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XXVIII International Scientific Conference of Young Scientists and Specialists

Modeling the survival rate of a heterogeneous population of neural stem cells in response to irradiation with ^{56}Fe particles

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INTRODUCTION

MODELING

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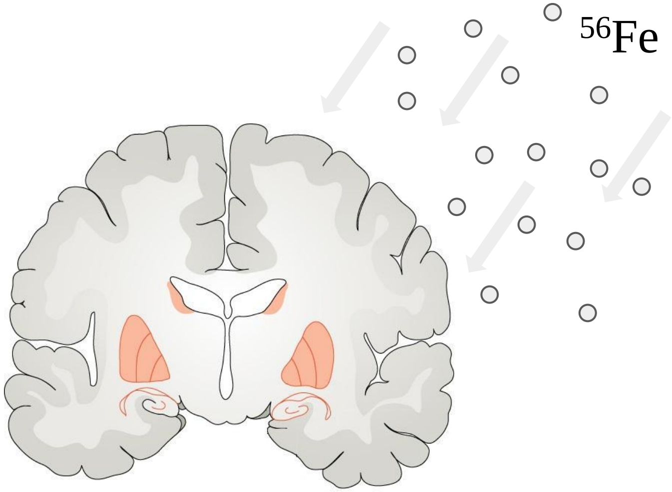
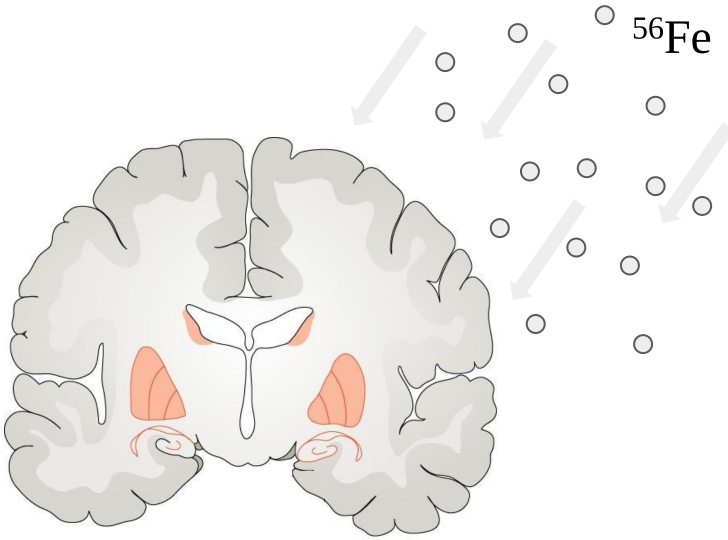
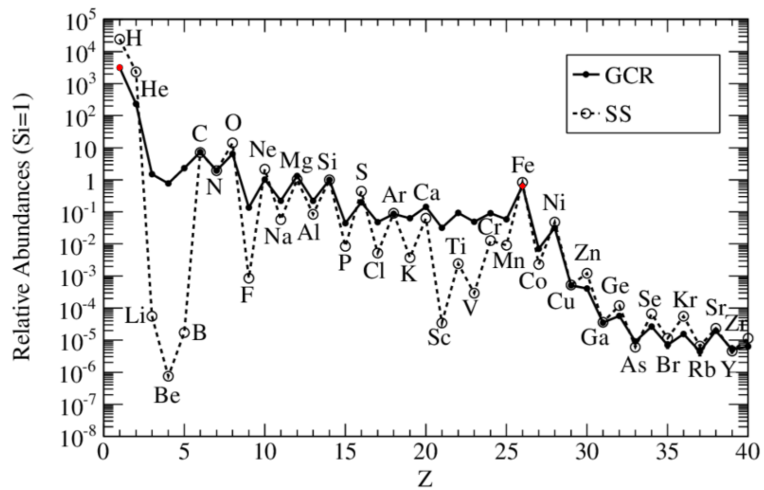
CONCLUSION



IRRADIATION WITH GALACTIC COSMIC RAYS





Solar System (SS) and Galactic cosmic ray (GCR) relative abundances at 2 GeV/nuc normalized to ^{14}Si = 1. The number of protons is more than 1000 times greater than the number of iron particles.

Galactic cosmic rays pose a potential danger to the health of astronauts who will participate in interplanetary flights. Iron particles, although they make up only a small part of cosmic rays, have high linear energy transfer and high energy, which makes them a significant factor in the overall biological effect of cosmic rays on the human health and cognitive functions.

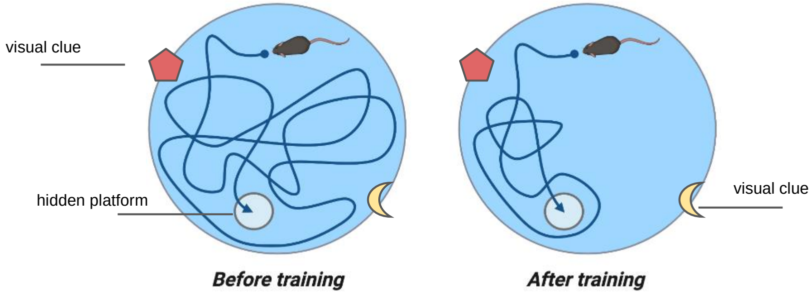
Left picture is taken from: *Denoth-Lippuner, Annina, and Sebastian Jessberger. Nature Reviews Neuroscience 22.4 (2021): 223-236.*
Right picture is taken from: *Rauch, B. F. PoS (ICRC2019) 678 (2019).*

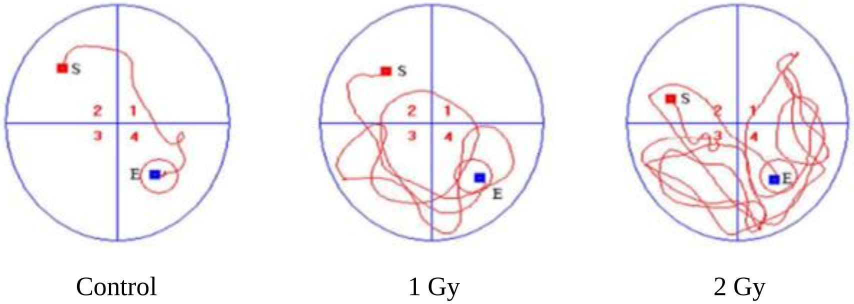
COGNITIVE IMPAIRMENT AFTER IRON IRRADIATION

The Morris Water Maze test measures the ability of rodents to learn and remember the spatial location of visual cues in a pool.

