UNIVERSITÀ DI PAVIA

PhD course in Physics

End Of the Year Seminars - 2025

Istituto Nazionale di Fisica Nucleare

When less is more: how irradiated volume shapes tissue damage in Radiotherapy

Supervisors: Mario Pietro Carante
Francesca Ballarini

Alice Casali

PhD cycle: XL

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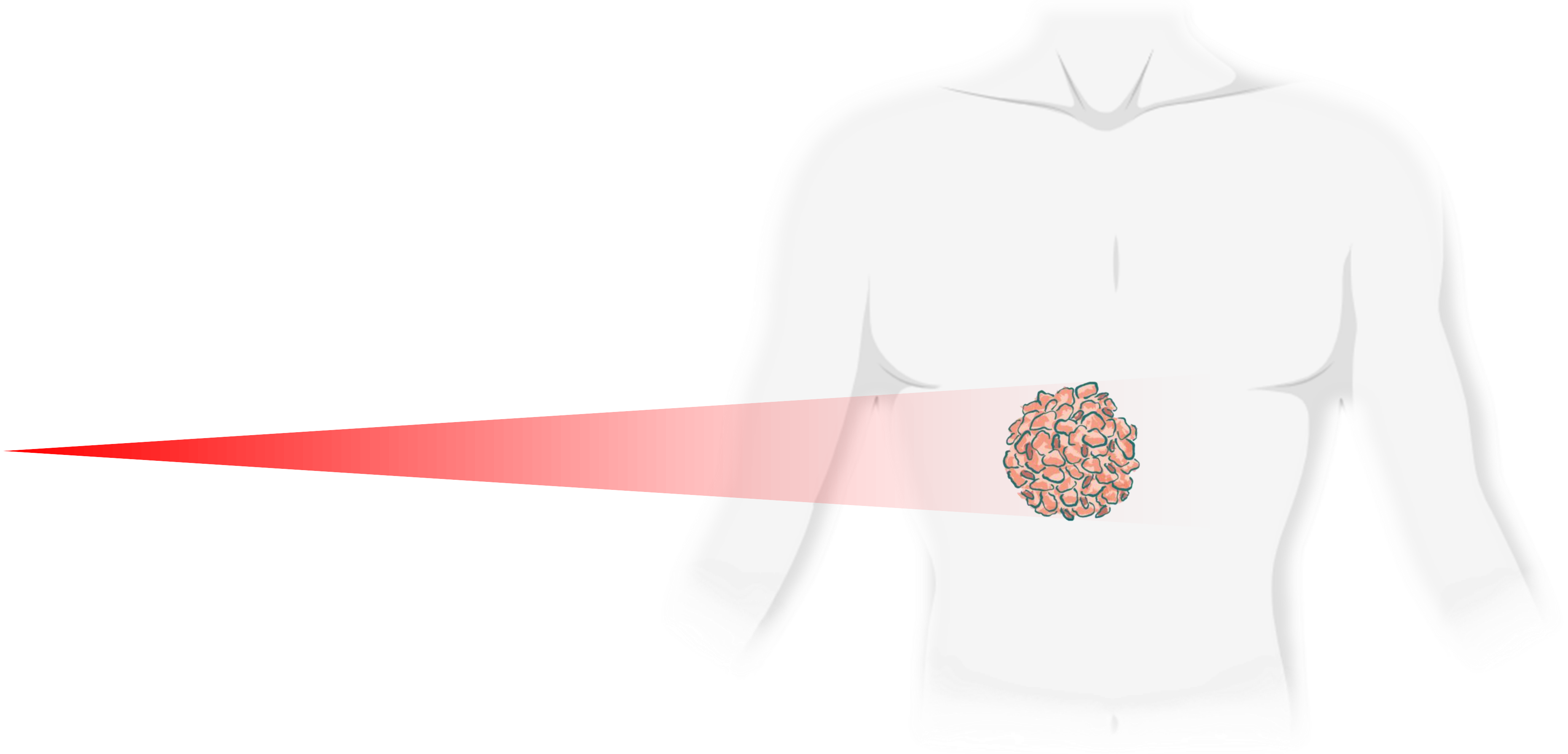
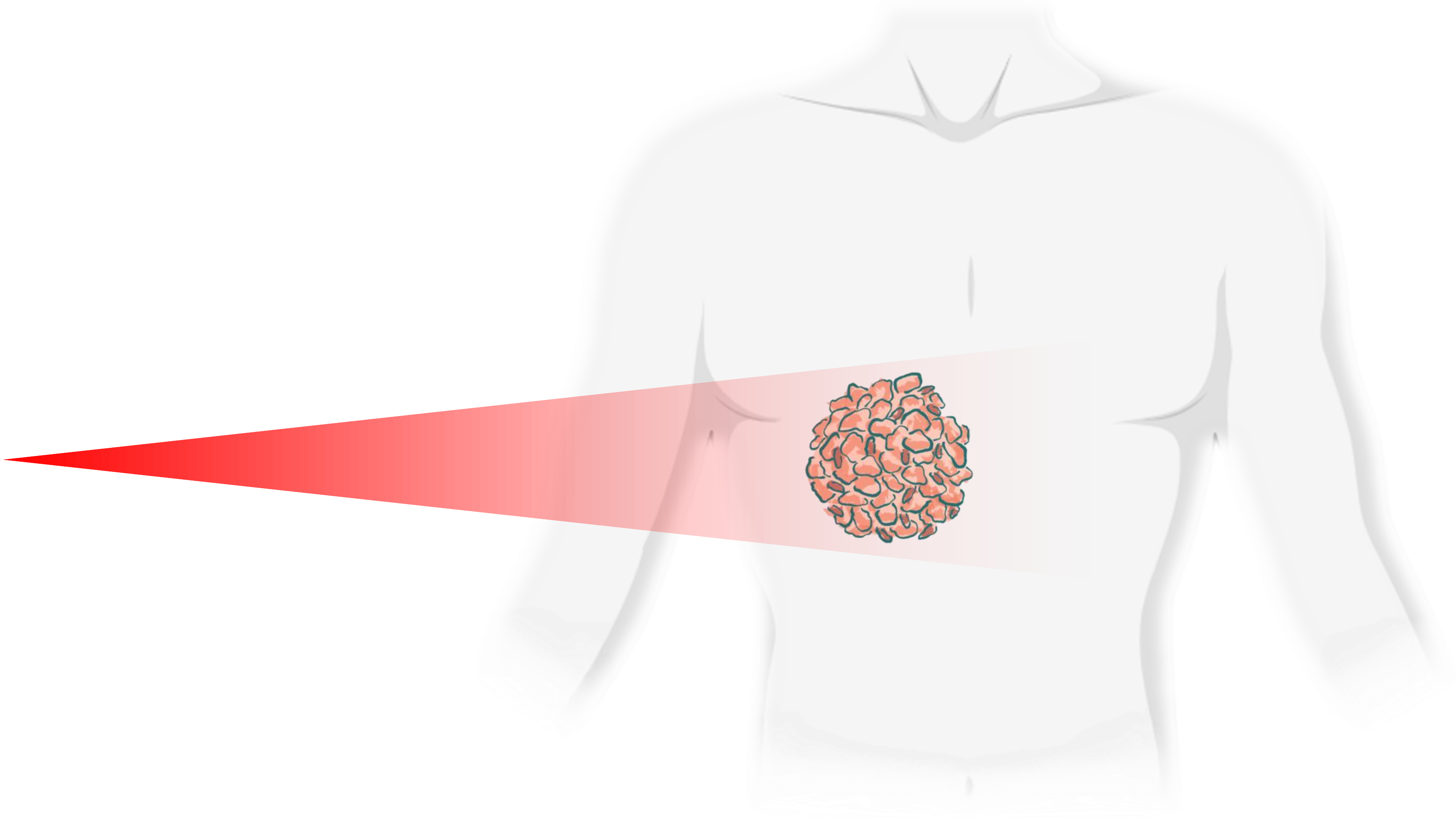
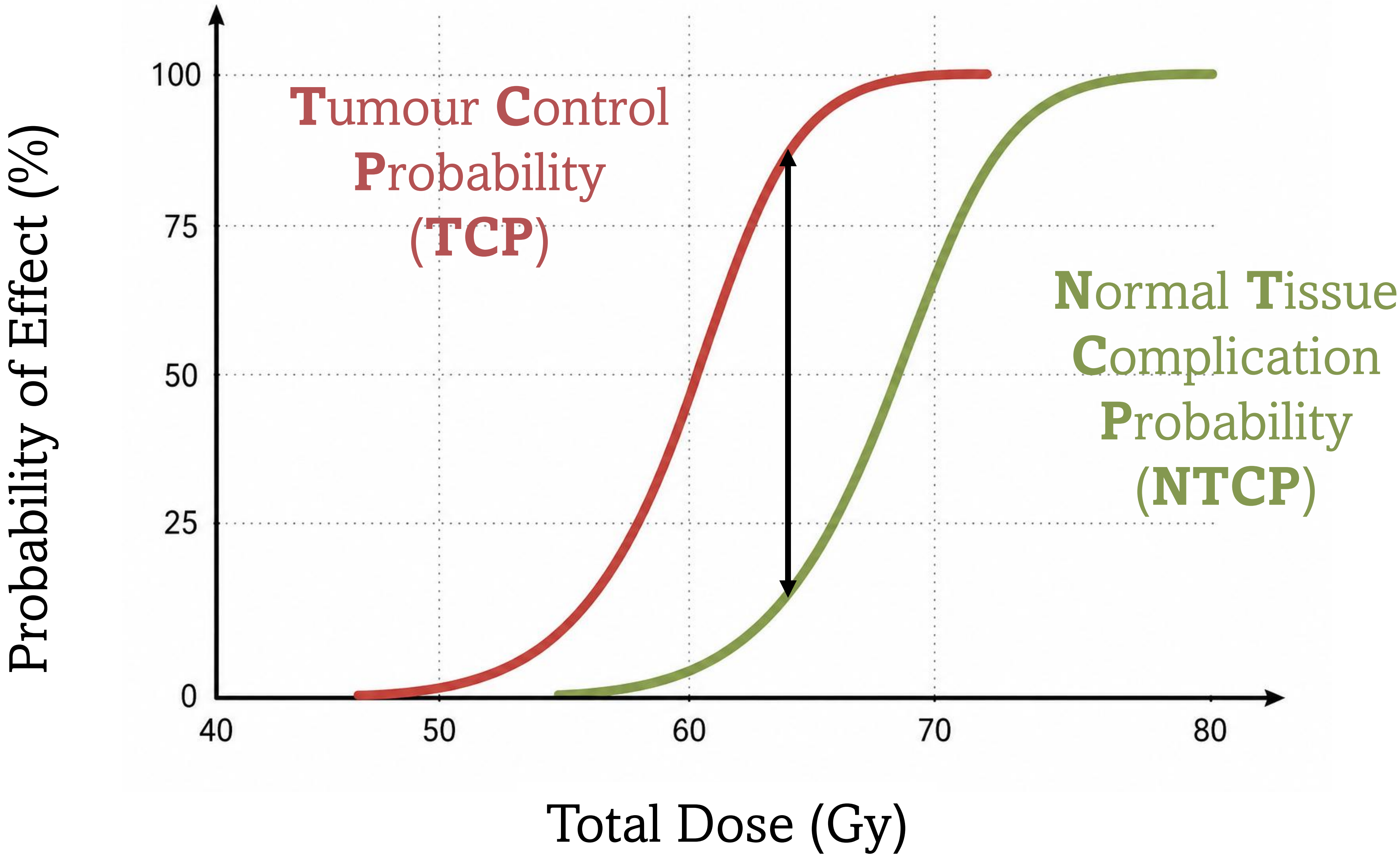


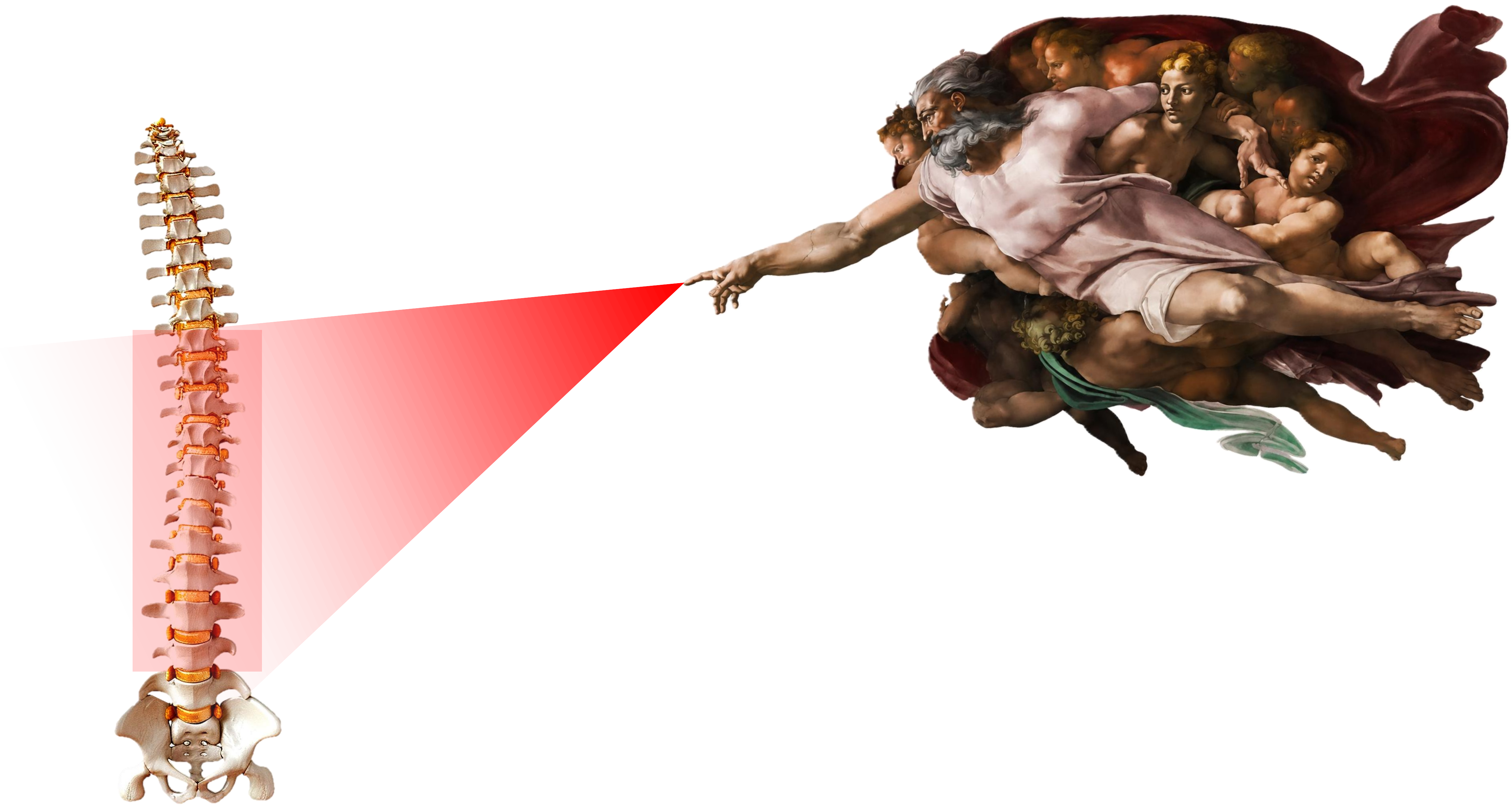
Dose

$$D = \frac{E}{m}$$



How much damage?


Probability of Effect (%)
100
75
50
25
0
40
50
60
70
80
Tumour Control Probability (TCP)
Normal Tissue Complication Probability (NTCP)
Total Dose (Gy)



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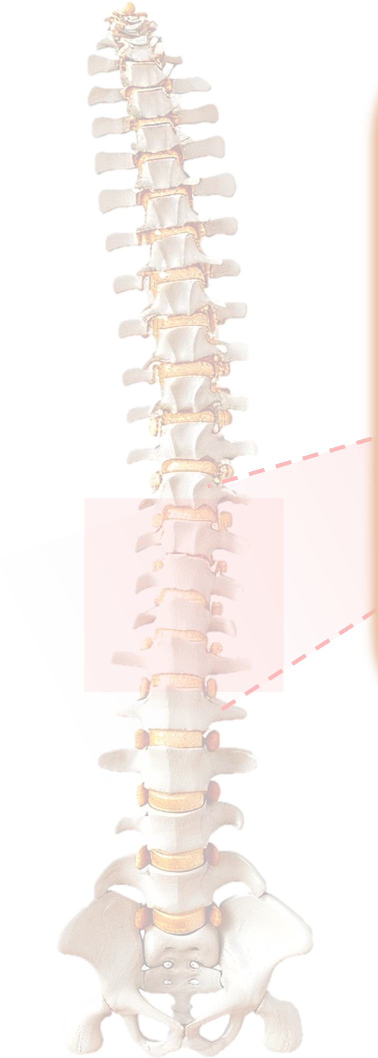
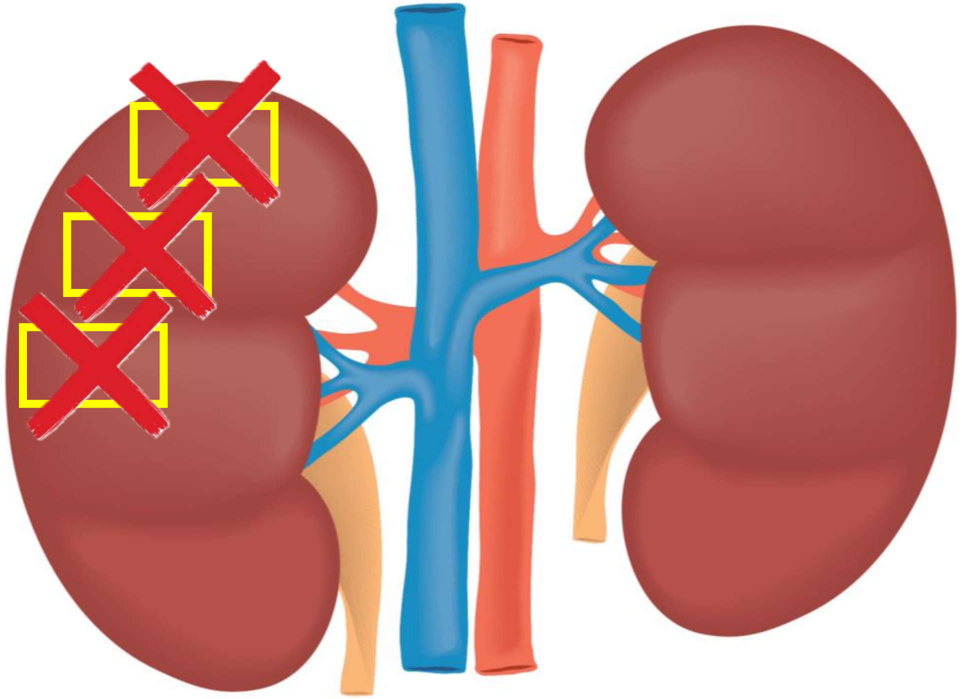
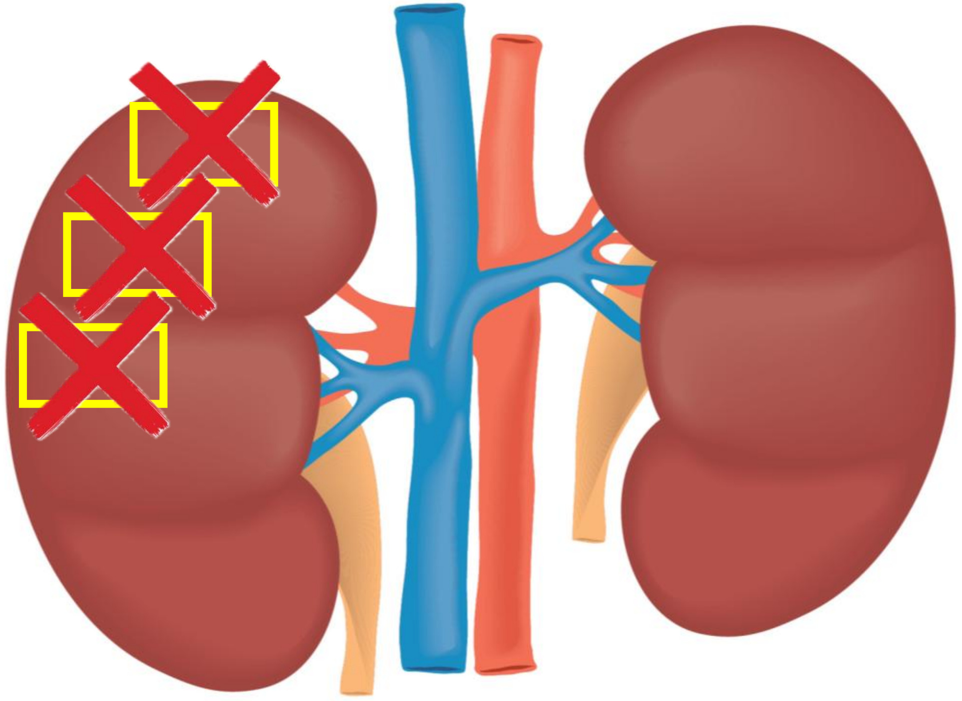


