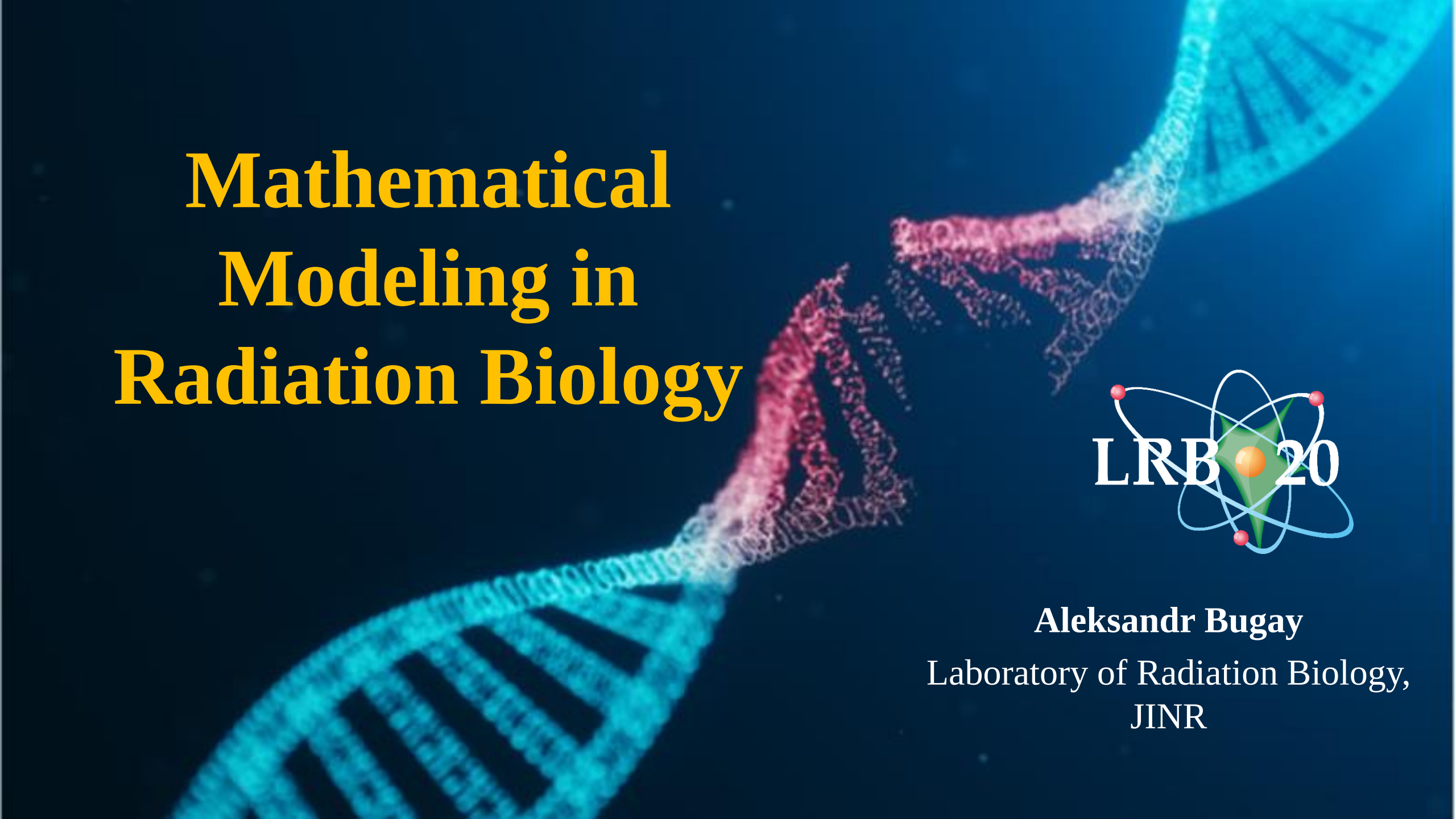
Mathematical Modeling in Radiation Biology

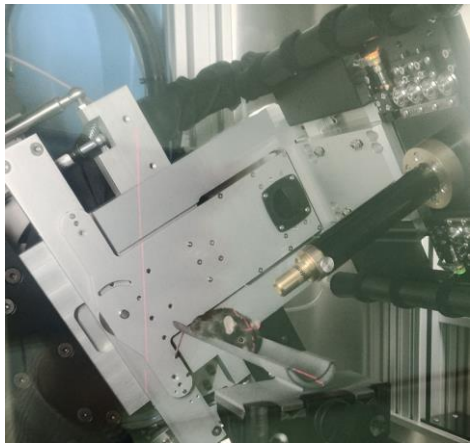


Aleksandr Bugay

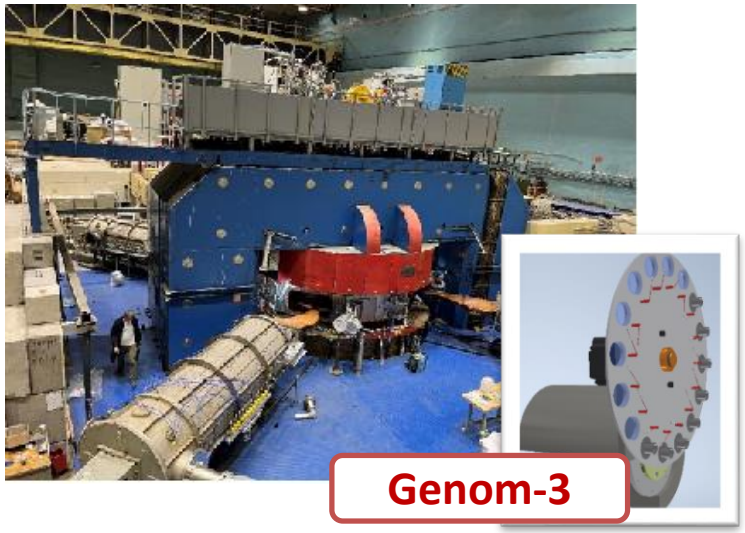
Laboratory of Radiation Biology, JINR

Research Infrastructure for Irradiation of Biological Samples

SARRP X-ray

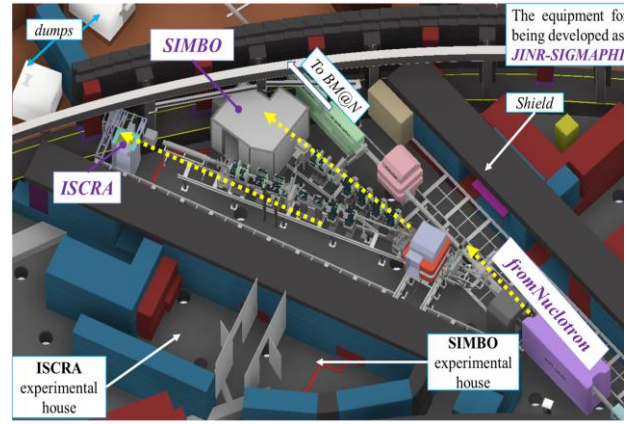


U-400M cyclotron
Ions, Li – Ar, 50 MeV/u



Nuclotron
Ions (C, Ar, Fe, Kr) 0.3-1 GeV/u





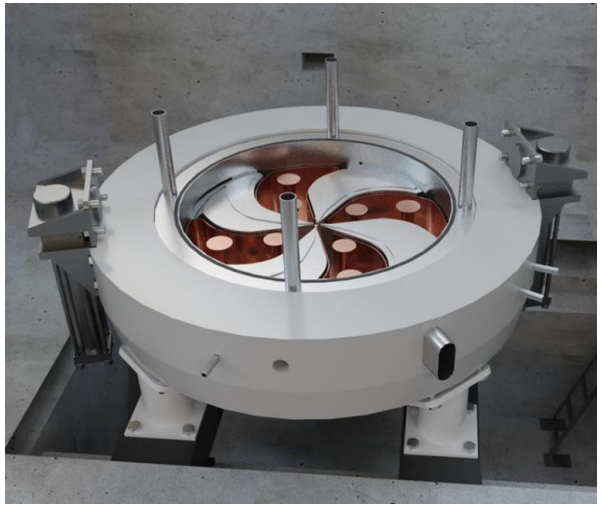
ARIADNA beamlines

SIMBO

Linac200
electrons 20-200 MeV



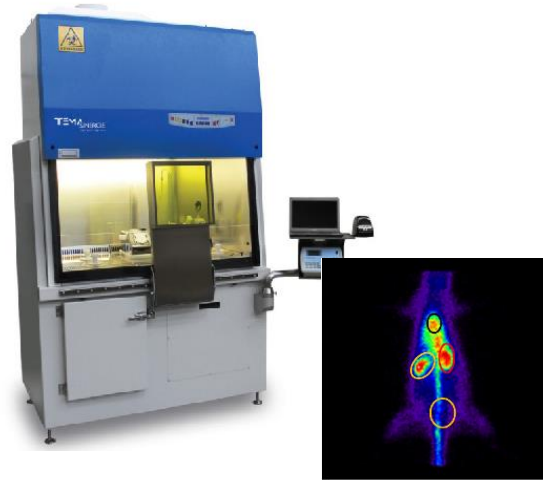
new MSC230 medical cyclotron
protons 230 MeV



