Improved Understanding of Biological Effectiveness in Charged Particle Therapy using Geant4 Simulations: four questions at the physics/biology interface

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Roger Barlow and Piyanud Thongjerm

Int. Inst. for Accelerator Applications
The University of Huddersfield

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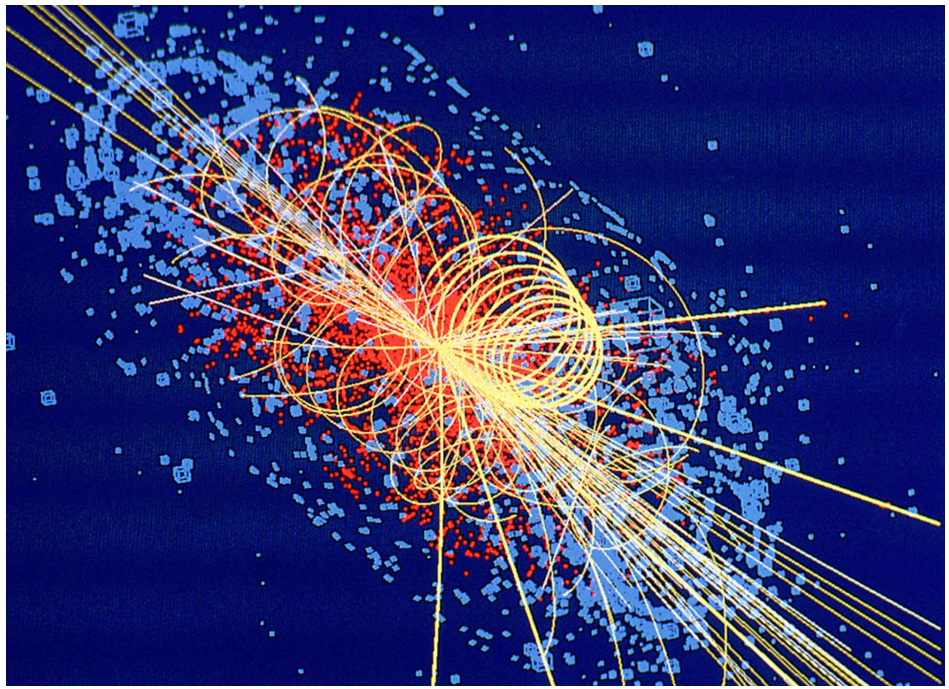
The Physics/Biology interface

Physics of charged particle interactions very well understood

Many years of experiment and theory: Bethe-Bloch, Landau, Vavilov....

Needed to make particle detectors work



Embodied in Geant4 Monte Carlo simulation program

What can this knowledge tell us about effect of radiation on cells?

Two Important Disclaimers

(1) Effects of ionisation in a cell are very complicated. To be approached with care and humility.

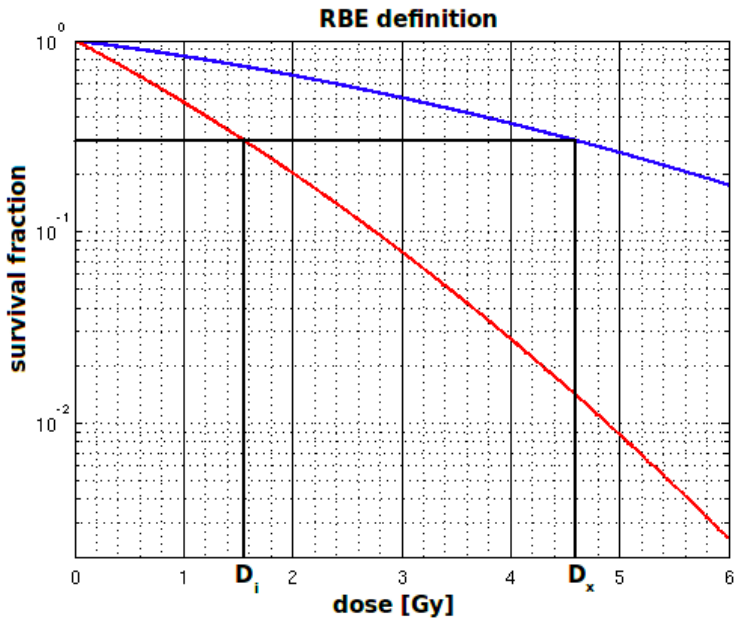
(2) Understanding behaviour of *in vitro* cells exposed to a single dose is a long way from understanding behaviour of a tumour (or healthy organ) exposed to a course of treatment. But it would be a start...

