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INFN Istituto Nazionale di Fisica Nucleare

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INSTITUT DE RADIOPROTECTION ET DE SÛRETÉ NUCLÉAIRE

HIGH LET SPECTRAL AND MICRODOSIMETRIC CHARACTERIZATION OF SECONDARIES IN THE TREATMENT OF ALZHEIMER'S DISEASE WITH NEUTRON CAPTURE THERAPY

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MEMBRE DE ETSON

FRAMEWORK

Alzheimer disease (AD)
neurodegenerative dementia
(affecting the central nervous
system & leading to cell death)

55 million affected today (2019 evaluation)
up to 139 million by 2050[1]

No cure to this day …

BUT : eradication of amyloids (Aβ aggregates) associated with reduction of cognitive & functional decline

NECTAR = **NE**utron **C**apture-enhanced **T**reatment of neurotoxic **A**myloid agg**R**egates
https://fisica.unipv.it/NECTAR-EU-FETOpen

Curative treatment based on neutron capture therapy targeting AD Aβ aggregates

(1) World Health Organization figures from World Alzheimer report 2022

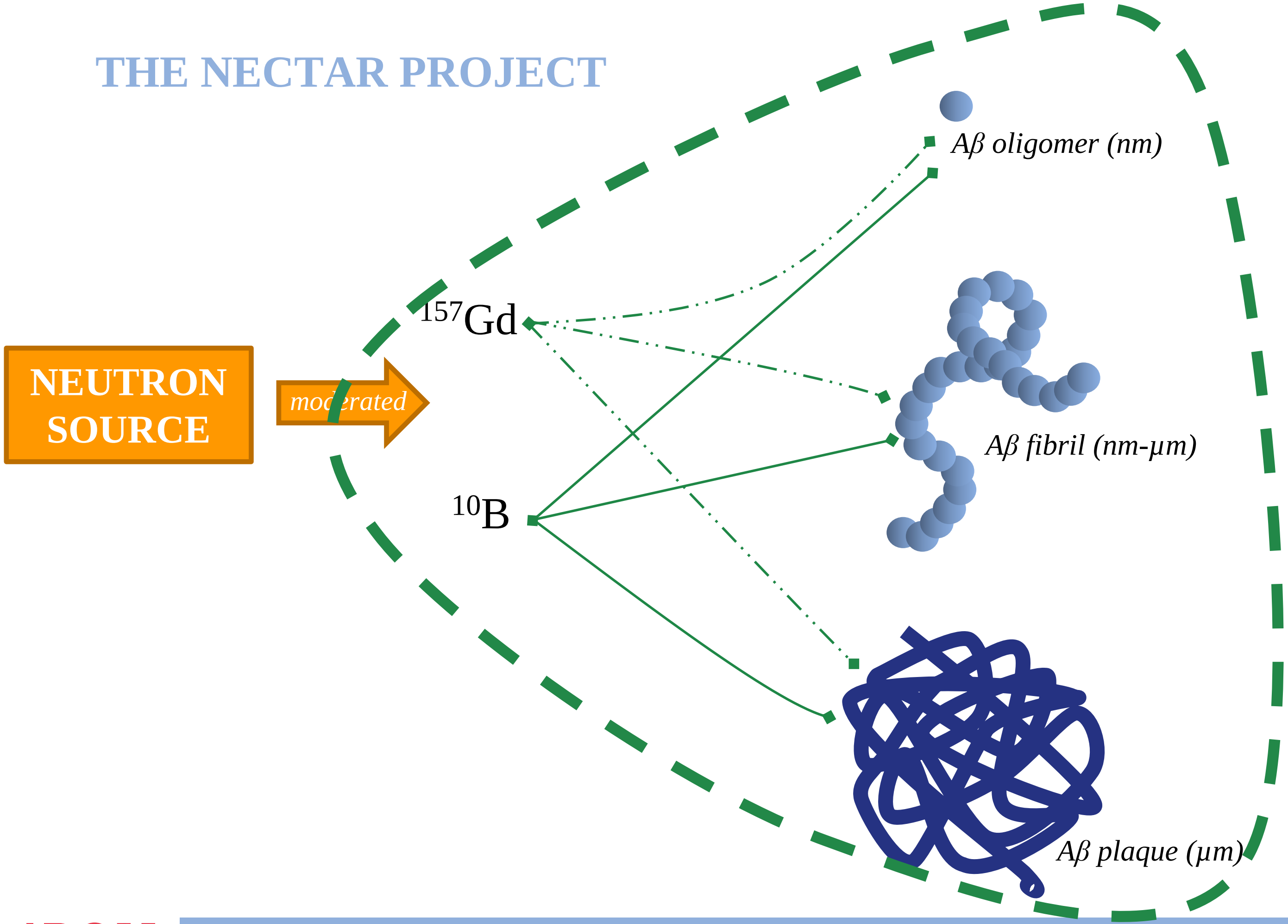
THE NECTAR PROJECT

^{157}Gd

NEUTRON SOURCE → *moderated*

^{10}B

THE NECTAR PROJECT



Gd/B carrier : selective binding on aggregates

THE NECTAR PROJECT

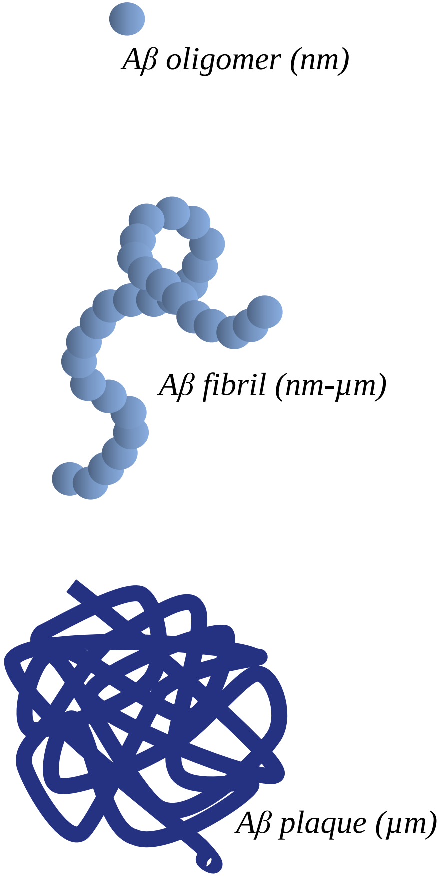
^{157}Gd

NEUTRON SOURCE → *moderated*

^{10}B

$^{157}Gd + n \rightarrow$
- *Auger electron + X rays*
- *Internal conversion electron*
- $^{158}Gd + \gamma + 7.9\ MeV$

$$^{10}B + n_{th} \rightarrow [^{11}B*] \begin{cases} \xrightarrow{6\%} {}^{4}He\,(1.78MeV) + {}^{7}Li\,(1.01MeV) \\ \xrightarrow{94\%} {}^{4}He\,(1.47MeV) + {}^{7}Li\,(0.84MeV) + \gamma(480keV) \end{cases}$$



THE NECTAR PROJECT

NEUTRON SOURCE → *moderated* → ^{157}Gd, ^{10}B

High LET & low range

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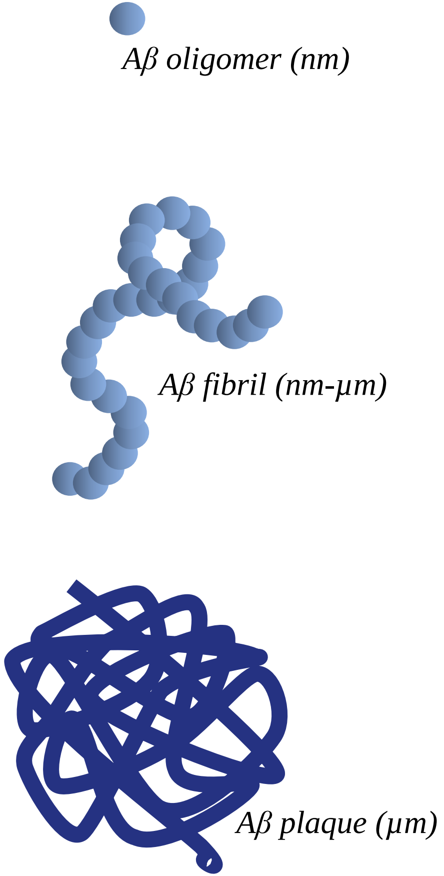

