June 16 – 20, 2025 | Hunguest Hotel Sun Resort
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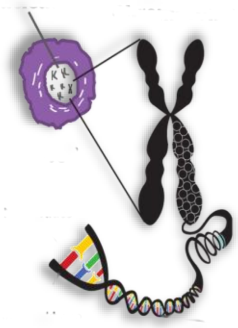
A mechanistic approach to predict the probability of complication in the rat spinal cord following particle irradiation



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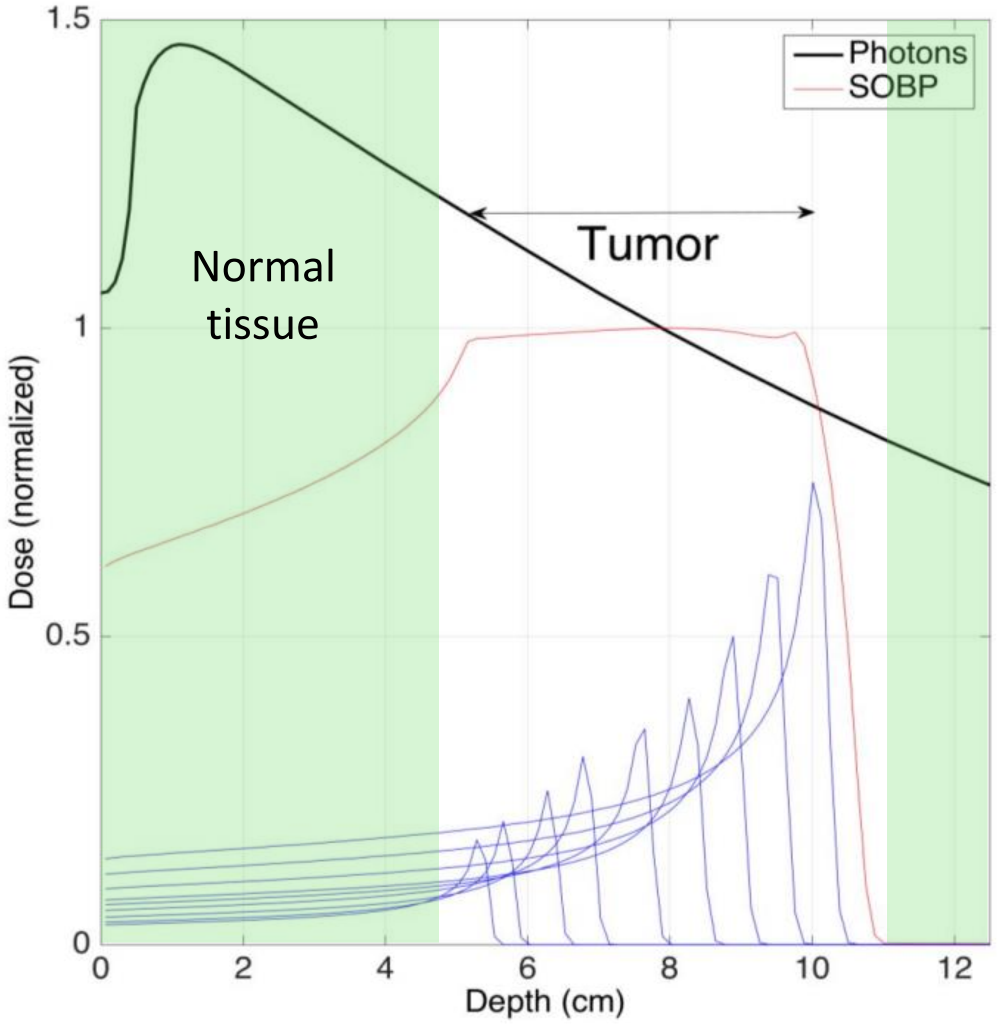
Introduction

Hadrontherapy

This study was conducted within the framework of **innovative radiotherapy** techniques, among which Hadrontherapy stands out.



[Image credit: E. Sterpin, Université catholique de Louvain]

Hadrontherapy =

charged particle irradiation

↓

✓ High radiation doses to tumour cells enabled by the Spread-Out Bragg Peak (**SOBP**) produced by charged particles

✓ Spare surrounding healthy tissues, compared to conventional photon radiotherapy

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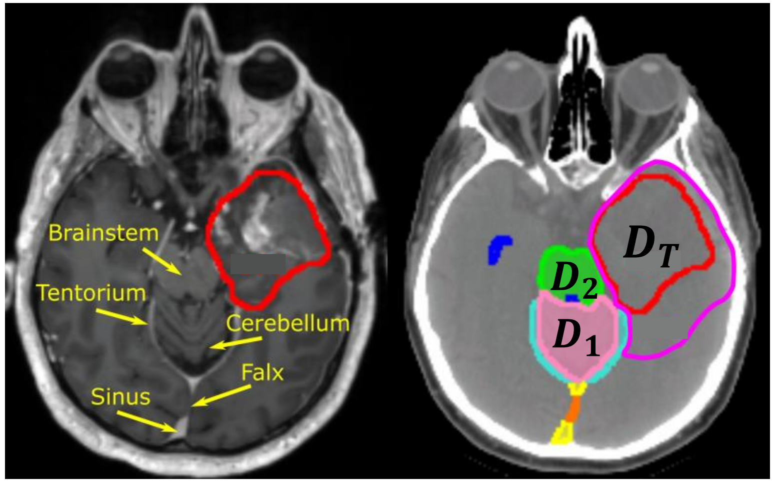
Well-suited for :

- pediatric tumours
- tumours located near organs at risk

Treatment planning in Hadrontherapy

TODAY



[Image credit: The Cancer Imaging Archive]

D_T = Tumour dose > 50 Gy

D_1 = OAR **1** < 2 Gy

D_2 = OAR **2** < 3 Gy

- Prescribed **reference dose** (D_T) to the tumor site
- Respecting certain **dose limits** in nearby organs at risk (e.g. D_1, D_2)

