Radiobiological Modeling in Voxel Constructs

Robert D. Stewart
and
Richard J. Traub

Pacific Northwest National Laboratory
Radiation and Health Technology
Richland, WA 99352

Monte Carlo 2000
Lisbon, Portugal
October 23-26, 2000

Acknowledgements

Work supported by the US Department of Energy under contract DE-AC06-76RLO 1830.

Battelle

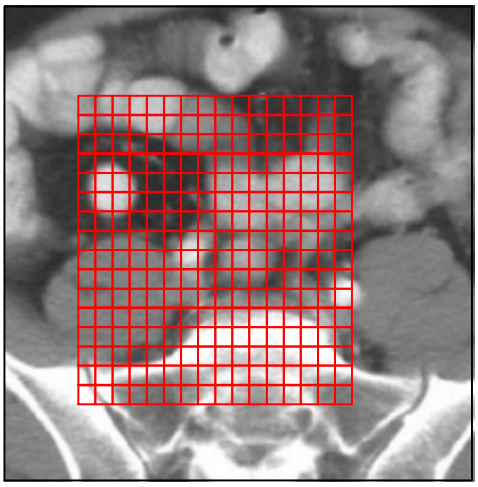
U.S. Department of Energy
Pacific Northwest National Laboratory

Overview

- VOXEL
  - 3D tumor response modeling software
- A prototypical application.
  - Biological optimization of the way dose fractions are delivery.
- Summary and concluding remarks.
  - Need for a DNA lesion database.
  - Future direction.

VOXEL
3D Tissue Modeling Software

- Sub-divide a region of tissue into many smaller (voxel) tissue regions.



CT Image courtesy of Justin Smith, M.D. First Hill Diagnostic Imaging.

- Construct an *absorbed dose rate* function to describe the radiation field experienced by cells in each voxel.
- Solve the LPL (cell killing) model to estimate the surviving fraction in all tissue regions.
- Use Poisson tumor control probability (TCP) model to estimate treatment effectiveness.

Lethal and Potentially Lethal (LPL) Model

$$\frac{dL_{pl}(t)}{dt} = \Sigma_{pl}\dot{D}(t) - l_{pl}L_{pl}(t) - e_{pl}L_{pl}(t)L_{pl}(t)$$

$$\frac{dL_f(t)}{dt} = \Sigma_f\dot{D}(t) + e_{pl}L_{pl}(t)L_{pl}(t)$$

$$L_f(0) = L_{pl}(0) = 0 \qquad S = \exp(-L_f)$$

SB Curtis, *Radiat Res* **106**(2):252-70 (1986). Published erratum appears in *Radiat Res* **119**(3):584 (1989).

Representative parameters for colon adenocarcinoma cells.

$$\Sigma_{pl} = 3.01 \text{ Gy}^{-1}\text{cell}^{-1}$$

$$\Sigma_f = 0.192 \text{ Gy}^{-1} \text{ cell}^{-1}$$

$$l_{pl} = 0.347 \text{ h}^{-1}$$

$$e_{pl} = 6.74 \times 10^{-3} \text{ h}^{-1}$$

Linear-Quadratic (LQ) Model

$$S = \exp\{-D(a + b\,D)\}$$

From the LPL model (SB Curtis 1986),

$$a = \Sigma_f + \Sigma_{pl} \exp\{-l_{pl} T_r\}$$

$$b = \frac{e_{pl} \Sigma_{pl}^2}{2\,l_{pl}} \left\{1 - \exp\left(-l_{pl} T_r\right)\right\}^2$$

T_r is the time available for damage repair.

Colon adenocarcinoma parameters*

$$a = 0.22 \text{ Gy}^{-1}$$
$$a / b = 3.26 \text{ Gy}^{-1}$$

* PJ Deschavanne *et al.*, *Radiat Res* **122**(1):29-37 (1990).

Tumor Control Probability (TCP) – Poisson Model

$$\text{TCP} = \{\text{prob. no tumor cells survive}\}$$

$$= \exp\left\{-\sum_{i=1}^{Q} N_i S_i(D)\right\}$$

$Q =$ Number of voxels.

$N_i =$ Initial number of tumor cells in the ith voxel ($\sim 10^9$ cells cm^{-3})

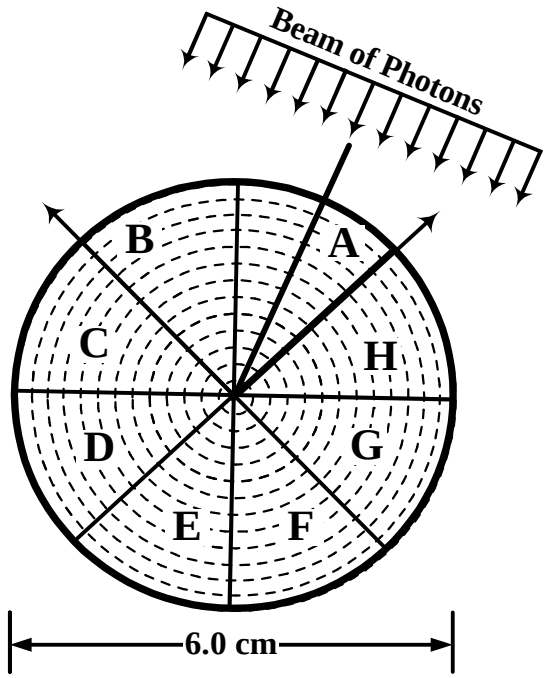
$S_i(D) =$ Surviving fraction of tumor cells in the ith voxel after dose D.

A Prototypical Application

Biological optimization of the way dose fractions are delivered.

Cylindrical tumor irradiated by 8 broad parallel beams of radiation.

- Scattering and attenuation of radiation beams produce dose gradients in the tumor.
- Takes at least a few seconds or minutes to move among beam and leaf configurations.

