Temporal Optimization of Radiotherapy Treatments

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Overview

- Key concepts in clinical radiobiology.
  - Dose, dose rate, and LET effects
  - Four R’s of radiation therapy.
- A next-generation radiobiological model.
  - Conceptual framework.
  - Relationship to other models.
  - Model calibration and testing.
- Temporal optimization of radiotherapy treatments.

Key Concepts in Radiobiology.

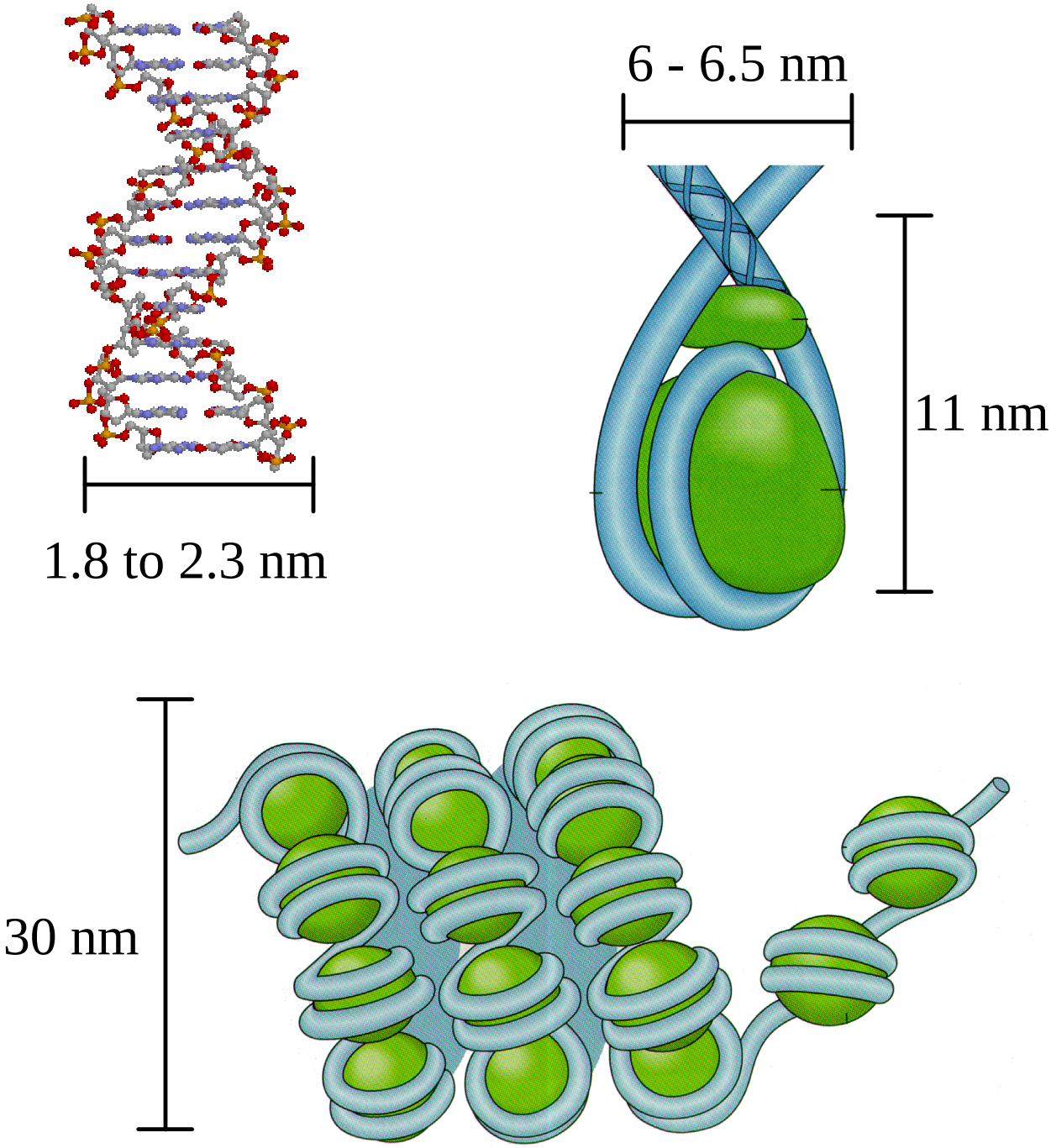
Biological effects of interest usually depend on

- Dose.
- Dose rate.
- Particle linear energy transfer (LET).

Four ***R***'s of Radiation Therapy

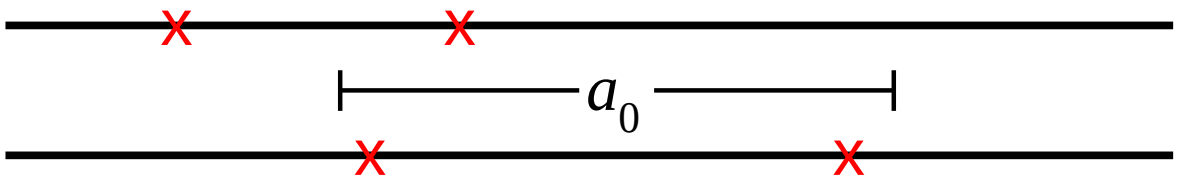
- ***R***epair Effects.
- Cell-Cycle ***R***edistribution Effects.
- ***R***epopulation Effects.
- Tissue ***R***eoxygenation Effects.

DNA and Chromatin

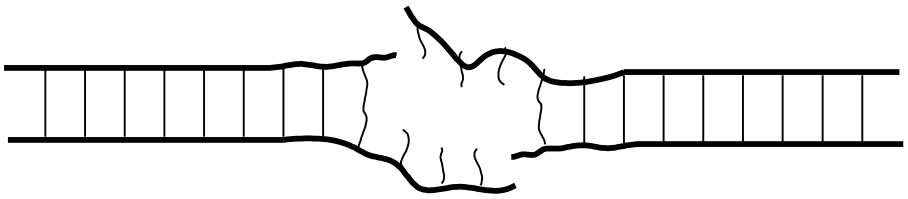


Pictures of chromatin adapted from SL Wolfe, *Molecular and Cellular Biology* (1993).

