Astrocytes modulate ionic homeostasis at active synapses

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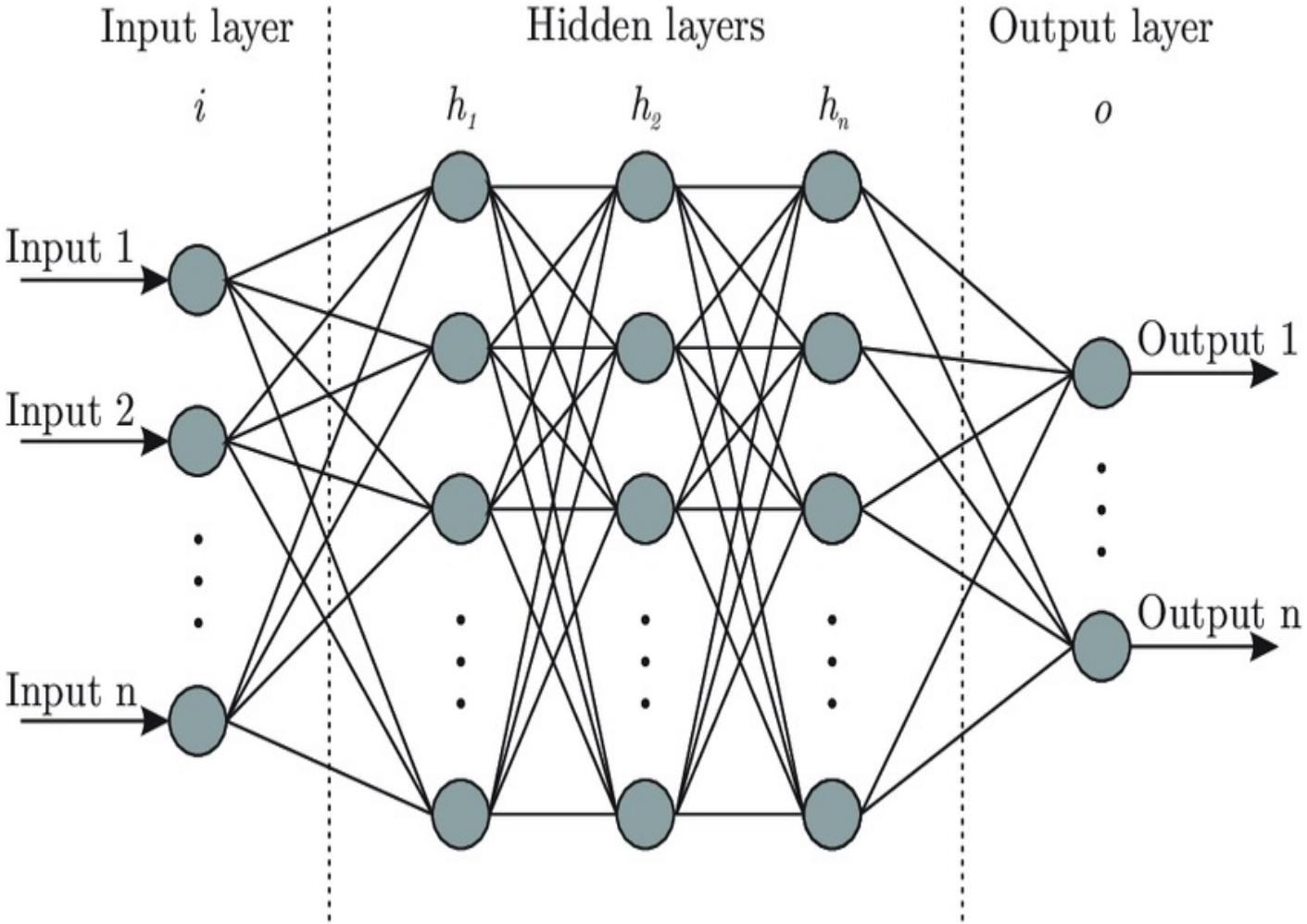
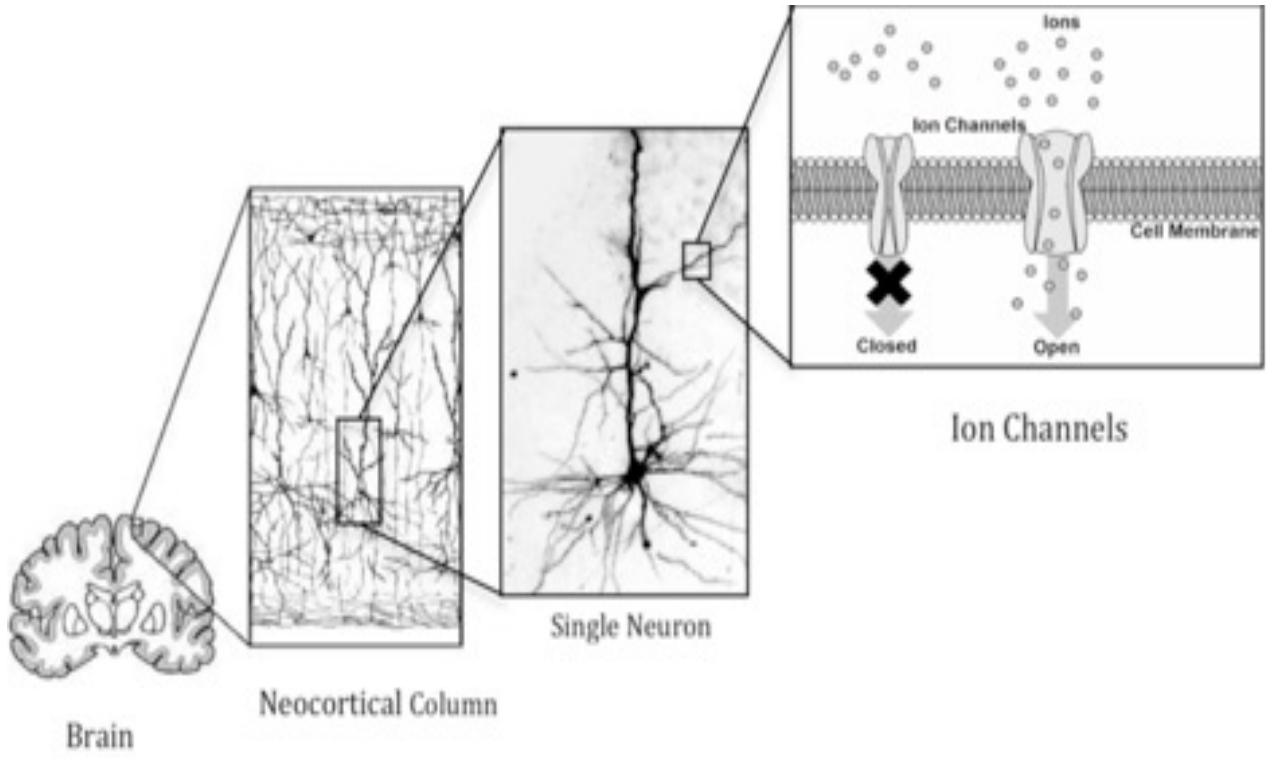
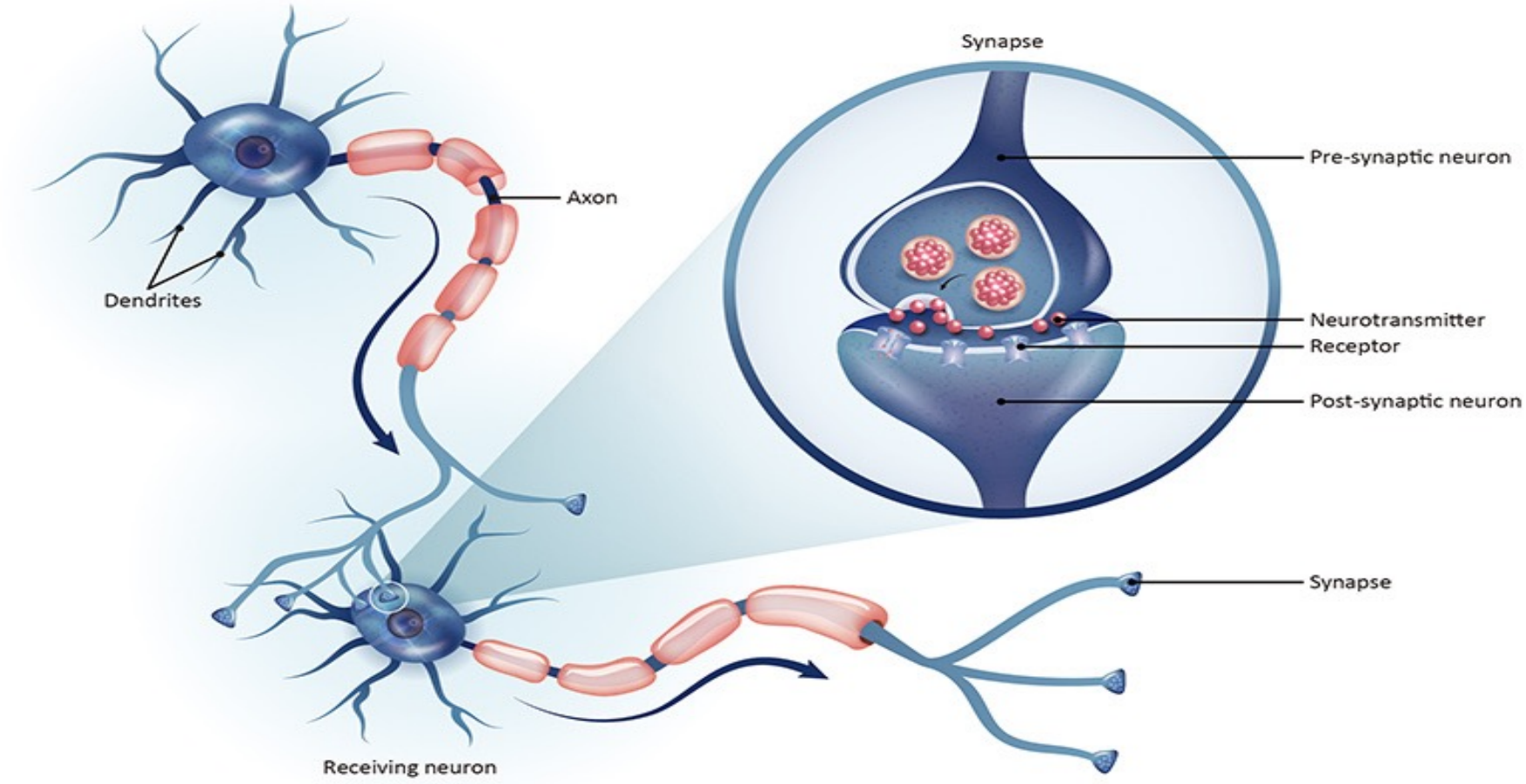
Neural Network Model



