Sodium-calcium exchangers modulate excitability of spatially distributed astrocyte networks

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In this work we combine two models of astrocytic calcium dynamics: the first one is based on the IP3-dependent exchange with the intracellular calcium storage, the second local model considers the sodium-calcium exchanger (NCX) and Na+ response to the synaptic glutamate. The proposed model proceeds to a spatially distributed astrocyte network.

Combined Mechanism-based model

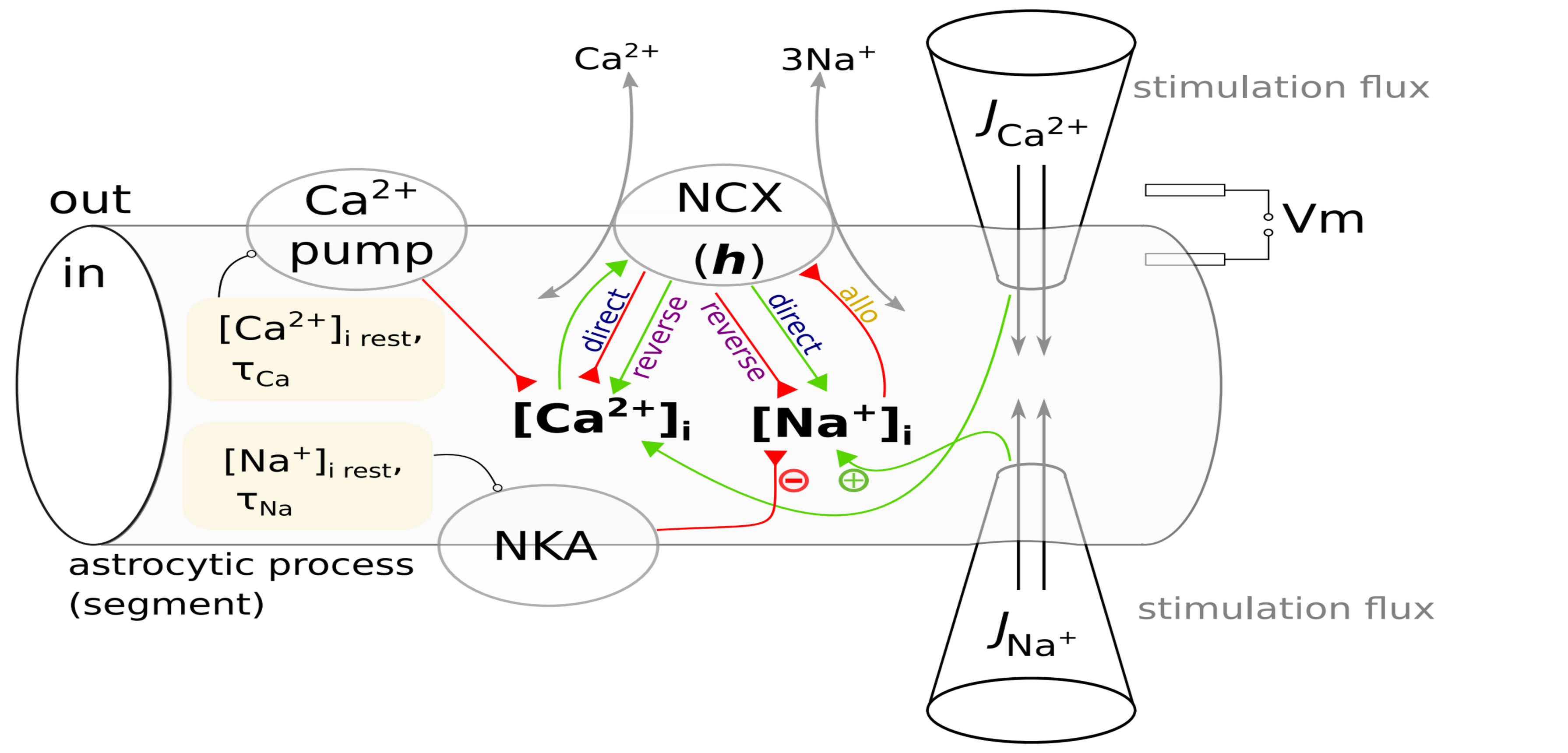
Na/Ca-exchanger (NCX) local model [1]

$$\frac{dCa_c}{dt} = J_{\rm ncx} + J_{\rm ext}^{\rm Ca} + \frac{Ca_{\rm rest} - Ca_c}{\tau_{\rm Ca}},$$

$$\frac{dNa}{dt} = J_{\rm ext}^{\rm Na} - 3J_{\rm ncx} + \frac{Na_{\rm rest} - Na}{\tau_{\rm Na}},$$

$$\frac{dg}{dt} = \frac{g_\infty - g}{\tau_g}$$

1. Ca^{2+} in cytoplasm – Ca_c
2. Na^+ in cytoplasm – Na
3. Na^+- dependent inactivation and Ca^{2+}- dependent deinactivation – g



