



WIR SCHAFFEN WISSEN – HEUTE FÜR MORGEN

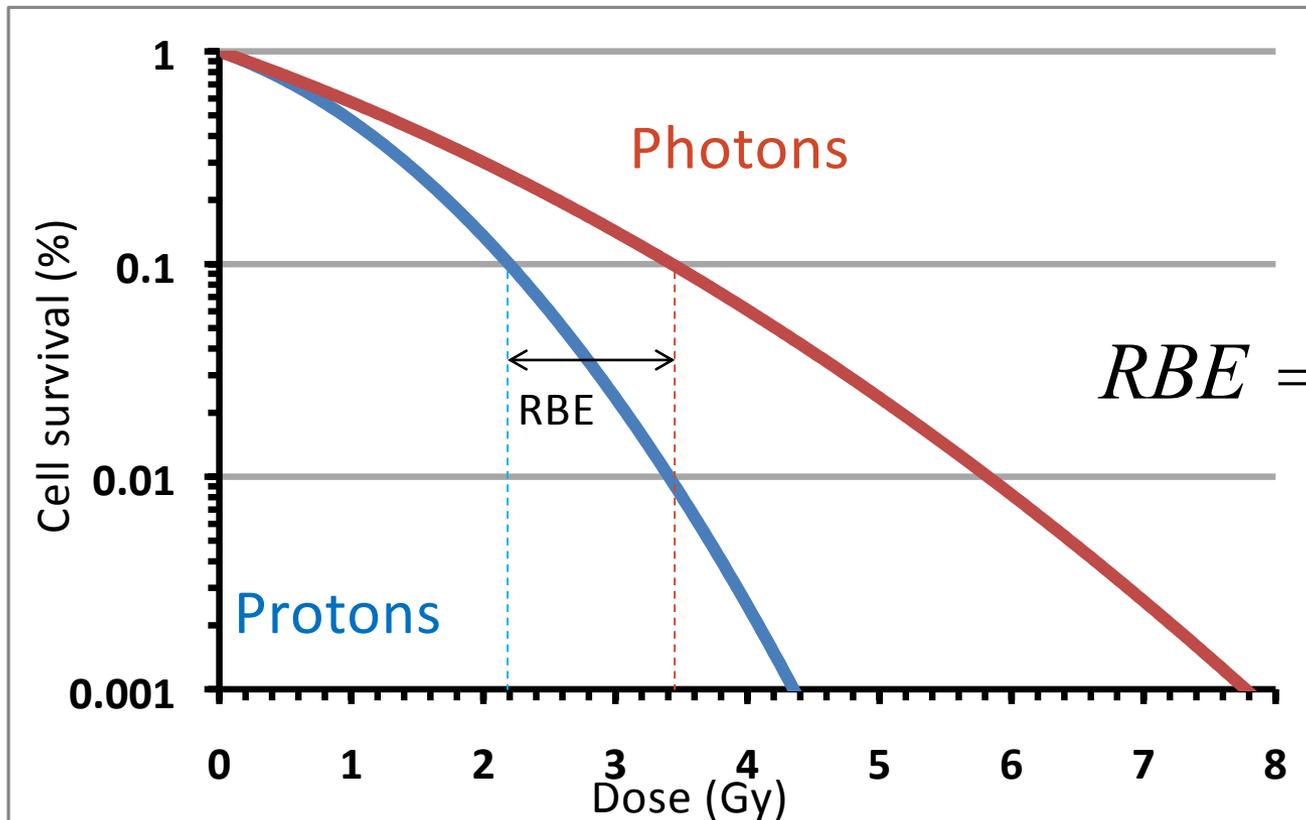
Tony Lomax :: Paul Scherrer Institute

Proton RBE: The physicist's-eye-view*

ICTR - 2016

* Title inspired by Michael Goitein

RBE is a simple concept, normally measured *in-vitro*

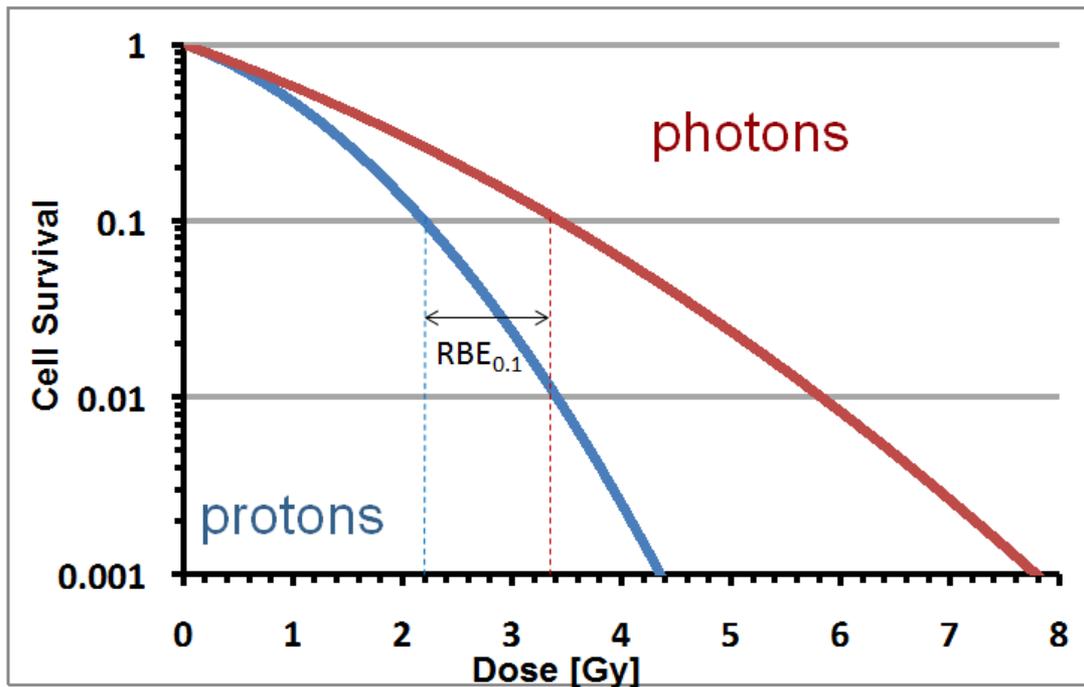


$$RBE = \frac{D_g}{D_{protons}} \langle effect \rangle$$

But is dependent on a few things...

In-vitro RBE is dependent on:

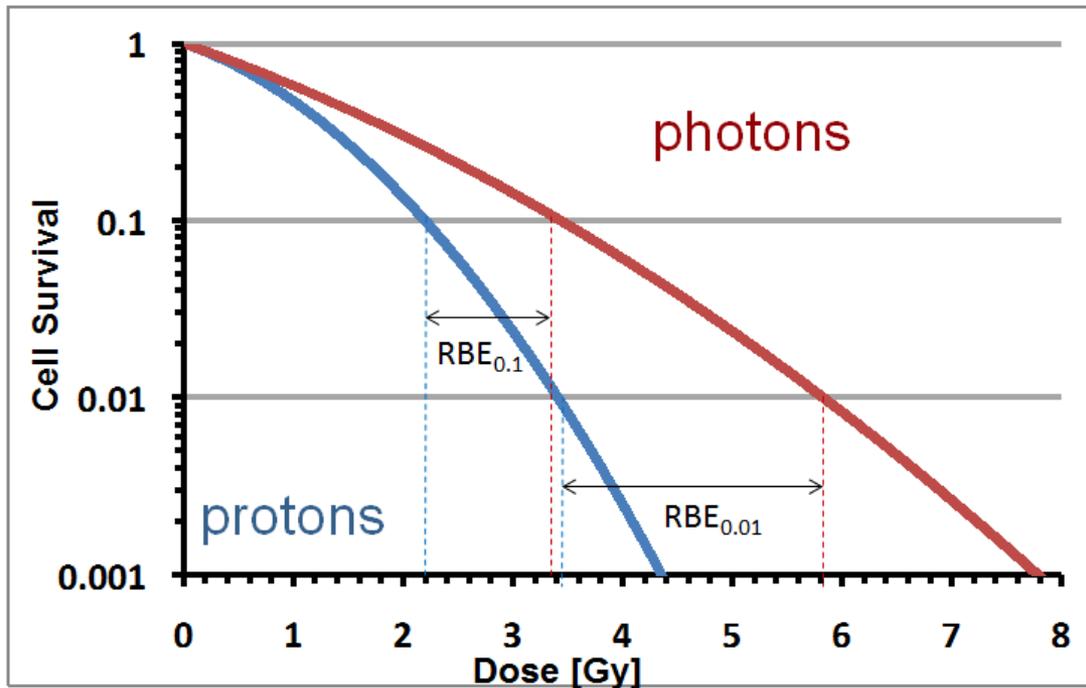
- Cell line



But is dependent on a few things...

In-vitro RBE is dependent on:

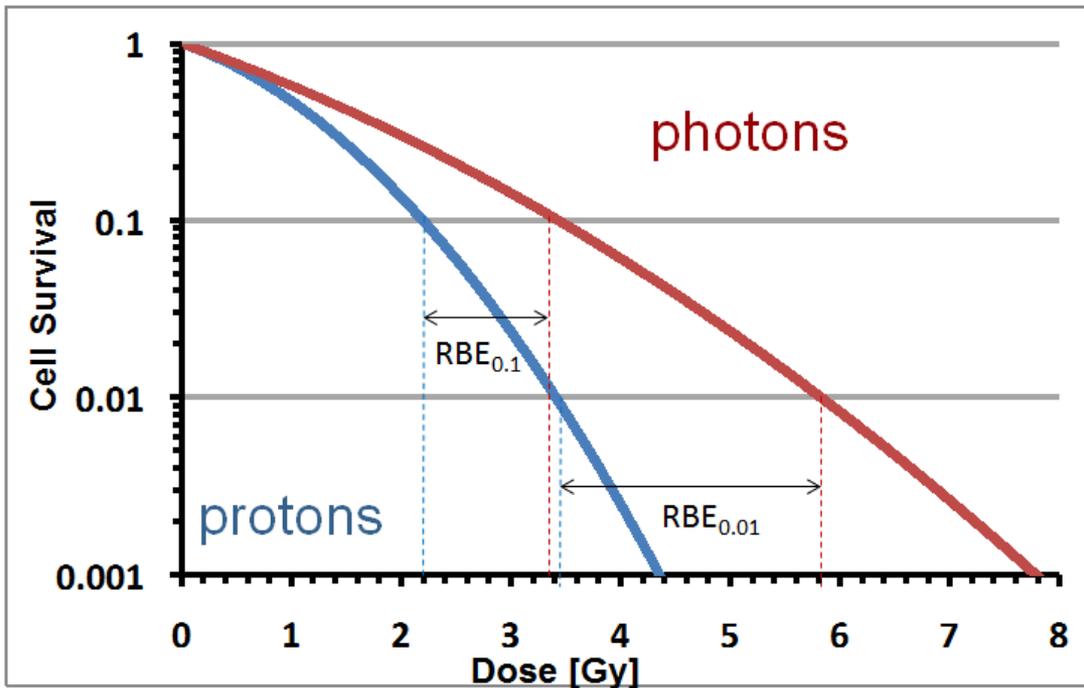
- Cell line
- End point



But is dependent on a few things...

