Faculté de physique et ingénierie
Université de Strasbourg

master PSA Physique Subatomique Astroparticules

Mesure de l'énergie du faisceau de la plateforme PRECy ; Étude des effets du serum d'ours hibernant sur la radiosensibilité des cellules humaines.

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Stage de master 2, sous la supervision de Marc Rousseau

Université de Strasbourg

24/06/2021

IPHC Institut Pluridisciplinaire Hubert CURIEN STRASBOURG

IRHIM

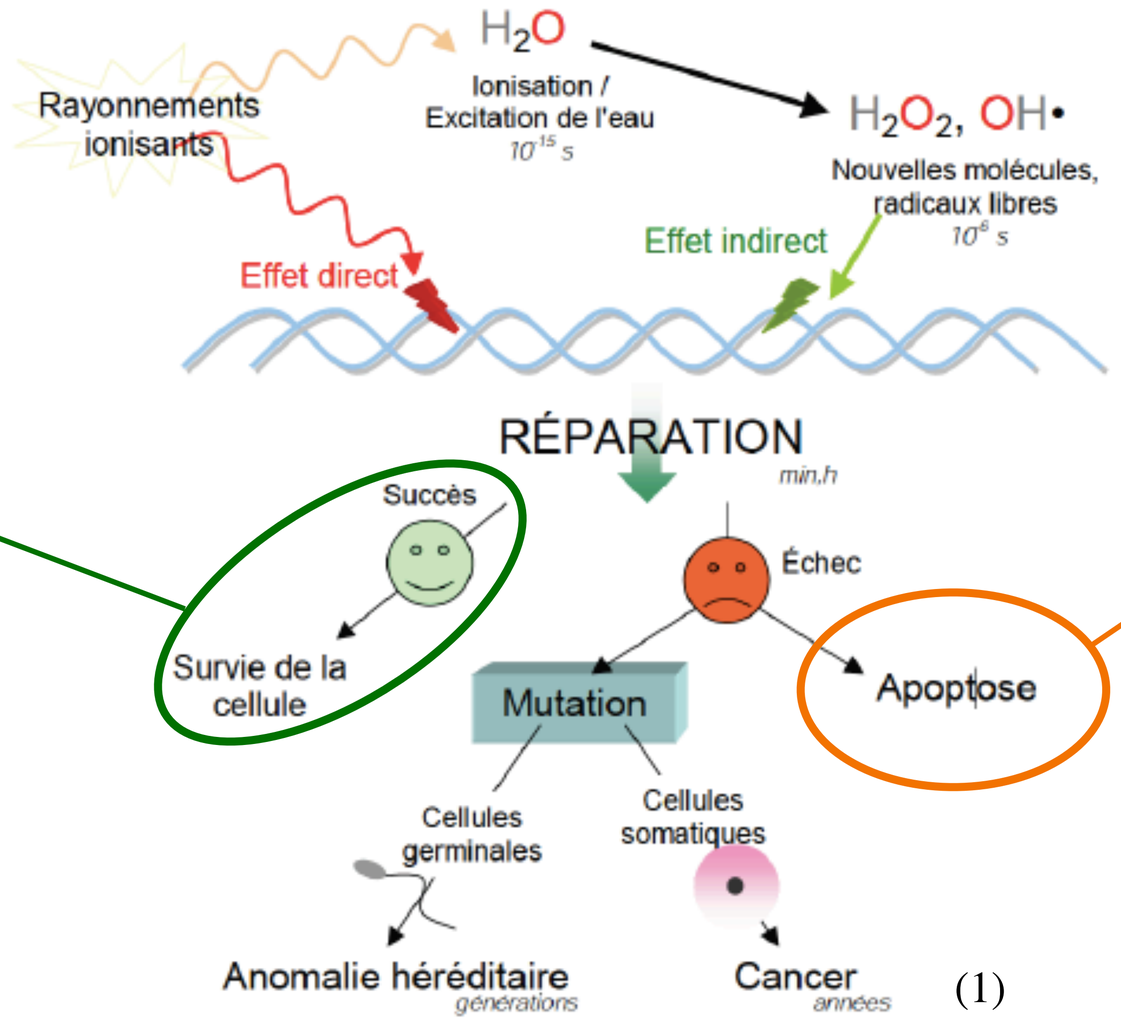
Overview

I - Context: ionizing radiations and protontherapy

II - Measure of the proton-beam energy at PRECy

III - Investigation of the radioprotective effects of bear serum

I - Context: Ionizing Radiations



Radioprotection

Cancer treatment

→ protect healthy cells

Cancer treatment

→ kill tumour cells

(1)

(1) : *Physique nucléaire appliquée à la biologie ou radiobiologie*, http://mon.ftp.a.moi.chez-alice.fr/Ecole/DEUG_SV2/Radiobio/Radio1.pdf

I - Context: Physical Quantities

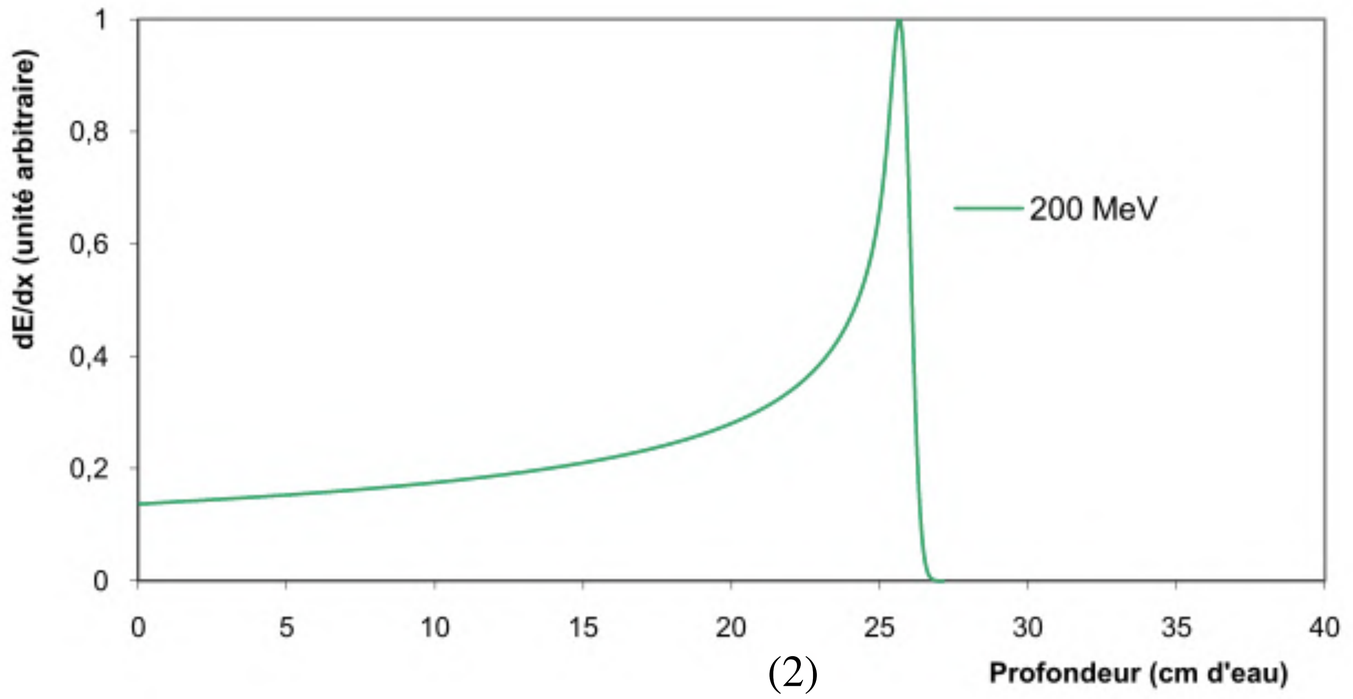
Dose

$$D = \frac{dE}{dm} \ [J/\mathrm{kg}]$$

Stopping Power

$$Sp(E) = -\frac{dE}{dx} \ [\mathrm{MeV/cm}]$$

$$D \propto Sp(E) \propto \frac{1}{E}$$



(2)

(2) : Y. Karakaya, *Étude des performances d'un système d'imageur proton dans le cadre de l'approche faisceau à faisceau*, PhD Thesis, Université de Strasbourg (2018)

Overview

I - Context: cancer, ionizing radiations and protontherapy

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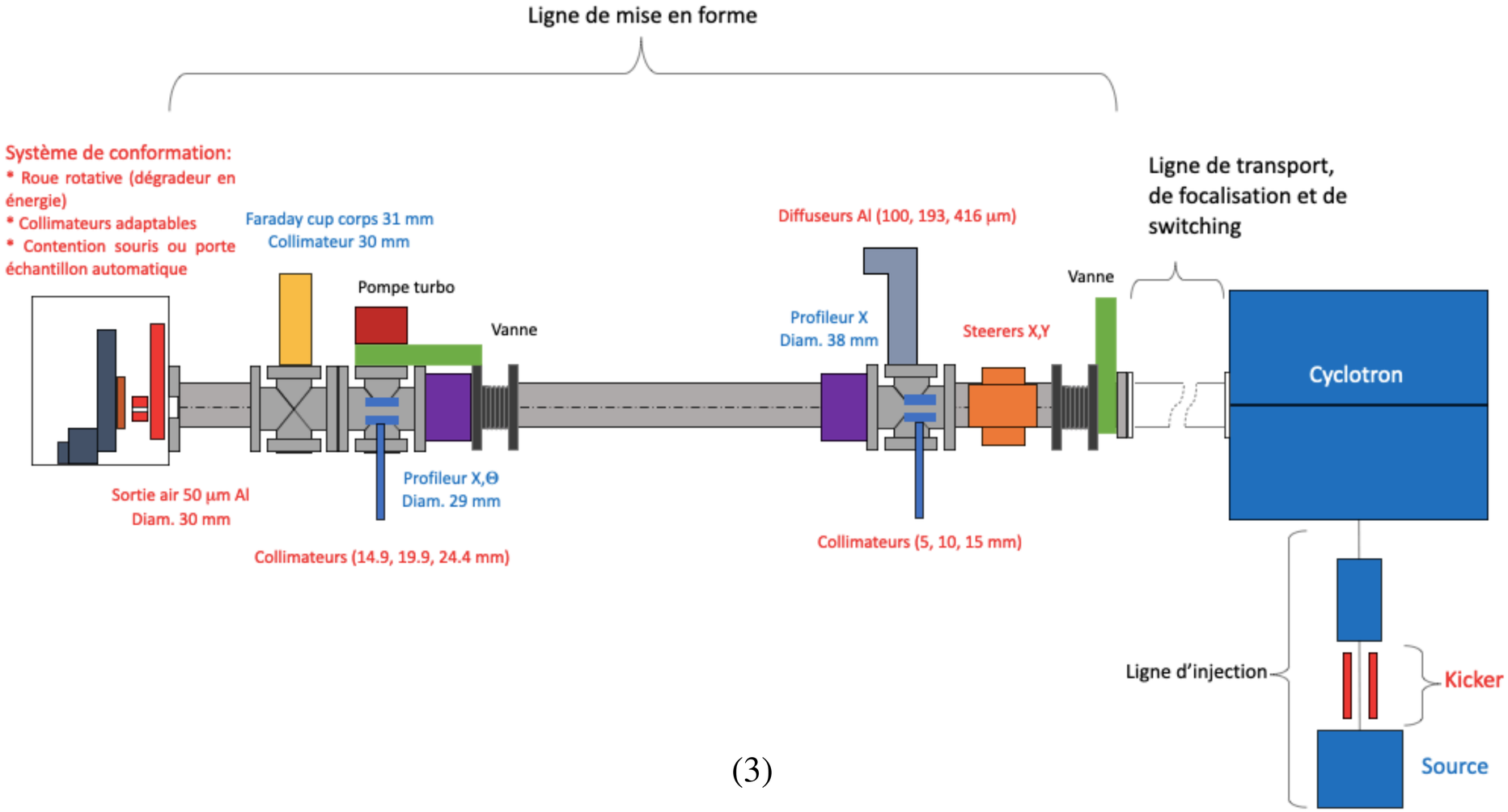
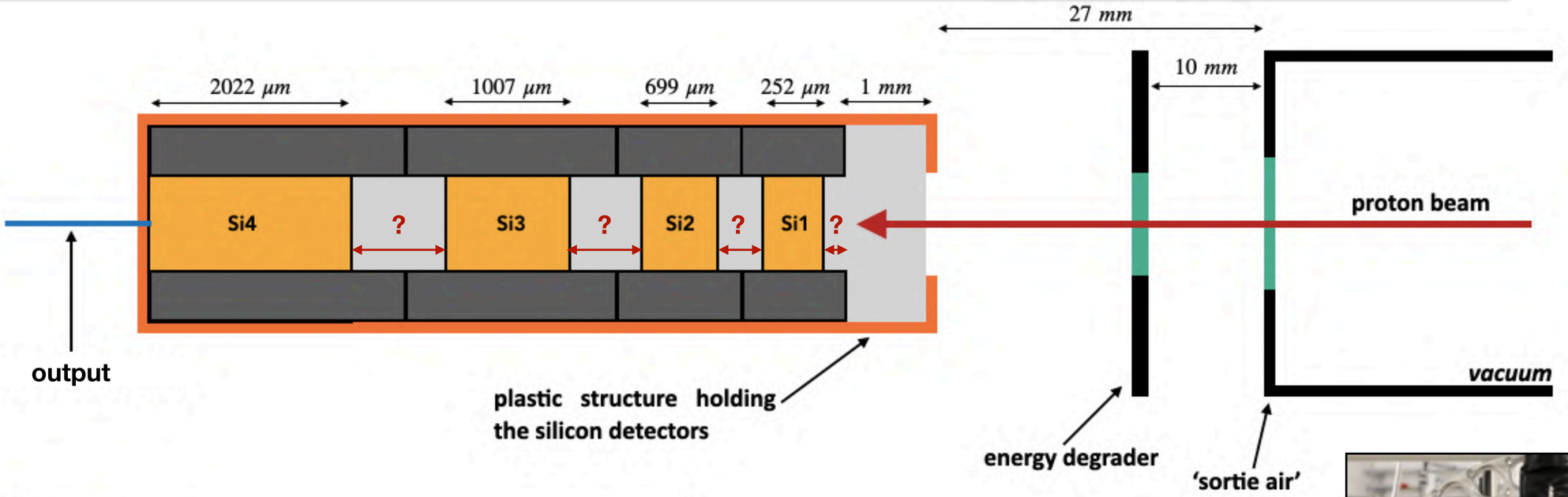
II - PRECy Irradiation Line



(3)

(3) : P. J. Jupille, *Validation dosimétriques des lignes d'irradiation de la plateforme PRECy*, Université de Strasbourg (2020)

II - Experimental Setup



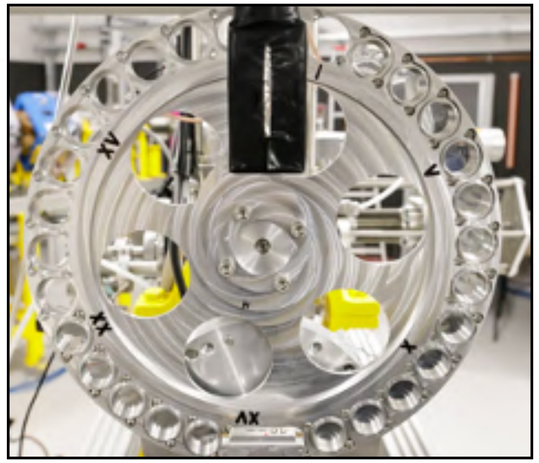
Legend :

: silicon thicknesses in the detectors

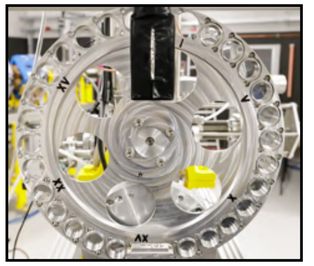
: air within the detection structure

: aluminium foils

Si1 : number of the detector



II - How to measure the energy ?