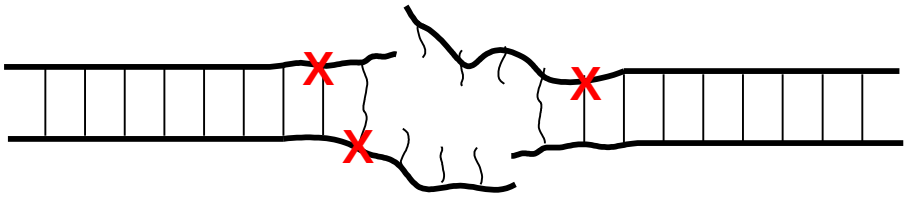
DNA Lesions



Idealized schematic of a group of four elementary damage sites forming a DNA lesion. Elementary damage sites are represented by an **x**.



Simple double strand break.



Complex double strand break.

Dose Effects

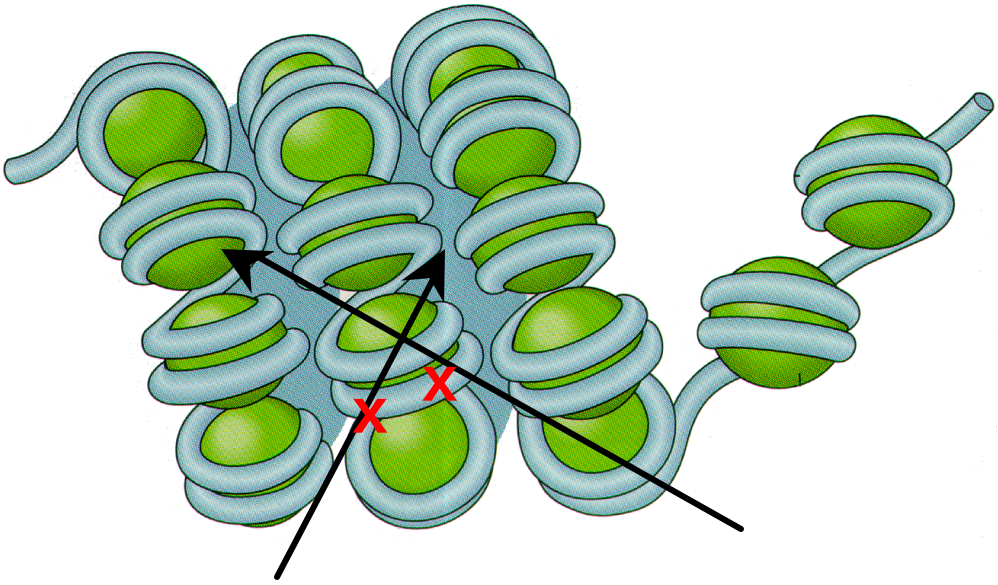
- Initial number of DNA lesions created in a cell increases linearly with absorbed dose.
- Expected number of lethal and non-lethal misrepaired damages produced in a cell tends to increase as a linear-quadractic function of dose (approximately).
- Under the assumption of Poisson distributed lethal DNA damages, cell survival decreases exponentially as the dose increases.

$$S(D) \cong \exp\{-D(\alpha + \beta D)\}$$

Dose-Rate Effects

Lesion Proximity and Damage Repair

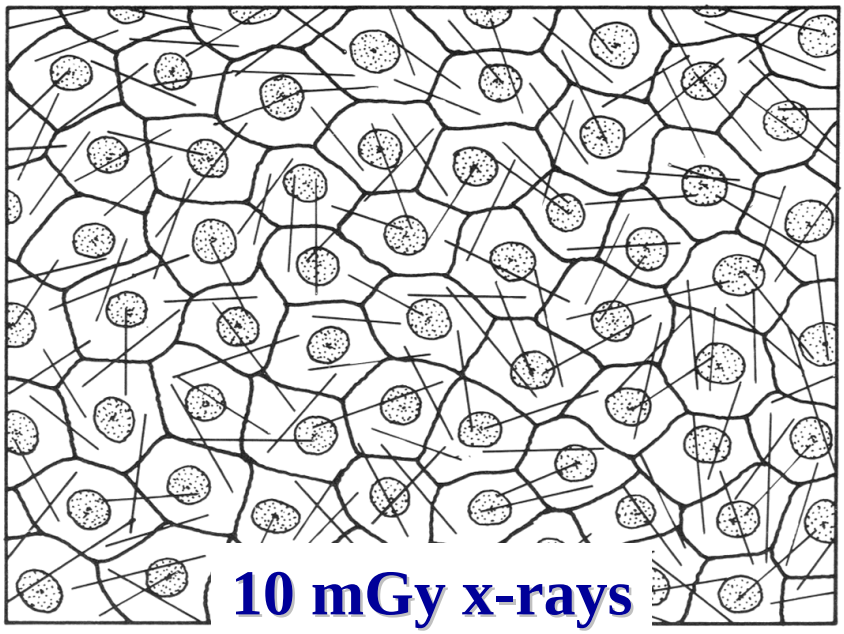
- As the dose rate increases, the peak number of unrepaired DNA lesions produced in a cell tends to increase.
- Pairwise damage interaction rate is a monotonically increasing, non-linear function of the number of unrepaired DNA lesions in a cell.
- Lesions formed in close temporal and spatial proximity are more likely to be misrepaired.