A platform is placed in the pool to prevent the mouse from seeing it. When a mouse first enters the pool, it swims aimlessly until it finds the hidden platform. Each time the mouse visits the pool, they get better at finding the platform. Using the clues on the wall, the mouse remembers where the platform is located.

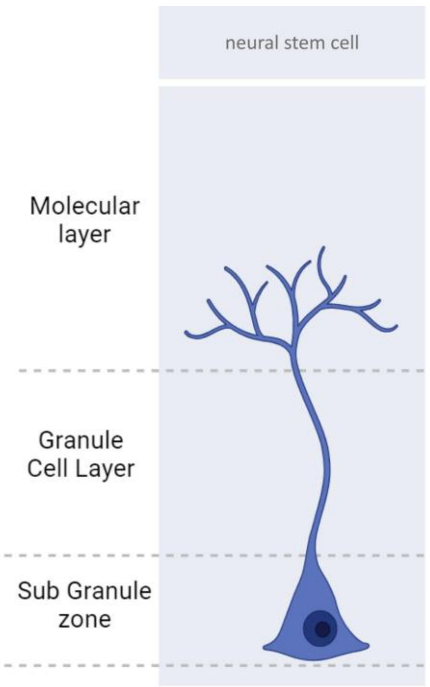
^{56}Fe ion radiation (E=600 MeV/nucleon) induced deficits of spatial learning and memory of kunming mice, one month after exposure. Mice in irradiated groups showed significant increment of escape latency on days 2 – 6 compared to control group.

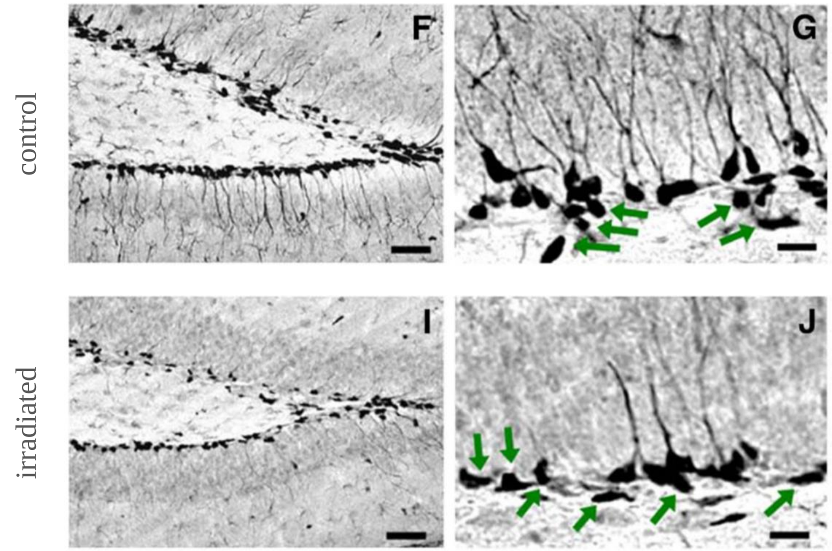




Top picture is taken from: *BioRender (2019). Morris Water Maze Test. https://app.biorender.com/biorender-templates/t-5e1f34bc6bca2300870629c0-morris-water-maze-test*
Bottom picture is taken from: *Yan, Jiawei, et al. Toxicology research 5.6 (2016): 1672-1679.*

IMPAIRMENT OF NEUROGENESIS AFTER IRON IRRADIATION

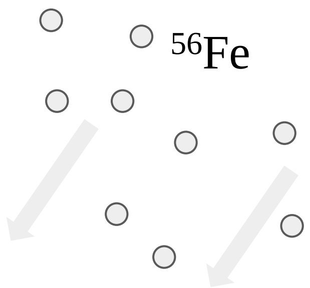




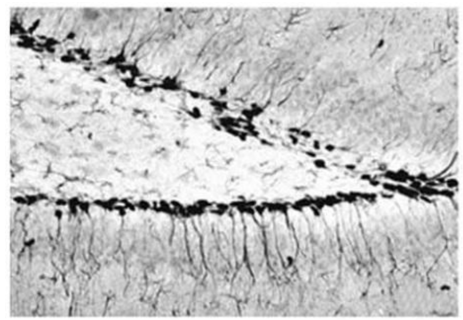
Representative photomicrographs of dentate gyrus sections from control (F, G) and irradiated (I, J) animals. ^{56}*Fe particle radiation decreases the number of neural stem cell and their progenitors (green arrows).*

Left picture is taken from: *Kasza, T. (2024). Adult Neurogenesis. https://app.biorender.com/biorender-templates/t-65bdaf5a5fafd26874044314-adult-neurogenesis*
Right picture is taken from: *Encinas, Juan M., et al. Experimental neurology 210.1 (2008): 274-279.*

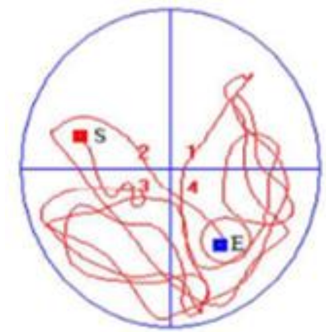
CONNECTION BETWEEN DATA



parameters of irradiation



quantitative experiments of cell survival



behavioral experiments

Ideally, we want to know how the number of neural stem cells changes after irradiation and what cognitive effects occur.

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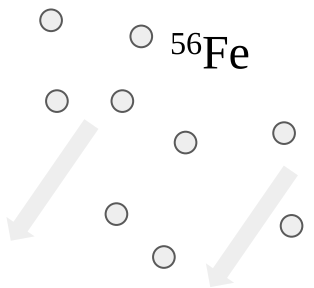
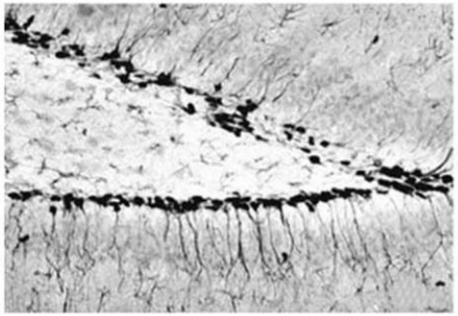


parameters of irradiation



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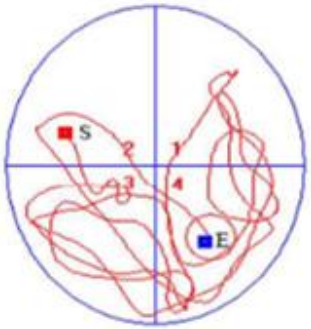

