THREE-DIMENSIONAL SIMULATION OF SYNAPTIC DEPRESSION IN AXON TERMINAL OF STIMULATED NEURON

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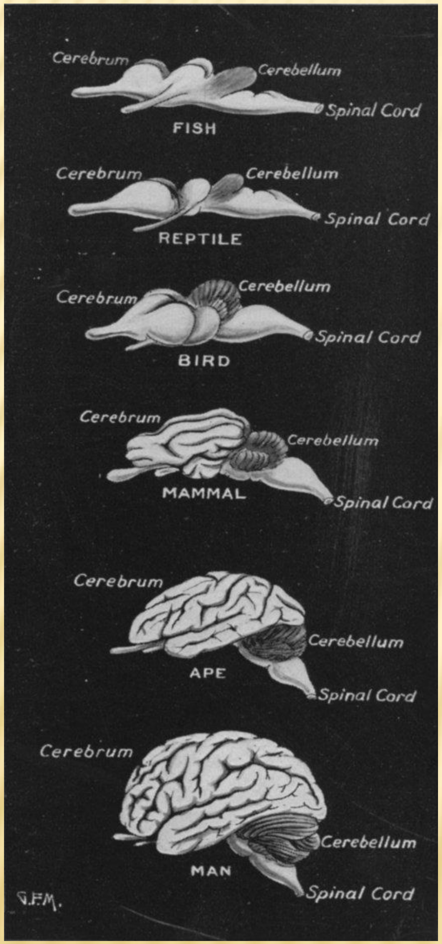
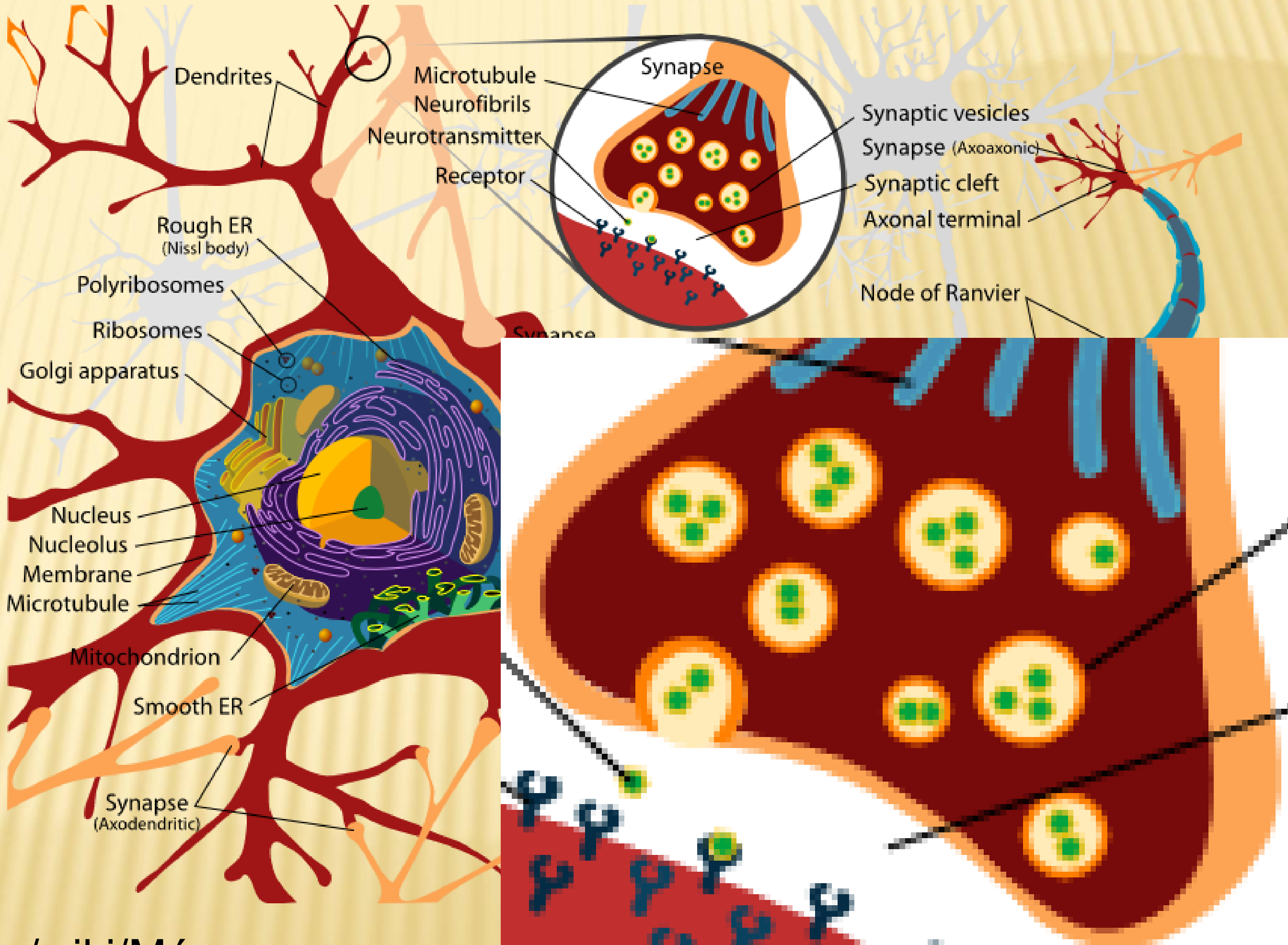
Subject of research (1)