THE NECTAR PROJECT

NEUTRON SOURCE → *moderated*

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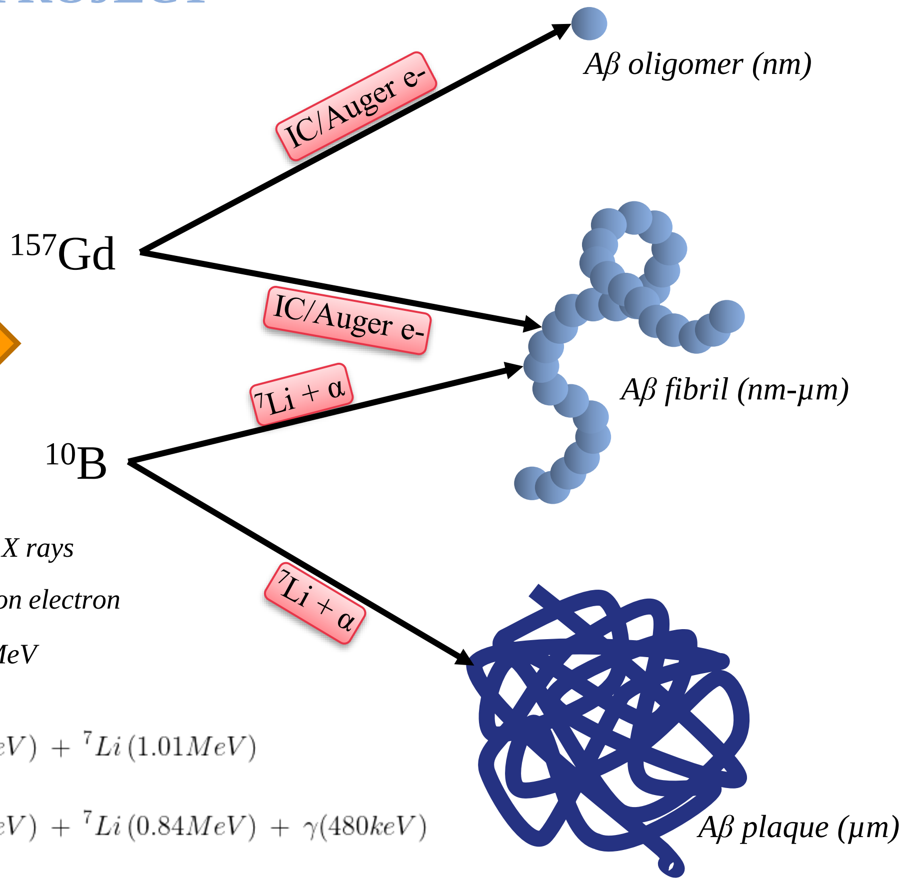

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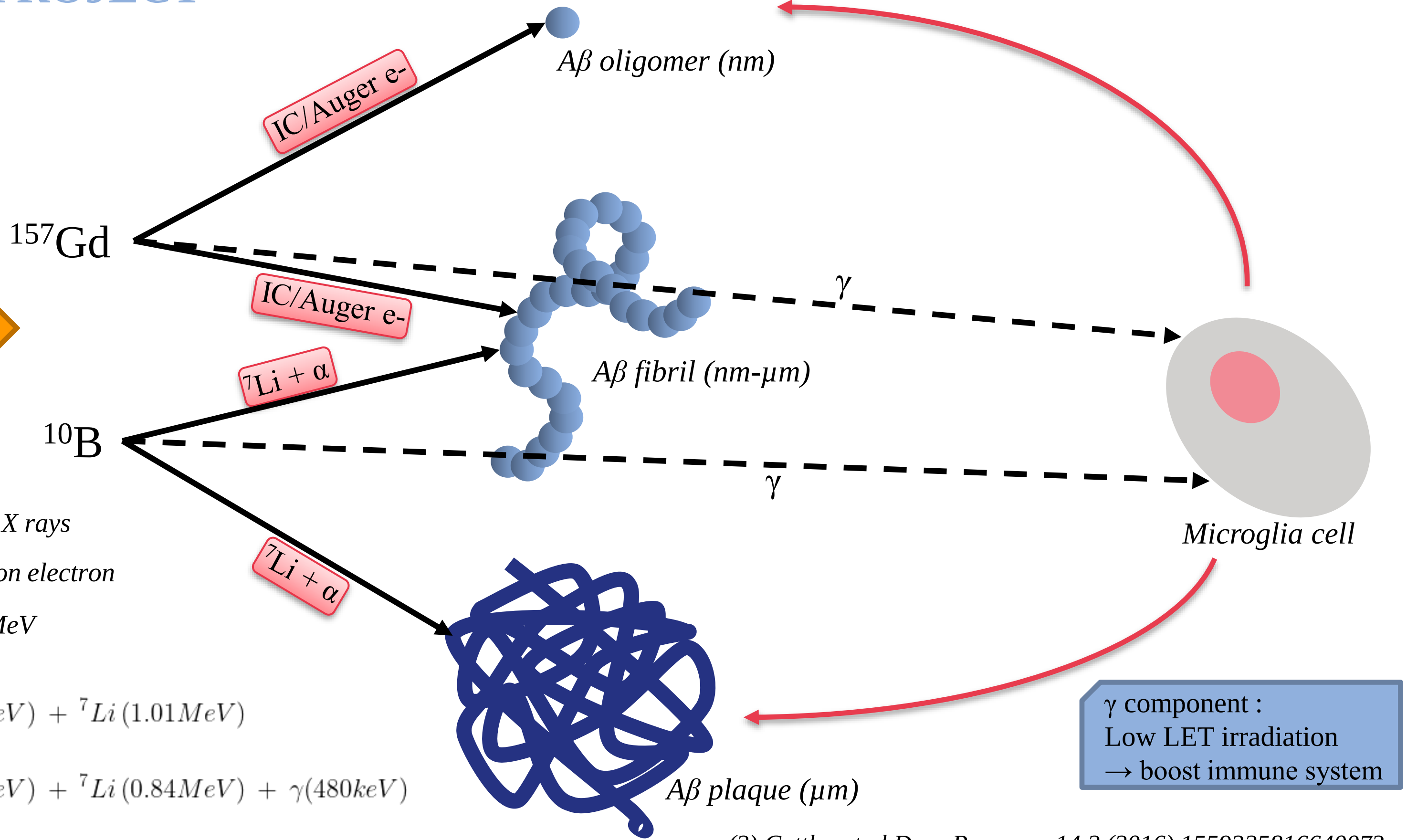
High LET & low range



