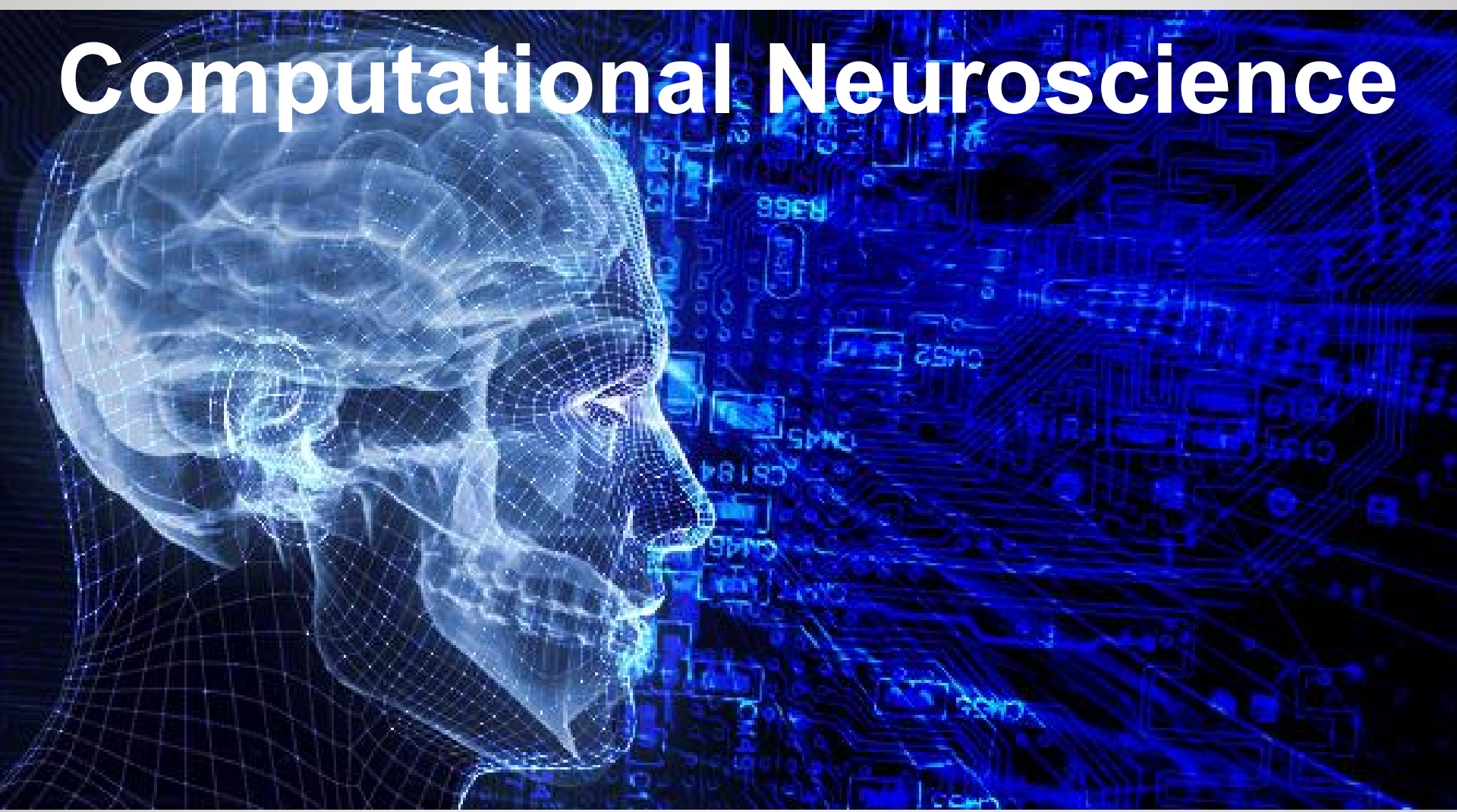
Neural Modeling

Astrocytes and the Tripartite Synapse

Nathan Crock

This is your Brain

Computational Neuroscience



Neuron

What is it?

Synapse

What is it?

The Biology

- Synapse - Point of connection between neurons
- Modeling synapses is key to modeling networks of neurons

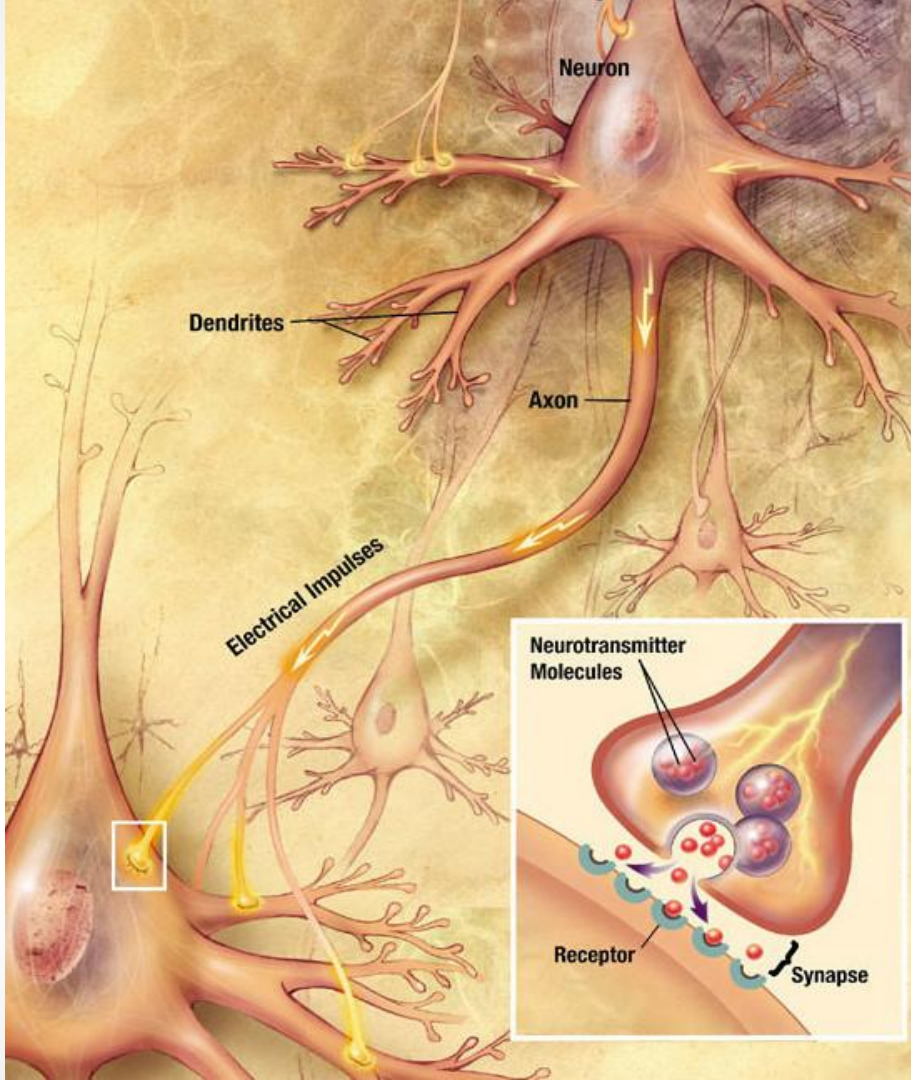
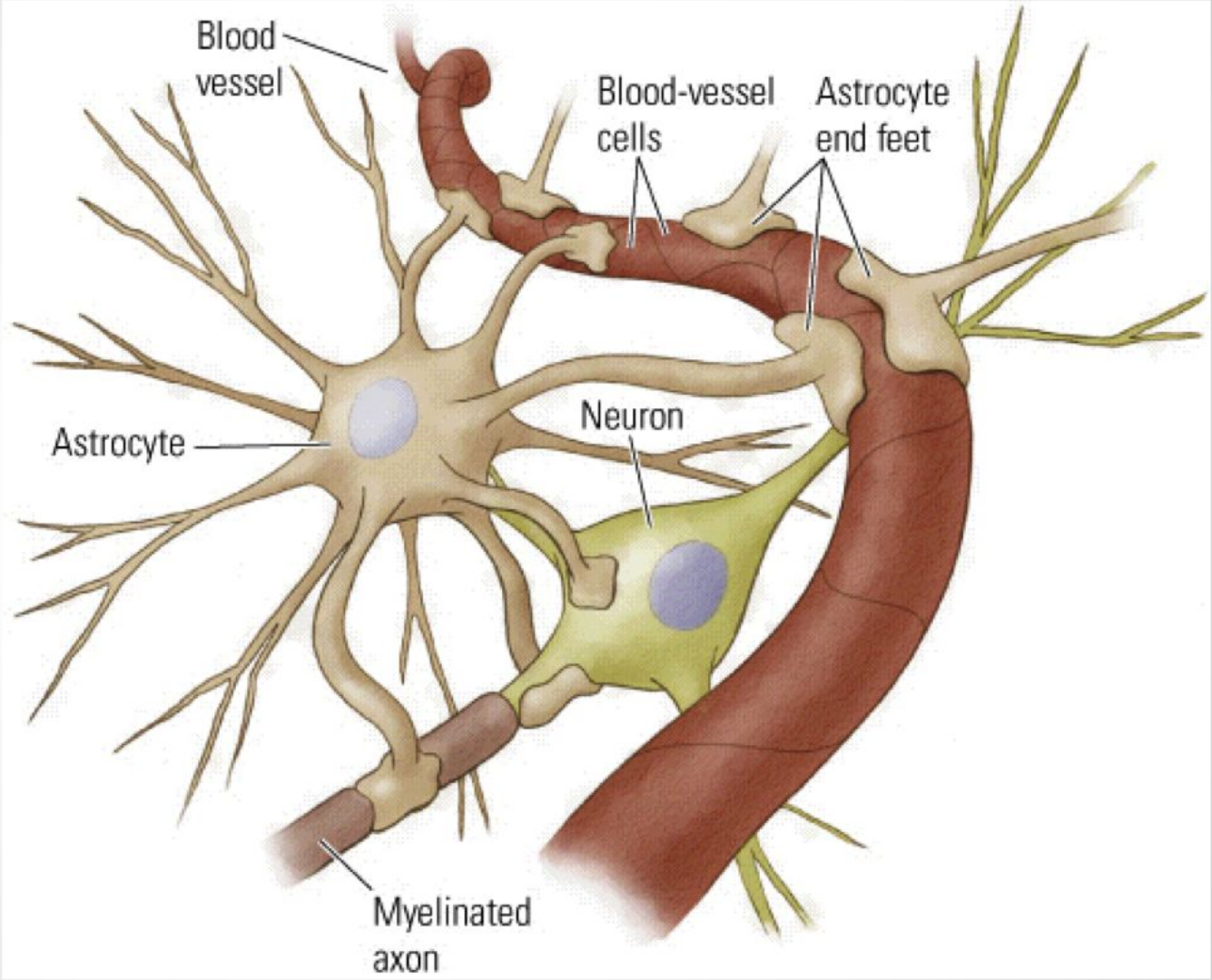


