*Lecture 5-1*

# Radiation Biology and Astrobiology

**Aleksandr Bugai**
Laboratory of Radiation Biology, JINR

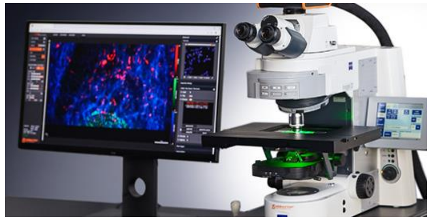
*International School on Nuclear Methods and Applied Research in Environmental, Material and Life Sciences (NUMAR-2024)*

# JINR Research Infrastructure

**U-400M cyclotron**
heavy ions 50 MeV/u

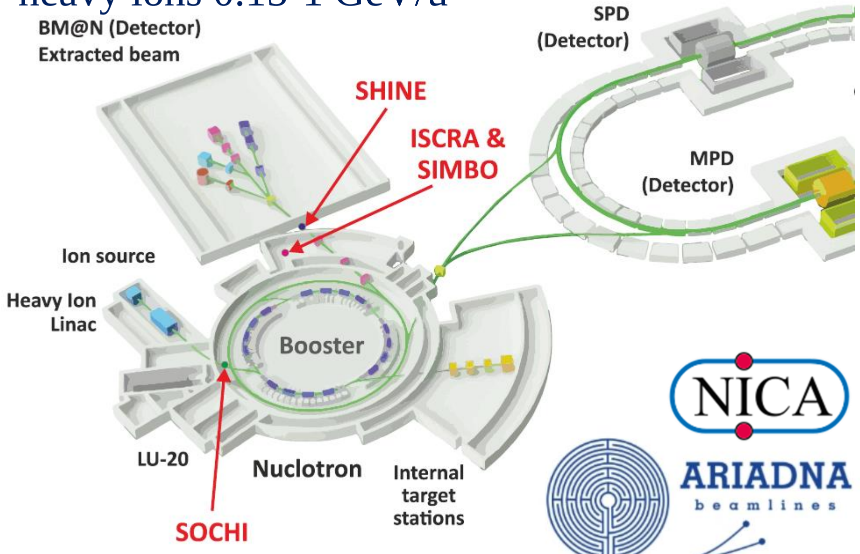
**Infrastructure for cellular and animal research**

Microscopy
Tomography
OMICS



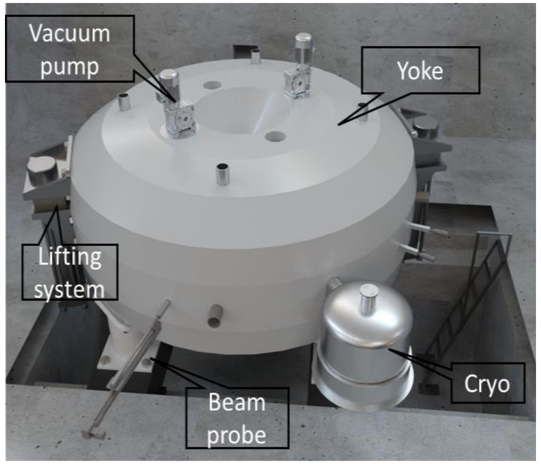
Vivarium

**Nuclotron**
heavy ions 0.15-1 GeV/u




NICA
ARIADNA
beamlines

**MSC230 cyclotron**
protons 230 MeV




**Linac200**
electrons
20-200 MeV

**MICC**
Supercomputer

**SARRP** X-ray

**IBR-2, IREN** neutrons

# JINR Life Science Research

### Dzhelepov Laboratory of Nuclear Problems

- Proton therapy of cancer
- Genetics
- Detectors and Tomography

### Laboratory of Radiation Biology

- Fundamental Radiobiology
- Radiation Neuroscience
- Clinical Radiobiology
- Mathematical Modeling
- Radiation Protection
- Astrobiology

Infrastructure for molecular, cellular and animal research

### Veksler and Baldin Laboratory of HEP

LHEP ЛФВЭ NICA ARIADNA beamlines

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

### Frank Laboratory of Neutron Physics

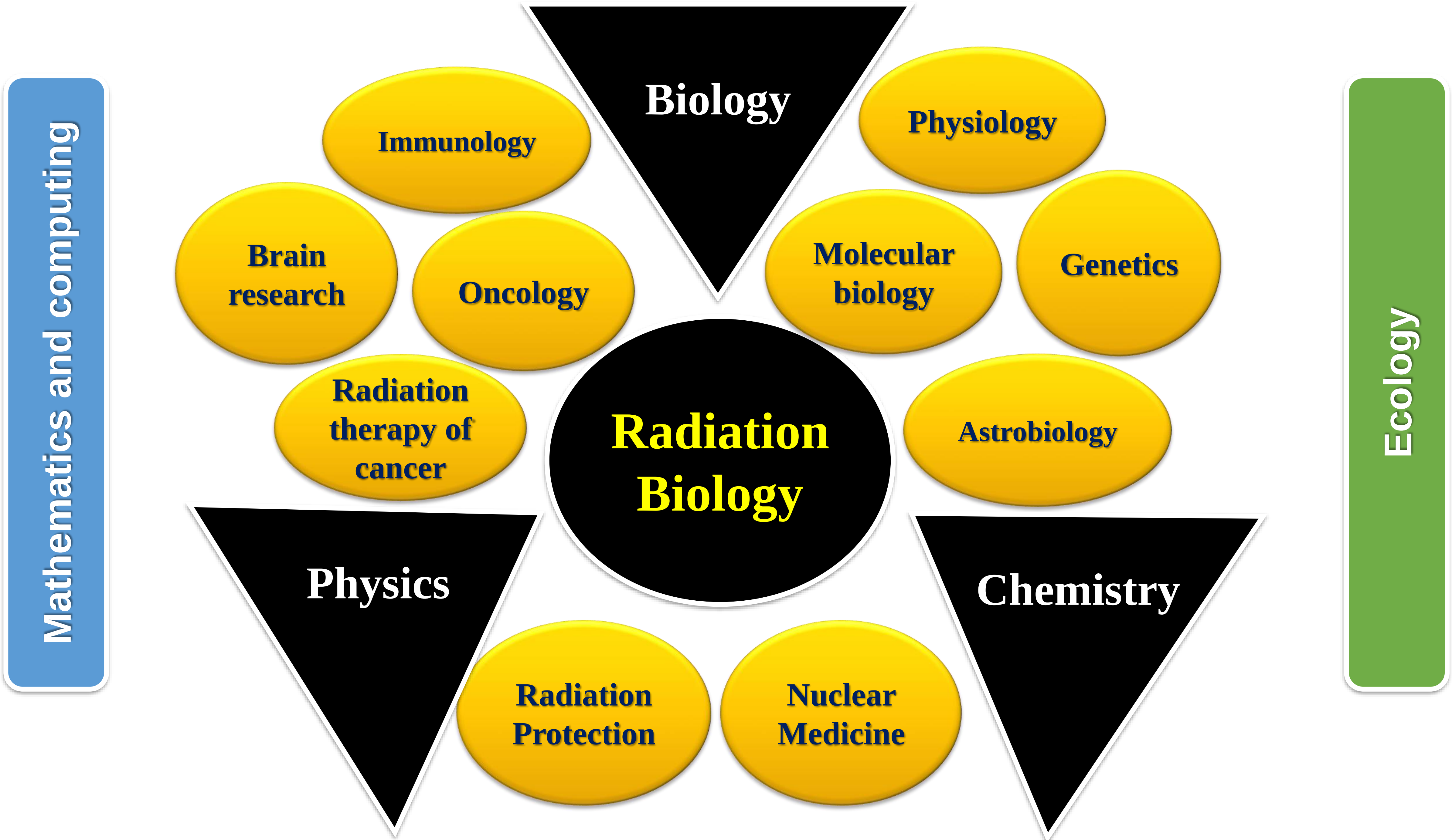
- Analysis in the structural biology and pharmacology
- Ecology

### Mecheryakov Lab. of Information Technologies

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

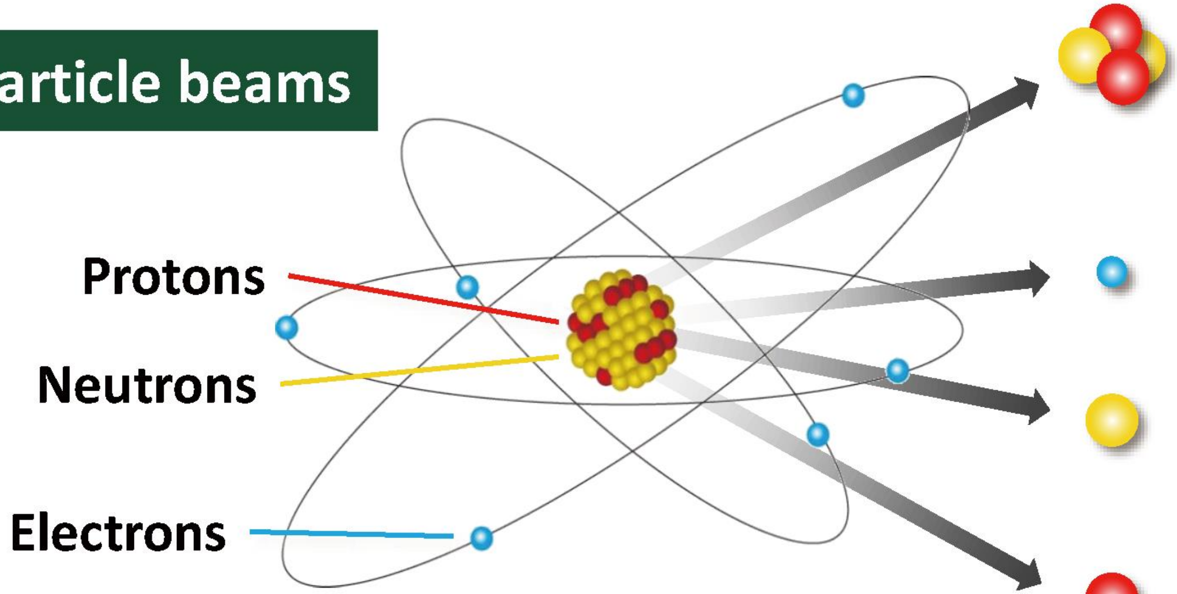
### Flerov Laboratory of Nuclear Reactions

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


Mathematics and computing
Biology
Immunology
Physiology
Brain research
Oncology
Molecular biology
Genetics
Radiation therapy of cancer
Radiation Biology
Astrobiology
Ecology
Physics
Chemistry
Radiation Protection
Nuclear Medicine

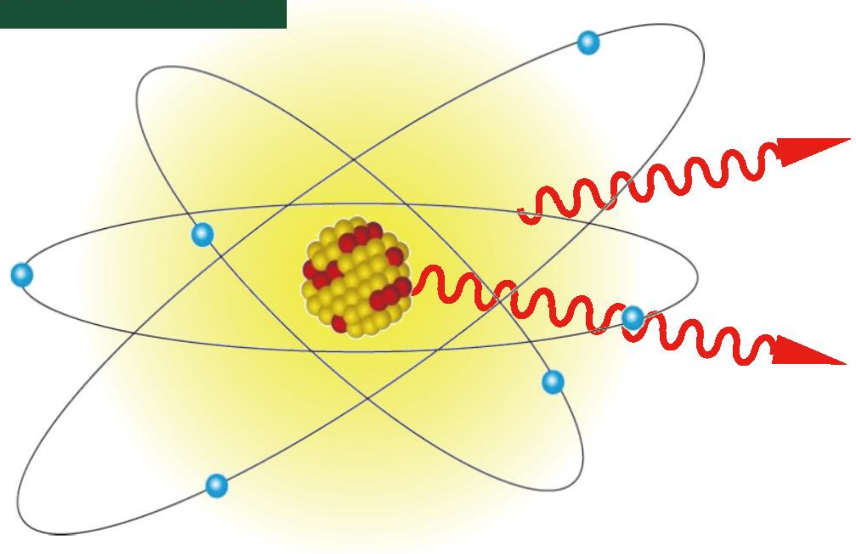
# Main types of ionizing radiations

## Particle beams




- α-particles (helium nuclei ejected from a nucleus)
- β-particles (electrons ejected from a nucleus)
- Neutron beams (produced in nuclear reactors, accelerators, etc.)
- Proton beams (produced in accelerators, etc.)

## Electromagnetic waves



- X-rays (generated outside a nucleus)
- γ-rays (emitted from a nucleus)

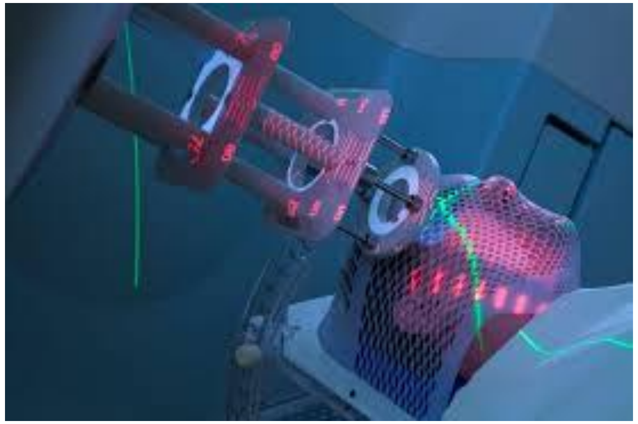
# Main tasks of radiation biology:

Nuclear and Radiation Technologies

Nuclear Waste

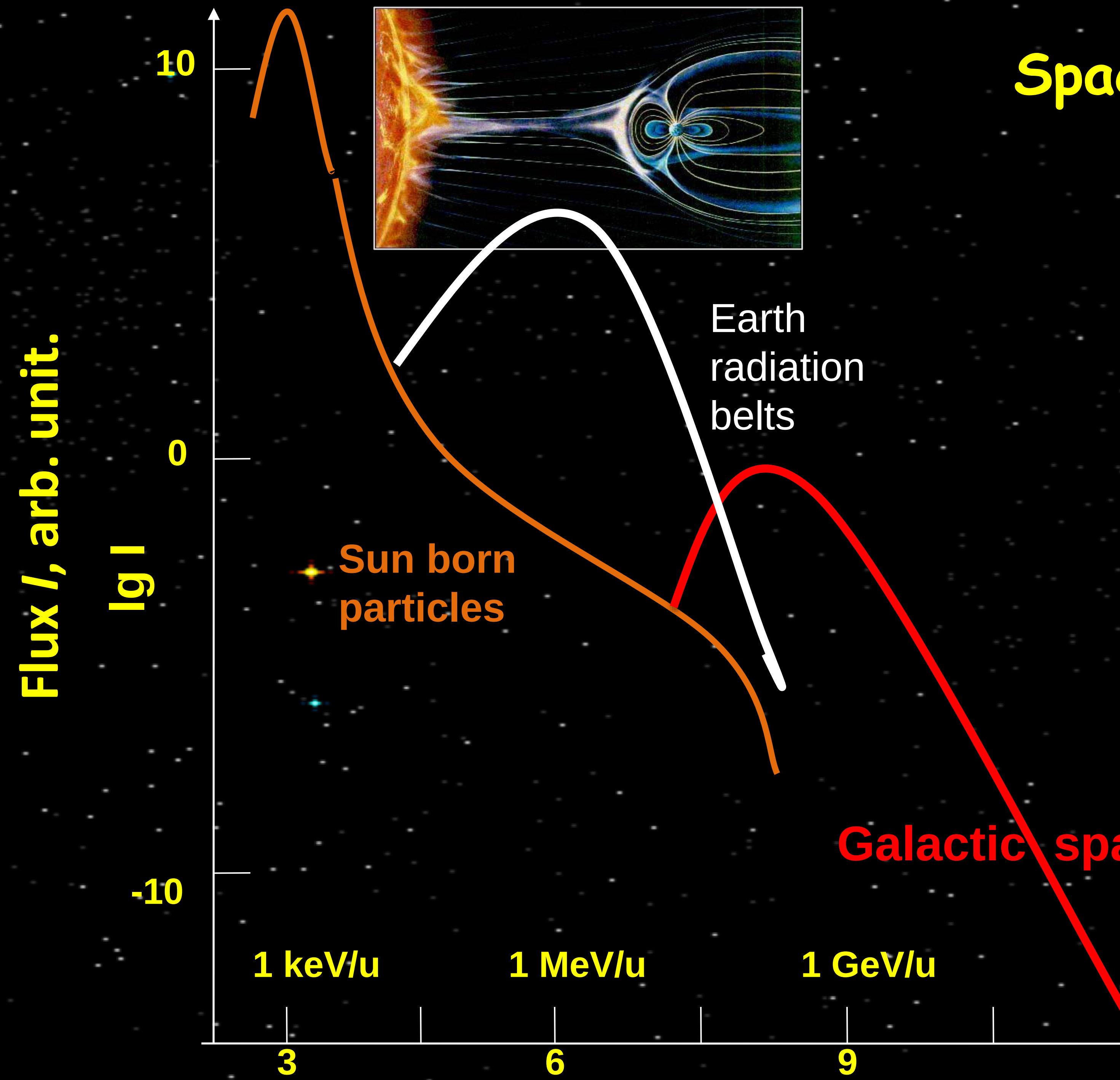
- **Fundamental research**
- **Evaluation of radiation risks**
- **Application of radiations in medicine**

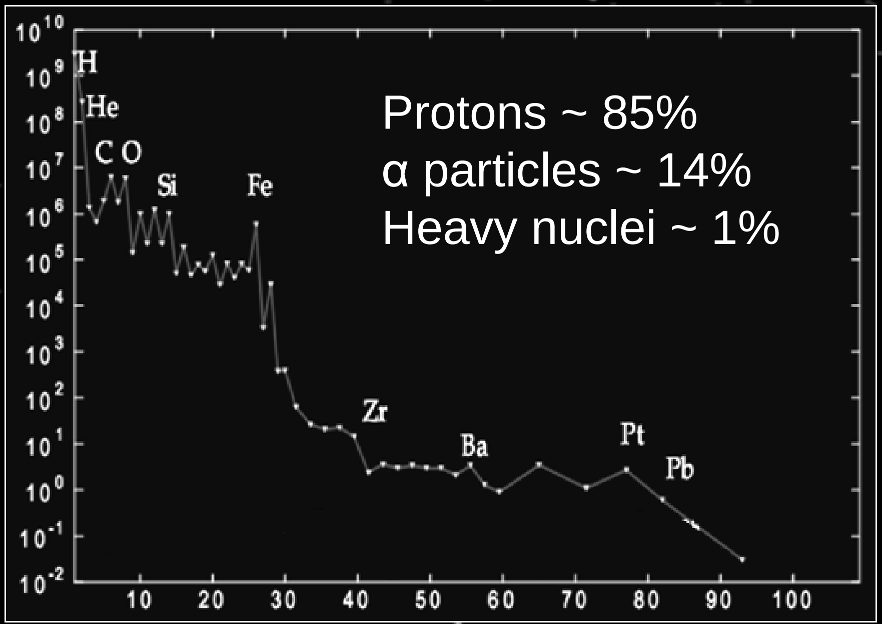
Diagnostics and Radiation therapy



Space Exploration

# Space radiation sources and spectra



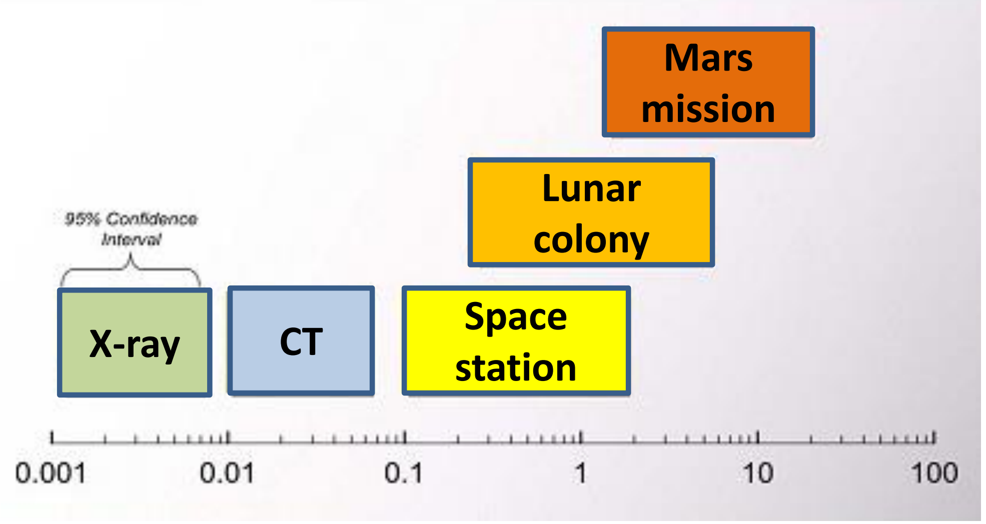




Charge spectrum of GCR particles

# Space radiobiology

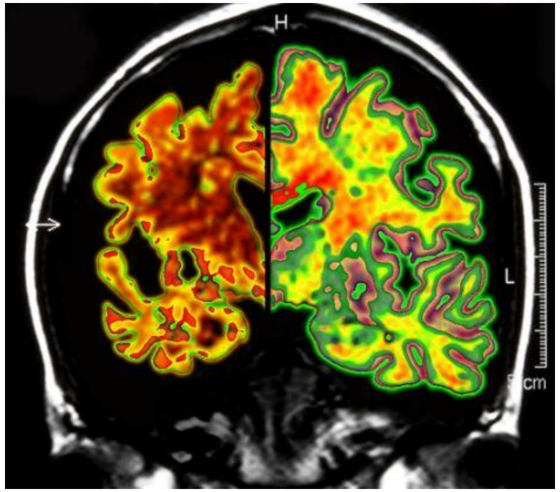
**New concept of radiation risk for deep space flights: Damage to the central nervous system (CNS)**

*Grygoriev, Krasavin, Ostrovskii, Bulletin of RAS 2017*




% Risk of cancer death

Paradigm shift



# JINR facilities for space radiobiology

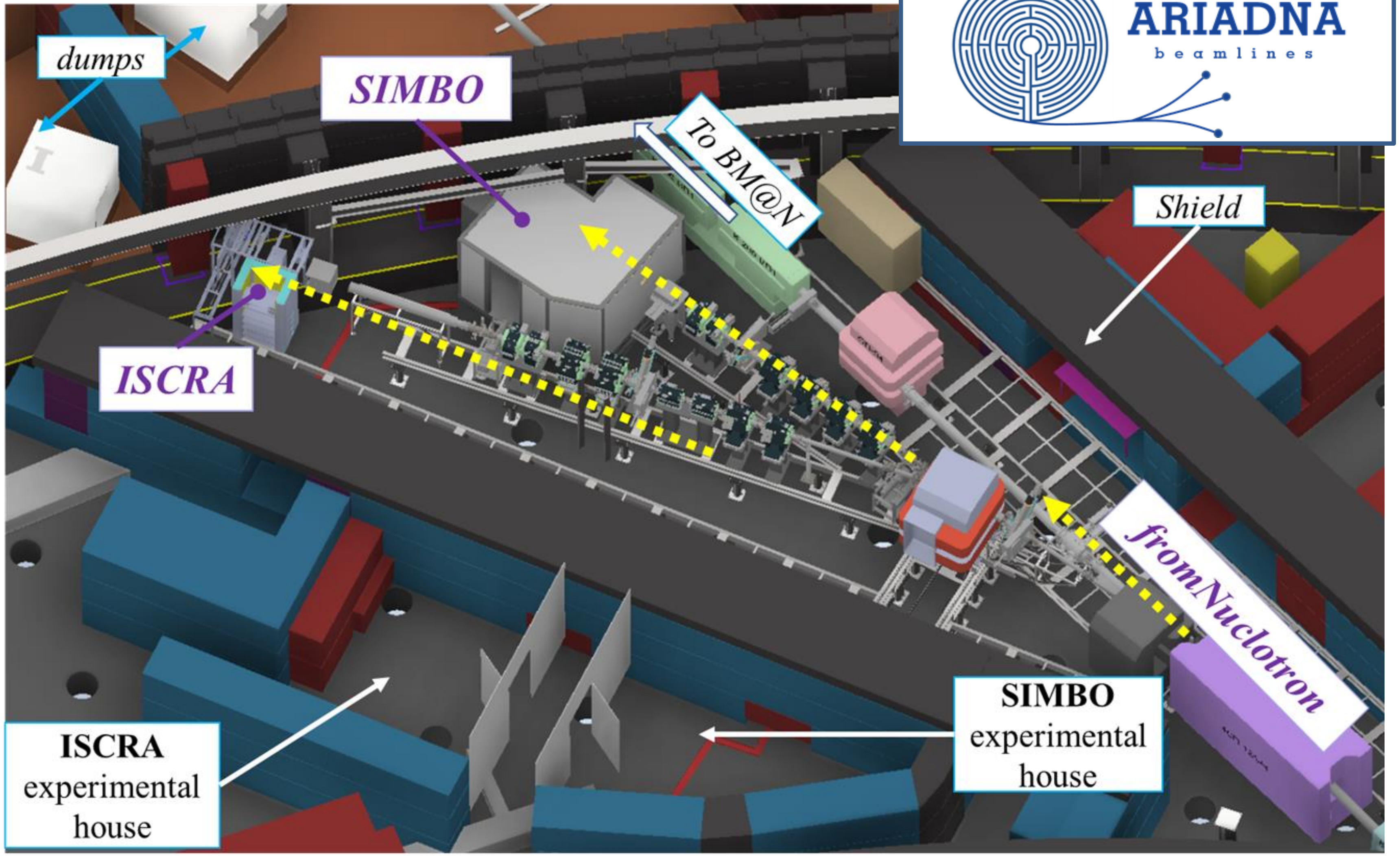
**S**tation of **I**nvestigation of **M**edico-**B**iological **O**bjects (**SIMBO**)

$^{12}C^{6+}$, $^{40}Ar^{18+}$, $^{56}Fe^{26+}$, $^{84}Kr^{36+}$

Ion energy 400-1100 MeV/n

Flux density $10^3$-$10^5$ particles/(cm$^2$.s)

Beam intensity, $10^6$-$3\times10^9$ particles per pulse

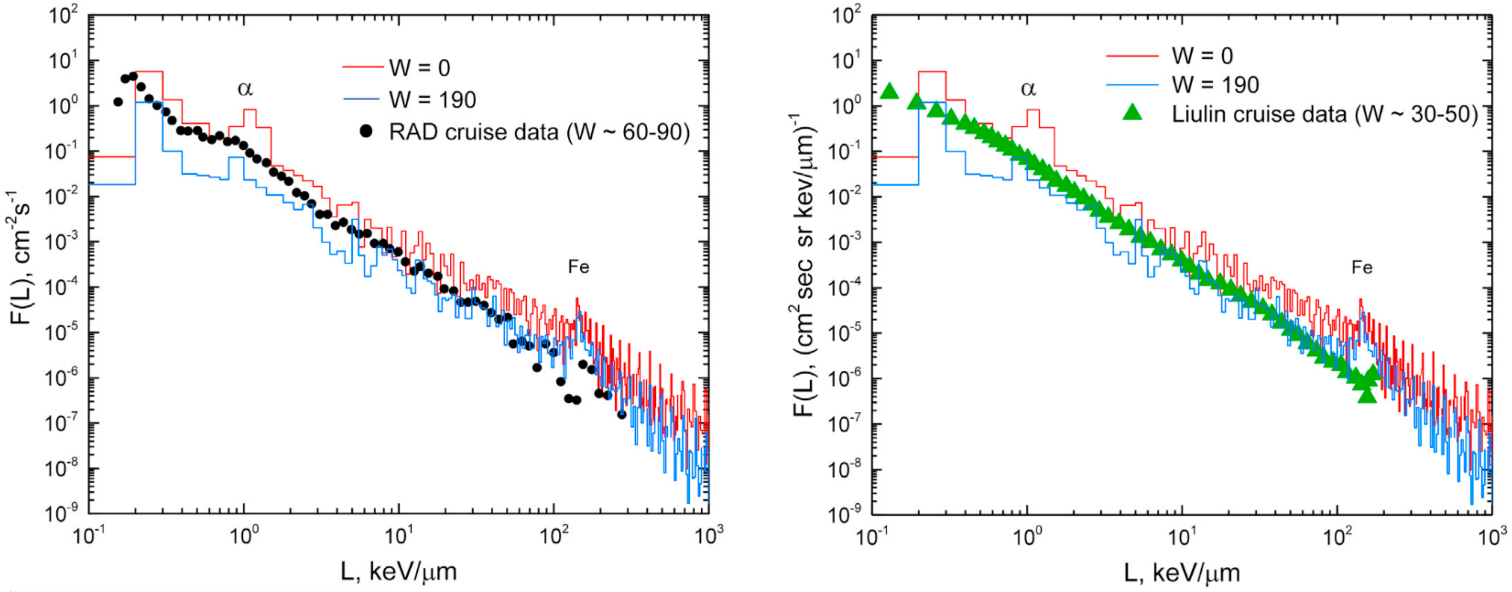


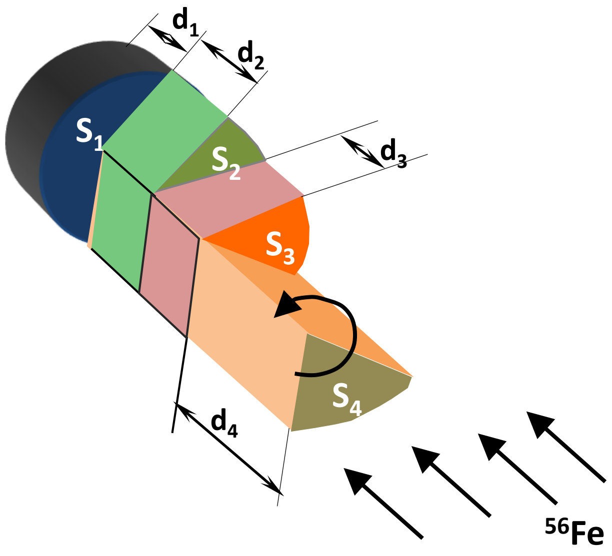

ARIADNA beamlines

# JINR facilities for space radiobiology

## New type of accelerator-based cosmic radiation field simulator

Comparison of simulated LET spectra with RAD and Liulin data




РОССИЙСКАЯ ФЕДЕРАЦИЯ

ПАТЕНТ

НА ИЗОБРЕТЕНИЕ

№ 2761376

Устройство моделирования на пучках тяжелых ионов высокой энергии полей смешанного излучения для целей экспериментальной радиобиологии

Патентообладатель: *Объединенный институт ядерных исследований (ОИЯИ) (RU)*

Авторы: *Тимошенко Геннадий Николаевич (RU), Гордеев Иван Сергеевич (RU)*

Заявка № 2021105845
Приоритет изобретения 05 марта 2021 г.
Дата государственной регистрации в Государственном реестре изобретений Российской Федерации 07 декабря 2021 г.
Срок действия исключительного права на изобретение истекает 05 марта 2041 г.

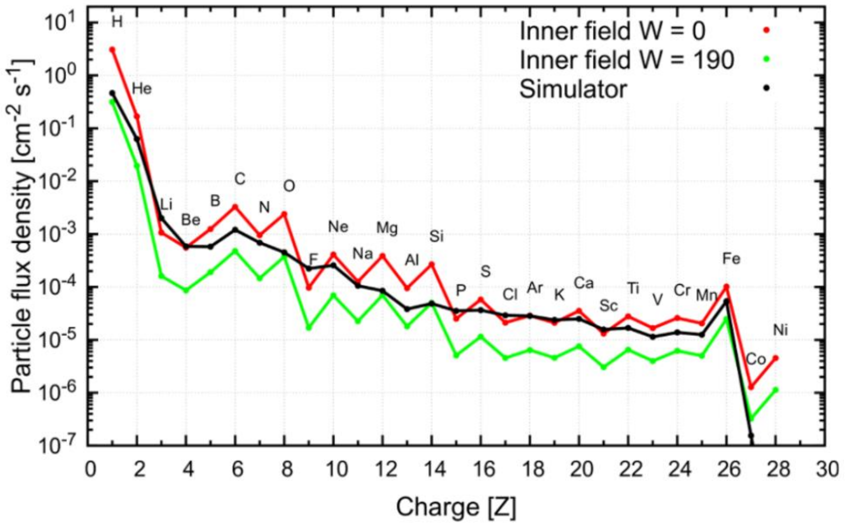
*Руководитель Федеральной службы по интеллектуальной собственности*

*Г.П. Ивлиев*

*Timoshenko G. N. and Gordeev I. S. // Planetary and Space Science. 2021. V. 199. P. 105190.*

*Timoshenko G., Gordeev I. // Life Sciences in Space Research, 2021, V.30, P.66*

***Patent No. 2761376***

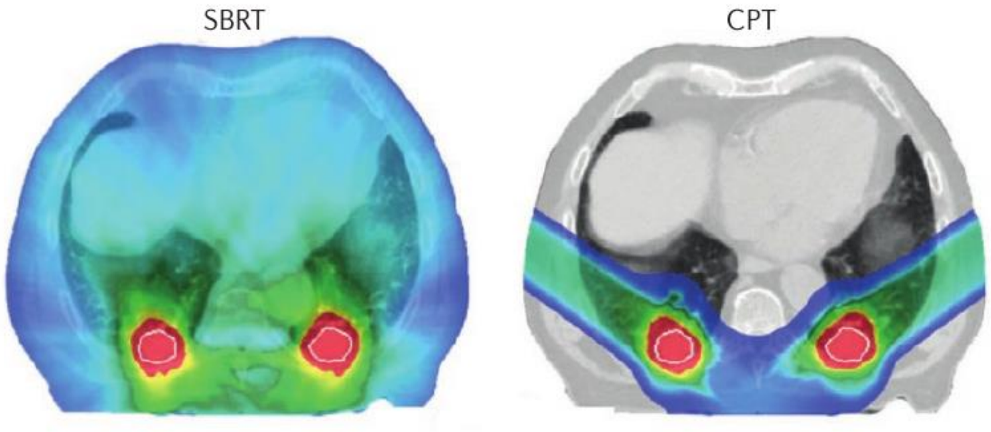



Comparison of simulator and space radiation charge spectra

# Clinical radiation biology

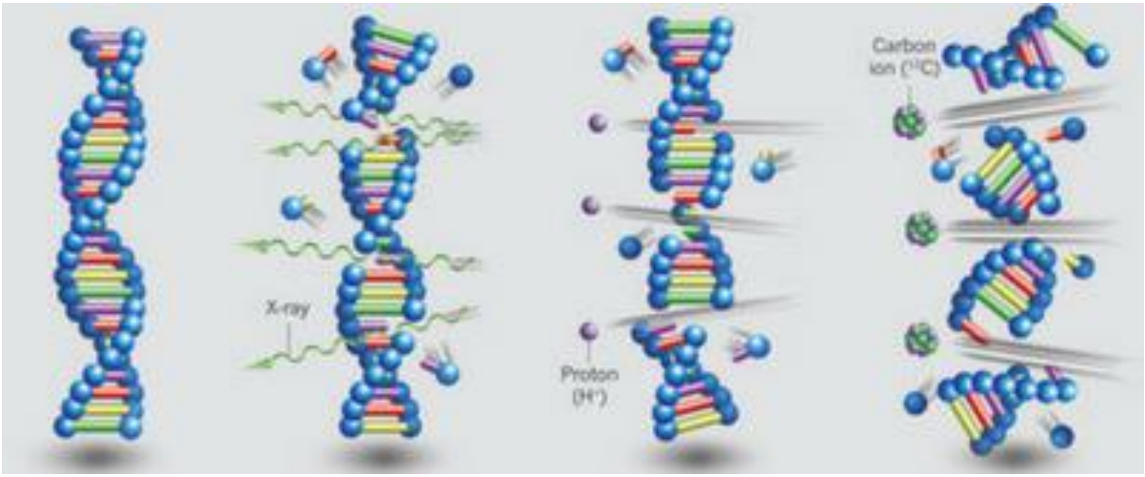
## I. Conformal dose delivery

Minimize damage to healthy tissue




## II. Biological efficiency of radiation

Maximize biological damage in tumor cells




| X-ray | protons | heavy ions |
|---|---|---|
| + | ++ | +++ |

# Ionizing radiations used in radiation medicine

## Distant radiation therapy and CT

### Conventional RT and CT

- $^{60}$Co gamma rays
- Electron linacs
- X-ray tubes

### Hadron therapy

- Fast neutrons 6-50 MeV
- Proton therapy 70-250МэВ
- Neutron capture therapy 0.025-1eV
- Ion beam (He,C,O) 250-400 MeV/nucleon

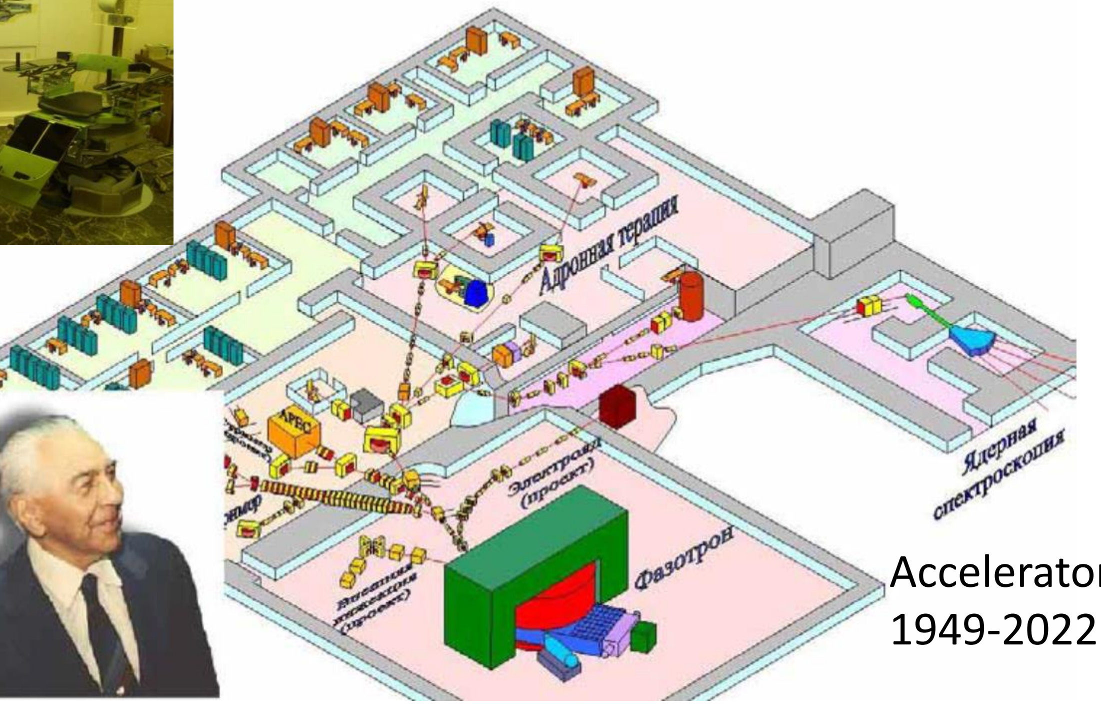
## Radionuclide therapy and diagnostics

*decay products:*

- Gamma rays and electrons (beta-emitters)
- Auger electrons
- Alpha particles

# JINR facilities for radiation medicine

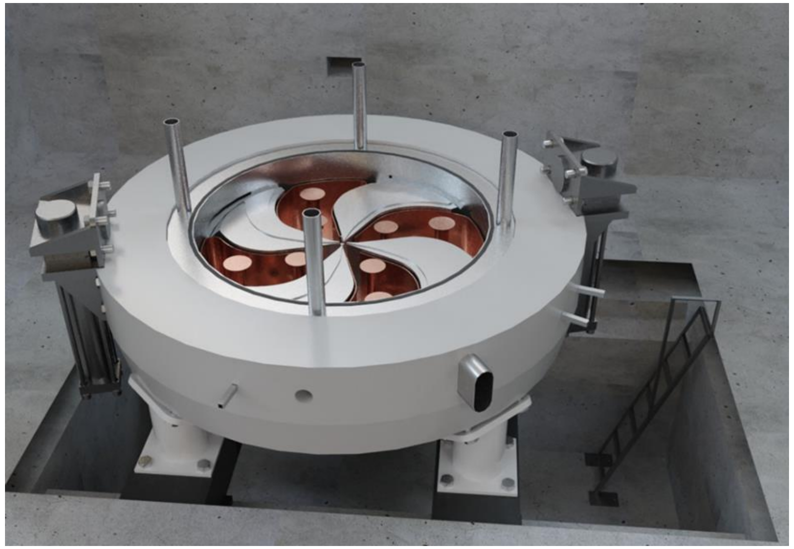
## Proton therapy




Accelerator phasotron
1949-2022

**The first proton beam in the USSR with the necessary parameters for therapy was formed in 1967 at JINR**

**During the operation of the medical proton beam in Dubna, more than 1,300 patients were treated**



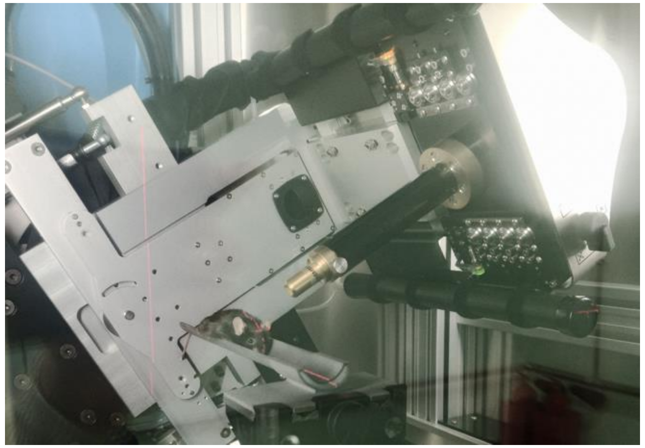
**JINR has developed a project for next generation superconducting compact proton cyclotron MSC-230 with parameters superior to foreign analogues. The production of a prototype is carried out jointly with NIIEFA named after. D.V. Efremova (Rosatom State Corporation).**

# JINR facilities for radiation medicine

## Preclinical research

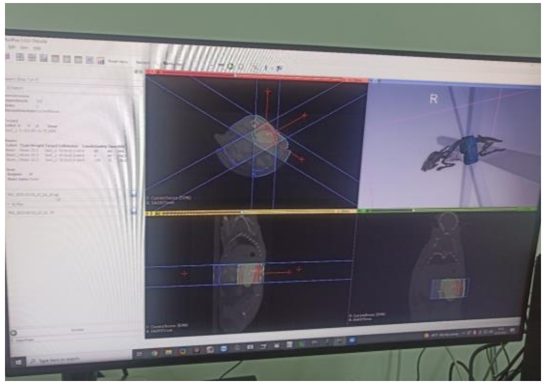
### SARRP (Small Animal Radiation Research Platform)


**SARRP** imitates modern X-ray radiation therapy systems for animal research



The 360° gantry and motorized stage allow for non-coplanar beam delivery from any angle.

