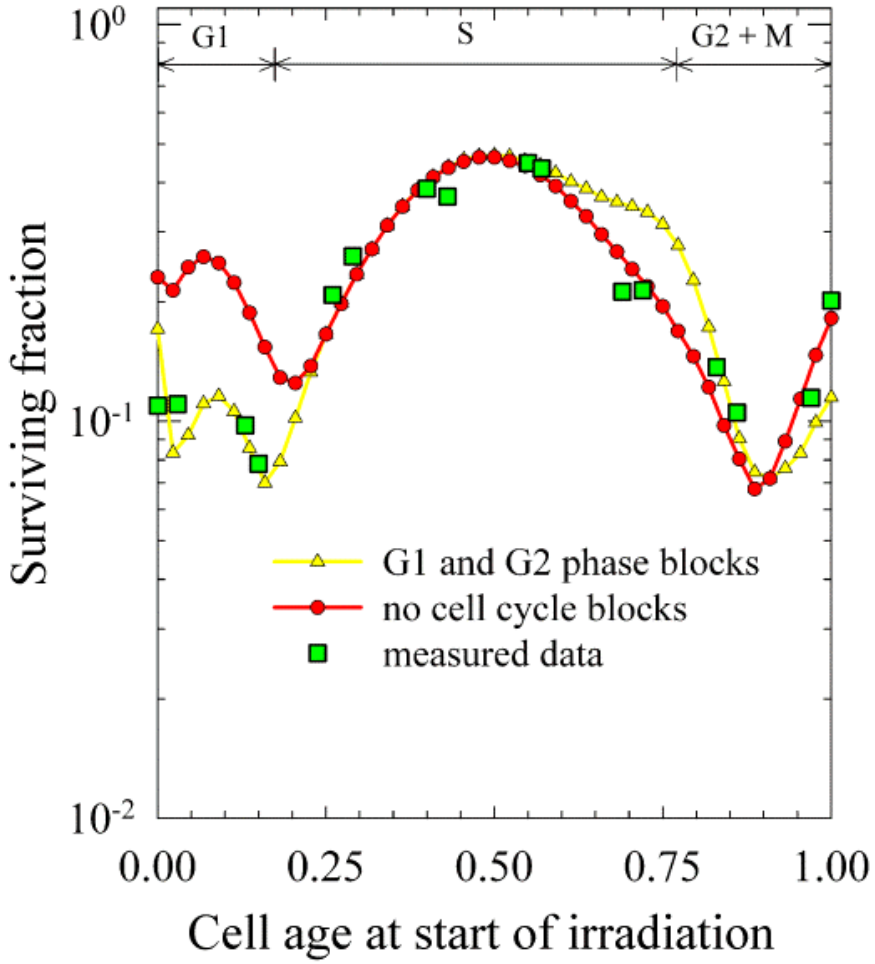
# Kinetic Biological Effects Modeling (KBEM) Software

***The software is the model...***




**Acknowledgements**

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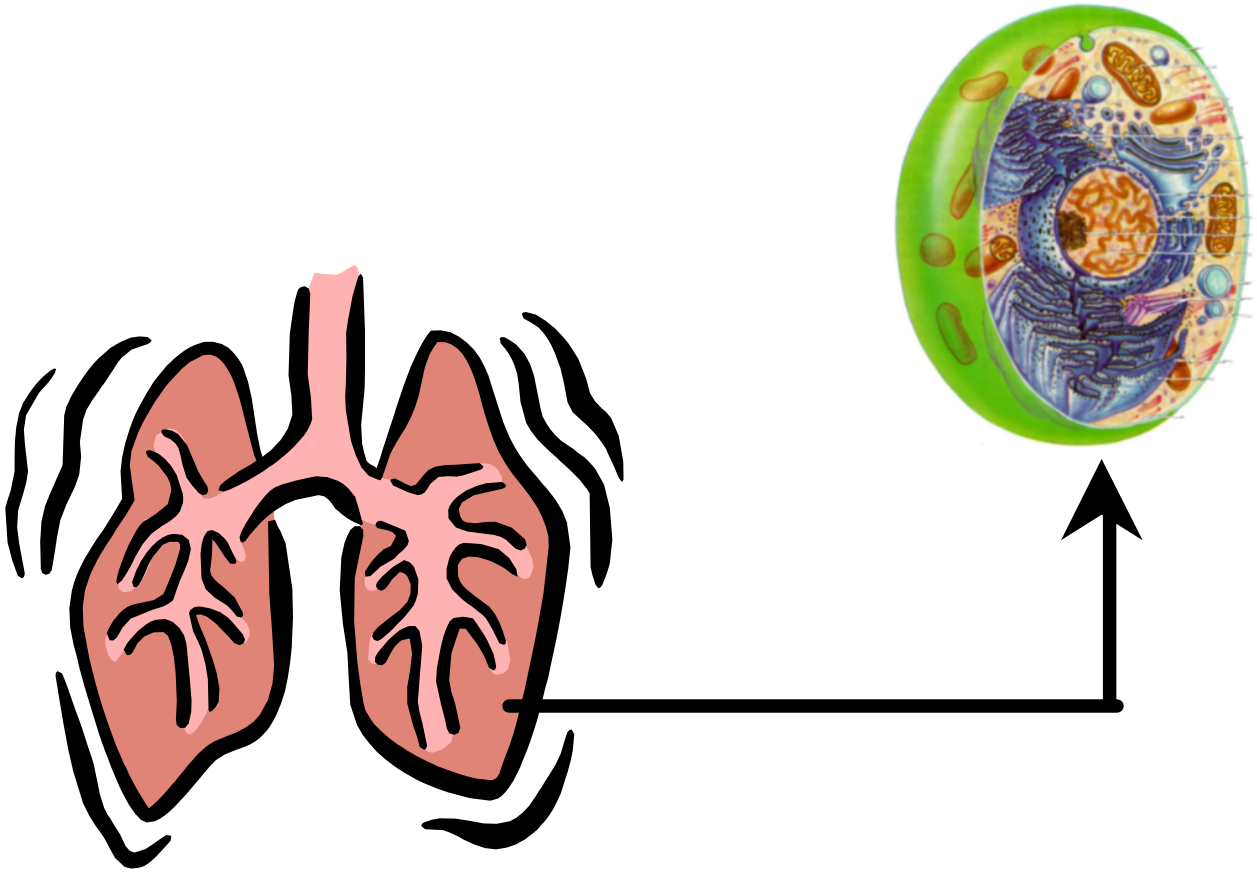
U.S. Department of Energy
Pacific Northwest National Laboratory

**Battelle**

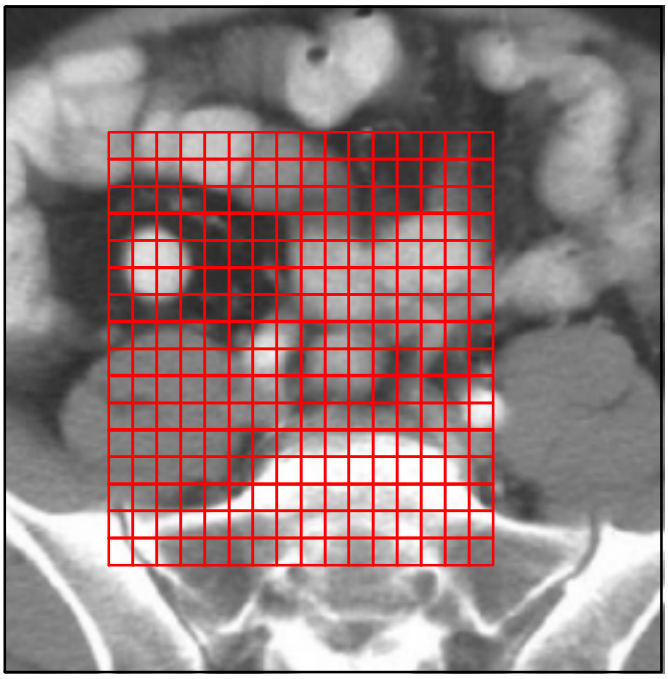
# Conceptual Framework
## *The Challenge...*

- Organs, tissues, and tumors are collections of one or more types of quiescent and proliferating cells that communicate with each other through a myriad of cell signaling pathways.



Picture of cell adapted from KM Van De Graaff and SI Fox, *Concepts of Human Anatomy and Physiology* (1986).

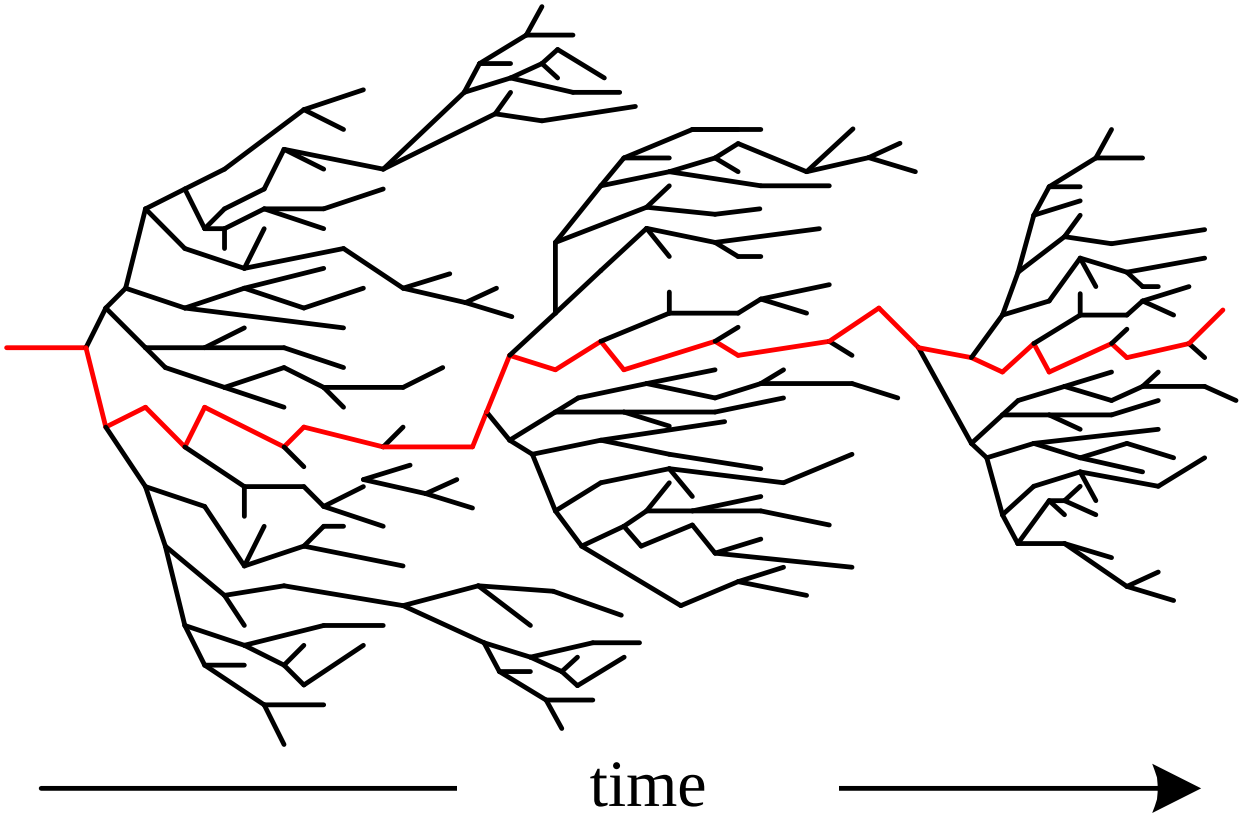
# Anatomical and Physiological Model



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

- Tissues of interest are sub-divided into three-dimensional regions (i.e., voxels).
- In each voxel, cells are exposed to a uniform amount of a chemical or radiological agent that periodically changes.
  - Chemical dosimetry (PBPK models).
  - External and internal radiation dosimetry.
  - Time steps on the order of 1 to 100 s.
- Cellular properties and partitioning of cells into different compartments adjusted after time steps on the order of 1 to 24 hours.