Image source: http://wikimedia.org

Astrocytes are “glial” cells

They are “helpers” to neurons



Motivation

- Ask what is memory? How do we learn?
- Identify neuron/synapse as the functional unit of the brain
- Understand that astrocytes modulate synaptic activity
- Hypothesize answers may be found in tripartite dynamics

Current Research Goal

Explore... Mathematical techniques for model reduction

Explore... The role of calcium in neuronal dynamics

Explore... The role of calcium in astrocytic dynamics

Explore... The dynamics of neuronal and astrocytic interplay

Develop a robust model of the tripartite synapse. Reduce the model and construct a large scale simulation of numerous tripartite synapses. LEARNING? MEMORY?

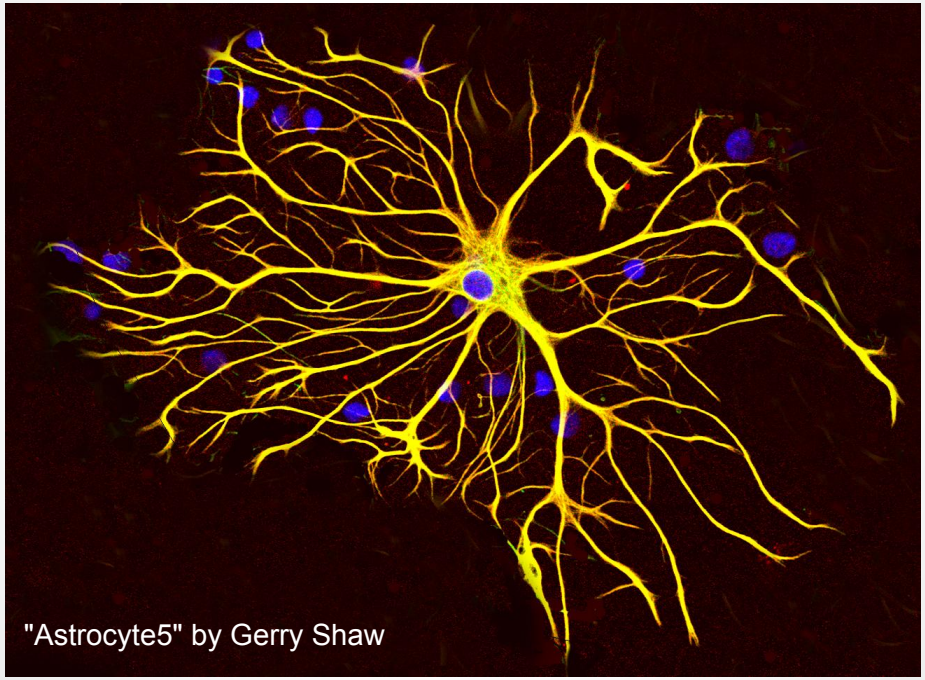
Outline

- What is an astrocyte?
- Astrocyte morphology
- Astrocyte functionality
- Neurons and astrocytes
  - Comparative morphology
  - Time and Spatial Scales
  - Communication
  - Motility
- Open questions

see what I did there?

What is an Astrocyte?

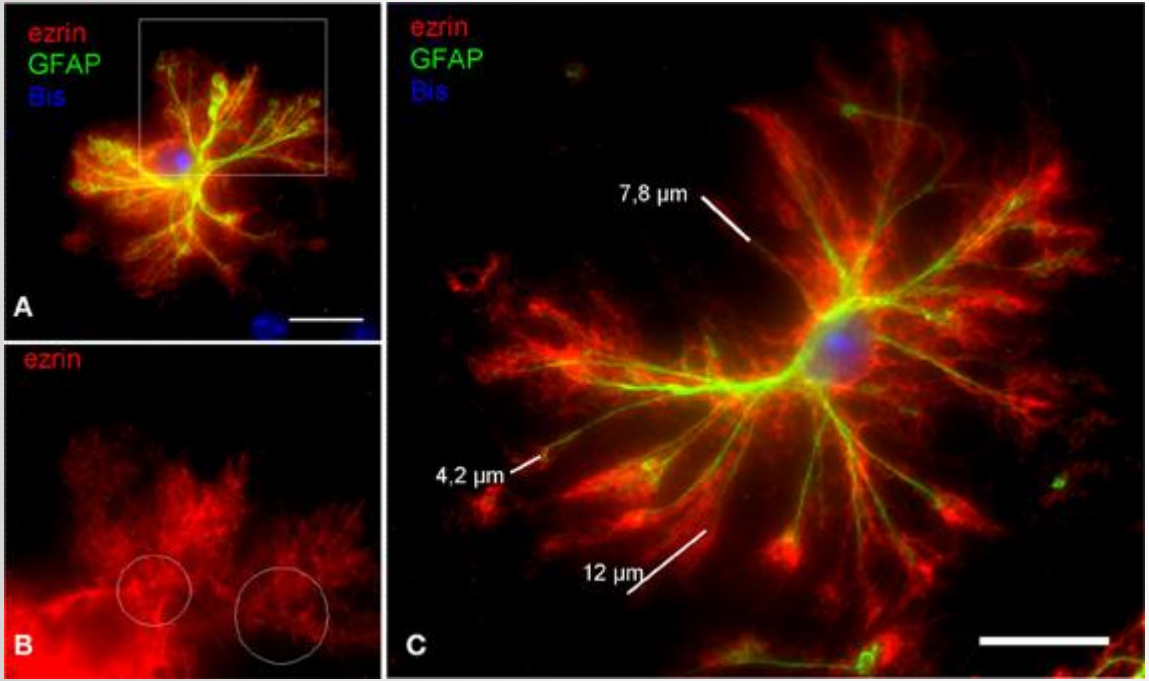
ASTRO
“star”



CYTE
“vessel”

A starlike cell found in the brain and spinal cord, or the central nervous system (CNS)

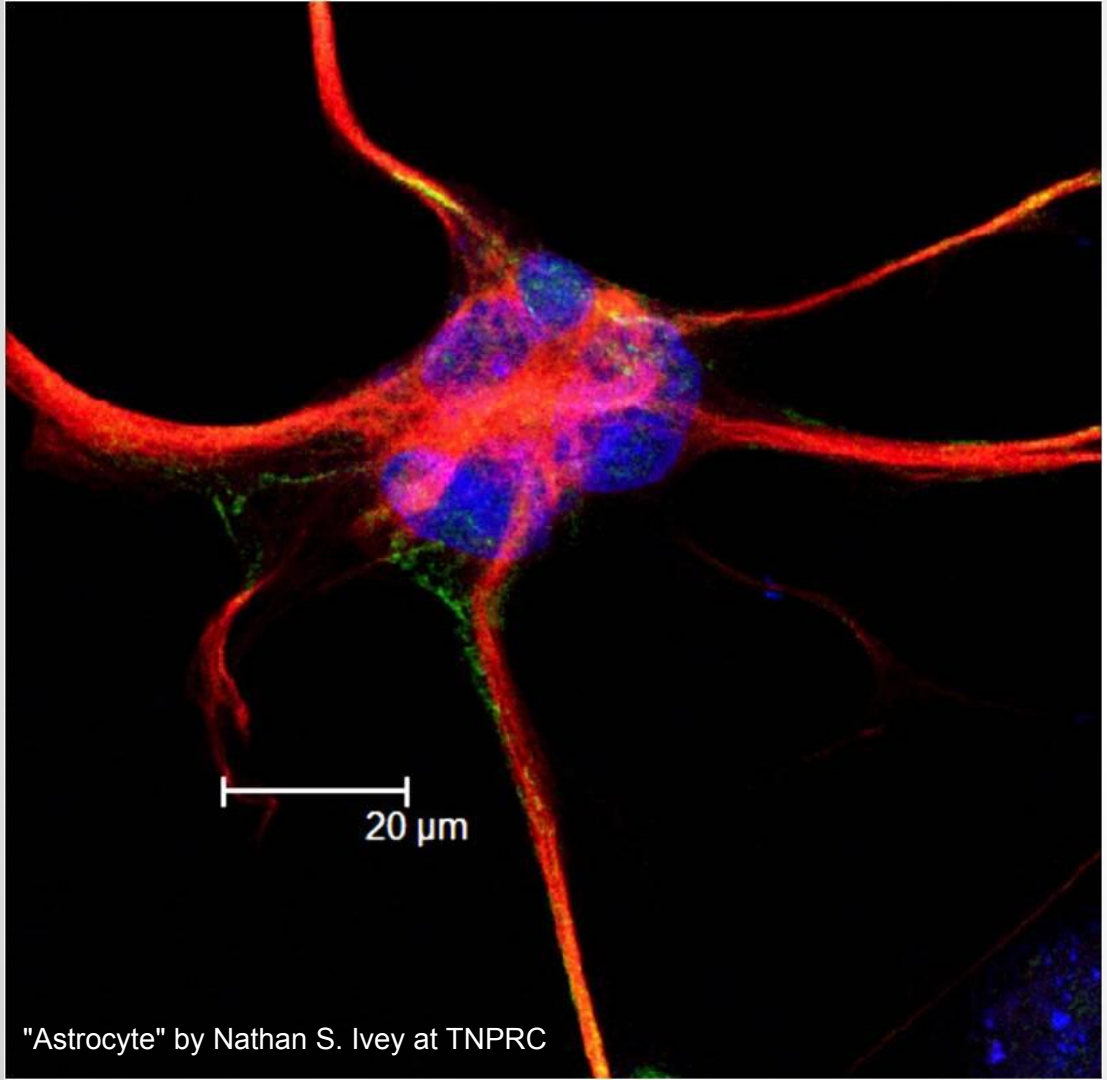
What do Astrocytes look like?



