Biologically Guided Radiation Therapy (BGRT)

Relative Biologically Effectiveness (RBE) and Oxygen Effects in Particle Therapy

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Friday April 23, 2010

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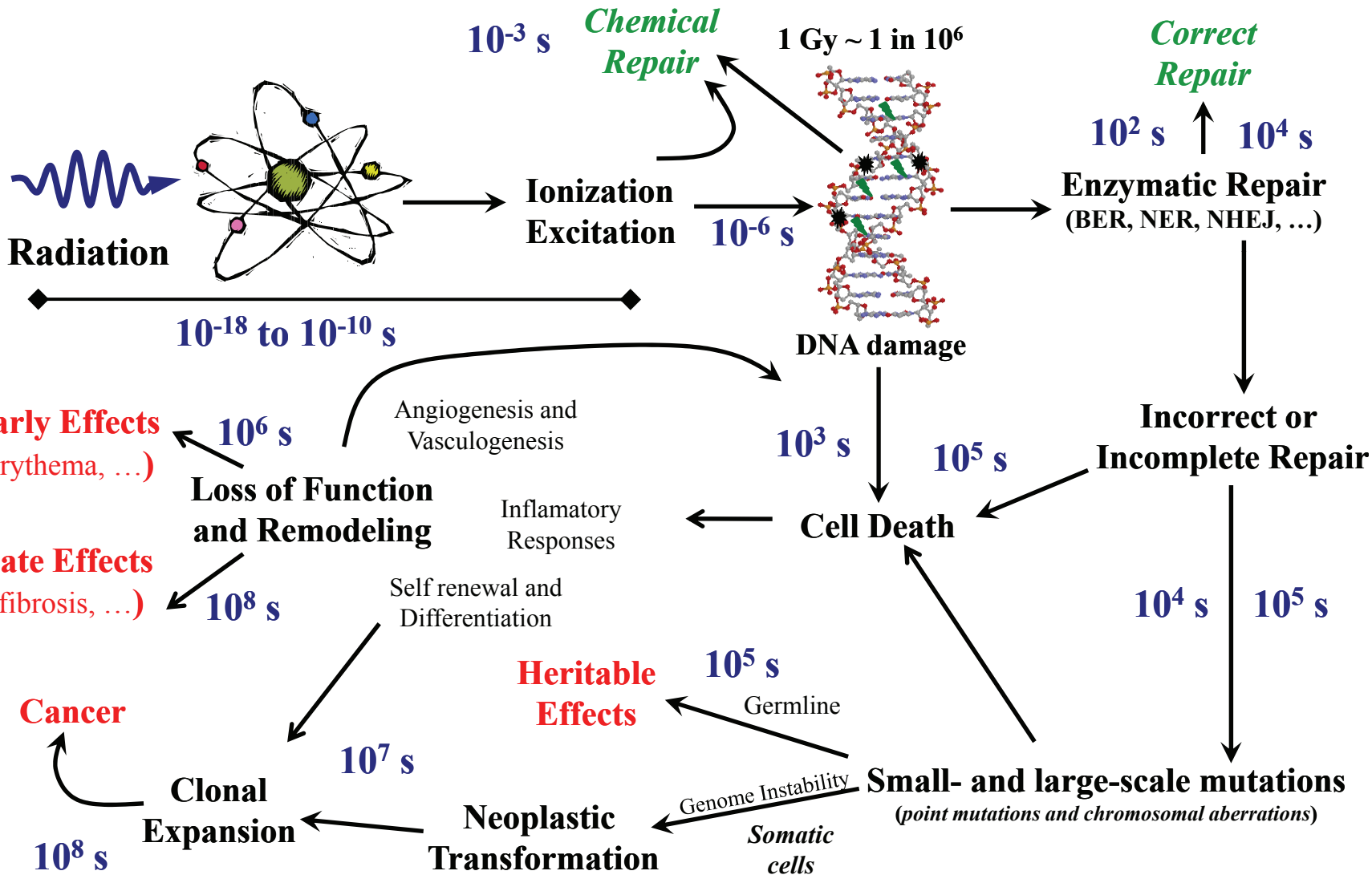
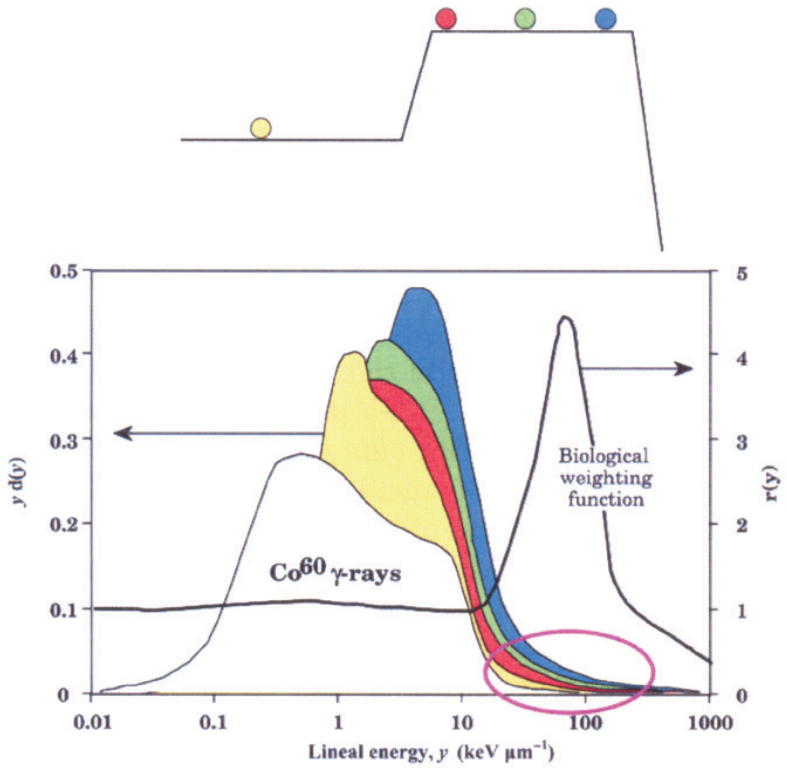
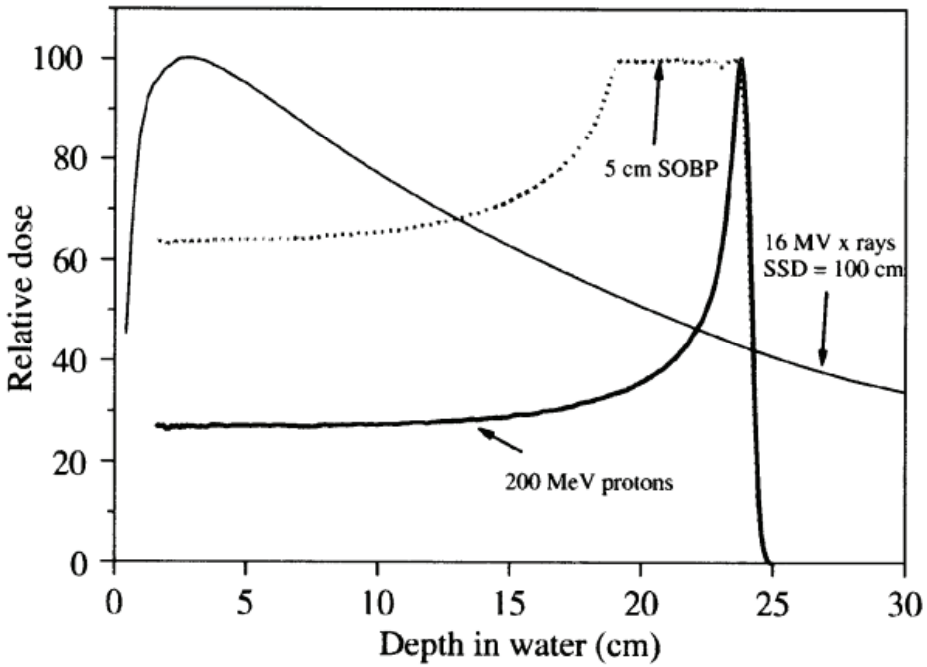
Physics → Chemistry → Biology → Clinic