Calibration with tri-alpha source → not sufficient !

Measurements with the energy degrader

FASTER[4] Data Acquisition system

→ **set of data (in channels)**

Python algorithm, input E_0

Computes iteratively the energy loss in the detectors

→ **set of energies (simulated)**

Setup simulation

→ measure of detectors structure

Pre-calibration with α-source

→ **reference points**

Plot channels VS energies

If **linear calibration relation** ⇒ right E_0 **found** in simulation

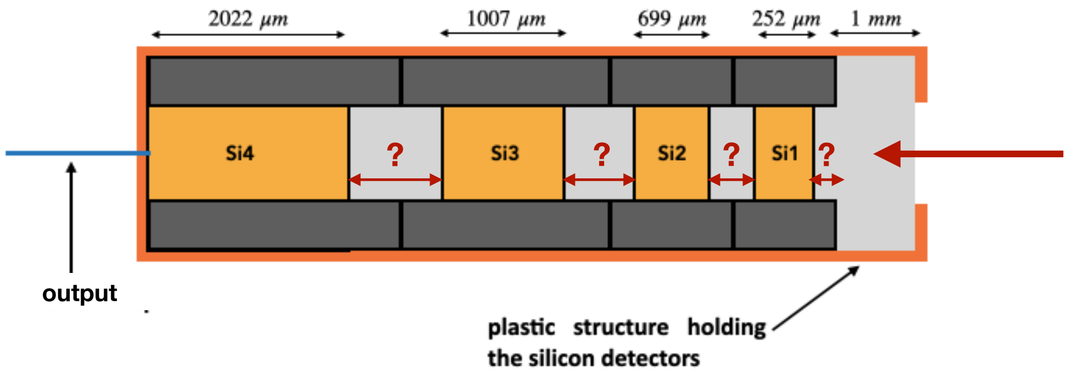
(4) : *Fast Acquisition System for nuclEar Research*, LPC (Caen), website : http://faster.in2p3.fr

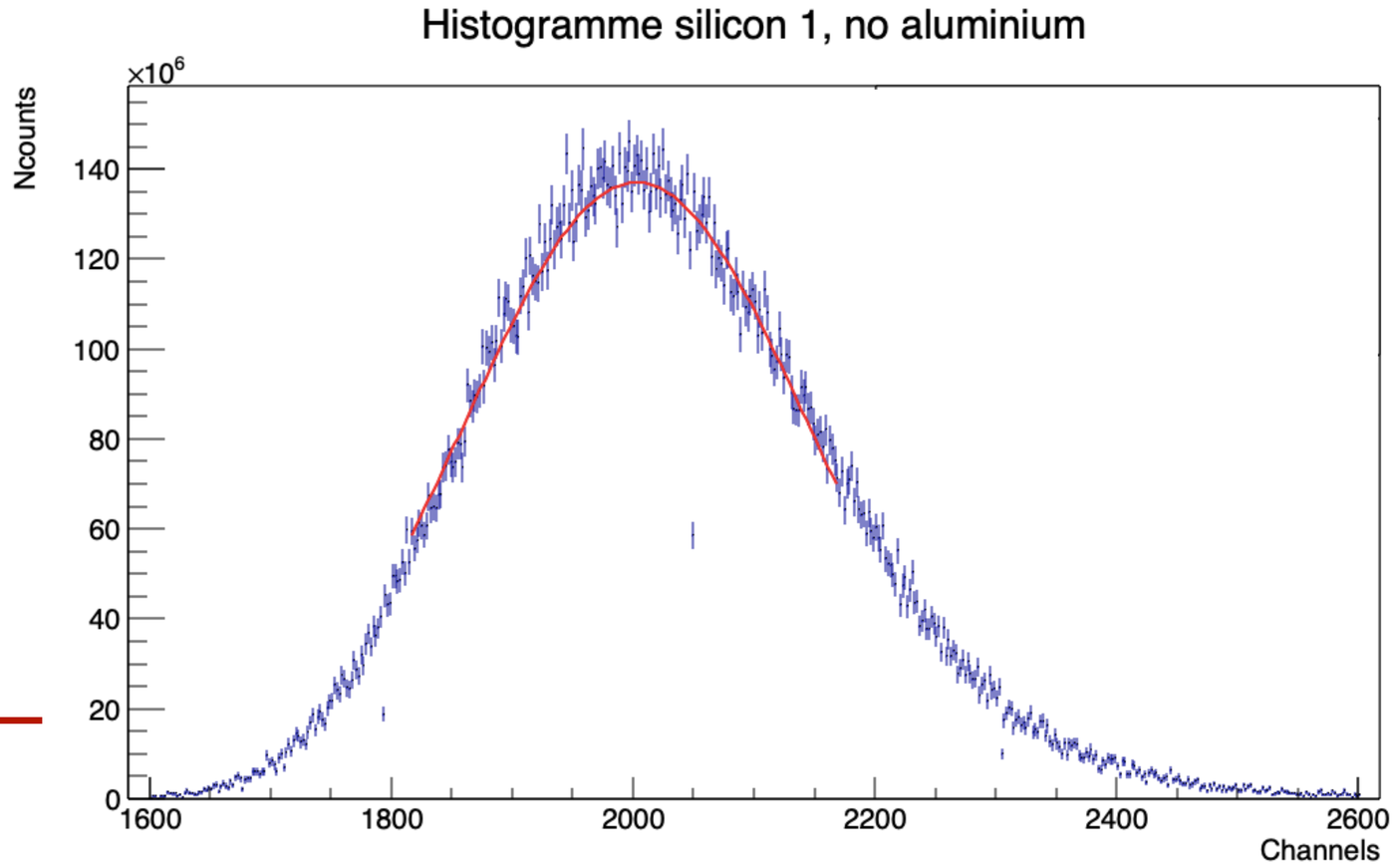
II - Measurements

- Data Acquisition System : FASTER
- Energy degrader → change energy
- 2 types of points:

  E- points (always in **Si4**)

  dE- points (always in **Si1**)





II - Simulation

- Python programme

  → *Input:* E_0 ('sortie air')

  → *For loop:* aluminum thicknesses

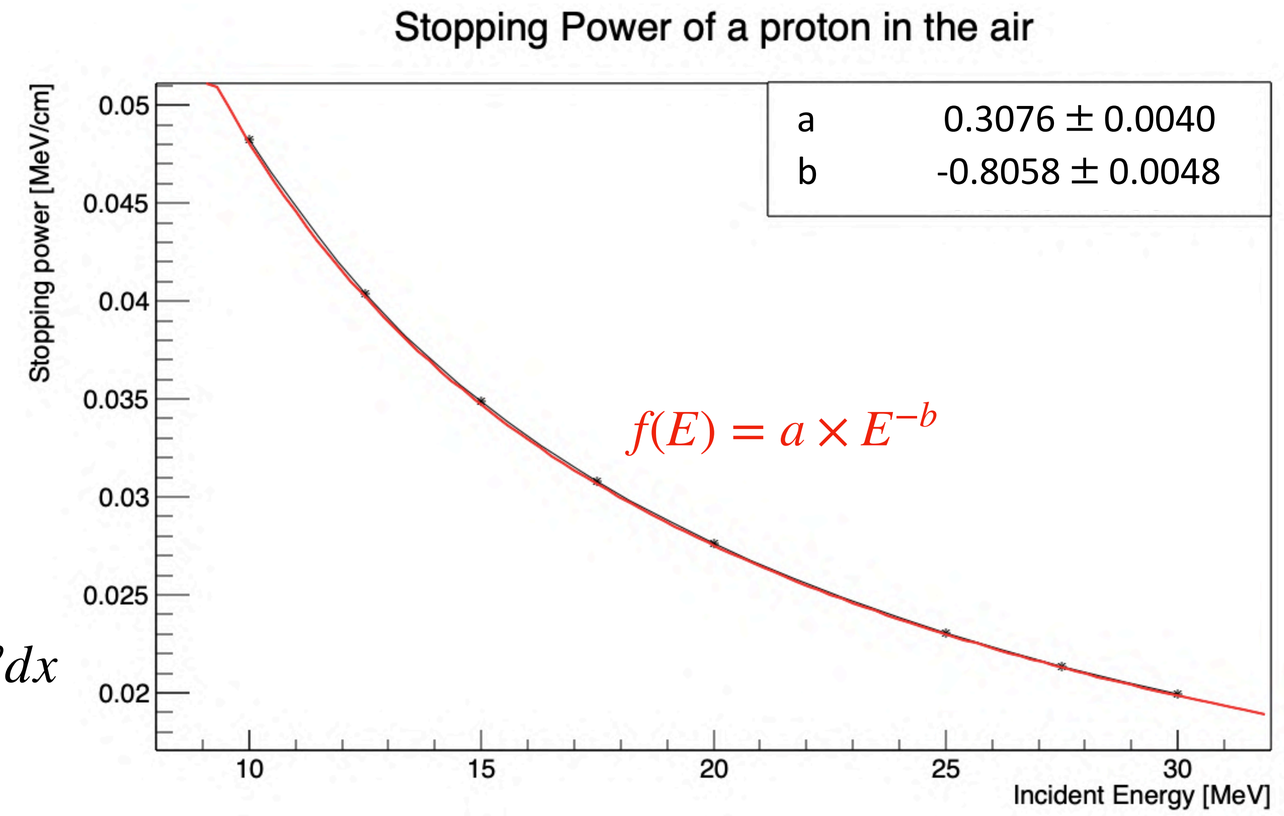
  Energy loss in structure

  $$dE_1 \;\; dE_2 \;\; dE_3 \;\; E_4$$

  Computed with stopping power[5]

  $$\Delta E = \int_0^{x_{Si}} \frac{dE}{dx} dx = \int_0^{x_{Si}} f(E)dx = \int_0^{x_{Si}} aE^{-b}dx$$

  → *End condition:* residual energy = 0

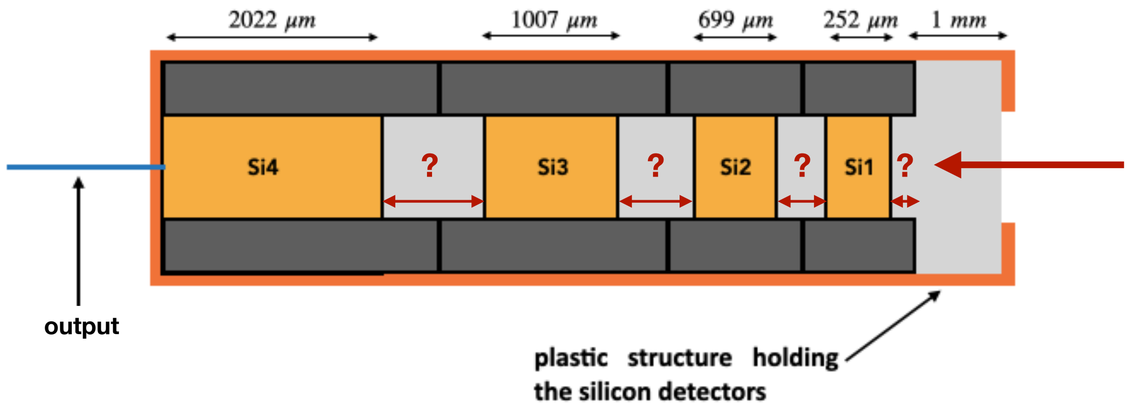


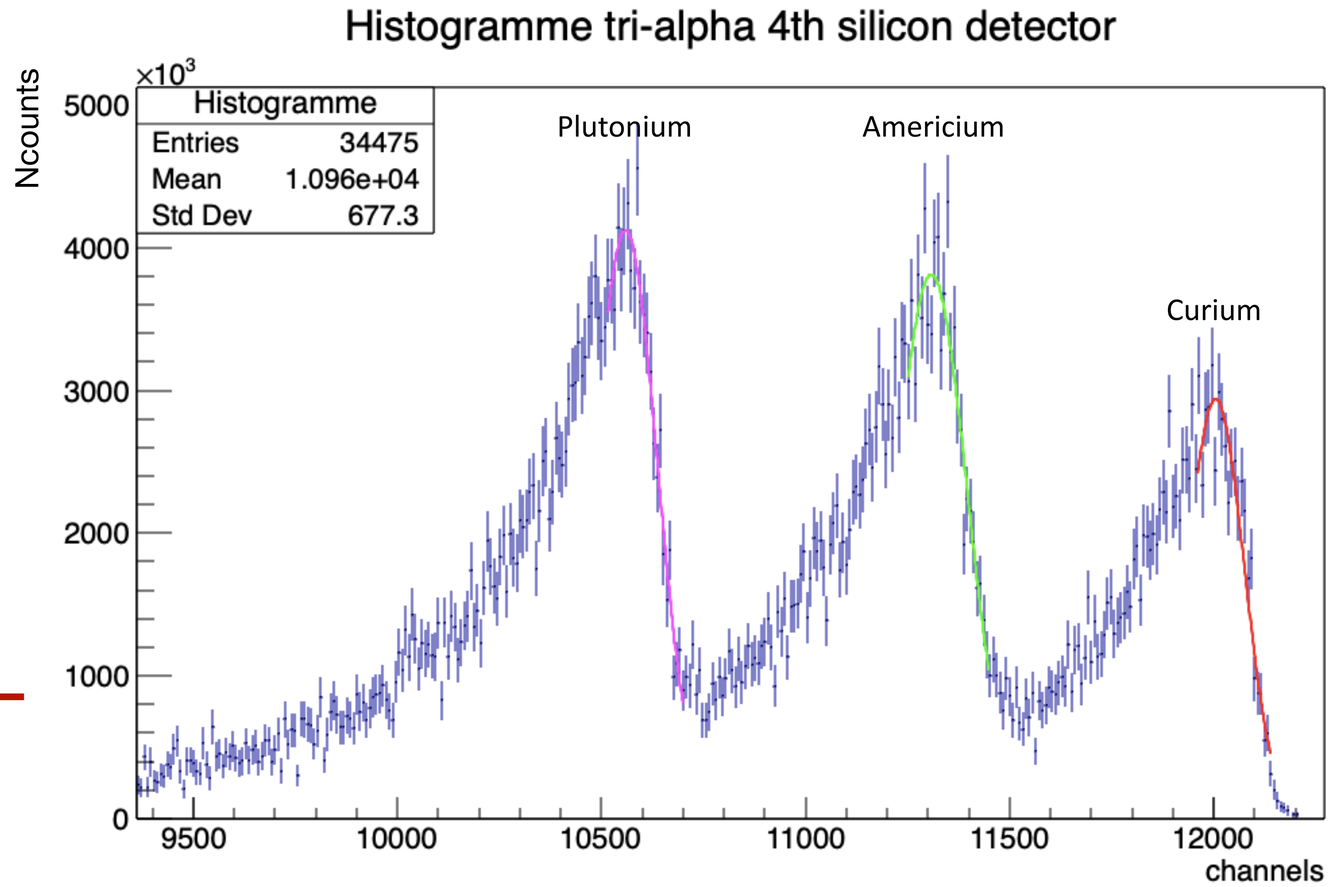
(5) : Pstar, Stopping Power and range tables for protons (2021) https://physics.nist.gov/PhysRefData/Star/Text/PSTAR.html