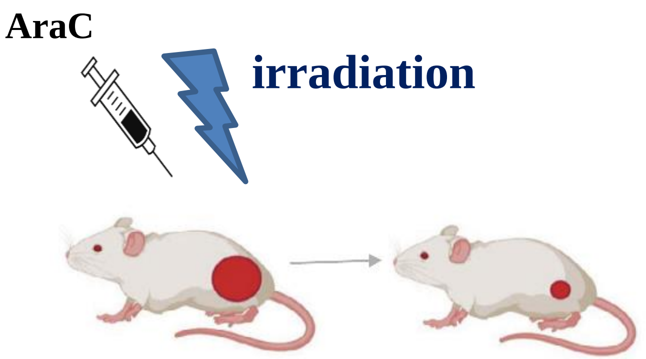
Techniques utilizing planar static beams, parallel opposed beams, continuous arc therapies, multiple isocenter treatments, and non-planar arcs can all be planned, evaluated, and delivered with SARRP

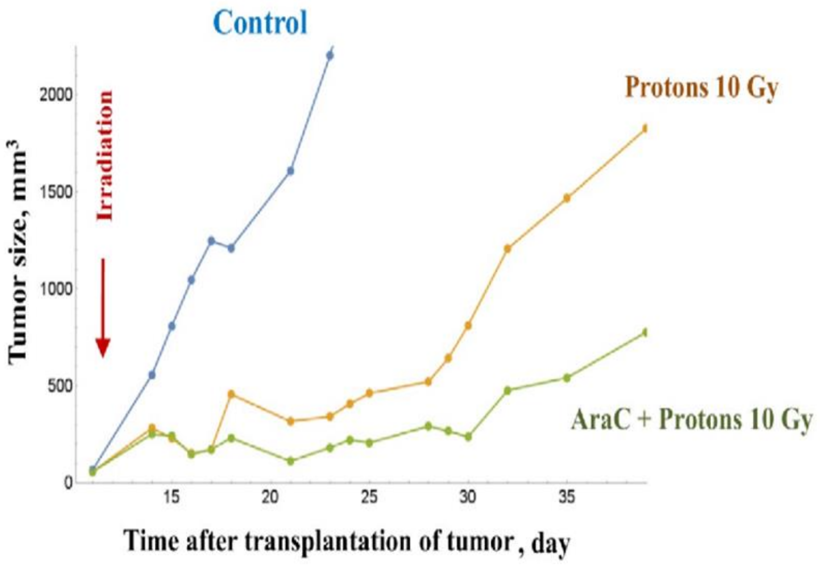


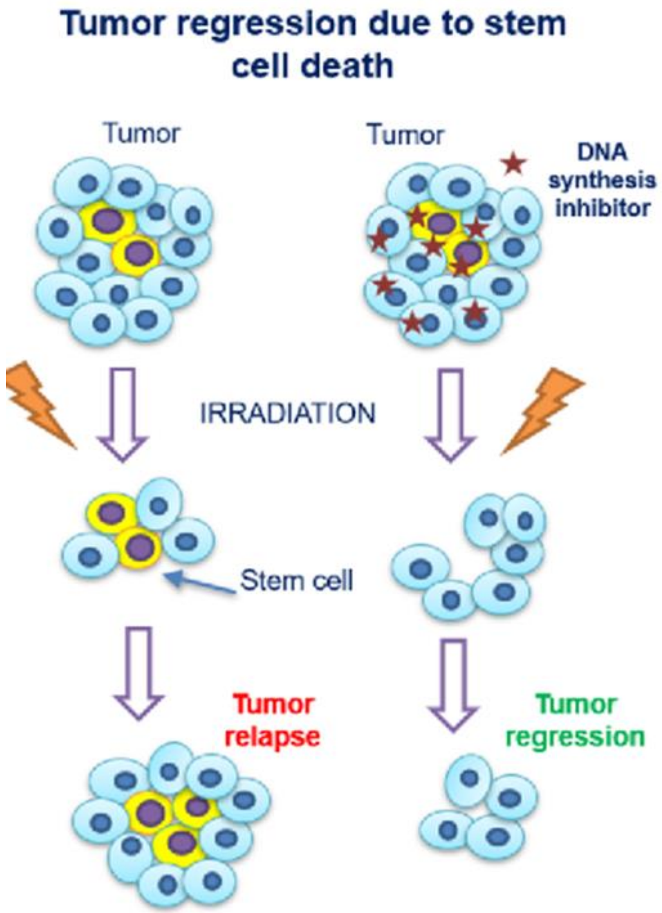
**Experiments on mice irradiation at SARRP**

# JINR expertise in radiation medicine

## A fundamentally new method to increase the efficiency of radiation therapy

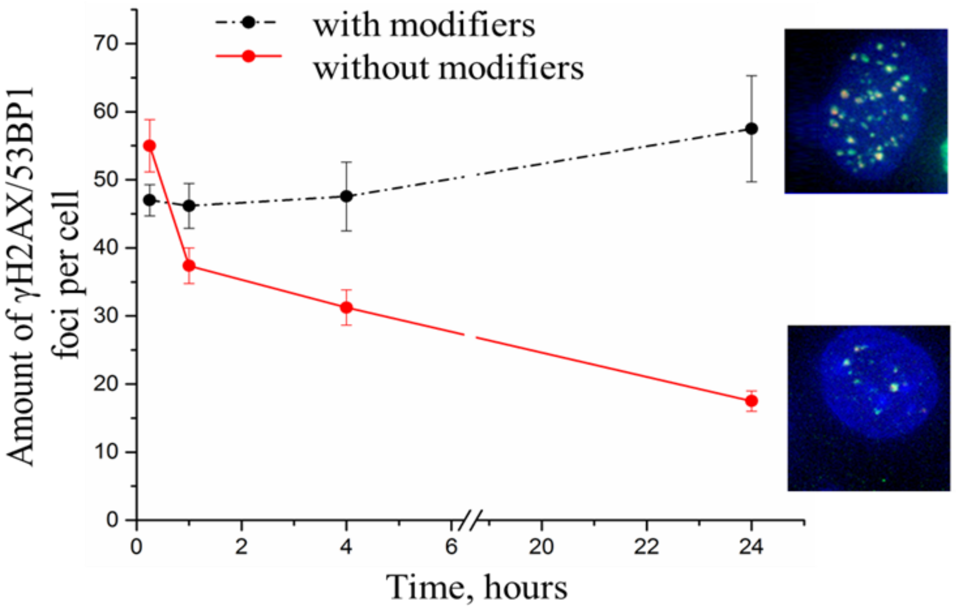


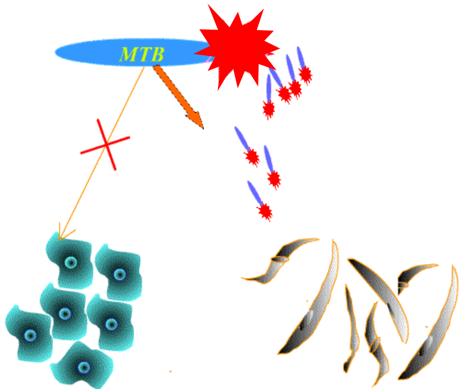

**Patents No.**
*2798733 (2023)*
*2774032 (2022)*
*2699670 (2019)*

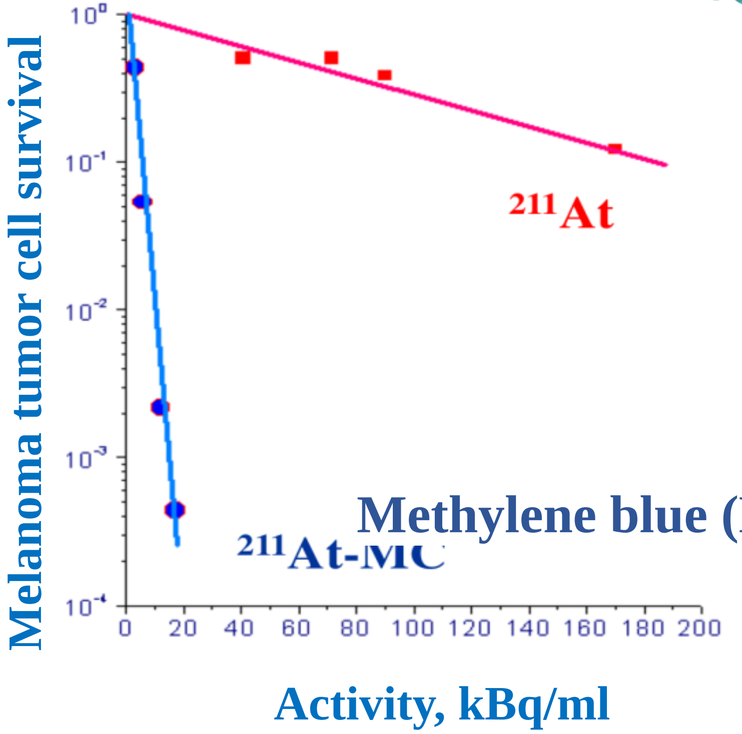
Glioblastoma tumor cells (U87) irradiated by medical proton beam (1.25 Gy)



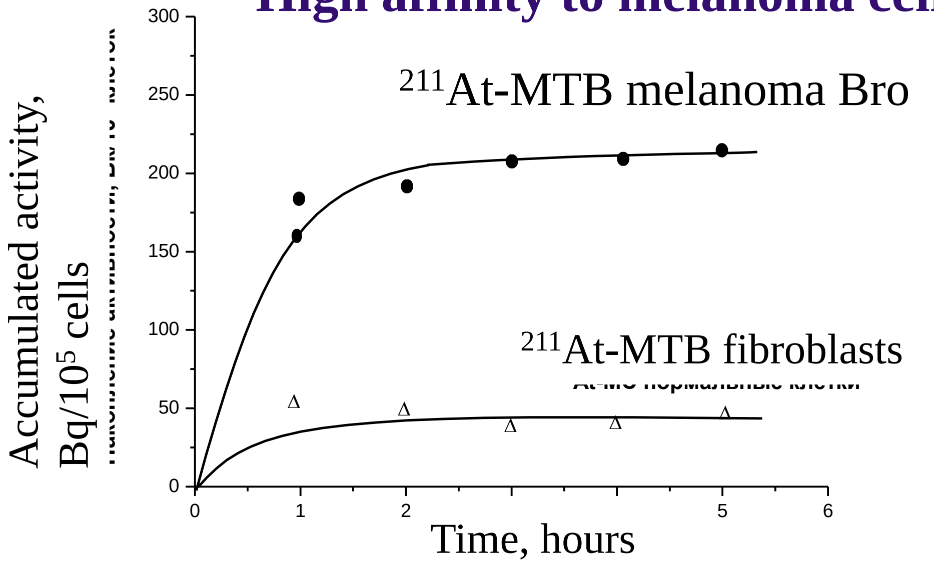
# JINR expertise in radiation medicine

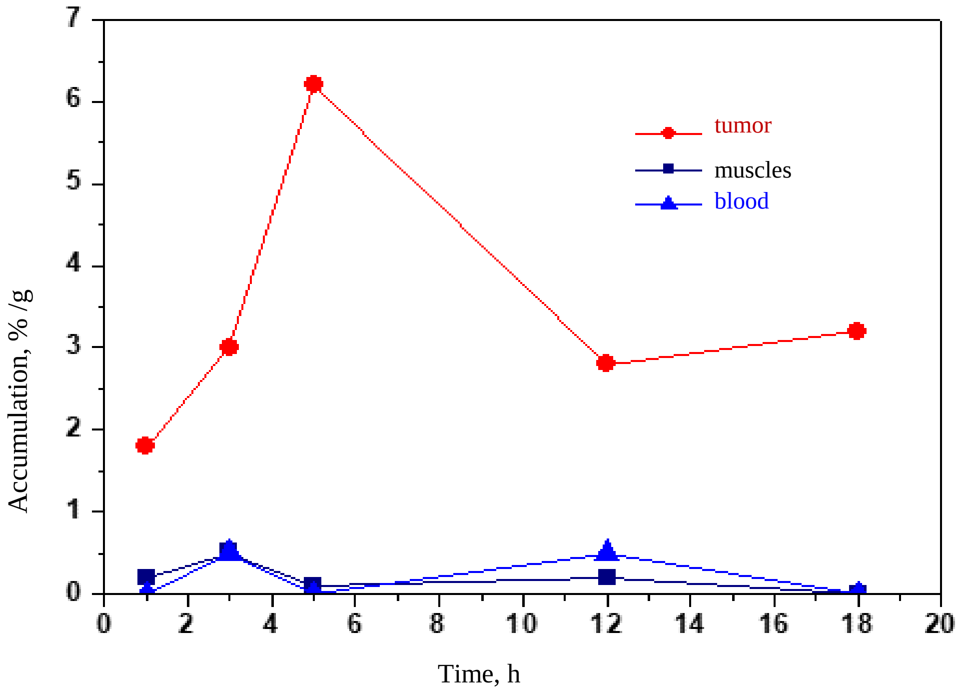
## System for targeted alpha-therapy of melanoma

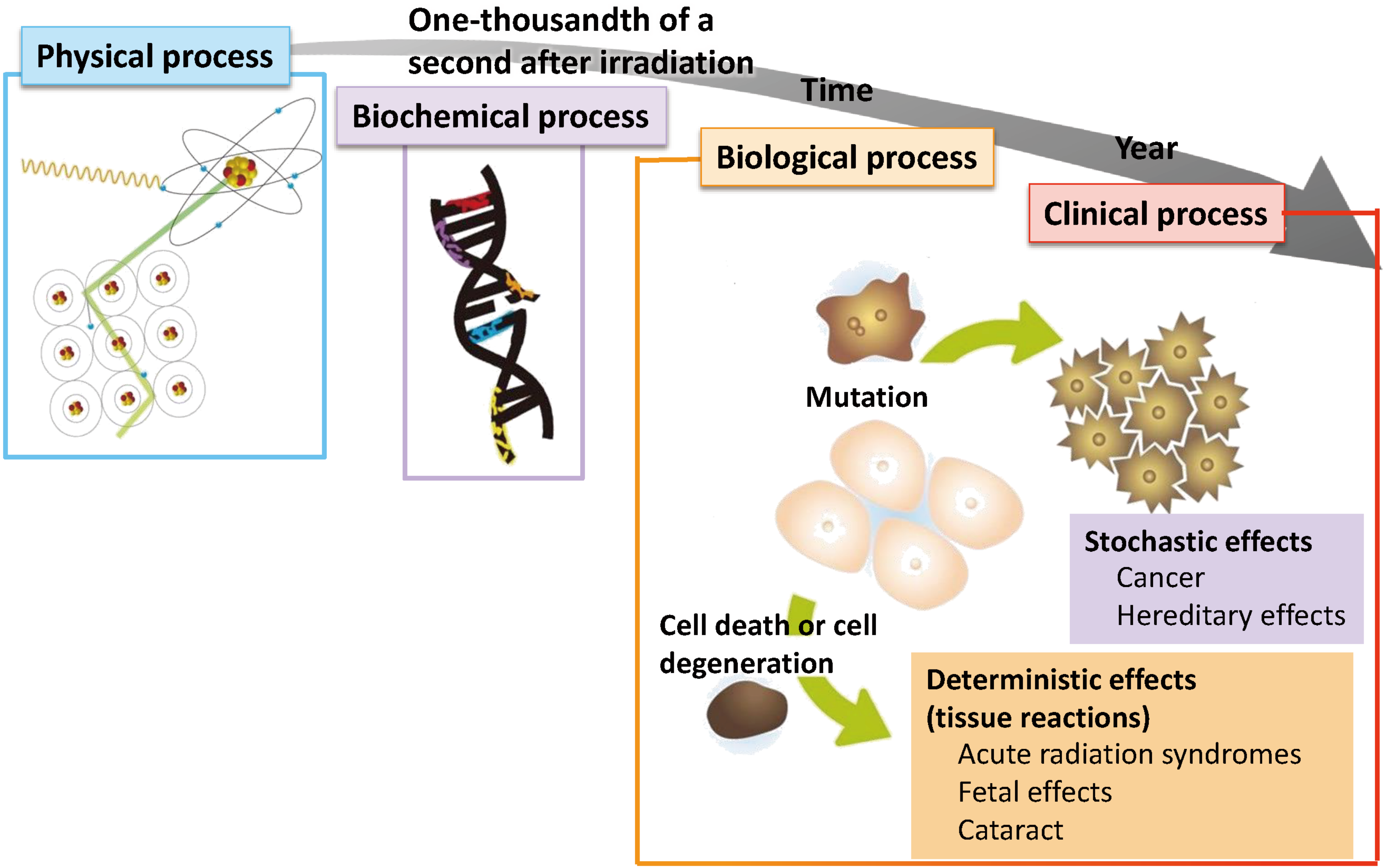


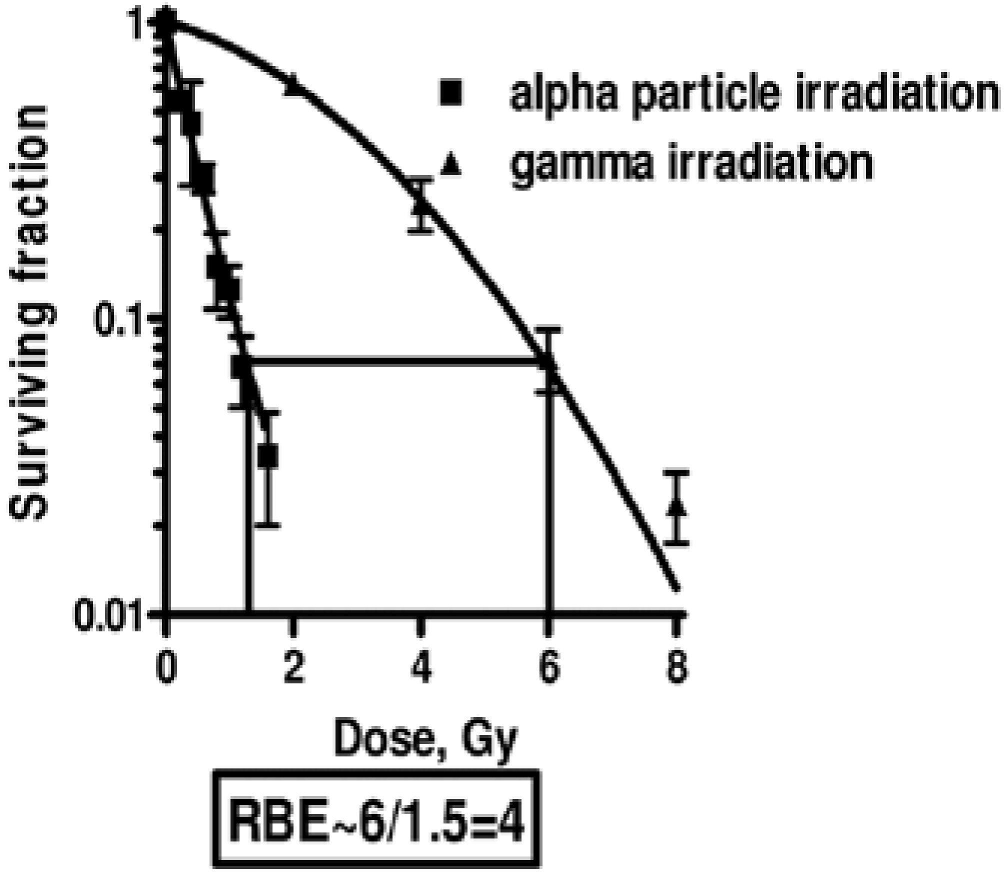

## High affinity to melanoma cells




One-thousandth of a second after irradiation
Time
Year
Physical process
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

# Relative biological effectiveness of ionizing radiations



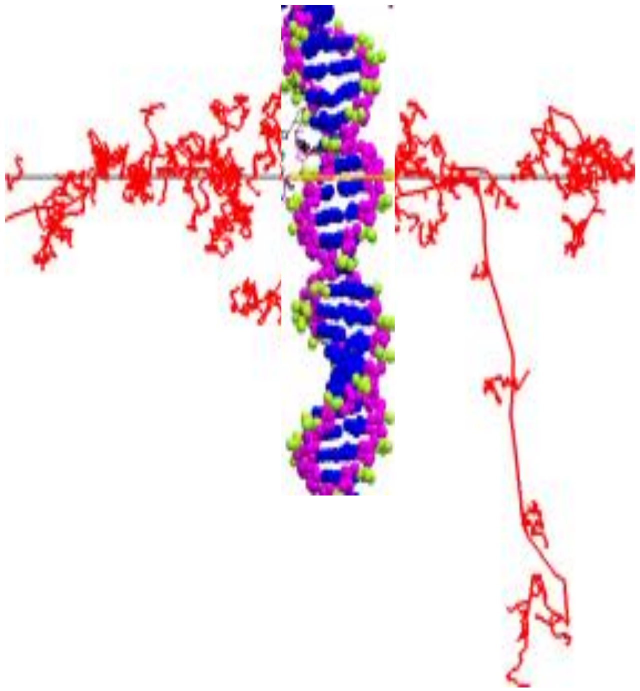

**The RBE value is determined by two factors - physical and biological.**

**The biological factor is dependent on the physical one.**

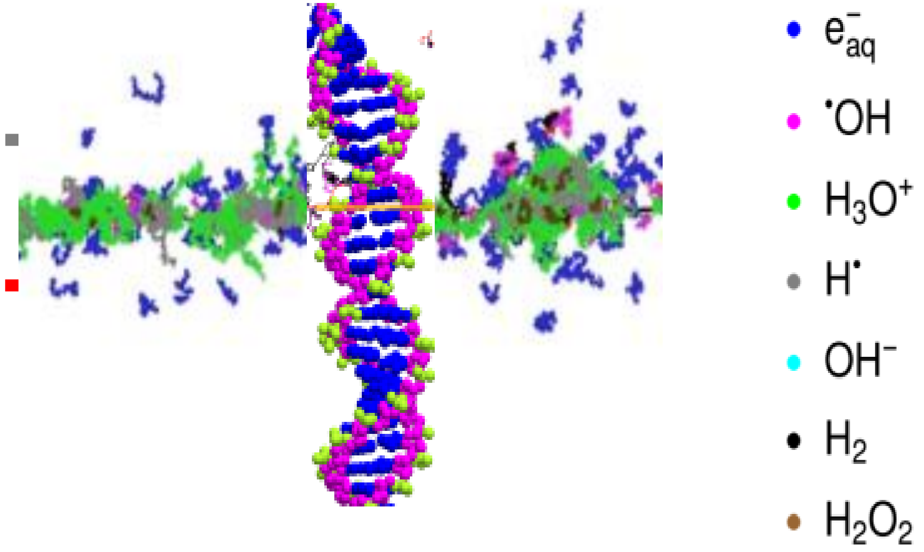
**DNA damage caused by photon and hadron radiation is qualitatively different**

# Biological efficiency of ionizing radiations
## Molecular basis

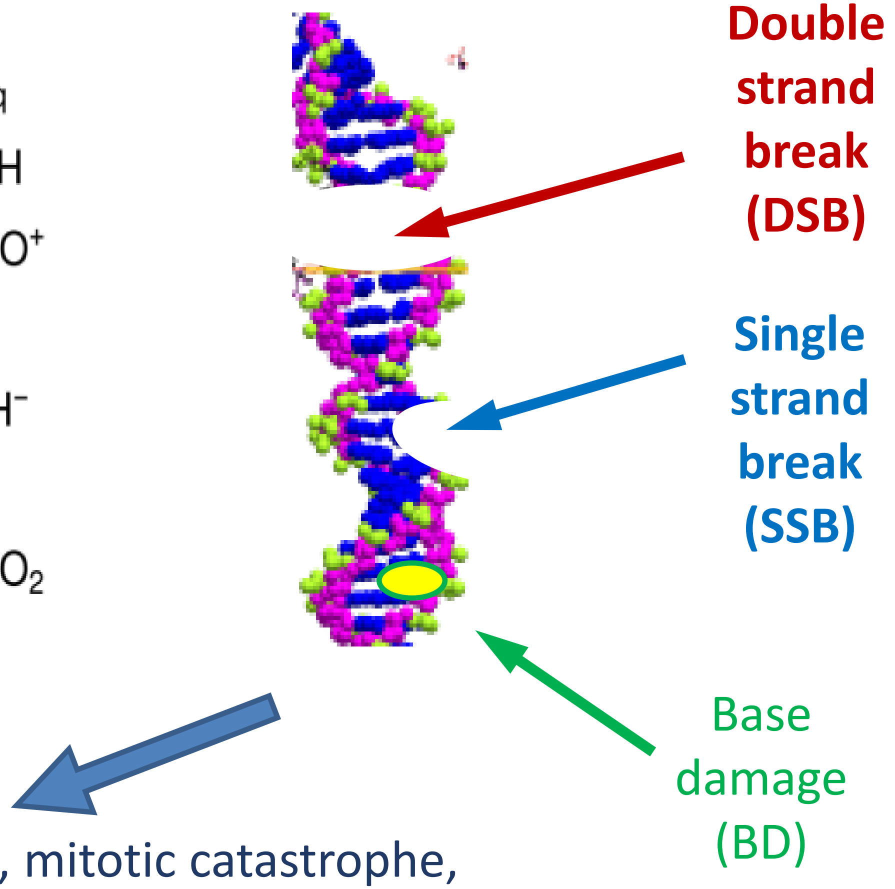
Ionization, bond breakage



Radical attack, indirect lesion




DNA lesions




Apoptosis, chromosome aberrations, mitotic catastrophe, cell death

# Important physical parameter – linear energy transfer (LET)

$$L = dE / dx$$

| Radiation tye | LET (keV/µm) |
|---|---|
| $^{60}Co$ γ-rays | 0,2 |
| 200 MeV protons | 0.45 |
| 290 MeV/u carbon ions | 12.9 |
| 600 MeV/u iron ions | 168 |
| 2,5 MeV α-particles | 166 |
| 1 MeV electrons | 0.25 |
| 10 keV electrons | 2.3 |
| 1 keV electrons | 12.3 |
| $^{235}U$ neutrons | 48 |

# LET of radionuclide decay products

| Radionuclide | Type | Half-life | $E_{max}$ (MeV) | Mean range (mm) | Imageable |
|---|---|---|---|---|---|
| $^{90}Y$ | β | 2.7 days | 2.3 | 2.76 | No |
| $^{131}I$ | β, γ | 8.0 days | 0.81 | 0.40 | Yes |
| $^{177}Lu$ | β, γ | 6.7 days | 0.50 | 0.28 | Yes |
| $^{153}Sm$ | β, γ | 2.0 days | 0.80 | 0.53 | Yes |
| $^{186}Re$ | β, γ | 3.8 days | 1.1 | 0.92 | Yes |
| $^{188}Re$ | β, γ | 17.0 h | 2.1 | 2.43 | Yes |
| $^{67}Cu$ | β, γ | 2.6 days | 0.57 | 0.60 | Yes |
| $^{225}Ac$ | α, β | 10 days | 5.83 | 0.04–0.10 | Yes |
| $^{213}Bi$ | α | 45.7 min | 5.87 | 0.04–0.10 | Yes |
| $^{212}Bi$ | α | 1.0 h | 6.09 | 0.04–0.10 | Yes |
| $^{211}At$ | α | 7.2 h | 5.87 | 0.04–0.10 | Yes |
| $^{212}Pb$ | β | 10.6 h | 0.57 | 0.60 | Yes |
| $^{125}I$ | Auger | 60.1 days | 0.35 | 0.001–0.020 | No |
| $^{123}I$ | Auger | 13.2 h | 0.16 | 0.001–0.020 | Yes |
| $^{67}Ga$ | Auger, β, γ | 3.3 days | 0.18 | 0.001–0.020 | Yes |

**LET ~ 0.1-1 keV/μm**

**LET ~ 50-200 keV/μm**

**LET ~ 5-25 keV/μm**

# Biological efficiency of ionizing radiations
## Amount of DNA damage

### Computer simulations

1) Base damage BD
2) Single strand breaks SSB
3) Clustered SSB
4) Double strand breaks DSB
5) Clustered DSB

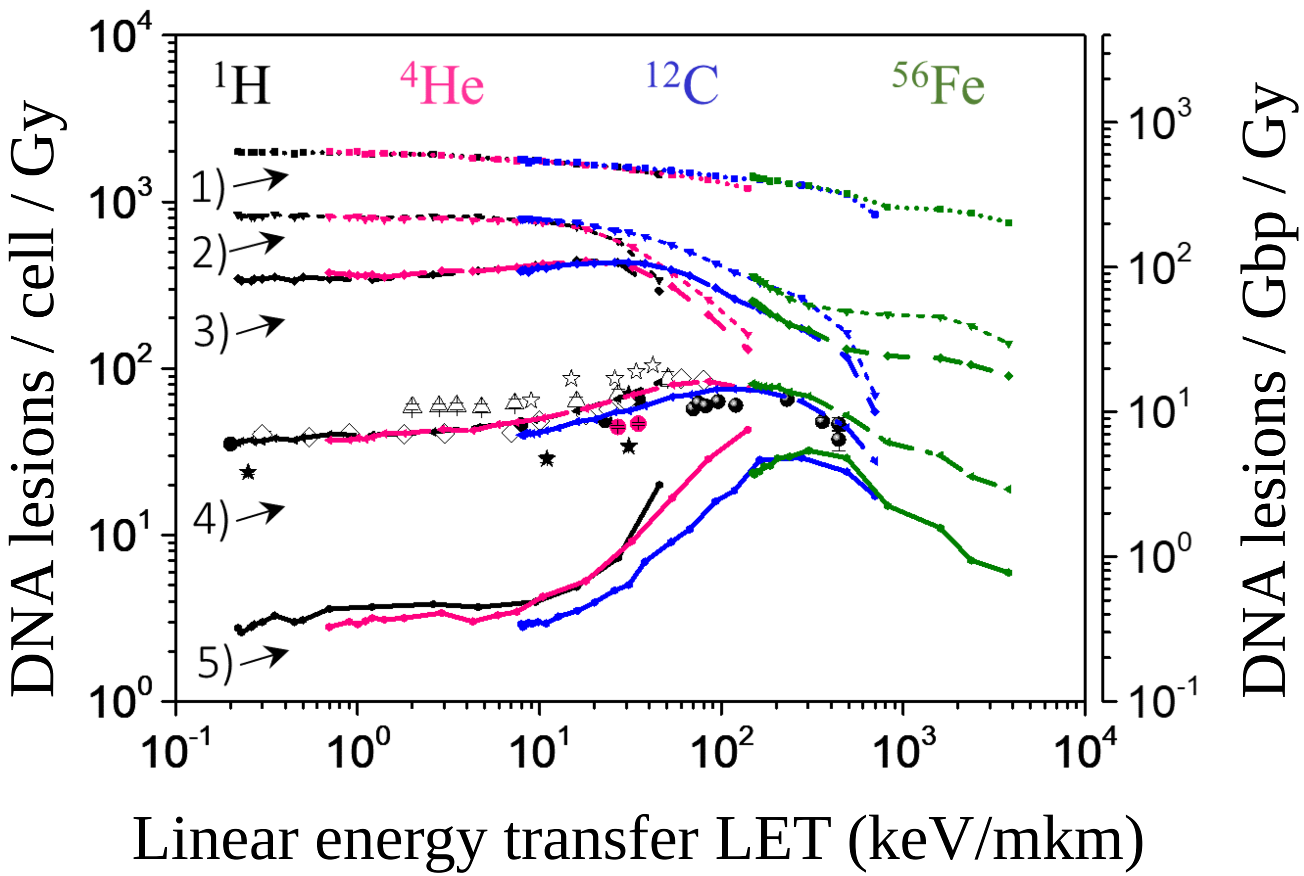
### Expeiments (DSB)

- ● Frankenberg 1999
- ★ Belli 2001
- ● Belli 2006
- ■ Bulanova 2019

Calculations (DSB)

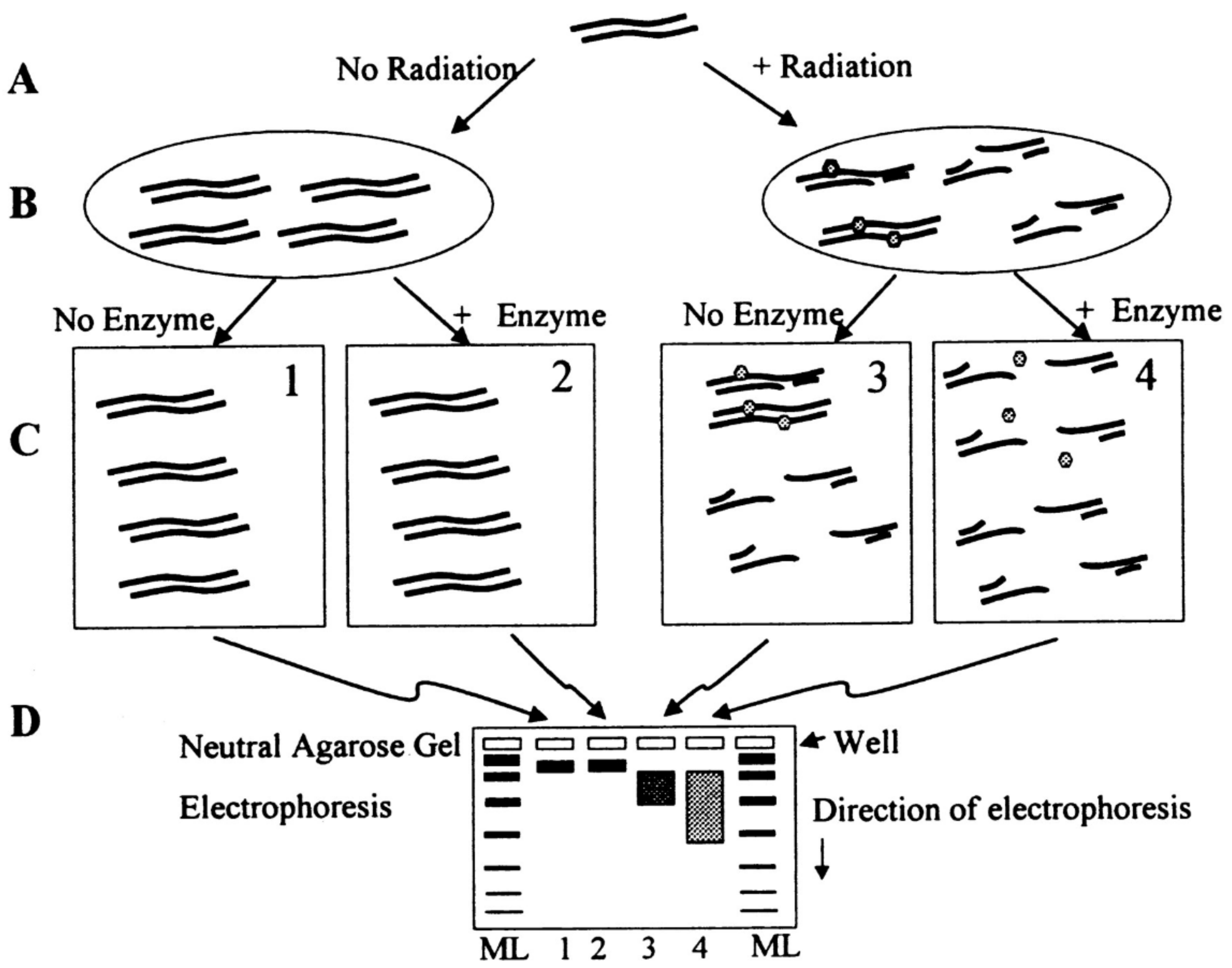
- --★--- Nikjoo 2001
- --◇--- Friedland 2011
- --△--- Rosales 2018

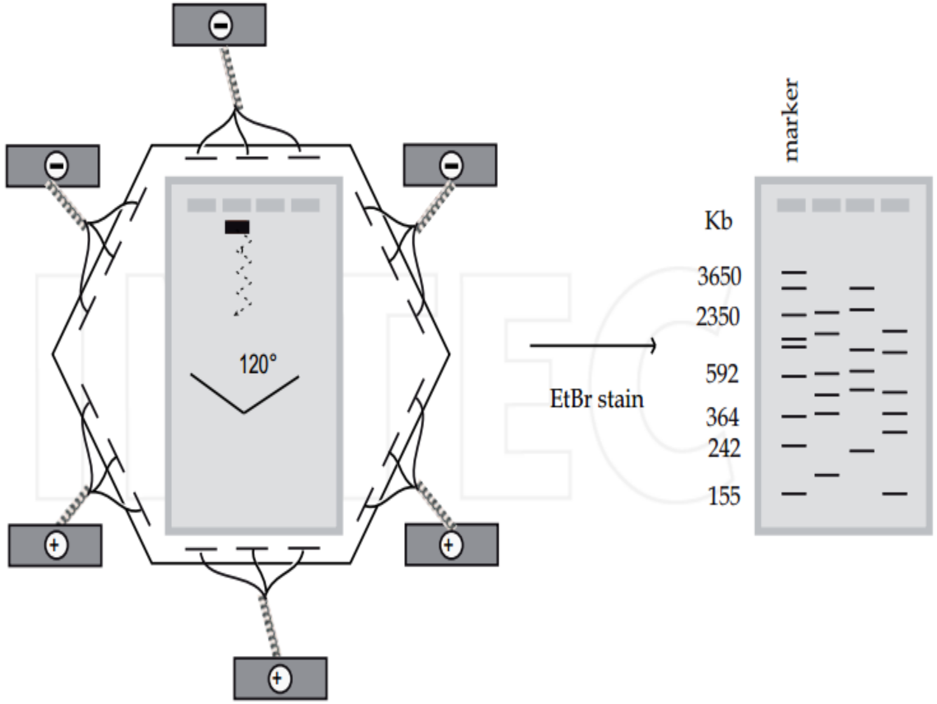
**1 DSB**
**:**
**10 SSB**
**:**
**100 BD**



# Measurement of DNA lesions

## 1. Pulsed-field gel electrophoresis



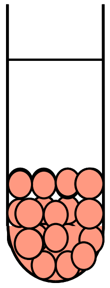




Electric field alternates 120° every 90 seconds for 18 to 24 hours at 14°C

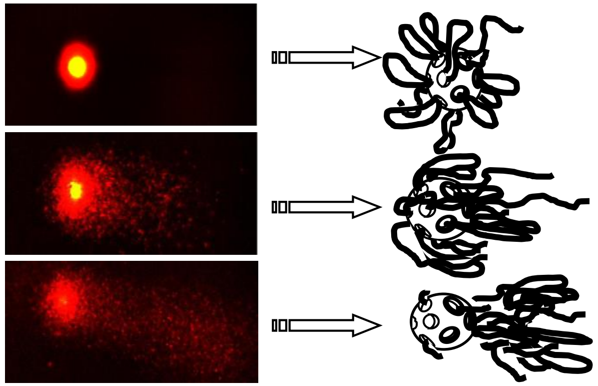
**Pulsed-field gel electrophoresis (PFGE) is a technique used for the separation of DNA fragments by applying to a gel matrix an electric field that periodically changes direction**

# Measurement of DNA lesions

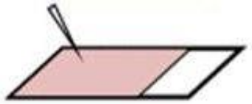
## 2. Comet assay
(single cell gel electrophoresis assay)



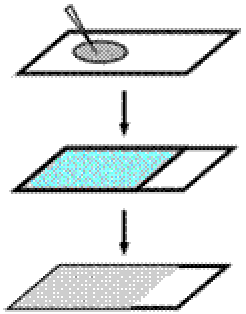
Cell culture



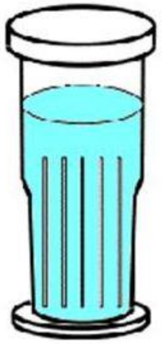
**the intensity of the comet tail relative to the head reflects the number of DNA breaks.**



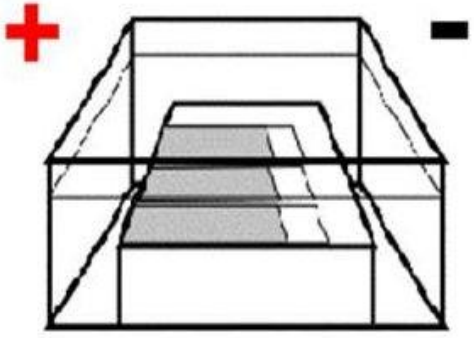
**Fluorescent staining**



**Encapsulation**



Cell lysis



Electrophoresis

Cells embedded in agarose on a microscope slide are lysed with detergent and high salt to form nucleoids containing supercoiled loops of DNA linked to the nuclear matrix. Electrophoresis at high pH results in structures resembling comets, observed by fluorescence microscopy;

# Measurement of DNA lesions

## 3. Immunofluorescent microscopy

**Irradiation**

↓

**Fixation of cells at different times post-irradiation (PI)**

↓

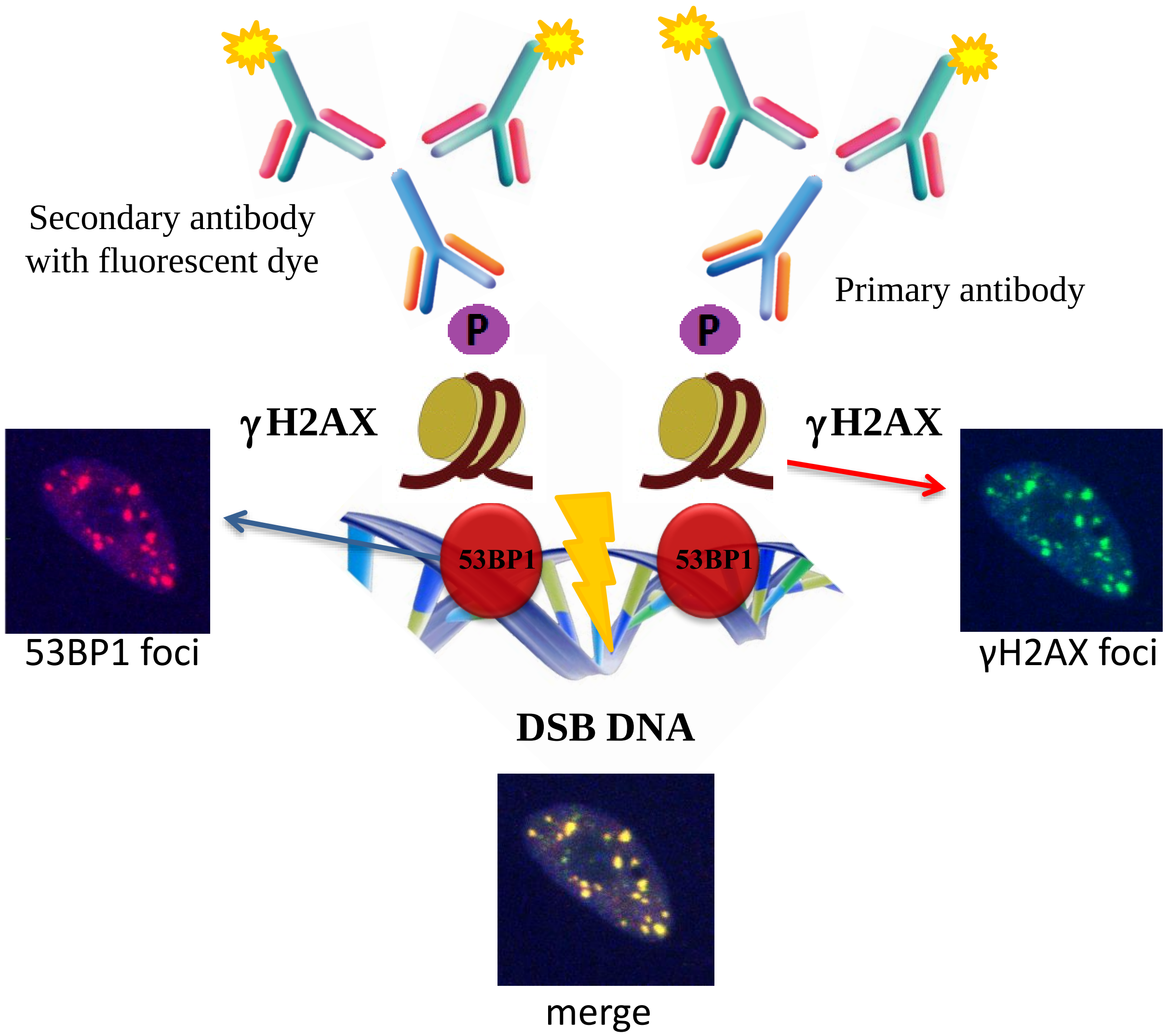
**Visualisation of induced DSBs (γH2AX/53BP1 foci)**

↓

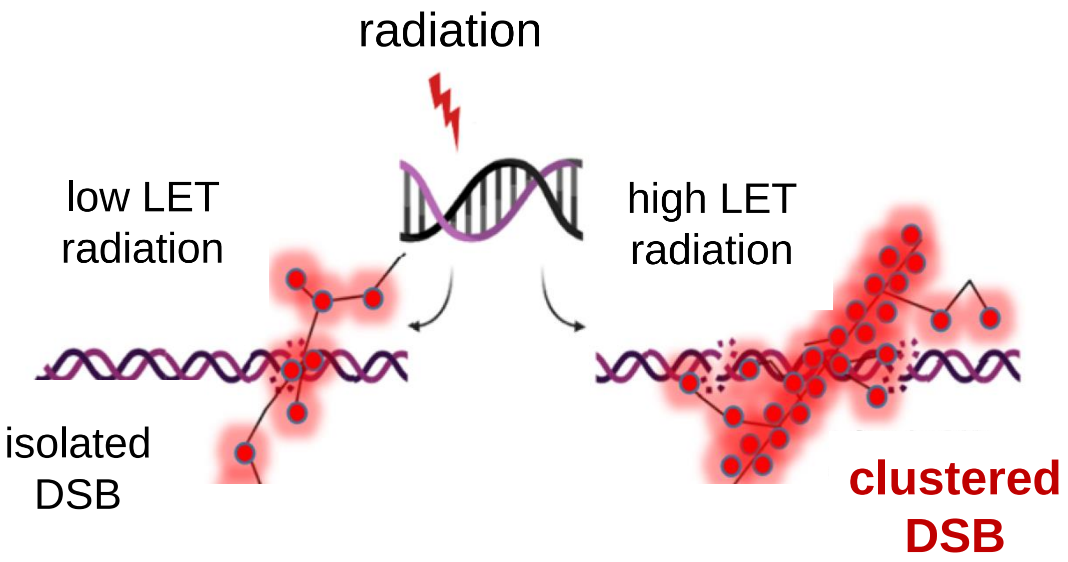
**Acquisition of images**

↓

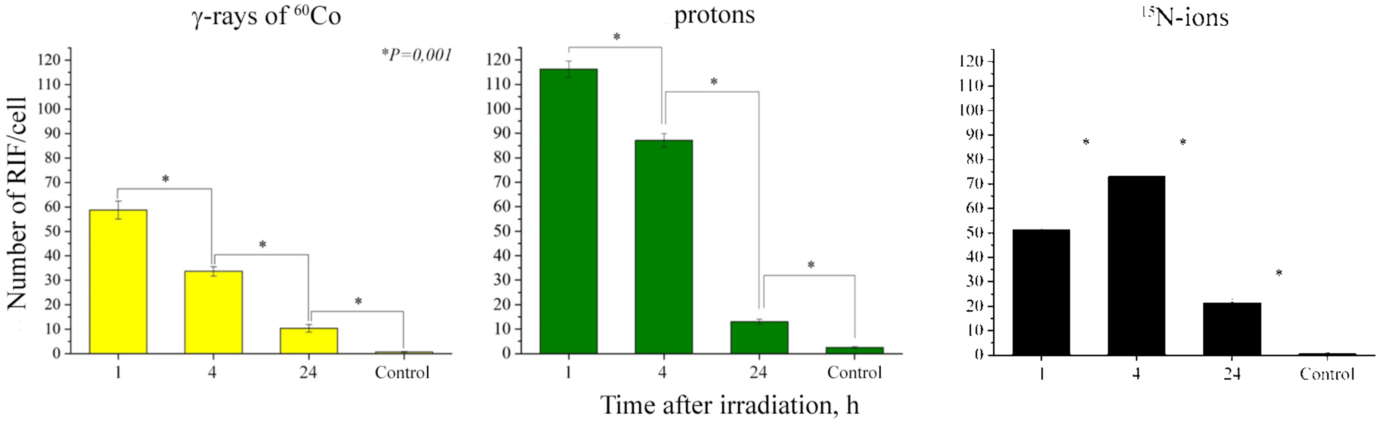
**3D analysis of induced γH2AX/53BP1 foci - Acquiarium**



