Examples of Mechanistically Motivated Models of Low-Dose Radiation Effects

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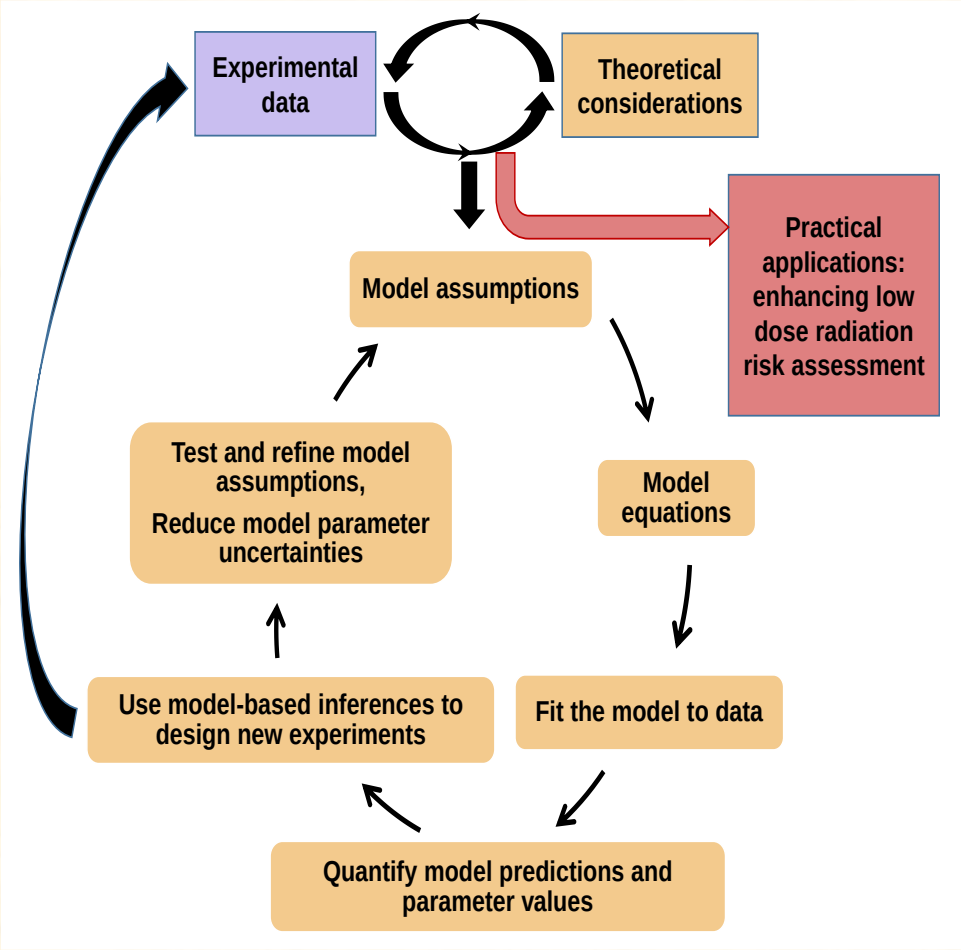
Integration of modeling with experimental and observational studies

- Mathematical modeling of ionizing radiation effects has a long history
- Models have several important roles, including making quantitative predictions for exposure conditions where directly measuring radiation effects is difficult (*e.g.* due to very large required sample sizes to detect effects statistically)
- Integration of models with experimental and observational studies in a "feedback cycle" can improve hypothesis generation and testing, and enhance risk estimation



Example 1: Modeling Cancer risks from space radiation using targeted (TE) and non-targeted effects (NTE)

I. Shuryak, A.J. Fornace, R.K. Sachs, D.J. Brenner

- Astronauts exploring space and distant planets (like Mars) will be exposed to complex mixed radiation fields
- Radiation doses (and especially dose rates) for such exposures are relatively low:

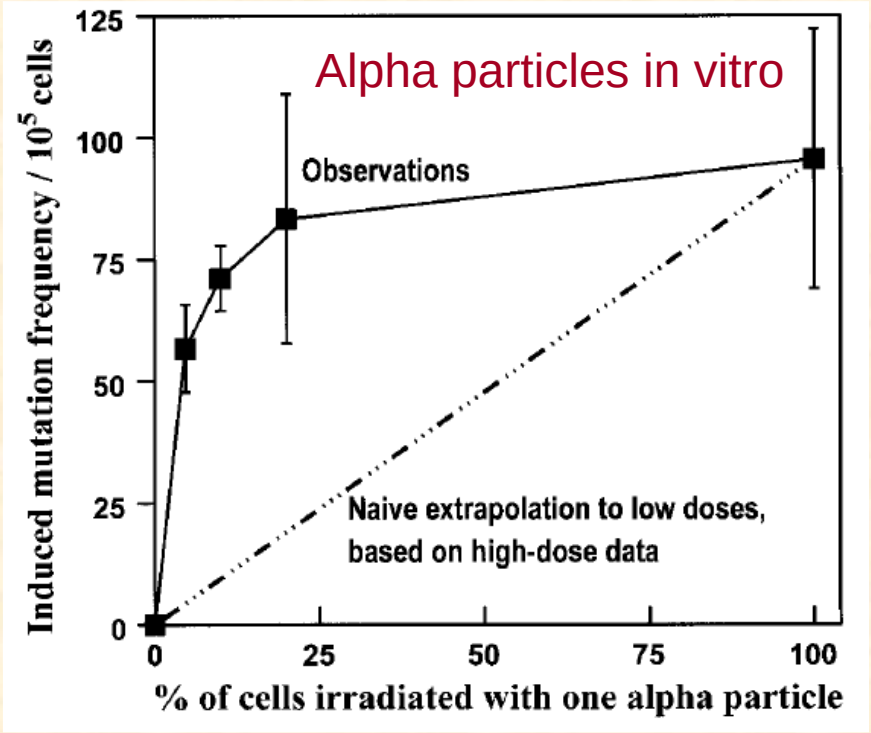
Charge group, Z	Habitat + 5-cm tissue		Transfer vehicle + 5-cm tissue	
	Dose fraction	Dose, mGy/y	Dose fraction	Dose, mGy/y
$Z = 1$	0.60	120.8	0.70	145.0
$Z = 2$	0.21	42.5	0.19	38.5
$3 \leq Z \leq 8$	0.11	22.7	0.08	16.3
$9 \leq Z \leq 14$	0.04	8.5	0.02	4.0
$15 \leq Z \leq 28$	0.04	7.4	0.01	2.9
Sum	1.00	201.9	1.00	206.7