Volume Effect

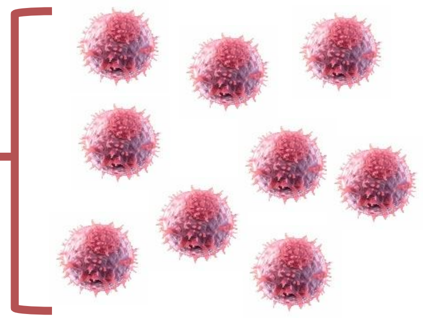
Parallel organs



Parallel organs

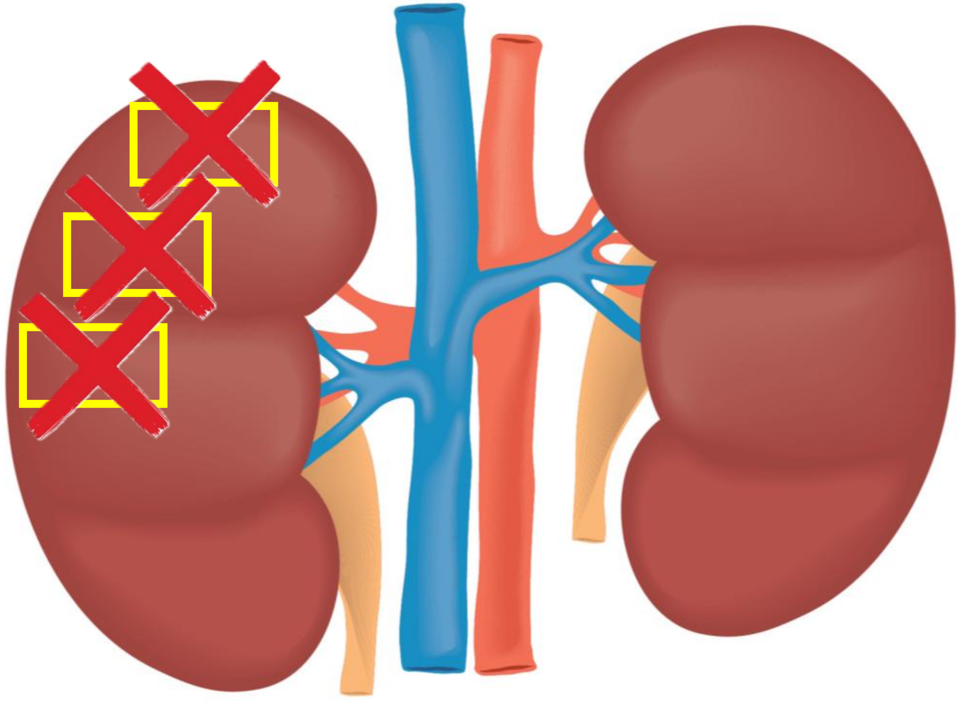


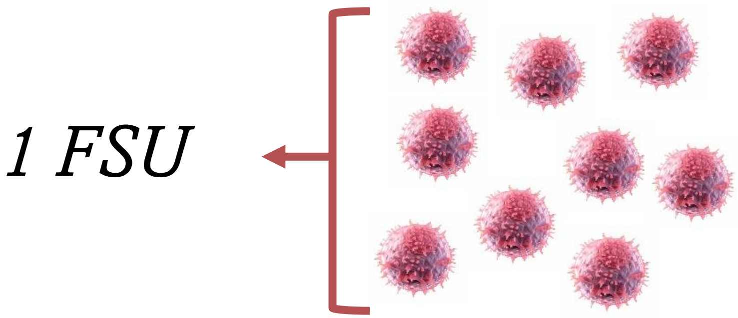
1 FSU



Parallel organs

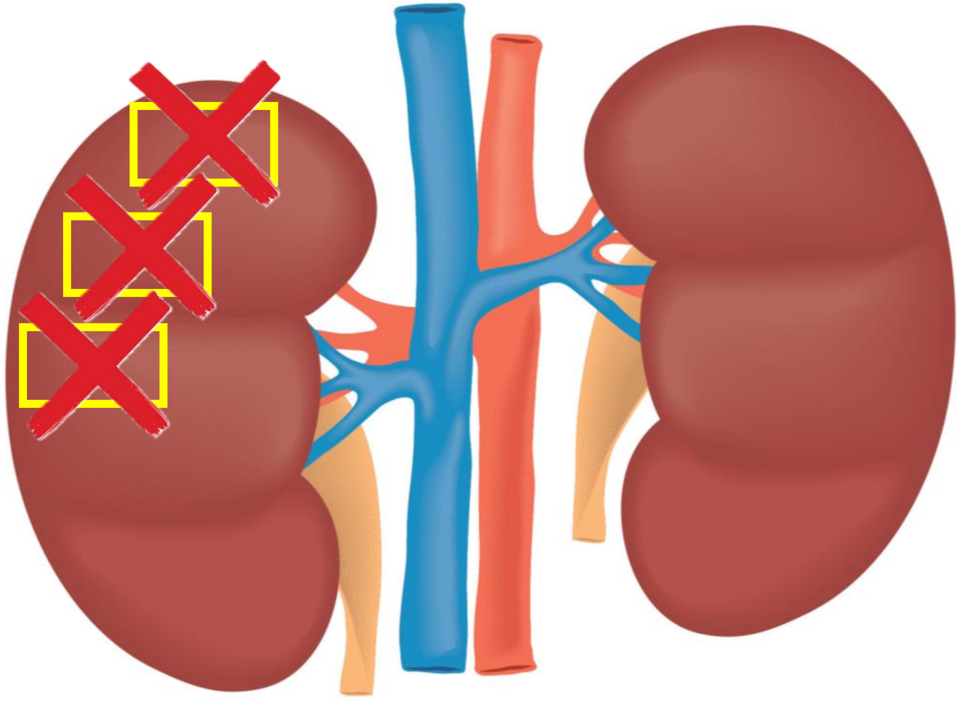
Serial organs



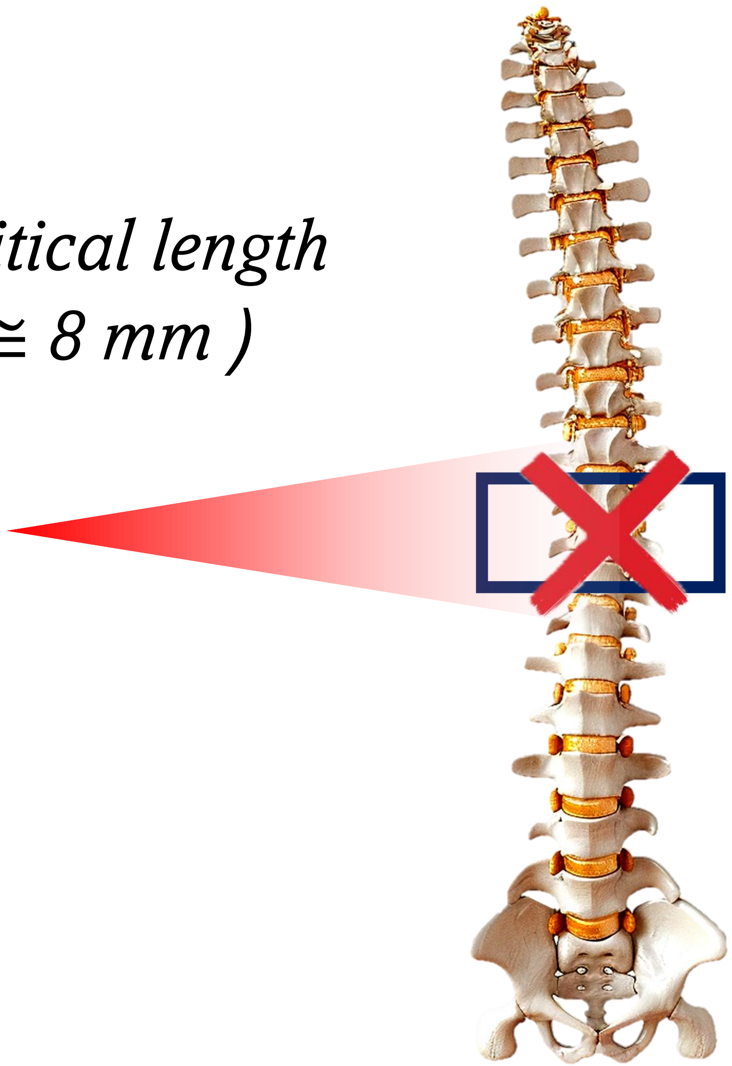


Parallel organs

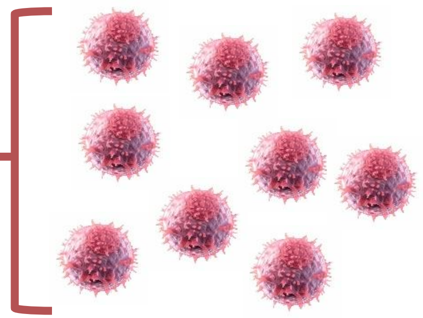
Serial organs

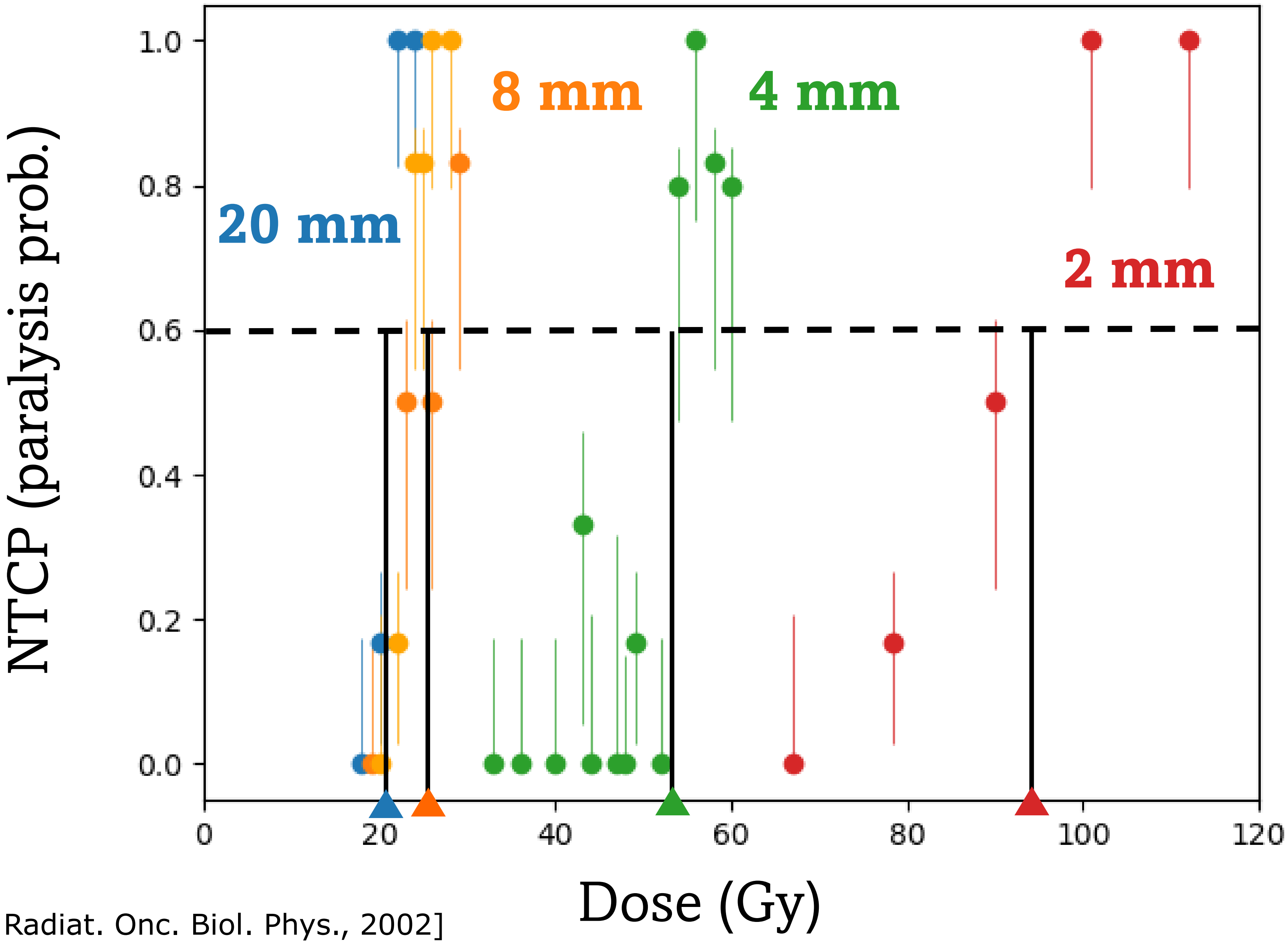


< critical length
(≅ 8 mm)

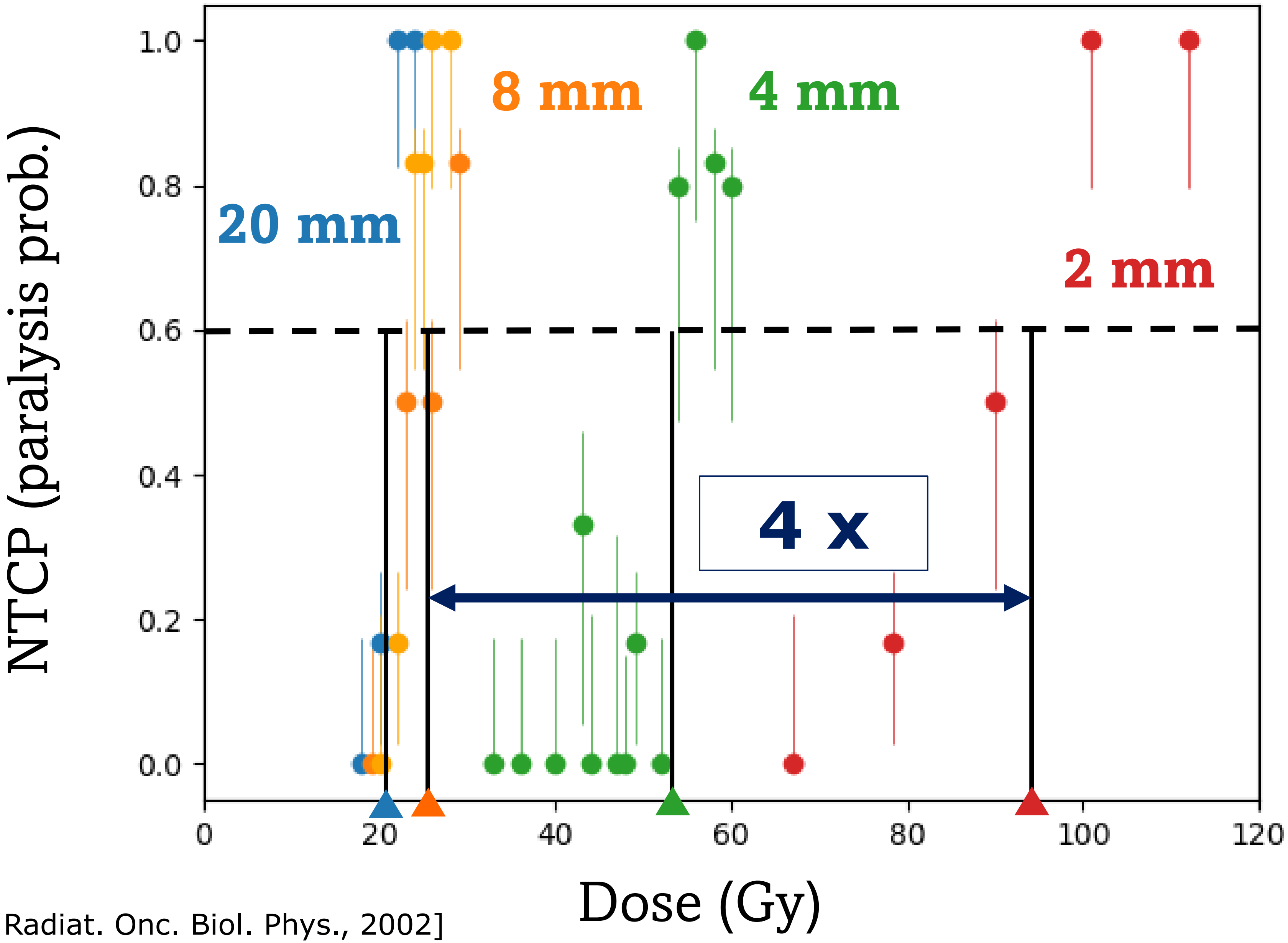


1 FSU

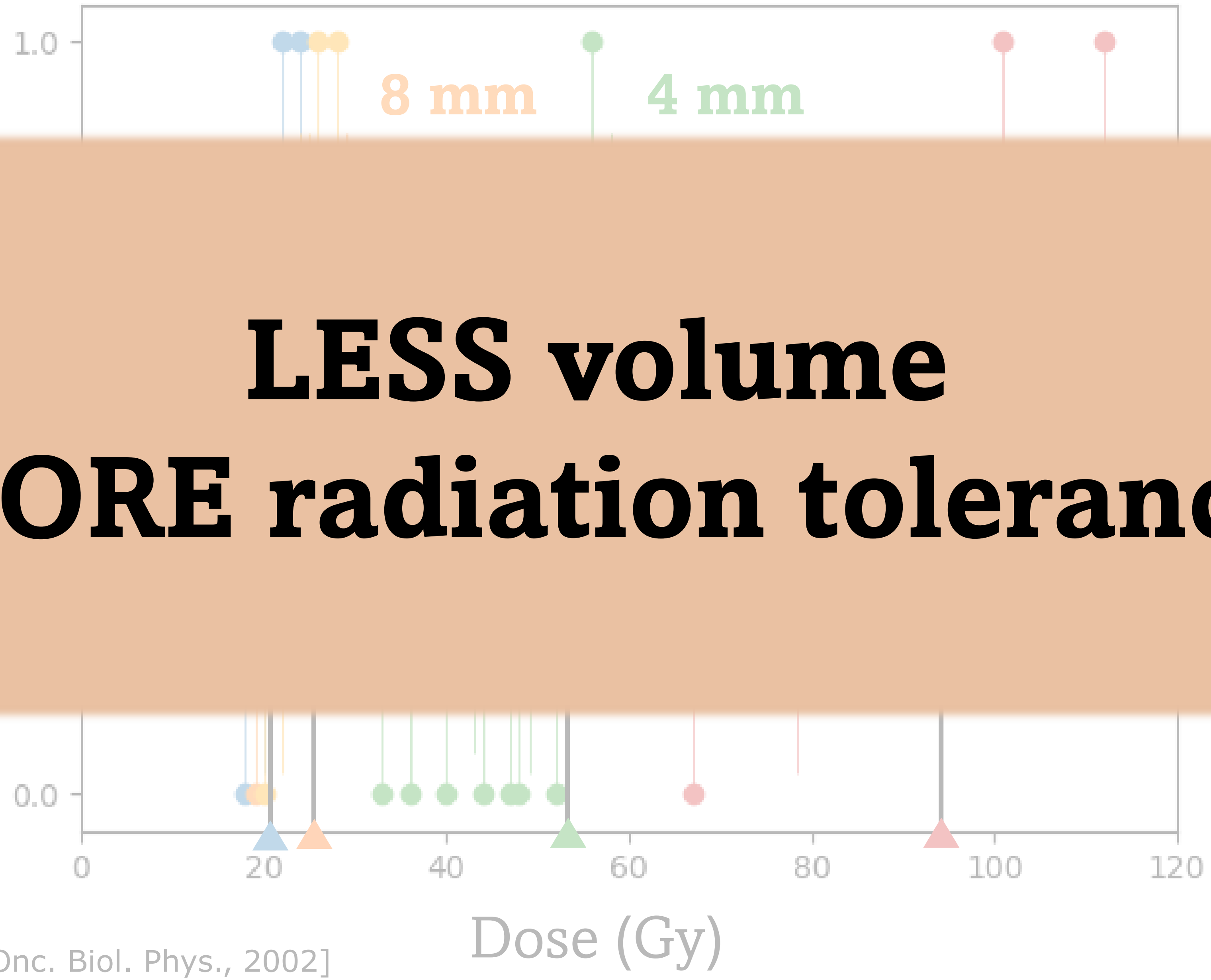




[Bijl et al., Int. J. Radiat. Onc. Biol. Phys., 2002]

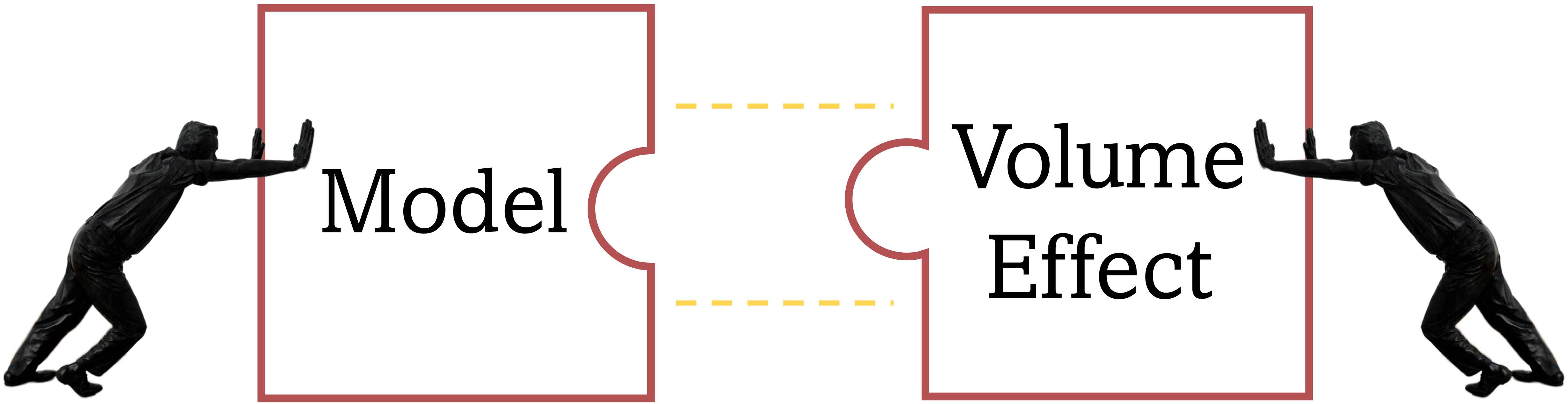


[Bijl et al., Int. J. Radiat. Onc. Biol. Phys., 2002]



LESS volume
MORE radiation tolerance

[Bijl et al., Int. J. Radiat. Onc. Biol. Phys., 2002]


Model
Volume Effect

Shirato model

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

Shirato model

Biological parameters from fit

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

Shirato model

Biological parameters from fit

Limited validation

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

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Shirato model

Biological parameters from fit

Limited validation

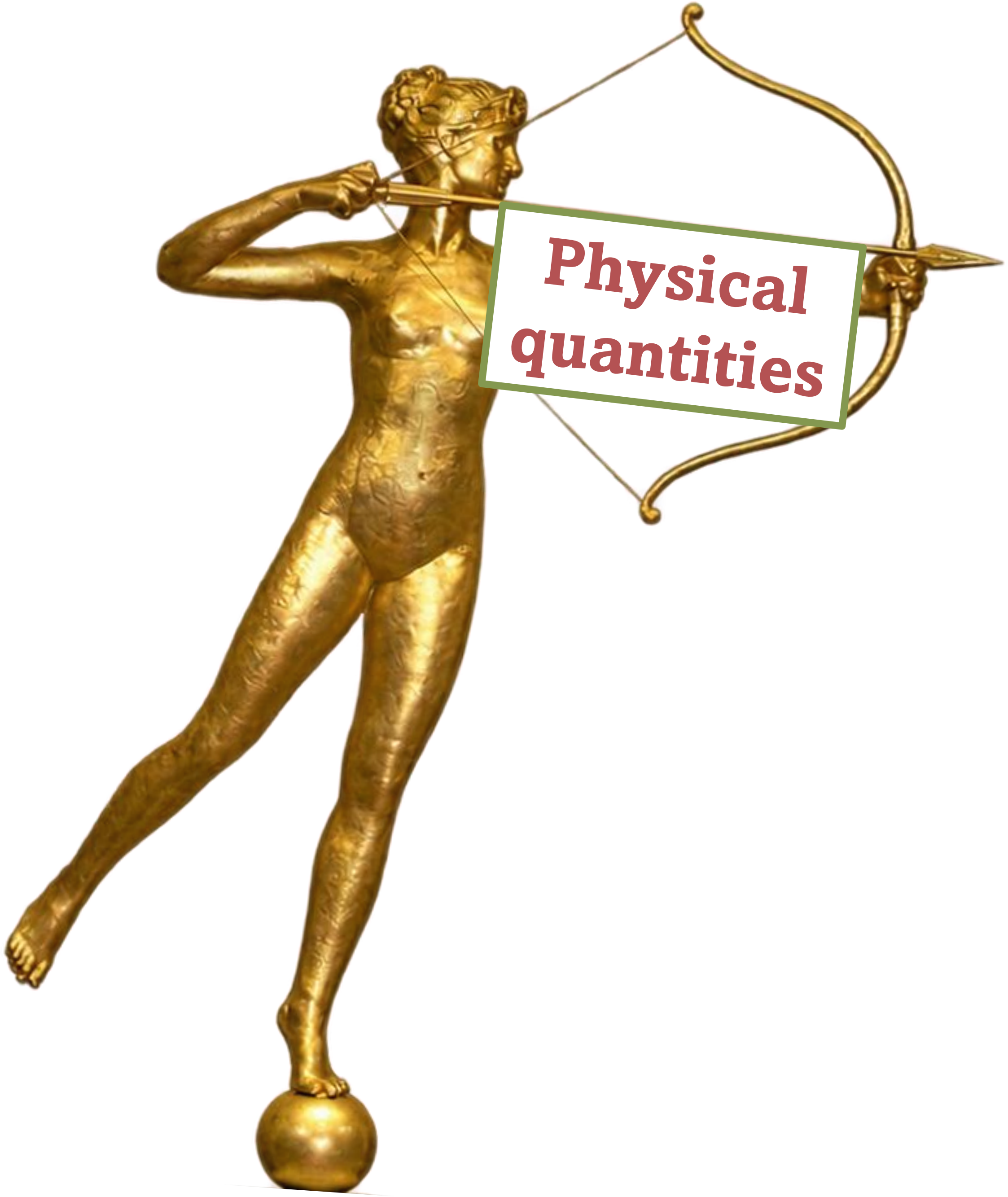
Parameter degeneracy

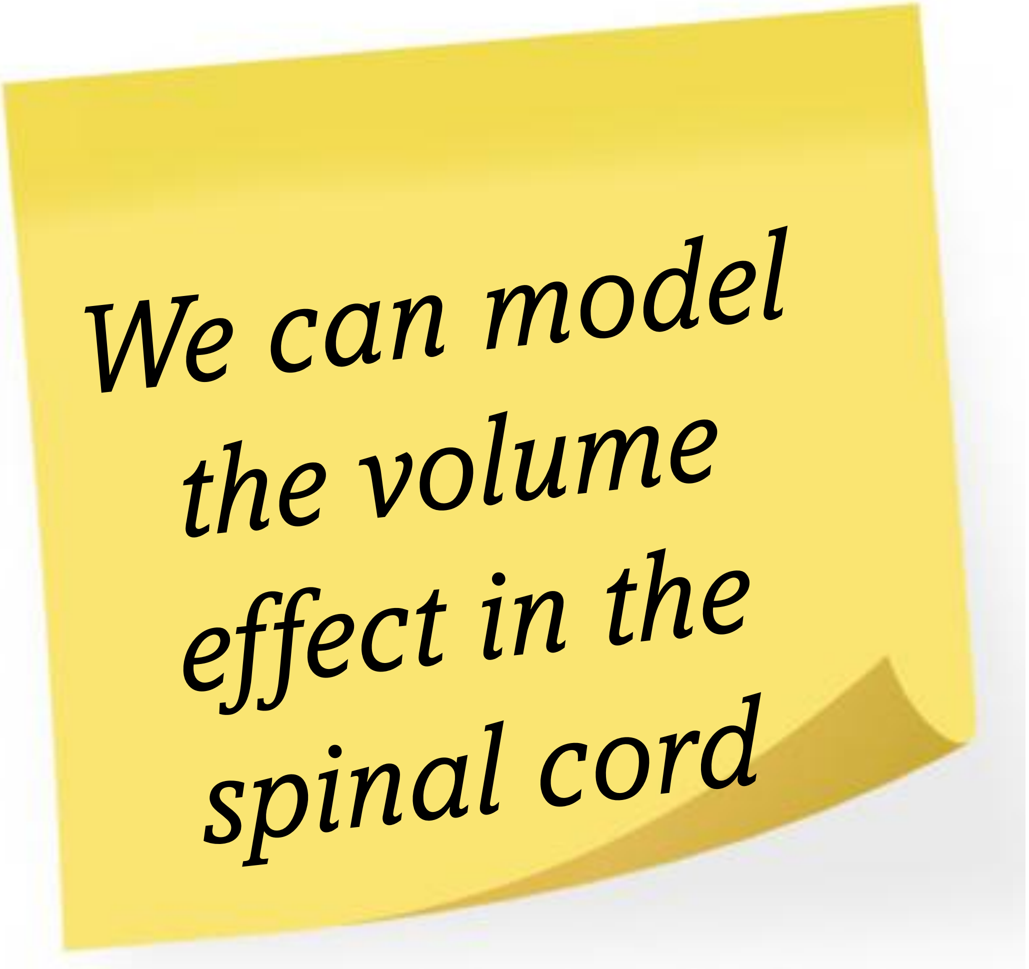
[Shirato et al., Radiotherapy and Oncology, 1995]

None *of the existing models is capable of describing the volume effect in serial organs.*

- Van der Kogel

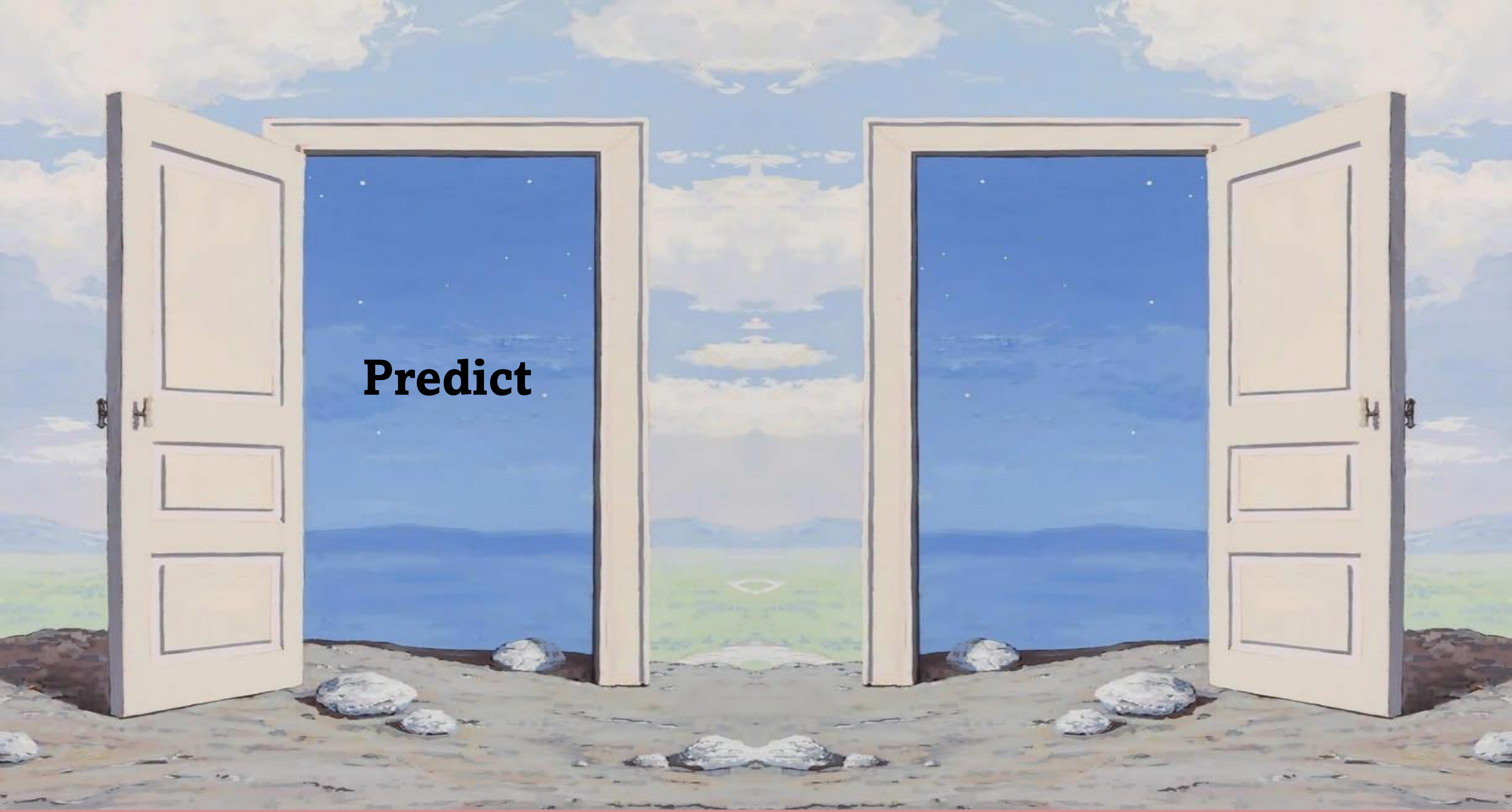
alice.casali01@universitadipavia.it Alice Casali