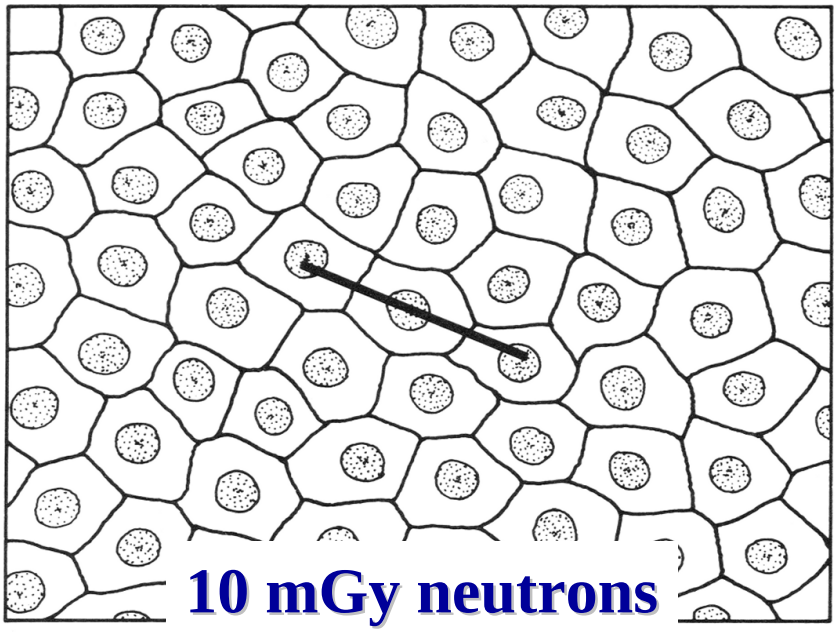


Picture of chromatin fiber adapted from SL Wolfe, *Molecular and Cellular Biology* (1993).

LET Effects

Spatial Pattern of Energy Deposits

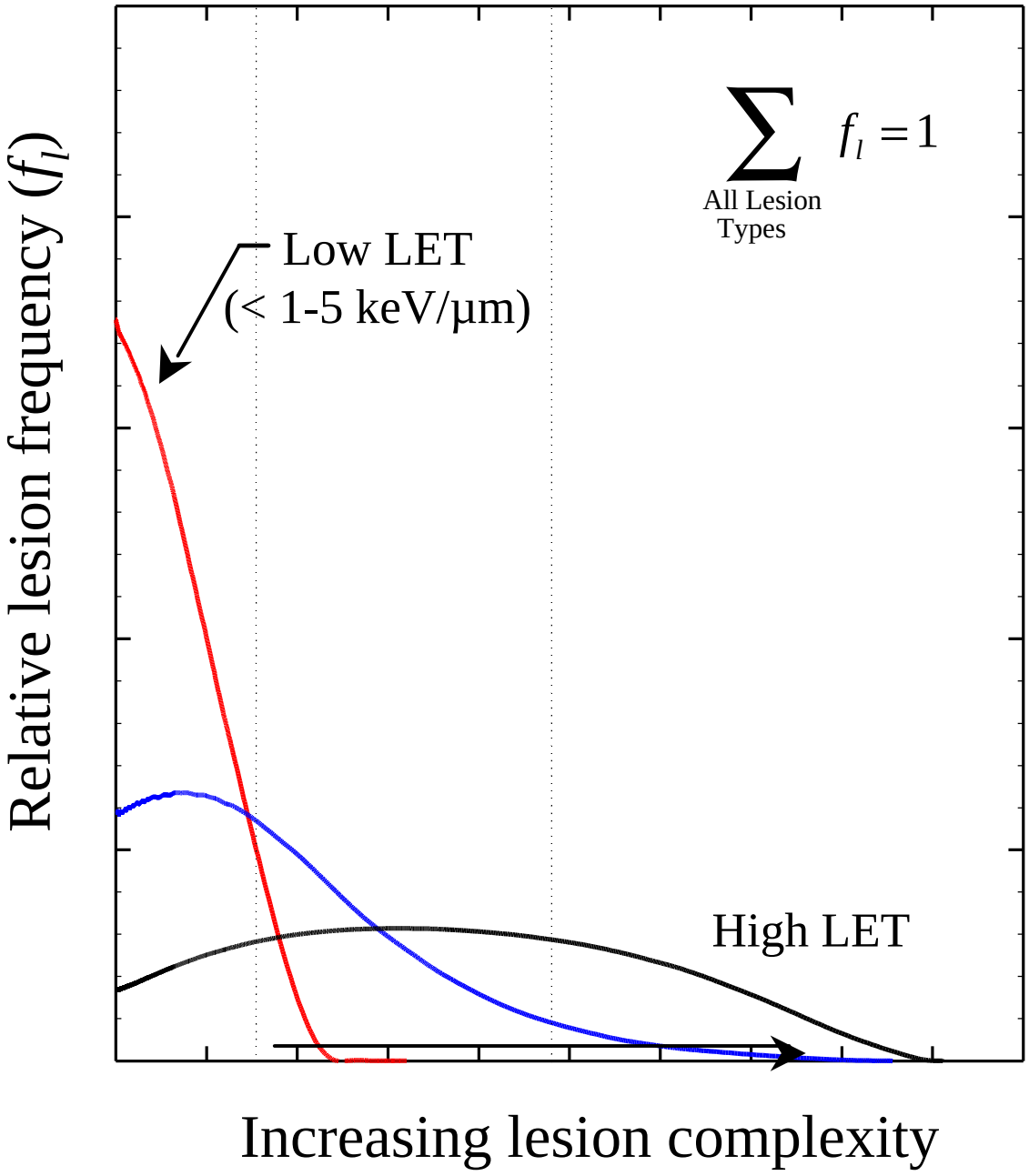




From *Moss' Radiation Oncology. Rationale, Technique, Results*. 7th Ed., p.9. James D. Cox, Editor. Mosby-Year Book, Inc. St. Louis MO. (1994).