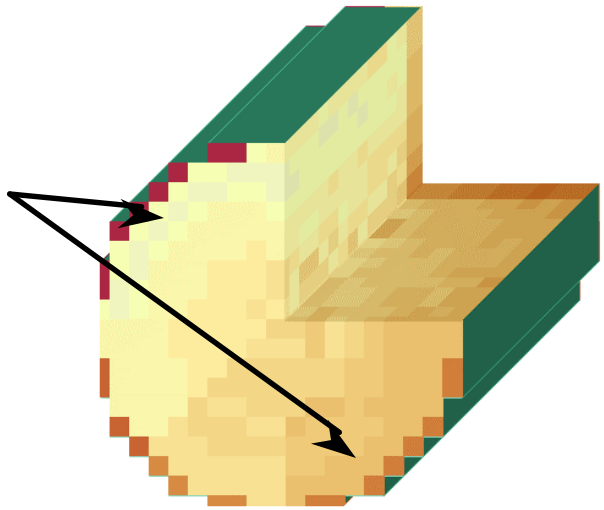


- Can beam sequence and dose protraction effects be exploited to improve radiation treatments?

Dosimetry

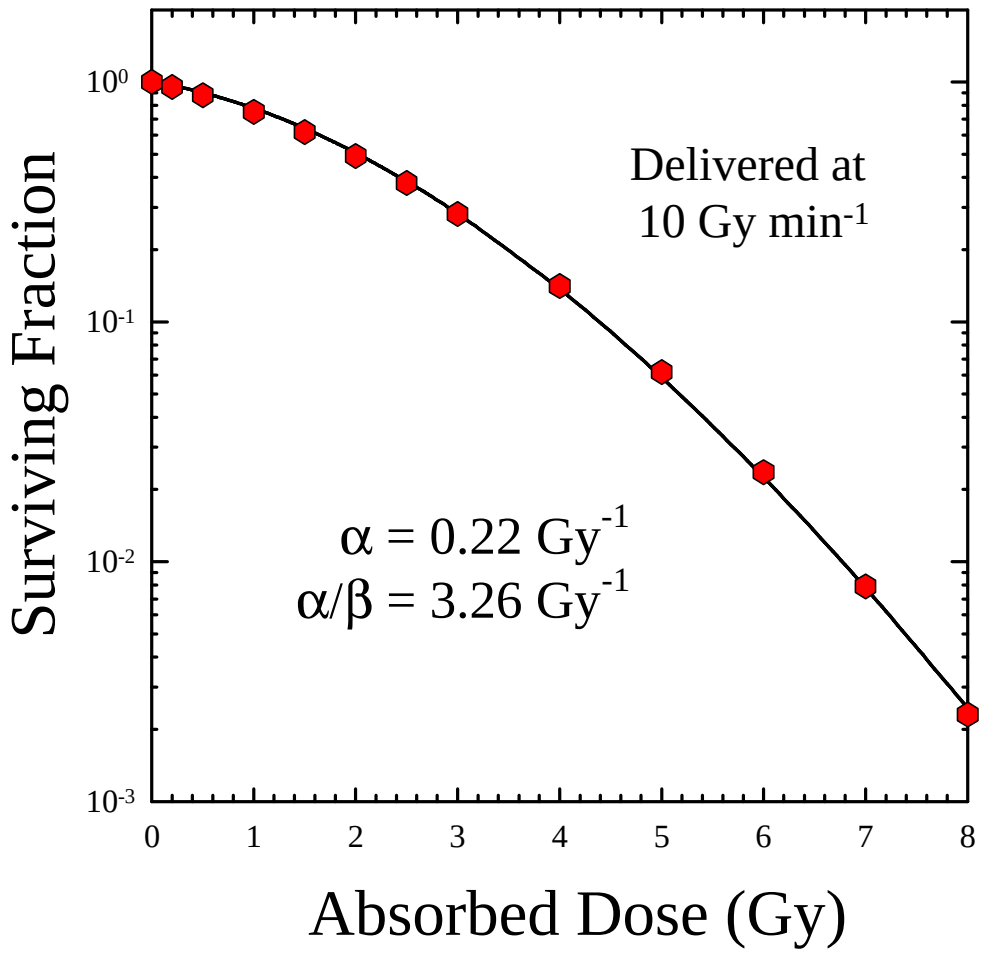
- Use MCNP™ to calculate absorbed dose distribution for each beam configuration (labeled A-H).
  - Monodirectional 1 MeV photon beams.
  - ICRU 4-element soft tissue at 1.04 g cm^{-3}.
- VOXEL application constructs an absorbed rate function for each voxel.
  - Beam sequence and beam reorient times are user configurable at run time.
  - Dose distribution scaled so that a voxel near the center of the tumor receives a prescribed dose.

Ratio of the maximum to minimum dose is 1.3



Intrinsic Radiosensitivity Parameters (low LET)