# Temporal Evolution of an Ensemble of Cells

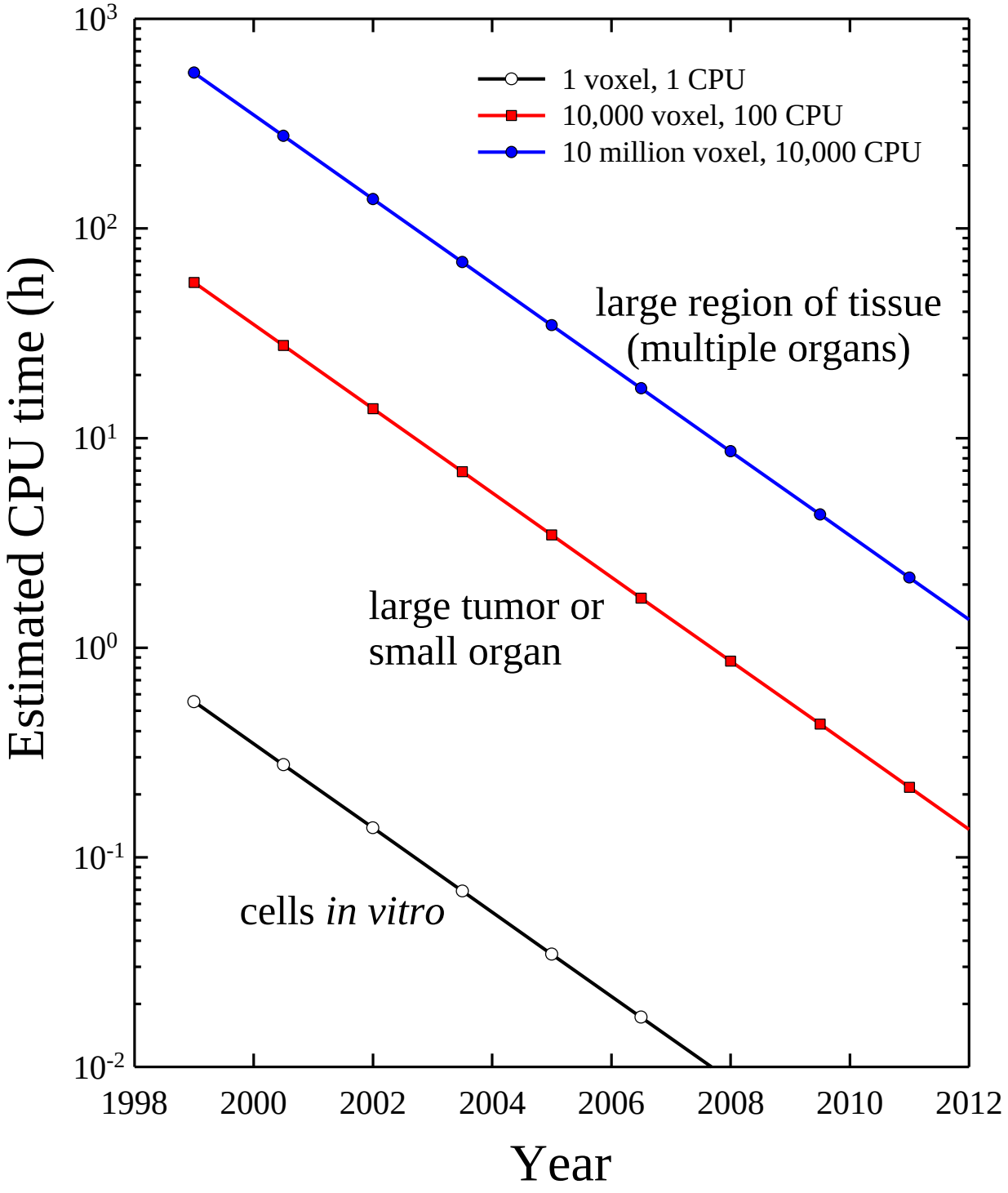



Idealized schematic illustrating the evolution of a population of cells from a single cell. “Forks” indicate the successful completion of mitosis and the creation of viable progeny cells. The length of the line segments indicates the amount of time it takes a cell to complete mitosis. The line segments shown in red indicate the “life history” of one particular cell.

# Dose-Response Behavior of an Ensemble of Cells

- Use a detailed biophysical model to simulate the behavior ("life history") of a large number of cells (and their progeny).
  - Update biophysical parameters in the dose-response model at periodic intervals to account for cell signaling and tissue/tumor microenvironment effects.
  - 10,000 to 100,000 cell histories to simulate behavior of cells in each voxel.
    - ➤Use cell-history splitting, roulette, or other variance reduction techniques to speed-up simulation.
- Evaluate quantities of interest at various times during the simulation.
  - Expected number of lethal and non-lethal genetic alterations per cell.
  - Expected number of transformed cells.
  - Expected number of cells killed.

# Is It Feasible?



# KBEM Software Overview

- Detailed multi-lesion, multi-pathway damage repair/misrepair model.
  - Chromatin structure and proximity effects.
  - Designed to facilitate future integration of effects such as inducible repair.
- Stochastic (Monte Carlo) cell proliferation model.
  - Cell-cycle blocking linked to amount of unrepaired DNA damage in a cell.
- Cell transformation and killing linked to the repair/misrepair of genotoxic damage.
  - How many lethal and non-lethal genetic alterations are produced under acute, high-dose and protracted low-dose conditions?
  - How many *randomly formed* genetic alterations are required to kill or transform a cell?

# Status of the KBEM Software

- Over 3,500 person-hours of effort to date.
- > 25,000 lines of Fortran source code sub-divided into 7 modules.

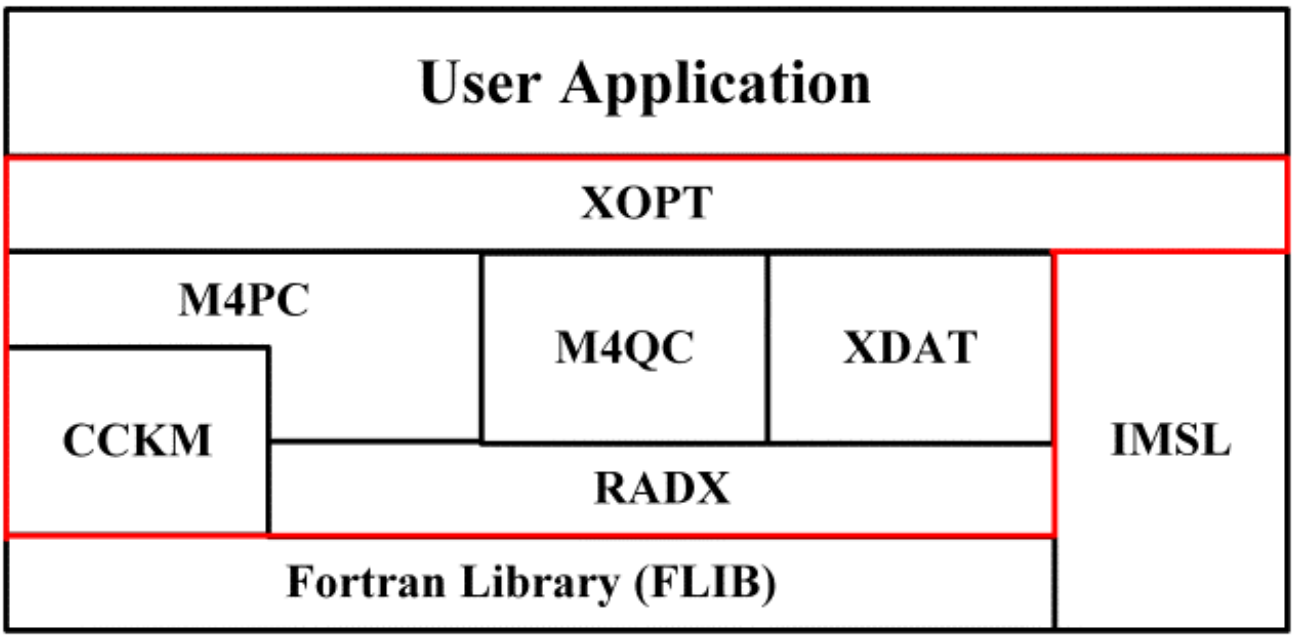
*Biophysical Simulation*

- RADX (beta).
- M4QC (beta).
- CCKM (prototype).
- M4PC (prototype).
- CHMX.

*Parameter Tuning*

- XDAT (alpha).
- XOPT (alpha).

# Organization of a Prototypical KBEM Application




- PNNL Fortran Library.
  - General purpose routines to manipulate alphanumeric character strings, generate random number sequences, display error and warning message, time and date routines, …
  - http://www.pnl.gov/berc/flib/index.html
- IMSL Math and Statistics Library
  - Differential equation solver.
  - http://www.vni.com/products/imsl/

# Linear Quadratic (LQ) Model

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

$\alpha \sim 0.3\ \mathrm{Gy}^{-1}$, $\beta \sim 0.05\ \mathrm{Gy}^{-2}$, 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.