II - Silicon Detectors Structures

- Tri-alpha source: ^{239}Pu, ^{241}Am, ^{244}Cm
- Alpha-energies E_i known[6]

$$E_{\alpha_{Pu}} = 5156.59 \pm 0.14 \text{ keV}$$
$$E_{\alpha_{Am}} = 5485.56 \pm 0.12 \text{ keV}$$
$$E_{\alpha_{Cm}} = 5804.77 \pm 0.5 \text{ keV}$$





(6) : bnl.gov data base, NuDat 2.8, access https://www.nndc.bnl.gov/nudat2/reCenter.jsp?z=78&n=104

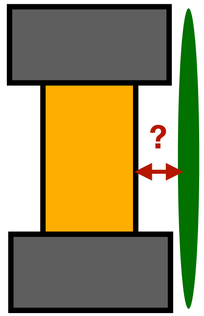
II - Silicon Detectors Structures

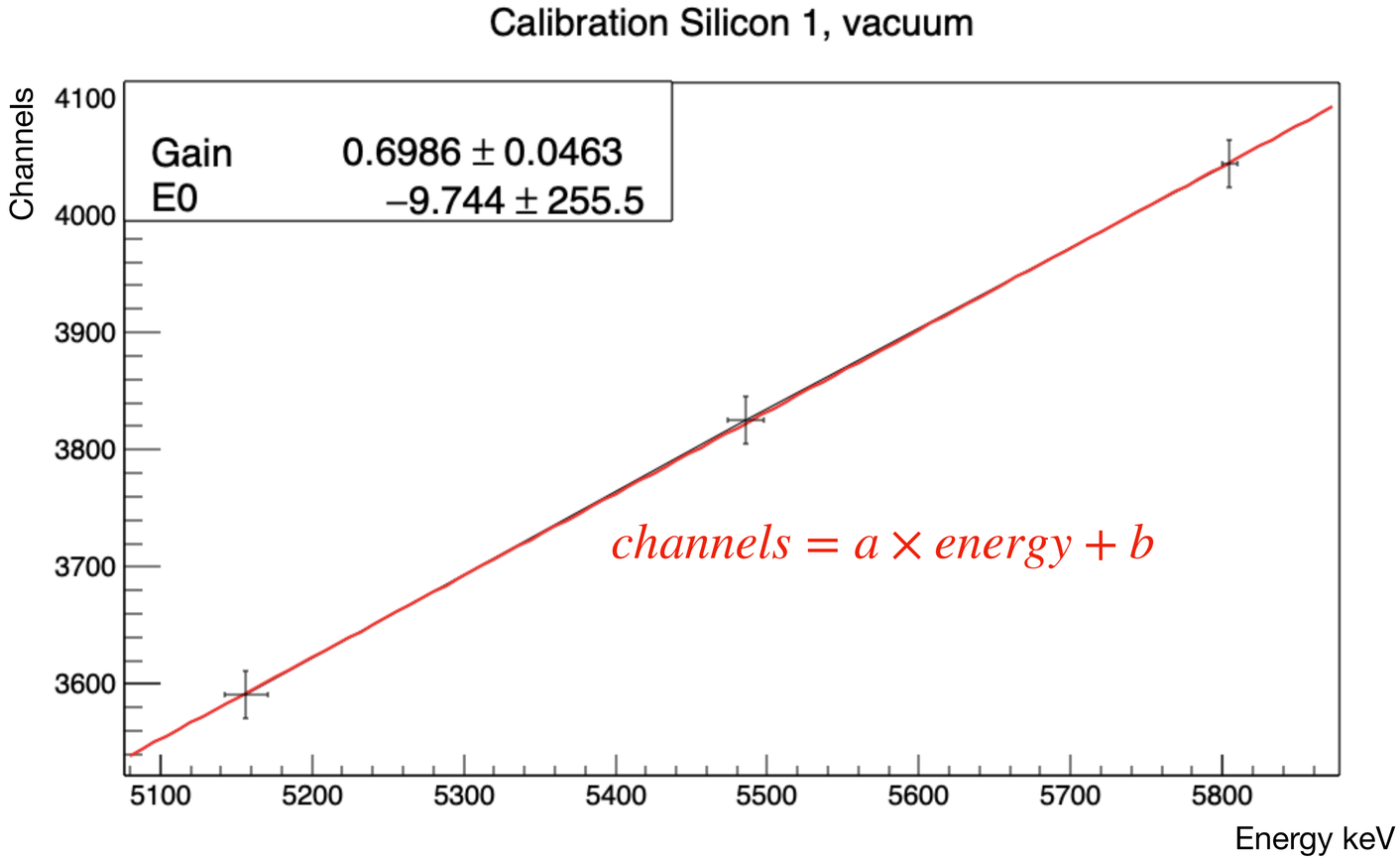
- Tri-alpha source: ^{239}Pu, ^{241}Am, ^{244}Cm
- Alpha-energies E_i known[6]

measure in vacuum
+
measure in air
} ΔE

⟶ Energy loss in air

$$\Rightarrow \quad \Delta x = \frac{Sp(E_i)}{\Delta E}$$





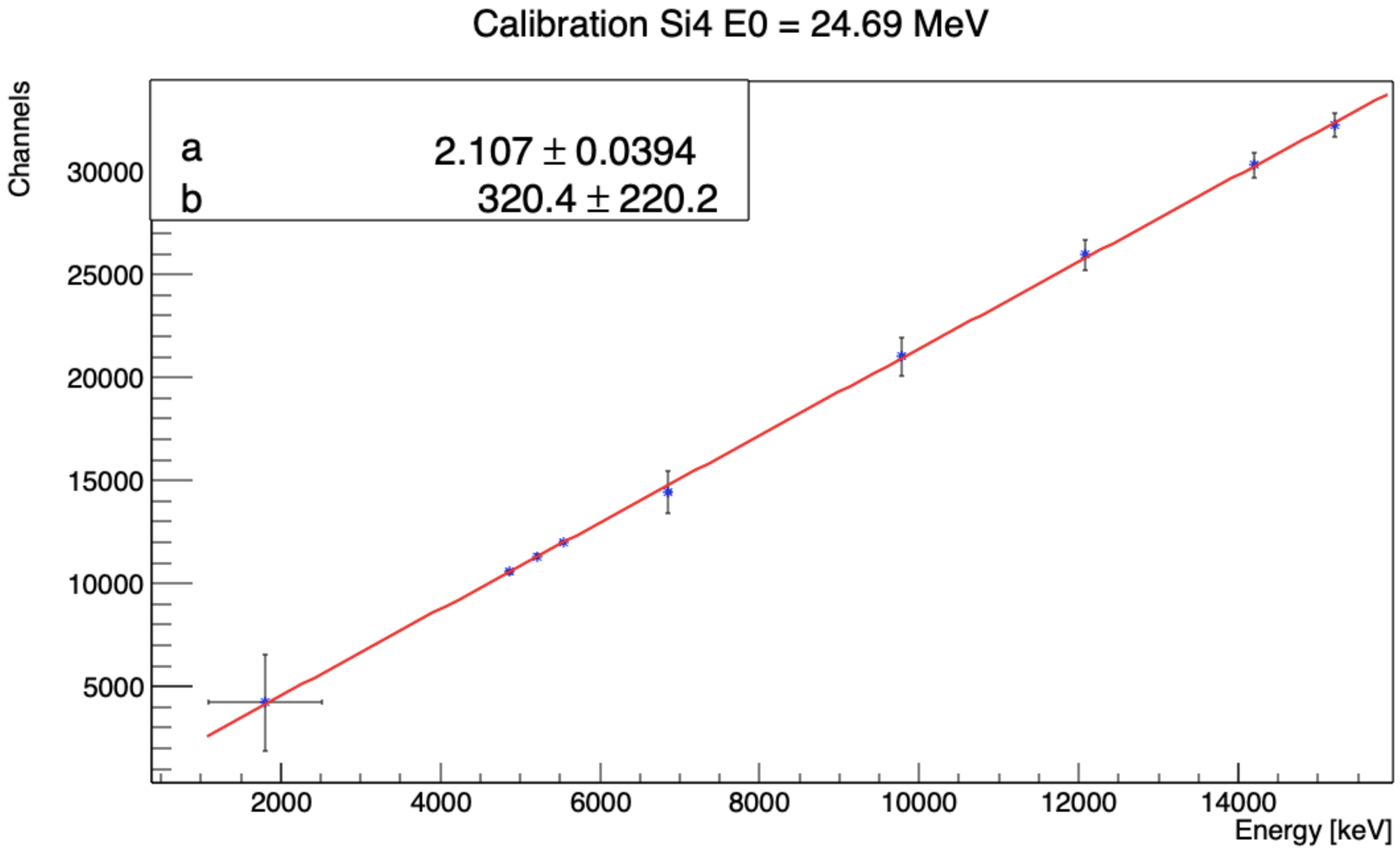
(6) : bnl.gov data base, NuDat 2.8, access https://www.nndc.bnl.gov/nudat2/reCenter.jsp?z=78&n=104

II - Calibration Results

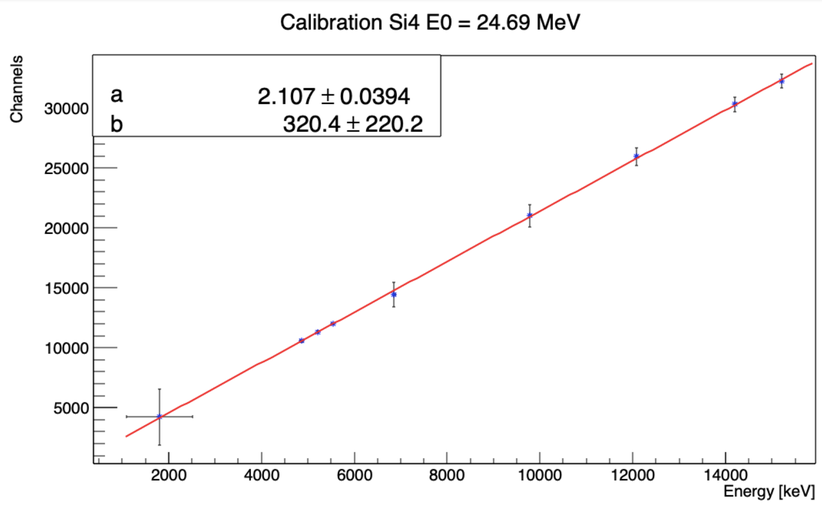
- **First:** align E-points and α-points in Si4.
  Check in other detectors.
  500 keV *steps on* E_0

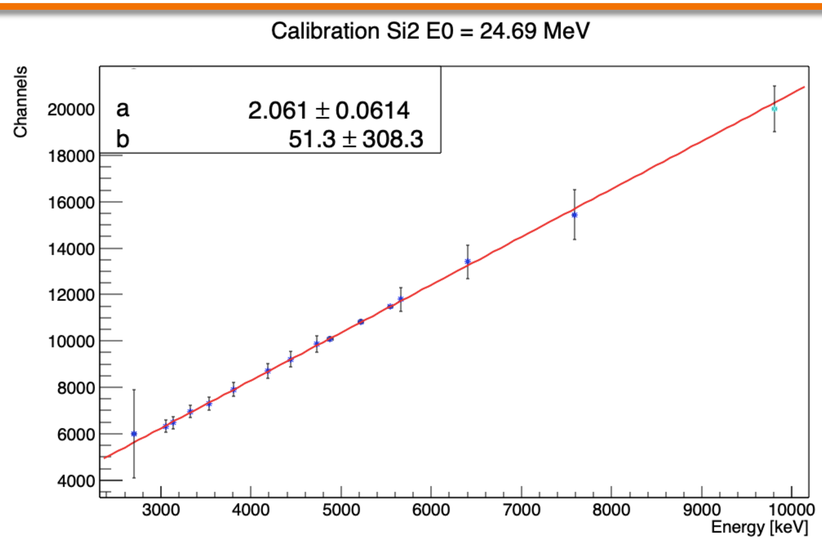
- **Second:** align E-points and dE -points in Si2 and Si3.
  50 keV *steps on* E_0

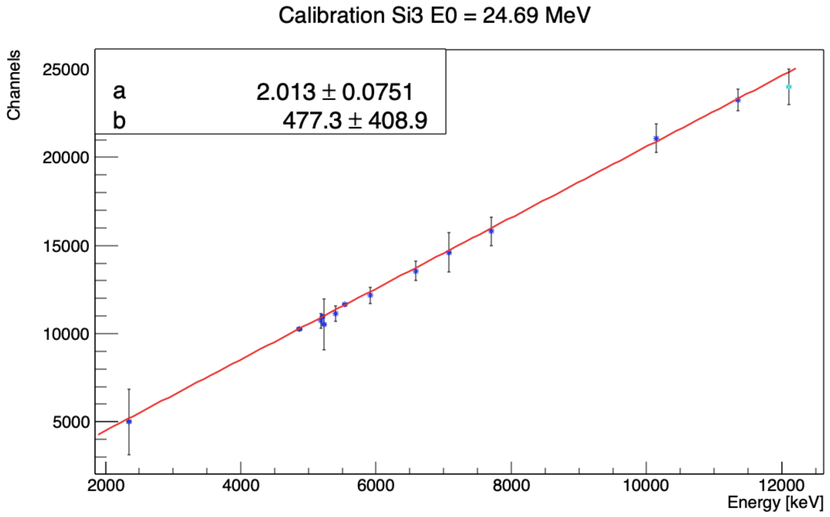
- **Third:** optimize alignment in the four detectors.
  10 keV *steps on* E_0

