Sponge astrocyte model: volume effects in a 2D model space simplification

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Astrocytes are the most abundant and versatile specialized glial cells, which contiguously tile the entire CNS where they may outnumber neurons. Real astrocytes are obviously not binary. There is a graded transition from thick branches to branchlets and to leaflets, primarily determined via the **surface-to-volume ratio** (SVR). Moreover, leaflet regions of the template contain not only astrocyte itself, but also the neuropil. We encode the astrocyte structural features by means of its color representation.

Mechanism-based model

Ullah local model [1-2] supplemented with Ca_{ER} and glutamate

$$\frac{dCa_c}{dt} = \varepsilon_1\left(J_{ch} + J_{leak} - J_{pump}\right) + \varepsilon_2\left(J_{in} - J_{out} + k[Glu]\right);$$

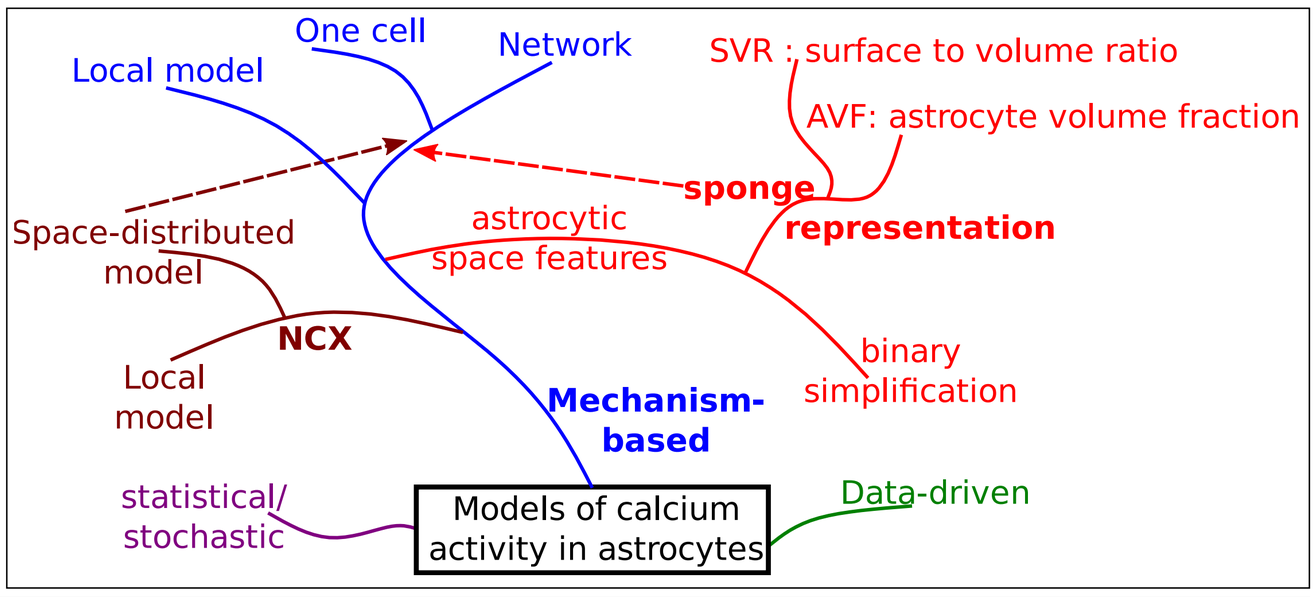
$$\frac{dCa_{ER}}{dt} = -\varepsilon_1\frac{J_{ch} + J_{leak} - J_{pump}}{c_1} + k_5(Ca_{ER_s} - Ca_{ER});$$

$$\frac{dIP3}{dt} = \varepsilon_3(J_{delta} + J_{glu}) - (IP - IP3_s)/\tau_r;$$

$$\frac{d[Glu]}{dt} = \frac{[Glu]_{amb} - [Glu]}{\tau_{Glu}} + \xi_p(t);$$

$$\frac{dh}{dt} = \frac{h_{inf} - h}{\tau_h}.$$

1. Ca^{2+} in cytoplasm – Ca_c
2. Ca^{2+} in endoplasmic reticulum – Ca_{ER}
3. IP_3 dynamics – IP_3
4. Extracellular glutamate – Glu
5. IP_3R inactivation variable (receptor of IP_3) – h



Calcium fluxes:

$m_{inf} = IP3/(IP3 + d_1); n_{inf} = Ca_c/(Ca_c + d_5)$

$J_{ch} = c_1 v_1 (Ca_{ER} - Ca_c)(m_{inf} n_{inf} h)^3$ — flux through channel

$J_{leak} = c_1 v_2 (Ca_{ER} - Ca_c)$ — leak of Ca from ER

$J_{pump} = v_3/(1 + (k_3/Ca_c)^2)$ — membrane Ca ATPase pump

$J_{out} = k_1 Ca_c$ — Ca extrusion from cytoplasm

$J_{in} = v_5 + v_6/(1 + (p_{k2}/IP3)^2)$ — Ca leak across plasma membrane

+ agonist-dependent IP3-stimulated Ca influx through Ca channel via IP3R

h-gate of IP3R

$Q_2 = d_2((IP3 + d_1)/(IP3 + d_3))$

$h_{inf} = Q_2/(Q_2 + Ca_c), \tau_h = 1/(a_2(Q_2 + Ca_c))$

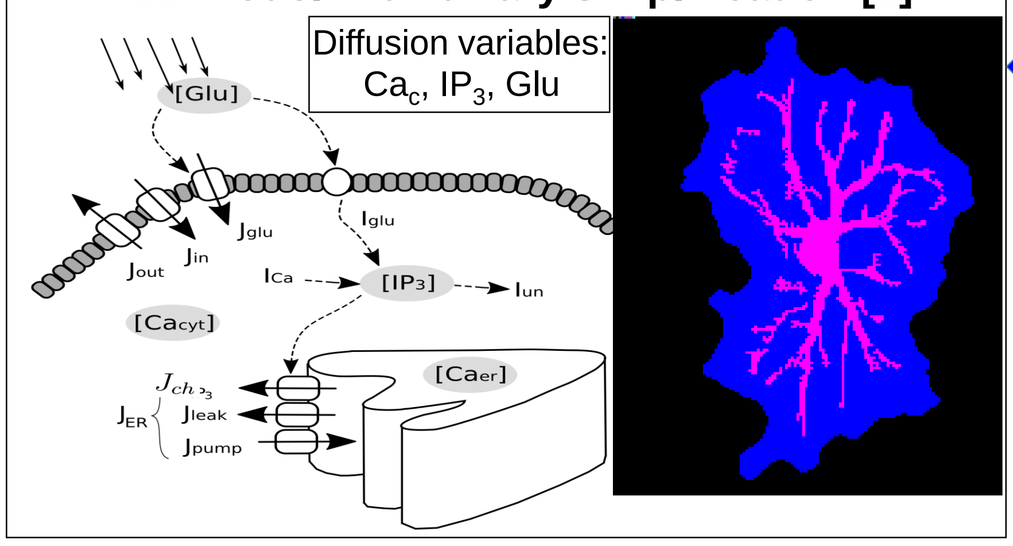
Cytosolic IP3

$J_{delta} = v_4(Ca_c + (1 - \alpha)k_4)/(Ca_c + k_4)$ — Ca stimulation of IP3 production

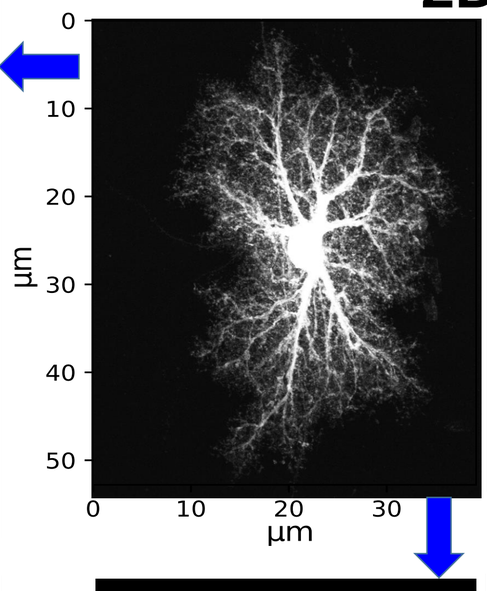
$J_{glu} = v_g(C_{glu}^{hill_{glu}})/(k_g^{hill_{glu}} + C_{glu}^{hill_{glu}})$ — synaptic glutamate stimulation of IP3 production

$\xi_p(t)$ – homogeneous Poisson process

2D model with binary simplification [2]