Brain → neuron → synapse → presynaptic bouton



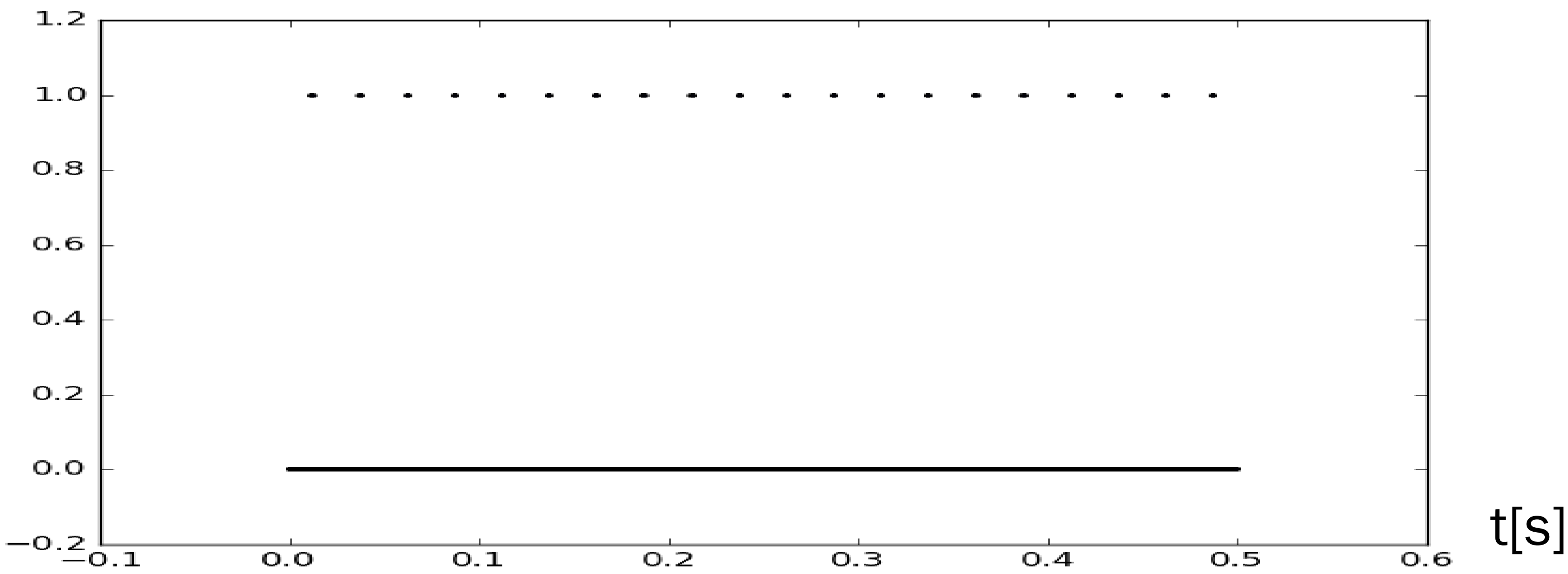


https://pl.wikipedia.org/wiki/Mózg

https://en.wikipedia.org/wiki/Neuron#/media/File:Complete_neuron_cell_diagram_en.svg

Subject of research (2)

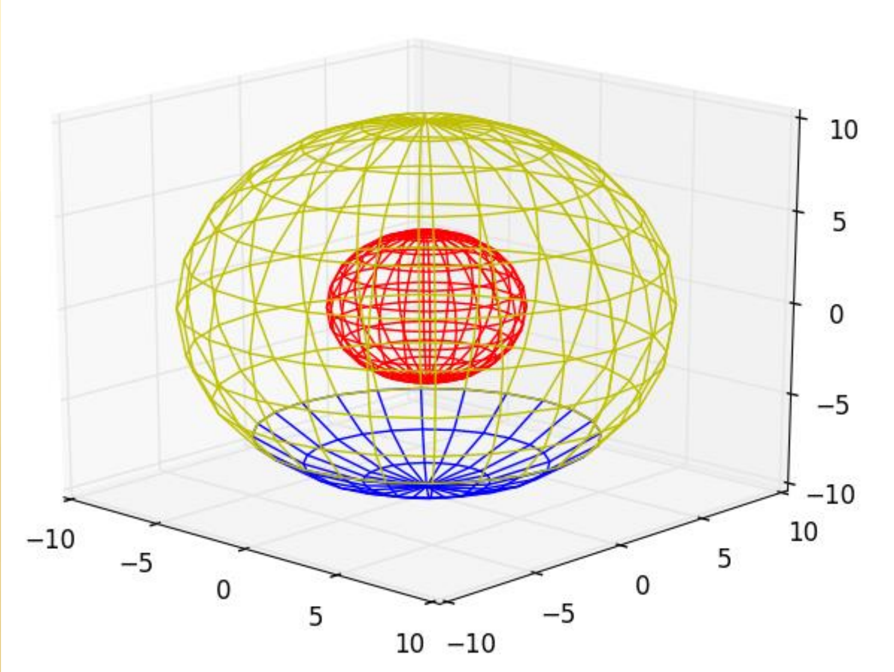
The purpose of the work was to present the solution of the simplest variant of a 3D model of neurotransmitter (**NT**) flow in the terminal bouton of a presynaptic neuron in response to periodical stimulation.



