Current Topics in Radiobiological Modeling

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Abstract

Exposure to ionizing radiation initiates a complex series of physical, chemical, and biological changes that may culminate in cell death, organ dysfunction, or cancer. Mechanistic models are needed to improve our understanding of, and ability to predict and mitigate, the human health risks of exposure to radiological hazards in the environment and workplace. Radiobiological models are also useful for socially beneficial applications such as the biological optimization of radiation treatments for cancer. Radiobiological models integrate and organize information from molecular and cellular studies and provide a self-consistent framework to extrapolate radiation effects from the higher dose and dose-rate conditions that are easily accessible in laboratory studies to the protracted, lower-dose exposure conditions relevant to health protection.

This presentation will give an overview of selected “hot topics” in radiobiology and discuss challenges associated with the development and testing of next-generation radiobiological models. The Virtual Cell (VC) radiobiology software (http://www.pnl.gov/berc/kbem/vc/) uses several molecular and cellular (component) models to predict early biological events following exposure to ionizing radiation. The component models used in the VC software have also been integrated into a prototype Virtual Life Form (VLF) computer program. The VLF computer program can be used to simulate radiation effects in three-dimensional tissue constructs derived from MRI and CT scans. Results illustrating the application of the VC and VLF software to problems in radiation therapy and relative-risk estimation will be presented. The presentation will conclude with a brief overview of some new and ongoing model development projects at the Pacific Northwest National Laboratory.

DOE Low-Dose Radiation Research Program

Goal: Support research that will help determine health risks from exposures to low levels of radiation.

- A 10 year program at $21 million/year.
- International in scope.
- To fund the best science (currently 59 projects/year).
- To understand biological mechanisms.
- To develop radiation standards based on risk.

http://lowdose.org

Courtesy Dr. A.L. Brooks.

2001 DOE Low-Dose Program

- Bystander Effects (4)
- Adaptive Response (5)
- Genomic Instability (6)
- DNA Damage and Repair (10)
- Tool Development (3)
- Genetic Susceptibility (3)
- Proteomics (3)
- Modeling (12)
- Communication (3)
- Gene Expression (5)

Courtesy Dr. A.L. Brooks.

Role of the "Modeler"

- Modelers convert caffeine (or sometimes ice cream) into mathematics and computer code.

$$\frac{d\bar{L}_1(t)}{dt} = 2\dot{D}(t)Y\Sigma_1 - \{e_1 + l_1\}\bar{L}_1(t) - \bar{L}_1(t)\left[h_1\bar{L}_1(t) + h_{1,2}\bar{L}_2(t)\right]$$

$$S = \exp\{-\bar{L}_f\}$$

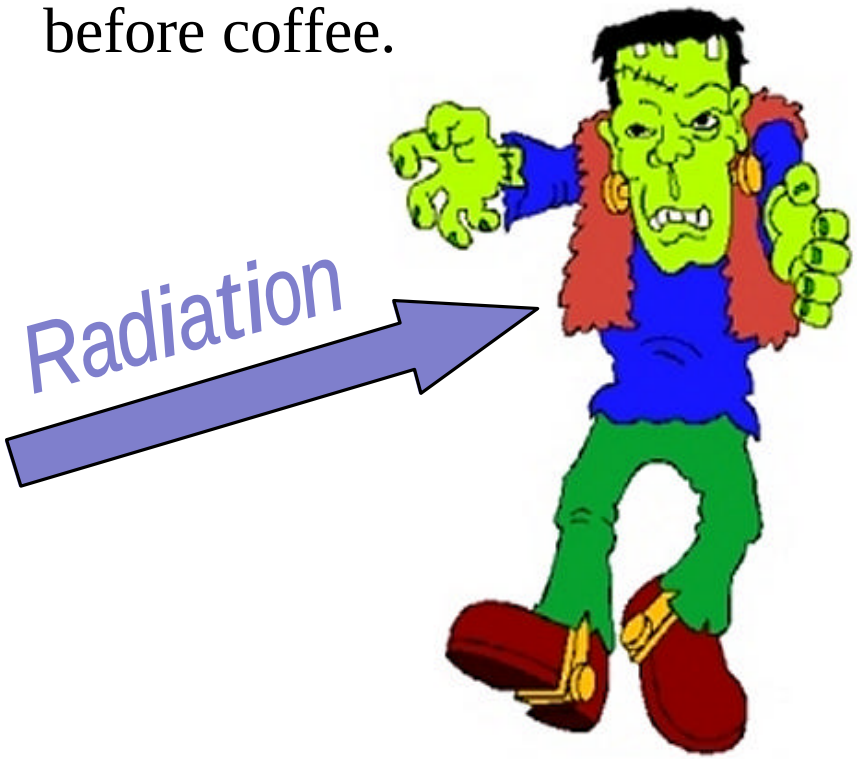
```
URL=zero
DO q=1,M4QC_NQ
  DO i=1,M4QC_NRL
    IF (LAMDA(i,q) > zero) THEN
        URL=URL + YR(i,q)
    ENDIF
  ENDDO
ENDDO
```

$$\mathrm{FAR} = F_{max}\left\{1 - \left[1 + K\bar{N}_{dsb}\left(1 - \frac{K}{M_0}\right)\right]\exp^{-K\bar{N}_{dsb}}\right\}$$

Suppose…

- A beam of radiation passes through the human body.

Typical Hanford employee before coffee.



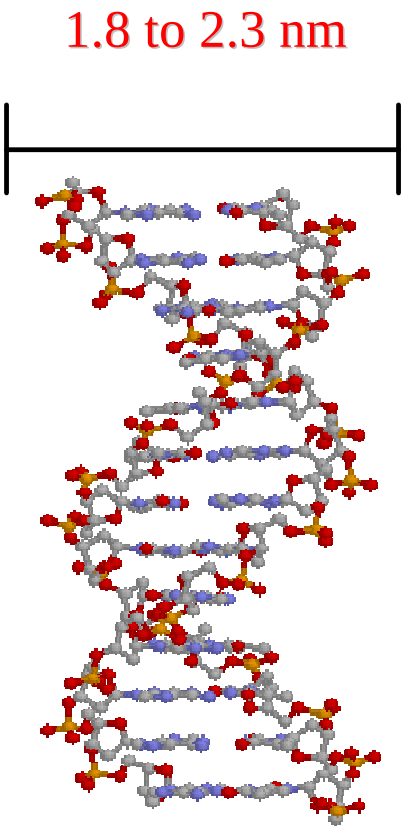
- Physiochemical stage
  - < 1 second after passage of particle through cell.
- Biological stage.
  - > 1 second after passage of particle through cell.

At the molecular (sub-cellular) level…

- Primary energy transfer events (excitation and ionization) occur within 10^{-17} to 10^{-16} s after radiation passes through a cell.
- Chemical changes are initiated in localized regions of matter termed spurs and blobs.
  - Spurs and blobs are roughly spherical regions of matter 4 to 7 nm in diameter.
  - Reactive chemical species such as the hydroxyl radical (•OH) are created.
  - Reactions are diffusion controlled.
  - Initial chemical reactions are finished within about 10^{-6} s after passage of the primary radiation.
- Chemical properties of the DNA (and other biomolecules) are directly or indirectly modified.

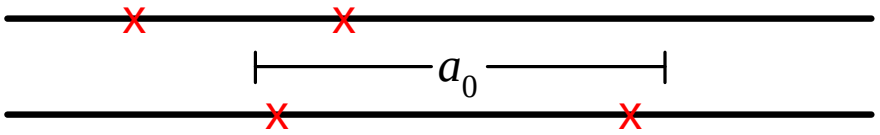
DNA – A critical target

- The fundamental chemical building block of DNA is the *nucleotide*:
  - Deoxyribose sugar unit,
  - Phosphate group that acts as a bridge between adjacent deoxyribose sugars, and a
  - Nitrogen-containing pyrimidine or purine base [Adenine (A), Cytosine (C), Guanine (G), and Thymine (T)].
- DNA structure is stabilized by
  - van der Waals forces,
  - hydrogen bonds between complementary organic bases (a base pair), and
  - hydrophobic interactions between the nitrogenous bases and the surrounding sheath of water.



Multiply Damaged Sites (MDSs)

- Deposition of energy by radiation is a stochastic (quantum mechanical) process.
  - Spatial pattern of spurs and blobs affects the configuration of DNA damage.
  - Average distance between adjacent spurs and blobs decreases as particle LET increases.
- Radiation creates many different spatial configurations of DNA damage (multiply damaged sites).
  - Five kinds of damaged or undamaged nucleotide: $(2 \times 30 \text{ bp})^5 \sim 10^8$ kinds of MDS.
  - Probability genetic information is lost may be different for each configuration of damage.



Idealized schematic of a group of four elementary damage sites forming a DNA lesion. Elementary damage sites are represented by an x. a_0 represents a 20 base pair (bp) section of the DNA.

Double Strand Breaks

- Double strand breaks are considered the most critical type of radiation damage.
  - Two strand breaks are created within about 10 to 20 bp and effectively cut the DNA into two pieces.
  - Radiation creates about 40 DSBs Gy^{-1} $cell^{-1}$.

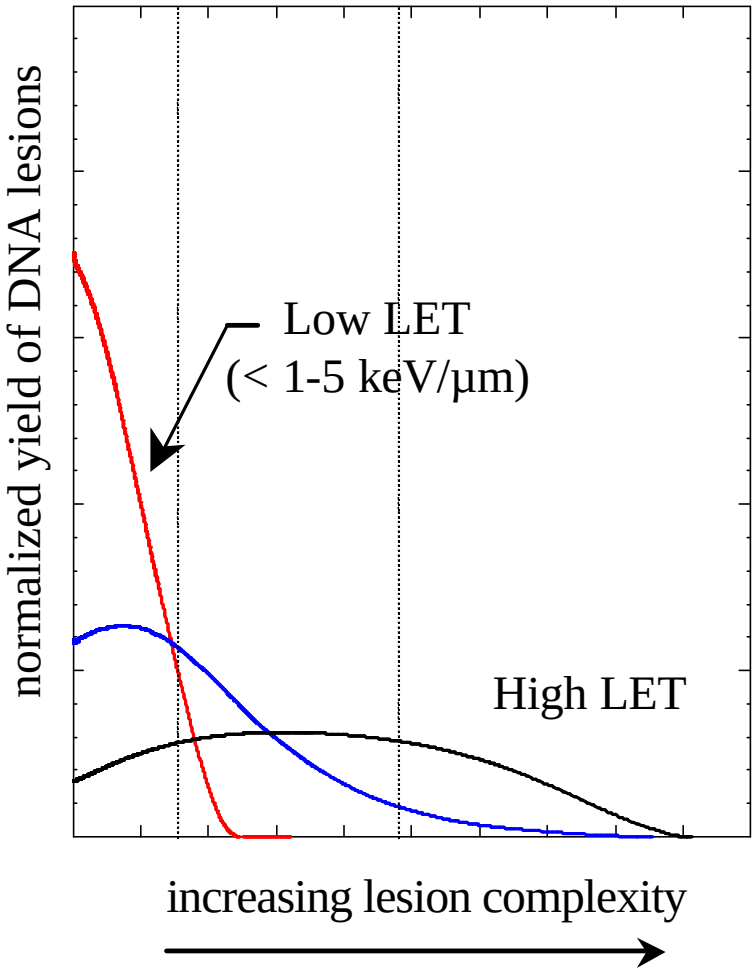
Idealized schematic of a double strand break (DSB)

Local complexity of the damage likely affects recognition or fidelity of repair.