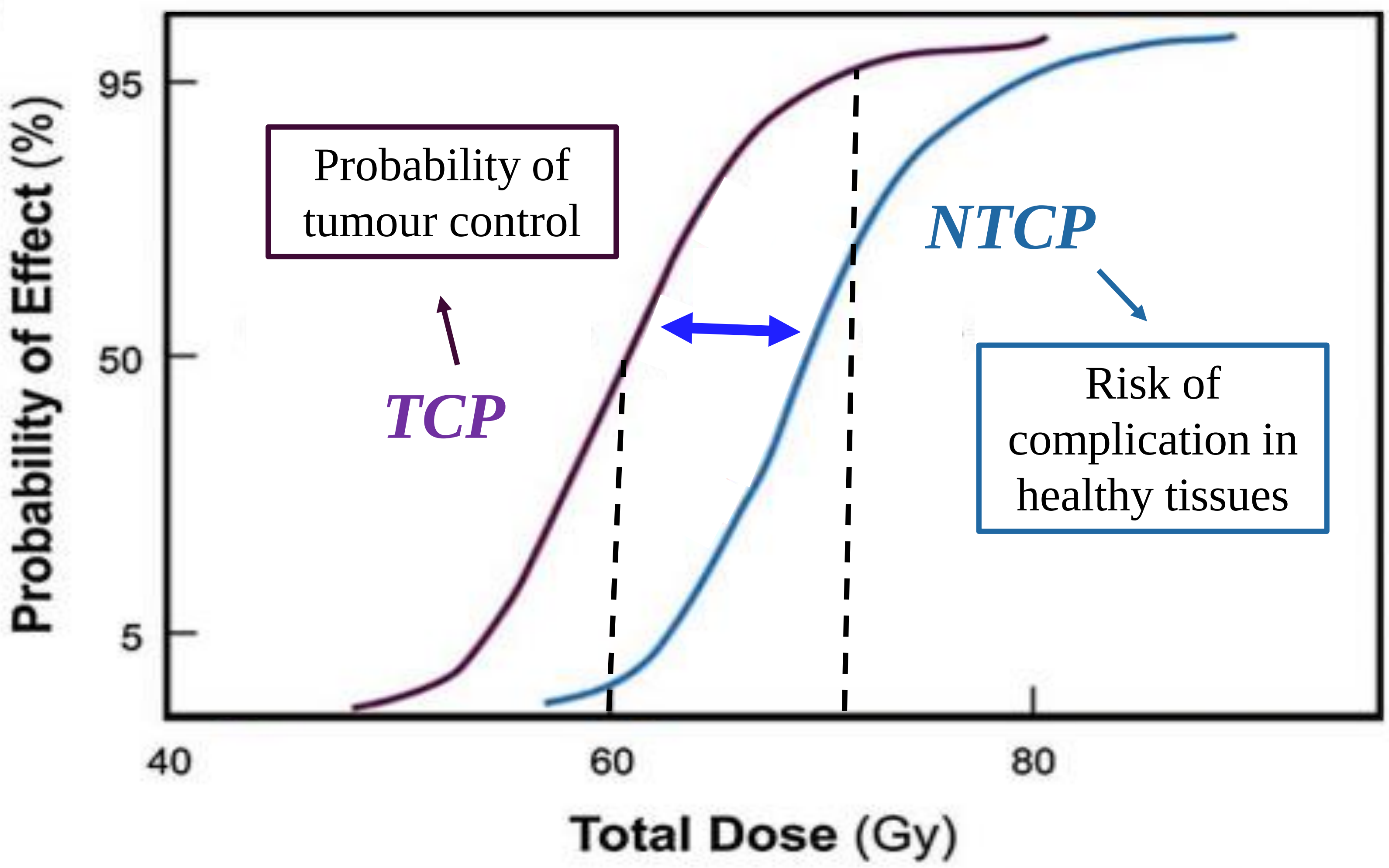
TOMORROW

To develop treatment plans directly based on the ***clinical outcomes***

Aim:

- optimize therapeutic efficacy
- minimize side effects
- develop more ***patient-specific*** treatment plans

To quantify the clinical *outcomes* → *Tumour Control Probability (**TCP**)*
*Normal Tissue Complication Probability (**NTCP**)*
curves



Hadrontherapy Aim:

- maximize **TCP**
- minimize **NTCP**

↓

increase TCP – NTCP gap as much as possible

AIM of the study

Development of a **novel approach** to **predict NTCP** curves for **late tissue reactions** following **Hadrontherapy**

For rat spinal cord irradiated with:

- Protons
  1.4 – 5.5 keV/μm
- Helium ions
  2.9 – 20.7 keV/μm
- Carbon ions
  13 – 125 keV/μm

In case of:

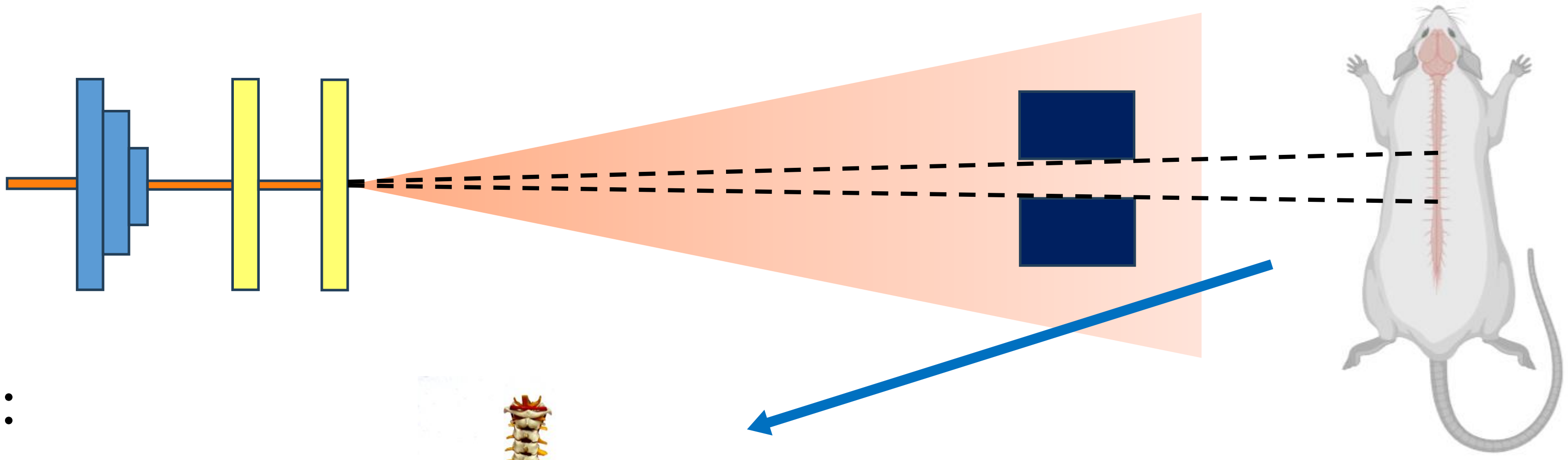
- Monochromatic irradiation
- Real mixed field

To directly incorporate biological *outcomes* into hadrontherapy treatment planning to improve **personalization** and clinical effectiveness

Materials and Methods

Experimental Data

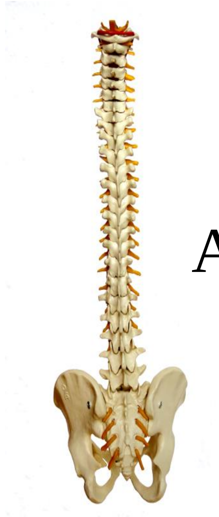
The experimental data, obtained from the literature, were used both for parameter calibration and for the validation of ion NTCP predictions. Further details can be found in [Karger et al., Int. J. Radiat. Onc. Biol. Phys., 2006, 10.1016/j.ijrobp.2006.08.045].



