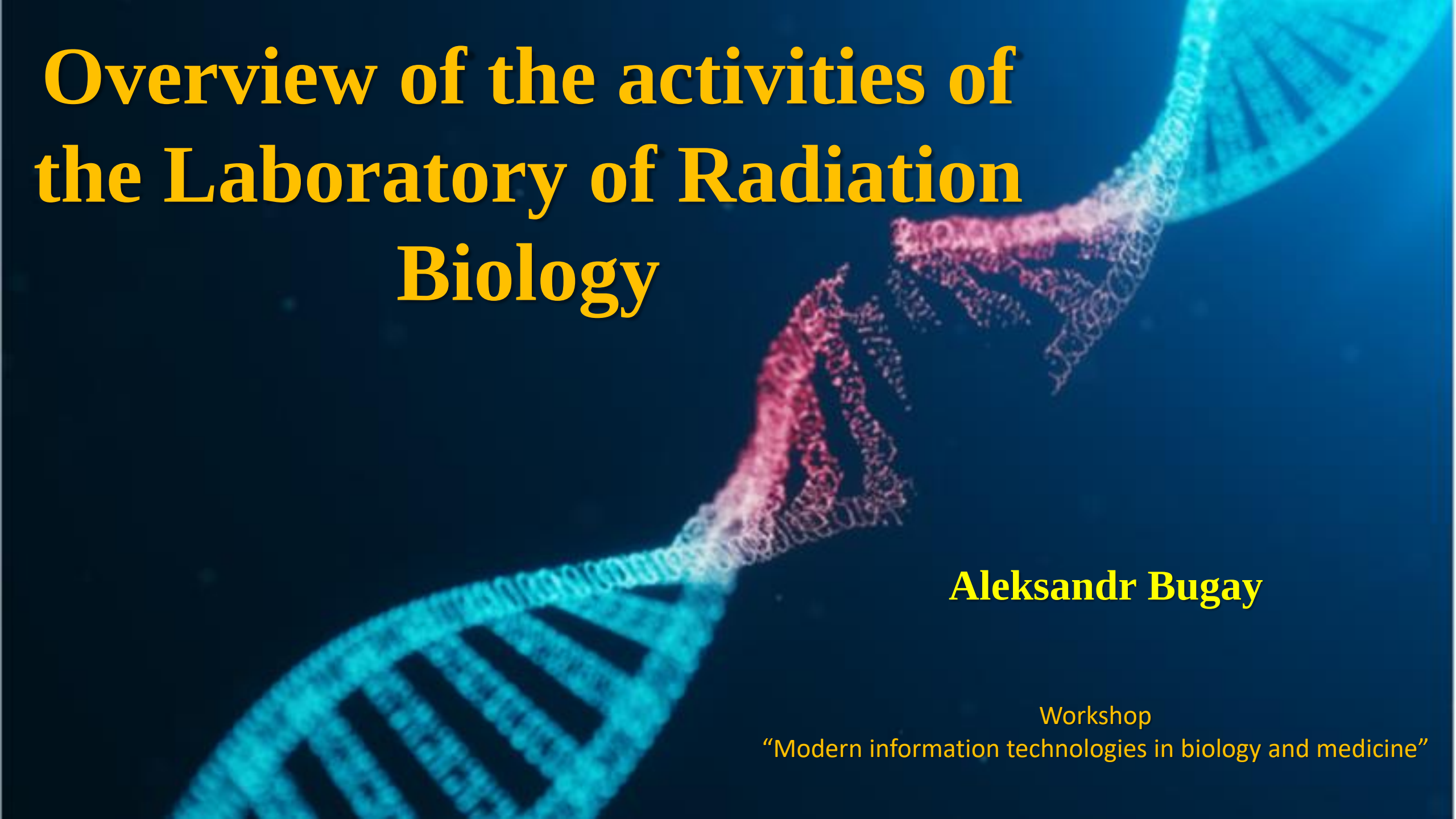
Overview of the activities of the Laboratory of Radiation Biology



Aleksandr Bugay

Workshop
"Modern information technologies in biology and medicine"

JOINT INSTITUTE FOR NUCLEAR RESEARCH

JINR in Figures:

- **19** Member States
- **5260** staff members
- **1200** researchers
- **1000** Doctors and Candidates of Sciences
- **2000** engineers and technicians
- **1500** scientific publications per year
- over **70** international conferences and workshops per year
- **800** partner universities, educational and research centres in more than 70 countries

Unique Park of Basic Facilities:

- World's Top Pulsed Neutron Source
- Heavy Ion Accelerators in a Wide Energy Range
- Megascience Project: Superconducting Collider NICA

7 JINR Laboratories, each being comparable with a large research institute in the scale of investigations performed

Frank Laboratory of Neutron Physics

flnph.jinr.ru

Veksler and Baldin Laboratory of High Energy Physics

lhep.jinr.ru

Flerov Laboratory of Nuclear Reactions

flerovlab.jinr.ru

Dzhelepov Laboratory of Nuclear Problems

dlnp.jinr.ru

Meshcheryakov Laboratory of Information Technologies

lit.jinr.ru

Bogoliubov Laboratory of Theoretical Physics

theor.jinr.ru

Laboratory of Radiation Biology

lrb.jinr.ru

Laboratory of Radiation Biology

lrb.jinr.ru

- 1959 - first radiobiological experiments (synchrocyclotron, LNP)
- 1978 - Biological Research Sector
- 1988 - Biological Division at DLNP
- 1995 - The Department of Radiation and Radiobiological Research
- **2005 - Laboratory of Radiation biology**

Founder:

Acad. E. A. Krasavin

krasavin@jinr.ru

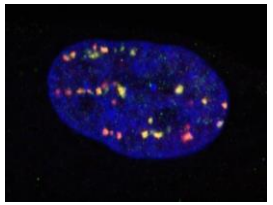
Director:

Prof. A. N. Bugay

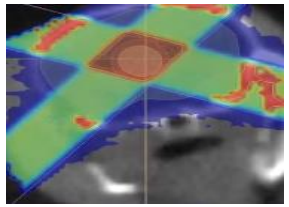
bugay@jinr.ru

Main Research Fields:

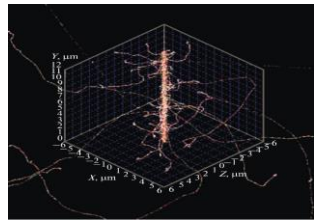
Molecular Radiobiology



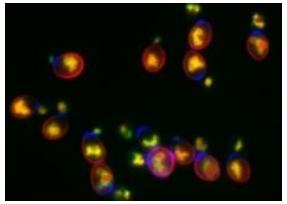
Clinical Radiobiology



Mathematical Modeling



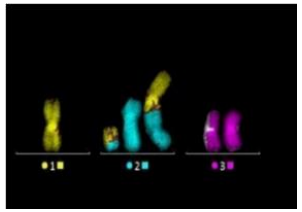
Radiation Genetics



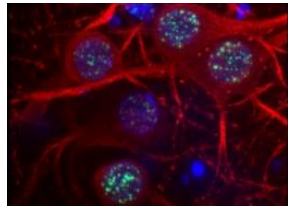
Radiation Physiology

Radiation Research

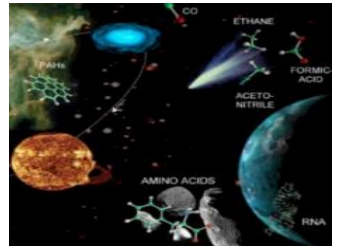
Radiation Cytogenetics



Radiation Neuroscience



Astrobiology



Interlaboratory Cooperation

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 Research**
- **Astrobiology**

Infrastructure for molecular, cellular and animal research

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

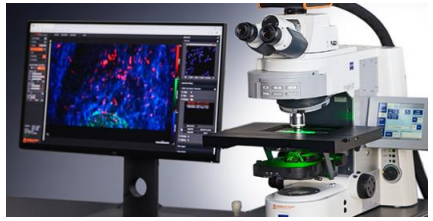
- Ion beams for cellular research
- Radionuclides synthesis for radiation medicine

JINR Research Infrastructure

U-400M cyclotron
heavy ions 50 MeV/u

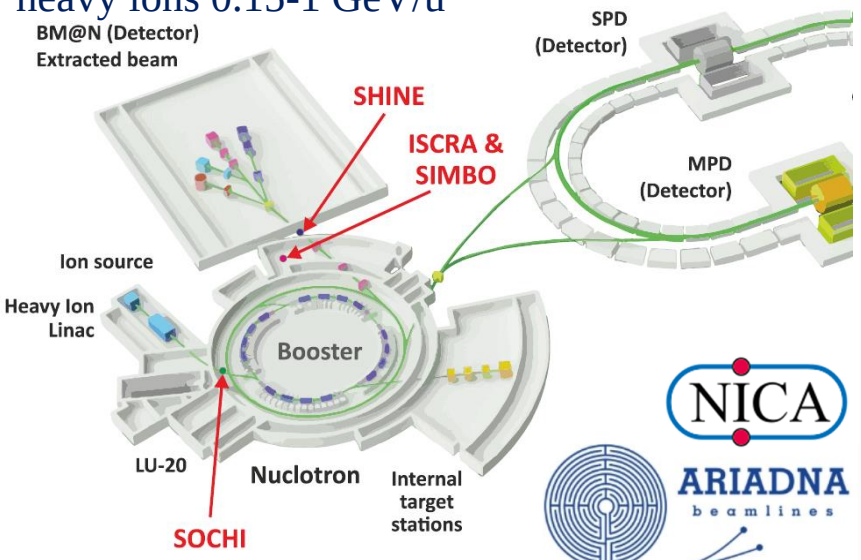
Infrastructure
for cellular and animal research

Microscopy
Tomography
OMICS

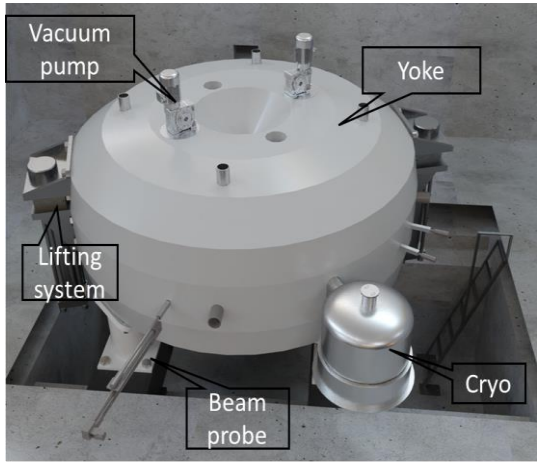


Vivarium

Nuclotron
heavy ions 0.15-1 GeV/u



MSC230 cyclotron
protons 230 MeV



Linac200
electrons
20-200 MeV

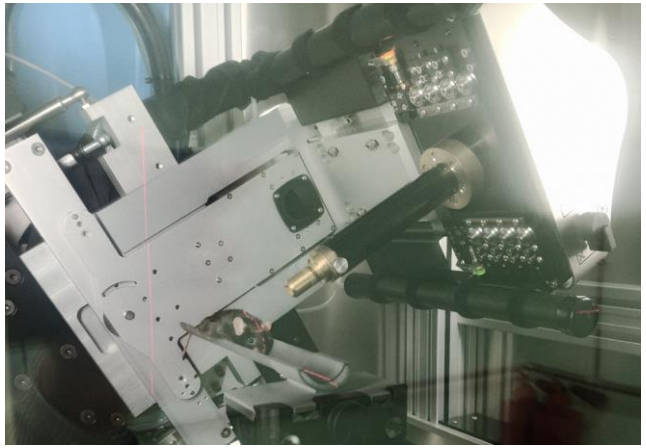
MICC
Supercomputer

SARRP X-ray

IBR-2, IREN neutrons

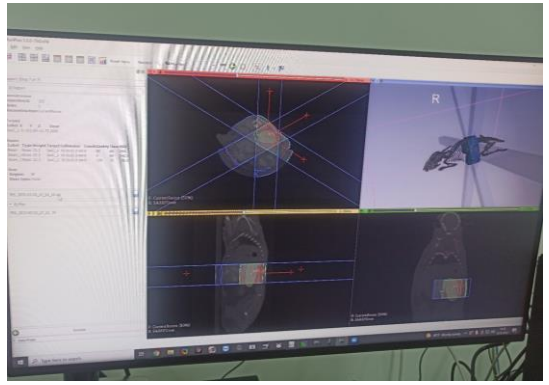
Basic facility of the LRB :
SARRP (Small Animal Radiation Research Platform)

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 tumor irradiation at SARRP

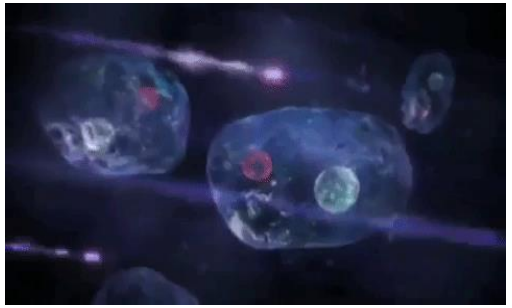
Molecular Radiobiology

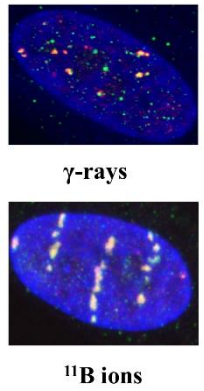
Molecular radiobiology

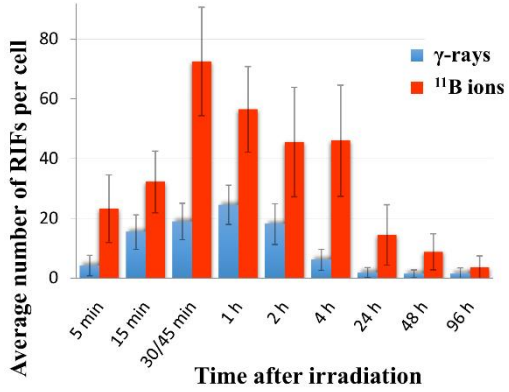
DNA damage, repair and regulatory mechanisms in normal and tumor cells,