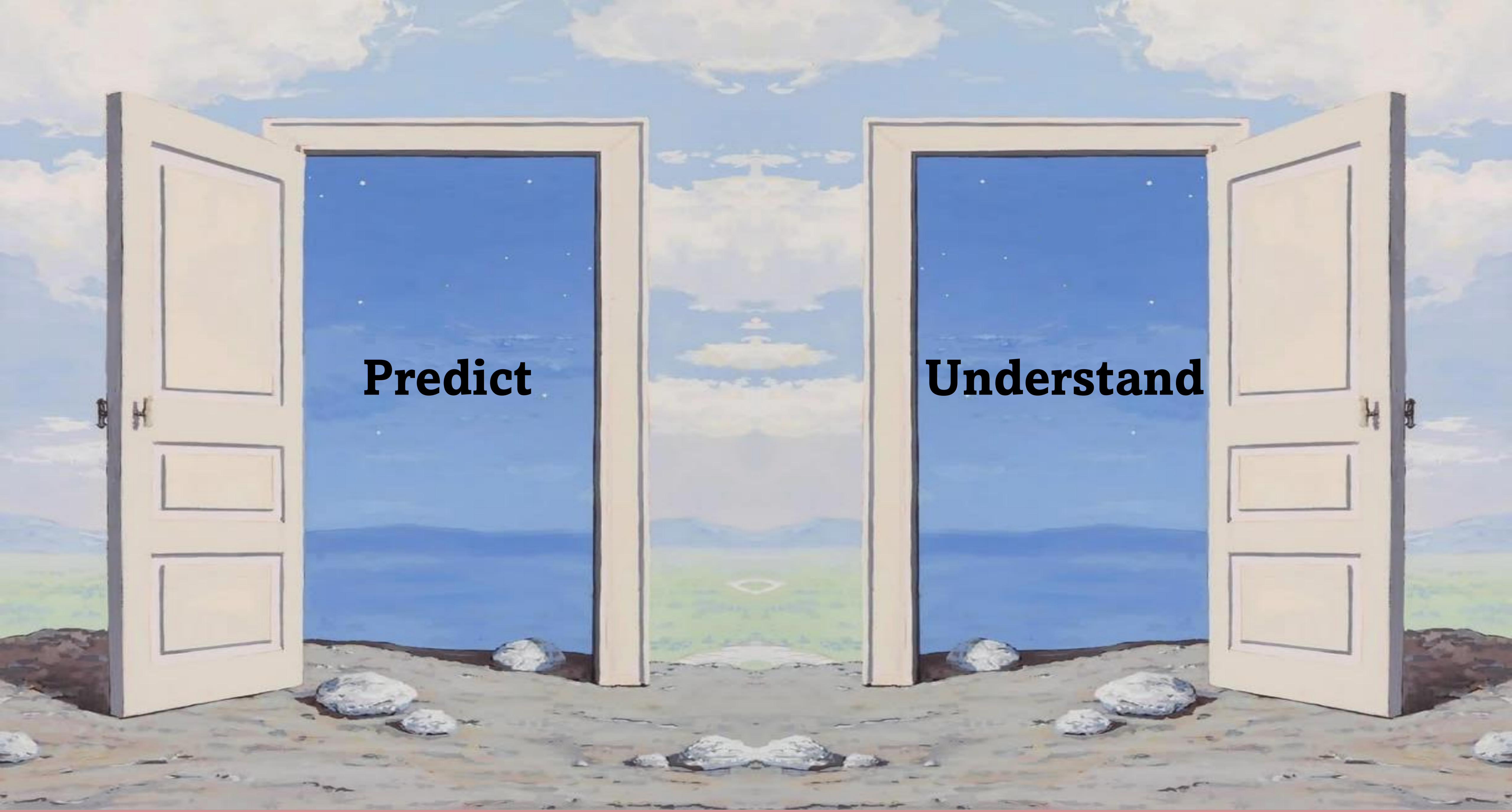

Physical quantities

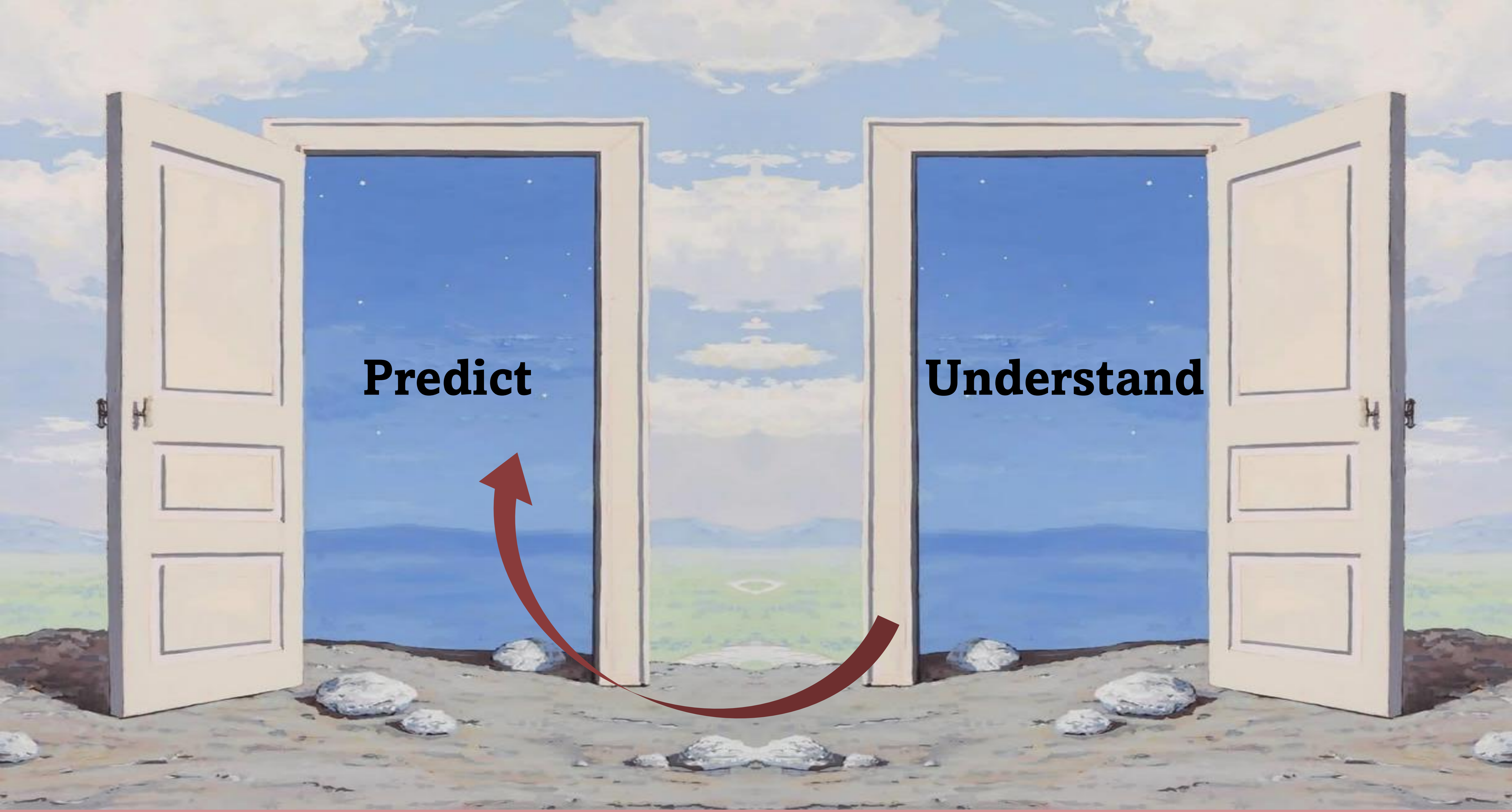

We can model the volume effect in the spinal cord

Why ?

Predict




Predict
Understand


Predict
Understand

How ?

NO
volume effect

Single length

l **>** *8 mm*

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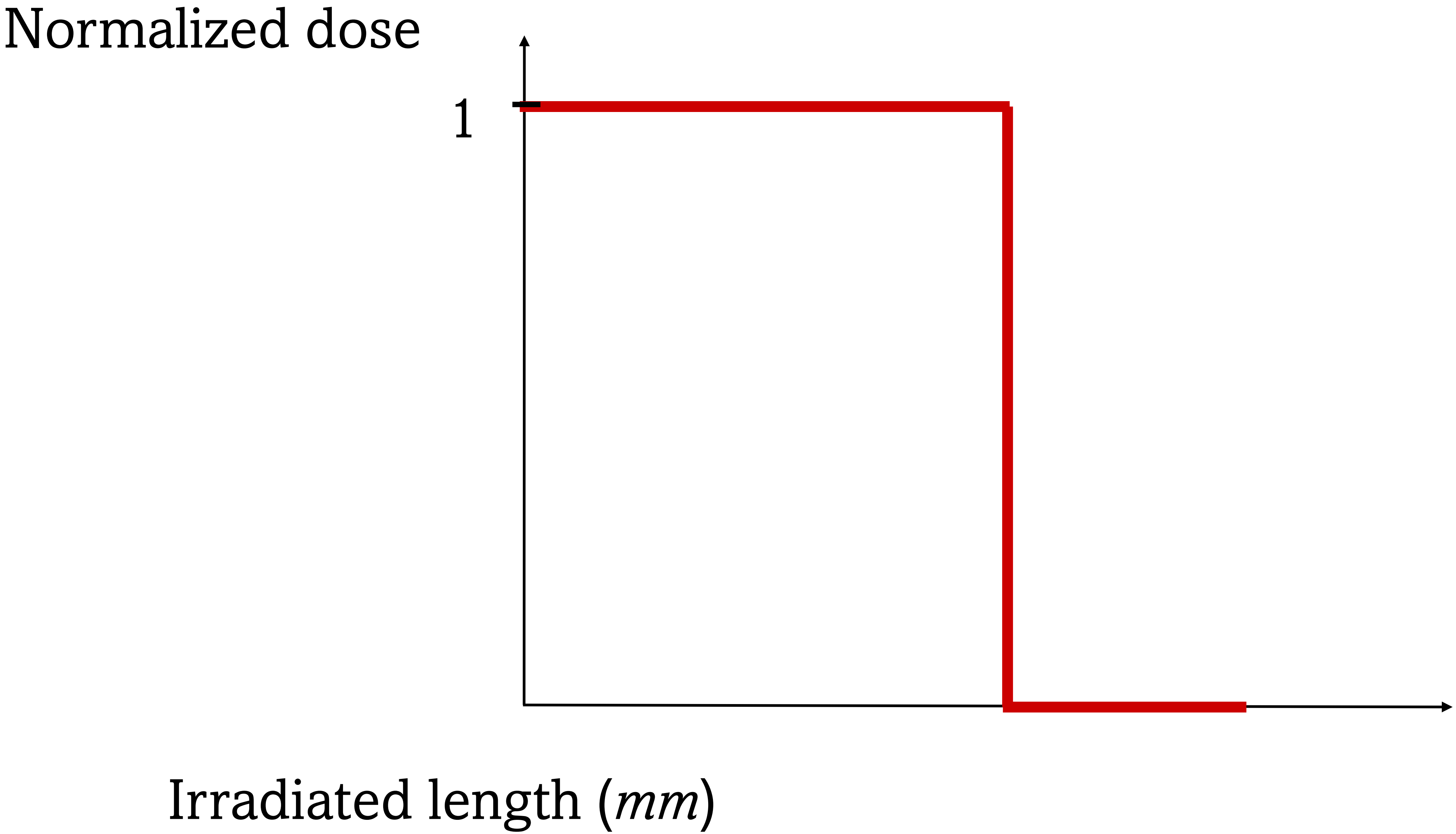
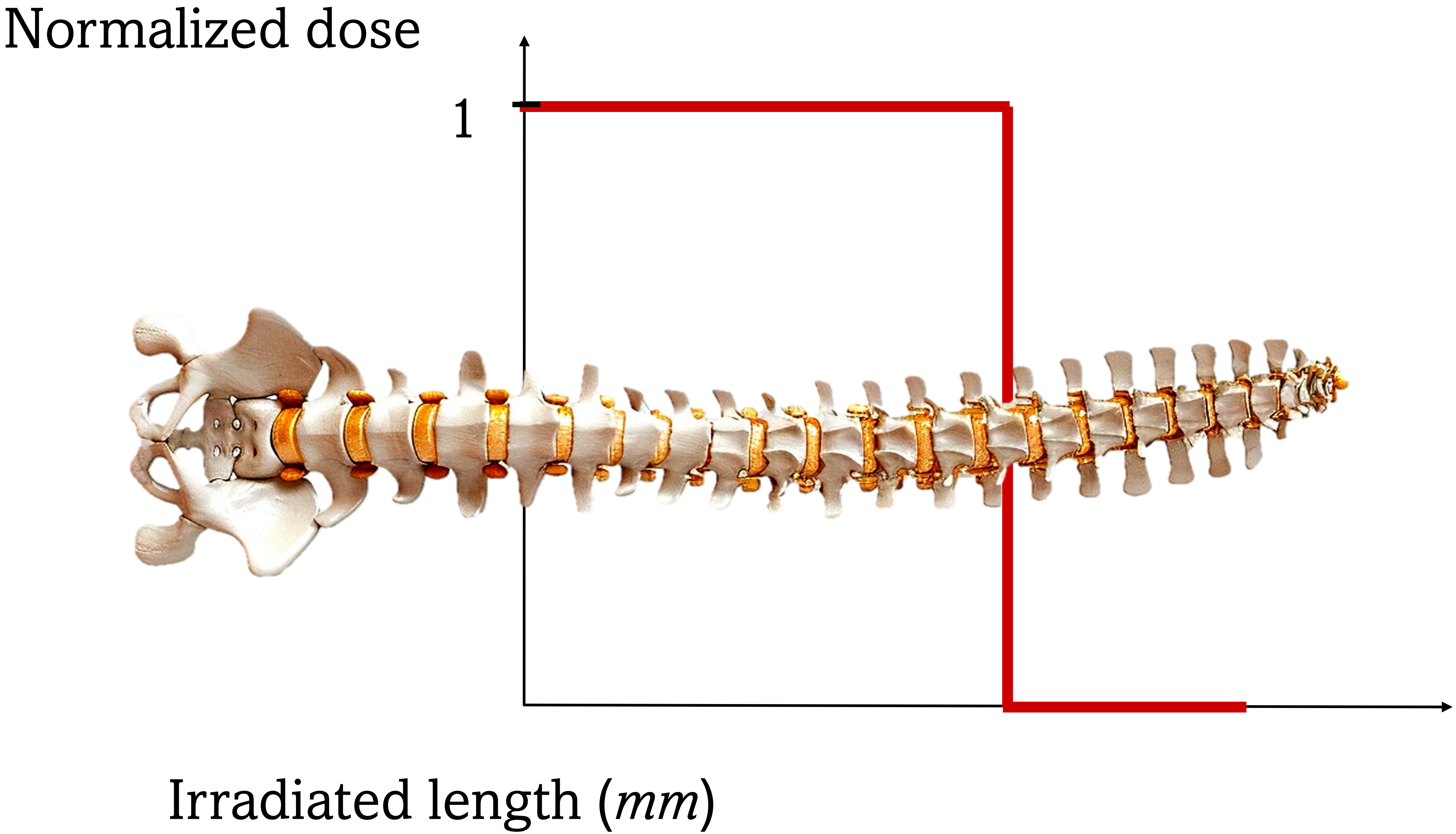
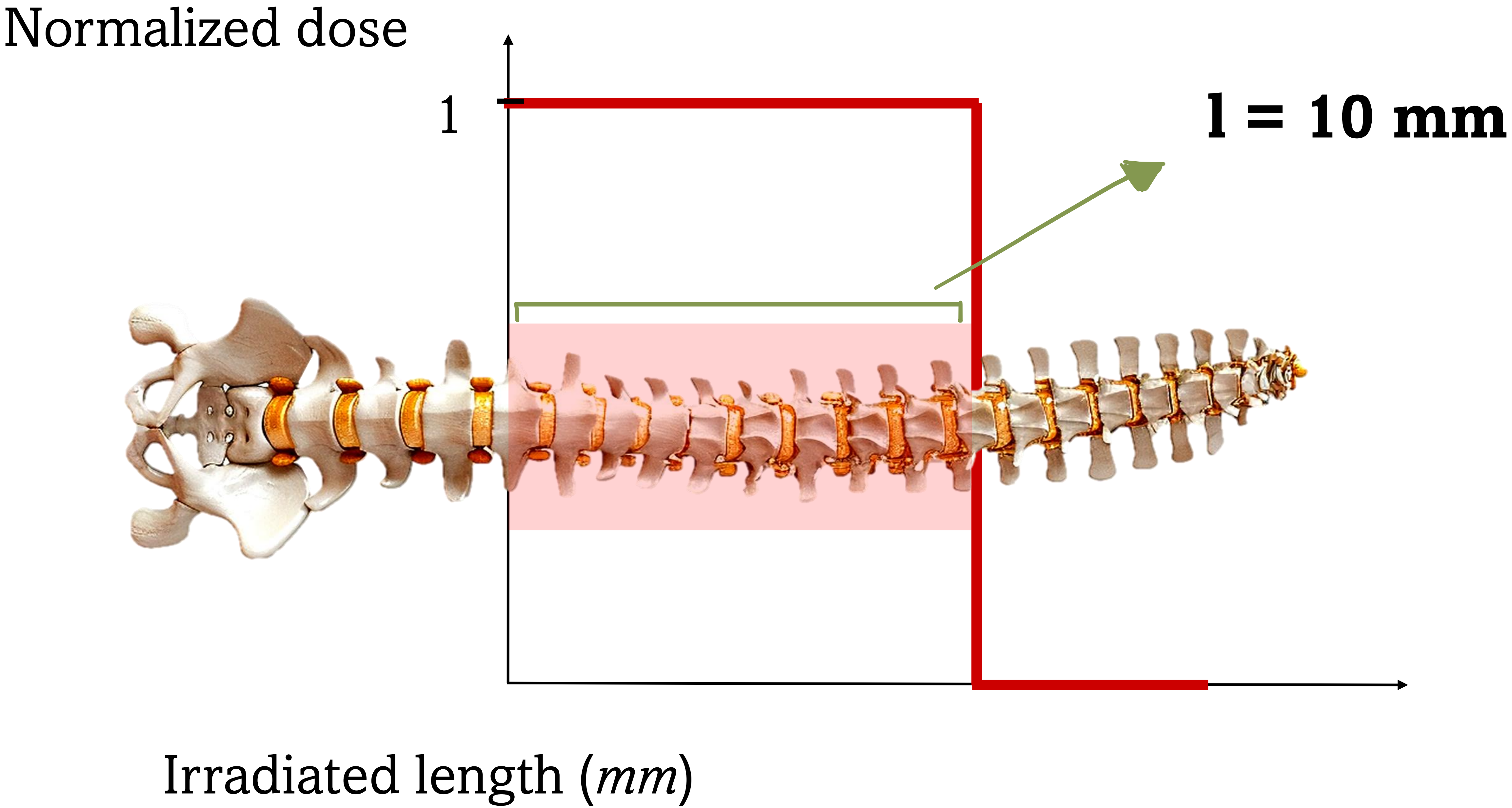
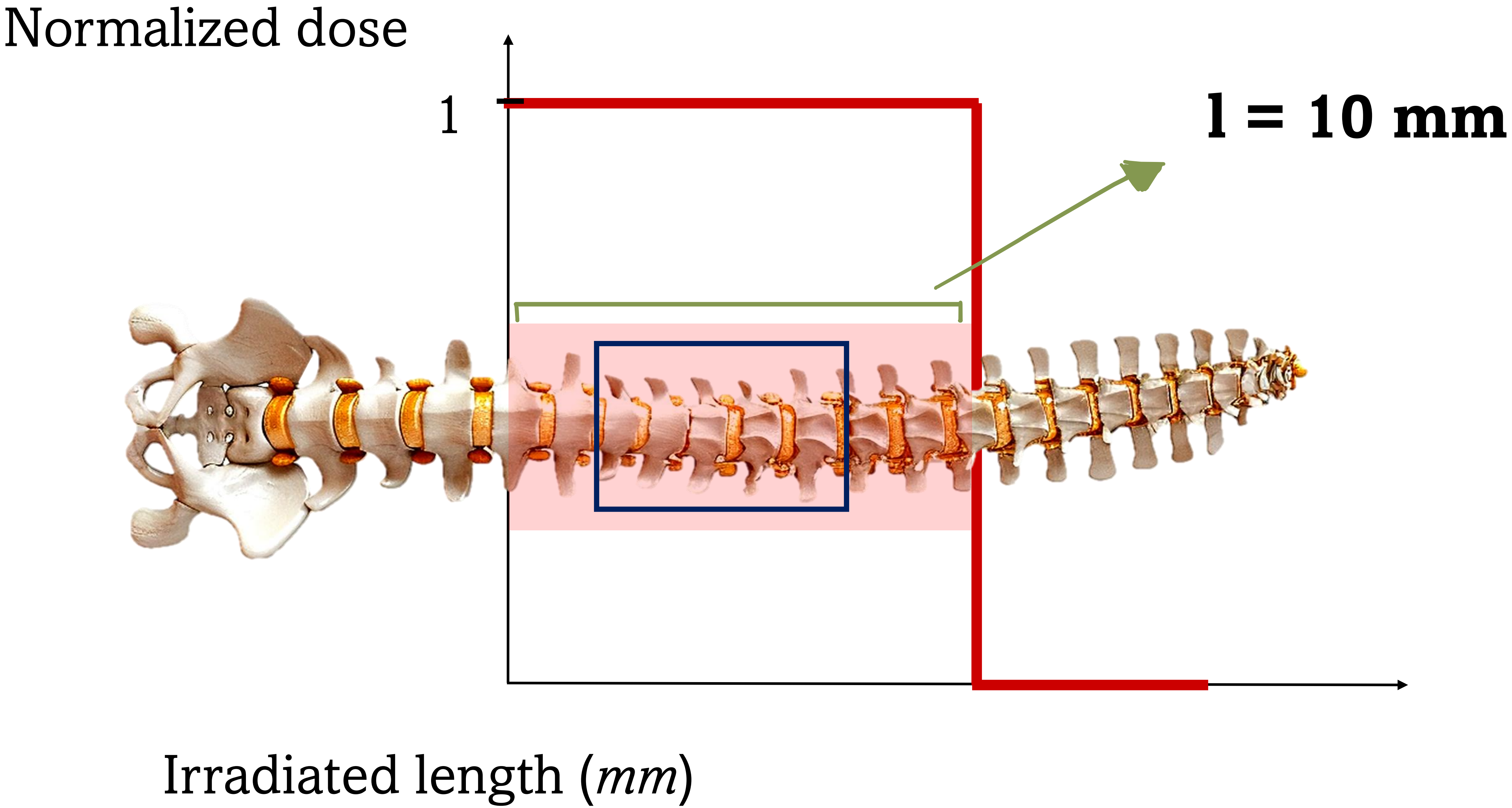

Normalized dose
1
Irradiated length (mm)


Normalized dose
1
Irradiated length (mm)


Normalized dose
1
l = 10 mm
Irradiated length (mm)


Normalized dose
1
l = 10 mm
Irradiated length (*mm*)

Critical Element Model

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

Critical Element Model

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

$$\mathbf{P_{cell}} = 1 - S = 1 - e^{-\alpha_i nd - \beta_i nd^2}$$

Critical Element Model

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

$$\mathbf{P_{cell}} = 1 - S = 1 - e^{-\alpha_i nd - \beta_i nd^2}$$

Linear – quadratic model

i = i-th particle type

Critical Element Model

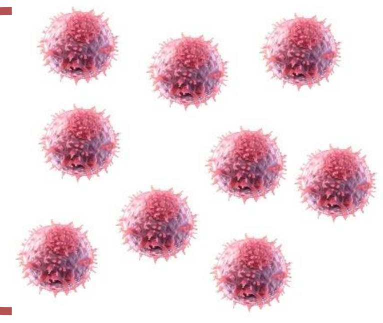
[Withers et al., Int. J. Radiat. Onc. Biol. Phys., 1988]

$$\mathbf{P_{cell}} = 1 - S = 1 - e^{-\alpha_i nd - \beta_i nd^2}$$

Linear – quadratic model

i = i-th particle type

1 FSU = t cells



Critical Element Model

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

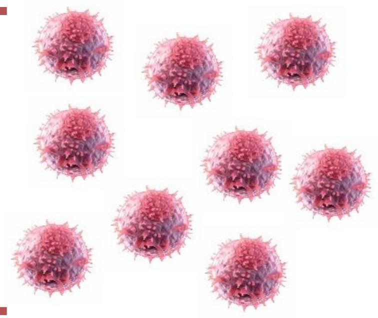
Linear – quadratic model

$$\mathbf{P_{cell}} = 1 - S = 1 - e^{-\alpha_i nd - \beta_i nd^2}$$

i = i-th particle type

$$\mathbf{P_{FSU}} = \left(1 - e^{-\alpha_i nd - \beta_i nd^2}\right)^t$$

1 FSU = t cells



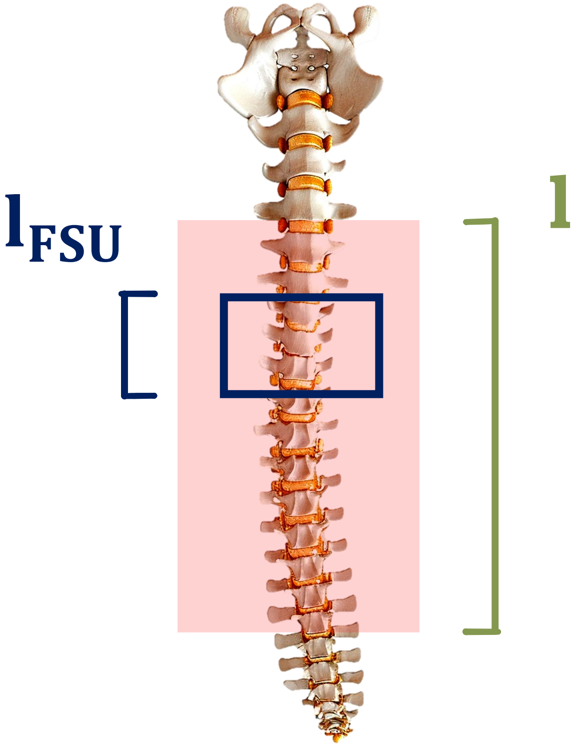
$$\mathbf{NTCP} = 1 - P_0 =$$

$$\mathbf{NTCP} = 1 - P_0 =$$

$$= 1 - \left(1 - \left(1 - e^{-\alpha_i nd - \beta_i nd^2} \right)^{t} \right)^{N}$$

$$\mathbf{NTCP} = 1 - P_0 =$$

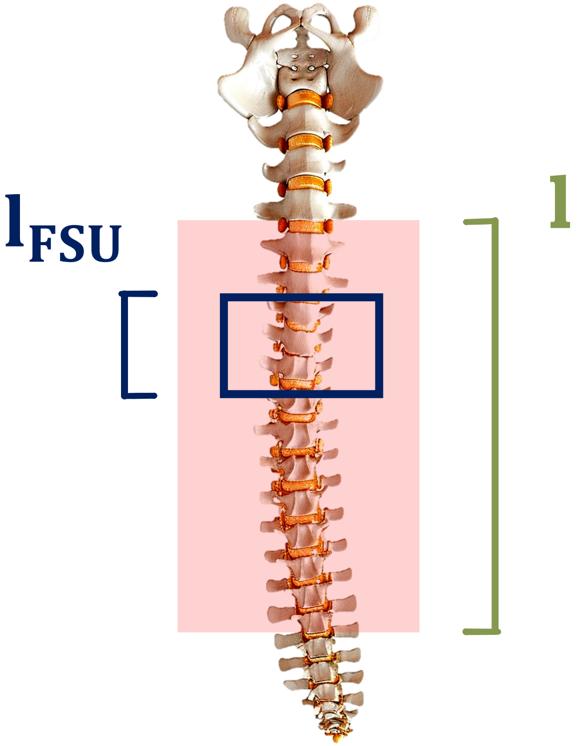
$$= 1 - \left(1 - \left(1 - e^{-\alpha_i nd - \beta_i nd^2}\right)^{t}\right)^{N}$$



$$N = \frac{l}{l_{FSU}}$$

$$\mathbf{NTCP} = 1 - P_0 =$$

$$= 1 - \left(1 - \left(1 - e^{-\alpha_i nd - \beta_i nd^2}\right)^{t}\right)^{N}$$