Cell body (soma)

Branches (processes)

“Synapse” (end feet)

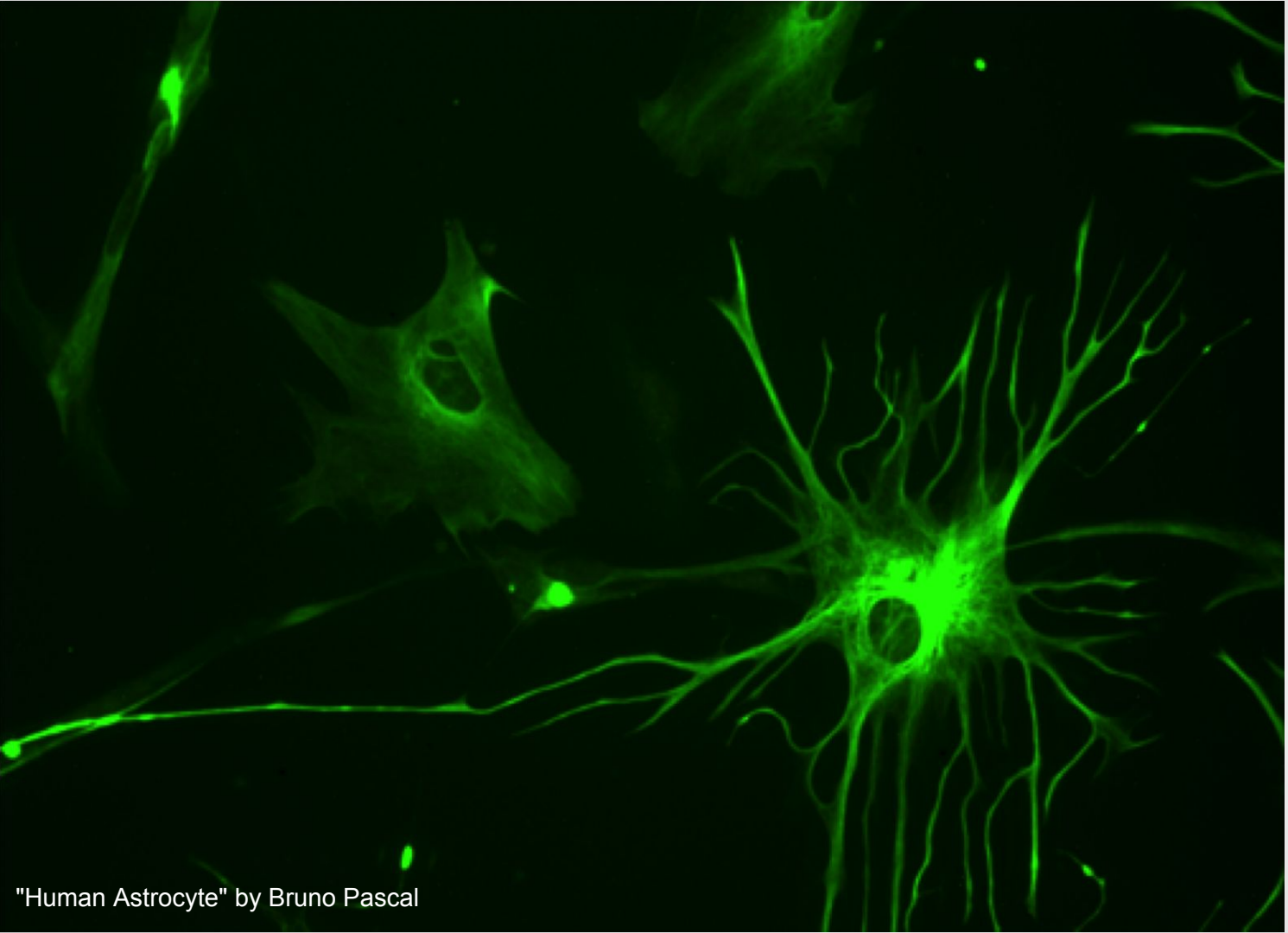


"Astrocyte" by Nathan S. Ivey at TNPRC

This is an astrocyte

The colors come from different stained proteins

~30-40 microns



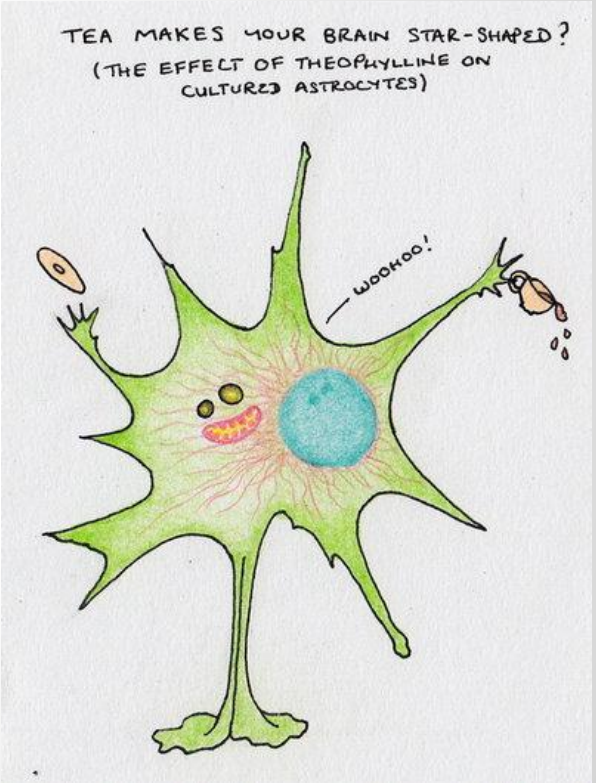
"Human Astrocyte" by Bruno Pascal

23 week human culture astrocyte

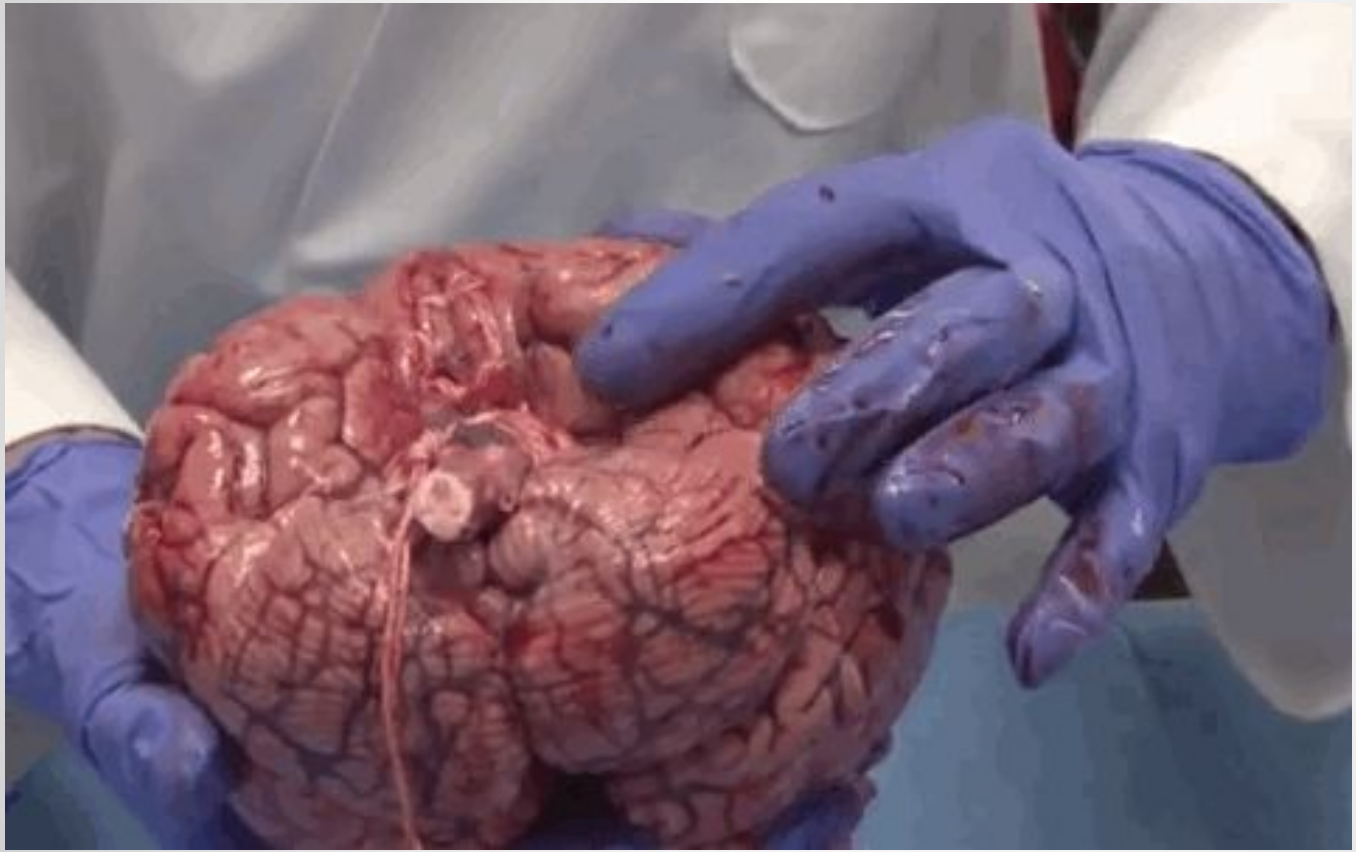
What do Astrocytes do?

- Scaffolding
- Scarring
- Blood Brain Barrier
- Homeostasis
- Clear Synapses

- Communication?