In-vitro RBE is dependent on:

- Cell line
- End point
- Dose

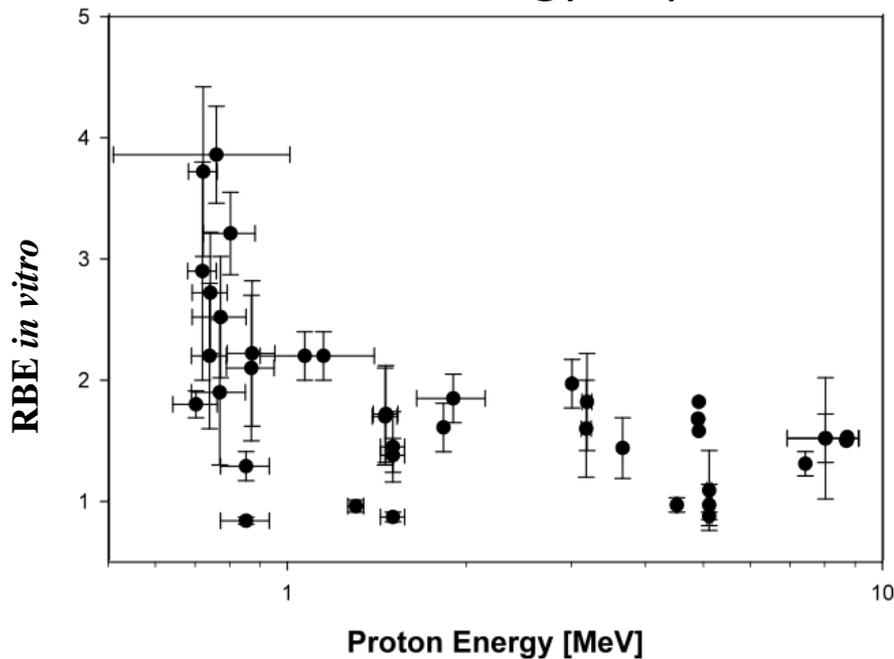


But is dependent on a few things...

In-vitro RBE is dependent on:

- Cell line
- End point
- Dose
- Energy

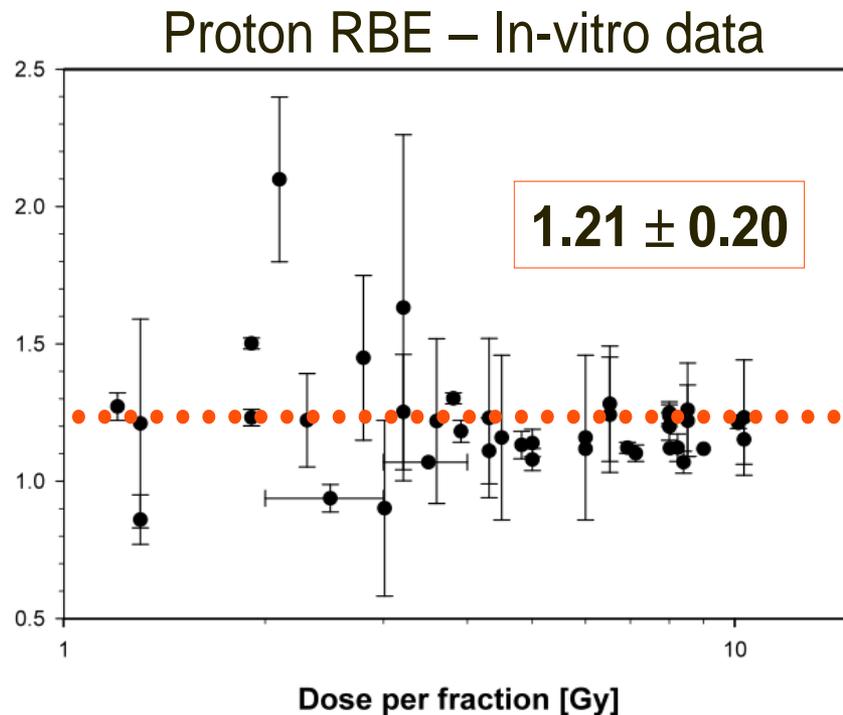
Proton RBE – energy dependence



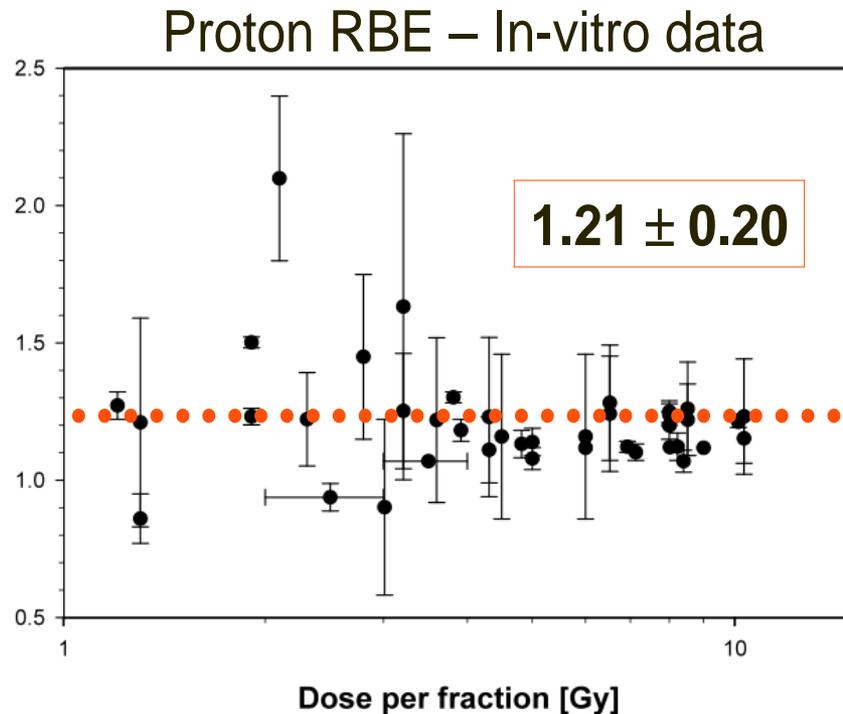
But is dependent on a few things...

In-vitro RBE is dependent on:

- Cell line
- End point
- Dose
- Energy
- Fractionation
- Dose rate
- α/β ratio
- ...

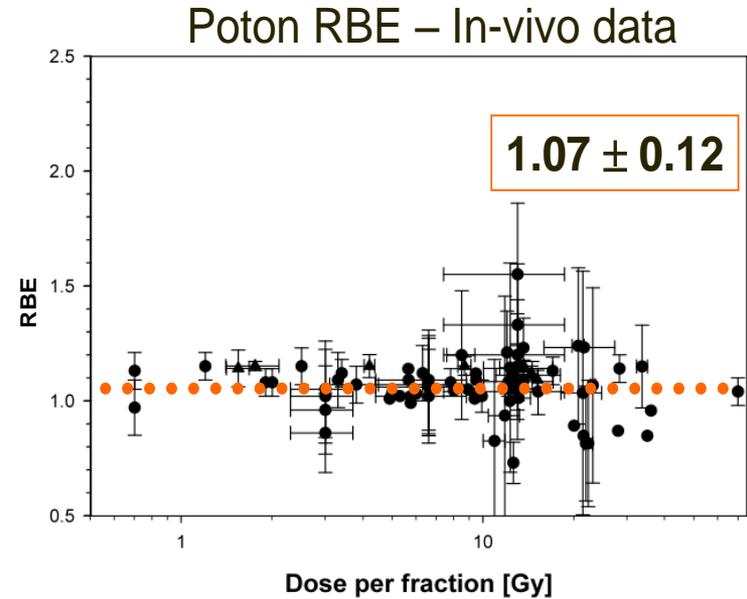
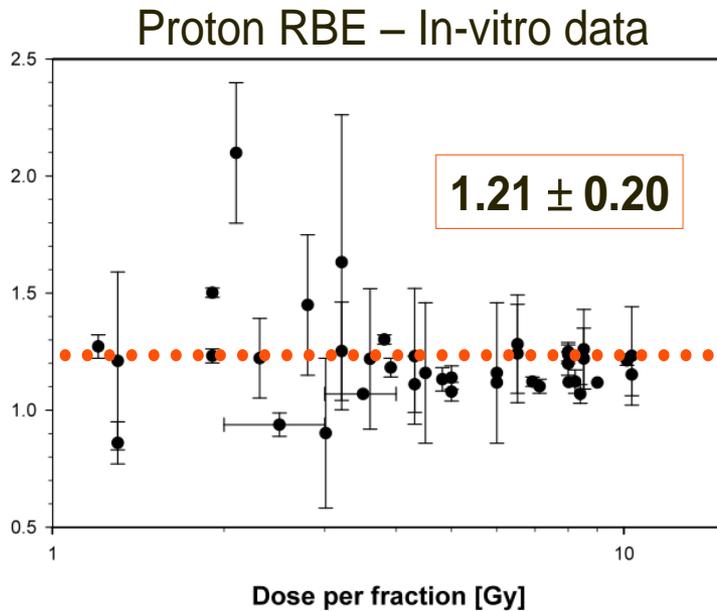


But is dependent on a few things...



In-vitro RBE is dependent on (at least) seven variables

What about *in-vivo* RBE?



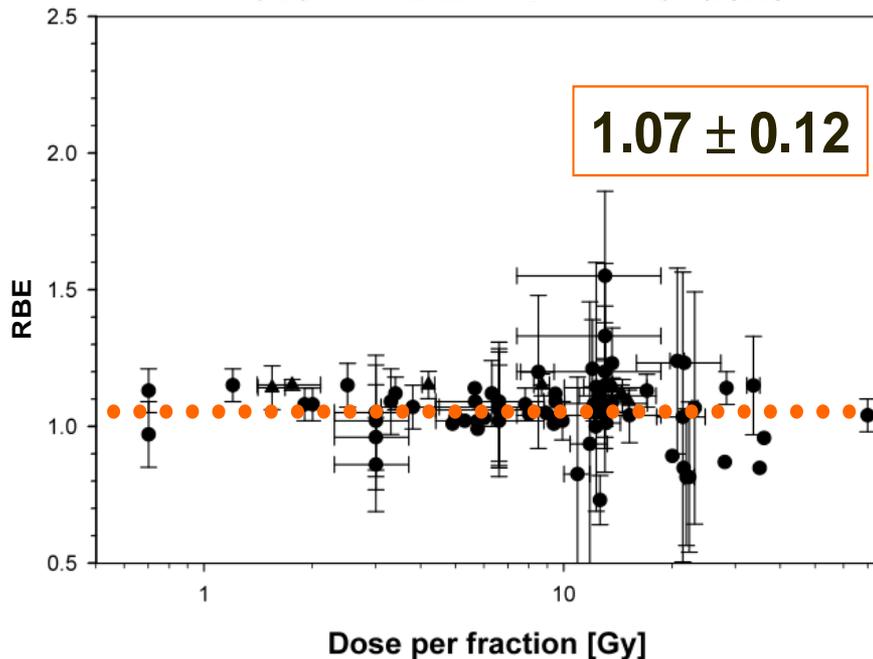
Endpoints: Lung tolerance, crypt regeneration, acute skin reactions...

What about *in-vivo* RBE?

In-vivo RBE is dependent on:

- Organ sensitivity
- Complication/control rate
- Dose
- Energy
- Effects of fractionation
- Dose rate
- Tissue α/β ratios
- ...