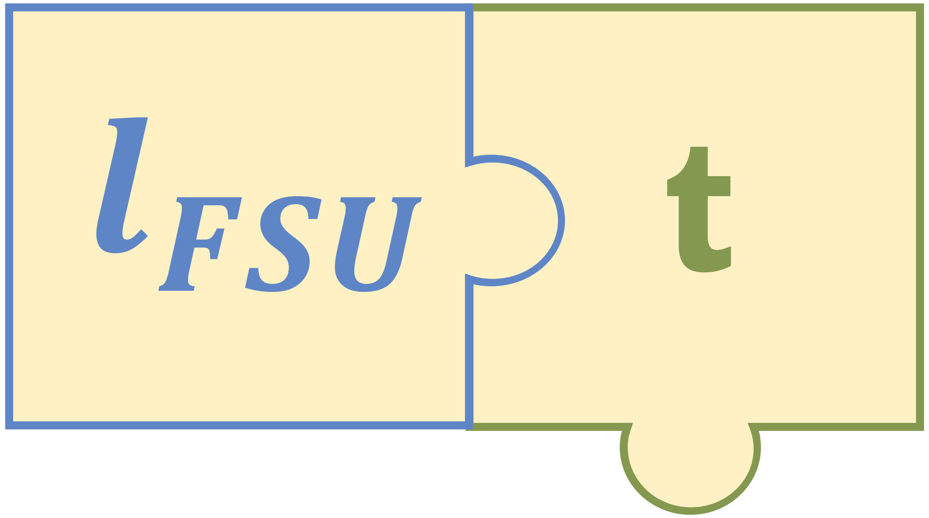
$$N = \frac{l}{l_{FSU}}$$

Model parameters

Model parameters

t = num. cells in 1 FSU

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



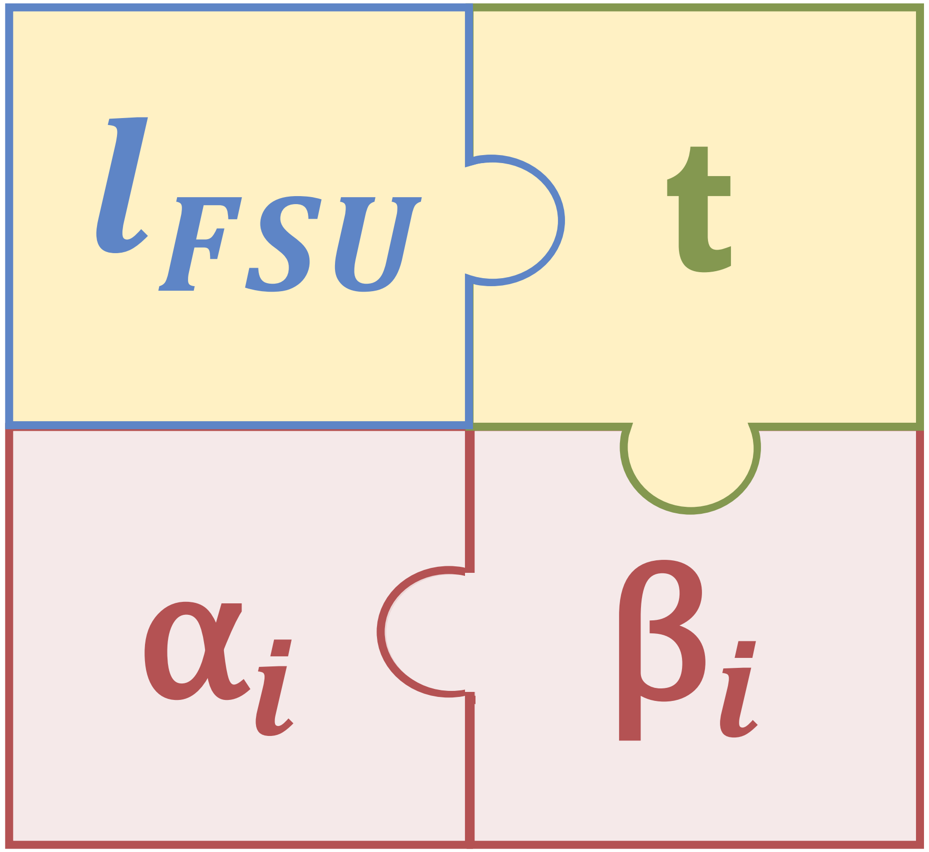
→ Photon NTCP data

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

Model parameters

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

t = num. cells in 1 FSU



→ **Photon NTCP data**

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

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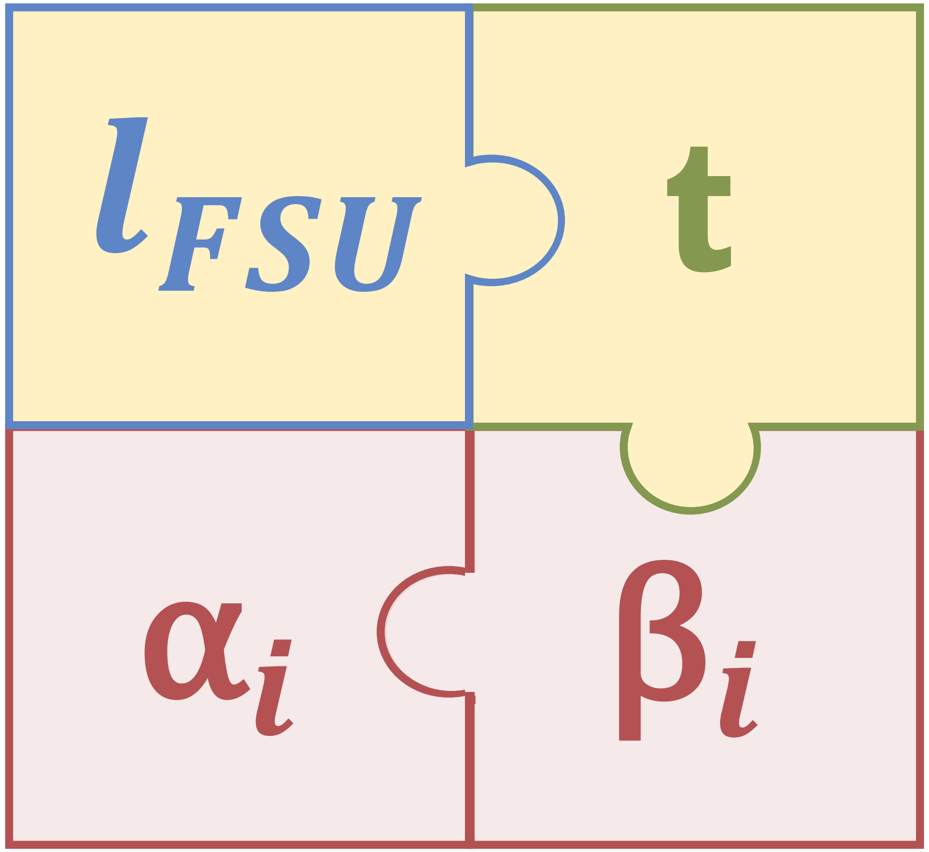
Model parameters

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

t = num. cells in 1 FSU



→ Photon NTCP data

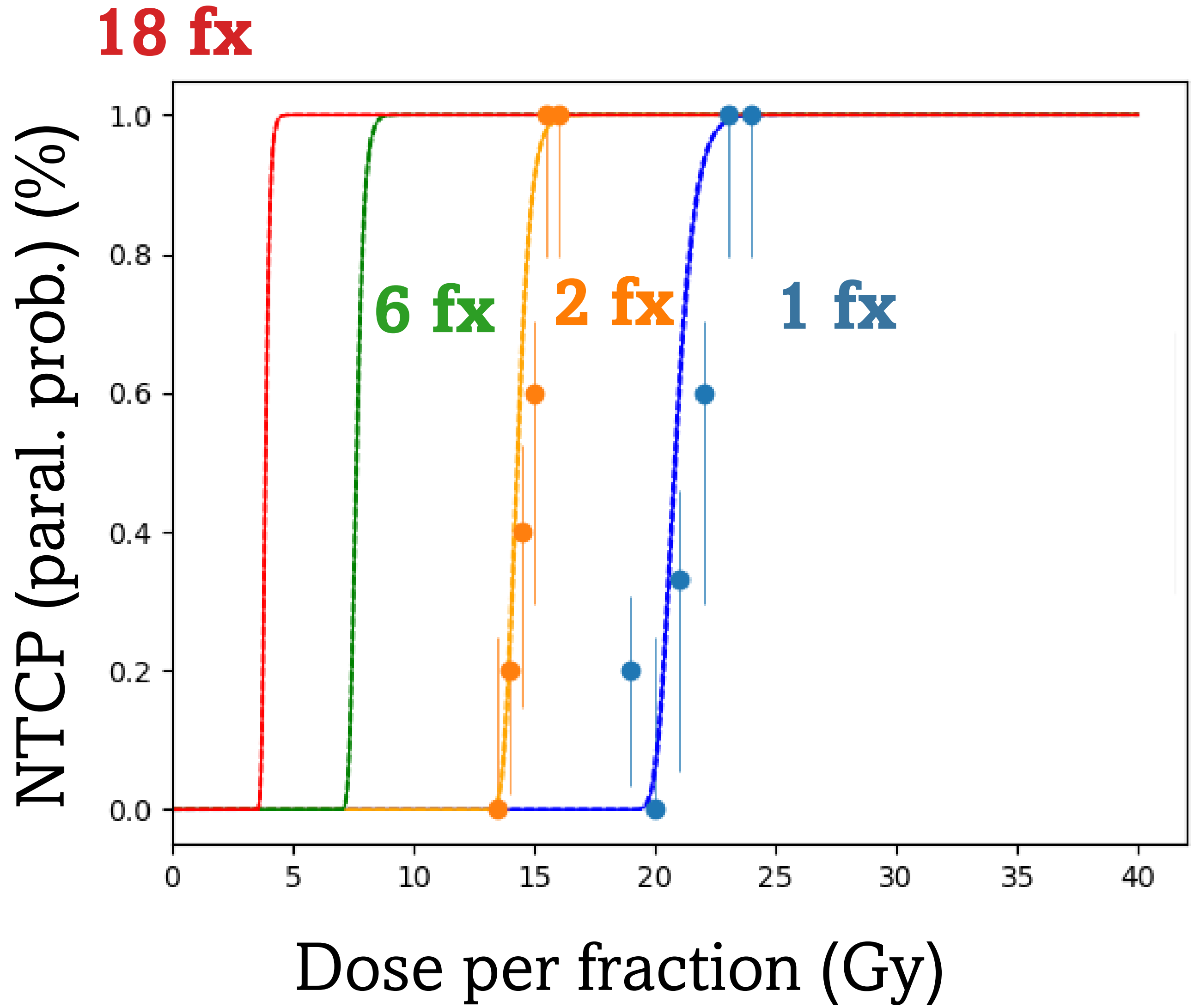
[Karger et al., Int. J. Radiat. Onc. Biol. Phys., 2006]

→ Photon NTCP data

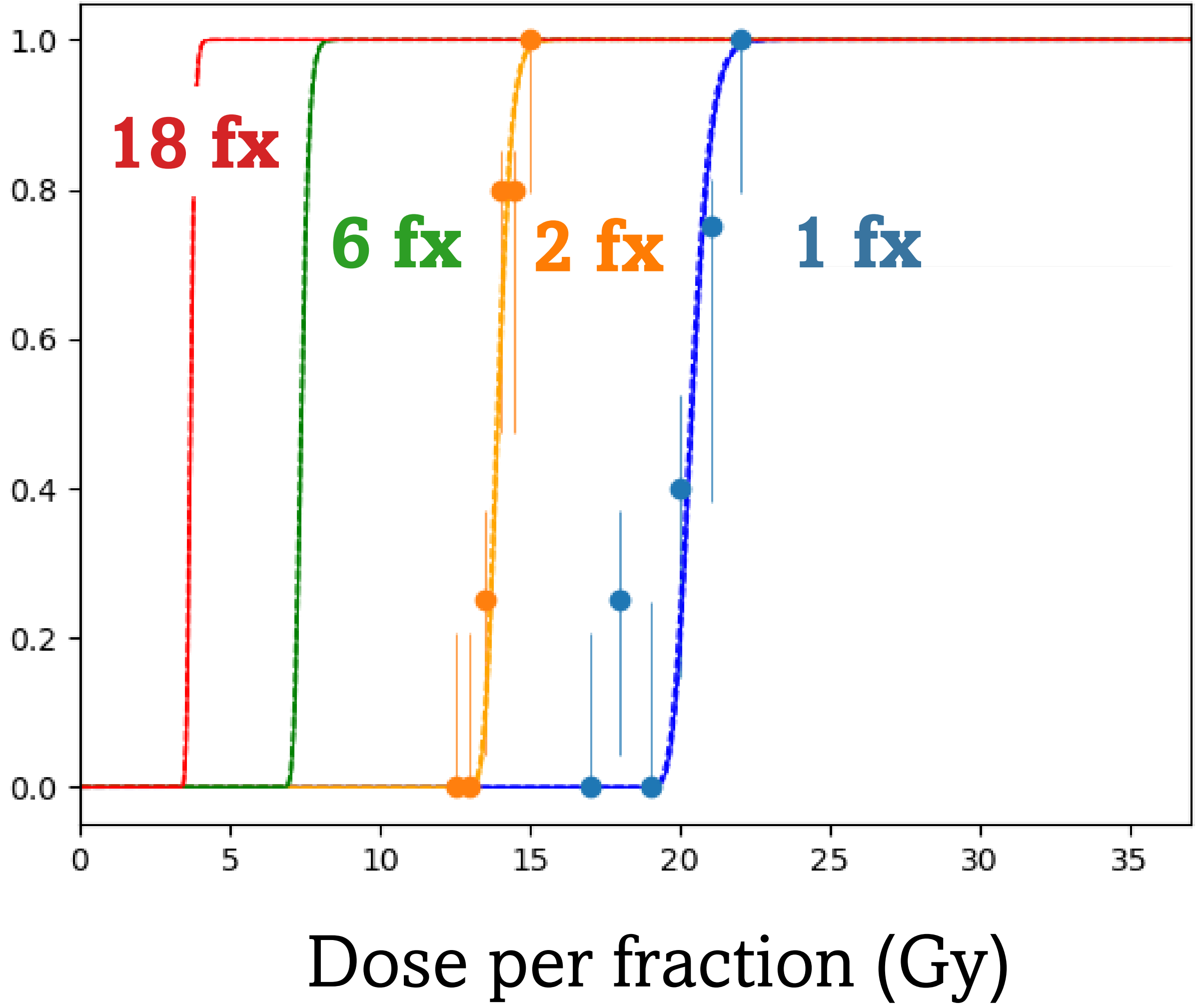
G4 – BIANCA interface

[**A. Casali** et al., Eur. Phys. J. Spec. Top., **2026**]

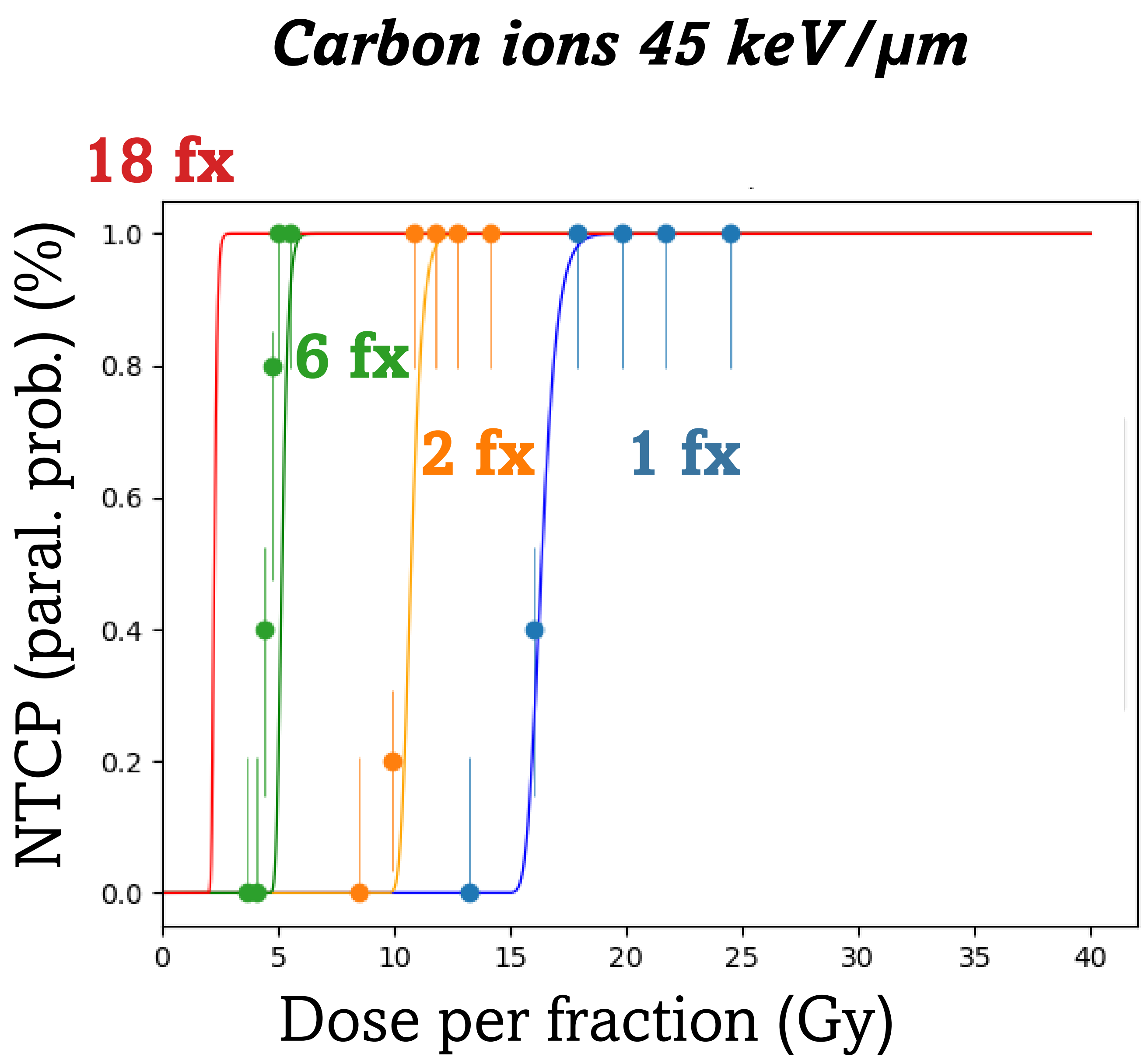
Protons 3.9 ± 0.2 *keV/µm*

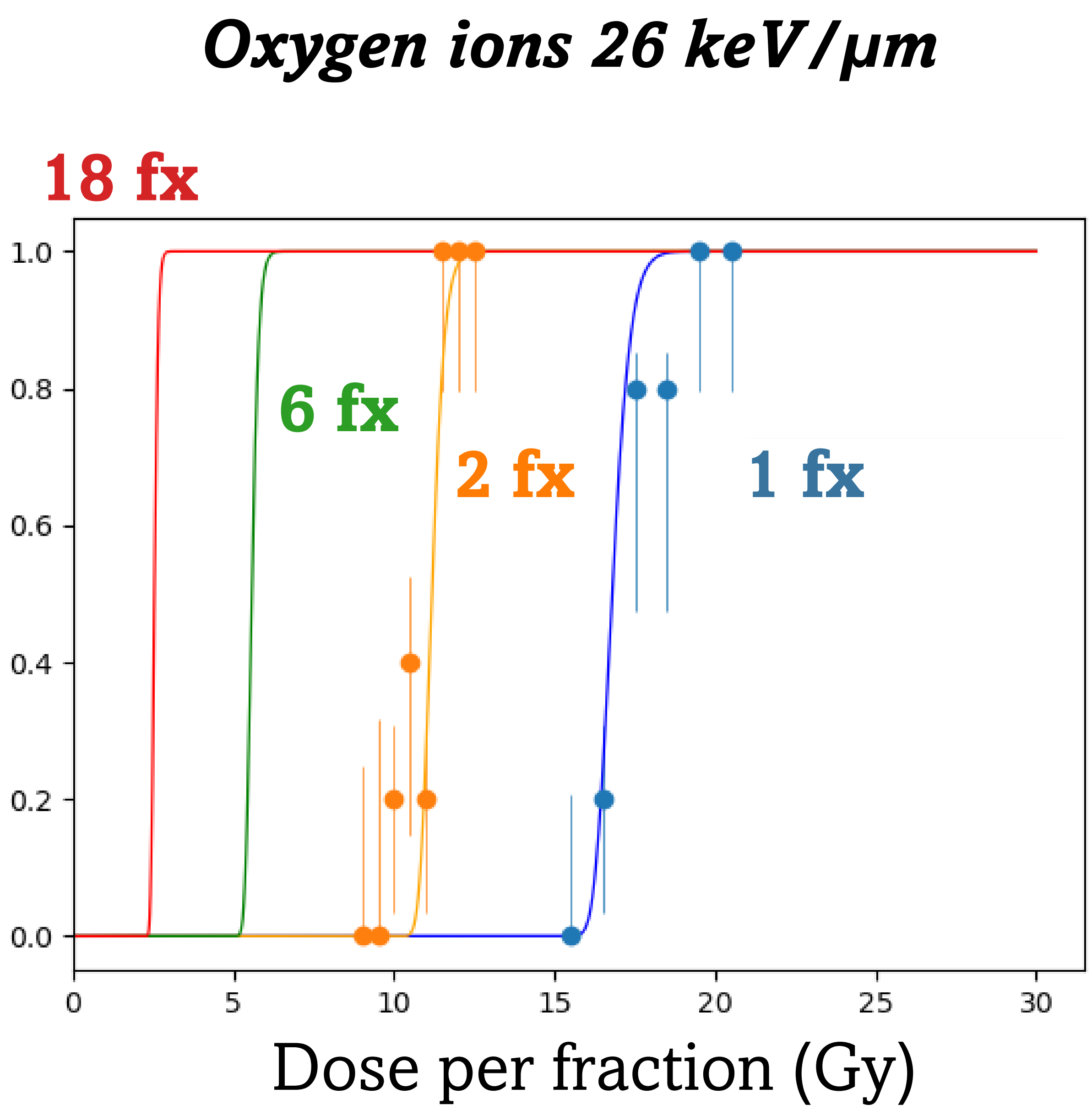


Helium ions $9.4^{+0.6}_{-1.4}$ *keV/µm*



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

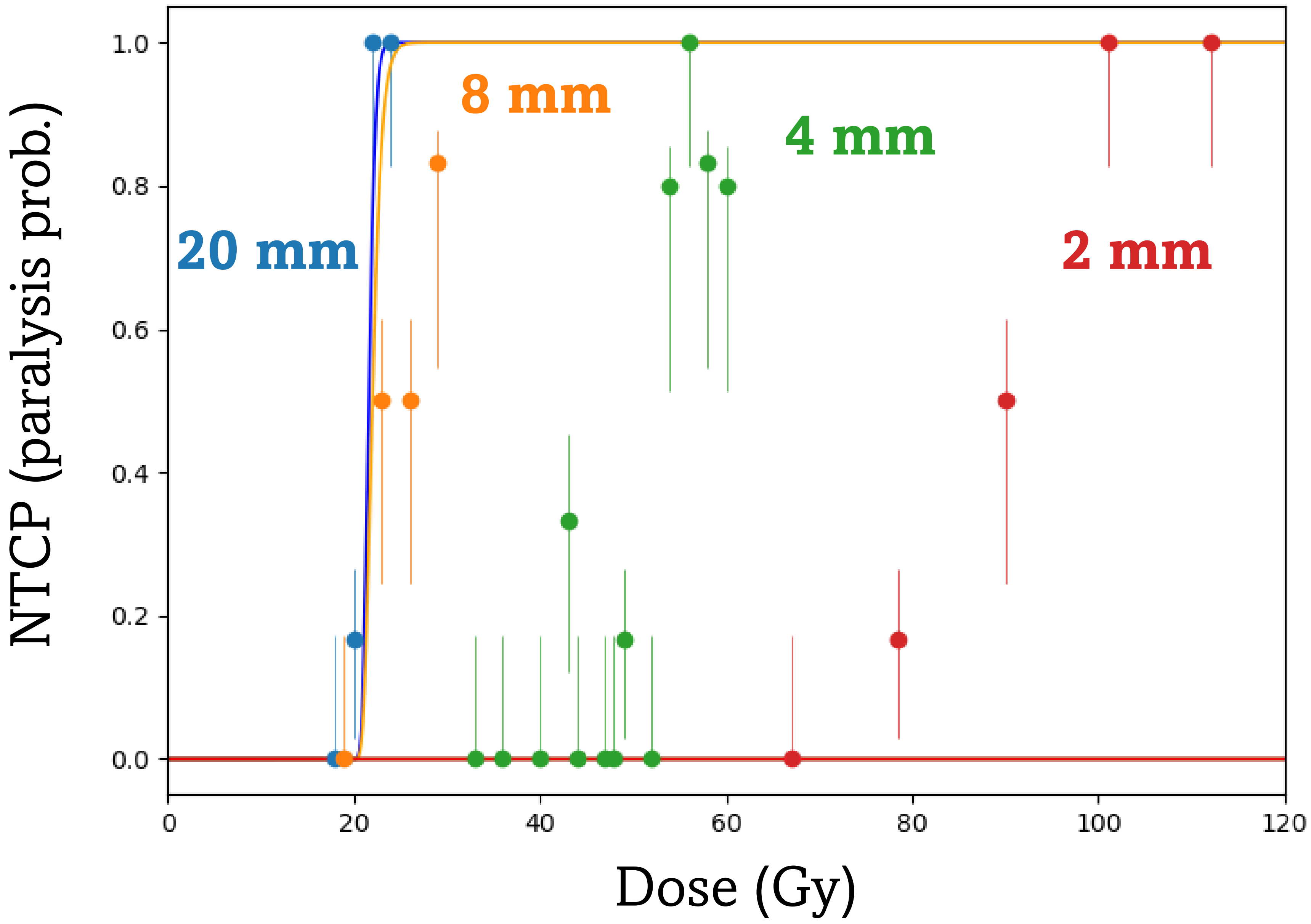




[Karger et al., Int. J. Radiat. Onc. Biol. Phys., 2006]

