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 $\alpha$, $\alpha/\beta$ and the pre-treatment number of tumor cells ($\rho V$) 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

Absorbed Dose

Radiation

10^{-18} to 10^{-10} s

Ionization

Excitation

10^{-6} s

Chemical Repair

10^{-3} s

O_2 fixation

1 Gy ~ 1 in 10^6

Correct Repair

Enzymatic Repair

(BER, NER, NHEJ, …)

10^2 s \uparrow 10^4 s

Acute hypoxia

Chronic hypoxia

(> 1-2 h)

Incorrect or Incomplete Repair

Non-Viable

10^3 s \rightarrow 10^5 s

Inflamatory Responses

Self renewal and Differentiation

Loss of Function and Remodeling

10^6 s

10^8 s

Early Effects

(erythema, …)

Late Effects

(fibrosis, …)

2nd Cancer

10^8 s

Clonal Expansion

Neoplastic Transformation

10^7 s

Viable

Small- and large-scale mutations
(point mutations and chromosomal aberrations)

Non-Viable

Germline

Heritable Effects

10^5 s

Chronic hypoxia

(> 4-10 h?)

Local Control

10^5 s

Viable

Clonal Expansion

Neoplastic Transformation

10^7 s

Heritable Effects

Germline Instability

Somatic cells

2nd Cancer

Clonal Expansion

Neoplastic Transformation

10^8 s

Late Effects

Clonal Expansion

Neoplastic Transformation

10^7 s

Viable

Small- and large-scale mutations
(point mutations and chromosomal aberrations)
The LQ in Radiation Therapy

Inaccurate and too simplistic (compared to known biology)

\[ S(D) = \exp(-\alpha D - \beta GD^2) \]

Dose-rate and dose-fractionation effects ("dose protraction factor")

one-hit damage inter-track damage interaction

Parameters (e.g., \( \alpha \) and \( \beta \)) 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)

\[ \alpha = 0.039 \text{ Gy}^{-1} \]
\[ \alpha/\beta = 1.49 \text{ Gy} \]
\[ S = 1.159 \times 10^{-3} (37 \times 2 \text{ Gy}) \]


\[ \alpha = 0.15 \text{ Gy}^{-1} \text{ (4X higher)} \]
\[ \alpha/\beta = 3.1 \text{ Gy} \text{ (2X higher)} \]
\[ S = 2.677 \times 10^{-8} \text{ (10^4 smaller)} \]
SF for a Heterogeneous Cell Population

Can’t use a single (average) set of LQ radiation sensitivity parameters ($\alpha$, $\alpha/\beta$) to predict overall shape of dose-response curve

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

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

\[ TCP = \exp\{-\rho VS(D)\} \]

product \( \rho V = \) pre-treatment number of tumor cells

Typical uncertainty in \( \rho V \)? 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 ($\alpha$ and $\alpha/\beta$) have a large impact on our ability to predict the TCP for individual patients.
Reproductive Death as a Surrogate for TCP?

Absorbed Dose
10^{-18} to 10^{-10} s

Radiation

Ionization
Excitation
10^{-6} s

Chemical
Repair

O_{2} fixation

1 Gy ~ 1 in 10^6

Acute hypoxia

DNA damage

Correct
Repair

10^2 s \uparrow 10^4 s

Enzymatic Repair
(BER, NER, NHEJ, …)

Incorrect or
Incomplete Repair

Chronic hypoxia
(> 1-2 h)

10^3 s 10^5 s

Non Viable

Local Tumor
Control

10^7 s (1 year) to 10^8 s (5 years)

Small- and large-scale mutations
(point mutations and chromosomal aberrations)

Chronic hypoxia
(> 4-10 h?)

10^4 s 10^5 s

Non Viable
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)

RMF Model → LQ Formula

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

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

\[ \beta = \frac{\kappa}{2} \Sigma^2 \]

\[ \frac{\alpha}{\beta} = \frac{2}{\Sigma} \left( \theta / \kappa \right) + 2 \bar{z}_F \]

**θ, κ** are adjustable cell- or tissue-specific parameters related to the biological processing of DNA damage *(independent of LET and O₂ concentration)*

**Σ** is the number of DSB Gy⁻¹ Gbp⁻¹ (or per cell) – *(strong function of LET and O₂ concentration)*

**\( \bar{z}_F \)** is the frequency-mean specific energy (in Gy) for the cell nucleus *(strong function of LET but independent of O₂ concentration)*

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

**Solid line:** two-parameter model fit to survival data ($\theta = 3.07 \times 10^{-2} \text{ Gbp/DSB}$, $\kappa = 7.05 \times 10^{-4} \text{ Gbp/DSB}$).

**Dashed lines:** *predicted* surviving fraction for higher LET radiations – estimate of $\theta$ and $\kappa$ from x-ray data

MCDS used to compute $\Sigma$ and $\bar{z}_F$ from “first principles.”

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

Measured data from Barendsen circa 1960-1966
Results-2 Human Kidney T1 Cells (anoxic)

\[ \alpha = \Theta \Sigma + \kappa \sum_{F} \Sigma^2 \]

\[ \beta = \frac{\kappa}{2} \sum^2 \]

\( \kappa \) and \( \theta \) determined from survival data for cells exposed to x-rays under aerobic conditions (i.e., same as previous slide). Use MCDS to compute \( \Sigma \) for anoxic conditions.
Patient-Specific TCP Guidance?

Even **small levels of uncertainty** in the biological parameters ($\alpha$ and $\alpha/\beta$) 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

\[ TCP(D_R) = TCP(D) \]

\[ \exp(-\rho VS(D_R)) = \exp(-\rho VS(D)) \]  Poisson TCP model

\[ \rho = \text{cell density (\# cm}^{-3}) \quad V = \text{tumor volume (cm}^3) \]

When comparing or ranking plans for the same patient, \( \rho V \) 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 (\( \rho \) and \( V \)) eliminated from modeling process (*uncertainty in \( \rho V \) doesn’t matter!*)

**For individual patients, iso-TCP = iso-(cell survival)**
**Iso-Survival Formula**

Reference Treatment = Alternate Treatment

\[ S(D_R) = S(D) \]

\[ \exp\left(-\alpha D_R - \beta GD_R^2\right) = \exp\left(-\alpha D - \beta GD^2\right) \]

**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 \( \alpha/\beta \).
Equivalent Prostate Tumor Doses – Effects of Uncertainty in $\alpha/\beta$

10,000 values for $\alpha/\beta$ sampled from a uniform pdf (range 1 to 10 Gy)

$\leftarrow$ 95% CI

$D_R = 79.2$ Gy (“clinical experience”)

$D_R = 60$ Gy (“clinical experience”)

Sufficiently accurate predictions are possible despite large uncertainties in $\alpha/\beta$

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

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

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., $\theta$ and $\kappa$) from multi-modality imaging before, during and/or after treatment?
  - Biology is not static
Selected Publications and Posters

- 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