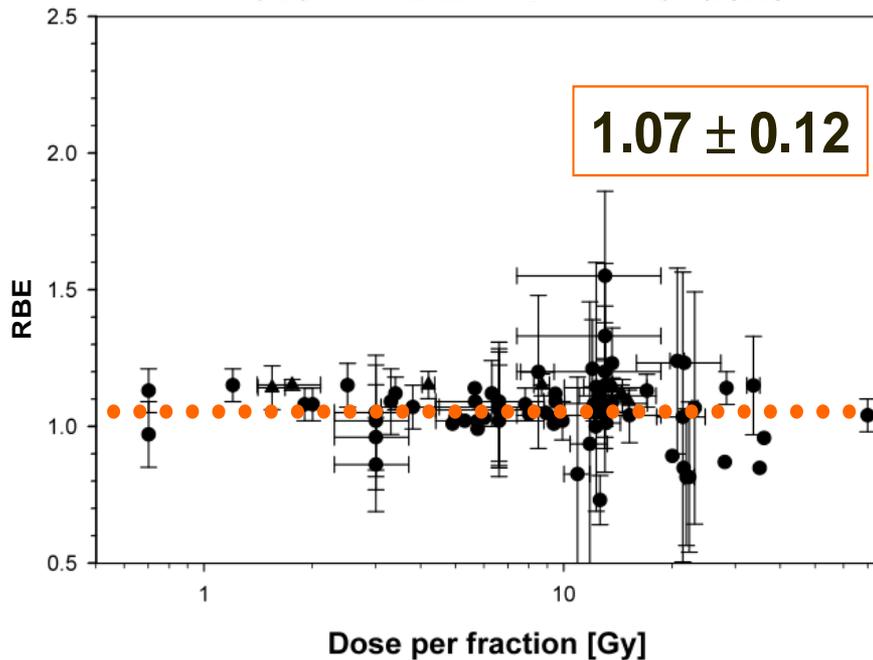
Proton RBE – In-vivo data



Endpoints: Lung tolerance, crypt regeneration, acute skin reactions...

In-vivo RBE - What we know and what we don't know

Proton RBE – In-vivo data

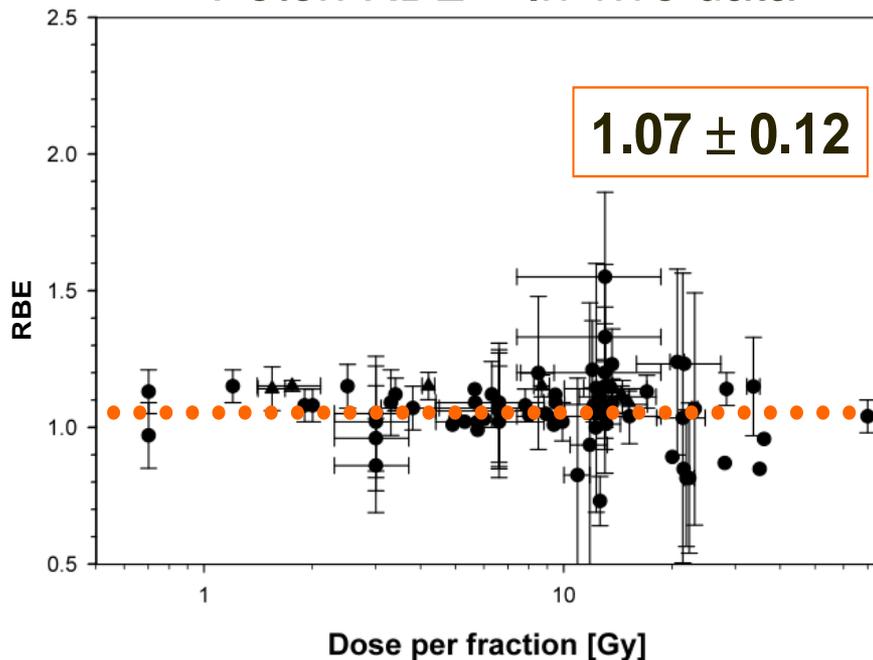


Endpoints: Lung tolerance, crypt regeneration, acute skin reactions...

- ✓ Dose
- ✓ Energy
- ✓ Dose rate
- ? Complication/control rate
- x Organ sensitivity
- x Effects of fractionation
- x Tissue α/β ratios
- x ...

In-vivo RBE - What we know and what we don't know

Proton RBE – In-vivo data

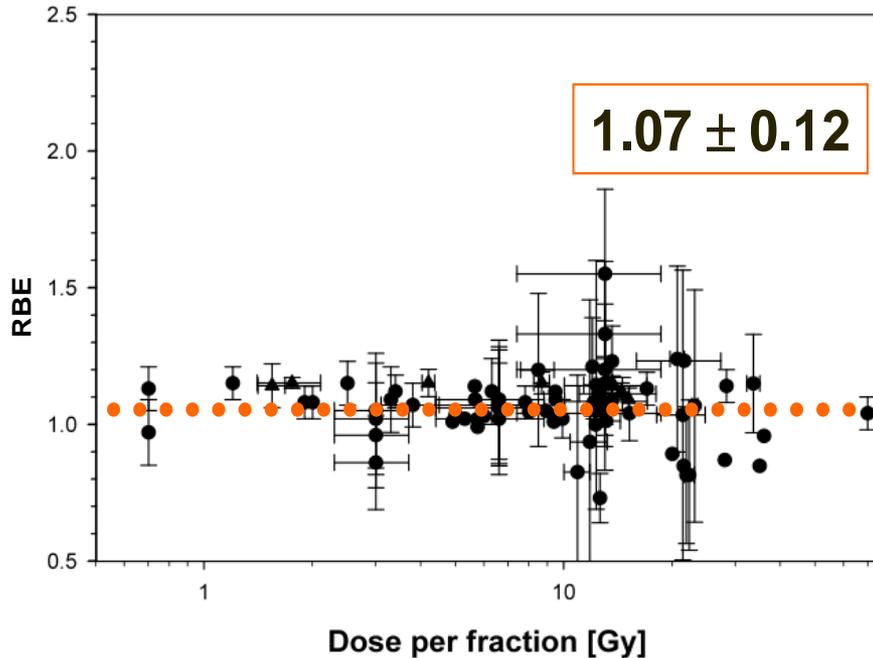


Endpoints: Lung tolerance, crypt regeneration, acute skin reactions...

Three of the seven variables affecting RBE *in-vivo* we don't really know

In-vivo RBE - What we know and what we don't know

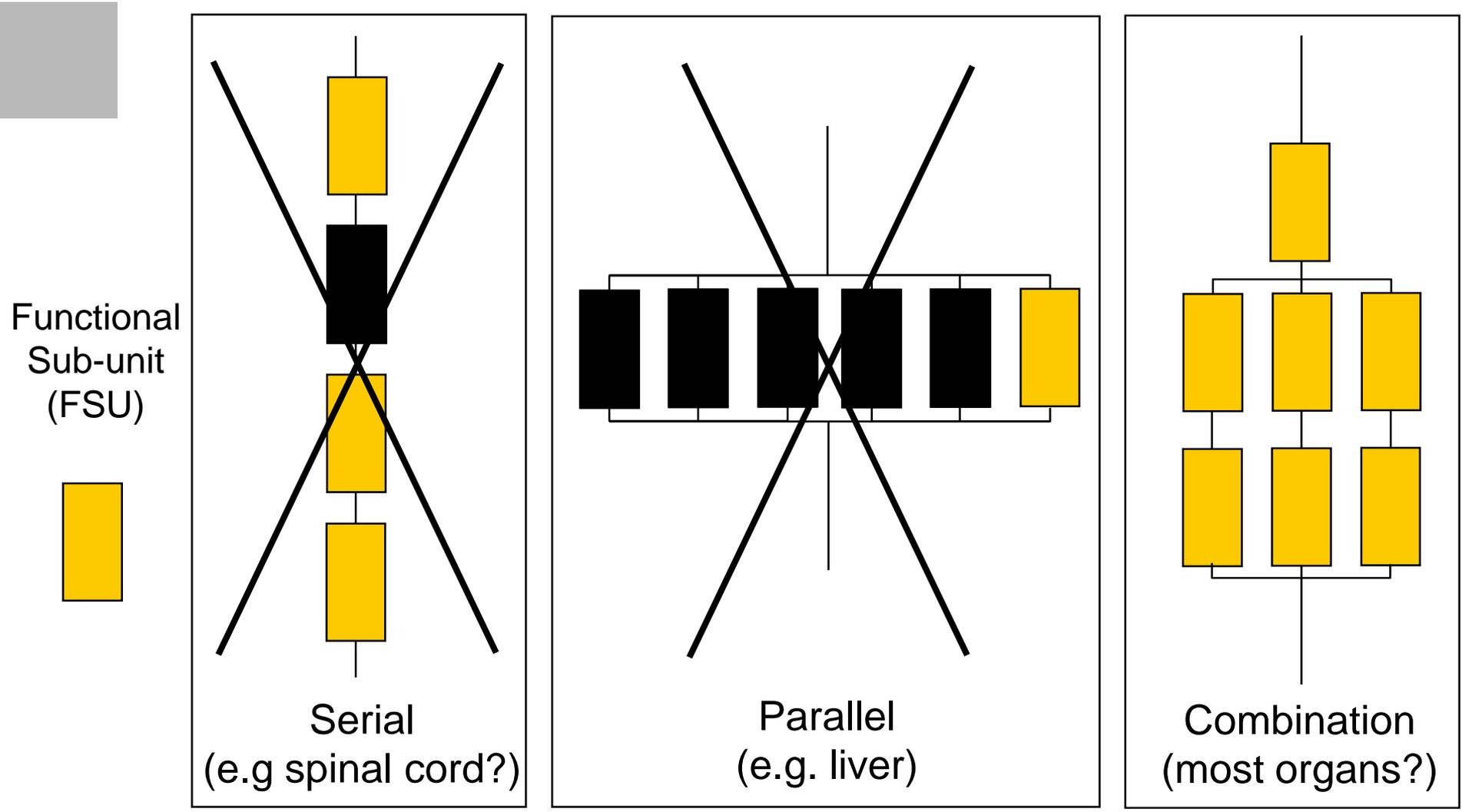
Proton RBE – In-vivo data



Endpoints: Lung tolerance, crypt regeneration, acute skin reactions...