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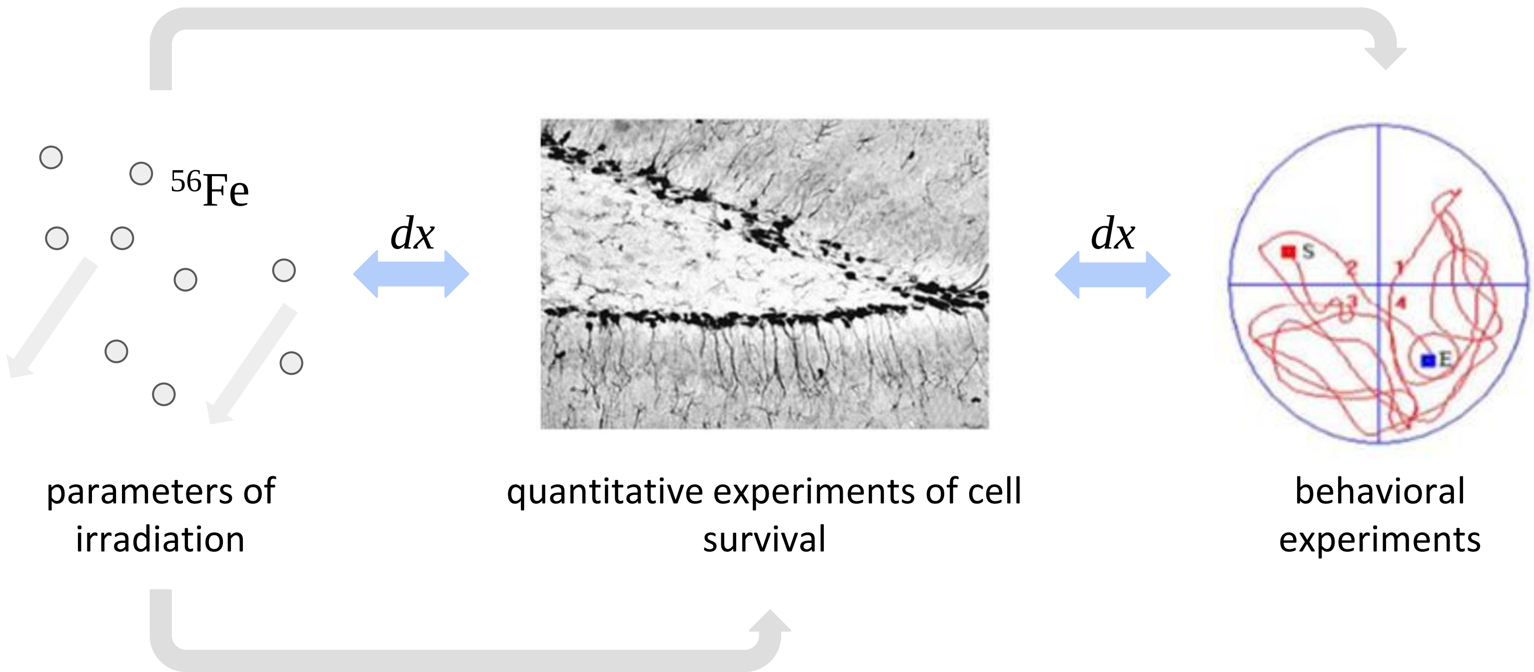

Ideally, we want to know how the number of neural stem cells changes after irradiation and what cognitive effects occur. However, in reality, most experimental work relates radiation parameters to the number of cells or to behavioral experiments. Mathematical modeling is used to try to reproduce the dependence of the influence of radiation on cell populations and animal behavior.

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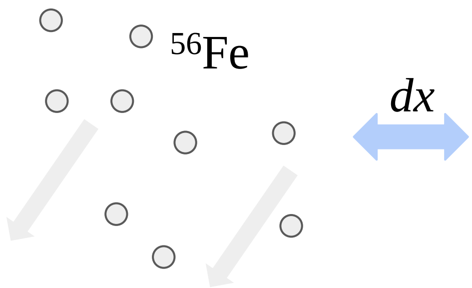
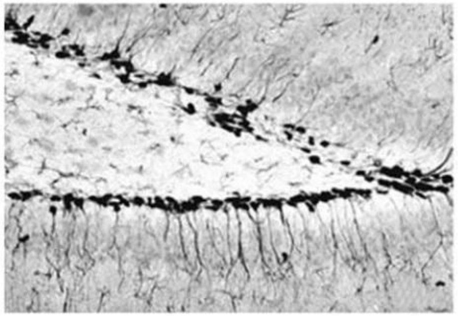
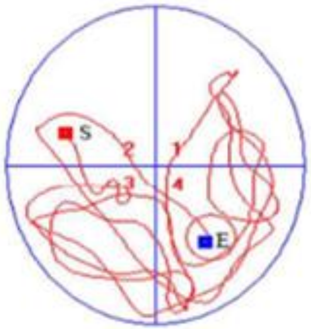






parameters of irradiation

quantitative experiments of cell survival

behavioral experiments

Ideally, we want to know how the number of neural stem cells changes after irradiation and what cognitive effects occur. However, in reality, most experimental work relates radiation parameters to the number of cells or to behavioral experiments. Mathematical modeling is used to try to reproduce the dependence of the influence of radiation on cell populations and animal behavior.

$$\frac{dQ(t)}{dt} = -t_{fd}Q(t) + \theta_{R_{1n}} t_c A_1(t)$$

$$\frac{dA_1(t)}{dt} = t_{fd}Q(t) - t_c A_1(t)$$

$$\frac{dA_{12}(t)}{dt} = \theta_{R_1} t_c A_1(t) - t_{bd_a} A_{12}(t) - t_{bd_{lt}} A_{12}(t)$$

$$\frac{dA_{2a}(t)}{dt} = \theta_a t_{bd_a} A_{12}(t) - t_c A_{2a}(t)$$

$$\frac{dA_{2rt}(t)}{dt} = \theta_{rt} t_{bd_a} A_{12}(t)$$

$$\frac{dA_{2lt}(t)}{dt} = \theta_{lt} t_{bd_{lt}} A_{12}(t) - t_c A_{2lt}(t)$$

$$\frac{dA_{23a}(t)}{dt} = \theta_{R_2} t_c A_{2a}(t) - t_{bd_a} A_{23a}(t)$$

$$\frac{dA_{23lt}(t)}{dt} = \theta_{R_2} t_c A_{2lt}(t) - t_{bd_{lt}} A_{23lt}(t)$$

$$\frac{dA_{3a}(t)}{dt} = t_{bd_a} A_{23_a}(t) - t_c A_{3a}(t)$$

$$\frac{dA_{3lt}(t)}{dt} = t_{bd_{lt}} A_{23_{lt}}(t) - t_c A_{3lt}(t)$$

$$\frac{dA_4(t)}{dt} = \theta_{R_3} t_c A_{3a}(t) + \theta_{R_3} t_c A_{3lt}(t) - \mathrm{t_{apop}}\, A_4(t)$$