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

# Lethal and Potentially Lethal (LPL) Model

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

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

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

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

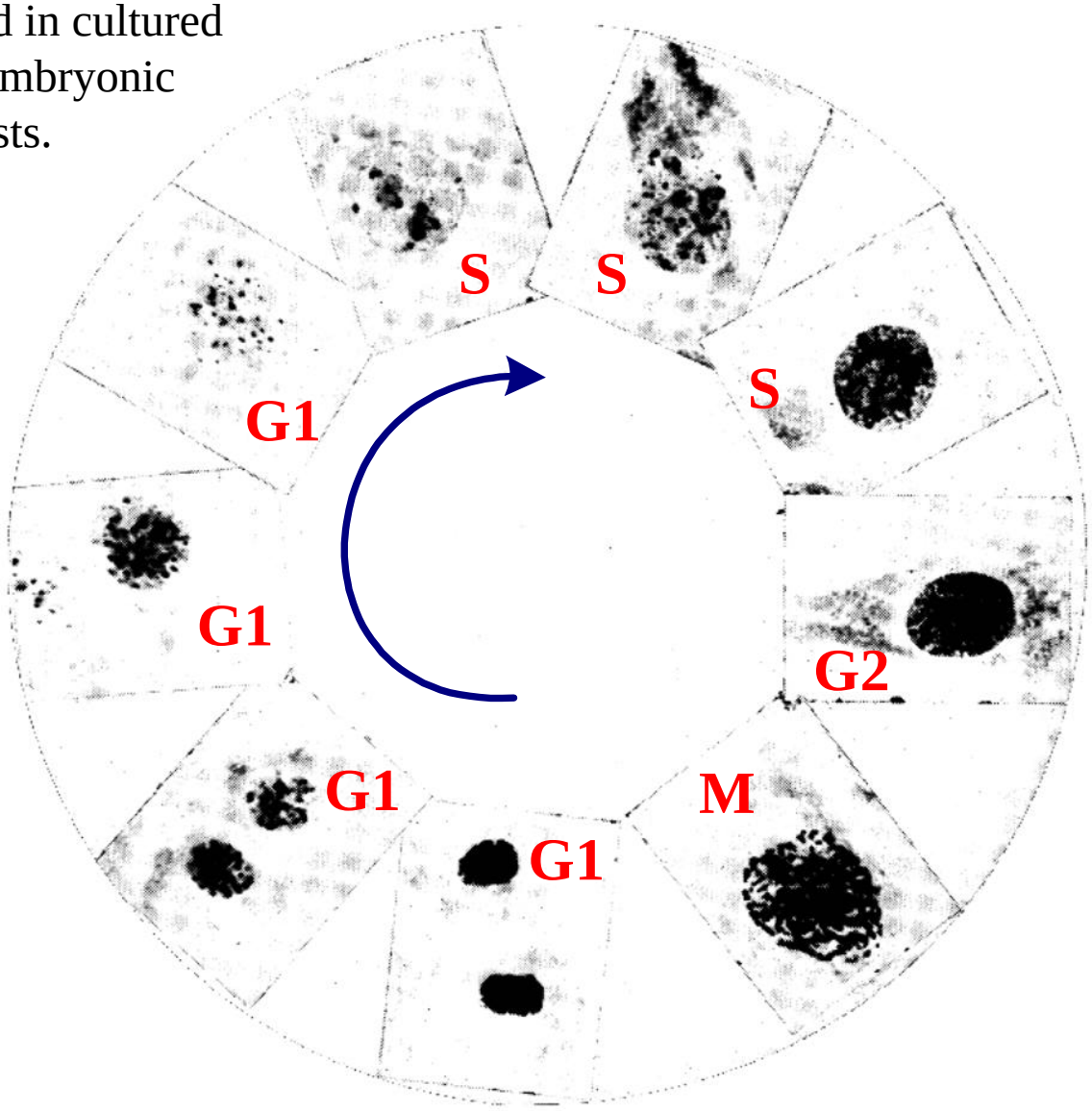
$$b = \frac{e_{pl}\Sigma_{pl}^2}{2 l_{pl}} \left\{ 1 - \exp\left( -l_{pl} T_r \right) \right\}^2$$

$T_r$ is the time available for damage repair.

From SB Curtis, *Radiat. Res.*, **106**, 252-270 (1986).

# Gross Temporal Changes in Chromatin Organization

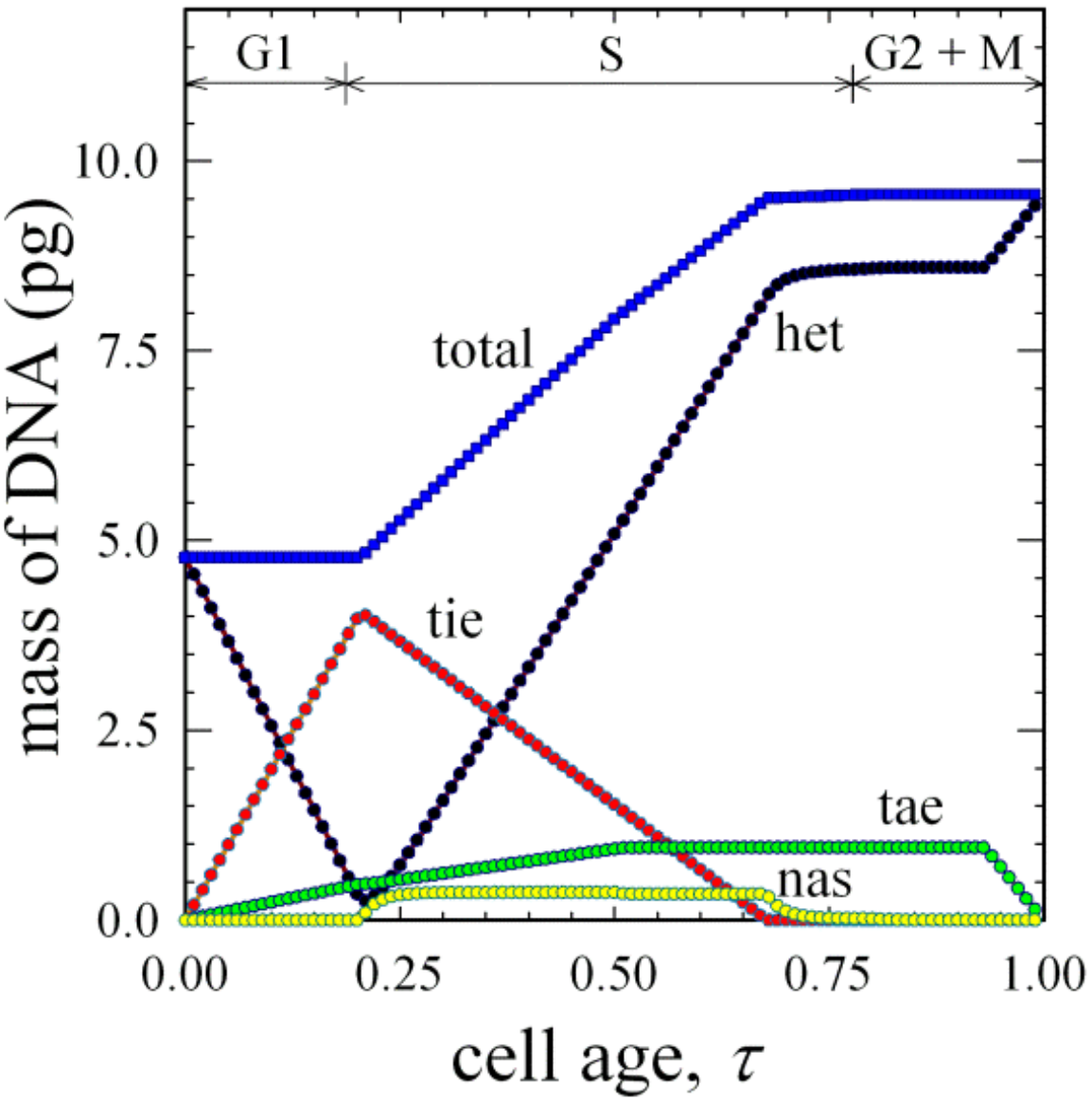
Temporal pattern of chromatin changes observed in cultured mouse embryonic fibroblasts.




Picture adapted from GC Moser and HK Meiss, “Nuclear Fluorescence and Chromatin Condensation..." In *Cell Biology: Genetic Expression in the Cell Cycle* (1982).