Critical Element Model

Volume effect in serial organs



Critical Element Model

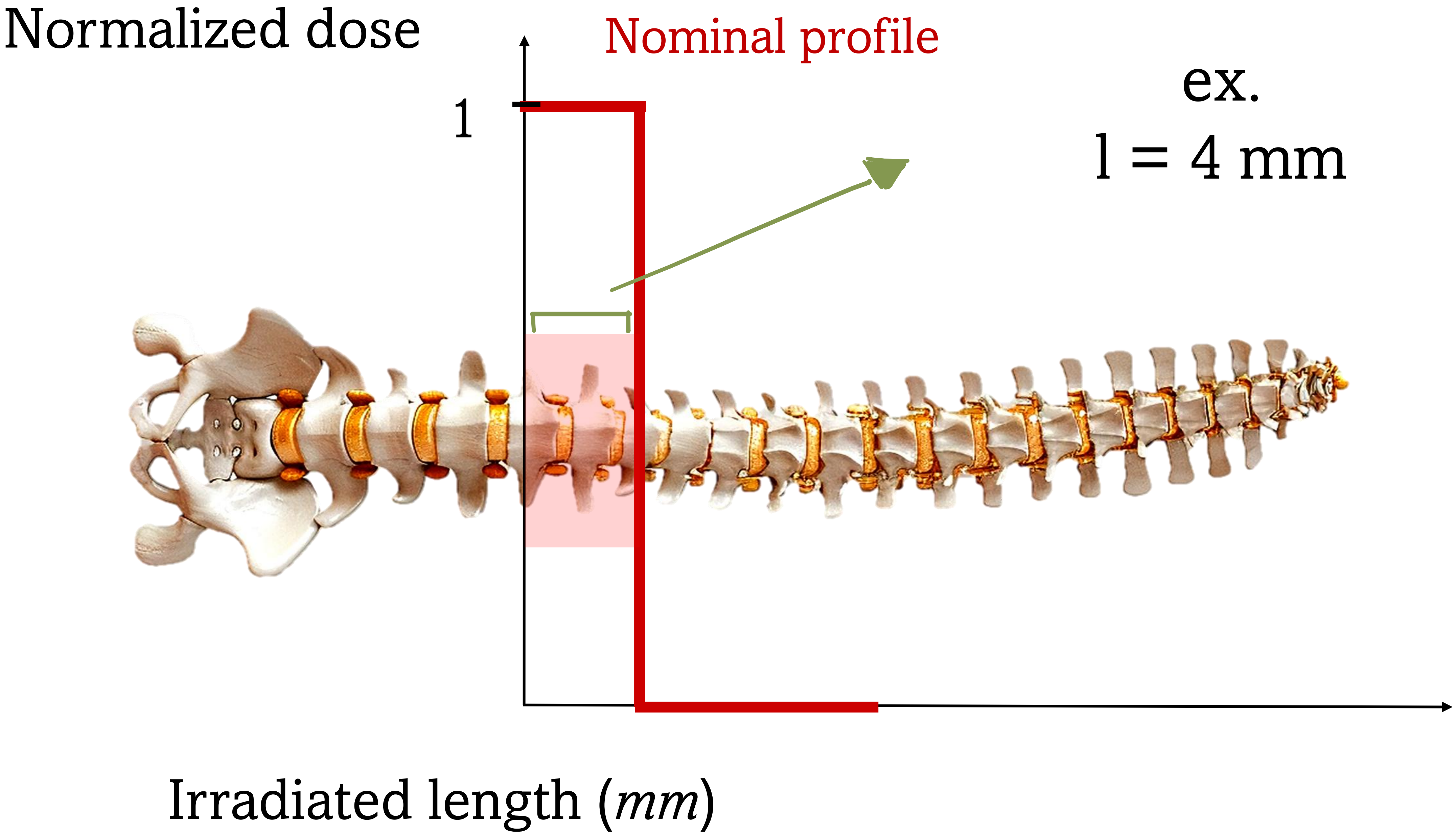
NO
volume effect

Single length

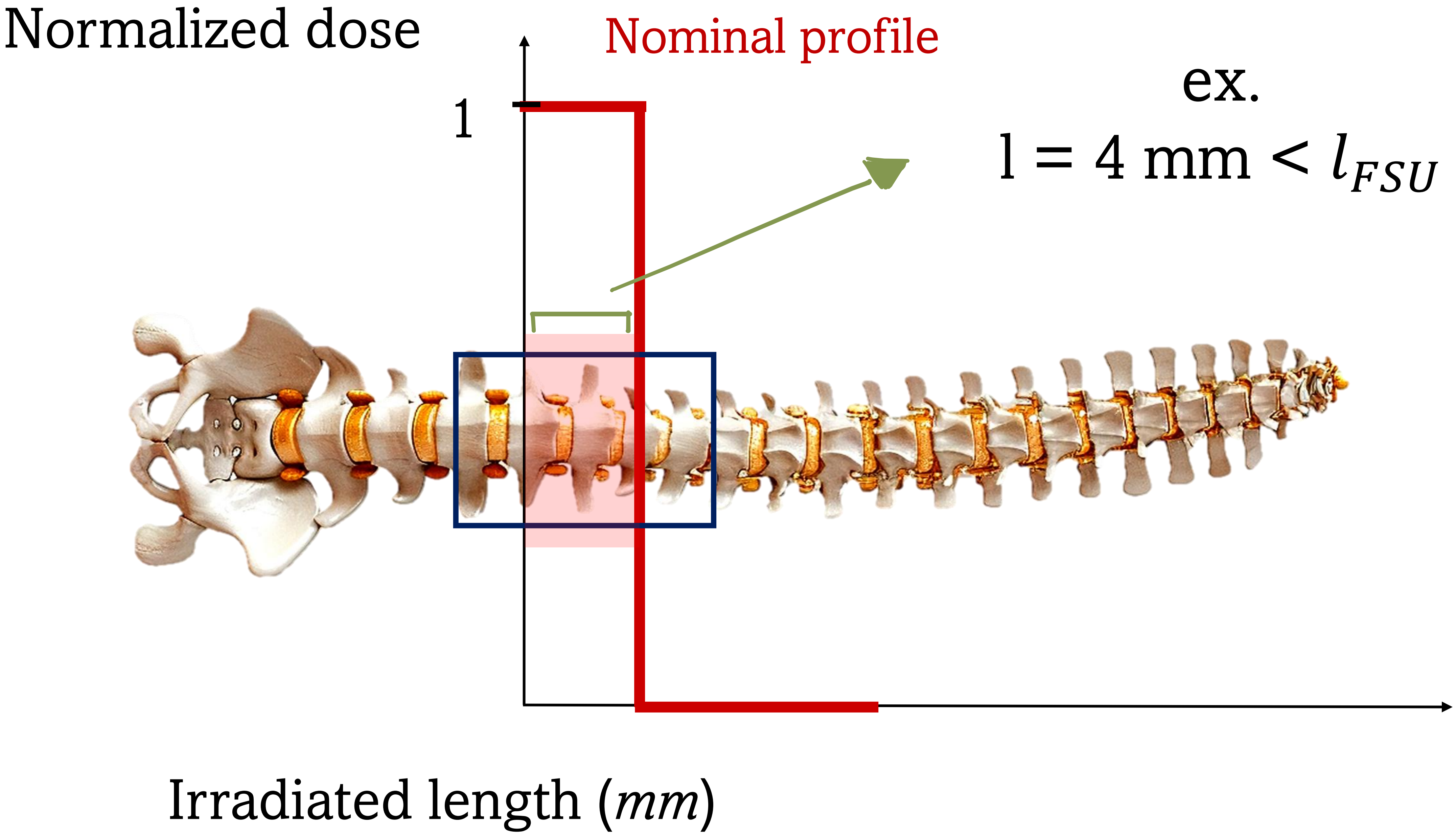
Volume effect

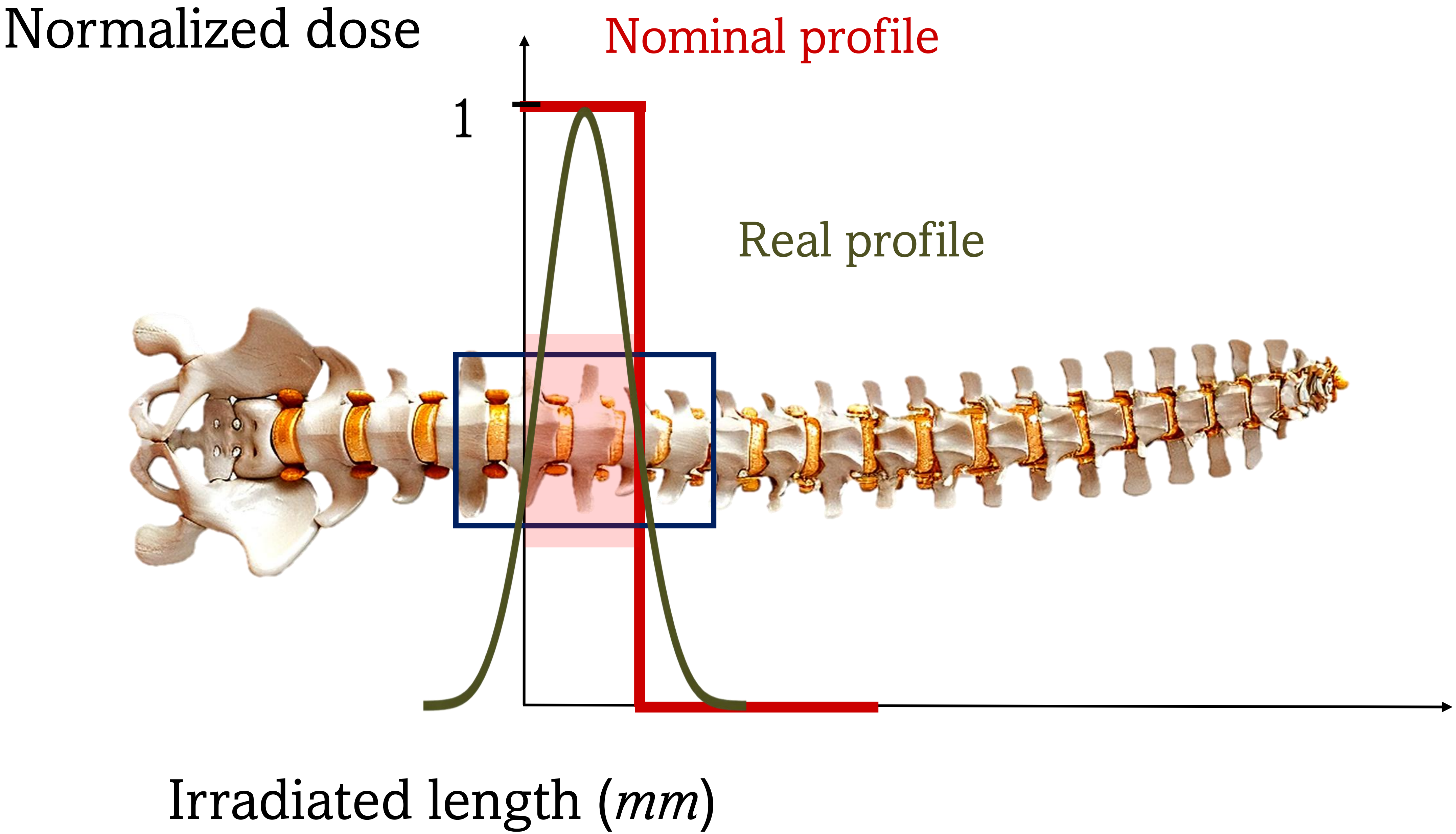
$l > 8\ mm$

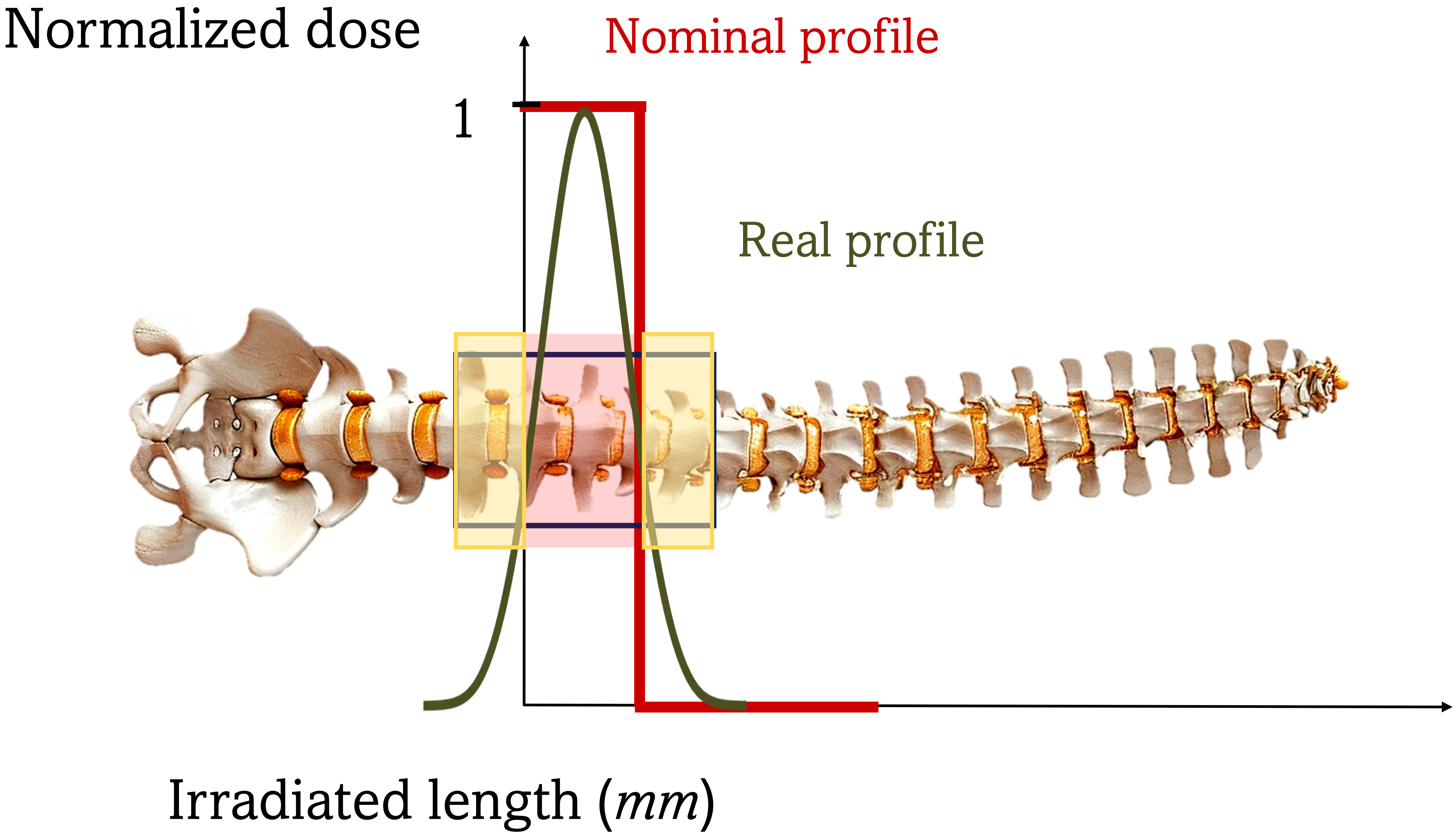
$l < 8\ mm$

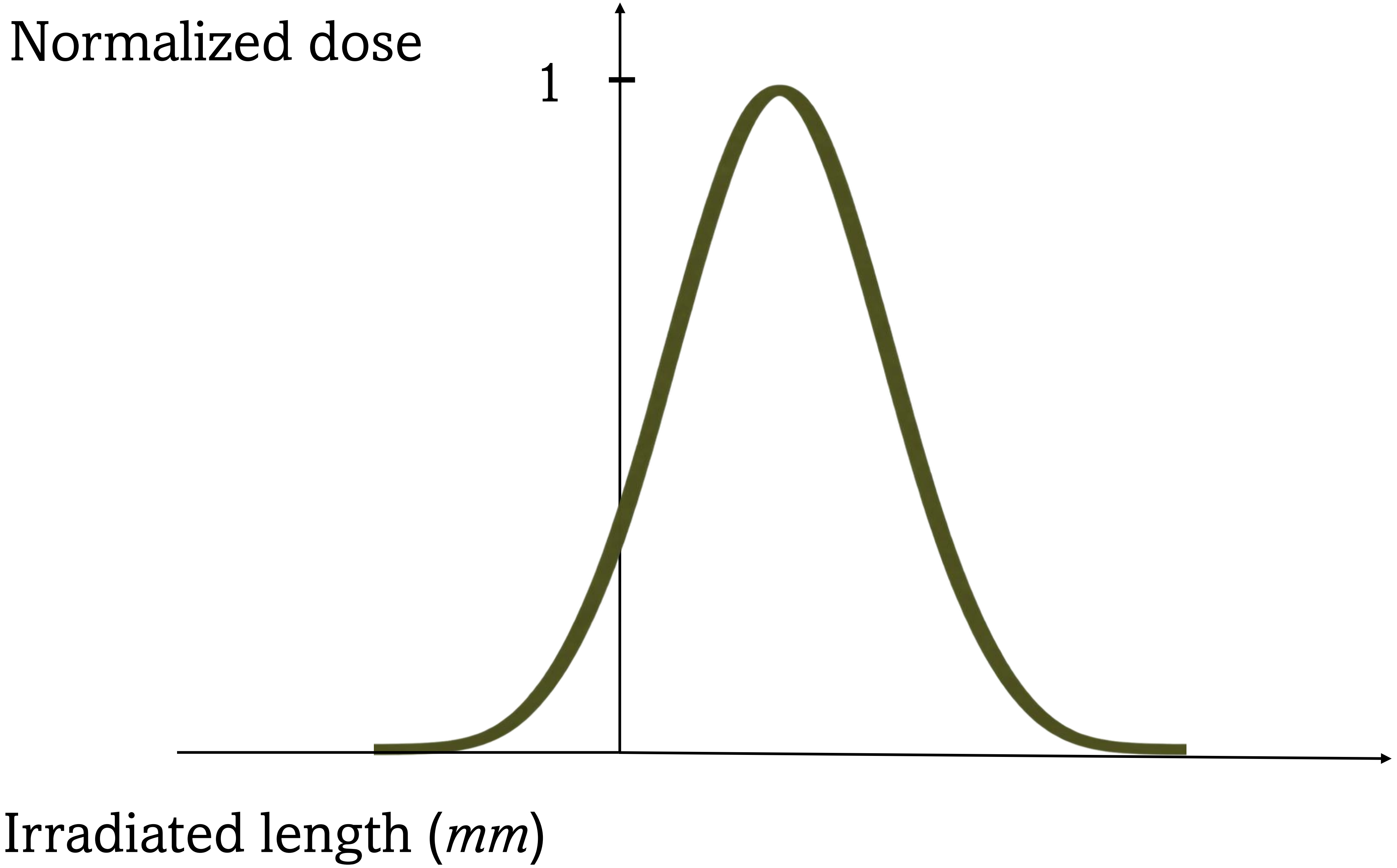


Normalized dose
Nominal profile
1
ex.
l = 4 mm
Irradiated length (*mm*)

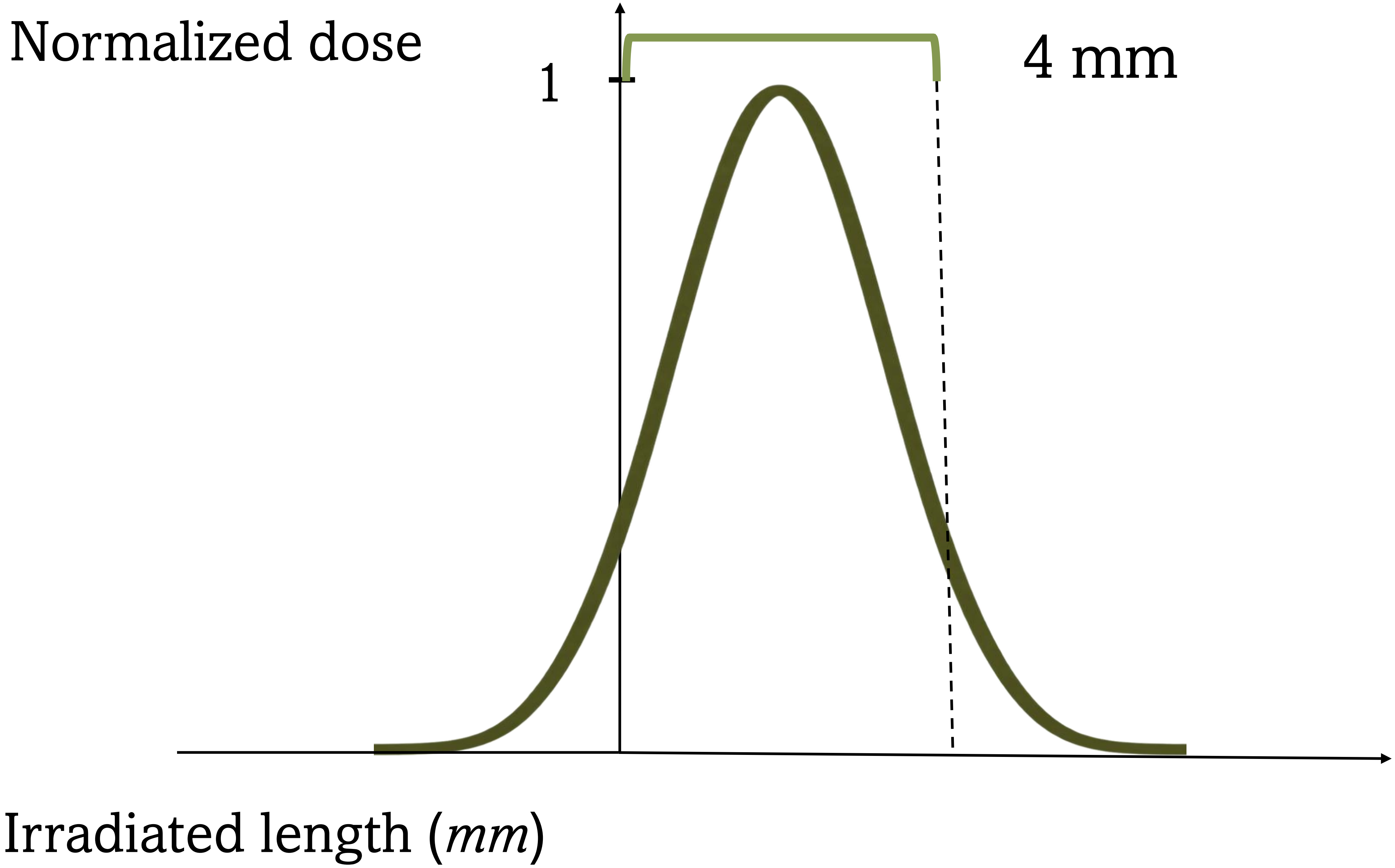

Normalized dose
Nominal profile
1
ex.
$l = 4 \text{ mm} < l_{FSU}$
Irradiated length (mm)

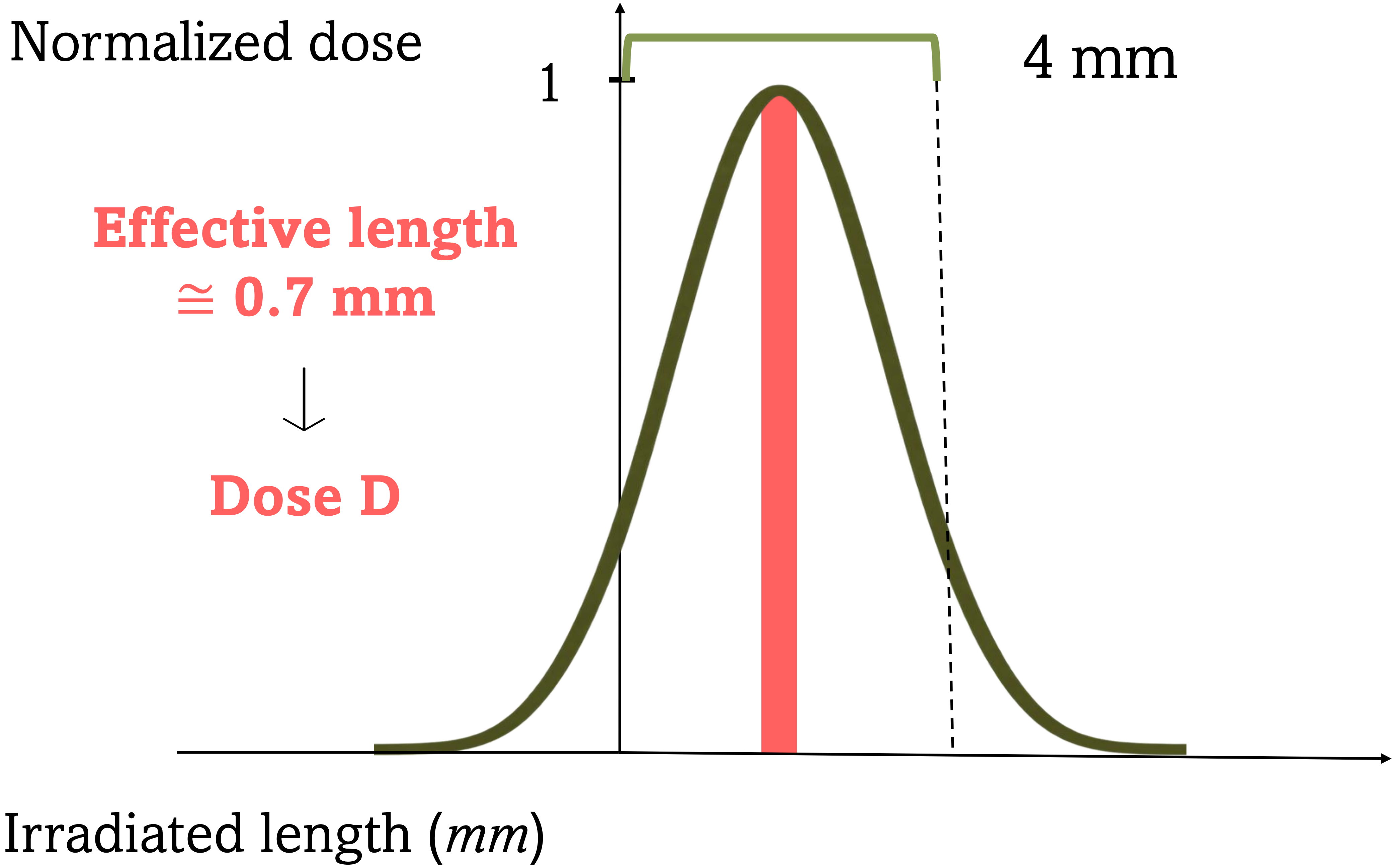

Normalized dose
Nominal profile
1
Real profile
Irradiated length (*mm*)


Normalized dose
Nominal profile
1
Real profile
Irradiated length (*mm*)



Normalized dose
1
Irradiated length (mm)


Normalized dose
1
4 mm
Irradiated length (mm)

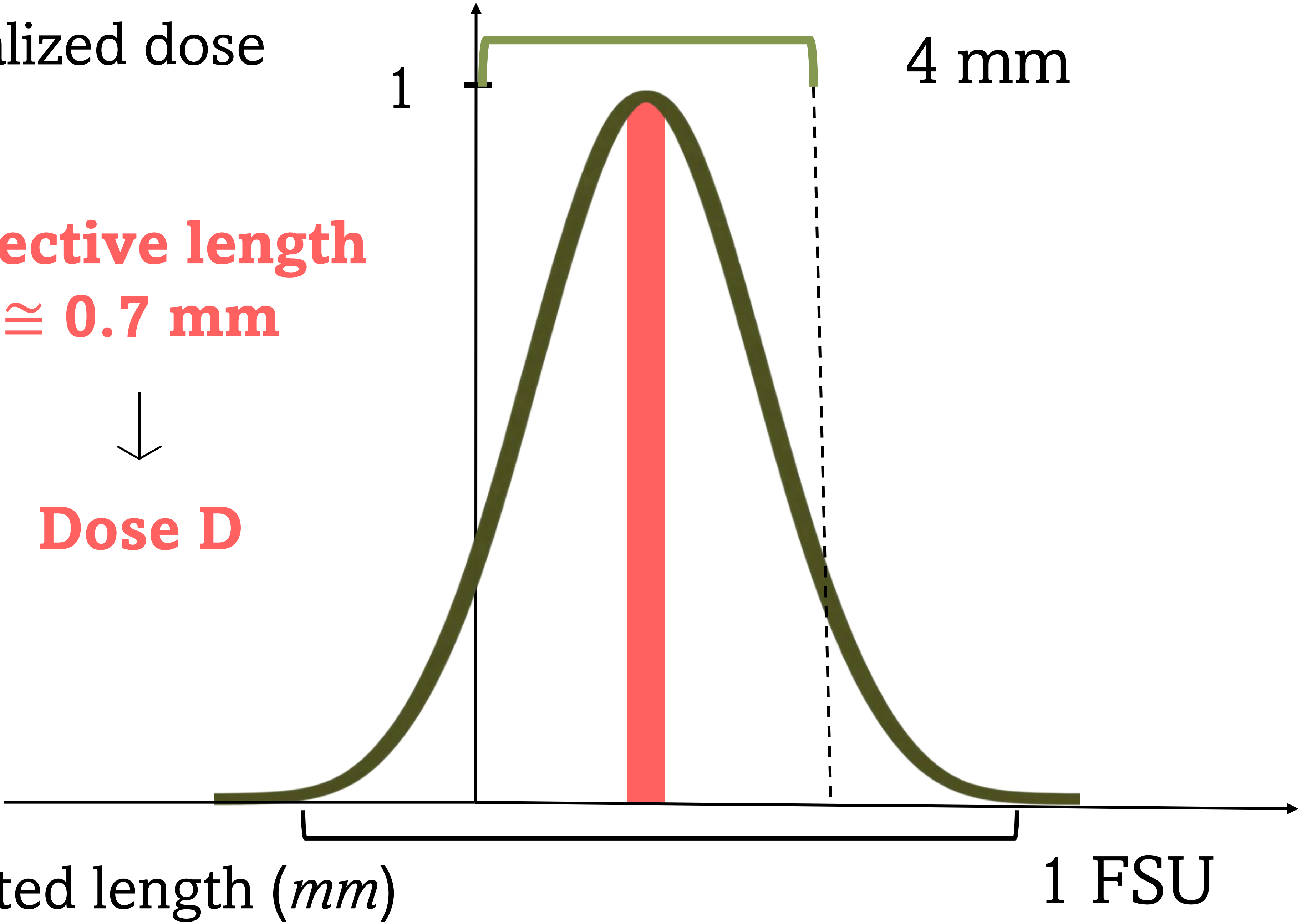

Normalized dose
1
4 mm
Effective length
≅ 0.7 mm
Dose D
Irradiated length (mm)