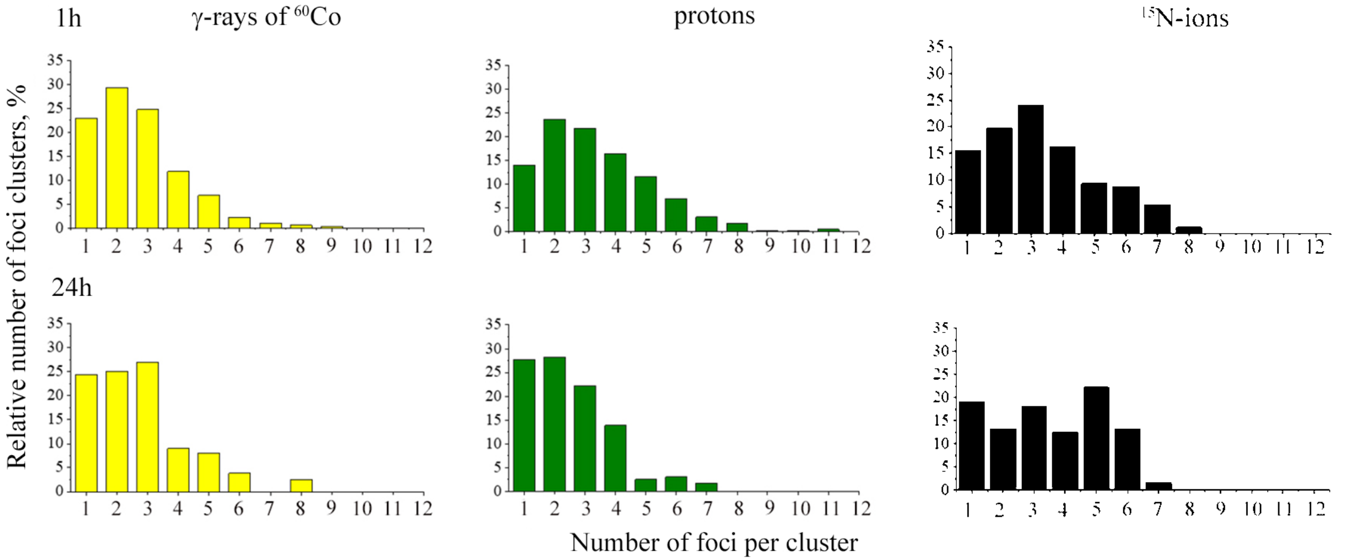
# DNA damage complexity. Clustered DNA double strand breaks



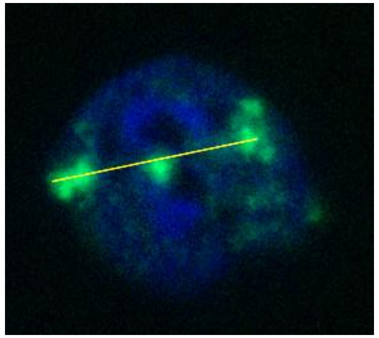

## Repair of DSBs



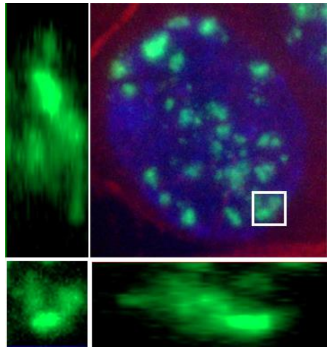

## Complexity level of clustered DSBs at different times




radiation-induced foci (RIF) in a track of nitrogen ions traversing neuron cell



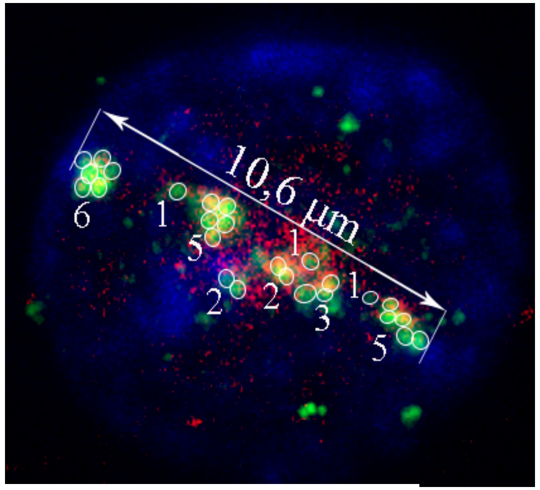
γH2AX foci cluster

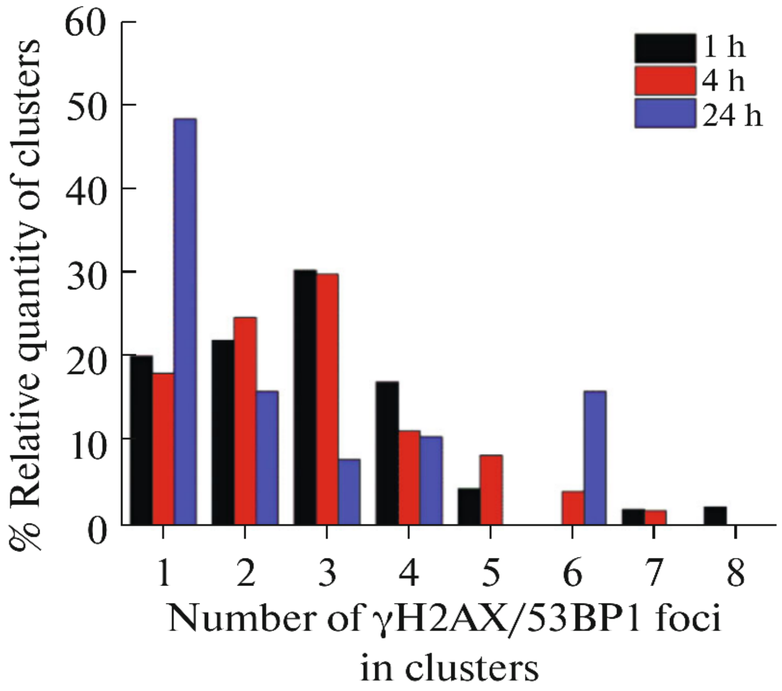


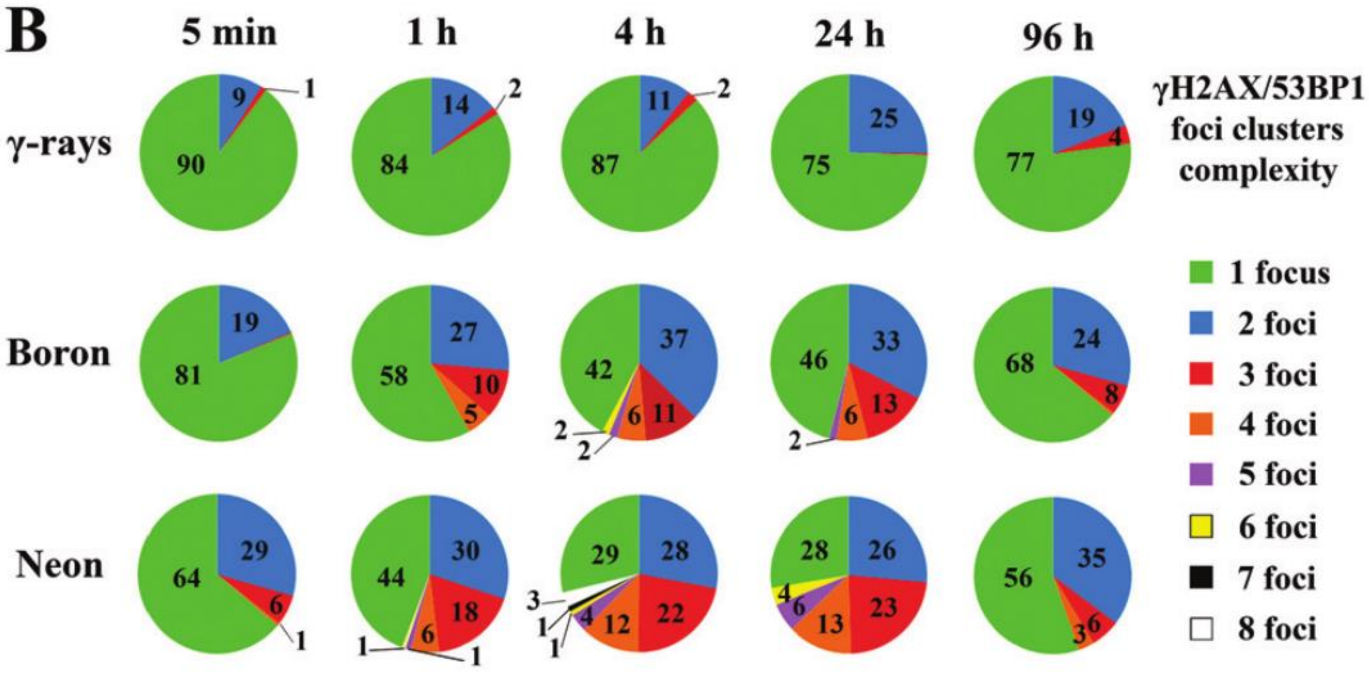
# DNA damage complexity. Clustered DNA double strand breaks

**A**

DNA damage in the rat hippocampus cells 1 hour after exposure to $^{78}$Kr ion beam

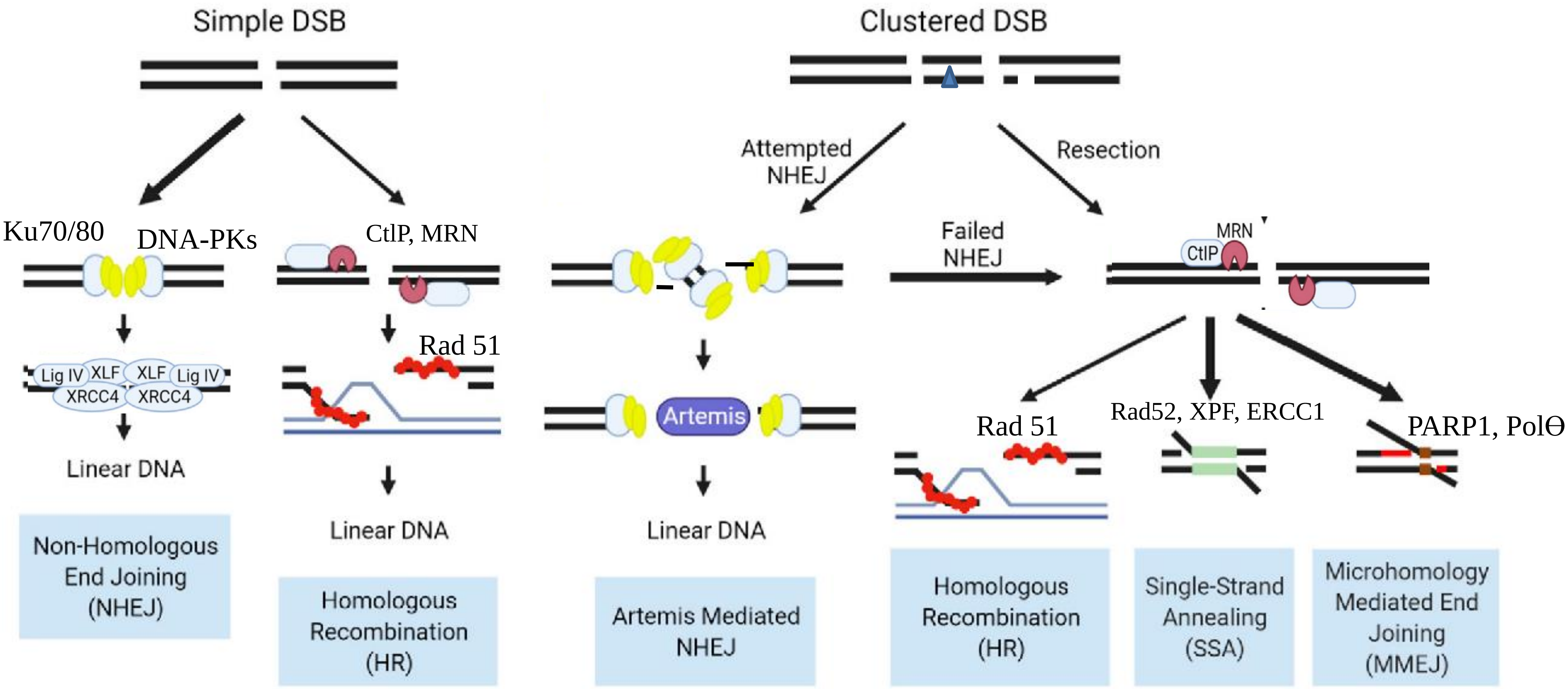



Ions with similar LET (~130 keV/mkm) generate foci clusters of different complexity

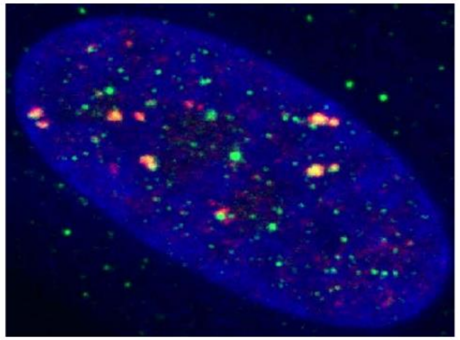
# DNA repair. Pathways of DNA DSB reparation



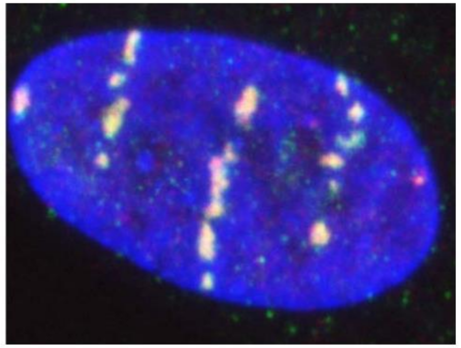

modified from Danforth et al(2022) Front. Cell Dev. Biol. 10:910440.

# Research on DNA repair

a)

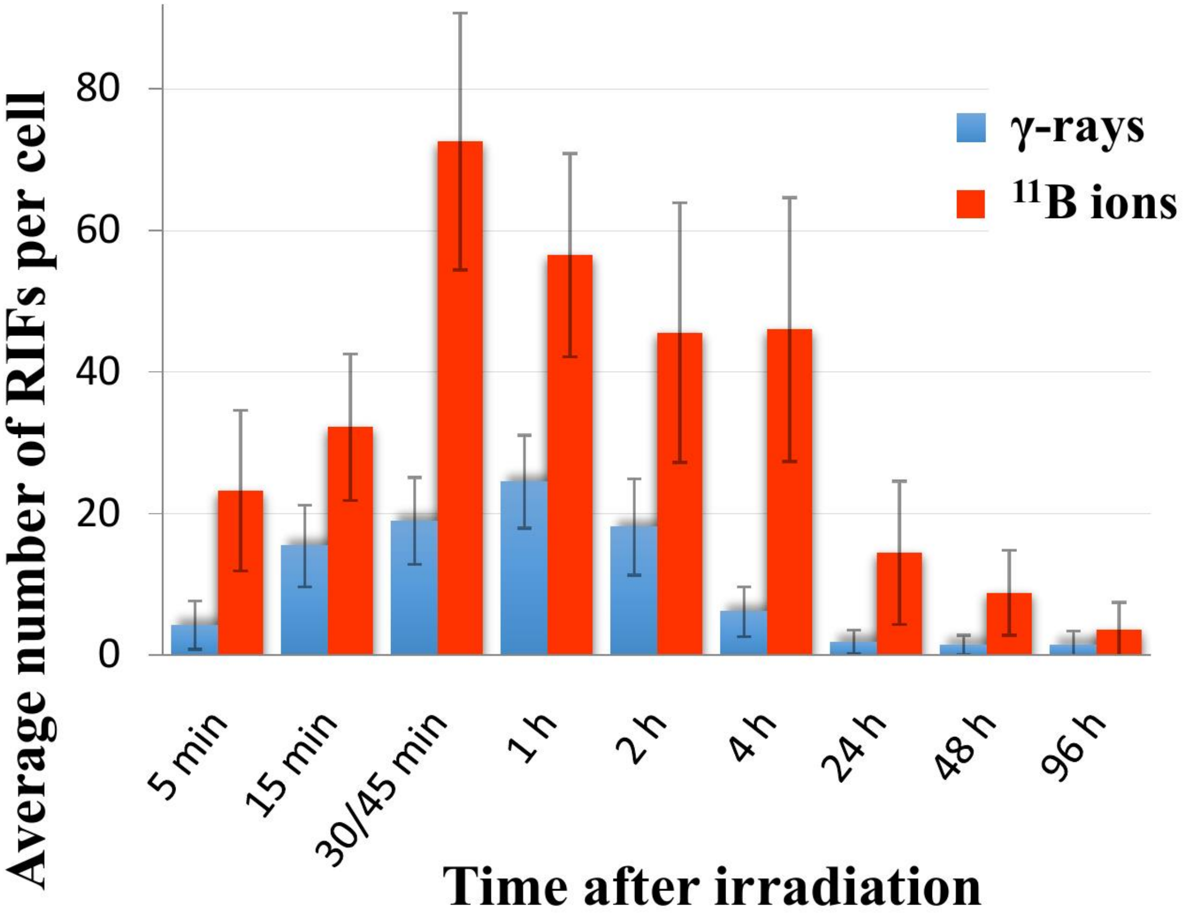


γ-rays



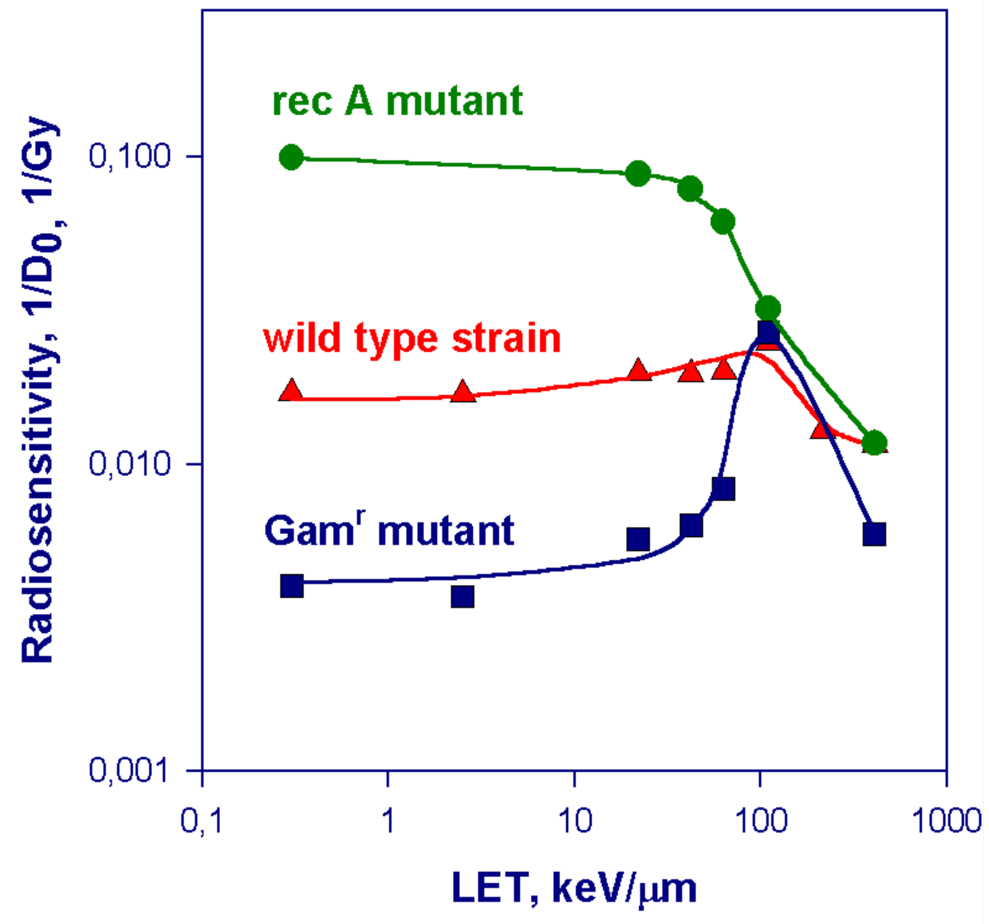
$^{11}$B ions

b)



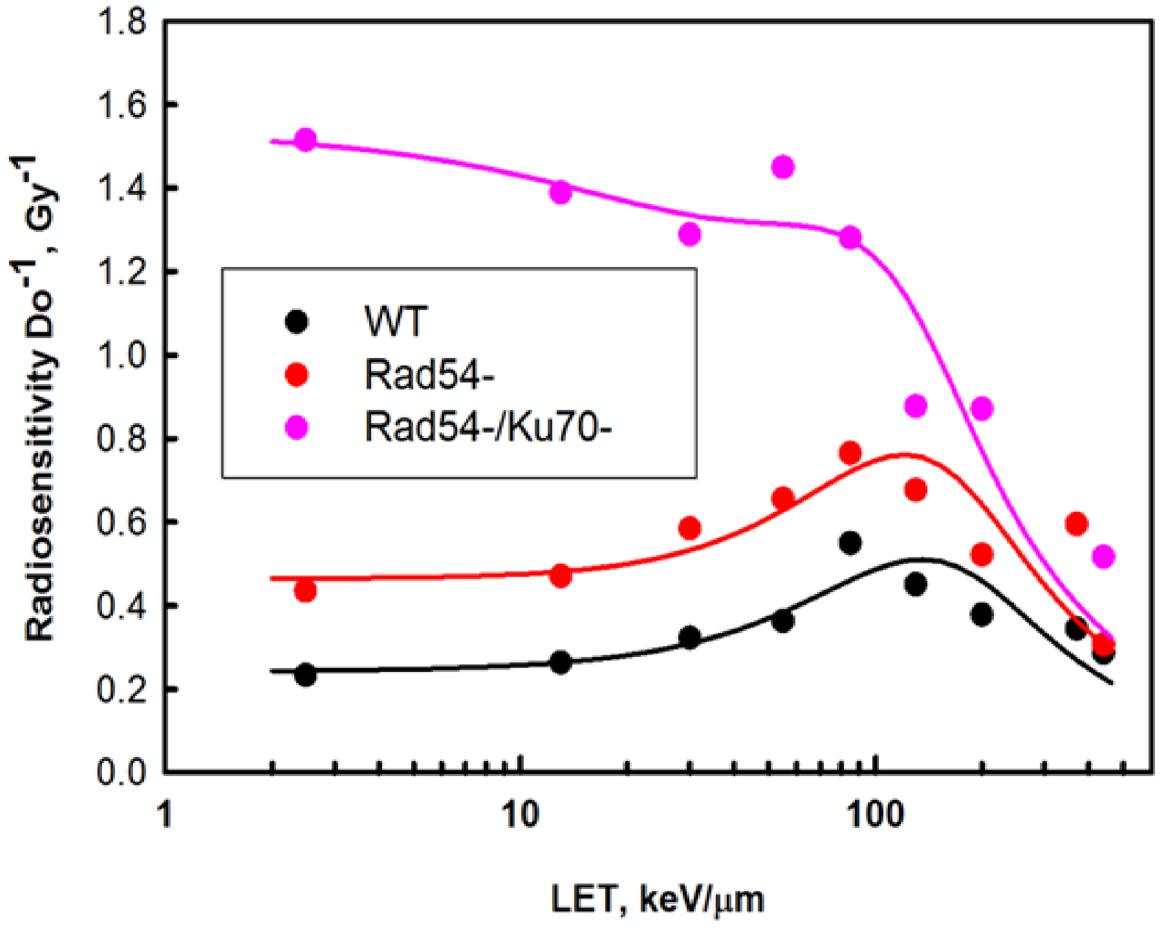
# Radiosensitivity and DNA repair

**E. Coli**




*Data source: LRB*

**B-lymphoma cells**

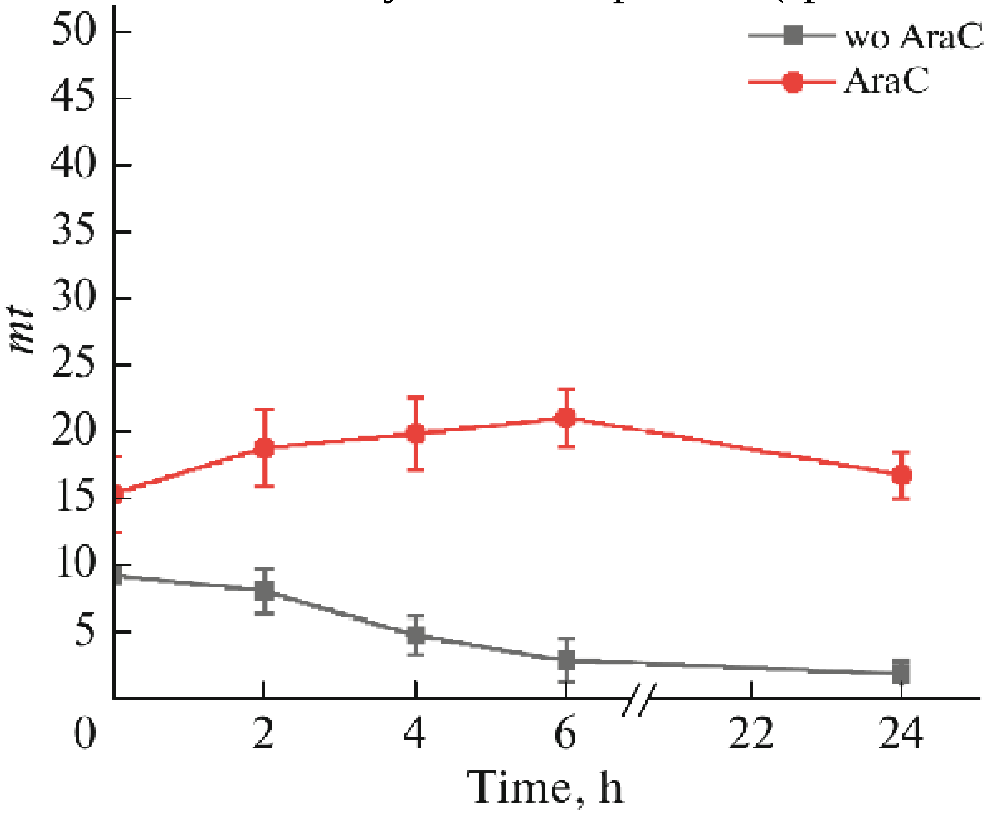



*Data source: Furusawa 2013*

# Effect of radiomodifier drugs on DNA damage

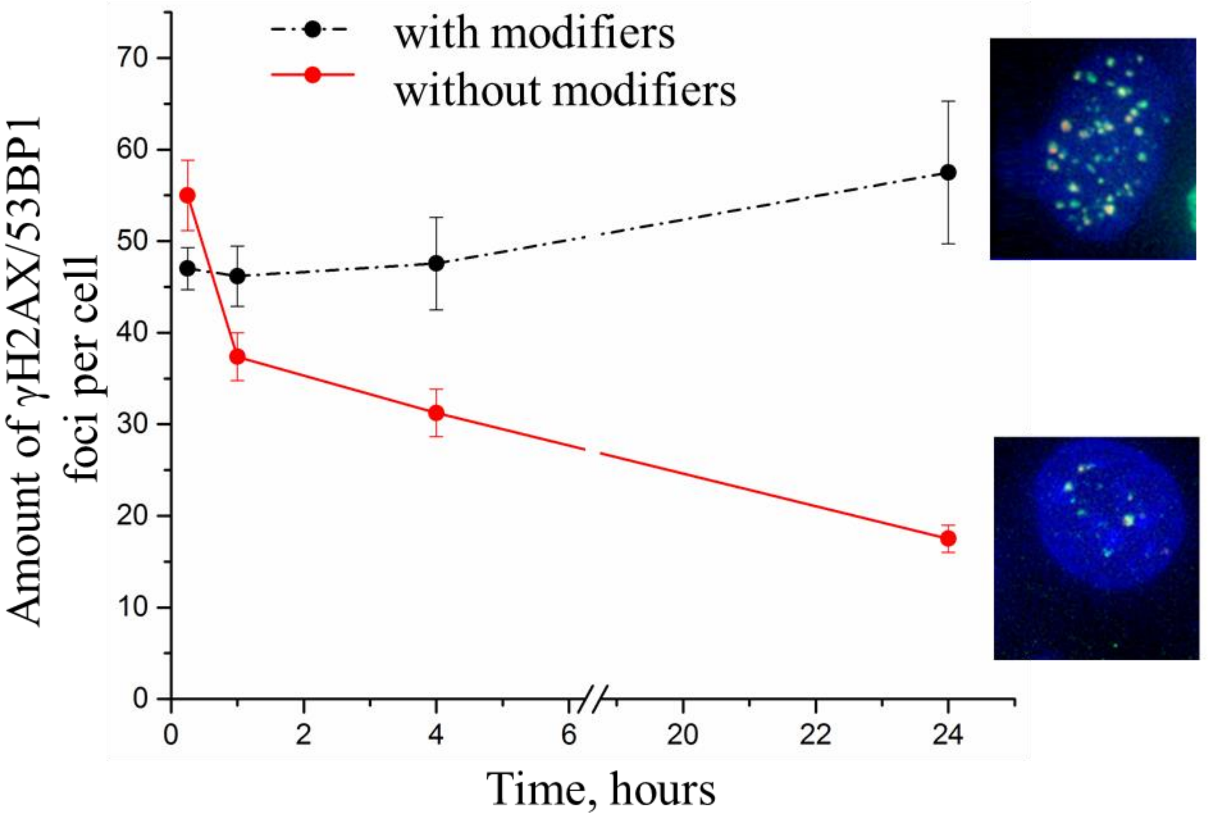
## Melanoma B16

5 Gy 170 MeV protons (spread out Bragg peak)




## Glioblastoma U87

1.25 Gy 170 MeV protons (spread out Bragg peak)




*E. A. Krasavin et al // Phys. Part. Nucl. Lett. (2019) 16: 153*

*R. A. Kozhina et al // Phys. Part. Nucl. Lett. (2022) 19: 590*

# Radiation Cytogenetics

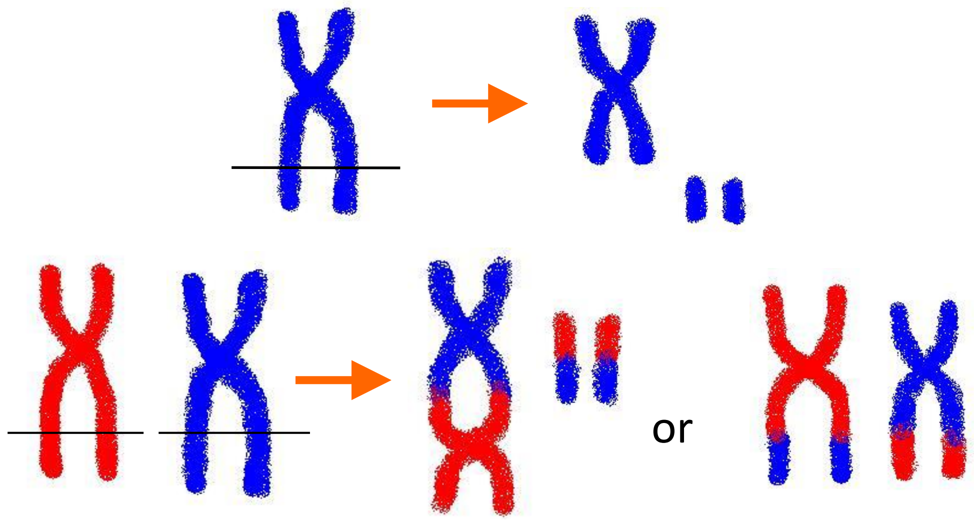
## Mutagenic effects radiations

- Radiation exposure to cell
- (Damage to DNA)
- Cells try to repair

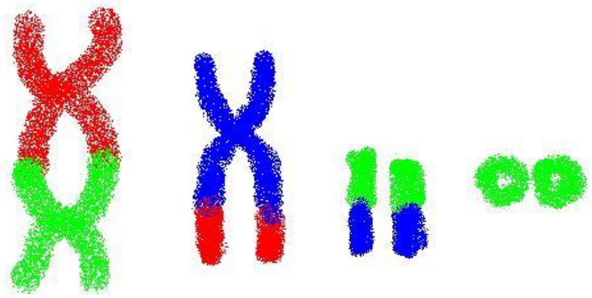
Repair successful | Repair failed | Cell death

Repair failed → eg chromosome aberrations

Examples of chromosome aberrations

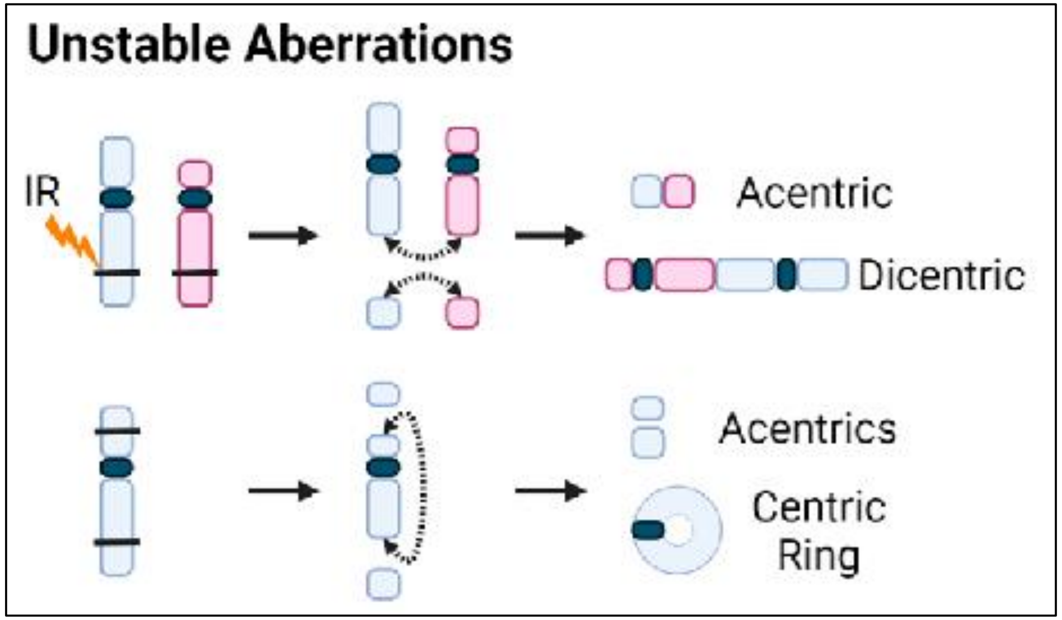


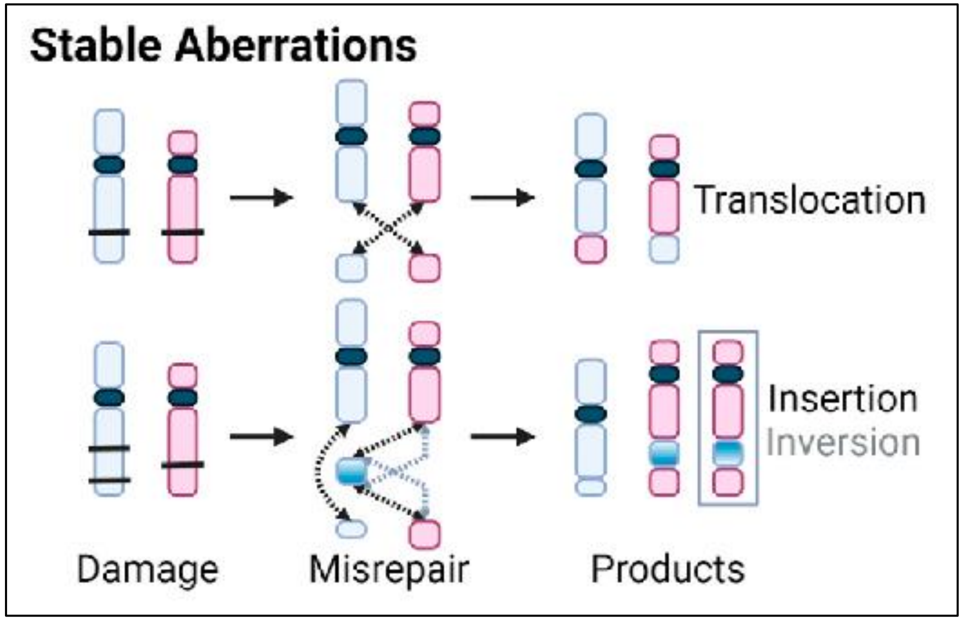

Following high LET exposure

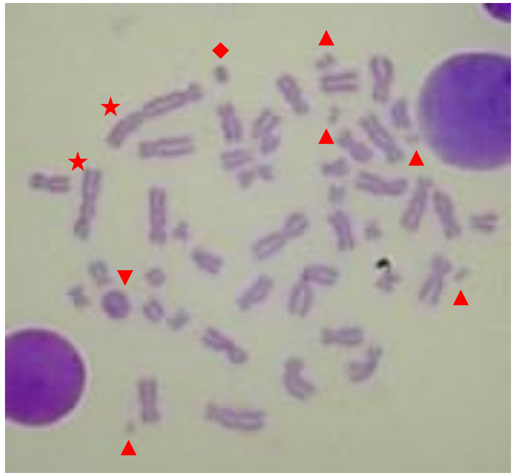


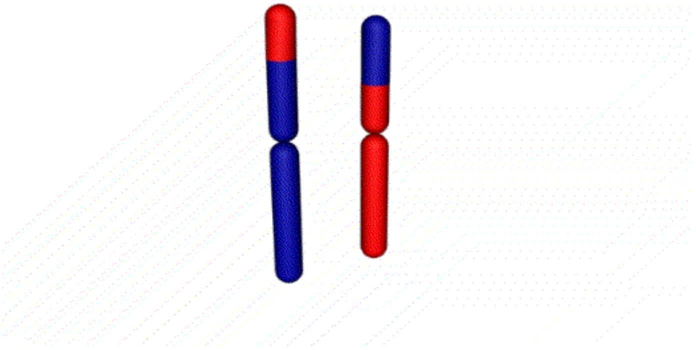
# Radiation Cytogenetics

Types of chromosome aberrations

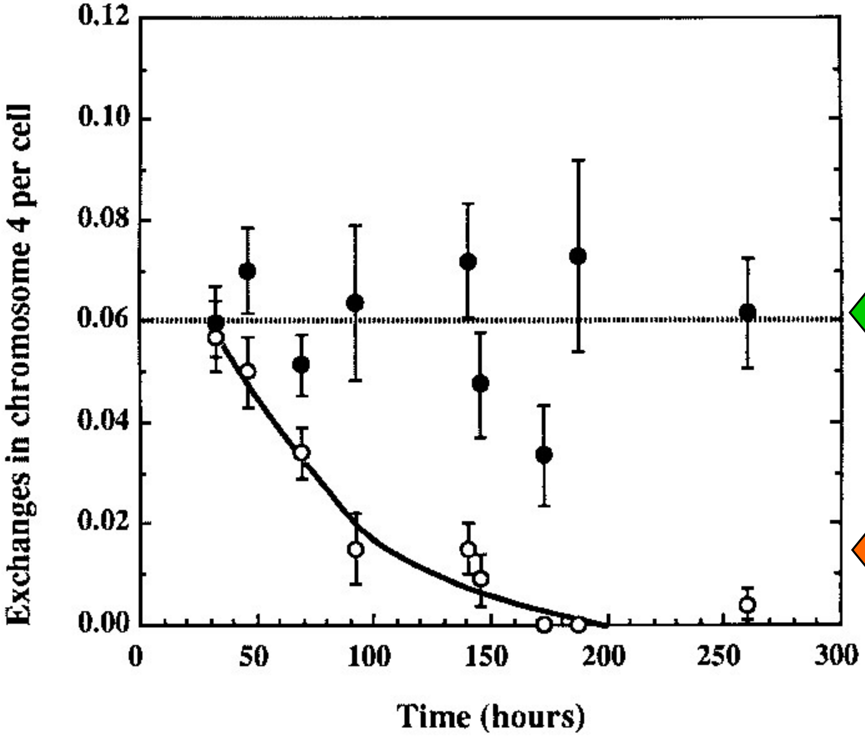


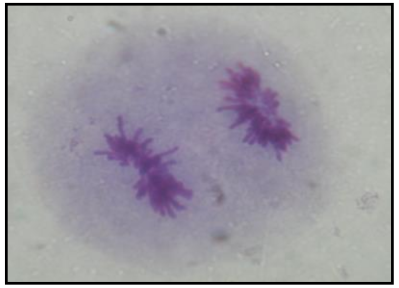





# Fate of stable and unstable aberrations

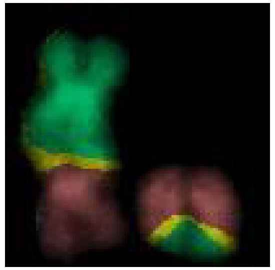



Aberrations in human fibroblasts
after gamma-ray exposure (6 Gy)
(*Kovacs et al. 1994*).



transmissible/stable
(translocations)

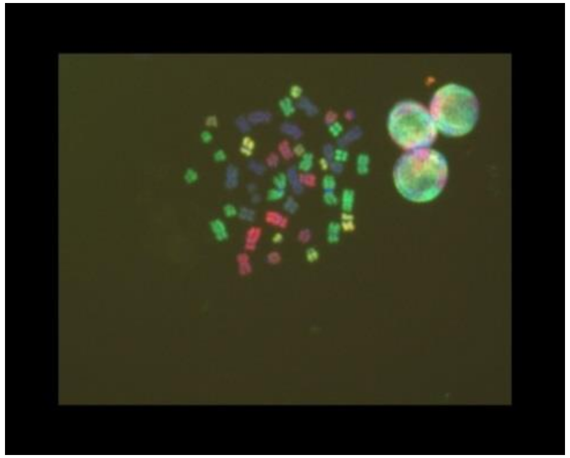
non-transmissible/stable
(dicentrics)

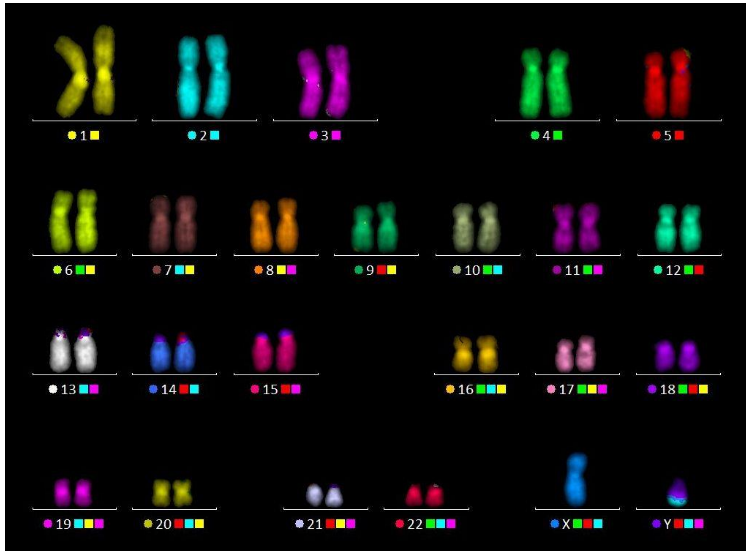


# Multicolor fluorescence *in situ* hybridization (mFISH)

- 5 types of probe DNA (≈150 - 400 bp long) labeled with 5 different fluorochromes **FITC SpO TR Cy5 DEAC**
- Specific binding to chromosomes (1 – 3 differently labeled DNA probes bind to each chromosome ⇒ 25 fluorochrome combinations)
- DAPI-counterstaining
- Images are captured at fluorescence microscope using a filter set
- resolution: ≈ 2,6 Mbp, depending on fluorochrome composition involved and hybridization quality

