High Performance Computing in Radiation Biology

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JINR Life Science Program: Basic and Applied Research

Laboratory of Radiation Biology

- **Fundamental Radiobiology**
- **Radiation Neuroscience**
- **Clinical Radiobiology**
- **Mathematical Modeling**
- **Radiation Research**
- **Astrobiology**

Infrastructure for molecular, cellular and animal research

Dzhelepov Laboratory of Nuclear Problems

- Proton therapy of cancer
- Genetics
- Detectors and Tomography

Veksler and Baldin Laboratory of HEP

- Heavy ion beamlines for space radiobiology, technologies for beam therapy

Frank Laboratory of Neutron Physics

- Analysis in the structural biology and pharmacology
- Ecology

Mecheryakov Lab. of Information Technologies

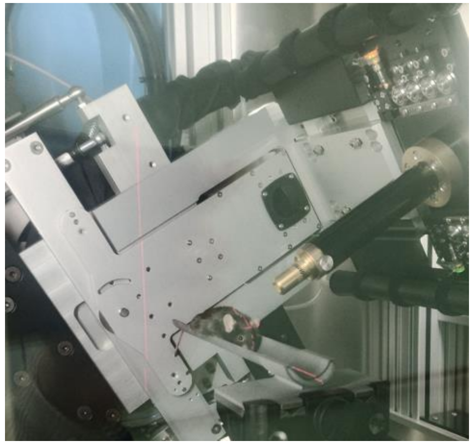
- High performance computing
- System for biological data storage and processing
- Bioinformatics, Machine Learning

Flerov Laboratory of Nuclear Reactions

- Ion beams for cellular research
- Radionuclides synthesis for radiation medicine

Research Infrastructure for Irradiation of Biological Samples

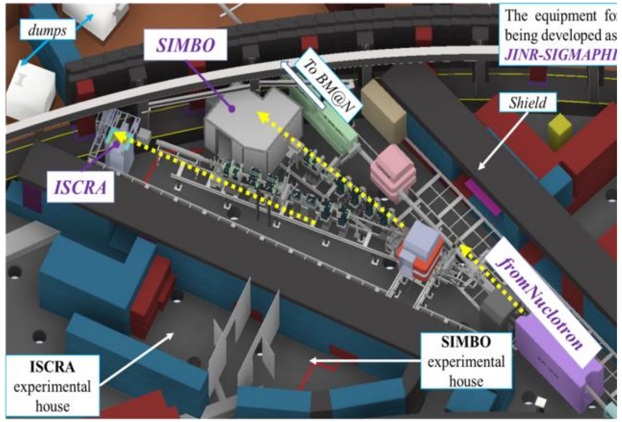
SARRP X-ray



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

Genom-3

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

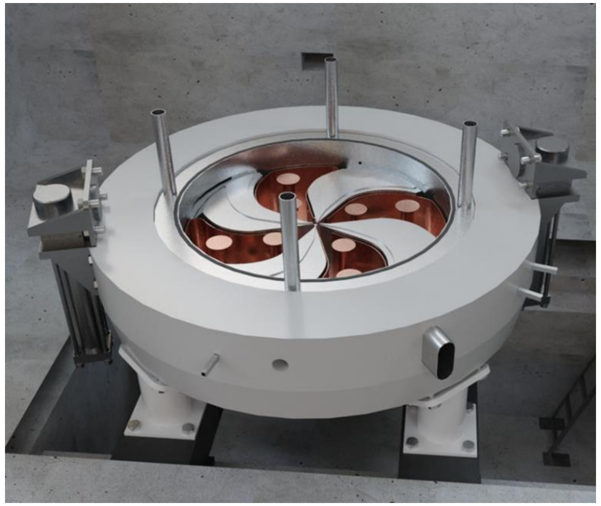


ARIADNA beamlines

SIMBO

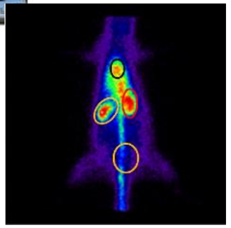
Linac200
electrons 20-200 MeV

new MSC230 medical cyclotron
protons 230 MeV



IBR-2, EG-5M neutrons

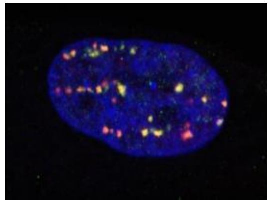
Radiopharmaceuticals



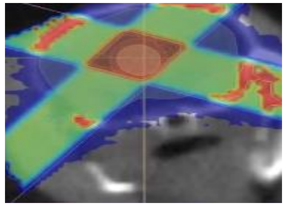
Laboratory of Radiation Biology

1. Establishment of integrative interrelations of **radiation-induced effects at different levels** of biological organization:
2. Identification of the mechanisms of the **radiations effects on brain** and the development of neurodegenerative diseases.
3. Assessment of **radiation risks** for various scenarios of manned space flights and mixed radiation fields of nuclear physics facilities.
4. Development of new methods to improve the **effectiveness of radiation and radionuclide therapy** of cancer.
5. Development of **new mathematical models** and computational approaches for radiobiology, bioinformatics, and radiation medicine.
6. Identification of mechanisms and pathways of **catalytic synthesis of prebiotic compounds** under the action of radiation.
7. Development of **new research protocols**, including omics technologies, bio-imaging, automated processing of biological data.

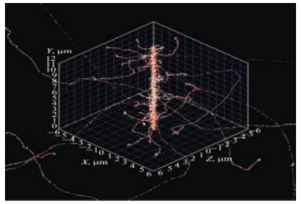
Molecular Radiobiology



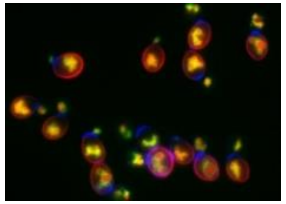
Clinical Radiobiology



Mathematical Modeling



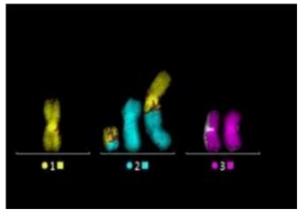
Radiation Genetics



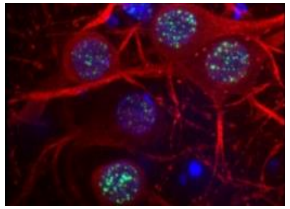
Radiation Physiology

Radiation Protection

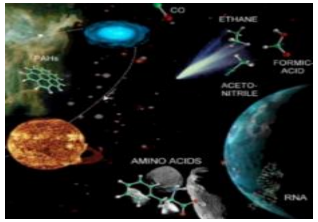
Radiation Cytogenetics



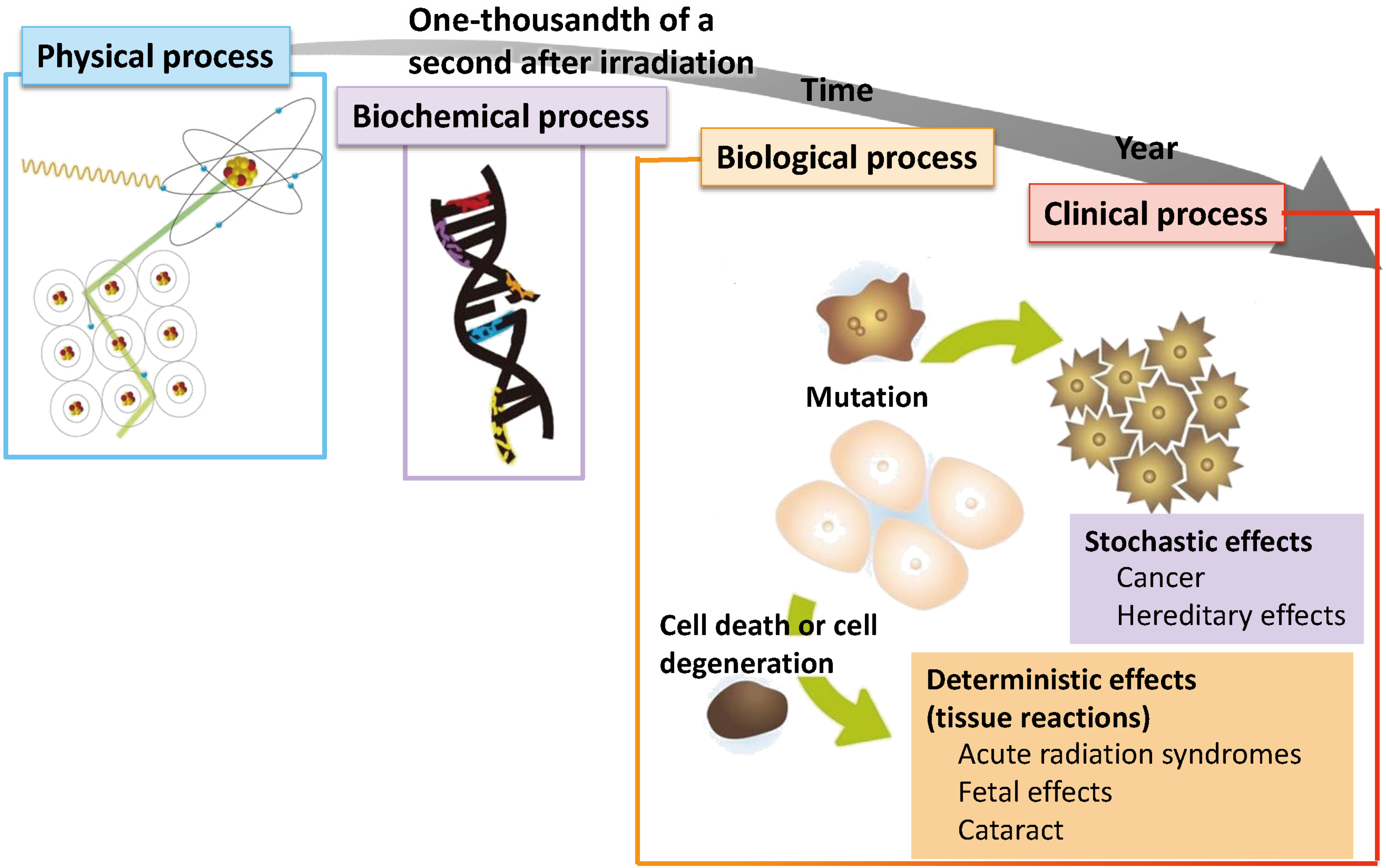
Radiation Neuroscience



Astrobiology

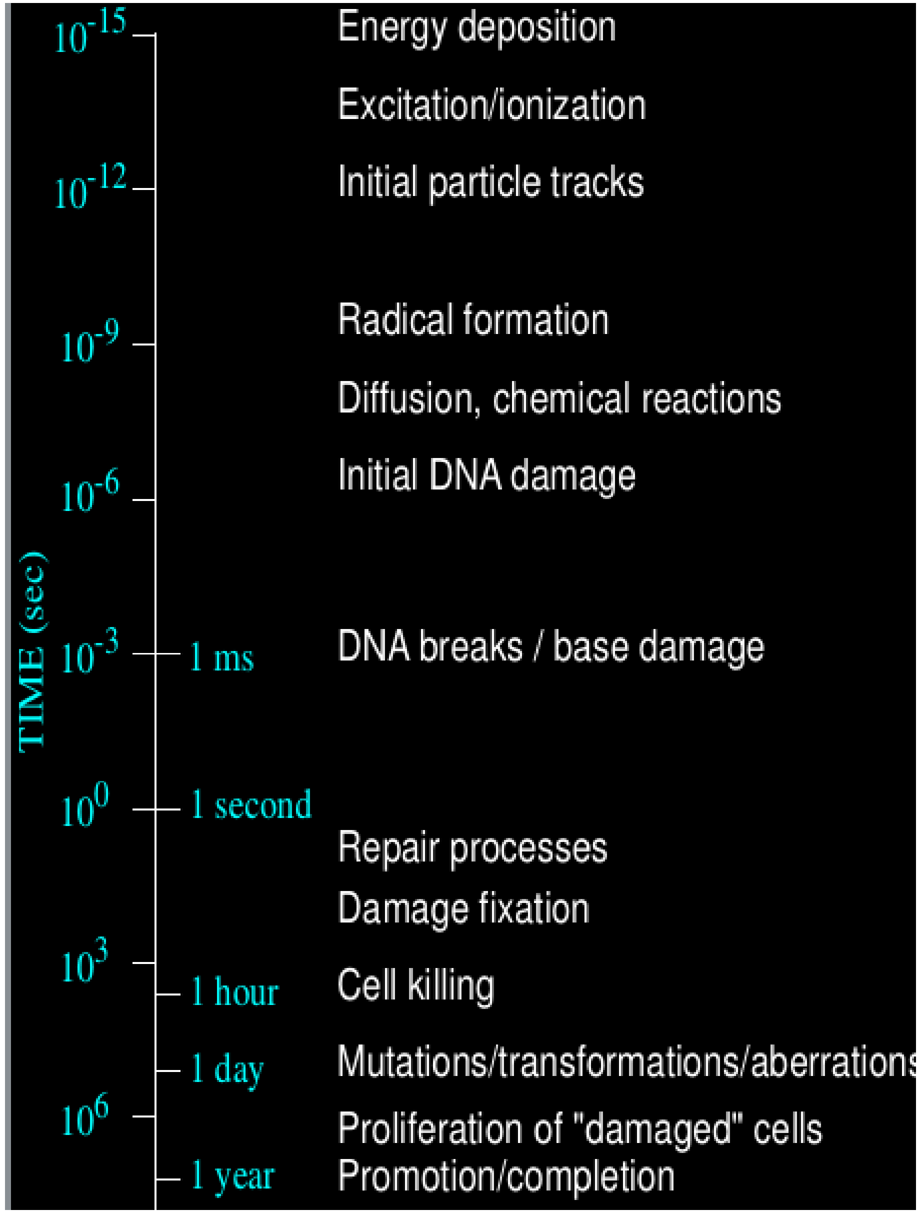


http://lrb.jinr.ru



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

Hierarchy in modeling the response to radiation



Monte Carlo simulations

GEANT4-DNA
A SIMULATION TOOLKIT

Molecular dynamics

NAMD
Scalable Molecular Dynamics

AMBER

Nonlinear dynamical systems

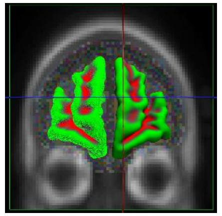
Wolfram Mathematica
MATLAB

PDE, neural networks, cellular automata …

Estimating final effect

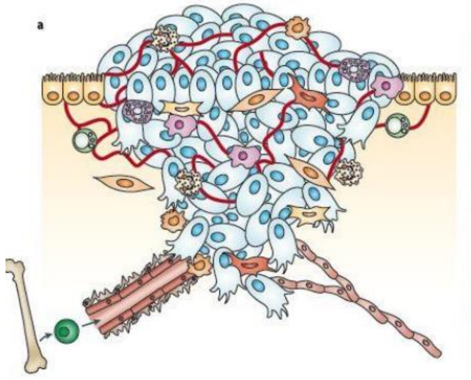
Radiation neuroscience:

Brain neural networks



Clinical radiobiology:

Complex models of tumor growth



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

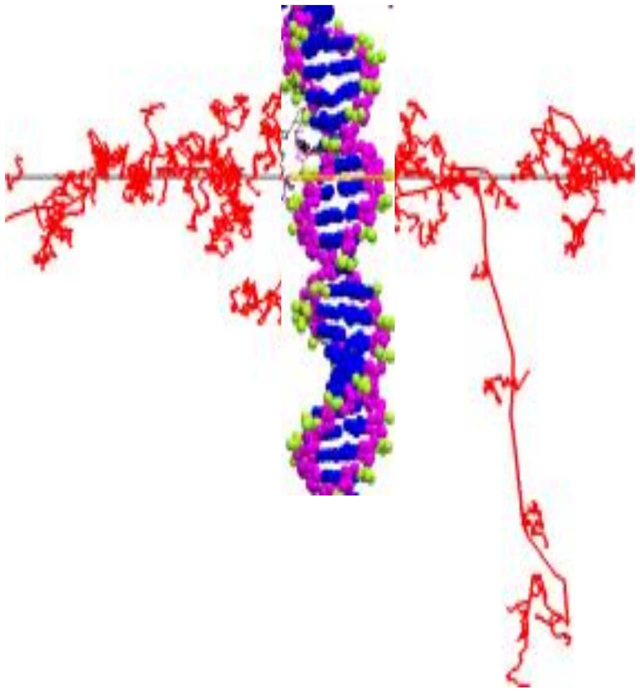
1. **Calculation of DNA damage formation**