Scaffolding



The astrocytes provide the structure which make up the brain and spinal cord (50% of CNS)

They are the “scaffolding” or the support for the rest of the cells in the CNS

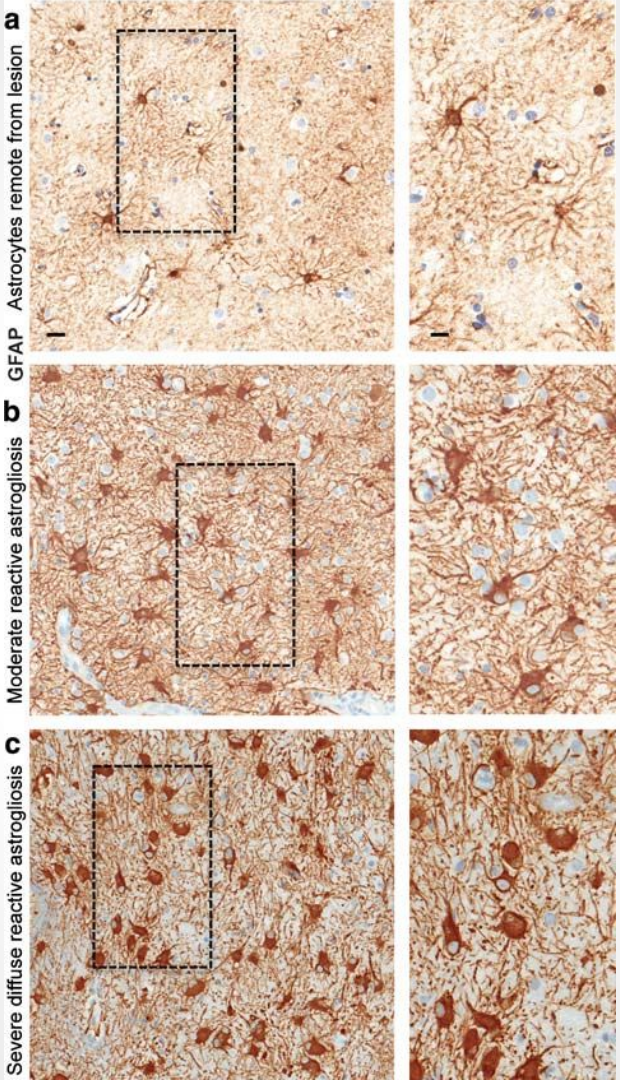
They create a spongy, mushroom like consistency

Glial Scarring

During CNS injury

- astrocytes proliferate
- migrate to the injury
- surround the area
- their processes thicken and elongate or “hypertrophy”
- all the processes connect to form a thick tissue that serve to wall off the area of injury “glial scar”

gliosis = astrogliosis = astrocytosis = reactive astrocytosis



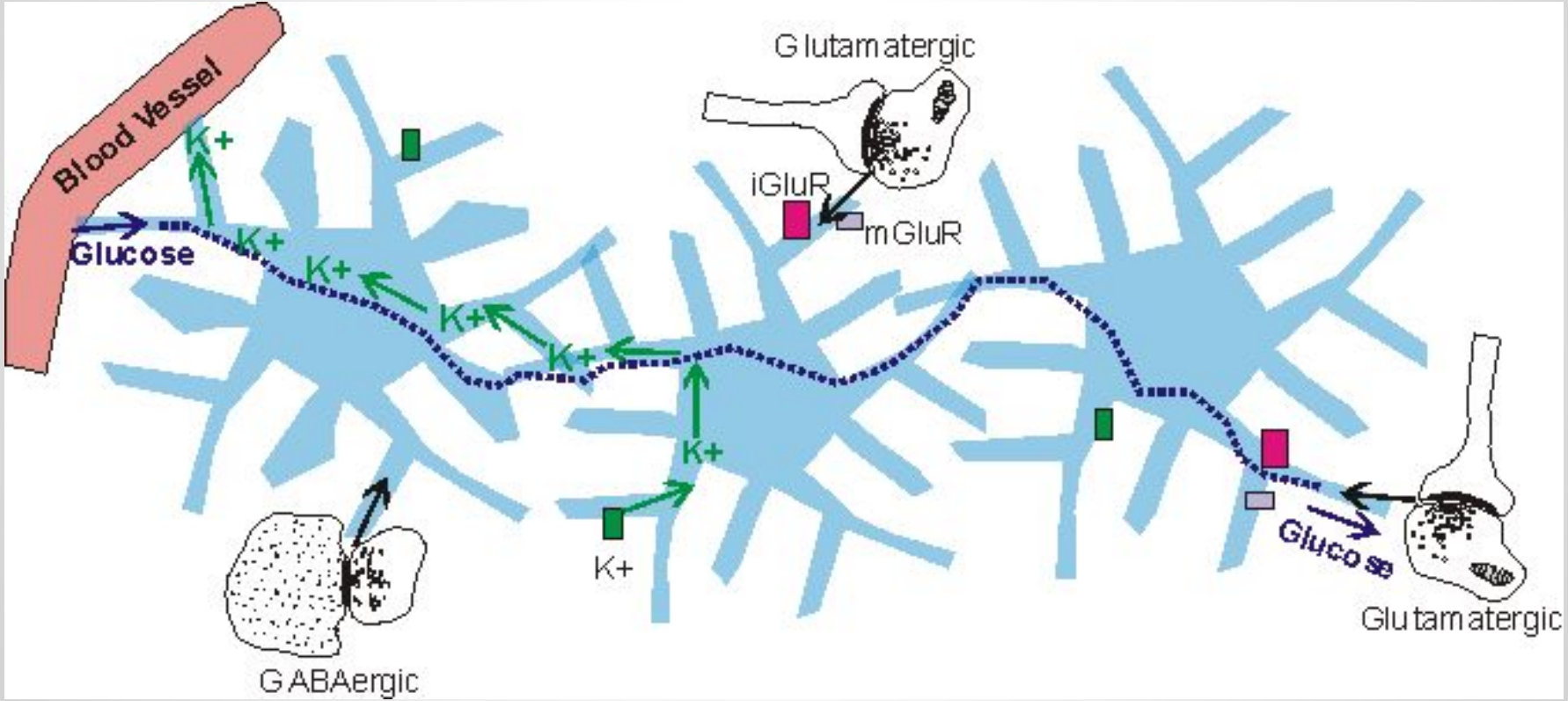
a) Appearance of astrocytes in tissue remote from a lesion and presumed healthy. Note that the territories of astrocyte processes do not overlap

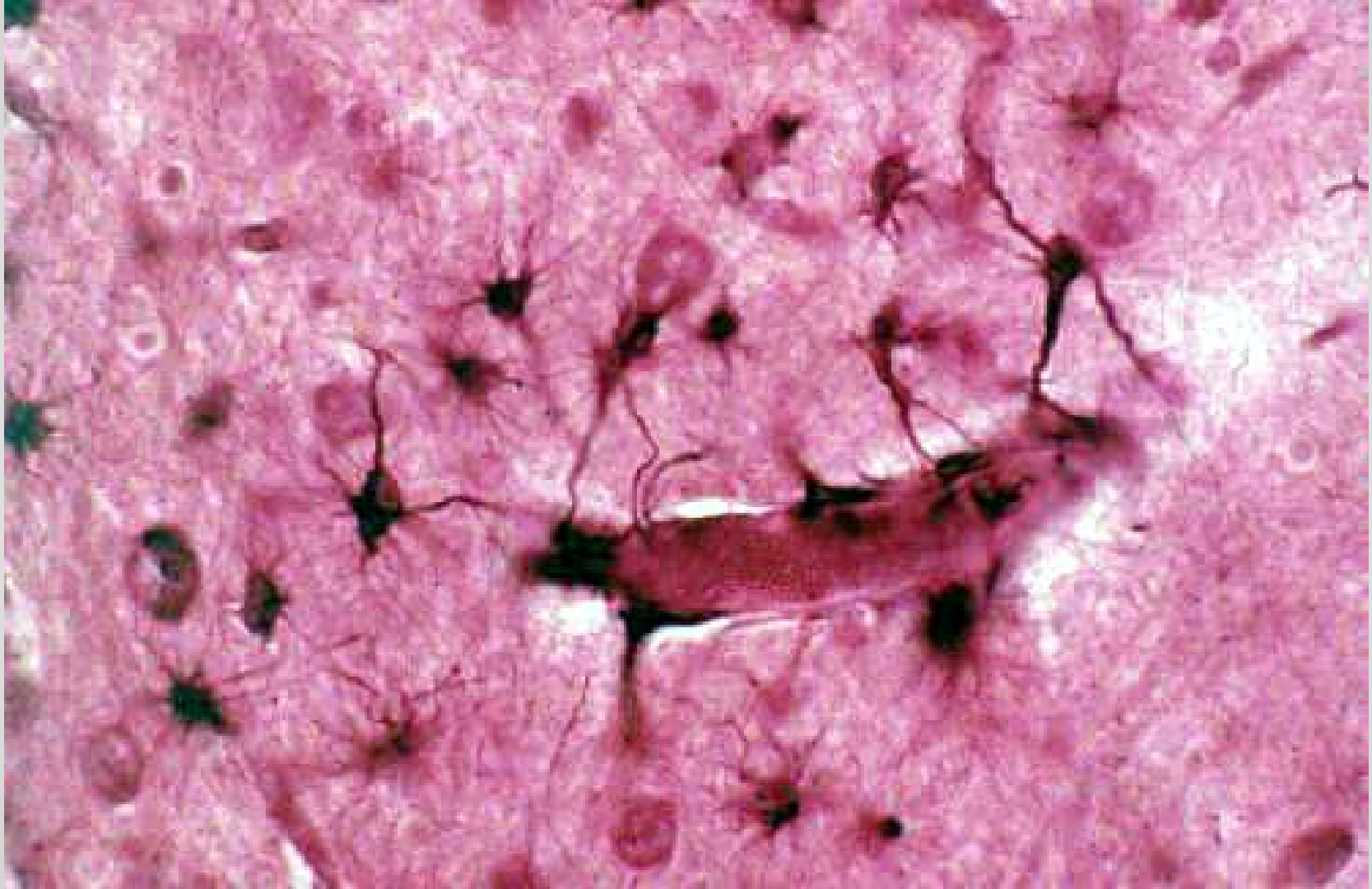
b) Moderately reactive astrogliosis in which most (if not all) astrocytes exhibit cellular hypertrophy, but with preservation of individual astrocyte domains and without pronounced overlap of astrocyte processes.