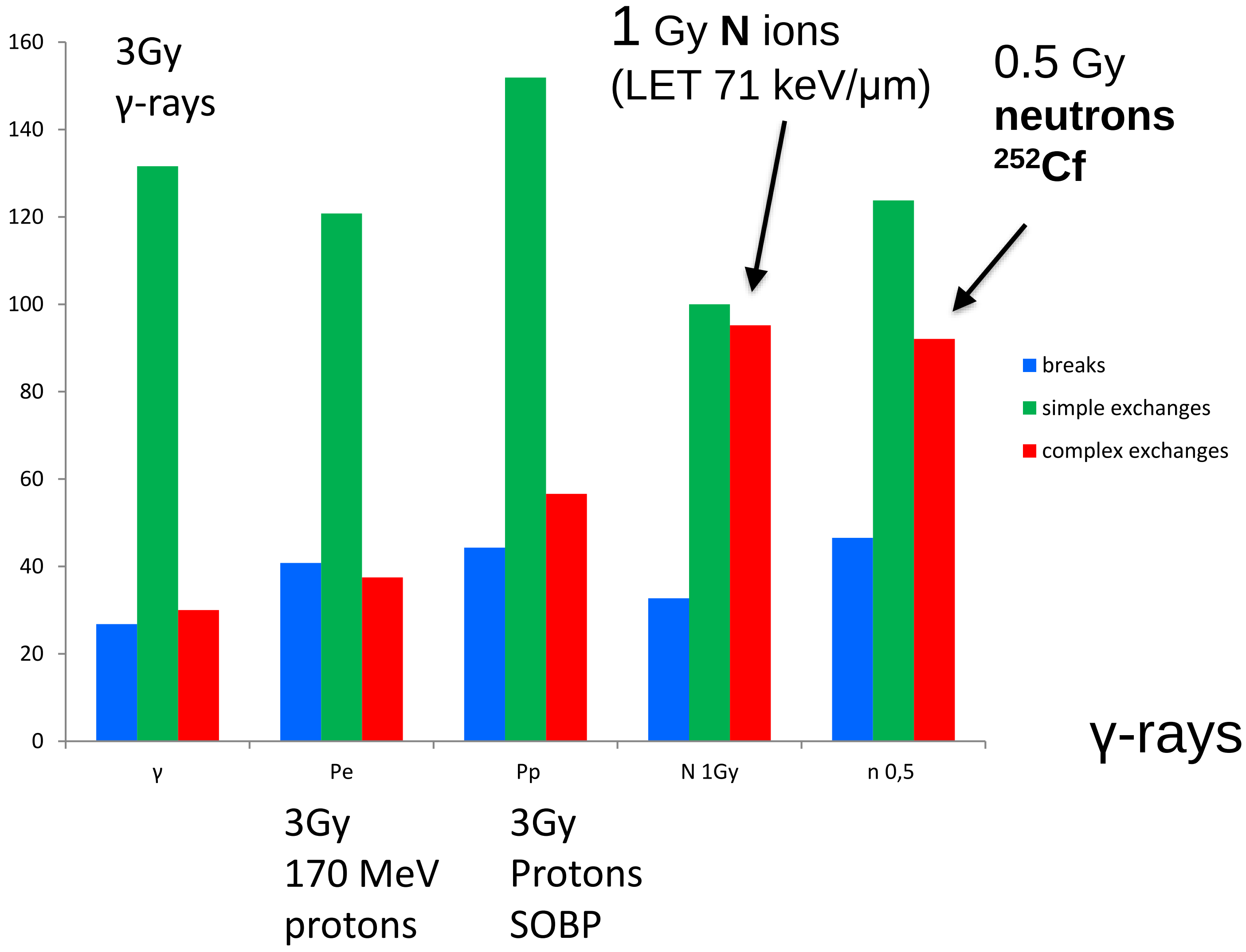
Probes and software of **MetaSystems, Germany**



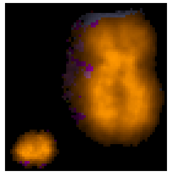



mFISH karyogram

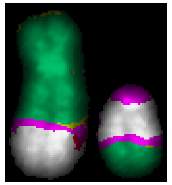
# RBE evaluation by mFISH



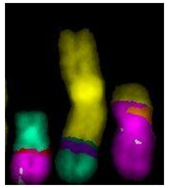

acentrics
(1 break)



simple exchanges
(2 breaks)



complex
aberrations
(≥3 breaks)



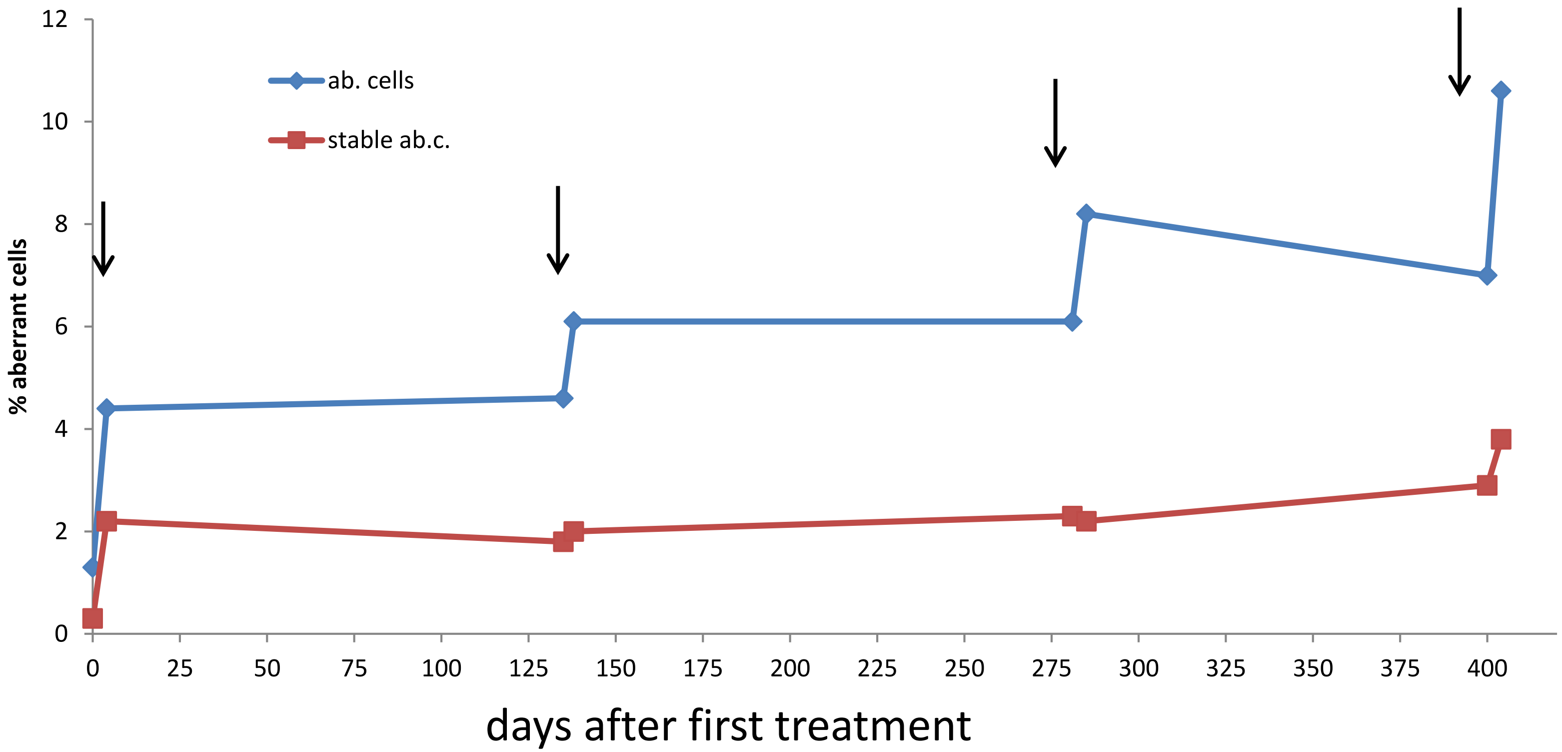
γ-rays and protons: 20 % / 60 % / 20 %

$^{14}$N ions: 14 % / 44 % / 42 %

# Cytogenetic risk evaluation:

## Prognosis of long-term consequences

(persistence of stable heritable CA in surviving cells)




Increase of % of aberrant cells during RIT (arrows mark I-IV $^{131}I$ courses)

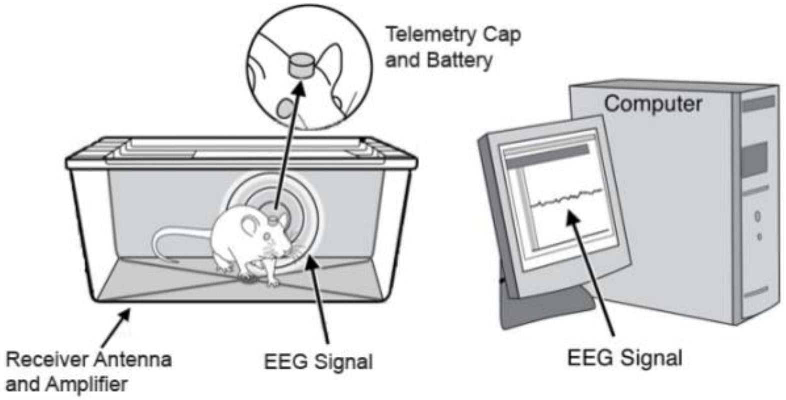
➢ **frequency of stable aberrant cells may serve as a prognostic marker of leukemogenesis**

# Set of equipment for the study of behavioral reactions and functional disorders of the central nervous system of animals

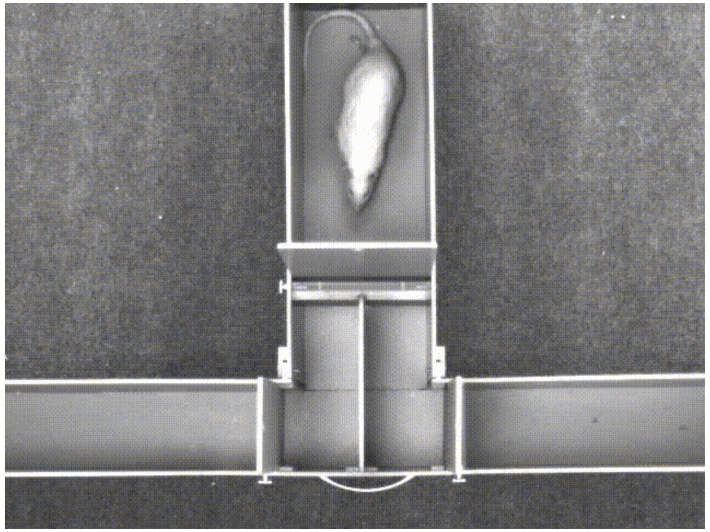
## Behavior test systems

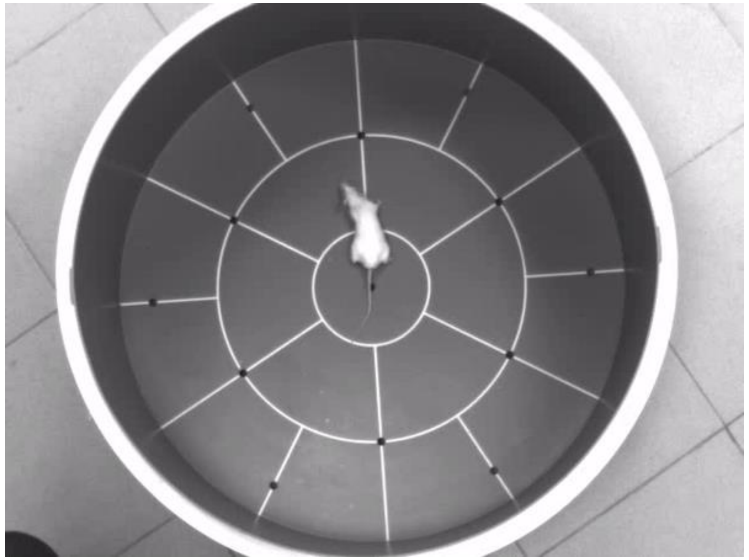
- Open field
- T - maze
- Morris water maze
- Barnes maze

## Electrophysiology studies



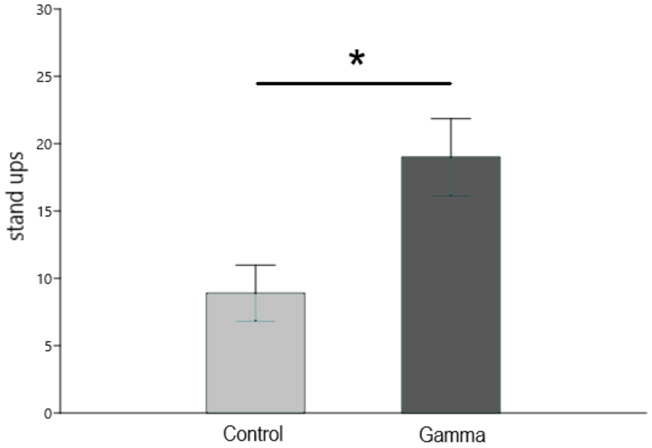


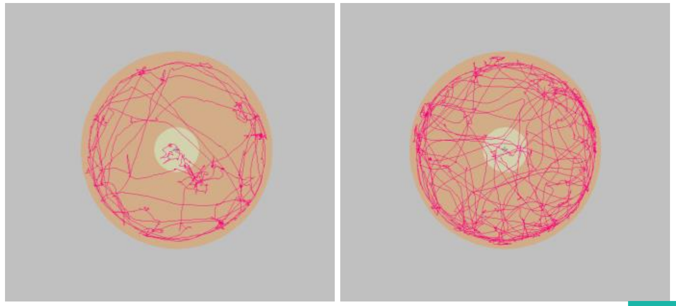




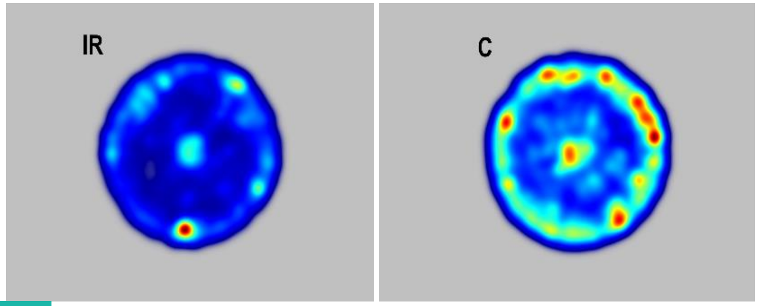
# Behavioral analysis

| **3 min** | *Grooming* | *Sectors crossings* | *Center entrance* | *Stand ups* | *Hole dipping* | *Freezing* | *Emotional status* | *Orientation-exploratory status* |
|---|---|---|---|---|---|---|---|---|
| Control | 8 |  | 7 |  | 5 |  | | |
| Irradiated | 5 | 4 | 6 | 3 | 4 | 0 | | |
| **6 min** | | | | | | | | |
| control | 5 | 1 | 4 |  |  | 1 | | |
| Irradiated | 2 | 5 | 4 | 9 | 7 | 1 | | |



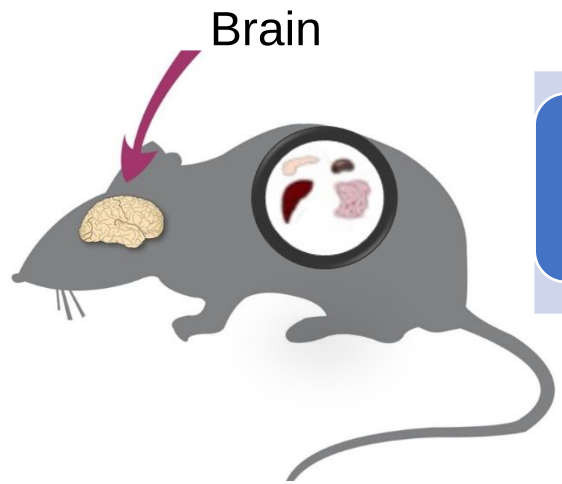
Tracking




EthoVision XT

Heatmap

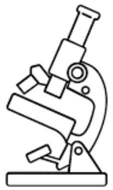
# Autopsy of laboratory rodents




visual estimation → taking an organ → tissue fixation → embedding or blocking out → staining → microscopy

thymus, spleen, brain

liver, small intestine, kidney brain



blood

# Histological methods

Paraffin block

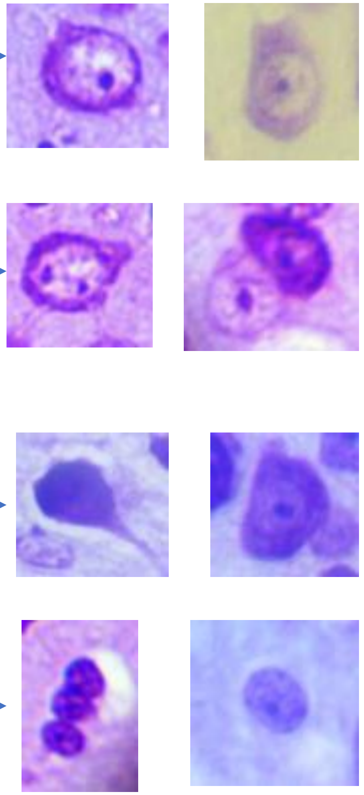
Histological slides

Staining

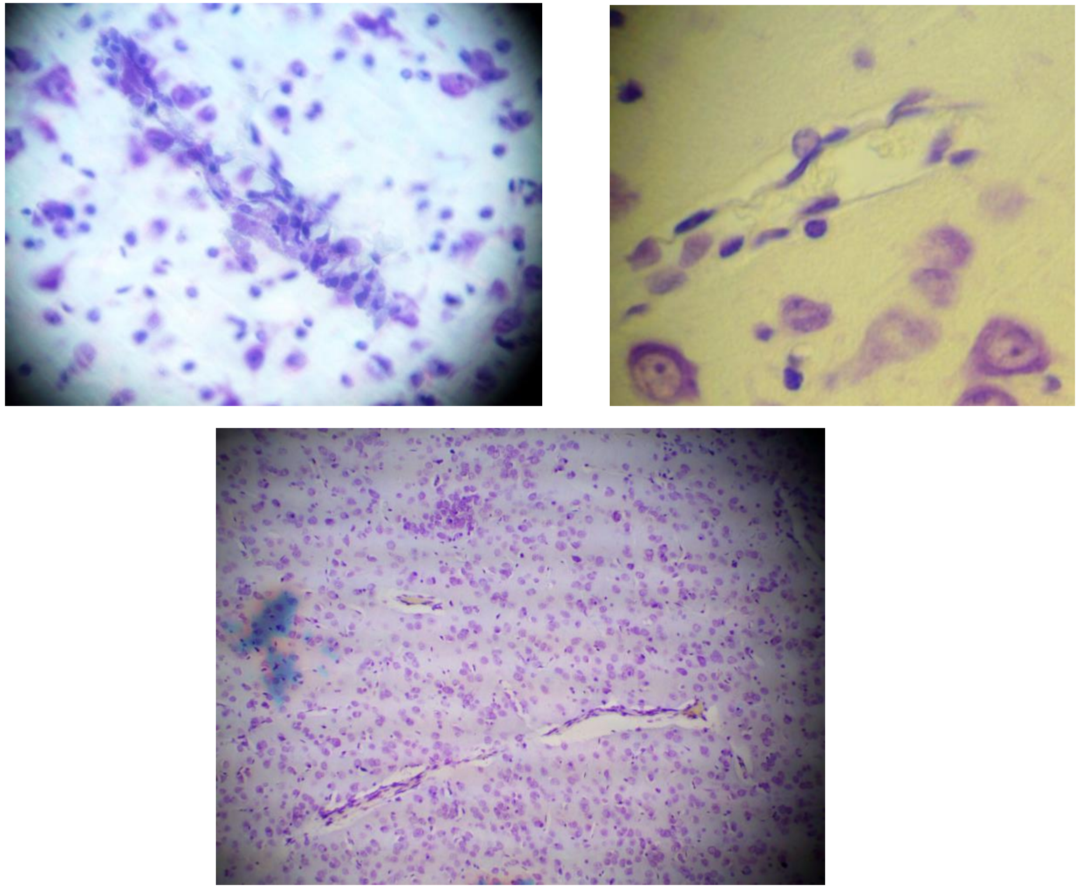
# Histological analysis of brain tissue

**Classification of brain cells:**

- normal
- altered
- degenerative
- glia

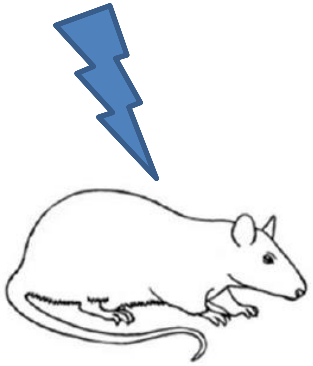


**Vascular changes:**



# Comparative Analysis of Behavioral Reactions and Morphological Changes in the Rat Brain after Irradiation

**Irradiation**



Dose: 1 Gy

LET: 0.2 keV/µm (gamma ray)
0.5 keV/µm (170 MeV protons)
1 keV/µm (70 MeV protons)

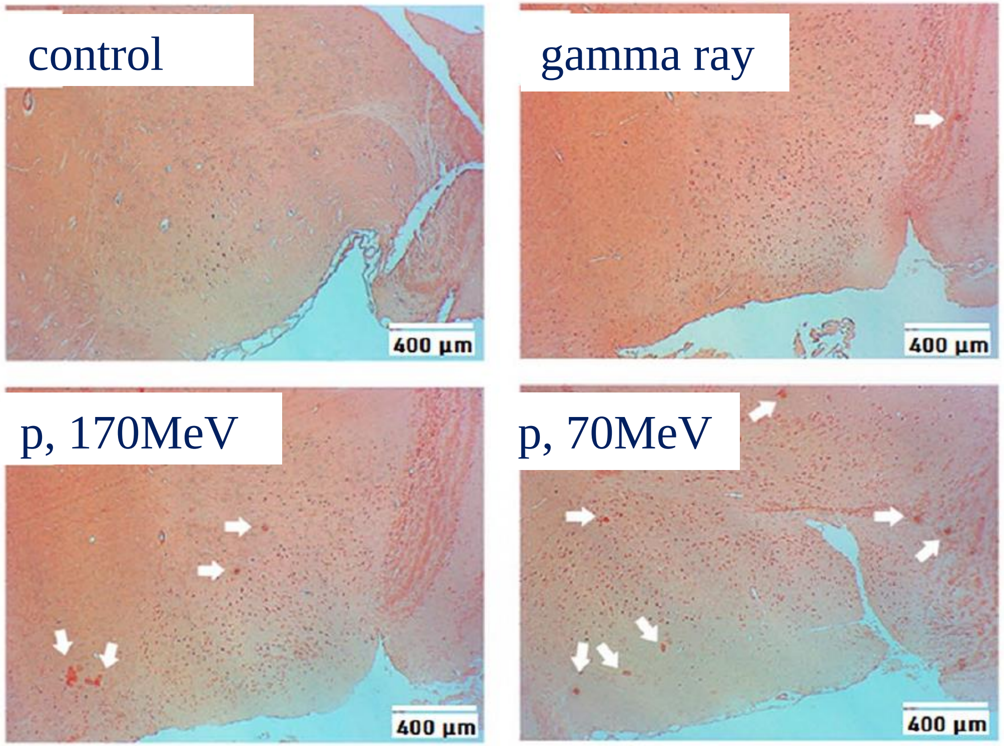
*after 1 month*

**Behavioral reactions:**

- impaired short-term memory
- decrease in overall motor activity
- decrease in exploratory behavior

**Morphological changes in the brain:**

- early amyloidosis
- autolysis of the ependymal layer
- neuronal hypertrophy
- increased dystrophic changes



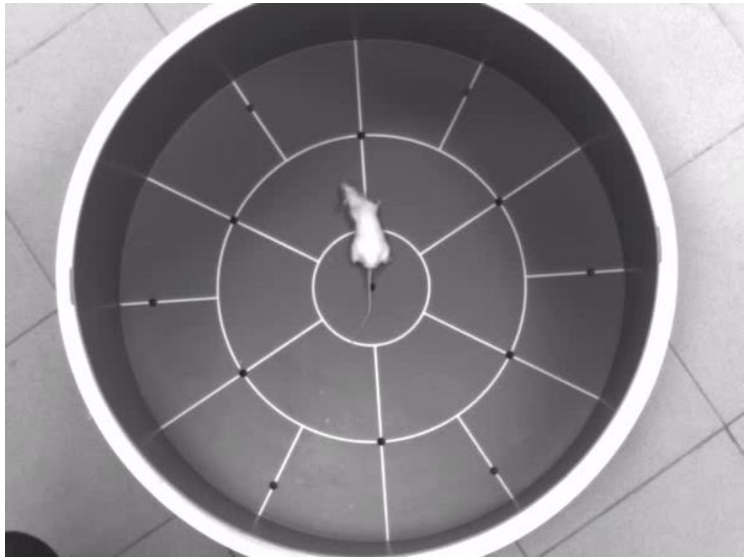

Amyloid plaques in the forebrain of rats (marked with white arrows)

**The neurodegeneration increases with LET of radiation**

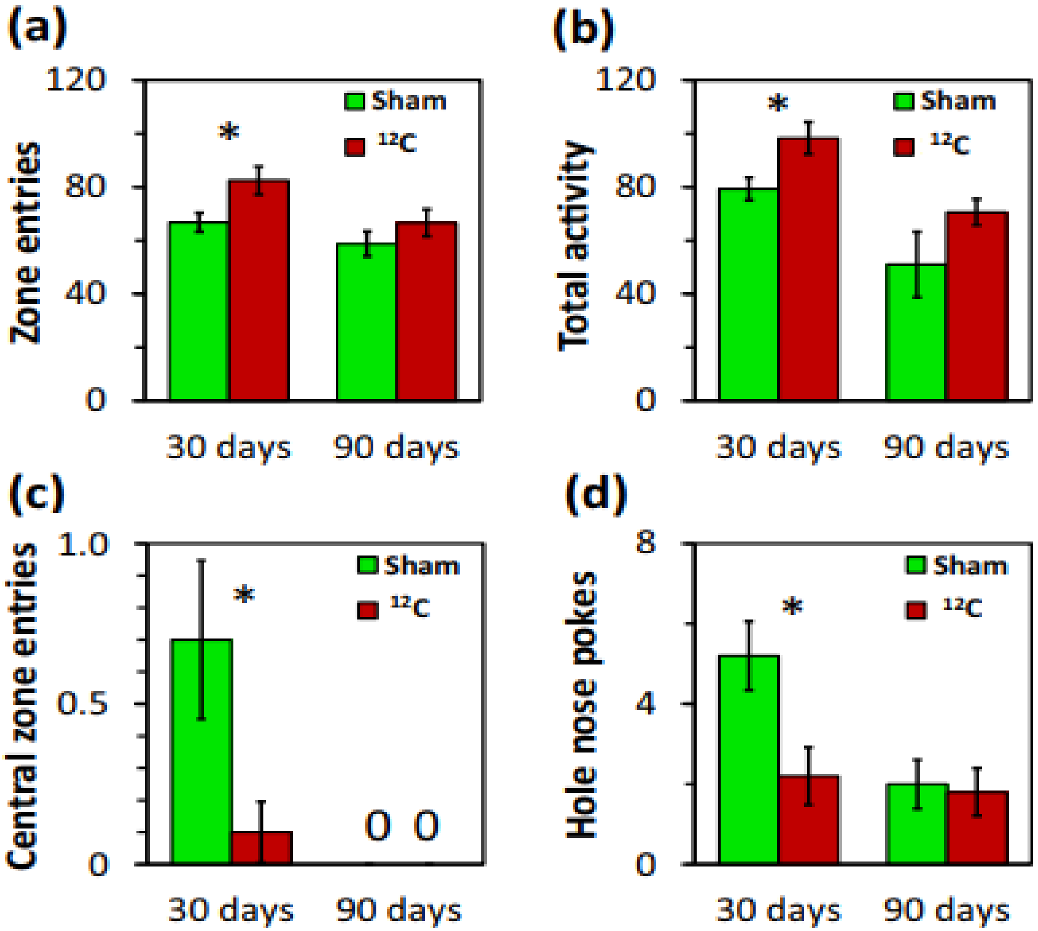
# Evaluation of radiation risks for deep space missions

The effect of 1 Gy 500 MeV/u $^{12}C$ particle radiation exposure on rats

Behavior and emotional status

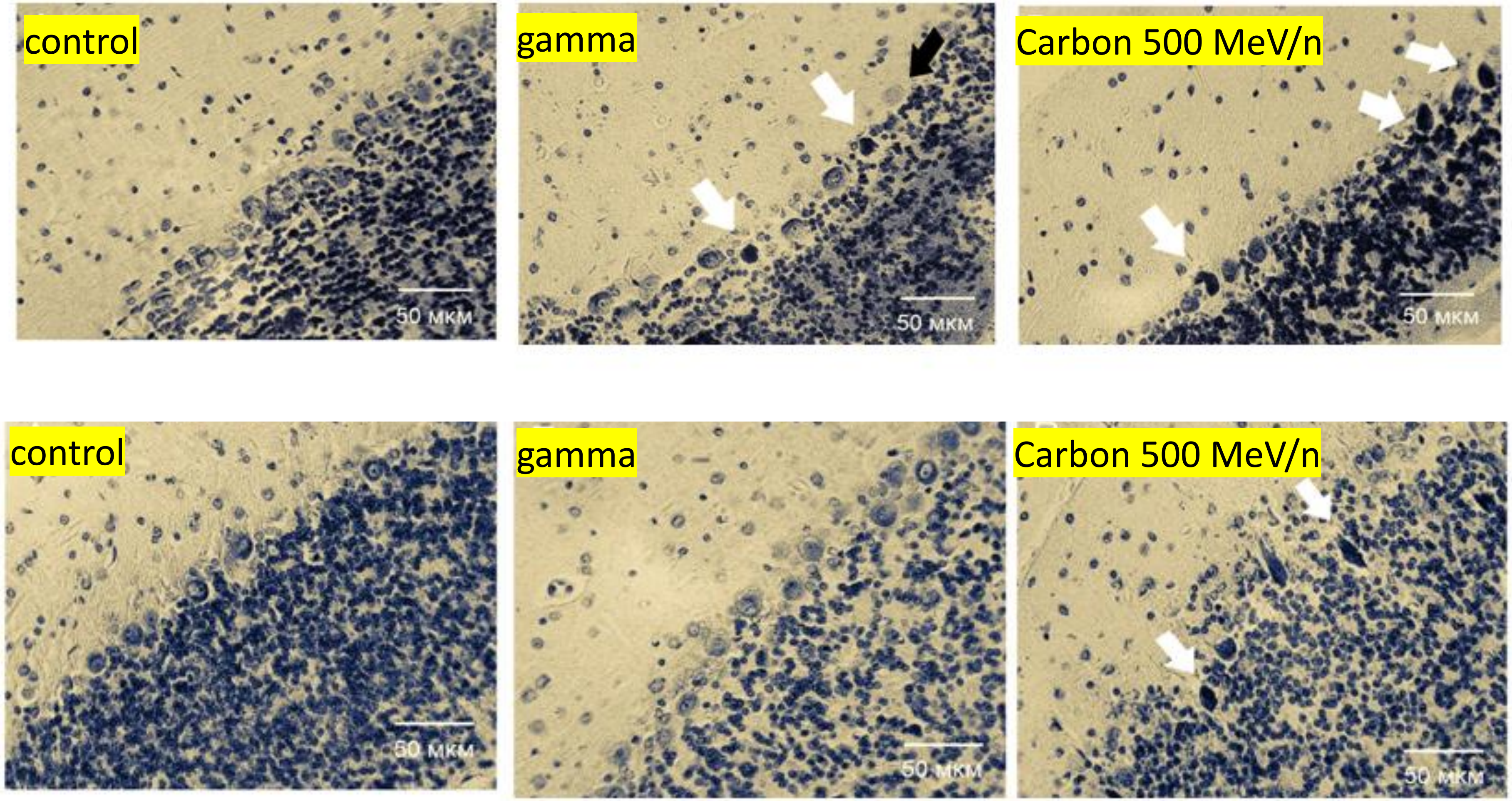


Open field test



# The effect of 1 Gy 500 MeV/u $^{12}C$ particle radiation exposure on rats

## Morphological changes in Purkinje cells in the cerebellar cortex 90 days after irradiation

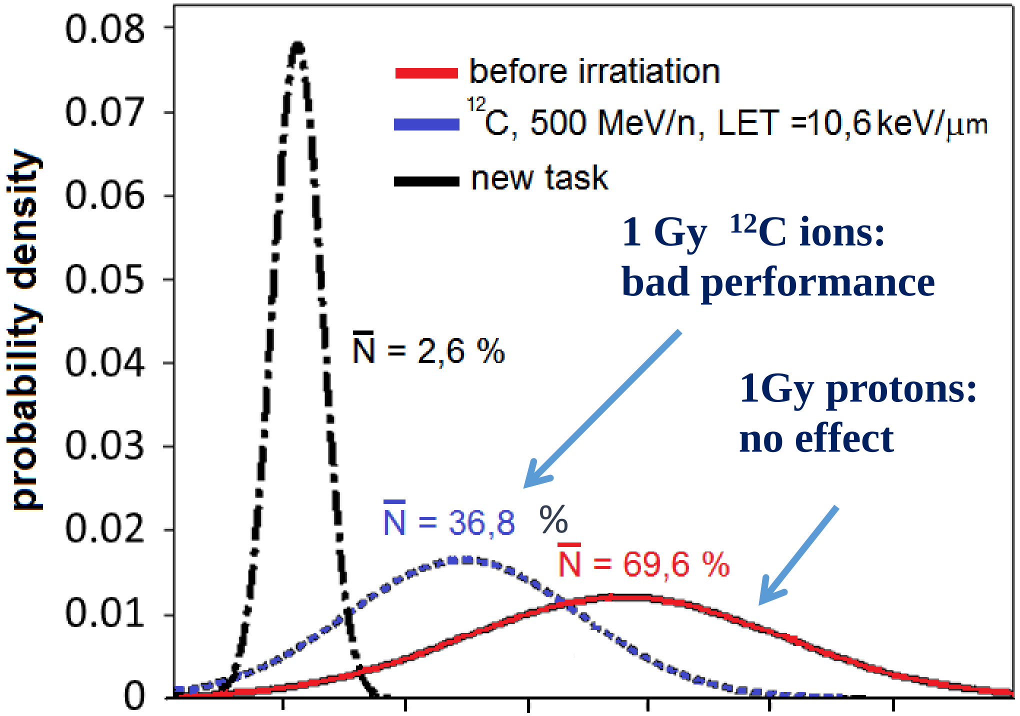


# Evaluation of radiation risks for deep space missions

## *Unique experiments on primates at LRB JINR*

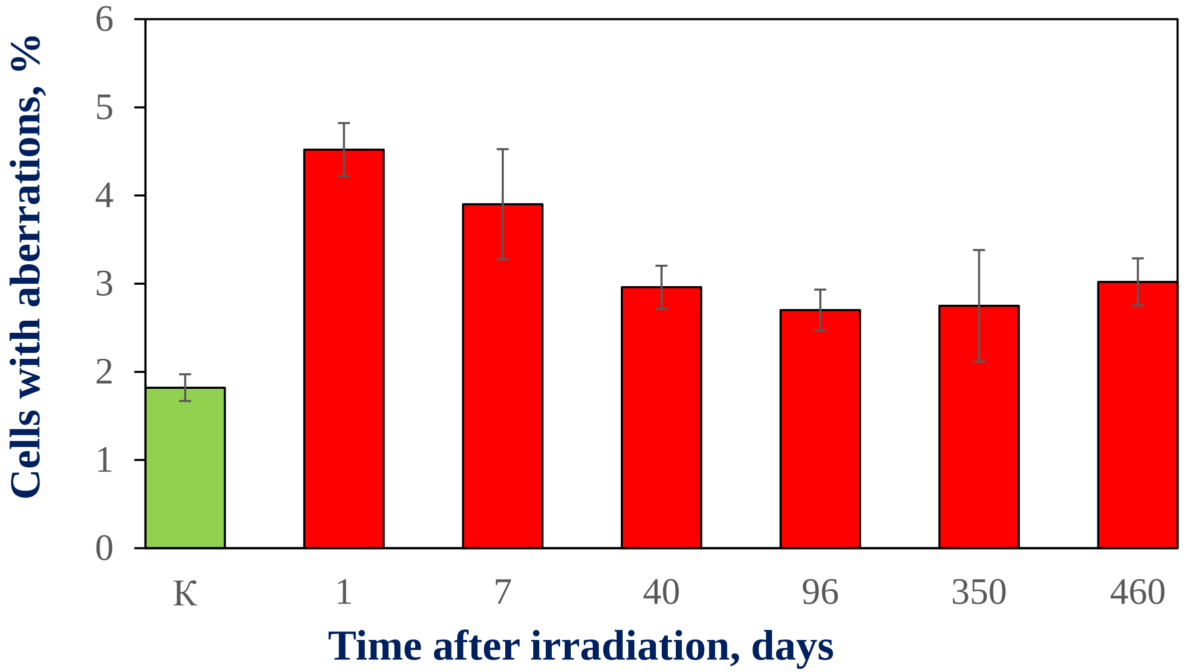
**Automated computer system for the simulation of operator activity during the flight**

**The monkeys were preliminarily trained to solve logical problems on a computer. The effect of exposure to 1 Gy of carbon ions with energy 500 MeV/u consisted in a significant suppression of the learning ability of monkeys. In experiments with gamma-rays and protons with energy 170 MeV at the same dose 1 Gy similar effect was not observed.**




RAS Institute of Biomedical Problems,
RAS Institute of Medical Primatology,
RAS Institute of Higher Nervous Activity and Neurophysiology,
Moscow State University

# Long-term cytogenetic and behavioral disorders in monkeys after brain irradiation with accelerated heavy ions




The level of chromosomal aberrations in peripheral blood lymphocytes of monkeys subjected to local action of accelerated krypton ions with an energy of 2.6 GeV/nucleon at a dose of 3 Gy at different periods of observation.

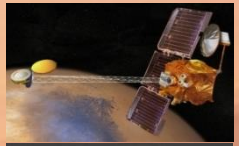
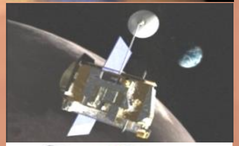
In the long term after irradiation of *certain areas of the brain of monkeys* (the hippocampus), most of the irradiated monkeys developed stable deviations from the standard behavior of animals which **persisted for 5 years** of the study.

# Astrobiology

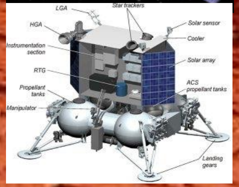
# Nuclear planetology instruments and search of water

**In cooperation with the FLNP and the Space Research Institute (Moscow), the LRB has been participating in the planetary surface research program for more than 15 years in accordance with the Implementation Agreements between the Roscosmos, NASA and ESA.**

- The High Energy Neutron Detector (HEND) aboard NASA's 2001 Mars Odyssey spacecraft to study the elemental composition of the Martian surface and search for water in orbit. The spacecraft was launched in February 2001.
- The Lunar Exploration Neutron Detector (LEND) aboard NASA's Lunar Reconnaissance Orbiter (LRO) to search for water from low orbit. The spacecraft was launched in June 2009 and the mission was very successful;
- Spectrometer of gamma-rays and neutrons (NS-HEND) of the Russian mission "Phobos-Grunt" to study the distribution of elements on the surface of Phobos. The spacecraft was launched in October 2011, but its mission was not completed.
- BTN-M1, BTM-M2 are designed for the BTN-Neutron experiment to study fast and thermal neutrons aboard the service module within the Russian orbital segment of the International Space Station (ISS).
- The Albedo Neutron Dynamics (DAN) instrument with a pulsed neutron generator aboard NASA's Mars Science Laboratory (Curiosity) rover to search for water directly in the Martian earth (Gail Crater). The rover landed on Mars in the fall of 2012.
- The Gamma Ray and Neutron Spectrometer (MGNS), which will be deployed on board the ESA's BepiColombo mission to Mercury in 2015. The main task is the orbital search for water at the poles of Mercury.
- ADRON-LR is designed to measure the local elemental composition of the lunar surface using active neutron and gamma spectrometry. This is a joint Russian-Indian project "Chandrayan-2".
- Luna Globe, ExoMars (with ESA), NORD (with NASA)



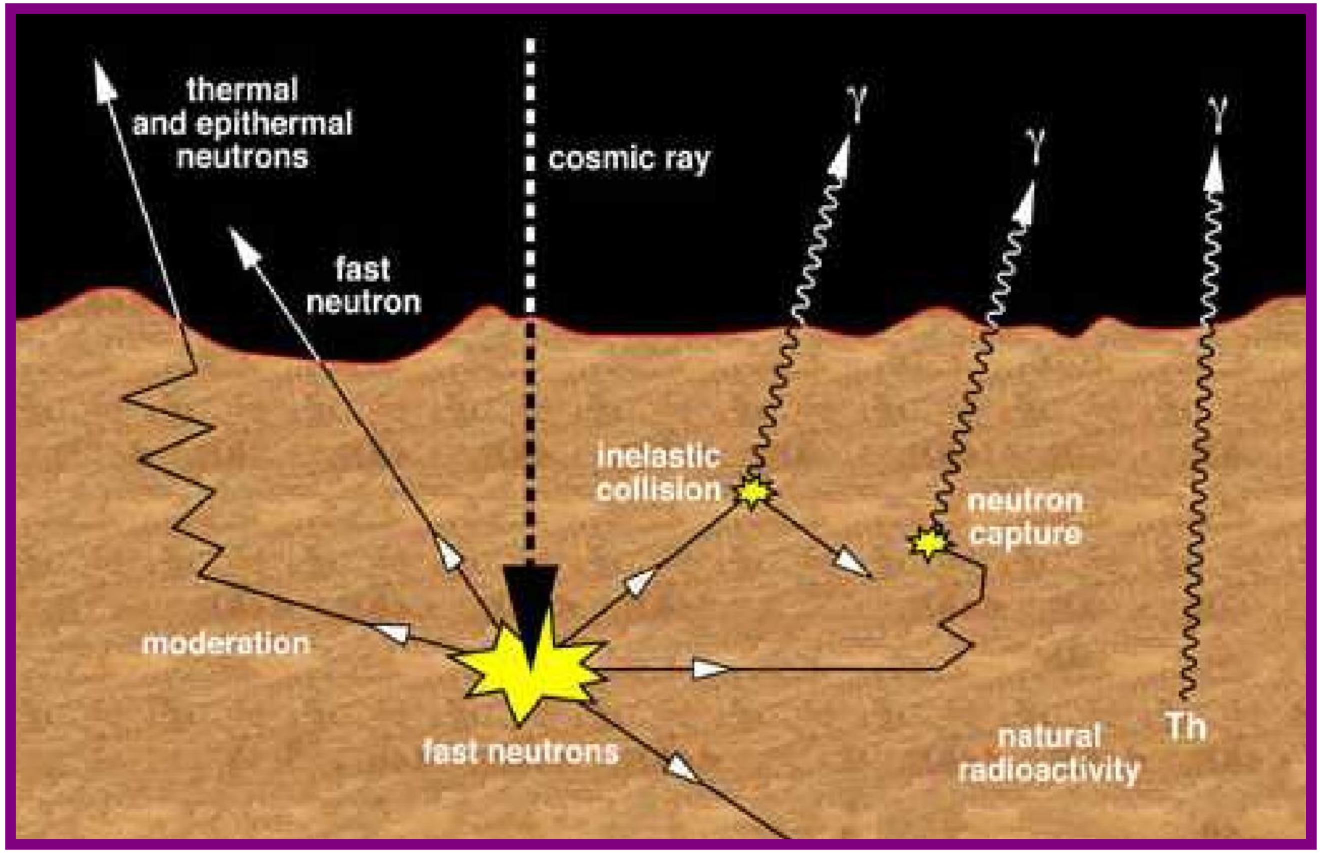
**Nuclear planetology** uses the methods of nuclear physics for study of planet elemental composition from the orbit or from the surface directly.

Overwhelming amount of H on the Earth is composed of water. Thus, search of H is search of water!