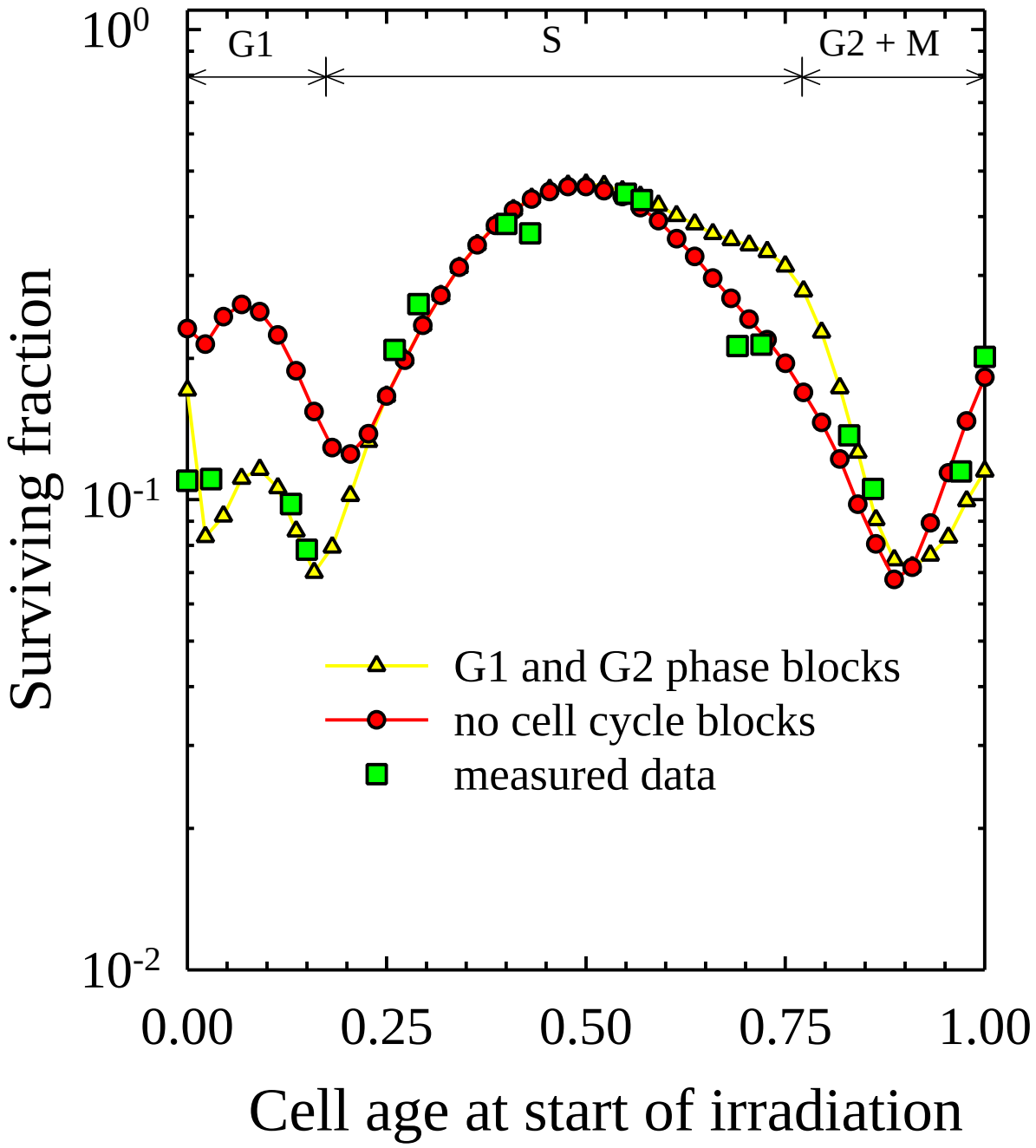
# Temporal Changes in the Chromatin

## *A Simple Model*



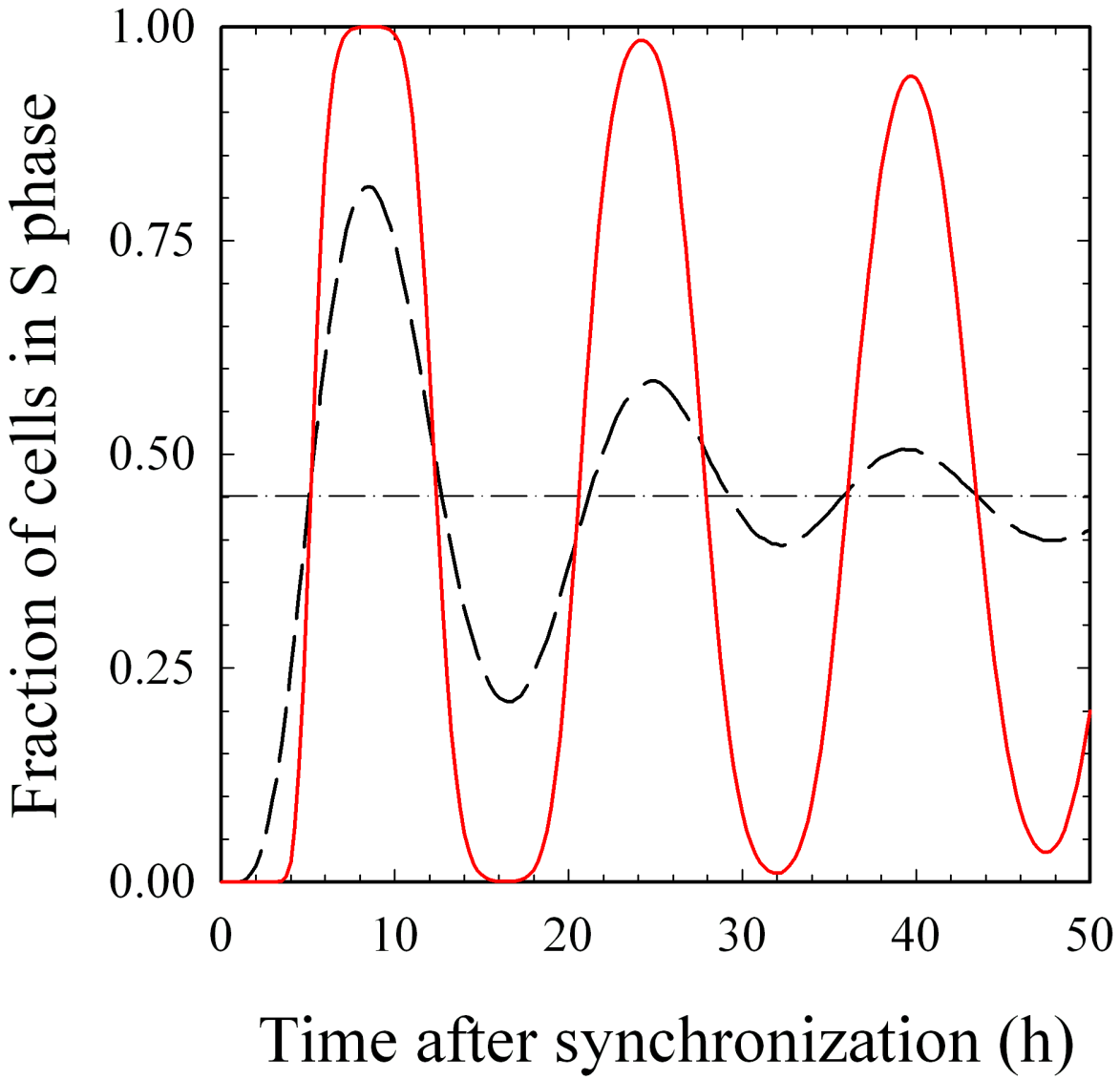

RD Stewart, *A Theoretical Investigation of Cell Cycle Effects and Interspecies Radiosensitivities*. Ph.D. dissertation. Kansas State University, October 1997.

# Cell-Cycle Effects in V79 Cells




RD Stewart, *A Theoretical Investigation of Cell Cycle Effects and Interspecies Radiosensitivities*. Ph.D. dissertation. Kansas State University, October 1997.

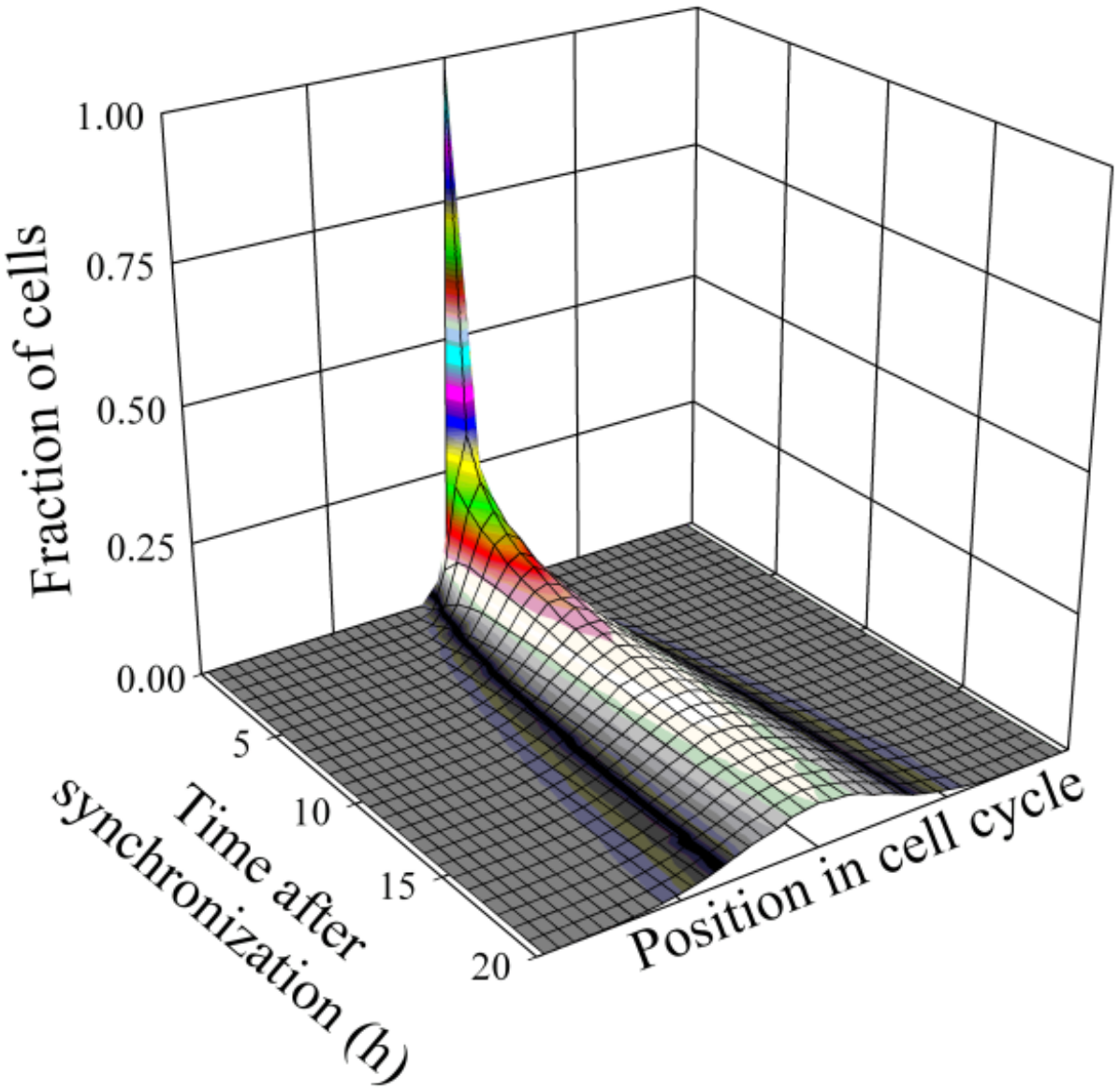
# Monte Carlo Simulated Redistribution of 25,000 Initially Synchronized Cells




The horizontal dash-dot reference line at 0.4516 is the equilibrium (fully asynchronous) fraction of a group of cells expected in the S phase.

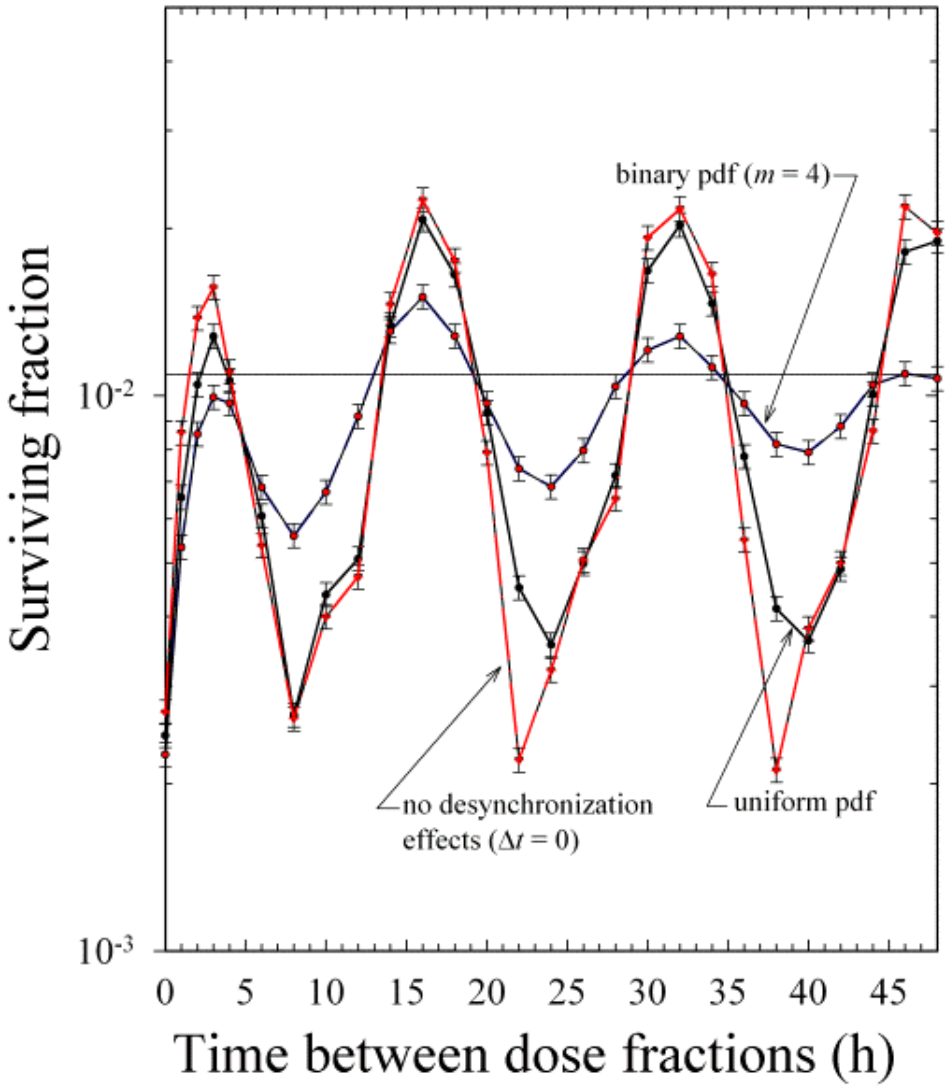
RD Stewart, *A Theoretical Investigation of Cell Cycle Effects and Interspecies Radiosensitivities*. Ph.D. dissertation. Kansas State University, October 1997.

# Monte Carlo Simulated Redistribution of 25,000 Initially Synchronized Cells




RD Stewart, *A Theoretical Investigation of Cell Cycle Effects and Interspecies Radiosensitivities*. Ph.D. dissertation. Kansas State University, October 1997.