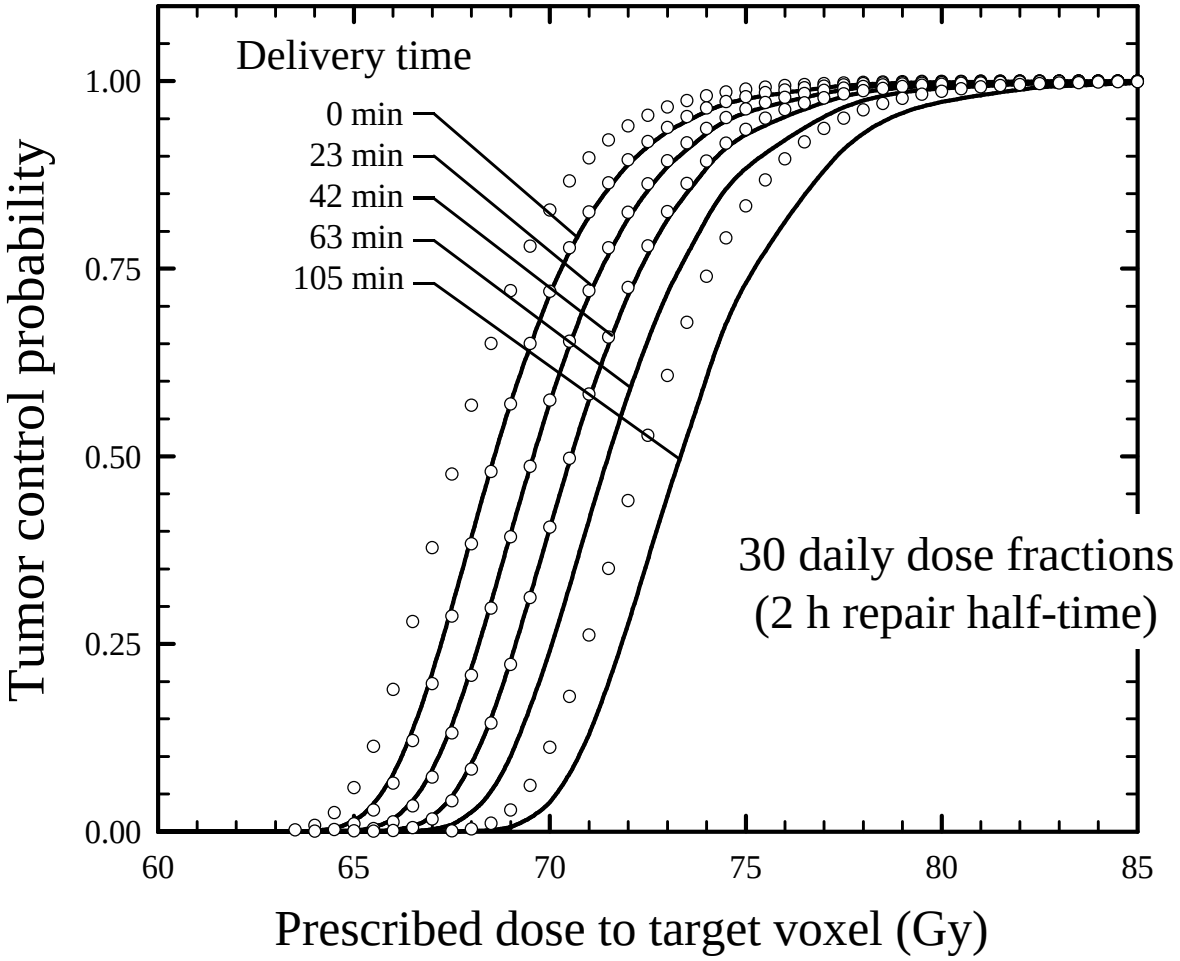
Colon adenocarcinoma cells



LQ and LPL models predict same level of cell killing for range of doses.

(•) LQ model (no repair); Solid lines LPL model (damage repair half-times of 1, 2, and 3 hours).

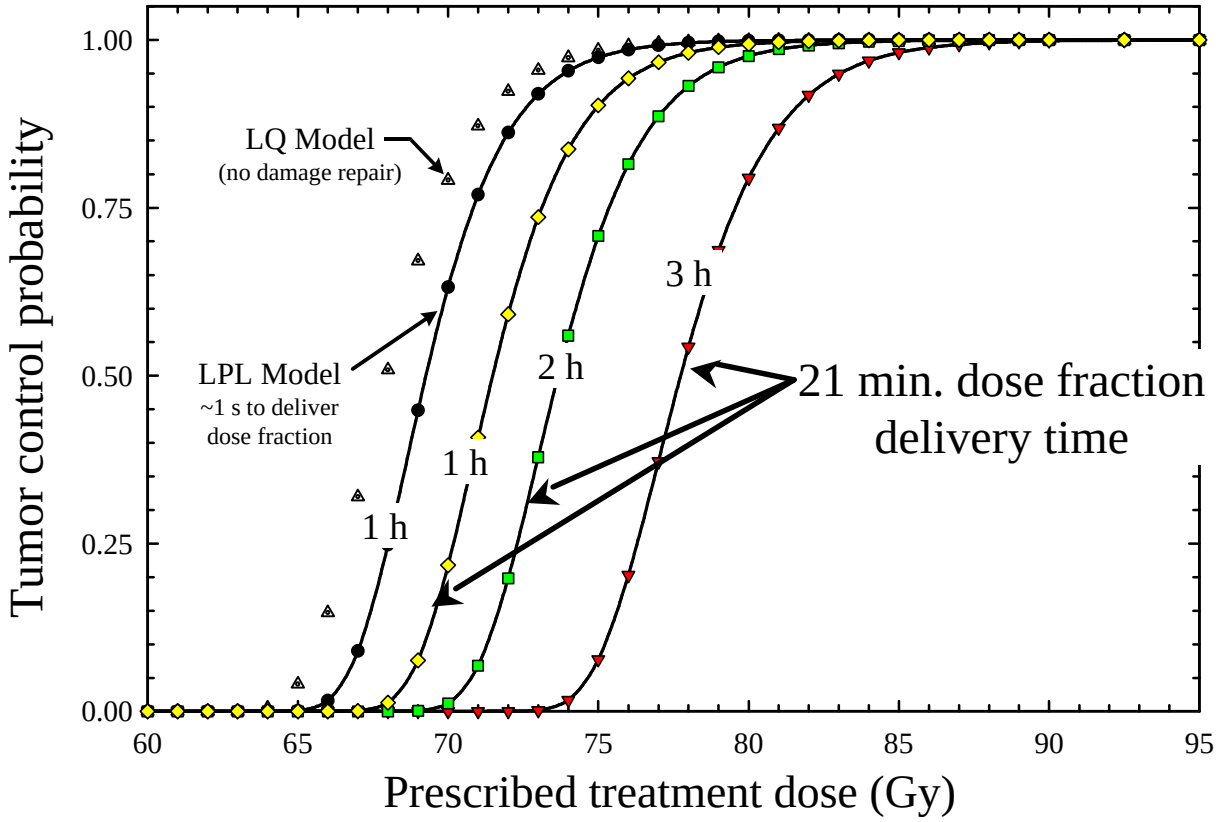
Effect of Dose Fraction Delivery Time



TCP for a tumor with homogeneous radiosensitivity properties.

Circles: all regions of the tumor experience exactly the same (prescribed) treatment dose.
Solid lines: MCNP-calculated absorbed dose distribution. Uniform dose to entire tumor (max. to min dose = 1.08).