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(2) Cuttler et al Dose Response 14.2 (2016) 1559325816640073.

THE NECTAR PROJECT

Main goals :

- **Synthetize** a Gd/B enriched molecule able to bind selectively with Aβ aggregates inside the brain
- In vitro **depolymerization** of the Aβ folded structures (from oligomers to plaque) with high LET particles irradiation
- **micro- & nano-dosimetric** calculations & measurements to understand the depolymerization process
- In vitro & in vivo **irradiation of AD biological models** to obtain a proof of concept for the developed Gd/B carrier
- Identifying **dose limits** (threshold & rate) to define the frame of a treatment plan

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MONTE CARLO MODELLING IN NECTAR

Main Goal : modelling high LET secondaries effects

- Fully characterize the production of the secondaries
- Determine the dosimetric impact
  - Secondaries characterization (specific energy, lineal energy)
  - Energy deposit at nm scale
- Consider various experimental condition (boron concentration, target size, neutron source…) → to validate the simulation approach & to perform the correlation with biological effects on the target

GEANT4 for neutrons : High precision package with thermal scattering process

GEANT4 A SIMULATION TOOLKIT

GEANT4-DNA A SIMULATION TOOLKIT

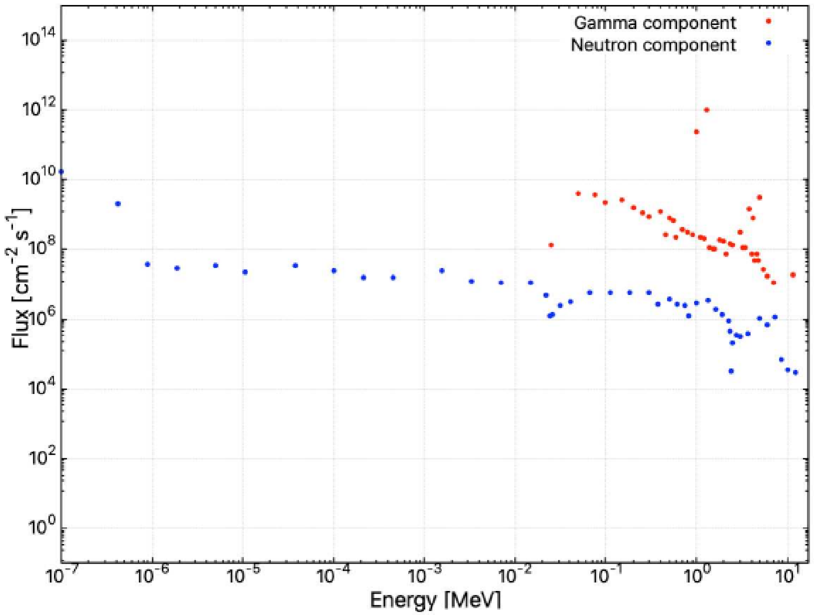
FIRST SIMPLIFIED SIMULATION SET UP

- Source :
  Neutron flux of the Pavia TRIGA Mark II research reactor

- Target : *plaque aggregate*
  100 µm radius sphere filled with water (inside water world)