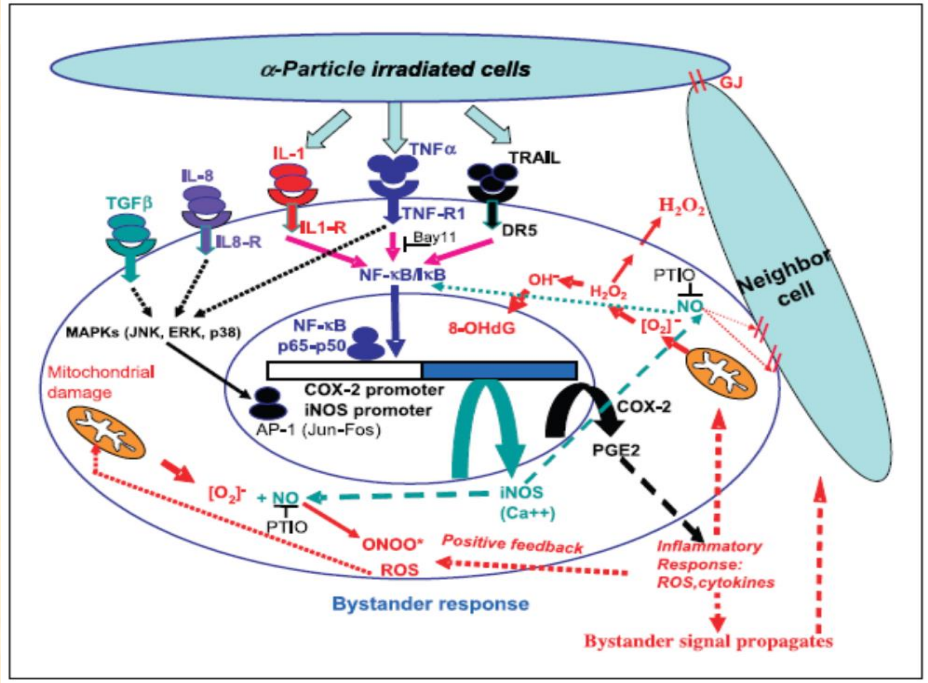
Kim et al 2015

- **However, space radiations (especially densely ionizing heavy ions) can be much more biologically damaging per unit dose than low-LET radiations**

Role of Non-Targeted (Bystander) Effects (NTE)

- ☑ At low doses of high-LET radiation, like heavy ions in space, a given cell's nucleus is only rarely traversed by a particle track core
- ☑ NTE can play an important role in such situations because unirradiated cells respond to signals emitted by irradiated cells
- ☑ This process can cause cells and organs to enter into a prolonged stressed state and potentially increase risks of cancer and other diseases





Zhou et al. *Cancer Res*, 2008

Simple TE + NTE modeling approach:

Applied to APC$^{1638N/+}$ mouse intestinal tumor data (from Fornace *et al.*, Georgetown University)

Radiation response for tumors/mouse (M): *D* = dose, *B* = background, *N* and *T* are NTE and TE parameters, and *s* is the NTE "slope" parameter:

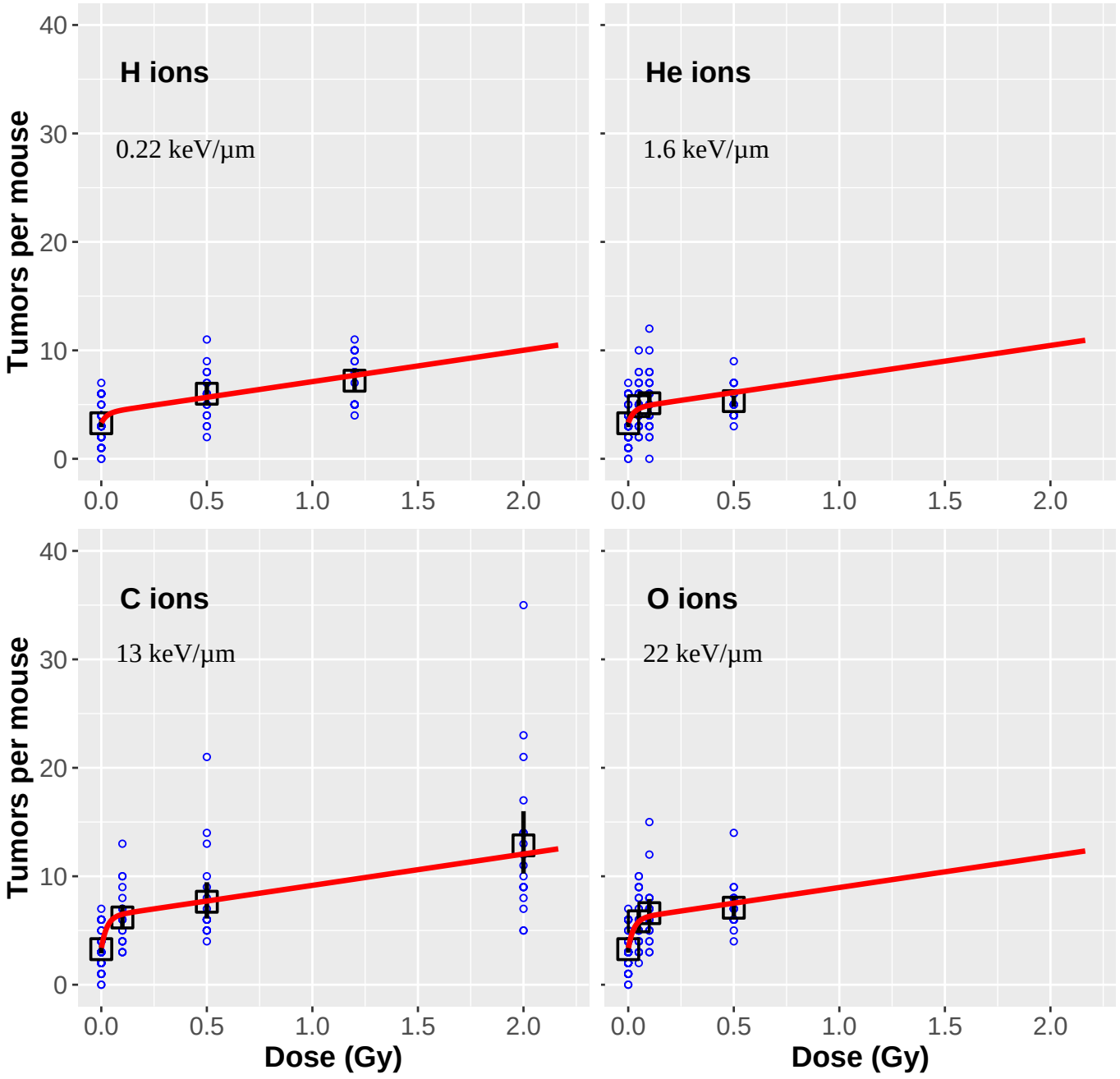
$$M = B \;+\; N\,(1 - \exp[-s\,D]) \;+\; T\,D$$