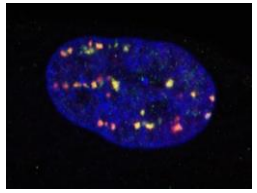
IBR-2, EG-5M **neutrons**

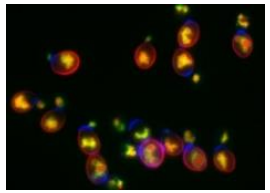


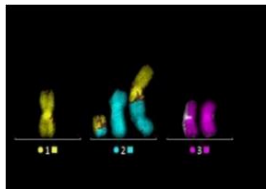
Radiopharmaceuticals

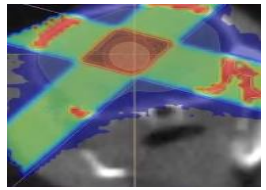


Scientific Program of the Laboratory of Radiation Biology

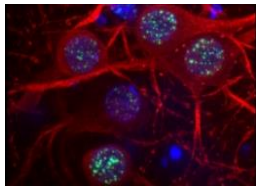

Molecular Radiobiology

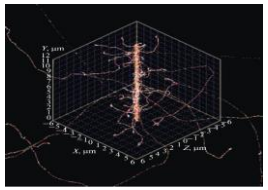

Radiation Genetics


Radiation Cytogenetics

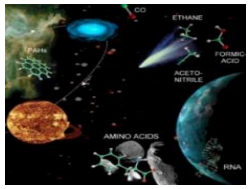

Clinical Radiobiology


Radiation Physiology


Radiation Neuroscience


Mathematical Modeling


Radiation Research



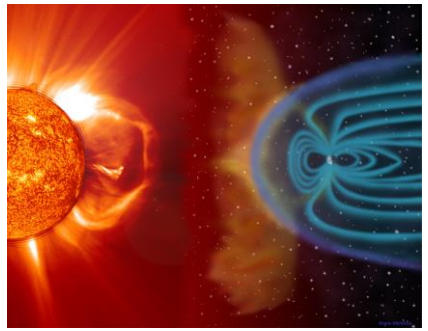
Astrobiology



Fundamental Research

Radiation Medicine

Radiation Risks


Space Radiobiology

Radiation Factors

X-ray therapy

proton and ion therapy

neutron-capture therapy

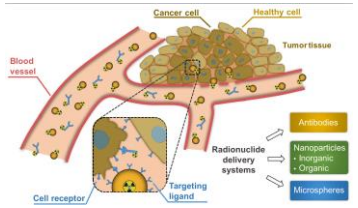
radionuclide therapy

Biological Pathways

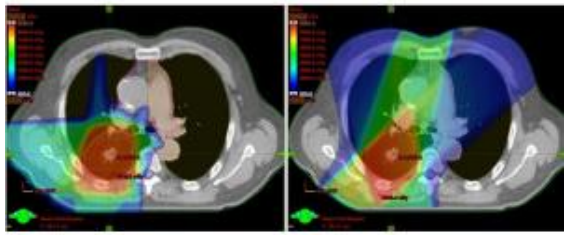


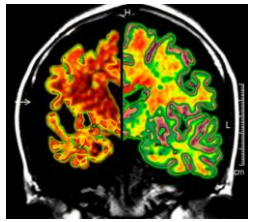
Radiosensitizers

Radioprotectors

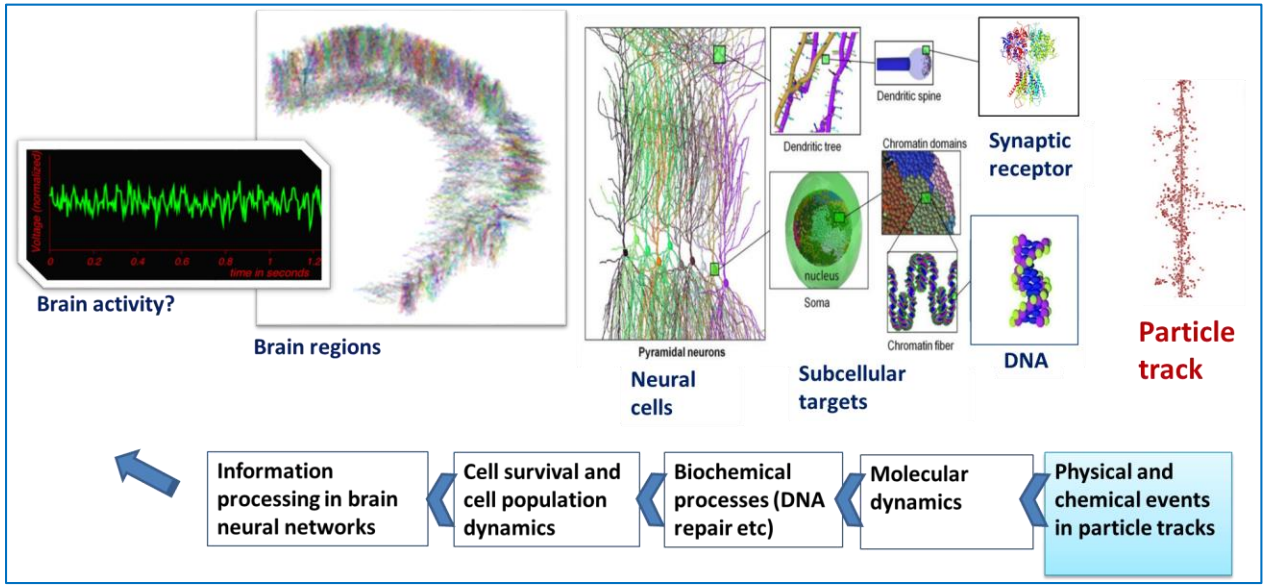


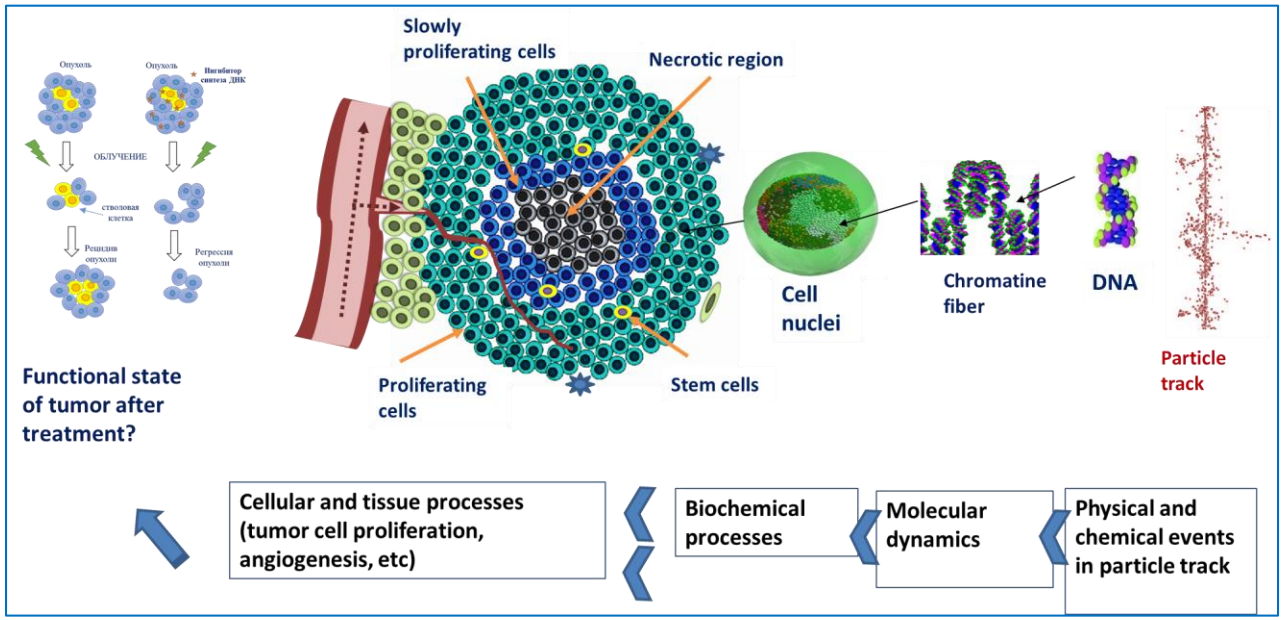
Targeted drug delivery


Side Effects of Radiotherapy


Radiation Neuroscience

Main tasks in Mathematical Modeling



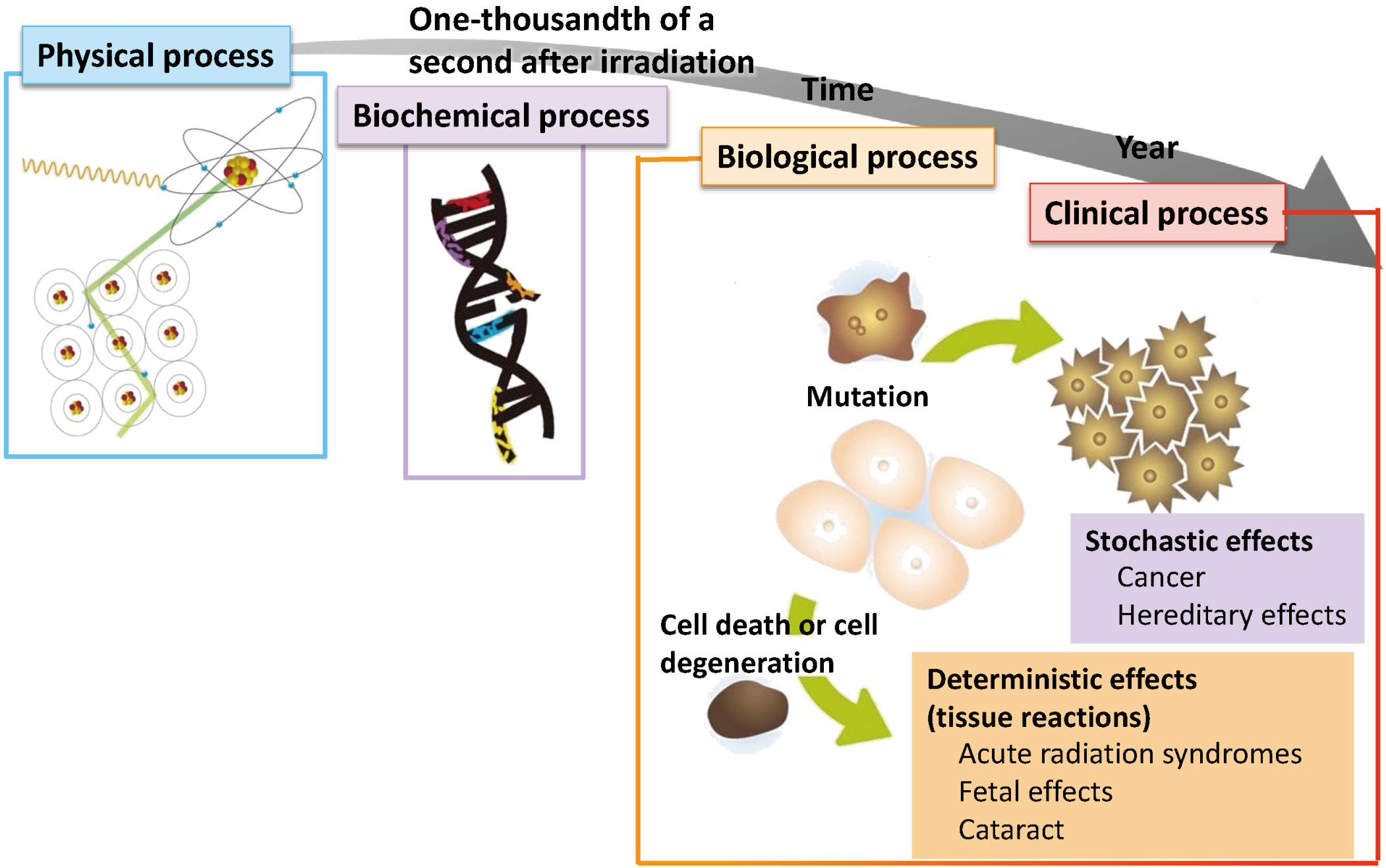


- A **hierarchy of mathematical models** to describe radiation-induced effects at different levels of biological organization and time scales

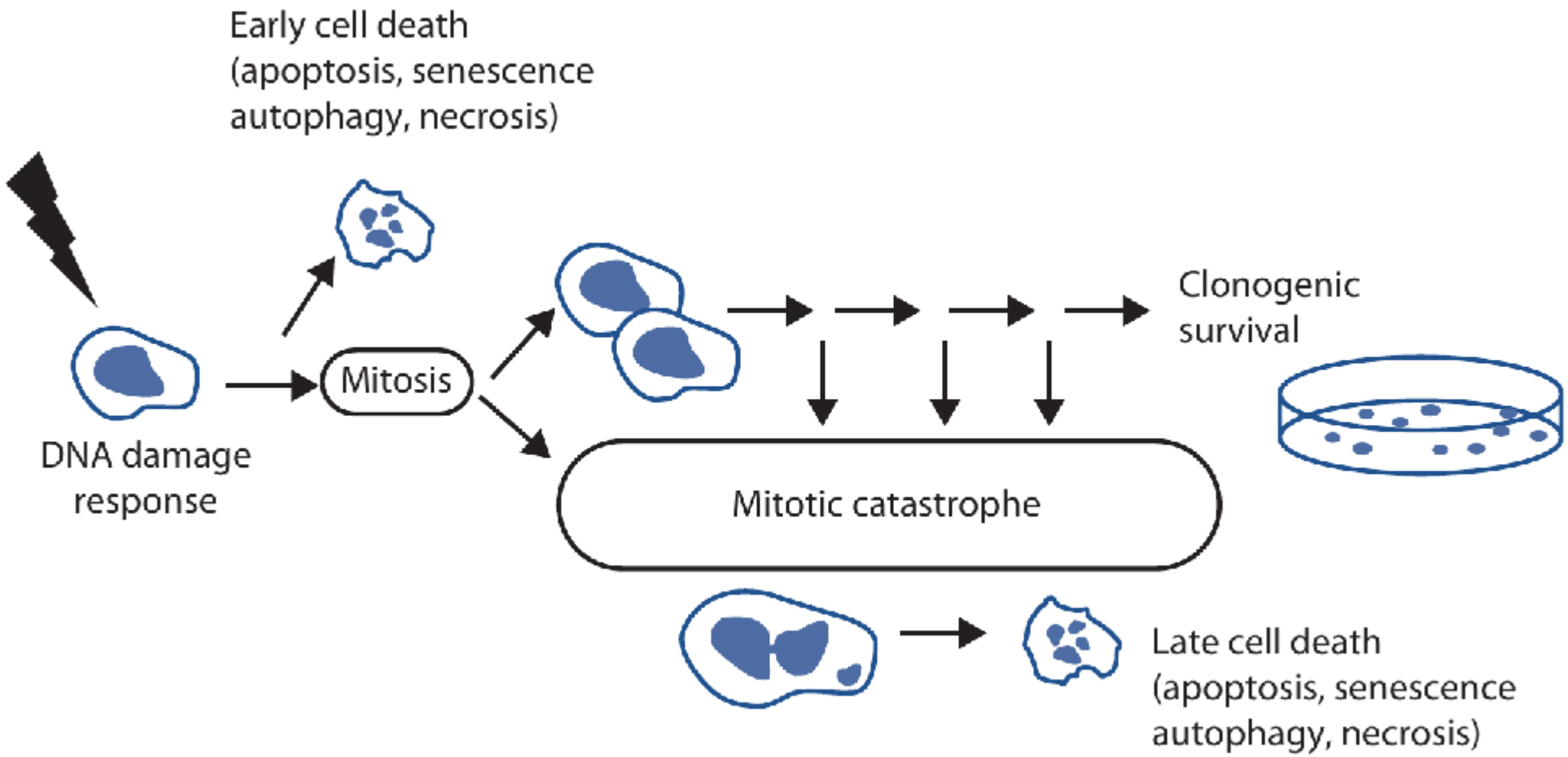
- Estimation of **radiation risks for normal tissues**
  - space radiation safety
  - side effects of radiation therapy

- Modeling of **tumor radiation response** for different modalities of particle and radionuclide therapy

- **Automatic processing of experimental data and parameter extraction**


Physical process
One-thousandth of a second after irradiation
Time
Year
Biochemical process
Biological process
Clinical process
Mutation
Stochastic effects
Cancer
Hereditary effects
Cell death or cell degeneration
Deterministic effects (tissue reactions)
Acute radiation syndromes
Fetal effects
Cataract

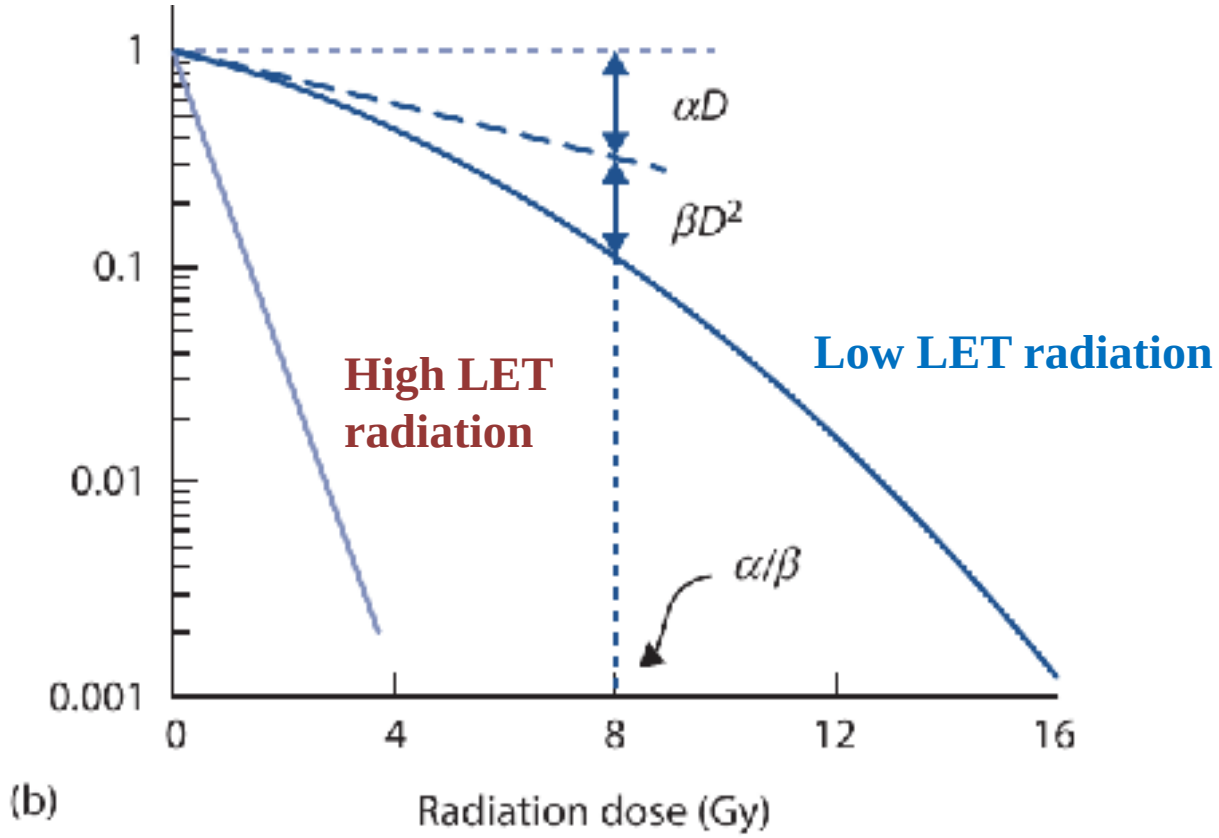
How radiation kills living cells



Empiric model of cell survival

Linear-quadratic model

$$S = e^{-\alpha D - \beta D^2}$$



A success of modern computations: From simple to very detailed models

Dose deposition ⇨ **Biological effect**

e.g. probability of cell survival

$$S = \exp(-\alpha D - \beta D^2)$$



Calculation of elementary events at the cellular and molecular level

1. Calculation of DNA damage formation

2. Models of DNA DSB repair and misrepair

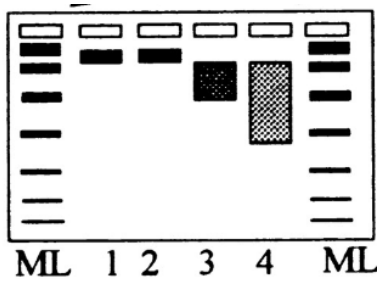
3. Cell survival ⇔ $\alpha = ?$ $\beta = ?$

Experimental protocols *in vitro*

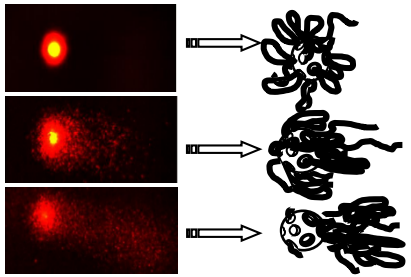
DNA lesions

Distribution of DNA fragments in electric field

Pulsed-field gel electrophoresis

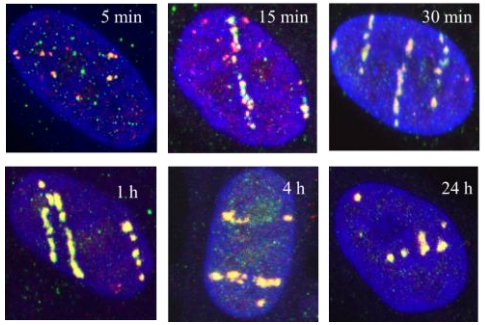


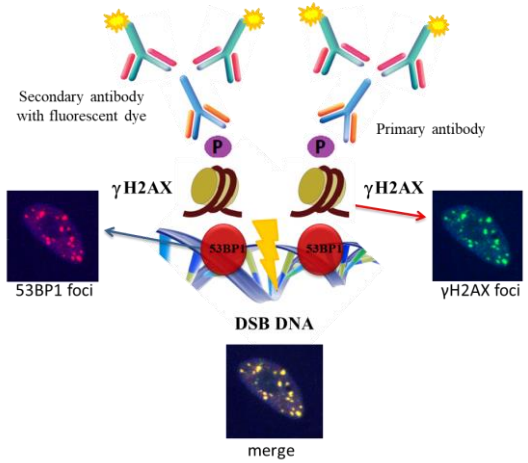
Comet assay



Fluorescent dyes + antibodies to DNA repair proteins

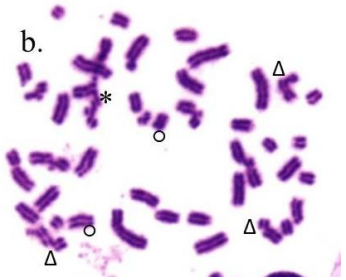
γH2AX foci





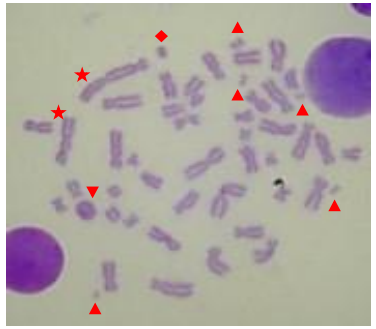
Chromatin breaks

Premature chromatin condensation PCC

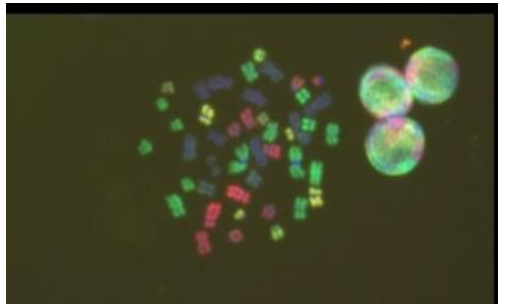


Chromosome aberrations

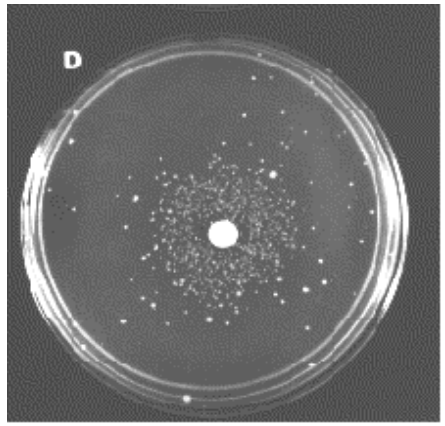
Metaphase assay



Multicolor fluorescence *in situ* hybridization mFISH

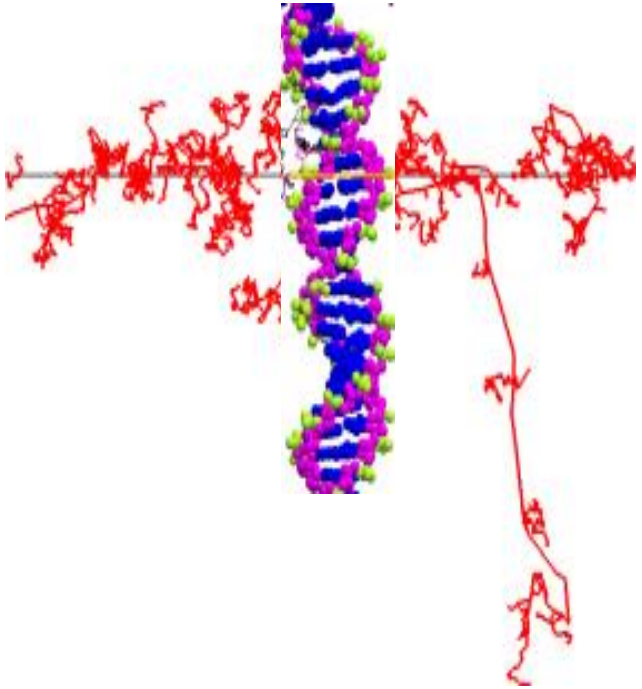


Cell survival

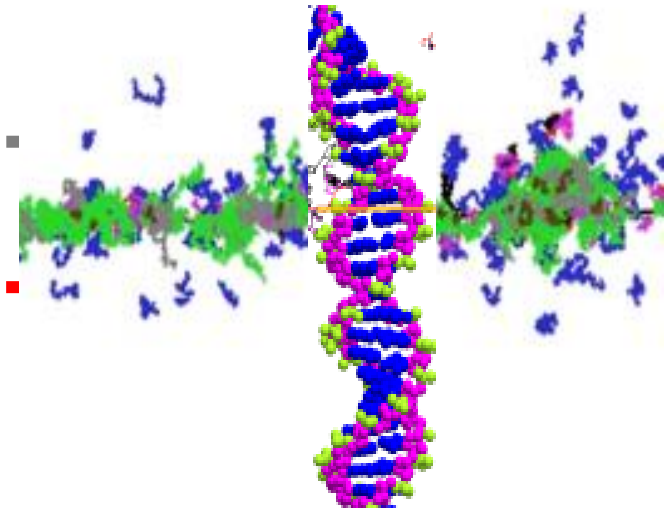


1. Monte Carlo simulation of radiation-induced DNA damage

Ionization, bond breakage

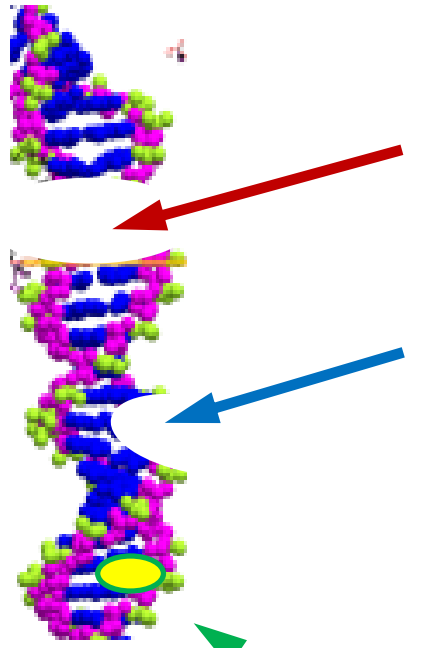


Radical attack, indirect lesion



- e^-_{aq}
- $^{\bullet}OH$
- H_3O^+
- $H^{\bullet}$
- OH^-
- H_2
- H_2O_2

DNA lesions



Double strand break (DSB)