RBE Effects in the SOBP

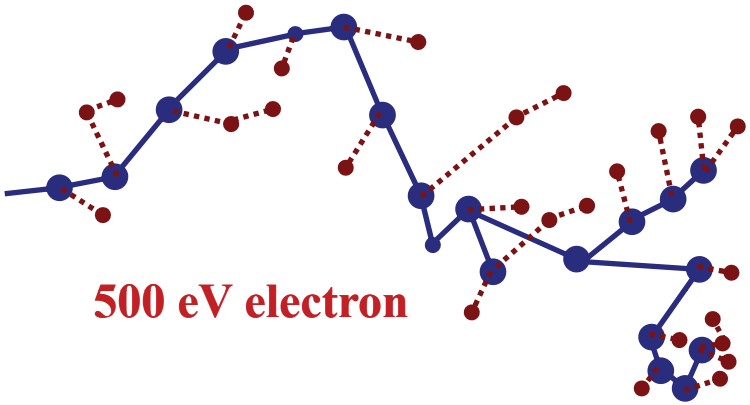
Delivered dose in the spread-out Bragg peak (SOBP) due to a mixture of low, intermediate and high energy protons



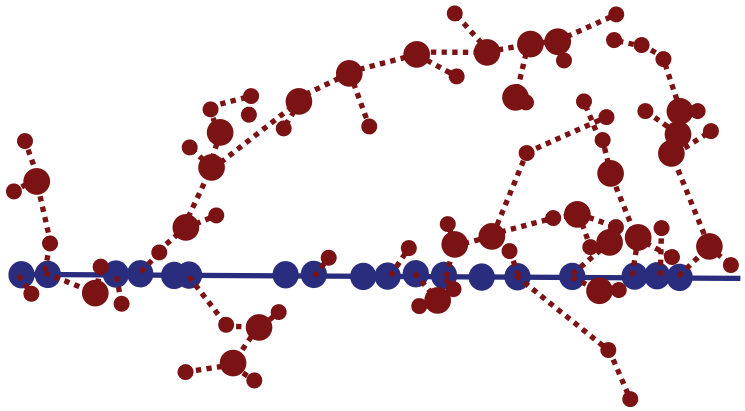


Source: ICRU 78 (2007)

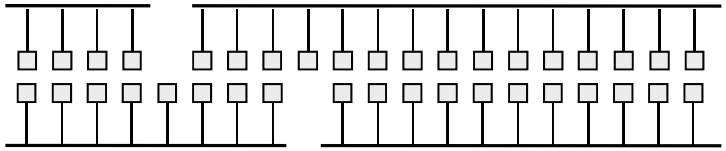
Effect of Radiation Quality (*1st level*)



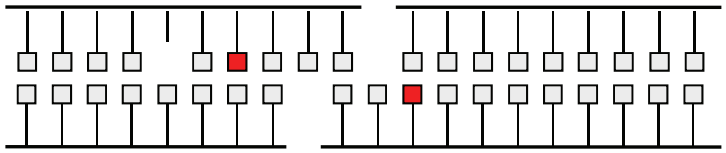
500 eV electron



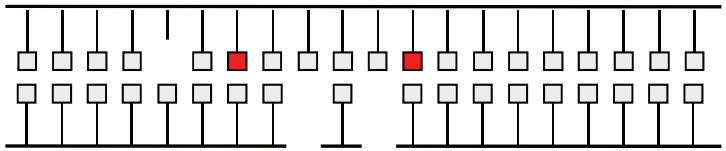
Segment of a 4 MeV α particle ($^4He^{2+}$)