To describe the complex pattern of variability of tumor count data, we used the following customized weighted negative binomial distribution, where *k* is number of tumors per mouse, $P_W(k)$ is the probability of *k*, Γ is the Gamma function, *M* is the radiation response function (above), *r* and *q* are parameters that describe the variance, and $Y = k + 1/r$:

$$P_w(k) = \frac{[(1 + r\,M)^{-Y}\,r^k\,M^{(k-1)}\,\Gamma(Y)\,(M + k\,q)]}{\left[\Gamma(1+k)\,\Gamma\left(\frac{1}{r}\right)\,(1+q)\right]}$$

Based on this, the **mean number of tumors per mouse (μ) is:**

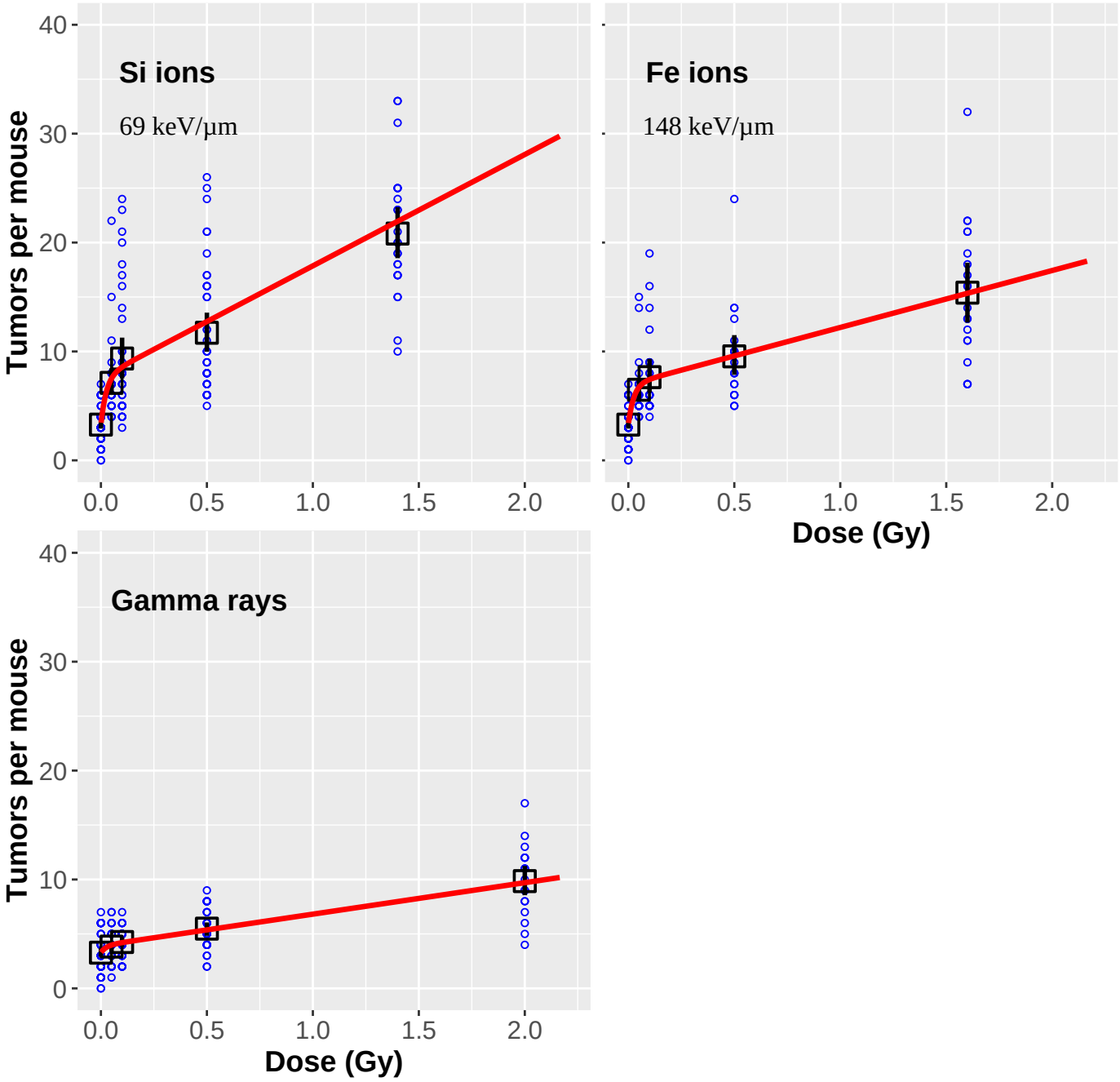
$$\mu = \frac{\left[M + q\left(1 + M\,(1+r)\right)\right]}{1+q}$$



Model Fits

Blue circles represent the number of tumors in individual mice.
Black squares and bars represent mean values and standard errors.
Red curves represent model fits.

A “bump” in tumor yield at low doses is attributed to NTE by the model.