Super-resolution microscopy

DNA double strand break formation and repair





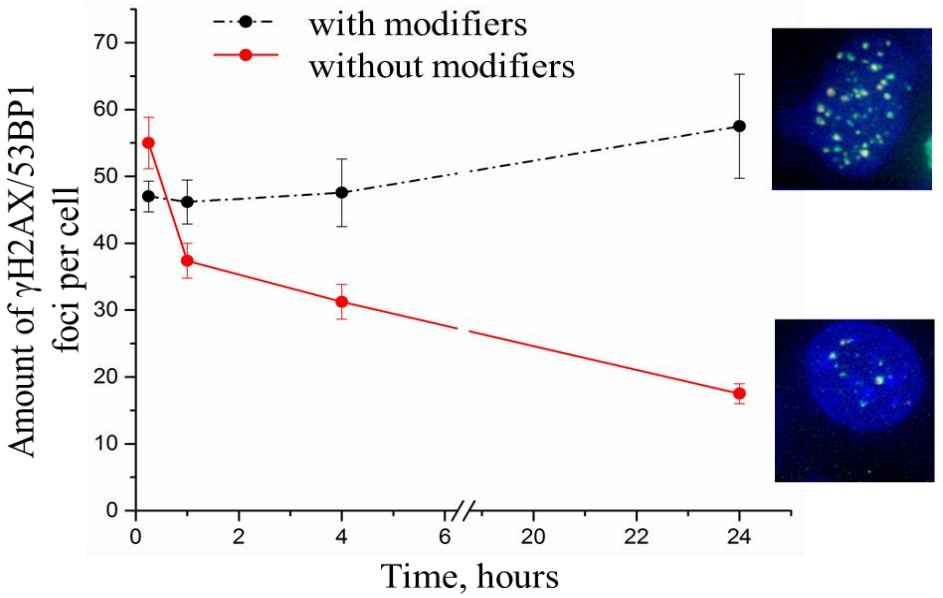


Mechanisms of radiomodification

molecular agents for radiation therapy of cancer

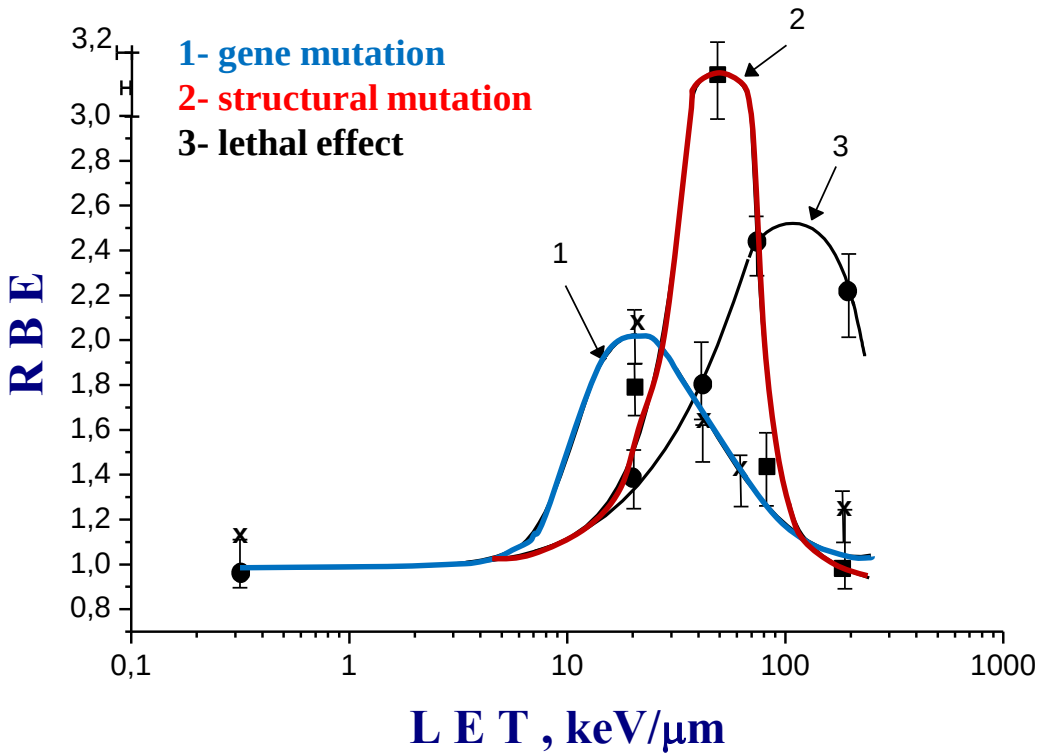
molecular mechanisms of radioprotection

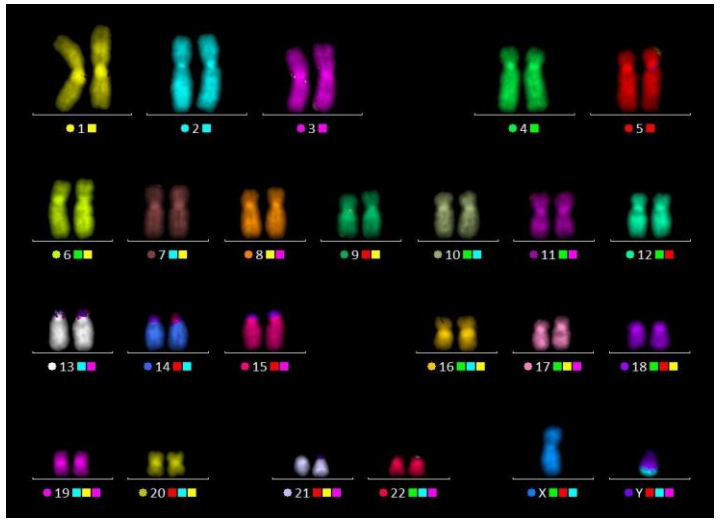
Glioblastoma tumor cells (U87)
irradiated by medical proton beam (1.25 Gy)

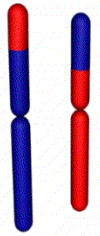


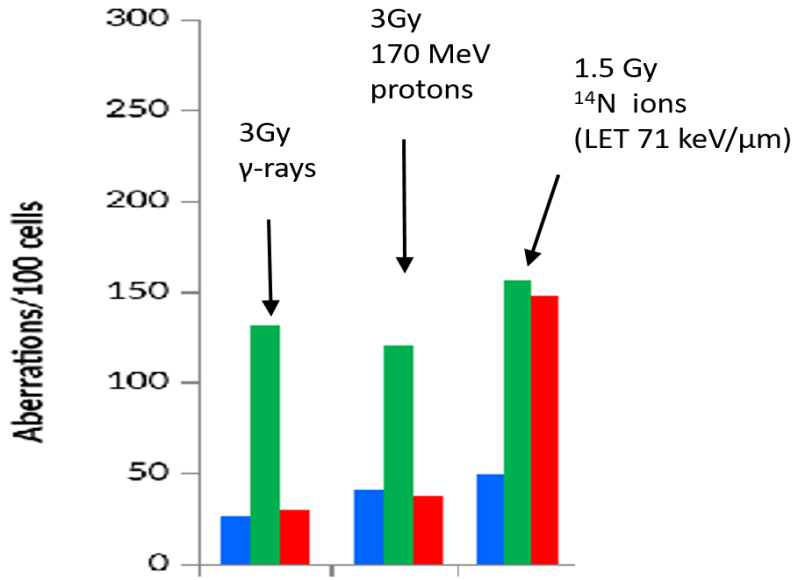
Radiation Genetics

Genetic and cytogenetic effects of radiation: gene mutations, complex chromosome aberrations, genome instability, long-term effects of radiation, biodosimetry





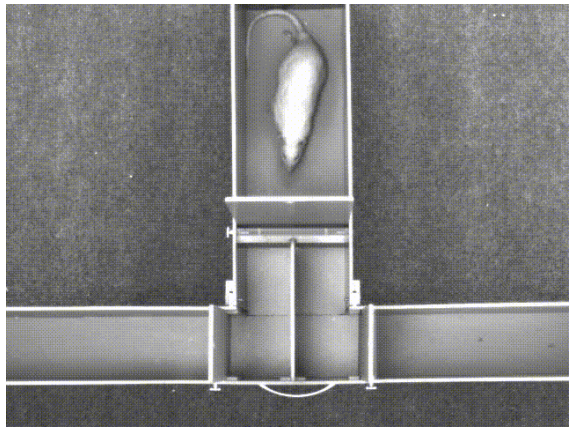




Complex chromosome aberrations (≥3 breaks)

Radiation Physiology and Neuroscience

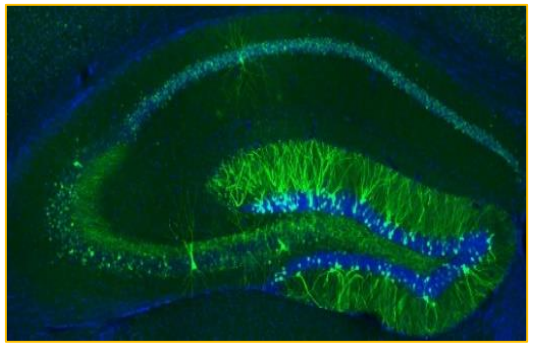
Radiation physiology: tissue and organismal pathologies, animal behavior

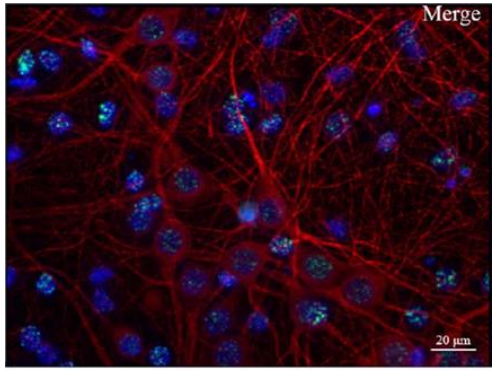


Behavioral tests

EEG records after irradiation

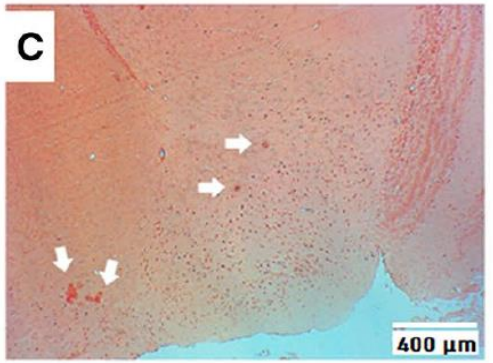
Radiation neuroscience: mechanisms of brain diseases and radiation-induced neurodegeneration





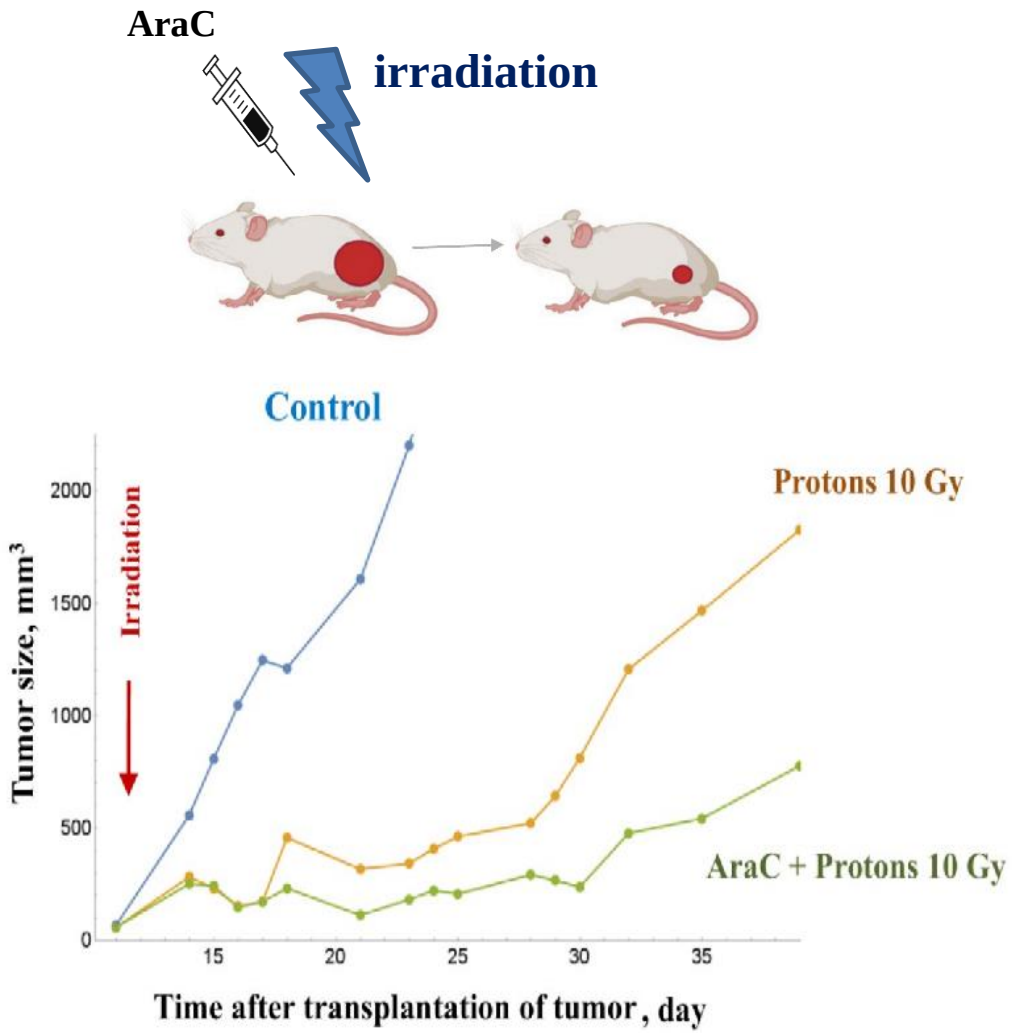
visualization of cell viability in hippocampal slice (right) and DNA damage in hippocampal cell culture (left)

