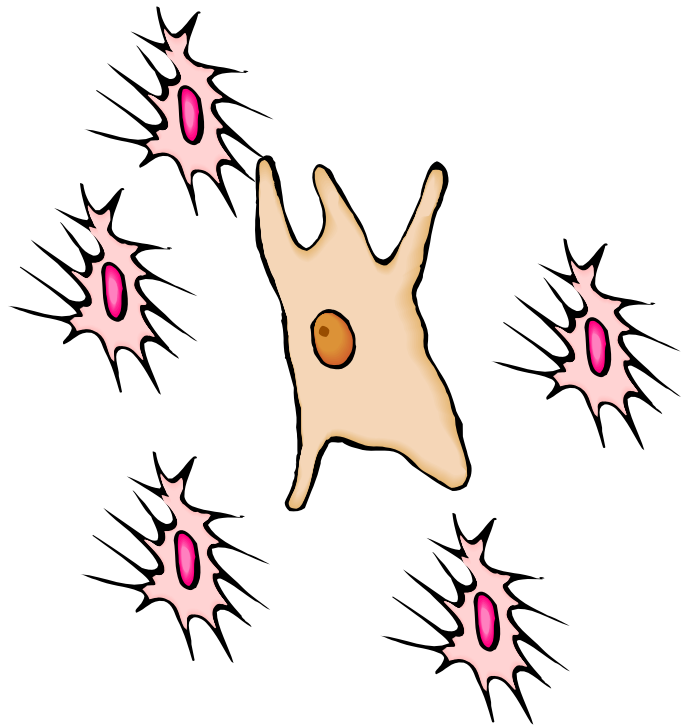
The Promise and Pitfalls of Mechanistic Modeling in Radiation Oncology



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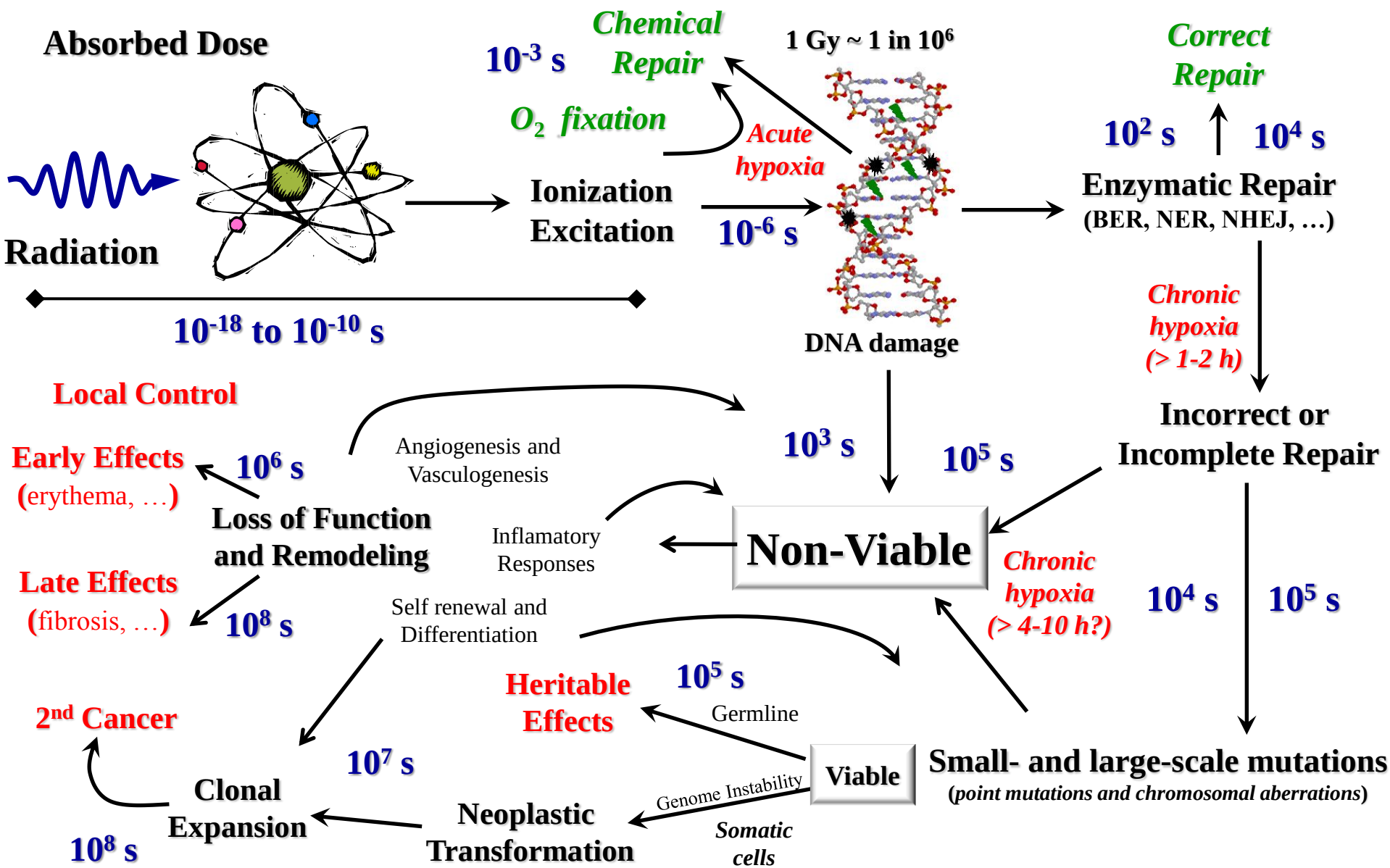
How Do We Couple Quantitative Imaging and Models of Tumor Response to Improve Multimodality Therapy?

Date and Time: Tuesday August 6, 2013, 2:00 pm to 3:50 pm
Location: Indianapolis, IN (Wabash Ballroom)

Conclusions

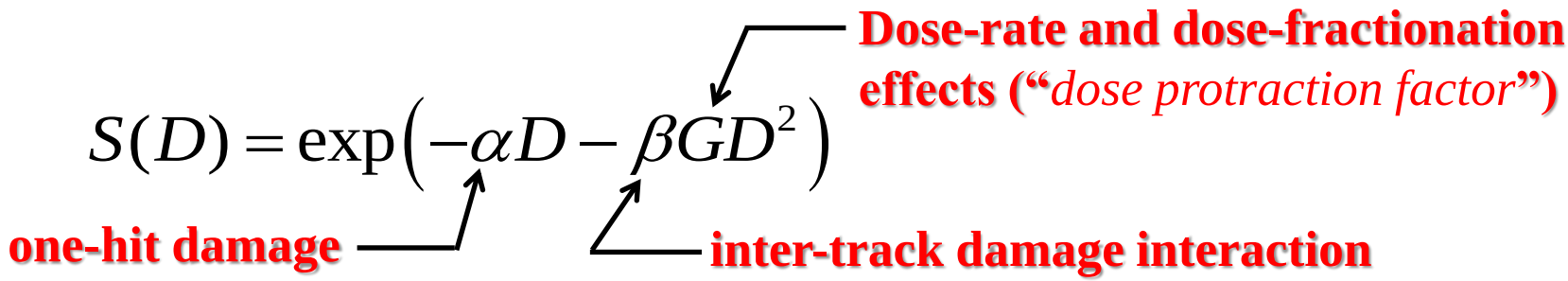
- **Local tumor control probability (TCP) modeling is not sufficiently accurate to provide patient- and tumor-specific guidance**
  - Cannot know α, α/β and the pre-treatment number of tumor cells (ρV) with sufficient accuracy
- **But… *relative* patient- and tumor-specific guidance derived from isoeffect calculations may very well be useful and practical**
  - Effects of (***1***) fraction size, (***2***) total dose, (***3***) particle linear energy transfer (LET), and (***4***) oxygen-related radiation resistance