Effect of Intrinsic Radiation Sensitivity

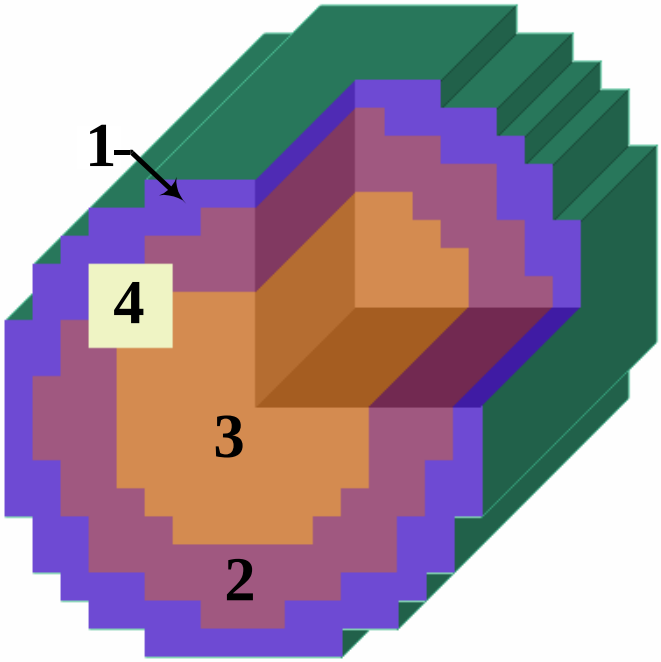


Tumor cells with the same apparent intrinsic radiosensitivity can respond very differently to the same radiation treatment.

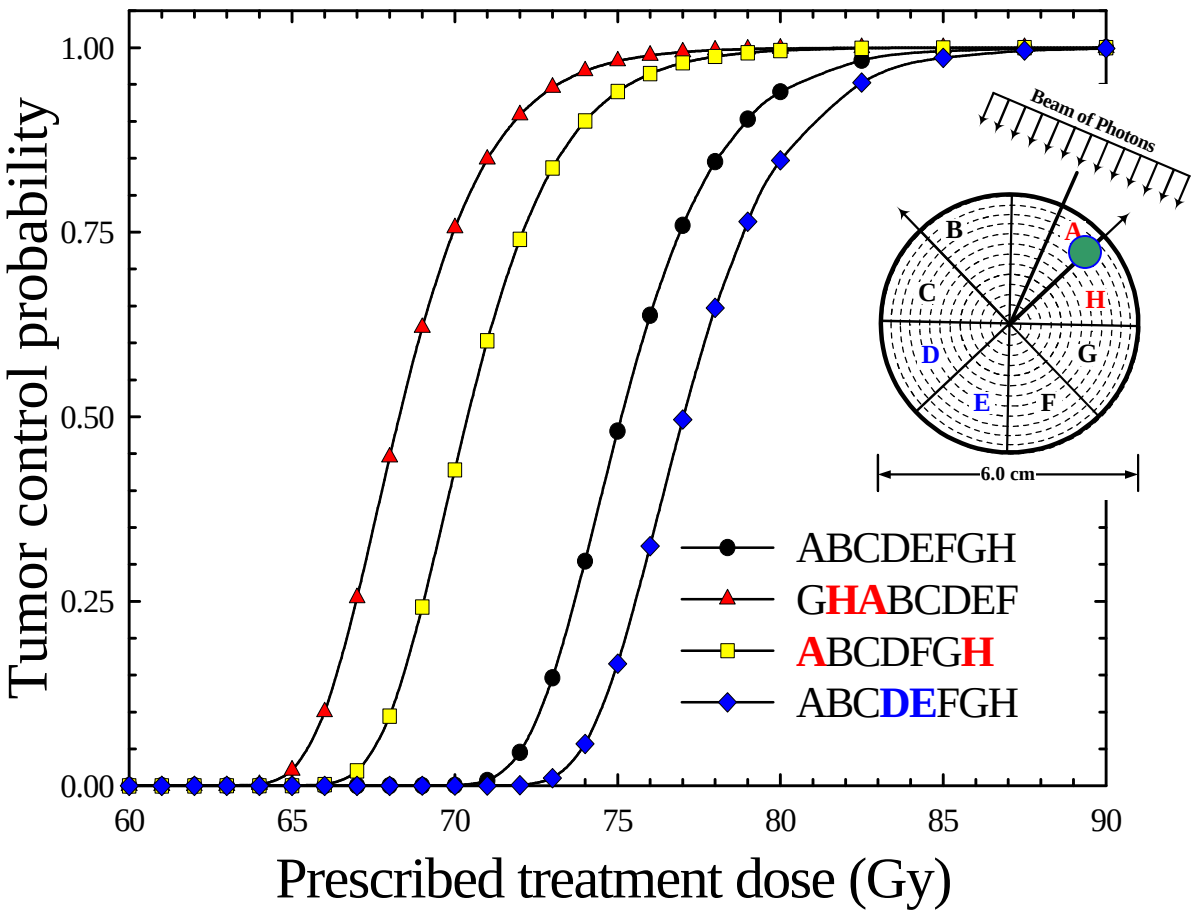
30 daily dose fractions
Homogeneous biophysical properties
Uniform prescribed dose to entire tumor

Idealized Tumor Model

- Cylindrical tumor 6 cm long with a diameter of 6 cm.
  - Tumor volume (~ 2300 voxels) is sub-divided into four smaller tissue regions.
  - The four tissue regions are assigned slightly different radiosensitivity characteristics.
    - ➤Tumor-cell density (~ 10^9 cells cm^{-3}).
    - ➤LPL “intrinsic radiosensitivity” parameters.



