Enhancing low dose risk assessment using mechanistic mathematical models of radiation effects

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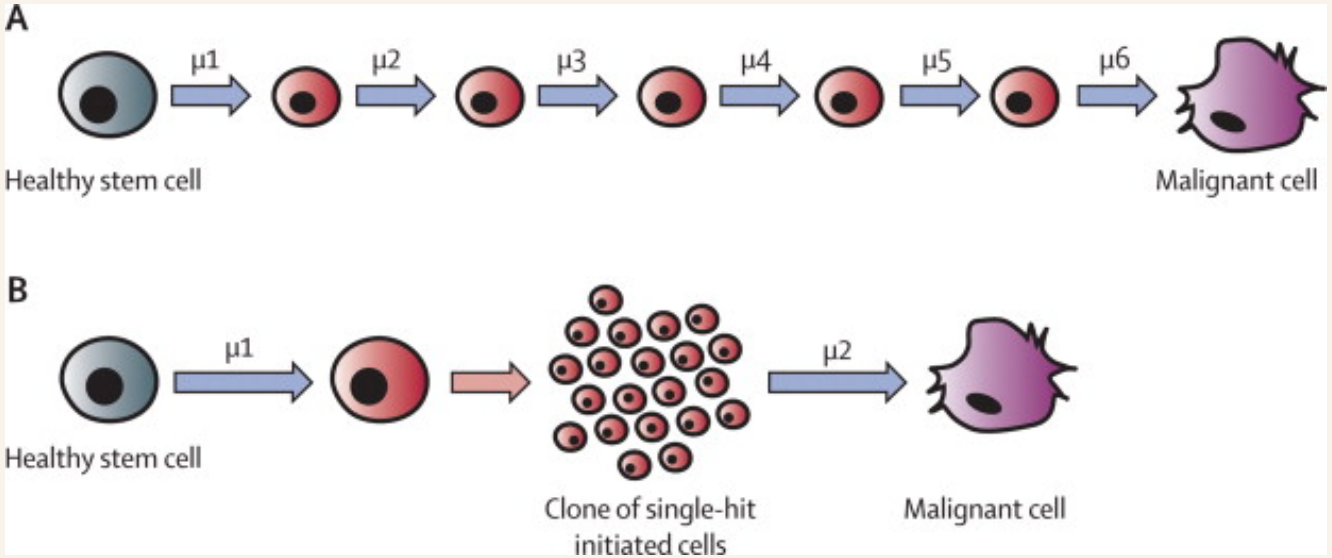
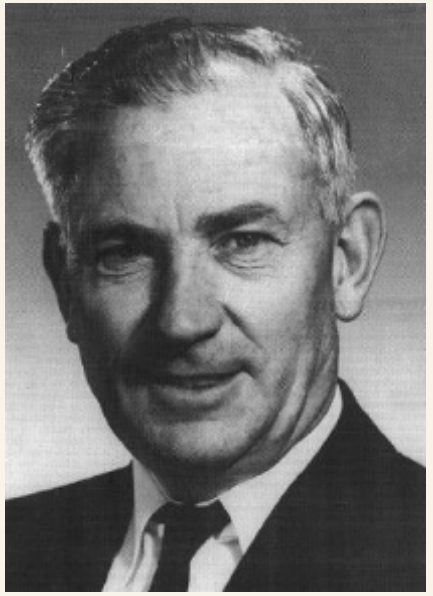
Mathematical modeling of ionizing radiation effects

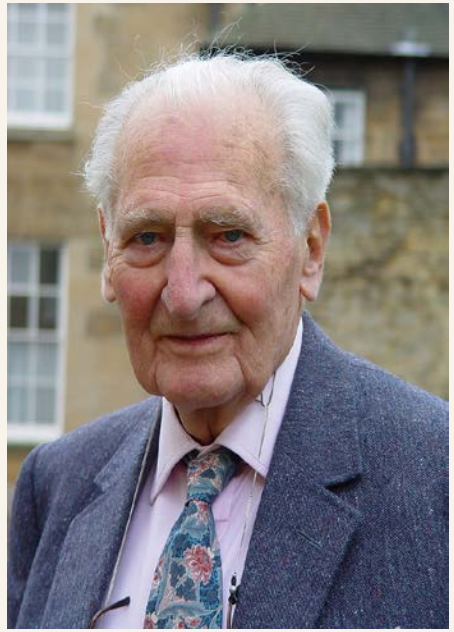
- Such modeling has a long history (e.g. Lea-Catcheside time factor, 1940s, multistage theories of carcinogenesis, 1950s)



From Hornsby et al. Lancet oncology, 2007.



D. G. Catcheside



R. S. Doll

- Models mathematically represent current knowledge and hypotheses about how radiation damages cells and organs
- Commonly modeled outcomes include clonogenic cell survival, chromosomal aberrations and carcinogenesis

Usefulness of modeling at low doses

- Low radiation doses are relevant for radiation protection
- However, very large sample sizes are needed to reliably measure radiation effects like cancer at such doses
- Mechanistically-motivated mathematical models are potentially very useful for risk prediction at low doses

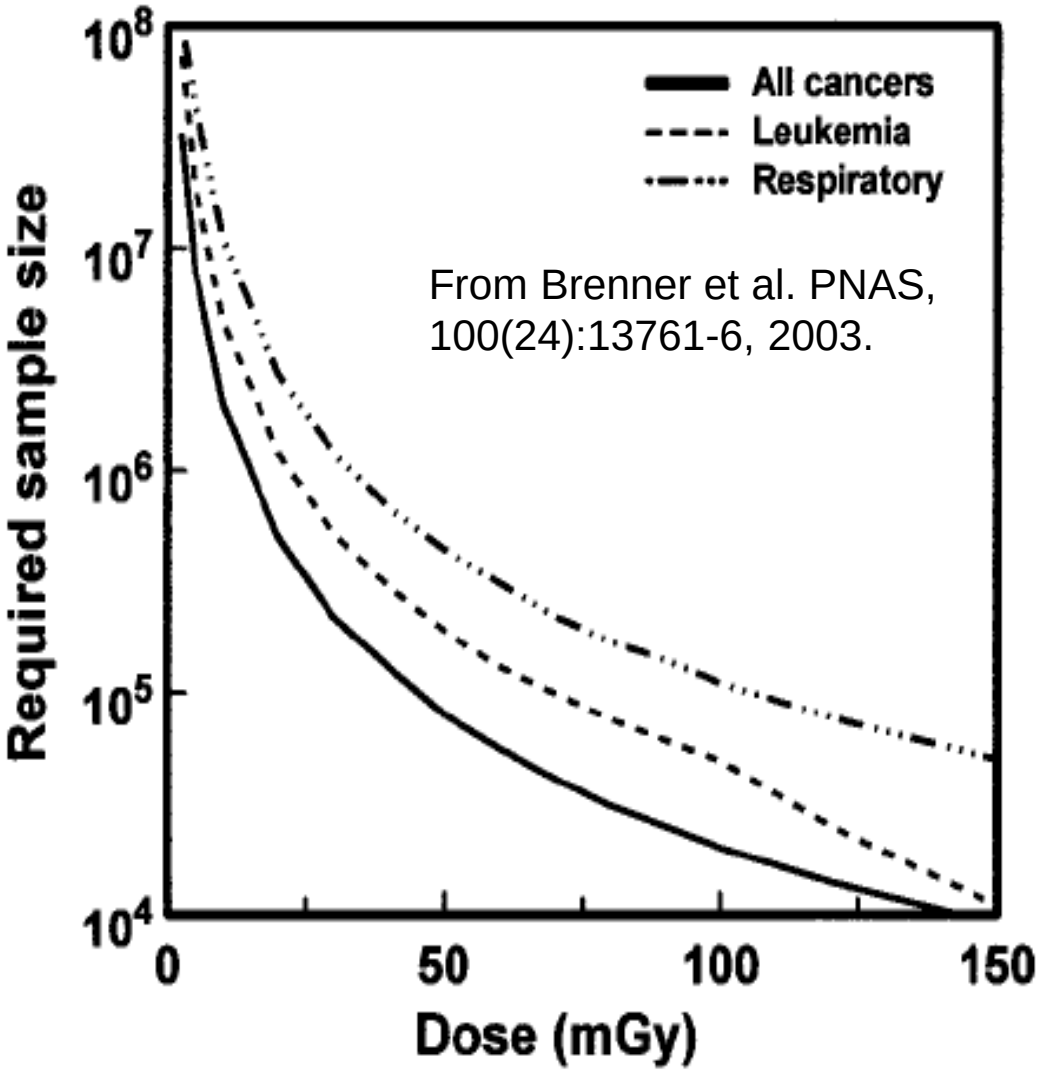
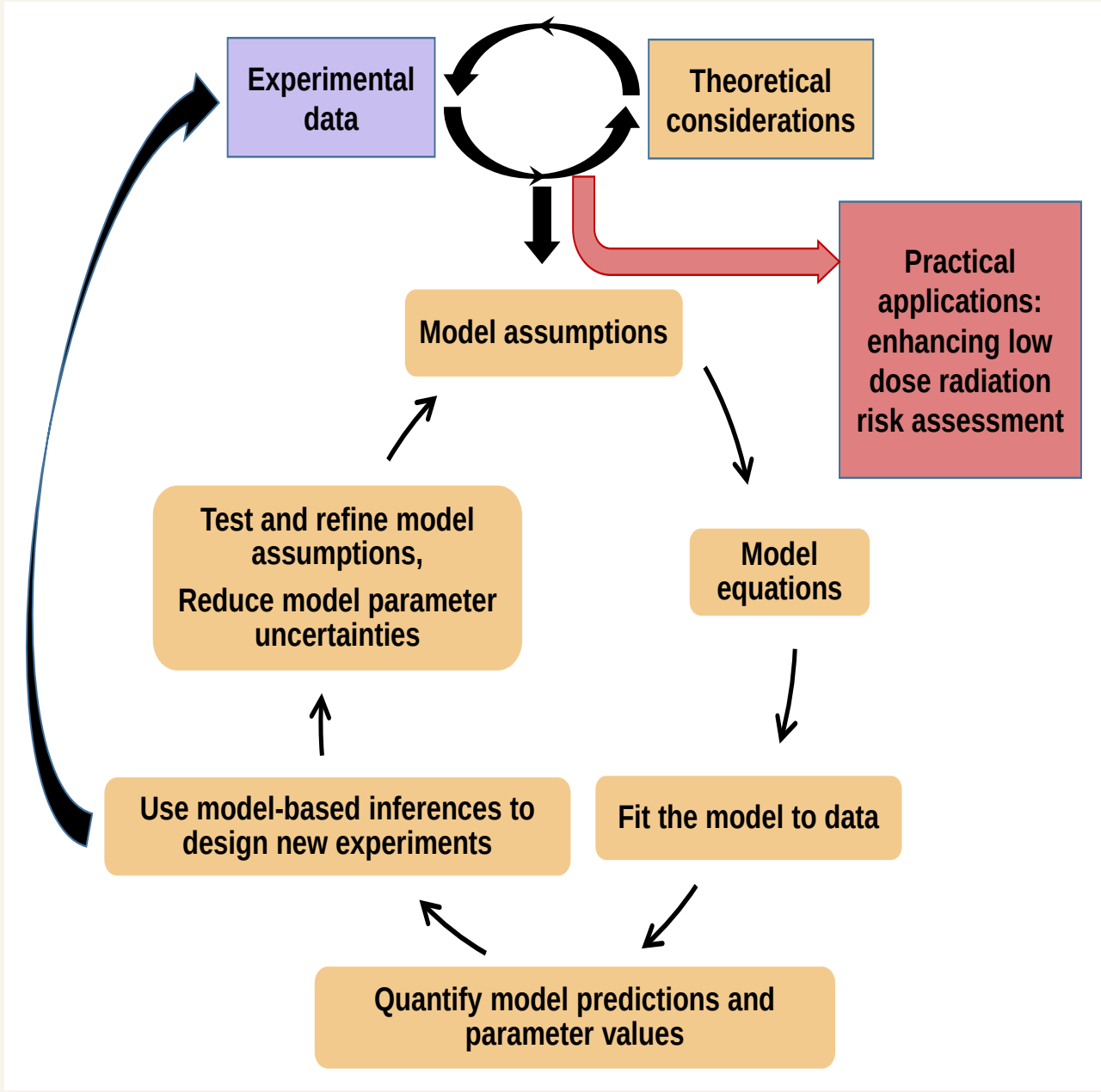