Radiation Biology is Complex



The LQ in Radiation Therapy

Inaccurate and too simplistic (*compared to known biology*)



Parameters (e.g., α and β**) derived from analysis of clinical outcomes are uncertain and averaged over a *heterogeneous* tumor and patient population**

JF Fowler, R Chappell, M Ritter,
IJROBP **50**, 1021-1031 (2001)

α = 0.039 Gy^{-1}

α/β = 1.49 Gy

***S* = 1.159 × 10^{-3} (**37 × 2 Gy**)**

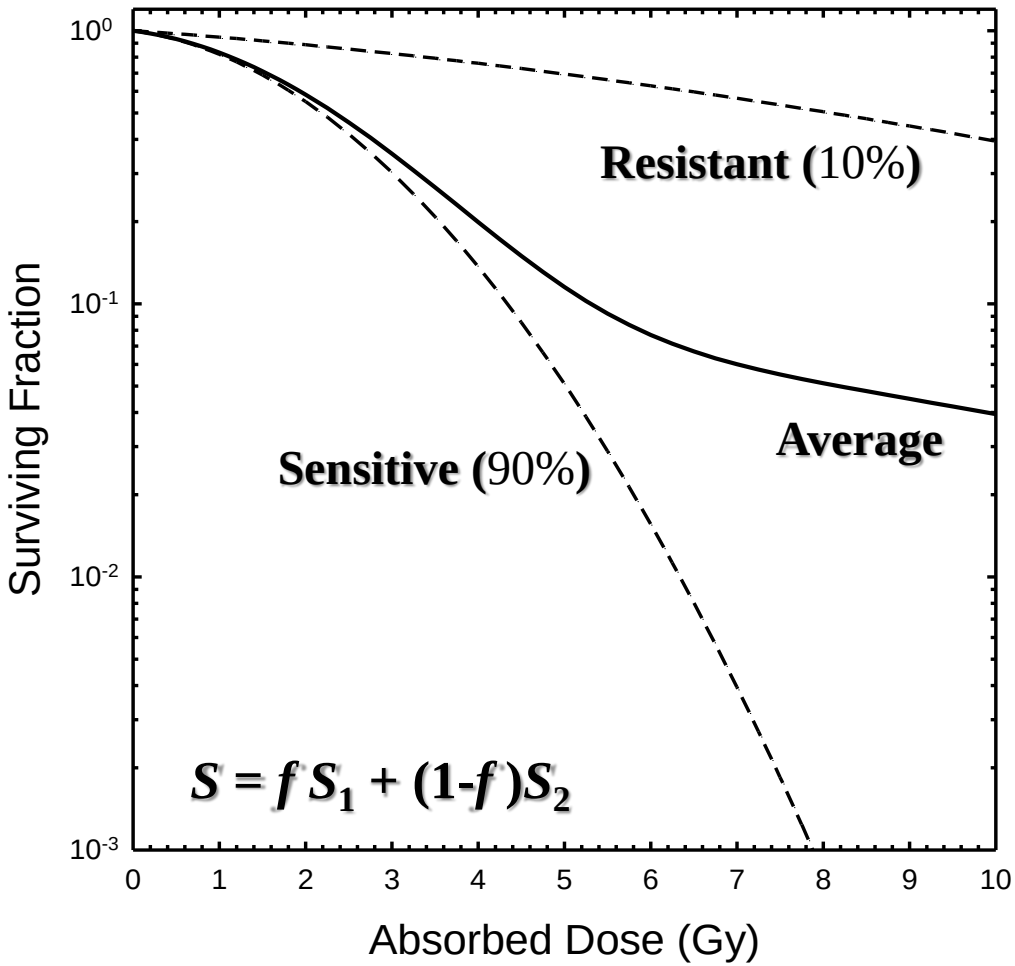
JZ Wang, M Guerrero, XA Li,
IJROBP **55**, 194-203 (2003)

α = 0.15 Gy^{-1} ***(4X higher)***

α/β = 3.1 Gy ***(2X higher)***

S* = 2.677 × 10^{-8}** ***(10^4 smaller)

SF for a Heterogeneous Cell Population

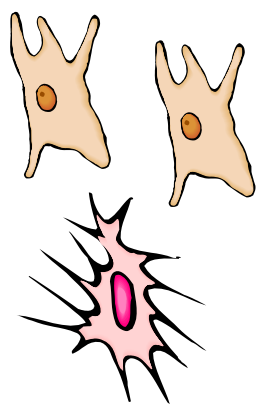


Can't use a single (*average*) set of LQ radiation sensitivity parameters (α, α/β) to predict overall shape of dose-response curve

$$S \neq \exp(-\alpha D - \beta G D^2)$$

Five Reasons (*many others possible*)

- **Genomic Instability**
- **Repair**
- **Repopulation**
- **Reassortment**
- **Reoxygenation**



Local Tumor Control Probability (TCP)

In the Poisson TCP model, the distribution of the *number* of tumor cells that survive a treatment is modeled as

$$TCP = \exp\{-\rho V S(D)\}$$

product ρV = pre-treatment number of tumor cells

Typical uncertainty in ρV? factor of 10^3 to 10^6!

Will even multi-modality imaging ever get us to a sufficiently accurate estimate of the number *and* spatial distribution of tumor cells?

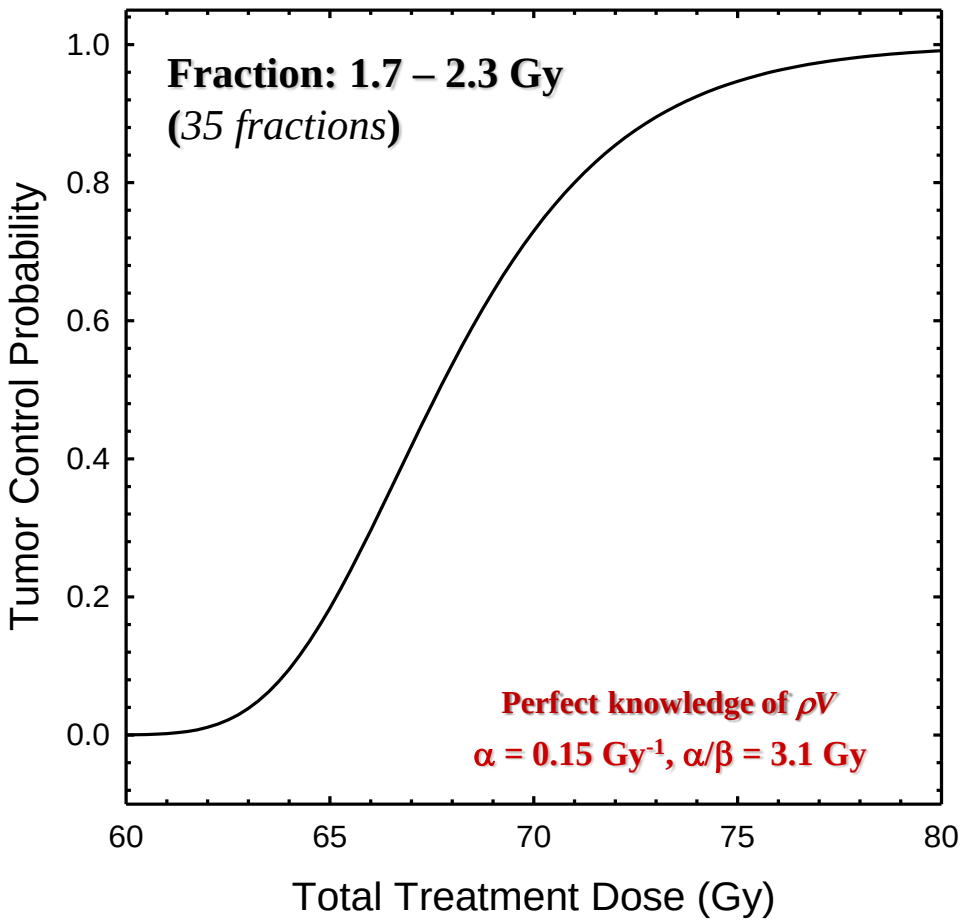
CT imaging → uncertainty in manually draw GTV and CTV contours

