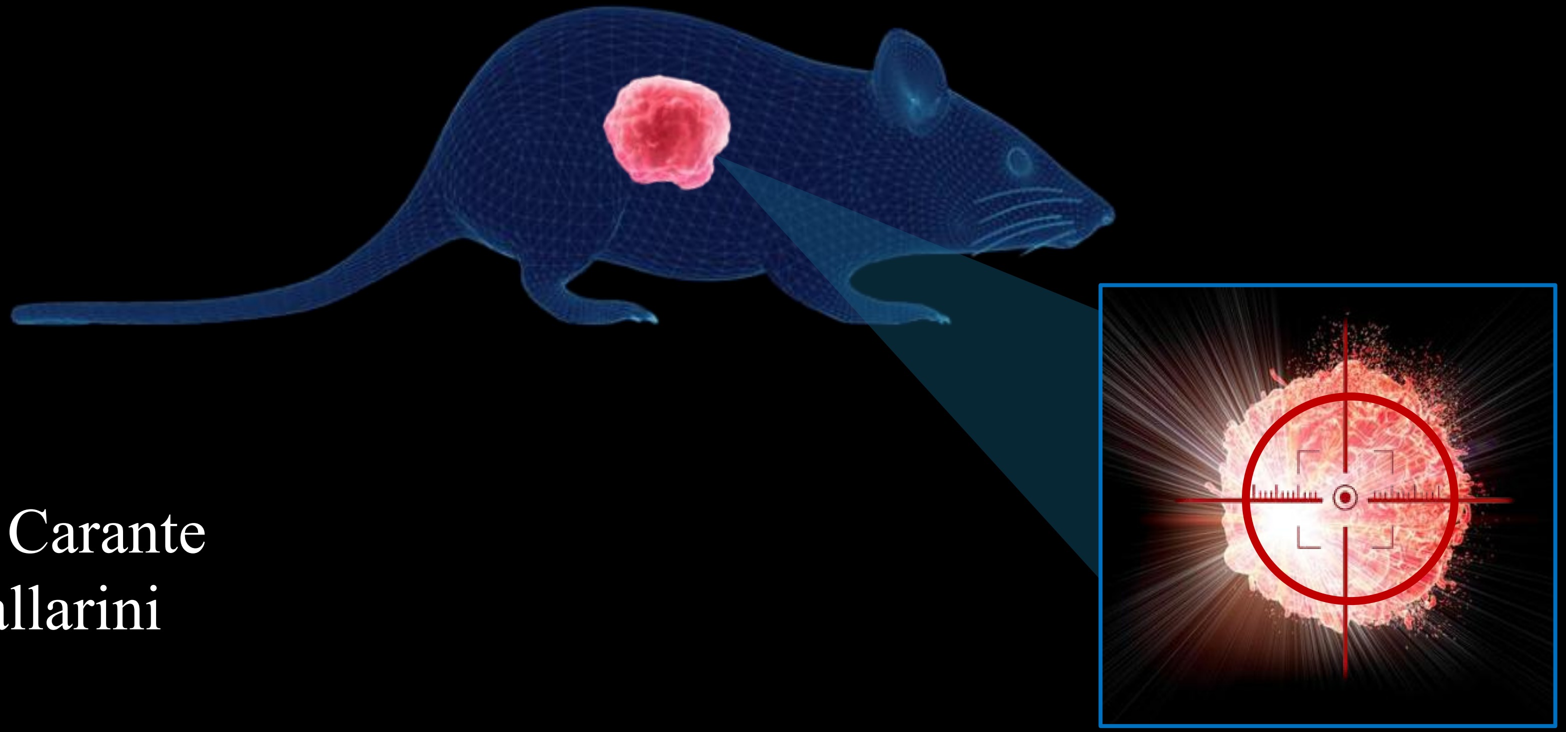
Università degli Studi di Pavia - PhD course in Physics

End Of the Year Seminars - 2025

For a safer Hadrontherapy



Supervisors:
Mario Pietro Carante
Francesca Ballarini

18 Sept 2025

Alice Casali

PhD cycle: XL

A.A. 2024 - 2025

What is Hadrontherapy?

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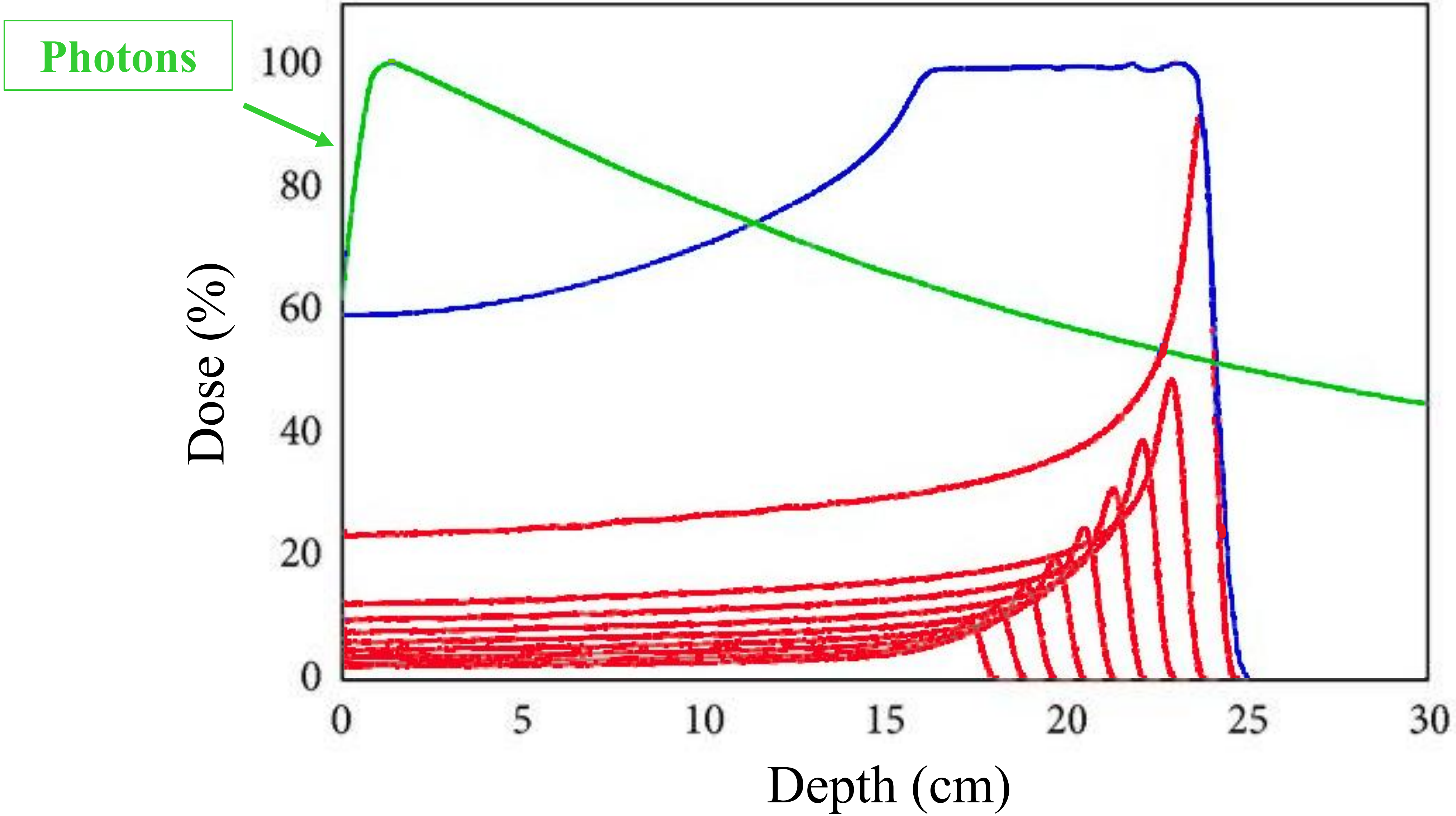
[Image credit: Grant et al., BioMed research international. (2014), 389048. 10.1155/2014/389048]



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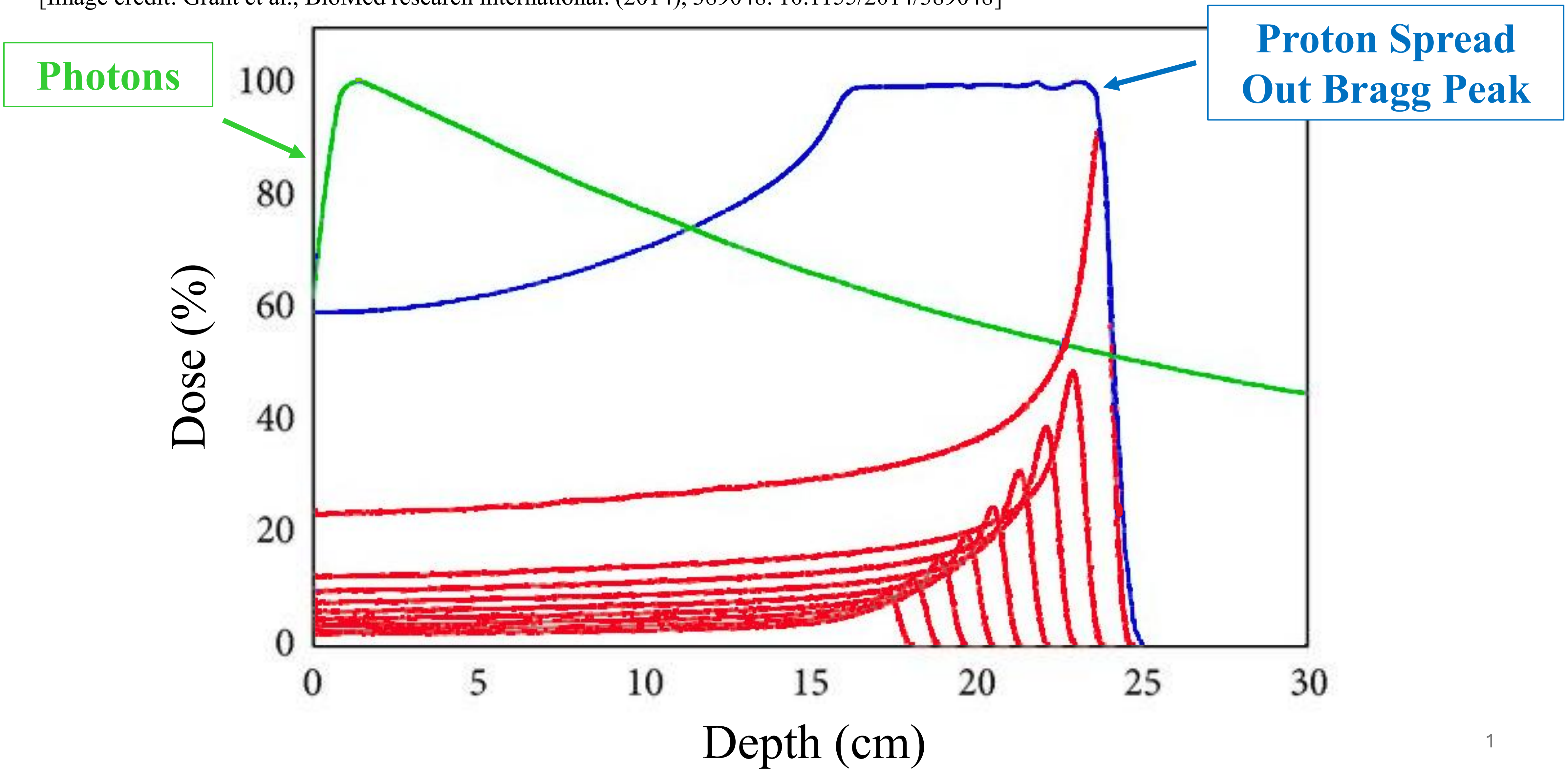

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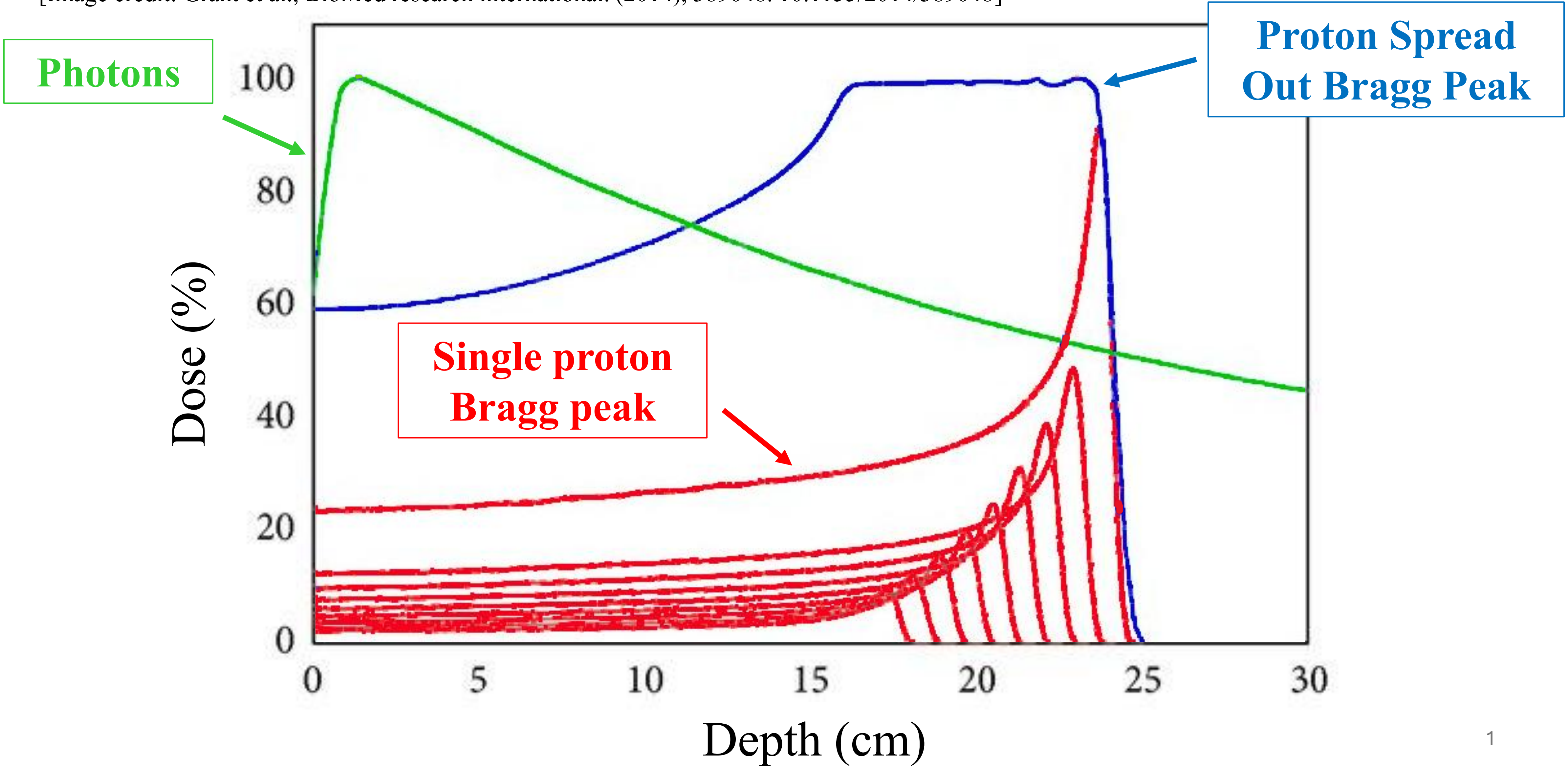

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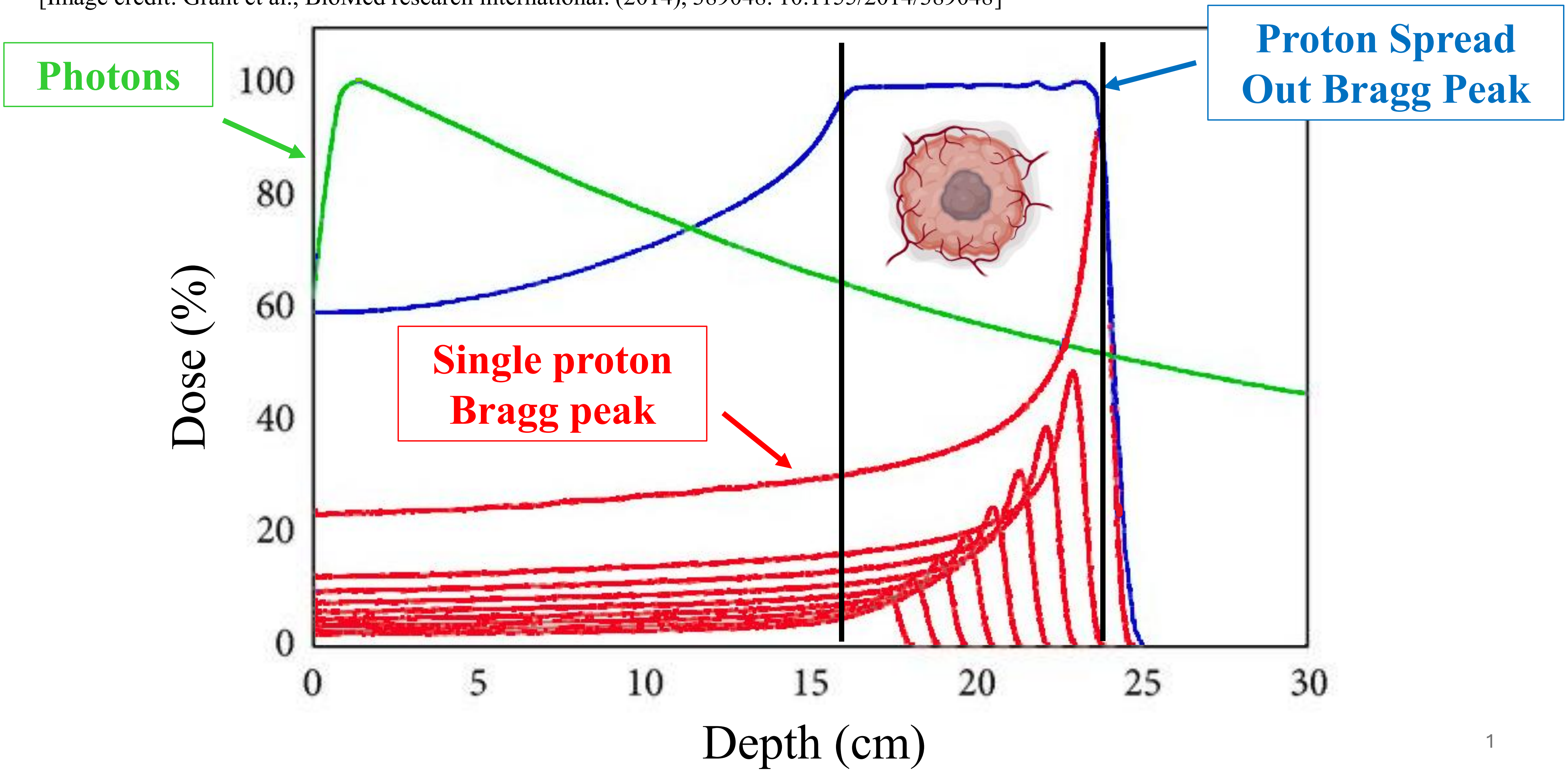

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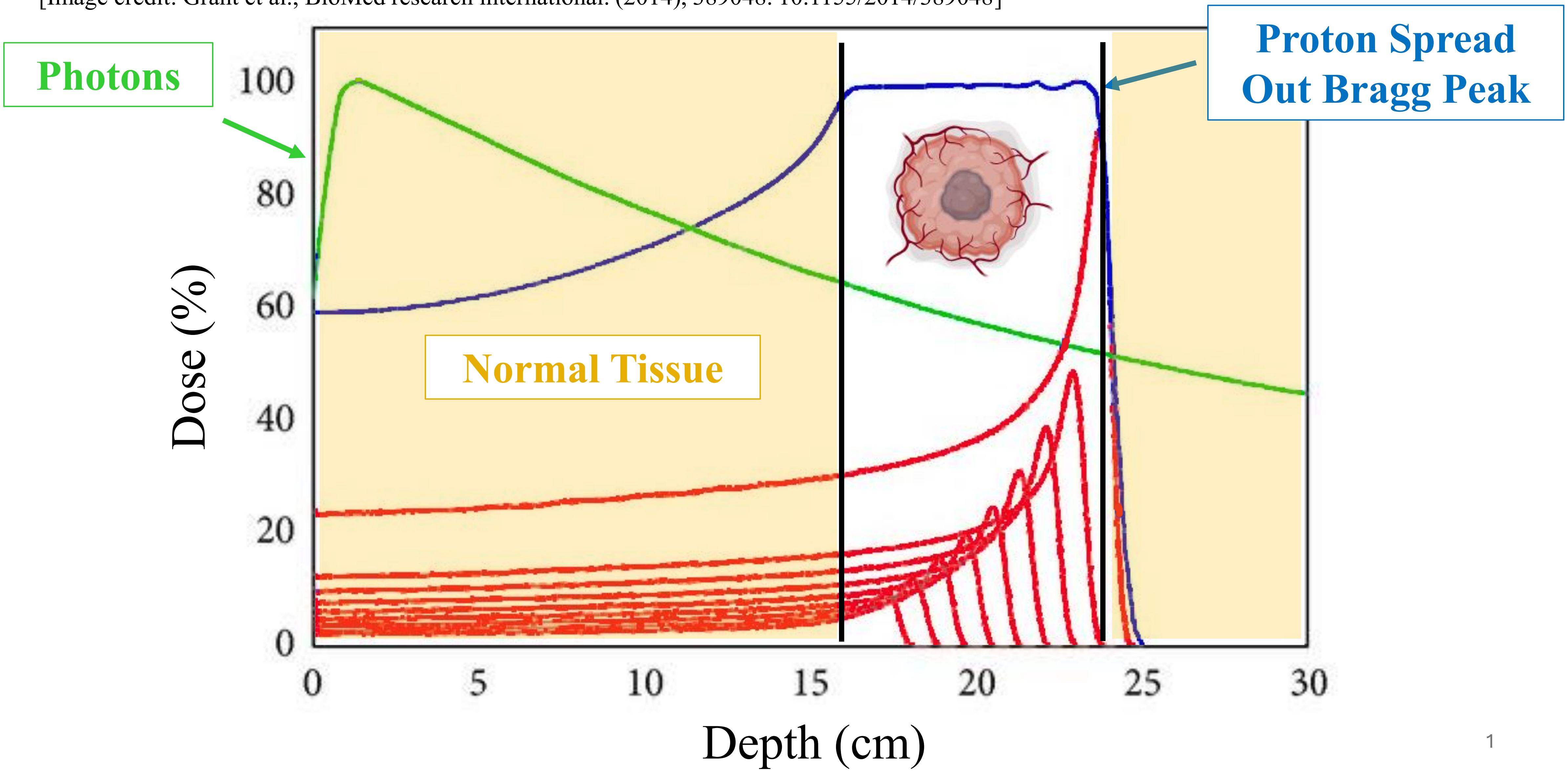
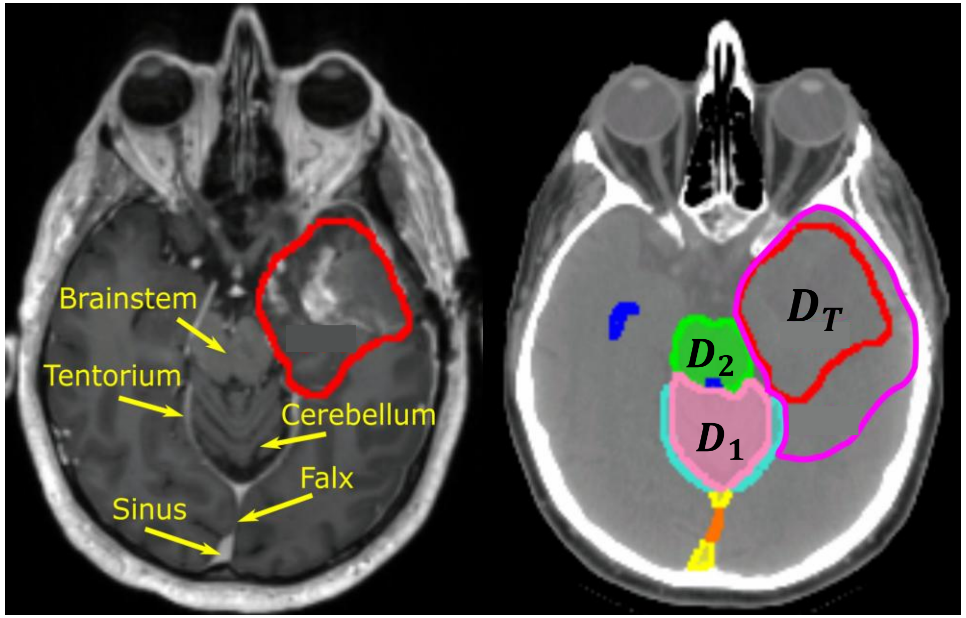


Treatment Planning

TODAY



D_T = Tumour dose > 50 Gy

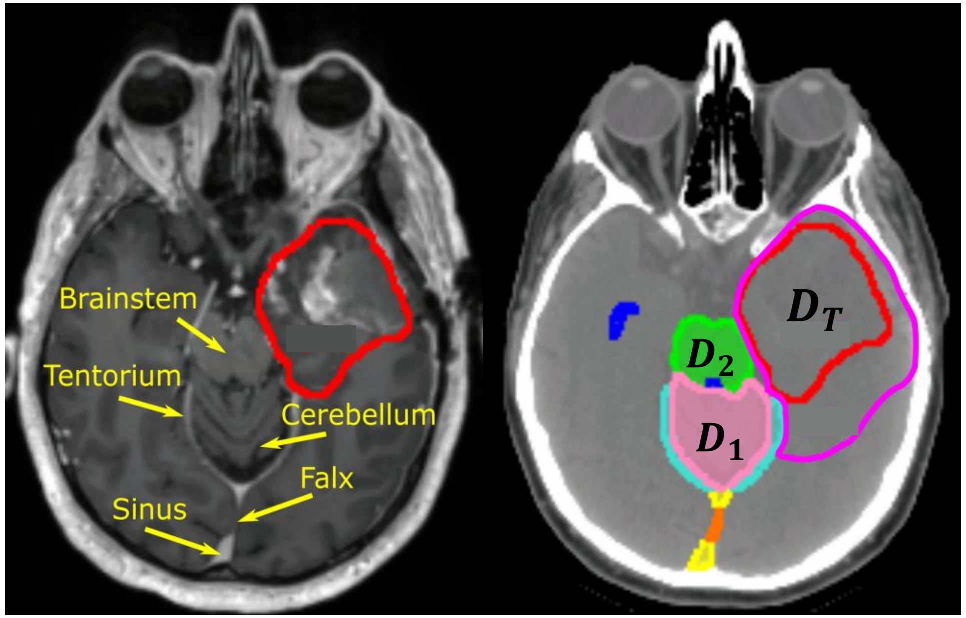
D_1 = OAR **1** < 2 Gy

D_2 = OAR **2** < 3 Gy

[Image credit: The Cancer Imaging Archive]

Treatment Planning

TODAY



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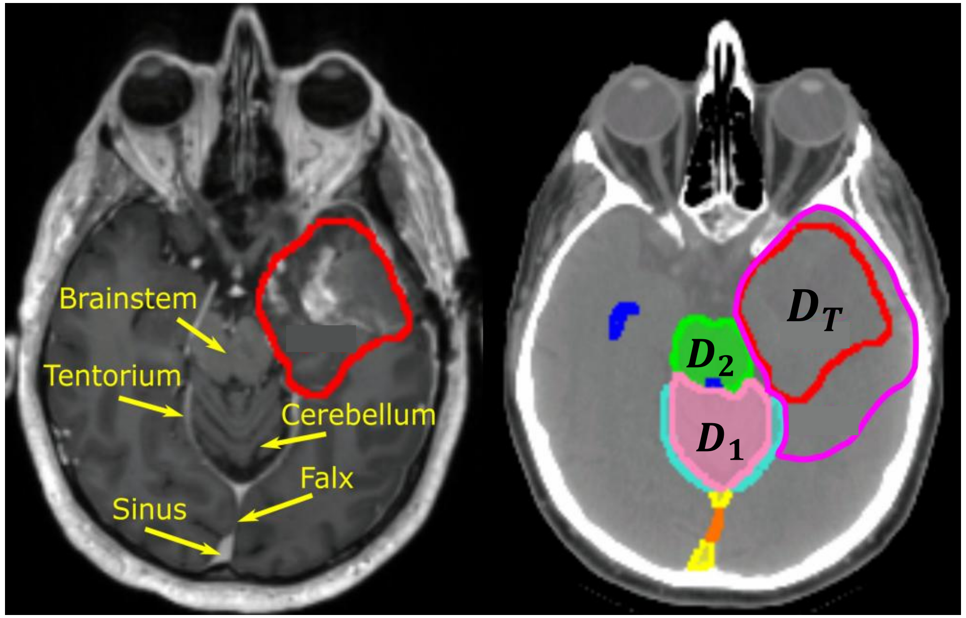
[Image credit: The Cancer Imaging Archive]

TOMORROW

Directly based on clinical ***outcomes***

Treatment Planning

TODAY



$\color{red}{D_T}$ = Tumour dose > 50 Gy

$\color{green}{D_1}$ = OAR **1** < 2 Gy

$\color{magenta}{D_2}$ = OAR **2** < 3 Gy

[Image credit: The Cancer Imaging Archive]

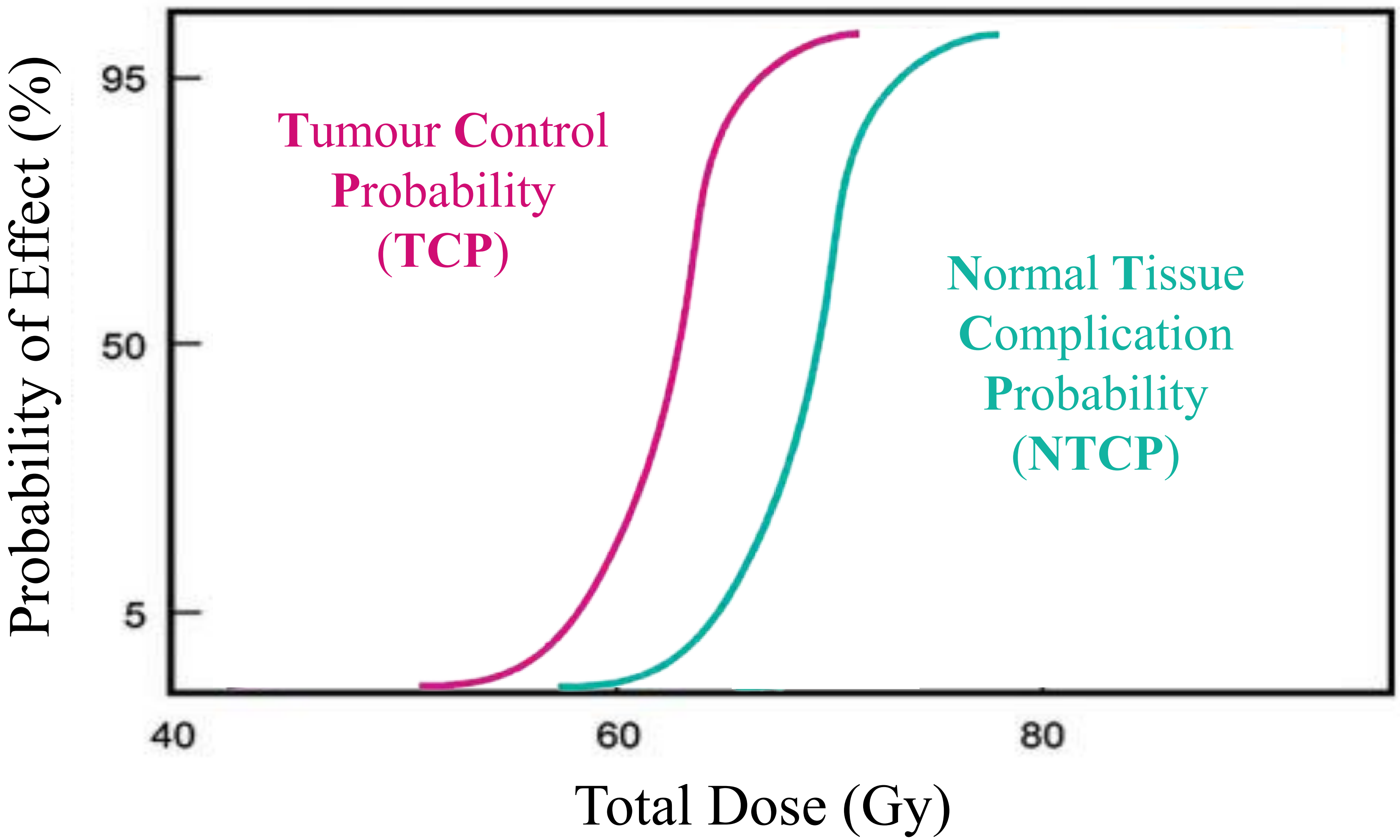
TOMORROW

Directly based on clinical ***outcomes***

Patient-specific treatment plans

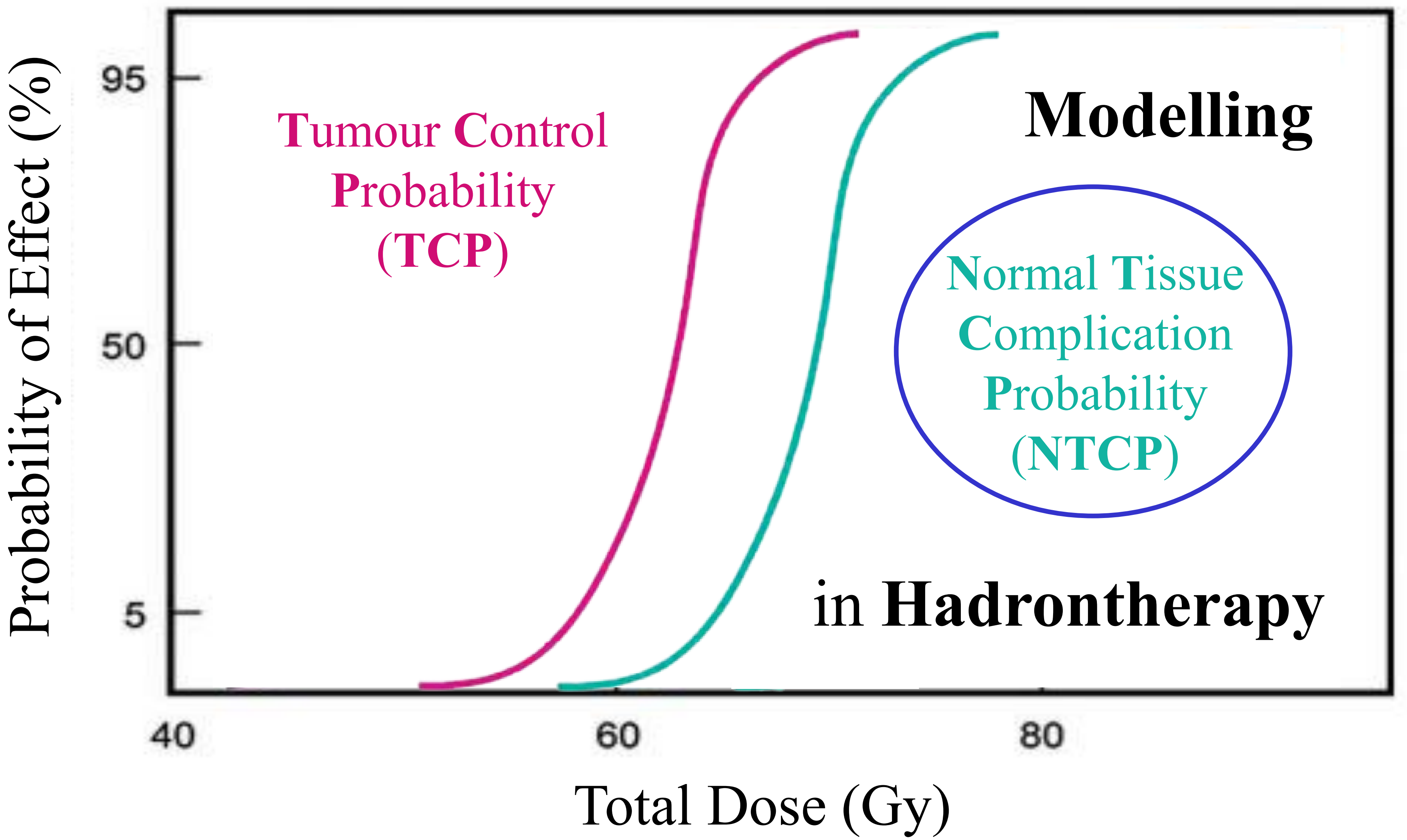
Quantification of clinical ***outcomes***

Quantification of clinical ***outcomes***



[Image credit: C. Chargari et al., Cancer Treatment Reviews. (2016), 10.1016/j.ctrv.2016.03.001]

Quantification of clinical *outcomes*



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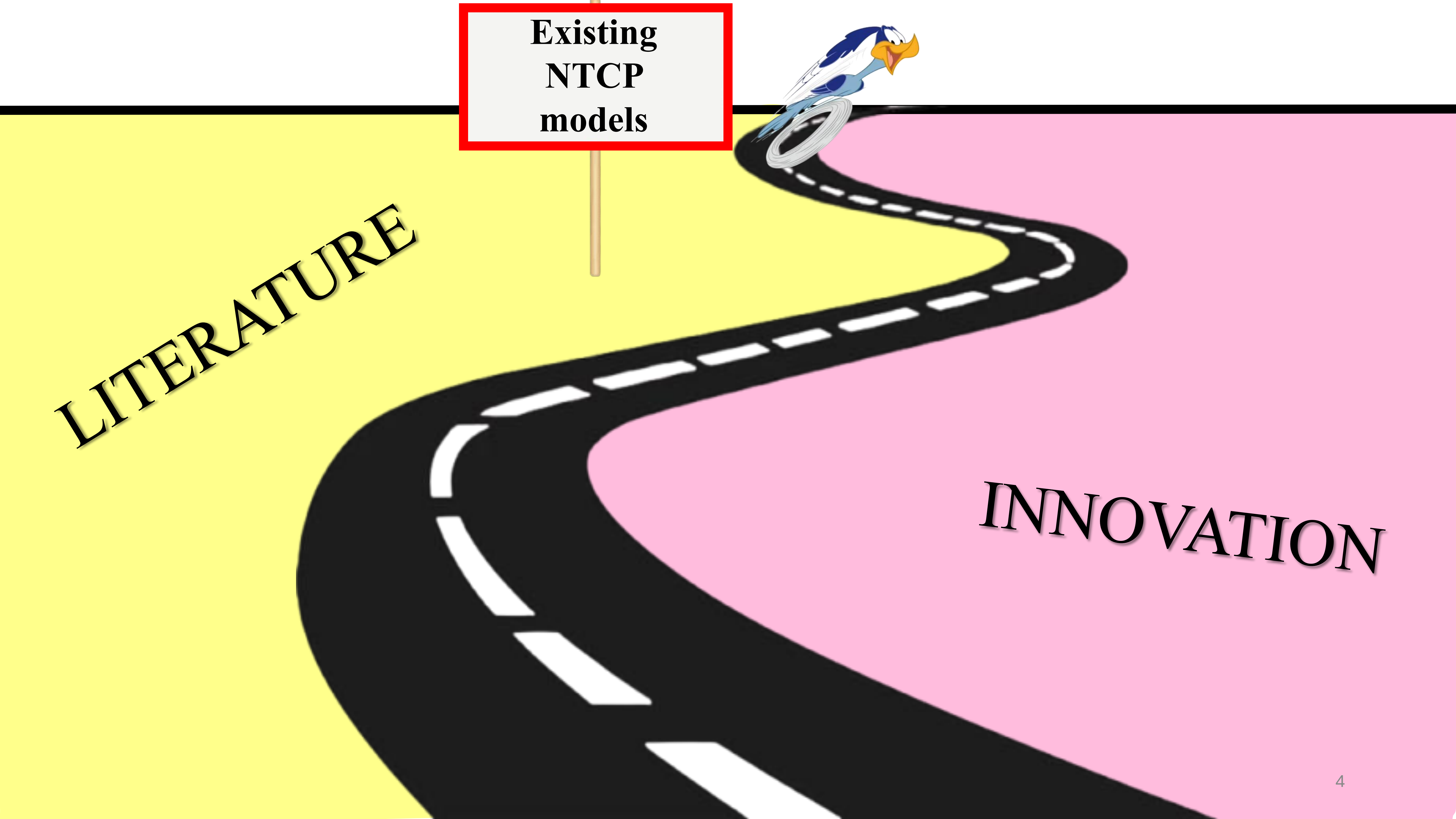