Simulation: 3D Presynaptic bouton model

Design of the general spherical bouton model ***(Python)***

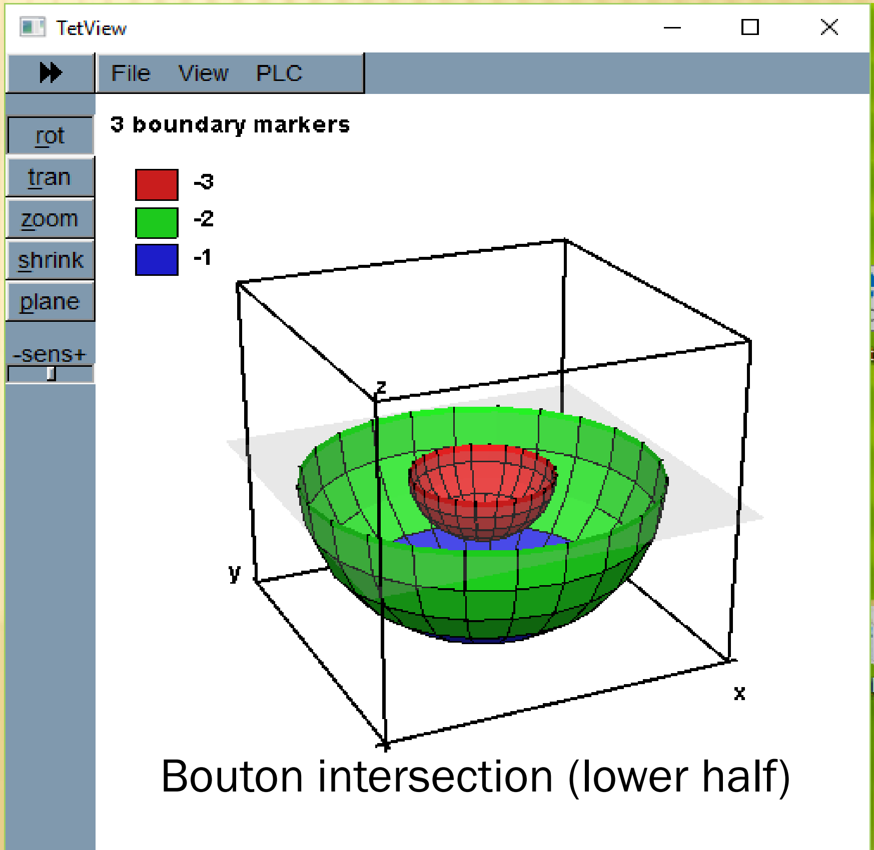
1. „Globe” wireframe model of the bouton (Ω) (yellow)
   - Radius – 10 units
   - 24 „meridians” at 15° intervals
   - 11 „circles of latitude” at 15° intervals
2. Model of the **NT** synthesis domain (Ω_3) (red)
   - Radius – 2,5 units
   - Same division as for (1.)
3. NT docking site ($\partial\Omega_d$) (blue)
   - Part of (1.)
   - Shape - spherical cap
   - Size: 90°S to 45°S



Simulation: before tetrahedralization

Generation of the spherical bouton model ***(Python): results***

1. **Bouton membrane** (including **docking site**) : R = 10
   - 266 nodes (1x„North Pole”+1x„South Pole”+11x24)
   - 288 segments (240 „rectangular”, 2 x 24 „triangular”)
2. **NT synthesis area boundary (denoted by Ω_3)**
   - 266 nodes, 288 segments
   - r = ¼ x radius of (1.)
1. **NT docking site ($\partial\Omega_d$)**
   - First part of (1.)
   - 1+3 x 24 = 73 nodes
   - 3 x 24 = 72 faces
2. **{Membrane} \ {docking site}**
   - 8 x 24+1 = 193 nodes
   - 9 x 24 = 216 faces



Bouton intersection (lower half)

Simulation: tetrahedralization

Generation of the tetrahedral mesh inside the bouton ***(TetGen® - C++ version)***