NCX flow $J_{\rm ncx} = \bar{J}_{\rm ncx} n_\infty({\rm Ca_c}) g J_{\Delta E}$

$n_\infty = \frac{1}{1+(\frac{K_n}{\rm Ca_c})^2}$ — deinactivation dependent on occupancy of the affinity Ca_c binding sites

$J_{\Delta E} = \frac{{\rm Na^3Ca_o} \exp\frac{\eta VF}{RT} - {\rm Na_o^3Ca_c} \exp\frac{(\eta-1)VF}{RT}}{K_X\left(1+k_{sat}\exp\frac{(\eta-1)VF}{RT}\right)}$ — net reaction rate of the ping-pong bi-bi cyclic reaction scheme

$$K_X = K_{M{\rm Ca}_o}{\rm Na_i^3} + K_{M{\rm Na}_o}{}^3{\rm Ca_c} + K_{M{\rm Na}}{}^3{\rm Ca_o}\left(1+\frac{\rm Ca_c}{K_{MCa_c}}\right) + K_{MCa_c}{\rm Na}_o^3\left(1+\frac{{\rm Na}_i^3}{K_{M{\rm Na}}{}^3}\right) + {\rm Na^3Ca_o} + {\rm Na}_o^3{\rm Ca_c}$$

$K_{M\cdot}$ are the corresponding Michaelis constants

$$\tau_g = 0.25 + \tau_0/(1+({\rm Ca_c}/K_\tau)^{H_\tau})$$

g-gate $g_\infty = 1 - \frac{1}{1+({\rm Ca_c}/K_{\rm Ca})^{H_{Ca}}}\frac{1}{1+(K_{\rm Na}/{\rm Na})^{H_{Na}}}$