Main techniques for search of H:

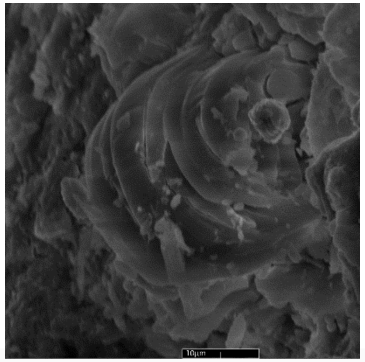
- Neutron radiometry and spectroscopy
- Gamma spectroscopy

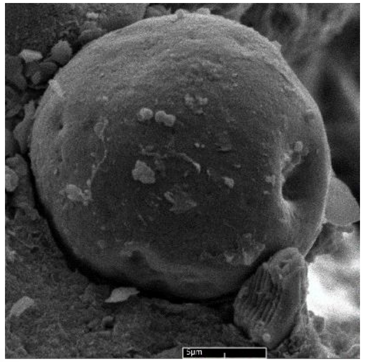
*Mechanism of gamma rays and neutrons generation within subsurface matter of planet*

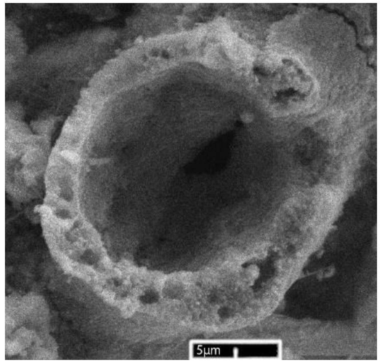


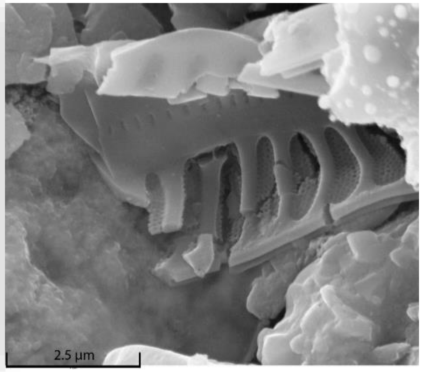

planetary ground facility DAN for testing nuclear planetology instruments

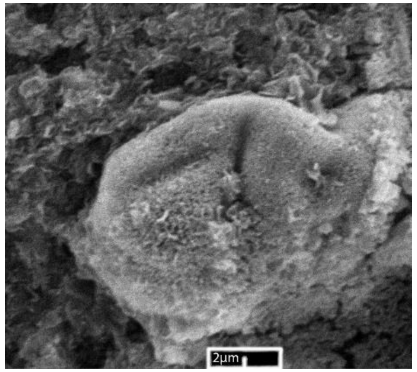
# Search for remains of living organisms (microfossils) in meteorites



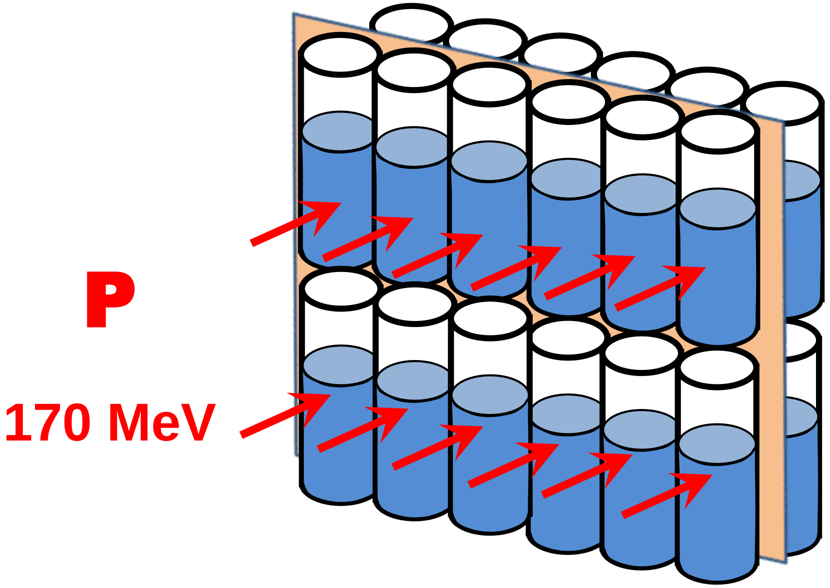


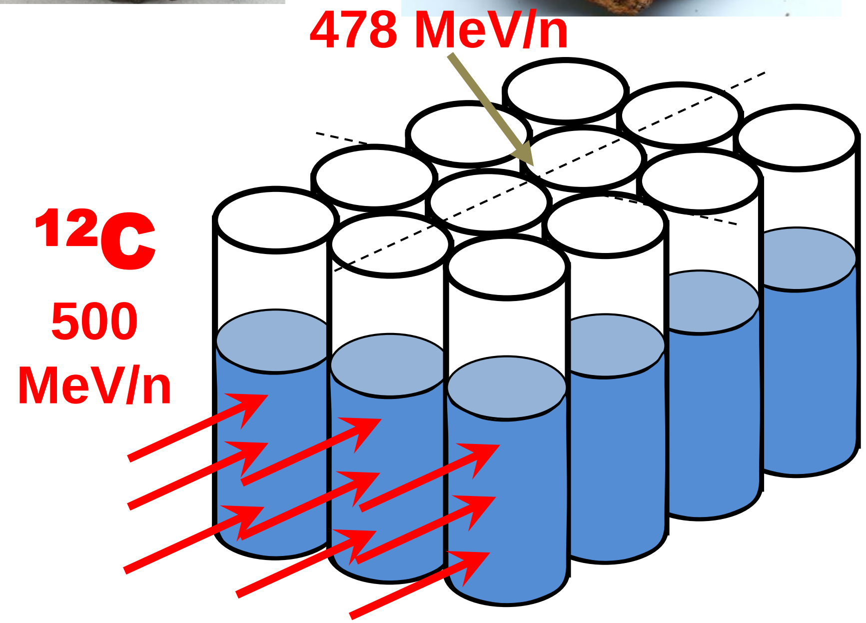




The Orgei meteorite is a unique phenomenon in the abundance and diversity of microfossils of prokaryotes and aquatic eukaryotes, including microalgae, protists, and even algae or fungal spores. The microfossils found are indigenous to the meteorite and not terrestrial biocontaminants. The consistency of the theory of panspermia is shown. The capabilities of SEM for the search and analysis of indigenous microfossils in meteorites are demonstrated.

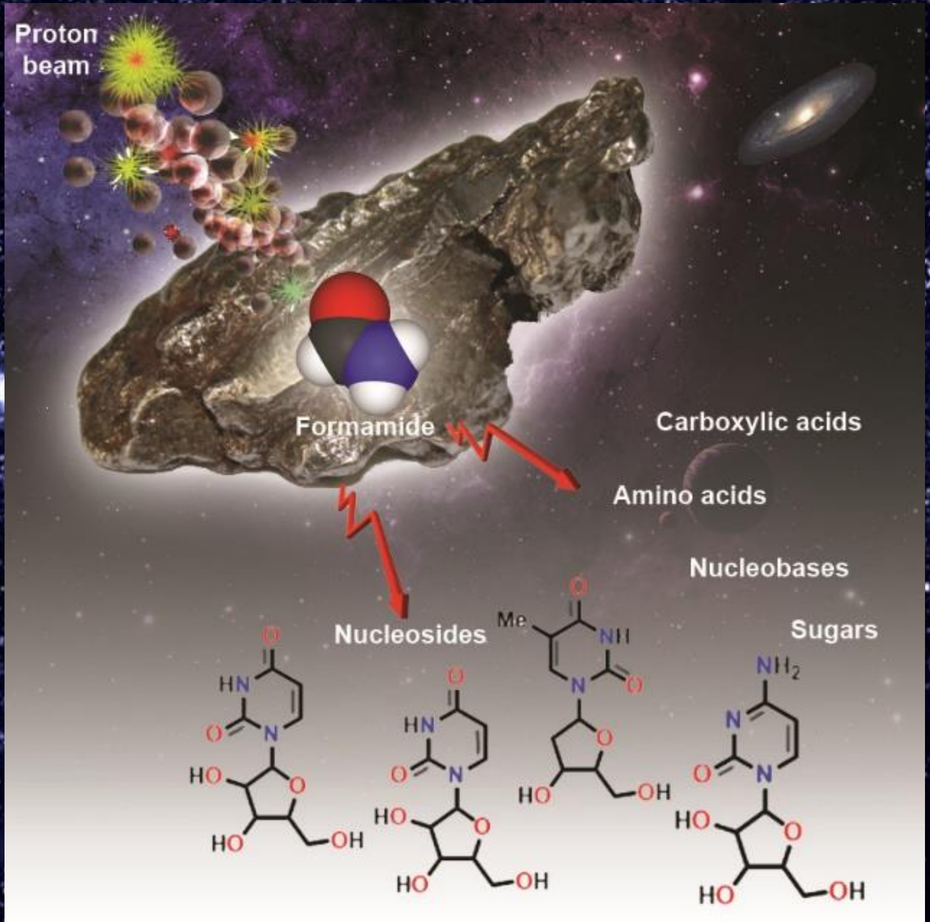
# Accelerator experiment: irradiation of formamide in the presence of space matter under the influence of cosmic types of ionizing radiation



# Prebiotic chemistry

Irradiation with protons with an energy of 170 MeV in the synthesis of formamide and meteoritic substances revealed precursors of nucleic acids, proteins, and metabolic cycles in appreciable amounts. In the absence of irradiation, prebiotic compounds are not formed.





nature

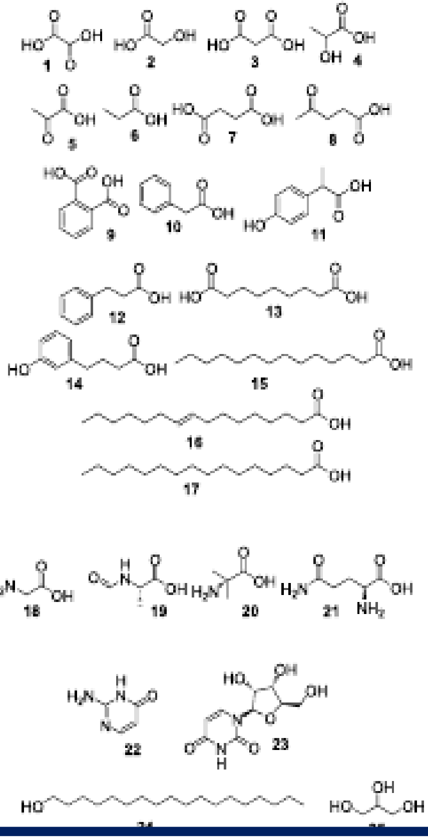
Acids (μg)

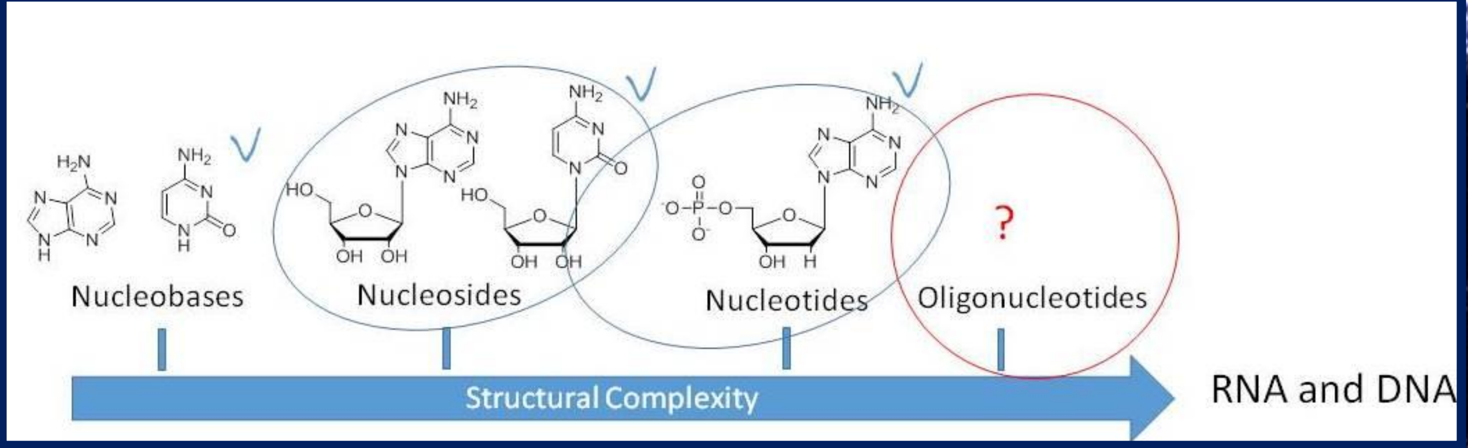
| n° atoms C | | |
|---|---|---|
| 2 | (1) Oxalic acid | 1,93 |
| | (2) Glycolic acid | 0,51 |
| 3 | (3) Malonic acid | 3,23 |
| | (4) Lactic acid | 5,89 |
| | (5) Pyruvic acid | 0,33 |
| | (6) Propionic acid | 0,18 |
| 4 | (7) Succinic acid | 0,32 |
| 5 | (8) 4-oxopentanoic acid | 0,58 |
| 8 | (9) Phthalic acid | 2,45 |
| | (10) Benzen acetic acid | 121,81 |
| 9 | (11) 4-hydroxyphenyl propionic acid | 1,13 |
| | (12) Hydrocinnamic acid | 0,4 |
| | (13) Azelaic acid | 0,58 |
| 10 | (14) 3-Hydroxy phenyl butyric acid | 1,16 |
| 14 | (15) Tetradecanoic acid | 1,43 |
| 16 | (16) Palmitelaidic acid | 0,64 |
| | (17)Hexadecanoic acid | 0,37 |

| Amino acids (μg) | |
|---|---|
| (18) Glycine | 0,86 |
| (19) Formyl-alanine | 5,56 |
| (20) 2-methyl alanine | 10,18 |
| (21) glutamine | 0,71 |

| Heterocycles (μg) | |
|---|---|
| | 75,6 |
| (22) Isocytosine | 3 |
| (23) Uridine | 0,54 |

Miscellanea (μg)

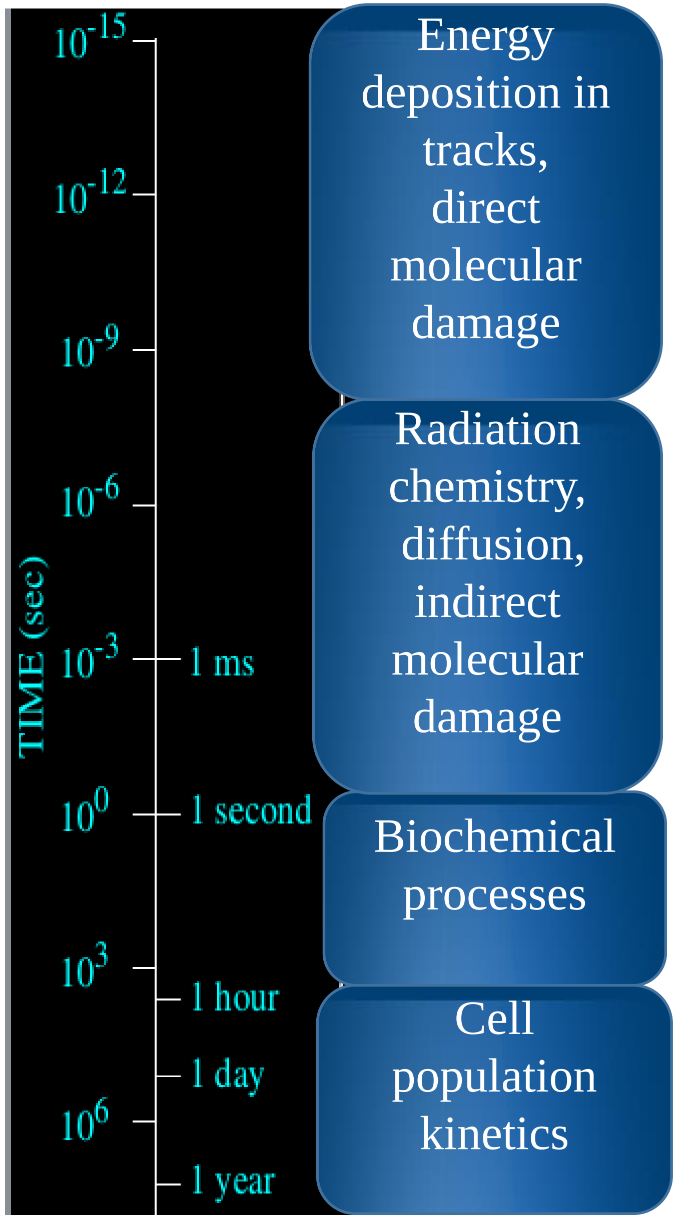




*Lecture 5-2*

# Modern Information Technologies in Biology and Medicine

# Hierarchy in mathematical modeling




**Monte Carlo radiation transport**

GEANT4-DNA

A SIMULATION TOOLKIT

**Molecular dynamics**

NAMD

Scalable Molecular Dynamics

AMBER

**Dynamical systems: ODE and PDE**

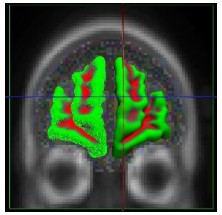
Wolfram Mathematica

MATLAB

Estimating final effect

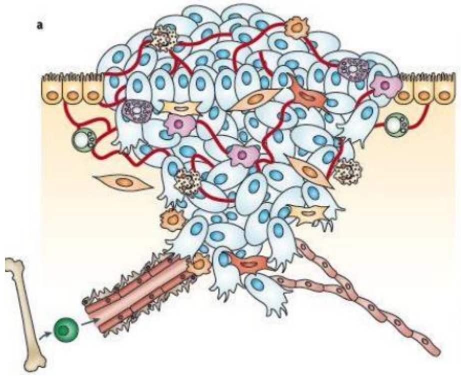
**Radiation neuroscience:**

**Brain neural networks**

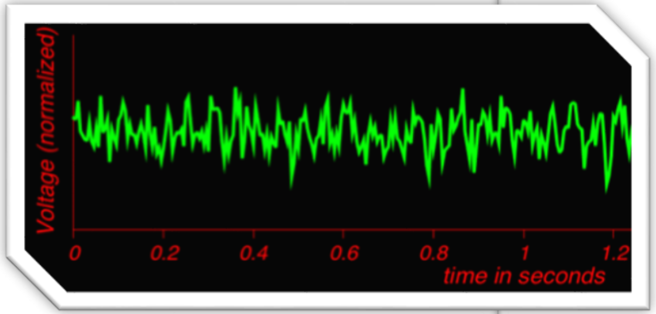


**Clinical radiobiology:**

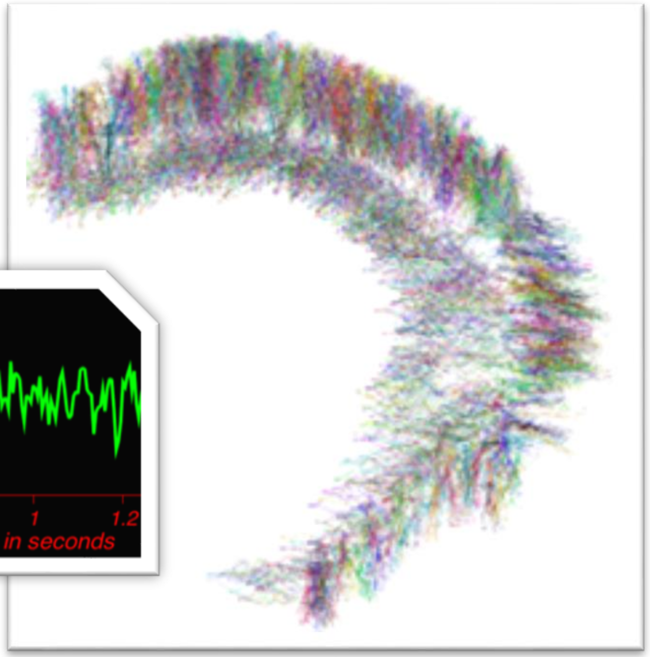
**Complex models of tumor growth**



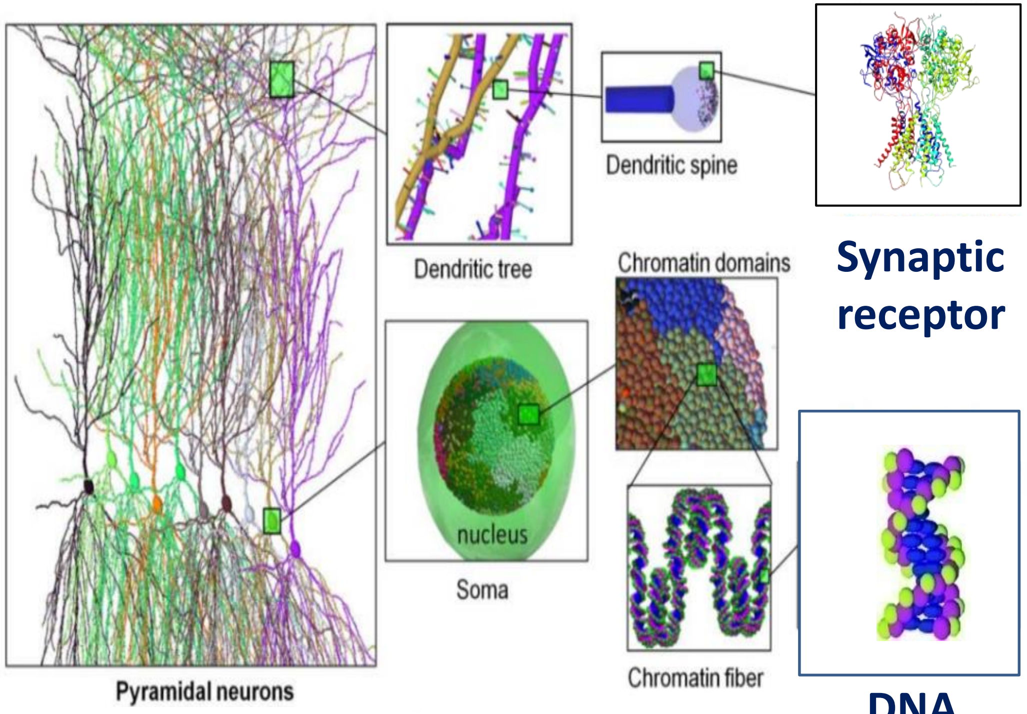
# Multiple scale modeling. Example 1




Brain activity?



Brain regions




Neural cells

Subcellular targets

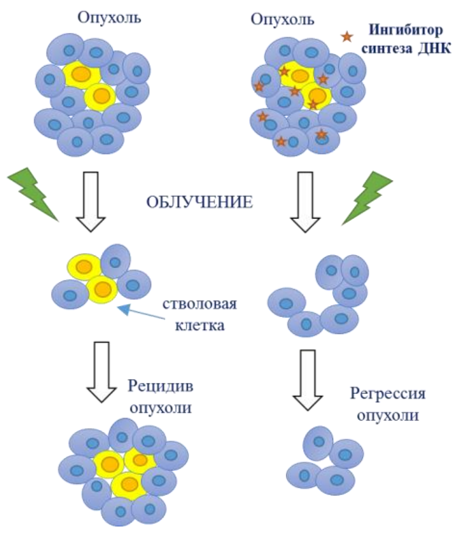
Synaptic receptor

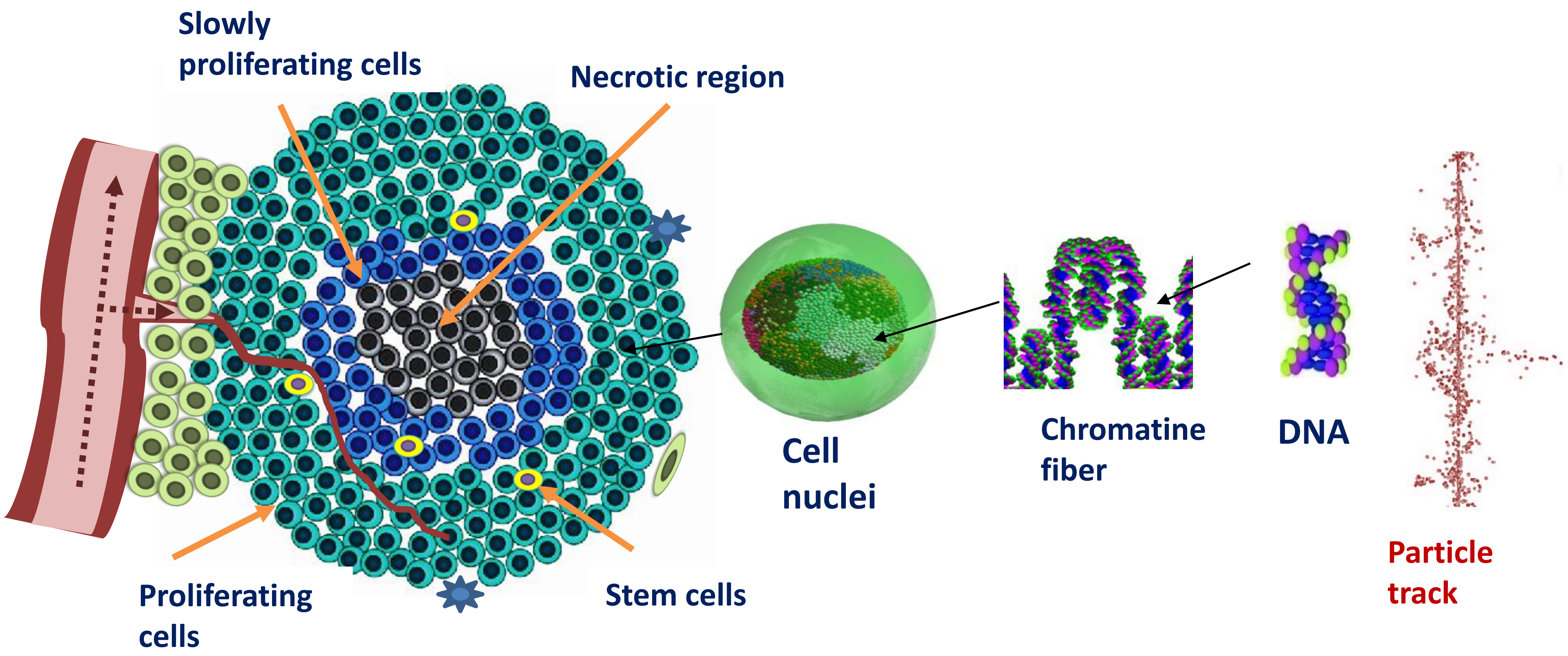
DNA

Particle track

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

# Multiple scale modeling. Example 2




**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**

# Phenomenological and detailed models

**Dose deposition** ⇨ **Biological effect**

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

⇩

**Calculation of elementary events at the cellular and molecular level**

1. **Calculation of DNA damage formation**

2. **Models of DNA DSB repair**

3. **Cell survival**

$\alpha = ?$

$\beta = ?$

# Monte Carlo simulation codes

| | |
|---|---|
| General purpose codes | **MCNP, EGS, GEANT, FLUKA, PENELOPE, PHITS, SHIELD …** |
| Treatment planning in radiotherapy | **PEREGRINE, DPM, VMC++, MCV, MMC, ORANGE …** |
| Low-energy codes for radiation biophysics | • Extensions of general purpose codes<br>**MCNP (v6), GEANT4-DNA, PENELOPE/penEasy, PHITS**<br>• Dedicated software<br>**NOREC, PARTRAC, RITTRACKS, TRAX, KURBUC …** |

**TRION** *Lappa, Bigildeev et al. (1993)*
**RADAMOL/TRIOL** *Bigildeev and Michalik (1996) @JINR*

**GEANT4-DNA/neuron** *Batmunkh et al, @LRB JINR*

# Methodology of simulation on example of Geant4-DNA

## Physical Interactions in Geant4-DNA

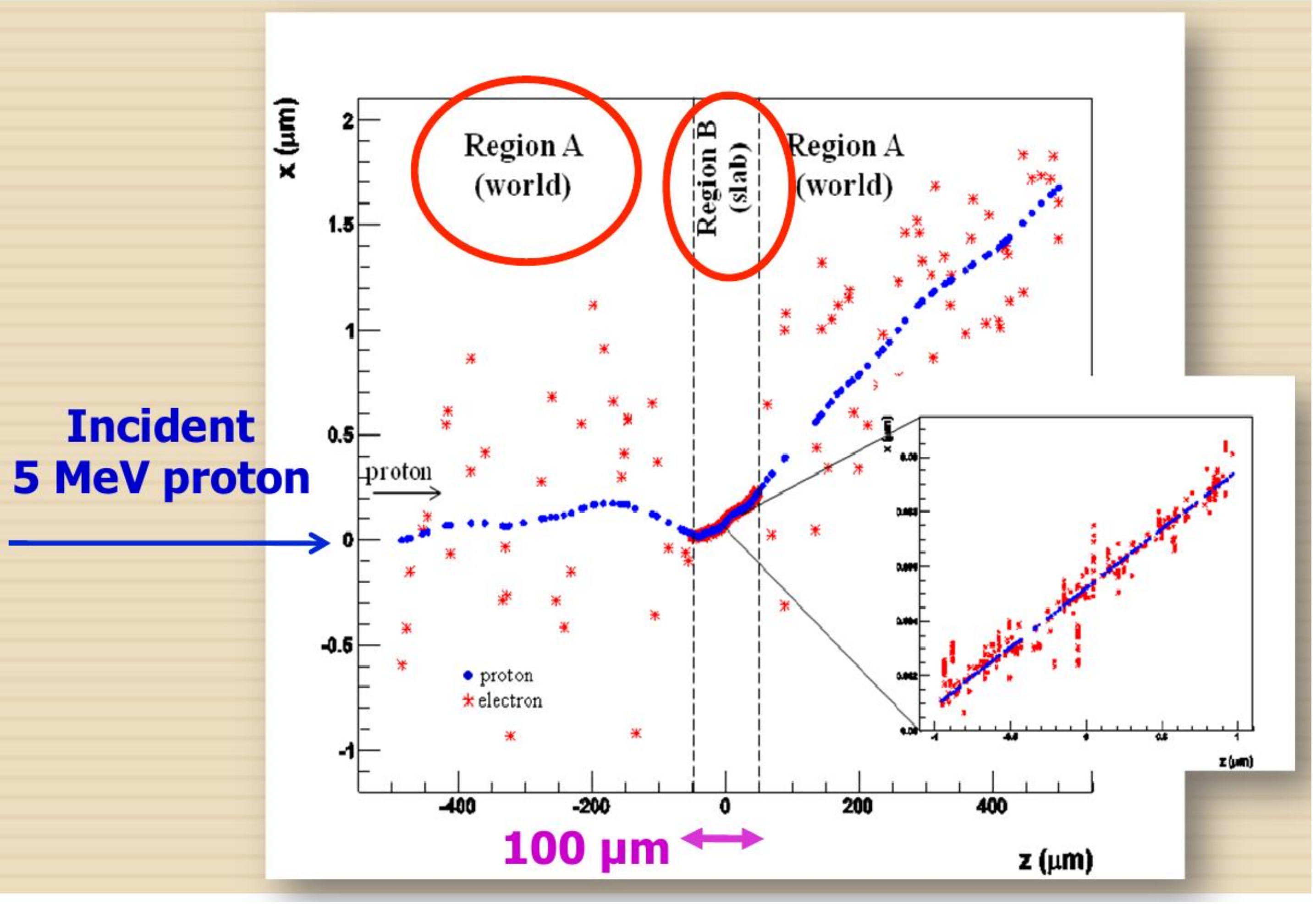
Geant4-DNA physics processes **simulate explicitly all interactions as purely discrete processes** and do not use condensed history approximations

One can combine in a single Physics list

**Geant4 EM Standard Physics** processes for electrons, protons, He, C, N, O, Fe and gammas

**Geant4 EM Low Energy Physics** processes for electrons and photons

**Geant4-DNA processes** for e-, p, H, $He^{q+}$, C, N, O, Fe




Allison 2006, Incerti 2009

# Methodology of simulation on example of Geant4-DNA

## Physical events

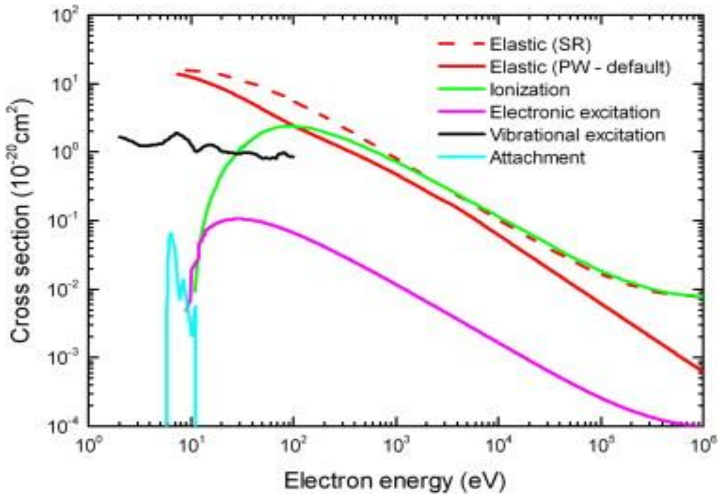
| Particle | Interaction | Model |
|---|---|---|
| $e^-$ | **ionization**<br>≥ 1МэВ<br>10 кэВ – 1 МэВ<br>10 эВ – 10 кэВ | (*Med. Phys. 2010*)<br>Moller-Bhabha<br>Born<br>Emfietzoglou |
| | **excitation**<br>10 кэВ – 1 МэВ<br>8 эВ – 10 кэВ | (*Med. Phys. 2010*)<br>Born<br>Emfietzoglou |
| | **elastic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

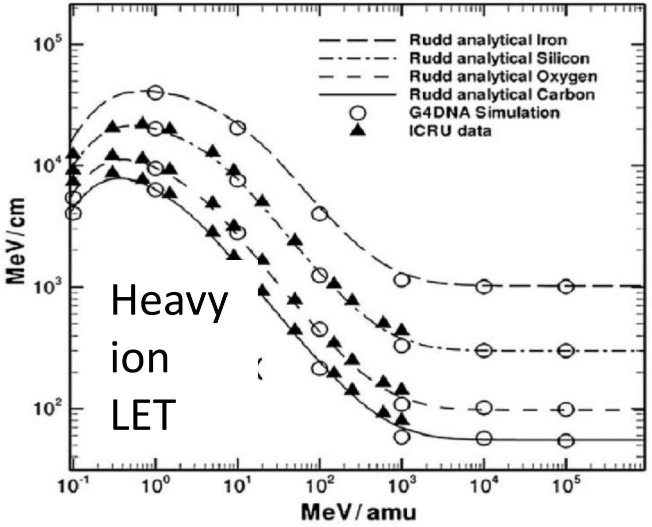
*Direct damage*

$P_{sb} = 1 - e^{-n}$ ; $n=(\varepsilon/\varepsilon_0)^2$

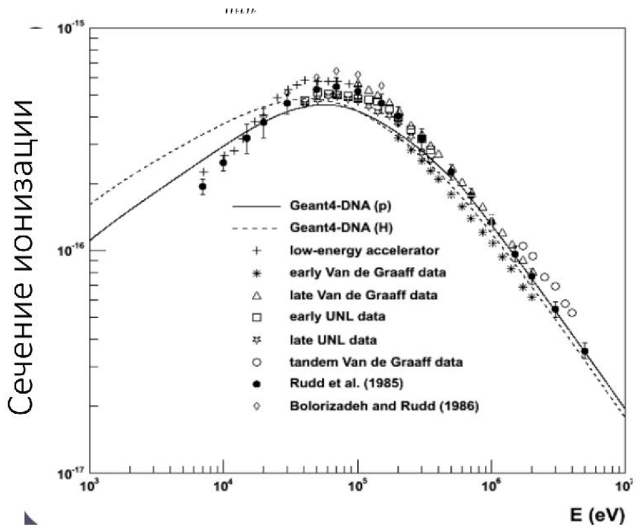
$\varepsilon_0 = 8.22$ eV

Electron cross sections




Ionization cross sections (protons)




### Двунитевые разрывы (ДР)

$P_{ДР} = 1 - e^{-(\varepsilon/\varepsilon_0)^2}$ ;

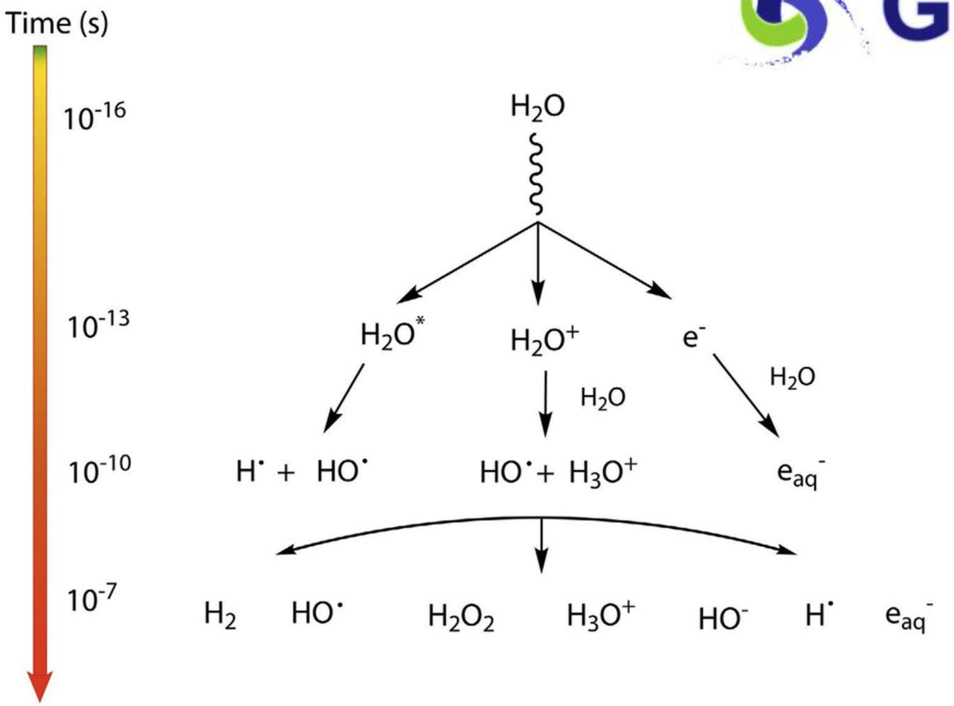
$\varepsilon$ – передача энергии (эВ) в ДНК

$\varepsilon_0$ =8.22– энергия разрыва связи

# 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 |



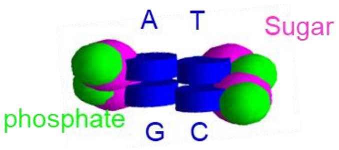

*Indirect damage*
$P_{OH}$ = 0.65

$${}^\bullet OH + DNA \rightarrow OHDNA$$

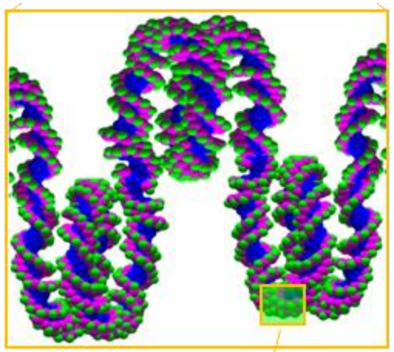
$$\frac{\partial p(r,t)}{\partial t} = \vec{\nabla} \cdot \left[ D \left[ \vec{\nabla} p(r,t) - \beta F(r)(r,t) \right] \right]$$

# Methodology of simulation on example of Geant4-DNA

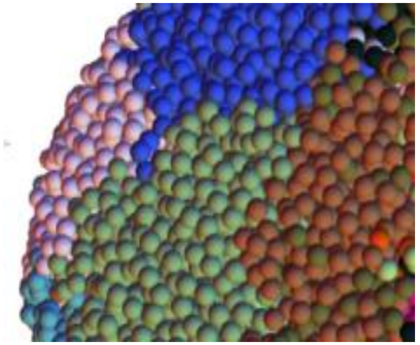
## Geometry of sensitive target



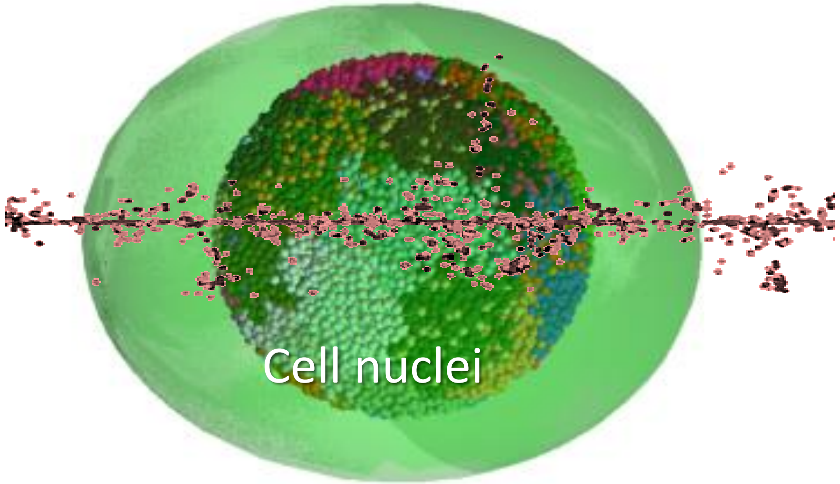

nucleoside



chromatine



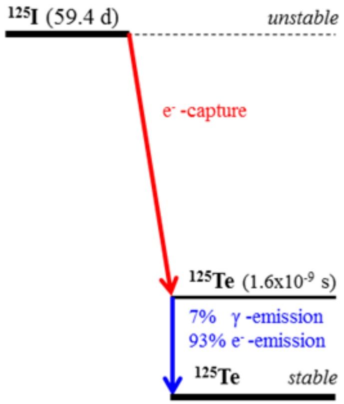
Chromosome domains

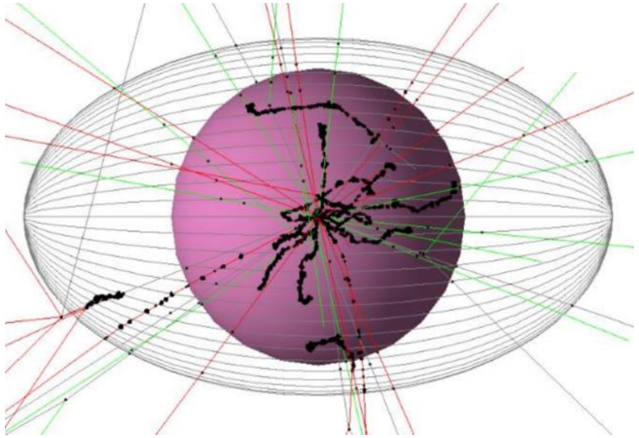



cell

# Methodology of simulation on example of Geant4-DNA

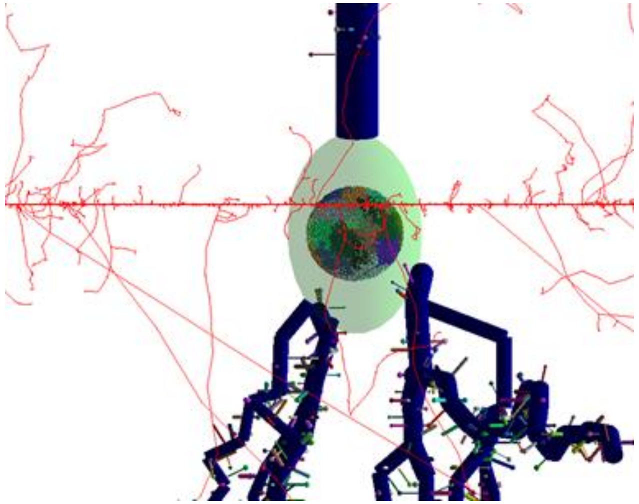
## Event counting

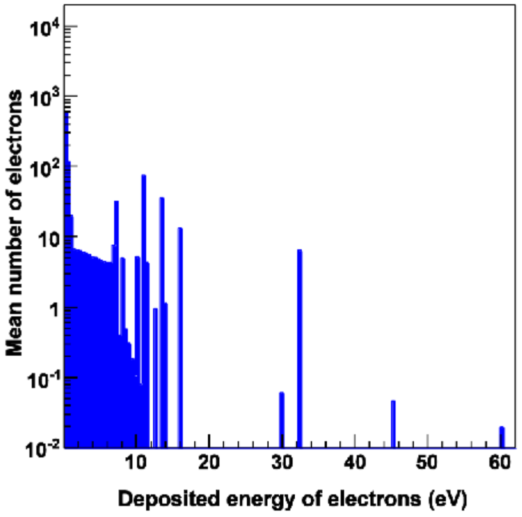


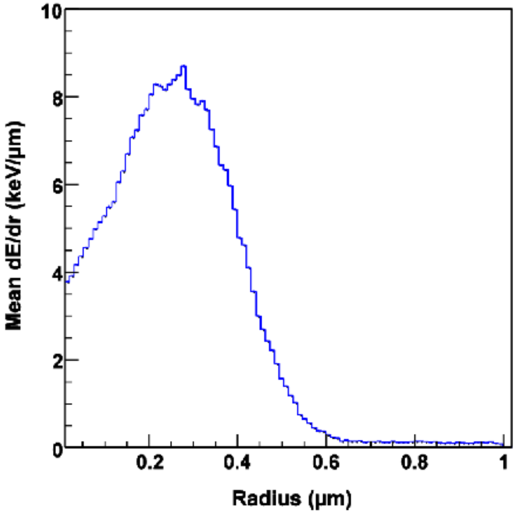



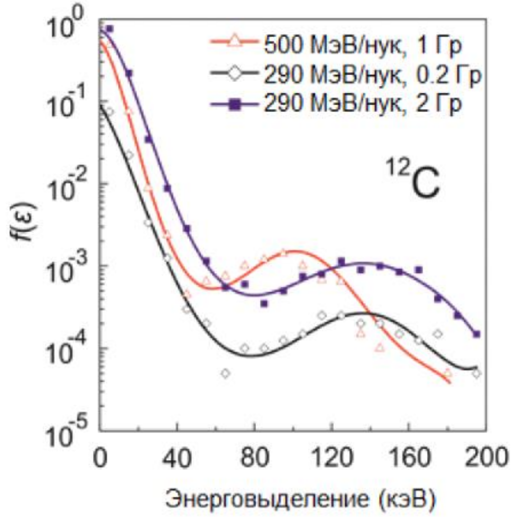
$^{125}$I

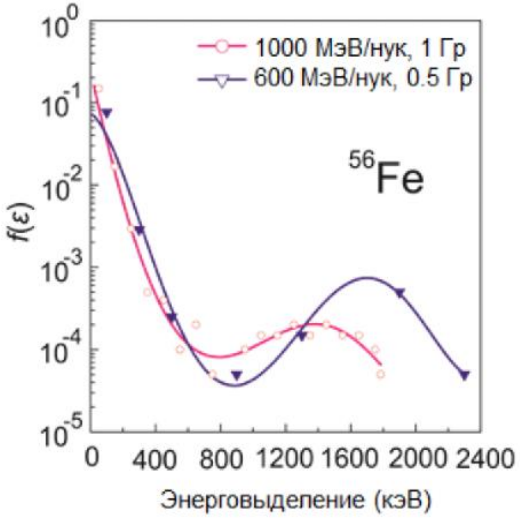
0,8 Бк/мкг



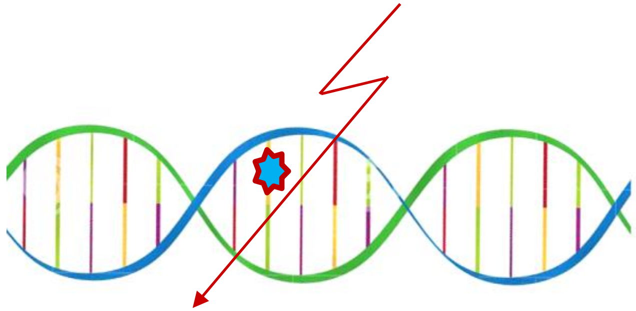


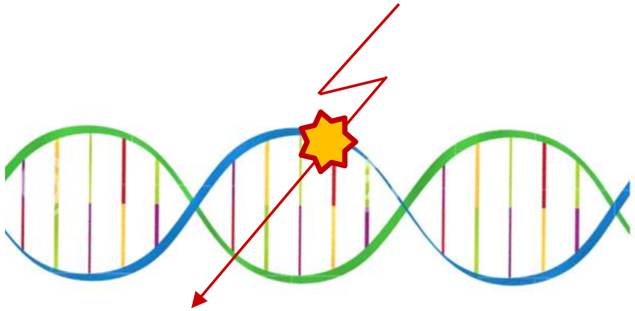



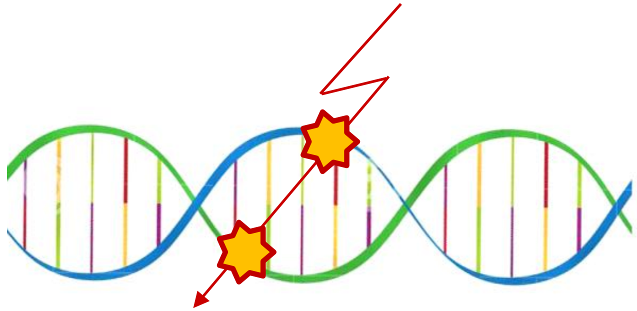
# Counting DNA lesions



Base damage (BD)