"Simple DSB" Opposed strand breaks within *about 10 bp*

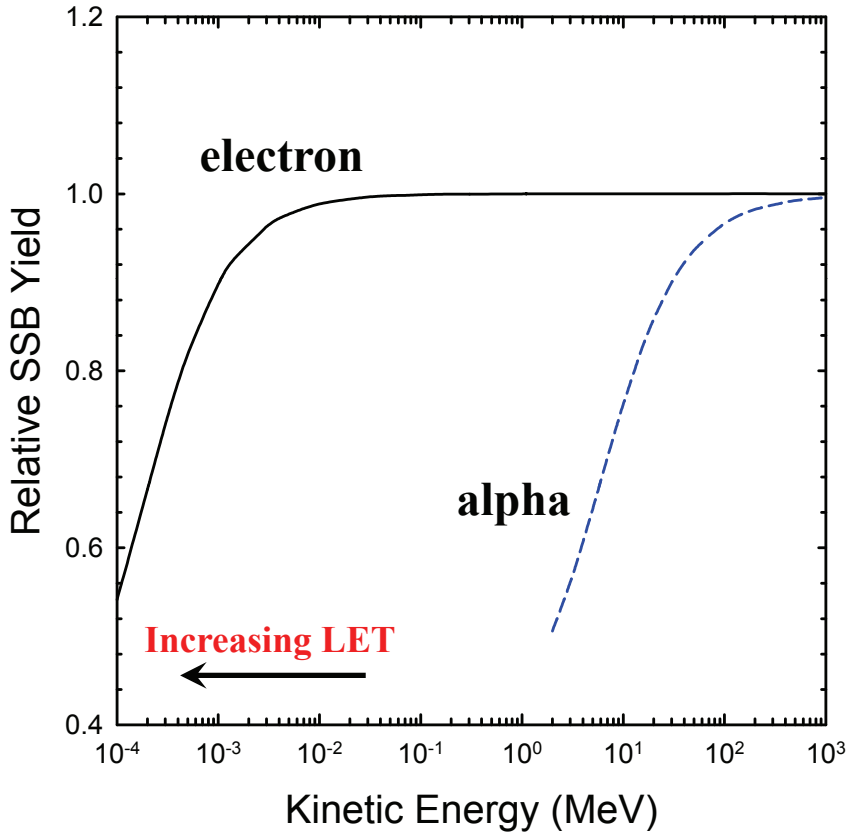


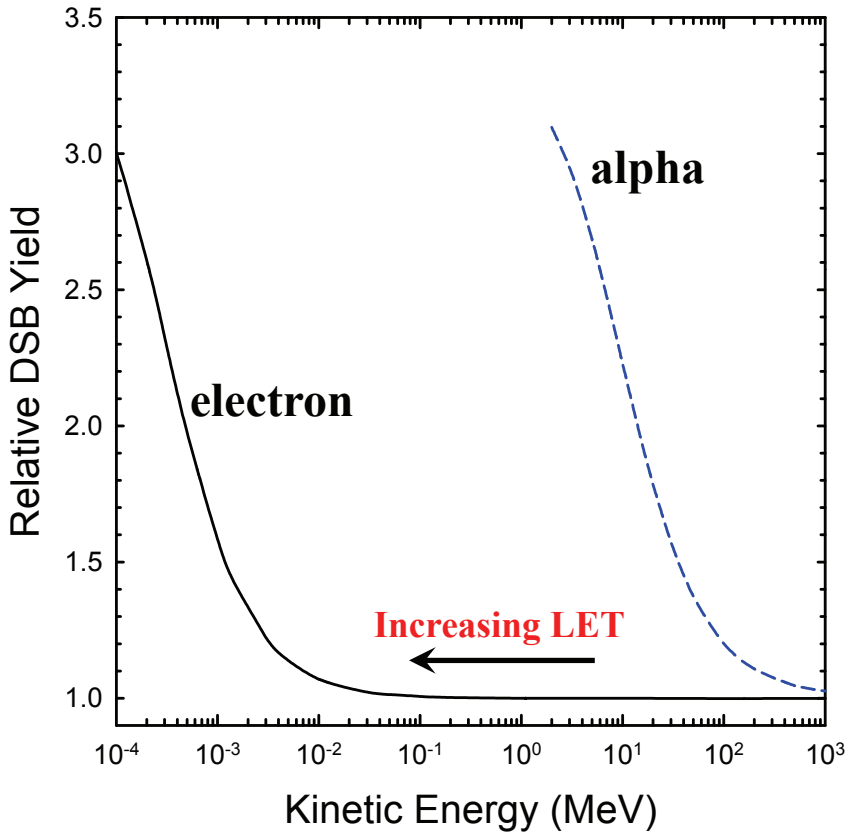
"Complex DSB" composed 2 strand breaks with collateral base damage in same or opposed strands



Complex SSB – one or more strand breaks (same side) with collateral abasic sites and base damage in the opposed strand

