RECENT PROGRESS IN COMPUTATIONAL STUDIES OF RADIATION-INDUCED DISORDERS IN THE CENTRAL NERVOUS SYSTEM

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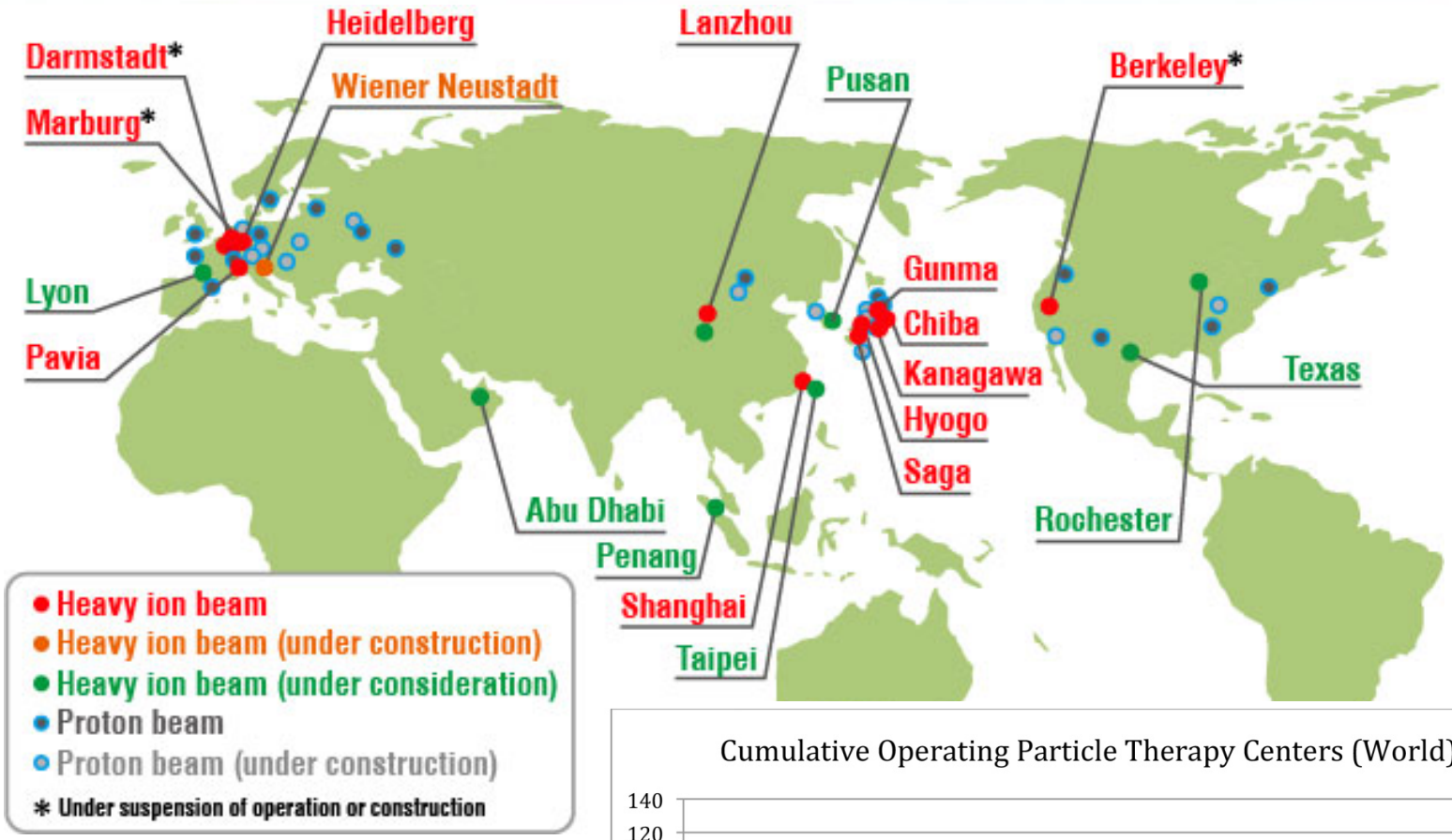
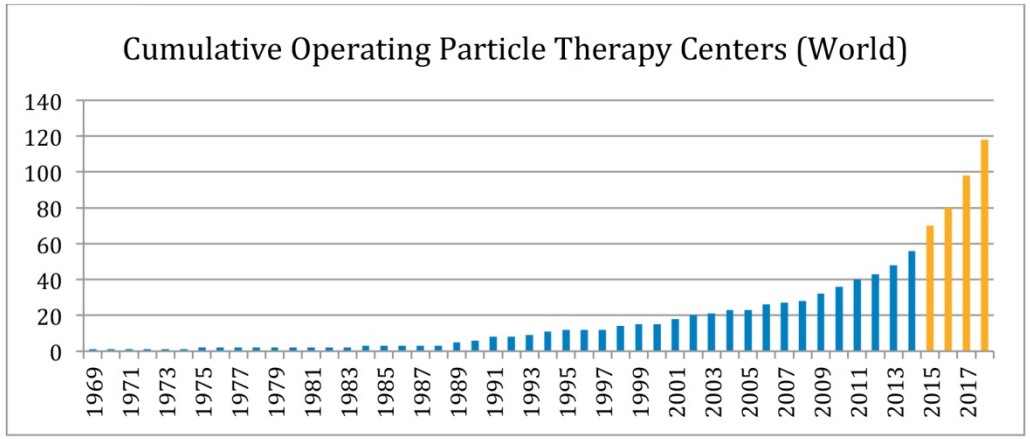
JINR, Dubna, Russia

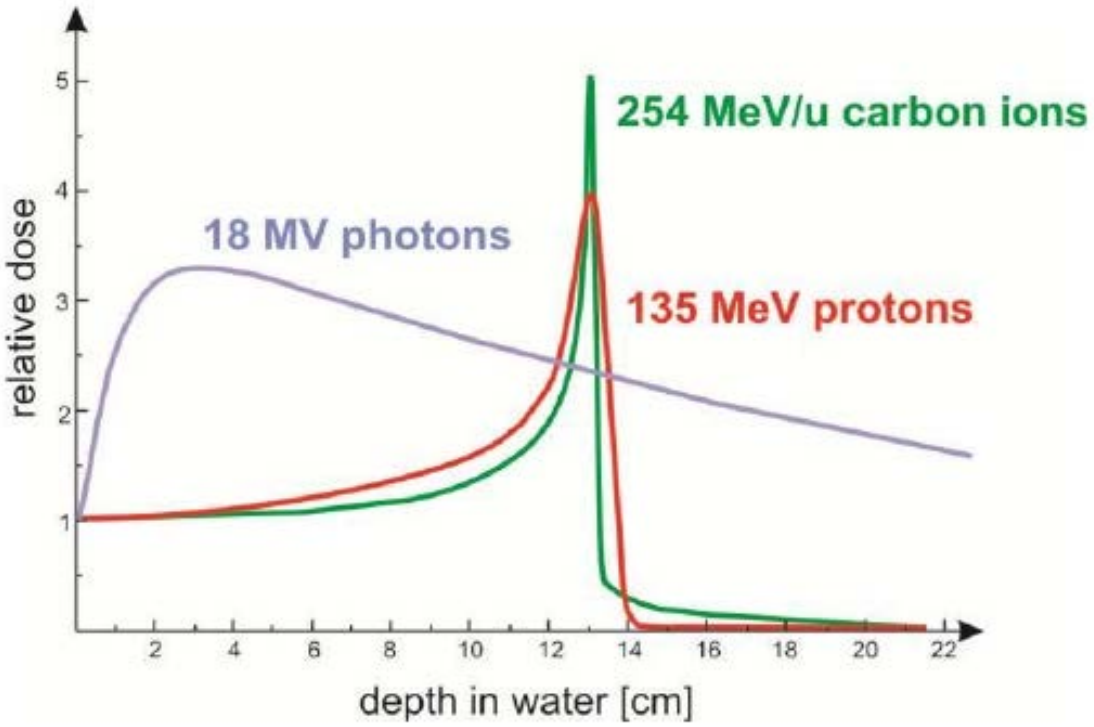
Radiation and brain: a cause for concern?

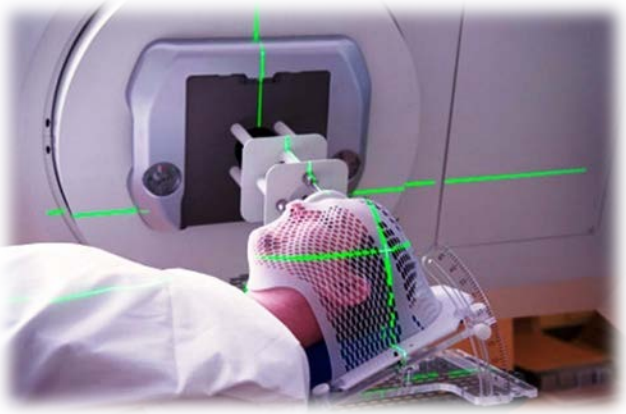
Radiation therapy boom



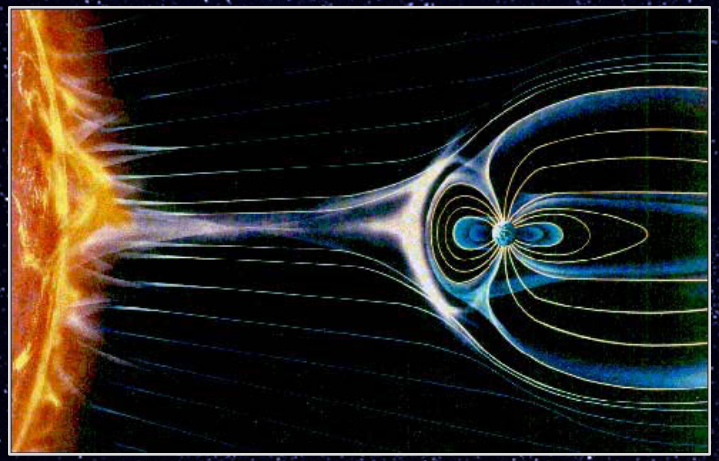


Principles of radiation therapy



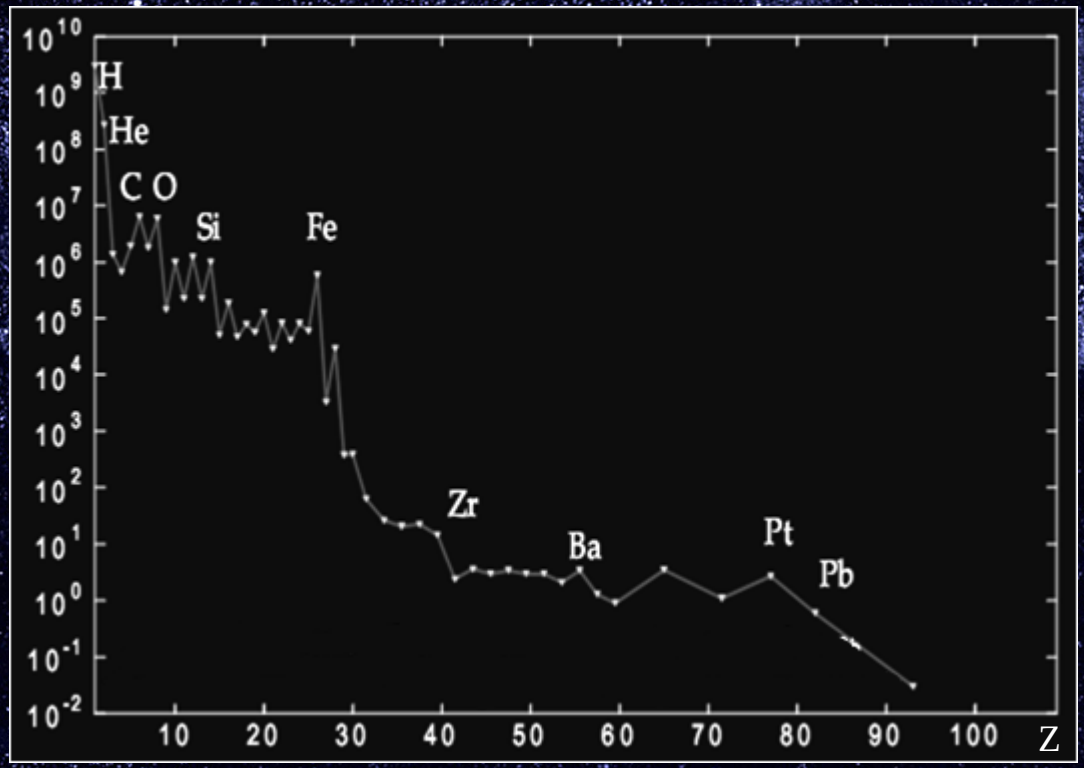


Space radiation and brain

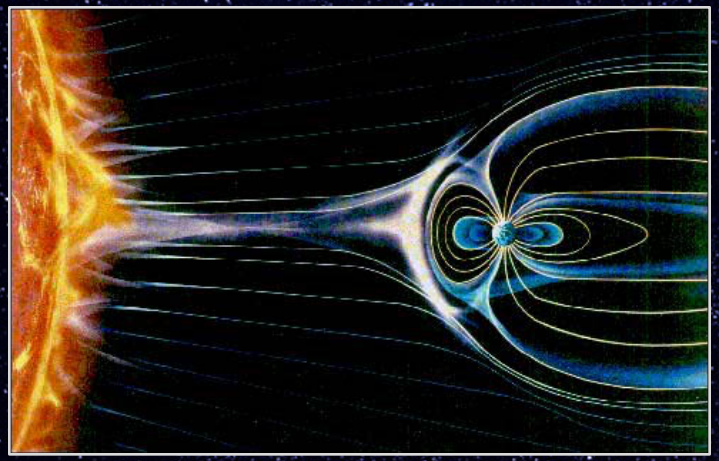


Galactic cosmic rays:

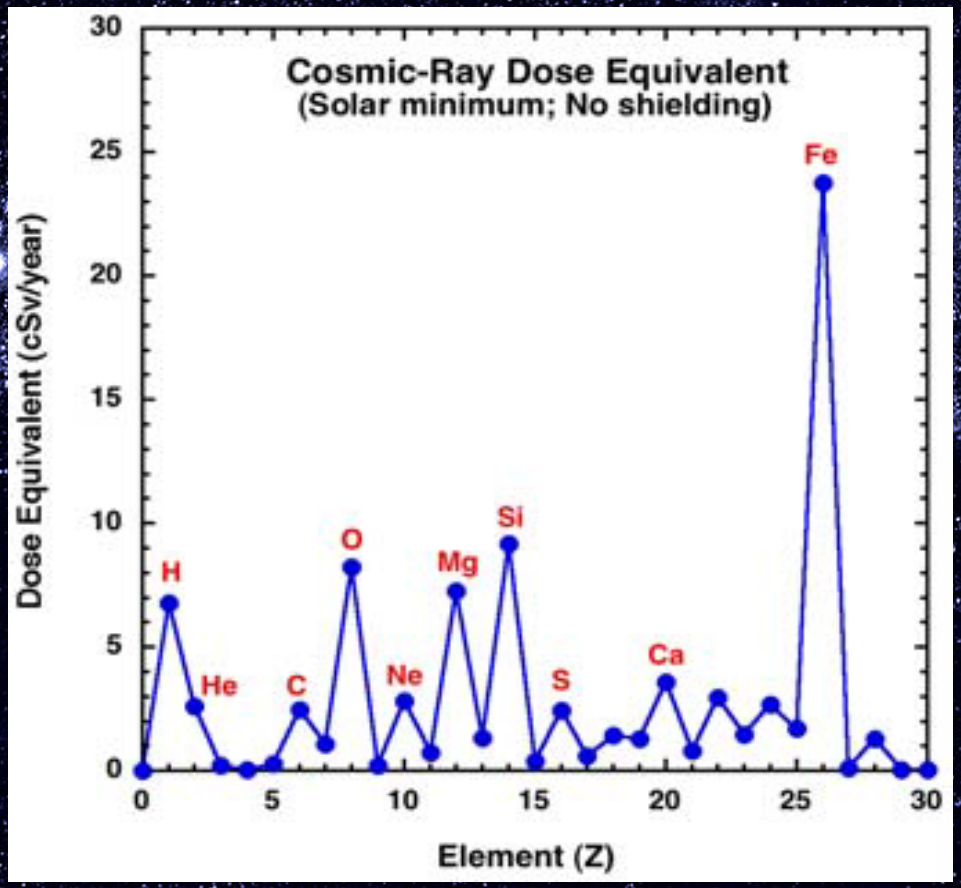
protons ~ 85%
α-particles ~ 14%
heavy nuclei ~ 1%