Single strand break (SSB)

Base damage (BD)

Apoptosis, chromosome aberrations, mitotic catastrophe, cell death

Methodology of simulation on example of Geant4-DNA

Physical events

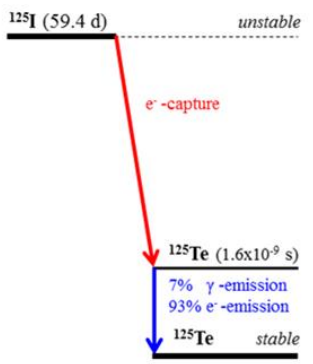
Particle	Interaction	Model
e^-	**ionization** ≥ 1МэВ 10 кэВ – 1 МэВ 10 эВ – 10 кэВ	(*Med. Phys. 2010*) Moller-Bhabha Born Emfietzoglou
	excitation 10 кэВ – 1 МэВ 8 эВ – 10 кэВ	(*Med. Phys. 2010*) Born Emfietzoglou
	elastic scattering 0.025 эВ – 1 МэВ	(*Rad. Phys. 2009*) Champion
^{1}H, ^{4}He, ^{7}Li, ^{9}Be, ^{11}B, ^{12}C, ^{14}N, ^{16}O, ^{28}Si, ^{56}Fe	**ionization** 1-1000 МэВ/нук	(*Rev. Phys. 1992*) Rudd
	Multiple scattering	(*J. Phys. 2010*) Urban

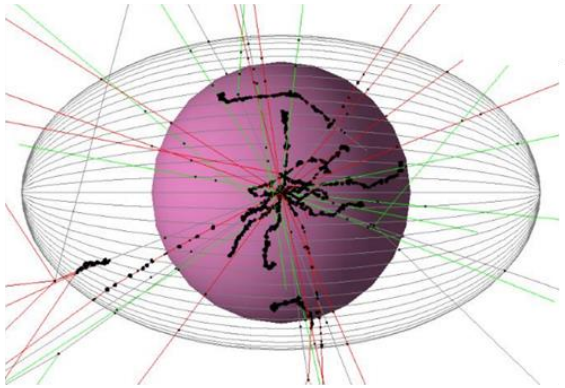
Double strand break probability

$P_{DSB} = 1 - e^{-\varepsilon/\varepsilon_0}$;

ε – energy deposition in event

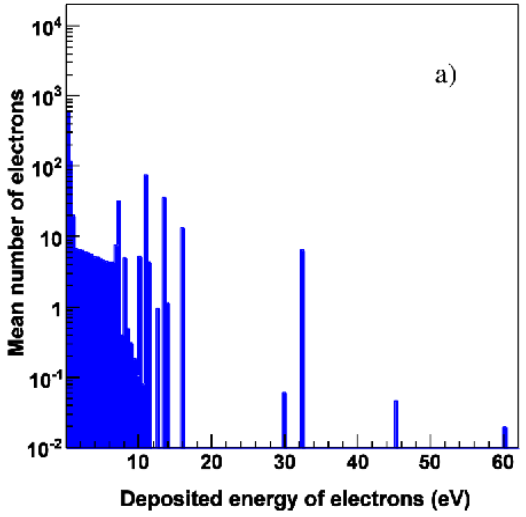
ε_0 =8.22– average bond dissociation energy

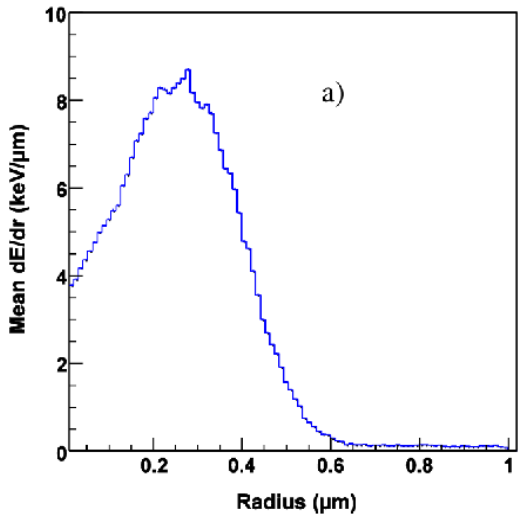




^{125}I

0,8 Bq/μg

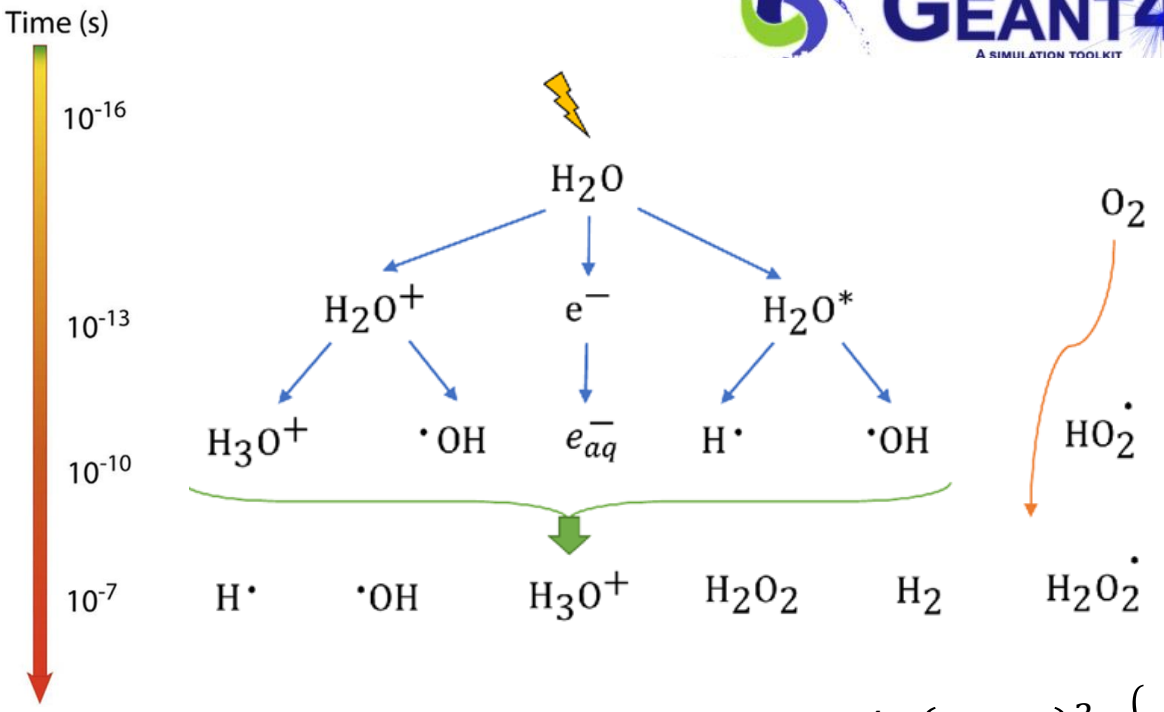




Methodology of simulation on example of Geant4-DNA

Radiolysis

Process	reaction coefficient, 10^{10} $M^{-1}s^{-1}$
$e^-_{aq} + e^-_{aq} + 2H_2O \rightarrow H_2 + 2OH^-$	0.5
$e^-_{aq} + H^\bullet + H_2O \rightarrow H_2 + OH^-$	2.65
$e^-_{aq} + {}^\bullet OH \rightarrow OH^-$	2.95
$e^-_{aq} + H_3O^+ \rightarrow H^\bullet + H_2O$	2.11
$e^-_{aq} + H_2O_2 \rightarrow OH^- + {}^\bullet OH$	1.41
${}^\bullet OH + {}^\bullet OH \rightarrow H_2O_2$	0.44
${}^\bullet OH + H^\bullet \rightarrow H_2O$	1.44
$H^\bullet + H^\bullet \rightarrow H_2$	1.2
$H_3O^+ + OH^- \rightarrow 2H_2O$	14.3



Indirect damage, main reaction channel
P_{DSB} = 0.65

DNA + ·OH → **(DNA)·**

Oxygen-dependent reaction channel1

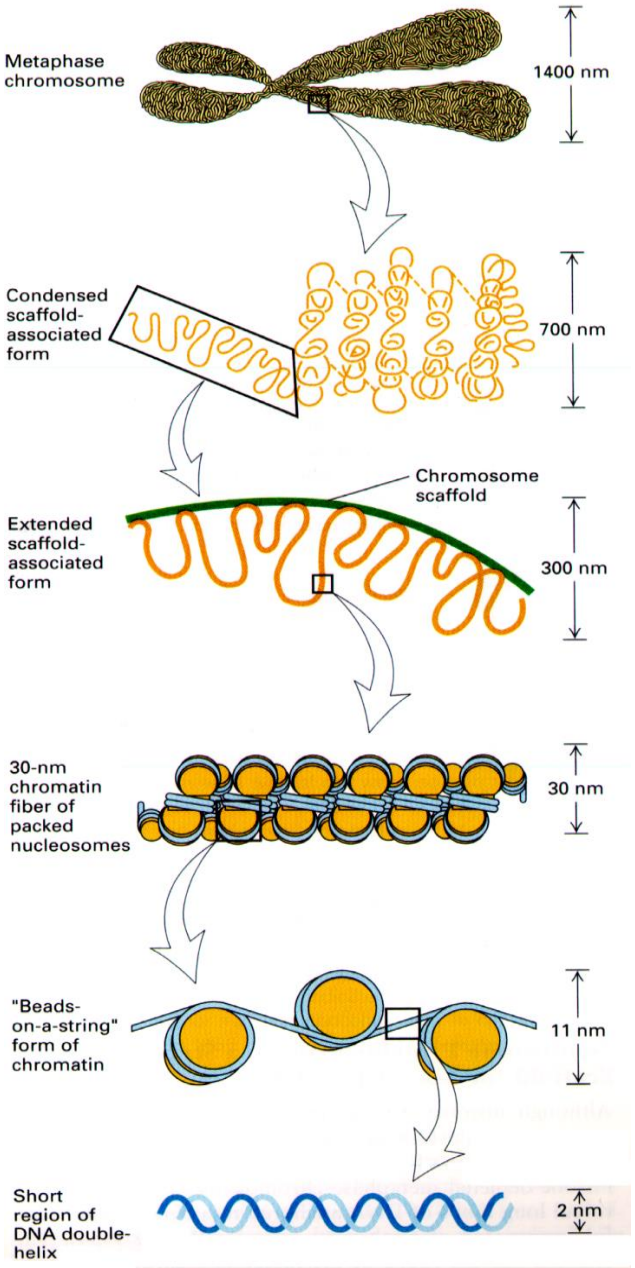
(DNA)· + [O_2] → (DNA)OO·

$$p(r,\Delta t|r_0) = \frac{4\pi(\mathrm{r}-r_0)^2}{(4\pi \mathrm{D}\Delta \mathrm{t})^{3/2}} \mathrm{e}^{\left\{\frac{-(\mathrm{r}-r_0)^2}{4D\Delta t}\right\}},$$

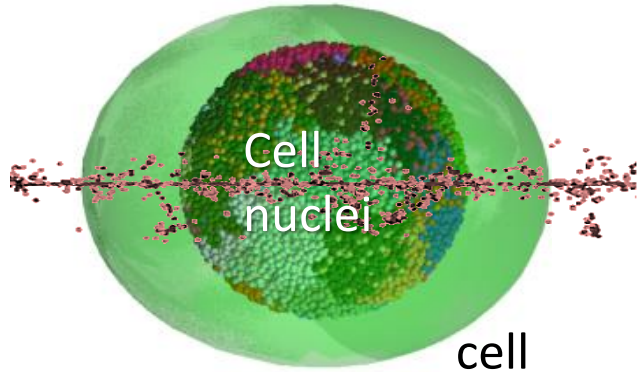
Reaction A+B occurs if $R_{AB} \leq R_e$

where $R_e = \frac{k}{4\pi N_A (D_A + D_B)}$ *or* $R_e = R_c/(e^{R_c/R_{AB}} - 1)$

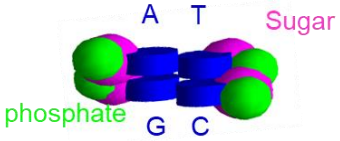
Methodology of simulation on example of Geant4-DNA



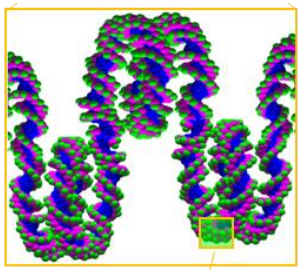
Geometry of sensitive target



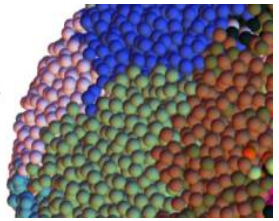
cell



nucleoside



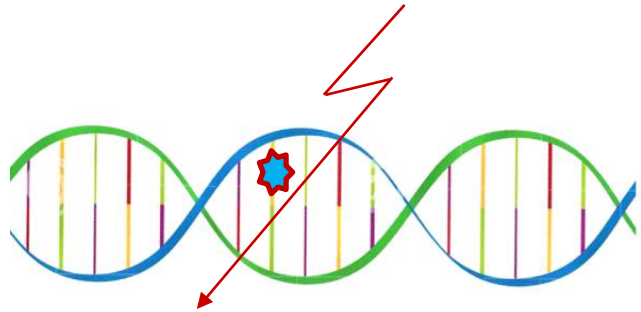
DNA in chromatin



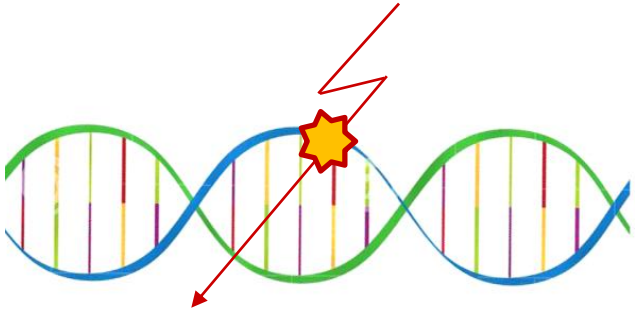
Chromosome domains

GEANT4-DNA
A SIMULATION TOOLKIT

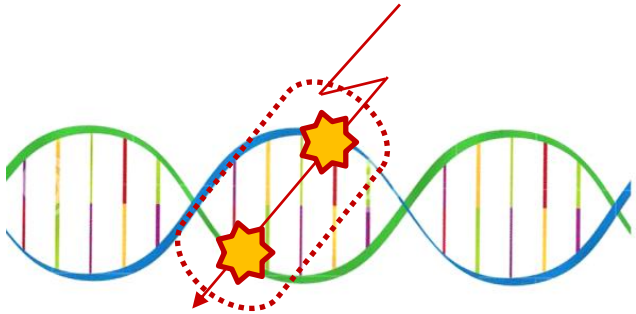
Counting DNA lesions



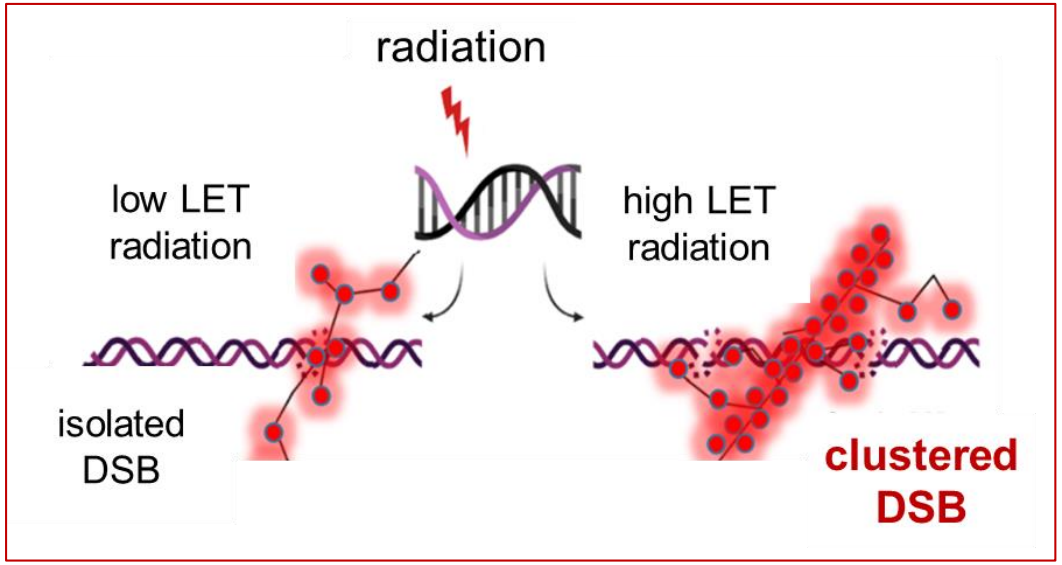
Base damage (BD)



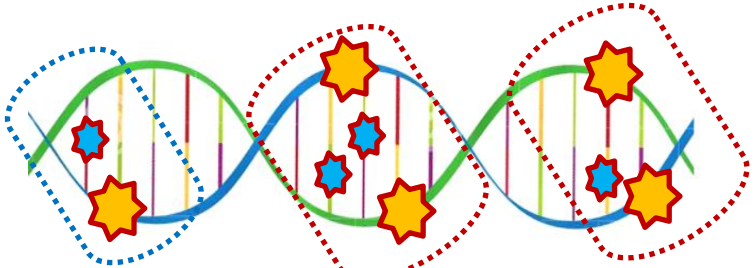
Single stand break (SSB)