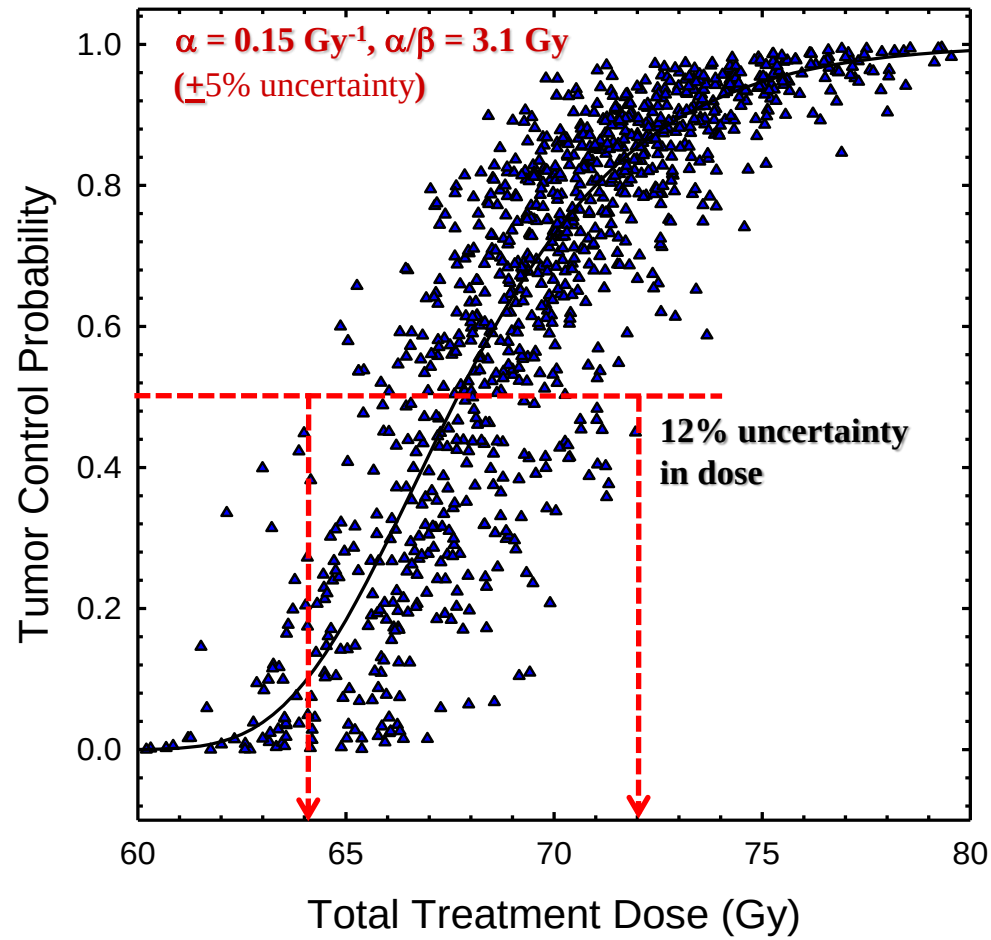
PET imaging → How is SUV related to cell density?

Do tightly packed tumor cells produce a different MR signal than normal tissue?

Can single- or multi-modality imaging differentiate ***cancer stem cells*** from the less important cells that make up the bulk of the GTV?

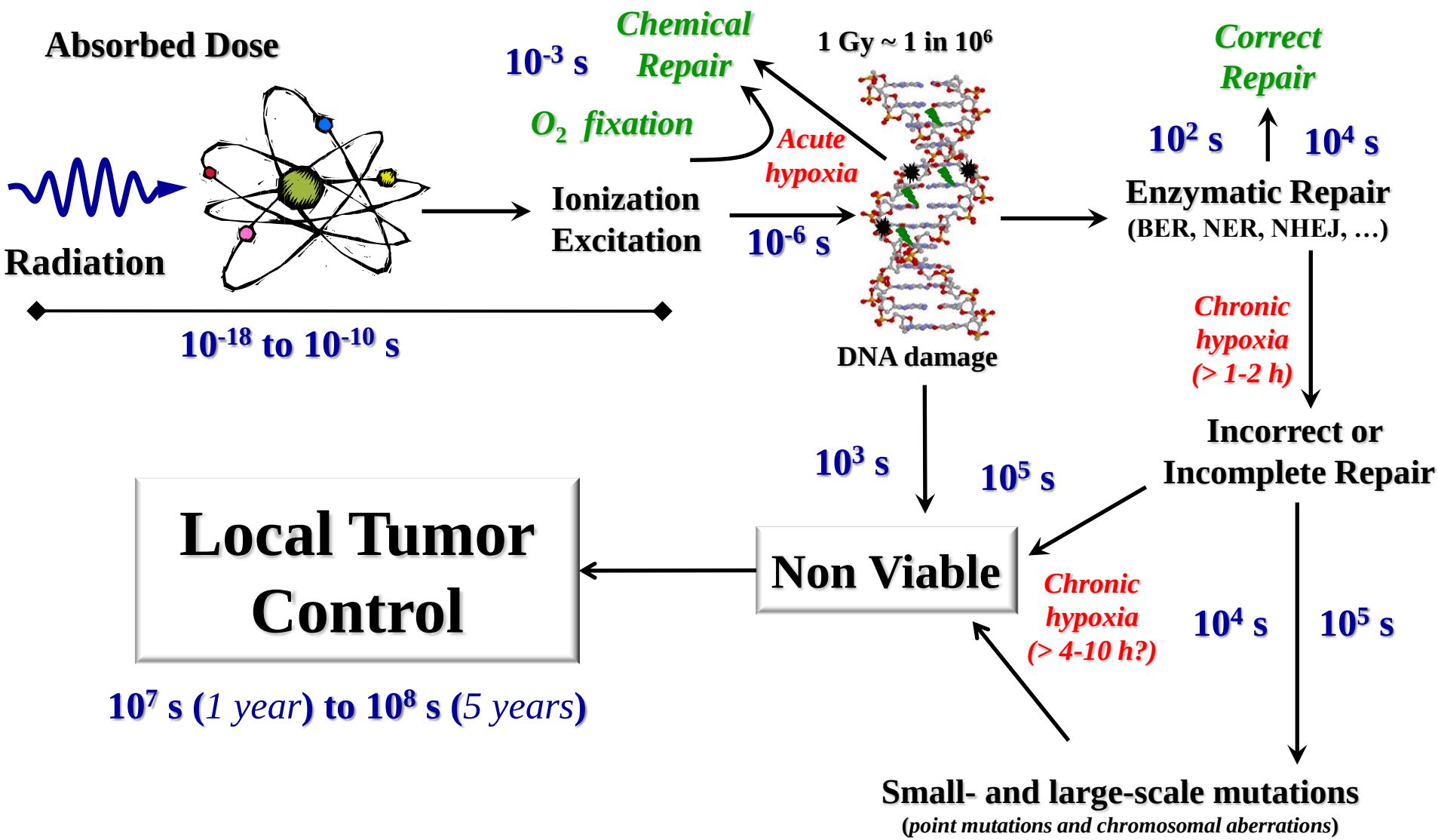
Accuracy of TCP Modeling (*The Pitfall…*)