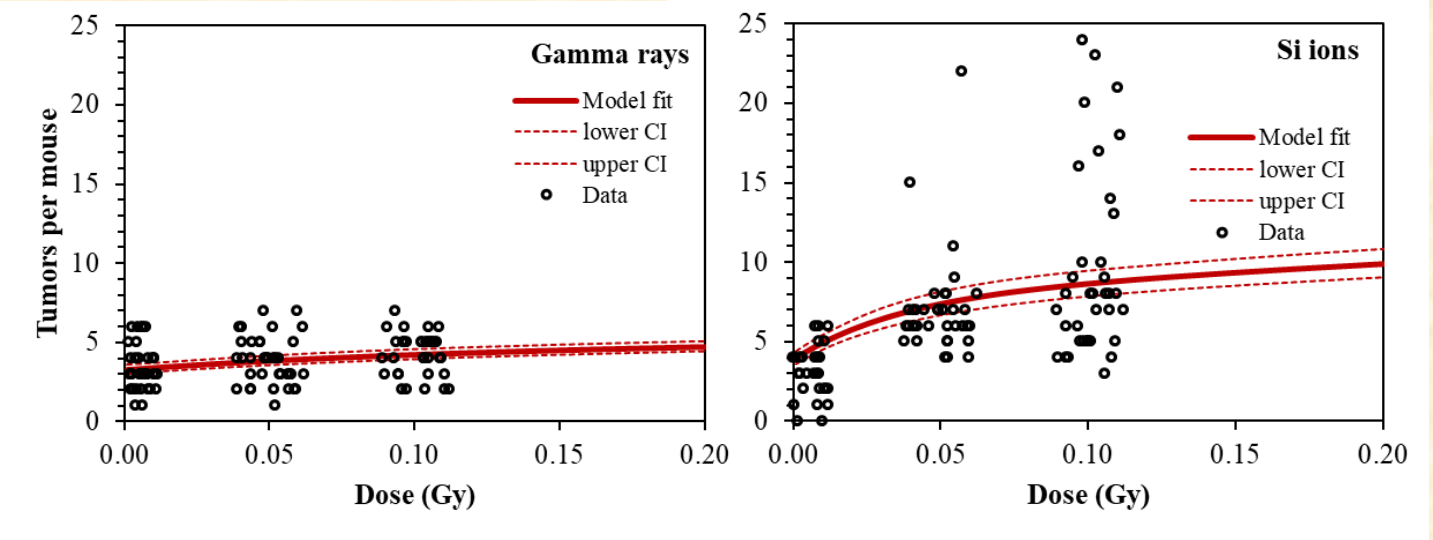


Two of the Si irradiated mice had >40 tumors (50 and 53), these points are not shown in the Si panel to improve visualization.

The dose response non-linearity at low doses is more prominent for Si and Fe ions.

Look More Closely at Low Doses

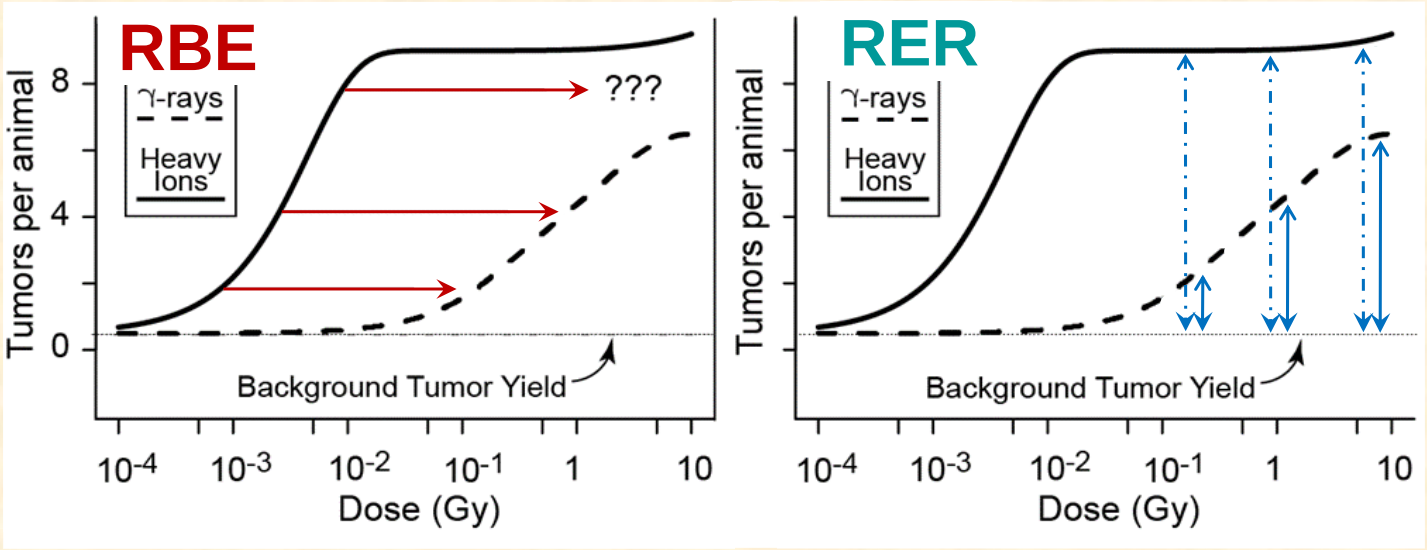
- ☑ Compare gamma rays (reference) with Si ions (most carcinogenic)



- ☑ Controls: mean = 3.28 tumors/mouse, SD = 1.63, var/mean = 0.81
- ☑ 0.05 Gy gamma rays: mean = 3.84, SD = 1.48, var/mean = 0.57
- ☑ 0.05 Gy Si ions: mean = 7.11, SD = 3.30, var/mean = 1.53
- ☑ 0.1 Gy gamma rays: mean = 4.26, SD = 1.36, var/mean = 0.42
- ☑ 0.1 Gy Si ions: mean = 9.35, SD = 5.38, var/mean = 3.10

