Biologically Guided Radiation Therapy (BGRT)
(Biologically Guided Extrapolation of Radiation Therapy Prescription Doses)

Rob Stewart, Ph.D.
Associate Professor
Director, Undergraduate Program in Radiological Health
School of Health Sciences
Purdue University
trebor@purdue.edu
http://rh.healthsciences.purdue.edu/faculty/rds.html

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X. Allen Li
Chief of Physics at the Medical College of Wisconsin

Vladimir Semenenko
Postdoctoral Fellow at the Medical College of Wisconsin

David J. Carlson
Medical Physics Resident at Stanford

George A. Sandison
Associate Dean, College of Pharmacy, Nursing and Health Sciences Head, School of Health Sciences Professor of Medical Physics

Current Ph.D. Students

Joo Han Park (Medical Physics)
Brock South (Medical Physics)
Yayun Hsaio (Physics)
Outline

- Physical and Biological Objectives
- Extrapolation of prescription dose
  - Short review
  - Significance of inter- and intra-patient heterogeneity
- Effects of radiation quality
  - Use of Monte Carlo DNA damage simulations to predict LQ parameters and relative biological effectiveness (RBE)
Biological Objectives → Physical Objectives

- Eradicate the tumor
  - Tumor control probability (TCP)

- Ensure normal tissue structures do not sustain unacceptable levels of damage
  - Normal tissue complication probability (NTCP)

**Increase dose to the tumor (TCP ↑)**
**Reduce dose to normal tissue (NTCP ↓)**
(reduce volume of normal tissue irradiated)

- Reasons local tumor control not achievable
  - Cure impractical because of normal tissue toxicity
  - Uncertain location of tumor cells, e.g., subclinical disease or metastasis
Biologically Guided Radiotherapy (BGRT)

- Exploit differential response of tumor and normal tissue structures or differences among patients
  - Keep TCP same (↔) and reduce NTCP (↓)
  - Keep NTCP same (↔) and increase TCP (↑)
  - Hypofractionation and accelerated hyperfractionation

- Save time and labor, increase patient convenience
  - Reduce number of fractions without altering TCP and NTCP
  - If a patient misses a treatment day, should we
    - Add a fraction to the end of the treatment?
    - Adjust size of remaining fractions?
    - If the latter, what fraction size should we use? Regardless, want same TCP and NTCP

- New modalities? Individualize treatment plans?
  - Effects of radiation quality (e.g., proton therapy)?
  - How can we best use information from functional imaging?

Dose and biologically motivated strategies are not mutually exclusive
Poisson TCP model

TCP = probability no tumor cells survive

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

- cell density \((< 10^9 \text{ cm}^{-3})\)
- Tumor volume
- Surviving fraction after total dose \(D\)

\(\rho VS(D) = \) average number of tumor cells that survive \(total\) treatment dose \(D\)

\[ S(D) = -\frac{\ln(TCP)}{\rho V} \]

Surviving fraction closely related to TCP

Model easily generalized to heterogeneous dose distributions
Linear Quadratic (LQ) Survival Model

\[ S(D) = \exp\left(-\alpha D - \beta GD^2 + \gamma T\right) \]

- **One-Track Damage**
- **Inter-Track Damage**
- **Repopulation effects**

- \( G \) depends on half-time for sub-lethal damage repair (\( \tau \)) and the temporal pattern of radiation delivery

\[ \gamma = \ln 2 / T_d \]

- Effective doubling time
Problem in a nutshell...

Analysis
(with highly non-linear models)

Clinical Outcomes
(small and noisy datasets)

Biological Parameters
(highly uncertain)

Prediction
(with highly non-linear models)

Clinical Outcome
(highly uncertain)

Surgery + RT
Chemo + RT

Seems hopeless, no?
Isoeffect Calculations ("extrapolation")

Variety of techniques used to perform isoeffect calculations
- Biologically effective dose (BED) and Equivalent Uniform Dose (EUD)
- Most, if not all, methods are related to the LQ survival model

Key Advantage: isoeffect calculations are relatively insensitive to uncertainties in biological parameters
**Iso-survival (special case)**

\[ S(D) = \exp\left(-\alpha D - \beta GD^2 + \gamma T\right) \cong \exp\left(-\alpha D\right) \]

\[ \alpha D >> \beta GD^2 - \gamma T \]

\[ \alpha D >> \beta GD^2 \quad \text{Slow growing tumors} \]

