Neuronal circuits: from reconstructions to design principles or how neuroanatomy is becoming an exact science

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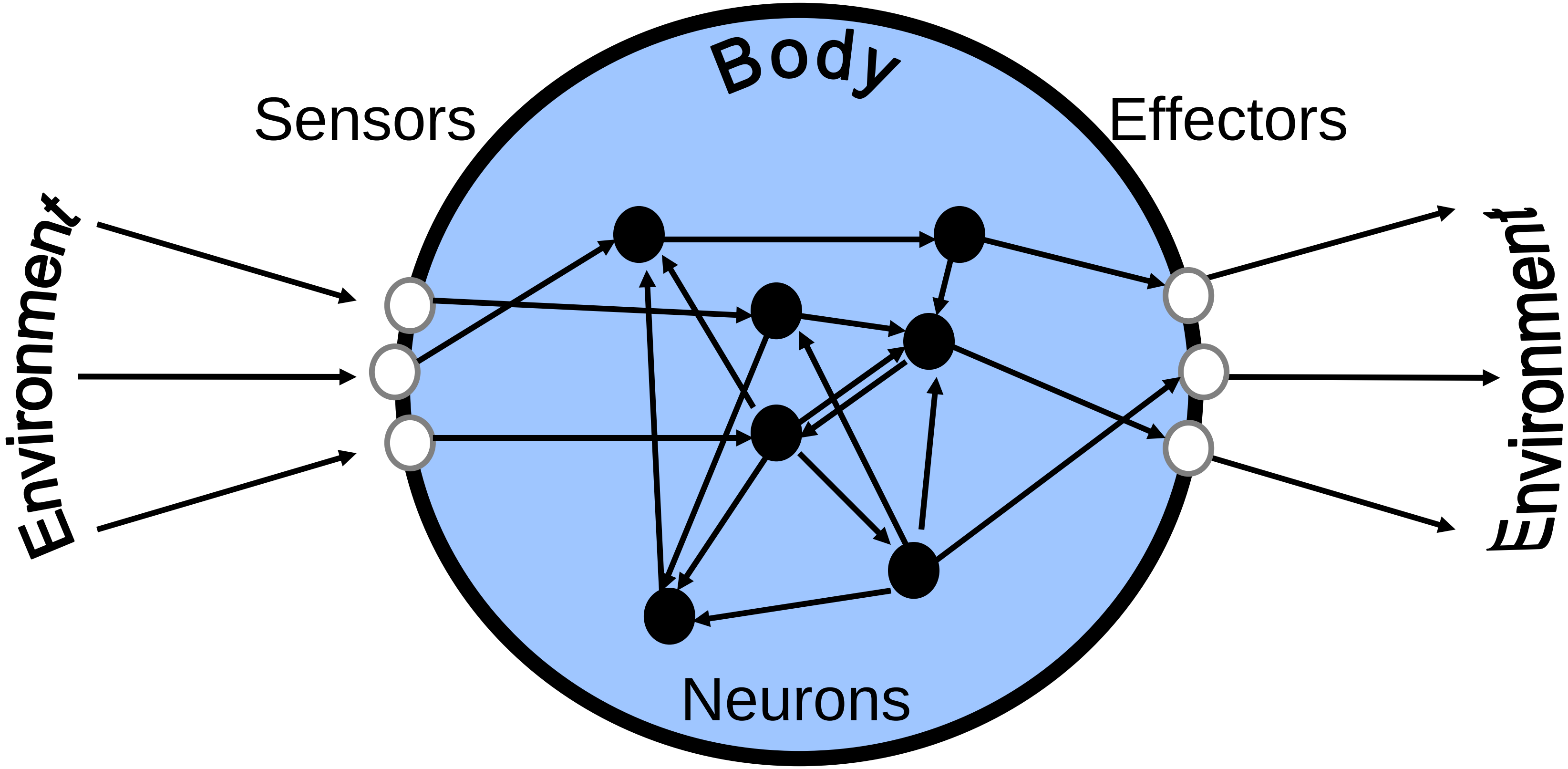
How does the brain generate behavior?



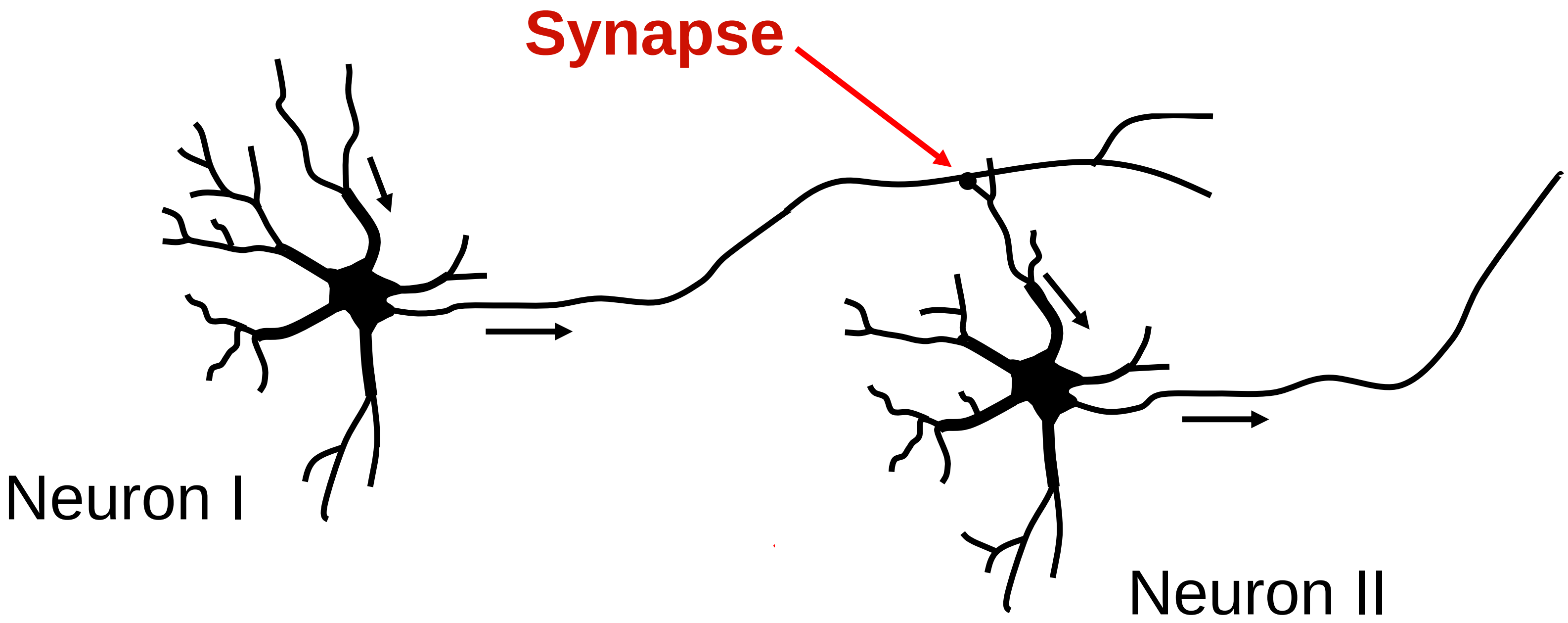
Electrical activity in neuronal circuits

Why cannot we predict behavior by modeling activity in neuronal circuits?

