Multiscale Modeling of Radiation Response
Effects of Radiation Quality and Hypoxia

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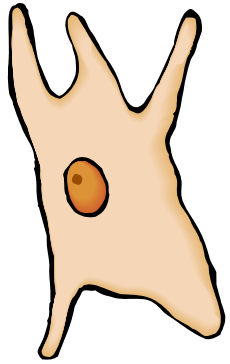


Presented at the

4th Modelling of Tumors (MOT) 2012 Meeting (Aug 2-4)

Date and Time: Saturday August 4, 9:00 to 10:00 am
Location: Hotel Grand Chancellor, 65 Hindley Street, Adelaide, South Australia
Website: *http://www.rah.sa.gov.au/cancer/mot.php*

Outline

As is sometimes done in Hollywood, the "Story" will be told from the end to beginning…

- **Literature Citations**
- **Conclusions**
- **Results**
- **Methods**
- **Future Direction**
- **Acknowledgements**

Presenter has no conflicts of interest to disclose

Literature Citations

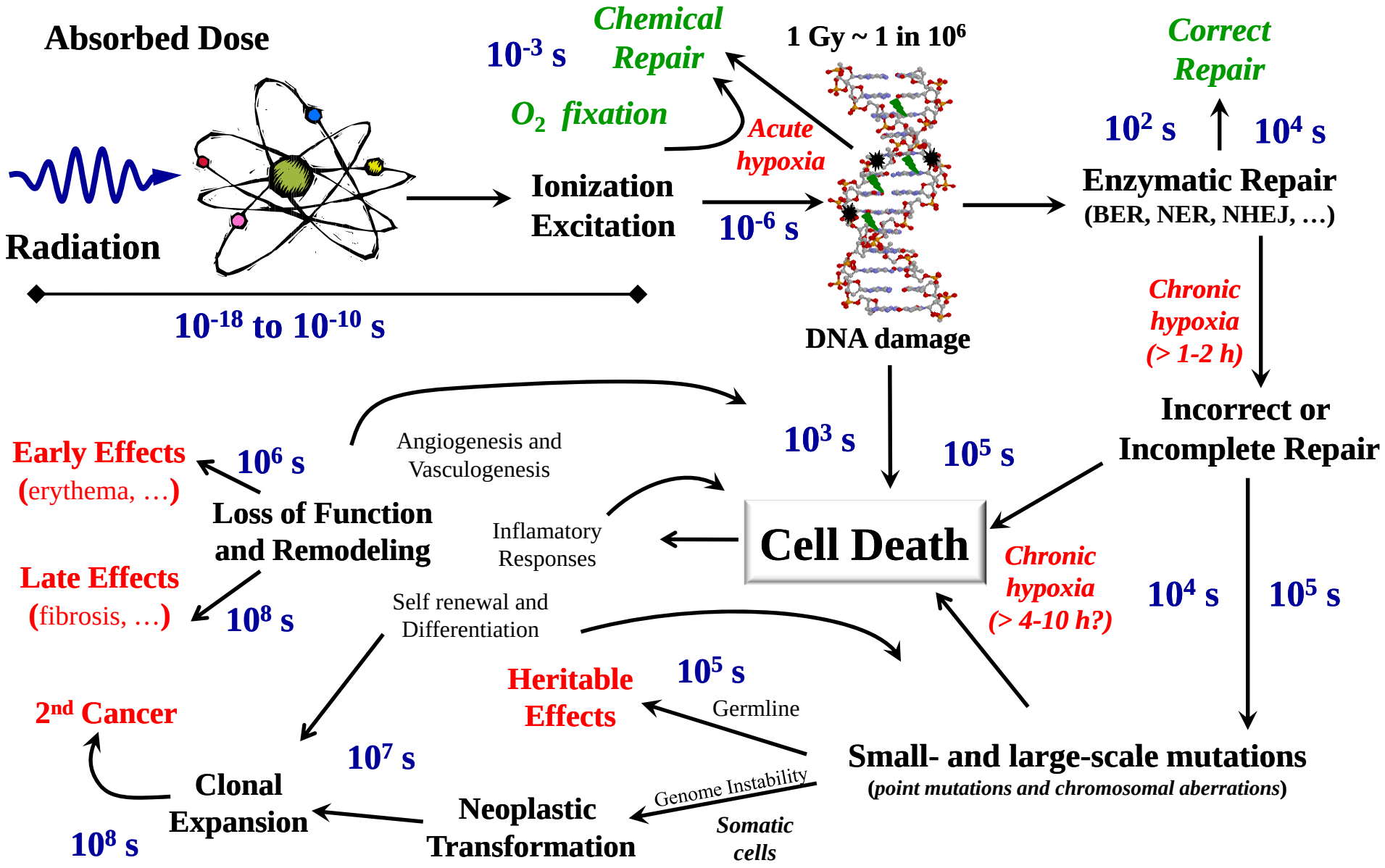
- M.C. Frese, V.K. Yu, R.D. Stewart, D.J. Carlson, A Mechanism-Based Approach to Predict the Relative Biological Effectiveness of Protons and Carbon Ions in Radiation Therapy, *Int. J. Radiat. Oncol. Biol. Phys., 83, 442-450 (2012).*
- R.D. Stewart, V.K. Yu, A.G. Georgakilas, C. Koumenise, J.H. Park, D.J. Carlson, Effects of Radiation Quality and Oxygen on Clustered DNA Lesions and Cell Death, *Radiat. Res. 176*, 587-602 (2011)
- D.J. Carlson, R.D. Stewart, V.A. Semenenko and G.A. Sandison, Combined use of Monte Carlo DNA damage simulations and deterministic repair models to examine putative mechanisms of cell killing. *Rad. Res. 169*, 447-459 (2008)
- Y Hsiao and R.D. Stewart, Monte Carlo Simulation of DNA Damage Induction by X-rays and Selected Radioisotopes. *Phys. Med. Biol. 53, 233-244 (2008)*
- V.A. Semenenko and R.D. Stewart. Fast Monte Carlo simulation of DNA damage formed by electrons and light ions. *Phys. Med. Biol.* **51**(7), 1693-1706 (2006)
- V.A. Semenenko and R.D. Stewart. Monte Carlo Simulation of Base and Nucleotide Excision Repair of Clustered DNA Damage Sites. II. Comparisons of Model Predictions to Measured Data. *Radiat. Res. 164, 194-201 (2005)*
- V.A. Semenenko, R.D. Stewart, E.J. Ackerman. Monte Carlo Simulation of Base and Nucleotide Excision Repair of Clustered DNA Damage Sites. I. Model Properties and Predicted Trends. *Radiat. Res. 164, 180-193 (2005)*
- V.A. Semenenko and R.D. Stewart. A fast Monte Carlo algorithm to simulate the spectrum of DNA damages formed by ionizing radiation. *Radiat Res. 161(4), 451-457 (2004)*
- R.D. Stewart, W.E. Wilson, J.C. McDonald, and D.J. Strom, Microdosimetric Properties of Ionizing Electrons in Water: A Test of the PENELOPE code system. *Phys. Med. Biol. 47(1), 79-88 (2002)*

Conclusions

- **We have successfully developed a multiscale system of *Monte Carlo* and *deterministic* models to link absorbed dose to reproductive cell death**
- **Captures many of the quantitative and qualitative features of cell survival curves**
  - Relative biological effectiveness (RBE), acute hypoxia, dose, dose rate and fractionation effects included (*cellular and sub-cellular effects*)
  - Bystander effects, adaptive responses, and many other (*larger-scale, multi-cellular and tissue*) effects neglected in current simulations

All models are incomplete (*wrong*) but some are useful…

Physics → Chemistry → Biology → Clinic



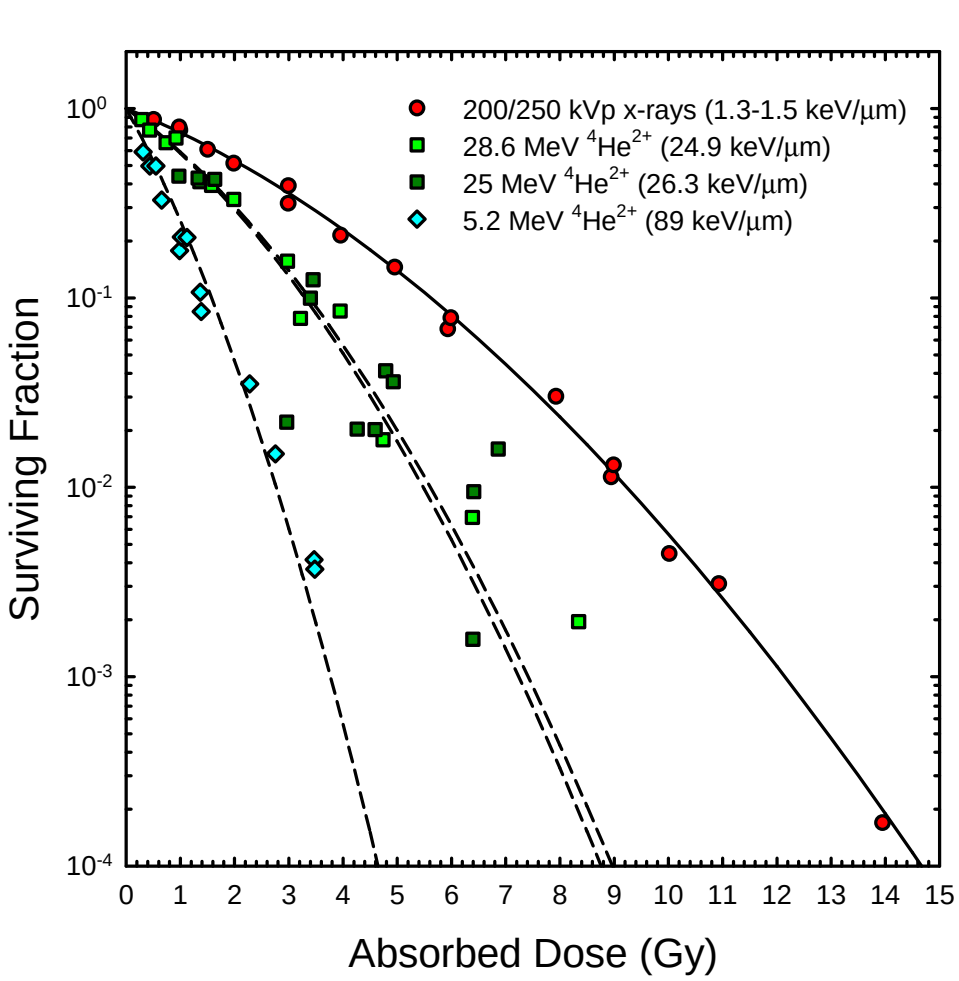
Advantages of a Multiscale Approach

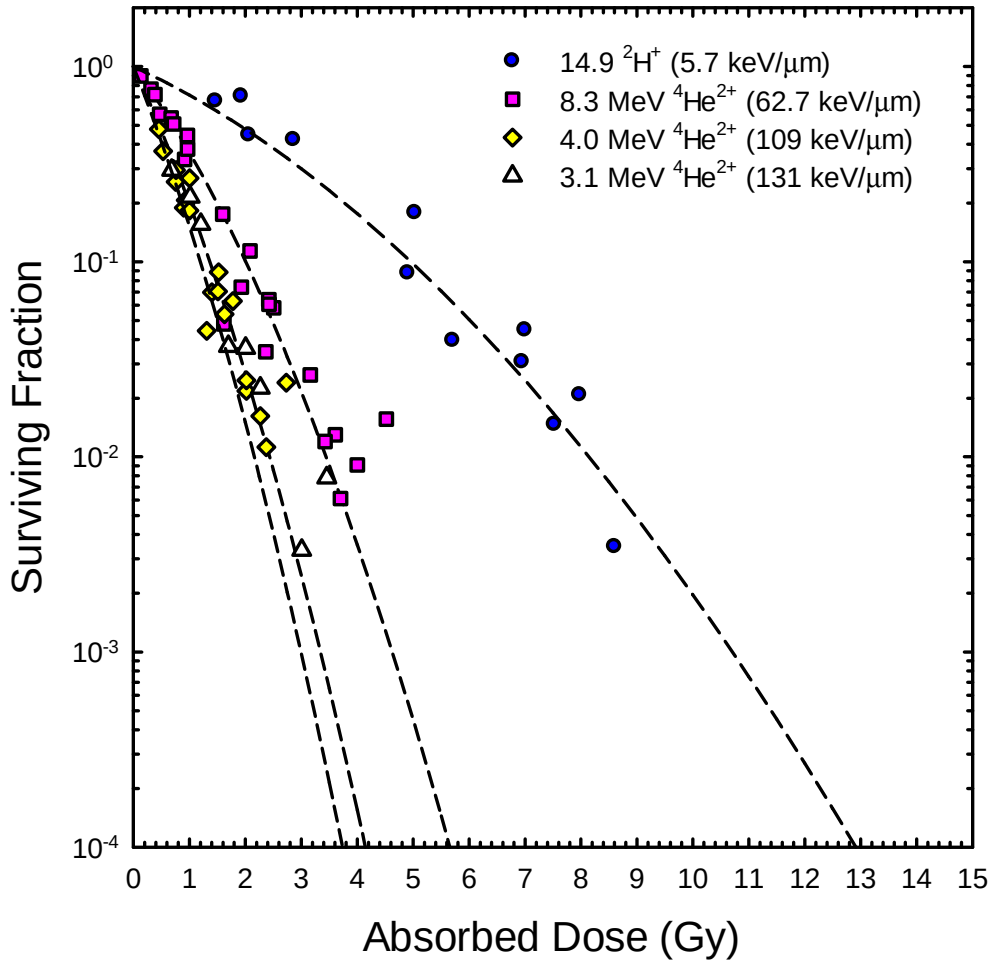
- **Modeled mechanisms at different levels in biological hierarchy can be independently tested against measured *in vitro* and *in vivo* data**
  - **Exploits idea that different biological endpoints are observable (*measurable*) on very different time scales after irradiation**
- **Proposed system of models ultimately has just two *critical* cell- or tissue specific adjustable parameters**
  - 2 parameters related to biological processing of DNA damage (***critical***)
  - 1 parameter related to dose rate effects (*repair half-time*) and one related to the microdosimetric deposition of energy within the cell nucleus (*most important for short-range, high LET radiations*)
  - All four adjustable parameters are independent of dose, dose rate, radiation quality (LET), and oxygen concentration

Why Might this be Useful?