Even small levels of uncertainty in the biological parameters (α and α/β) have a large impact on our ability to predict the TCP for individual patients

Reproductive Death as a Surrogate for TCP?



Methods – A Multiscale Approach

- **Monte Carlo Damage Simulation (MCDS)**
  - Effects of LET and Oxygen on DNA double strand break (DSB) induction
  - Microdosimetry (lineal energy, frequency-mean specific energy, CSDA range)
- **Repair-Misrepair-Fixation (RMF) Model**
  - Motivated by the breakage and reunion theory of chromosomal aberrations
  - Coupled system of non-linear differential equations link DSB induction to the formation of lethal and non-lethal chromosomal aberrations
  - RMR (CA Tobias) and LPL (S Curtis) models (circa -1980-1985) are special cases of the RMF
    - In the RMF, DSB induction is modeled with a compound Poisson distribution instead of a Poisson distribution (LPL and RMR models)

R.D. Stewart, V.K. Yu, A.G. Georgakilas, C. Koumenise, J.H. Park, D.J. Carlson, *Radiat. Res.* **176**, 587-602 (2011). D.J. Carlson, R.D. Stewart, V.A. Semenenko and G.A. Sandison, *Rad. Res.* **169**, 447-459 (2008)

RMF Model → LQ Formula

LQ model is a low dose approximation to the RMF system of non-linear differential equations (Carlson *et al.* 2008)

Intra-track chromsomal aberrations

$$\alpha = \theta\Sigma + \kappa\bar{z}_F\Sigma^2$$

Unrepairable and misrepaired damage

$$\beta = \frac{\kappa}{2}\Sigma^2$$

Inter-track aberrations

$$\frac{\alpha}{\beta} = \frac{2}{\Sigma}(\theta/\kappa) + 2\bar{z}_F$$

Cell sensitivity to changes in fraction size and dose rate

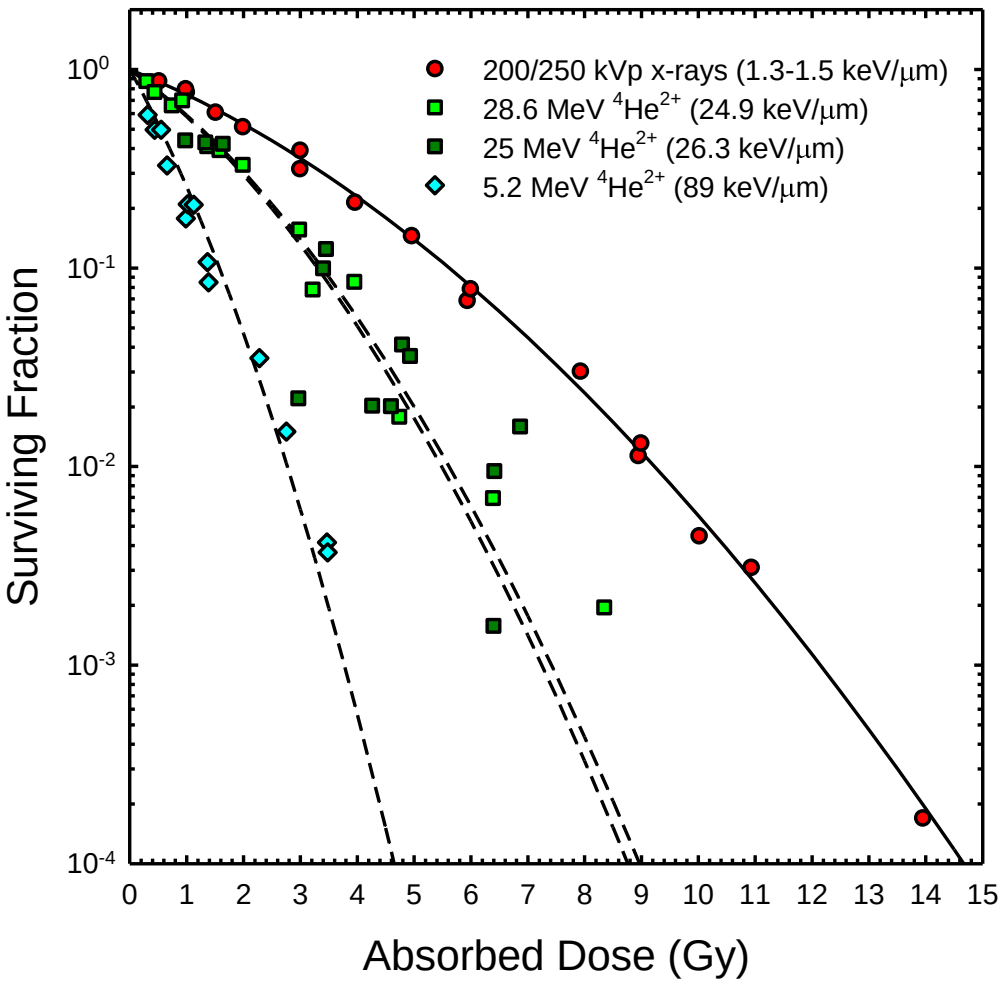
θ, κ are *adjustable cell- or tissue-specific* parameters related to the biological processing of DNA damage (*independent* of LET and O_2 concentration)

Σ is the number of DSB Gy^{-1} Gbp^{-1} (or per cell) – (*strong* function of LET and O_2 concentration)

$\bar{z}_F$ is the frequency-mean specific energy (in Gy) for the cell nucleus (*strong* function of LET but independent of O_2 concentration)

D.J. Carlson, R.D. Stewart, V.A. Semenenko and G.A. Sandison, *Rad. Res.* 169, 447-459 (2008)

Results-1 Human Kidney T1 Cells (*aerobic*)



Solid line: two-parameter model fit to survival data ($\theta = 3.07\times10^{-2}$ Gbp/DSB, $\kappa = 7.05\times10^{-4}$ Gbp/DSB).

