Zespół BIOSIG – część I

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Epistemologia a symulacja w skali subkomórkowej

Bielecki A., Gierdziewicz M., 2025. Computer Simulations in Subcellular Biology - Meta-Research Perspectives and Possible Role in Biological Studies (gotowa do wysłania)

Modelowanie struktur i procesów w synapsie

Zagadnienia:

1. Optymalizacja siatki do symulacji numerycznych w kolbce presynaptycznej.
2. Modelowanie transportu w kolbce presynaptycznej przy użyciu heterogenicznego automatu komórkowego

Superkomputery ACK Cyfronet Kraków – *mars* (2016, 2017), *prometeusz* (2024), *ares* (2025)

Publikacje:

Bielecki A., Gierdziewicz M. *Simulation of Neurotransmitter Flow in a Presynaptic Bouton of a Neuron with Cellular Automaton. Sixteenth ACC Cyfronet AGH HPC Users'Conference, Zakopane,13-15 March 2024.*

Bielecki A., Gierdziewicz M. *Cellular Automaton Approach to Estimation of Neurotransmitter Flow Parameters in a Presynaptic Bouton of a Neuron. Sixteenth ACC Cyfronet AGH HPC Users'Conference, Zakopane,2-4 April 2024.*

Gierdziewicz M., Bielecki A., Bielecki P. (2025) *Heterogeneous Cellular Automaton as a Tool for Modeling Signal Processing in the Presynaptic Bouton* (gotowe do wysłania w kwietniu)

Bielecki A., Gierdziewicz M., Bielecki P., Pachel I. (2025) *The use of a membrane cellular automaton for neurotransmitter flow in the realistic model of the presynaptic bouton* (w przygotowaniu)

Plan: wykorzystanie superkomputerów ACK Cyfronet – *atena, helios*

Agenda

- Various approaches to the problem
- Biological environment
- The object of the study
- Theoretical foundations
- Example model parameters
- History of cellular automata
- Description of the cellular automaton
- Geometrical model – updates
- Simulation updates
- Previous results – for comparison
- Results – total amount nd distribution of neurotransmitter
- Concluding remarks

Various approaches

- Ordinary Differential Equations
- Partial Differential Equations
- **Cellular Automaton**
- Membrane Computing

Biological environment

- Highly heterogeneous environment in the neuron
  - including the synapse
  - its various parts have various properties
- Diffusion coefficients (*a*) vary significantly due to the existence of organelles
  - *Trovato et al., 2014. Diffusion within the Cytoplasm: A Mesoscale Model of Interacting Macromolecules.*
- Values of *a* differ between organelles and cytoplasm
- Microfilaments and microtubules >>
  - inter-organelle space: heterogeneous and anisotropic;
  - complicated by the intracellular membranes system.
  - External membrane active transport of Ca, Na, K

The object of the study

- PROCESS
  - Reaction-diffusion processes
    - transport component
    - reaction component
  - production (supply) processes etc.

In this paper the transport processes inside the presynaptic bouton of the neuron are modeled.

- OBJECT
  - Bouton
    - first of 3 elements that make up the synapse
  - The other two are
    - synaptic cleft
    - postsynaptic dendrite receptor

Theoretical foundations

- The process of conducting nerve impulses in the presynaptic bouton may be split into four stages.
  - The appearance of synaptic vesicles containing NT molecules inside the presynaptic bouton after they have been delivered there.
  - Diffusion process, supported in part by actin filaments.
  - Exocytosis:
    - electrical impulse;
    - some vesicles empty their content into the synaptic cleft
  - NT reuptake from the cleft.
- The first three processes are considered here.
  - So far, ODE and PDE were used for their modeling

Example 3D bouton model parameters

- Total surface: $S \approx 6.78\ \mu m^2$
- Active zone: $S_{AZ} \approx 0.24\ \mu m^2$
- Mesh size: $N = 77418$
- Total volume: $V \approx 0.9029\ \mu m^3$
- Volume of supply zone: $V_s \approx 0.0198\ \mu m^3$

Initial neurotransmitter density

- $\rho(x,0) = \rho_0 = A\, e^{-br^2}$ [vesicles / μm^3]
- $A = 300\ \mu m^{-3}$
- $b = -0.28 \mu m^{-2}$
- r = distance from the center of the bouton