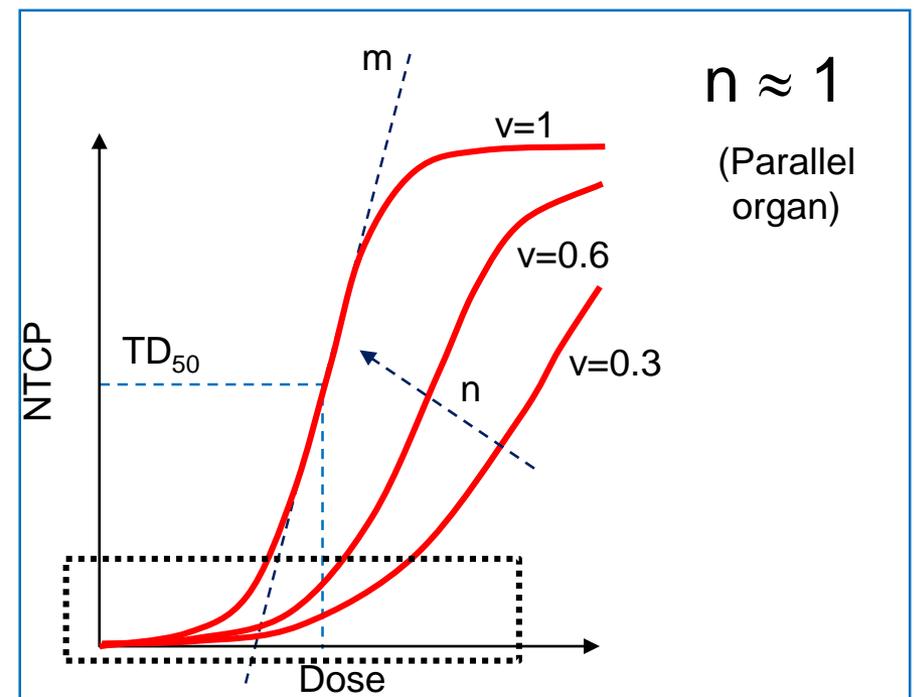
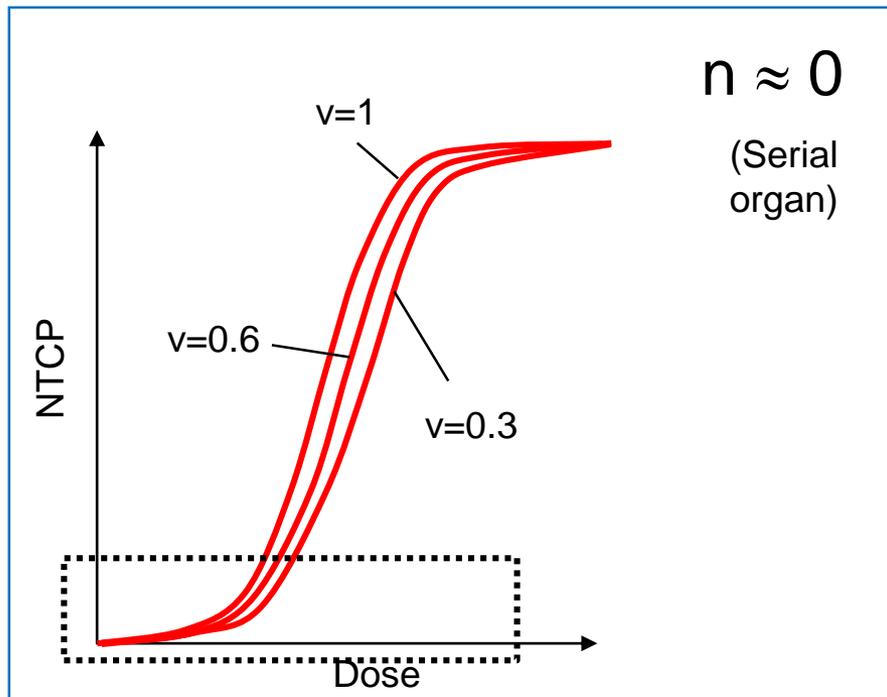
In fact, it is even worse, as there will also be an interplay with the underlying tissue architecture of the involved organ...

The biological effect of tissue architecture



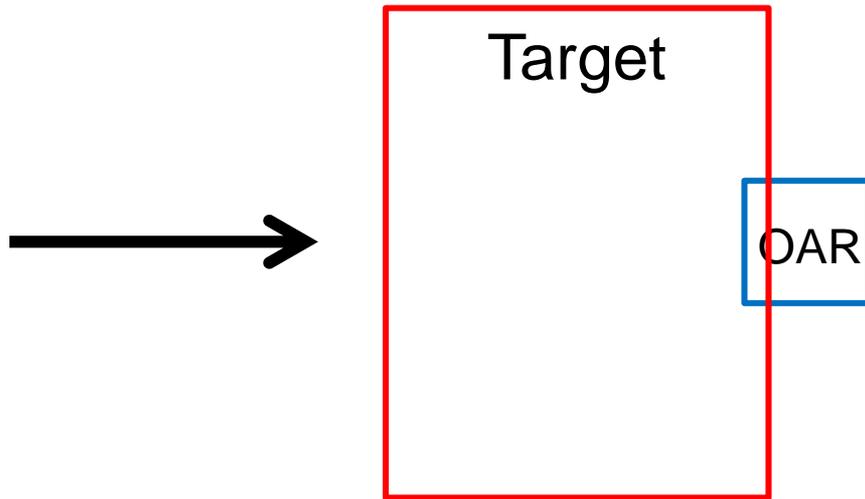
The biological effect of tissue architecture

e.g. The 'Lyman-Kutcher-Burmann' model for NTCP



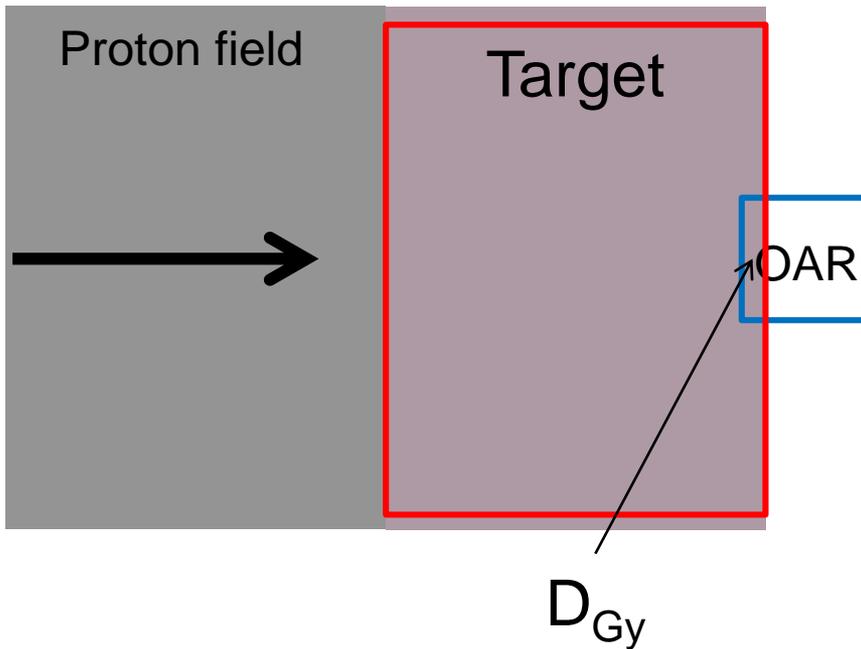
The interplay of tissue architecture and RBE

A thought experiment...



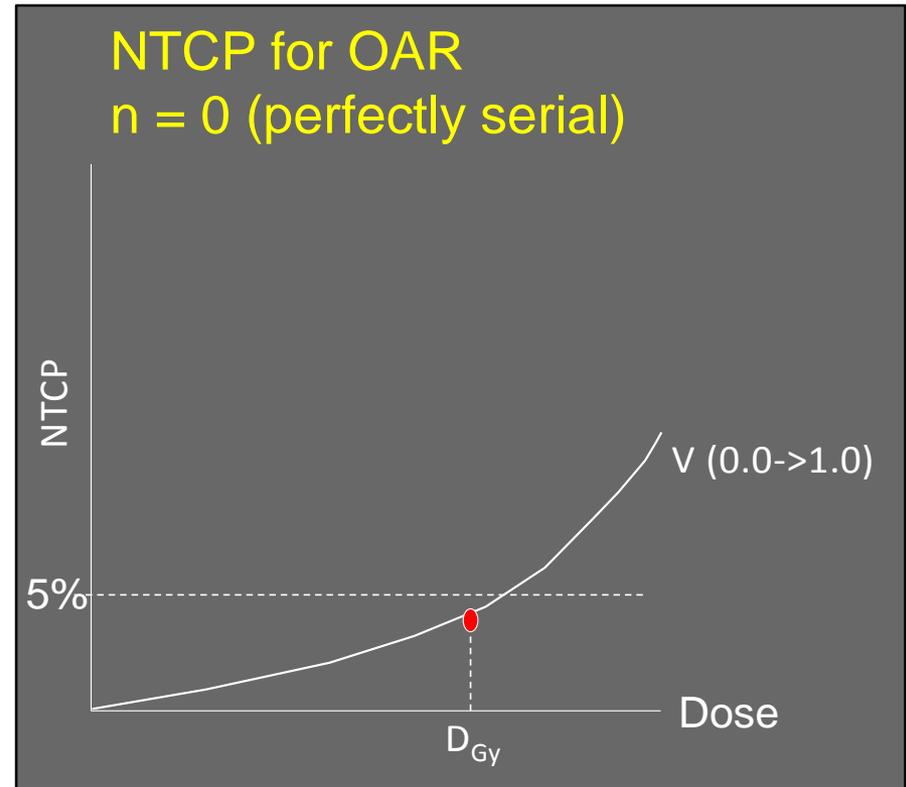
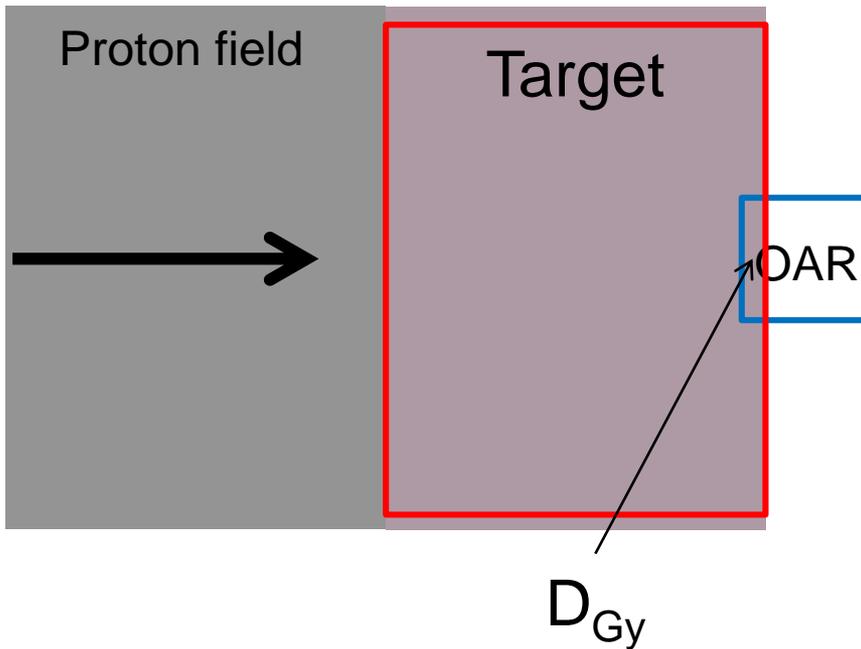
The interplay of tissue architecture and RBE

A thought experiment...