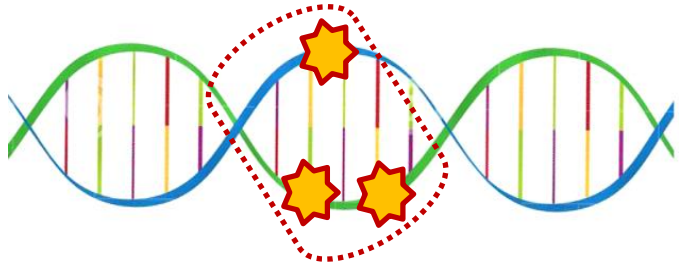
Double strand break (DSB)



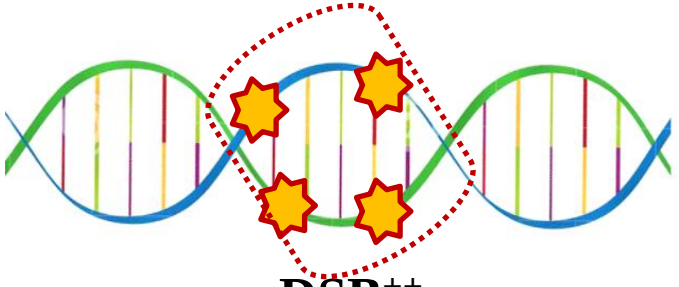
Complex and clustered damage (size < 10 bp)



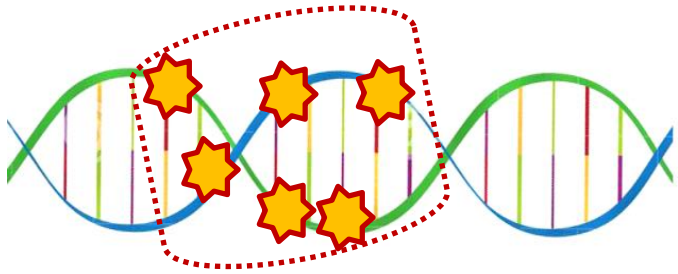
SSB* **DSB**** **DSB***



DSB^{+}

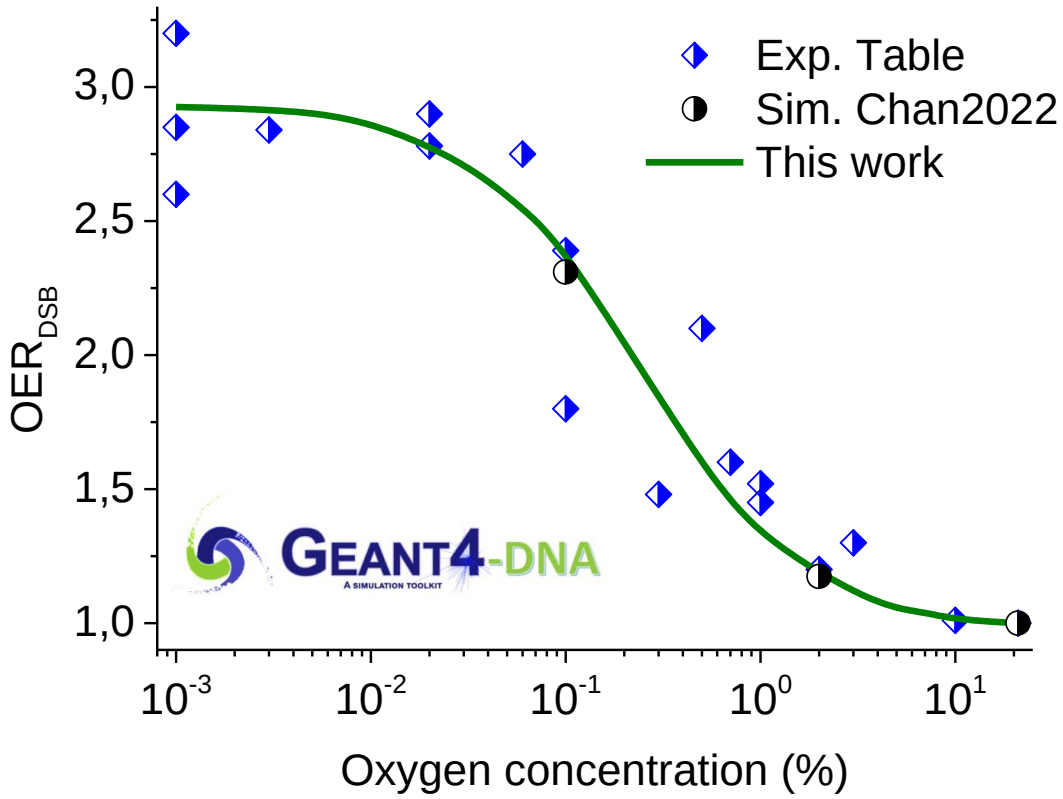


DSB^{++}

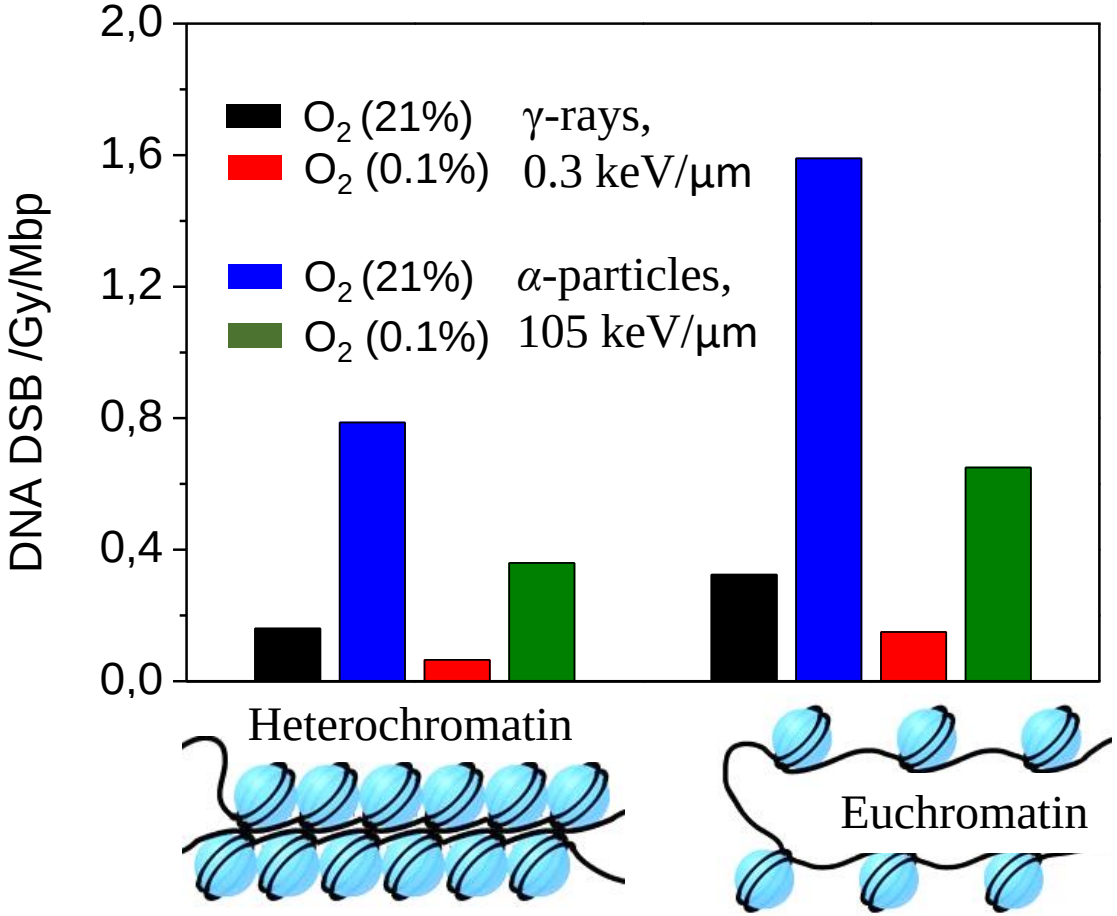


DSB^{++++}

Oxygen-Dependent Damage and Chromatin Structure



Comparison of measured and calculated oxygen enhancement ratio OER determined by double strand break (DSB) yields after γ-irradiation



Effect of oxygen concentration and chromatin structure on amount of DNA double strand breaks induced by low- and high-LET radiations

DNA lesion distribution by type

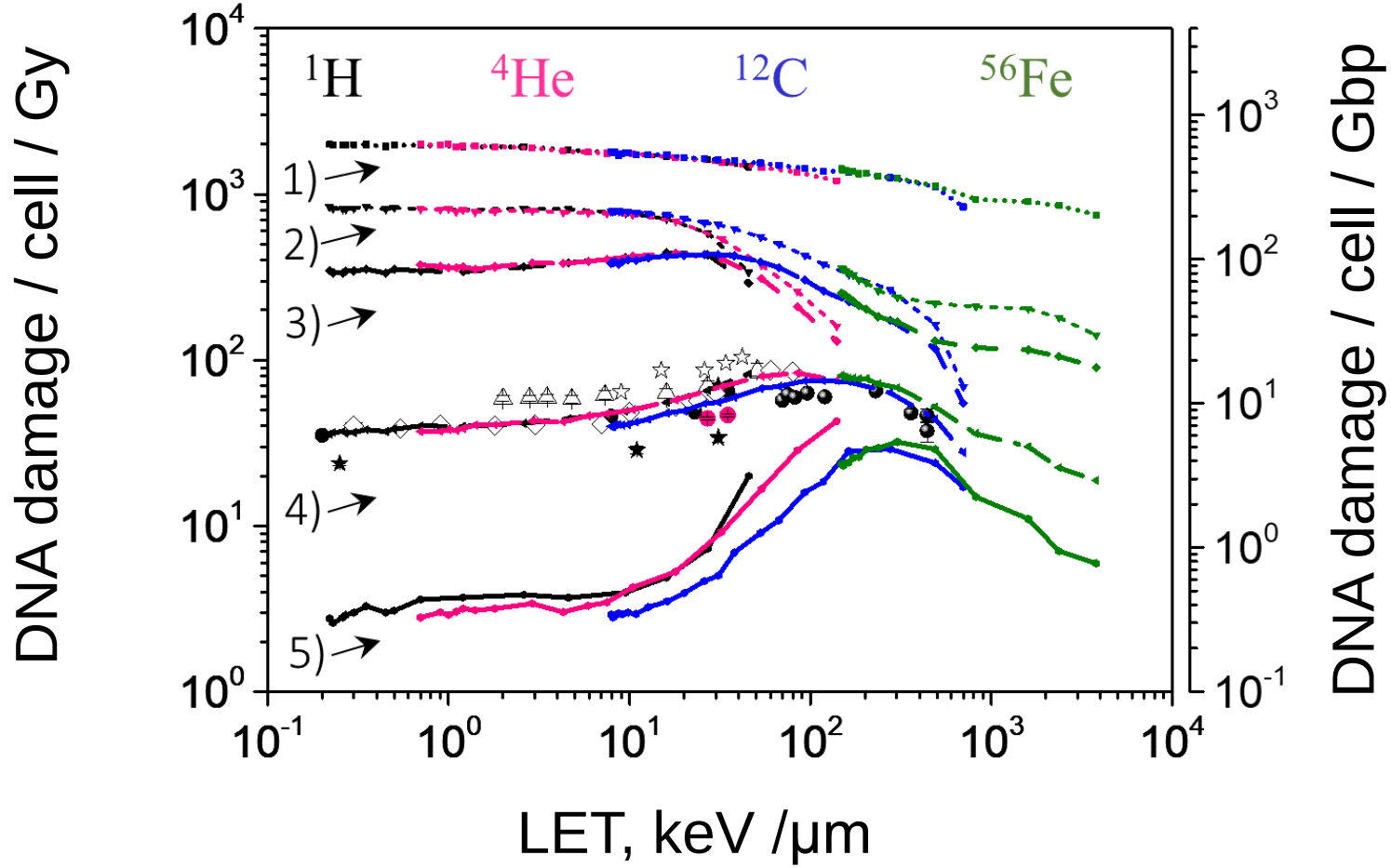
1) DNA base damage (BD)
2) Single strand break (SSB)
3) Clustered SSB
4) Double strand breaks (DSB)
5) Clustered DSB

Experimental data

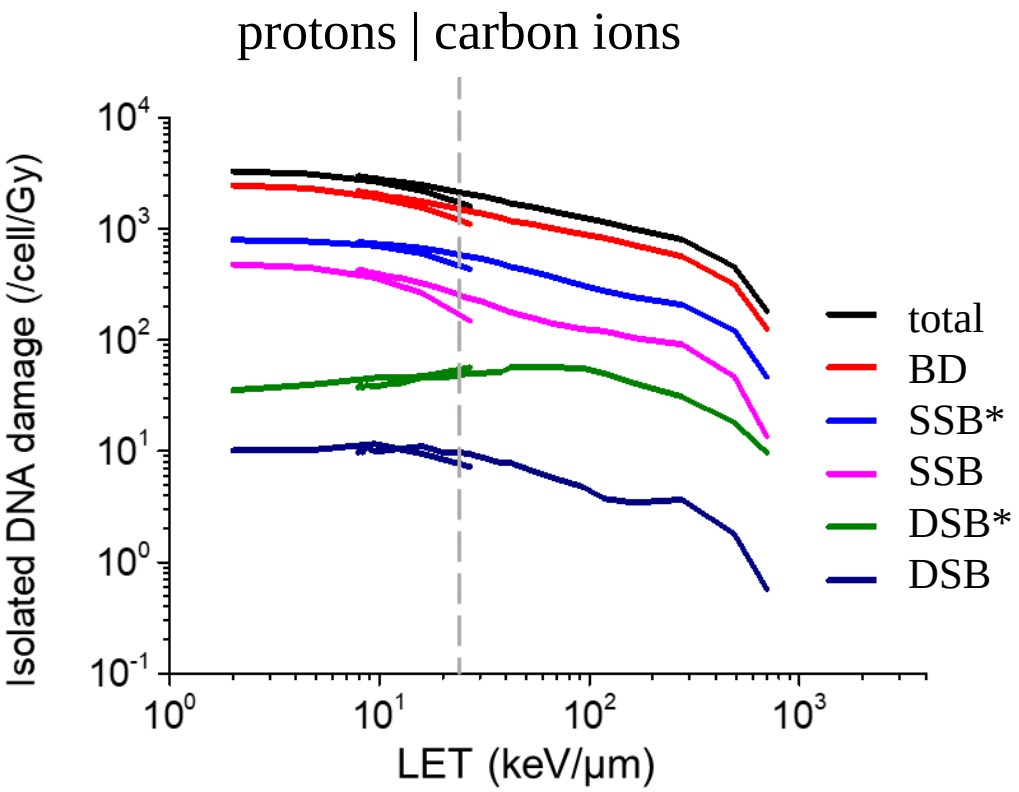
- Frankenberg 1999
- Belli 2001
- Belli 2006

