Laboratory of Radiation Biology,
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# CALCULATION OF DNA DAMAGE IN THE TUMOR CELL ON BORON NEUTRON CAPTURE THERAPY

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# Content

# Background

## Diseases at higher risk for human life

Cancer is a leading cause of death worldwide, accounting for nearly 10 million deaths in 2020, or nearly 1 in 6 deaths [1]

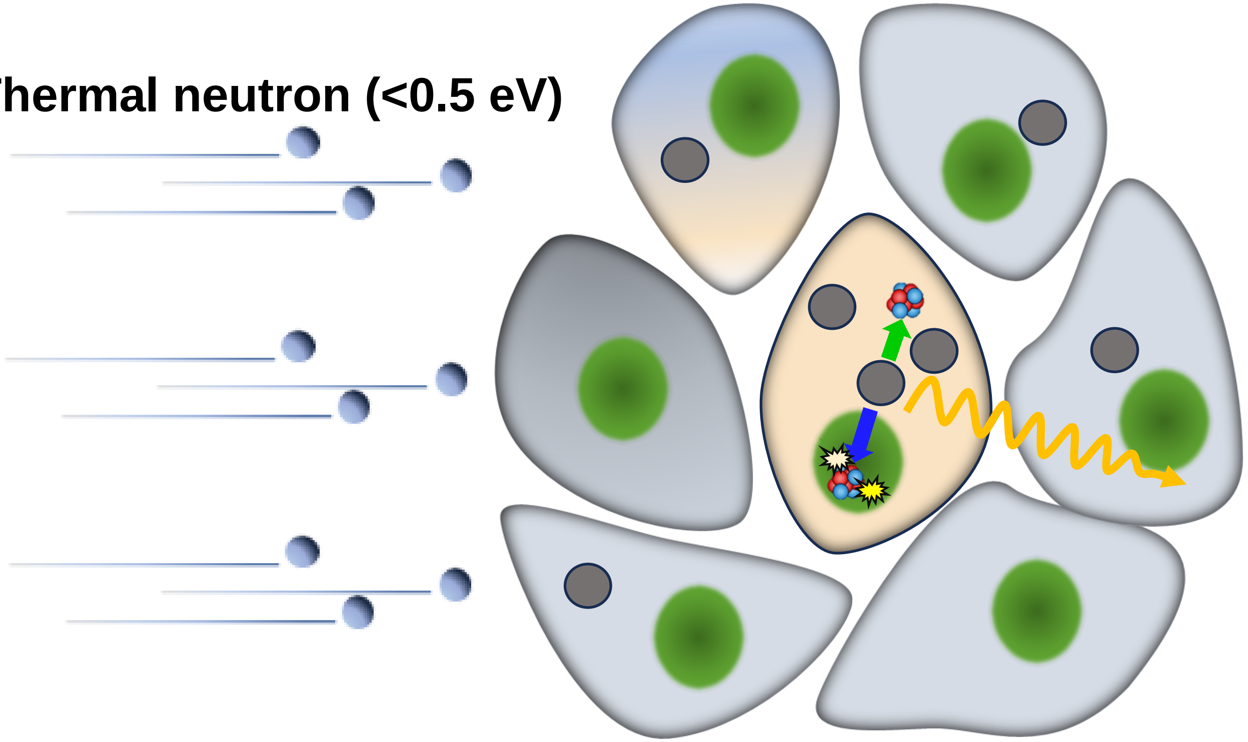
## Radiation therapy

Radiotherapy remains one of the most common and effective treatment modalities for cancer [2]

[1] www.who.int
[2] Baskar R. et .al, (2012)

## Boron neutron capture therapy (BNCT)

**Thermal neutron (<0.5 eV)**



- Tumor cell
- Normal cells
- $^{10}B$
- Cell nucleus
- DNA damage caused by high energetic particles

$^{10}B$ ratio in tumor and normal cell: > **3/1** [3]

**Boron neutron capture reaction**

$$^{1}n + ^{10}B \longrightarrow ^{11}B \longrightarrow ^{7}Li\ (0.84\ MeV) + ^{4}He\ (1.47\ MeV) + \gamma\ (0.48\ MeV) \quad 93.7\ \%$$

$$^{1}n + ^{10}B \longrightarrow ^{11}B \longrightarrow ^{7}Li\ (1.01\ MeV) + ^{4}He\ (1.77\ MeV) \quad 6.3\ \%$$

[3] IAEA (2023)

# Background

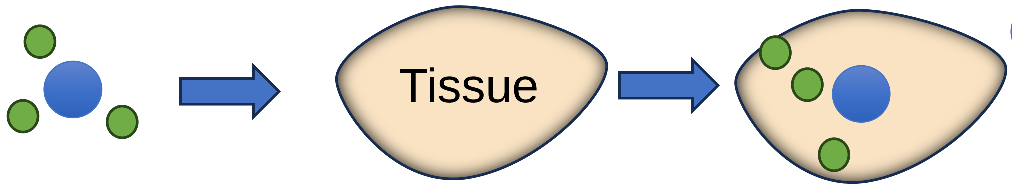
## In brief review

- Gordon Locher first elaborated the idea and principle of neutron capture therapy (NCT) in 1936 (4).
- In-vivo studies, the first clinical trial of BNCT was initiated by Farr and Sweet et al. in 1951 (5).
- In-silico study, last few decade the Monte-Carlo codes for BNCT has been mainly demonstrated dose effectiveness in the tumor scale.

[4] Locher G, et.al (1936)
[5] Wang S, et.al (2022)

# Background

## What is a $^{10}$B agents?

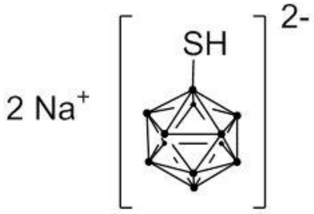


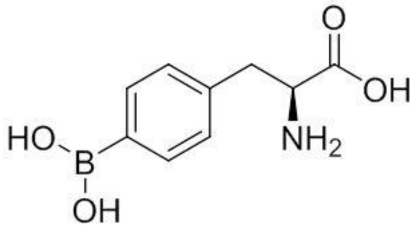

$^{10}$**B** (useful)

conjugated elements

I) Two low molecular weight boron-containing drugs currently are being used clinically, sodium borocaptate and boronophenylalanine (L-BPA) [6]