Existing
NTCP
models
LITERATURE
INNOVATION

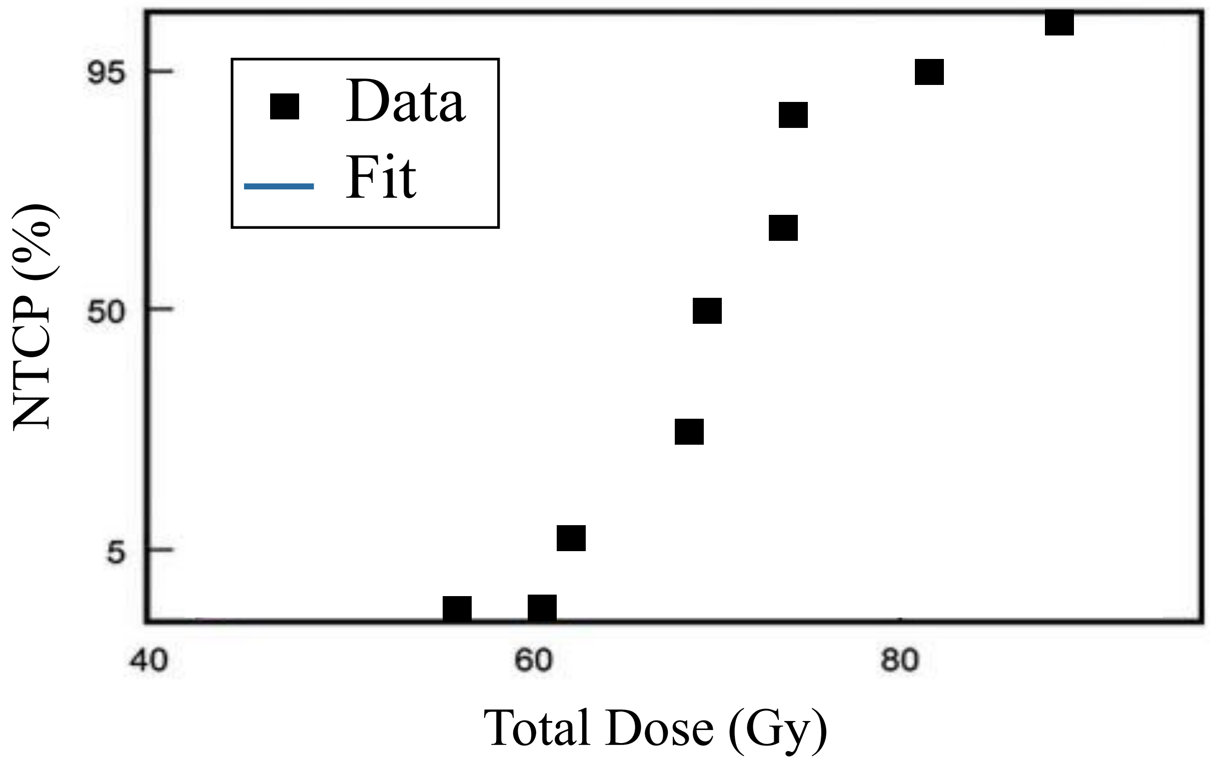
Existing NTCP Models

Phenomenological

Mechanistic

Existing NTCP Models

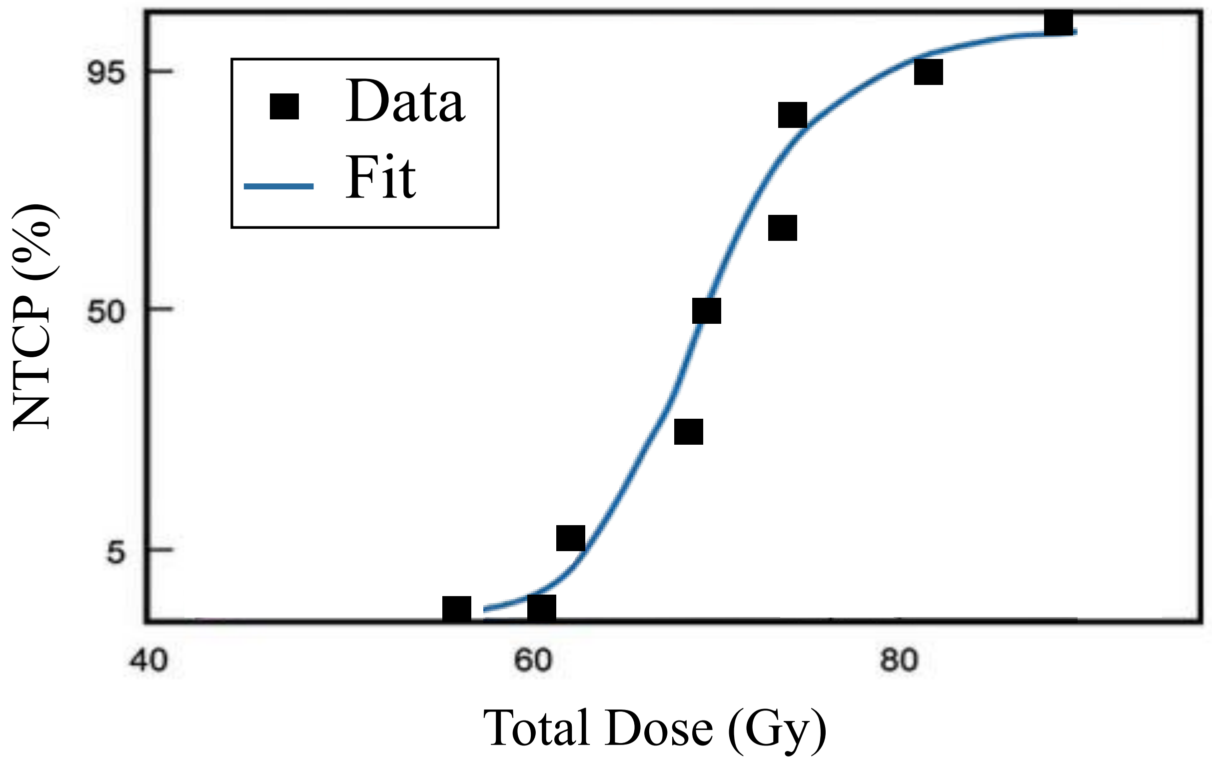
Phenomenological



Mechanistic

Existing NTCP Models

Phenomenological



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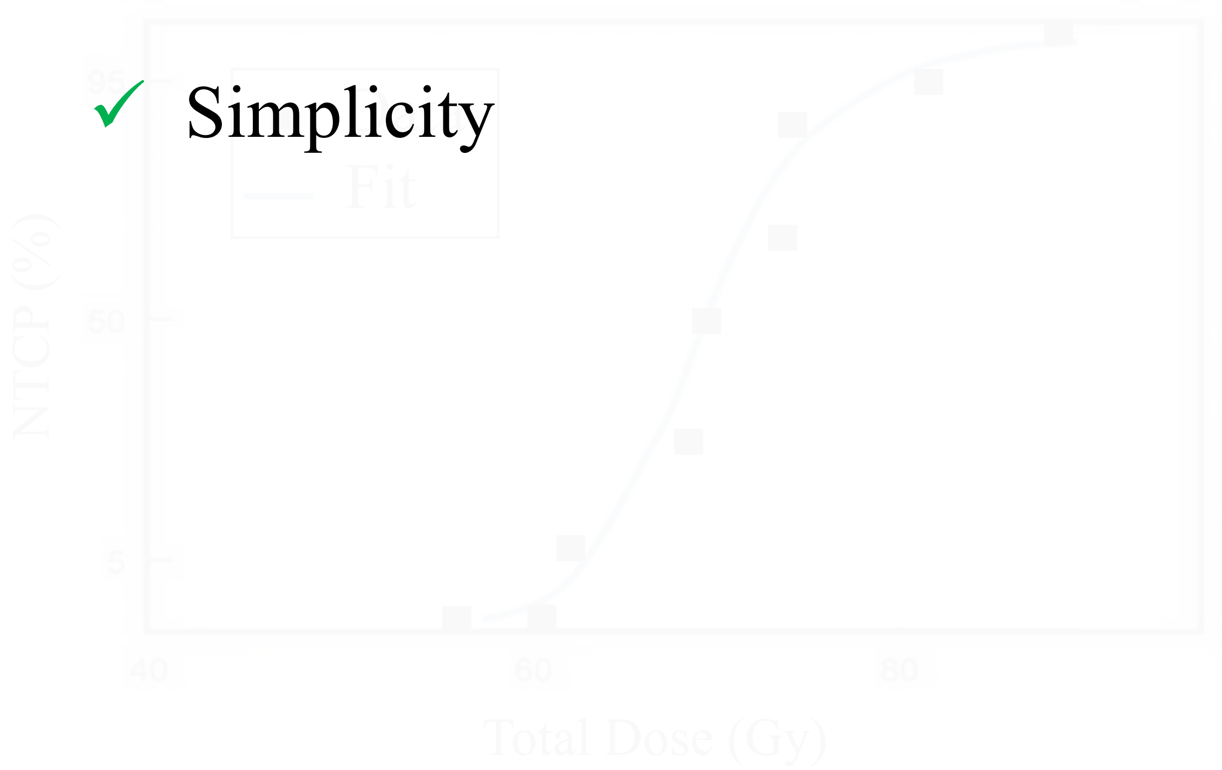


✓ Simplicity

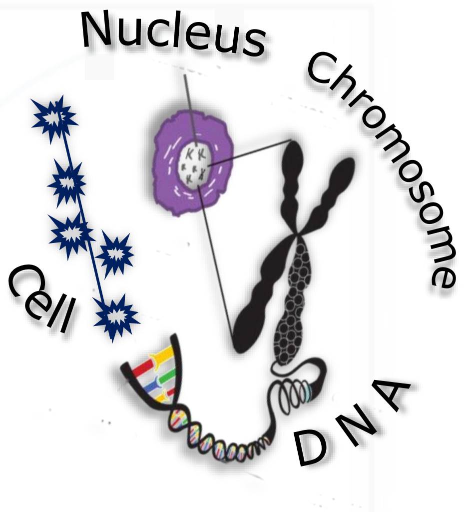
Mechanistic

Existing NTCP Models

Phenomenological

✓ Simplicity

✓ Not account for biological mechanisms



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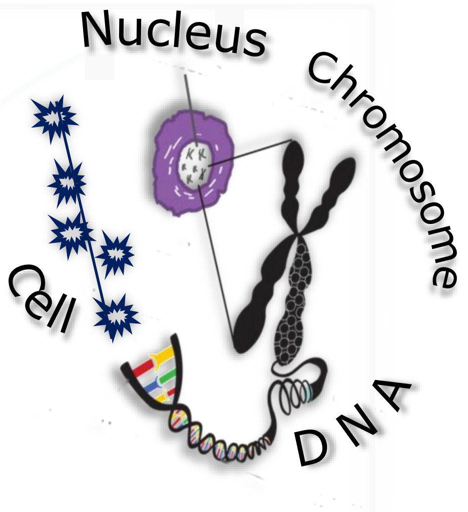
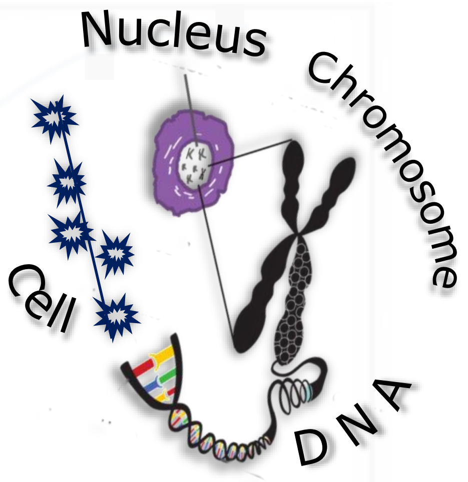


✗ Predictions in situations deviating from the validation dataset

Existing NTCP Models

Phenomenological

- ✓ Simplicity
- ✓ Not account for biological mechanisms
- ✗ Predictions in situations deviating from the validation dataset



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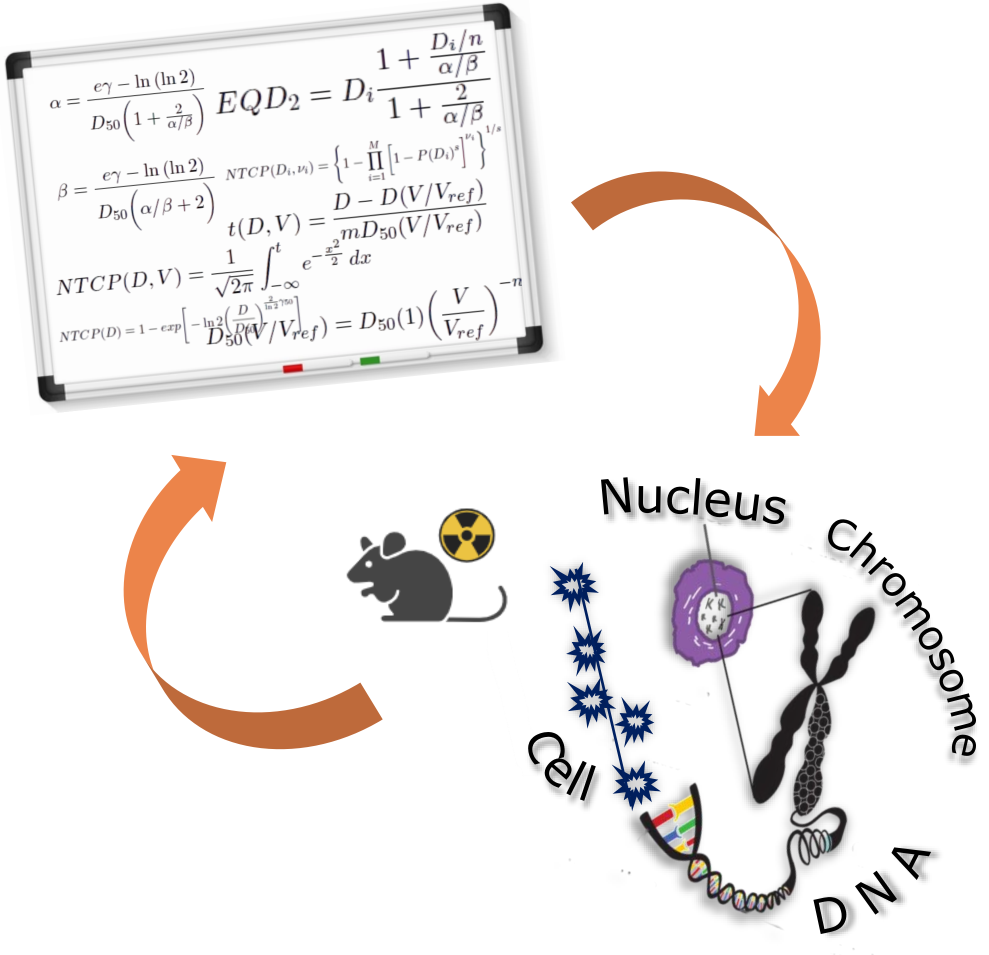

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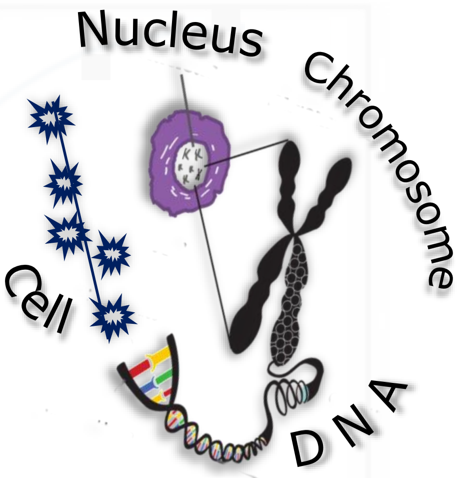

- ✗ Predictions in situations deviating from the validation dataset

Mechanistic

- ✓ Parameters with physical and biological meanings

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✓ Simplicity

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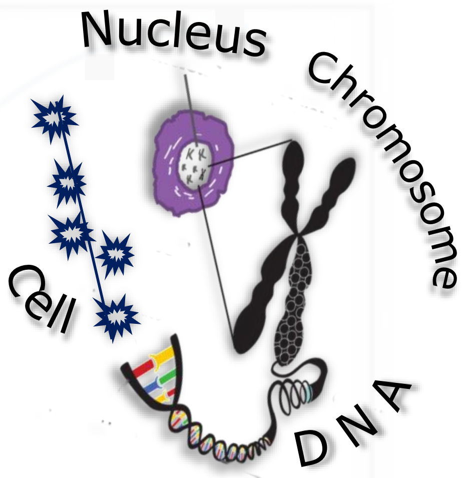

✗ Predictions in situations deviating from the validation dataset

Mechanistic

✓ Parameters with physical and biological meanings

✓ Predictions

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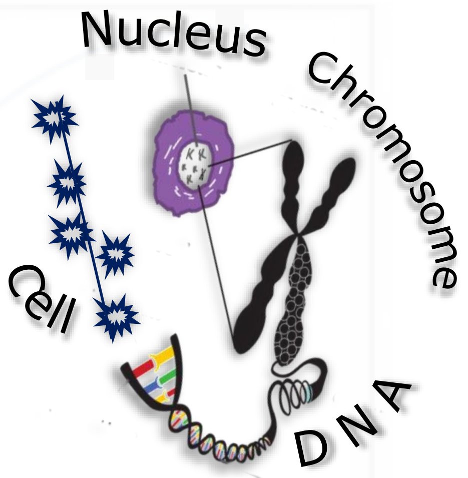


- ✗ Predictions in situations deviating from the validation dataset

Mechanistic

- ✓ Parameters with physical and biological meanings
- ✓ Predictions
- ✗ Optimal parameters?

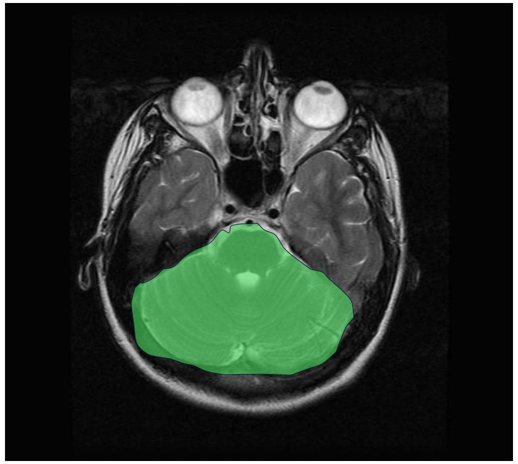
Lyman – Kutcher - Burman (LKB) model

Phenomenological

Lyman – Kutcher - Burman (LKB) model

Phenomenological

Uniform dose distribution



[Image credit: B.V. Prakash et al., Sci Rep 13. (2023), 10.1038/s41598-023-41576-6]

Assumptions:

[J. T. Lyman, Radiat. Res., 1985]

Lyman – Kutcher - Burman (LKB) model

Phenomenological

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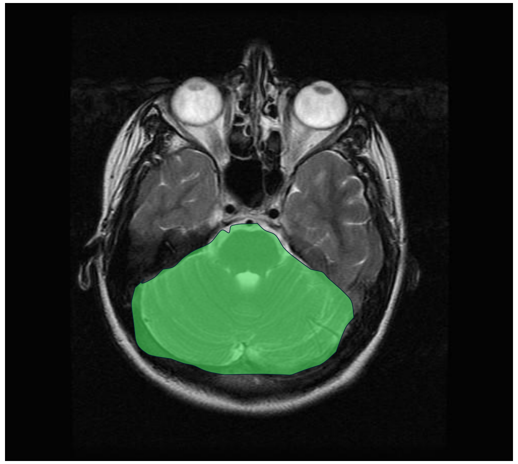

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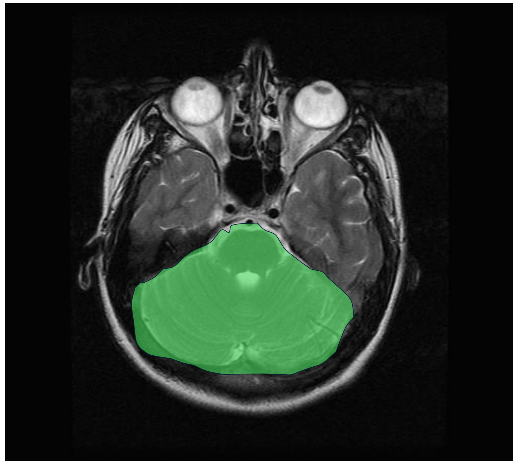

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Power law $D_{50}(V) = \frac{D_{50}(1)}{V^n}$

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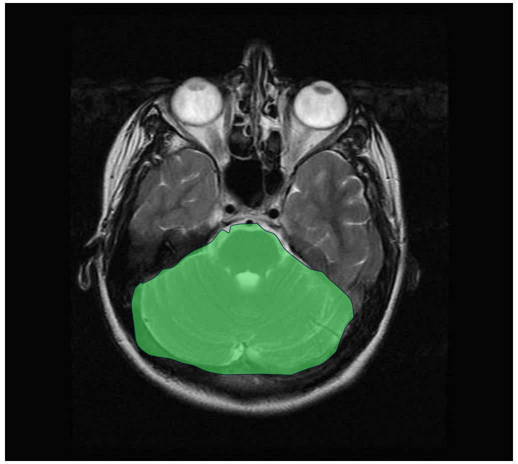

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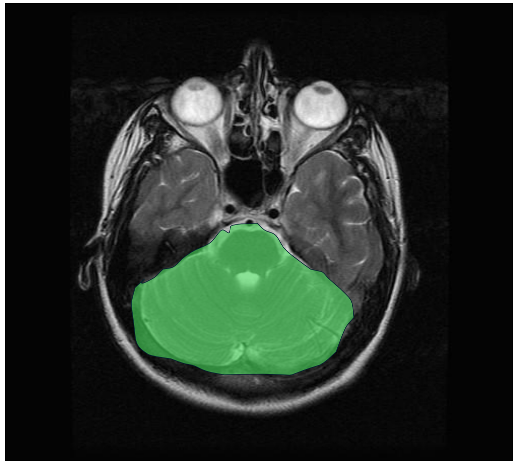

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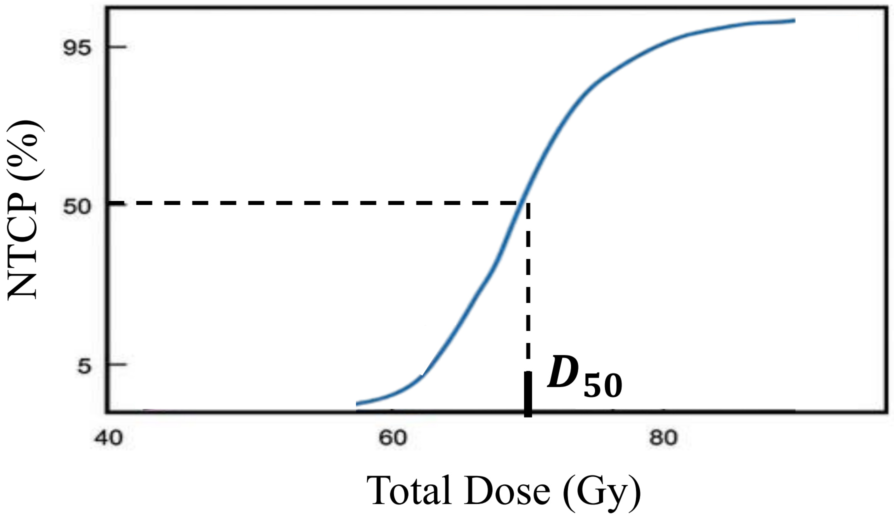

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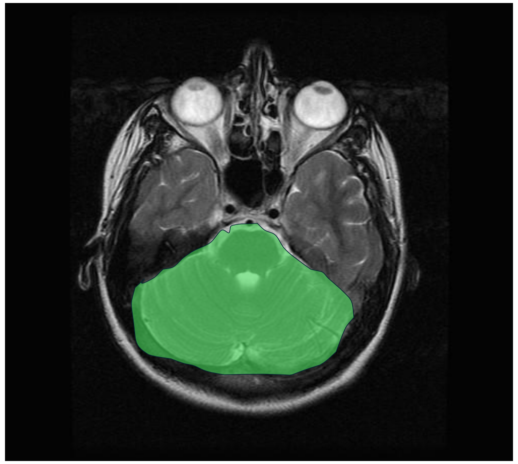

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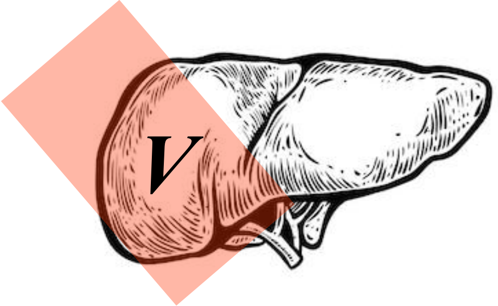

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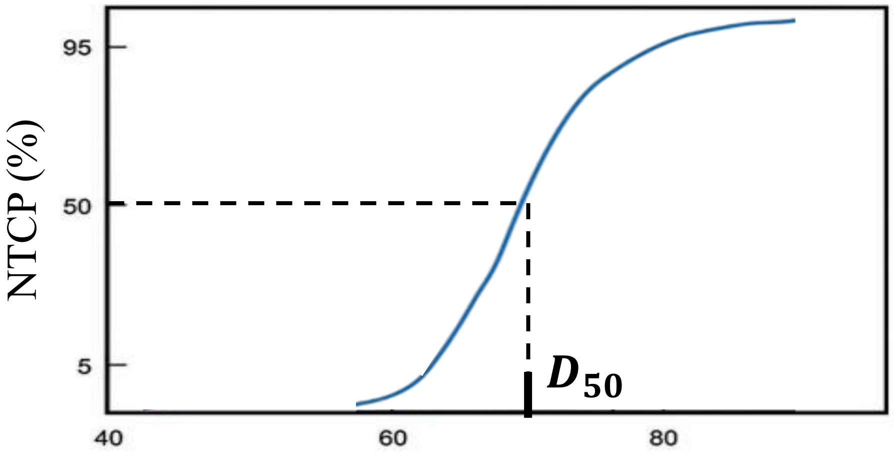

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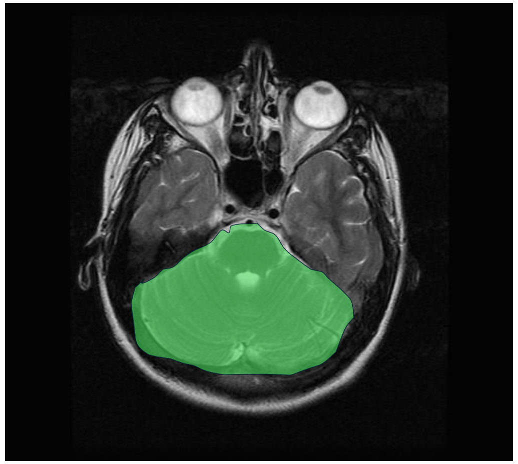

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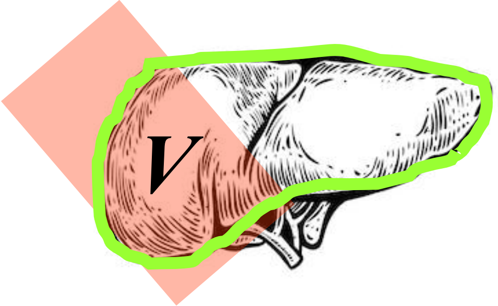

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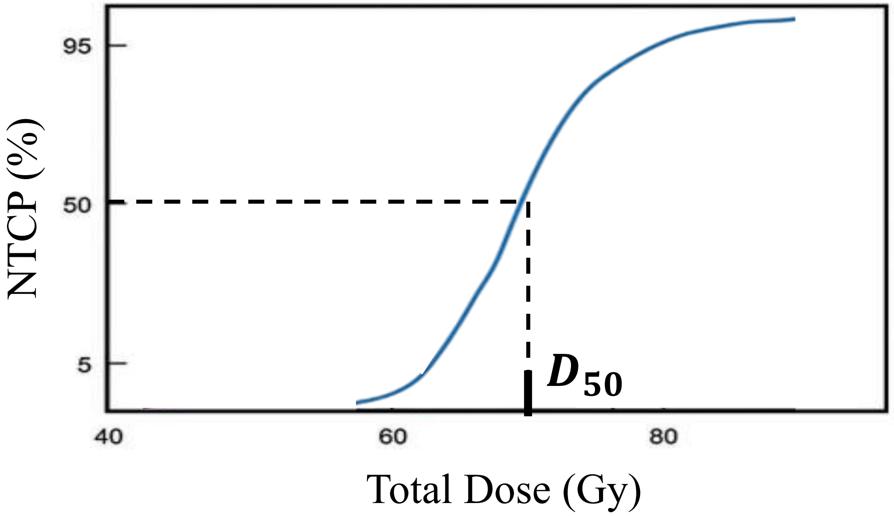

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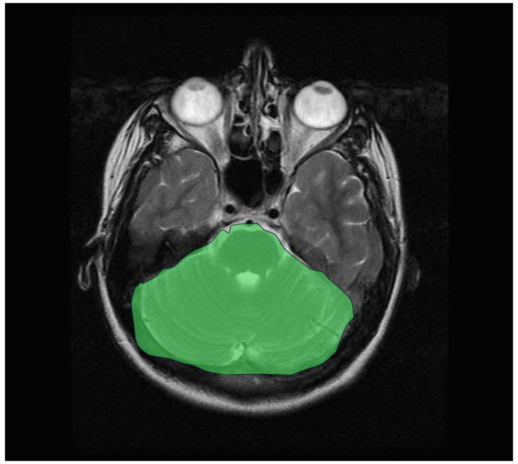

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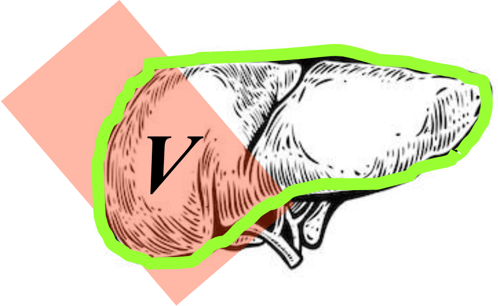

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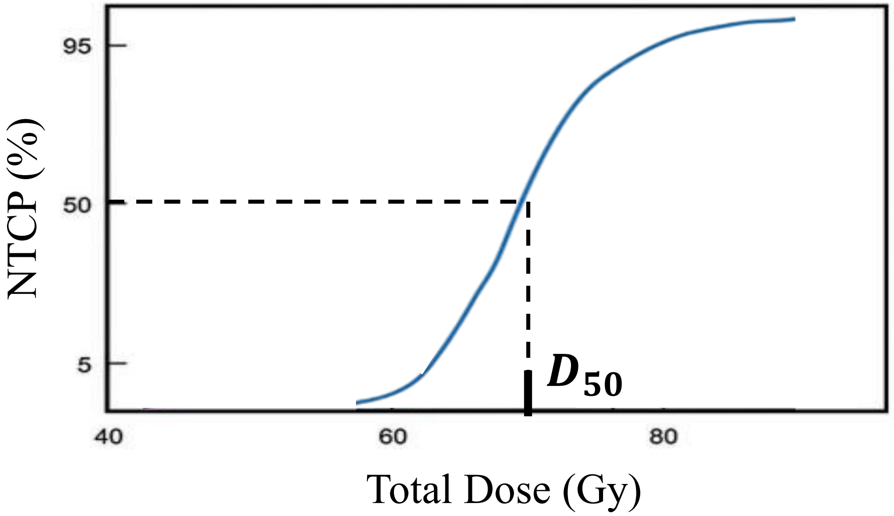

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$$NTCP(D,V) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} exp\left(-\frac{x^2}{2}\right) dx$$

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where $t(D,V) = \frac{D - D_{50}(V)}{m\, D_{50}(V)}$

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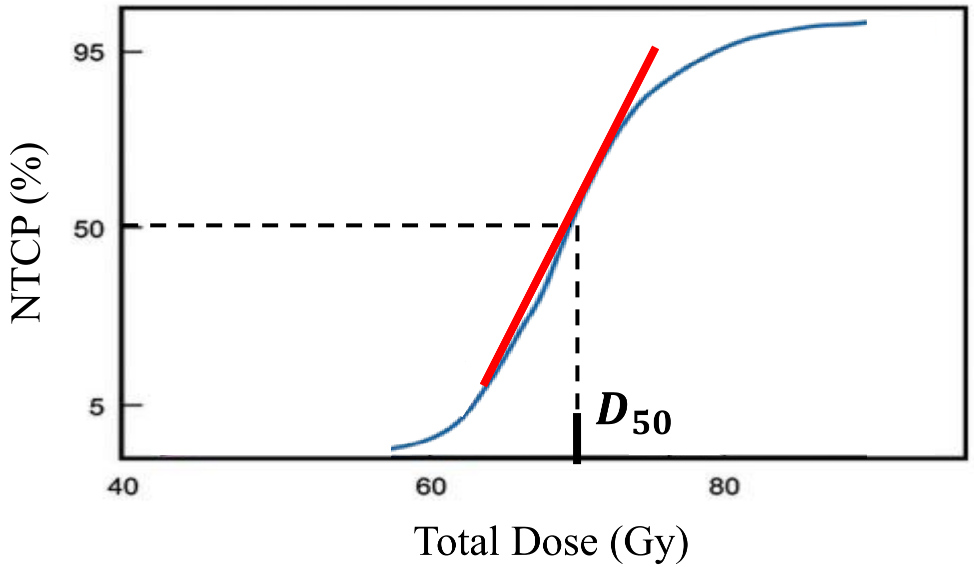

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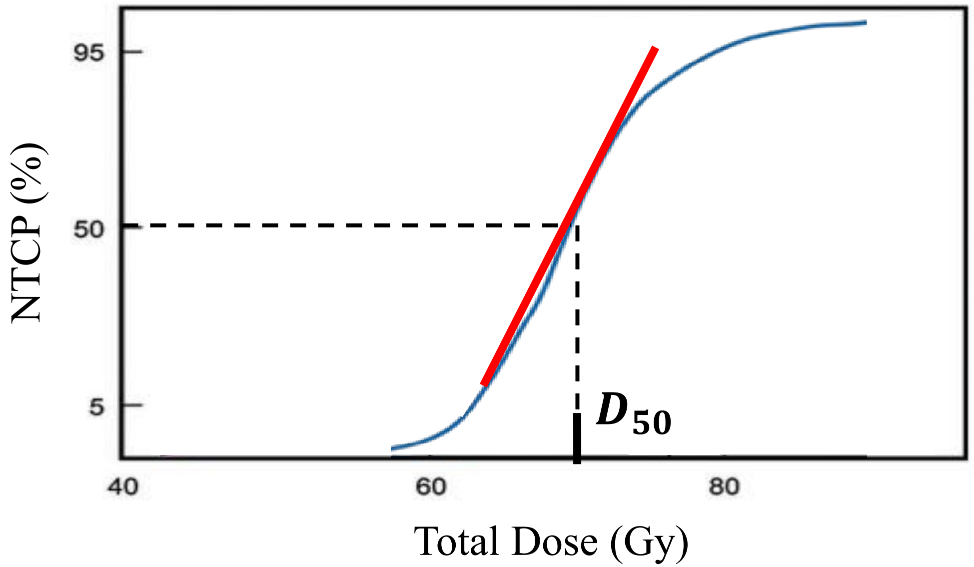

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Phenomenological

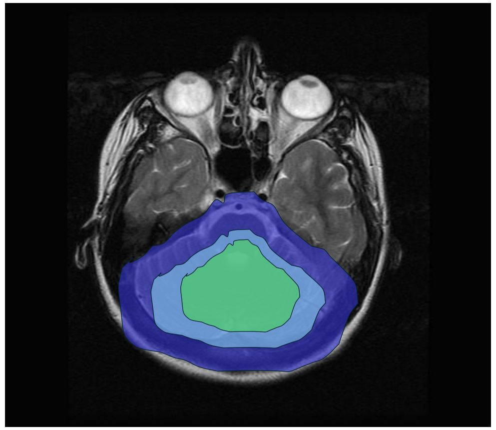
[G. J. Kutcher and C. Burman, Int. J. Radiation Oncology Biol. Phys.,1989]

Lyman – **Kutcher - Burman** (LKB) model

Phenomenological

NON - uniform dose distribution

<u>Assumption:</u>



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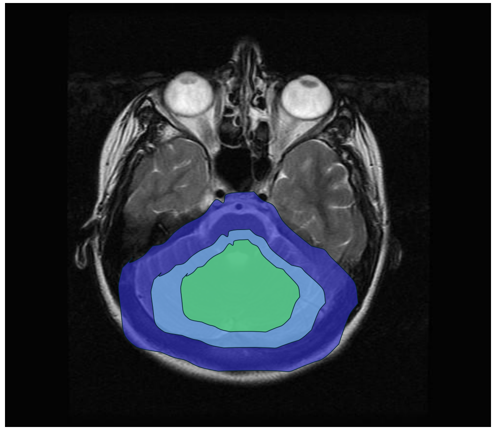

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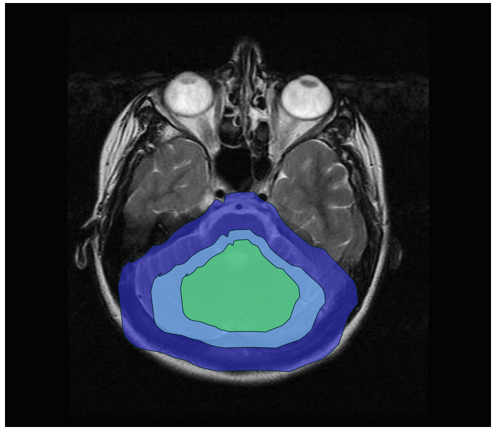