# Cell-Cycle Redistribution Effects

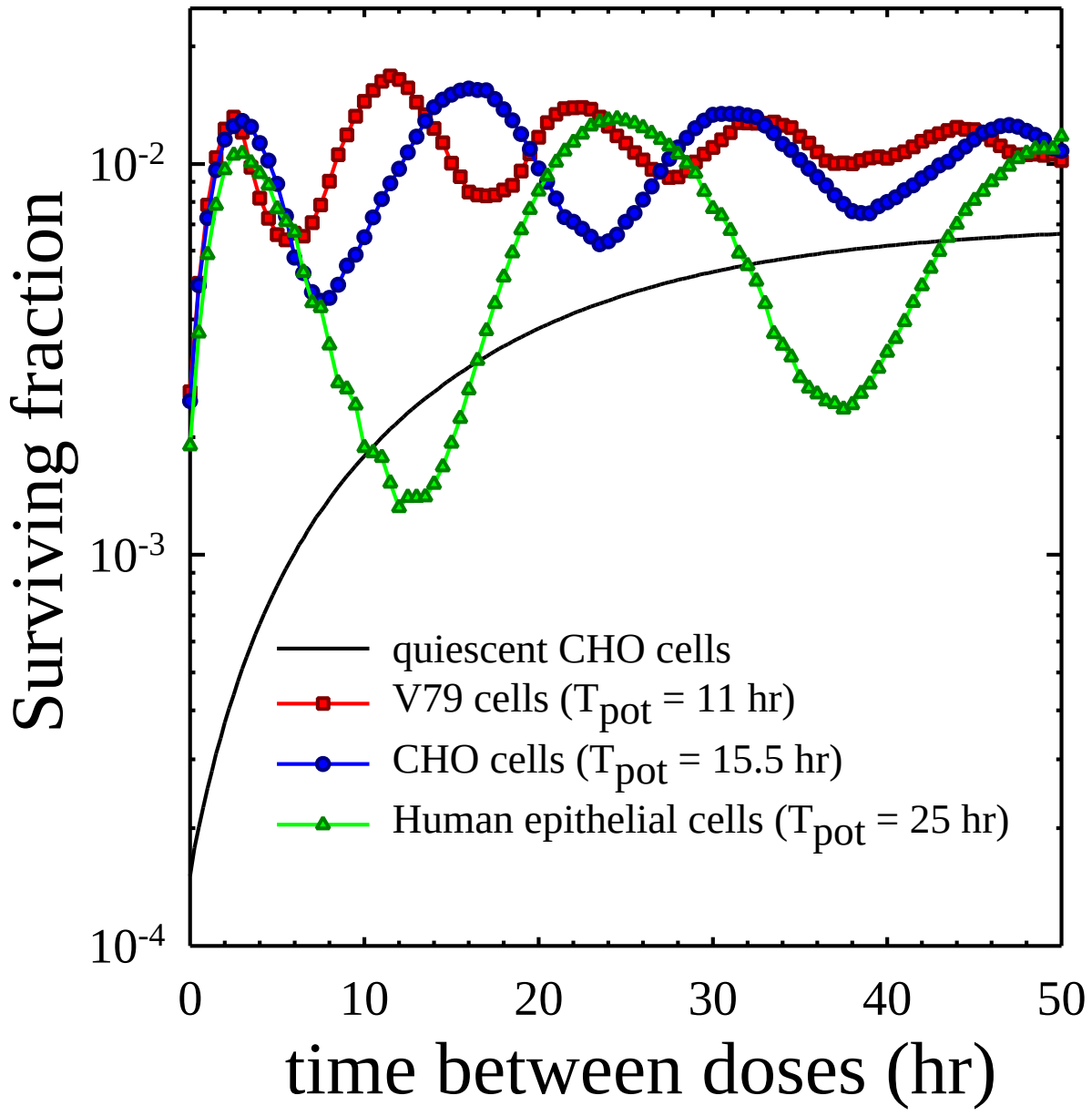



Survival response pattern of an initially asynchronous group of CHO cells exposed to 20 Gy of low-LET radiation delivered in two acute 10 Gy fractions.

RD Stewart, *A Theoretical Investigation of Cell Cycle Effects and Interspecies Radiosensitivities*. Ph.D. dissertation. Kansas State University, October 1997.

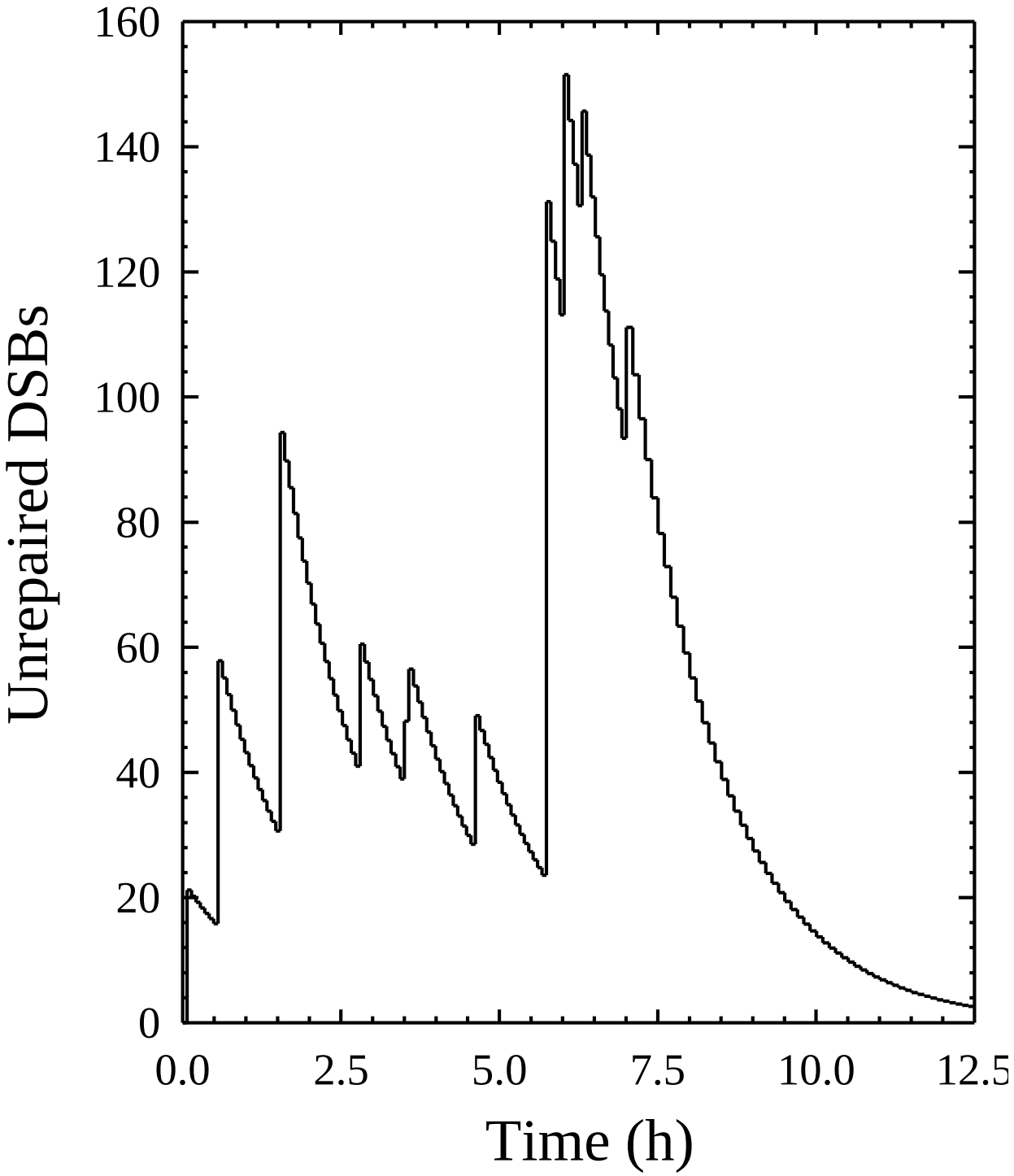
# A Split-Dose Simulation

## — *20 Gy in two 10 Gy fractions*



# KBEM Example 1

*DSB Rejoining Kinetics*



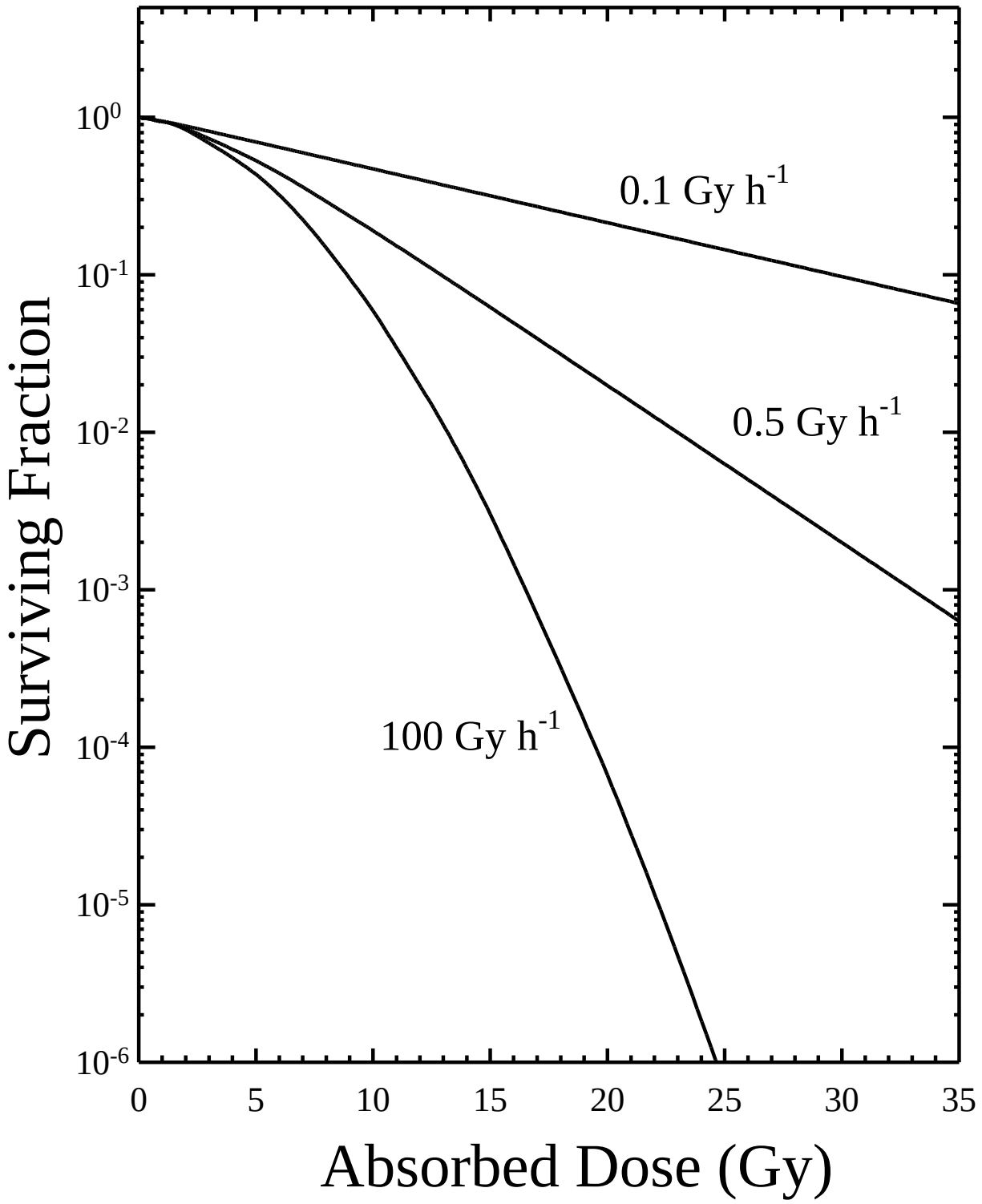
# KBEM Example 1

## *Input File*

```
<!
  Lethal and Potentially Lethal (LPL)
  Example 1 Input File
  26-APR-2000

  Rob Stewart, Ph.D.
  Pacific Northwest National Laboratory (PNNL)
  PO Box 999, MSIN K3-55
  Richland, WA 99352-0999  USA
  trebor@pnl.gov
  http://www.pnl.gov/berc/staff/rds.html
!>

CELL DNA=4682.0D+06 !DNA content (bp)
IRAD   CL = 40.0
CLRP   RHT = 1.0  BMR=1E-04
SOLVER DBLV=0 ETOL=1.0E-09 MXSS=999999 HMAX=10.0
SIMCON FSDX=0.01 TSAX=0.10 TCUT=25

RADX  AD=RX1 ADR=100 TMX=RX2 RND=RX3 OPT=3
RX1 = 1,2, 3,1, 1,1, 5,2, 1,1  /
RX2 = 0.00 0.50 1.50 2.75 3.50
      4.60 5.70  6.00 6.25 7.0 /
RX3 = 10 /  !Total dose (Gy)
```