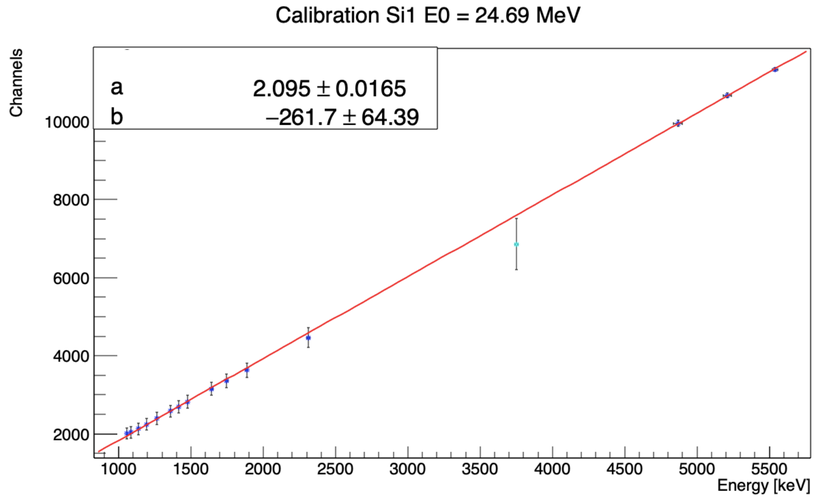


II - Calibration Results









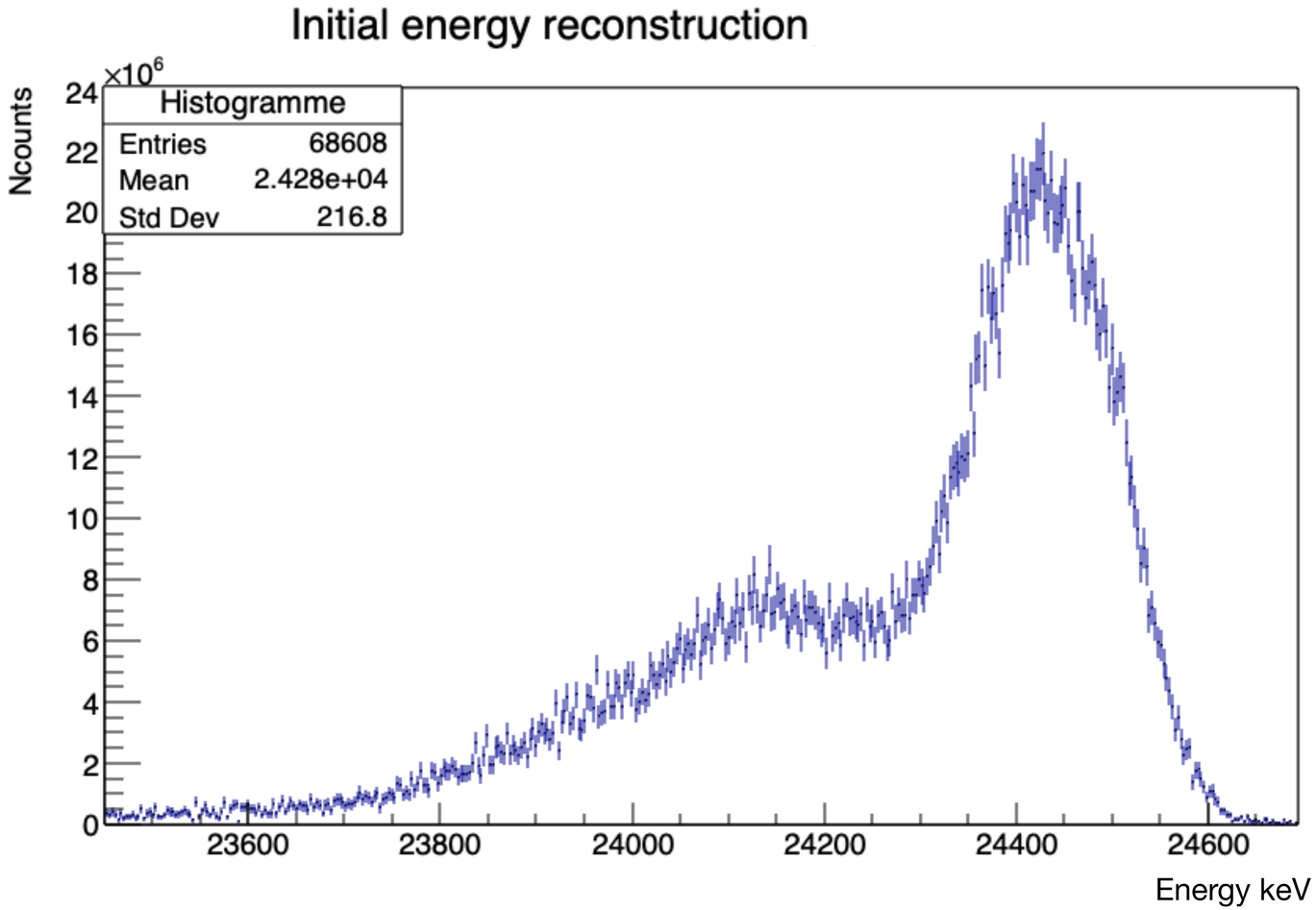
II - Proton Beam Energy

- Energy of the beam:

$$E_0 = 24.69 \pm 0.08 \text{ MeV}$$

$$\Rightarrow E_{\text{beam}} = 24.91 \pm 0.08 \text{ MeV}$$

- Consistent with previous measurements:
  24.85 ± 0.14 MeV[7]



(7) : J. Constanzo, M. Vanstalle, C. Finck, D. Brasse, M. Rousseau, *Dosimetry and characterization of a 25-MeV proton beam line for preclinical radiobiology research*, Medical Physics, 46, 2356 (2019)

Overview

I - Context: cancer, ionizing radiations and protontherapy

II - Measure of the proton-beam energy at PRECy

III - Investigation of the radioprotective effects of bear serum

III - Bear Serum: What for ?

- Hibernation → muscular mass conservation[8]
  ↳ Astronauts, sick people, *etc*.

- Hibernating bear serum → radioprotection properties
  → hypometabolism[9] ?

⇒ Human cells cultures with bear serum treatments

(10) : © Getty Images/iStockphoto

Collaboration:
IPHC (Institut Pluridisciplinaire Hubert-Curien, DRHIM and DSA departments) laboratory in Strasbourg (IN2P3)
CarMeN (Cardiologie, Métabolisme, Diabétologie et Nutrition) laboratory in Clermont Ferrand (INRA)
LPC (Laboratoire de Physique Corpusculaire) laboratory in Clermont Ferrand (IN2P3)

(8) : S. Chanon, B. Chazarin, B. Toubhans et. al., *Proteolysis inhibition by hibernating bear serum leads to increased protein content in human muscle cells*, Nature Scientic Reports (2018)
(9) : X.J. Musacchia, R.E. Barr, *Survival of whole-body-irradiated hibernating and active ground squirrels; Citellus tridecemlineatus*, Radiat Res., 33(2):348-56 (1968)

III - Bear Serum: Experiments at PRECy

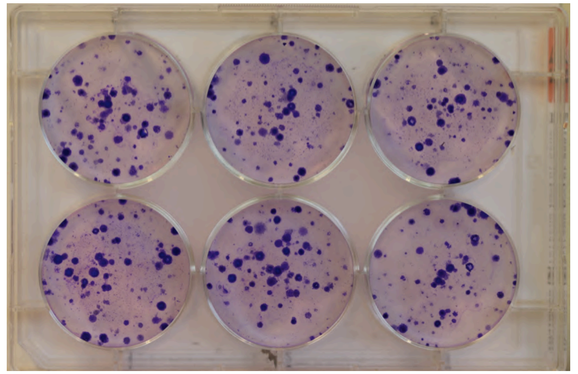
- <u>Immunofluorescence:</u>

Cells irradiation → DNA damages

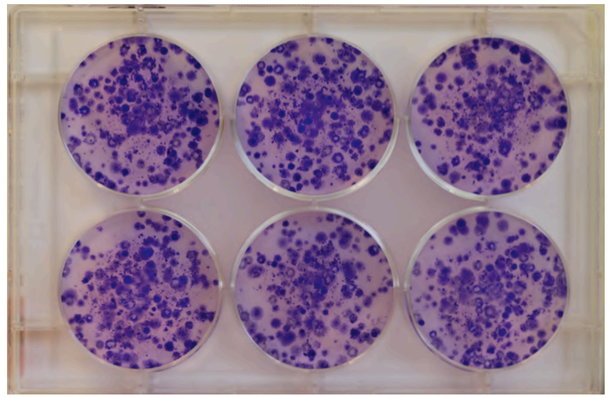
Which processes/molecule involved in DNA repair ?

- <u>Clonogenicity:</u>

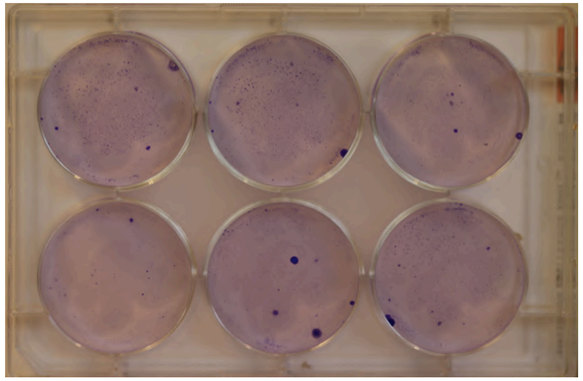
Survival rate depending on the dose



2 Gy



0 Gy

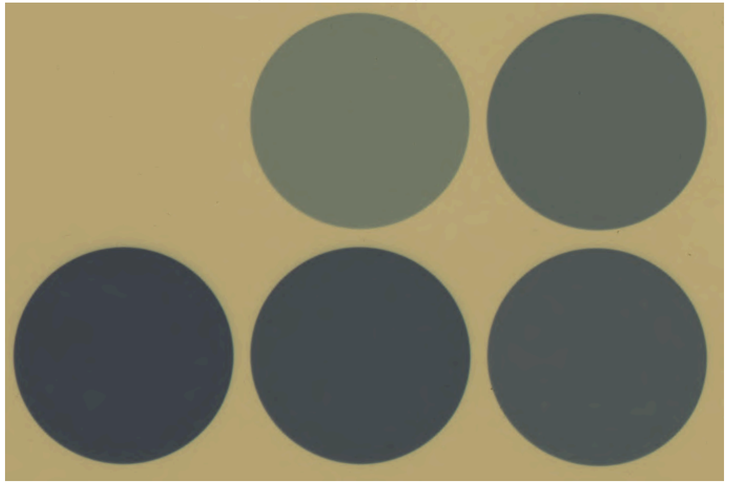


10 Gy

Comparison { Three sera tested → *FBS*, *WBS*, *SBS*
Cancerous tissues and healthy tissues irradiated

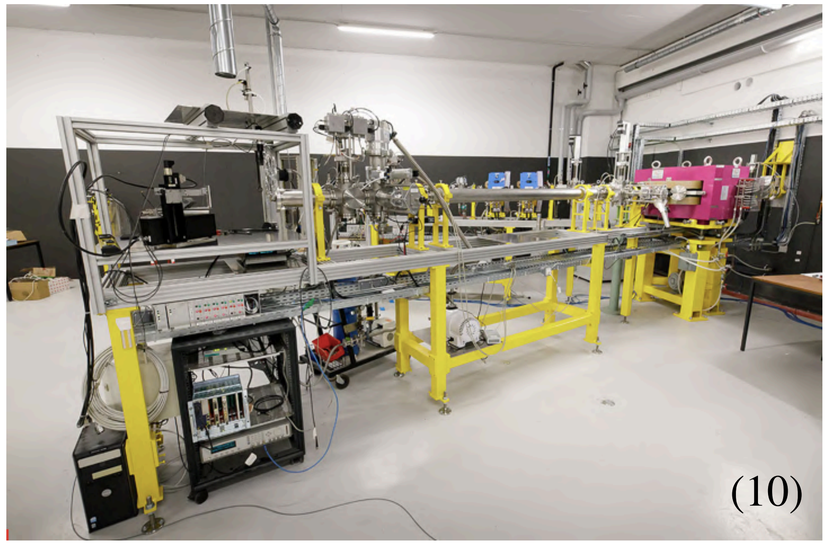
Conclusion

Radiochromic film used for dose control



Bear-serum investigation:

- Two experiments performed
  - ⟶ immunofluorescence
  - ⟶ clonogenicity
- Active role played during irradiation time and cells counting



PRECy proton-beam energy measurement:

- Measurements performed at PRECy
- Python algorithms developed
- Energy of the beam determined
- Beam profile reconstructed

(10) : Ligne de radiobiologie de la plateforme Precy. Image Nicolas Busser, IPHC, Photothèque IN2P3

Acknowledgments

Thank you for your attention !

Special thanks to:

- **Marc Rousseau:** for your ionizing supervision
- **David Brasse:** enriching physical introspection
- All members of the **DRHIM TEAM**
- The biologists: **Estelle Stantiago**, **Laurent Daeffler** and **Fabrice Bertile** (how much fun it was counting cells !)
- **Michel Pellicioli** and **Jacky Schuller:** impressive proton-beam pilots

Back up slides

BackUp: ionizing radiations

- Radiations with enough energy to ionize matter

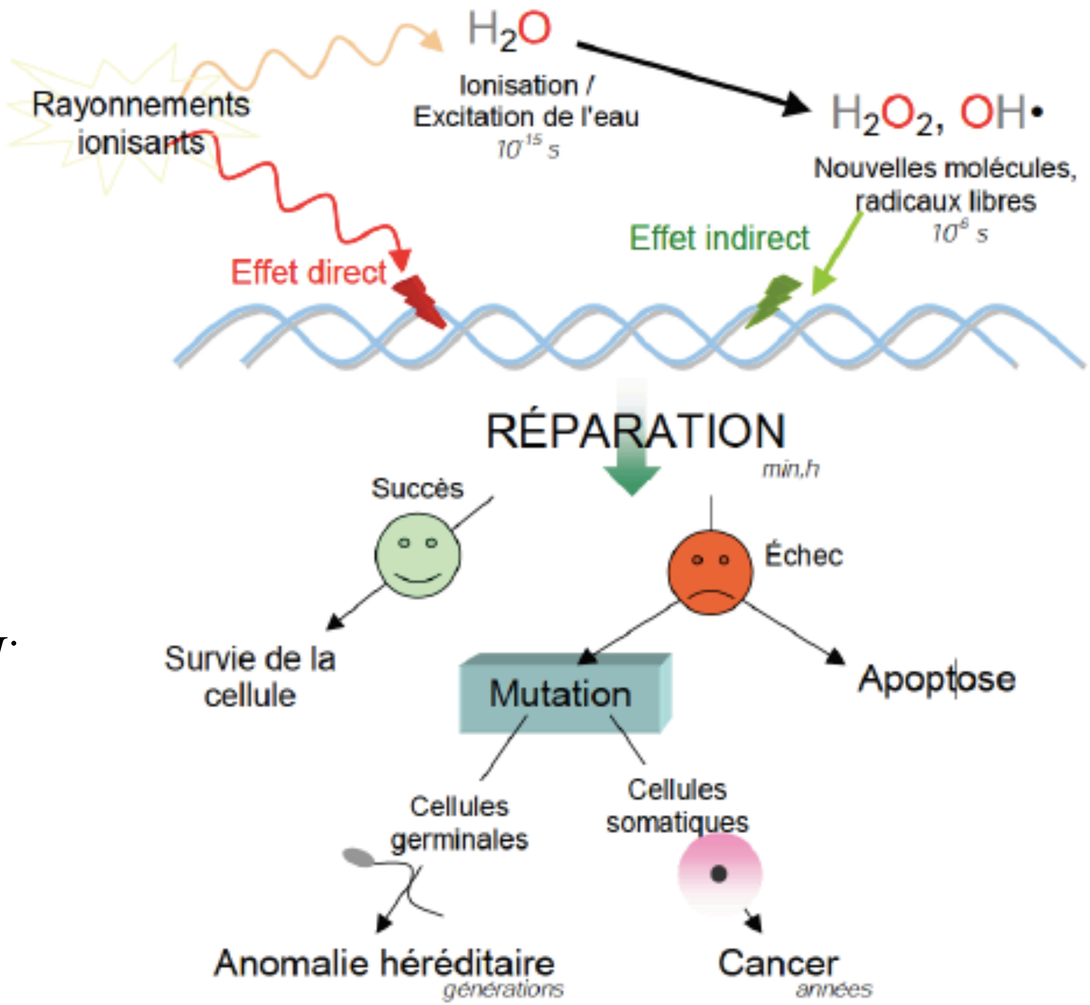
directly → ionize DNA → **Bonds breaking** between DNA components

indirectly → Radiolysis of water: → **Bonds breaking** between DNA components

H_2O excitation/ionization

free radicals created *e.g.* $OH^{\cdot}$

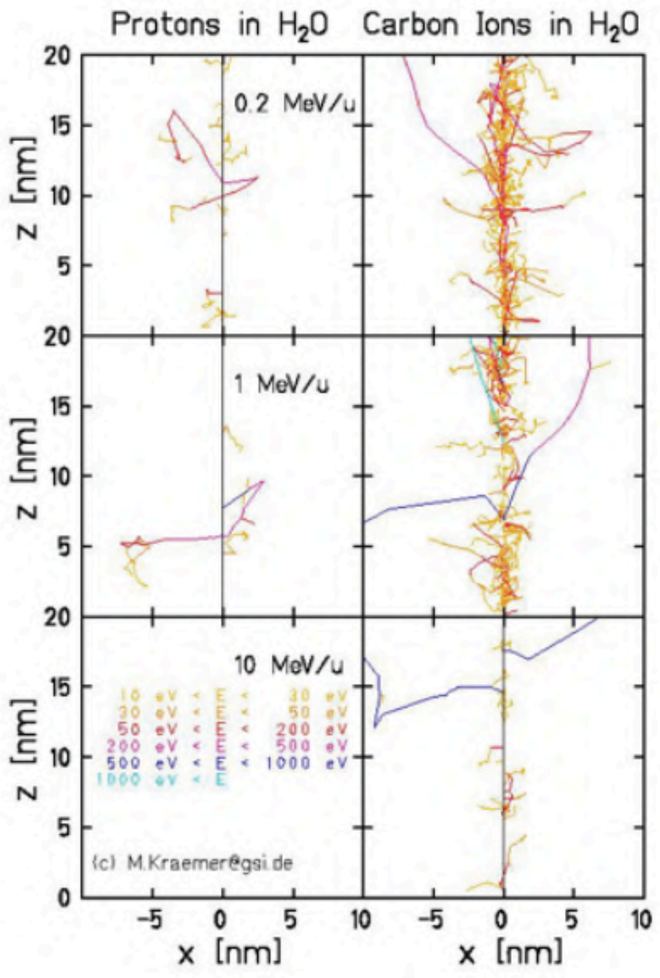
oxydiser interacts with ADN



BackUp: Dose, LET and Stopping Power

$$D = \frac{dE}{dm} = \frac{1}{\rho}\frac{dE}{dV} = \frac{1}{\rho S}\frac{dE}{dx}$$

$$\Rightarrow D = \underbrace{\frac{1}{S}}_{\text{Fluence}} \times \underbrace{\frac{1}{\rho}\frac{dE}{dx}}_{\text{Stopping Power}}$$