Irradiation with:

- Photons (for parameter calibration)
- Protons
- Helium ions
- Carbon ions

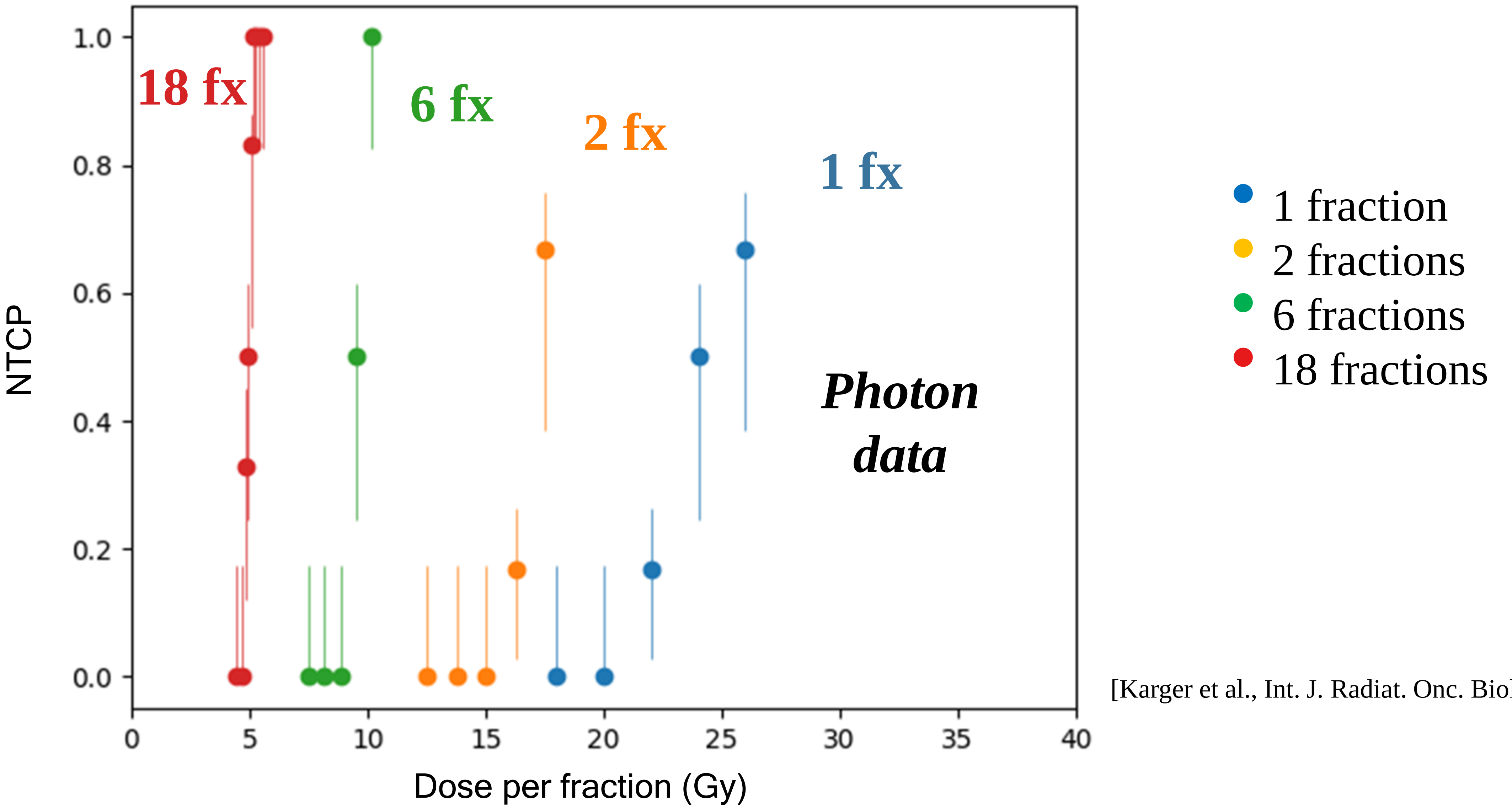
→ for ion NTCP validation (Protons, Helium ions, Carbon ions)



A portion of the rat spinal cord was irradiated

→ *Clinical outcome*: **paresis of grade II**, which is a late tissue reaction

e. g. Experimental Data



[Karger et al., Int. J. Radiat. Onc. Biol. Phys., 2006]

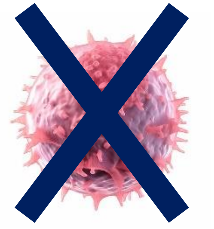
Critical Element NTCP Model

[Withers et al., Int. J. Radiat. Onc. Biol. Phys., 1988]

We selected the Critical Element NTCP model, which is based on the concept of Functional Sub-Units (FSUs).