Relative SSB and DSB induction

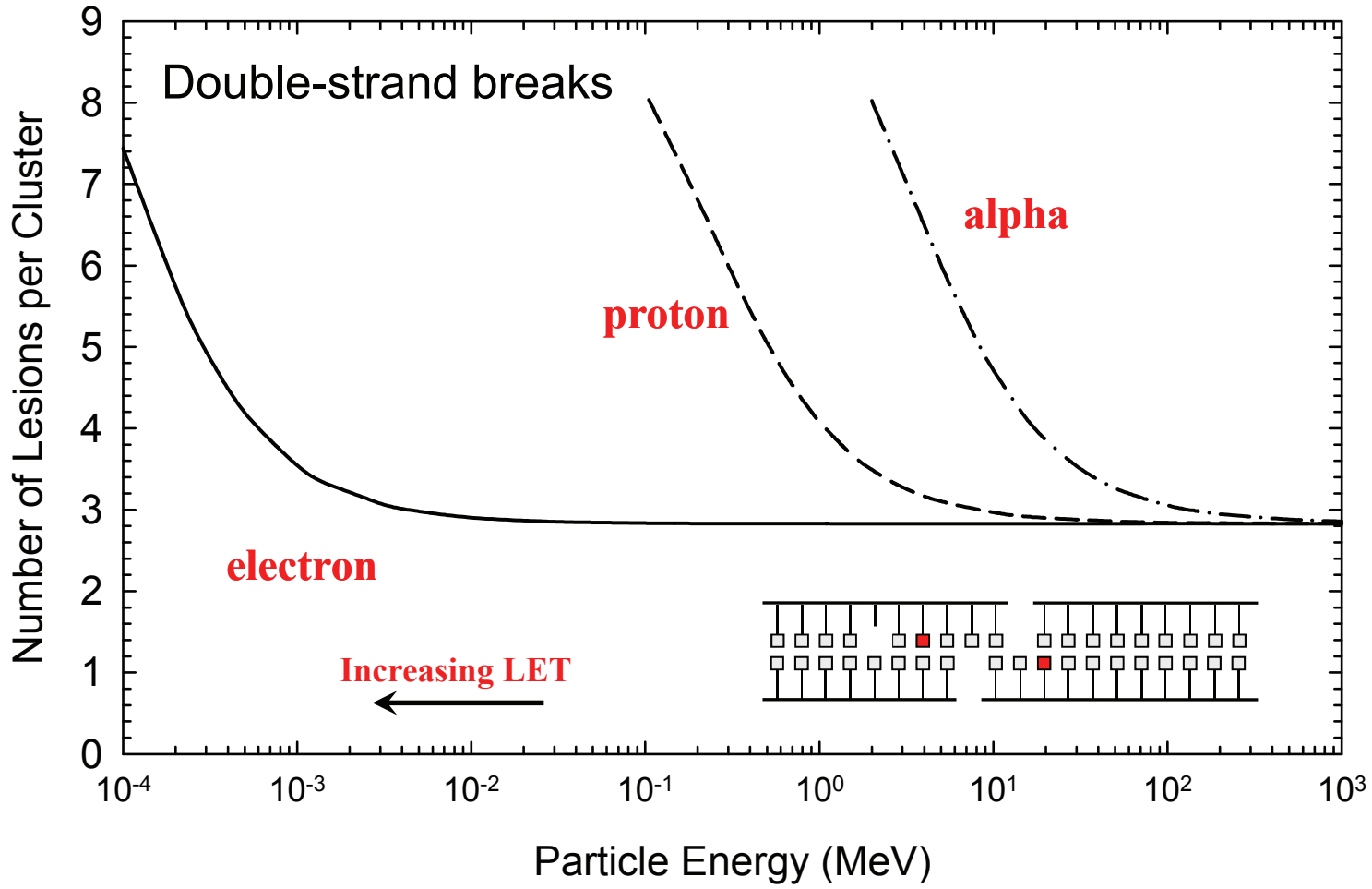




Ratio of SSB per DSB decreases with increasing LET

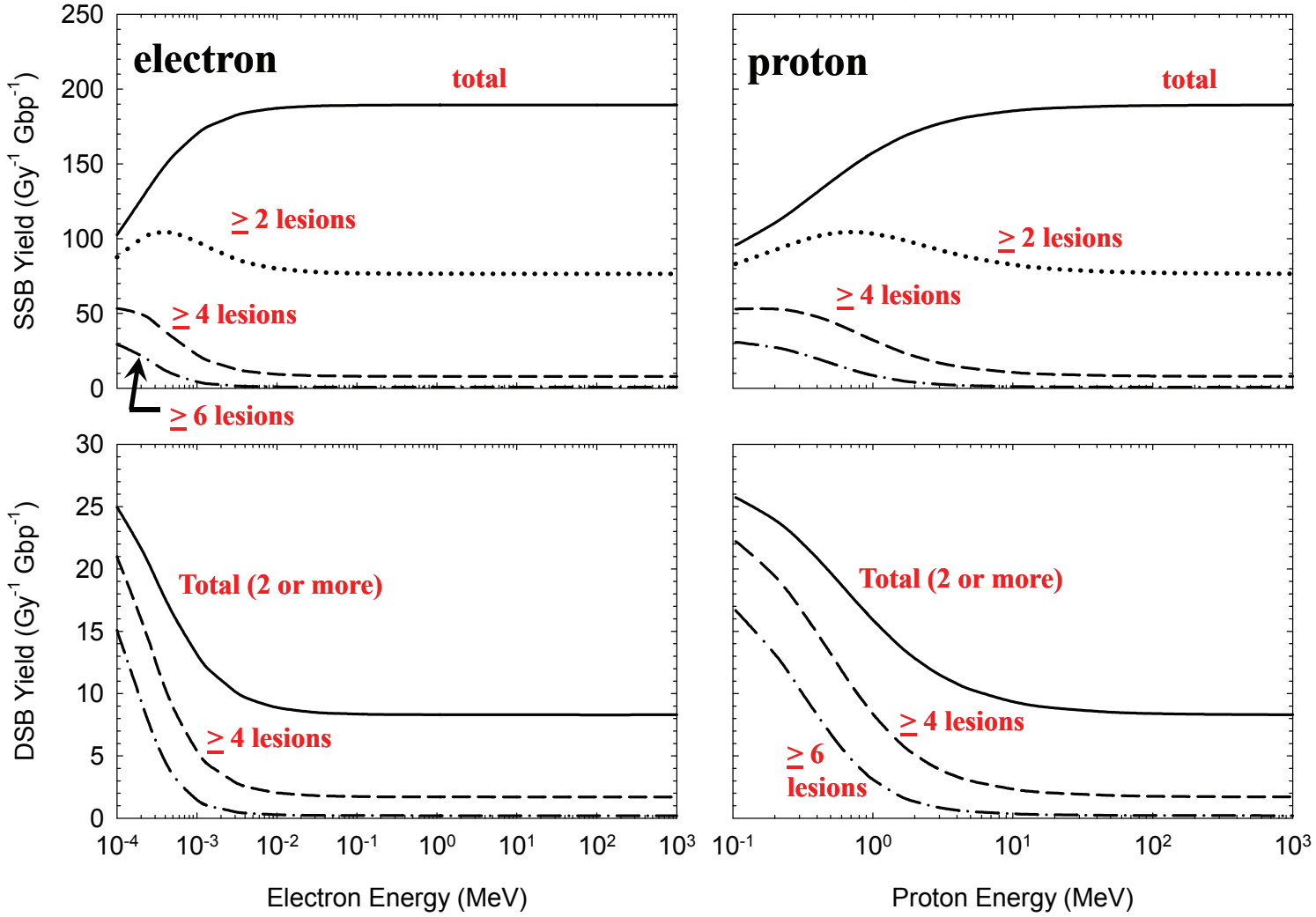
V.A. Semenenko and R.D. Stewart. Fast Monte Carlo simulation of DNA damage formed by electrons and light ions. *Phys. Med. Biol.* **51**(7), 1693-1706 (2006)

DSB complexity



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)

SSB and DSB yield

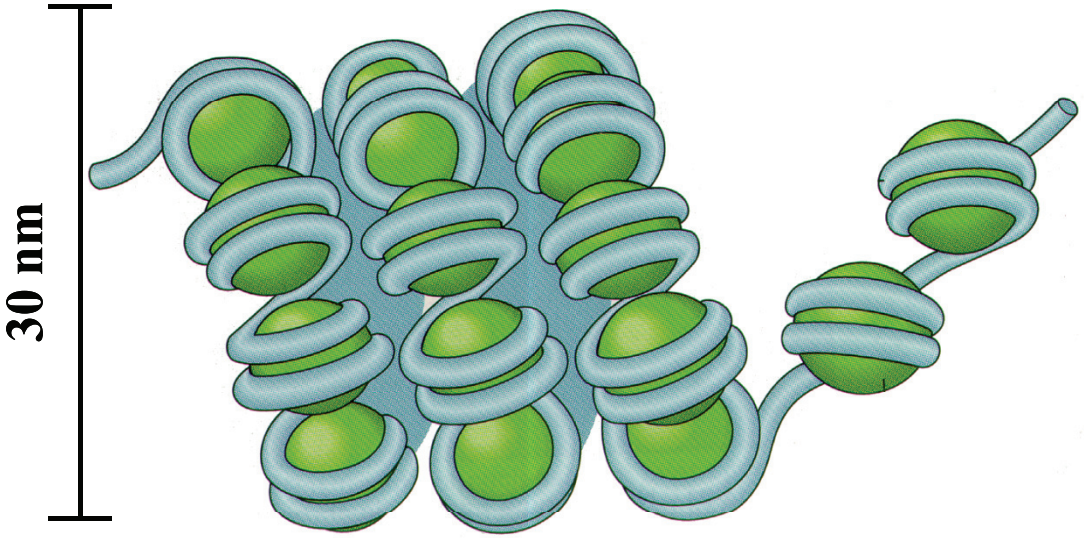


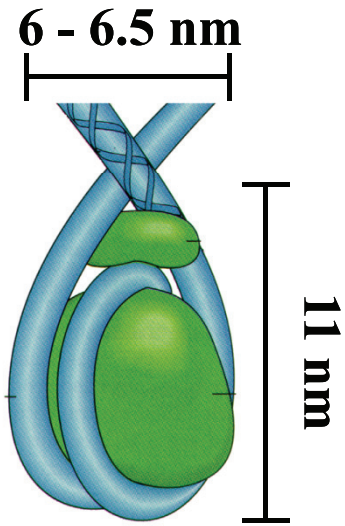
V.A. Semenenko and R.D. Stewart. Fast Monte Carlo simulation of DNA damage formed by electrons and light ions. *Phys. Med. Biol.* **51**(7), 1693-1706 (2006)

DNA and Chromatin

Induction of individual and clustered DNA lesions by ionizing radiation related stochastic events and processes on

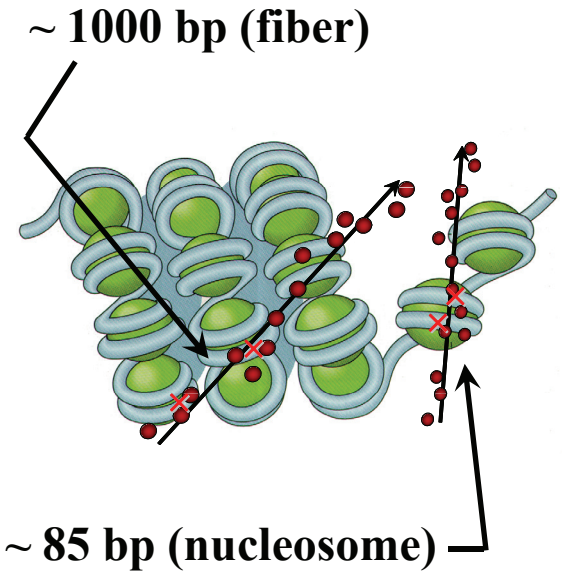
- **Spatial scale < 10 nm (*100 to 1000 nucleotides*)**
- **Time scales < 10^{-3} s**