1. We do not know the wiring diagram

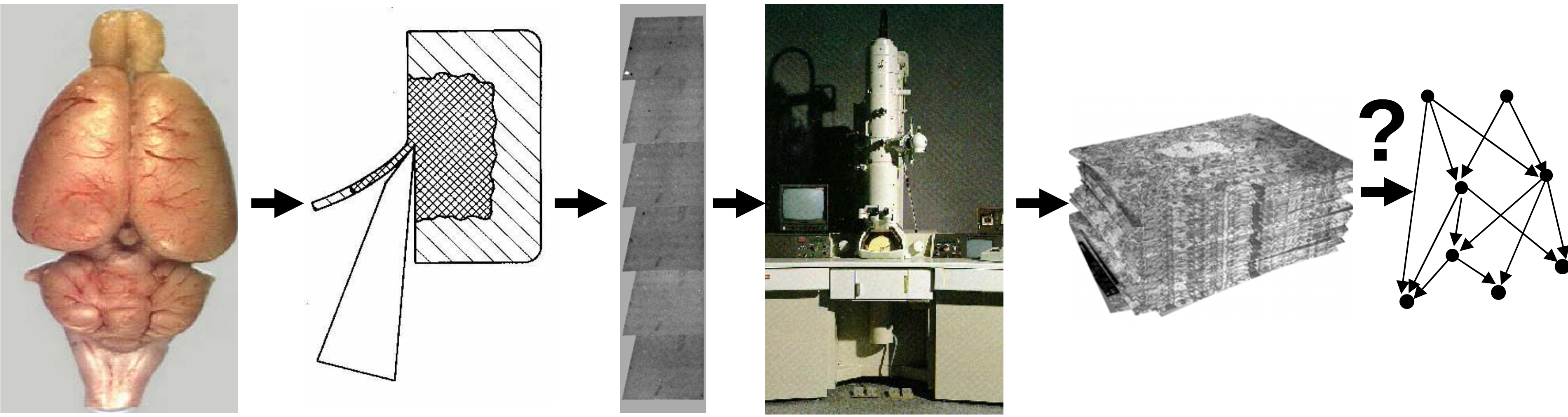
   -> circuit reconstructions

Anatomy of the circuit

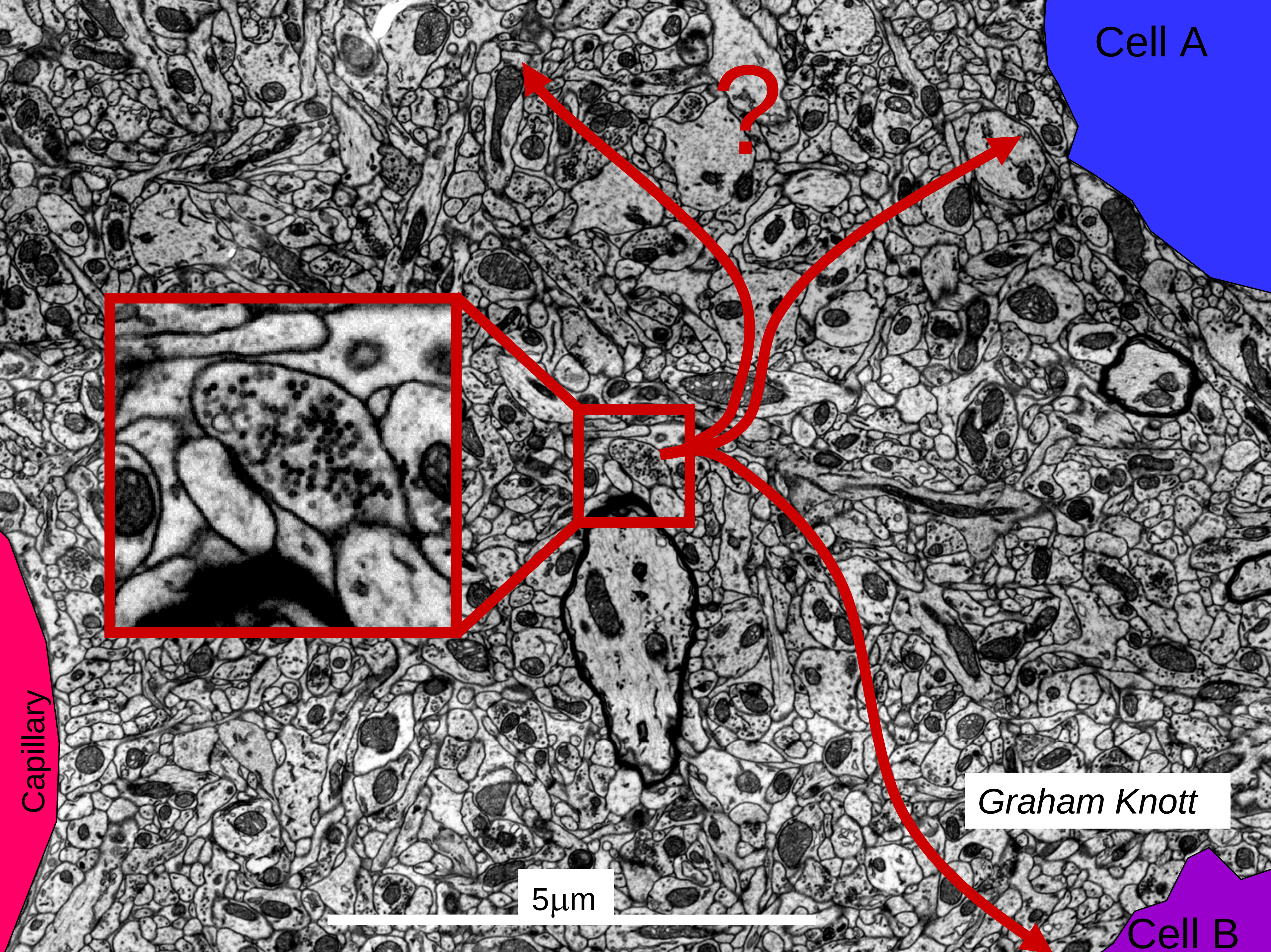


Human brain contains 10^{11} neurons connected by 10^{15} synapses

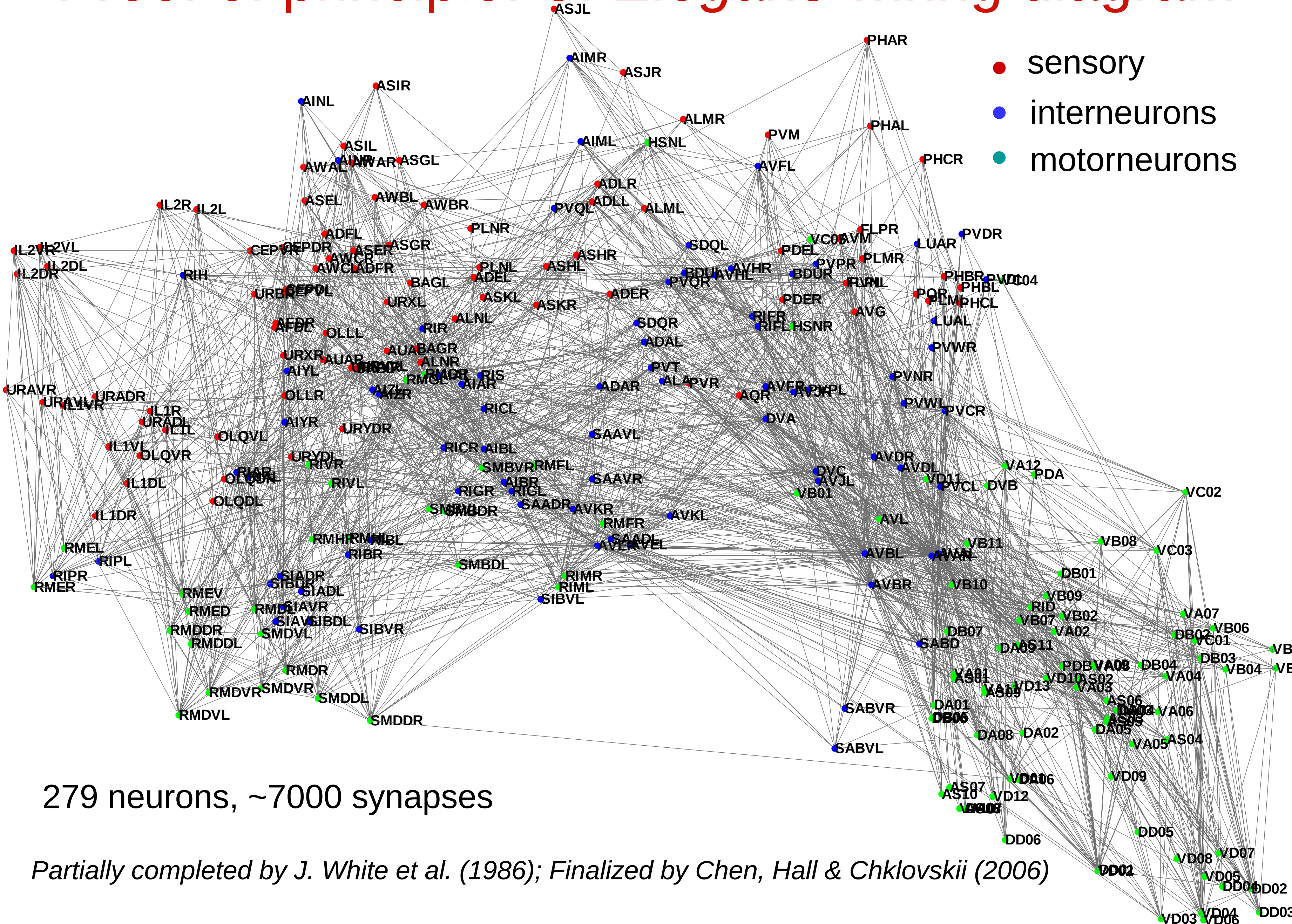
Due to sub-micron size an unequivocal identification of synapses requires the resolution of an electron microscope



Reconstructing circuits from huge datasets is a major computational challenge


Cell A
?
Capillary
Graham Knott
5μm
Cell B

Proof of principle: *C. Elegans* wiring diagram



279 neurons, ~7000 synapses

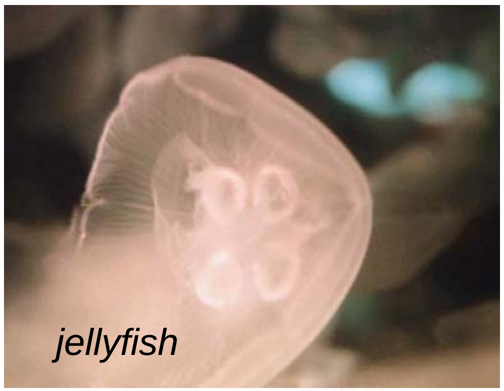
Partially completed by J. White et al. (1986); Finalized by Chen, Hall & Chklovskii (2006)

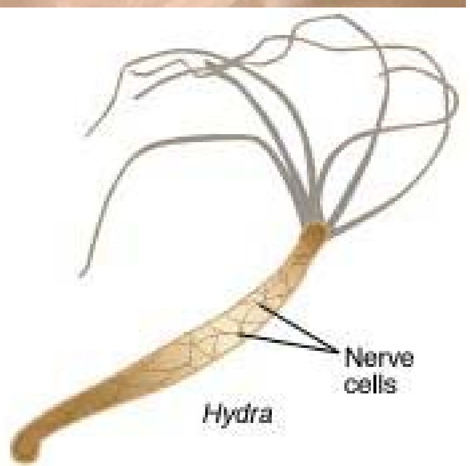
Why cannot we predict behavior by modeling activity in neuronal circuits?

