Evolution as the blind engineer: wiring minimization in the brain

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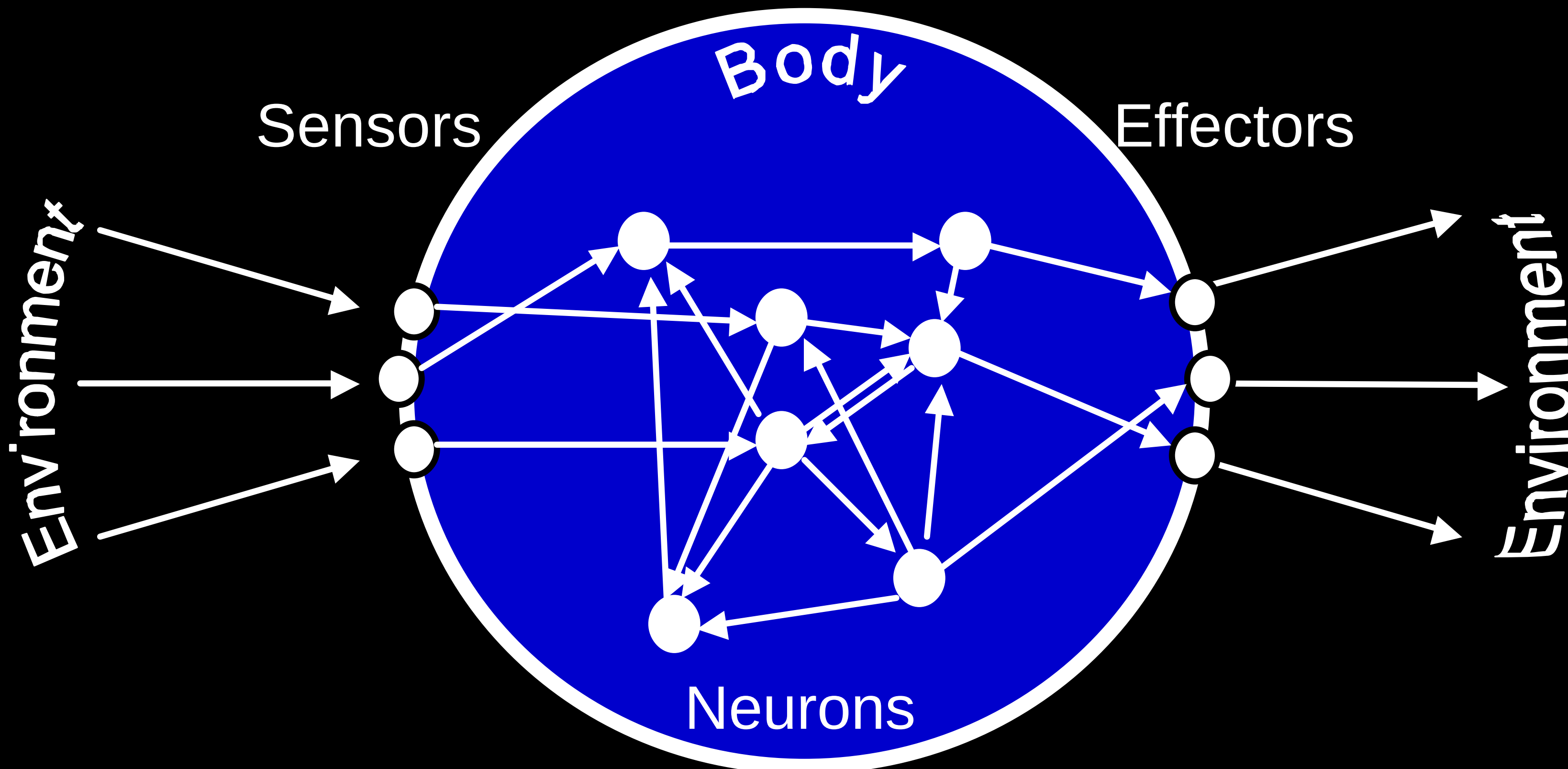
Optimization is a powerful theoretical tool for understanding brain design

- Evolutionary theory: survival of the fittest
- Maximize fitness to predict animal design
- Fitness ~ functionality – cost
- Minimize cost for given functionality

Brain as a neuronal network



Network functionality is captured by neuronal connectivity

Evolutionary cost of wiring

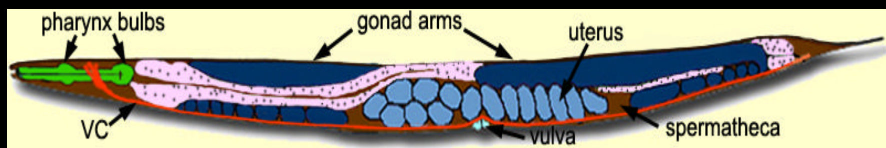
- Signal delay and attenuation
- Metabolic requirements
- Space constraints
- Guidance defects in development

Wiring cost grows with the distance between connected neurons

For given functionality minimize wiring length

C. elegans as Model System

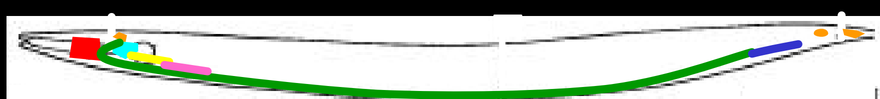
Anterior Posterior



1mm

Nervous system

A



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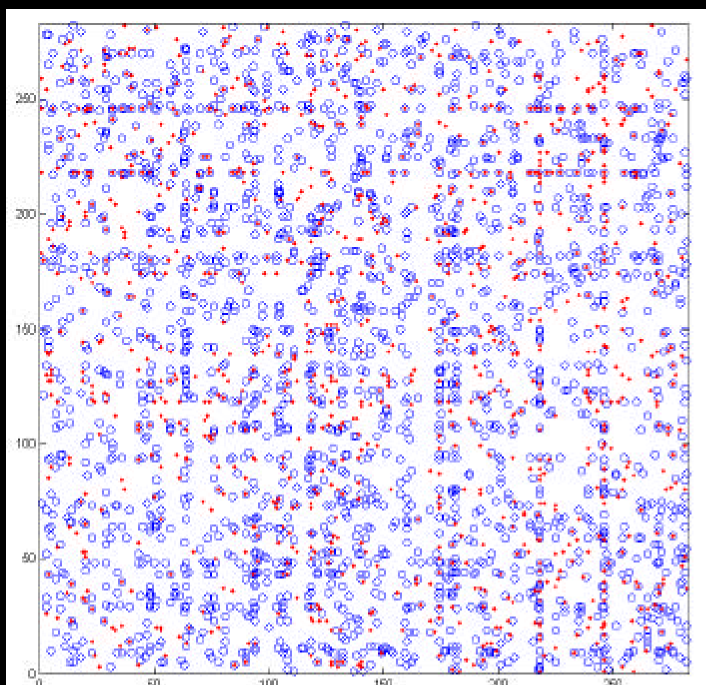
- Well documented
  - Wiring diagram
  - Neuronal map
- Simple system
  - 302 neurons
  - 11 gangalia
- One-dimensional problem

Can wiring minimization predict neuronal placement?