Functional Sub-Unit (FSU) → Basic unit that can maintain organ functionality

Probability of killing 1 cell



→ $$\boldsymbol{P_{cell}} = 1 - S = 1 - e^{-\alpha n d - \beta n d^2}$$

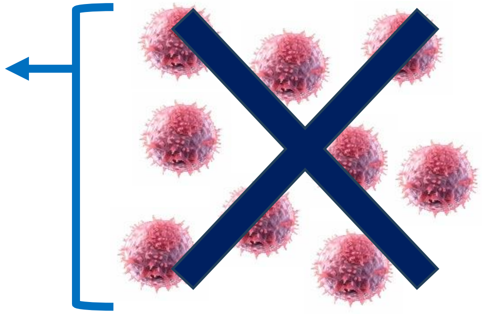
S: Linear-Quadratic cell survival model (**LQ**)

Assumption:

1 FSU

=

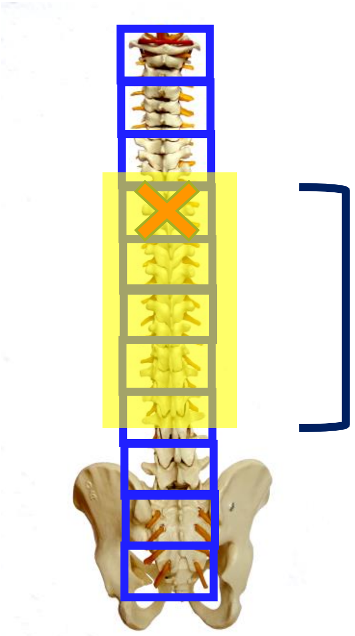
k cells



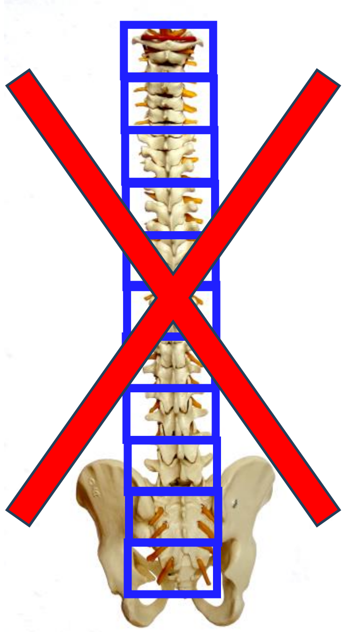
Probability of depleting 1 FSU = probability of killing all its k cells

$$P_{FSU} = (1 - e^{-\alpha n d - \beta n d^2})^k$$

For **serial organs**, like the spinal cord, the loss of a single FSU is sufficient to lack the functionality of the entire organ



***N**: # tot irradiated FSUs*



$$\mathbf{NTCP} = 1 - (1 - P_{FSU})^{N} = 1 - \left[1 - \left(1 - e^{-\alpha n d - \beta n d^2}\right)^{k}\right]^{N}$$

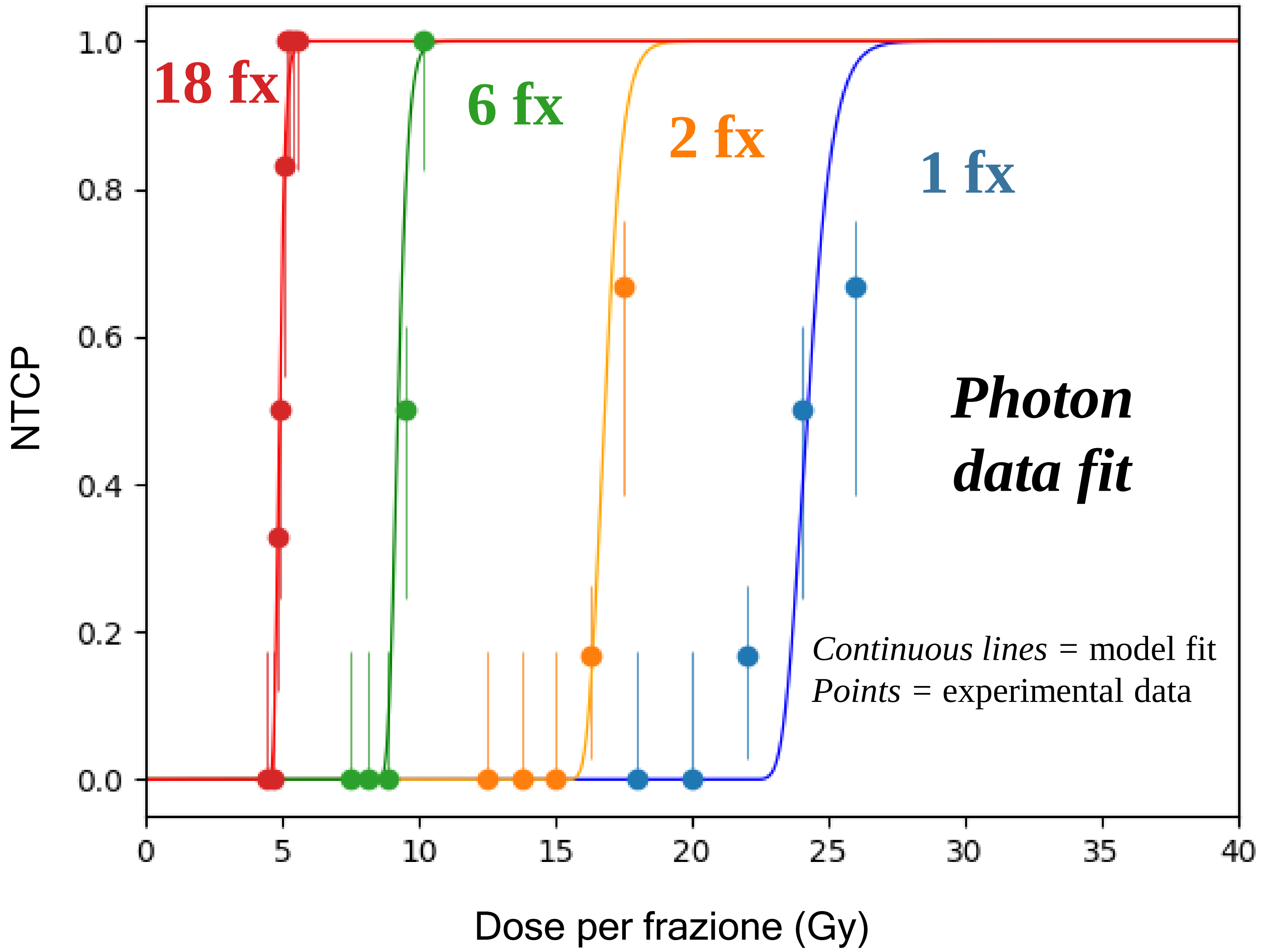
NTCP model that depends on only 4 parameters

↓

Model parameter estimation for ion NTCP predictions:

One set of ion **α, β, *k, N*** parameters for all the fractionation schemes

k and N estimation for ion NTCP predictions



Photon data **fitted** with the *Critical Element NTCP Model*

Resulting parameters

Photon **k, N** depending only on tissue features

Photon α_X and β_X

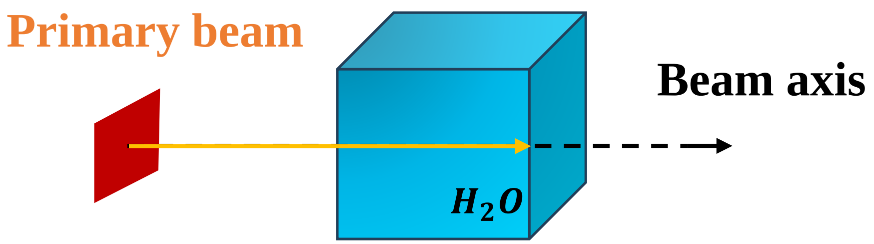
Fixed for ion NTCP predictions

Ion α and β estimation for ion NTCP predictions

In case of

1 **Monochromatic irradiation**

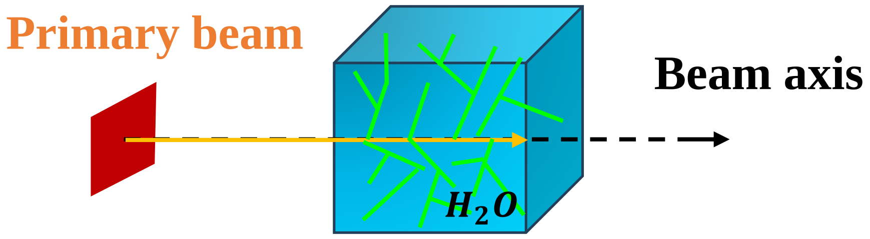
- Only primary beam particles at fixed energy were considered



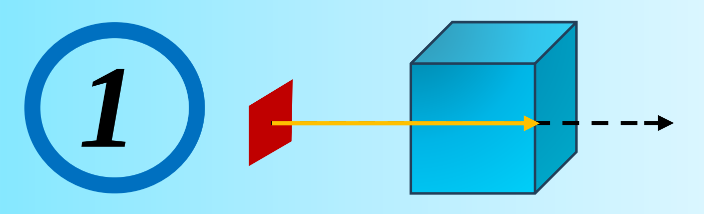
BIANCA

2 **Real Mixed Field**

- All secondary particles produced by the interaction of the primary beam with the water phantom were included
- The SOBP results from the superposition of Bragg peaks at different energies



Interface BIANCA - GEANT4



Monochromatic Field

Ion α and β ⟶ calculated by applying **BIANCA** model

BIANCA: biophysical model developed by the Computational Radiobiology group of Pavia University [Ballarini, Carante, Radiat. Phys. And Chem., 2016]

BIANCA input

Photon α_X and β_X derived by fitting the photon data using the Critical Element NTCP model

Z=1 A=1,2,3

LET	alfa	beta
5	0.161168003608071	0.034227925863557
7.5	0.219155512347106	0.031807059167825
10	0.277730304065006	0.026062986984213
12.5	0.324223249128924	0.031963531745716
15	0.370061833526514	0.032195025167274
17.5	0.421451839190716	0.031121716722449
20	0.482515824349661	0.028525693688078
22.5	0.560520033338037	0.018863044675061
25	0.613244623202487	0.019486893814967
27.5	0.670278414247874	0.018719108913174
30	0.723636950773347	0.019048357687813

Z=2 A=3 (He3)

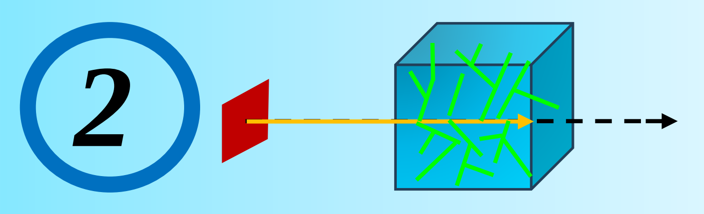
LET	alfa	beta
5	0.134484868252636	0.033328267759041
10	0.144914045351193	0.039167916406686
20	0.195309536204132	0.055766427339300
30	0.254263496879065	0.086614721872234
40	0.346232798363745	0.110820821623133
50	0.461751927355611	0.125899692117198
60	0.577156328111620	0.149414730517834
70	0.688177599469057	0.170307321062664
80	0.831202131850177	0.173711239896555
90	0.958976414546513	0.178987749762615

Z=2 A=4 (He4)

LET	alfa	beta
5	0.122919965474113	0.0282243396663055
10	0.164742642147497	0.0320256389518587

BIANCA output

Dataset of α and β for each **particle** and **LET** value

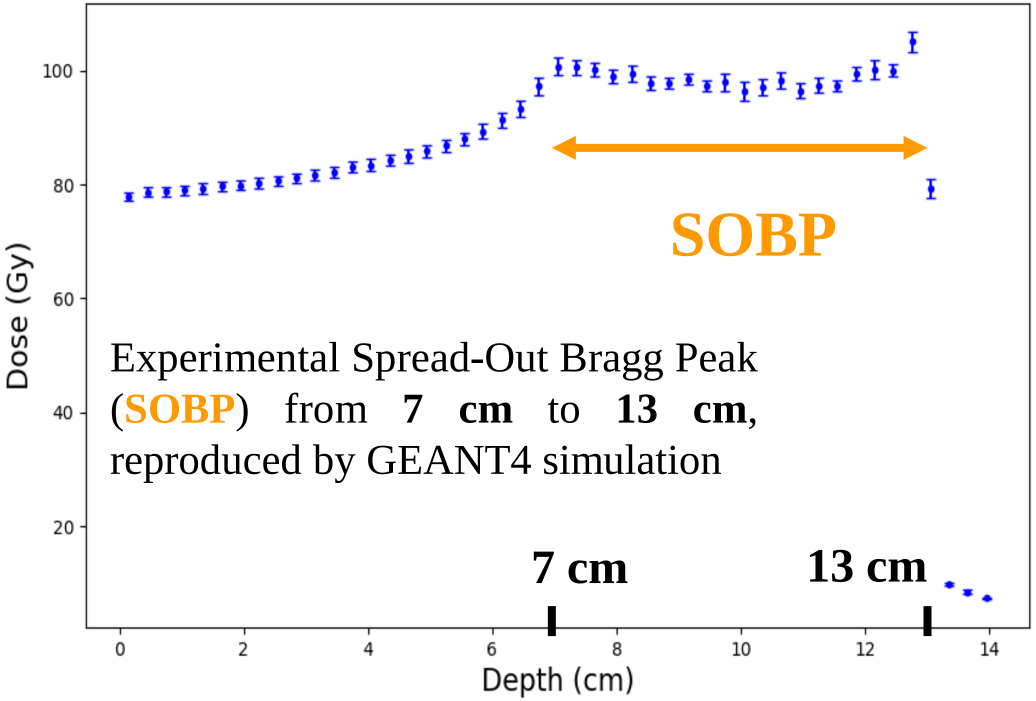


Real Mixed Field

Ion α and β → calculated by **BIANCA – GEANT4** interface

GEANT4 irradiation simulation:

To reproduce the **experimental conditions** and identify the secondary particles generated →



BIANCA α and β table for each particle, as a function of energy value

The ion $\overline{\alpha}$ and $\overline{\beta}$ values for the mixed field were calculated by averaging, over dose, the α and β values read from the BIANCA table **for each energy and particle type** produced in the GEANT4 simulation

Ion NTCP predictions

- All four parameters required for ion NTCP predictions have been estimated

$\boldsymbol{\alpha, \beta}$ Monochromatic Field
from BIANCA

$\boldsymbol{k, N}$
from Photon data fit

$\bar{\boldsymbol{\alpha}}, \bar{\boldsymbol{\beta}}$ *Real Mixed Field*
from BIANCA-GEANT4

- **Monochromatic Field**

$$\mathbf{NTCP} = 1 - \left[1 - \left(1 - e^{-\alpha n d - \beta n d^2}\right)^k\right]^N$$

- **Real Mixed Field**

$$\mathbf{NTCP} = 1 - \left[1 - \left(1 - e^{-\bar{\alpha} n d - \bar{\beta} n d^2}\right)^k\right]^N$$

NO free - parameters → Full **predictions** of ion NTCP curves

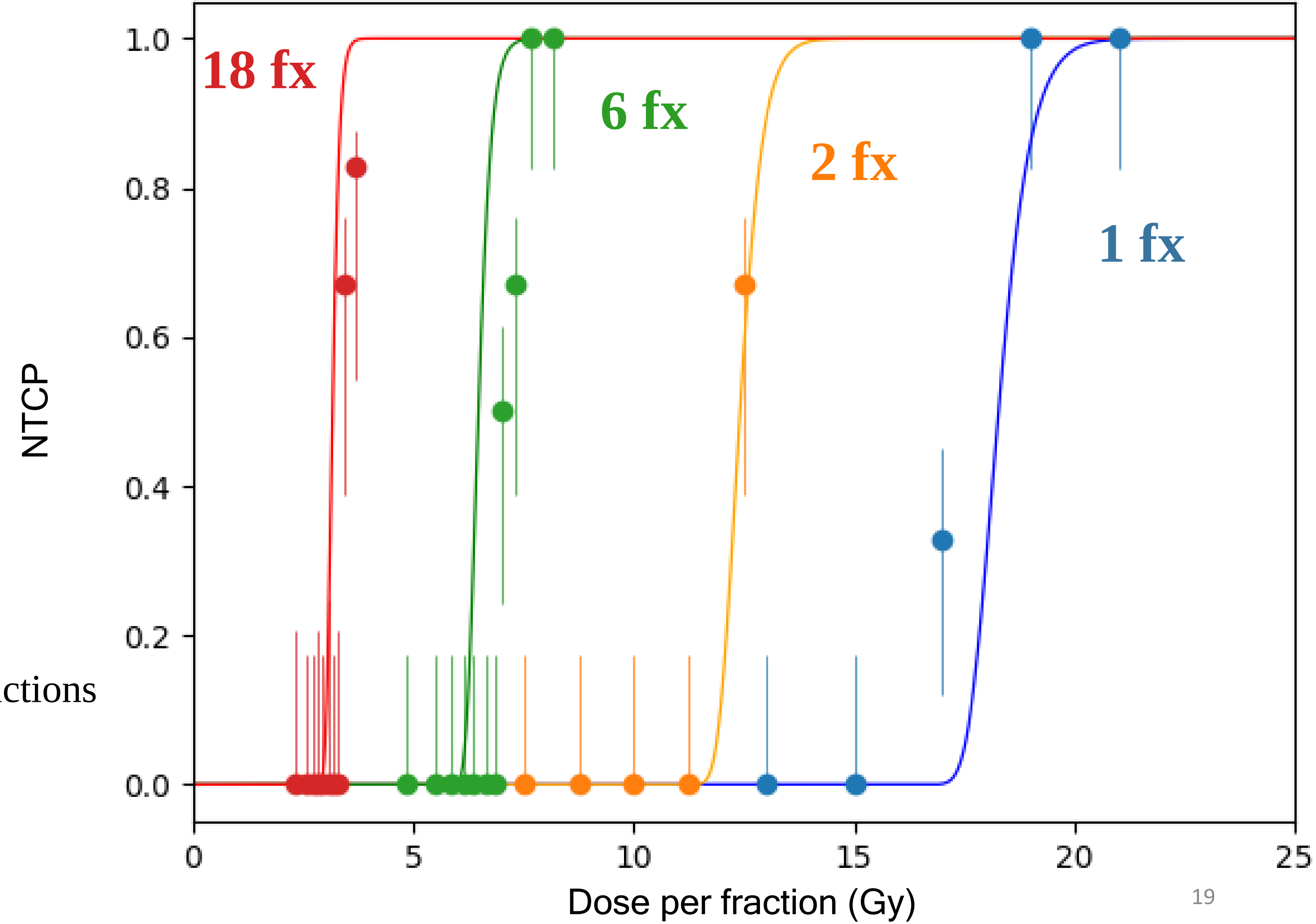
Results

[**A. Casali** et al., Phys. Med. Biol., **2024**]