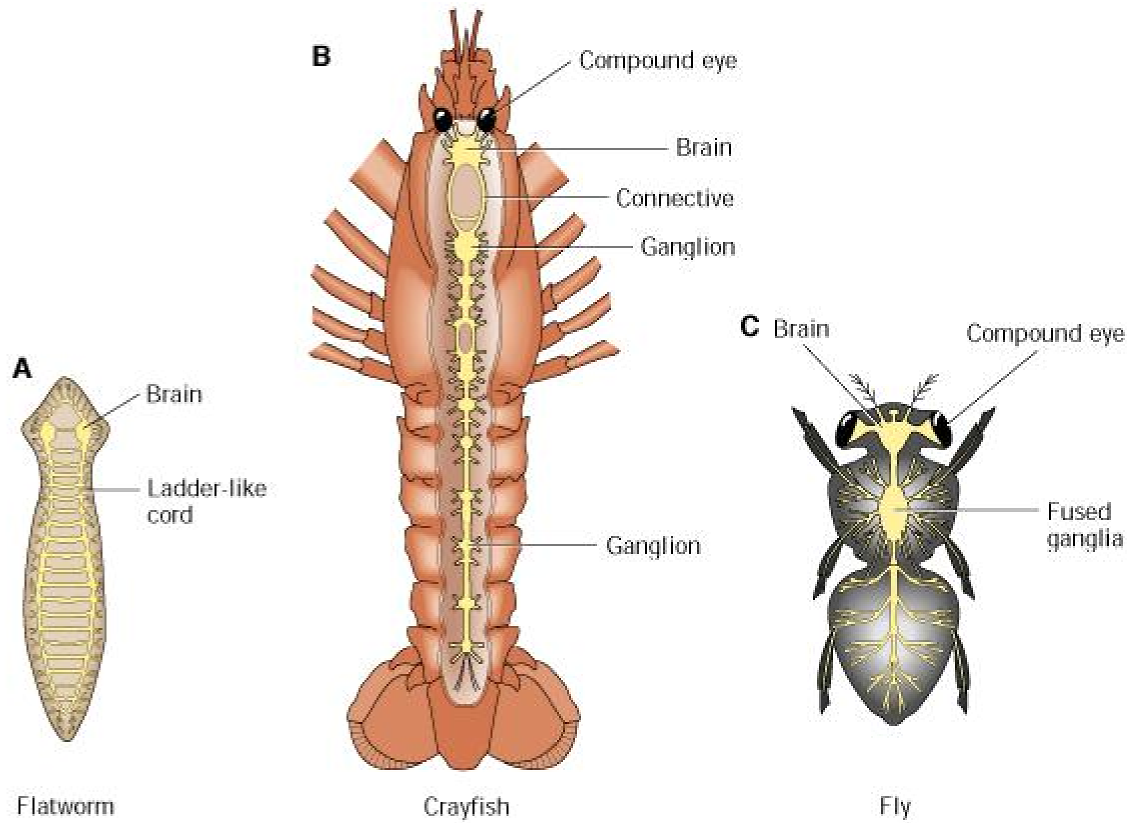
1. We do not know the wiring diagram
   -> circuit reconstructions
2. We do not know the appropriate level of abstraction

-> answers to *why* questions using constrained optimization

Distributed vs. centralized nervous systems (Cajal 1899)





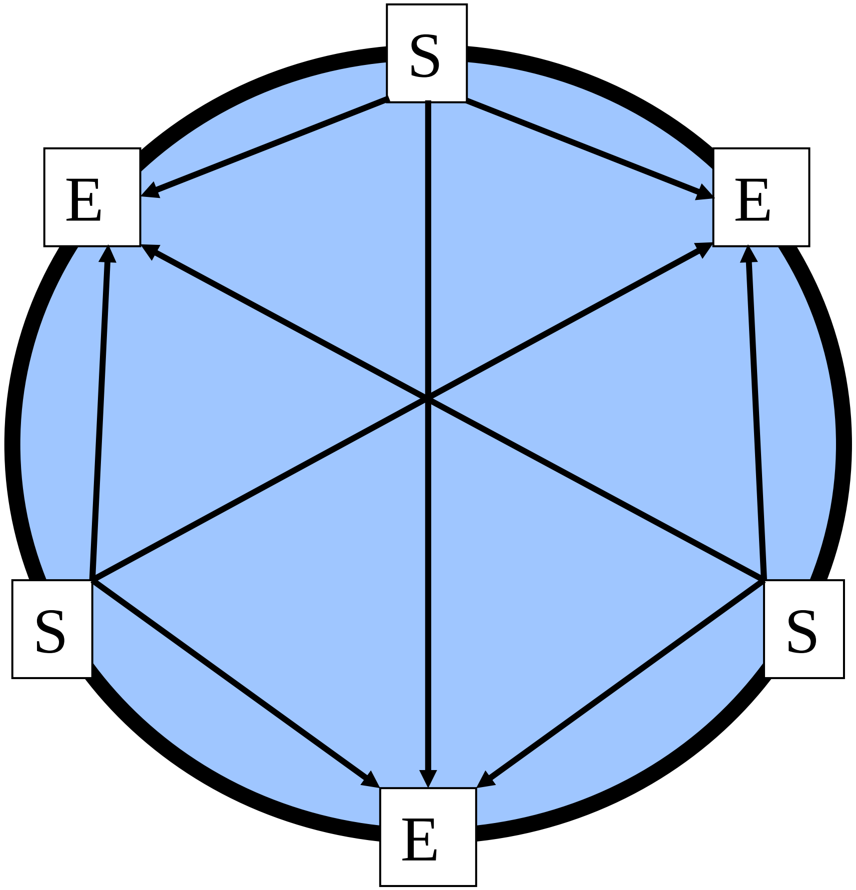


10^3 neurons

10^5 neurons

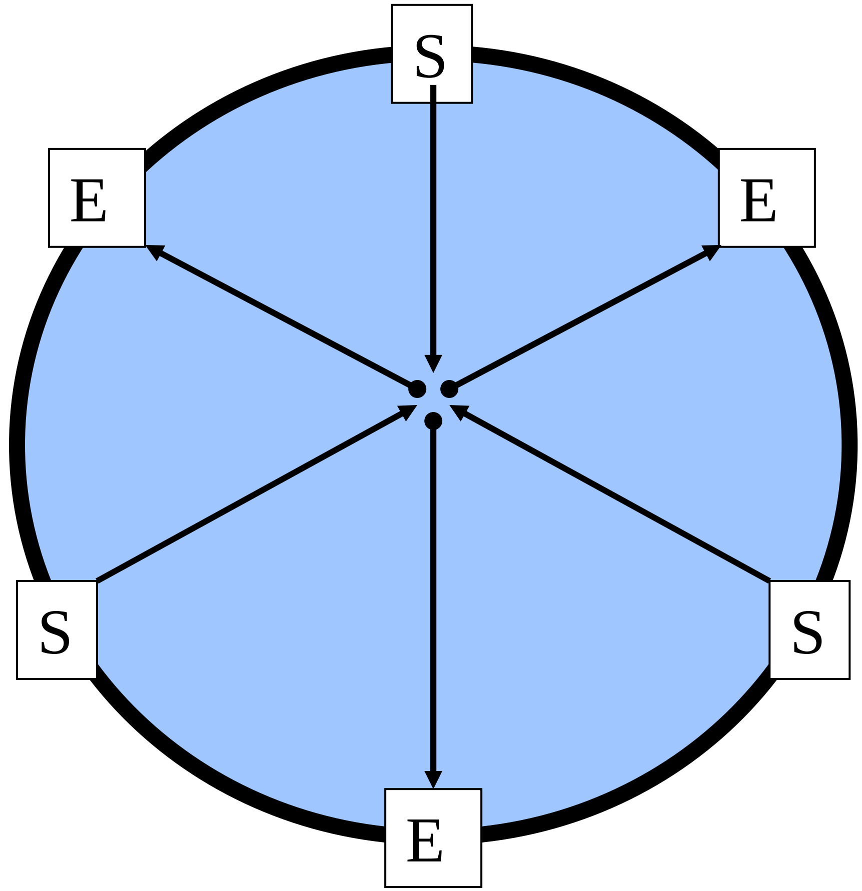
Which design is less costly?