Complex DSB

Effect of Linear Energy Transfer (LET)

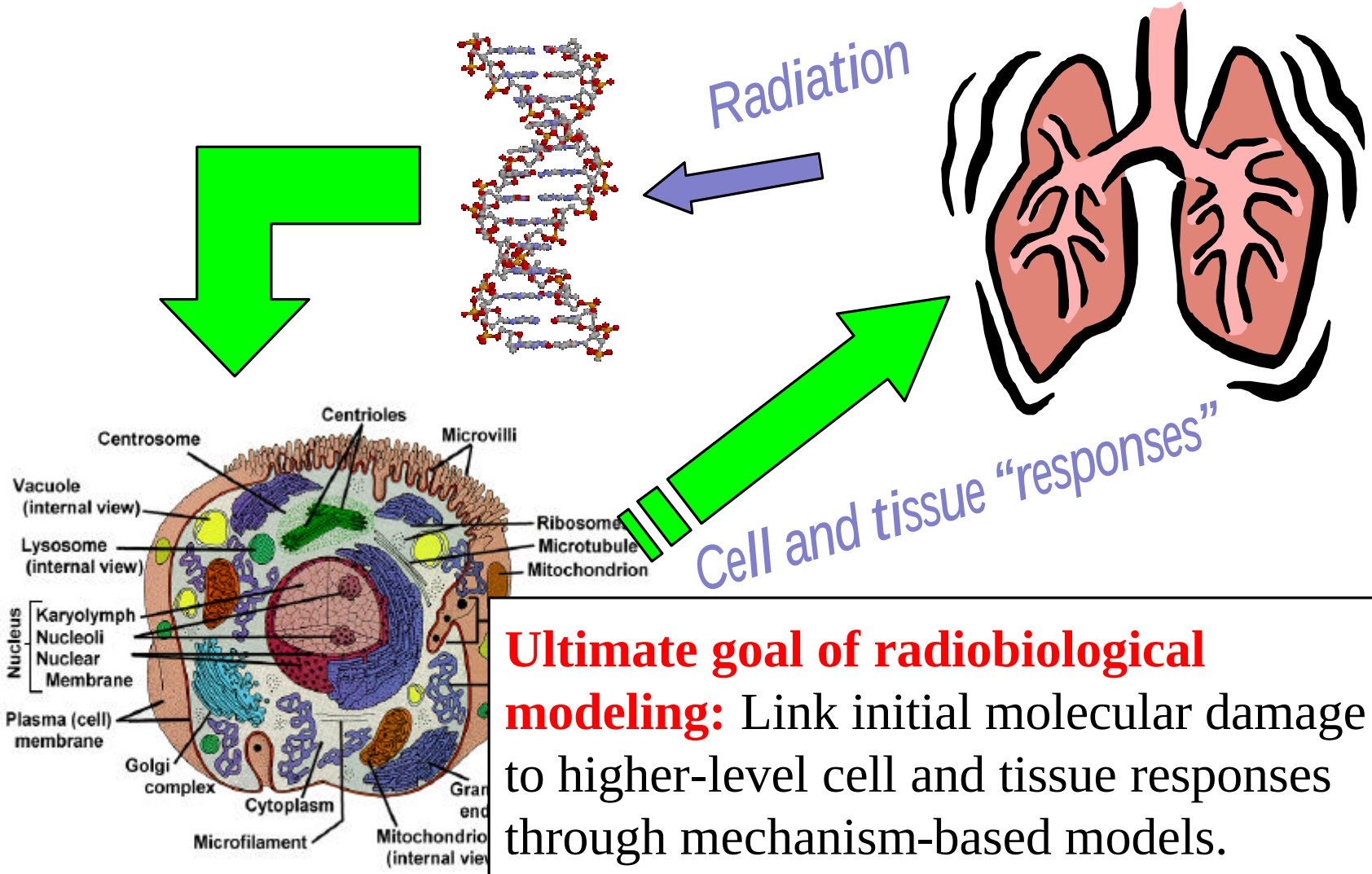
- As particle LET increases, the yield of multiply damaged (complex) DNA lesions to singly damaged (simple) DNA lesions increases.



Elapsed time since irradiation < 1 second.

- Initial physics and chemistry that results in DNA damage is relatively well understood.
  - Event by event Monte Carlo simulations are the gold standard.
- Cells don’t even “know” that they have been damaged yet.
- Modeling of the physiochemical stage of radiobiology can be decoupled from the biological stage.

Biological Stage



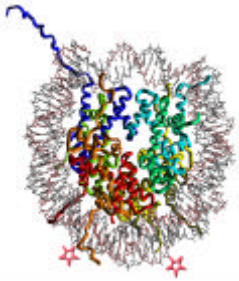
Ultimate goal of radiobiological modeling: Link initial molecular damage to higher-level cell and tissue responses through mechanism-based models.

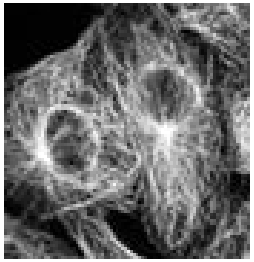
"Early" Cellular Responses

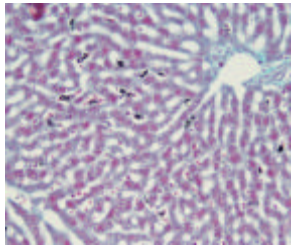
10^{-9} 10^{-6} 10^{0}

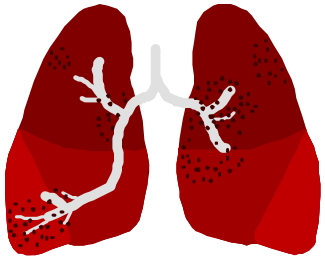
Spatial scale (m)

molecules **cells** **tissues** **organs**









intracellular signaling

intercellular signaling (bystander effects)

Time (seconds)

10^{-3} 10^{0} 10^{3} 10^{6} 10^{9}

protein kinetics

DNA damage recognition and repair

tumor promotion and progression

initial DNA and cellular damage

apoptosis, necrosis, reproductive death

microenvironmental and systemic changes

cell proliferation and differentiation

physiochemical stage

genome instability and oncogenic transformation

biological stage

1 h ~ 10^3 s
1 d ~ 10^5 s
1 y ~ 10^7 s

Cells adapt and respond

- Cells sometimes alter gene expression in response to
  - external stimuli (radiation, heat, chemical toxicants),
  - changes in their local environment (extracellular matrix), and
  - systemic factors (age, diet, health status, diet).
- Proteins networks regulate essential cellular processes such as DNA repair, apoptosis, and cell growth and differentiation.
  - How does radiation disrupt or alter information processing in relevant signaling networks?
  - What are the initiating events for early cellular responses to radiation? How does the induction frequency for these initiating events change as a function of dose and dose rate?
  - Does exposure to radiation activate additional (or suppress some) damage repair or tolerance mechanisms? Thresholds?

Bystander effects

- Cells communicate with each other through gap junctions and by secreting messenger molecules (hormones, cytokines, growth factors) into the extracellular environment.

Cancer is a multistep process

DNA damage

Early events (minutes to days)

Damage repair/fixation
- [Temperature, microwaves
+ [Caffeine, hyperthermia, hydroxyurea

Cell-cycle control

Cell reproduction
+ [Caffeine

Apoptosis inhibition

Membrane damage
+ [Heat, mineral fibres, dust, lead

Mutation/initiation
+ [Tobacco, UV, benzene, mutagens

Late events (weeks to years)

Promotion of neoplasia
- [Vitamin A, E, K, selenium, low-fat diet
+ [Tobacco, abestos, mineral fibres, hormones, dust

Enhanced instability

Tumor growth
+ [Mutagens, tobacco, asbestos, benzo(a)pyrene

Immune system surveillance
+/- [UV/ Vitamin A, endotoxins, dietary factors

Metastases
- [Anoxia, selenium
+ [Mechanical irritation, dust, mitogens

- Many intrinsic and extrinsic factors affect tumorigenesis in more (+) or less (-) than additive fashion.
  - How much do low doses of radiation impact on the promotion of neoplasia, tumor growth, or the immune system?

Adapted from UNSCEAR 2000 Volume II Annex H (Figure V.), p. 198.

How to model something you don't completely understand

- Start with what you know (or think you know).
- Ockham's Razor.
  - Keep the number of "adjustable" model parameters to the minimum required to explain the available data.
  - However, number of adjustable model parameters inevitably increases as the amount of detail incorporated into the model increases.
- Refine the model(s) as more information becomes available.
  - Process of iterative model refinement is something of an "art" and many approaches are possible.

Models to link radiation damage to cell killing

- Linear-quadratic (LQ) model.
- Lethal and potentially lethal (LPL) model.
- Two Lesion Kinetic (TLK) model.
- Some tests of the LPL and TLK model(s).
- Biological optimization of radiation therapy treatments for cancer.

Virtual Cell (VC) radiobiology software

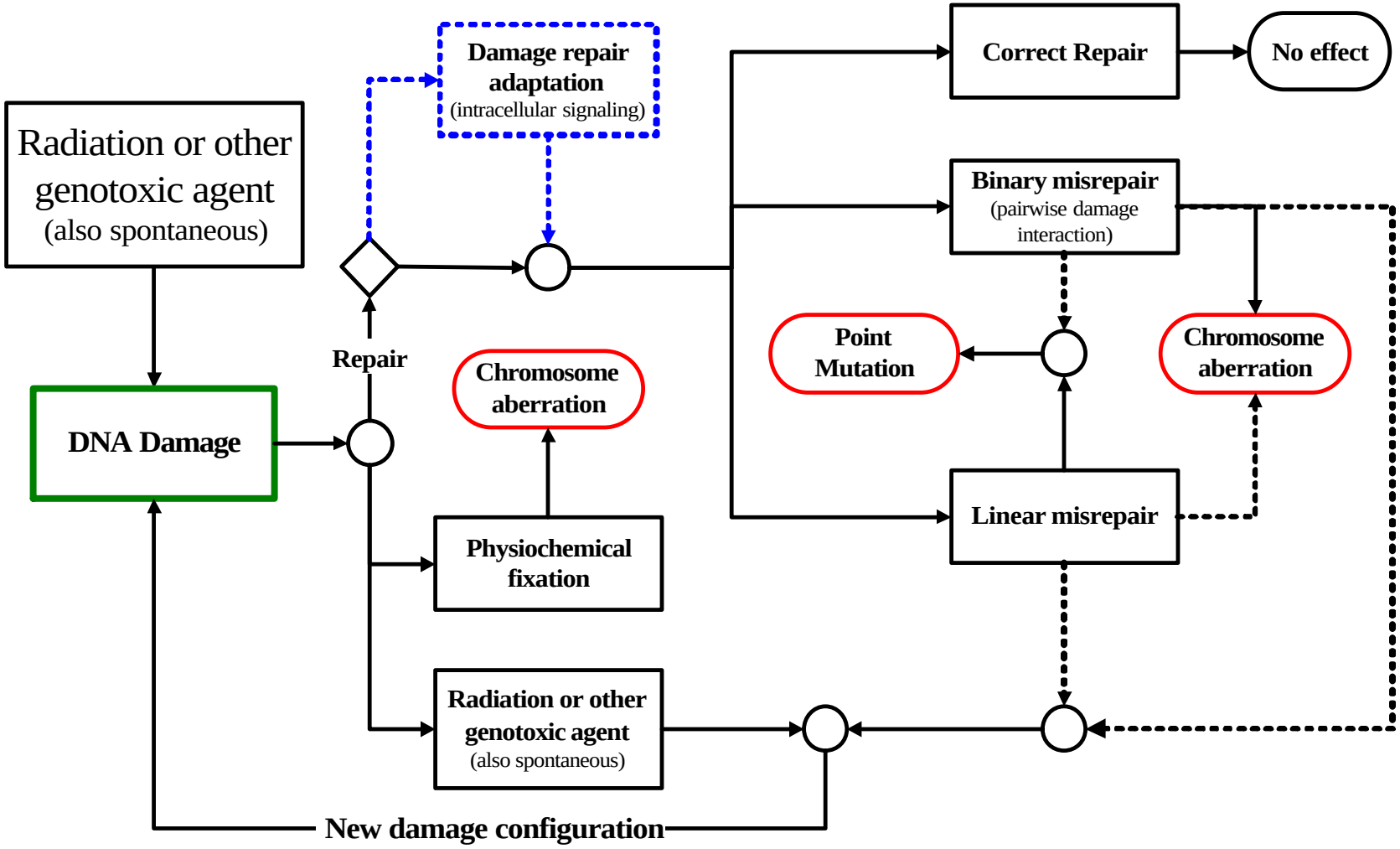
- **Complete computer program to simulate radiation effects in a homogeneous population of cells exposed to ionizing radiation.**
  - Double-strand break (DSB) rejoining kinetics.
  - Yield of lethal and non-lethal mutations by mechanism of action.
  - Genome instability and oncogenic (neoplastic) transformation.
  - Cell killing.
- **Available repair models**
  - LPL Model (Curtis 1986)
  - RMR (Tobias 1985)
  - TLK (Stewart 2001)

R.D. Stewart, Virtual Cell (VC) Radiobiology Software. PNNL-13579, July 2001. Available at http://www.pnl.gov/berc/kbem/vc/

Virtual Life Form (VLF) software

- **Complete computer program to simulate radiation effects in three-dimensional tissue constructs.**
  - Imports a dose distribution for a voxel tissue construct.
  - Simulates DNA repair and the killing or transformation of cells.
    - LPL Model (Curtis 1986)
    - RMR (Tobias 1985)
    - TLK (Stewart 2001)
  - Poisson tumor control probability (TCP) model.
  - Different regions of the tissue construct can be assigned different radiosensitivity parameters.