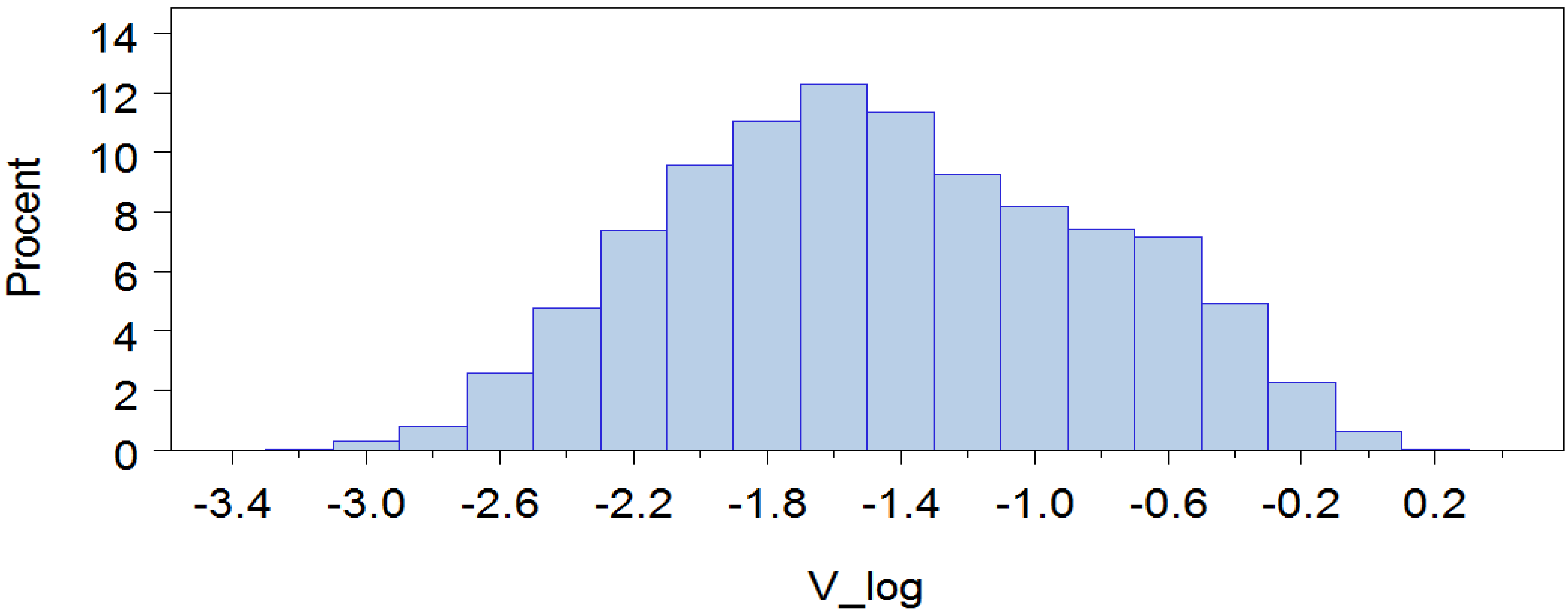
1. Parameters passed to TetGen® execution
   - **`$ ./tetgen -pq4.0/19VAa4.0 param29.poly`**
   - Explanation of the parameters:
     - pq refined mesh (face angle ≥ 14°)
     - 4.0/19 max. R/edge ratio, min. dihedral angle [°]
     - V print tetrahedron volume statistics
     - A assign attributes to regions
     - a4.0 max. tetrahedron volume

Simulation: after tetrahedralization

Mesh generation inside the bouton ***(TetGen® in C++)***

- 7523 points (vertices), 42801 tetrahedra
- Distribution of log(volume) of tetrahedra logV ***(SAS®)***
- Mean(V)=0,095; mean(logV)= –1,442 (V=0,036)

Hardware: IBM BladeCenter („mars”) – ACK Cyfronet



Simulation: before applying FEM

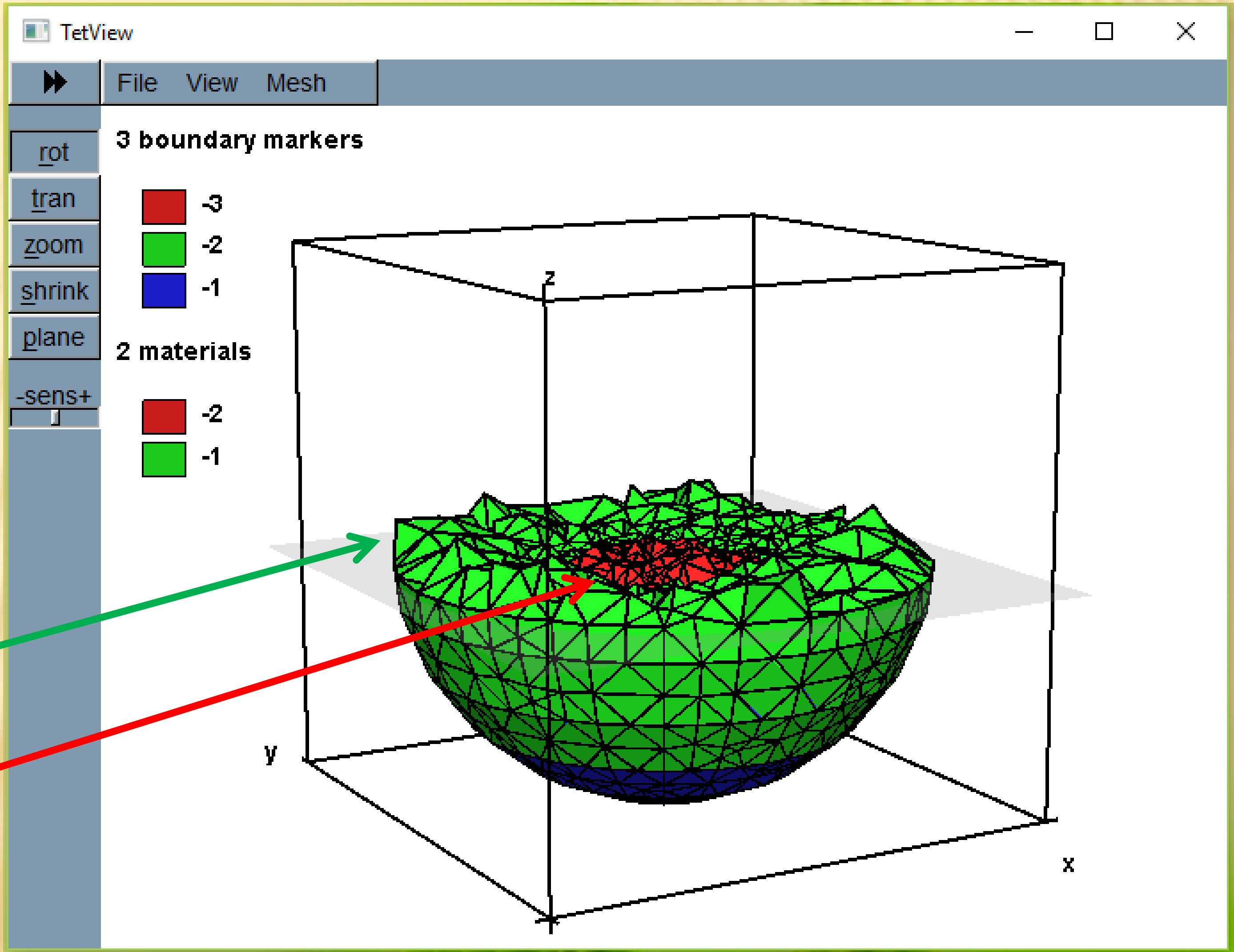
The view of the generated mesh ***(TetView®)***