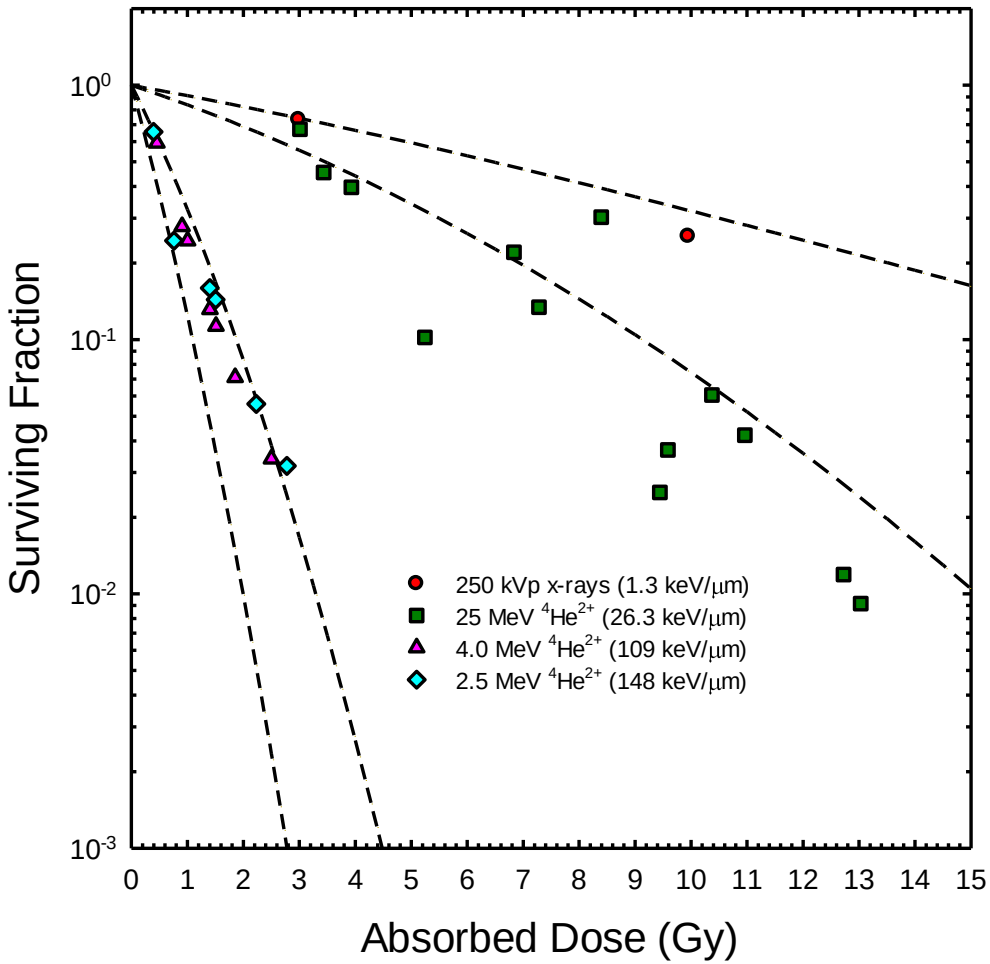
Dashed lines: *predicted* surviving fraction for higher LET radiations – estimate of θ and κ from x-ray data

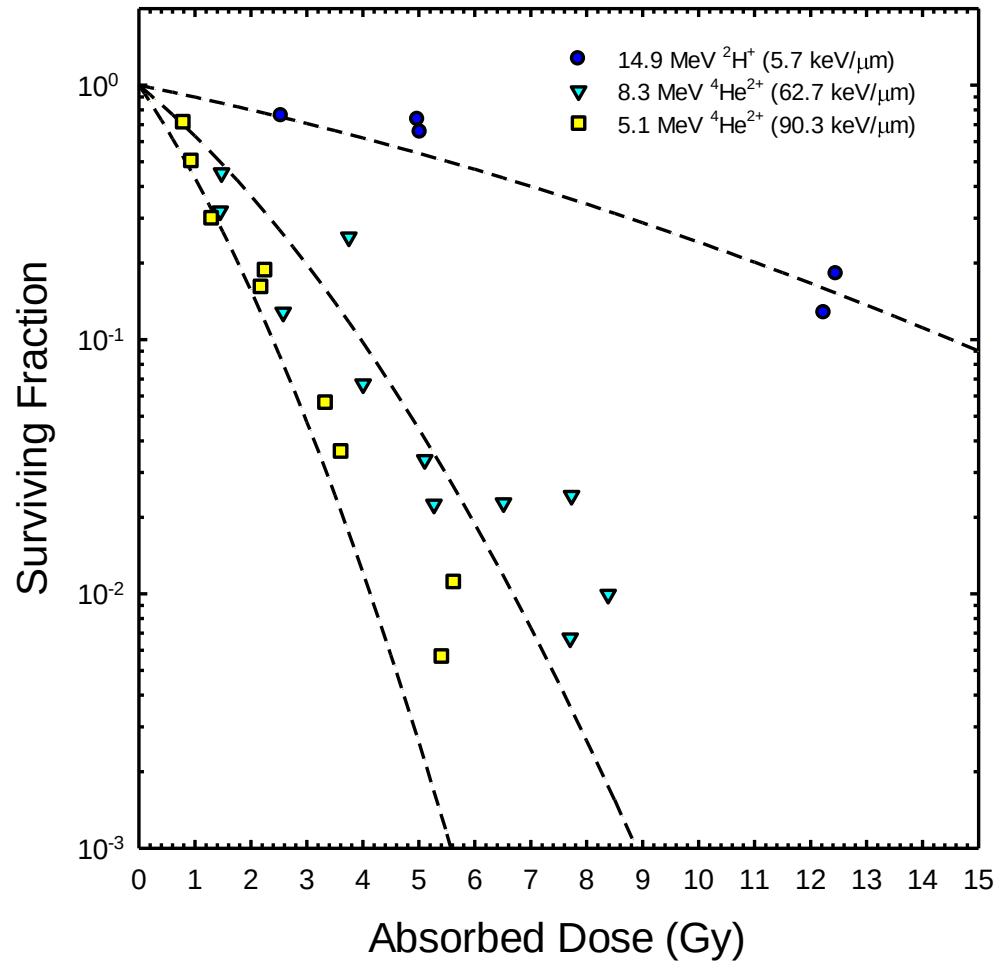
MCDS used to compute Σ and $\bar{z}_F$ from "first principles."

$$\alpha = \theta\Sigma + \kappa\bar{z}_F\Sigma^2 \qquad \beta = \frac{\kappa}{2}\Sigma^2$$

Measured data from Barendsen circa 1960-1966

Results-2 Human Kidney T1 Cells (*anoxic*)





