Geometry-based estimates of glutamate transporter density in astrocytes

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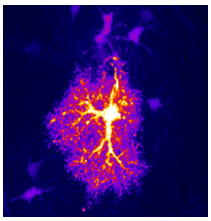
Glutamate is the main excitatory neurotransmitter released in the brain. Its removal from the extracellular space is important to terminate synaptic transmission between neurons, and prevent build-up of neurotoxicity. The removal process is intermediated by non-neuronal cells called astrocytes. These take in the excess extracellular glutamate via tiny cross-membrane transporters densely expressed in the wall of the cell membrane. To understand their impact on neurotransmission efficiency, one needs to estimate the density of transporters for an average astrocyte [1, 2].

Existing computations are based on simplifying assumptions of spherical cellular shape. However, the actual, 3-dimensional fractal geometry of a typical astrocyte may drastically reduce this number, due to the rigidity implied by the condition that transporters cannot collide with each other. We use a geometric modeling argument, based on the known crystal structure of the transporter, to study how the structural complexity of astrocytic processes influences the surface density of transporters. Making only basic simplifying assumptions of regularity and symmetry for the cell geometry, we consider a cell model built around a spherical soma, surrounded by a three-dimensional branching tree. The geometry of the branching processes follows certain spatial restrictions, and the length and diameter of the branches depend on their position in the tree (e.g., generational distance from the soma). The transporters can be well approximated to have prismatic shape, with an equilateral triangular base. Using a combination of trigonometry and a variety of traditional and new integration algorithms, we compute the number and fraction of the cellular membrane occupied by transporters, under the geometric constraint that the intra-cellular ends of the transporters cannot meet.



We compare our results to existing empirically-based estimates based on assumptions of simpler geometry, and we discuss the significance of the improvement that geometrically-informed estimated may bring to the field. We use Monte Carlo reaction-diffusion simulations to determine whether our theoretical estimates challenge our knowledge of how glutamate transporters shape efficiency of synaptic transmission.

References

[1] J.S. Diamond. Deriving the glutamate clearance time course from transporter currents in CA1 hippocampal astrocytes: transmitter uptake gets faster during development. *The Journal of Neuroscience*, 25(11) 2906-2916, 2005.

[2] A. Scimemi et al. Neuronal transporters regulate glutamate clearance, NMDA receptor activation, and synaptic plasticity in the hippocampus. *The Journal of Neuroscience*, 29(46) 14581-14595, 2009.