Total treatment dose \( D \) needed to achieve same \( S \) is independent of the temporal pattern of radiation delivery (e.g., Brachytherapy vs IMRT)

\[ D = -\frac{\ln S}{\alpha} \equiv BED \text{ (biologically equivalent dose)} \]
**Iso-survival (general formula)**

\[ S(D) = \exp \left( -\alpha D - \beta GD^2 + \gamma T \right) \]

Take logarithm, apply quadratic formula and rearrange terms

\[ D = \frac{\alpha / \beta}{2G} \left\{ -1 + \sqrt{1 - \frac{4G(\ln S - \gamma T)}{\alpha(\alpha / \beta)}} \right\} \]

\[ = \frac{\alpha / \beta}{2G} \left\{ -1 + \sqrt{1 + \frac{4G}{(\alpha / \beta)} \left( \frac{BED + \gamma T}{\alpha} \right)} \right\} \]
**Protraction Factor** *(external beam therapy)*

\[
G = \frac{2}{D^2} \left( \int_{-\infty}^{t} dt \; \dot{D}(t) \right) \left( \int_{-\infty}^{t} dt' \; \dot{D}(t') \exp\{-\lambda(t-t')\} \right)
\]

- \(\lambda = \frac{\ln 2}{\tau}\) Repair half-time
- Instantaneous absorbed dose rate (e.g., Gy/h) at time \(t\)
- Absorbed dose (Gy)

**Dose \(d\) (fraction size) delivered during time interval \(\Delta t\) (fraction delivery time)**

\[
G_1 = 2(e^{-x} + x - 1) / x^2
\]

\[x \equiv \lambda \Delta t = \Delta t \ln 2 / \tau\]

**Series of \(n\) daily fractions**

\[
G_n = G_1 \approx \frac{1}{n} \quad \text{(assumes repair complete between fractions)}
\]

\(G\) is always between 0 *long irradiation time* and 1 *short irradiation times*.
$D \rightarrow S$ for Prostate Cancer

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

$\alpha = 0.039 \ \text{Gy}^{-1}$

$\alpha/\beta = 1.49 \ \text{Gy}$

$\tau = 1.9 \ \text{h}$

$T_d \approx \infty$


$\alpha = 0.15 \ \text{Gy}^{-1}$

$\alpha/\beta = 3.1 \ \text{Gy}$

$\tau = 0.267 \ \text{h}$

$T_d \approx 42 \ \text{day}$

\[
G_n \approx \frac{1}{37} \quad \Rightarrow 
S = 1.159 \times 10^{-3}
\]

\[
G_n \approx \frac{1}{37} \quad \Rightarrow 
S = 2.677 \times 10^{-8}
\]
$S \rightarrow D$ for Prostate Cancer (37 fx $\times$ 2 Gy)

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

\[
D = \frac{\alpha / \beta}{2G} \left\{-1 + \sqrt{1 - \frac{4G(\ln S - \gamma T)}{\alpha(\alpha / \beta)}}\right\}
\]

2 Gy per fx

\[
= \frac{1.49 \text{ Gy}}{2(1/37)} \left\{-1 + \sqrt{1 - \frac{4(1/37)(\ln 1.159 \times 10^{-3})}{0.039 \text{ Gy}^{-1}(1.49 \text{ Gy})}}\right\} = 74.00 \text{ Gy}
\]


\[
D = \frac{3.1 \text{ Gy}}{2(1/37)} \left\{-1 + \sqrt{1 - \frac{4(1/37)(\ln 2.677 \times 10^{-8} - 50 \text{ day} \cdot \ln 2 / 42 \text{ day})}{0.15 \text{ Gy}^{-1}(3.1 \text{ Gy})}}\right\}
\]

= 74.00 Gy

divide by 37
Isoeffect Loop \((D \rightarrow S \rightarrow D)\)

\[
D = 74 \text{ Gy}
\]

\[
S = \exp \left\{ -\alpha D \left( 1 + \frac{GD}{\alpha / \beta} \right) + \gamma T \right\}
\]

\[
D = 74 \text{ Gy}
\]

\[
D = \frac{\alpha / \beta}{2G} \left\{ -1 + \sqrt{1 - \frac{4G(\ln S - \gamma T)}{\alpha(\alpha / \beta)}} \right\}
\]