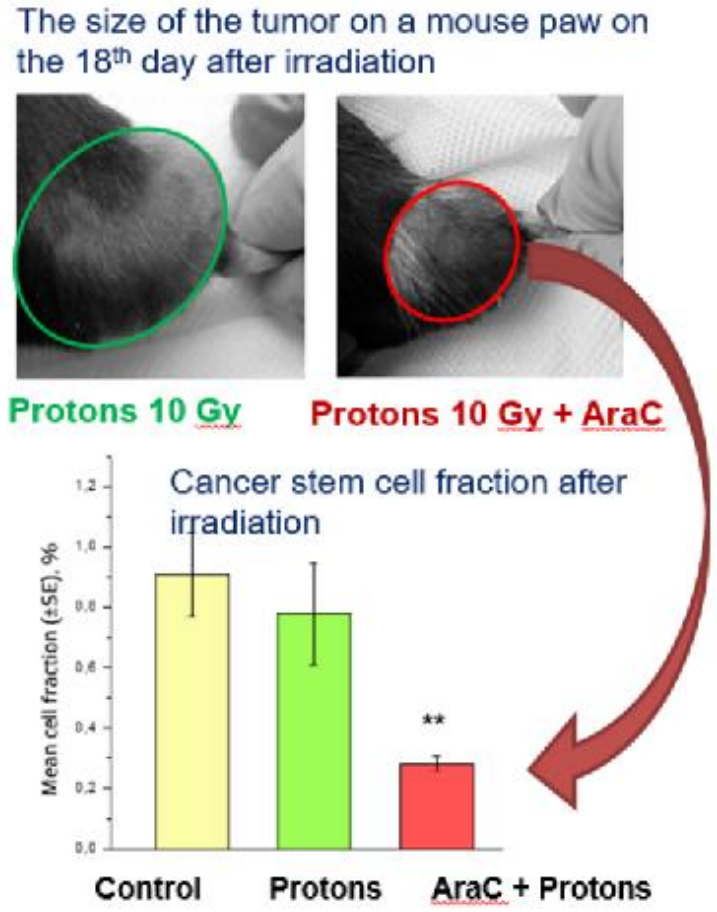
Amyloid plaques in the forebrain of rats after 170 MeV proton irradiation

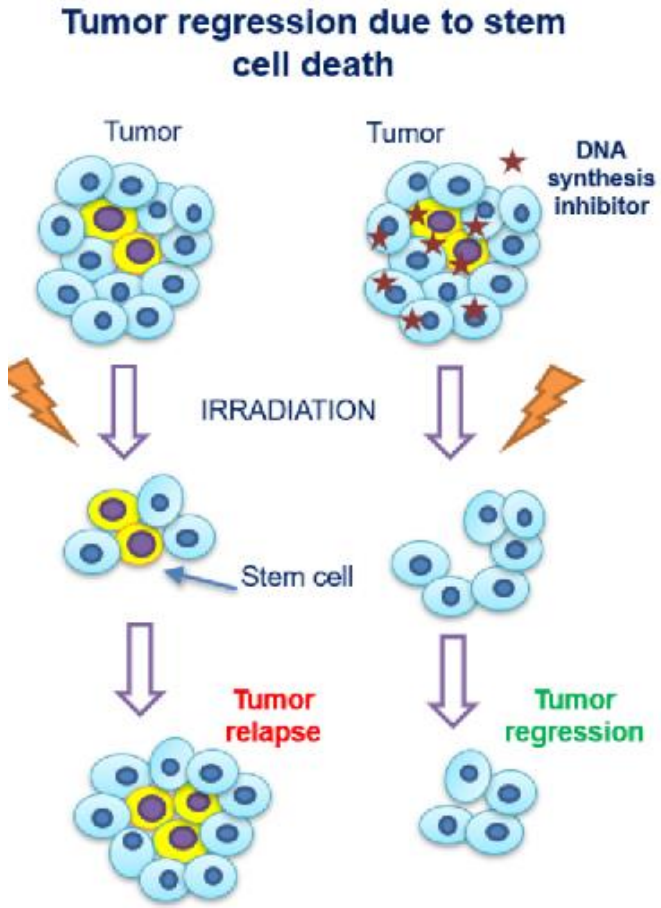


Radiation Medicine

Novel methods to improve the efficiency of radiation therapy of cancer

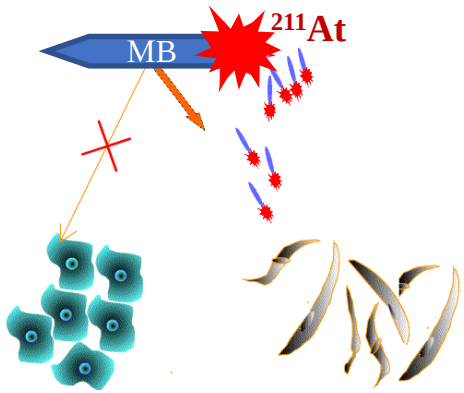


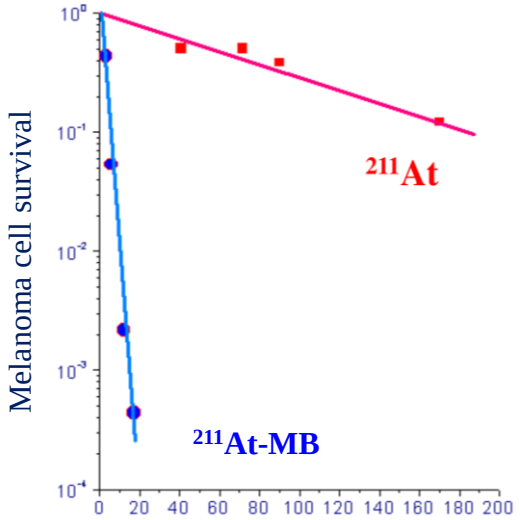




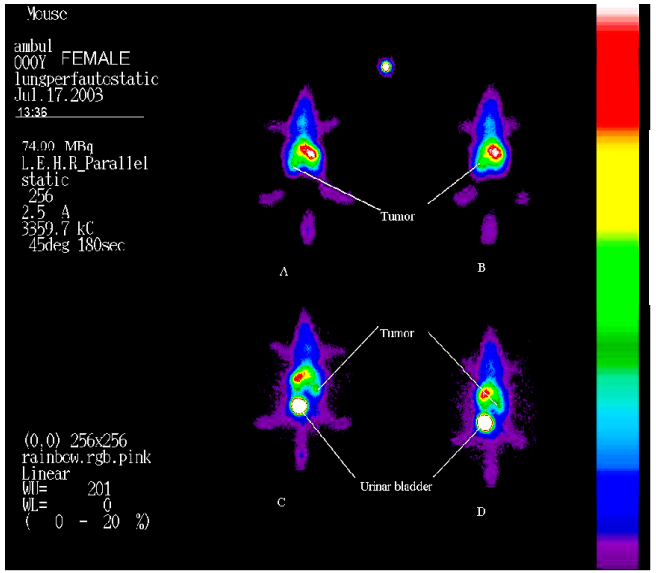
Radiation Medicine

Targeted therapy of melanoma

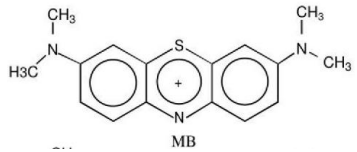




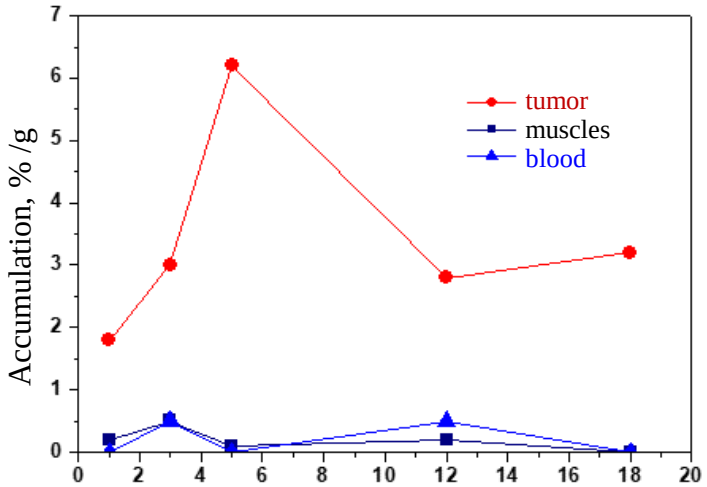
Volumetric activity of the isotope, kBq/mL



Visualization of ^{131}I-MB accumulation in tissues of animals with inoculated melanoma



Methylene blue (MB)

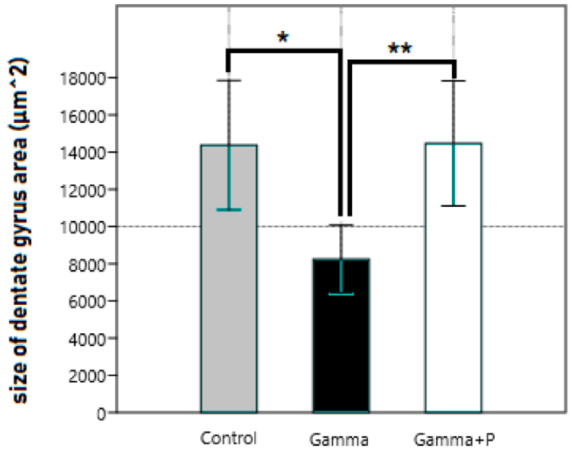


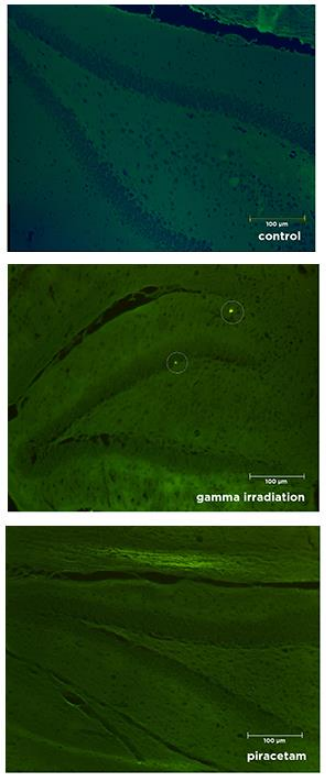
Time, h

Radiation Protection

Radioprotectors:

regulatory mechanisms and pharmacological modulations of radiation effects

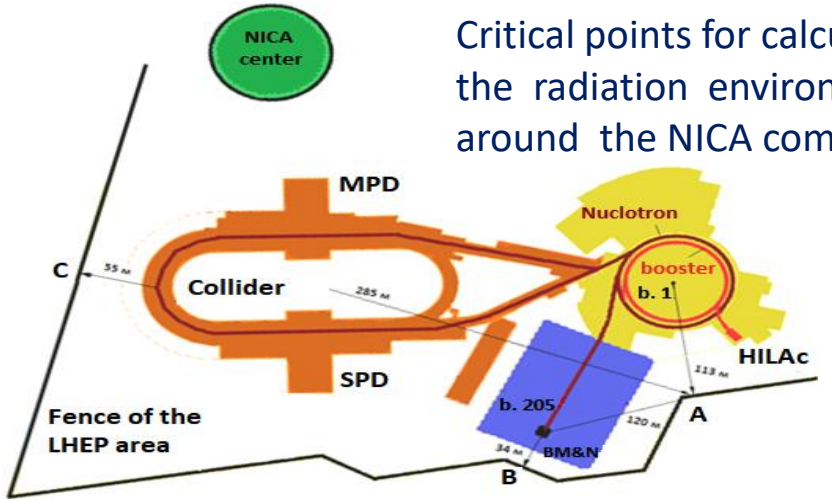




The effect of 2 week - piracetam injection after irradiation on size of DG area of hippocampus

Radiation Research:

evaluation of radiation risks at nuclear objects, accelerator complexes, and spacecraft