Lyman model

$$t(D_i, v_i) = \frac{EUD - D_{50}(1)}{m\, D_{50}(1)}$$

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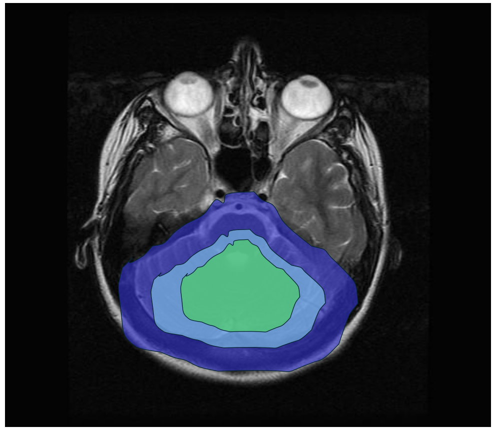

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$$t(D_i, v_i) = \frac{EUD - D_{50}(1)}{m\, D_{50}(1)} \quad \longrightarrow \quad EUD = \left(\sum_{i=1}^{m} v_i D_i^{1/n}\right)^n$$

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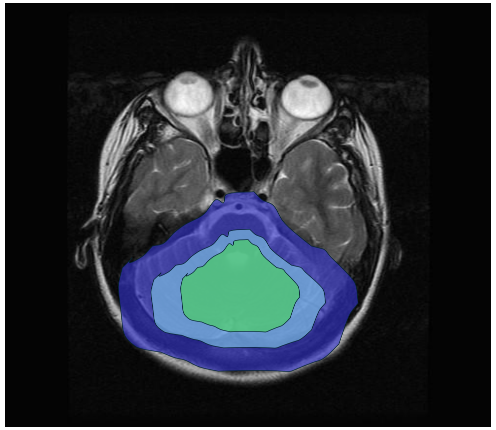

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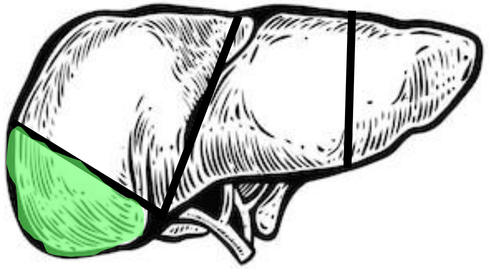

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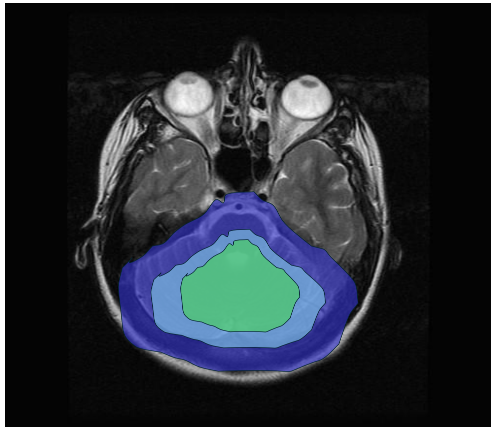

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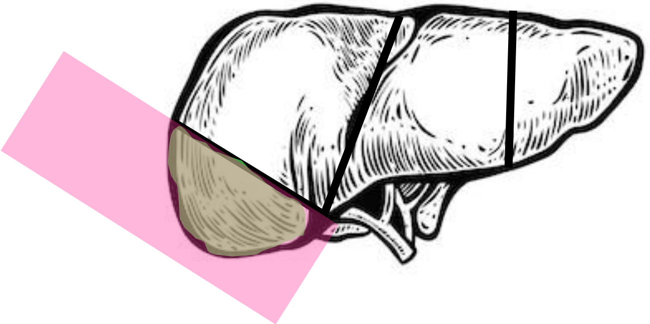

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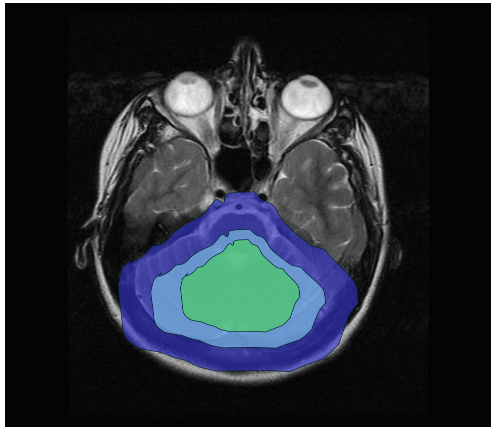

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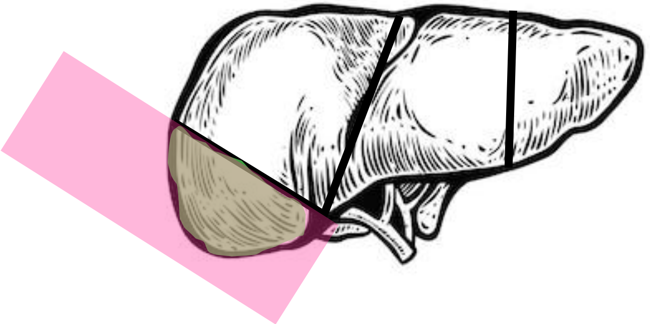
Lyman model

$$t(D_i, v_i) = \frac{EUD - D_{50}(1)}{m\, D_{50}(1)} \longrightarrow EUD = \left(\sum_{i=1}^{m} v_i D_i^{1/n}\right)^{n}$$



[G. J. Kutcher and C. Burman, Int. J. Radiation Oncology Biol. Phys.,1989]

Relative Seriality model

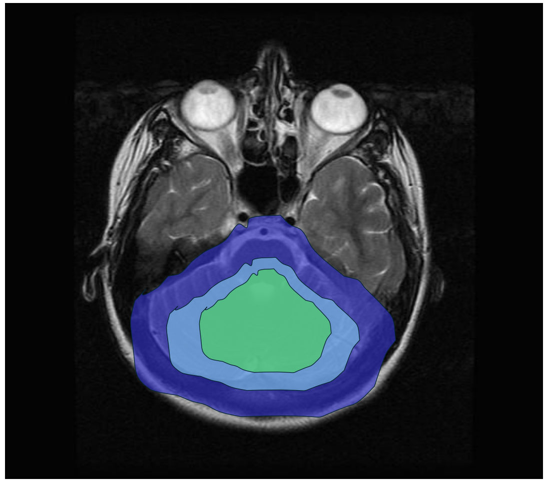
Phenomenological / Mechanistic

[P. Källman, Int. J. Radiat. Biol.,1992]

Relative Seriality model

Phenomenological / Mechanistic

<u>Assumption:</u> NON - uniform dose distribution



[Image credit: Biorender]

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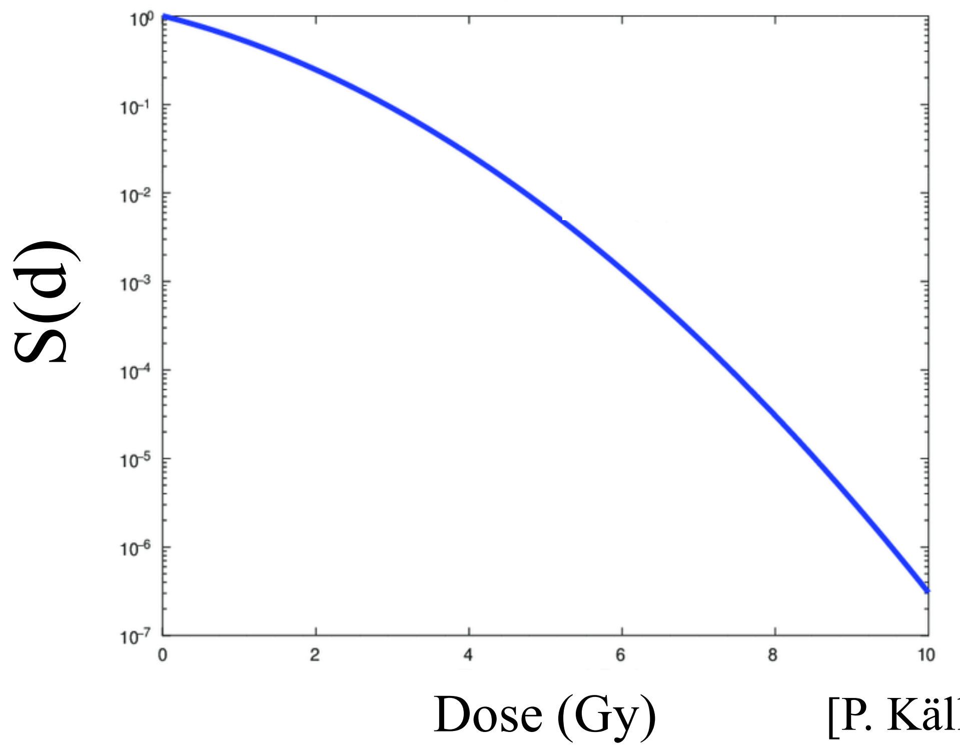

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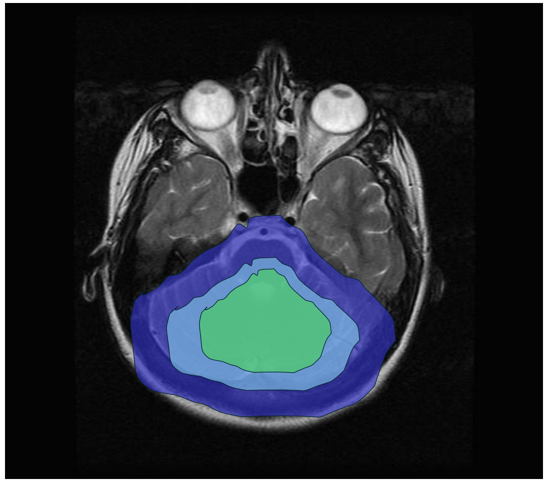


[Image credit: Biorender]

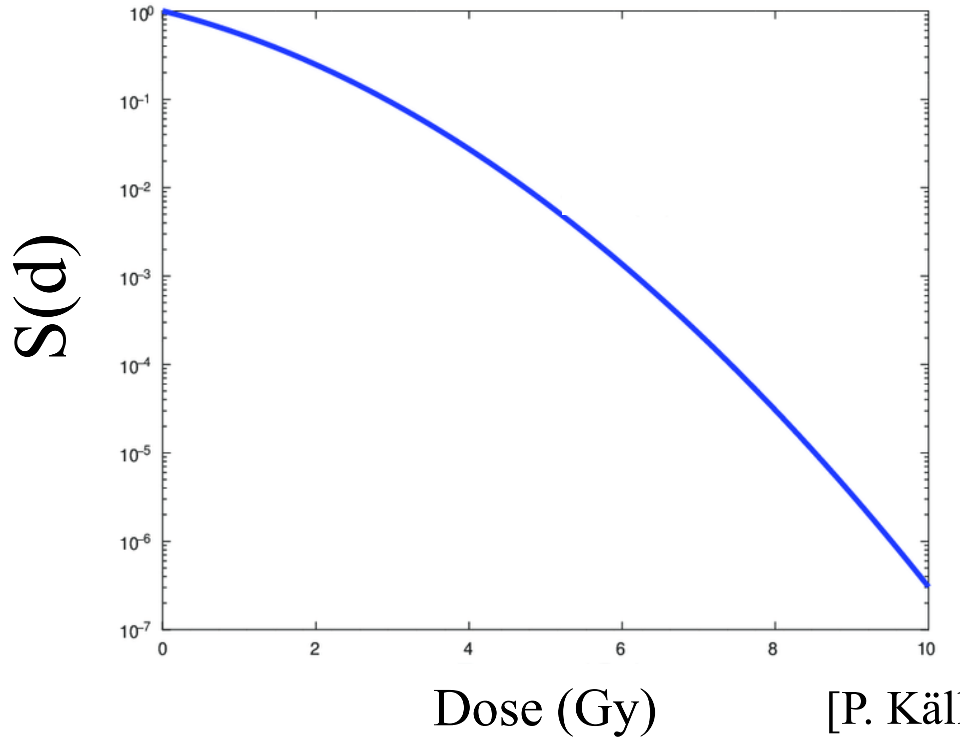
Relative Seriality model

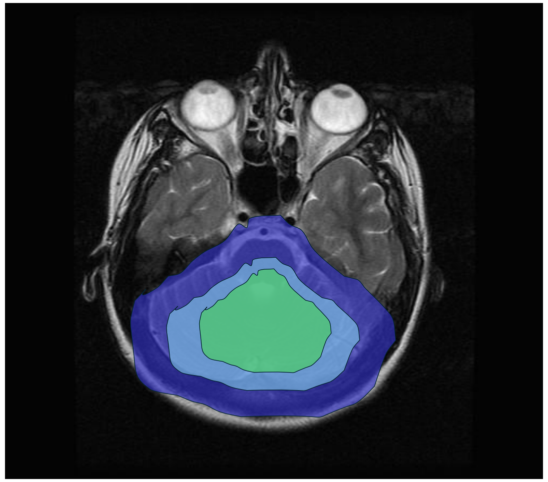
Phenomenological / Mechanistic

<u>Assumption:</u> NON - uniform dose distribution

Linear – Quadratic *(LQ) cell survival model*

$$S(d) = e^{-\alpha n d_i - \beta n d_i^2}$$



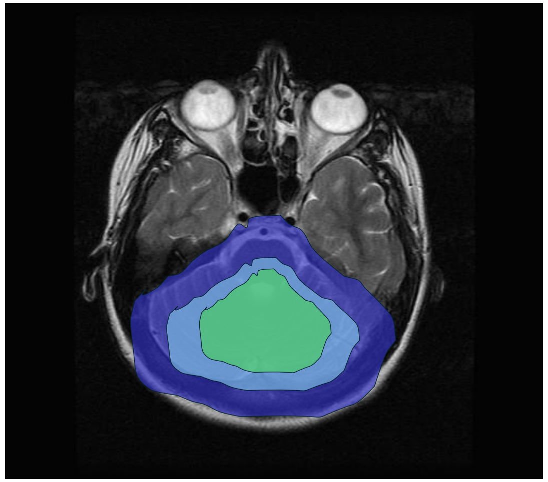


[P. Källman, Int. J. Radiat. Biol.,1992]

[Image credit: Biorender]

Relative Seriality model

Phenomenological / Mechanistic



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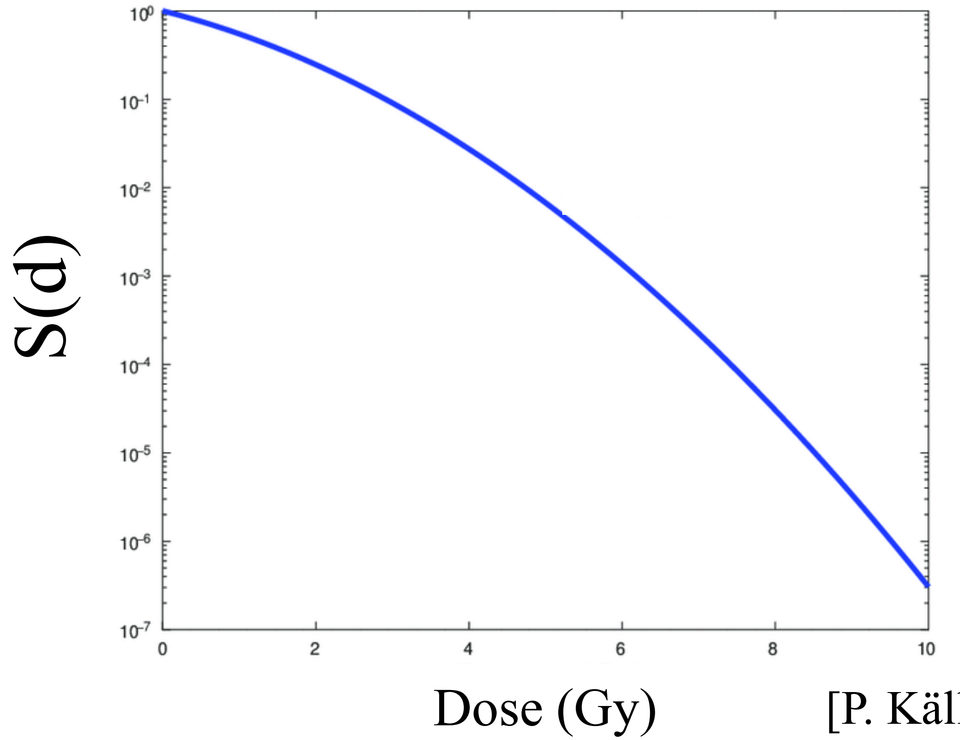
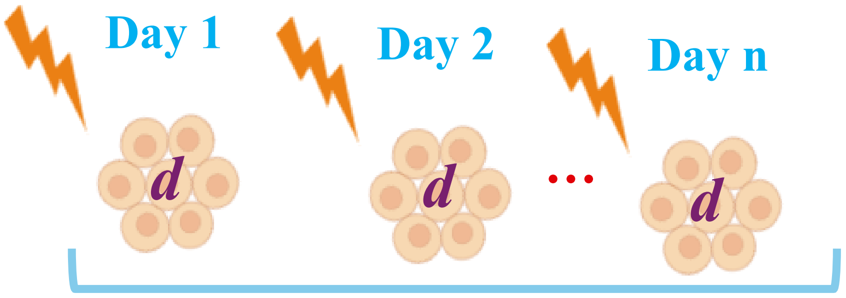
$$S(d) = e^{-\alpha \boldsymbol{n} d_i - \beta \boldsymbol{n} d_i^2}$$





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[Image credit: Biorender]

Relative Seriality model

Phenomenological / Mechanistic

Assumption: NON - uniform dose distribution

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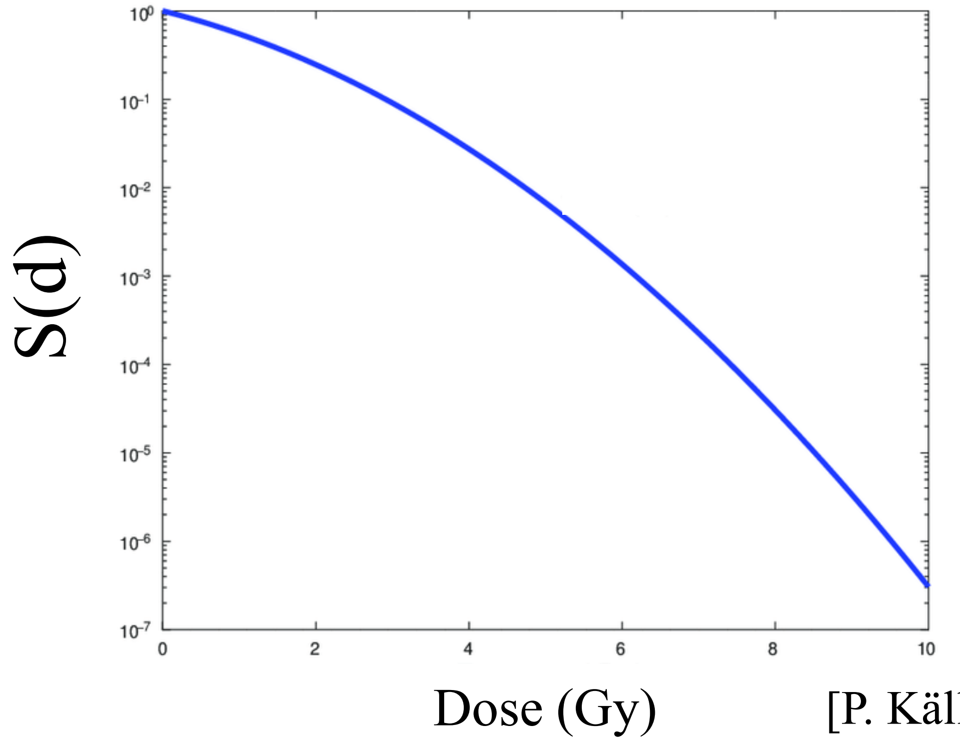

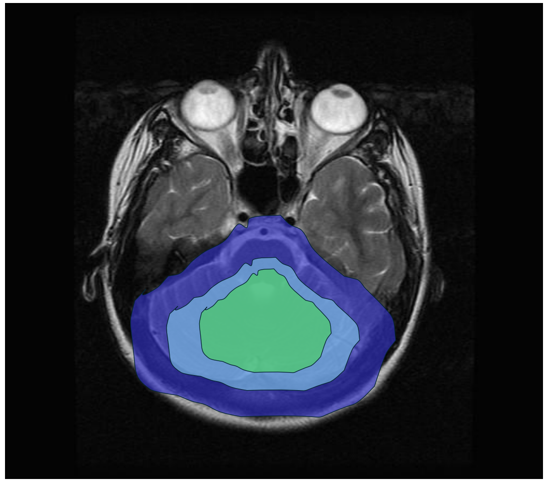

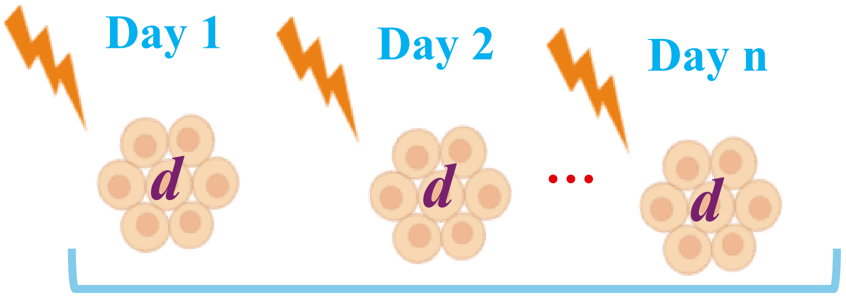

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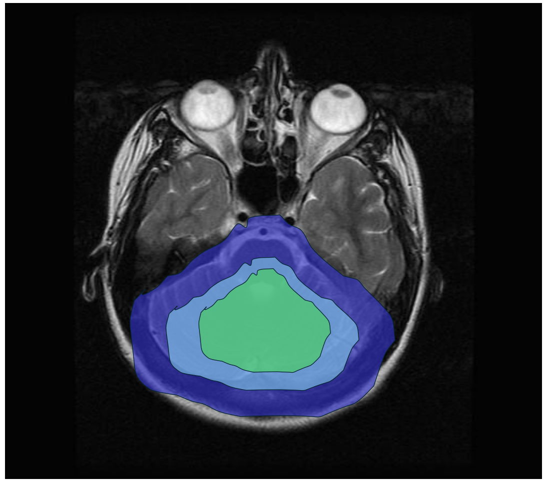
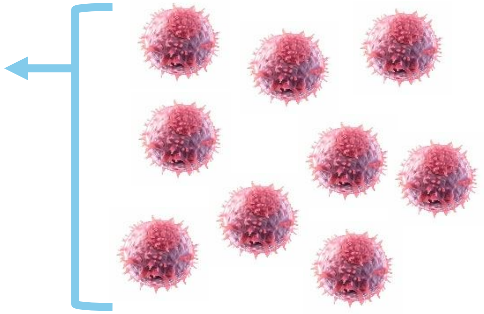
Relative Seriality model

Phenomenological / **Mechanistic**



Assumption: NON - uniform dose distribution

1 FSU
=
k cells

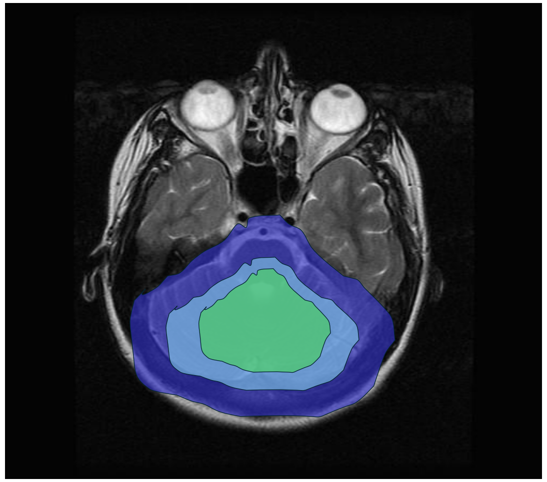


[Image credit: Biorender]

[P. Källman, Int. J. Radiat. Biol.,1992]

Relative Seriality model

Phenomenological / **Mechanistic**



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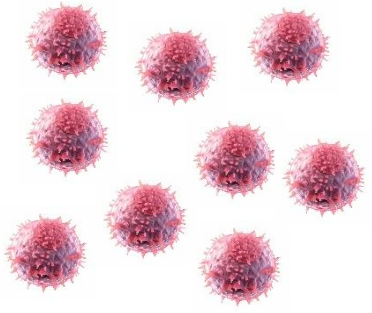


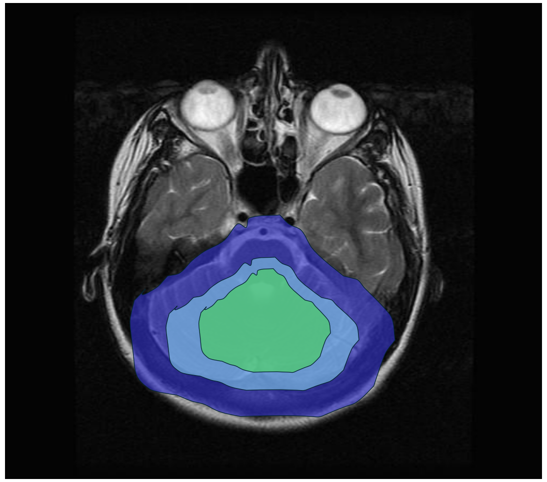
$$P(d_i)_{FSU} = e^{-ke^{-\alpha n d_i - \beta n d_i^2}}$$

[Image credit: Biorender]

[P. Källman, Int. J. Radiat. Biol.,1992]

Relative Seriality model

Phenomenological / **Mechanistic**



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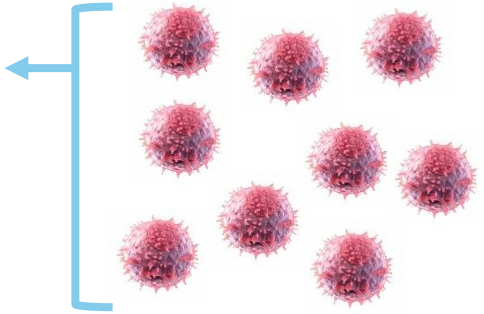

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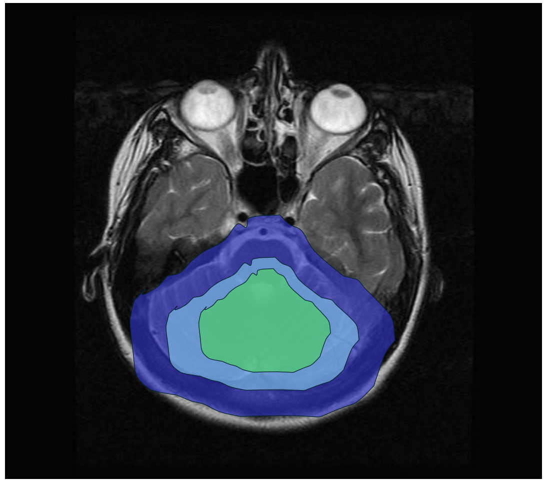
[Image credit: Biorender]

[P. Källman, Int. J. Radiat. Biol.,1992]

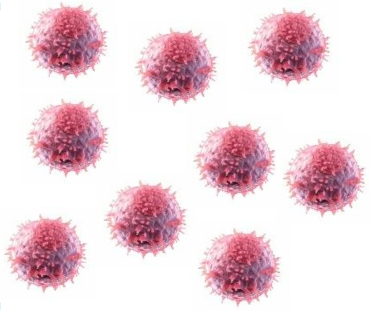
Relative Seriality model

Phenomenological / **Mechanistic**



<u>Assumption:</u> NON - uniform dose distribution

1 FSU = *k cells*



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LQ cell survival model

[Image credit: Biorender]

[P. Källman, Int. J. Radiat. Biol.,1992]

Relative Seriality model

Phenomenological / Mechanistic

$$(\boldsymbol{P}(\boldsymbol{d}_{\boldsymbol{i}})_{\boldsymbol{FSU}})^{\boldsymbol{s}}$$

[P. Källman, Int. J. Radiat. Biol.,1992]

Relative Seriality model

Phenomenological / Mechanistic

$$[1 - (P(d_i)_{FSU})^{s}]$$

[P. Källman, Int. J. Radiat. Biol.,1992]

Relative Seriality model

Phenomenological / Mechanistic

$$[\mathbf{1} - (\boldsymbol{P}(\boldsymbol{d_i})_{\boldsymbol{FSU}})^{\boldsymbol{s}}]^{\boldsymbol{v_i}}$$

[P. Källman, Int. J. Radiat. Biol.,1992]

Relative Seriality model

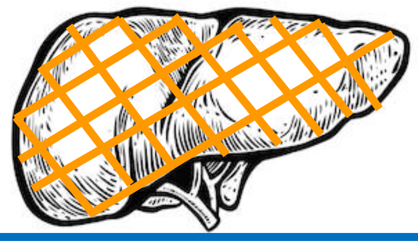
Phenomenological / Mechanistic

$$NTCP(d_i, v_i) = \left\{1 - \prod_{i=1}^{m}[1 - (P(d_i)_{FSU})^{s}]^{v_i}\right\}^{1/s}$$

[P. Källman, Int. J. Radiat. Biol.,1992]

Relative Seriality model

Phenomenological / Mechanistic

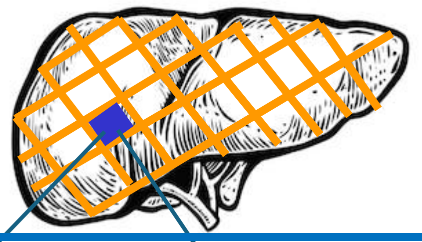


$$NTCP(d_i, v_i) = \left\{1 - \prod_{i=1}^{m}\left[1 - \left(e^{-ke^{-\alpha n d_i - \beta n d_i^2}}\right)^s\right]^{v_i}\right\}^{1/s}$$

[P. Källman, Int. J. Radiat. Biol.,1992]

Relative Seriality model

Phenomenological / Mechanistic



$$NTCP(d_i, v_i) = \left\{1 - \prod_{i=1}^{m} \left[1 - \left(e^{-ke^{-\alpha n d_i - \beta n d_i^2}} \right)^s \right]^{v_i} \right\}^{1/s}$$

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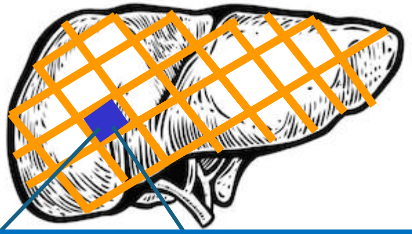
Relative Seriality model

Phenomenological / Mechanistic



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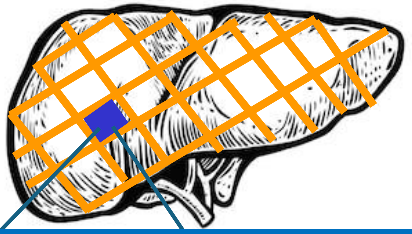
Serial organ

[P. Källman, Int. J. Radiat. Biol.,1992]

Relative Seriality model

Phenomenological / Mechanistic



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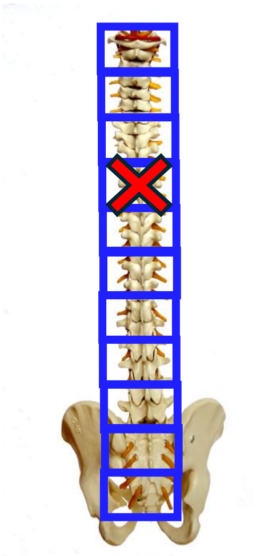

Serial organ

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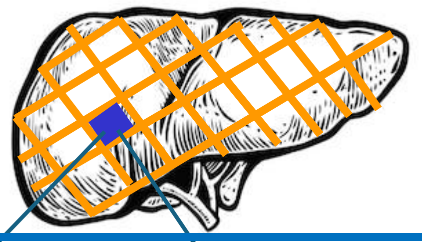
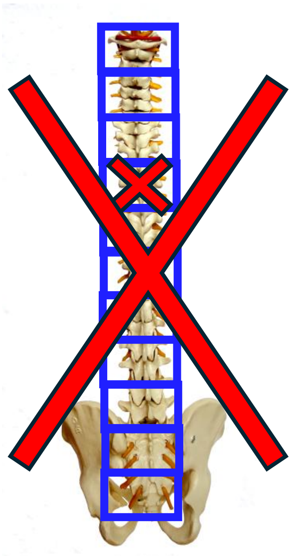
Relative Seriality model

Phenomenological / Mechanistic



$$NTCP(d_i, v_i) = \left\{1 - \prod_{i=1}^{m}\left[1 - \left(e^{-ke^{-\alpha n d_i - \beta n d_i^2}}\right)^s\right]^{v_i}\right\}^{1/s}$$



Serial organ

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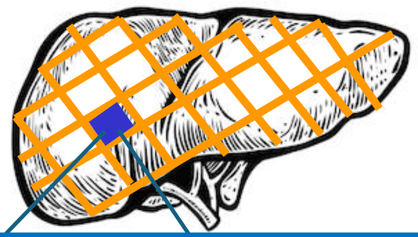
Relative Seriality model

Phenomenological / Mechanistic



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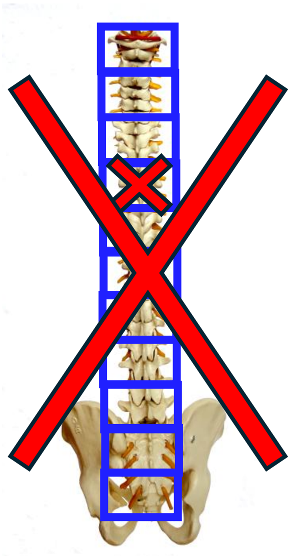


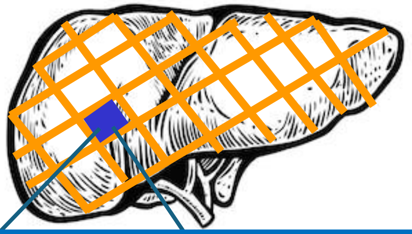
Serial organ

S* = *1

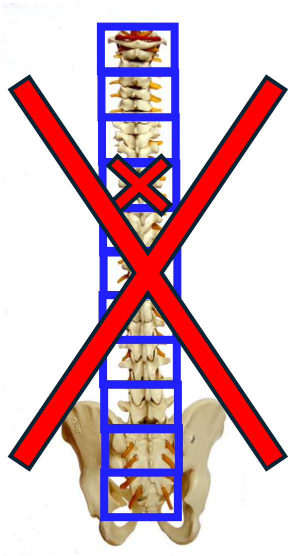
[P. Källman, Int. J. Radiat. Biol.,1992]

Relative Seriality model

Phenomenological / Mechanistic



$$NTCP(d_i, v_i) = \left\{1 - \prod_{i=1}^{m}\left[1 - \left(e^{-ke^{-\alpha n d_i - \beta n d_i^2}}\right)^s\right]^{v_i}\right\}^{1/s}$$



Serial organ

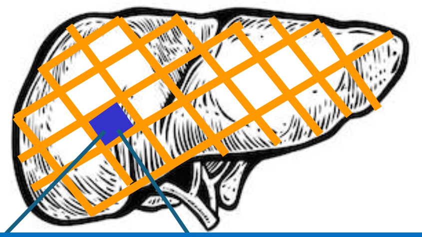
S* = *1

Parallel organ

[P. Källman, Int. J. Radiat. Biol.,1992]

Relative Seriality model

Phenomenological / Mechanistic



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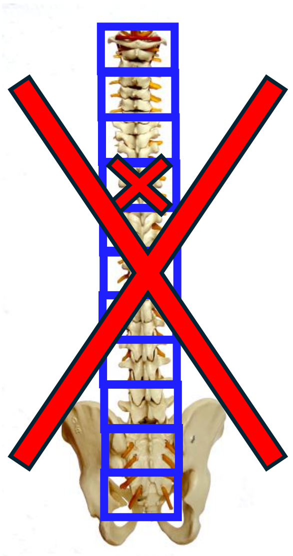
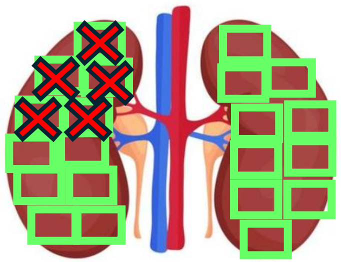


Serial organ

S = 1

Parallel organ



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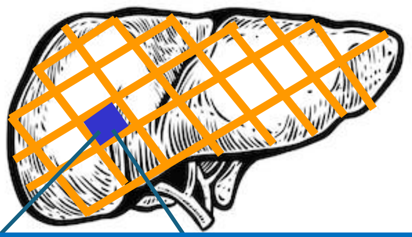
Relative Seriality model

Phenomenological / Mechanistic



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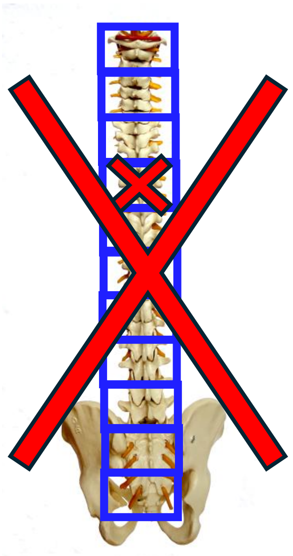
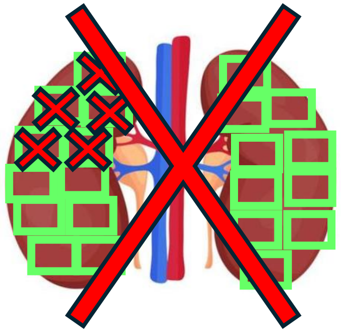


Serial organ

S = 1

Parallel organ



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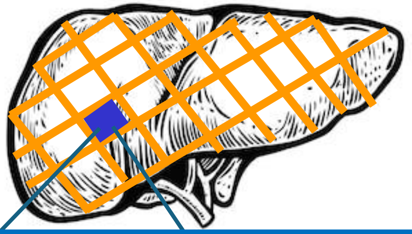
Relative Seriality model

Phenomenological / Mechanistic



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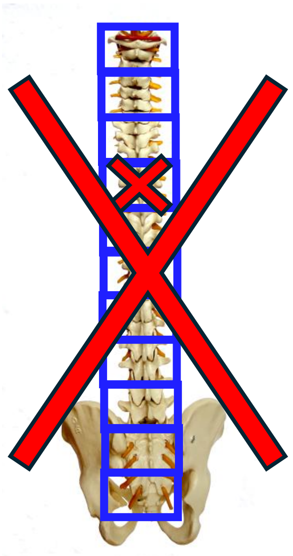
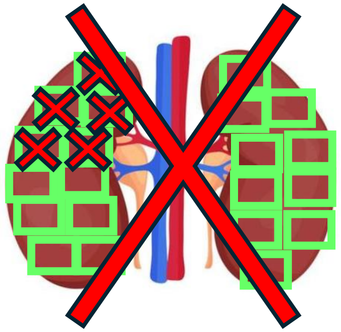


Serial organ

$S = 1$

Parallel organ

$S \rightarrow 0$



[P. Källman, Int. J. Radiat. Biol.,1992]