Carbon ions 13 keV/μm

Monochromatic Field

- 1 fraction
- 2 fractions
- 6 fractions
- 18 fractions

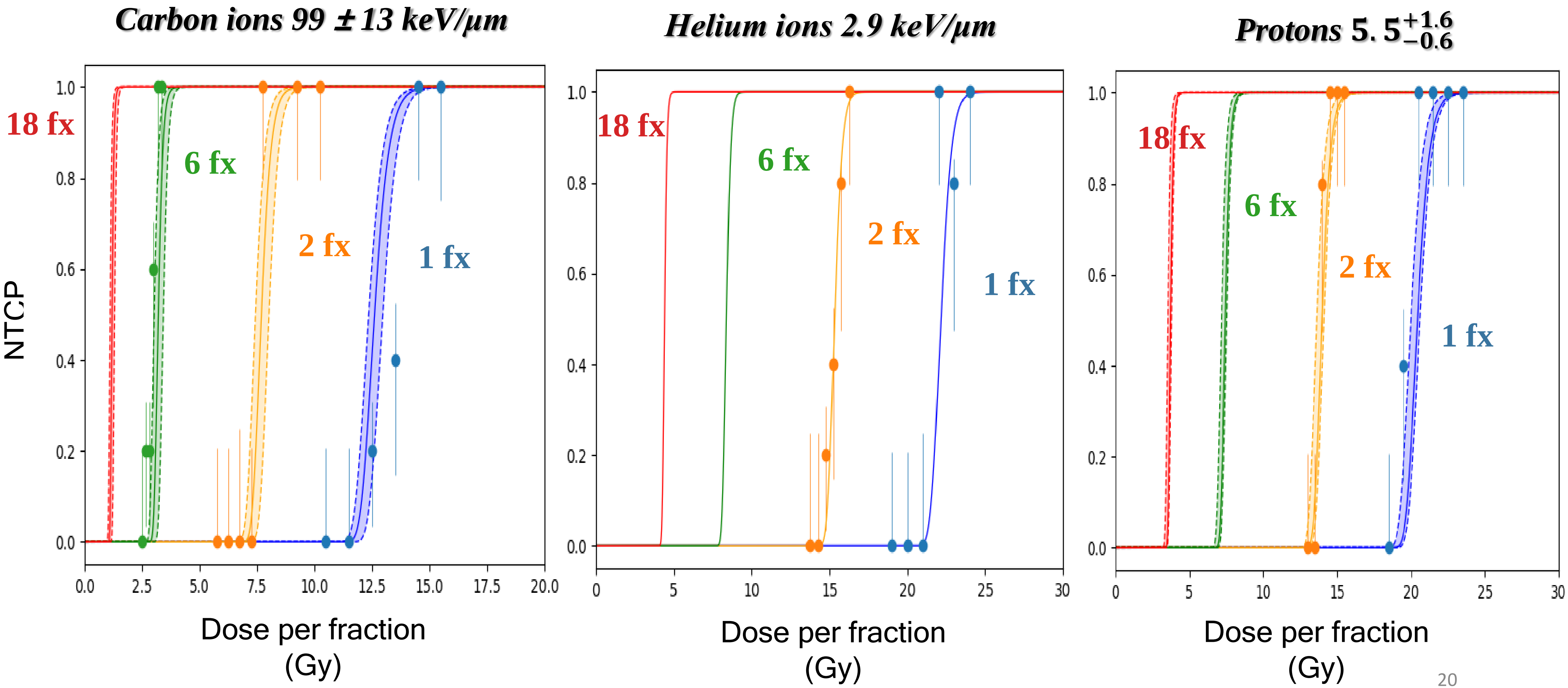


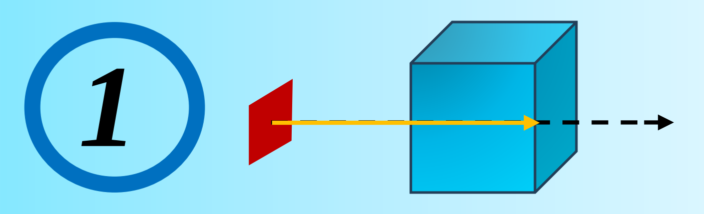
Continuous lines: model predictions
Points: experimental data

[**A. Casali** et al., Phys. Med. Biol., **2024**]

Monochromatic Field

Results for other particles and LET values



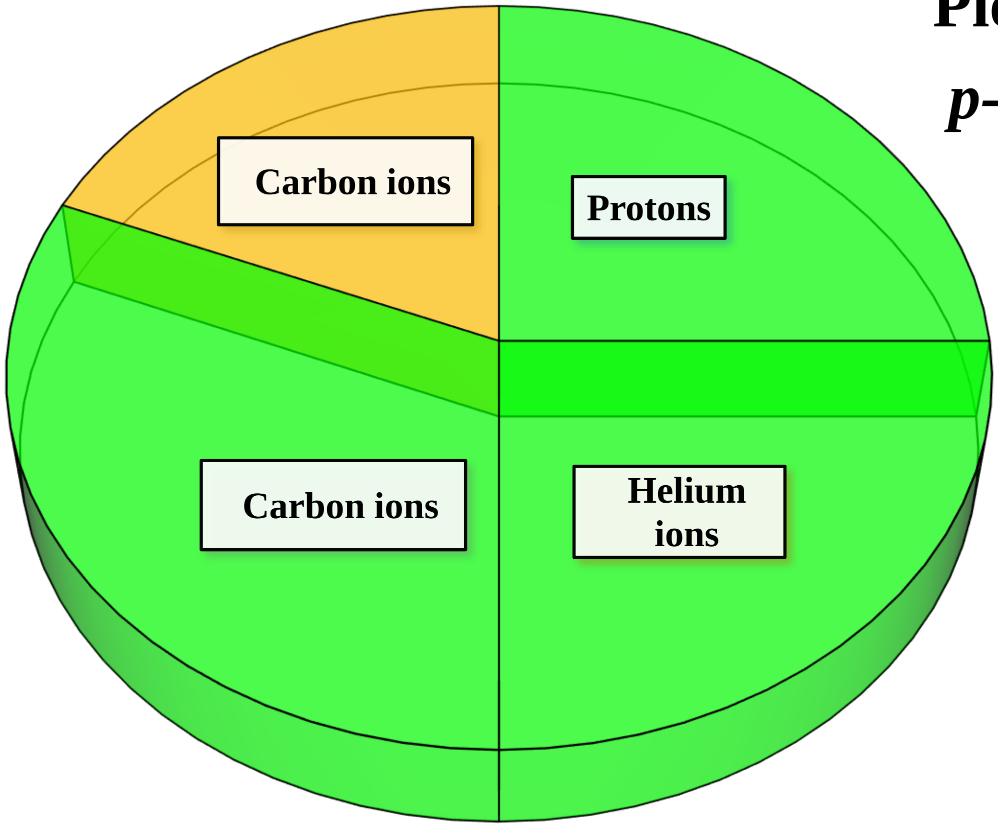


Statistical analysis

Monochromatic Field

P-values assessing the agreement between experimental data and our approach predictions under monochromatic ion irradiation were obtained via Monte Carlo simulation.