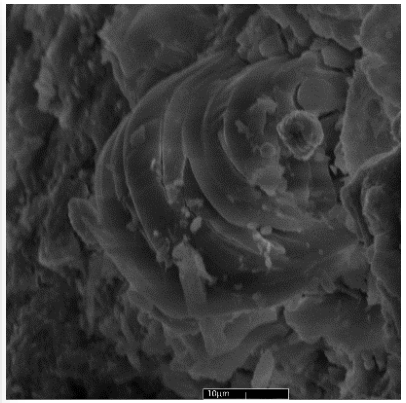


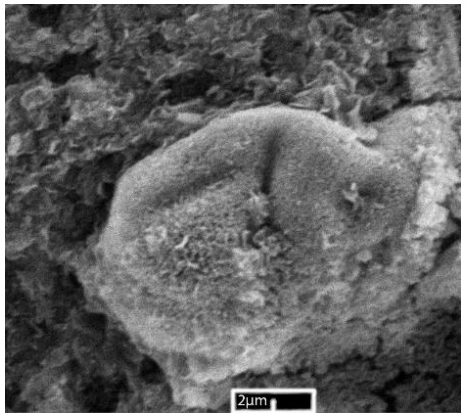
Critical points for calculation of the radiation environment around the NICA complex

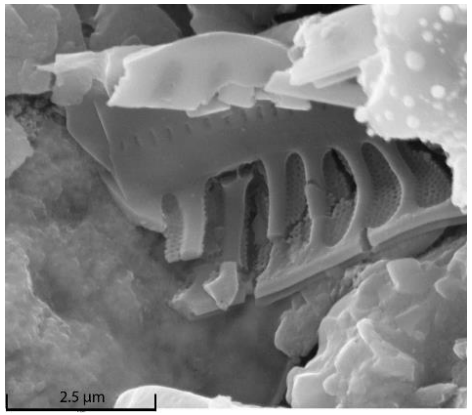
Instruments for neutron dosimetry and nuclear planetology

Astrobiology

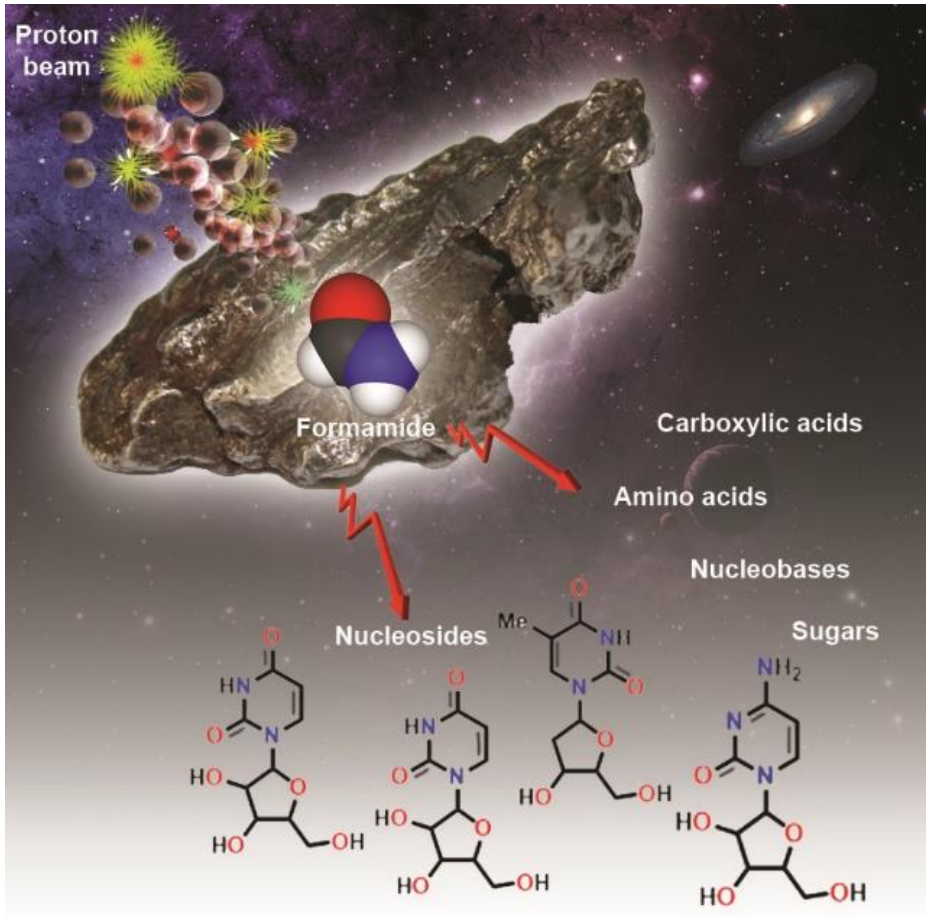
search for biofossils in cosmic matter







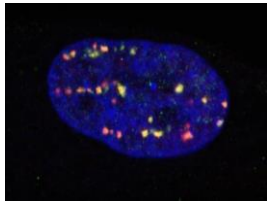
accelerator-based simulation of prebiotic compounds synthesis



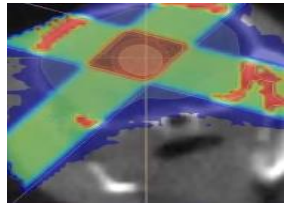
Research Program of the Laboratory of Radiation Biology

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.

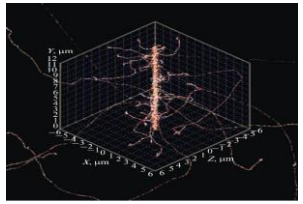
Molecular Radiobiology



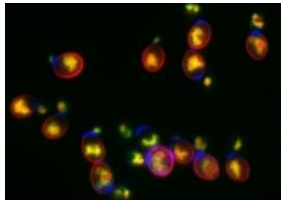
Clinical Radiobiology



Mathematical Modeling



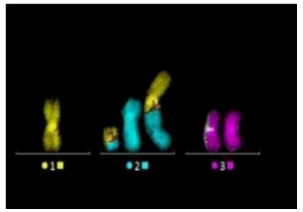
Radiation Genetics



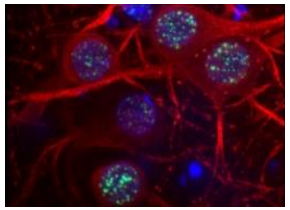
Radiation Physiology

Radiation Protection

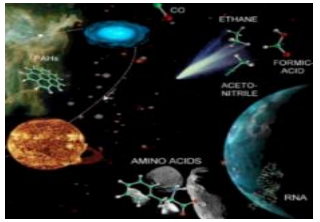
Radiation Cytogenetics



Radiation Neuroscience



Astrobiology

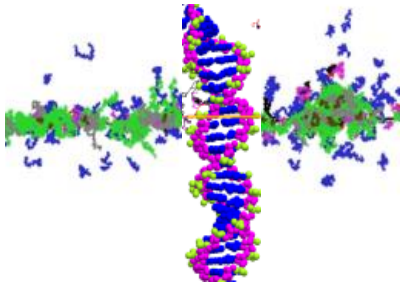


http://lrb.jinr.ru

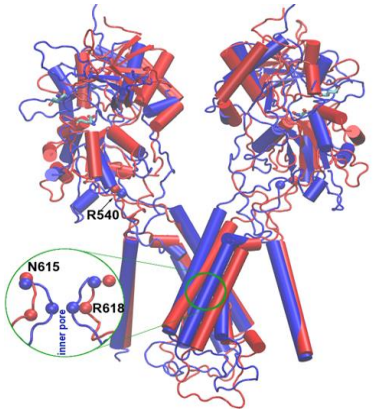
1. Mathematical Modeling

Problems:

- formation of DNA damage and its repair
- induction of mutations and chromosome aberrations
- prediction of structure and functions of mutant proteins
- molecular and cellular mechanisms of radiomodification

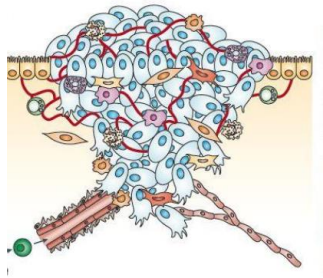


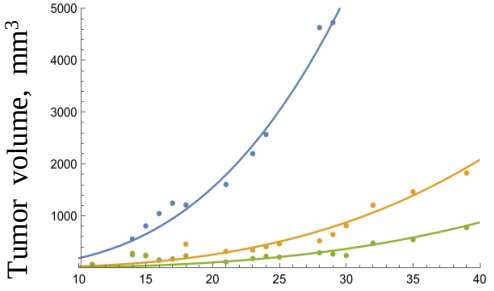
Model of particle track and DNA damage induction



Mutant NMDA receptor protein

- simulations of tumor growth dynamics after treatment with medical radiation beams or radionuclides



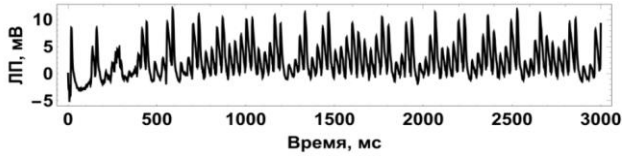


Model of tumor growth

- theoretical evaluation of radiation-induced disorders of the CNS

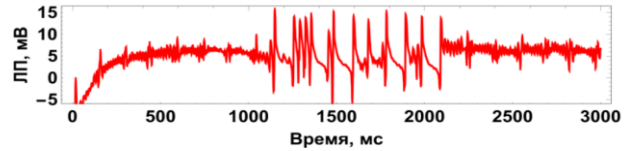
Effect of mutations on brain electric activity

Native

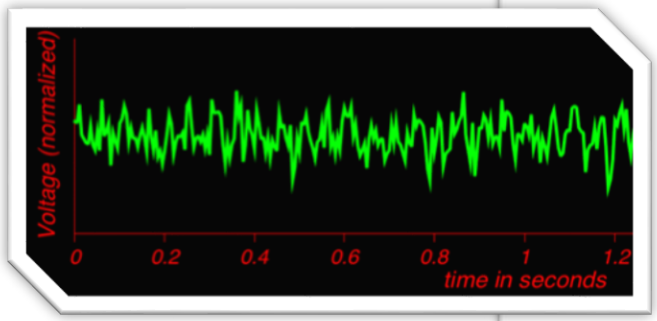


p.ASN615LEU

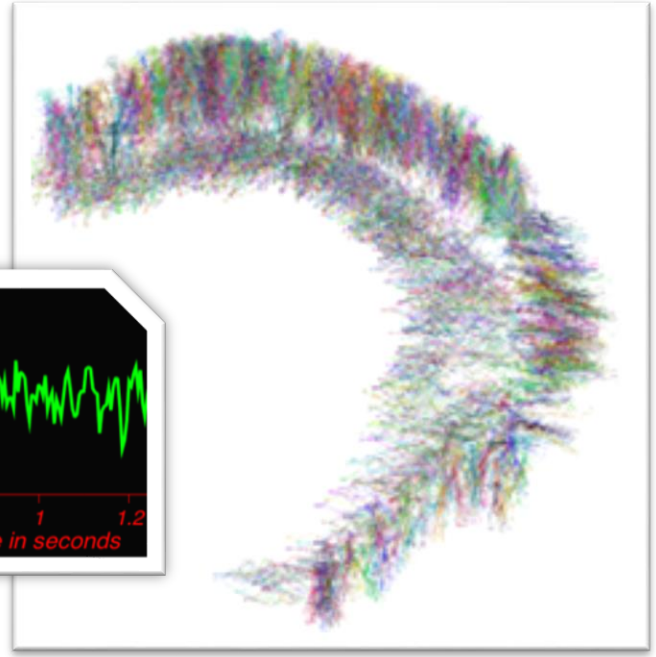
Epileptic seizure



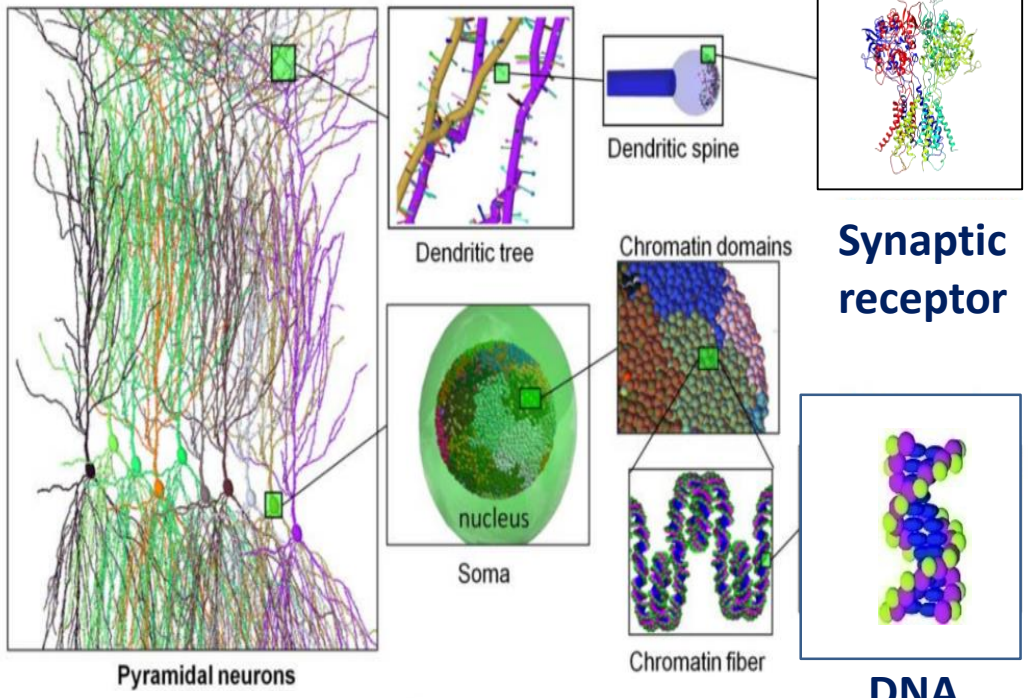
Multiple scale modeling



Brain activity?