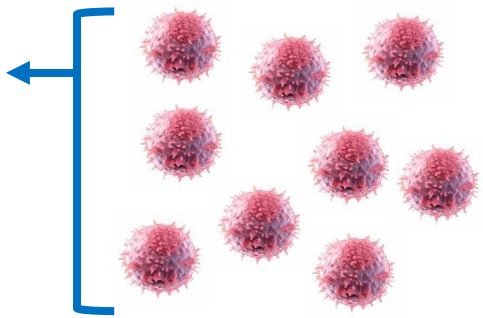
Critical Volume model

Mechanistic

1 FSU

=

k cells



[Withers et al., Br. J. Radiol., 1986]

Critical Volume model

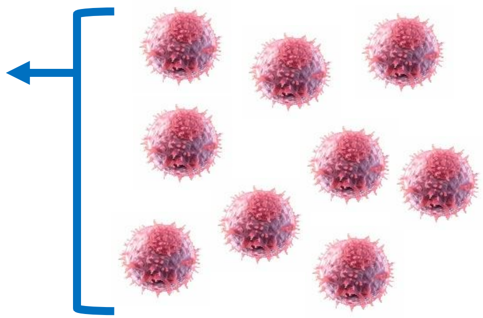
Mechanistic

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

1 FSU

=

k cells



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Critical Volume model

Mechanistic

LQ cell
survival model

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

1 FSU
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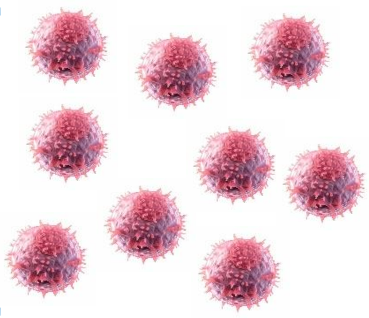

[Withers et al., Br. J. Radiol., 1986]

Critical Volume model

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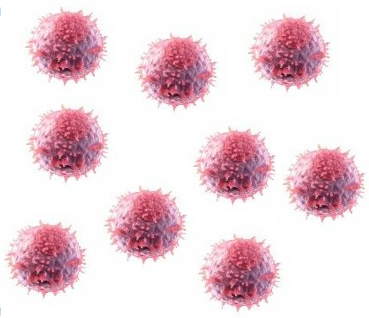


$$NTCP = \sum_{t=M}^{N} \binom{N}{t} P_{FSU}{}^{t} (1 - P_{FSU})^{N-t}$$

Binomial cumulative
probability

[Withers et al., Br. J. Radiol., 1986]

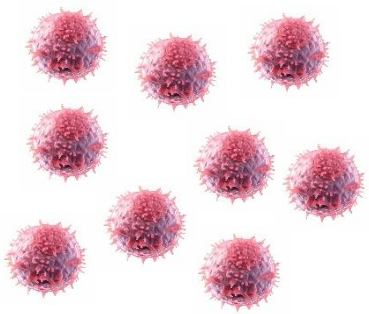
Critical Volume model

Mechanistic

LQ cell survival model

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

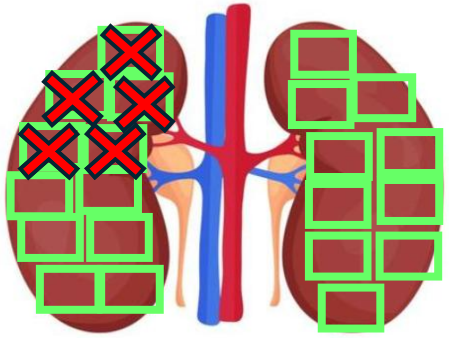
1 FSU = k cells



$$NTCP = \sum_{t=M}^{N} \binom{N}{t} P_{FSU}{}^{t} (1 - P_{FSU})^{N-t}$$

Binomial cumulative probability

Parallel organs



[Withers et al., Br. J. Radiol., 1986]

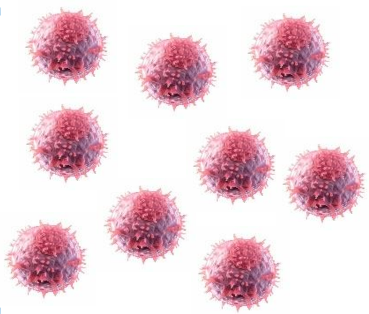
Critical Volume model

Mechanistic

LQ cell survival model

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

1 FSU = k cells



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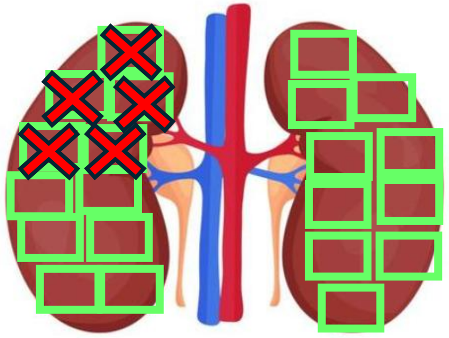
Binomial cumulative probability

Parallel organs



[Withers et al., Br. J. Radiol., 1986]

Critical Volume model

Mechanistic

LQ cell
survival model

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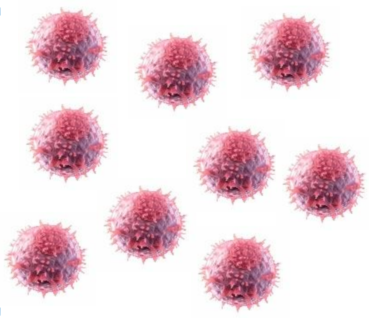
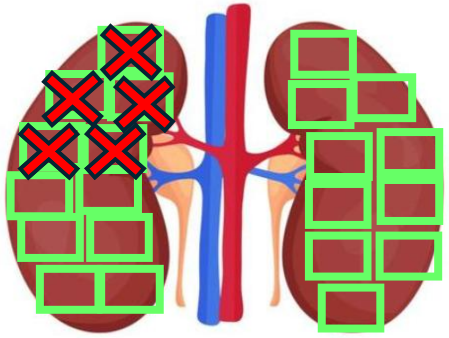


$$NTCP = \sum_{t=M}^{N} \binom{N}{t} {P_{FSU}}^{t} (1 - P_{FSU})^{N-t}$$

Binomial cumulative
probability

Parallel organs



[Withers et al., Br. J. Radiol., 1986]

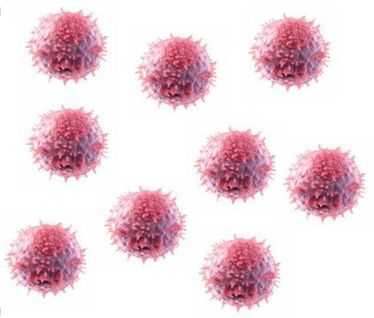
Critical Volume model

Mechanistic

LQ cell
survival model

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

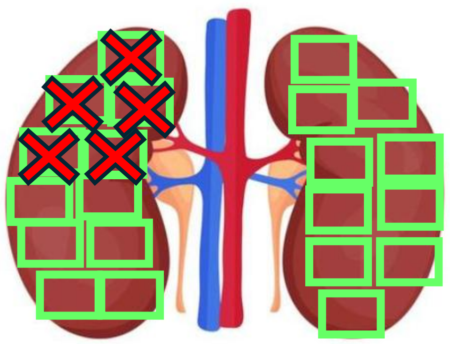
1 FSU
=
k cells



$$NTCP = \sum_{t=M}^{N} \binom{N}{t} P_{FSU}{}^{t} (1 - P_{FSU})^{N-t}$$

Binomial cumulative
probability

Parallel organs



[Withers et al., Br. J. Radiol., 1986]

Critical Volume model

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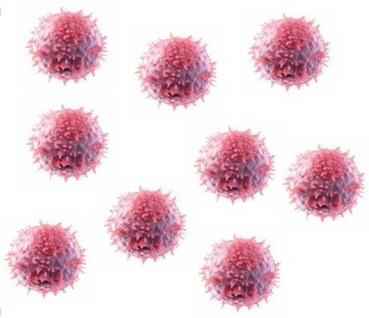

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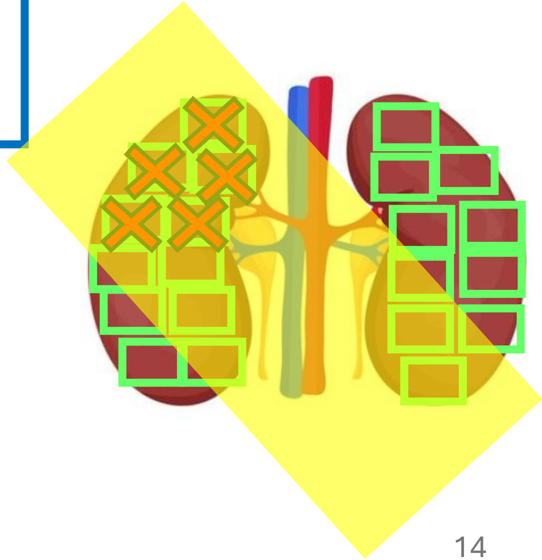
Binomial cumulative probability

Parallel organs



[Withers et al., Br. J. Radiol., 1986]

Critical Element model

Mechanistic

$$\boldsymbol{NTCP} = \sum_{t=M}^{N} \binom{N}{t} {P_{FSU}}^{t} (1 - P_{FSU})^{N-t}$$

Critical Volume Model

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

Critical Element model

Mechanistic

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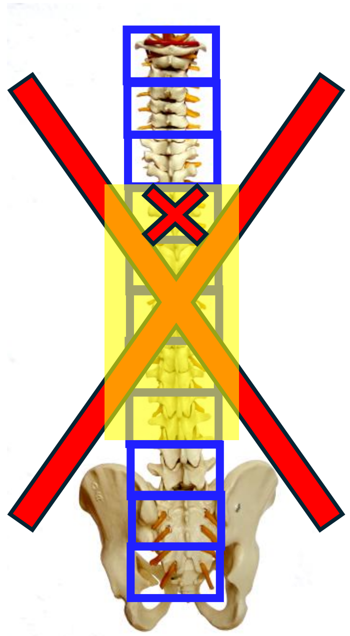
Critical Volume Model

Serial organs



M = 1

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

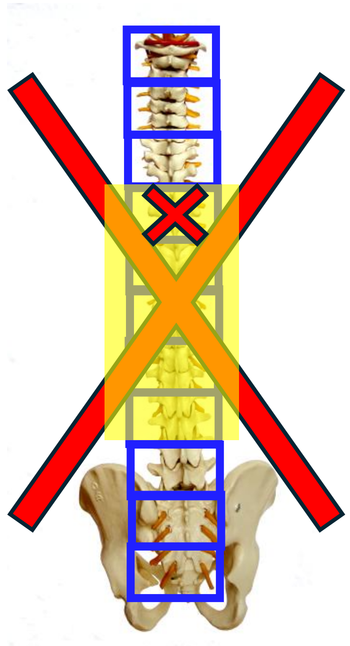
Critical Element model

Mechanistic

$$\boldsymbol{NTCP} = \sum_{t=M}^{N} \binom{N}{t} {P_{FSU}}^{t} (1 - P_{FSU})^{N-t}$$

Critical Volume Model

Serial organs



M = 1

$$\textbf{NTCP} = 1 - P_0 = 1 - (1 - P_{FSU})^N$$

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

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

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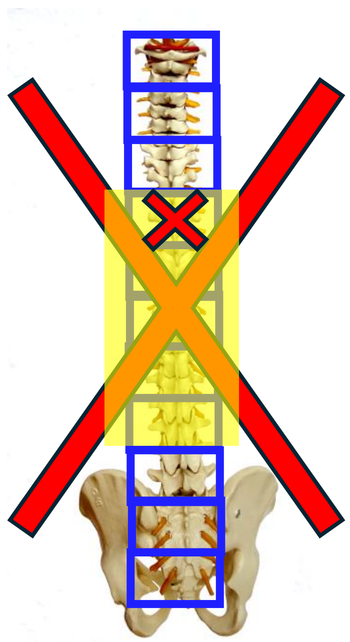
Critical Volume Model

Serial organs



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

Open Problems

Mechanistic

- ✓ Parameters with physical and biological meanings
- ✓ Predictions

❌ Optimal parameters?

Open Problems

How to estimate the model parameters to make predictions?

Mechanistic

- ✓ Parameters with physical and biological meanings
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- ✗ Optimal parameters?

Open Problems

How to estimate the model parameters to make predictions?

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✓ Parameters with physical and biological meanings

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[Image credit: Biorender]

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How to estimate the model parameters to make predictions?

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[Image credit: Biorender]

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[Image credit: Biorender]

Mechanistic

- ✓ Parameters with physical and biological meanings
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✗ Optimal parameters?

Open Problems

How to estimate the model parameters to make predictions?

Mechanistic

- ✓ Parameters with physical and biological meanings
- ✓ Predictions

cells in 1 FSU
= 100 ???

✗ Optimal parameters?

[Image credit: Biorender]

Aim PhD Project

Development of a **novel approach** to estimate the **parameters** to **predict NTCP** curves following **Hadrontherapy**

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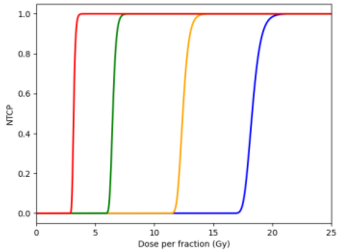
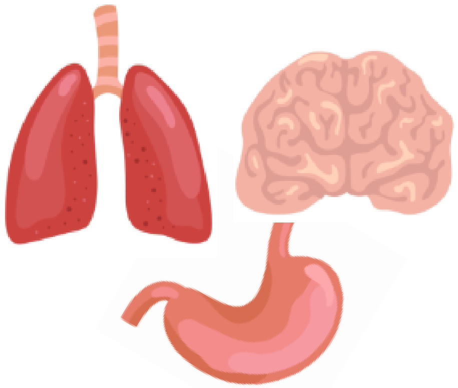
Development of a **novel approach** to estimate the **parameters** to predict **NTCP** curves following **Hadrontherapy**

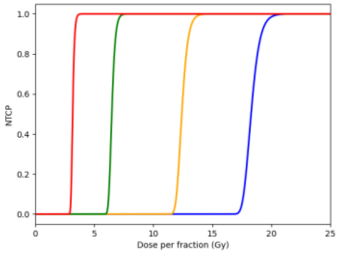


Aim PhD Project

Development of a **novel approach** to estimate the **parameters** to **predict NTCP** curves following **Hadrontherapy**

Several organs





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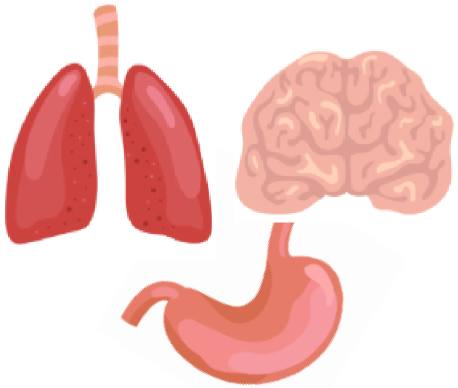
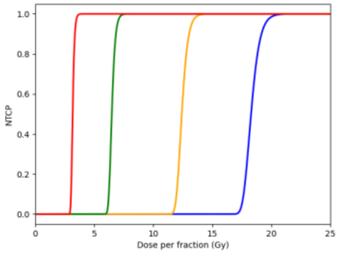
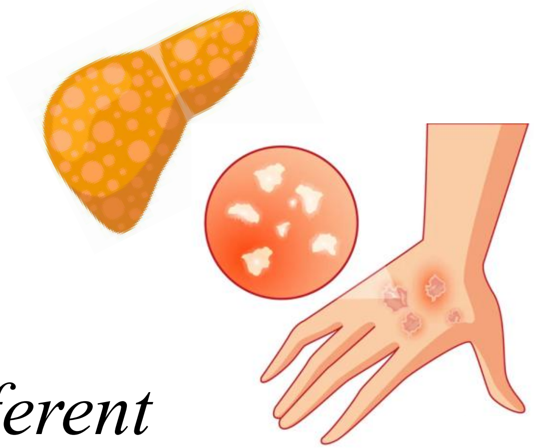
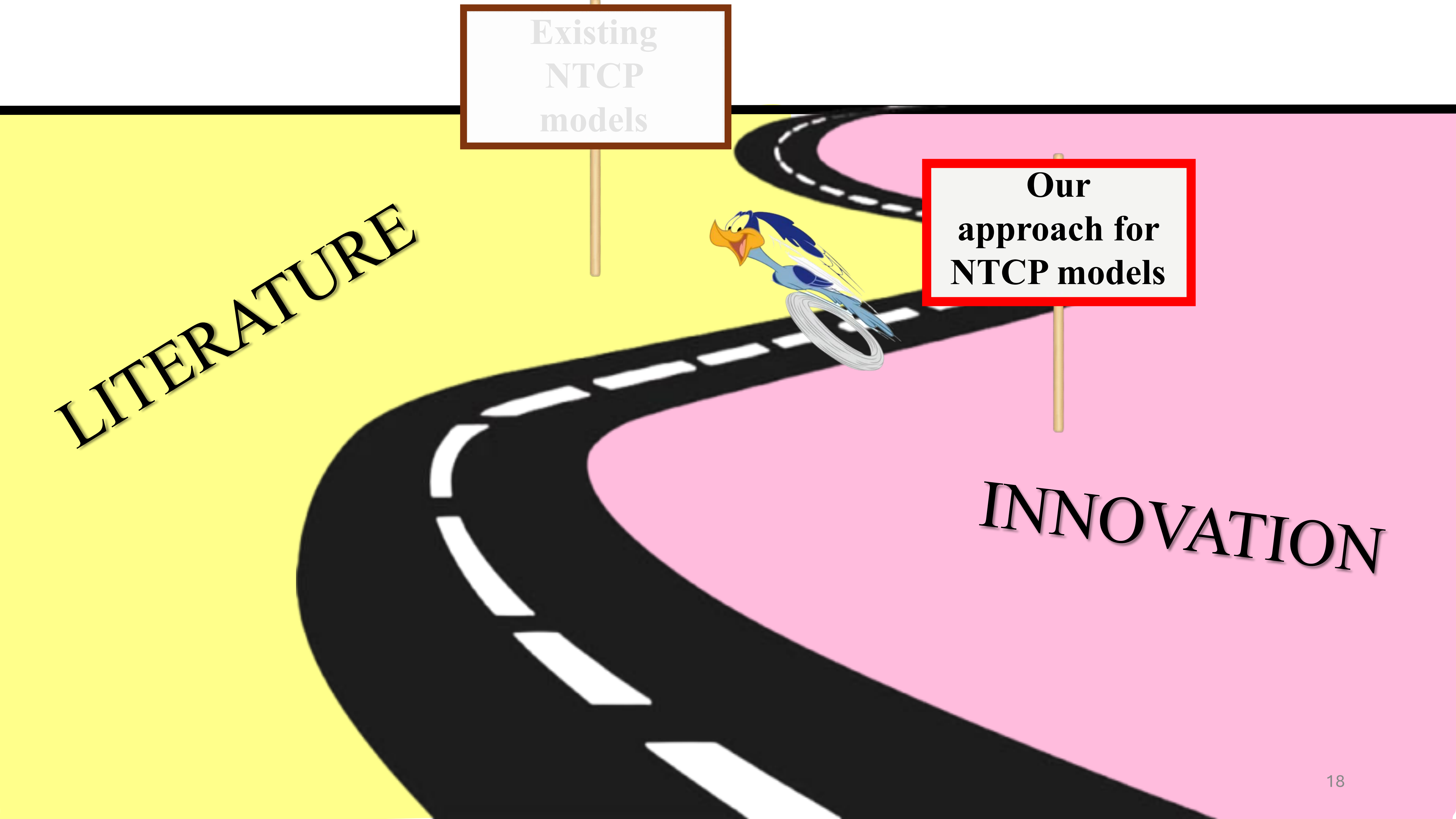
Several organs



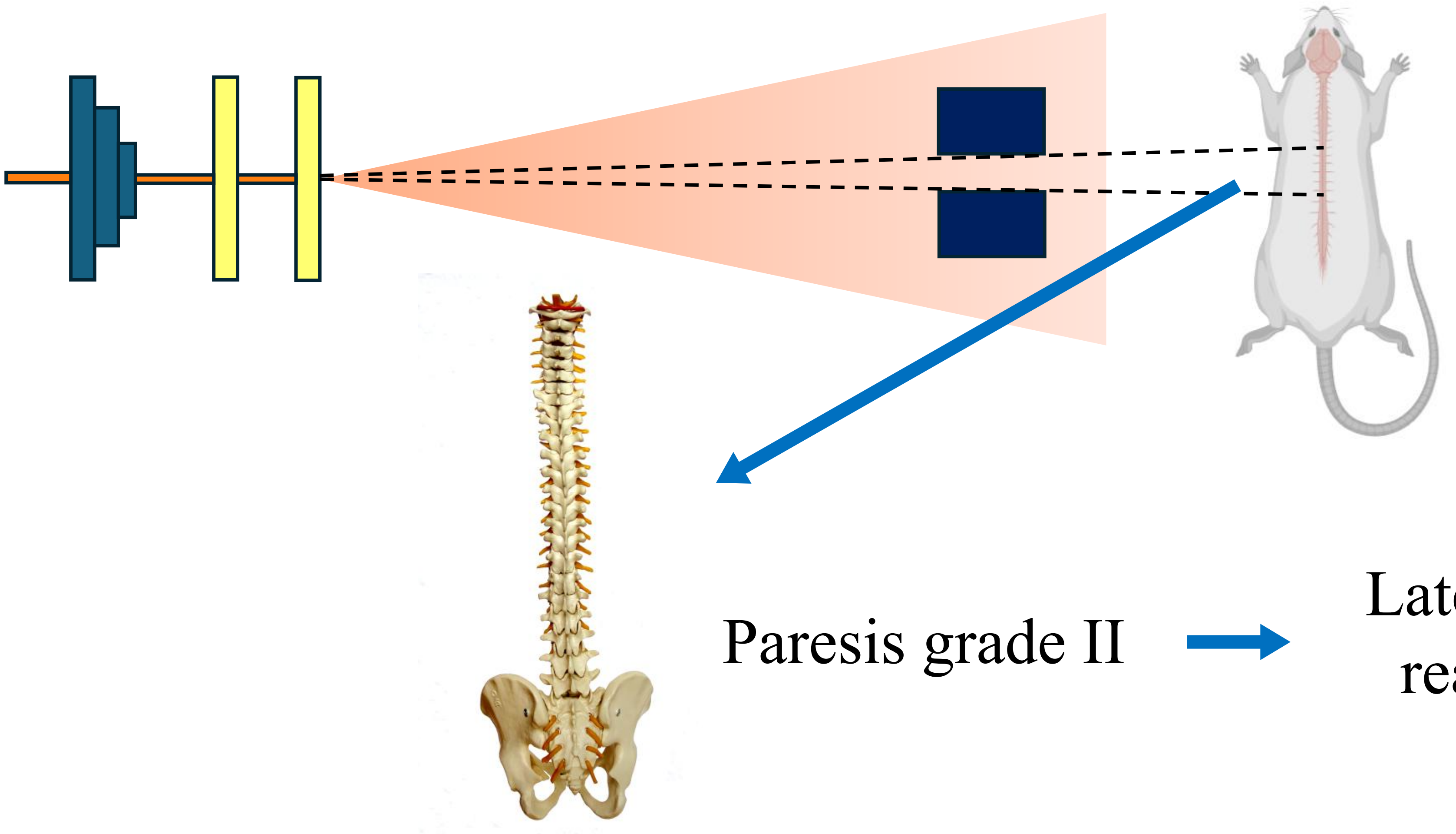




Different endpoints


Existing
NTCP
models
Our
approach for
NTCP models
LITERATURE
INNOVATION

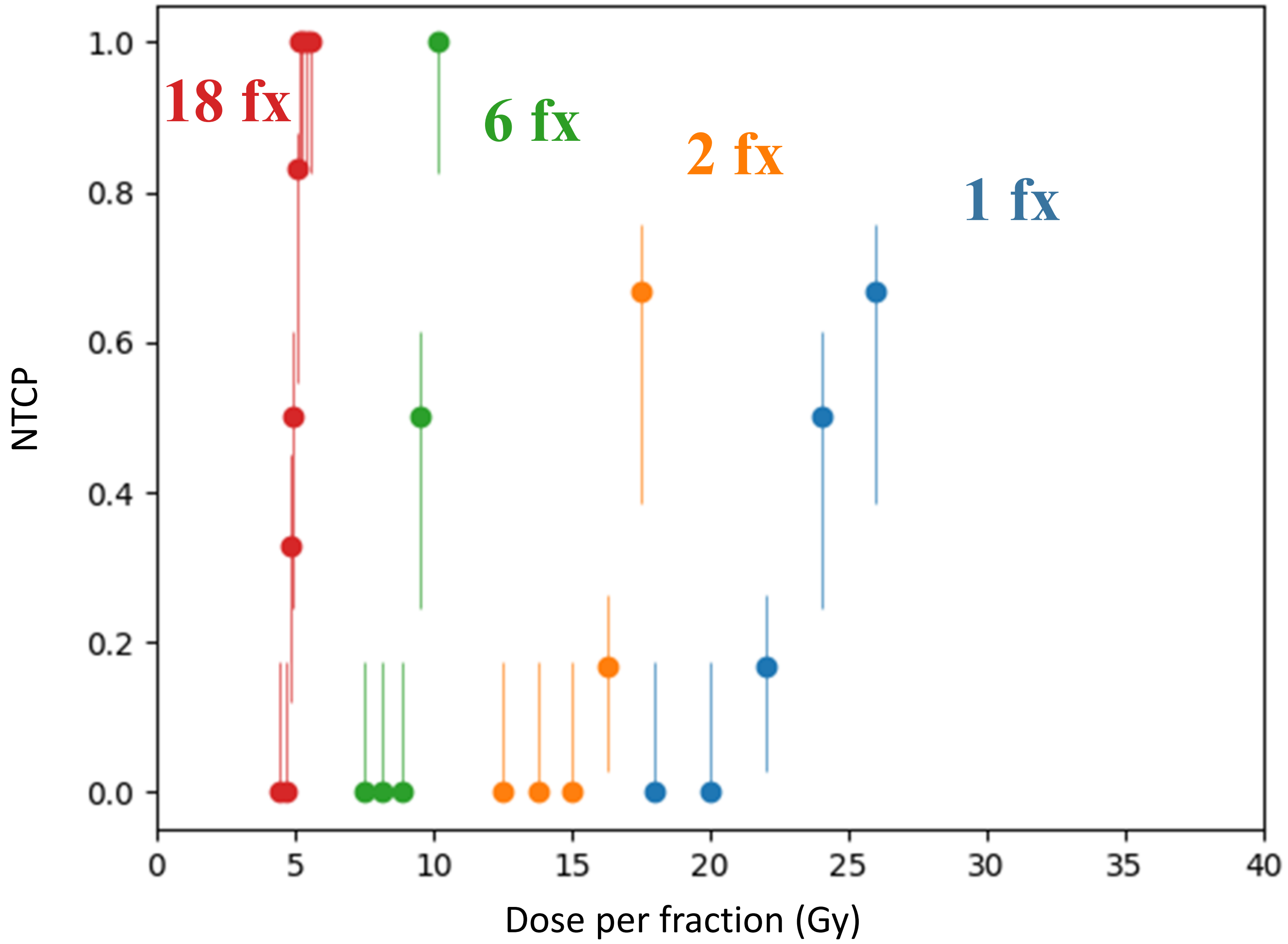
Experimental Data



Paresis grade II → Late tissue reaction

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

Experimental photon data

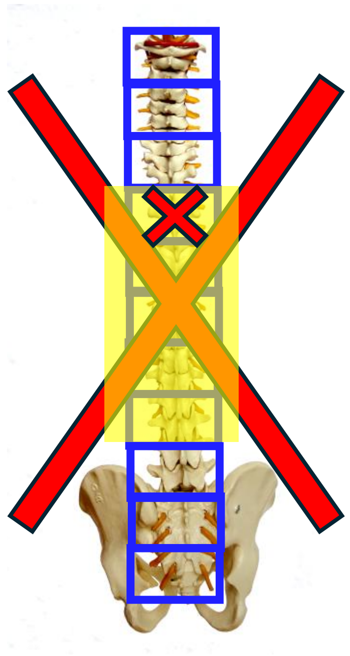


[Karger et al., Int. J. Radiat. Onc. Biol. Phys., 2006]

Critical Element model

Mechanistic

Serial organ



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

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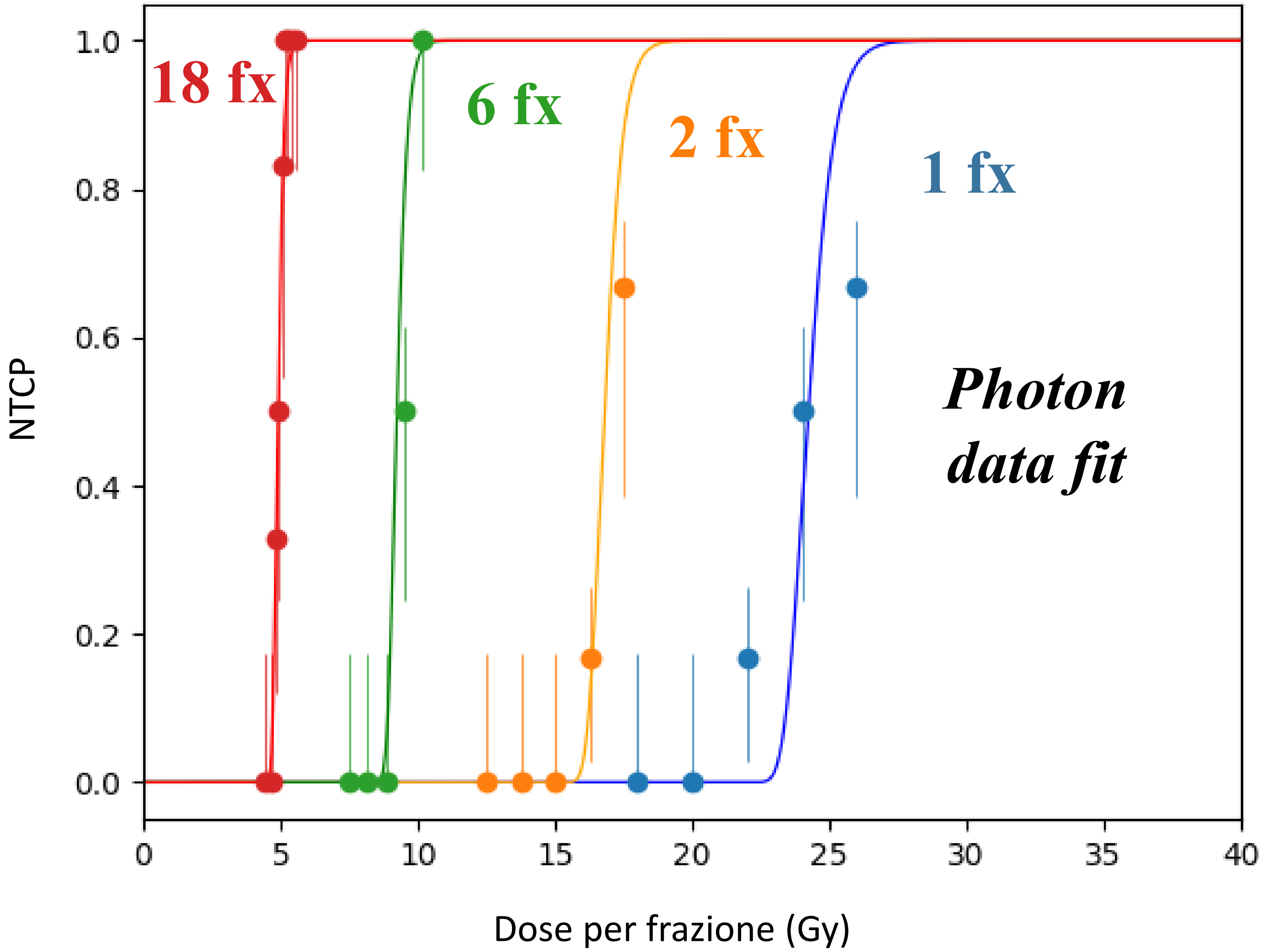
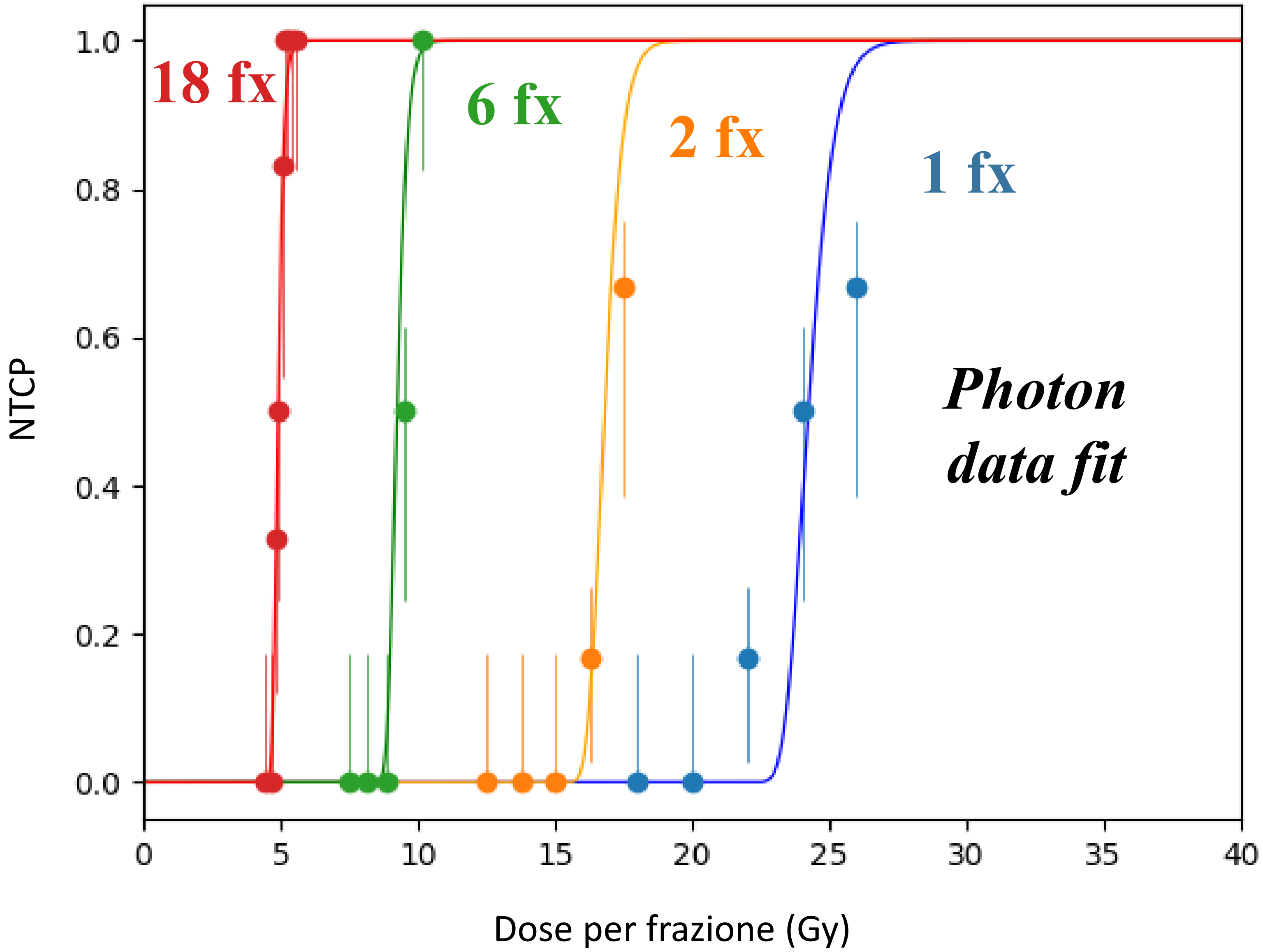
Parameter estimation for ion NTCP predictions

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



Parameter estimation for ion NTCP predictions



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Photon **k, N** fixed for ion NTCP predictions

Parameter estimation for ion NTCP predictions

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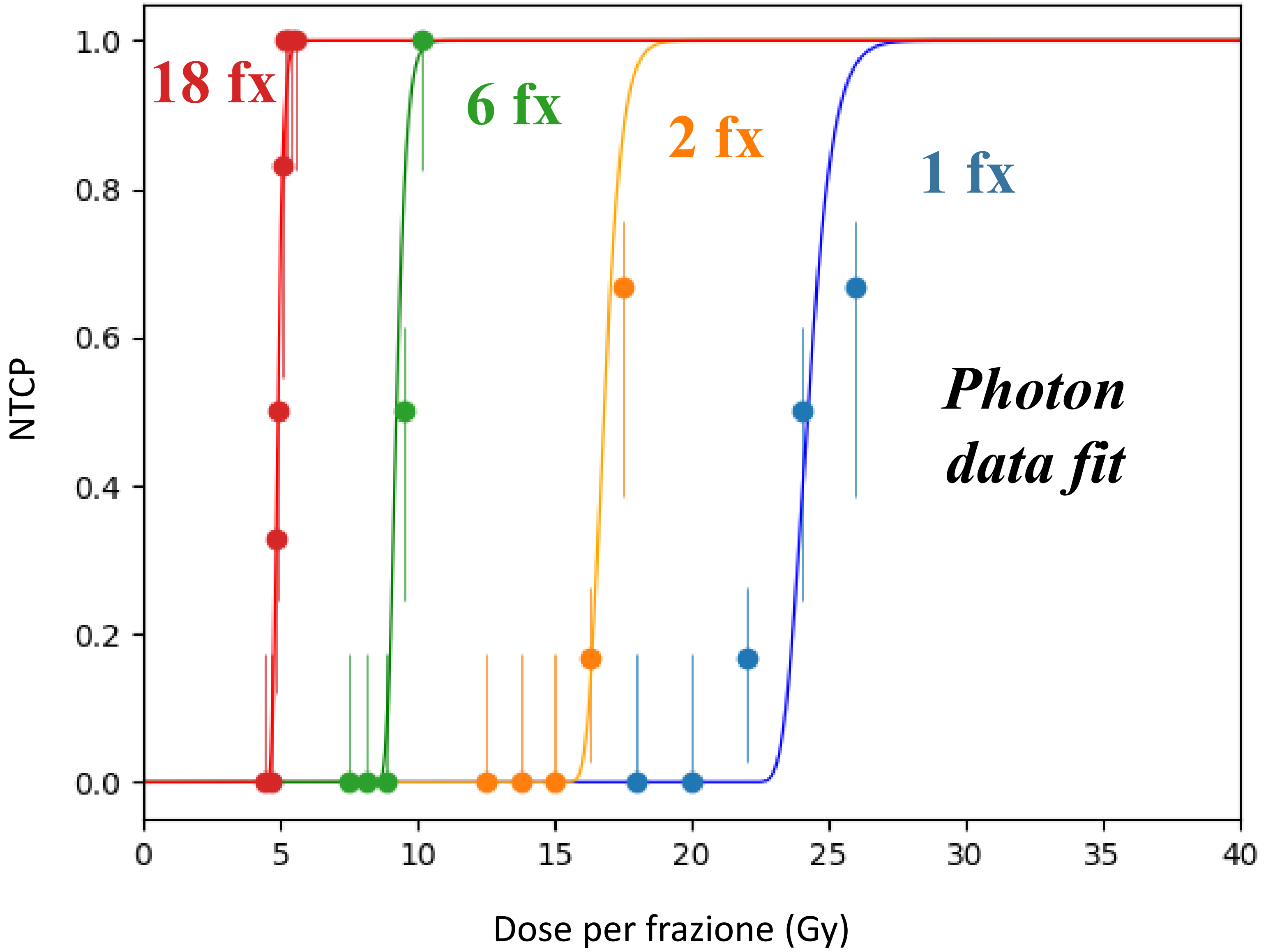


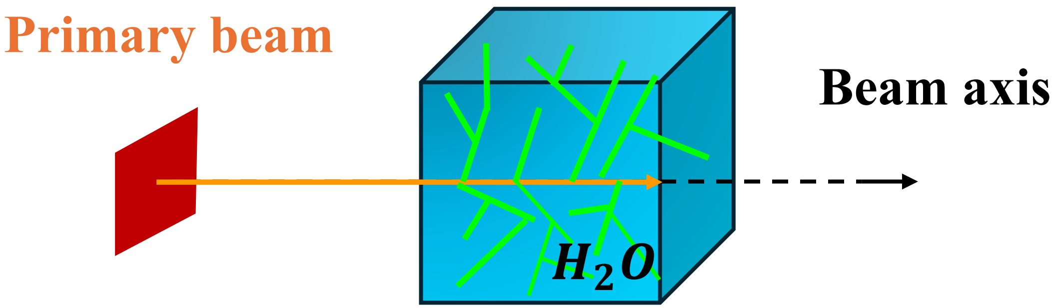
Photon **k, N** fixed for ion NTCP predictions

$\boldsymbol{\alpha_X}$ e $\boldsymbol{\beta_X}$

Ion α and β estimation

Ion α and β estimation

Real Mixed Field



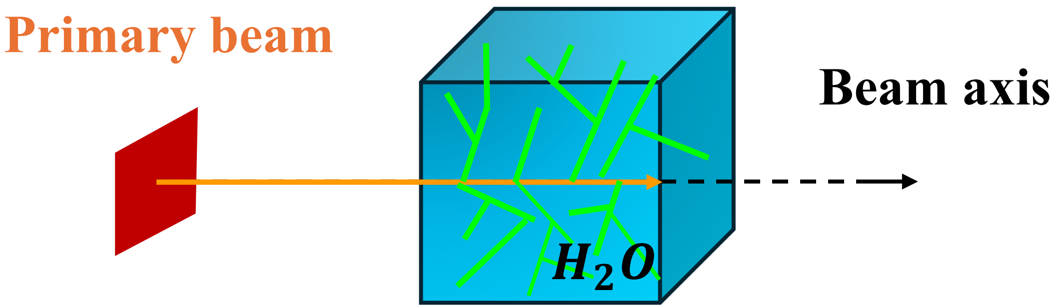
Real Mixed Field

Ion α and β estimation

BIANCA-Geant4 interface

[in collaboration: GEANT4INFN project]

Real Mixed Field



Real Mixed Field

BIANCA

[Ballarini, Carante, Radiat. Phys. And Chem., 2016]

By knowing
α_X e β_X →

BIANCA

[Ballarini, Carante, Radiat. Phys. And Chem., 2016]

By knowing α_X e β_X

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

Table of α and β for several particles and LET values

LET [keV/μm] = ***Stopping power***

BIANCA

[Ballarini, Carante, Radiat. Phys. And Chem., 2016]

By knowing α_X e β_X

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Z=2 A=4 (He4)

LET	alfa	beta
5	0.122919965474113	0.0282243396663055
10	0.164742642147497	0.032025638951858?