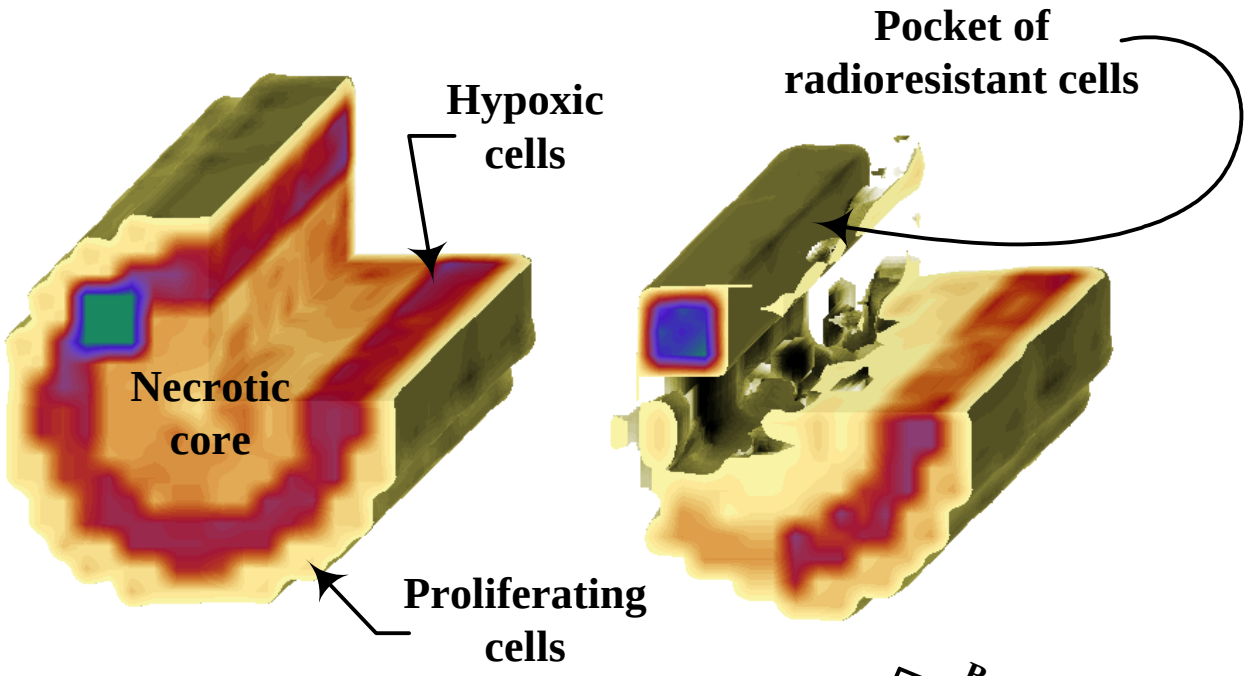
Beam Sequence Effects

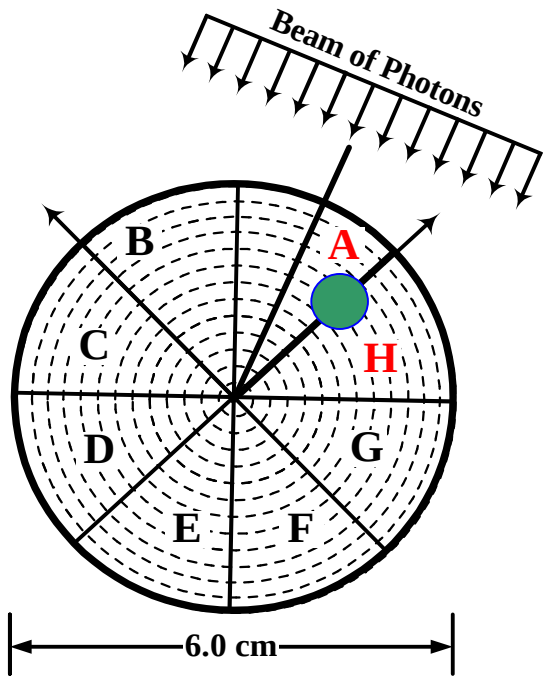


For some tumors, beam sequences effects could be used to modulate tumor response. Isoeffect dose factors from ~ 5 to 20%.

30 daily dose fractions
28 minute dose fraction delivery time
Tumor sub-divided into 4 radiosensitivity regions.

Tumor Cell Survival After a 55 Gy Radiation Treatment





Left panel: Uniform dose to entire tumor (all beams same strength).
Right panel: Strength of beams **A** and **H** increased 10-fold to preferentially target pocket of radioresistant cells.

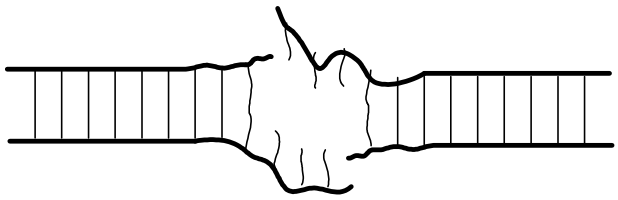
30 daily dose fractions, 28 min. dose-fraction delivery time

Summary

- Tumor cells with the same apparent intrinsic radiosensitivity (e.g., SF2) may respond very differently to the same radiation treatment.
- Biological optimization of the way *dose fractions* are delivered could increase treatment effectiveness.
  - Isoeffect dose factors from ~ 5 to 20% seem possible for some tumors.
    - ➤Deliver radiation to the tumor as rapidly as possible (~ 1 to 5% increase in TCP).
    - ➤Select a beam sequence and dose distribution that preferentially targets radioresistant portions of the tumor.
  - Could also (or alternatively) select a dose-fraction delivery scheme that minimizes damage to critical organ and tissues.

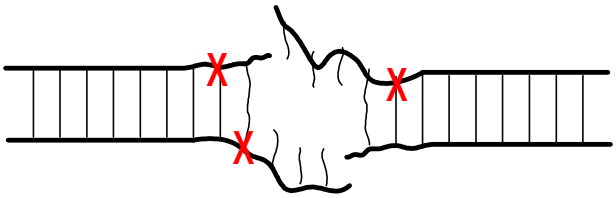
Room for Improvement...

- Damage repair effects play an important role in determining treatment outcome.
- Chromatin structure, proximity and damage complexity effects most likely affect the rate and fidelity of damage repair.