(11)

(11) : M. Krämer, M. Durante, *Ion beam transport calculations and treatment plans* in particle therapy, Eur. Phys. J. D., 60, 195-202 (2010)

BackUp: Bethe-Bloch

$$E = \frac{1}{2}mv^2$$

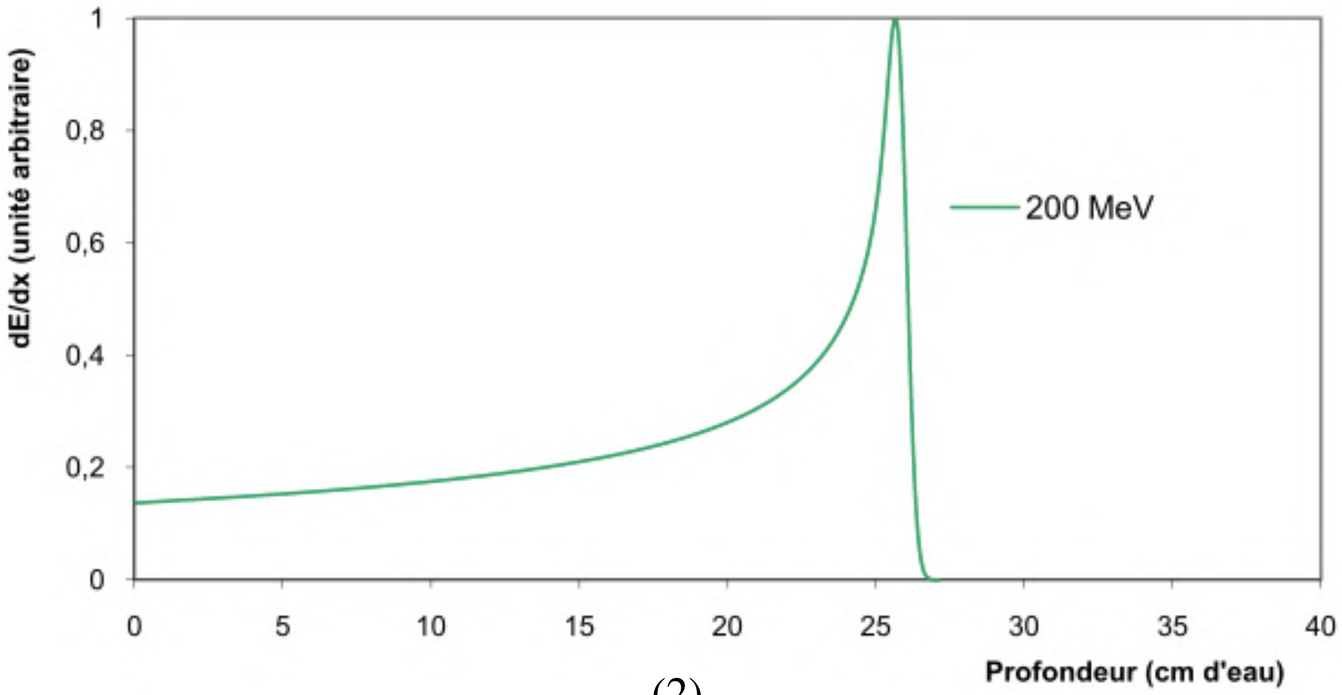
$$\Rightarrow E \propto v^2$$

$$\Rightarrow \frac{dE}{dx} \propto \frac{1}{E}$$

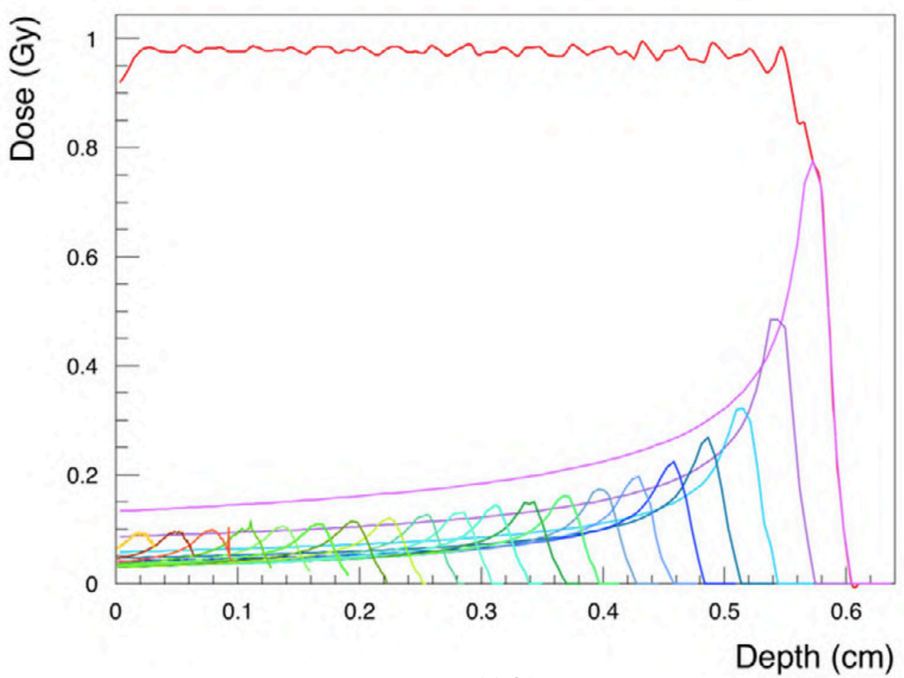
$$-\frac{dE}{dx} = \frac{4\pi e^4 z^2 n}{(4\pi\epsilon_0)^2 m_e v^2} \times \left[\ln\left(\frac{2m_e v^2}{I}\right) - \ln(1-\beta^2) - \beta^2\right]$$

$$\Rightarrow \frac{dE}{dx} \propto \frac{1}{v^2}$$

I - Context: Protontherapy and SOBP



(2)



(12)

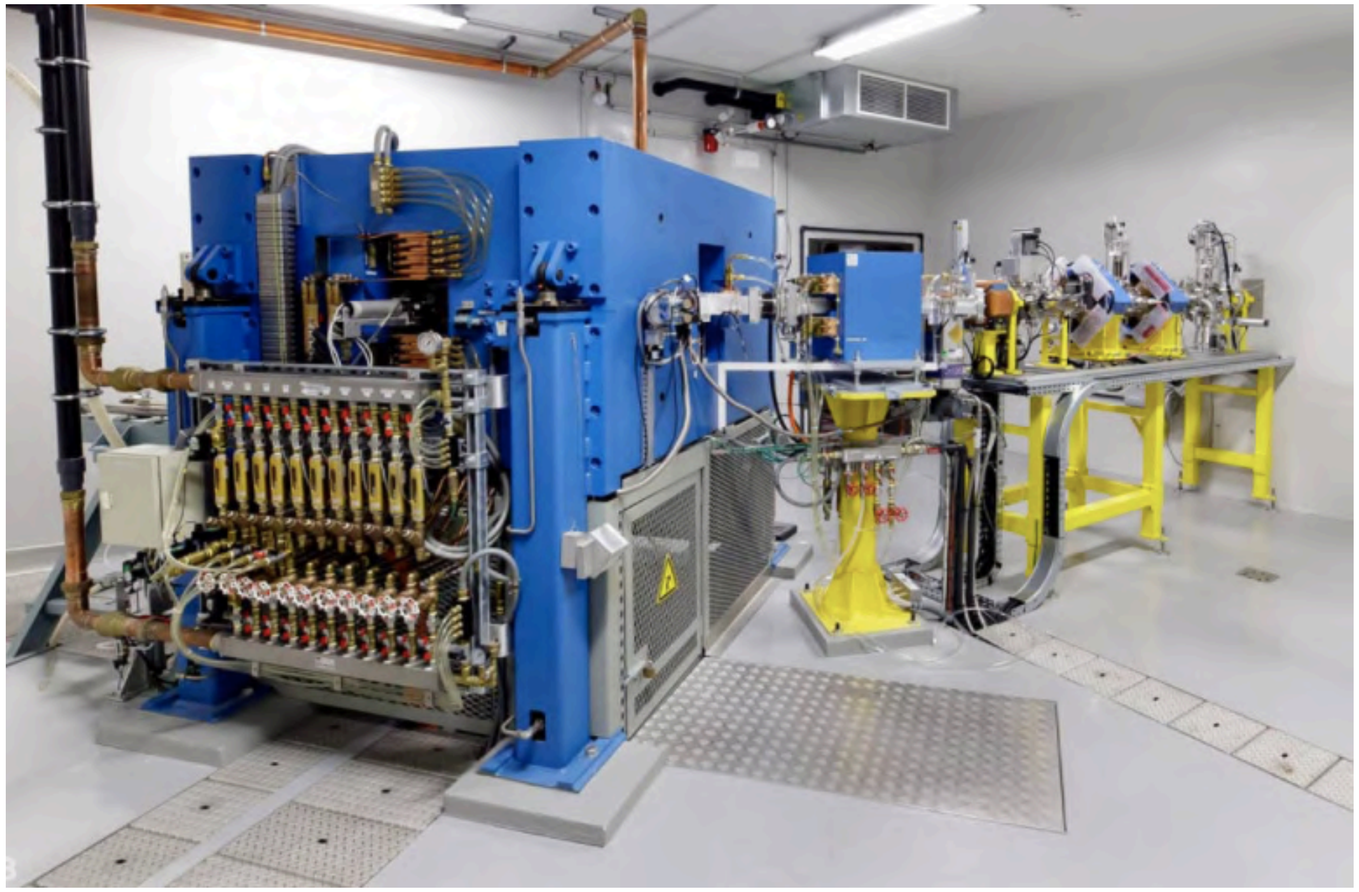
Bragg peak → localized deposited energy

SOBP → uniform dose deposition
(*Spread Out Bragg peak*)

(2) : Y. Karakaya, *Étude des performances d'un système d'imageur proton dans le cadre de l'approche faisceau à faisceau*, PhD Thesis, Université de Strasbourg (2018)
(12) : J. Constanzo, M. Vanstalle, C. Finck, D. Brasse, M. Rousseau, *Dosimetry and characterization of a 25-MeV proton beam line for preclinical radiobiology research*, Medical Physics, 46, 2356 (2019)

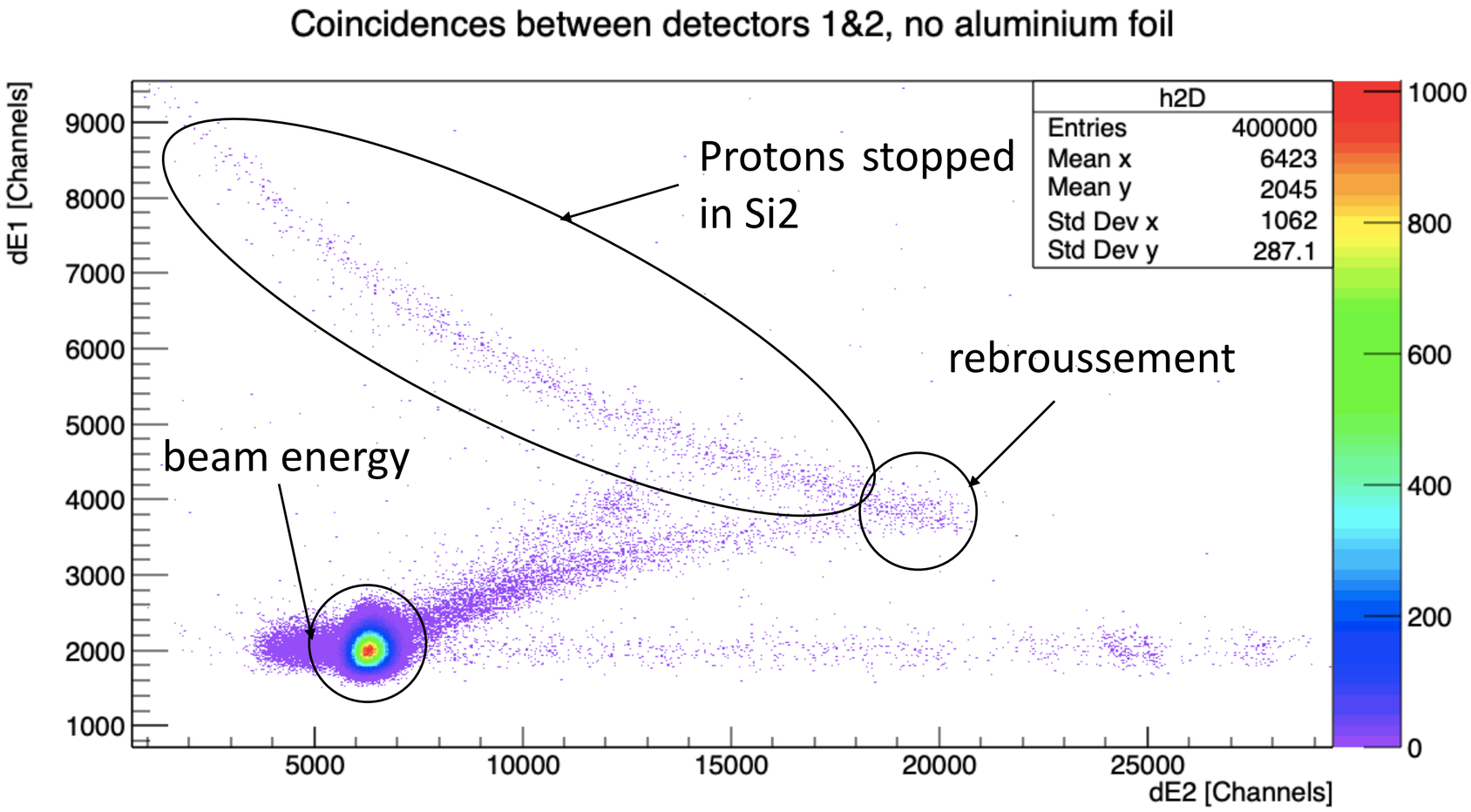
BackUp: CYRCé Cyclotron

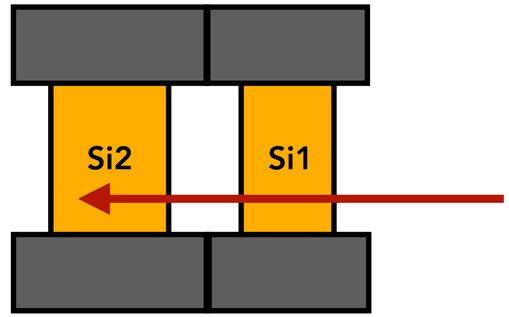
- H^- source $\rightarrow$ accelerating electric field
  + magnetic field
- carbon foil $\rightarrow$ two e^- stripped away
- $H^+ \rightarrow$ injected in irradiation lines
- $E_{\text{protons}} \in [16\ MeV,\ 24\ MeV]$