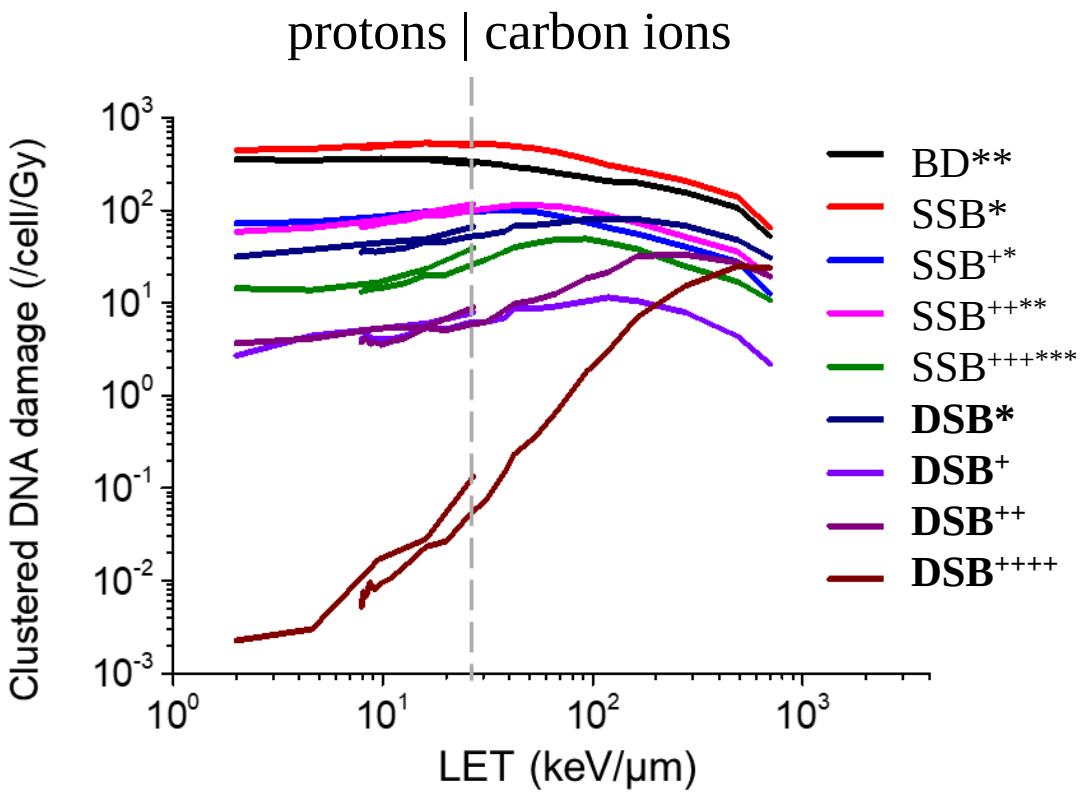
Other simulation codes

- Nikjoo 2001
- Friedland 2011
- Rosales 2018

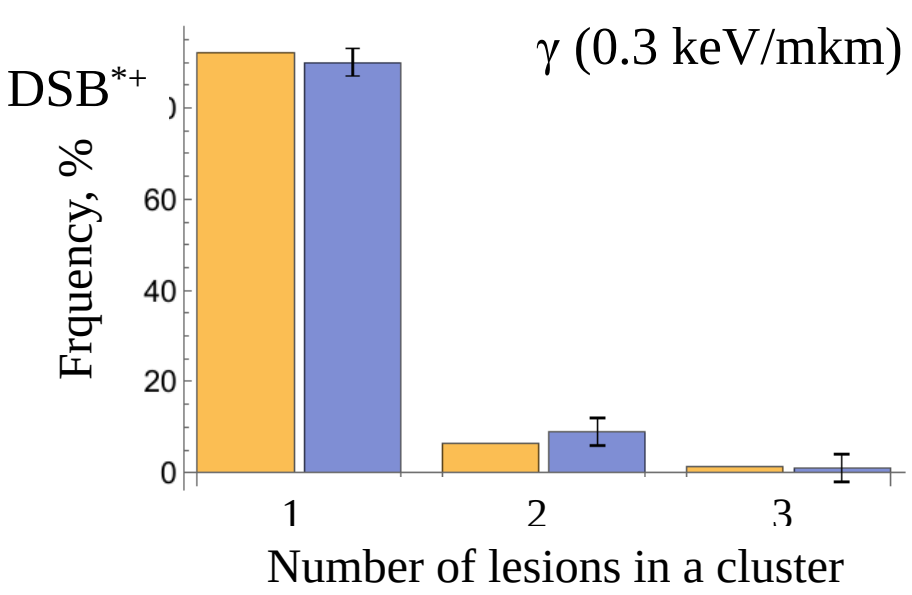


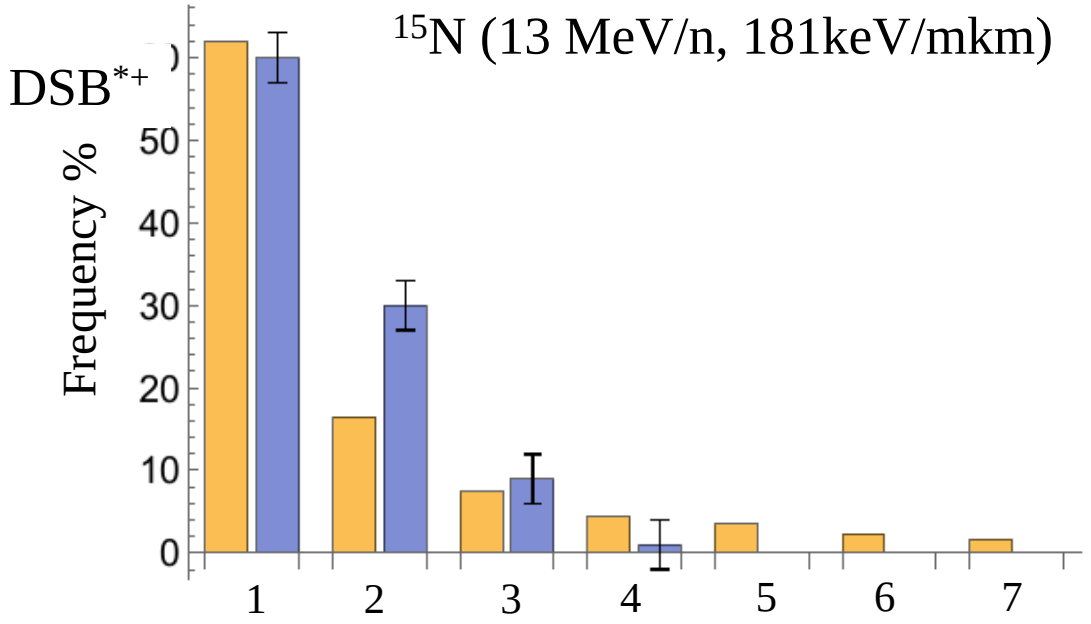
Complexity of clustered DNA damage





Complexity of clustered DNA damage



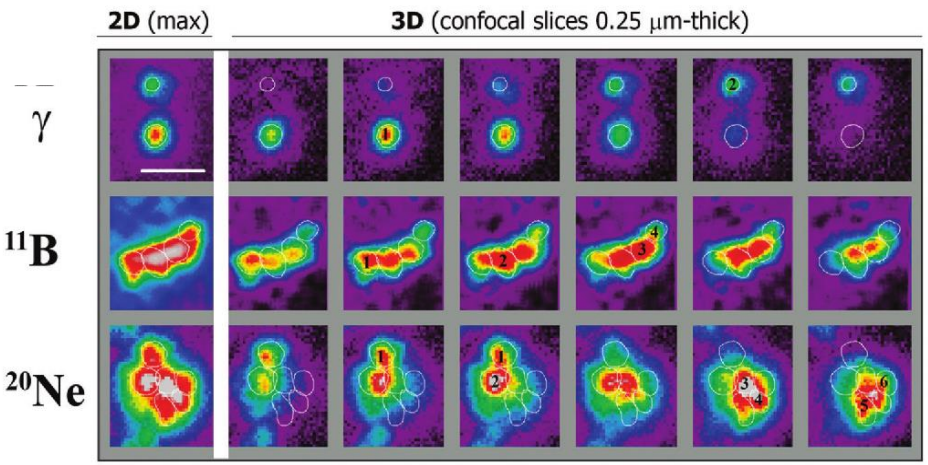


Model

Experiment

Boreyko A.V. et al, PEPAN Lett, 2022, Vol. 19, p. 440.

Nanoscale, 2018, 10, 1162–1179 |



2. Principles of DNA repair modeling

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

2. Differential Equations

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

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

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

3. Initial conditions

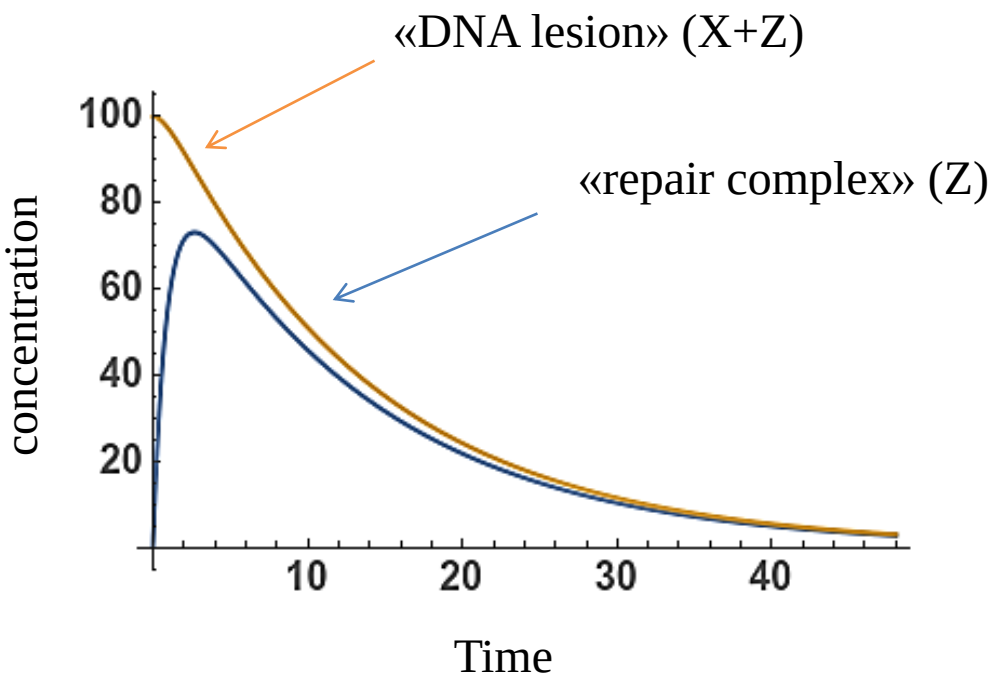
$$X(0) = N_0$$

$$R(0) = R_0$$

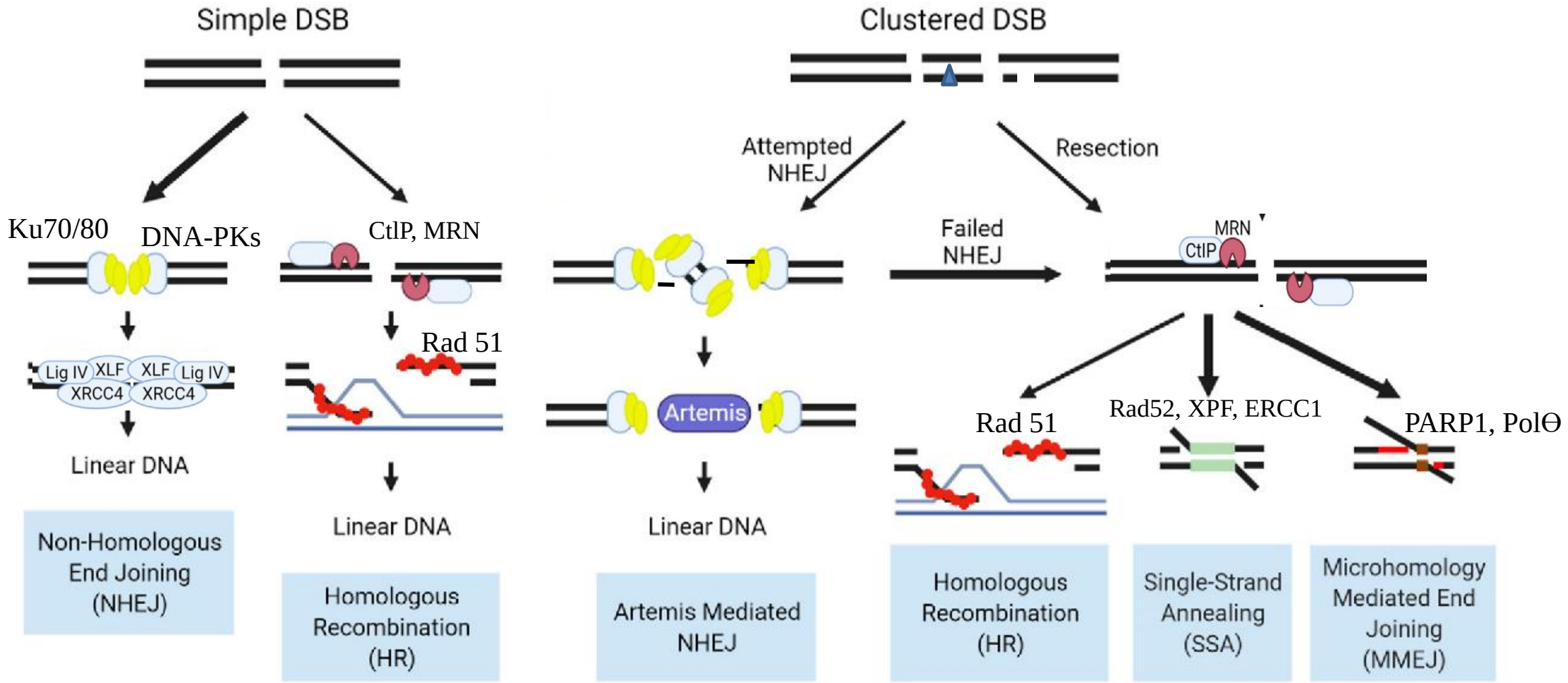
$$Z(0) = 0$$

4. Determination of parameters

k_+ k_- q

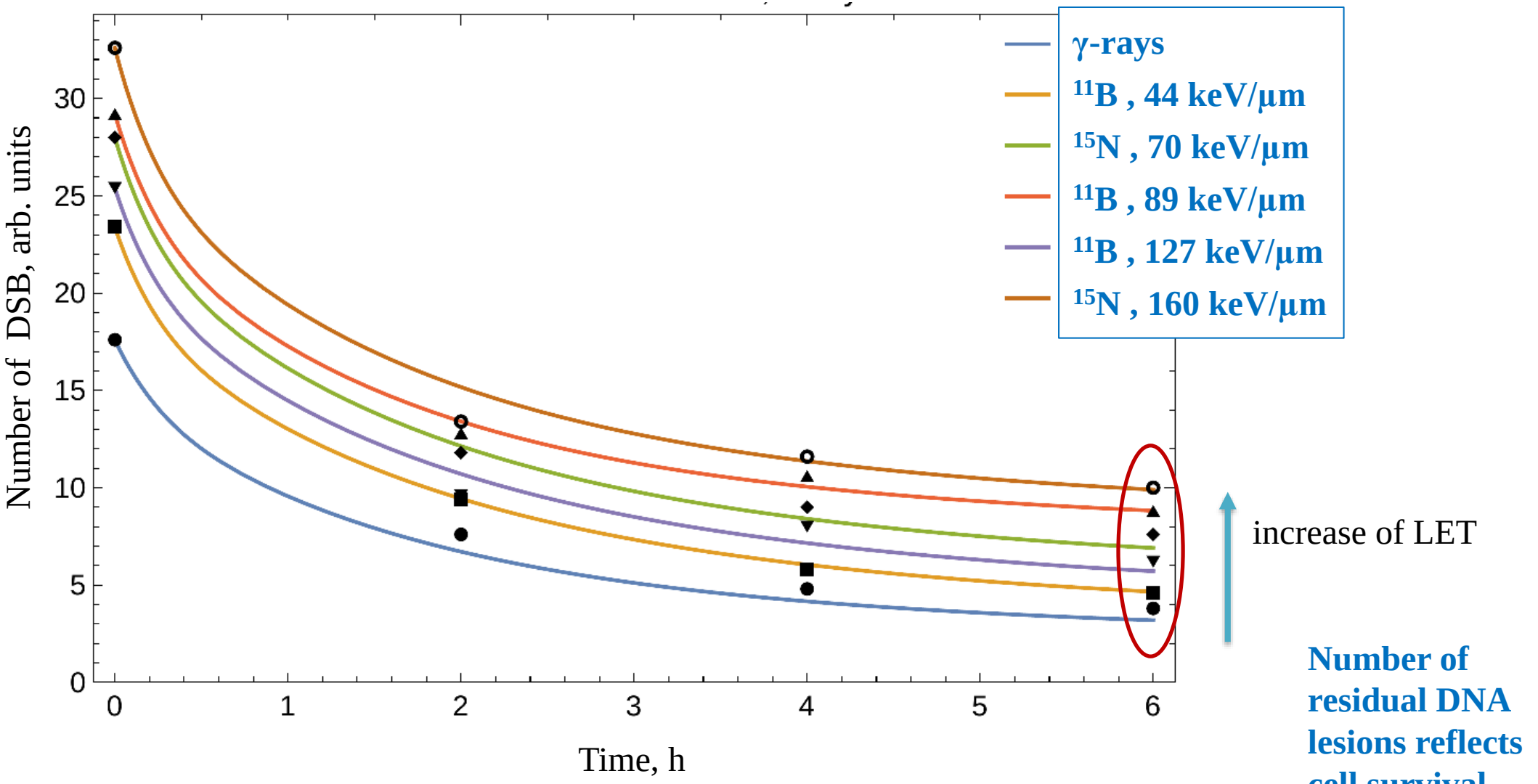


Pathways of DNA double strand break repair



modified from Danforth et al(2022) Front. Cell Dev. Biol. 10:910440.

DNA repair modeling



Number of residual DNA lesions reflects cell survival

3. Cell survival modeling

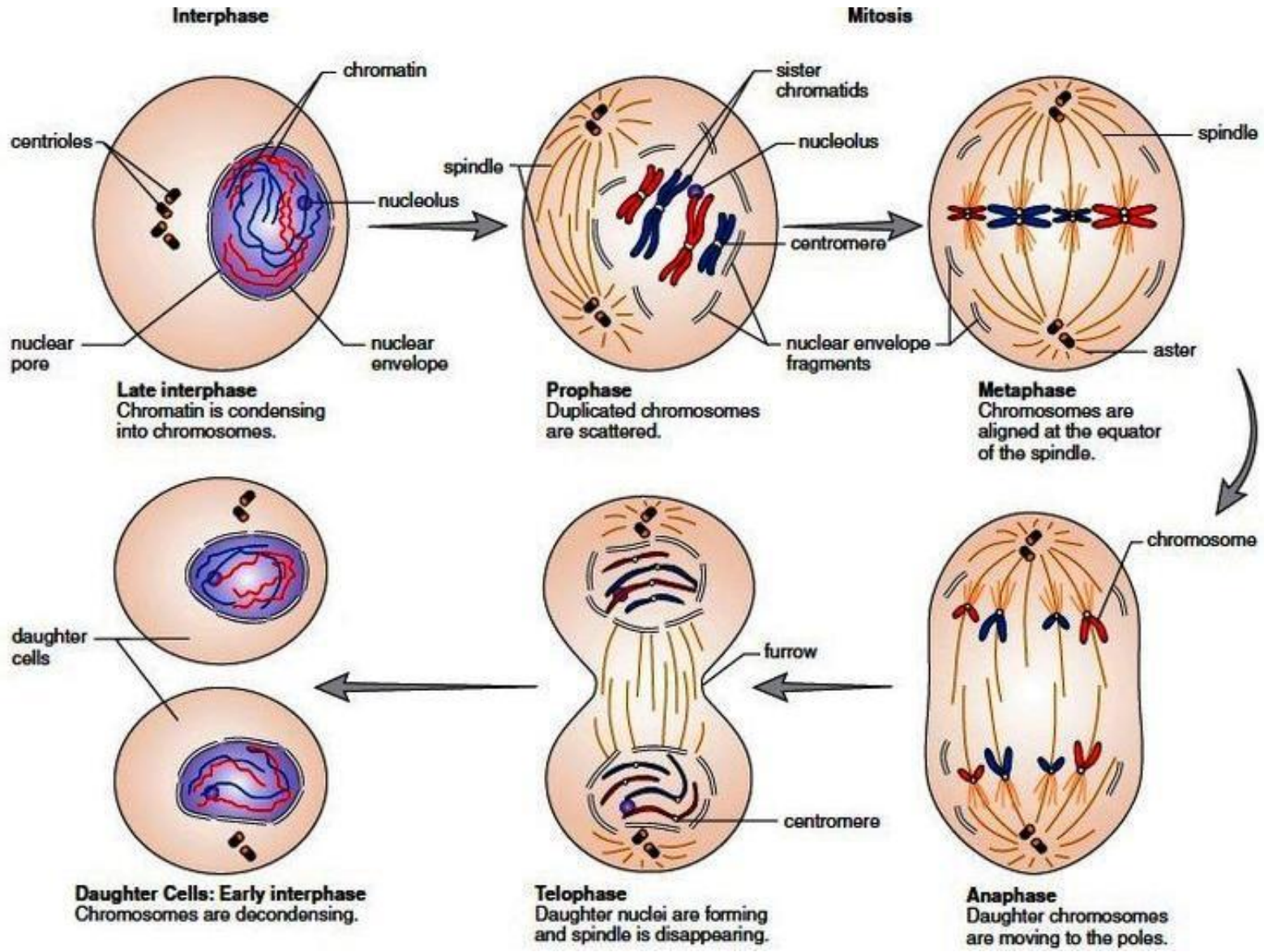
$$S = e^{-p_{i,p,m,a}N - N_{mis}}$$

N - number of DSBs remaining

$N_{mis} \sim N_{chrom\ aber}$

- number of misrepaired DSBs

Scheme of cell cycle



3. Cell survival modeling

Example of simple semi-analytical model

$$S(D, N_{DSB}, n_{particle}) \approx \exp(-\alpha D - \beta D^2)$$

$$\alpha = Y \times \left(\frac{1 - e^{-\zeta \lambda_p}}{\zeta \lambda_p} \right) \times \left(1 - \mu_x \left(\frac{1 - e^{-\xi \lambda_p}}{\xi \lambda_p} \right) \right) \times \mu_y$$

$$\beta = \frac{1}{2} \eta(\lambda_p) \frac{Y}{\lambda_p} \times Y \times \left(\frac{1 - e^{-\zeta \lambda_p}}{\zeta \lambda_p} \right) \times \left(\frac{1 - e^{-\xi \lambda_p}}{\xi \lambda_p} \right) \times \mu_x \mu_y$$

