangement

Extremely regular grid-like networks of neurons in the hippocampus exhibit spatially repetitive firing patterns that constitute an internal representation of the external local environment [the subject of this year's Nobel]. While this is an extreme example of spatial organisation, it has been found that a great majority of the interconnections between the areas/layers of the cortex (discussed above) are performed over very small physical distances. There is a metabolic (energy) cost ("wiring cost") associated with the distance between connected neurons that results in an exponential distance rule, favouring shorter connections, especially between distinct cortical areas [ref].

Similarly, the molecular network is dominated by spatial organisation in terms of the transport, processing, and final localisation of RNAs and proteins. This is well exemplified by the cell's use of signal recognition particles to localise the translation of membrane proteins at the endoplasmic reticulum [ref] and can be though of as a mechanism to minimise the cost of transporting these proteins to their intended destination (compare to stochastic movements through the cytoplasm). Additionally, local translation of mRNAs at the synapse [ref] provides the neuron an efficient mechanism for delivering protein far away from the nucleus with the shortest time-delay.

However in both the molecular and the neuroanatomical network, proximity must not always be assumed to infer interaction or association. Proteins co-localised to the same cellular compartment may not interact if they do not share a common binding domain, just as neurons in the same small volume of tissue may perform distinct, and sometimes opposing [ref], functions.

Wrap-up

One thing that is clear that the resolution of molecular interrogation of the CNS must increase dramatically before they can be of significant benefit to studies of neurodegeneration and disease. This increase in resolution of course includes increasing the spatial precision of fMRI and molecular profiling to assay single cell-types in the brain, but also relies on the tighter integration of these different, but highly complementary, data modalities. There exists significant advantages to the non-invasive monitoring of electrical and chemical activity in the mammalian CNS, but complementary molecular profiling is necessary for true mechanistic understanding of these signals [ref - our NN review].

Other topics (?):

- Redundancy in physical (e.g. rewiring after a stroke) and molecular networks - how to model this?

Comparison

Small-world networks have been scale free?
connectivity?
some analyses work on some things but not on others (?)
compare timescales, sizes/complexity of physical vs molecular networks
attached PDF to Mark by Wed @4pm