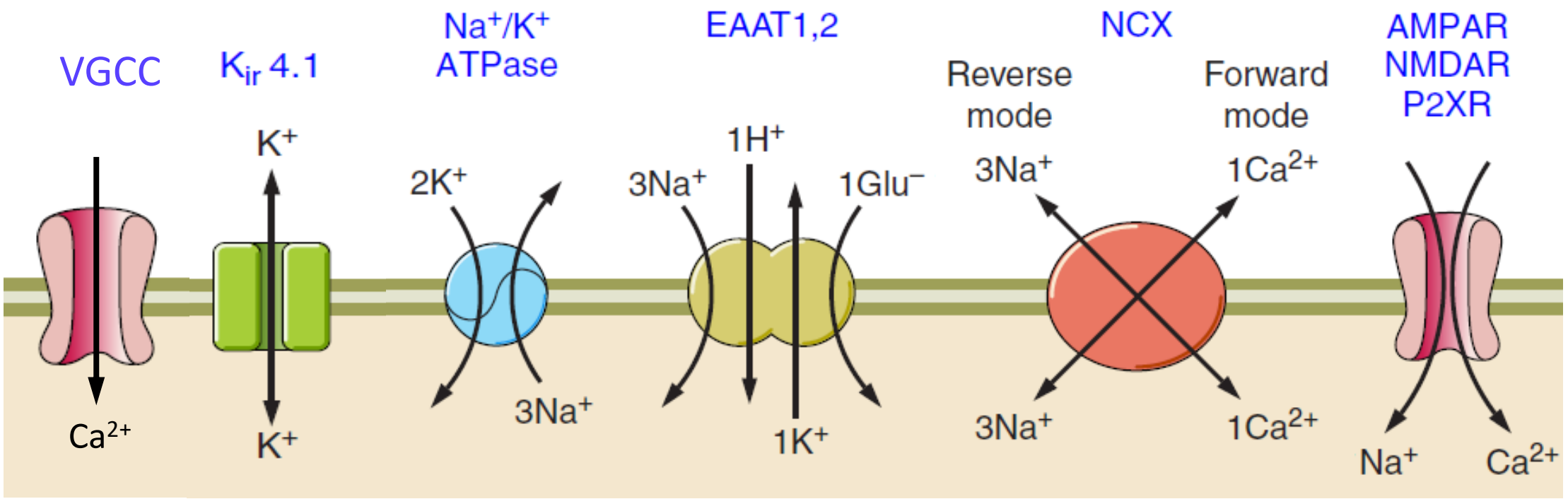
Model Abstraction Level



Synaptic Junction between two Neurons



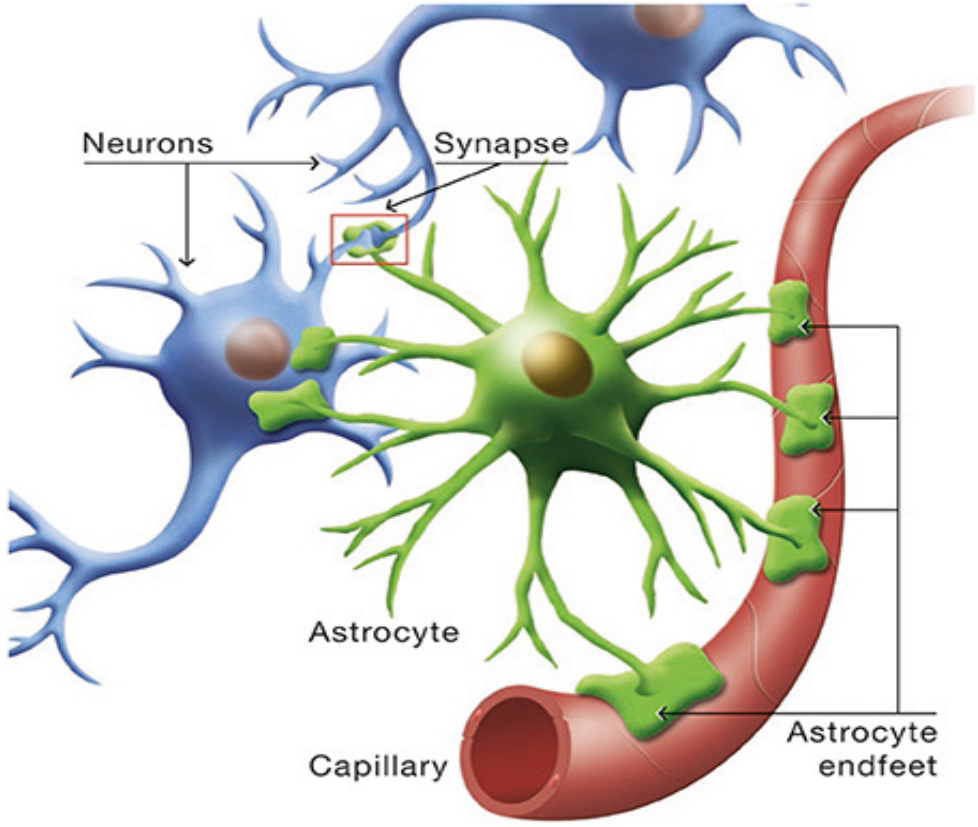
Ionic Transport Across Cell Membranes



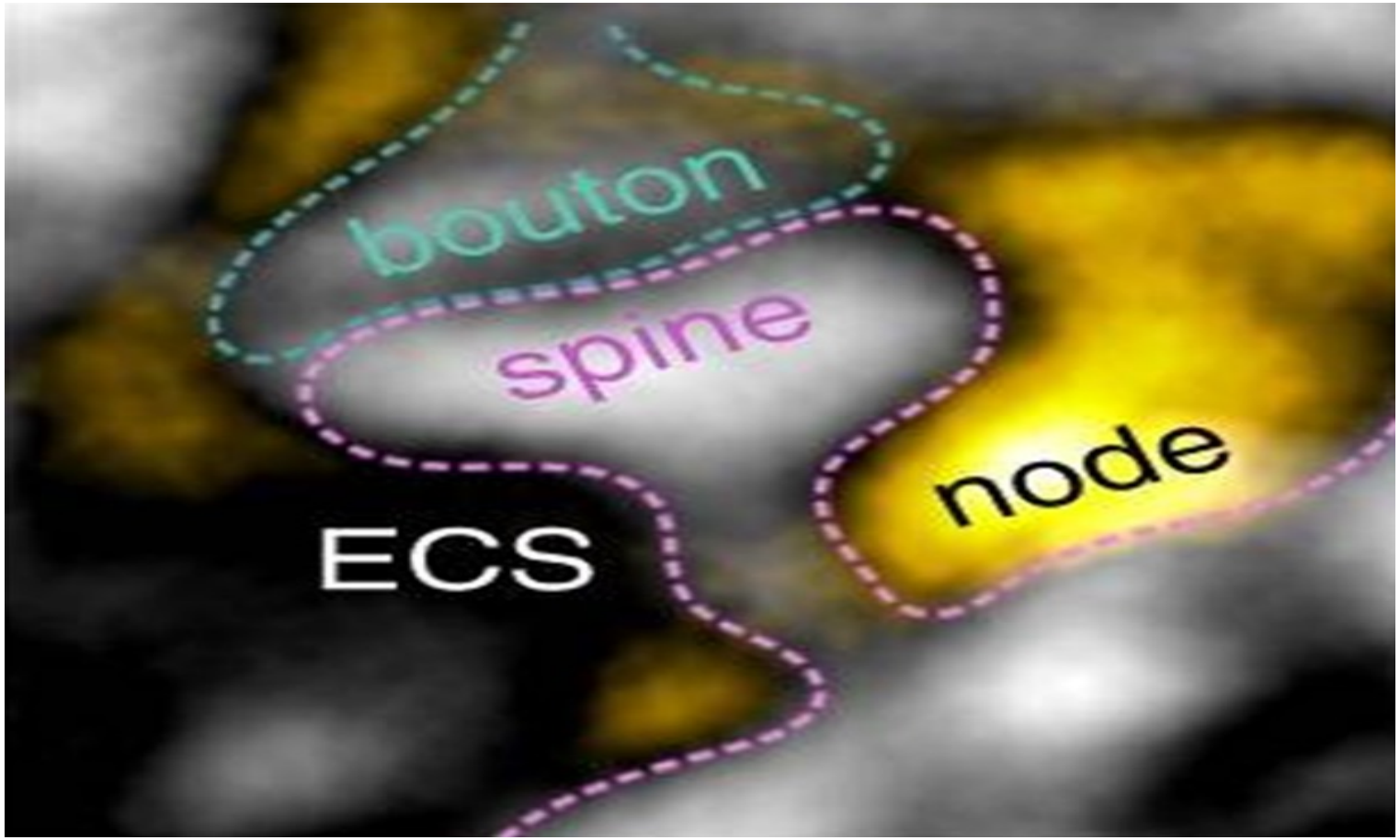
Reference: **Verkhratsky A, Nedergaard M.** Physiology of Astroglia. *Physiol Rev* 98: 239–389, 2018. doi:10.1152/physrev.00042.2016.

New Player-Astrocyte

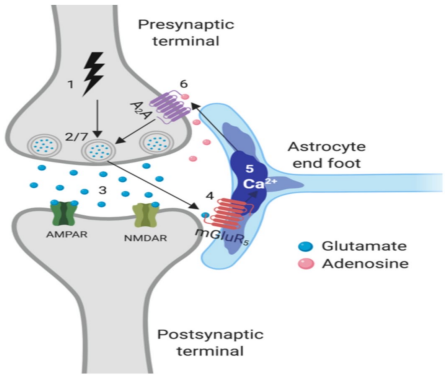
- Astrocytes - type of glial cell that enwraps neuronal synapses
- Astrocytes semi-isolate synapses
- Homeostatic control of different ionic species like Ca^{2+}, Na^{+} and K^{+}
- Thin processes ($\backsim$50nm) play a crucial role in ionic flow – effectively semi-isolate cradle from soma

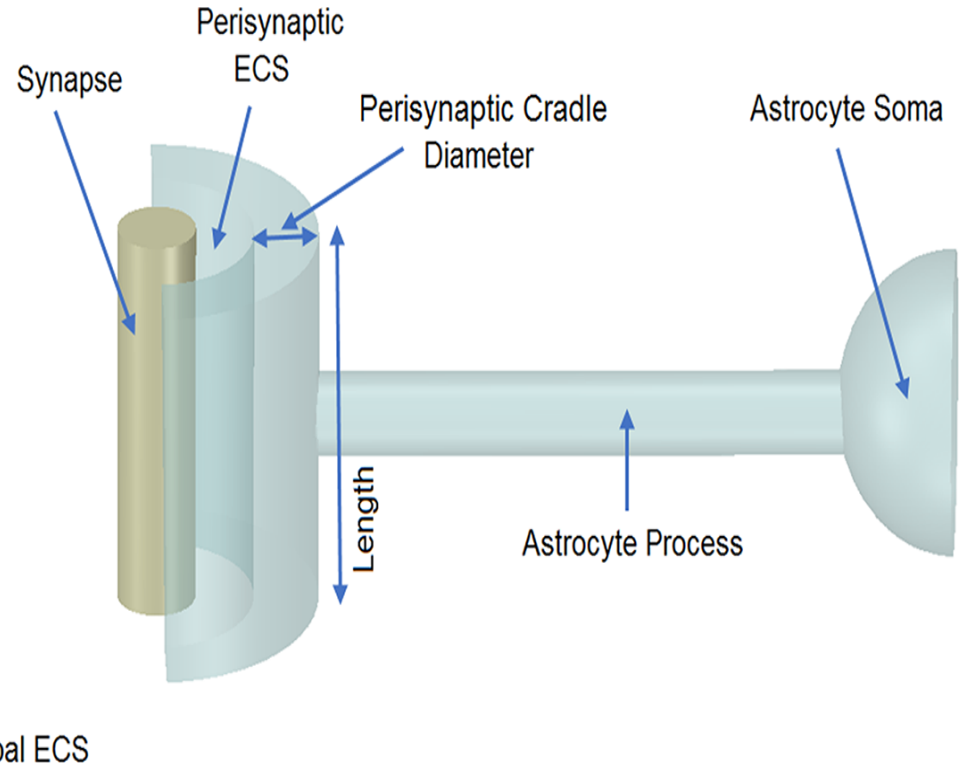


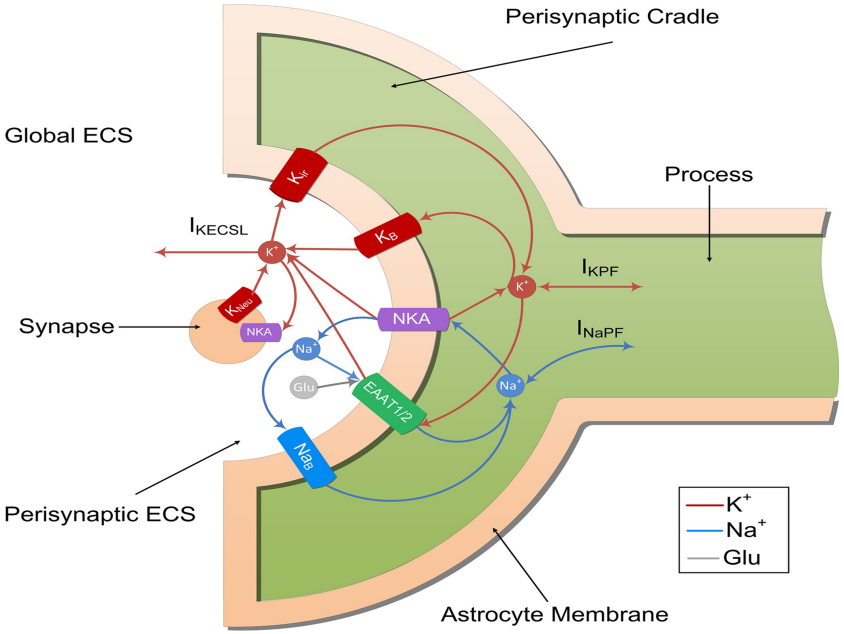
Astrocyte Coverage at Tripartite Synapses