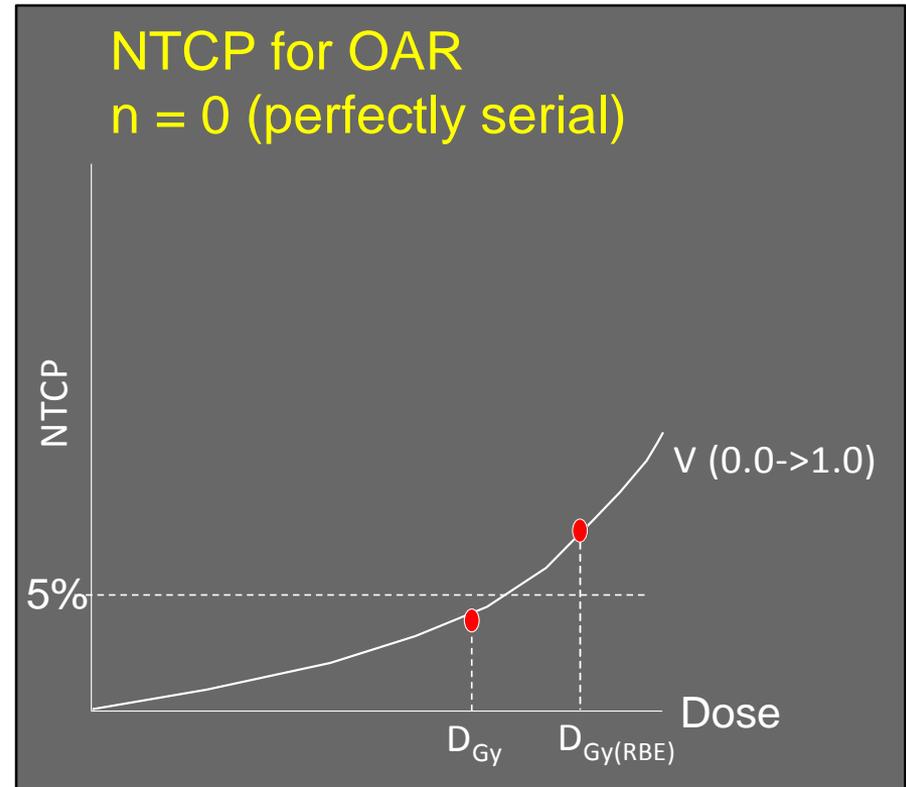
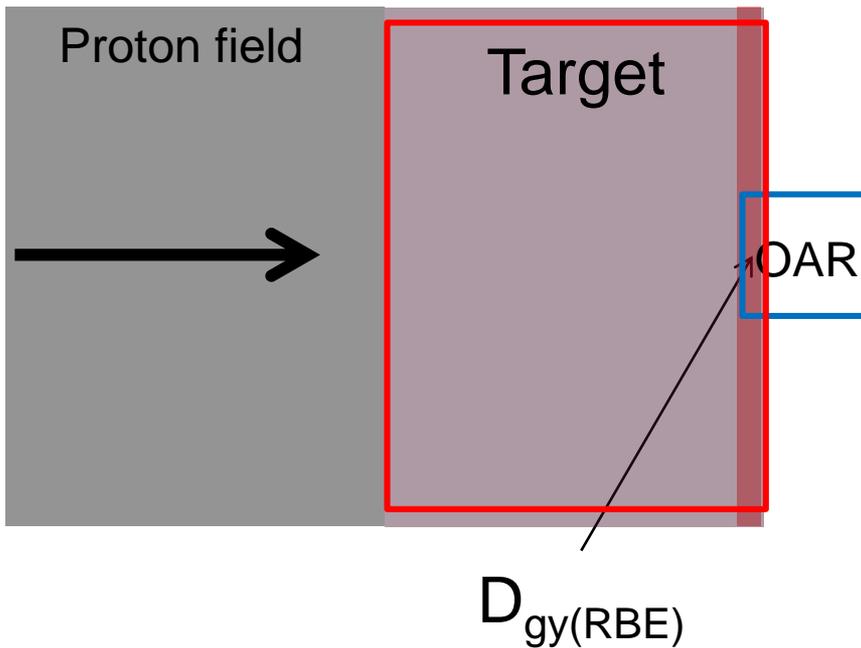
The interplay of tissue architecture and RBE

A thought experiment...



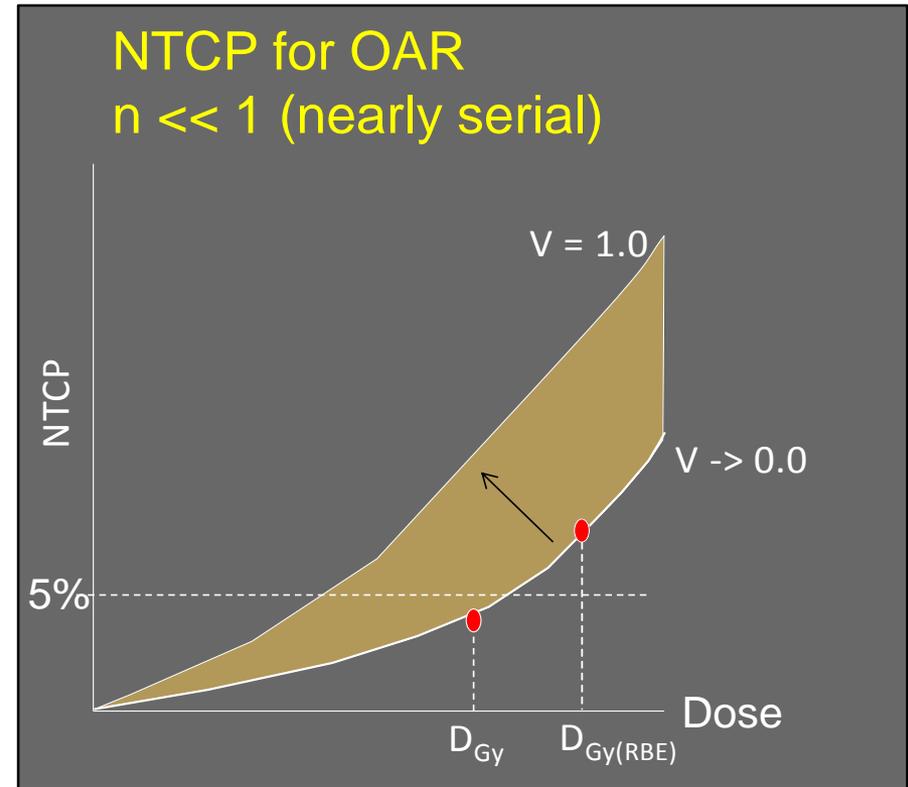
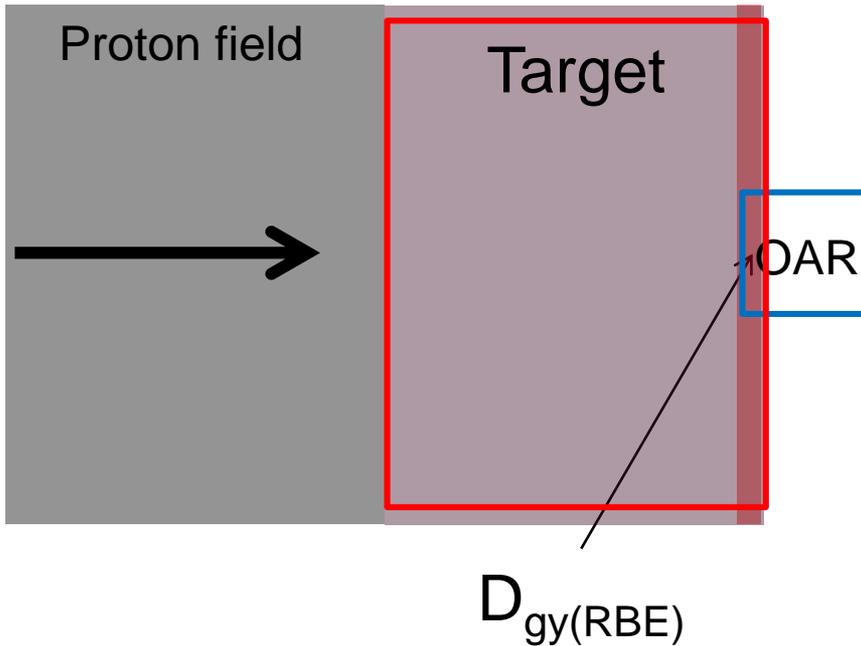
The interplay of tissue architecture and RBE

A thought experiment...



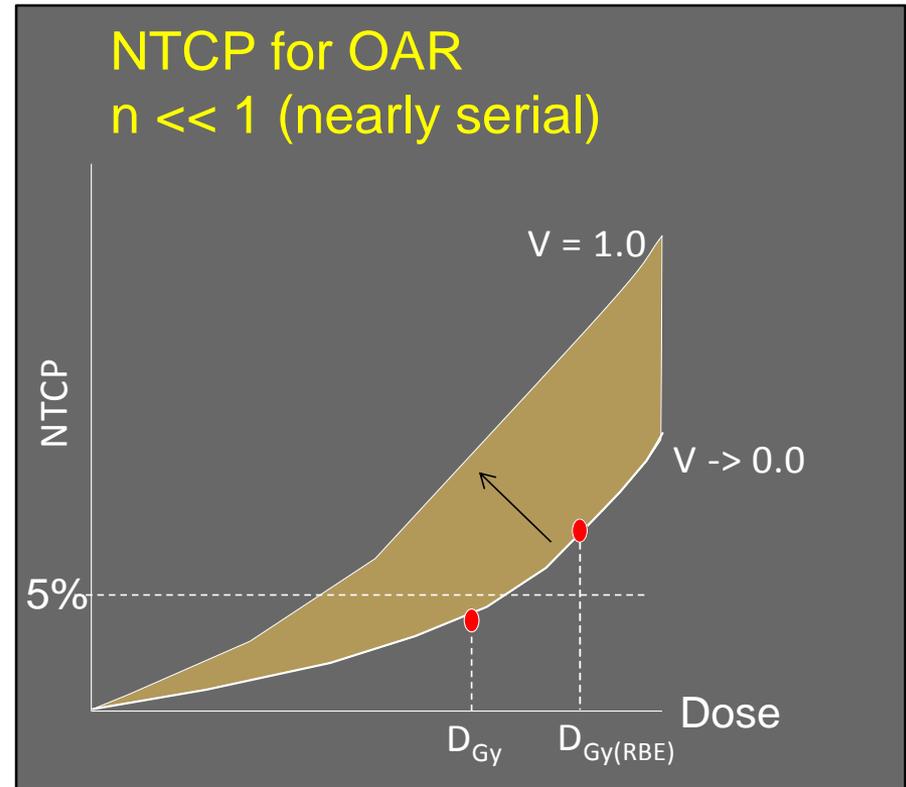
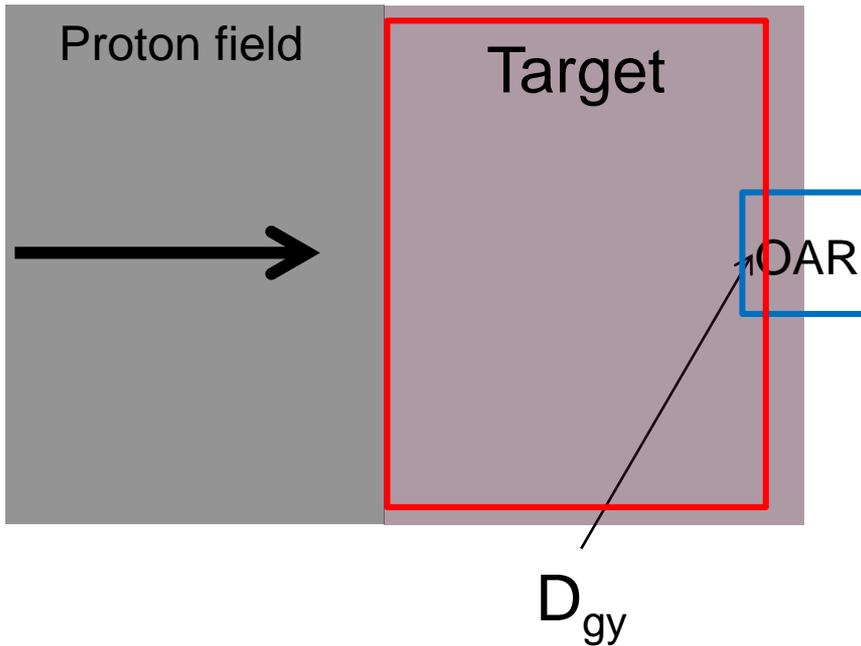
The interplay of tissue architecture and RBE

A thought experiment...