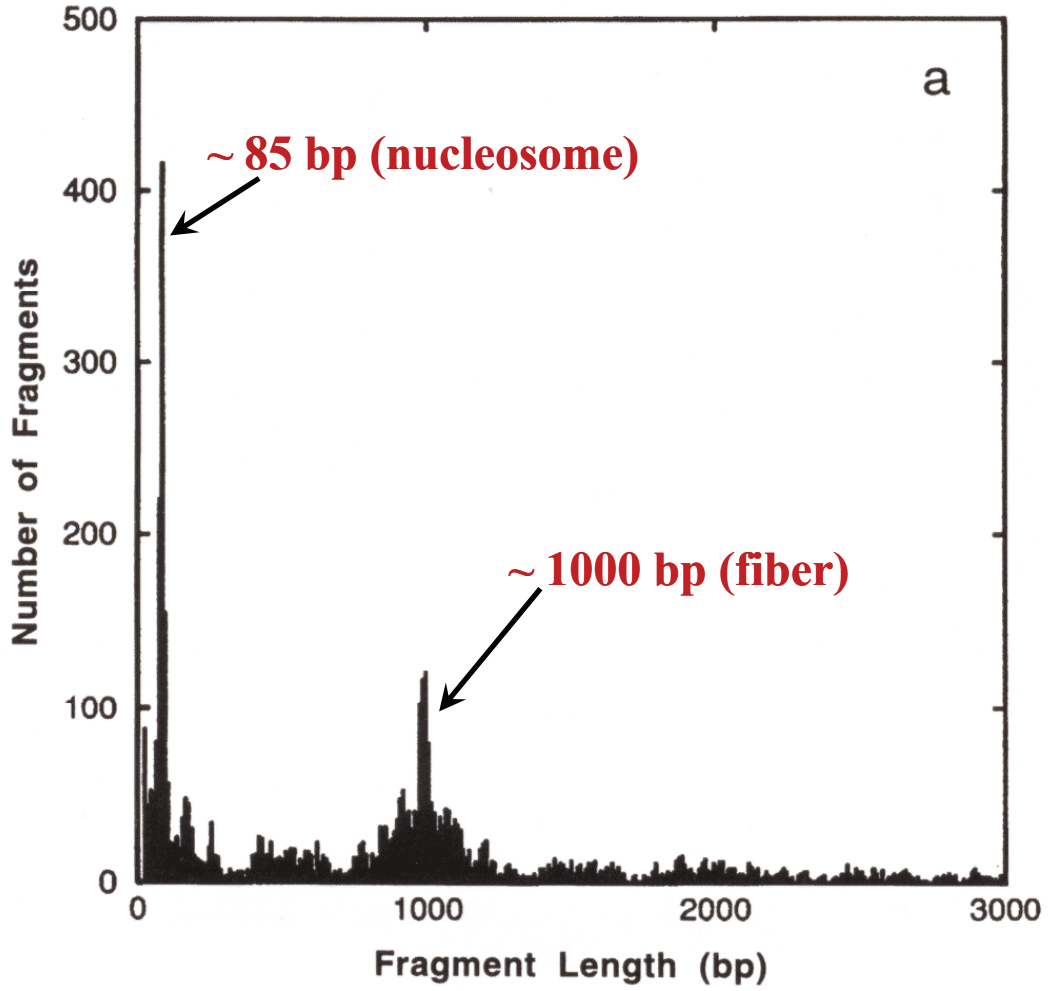




Nucleosome
(146 ± 1 bp)

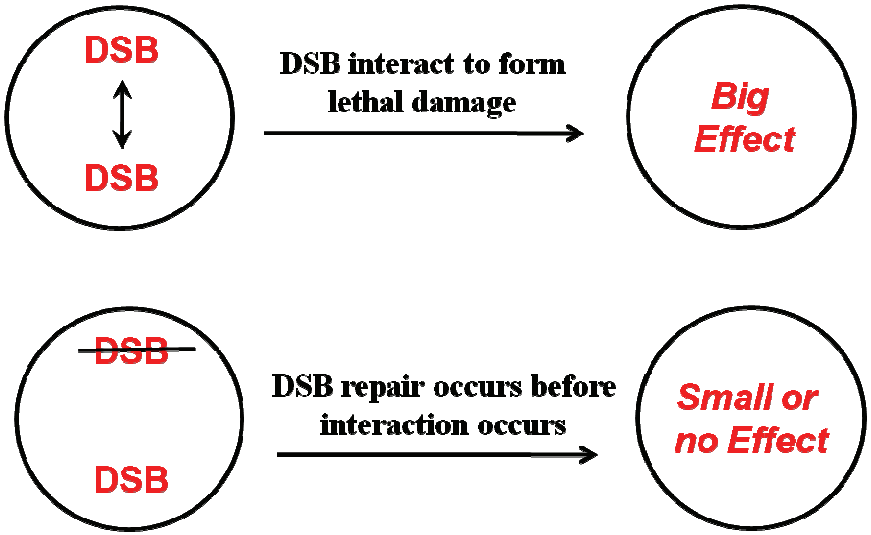
Radiation Quality and Fragment Size Distributions (*2nd level*)





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).

RMDS and DSB Proximity – Significance?

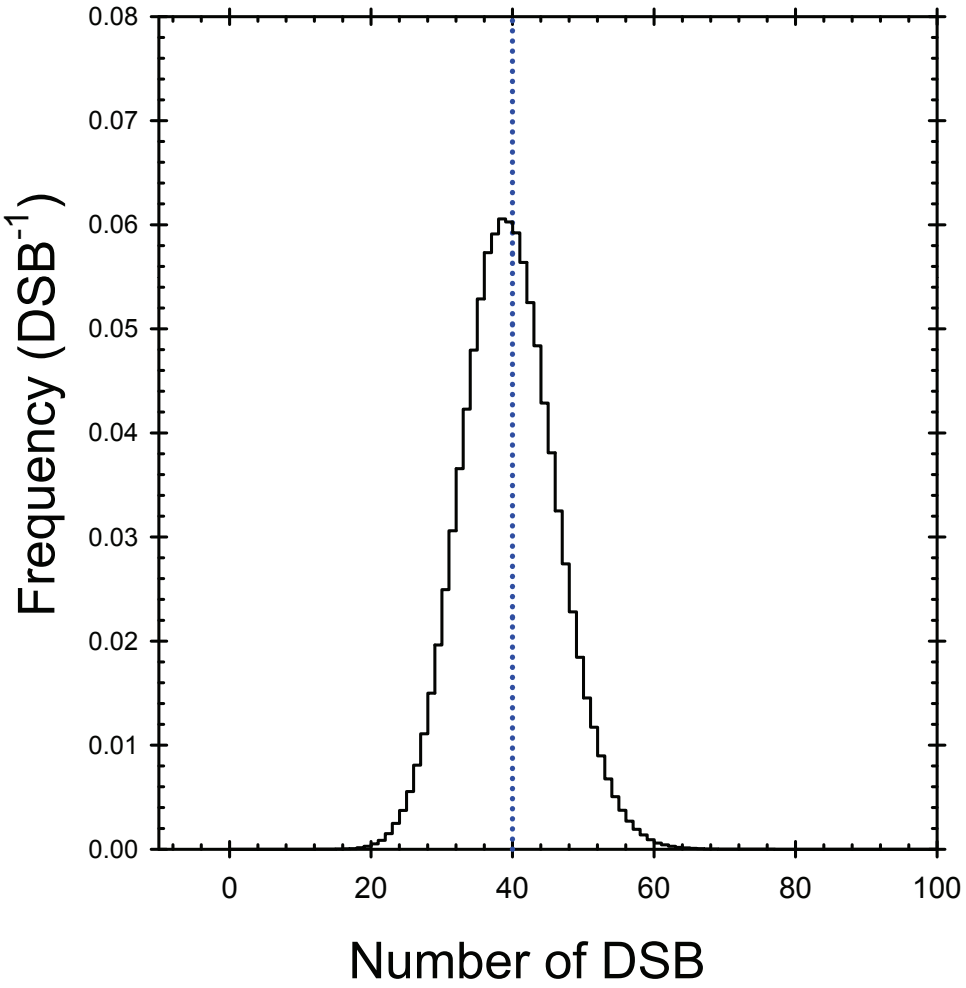


DSB in close spatial proximity are more likely to interact (*less likely to be correctly repaired*) than DSB separated by large distances

