Computational modeling of neuron-astrocyte interactions in large neural populations using the NEST simulator

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ASTROCYTES AND NEURON-ASTROCYTE INTERACTION IN CORTICAL CIRCUITS:

Astrocytes, the most common type of glial cells in the cortex, have been shown to interact with the neighboring synapses, neurons and glia through complex cellular machinery [1]. Astrocytic processes are positioned closely to the synaptic contacts and in some conditions enwrap the whole synapse, sense synaptic transmission, and modulate the synaptic signal by releasing signaling molecules (e.g. astrocytic glutamate, GABA, ATP and D-serine). Recent experimental studies demonstrated coordinated neuronal and astrocytic activity *in vivo* [2] suggesting the active role of astrocytes and neuron-astrocyte interactions in behaviorally relevant tasks. Integrating the knowledge about the subcellular, cellular and circuit level astrocytic mechanisms, and understanding their contribution to functions of cortical circuits requires combining the experimental studies with computational modeling. Reproducible, reusable, systematically developed and well documented computational models of neuron-astrocyte circuits are facilitated by adequate open-source simulation tools. For review of models, tools and challenges in astrocyte modeling see [3-5].

OUR GOALS:

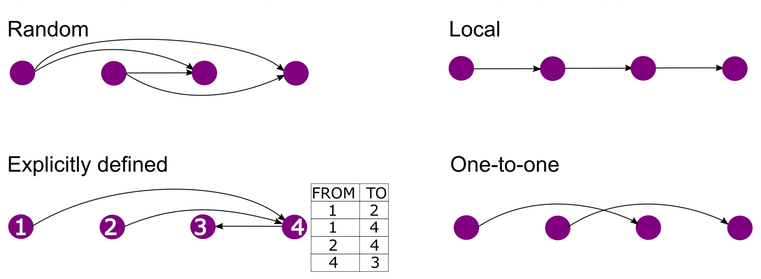
We develop a new astrocyte module for the **NEST simulator** (https://www.nest-simulator.org/) [6], an open-source simulator of large-scale brain circuit models [7]. The new module allows the simulation of astrocytic calcium dynamics, the mechanisms of neuron-astrocyte interactions, and the activity of brain circuits of realistic size. Our goals are:

- To provide an efficient tool for building and simulating large-scale models of cortical circuits composed of neuronal and astrocytic cells
- To expand the existing open access tools capable of modeling selected astrocytic mechanisms and functions
- To support reproducibility, reuse and sharing of neuron-astrocyte models
- To build infrastructure that can be easily extended with new mechanisms and models as they get confirmed by the new experimental evidence

EXPERIMENTAL FINDINGS THAT SUPPORT NEURON-ASTROCYTE CIRCUIT MODELING:

- Astrocytes form non-overlapping microdomains [8,9], the average microdomain is in contact with several hundreds of neurons and ~100,000 synapses (rodent data, [8]).
- Versatile types of synapse to astrocyte contacts: astrocytic processes may form contacts with different types of synaptic elements, some synapses may not be in contact with astrocytes [10].

NEURONAL-ASTROCYTE INTERACTION SCHEMES USED IN COMPUTATIONAL MODELS:



Computational literature explores versatile neuron-astrocyte network organizations, including deterministic and probabilistic schemes that may or may not depend on the physical location of the cells.

NEST module allows efficient generation of large populations that take into account the experimental data and modeler's needs to explore versatile model configurations.

OVERVIEW OF THE SIMULATION TOOLS THAT SUPPORT ASTROCYTE MODELING:

For a review of tools and models see [5]. NEST module provides efficient routines for constructing large neuron-astrocyte circuits.