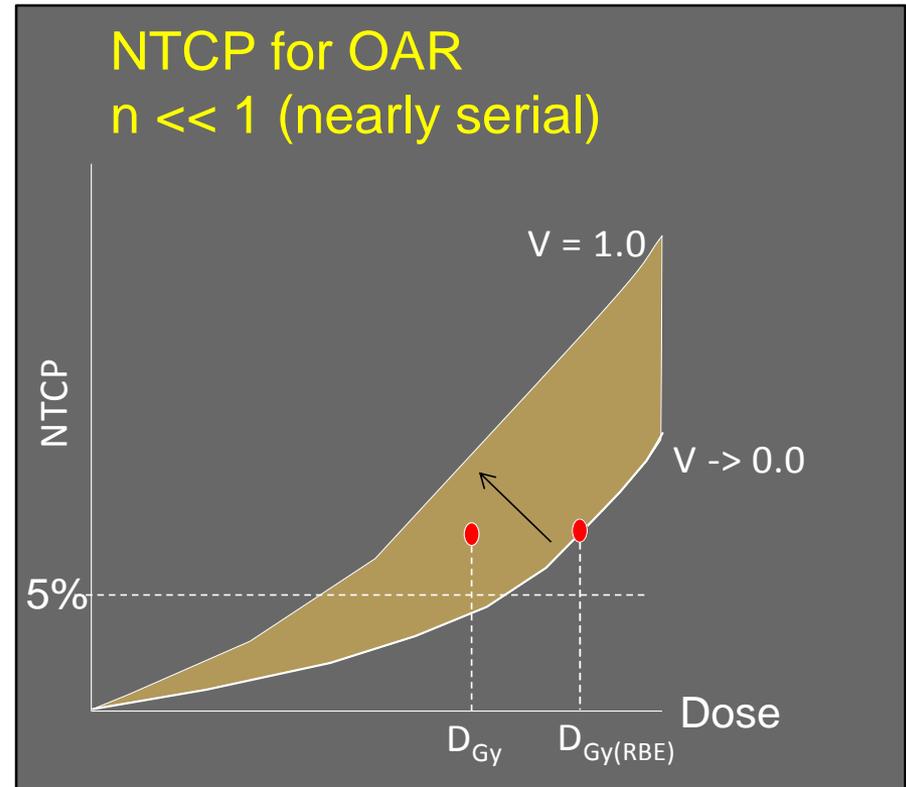
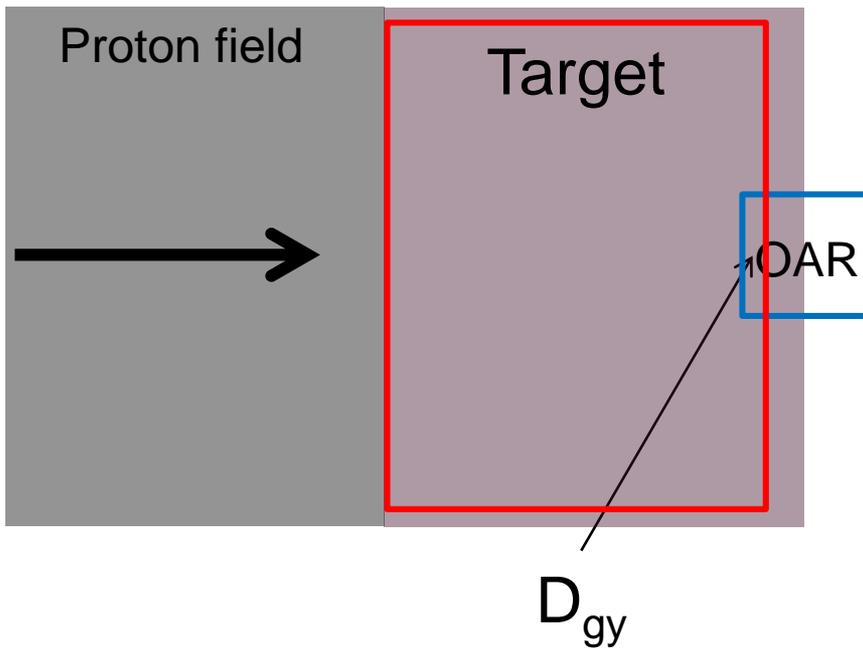
The interplay of tissue architecture and RBE

A thought experiment...



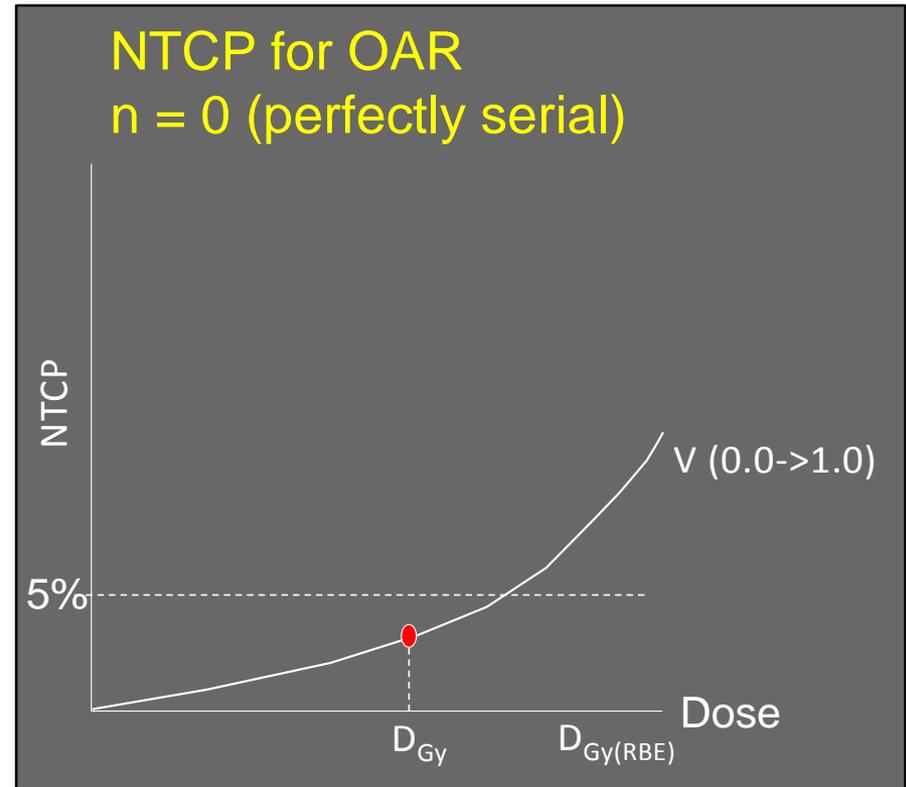
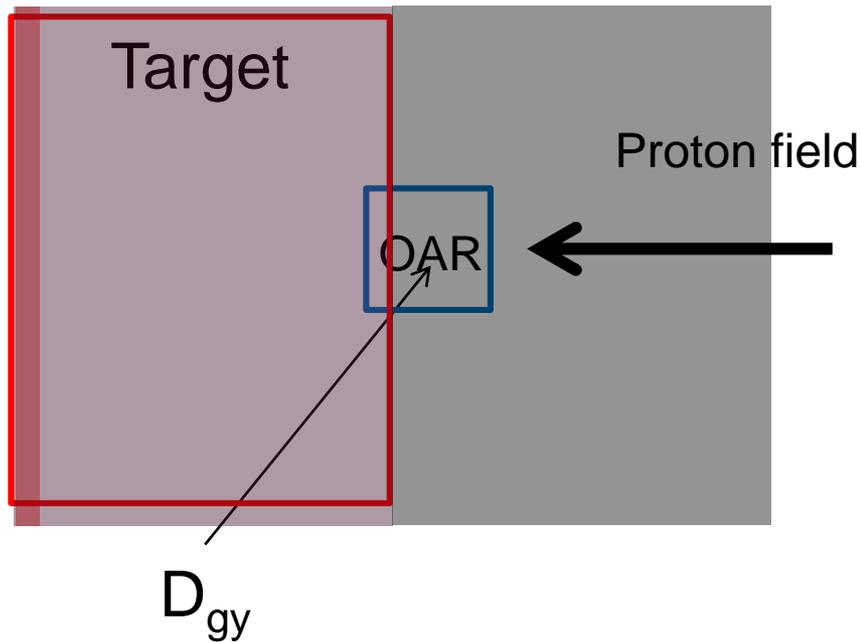
The interplay of tissue architecture and RBE

A thought experiment...



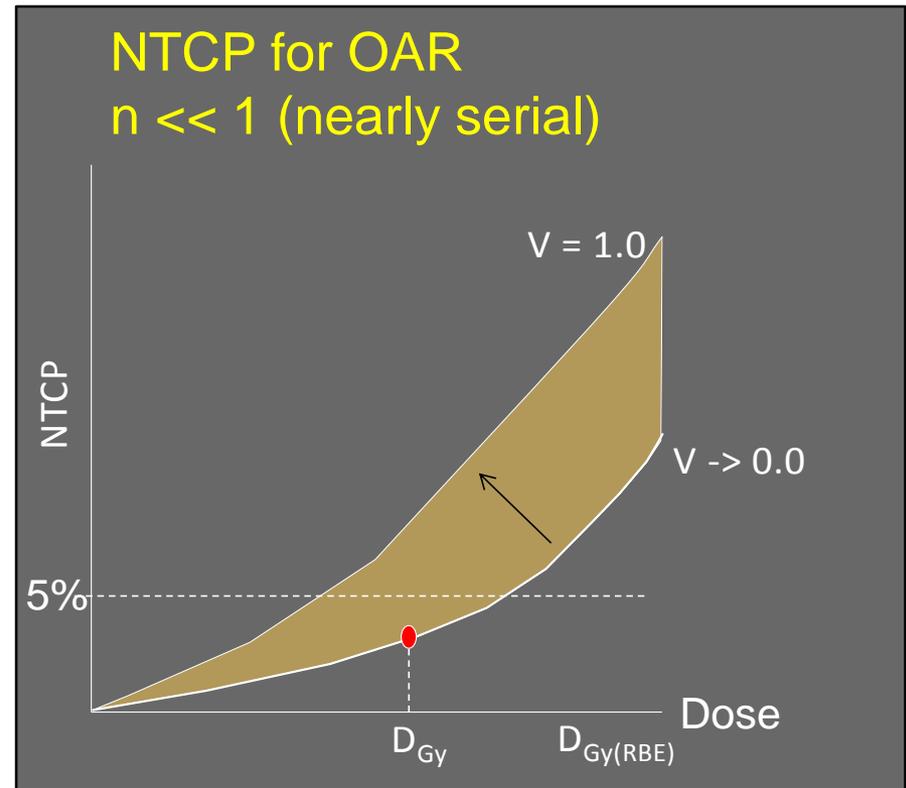
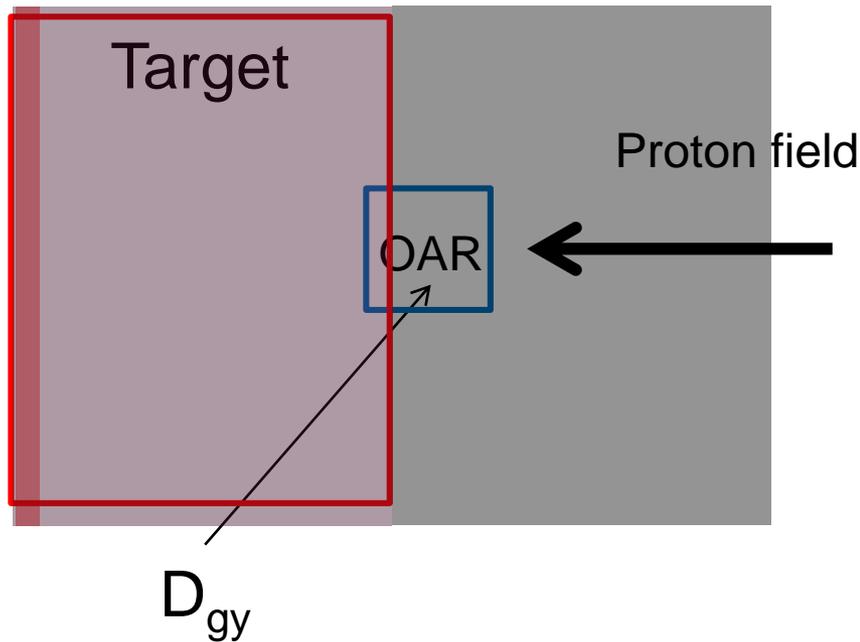
The interplay of tissue architecture and RBE

A thought experiment...