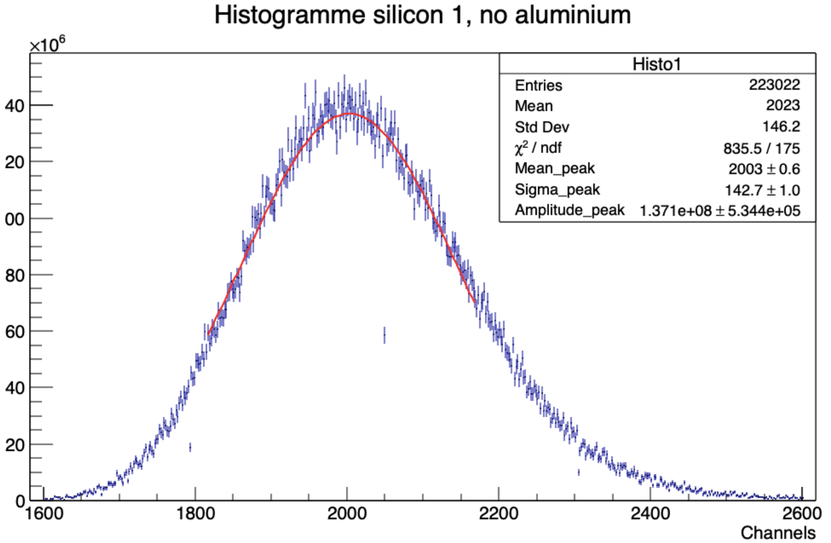


(13) : Cyclotron TR24 ACSI et tronc commun des lignes d'irradiation, Image Nicolas Busser, IPHC, Photothèque IN2P3

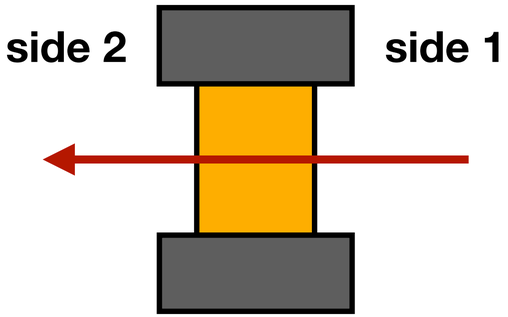
BackUp: Coincidences







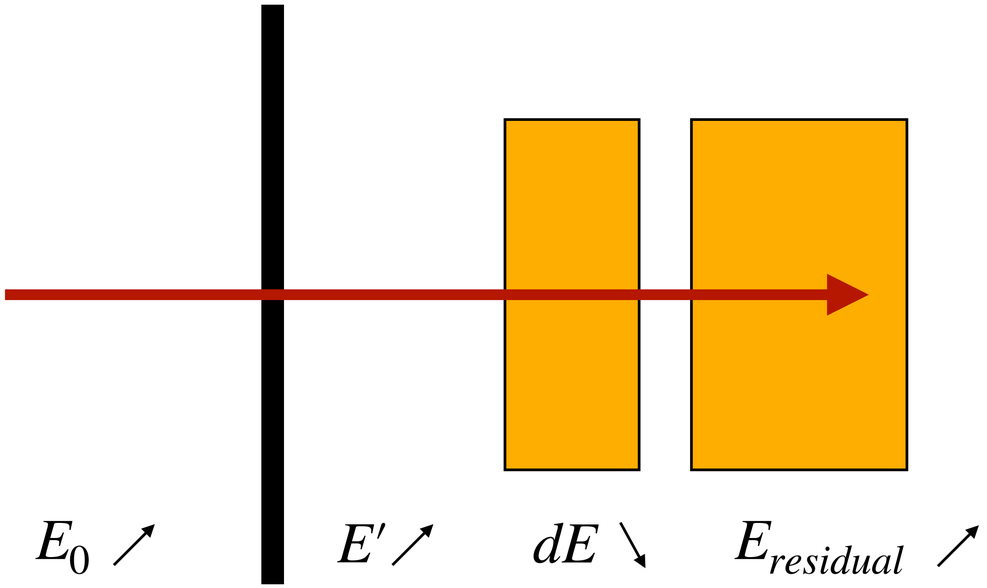
BackUp: Air Thicknesses Results

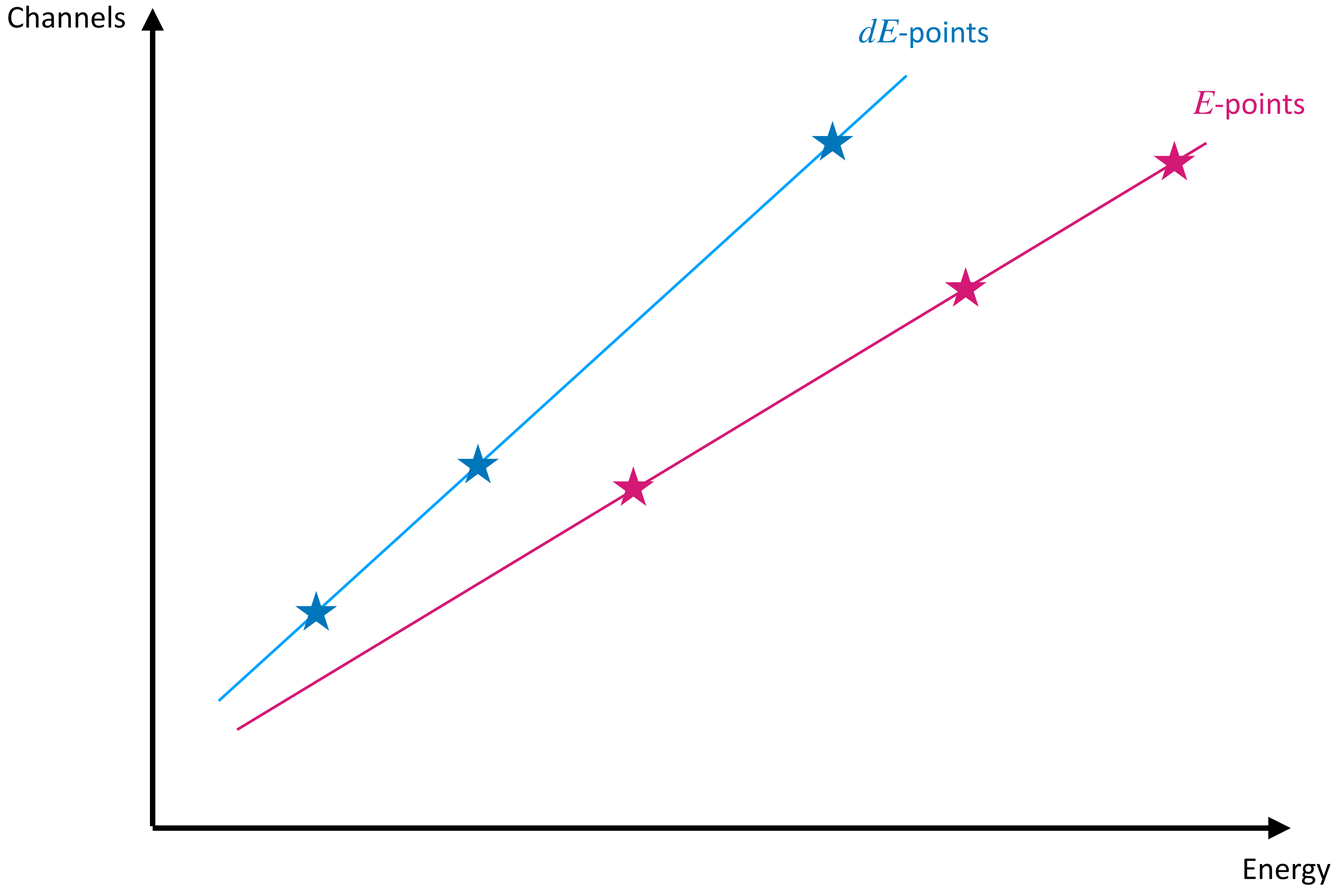


	Δx side 1 (in cm)	Δx side2 (in cm)
Si1	0.317 +/- 0.017	0.522 +/- 0.017
Si2	0.305 +/- 0.017	0.519 +/- 0.017
Si3	0.318 +/- 0.017	0.490 +/- 0.017
Si4	0.317 +/- 0.017	-