• B/BH



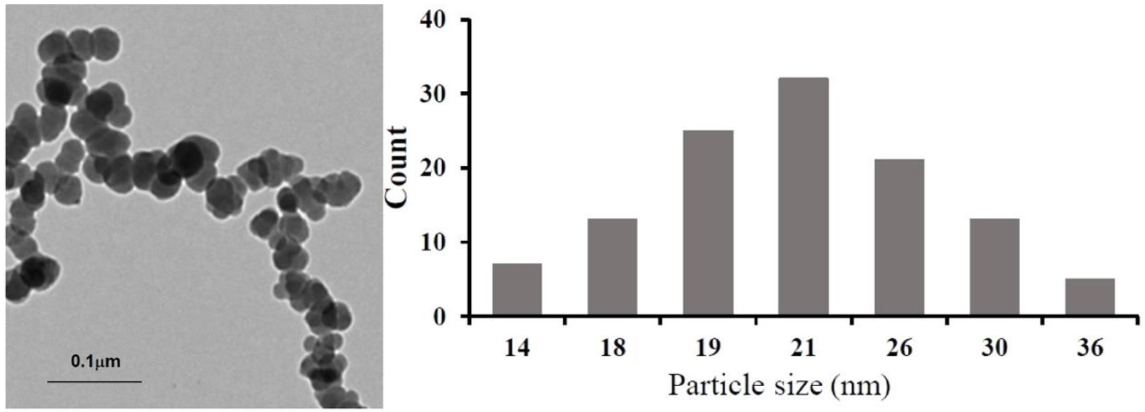




Sodium borocaptate (BSH)

L-4-Dihydroxyboronophenylalanine (L-BPA)

- L-Boronophenylalanine ($C_9H_{12}$**B**$NO_4$)
- Sodium borocaptate ($Na_2$**$B_{12}$**$H_{11}SH$)

II) Average diameter of BNPs about 21 nm [7,8]




III) Average concentration of $^{10}$**B** for BNCT

Each tumor cell contains more than 30-40 µg/g ($10^9$ $^{10}$**B** atoms) [6,9]

[6] Barth, R.F., et.al, Cancer Commun 38 (2018)
[7] Yinghuai Zhu, et.al, ACS Omega (2022
[8] ) Liu, X., et.al, Journal of Colloid and Interface Science (2009)
[9] Farr LE., et.al, (1954)

# Aim of the work

To estimate DNA damage in the glial cell model after irradiation with low energetic neutrons

# Monte Carlo method

## Verification of total cross-section of $^{10}B$

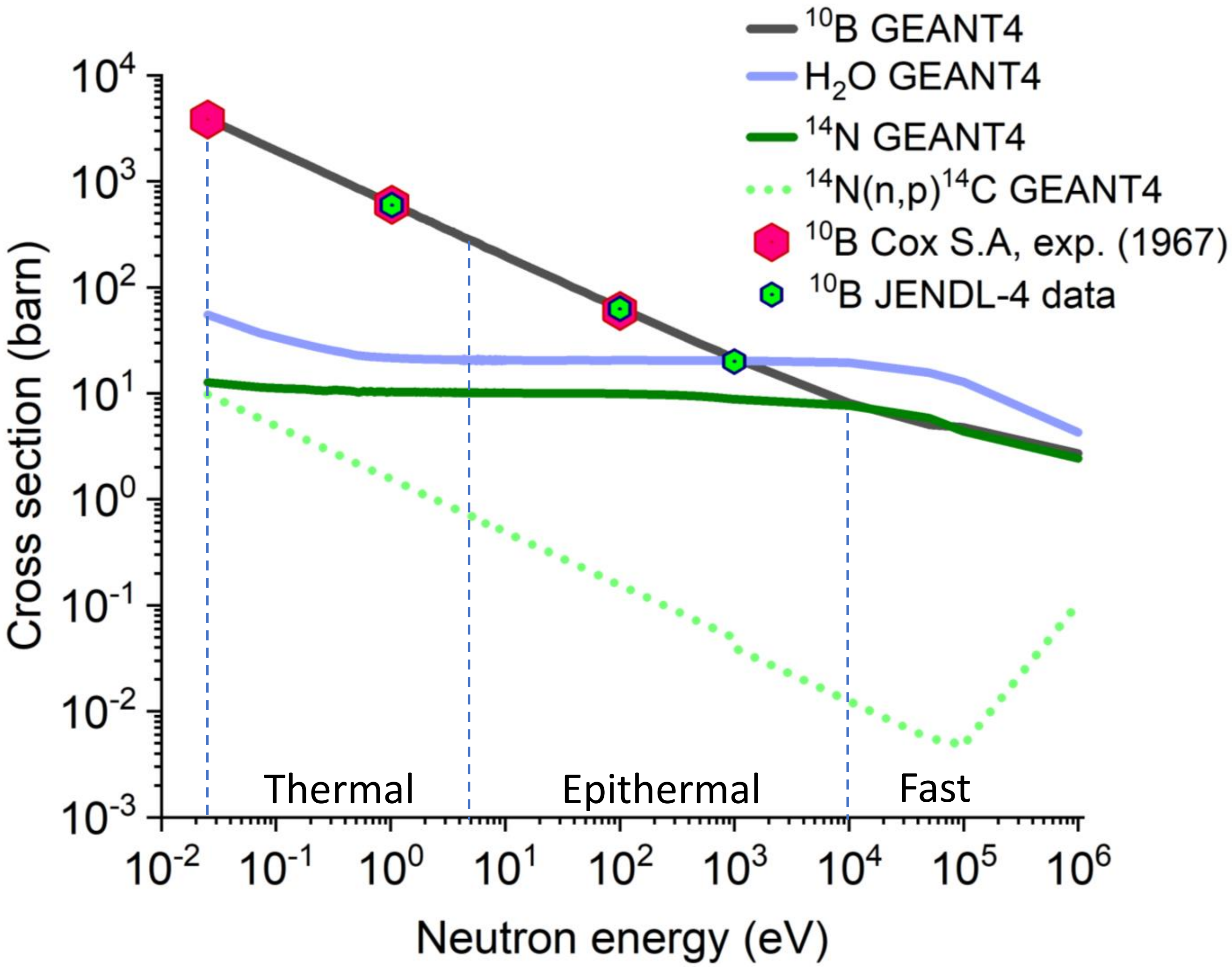



**Figure 1**. Neutron absorption cross section

**NeutronHP physics:** <20 MeV, including TENDL, JENDL cross sectional data library

**NUCLEAR PROCESSES:**

- Neutron elastic scattering (no absorption)
- Neutron inelastic scattering (absorption)

$^{10}B(n,\alpha)^{7}Li$ process dominant for boron

The highest value of total cross section is **3886** barn at 0.0253 eV, error with **1.25%.**