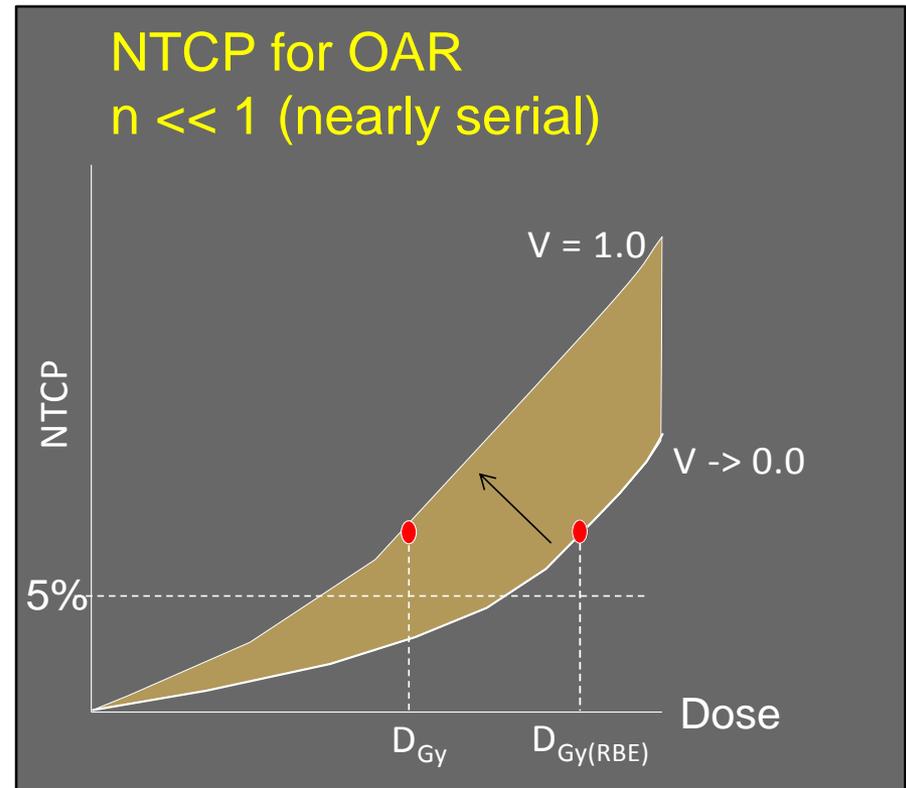
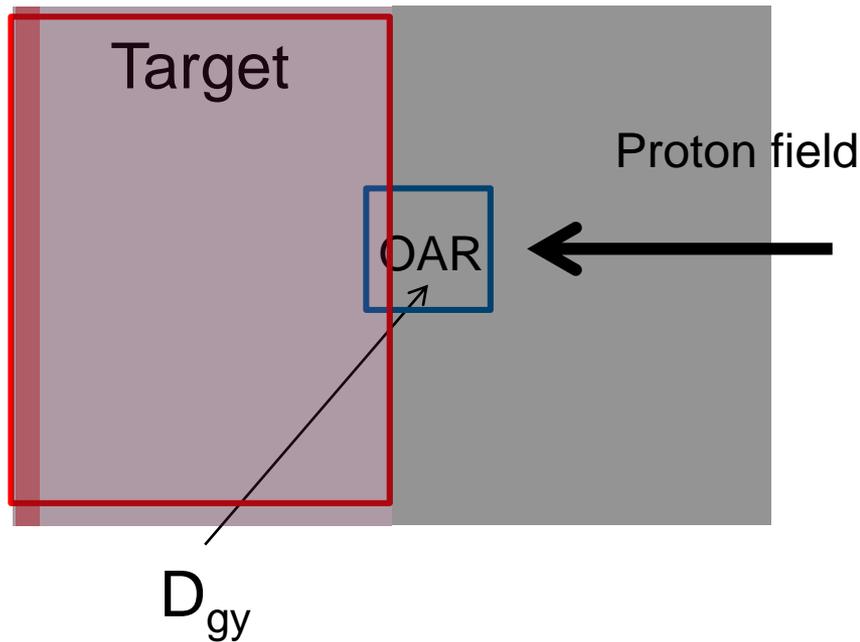
The interplay of tissue architecture and RBE

A thought experiment...



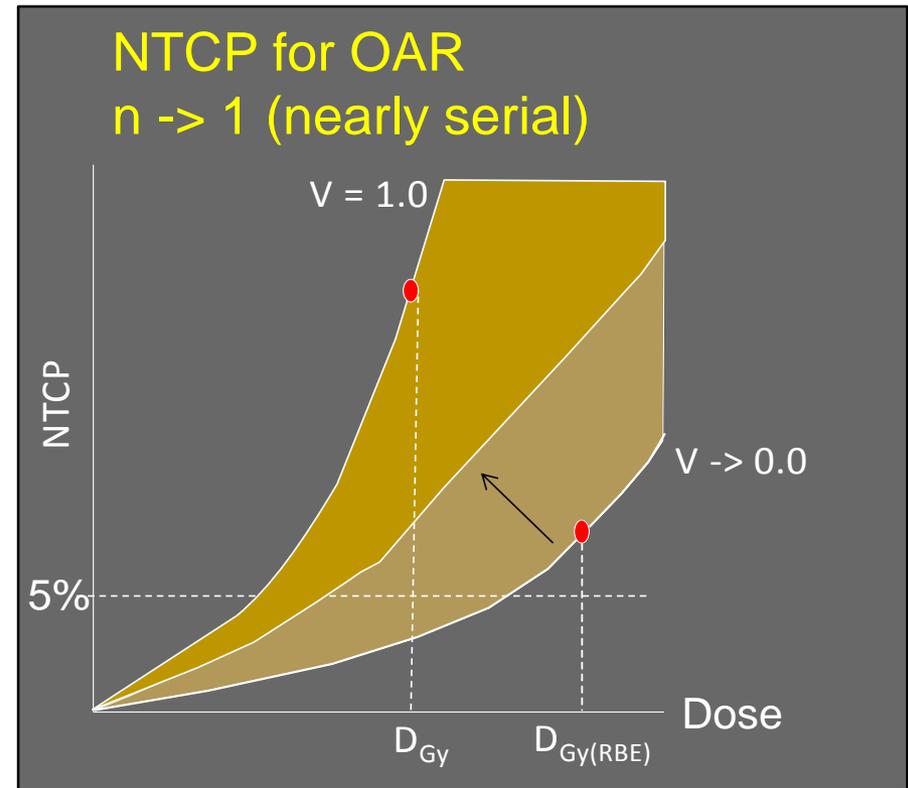
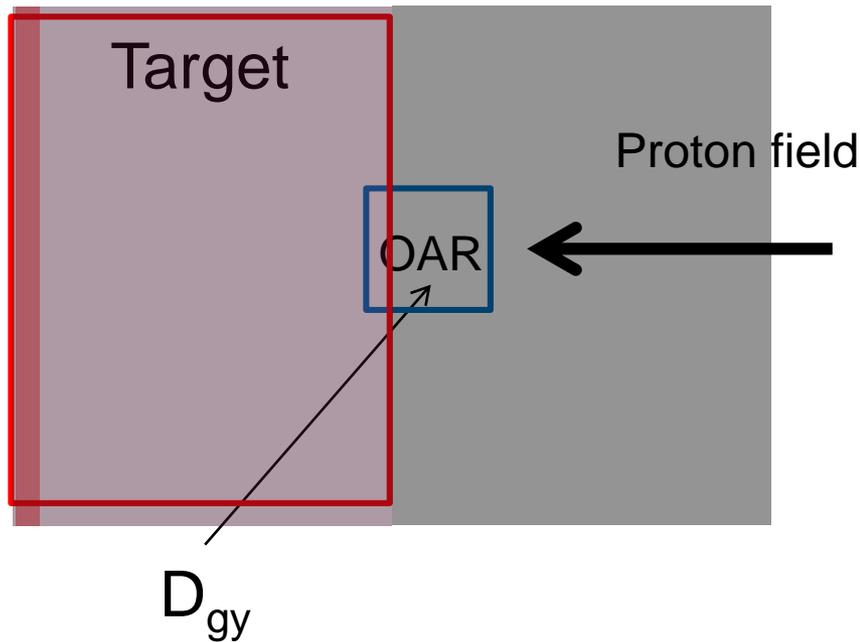
The interplay of tissue architecture and RBE

A thought experiment...



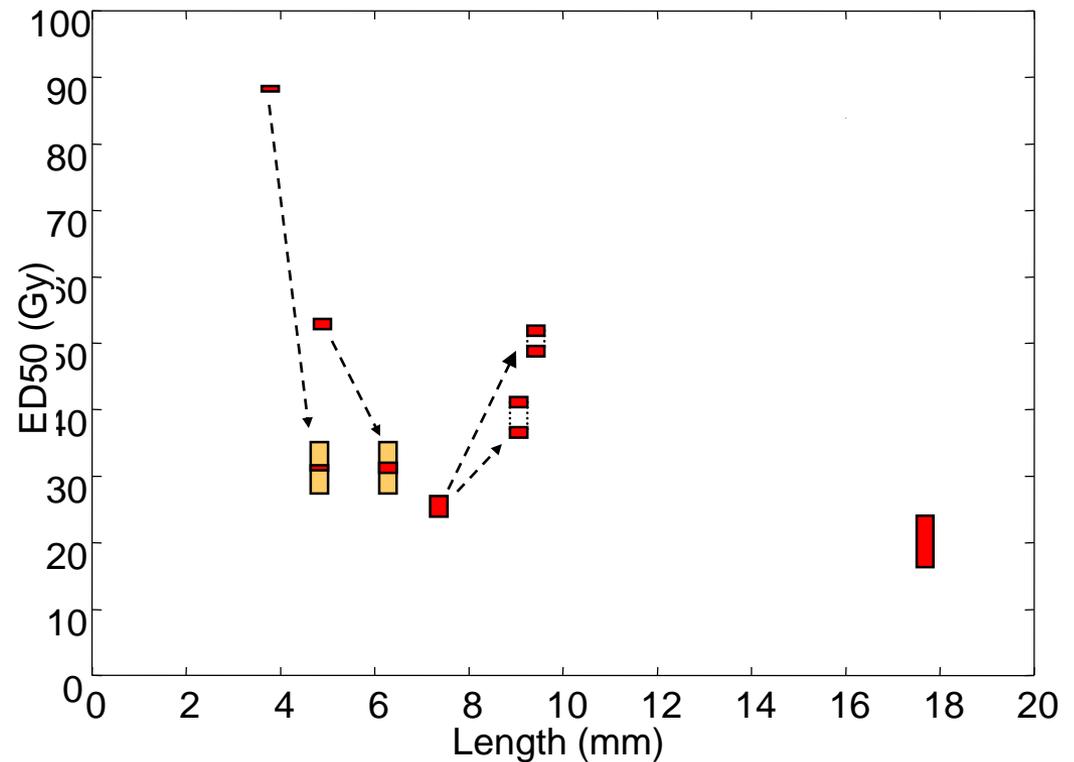
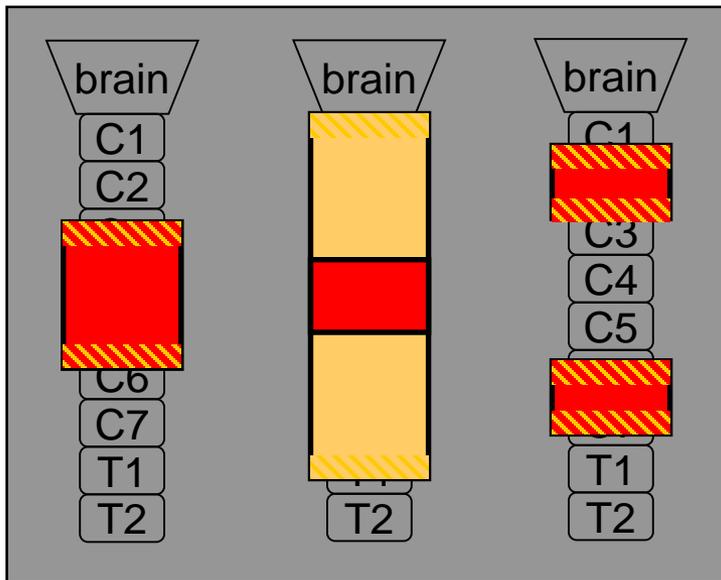
The interplay of tissue architecture and RBE