c) Severe diffuse reactive astrogliosis with astrocyte hypertrophy, astrocyte proliferation and pro- nounced overlap of astrocyte processes resulting in disruption of individual astrocyte domains. Scale bars surveys = 25 lm, details = 10 lm

Sofroniew, Michael V., and Harry V. Vinters. "Astrocytes: biology and pathology." Acta neuropathologica 119.1 (2010): 7-35. Fig. 3

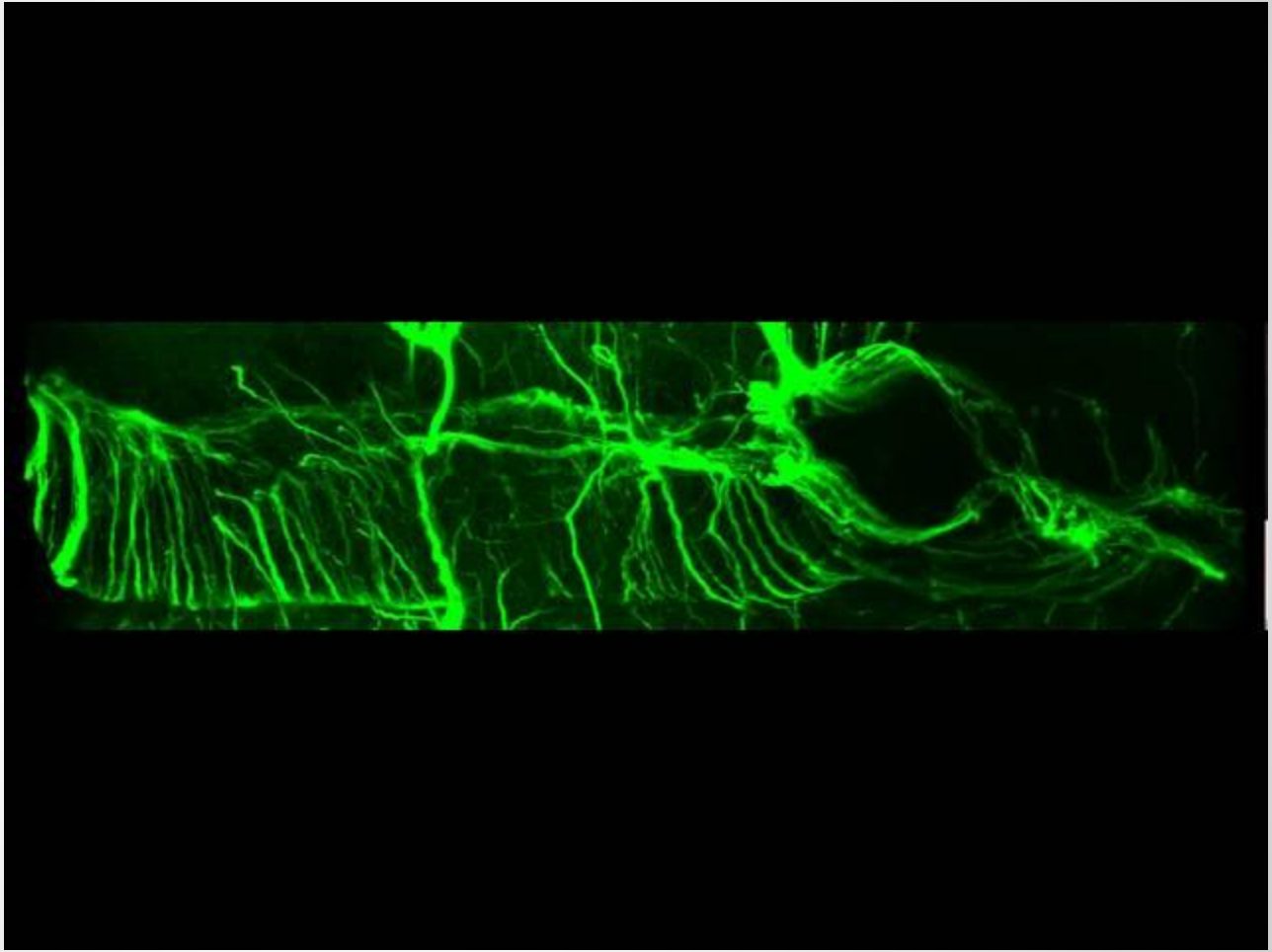
Blood Brain Barrier



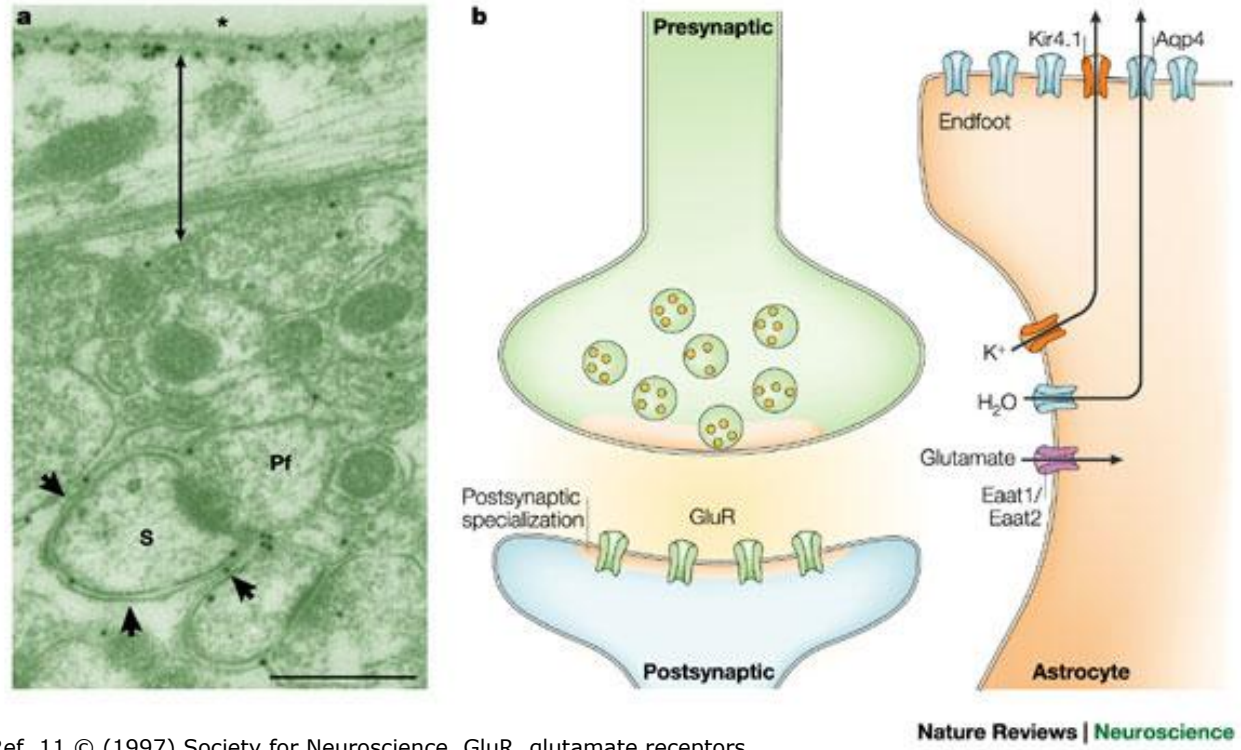


The CLARITY protocol was used to clear the brain, which was then stained for GFAP. This reveals astrocyte processes enveloping a blood vessel as a part of the blood-brain barrier.

Produced by the Naus Lab at UBC.



Homeostasis



Ref. 11 © (1997) Society for Neuroscience. GluR, glutamate receptors.

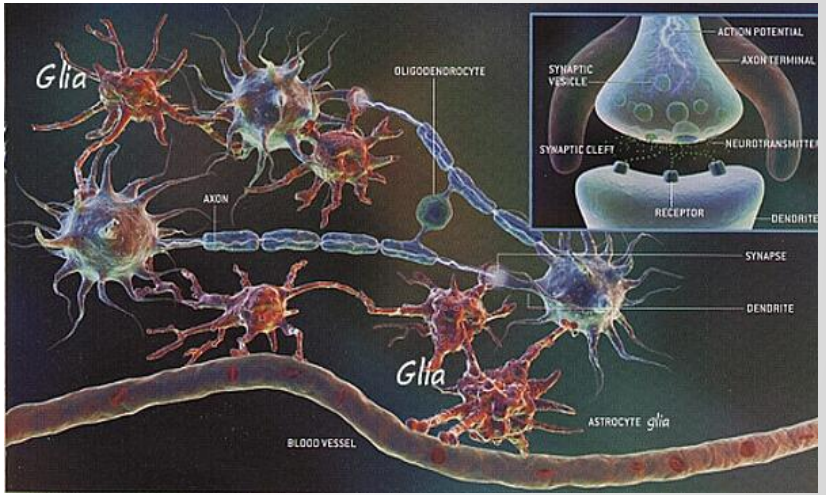
Monitor interstitial fluid and regulate its ion balance

a) Gold particles labelling Aqp4 occur in astrocytic lamellae (arrowheads) ensheathing synapses between parallel fibers (Pf) and Purkinje cell spines (S), and, at higher density, in endfeet membranes facing the pia and the subarachnoidal space (asterisk). The double arrow indicates subpial endfoot.

