Introduction to Radiation Biology

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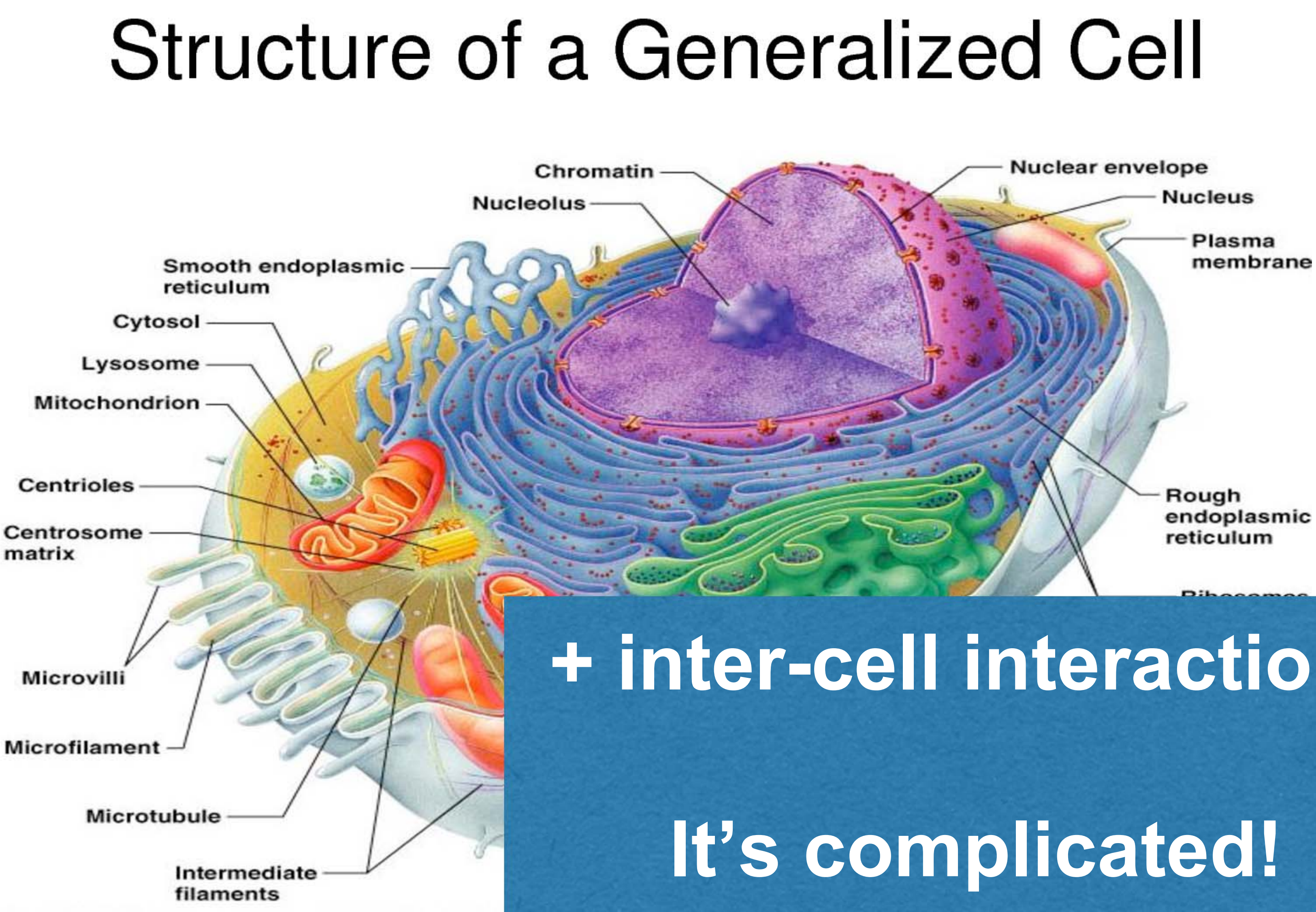
RADIATION ONCOLOGY

HARVARD MEDICAL SCHOOL

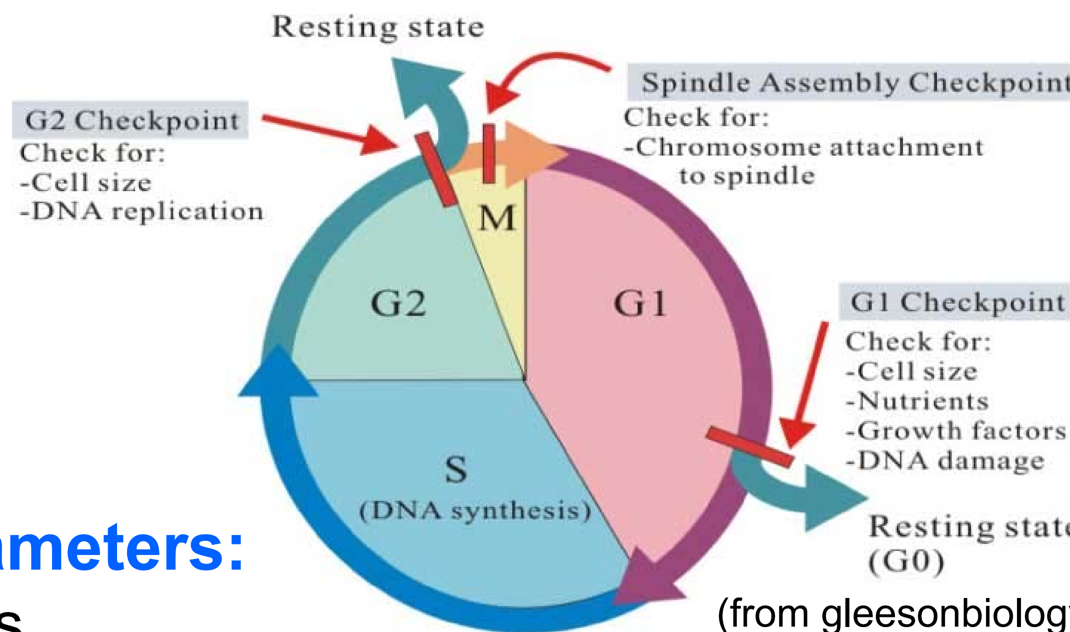


+ inter-cell interactions

It's complicated!

Cell Cycle

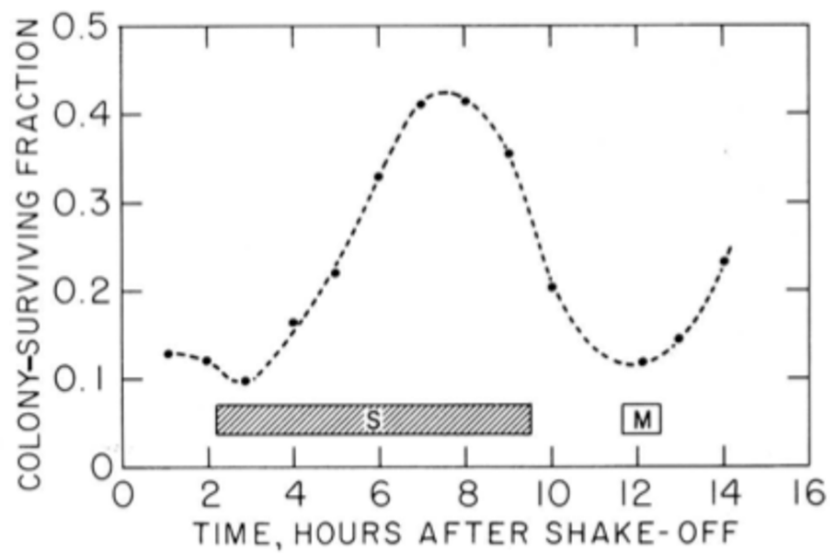
Cell Cycle Stages:



(from gleesonbiology)

Typical Cell Cycle Parameters:

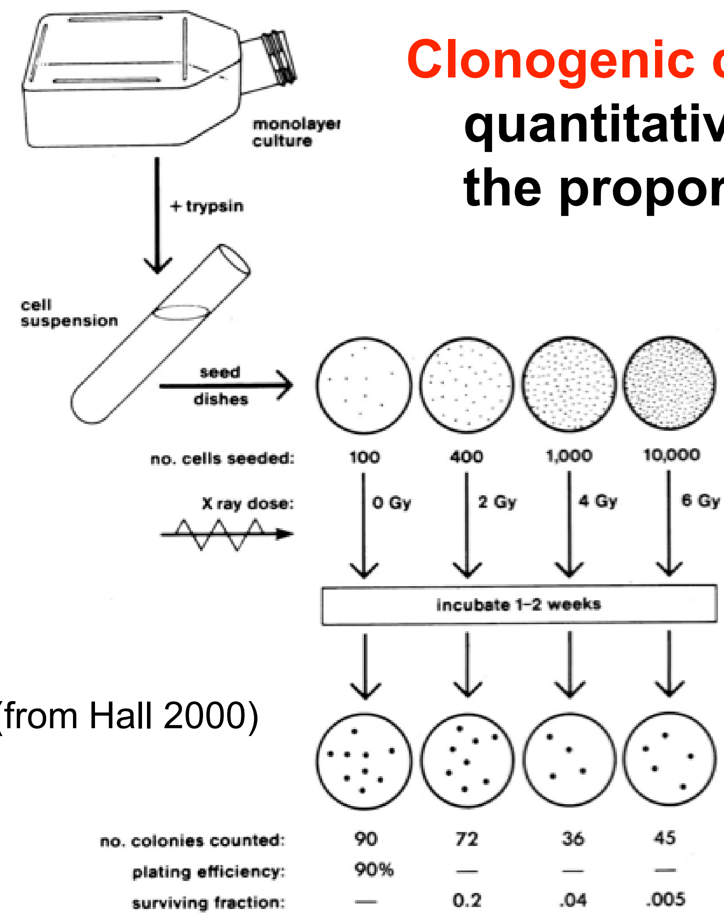
T_C	10 hours - 10 days
T_{G1}	1 - 150 hours
T_S	6 - 10 hours
T_{G2}	1 - 2 hours
T_M	1 hour