Monochromatic Field

Table of α and β for several particles and LET values

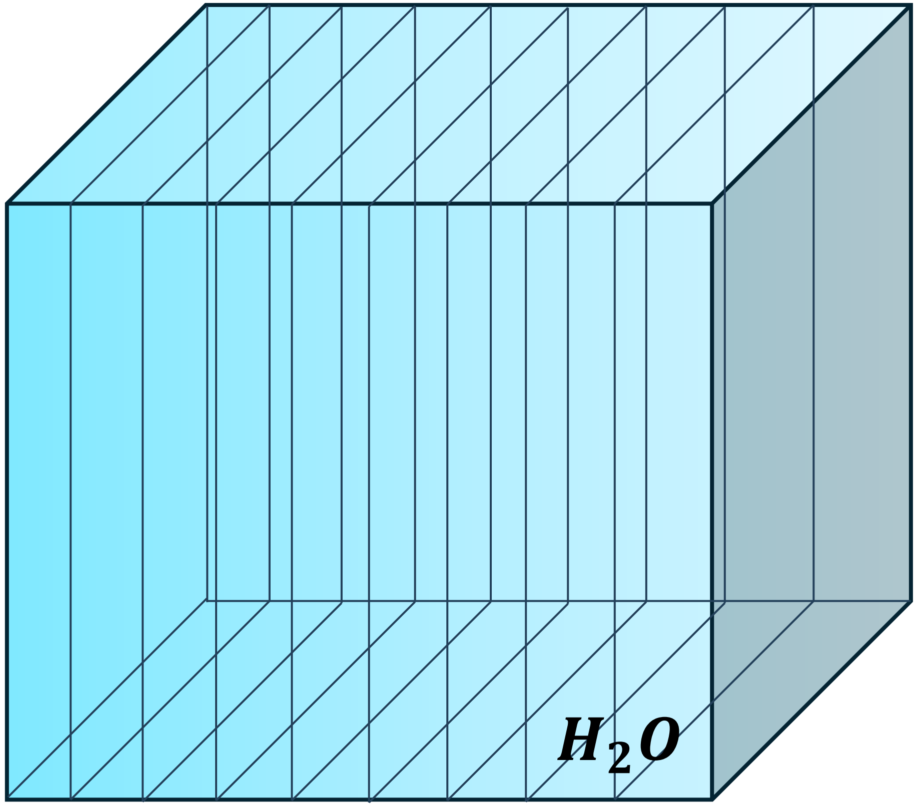
LET [keV/μm] = ***Stopping power***

Interface BIANCA - GEANT4

GEANT4 simulation

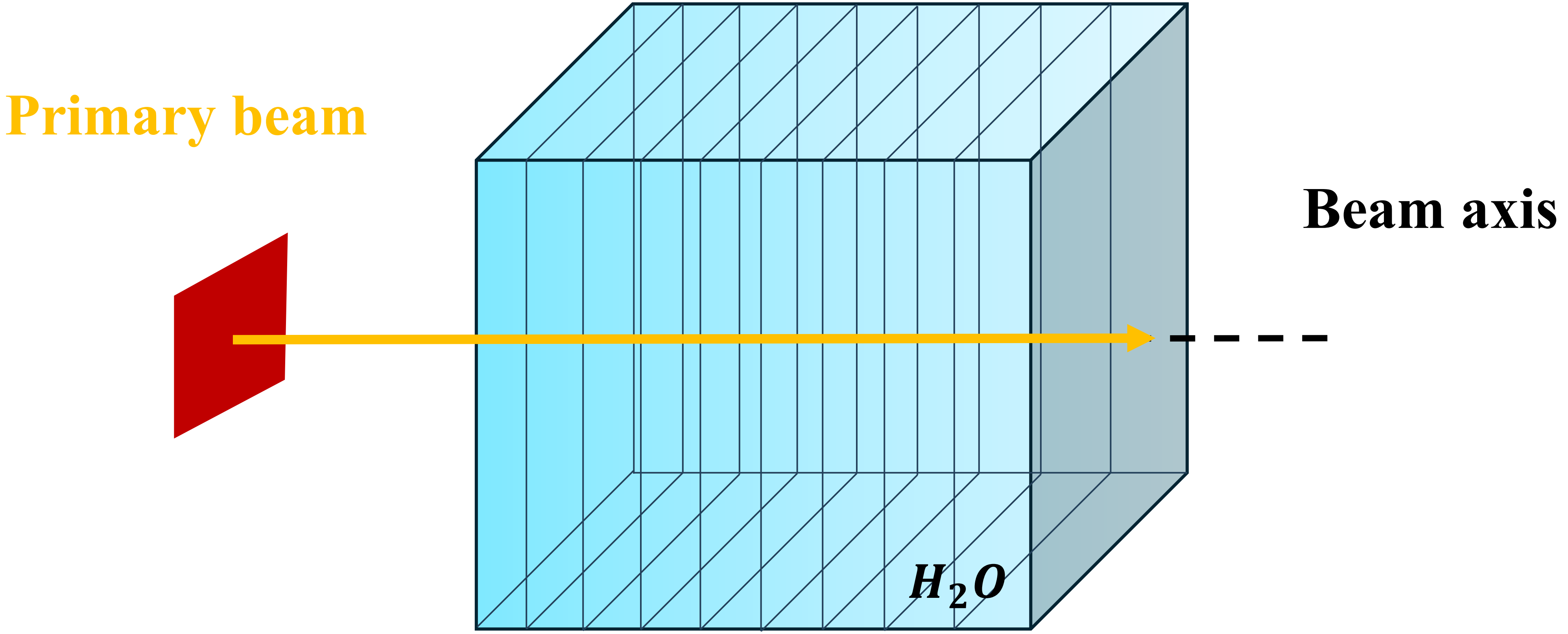
Interface BIANCA - GEANT4

GEANT4 simulation



Interface BIANCA - GEANT4

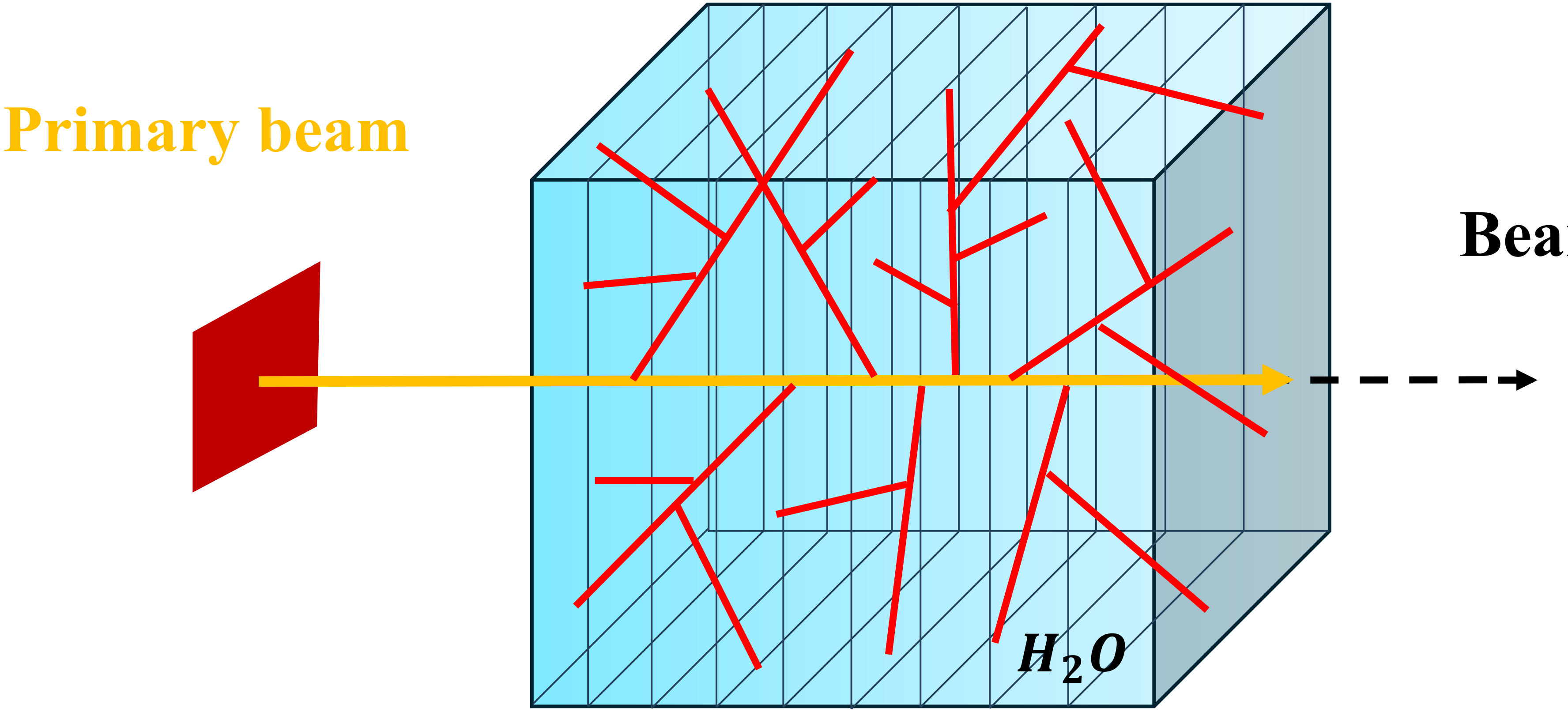
GEANT4 simulation



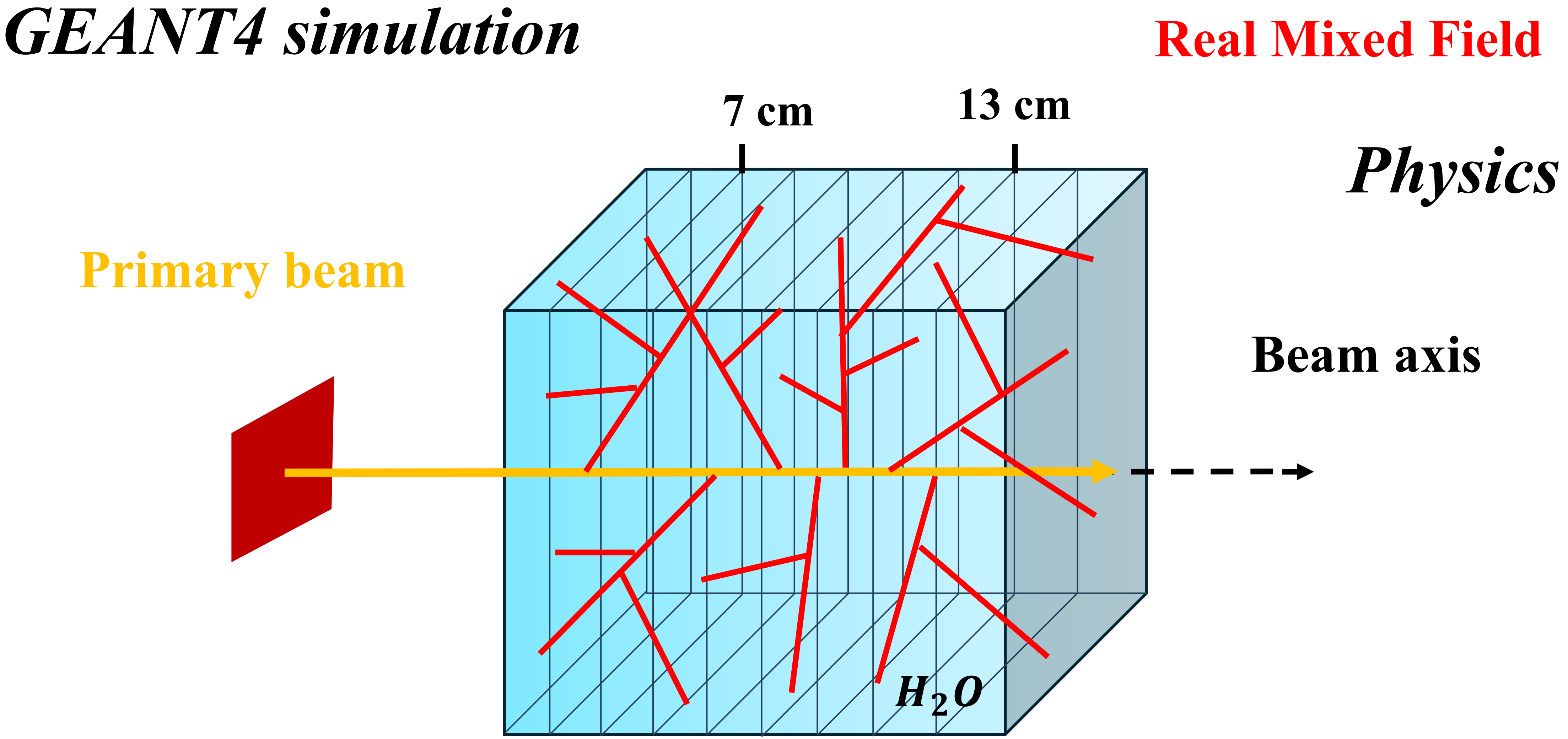
Interface BIANCA - GEANT4

GEANT4 simulation

Real Mixed Field



Interface BIANCA - GEANT4



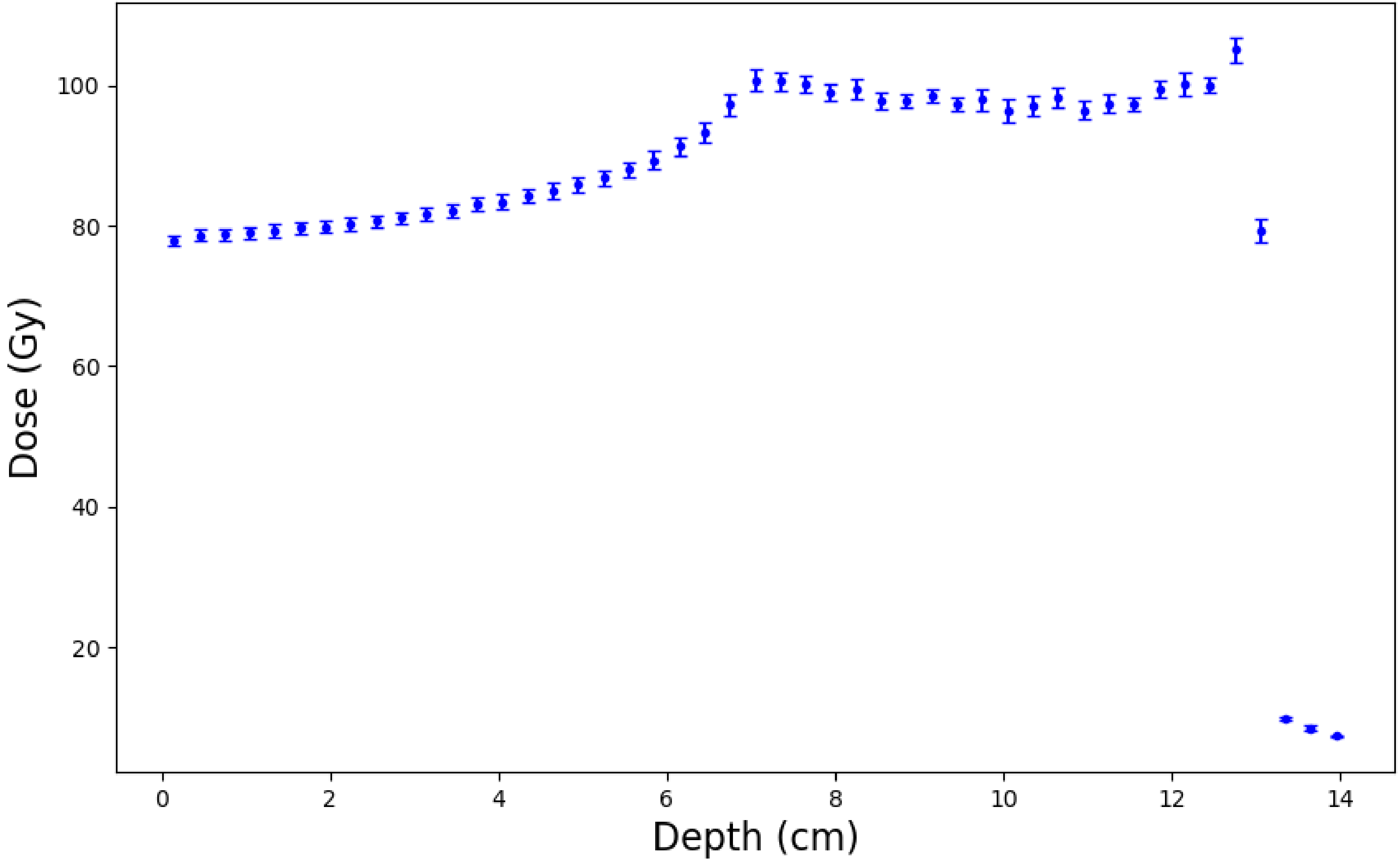
Interface BIANCA - GEANT4

e.g. Carbon ions

Physics

Interface BIANCA - GEANT4

e.g. Carbon ions

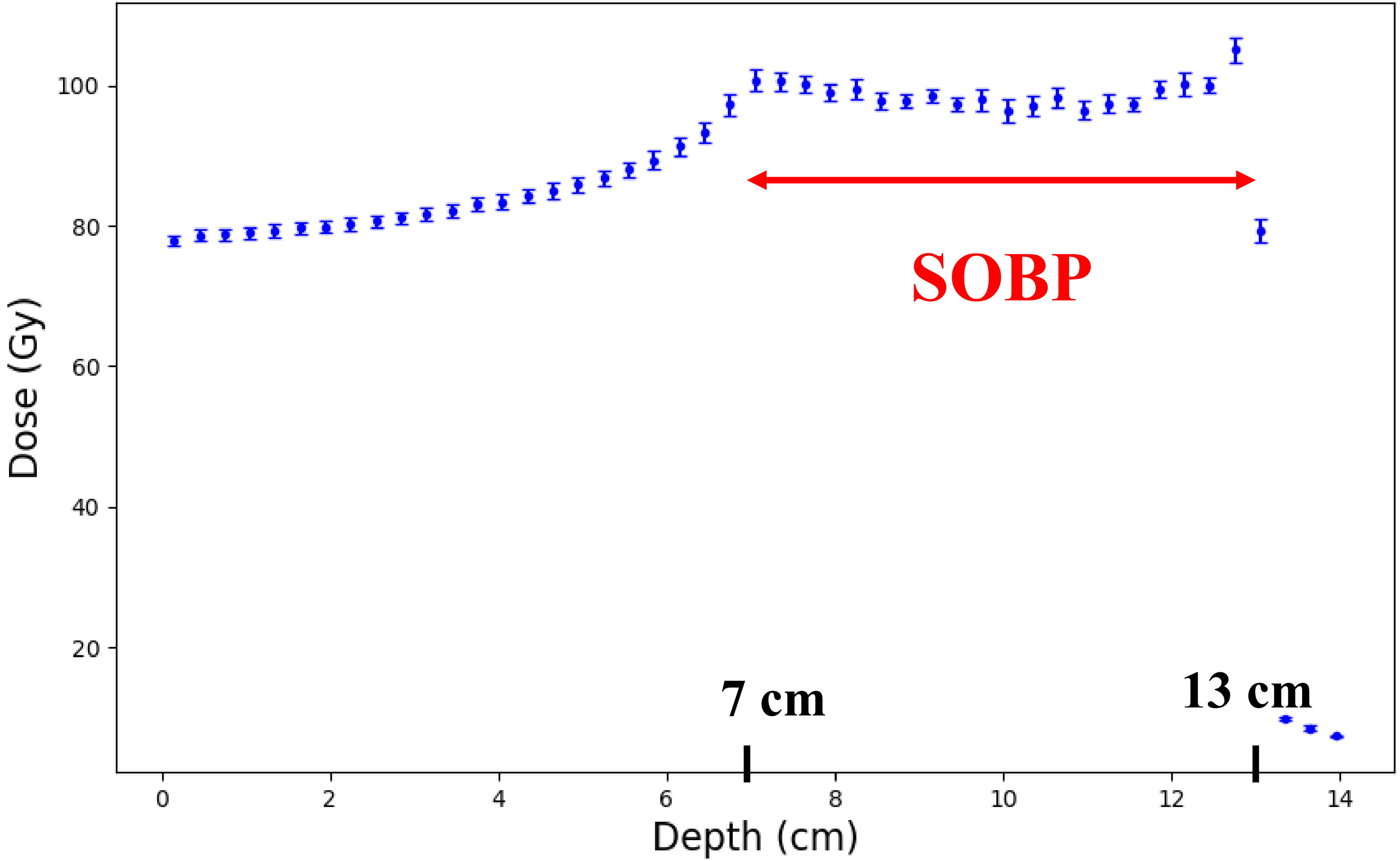


Physics

Interface BIANCA - GEANT4

e.g. Carbon ions

Physics



Interface BIANCA - GEANT4

Radiobiology

Interface BIANCA - GEANT4

Radiobiology

Averaged ion

$\boldsymbol{\overline{\alpha}, \overline{\beta}}$

Interface BIANCA - GEANT4

Radiobiology

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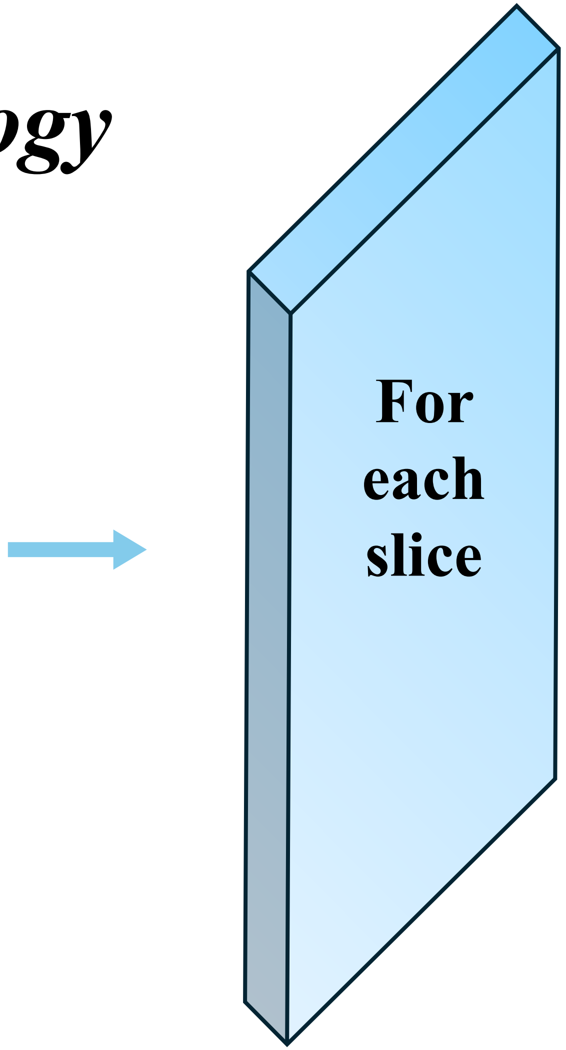
$\bar{\alpha}, \bar{\beta}$



Interface BIANCA - GEANT4

Radiobiology

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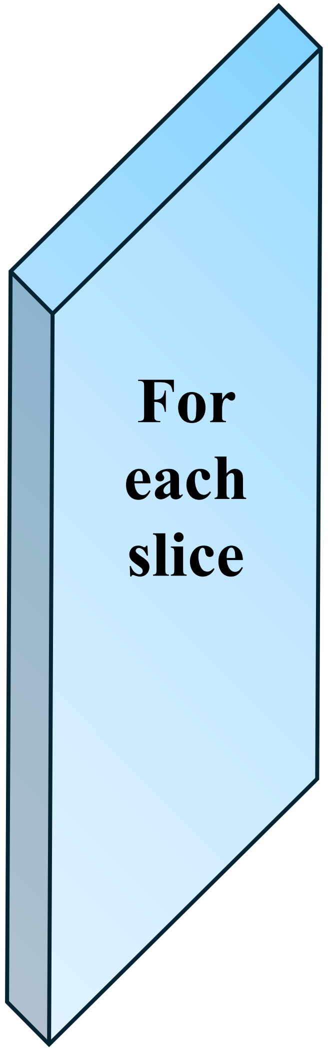
$\bar{\alpha}, \bar{\beta}$



$$\bar{\alpha} = \frac{\sum_{i=1}^{n} \sum_{j=1}^{m} \alpha_{i,j} D_{i,j}}{\sum_{i=1}^{n} \sum_{j=1}^{m} D_{i,j}}$$

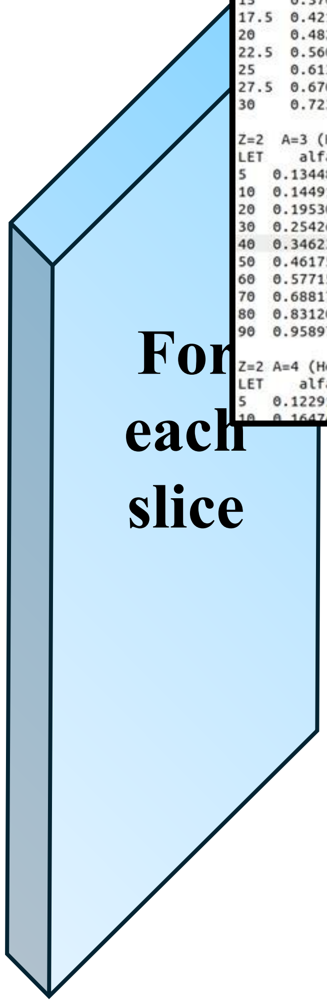
$$\bar{\beta} = \left(\frac{\sum_{i=1}^{n} \sum_{j=1}^{m} \sqrt{\beta_{i,j}} D_{i,j}}{\sum_{i=1}^{n} \sum_{j=1}^{m} D_{i,j}} \right)^2$$

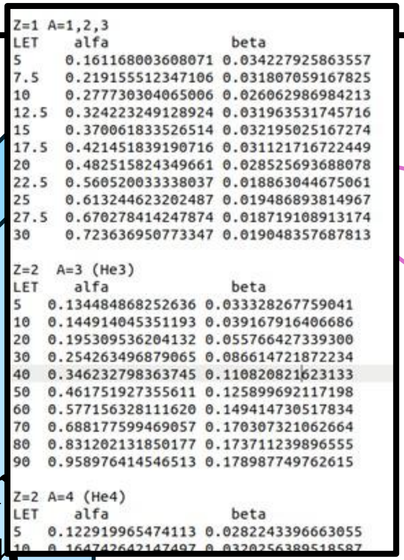
Interface BIANCA - GEANT4

Radiobiology

Averaged ion

$\bar{\alpha}, \bar{\beta}$





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90	0.958976414546513	0.178987749762615

Z=2 A=4 (He4)

LET	alfa	beta
5	0.122919965474113	0.028224339666305

BIANCA

$$\bar{\alpha} = \frac{\sum_{i=1}^{n}\sum_{j=1}^{m} \alpha_{i,j} D_{i,j}}{\sum_{i=1}^{n}\sum_{j=1}^{m} D_{i,j}}$$

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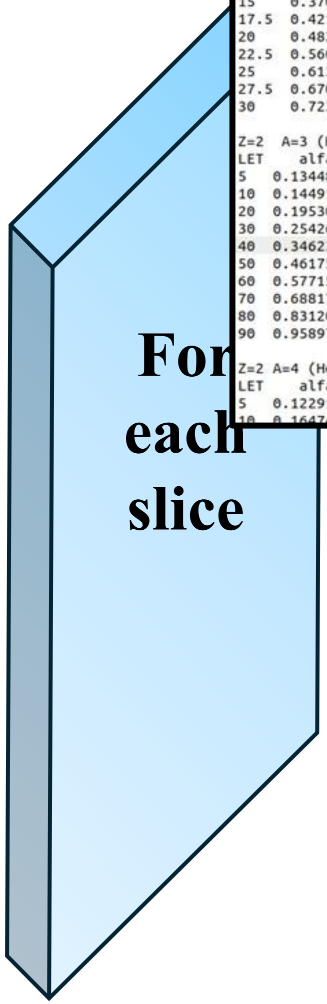
Interface BIANCA - GEANT4

Radiobiology

Averaged ion

$\bar{\alpha}, \bar{\beta}$



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LET	alfa	beta
5	0.122919965474113	0.028224339666305 5

BIANCA

$$\bar{\alpha} = \frac{\sum_{i=1}^{n}\sum_{j=1}^{m} \alpha_{i,j} D_{i,j}}{\sum_{i=1}^{n}\sum_{j=1}^{m} D_{i,j}}$$

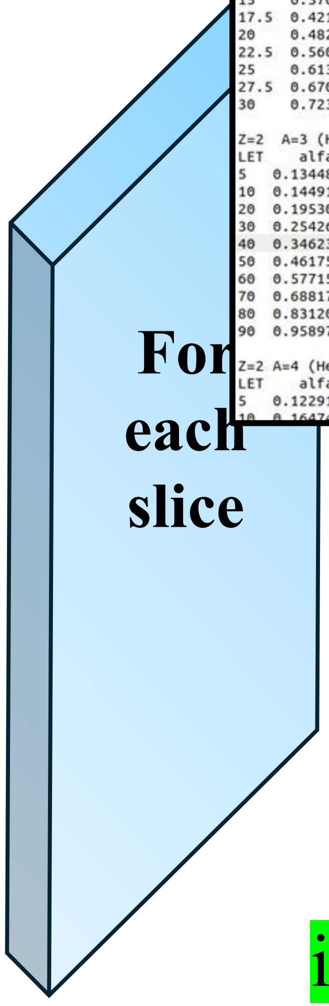
$$\bar{\beta} = \left(\frac{\sum_{i=1}^{n}\sum_{j=1}^{m} \sqrt{\beta_{i,j}} D_{i,j}}{\sum_{i=1}^{n}\sum_{j=1}^{m} D_{i,j}}\right)^2$$

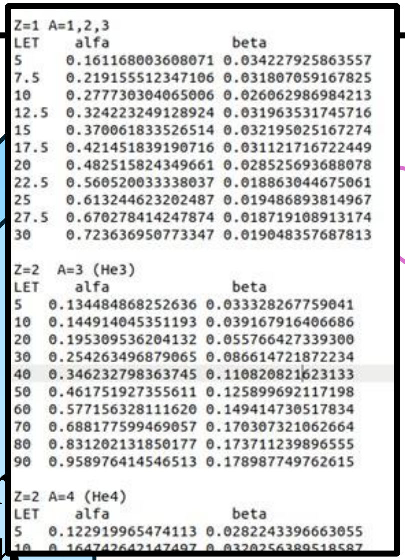
Interface BIANCA - GEANT4

Radiobiology

Averaged ion

$\bar{\alpha}, \bar{\beta}$





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	0.028224339666305 5
10	0.164742642147497	0.0320256389518587

BIANCA

$$\bar{\alpha} = \frac{\sum_{i=1}^{n} \sum_{j=1}^{m} \alpha_{i,j} D_{i,j}}{\sum_{i=1}^{n} \sum_{j=1}^{m} D_{i,j}}$$

$$\bar{\beta} = \left(\frac{\sum_{i=1}^{n} \sum_{j=1}^{m} \sqrt{\beta_{i,j}} D_{i,j}}{\sum_{i=1}^{n} \sum_{j=1}^{m} D_{i,j}} \right)^2$$

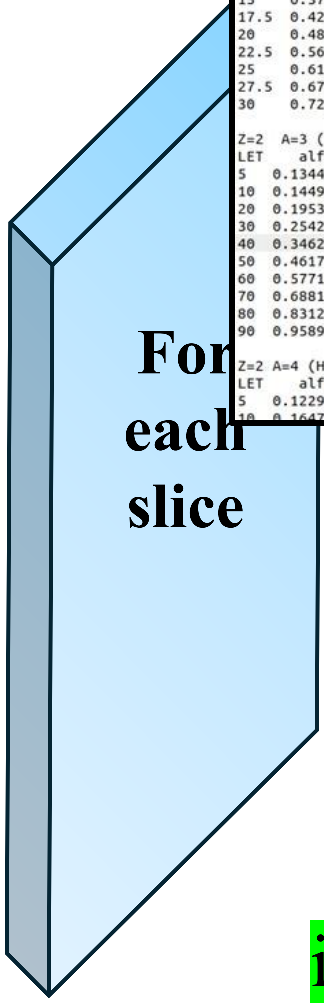
i – th particle

Interface BIANCA - GEANT4

Radiobiology

Averaged ion

$\bar{\alpha}, \bar{\beta}$




```
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)
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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
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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 0.028224339666305
10  0.164742642147497 0.0320256389518587
```