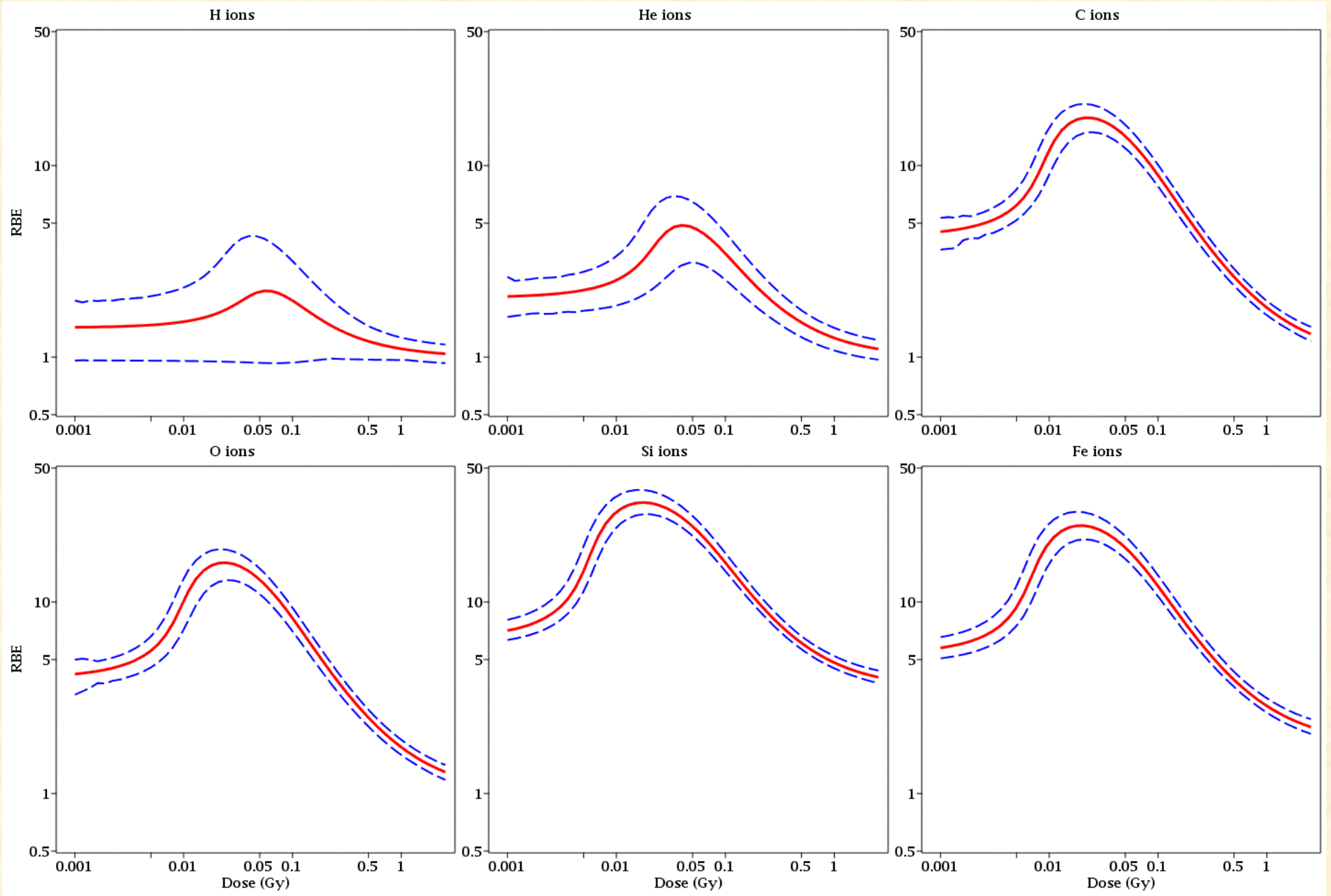
Metrics for Comparing Carcinogenic Effectiveness of Different Radiations

- ***RBE = Ratio of doses that produce equal effects***
- **Another way: Radiation Effects Ratio (RER), compares effects of two radiations *at the same dose***

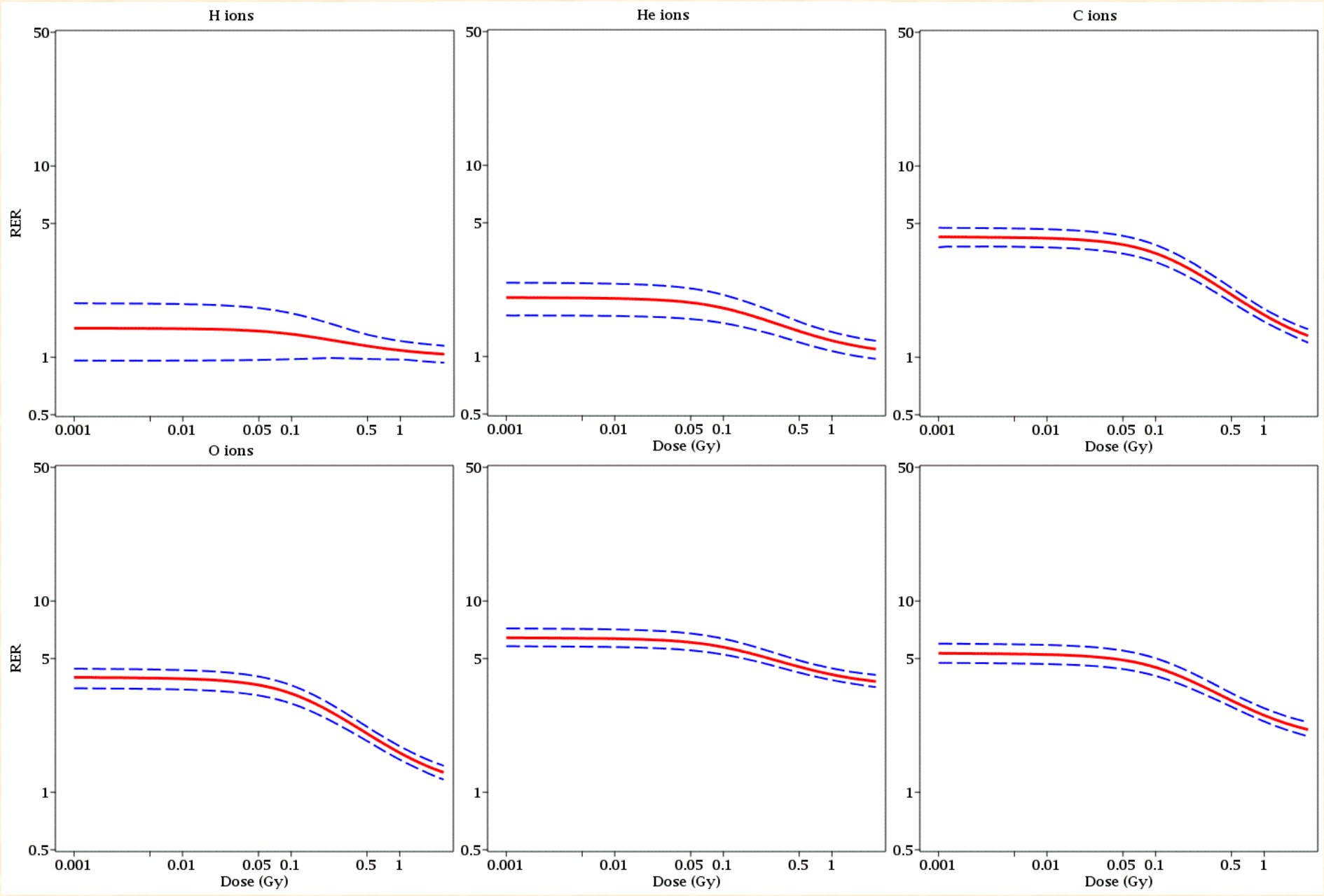


- **"Horizontal" vs "vertical" scaling**
- **If the dose responses are both linear, then RBE=RER**
- **RBE is not always possible to calculate (*e.g.* if dose responses plateau or decrease at high doses), but RER avoids this issue**

RBE estimates for mouse intestinal tumors



RER estimates



Example 2: Applying Similar TE + NTE Concepts to Modeling Space Radiation Induced Cognitive Dysfunction

I. Shuryak, D.J. Brenner, S.R. Blattnig, B. Shukitt-Hale, B.M. Rabin

- Radiation-induced cognitive dysfunction is an important risk for human exploration of distant planets like Mars.
- Although the mechanisms of radiation-induced CNS dysfunction are not yet fully understood and are being actively studied, non-targeted effects (NTE) may be involved in this phenomenon.
- Experimental evidence supporting this hypothesis: body-only exposure to space-relevant radiation, which does not traverse the brain, can nevertheless affect cognitive functioning in rodents.
- The molecular mechanisms of this phenomenon likely involve radiation-induced oxidative stress and neuroinflammation, which, in turn, affect neuronal function.

