On the computational role of astrocyte – neuron coupling in brain function

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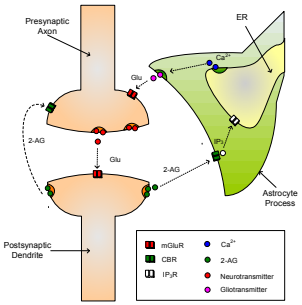
Understand/capture the functional significance of astrocyte-neural interactions

The tripartite synapse model showing indirect and direct signaling of 2-AG.

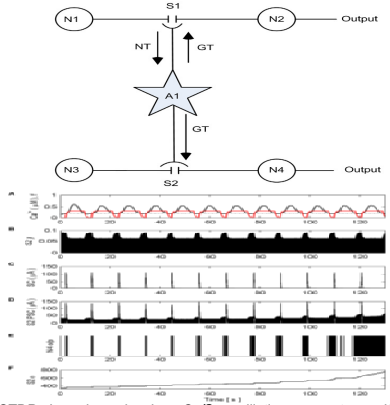


Research Objective:

► To develop a computational model of astrocyte-neuron interactions and demonstrate how these interactions underpin Learning, Synchrony and Self-Repair.

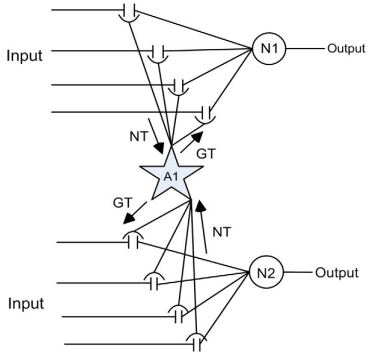
STDP Learning

Li and Rinzel Calcium model - relates calcium dynamics to IP_3
Gatekeeper model - glutamate to mGLu receptors/generation of IP_3
Gating variable f effect probability of transmitter release into the cleft



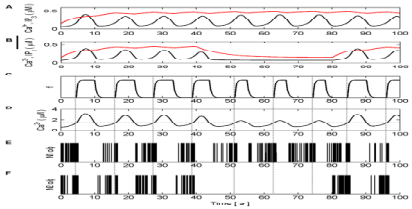
STDP Learning showing Ca^{2+} oscillation, neurotransmitter (y) released, NMDA-mediated SICs, PSC (Post-Synaptic Currents) comprising EPSCs and SICs, firing activity,weigh potentiation.

Dynamic Coordination (Synchrony)



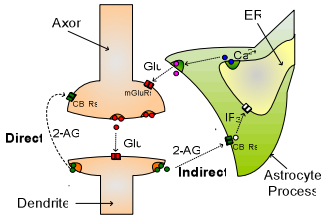
Dynamic coordination in the AN model. All synapses connected to the astrocyte can communicate via bidirectional signaling of neurotransmitter (NT) and gliotransmitter (GT).

Dynamic Coordination (Synchrony)

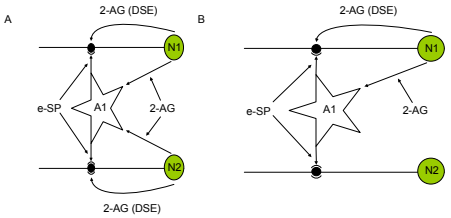


- Ca2+ oscillations (black line) and IP3 levels (red line) at a synapse from N1 stimulated by 7 Hz Poisson spike train for 100s
- Ca2+ oscillations at a synapse from N2 which is only stimulated from 0–40 s and 80–100 s with a 7 Hz Poisson spike train
- Activity of the gating function f which is activated when the total level of Ca2+ (D) within the astrocyte passes the threshold
- (D-black dashed line)
- (E and F) The output firing activity of neurons N1 and N2. Note that when the total Ca2+ oscillation crosses the threshold from
- below both neurons fire with a significantly higher frequency of activity; a result of the global release of glutamate and NMDA
- SIC activation. These are the only times that the neurons are highly coordinated. Furthermore it can be seen that there are
- extended periods of silence from both neurons after firing in bursts. This is a result of the negative feedback from f which depresses
- the release of neurotransmitter from the synapses and remains active until the Ca2+ oscillation crosses the threshold from above

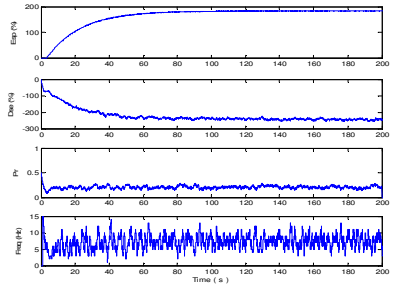
Endocannabinoid Mediated Self-Repair



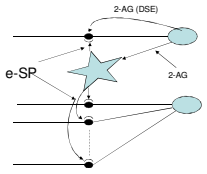
Network illustrating endocannabinoid mediated self-repair:(A) Network be fore fault. **(B)** Network after fault. Note 2-AG is a local signal associated with each synapse connected to either neuron N1 or N2,whereas e-SP is a global signal associated with all synapses connected to the astrocyte A1.



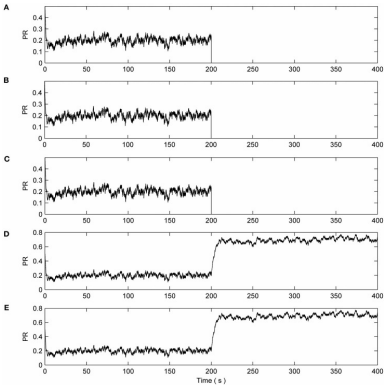
Network with no fault.(A) e-SP function of both N1and N2. Since e-SP is a global function and relates to all synapses connected by the astrocyte it is the same for N1 and N2 **(B)** DSE function of N1 and N2. Since DSE is only local to all synapses connected to a neuron, DSE is different in N1 and N2 and is driven by the output of each neuron. **(C)** The probability of a synapse connected to N1 and N2. This probability is the summation of e-SP and DSE presented to the neuron. Note how the probability isr educed by ~50% which results in an overall reduction of the firing rate of N1 and N2 as seen in **(D)**.



Endocannabinoid Mediated Self-Repair



Network fragment with multiple synaptic inputs where a fraction is set to fail while other compensate through the endocannabinoid process



►PR values of synapses of N2.
(A–C) Show three faulty synapses where the fault is induced at time 200s.
(D,E) Demonstrates the PR of the remaining nonfaulty synapses increasing to compensate for the net loss of **(A–C)**, thereby restoring the functionality of N2.

References:

► Wade John, McDaid Liam, Harkin Jim, Crunelli Vincenzo Kelso Scott, "Self-repair in a bidirectionally coupled astrocyte-neuron (AN) system based on retrograde signaling", Frontiers in Computational Neuroscience, published: 26 September 2012

► Wade, John, McDaid, Liam, Harkin, Jim, Crunelli, Vincenzo and Kelso, J A Scott (2011) Bidirectional Coupling between Astrocytes and Neurons Mediates Learning and Dynamic Coordination in the Brain: A Multiple Modeling Approach. PLoS One, 6 (12). e29445.

► Wade, John, McDaid, Liam, Harkin, Jim, Crunelli, V, Kelso, S and Beiu, V (2011) Exploring Retrograde Signaling via Astrocytes as a Mechanism for Self Repair. In: International Joint Conference on Neural Networks (IJCNN), , California, USA. IEEE. 6 pp.