BIANCA

$$\bar{\alpha} = \frac{\sum_{i=1}^{n} \sum_{j=1}^{m} \alpha_{i,j} D_{i,j}}{\sum_{i=1}^{n} \sum_{j=1}^{m} D_{i,j}}$$

$$\bar{\beta} = \left(\frac{\sum_{i=1}^{n} \sum_{j=1}^{m} \sqrt{\beta_{i,j}} D_{i,j}}{\sum_{i=1}^{n} \sum_{j=1}^{m} D_{i,j}} \right)^2$$

i – th particle   j – th energy value

Ion NTCP predictions

Real Mixed Field

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

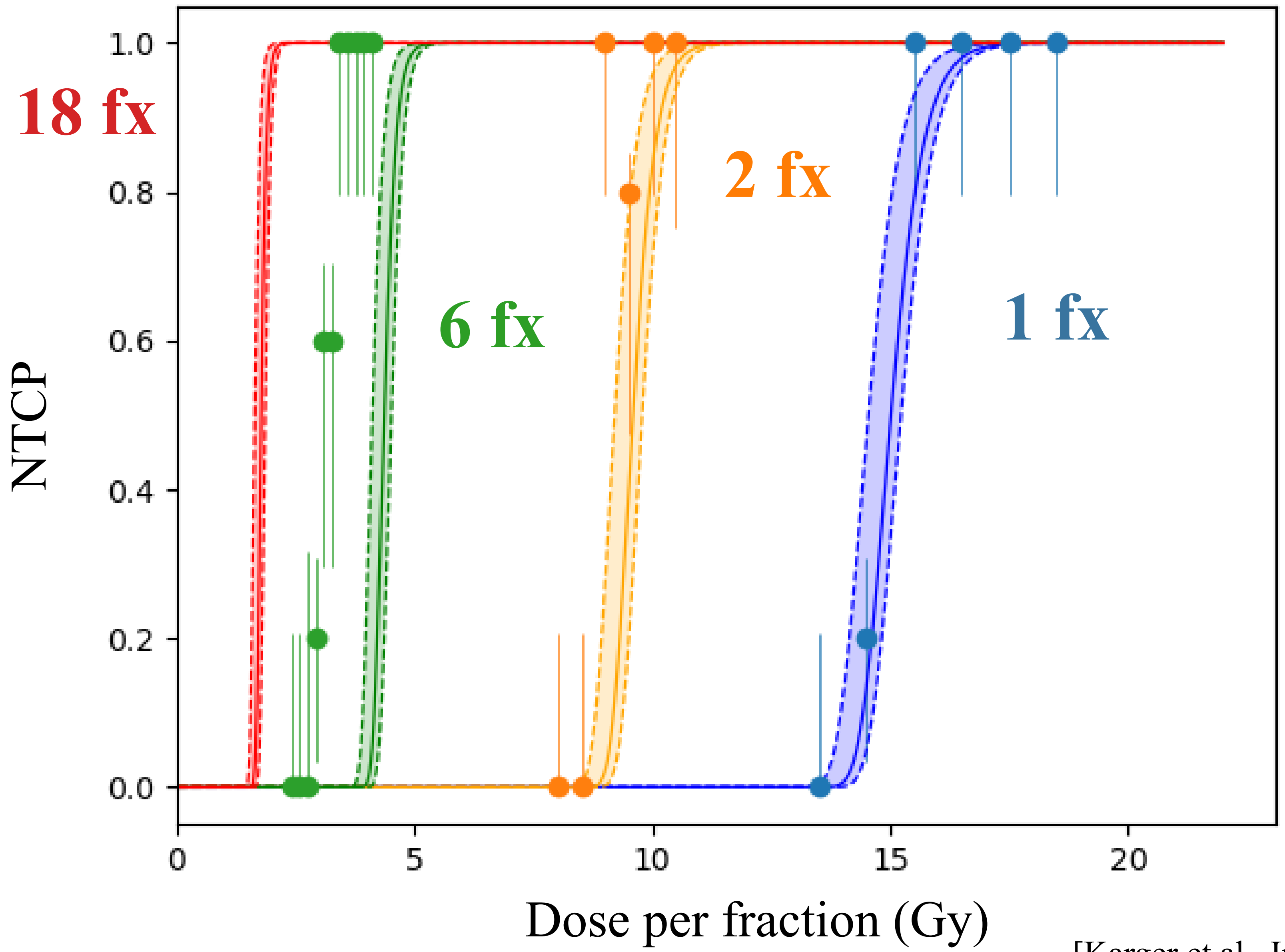
Ion NTCP predictions

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

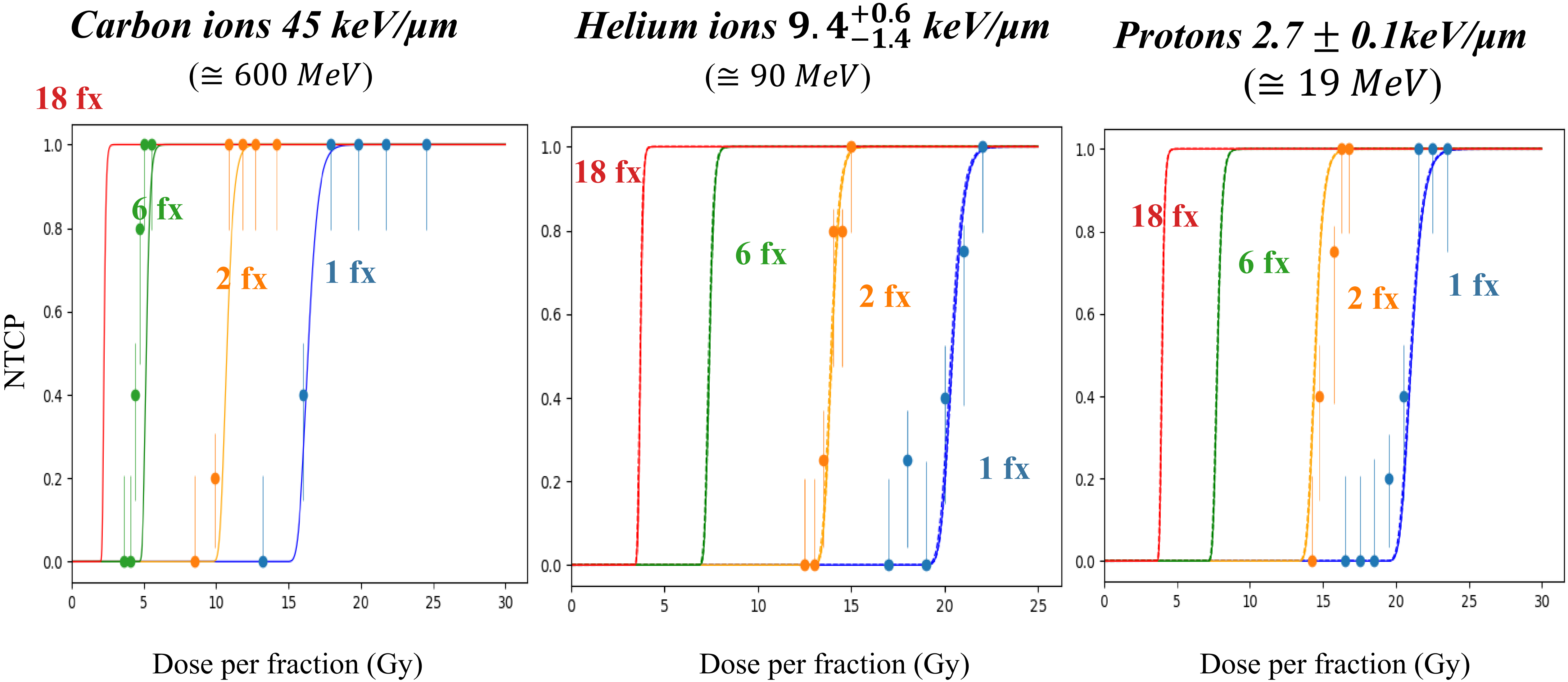
Carbon ions 66 ± 6 keV/μm $(\cong 375\ MeV)$



[**A. Casali** et al., European Physical Journal Special Topics., submitted, **2025**]

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

For other particles and LET values



Validation on other data

Validation on other data

Collected by
another
research group

[Leith et al., Radiation Research, 1982]

Validation on other data

Collected by **another research group**

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

BIANCA – Geant4 interface

[Leith et al., Radiation Research, 1982]

Validation on other data

Collected by
another
research group

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

BIANCA – Geant4 interface

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
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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	0.028224339666305 5
10	0.164742642147497	0.0320256389518587

Previous dataset

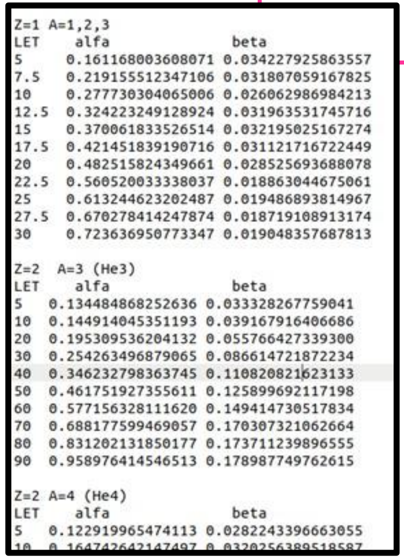
[Leith et al., Radiation Research, 1982]

Validation on other data

Collected by **another research group**

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

BIANCA – Geant4 interface



```
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
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80  0.831202131850177 0.173711239896555
90  0.958976414546513 0.178987749762615

Z=2 A=4 (He4)
LET    alfa               beta
5   0.122919965474113 0.028224339663055
10  0.164742642147497 0.032025638951858
```

Previous dataset

Previous dataset

[Leith et al., Radiation Research, 1982]

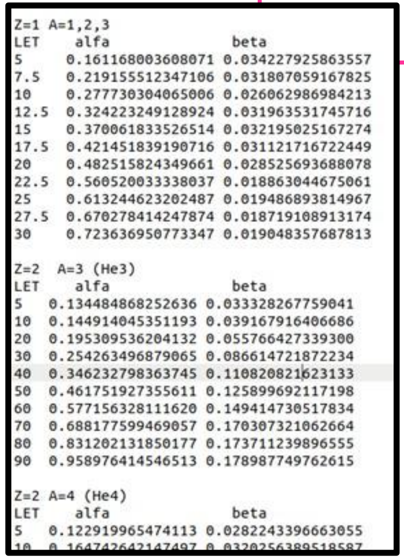
Validation on other data

L

Collected by **another research group**

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

BIANCA – Geant4 interface



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LET	alfa	beta
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10	0.277730304065006	0.026062986984213
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Z=2 A=4 (He4)

LET	alfa	beta
5	0.122919965474113	0.028224339663055
10	0.164742642147497	0.032025638951858

Previous dataset

Previous dataset

$\propto$ ***L***

irradiated length

[Leith et al., Radiation Research, 1982]

Validation on other data

L

Collected by **another research group**

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

BIANCA – Geant4 interface ($\bar{\alpha}$, $\bar{\beta}$)

Previous dataset (k)

Previous dataset (N)

$\propto$ ***L*** irradiated length

Z=1 A=1,2,3

LET	alfa	beta
5	0.161168003608071	0.034227925863557
7.5	0.219155512347106	0.031807059167825
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70	0.688177599469057	0.170307321062664
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90	0.958976414546513	0.178987749762615

Z=2 A=4 (He4)

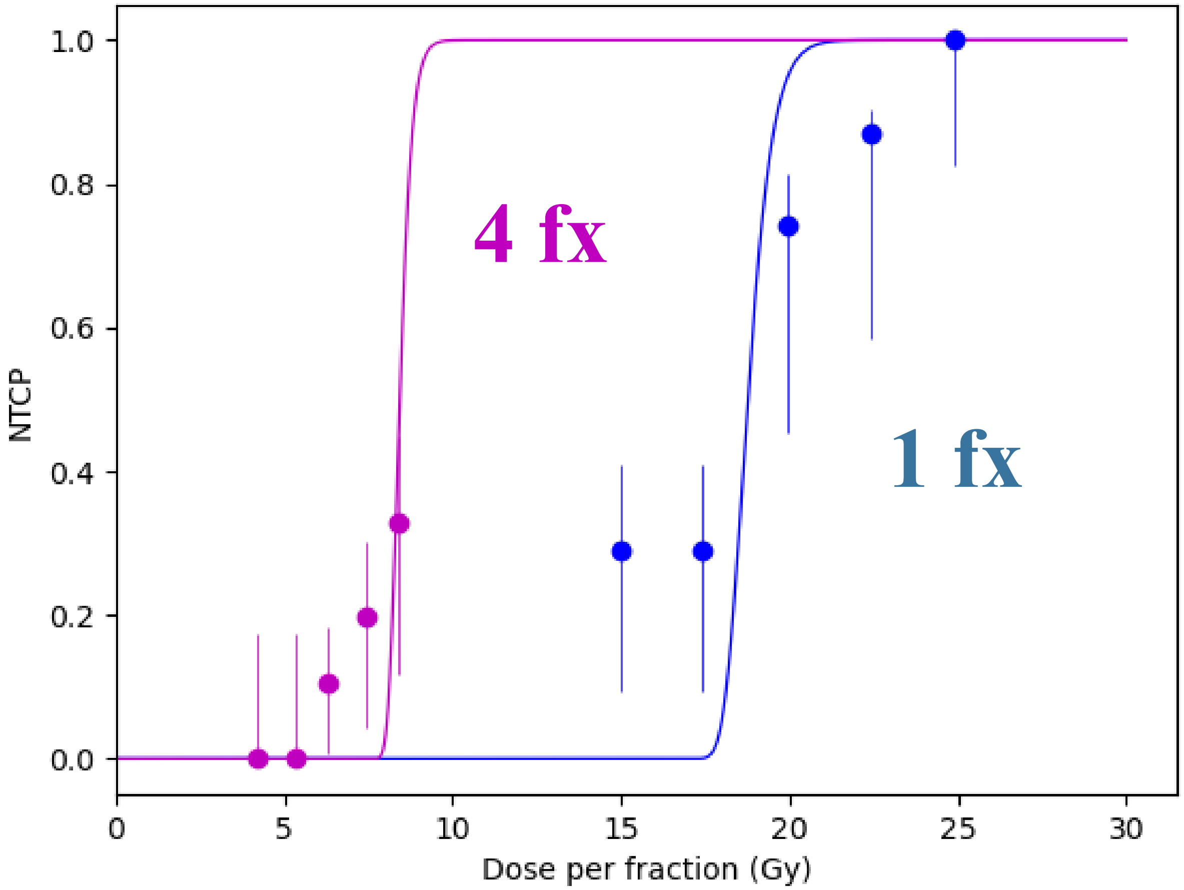
LET	alfa	beta
5	0.122919965474113	0.028224339663055
10	0.164742642147497	0.0320256389518587

Previous dataset

[Leith et al., Radiation Research, 1982]

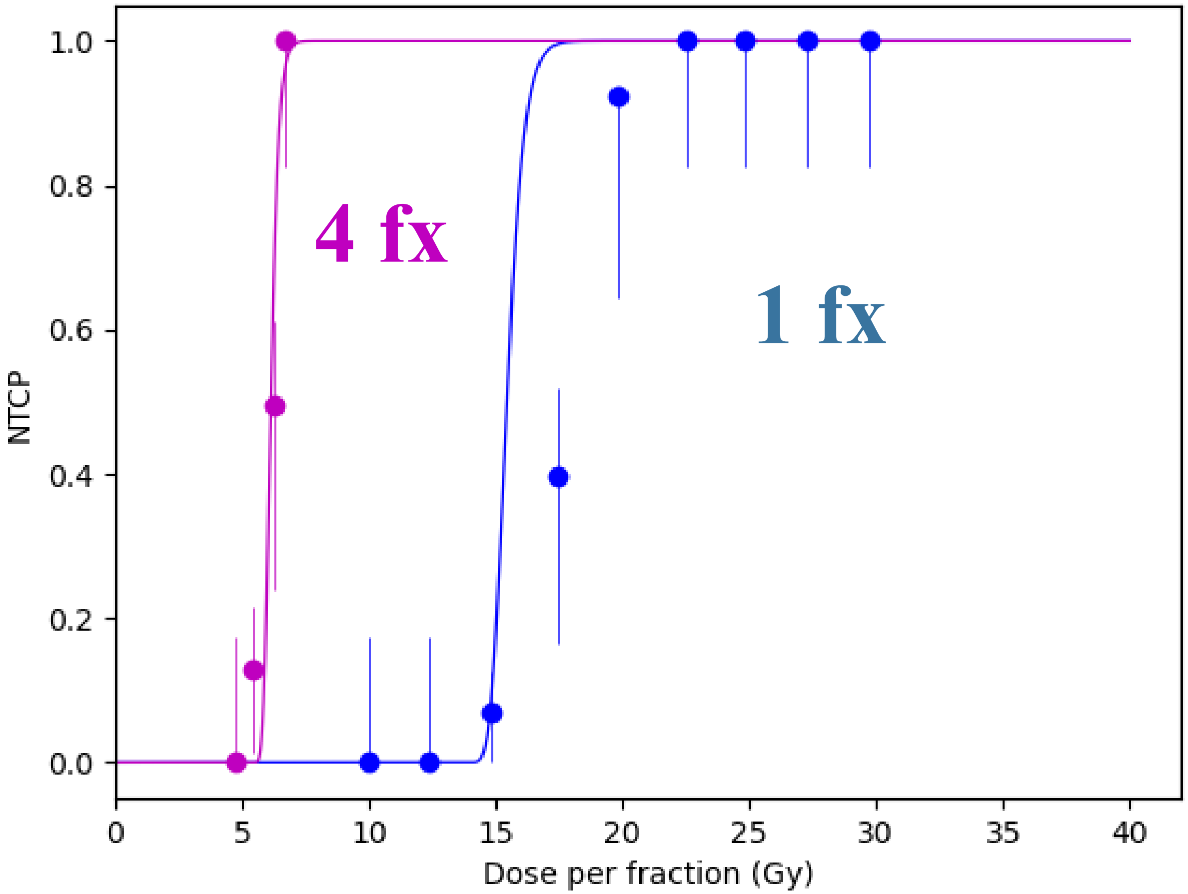
Carbon ions 10 keV/μm

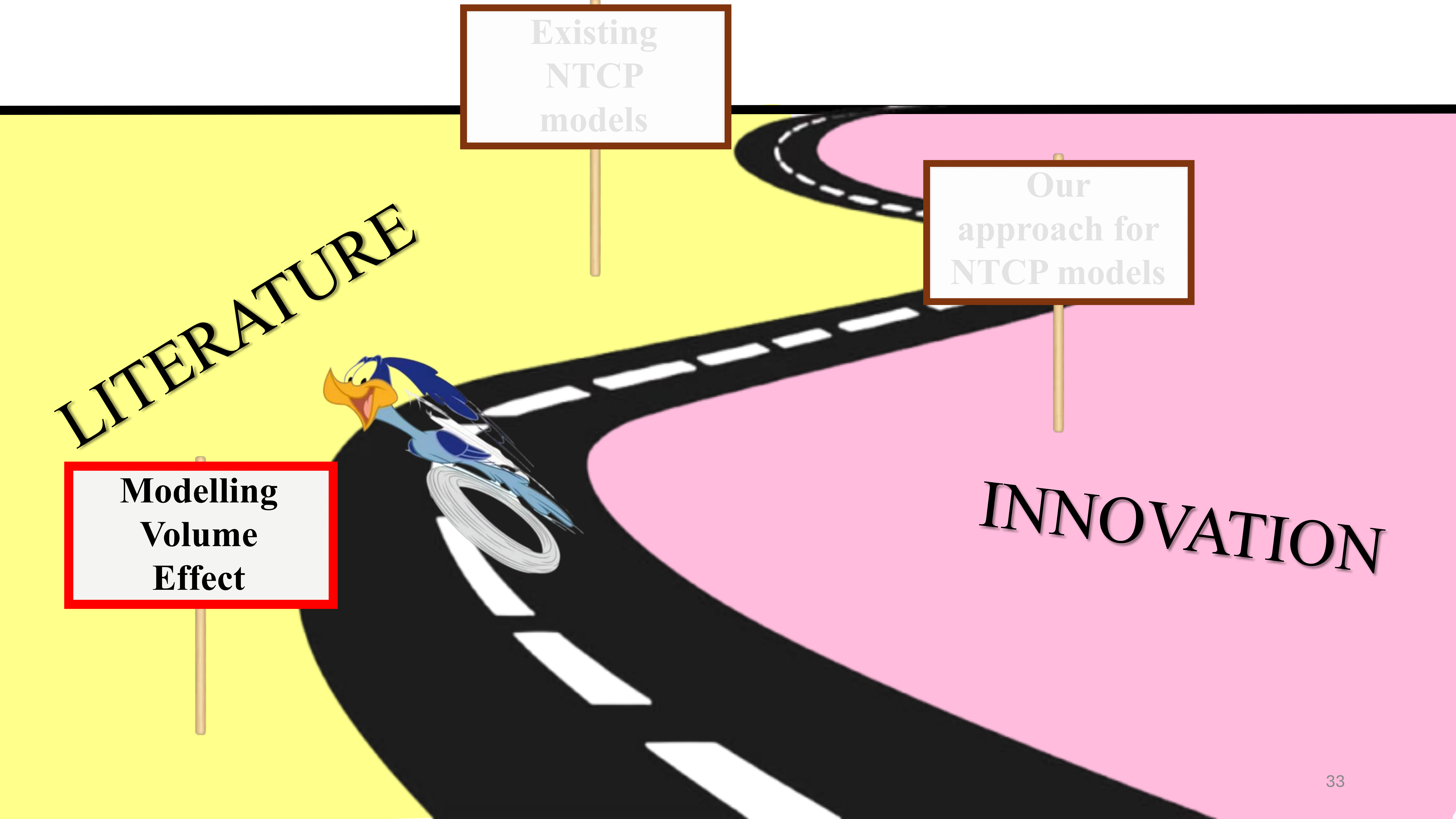
$(\cong 5500\ MeV)$



Carbon ions 80 keV/μm

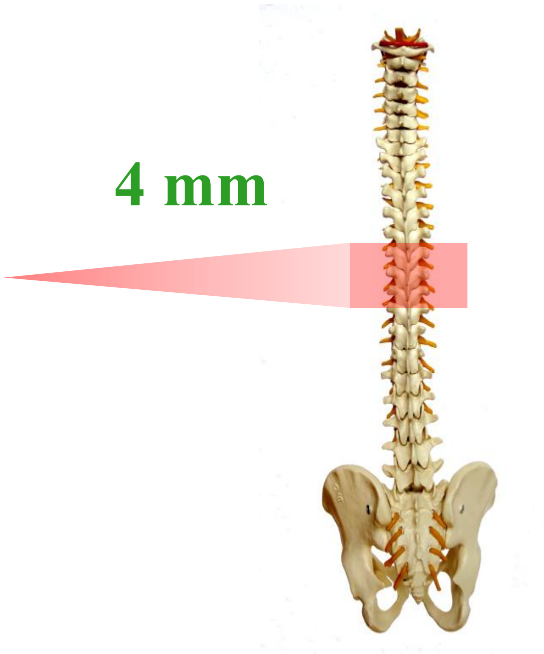
$(\cong 285\ MeV)$



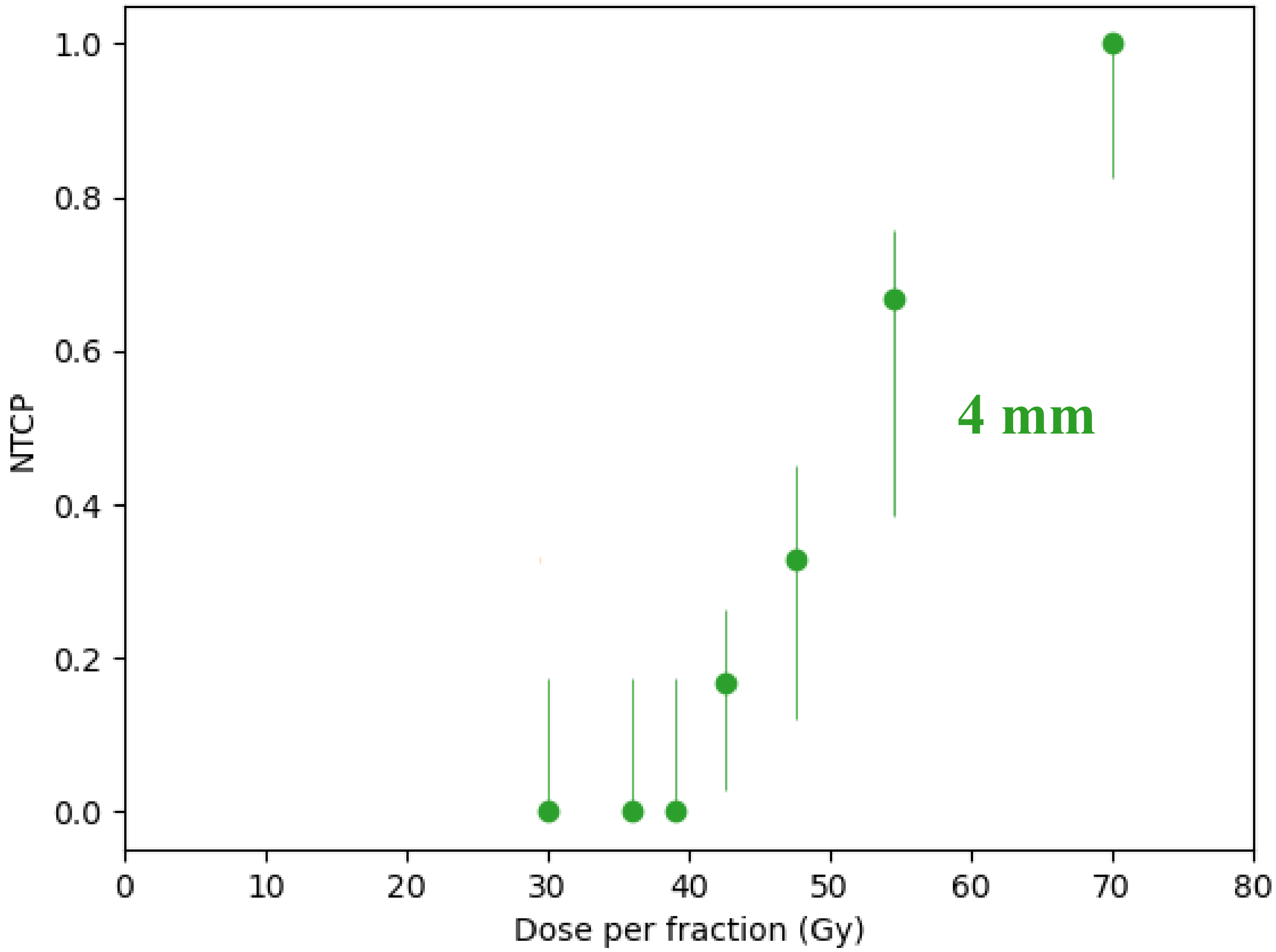


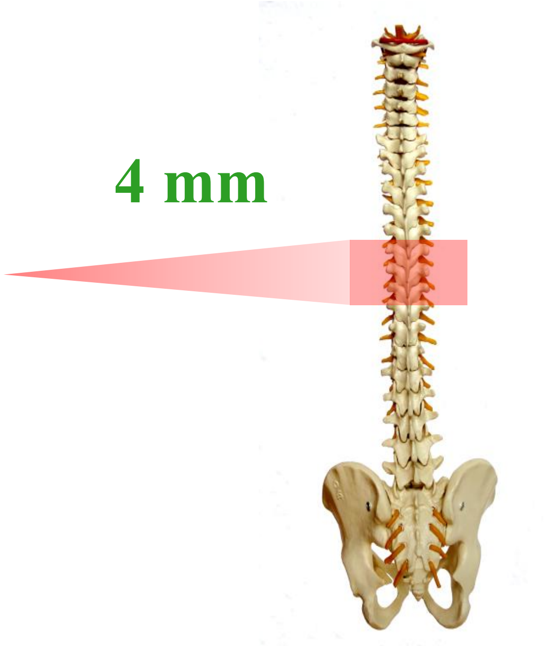
Existing NTCP models
Our approach for NTCP models
LITERATURE
Modelling Volume Effect
INNOVATION

Open Problems: *Volume Effect*



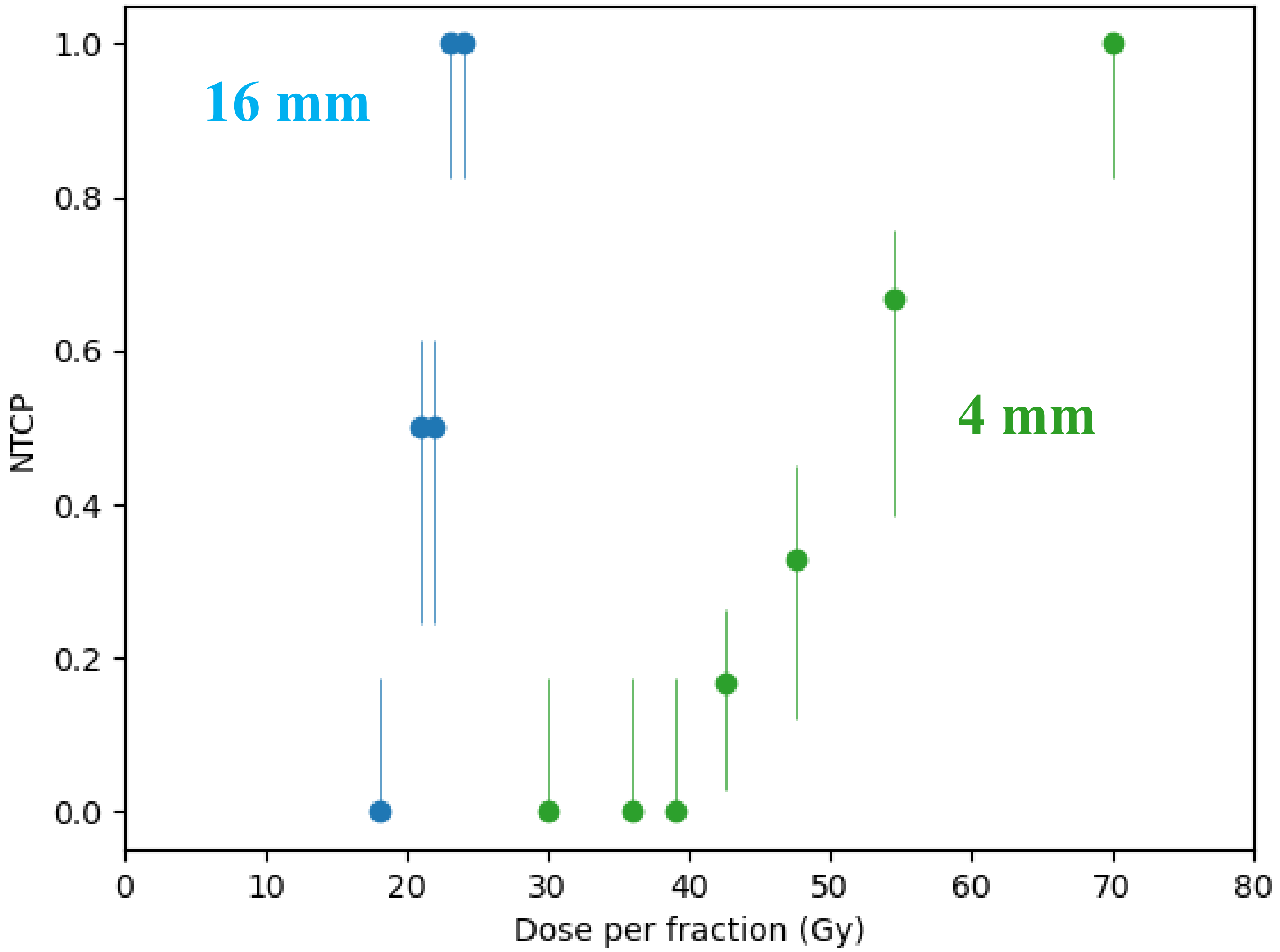
Open Problems: Volume Effect

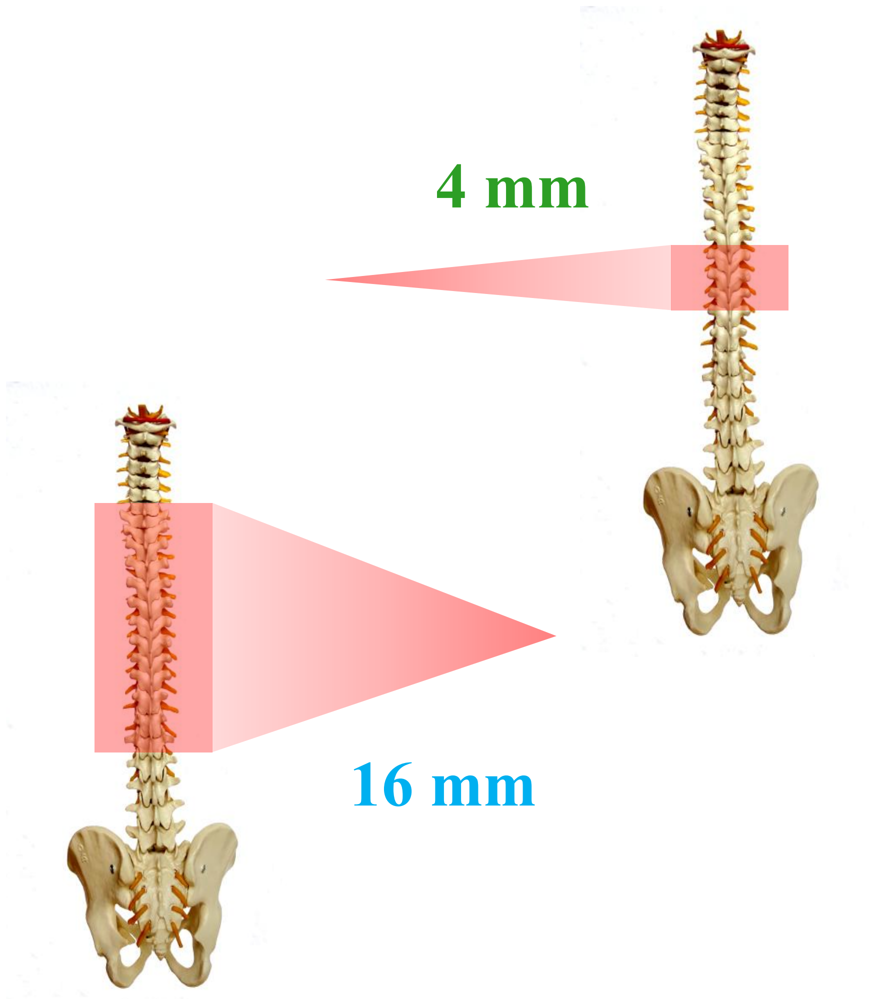




[Hopewell et al., The British Journal of Radiology, 1987]

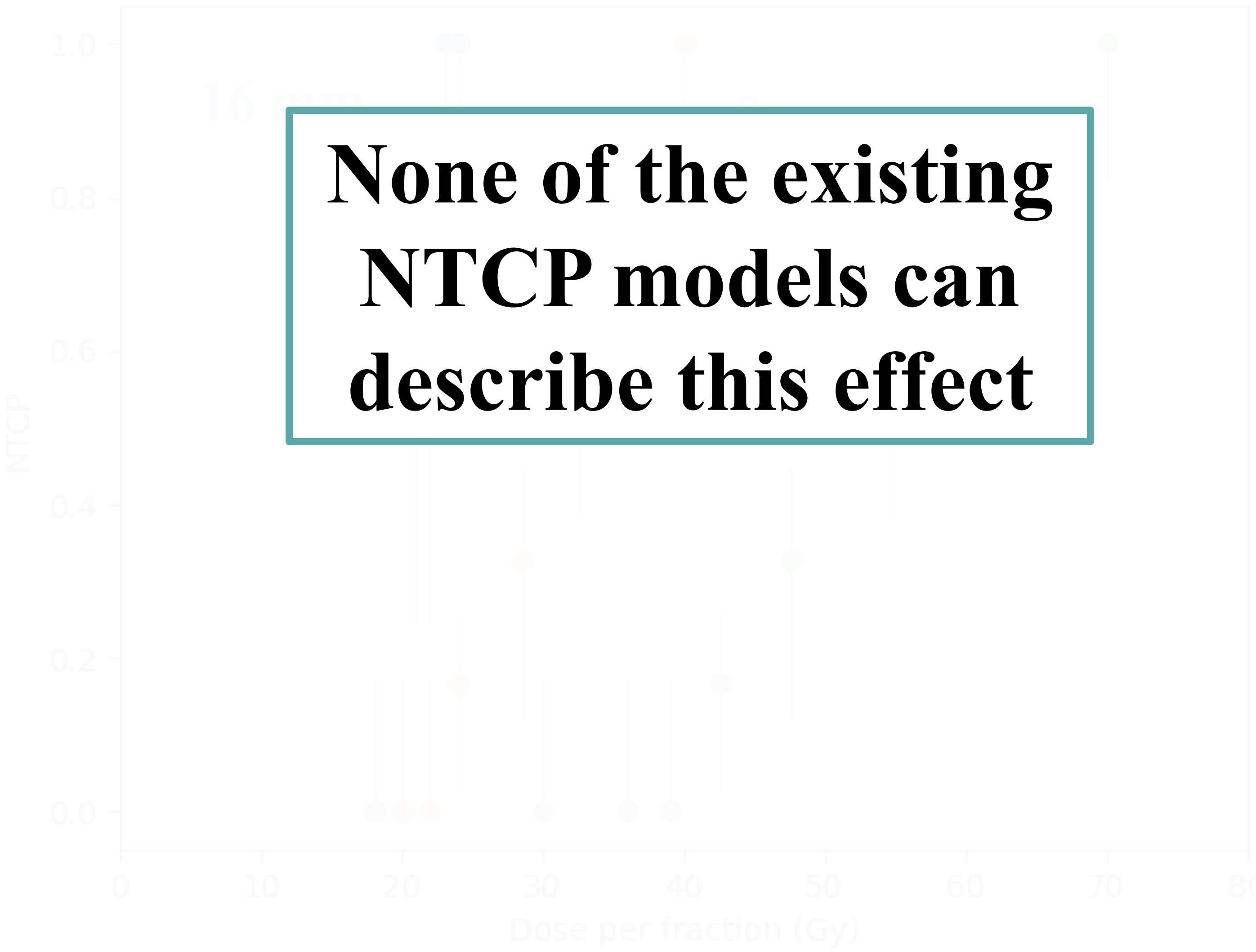
Open Problems: *Volume Effect*





[Hopewell et al., The British Journal of Radiology, 1987]

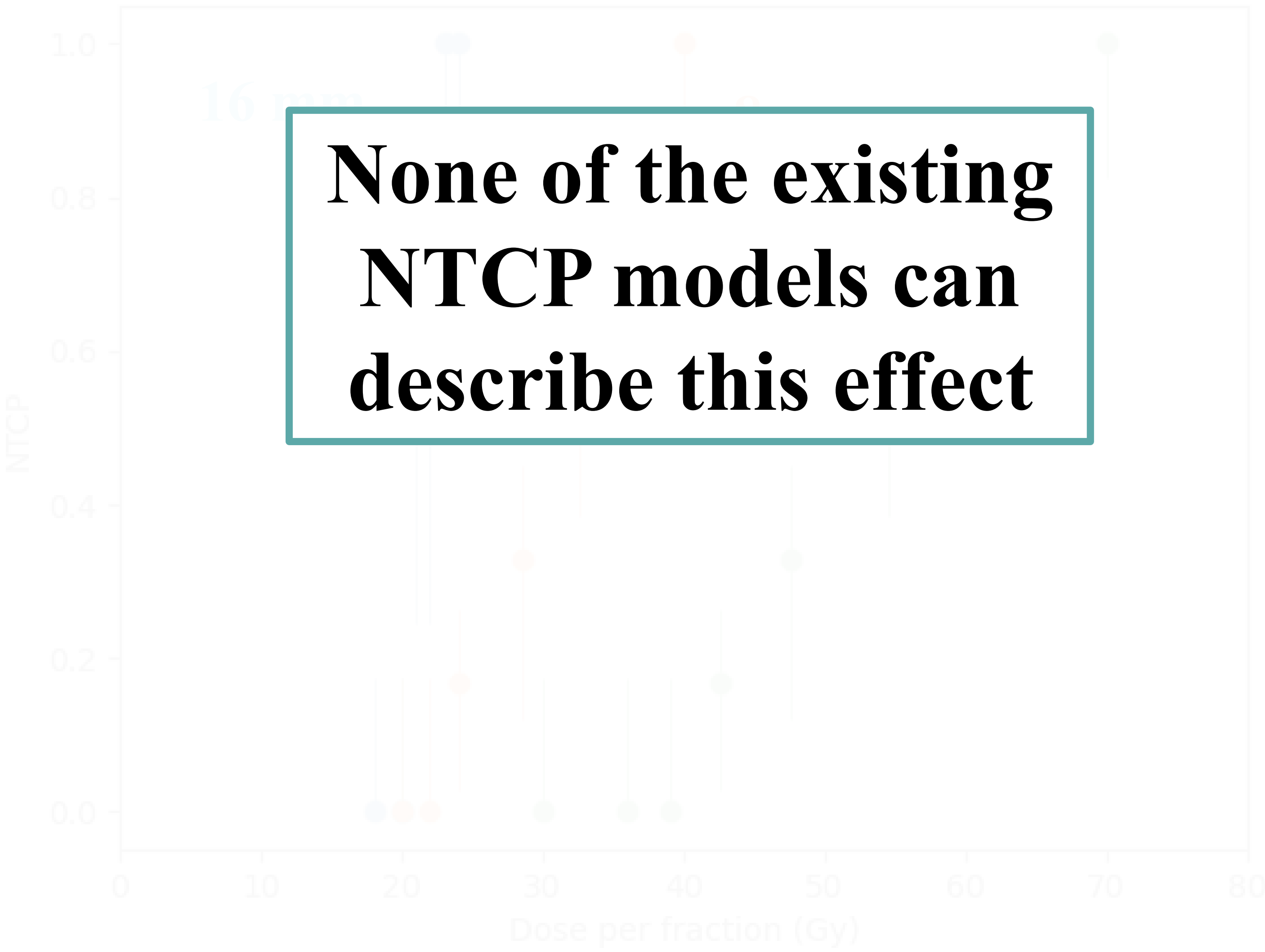
Open Problems: *Volume Effect*



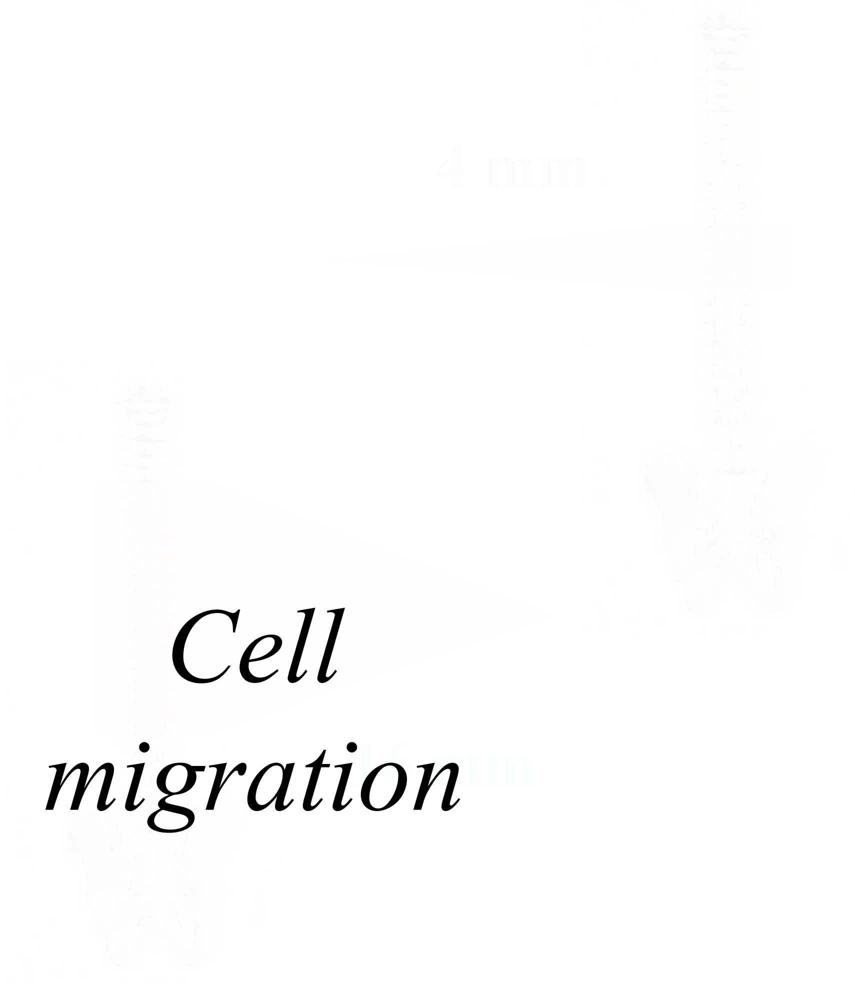
None of the existing NTCP models can describe this effect