×

OLD APPROACH FOR MODELING OF NSC POPULATION

quiescent

$$\frac{dn_1(t)}{dt} = -d_1 n_1(t) + p_1 n_1(t)$$

activation proliferation

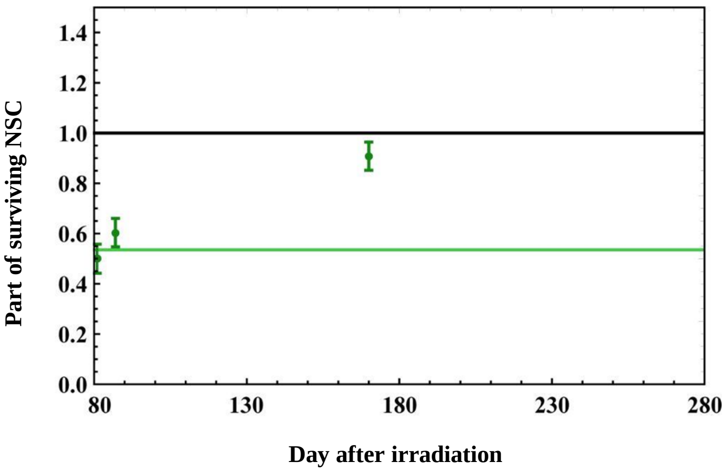
Equation of dynamic of NSCs population [Cacao2016]

quiescent

$$\frac{dA(t)}{dt} = -k_a A(\mathrm{t})$$

activation

Equation of dynamic of NSCs population [Glebov2022]

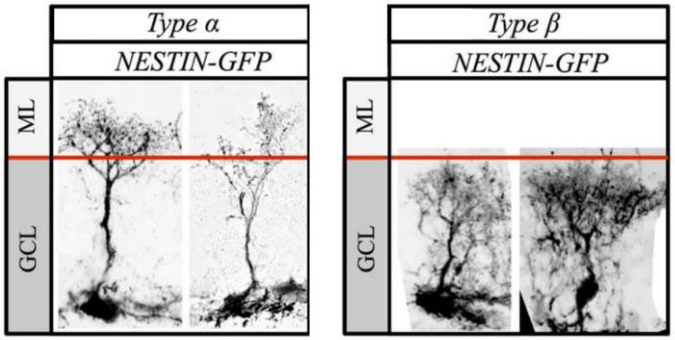


The results of modeling the part of surviving neural stem cells after ^{56}Fe irradiation with dose 1 Gy. Experimental data takes from [DeCarolis2014]. Population dynamic are calculated based on a model of a neurogenesis [Glebov2022].

Equation is taken from: *Cacao, Eliedonna, et al. Radiation research 186.6 (2016): 624-637. // Glebov, A. A., et al. Physics of Particles and Nuclei Letters 19.4 (2022): 422-433.*
Experimental data is taken from: *DeCarolis, Nathan A., et al. Life sciences in space research 2 (2014): 70-79.*

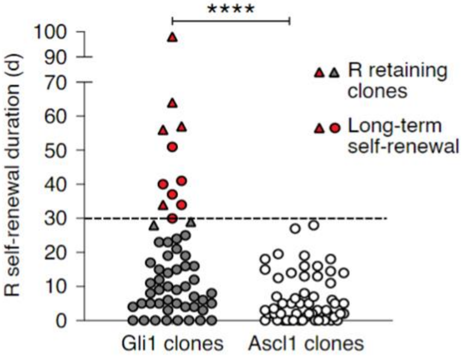
DIFFERENT TYPES OF NEURAL STEM CELLS

Differences in morphology



Confocal maximal projection micrographs of types α and β neural stem cells in Nestin-GFP mice.

Differences in rate of dividing



Time (days) between first and last division in each lineage of Gli1- and Ascl1-targeted R cells. Triangles depict clones where R cells were still present at the end of the imaging. Red circles depict R cells showing long-term self-renewal. The dashed line represents a long-term self-renewal threshold.

Left picture is taken from: *Gebara, Elias, et al. Stem cells 34.4 (2016): 997-1010.*
Right picture is taken from: *Bottes, Sara, et al. Nature neuroscience 24.2 (2021): 225-233.*

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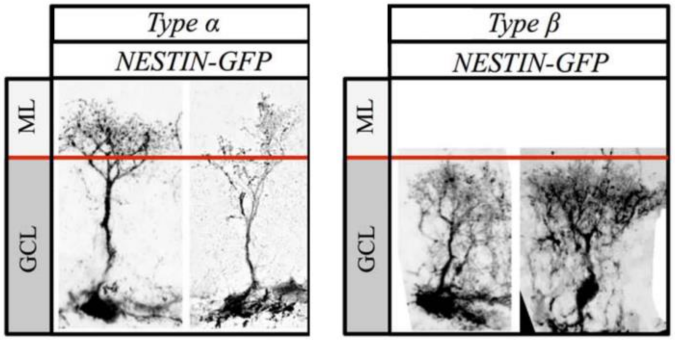

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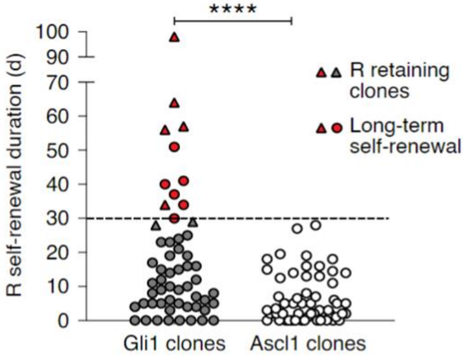