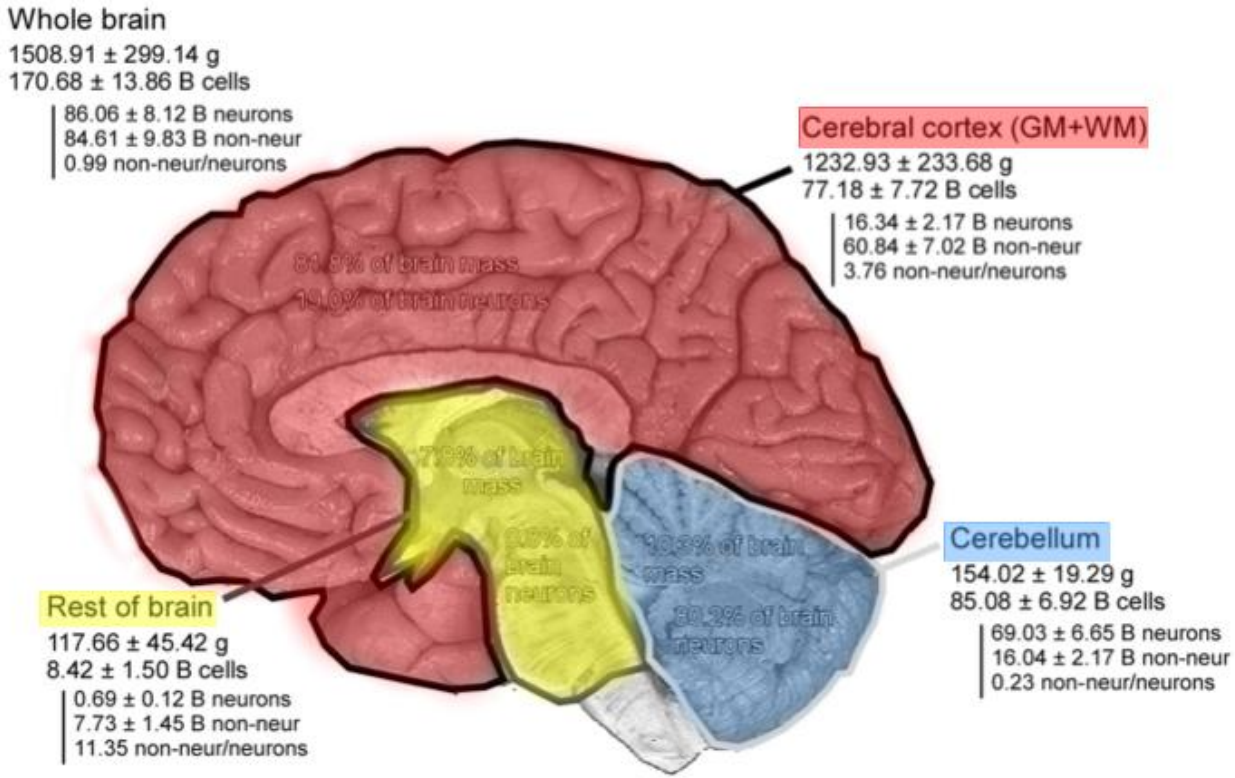
b) Drawing showing a simplified glutamatergic synapse along with an astrocyte with different molecules (inwardly rectifying K^+ channel (Kir) 4.1 and glutamate transporters Eaat1 and 2) that are believed to take part in the clearance of $K^+$and glutamate. Scale bar, 0.5 m.

Neuron-Astrocyte Relationship

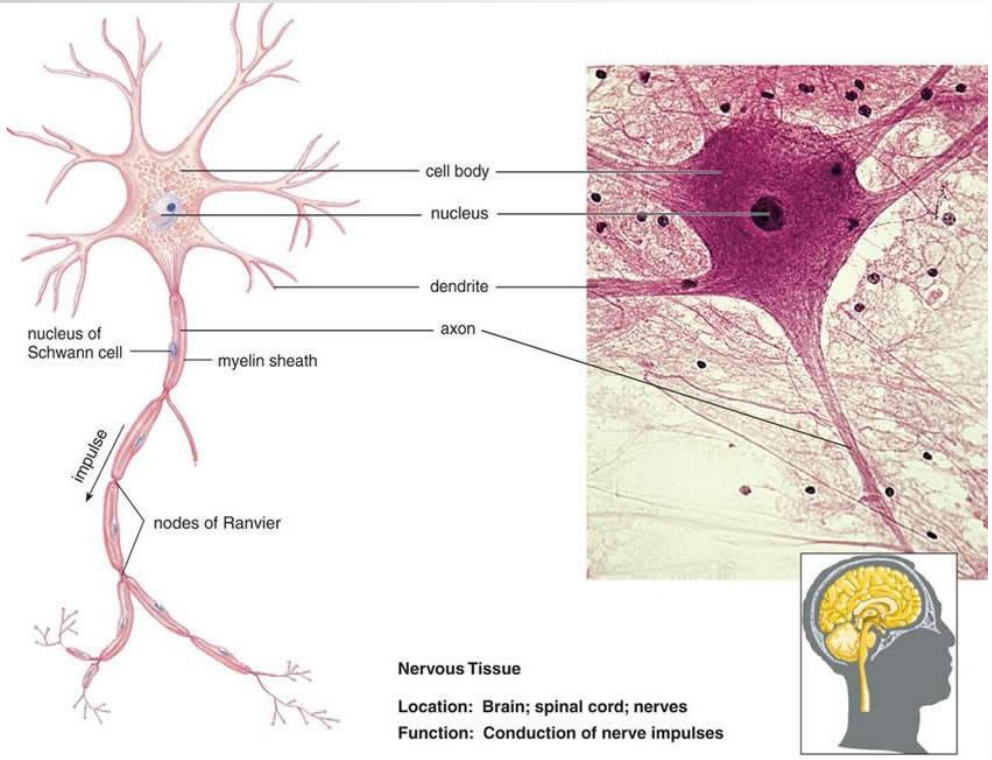
- Representation
- Comparative morphology
  - Size
  - Synapses vs End Feet
- Motility
- Communications



Representation

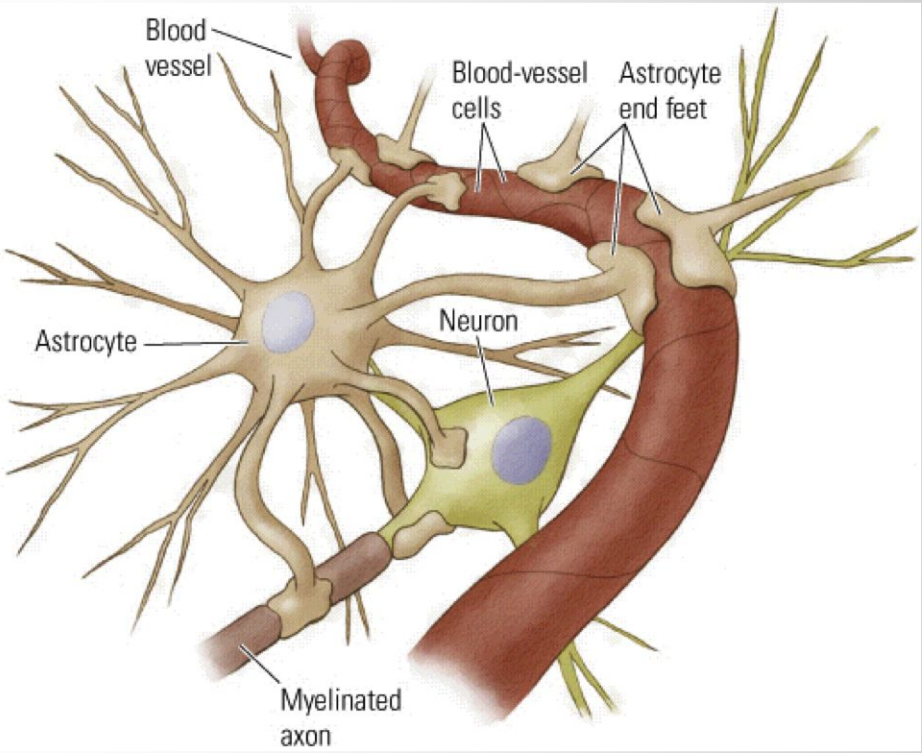


Typical Neuronal Morphology



Anywhere from 4 microns to 100 microns in diameter

Typical Astrocyte Morphology



Anywhere from 30 microns to 50 microns in diameter

Neurons vs Astrocytes

- Number of synapses
  - 1,000 - 100,000
- Contacts ? astrocytes
- *Cannot* move on their own
- Communicate via *neurotransmitters*
- 4 - 100 microns in diameter

- Number of end feet
  - ?
- Contacts ~100,000 neurons
- *Can* move on their own
- Communicate via *gliotransmitters*
- 30 - 50 microns in diameter
- Astrocytes control all phases of synapses – forming, maturation, neuroplasticity, and pruning


Astrocytes are a type of glial cells.
100 µm

Time Scales

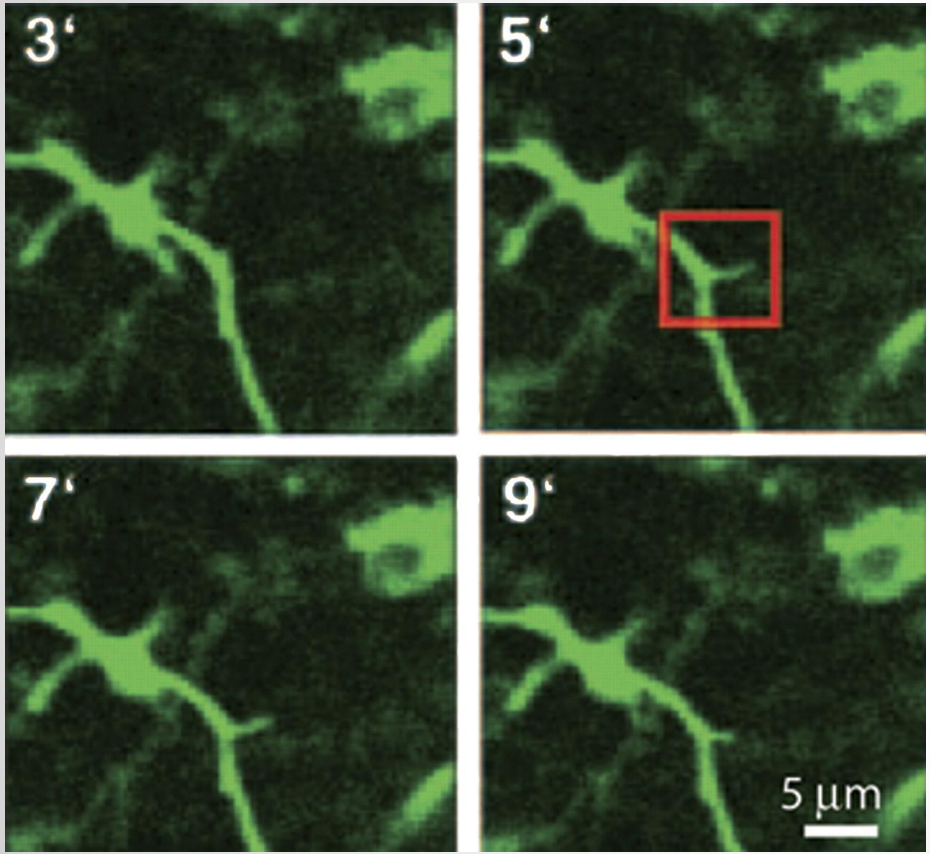
Neurons

Astrocytes

Distal astrocytic processes can undergo morphological changes in a matter of minutes a remodeling that modifies the geometry and diffusion properties of the extracellular space and relationships with adjacent neuronal elements, especially synapses.