Distributed nervous system



$$N_{Wires} = N_S N_E$$

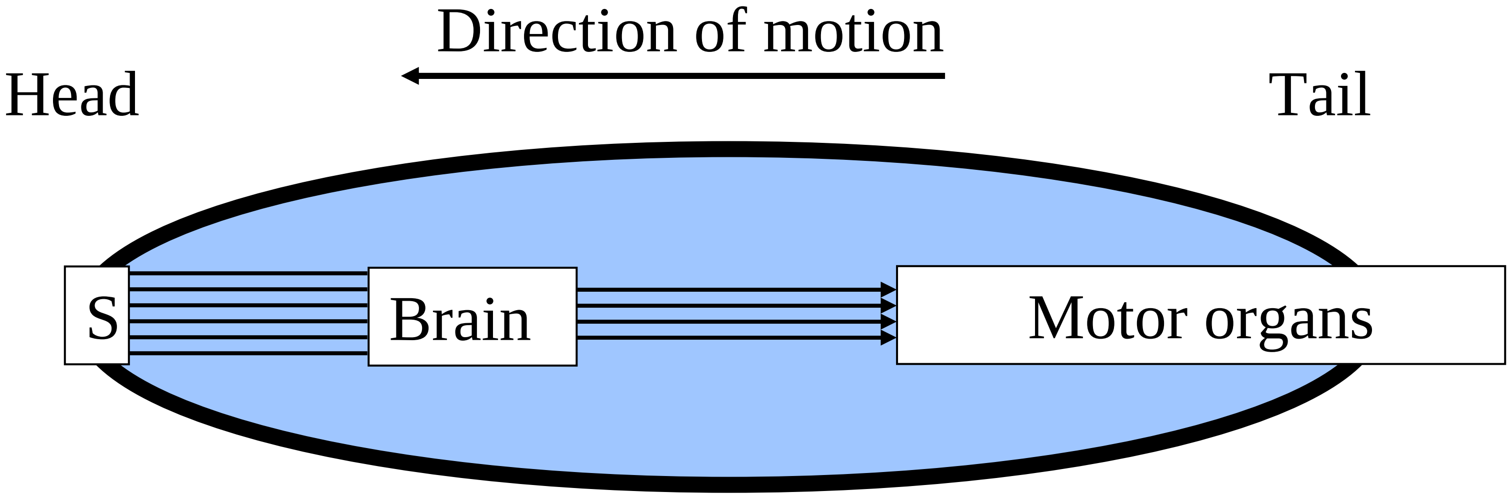
Centralized nervous system



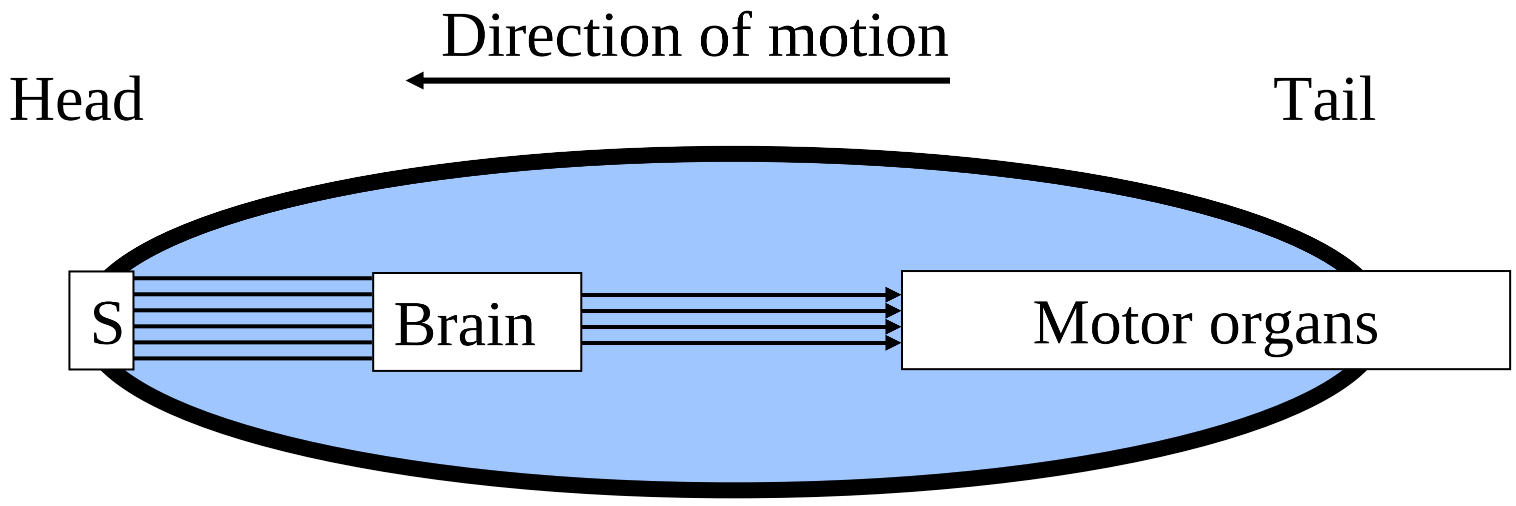
$$N_{Wires} = N_S + N_E$$

$N_S = N_E = 10^6$: 10^{12} $2\text{x}10^6$

What determines brain placement?



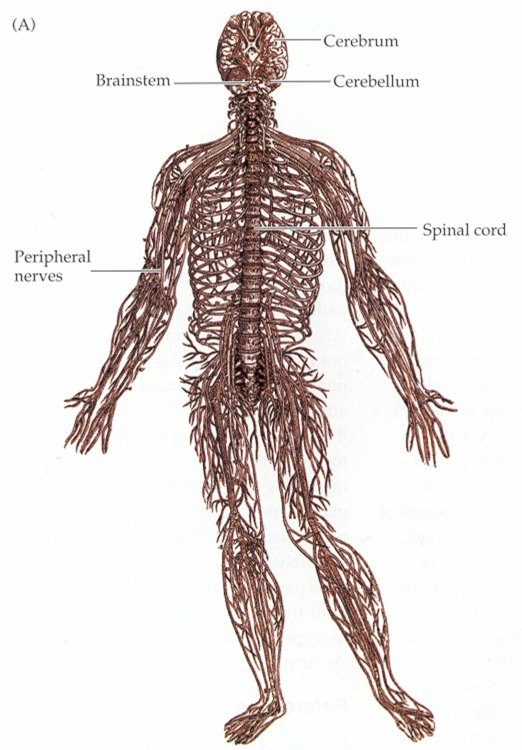
What determines brain placement?



Brain location is biased towards the dominant source of connections

Numbers of connections to the human brain

Anterior: Cranial nerves	
Olfactory	10,000K
Optic	2,000K
Oculomotor	60K
Trochlear	6K
Trigeminal	300K
Abducens	14K
Facial	20K
Cochlear	60K
Vestibular	40K
Glossopharyngeal	7K
Vagus	70K
Accessory	7K
Hypoglossal	15K