# KBEM Example 2

*Quiescent CHO 10B2 Cell Killing*



# KBEM Example 2

## *LPL Input File for CHO 10B2 cells*

```
/*
  Lethal and Potentially Lethal (LPL)
  EXAMPLE #2
  DATE: 26-APR-2000

  AUTHOR:
    Rob Stewart, Ph.D.
    Pacific Northwest National Laboratory (PNNL)
    PO Box 999, MSIN K3-55
    Richland, WA 99352-0999  USA
    trebor@pnl.gov
    http://www.pnl.gov/berc/staff/rds.html
*/

CELL DNA=4682.0D+06
IRAD CL=3.0108733E+00 FL=3.5553375E-02
CLRP RHT=5.5350273E+00  BMR=7.6838979E-04
SOLVER DBLV=0 ETOL=1.0E-09 MXSS=999999 HMAX=10.0
SIMCON FSDX=0 TSAX=10 TCUT=100 RCUT=1.0D-09

RADX AD=RX1 ADR=RX2
RX1= 0,0.1,0.2,0.5,1.0,2.0,5.0,7.5,
     10.0,12.5,15.0,20.0,25,30.0,35.0 /
RX2= 0.1, 0.5, 100 /
```

# Multi-Objective Parameter Tuning

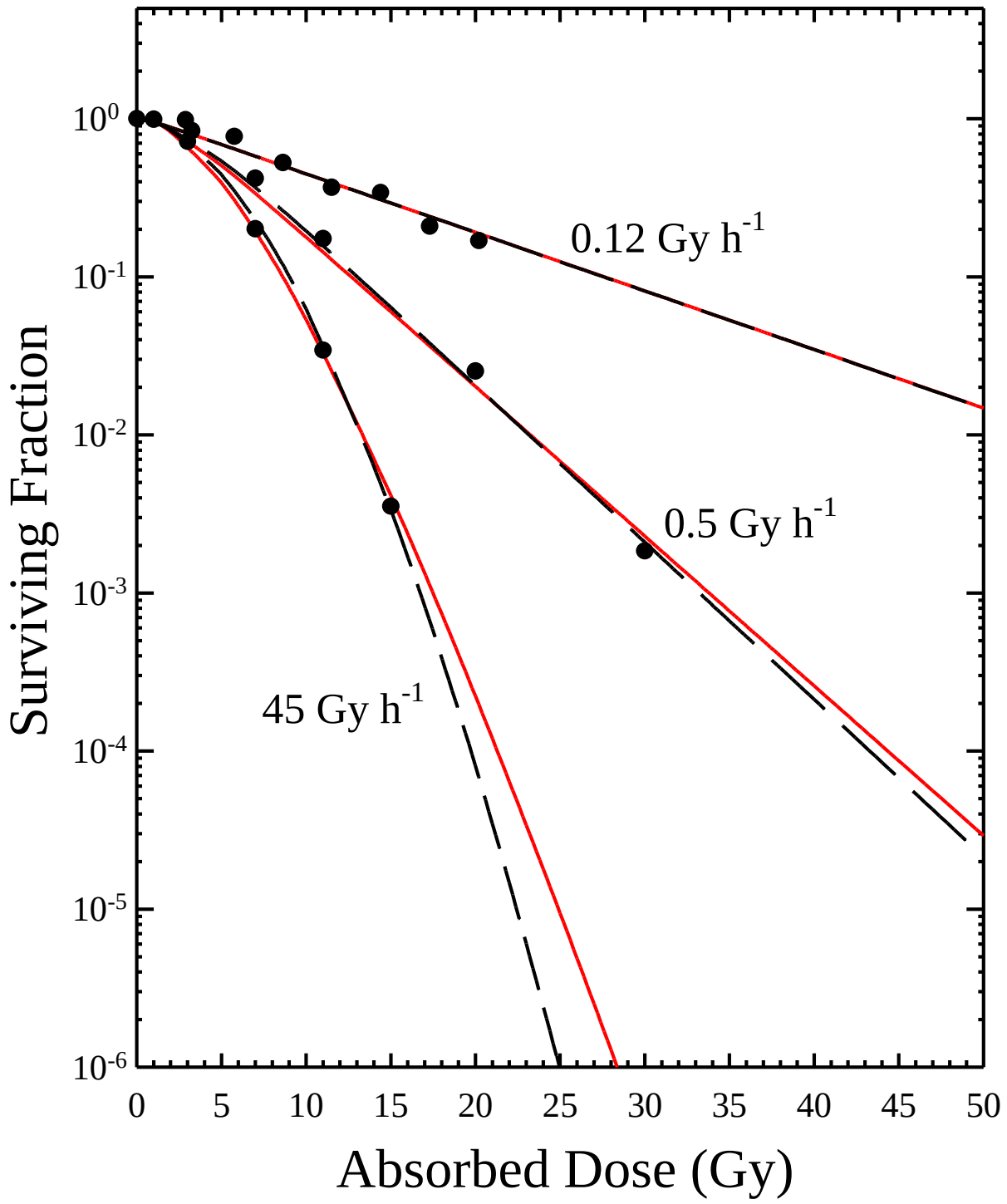
- Formulate a figure of merit (FOM).

$$\mathrm{FOM}^2 = \sum_{i=1}^{N} w_i \left( M_i - P_i \right)^2$$

- Use multi-parameter optimization techniques to minimize the figure of merit.
  - Gradient techniques.
  - Simulated annealing.
  - Genetic algorithms.
- Model(s) are “mechanistic.”
  - model inputs can be constrained to a relatively narrow range of values.
- Seek a parameter set consistent with values obtained through direct (independent) measurement.