$^{1}H(n,n')^{1}H'$ recoil process mainly for water

$^{14}N(n,p)^{14}C$ process higher only at thermal energies for nitrogen

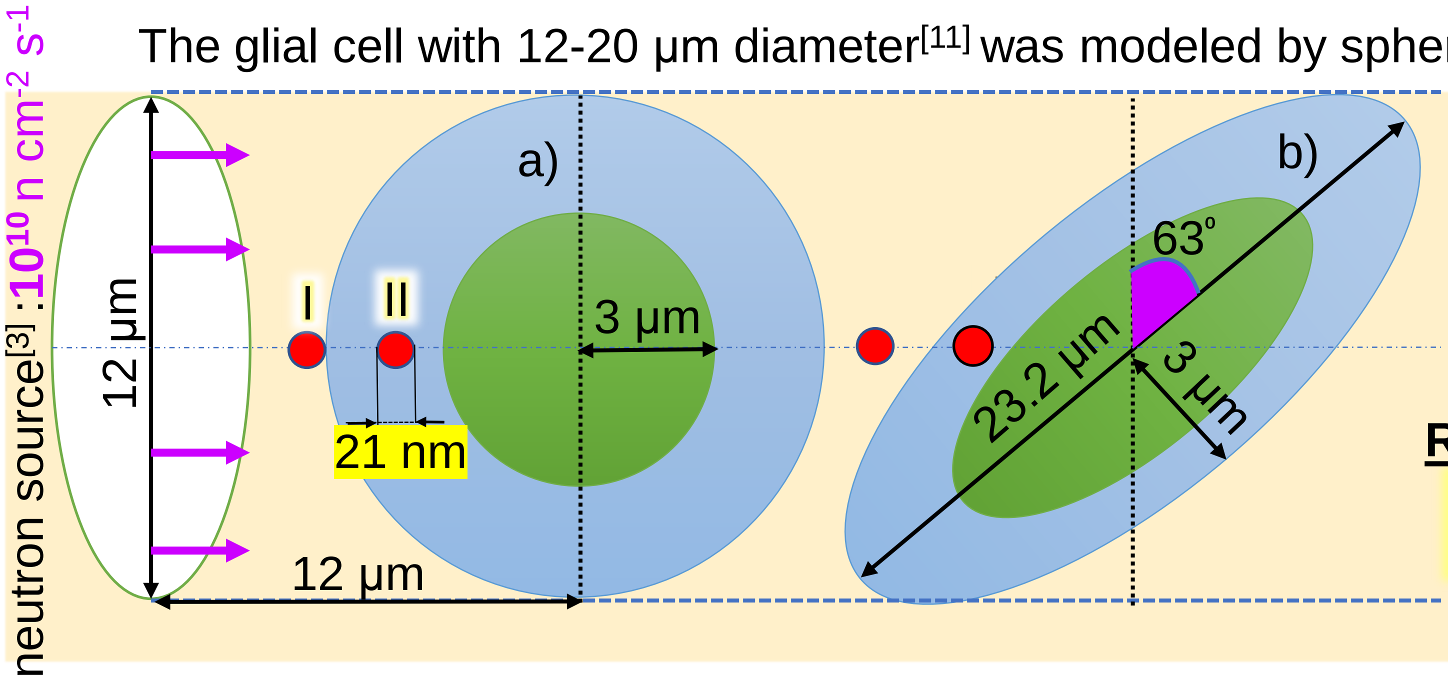
JENDL- Japanese Evaluated Nuclear Data Library (JAEA)
TENDL- TALYS Evaluated Nuclear Data Library
1 barn = $10^{-28}$ m$^2$

[10] Cox, S.A (1967)

# Monte Carlo method

## Simulation setup on the GEANT4

The glial cell with 12-20 μm diameter[11] was modeled by sphere (a) and ellipsoid (b).




- Cytoplasm
- Nucleus (**DNA:6 Gbp**)
- Tissue
- Representation of BNPs (4513 $^{10}$**B** atoms)