2. **Models of DNA DSB repair and misrepair**

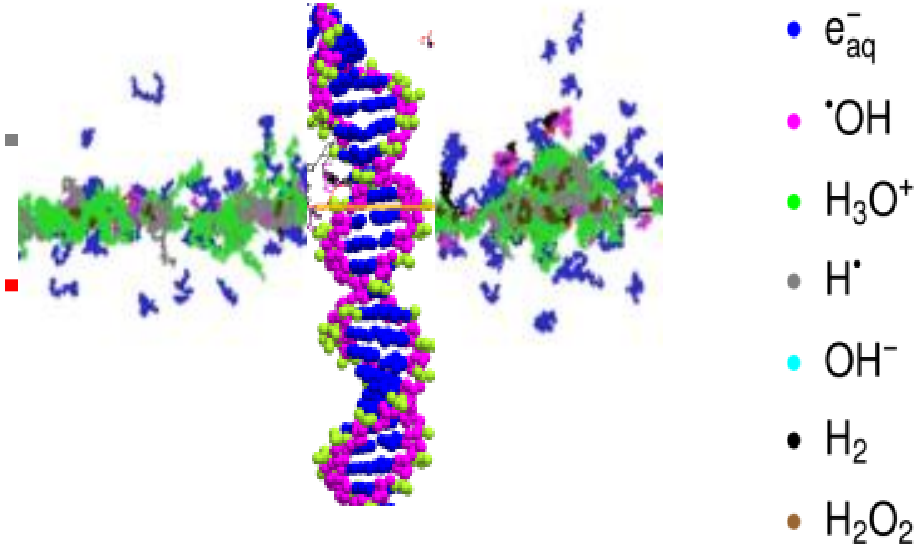
3. **Cell survival** ⇔ $\alpha = ?$ $\beta = ?$

1. Monte Carlo simulation of radiation-induced DNA damage

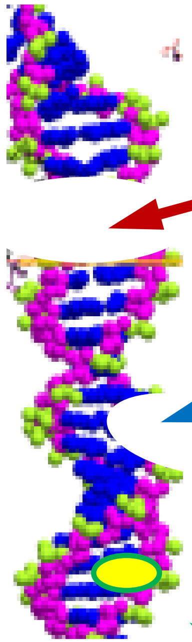
Ionization, bond breakage



Radical attack, indirect lesion



DNA lesions



Double strand break (DSB)

Single strand break (SSB)

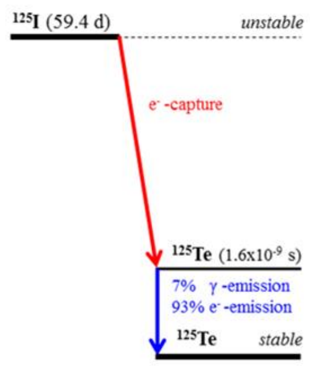
Base damage (BD)

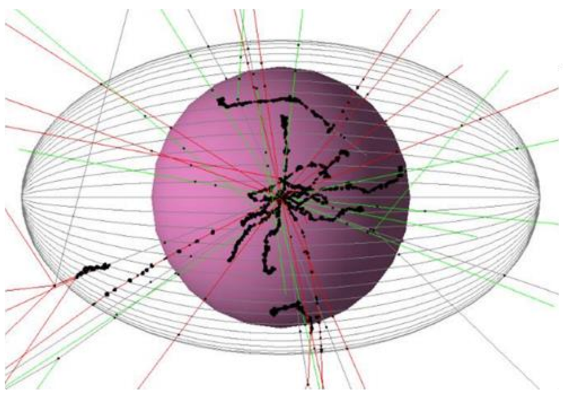
Apoptosis, chromosome aberrations, mitotic catastrophe, cell death

Methodology of simulation on example of Geant4-DNA

Physical events

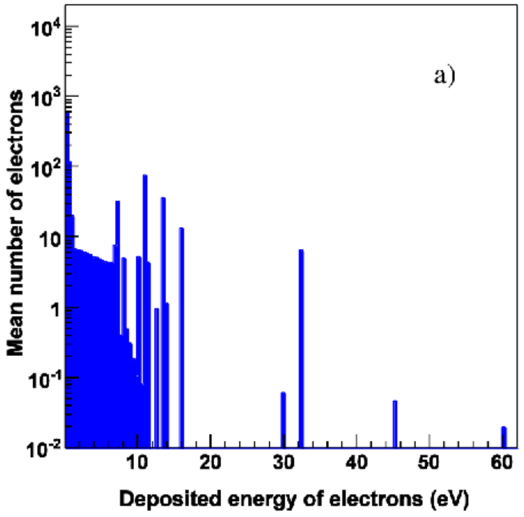
Particle	Interaction	Model
e^-	**ionization** ≥ 1МэВ 10 кэВ – 1 МэВ 10 эВ – 10 кэВ	(*Med. Phys. 2010*) Moller-Bhabha Born Emfietzoglou
	excitation 10 кэВ – 1 МэВ 8 эВ – 10 кэВ	(*Med. Phys. 2010*) Born Emfietzoglou
	elastic scattering 0.025 эВ – 1 МэВ	(*Rad. Phys. 2009*) Champion
^{1}H, ^{4}He, ^{7}Li, ^{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

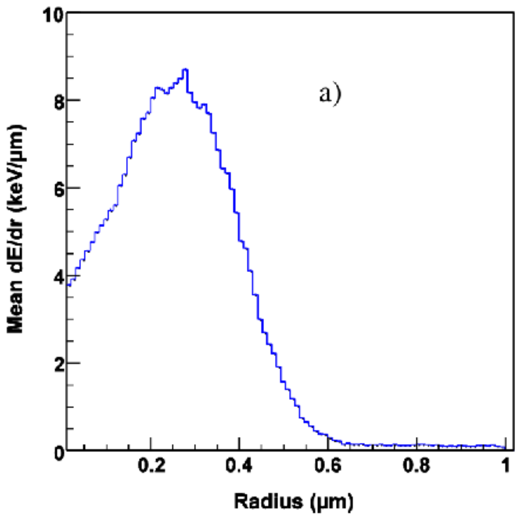




^{125}I

0,8 Bq/μg





Double strand break probability

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

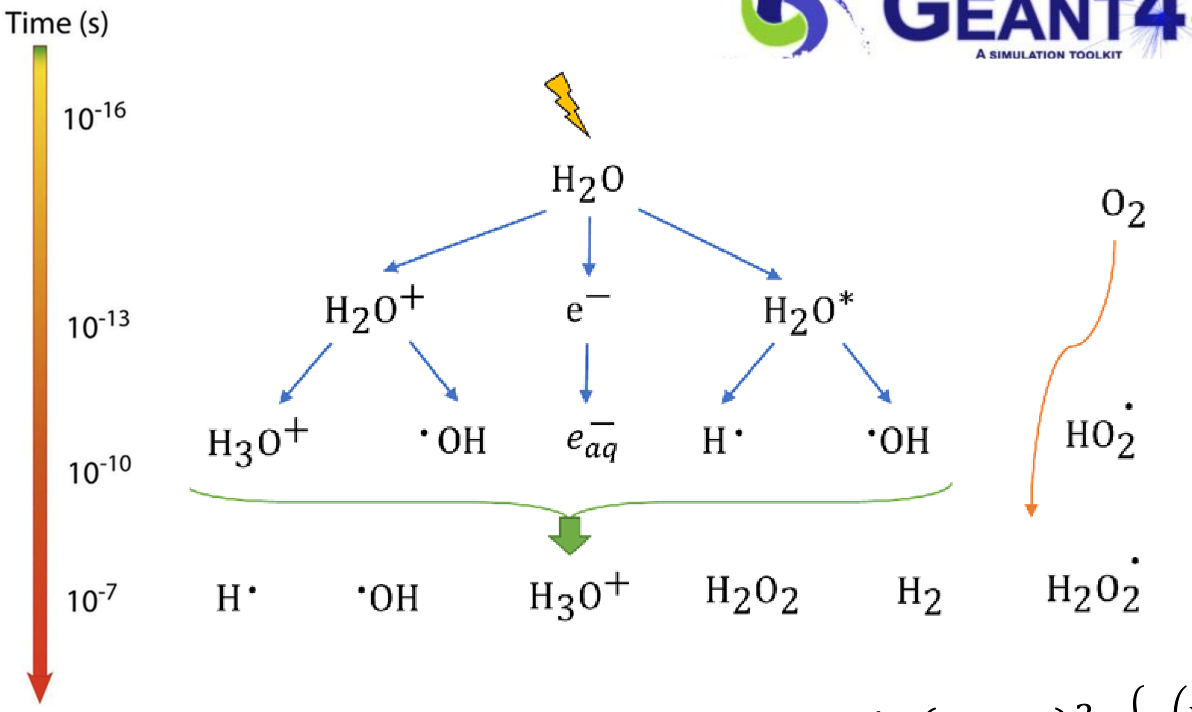
ε – energy deposition in event

ε_0 =8.22– average bond dissociation energy

Methodology of simulation on example of Geant4-DNA

Radiolysis

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



Indirect damage, main reaction channel

$P_{DSB} = 0.65$

DNA + $^\bullet$OH → **(DNA)$^\bullet$**

Oxygen-dependent reaction channel1

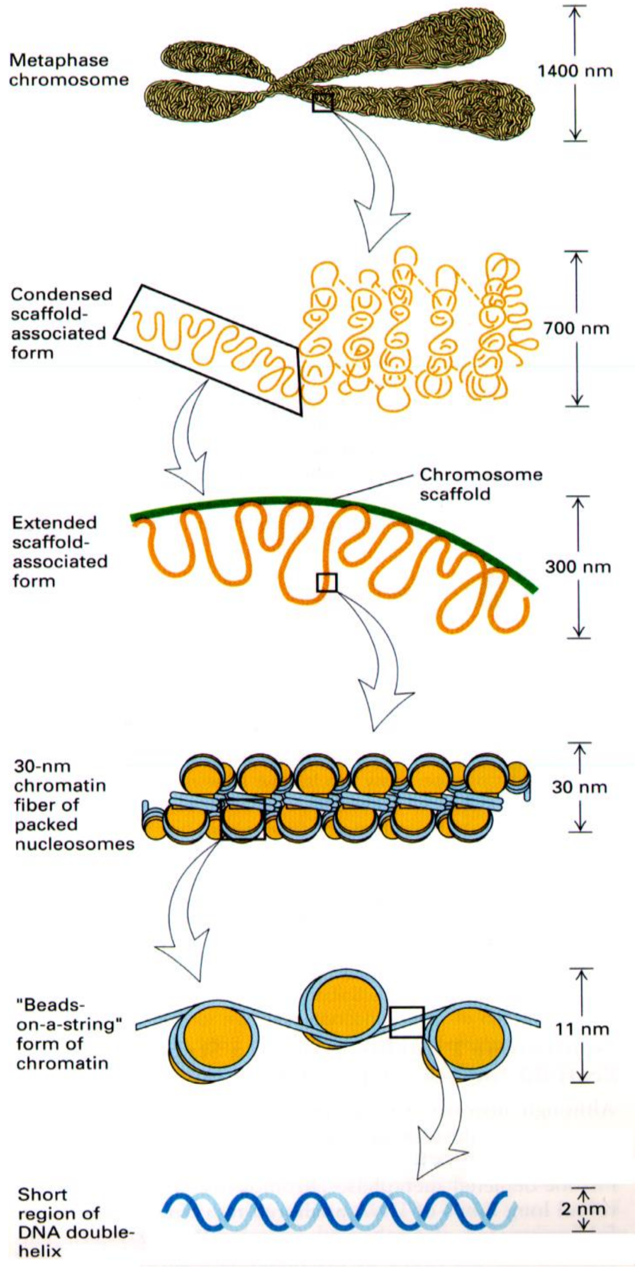
(DNA)$^\bullet$ + $[O_2]$ → (DNA)OO$^\bullet$

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

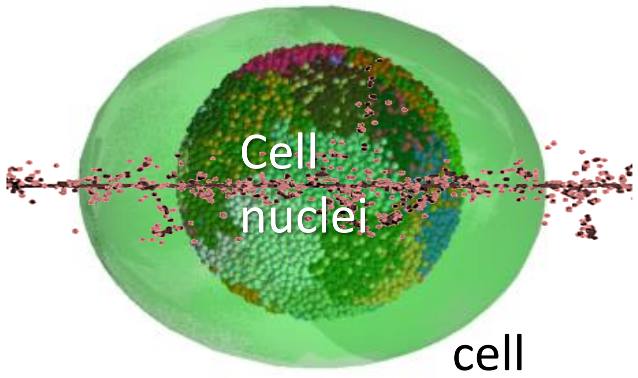
Reaction A+B occurs if $R_{AB} \le R_e$

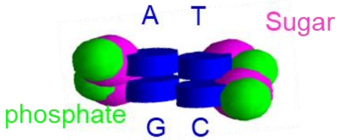
where $R_e = \dfrac{k}{4\pi N_A(D_A + D_B)}$ *or* $R_e = R_c/(e^{R_c/R_{AB}} - 1)$

Methodology of simulation on example of Geant4-DNA

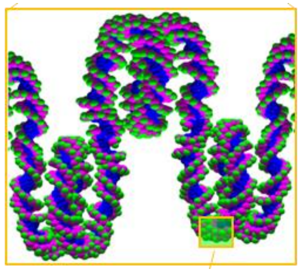


Geometry of sensitive target

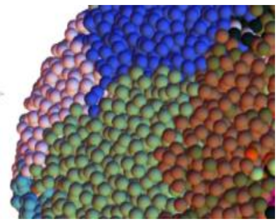




nucleoside



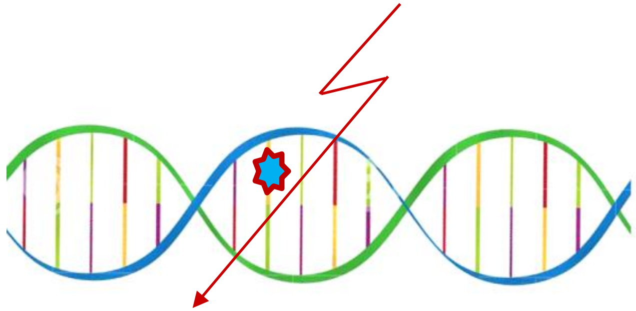
DNA in chromatin



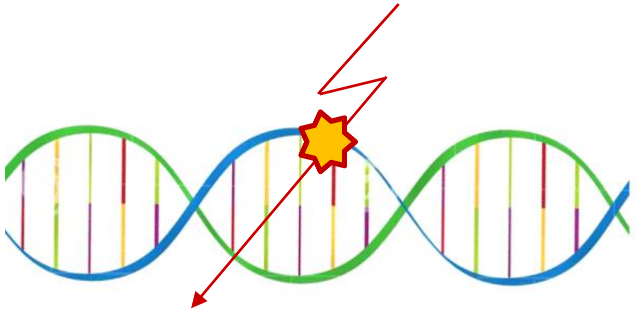
Chromosome domains

GEANT4-DNA A SIMULATION TOOLKIT

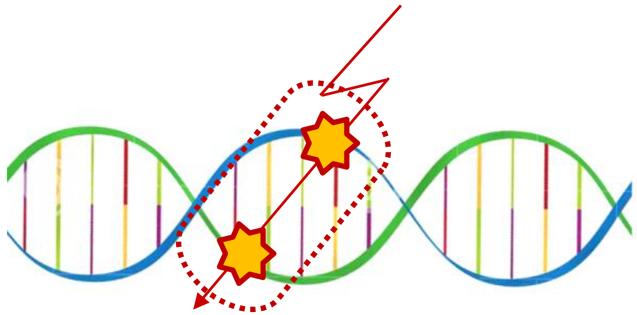
Counting DNA lesions



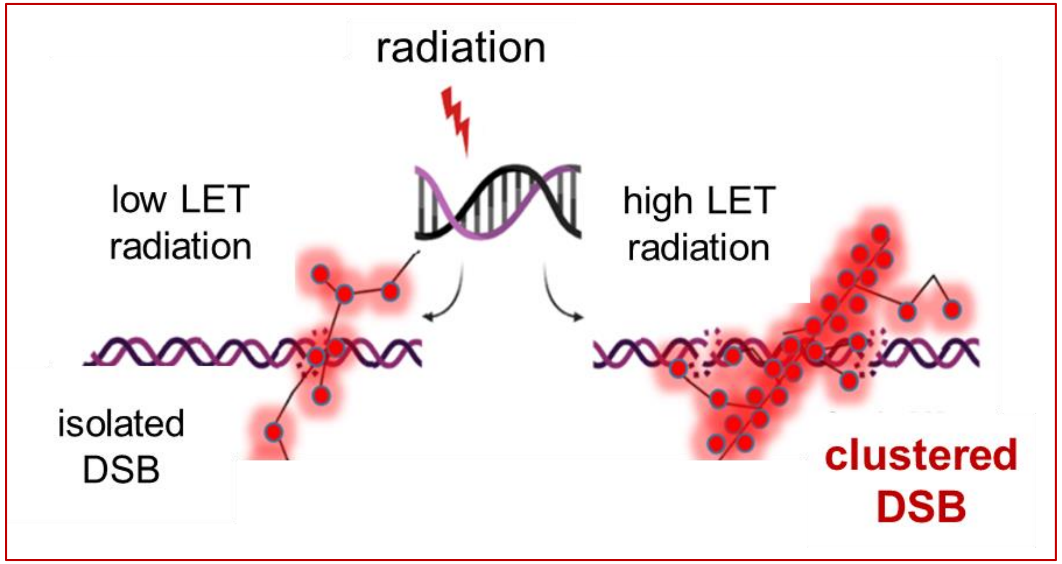
Base damage (BD)