- **Critical biological parameters can be estimated from survival data for low LET radiations**
  - Use parameters unchanged in simulations for higher LET radiations under the *same or different* oxygen concentrations
- **Easy to incorporate RBE and O_2 information from simulations into isoeffect (**BED, EUD, …**) and outcome (**TCP and NTCP**) calculations**
- **Hypothesis**
  - For the endpoint of reproductive death, *in vitro* and *in vivo* radiation sensitivity mainly differ because of differences in the way cells *in vitro* and *in vivo* process and/or express the initial sub-cellular damage

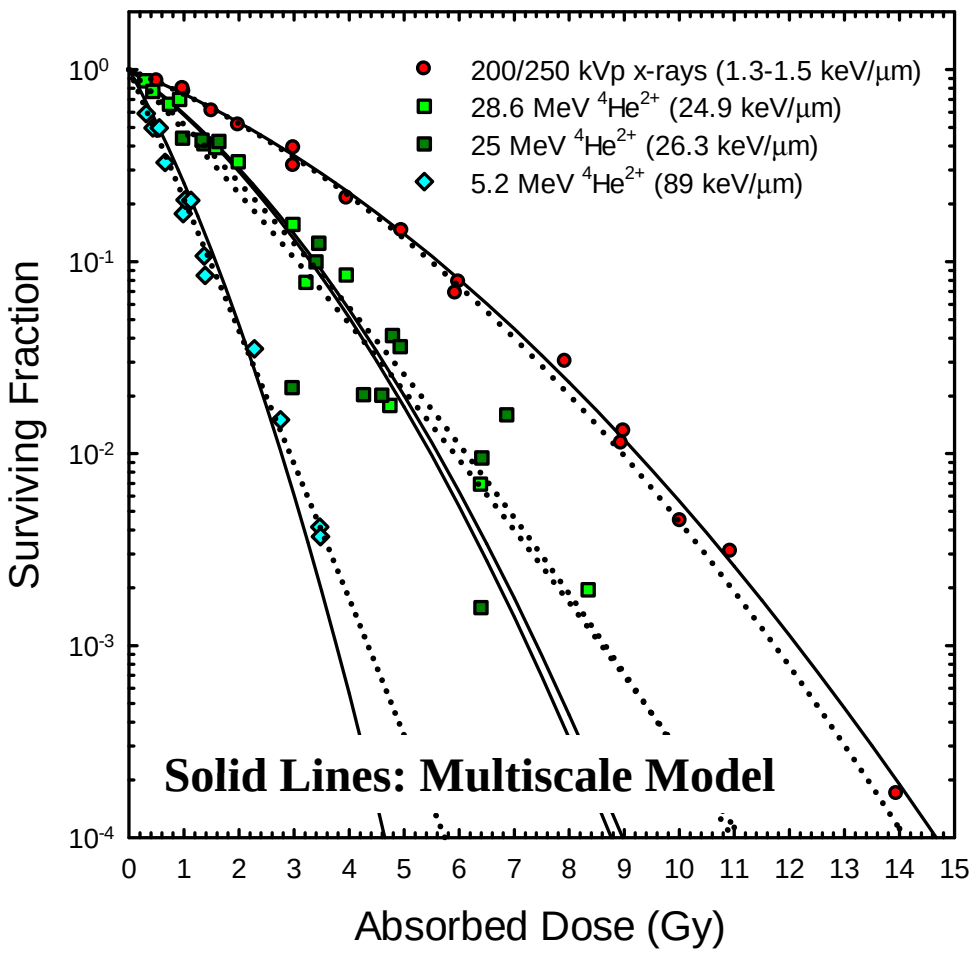
Results-1 Human Kidney T1 Cells (*aerobic*)

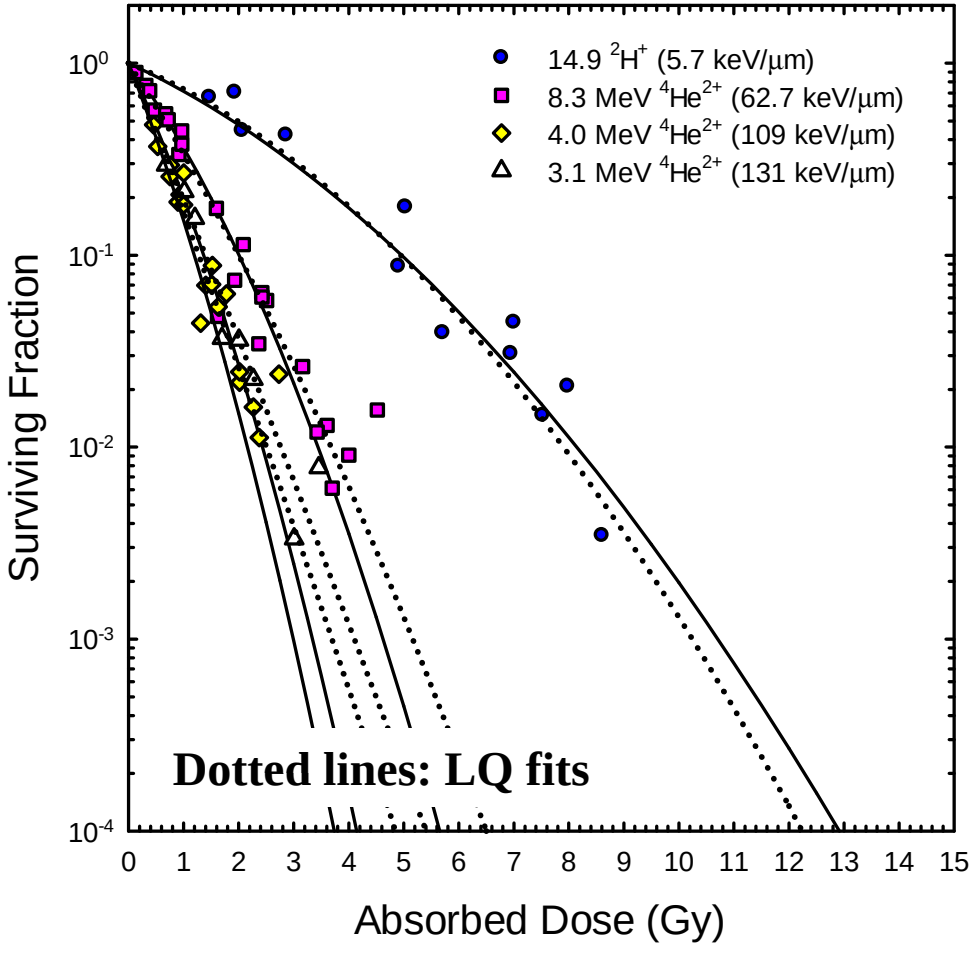




In vitro irradiation of T1 cells by selected ions (Barendsen circa 1960-1966). Simulation parameters: $\theta = 3.07\times10^{-2}$ Gbp/DSB, $\kappa = 7.05\times10^{-4}$ Gbp/DSB, $\tau = 2$ h, ndia=3.5 μm. Equivalent x-ray LQ parameters: α_X=0.265 Gy^{-1}, α/β_X=10.1 Gy

Results-1 Comparison to LQ fits (*aerobic*)





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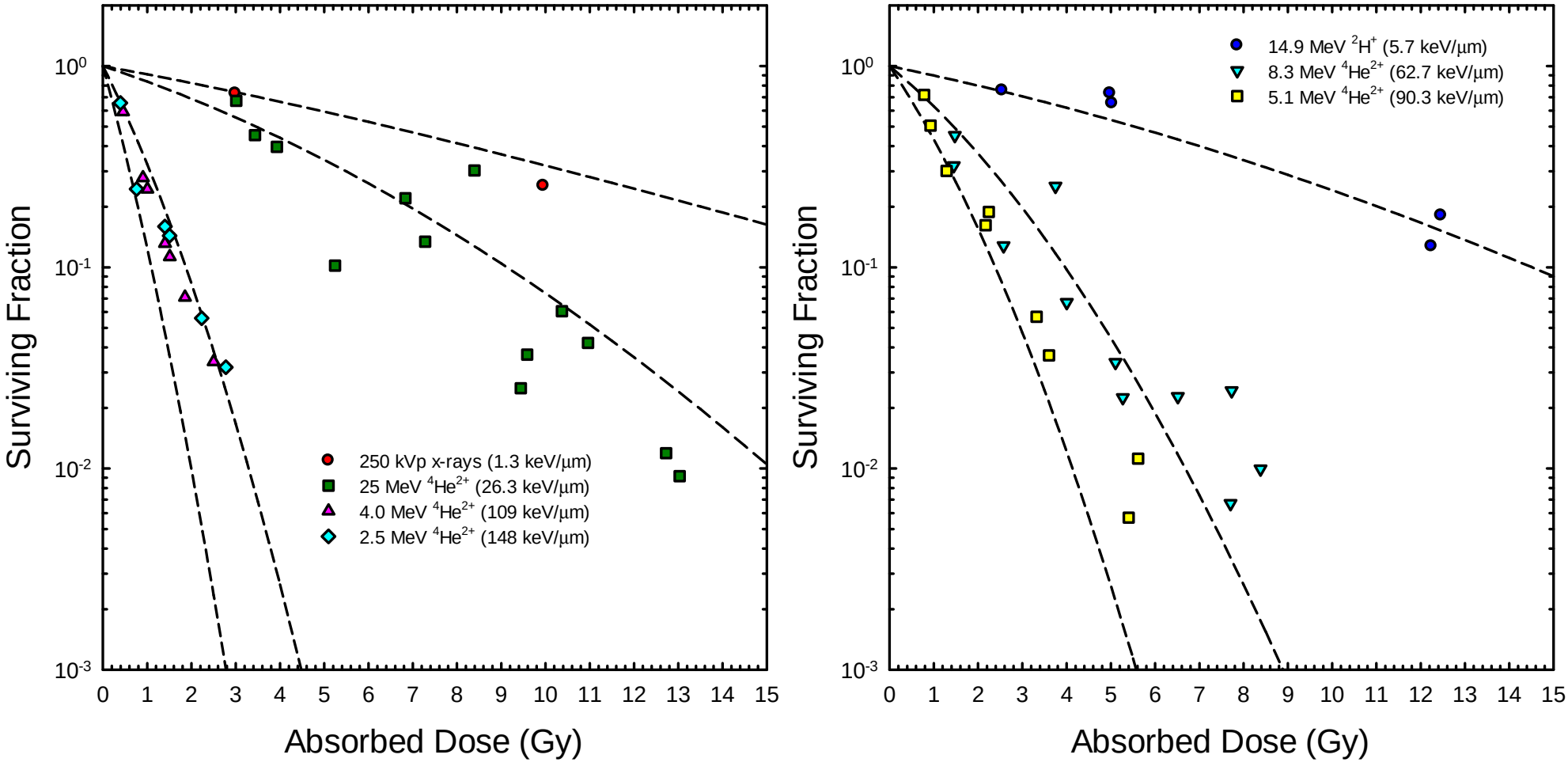
Results-1a Human Kidney T1 Cells (*hypoxic*)



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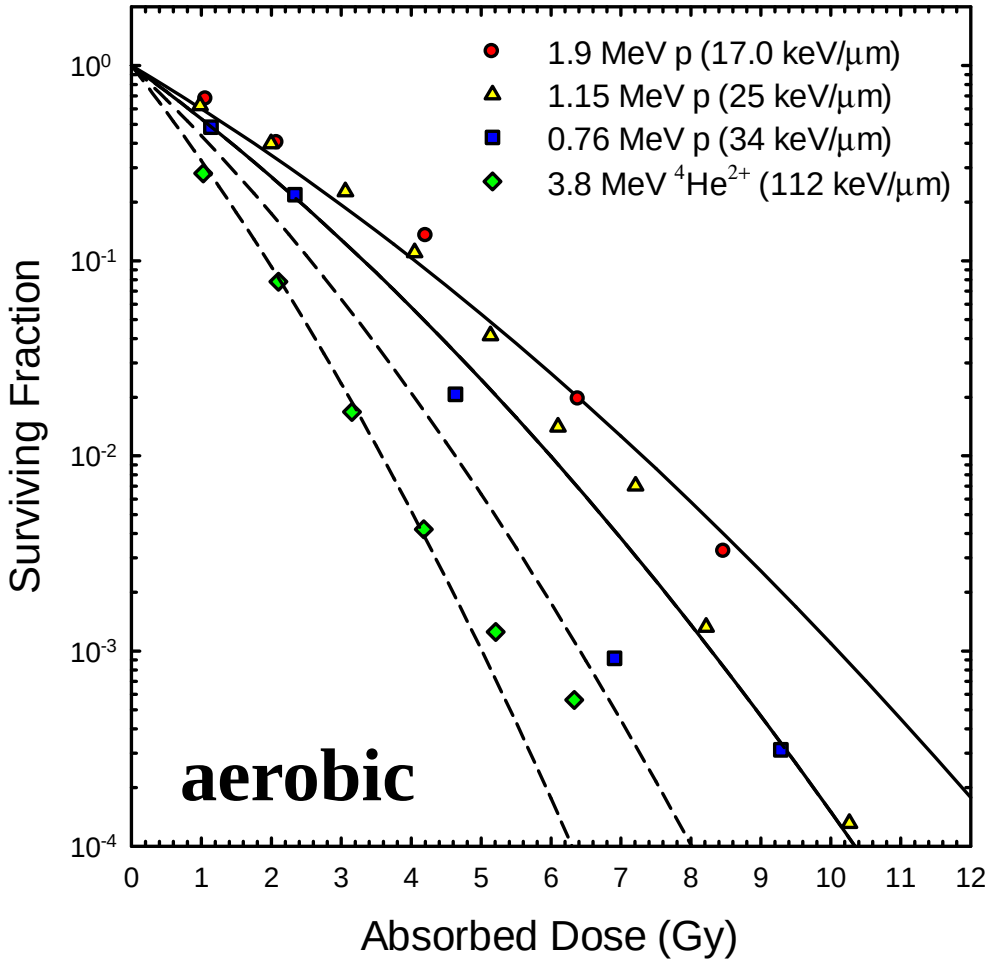
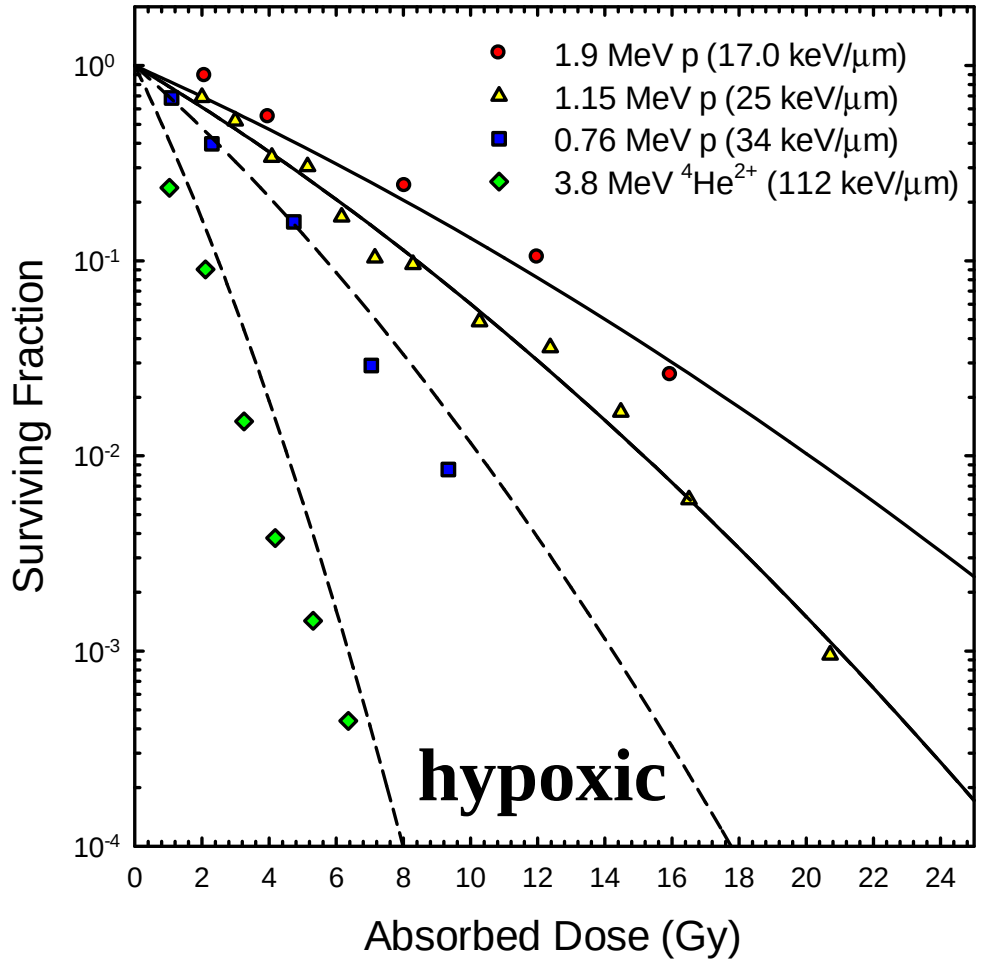
Results 1 - Some Observations