Cells most sensitive in G2/M
Cells most resistant in late S

Radiobiology experiments: Cell Survival

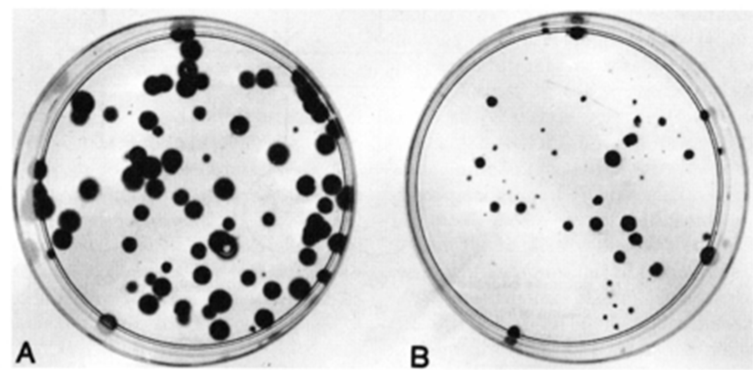
Measuring a cell survival curve



(from Hall 2000)

Clonogenic cell survival curve

quantitative relationship between radiation dose and the proportion of cells that survive (form a colony)



Cell death

loss of reproductive capacity; loss of ability to form a colony

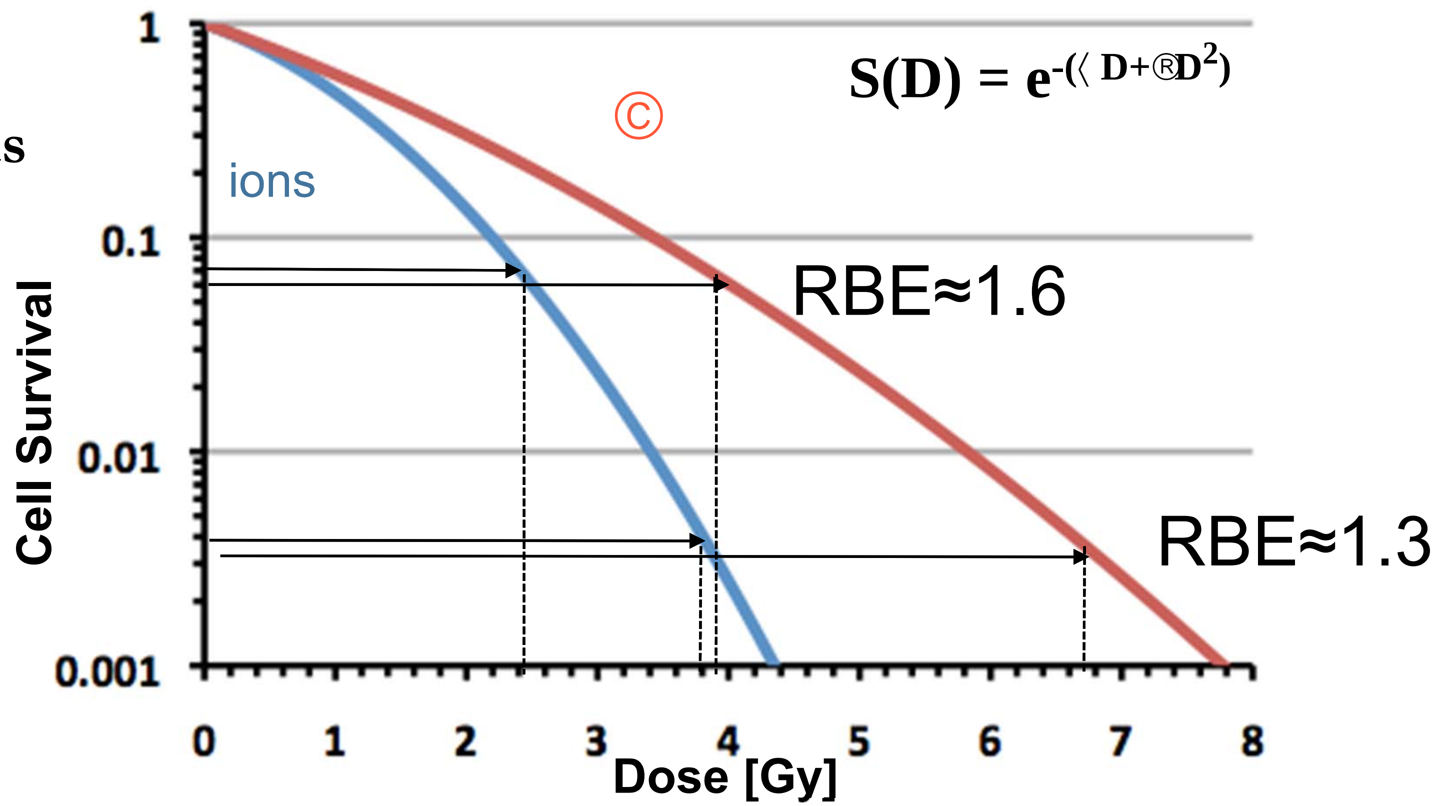
In unirradiated control: Plating Efficiency (PE) = # colonies/# cells plated

In irradiated samples: Surviving Fraction = # colonies/(# cells plated x PE/100)

Relative Biological Effect - RBE

RBE is a concept to relate radiation effectiveness of proton and ion t

RBE depends on dose



$$\text{RBE} = \text{Relative Biological Effect} = \frac{D_\gamma}{D_{protons}} \langle effect \rangle$$

Linear Quadratic Model

Assumption – two components to cell killing by IR

One (α) proportional to dose

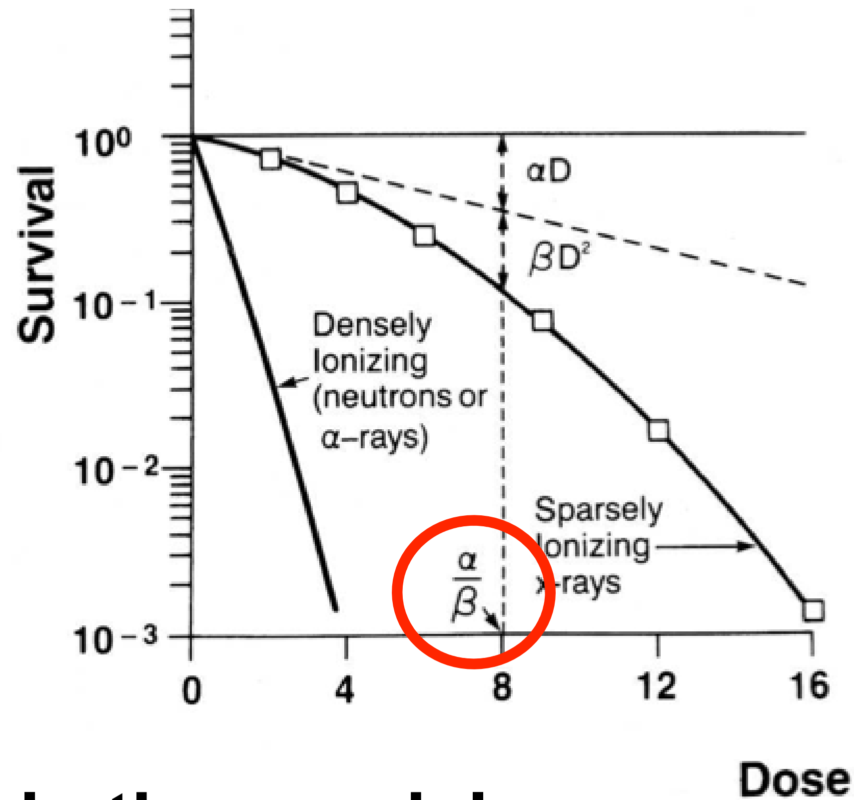
One (β) proportional to square of the dose

$$SF = e^{-(〈 D + ® D^2)}$$

〈 = initial slope at low doses

® = slope at high doses

〈 /® ratio = dose at which linear and quadratic components are equal (describes the “curviness” of the survival curve)



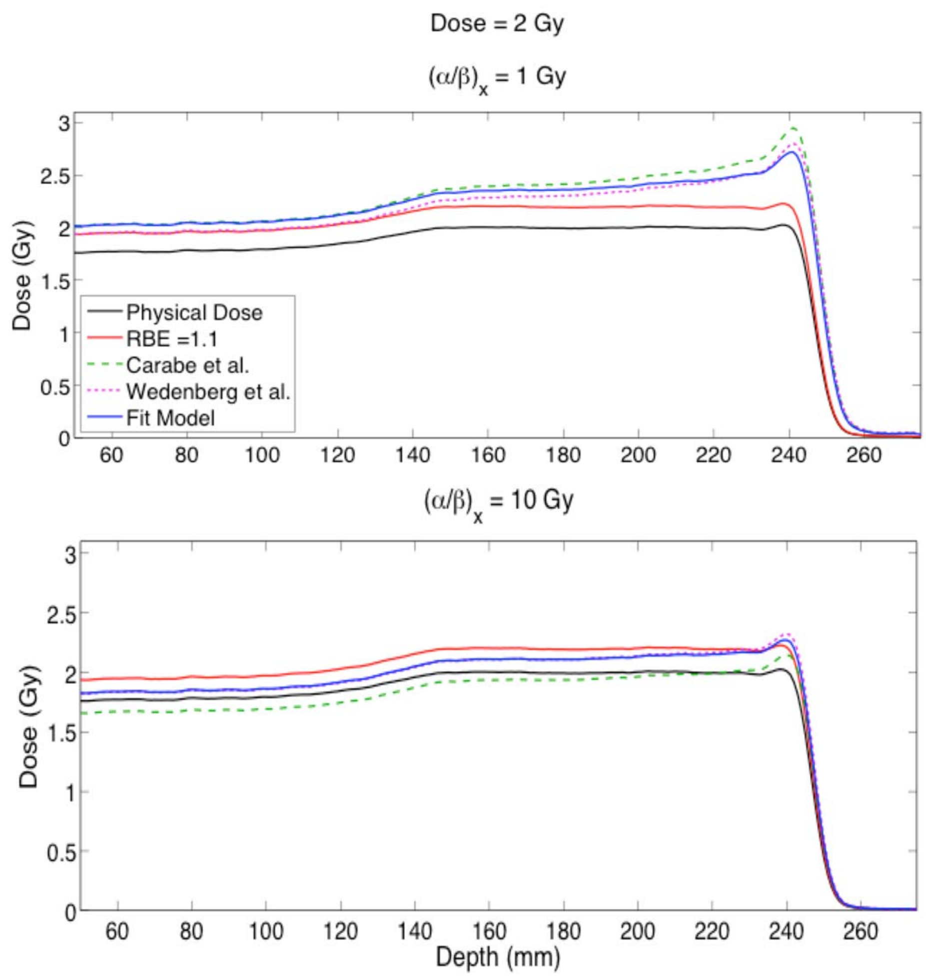
There are several other models

Clinical application of RBE in proton therapy

- Doses in particle therapy are corrected for RBE
- For proton therapy a generic RBE=1.1 is used
- RBE at center of an SOBP is ~1.1
- assuming a constant RBE may not be sufficient for more advanced therapy approaches