Data set: Novel object recognition

- We chose to analyze a large published data set on novel object recognition (NOR) testing in rats.
- The rats were exposed to multiple space-relevant radiation types (H, C, O, Si, Ti and Fe ions), covering wide ranges of linear energy transfer (LET) (0.22-181 keV/μm) and dose (0.001-2 Gy).
- NOR is a standard measure of cognitive performance in animal studies.
- The outcome variable in the analyzed data set was the fraction of time that a rat spent exploring the novel object (F_{nov}).
- We log-transformed this variable to create a more continuously distributed response variable:

$$\boldsymbol{R = -ln[F_{nov}]}$$

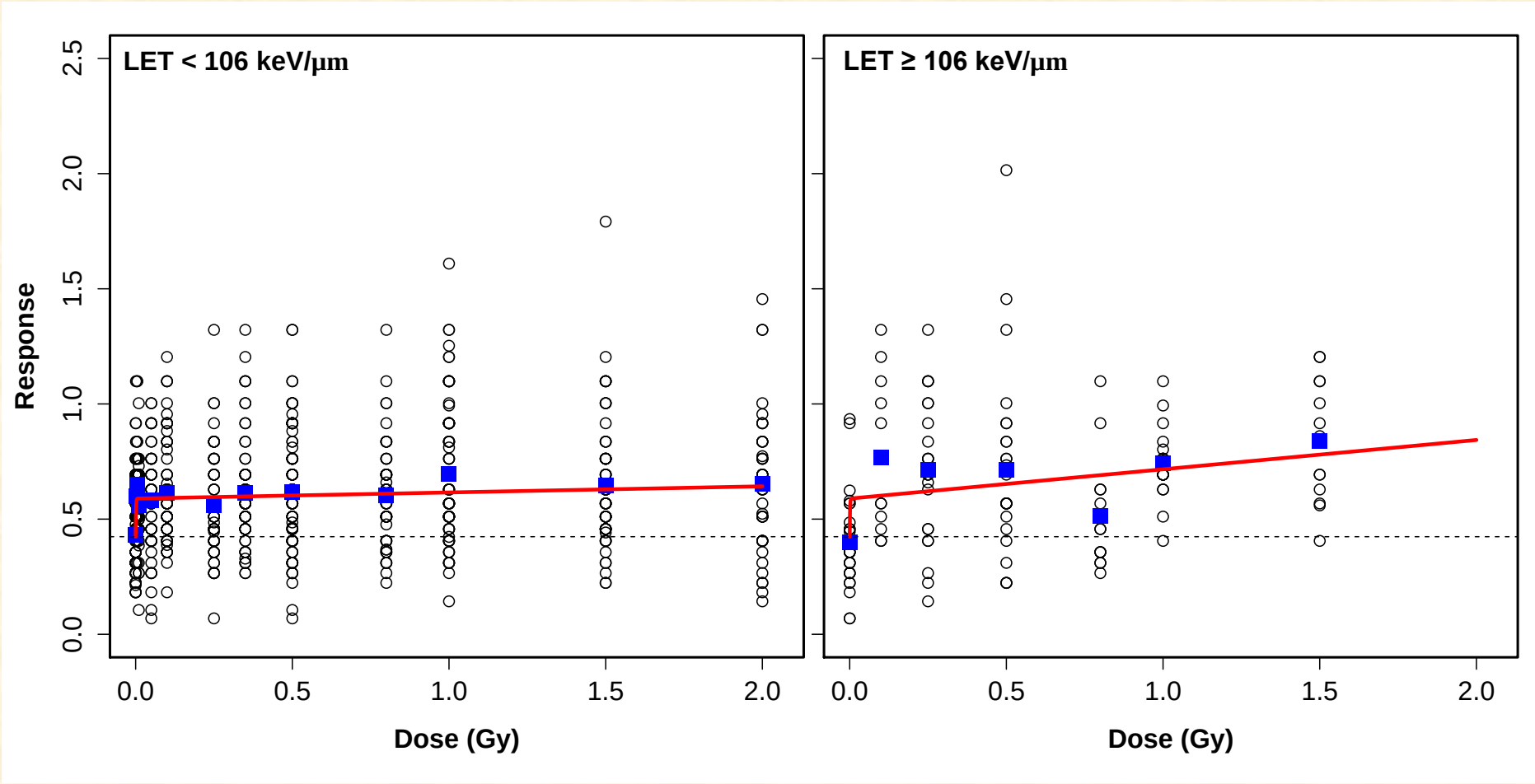
Modeling approaches

- We compared 18 dose response model variants based on TE/NTE concepts described above using the Akaike information criterion.
- **The strongest support was found for a model where NTE saturate at low doses (~0.01 Gy) and occur at all tested LETs, whereas TE depend on dose linearly with a slope that increases with LET.** The model structure is:

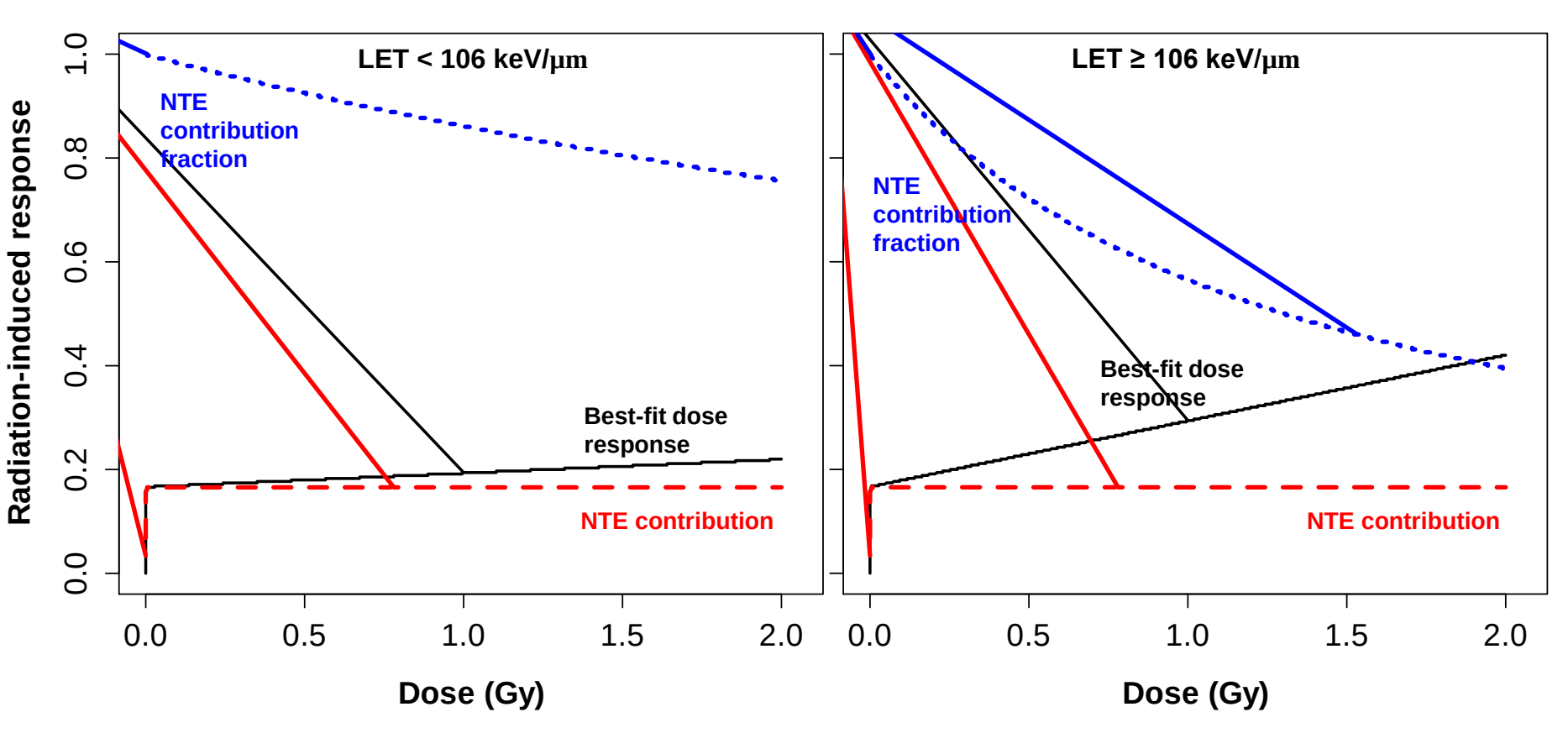
$$\boldsymbol{R = B + N\,(1 - \exp[-s\,D]) + \sum_{i=LMH,VH} T_i\,D_i}$$

- Here *D* is radiation dose, *R* is the response variable, *B* is background, *T* is a parameter for TE, *N* is a parameter for NTE, and *i* is the LET category (L=0.22, M=13-16, H=41-50, VH=106-181keV/μm).
- The NTE "slope" parameter *s* attained a very high value with a very large uncertainty, so we fixed it at 10^3 Gy^{-1}. This allows the response to rapidly increase and saturate at low doses, but retains the model's properties as a smooth function.
- Three other model variants had support values close to the best model (ΔAICc <6).The first two assume more detail for the linear TE slope variation by LET categories, and the last one assumes a quadratic TE dose response.

Best-supported model fits (red). Blue squares = mean response values. The model assumes that the TE dose response "slope" differs by LET category, whereas NTE occur at all LETs.



NTE contribution (absolute, red dashed curves, and fractional, blue dashed curves) to the dose response predictions (black curves) of the best-supported model. Baseline response in unirradiated rats (parameter B) was subtracted for improved visualization.



Some Thoughts About Other Endpoints: Cell Killing

I. Shuryak, M.N. Cornforth

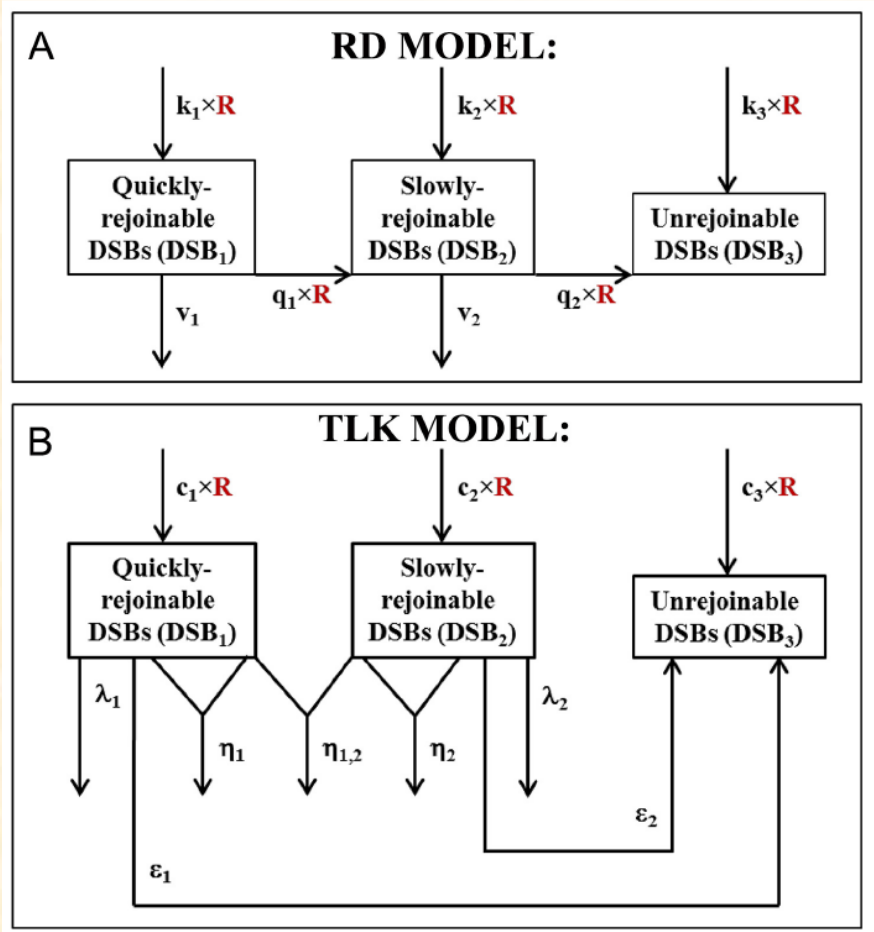
- Cell killing by radiation is commonly described by the linear quadratic (LQ) model, assuming a Poisson distribution of lethal events/cell.
- However, overdispersion of lethal events/cell (*i.e.* variance/mean >1) is known to occur for high-LET and sometimes even low-LET irradiation.
- After analyzing several cell killing and chromosome aberration data sets (Front Oncol. 2017 Dec 21;7:318; Int J Radiat Biol. 2021;97(1):50-59), we found that changing the error distribution (*e.g.* from Poisson to negative binomial), while keeping the LQ dose dependence for the mean, improved LQ model performance.
- **This approach improved estimation of the α parameter, which can produce more reliable predictions of low dose/dose rate effects that are of major concern for radiation protection.**