Fig. 1. Size of a cohort exposed to different radiation doses, which would be required to detect a significant increase in cancer mortality in that cohort, assuming lifetime follow-up (9).

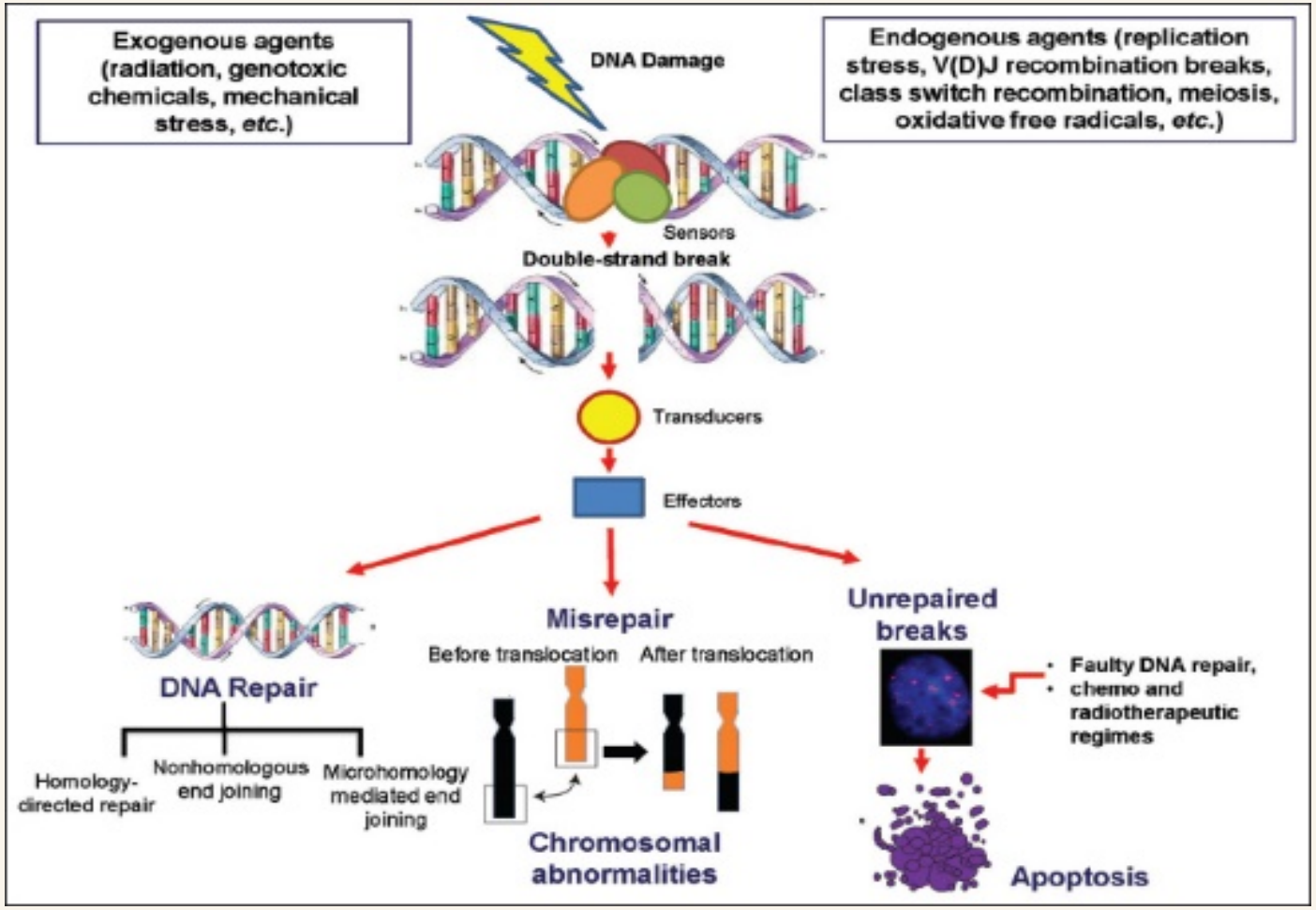
Integration of modeling with experimental and observational studies

- By design, models never form a complete description of the complex biological system, but focus on specific aspects of radiation effects
- Arguably, such simplicity is a strength, not a weakness
- The simplifying approximations provide insights into which components of the system are responsible for a particular behavior
- Integration of models with experimental and observational studies in a “cycle” can improve hypothesis generation and testing, and enhance risk estimation



DNA double strand breaks (DSBs)

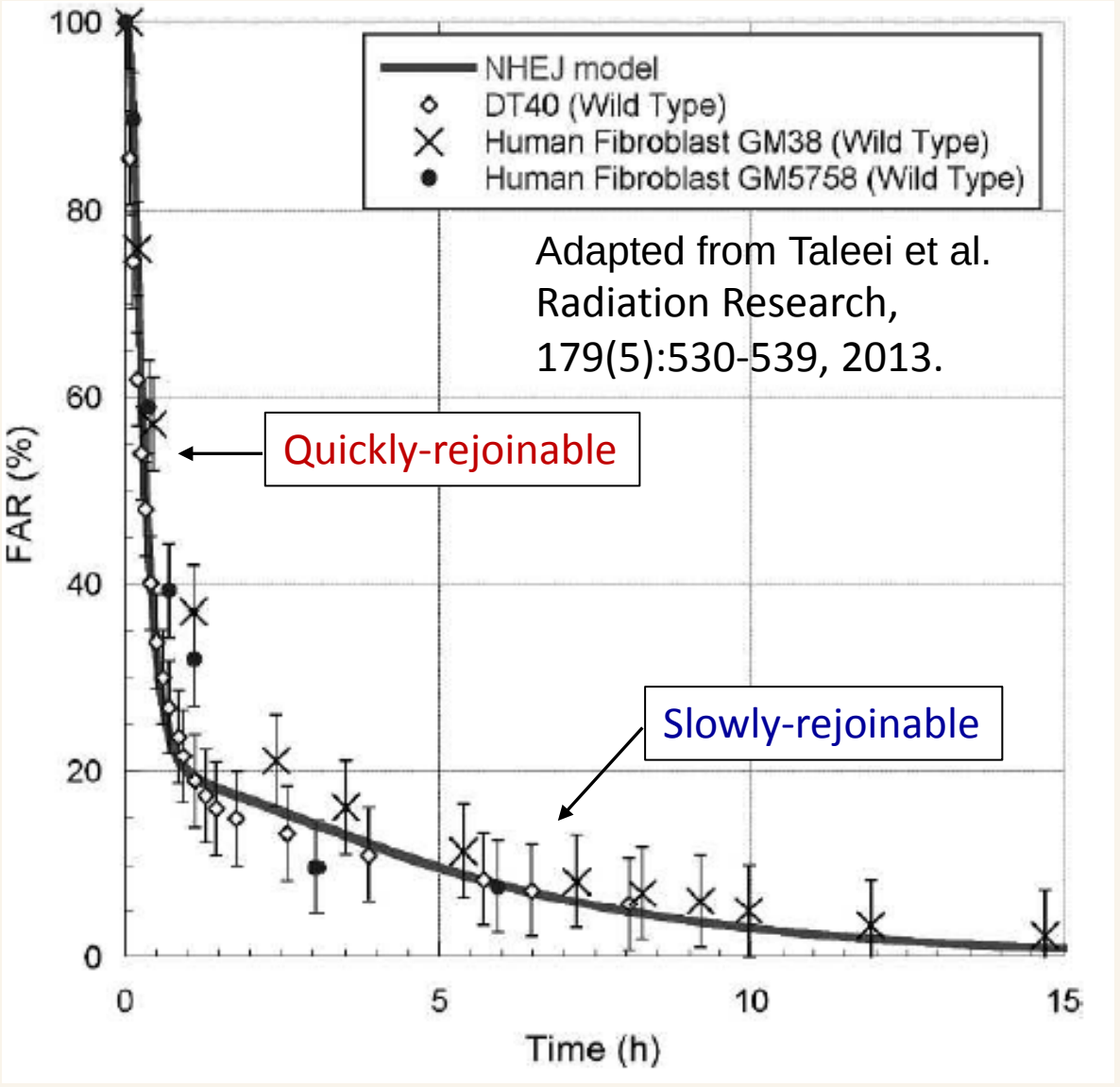
- DSBs are not the most common type of radiation-induced DNA damage
- However, DSBs are important because of their severity: disrupt DNA integrity
- Mistakes in DSB repair can cause cell death, chromosomal aberrations and carcinogenesis



From Pandey et al. DNA double-strand break repair in mammals. Journal of radiation and cancer research, 2017.