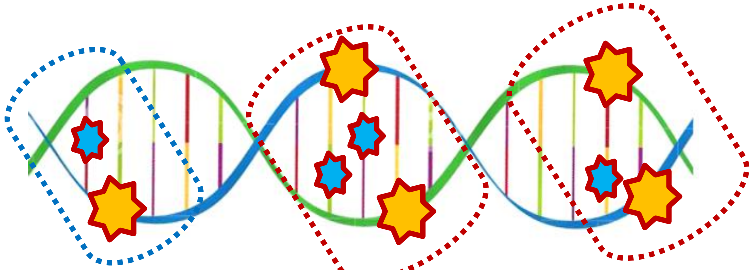
Single stand break (SSB)



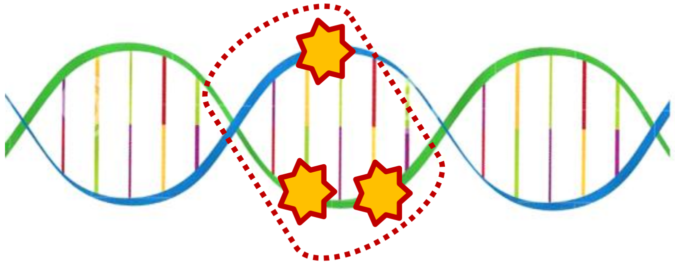
Double strand break (DSB)



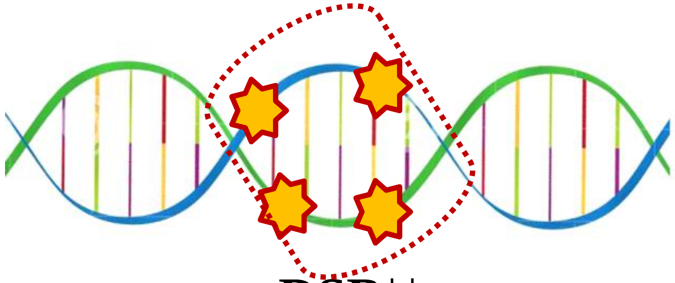
Complex and clustered damage (size < 10 bp)



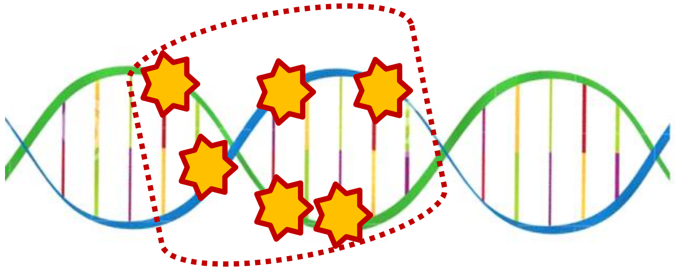
SSB* **DSB**** **DSB***



DSB^{+}

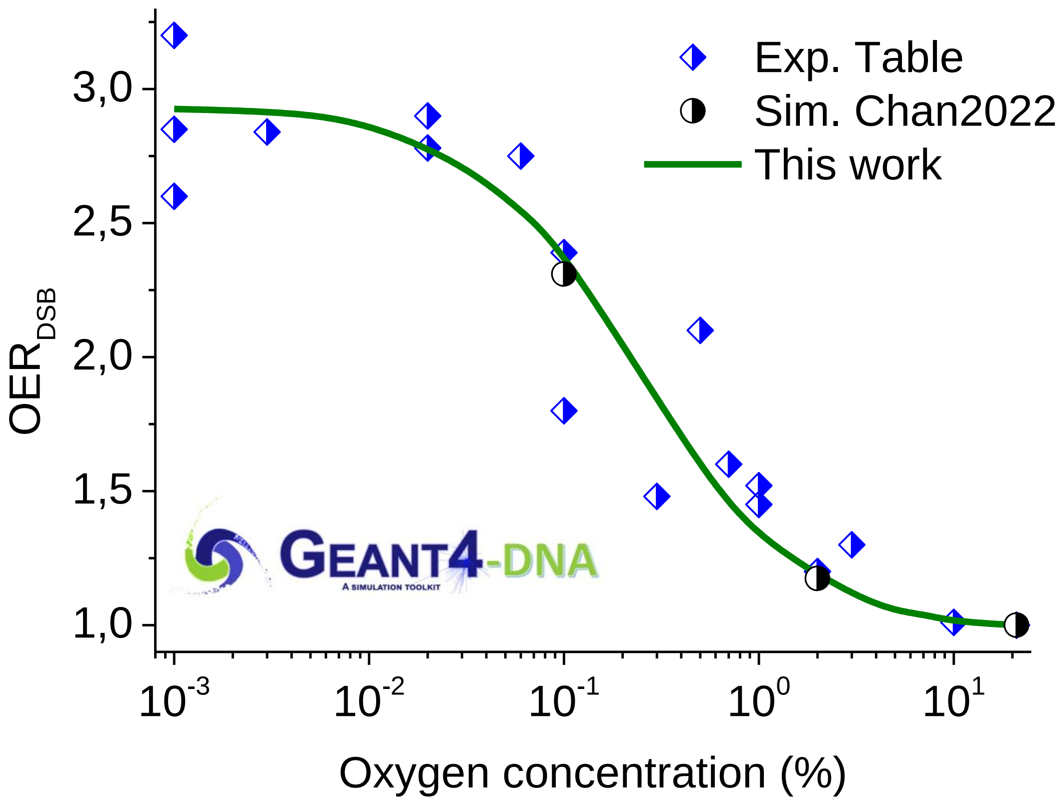


DSB^{++}

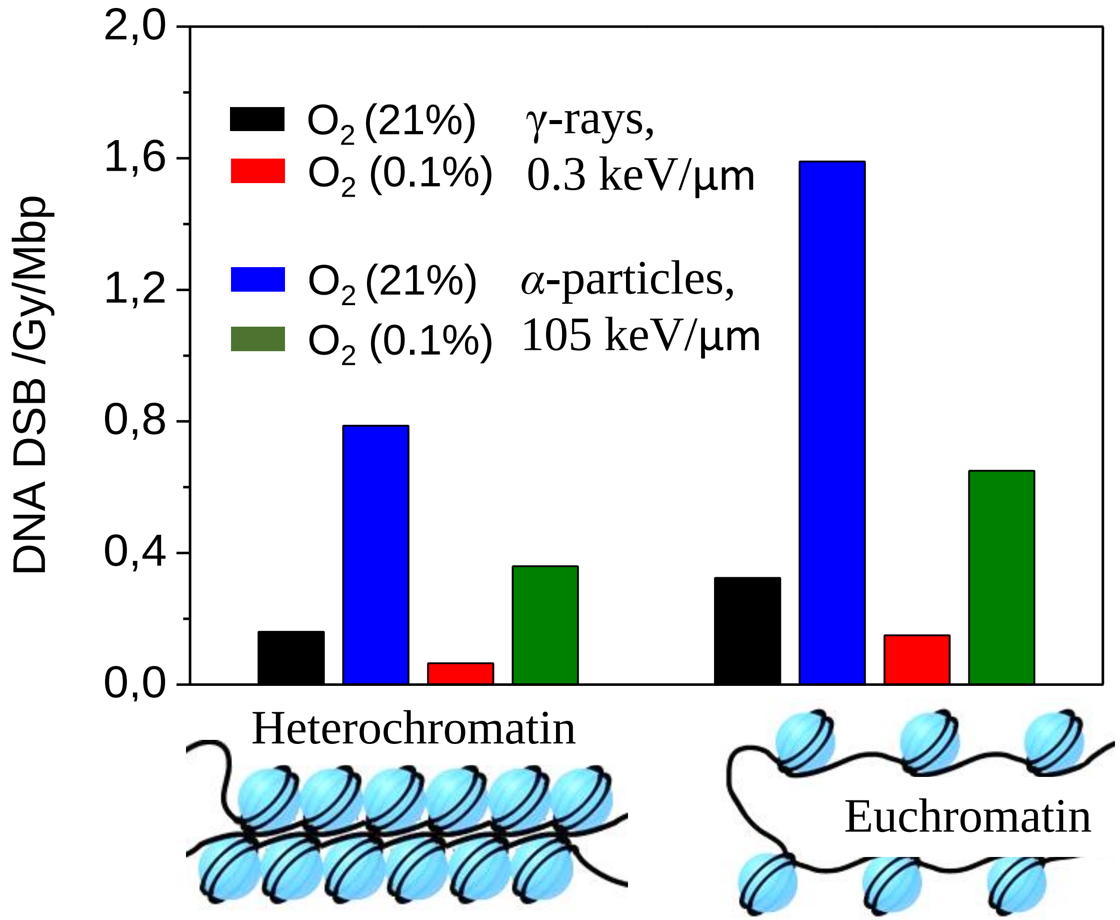


DSB^{++++}

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

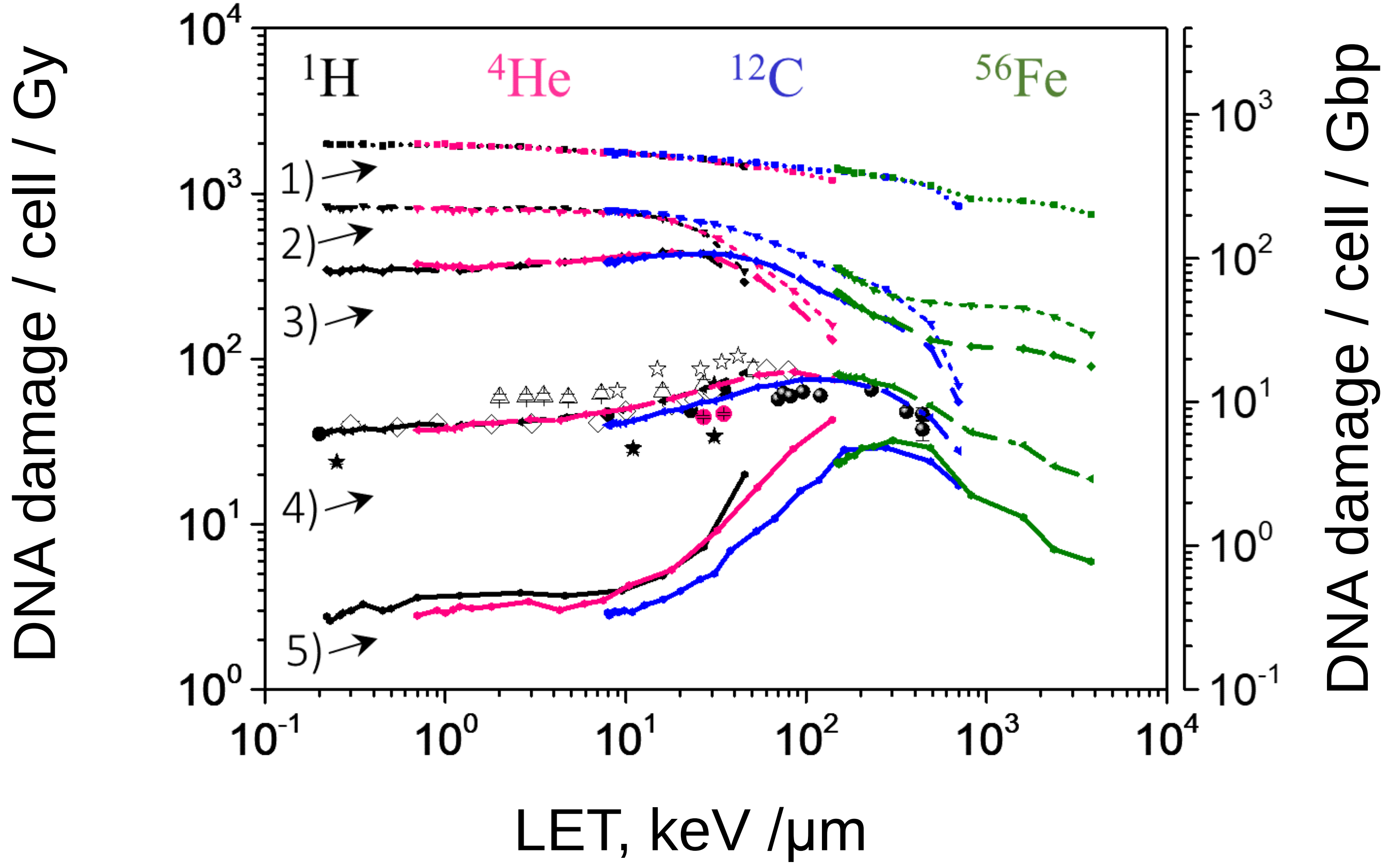
1) DNA base damage (BD)
2) Single strand break (SSB)
3) Clustered SSB
4) Double strand breaks (DSB)
5) Clustered DSB

Experimental data

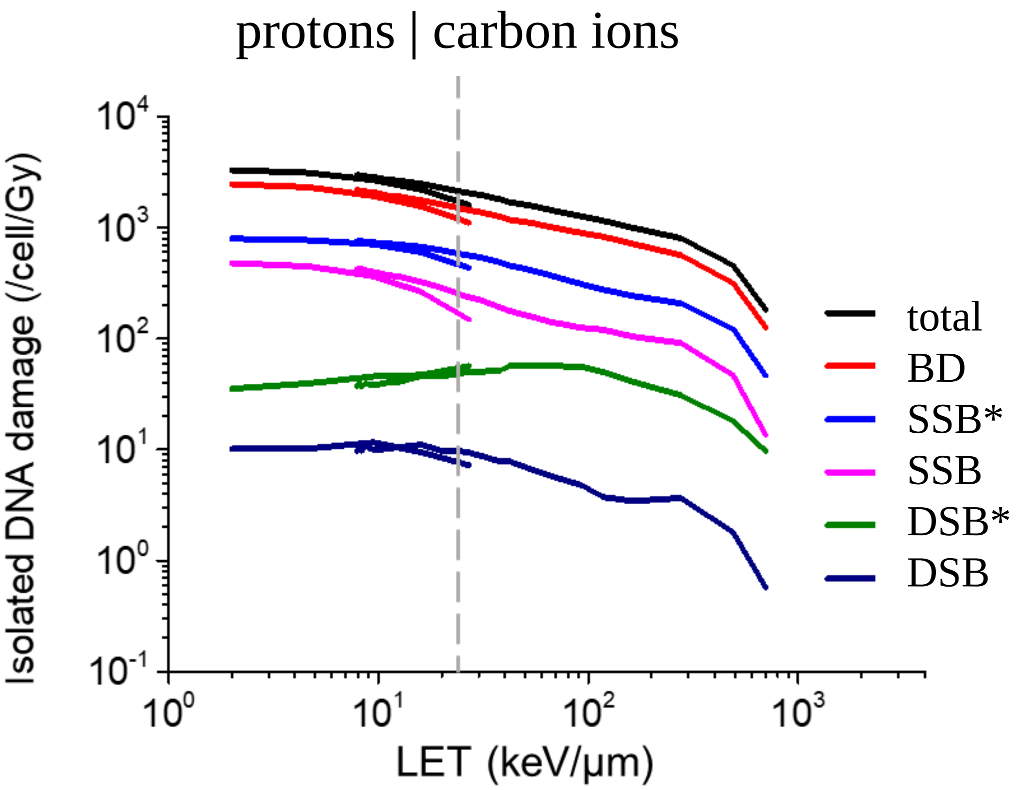
- Frankenberg 1999
- Belli 2001
- Belli 2006