From the wiring diagram…

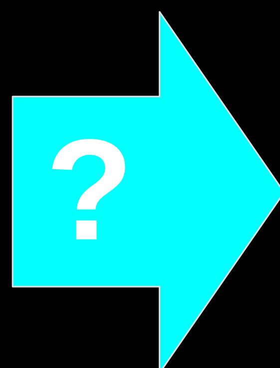


Pre-synaptic Neuron

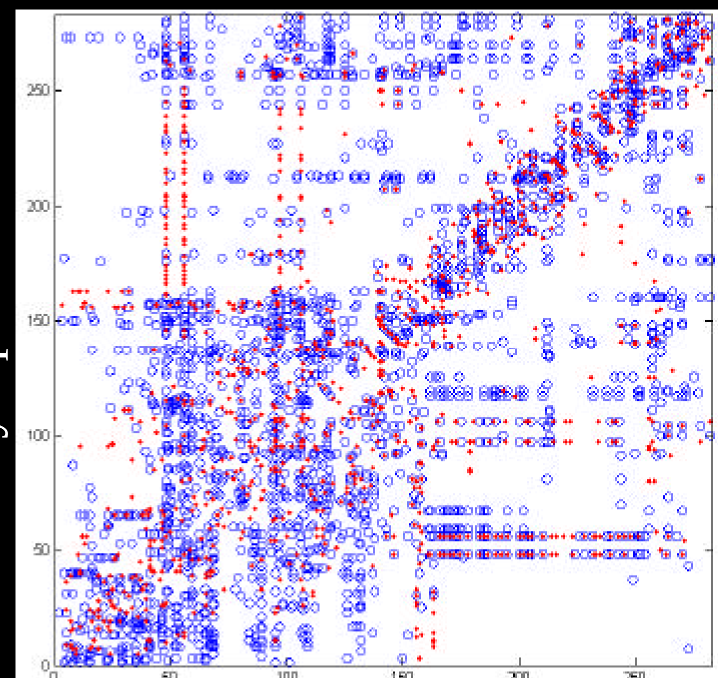
Post-synaptic Neuron

○ Chemical synapse

• Electrical synapse



To the actual placement…



Pre-synaptic Neuron

Post-synaptic Neuron

A  P

Quadratic Cost Function

$$E = \left[\frac{1}{2} \sum_{i,j} A_{ij} (r_i - r_j)^2 \right] + \left[\sum_{k,l} B_{kl} (r_k - f_l)^2 \right]$$

Internal wiring cost (first bracket); External constraints (second bracket)