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MODELING OF A HETEROGENEOUS POPULATION OF NSC

quiescent cells

$$\frac{dQ(t)}{dt} = -t_{fd}Q(t) + \theta_{R_{1n}} t_c A_1(t)$$

activation

proliferation

$$\frac{dA_1(t)}{dt} = t_{fd}Q(t) - t_c A_1(t)$$

$$\frac{dA_{12}(t)}{dt} = \theta_{R_1} t_c A_1(t) - t_{bd_a} A_{12}(t) - t_{bd_{lt}} A_{12}(t)$$

fast divisions

$$\frac{dA_{2a}(t)}{dt} = \theta_a t_{bd_a} A_{12}(t) - t_c A_{2a}(t)$$

$$\frac{dA_{23a}(t)}{dt} = \theta_{R_2} t_c A_{2a}(t) - t_{bd_a} A_{23a}(t)$$

$$\frac{dA_{3a}(t)}{dt} = t_{bd_a} A_{23_a}(t) - t_c A_{3a}(t)$$

resting cells

$$\frac{dA_{2rt}(t)}{dt} = \theta_{rt} t_{bd_a} A_{12}(t)$$

slow divisions

$$\frac{dA_{2lt}(t)}{dt} = \theta_{lt} t_{bd_{lt}} A_{12}(t) - t_c A_{2lt}(t)$$

$$\frac{dA_{23lt}(t)}{dt} = \theta_{R_2} t_c A_{2lt}(t) - t_{bd_{lt}} A_{23lt}(t)$$

$$\frac{dA_{3lt}(t)}{dt} = t_{bd_{lt}} A_{23_{lt}}(t) - t_c A_{3lt}(t)$$

$$\frac{dA_4(t)}{dt} = \theta_{R_3} t_c A_{3a}(t) + \theta_{R_3} t_c A_{3lt}(t) - \mathrm{t_{apop}}\, A_4(t)$$

apoptosis

×

A scheme of the process of division of neural stem cells, where:

Q - quiescence cells

A_a - active fast dividing cells

A_{lt} - active slow dividing cells

A_{rt} - resting cells

Calculation of dynamics were performed for adult mice starting from the sixtieth day of life.

The initial number of cells in population Q was 1, while the numbers of cells in the remaining populations were 0.

MODELING OF A HETEROGENEOUS POPULATION OF NSC

Rate of processes:

$t_{fd} = 1/24.98\ d^{-1}$	-	activation rate of first division of NSC
$t_c = 1/0.95\ d^{-1}$	-	rate of cell cycle of NSC
$t_{bd_a} = 1/10.11\ d^{-1}$	-	activation rate of second and third division of fast dividing NSC
$t_{bd_{lt}} = 1/17.80\ d^{-1}$	-	activation rate of second and third division of slow dividing NSC
$t_{apop} = 1/176\ d^{-1}$	-	rate of apoptosis

Proportion of cell formed:

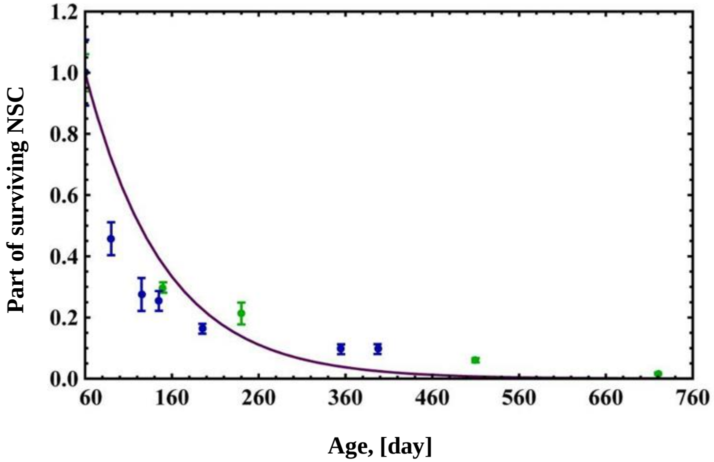
$\theta_{R_{1n}} = 0.1852$	-	proportion of newborn NSC
$\theta_{R_1} = 0.7778$	-	proportion of NSC after first division
$\theta_a = 0.7144 - 0.0014 * t$	-	proportion of active fast dividing NSC
$\theta_{lt} = 0.1964 + 0.0007 * t$	-	proportion of active slow dividing NSC
$\theta_{rt} = 0.0892 + 0.0007 * t$	-	proportion of resting NSC
$\theta_{R_2} = 0.4737$	-	proportion of NSC after second division
$\theta_{R_3} = 0.6364$	-	proportion of NSC after third division

The rate of processes and the proportion of cells formed is taken from: *Wu, Yicheng, et al. Nature Aging 3.4 (2023): 380-390.*
Duration of the NSC cell cycle is taken from: *Brandt, Moritz D., et al. Stem cells 30.12 (2012): 2843-2847.*

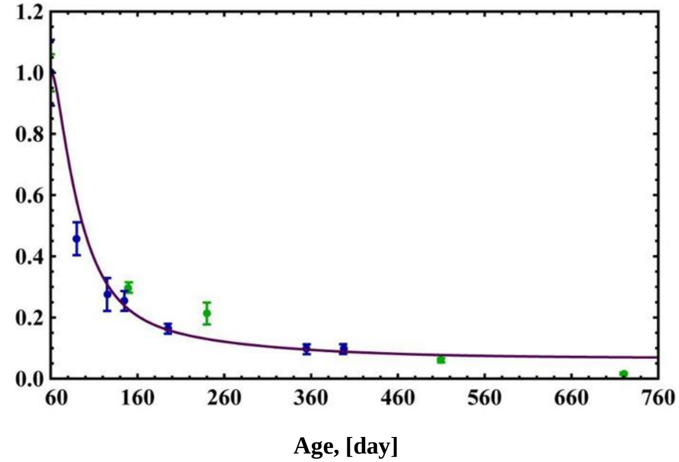
CALCULATED SURVIVAL OF NEURAL STEM CELLS

AGE-RELATED DYNAMICS OF NEURAL STEM CELLS SURVIVING

HOMOGENEITY MODEL OF NSC



HETEROGENEITY MODEL OF NSC



Results of modeling the part of surviving neural stem cells depending on age.
Left - taking into account the homogeneity of neural stem cells, right - taking into account the heterogeneity of neural stem cells.

Experimental data is taken from:

green dots	*Encinas, Juan M., et al. Cell stem cell 8.5 (2011): 566-579.*
blue dots	*Ziebell, Frederik, et al. Development 145.1 (2018): dev153544.*

MODELING OF RESPONSE TO RADIATION

Cell response

The initial number of cells after irradiation was calculated based on the age-dependent dynamics of the NSC number at 0 Gy. The exponential term in the equation takes into account the instantaneous death of cells after irradiation.

absorbed dose

$$n_{IR_X}(t,dz) = n_{0_X}(t,0) \times \exp\left[-\frac{dz}{D_{37}}\right]$$

number of cells in population X after irradiation

number of cells in population X before irradiation

characteristic dose (dose at with 37% of cell is survived)

Microenvironment response

We found that changing the rate of the first division activation significantly modifies the dynamic curve. Therefore, we fitted this parameter depending on the absorbed dose of radiation.

rate of first division activation

$$\frac{dQ(t)}{dt} = -t_{fd} Q(t) + \theta_{R_{1n}} t_c A_1(t)$$

Transcriptomic studies have shown that quiescent NSCs are actively integrating signals from their microenvironment. Activation of NSCs leads to a shut down of their ability to respond to external stimuli, switching the expression of genes from the membrane to the nucleus.