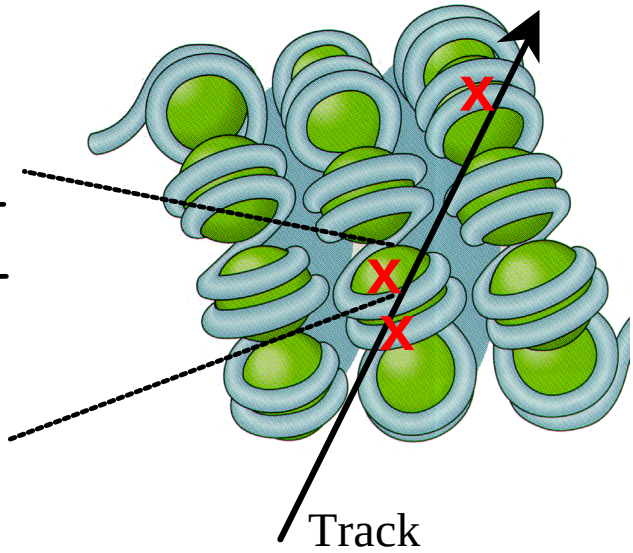


Simple double strand break

Regional multiple damaged sites

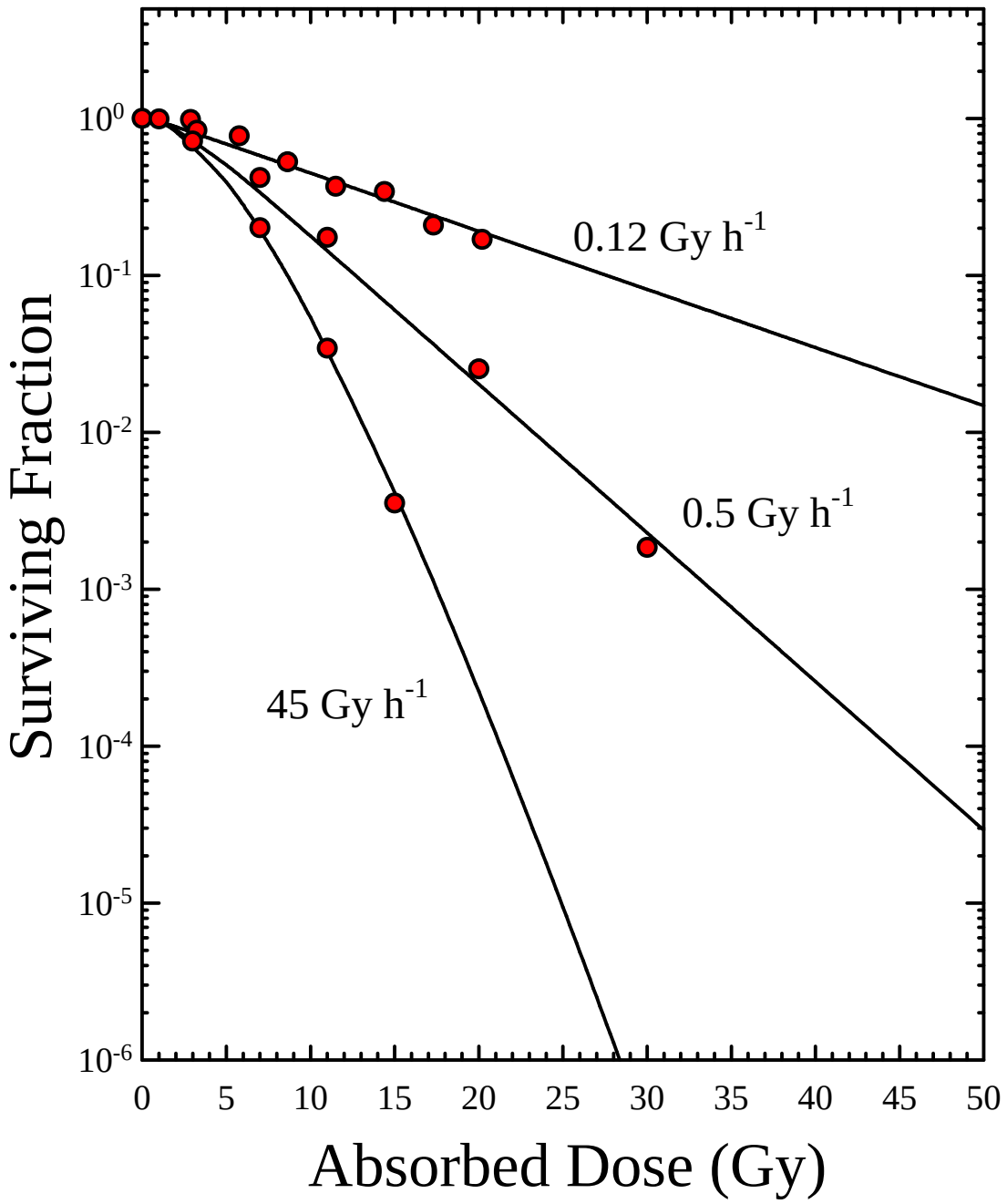


Complex double strand break

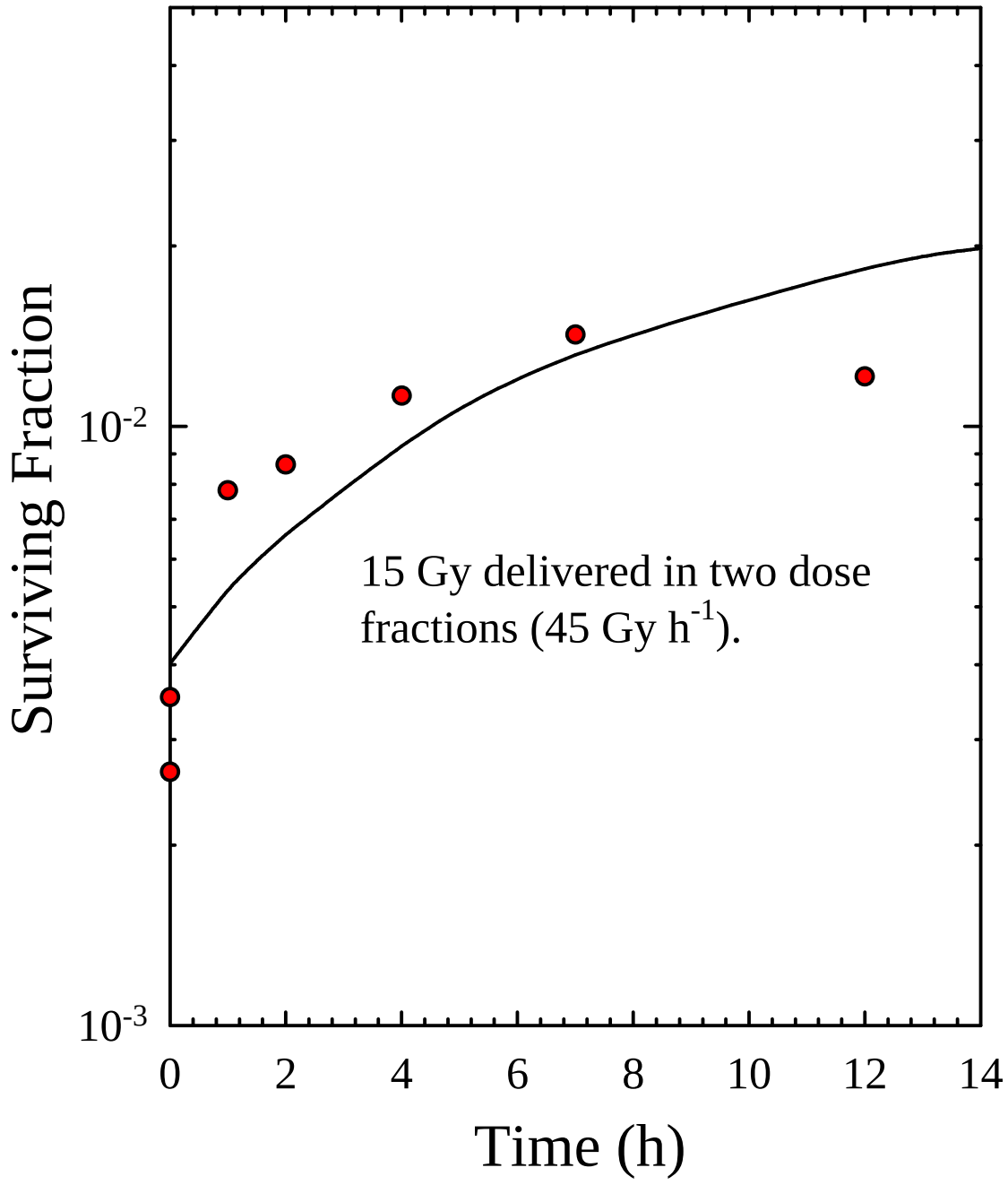