r_i = position of neuron i

f_l = position of sensor/effector l

A_{ij} = neuron i to neuron j connection matrix

B_{kl} = neuron k to sensor/effector l connection matrix

For symmetrized A, rewrite into matrix form…

$$E = [r^T \underbrace{(D_A - A)}_{L} r] + [r^T D_B r - 2 r^T B f + const]$$

L: Laplacian of A

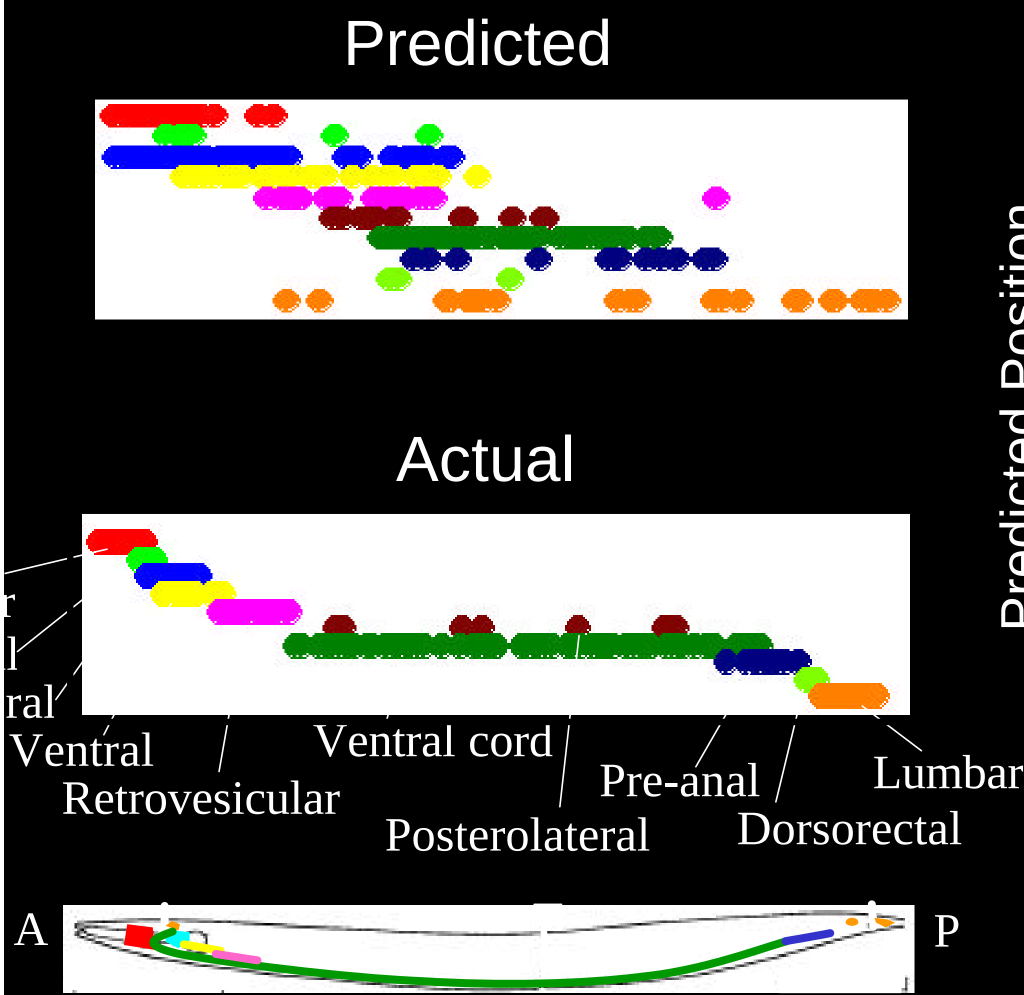
$$D_{A\,ij} = d_{ij} \sum_p A_{ip}$$

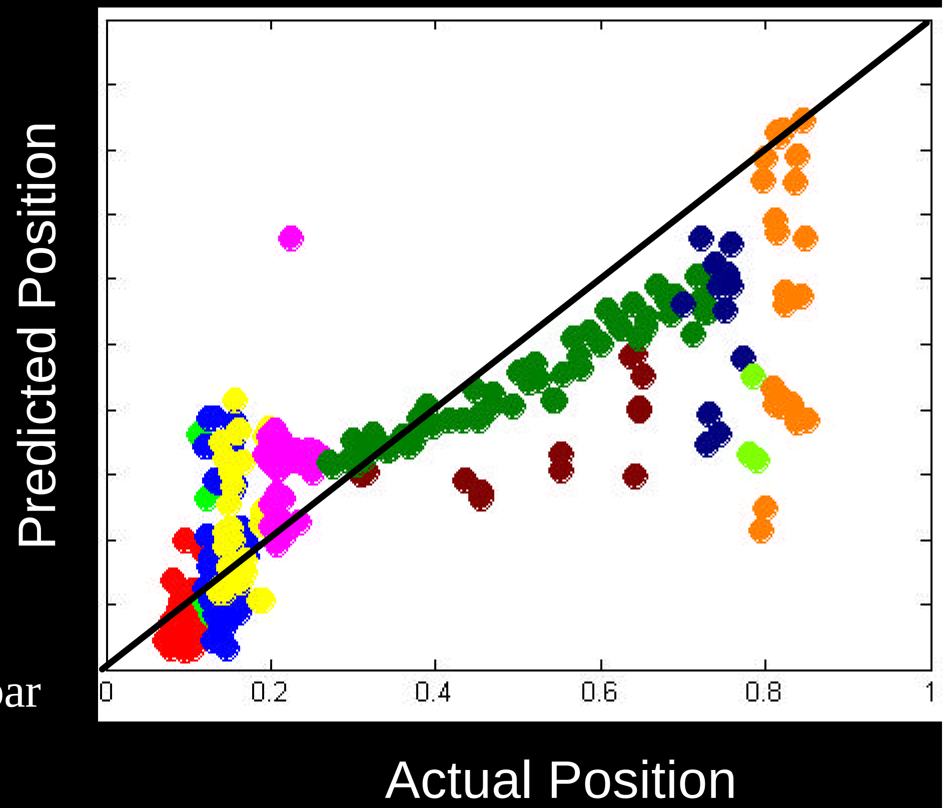
$$D_{B\,ij} = d_{ij} \sum_p B_{ip}$$

Optimal placement coordinates:

$$r = \left(L + D_B \right)^{-1} B f$$

Actual vs. Predicted Neuron Positions





Wiring minimization is reasonable but not perfect

Why is not wiring minimization prediction perfect?

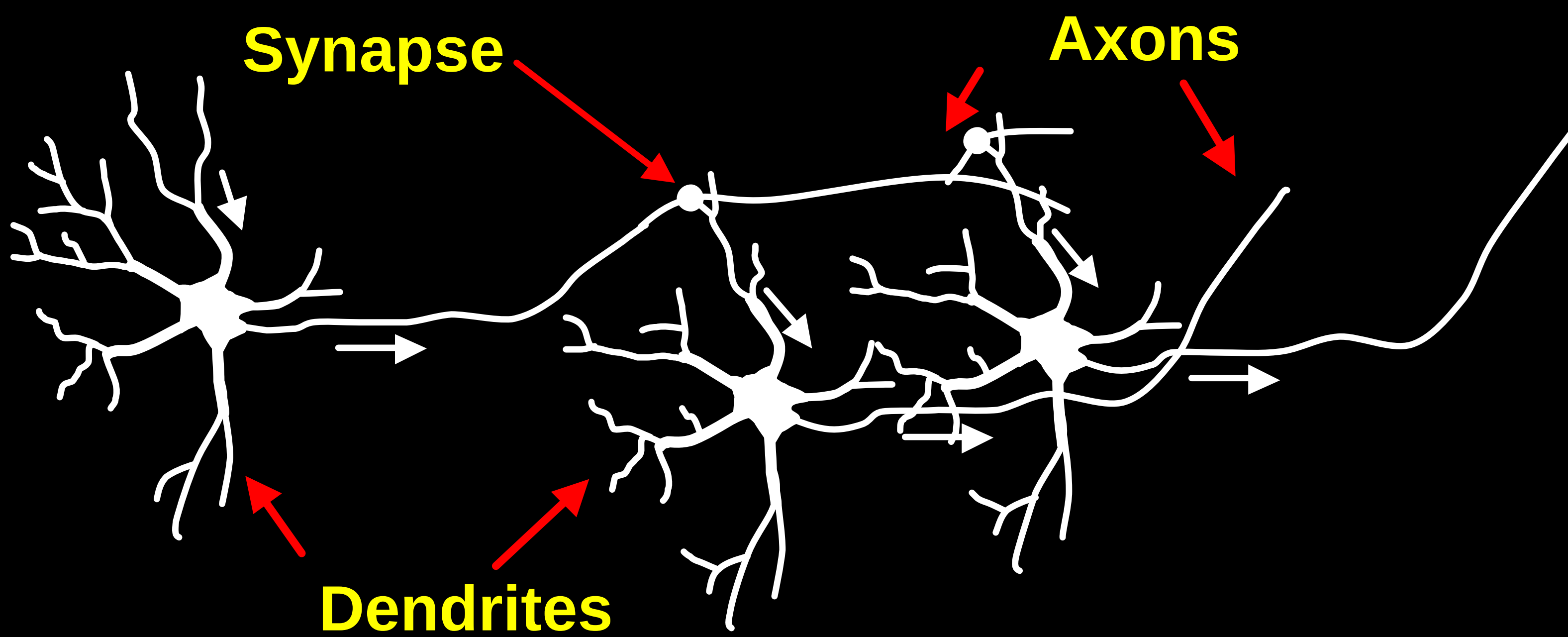
- Nervous system may be sub-optimal
- Other constraints may be important

  (e.g. development)
- Quadratic cost function may be incorrect
- Routing optimization may affect placement