**Gbp-10⁹ basepair**

**Random distributions**

I) In the cytoplasm
II) Outside of the cell

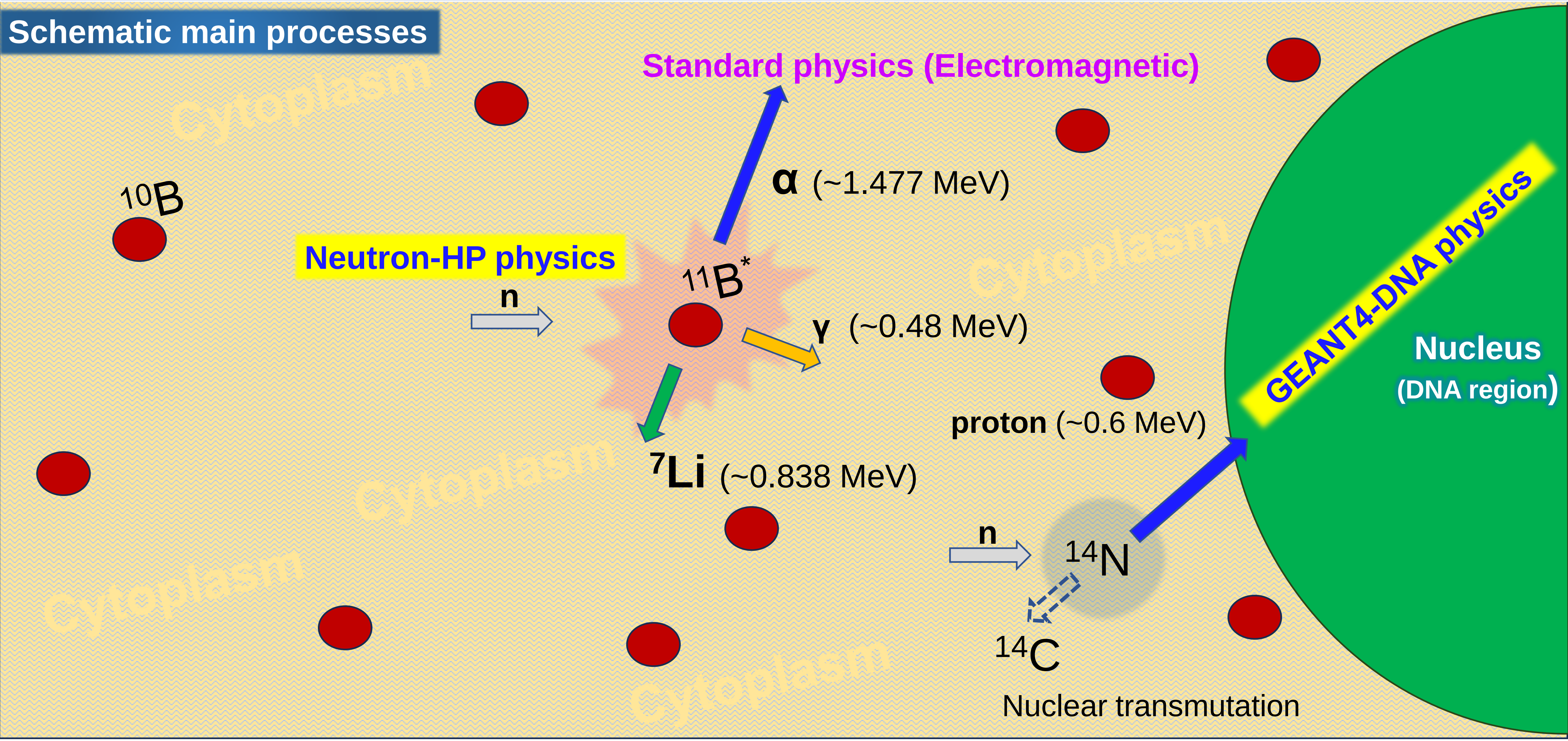
**Concentrations**

I) 100 μg/g
II) 50 μg/g
III) 10 μg/g

| Material name | Mass fraction of each element (%) | | | | | | | | | | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | $^{1}$H | $^{10}$B | $^{12}$C | $^{14}$N | $^{16}$O | $^{23}$Na | $^{31}$P | $^{32}$S | $^{35}$Cl | $^{39}$K | |
| Water (Nucleus) | 66.67 | | - | | 33.33 | | | - | | | 100 |
| Soft tissue (Cytoplasm) | 10.5 | - | 25.6 | 2.7 | 60.2 | 0.1 | 0.2 | 0.3 | 0.2 | 0.2 | 100 |
| BNPs (L-BPA) | + | + | + | + | + | | | - | | | 100 |

[3] IAEA (2023) [11]. M. Pruimboom-Brees, (2004)

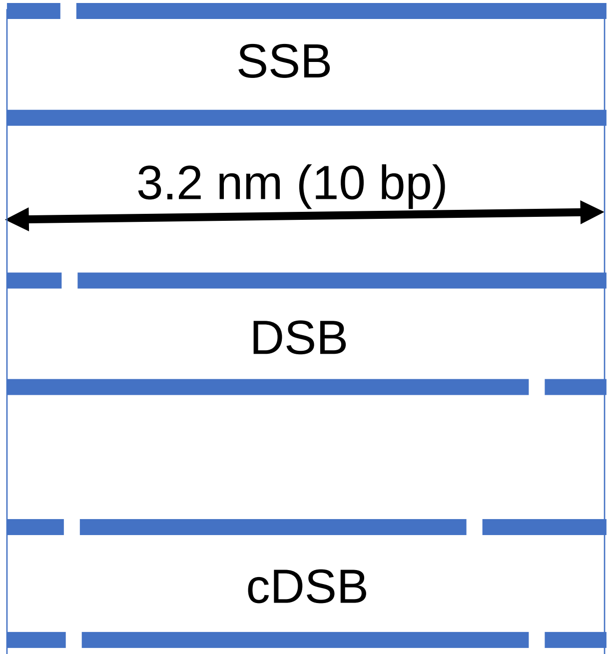
# Monte Carlo method



# Monte Carlo method

## Clustering algorithm (DBSCAN)

| Parameter name | Parameter definition | Value | Reference |
|---|---|---|---|
| Eps | Radius of the cluster | 3.2 nm | Francis et.al (2011) |
| MinPts | Minimum points per cluster | 2 | |
| SPointsProb | Probability of energy deposition point in DNA region | 5.78% (sphere cell)<br>4.94% (ellipsoid cell) | |
| EMinDamage | Minimum energy inducing a **SSB** | 5 eV | W. Friedland et.al (2005) |
| EMaxDamage | The lowest energy inducing a **SSB** with probability as 1 | 37.5 eV | W. Friedland et.al (2005) |




- Single Strand Break (SSB)
- Double Strand Break (DSB)
- clustered DSB (cDSB)