DSB rejoining kinetics

- Most radiation-induced DSBs are quickly-rejoinable (within the first 1–2 hours after acute exposure)
- Others are slowly-rejoinable (persist for several hours), or essentially unrejoinable (persist for >24 hours)
- Possible reasons for such multi-phasic behavior:
  - Different rejoining mechanisms (e.g. nonhomologous, homologous)
  - Different DSB types/complexities (e.g. due to spatial proximity between DSB and/or chemical aspects like base damage close to a DSB)
  - Different accessibilities of DSBs to repair machinery (e.g. DSB location in heterochromatin versus euchromatin)

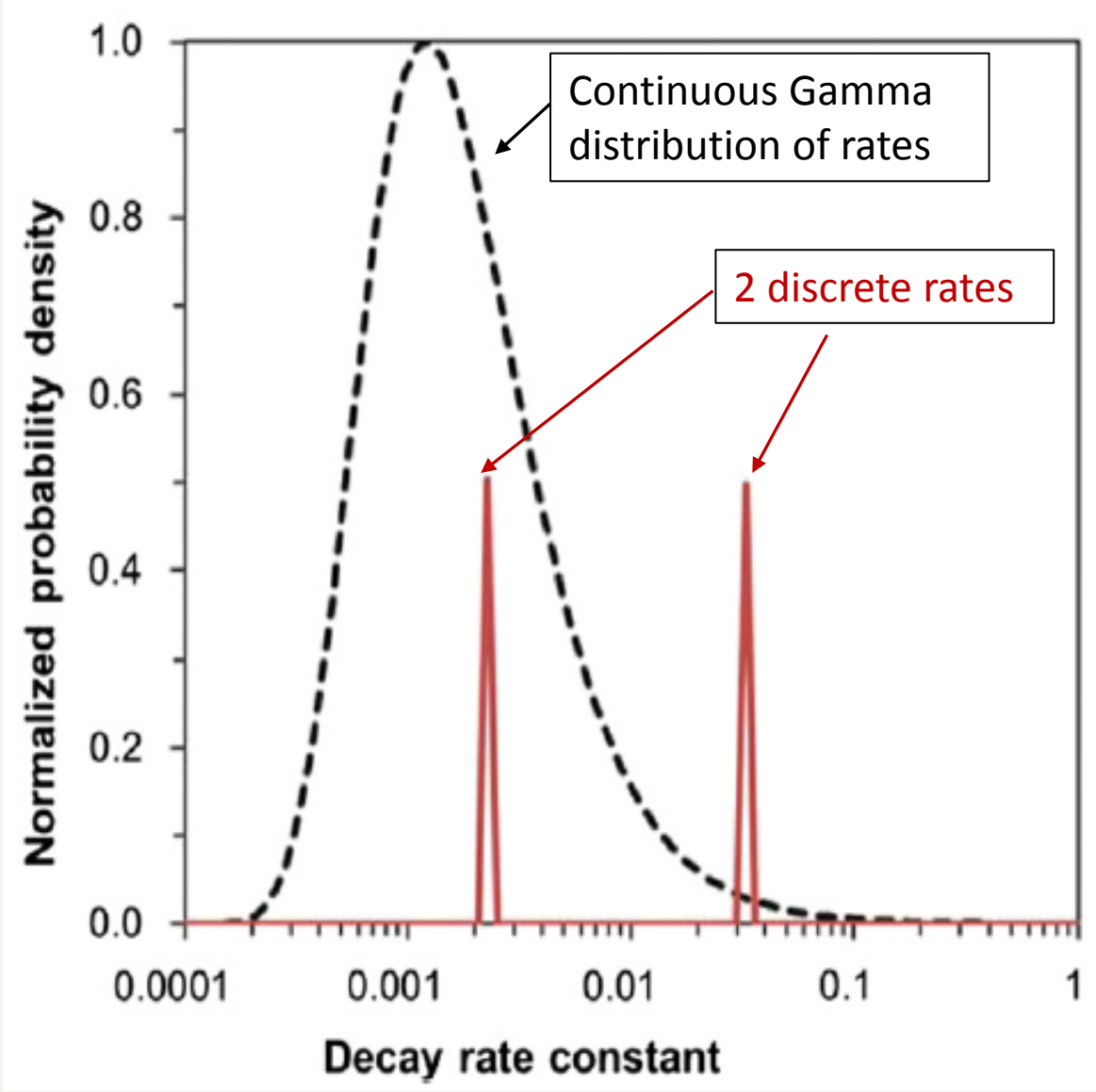


Importance of modeling DSB rejoining

- Quantitative and mechanistic understanding of DSB rejoining are important at both high and low radiation doses
- For example, when radiotherapy doses are given in fractions with short inter-fraction intervals
- Or when radiation exposure is protracted over long time periods:
  - occupational exposures
  - radioactive contamination from nuclear accidents or attacks
  - long duration space missions
- Importantly, the dependences of DSB rejoining kinetics on radiation dose and dose rate remain incompletely understood:
  - older studies using gel electrophoresis were limited to high doses
  - newer studies at lower doses rely on surrogate DSB markers like gamma-H2AX foci

Discrete rejoining rates vs continuous rate distributions

- DSB rejoining is often modeled by the sum of discrete exponential (first order) rates
- However, complex decay patterns may result from a continuous probability distribution of first-order rates
- This approach is consistent with the concepts of multiple DSB types/ complexities (chemical and spatial) and multiple repair pathways
- A schematic example is shown on the right



Model comparisons

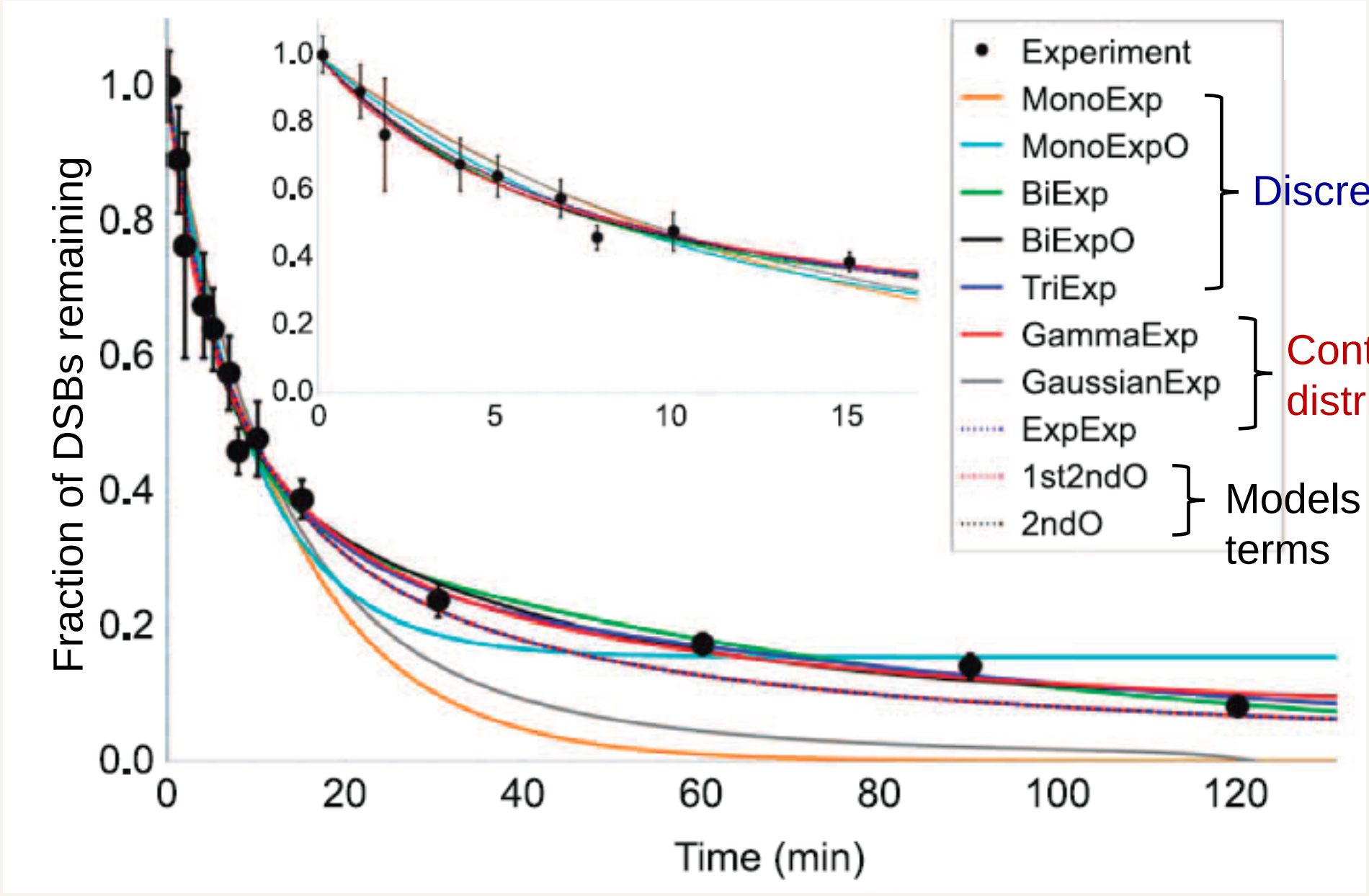
- The concept of continuous rate distributions is not new, but it was not previously applied to DSB rejoining in detail
- We did this in the following paper:

Herr, L., Shuryak, I., Friedrich, T., Scholz, M., Durante, M. and Brenner, D. J. New Insight into Quantitative Modeling of DNA Double-Strand Break Rejoining. *Radiat. Res.* 184, 280–295 (2015).