RBE is not useful (at this level)

$$RBE = \frac{\text{Effect of protons}}{\text{Effect of X} - \text{rays}}$$

(1) Not a constant as dose-dependent.

Ratio depends on where you draw the horizontal line



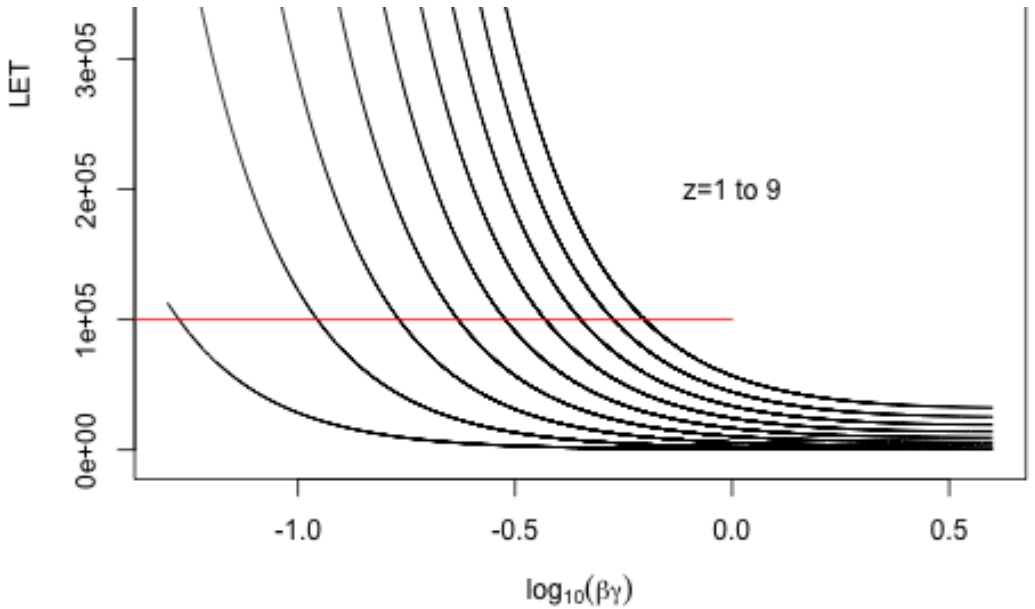
Taken from Wikipedia

Photons and carbon ions on CHO-K1 cell line

(2) Denominator is also complicated

Question 1: Does the effectiveness of a charged particle track depend on the energy deposition pattern as well as the LET?

$$\langle LET \rangle = \frac{4\pi x N r_e^2 \rho Z z^2 m_e}{A\beta^2} \left(\ln \frac{2 m_e \beta^2 \gamma^2}{I} - \beta^2 \right)$$

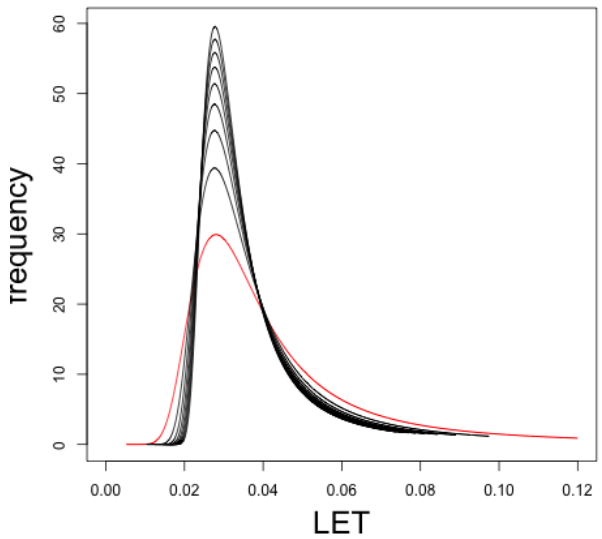


LET increases with charge z and decreases with velocity β

A slow proton can have the same LET as a fast alpha particle

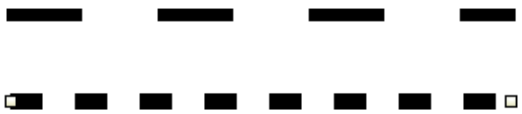
Do they have the same cell-killing power?