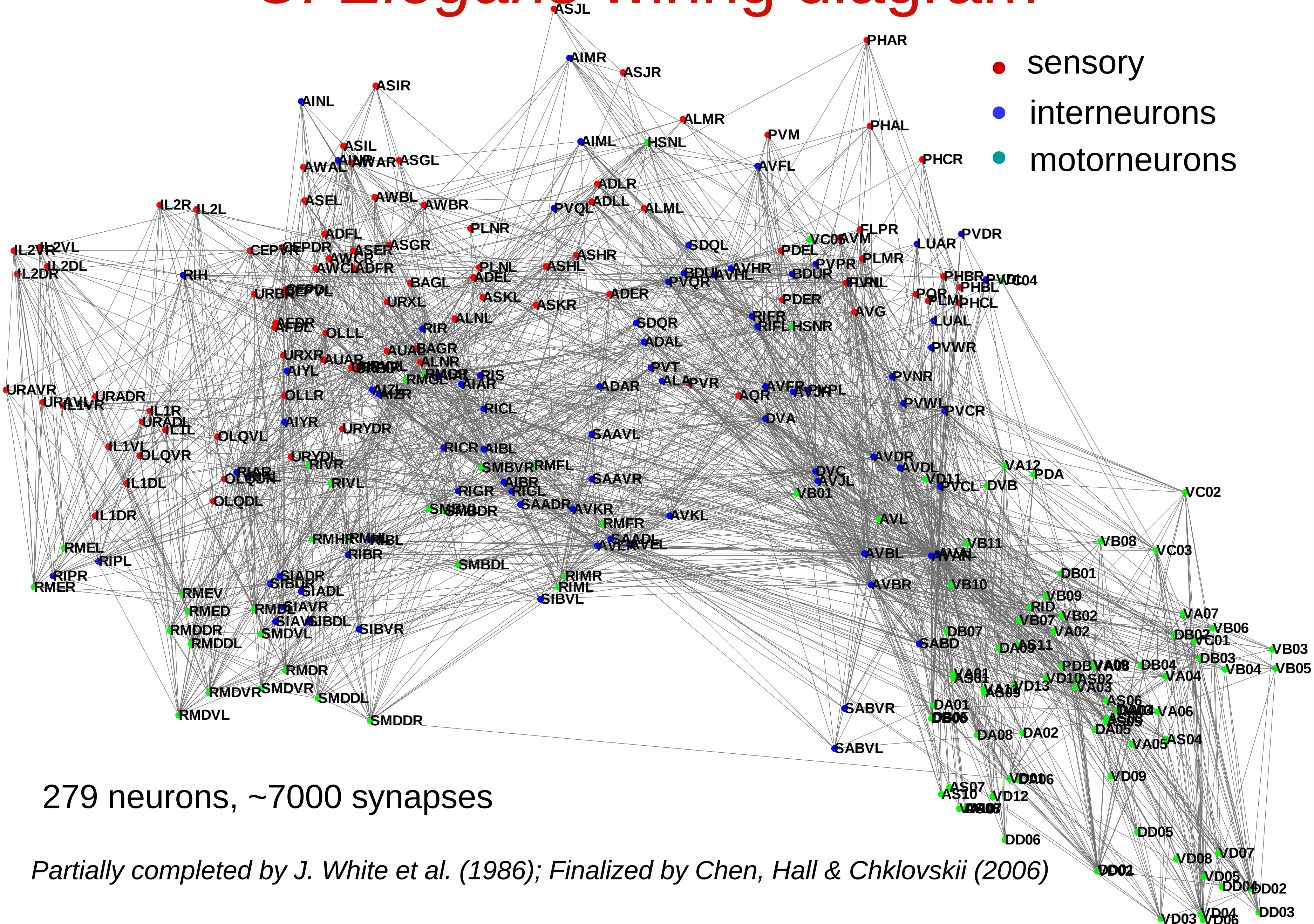


Posterior: Spinal cord	
Dorsal	2,000K
Ventral	400K

Anterior/posterior ratio > 1 is consistent with forward brain placement

Cherniak, 1994

C. Elegans wiring diagram



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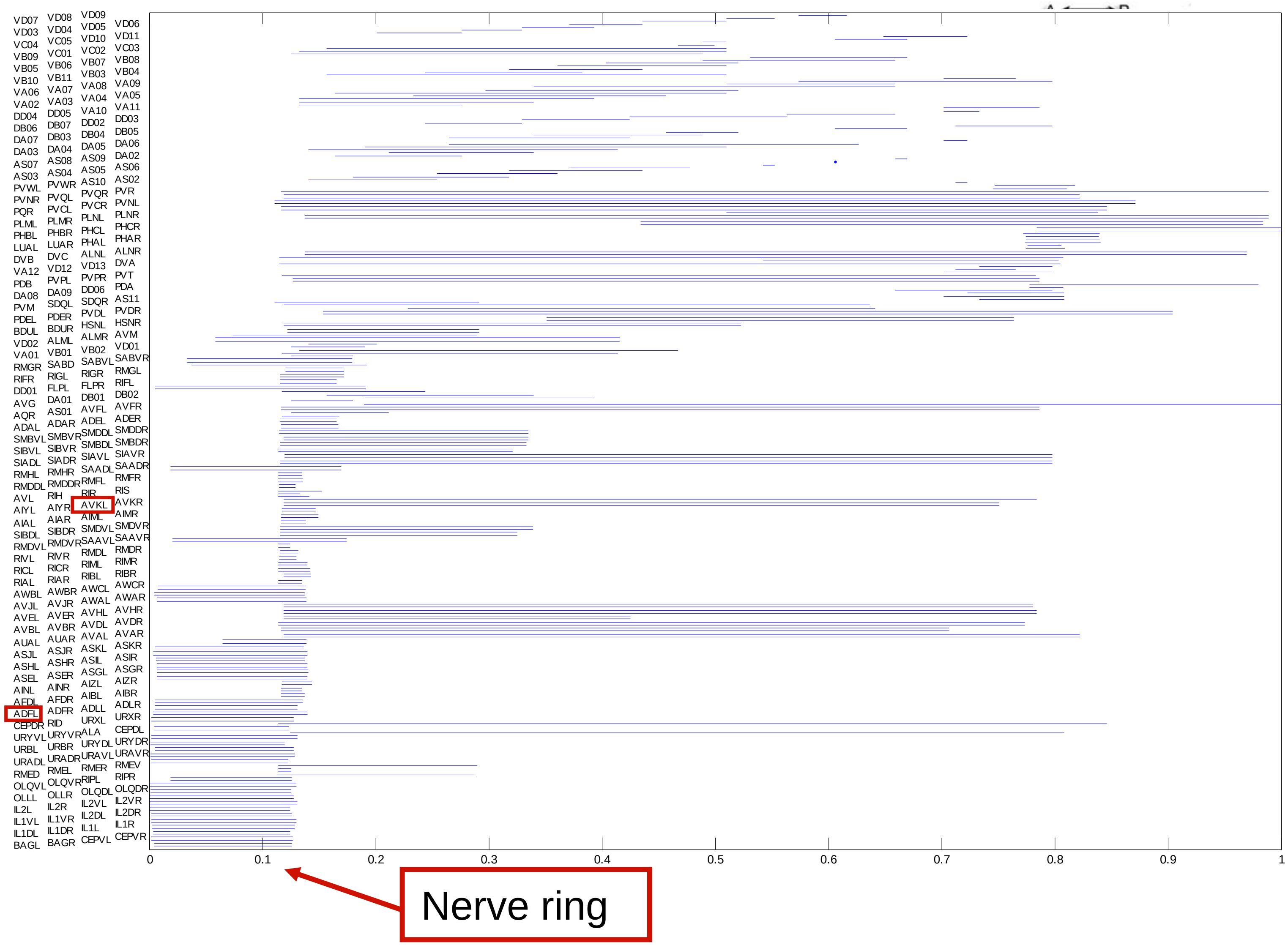
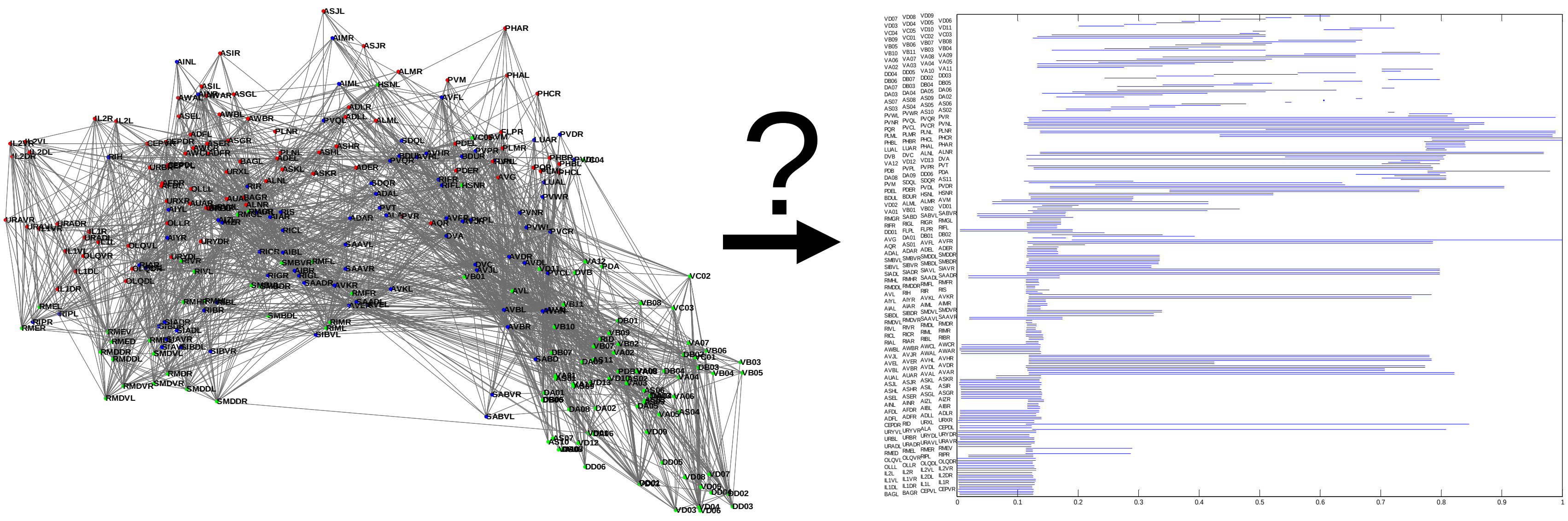
C. elegans neuronal layout reduced to 1D



Can the wiring diagram predict neuronal shape and layout?

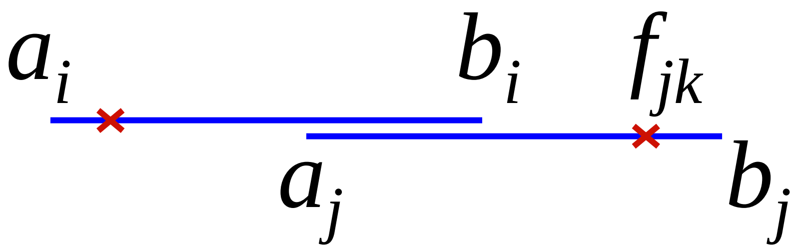


Method: Minimizing the cost of wiring

Wiring optimization approach

- Minimize total wiring length:

$$L = \sum_i | b_i - a_i |$$



- Given connectivity constraints:

If neurons i and j are connected

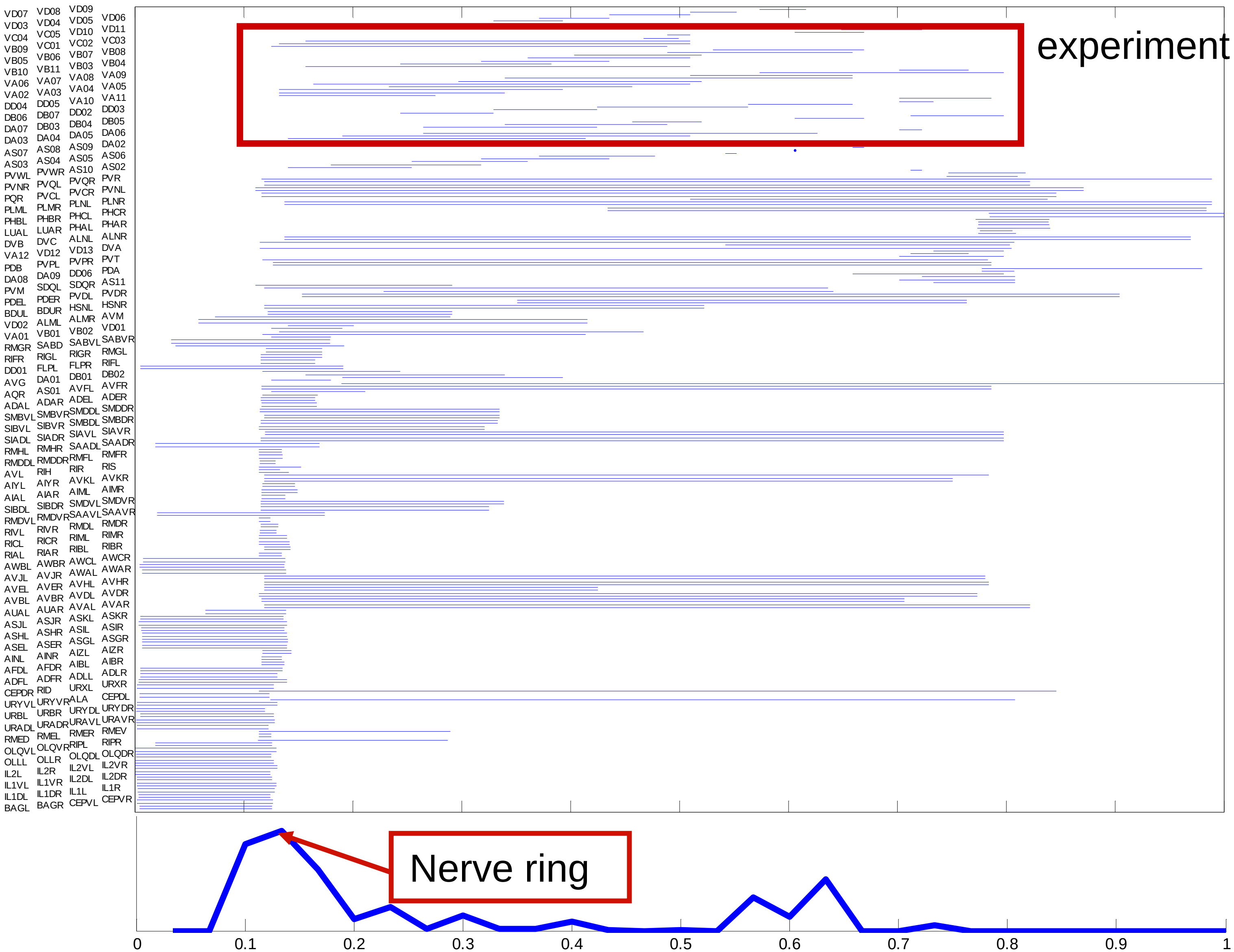
$$a_j \leq b_i$$

$$a_i \leq b_j$$

If neuron j has a sensory ending or a neuromuscular junction

$$a_j \leq f_{jk} \leq b_j$$

Optimized layout is close to actual

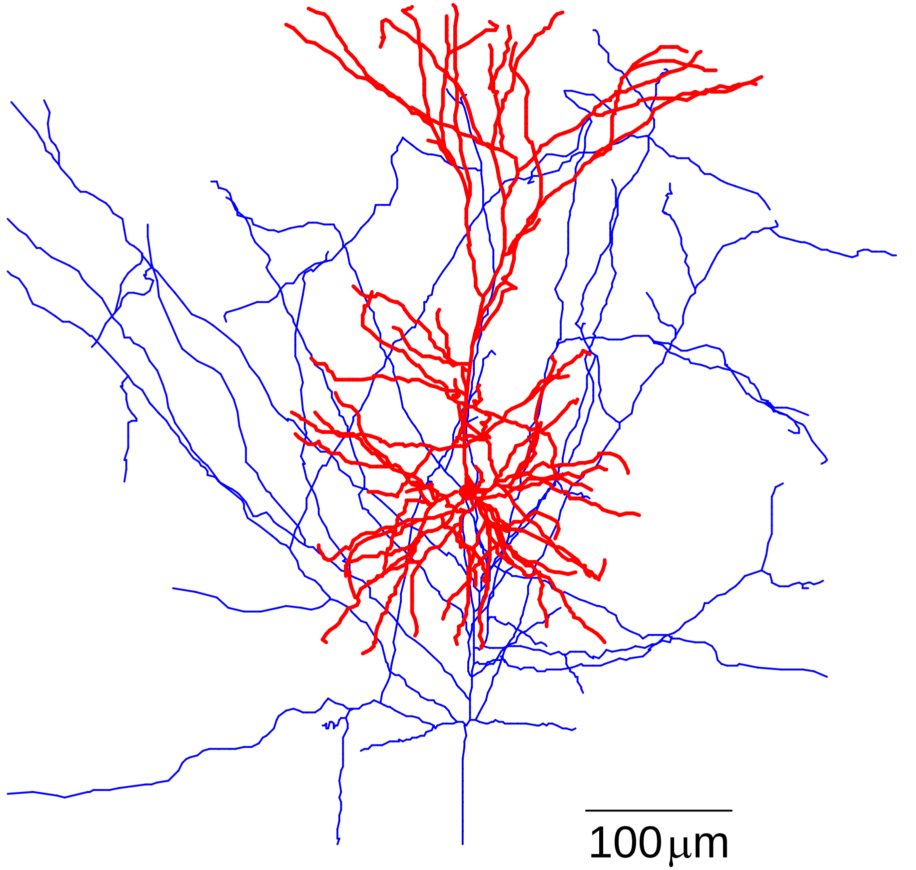


Is wiring diagram an appropriate level of abstraction for understanding brain function?

- Neurons can be represented as network nodes characterized by a single parameter (membrane potential)
- Neurons contain electrically coupled compartments characterized by multiple parameters and perform complicated computations determined by their shape and the location of synapses on a neuron

Our success in predicting neuronal shape and layout from the wiring diagram points towards the first scenario

What determines the shape of axons and dendrites in cortical neurons?



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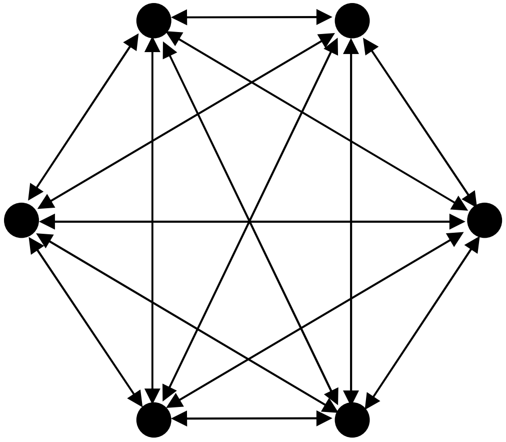
Although the shape of cortical neurons is different from those in *C. elegans*, it is also subject to wiring optimization

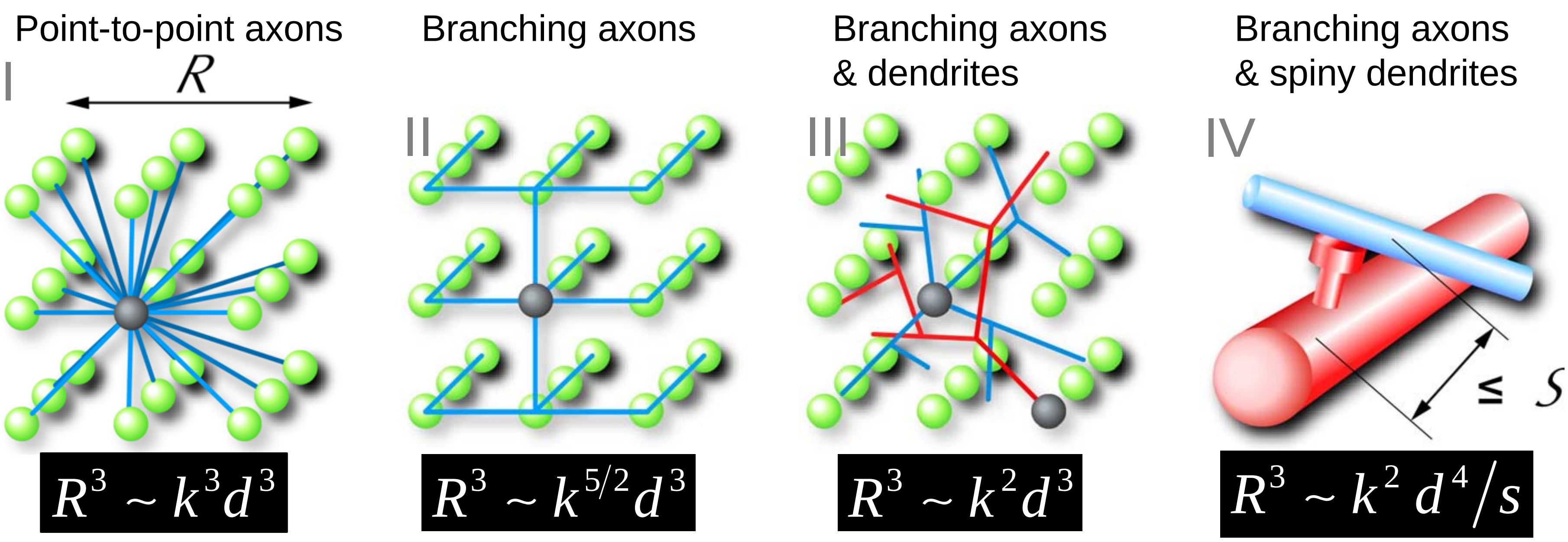
Wiring problem

What is the volume of the all-to-all connected network of *k* neurons with wires of diameter *d* ?