Space radiation and brain



Galactic cosmic rays
dose equivalents

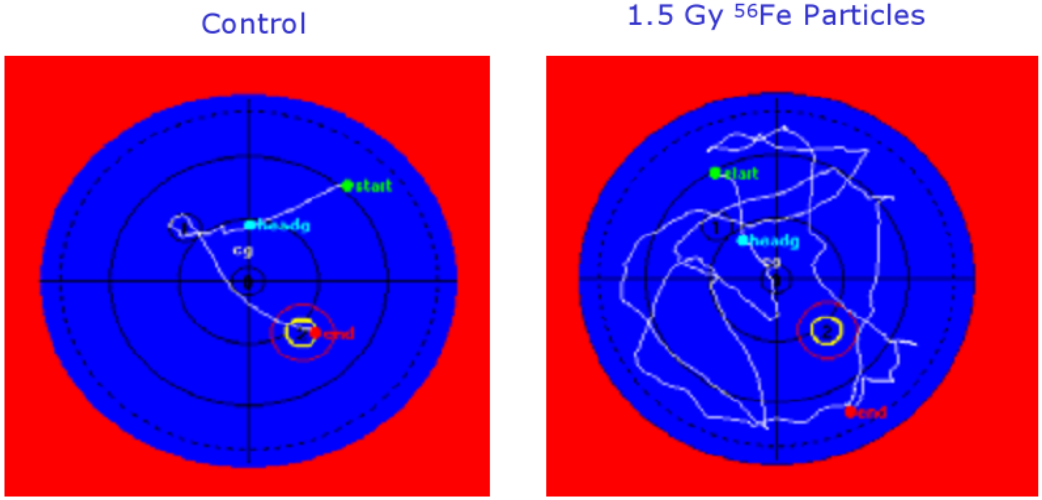


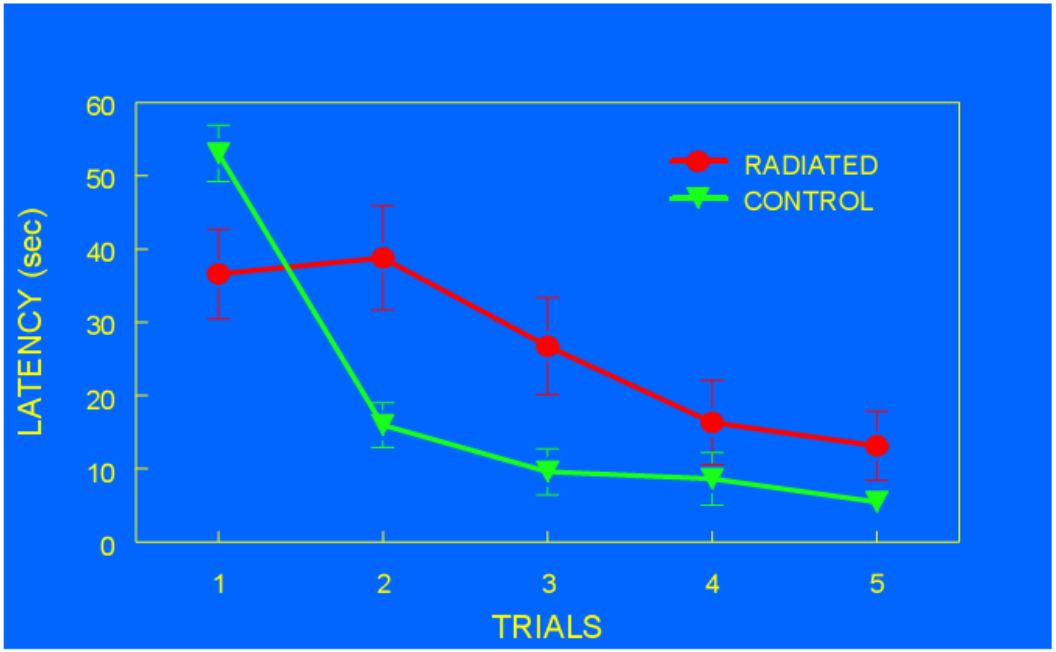
Persistent reduction in the spatial learning ability of rats after ^{56}Fe ion irradiation

➢ Morris water maze

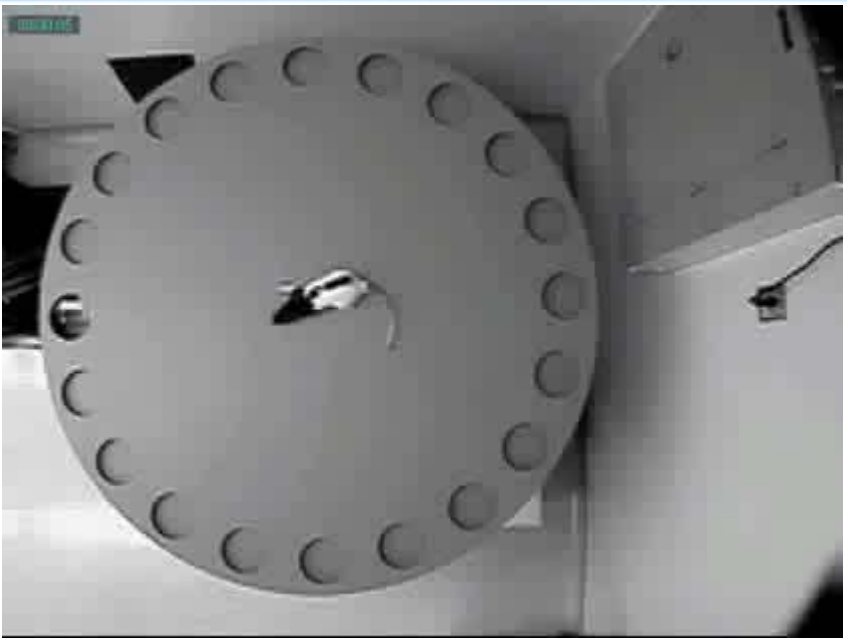
1GeV/u , 1.5 Gy, ^{56}Fe
After 1 month

M. Rabin. 2005



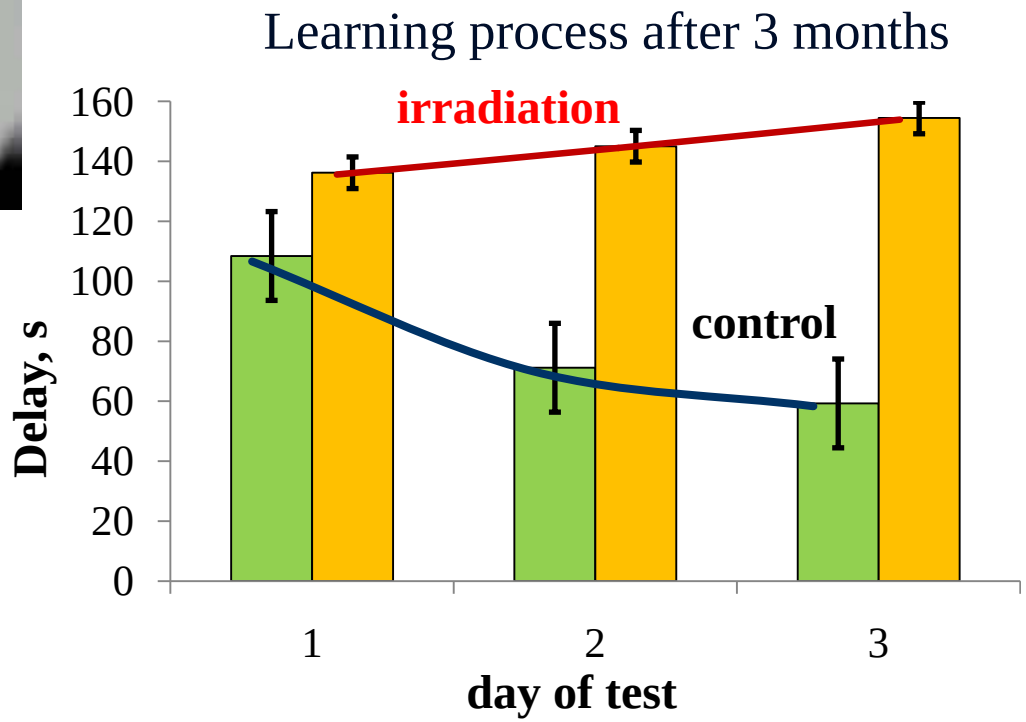


Persistent reduction in the spatial learning ability of rats after ^{56}Fe ion irradiation



20 cGy 1GeV/u ^{56}Fe

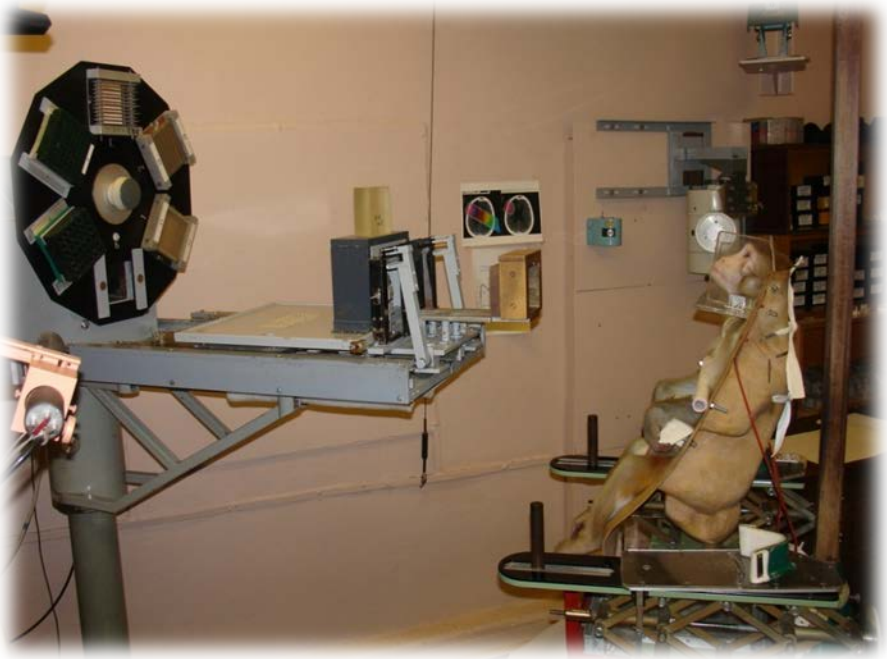
$\Phi \approx 10^5/cm^2$



R. Britten et al., 2012

First experiments with monkeys

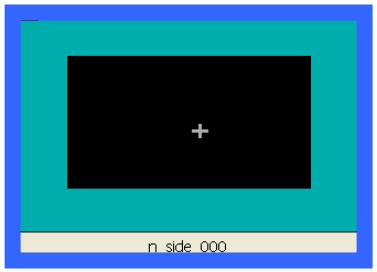
Proton beam
170 MeV, 3 Gy

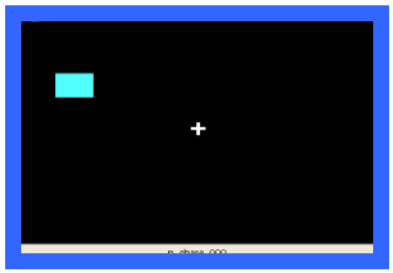


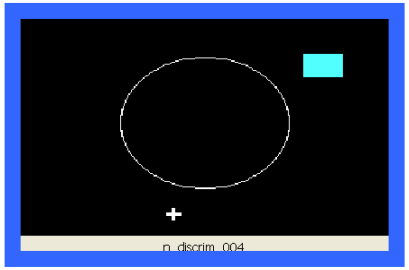
^{12}C ions
500 MeV/u, 1 Gy

Gaming tests
(an automated computer system)

Psychological Test System — a series of 18 computer gaming tasks of increasing difficulty to simulate the basic elements of the operator's activity

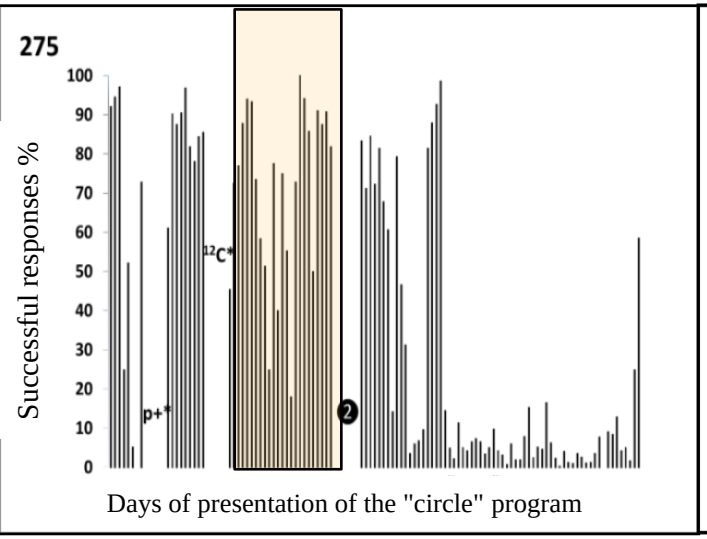


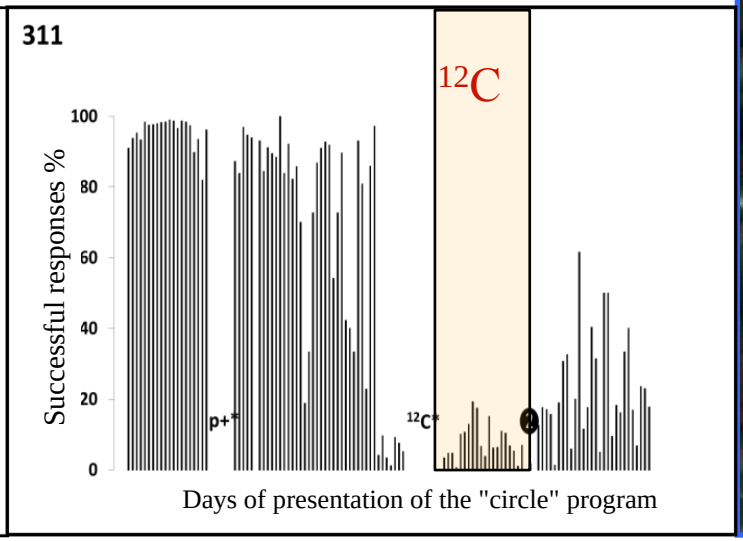




The test is based on the development of complex instrumental conditioned reflexes, associated with the precise coordination of movements on the video stimuli of different configurations

Macaca mulatta irradiation (^{12}C ions, 500 MeV/nucleon)





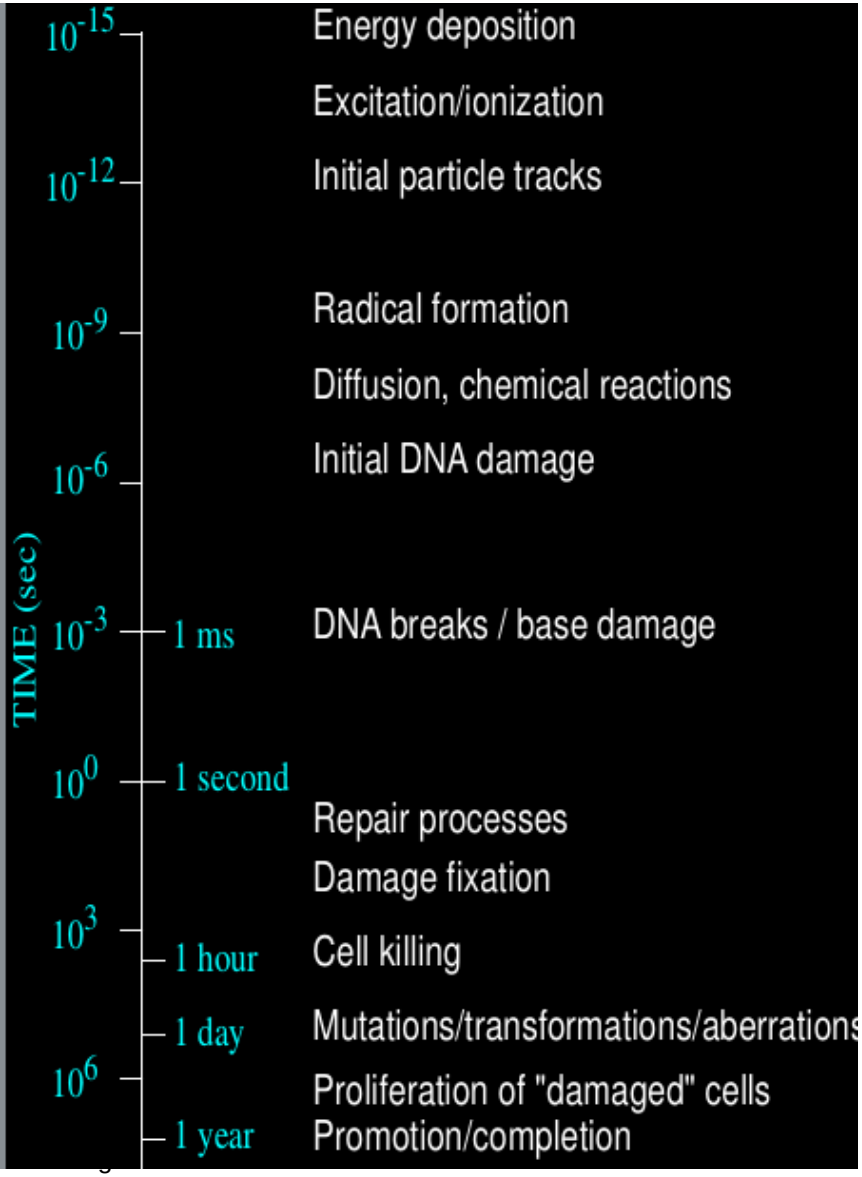
control **exposure** **Dose: 1 Gy**

Indicators of cognitive functions in the irradiated and control monkey groups

p + — proton irradiation day; ^{12}C — carbon ion irradiation day; 2 — a new level of the game program difficulty.