Brain regions

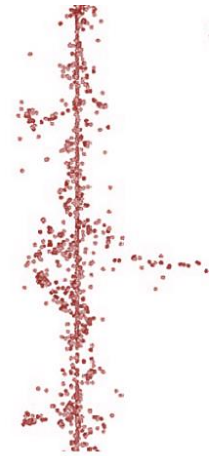


Neural cells

Subcellular targets

Synaptic receptor

DNA



Particle track

Information processing in brain

Cell survival and cell population dynamics

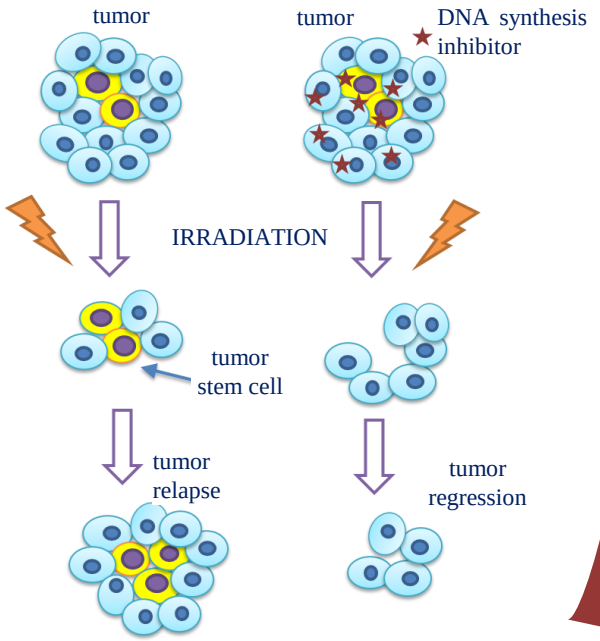
Biochemical processes (DNA repair etc)

Molecular dynamics

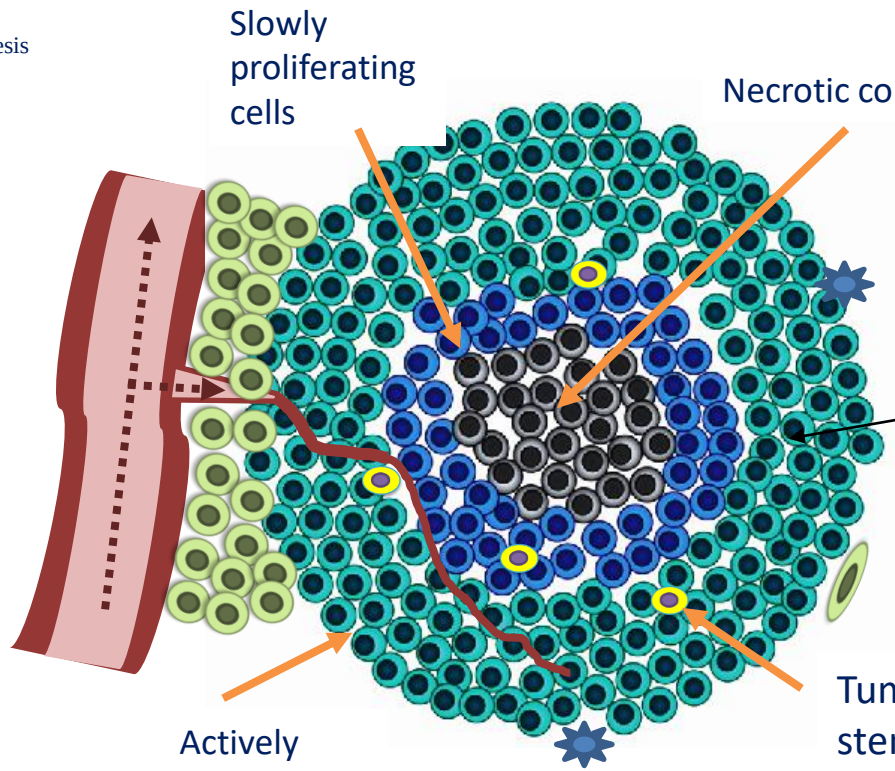
Physical and chemical events in particle tracks

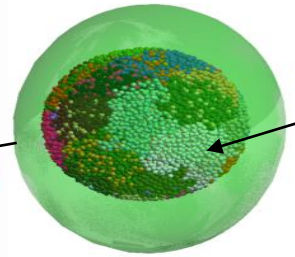
Multiple scale modeling

Tumor regression due to stem cell death

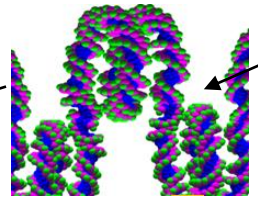


Functional state of tumor after treatment?

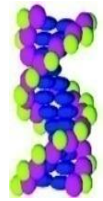




cell



chromatine



DNA

Particle track

- **PDE-based modeling**
- **Single-cell based modeling**

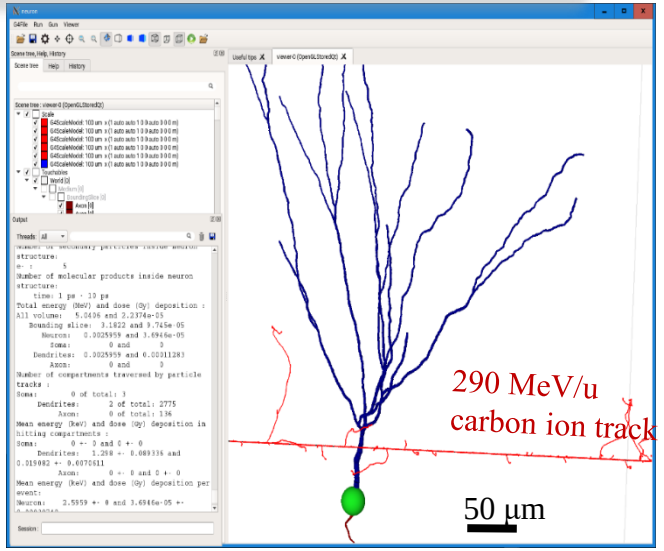
Biochemical kinetics ← **Molecular dynamics** ← **Physical and chemical events in particle tracks**

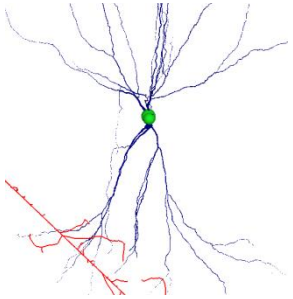
Monte Carlo simulations particle interactions with cells

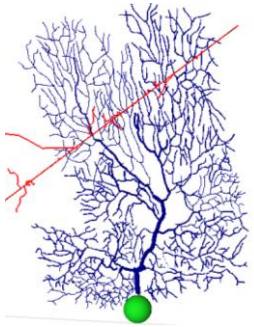
«Neuron» — new application of GEANT4-DNA

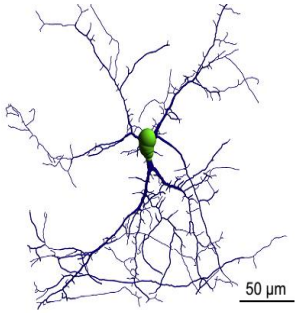
- The Geant4 « **neuron** » **extended/medical/dna** example shows how to simulate **a neural network including physics and radiolysis.**

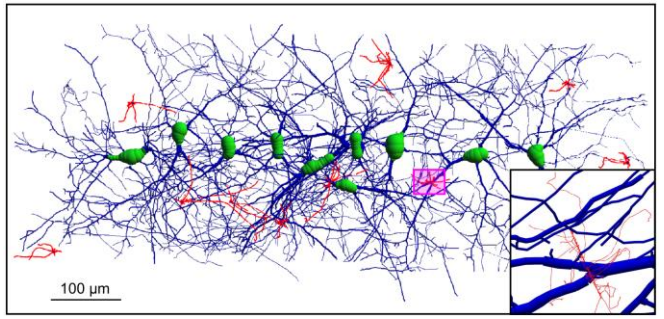
https://geant4.web.cern.ch:
http://geant4-dna.org/examples/neuron