1. Synthesis
2. Docking
3. Other

Rescaled Bouton: (unit=0,16µm)

R = 0,16x10µm = 1,6 µm

r = 0,16x4µm = 0,64 µm



Outline of the applied FEM - model

1. Details of the simulation model
   - Partial differential equation

$$\frac{\partial \rho(x,t)}{\partial t} = \sum_{i,j=1}^{3} \frac{\partial}{\partial x_i}\left(a_{ij}(x) \frac{\partial \rho(x,t)}{\partial x_j} \right) + f(x)\left(\bar{\rho} - \rho(x,t)\right)^{+}$$

2. Explanation of terms used in the model equation
   - $x = [x_1, x_2, x_3]$ or $[x,y,z]$ – point in Ω (in the bouton)
   - t – simulation time [s]
   - $\rho(x,t)$ *(rho)* : NT vesicle density (ves/μm^3)
   - a_{ij} : diffusion tensor (diagonal) (μm^2/s)
   - $f(x)=\beta(x)$: time distribution of synthesis rate
     - uniform distribution assumed $\beta(x) = \beta_0$ (1/s)
   - $\bar{\rho}$: synthesis threshold (ves/μm^3)

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Outline of the applied FEM – model (2)

1. Requirements for the simulation model
   - Total amount of NT ≈ 84000 [vesicles]
   - Amount of NT released during τ = 0,4μs stimulation:
   - $$\int \rho(x,t)\,dx\,dt \approx 300[vesicles]$$

$(x, t) \in \partial\Omega_d \times [t_0, t_0 + \tau]$

   - Stimulations occur *only* in the middle of each 0,025s time period (stimulation frequency = 40Hz)
   - The values of the parameters of the simulation were chosen to meet the above assumptions*.

* Aristizabal F, Glavinovic MI (2004) Simulation and parameter estimation of dynamics of synaptic depression. *Biol Cybern* 90:3–18

Outline of the applied FEM – model (3)

1. Parameters of the simulation model

$$\frac{\partial\rho(x,t)}{\partial t} = \sum_{i,j=1}^{3} \frac{\partial}{\partial x_i}\left(a_{ij}(x)\frac{\partial\rho(x,t)}{\partial x_j}\right) + f(x)(\bar{\rho} - \rho(x,t))^{+}$$

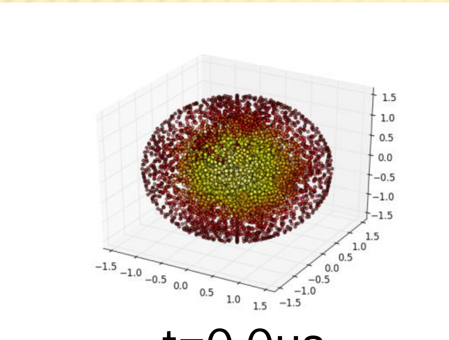
2. Parameter values:
   - $\rho(x,0) = 7200\mu m^{-3}\, e^{(-0{,}28/\mu m^2) r^2}$ $(r^2 = x^2 + y^2 + z^2)$
   - a_{ij} : diffusion tensor (diagonal) $[300\mu m^2/s]/[10^k]$ (k=2)
   - f(x) : spatial distribution of synthesis rate
     - $f(x) = \beta_0$ for $\rho(x,t) < \bar{\rho}$
   - $\bar{\rho} = 6000\ (1/\mu m^3)$
   - Release of NT ➔
     - ($\alpha = 20{,}8\ \mu m^3/s$)
   - $\beta_0 = 3{,}12 (1/s)$