Isoeffect “loop” is exact, regardless of values used for \(\alpha\), \(\alpha/\beta\), \(\lambda\) (or \(\tau\)) and \(\gamma\)
Extrapolation of prescription dose

Compute $S_R$ for a reference treatment used in clinic (e.g., 2 Gy $\times$ 37 fx)

$$D = \frac{\alpha / \beta}{2G} \left\{ -1 + \sqrt{1 - \frac{4G(\ln S_R - \gamma T)}{\alpha(\alpha / \beta)}} \right\}$$

Extrapolate to alternate fractionation schedule or treatment modality by selecting appropriate physical parameters for $G$ and $T$

$$G \approx \frac{1}{n} \quad T = n - 1 + 2 \text{int} \left( \frac{n - 1}{5} \right)$$

Total treatment time skipping weekends

Hypothesis: treatments with same $S_R$ have same clinical outcome ($S_R$ is a surrogate for clinical outcome)
Eqv. Prostate Treatments ("average patient")

For 23 to 50 fractions, doses are within 3% of each other *despite* almost 5 orders of magnitude difference in $S_R$ ($10^{-3}$ vs $10^{-8}$)
Inter-patient heterogeneity?

Distribution of biological parameters ($\alpha$, $\alpha/\beta$, $\tau$, $T_d$) among patient population

$S_{R,i} = \exp\left\{-\alpha_i D_R \left(1 + \frac{G_i D_R}{(\alpha / \beta)_i}\right) + \gamma_i T_R\right\}$

Clinical response of $i$th patient

$D_i = \frac{(\alpha / \beta)_i}{2G_i} \left\{-1 + \sqrt{1 - \frac{4G_i \left(\ln S_{R,i} - \gamma_i T\right)}{\alpha_i (\alpha / \beta)_i}}\right\}$

Iso-effective dose for $i$th patient

Use same biological parameters to compute $S_R$ and $D$, i.e., same outcome in same patient but not necessarily same outcome in different patients
Equivalent prostate treatments (*population*)

Patient population simulated by randomly sampling of 95% CI associated with Fowler *et al.* 2001 or Wang *et al.* 2003 parameters.
What about intra-tumor heterogeneity?

Suppose we sub-divide our tumor into $N$ regions. Each region has it’s own radiosensitivity parameters…

Conceptually, we can sub-divide the tumor into regions that are so small that they contain a single cell, i.e., *every cell in the tumor has it’s own unique biological characteristics*.

**Hypothesis:** overall treatment effectiveness remains the same as long as the surviving fraction in each region is the same

$$TCP = \prod_{i=1}^{N} TCP_i = \prod_{i=1}^{N} \exp\left(-\rho_i v_i S_i\right) = \exp\left(-\sum_{i=1}^{N} \rho_i v_i S_i\right)$$
What about intra-tumor heterogeneity?

Compute the dose to each region required to produce the same $S$ as a reference treatment.

Uniform dose $D_R$ to entire tumor
Radiosensitivity parameters depend on region

Surviving fraction in region $i$ (reference treatment)

$$S_{R,i} = \exp \left\{ -\alpha_i D_R \left( 1 + \frac{G_i D_R}{(\alpha / \beta)_i} \right) + \gamma_i T_R \right\}$$

$$D_i = \frac{(\alpha / \beta)_i}{2G_i} \left\{ -1 + \sqrt{1 - \frac{4G_i \left( \ln S_{R,i} - \gamma_i T \right)}{\alpha_i (\alpha / \beta)_i}} \right\}$$

Dose in region $i$ to achieve same $S$ as reference treatment

Change $G$ and $T$
Equivalent DVH (intra-tumor heterogeneity)

Tumor sub-divided into $10^4$ regions

For each region, biological parameters randomly sampled from

- $\alpha = 0.1-0.3$ Gy$^{-1}$
- $\alpha/\beta = 1-10$ Gy
- $\tau = 0.1-6$ h
- $T_d = 30-365$ d

Reference treatment

- $n = 37$  $d = 2$ Gy
- $D = 74$ Gy  $\Delta t = 10$ min

- $n = 15$  Intermediate Risk
- $n = 30$  Low Risk
- $n = 5$  High Risk
Summary – dose extrapolation

- Isoeffect calculations are a robust way to guide the selection of equivalent treatments (tumor control)
  - Equivalent treatments produce the same distribution of patient outcomes (not same outcome in all patients)
  - Can assess sensitivity (robustness) by sampling biological parameters from distributions
  - Relatively insensitive to inter-patient heterogeneity
  - Relatively insensitive to intra-tumor heterogeneity

- Easy way to manage risks associated with extrapolation of prescription doses
  - \( n = 37 \) to \( n = 30 \) (low risk)
  - \( n = 37 \) to \( n = 5 \) (high risk)
Effects of radiation quality?

