Simulation of Astrocytic Calcium Dynamics in Lattice Light Sheet Microscopy Images

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IEEE - ISBI 2021
International Symposium on Biomedical Imaging

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ABSTRACT

Astrocytes regulate neuronal information processing through a variety of **spatio-temporal calcium signals**. Advances in calcium imaging started to reveal astrocytic activities, but the complexity of the recorded data strongly call for computational analysis tools. Their development is hindered by the lack of reliable annotations that are essential for their evaluation and for the design of learning-based methods. To overcome the labeling problem, we present a framework to **simulate realistic astrocytic calcium signals in 3D+time lattice light sheet microscopy (LLSM) images** by closely modeling **calcium kinetics** in **real** astrocytes.

METHOD

Simulation of Calcium Puffs

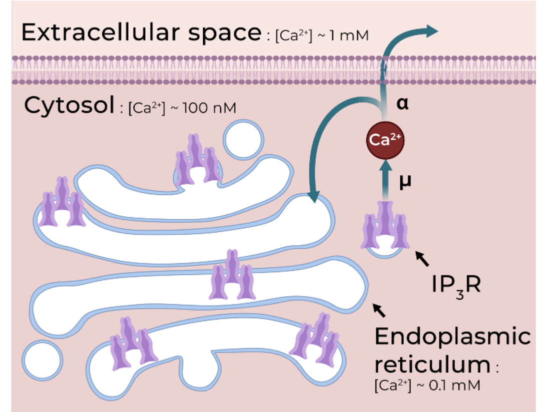
Kinetic model (nanoscale) | **Simulation (microscale)**

- Stimulus at time t_0 and location $\mathbf{x}_c$ of an astrocyte triggering a γ variation of $[Ca^{2+}]$

$$g(\mathbf{x}) = \begin{cases} \gamma e^{-\left(\frac{\|\mathbf{x}-\mathbf{x}_c\|^2}{2\sigma^2}\right)} & \text{if } \mathbf{x} \in \mathcal{A}, \\ 0 & \text{otherwise.} \end{cases}$$

$\mathcal{A}$: set of points belonging to astrocytes

- Cytosolic calcium fluxes:



$$\Delta t_e \left(\sum_{n=1}^{N_c} \mu \, \mathbb{1}_{\mathcal{O}_t}(n) - \alpha \right)$$

$\mathbb{1}_{\mathcal{O}_t}$: indicator function of the subset $\mathcal{O}_t$
$\mathcal{O}_t$: set of open IP_3Rs at time t
Δ_{t_e}: temporal resolution
N_c : number of IP_3Rs in a cluster

- Brownian motion

$$\begin{cases} \frac{\partial f_e(\mathbf{x},t)}{\partial t} = \text{div}\left(c(\|\nabla f_e(\mathbf{x},t)\|)\nabla f_e(\mathbf{x},t)\right) \\ f_e(\mathbf{x},t_0) = g(\mathbf{x}) + \beta \, \mathbb{1}_{\mathcal{E}}(\mathbf{x}), \end{cases}$$

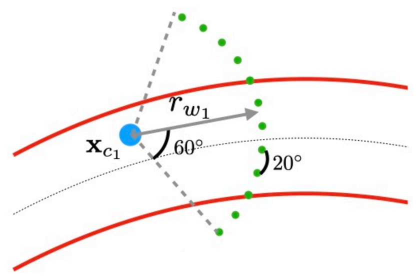
Anisotropic Perona-Malik diffusion

f_e : sequence simulating one calcium event
div(·) : divergence operator
$\mathcal{E}$: set of points belonging to astrocytes' edges
β : maximum intensity
$c(u) = \exp\left(-\left(\frac{u}{\kappa}\right)^2\right)$: conductivity function

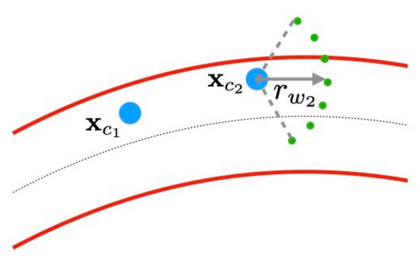
$$f_e(\mathbf{x}, t+\Delta t_e) = f_e(\mathbf{x},t) + \Delta t_e \frac{\partial f_e(\mathbf{x},t)}{\partial t} + \Delta t_e \left(\sum_{n=1}^{N_c} \mu \, \mathbb{1}_{\mathcal{O}_t}(n) - \alpha \right) \quad (1)$$