[Hopewell et al., The British Journal of Radiology, 1987]

Open Problems: *Volume Effect*



None of the existing NTCP models can describe this effect



Cell migration

[Hopewell et al., The British Journal of Radiology, 1987]

Shirato model

Critical Element model

$$\mathbf{NTCP} = 1 - \left[1 - \left(1 - e^{-\alpha n d - \beta n d^2}\right)^k\right]^{\frac{L}{L1}}$$

[Shirato et al., Radiotherapy and Oncology, 1995]

Shirato model

Critical Element model

$$\mathbf{NTCP} = 1 - \left[1 - \left(1 - e^{-\alpha n d - \beta n d^2}\right)^k\right]^{\frac{L}{L1}}$$

N

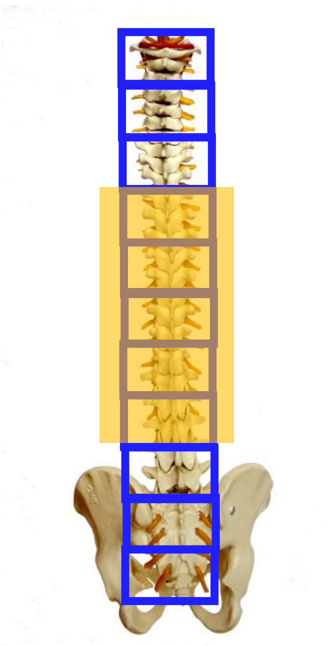
[Shirato et al., Radiotherapy and Oncology, 1995]

Shirato model

Critical Element model

$$\mathbf{NTCP} = 1 - \left[1 - \left(1 - e^{-\alpha n d - \beta n d^2}\right)^k\right]^{\frac{L}{L1}}$$

N



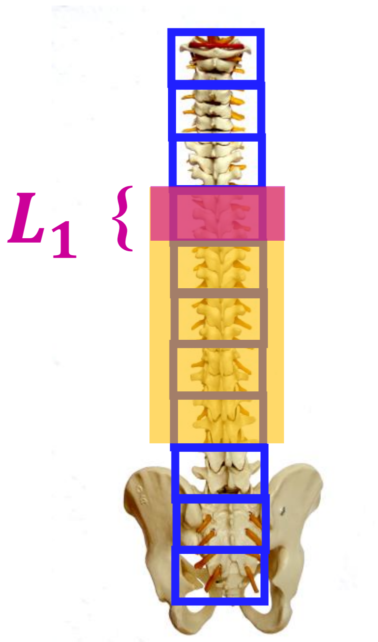
[Shirato et al., Radiotherapy and Oncology, 1995]

Shirato model

Critical Element model

$$\mathbf{NTCP} = 1 - \left[1 - \left(1 - e^{-\alpha n d - \beta n d^2}\right)^k\right]^{\frac{L}{L1}}$$

N



[Shirato et al., Radiotherapy and Oncology, 1995]

Shirato model

Probability of killing 1 cell

Migration term

$$\mathbf{NTCP} = 1 - \left[1 - \left[\left(1 - e^{-\alpha n d - \beta n d^2}\right)\boldsymbol{M(I)}\right]^k\right]^{\frac{L}{L1}}$$

[Shirato et al., Radiotherapy and Oncology, 1995]

Shirato model

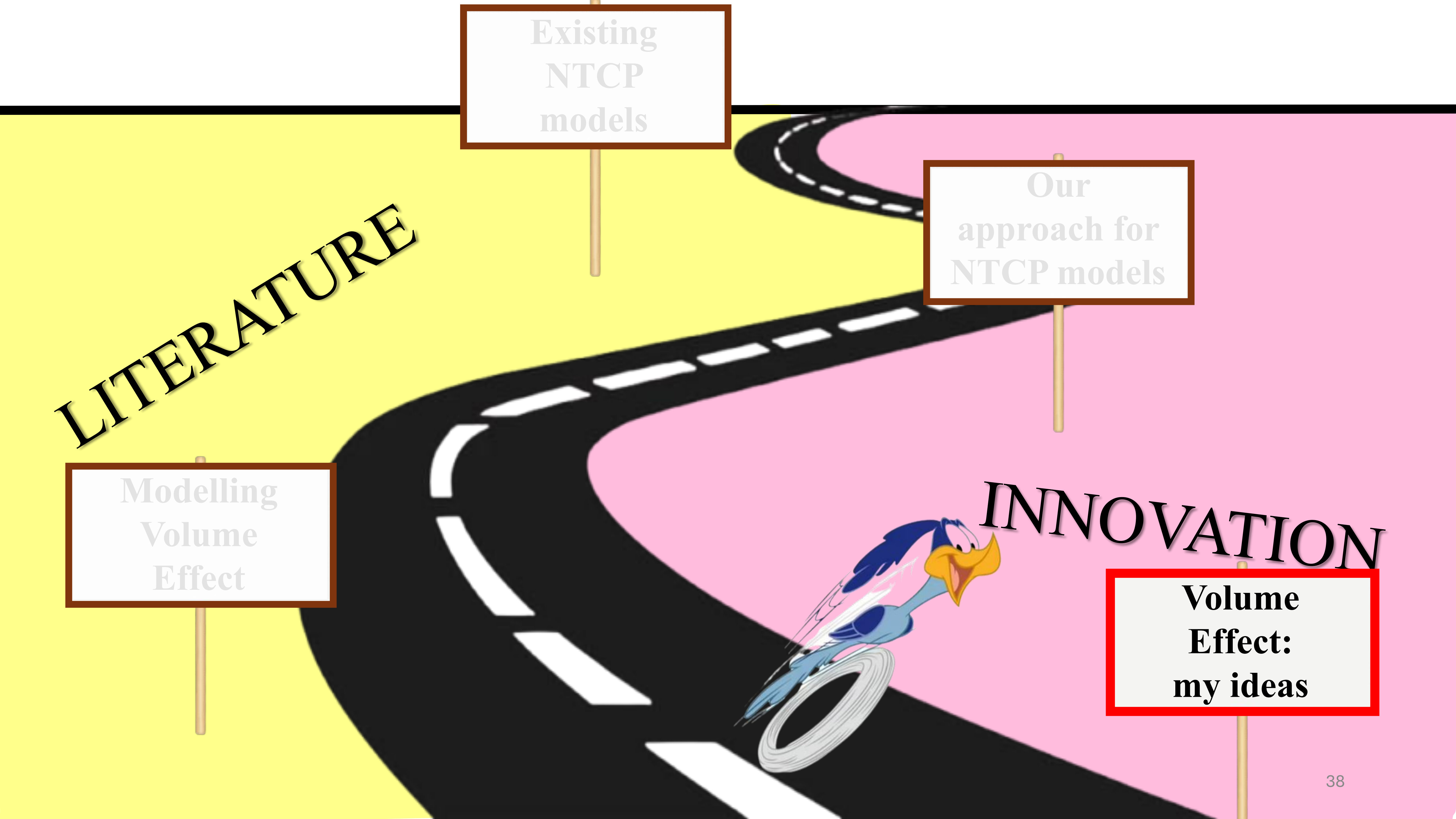
Probability of killing 1 cell

Migration term

$$\mathbf{NTCP} = 1 - \left[1 - \left[\left(1 - e^{-\alpha n d - \beta n d^2}\right) \boldsymbol{M}(\boldsymbol{I})\right]^{k}\right]^{\frac{L}{L1}}$$

- ✕ I from fit
- ✕ Validation limited to one dataset
- ✕ Multiple parameter sets fit the data

[Shirato et al., Radiotherapy and Oncology, 1995]



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Volume Effect: my ideas

***Volume Effect**: my ideas*

Critical Element model

$$\mathbf{NTCP} = 1 - \left[1 - \left(1 - e^{-\alpha n d - \beta n d^2}\right)^k\right]^{\frac{L}{L1}}$$

***Volume Effect**: my ideas*

Critical Element model

$$\mathbf{NTCP} = 1 - \left[1 - \left(1 - e^{-\alpha n d - \beta n d^2}\right)^k\right]^{\frac{L}{L1}}$$

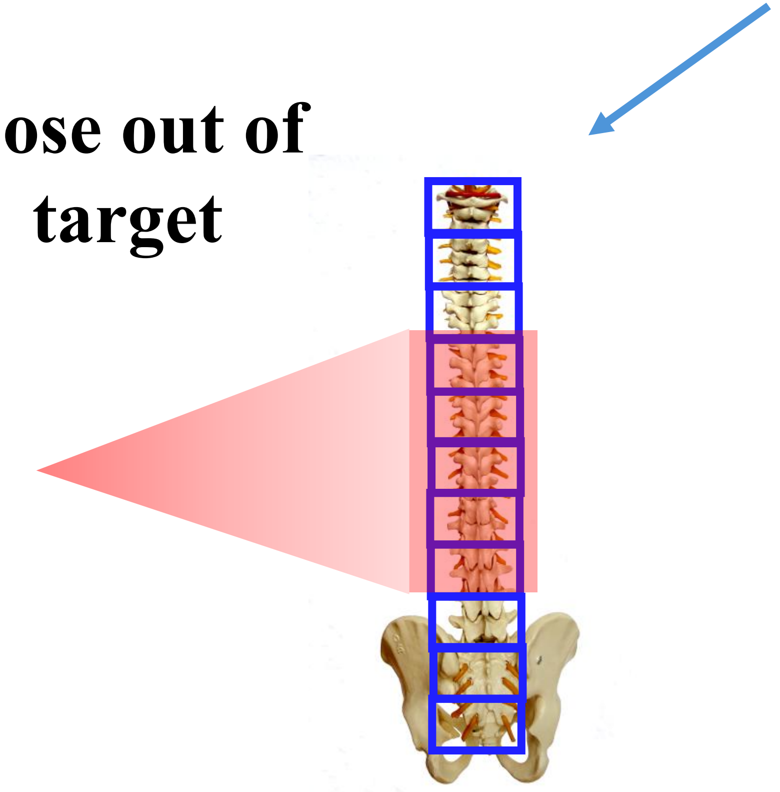
Dose out of target

***Volume Effect**: my ideas*

Critical Element model

$$\mathbf{NTCP} = 1 - \left[1 - \left(1 - e^{-\alpha n d - \beta n d^2}\right)^k\right]^{\frac{L}{L1}}$$

Dose out of target

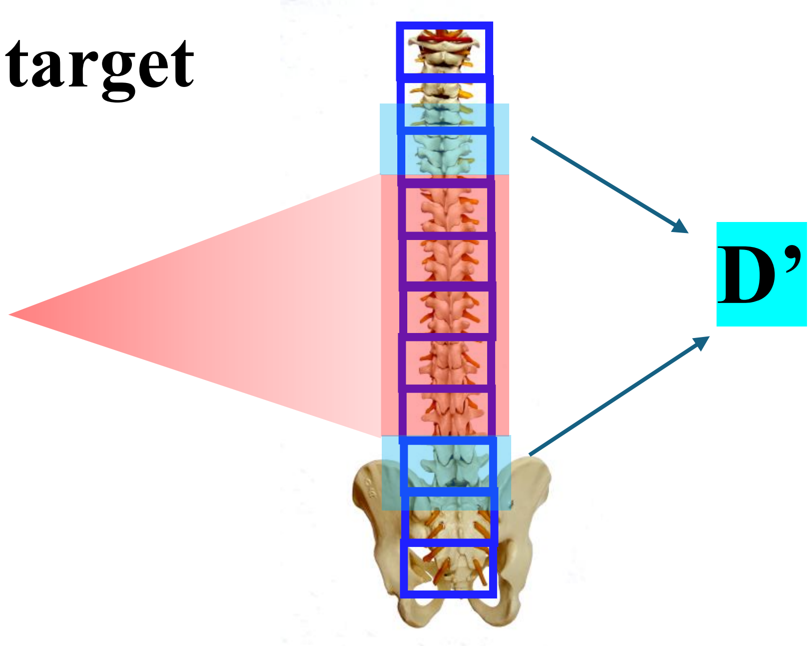


Volume Effect: my ideas

Critical Element model

$$\mathbf{NTCP} = 1 - \left[1 - \left(1 - e^{-\alpha n d - \beta n d^2}\right)^k\right]^{\frac{L}{L1}}$$

Dose out of target

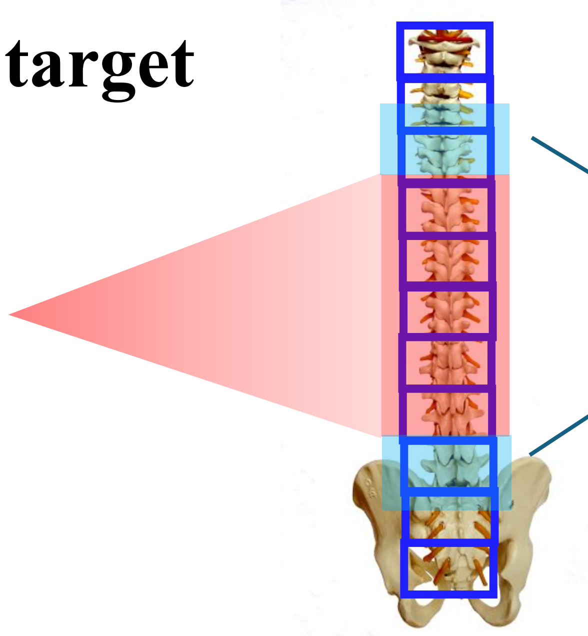


Volume Effect: *my ideas*

Critical Element model

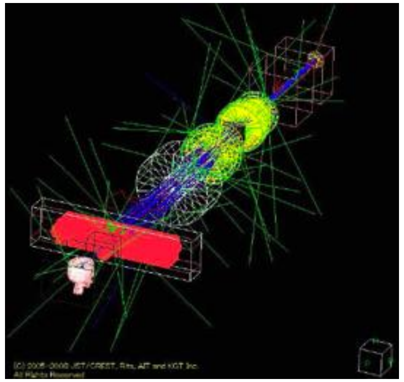
$$\mathbf{NTCP} = 1 - \left[1 - \left(1 - e^{-\alpha n d - \beta n d^2}\right)^k\right]^{\frac{L}{L1}}$$

Dose out of target



D’

GEANT4
A SIMULATION TOOLKIT



Volume Effect: my ideas

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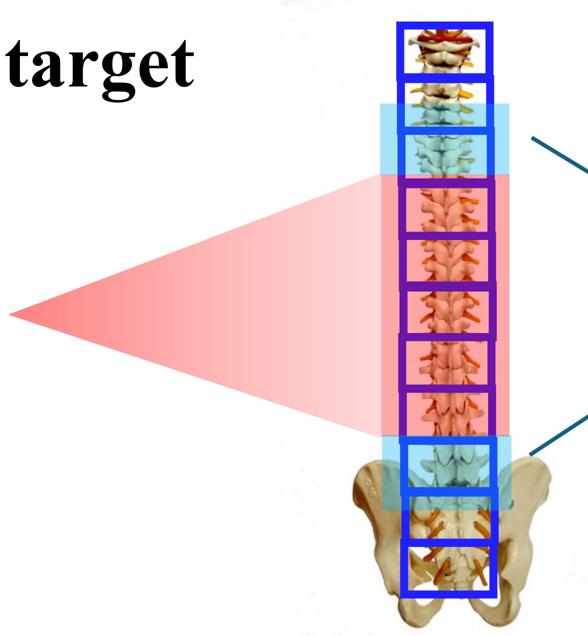
Dose out of target

Cell migration probability



D'

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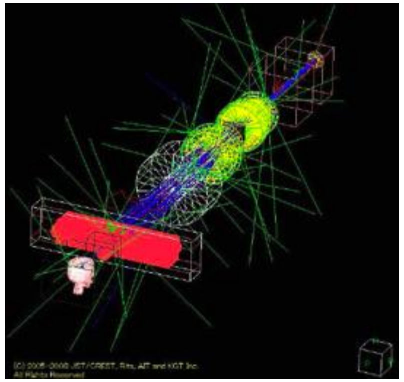
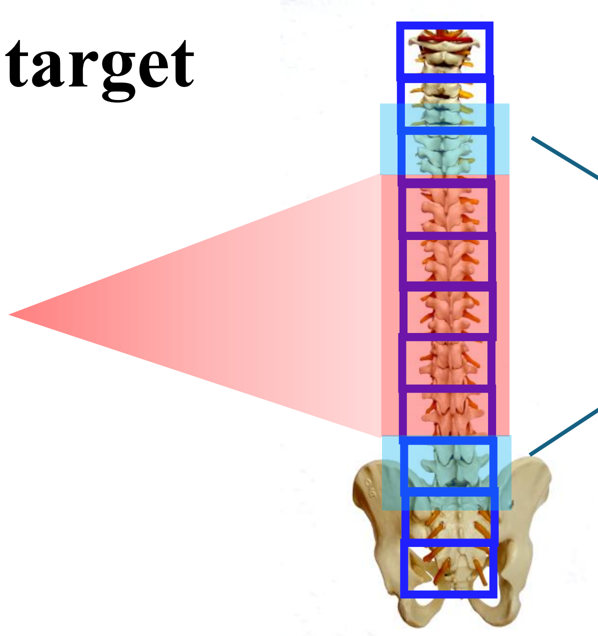


Volume Effect*: my ideas*

Critical Element model

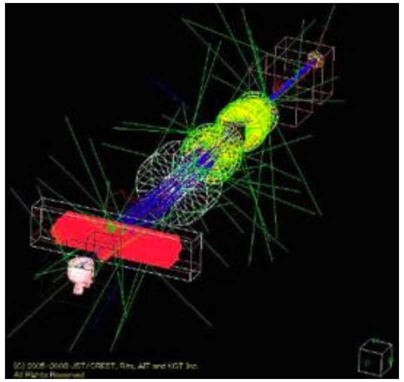
$$\mathbf{NTCP} = 1 - \left[1 - \left(1 - e^{-\alpha n d - \beta n d^2}\right)^k\right]^{\frac{L}{L1}}$$

Dose out of target



D'

GEANT4
A SIMULATION TOOLKIT



From experiment $d_c \sim 2\ mm$

Cell migration probability

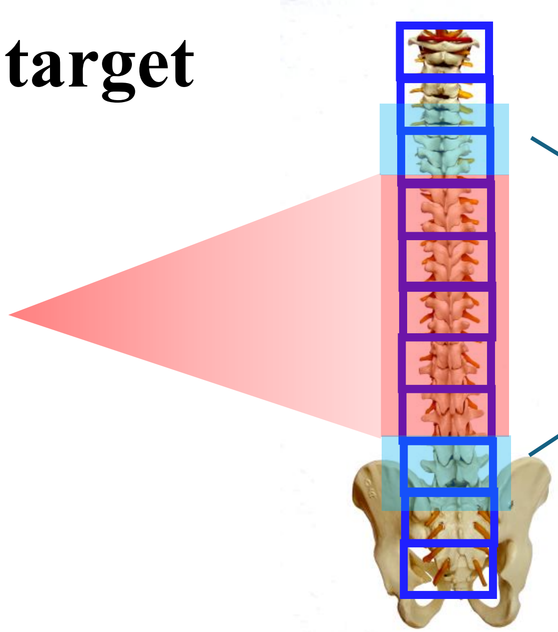
$\propto d_c$
critical distance

Volume Effect: my ideas

Critical Element model

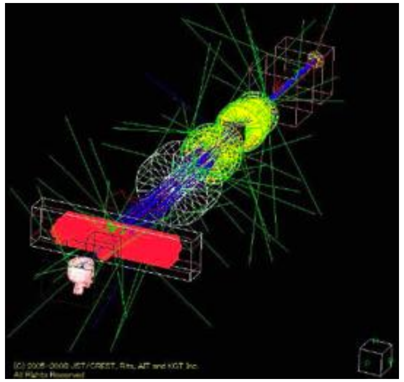
$$\mathbf{NTCP} = 1 - \left[1 - \left(1 - e^{-\alpha n d - \beta n d^2}\right)^k\right]^{\frac{L}{L1}}$$

Dose out of target



D'

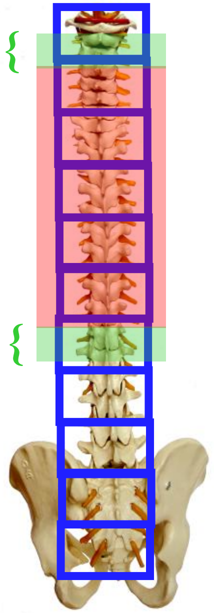
GEANT4
A SIMULATION TOOLKIT



From experiment
$d_c \sim 2\ mm$

Cell migration probability

$\mathbf{d_c}$



$\propto d_c$
critical distance

Take home messages

Our approach

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

[**A. Casali** et al., European Physical Journal Special Topics., submitted, **2025**]

Take home messages

Our approach

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Patient-specific
treatment plans

Take home messages

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Patient-specific
treatment plans

NTCP (k, N, α, β)
few parameters

Take home messages

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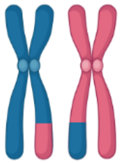
Patient-specific
treatment plans

NTCP (k, N, α, β)
few parameters

BIANCA
for chromosome
damages



Take home messages

Our approach

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Patient-specific
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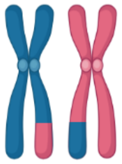


Stochastic effects

e.g. radiation-induced tumours

Take home messages

Our approach

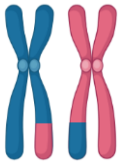
[**A. Casali** et al., Phys. Med. Biol., **2024**]

[**A. Casali** et al., European Physical Journal Special Topics., submitted, **2025**]

Patient-specific
treatment plans

NTCP (k, N, α, β)
few parameters

BIANCA
for chromosome damages



Stochastic effects

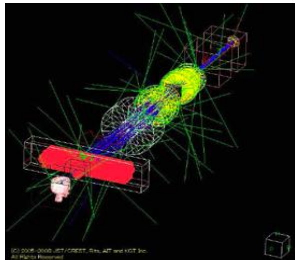
e.g. radiation-induced tumours

Worth implementing to make it as general as possible

PhD project: *detailed steps*

PhD project: detailed steps

BIANCA – Geant4
NTCP in
mixed field



Start

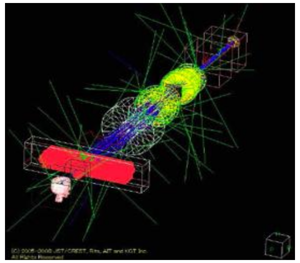
Finish

PhD project: *detailed steps*

✅ **BIANCA – Geant4**

NTCP in
mixed field

GEANT4
A SIMULATION TOOLKIT

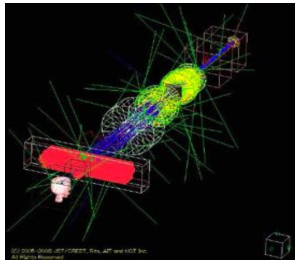


Start

Finish

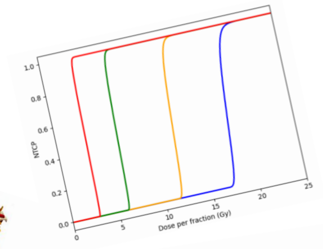
PhD project: detailed steps

BIANCA – Geant4
NTCP in
mixed field



Start

Finish

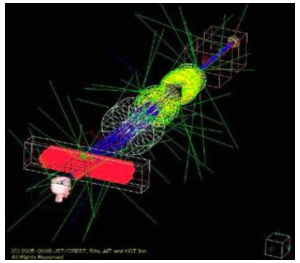


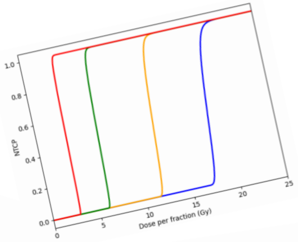
Apply our
approach to
additional **organs**,
endpoints and **ion**
irradiation

PhD project: detailed steps

Start

BIANCA – Geant4
NTCP in
mixed field





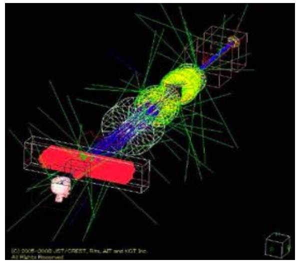
SOON

Apply our approach to additional **organs**, **endpoints** and **ion** irradiation

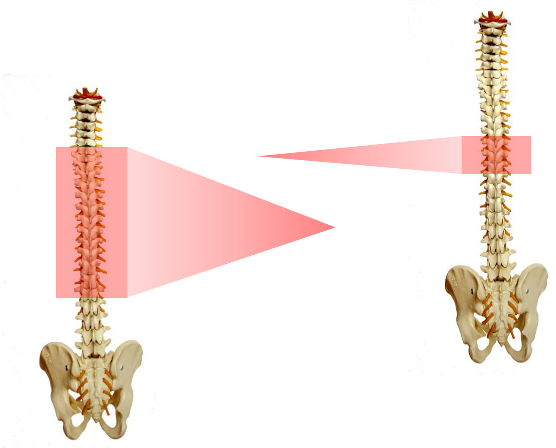
Finish

PhD project: detailed steps

BIANCA – Geant4
NTCP in
mixed field

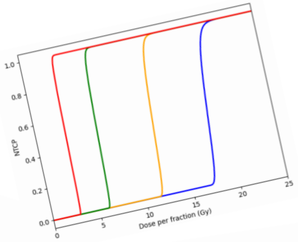


Reproduce the
Volume Effect



Start

Finish



SOON

Apply our
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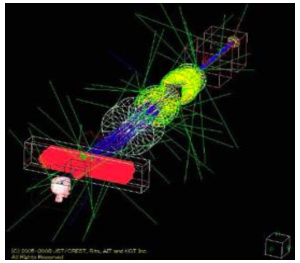
additional **organs**,
endpoints and **ion**
irradiation

PhD project: detailed steps

BIANCA – Geant4
NTCP in
mixed field



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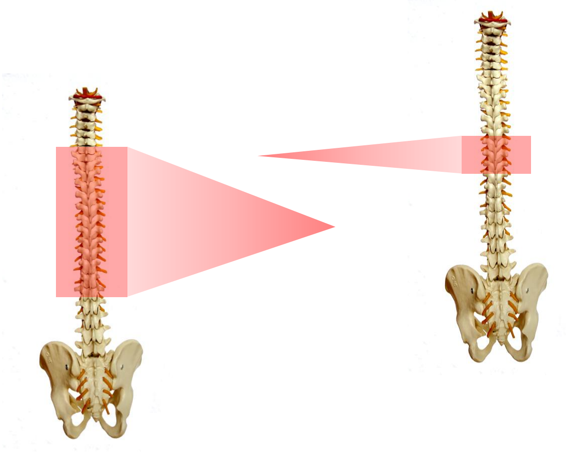
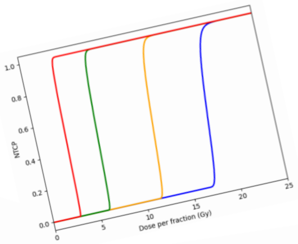


Start

Finish



SOON

Apply our
approach to
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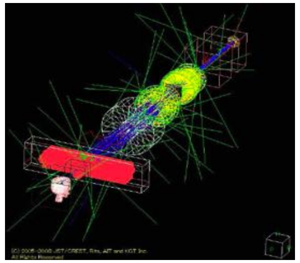
irradiation

PhD project: detailed steps

Start

BIANCA – Geant4
NTCP in
mixed field

GEANT4
A SIMULATION TOOLKIT



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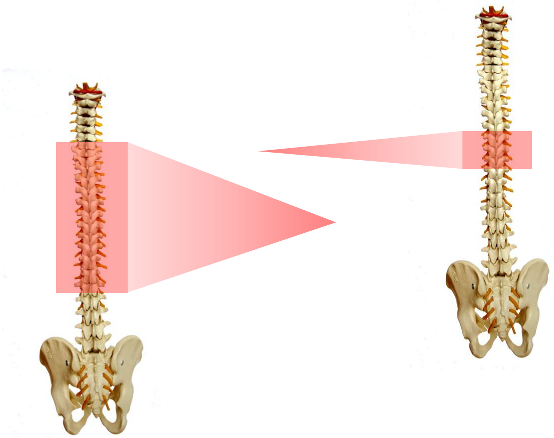
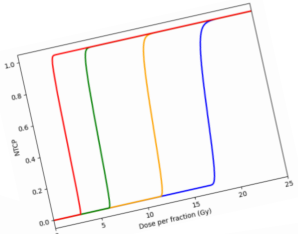


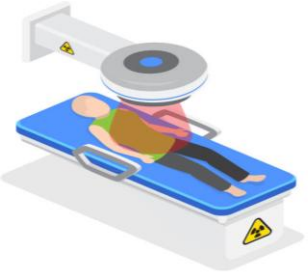
Finish



SOON

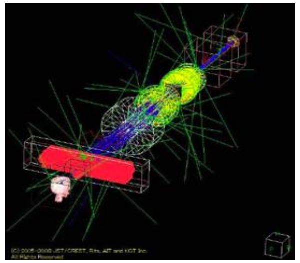
Apply our
approach to
additional **organs**,
endpoints and **ion**
irradiation

Apply our
approach to
human data

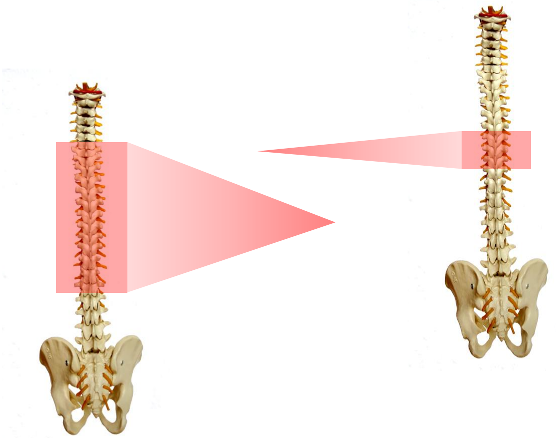


PhD project: detailed steps

BIANCA – Geant4
NTCP in mixed field

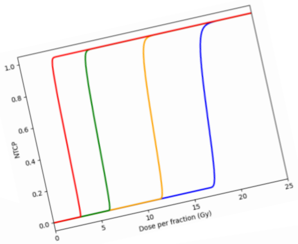


Reproduce the
Volume Effect



Start

Finish



SOON

Apply our approach to additional **organs**, **endpoints** and **ion** irradiation

SOON

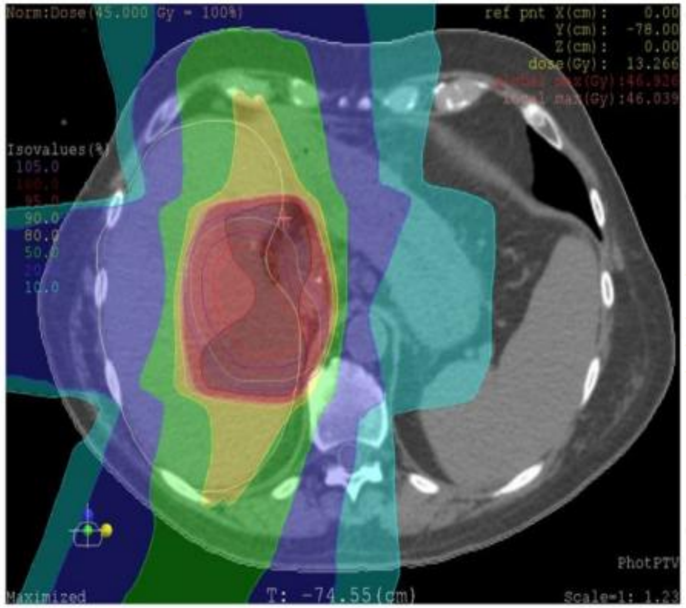
Apply our approach to **human data**

Back up slides

What is Hadrontherapy?