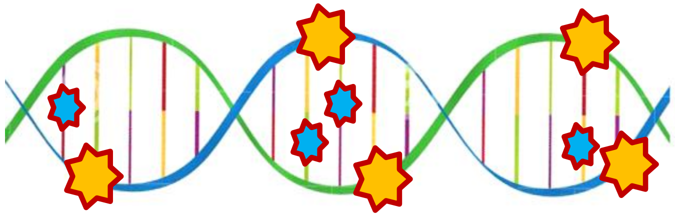


Single stand break (SSB)

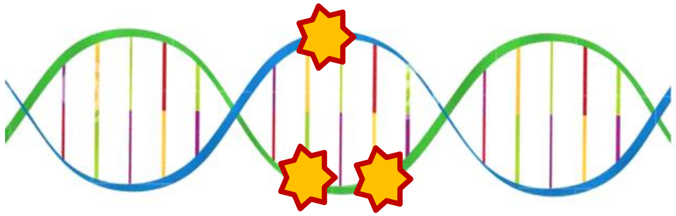


**Double strand break (DSB)**

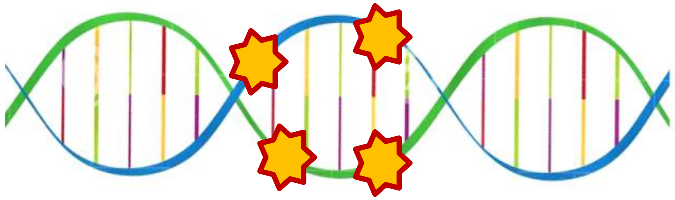
## Complex and clustered damage (size < 10 bp)



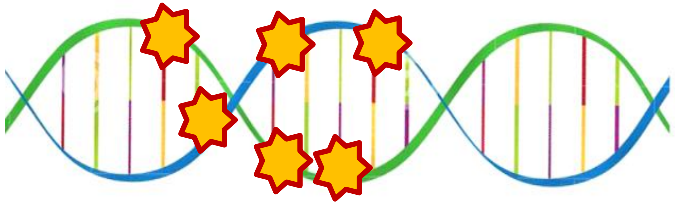
**SSB***  **DSB****  **DSB***



**DSB$^{+}$**



**DSB$^{++}$**



**DSB$^{++++}$**

# Amount of DNA damage

## Computer simulations

1) Base damage BD
2) Single strand breaks SSB
3) Clustered SSB
4) Double strand breaks DSB
5) Clustered DSB

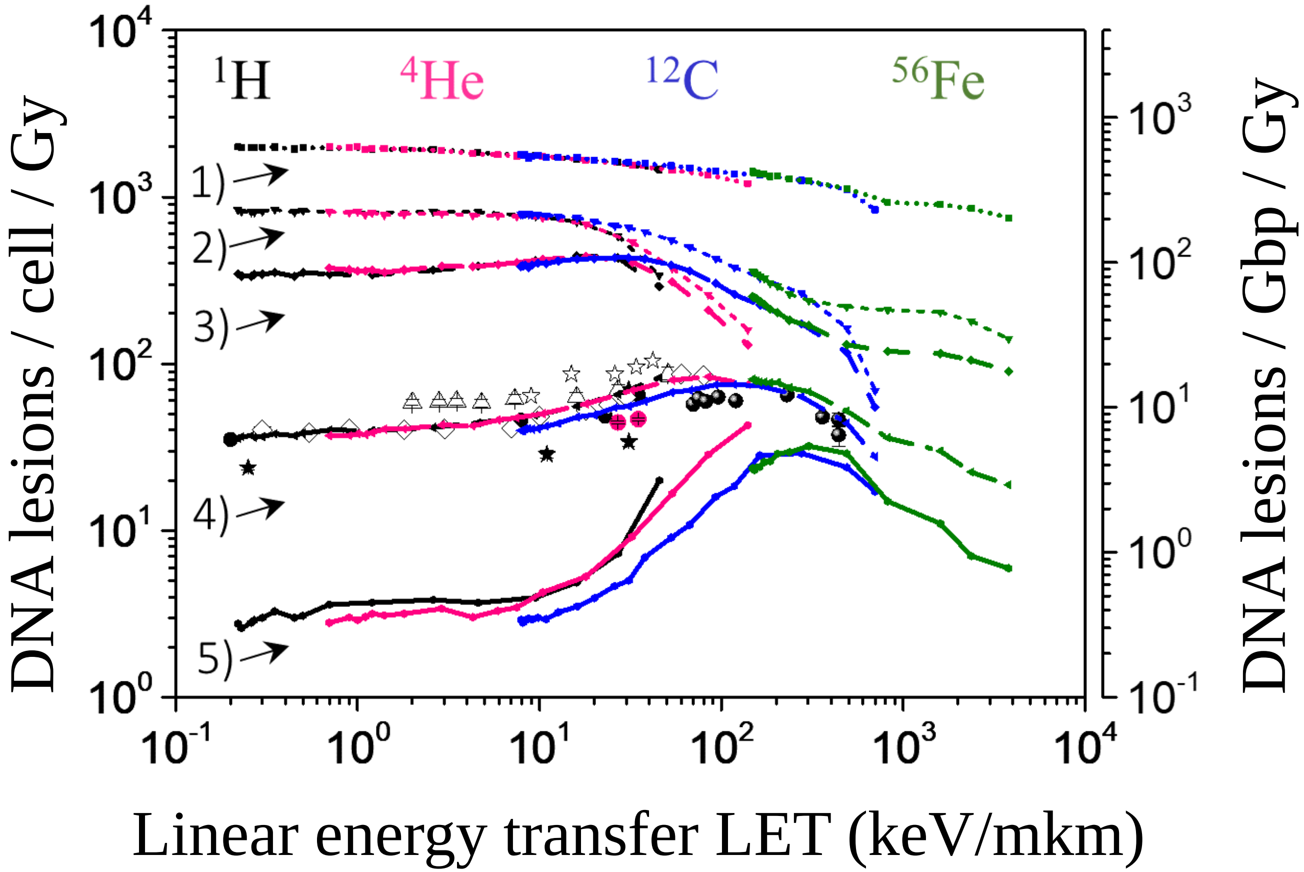
Expeiments (DSB)

- ● Frankenberg 1999
- ★ Belli 2001
- ● Belli 2006
- ■ Bulanova 2019

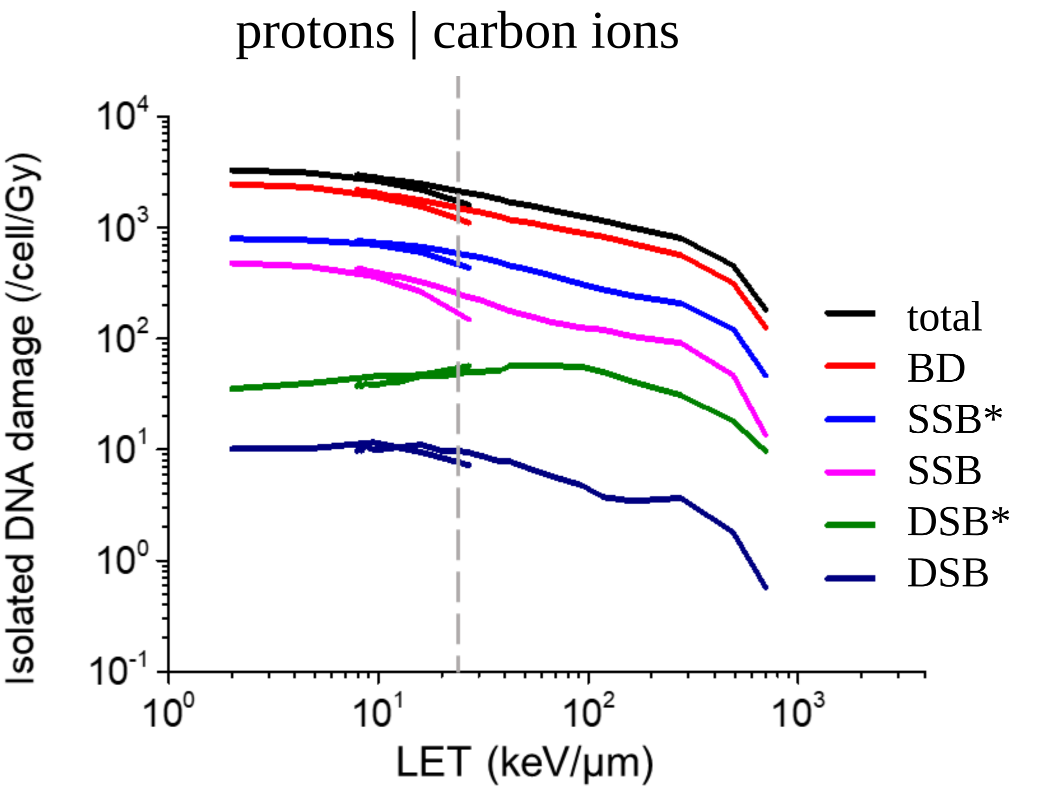
Calculations (DSB)

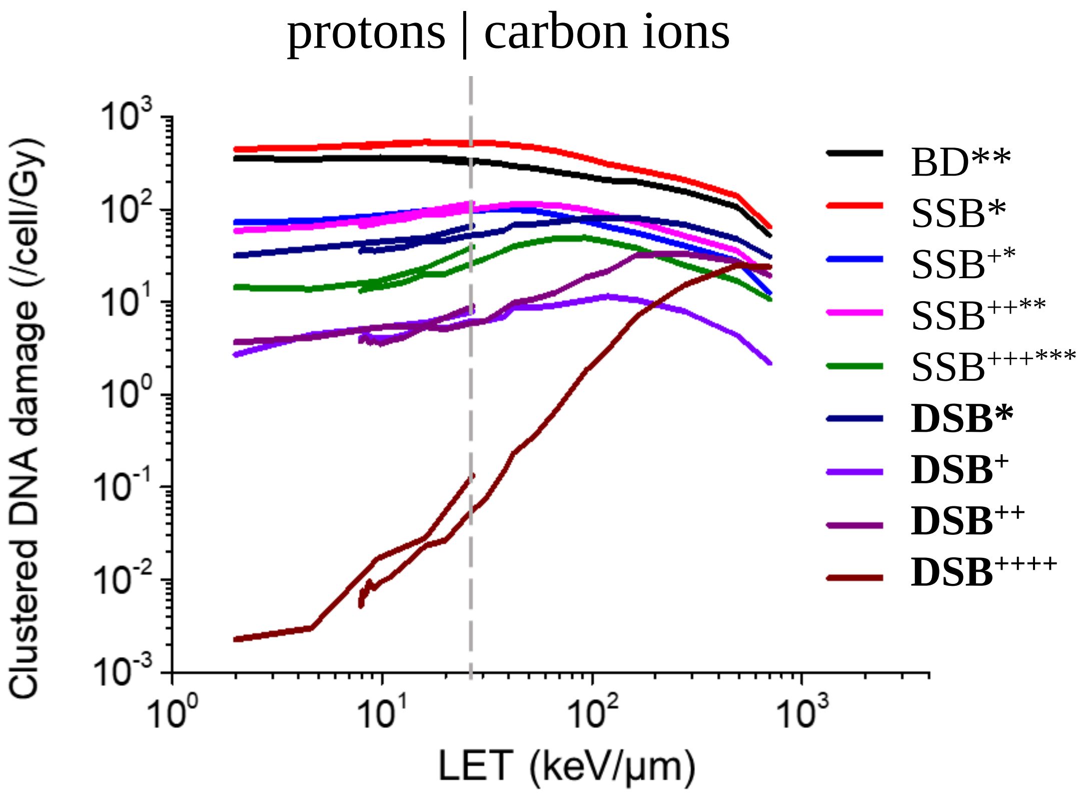
- --★--- Nikjoo 2001
- --◇--- Friedland 2011
- --△--- Rosales 2018

**1 DSB**
**:**
**10 SSB**
**:**
**100 BD**

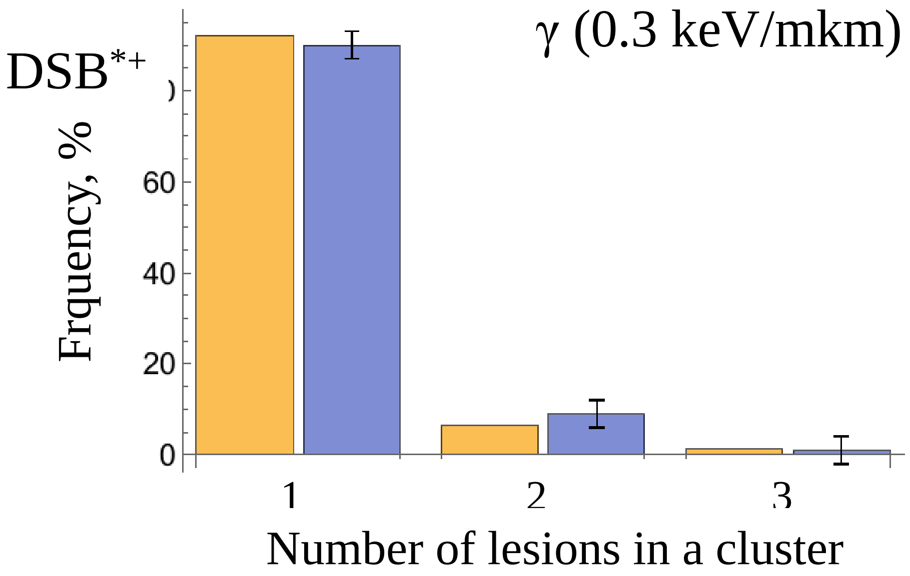


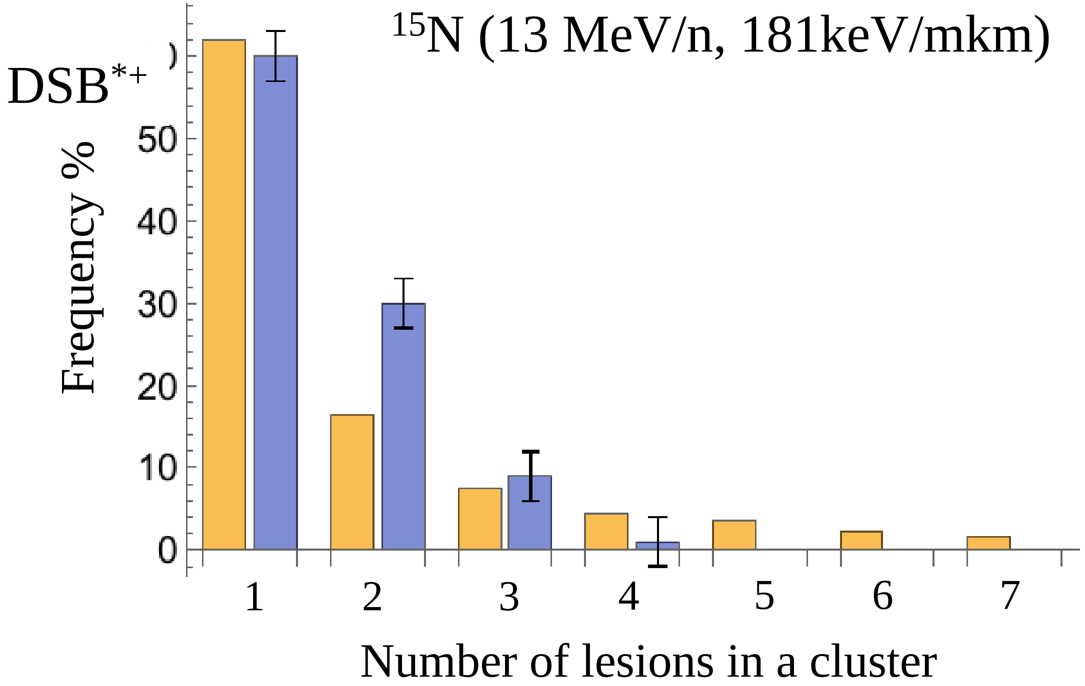
# Complexity of clustered DNA damage



# Complexity of clustered DNA damage

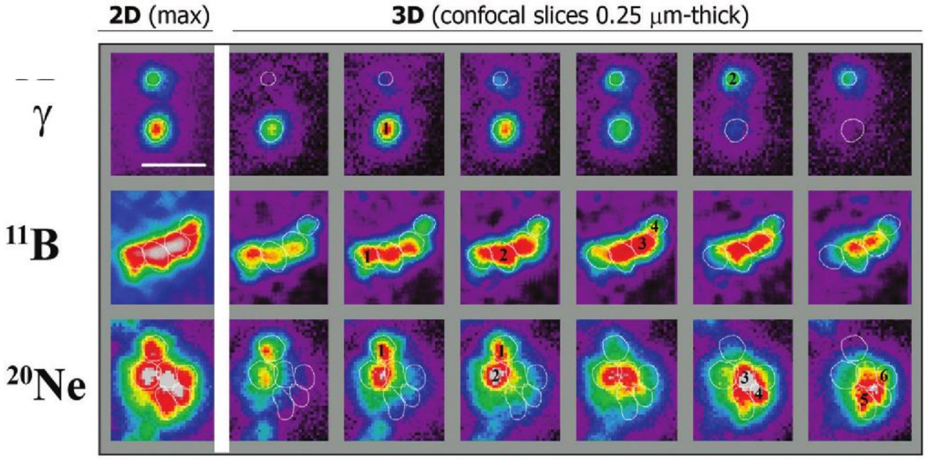



Model

Experiment

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




*Nanoscale, 2018, 10, 1162–1179* |

# Principles of DNA repair modeling

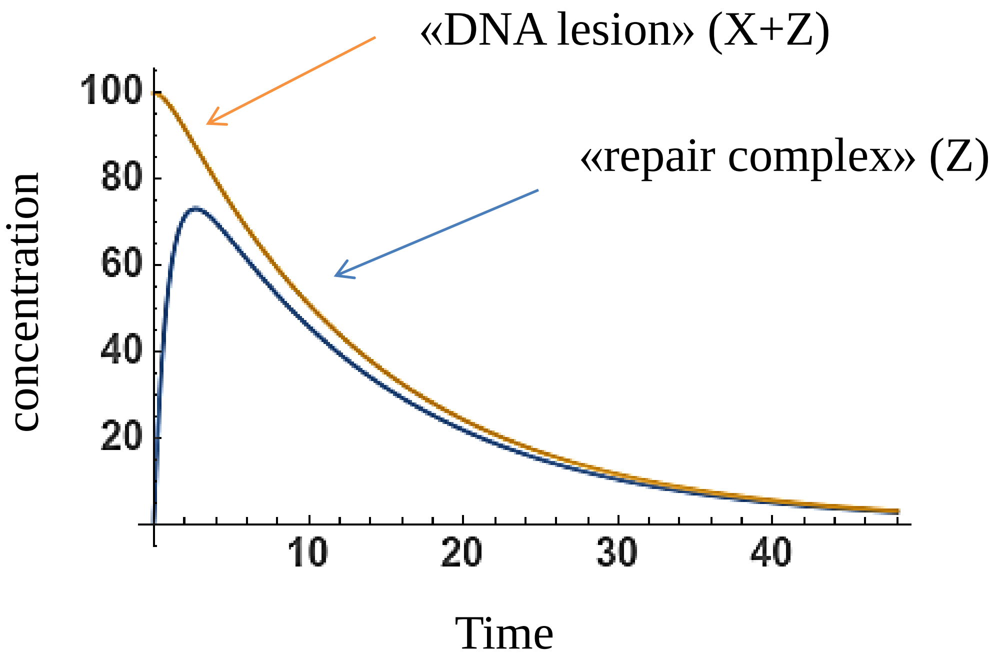
**1. Reaction scheme** $X + R \underset{k_-}{\overset{k_+}{\rightleftarrows}} Z \xrightarrow{q} R$

**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**

$$X(0) = N_0$$

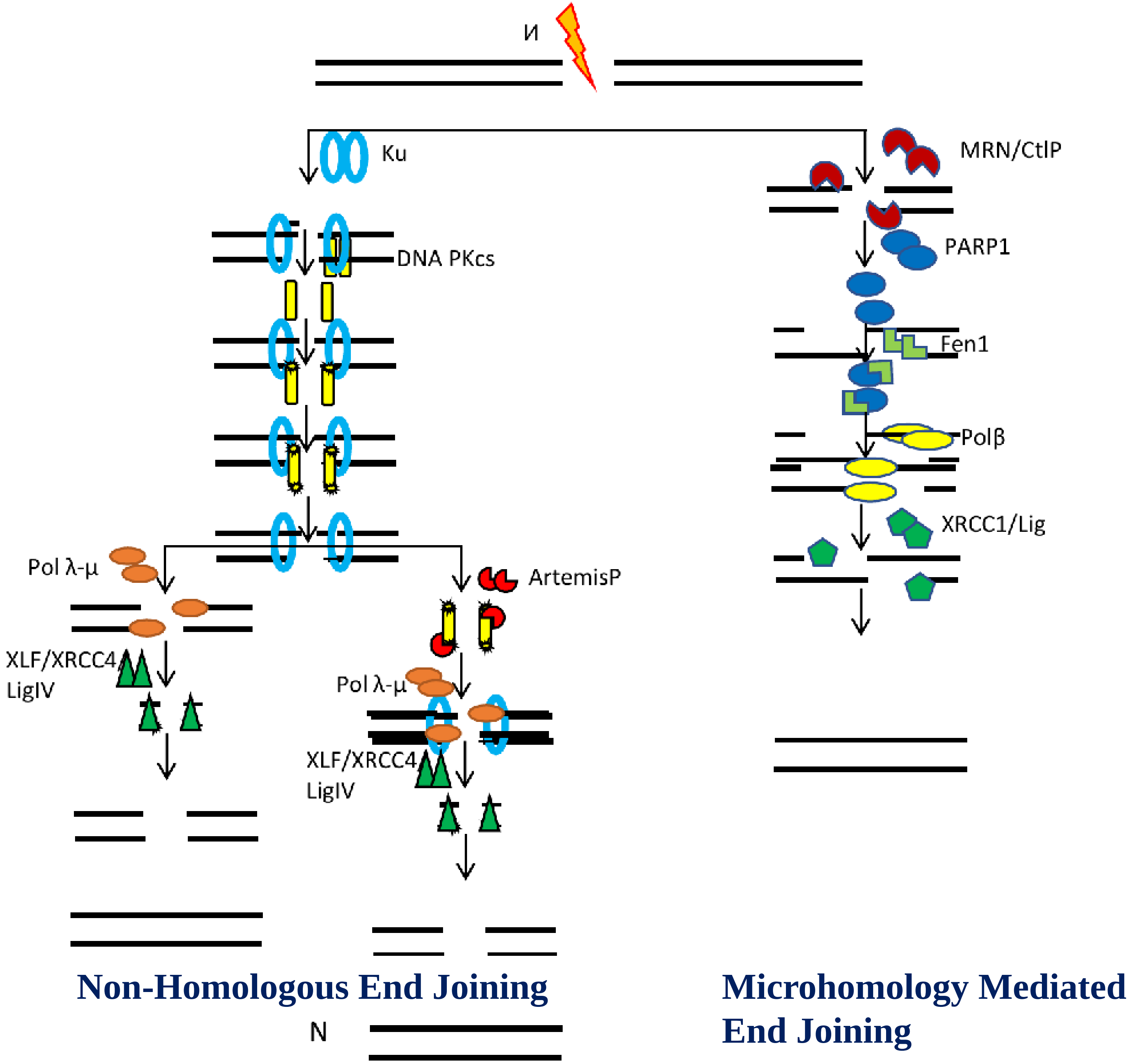
$$R(0) = R_0$$

$$Z(0) = 0$$

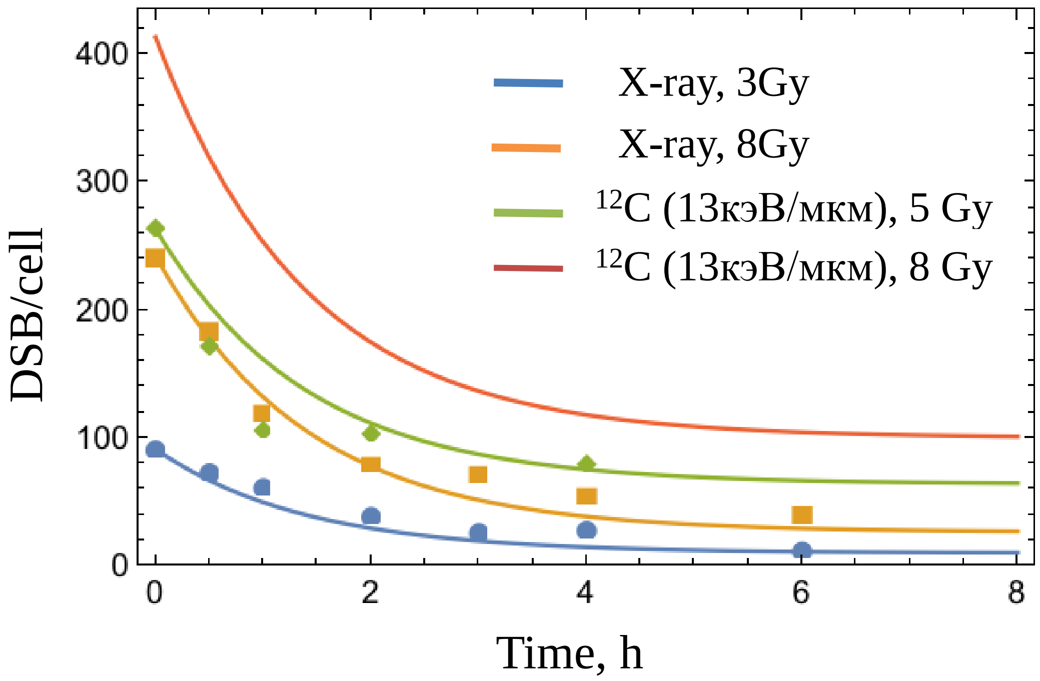
**4. Determination of parameters**

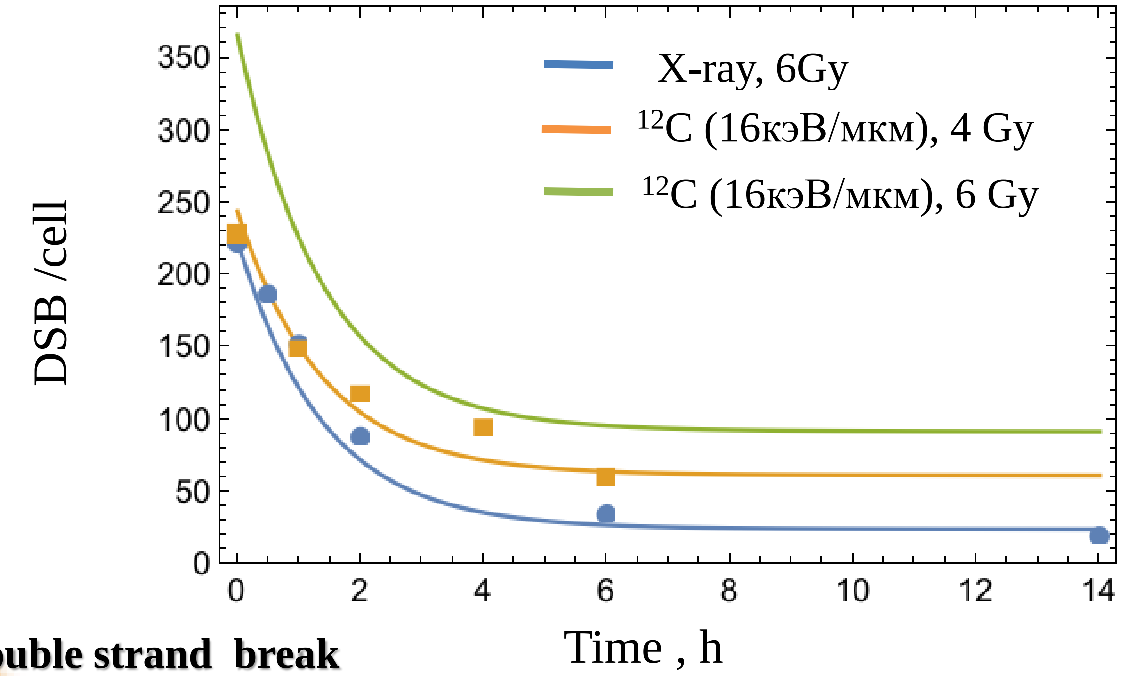
$k_+ \quad k_- \quad q$

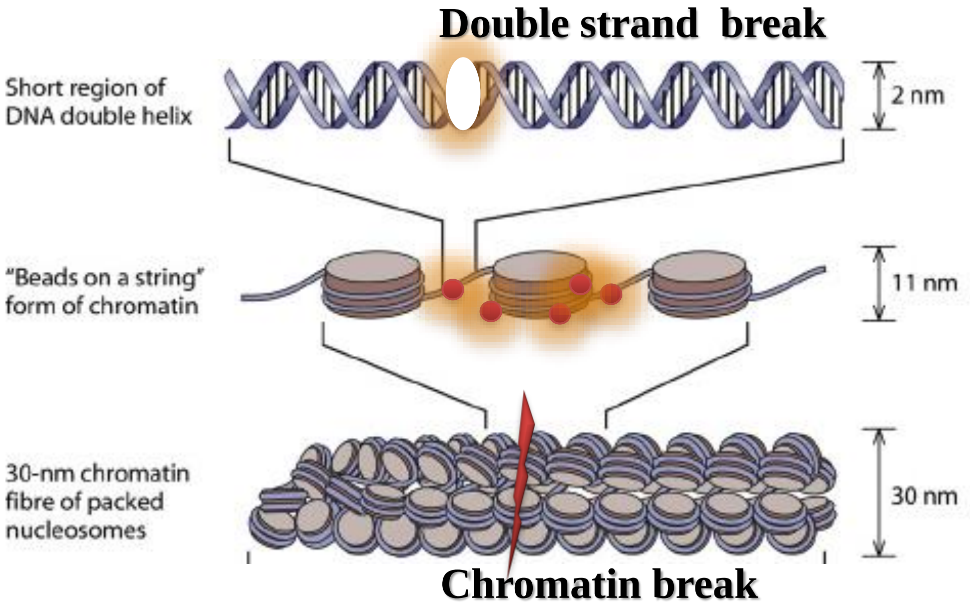
# DNA repair in G0/G1 phase



# DNA repair modeling: comparison DSB and chromatin breaks




V79 cells

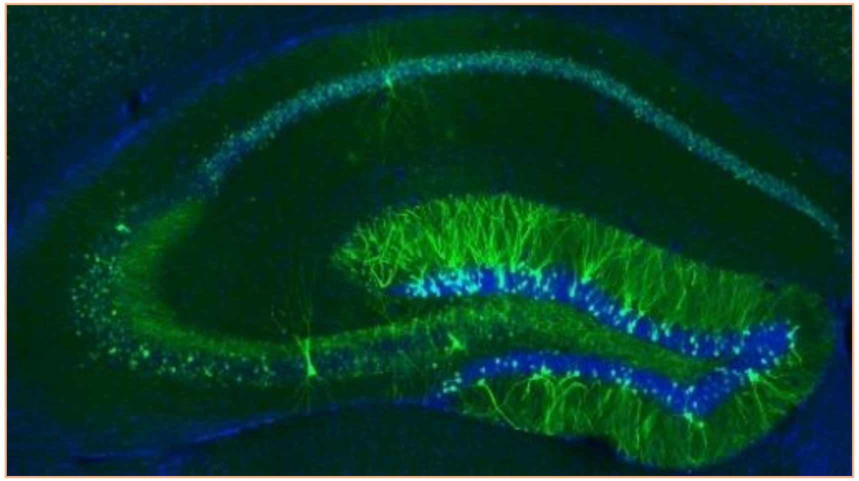
$$\frac{N_{dsb}}{N_{pcc}} = 10$$

Human fibroblasts

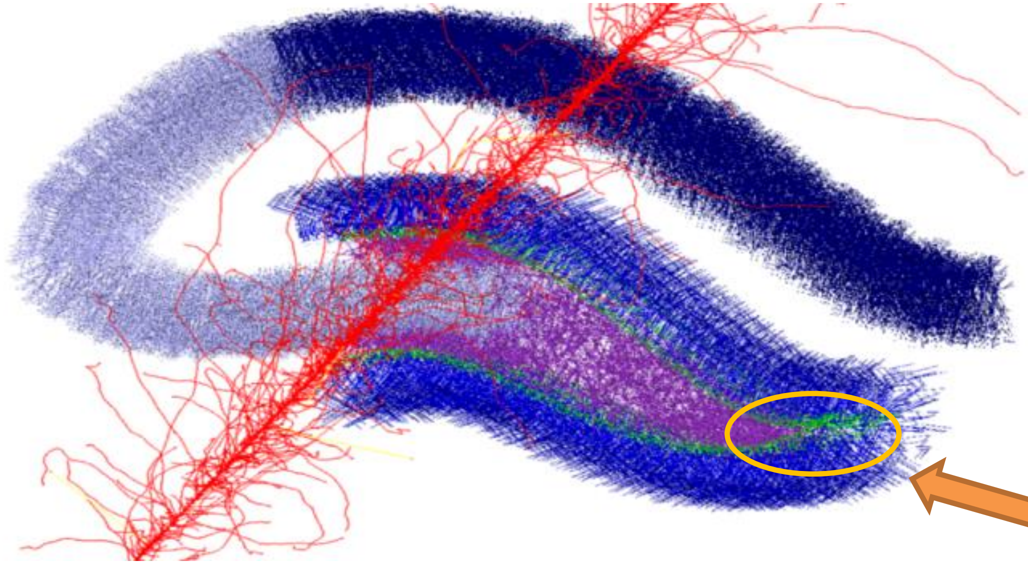
$$\frac{N_{dsb}}{N_{pcc}} = 7.4$$

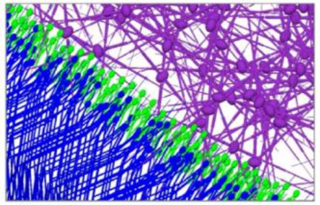
# Survival of radiosensitive cells

Hippocampus – critical target in brain



$^{56}$Fe 0.6 ГэВ/н

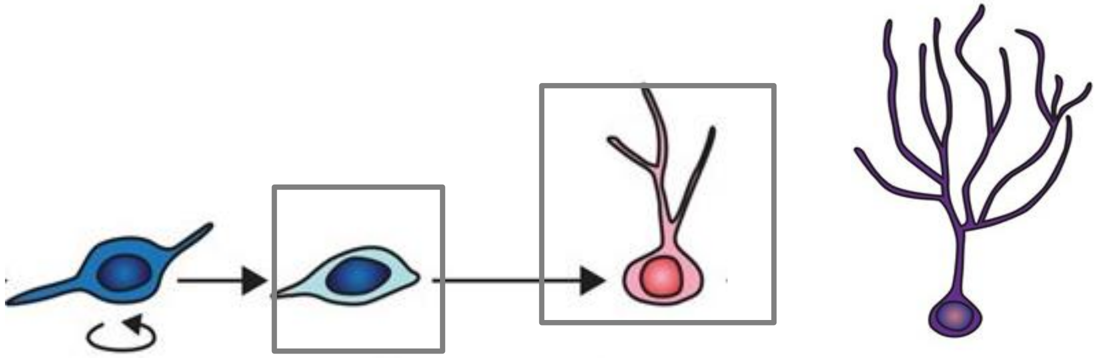




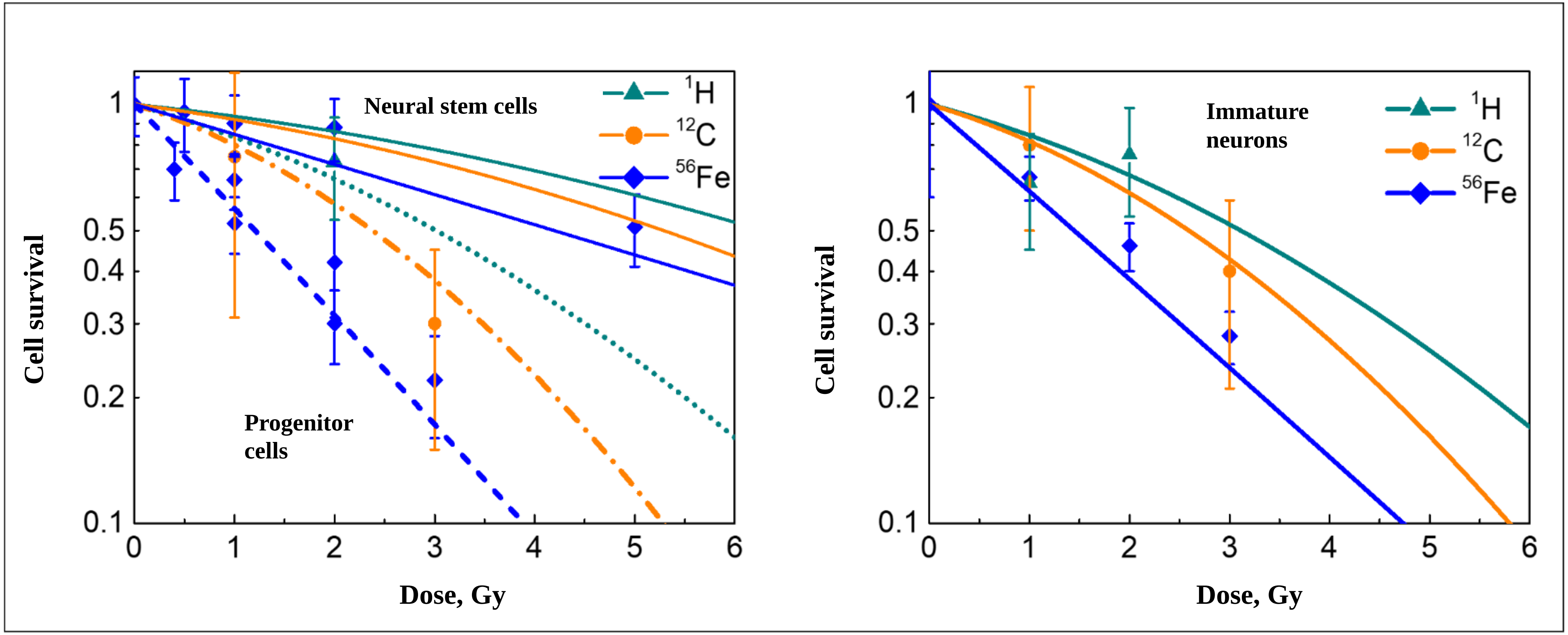
$$S\,(D, Y_{DSB}, N_{particle}) = \exp(-\alpha D - \beta D^2)$$

$$\alpha = Y_{DSB} \cdot P_{contrib} \cdot (1-P_{correct})$$
$$\beta = 0.5 \cdot Y_{DSB} \cdot P_{contrib} \cdot Y_{DSB} \cdot P_{correct} / N_{particle}$$

$$P_{contrib} = 1-\exp(-Y_{DSB})$$
$$P_{correct} = [1-\exp(-N_{particle})] \cdot [1-\exp(-Y_{DSB})]$$



# Survival of radiosensitive cells



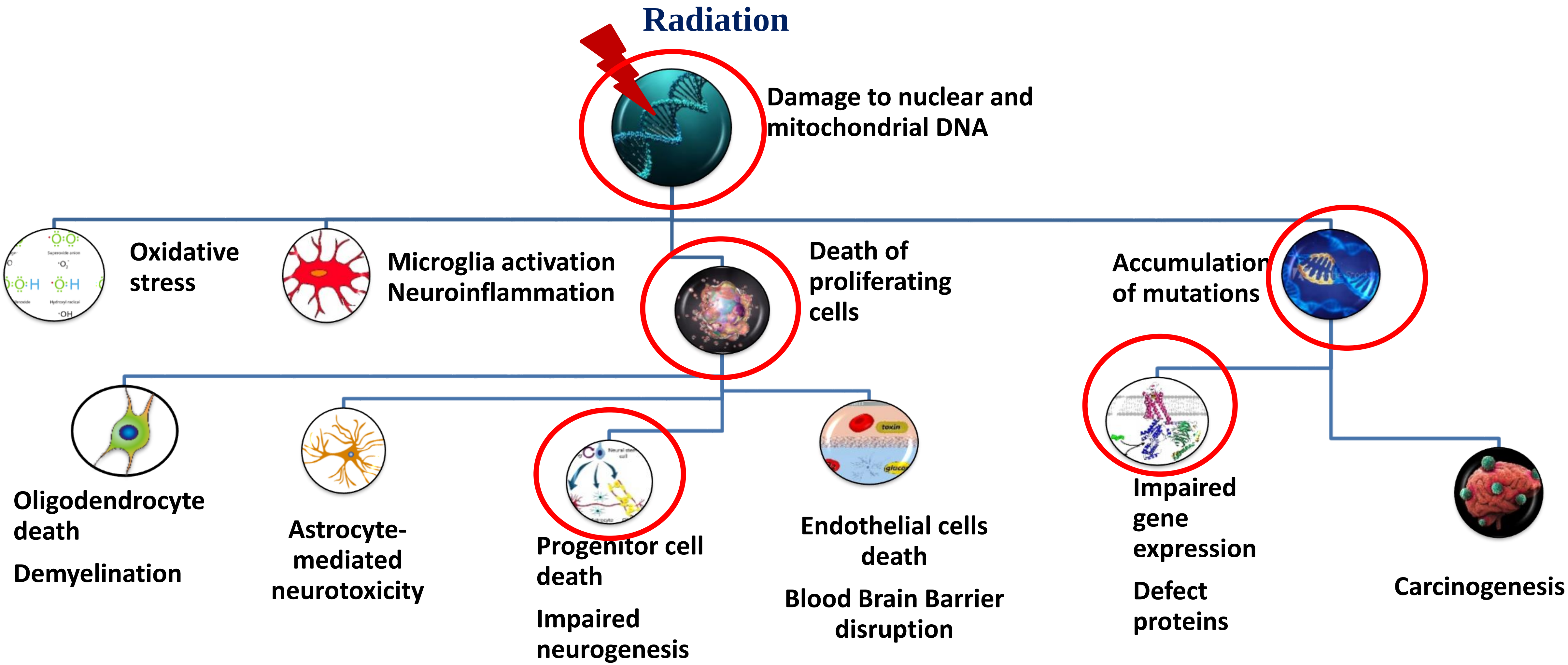

Calculated survival of radiosensitive cells (neural stem cells, neural progenitor cells, immature neurons) after action of 1000 MeV protons, 290 MeV/u carbon ions, 600 MeV/u iron ions as compared with experimental data [Rola 2004, 2005, Tseng 2014].