Dose in particle therapy is prescribed as Gy(RBE) or GyE

prediction using RBE=1.1 and different RBE models



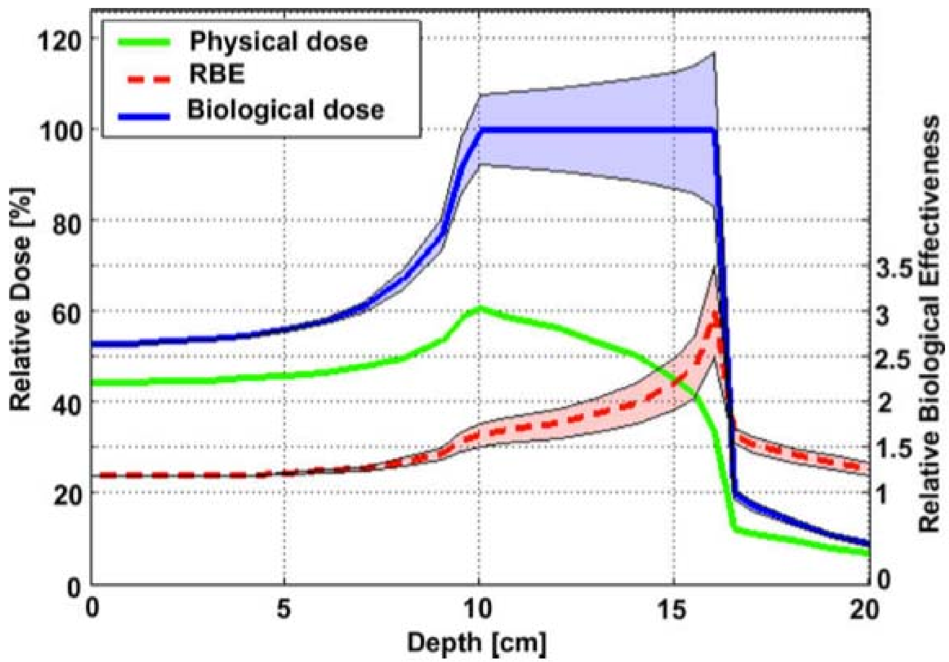
Clinical application of RBE in ion therapy

- RBE of ion fields varies strongly across treatment field
- Treatments prescribed to achieve constant biological dose in target
- Need to model RBE to prescribe treatment

RBE of ions?

... it's complicated

Impact of 2.5< α/β <3.5

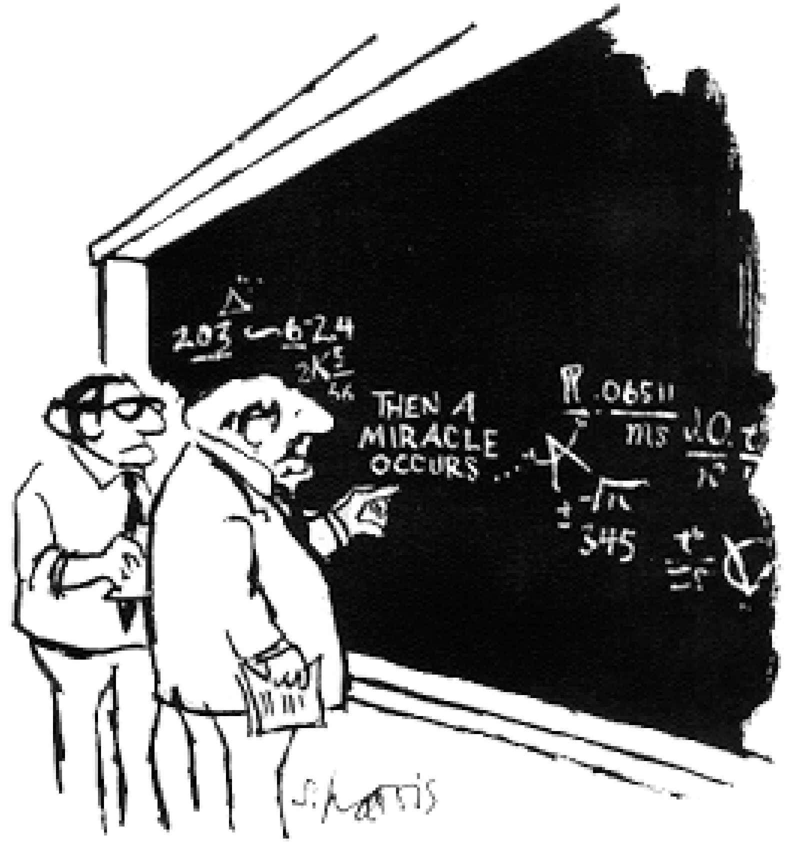


H. Suit et al, Radiother Onc (2010)

Relative Biological Effect

RBE depends on

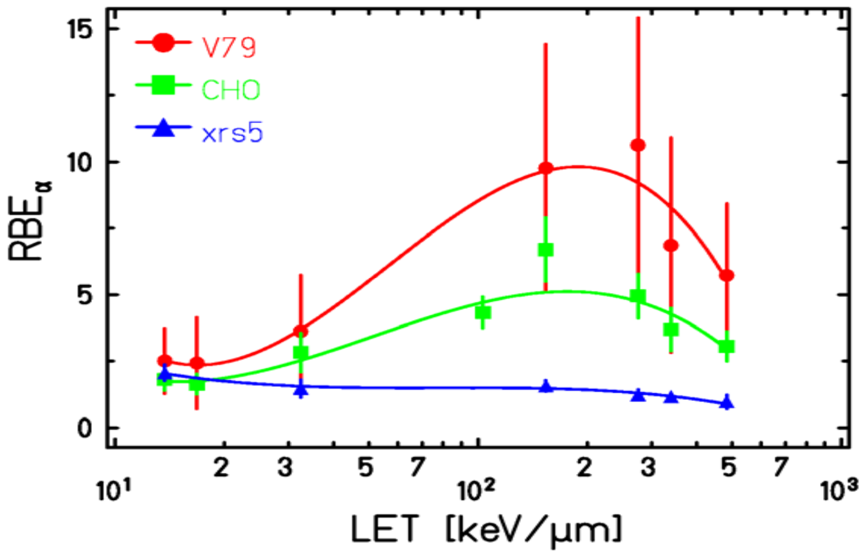
- tissue
- radiation type
- dose
- energy/LET
- endpoint
- fractionation
- etc.



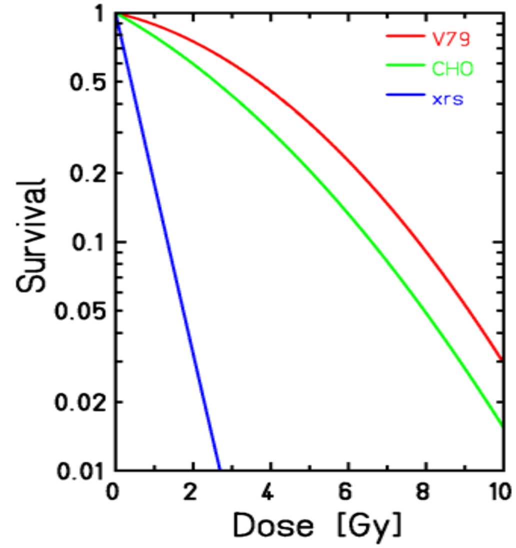
"I think you should be more explicit here in step two."

RBE as a function of tissue/endpoint

Carbon ions

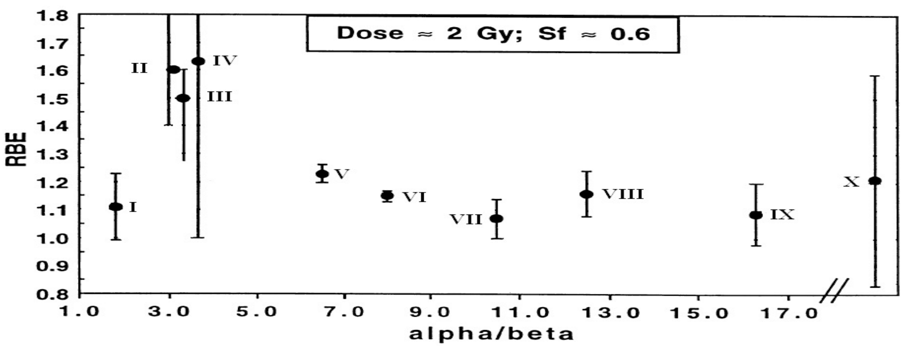


Photons



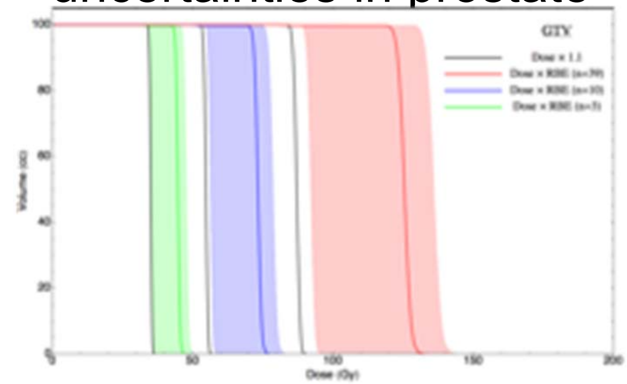
W. Kraft-Weyrather

α/β ratio



Gerweck and Kozin *Radiother. Oncol.* 1999

Uncertainties due to α/β ratio uncertainties in prostate



A Carabe, S España, C Grassberger, H Paganetti
Physics in Medicine and Biology 2013 58: 2103-2117

RBE as a function of tissue/endpoint

RBE is a concept to relate radiation effectiveness of proton and ion t

RBE is generally determined from:

- Colony formation
- **Foci formation**
- **Micronuclei formation**

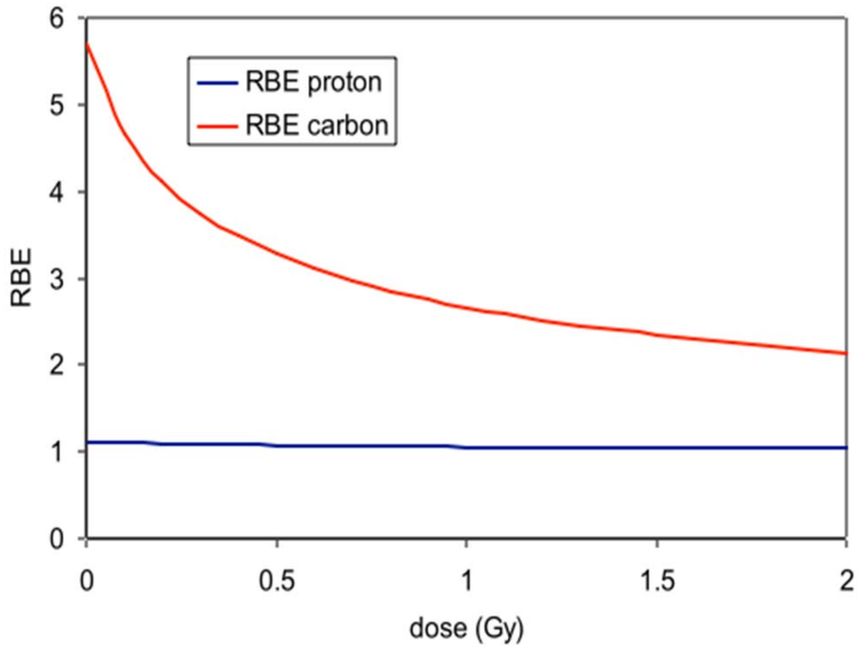
↓ **Scale-mismatch**

The relevant endpoints are clinical:

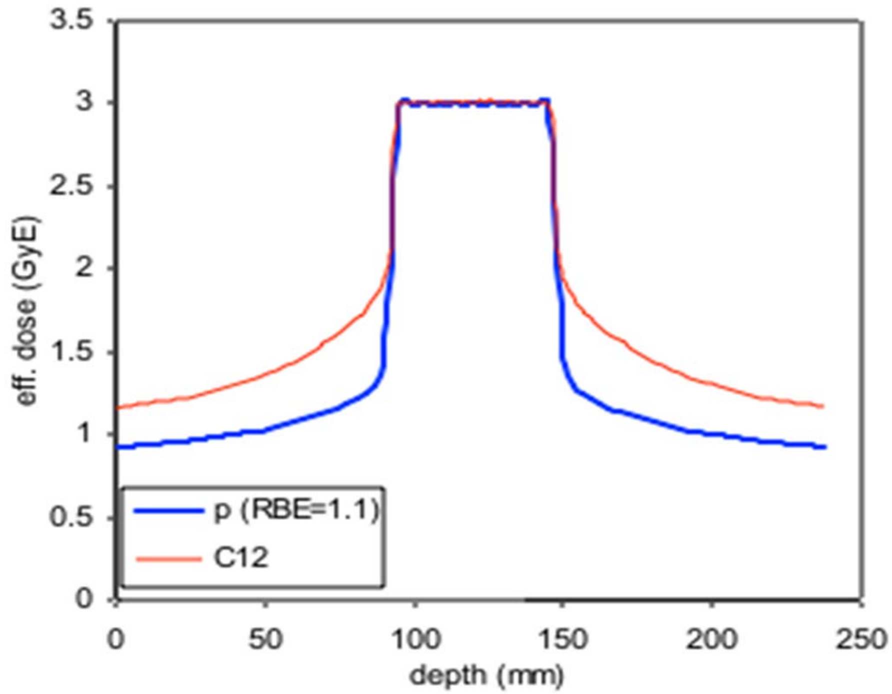
- **tumor control**
- **normal tissue complications**
  - **early effects such as erythema**
  - **late effects such as lung fibrosis, lung function, spinal cord injury, or necrosis**

RBE as a function of dose

- **RBE decreases with increasing dose**
- **The lower the LET, the smaller the effect**



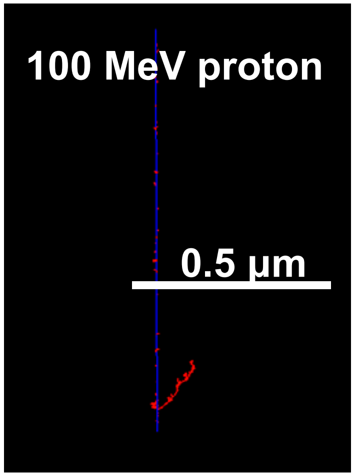
Higher RBE for OAR (lower doses)



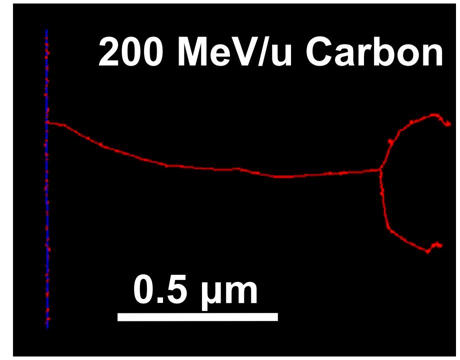
Wilkins and Oelfke:
Int. J. Radiat. Oncol. Biol. Phys. 2008

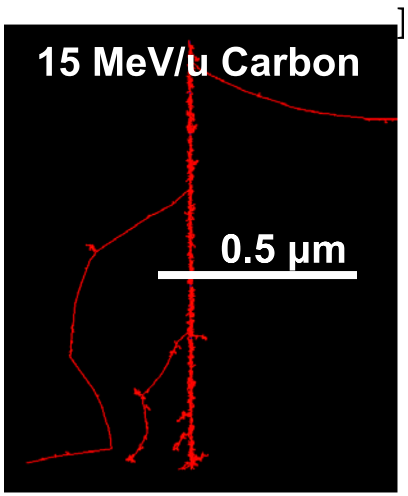
The effective dose out of field is lower for proton therapy than Carbon therapy!

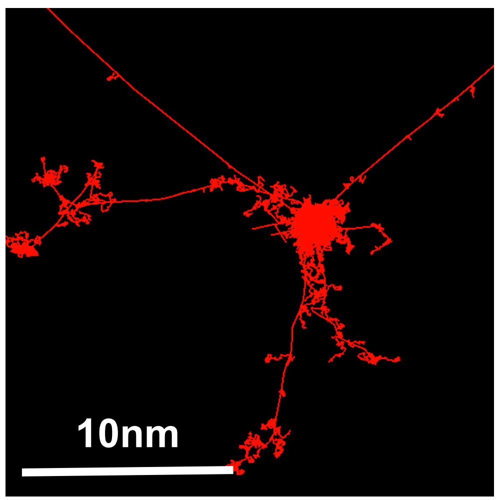
RBE as a function of energy/LET

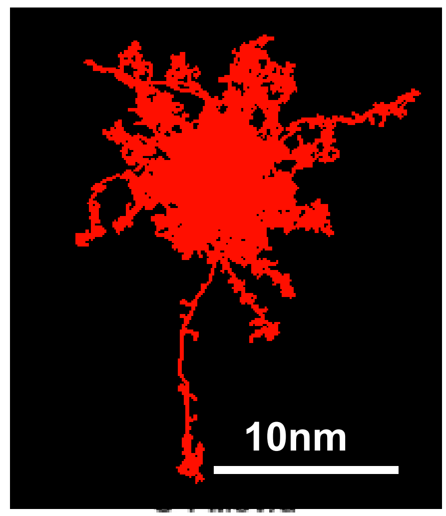


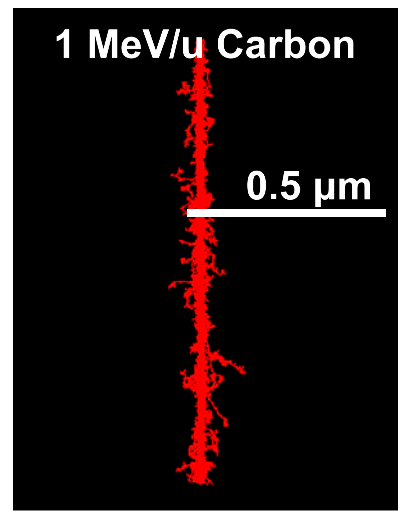
Simulated with TOPAS











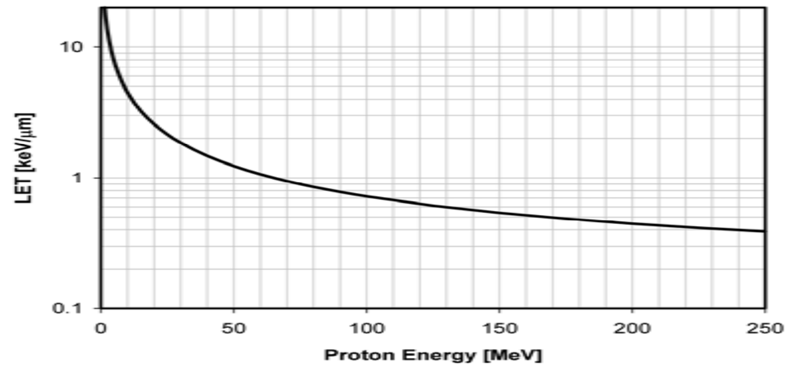
Radiation is more effective when energy depositions are more concentrated in space