Example, $k = 6$:



Wiring designs for an all-to-all network

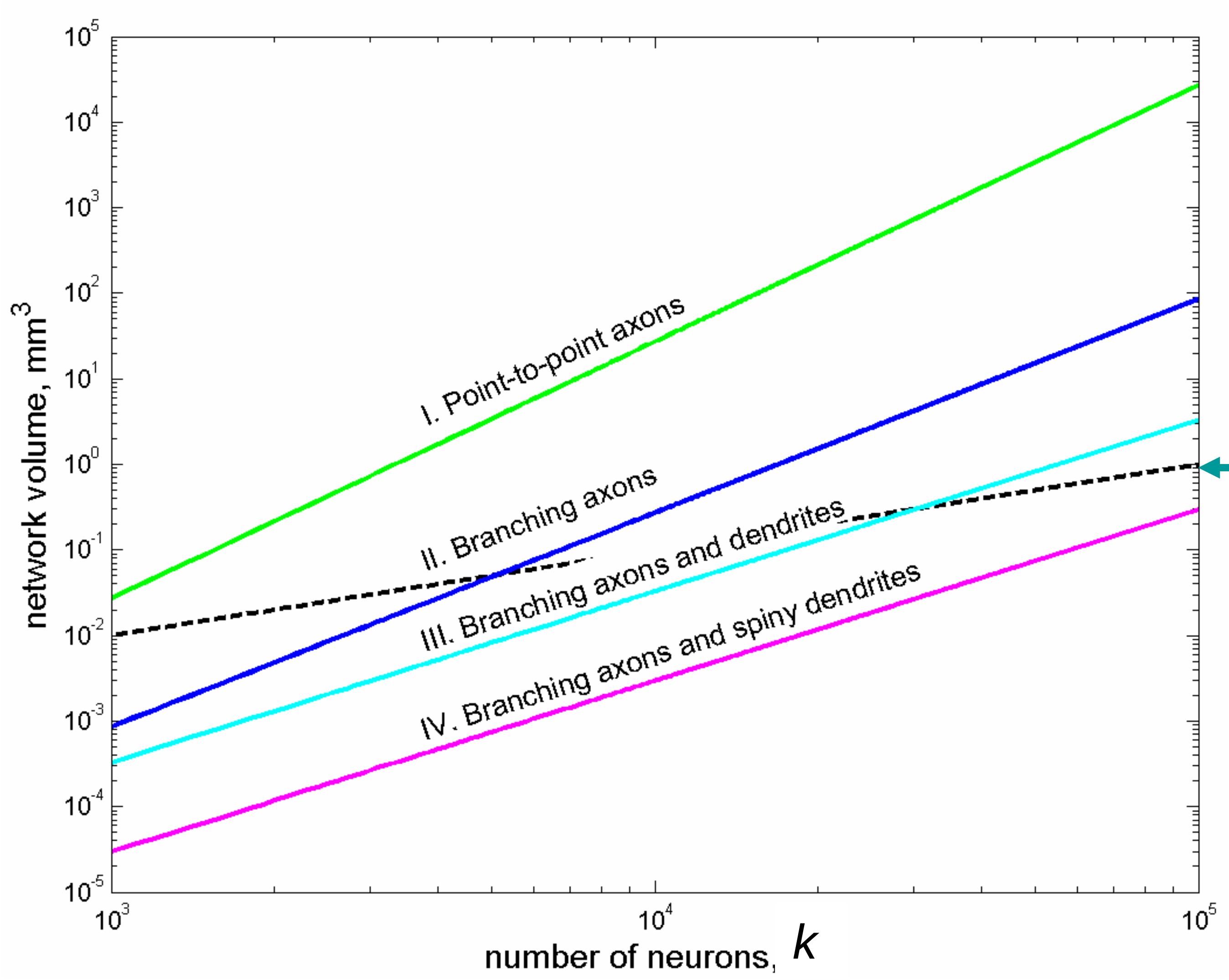


Cortical column: $k=10^5$, $d=0.3\mu m;1\mu m$, $s=2.5\mu m$, $R=1mm$

30,000mm^3 100mm^3 2mm^3 0.6mm^3

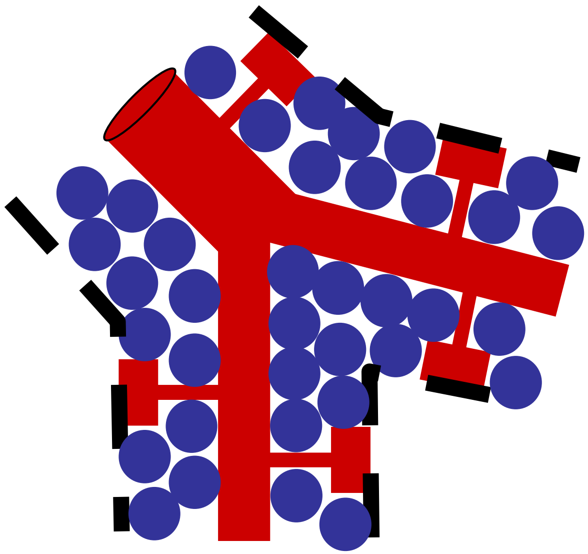
Chklovskii, 2004

Network volume for different designs

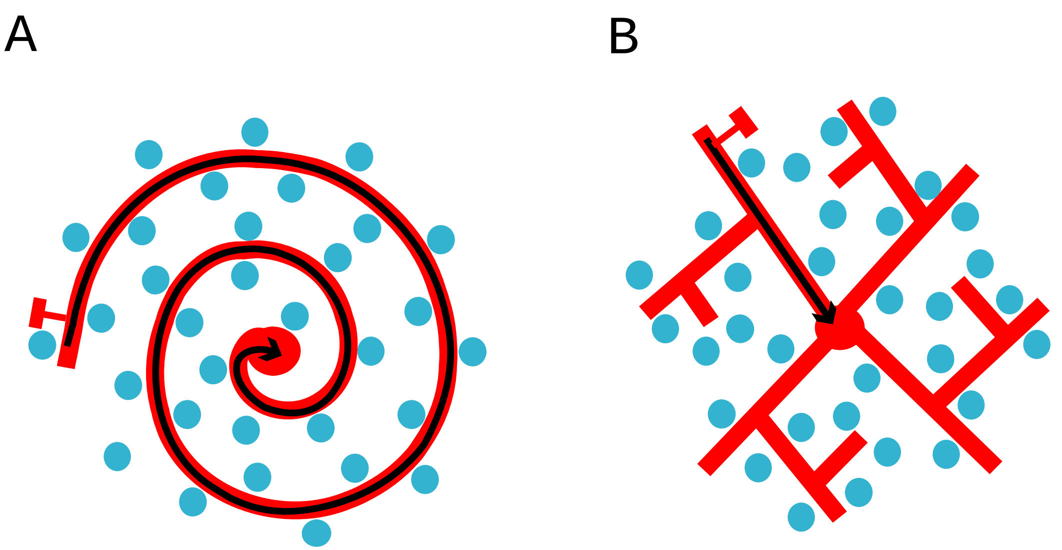


Actual volume

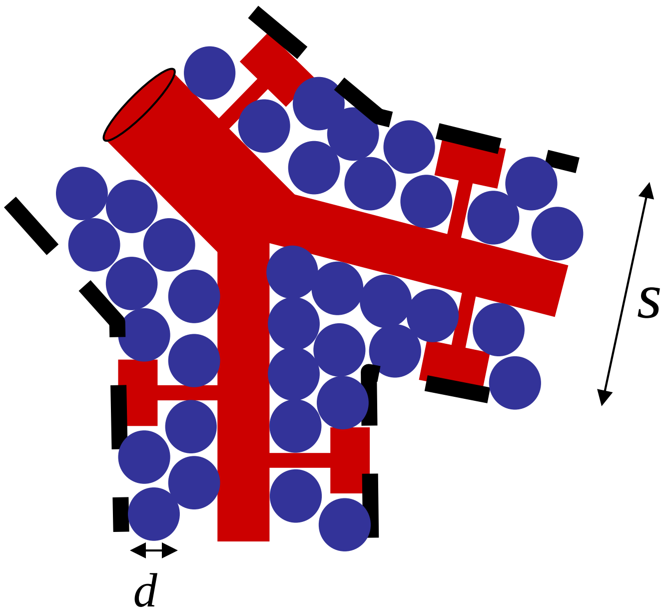
Dendrites should be long enough for axons to fit within the spine-reach zone - the airport terminal theory