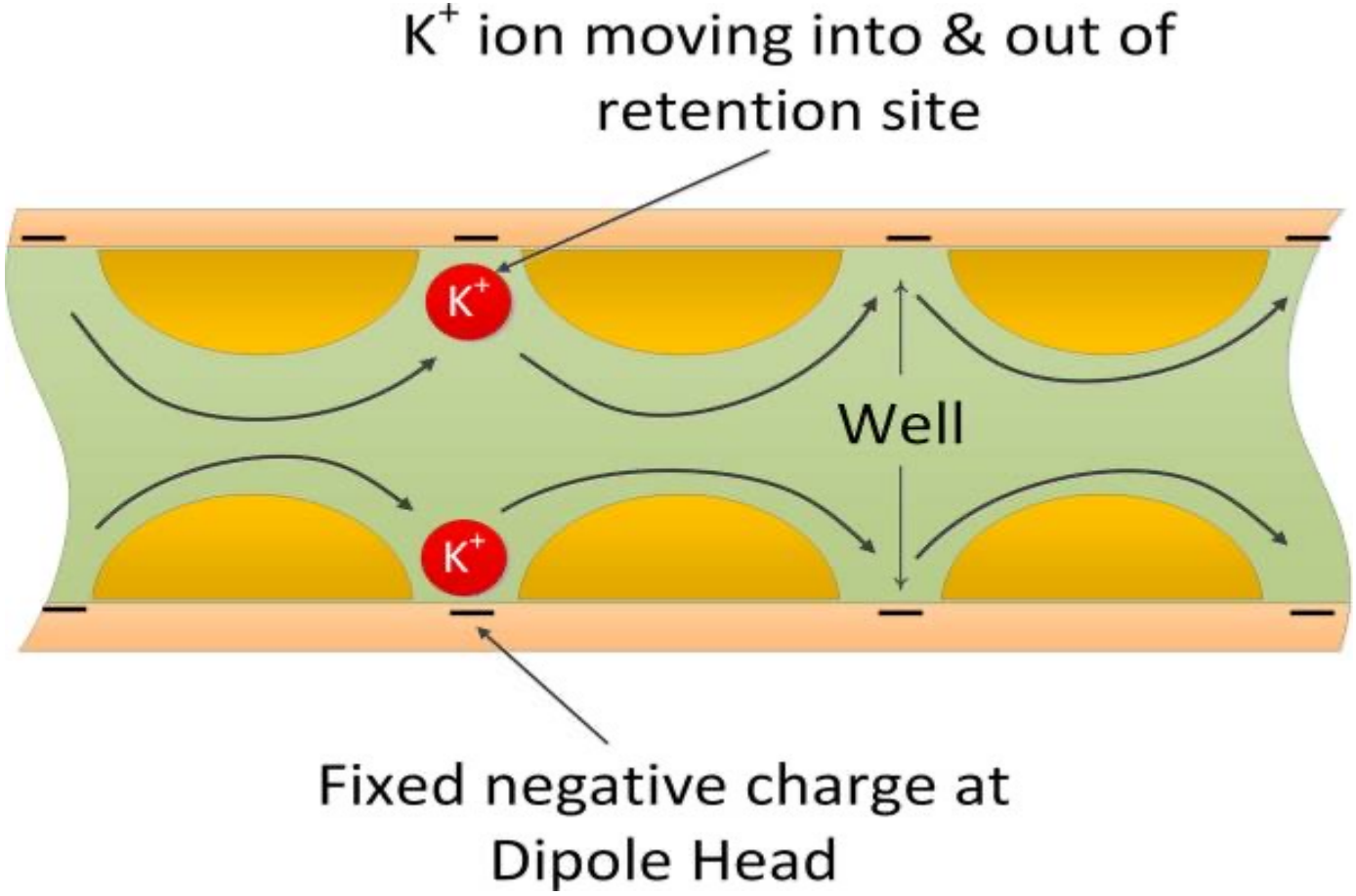
Tripartite Synapse Model







Retention Sites in Thin Processes



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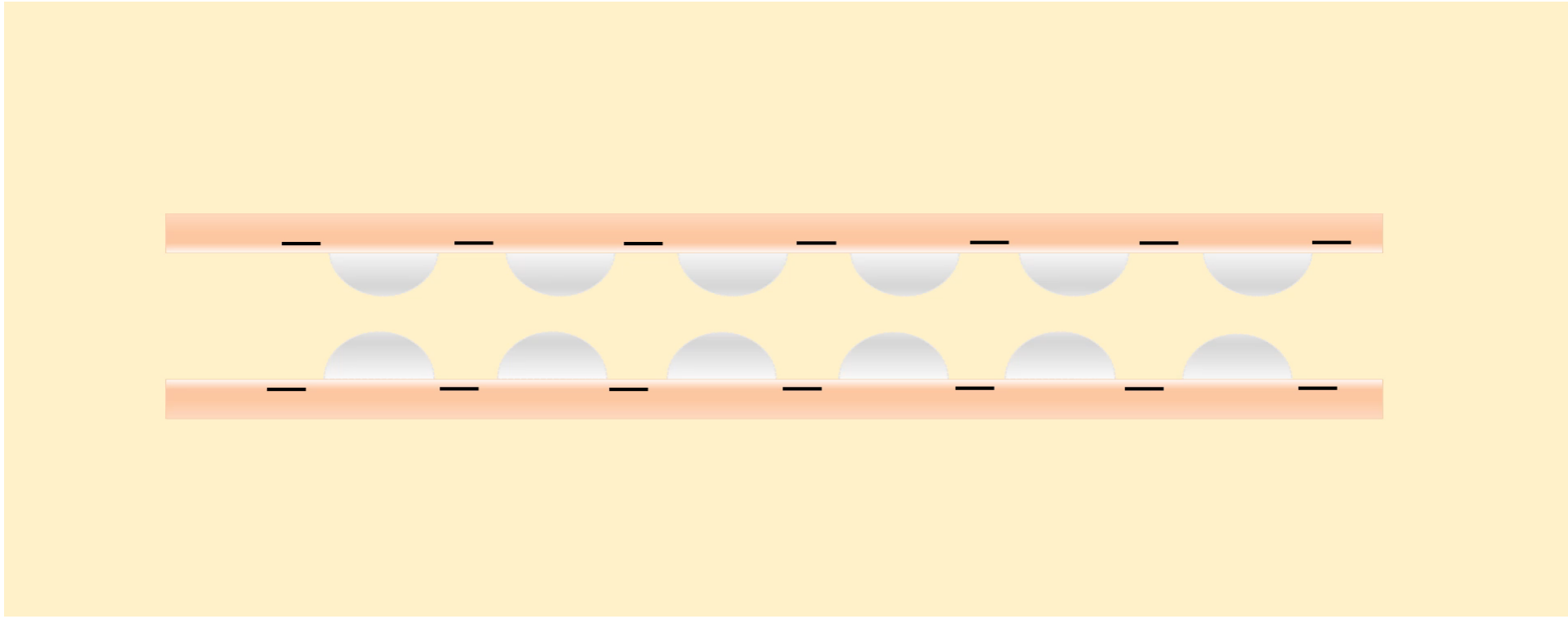
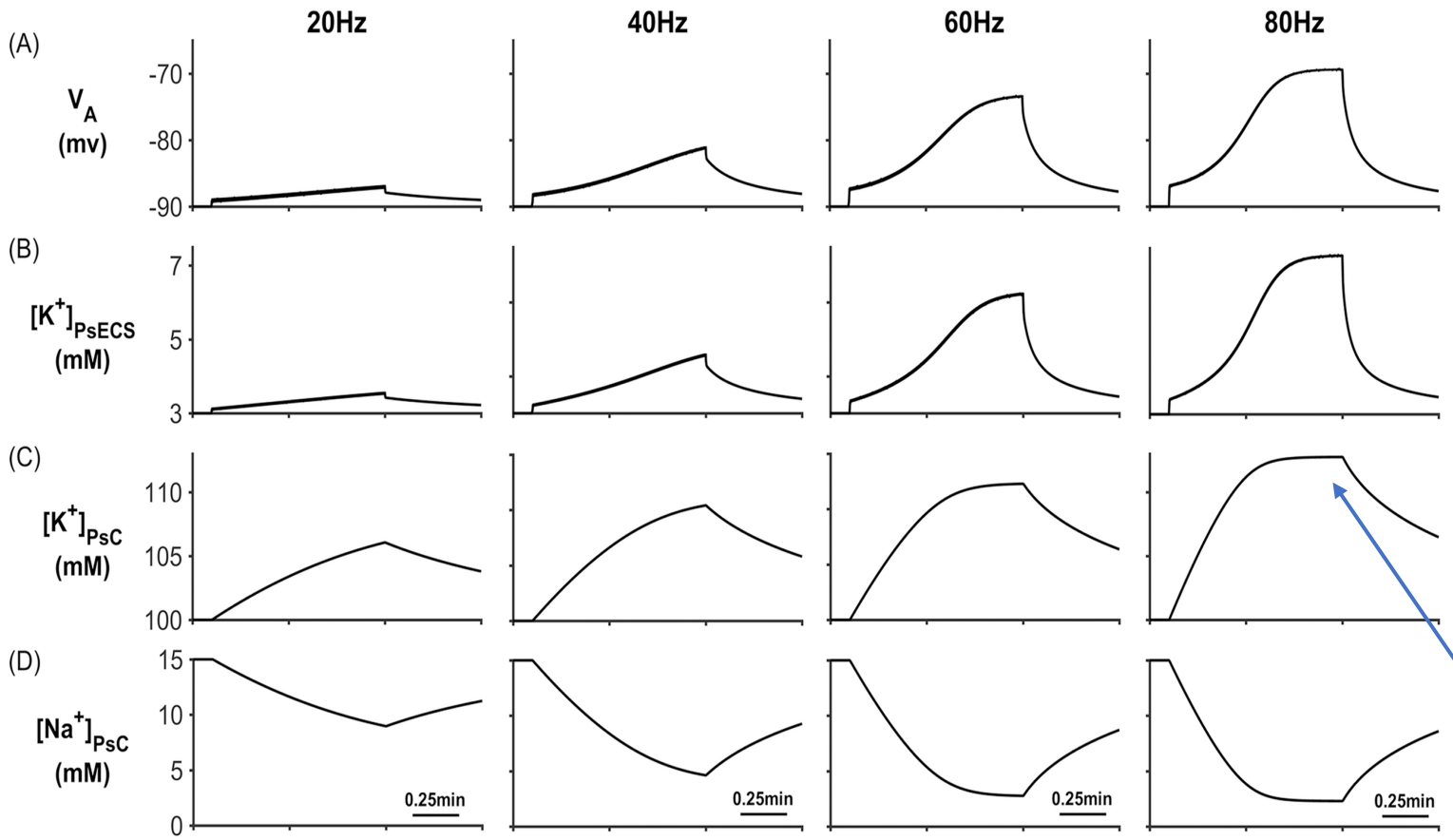
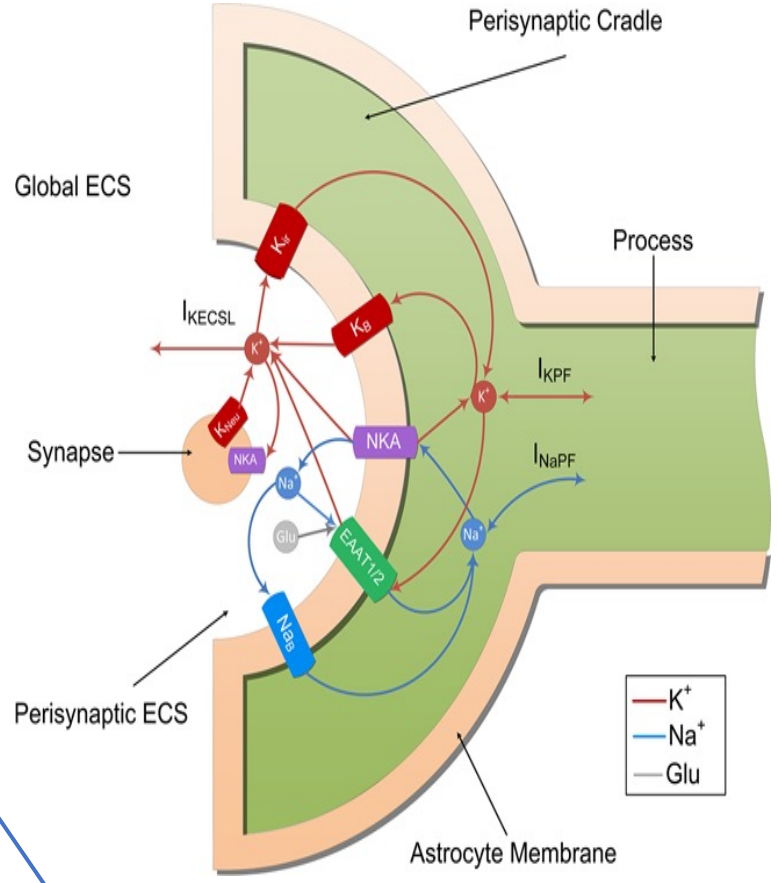