How to explain and predict radiation-induced disorders?

Principles of modeling



Physical stage

Chemical stage

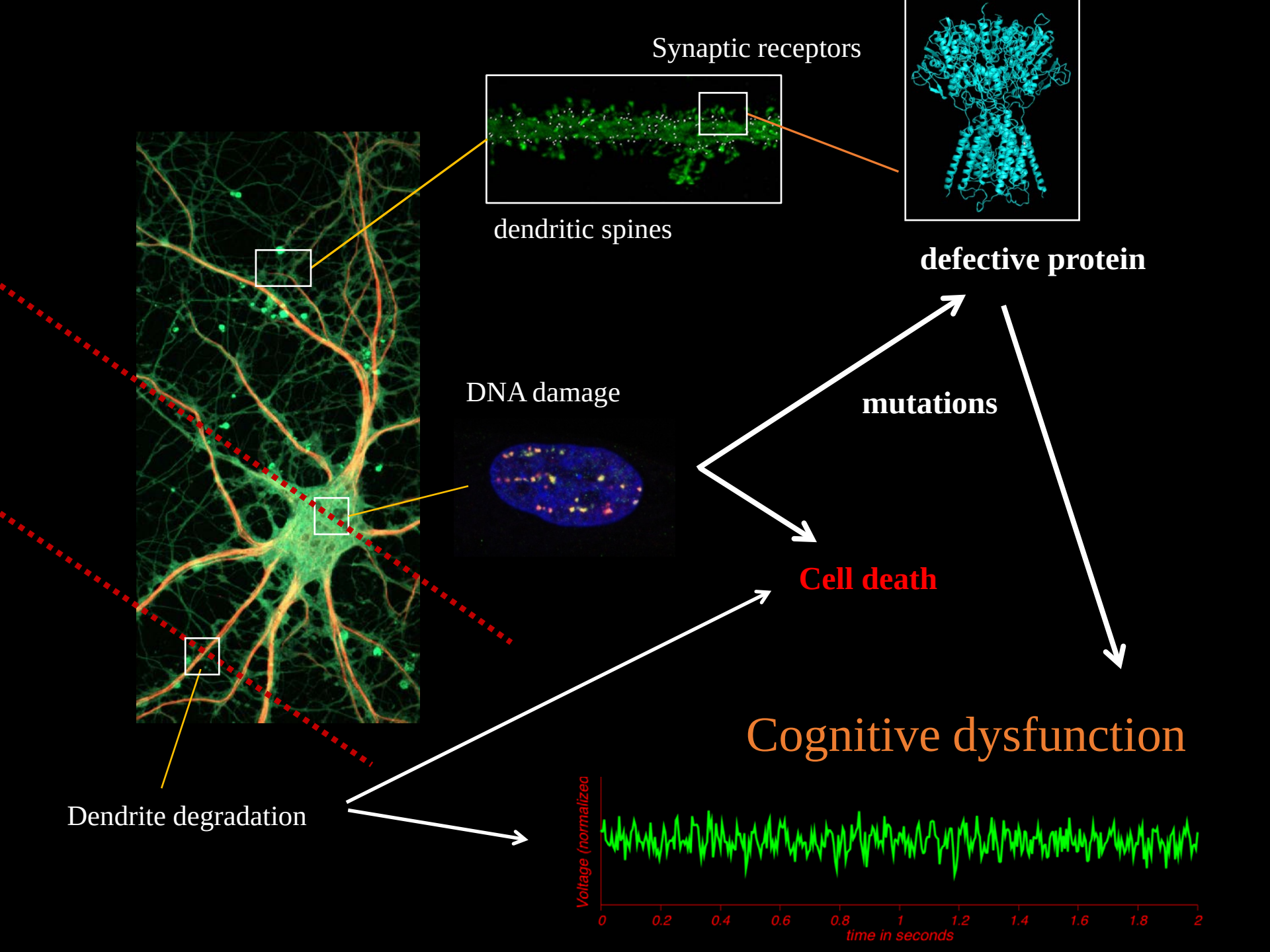
Biological stage

?

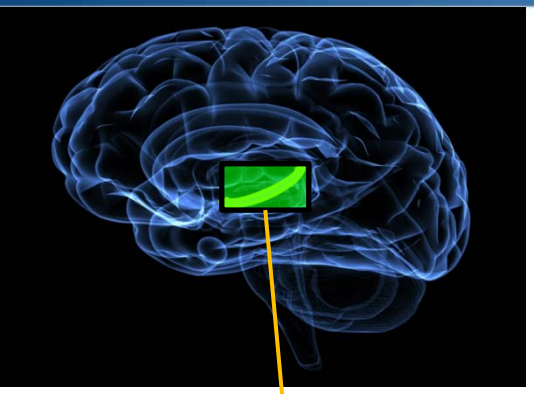
Functional activity of CNS

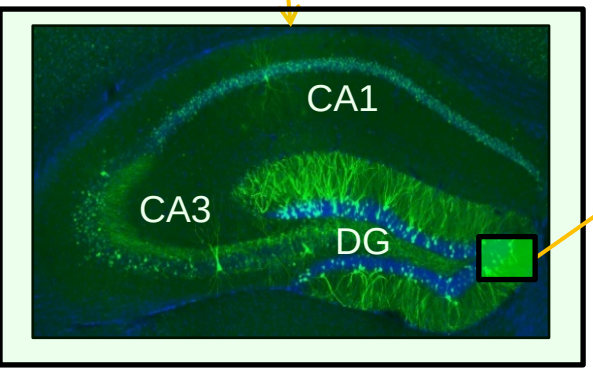
Neural network modeling

Estimating risks

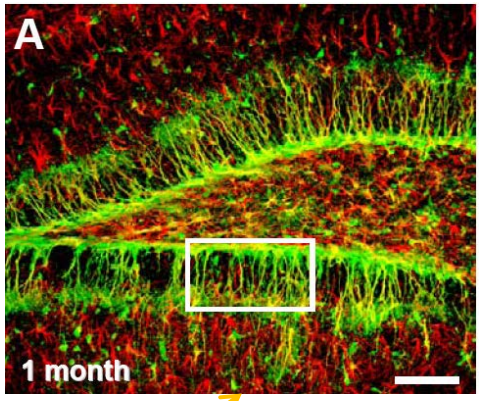

Synaptic receptors
dendritic spines
defective protein
DNA damage
mutations
Cell death
Cognitive dysfunction
Dendrite degradation
Voltage (normalized)
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
1.8
2
time in seconds

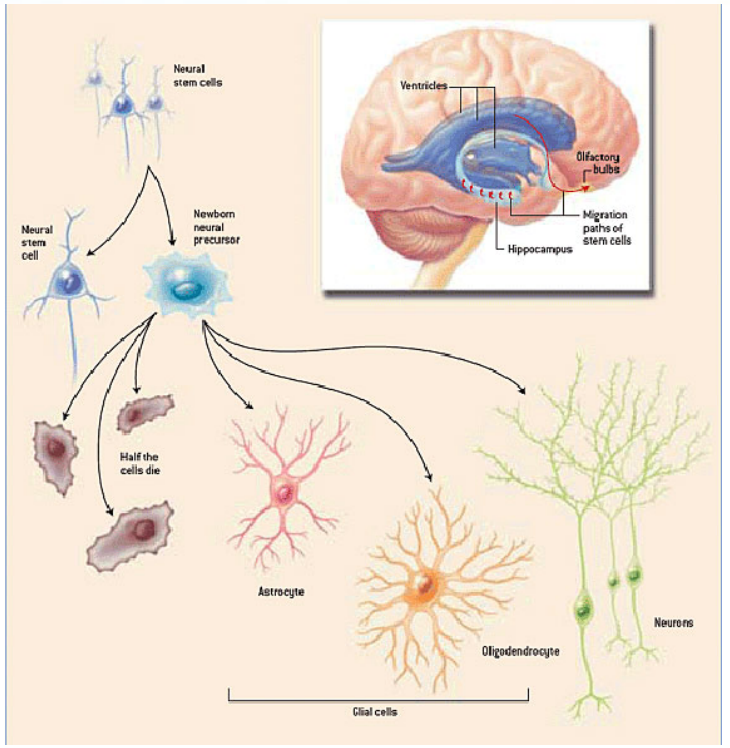
Critical parts of brain





J.Encinas et al., 2011



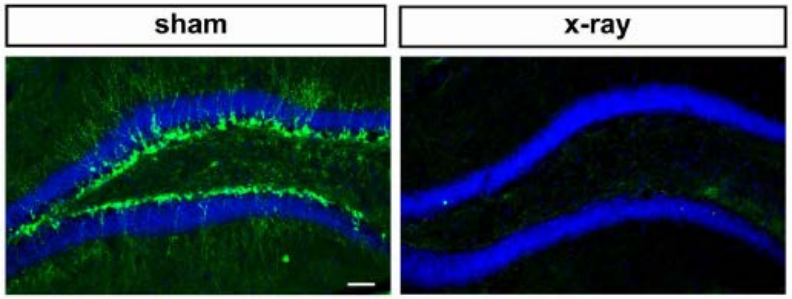


Hippocampus

- Key role in “short-term” and “long-term” memory, integrating processes and plasticity of the brain

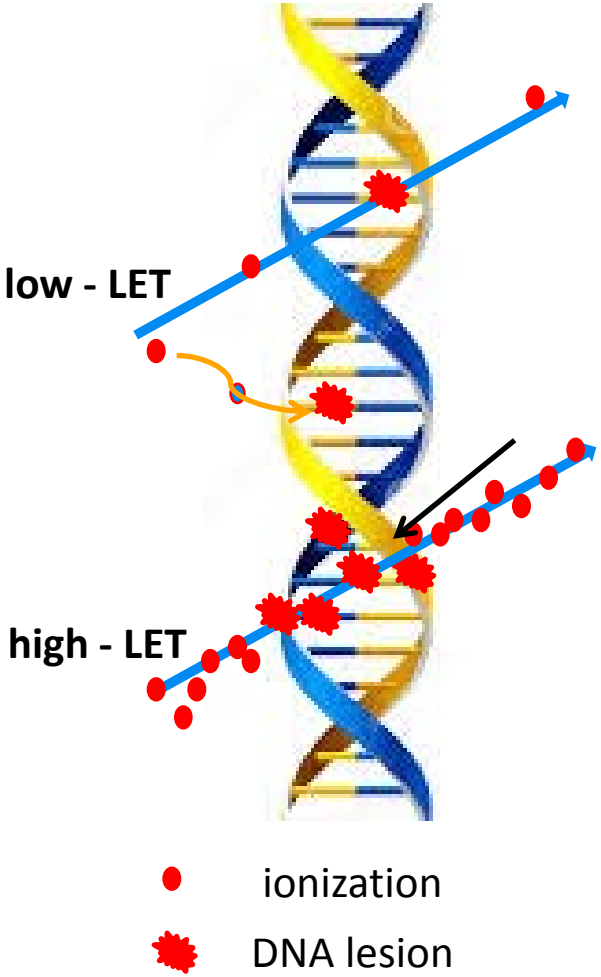
Neuronal Stem Cells

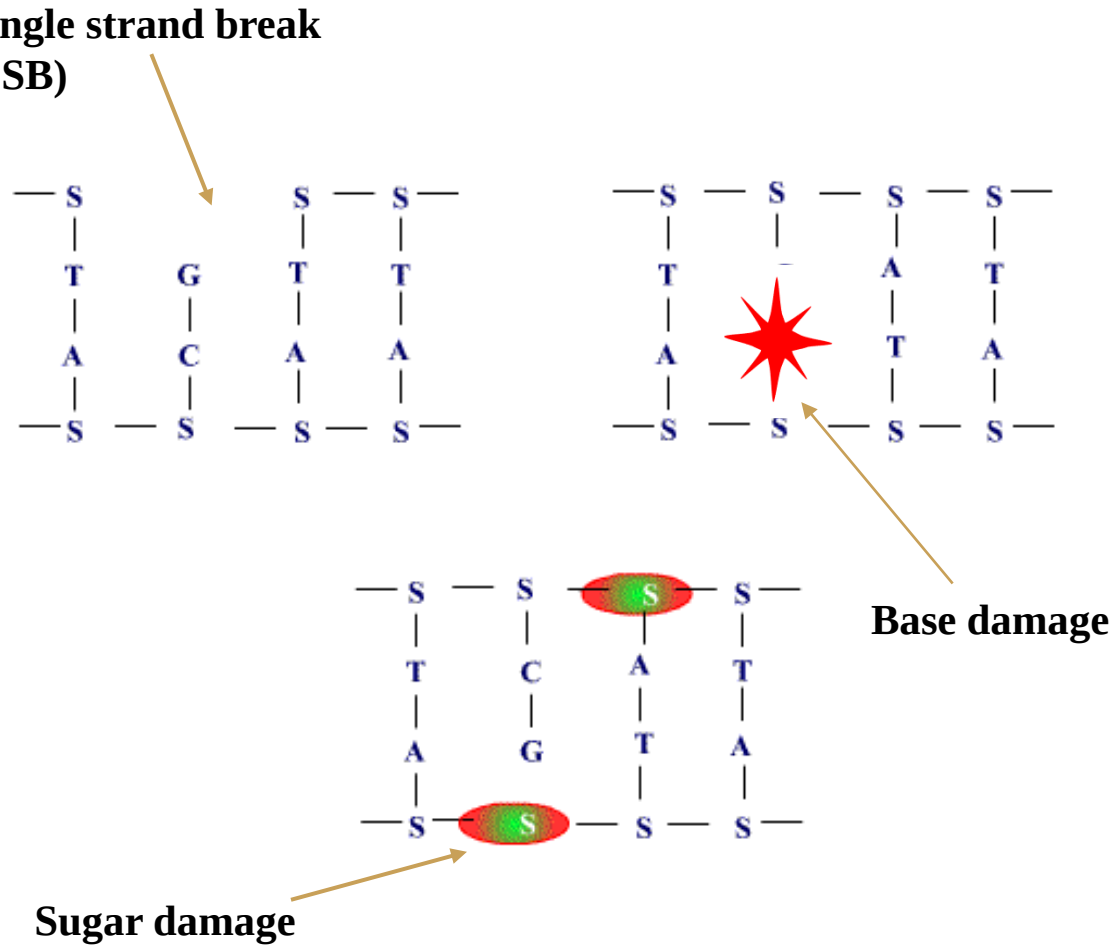
- are localized in the special zones of hippocampus and constantly produce new neurons
- highly radiosensitive!