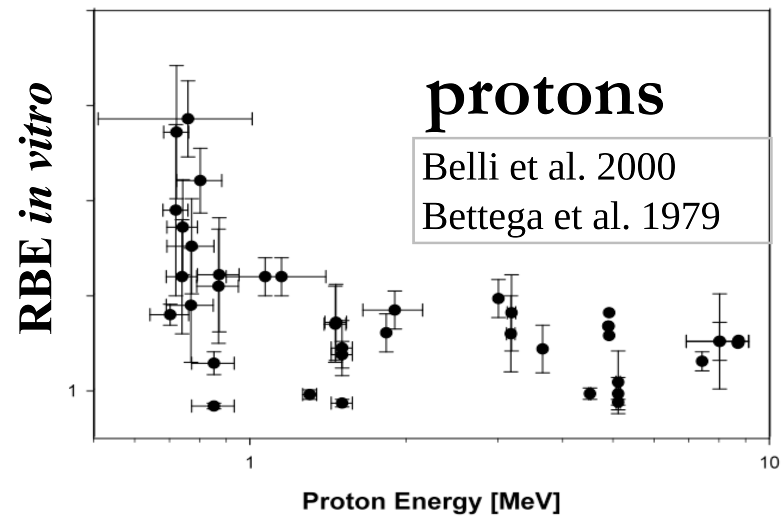
RBE as a function of energy/LET

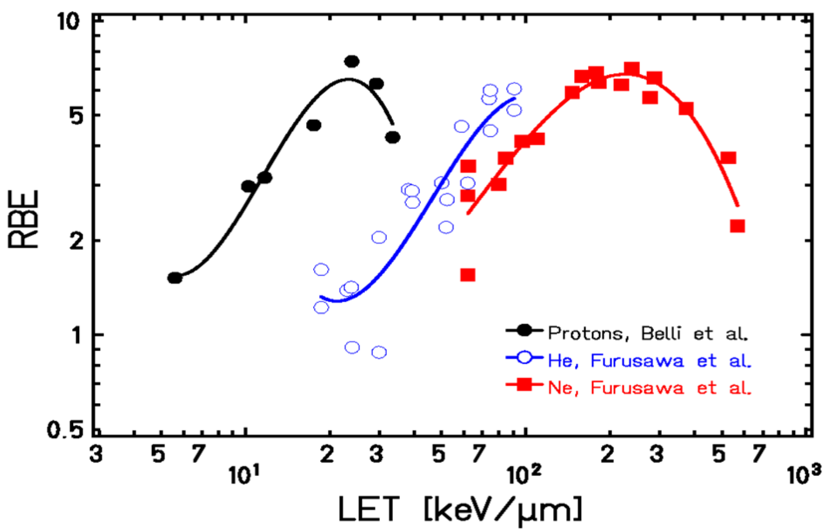
LET □ Energy

Radiation	LET (keV/μm)
Photons	
^{60}Co (~1.2 MeV)	0.3
200-keV X-ray	2.5
Electrons	
1 MeV	0.2
100 keV	0.5
10 keV	2
1 keV	10
Charged particles	
proton 2 MeV	17
alpha 5 MeV	90
carbon 100 MeV	160
Neutrons	
2.5 MeV	15–80
14.1 MeV	3–30

RBE increases with LET







protons create lower energy ™-rays (smaller track halo) compared to heavy ions at a given LET

®higher local dose

®proton RBE > ion RBE at a given LET

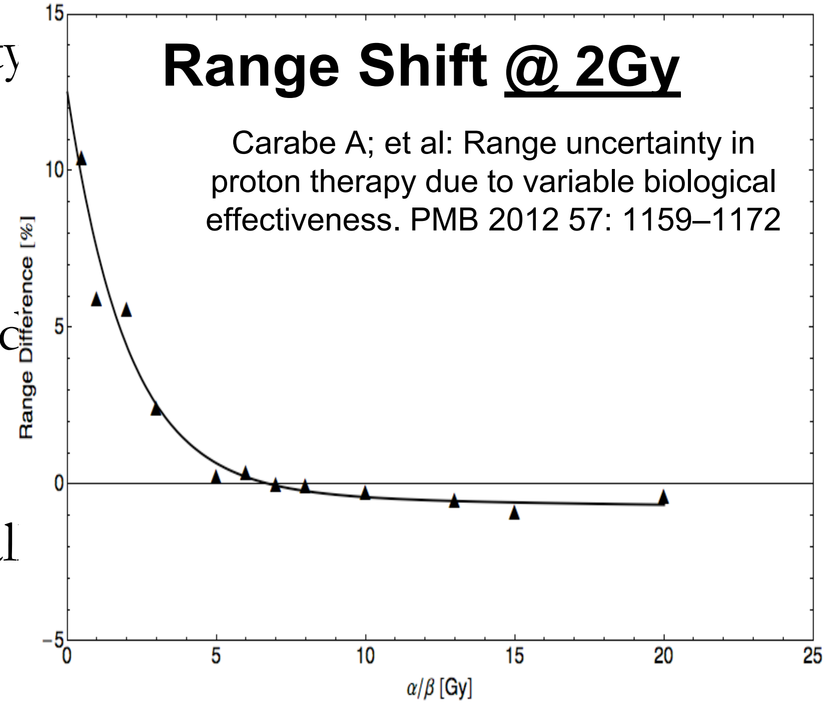
RBE as a function of energy/LET

- Increased effectiveness as a function of depth

- Extended beam range (i.e. range uncertainty to be considered when pointing a field towards a critical structure)

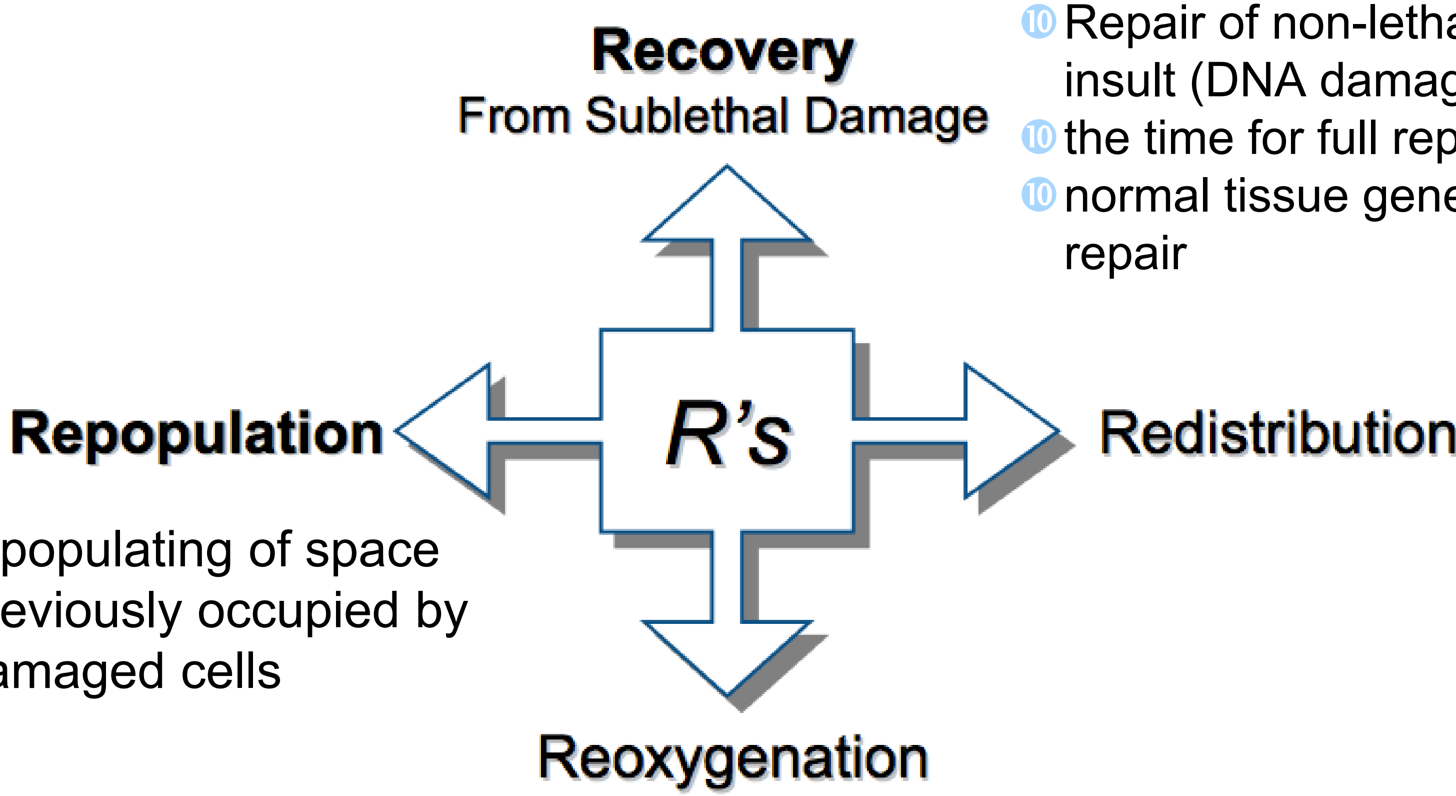
- RBE might be higher close to the 'target' ec (mainly in OAR)

- LET is well understood and could potential used in biological treatment optimization