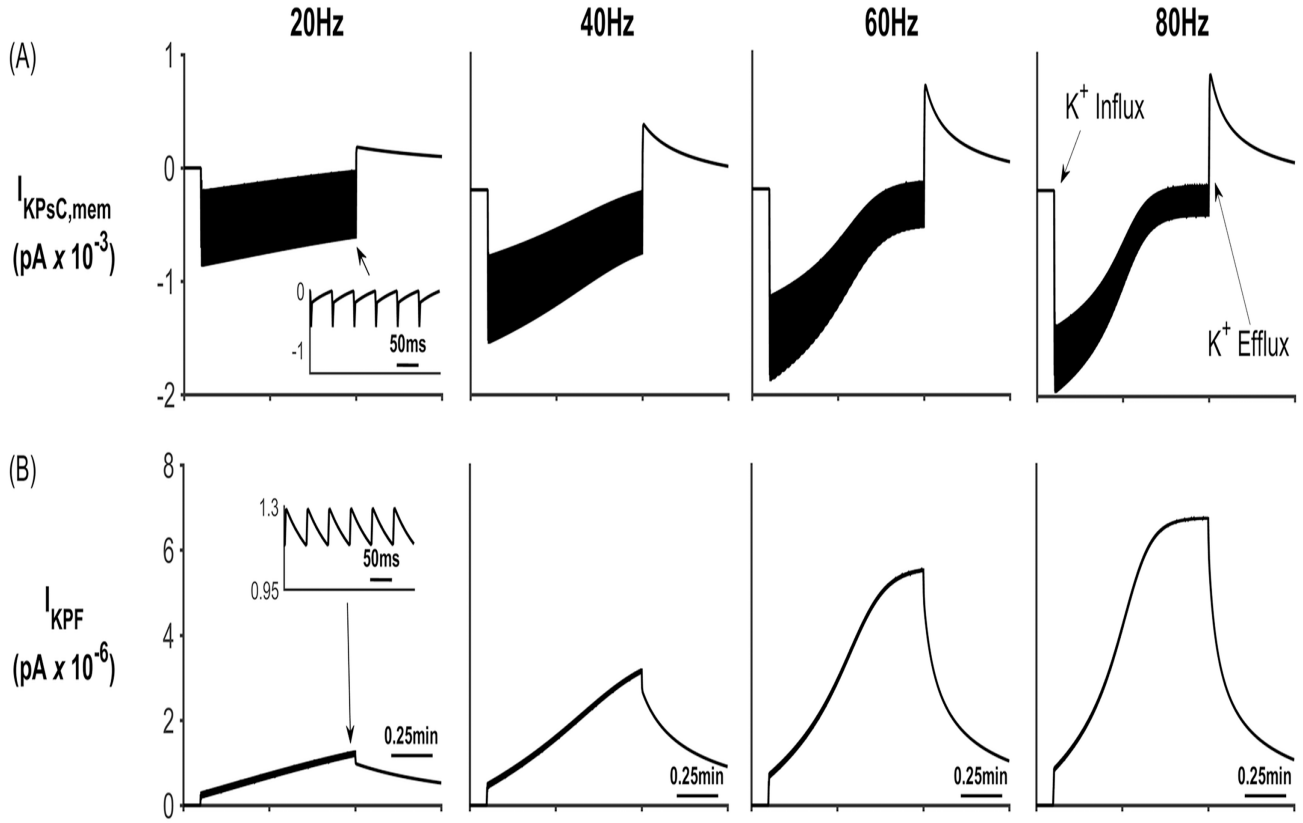
Potassium Buffering

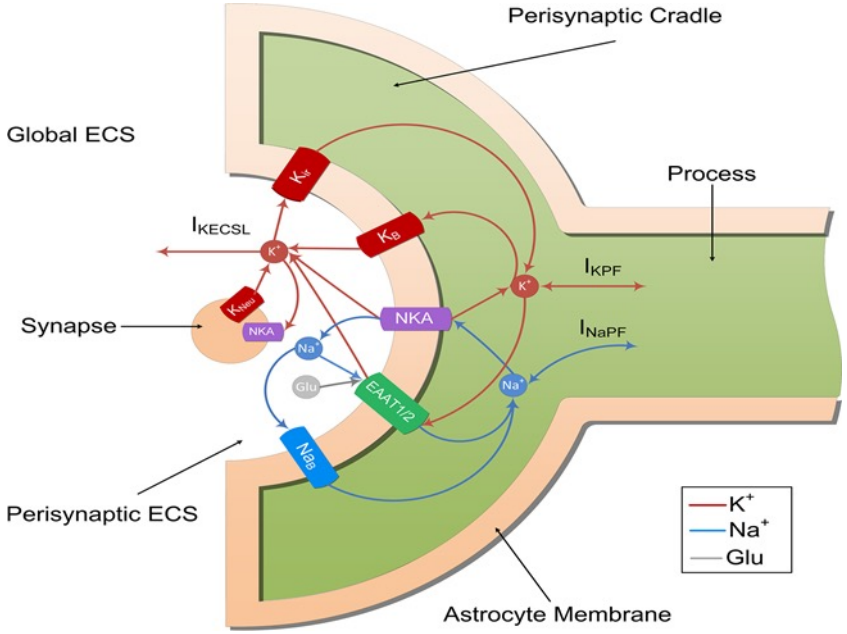




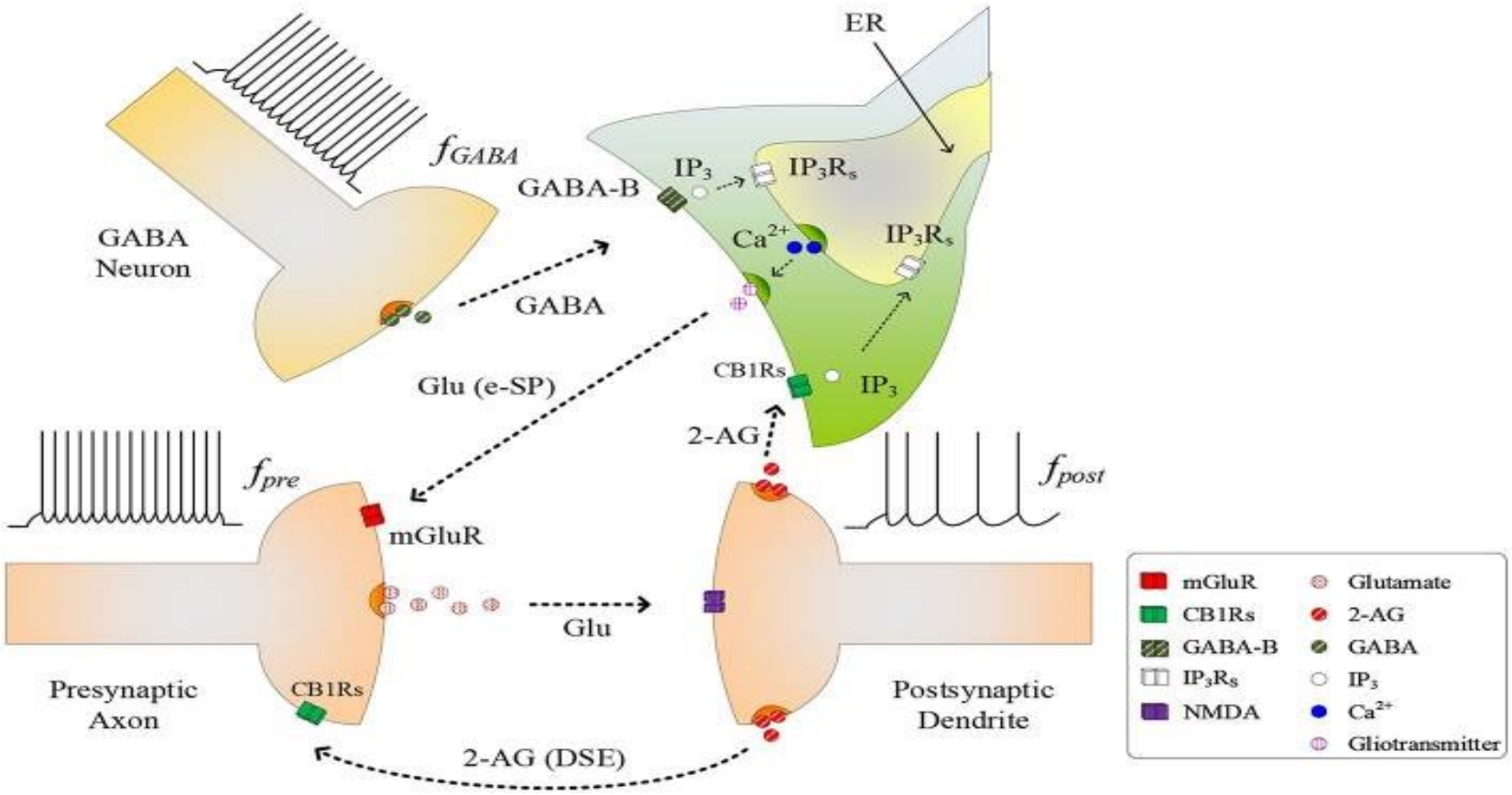
Microdomain

Potassium Buffering

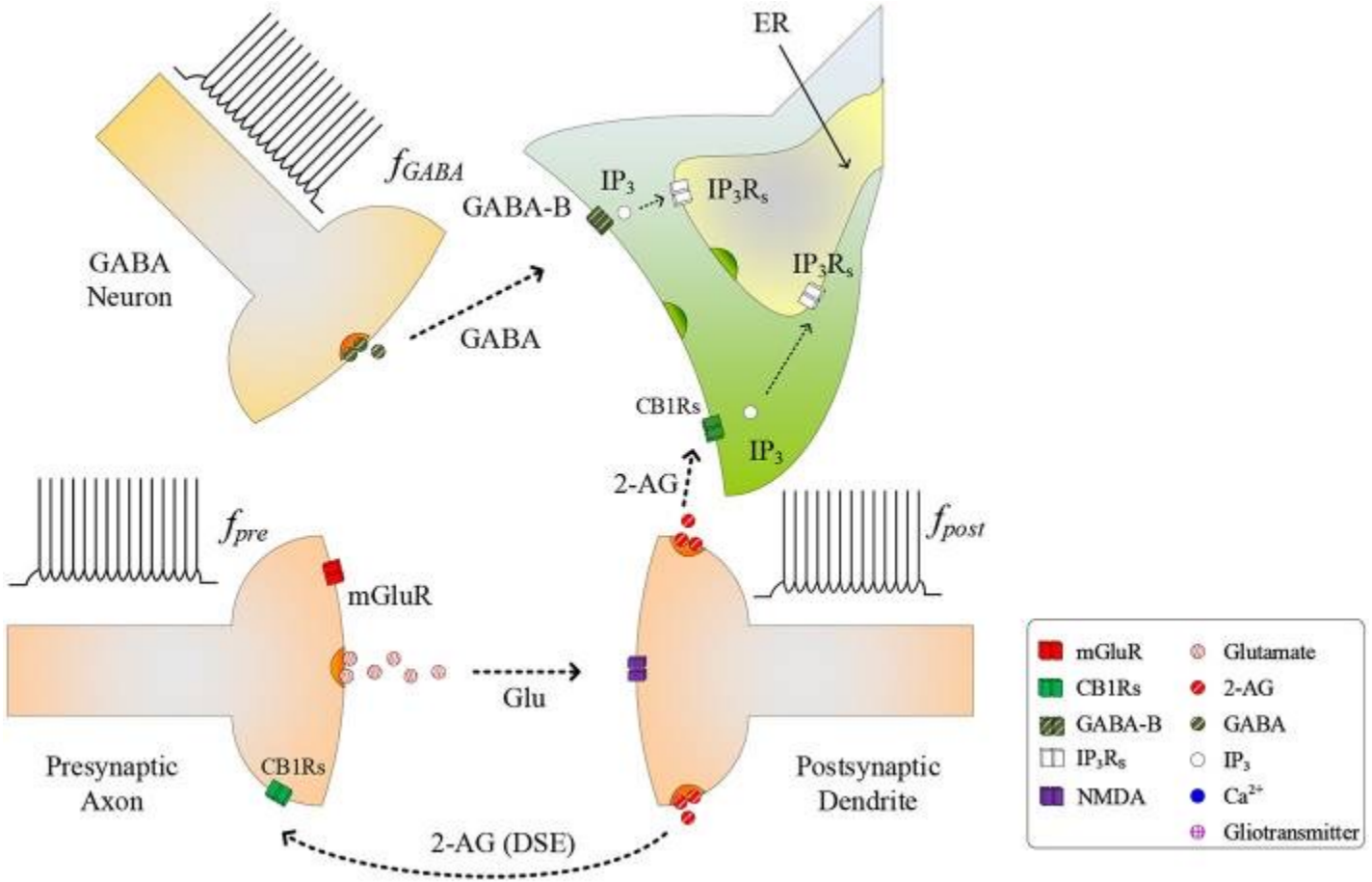




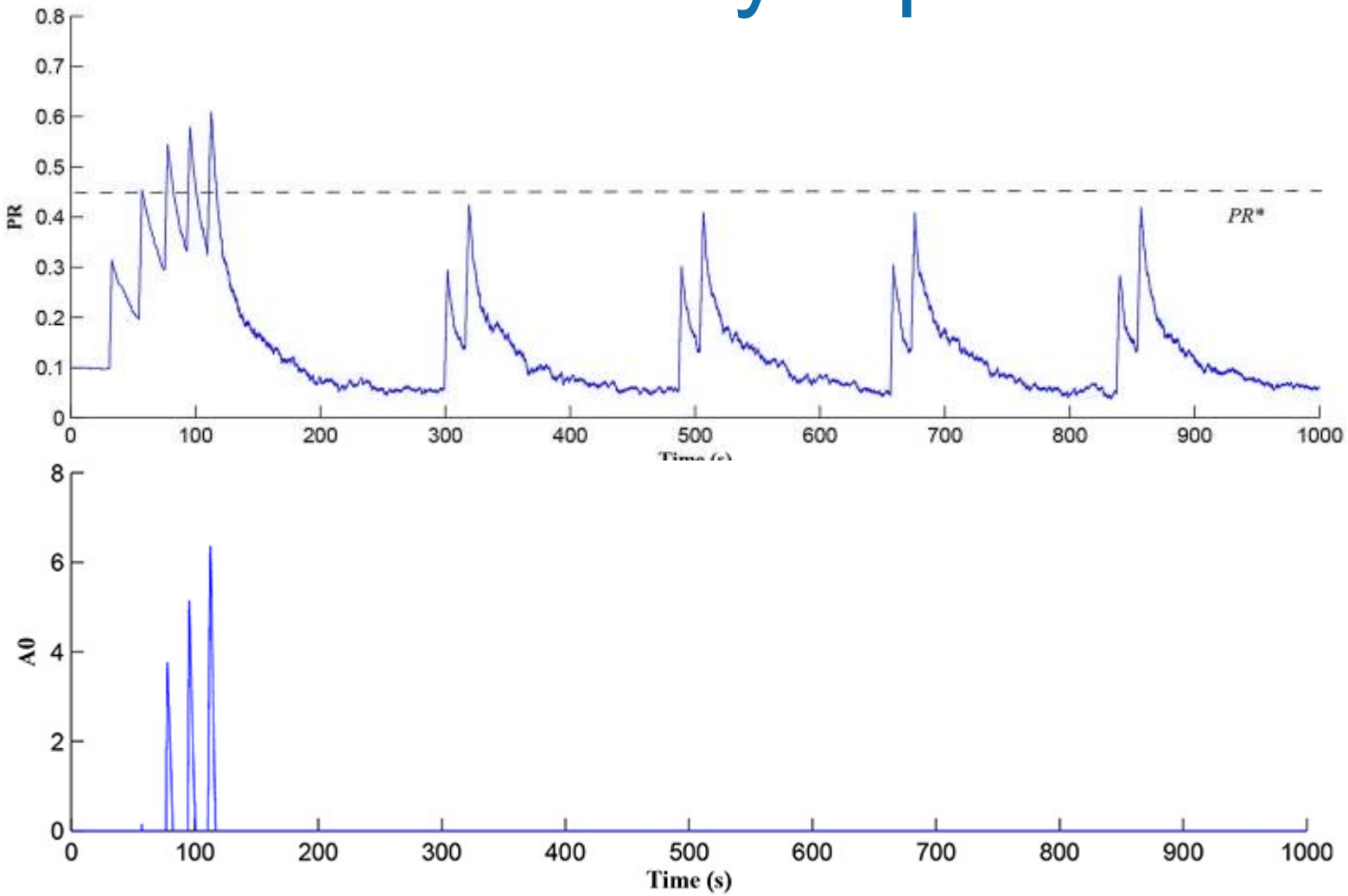
GABA Interneurons - Tripartite synapse