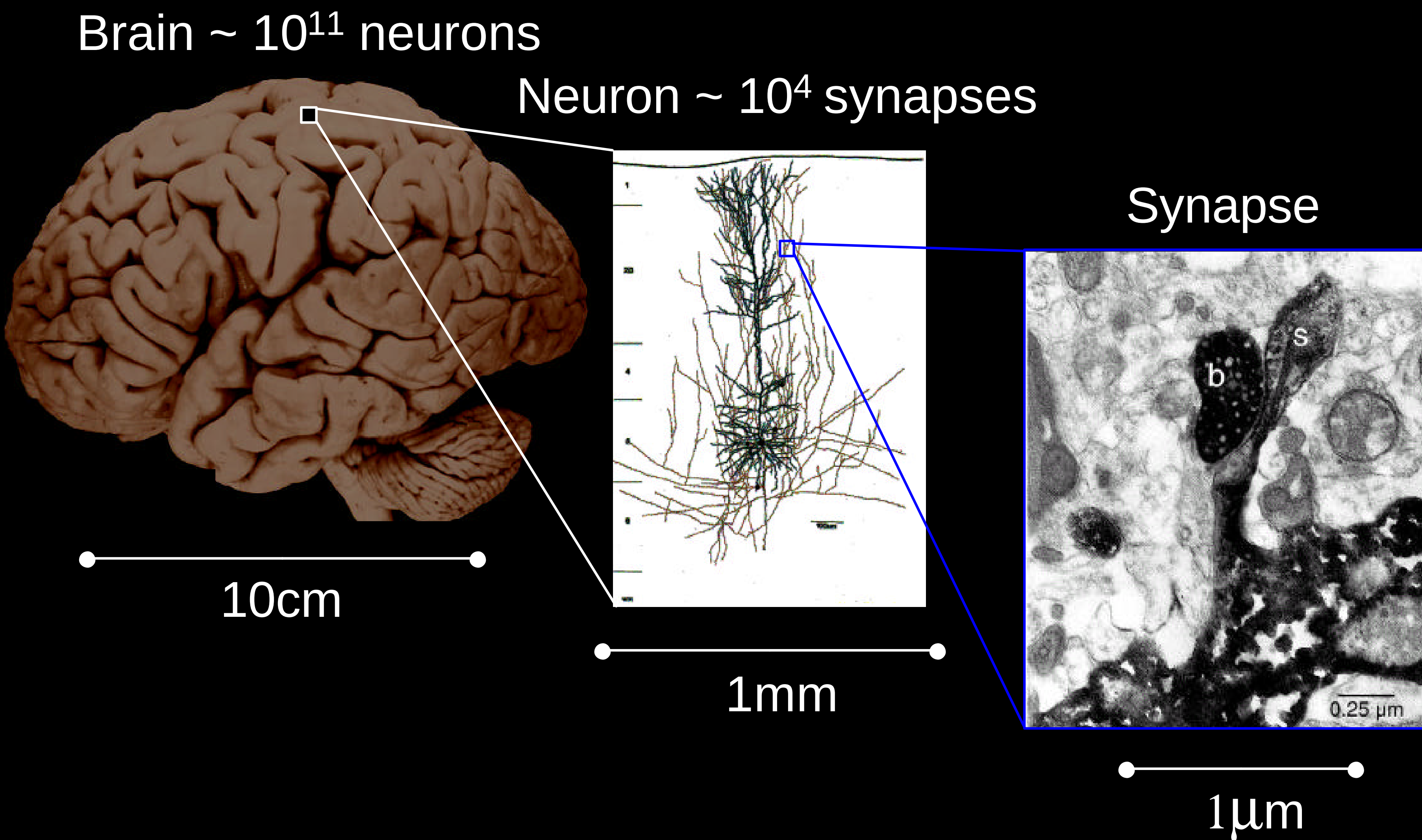
Routing or neuronal shape

point neurons

actual neurons



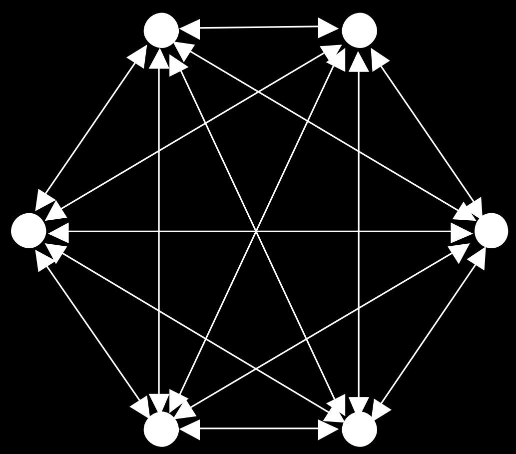
Big brains - large numbers



Assembling the wiring diagram will take many years

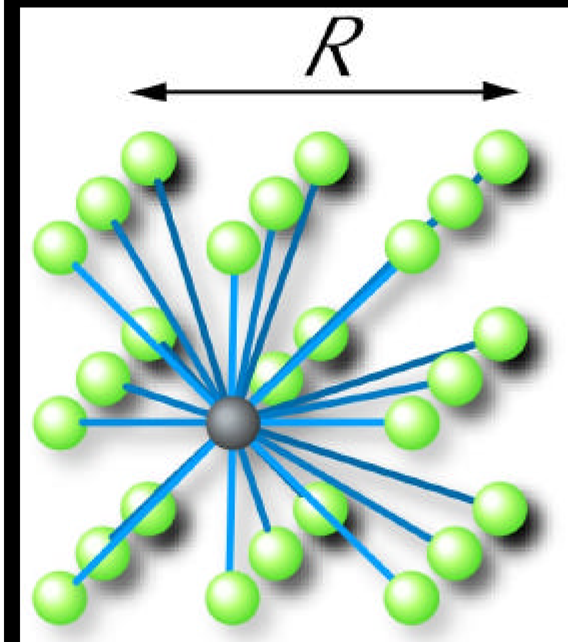
Routing problem

- Network of N neurons
- Fully connected (all-to-all)
- Fixed wire diameter, d



Find wiring design minimizing network volume

Design I: Point-to-point axons



Number of neurons: N

Wire diameter: d

Axon length per neuron: $l \sim NR$

Total wiring volume: $R^3 \sim Nld^2$

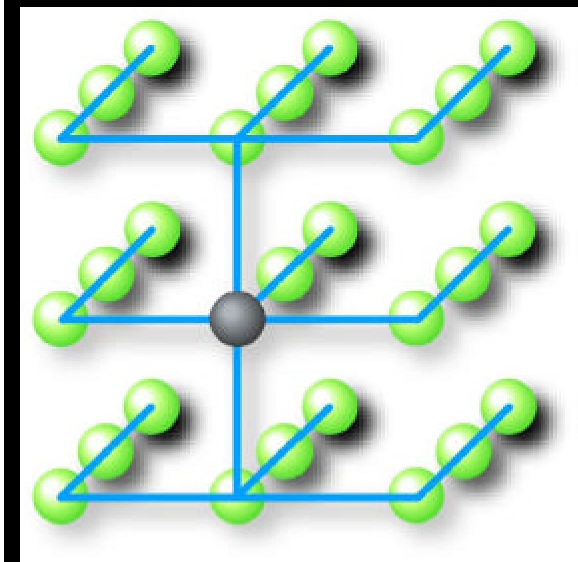
$\Rightarrow$

$\Rightarrow$ Network size: $\boxed{R \sim Nd}$

Mouse cortical column (1mm³): $N=10^5$, $d=0.3\mu m \Rightarrow$

$\Rightarrow R=3cm$ ☹

Design II: Branching axons (multi-pin nets)