$$\alpha = \theta\Sigma + \kappa\bar{z}_F\Sigma^2$$

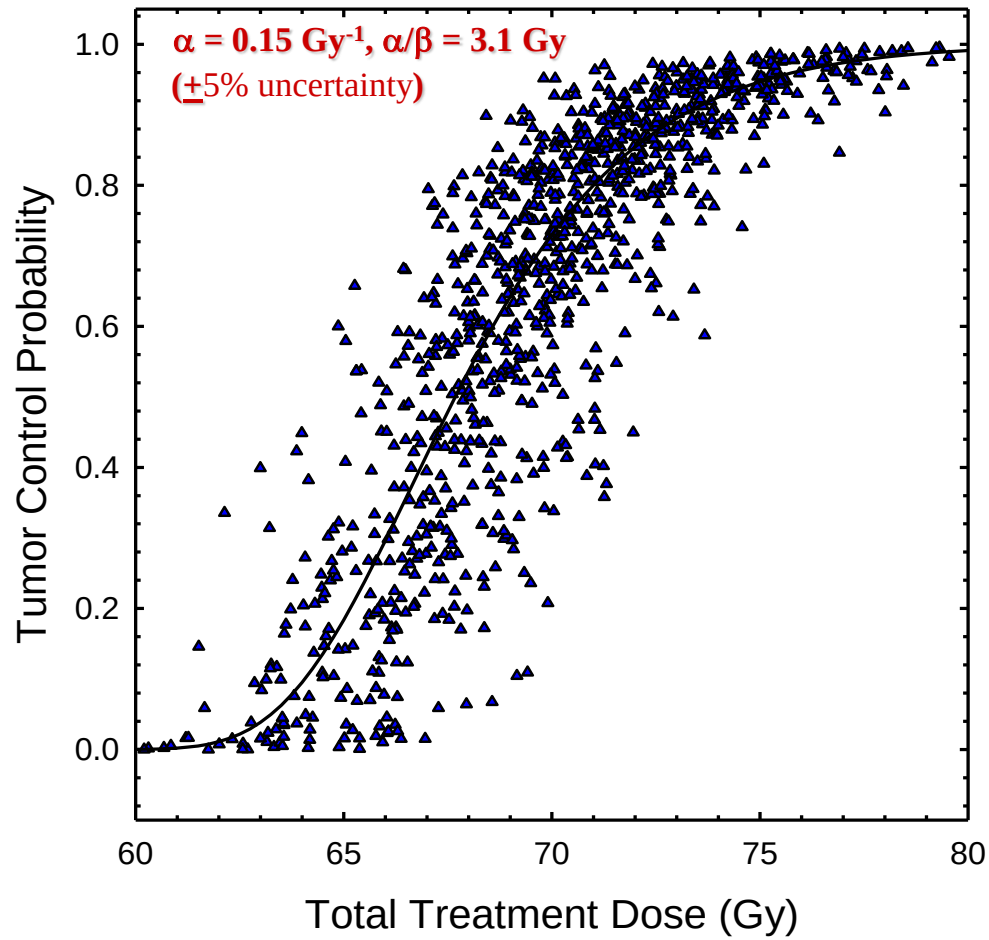
$$\beta = \frac{\kappa}{2}\Sigma^2$$

κ and θ determined from survival data for cells exposed to *x-rays under aerobic conditions* (*i.e., same as previous slide*). Use MCDS to compute Σ for anoxic conditions.

Patient-Specific TCP Guidance?

Even *small levels of uncertainty* in the biological parameters (α and α/β) have a *large impact* on our ability to predict the TCP for individual patients

Is there a clever way to overcome the uncertainty?



Iso-TCP Calculations ↔ Equivalent Tumor Dose

What dose should be delivered to achieve the same level of local control as another treatment?

Reference Treatment *Alternate Treatment*

$$TCP(D_R) = TCP(D)$$

$$\exp\left(-\rho VS(D_R)\right) = \exp\left(-\rho VS(D)\right)$$ *Poisson TCP model*

ρ = *cell density* (# cm^{-3}) V = *tumor volume* (cm^3)

When comparing or ranking plans for the *same patient*, ρV may be considered *modality and plan independent* constants (*same number of diseased cells regardless of treatment modality and plan*).**

$$S(D_R) = S(D)$$

Two biological parameters (ρ and V) eliminated from modeling process (*uncertainty in ρV doesn't matter!*)

For individual patients, iso-TCP = iso-(cell survival)

Iso-Survival Formula

Reference Treatment = Alternate Treatment

$$S(D_R) = S(D)$$

$$\exp\left(-\alpha D_R - \beta G D_R^{\,2}\right) = \exp\left(-\alpha D - \beta G D^2\right)$$

α and β (or α/β**) characterize *intrinsic radiation sensitivity***

G* is the *dose protraction factor

Take logarithm, apply quadratic formula and rearrange terms

$$D = \frac{n}{2}(\alpha/\beta)\left\{-1+\sqrt{1+\frac{4D_R}{n(\alpha/\beta)}\left(1+\frac{D_R}{n_R(\alpha/\beta)}\right)}\right\}$$

Reference Treatment
(“*clinical experience*”)

***D*$_R$ = total dose (Gy)**

***n*$_R$ = number fractions**

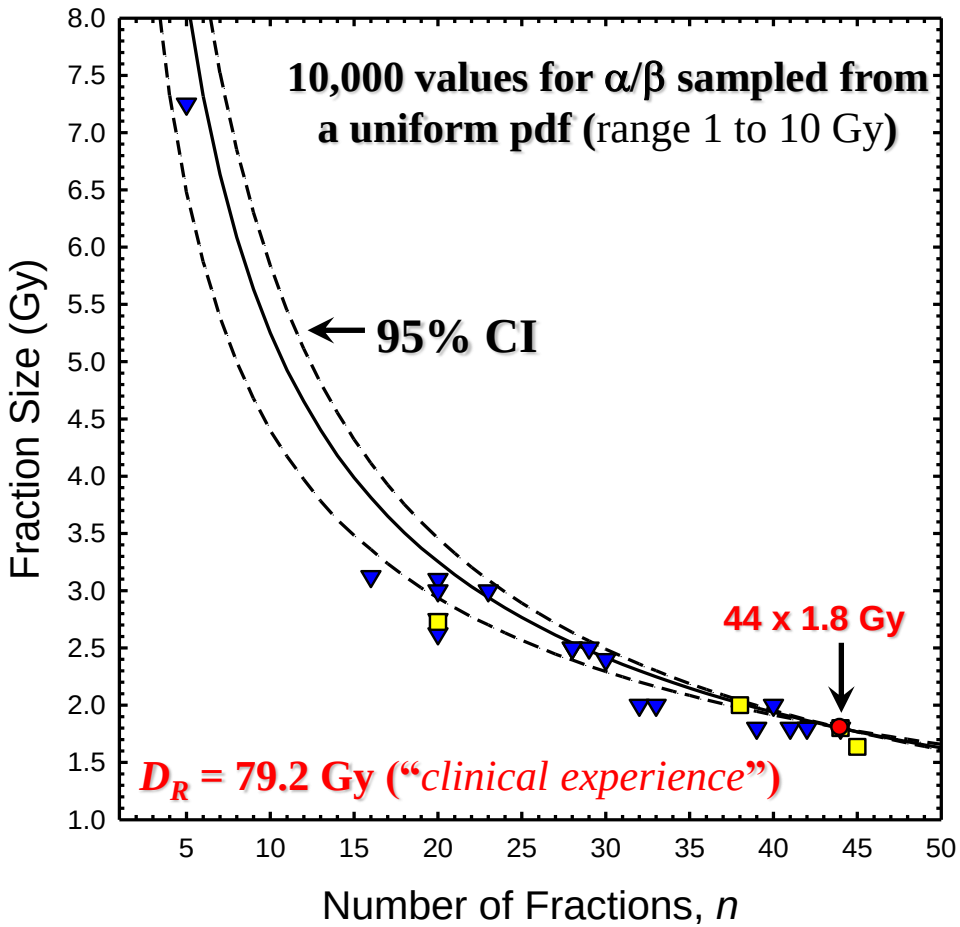
***d*$_R$ = *D*$_R$/*n*$_r$ (*fraction size*)**