Biochemical processing of DNA damage



Linear Quadratic (LQ) Model

$$S(D) = \exp\left\{-D\left(a + bGD\right)\right\}$$

a ~ 0.3 Gy^{-1}, b ~ 0.05 Gy^{-2}, and G is the Lea-Catcheside dose protraction factor

$$G = (2/D)^2 \int_{-\infty}^{\infty} dt\, \dot{D}(t) \int_{-\infty}^{t} dt'\, \dot{D}(t') \exp\left\{-l\,(t-t')\right\}$$

For two acute doses D_1 and D_2 separated by time interval T

$$G = \left\{D_1^2 + D_2^2 + 2D_1D_2e^{-lT}\right\}(D_1 + D_2)^{-2}$$

G = 1 for a single acute dose of radiation.

RK Sachs, P Hahnfeld, and DJ Brenner, *Int. J. Radiat. Biol.*, **72**, 351-374 (1997).

Lethal and Potentially Lethal Model

In the 4-parameter LPL Model...

$$\frac{dL_{dsb}(t)}{dt} = \Sigma_{dsb}\dot{D}(t) - L_{dsb}(t)\left\{ l_{dsb} + e_{dsb} L_{dsb}(t) \right\}$$

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

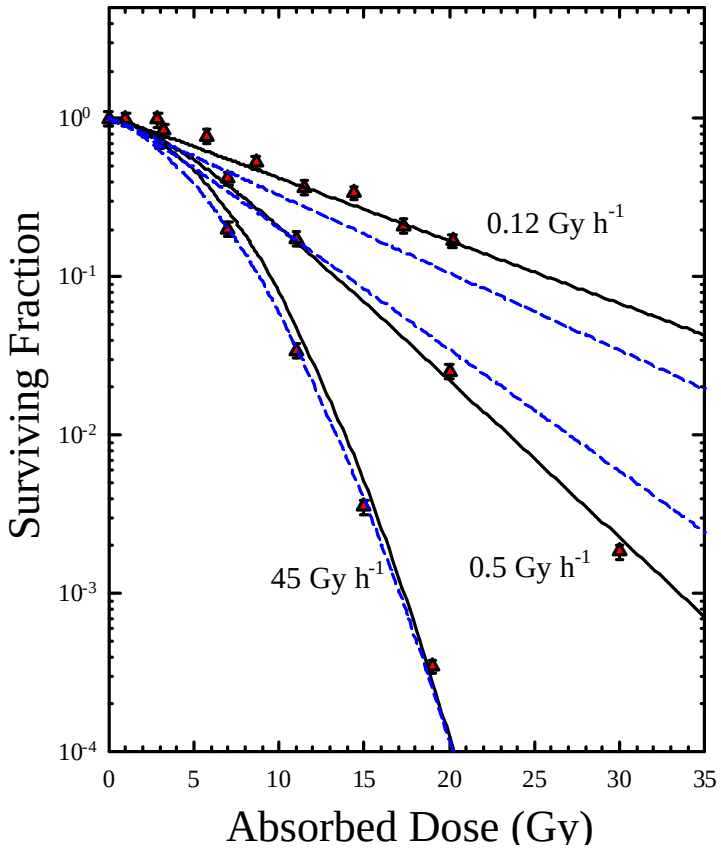
$$L_f(0) = L_{dsb}(0) = 0 \qquad S = \exp(-L_f)$$

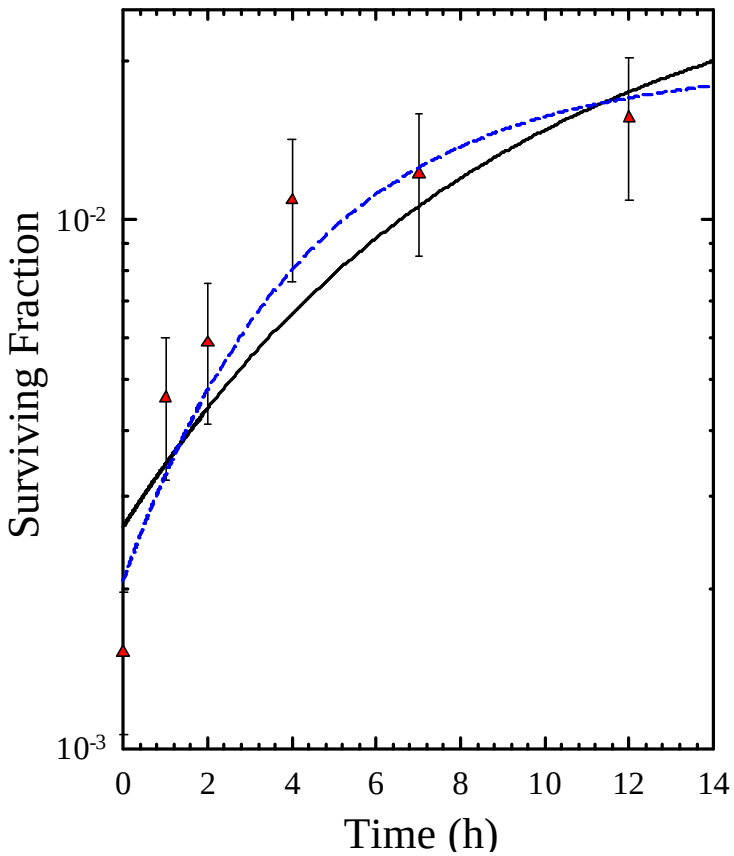
$$a = \Sigma_f + \Sigma_{dsb} \exp\left\{ -l_{dsb} T_r \right\} \qquad Gb = \frac{e_{dsb}\Sigma_{dsb}^2}{2 l_{dsb}} \left\{ 1 - \exp\left(-l_{dsb} T_r \right) \right\}^2$$

T_r is the effective time available for repair.

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

Calibration of the LPL model

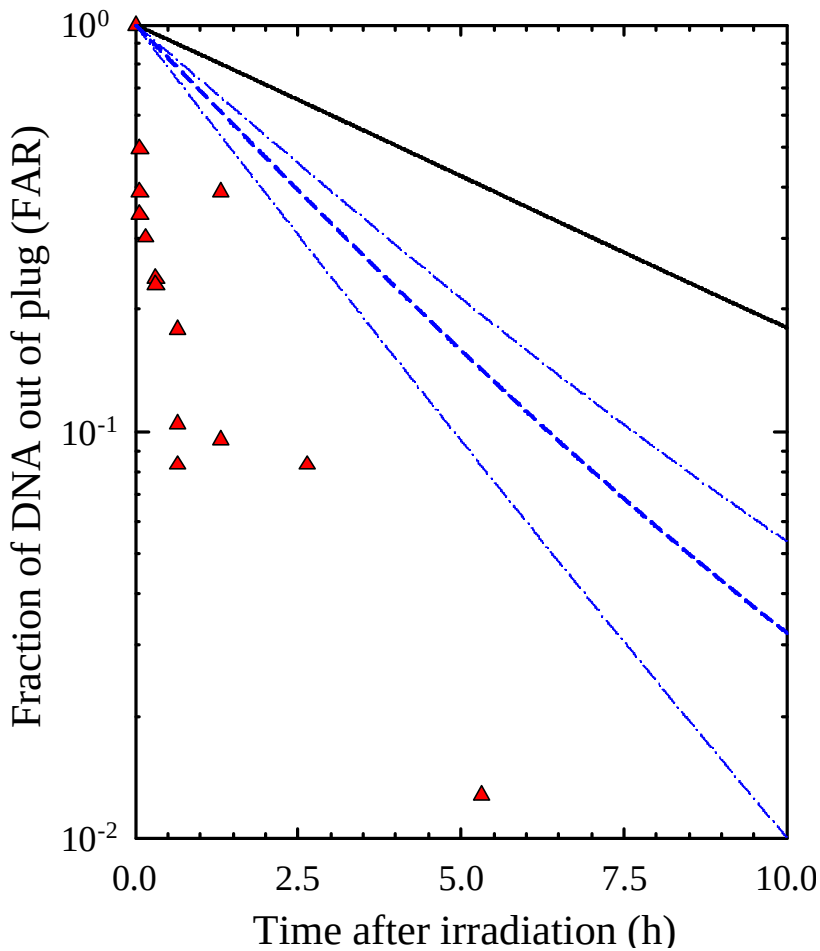




Survival of plateau phase CHO 10B2 cells irradiated by ^{137}Cs gamma-rays. ***Solid line:*** three-parameter LPL model fit ($2Y\Sigma_{dsb}$ = 25 cell^{-1} Gy^{-1}). ***Dashed line:*** two-parameter LPL model fit [$2Y\Sigma_{dsb}$ = 25 cell^{-1} Gy^{-1}, l_{dsb} = 0.231 h^{-1} (3 h DSB repair half-time)].

Adapted from R.D. Stewart, *Radiat. Res.* **156**(4), 365-378 October 2001.

A Test of the LPL model



DSB rejoining kinetics in plateau phase CHO 10B2 cells following irradiation by 20 Gy dose delivered at 356.1 Gy h^{-1}.

Solid line: three-parameter LPL model fit ($2Y\Sigma_{dsb}$ = 25 $cell^{-1}$ Gy^{-1}).

Dashed line: two-parameter LPL model fit [$2Y\Sigma_{dsb}$ = 25 $cell^{-1}$ Gy^{-1}, λ_{dsb} = 0.231 h^{-1} (3 h DSB repair half-time)].

Dash-dot lines: estimated lower and upper bounds on LPL model rejoining kinetics.

Conclusion: LPL model does not provide a satisfactory formalism to link biochemical processing of the DSB to cell killing.

Adapted from R.D. Stewart, *Radiat. Res.* **156**(4), 365-378 October 2001.

Two-Lesion Kinetic Model

$$\text{DSBs}\begin{cases} \dfrac{d\bar{L}_1(t)}{dt} = 2\dot{D}(t)Y\Sigma_1 - \left\{ l_1 + h\left[\bar{L}_1(t) + \bar{L}_2(t)\right]\right\}\bar{L}_1(t) \\ \dfrac{d\bar{L}_2(t)}{dt} = 2\dot{D}(t)Y\Sigma_2 - \left\{ l_2 + h\left[\bar{L}_1(t) + \bar{L}_2(t)\right]\right\}\bar{L}_2(t) \end{cases}$$

$$\frac{d\bar{L}_f(t)}{dt} = b_1 l_1 \bar{L}_1(t) + b_2 l_2 \bar{L}_2(t) + gh\left[\bar{L}_1(t) + \bar{L}_2(t)\right]^2$$

$$\frac{d\bar{L}_m(t)}{dt} = (1 - b_1) l_1 \bar{L}_1(t) + (1 - b_2) l_2 \bar{L}_2(t) + (1 - g)h\left[\bar{L}_1(t) + \bar{L}_2(t)\right]^2$$

$$b_1 = b_2$$

$$2Y(\Sigma_1 + \Sigma_2) \sim 40 \text{ DSB Gy}^{-1} \text{ cell}^{-1}$$

$$\bar{L}_1(0) = \bar{L}_2(0) = \bar{L}_f(0) = 0$$

$$S(t) = \exp\left\{-\bar{L}_f(t)\right\}$$

R.D. Stewart, *Radiat. Res.* **156**(4), 365-378 October 2001.