Cell type	DU145	CP3	U373MG	CHOAA8	Yeast	Yeast
Radiation type	x-rays (250 kVp)				x-rays (70 kVp)	^{241}Am α-particles
Poisson model	3.0×10^{-3}	6.5×10^{-5}	8.0×10^{-5}	0.532	2.0×10^{-16}	1.0×10^{-11}
NB model	0.253	0.468	0.184	0.130	5.8×10^{-6}	0.389
MNB model	0.319	0.427	0.230	0.136	2.5×10^{-6}	0.610
PLQ model	0.334	0.102	0.324	0.129	7.9×10^{-10}	2.5×10^{-4}
2C model	0.0909	2.89×10^{-3}	0.262	0.0728	~1.00	1.3×10^{-3}

Cell type		DU145[a]	CP3[a]	U373MG[a]	CHOAA8[a]	Yeast[b]	Yeast[b]
Poisson model parameters	**α** (dose^{-1})	**0.22**	**0.14**	**0.16**	**0.18**	**1.24**	**9.10**
	95% CIs	0.20	0.10	0.14	0.17	0.79	7.85
		0.24	0.18	0.18	0.20	1.70	10.38
	α/β (dose)	**18.59**	**3.22**	**8.04**	**10.04**	**0.46**	**1.63**
	95% CIs	14.87	2.28	6.14	8.37	0.29	0.86
		22.87	4.89	10.53	12.05	0.84	2.75
NB model parameters	**α** (dose^{-1})	**0.16**	**0.00**	**0.08**	**0.18**	**0.00**	**2.05**
	95% CIs	0.12	0.00	0.04	0.16	0.00	0.42
		0.20	0.05	0.12	0.20	0.11	3.65
	α/β (dose)	**5.70**	**0.00**	**1.68**	**9.84**	**0.00**	**0.04**
	95% CIs	3.15	0.00	0.88	8.20	0.00	0.02
		10.26	0.01	4.31	14.17	0.00	0.23

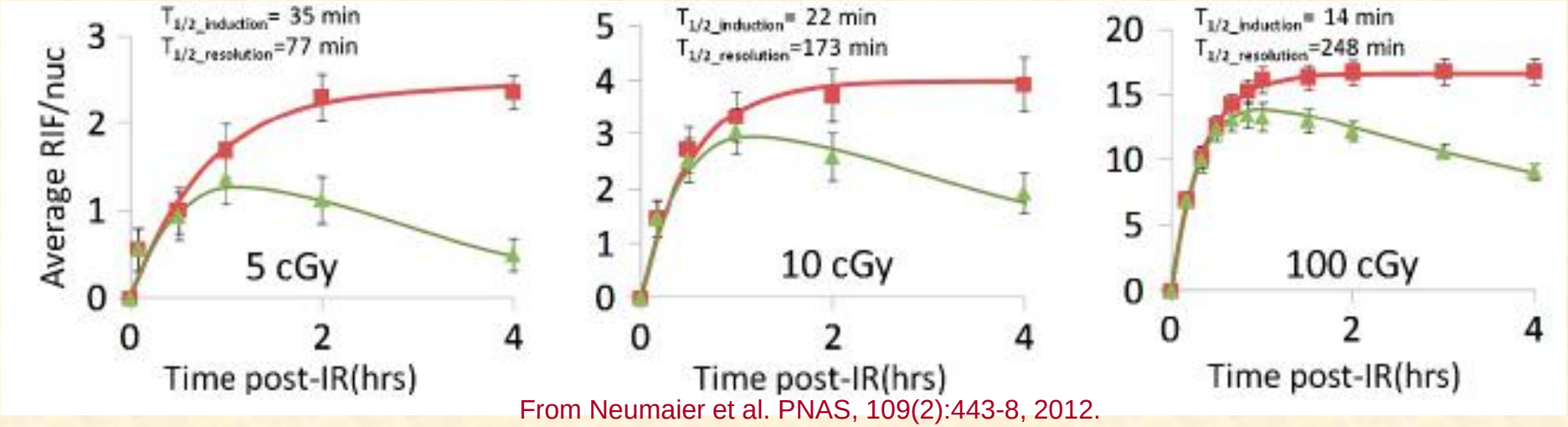
DNA double strand break (DSB) repair

- **There is some evidence that DSB repair pathway choice and rate(s) can depend on radiation dose / dose rate.**
- For example, this can be seen is yeast (*S. cerevisiae*) which mostly rely on homologous recombination (HR).
  - We analyzed yeast DSB rejoining data using a new radiation-dependent (RD) model for three DSB rejoining rate classes: quickly, slowly and unrejoinable
  - Radiation converts DSBs from one class to another
  - We used yeast data for 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
  - **The RD model described all tested low-LET and high-LET radiation data significantly better than the TLK model**



Shuryak, PLOS One, 2016.

- So, in yeast DSB rejoining is dose-dependent
- In mammalian cells the evidence is less clear, but some studies suggest this, which is potentially relevant for low dose radiation effect predictions



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

Analysis of chromatid-break-repair detects a homologous recombination to non-homologous end-joining switch with increasing load of DNA double-strand breaks

Mutation Research - Genetic Toxicology and Environmental Mutagenesis 867 (2021) 503372

Tamara Murmann-Konda [b], Aashish Soni [a,b,*], Martin Stuschke [a,c], George Iliakis [a,b,*]

"When G2-phase cells are irradiated, only about 10 % of the induced DSBs break the chromatids. At doses <2 Gy, HR is the main option in the processing of the subset of DSBs generating chromatid breaks and that a pathway switch at doses between 4–6 Gy allows the progressive engagement of c-NHEJ. "

Conclusions

- Mathematical models of radiation effects can have many forms and varying degrees of mechanistic detail
- Models can be quite useful for making predictions at low radiation doses / dose rates, where radiation effects are difficult to detect and measure
- In general, such models do not form a complete description of the complex biological system, but focus on specific aspects of radiation effects
- The simplifying approximations provide insights into which components of the system may be responsible for a particular behavior (*e.g.* NTE vs TE)
- These insights can potentially generate testable hypotheses and improve scientific understanding, as well as accuracy of predictions
- Thank you very much for your interest!