Parameters taken from Geant4-DNA data per cell

D – absorbed dose

Y – number of DSBs per cell per 1 Gy

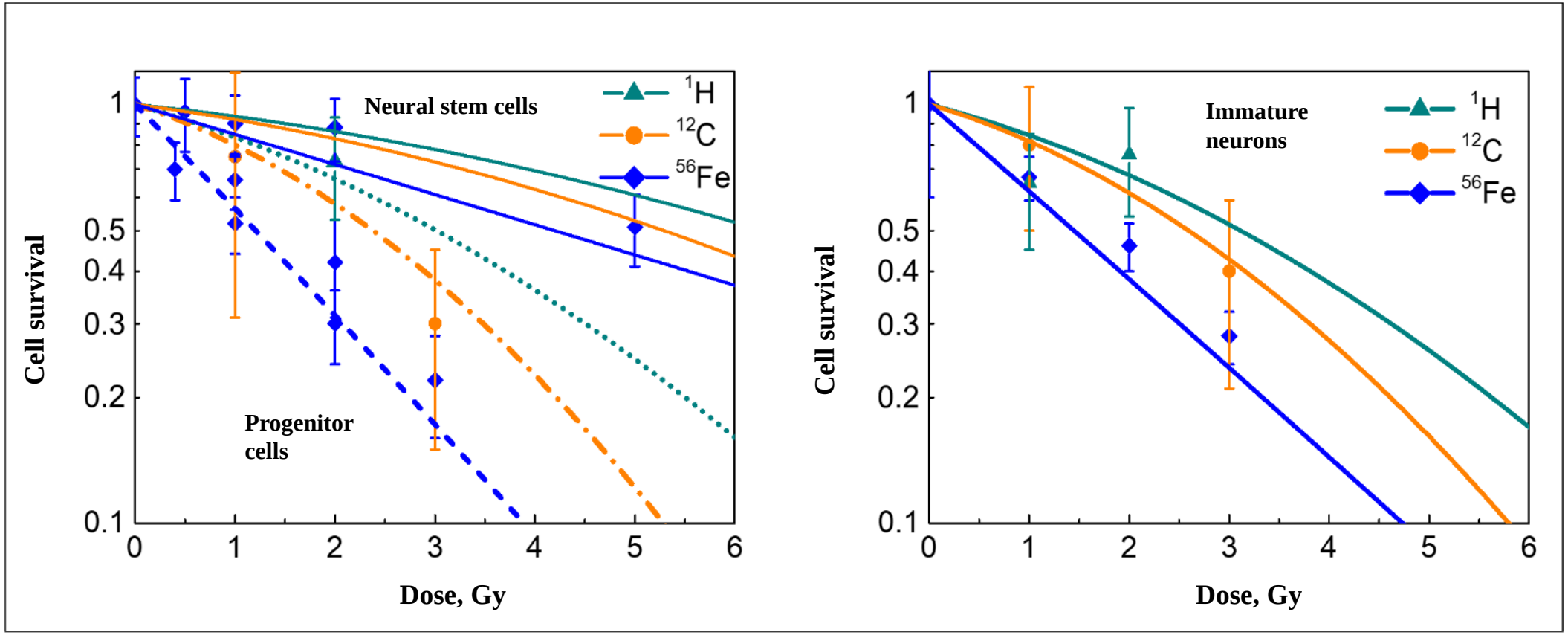
λ_p – number of DSBs induced by 1 particle

$\zeta \lambda_p$ – contribution to cell death, μ_y – sensitivity (depends on cluster complexity)

$\xi \lambda_p$ – joining probability in the same track, μ_x – repair fidelity (e.g. for HR , μ_x =1)

η - joining probability in different tracks

Survival of radiosensitive cells



Calculated survival of radiosensitive cells (neural stem cells, neural progenitor cells, immature neurons) after action of 1000 MeV protons, 290 MeV/u carbon ions, 600 MeV/u iron ions as compared with experimental data [Rola 2004, 2005, Tseng 2014].

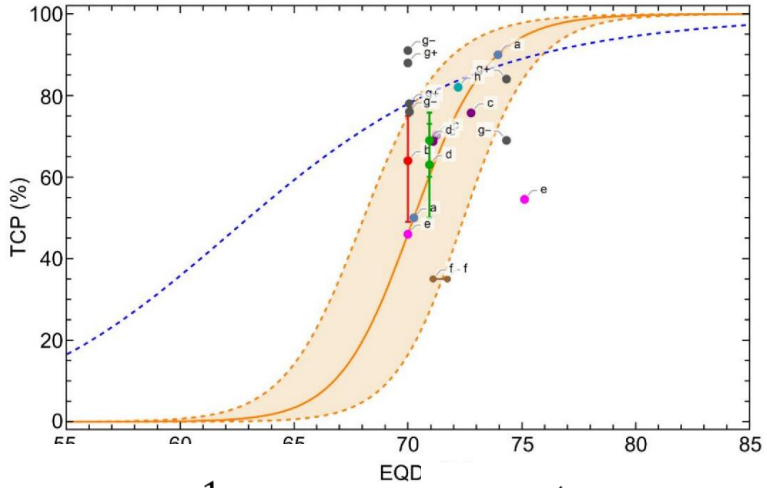
Transition from cell culture to tissue - is there any workaround?

Data-driven approach

Clinical / laboratory data

Predictive power limited by database!

Empirical model formula, or software (e.g. machine learning)



$$TCP = \frac{1}{1 + \left(\frac{TCD_{50}}{EUD}\right)^{4\gamma_{50}}}$$

$$EUD = \left(\sum_i v_i \left(D_i \frac{\alpha/\beta + D_i/n_f}{2 + \alpha/\beta}\right)^a\right)^{1/a}$$

Model of A. Niemierko et al

Model-driven approach

Hierarchy of complex models

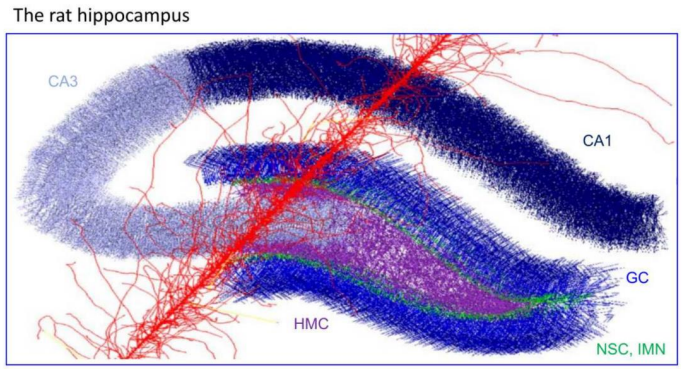
Input data rely on current scientific knowledge!

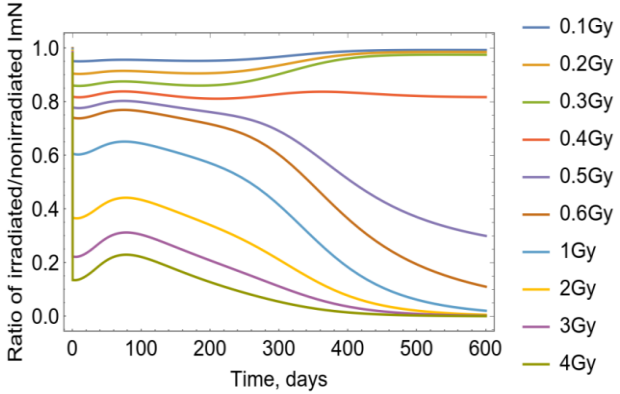
Insufficient computing power!

Simplification

Requires verification!

Software or fit to simple formula





Tissue and organ effects of radiation

An example of model-driven approach

Radiation damage to the central nervous system:

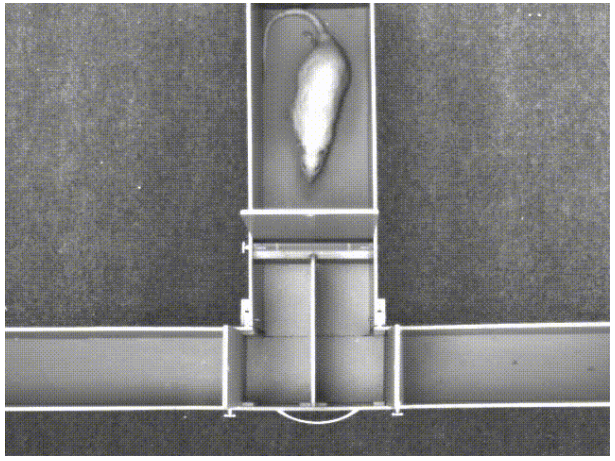
Radiosensitive cells - neural stem cells

1. **Amount of cells with lesions**
2. **Calculation of cell survival**
3. **Effect of neurogenesis impairment on brain electric activity**