Proposed model

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

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

$$\frac{dIP3}{dt} = \text{SVR}(J_{delta} + J_{glu}) - (IP3 - IP3_s)/\tau_r,$$

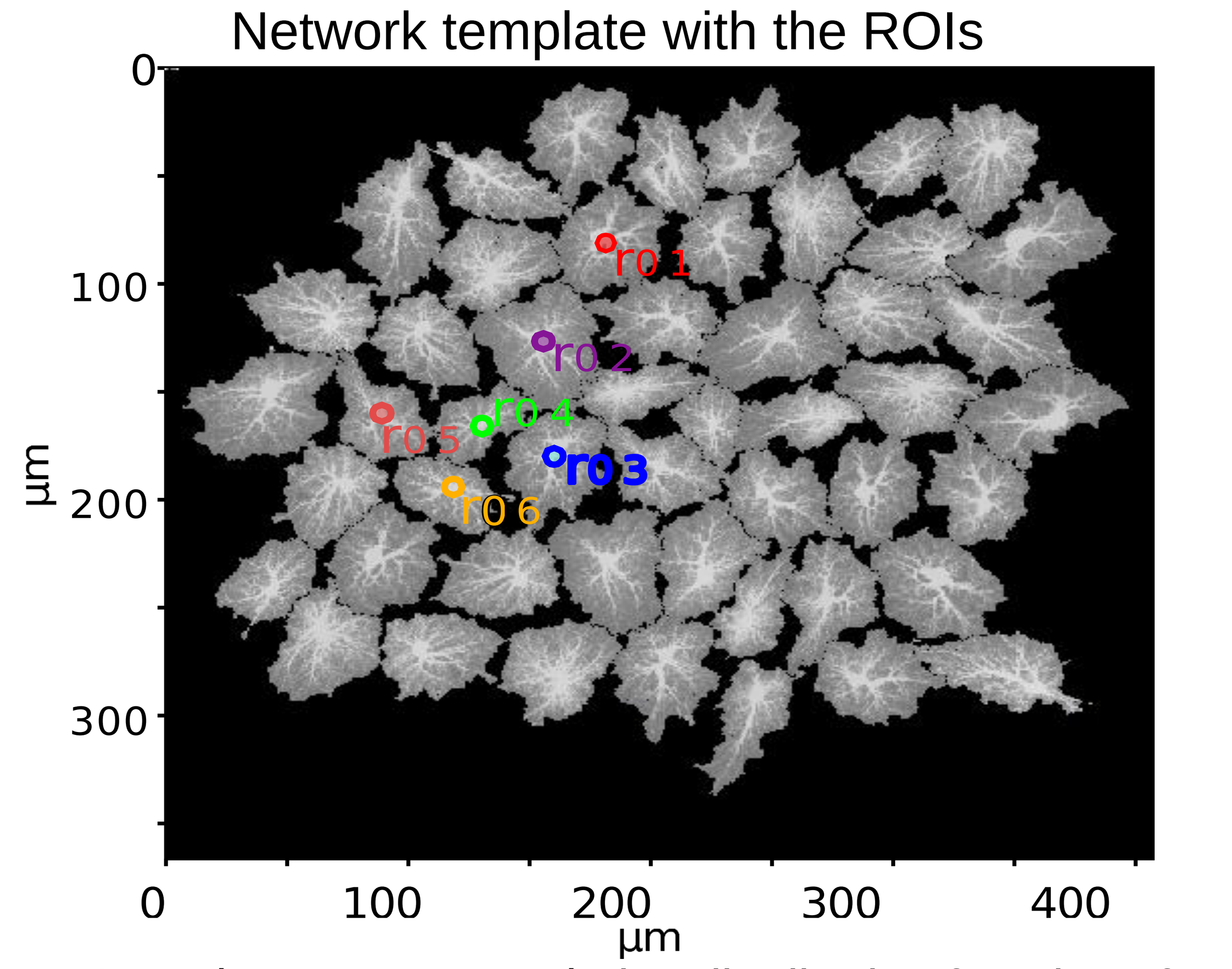