LET Effects

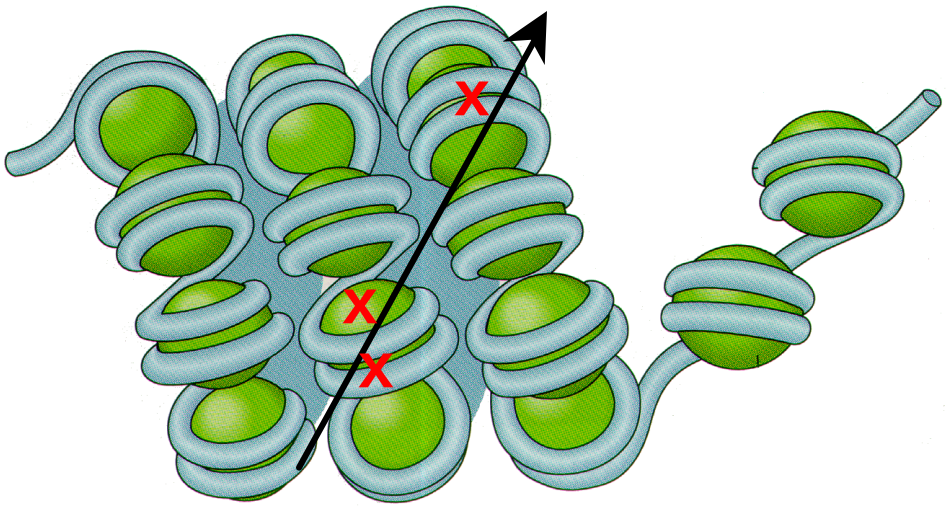
A Spectrum of DNA Lesions



LET Effects

Lesion Type and Spatial Proximity

- Lesions formed in close temporal and spatial proximity are more likely to be misrepaired.
- Complex lesions formed by high-LET radiation may be repaired more slowly than the “simple” lesions formed by low-LET radiation.
  - More time for pairwise damage interaction and lesion fixation.
- High-LET radiation is more effective at producing spatially correlated DNA lesions than low-LET radiation.



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

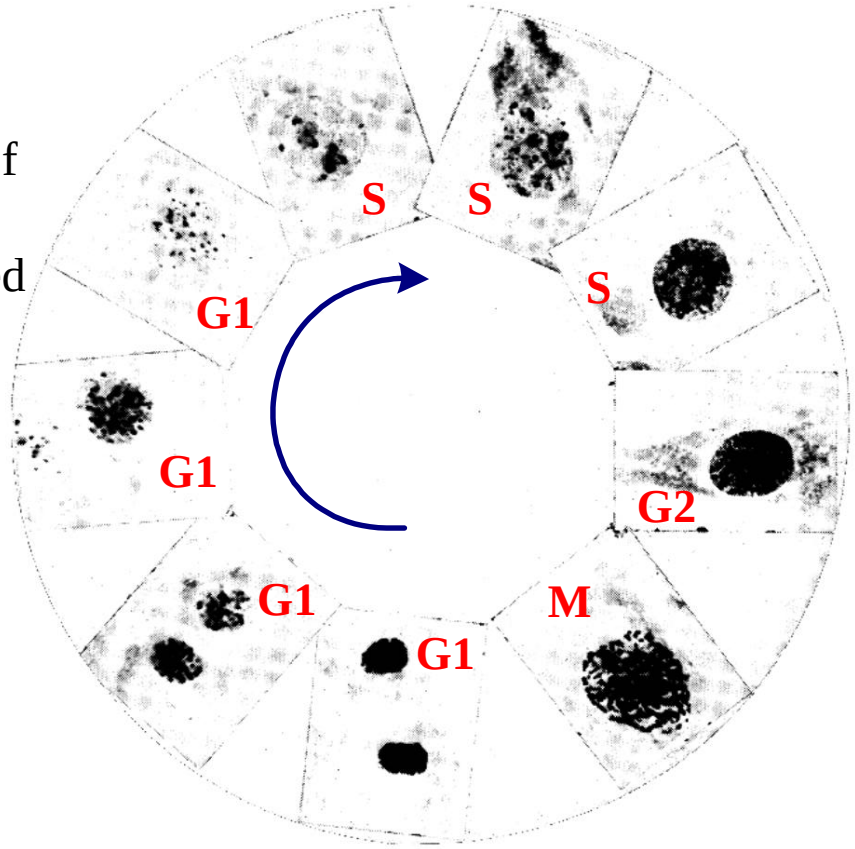
LET Effects
A Summary

- As particle LET increases,
  - Number of cells damaged per unit absorbed dose *decreases*.
  - But the expected number of DNA lesions per damaged cell *increases*.
  - Fidelity of damage repair tends to decrease (probability of damage misrepair increases) because of intra-track proximity effects.
- As particle LET increases, the lesion spectrum "hardens."
  - Simple DNA lesions are repaired more accurately than complex lesions.
  - The overall (lesion-spectrum averaged) probability of damage misrepair tends to increase.
- If a high-LET particle passes through a cell, there is a good chance the cell will be killed.