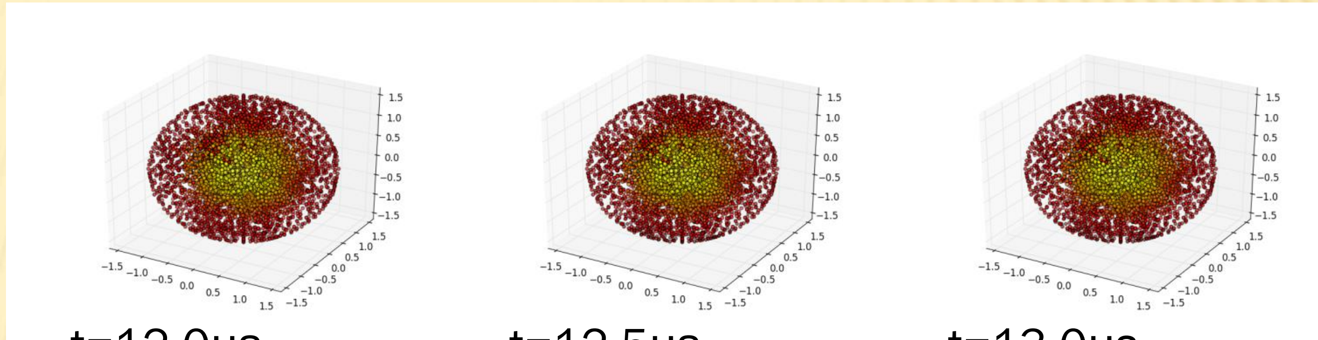
$$\sum_{i,j=1}^{N} a_{ij}\frac{\partial\rho(x,t)}{\partial x_j} n_i = \alpha\rho(x,t) \quad \text{for}$$

$$(x,t) \in \partial\Omega_d \times [t_0, t_0 + \tau].$$

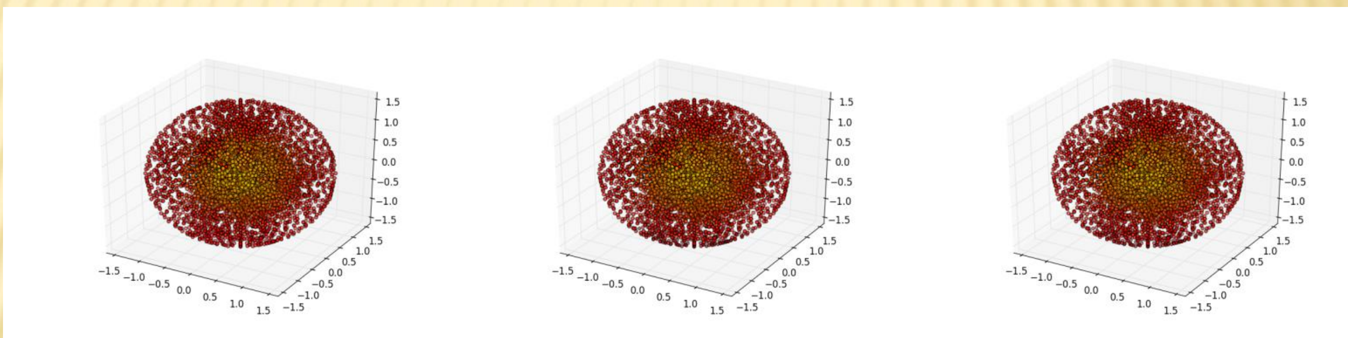
Results (1) – flattening distribution ρ(x,t)