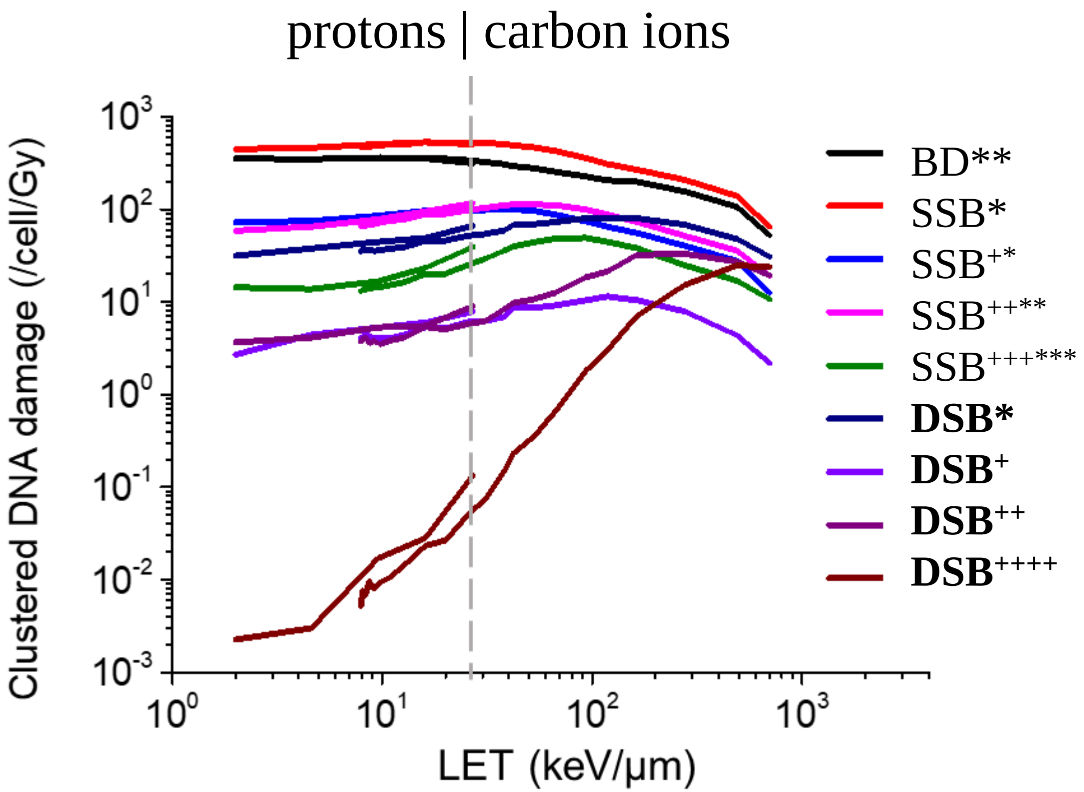
Other simulation codes

- Nikjoo 2001
- Friedland 2011
- Rosales 2018

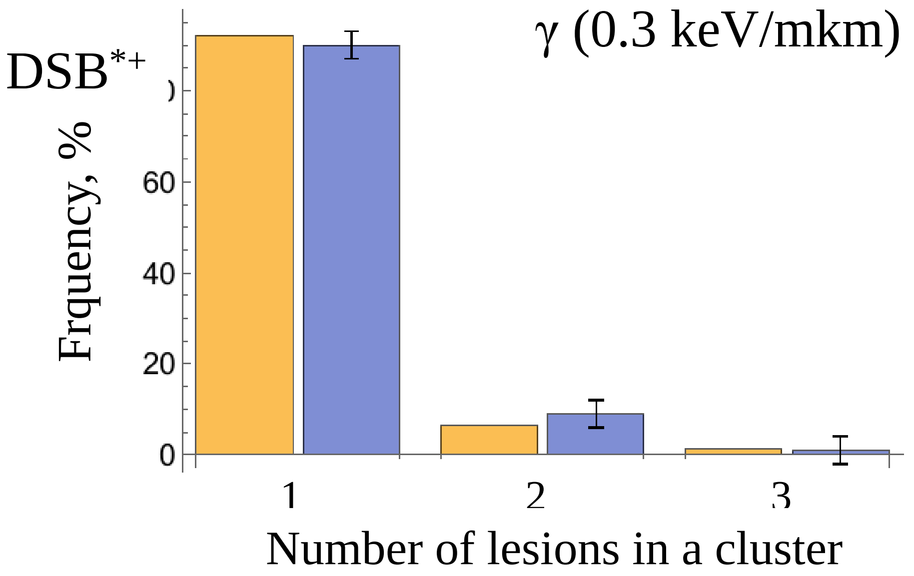


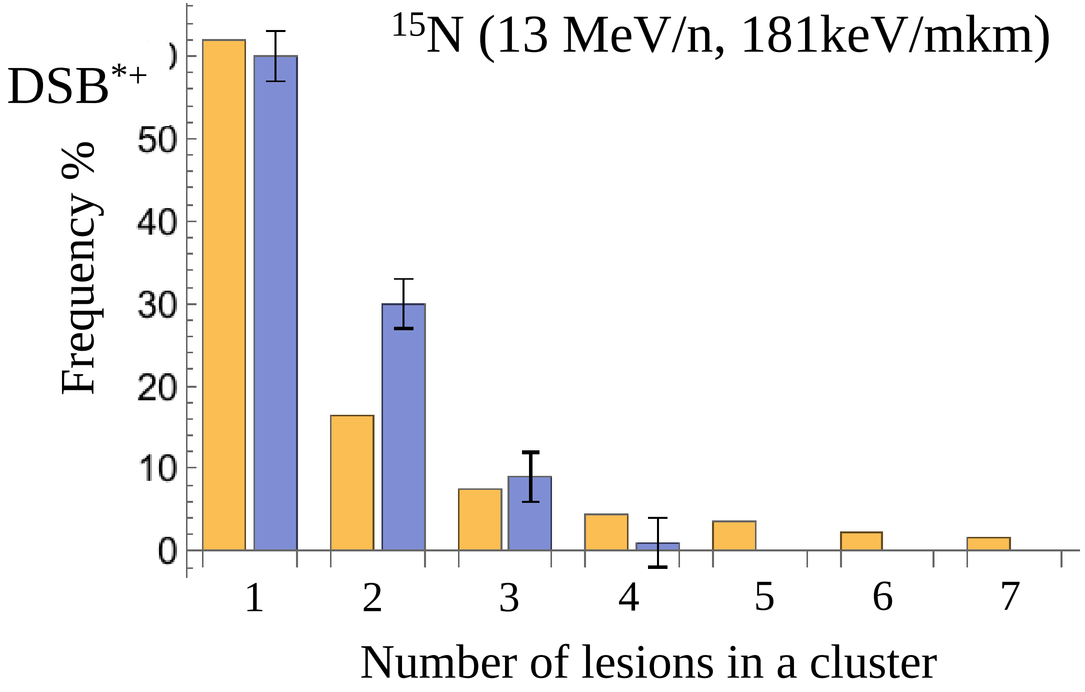
Complexity of clustered DNA damage





Complexity of clustered DNA damage



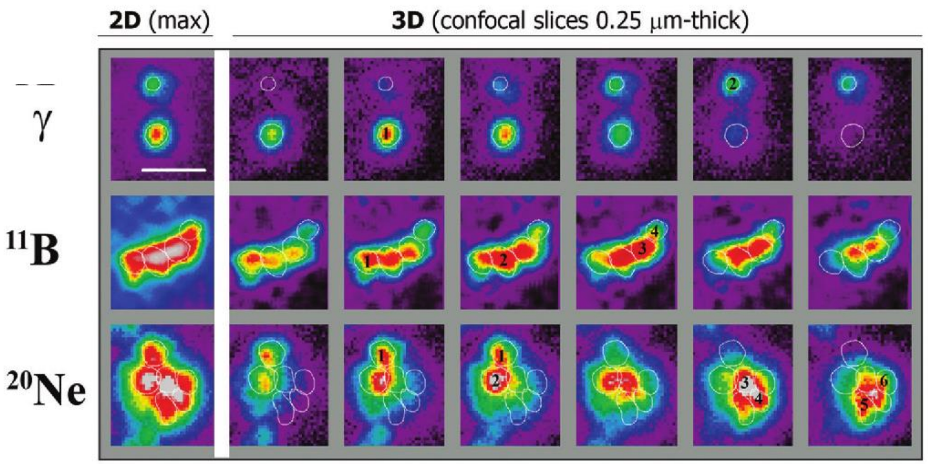


Model

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

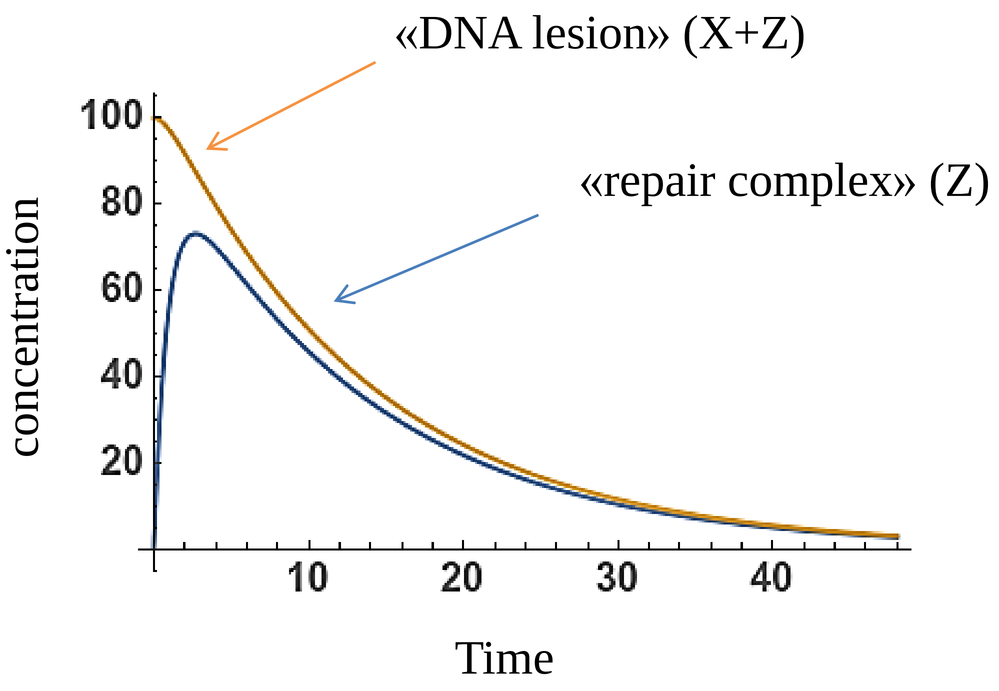
$$X + R \underset{k_-}{\overset{k_+}{\rightleftarrows}} Z \xrightarrow{q} R$$