Cell-Cycle Effects

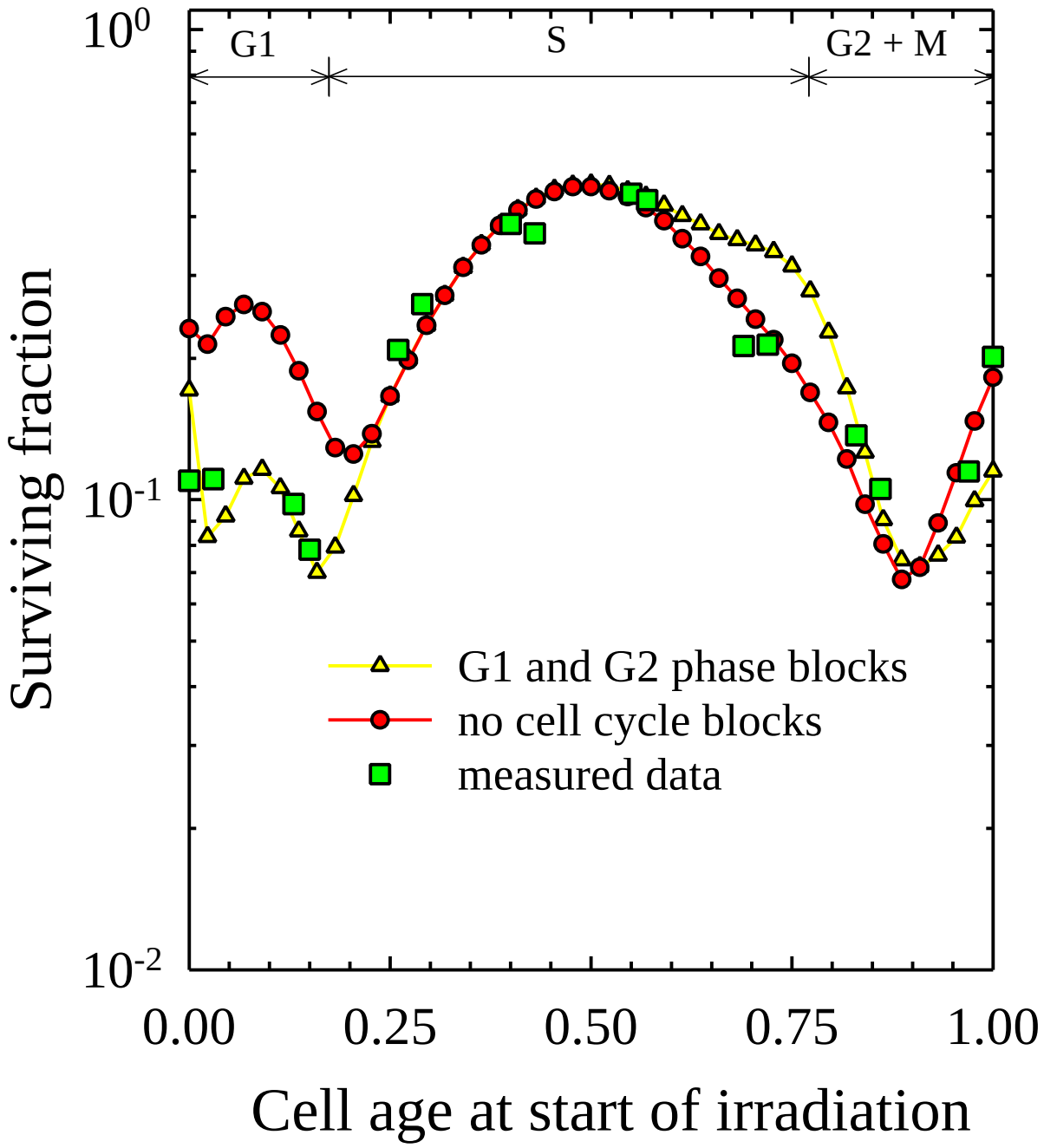
- As cells move through the cell division cycle (G1, S, G2, and M), fluctuations in the initial yield of DNA damages and the subsequent rate and fidelity of damage repair produce characteristics changes in cell killing (and other endpoints).

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).

Cell-Cycle Effects in V79 Cells

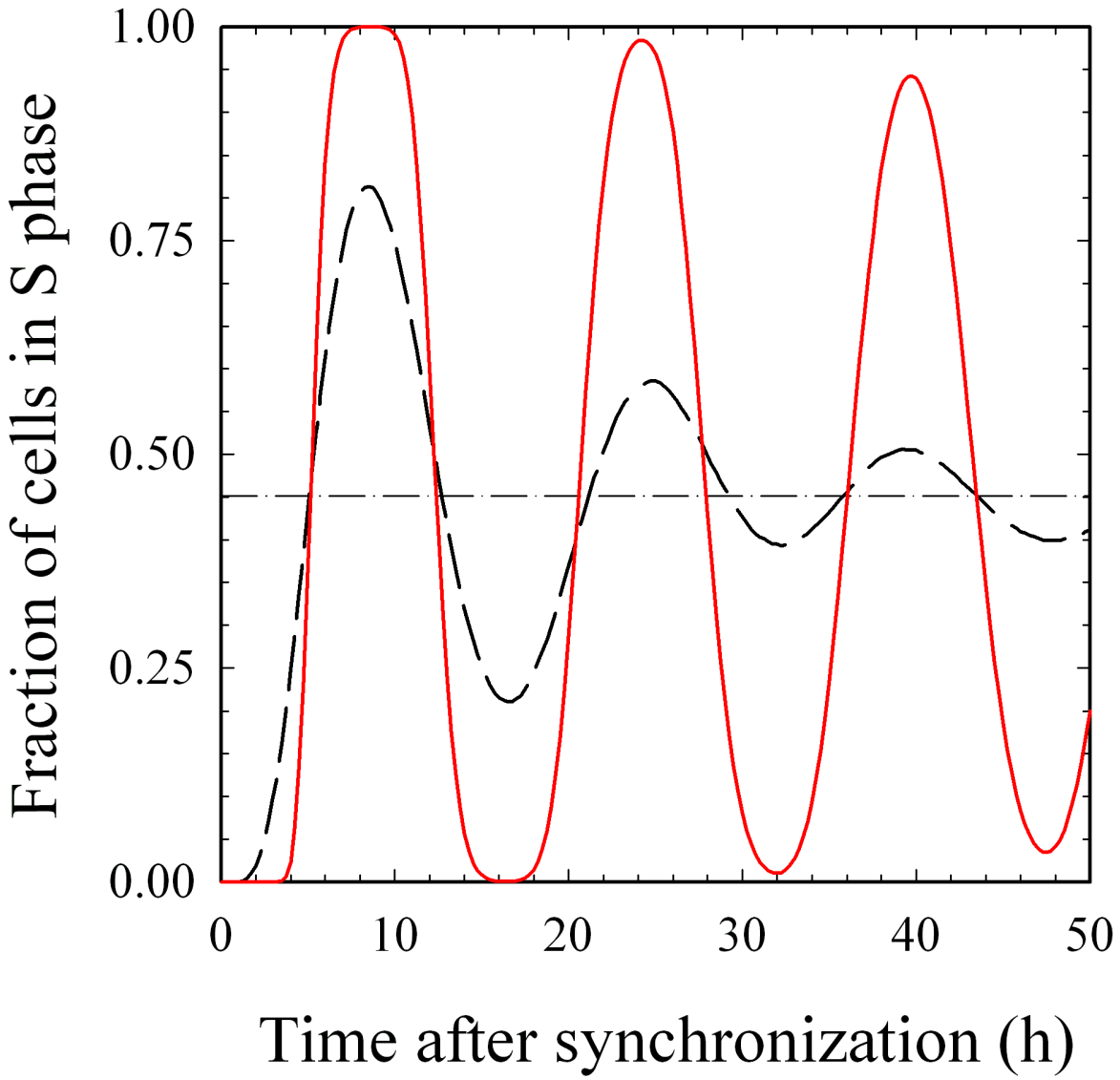


RD Stewart, *A Theoretical Investigation of Cell Cycle Effects and Interspecies Radiosensitivities*. Ph.D. dissertation. Kansas State University, October 1997.