- Boron concentration :
  100 ppm (^{10}B)

- Characteristic quantity :
  energy deposit per neutron source & unit mass inside the target

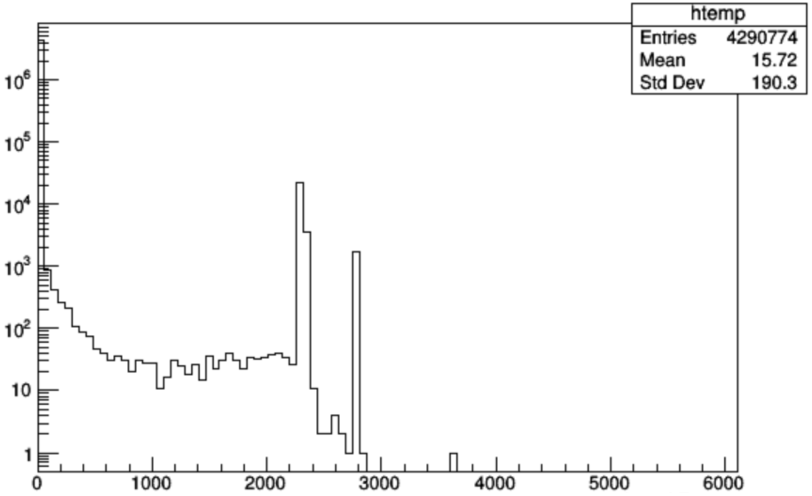


From : V. Pascali - Monte Carlo simulations ranging from microscopic up to macroscopic level for the irradiation of protein aggregates exploiting neutron capture reactions - 2021

FROM ENERGY DEPOSIT TO SPECIFIC ENERGY [z = ε (energy deposit) / m (target mass)]

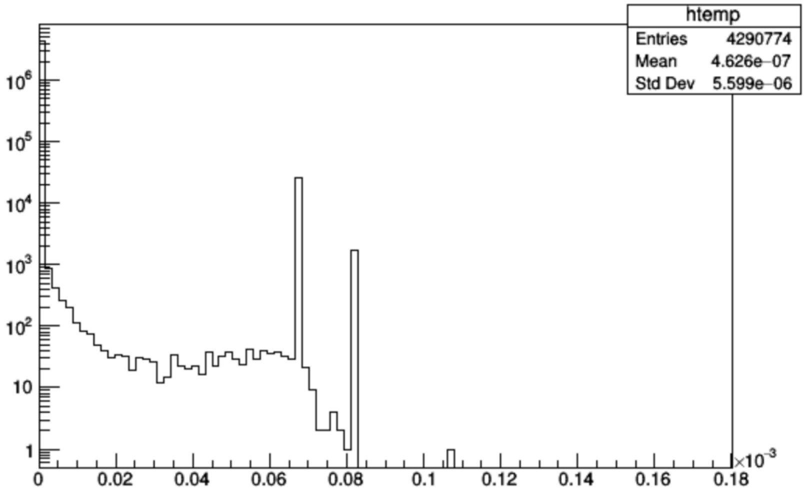
ENERGY DEPOSIT (keV)

Per neutron source



SPECIFIC ENERGY (Gy)