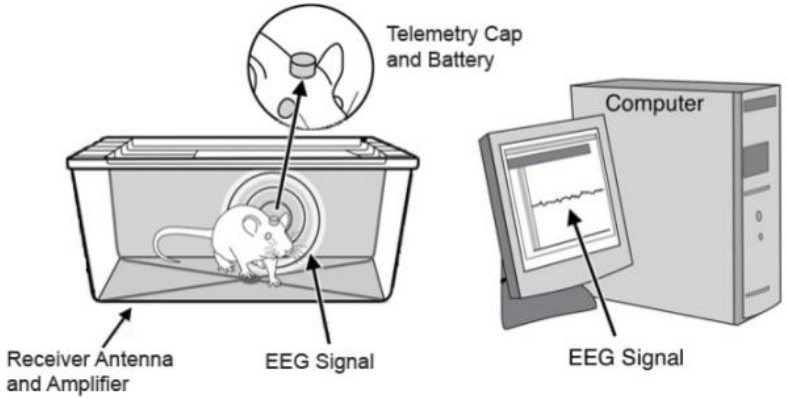
Experimental protocols *in vivo*

Behavior Test Systems

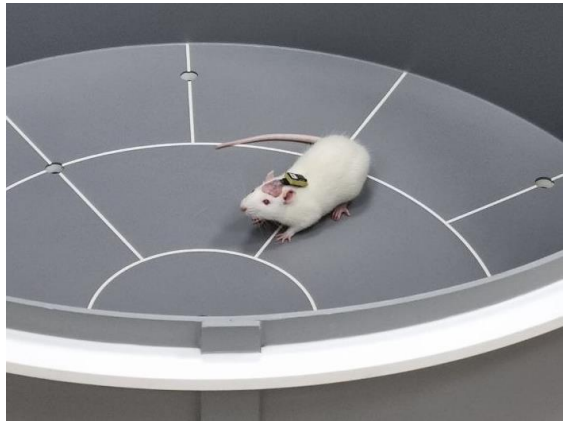




EEG records

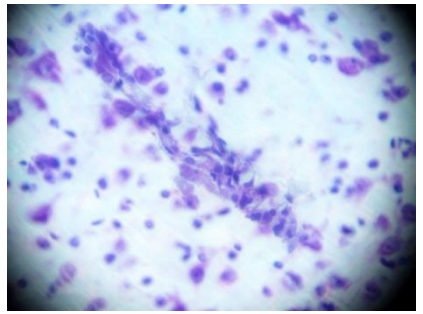


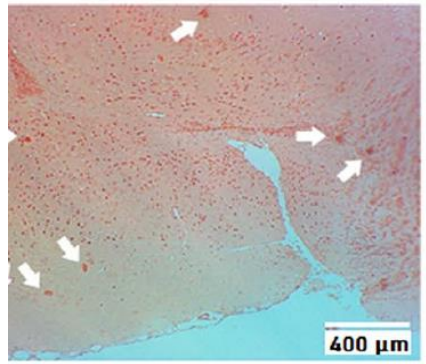


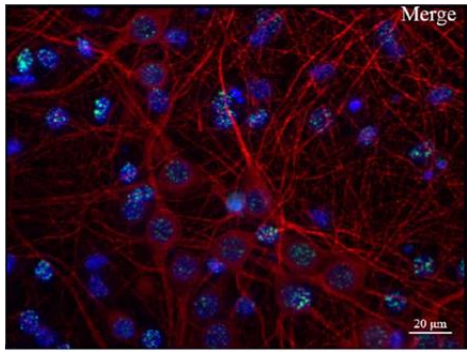


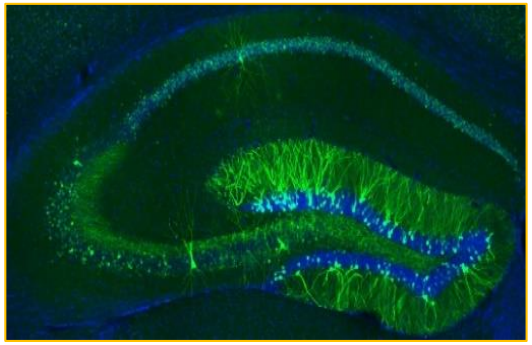
Tomography and histological analyis





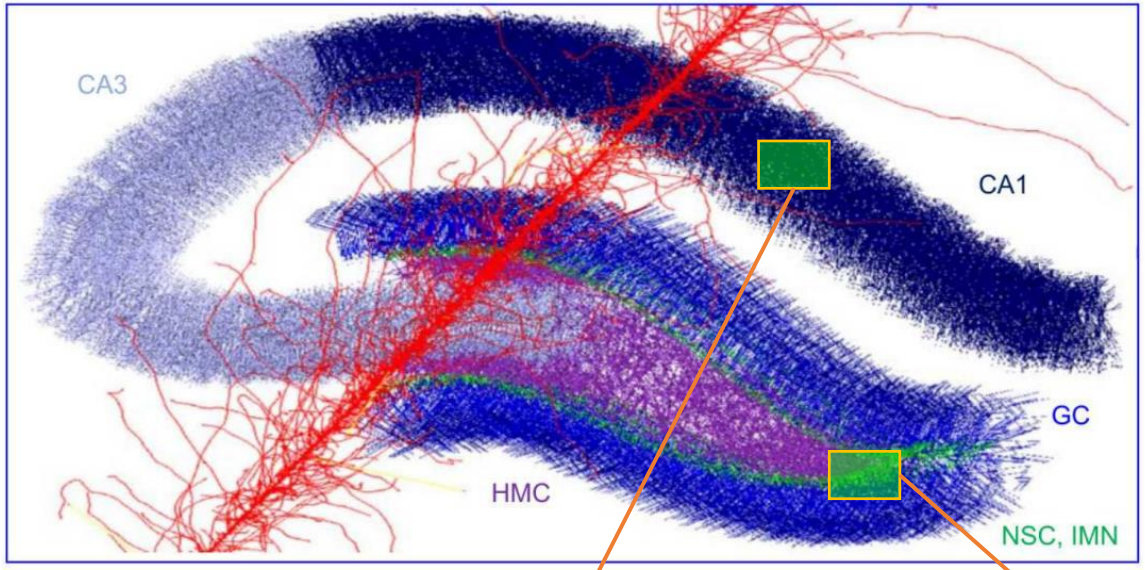


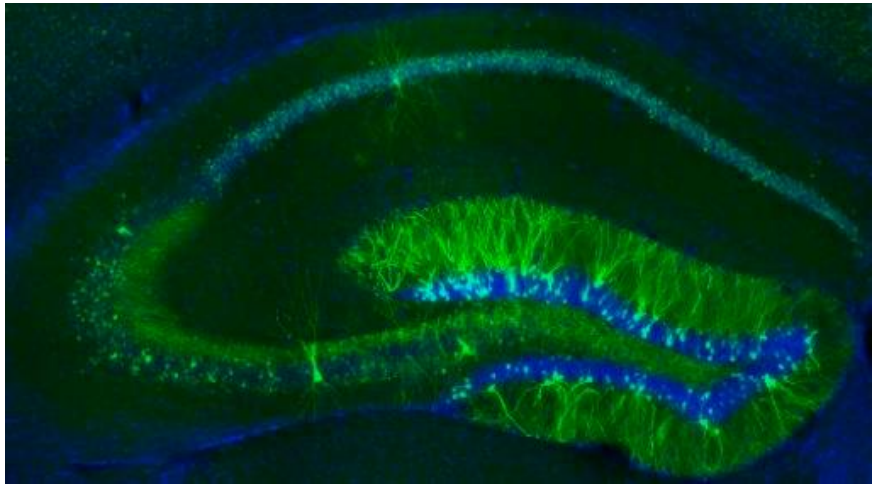




Geometry of rodent hippocampus for use in GEANT4-DNA

3D model of rat hippocampus traversed by 600 Mev/u ^{56}Fe ion track

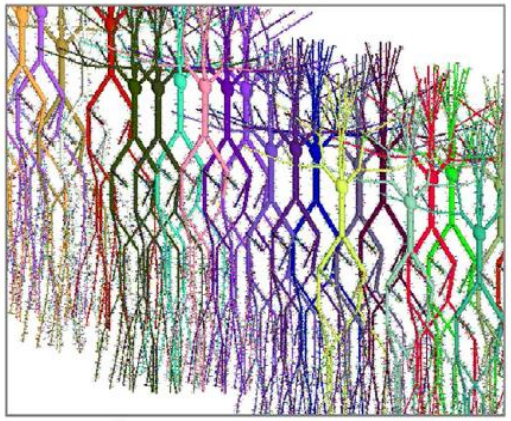


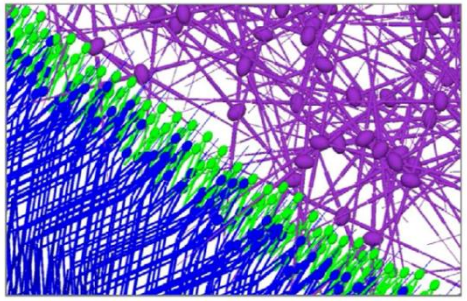


Fluorescent image of hippocampus slice

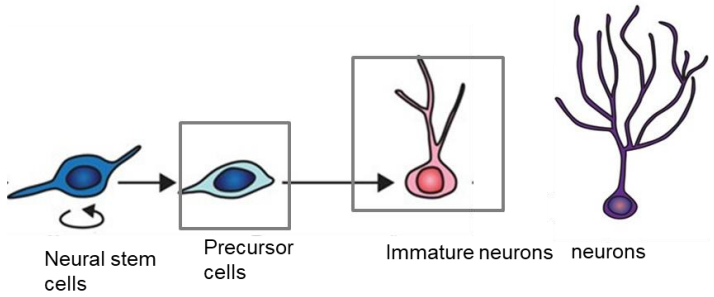
Scale 1:100

~ 20 000 cells

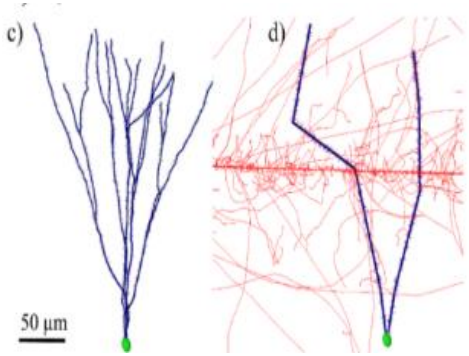


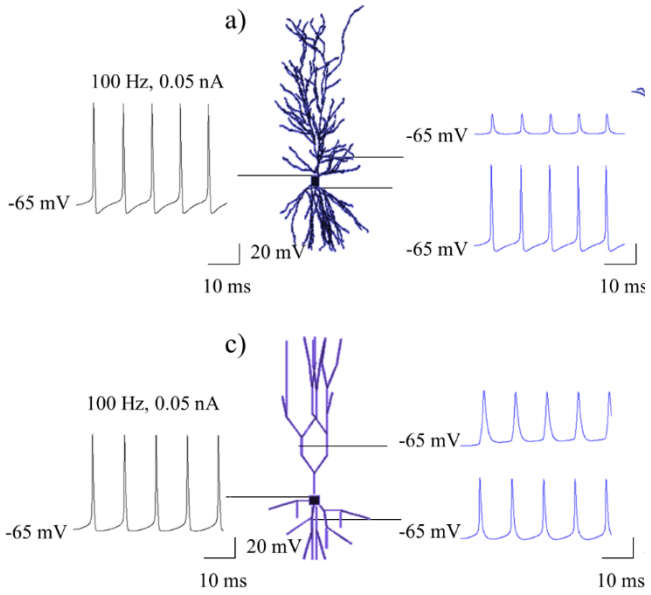


Neurogenesis region
Sensitive to Radiation!

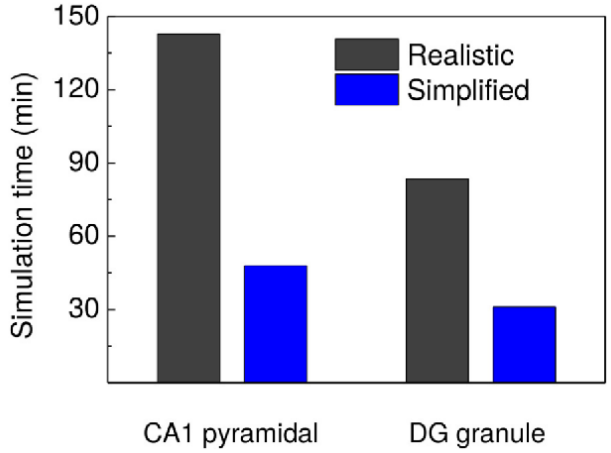


Scalability – way to success

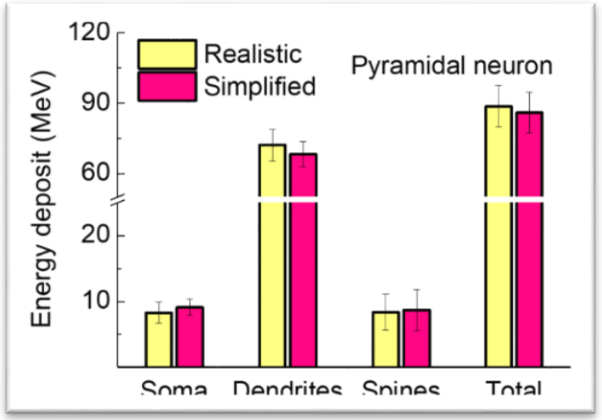




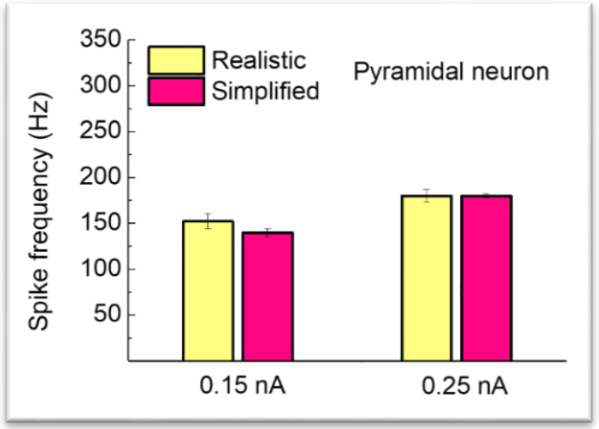
100 cell benchmark

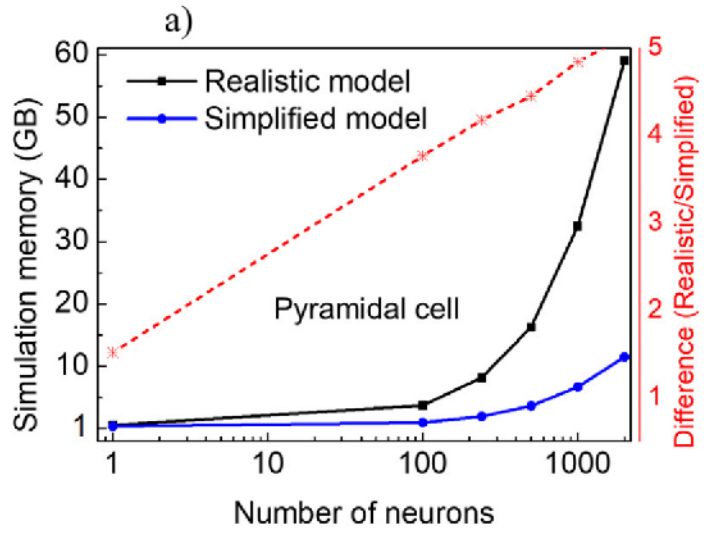


Microdosimetry scaling

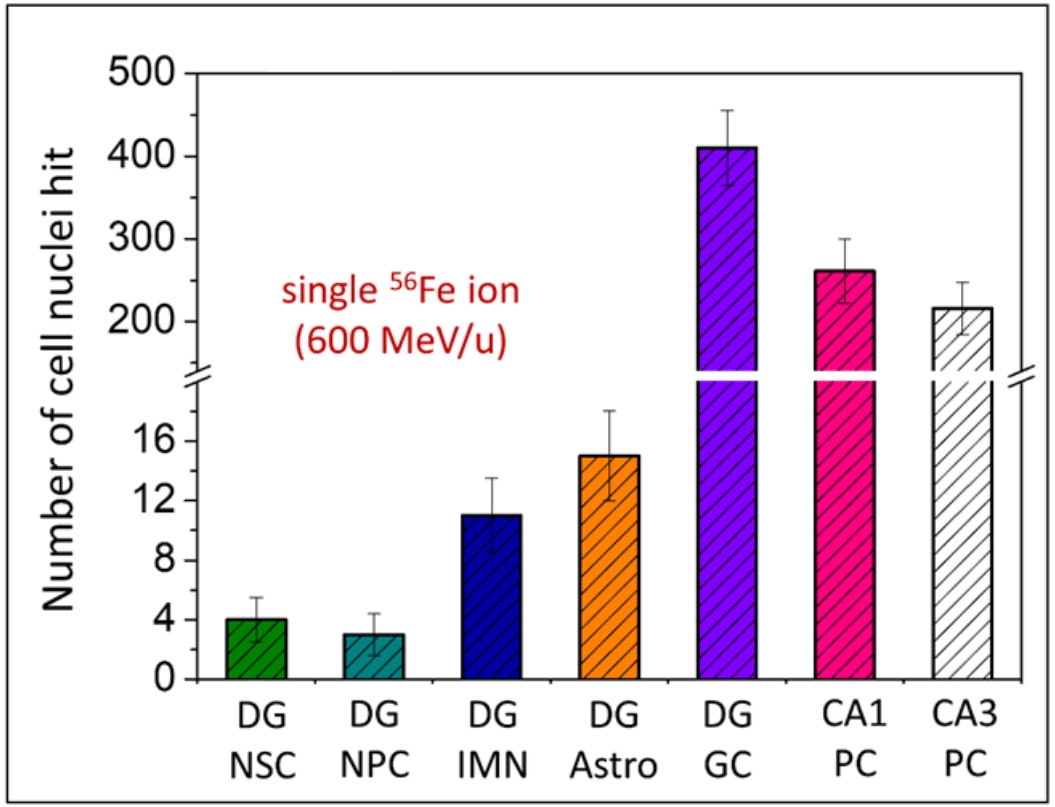


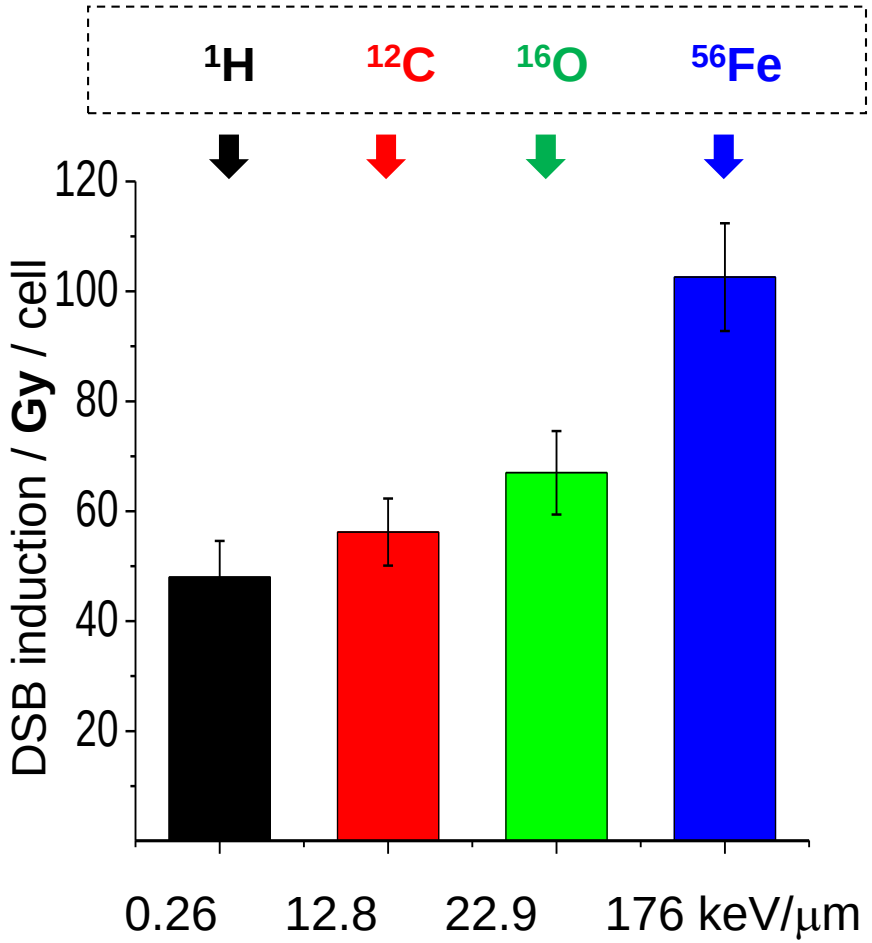
Electrophysiology scaling



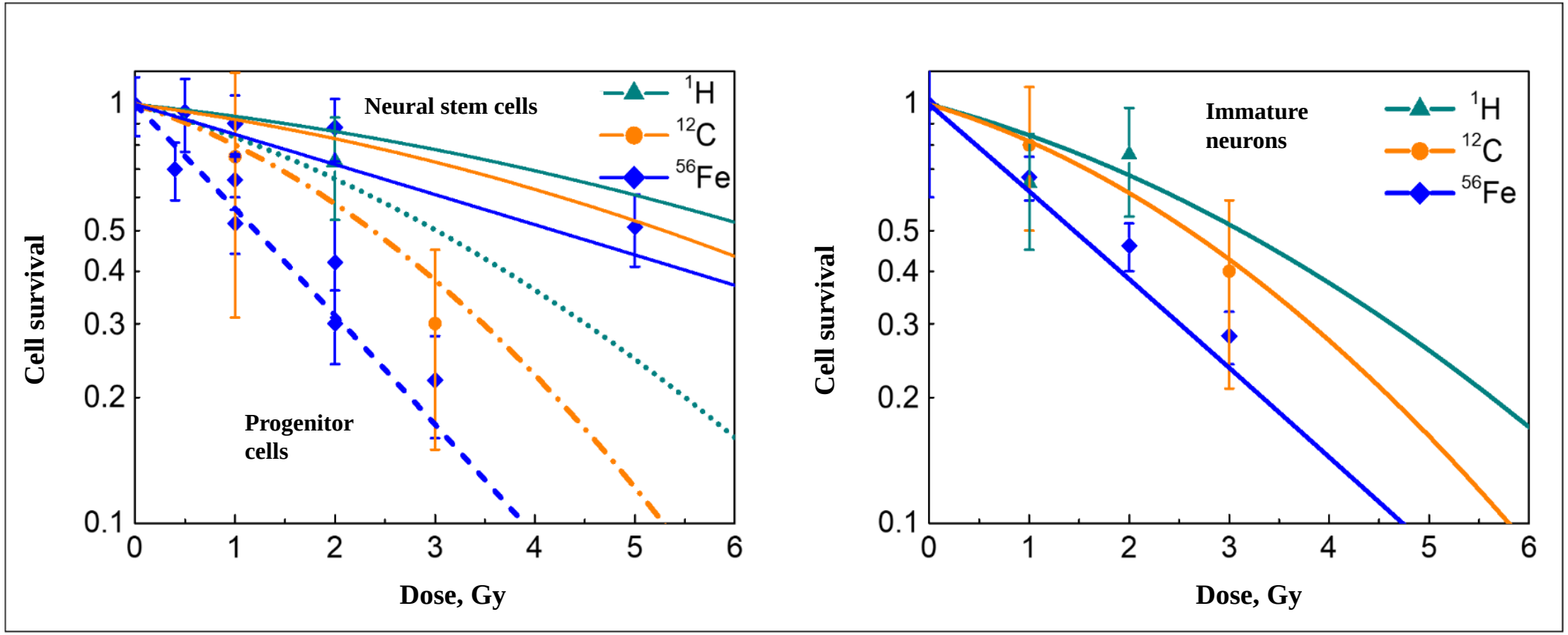


DNA damage computation



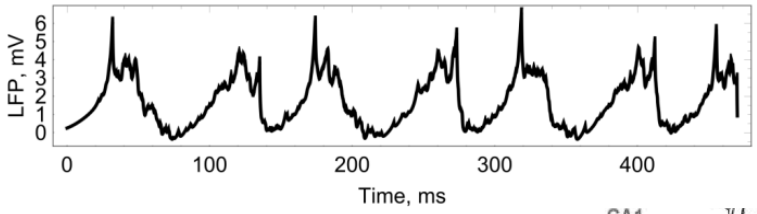


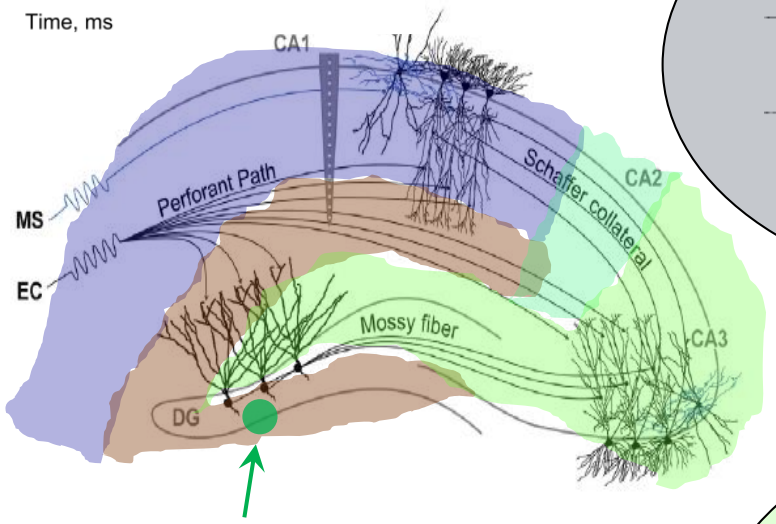
Survival of radiosensitive cells



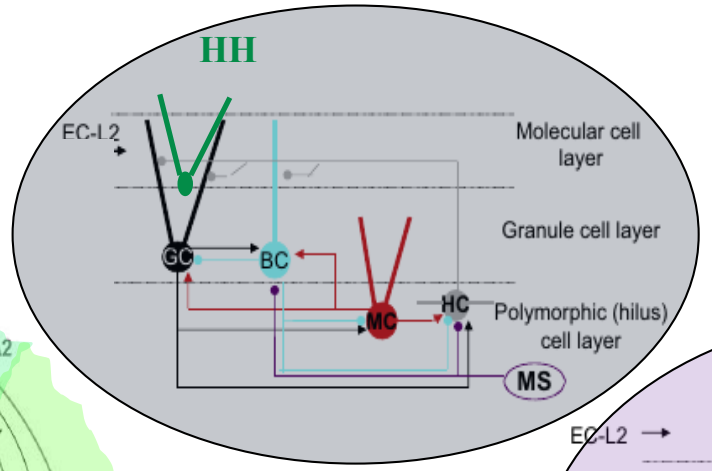
Calculated survival of radiosensitive cells (neural stem cells, neural progenitor cells, immature neurons) after action of 1000 MeV protons, 290 MeV/u carbon ions, 600 MeV/u iron ions as compared with experimental data [Rola 2004, 2005, Tseng 2014].