DSBs ↔ Fractional Activity Released (FAR)

- Random breakage model used to convert unrepaired DSBs into an estimate of the fractional activity released out of well (FAR).
  - Relate measured and model-predicted quantities.

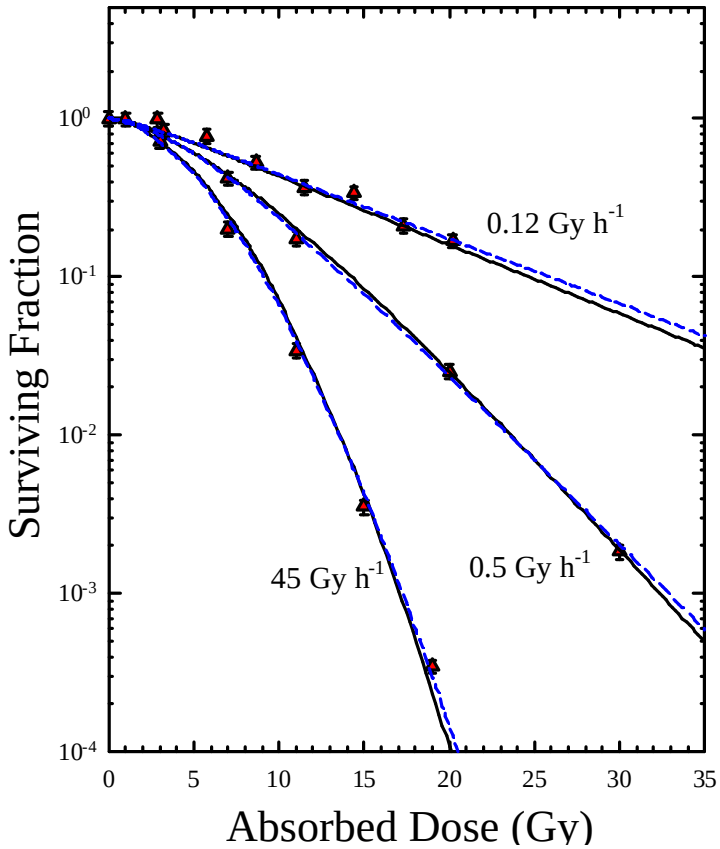
$$\mathrm{FAR} = F_{max}\left\{1-\left[1+K\bar{N}_{dsb}\left(1-\frac{K}{M_0}\right)\right]\exp^{-K\bar{N}_{dsb}}\right\}$$

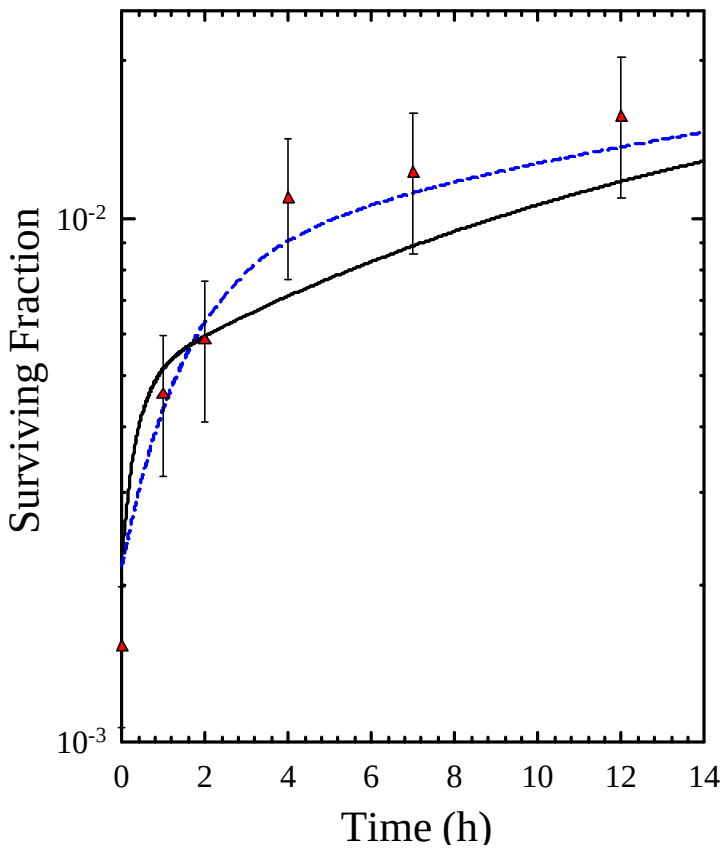
F_{max} = maximum fraction of the cellular DNA that can enter the gel.
M_0 = average chromosome size (base pair).
K = gel exclusion size (DNA fragments larger than K do not move out of the well).

$$\bar{N}_{dsb} = \bar{L}_{dsb}(t)/Y \text{ or } [\bar{L}_1(t)+\bar{L}_2(t)]/Y$$

Belli M, Cherubini R, Dalla Vecchia M, Dini V, Moschini G, Signoretti C, Simone G, Tabocchini MA, Tiveron P. DNA DSB induction and rejoining in V79 cells irradiated with light ions: a constant field gel electrophoresis study. *Int. J. Radiat. Biol.* **76**(8):1095-104 (2000).

Calibration of the TLK model

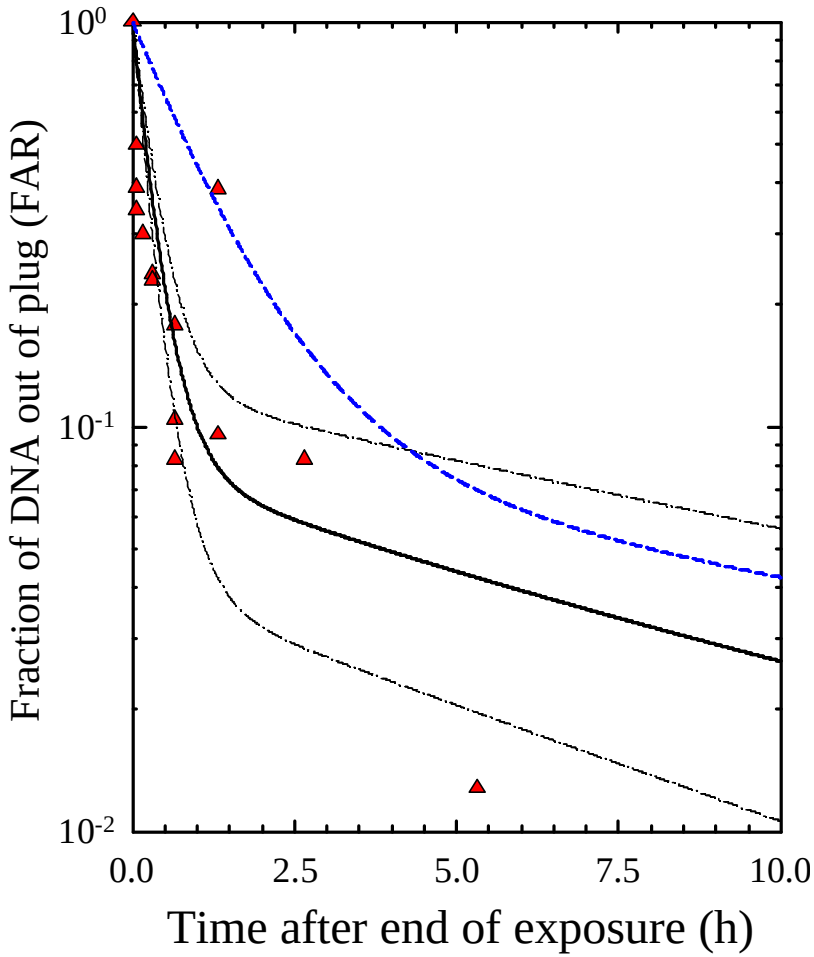




Survival of plateau phase CHO 10B2 cells irradiated by ^{137}Cs gamma-rays. ***Solid lines:*** five-parameter TLK model calibration, $2Y(\Sigma_1 + \Sigma_2)$= 24 cell^{-1} Gy^{-1} (increased simple DSB repair parameter, l_1). ***Dashed lines:*** six-parameter TLK model fit [$2Y(\Sigma_1 + \Sigma_2)$= 25 cell^{-1} Gy^{-1}].

Adapted from R.D. Stewart, *Radiat. Res.* **156**(4), 365-378 October 2001.

A Test of the TLK model



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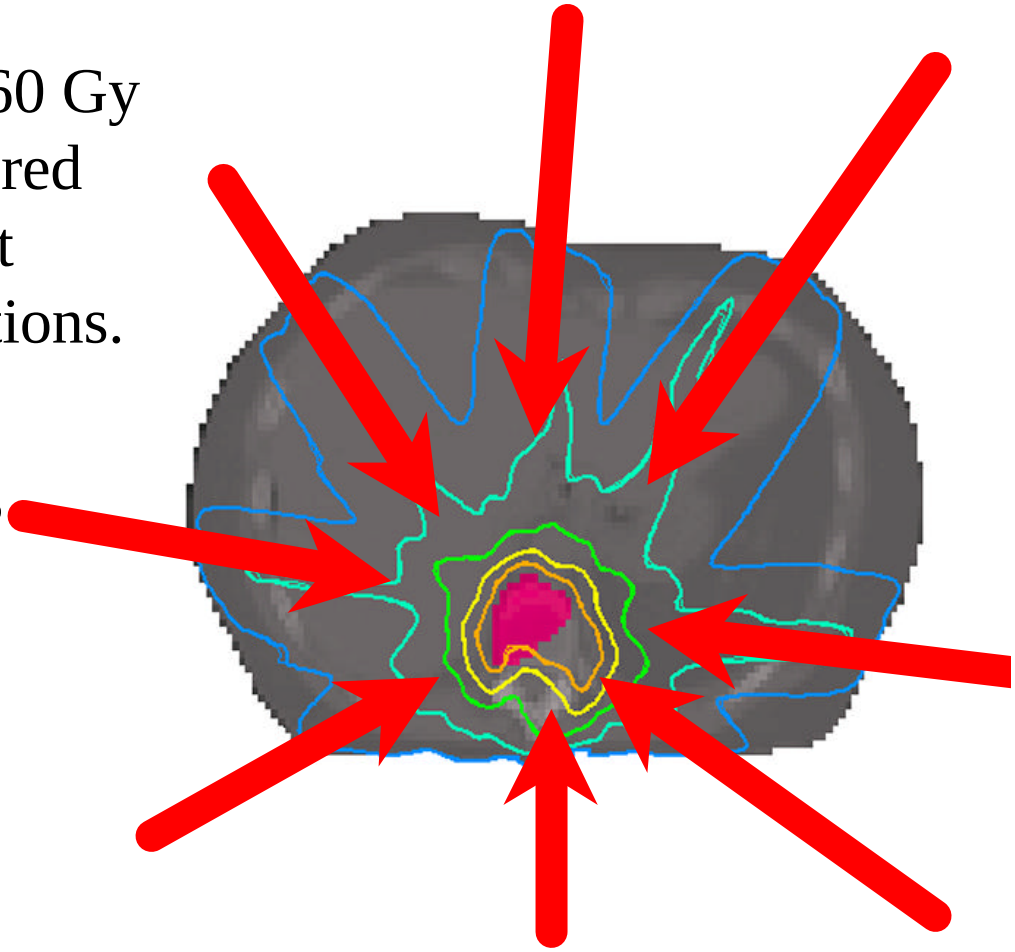
Adapted from R.D. Stewart, *Radiat. Res.* **156**(4), 365-378 October 2001.

Radiation therapy for the treatment of cancer

- Radiation treatments are often delivered as a series of daily dose fractions.
  - ~ 2 Gy/day x 30 days = 60 Gy
  - Dose fractions are delivered using a series of different leaf and beam configurations.

Cells experience a series of radiation "pulses" separated by seconds or minutes.