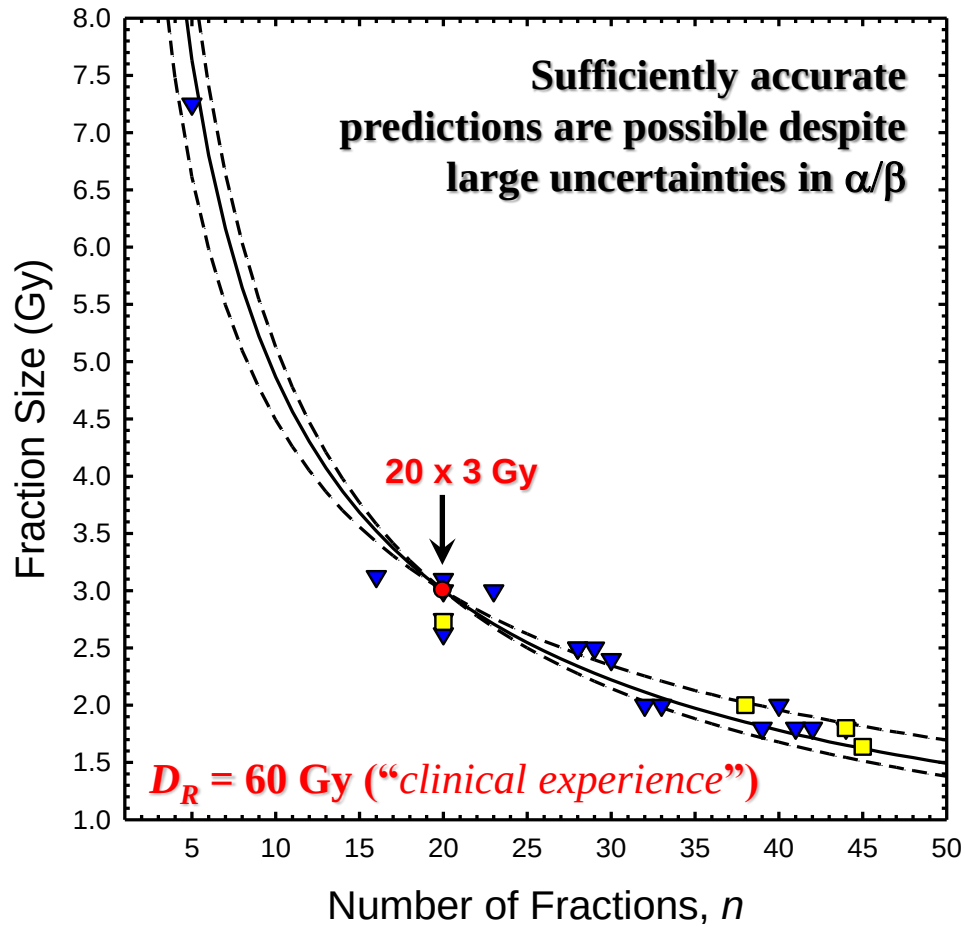
New (alternate) Treatment

***n* = desired number fractions**

Uncertainty in *D* arises from uncertainties associated with α/β.

Equivalent Prostate Tumor Doses – Effects of Uncertainty in α/β



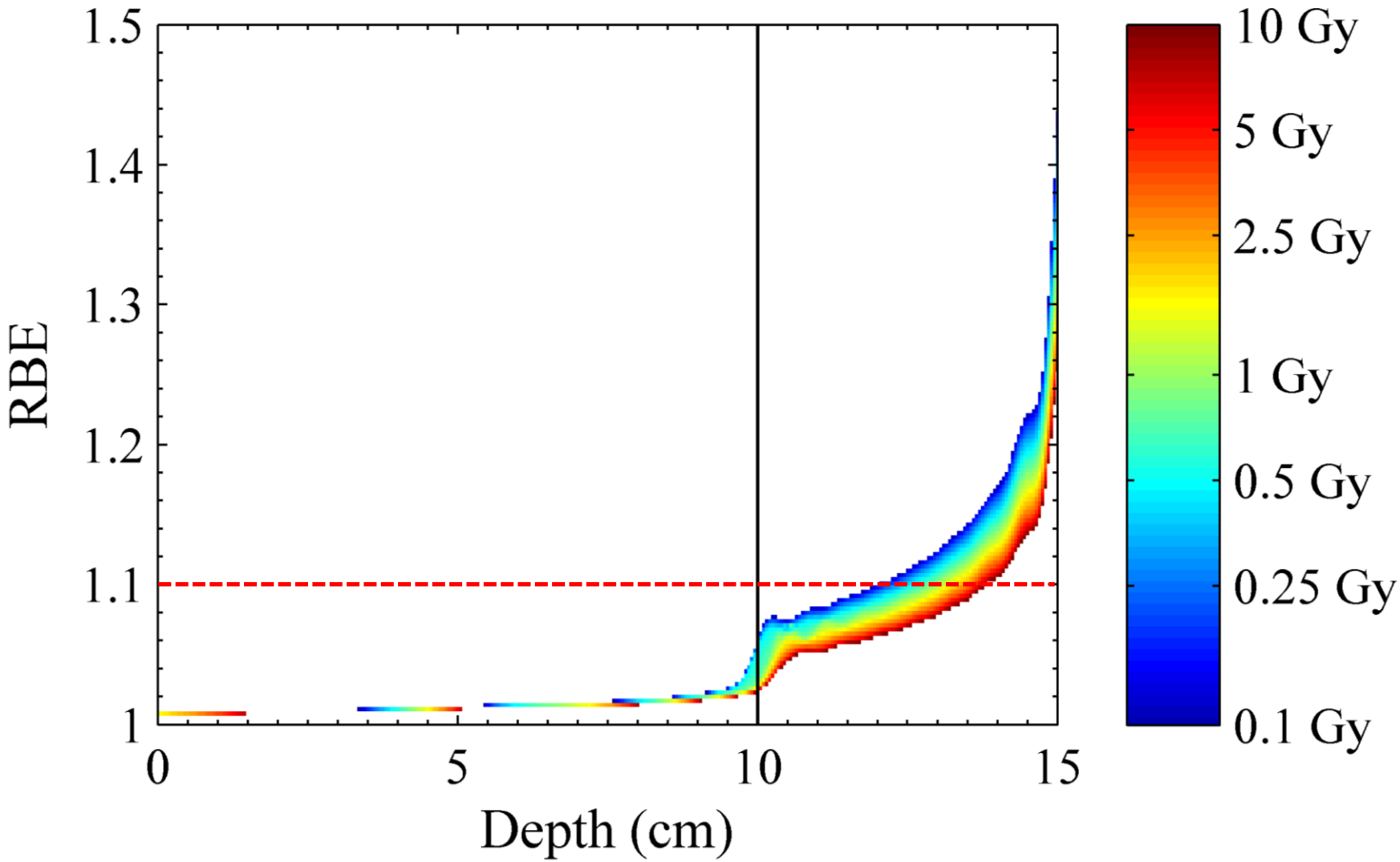


$$D = \frac{n}{2}(\alpha/\beta)\left\{-1+\sqrt{1+\frac{4D_R}{n(\alpha/\beta)}\left(1+\frac{D_R}{n_R(\alpha/\beta)}\right)}\right\}$$

Clinical Application of the MCDS+RMF?