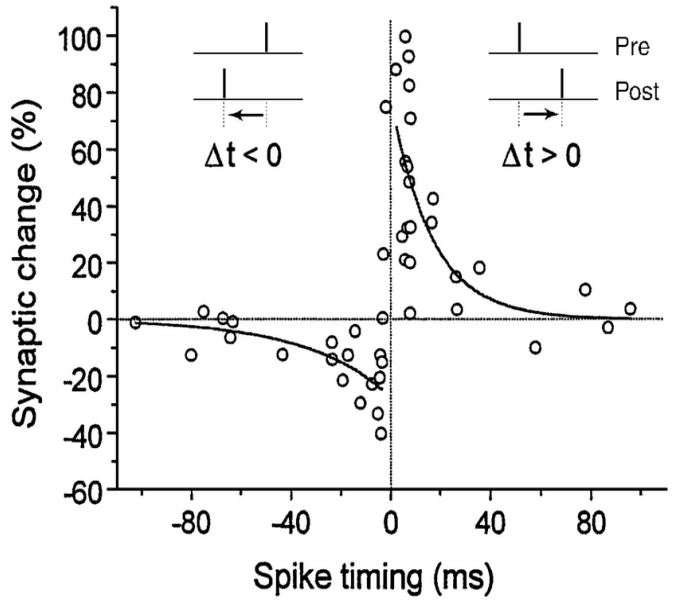


GABA Interneurons - Tripartite synapse

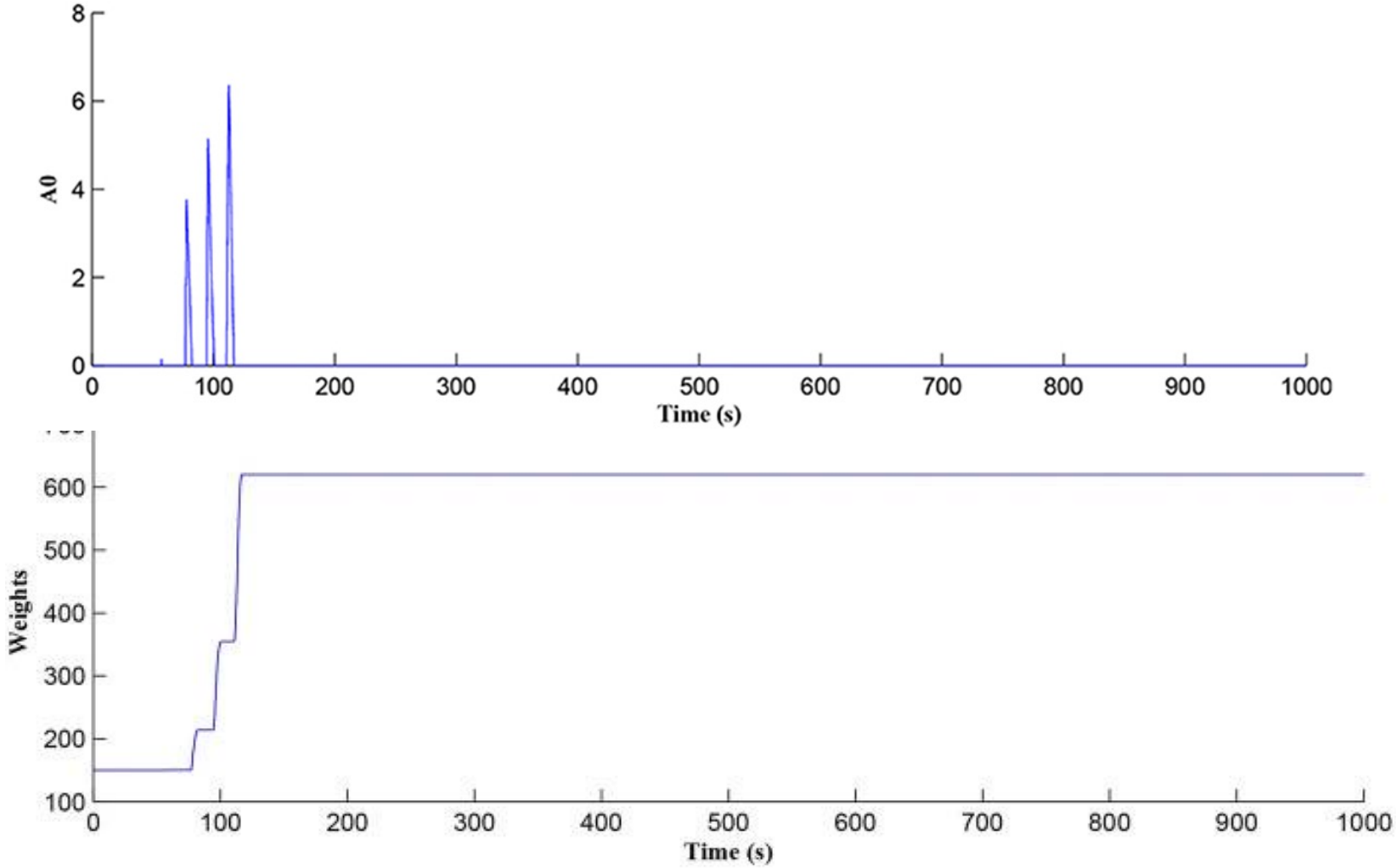


STDP - Synaptic Potentiation

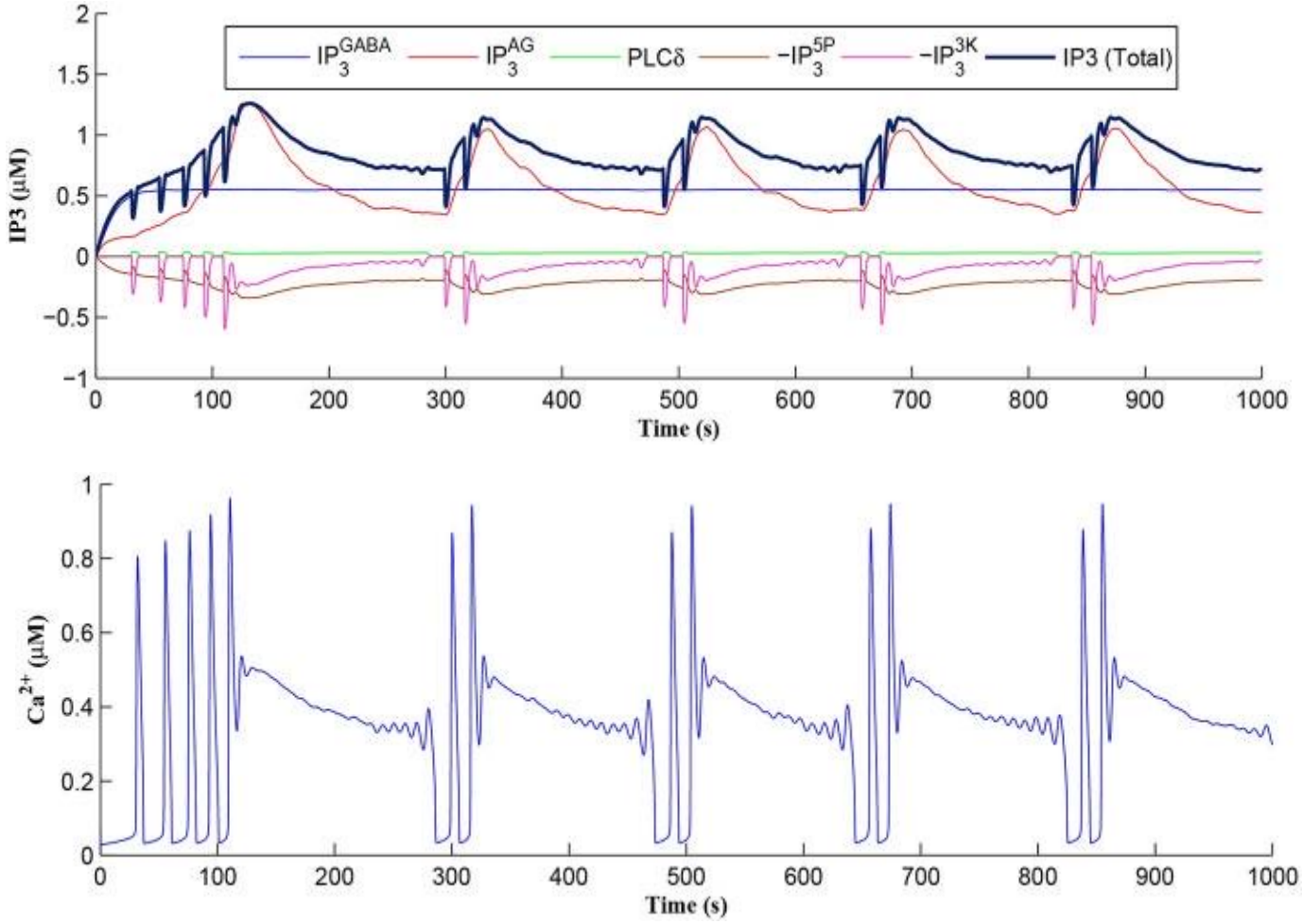


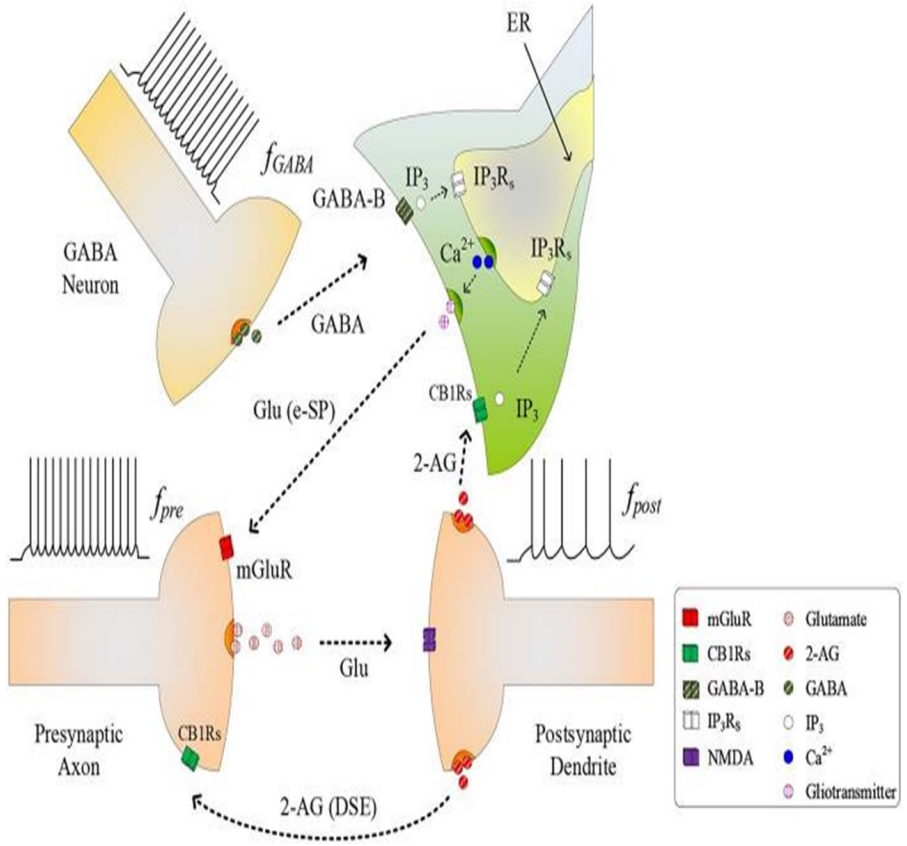


Weight Potentiation When STDP Window Open

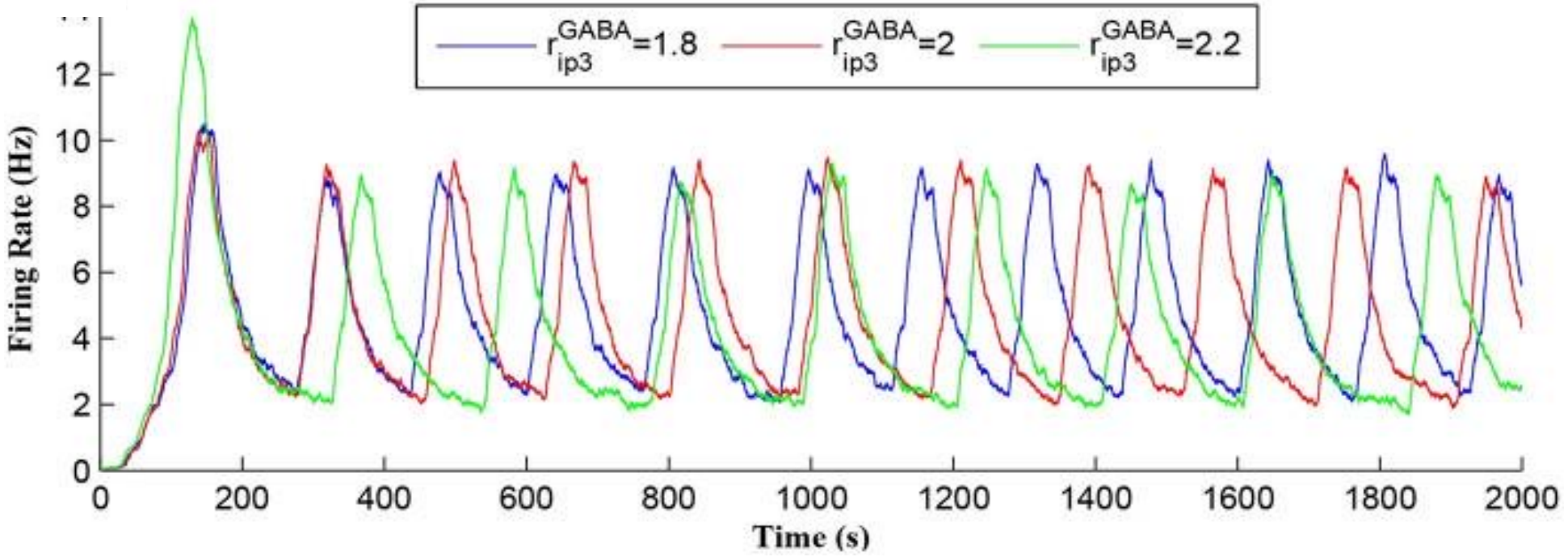