History of cellular automata (CA)

- The history of CA dates back to the 1940s
- The concept further developed by Ulam (1962)
- Ulam's ideas used by John von Neumann (1966):
  - 5 models of self-replicating automata
  - space and time discretization based on Ulam's work
- Codd (1968)
  - much simpler self-replicating structure
- „The game of life" (Martin Gardner, 1970)

Cellular automata allow for flexible creation of models using discrete time scale, space and states, so they have found a number of applications

Description of cellular automaton (I)

The general form of diffusion-reaction formula applied in our CA is shown below.

$$\partial_t q = D\nabla^2 q + R(q)$$

where:

q - the vector of unknowns;

D - diagonal matrix of diffusion coefficients;

R - contains all local reactions.

Description of cellular automaton (II)

The above type of equation has been solved to reveal:

patterns forming into sliding waves;

patterns forming into other self-organizing stripes;

patterns forming into polygons;

commonly referred to as ***Turing patterns***

since the 1950s until today, in various objects:

- animals (zebrafish),
- vegetable patterns (ecology),
- atomic monolayers

(Nakamasu et al. 2009, Campagna et al. 2017, Fuseya et al. 2021}.

Description of cellular automaton (III)

- In our paper, CA were used to model diffusion-reaction flows. The flows of this kind occur quite widely in biology:
  - neurotransmitter transport;
  - skin pigmentation;
  - description of ecological invasions;
  - spreading of epidemics;
  - growth of tumors and cancer cells;
  - wound healing;
  - etc…

  They may be described by partial differential equations, the general form of which was shown before.

Description of cellular automaton (IV)

- More advanced **heterogeneous CA** *(in complex systems)*
  - cell attributes: age, decay, or other…
  - transition functions: various kinds
- Heterogeneous CA are used to study
  - traffic (Malli et al. 2009);
  - fire spread (Jiang et al. 2021);
  - epithelial cells growth (Lange et al. 2024);
  - cells evolution (Shrestha et al. 2024);
  - urban growth (Gao et al. 2020); …
- *Such models, however, have not been used so far to examine neurotransmitter reaction and diffusion in the presynaptic bouton of the neuron.*

Formulas for CA model

- Cell *i,* volume V_i , exocytosis rate α, impulse starts for $t = t_0+kT$, ends for $t = t_0+kT+\tau$
- Change of m_i in cell *i* pertinent to diffusion
  - $\Delta_1 m_{ij} = \Sigma (a\, s_{ij}\, \Delta t / r_{ij}) (\rho_j - \rho_i)$ ← *sum for* $j \in NC_{i;}$ *(NC – neighboring cell)*
- Change of m_i pertinent to supply: $\Delta_2 m_i = \beta (\overline{\rho} - \rho_i)$
- Change of m_i pertinent to exocytosis: $\Delta_3 m_i = -3\alpha\, s_{i.}\, \rho_i$ if $\Delta_t \subset < t_0+kT;\ t_0+kT+\tau >$
  - k = positive integer number; T – time interval
- new m_i value: $\Delta m_i = \Delta_1 m_i + \Delta_2 m_i + \Delta_3 m_i$; $m_i' = m_i + \Delta m_i$
- New density value: $\rho_i' = m_i' / V_i$

Geometrical model – updates since 2024

Intended bouton volume=1.1 μm^3 => the intended radius of the outer sphere 0.64µm
Inner sphere („supply zone") approx. 0.256 µm.
Generated mesh: 3102 vertices, 2528 faces and 16273 tetrahedra
Previous version: 7525 vertices, 4090 faces and 42801 tetrahedra
Real progress – more optimal 3D mesh
Release site („Active Zone = AZ):
spherical cap around the "South Pole" up to 45^O
Surface of AZ about 0,754 μm^2
same order of magnitude as in literature
(Gundel et al. 2009, Holderith et al. 2012)
Initial NTdensity [vesicles/μm^3]: $36 \exp(-0.28r^2)$
depending on the distance r from the globe centre.
Result: a total of about 400 synaptic vesicles
This is in agreement with experimental findings (Wilhelm 2013)

