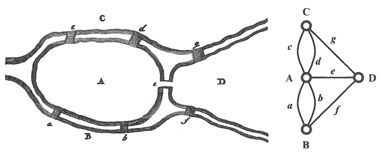
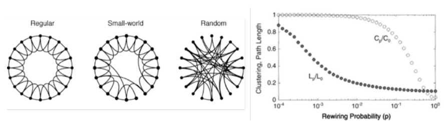
Connectomics



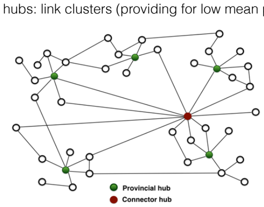
Networks and Graph Theory

- A network is a set of nodes connected by edges
- The field of graph theory has developed a number of measures to analyze networks
  - *Mean shortest path length*: the average fewest number of edges that must be traversed between nodes
  - *Cluster coefficient*: the percentage of its neighbors to which a node is connected
- In the mid-20th century most focus was on regular lattices and random networks
  - In 1998 Watts and Strogatz characterized many real world networks as small world networks
    - Like regular lattices, they exhibit high clustering
    - Like random networks, they exhibit short path length



Network Hubs

- Another measure of network structure is *degree*
  - the number of edges connecting to a node
- Traditionally it was assumed that degree would be distributed normally
  - But in 1999 Barabási found that in many real world networks degree fits a power law
    - Most nodes have just a few connections
    - A few nodes have a great many connections
  - In such networks, those nodes with many connections constitute hubs
    - Provincial hubs: core of clusters
    - Connector hubs: link clusters (providing for low mean path length)



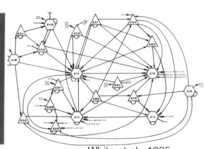
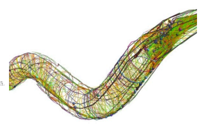
Clicker Question

What makes the connectome of the round worm (*C. elegans*) of sepial interest to neuroscientists?

- One can do direct electrophysiological recording from individual neurons and determine their role in behavior
- It is the only species for which we have a complete connectome
- The connections in the worm keep changes with experience, allowing researchers to figure out what changes as the worm learns

Why the interest in *C. elegans?*

- *C. elegans* (round worm)
  - The hermaphrodite has only 302 neurons
  - Regular from worm to worm
- Sydney Brenner and his graduate student, John White, used serial electron micrographs to trace 279 neurons linked by 6,393 chemical synapses, 890 electrical junctions, and 1,410 neuromuscular junctions
- They then extracted wiring diagrams for circuits such as that involved in chemoreception

White et al., 1985

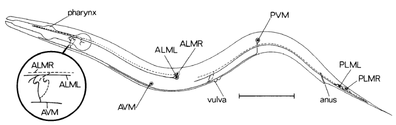
Discussion Question

Of what possible use is having the connectome of the worm?

- It provides a basis for conducting experiments directed at understanding the mechanisms involved in the worm's behavior
- By showing how the nervous system is wired it offers a basis for theorizing (mathematically modeling) about the mechanisms underlying behavior in the worm
- It provides a model of what can be done to understand the wiring diagram of more complex species, including humans
- It is of limited use since by itself it offers little in the way of explanation

From the Wiring Diagram to Function

- In 1985 Martin Chalfie used the just-developed wiring diagram of *C. elegans* to identify the touch circuit
- From the wiring diagram
  - 6 touch receptors (distinctive microtubule cells)
  - 5 pairs of interneurons
  - 69 motor neurons
- Used laser microbes to kill individual neurons and determine effect
  - At the time researchers could not do electrophysiological studies because of the size of the organism



What is the Value of a Connectome?

