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.
Proof of principle: *C. Elegans* wiring diagram

- sensory
- interneurons
- motorneurons

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)

- Jellyfish: 10^3 neurons
- Hydra: 10^3 neurons
- Flatworm: 10^5 neurons
- Crayfish: 10^5 neurons
- Fly: 10^5 neurons
Which design is less costly?

- Distributed nervous system
  
  \[ N_{\text{Wires}} = N_S N_E \]
  
  \[
  N_S = N_E = 10^6: \quad 10^{12}
  \]

- Centralized nervous system
  
  \[ N_{\text{Wires}} = N_S + N_E \]
  
  \[
  2 \times 10^6
  \]
What determines brain placement?

Direction of motion

Head

Tail

S

Brain

Motor organs
What determines brain placement?

Brain location is biased towards the dominant source of connections.
Numbers of connections to the human brain

<table>
<thead>
<tr>
<th>Anterior: Cranial nerves</th>
<th>Posterior: Spinal cord</th>
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</thead>
<tbody>
<tr>
<td>Olfactory</td>
<td>Dorsal</td>
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<tr>
<td>Optic</td>
<td>2,000K</td>
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<tr>
<td>Oculomotor</td>
<td>Ventral</td>
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<tr>
<td>Trochlear</td>
<td>400K</td>
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<td>Trigeminal</td>
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<td>Abducens</td>
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<td>Facial</td>
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<td>Cochlear</td>
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<td>Vestibular</td>
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<td>Vagus</td>
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<tr>
<td>Accessory</td>
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<tr>
<td>Hypoglossal</td>
<td></td>
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</tbody>
</table>

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

Cherniak, 1994
C. Elegans wiring diagram

- sensory
- interneurons
- motorneurons

279 neurons, ~7000 synapses

Partially completed by J. White et al. (1986); Finalized by Chen, Hall & Chklovskii (2006)
C. elegans neuronal layout reduced to 1D

Nerve ring
Can the wiring diagram predict neuronal shape and layout?

Method: Minimizing the cost of wiring
Wiring optimization approach

• Minimize total wiring length:

\[ L = \sum_{i} |b_i - a_i| \]

\[ a_i \]
\[ a_j \]
\[ b_i \]
\[ f_{jk} \]
\[ b_j \]

• 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

Nerve ring
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?

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

Point-to-point axons

Branching axons

Branching axons & dendrites

Branching axons & spiny dendrites

\[ R^3 \sim k^3 d^3 \]

\[ R^3 \sim k^{5/2} d^3 \]

\[ R^3 \sim k^2 d^3 \]

\[ R^3 \sim k^2 d^4 / s \]

Cortical column: \( k=10^5 \), \( d=0.3 \mu m; 1 \mu m \), \( s=2.5 \mu m \), \( R=1 \text{mm} \)

30,000mm\(^3\)  
100mm\(^3\)  
2mm\(^3\)  
0.6mm\(^3\)

Chklovskii, 2004
Network volume for different designs

- I. Point-to-point axons
- II. Branching axons
- III. Branching axons and dendrites
- IV. Branching axons and spiny dendrites
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: $k=10^5$ $d=0.3\mu m$ $s=2.5\mu m$ $\Rightarrow l=4mm$

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

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.
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
Acknowledgements

• Armen Stepanyants, CSHL (now at Northeastern)
• Yuriy Mishchenko, CSHL
• Beth Chen, CSHL
• Quan Wen, CSHL
• Lav Varshney, MIT