A thought experiment...

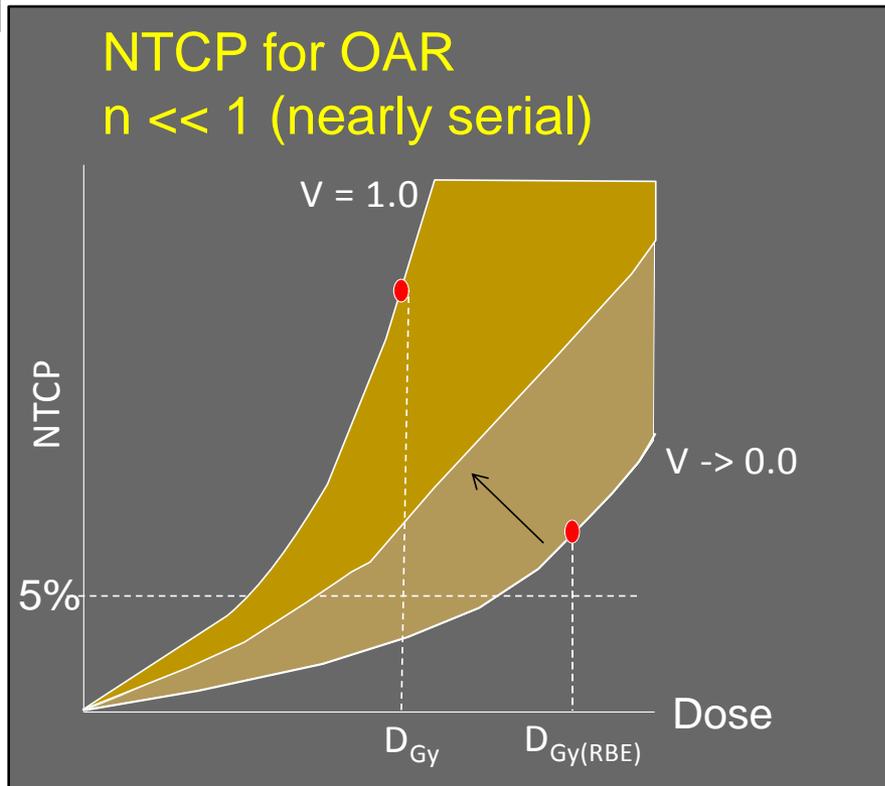


The interplay of tissue architecture and RBE

In-vivo rat spinal cord irradiations using collimated proton beams



In-vivo RBE - What we don't know



- x Tissue architecture and response
- x Organ sensitivity
- x Effects of fractionation
- x Tissue α/β ratios
- x ...

Unfortunately, that's not the end of the story...

Other confounding factors (e.g. for brain necrosis)* ...

- Concomitant targeted therapy or chemotherapy
- Pre-radiation organ condition (arteriosclerosis vessels/brain; cortical hypotrophy)
- Regional radio sensitivity within the organ
- Smoking
- Hypertension
- Diabetes
- Number of surgeries
- Age
- ...

*Courtesy of Prof Damien Weber

To summarise.

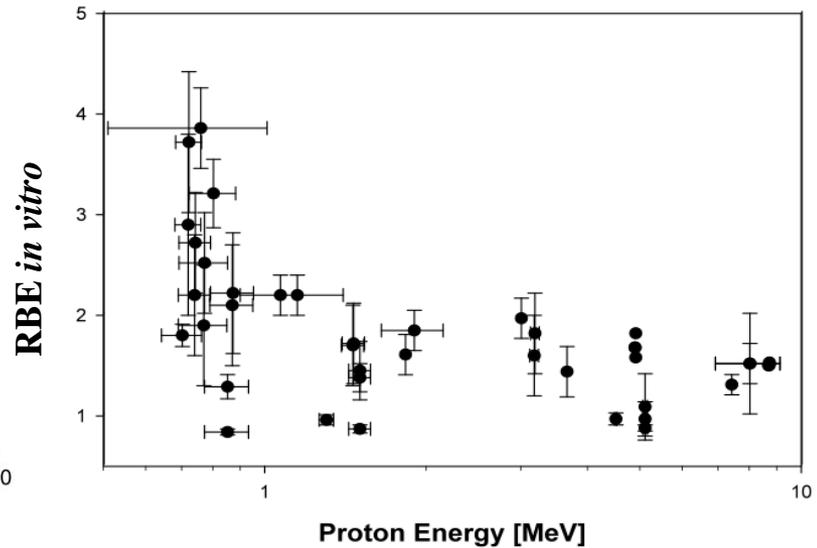
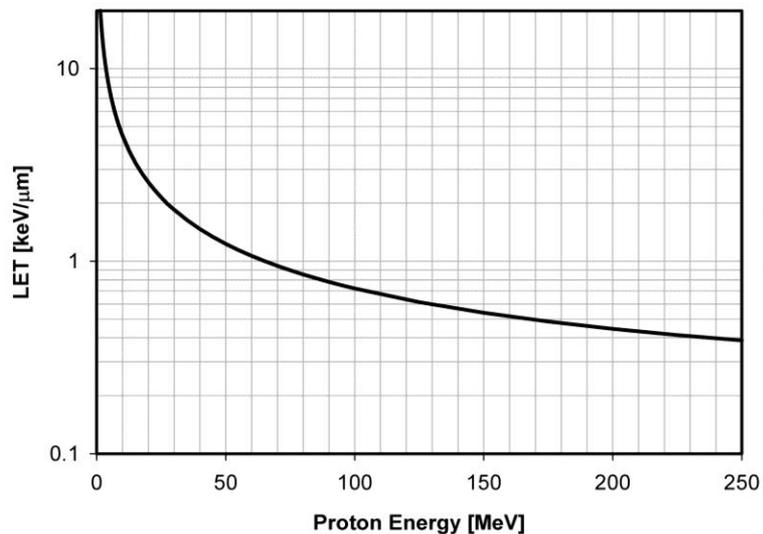
- There are (at least) 4 unknown factors that can influence in-vivo RBE
- There are (at least) 8 additional confounding factors that can influence patient outcomes
- In the end, the biological differences between protons and photons are more complicated than can be expressed in a single value

With (at least) 12 factors that can influence RBE and/or positive/negative biological effects observed in patients, is it likely that we will ever know RBE in-vivo?

The way forward?

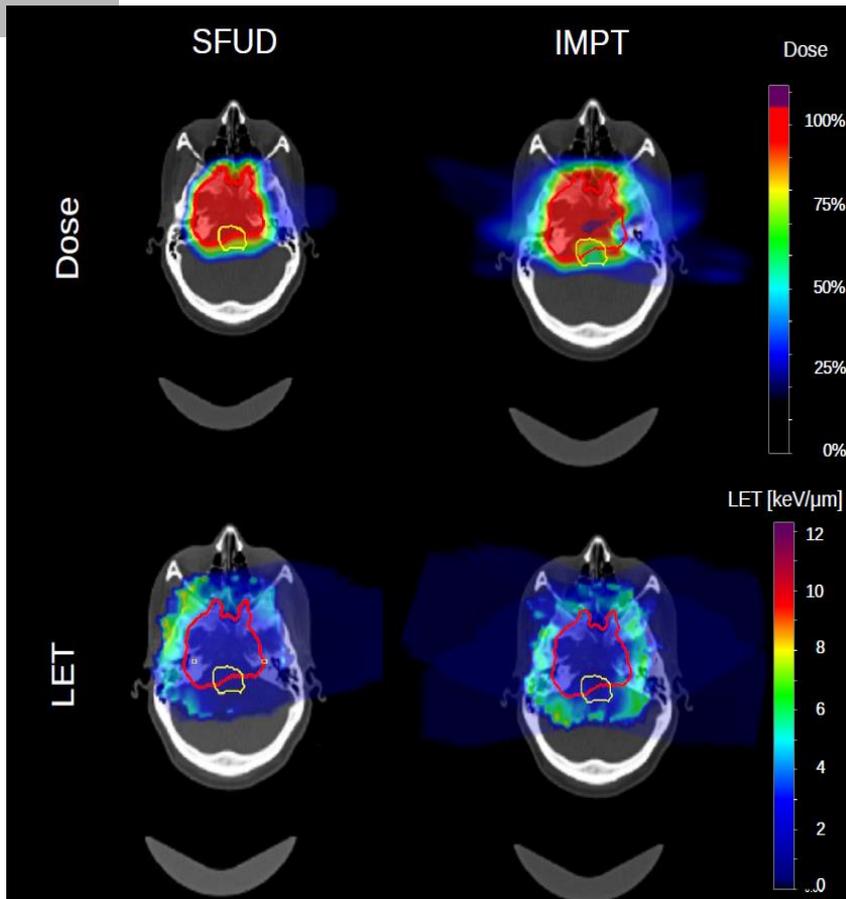
Work with what we know

✓ Dose ✓ Energy/LET



The way forward?

Work with what we know



- Dose and LET are parameters that can be accurately defined and localised
- Analyse outcomes of particle therapy in terms of dose and (e.g.) LET
- If need arises, derive dose/LET constraints for organs as result of outcome analysis

The Lomax-eye-view

- Although global RBE may be derivable for tumour control, given the generally low rate of severe side effects it is highly unlikely that localised RBE's in the patient can ever be deduced (small sample size, large number of unknowns)
- Therefore, if unexpected outcomes occur, we should relate these to known and measurable parameters (e.g. dose and LET) and define corresponding tumour/organ specific constraints

Once we have these, maybe we don't need RBE any more...

Thanks for your attention