# Tuned LPL Parameters (Case 1)

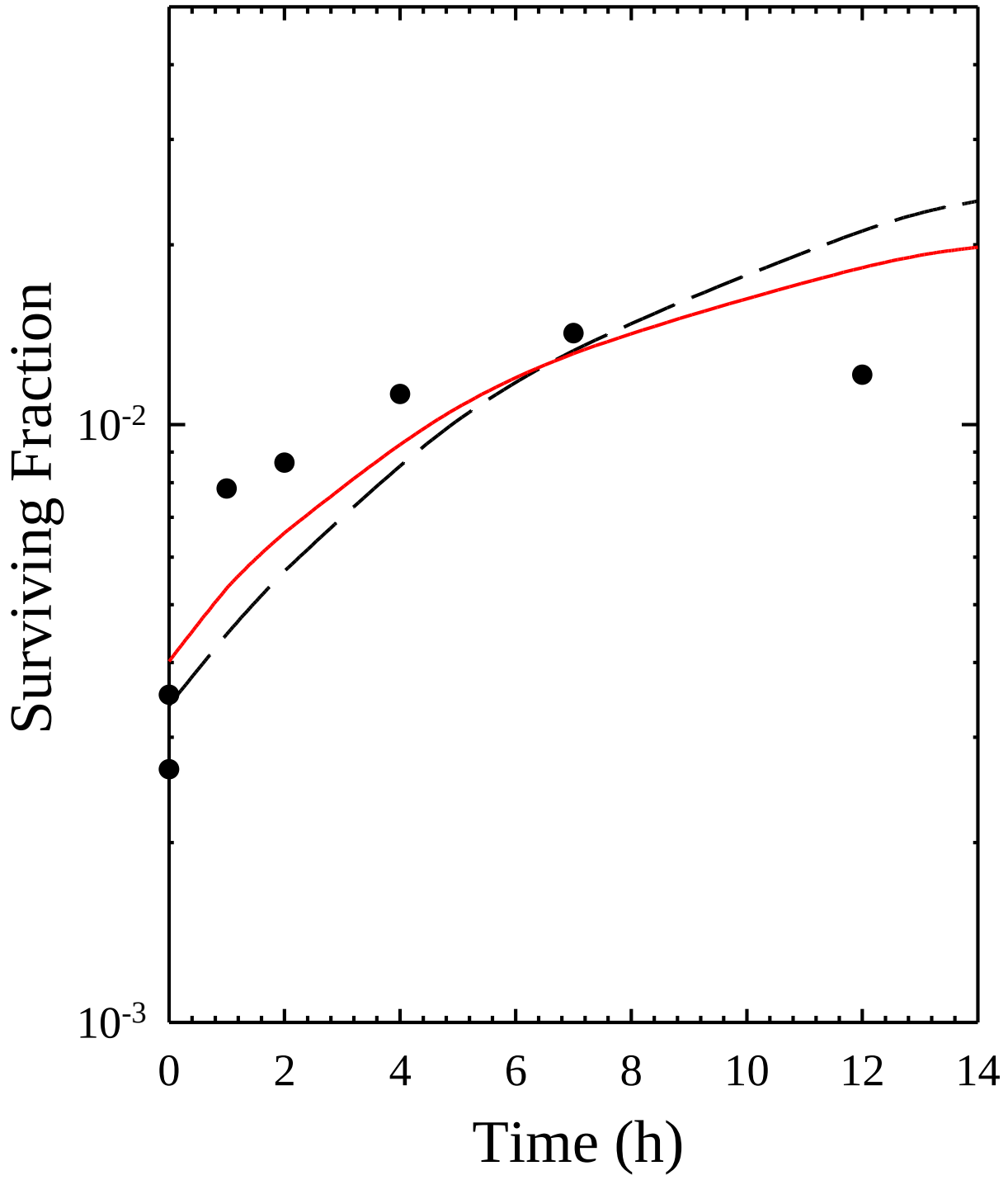
## *Cell Killing (single dose)*




***CHO 10B2 cells***

# Tuned LPL Parameters (Case 1)

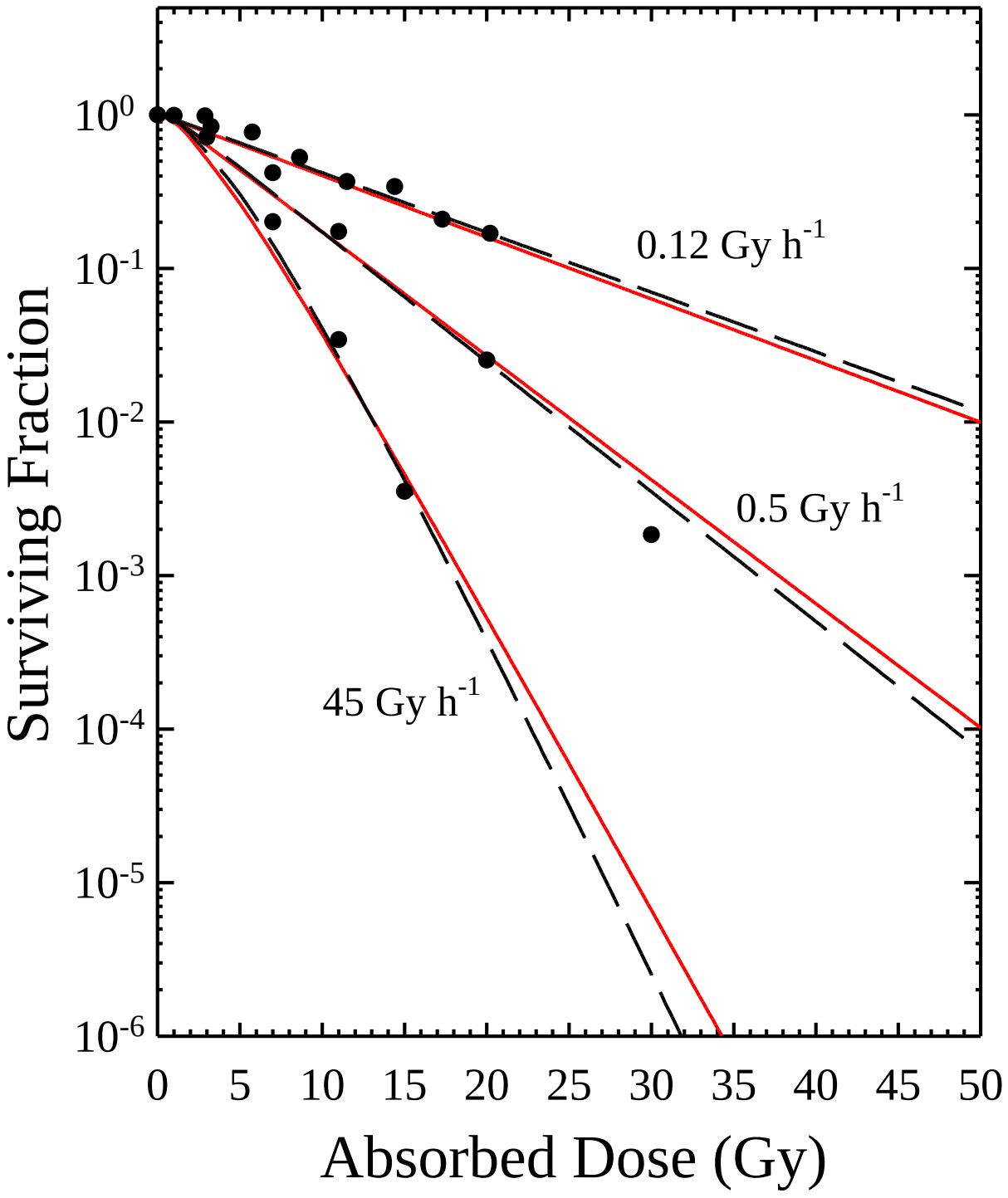
*Cell Killing (split-dose)*




***CHO 10B2 cells***

# Tuned LPL Parameters (Case 2)

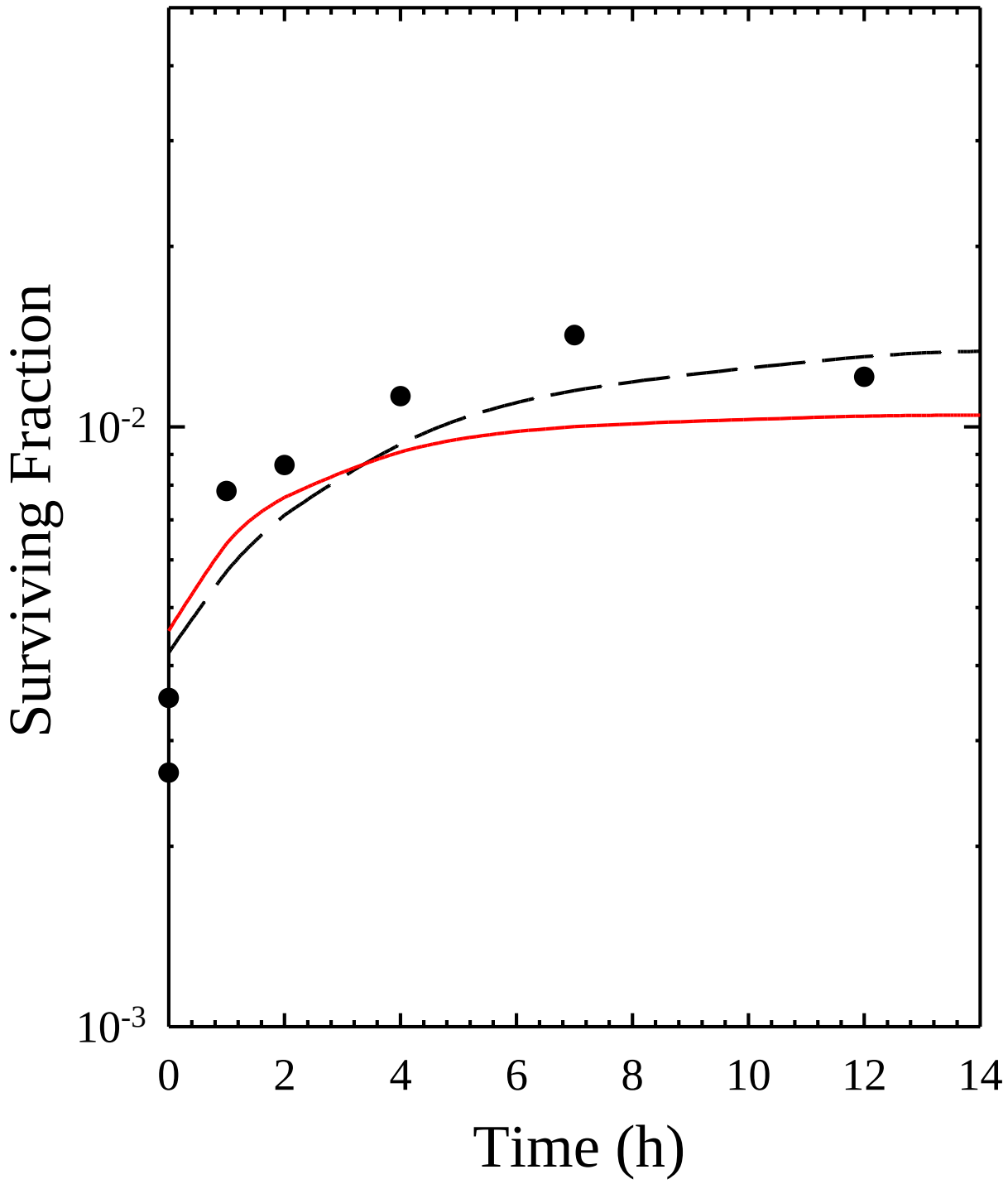
## *Cell Killing* (*3 h repair half-time*)