Calcium Oscillations



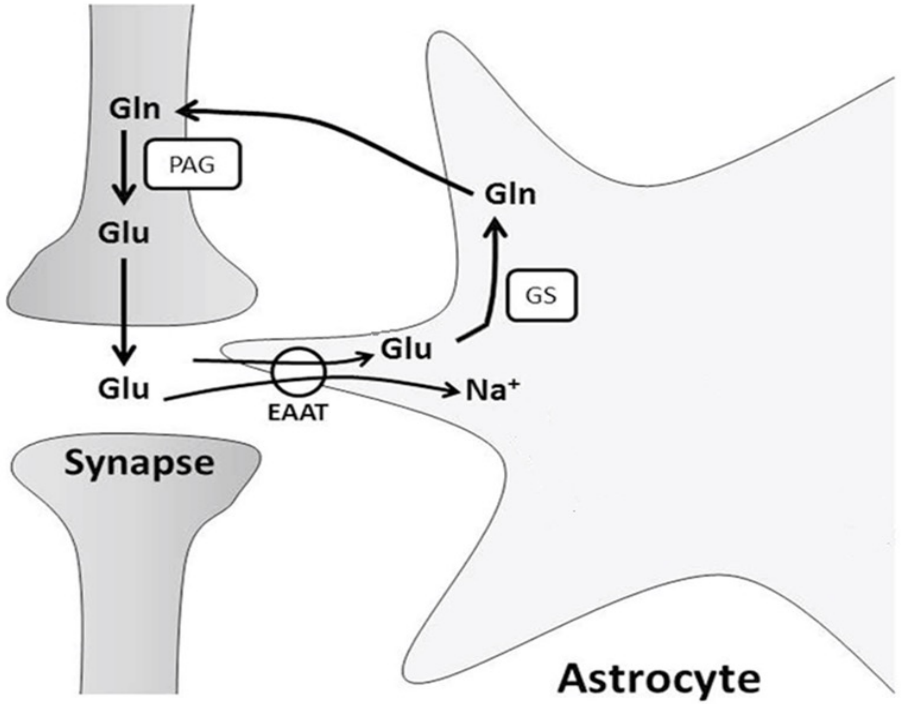


Neuronal Burst Firing



Change in GABA production rate r_{ip3}^{GABA} leads to a change in burst firing rate –look at the first 1000 seconds - $r_{ip3}^{GABA} = 1.8$ gives 6 bursts, $r_{ip3}^{GABA} = 2$ gives 5 bursts while $r_{ip3}^{GABA} = 2.2$ gives 4 bursts