**Step 1:** Compute $S_R$ for dose of low LET radiation (e.g., IMRT with photons)

\[
S_R = \exp\left\{-\alpha_L D_L \left(1 + \frac{G_L D_L}{(\alpha / \beta)_L}\right) + \gamma T\right\}
\]

Use LQ parameters for low LET radiation

**Step 2:** Compute equivalent treatment dose for higher LET radiation

\[
D_H = \frac{(\alpha / \beta)_H}{2G_H} \left\{-1 + \sqrt{1 - \frac{4G_H \left(\ln S_R - \gamma T\right)}{\alpha_H (\alpha / \beta)_H}}\right\}
\]

Use LQ parameters for high LET radiation (assume $\gamma$ is same for low and high LET)

Dose of high LET radiation to achieve same $S$ as low LET treatment

**NOTE:** $\text{RBE} \equiv D_L / D_H$

Need a method to predict *trends* in $\alpha$, $\alpha/\beta$ and $\tau$ as a function of radiation quality
DSB Induction and LQ parameters

Repair-misrepair-fixation (RMF) models predicts

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

\[ \bar{z}_F = 0.204 \frac{LET}{\rho d^2} \]

\[ \beta = \kappa \Sigma^2 / 2 \]

\[ \Sigma = \text{DSB Gy}^{-1} \text{ cell}^{-1} \]

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

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

As expected

\[ \lim_{\alpha / \beta \gg GD} \exp \left\{ -\alpha D \left( 1 + \frac{GD}{\alpha / \beta} \right) \right\} = \exp \{ -\alpha D \} \]

Simulation of DSB induction

- Monte Carlo Damage Simulation (MCDS)

- Nucleotide-level maps of SSB, DSB and other forms of clustered damage for electrons, protons and α particles up to ~ 1 GeV

\[ \alpha = \theta \sum + \kappa \sum^2 \]

**Hypothesis:** θ and κ are independent of radiation quality
Human kidney T–1 cells irradiated in vitro

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

\[ \theta = 5.93 \times 10^{-3} \]

\[ \kappa = 5.24 \times 10^{-5} \]

DJ Carlson, RD Stewart, VA Semenenko and GA Sandison, Combined use of Monte Carlo DNA damage simulations and deterministic repair models to examine putative mechanisms of cell killing. Submitted *Radiation Research* (2007)
LQ parameters for protons

\[ \alpha = \theta \Sigma + \kappa \bar{z}_F \Sigma^2 \]
\[ \theta = 7.66 \times 10^{-4} \]
\[ \kappa = 6.26 \times 10^{-4} \]

Adjusted \( \theta \) and \( \kappa \) to match \( \alpha \) and \( \alpha/\beta \) reported by Fowler et al. (2001) – two equations and two unknowns (\( \theta, \kappa \))

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

\[ \lim_{\alpha/\beta \gg GD} \quad S = \exp\{-\alpha D\} \]
Predicted RBE for protons

\[ RBE \equiv \frac{D_L}{D_H} \]

\( 37 \times 2 \text{ Gy} \)

\( 15 \times 3.88 \text{ Gy} \)

\( 5 \times 8.03 \text{ Gy} \)

Kinetic Energy (MeV)

CSDA Range (mm)

100 cell diameters
Summary – effects of radiation quality

- May be feasible to use Monte Carlo DNA damage simulations to predict trends in LQ parameters (and hence RBE)
  - Additional testing of approach is needed
- RBE may be lower than unity for protons with kinetic energies above ~ 10 MeV
  - Potential for biological cold spots?
- Proton RBE may increase rapidly with decreasing kinetic energy below 20 MeV
  - Tail of the proton track has a real sting!
  - Effects a few hundred cells per proton
Biologically Guided Radiation Therapy

The future is fast approaching…

DCE-CT image of blood perfusion in a MCF-7wt tumor
(courtesy M. Cao)

PDF of presentation available at
http://rh.healthsciences.purdue.edu/faculty/rds.html