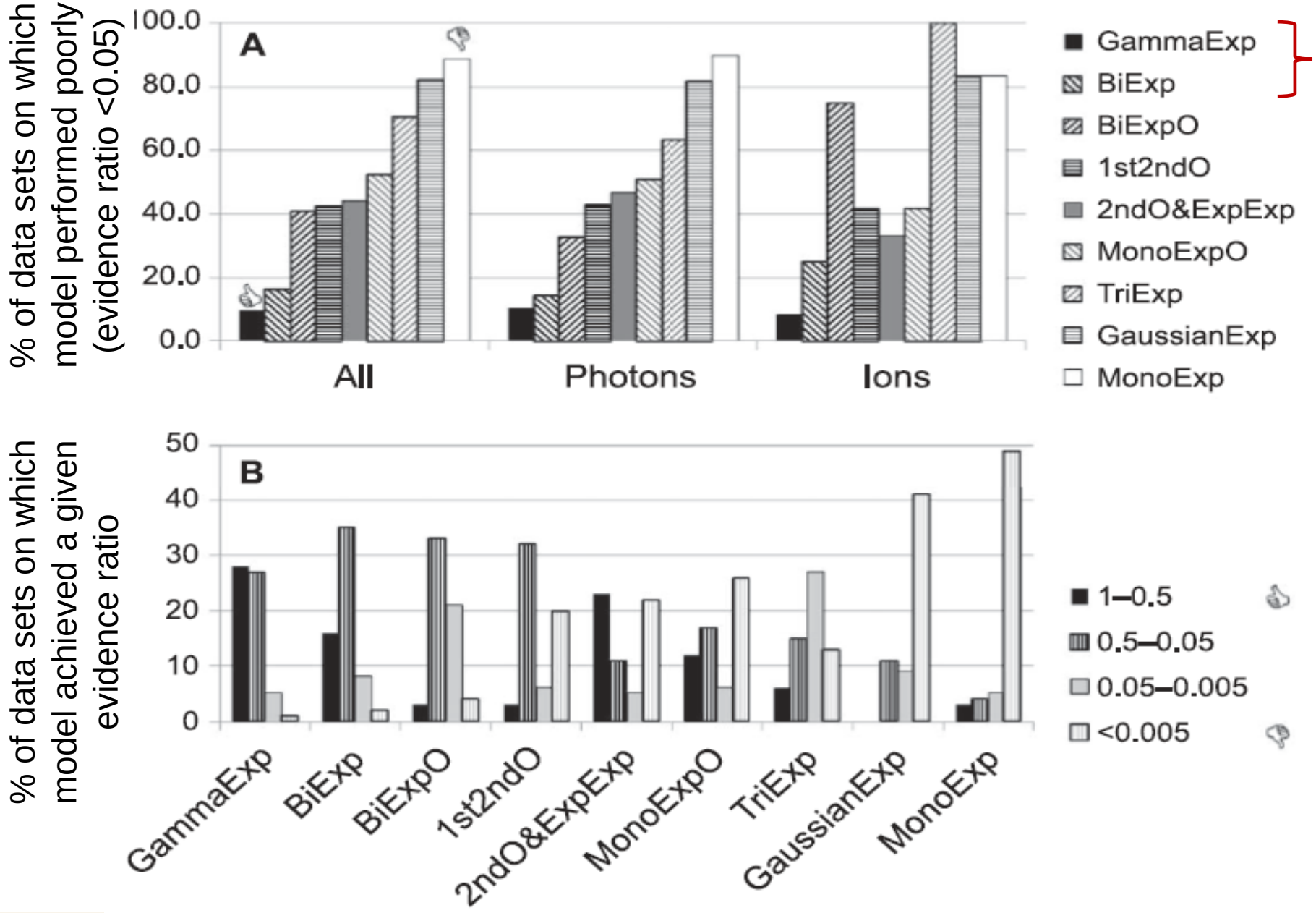
- We compared 10 DSB rejoining models using published data from 61 mammalian cell lines after high dose rate photon or heavy ion irradiation
- The set of models included formalisms with:
  - one, two or three discrete first-order rejoining rates
  - continuously distributed first-order rejoining rates (using Gaussian, Exponential or Gamma distributions)
  - second-order rejoining rates

Here are fits from all models to a sample data set on CHO-K1 cells

(gel electrophoresis, 40 Gy)



Summary of model performances on all data sets



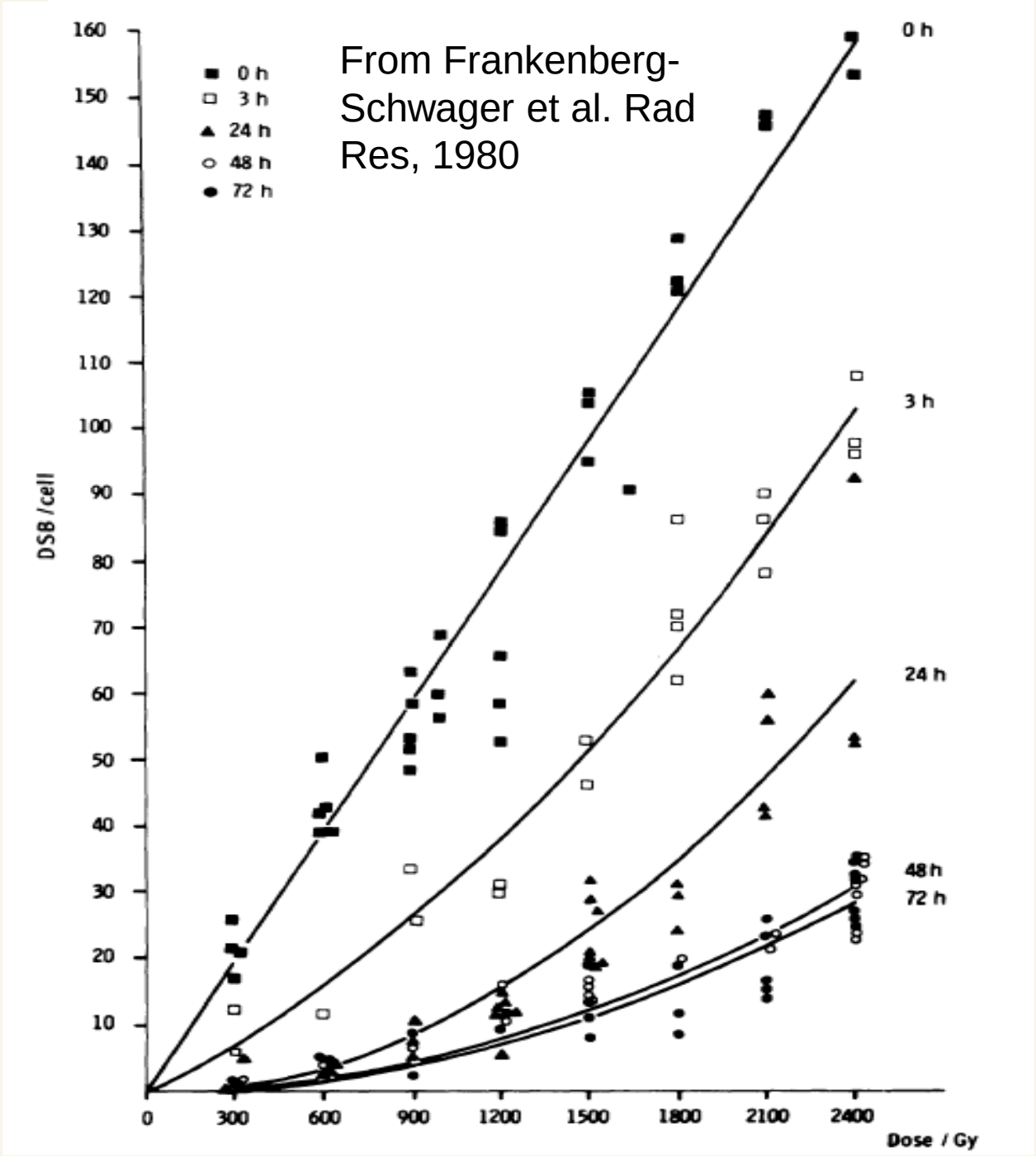
Best-performing models

DSB rejoining: conclusions

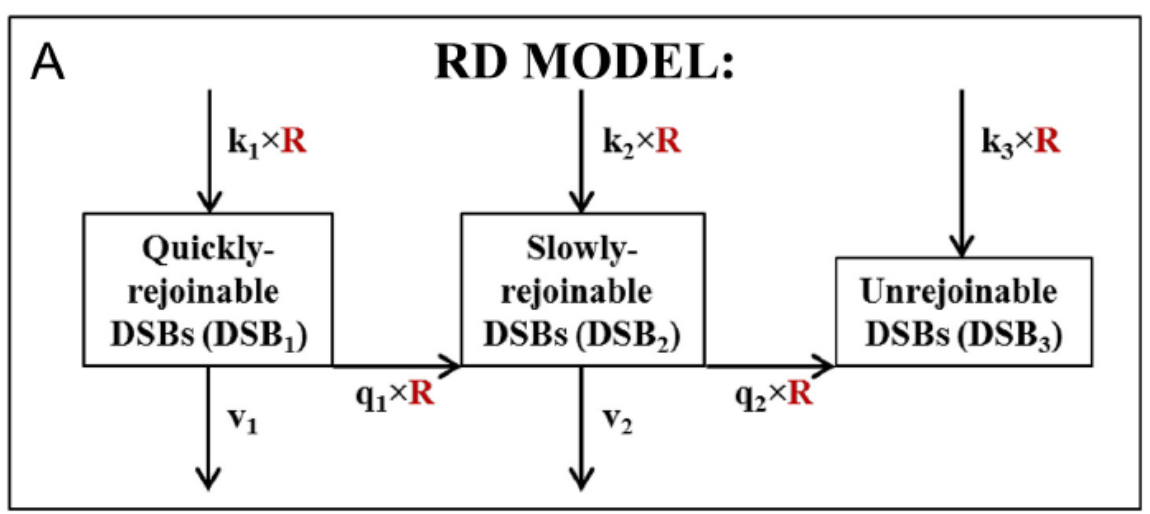
- The model with a gamma-distributed decay rate, and the bi-exponential model, performed well on most tested DSB rejoining data sets
- Compared with the bi-exponential model, the gamma-distributed model has one parameter less, and does not systematically underestimate data at long times after irradiation
- In contrast, the following model types performed poorly:
  - ❖ One decay rate or a decay rate that shows small deviations from an expected value
  - ❖ Second-order kinetics (pairwise DSB interactions)
  - ❖ Too many adjustable parameters (e.g. multiple discrete rejoining rates)