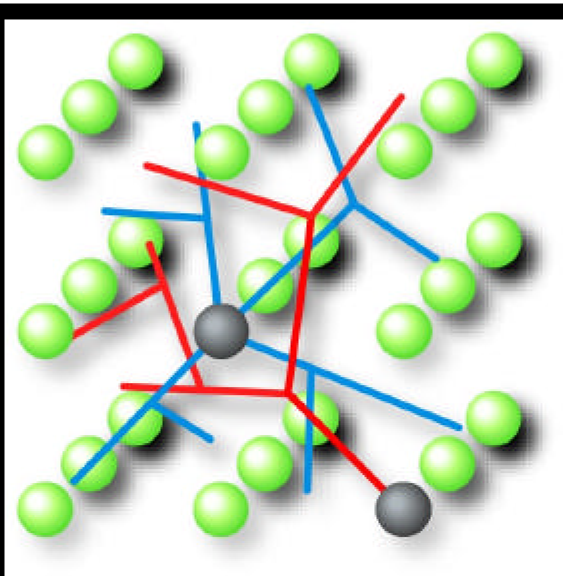
Inter-neuron distance: $R / N^{1/3}$

Axon length per neuron: $l = R N^{2/3}$

Total wiring volume: $R^3 \sim N l d^2$

$\Rightarrow$ Network size: $\boxed{R \sim N^{5/6} d}$

Cortical column: $N = 10^5 \;\; d = 0.3\mu\text{m} \Rightarrow R = 4.4\text{mm}$ ☹



Design III: Branching axons and dendrites

Total number of voxels: R^3 / d^3

Number of voxels containing axon: l/d

Fraction of voxels containing axon: ld^2 / R^3

Fraction of voxels containing dendrite: ld^2 / R^3

Number of voxels containing axon and dendrite: $l^2 d / R^3 \sim 1$

Total wiring volume: $R^3 \sim Nld^2$

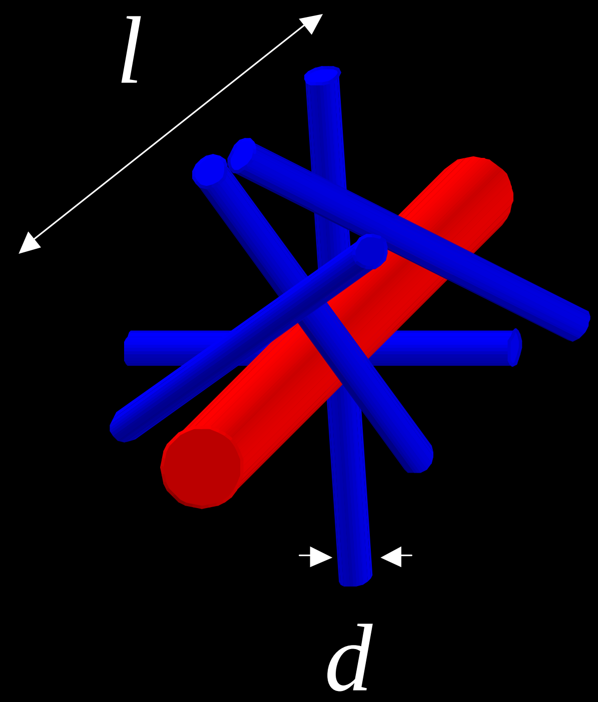
$\Rightarrow$ Network size: $R \sim N^{2/3} d$

Cortical column: $N = 10^5$ $d = 0.3;1\mu\text{m}$ $\Rightarrow R = 1.6\text{mm}$ ☹

Is it possible to improve on Design III?

In Design III, dendrite length can be found…

$$\left.\begin{array}{l} R^3 \sim Nld^2 \\ R \sim N^{2/3} d \end{array}\right\} \Rightarrow l \sim Nd$$

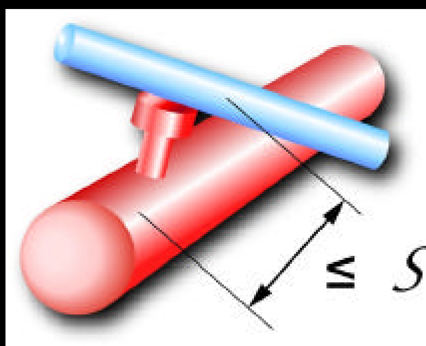


…to be smallest possible:

$$L \gtrsim Nd$$

Design III cannot be improved if dendrites are smooth

Design IV: Branching axons and spiny dendrites



Number of voxels containing axon and dendrite: $l^2 s / R^3 \sim 1$

Total wiring volume: $R^3 \sim N l d^2$

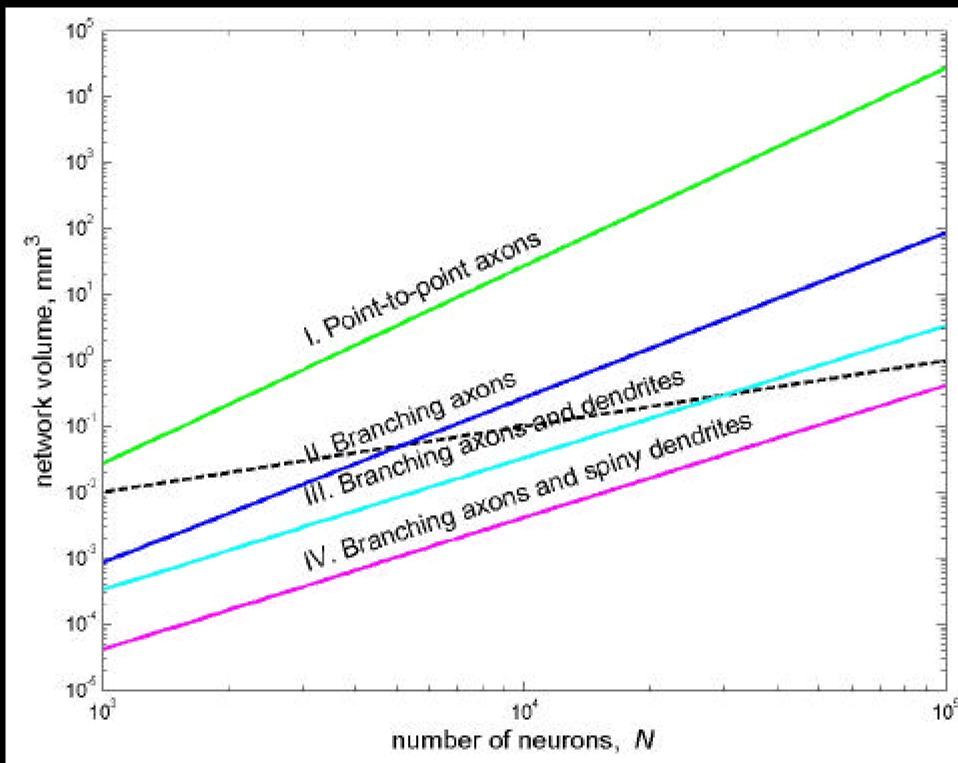
$\Rightarrow$

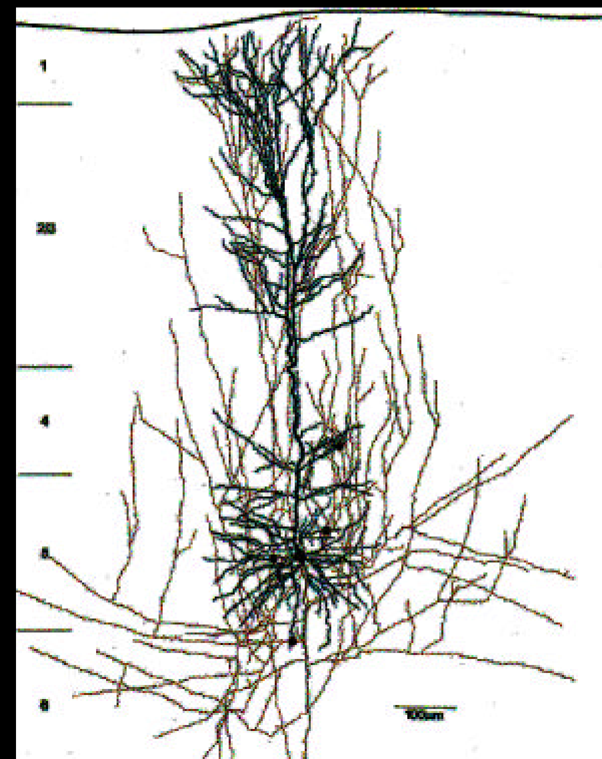
$\Rightarrow$ Network size: $R \sim N^{2/3} d^{4/3} / s^{1/3}$

Cortical column: $N = 10^5$ $d = 0.3;1\mu\text{m}$ $s = 2.5\mu\text{m}$ $\Rightarrow$

$\Rightarrow$ $R = 0.8\text{mm}$ ☺

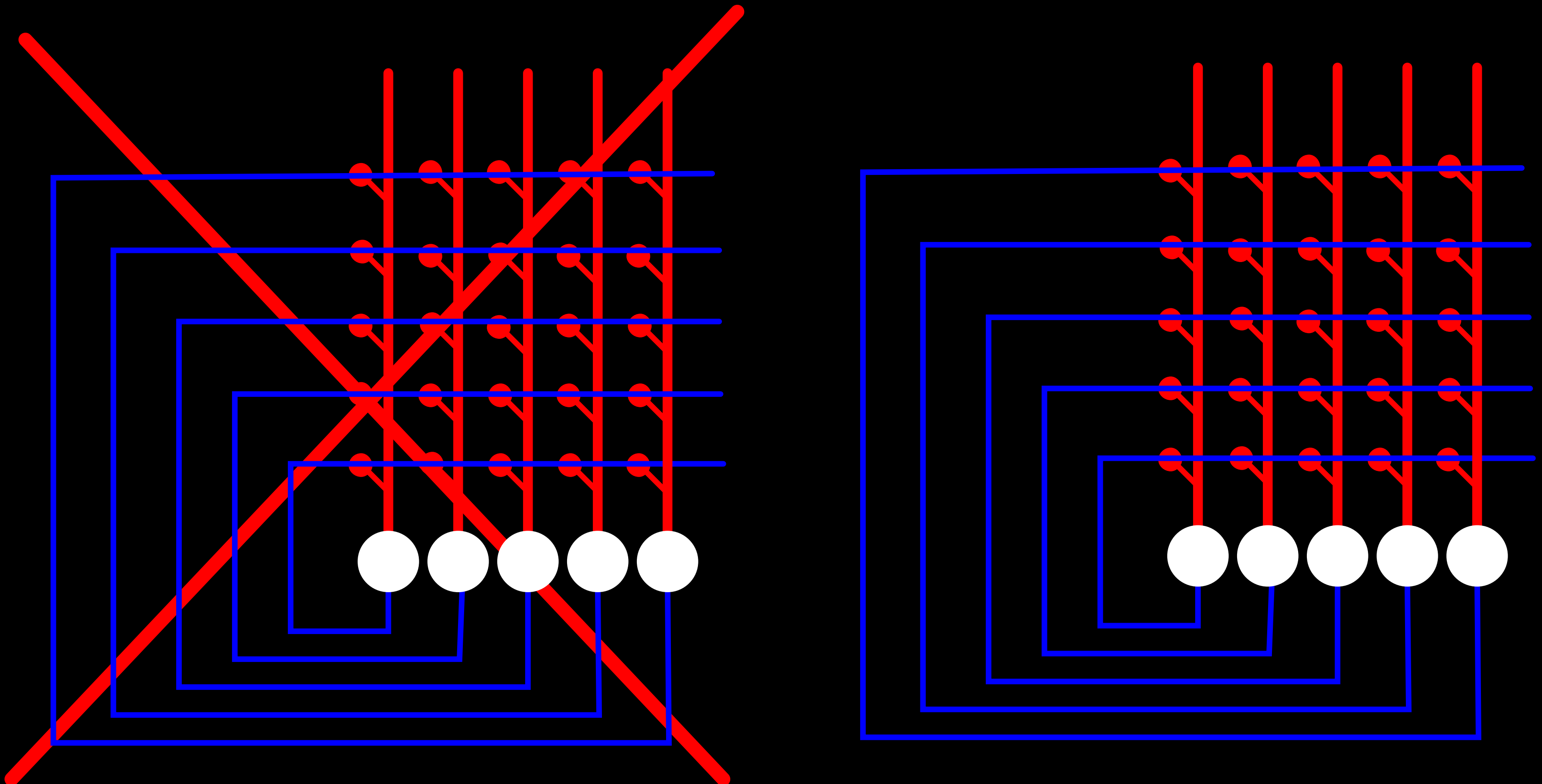
Network volume for various wiring designs