Branching minimizes path length from synapses to cell body



Minimal length of a dendrite with N potential synapses: $l \sim kd^2/s$



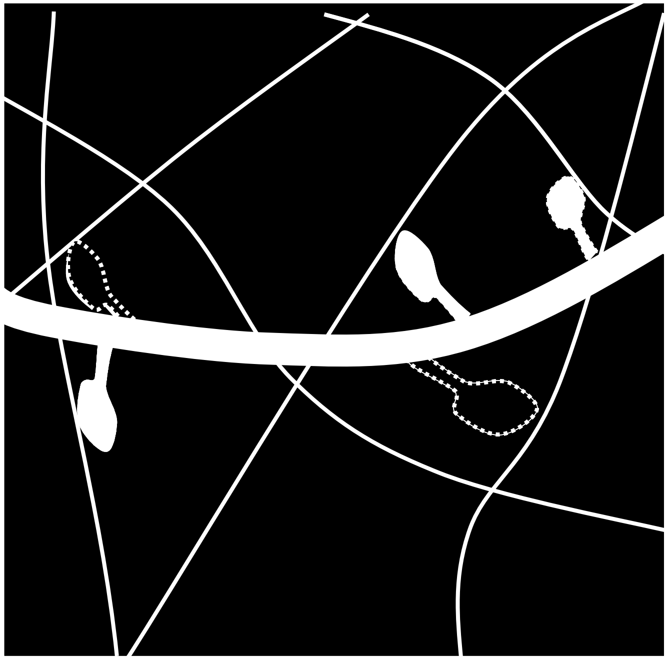
Dendrites: k=10^5 d=0.3μm s=2.5μm $\Rightarrow l$=4mm

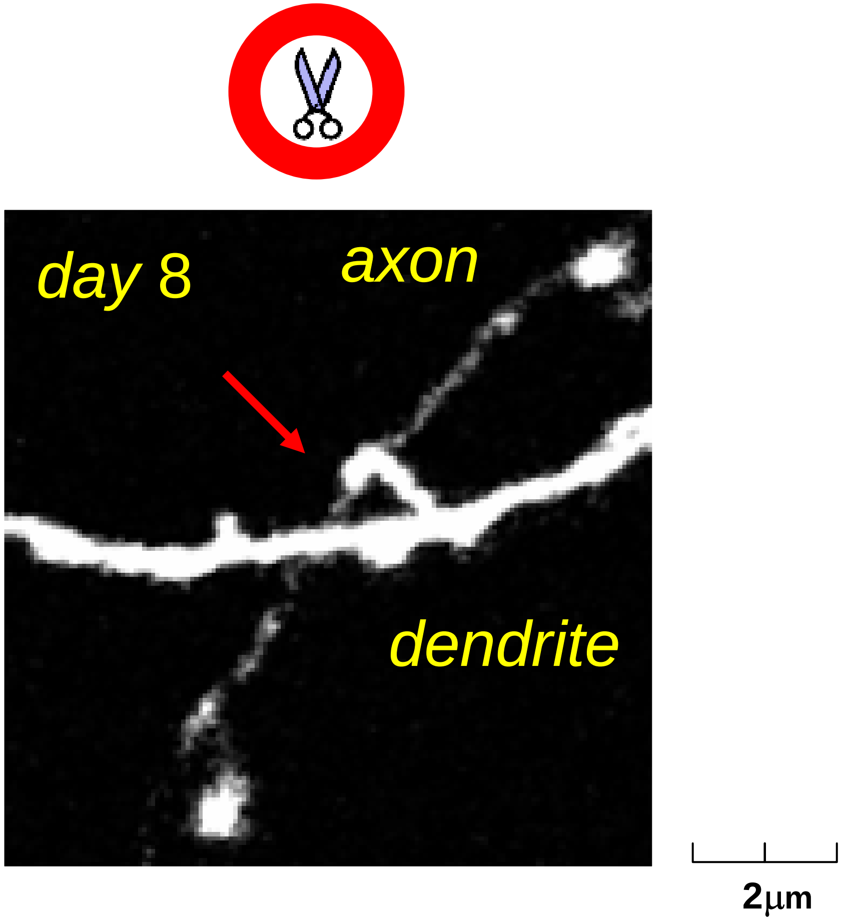
Axons: k=10^5 d=1μm s=2.5μm $\Rightarrow l$=4cm

More precise measurements revealed an excess of available axons relative to synapses

(Stepanyants, Hof, Chklovskii, 2002)

Small synapse-to-available axon ratio ensures room for synapse re-arrangement

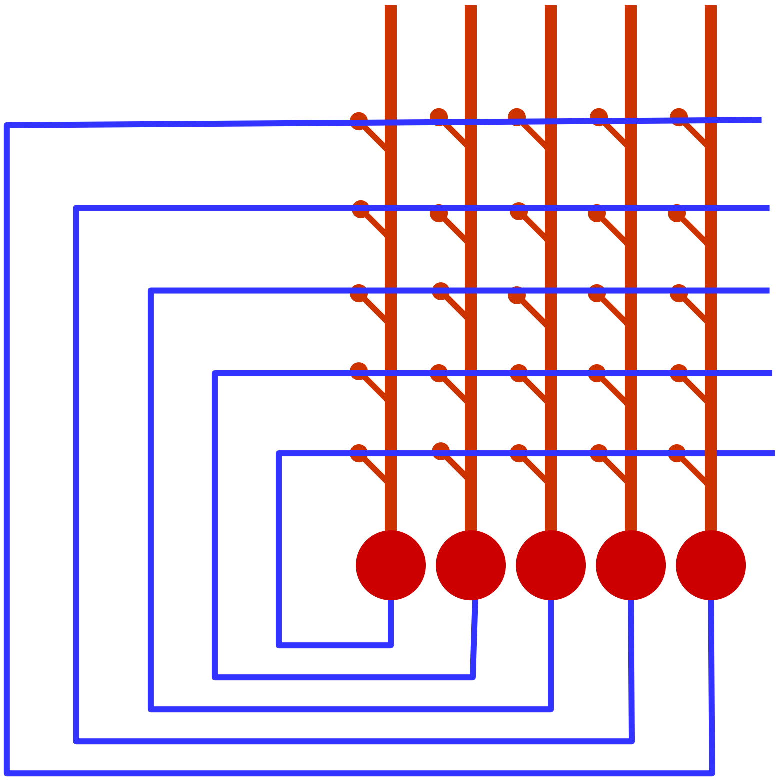




Stepanyants, Hof, Chklovskii, 2002

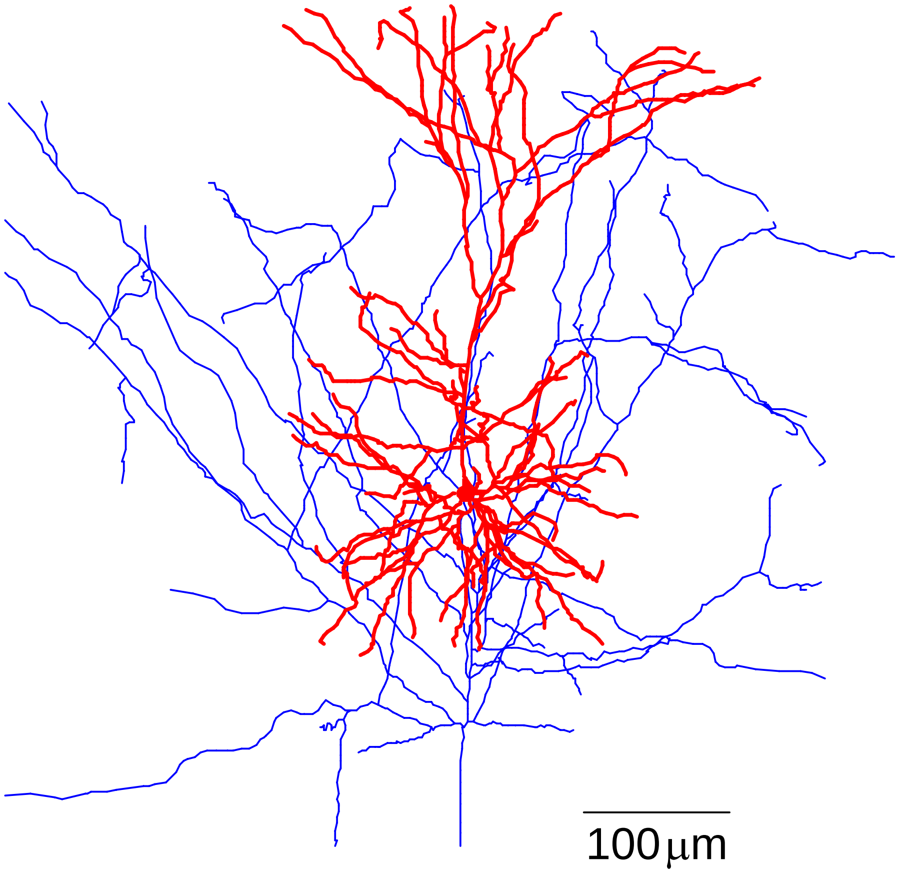
Trachtenberg, Chen, Knott, Feng, Sanes, Welker, Svoboda, 2002

The number of available circuits quantifies information storage capacity



Sparse network has high information storage capacity

The shape of cortical neurons minimizes wiring cost and maximizes the number of potential connectivity patterns



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Summary

- We perform large-scale reconstructions of neuronal circuits, a necessary step to understand brain function
- We explain brain design using optimization principles such as minimum wiring cost and maximum information storage capacity, which will help building models of brain function

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