Normalized dose

Effective length
≅ 0.7 mm

↓

Dose D



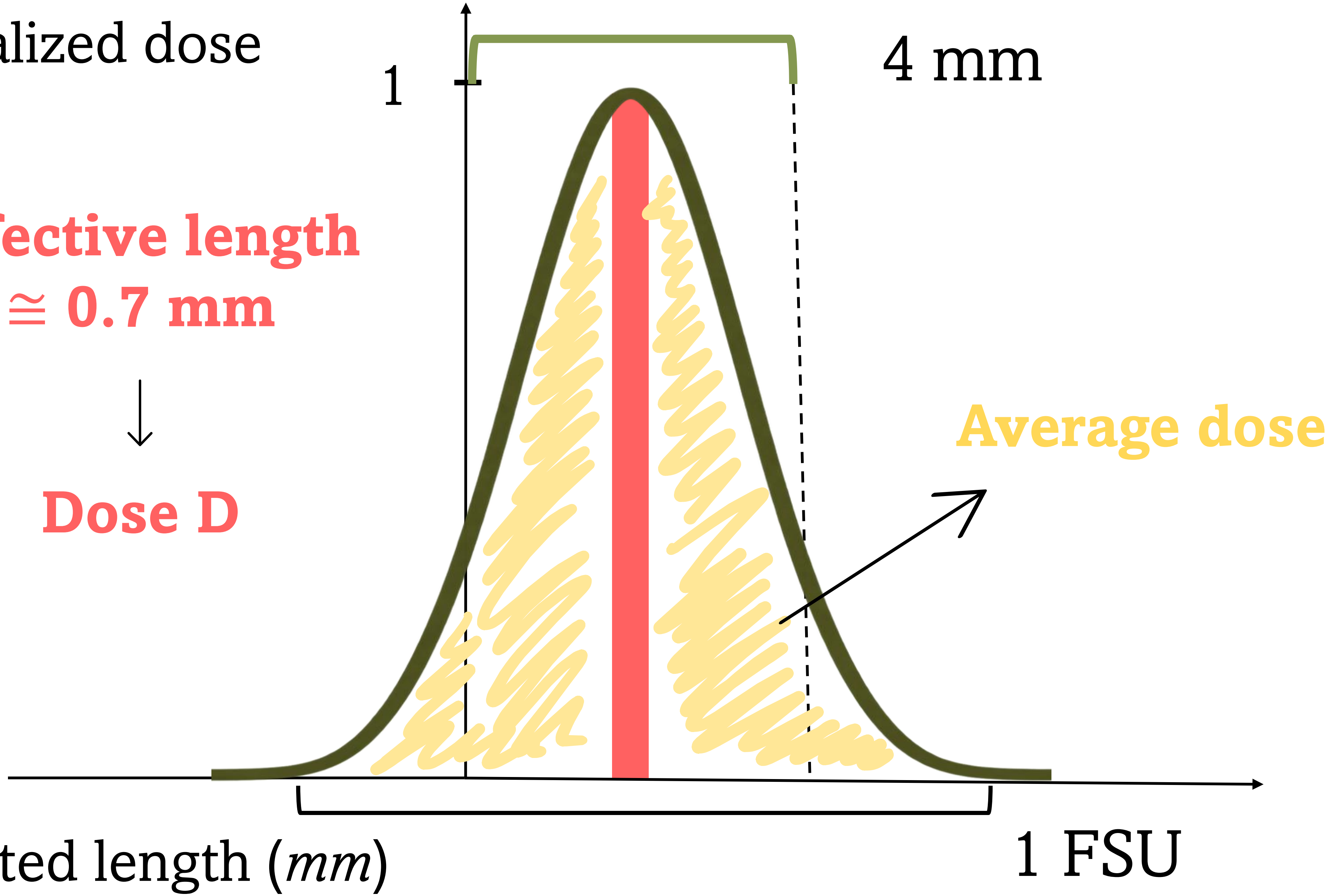
Irradiated length (mm)

Normalized dose

Effective length ≅ 0.7 mm

↓

Dose D



Irradiated length (*mm*)

Dose profiles

Our **new** NTCP model

Paralysis probability

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Alice Casali

New Model for the Volume Effect

New Model for the Volume Effect

$$\mathrm{NTCP} = 1 - \left(1 - \left(1 - e^{-\alpha_i nd - \beta_i nd^2} \right)^{p \cdot t} \cdot \left(1 - e^{-\alpha_i nd_{part} - \beta_i nd_{part}^{\;2}} \right)^{(1-p) \cdot t} \right)^{1}$$

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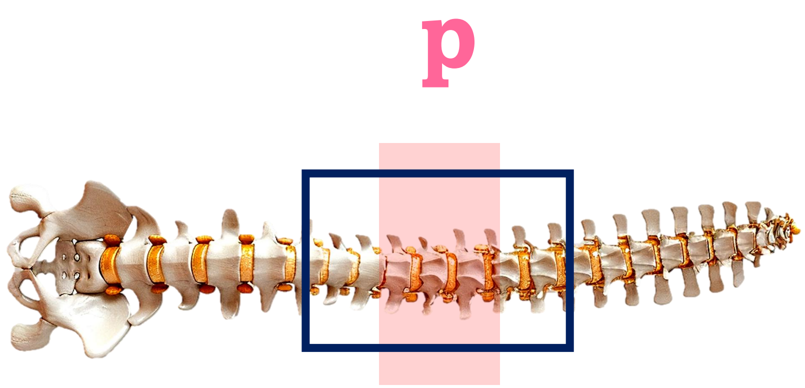
Alice Casali

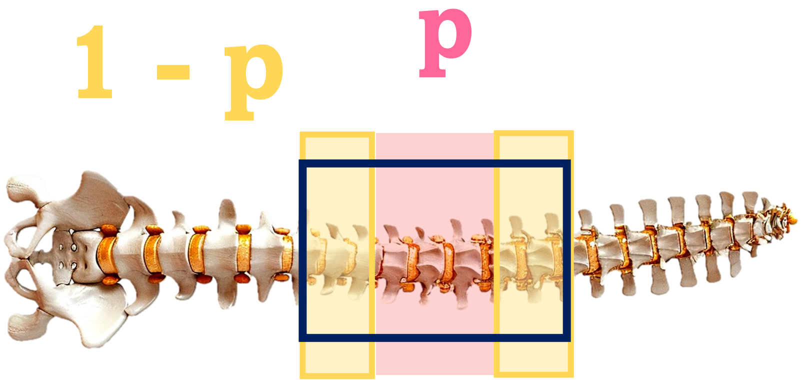
New Model for the Volume Effect

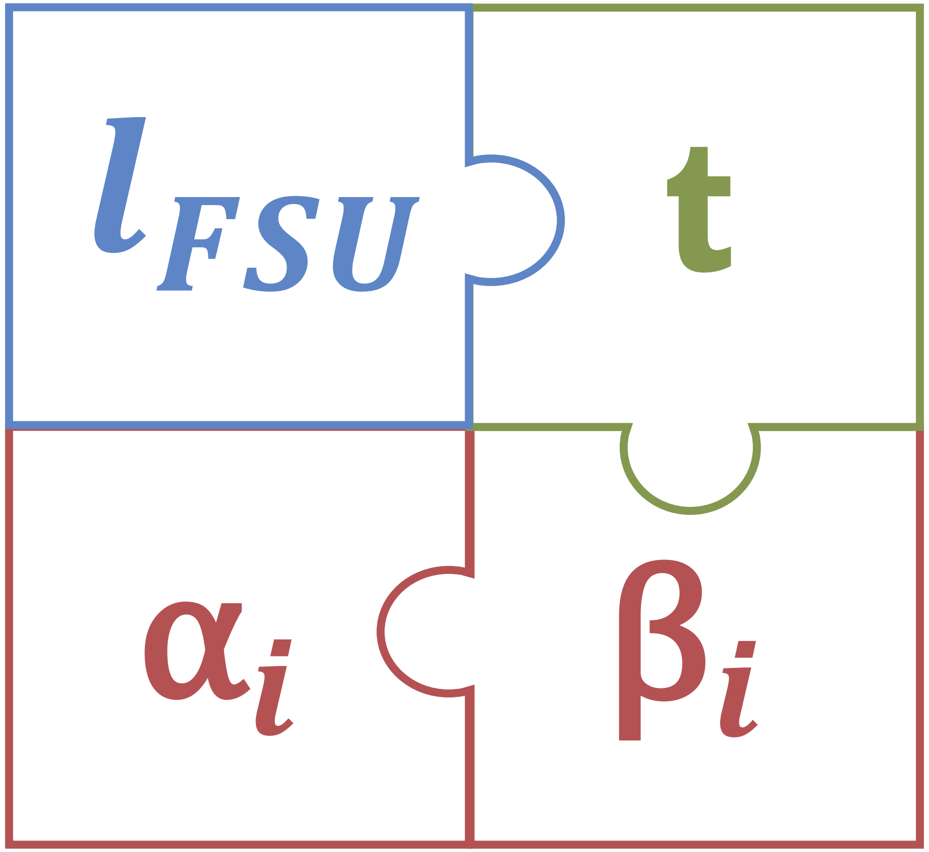
$$\mathrm{NTCP} = 1 - \left(1 - \left(1 - e^{-\alpha_i n d - \beta_i n d^2}\right)^{p \cdot t} \cdot \left(1 - e^{-\alpha_i n d_{part} - \beta_i n d_{part}^{\;2}}\right)^{(1-p) \cdot t}\right)^{1}$$



New Model for the Volume Effect

$$
NTCP = 1 - \left(1 - \left(1 - e^{-\alpha_i n d - \beta_i n d^2} \right)^{p \cdot t} \cdot \left(1 - e^{-\alpha_i n d_{part} - \beta_i n d_{part}{}^2} \right)^{(1 - p) \cdot t} \right)^1
$$



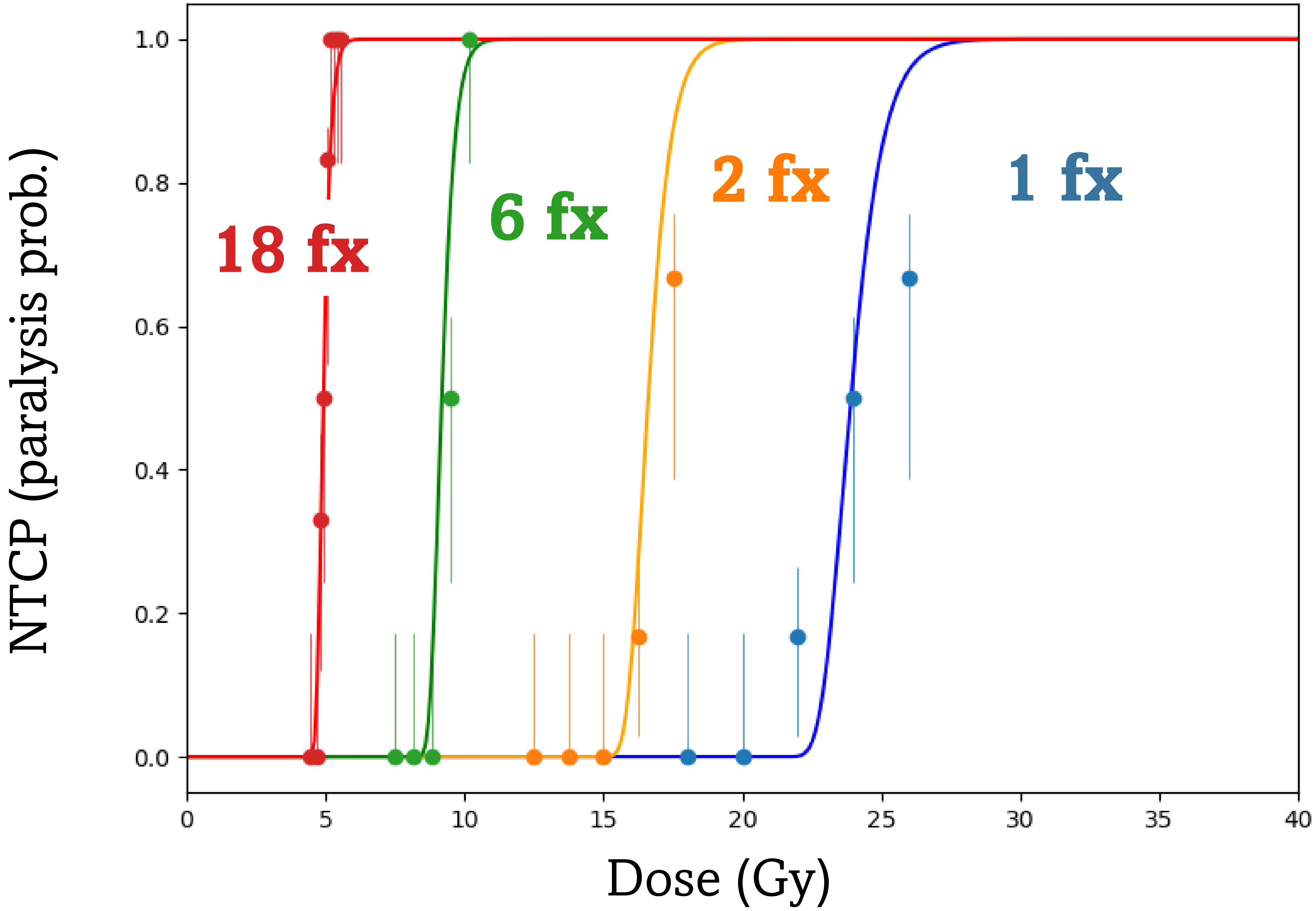

l_{FSU}
t
α_i
β_i

Fit **new** model

Photon NTCP data

1 irradiation length

> 8 mm

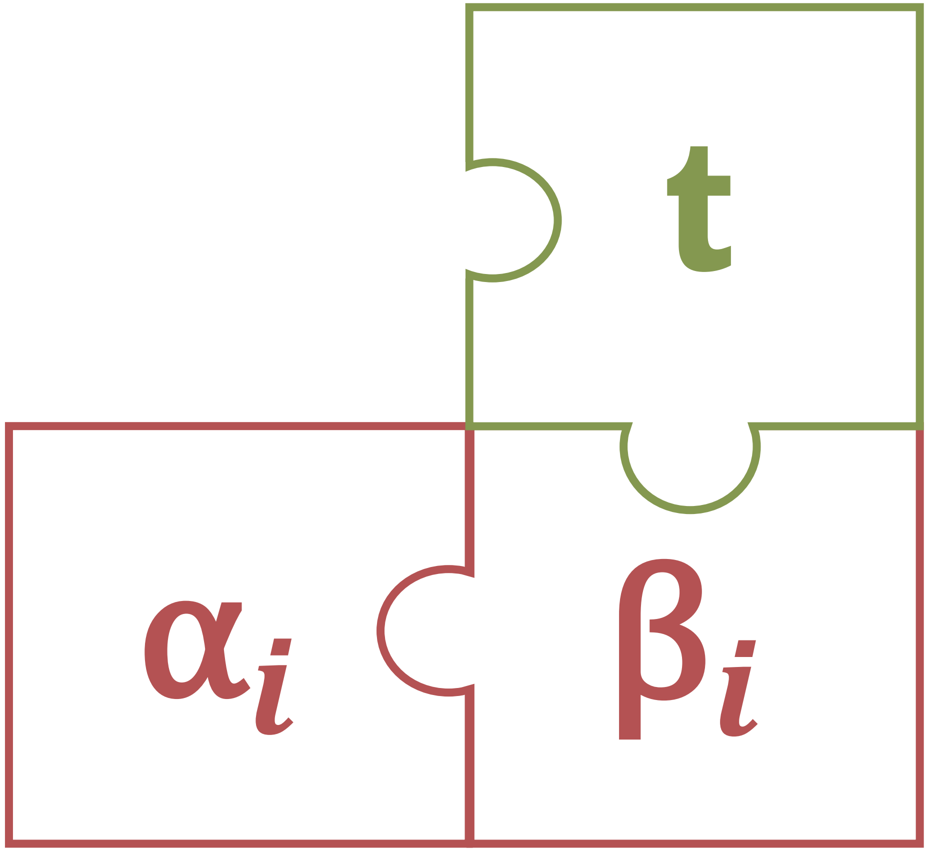

NTCP (paralysis prob.)
1.0
0.8
0.6
0.4
0.2
0.0
18 fx
6 fx
2 fx
1 fx
0
5
10
15
20
25
30
35
40
Dose (Gy)

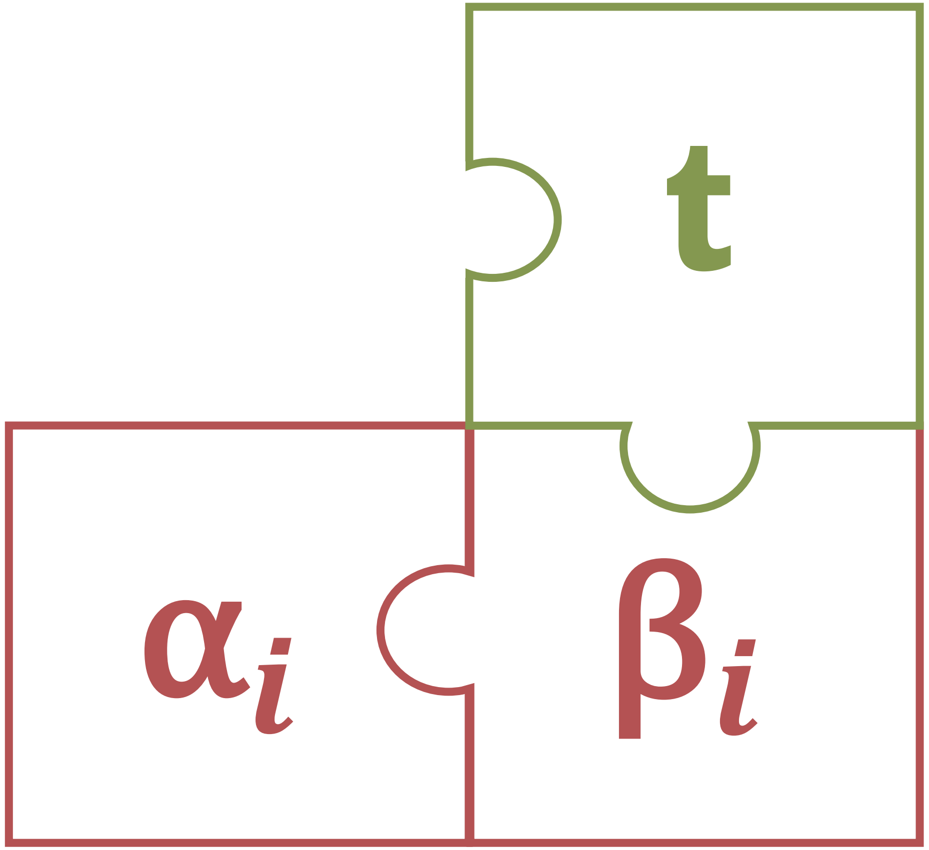
Fit **new** model

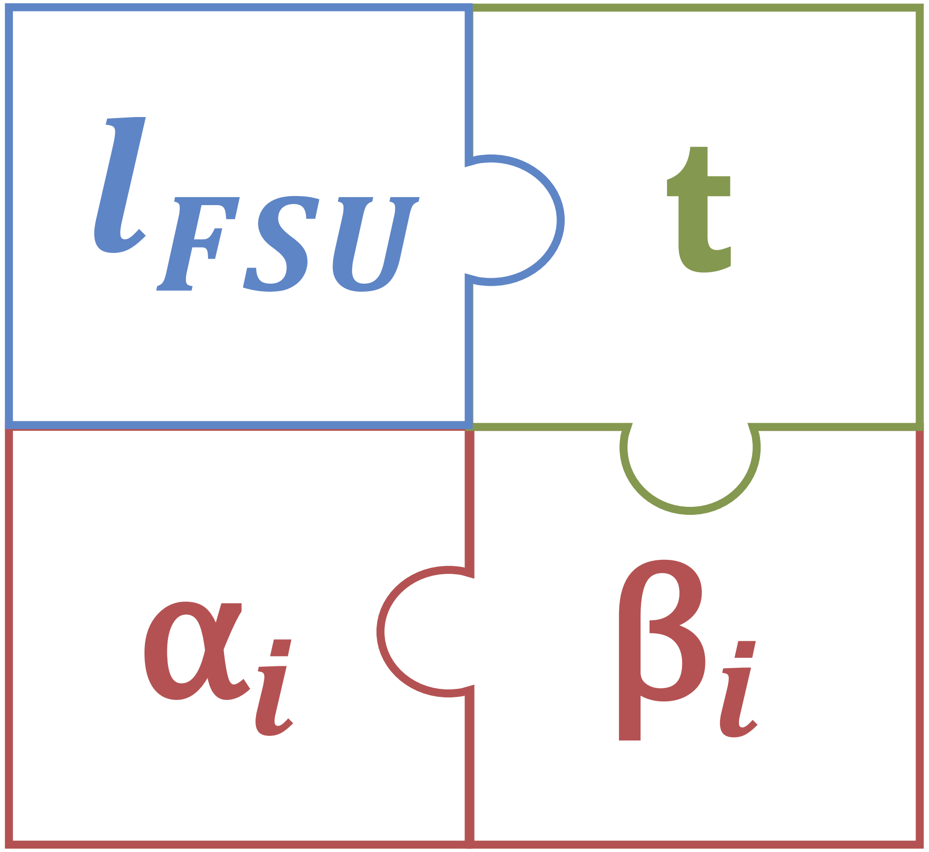
Photon NTCP data

1 irradiation length
> 8 mm

→

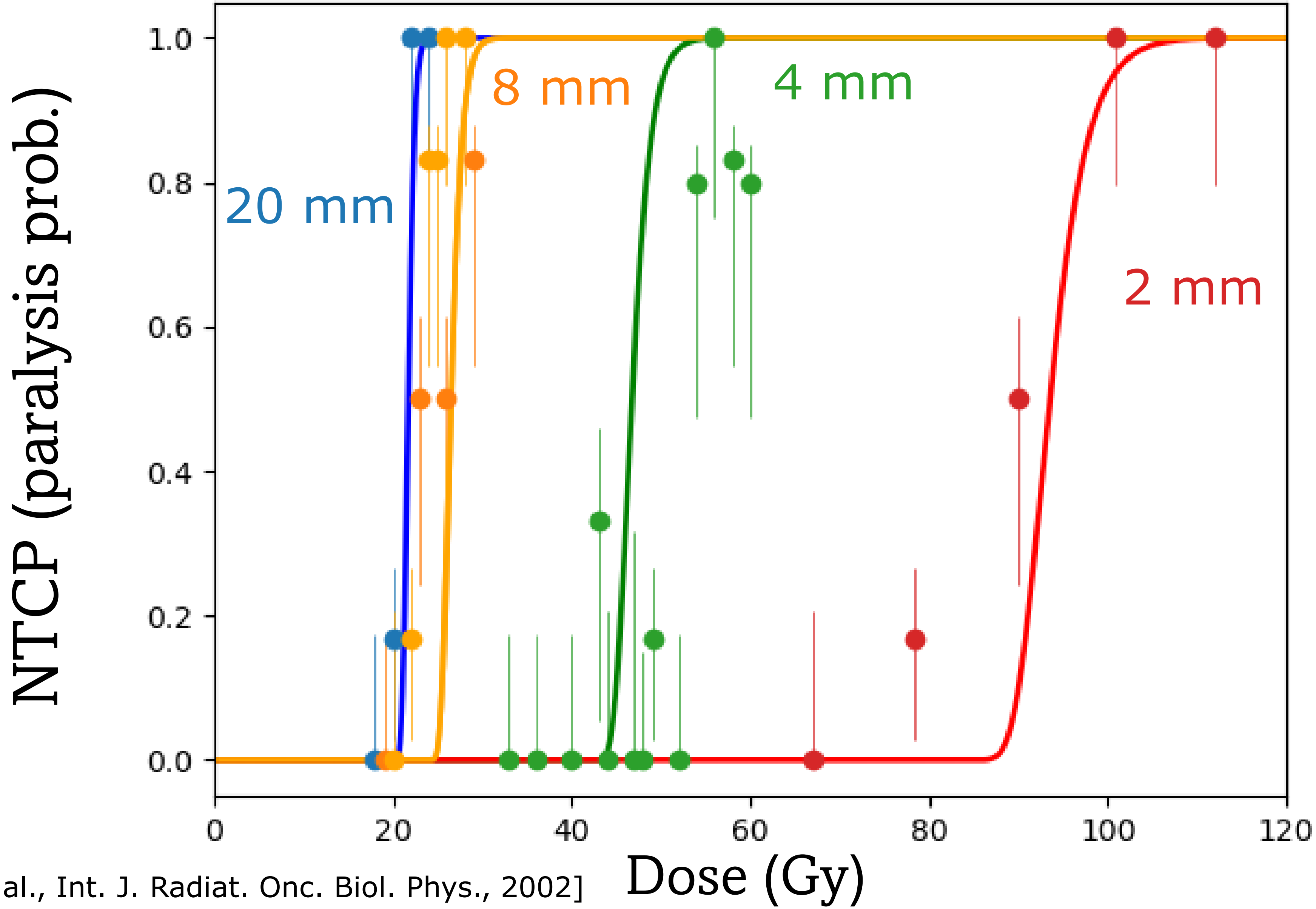



t
α_i
β_i



Multiple irradiation lengths < 8 mm

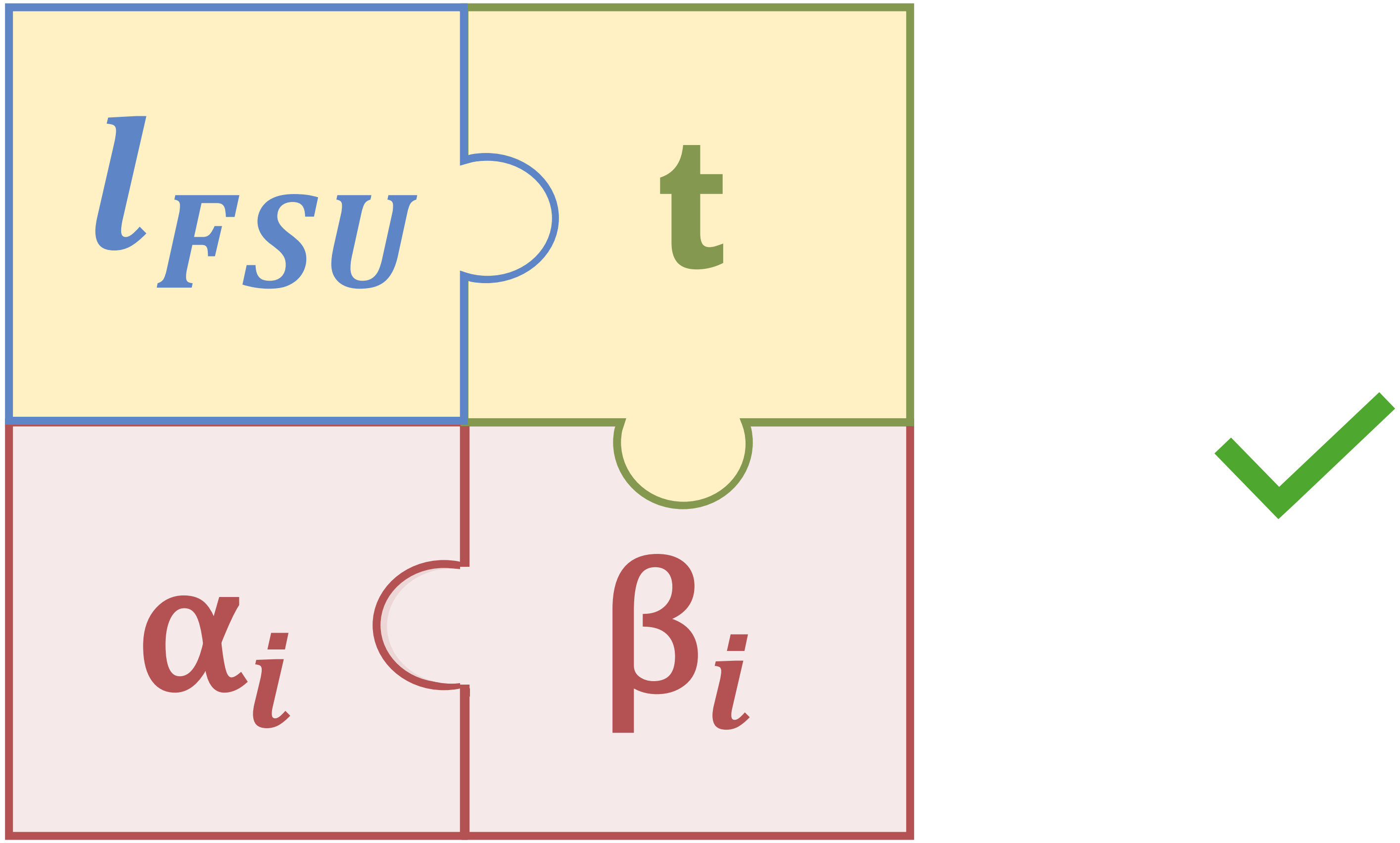
Fit across multiple irradiated lengths



1 free parameter

$l_{FSU} \cong 7.5$ mm

[Bijl et al., Int. J. Radiat. Onc. Biol. Phys., 2002]


l_{FSU}
t
α_i
β_i

Predictions

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Alice Casali

Predictions

Bath and shower

[Bijl et al., Int. J. Radiat. Onc. Biol. Phys., 2003]