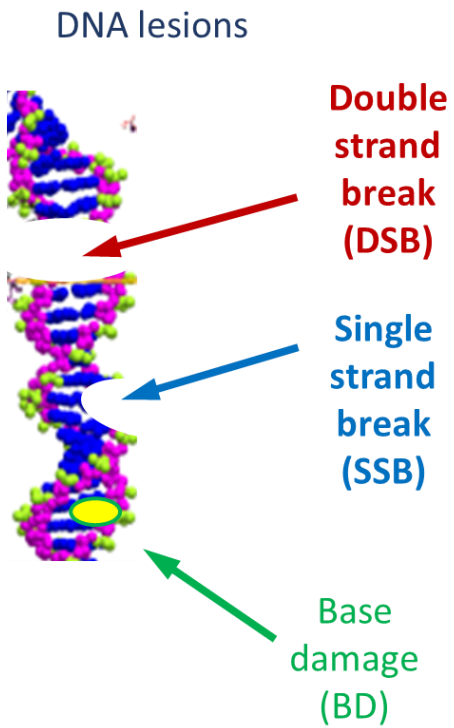


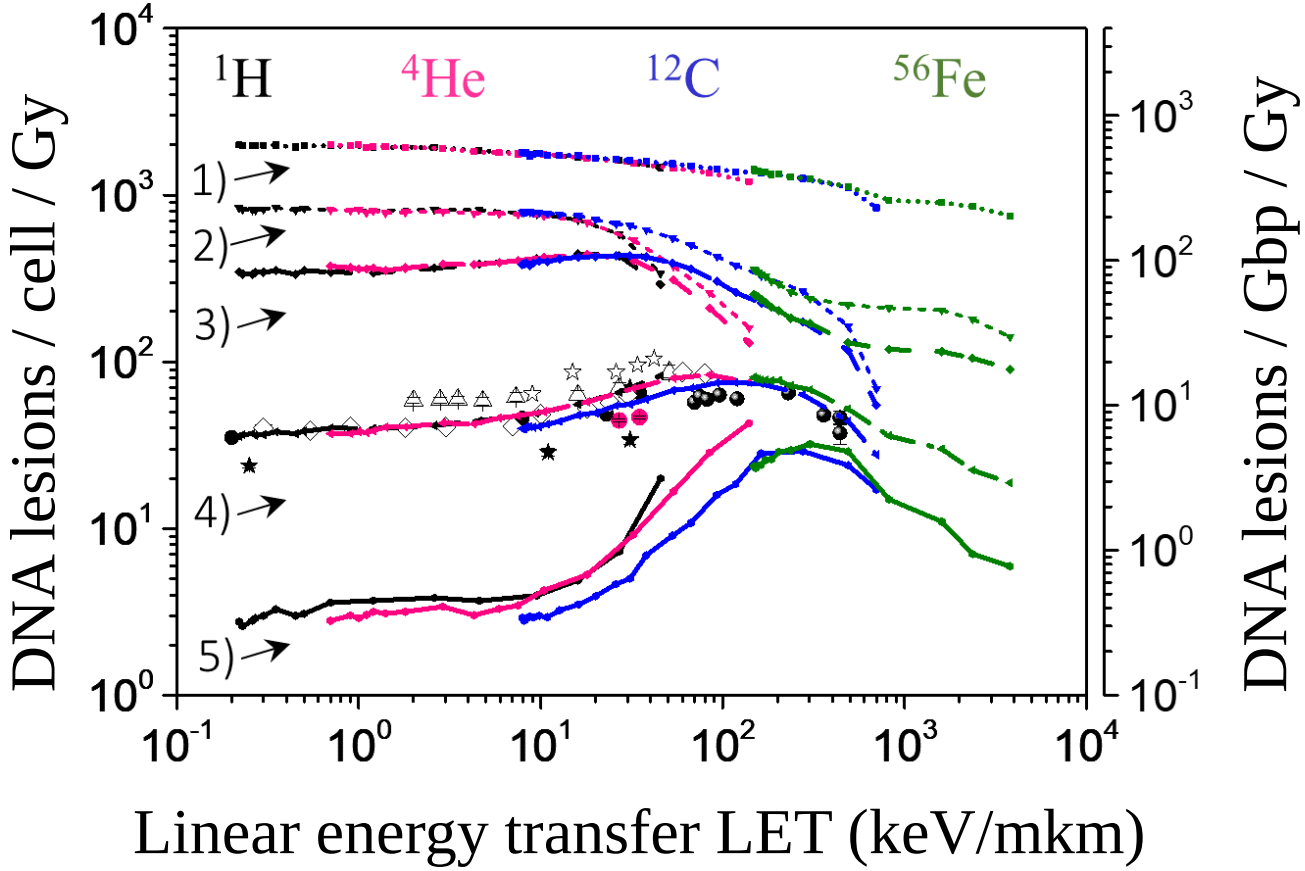


Monte Carlo simulations particle interactions with cells
Amount of DNA damage

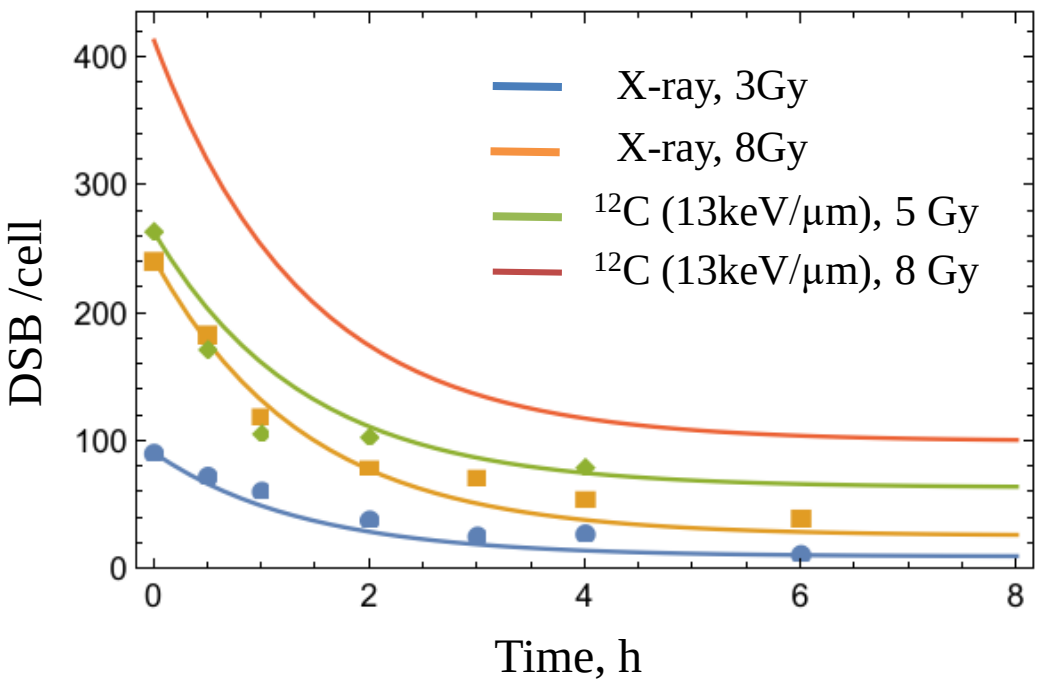
Computer simulations

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



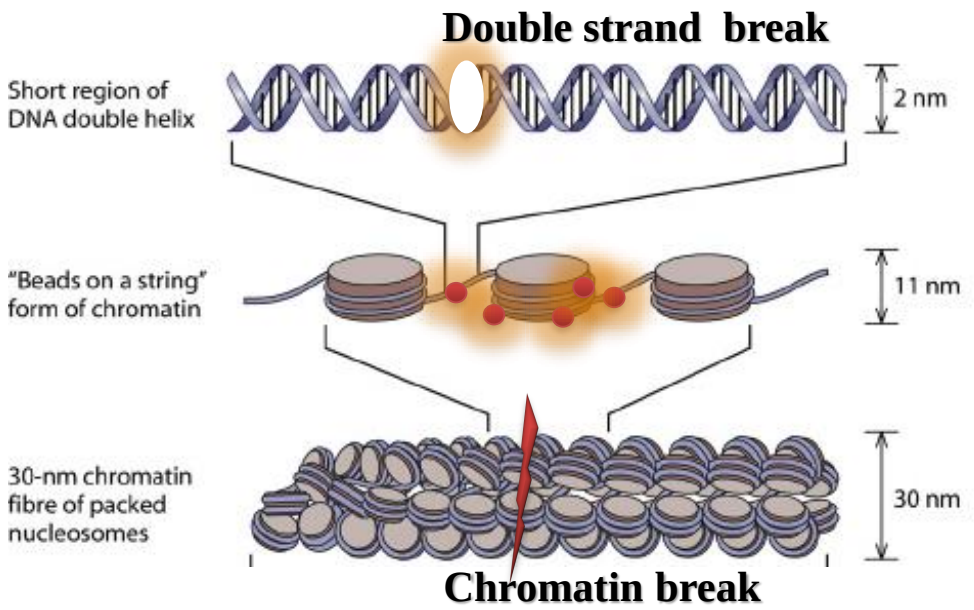


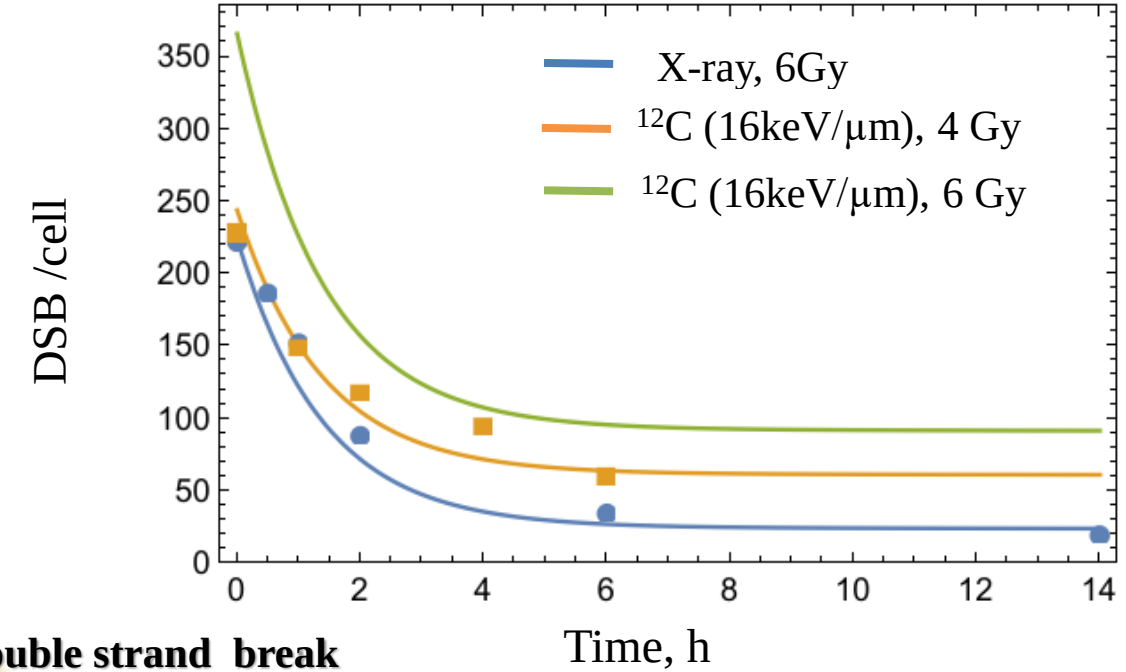
Modeling of DNA repair



V79 fibroblasts

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



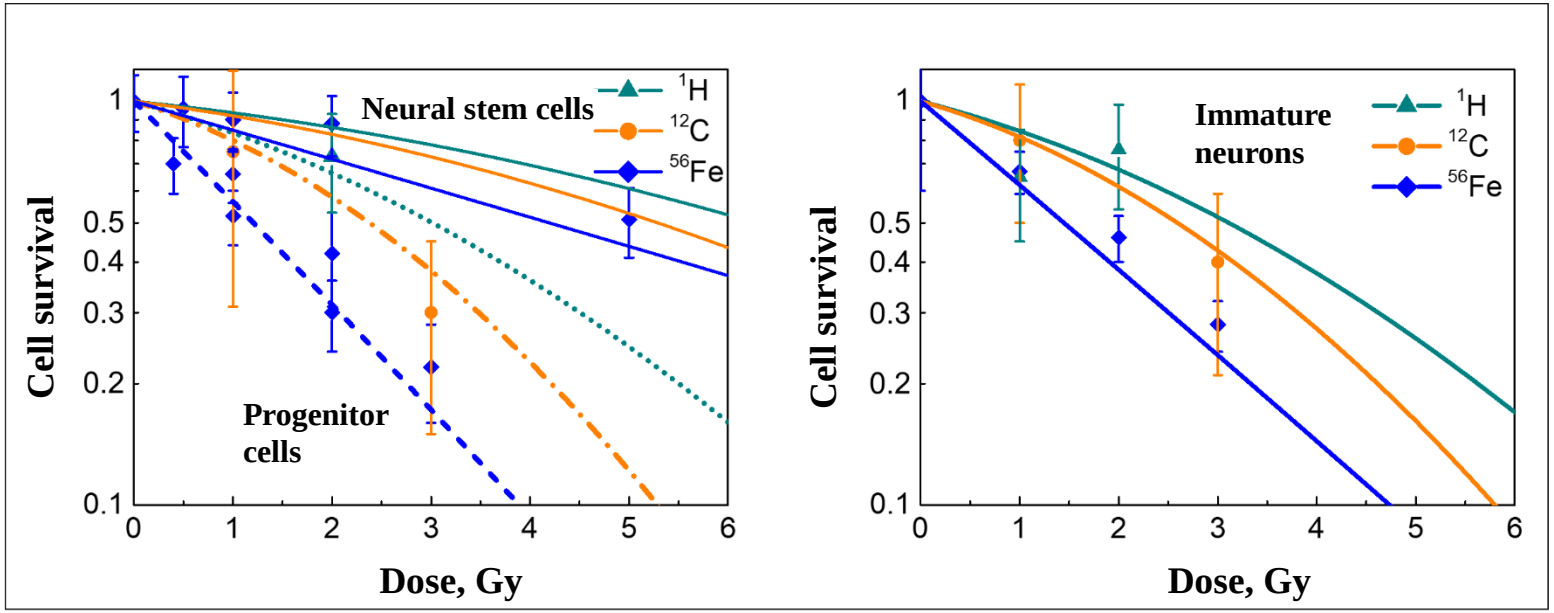


Human fibroblasts

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

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].



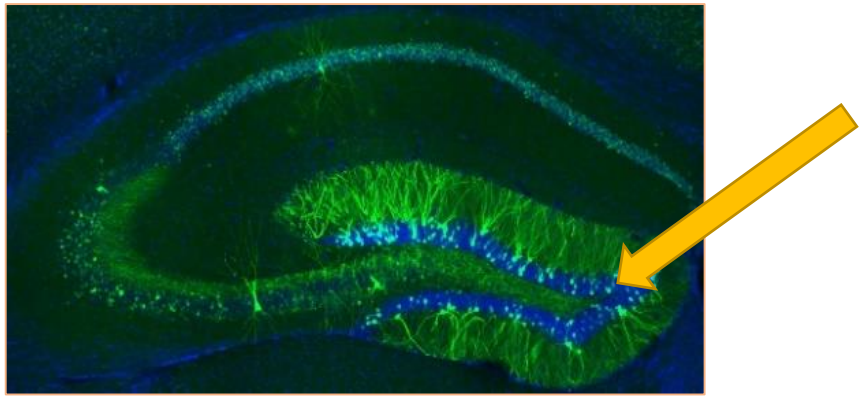
$$S(D, Y_{DSB}, N_{particle}) = \exp(-\alpha D - \beta D^2)$$

$$\alpha = Y_{DSB} \cdot P_{contrib} \cdot (1 - P_{correct})$$

$$\beta = 0.5 \cdot Y_{DSB} \cdot P_{contrib} \cdot Y_{DSB} \cdot P_{correct} / N_{particle}$$