Simulations – updates since 2024

- 200*Hz* stimulation frequency
- Correcting factors introduced to account for mesh geometry *and the chosen method – FE or CA*.
- The computer ***Ares*** was used for simulations.
- The computing grant was ***plgneuron2024***
- The programming language was Python.
- The simple experiments took about 2GB RAM and
  - 58’ (FE, large bouton), 42’ (CA, large bouton);
  - 62’ (FE, average bouton), 58’ (CA, average bouton)

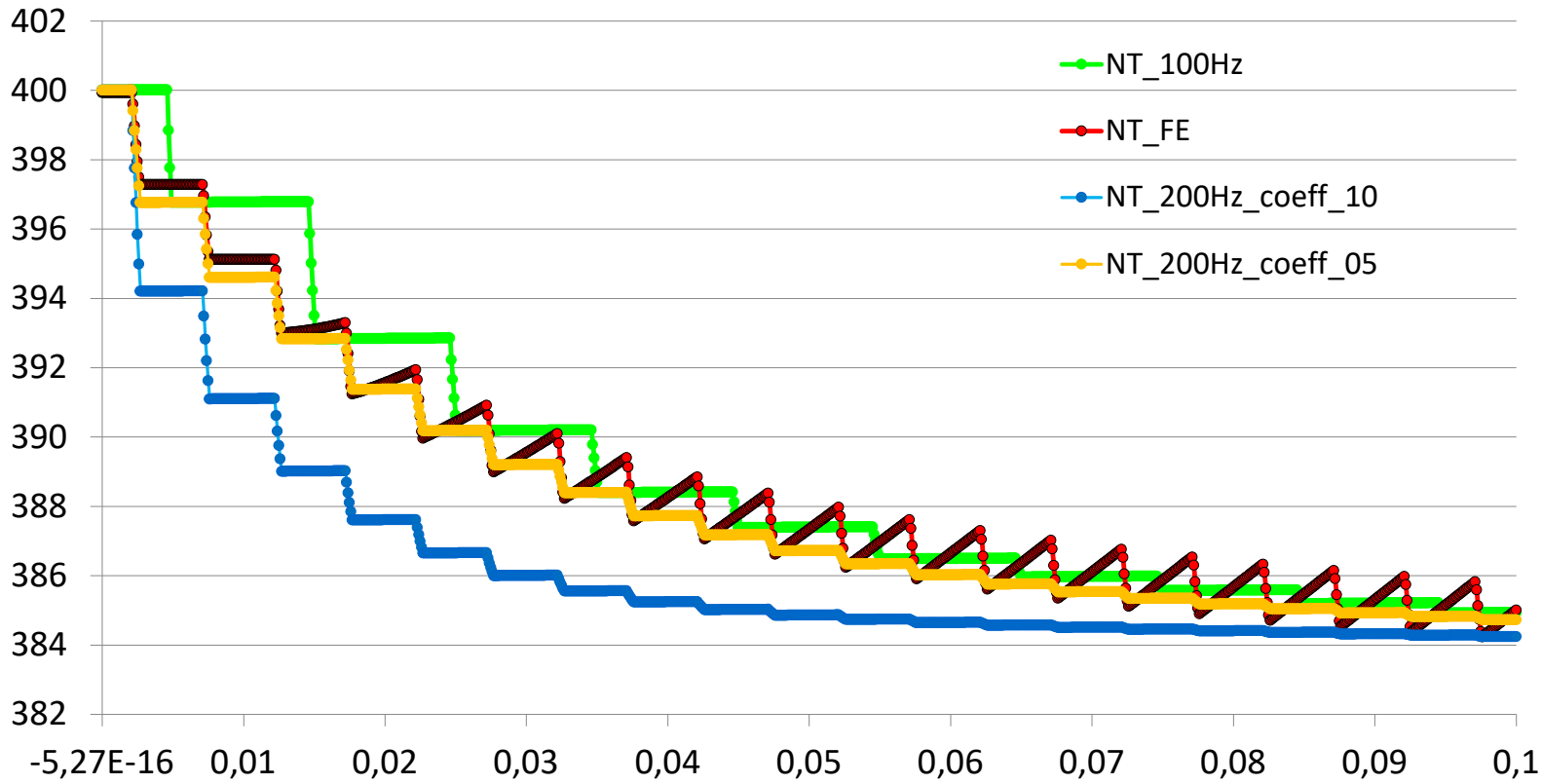
(last year version: over 400 minutes simulation time)