Simulation of Calcium Waves

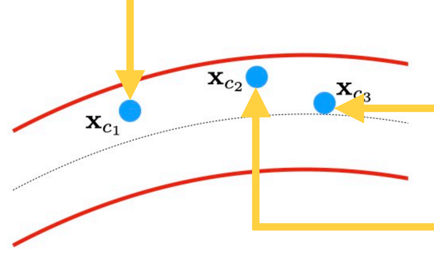
- Propagation of calcium puffs from a IP_3R cluster to the neighboring ones



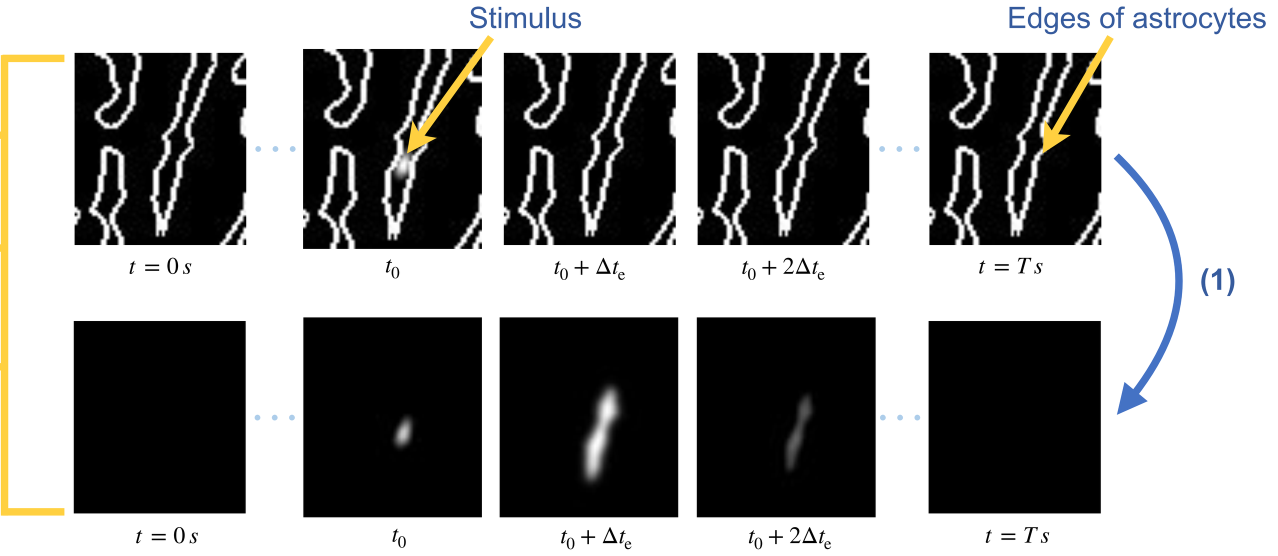
Determination of $\mathbf{x}_{c_2}$



Determination of $\mathbf{x}_{c_3}$

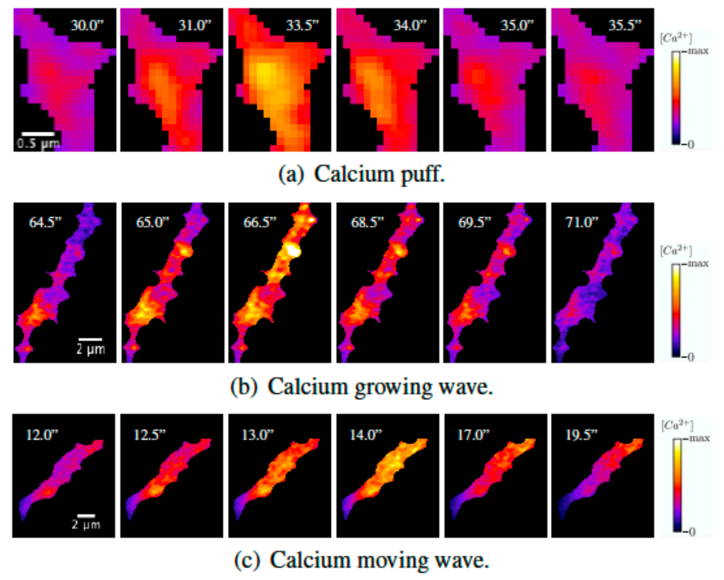