- **Direct LQ fits to survival data are comparable to fits obtained from the multiscale model. But…**
  - LQ fits: 15 x 2 parameters = 30 adjustable parameters (*one set for each particle type, energy and oxygen condition*).
  - Multiscale model: 2 adjustable parameters (θ *and* κ), which can be estimated from x-ray cell survival data for aerobic conditions
- **For short-range (*higher LET*) particles, direct LQ fits to cell survival data are sensitive to**
  - Uncertainties in dosimetry
  - Experimental artifacts in the measured data (e.g., “floaters”)
- **Global (*simultaneous*) fits of the multiscale model are possible but produce modest improvements in quality of fit.**

Results-2 V79 Cells (protons and $^4He^{2+}$)



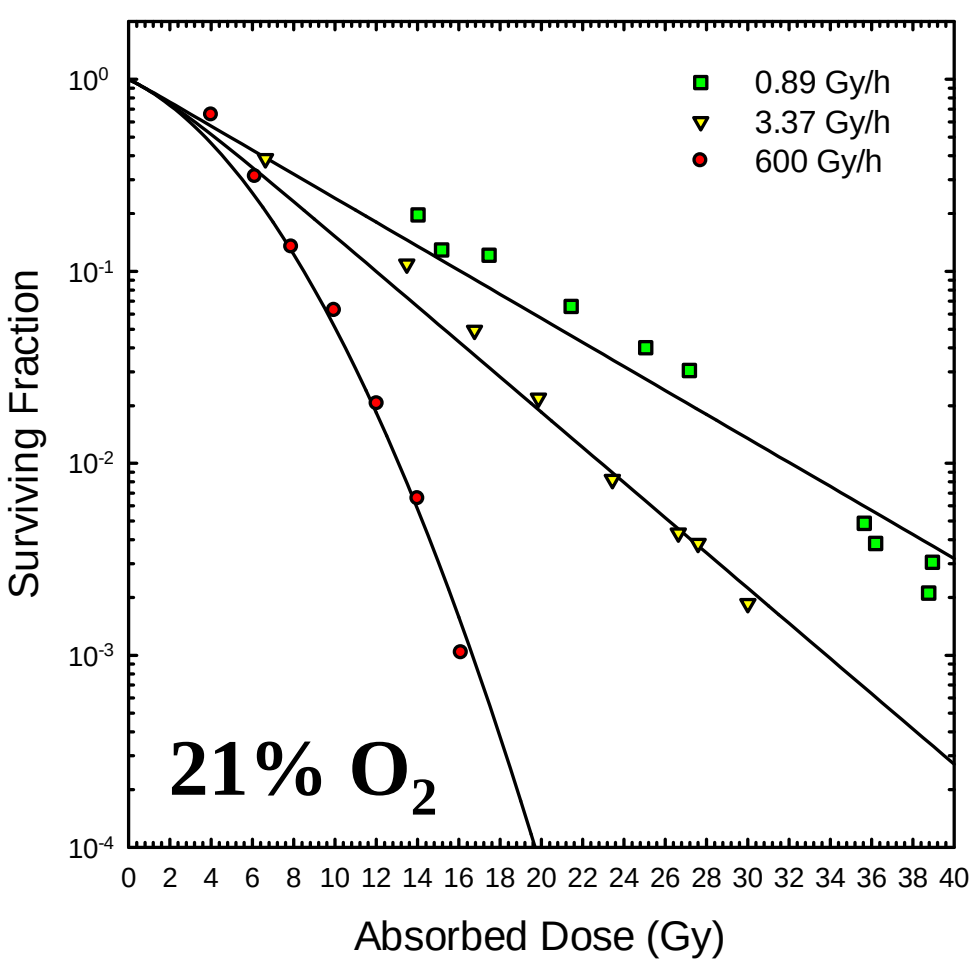


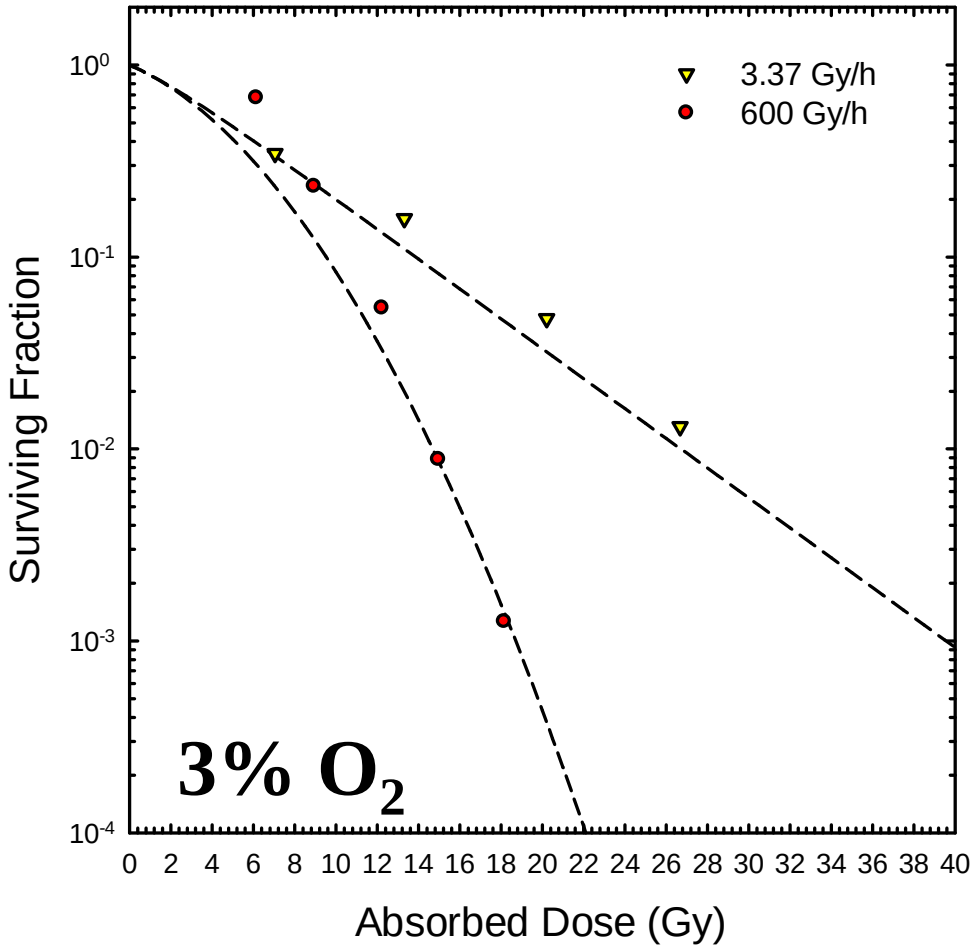
In vitro irradiation of V79 cells under aerobic and hypoxic conditions by selected ions (Prise *et al.* IJRB **58**, 261-277 1990). Simulation parameters: $\theta = 3.71\times10^{-2}$ Gbp/DSB, $\kappa = 2.32\times10^{-4}$ Gbp/DSB, $\tau = 2$ h, ndia = 4 µm.

Results 2 - Some Observations

- **Can perform simultaneous fits to aerobic and hypoxic data for one or more particle types**
  - For the smaller, often noisy, datasets common for higher LET radiations, simultaneous fits to multiple particle types provide more accurate estimate of parameters than fits to data for a single particle type.
- **Anecdotal testing of the model suggests that estimates of κ parameter (**related to β in the LQ**) are more accurate when survival data for low LET radiations available**
  - Dosimetry more accurate for low LET radiations than for high LET radiations
  - Low LET radiations not so sensitive to “floaters” and other experimental artifacts
  - Datasets usually larger for low LET radiations than high LET radiations

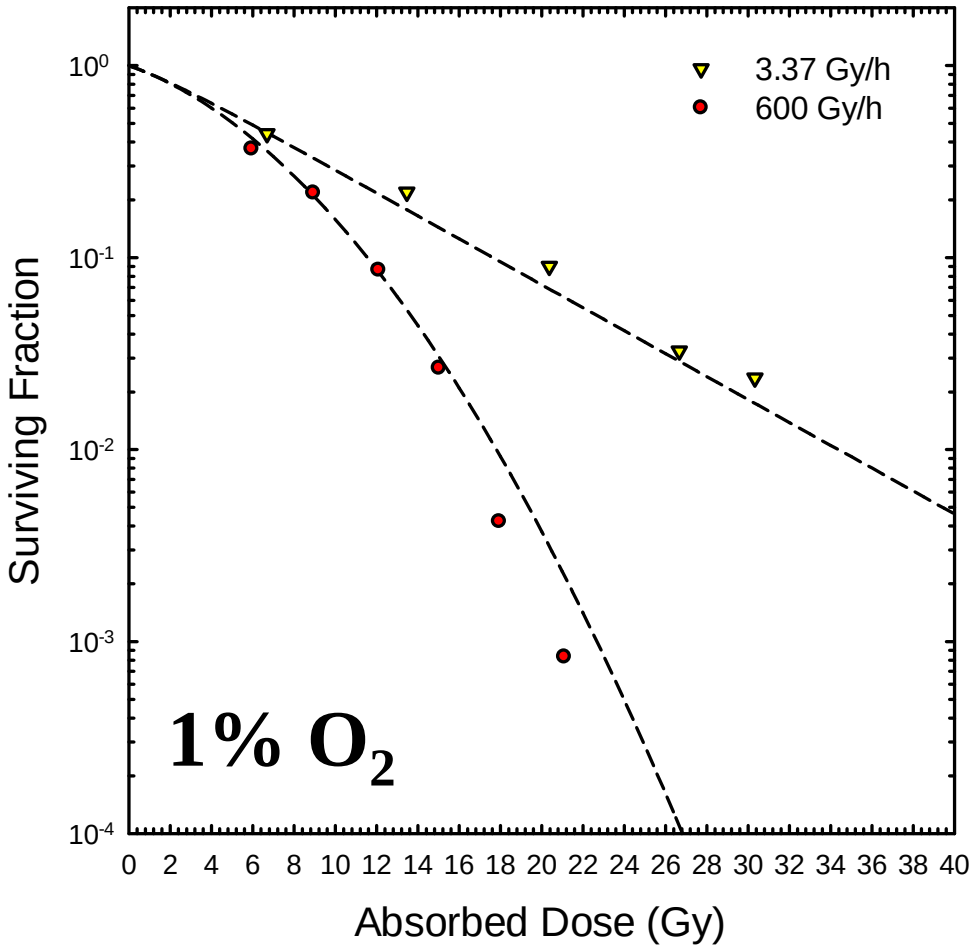
Results 3a - Dose Rate and Hypoxia (low LET)

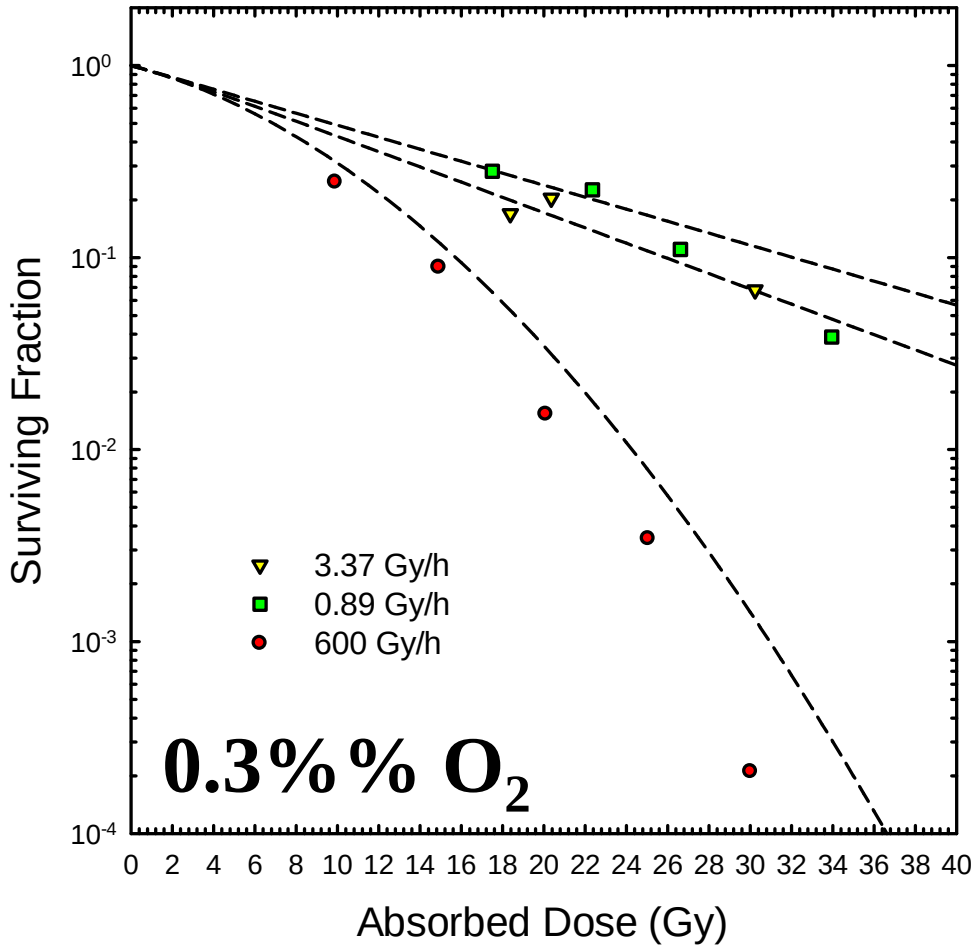




In vitro irradiation of V79 cells by 10 MV x-rays or ^{137}Cs γ-rays under aerobic and hypoxic conditions by selected ions (Spiro *et al.* BJR **58**, 357-363 1985). Simulation parameters: $\theta = 1.48\times10^{-2}$ Gbp/DSB, $\kappa = 5.42\times10^{-4}$ Gbp/DSB, $\tau = 0.523$ h, ndia = 3.5 μm.