# Results

## Cell dose

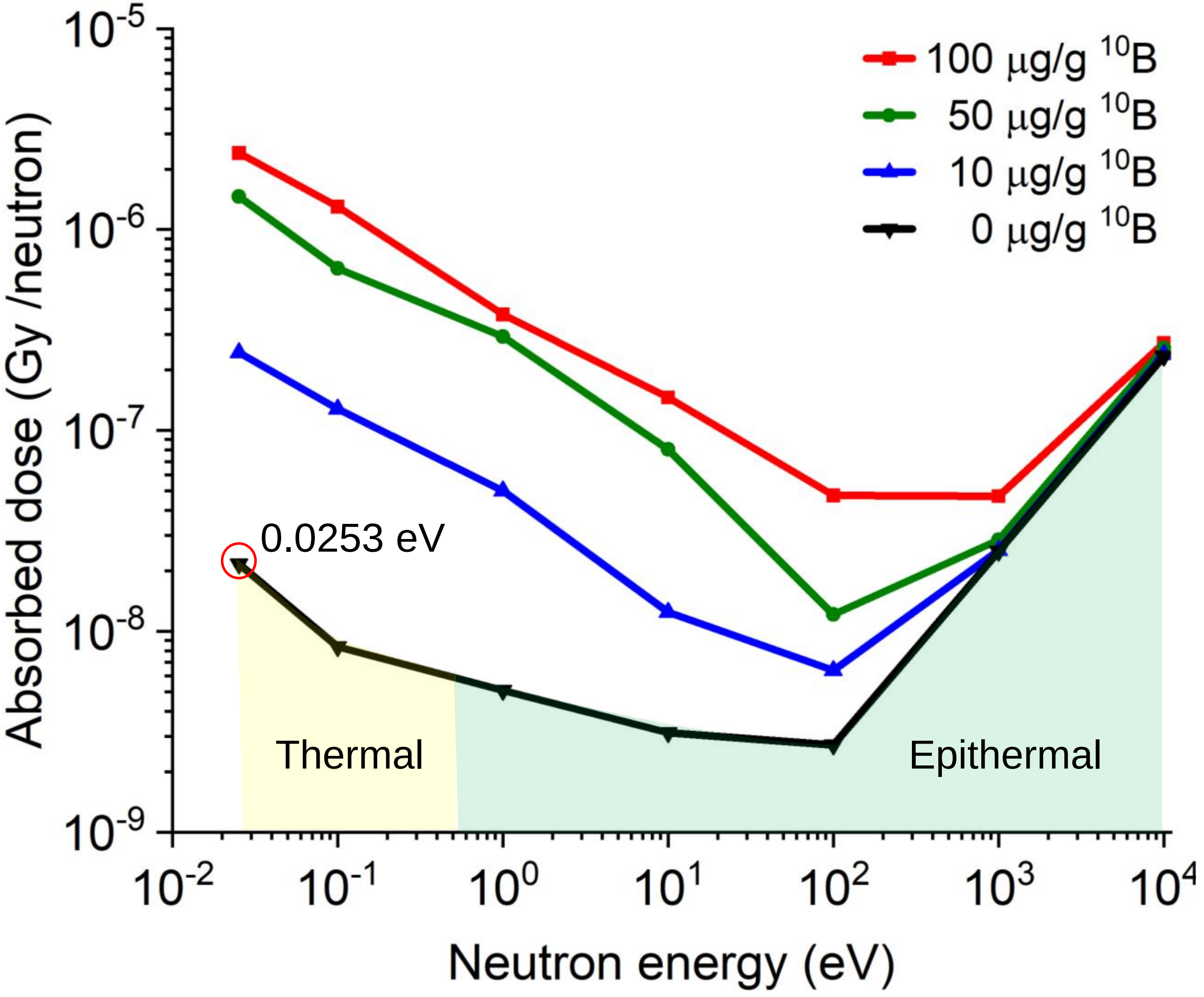



**Figure 2**. BNPs located in the cytoplasm

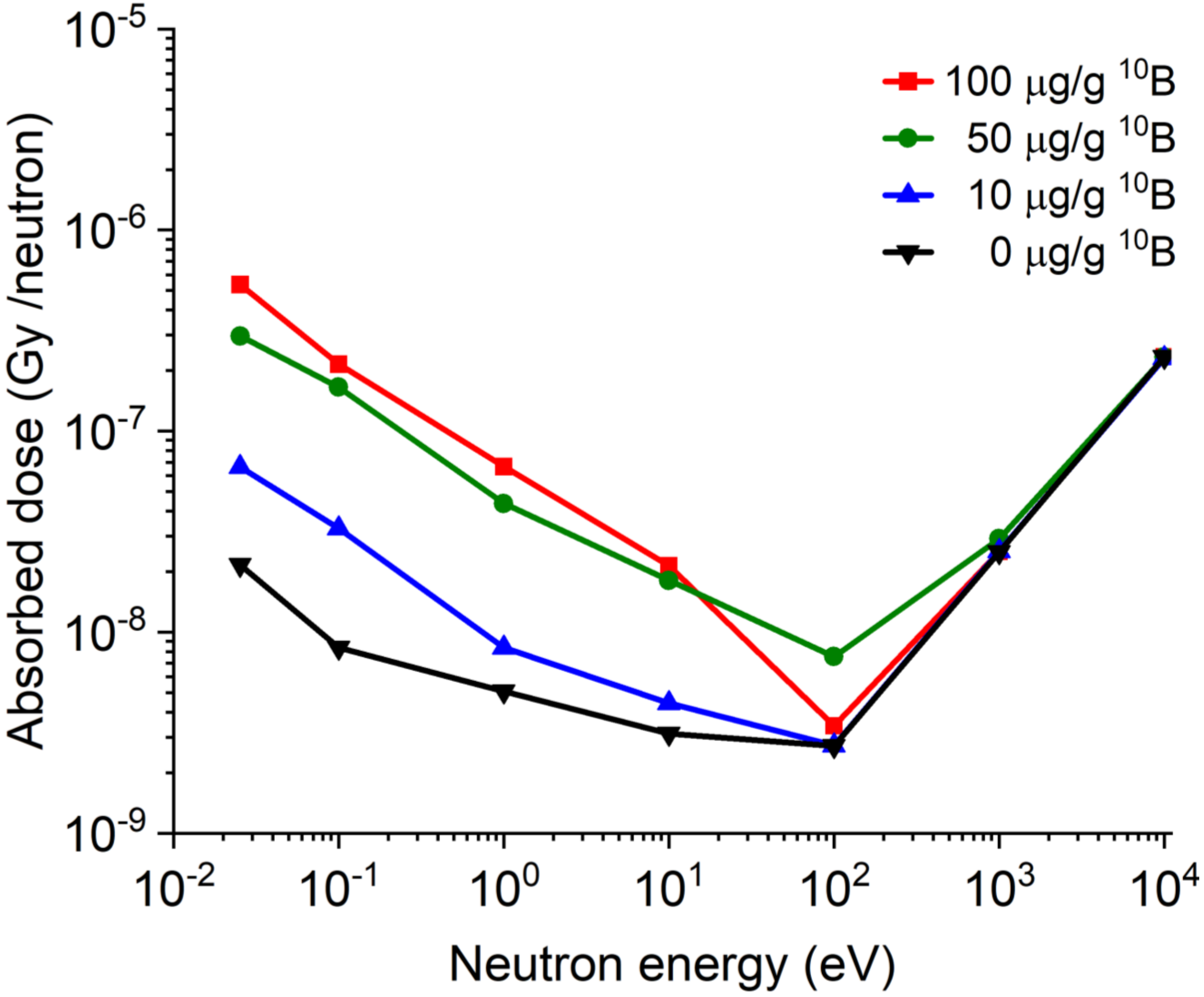



**Figure 3**. BNPs located outside the cell

# Results

## Dose contribution by $^{10}B$

- $^{10}B(n,\alpha)^{7}Li$ boron dose $D_B$,
- $^{1}H(n,n')^{1}H$ neutron dose $D_n$,
- $^{14}N(n,p)^{14}C$ to the called proton dose $D_p$,
- $^{1}H(n,\gamma)^{2}H$ reaction and
  $^{10}B(n,\gamma)^{7}Li$ to the called gamma dose $D_\gamma$

$$D_t = \underbrace{D_n + D_p + D_\gamma}_{\text{Dose when 0 μg/g BNPs}} + \boxed{D_B}$$