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

$$X(0) = N_0$$

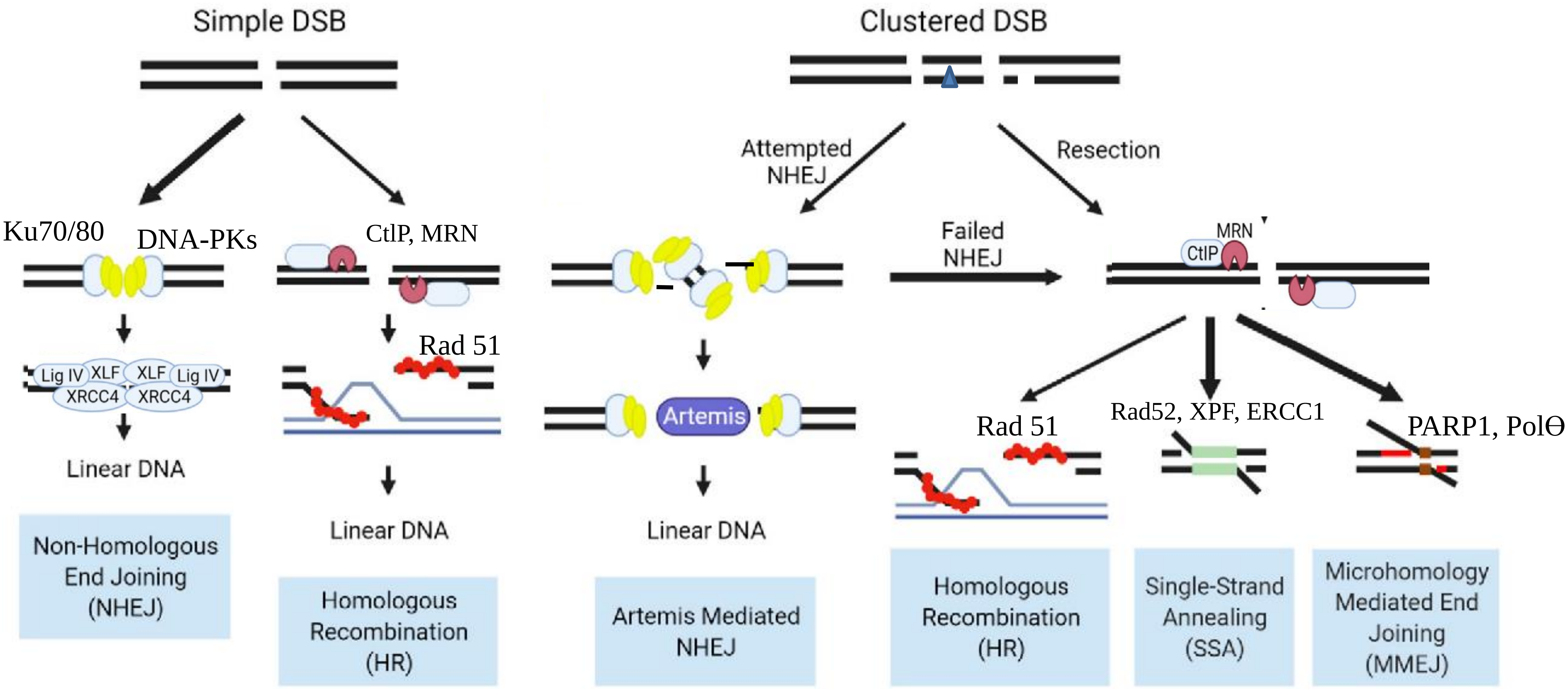
$$R(0) = R_0$$

$$Z(0) = 0$$

4. Determination of parameters

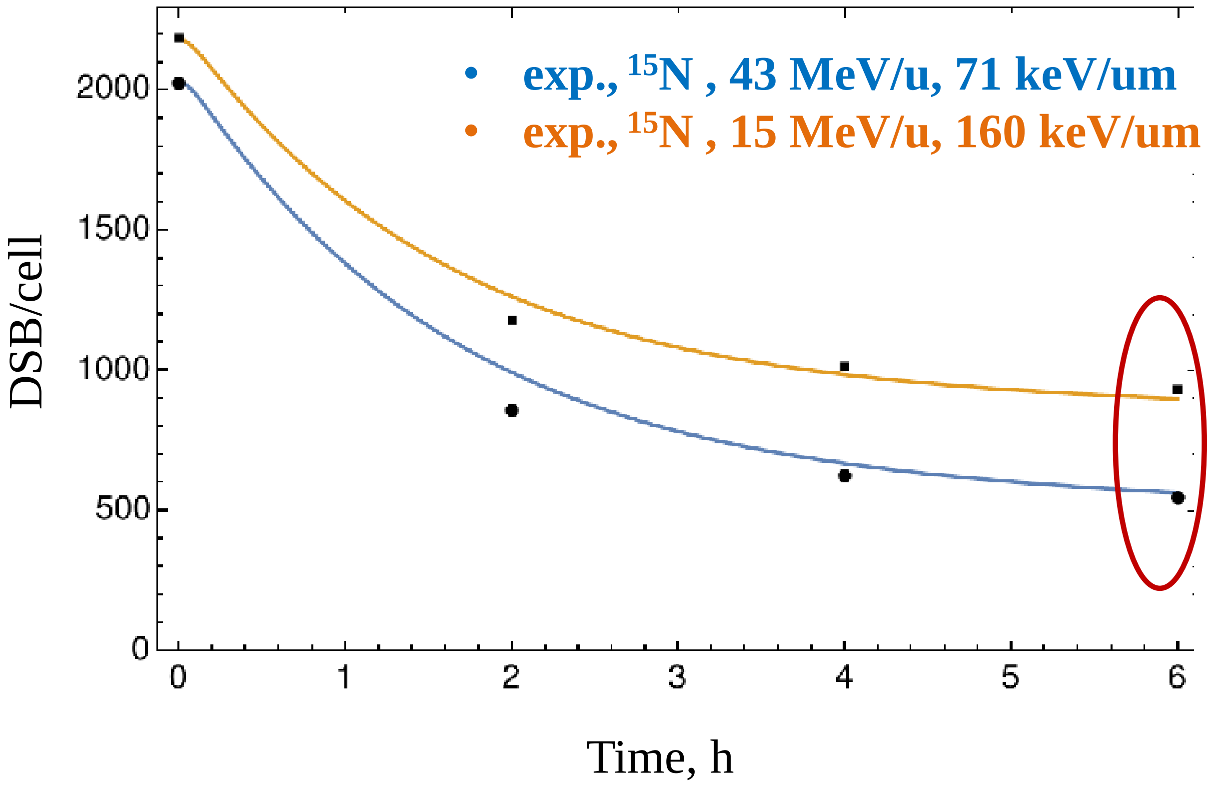
$k_+ \quad k_- \quad q$

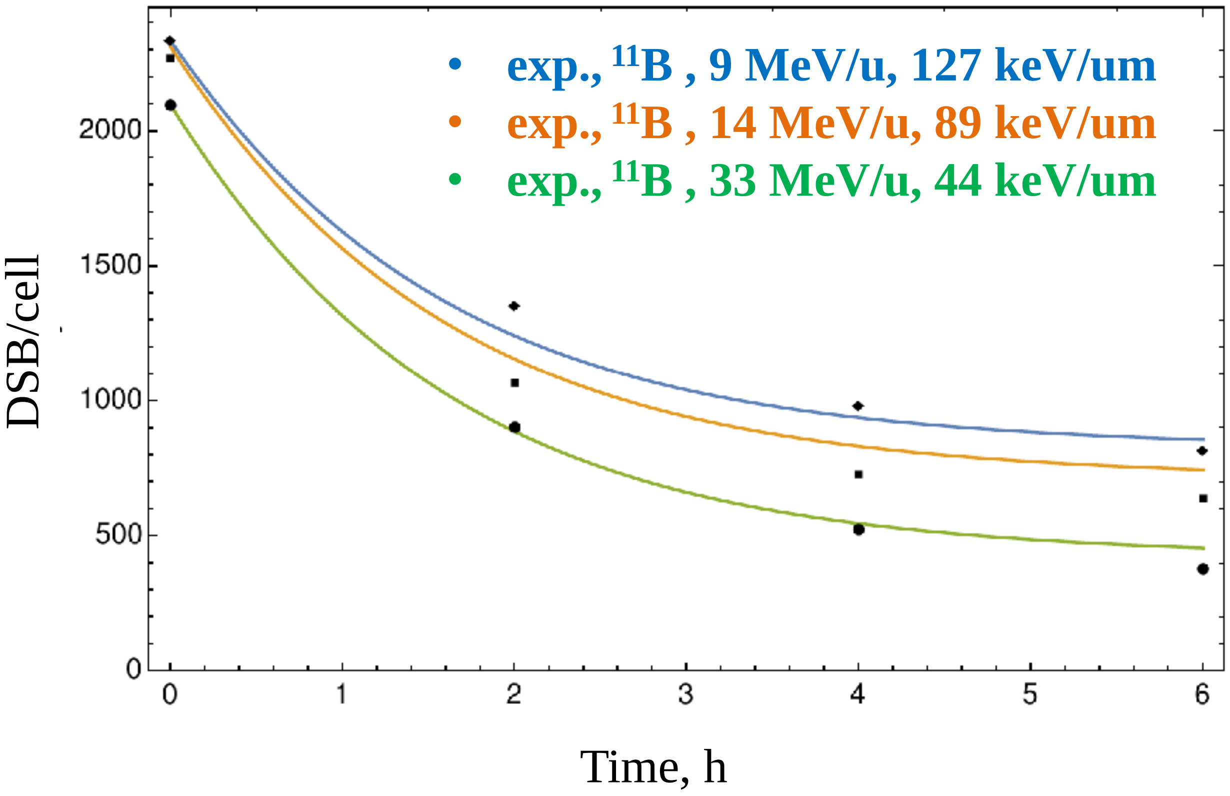
Pathways of DNA double strand break repair



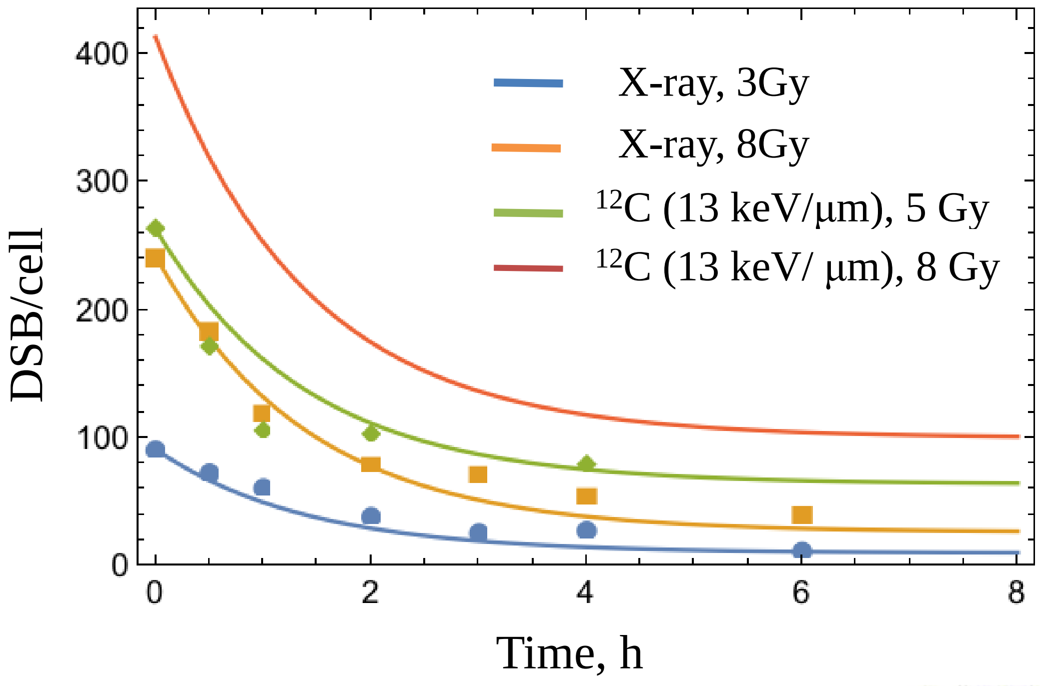
modified from Danforth et al(2022) Front. Cell Dev. Biol. 10:910440.

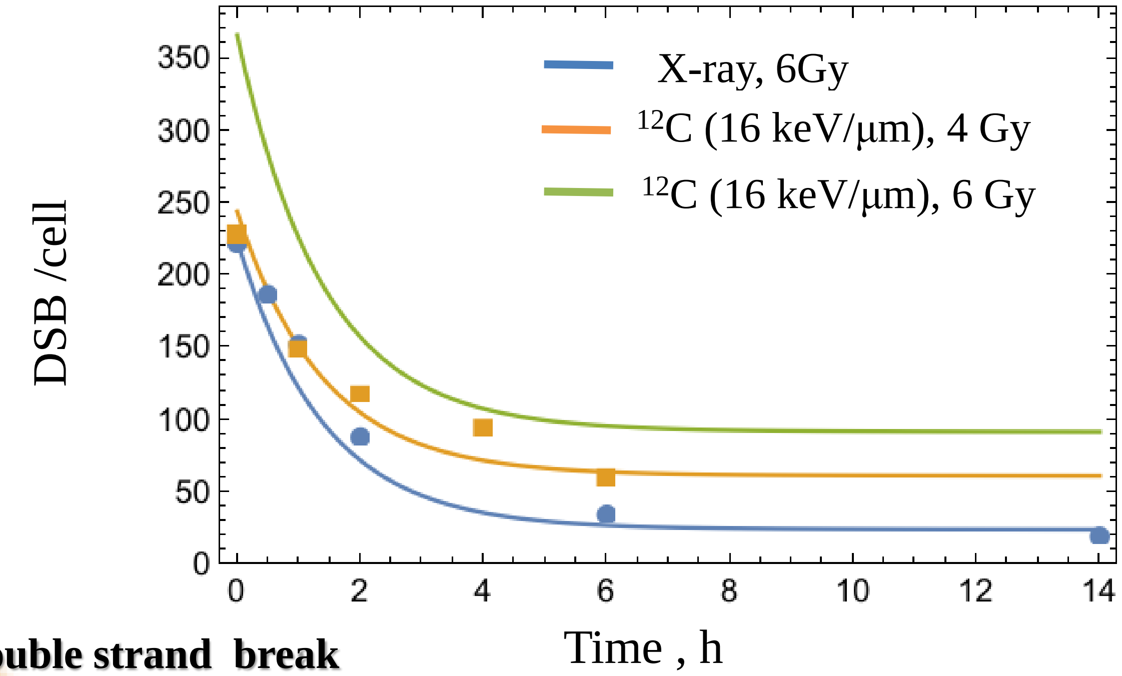
DNA repair modeling

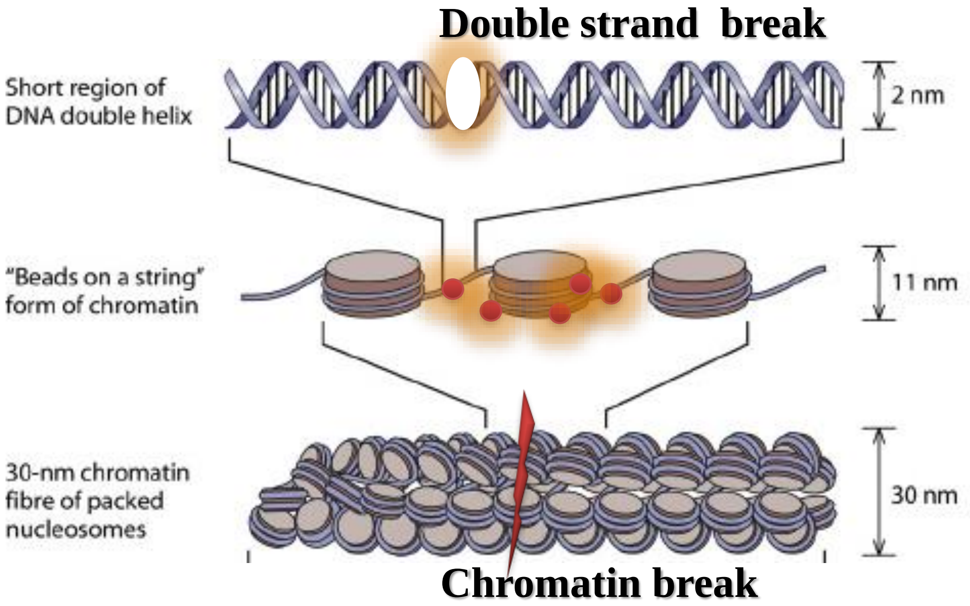




DNA repair modeling: comparison of DSB and chromatin breaks







V79 cells

$$\frac{N_{dsb}}{N_{pcc}} = 10$$

Human fibroblasts

$$\frac{N_{dsb}}{N_{pcc}} = 7.4$$

3. Cell survival modeling

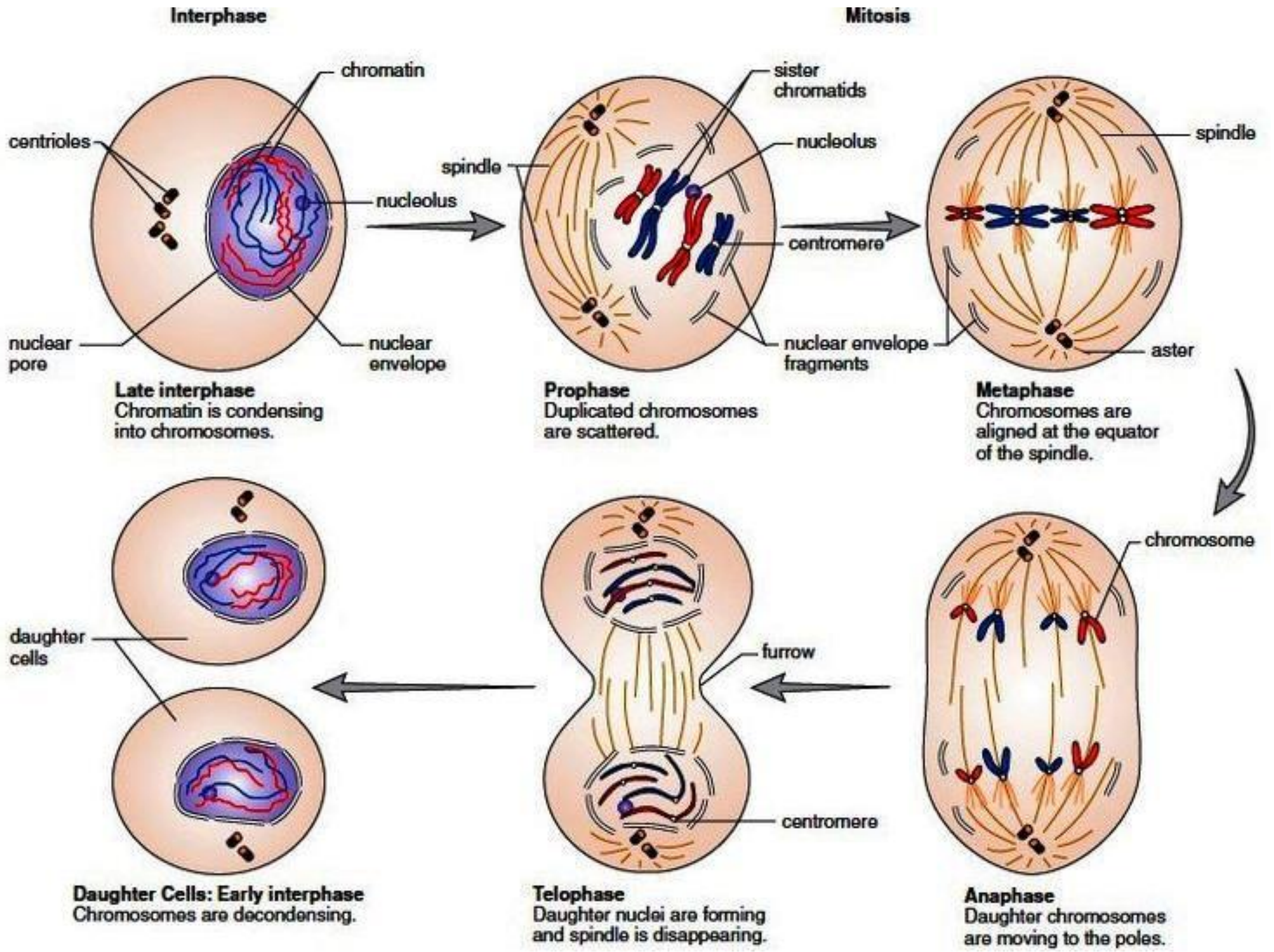
Scheme of cell cycle

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

N - number of DSBs remaining

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

- number of misrepaired DSBs



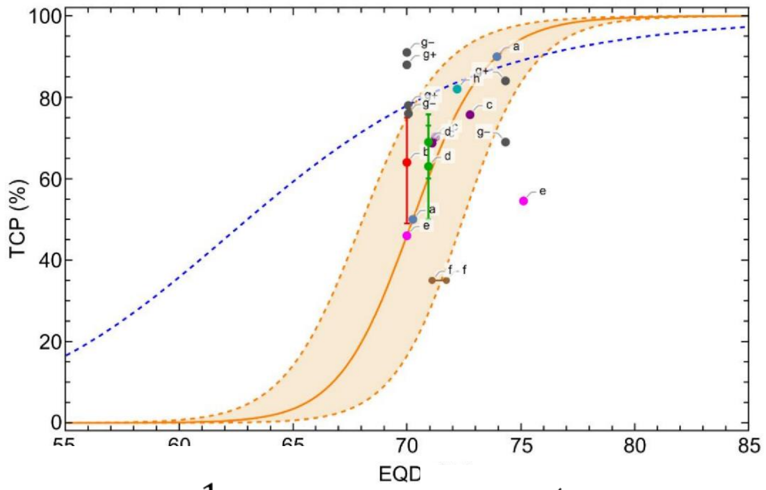
Transition from cell culture to tissue - is there any workaround?

Data-driven approach

Clinical / laboratory data

Predictive power limited by database!