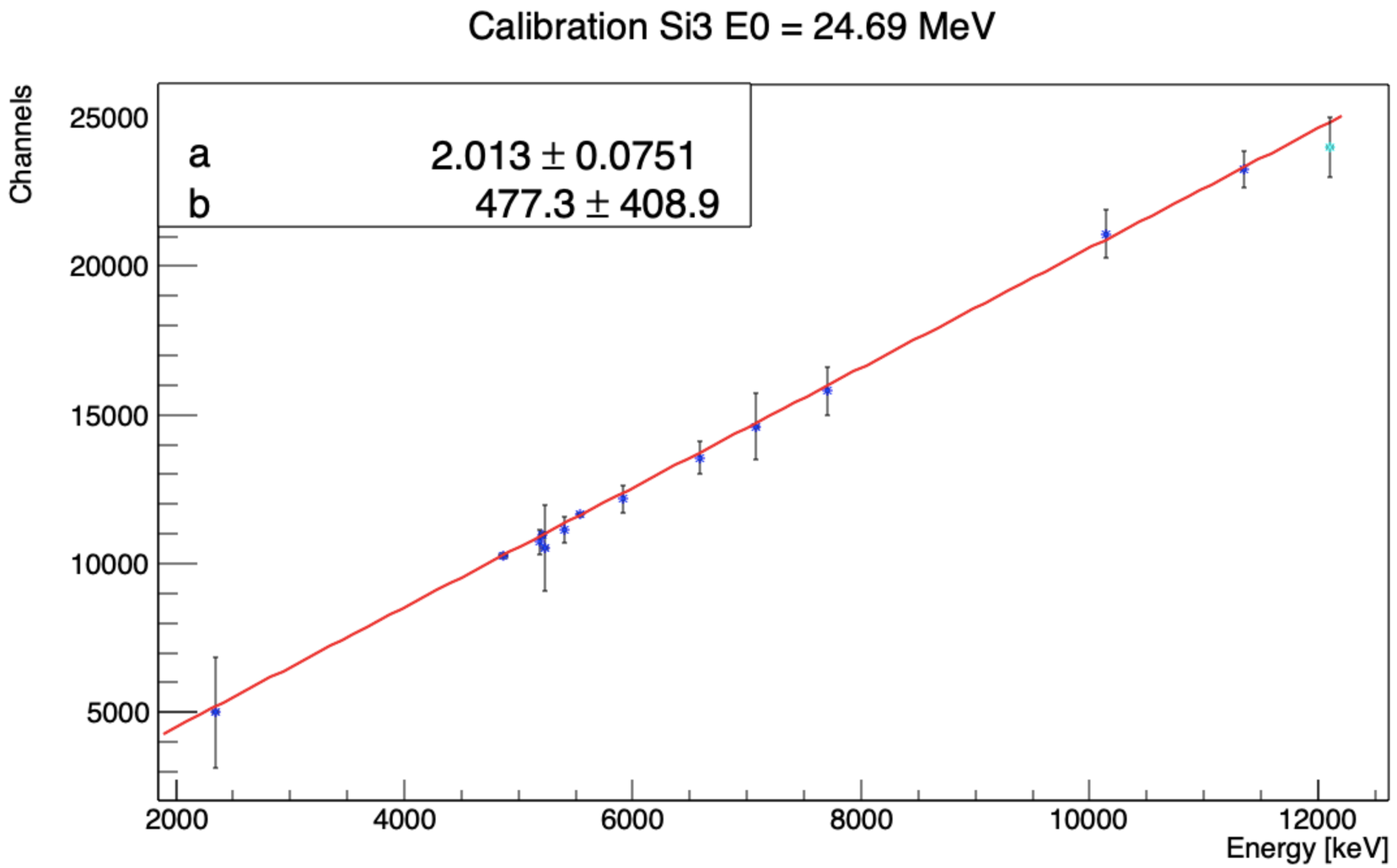
BackUp: Calibration Method

Case where E_0 from simulation is too low

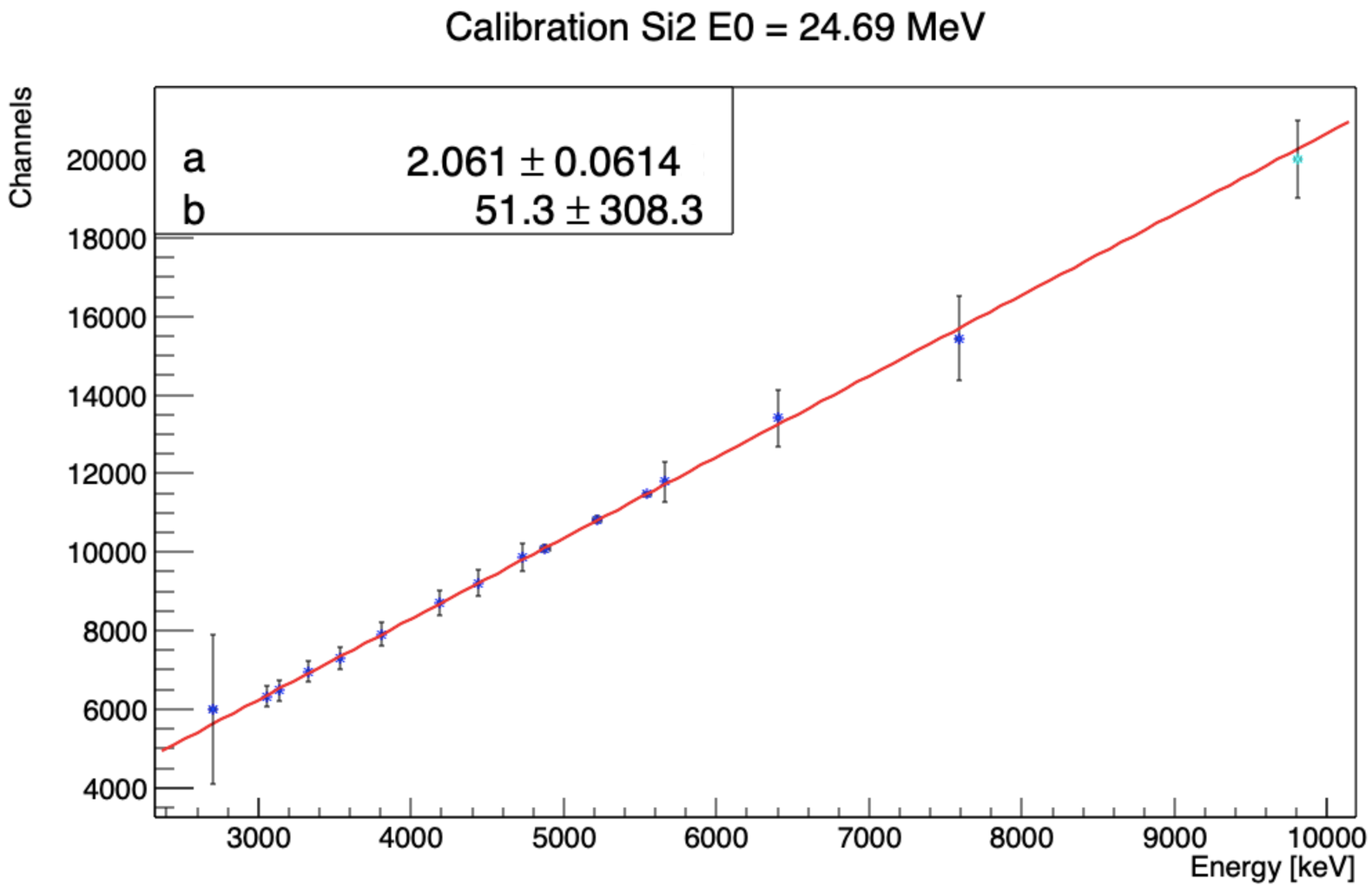




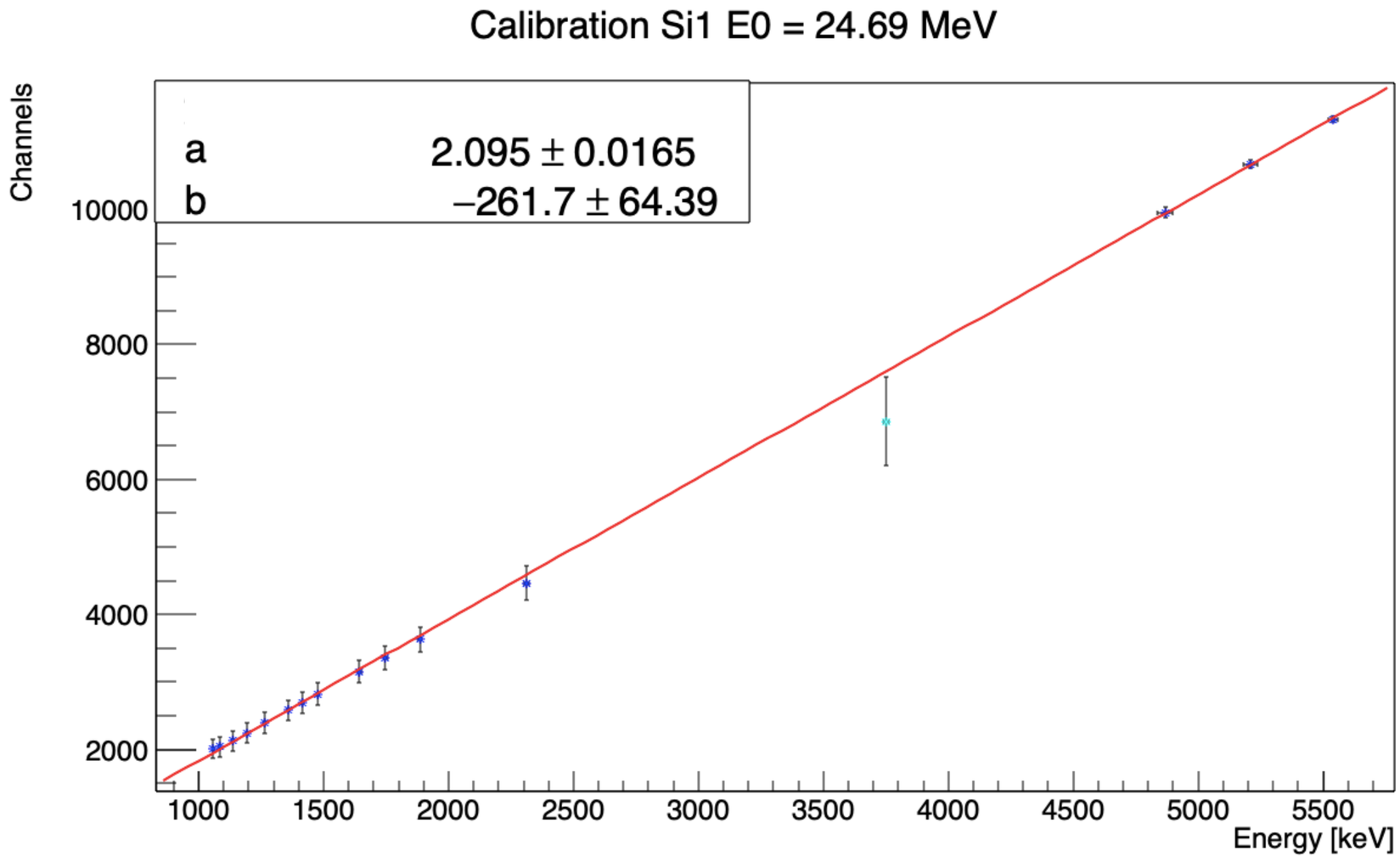
BackUp: Calibration Results



BackUp: Calibration Results

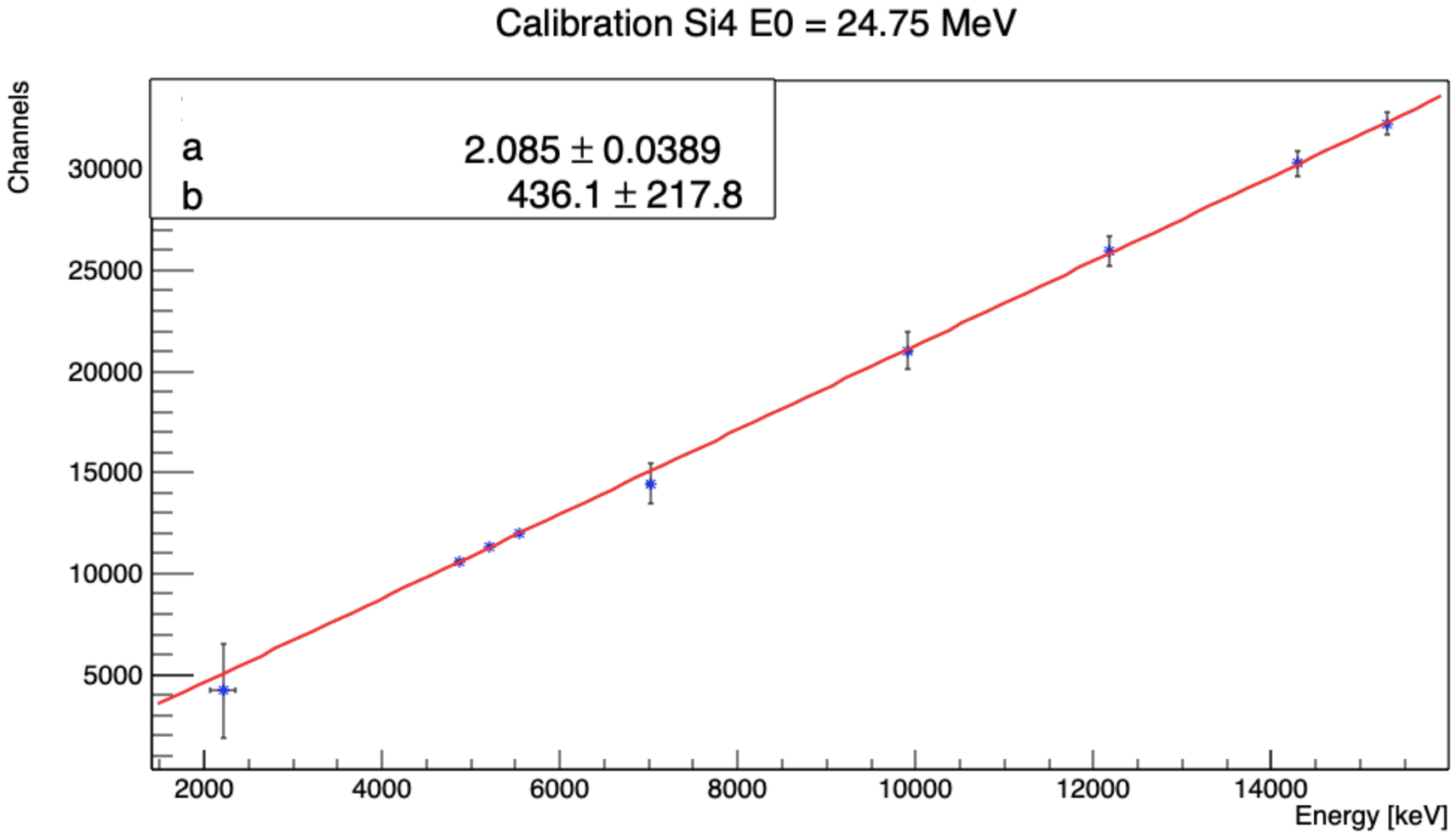


BackUp: Calibration Results



BackUp: Calibration Results - wrong energy

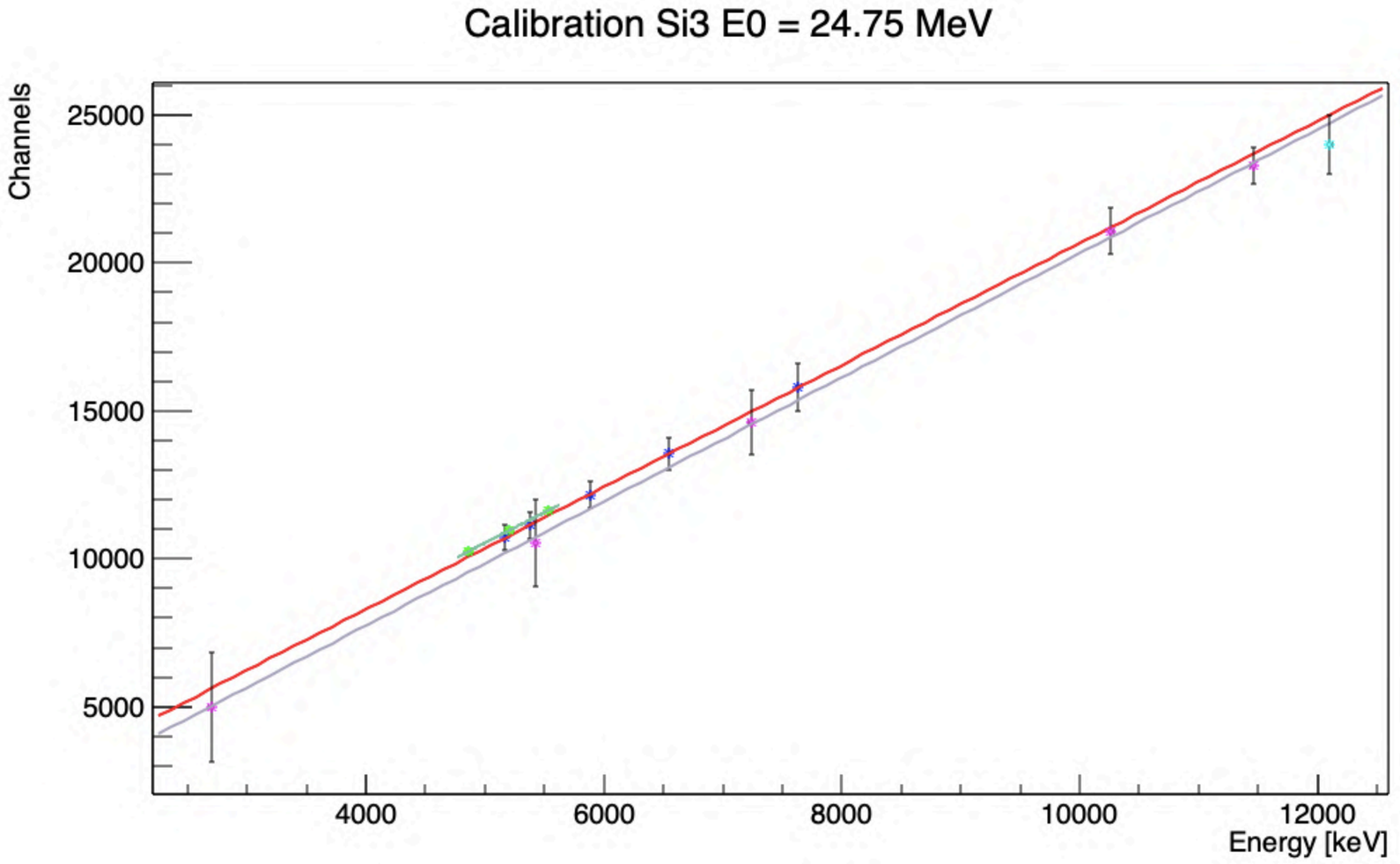
Wrong $E_0 \Rightarrow$ points not aligned



BackUp: Calibration Results - wrong energy

Wrong $E_0 \Rightarrow$ points not aligned

- Green $\rightarrow \alpha$-points
- Dark blue $\rightarrow dE$-points
- Magenta $\rightarrow E$-points