Results 3b - Dose Rate and Hypoxia (low LET)





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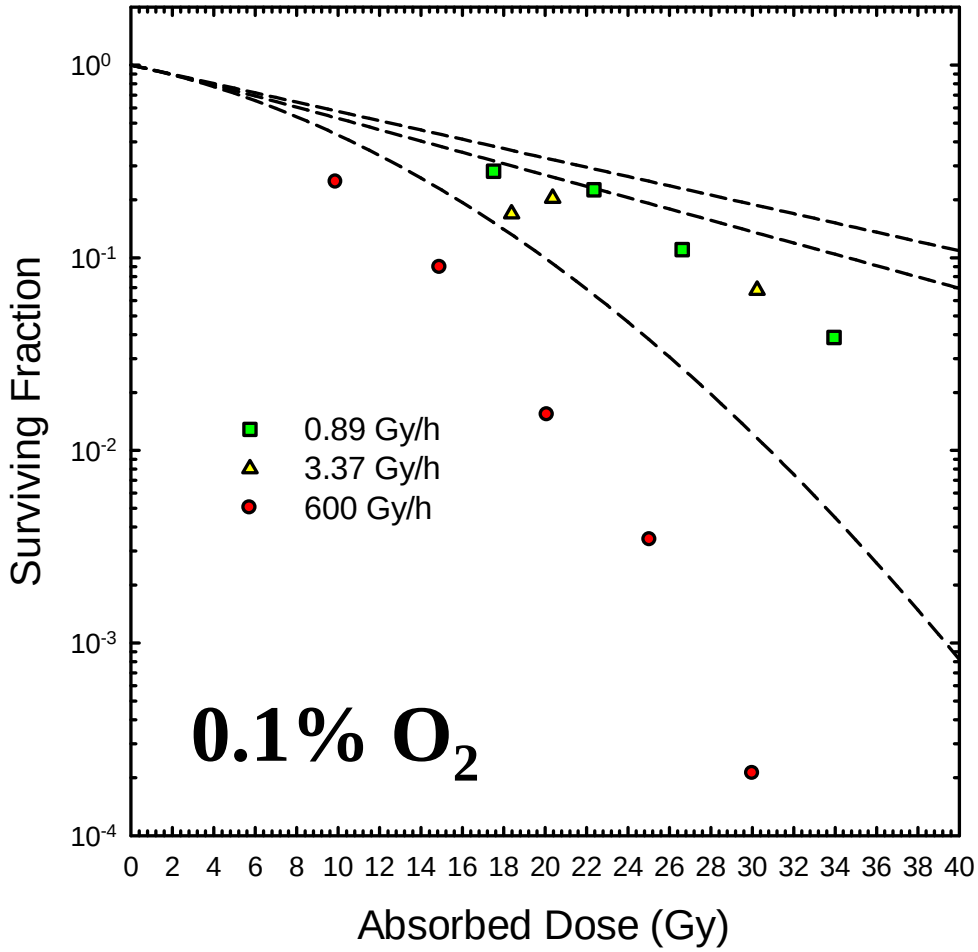
Results 3c - Dose Rate and Hypoxia (low LET)



Poor agreement for extreme hypoxia may be due to a slowing of repair process (acute vs chronic hypoxia**) or modulation of cell death modes not related to DNA damage induction** (plating efficiency substantially reduced under extreme hypoxia)

In vitro irradiation of V79 cells by 10 MV x-rays or ^{137}Cs γ-rays under aerobic and hypoxic conditions by selected ions (Spiro *et al.* BJR **58**, 357-363 1985). Simulation parameters: $\theta = 1.48\times10^{-2}$ Gbp/DSB, $\kappa = 5.42\times10^{-4}$ Gbp/DSB, $\tau = 0.523$ h, ndia = 3.5 μm.

Overall Summary of Results

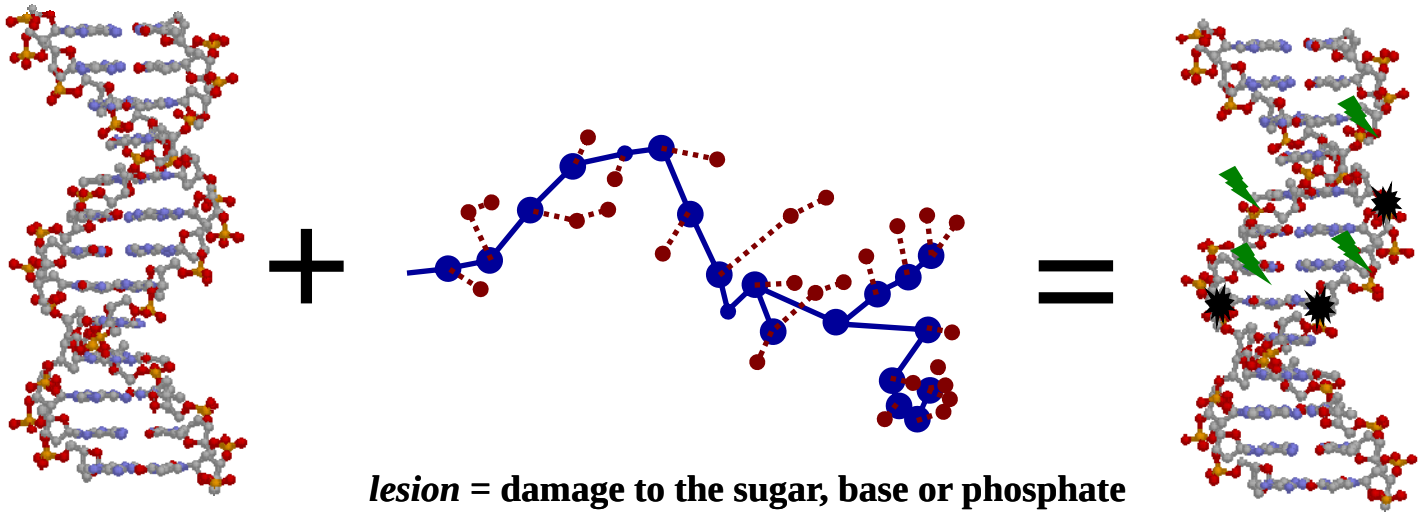
- **Model appears to have substantial predictive power**
  - Fit model to low LET survival data under aerobic conditions
  - Predict cell survival for other types of radiation and oxygen conditions
- **Accuracy of model predictions can be improved somewhat by fitting the model to data for multiple particle types and/or O_2 conditions**
  - **Such datasets are available *in vitro* but scarce for *in vivo* models (**including humans ;**)**
- **May need to incorporate a model for the effects of reduced oxygen on the rate of damage repair and/or modulation of cell death modes (**e.g., apoptosis vs mitotic death**)**

Methods

- **Monte Carlo Damage Simulation (MCDS)**
  - Effects of LET and Oxygen on DNA damage induction
  - Microdosimetry (lineal energy, frequency-mean specific energy, CSDA range)
- **Repair-Misrepair-Fixation (RMF) Model**
  - Motivated by the breakage and reunion theory of chromosomal aberrations
  - DNA damage induction linked to cell killing through a couple system of deterministic non-linear differential equations
    - Cell survival curves are LQ for low doses and become linear at high dose
  - RMR (CA Tobias) and LPL (S Curtis) models (circa 1985) are special cases of the RMF
    - Compound Poisson distribution for damage induction (RMF) instead of Poisson
  - As with the RMR and LPL, the linear-quadratic (LQ) is a low dose or low dose rate approximation for the RMF.

Clustered DNA lesions

Groups of several DNA lesions within one or two turns of the DNA are termed *clustered DNA lesions**



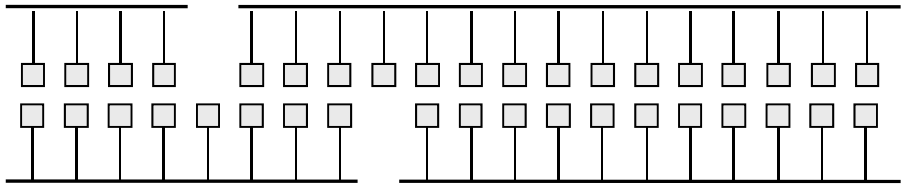
lesion = damage to the sugar, base or phosphate group of a single nucleotide

* Clustered DNA lesions are also referred to as *locally multiply damaged sites* (LMDS), *multiply damaged sites* (MDS) or just "*clusters*"

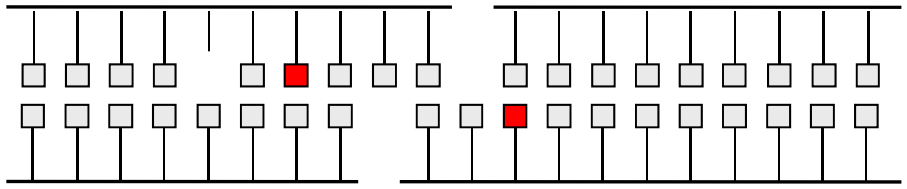
Interesting Trivia: Over 10^{12} (!) possible types of clustered DNA lesion, i.e., the number of possible ways a 10 bp segment of DNA (*20 nucleotides*) can be damaged is on the order of $4^{20} = 10^{12}$ possible types of cluster. Most of the DNA clusters formed by ionizing radiation, including single- and double-strand breaks, are composed of 3 or more individual lesions.

MCDS – General Features and Capabilities (1)

Developed to simulate number and small-scale spatial distribution of lesions forming clusters ("*nucleotide-level maps*")



Simple DSB (*2 lesions*)



Complex DSB (*5 lesions*)

- **Individual particles or arbitrary mixtures of charged particles up to and including ^{56}Fe (*new in 2011*)**
  - **Simulate damage from neutral particles using the distribution of secondary charged particles (**e.g., see Hsaio and Stewart, PMB **53**, 233-244, 2008**)**

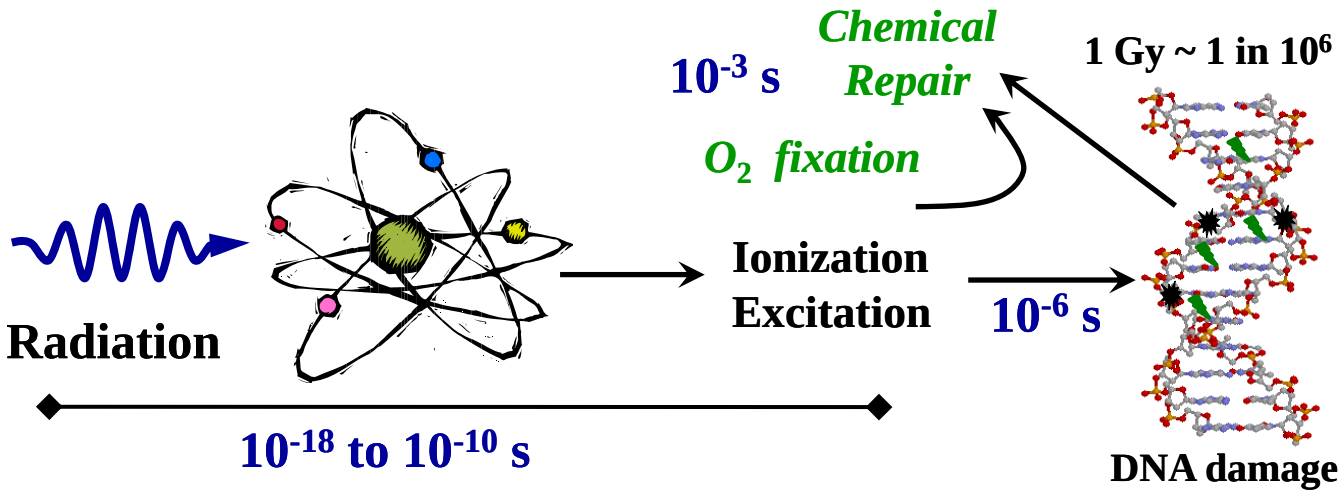
Additional Information and Software Available at

http://faculty.washington.edu/trawets/mcds/

"trawets" = "stewart" backwards

MCDS – General Features and Capabilities (2)

- **Simulates the effects on cluster formation of O_2 fixation and chemical repair (*new in 2011*) – "*oxygen effects*"**



First and only (*at present*) MC simulation to account for the effects of oxygen concentration on clusters

MCDS – General Features and Capabilities (3)

- **Particle and Dosimetric Information (*new in 2011*)**
  - **Stopping power in water, CSDA range, absorbed dose per unit fluence, mean specific energy, energy imparted per radiation event, and lineal energy**

Particle Type	Kinetic Energy		$S - S_{rad}$ (keV/μm)	CSDA Range (μm)	$\bar{z}_F$ (Gy)	
	MeV	MeV/u			MCDS	Analytic
e^-	2.56×10^{-5}	–	21.13	2×10^{-3}	$< 10^{-11}$	0.17
^{1}H	6.47×10^{-3}	6.47×10^{-3}	34.2	0.28	$< 10^{-4}$	0.29
$^{4}He^{2+}$	0.294	7.35×10^{-2}	186	2.70	0.14	1.53
$^{12}C^{6+}$	14.8	1.23	612	21.13	5.32	5.08
$^{16}O^{8+}$	38.1	2.38	711	42.03	6.01	5.86
$^{20}Ne^{10+}$	78.4	3.92	792	73.14	6.60	6.50
$^{56}Fe^{26+}$	1750	31.3	1148	963.7	9.35	9.34

Analytic Formula: $\bar{z}_F = 0.204\left[S - S_{rad}\right] / \rho d^2$

Chemical Basis of the Oxygen Effect

Competition between oxygen fixation and chemical repair modeled in the MCDS using a scheme that mimics the pathways suggested by von Sonntag (2006)**)**

(*1***) DNA + ionizing radiation → DNA lesion (***biochemical repair required***)**

(*2***) DNA + ionizing radiation → DNA· (***various***)**

Lesions and DNA radicals formed through direct and indirect interaction mechanisms

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(*3***) DNA· + O_2 → DNA-O_2 (***"oxygen fixation" – biochemical repair required***)**