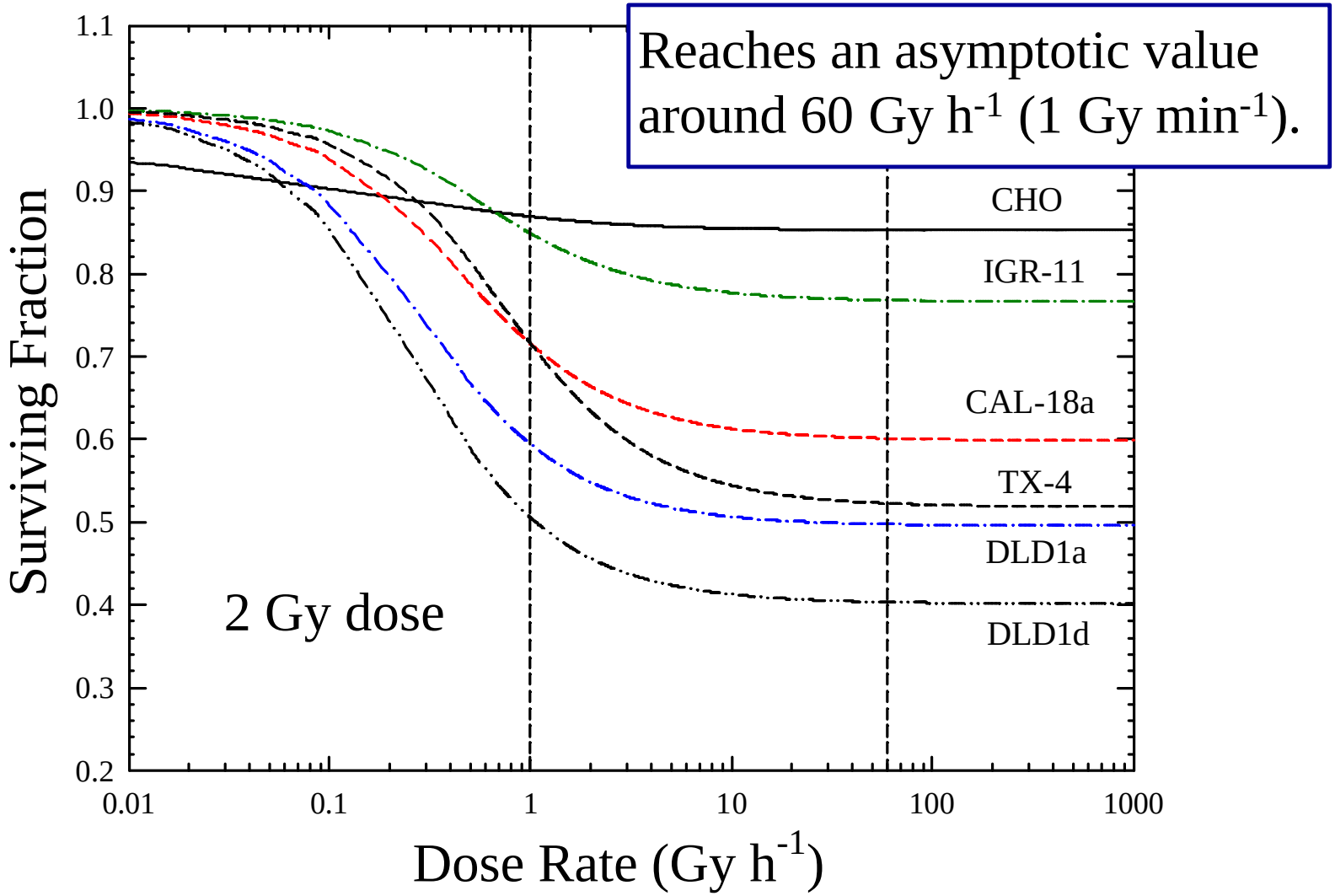


Effective (average) dose rate

	Dose fraction size (Gy)				
Dose fraction delivery time (min.)	**1.5**	**2.0**	**3.0**	**4.0**	**5.0**
1	90.00	120.00	180.00	240.00	300.00
2	45.00	60.00	90.00	120.00	150.00
5	18.00	24.00	36.00	48.00	60.00
8	12.00	16.00	24.00	32.00	40.00
10	9.00	12.00	18.00	24.00	**30.00**
15	6.00	8.00	12.00	16.00	20.00
20	4.50	6.00	9.00	12.00	15.00
30	**3.00**	4.00	6.00	8.00	10.00
45	2.00	2.67	4.00	5.33	6.67
60	1.50	2.00	3.00	4.00	5.00
90	1.00	1.33	2.00	2.67	3.33
120	0.75	1.00	1.50	2.00	2.50

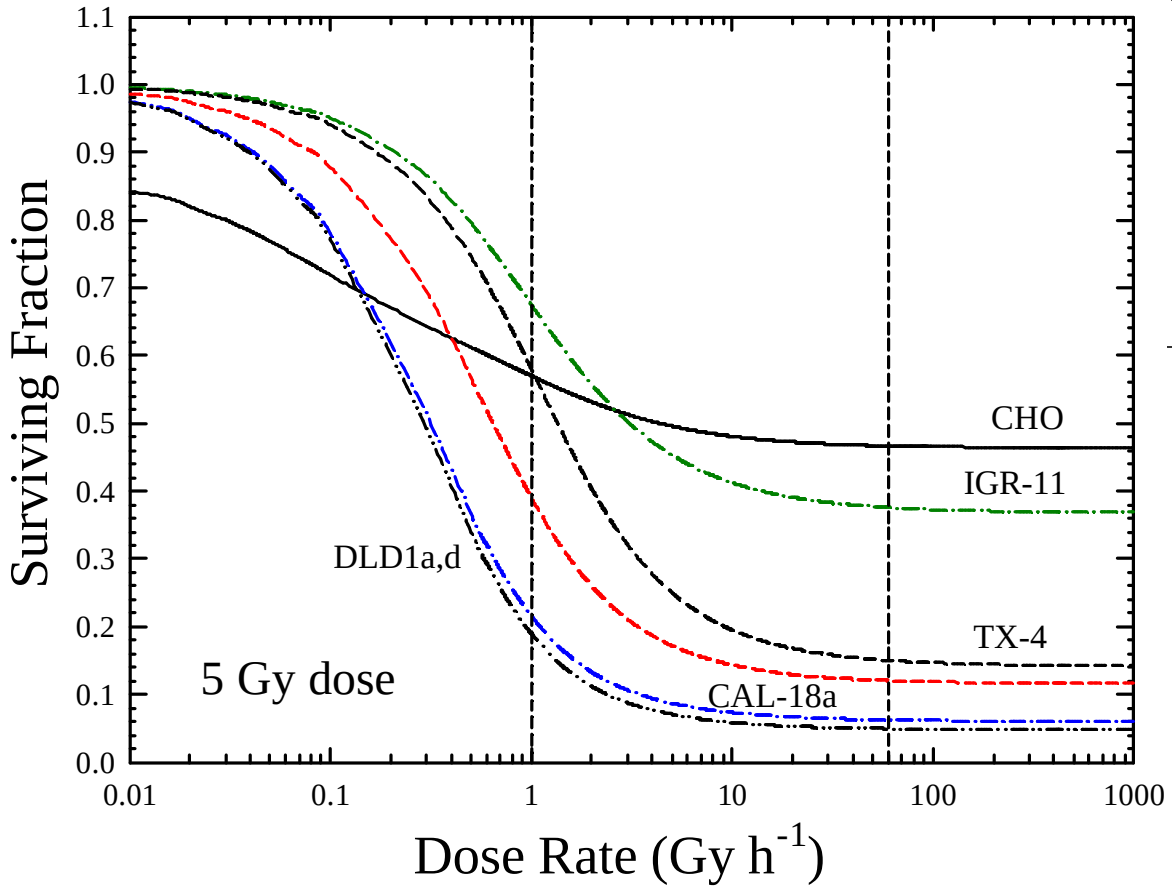
Effective dose rate (EDR) is the absorbed dose to a region of tissue divided by the total time to delivery the dose of radiation.

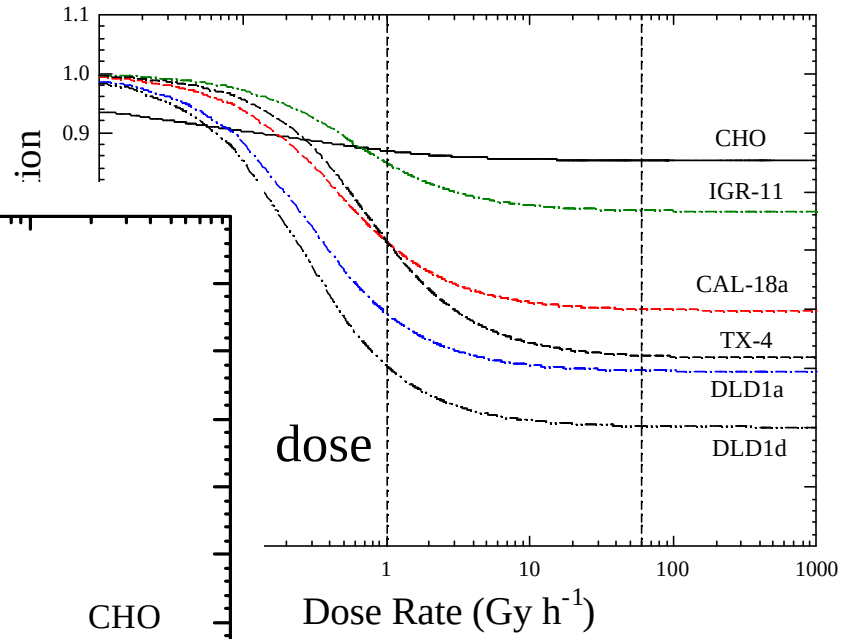
Effect of dose rate on tumor-cell killing



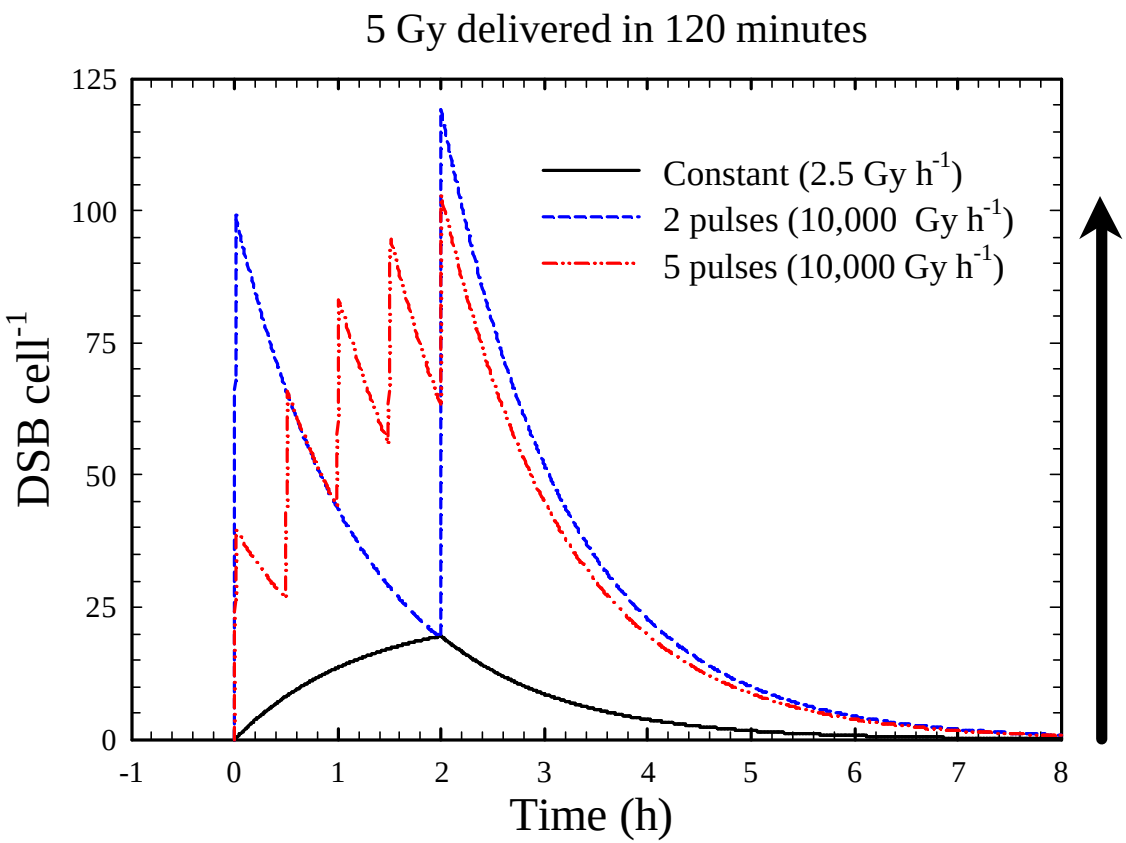
Effect of dose rate on tumor-cell killing (5 Gy)

Shape of survival curve depends on the intrinsic radiosensitivity and dose.