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Predictions

Bath and shower

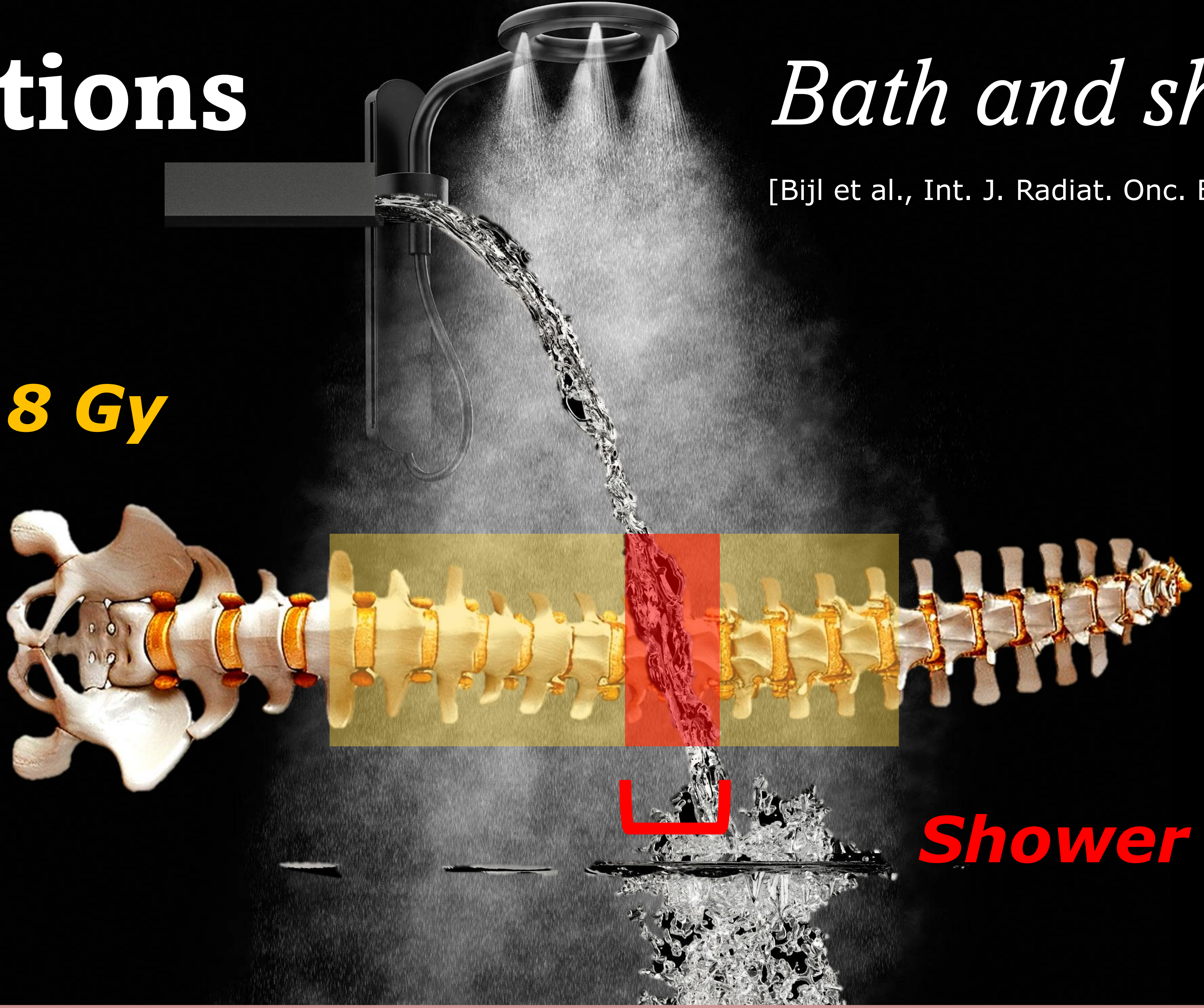
[Bijl et al., Int. J. Radiat. Onc. Biol. Phys., 2003]

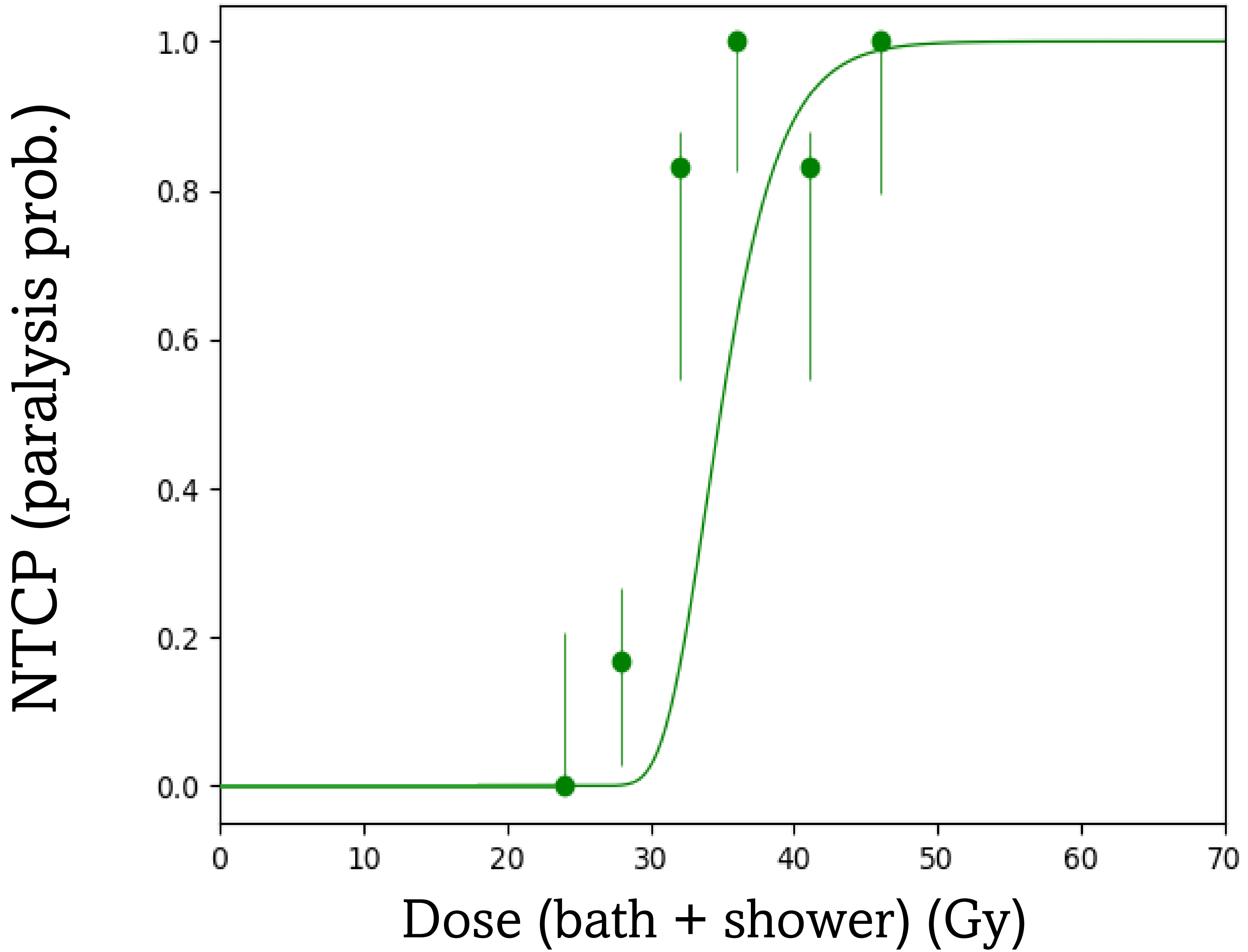
Bath 18 Gy

Predictions

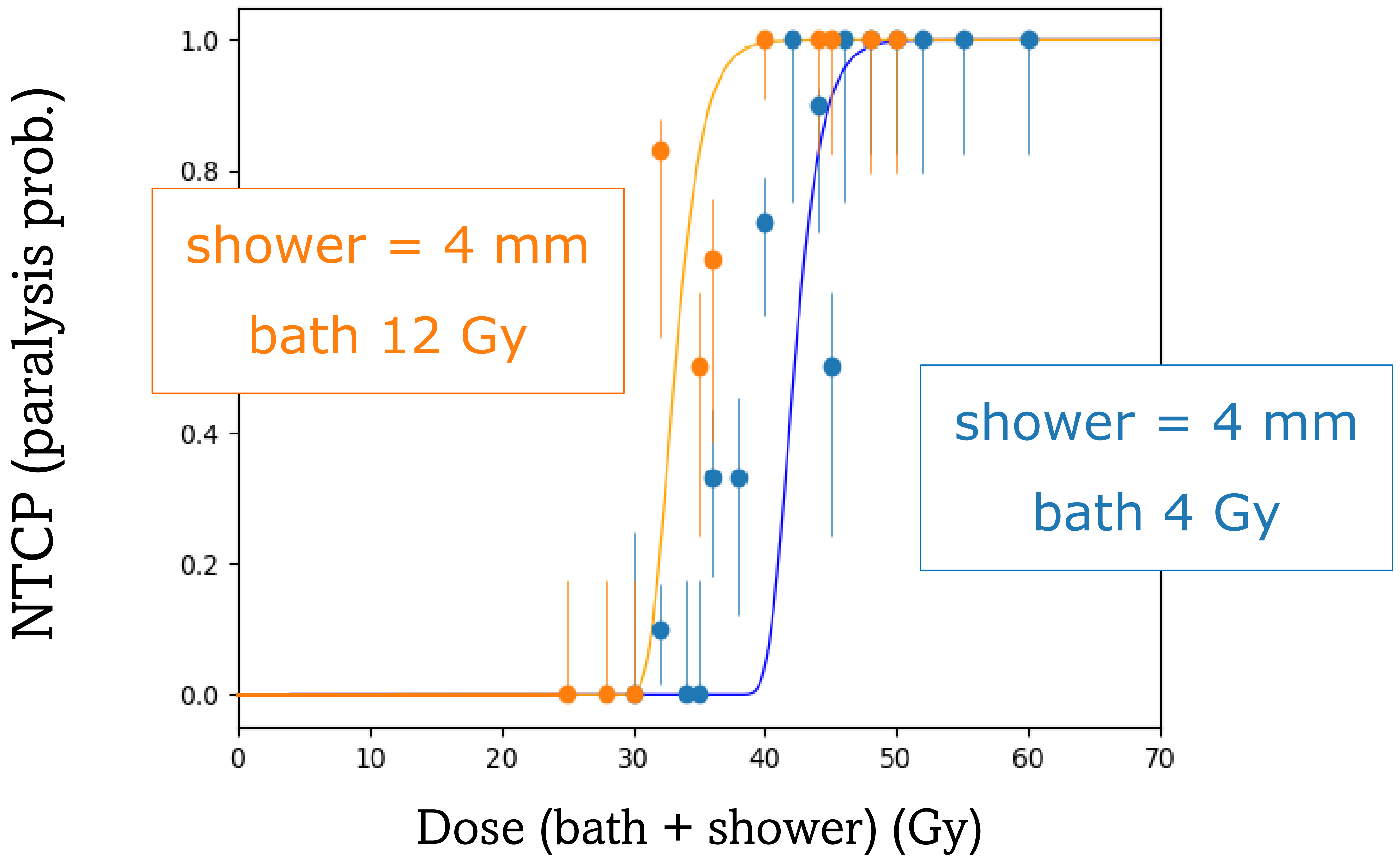
Bath and shower

[Bijl et al., Int. J. Radiat. Onc. Biol. Phys., 2003]



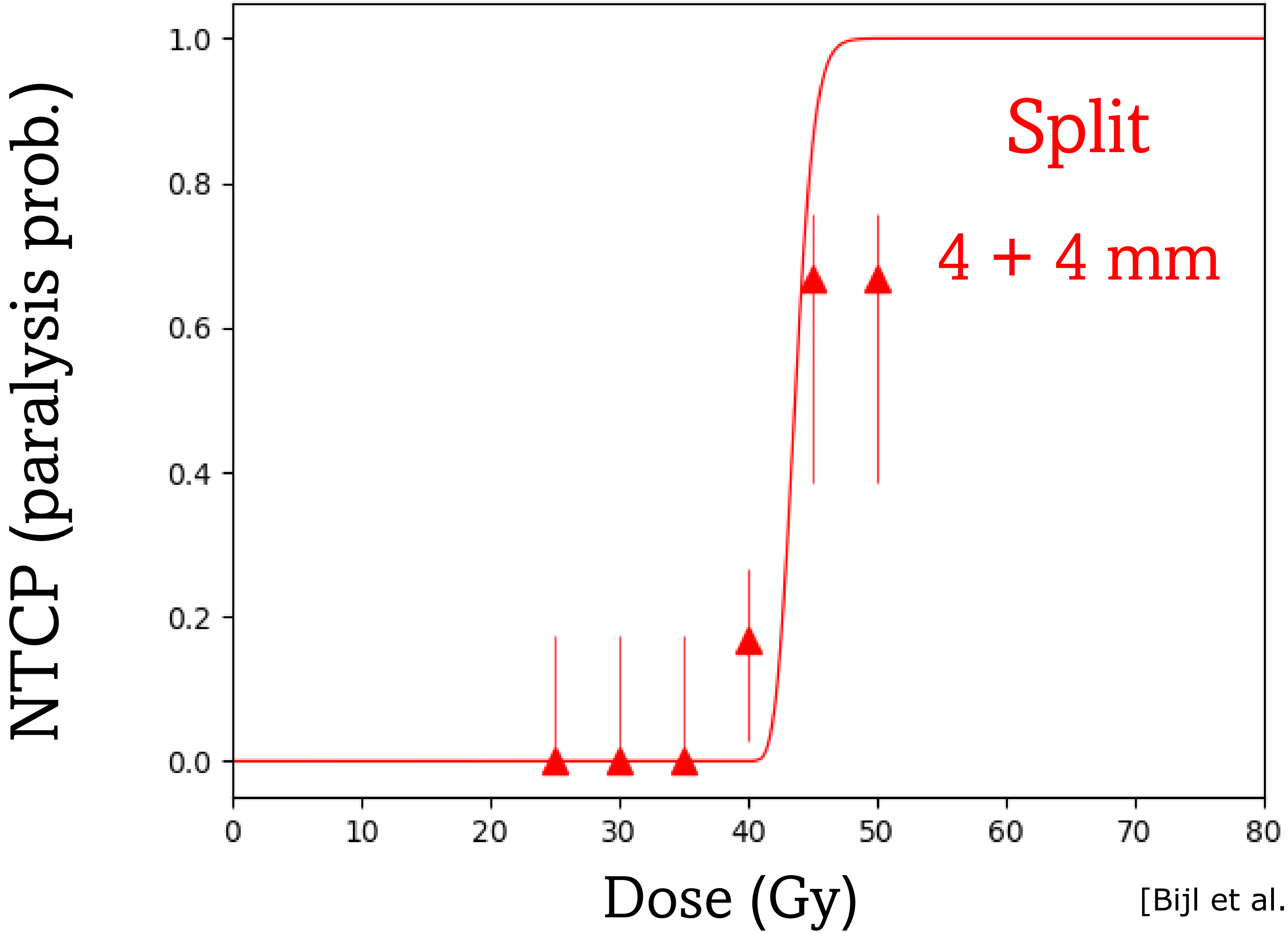


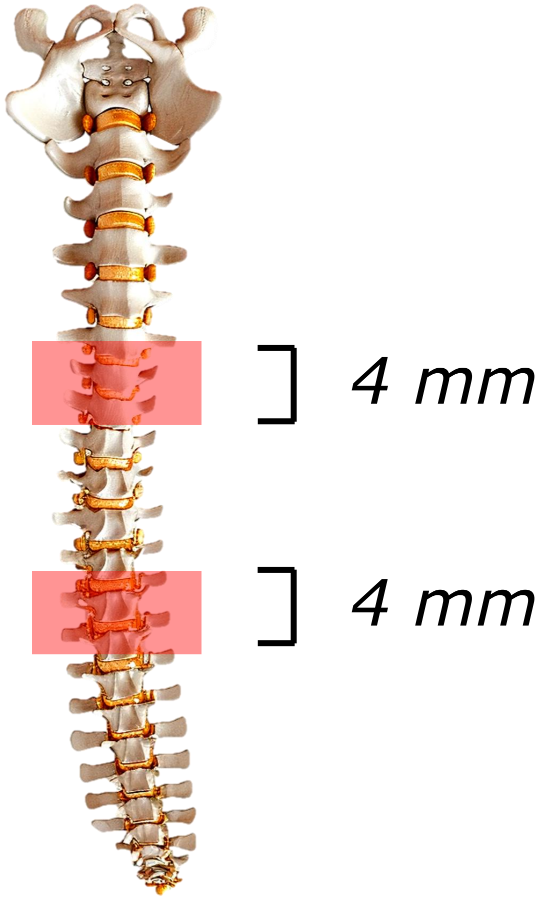
NO free parameters



NTCP (paralysis prob.)
1.0
0.8
0.4
0.2
0.0
0
10
20
30
40
50
60
70
Dose (bath + shower) (Gy)
shower = 4 mm
bath 12 Gy
shower = 4 mm
bath 4 Gy

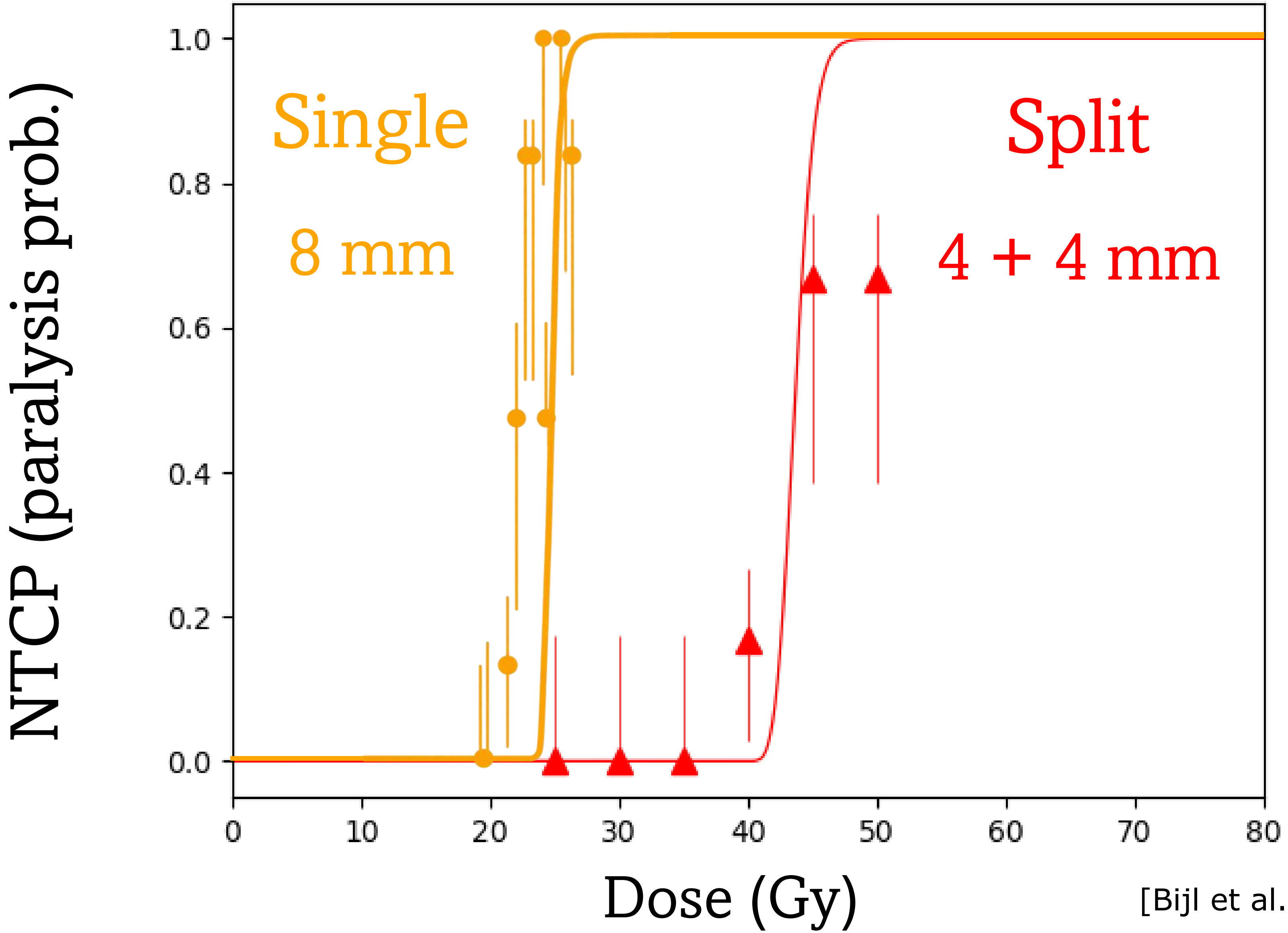
Split field

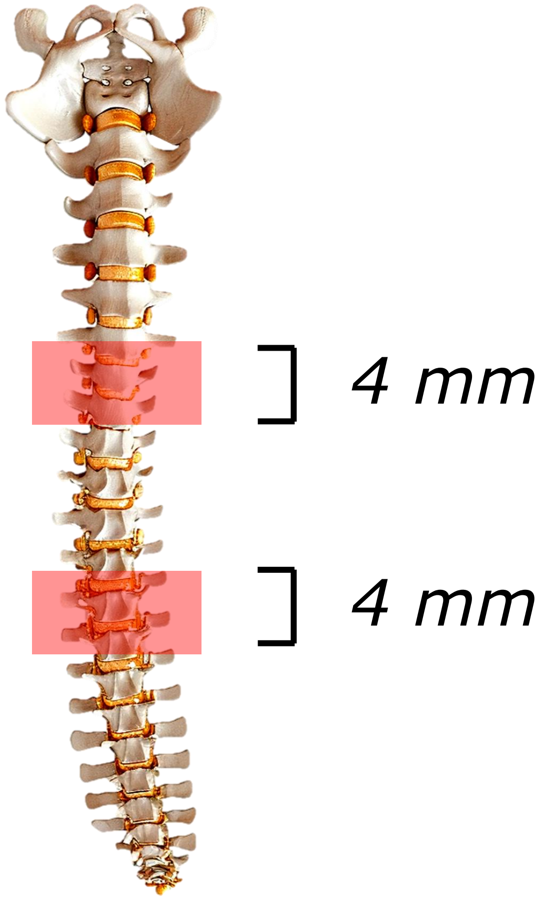




[Bijl et al., Int. J. Radiat. Onc. Biol. Phys., 2003]