Cell-Cycle Redistribution Effects

- Cells tend to “pile up” in certain portions of the cell cycle (G1/S and S/G2) because of cell-cycle blocking phenomena.
- Random-seeming fluctuations in the rate that cells progress through the cell division cycle tend to redistribution cells in the cell cycle.
- For prolonged and multi-fraction exposure conditions, the overall response of a cell population (e.g., the ensemble of cells forming a tumor) is a complicated function of several cell-cycle kinetics parameters *and* the irradiation “history.”
  - Inverse dose-rate effects
  - Resonance effects.

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.

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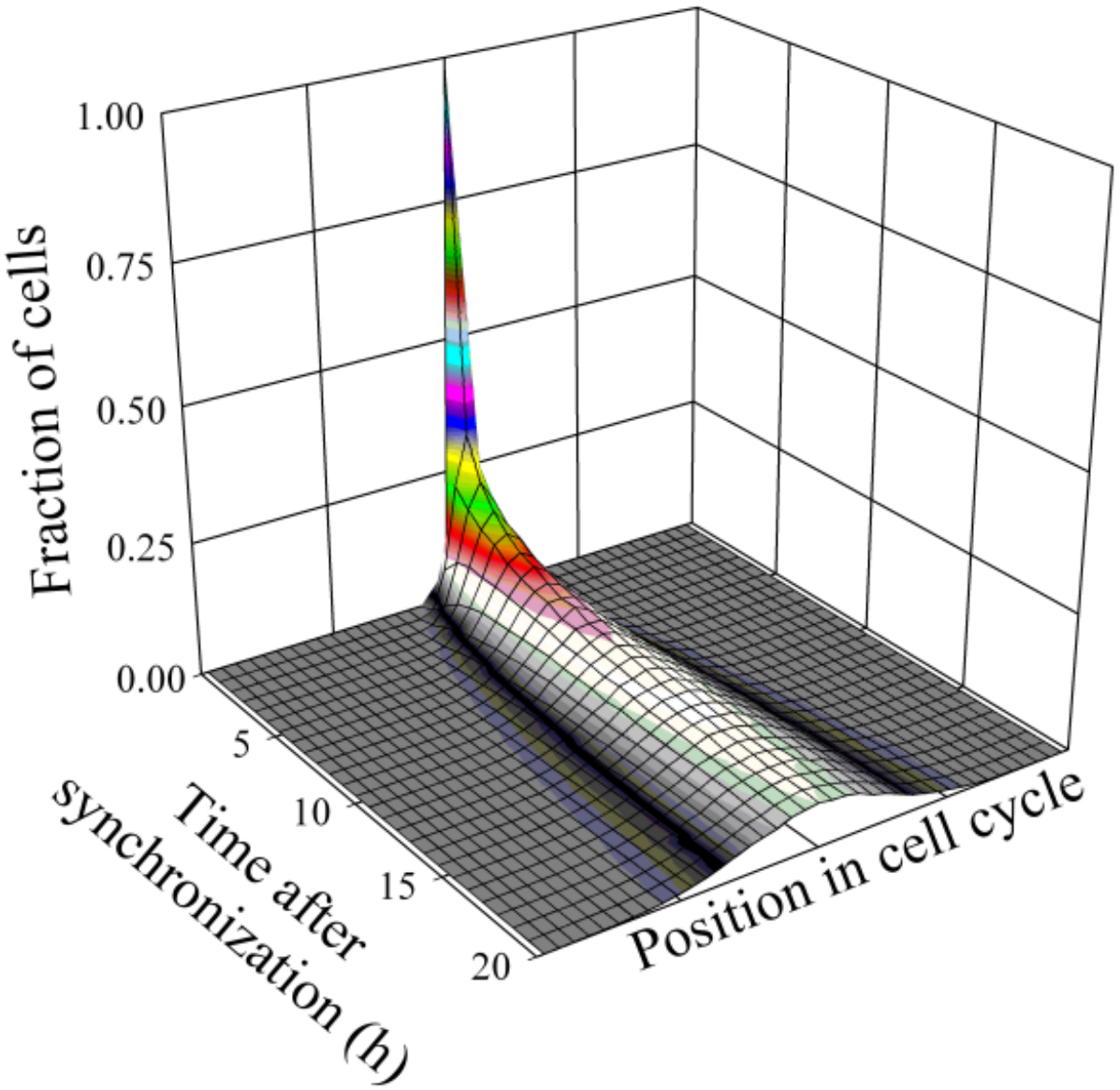
Monte Carlo Simulated Redistribution of 25,000 Initially Synchronized Cells