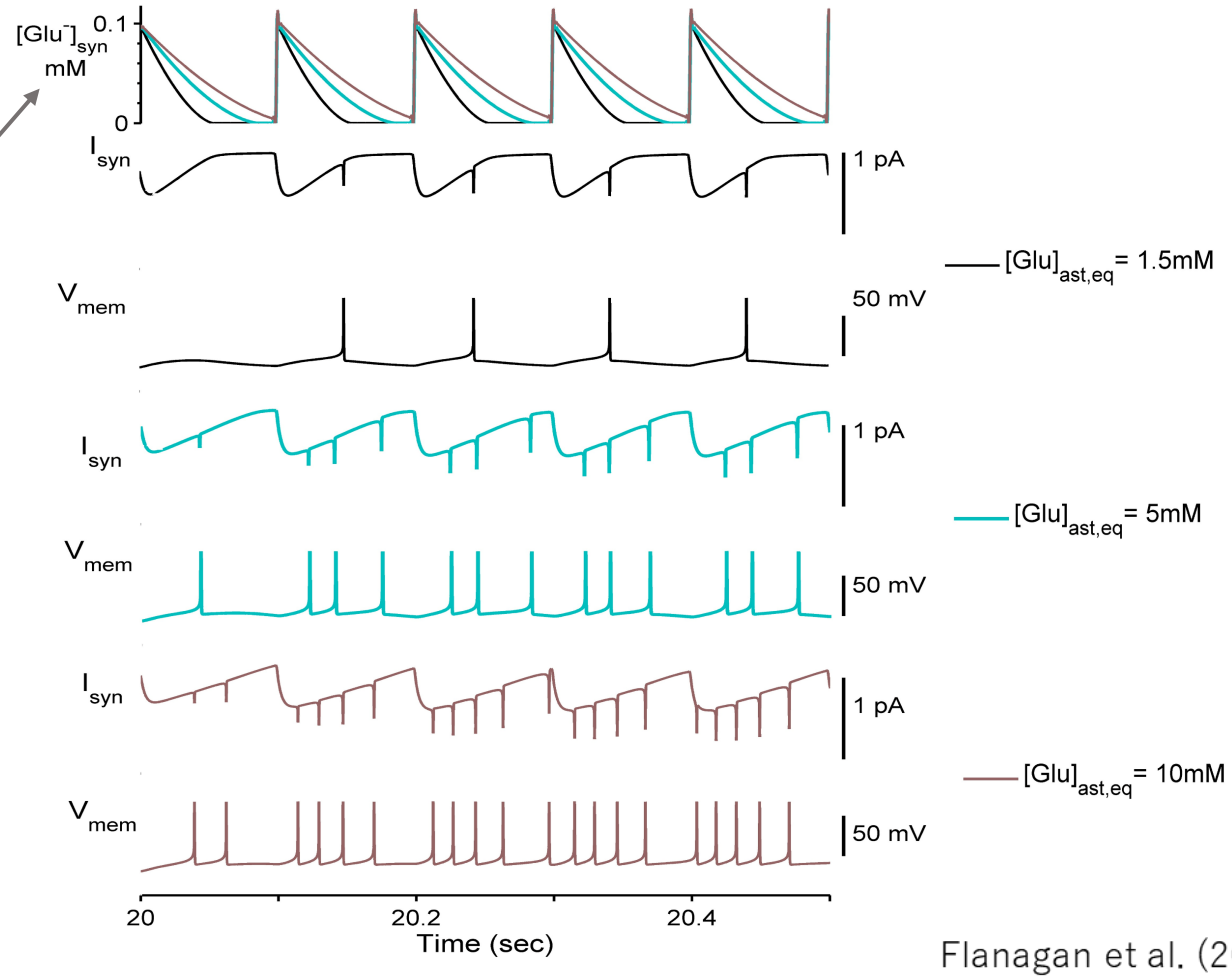
Astrocytic Glutamate Uptake



Adapted from: Stobart & Anderson (2013) Multifunctional role of astrocytes as gatekeepers of neuronal energy supply

Glutamate Clearance and Neuronal Excitability

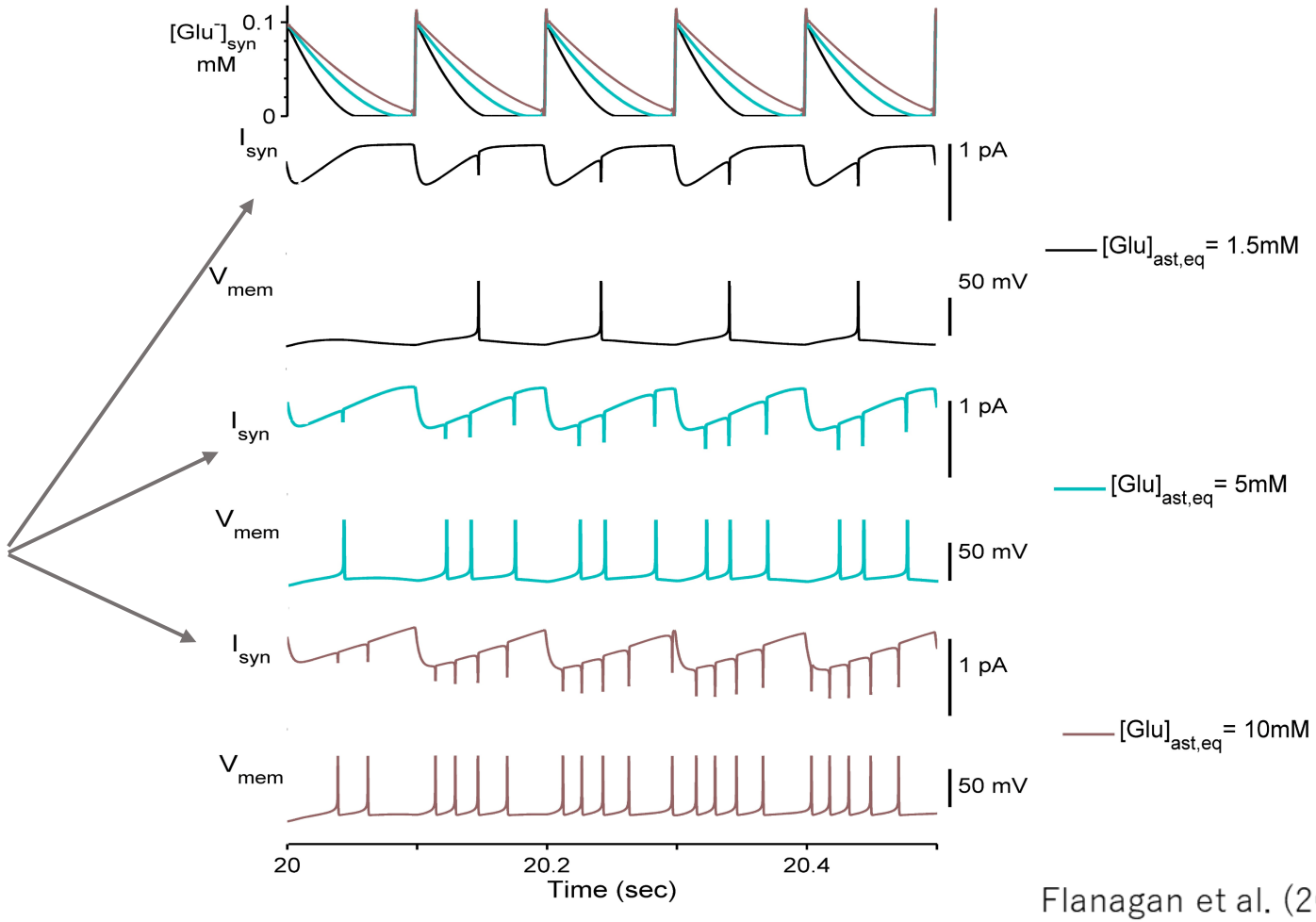
- Increased astrocytic glutamate resulted in slower glutamate clearance at the synapse.



Flanagan et al. (2018)

Glutamate Clearance and Neuronal Excitability

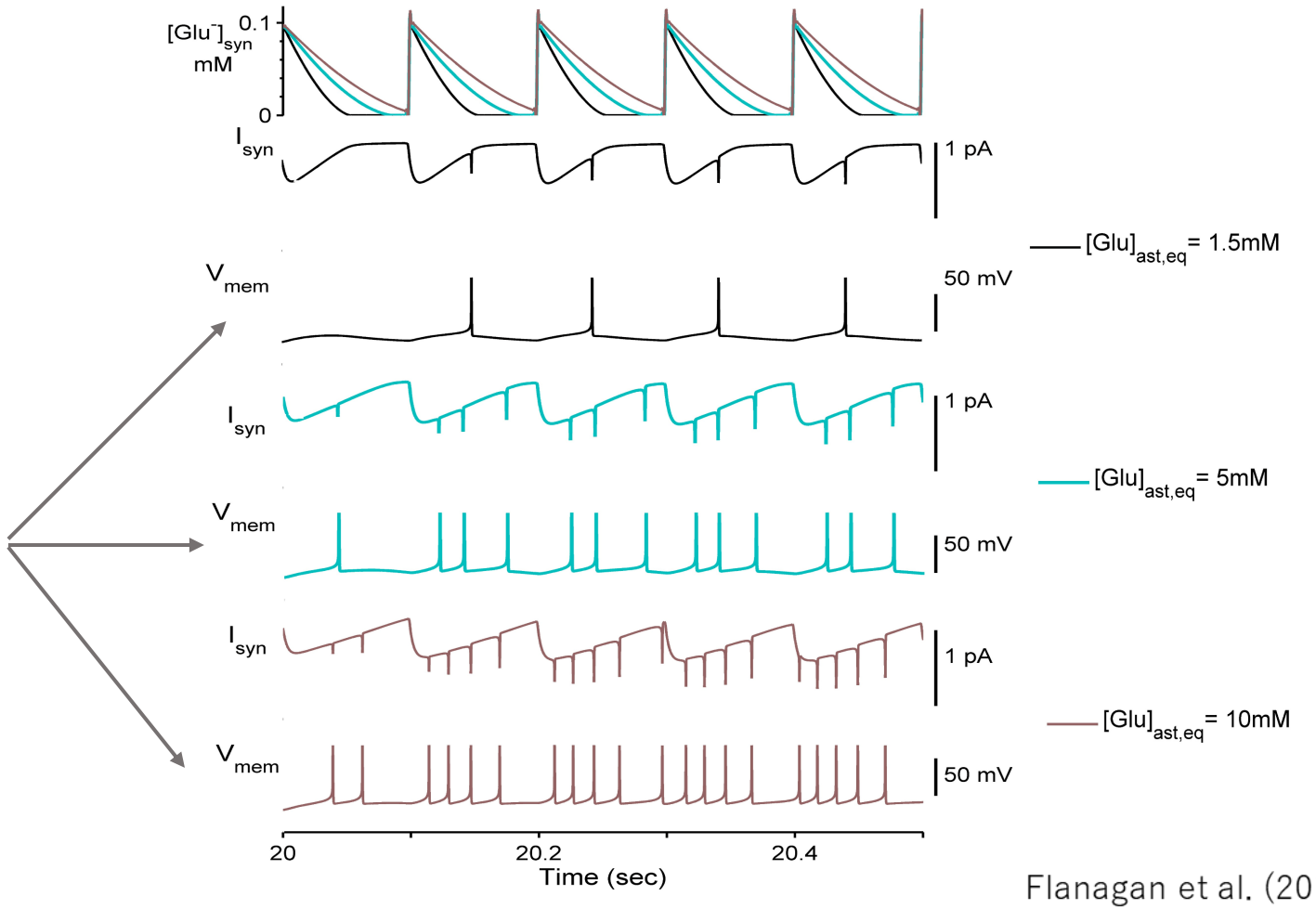
- Prolonged synaptic glutamate-mediated currents due to delayed glutamate clearance.



Flanagan et al. (2018)

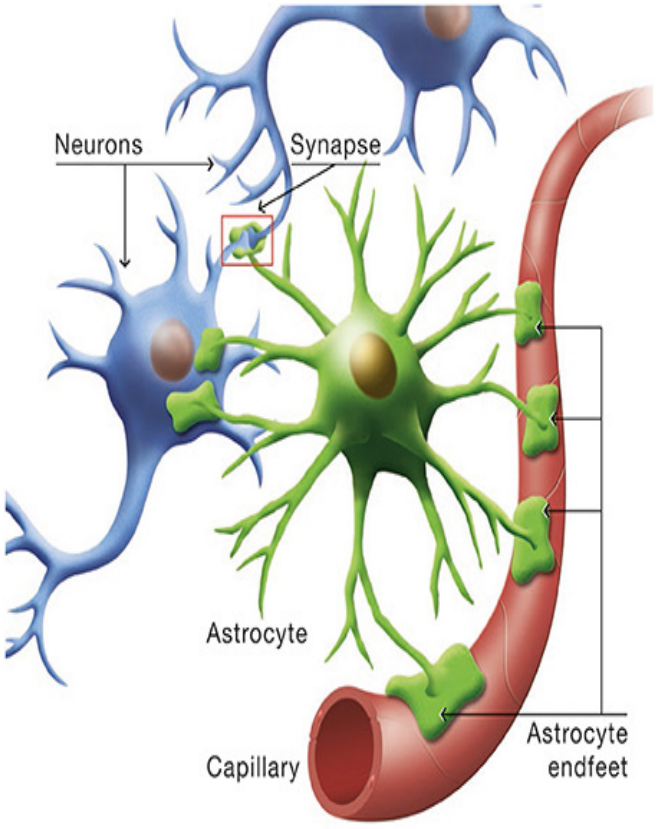
Glutamate Clearance and Neuronal Excitability

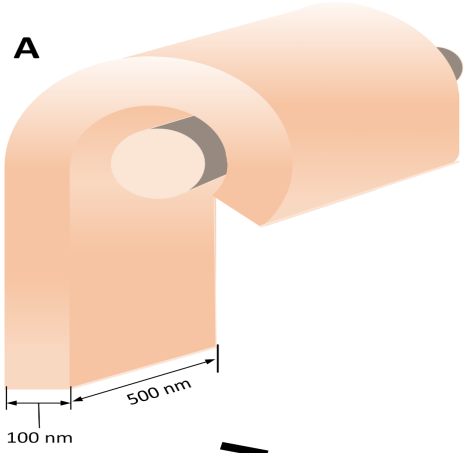
- Increased astrocytic glutamate resulted in slower glutamate clearance at the synapse.
- Prolonged synaptic glutamate-mediated currents due to delayed glutamate clearance.
- Increased neuronal firing as a result of these currents.