$$\frac{dNa}{dt} = \text{SVR}(J_{\rm ext}^{\rm Na} - 3J_{\rm ncx}) + \frac{Na_{\rm rest} - Na}{\tau_{\rm Na}}$$

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

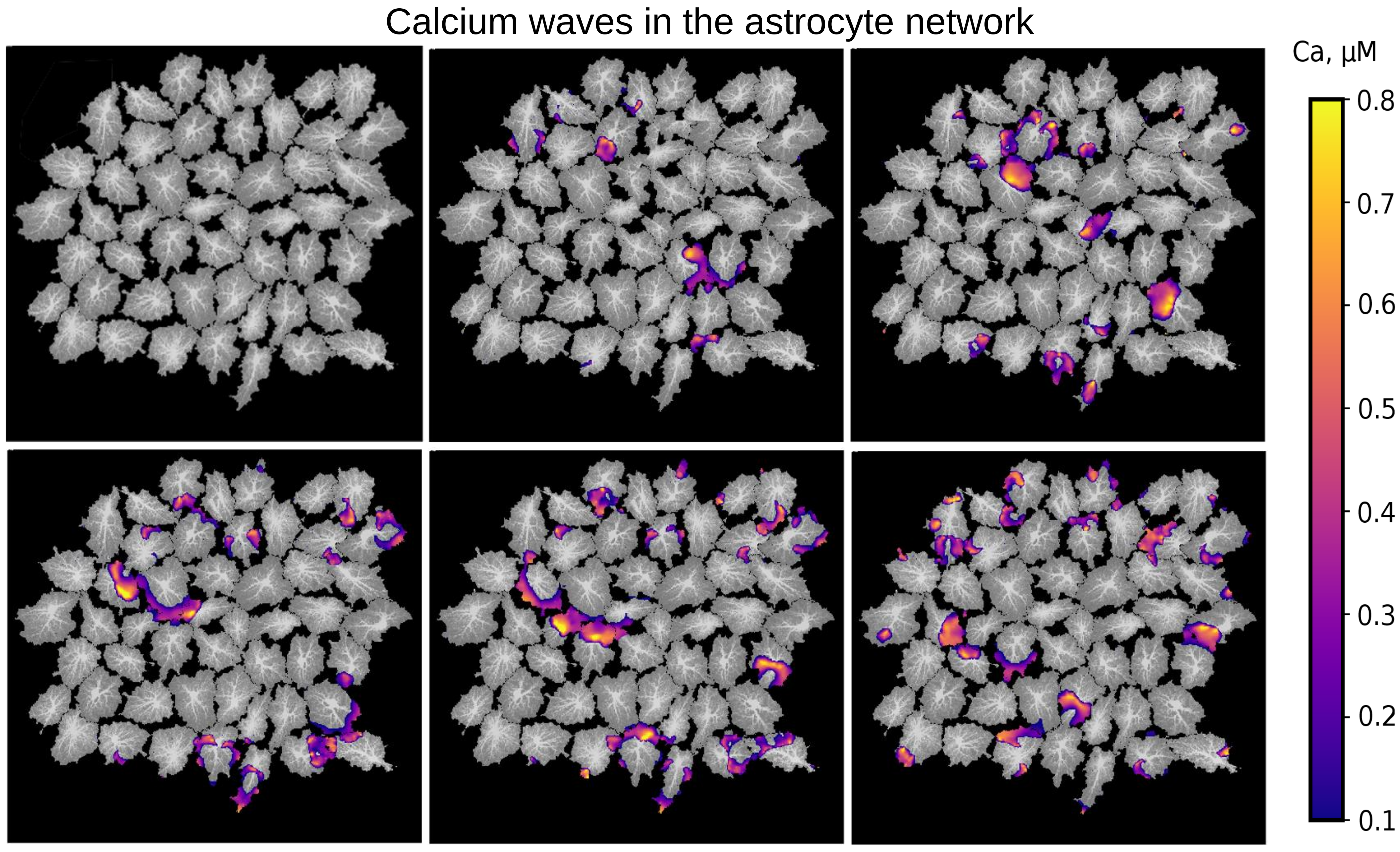
$$\frac{dh}{dt} = \frac{h_{inf} - h}{\tau_h} \qquad \frac{dg}{dt} = \frac{g_\infty - g}{\tau_g}$$