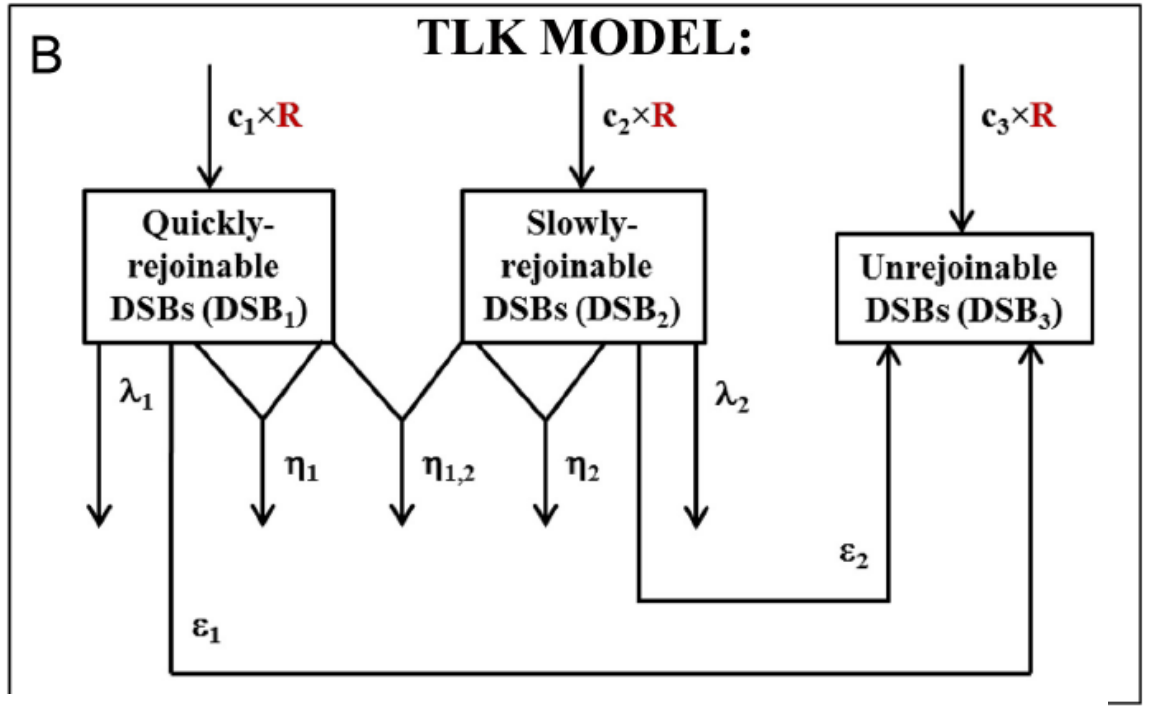
DSB rejoining: yeast

- Yeast (*S. cerevisiae*) represent an interesting case because DSB rejoining can be measured by gel electrophoresis at the same doses as cell survival, which is not possible for mammalian cells
- The dose response for DSBs is **linear** just after irradiation, but becomes more and more **curved** at longer rejoining times
- This pattern suggests dose dependent DSB rejoining kinetics



- We analyzed these data using a new radiation-dependent (RD) model for three DSB classes: quickly-rejoinable, slowly-rejoinable and unrejoinable
- Radiation converts DSBs from one class to another
- We used yeast data for low-LET and high-LET radiations to compare the performances of the RD model with a more “standard” two-lesion kinetic (TLK) model
- The TLK model also has three DSB classes, but no radiation-dependent conversion between them

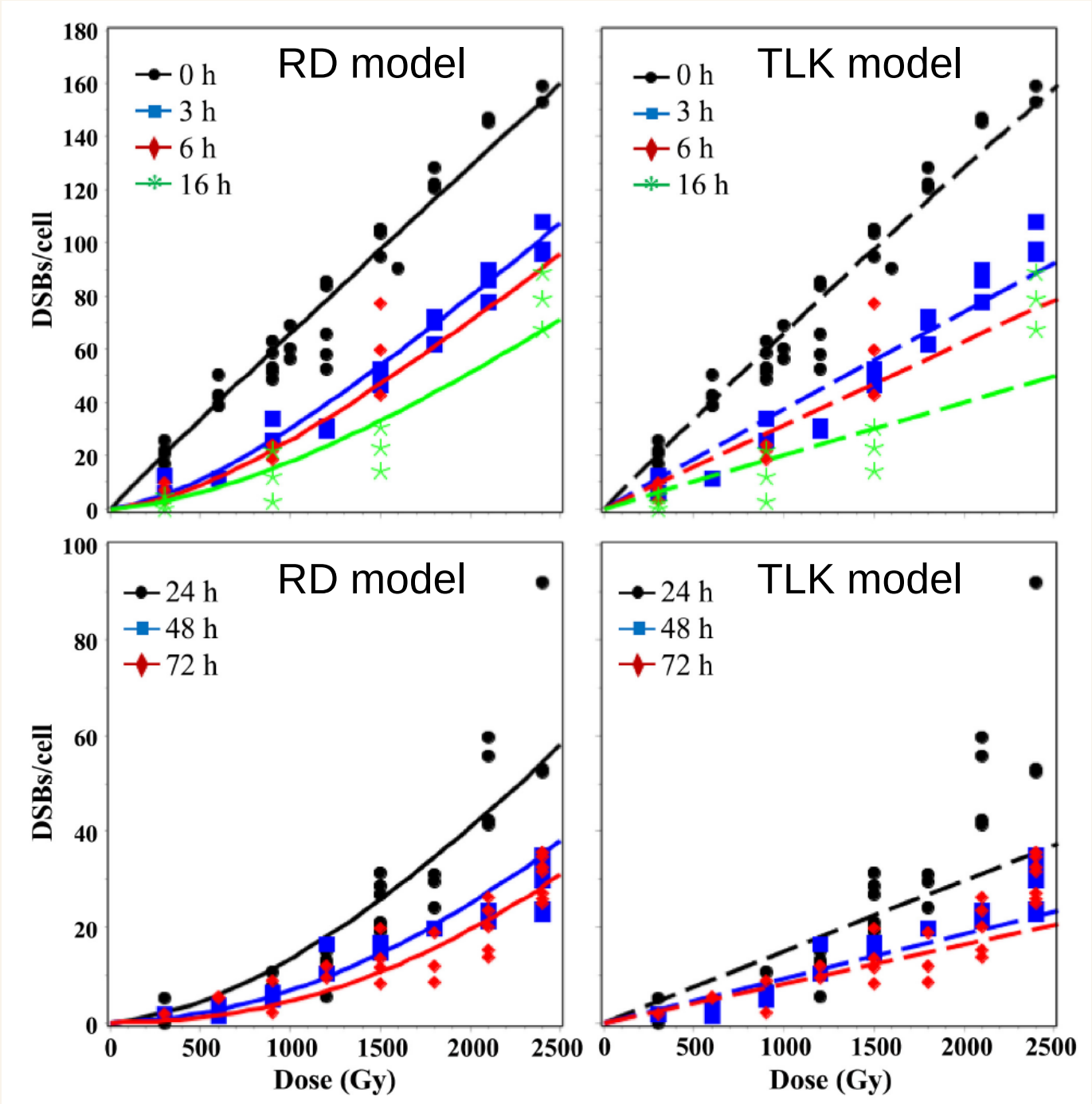




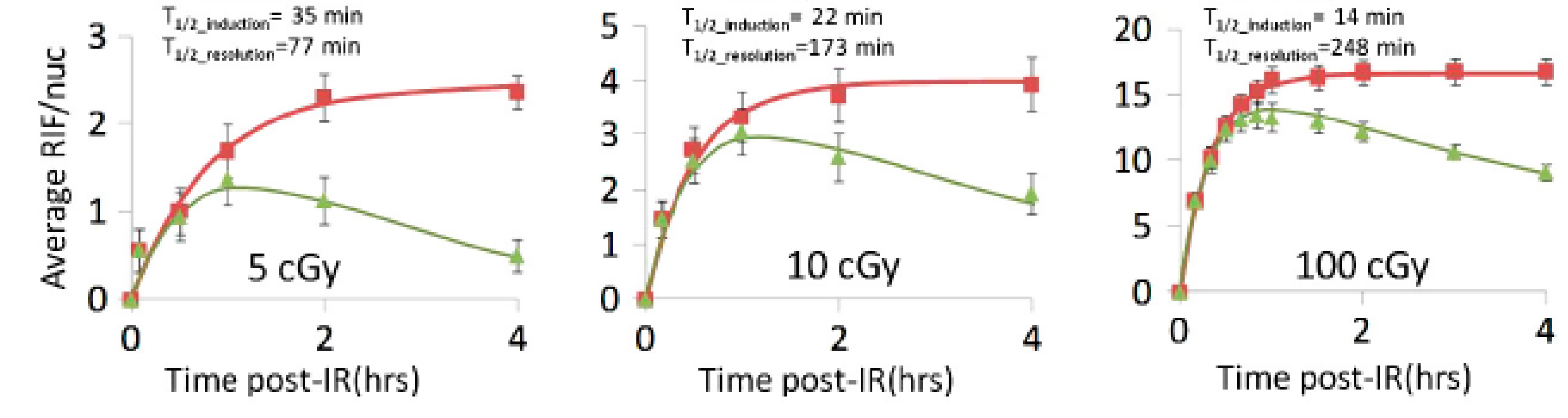
Shuryak, Mechanistic Modeling of Dose and Dose Rate Dependences of Radiation-Induced DNA Double Strand Break Rejoining Kinetics in *Saccharomyces cerevisiae*, PLOS One, 2016.

RD and TLK comparisons

- The RD model described all tested data sets significantly better than the TLK model
- This occurred because the RD model:
  - reproduced the observed **curving** dose responses for DSBs at long times after irradiation, whereas the TLK model predicted **linear** shapes
  - adequately described DSB yields at both high and low **dose rates** using one parameter set, whereas the TLK model overestimated low dose rate data



- So, in yeast there is clear evidence that DSB rejoining is dose-dependent:
  - ❖ The fraction of slowly-rejoinable and/or unrejoinable DSBs increases with increasing dose/dose rate
- In mammalian cells this is less clear, but some studies with repair foci kinetics at **low doses** also suggest dose dependence