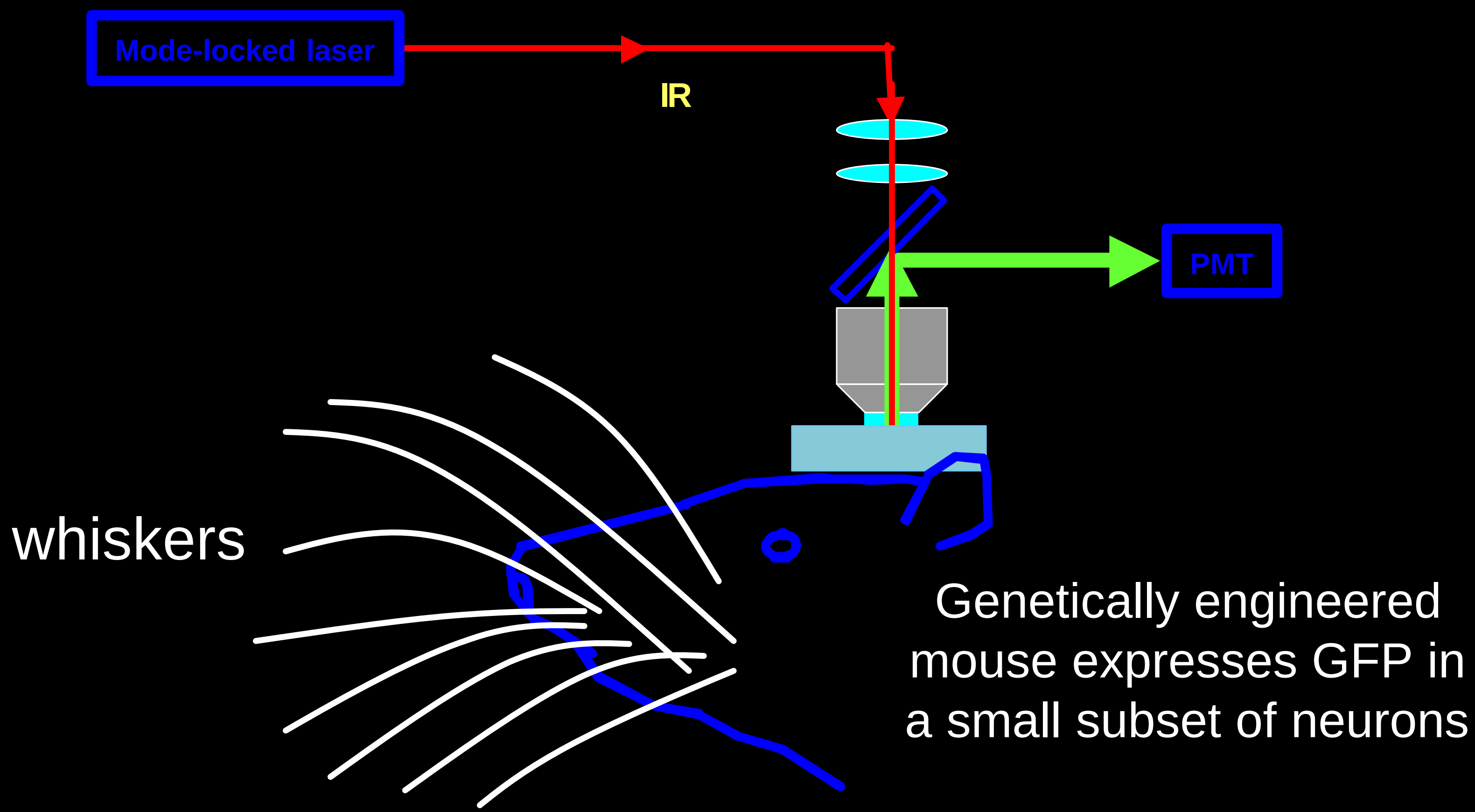
Neuronal shape is a routing solution implementing high inter-connectivity

Cortical architecture is optimized for high inter-connectivity



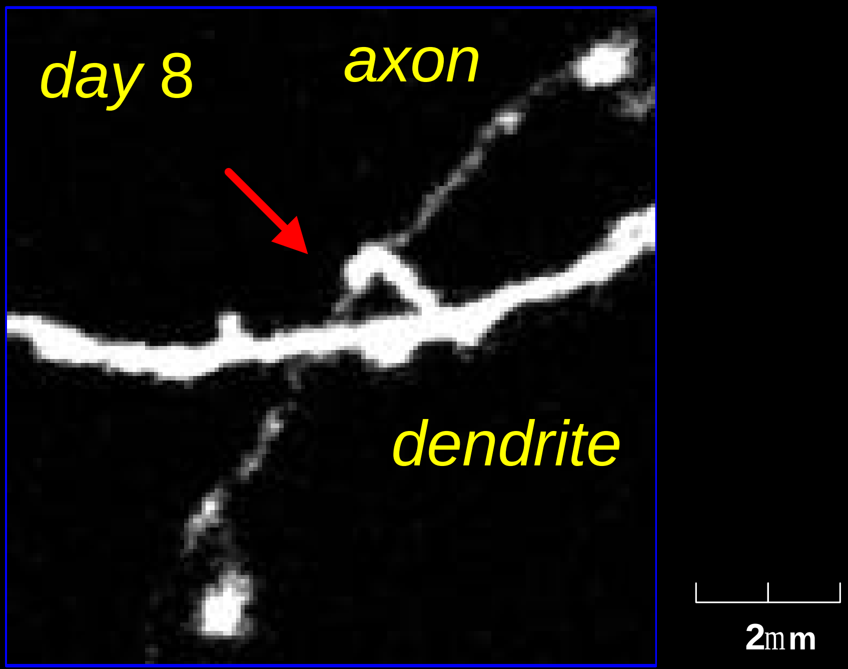
Synapse re-arrangement is potential memory mechanism with high information storage capacity (Stepanyants, Hof, Chklovskii, 2002)

Experiments on synapse re-arrangement



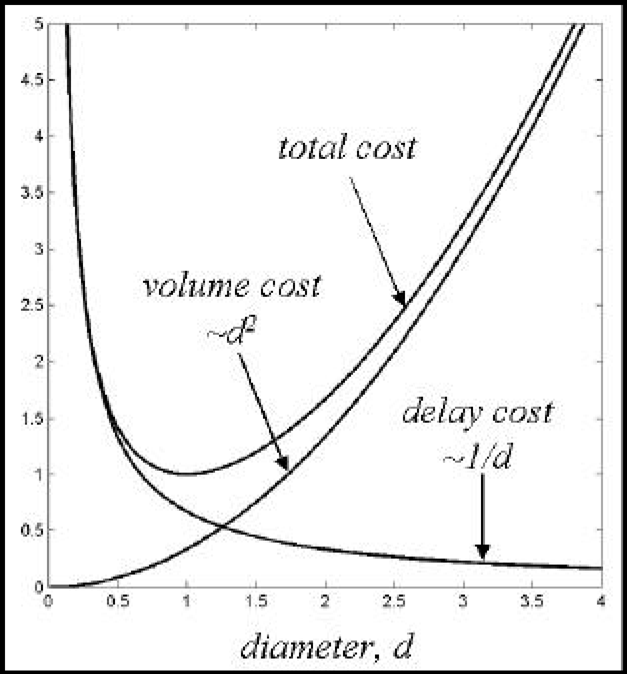
Two-photon microscope provides *in vivo* images with single-synapse resolution