DSB formation and repair in a mammalian cell

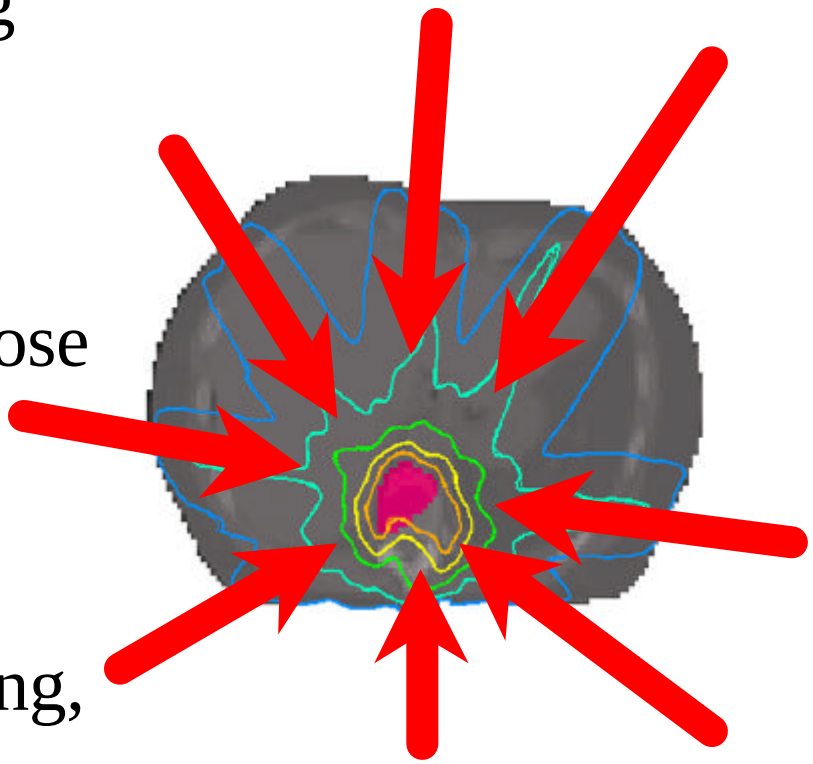


Rate of lethal DSB misrepair increases.

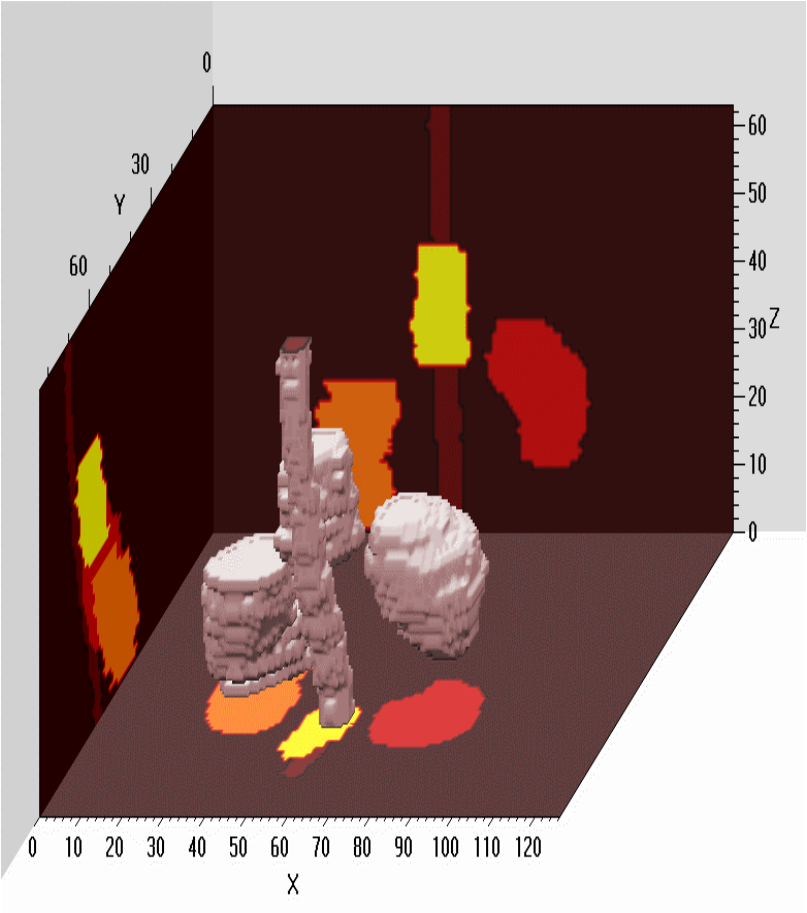
- Timing and size of the pulses affects cell killing because of damage repair (dose rate) effects.

Strategies to exploit damage repair effects

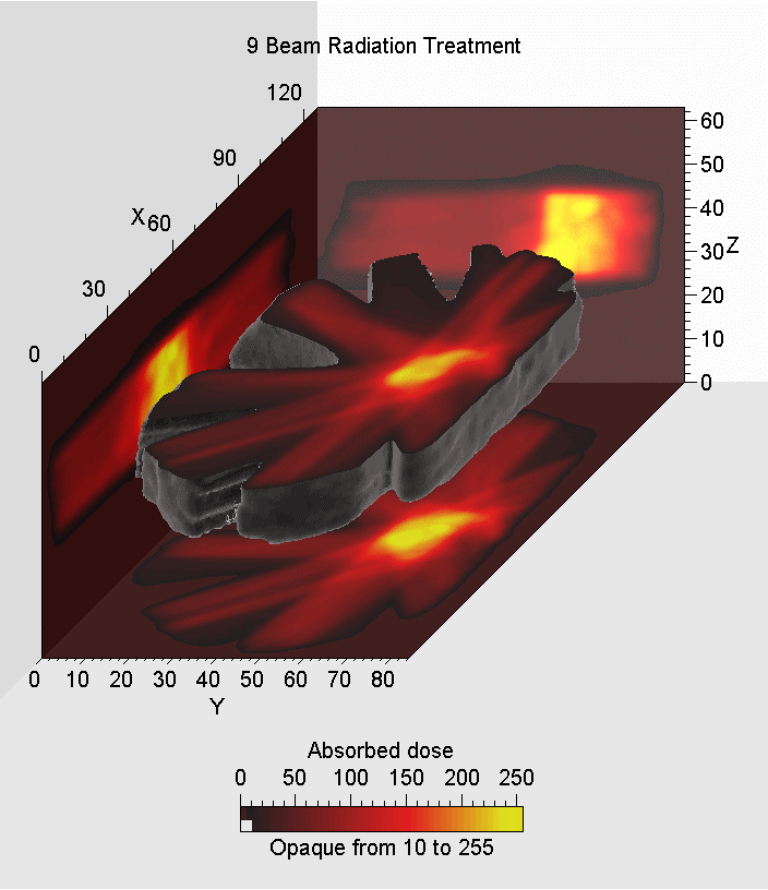
- Maximize tumor-cell killing by minimizing the dose delivery time.
- Minimize normal tissue damage by increasing the dose delivery time.
  - Multiple daily fractions.
- Use biological models to optimize the sequence, timing, and intensity of the beams.



A representative 3-D tissue construct



Intrinsic radiosensitivity and cell density parameters is the same within all tissue regions.



EGS4 Monte Carlo code used to compute dose distribution.

Tumor Control Probability (TCP)

Probability the tumor is eradicated can be expressed as

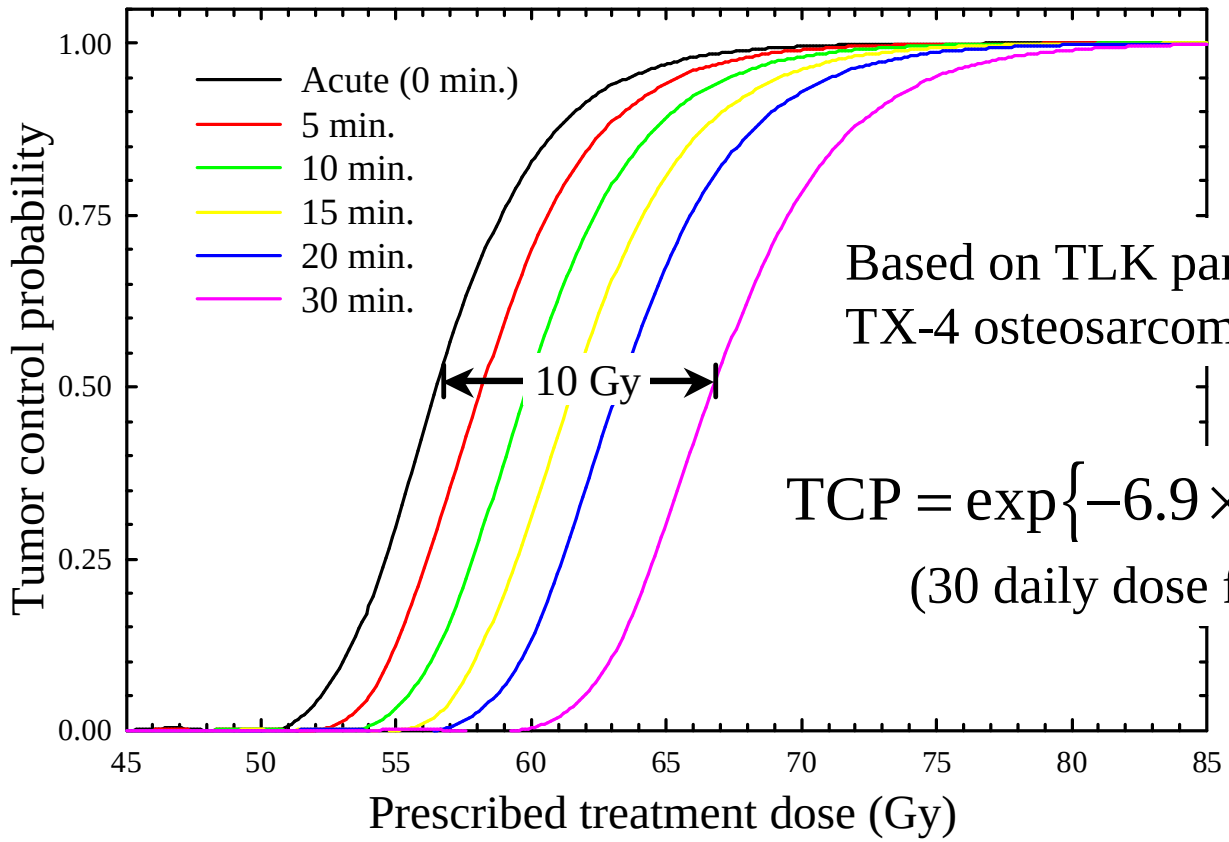
$$\mathrm{TCP} = \exp\left\{-\sum_{i=1}^{Q} N_i S_i(D)\right\}$$

$Q =$ Number of voxels.

$N_i =$ Initial number of tumor cells in the *i*th voxel.

$S_i(D) =$ Surving fraction of tumor cells in the *i*th voxel after dose *D*.

Effect of dose-fraction delivery time



Based on TLK parameters for TX-4 osteosarcoma cells.