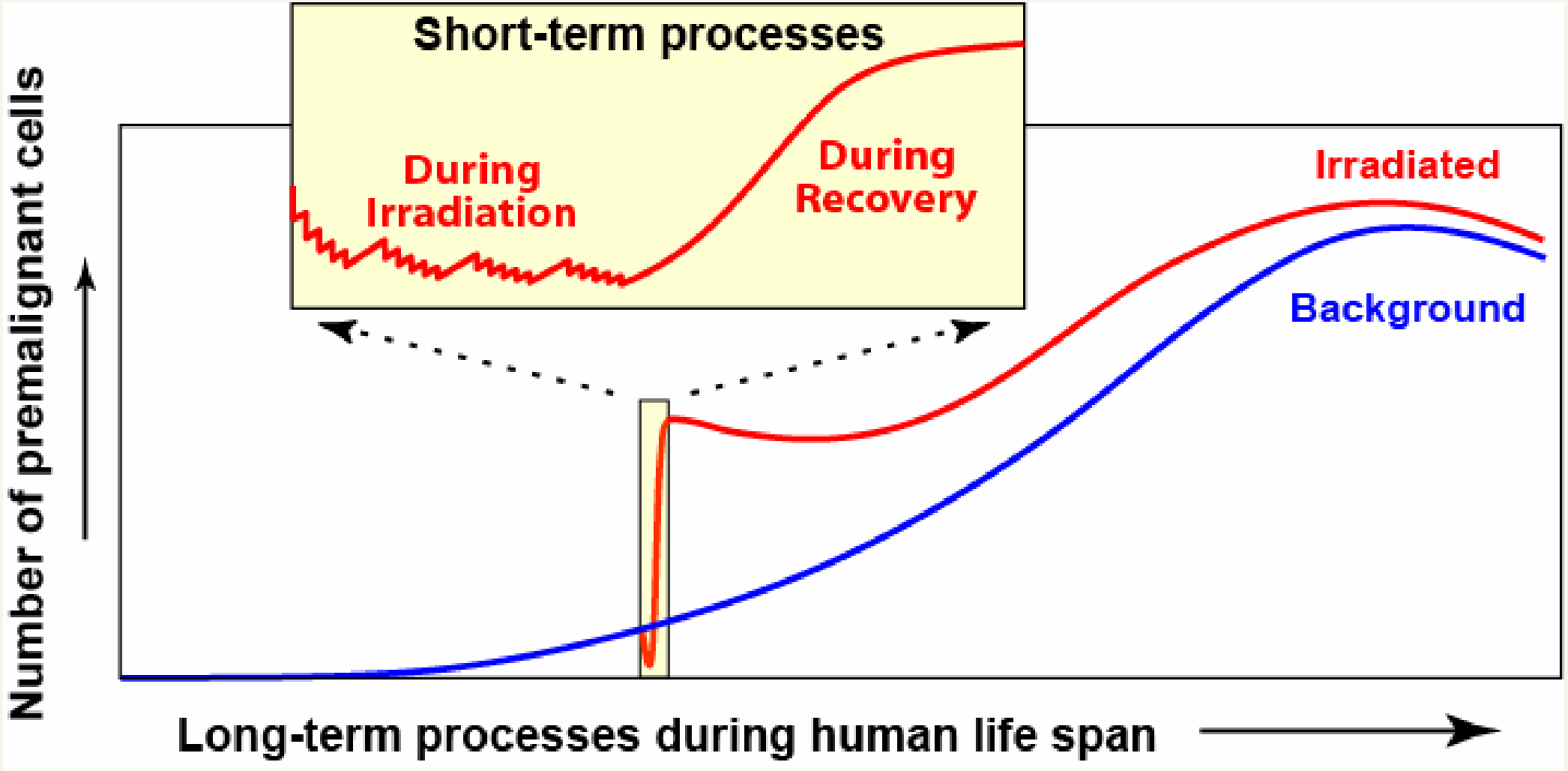


From Neumaier et al. PNAS, 109(2):443-8, 2012.

Radiation carcinogenesis

- Cancers may eventually arise from cells with mis-rejoined DSBs or other radiation-induced damage through a lengthy evolution
- Many mechanistic carcinogenesis models have been developed over several decades
- They can be roughly grouped into **two categories**:
- ***Short-term:*** **Only the period of radiation exposure, and perhaps initial tissue recovery (seconds to weeks) is analyzed in detail**
  - **Help to understand dose response shape, effects of radiation quality, dose rate, fractionation**
- ***Long-term:*** **Entire life span (many years) is modeled, but the irradiation / recovery period is treated simply as an instantaneous perturbation of background carcinogenesis rates**
  - **Help to understand modulation of background cancer rates, effects of age at exposure, time since exposure**

Schematic of short- and long-term processes



Background processes → short-term dose response → modulation of dose response by long-term processes

An attempt to combine short- and long-term models

Shuryak I, Hahnfeldt P, Hlatky L, Sachs RK, Brenner DJ. *Radiat Environ Biophys*. 2009

Advantages of combined approach:

1) **background risks are modeled directly**
2) **modulation of short-term dose response by long-term processes is included**
3) **enhanced insight into carcinogenesis mechanisms**

The particular approach here tracks carcinogenesis processes as follows:

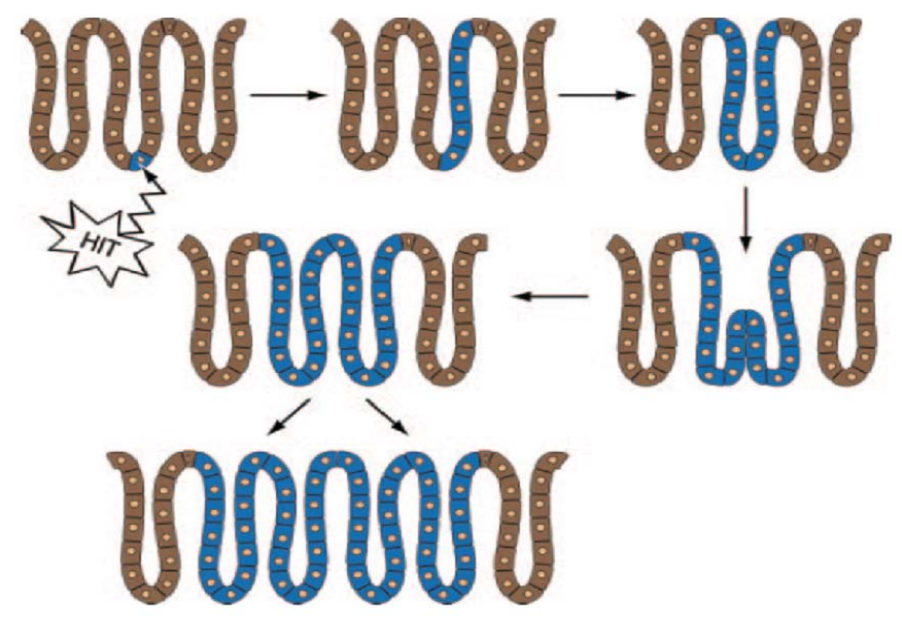
1. **From birth to irradiation (long-term model)**
2. **During, and shortly after, irradiation (short-term model)**
3. **From irradiation to old age (long-term model)**

Model assumptions

- **Short-term part (radiation + recovery; stochastic equations):**
  - **Initiation (spontaneous + radiogenic), inactivation (killing), repopulation (*iir*)**
- **Long-term part (before and after radiation + recovery; deterministic equations):**
  - **Pre-malignant cells can fill an entire "niche" and/or can invade an adjacent one (clonal expansion)**
  - **Radiation can modulate the homeostatic regulation of pre-malignant niche sizes (promotion)**
  - **Pre-malignant cells can become fully malignant (transformation)**

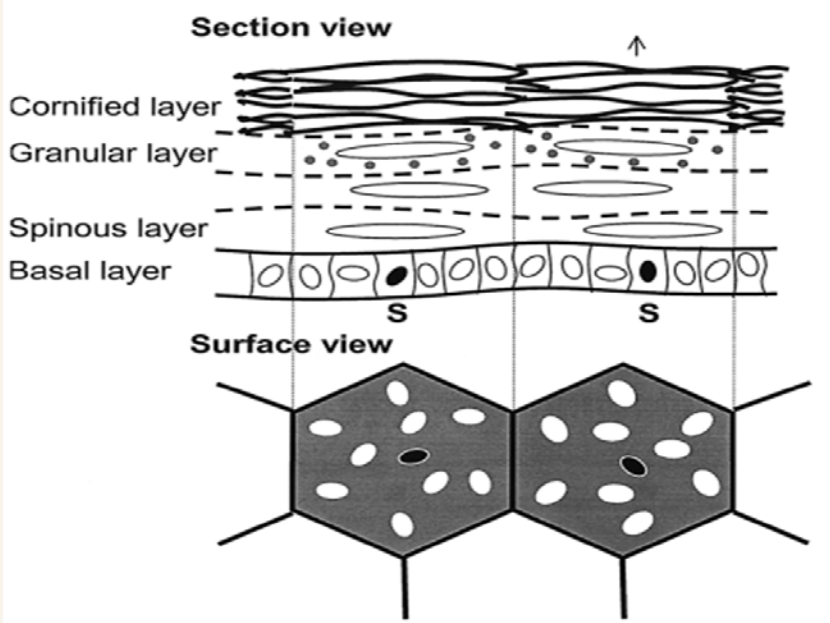
Examples of niches:

Colon crypts



Greaves et al., *PNAS*, 2006

Epidermal proliferative units



Potten and Booth, *J Invest Dermatol,* 2002

Even for tissues which have no well defined niches, there may be functionally similar size restrictions on individual pre-malignant clones