(*4***) DNA· + RSH → DNA (***"chemical repair" – restoration of the DNA****)**

(*5***) DNA· → DNA lesion (***biochemical repair required***)**

*** Von Sonntag notes that donation of a proton to a DNA radical may or may not restore the original chemical structure of the DNA. But, the chemical repair process evidently converts the DNA radical (***or cluster of radicals?***) into a form that is more amenable to biochemical repair and reduces the number of strand breaks.**

Clemens von Sonntag, Free-Radical-Induced DNA Damage and its Repair – A chemical perspective. Springer-Verlag, New York, NY (2006)

RBE and *HRF* (induction of DNA damage)

Relative Biological Effectiveness (*RBE*) for the *i*th type of cluster

$$RBE_i(q) = \frac{\Sigma_i(q)}{\Sigma_i(q_0)}$$

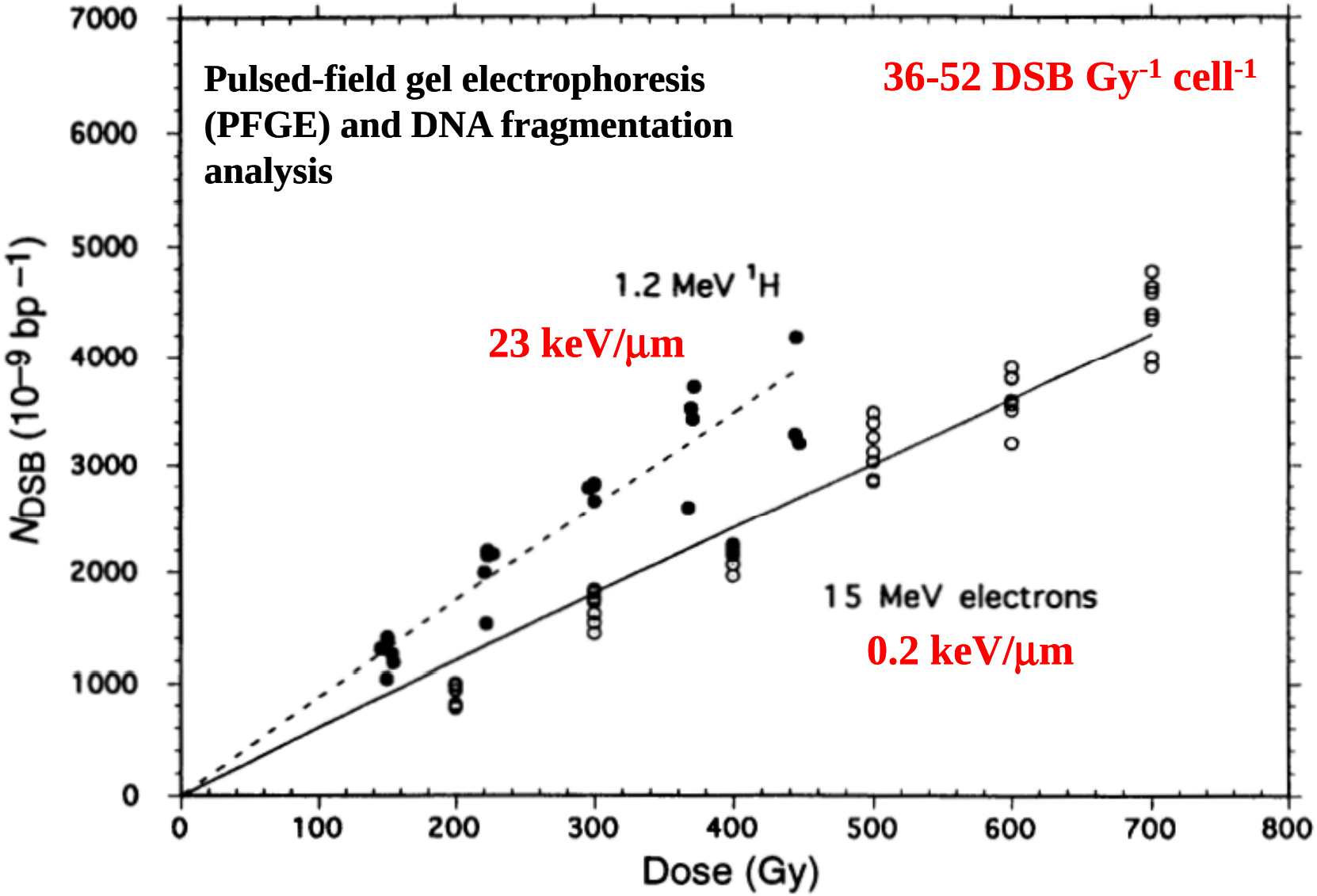
Hypoxia Reduction Factor (*HRF*) for the *i*th type of cluster

$$HRF_i([O_2]) = \frac{\Sigma_i(100\%\,O_2)}{\Sigma_i([O_2])}$$

Σ_i = Measured or MC simulated number of the *i*th type of cluster Gy^{-1} Gbp^{-1} (*or per cell*), *q* denotes radiation quality of the particle of interest (*e.g., a proton or neutron*), and q_0 denotes the radiation quality of the reference radiation (typically high-energy x-rays or γ-rays from ^{60}Co or ^{137}Cs**)**

In general, the RBE and HRF varies with endpoint (cell killing vs DNA damage**) and even the type of damage (*e.g., SSB vs DSB*). For DNA damage induction up to doses of at least a few hundred Gy, little if any good evidence that the *RBE* or *HRF* depend on dose or dose rate.**

DSB induction in human skin fibroblasts



Frankenberg D, Brede HJ, Schrewe UJ, Steinmetz C, Frankenberg-Schwager M, Kasten G, Pralle E. Induction of DNA double-strand breaks by 1H and 4He ions in primary human skin fibroblasts in the LET range of 8 to 124 keV/microm. *Radiat Res.* 151(5), 540-549 (1999).

DNA Damage and Hypoxia

Presence of oxygen within a cell substantially enhances the initial yield of DNA damage

100% O_2

2.91 DSB Gbp^{-1} Gy^{-1}

100% N_2

1 DSB Gbp^{-1} Gy^{-1}

DSB induction is proportional to dose up to at least 2400 Gy under aerobic *and* hypoxic conditions

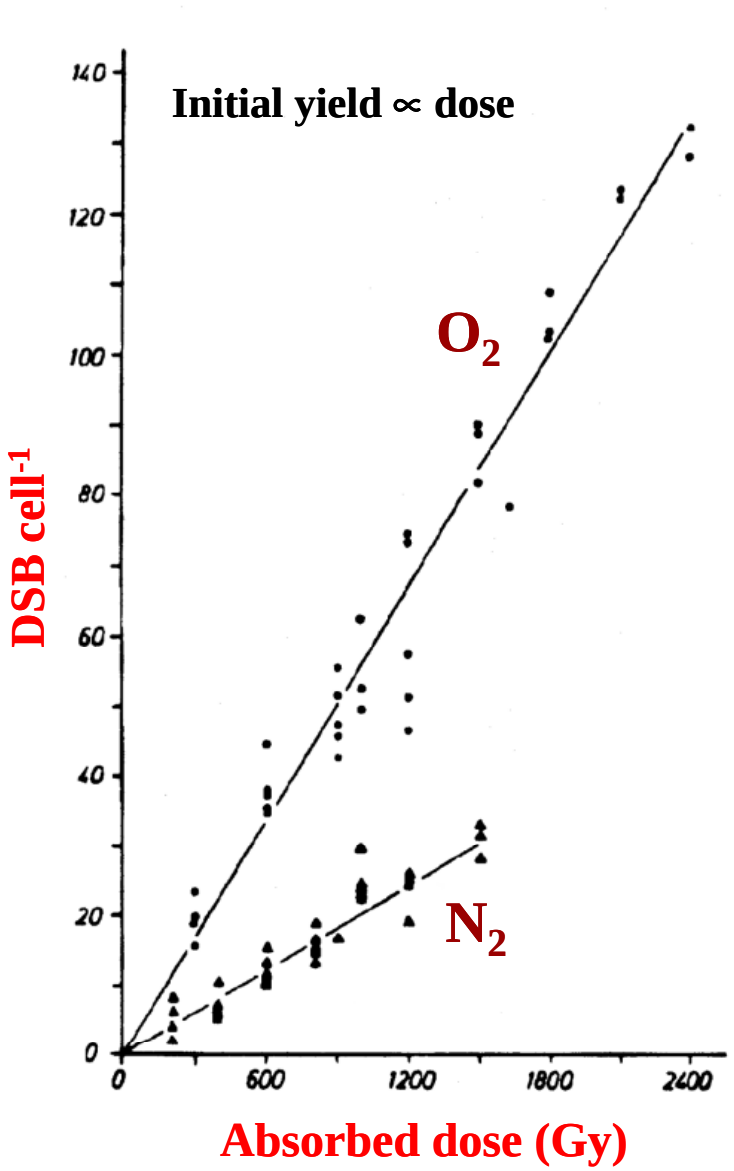
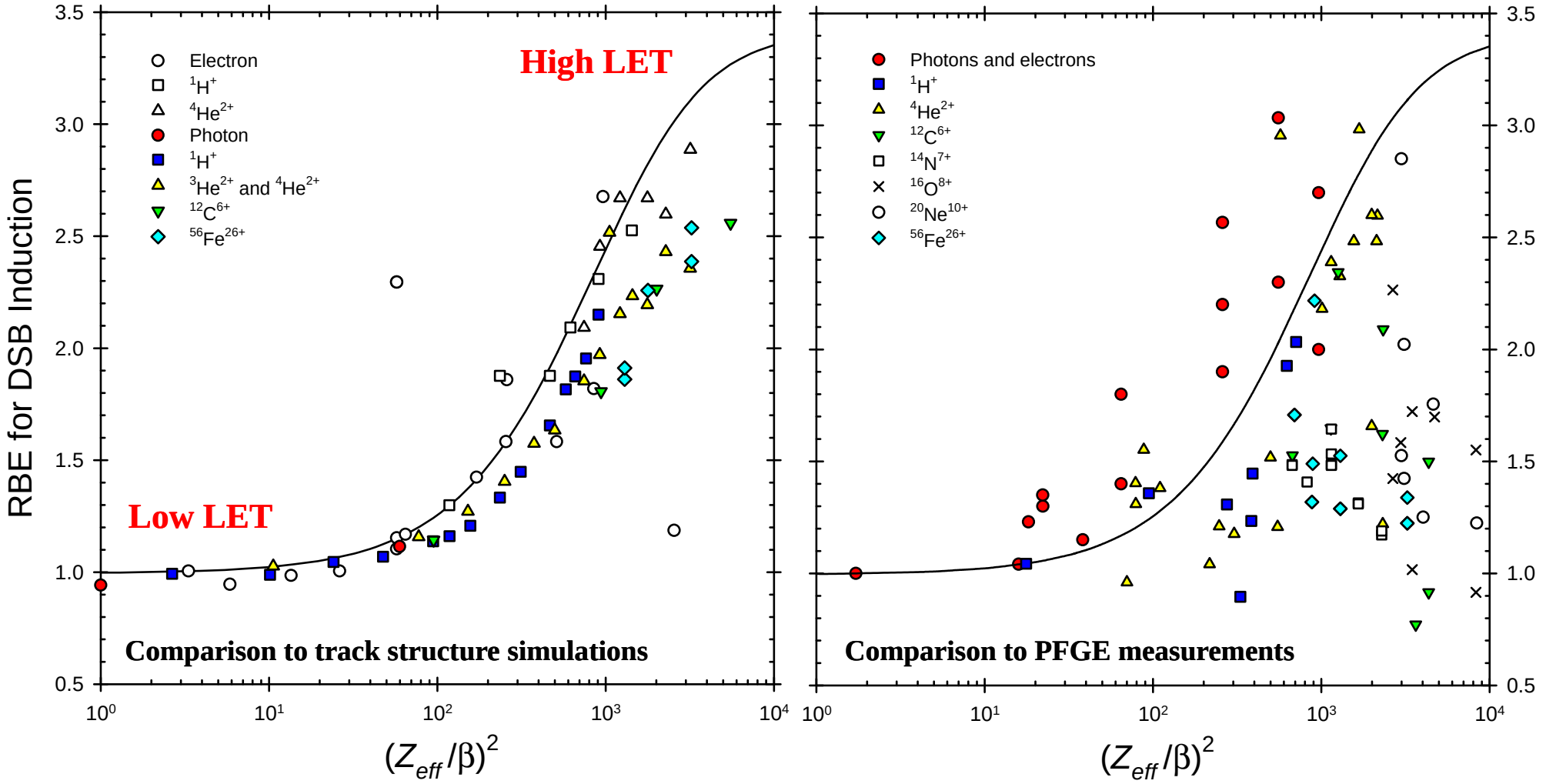


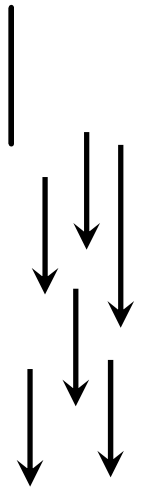
Figure adapted from Frankenberg D, Frankenberg-Schwager M, Blocher D, Harbich R. Evidence for DNA double-strand breaks as the critical lesions in yeast cells irradiated with sparsely or densely ionizing radiation under oxic or anoxic conditions. *Radiat Res.* 88(3), 524-532 (1981)

RBE for DSB Induction



Many of the published experimental studies (symbols, right panel**) detect a subset of the total number of DSB because not all DNA fragments counted**

DNA Fragmentation Analysis

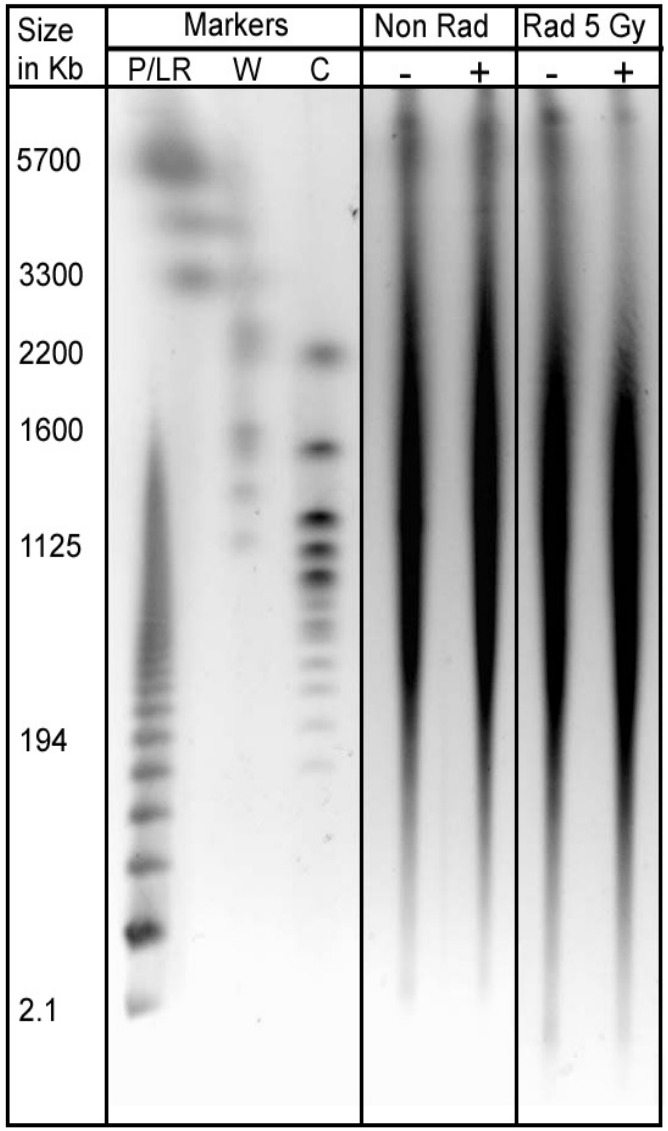


Agarose plug containing irradiated DNA isolated from cells

Fragments migrate out of the gel because of the negative charge carried by the sugar-phosphate backbone of DNA