The same but different



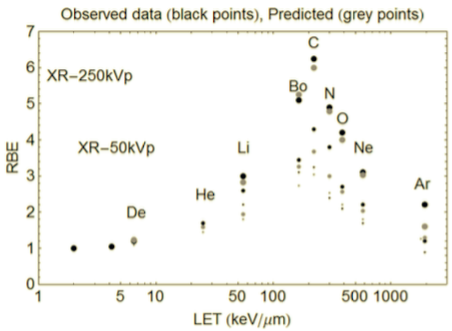
LET distributions predicted by Landau formula for z=1,2,3..9 in a 1μ distance at different β but the same $< LET >$

Proton distribution is broadest



Uses simple Landau formula - need full G4 to include geometrical effects.

Same LET, same dose, different ion/energy. Experiments need to be done.



Results (either way) would be very informative

Difference in effectiveness for different ions confuses effects of LET and of deposition pattern

Todd's data, taken from Bleddyn Jones

Question 2: Why fractionate for proton/ion therapy?

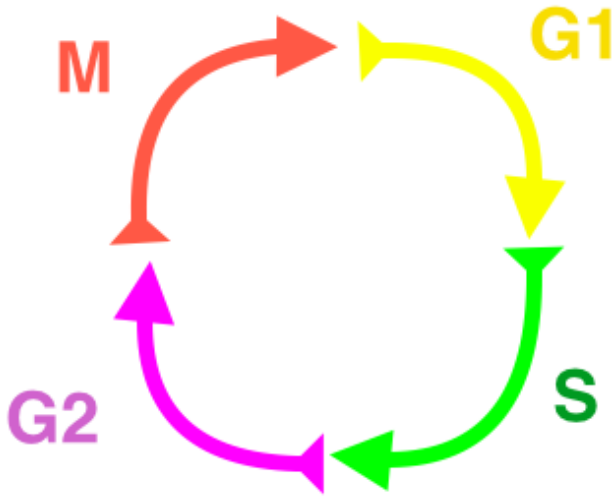
The Five R's of Radiobiology

- **Repair** Healthy cells repair themselves better than tumour cells. So with repeated equal doses, they win. But with targeted doses this is not necessary.
- **Reoxygenation** Oxygen needed to make OH radicals. Gets used up and needs time to get replenished. Important only if OH radicals are key, i.e. photons not protons/ions.
- **Repopulation** Malignant cells (often) repopulate faster than healthy ones. Argument for large fractions.
- **Radiosensitivity** - remember cell types are different
- **Redistribution** between different parts of the cell cycle. Changing radiosensitivity during the cell cycle; cells in resistant phase hit by subsequent dose.

The Cell Cycle

Growth 1
Synthesis : DNA replicates
Growth 2
Mitosis : nucleus and then cell splits

Timescale hours



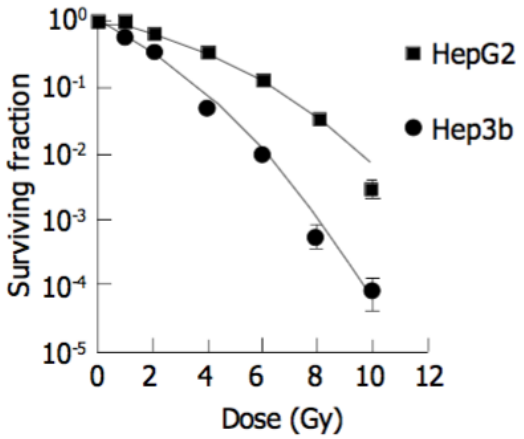
Sensitivity $M > G_2 > G_1 > S$.
Due to many factors including DNA target size
G4-DNA can study effect of different target sizes. Include in analysis of differing sensitivity. Use for planning large fraction treatment.

Question 3: Is the LQ model always valid?

prescriptive or *descriptive* ?