... but there is more

The 4 R's of Fractionated Radiation Therapy

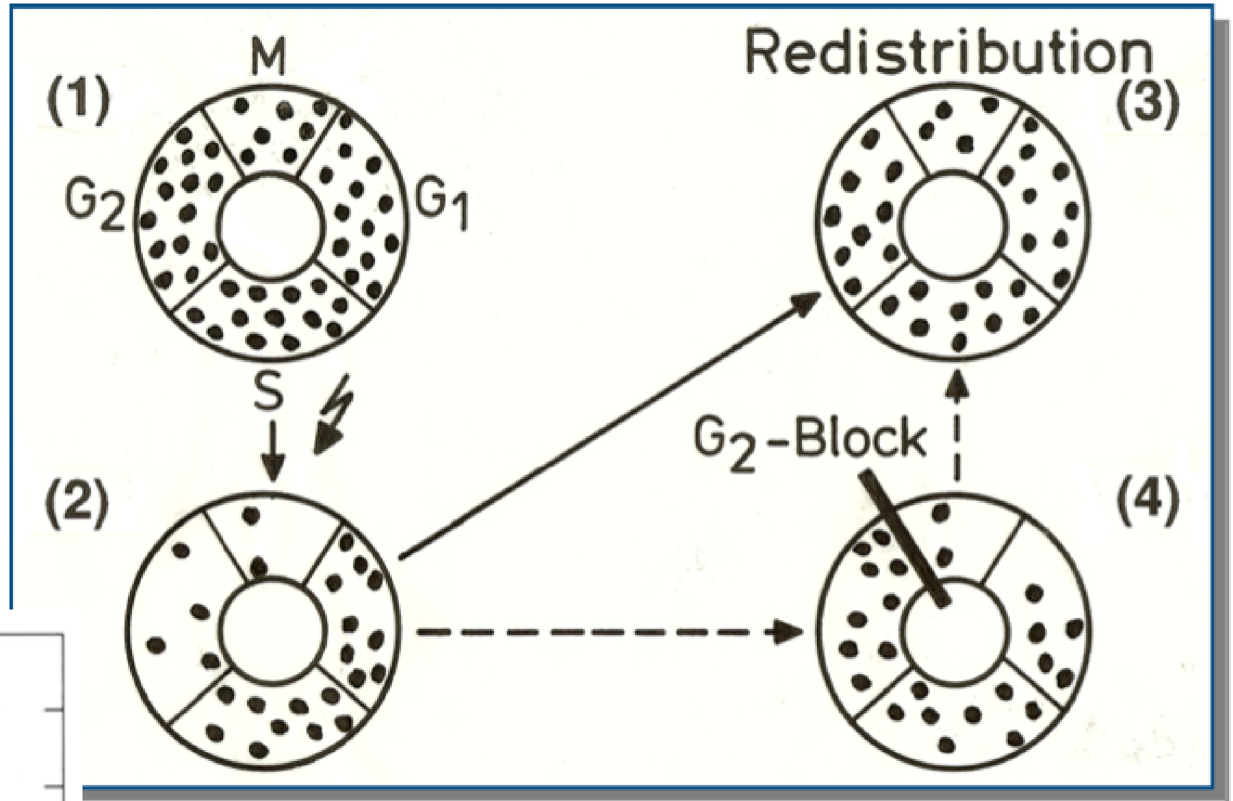


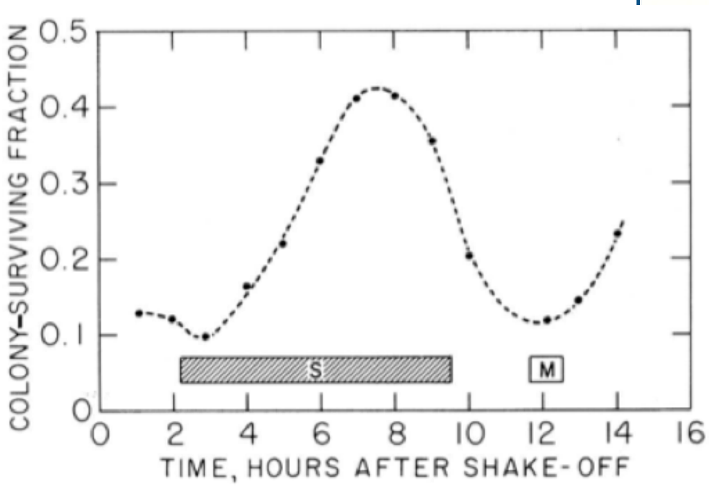
- Repair of non-lethal radiation insult (DNA damages) in cells
- the time for full repair is ~6 hours
- normal tissue generally better at repair

- repopulating of space previously occupied by damaged cells

Redistribution or Reassortment in Tumors

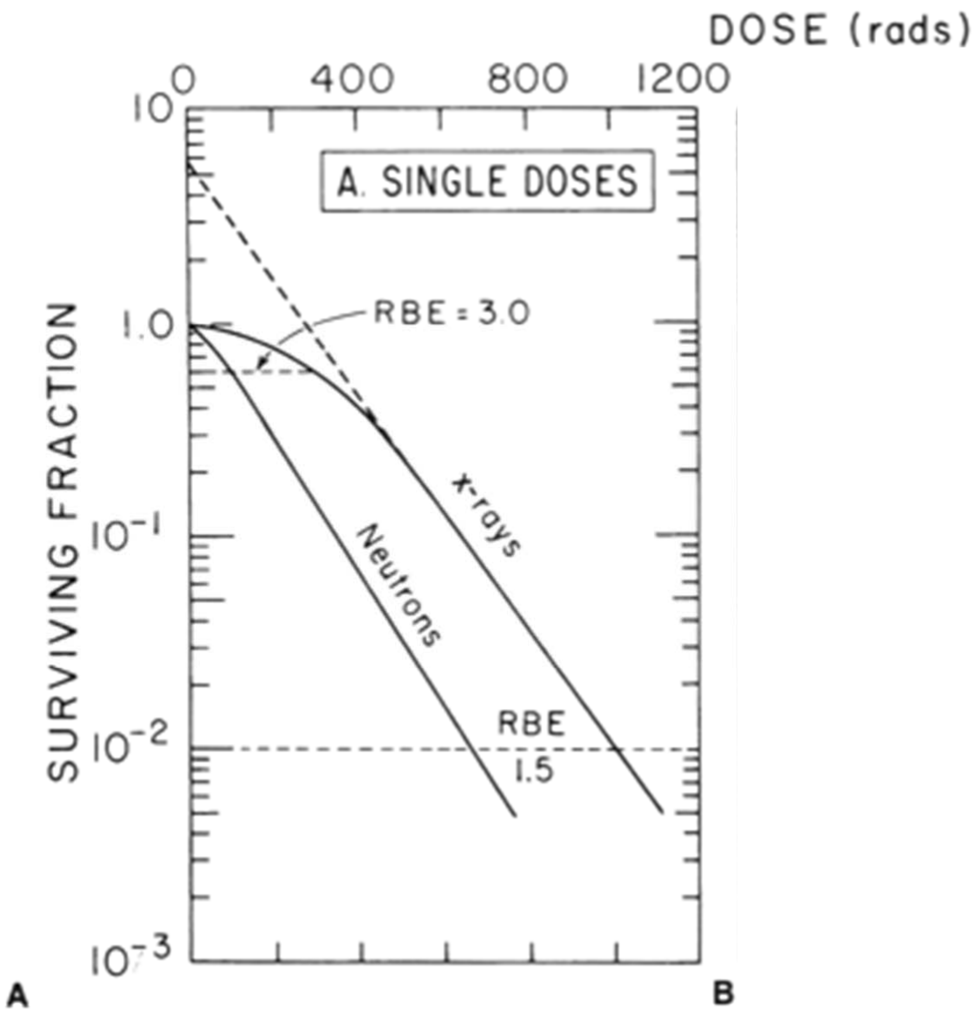
- radiation damage changes the distribution of the cell stages due to different radiation sensitivities
- over time, cell stages get redistributed





- potential G2-block, avoids cells going into mitosis before damages are repaired

RBE depends on Fractionation

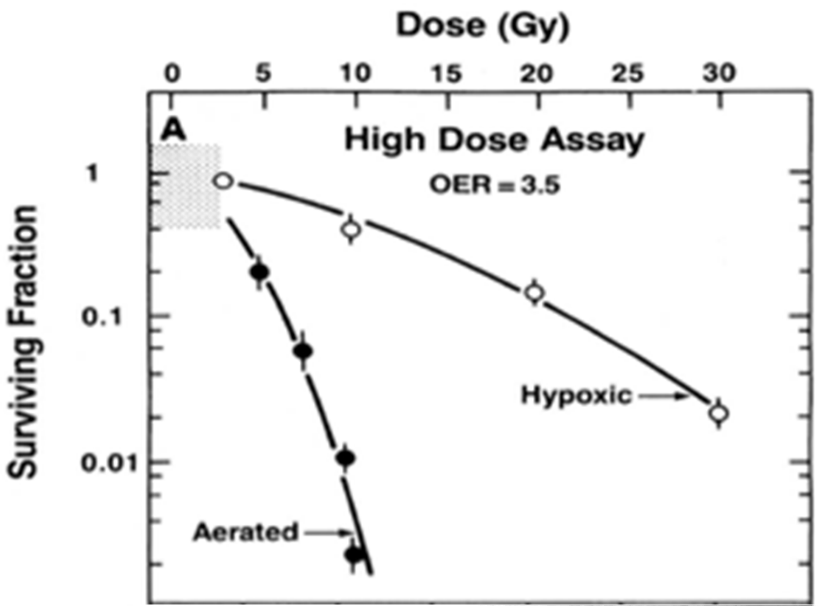


RBE increases with fractionation.

Effect is due to shoulder on the X-ray curve.

(from Hall 2000)

Oxygen Effect



Oxygen is the best known and most general radiation sensitizer.

The Oxygen Effect Ratio (OER) is:

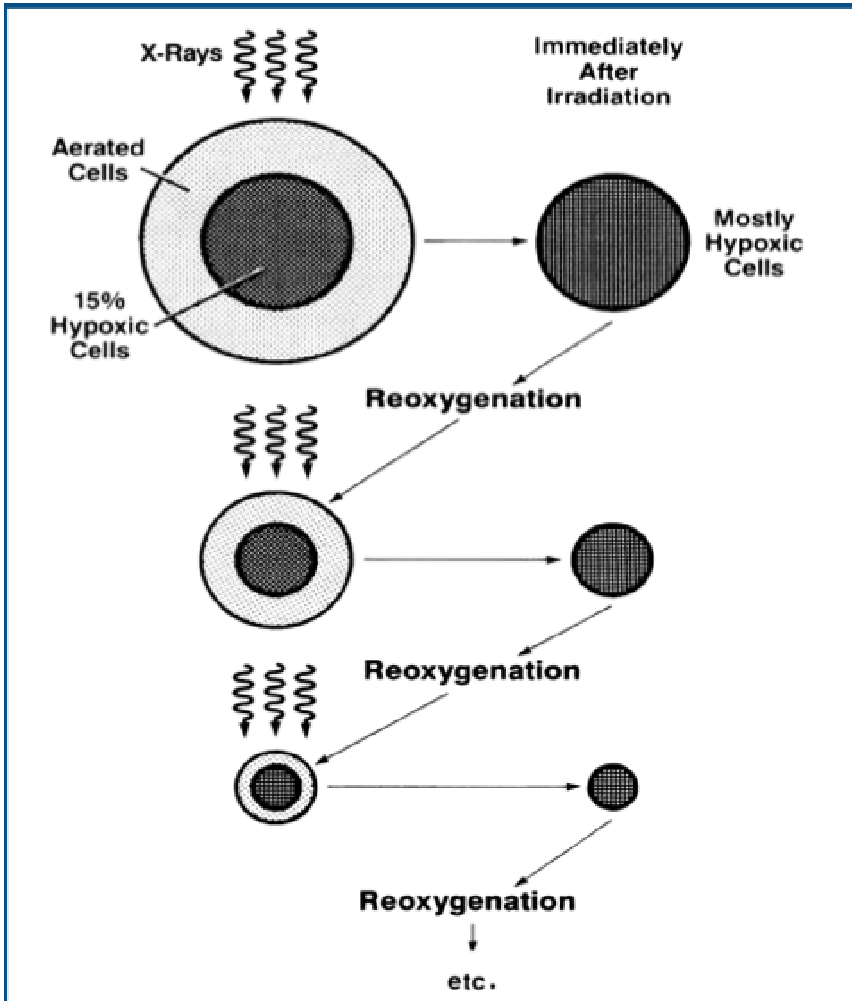
$$OER = \frac{\text{Dose(hypoxia)}}{\text{Dose(oxygenated)}}$$

OER is usually about 3 at high radiation doses, but can be lower at low doses.