The three calcium puff sites of the wave

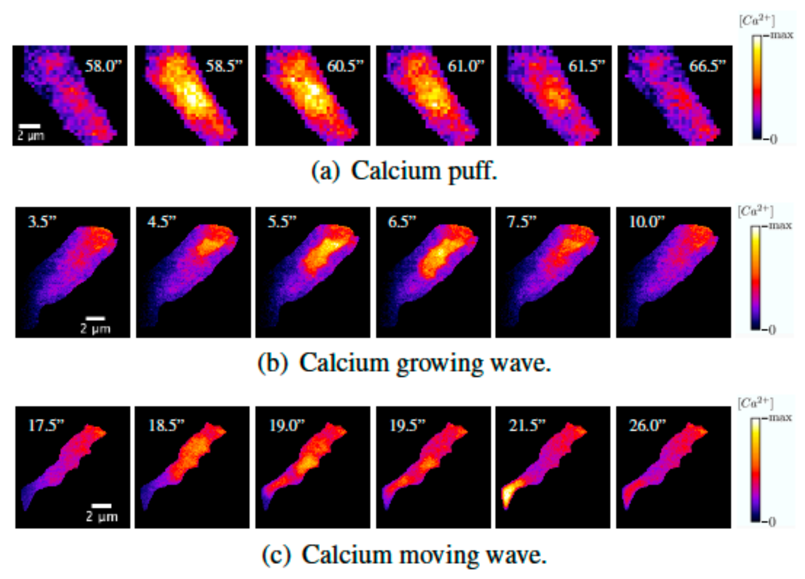


RESULTS

Figure 1

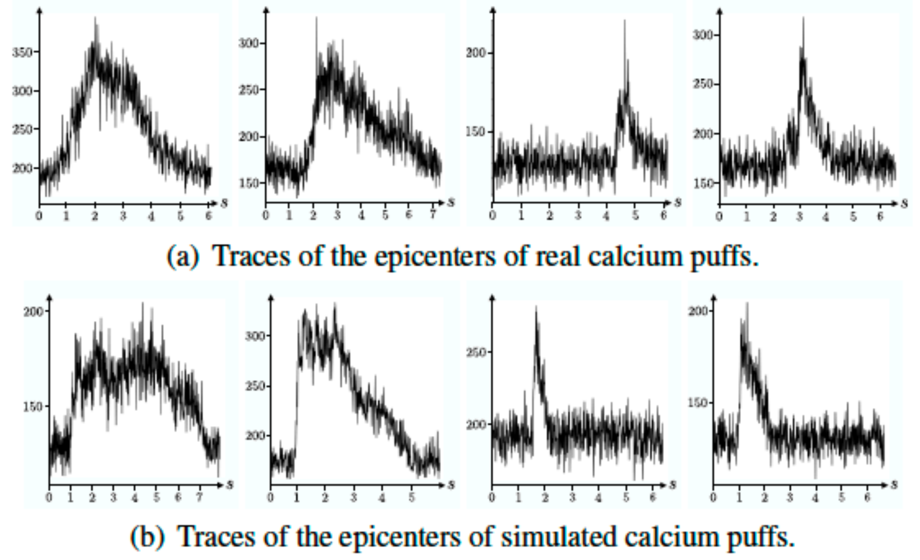


Maximum intensity projections of calcium puff (a) and waves (b)-(c) from real 3D+time lattice light sheet microscopy images ($\Delta t = 0.5\ s$).