***CHO 10B2 cells***

# Tuned LPL Parameters (Case 2)

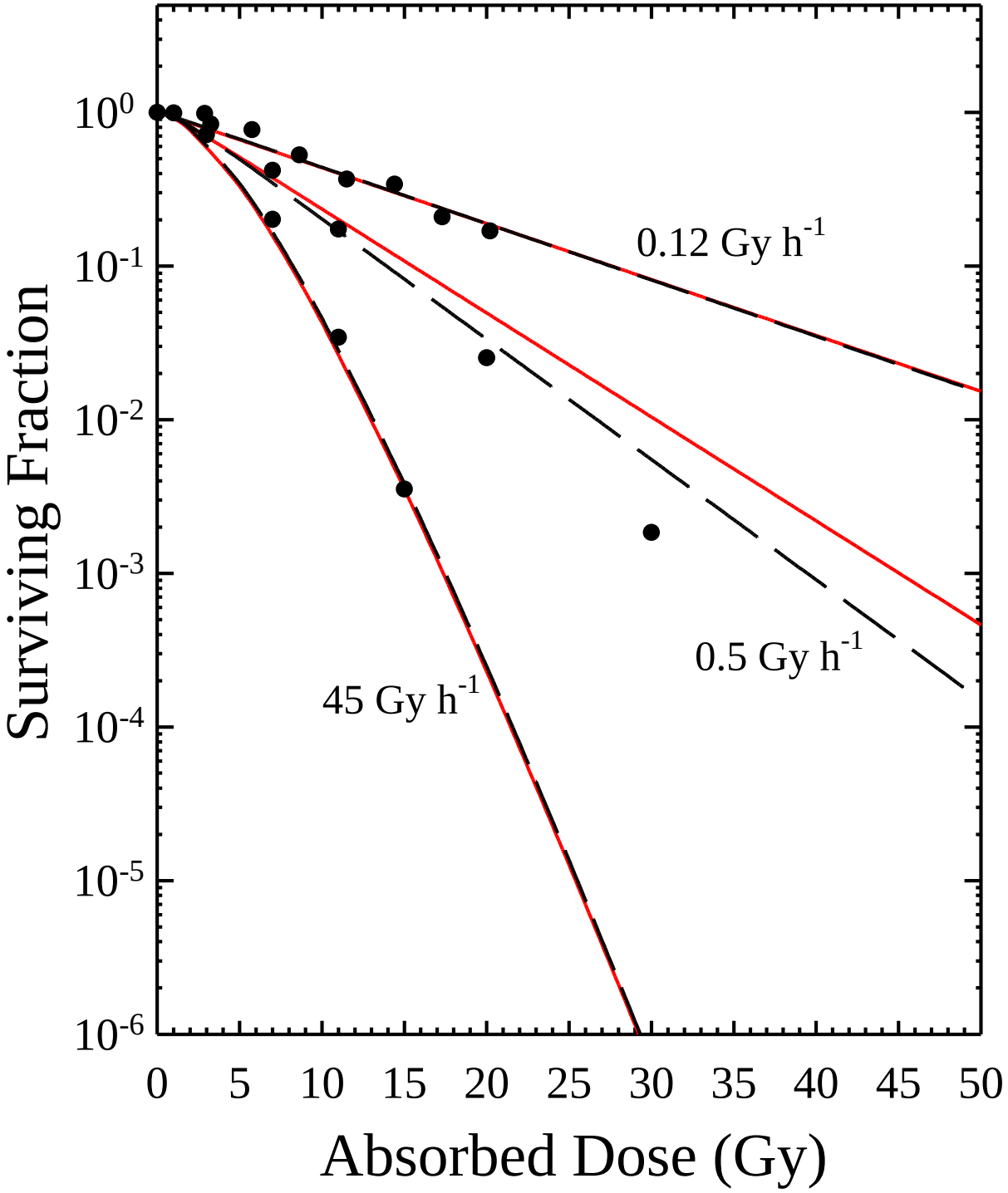
*Cell Killing (split-dose)*




***CHO 10B2 cells***

# Tuned LPL Parameters (Case 3)

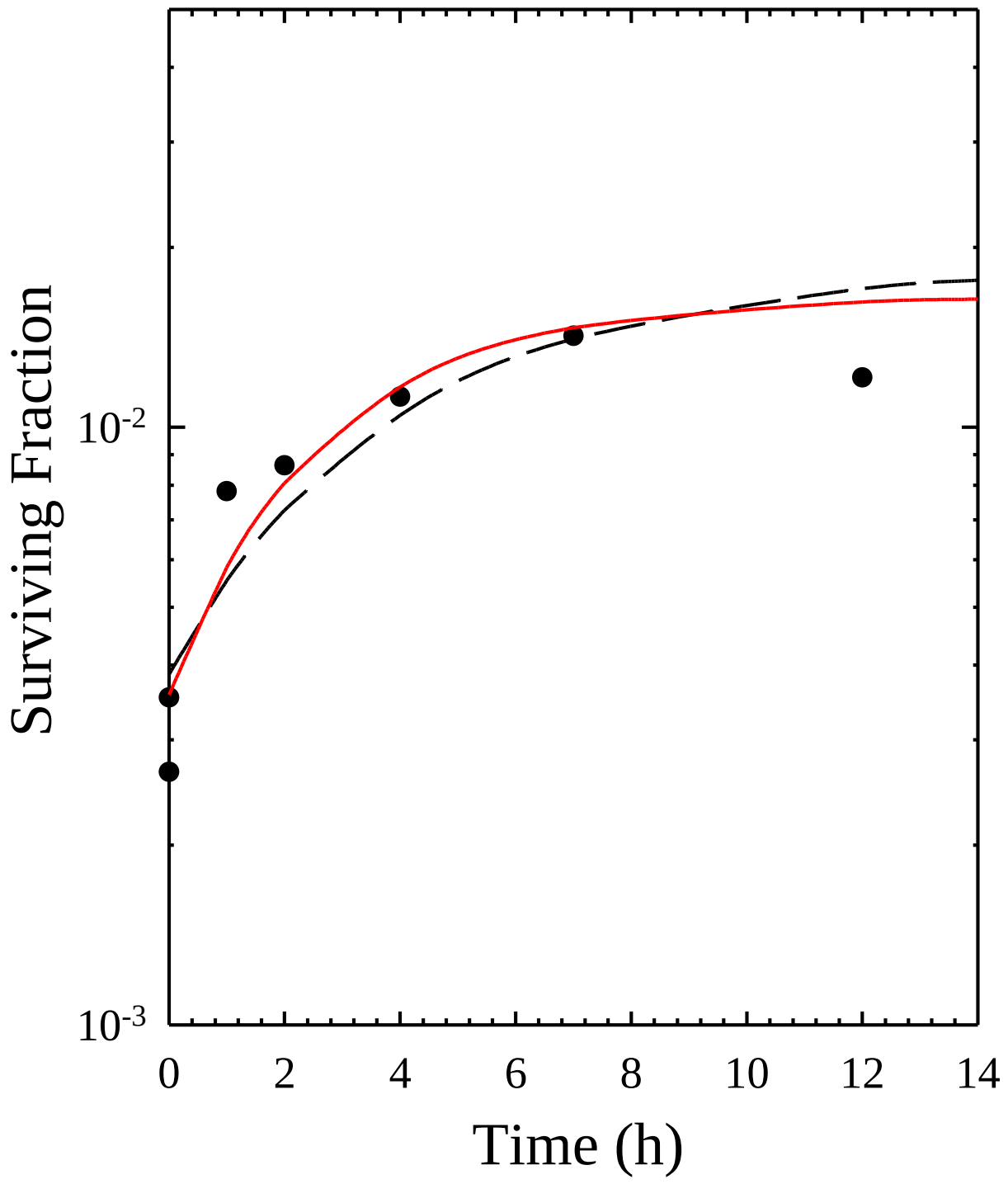
## *Cell Killing (3 h repair half-time)*




***CHO 10B2 cells***

# Tuned LPL Parameters (Case 3)

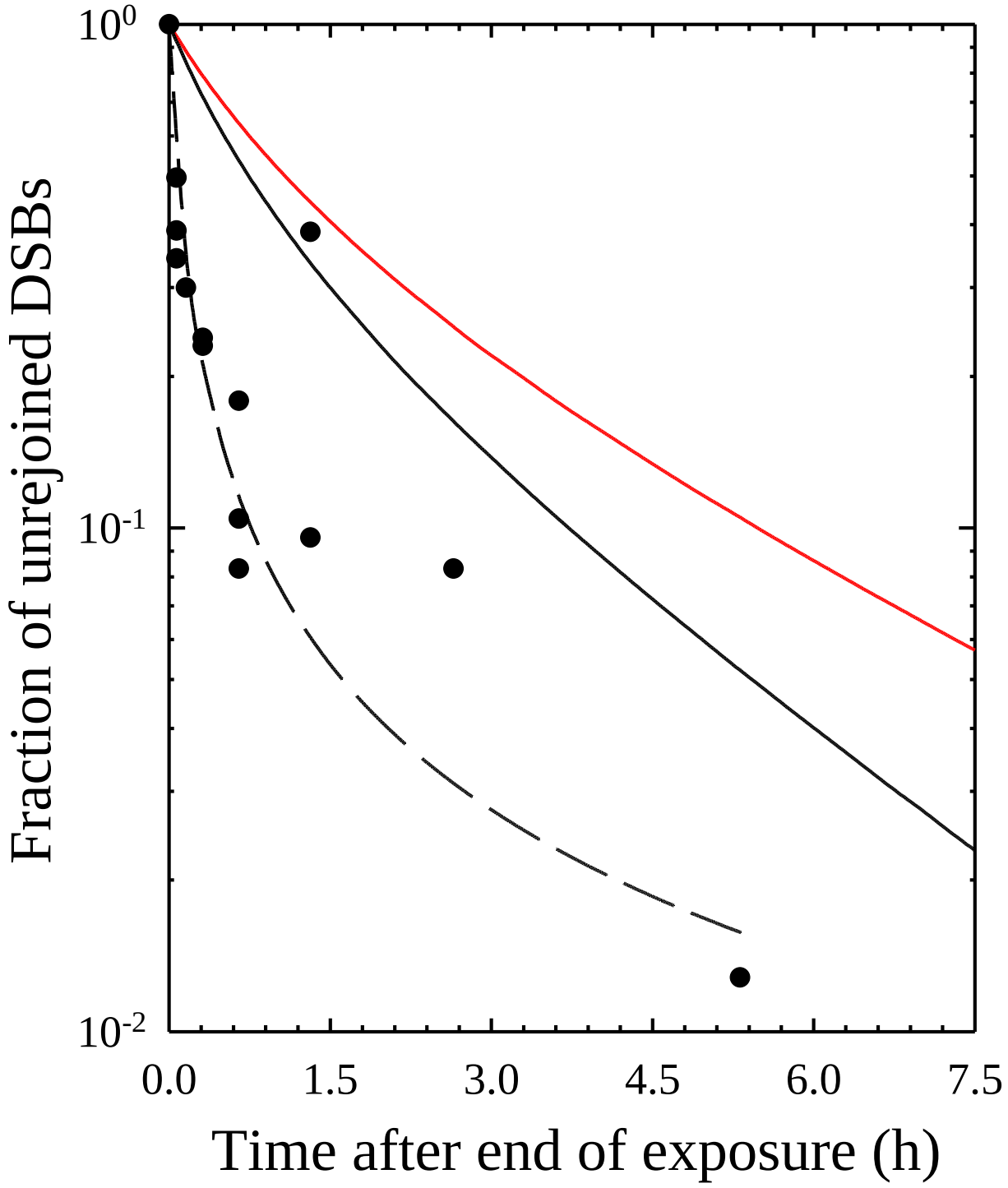
*Cell Killing (split-dose)*




***CHO 10B2 cells***

# Tuned LPL Parameters (Case 3)

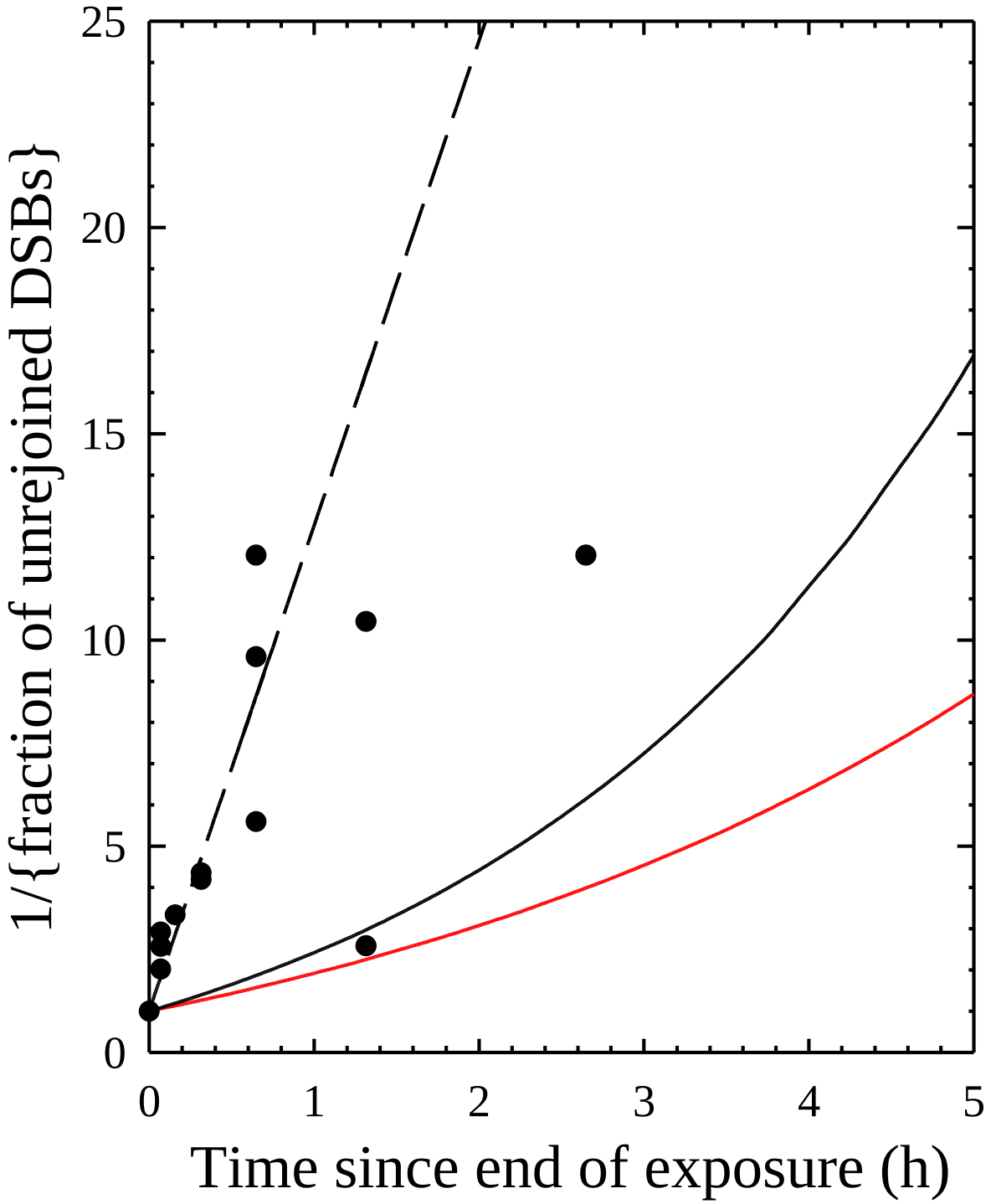
## *DSB Rejoining*




***CHO 10B2 cells***

# Tuned LPL Parameters (Case 3)

## *DSB Rejoining* (*Fowler Plot*)




***CHO 10B2 cells***

JF Fowler, *Radiat. Res.* **152**, 124-136 (1999).

# Multi-Objective Parameter Tuning
## *Conclusions and Conjecture*

- Quickly determine an “optimal” parameter set.
  - A more thorough examination of model behavior in different regions of the parameter space.
  - Help identify strengths and weaknesses of different models.
  - 4-6 model inputs can be tuned using just survival data and/or cell transformation data.
- Model inputs can be simultaneously tuned to reflect data from a variety of sources.
  - DSB $Gy^{-1}$ cell $^{-1}$ (PFGE).
  - DSB rejoining after an exposure (PFGE).
  - Chromosome aberrations (FISH).
  - Cell killing as a function of dose, dose-rate, and or dose-fractionation.
  - Cell transformation as a function of dose, dose-rate, and or dose-fractionation.