ρ(x,t)[μm^{-3}]=3000 4000 5000 6000 7000 8000

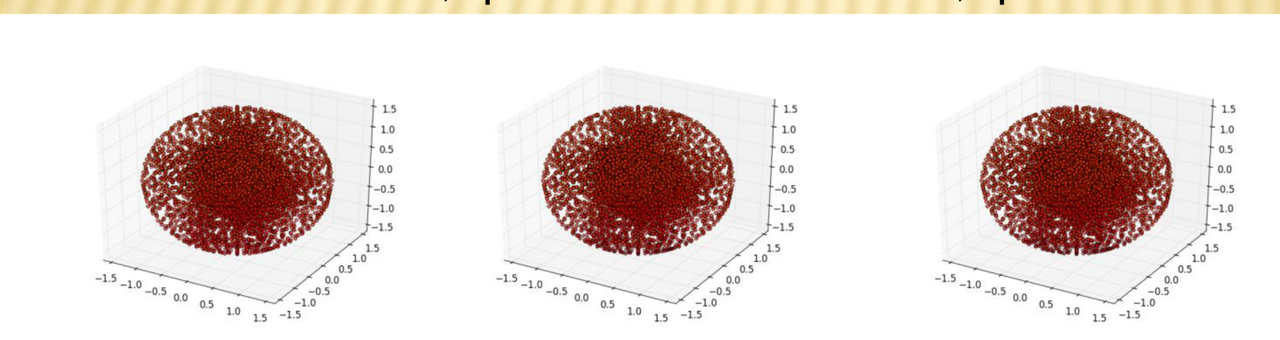


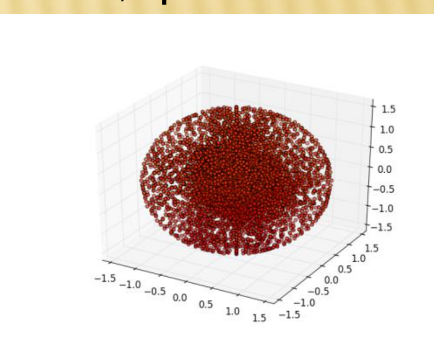


t=0,0μs … t=12,0μs t=12,5μs t=13,0μs …



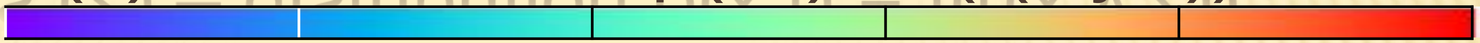
t=37,0μs t=37,5μs t=38,0μs …



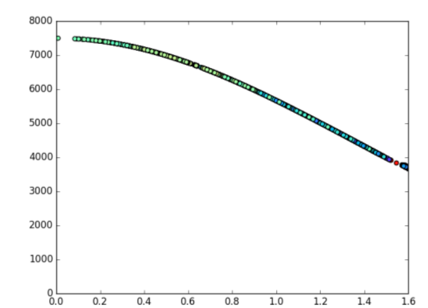


t=487,0μs t=487,5μs t=488,0μs … t=500,0μs

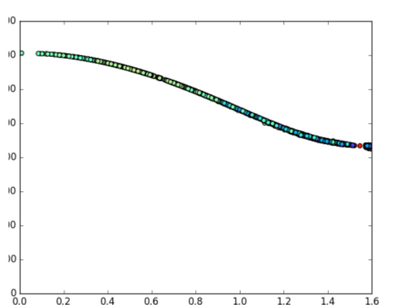
Results (2) – distribution ρ(x,t) = f(r(x,y,z))