Simulator	ARACHNE	ASTRO	Brian 2	NEST	STEPS
Modeling formalism, supported models	neuron-glia networks	detailed synapse and multi-compart. cell models	neuron-glia networks	neuron-glia networks	detailed synapse multi-compart. cell models
Programming language	C++, MATLAB	NEURON, C++, MATLAB	Python	Python, C/C++	Python, C/C++
Web address	https://github.com/LeonidSavtchenko/Arachne	https://github.com/LeonidSavtchenko/Astro	https://brianssimulator.org	https://www.nest-simulator.org	http://steps.sourceforge.net/STEPS/default.php
Reference	Aleksin et al. (2017)	Savtchenko et al. (2018)	Goodman and Brette (2008)	Gewaltig and Diesmann (2007)	Hepburn et al. (2012)

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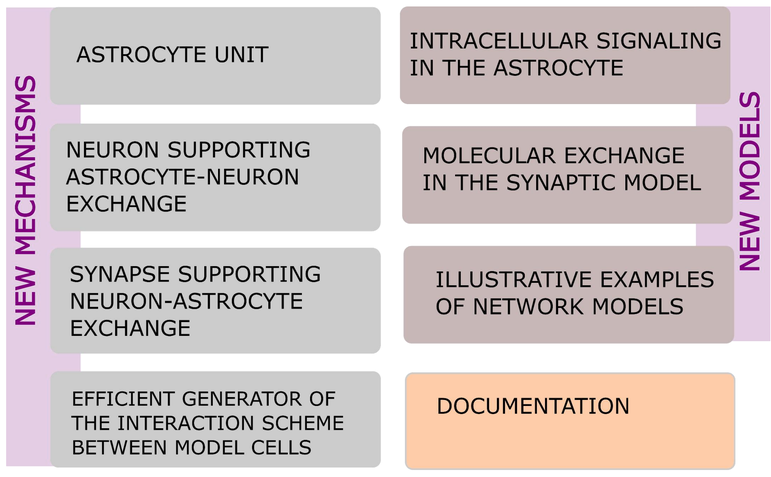
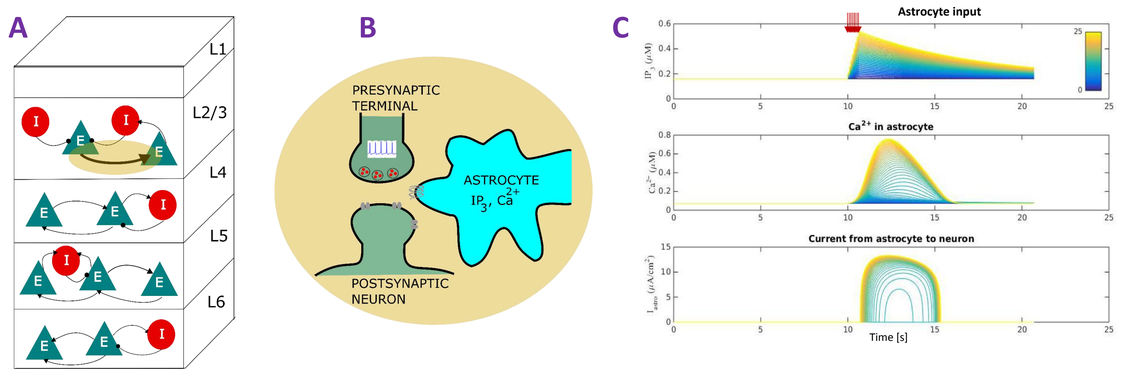
NEW MECHANISMS AND MODELS IN NEST:



ASTROCYTE UNIT AND NEURON-ASTROCYTE EXCHANGE:

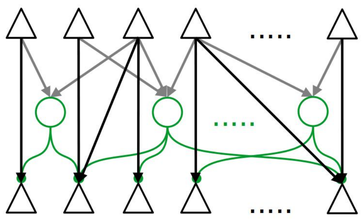
A-B: NEST synapse model is extended to interact with an astrocytic process.
C: Illustration of astrocyte model dynamics when stimulated with synaptic events. Panels from top down: astrocyte input expressed as the increasing concentration of astrocytic IP_3 induced by synaptic events (event times marked by red arrows), calcium concentration in the astrocyte, increased astrocytic calcium induces a current (I_{astro}) in the nearby neuron. Color code – efficiency of neuron to astrocyte interaction (the IP_3 production rate expressed in μM/s).