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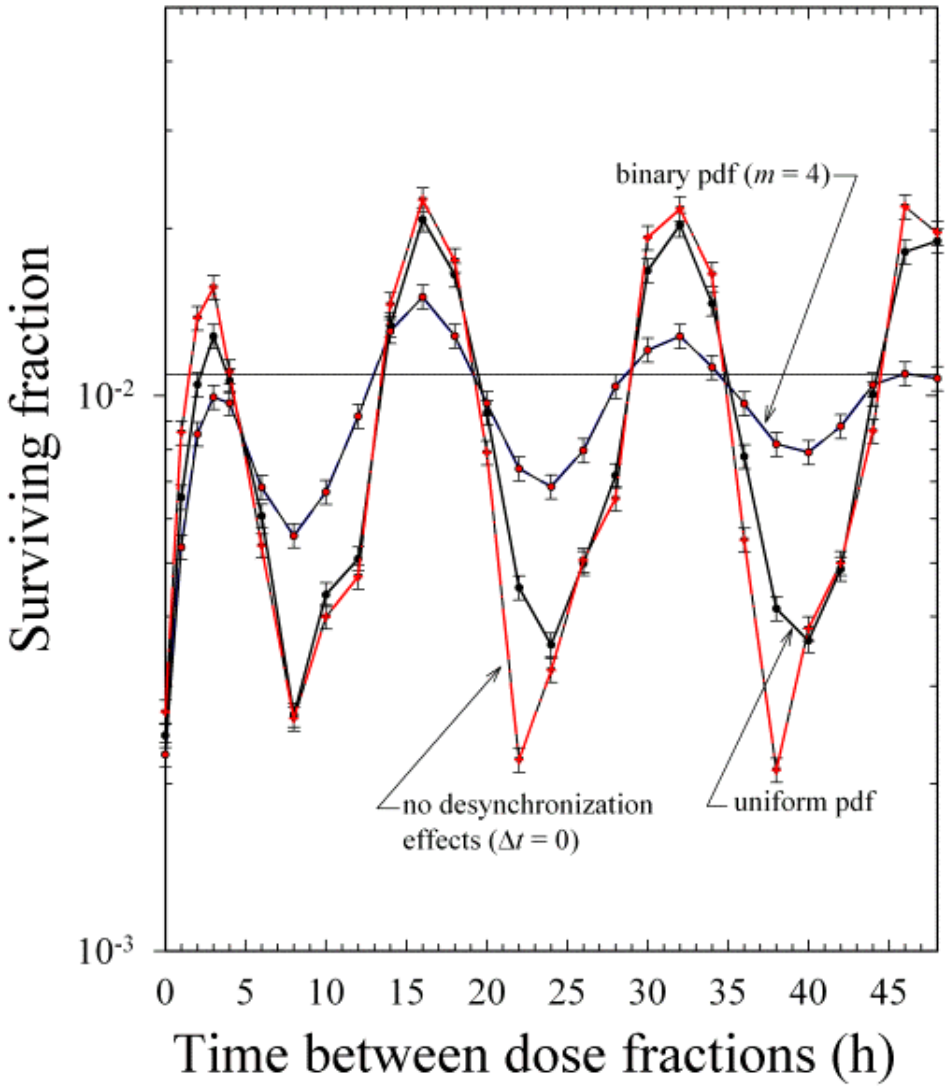
Cell-Cycle Redistribution Effects



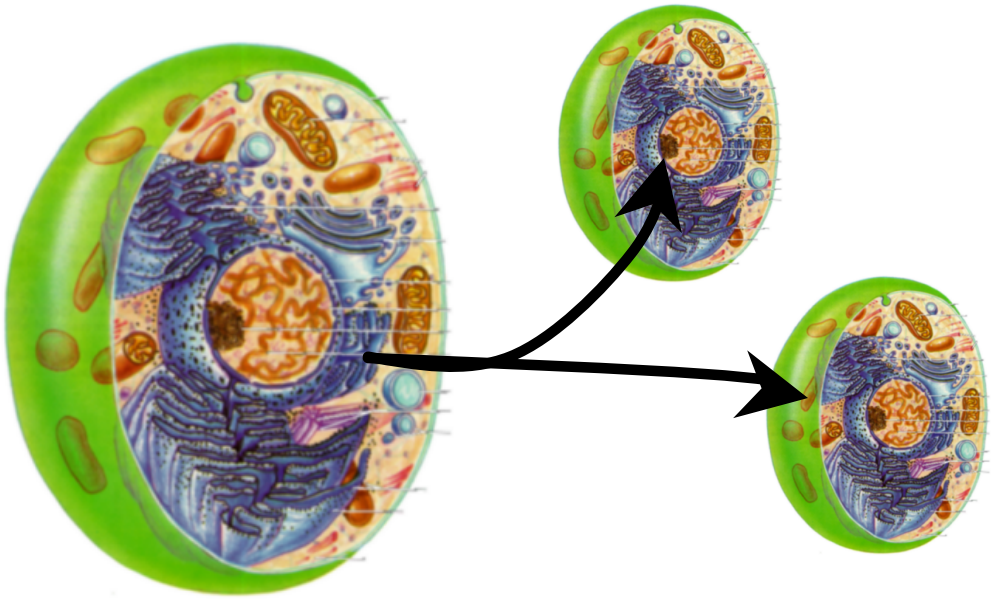
Survival response pattern of an initially asynchronous group of CHO cells exposed to 20 Gy of low-LET radiation delivered in two acute 10 Gy fractions.

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

Repopulation Effects

For prolonged and multi-fraction exposure conditions, the number of (target) cells changes.

- All other factors being equal, the number of survivor cells tends to increase as the exposure duration increases.
- "Surviving fraction" can be greater than unity!
  - ➤ more viable cells are present at the end of an exposure (treatment) than at the beginning.