Picture of chromatin adapted from SL Wolfe, *Molecular and Cellular Biology* (1993).

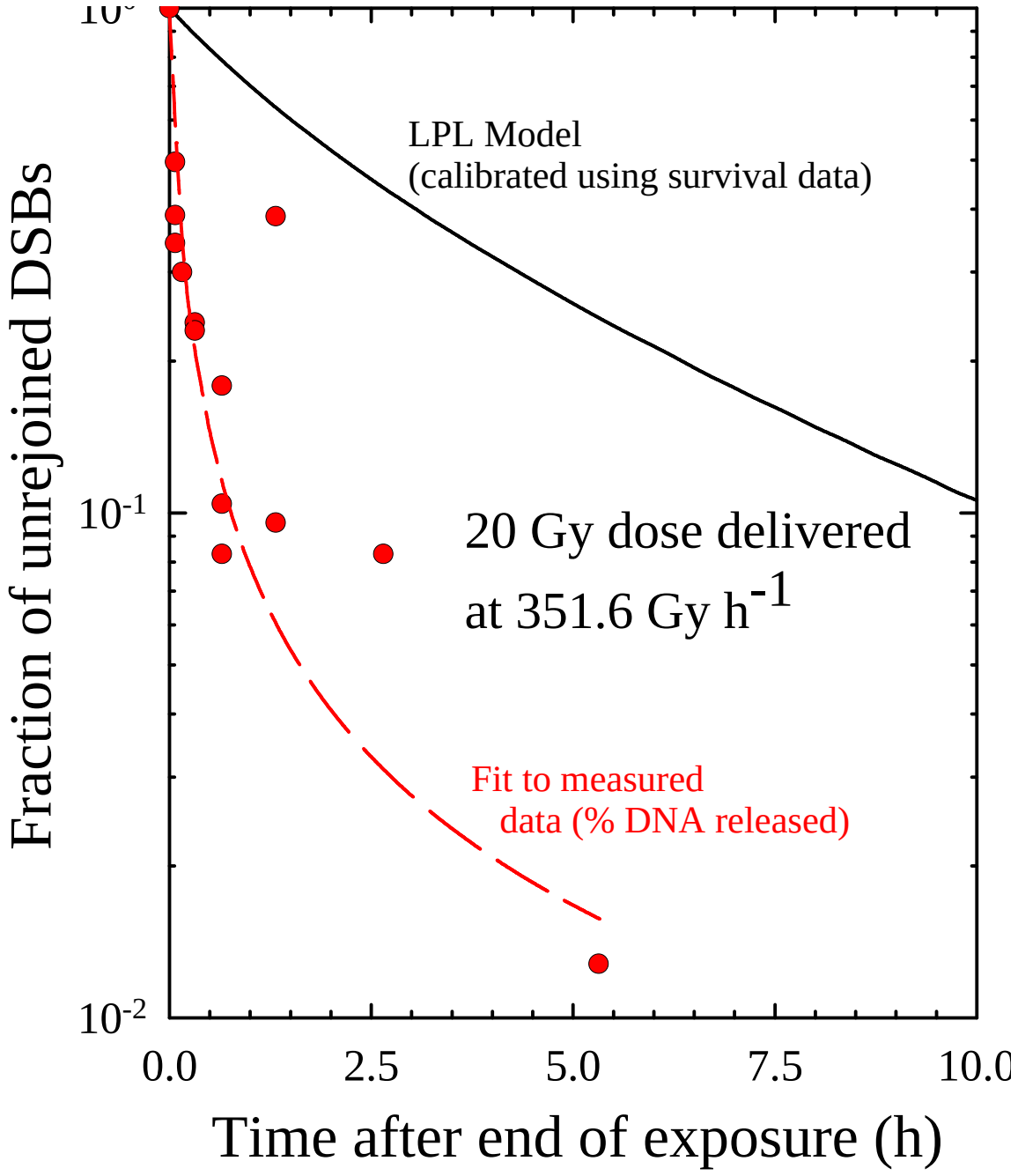
LPL Model Calibration
CHO 10B2 cells (low LET)



LPL Model Calibration
CHO 10B2 cells (low LET)