Diffusion variables: Ca_c, IP_3, Glu, Na

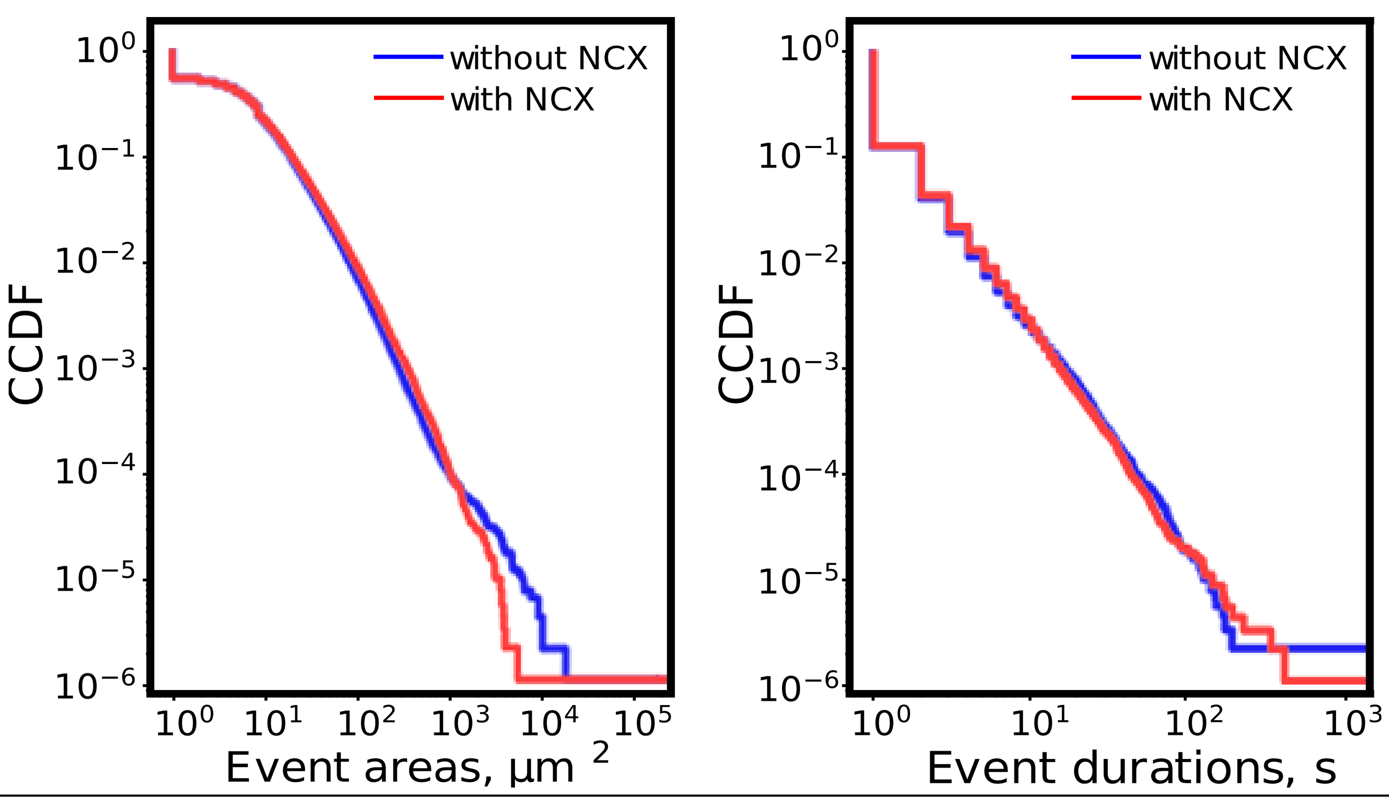
Network template with the ROIs



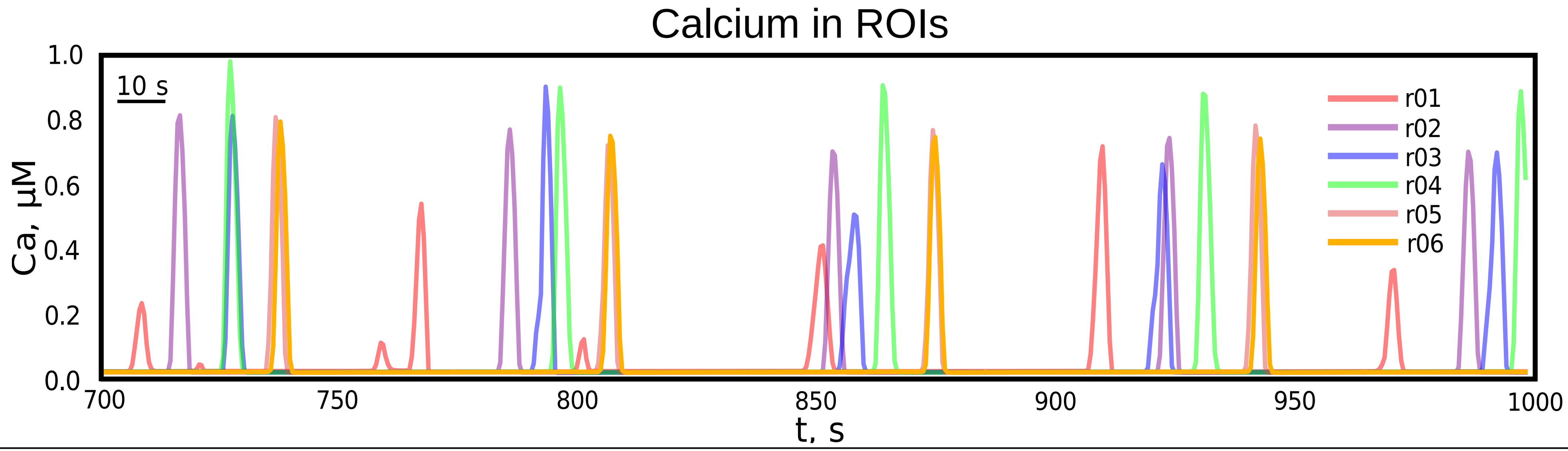
Calcium waves in the astrocyte network



Complementary cumulative distribution functions for areas and durations of calcium excitation



Calcium in ROIs



Conclusions

The results of the unified model numerical solution confirm the emergence of calcium waves, which occur due to the synaptic activity and spread over the astrocyte network (calcium excitation wave captures the entire astrocyte network, along with local waves, which exist only within one cell and terminate beyond its borders). The presence of NCX leads to a decrease in the average areas that are affected by a global calcium wave during excitation, while the number of events with equal duration time is the same on average for both models. However, the Na/Ca-exchanger stimulates calcium waves, making possible the formation of more long-lived waves.

Acknowledgements

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1. A. R. Brazhe, A. Yu. Verisokin, D. V. Verveyko, and D. E. Postnov. Sodium-calcium exchanger can account for regenerative Ca^{2+} entry in thin astrocyte processes. *Front Cell Neurosci.* 2018, 12: 250.