Split field

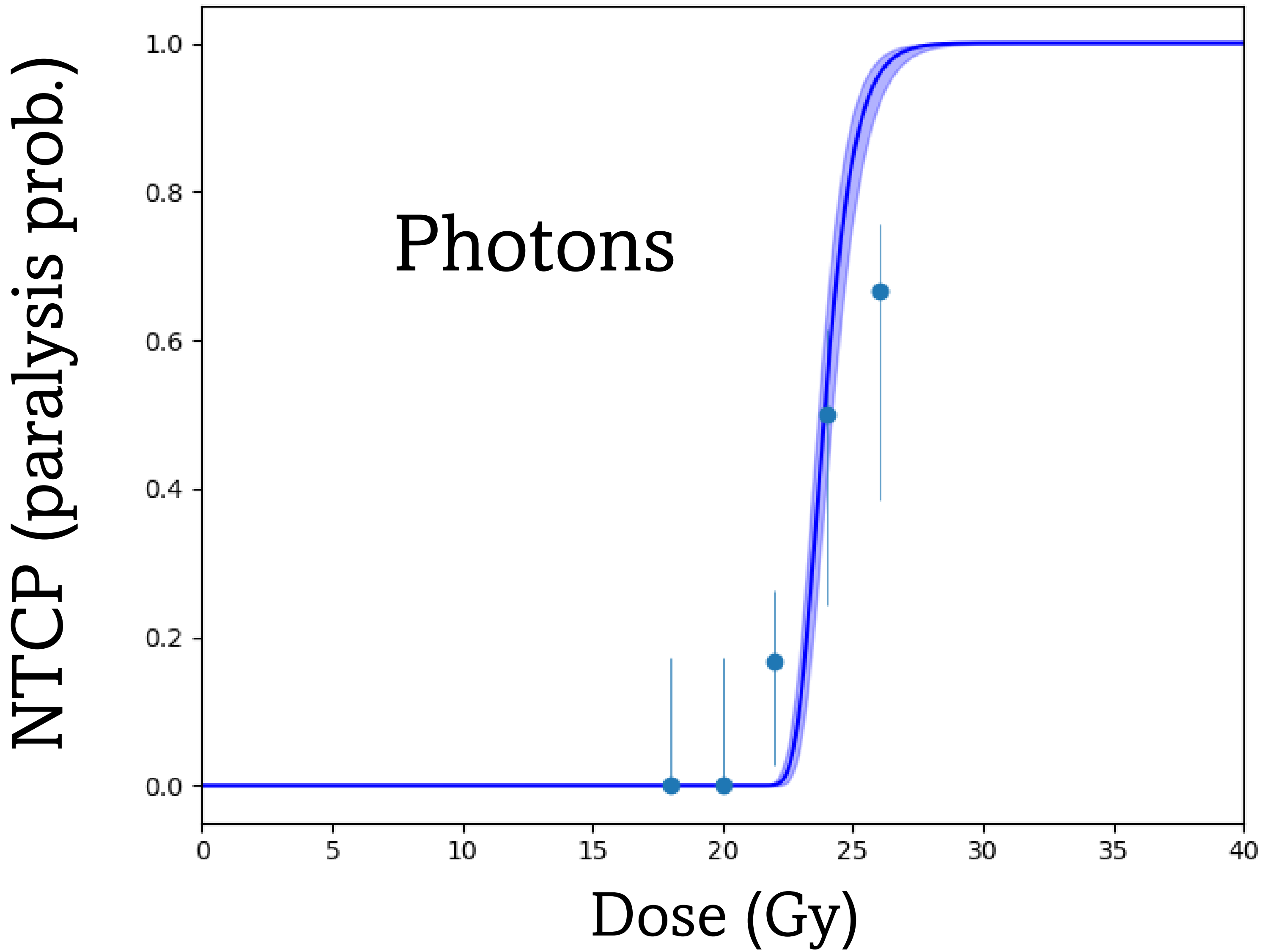




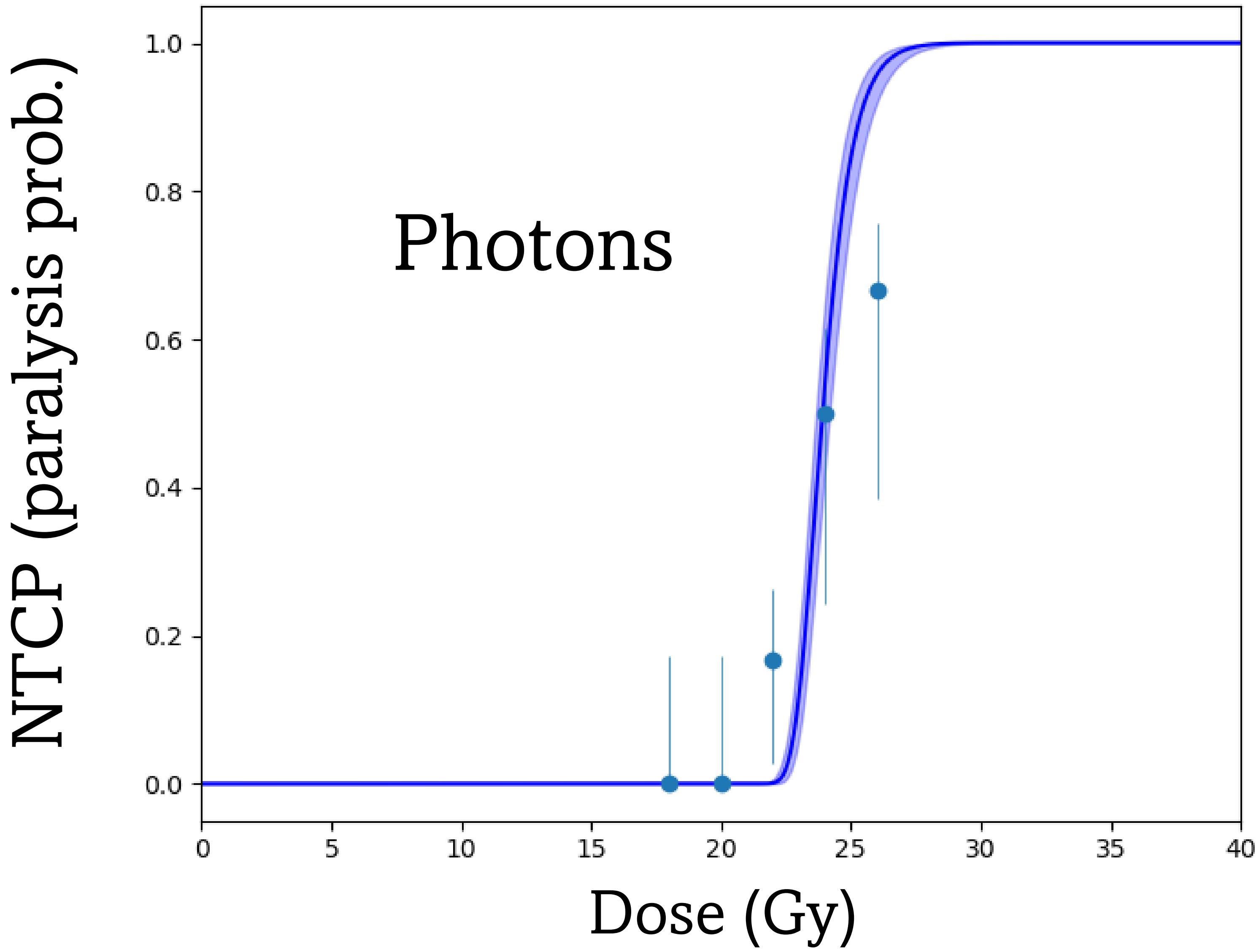
[Bijl et al., Int. J. Radiat. Onc. Biol. Phys., 2003]

How accurate are our predictions ?

Markov Chain Monte Carlo (MCMC)

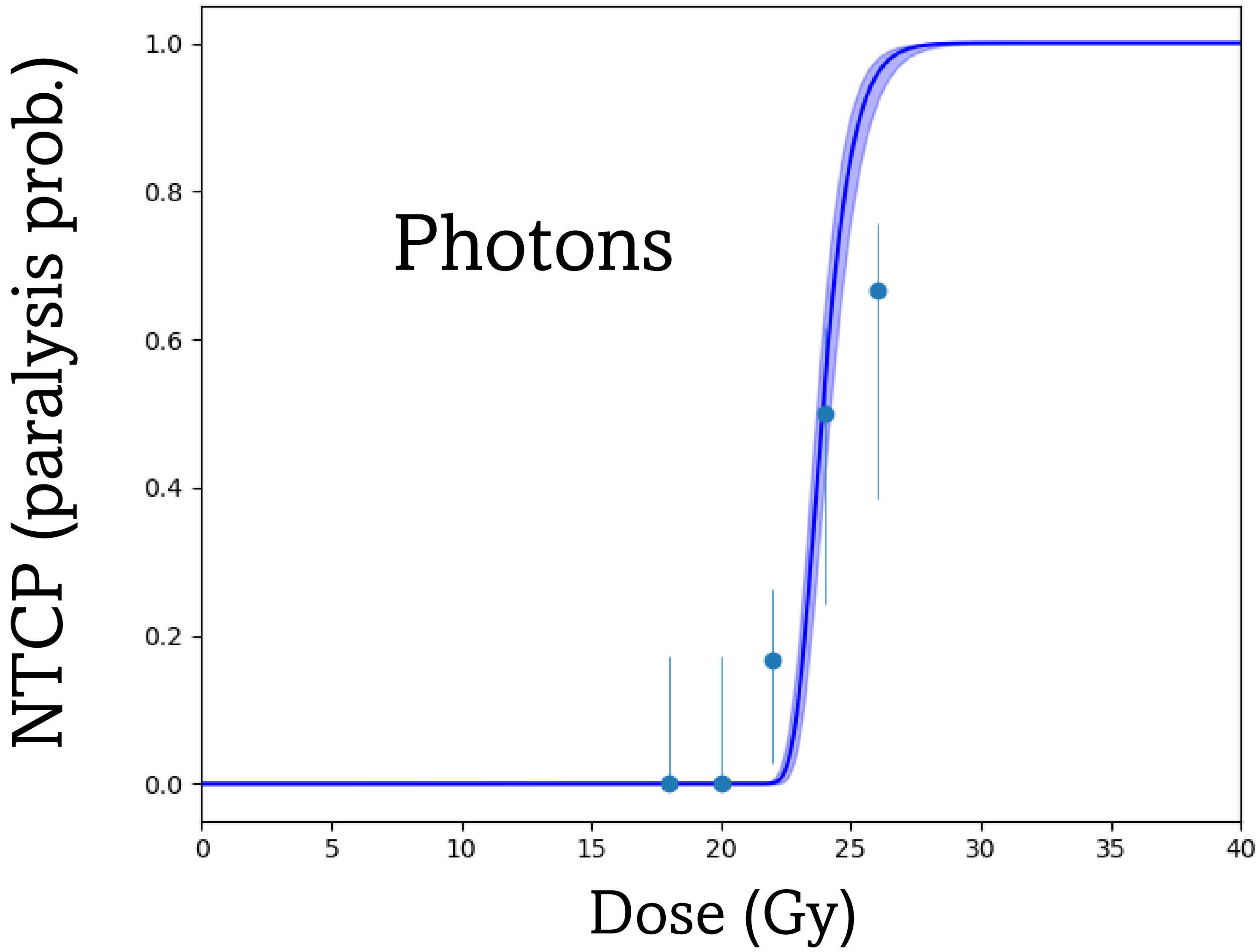


Markov Chain Monte Carlo (MCMC)



16° - 50° - 84°
percentiles

Markov Chain Monte Carlo (MCMC)



16° - 50° - 84°
percentiles

↓

1 σ

Other particles

Other particles

MCMC

$$(\alpha_X, \beta_X)_1$$
$$(\alpha_X, \beta_X)_2$$
$$\vdots$$
$$(\alpha_X, \beta_X)_n$$

Other particles

MCMC

$$\begin{bmatrix} (\alpha_X, \beta_X)_1 \\ (\alpha_X, \beta_X)_2 \\ \vdots \\ (\alpha_X, \beta_X)_n \end{bmatrix} \qquad \begin{bmatrix} (\alpha_i\ \beta_i)_1 \\ (\alpha_i, \beta_i)_2 \\ \vdots \\ (\alpha_i, \beta_i)_n \end{bmatrix}$$

Other particles

MCMC

$$\begin{bmatrix} (\alpha_X, \beta_X)_1 \\ (\alpha_X, \beta_X)_2 \\ \vdots \\ (\alpha_X, \beta_X)_n \end{bmatrix} \dashrightarrow \textbf{BIANCA} \dashrightarrow \begin{bmatrix} (\alpha_i\ \beta_i)_1 \\ (\alpha_i, \beta_i)_2 \\ \vdots \\ (\alpha_i, \beta_i)_n \end{bmatrix}$$

Other particles

MCMC

$(\alpha_X, \beta_X)_1$

1000000 h

BIANCA ----→

$(\alpha_i\ \beta_i)_1$

$(\alpha_i, \beta_i)_2$

⋮

$(\alpha_i, \beta_i)_n$

Other particles

MCMC

$(\alpha_X, \beta_X)_1$

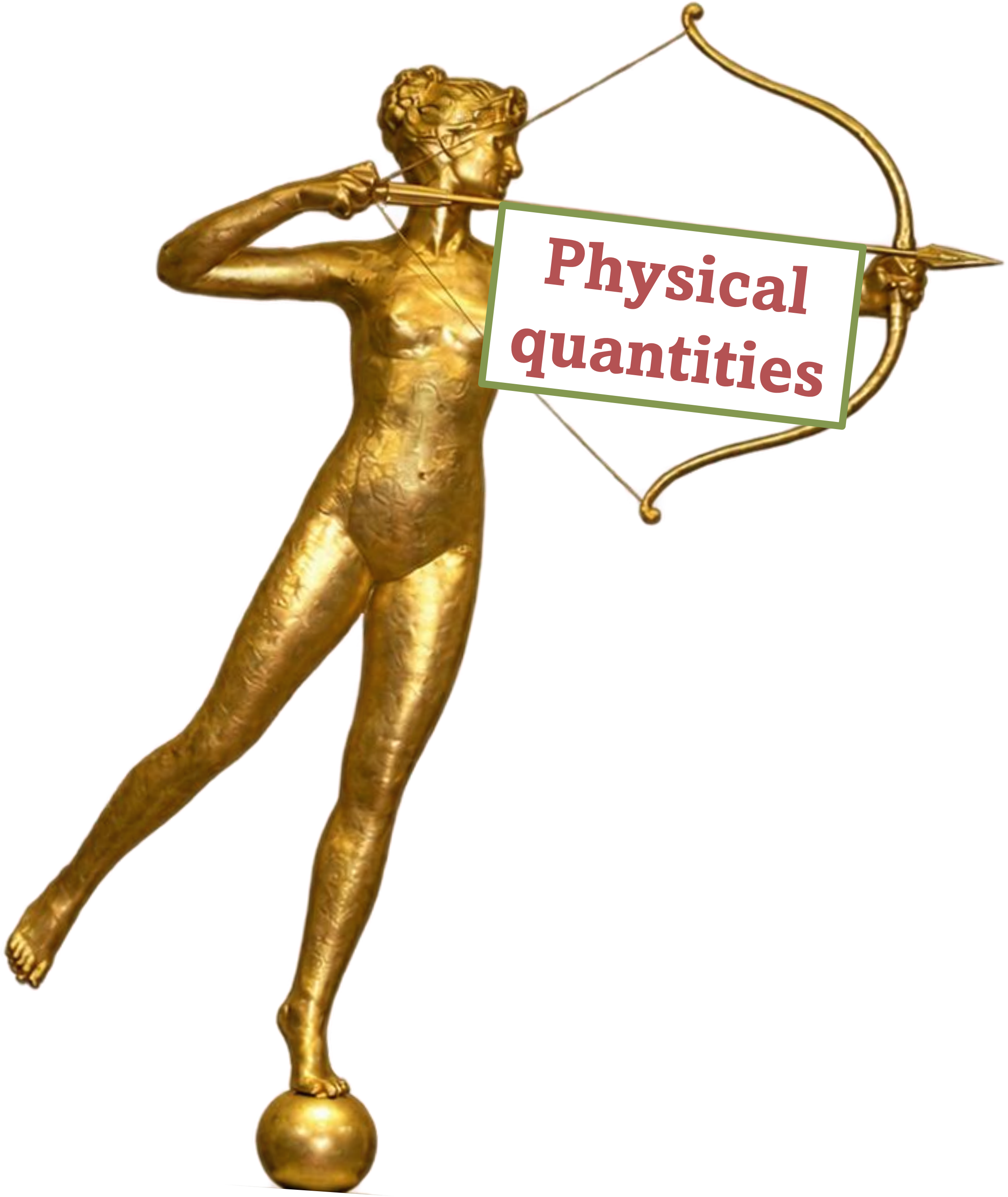
AI Transformer

BIANCA ----▸

⋮

$(\alpha_i, \beta_i)_n$

1000000 h



We can model the volume effect in the spinal cord

Physical quantities

We can model the volume effect in the spinal cord

What's next..?

Single length

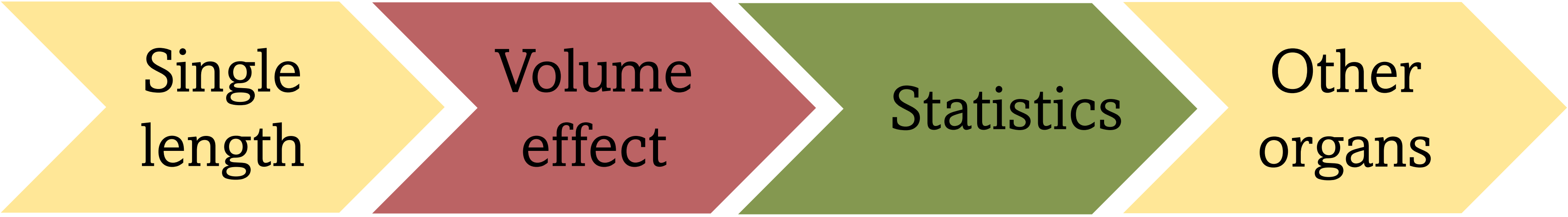
Volume effect

Statistics

$l > 8\ mm$

$l < 8\ mm$

What’s next..?



l **>** *8 mm*

l **<** *8 mm*

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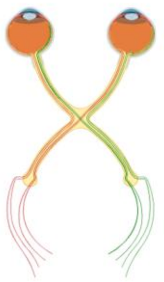
What’s next..?

Single length → Volume effect → Statistics → Other organs

l **>** *8 mm*

l **<** *8 mm*



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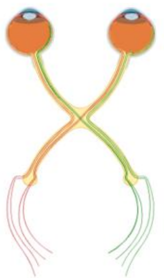
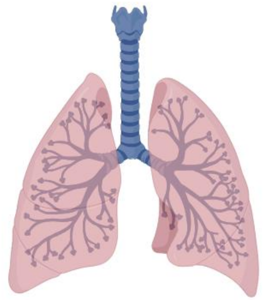
What's next..?

Single length → Volume effect → Statistics → Other organs

$l > 8\ mm$

$l < 8\ mm$





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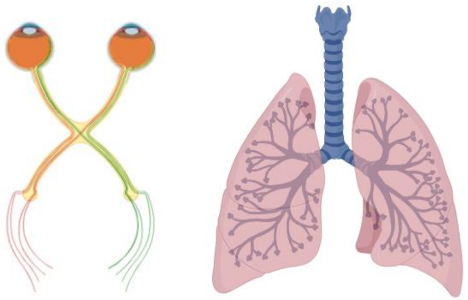
What's next..?

Single length → Volume effect → Statistics → Other organs

l **>** *8 mm*

l **<** *8 mm*



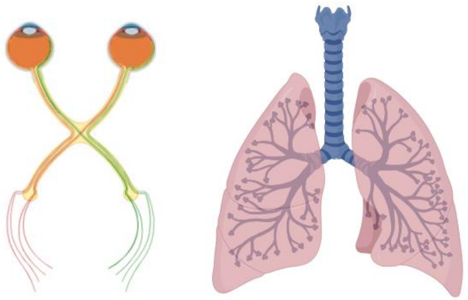
[INFN-GEANT4 project]

What's next..?

Single length → Volume effect → Statistics → Other organs → Other outcome

l **>** *8 mm*

l **<** *8 mm*



[INFN-GEANT4 project]

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Back up slides

“ .. none of the existing models […] is capable of adequately describing the volume effect data, the spinal cord being a good example. ”

- Van der Kogel

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Alice Casali

Markov Chain Monte Carlo (MCMC)

$(\alpha_X, \beta_X, t)_1$
$(\alpha_X, \beta_X, t)_2$
$\vdots$
$(\alpha_X, \beta_X, t)_n$

MCMC $\longrightarrow$

$NTCP_1(D_1)$ $NTCP_1(D_2)$ $\cdots$
$\vdots$
$NTCP_n(D_1)$

$NTCP_1\ (\boldsymbol{D_1}) \quad NTCP_1\ (\boldsymbol{D_2}) \quad \cdots \quad NTCP_1\ (\boldsymbol{D_m})$

$\vdots$

$NTCP_n\ (\boldsymbol{D_1}) \quad NTCP_n\ (\boldsymbol{D_2})$

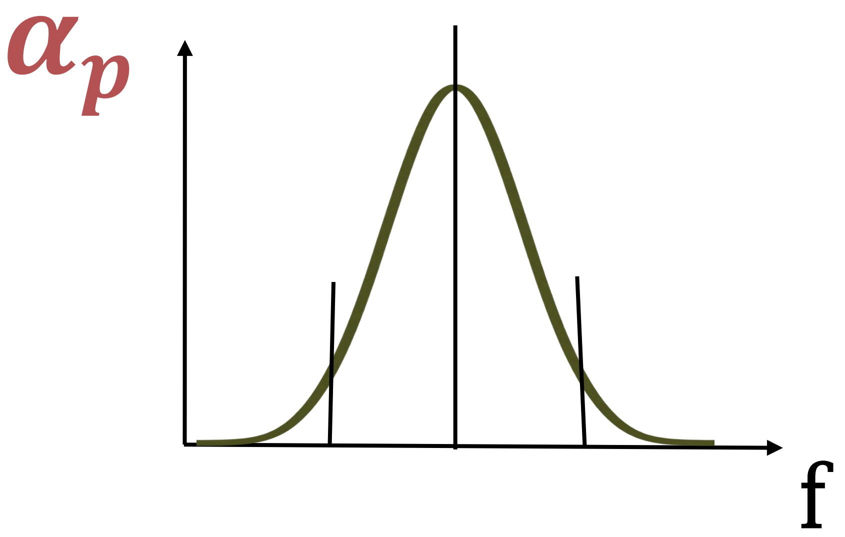
16° - 50° - 84°   16° - 50° - 84°   …   16° - 50° - 84°

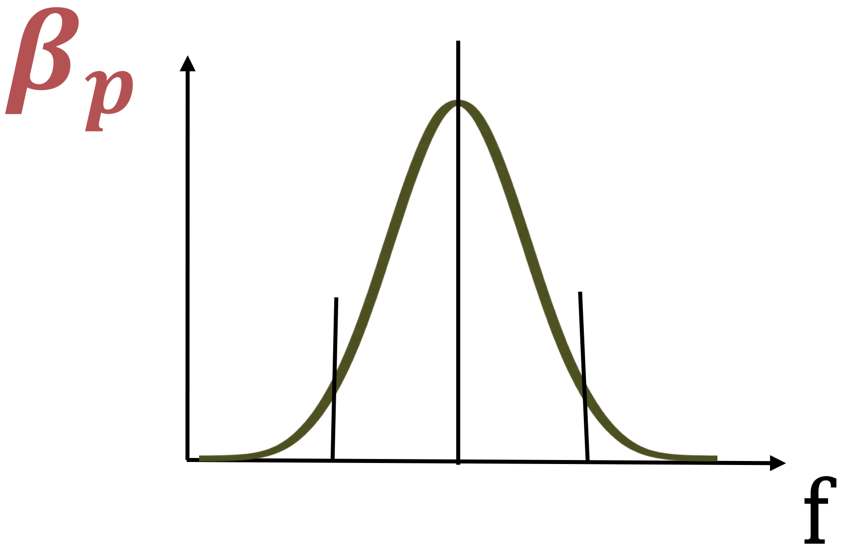
↓

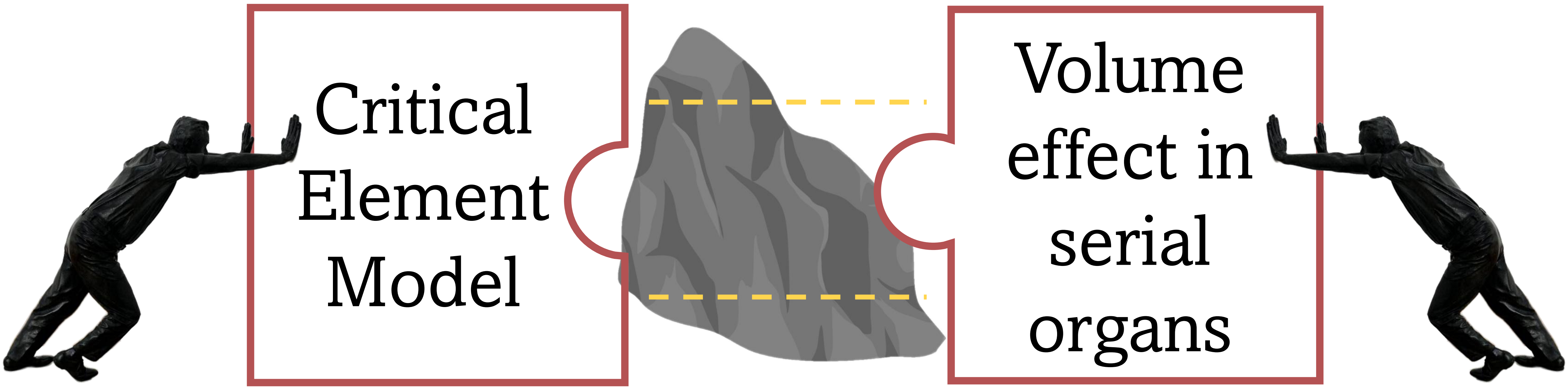
Three NTCP curves reconstructed

MCMC

$$\begin{bmatrix} (\alpha_X, \beta_X)_1 \\ (\alpha_X, \beta_X)_2 \\ \vdots \\ (\alpha_X, \beta_X)_n \end{bmatrix} \longrightarrow \boxed{\text{BIANCA}}$$





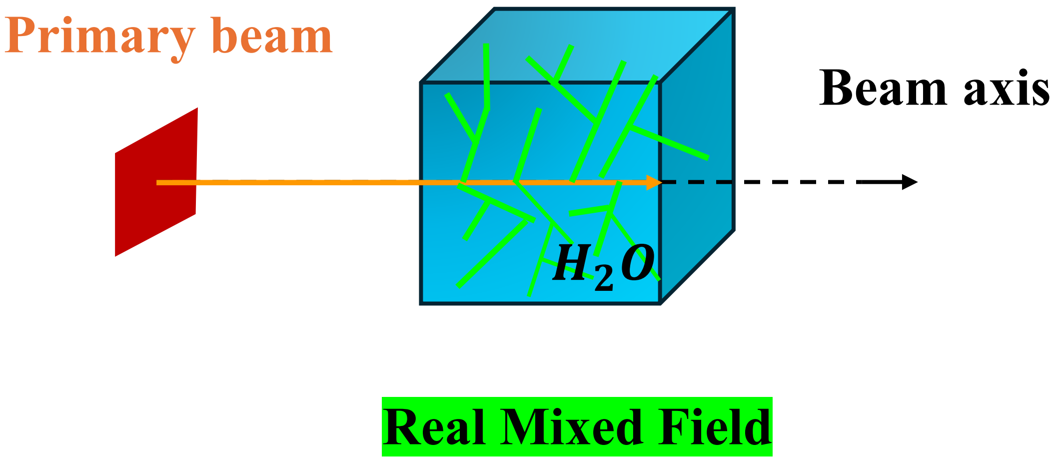

Critical Element Model
Volume effect in serial organs

Ion α and β estimation

BIANCA-Geant4 interface

[in collaboration: GEANT4INFN project]

Real Mixed Field



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	0.028224339666305
10	0.164742642147497	0.032025638951858

Monochromatic Field

Table of α and β for several particles and LET values

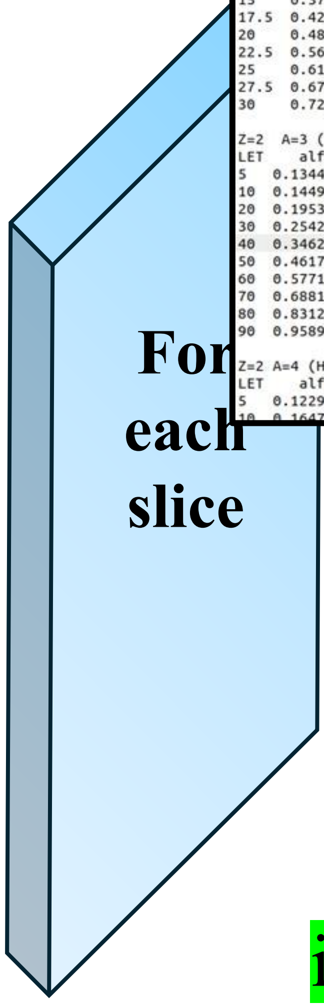
LET [keV/μm] = ***Stopping power***

Interface BIANCA - GEANT4

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

j – th energy value