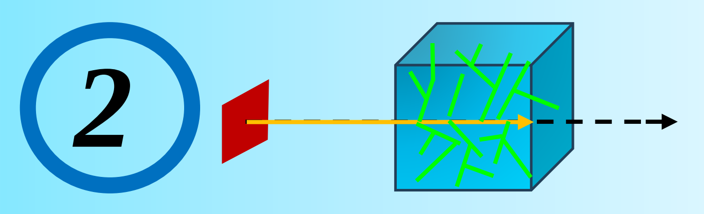
Pie chart of *p-values*



p - value > 5%

p - value > 1% **OK**

In general, the proposed approach exhibits **good predictive power** across the entire set of experimental data.



Statistical analysis

Real Mixed Field

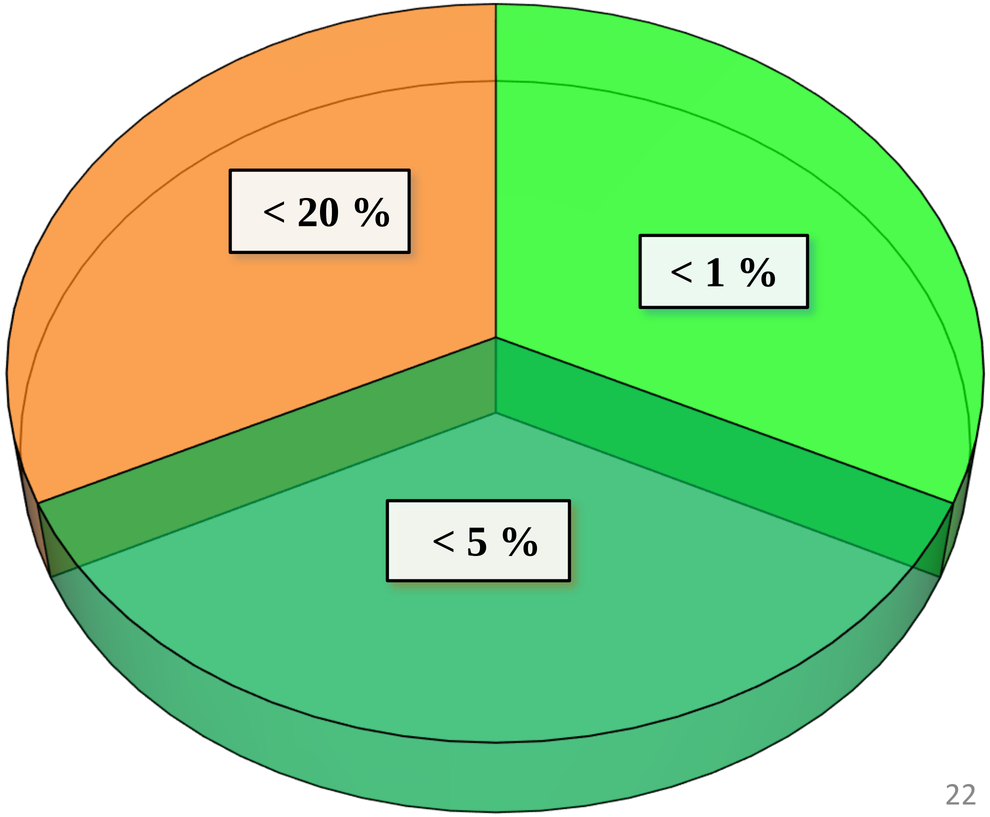
Regarding real mixed-field ion irradiation, only the percentage difference between the monochromatic and mixed-field cases was evaluated.

$$\textbf{Percentage difference} = \frac{|D_{50}^{mixed} - D_{50}^{mono}|}{D_{50}^{mono}} 100$$

D_{50}^{mixed} : dose at a NTCP of 50% in case of real mixed field

D_{50}^{mono} : dose at a NTCP of 50% in case of monochromatic field

Pie chart of percentage difference mixed-mono



Out of 56 datasets, 47 show **NO significant difference** (< 5%) between the two scenarios. Differences > 5% but < 20% were observed only in few C-ions cases with high LET, where mixed-field plays an important role.

Conclusions

Take home messages

Integration of
biological models
(TCP / NTCP)
into ***treatment planning***

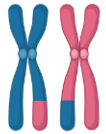
To enable
patient-specific
treatment plans

Strengths of
our approach
[A. Casali et al., Phys. Med. Biol., 2024]

NTCP (k, N, α, β)
- ✓ few parameters
- ✓ high predictive power

Advantage of using
BIANCA over other
biophysical models

BIANCA simulates also
chromosome aberrations

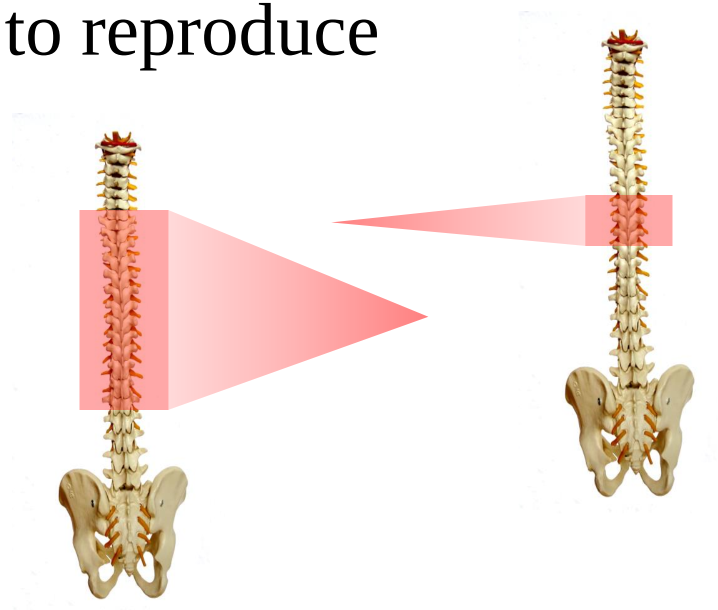


To predict
stochastic effects

Future perspectives

- Apply NTCP *Critical Element Model* + LQ model + BIANCA to →
  - Human data
  - Other *tissue reactions* endpoints
  - Other *irradiated organs*

- Modify the NTCP model mathematical expression to reproduce
  - **Stochastic effects** (es. radiation-induced tumours)
  - **Volume Effect**



Thank you for your attention!

If you have any doubts, questions, or if you want more information, please don't hesitate to contact me

↓

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