Simulations – updates (continued)

- The example values of simulation parameters:
  - Diffusion coefficient $a = 6\ \mu m^2/s$;
  - Permeability coefficient $\alpha = 63\ \mu m^3/s$;
  - Supply rate $\beta = 50/s$;
  - Supply threshold $\rho = 30$ vesicles/μm^3.
  - *Initial NT density:* $\rho_0(x) = A \exp(-B r^2)$, where:
    - $A = 36$ vesicles/μm^3; $B = 0.28/\mu m^2$; $r^2 = x_1^2 + x_2^2 + x_3^2$

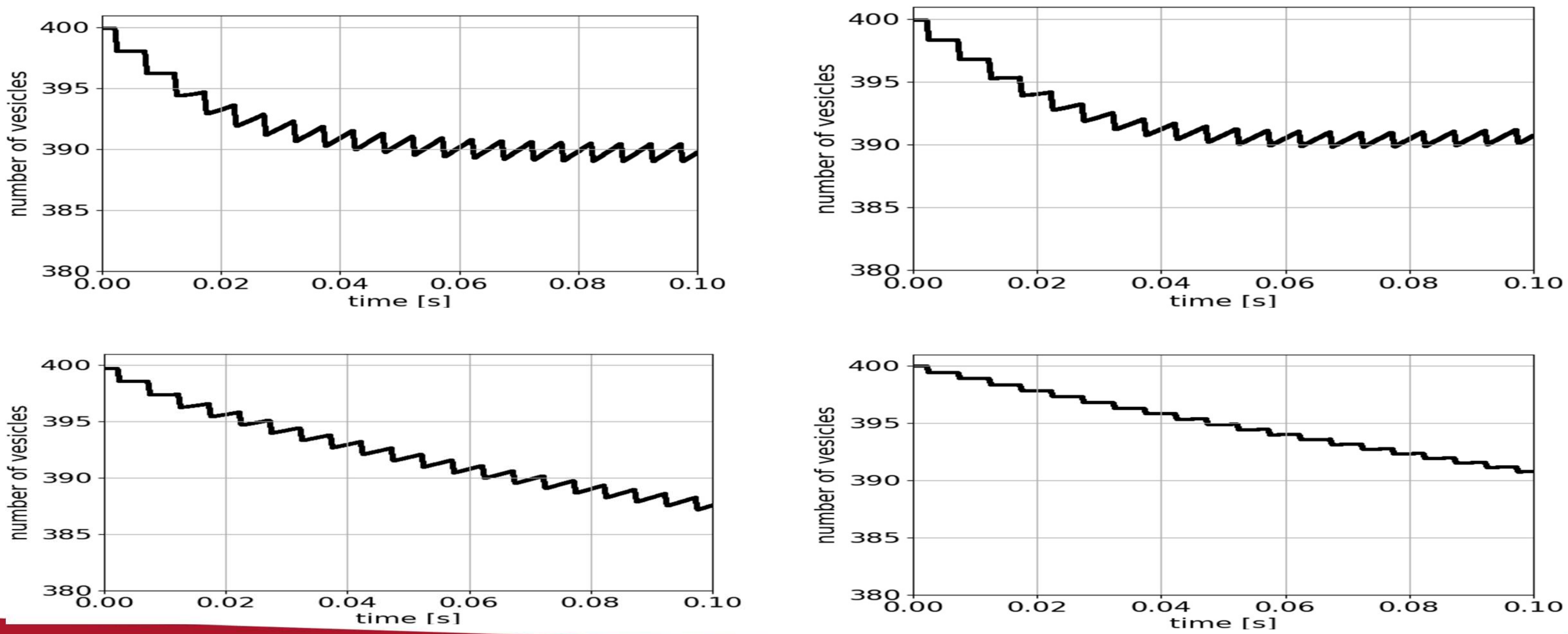
Total amont of NT [vesicles]

four example experiments in 2024 (*simulation time* 0.1000*s; red = finite elements*)