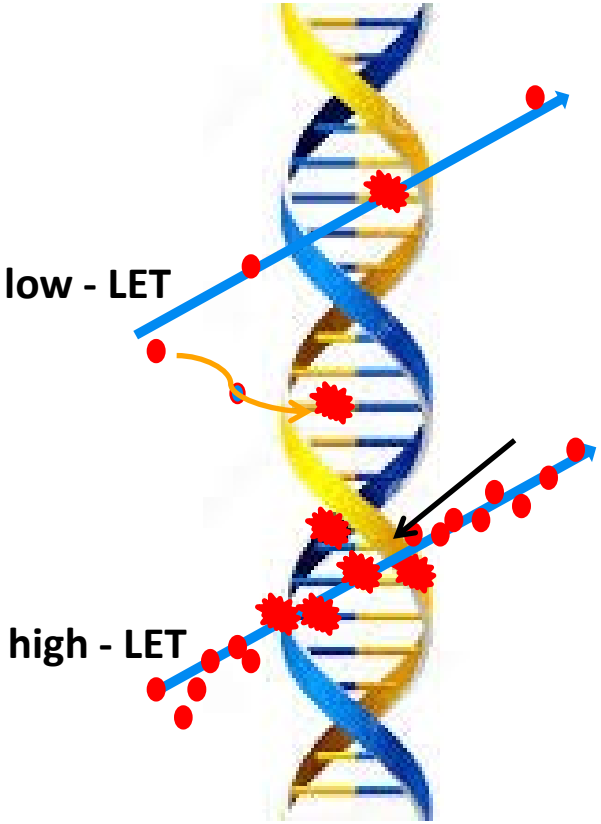
Computing DNA damage

Isolated DNA damage



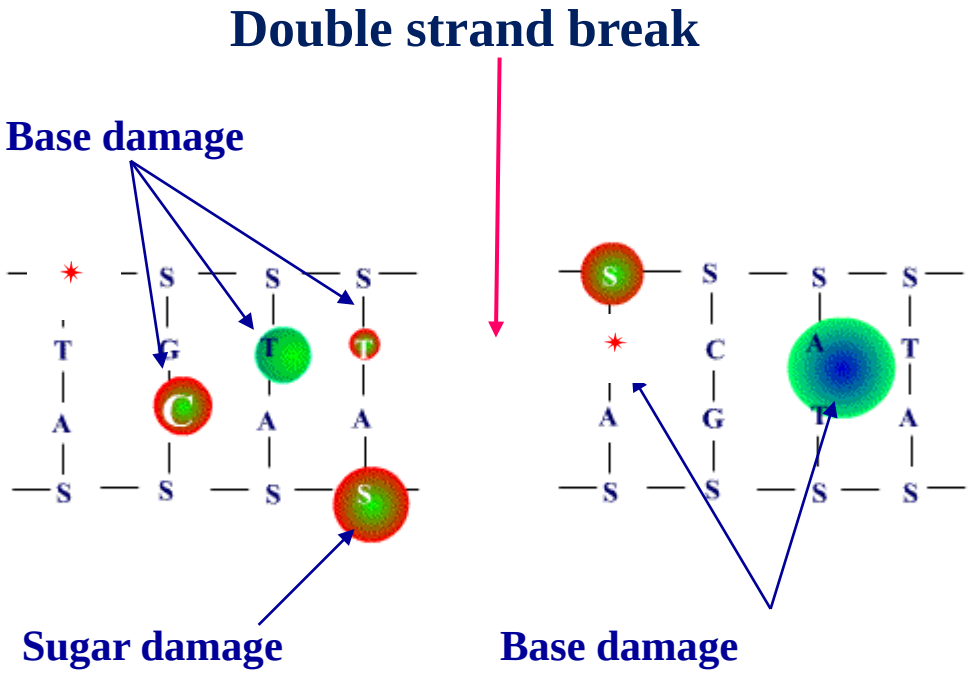


Clustered DNA damage



ionization

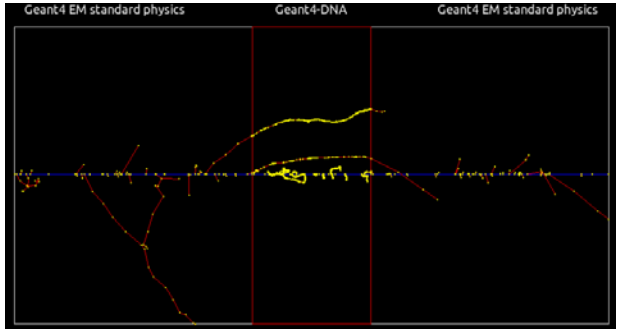
DNA lesion



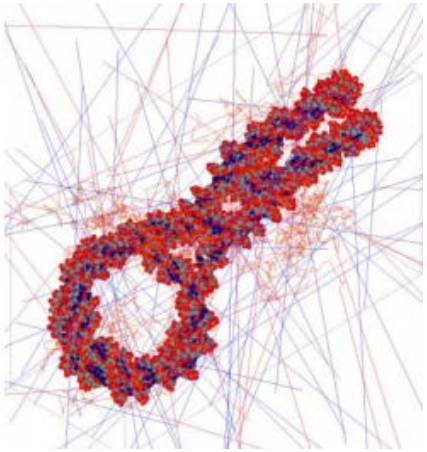
Frequency of damage induction per cell per Gy:
SSB – 1000; DSB – 30-40; DNA-protein cross-links – 50;
complex damage (SSB+base lesions) - 60

Geant4-DNA Monte Carlo radiation transport code for biophysical simulations

MICRODOSIMETRY
S. Incerti et al. (2008)

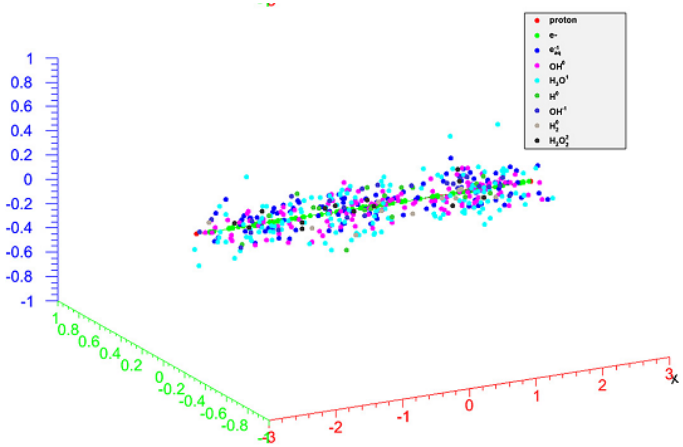


PDB4DNA
E. Delage et al. (2015)

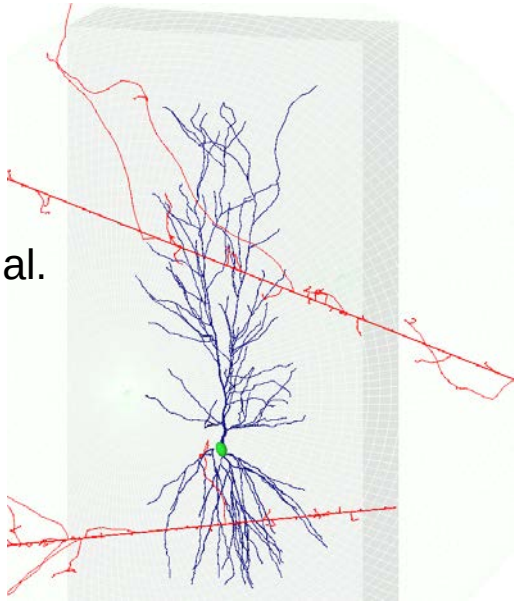


GEANT4-DNA : EXTENDING THE GEANT4 MONTE CARLO SIMULATION TOOLKIT FOR RADIOBIOLOGY

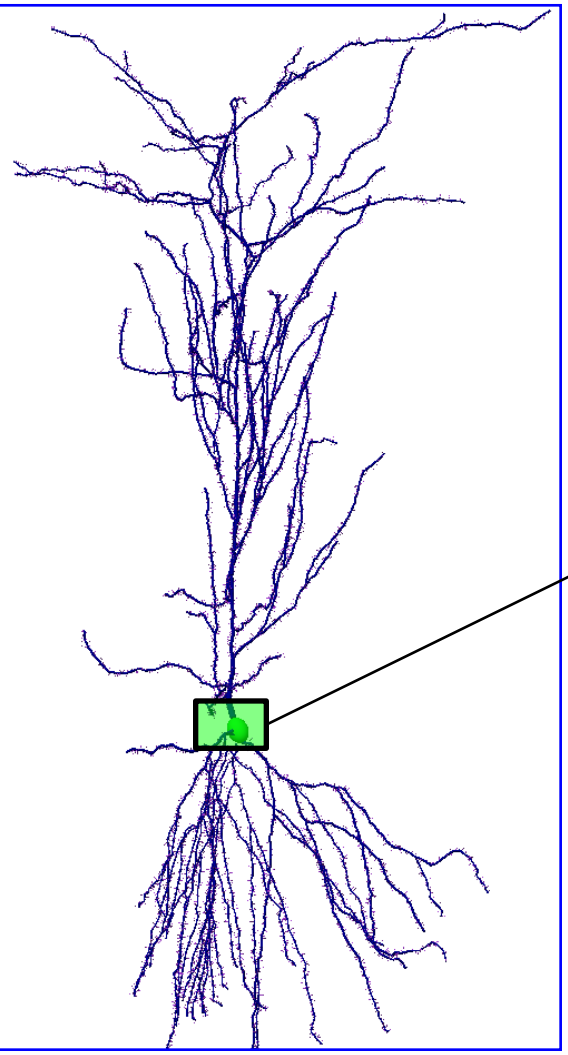
CHEMISTRY
M. Karamitros et al. (2015)



NEURON
M. Batmunkh et al. (2014-2017 at LRB, JINR)



Simulating DNA damage in neurons of the rat hippocampus

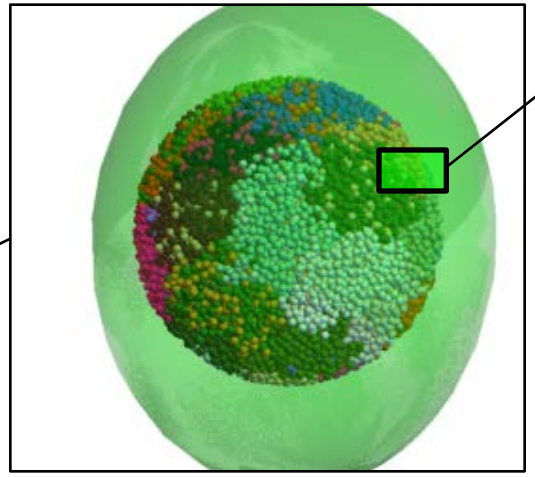


soma: 248.07 ± 27.44 µm^2

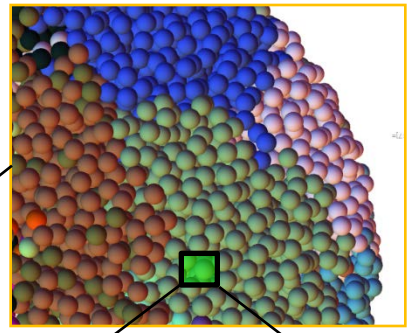
nucleus: 101.41 ± 9.61 µm **^{2}**

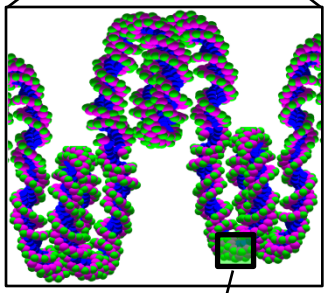
genome length: 5439.67 Mbp

42 chromosomes (rat)



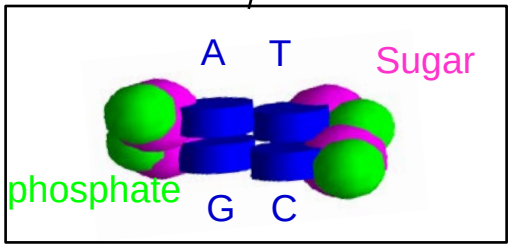
Chromatin domains



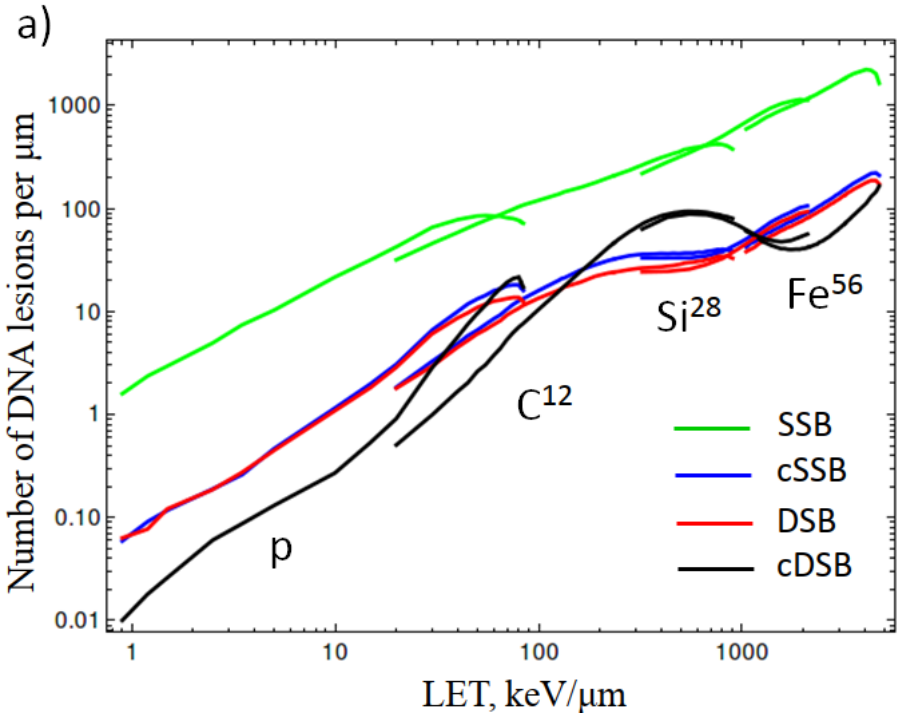


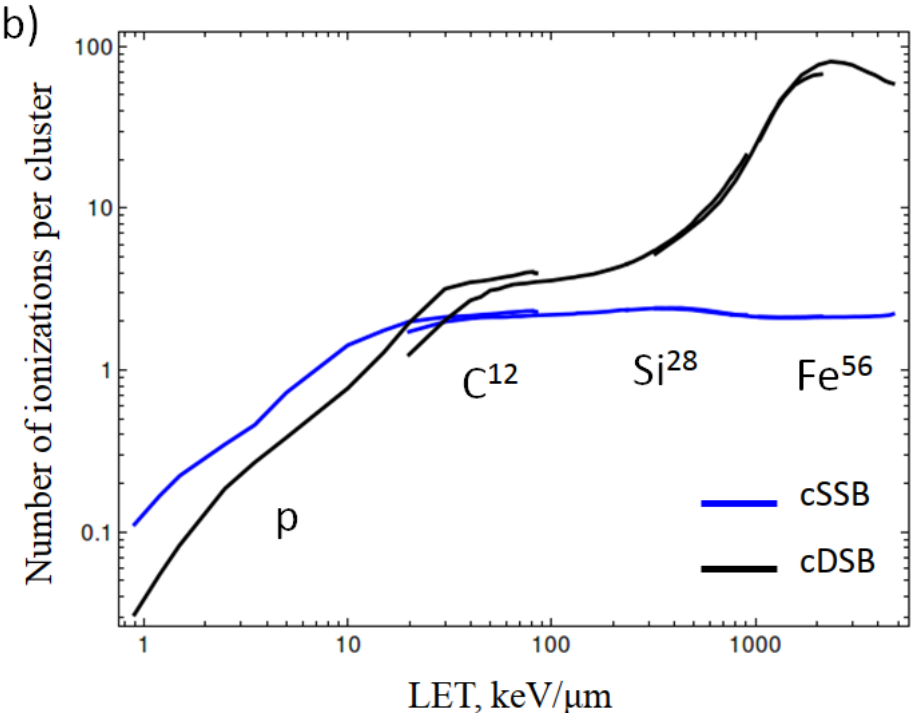
Chromatin fiber

Base pair



DNA damage dependence on LET





SSB – single strand break
cSSB – cluster of single strand breaks
DSB – double strand break
cDSB – cluster with double strand breaks

Cell injury in rat hippocampus after irradiation

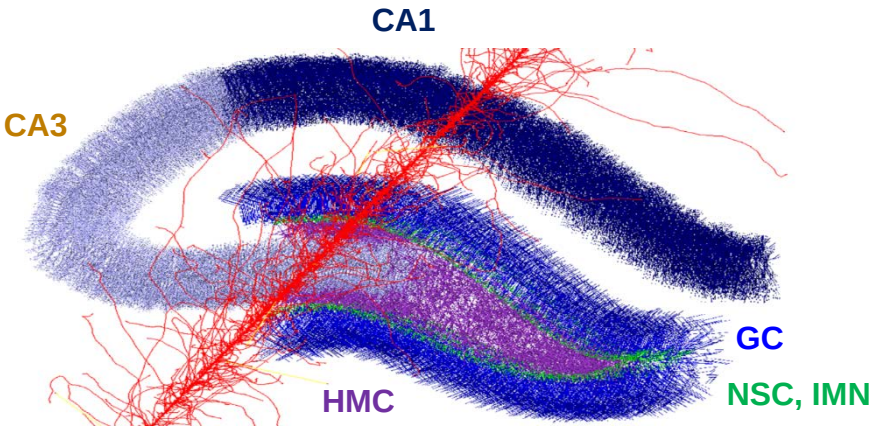
Particle energy and fluence:

^{1}H (150 MeV), 10^{8} particles/cm^{2}

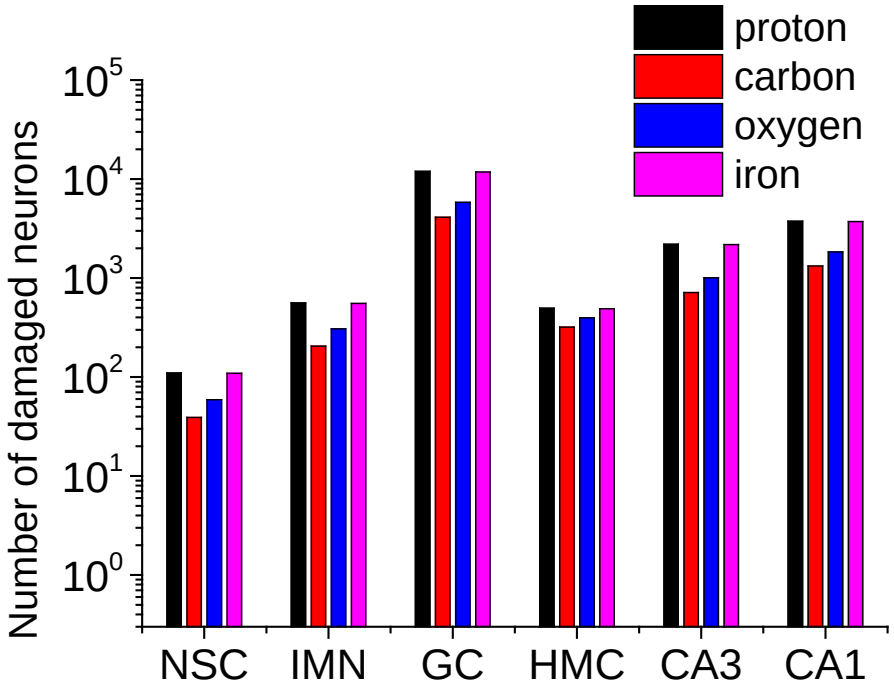
^{12}C (300 MeV/u), 10^{5} particles/cm^{2}

^{16}O (300 MeV/u), 10^{5} particles/cm^{2}

^{56}Fe (600 MeV/u), 10^{5} particles/cm^{2}



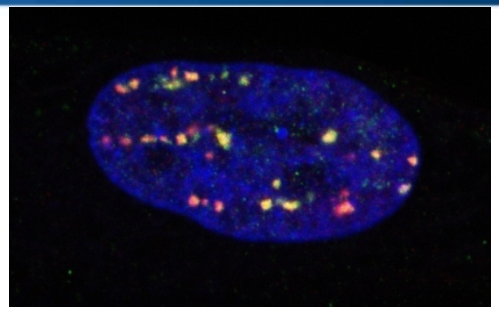
at least one strand break of DNA



DNA repair

Basic principles of modeling repair kinetics

Reaction scheme $X + R \underset{k_-}{\overset{k_+}{\rightleftarrows}} Z \xrightarrow{q} \ldots \rightarrow R$



experimental visualization of DNA damage with γH2AX-foci

Differential equations

$$\frac{dX}{dt} = -k_+ XR + k\_Z$$

$$\frac{dR}{dt} = -k_+ XR + k\_Z + qZ$$

$$\frac{dZ}{dt} = k_+ XR - k\_Z - qZ$$

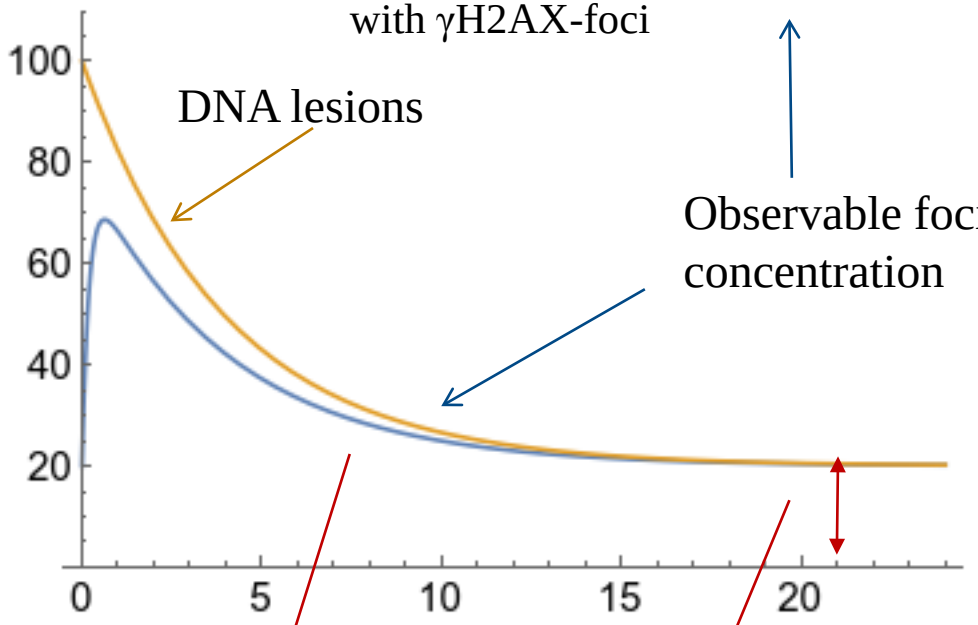
Initial conditions

$$X(0) = N_0$$

$$R(0) = R_0$$

$$Z(0) = 0$$

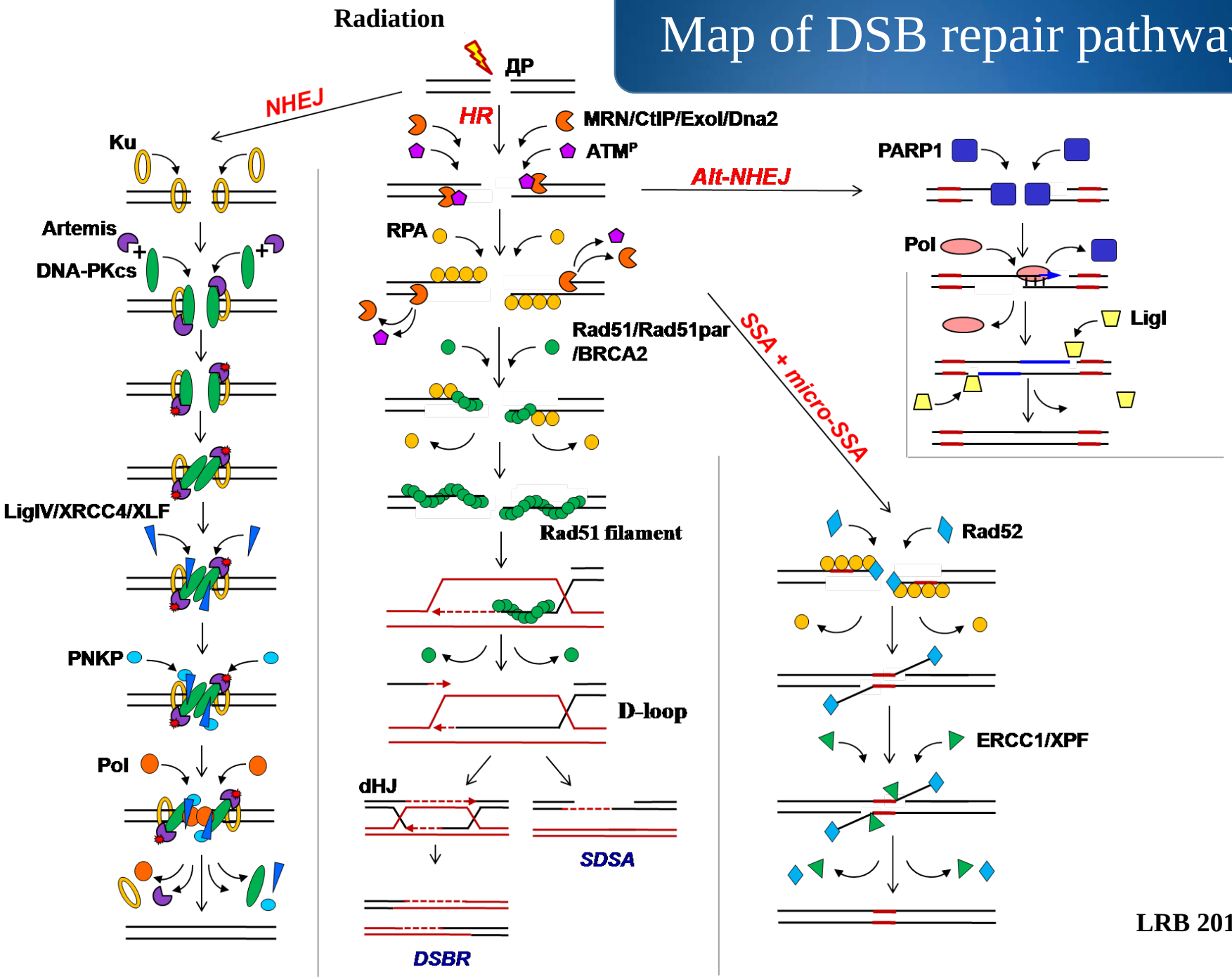
$$\ldots$$



$$N_{mut} = \int_0^t z\ p(z)dt'$$

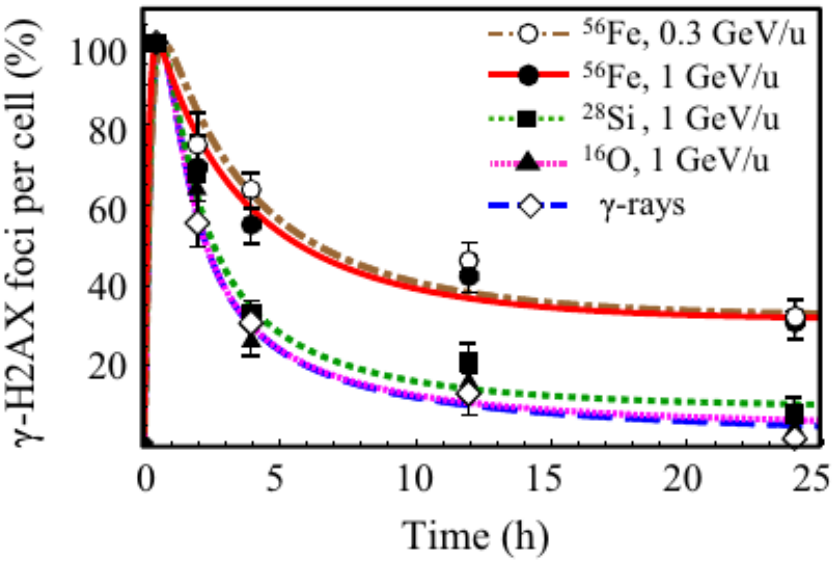
N_{nonrep}

Map of DSB repair pathways



Comparison of simulation and experiment

γ-H2AX

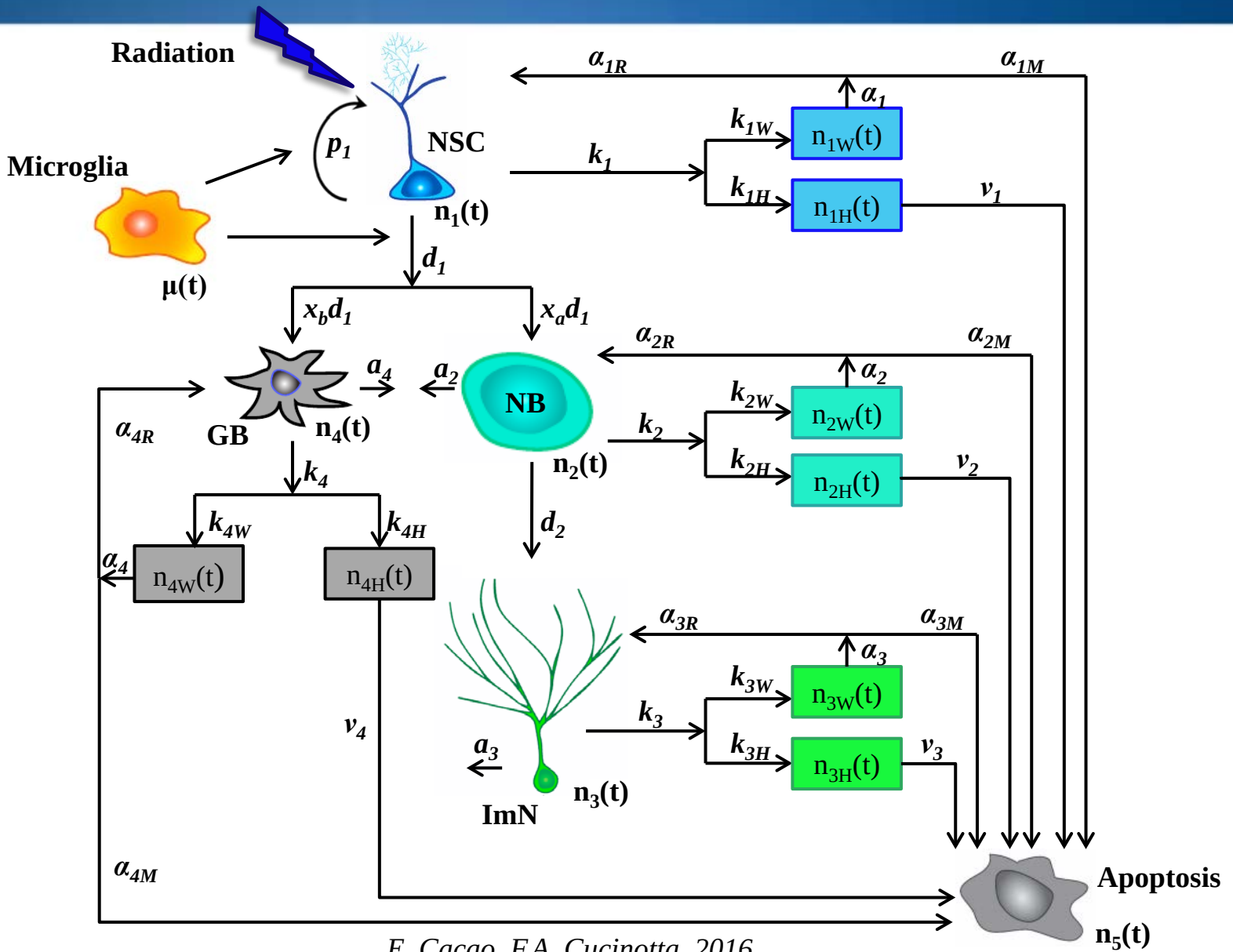


Belov O.V. et al // J.Theor. Biology 2015, 366, 115-130

The kinetics of γH2AX-foci in human skin fibroblast culture induced by 1 Gy ionizing irradiation with different physical characteristics
(the dots are experimental data (Asaithamby et al.,2008));

Calculation of neuron loss
Neurogenesis

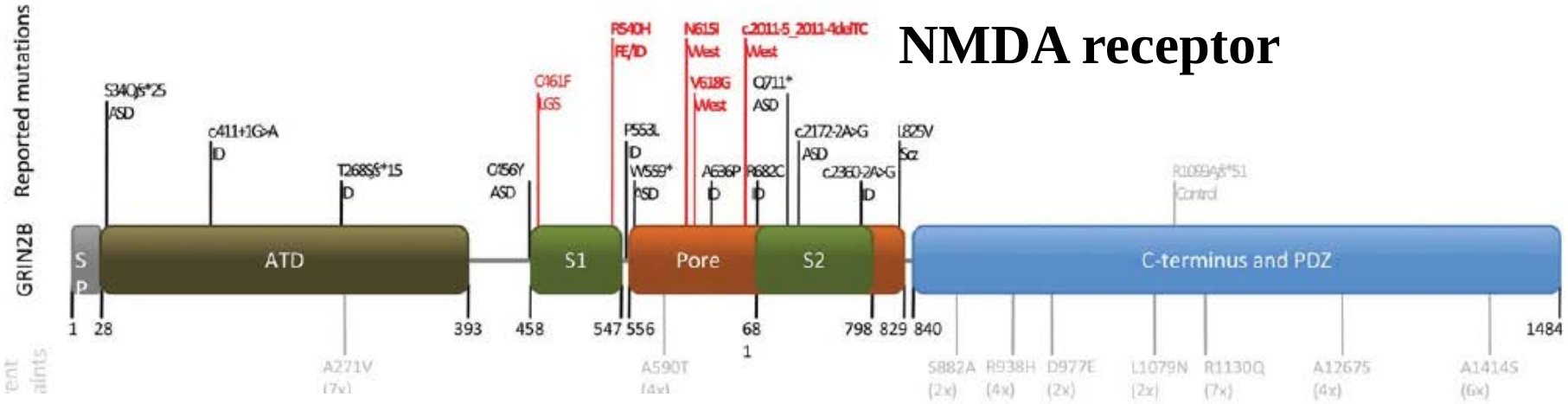
Hippocampal neurogenesis model after irradiation