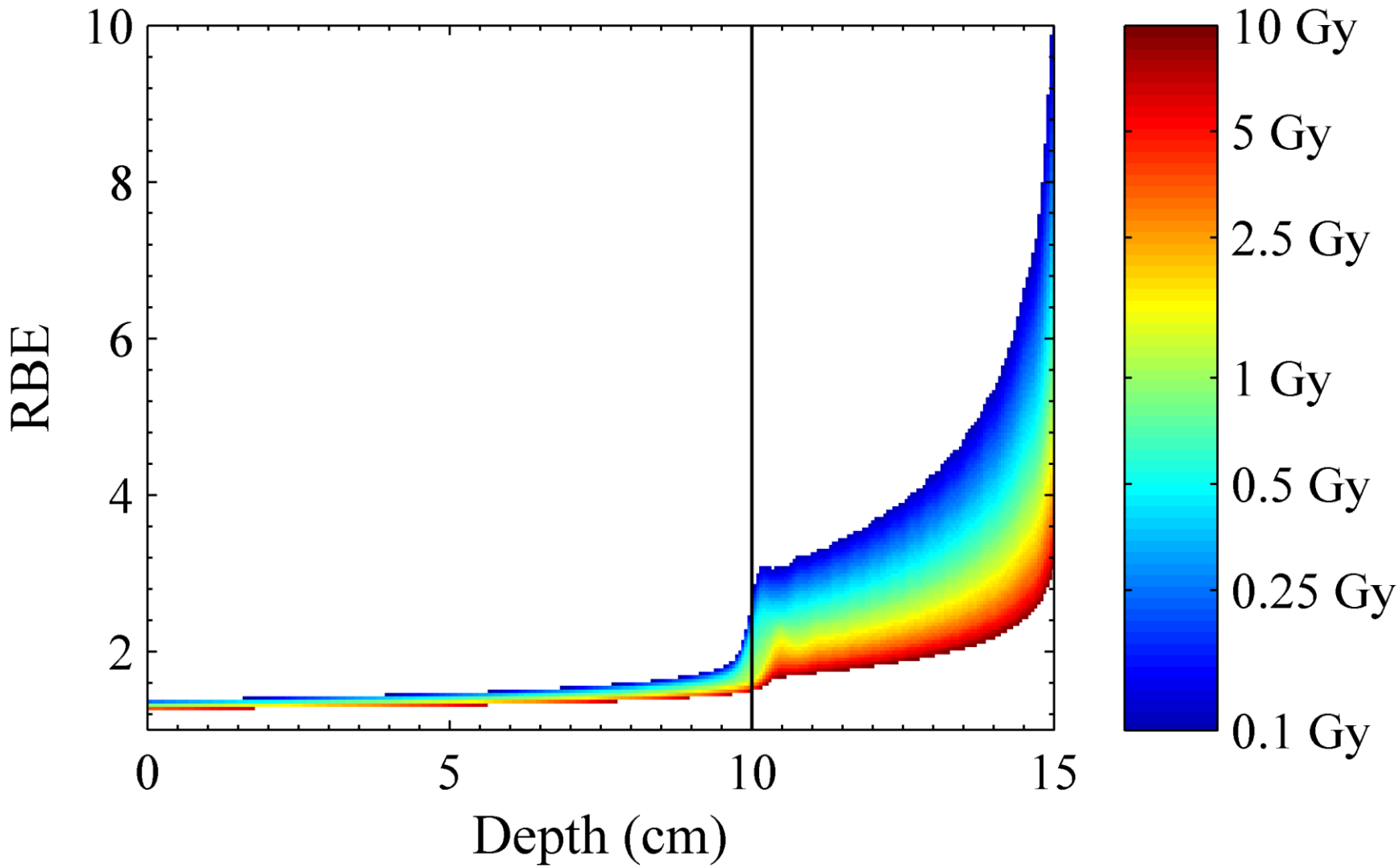
- **MCDS+RMF is a useful, mechanistic system of models to link DSB induction to reproductive cell death *in vitro***
  - Independent testing of the MCDS against measured data for the number of DSB
  - Additional testing of the MCDS+RMF against cell survival data
  - Substantial predictive power with *two adjustable parameters* (θ and κ). Effects of *fraction size, dose rate, total dose, LET and oxygen-related radiation resistance*
- ***Virtual Clinical Trials***
  - Fit θ and κ to *clinical data* for x-rays (100+ years of experience)
  - Use *isoeffect calculations* to compare *relative effectiveness* of alternate plans and modalities (IMRT, IMPT, SBRT, …)
  - Use quantitative imaging to help quantify spatial variations in α and α/β and among patients (*imaging as a surrogate endpoint*) – predictions becomes more individualized (and accurate?)

MV x-ray RT → Proton RT (5 cm SOBP)



M.C. Frese, V.K. Yu, R.D. Stewart, D.J. Carlson, A Mechanism-Based Approach to Predict the Relative Biological Effectiveness of Protons and Carbon Ions in Radiation Therapy, *Int. J. Radiat. Oncol. Biol. Phys.*, **83**, 442-450 (2012)

MV x-ray RT → ^{12}C ion RT (5 cm SOBP)



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Food for Thought (*Discussion*)

- **Is it reasonable to use a surrogate endpoint, such as reproductive cell death, to provide patient-specific guidance on the effects of one treatment *relative* to another (**isoeffect calculation**)?**
  - Equivalent tumor doses?
  - Equivalent tolerance doses for normal tissue?
- **How best might we derive patient-specific estimates of radiation sensitivity parameters (**e.g., θ and κ**) from multi-modality imaging before, during and/or after treatment?**
  - Biology is not static

Selected Publications and Posters

- D Corwin, C Holdsworth, R Rockne, **RD Stewart**, M Phillips, KR Swanson, Optimizing Radiotherapy for Glioblastoma Using A Patient-Specific Mathematical Model. AAPM Poster SU-E-T-295
- C Kirkby, E Ghasroddashti, Y Poirier, M Tambasco, **RD Stewart**, Monte Carlo Simulations of Relative DNA Damage From KV CBCT Radiation *Phys. Med. Biol.* **58**, 5693-5704, 2013. AAPM poster SU-E-T-495
- A.G. Georgakilas, P. O'Neill, and **R.D. Stewart**, Induction and Repair of Clustered DNA Lesions: What Do We Know So Far? *Radiat. Res.* **180**, 100-109 (2013)
- S Streitmatter, **R Stewart**, G Sandison, Relative Biological Effectiveness (RBE) of Protons in Pristine Bragg Peaks. AAPM talk WE-E-108-3 Wednesday 2:00PM - 3:50PM Rm 108
- M.C. Frese, V.K. Yu, **R.D. Stewart**, D.J. Carlson, A Mechanism-Based Approach to Predict the Relative Biological Effectiveness of Protons and Carbon Ions in Radiation Therapy, *Int. J. Radiat. Oncol. Biol. Phys.*, **83**, 442-450 (2012)
- **R.D. Stewart**, V.K. Yu, A.G. Georgakilas, C. Koumenise, J.H. Park, D.J. Carlson, Effects of Radiation Quality and Oxygen on Clustered DNA Lesions and Cell Death, *Radiat. Res.* **176**, 587-602 (2011)
- D.J. Carlson, **R.D. Stewart**, V.A. Semenenko and G.A. Sandison, Combined use of Monte Carlo DNA damage simulations and deterministic repair models to examine putative mechanisms of cell killing. *Rad. Res.* **169**, 447-459 (2008)
- Y Hsiao and **R.D. Stewart**, Monte Carlo Simulation of DNA Damage Induction by X-rays and Selected Radioisotopes. *Phys. Med. Biol.* **53**, 233-244 (2008)

http://faculty.washington.edu/trawets/