# Effect of radiation at the system level

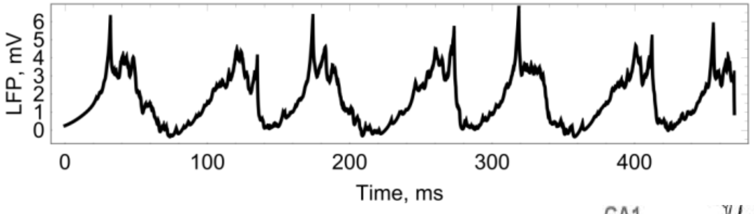
**Radiation damage to the central nervous system:**

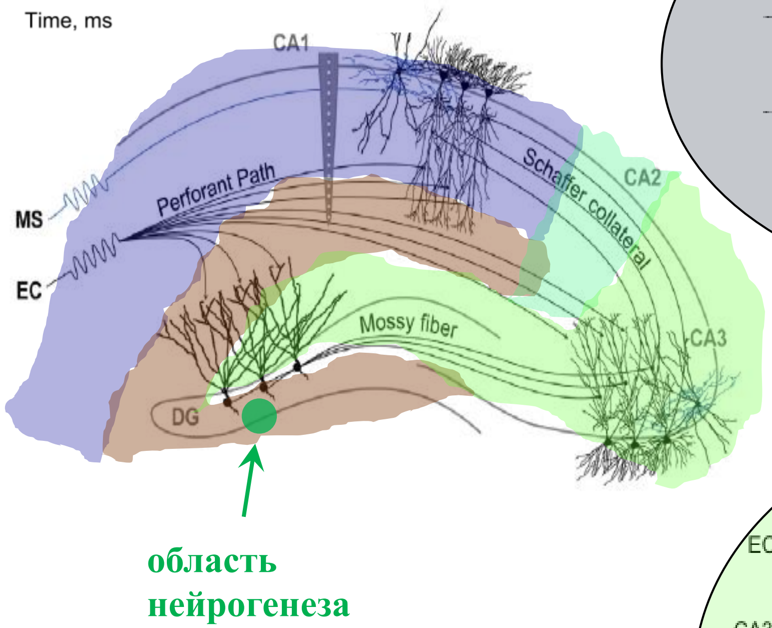
- **molecular level**
- **cellular level**
- **functional level**

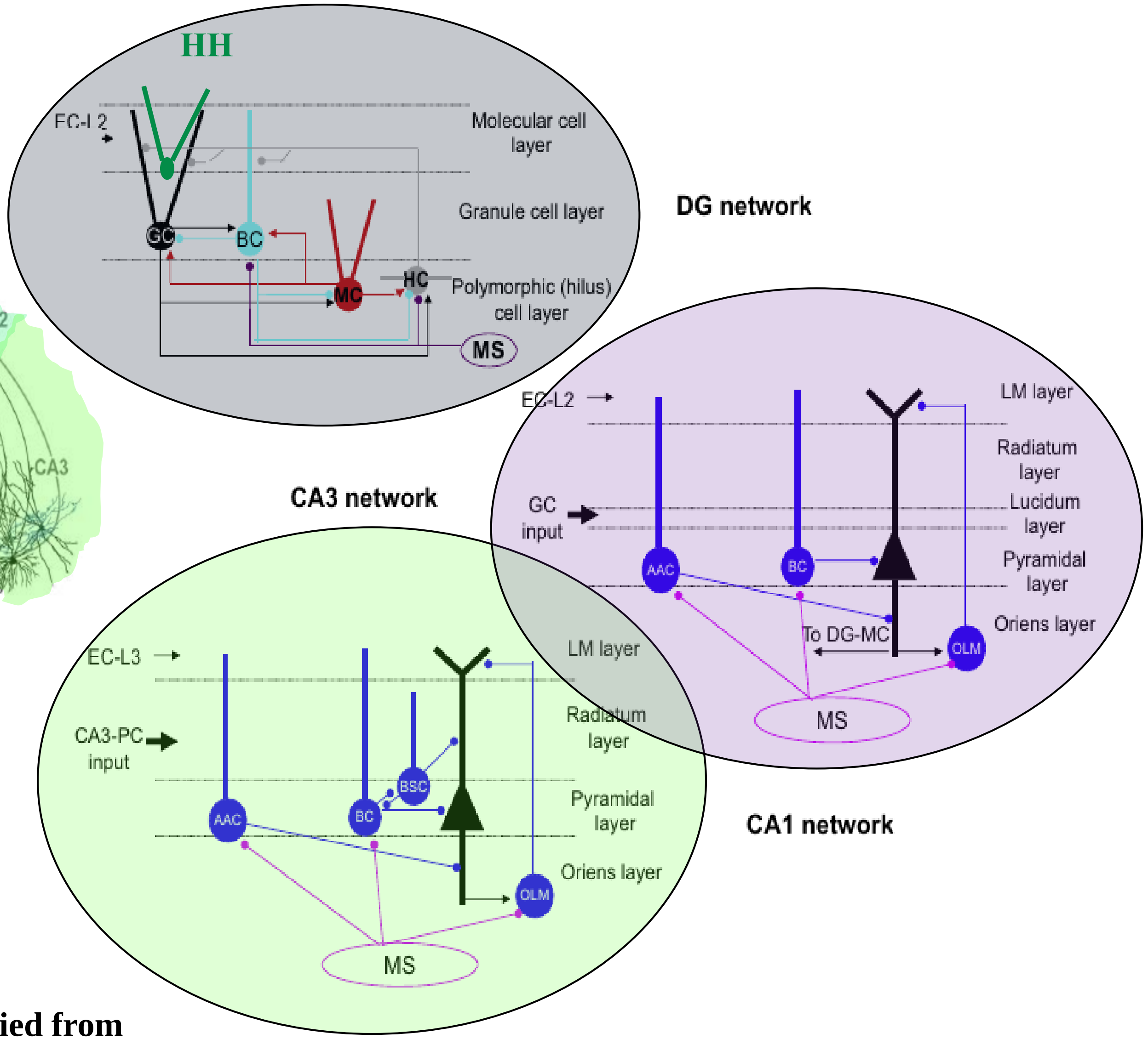
# Mechanisms of radiation damage to the central nervous system



# <u>Biological neural network</u> of hippocampus: a model for electrophysiological activity



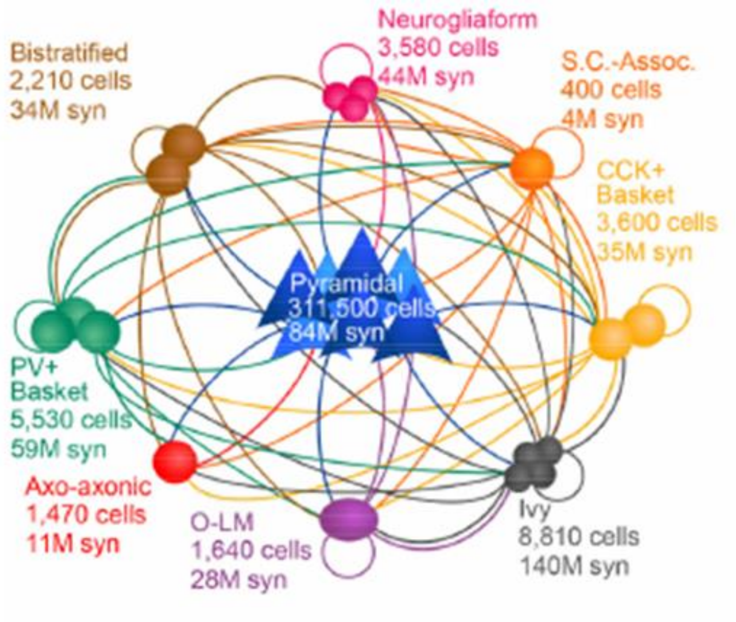



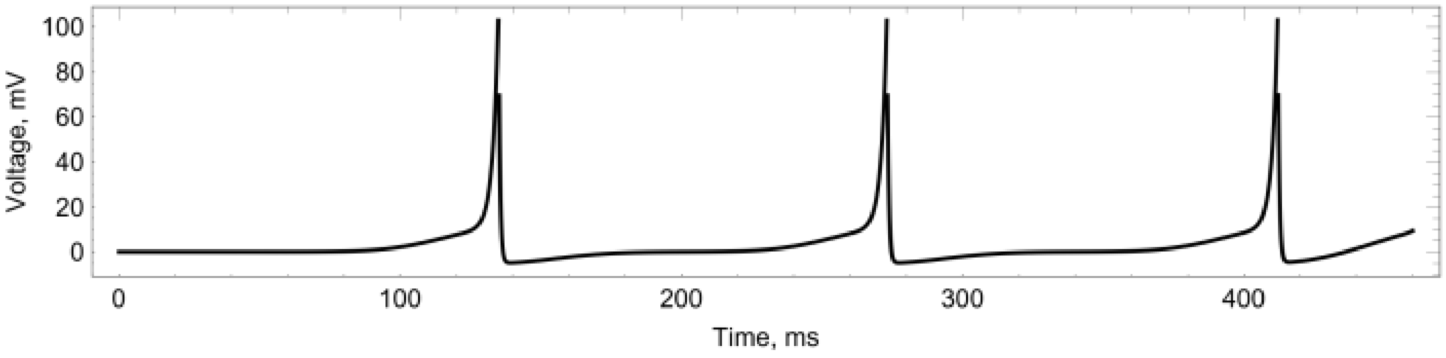




**Modified from**

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

# Mathematical description of neural network elements



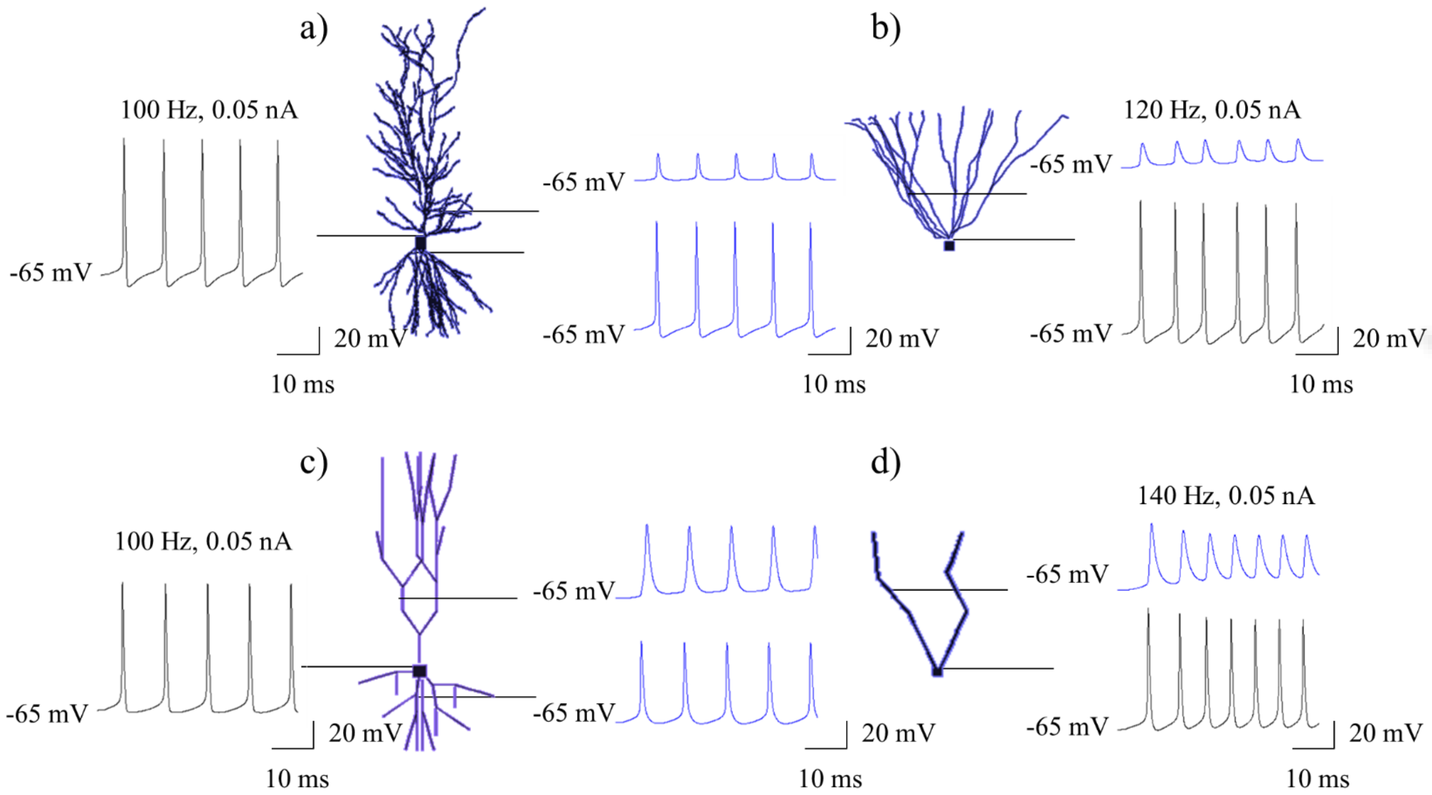

$$C\frac{dV_p}{dt} = g_{Na} m_p^{\,3} h_p (E_{Na} - V_p) + (g_K n_p^4 + g_{K(A)} a_p b_p)(E_K - V_p)$$

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

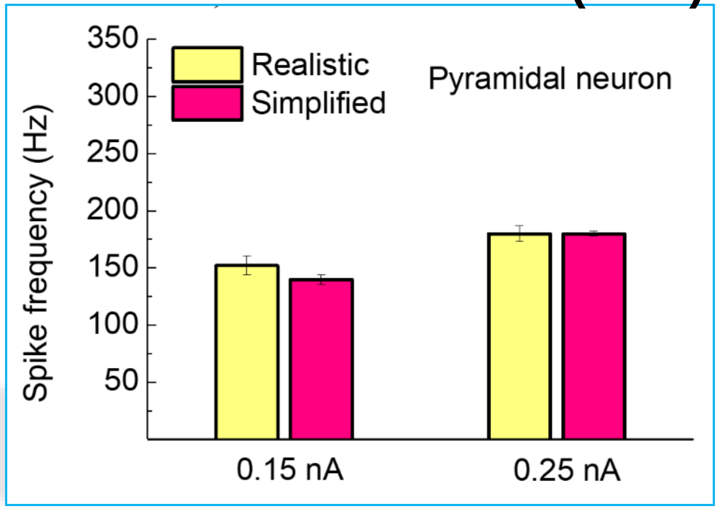
Synaptic connections between neurons

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

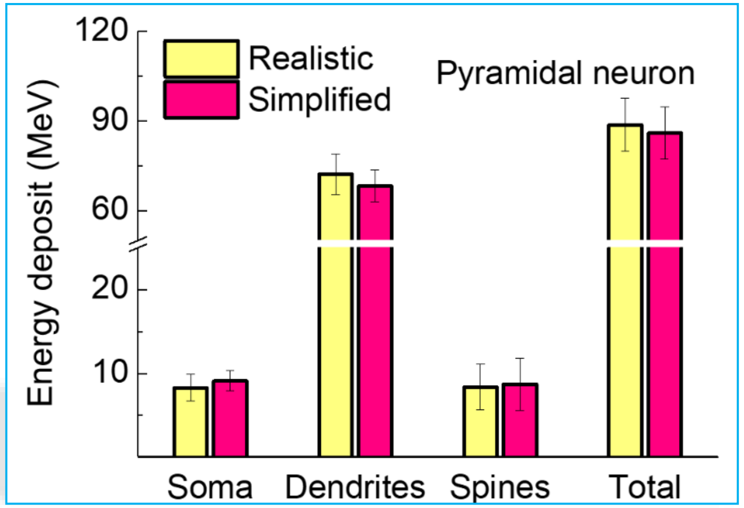
# Compartment models of neurons can be used both for calculating absorbed dose and for analyzing electrical activity




NEURON (v.7.4)

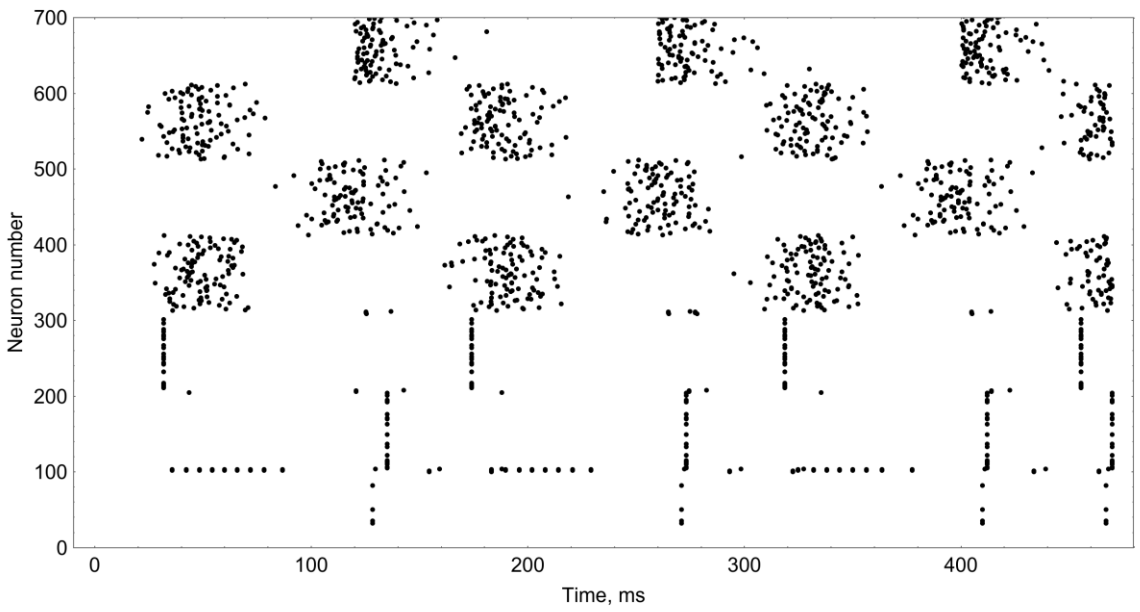



GEANT4 (v.10.4)

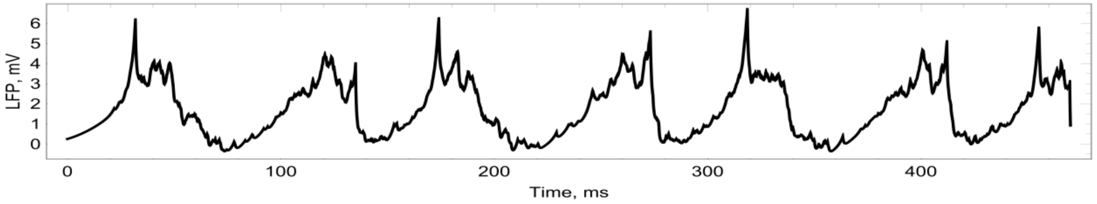


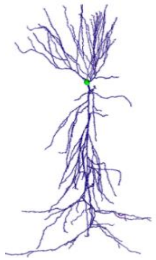

600 MeV/n $^{56}Fe$, flux $3.2 \times 10^5$ $cm^{-2}$

# Neural network electric activity

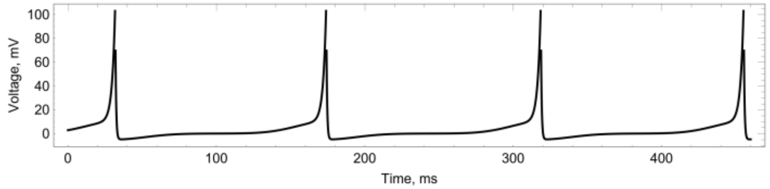


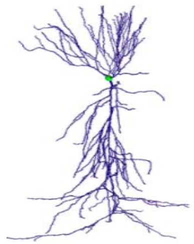

Integral signal (theta-rhytm)



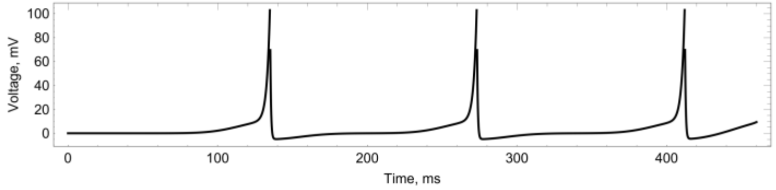



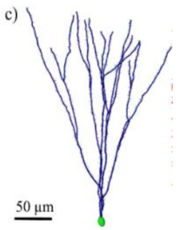
Pyramidal neuron CA1



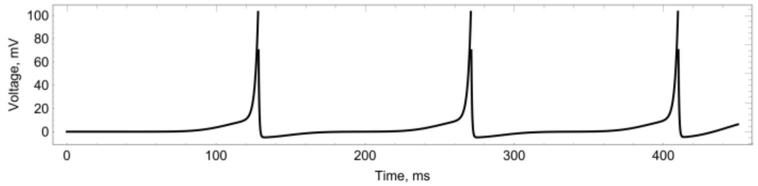



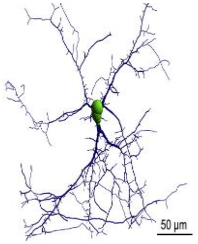
Pyramidal neuron CA3



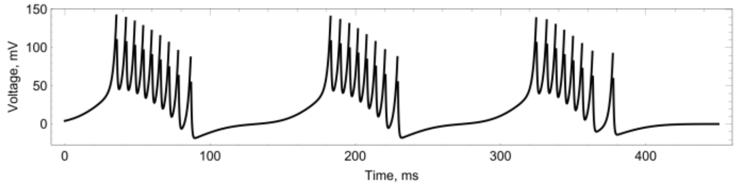




Granular cell



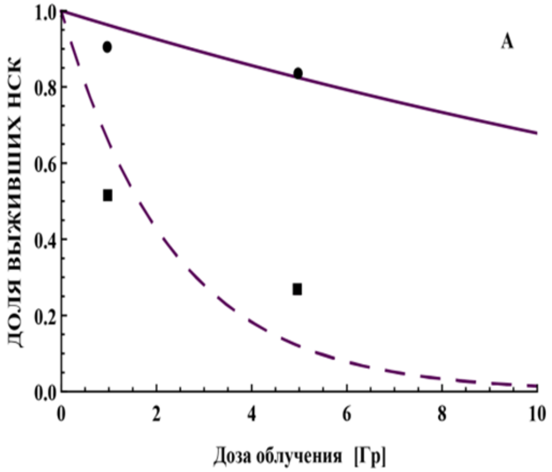



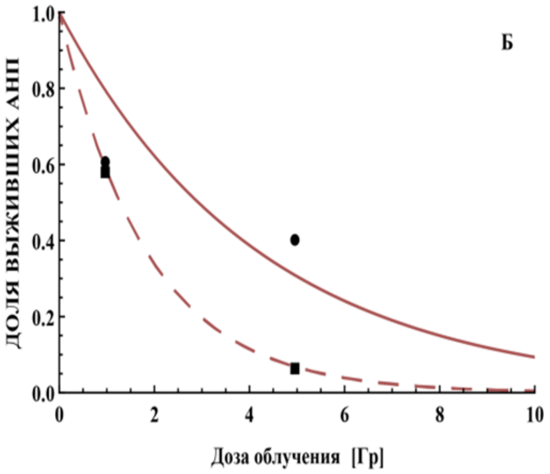

Basket cell

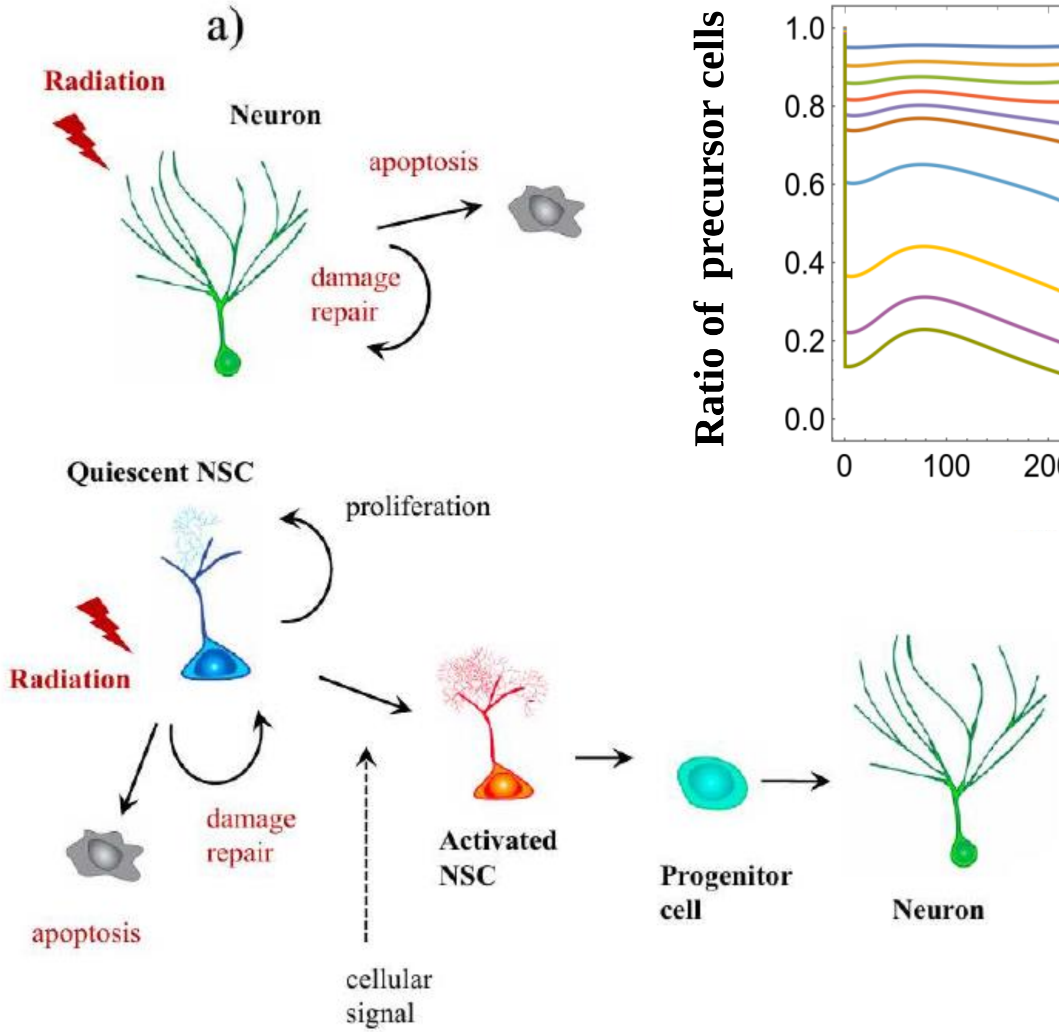


# Mathematical modeling of radiation-induced neurogenesis impairment

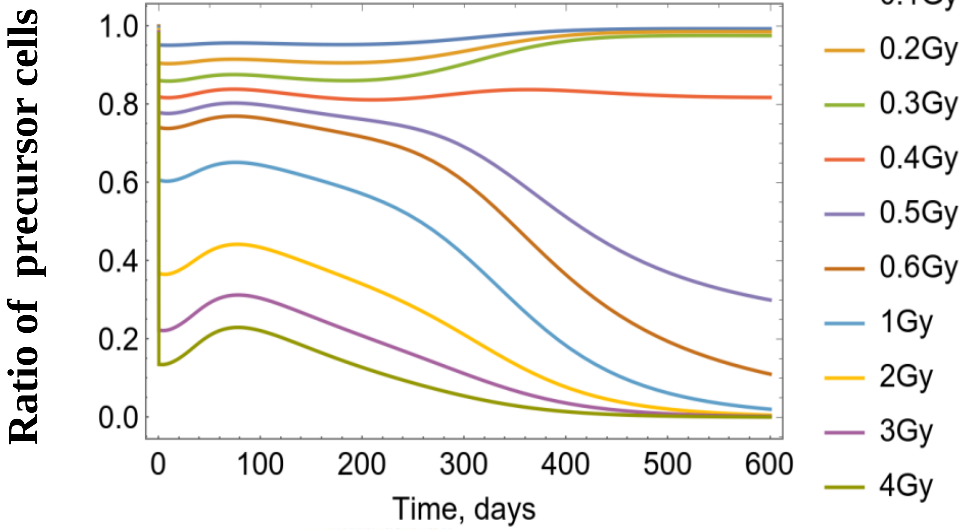
X-ray: theory vs experiment



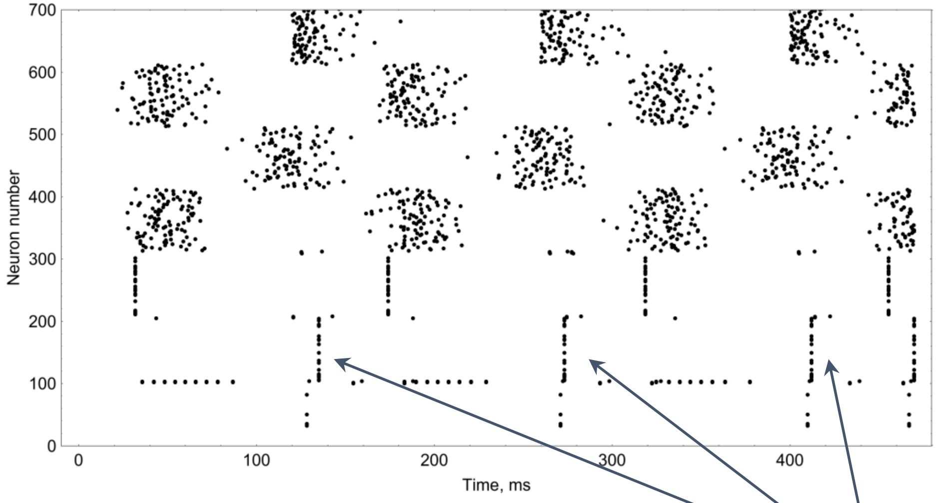




$^{56}Fe$ ions 600 MeV/u

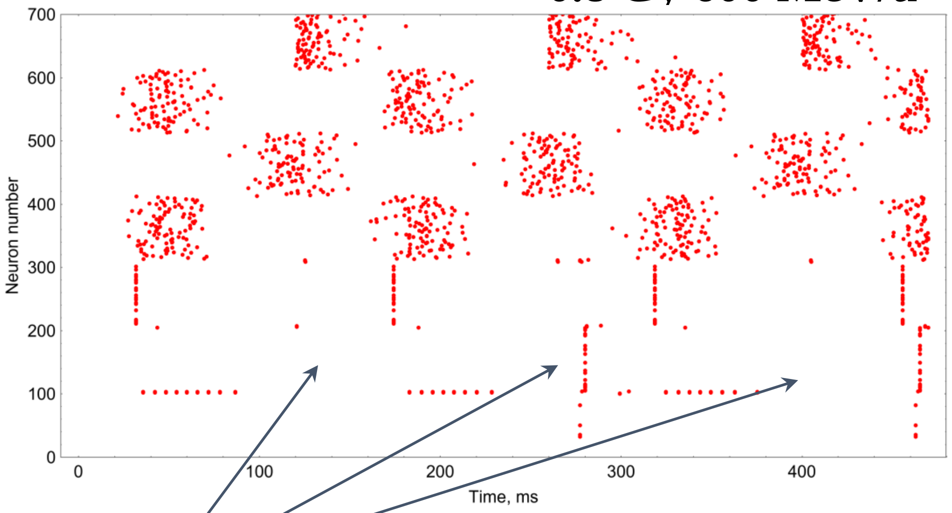


# Influence of immature cell loss on information processing

**Control**

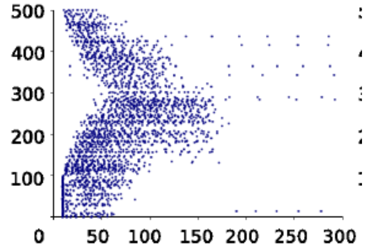



**0.8 Gy 600 MeV/u $^{56}Fe$**

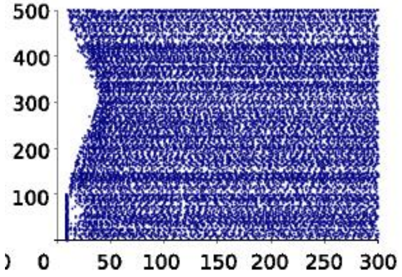



**Encoded patterns**

**10% of newborn GC**

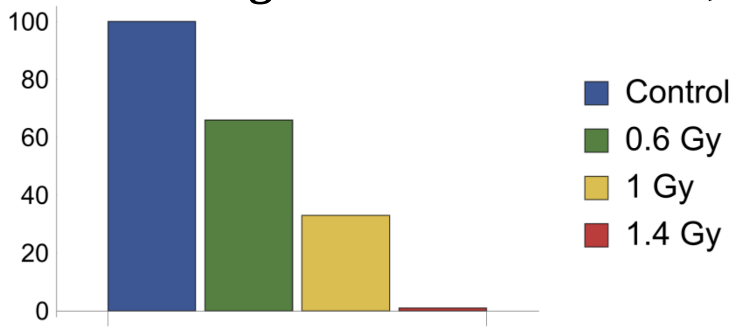



**50% of newborn GC**

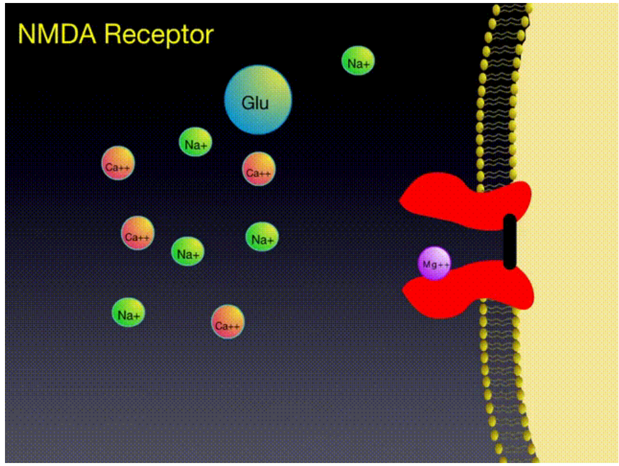



**Local effect of immature neuron loss**

**Encoding and retrieval success, %**



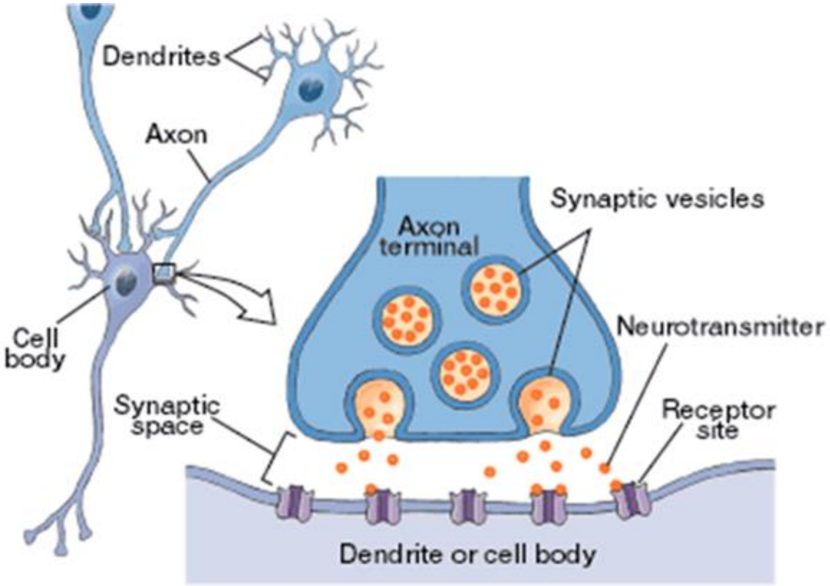
# Effects of mutations in synaptic receptors: molecular dynamics simulation

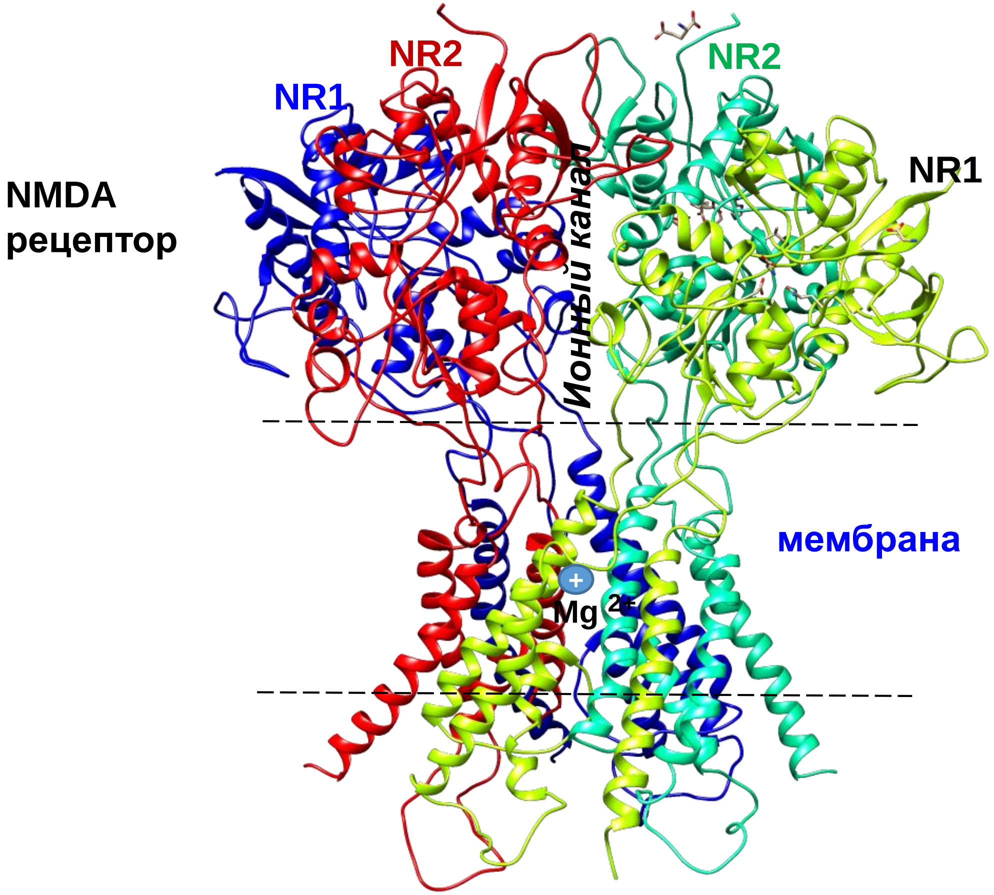



## NMDA receptor

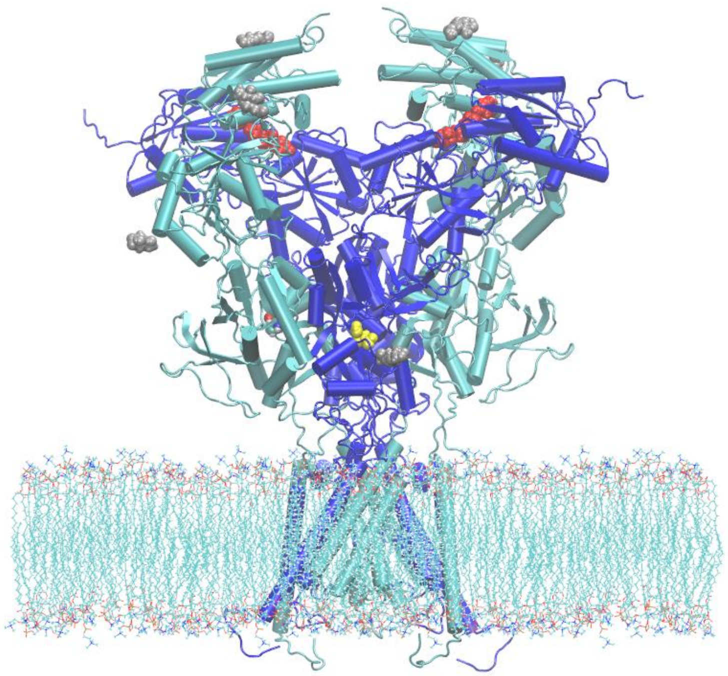
NR1 subunit
*GRIN1* chr9, 30373 bp

NR2B subunit
*GRIN2B* chr12, 443027 bp



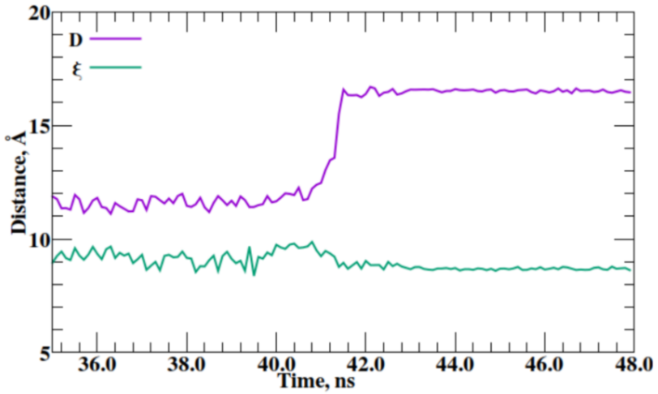



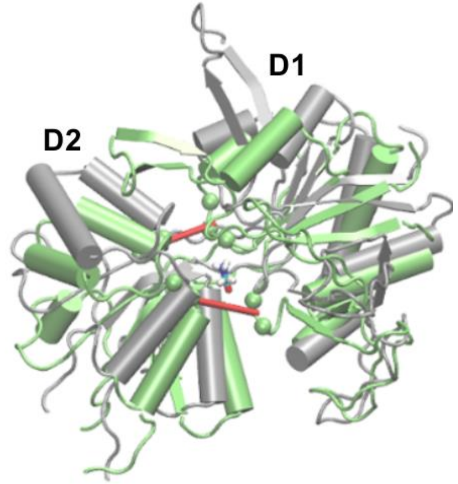
# Opening of transmembrane ion channel

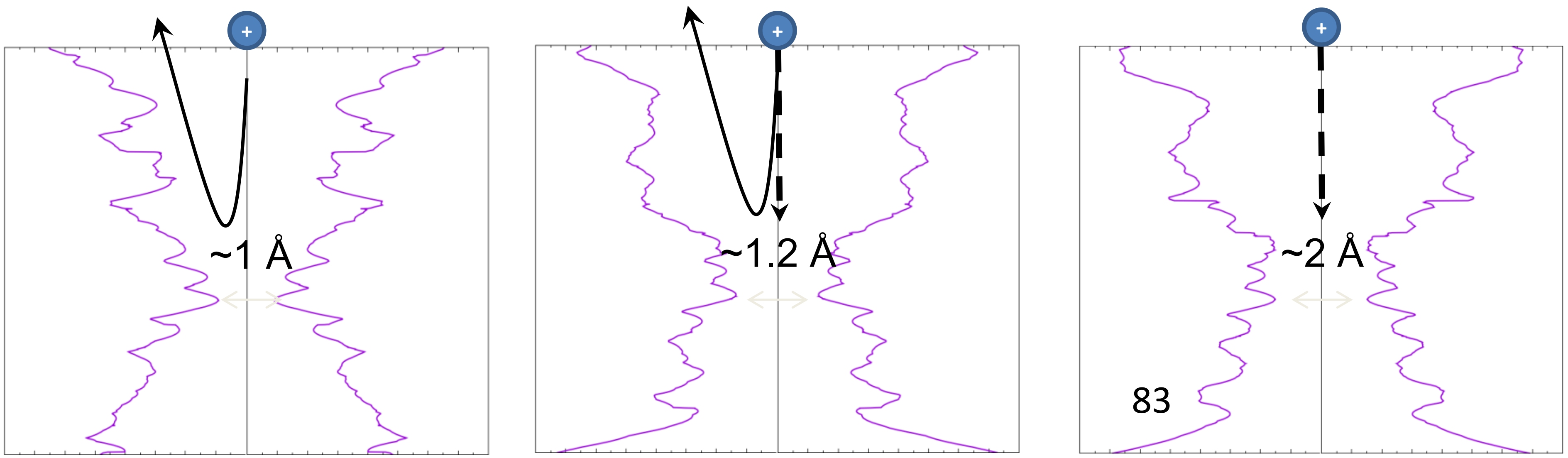


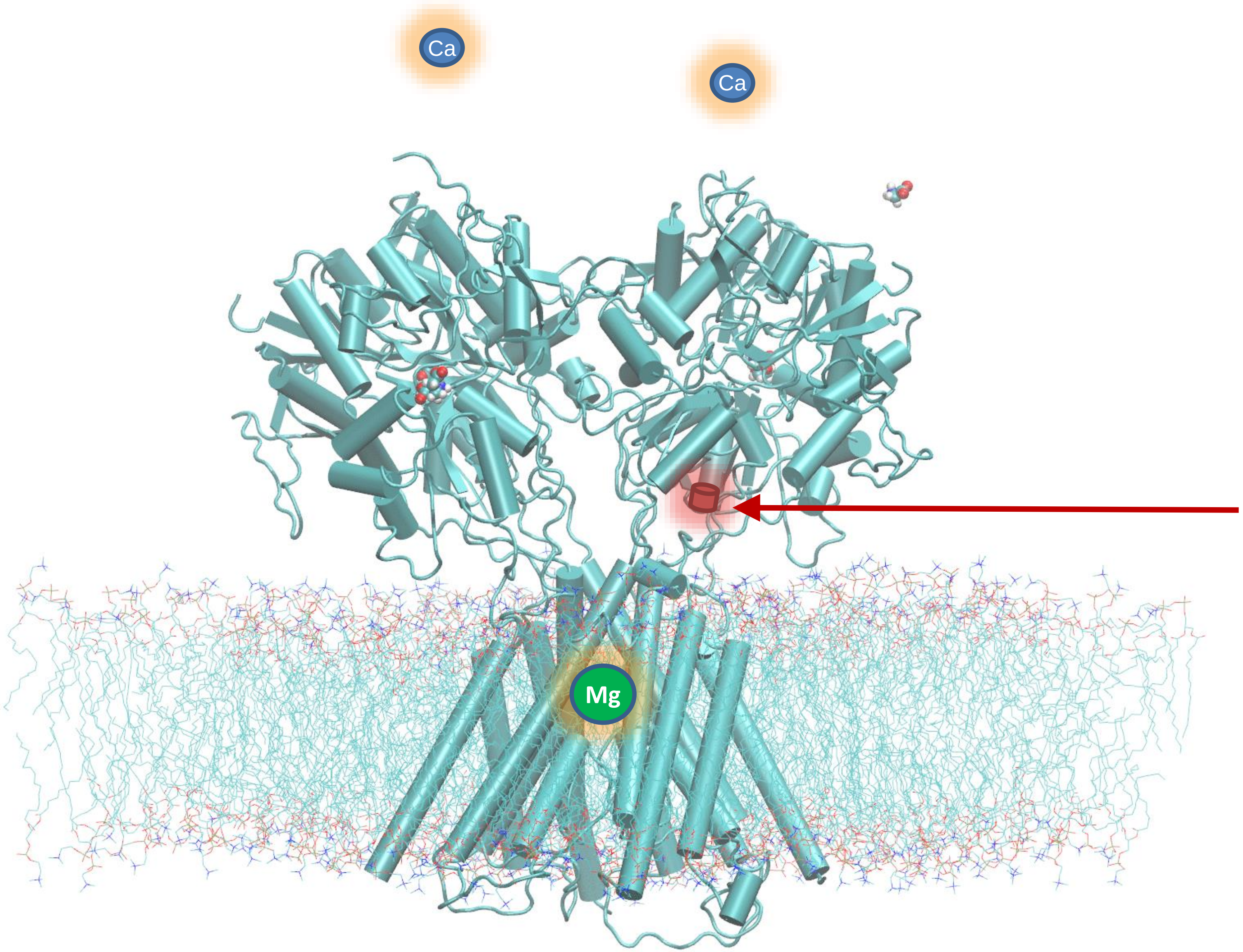
5FXJ crystal structure from the Protein Data Bank (PDB)