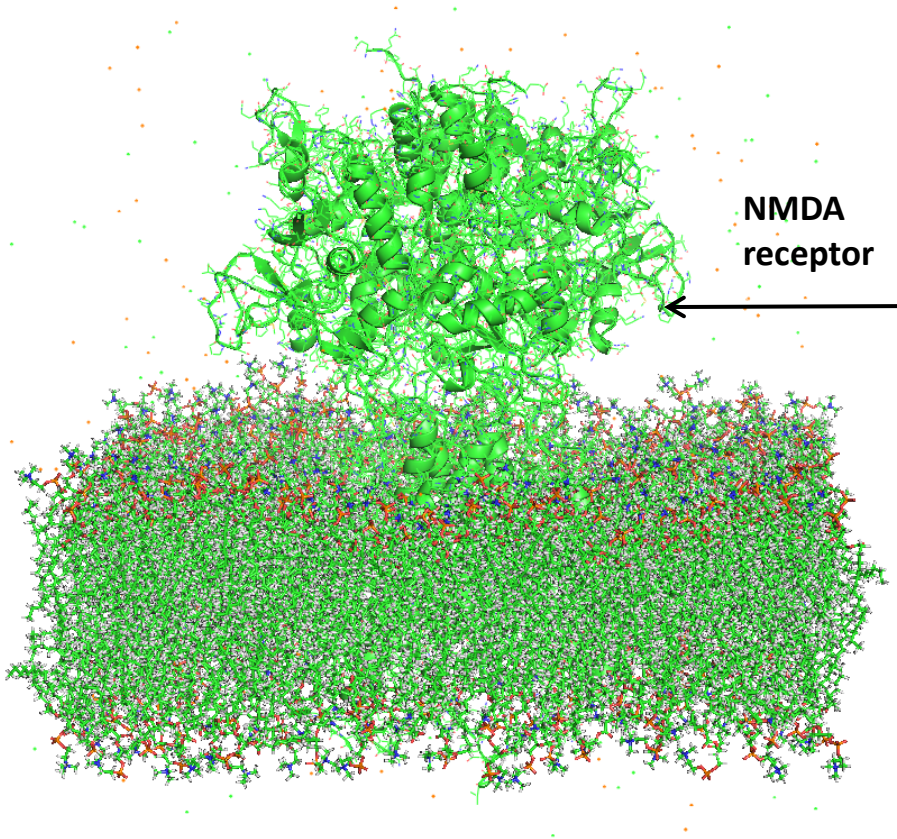


E. Cacao, F.A. Cucinotta, 2016

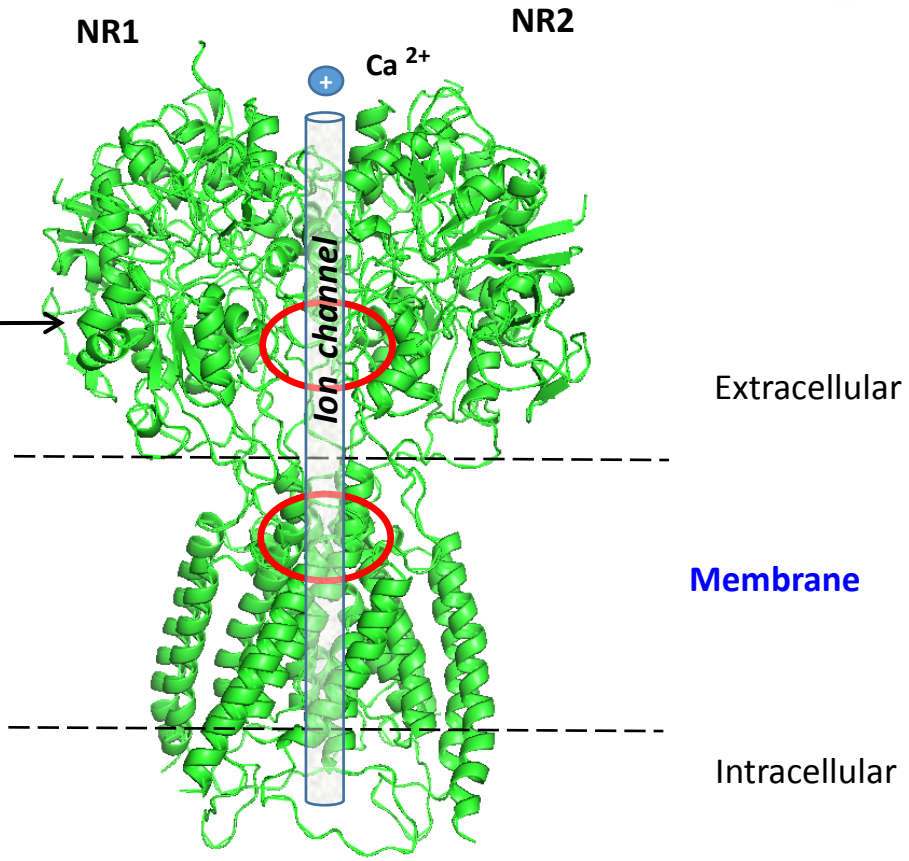
Predicting structure and function of mutant proteins: molecular dynamics simulations

NMDA receptor





NMDA receptor



LRB 2017

MD software. GPU computing

NAMD
Scalable Molecular Dynamics

http://www.ks.uiuc.edu/Research/namd/

VMD
Visual Molecular Dynamics

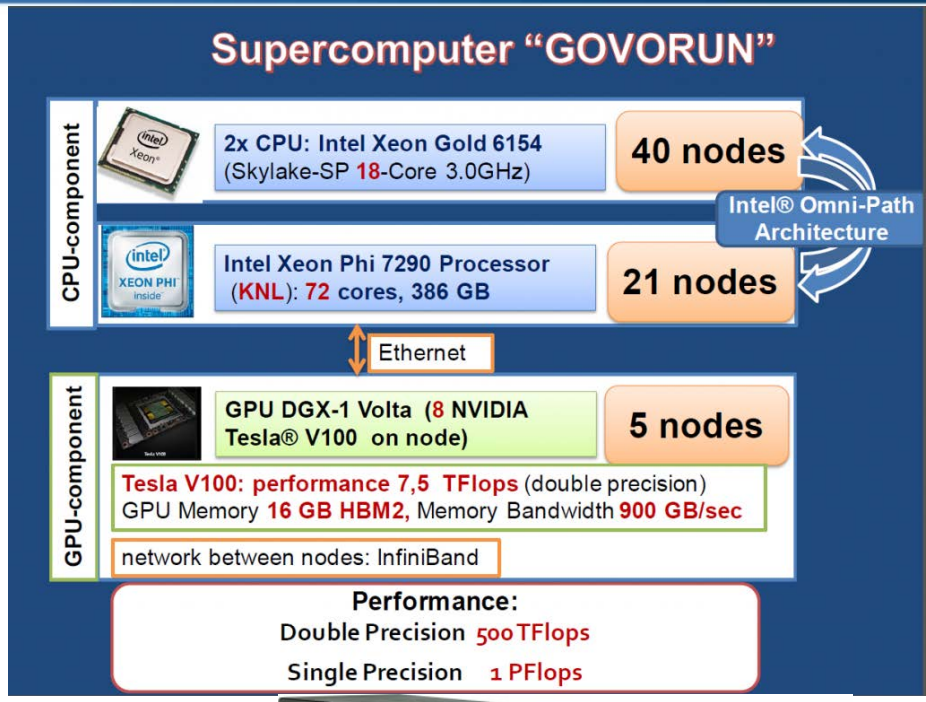
http://www.ks.uiuc.edu/Research/vmd/

GROMACS FAST. FLEXIBLE. FREE.

http://www.gromacs.org/

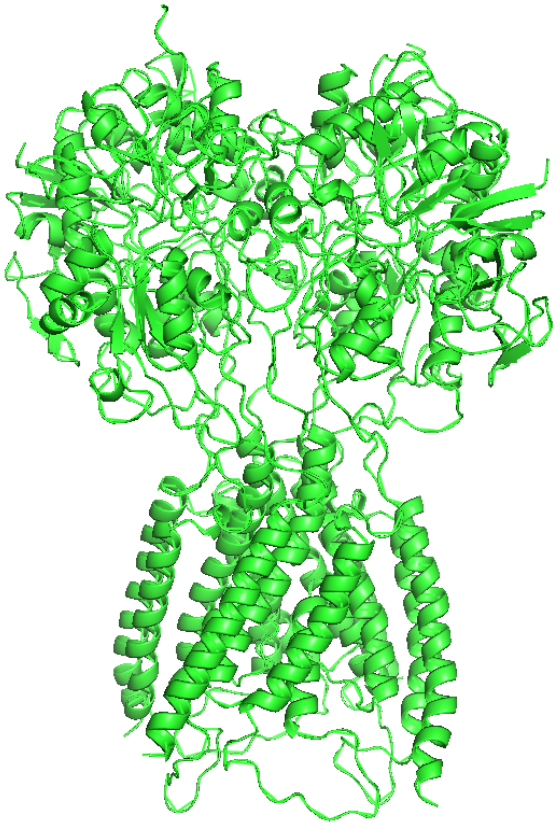
AMBER

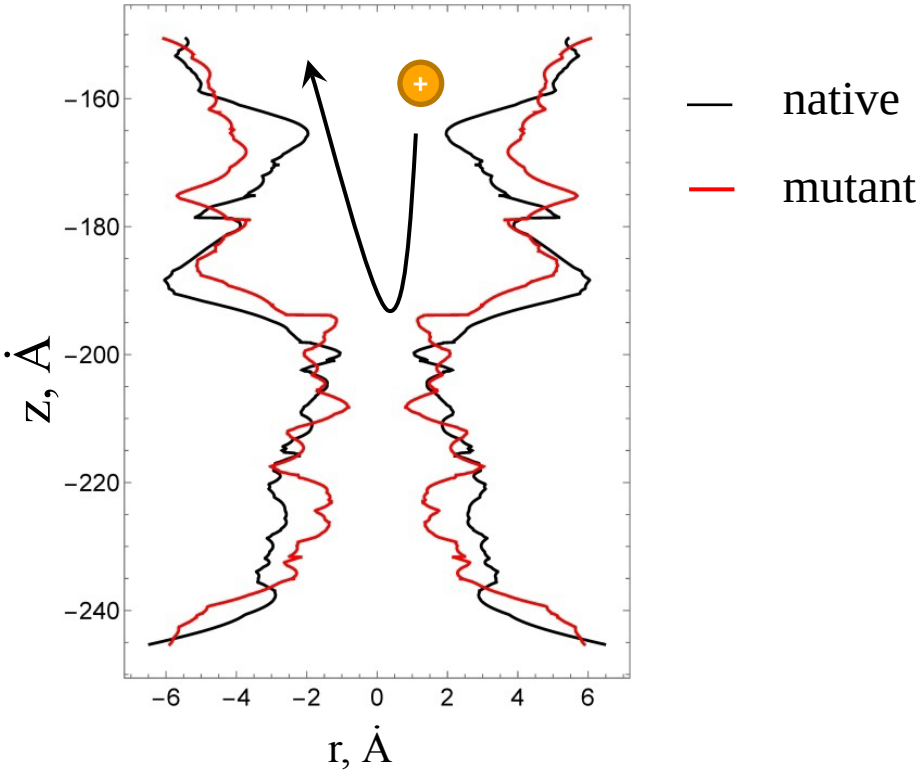
http://ambermd.org/



GPU workstation

Channel conductance is changed!



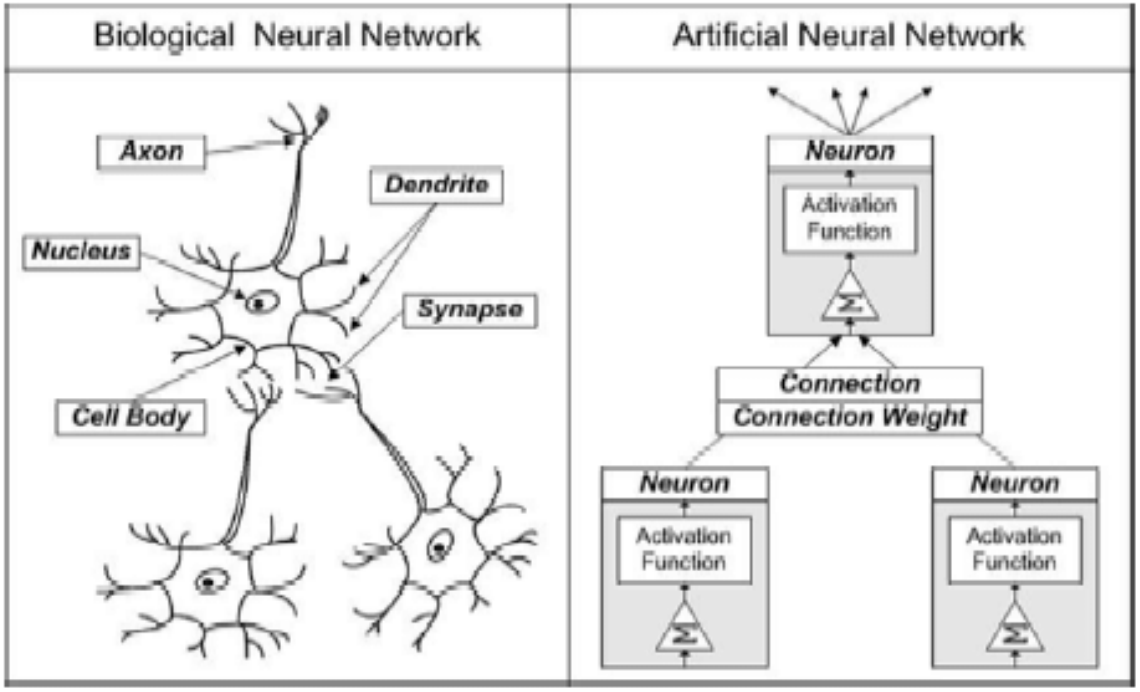


Neural networks

Neural networks

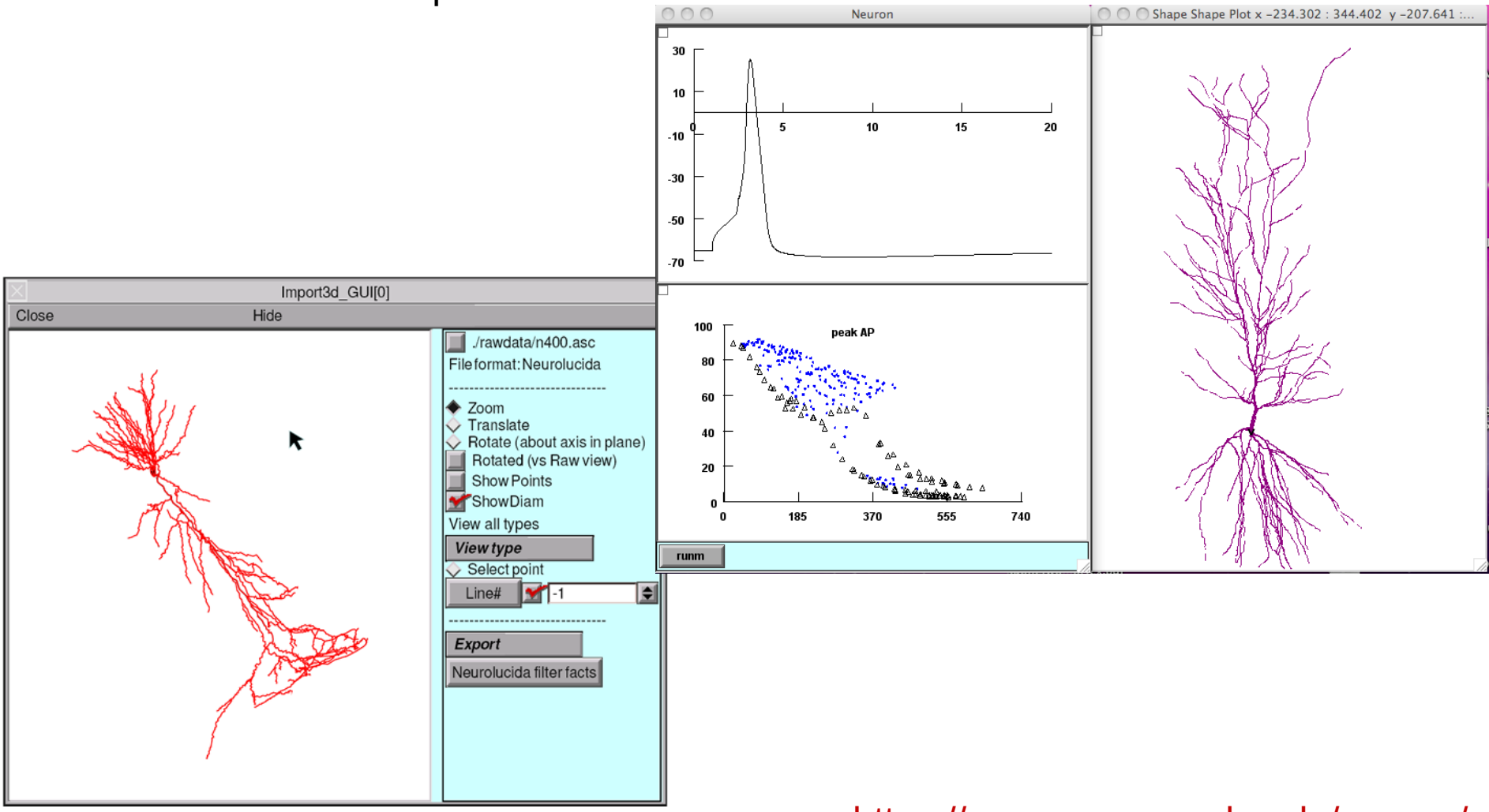
In neuroscience, a **biological neural network** is a series of interconnected neurons whose activation defines a recognizable linear pathway. The interface through which neurons interact with their neighbors usually consists of several axon terminals connected via **synapses** to dendrites on other neurons. If the sum of the input signals into one neuron surpasses a certain threshold, the neuron sends an action potential at the axon hillock and transmits this electrical signal along the axon.