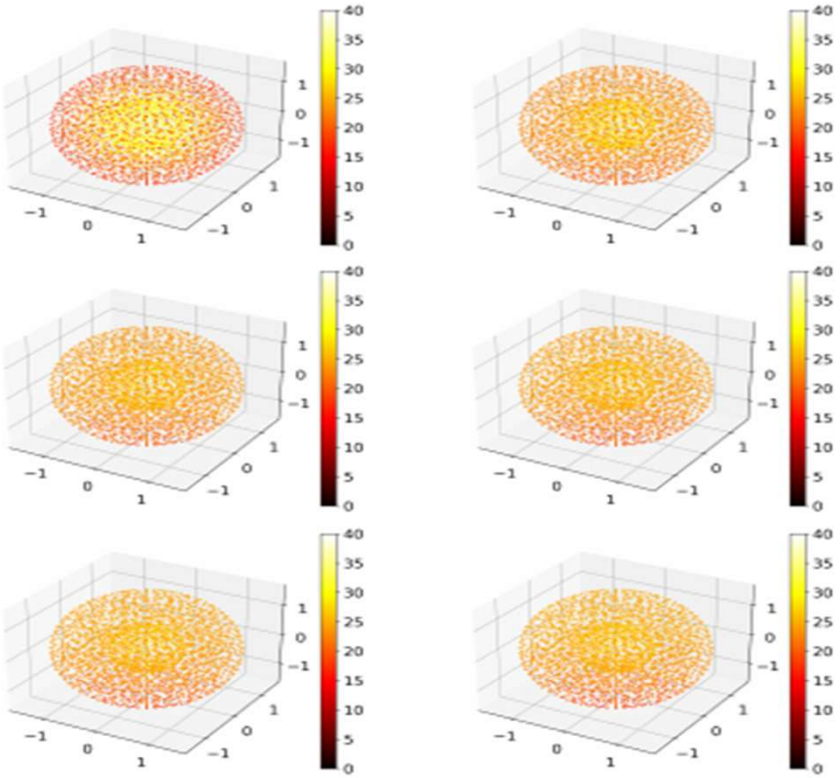


Total amont of NT [vesicles] (*simulation time* 0.1000*s*)

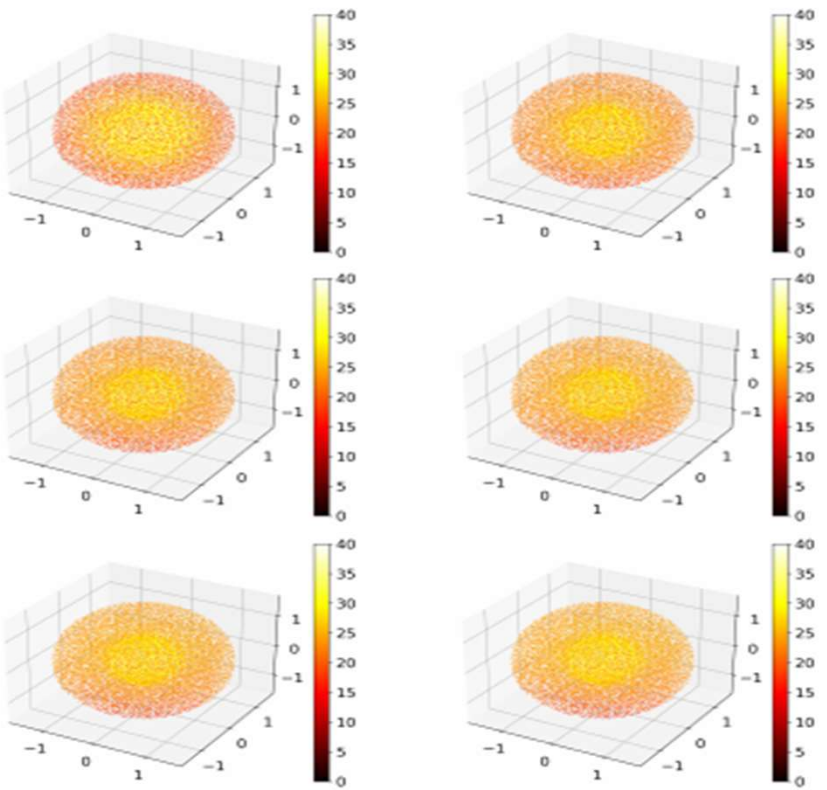
top-large bouton; bottom–small bouton; left-FE, right-CA