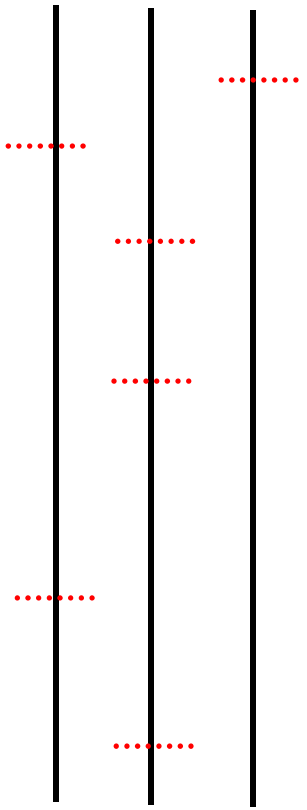
Short fragments quickly migrate
Larger fragments slowly migrate

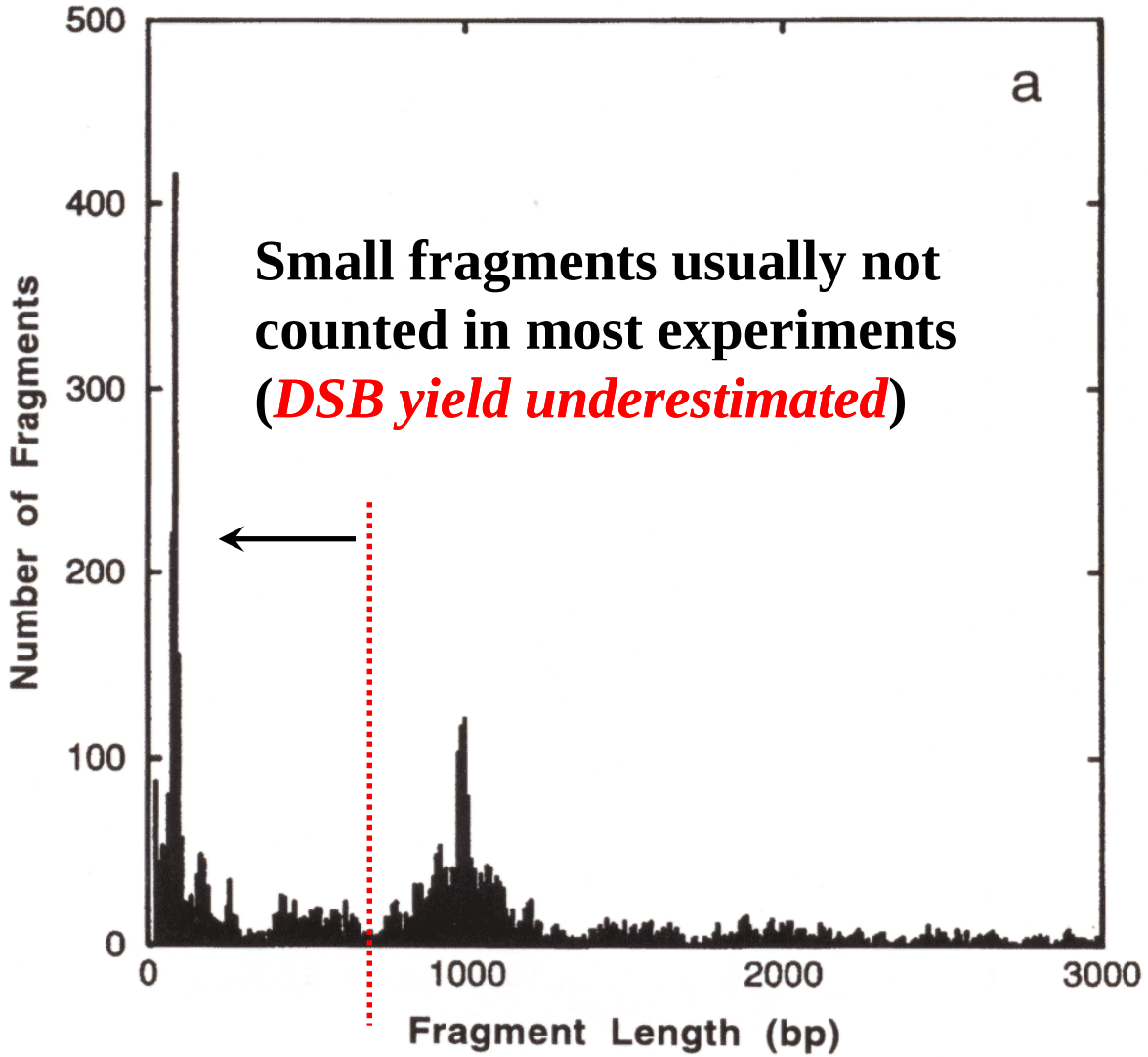
Quantify number and sizes of fragments



Courtesy A. Georgakilas (ECU)

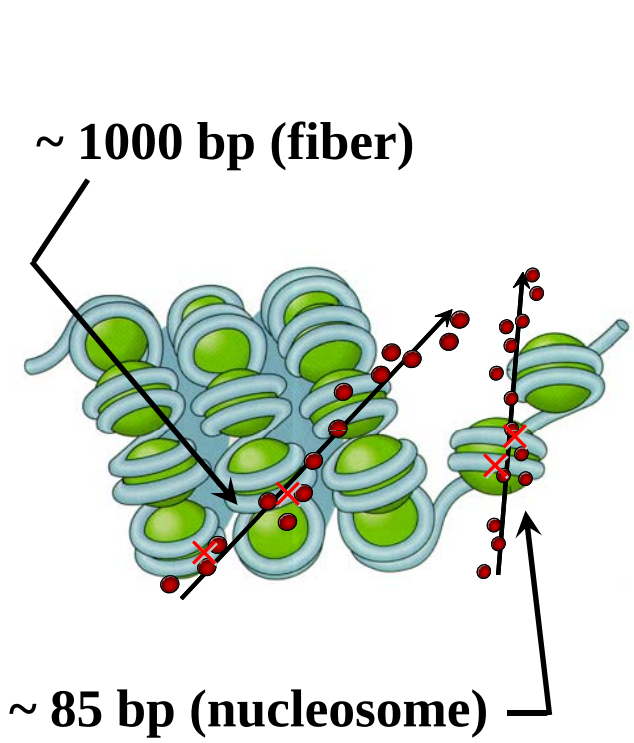
Fragment size distributions

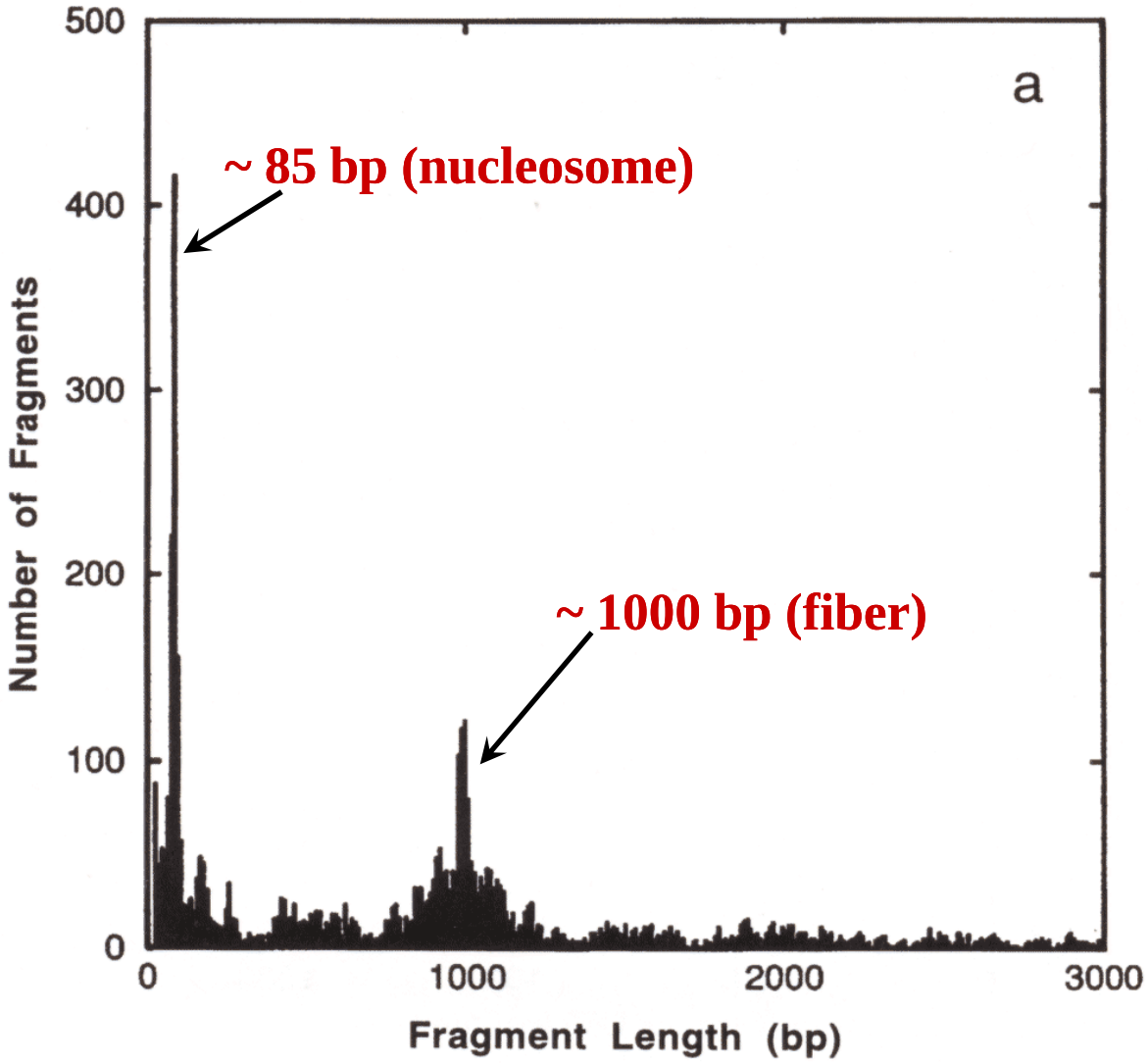




Holley WR, Chatterjee A. Clusters of DNA induced by ionizing radiation: formation of short DNA fragments. I. Theoretical modeling. *Radiat Res.* 145(2):188-99 (1996). Rydberg B. Clusters of DNA damage induced by ionizing radiation: formation of short DNA fragments. II. Experimental detection. *Radiat Res.* 145(2):200-9 (1996).

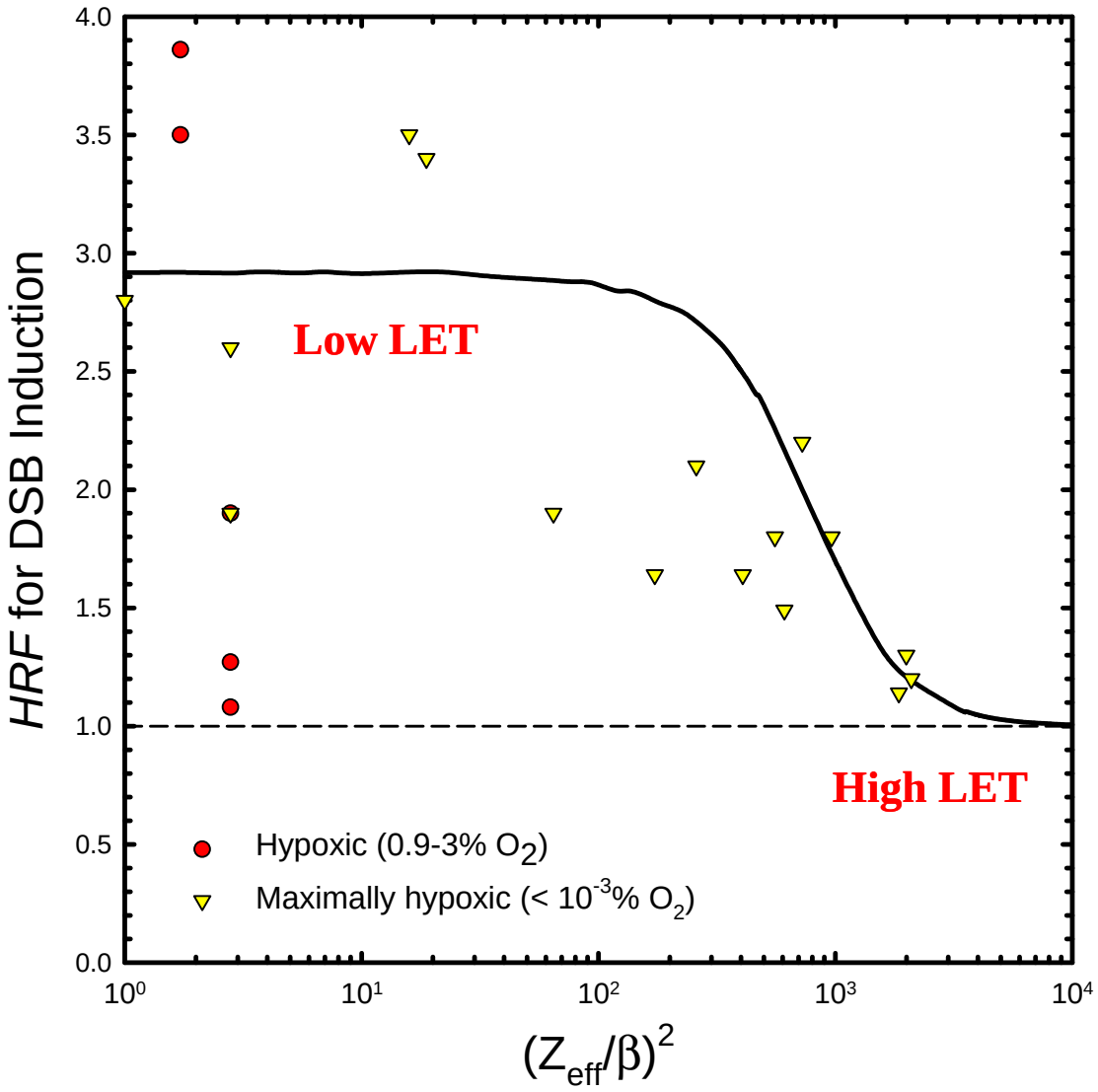
Fragment size distributions





Holley WR, Chatterjee A. Clusters of DNA induced by ionizing radiation: formation of short DNA fragments. I. Theoretical modeling. *Radiat Res.* 145(2):188-99 (1996). Rydberg B. Clusters of DNA damage induced by ionizing radiation: formation of short DNA fragments. II. Experimental detection. *Radiat Res.* 145(2):200-9 (1996).