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



$$TCP = \frac{1}{1+\left(\frac{TCD_{50}}{EUD}\right)^{4\gamma_{50}}} \qquad EUD = \left(\sum_i v_i \left(D_i \frac{\alpha/\beta + D_i/n_f}{2+\alpha/\beta}\right)^a\right)^{1/a}$$

Model of A. Niemierko et al

Model-driven approach

Hierarchy of complex models

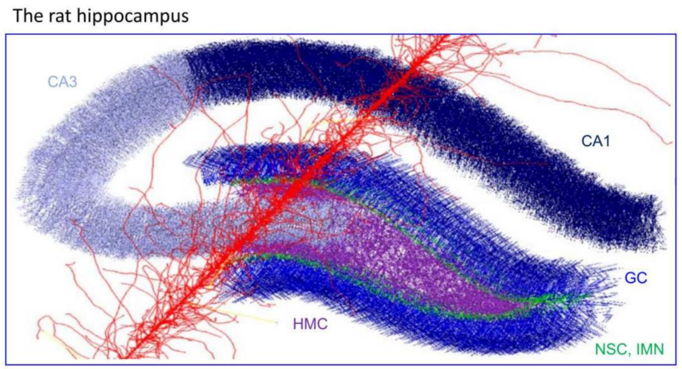
Input data rely on current scientific knowledge!

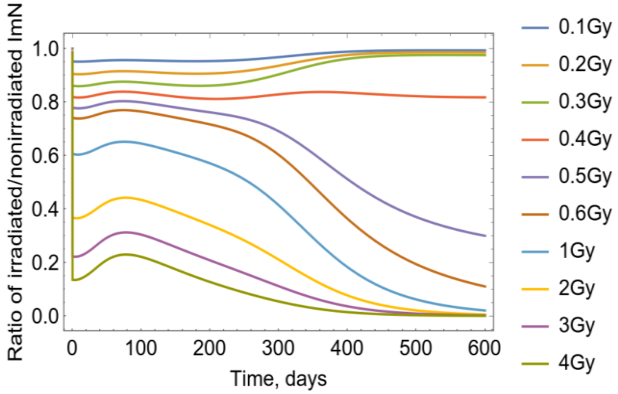
Insufficient computing power!

Simplification

Requires verification!

Software or fit to simple formula





Tissue and organ effects of radiation

An example of direct modeling scheme

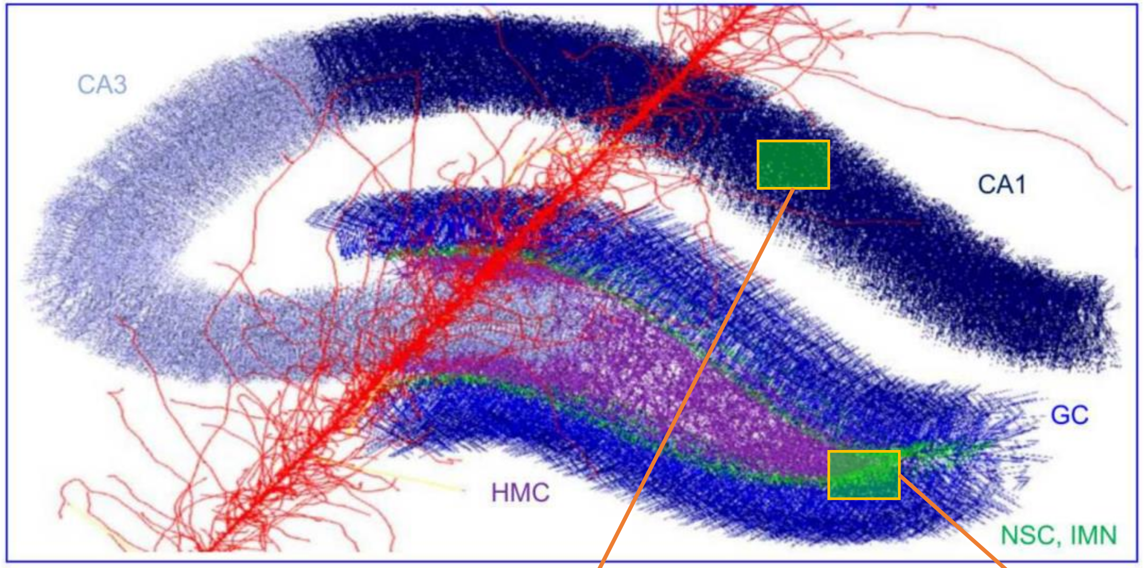
Radiation damage to the central nervous system:

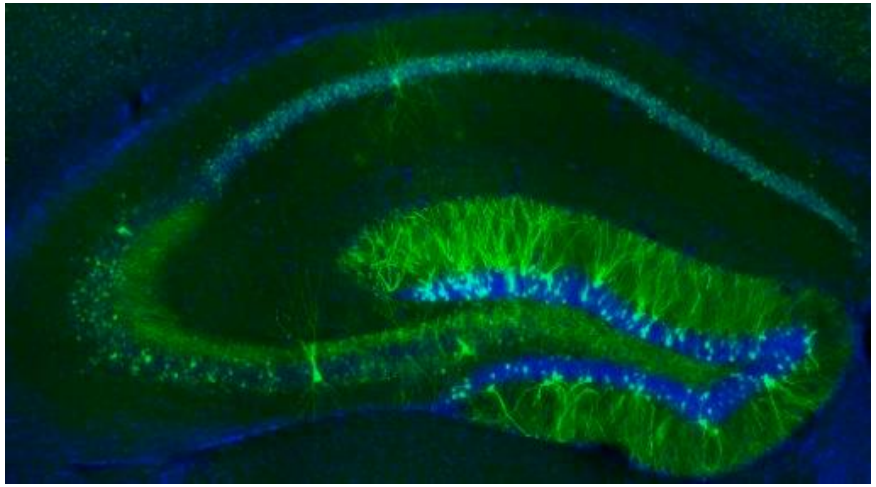
Radiosensitive cells - neural stem cells

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

Geometry of rodent hippocampus for use in GEANT4-DNA

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

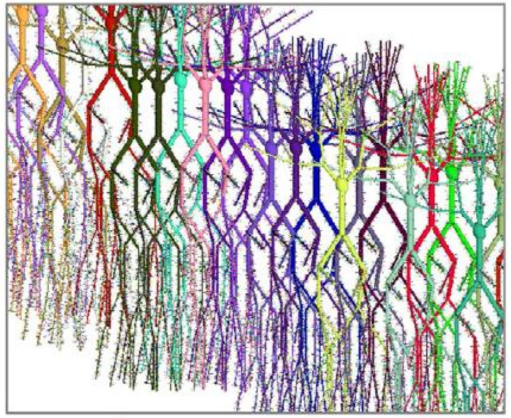


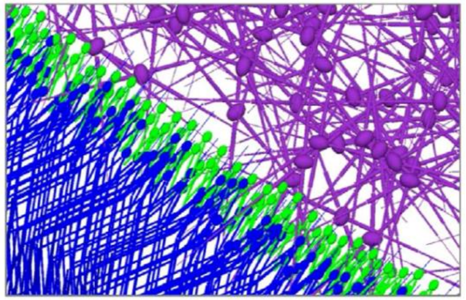


Fluorescent image of hippocampus slice

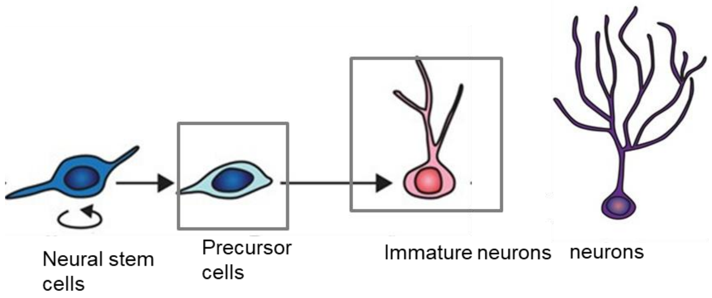
Scale 1:100

~ 20 000 cells

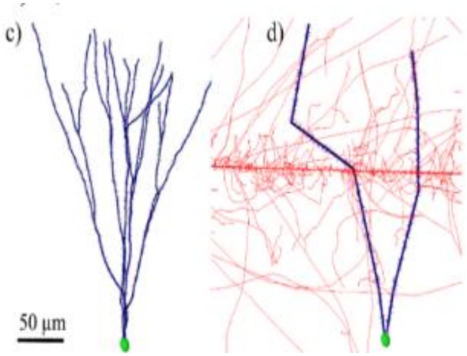


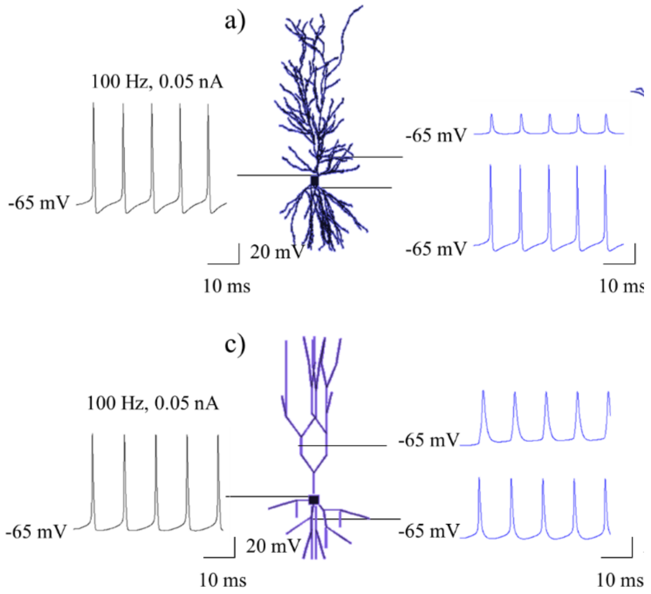


Neurogenesis region
Sensitive to Radiation!