(hypoxia means low oxygen;
anoxia means no oxygen)

(from Hall 2000)

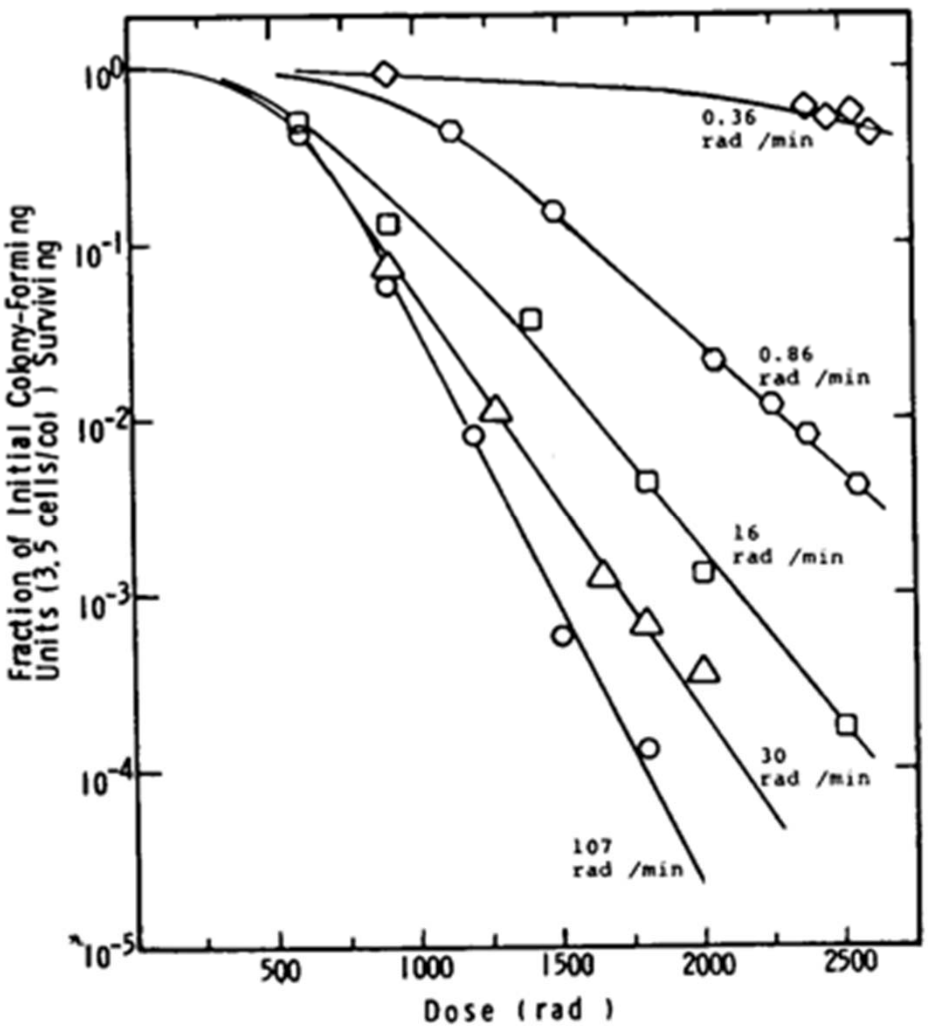
Reoxygenation in Tumors



- Phenomenon by which hypoxic cells become oxygenated after a dose of radiation
- Human tumors may contain 10-15% hypoxic cells
- Time interval between fractions needs to be long enough to allow complete reoxygenation
- “Fast” reoxygenation: One mechanism may reflect reperfusion of temporarily closed vessels
- “Slow” reoxygenation of chronically hypoxic cells may occur as the tumor shrinks

Hall textbook

Dose Rate Effect



As dose rate is reduced:
- slope of survival curve decreases
- shoulder decreases

At very low dose rates:
- all sub-lethal damage is repaired during exposure
- repopulation may increase survival or tumor growth

RBE Summary

RBE depends on

Tissue:	RBE increases with decreasing α/β
Dose:	RBE increases with decreasing dose
LET:	RBE increases as a function of depth
Dose Rate:	Higher dose rate, higher cell kill
Particle Type:	Higher LET, higher RBE (up to threshold)
Fractionation:	RBE increases with increase in fractions

- For an optimal treatment plan, we need to consider all of these parameters at the same time
- Many more biological factors to be considered

- How do we use RBE in clinical treatment planning?
  - Protons: RBE = 1.1
  - Ions model RBE

HIT: Local Effect Model (LEM) for calculation of RBE

- Idea:
  - Determine number of lethal damages in the nucleus
  - Use radial dose distributions around ion tracks (ion dependent)
  - Combine photon dose response and microscopic dose distribution
  - Overlay tracks and integrate lethal damages in nucleus

Local biological effect:

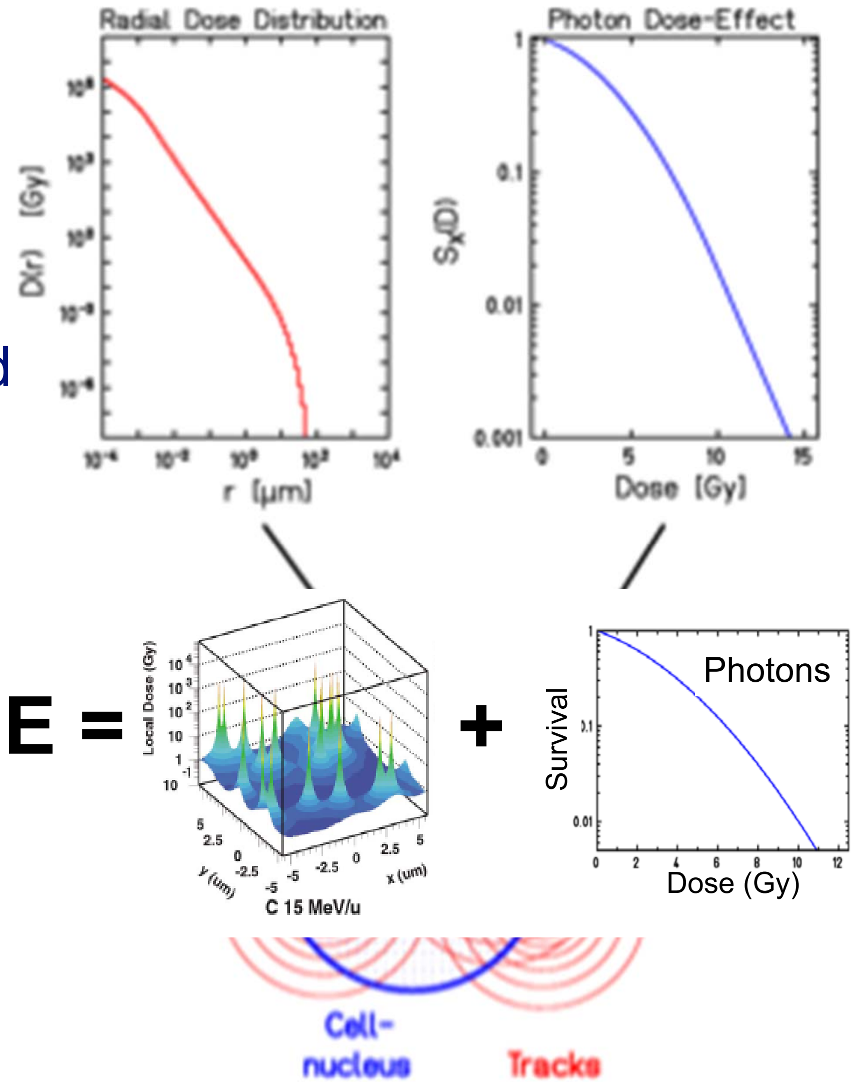
$$S = e^{-\bar{N}_{lethal}}$$

$$\bar{N}_{lethal} = \int \frac{-\ln S_X(d(x,y,z))}{V_{Nucleus}} dV_{Nucleus}$$

d(x,y,z): local dose

M. Scholz et al.

RBE =



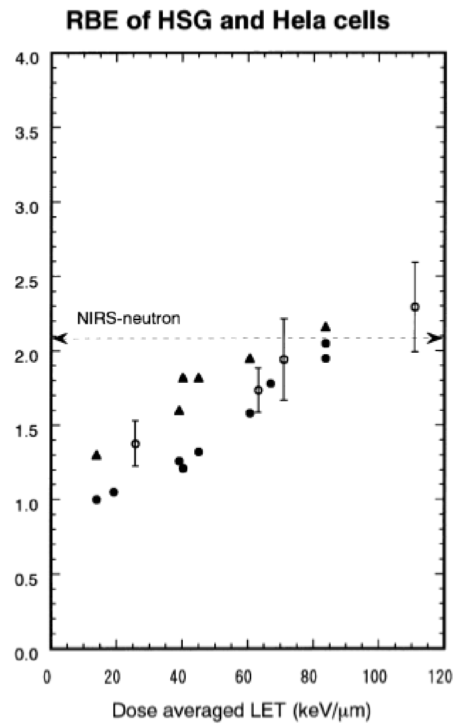
Carbon therapy at HIMAC

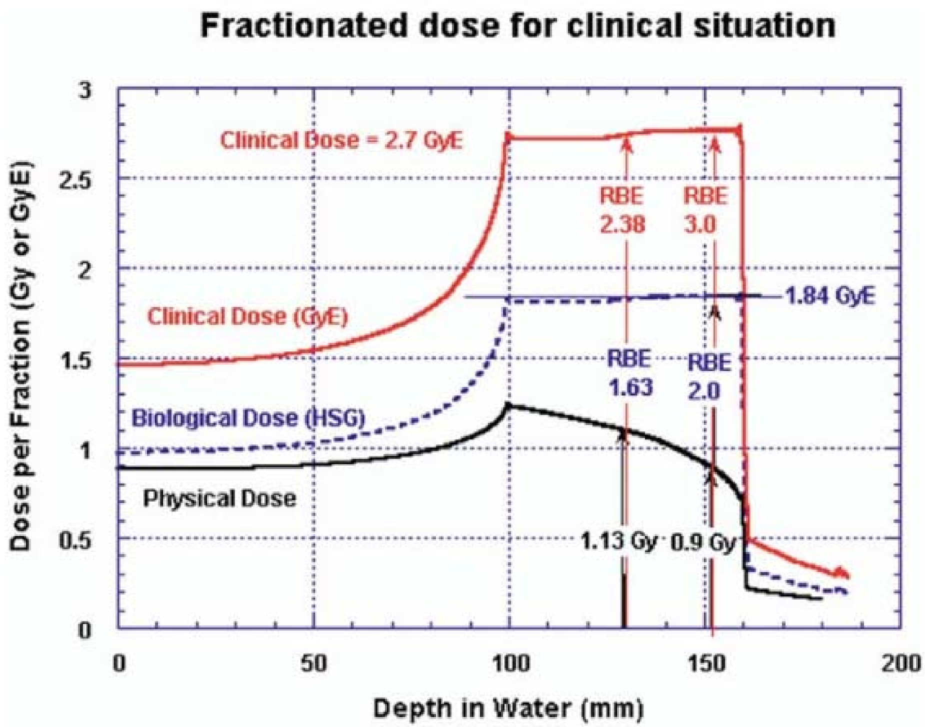
Start with experience from neutron treatment at NIRS