NAMD Scalable Molecular Dynamics



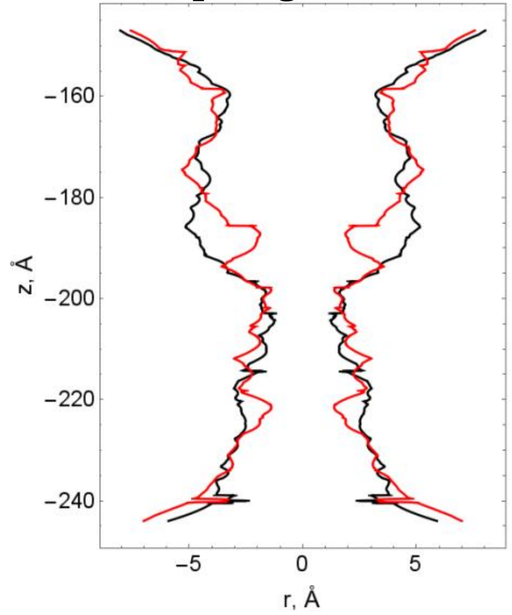



Microdeletion of p.Phe671_Gln672del results in the loss of two amino acids: phenylalanine and glutamine

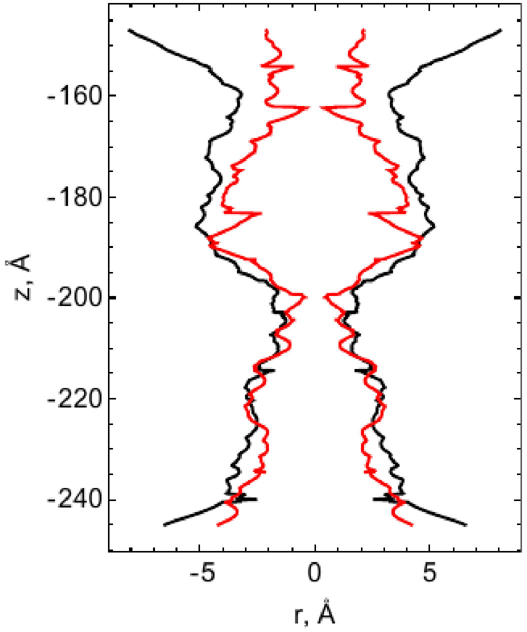
Protein conformation change!

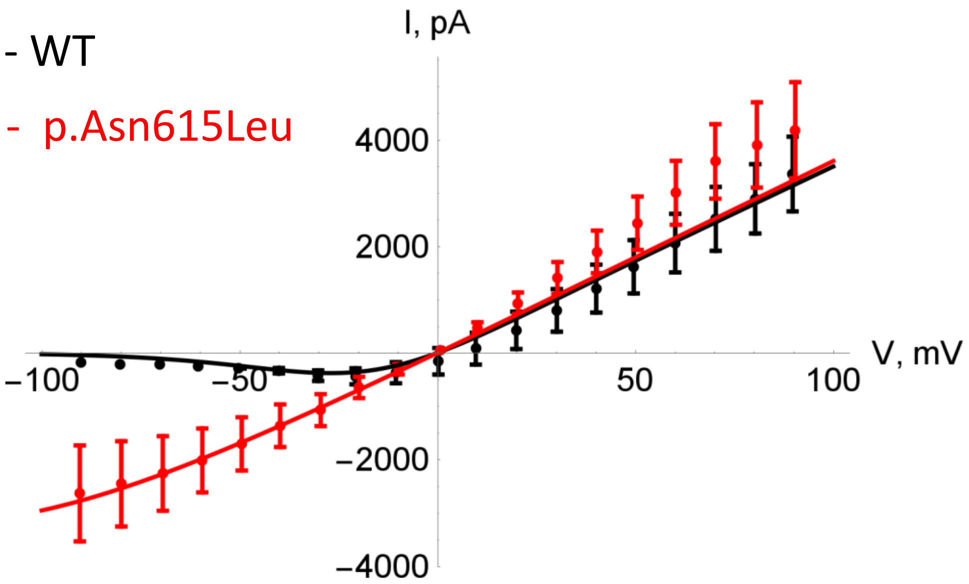
# Ion channel properties for specific mutations

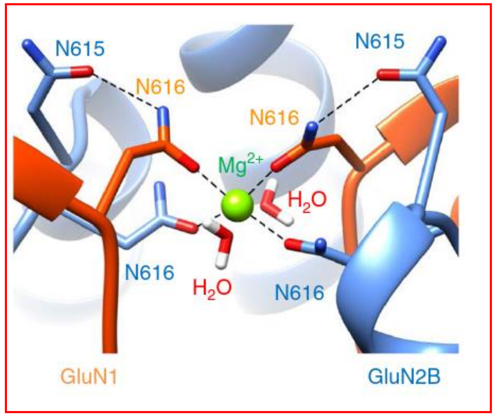
**p.Arg540His**

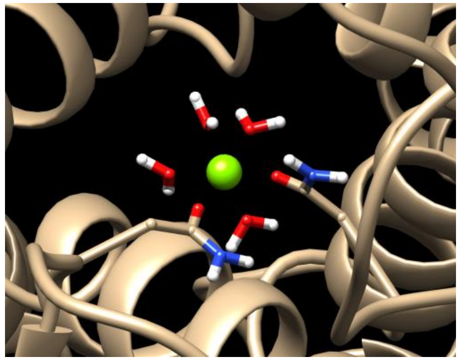


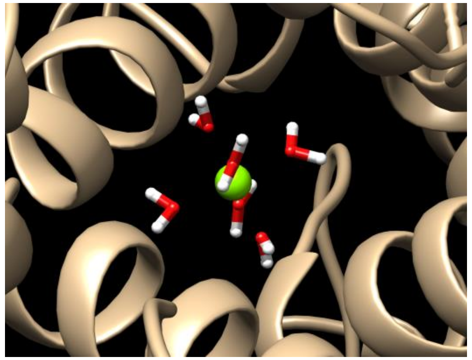

**p.Phe671_Gln672del**





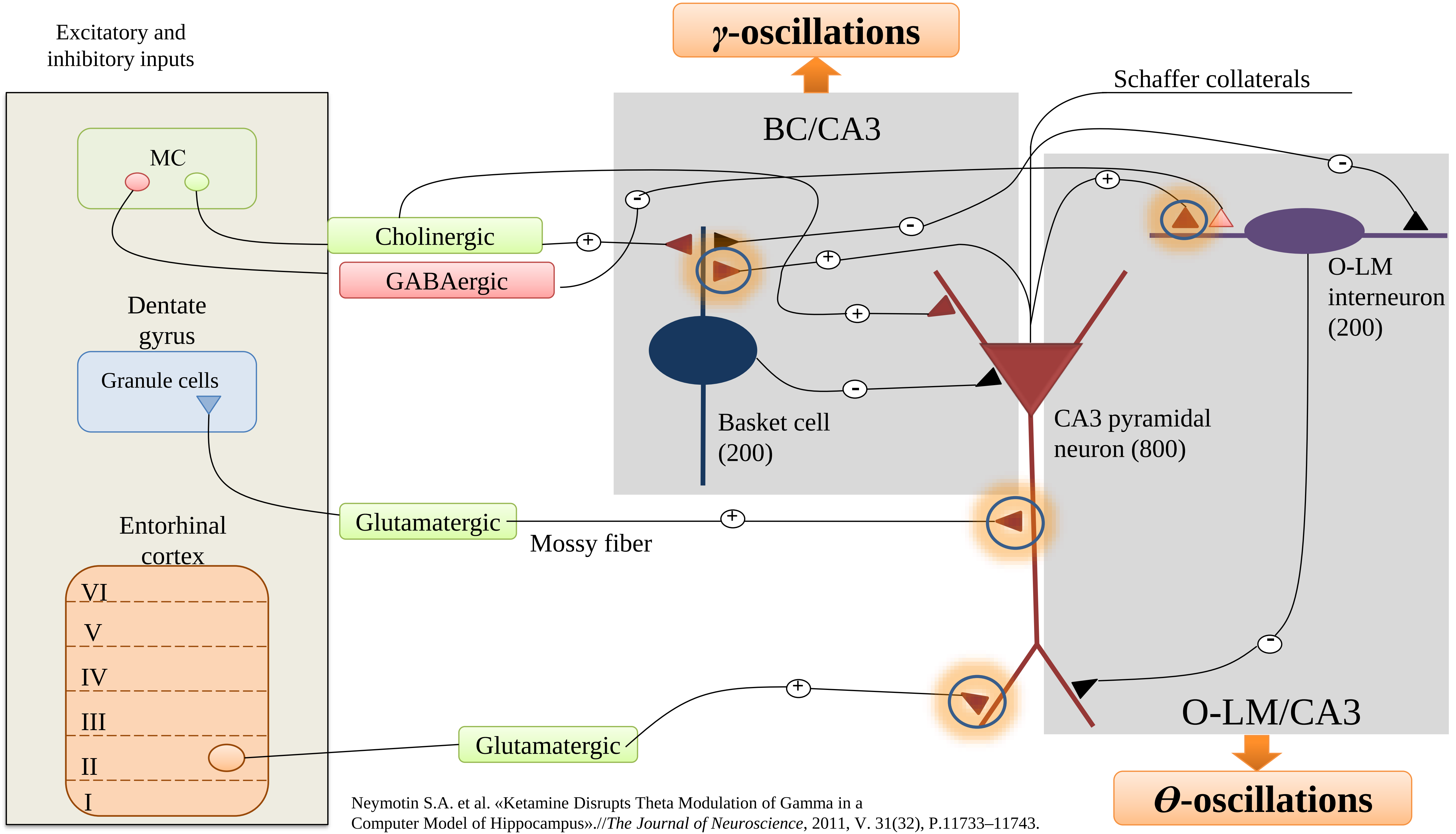
**p.Arg540His** **p.Asn615Leu**

Maximum conductivity **G**

$$I_{NMDA} = \frac{G\ P(V_{pre})(V - V_e)}{1 + c[Mg^{2+}]\exp[-qV]},$$

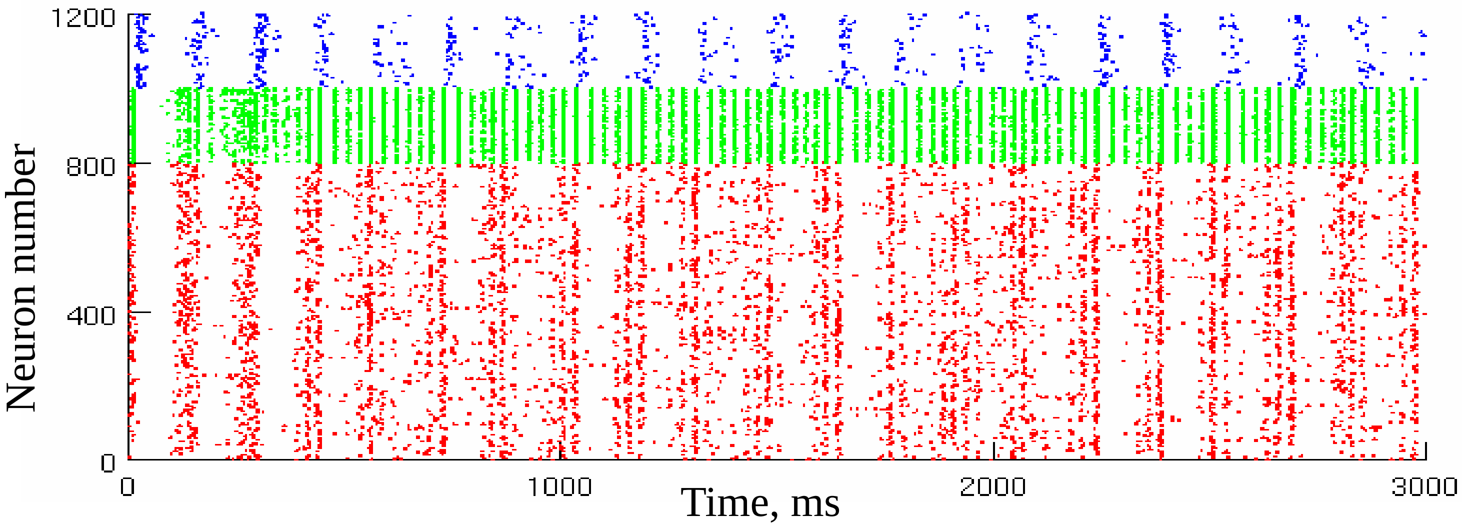
$Mg^{2+}$ binding

*Batova, Bugay et al*, J. Bioinf. Comp. Biol. 2019

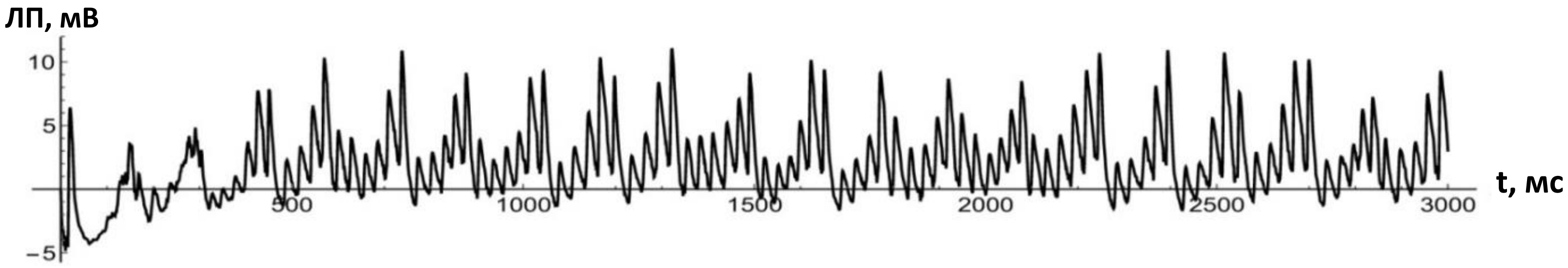



Neymotin S.A. et al. «Ketamine Disrupts Theta Modulation of Gamma in a Computer Model of Hippocampus».//*The Journal of Neuroscience*, 2011, V. 31(32), P.11733–11743.

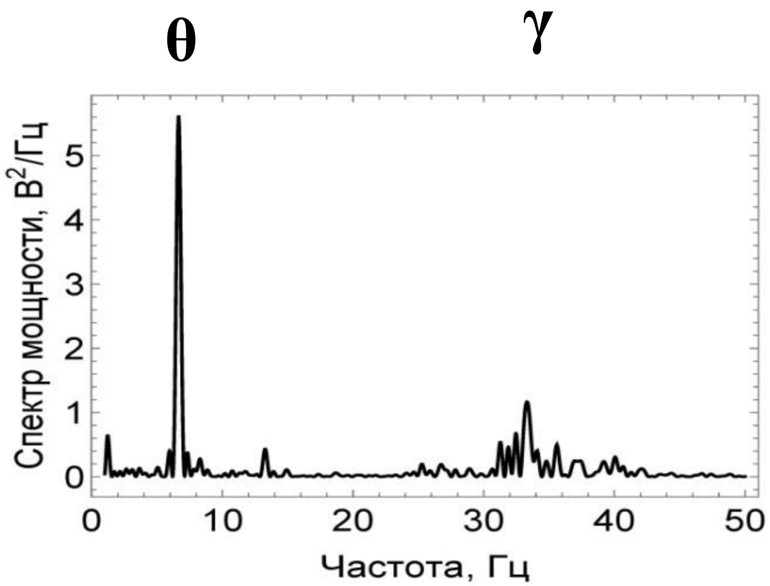
# Normal dynamics of brain activity




Spike generation over time and neuron number




Local field potential

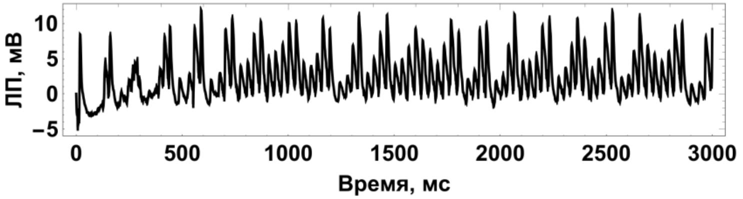



Spectra of brain rhythms

# Effect of mutant synaptic receptors on brain electric activity

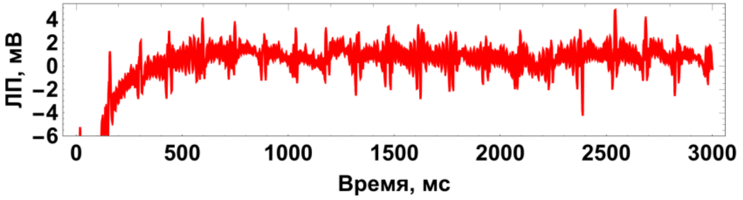
## EEG signals in hyppocampus

**Effect of mutant receptors**




(a)

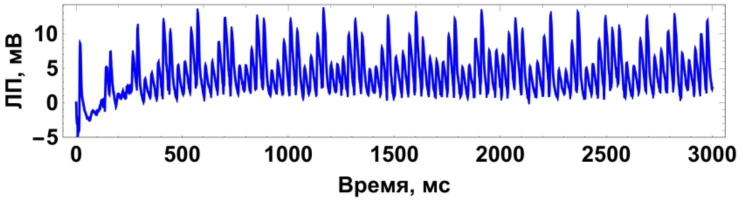
control




(b)

**p.ASN615LEU**

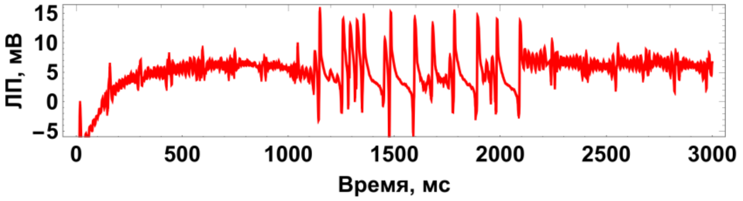
West syndrome




(c)

**p.PHE671_GLN672del**

Mild ID, autism

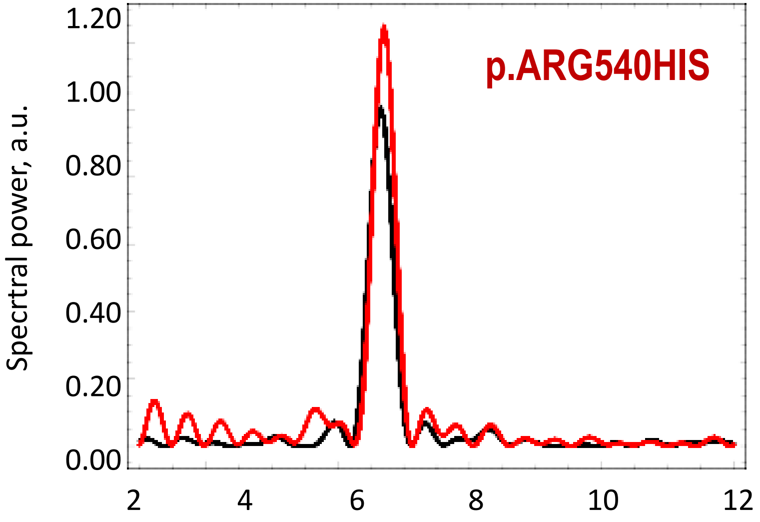


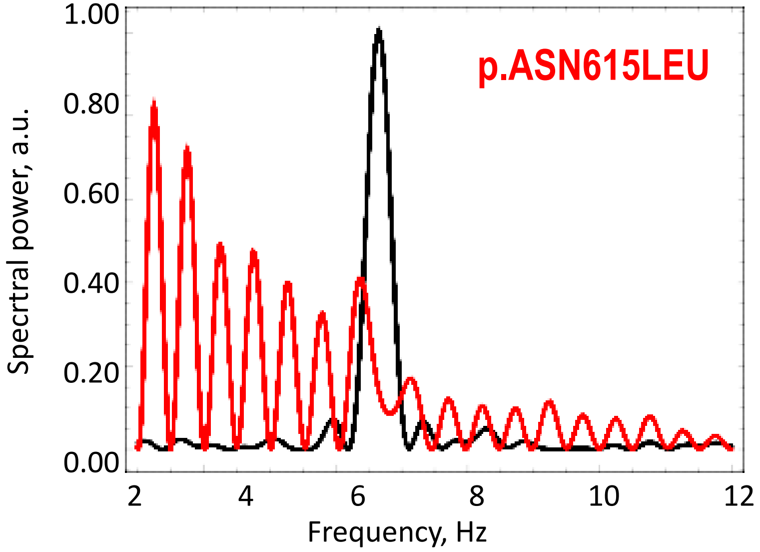

(d)

**p.ASN615LEU**

Epileptic seizure

- control
- **mutant**



# Machine learning in biological data analysis

BIOHLIT

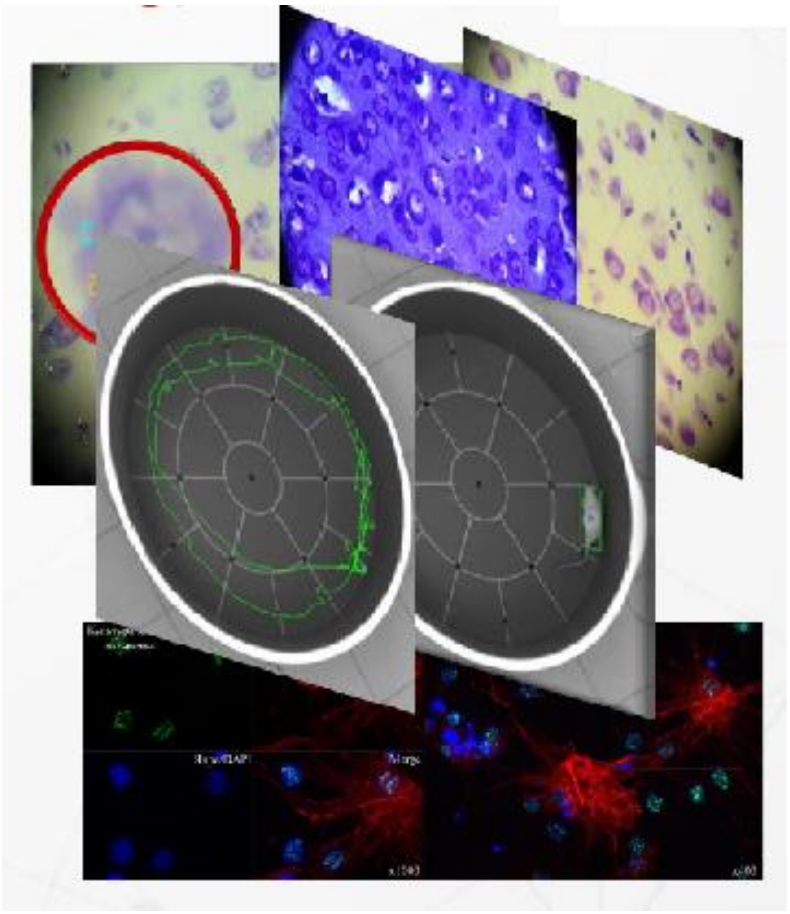
[https://it4bio.jinr.ru](https://it4bio.jinr.ru)

## Information system BIOHLIT

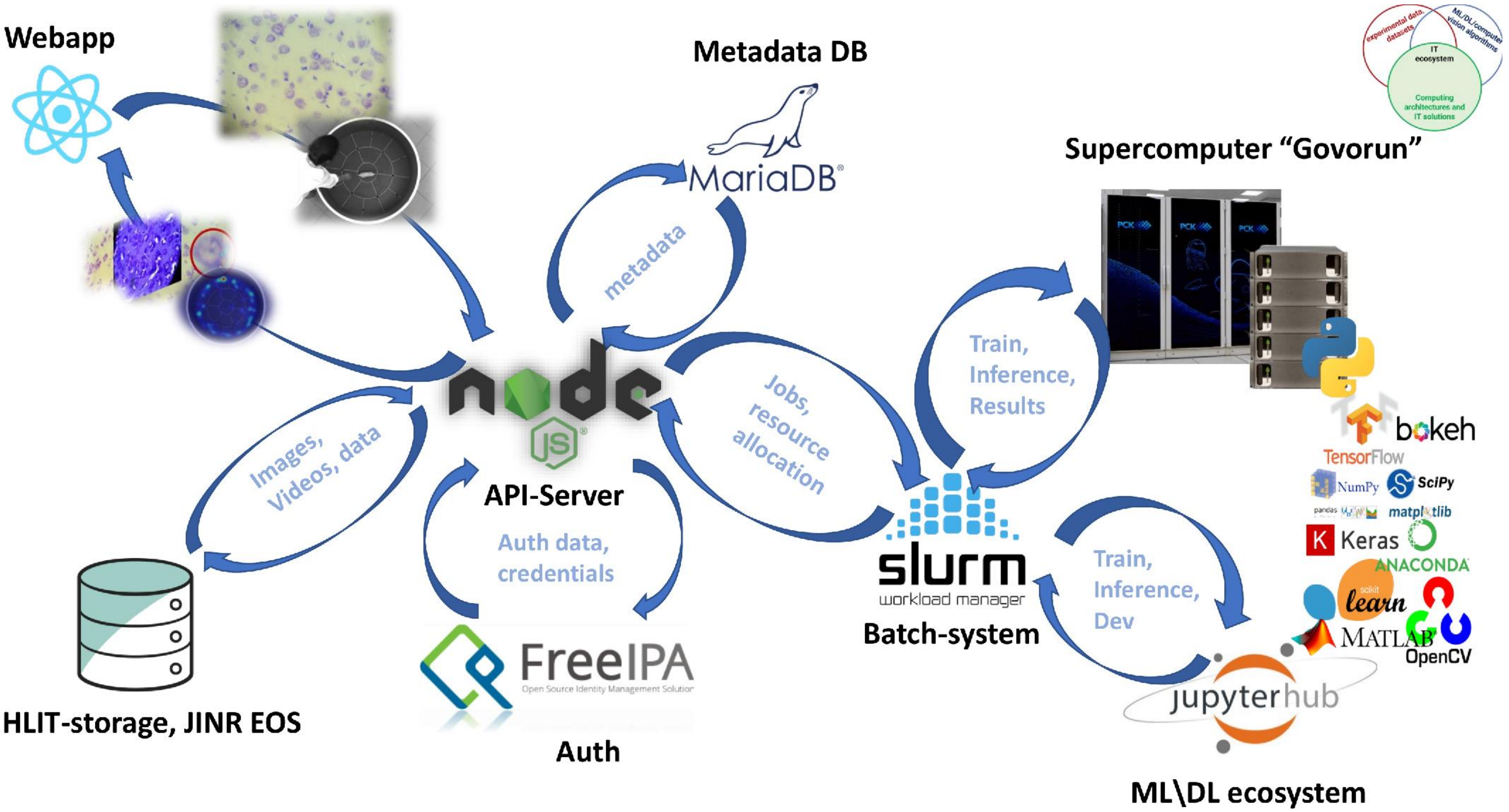
- computer vision algorithms based on machine learning and deep learning technologies;
- modern IT solutions for storing, processing and visualizing data;

Data used

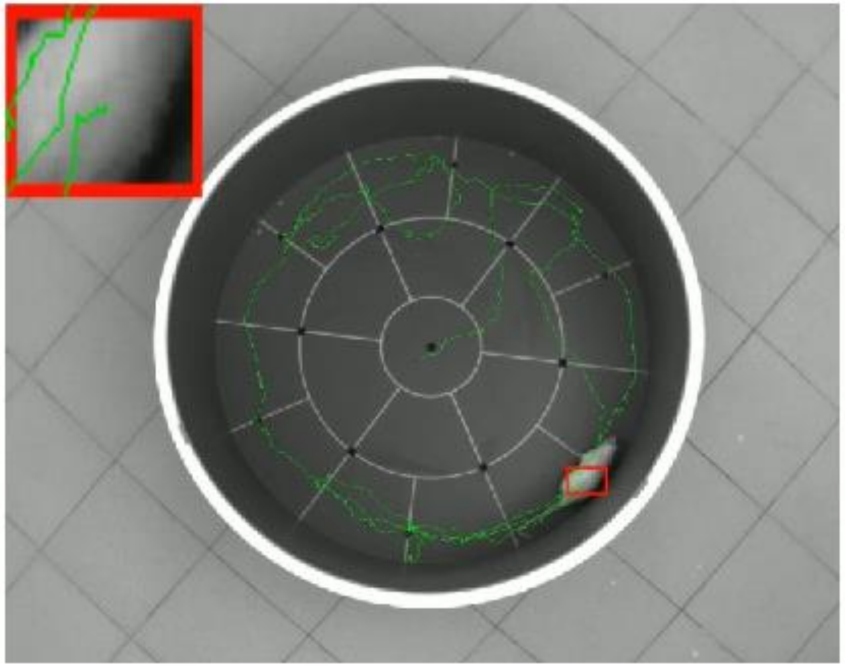
- ❑ video recordings of animal behavior
- ❑ photo of histological sections
- ❑ confocal microscopy images



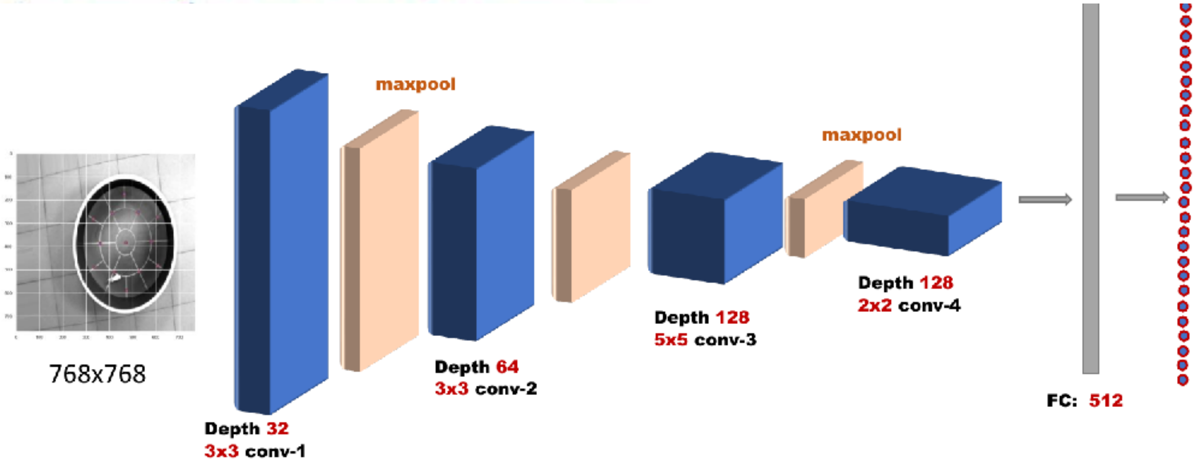
# Architecture of BIOHLIT

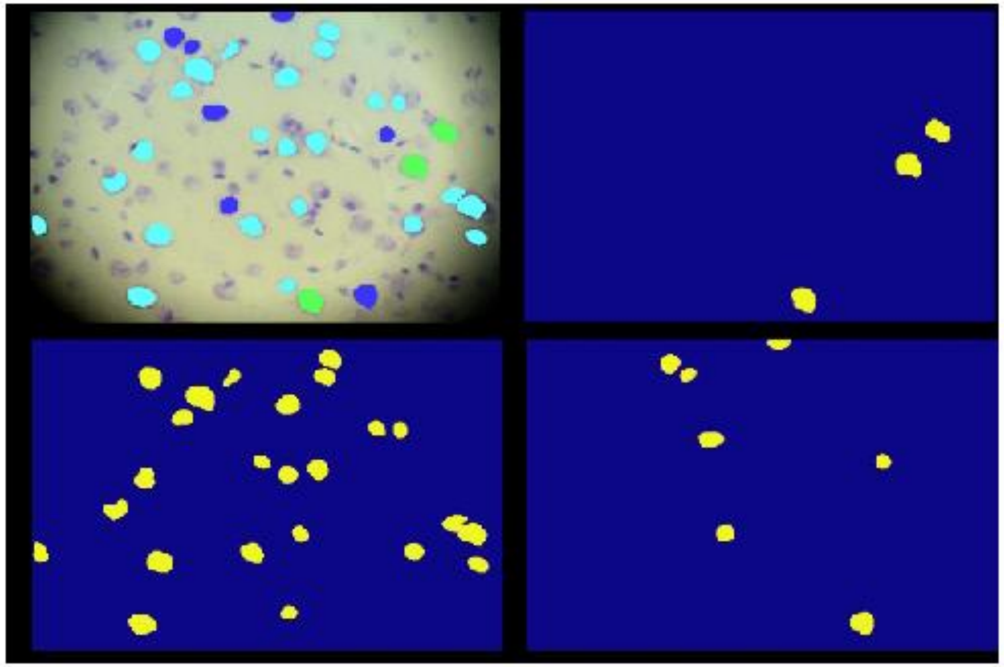


# ML/DL/computer vision algorithms



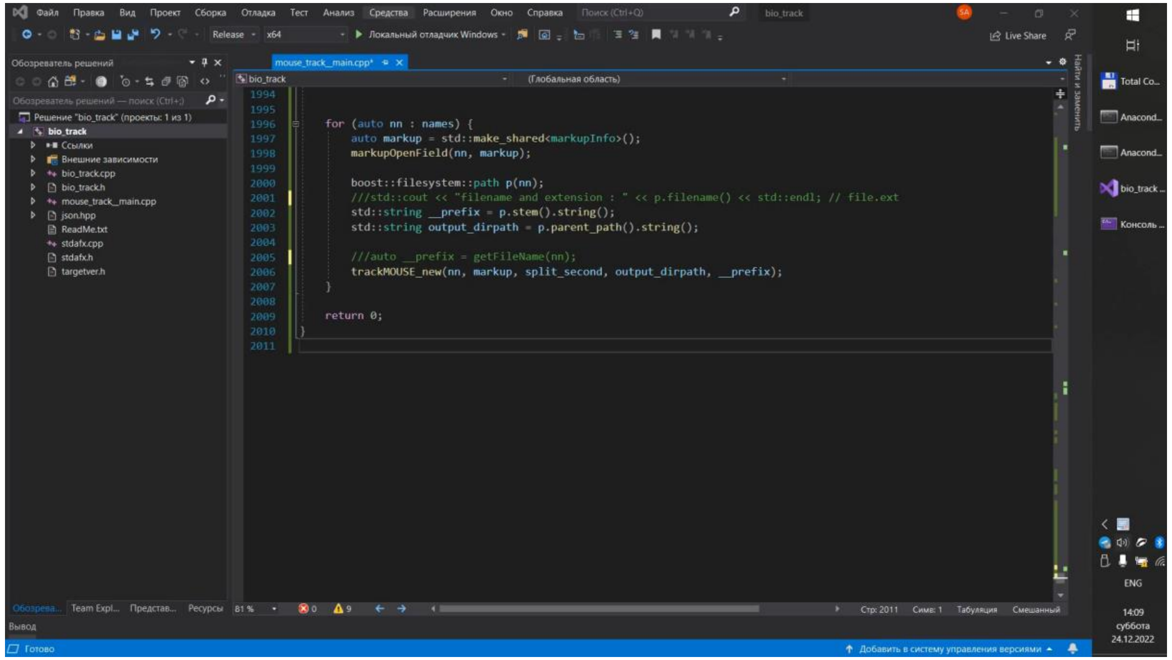
Tracking a laboratory animal:

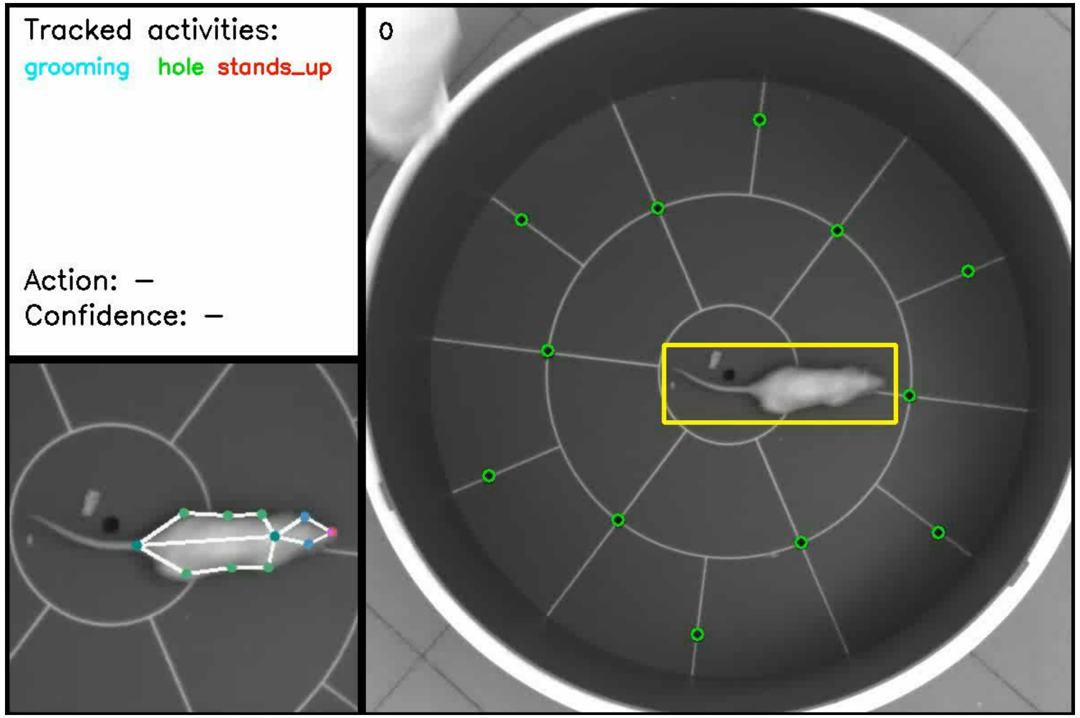


Neural networks for the task of neuron segmentation on brain slice images

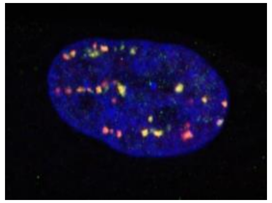
# Examples of automated video data analysis



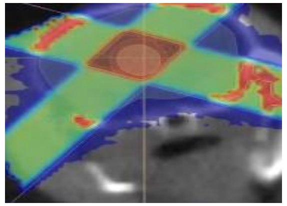



# Laboratory of Radiation Biology

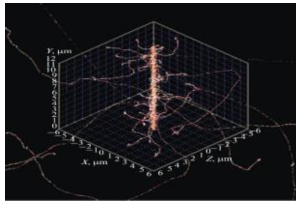
**Molecular Radiobiology**



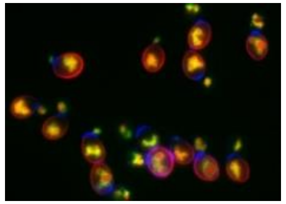
**Clinical Radiobiology**



**Mathematical Modeling**



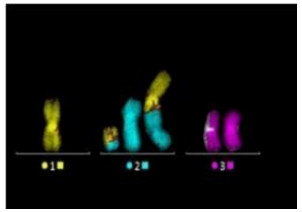
**Radiation Genetics**



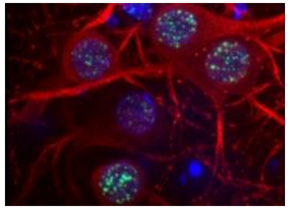
**Radiation Physiology**

**Radiation Protection**

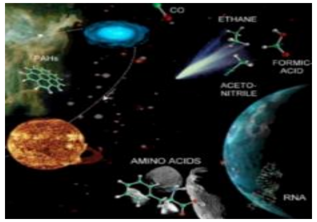
**Radiation Cytogenetics**



**Radiation Neuroscience**



**Astrobiology**




Contacts:

Prof. A. N. Bugay
LRB Director,
JINR executive for contacts with Cuba
**bugay@jinr.ru**

http://lrb.jinr.ru


Gracias por su atención!