Transcriptomic studies is taken from: Shin, Jaehoon, et al. *Cell stem cell* 17.3 (2015): 360-372.

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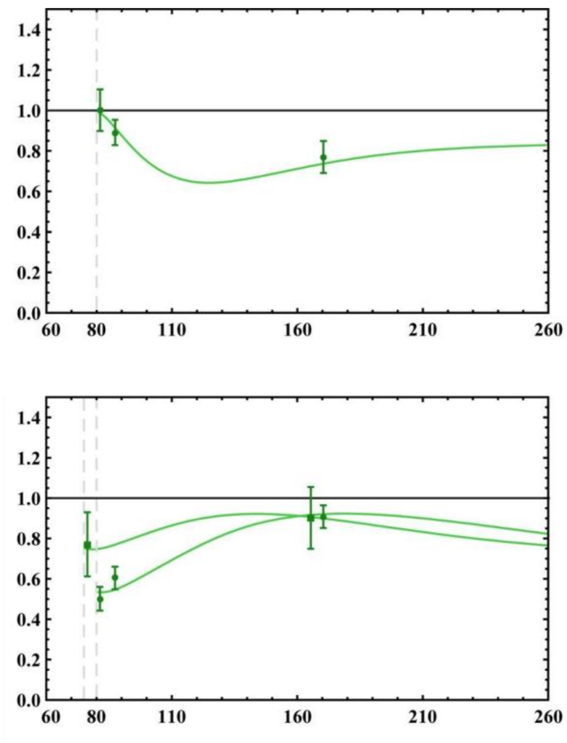
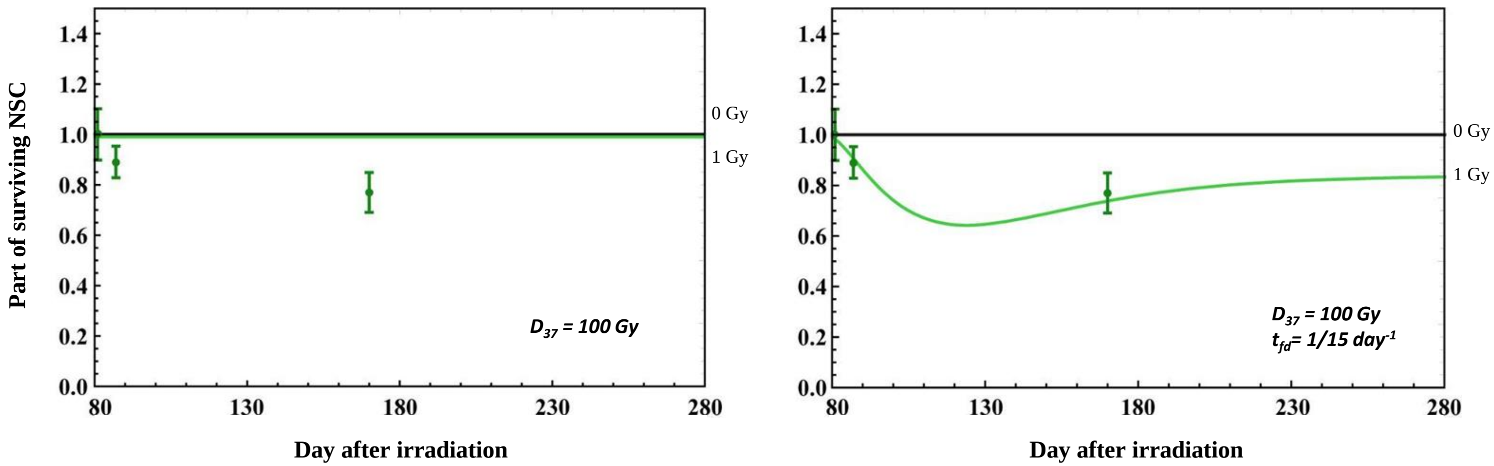


CALCULATED SURVIVAL OF NEURAL STEM CELLS

SHORT- AND MEDIUM-TERM SURVIVAL OF NSC AFTER ^{56}FE PARTICLE IRRADIATION

E = 1000 MeV/nucleon, LET = 148 keV/µm

HOMOGENEITY MODEL OF NSC *HETEROGENEITY MODEL OF NSC*



The results of modeling the part of surviving neural stem cells after ^{56}Fe irradiation. On the left - taking into account the homogeneity of the NSC, on the right - taking into account the heterogeneity of the NSC. D_{37} is the characteristic dose of NSCs, t_{fd} is the rate of the first division activation.

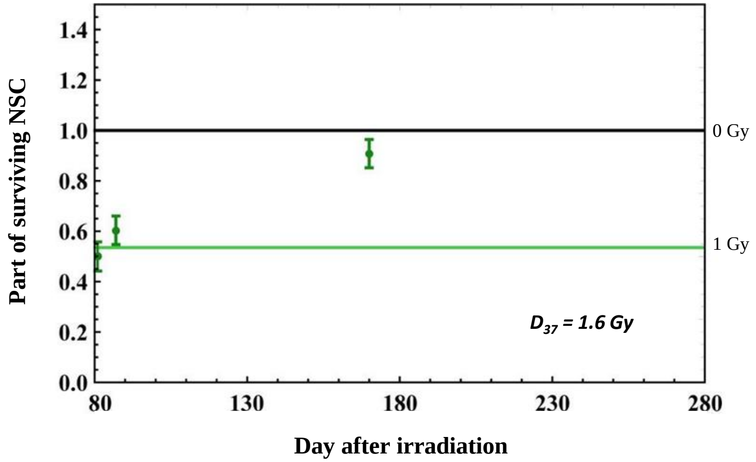
Experimental data is taken from: *DeCarolis, Nathan A., et al. Life sciences in space research 2 (2014): 70-79.*