Spatial distribution of NT - large bouton (*t*=0.0000*s;* 0.0020*s;* 0.0040*s;…;* 0.0100*s;*)

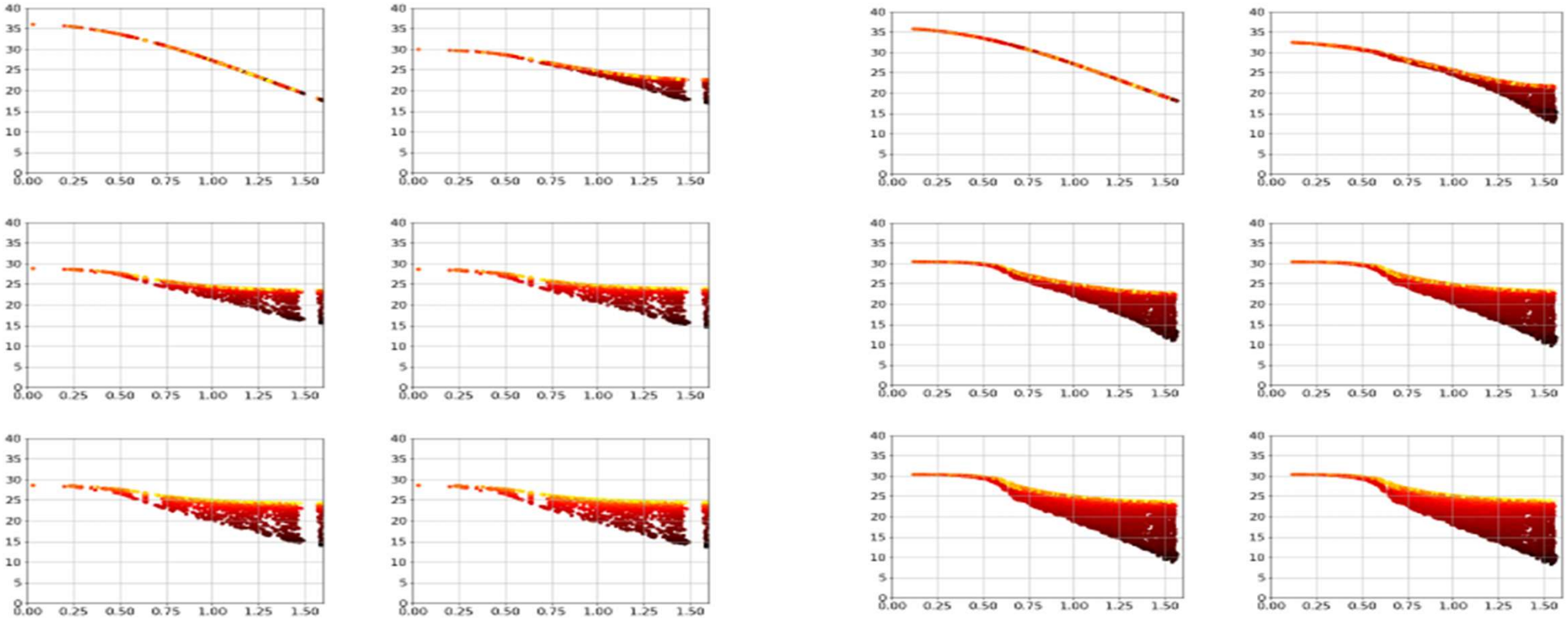


FE



CA

Radial distribution of NT - large bouton (*t*=0.0000*s;* 0.0020*s;* 0.0040*s;…;* 0.0100*s;*)



FE CA

Concluding remarks

- *The simulations confirmed again the occurence of the synaptic depression.*
- *The hardware-software progress speeded up simulations.*
- *The improvement of the tertrahedral mesh of the examined object also contributed to the gain in computations speed.*
- *If two presynaptic boutons of different sizes, but with maintained proportions, are filled with the same number of synaptic vesicles, it is likely that the smaller one gets rid of NT faster.*
- *The cellular automaton model is simpler and faster; however, it may need more iterations with the shorter time step to achieve similar accuracy of prediction of synapse behaviour.*