High-LET radiation is more effective at producing *spatially and temporally* correlated DSB than low LET radiation

On average, DSB formed by high-LET radiation are more likely to cause harm than DSB from low-LET radiation

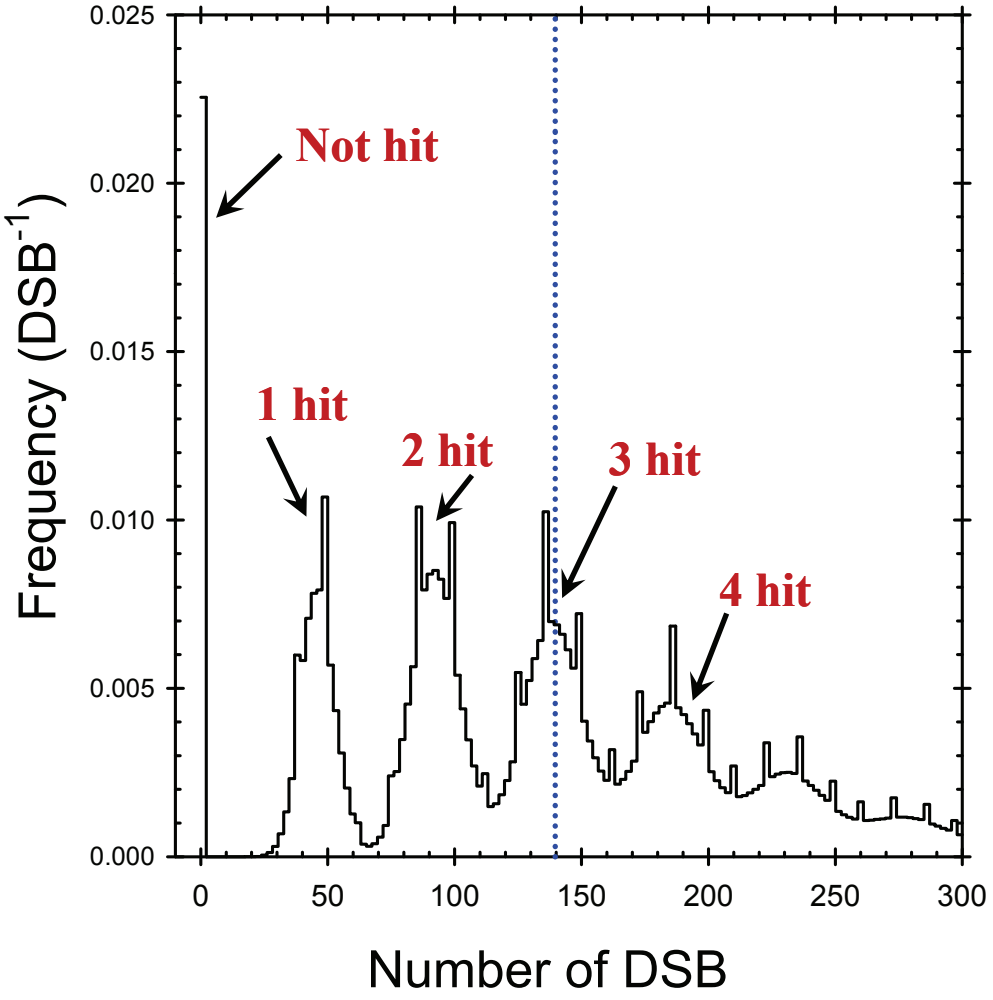
Damage Distribution Among Cells (*3rd level*)



- 1 Gy absorbed dose
- Low LET (1 keV/μm)
- 40 DSB cell^{-1}
- **490.2 tracks**
- 0.0816 DSB track^{-1}

$$\bar{z}_F = 2.04 \text{ mGy}$$

DSB distribution (1 Gy, 2 MeV α particle)



- 1 Gy absorbed dose
- High LET (162.5 keV/μm)
- 139.64 DSB cell^{-1}
- **3.02 tracks**
- 46.3 DSB track^{-1}

$\bar{z}_F = 331.49$ mGy

Nucleus 5 μm in diameter

Effects of Radiation Quality on α and α/β

RADIATION RESEARCH 169, 447–459 (2008)
0033-7587/08 $15.00

Combined Use of Monte Carlo DNA Damage Simulations and Deterministic Repair Models to Examine Putative Mechanisms of Cell Killing

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$$\alpha = \Sigma\theta\left(1 + \frac{\bar{z}_F \Sigma}{\theta / \kappa}\right)$$

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

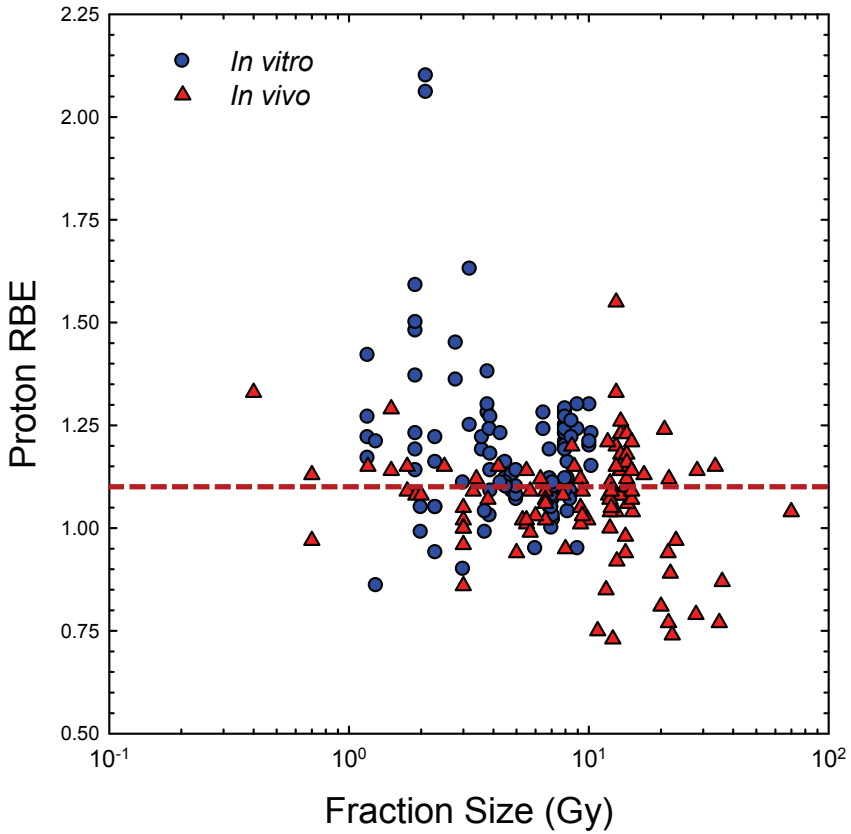
$$\bar{z}_F \cong 0.204 \frac{LET}{d^2}$$

Σ = number of DSB Gy^{-1} cell^{-1} (*estimated using Monte Carlo simulations*)

θ and κ are dimensionless, cell-specific biological constants that are independent or a weak function of LET up to about 80-100 keV/μm

frequency-mean specific energy (Gy)