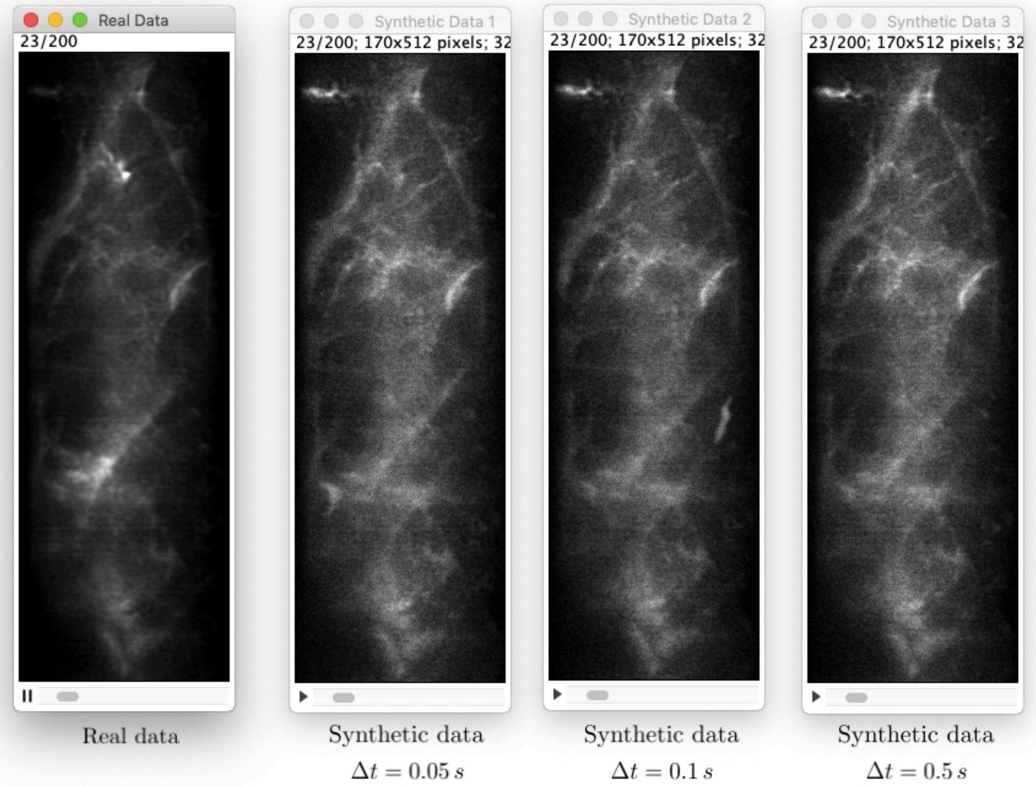
Maximum intensity projections of calcium puff (a) and waves (b)-(c) from our simulated 3D+time lattice light sheet microscopy images ($\Delta t = 0.5\ s$)

Figure 2

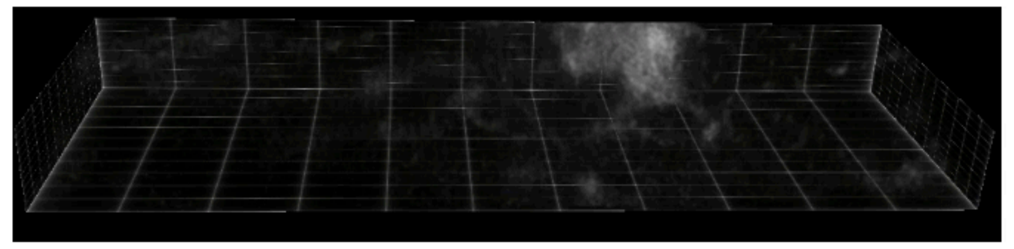


Traces of the epicenters of calcium puffs present in real (a) and synthetic (b) 2D+time lattice light sheet microscopy images ($\Delta t = 0.01\ s$)

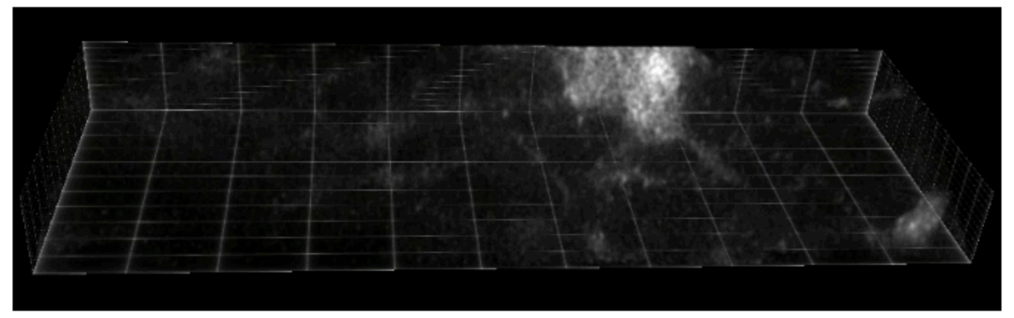
Video 1: 2D+time sequences



Video 2: 3D+time sequences



Real data
$\Delta t = 0.05s$



Synthetic data
$\Delta t = 0.05s$

CONCLUSIONS

Contributions

- Generation of 3D+time **LLSM images depicting astrocytic activity**. First simulator of its kind
- Driven by a **calcium kinetic model** that we adapted from nanoscale to microscale
- Image background made of **real astrocytic ramifications**
- Simulation of **experimental conditions** of LLSM acquisitions (*e.g.*, noise and blur)
- Implementation as an **ImageJ plugin** with parameters and user interface

Results

- Variety of synthetic datasets that **realistically represents the complexity** of experimental data
- Helpful to **develop computerized learning-based methods** to analyze astrocytic calcium signals in 3D+time images

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