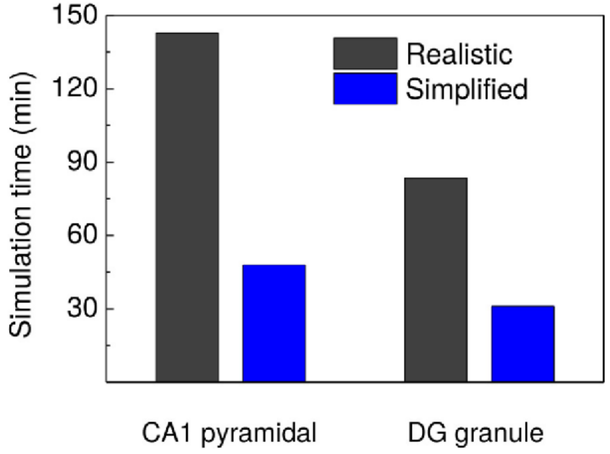


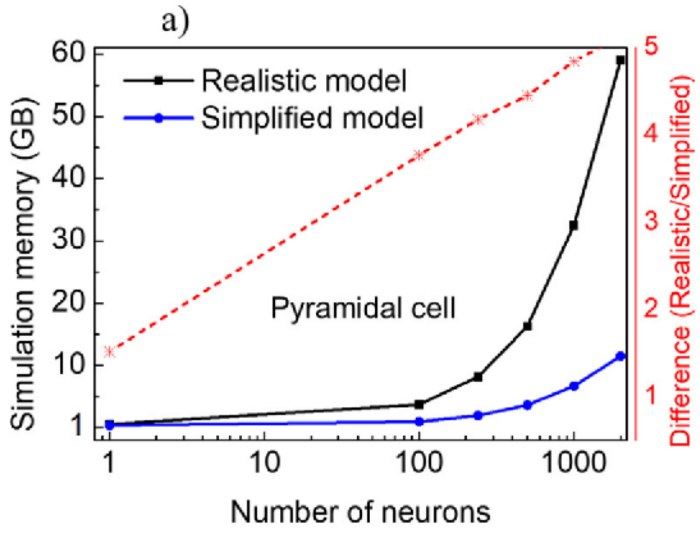
Scalability – way to success



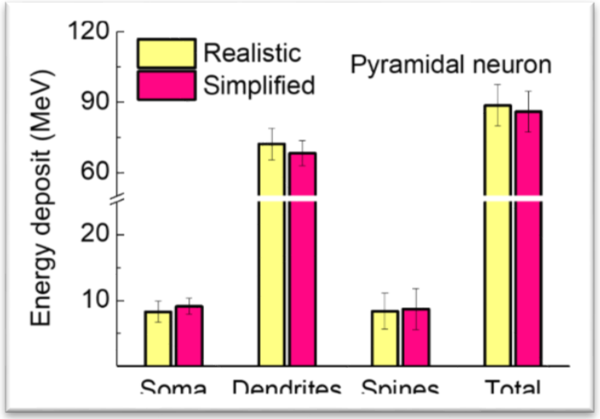


100 cell benchmark

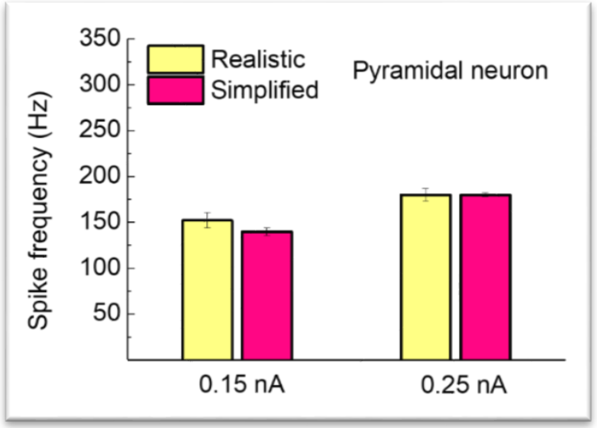




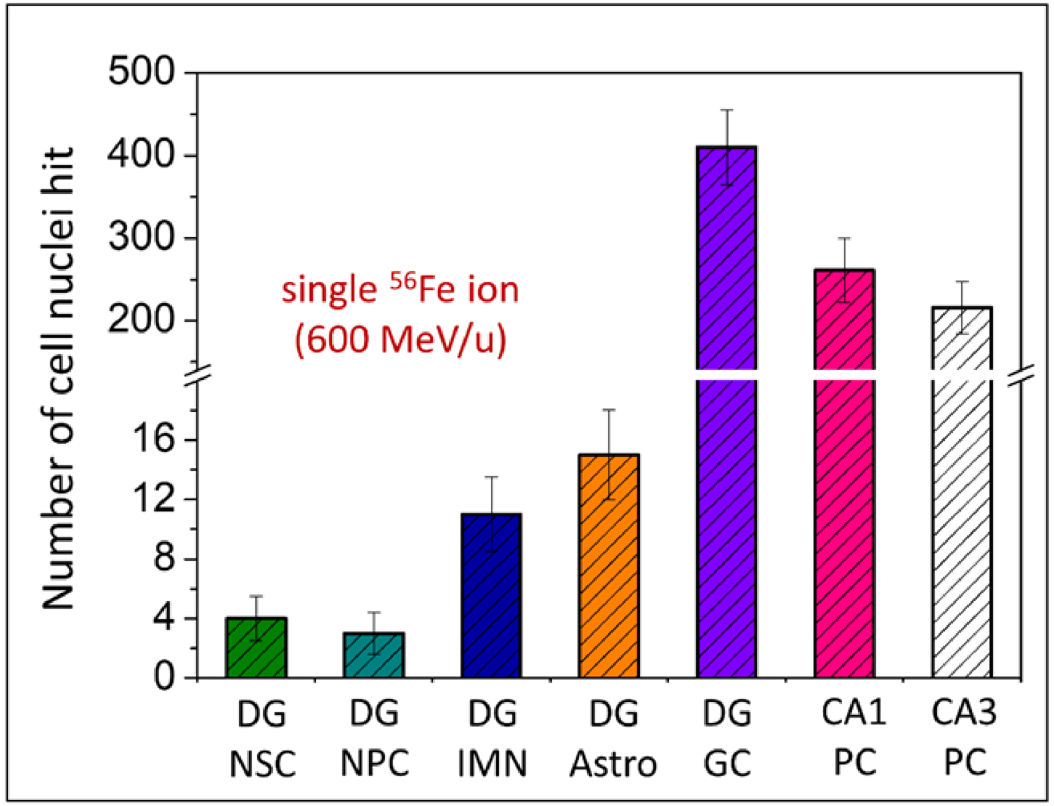
Microdosimetry scaling

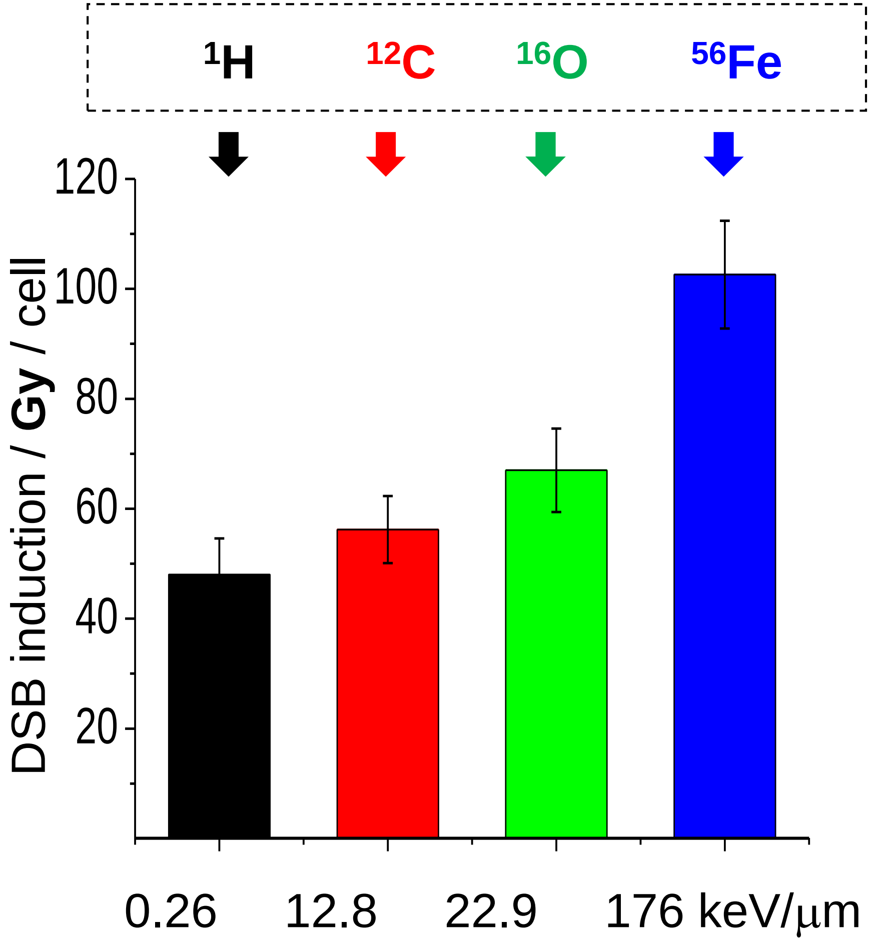


Electrophysiology scaling

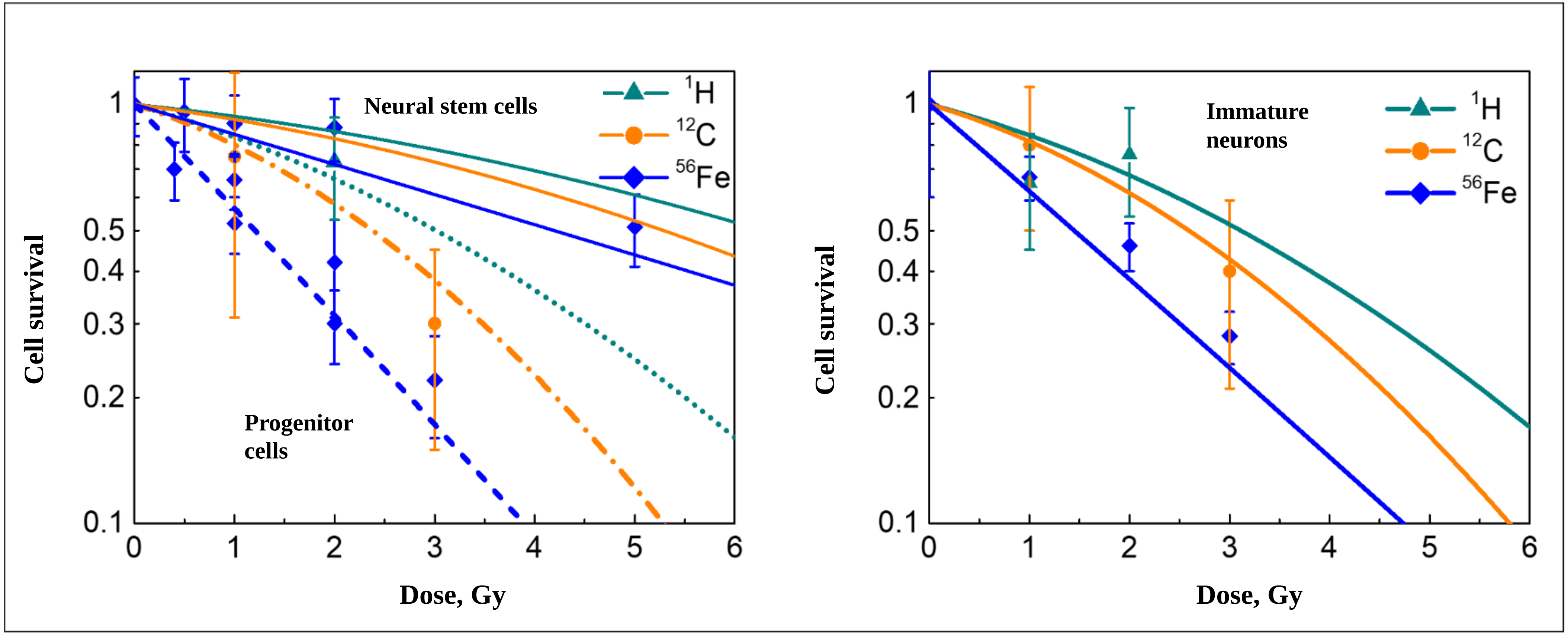


DNA damage computation



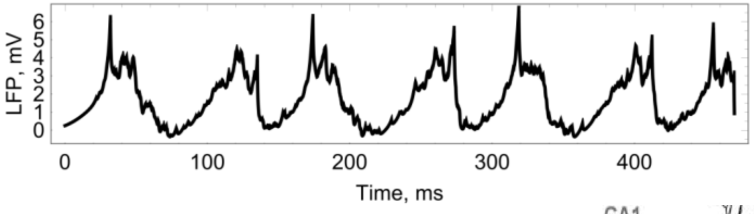


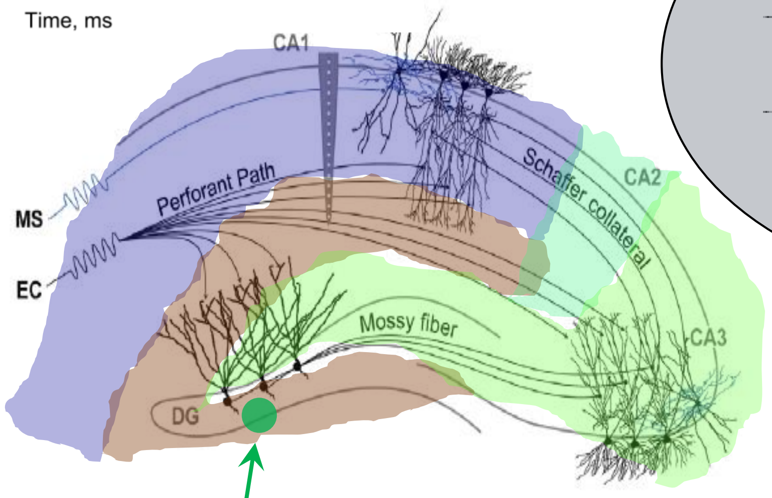
Survival of radiosensitive cells



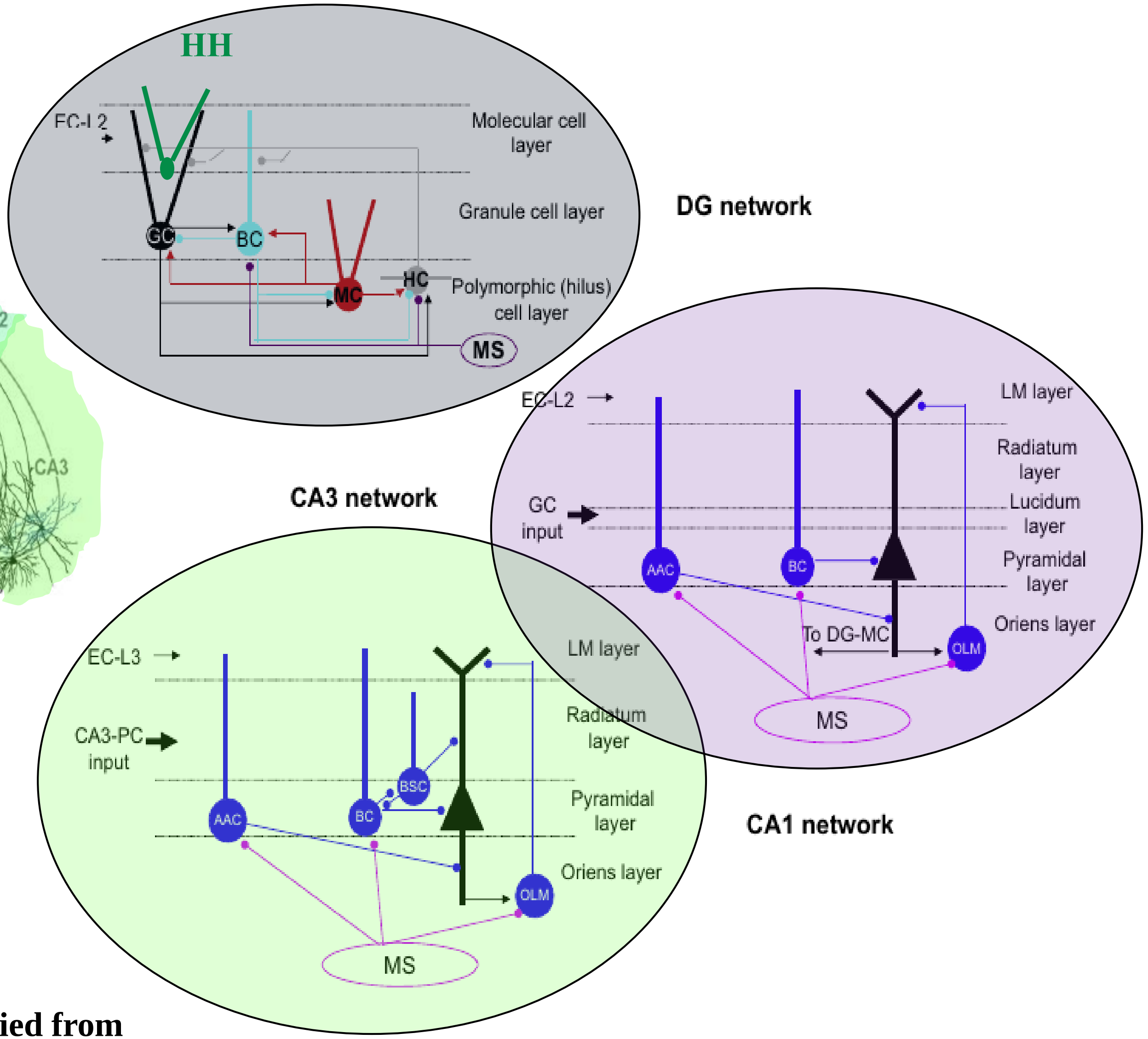
Calculated survival of radiosensitive cells (neural stem cells, neural progenitor cells, immature neurons) after action of 1000 MeV protons, 290 MeV/u carbon ions, 600 MeV/u iron ions as compared with experimental data [Rola 2004, 2005, Tseng 2014].

Biological neural network of hippocampus: a model for electrophysiological activity



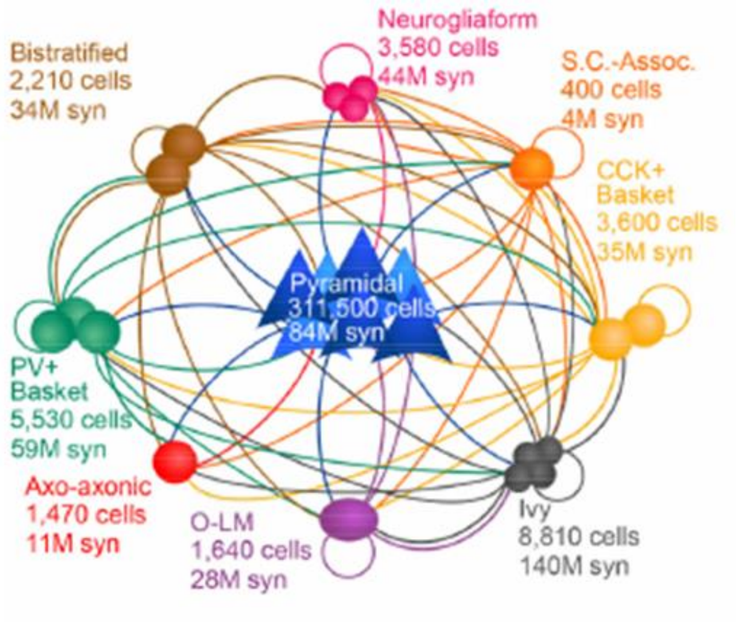


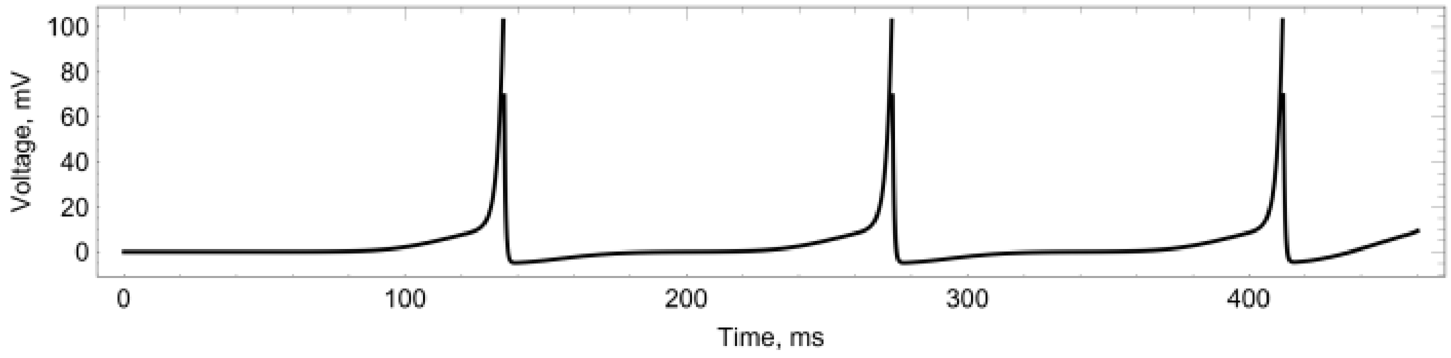
Zone of neurogenesis



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

Mathematical description of neural network elements





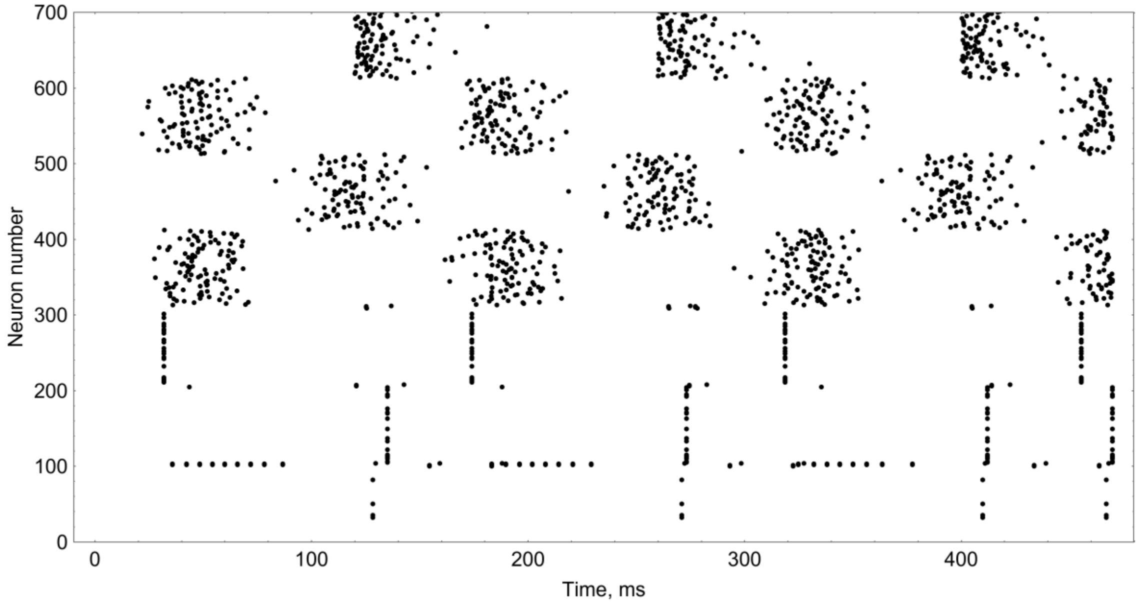
$$C\frac{dV_p}{dt} = g_{Na} m_p^{\,3} h_p (E_{Na} - V_p) + (g_K n_p^4 + g_{K(A)} a_p b_p)(E_K - V_p)$$