HRF for DSB Induction

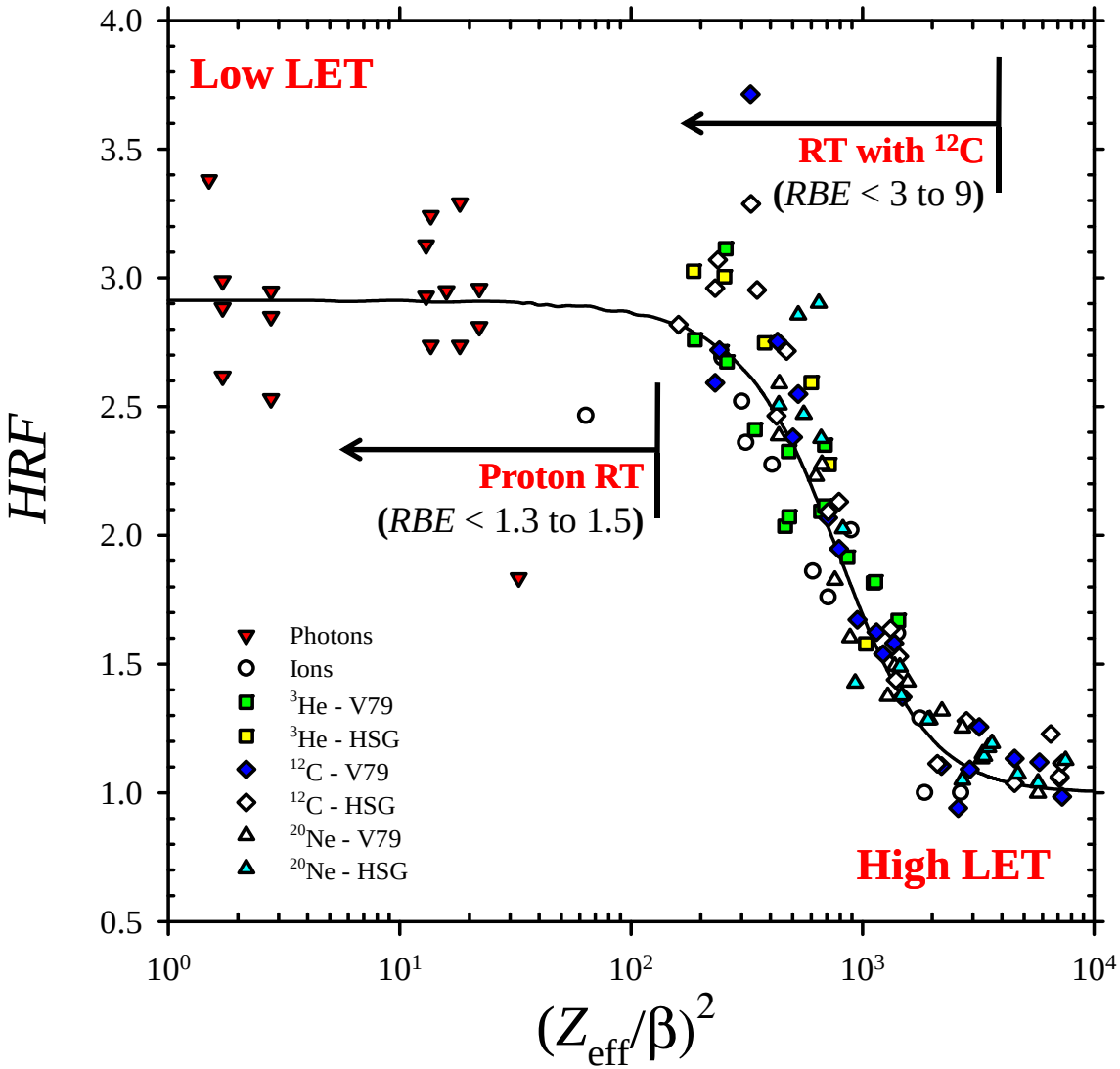


For low LET radiations, DSB induction is about 3-fold lower under maximally hypoxic conditions than in well oxygenated cells (i.e., $HRF \cong 3$**).**

***HRF* decreases towards unity (**O_2 concentration has no effect**) as particle LET increases.**

Filled *symbols* are data from PFGE experiments. *Solid line* is the MCDS predicted *HRF* for a range of particle types and energies.

HRF for Cell Survival and DSB Induction



Solid Black Line: *HRF* for DSB induction predicted by the MCDS (0% O_2 concentration)

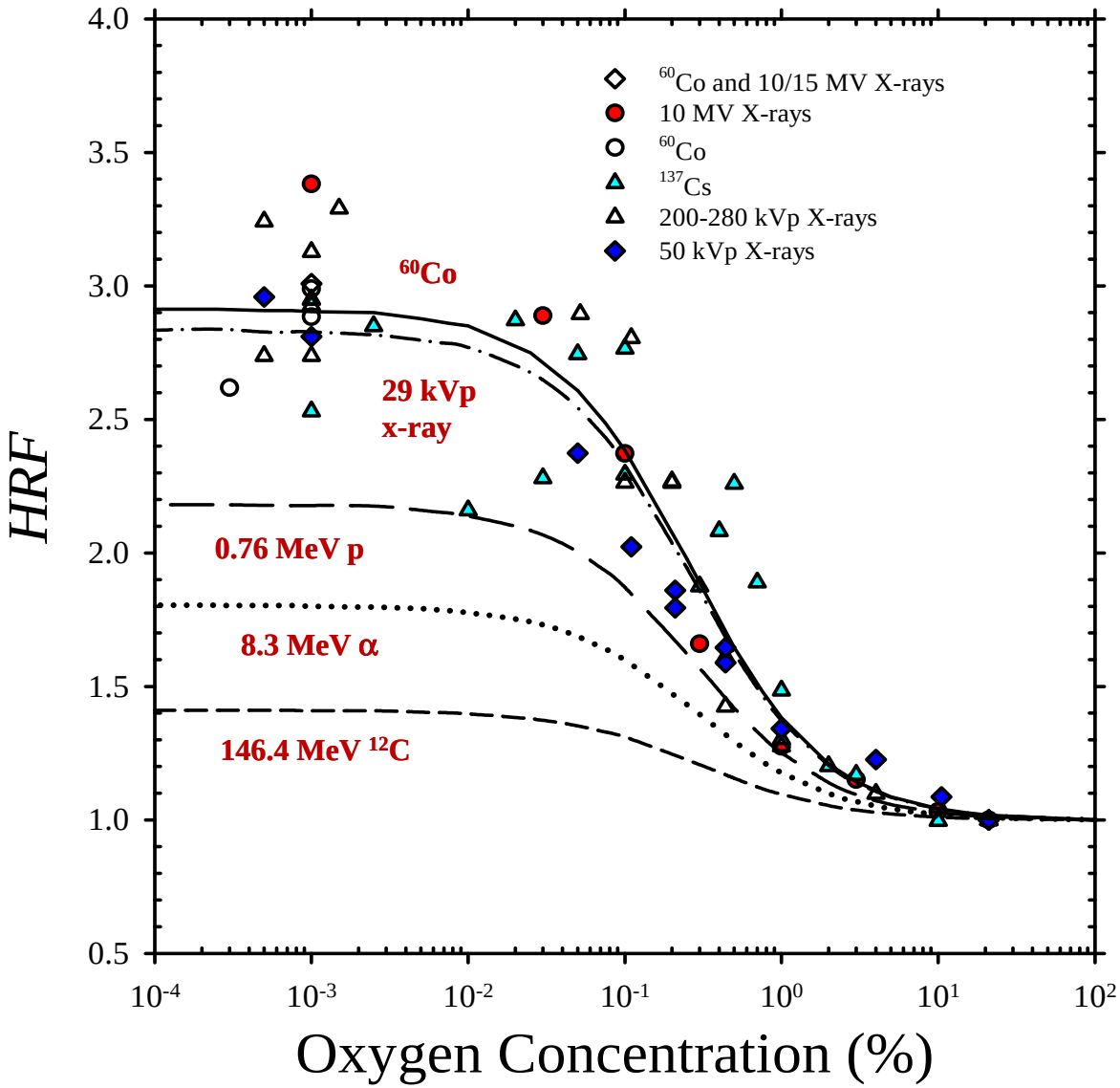
Symbols: *HRF* derived from published clonogenic survival data (negligible O_2 concentration)

$$\alpha_H = \alpha_A / HRF_\alpha$$

$$(\alpha/\beta)_H = (\alpha/\beta)_A \cdot HRF_{\alpha/\beta}$$

$$HRF_\alpha \cong HRF_{\alpha/\beta}$$

Effect of Oxygen Concentration on the *HRF*



Symbols: *HRF* derived from published clonogenic survival data

Solid, dotted and dashed black lines: *HRF* for DSB induction predicted by the MCDS for selected particle types

Low Dose Approximation to the RMF

Trends in DSB induction with radiation quality and oxygen concentration are closely related and predictive of general trends in Linear-Quadratic (LQ) survival parameters α and α/β (e.g., Carlson *et al.* 2008**)**

***Intra*-track chromsomal aberrations**

$$\alpha = \theta\Sigma + \kappa\bar{z}_F\Sigma^2 \qquad \beta = \frac{\kappa}{2}\Sigma^2 \qquad \frac{\alpha}{\beta} = \frac{2}{\Sigma}(\theta/\kappa) + 2\bar{z}_F$$

Unrepairable and misrepaired

***Inter*-track aberrations**

θ, κ are *adjustable cell- or tissue-specific* parameters related to biological processing of DNA damage (*independent of LET and O_2 concentration***)**

Σ is the number of DSB Gy^{-1} Gbp^{-1} (or per cell**) and is estimated using the MCDS (***strong function of LET and O_2 concentration***)**

$\bar{z}_F$ is the frequency-mean specific energy (in Gy**) for the cell nucleus (***strong function of LET but independent of O_2 concentration***) – estimate with the MCDS or other Monte Carlo code(s)**

D.J. Carlson, R.D. Stewart, V.A. Semenenko and G.A. Sandison, Combined use of Monte Carlo DNA damage simulations and deterministic repair models to examine putative mechanisms of cell killing. *Rad. Res.* **169**, 447-459 (2008)

Strategies to estimate θ and κ measured data

(*1*) Non-linear regression analysis of LQ to survival data for particles of one or more radiation quality and one or more O_2 concentrations

$$S(D) = \exp\left\{-\alpha D - \beta G D^2\right\} = \exp\left\{-\left(\theta\Sigma + \kappa \bar{z}_F \Sigma^2\right) D - \frac{\kappa}{2}\Sigma^2 G D^2\right\}$$

Estimate Σ and $\bar{z}_F$ *a priori* using MCDS or other methods. Potentially most accurate. BUT… can be sensitive to uncertainties in microdosimetry for short-range (*high LET*) radiations

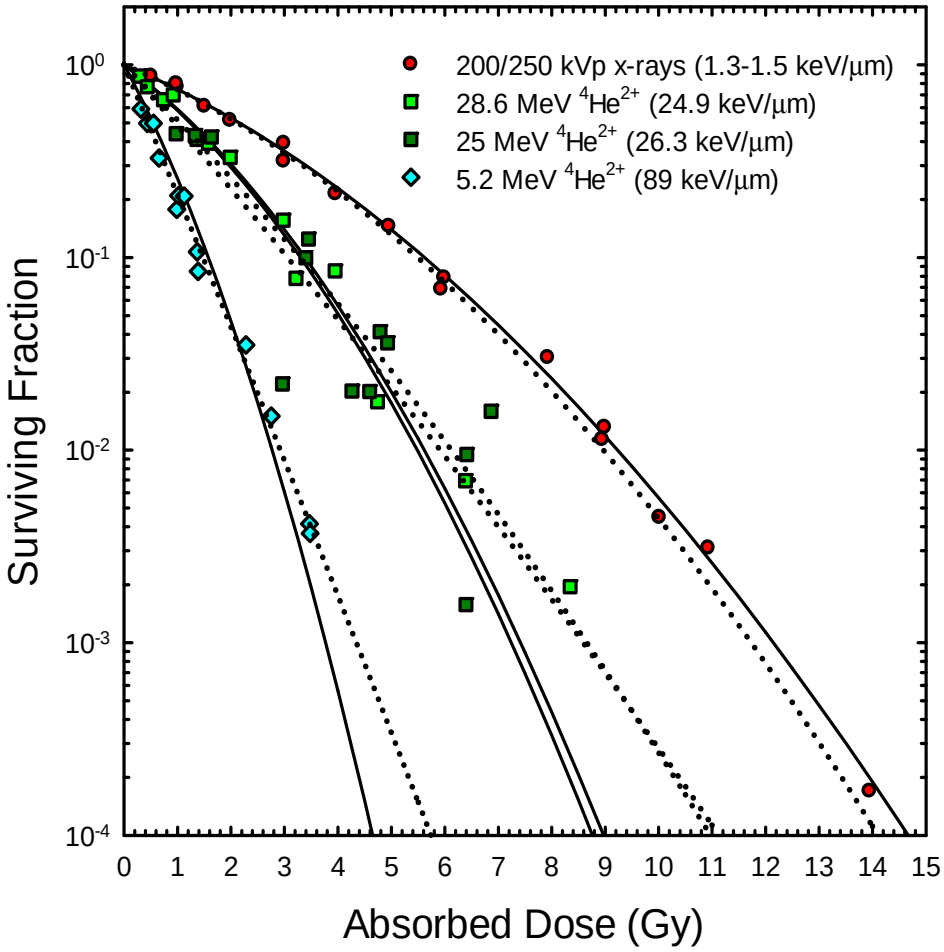
(*2*) Use analytical formulas to estimate θ and κ from published LQ parameters for a reference radiation (*clinical*, *animal*, *in vitro*)

$$\theta = \frac{1}{\Sigma}\left(\alpha - \kappa \bar{z}_F \Sigma^2\right) \cong \frac{\alpha}{\Sigma} \qquad \kappa = \frac{2\beta}{\Sigma^2} = \frac{2\alpha / \Sigma^2}{(\alpha / \beta)}$$

Estimate Σ and $\bar{z}_F$ *a priori* using MCDS or other methods. In practice, insensitive to uncertainties in microdosimetry because for most low LET radiations

$$\frac{\alpha}{\Sigma} \gg \kappa \bar{z}_F \Sigma^2$$

Importance of Good Dosimetry (*high LET*)



LQ fits to data for each particle type relatively insensitive to systematic dosimetry errors – it's the product of αD and βD^2 that matters!