2D One cell Sponge Model

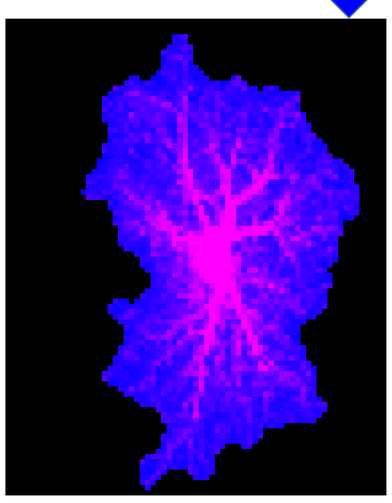


$$\frac{dCa_c}{dt} = (1 - SVR)\left(J_{ch} + J_{leak} - J_{pump}\right) + SVR\left(J_{in} - J_{out} + k[Glu]\right);$$

$$\frac{dCa_{ER}}{dt} = -(1 - SVR)\frac{J_{ch} + J_{leak} - J_{pump}}{c_1} + k_5(Ca_{ER_s} - Ca_{ER});$$

$$\frac{dIP3}{dt} = SVR(J_{delta} + J_{glu}) - (IP - IP3_s)/\tau_r;$$

$$\frac{d[Glu]}{dt} = \frac{[Glu]_{amb} - [Glu]}{\tau_{Glu}} + \xi_p(t); \qquad \frac{dh}{dt} = \frac{h_{inf} - h}{\tau_h}.$$

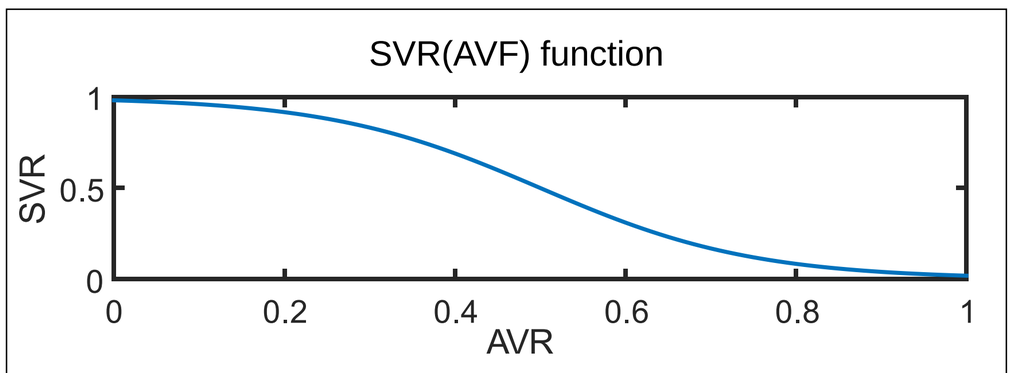


Blue channel - the presence / absence of a cell (astrocyte).
Brightness of the red channel reflects the AVF,
i.e. the percent of voxel volume that is occupied by the cell.

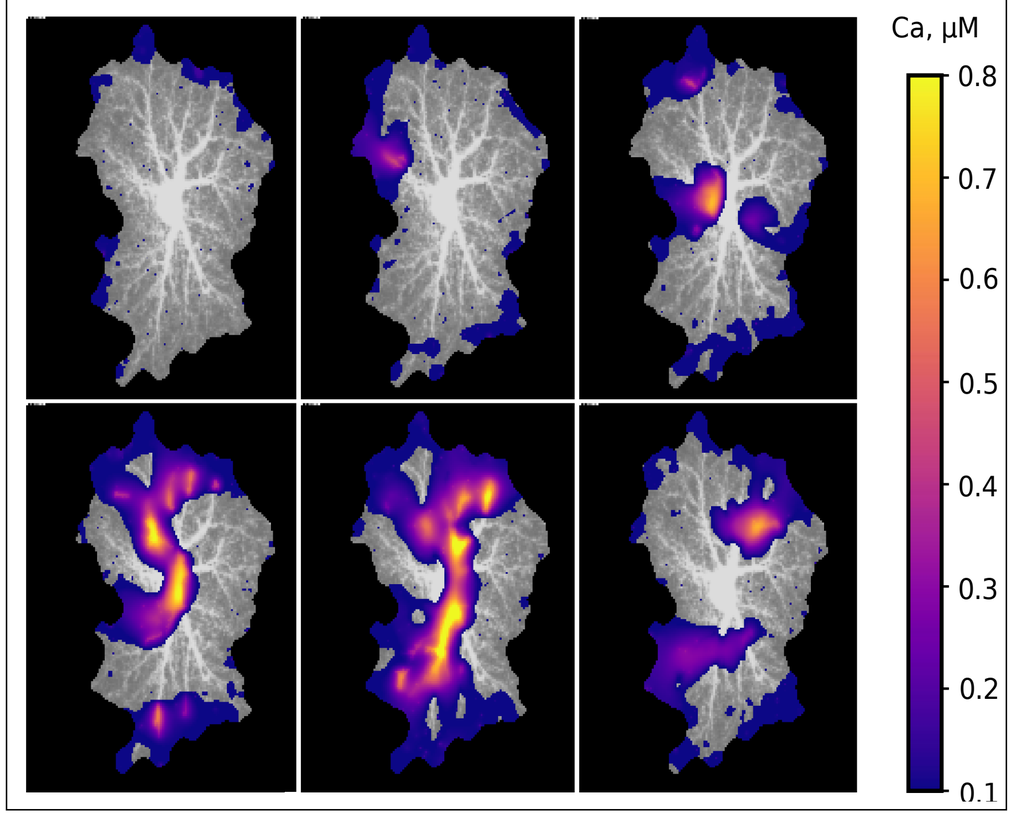
AVF changes the diffusion for Ca_c and IP_3.
SVR determines the contribution of ER and PM processes.