[Image credit: Grant et al., BioMed research international. (2014), 389048. 10.1155/2014/389048]

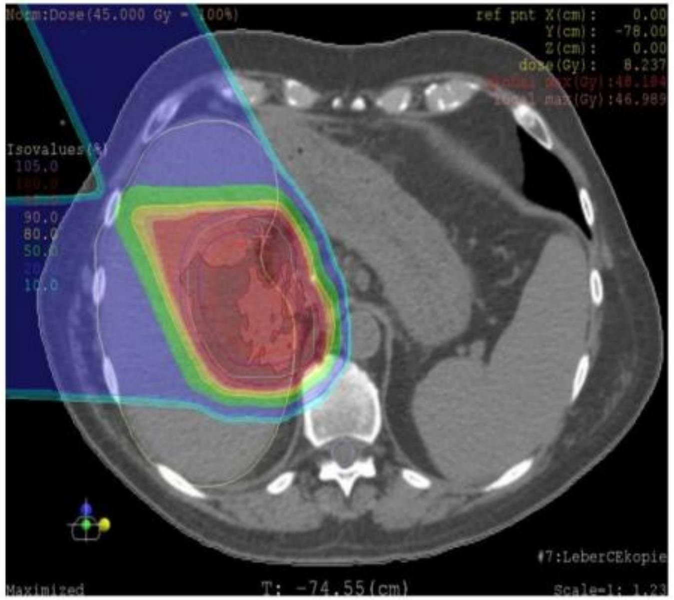
Photons



- 3 Beams

Proton Spread Out Bragg Peak

- 2 Beams



[Image credit: H. Rocken, Vrian Medical Systems]

Lyman – Kutcher - Burman (LKB) model

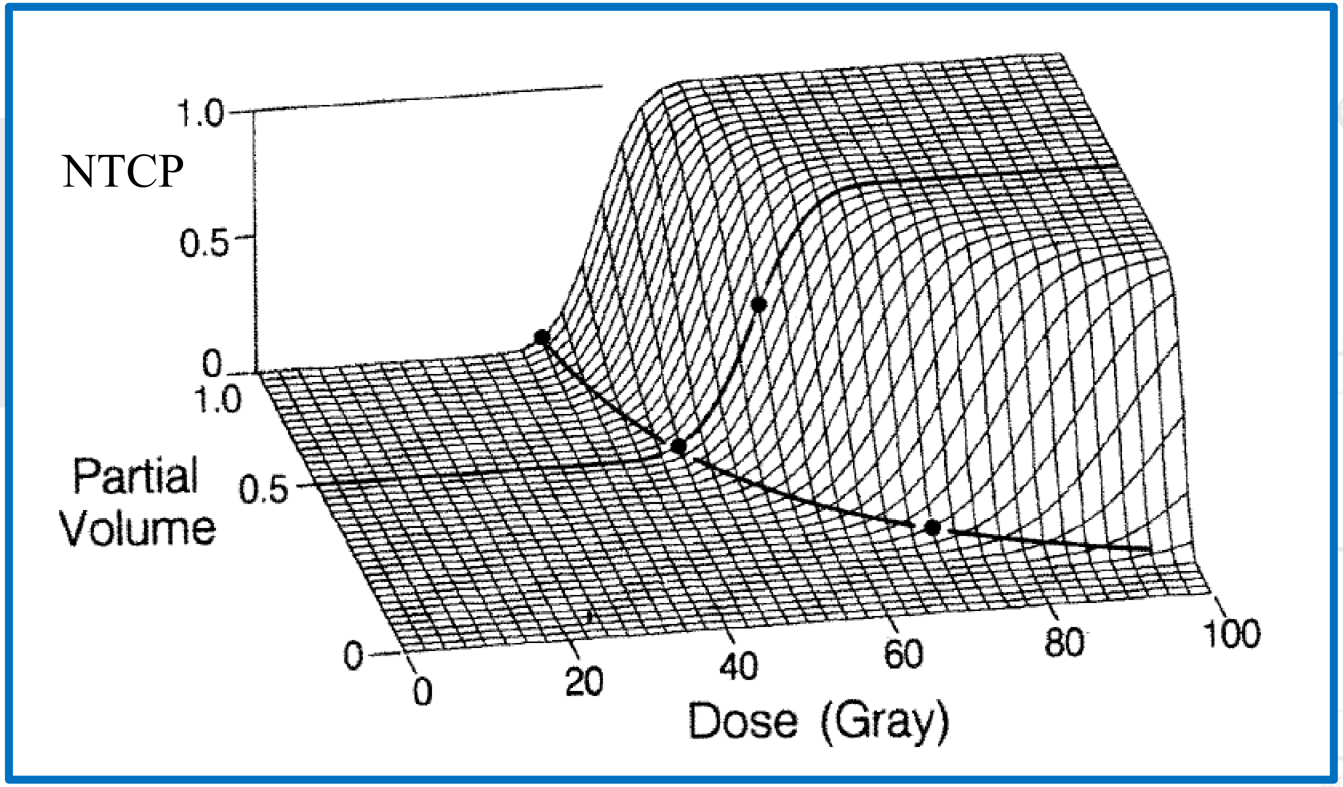
Phenomenological

$$NTCP(D,V) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} exp\left(-\frac{x^2}{2}\right) dx$$

Assumptions:

Uniform dose

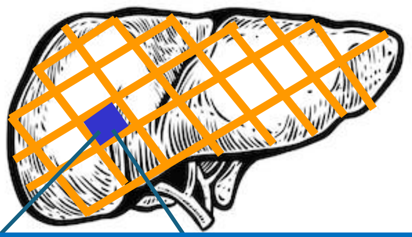
$$t(D,V) = \frac{D - D_{50}(V)}{m\, D_{50}(V)}$$



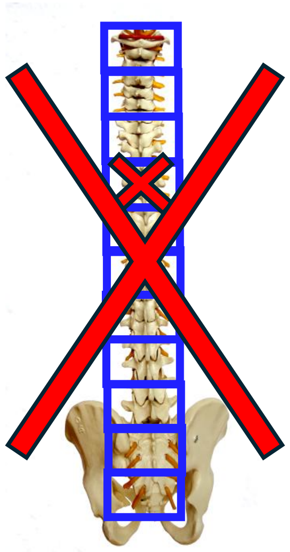
[J. T. Lyman, Radiat. Res., 1985]

Relative Seriality model

Phenomenological / Mechanistic



$$NTCP(d_i, v_i) = \left\{1 - \prod_{i=1}^{m}\left[1 - \left(e^{-ke^{-\alpha n d_i - \beta n d_i^2}}\right)^{s}\right]^{v_i}\right\}^{1/s}$$

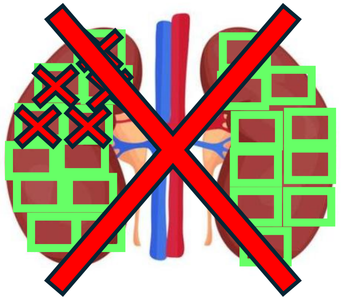


Serial organ **s = 1**

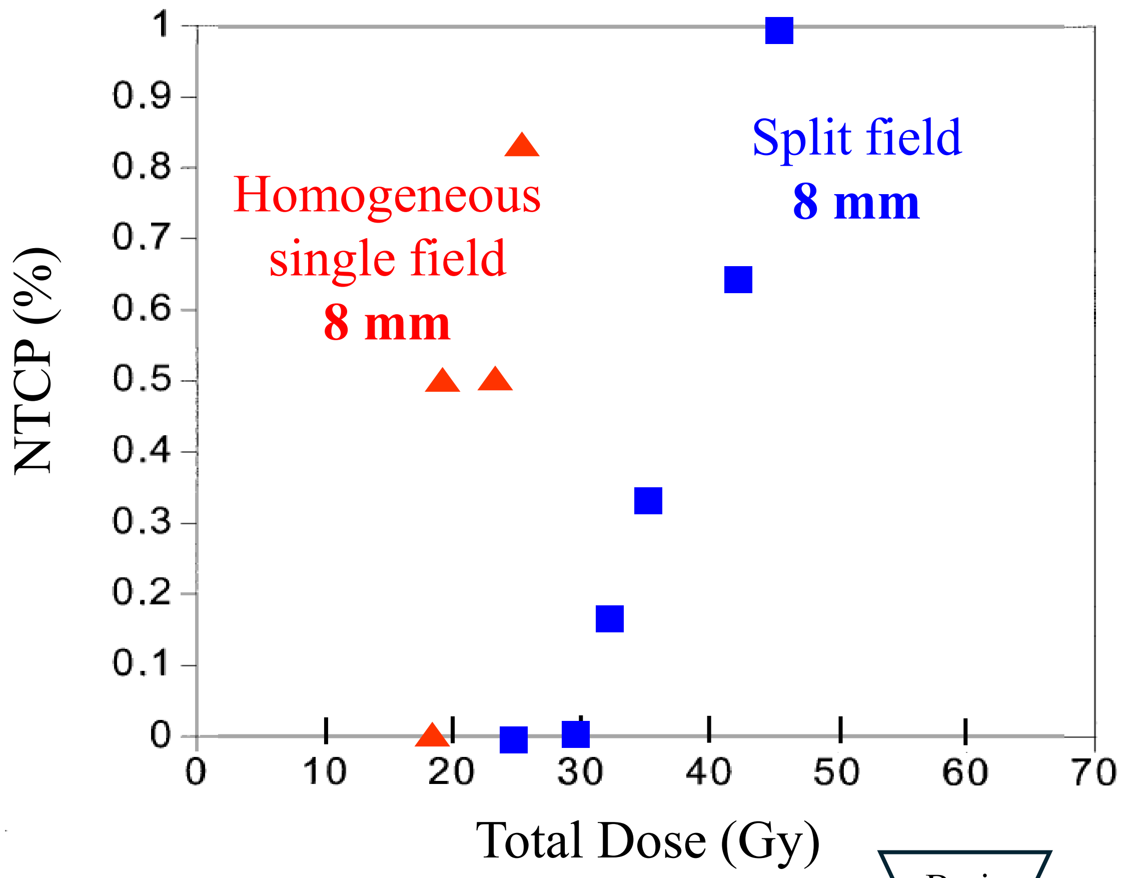
$$P(d_i)_{FSU} = 1 - \prod_{i=1}^{m}[1 - P(d_i)_{FSU}]^{v_i}$$

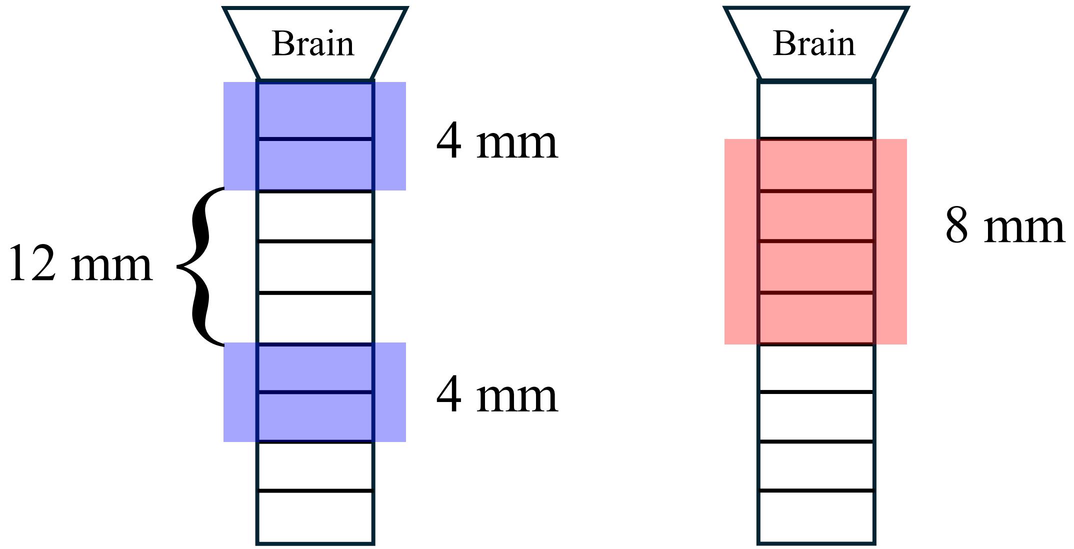
Parallel organ **s → 0**

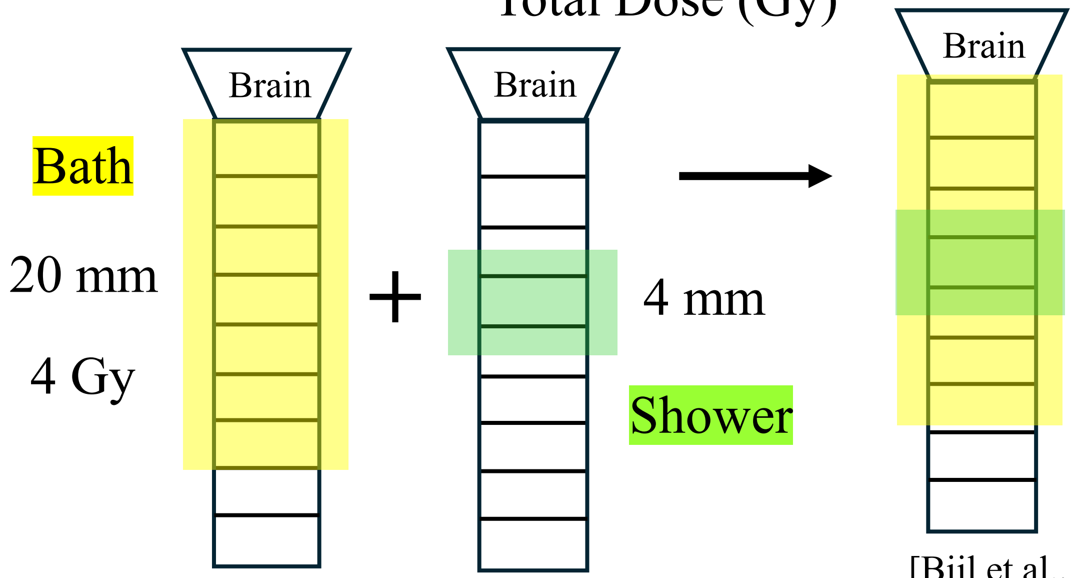
$$P(d_i)_{FSU} = 1 - \exp\left[\sum_{i=1}^{m} v_i P(d_i)_{FSU}\right]$$

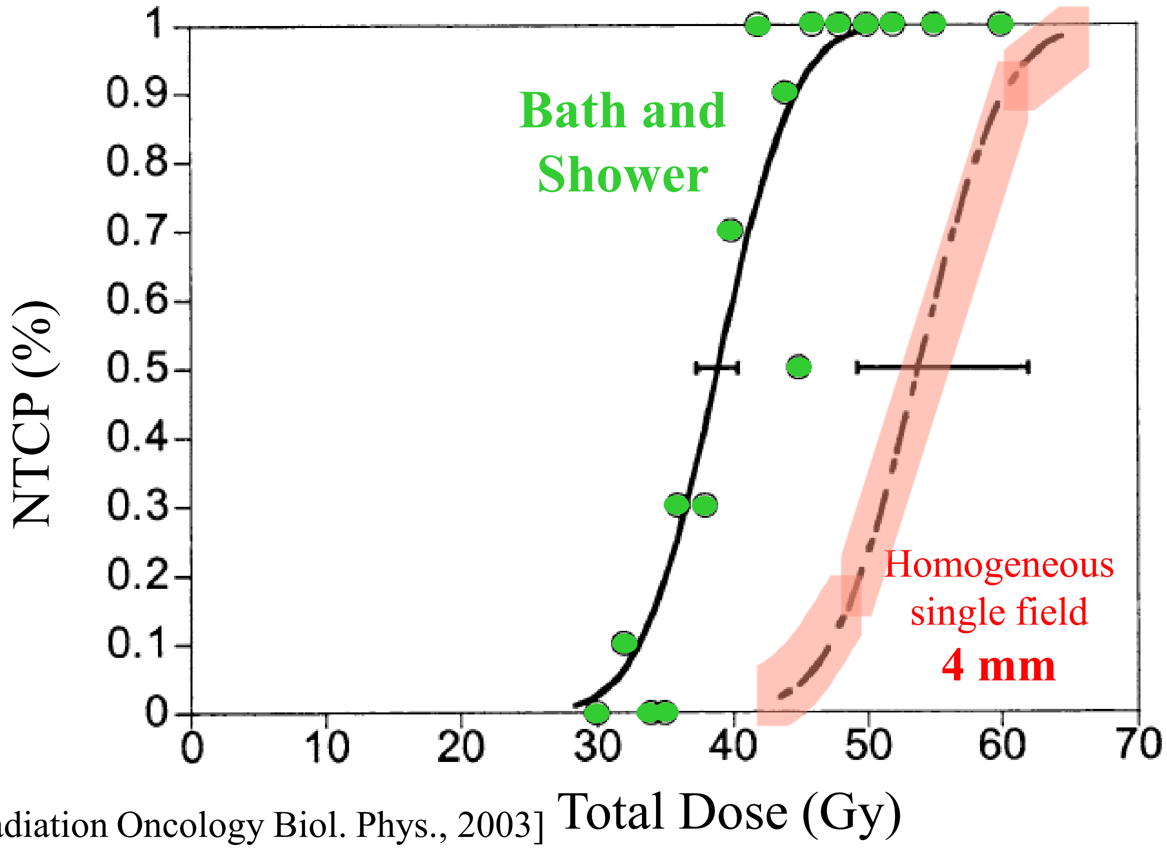


[P. Källman, Int. J. Radiat. Biol.,1992]









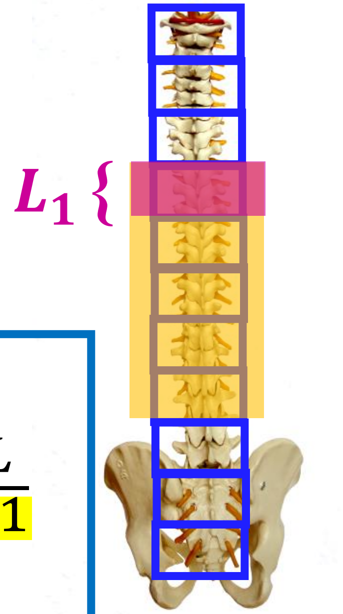
[Bijl et al., Int. J. Radiation Oncology Biol. Phys., 2003]

Shirato model

Critical Element model

$$\mathbf{NTCP} = 1 - \left[1 - \left(1 - e^{-\alpha n d - \beta n d^2}\right)^k\right]^{\frac{L}{L1}}$$

N



Prob. to kill 1 cell

$$\mathbf{NTCP} = 1 - \left[1 - \left[\left(1 - e^{-\alpha n d - \beta n d^2}\right)\left(1 - e^{\left(-\alpha n d - \beta n d^2\right)N \cdot I}\right)\right]^k\right]^{\frac{L}{L1}}$$

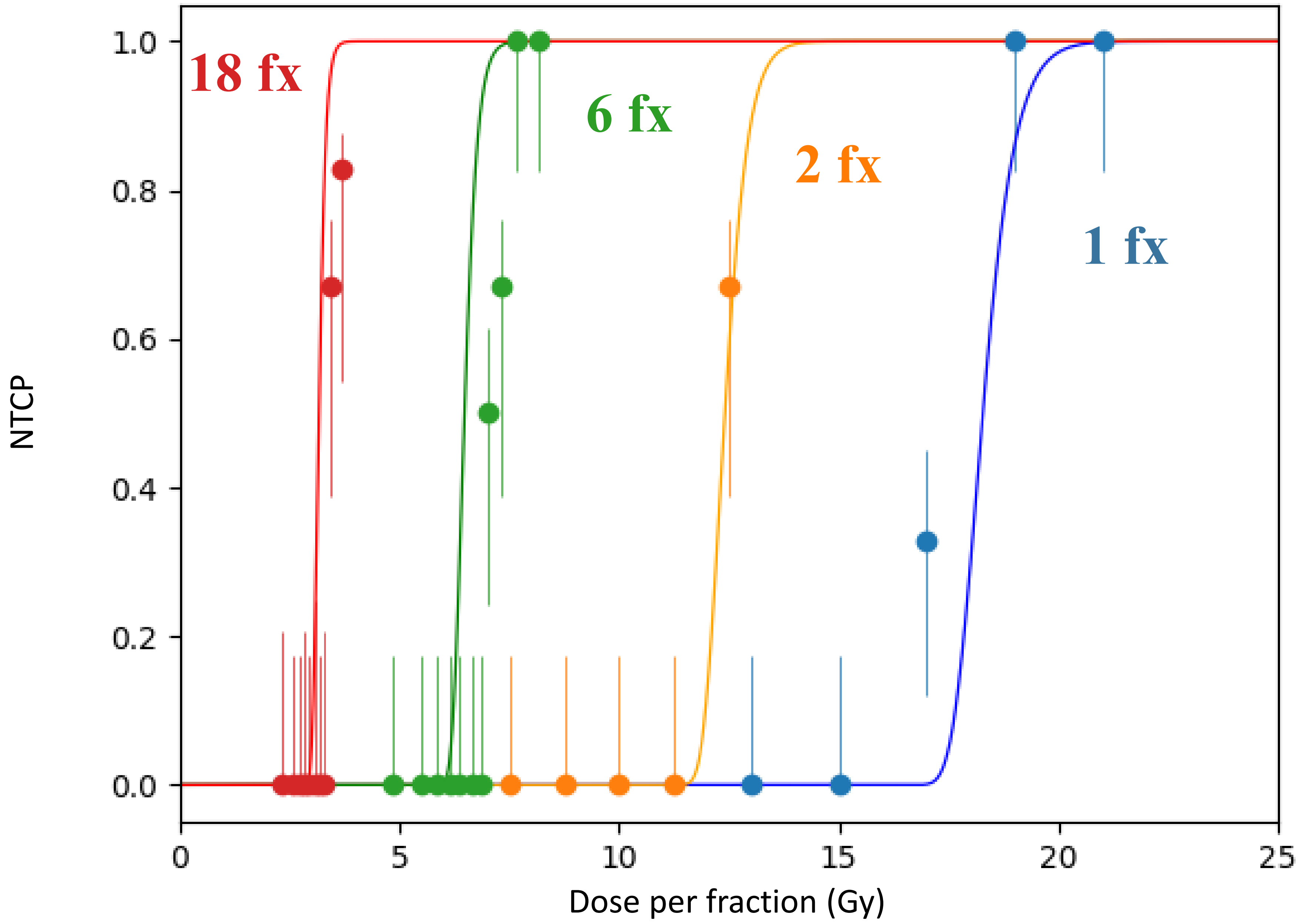
Migration term

[Shirato et al., Radiotherapy and Oncology, 1995]

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

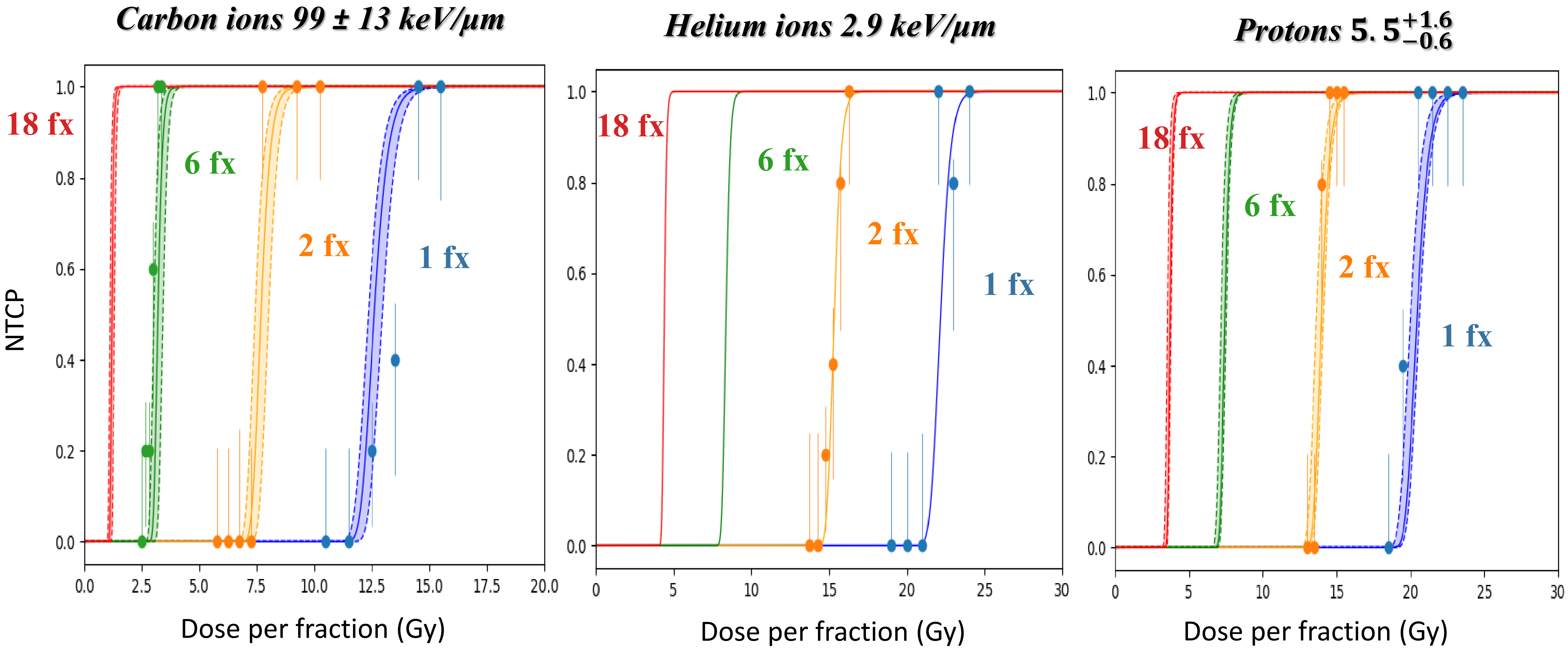
Carbon ions 13 keV/μm

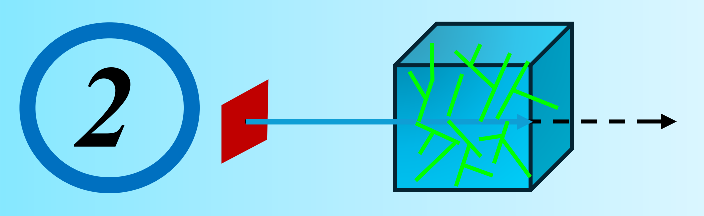
Monochromatic Field



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

Monochromatic Field

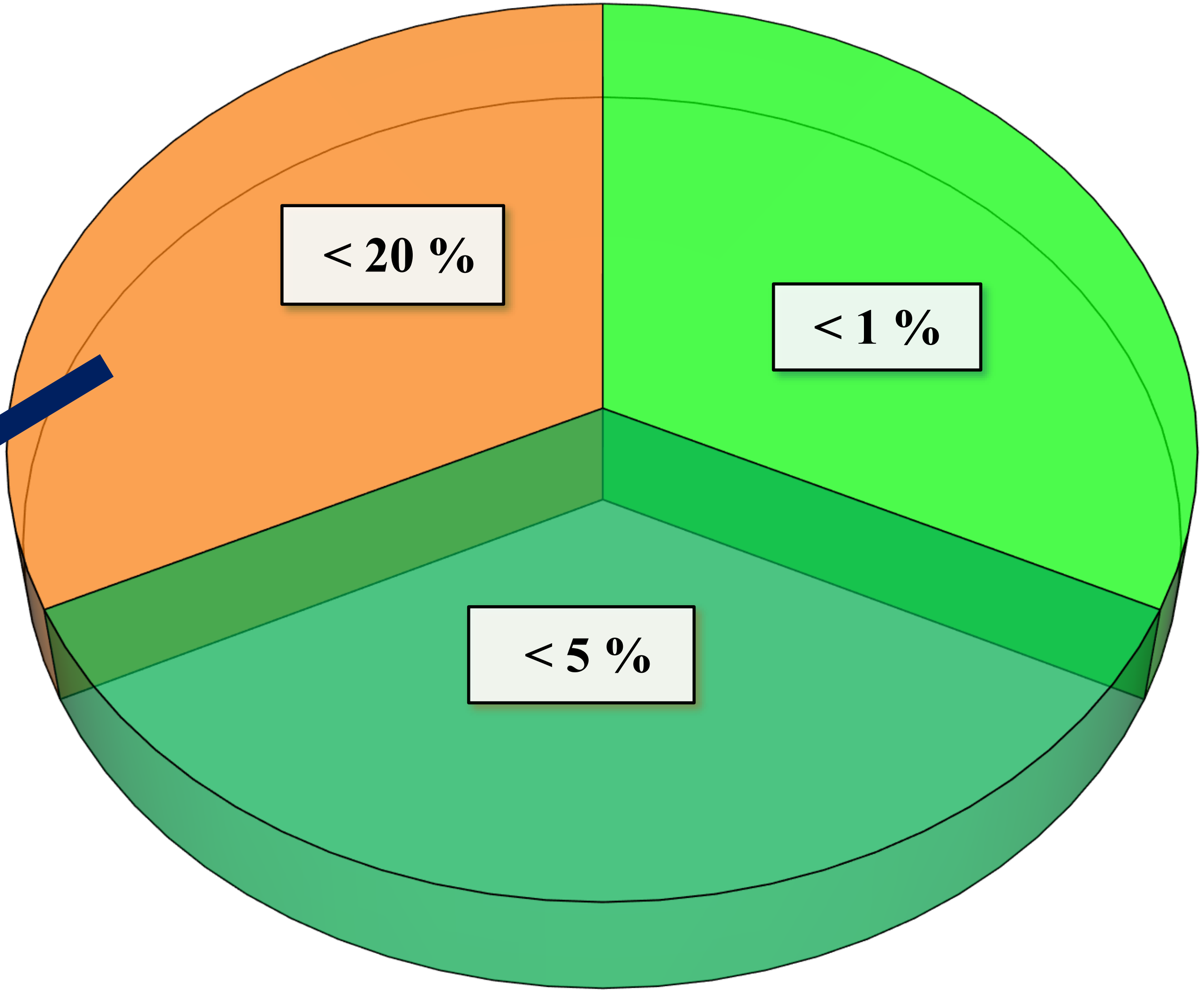




Statistical analysis

Real Mixed Field

$$\frac{| D_{50}^{mixed} - D_{50}^{mono} |}{D_{50}^{mono}} \, 100$$



C ions high LET

47 / 56 NOT significant difference mono - mixed

MC simulation for p-values

1. NTCP simulated experimental data:

Binomial distribution → b (x; **n**, **p**) → x / n = NTCP

n: Number of irradiated rats for a certain *dose level*

p: NTCP with *Critical Element Model*

2. N repeated extractions

MC simulation for p-values

3. χ_R^2 between simulated NTCP and NTCP predicted with the model

4. Count $\chi_{R_{sim}}^2 > \chi_{R_{sperim}}^2$ *(c)*

5. Divide *c* for the repetition number (N) → *P-value*

P-values

p - value > 5%

Particella	LET (keV/μm)	*p-values* (%)
Ioni carbonio	13	– 2.9
	16	– 1.3
	21	↑ 18.5
	36	↑ 5.6
	45	↑ 20.6
	66 ± 6	– 3.3
	99 ± 13	↑ 15.6
	125 ± 25	↑ 59.0

Particella	LET (keV/μm)	*p-values* (%)
Protoni	1.4	↑ 18.4
	2.7 ± 0.1	↑ 47.4
	3.9 ± 0.2	↑ 48.4
	$5.5^{+1.6}_{-0.6}$	↑ 59.0

Particella	LET (keV/μm)	*p-values* (%)
Ioni elio	2.9	↑ 30.9
	$9.4^{+0.6}_{-1.4}$	↑ 70.8
	$14.4^{+1.1}_{-1.9}$	↑ 23.3
	$20.7^{+7.3}_{-2.2}$	↑ 89.3

Clopper-Pearson equations

$$\sum_{k=x}^{n} \binom{n}{k} p_1^{\,k} (1 - p_1)^{n-k} = \frac{1 - CL}{2}$$

x = n. rats with paresis

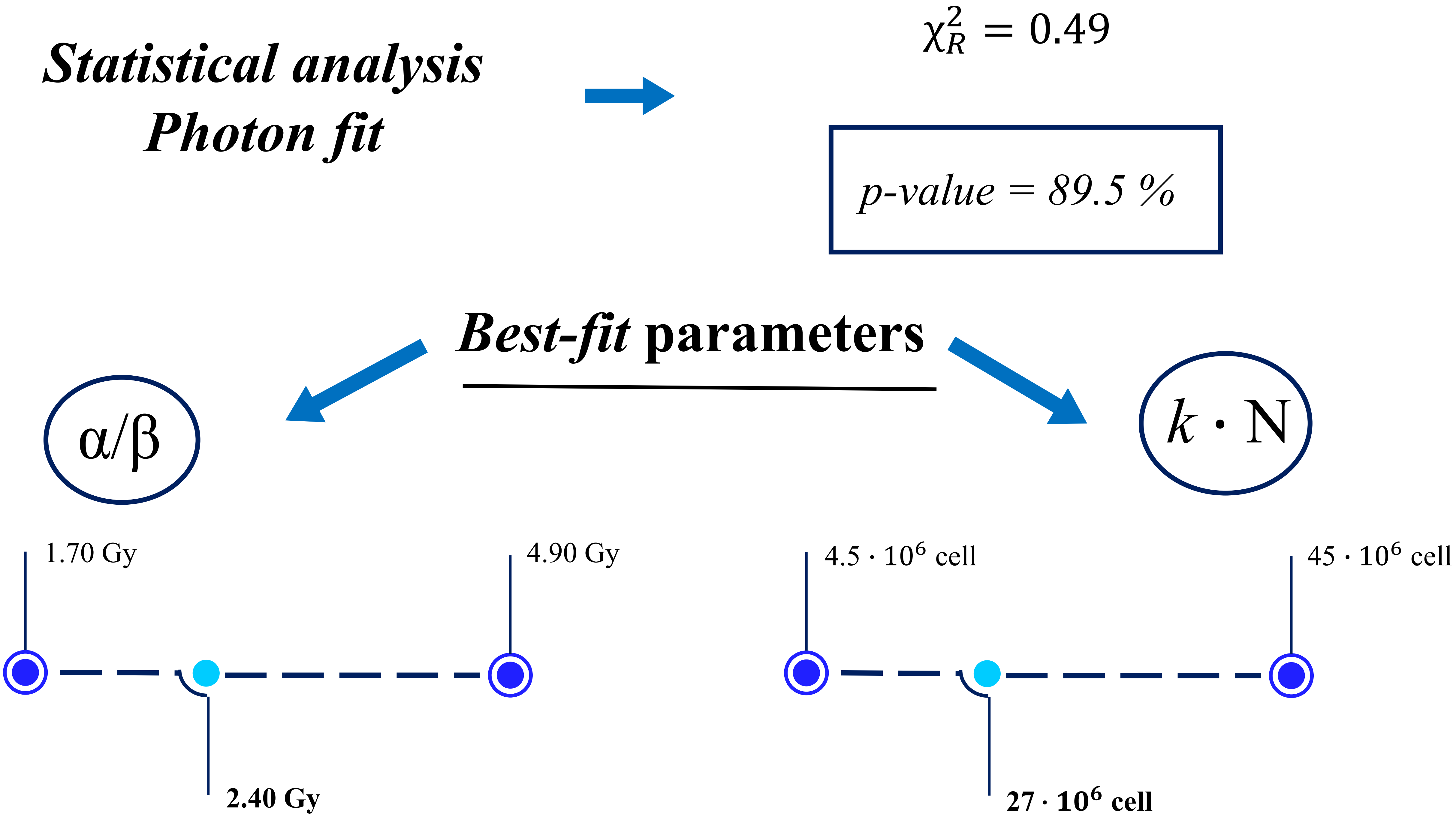
n = n. irradiated rats

$$\sum_{k=0}^{x} \binom{n}{k} p_2^{\,k} (1 - p_2)^{n-k} = \frac{1 - CL}{2}$$

X = 0 → $p_1 = 0$ $p_2 = 1 - \sqrt[n]{1 - CL}$

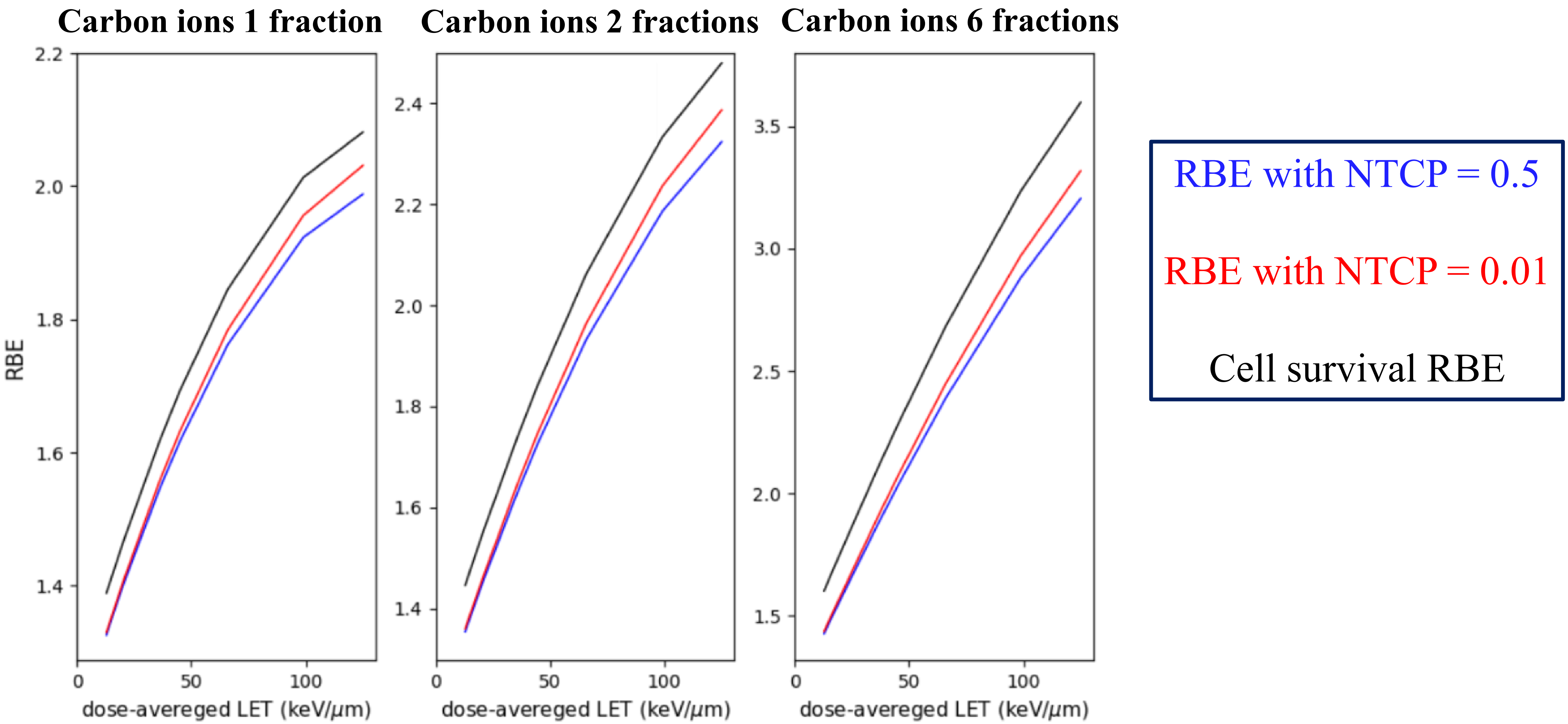
X = 1 → $p_1 = \sqrt[n]{1 - CL}$ $p_2 = 1$

Incomplete Beta Function $I_p(x, n - x + 1) = \sum_{k=x}^{n} \binom{n}{k} p^k (1 - p)^{n-k}$

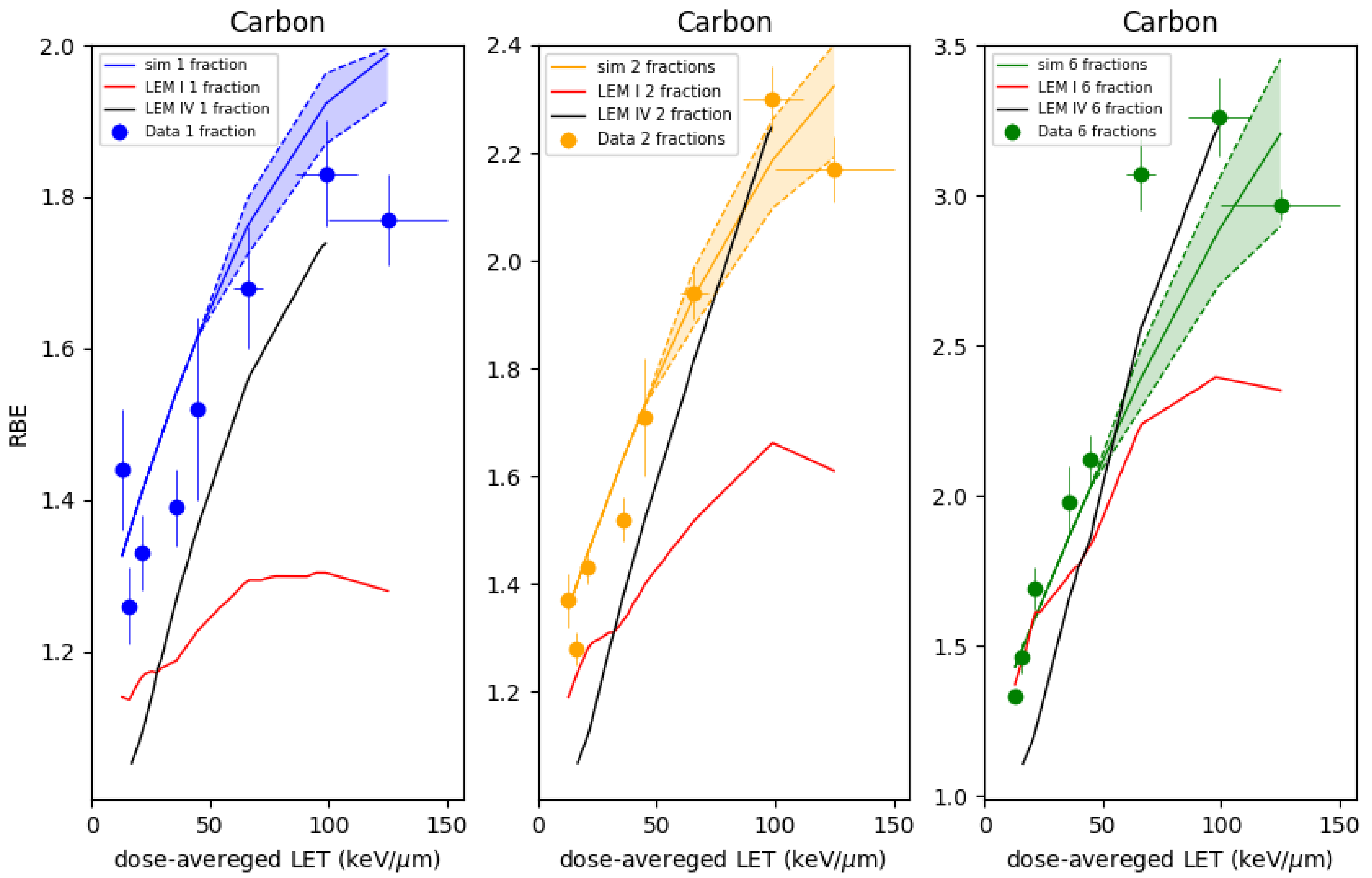


Statistical analysis
Photon fit
$\chi^2_R = 0.49$
p-value = 89.5 %
Best-fit parameters
α/β
k · N
1.70 Gy
4.90 Gy
2.40 Gy
4.5 · 10^6 cell
45 · 10^6 cell
27 · 10^6 cell

RBE (different *outcome* levels)



RBE (cfr LEM)



Carbon
sim 1 fraction
LEM I 1 fraction
LEM IV 1 fraction
Data 1 fraction
RBE
dose-avereged LET (keV/μm)
Carbon
sim 2 fractions
LEM I 2 fraction
LEM IV 2 fraction
Data 2 fractions
dose-avereged LET (keV/μm)
Carbon
sim 6 fractions
LEM I 6 fraction
LEM IV 6 fraction
Data 6 fractions
dose-avereged LET (keV/μm)