GENERATING INTERACTIONS IN NEURON-ASTROCYTE POPULATIONS:

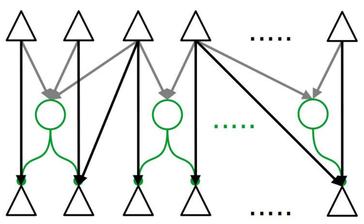
We extend the NEST Create() function to be able to generate astrocyte populations, and Connect() function to be able to establish interactions between neurons and astrocytes in addition to connecting neurons in the model. The figure below illustrates various interaction schemes that can be specified by Connect(). We provide a probabilistic rule to select the interacting neurons and astrocytes, with an option to limit the max number of astrocytes interacting with a postsynaptic neuron.

(1) Probabilistic interactions



```
nest.Connect(
    pre_neurons, post_neurons,
    conn_spec={
        "rule": "pairwise_bernoulli_astro",
        "astrocyte": astrocytes
        "p": #,
        "p_astro": 1
    }
)
```

(2) Setting a max number of astrocytes for each postsynaptic neuron

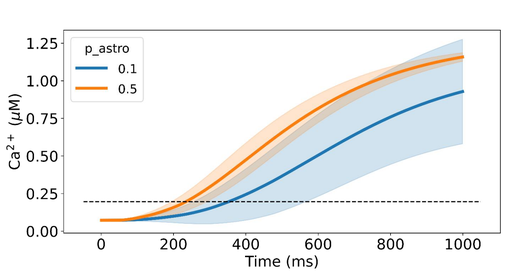


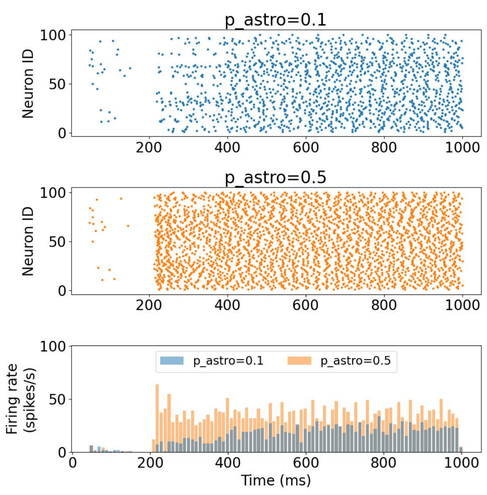
```
nest.Connect(
    pre_neurons, post_neurons,
    conn_spec={
        "rule": "pairwise_bernoulli_astro",
        "astrocyte": astrocytes
        "p": #,
        "p_astro": 1,
        "max_astro_per_target": 1
    }
)
```

Notation	Meaning
△ pre_neurons, post_neurons	Presynaptic and postsynaptic neurons (could be the same population)
○ astrocytes	Astrocyte population generated by calling NEST Create() function
⇉	Neuron→neuron (black) and neuron→astrocyte (grey) interactions
—●	Astrocyte→neuron interactions
rule	Rule that determines the interaction matrix of the neuron-astrocyte network
p	Probability of neuron→neuron interactions
p_astro	Probability that a neuron→neuron interaction is paired with an astrocyte. Example: all are paired with astrocytes (p_astro=1)
max_astro_per_target	Max number of astrocytes that can interact with a postsynaptic neuron. When not given, all astrocytes can interact.

EXAMPLES OF POPULATION DYNAMICS IN NEURON-ASTROCYTE MODELS:

Increased probability of neuron to astrocyte interaction increases the overall spiking activity in the modeled neuronal population.





Left: increase of p_astro leads to increase of neuronal inputs to astrocytes, which induces higher calcium levels in astrocytes (dashed line: threshold of calcium for the generation of I_{astro}).

Right: increase in astrocytic calcium induces excitatory input to neurons, which leads to higher population activity and overall firing rates.