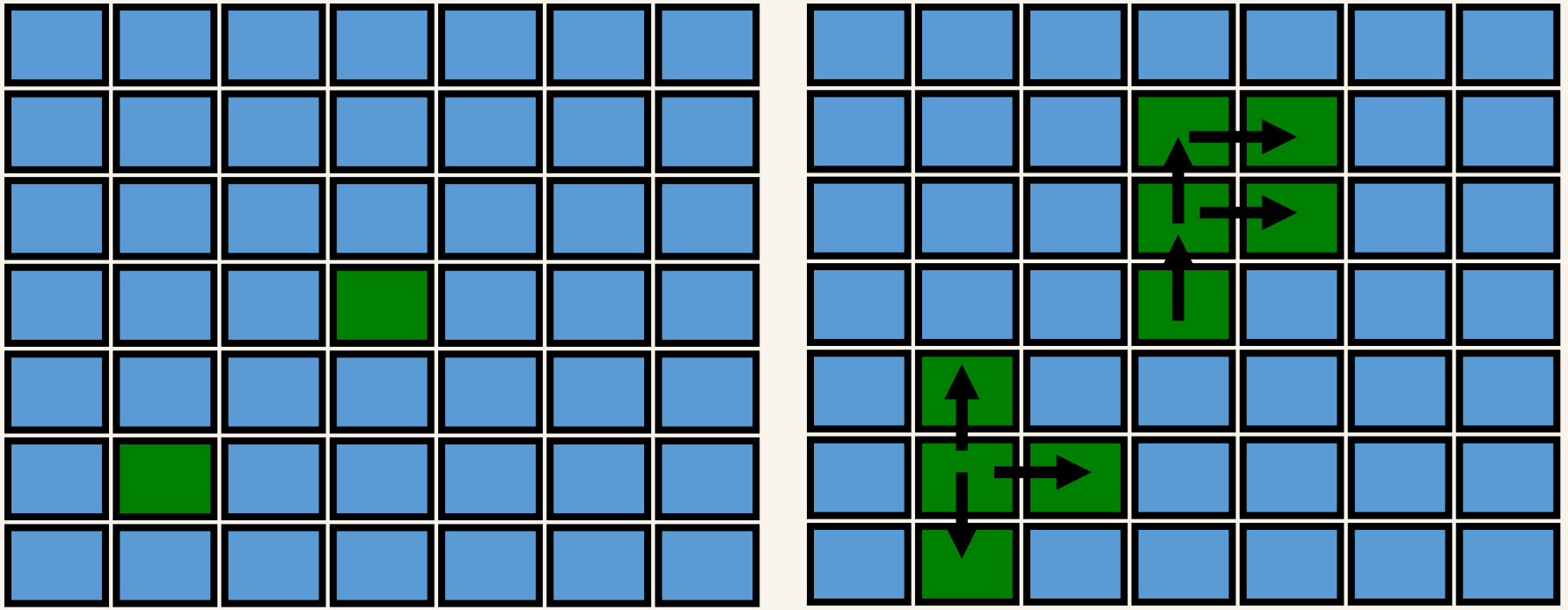
MODEL SCHEMATIC: Before irradiation

Niches filled with normal cells

Niches filled with spontaneously-initiated pre-malignant cells

Spontaneous initiation

Clonal expansion



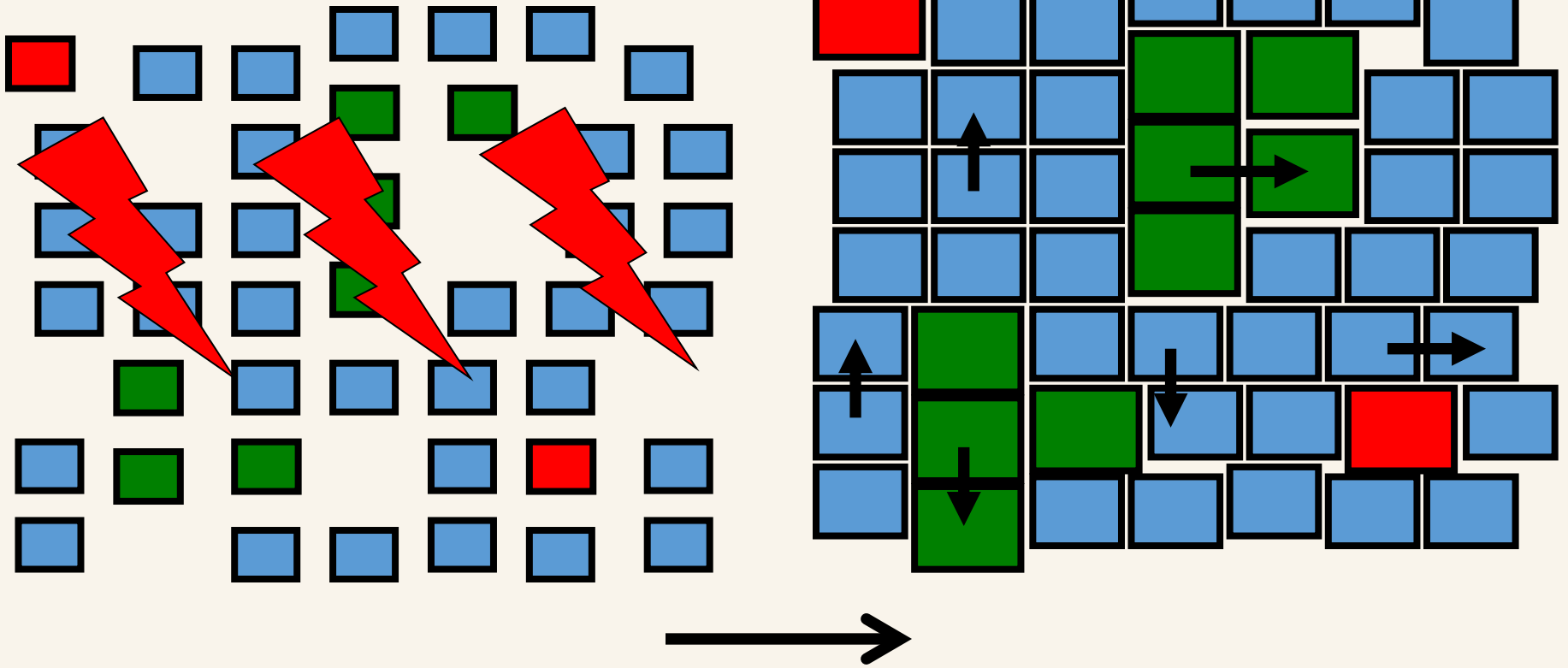
Time

Radiation effects

Niches filled with radiation-initiated pre-malignant cells

Radiogenic initiation and inactivation

Repopulation, promotion

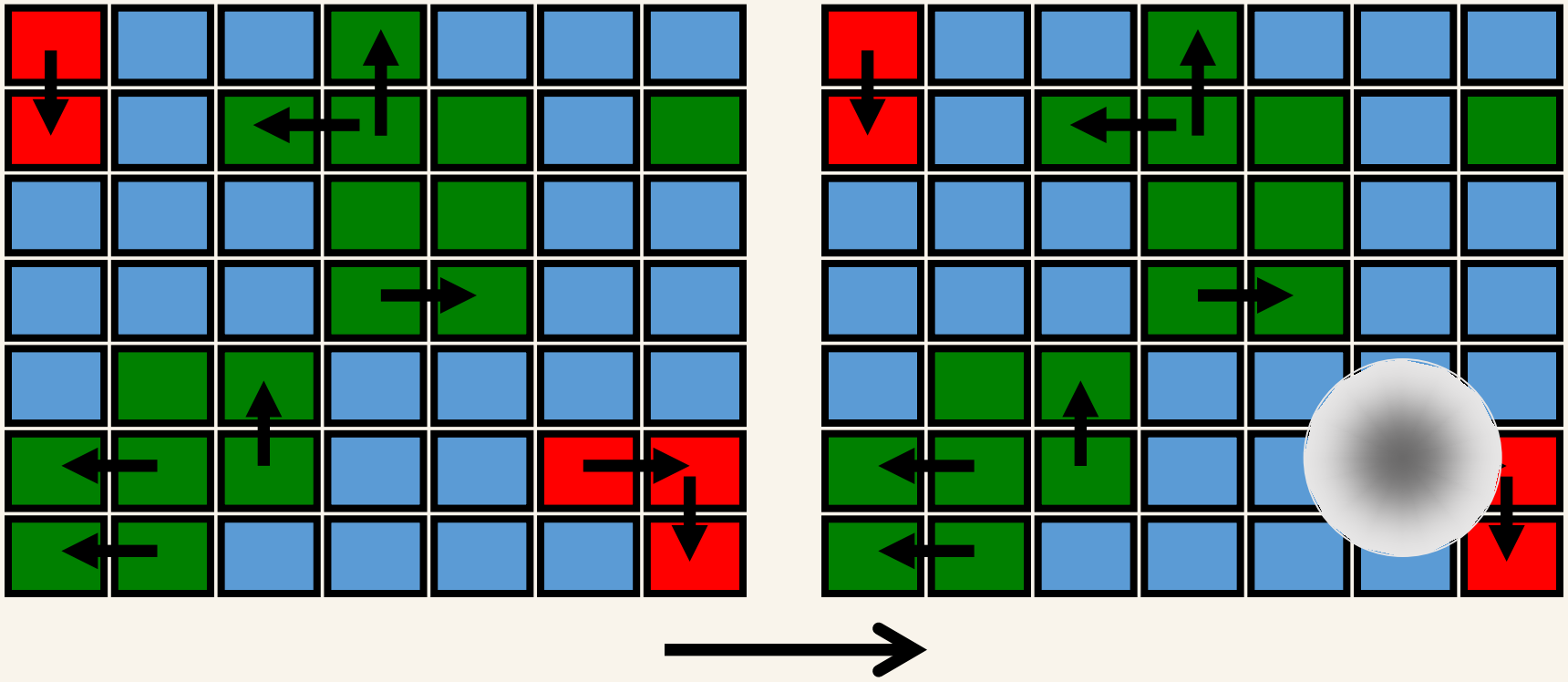


After irradiation

Continued clonal expansion + spontaneous initiation; possible reversal of promotion (homeostatic regulation)