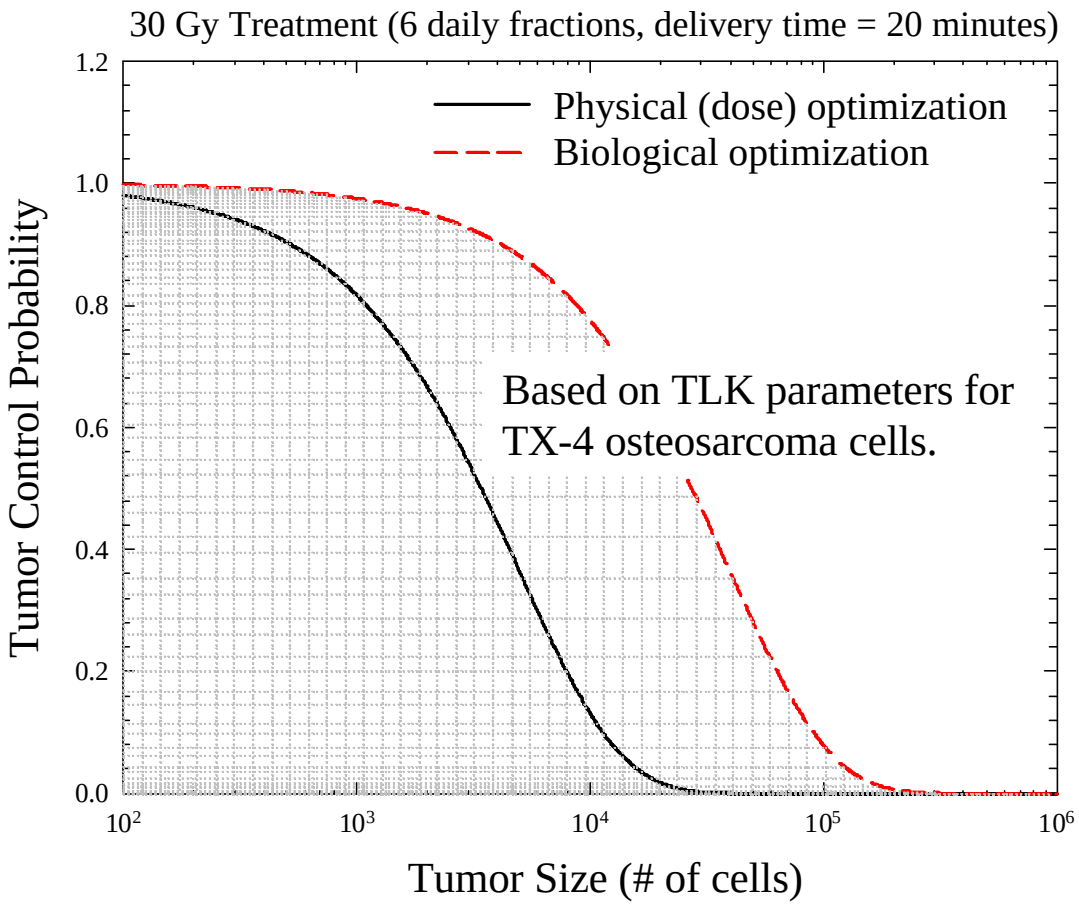
$$\mathrm{TCP} = \exp\left\{-6.9\times10^{7}\,S(D)^{30}\right\}$$

(30 daily dose fractions)

- Treatment effective *increases* as dose fraction delivery time *decreases*.

Biological optimization

- Tumor response can be modulated by altering the sequence and intensity of the beams.
- Uniform dose to the tumor may not be optimal.



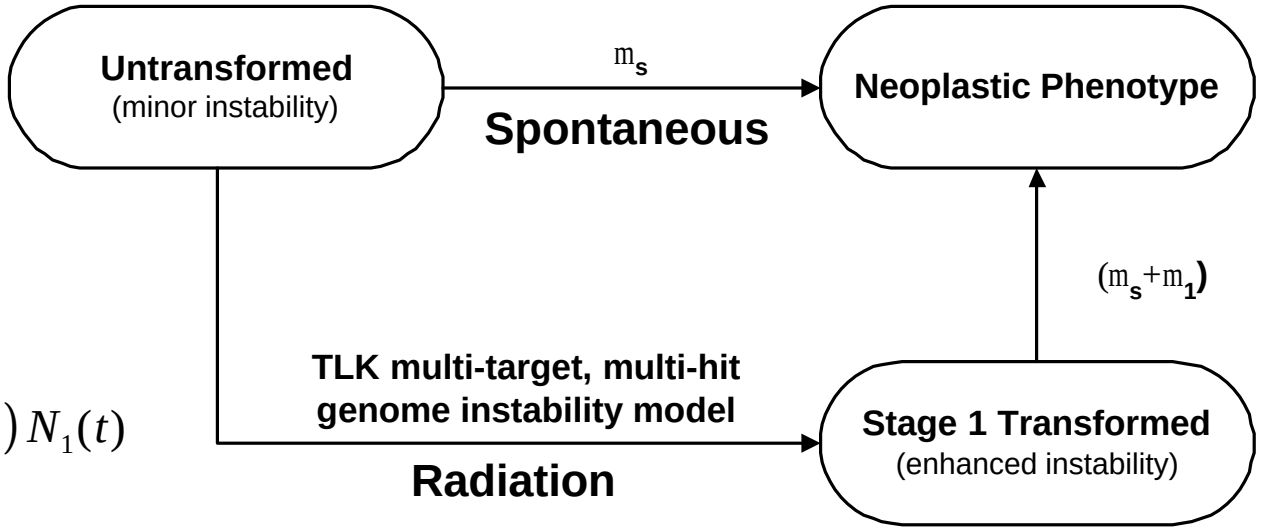
Summary

- Damage repair can affect tumor and normal tissue response even for dose delivery times as short as 5 or 10 minutes.
  - Magnitude of the effect depends on the intrinsic radiosensitivity of cell and increases with increasing dose delivery time.
- For some tumors, biological optimization of the beam sequence and intensities has the potential to significantly impact treatment outcome.
  - Maximize TCP, minimize normal tissue damage, or both.
- Additional work needed to identify clinical strategies to exploit damage repair effects.
  - Develop effective strategies to identify biological inputs.
  - Retrospective and prospective studies to test model predictions.
  - Practical constraints on dose-timing schemes.

Radiation protection – Early events along the path to cancer.

- Cancer is a multi-step process.
- How many cell transformation steps (stages) are needed to convert a normal cell into one capable of forming a malignant growth?
- How many random genetic hits are required to promote cells in one stage of the “cancer pipeline” to the next?
  - Activation proto-oncogenes (gain of function).
  - Inactivation of tumor supressor genes (loss of function).
- How do cellular characteristics change as cells are promoted from one stage to the next?
  - Different genomic instability states.
  - Intrinsic radiosensitivity (cell cycle blocks, contact inhibition, up or down regulation of DNA repair and apoptosis, …).

A simple neoplastic transformation model



$$\frac{dN_0(t)}{dt} = -m_s N_0(t)$$

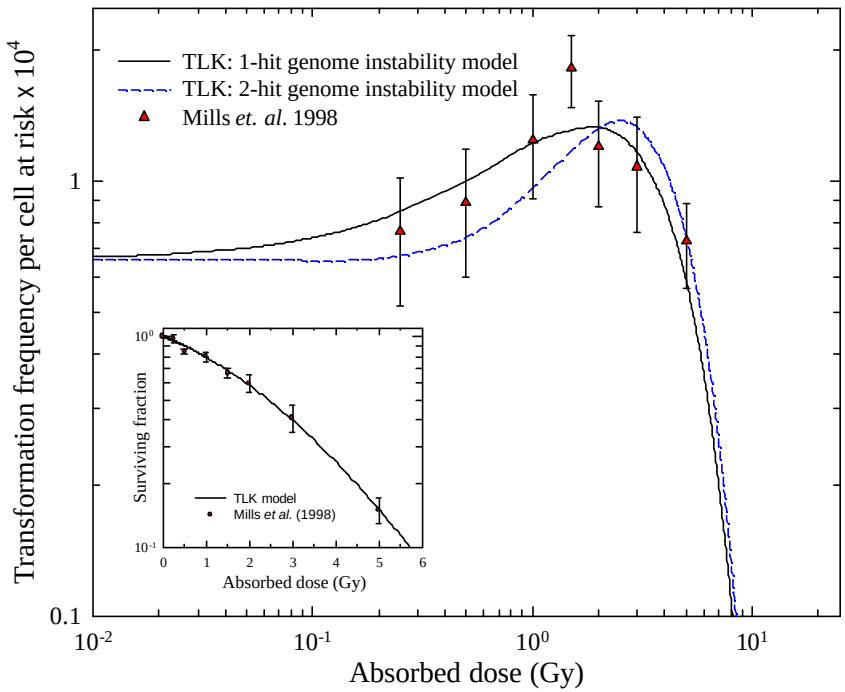
$$\frac{dN_1(t)}{dt} = -\left(m_s + m_1\right) N_1(t)$$

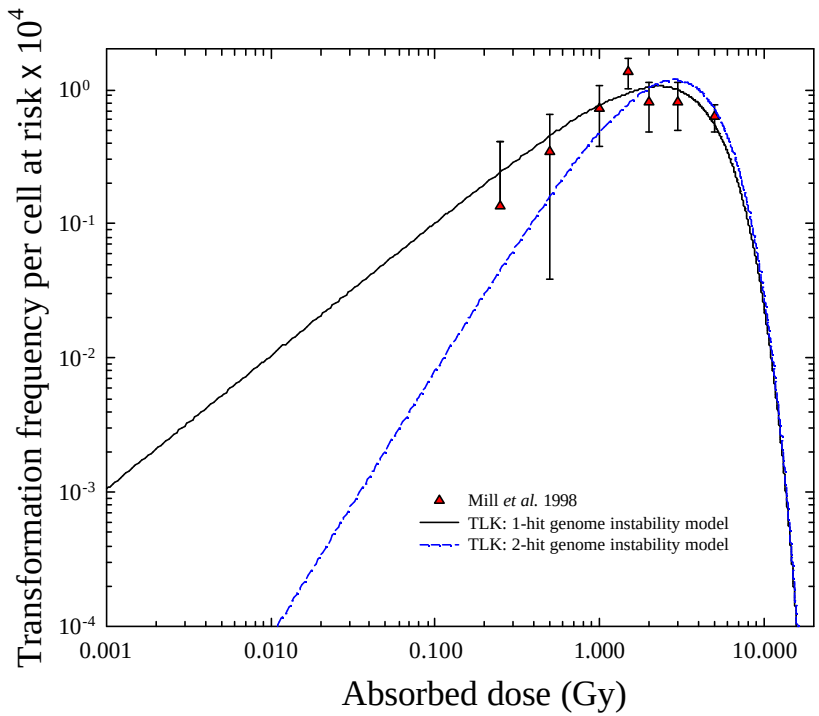
$$\frac{dN_{neo}(t)}{dt} = \left(m_s + m_1\right) N_1(t) + m_s N_0(t)$$

Number of neoplastic cells at time t equals

$$N_{neo}(t) = \left(1 - p_{gi}\right)\left\{1 - \exp\left[-m_s\left(t - t_0\right)\right]\right\} + p_{gi}\left\{1 - \exp\left[-\left(m_s + m_1\right)\left(t - t_0\right)\right]\right\}$$