Biological neural network of hippocampus: a model for electrophysiological activity

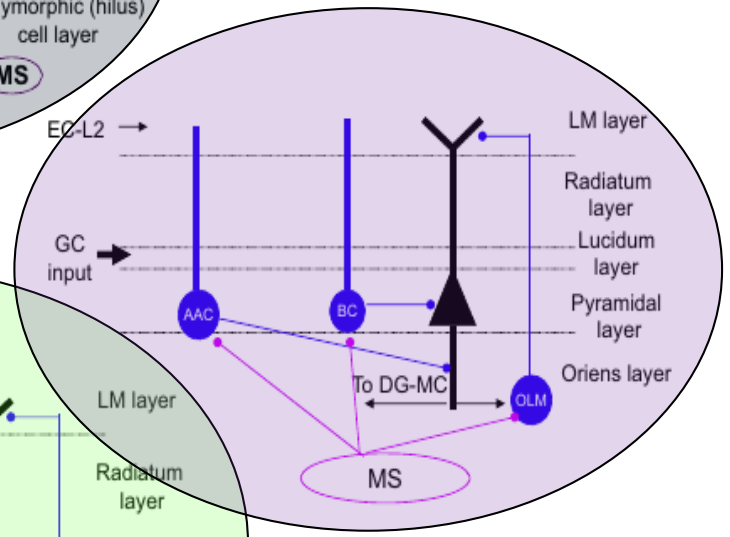




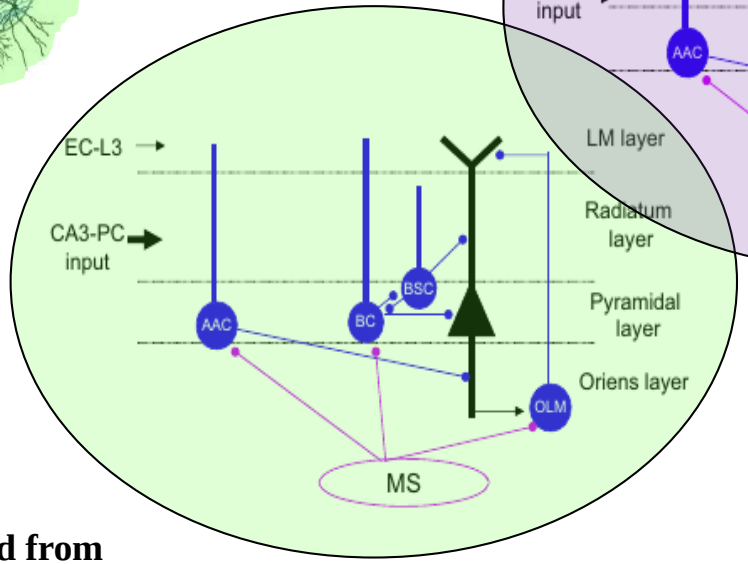
Zone of neurogenesis



DG network



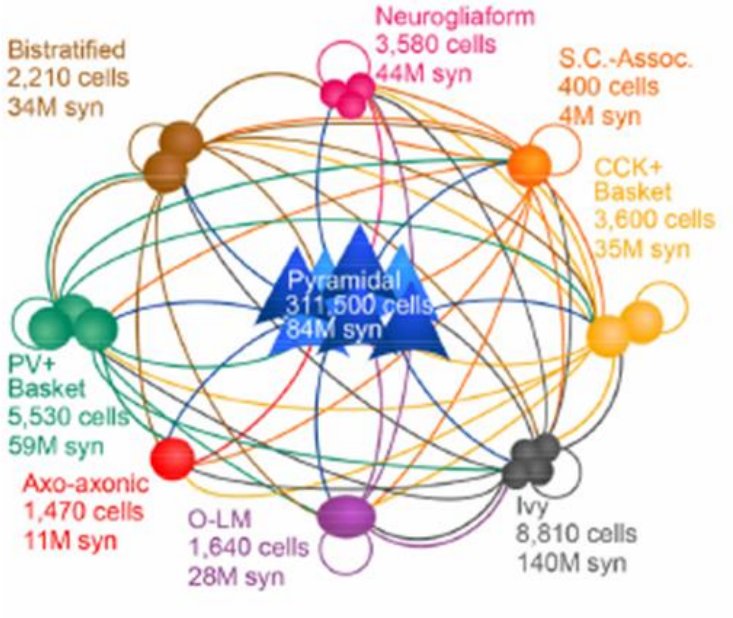
CA3 network

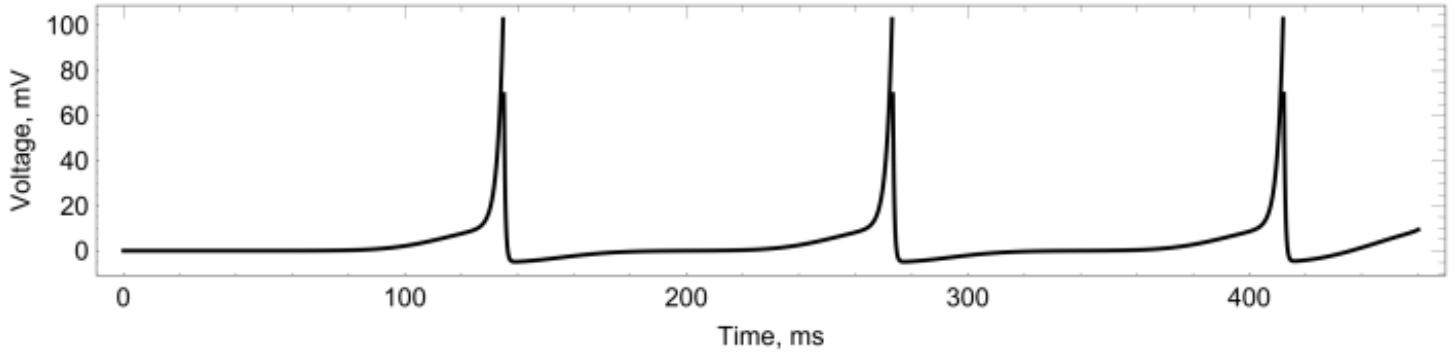


CA1 network

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

Mathematical description of neural network elements





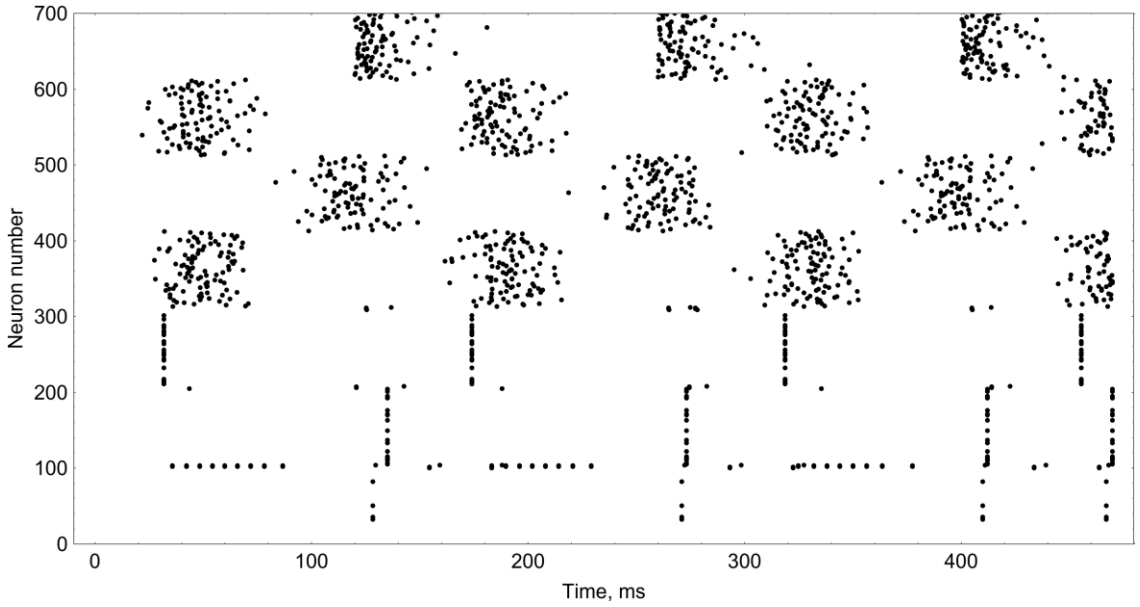
$$C\frac{dV_p}{dt} = g_{Na}m_p{}^3h_p(E_{Na}-V_p)+(g_K n_p^4 + g_{K(A)}a_p b_p)(E_K - V_p)$$

$$+ g_h r_p(E_h - V_p) + g_L(E_L - V_p) + \sum_{p,n,m} g_m(V_p) w_{p,n} s_{n,m}(t)(E_m - V_p) + I_{ext}$$

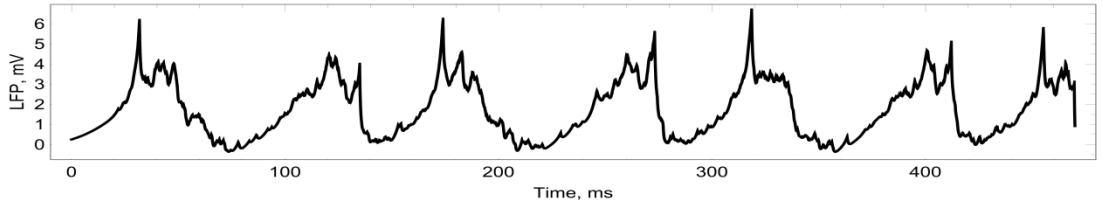
Synaptic connections between neurons

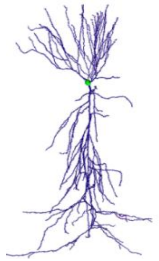
$$\frac{ds_i}{dt} = \rho(V_i)\frac{1-s_i}{\tau_R} - \frac{s_i}{\tau_D}$$

Neural network electric activity

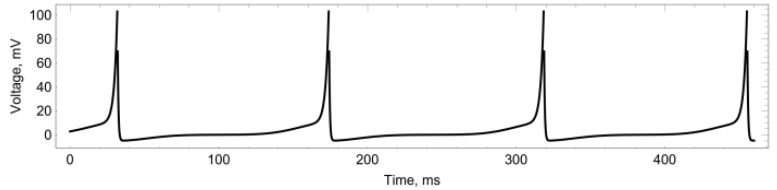


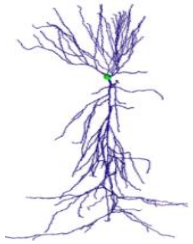
Integral signal (theta-rhythm)



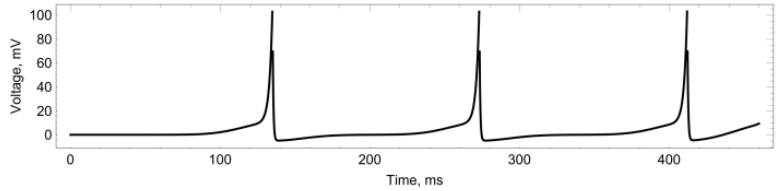


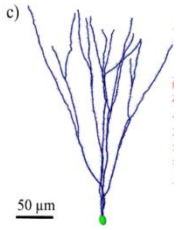
Pyramidal neuron CA1



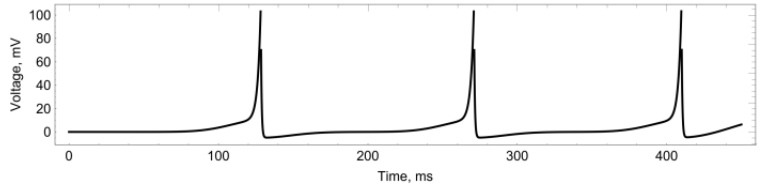


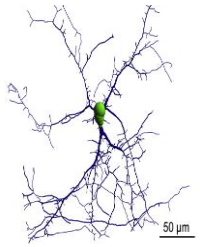
Pyramidal neuron CA3



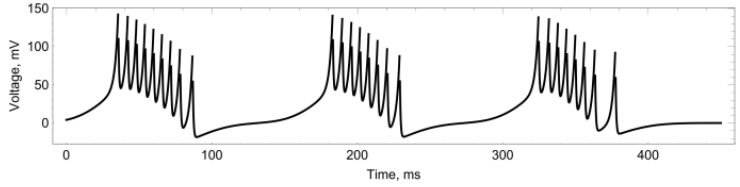


Granular cell



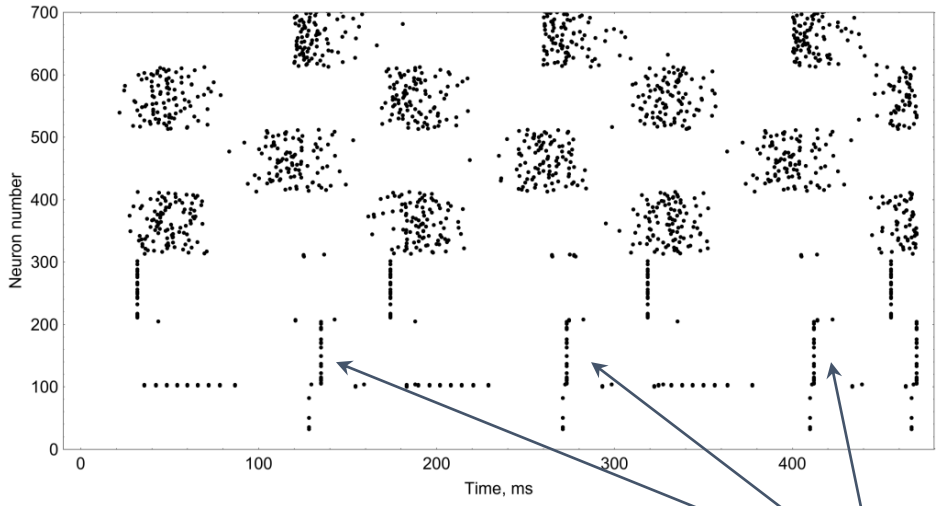


Basket cell

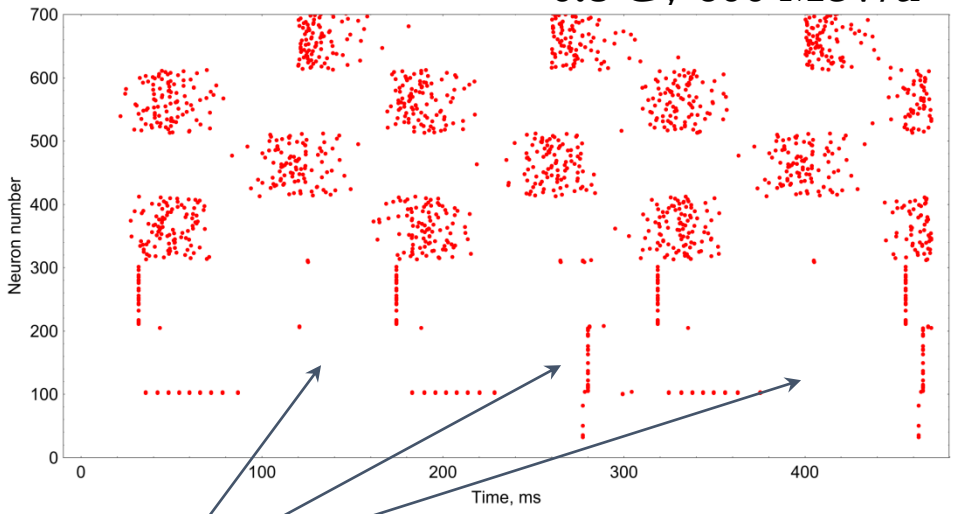


Influence of immature cell loss on information processing

Control

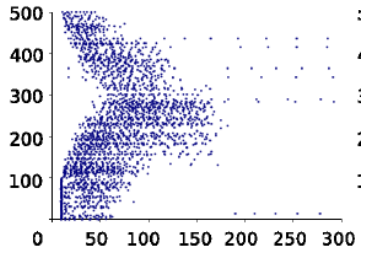


0.8 Gy 600 MeV/u ^{56}Fe

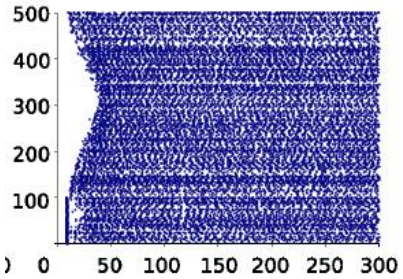


Encoded patterns

10% of newborn GC

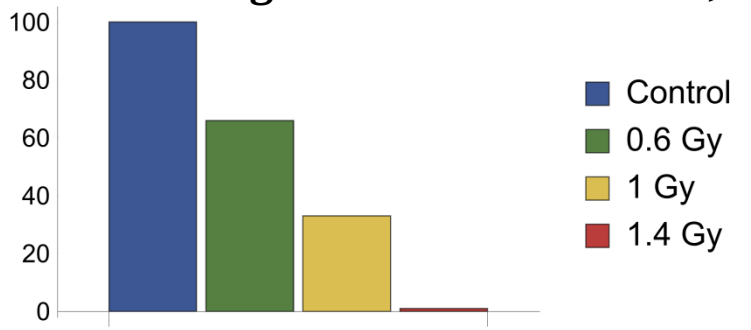


50% of newborn GC



Local effect of immature neuron loss

Encoding and retrieval success, %



Summary

✓ **Cell culture simulations**

+ direct/indirect DNA lesions
+ repair/misrepair (kinetics, effect of inhibitors, mutations)
+ cell survival (e.g. computation of α, β values)

○ **Tissue effects**

± empiric models (lack of data for new protocols)
± detailed models of tumor growth (semi-empiric, extremely high computation power)
- detailed models of normal tissue damage (strongly depends on tissue, hard to verify)

– **Organism level**

– **Translation from rodents to human**



Thank you for the attention!