Prescriptive Model $\Longleftrightarrow$ Data

Data $\rightarrow$ descriptive model



$$Survival = e^{-\alpha D - \beta D^2}$$

(This data from : X-K Zheng et al, World J Gastroenterol 2005;11(10):1452-1456)

Claims to be prescriptive

... the survival fraction function for a two-stage mechanism carries an exponent proportional to the square of dose.

For single events $P(0) = e^{-\alpha D}$ but for double events (2-target model)$P(0) + P(1) = e^{-\beta D} + \beta D e^{-\beta D} \neq e^{-\beta' D^2}$

Or: damage repaired over time - fraction of damaged cells proportional to D so probability of second hit proportional to D^2 - very specific model

LQ is descriptive

Not straight line? Try parabola

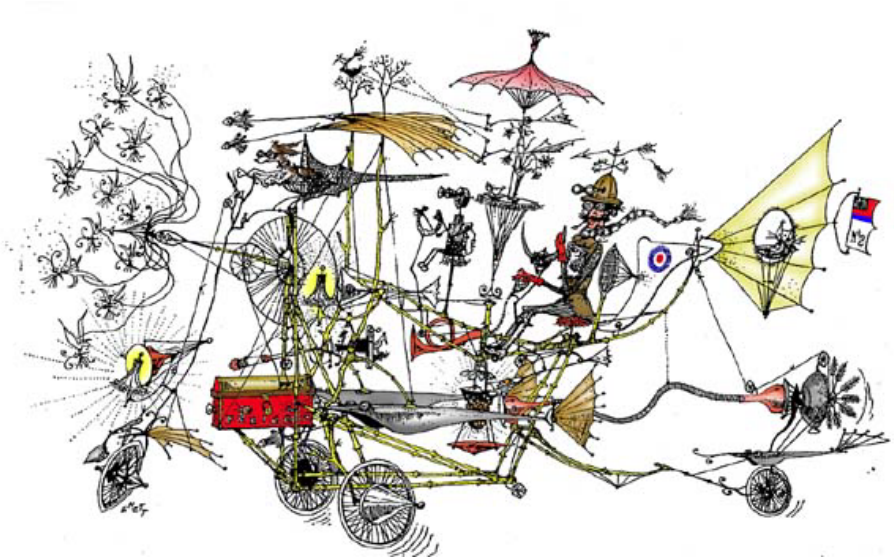
Extrapolation is dangerous
Use at high doses is contentious

D. J. Brenner, "The linear-quadratic model is an appropriate methodology for determining isoeffective doses at large doses per fraction," Semin. Radiat. Oncol. 18, 234-239 (2008).
J. P. Kirkpatrick, J. J. Meyer, and L. B. Marks, "The Linear-quadratic model is inappropriate to model high dose per fraction effects in radiosurgery," Sem. Radiat. Oncol. 18, 240-243 (2008).

Would like to establish range of validity - and possible refinements?
No shortage of (prescriptive) suggestions
Resolution needs much more data with better quality - but the experiments are SERIOUSLY difficult

Let's build a model with all the bells and whistles

Use in-silico prescriptive stochastic modelling to get on top of the mathematical arguments on descriptive models: then confront real data



General prescriptive model of what happens (or might be happening)
Using G4-DNA we can run with high statistics and controlled systematics, put in all the mechanisms anyone suggests, and investigate where the model remains valid, where alternatives may be needed, and the best form for those alternatives.

Prescriptive Model $\Longleftrightarrow$ Descriptive Model $\leftarrow$ Data

Question 4: Do radicals care about their past history?

Effect of dose depends in complicated way on particle type (photons, protons, alphas...) and energy.

Part of complication due to having both indirect effects from radical (OH) production and direct effects on the DNA.

Plausible that OH radicals produced by a proton will behave the same as OH radicals produced by a photon.

Likewise that a directly broken DNA strand doesn't care how it got broken

Can the effects of multiple different particles be reduced to just two separate effects?

Use G4 to quantify OH + other radical production for X rays and protons and other ions. Likewise DNA breaks. Analyse measurements from this viewpoint.

Conclusions

Four ideas

- Study effect of tracks with the same $< LET >$ but different patterns of energy loss
- Hypofractionate proton/ion treatment, but has to match the cell cycle
- Put the LQ model (and proposed upgrades) through its paces on simulated data
- Reduce multifold ion+energy behaviour to direct + indirect contributions

Work in progress - Watch this space!

Happy to talk