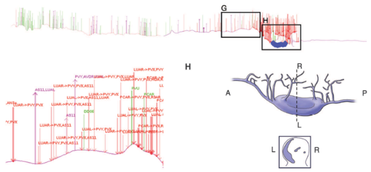
- Movshon:
  - "I think it's fair to say...that our understanding of the worm has not been materially enhanced by having that connectome available to us. We don't have a comprehensive model of how the worm's nervous system actually produces the behaviors. What we have is a sort of a bed on which we can build experiments—and many people have built many elegant experiments on that bed. But that connectome by itself has not explained anything."
- A complaint much like that issued against the human genome project

"Decision Making" in the *C. elegans* male

- Jarrell et al. (2012) focused on mating behavior in the male worm
  - specific behaviors: locating the hermaphrodite's vulva, inserting its spicules, and transferring sperm
  - Followed the same approach as White and Benner to map the circuit in the male
- Male contains the same 302 neurons as the hermaphrodite, plus 81 additional neurons, all located along the posterior nervous system and thought to be involved in regulating mating behavior
  - These 81, plus 89 also found in the hermaphrodite, identified as a circuit linking sensory inputs to muscle and gonad involved in mating

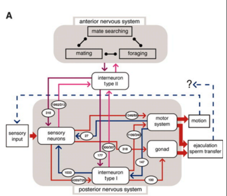
Mapping the Mating Network

- Jarrell et al. also measured the size of synapses or gap junctions (number of sections crossed) and used that as a proxy for the strength of each connection
  - Below are the results for one interneuron (PVX), with length of vertical lines indicating strength and color the type of connection (red, chemical input; magenta, chemical output; green, gap junction)



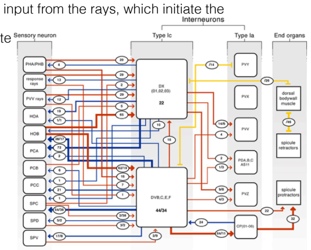
Rendering Network as a Graph

- Jarrell et al. integrated their results in several graph representations with chemical synapses as directed edges and gap junctions as undirected edges
  - Demonstrated a small-world network (short path length and high clustering)
- Developed models of the flow of information
  - Red arrows are forward projections
  - Blue are recurrent projections
  - Numbers indicate number of serial sections for the connection (chemical synapses/gap junctions)
    - Proxy for strength
  - Many projections directly from senses to motor neurons
  - Few recurrent projections



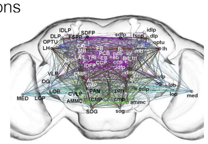
From Connectome to Functional Story

- At a more fine-grained level, Jarrell et al. differentiate two classes of interneurons and offer a narrative of how the mechanism might work
  - Both sets of interneurons receive input from the rays, which initiate the response step in mating, and the hook, previously shown to promote vulva search behavior when vulva contact is lost
  - DVB, is known to be GABAergic (GABA is often inhibitory), suggesting that these interneurons may serve to inhibit the spicule protractor muscles
  - DX (01-03) have gap junctions to the dorsal body wall muscles, which in turn have gap junctions onto the spicule retractors
  - Proposal: circuit inhibits spicule protractors and initiates spicule retraction in response to signals indicating the need to pursue earlier steps in the mating behavior



Can Connectome Research Scale?

- *C. elegans*: 302 neurons, 7,000 connections
- *Drosophila* (fruit fly): ~100,000 neurons
- *Apis* (honey bee) ~1,000,000 neurons
- *Mus* (mouse): ~71,000,000 neurons, ~4,000,000 in cortex
- *Rattus* (rat) ~200,000,000 neurons, 18,000,000 in cortex
- *Macque* (monkey) 6,376,000,000, 480,000,000 in cortex
- *Homo sapiens* (human): ~86,000,000,000 neurons; ~21,000,000,000 in cortex (~100,000,000,000,000 connections)



- *C. elegans* reveals a constant wiring pattern across individuals, but other organisms exhibit a dynamic pattern
  - connections change over time (reflecting learning)

Discussion Question

What strategy should researchers follow to develop a connectome for mammals, primates, humans given the much larger number of neurons?