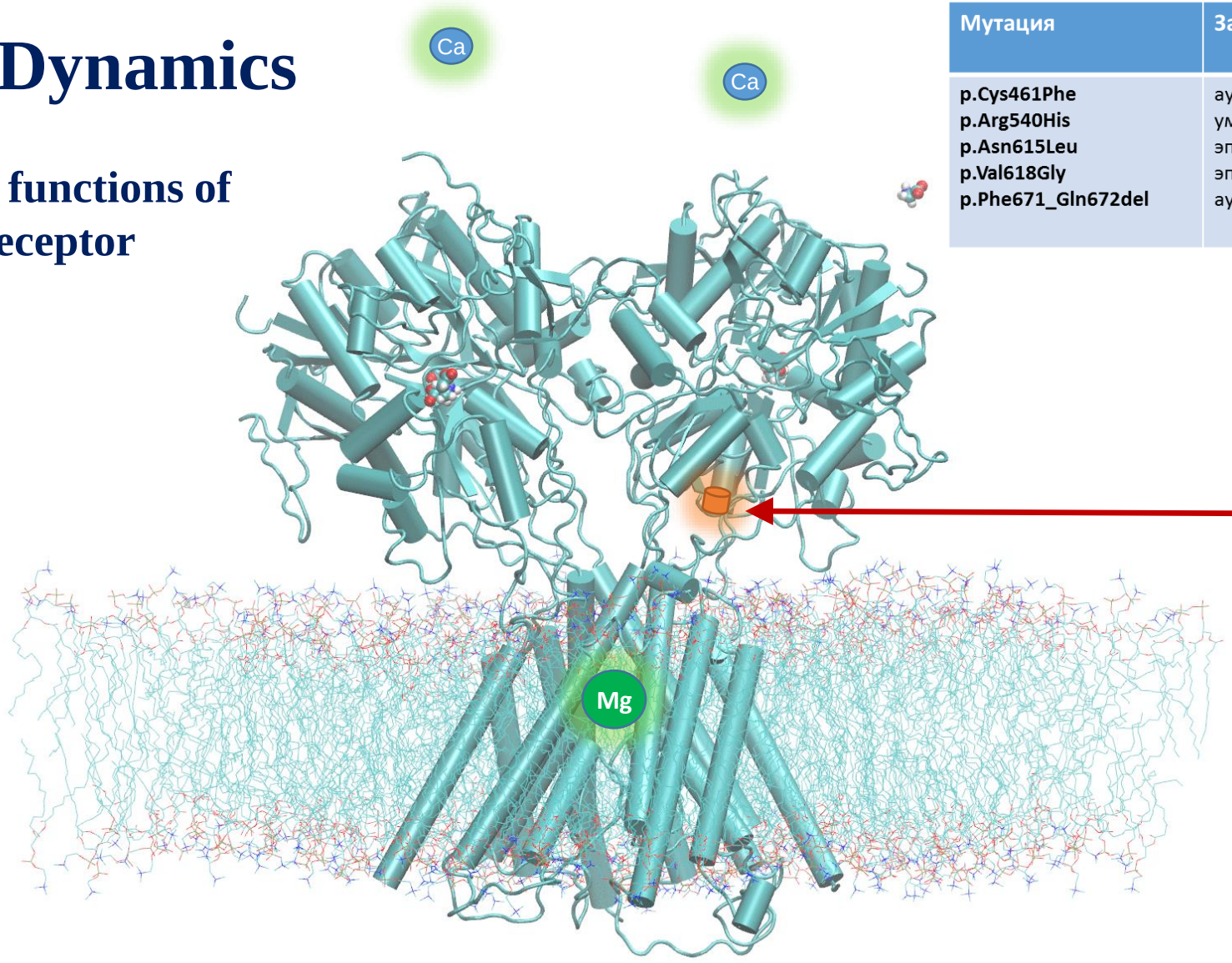
$$P_{contrib} = 1 - \exp(-Y_{DSB})$$

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



Molecular Dynamics

Structure and functions of NMDA receptor



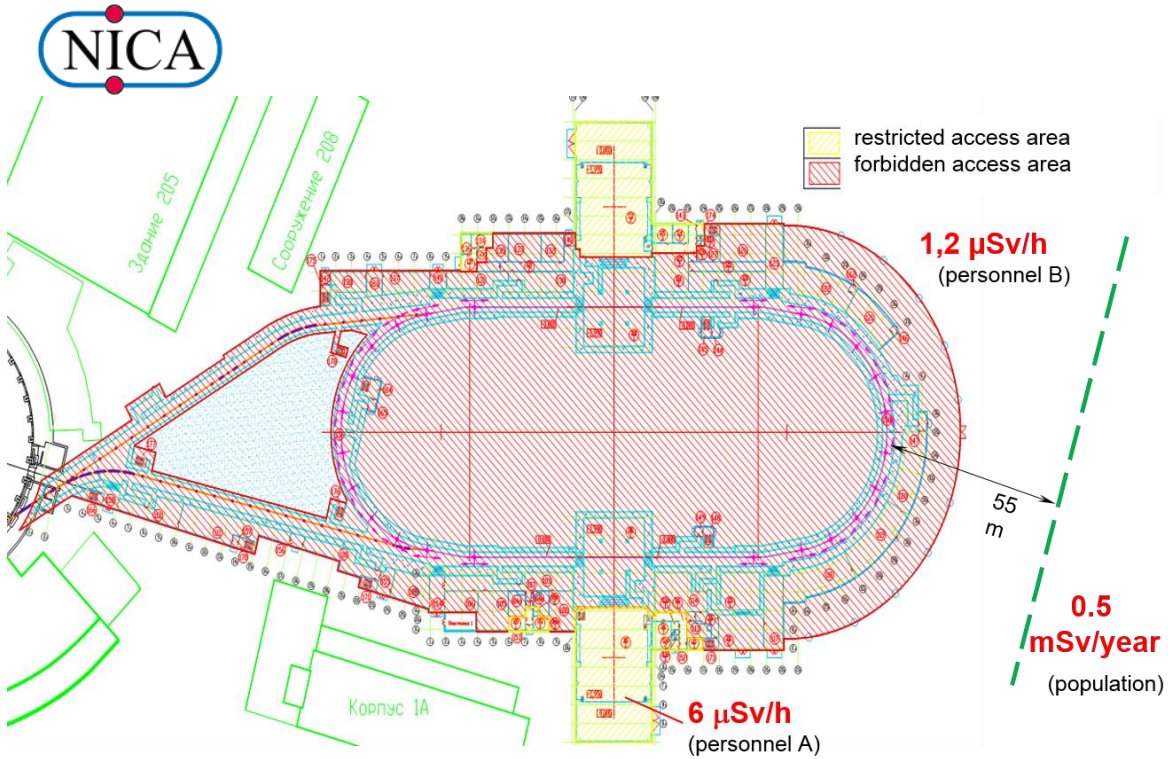
Мутация	Заболевания
p.Cys461Phe	аутизм
p.Arg540His	умственная отсталость, фокальная эпилепсия
p.Asn615Leu	эпилепсия (синдром Веста, инфантильные спазмы)
p.Val618Gly	эпилепсия (синдром Веста, инфантильные спазмы)
p.Phe671_Gln672del	аутизм , умственная отсталость

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

Protein conformation change!

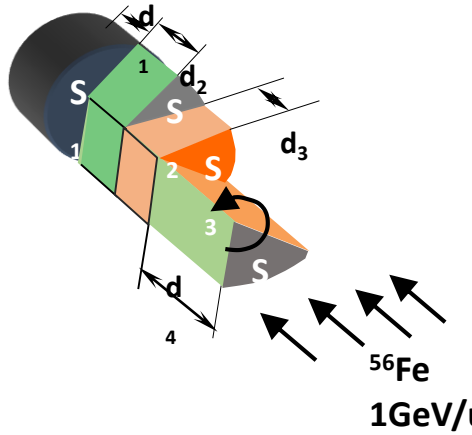
The function of synapses with a mutant receptor protein is impaired

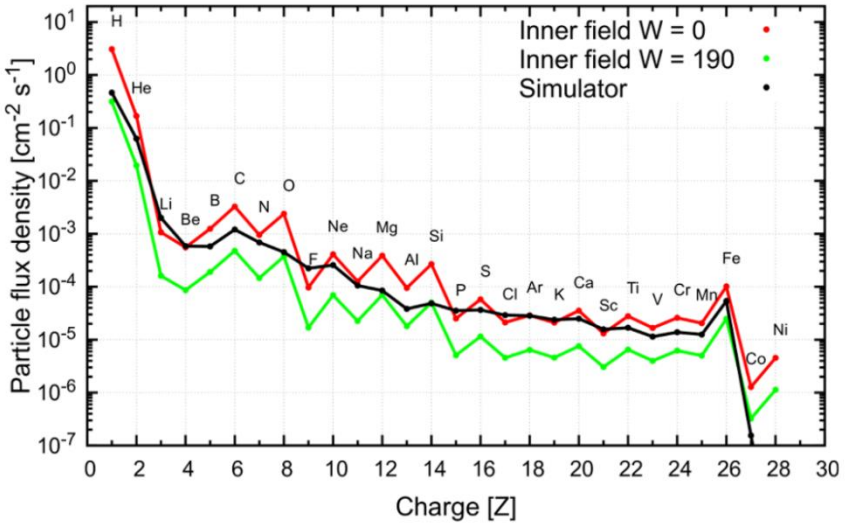
Radiation protection and dosimetry



Radiation zoning around the collider

A scheme of **Space Radiation Simulator** target to be installed at SIMBO station



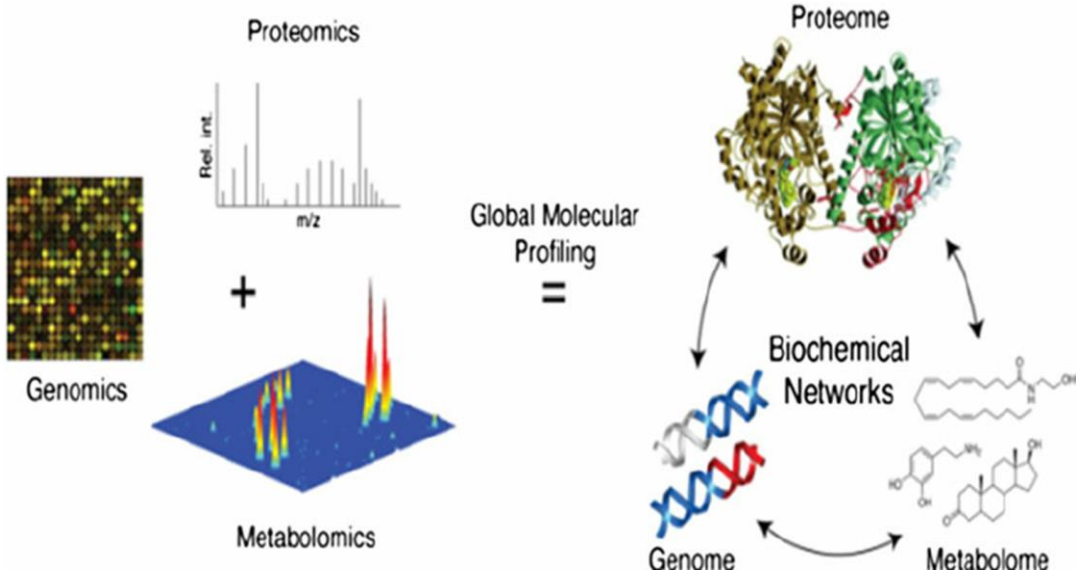


Comparison of space radiation charge spectra and simulator radiation field

RaDAT: Radiation Dose Assessment Team

Calculations of radiation environment around NICA complex and other JINR high energy accelerators

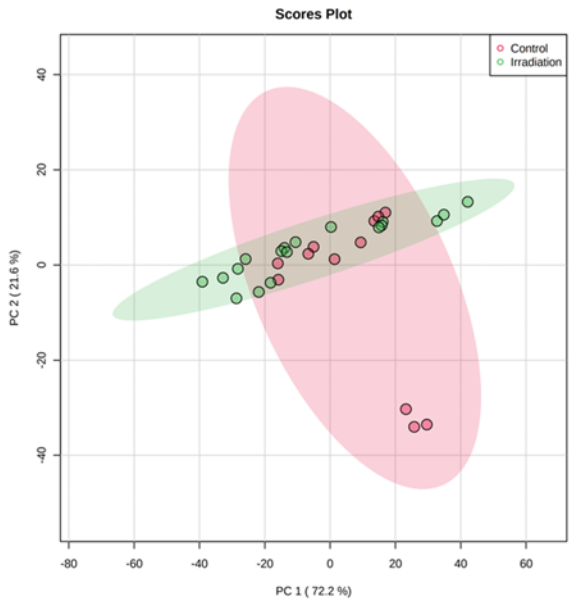
2. Data mining in OMICS

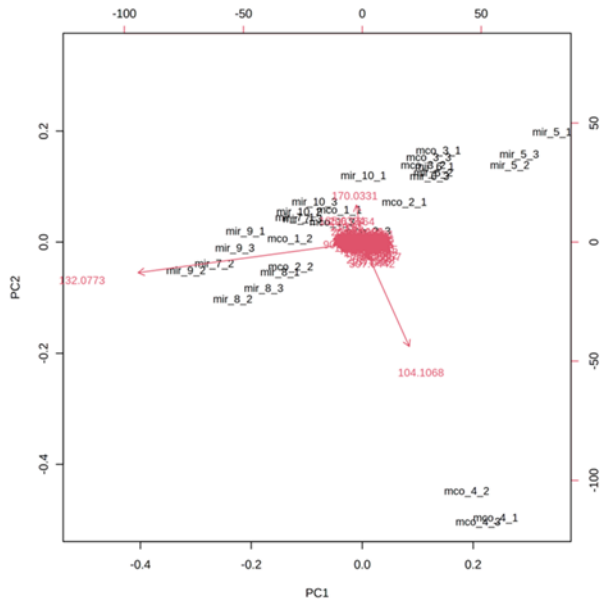


OMICS technologies:

Data-driven analysis of complex biological networks

Analysis of LS-MS data obtained from mouse brain metabolome after proton irradiation