Biological neural networks have inspired the design of **artificial neural networks**.



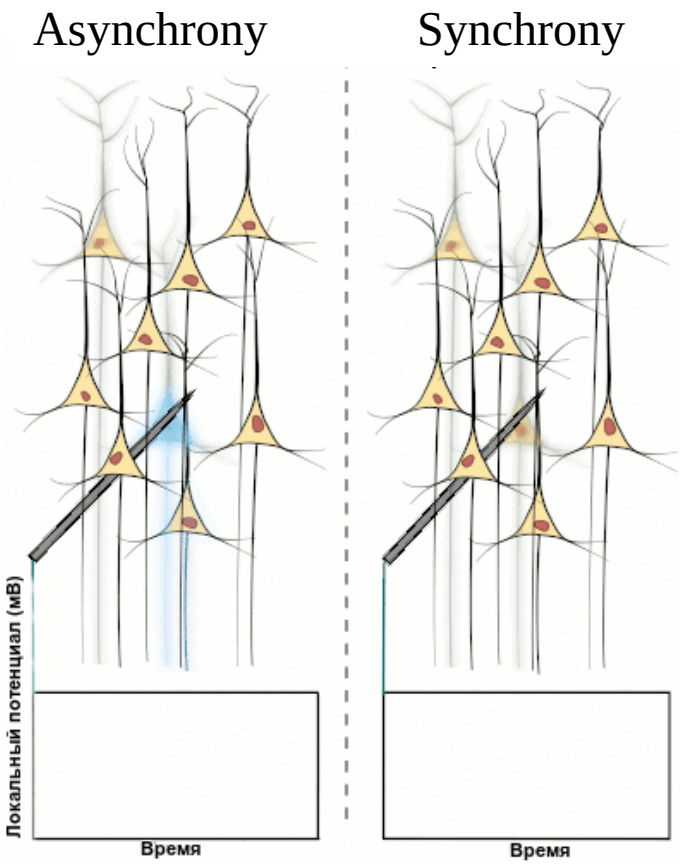
NEURON: empirically based simulations of neurons and networks

NEURON interface samples

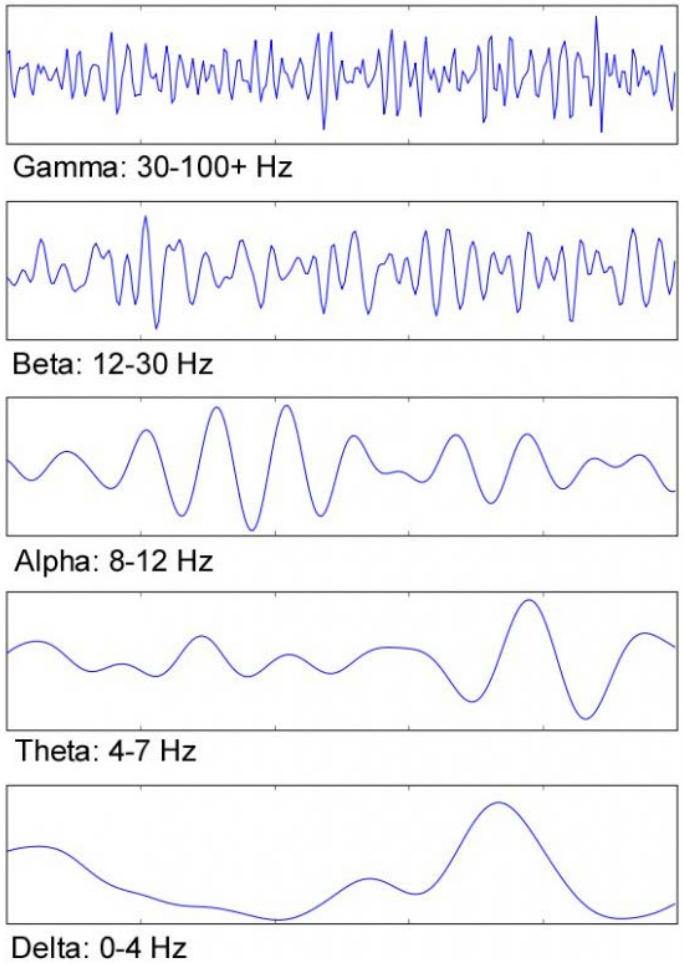


https://www.neuron.yale.edu/neuron/

Synchronization of neuron oscillations

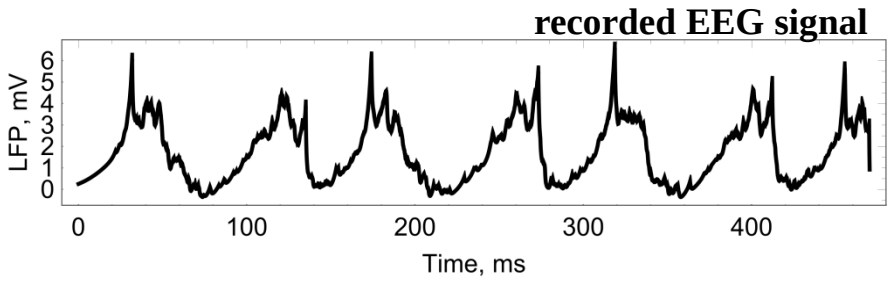


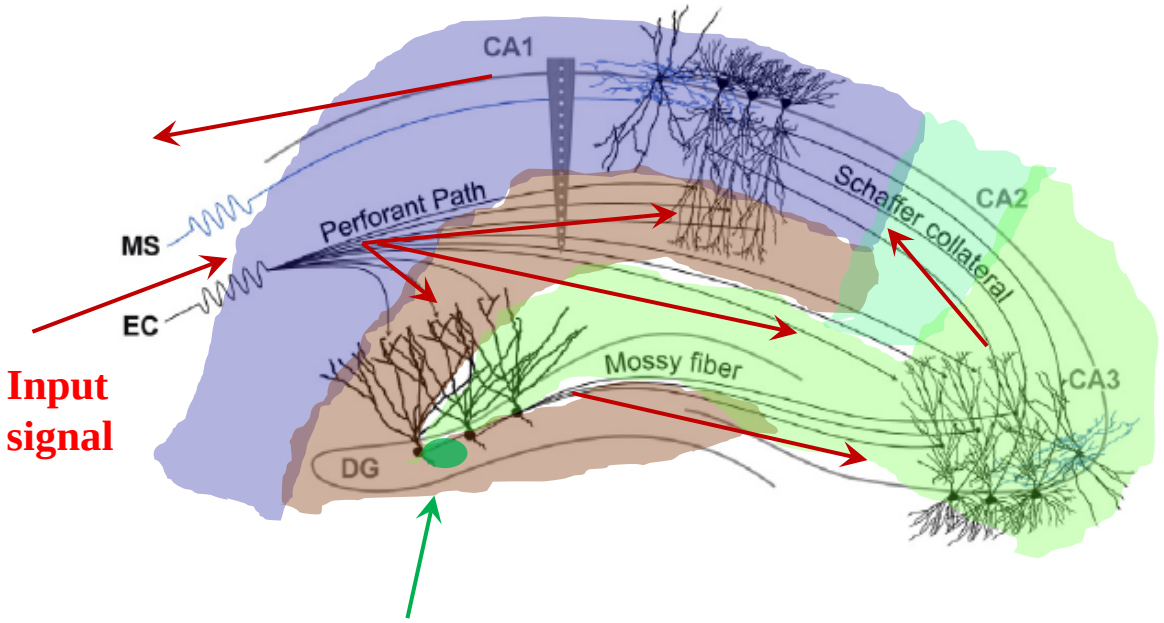
Local field potential (EEG)



Electroencephalography (EEG) signal bands

Hippocampal neural networks





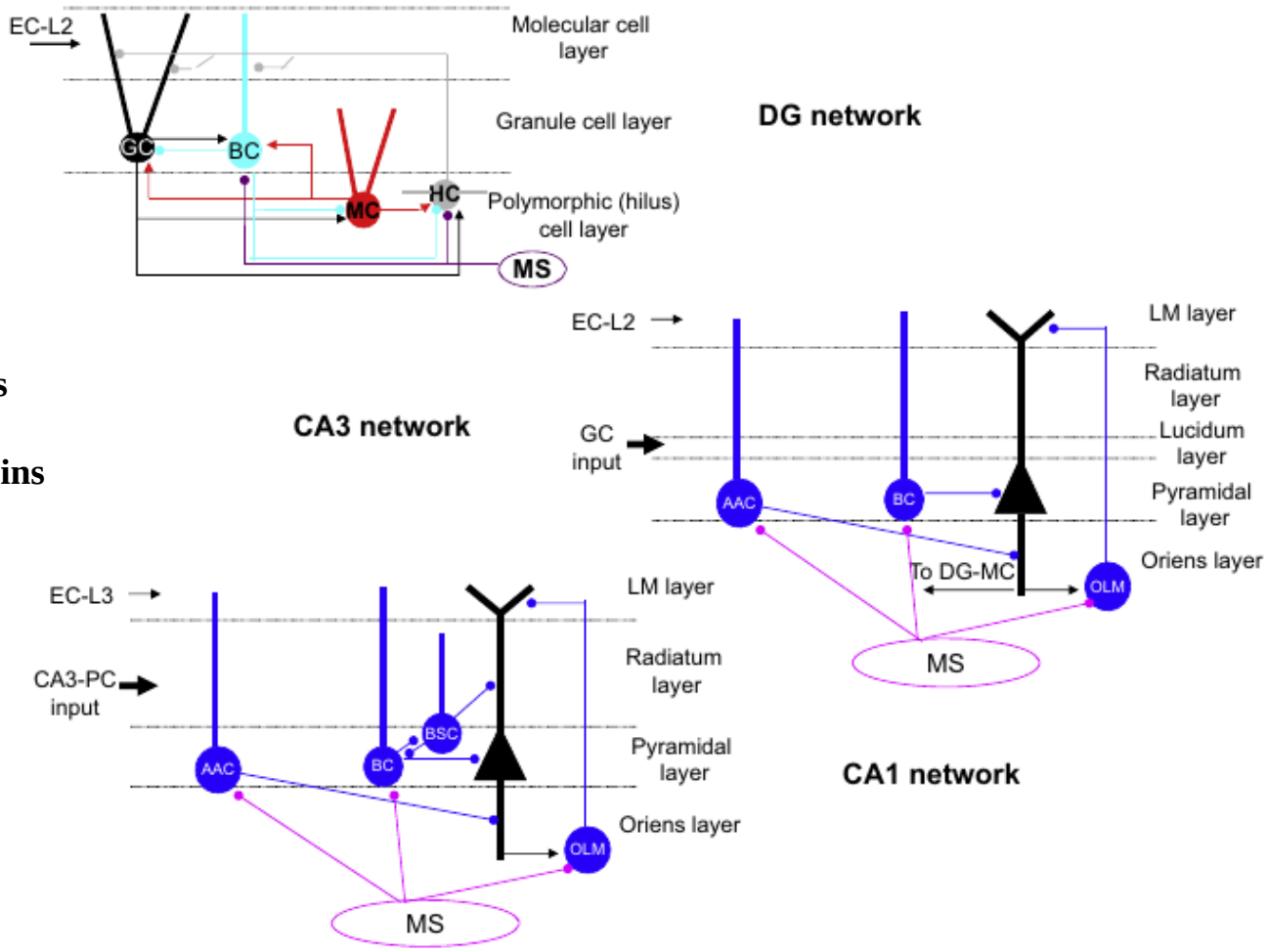
Neural network architecture

+ **Cell death**

+ **Immature granular cells**

+ **Modified synaptic proteins**

+ **???**



Modified from
***V. Cutsuridis, P. Poirazi* // Neurobiology of Learning and Memory 120 (2015) 69–83**

A sample of model equations for CA3 network

Potential at each neuron:

$$C\frac{dV_p}{dt} = g_{Na}{m_p}^3 h_p(V_p - E_{Na}) + g_K{n_p}^4(V_p - E_K) + g_{K(A)}a_p b_p(V_p - E_K) +$$
$$+g_h r_p(V_p - E_h) + g_L(V_p - E_L) + I_{ext} + I_{syn} + I_{syn(noise)}$$

Pyramidal neurons

$$C\frac{dV_b}{dt} = g_{Na}m_{(\infty)b}(V)^3 h_b(V_b - E_{Na}) + g_K{n_b}^4(V_b - E_K) + g_L(V_p - E_L) +$$
$$+I_{syn} + I_{syn(noise)}$$

Basket interneurons

$$C\frac{dV_O}{dt} = g_{Na}m_{(\infty)O}(V_O)^3 h_O(V_O - E_{Na}) + g_K{n_O}^4(V_O - E_K) +$$
$$+g_{K(AHP)}{q_O}^2(V_O - E_K) + g_{Ca}s_{(\infty)O}(V_O)^2(V_O - E_{Ca}(V_O)) +$$
$$+g_h r_O(V_O - E_h) + g_L(V_O - E_L) + I_{ext} + I_{syn} + I_{syn(noise)}$$

Oriens-lacunosum moleculare (OLM) interneurons

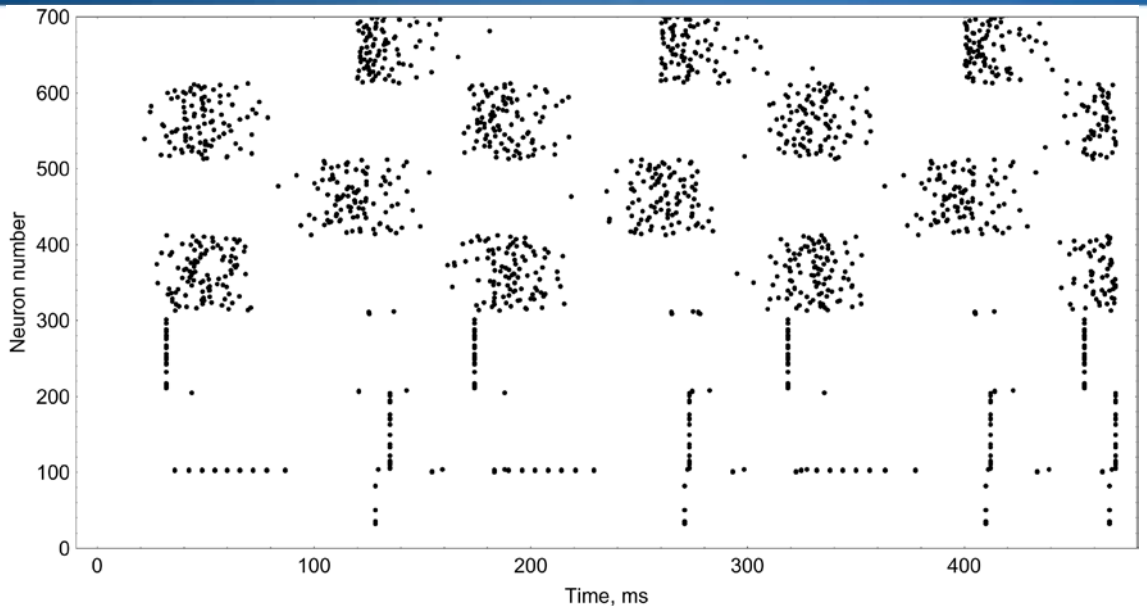
Synaptic currents:

$$I_{syn} = I_{NMDA} + I_{AMPA} + I_{GABA_{(A)}} = \sum g_{ij}s_i(t)\left(V_j - V_{syn}\right)$$

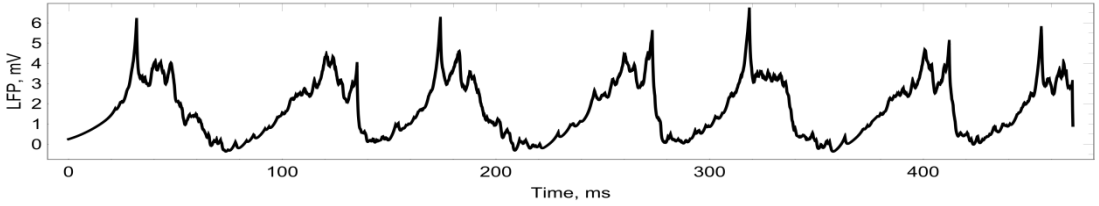
$$\frac{ds_i}{dt} = \rho(V_i)\frac{1 - s_i}{\tau_R} - \frac{s_i}{\tau_D}$$