CALCULATED SURVIVAL OF NEURAL STEM CELLS

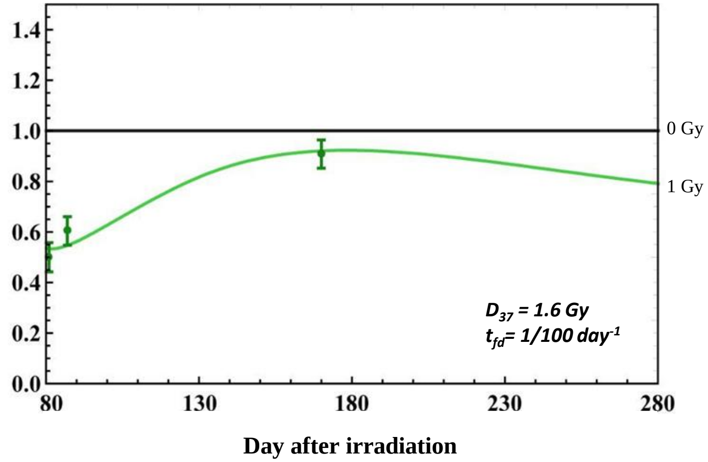
SHORT- AND MEDIUM-TERM SURVIVAL OF NSC AFTER ^{56}FE PARTICLE IRRADIATION

E = 300 MeV/nucleon, LET = 240 keV/µm

HOMOGENEITY MODEL OF NSC



HETEROGENEITY MODEL OF NSC



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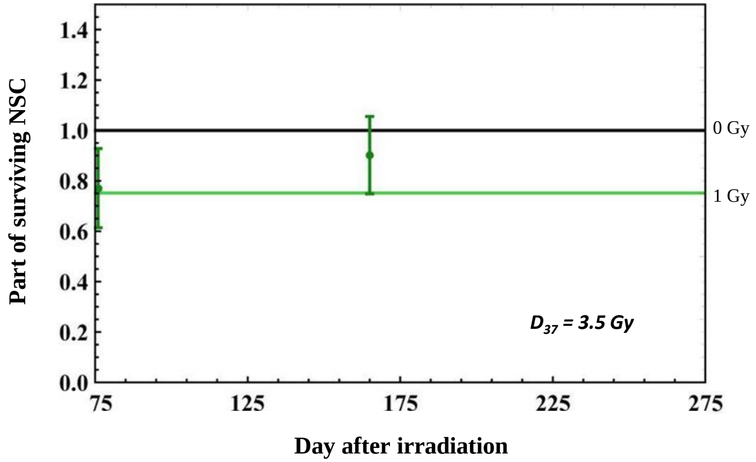
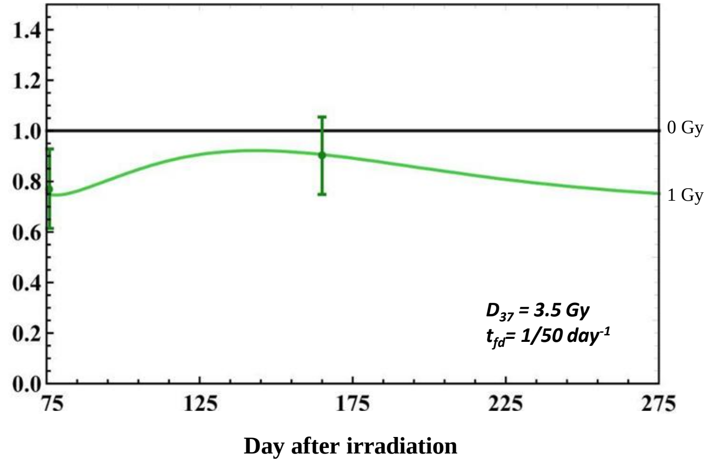


HETEROGENEITY MODEL OF NSC

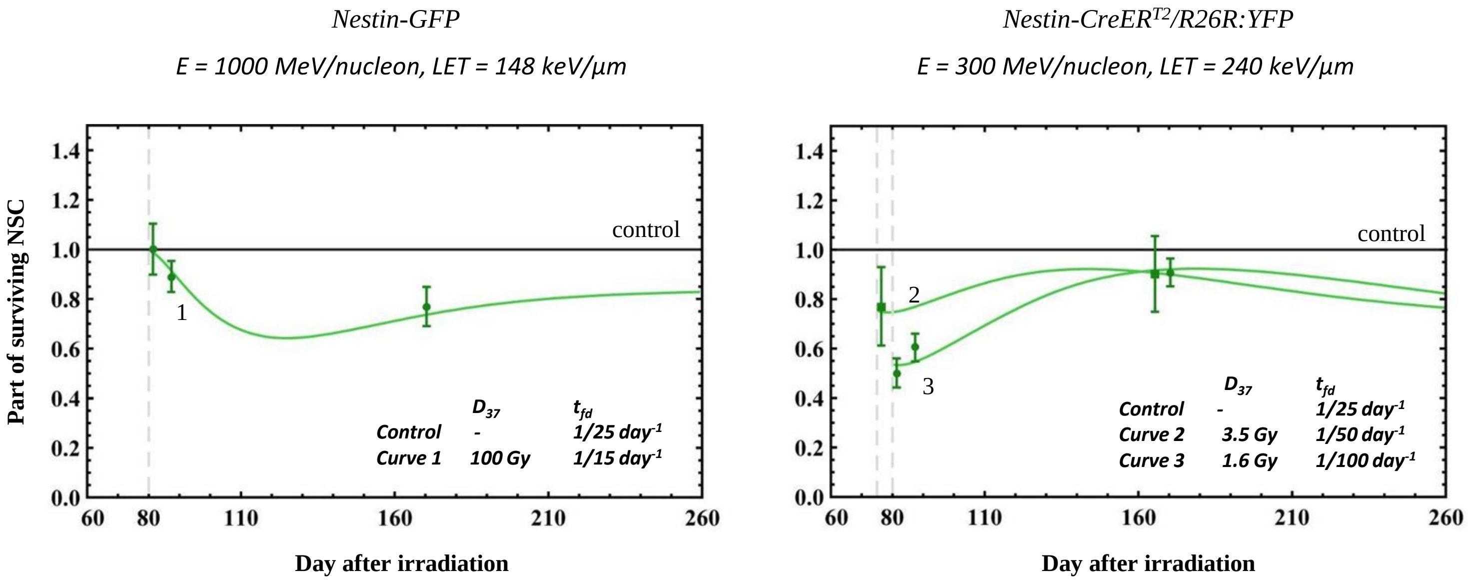


The results of modeling the part of surviving neural stem cells after ^{56}Fe irradiation. On the left - taking into account the homogeneity of the NSC, on the right - taking into account the heterogeneity of the NSC. D_{37} is the characteristic dose of NSCs, t_{fd} is the rate of the first division activation.