But when attempting to *predict* effects for high LET radiations from lower LET radiations, good absolute dosimetry is important – *rejoice physicists*!

$$\alpha D = (\theta\Sigma + \kappa\bar{z}_F\Sigma^2)D$$

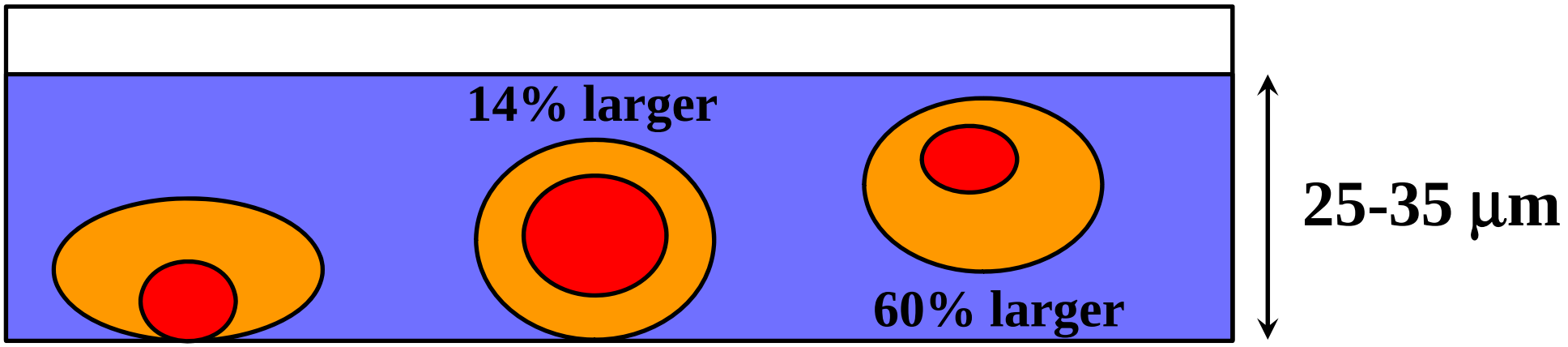
macrodosimetry

microdosimetry

Cellular and Sub-cellular Dosimetry

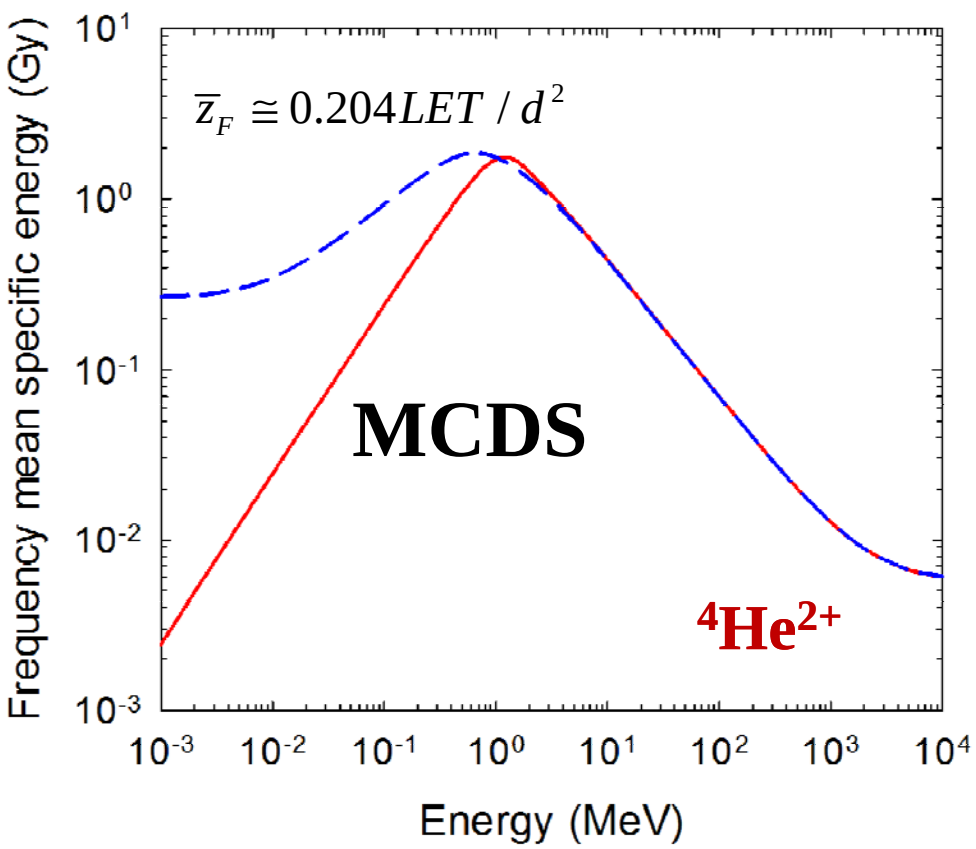
		Dose per Unit Fluence (nGy per cm^2)		
Particle	Range (um)	Entrance	Exit	Average
1.9 MeV p	67.90	26.90	27.70	27.20
1.15 MeV p	30.00	39.00	41.70	40.00
0.76 MeV p	15.90	52.90	59.40	54.60
3.8 MeV α	25.30	174.20	189.30	179.50

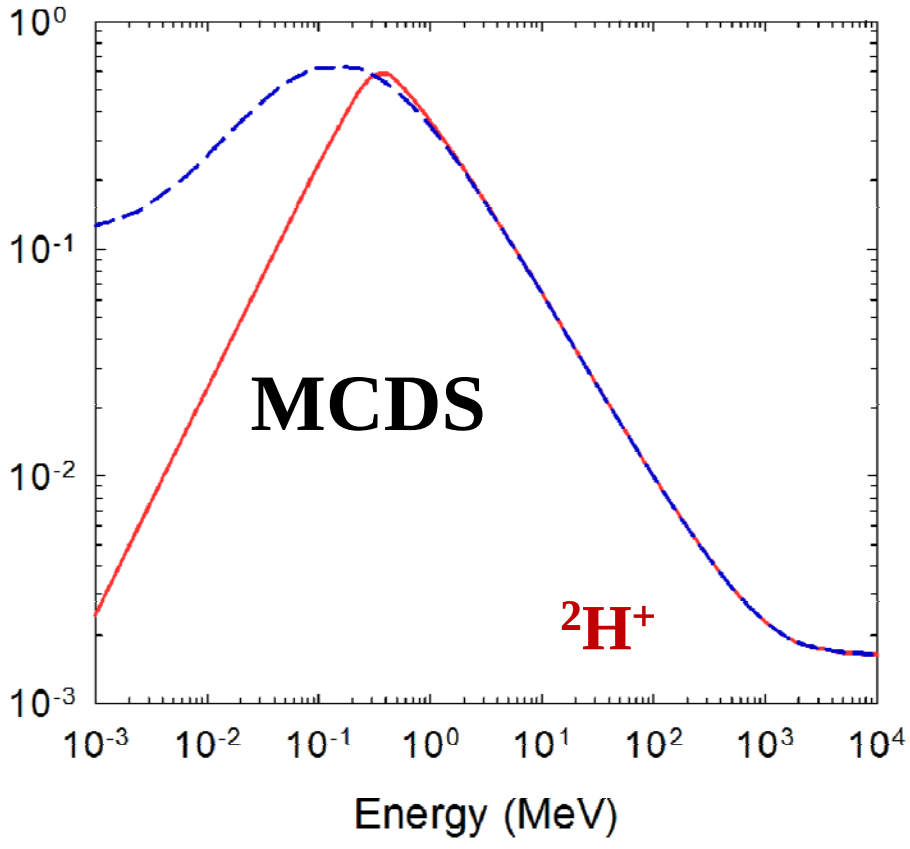
< 2-3% difference in entrance vs exit dose for G1 phase cell



G1 phase **M phase** **“floater”**

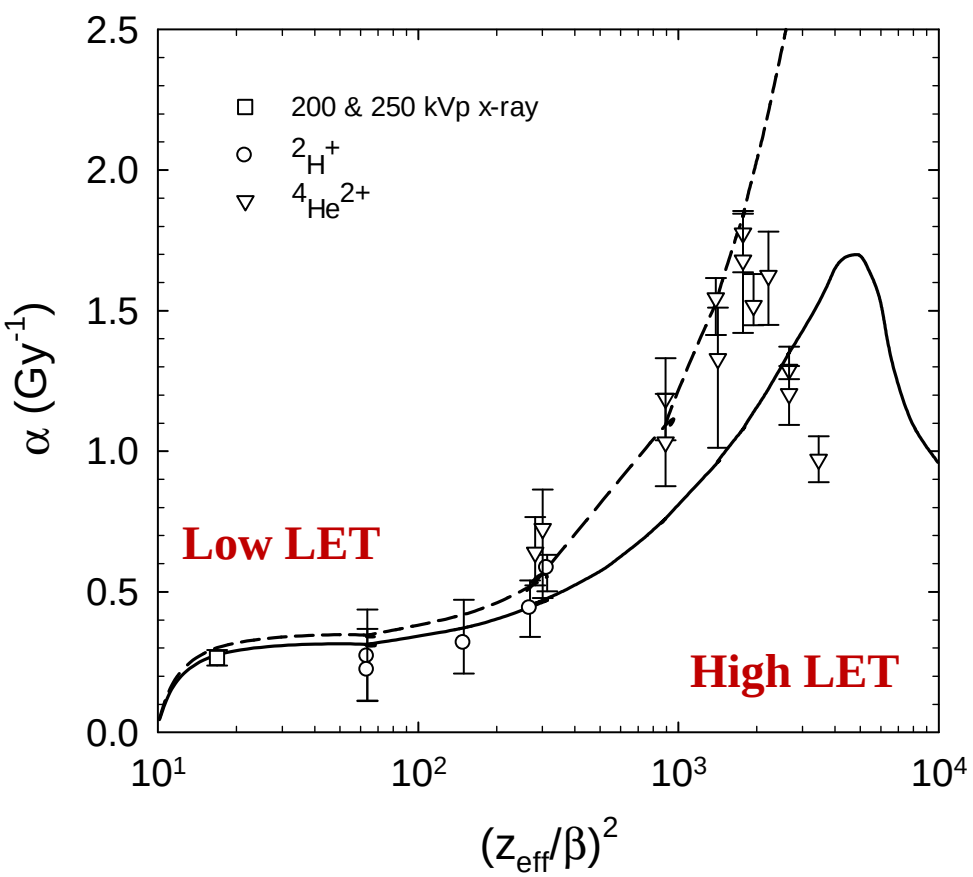
Microdosimetry → $\alpha D = (\theta\Sigma + \kappa\bar{z}_F\Sigma^2)D$

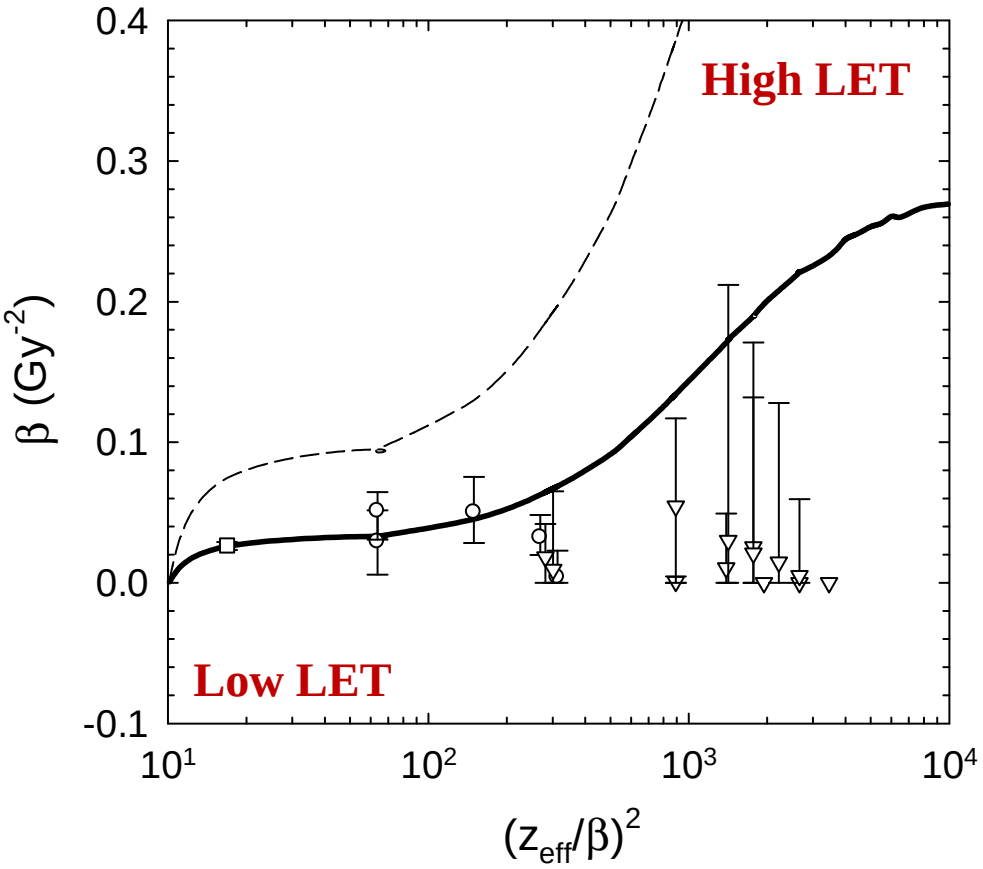




Analytic formula neglects changes in stopping power while particle passes through target. Also assumes particle passes all the way through target. MCDS accounts for "stoppers" and changes in stopping power within target

Predicted Tends in LQ Parameters





(*1*) Contrary to conventional wisdom, RMF predicts that β tends to increase with increasing LET. (*2*) Multiple combinations of LQ parameters fit measured data about equally.

Future Direction

- **Additional testing and refinement of MCDS+RMF**
  - Numerical solution of the RMF system of differential equations instead of low dose LQ approximation
  - Effects of chronic hypoxia (?)
- **Combine MCDS+RMF model with MCNPX radiation transport code**
  - RBE and O_2 effects in pristine and spreadout proton and carbon ion Bragg peaks (see also Frese et al. IJROBP, 83, 442-450. 2012).
  - RBE and O_2 effects in the fast neutron beamline at UWMC
    - Estimate neutron tolerance doses from first principles
    - Compare to clinical experience and RBE estimates from in vitro experiments
  - Dosimetry and biological modeling support for small animal proton irradiation facility under development at UWMC

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