Follow the same strategy as in the worm—developing a map of individual neurons, recognizing that this may take a long time

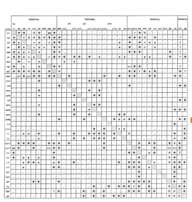
Start in the peripheral nervous system and work up from there to the brain, tracing individual neurons

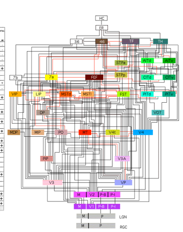
Move to a higher level of organization, focusing on brain regions (V1, V4, MT, etc.) and the pathways between them

Other

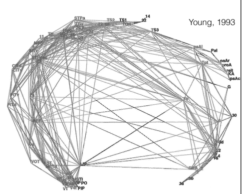
Mapping the Macaque Visual Cortex

- In 1991 Felleman and van Essen synthesized information about the connections between visual areas in the Macaque, generating a hierarchical map
- Young (1993) used multi-dimensional scaling to identify areas that exhibited similar connectivity





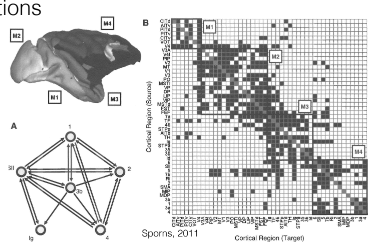
Felleman and van Essen, 1991



Young, 1993

Small Worlds in Macaque Cortex

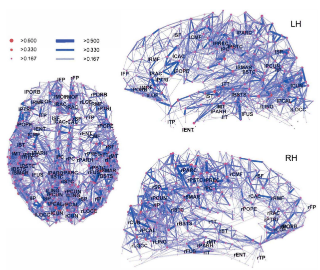
- By examining the pattern of connectivity between brain regions in the full macaque brain, Sporns and his collaborators identified a small world architecture
  - Most connections are within modules
  - But a few connections go between modules



Sporns, 2011

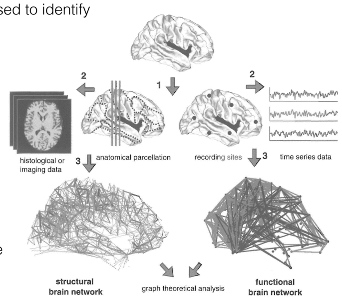
The Connectome Project

- In 2005 Sporns, Tononi, and Kotter advanced the proposal to identify the human connectome: graph representations of the structural connectivity in the human brain
- Multiple spatial scales from individual neurons to brain regions
- Macro-scale connectome to be based on structural and diffusion tensor MRI



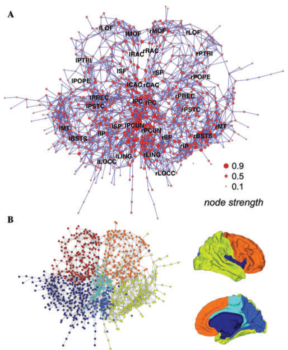
Relating Structural and Functional Maps

- The structural techniques being applied to create the human connectome and functional techniques used to identify functional networks that can be analyzed in graph theory terms
- These maps are highly correlated, indicating that the structural networks may be the basis for functional processing in the brain
- Both techniques reveal small-world organization with hubs
- There is increasing evidence that such organization can facilitate sustained complex dynamical behavior



Identifying Modules

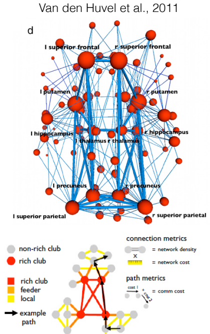
- Start with a structural connection matrix
  - Apply an algorithm (A) that treats connections like springs and minimizes total force
    - That preserves some degree of spatial organization (separation of hemispheres)
  - Indicate separate modules with colors (B) and map those on right onto anatomy of right hemisphere



Rich Club Organization in Human Cerebral Cortex

- Sporns and others discovered a small set of highly connected brain regions (the rich club) that are densely interconnected: includes portions of the precuneus, anterior and posterior cingulate cortex, superior frontal cortex, superior parietal cortex and the insula
  - Maintaining this rich club costs energy, demanding 40% of the brain's total communicative cost (Collin et al., 2013)
  - 69% of all communication paths go through the rich club
  - Physiological properties of nodes in the rich club suggest they play an integrating role
  - The rich club is hypothesized to enable efficient routing of information through local decision making

Van den Huvel et al., 2011



Van den Huvel et al., 2012

Discussion Question

Why might there be a rich club structure in the brains of higher organisms?

It might just well be an accident of the way the neurons send out projections

It provides a network through which the results of processing in one brain region can be passed on to other regions

It provides a network through which activities in multiple brain regions can be coordinated

Other