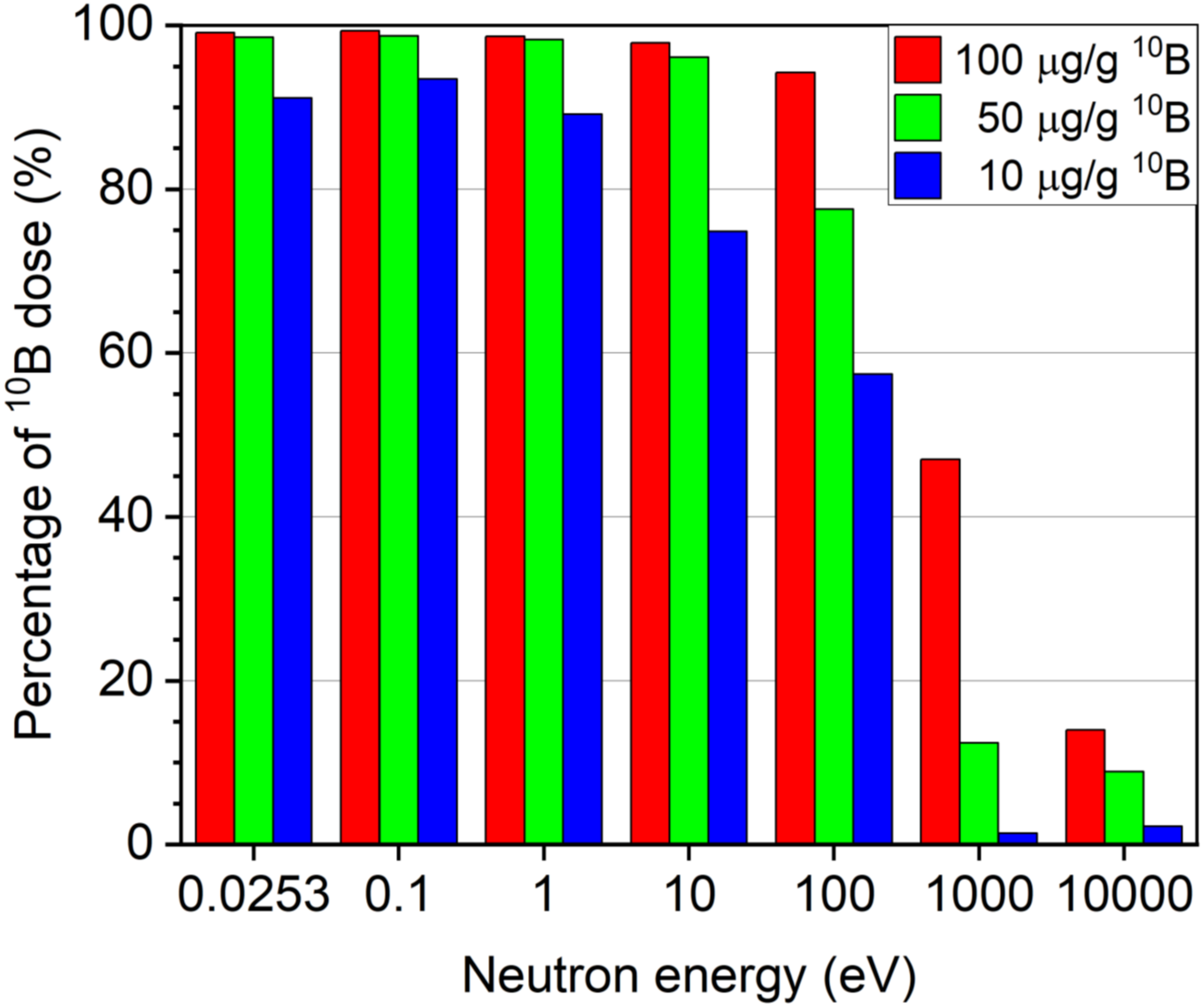



**Figure 4.** BNPs in the cytoplasm

# Results

## DNA damage yield per gray dose and each $10^9$ basepairs

DNA damage depends on the position and concentration of BNPs in the sphere cell