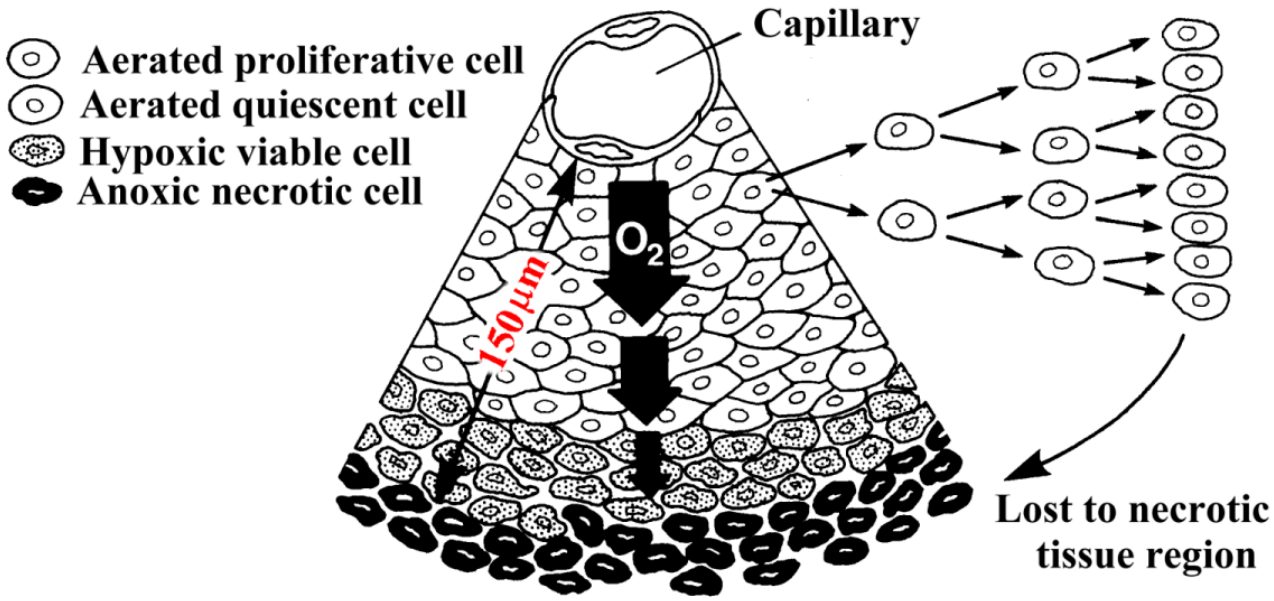


Picture of cell adapted from KM Van De Graaff and SI Fox, *Concepts of Human Anatomy and Physiology* (1986).

Reoxygenation Effects

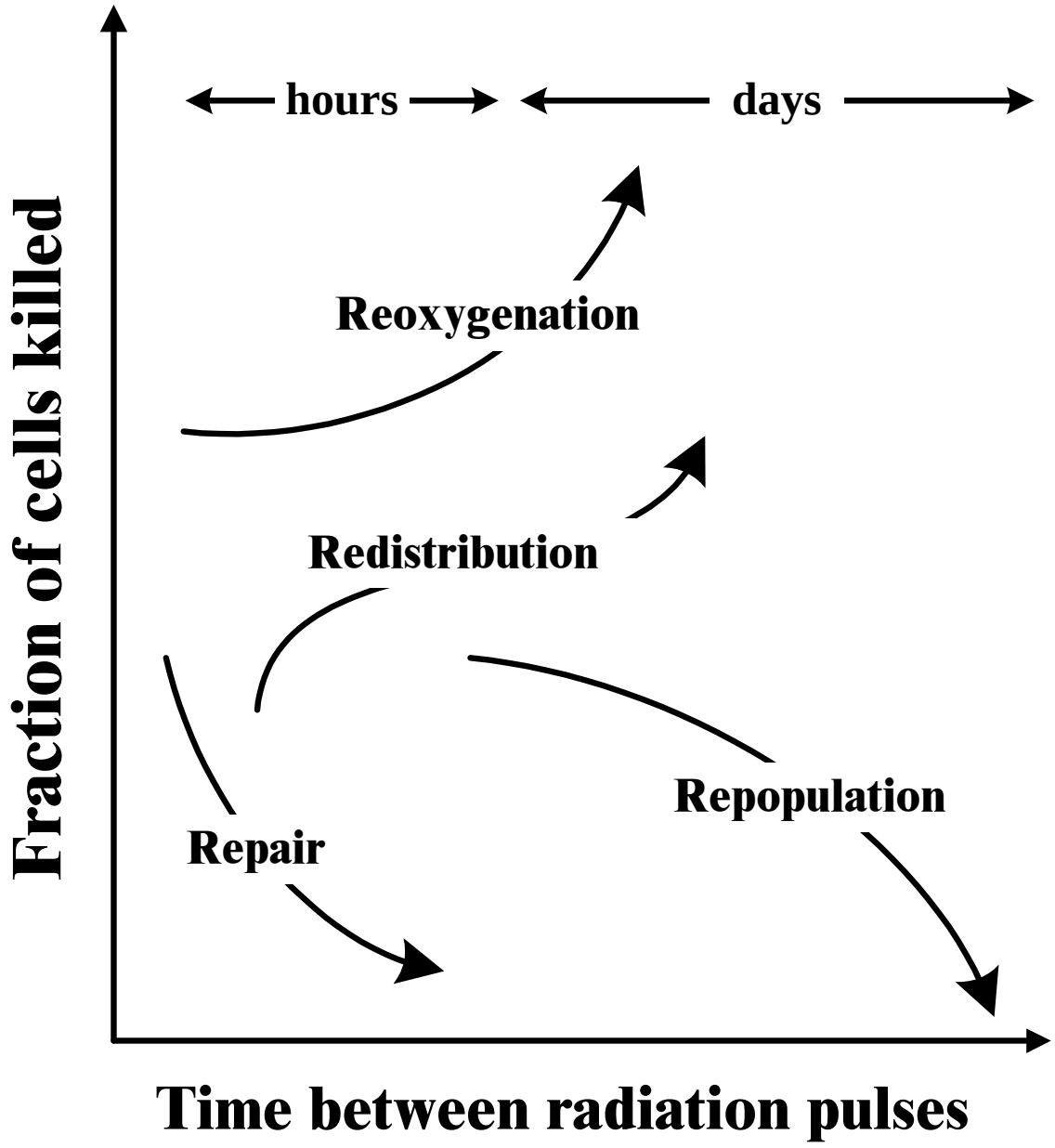
For prolonged and multi-fraction exposure conditions, the number of aerated and hypoxic cells changes.

- Aerated cells are more radiosensitive than hypoxic cells.



Schematic from *Moss' Radiation Oncology. Rationale, Technique, Results*. 7th Ed., p.22. James D. Cox, Editor. Mosby-Year Book, Inc. St. Louis MO. (1994).

Four *R*'s of Radiation Therapy



An idealized schematic illustrating trends in cell killing as a function of time between radiation pulses (treatment fractions).