CHO 10B2 DSB Rejoining Kinetics

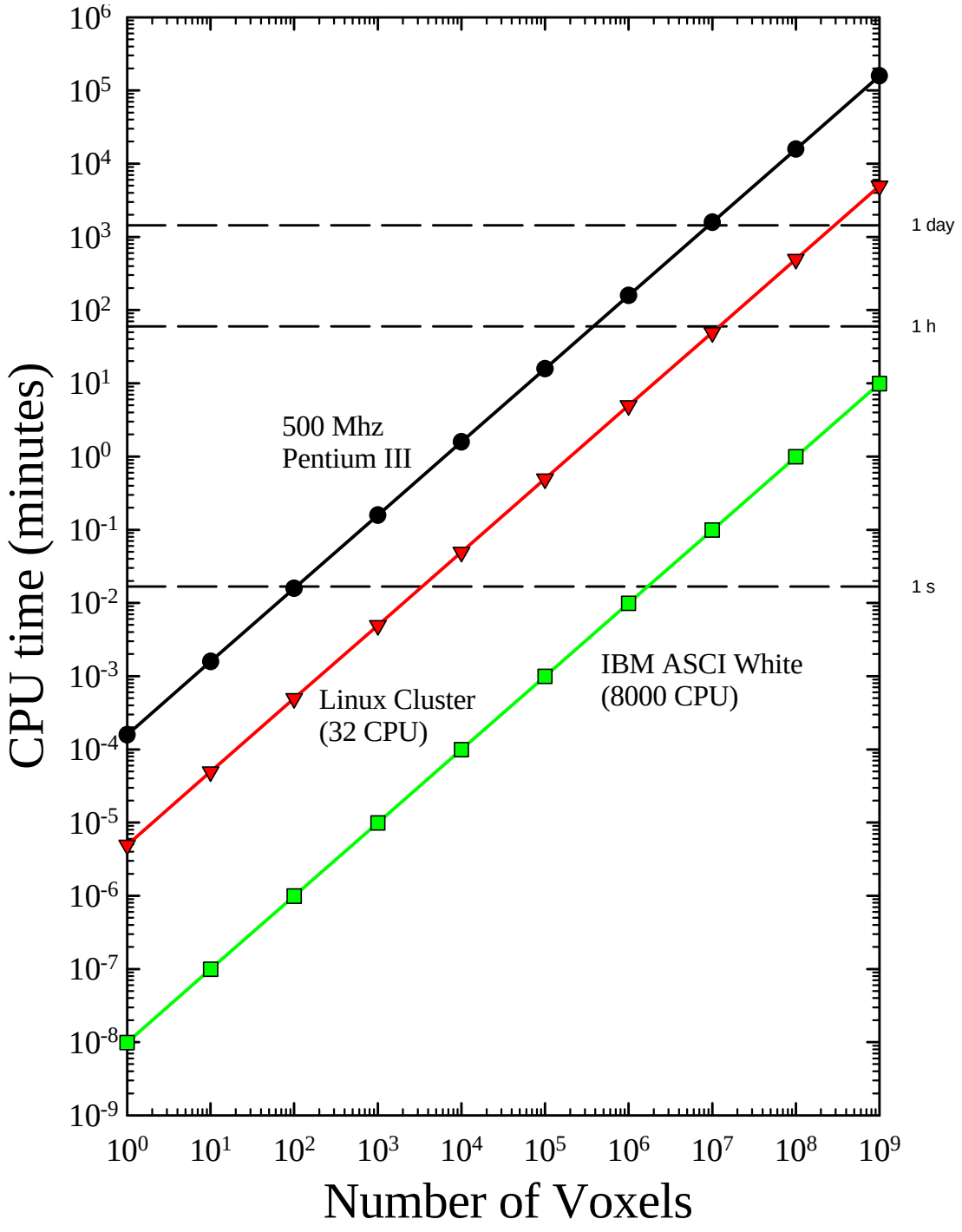


A DNA Lesion Database

- Need an evaluated database of lesion "cross sections."
  - Initial types and geometric extent of DNA damages as a function of
    - Radiation type and energy
    - Chromatin organization/structure
  - Need a suitable computational algorithm to group the multitude of possible DNA lesion types into biologically meaningful categories.
- Database would play a role in biophysical modeling analogous to the role of ENDF/B-VI cross section tables in radiation transport modeling.
  - Reduce number of adjustable parameters in biophysical models.
  - Could be used to help resolve open questions about the role of proximity effects and lesion complexity in cell killing, transformation, …

Challenge

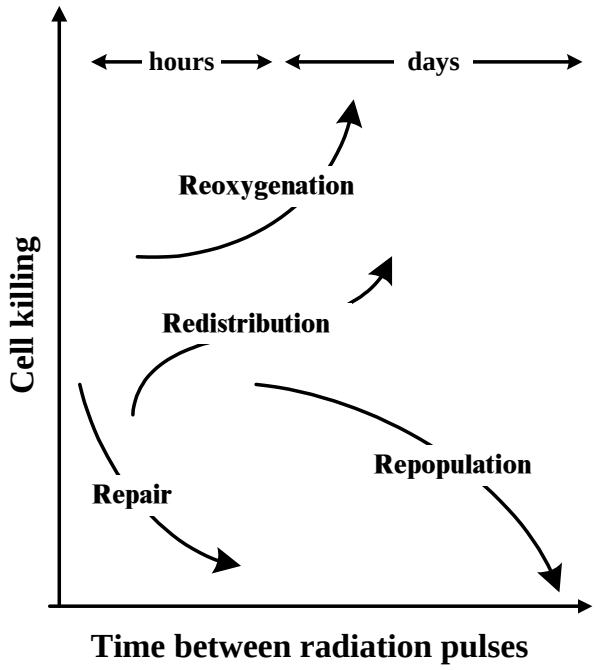
CPU time per TCP calculation



Extrapolation based on VOXEL 1.00C running on a Pentium III computer.

Future Direction

- Need to establish a set of standardized file formats to exchange absorbed dose distribution information among institutions.
  - Release initial (beta?) version of VOXEL application in next 2-3 months?
  - http://www.pnl.gov/berc/
- Software and model refinements to account for additional biophysical phenomena.
  - Four R's of radiation therapy.
  - Cell signaling (bystander) effects.
  - Apoptosis, transformation, …



An idealized schematic illustrating trends in cell killing associated with the Four R effects.