Proton RBE (*experimental*)



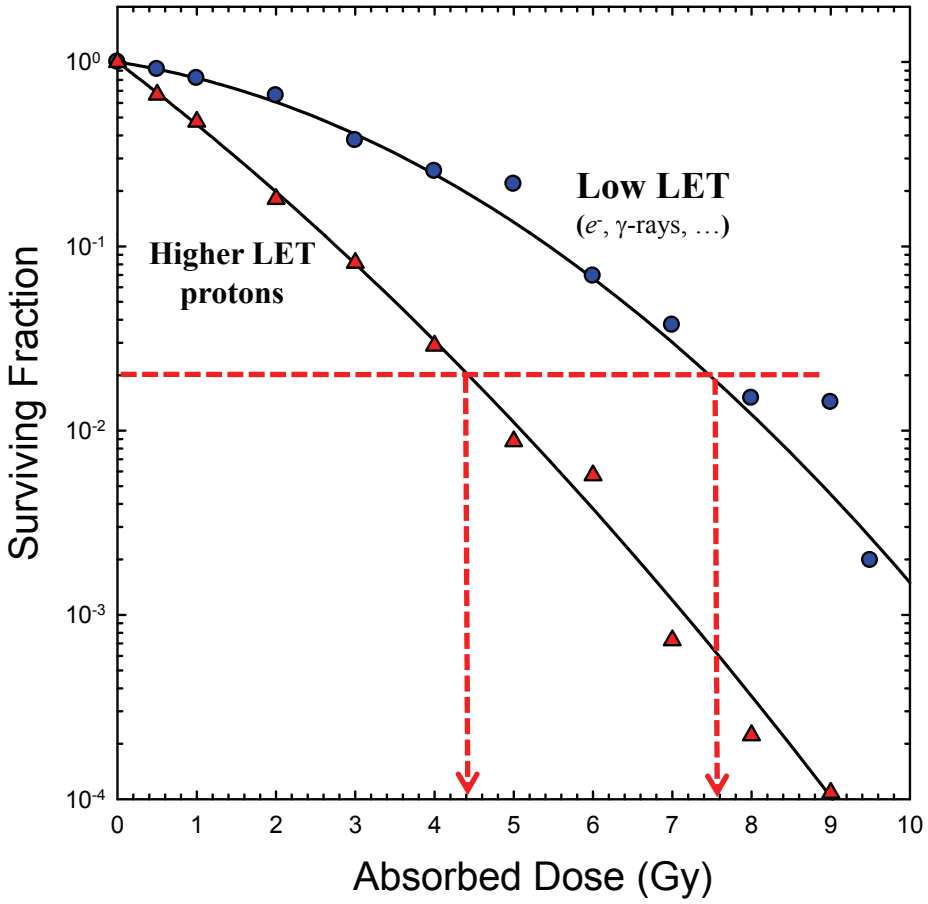
Paganetti H, Niemierko A, Ancukiewicz M, Gerweck LE, Goitein M, Loeffler JS, Suit HD. Relative biological effectiveness (RBE) values for proton beam therapy. *Int J Radiat Oncol Biol Phys.* **53**(2), 407-421 (2002)

In vitro: 1.2 ± 0.2 (0.8, 1.5)

In vivo: 1.1 ± 0.1 (0.8, 1.3)

ICRU 78 (2007) recommends an RBE = 1.1

RBE for Clonogenic Survival



$$RBE \equiv \frac{D_\gamma}{D_p} \cong \frac{7.6\ \text{Gy}}{4.4\ \text{Gy}} = 1.7$$

Equivalent Dose of the Reference Radiation

Outcome reference radiation = Outcome mixture of protons

$$S(D_\gamma) = S(D_1)S(D_2)S(D_3)\cdots S(D_n) = \prod_{i=1}^{n} S(D_i)$$

$$\exp\left[-\alpha_\gamma D_\gamma - \beta_\gamma G_\gamma D_\gamma^{\,2}\right] = \exp\left[\sum_i -\alpha_i D_i - \beta_i G_i D_i^{\,2}\right]$$

Take logarithm, apply quadratic formula and rearrange terms

$$D_\gamma = \frac{(\alpha/\beta)_\gamma}{2G_\gamma}\left\{-1+\sqrt{1+\frac{4G_\gamma}{\alpha_\gamma(\alpha/\beta)_\gamma}\sum_i \alpha_i D_i\left(1+\frac{G_i D_i}{(\alpha/\beta)_i}\right)}\right\}$$

Formula has *explicit* corrections for total dose, fraction size, and dose rate effects
Effect of radiation quality *implicit* in the biological parameters.

α_i/α_γ, $(\alpha/\beta)_i$, $(\alpha/\beta)_\gamma$

RBE for a Mixture of Protons

Define $f_i \equiv \alpha_i / \alpha_\gamma$, $D_p \equiv \sum_{i=1}^{n} D_i$, $G_\gamma \cong \frac{1}{n_\gamma}$, **and** $G_i \cong \frac{1}{n_p}$

$$RBE \equiv \frac{D_\gamma}{D_p} = \frac{n_\gamma (\alpha/\beta)_\gamma}{2D_p}\left\{-1+\sqrt{1+\frac{4}{n_\gamma (\alpha/\beta)_\gamma}\sum_i f_i D_i\left(1+\frac{D_i}{n_p (\alpha/\beta)_i}\right)}\right\}$$

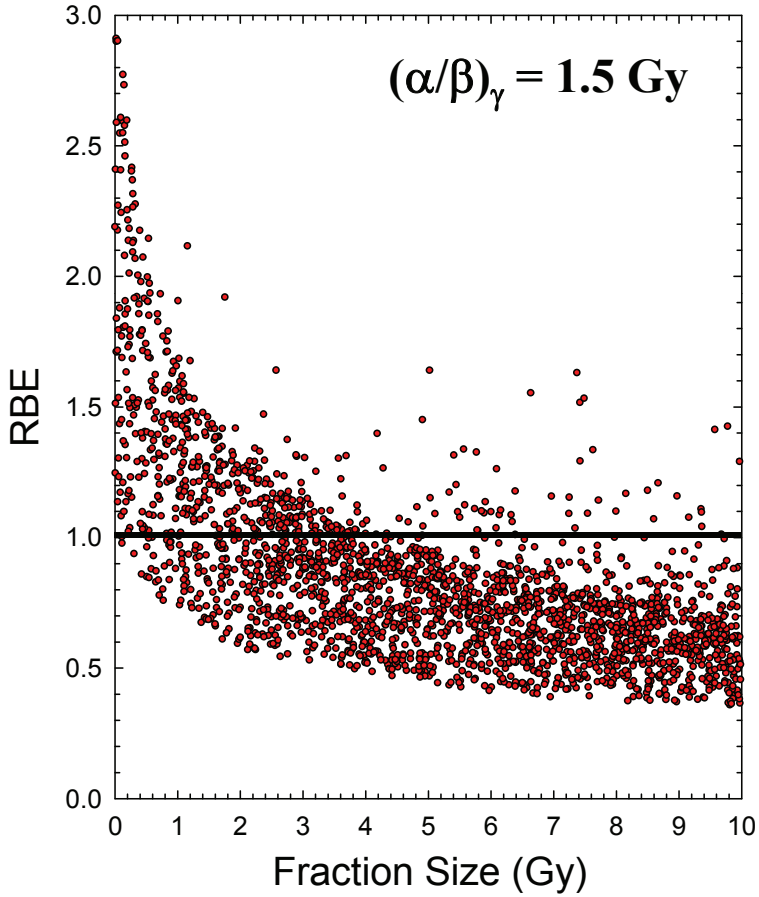
physical parameters: n_γ, n_p, D_p, D_i

biological parameters: f_i, $(\alpha/\beta)_\gamma$, $(\alpha/\beta)_i$

Similar RBE formula derived by Wilkens and Oelfke (2004) and references therein.