Malignant tumor

Malignant transformation

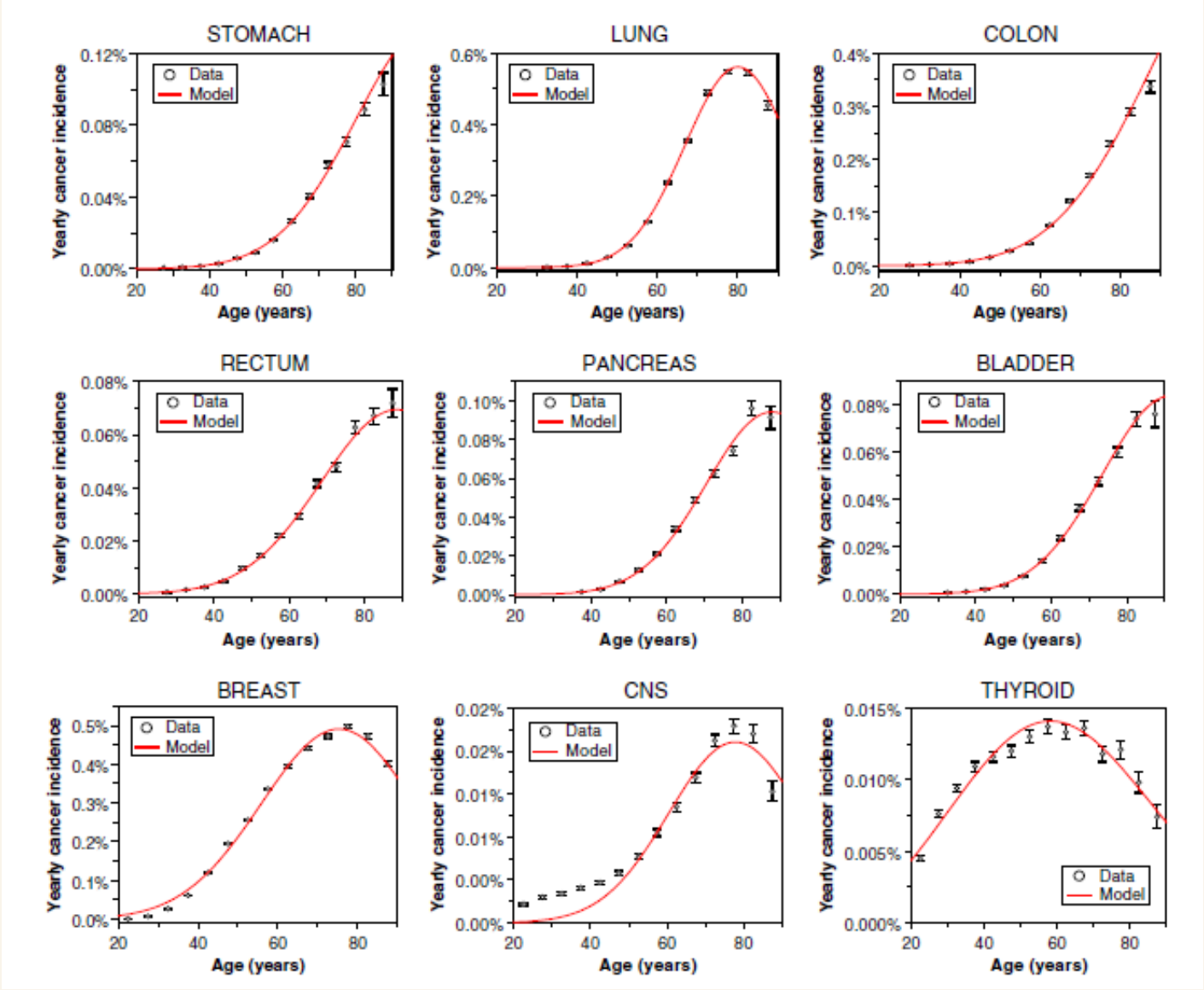


Modeling approach summary

- Deterministic long-term equations provide the mean number of niches filled with pre-malignant cells, and the mean number of pre-malignant cells per niche, just before radiation
- Stochastic short-term equations provide the number of these niches eradicated by the radiation, as well as the number of pre-malignant clones that are induced by and survive the irradiation
- The mean number of pre-malignant niches is the initial condition for deterministic long-term equations, which are applied from this point until old age / death
- The model was fitted to three types of data together:
  - Background cancer incidence (SEER)
  - Radiation-induced ERRs at low doses (Atomic bomb survivors)
  - Radiation-induced ERRs at high doses (second cancers after radiotherapy)

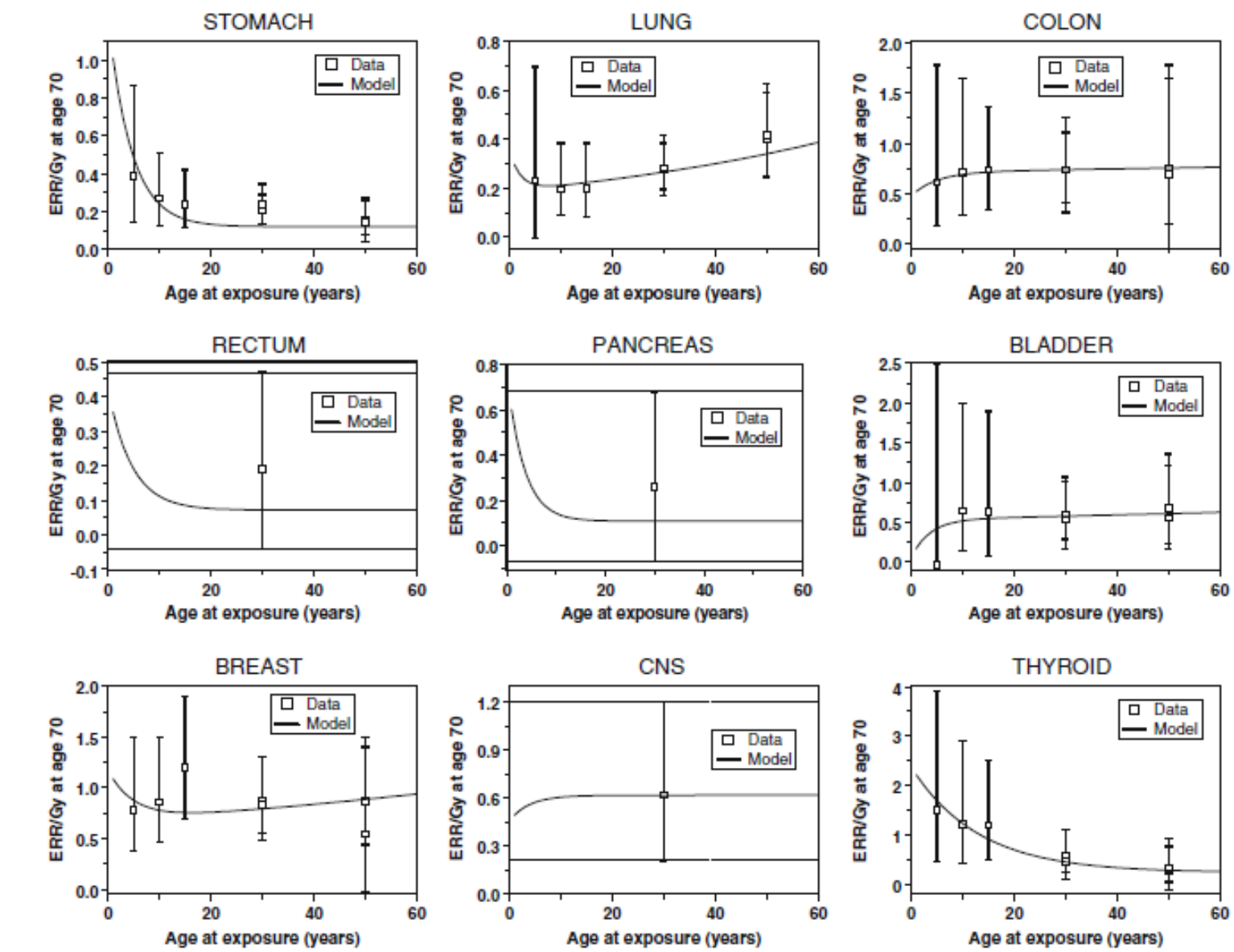
Results

Background cancers: *Three parameters*

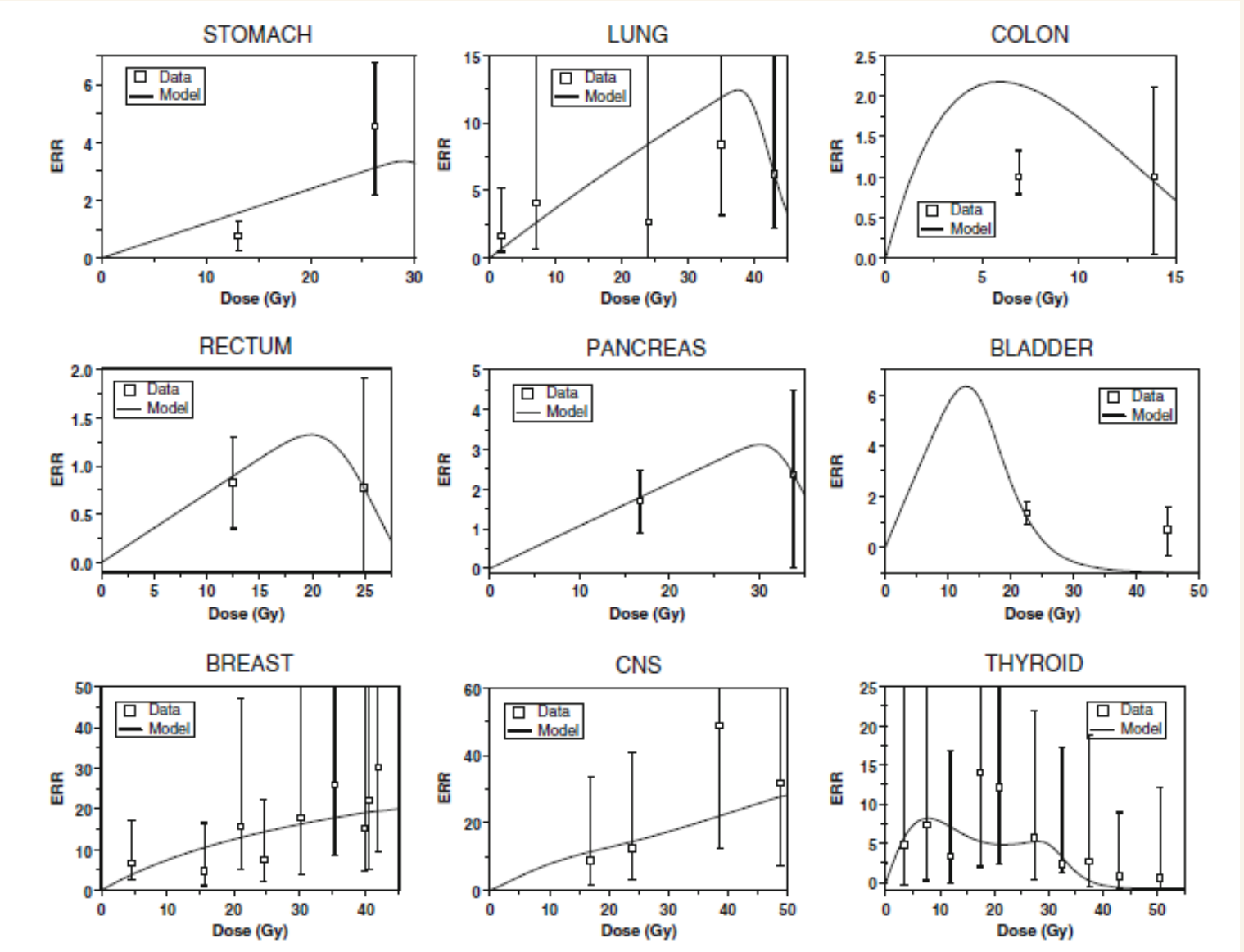


Data from SEER

Used Atomic bomb survivor data + background parameters to quantify radiation risk at low doses: *Three more parameters*



Used data on radiotherapy-induced second cancers to quantify risks at high doses: *One more adjustable parameter + previously determined parameters + cell killing parameters from radiobiological literature*



Conclusions

DSB rejoining:

- There may be more than two (perhaps a whole spectrum) of DSB rejoining rates, which can be summarized by a continuous probability distribution
- DSB rejoining kinetics may depend on dose / dose rate

Carcinogenesis:

- Both short-term and long-term models are becoming more advanced
- Combining models from both classes seems like a promising way forward for quantifying radiation risks and providing mechanistic insights into dose response shapes and behaviors