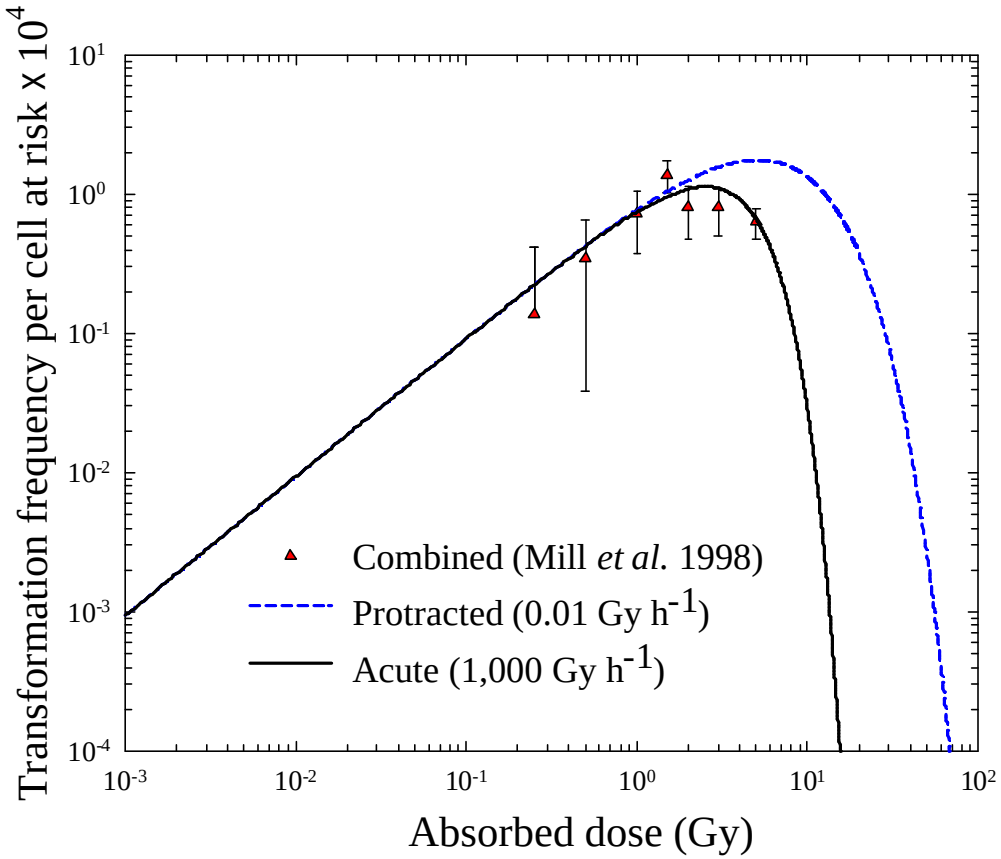
Transformation of C3H 10T1/2 cells





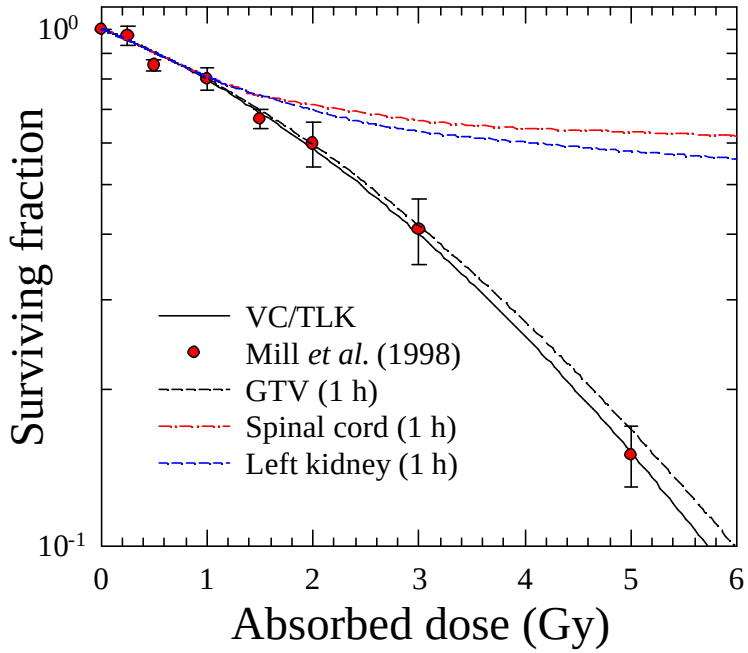
Comparison of model-predicted and measured data for the transformation frequency of C3H 10T1/2 cells (manuscript in preparation). Left panel: spontaneous plus radiation-induced cell transformation. Inset figure shows the cell surviving fraction after an acute dose of low-LET radiation; the same radiation source and dose rate was used for the cell transformation and survival studies. Right panel: radiation-induced cell transformation (no spontaneous transformation). The same TLK model parameters were used to predict cell transformation and killing. Cell transformation and killing data are from A.J. Mill *et al.*, *J Radiol Prot.* **18**(2):79-100 (1998).

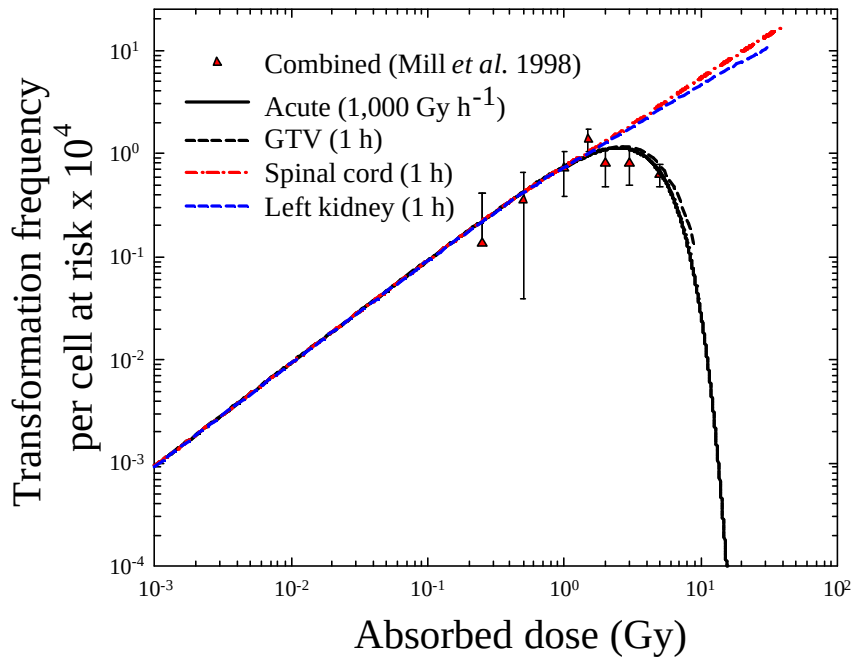
Effect of dose rate



- For doses below about 1 Gy, cell transformation is proportional to dose and independent of dose rate.
- For higher doses, cell killing overtakes cell transformation and the dose response curve bends downward.

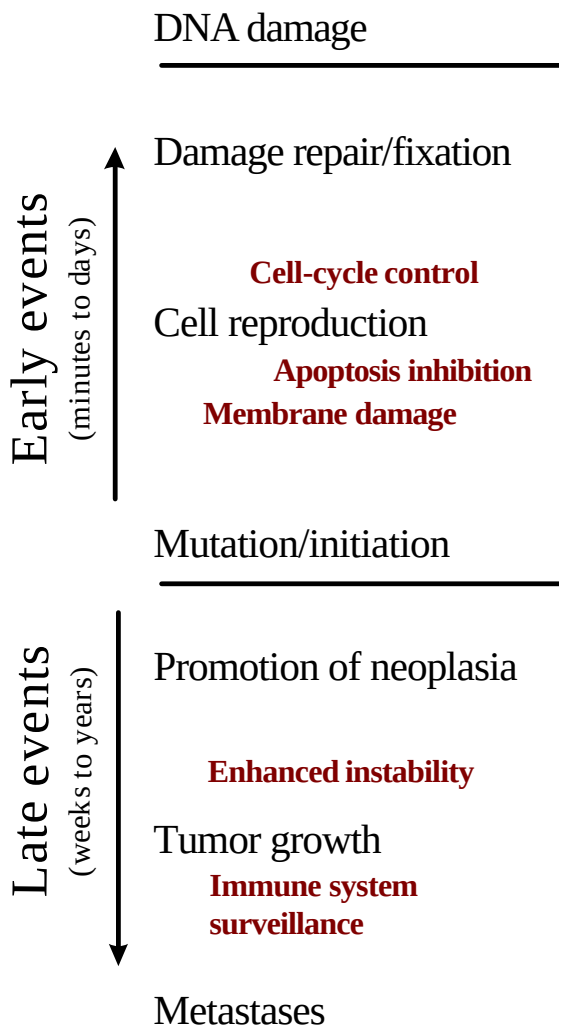
Effect of partial tissue irradiation





- Partial tissue irradiation alters the shape of the response curve at higher doses because of changes in tissue-averaged cell killing.

Summary



- *As a first-order approximation*, cell transformation is
  - Proportional to dose
  - Independent of dose rate below about 1 Gy.
  - Linear no-threshold (LNT) model is probably not too bad.
- Cancer is the result of a multi-step process that occurs over many months or years.
  - Many endogenous and exogenous factors affect the probability a transformed cell will eventually develop into a tumor.

2nd order refinements (Early events)

- Does DNA damage other than the DSB contribute significantly to the mutagenic potential of radiation?
- Up regulation of DNA repair in response to damage (i.e., inducible repair).
  - Some repair mechanisms may be up regulated while others are not.
  - Repair may shift from slow, high-fidelity mechanisms to faster but more error prone mechanisms (increases cell transformation, decreases cell killing) or vice versa.
- Cell cycle effects.
  - Initial yield, rate, and fidelity of damage repair are different in G1, S, G2, and M phases of the cell cycle.

More 2nd order refinements

- Repopulation effects.
  - Cells may produce viable progeny during the course of a protracted radiation exposure.
- Apoptosis.
  - Cells recognize they are damaged and initiate a self-destruct sequence.
  - Tends to suppress cell transformation.
- Bystander effects.
  - Cells not directly hit by radiation display changes in gene expression, increases in sister chromatid exchanges, and chromosomal instability.
  - Tends to increase number of cells transformed at lower doses.

Conclusions

- Accuracy of cancer risk estimates for low doses of radiation remains a contentious issue.
  - Quite a lot is known about early events involved in the pathogenesis of cancer.
    - As a first approximation, linear no-threshold (LNT) model isn't too bad for early events.
  - Many of the details of how cells and *collections of cells* adapt and respond to radiation are not yet known.
- We're a long way from the radiobiological equivalent Einstein's General Theory of Relativity.
  - Predicting the development of cancer is more like predicting the weather than predicting the orbits of planets and stars.

Acknowledgements

- Dr. A.L. Brooks, WSU-TC.
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Some new and ongoing projects at PNNL

- Virtual Respiratory Tract (VRT).
  - PNNL Laboratory Directed Research and Development (LDRD) project.
  - R.A. Corley, C. Timchalk, H.E. Trease, K.R. Minard, D.N. Rommereim
- ADAM – Advanced Dosimetry Assessment Model
  - PNNL Laboratory Directed Research and Development (LDRD) project.
  - R.D. Stewart, J. Malard, H.E. Trease, and T. Palmer (OSU).
- Kinetic Modeling of Damage Repair, Genome Instability, and Neoplastic Transformation
  - U.S. Department of Energy, Low Dose Radiation Research Program (http://www.lowdose.org).
  - R.D. Stewart (P.I.), E.J. Ackerman (co-PI), J. Malard, X.C. Lei, A. Chatterjee (LBNL), P.K. Cooper (LBNL), B.R. Scott (LRRI).

Kinetic modeling of damage repair…

- Objective: Develop new modeling tools to study the putative effects of
  - inducible repair phenomena.
  - DNA repair-pathway interactions.
- Specific aims:
  - Develop Monte Carlo base and nucleotide excision repair models.
    - Estimate the repair fidelity of damages other than the DSB.
  - Develop pathway specific kinetic models to relate biochemical processing of DNA damage to
    - the onset of genomic instability.
    - transformation or killing of cells.
  - Conduct an uncertainty analyses to help identify the critical experimental inputs for future studies.
    - Multi-objective optimization (genetic algorithms, gradient methods).
    - Latin hypercube sampling.

Additional Information

- Biological Effects of Radiation and Chemicals
  - http://www.pnl.gov/berc/
- Virtual Cell Radiobiology Software
  - http://www.pnl.gov/berc/kbem/vc/
- Rob Stewart
  - http://www.pnl.gov/berc/staff/rds.html