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

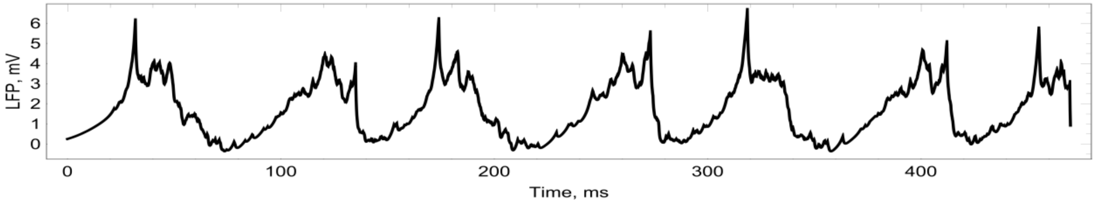
Synaptic connections between neurons

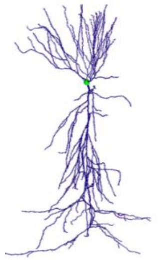
$$\frac{ds_i}{dt} = \rho(V_i)\frac{1 - s_i}{\tau_R} - \frac{s_i}{\tau_D}$$

Neural network electric activity

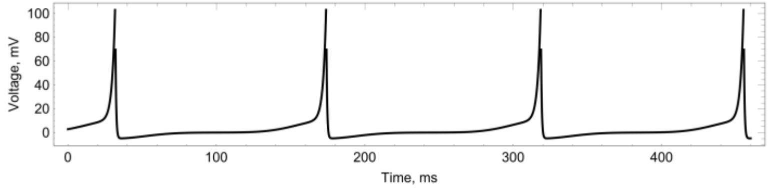


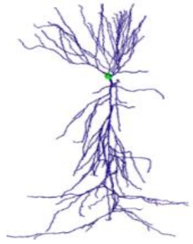
Integral signal (theta-rhythm)



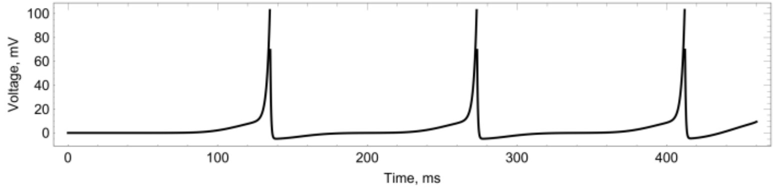


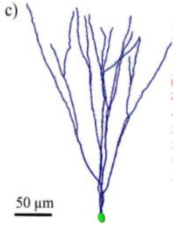
Pyramidal neuron CA1



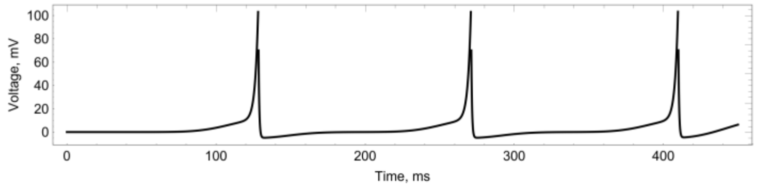


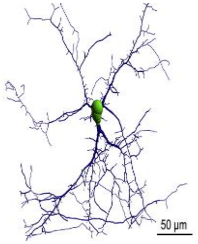
Pyramidal neuron CA3



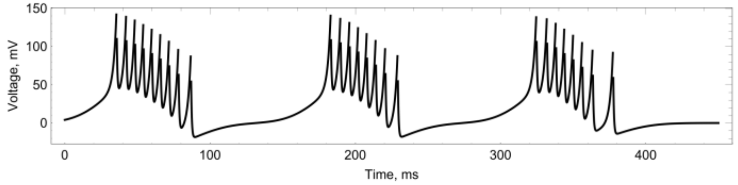


Granular cell



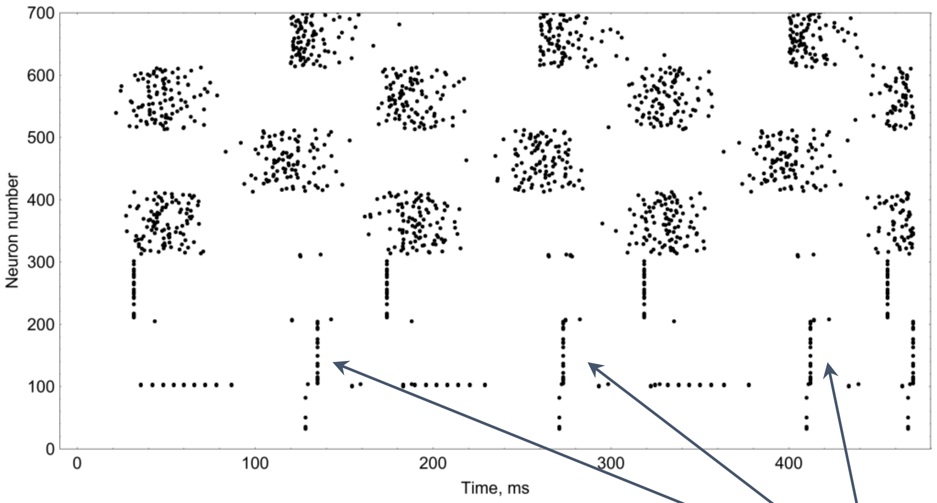


Basket cell

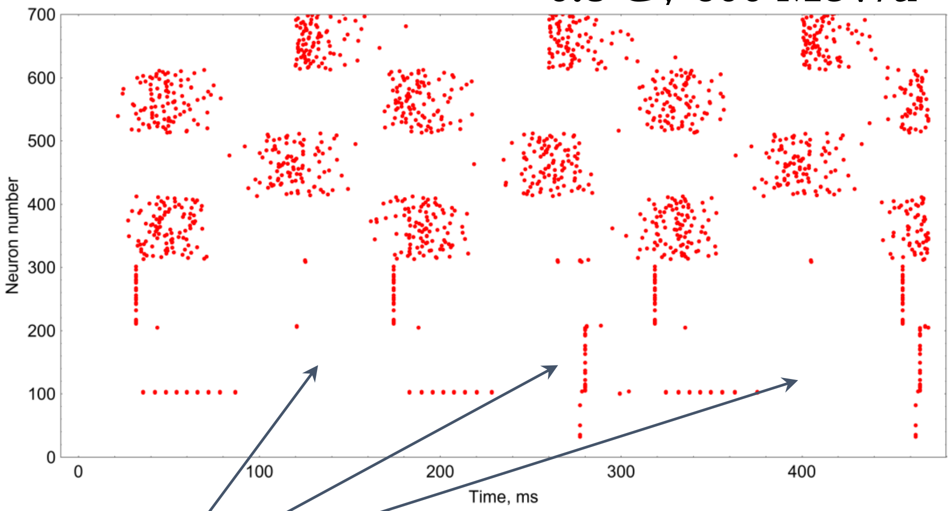


Influence of immature cell loss on information processing

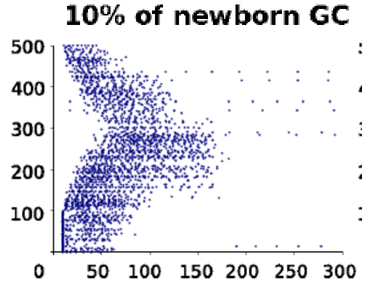
Control

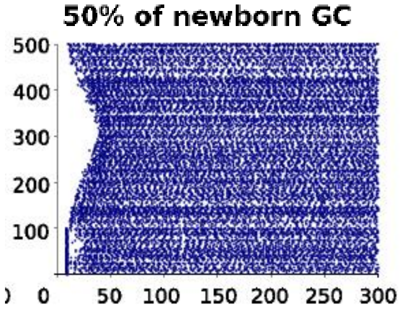


0.8 Gy 600 MeV/u ^{56}Fe



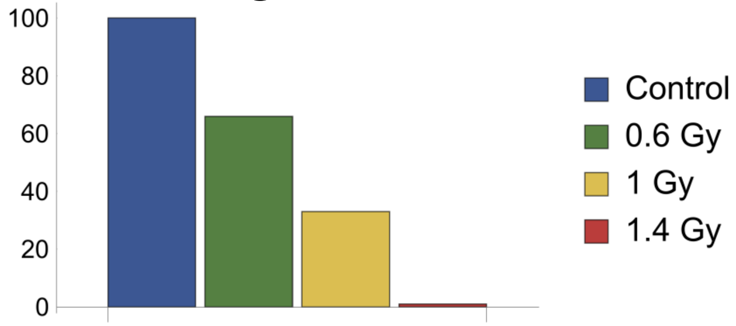
Encoded patterns



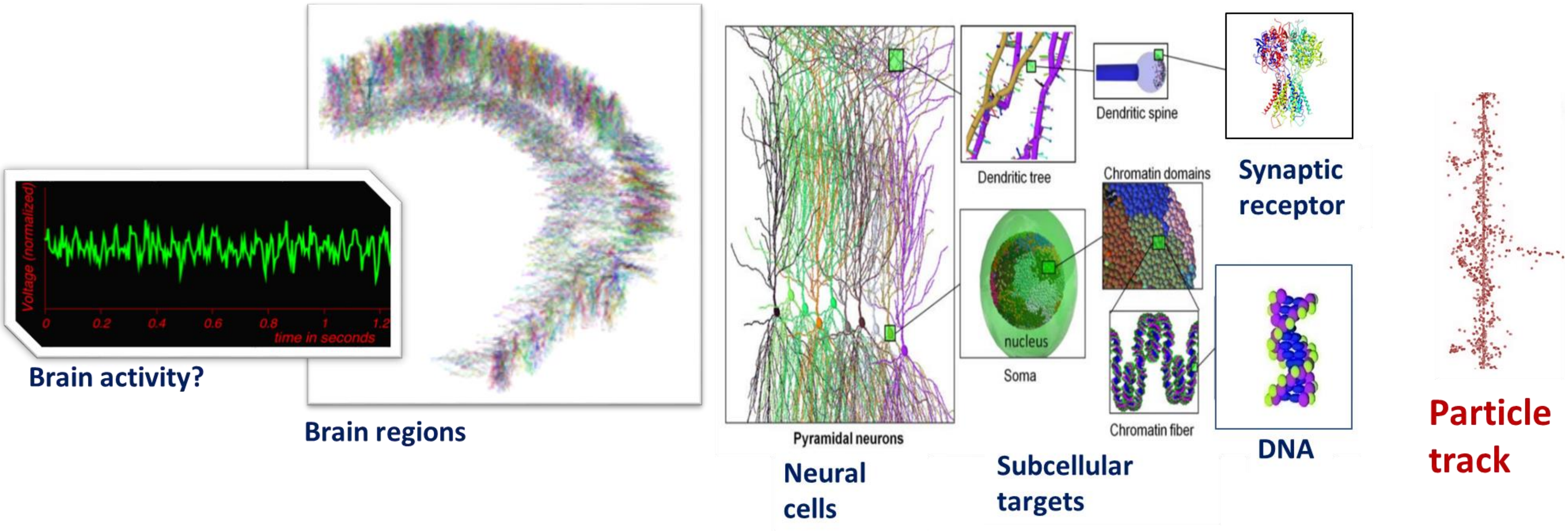


Local effect of immature neuron loss

Encoding and retrieval success, %



Future plans: 1) radiation-induced brain disorders



Information processing in brain neural networks

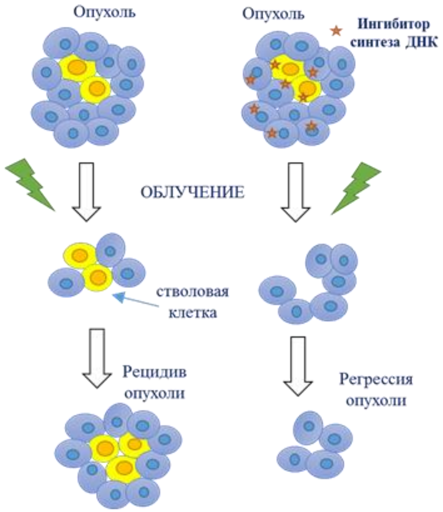
Cell survival and cell population dynamics

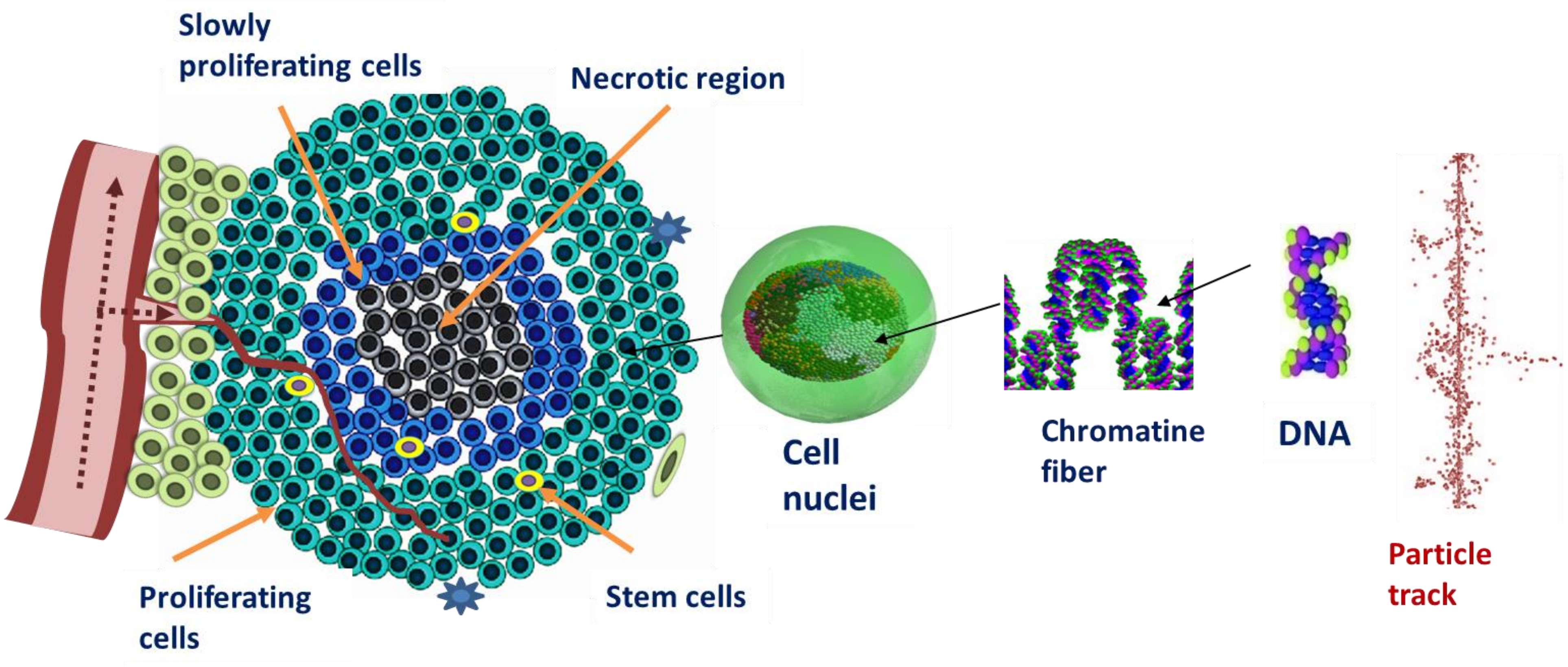
Biochemical processes (DNA repair etc)

Molecular dynamics

Physical and chemical events in particle tracks

Future plans: 2) response of tumors to radiation





Functional state of tumor after treatment?

Cellular and tissue processes (tumor cell proliferation, angiogenesis, etc)

Biochemical processes

Molecular dynamics

Physical and chemical events in particle track

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!

@LRB_JINR