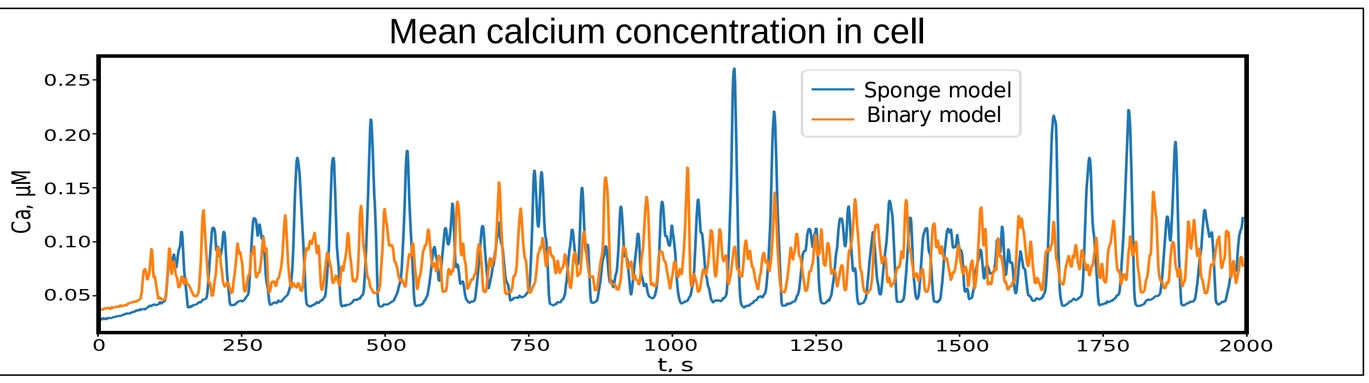
We don't consider the separate thin branches,
AVF defines the relative “density” of branches in cell.

Cell is considered as a “sponge”.



Calcium waves in the astrocyte cell





The AVF role:
- large AVF (and small SVR) leads to less contribution from plasma membrane (PM) versus ER
- large AVF leads to the less Ca and IP3 concentration change through the diffusion from the neighboring compartment
- small AVF leads to the slower diffusion due to the “jagged” volume;
the exchange is faster on thick branches

Conclusions

Simulations show the formation of calcium waves. In contrast to the binary segmentation model, calcium elevation response in the proposed biophysically more realistic sponge model is greater, i.e. the intensity of the formed waves is higher, but the basal calcium level is lower. The threshold of stable wave existence grows because increasing AVF works like a blocking barrier for a small glutamate release reducing the number of wave sources. Nevertheless, large enough glutamate release leads to a wide-area wave quickly occupying the leaflets moving to the astrocyte soma.

Acknowledgements

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1. G. Ullah, P. Jung, A.H. Cornell-Bell. Anti-phase calcium oscillations in astrocytes via inositol (1, 4, 5)-trisphosphate regeneration. *Cell Calcium* 2006, 39: 197-208.
2. A. Yu. Verisokin, D. E. Postnov, D. V. Verveyko, and A. R. Brazhe. Raindrops of synaptic noise on dual excitability landscape: an approach to astrocyte network modelling. *Proc. of SPIE* 2018, 10717: 107171S-1