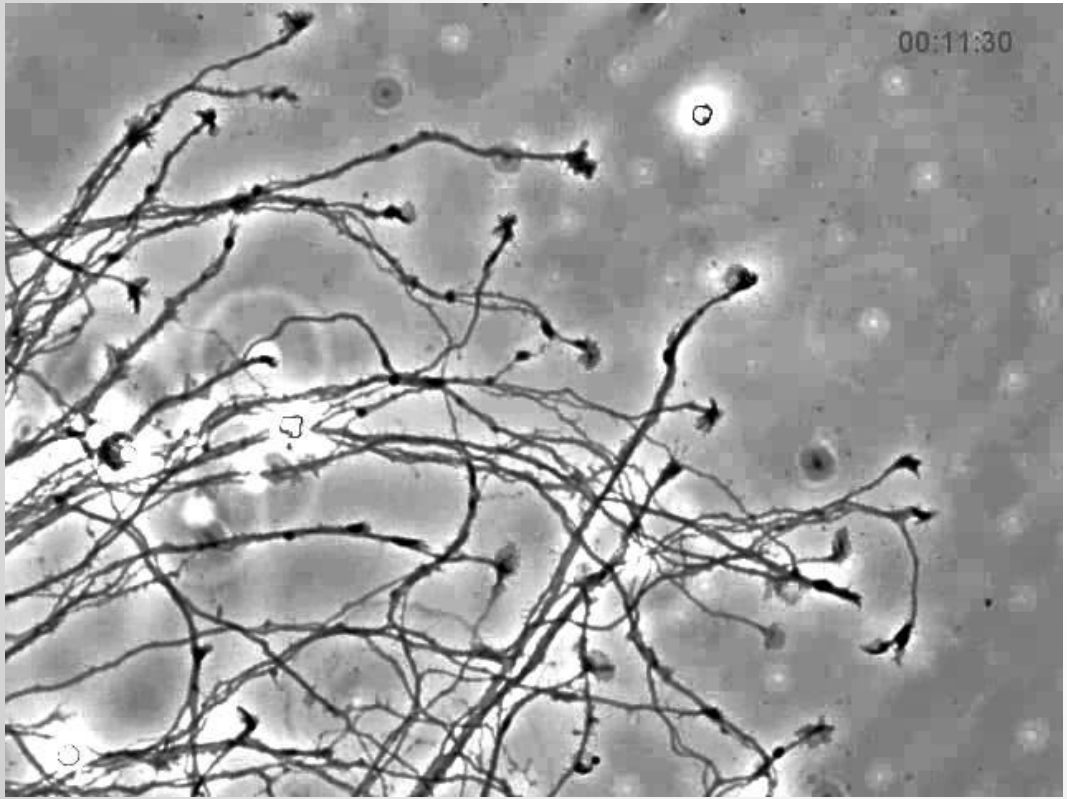
Where astrocytic processes are mobile then, astrocytic-neuronal interactions become highly dynamic, a plasticity that has important functional consequences since it modifies extracellular ionic homeostasis, neurotransmission, gliotransmission, and ultimately neuronal function at the cellular and system levels.

Astrocyte Motility



Evidence for astrocytic movement has been observed in vitro, where astrocytes change shape by developing filopodial extensions when exposed to neurotransmitter. The direction of filopodial growth is vectored up the concentration gradient of the applied neurotransmitter.

Neuron Motility



A time-lapse sequence of various motile behaviors of the growth cone in culture. The explant cultures were made from rat pontine nuclei and plated on laminin substrate. Many axons emerged from the explants within 24 h after plating, and each of them exhibits a motile growth cone. Different motile behaviors of the growth cones are indicated by the number labels:

(1) rapid extension

(2) pausing/stalling

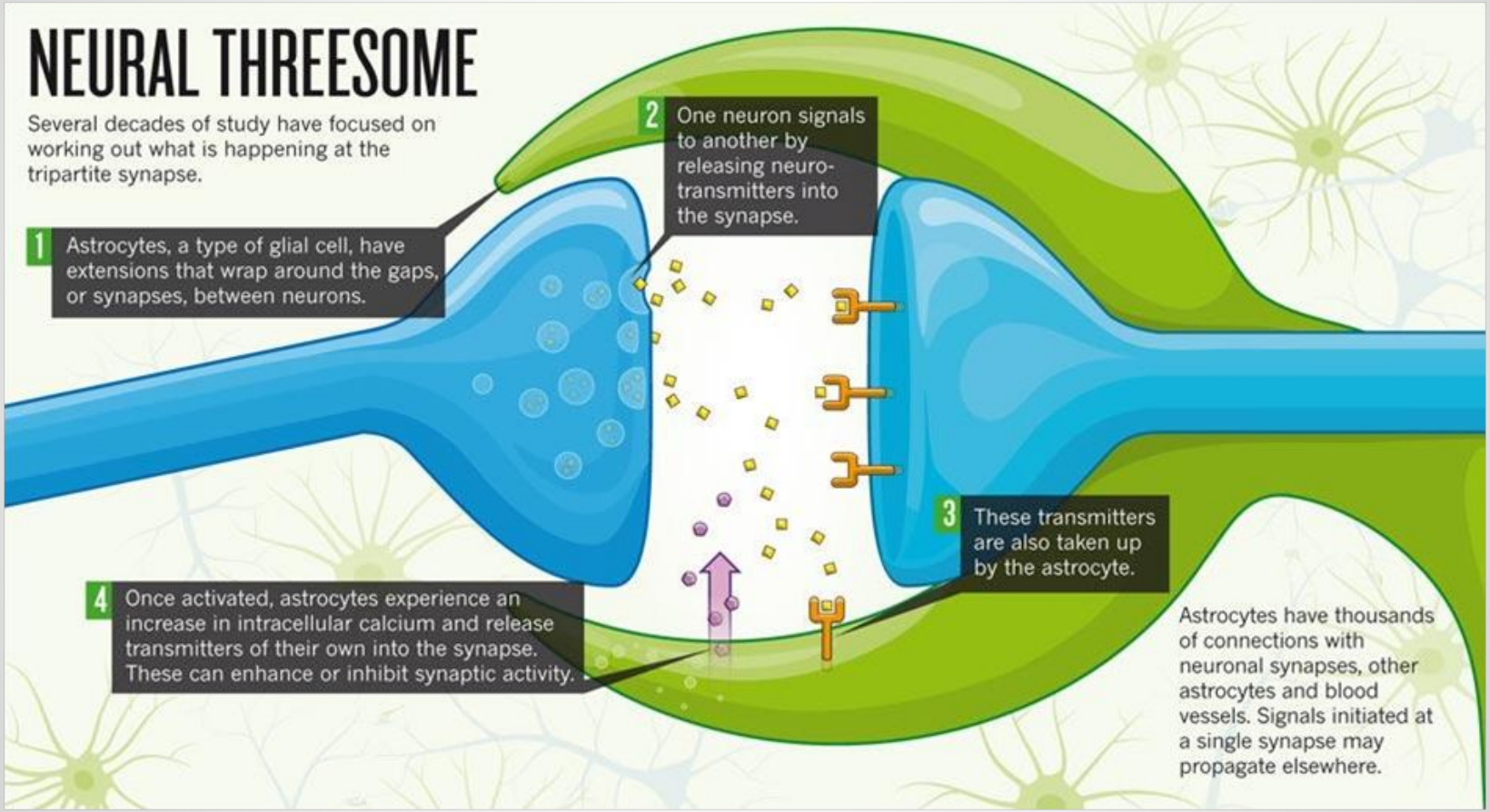
(3) rapid migration along other axon

(4) selective fasciculation

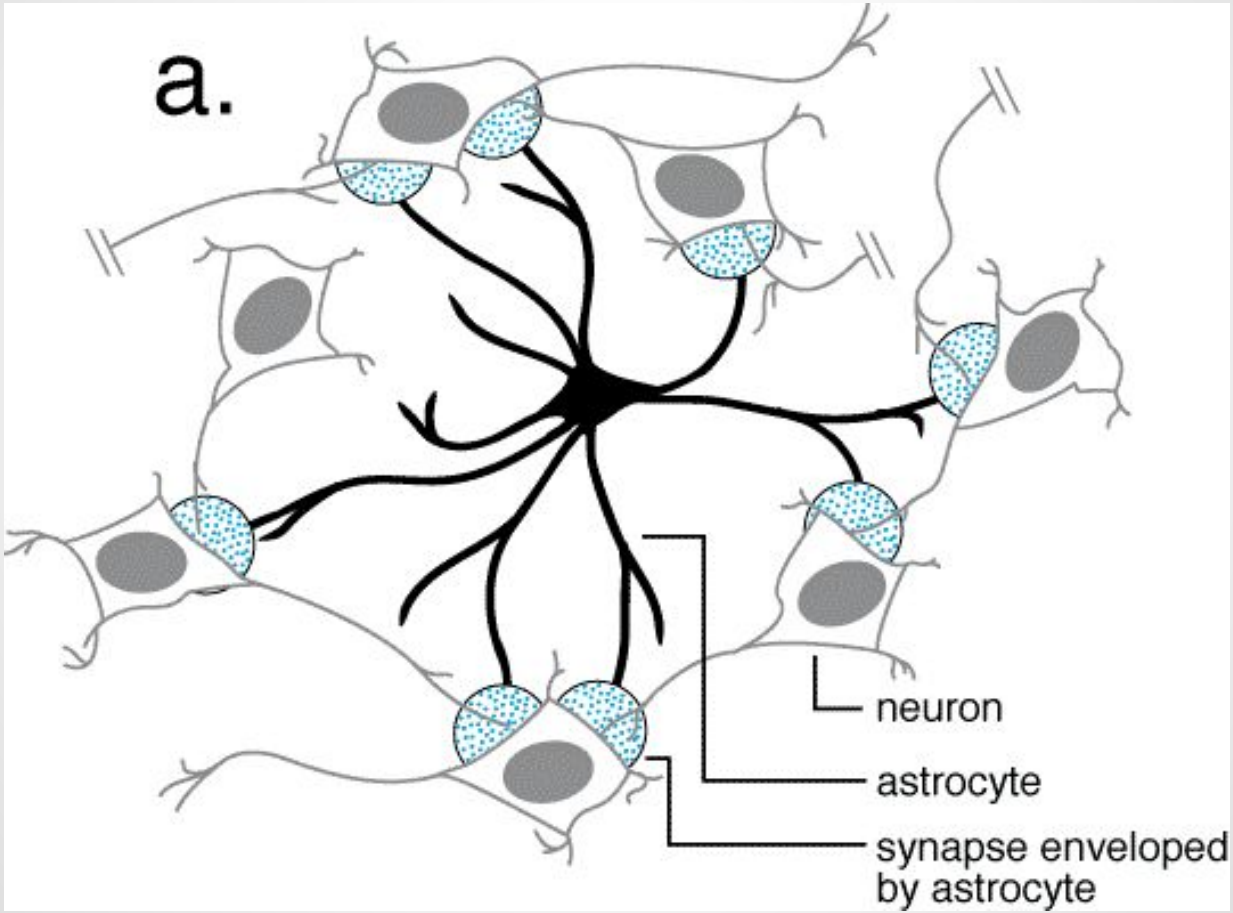
(5) collapse.

The playback speed is 190 times of the real time.

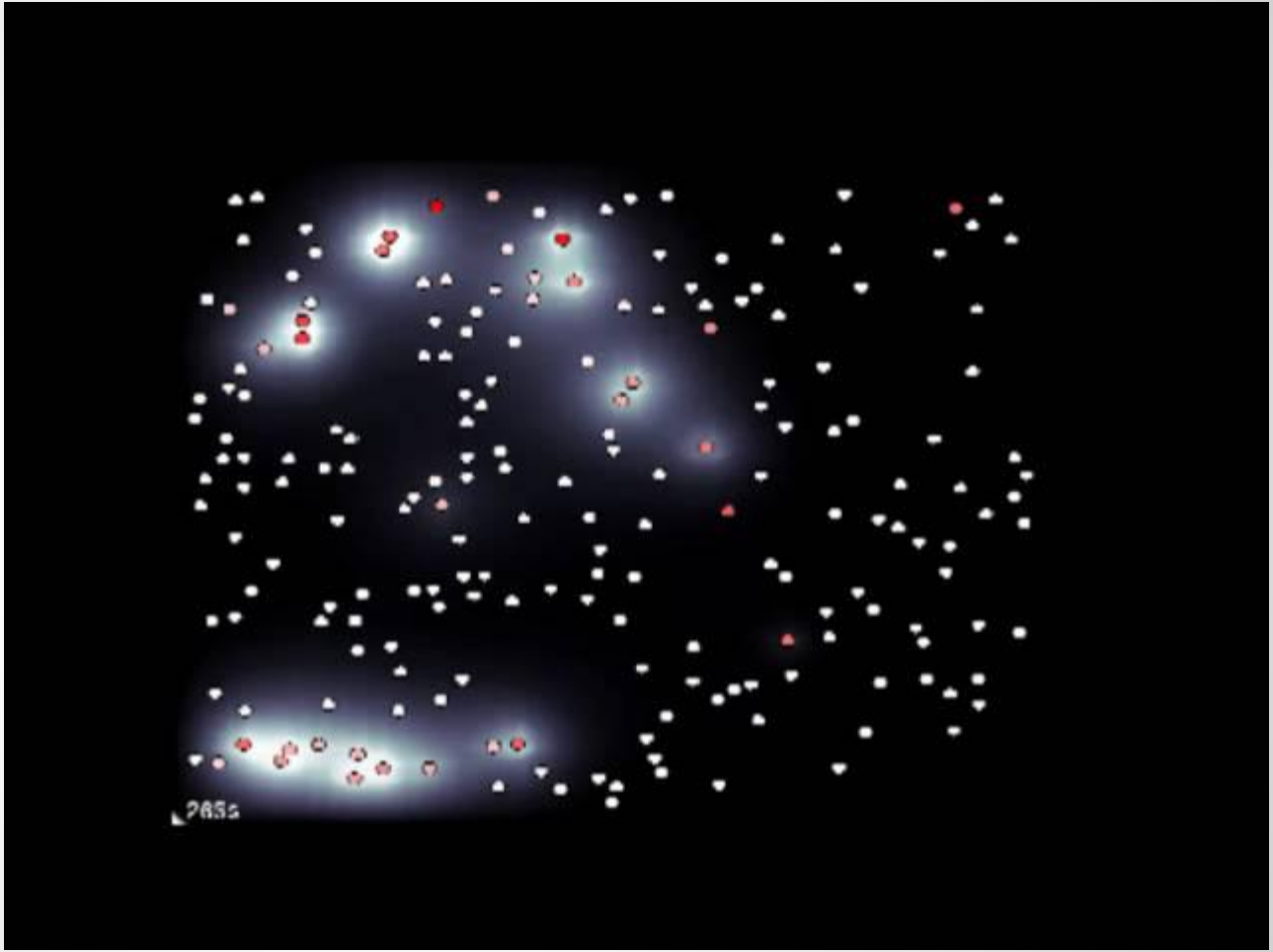
Neuron-Astrocyte Communication

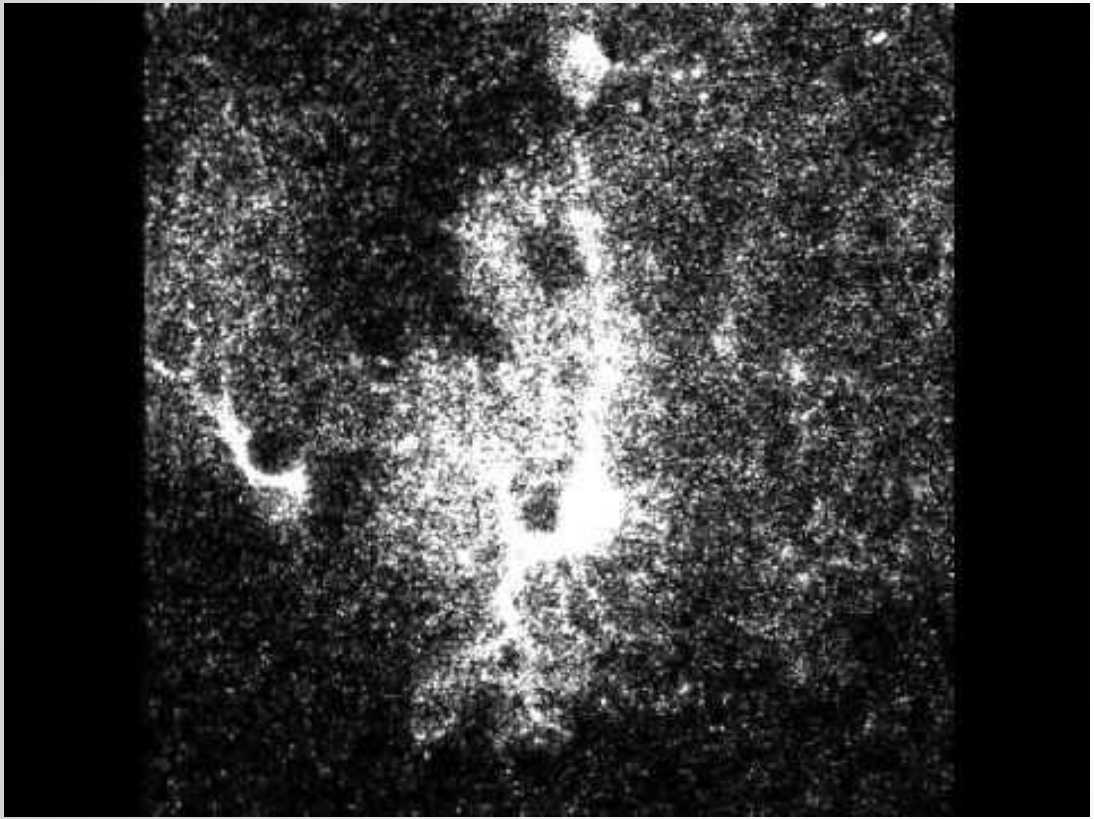


Network Communication



The bioengineers found that amyloid beta peptides (Aβ) spontaneously trigger calcium waves in purified cultures of astrocyte cells extracted from the cortex region of rat brains and grown in the lab. These calcium waves could be relevant for understanding the origin of Alzheimers disease.





This video shows astrocytes in the hippocampus, keeping tabs on neuronal conversations. The flashes of light indicate changes in calcium levels within the astrocytes. When neurons show a burst of activity, calcium levels dramatically increase in the astrocyte, lighting up the entire cell.

Video courtesy of Baljit S.

Open Questions

- Quantity of end-feet per astrocyte
- Astrocytic role in neurotransmission
- What kind of brain activity are astrocytes related to?
- What are their cellular/molecular sources?
- What is the role of astrocytes in plasticity?
- What is the precise role of astrocytes in axonal pruning?
- The details between astrocyte-astrocyte communication