Experimental data is taken from: *Rivera, Phillip D., et al. Radiation research 180.6 (2013): 658-667.*

CALCULATED SURVIVAL OF NEURAL STEM CELLS

SHORT- AND MEDIUM-TERM SURVIVAL OF NSC AFTER ^{56}FE PARTICLE IRRADIATION



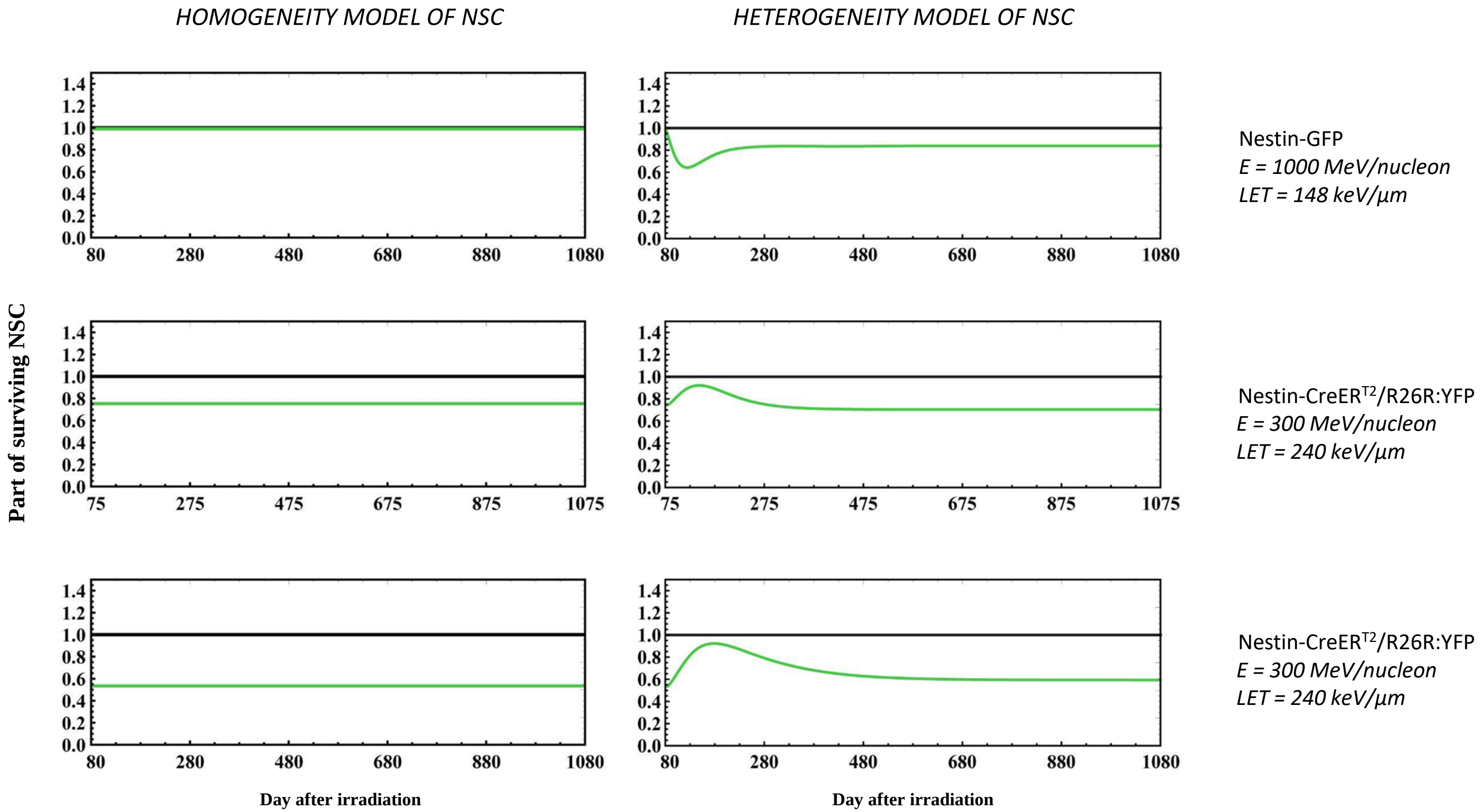
The results of modeling the part of surviving neural stem cells after irradiation with iron particles, taking into account the heterogeneity of NSCs. On the left - for transgenic Nestin-GFP mice, on the right - for transgenic Nestin-CreER^{T2}/R26R:YFP mice. The green curve for all presented graphs corresponds to a dose of 1 Gy. D_{37} is the characteristic dose of NSCs, t_{fd} is the activation rate of the first division of neural stem cells.

Experimental data is taken from:

Left picture	*green dots*	*DeCarolis, Nathan A., et al. Life sciences in space research 2 (2014): 70-79.*
Right picture	*green squares*	*Rivera, Phillip D., et al. Radiation research 180.6 (2013): 658-667.*
	green dots	*DeCarolis, Nathan A., et al. Life sciences in space research 2 (2014): 70-79.*

CALCULATED SURVIVAL OF NEURAL STEM CELLS

LONG-TERM SURVIVAL OF NSC AFTER ^{56}FE PARTICLE IRRADIATION



The results of modeling the part of surviving neural stem cells after ^{56}Fe irradiation. On the left - taking into account the homogeneity of the NSC, on the right - taking into account the heterogeneity of the NSC. The green curve for all presented graphs corresponds to a dose of 1 Gy.

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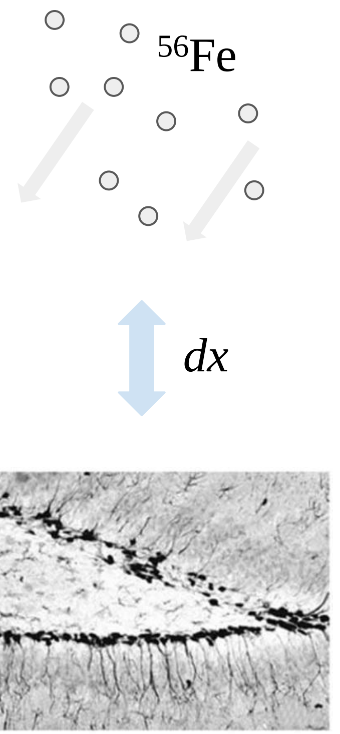

CONCLUSION

1.

Modeling the number of neural stem cells taking into account their heterogeneity makes it possible to reproduce age-related changes in the number of cells

2.

The dependence of the first division activation rate parameter on the dose allows us to reproduce experimental data on the number of neural stem cells after irradiation with iron particles of different energies

3.

Depending on the energy of the particles, neural stem cells can restore their numbers by accelerating the entry into division or preserving cell divisions

Further development of the model and comparison of the results with behavioral experiments will help to assess the risk of cognitive impairment in people during interplanetary flights

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THANK YOU
FOR ATTENTION