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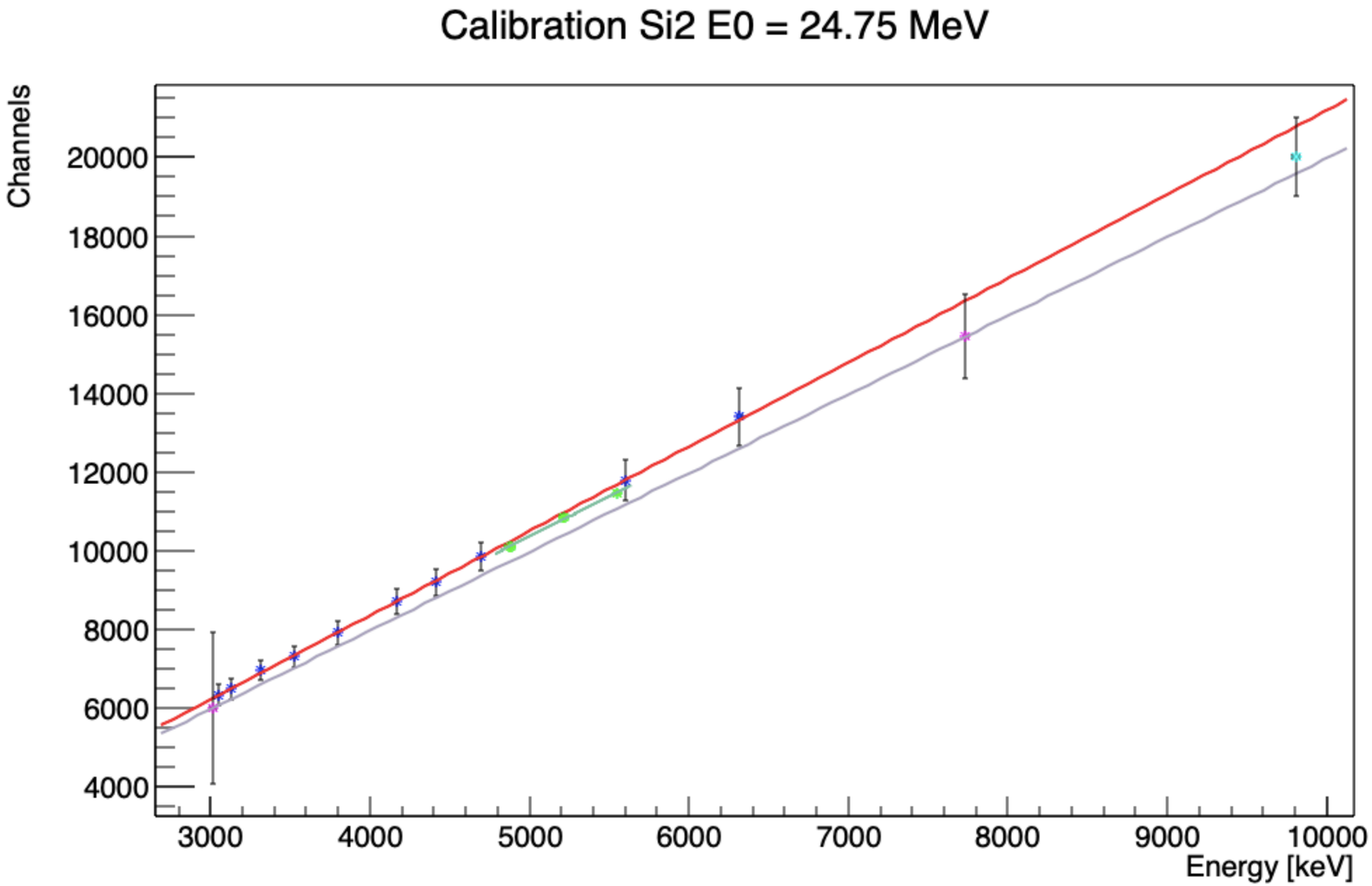
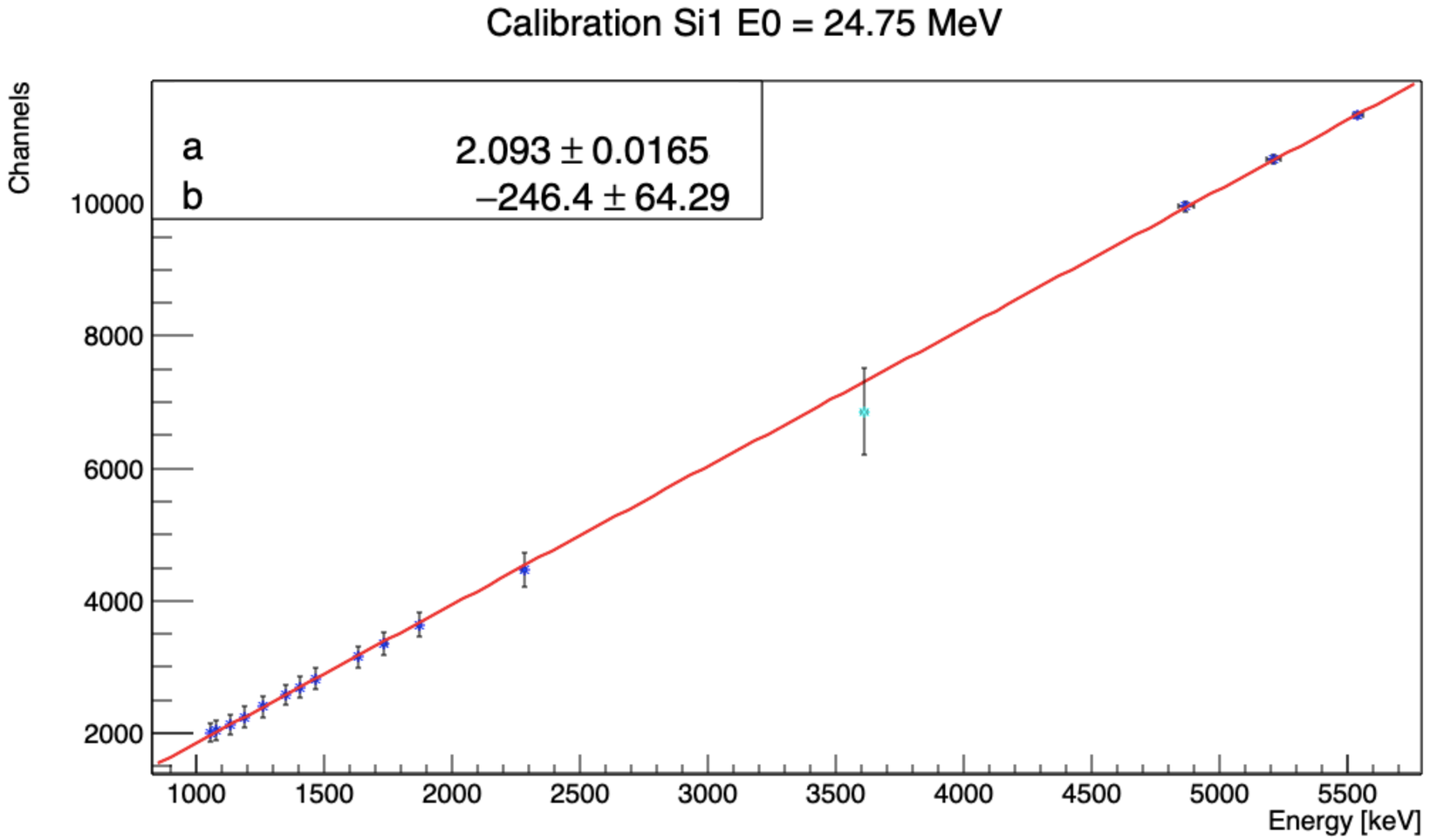
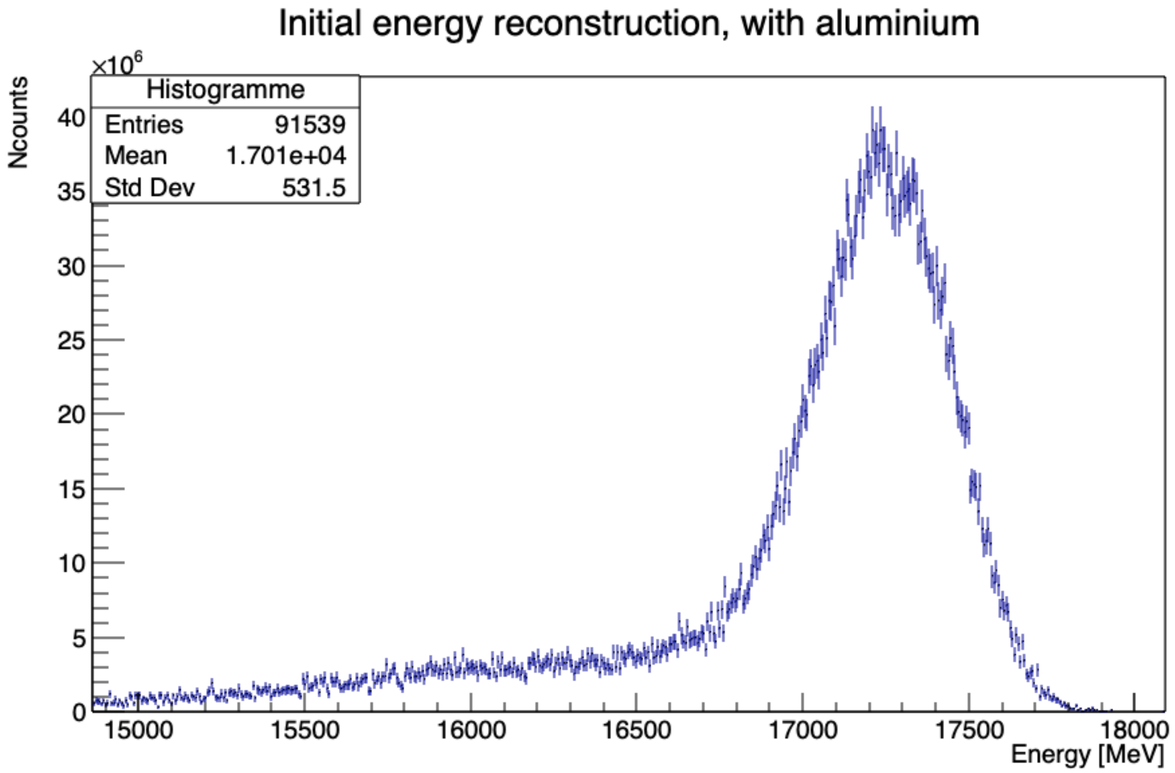


BackUp: Calibration Results - wrong energy

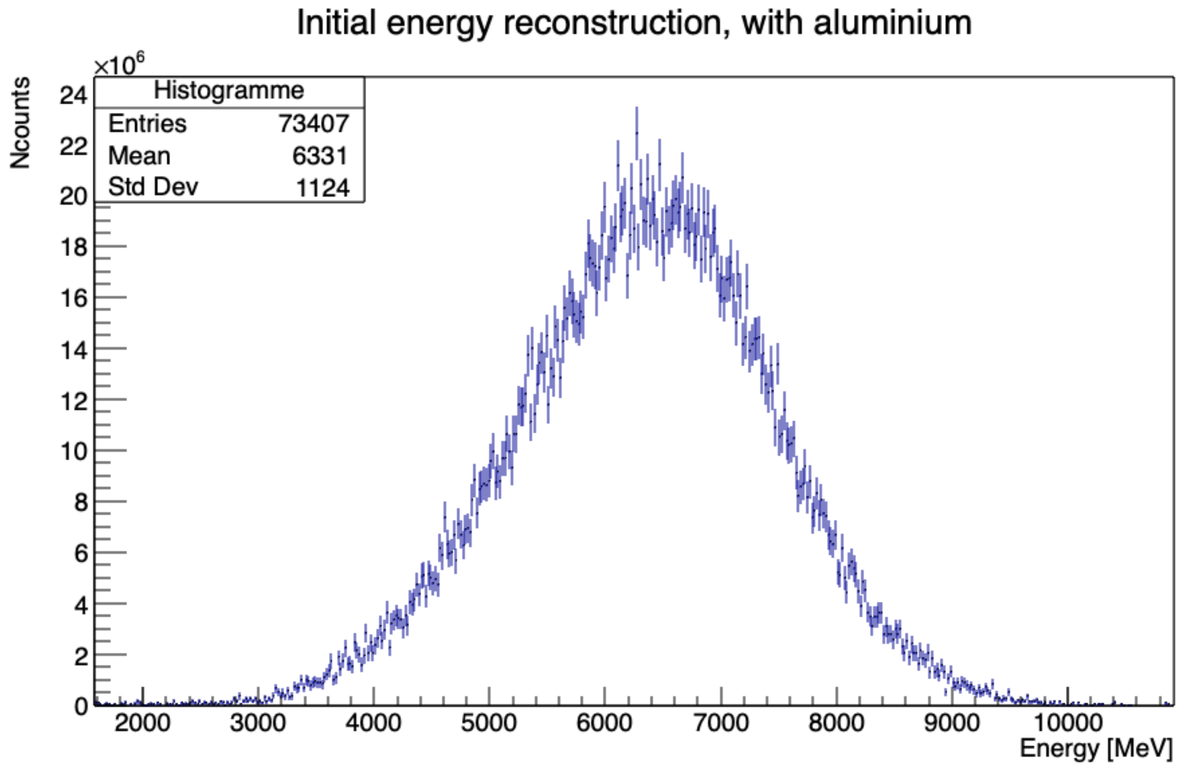
Wrong $E_0 \Rightarrow$ points not aligned



BackUp: Energy Profile

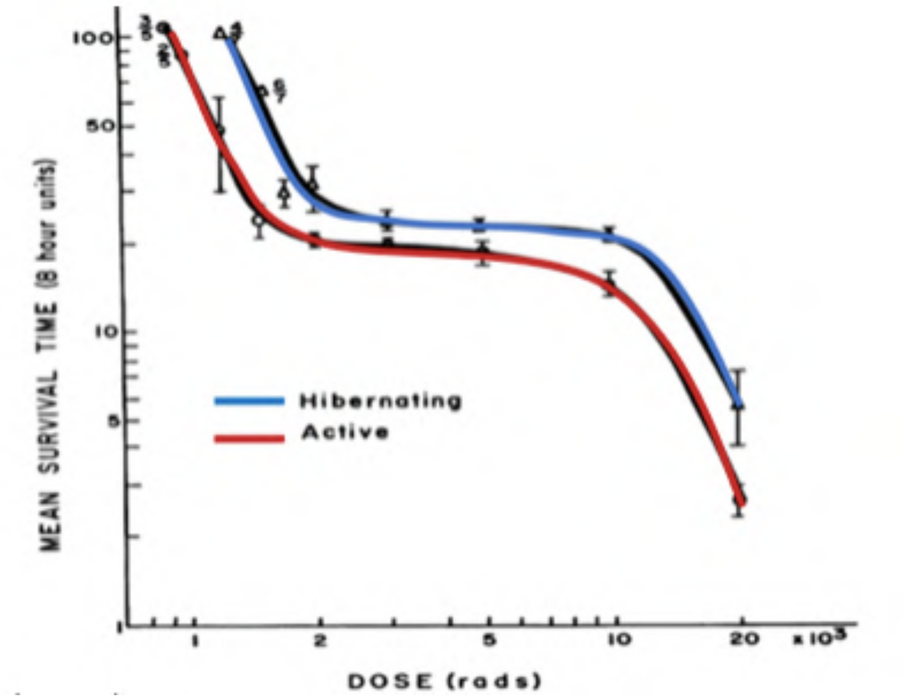


With $1.424\ \mu m$ of aluminium



With $2.761\ \mu m$ of aluminium

BackUp: Bear Serum



(14)

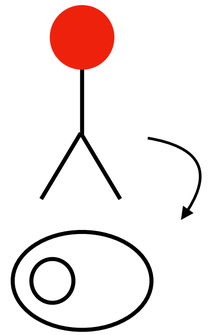
Better resistance of small hibernating animals during hibernation.

→ hypometabolism and hypothermia

(14) : X.J. Musacchia, R.E. Barr, *Survival of whole-body-irradiated hibernating and active ground squirrels; Citellus tridecemlineatus*, Radiat Res., 33(2):348-56 (1968)

BackUp: Immunofluorescence

- Immunofluorescence: Antibodies + colored markers → target DNA damages



- Tested Sera:

  FBS: Fœtal Bovine Serum

  SBS: Summer Bear Serum

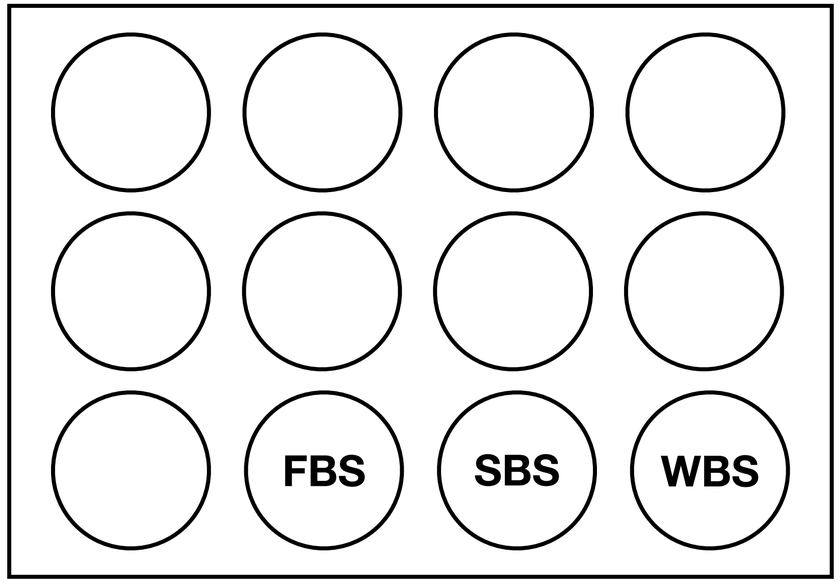
  WBS: Winter Bear Serum

- Irradiation:

  timepoints: 6h, 3h, 1h, 30min, 0s

  reaction mechanisms stopped with formaldehyde

  plates go to Clermont-Ferrand



BackUp: Clonogenicity

- Probe cellular survival rate after irradiation

→ 3 sera

→ Dose $\in [0\ \mathrm{Gy},\ 10\ \mathrm{Gy}]$

→ Dose rate = $2\ \mathrm{Gy/s}$

→ Count number of cells before and after irradiation