Per neutron source



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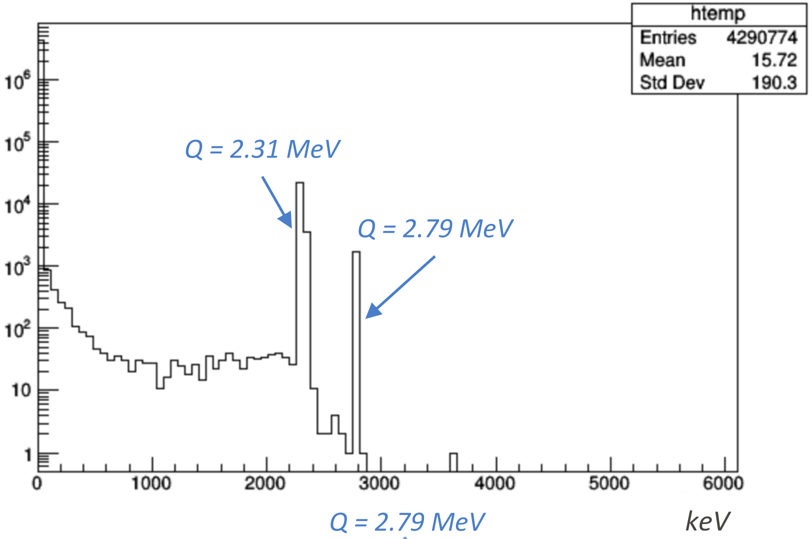
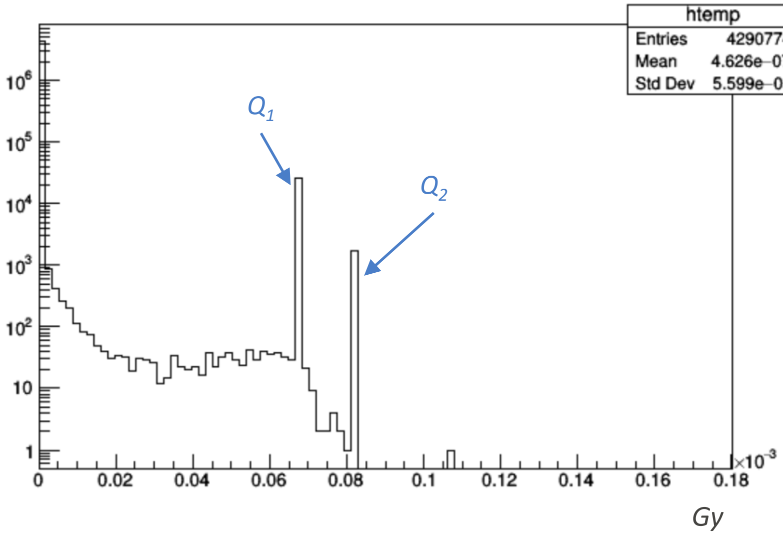


SPECIFIC ENERGY (Gy)

Per neutron source



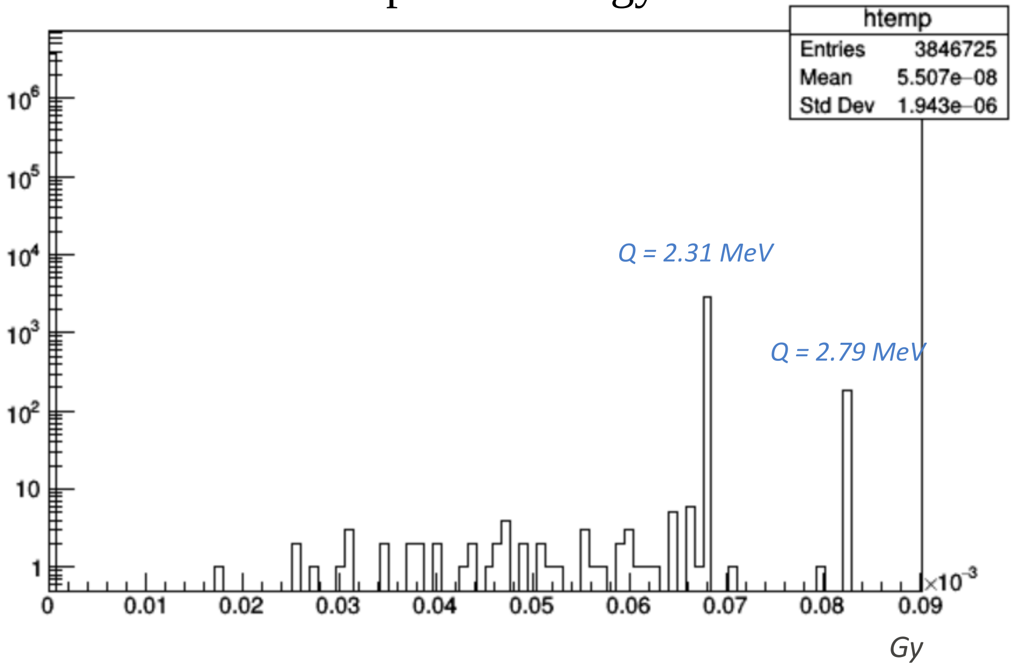
$$^{10}B + n_{th} \rightarrow [^{11}B*] \begin{cases} \xrightarrow{6\%} \underbrace{^{4}He\,(1.78MeV) + {}^{7}Li\,(1.01MeV)}_{Q\,=\,2.79\ MeV} \\ \xrightarrow{94\%} \underbrace{^{4}He\,(1.47MeV) + {}^{7}Li\,(0.84MeV)}_{Q\,=\,2.31\ MeV} + \gamma(480keV) \end{cases}$$