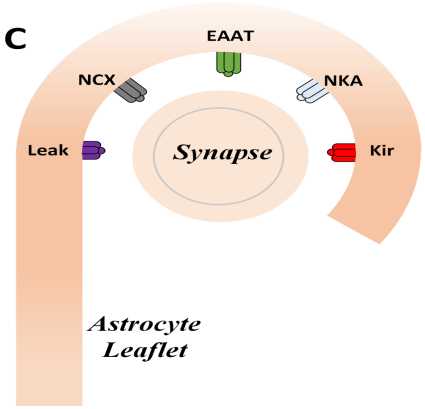


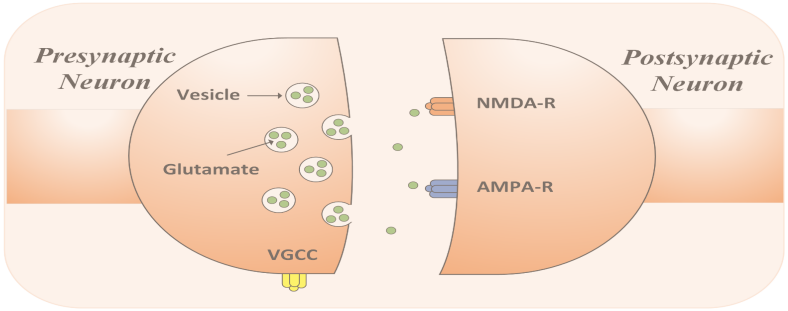
Flanagan et al. (2018)

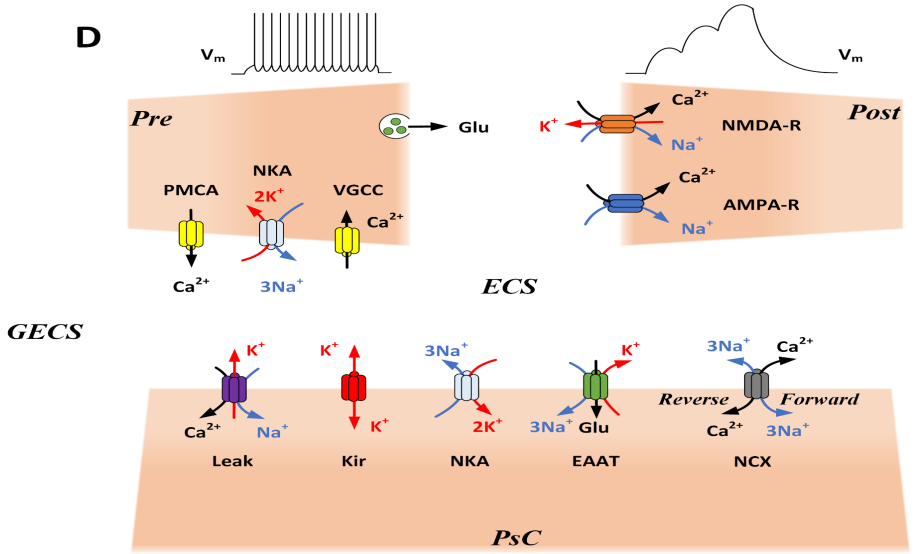
Influence of Astrocytic leaflet motility on ionic homeostasis at synapses



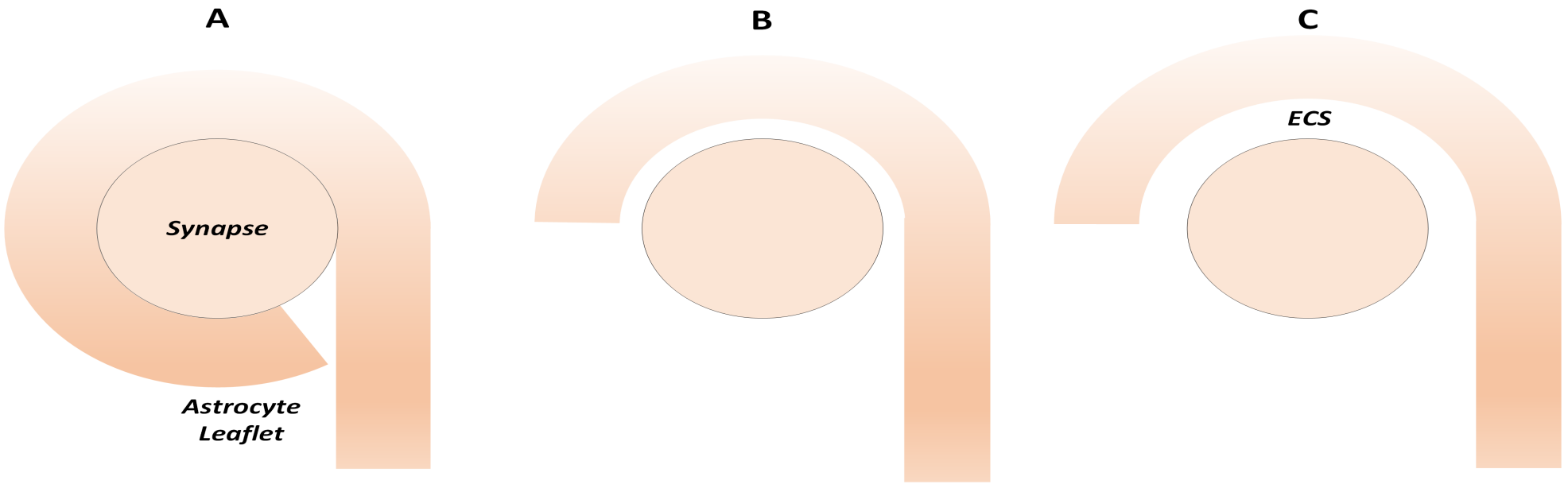






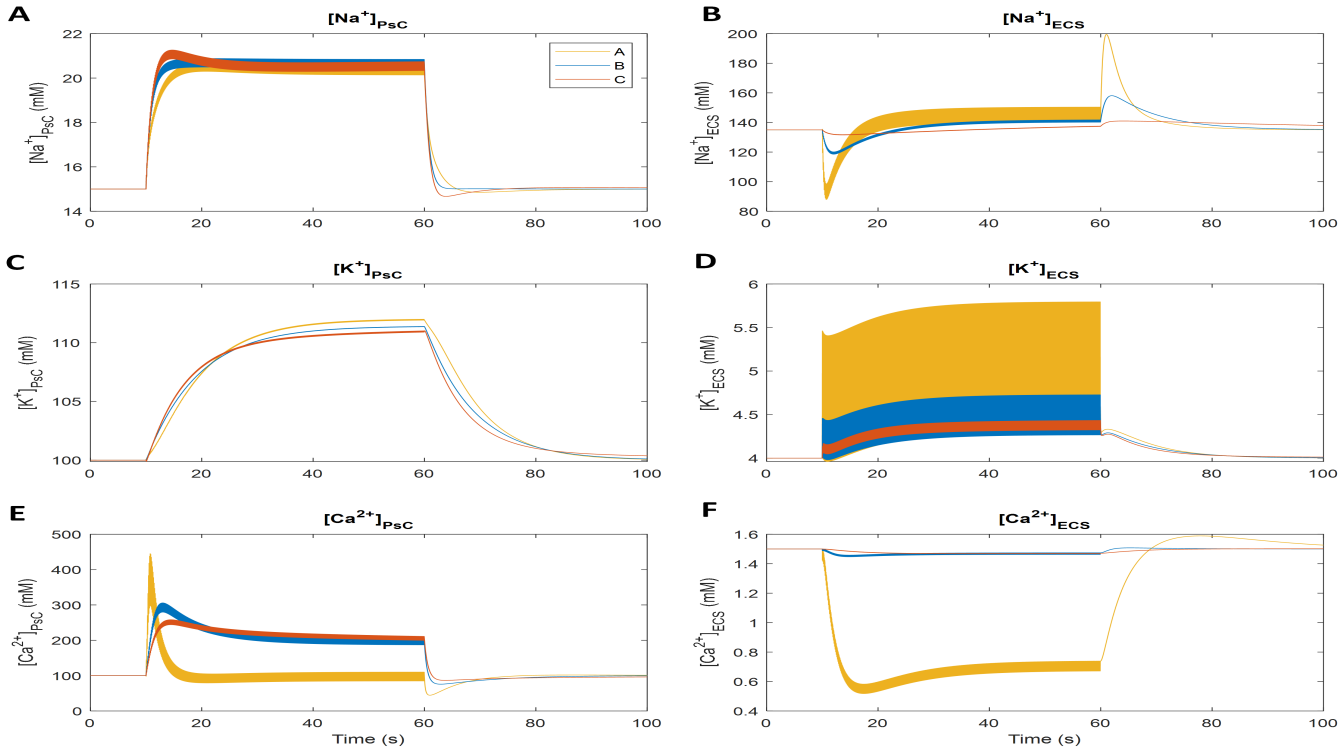


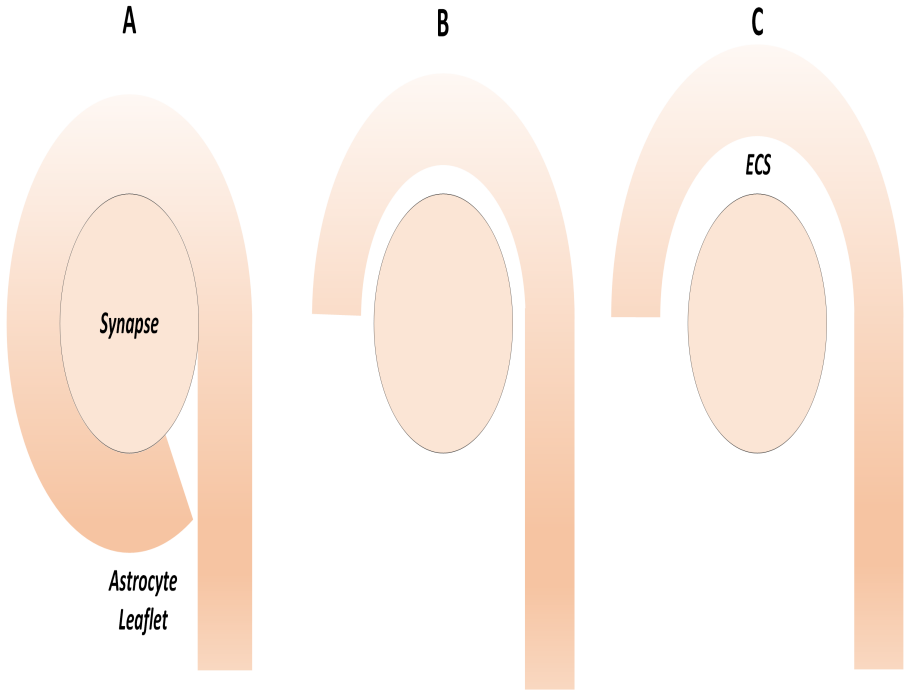
Astrocytic leaflet motility



Schematic showing varying degrees of synaptic coverage by PsC.
(A) – almost completely enwrapped
(B) - semi enwrapped
(C) - loosely enwrapped
To simulate the various astrocyte-synapse couplings, the ECS volume and extracellular diffusion surface area is increased as the PsC moves away from the synapse.

Ionic concentrations vs Leaflet coverage





(A) yellow line - ECS = cleft volume
(B) blue line - ECS = 7 x cleft volume
(C) orange line - ECS = 49 x cleft volume

The protein actin forms filaments that provide cells with mechanical support and driving forces for movement.

Conclusion

- Neurons are no longer the celebrities in the crowd – need to consider Glia cells

  - Astrocyte-synapse spatial relationship affects astrocytic homeostasis
  - PsC clears potassium from the cleft – PsC acts as a temporary store for potassium – thin processes
  - Interneurons (GABA) with endocannabinoids can modulate plasticity – regulates burst firing across neuron populations
  - NCX reversal results in calcium influx to the PsC - may play a role in motility through the driving force of the protein actin - drop in calcium in cleft self regulates motility

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Questions