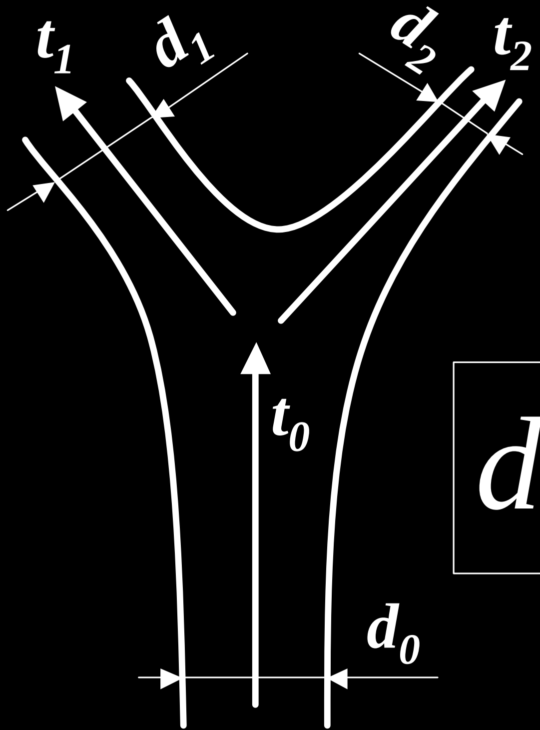
Spine remodeling indicates synapse re-arrangement *in vivo*



Trachtenberg, …, Svoboda, 2002

What determines axon (dendrite) diameter?





$$d_0^3 = d_1^3 + d_2^3$$

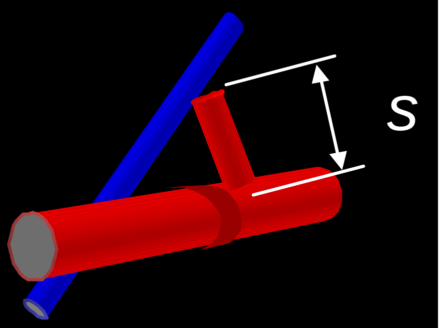
Axon diameter minimizes the combined cost of wiring volume and conduction delays

Summary

Wiring minimization is a key factor determining brain architecture

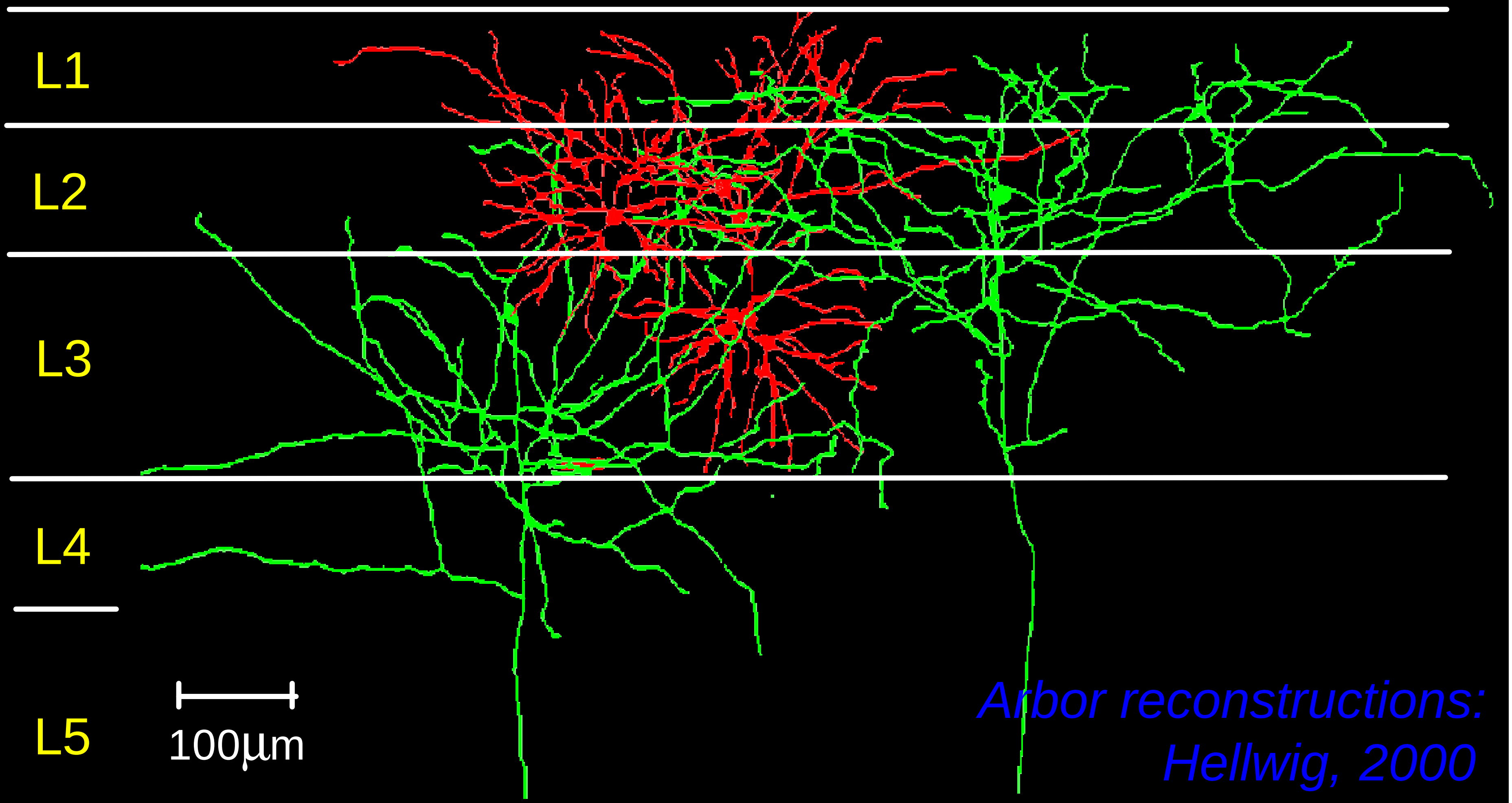
Complexity of neuronal networks poses challenging wiring minimization problems

Potential synapse is a location where axon comes within a spine length of a dendrites



- Potential synapse is a necessary (but not sufficient) condition for an actual synapse
- Potential synaptic connectivity is more stable than actual
- Potential synaptic connectivity can be evaluated geometrically

90% potential connectivity neighborhood



“Potential” definition of a cortical column

What is the correct cost function?

Biology: $\text{Min}\{V\} \rightarrow \text{Min}\{C = V - \lambda \log N\}$

Physics: $\text{Min}\{E\} \rightarrow \text{Min}\{F = E - TS\}$

Constrained optimization is a powerful tool for building a theory of brain function

Acknowledgments

Armen Stepanyants

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