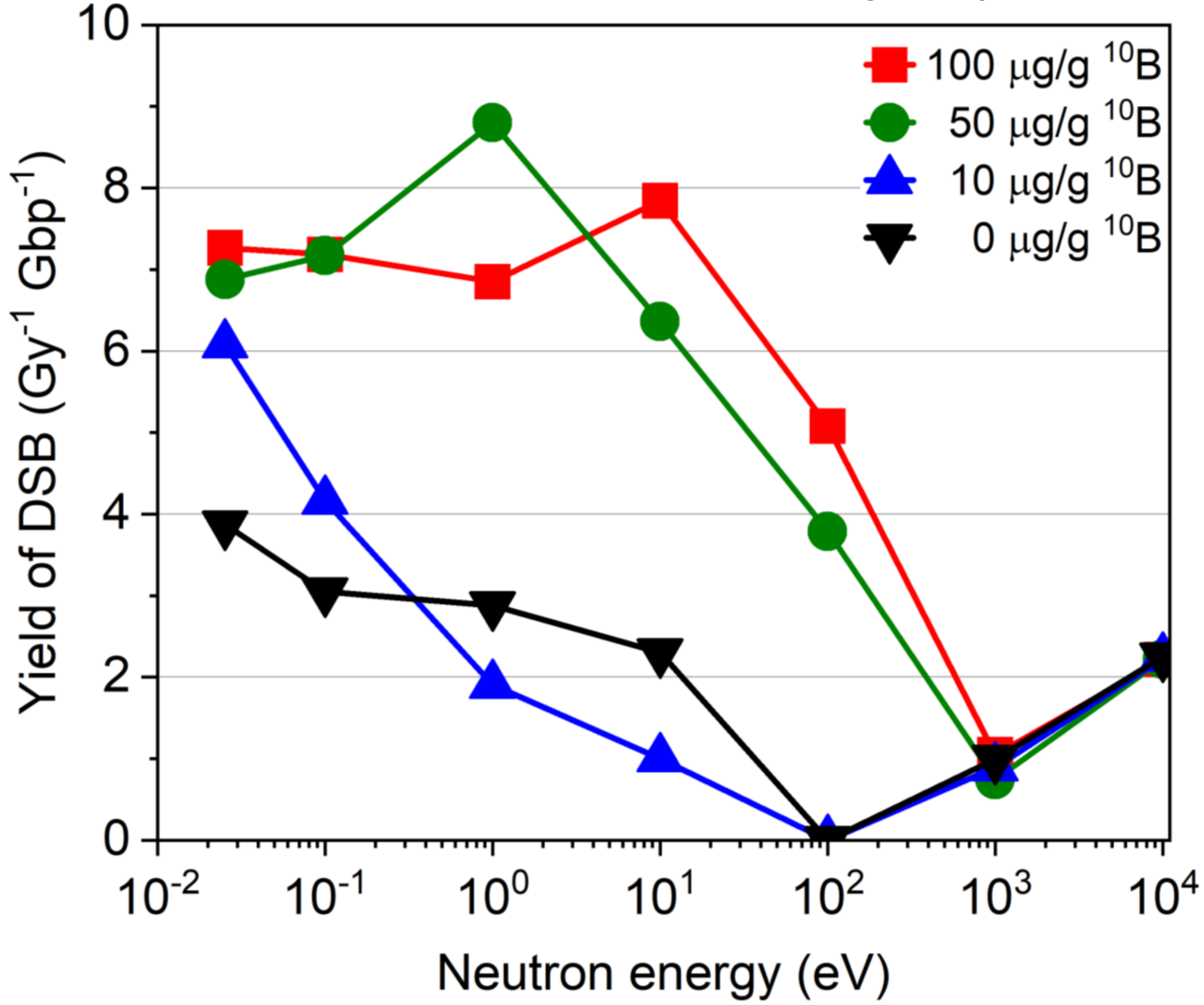



**Figure 5.** BNPs located in the cytoplasm

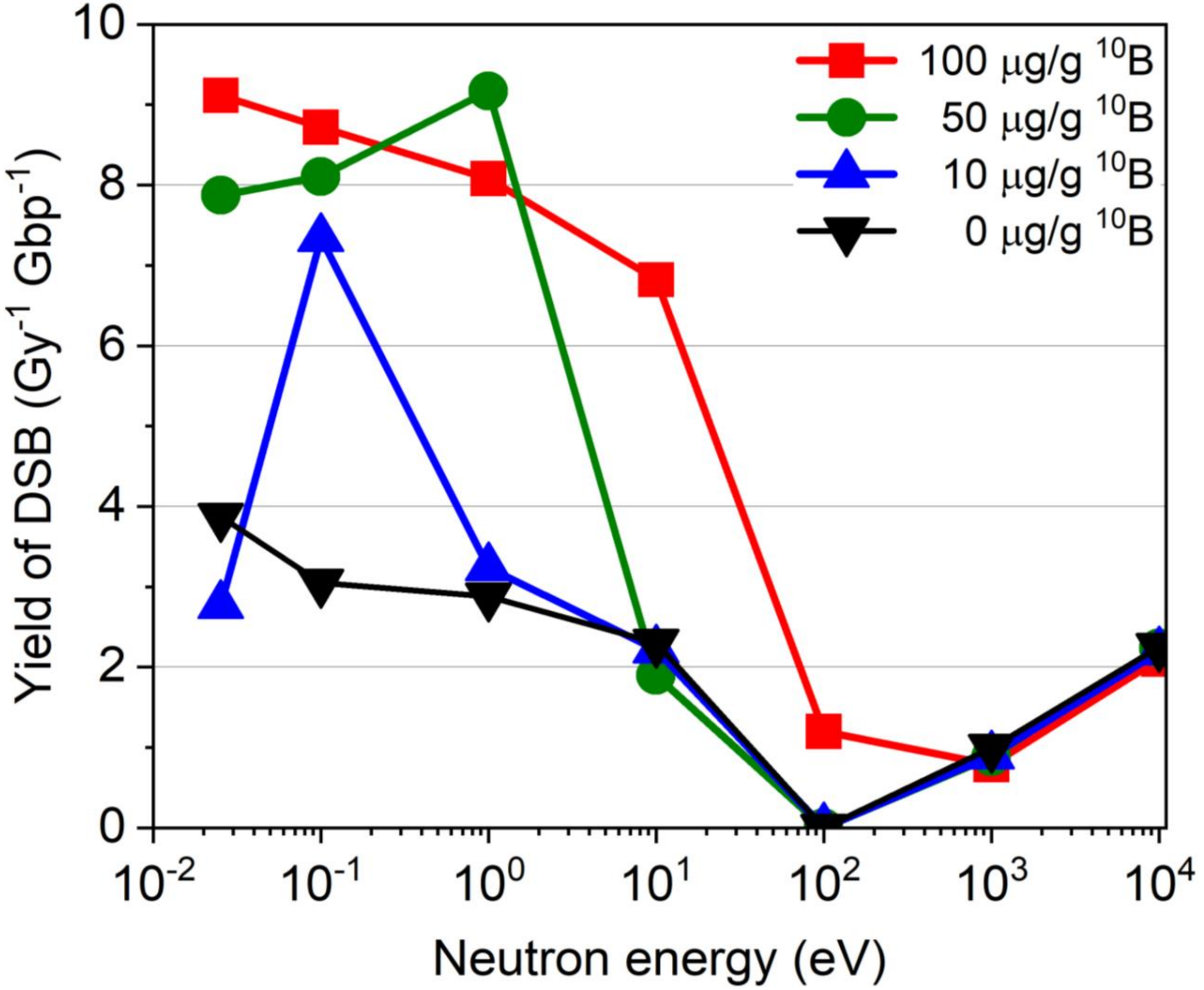
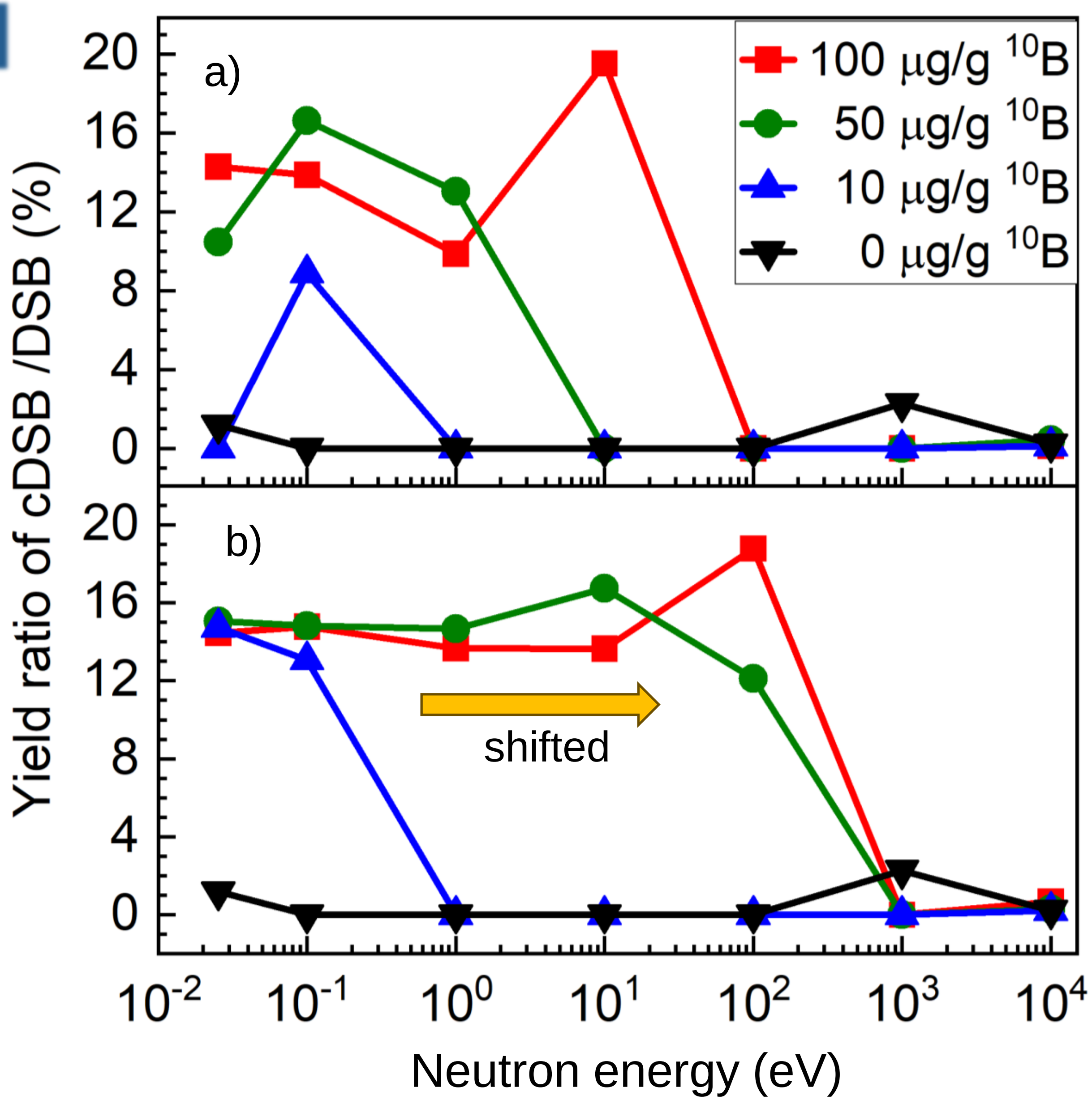