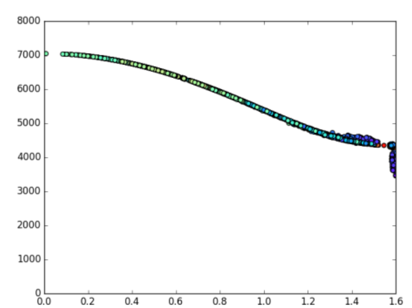
z[μm] = -1,6 -0,96 -0,32 0,32 0,96 1,6



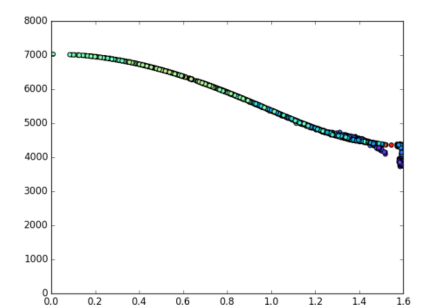
t=0,0μs …



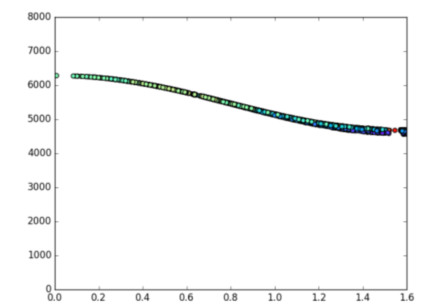
t=12,0μs



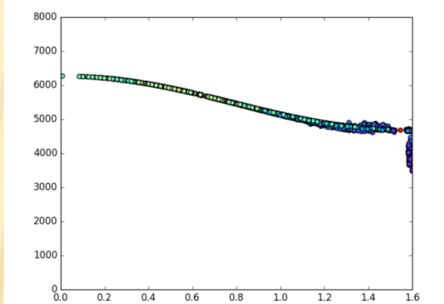
t=12,5μs



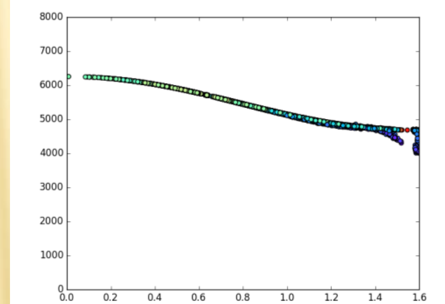
t=13,0μs …



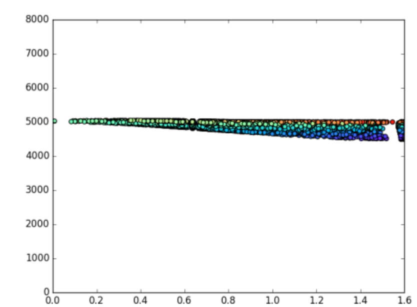
t=37,0μs



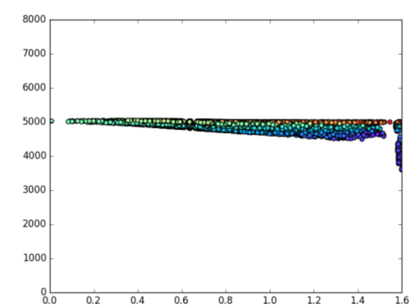
t=37,5μs



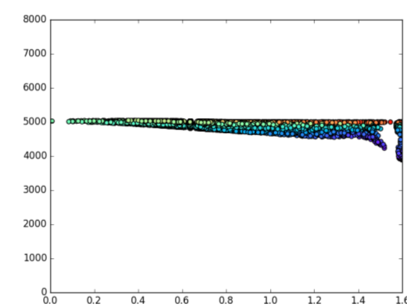
t=38,0μs …



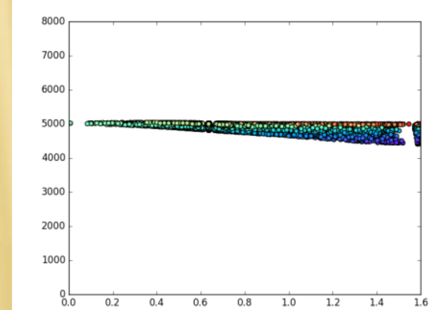
t=487,0μs



t=487,5μs

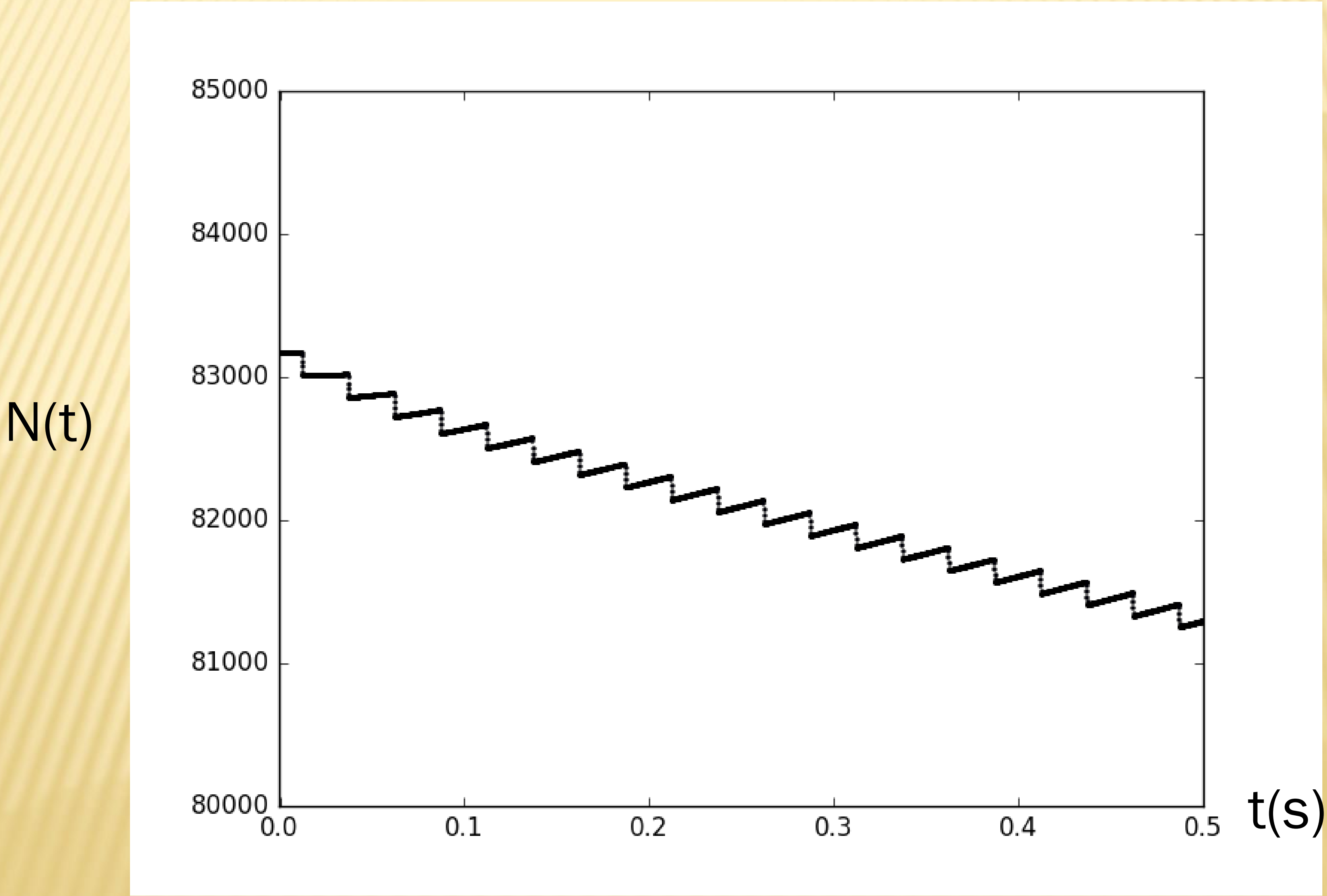


t=488,0μs …



t=500,0μs

Results(3) – Total number of vesicles N = N(t)



Concluding remarks

1. *After some time delay the stimulated neuron begins to restore its synaptic vesicle pool .*
2. *HOWEVER, in some cases, frequent stimulation may lead to the synaptic depression, and smaller release ability in response to the next arriving action potentials.*
3. *The model is suitable for performing a number of experiments in order to verify the effect of:*
   1. *production rate of the neurotransmitter ;*
   2. *release rate of the neurotransmitter ;*
   3. *the size of secretion zone*

   on the ability to maintain the neuron response to frequent stimulation.

THANK YOU FOR YOUR ATTENTION …