Carbon ions most like neutrons

Same biological effect at Carbon beam at LET ~ 80keV/μm
Neutron RBE = 3

Kanai et al, IJROBP 1999 and 2006

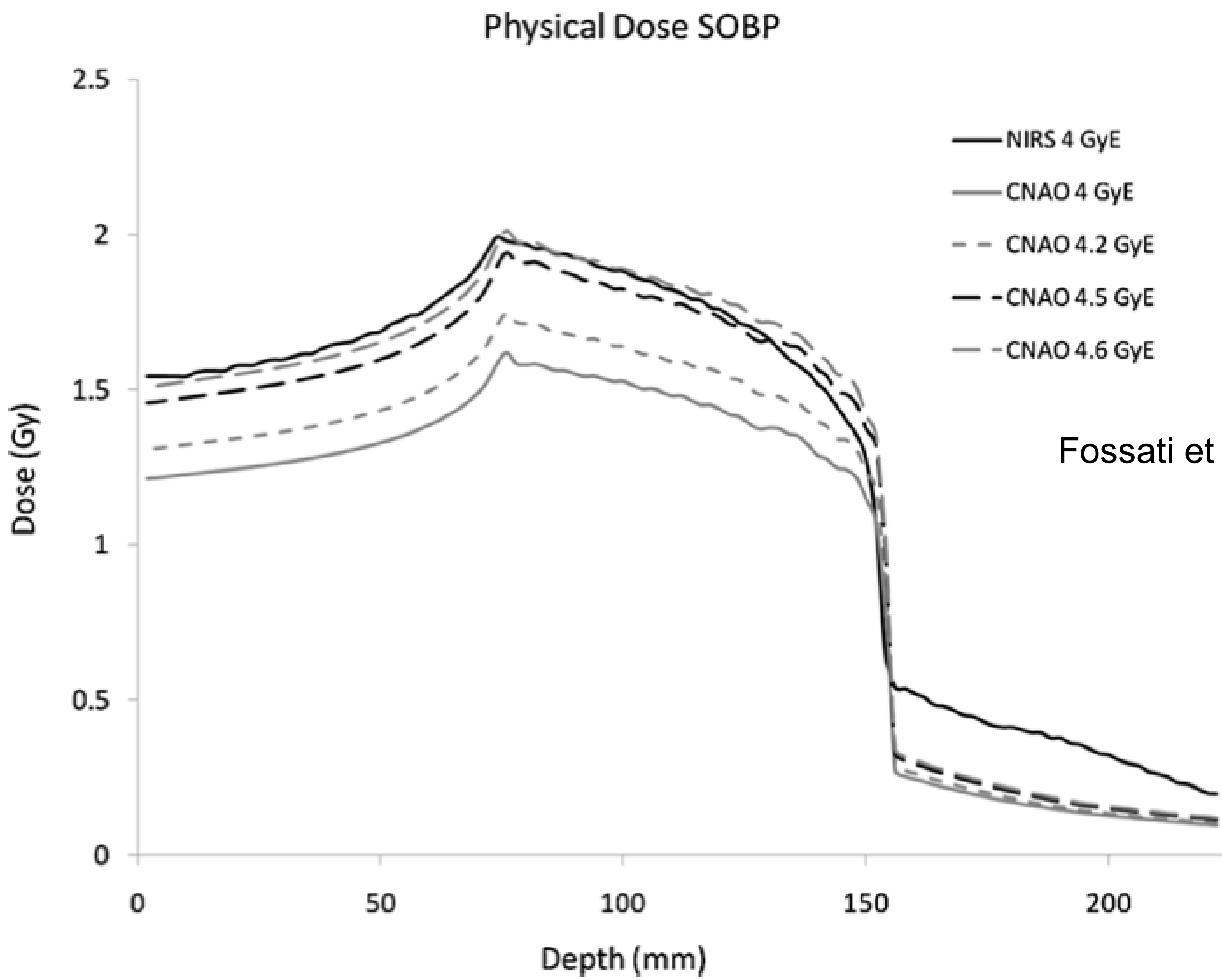




Recently some efforts to use a modified MKM model

Kase et al, J.Rad.Res. 2011

Comparing LEM and NIRS (HIMAC)



Fossati et al. PMB 2012

Similar physical dose for LEM corresponds to higher RBE-weighted dose
Steeper falloff for NIRS

Input parameters for LEM and HIMAC

LEM Input Parameters:

X-ray Survival Curves:

Experimental data according to LQ

$$S = e^{-(\alpha D + \beta D^2)},$$

D_t : dose threshold

additional assumption: Transition from shoulder to exponential shape at high doses

$$S = e^{-s_{max}(D - D_t)}, \quad D \geq D_t$$

Radial Dose Distribution (~ $1/r^2$)

Monte-Carlo (M. Krämer), Analytical Models (Katz, Kiefer), Experimental Data

Target Size (Nuclear Size)

Experimental Data

HIMAC Input Parameters:

Neutron RBE as observed for HSG cells at NIRS

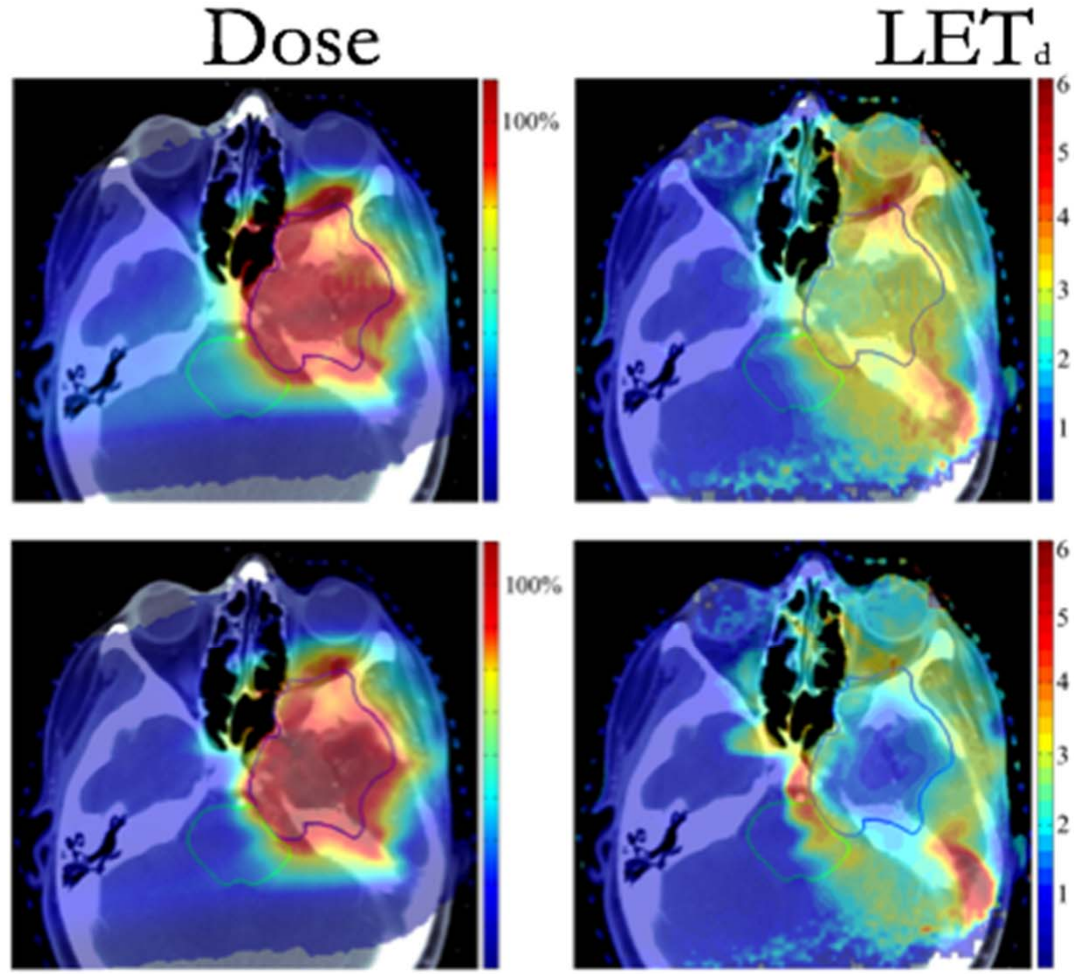
Normalize Carbon RBE to neutron RBE at 80 keV/µm

Neutron RBE = 3

Outlook (protons)

IMPT Plan 1

IMPT Plan 2



Grassberger et al., IJROBP, 80, 1559 (2011)

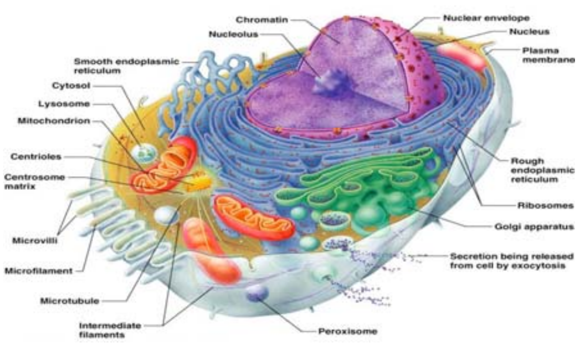
LET is highest at end of range → RBE increases

Same dose distribution does not mean same LET distribution

Take away messages, to remember when planning:

- We need to understand the biological processes better
  - currently modeling protons with constant RBE
  - Carbon RBE from limited data
  - Should use: ion specific biological effect (n/a)

Structure of a Generalized Cell



- Include advanced imaging
  - advanced imaging could determine regions of hypoxia and other tumor heterogeneities

- To go towards biological effect based plans we need to:
  - stop using flat dose distribution
  - use all the information that we can obtain
  - rethink what is possible: determine biology from the bottom up?

Thanks

For providing a lot of material shown today to:

- **Harald Paganetti**
- **Kathy Held**
- **Henning Willers**