**Figure 6.** BNPs located outside of the cell

# Results

## Percentage of cDSB

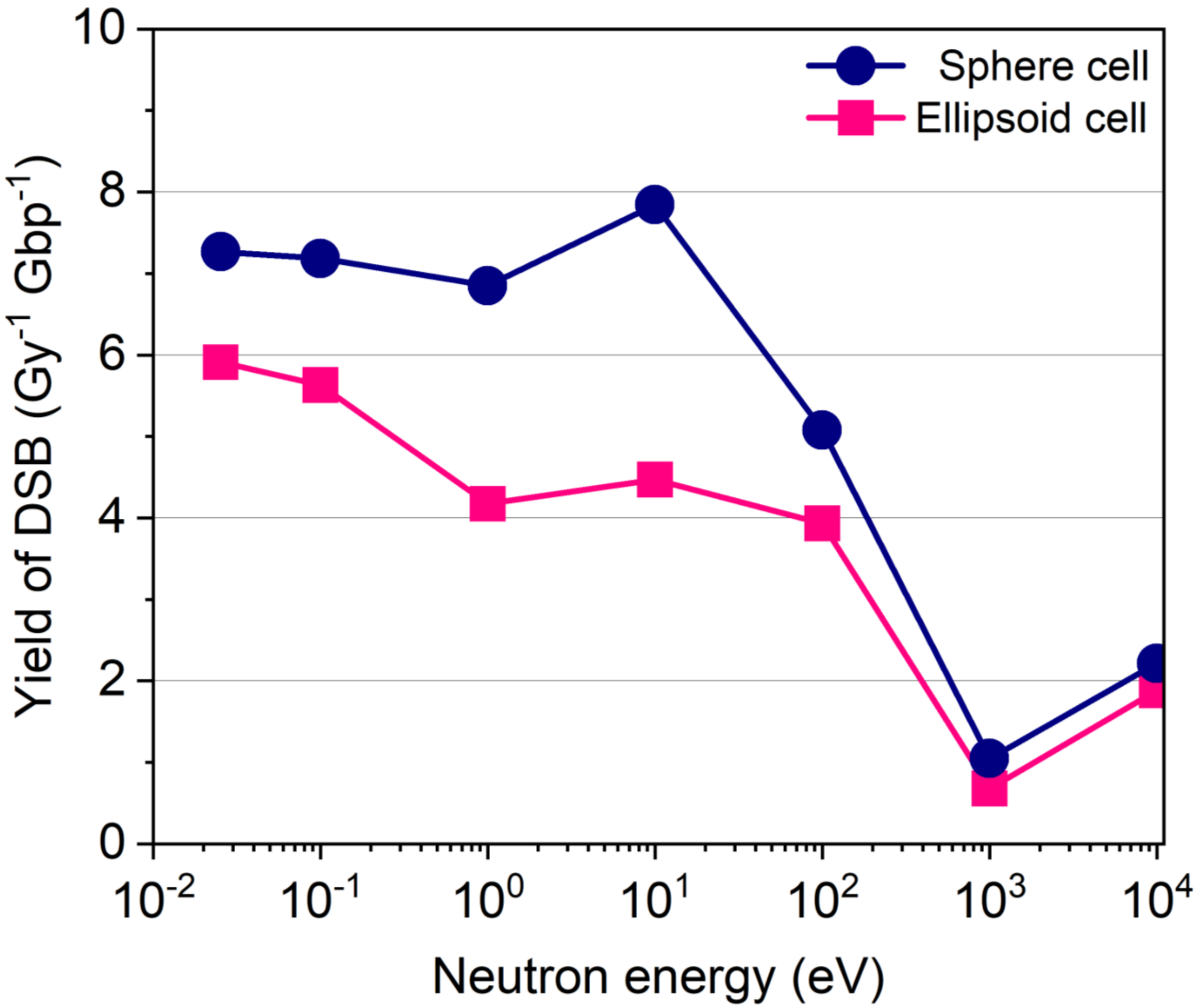



- Characteristics of the particles (LET)
- Traverse range (closer to the cell nucleus)

**Figure 7.** Clustered DSB estimated when BNPs located outside the cell (a) and in the cytoplasm (b) for sphere cell

# Results

## Comparison DNA damage yield in different nuclei geometries




- Geometrical advantage of sphere cell
- The ellipse nucleus size bigger than spherical (DNA contains of density lower at 0.36%)
- The nucleus and cytoplasm of sphere cell wider along incident particles in this case

**Figure 8.** Calculated DSB yield at 100 μg/g $^{10}B$ when BNPs distributed in the cytoplasm

# Conclusion

In this work, we estimated the absorbed dose effectiveness and DNA damages into the cellular volume after nuclear interaction between neutrons and boron nanoparticles.

The highest dose deposition of secondary particles resulting from nuclear reactions between neutrons and boron nanoparticles was corresponded to highest boron concentration. Then we estimated the absorbed boron dose at neutron energy with 100 eV and increased by 99% concentration at 100 μg/g while by 57% percent than 10 μg/g $^{10}B$ in cytoplasm.

Yield of DSB was more effective when BNPs located in cytoplasm. Additionally, DNA damage in the sphere cell with 100 μg/g boron was found more than ellipsoid depending on optimal shape.

# References

[1] www.who.int

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[5] Farr LE, Sweet WH, Robertson JS, Foster CG, Locksley HB, Sutherland DL, Mendelsohn ML, Stickley EE (1954) Neutron capture therapy with boron in the treatment of glioblastoma multiforme. AJR 71: 279–293

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[11] Pruimboom-Brees IM, Brees DJ, Shen AC, Ibebunjo C. Malignant astrocytoma with binucleated granular cells in a Sprague- Dawley rat. Vet Pathol. 2004 May;41(3):287-90. doi: 10.1354/vp.41-3-287. PMID: 15133182.

# Thank you for your attention