- Two peaks corresponding to a high energy deposit from $^{10}B(n,\alpha)^{7}Li$

MONOENERGETIC BEAMS – 10 eV NEUTRONS

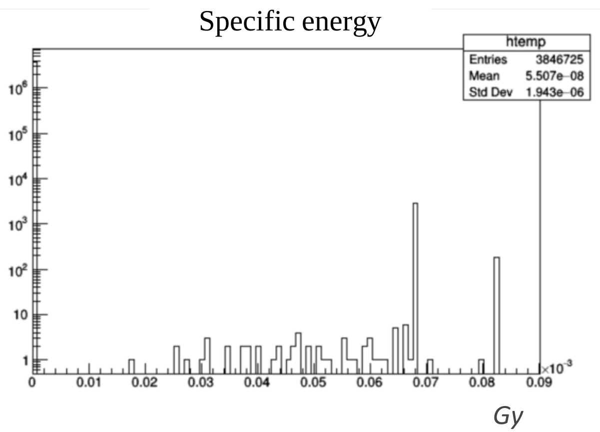
- Neutron source @ 10 eV
- Population below Q = 2.31MeV peak : α particles & ^{7}Li that are exiting the target
- Very low Gy bin : neutron elastic scattering on hydrogen or oxygen in water

Specific energy

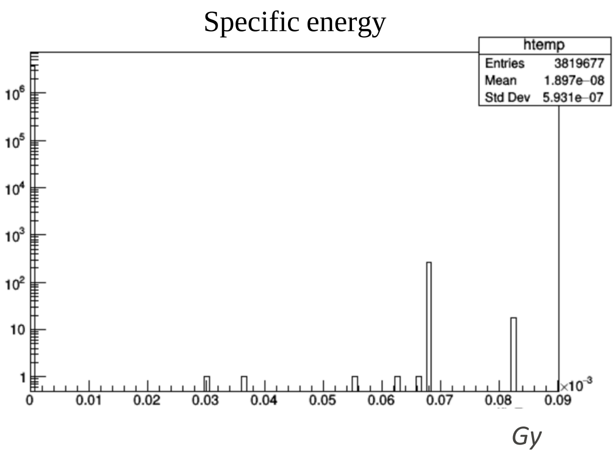


SPECIFIC ENERGY AS FUNCTION OF THE INITIAL NEUTRON ENERGY

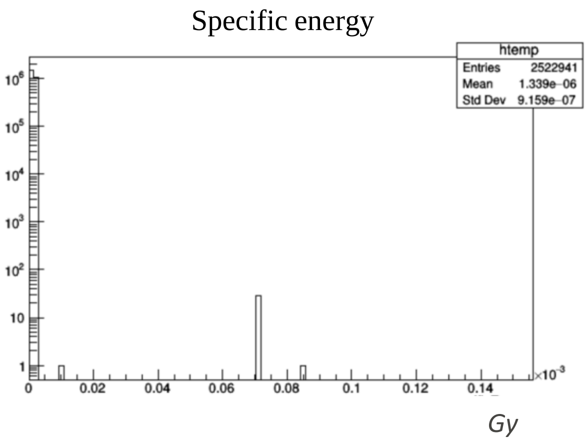
10 eV



1 keV



100 keV



- Neutron energy ↗ → number of events where all the energy available is not deposit in the target ↘

- Neutron capture on ^{10}B is located deeper in the target → α particles & ^{7}Li stay in the volume

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PERSPECTIVES

On going work and following steps

Secondaries discrimination & associated effects on microdosimetric values

Target specification, different size models & boron concentration

Nanodosimetry calculations with GEANT4-DNA ↔ depolymerization process

In parallel : work/discussion with experimentalist on the project to obtain validated & possible experimental conditions

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THANK YOU FOR YOUR ATTENTION

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