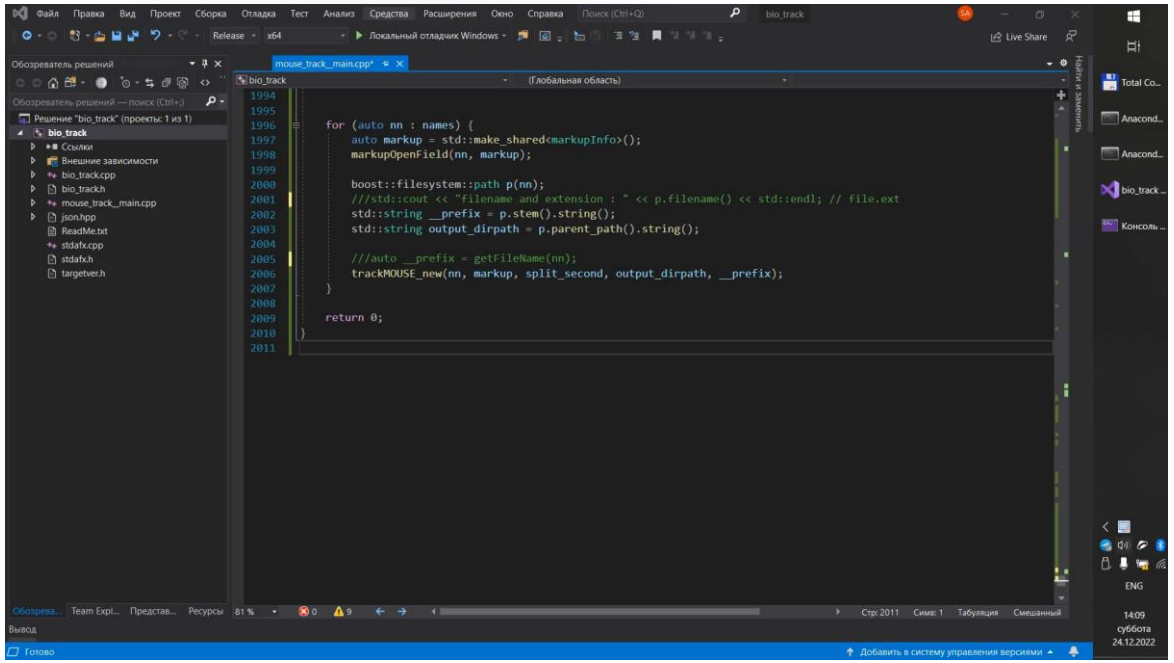


3. Machine learning for automated biological data processing

The joint activity of MLIT and LRB aims to create an information system for analyzing behavioral and pathomorphological changes in irradiated animals

https://it4bio.jinr.ru

The information system is based on:
- computer vision algorithms based on machine learning and deep learning technologies;
- modern IT solutions for storage, processing and visualization data;



Main tasks

- Development of an information system;
- Development of protocols for labeling images and video materials;
- Testing of implemented algorithms and software designed for automated data processing.

JINR - Serbia
Ongoing projects

JOINT INSTITUTE FOR NUCLEAR RESEARCH

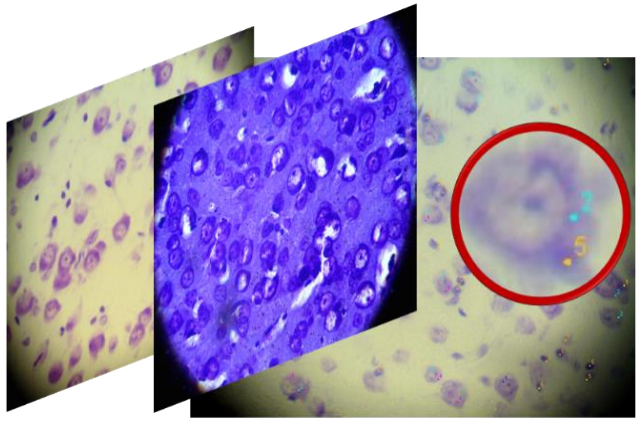
РЕПУБЛИКА СРБИЈА

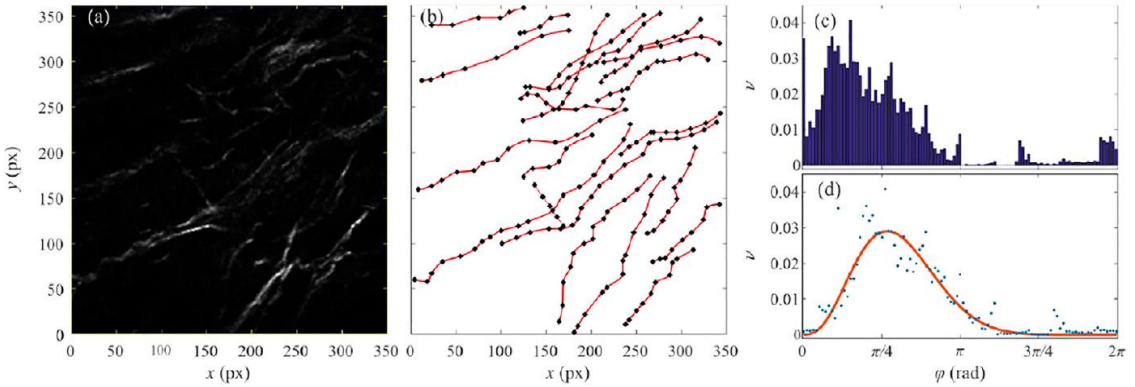
Project
The Computer-Assisted Identification, Characterization, and Modeling of the Histological Data

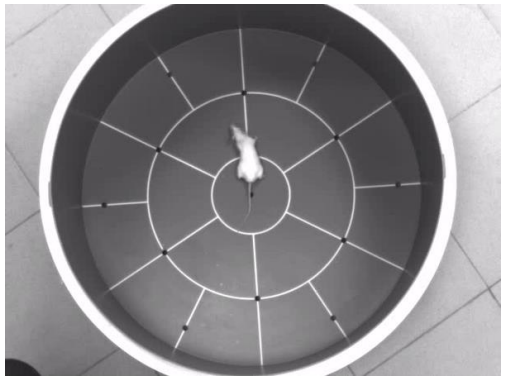
BIOHLIT VINČA

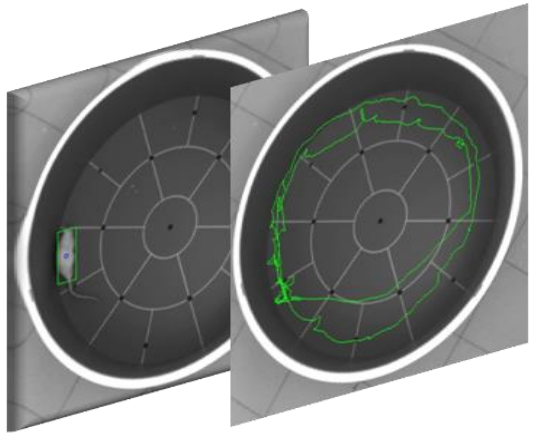
https://it4bio.jinr.ru

IT ecosystem for automated processing of histological data and animal behavior

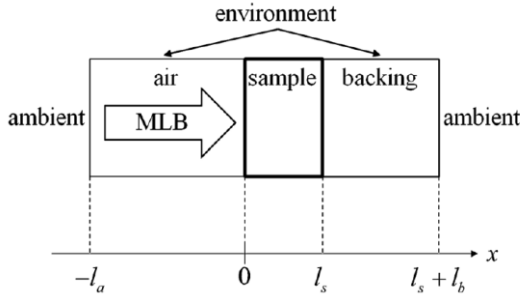








Project
Heat transfer across biological systems: development *in vivo* photothermal diagnostic

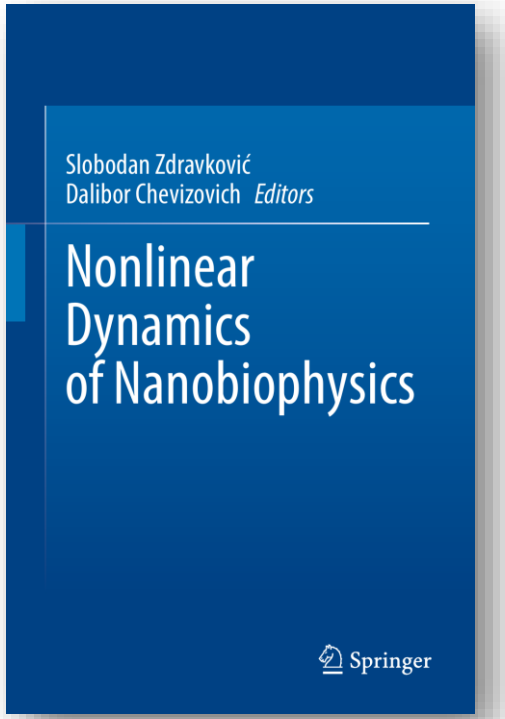


$$\frac{\partial^2 T_a(x,t)}{\partial x^2} - \frac{1}{D_a}\left[\frac{\partial T_a(x,t)}{\partial t} + \tau_a \frac{\partial^2 T_a(x,t)}{\partial t^2}\right] = 0$$

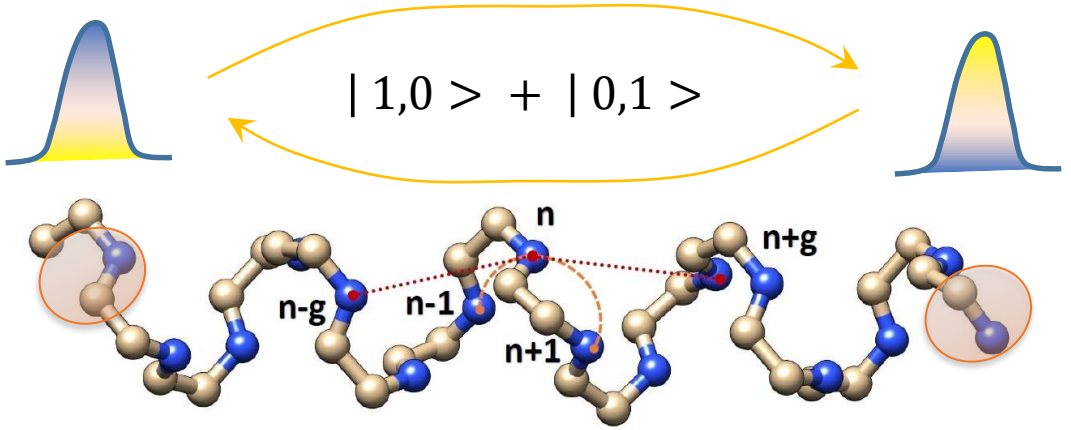
JINR - Serbia
Ongoing projects

JOINT INSTITUTE FOR NUCLEAR RESEARCH

РЕПУБЛИКА СРБИЈА

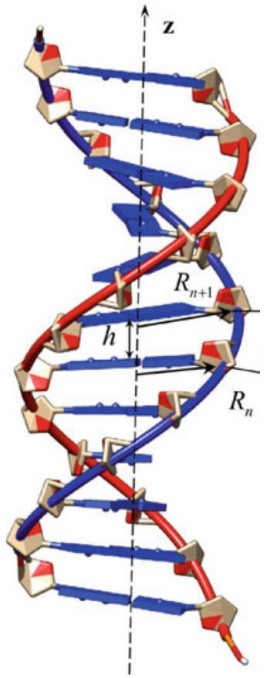


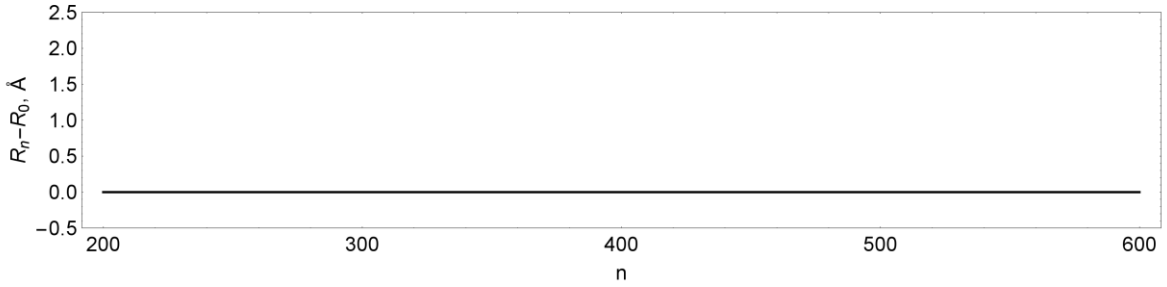
Monography on biomolecules, 2022:
- biophysics,
- bioinformatics,
- nonlinear dynamics,
- quantum correlations

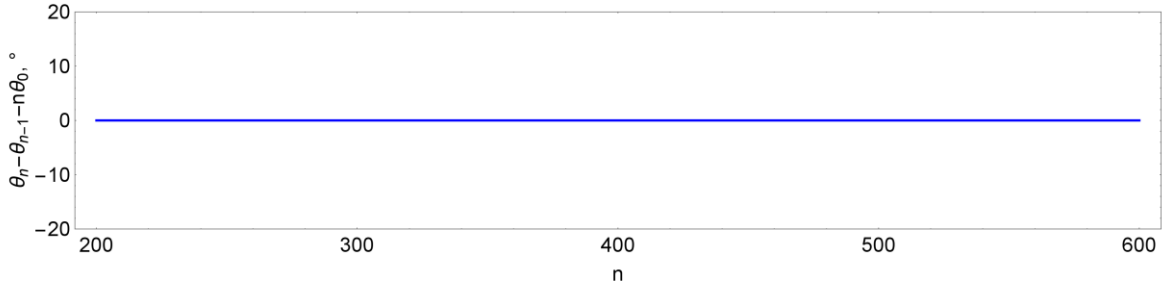


Project
The role of quantum coherence in charge and energy transport in biological macromolecules

Quantum correlations in a model of protein alpha helix







Project
Solitons and chaos in nonlinear dynamics of biomolecules

Collective excitation (soliton) in DNA chain

Thank you for the attention!

JOINT INSTITUTE
FOR NUCLEAR RESEARCH

Dubna

Volga river