NMDA receptor conductance: $g_{NMDA}(t) = g_{ij}s_i(t)\cdot F([Mg^{2+}], V_j)$

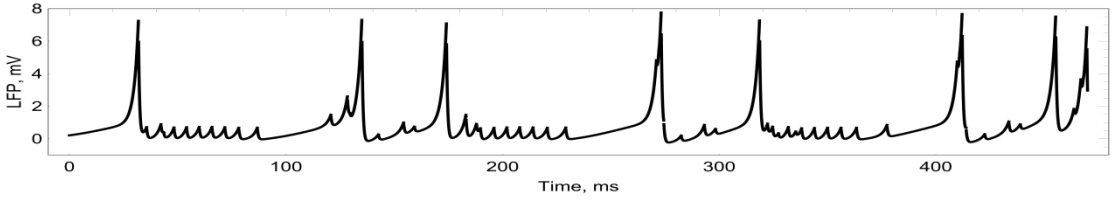
Neural network activity



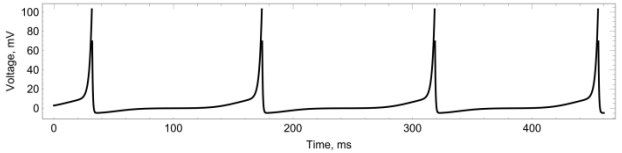
EEG signal (theta wave)



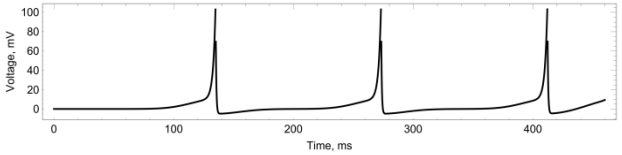
hippocampal local field potential



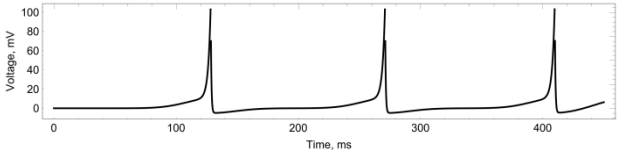
CA1 pyramidal cell



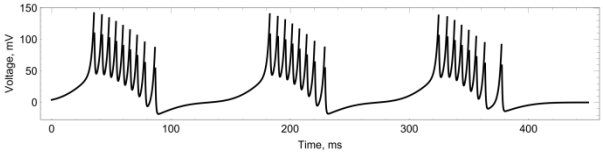
CA3 pyramidal cell



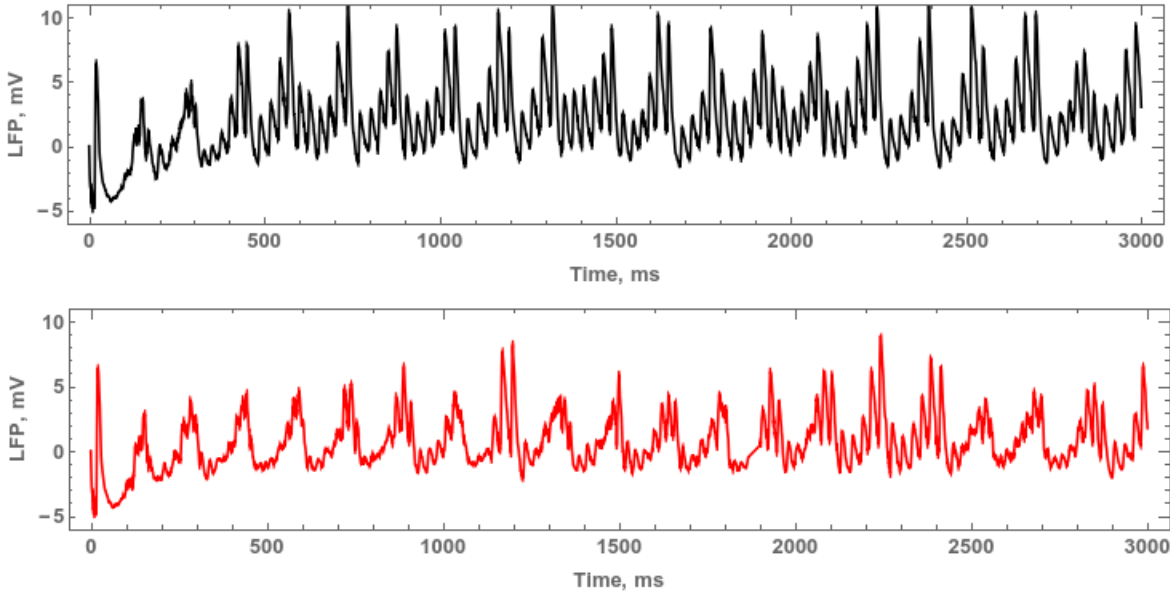
DG granule cell



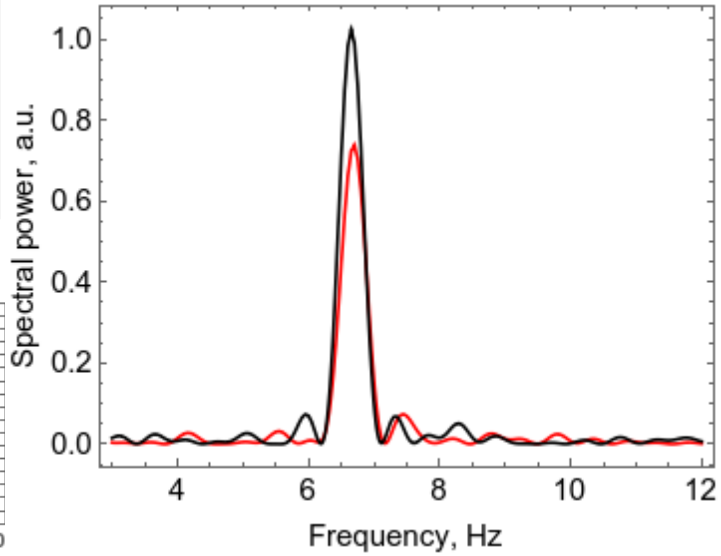
DG basket cell



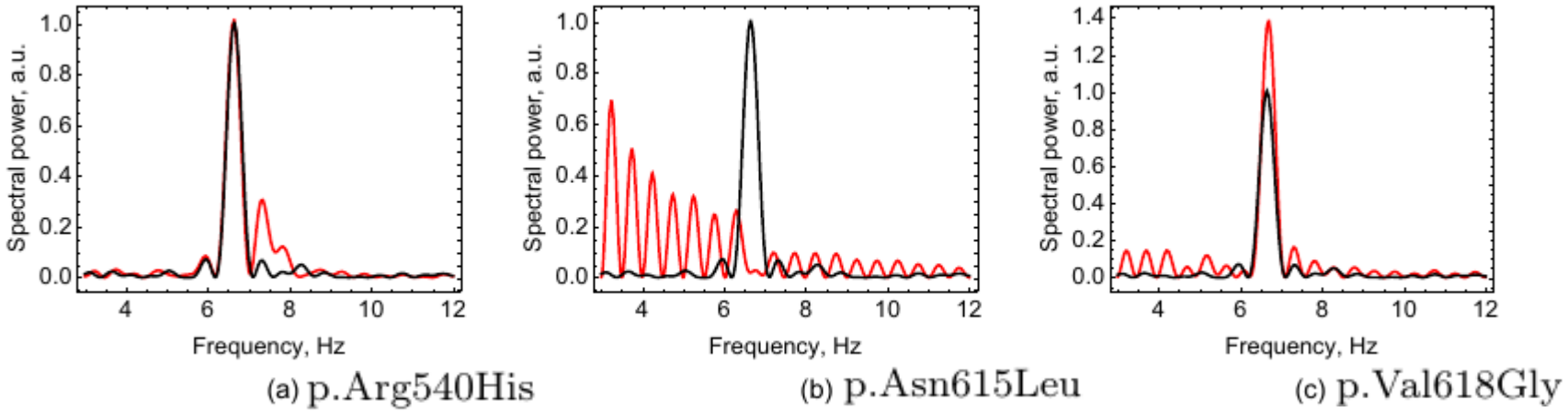
Influence of cell loss on theta-wave amplitude

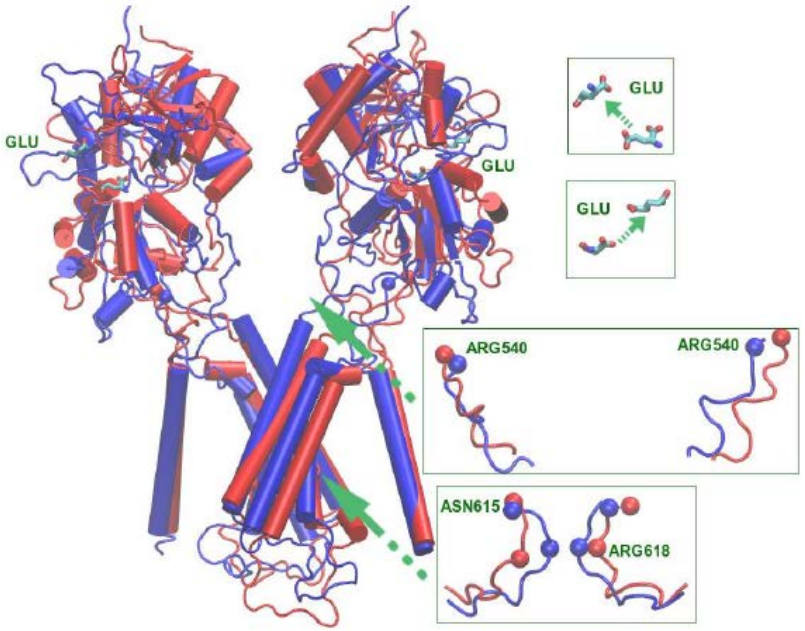


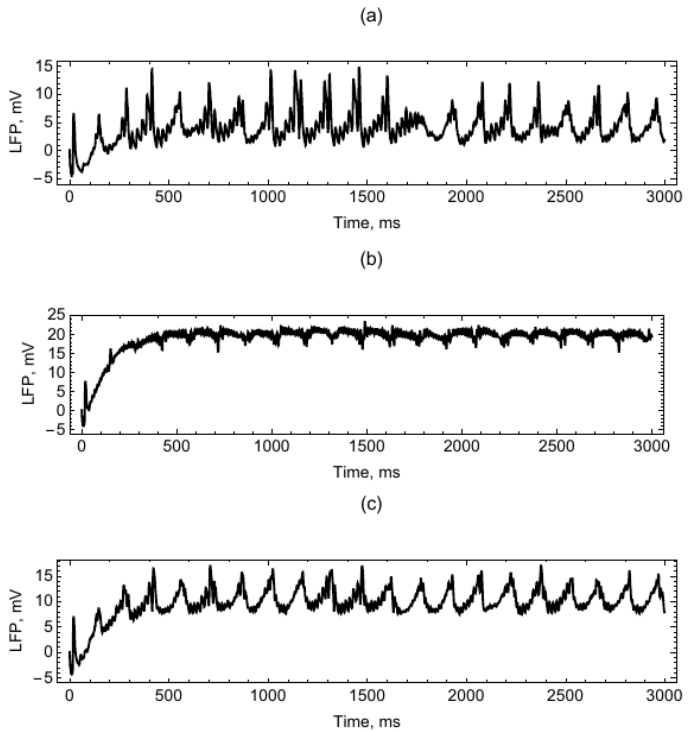
1.5 Gy 600 MeV/u ^{56}Fe



Effect of different mutations on EEG spectra



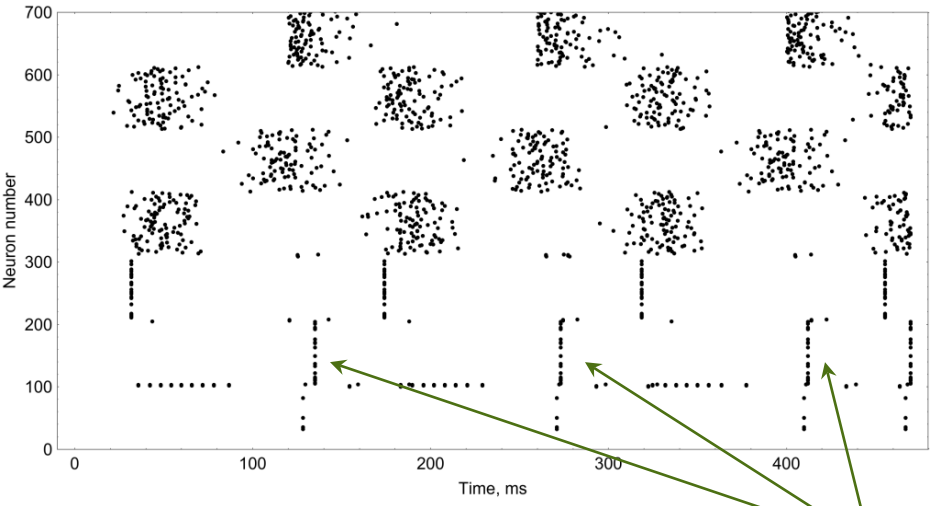




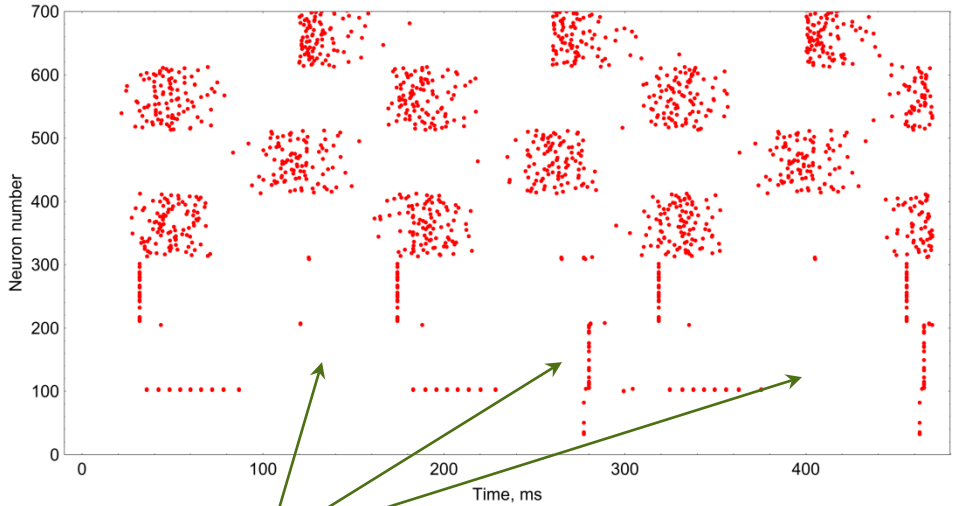
P

Influence of immature cell loss on information processing

Control

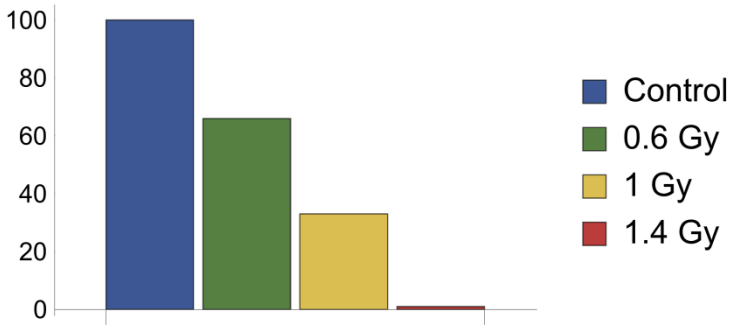


0.8 Gy 600 MeV/u ^{56}Fe

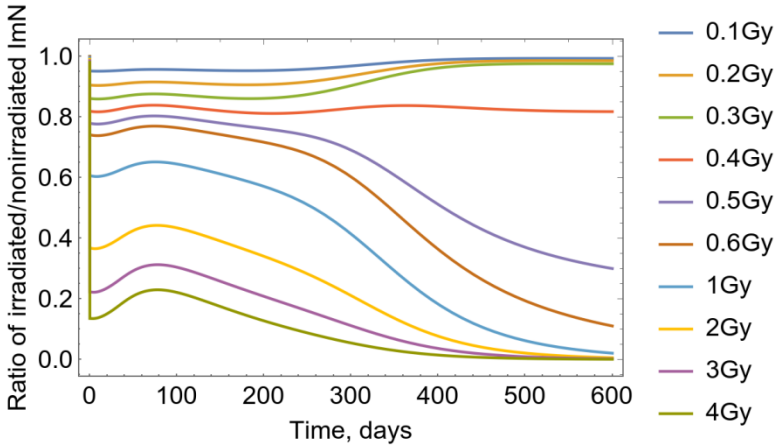


Encoded patterns

Encoding and retrieval success, %



Amount of survived immature neurons



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Thank you for the attention!