Wilkens JJ, Oelfke U, A phenomenological model for the relative biological effectiveness in therapeutic proton beams. *Phys Med Biol.* **49**(13), 2811-2825 (2004).

Possible proton RBE range

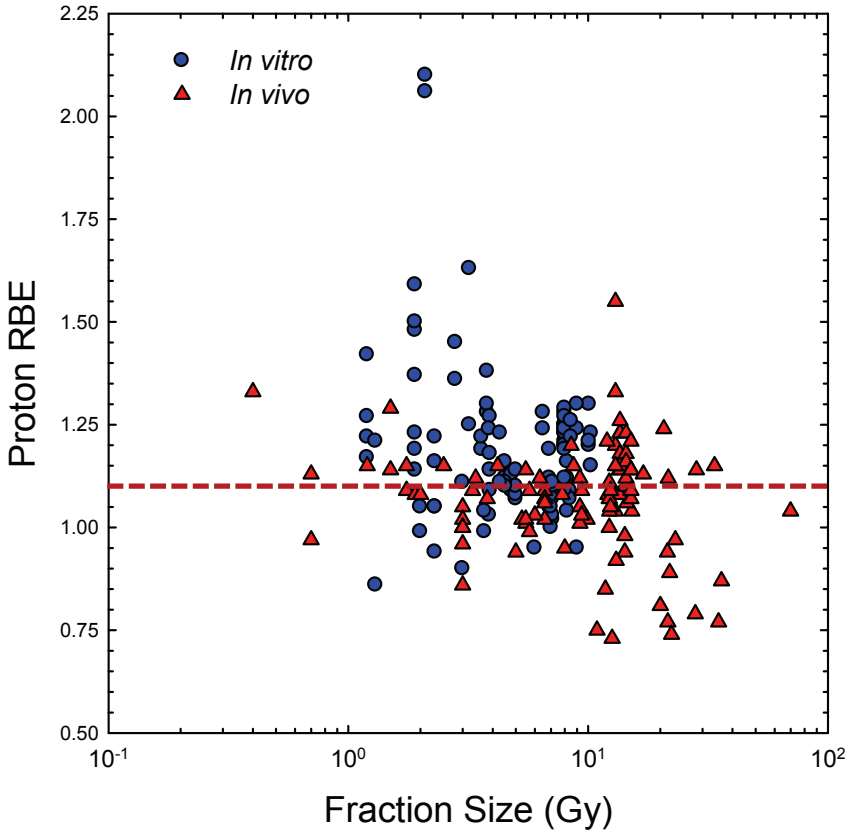


$0.35\ Gy^{-1} \geq \alpha_p \geq \alpha_\gamma$

$100\ Gy \geq (\alpha/\beta)_p \geq (\alpha/\beta)_\gamma$

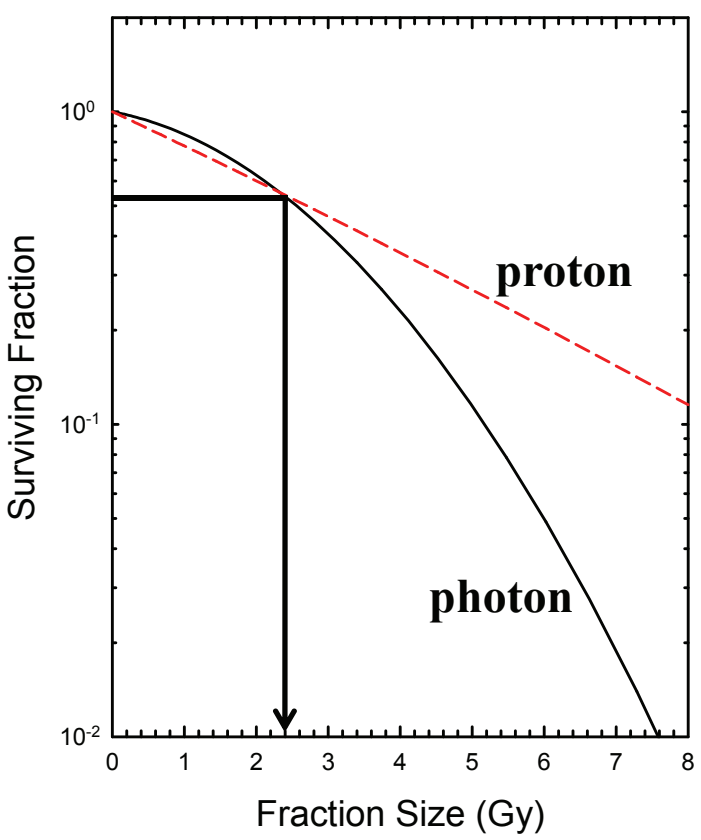
$\alpha_\gamma = 0.1\ Gy^{-1}$

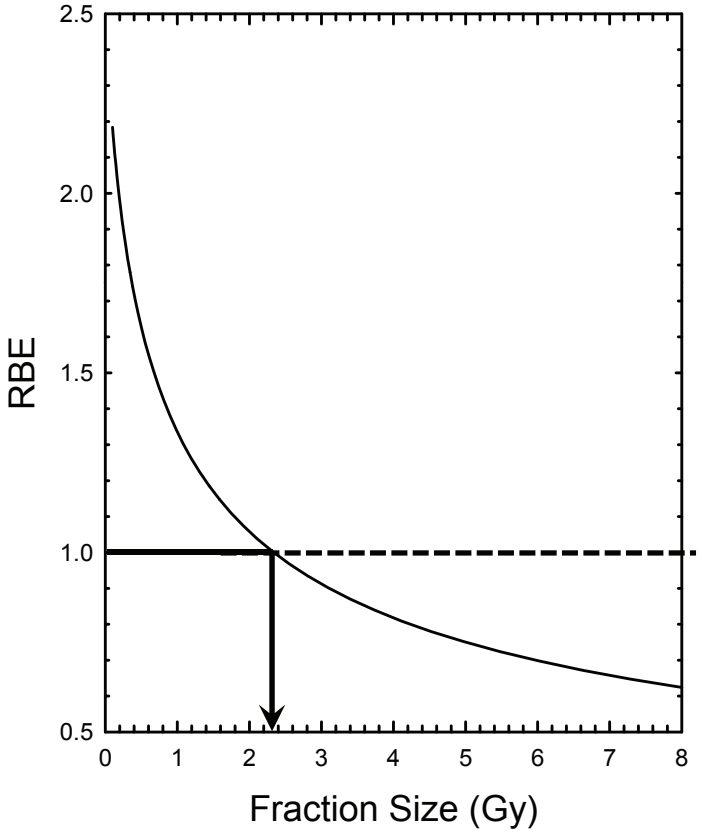
Sampled using MC methods



Paganetti H, Niemierko A, Ancukiewicz M, Gerweck LE, Goitein M, Loeffler JS, Suit HD. Relative biological effectiveness (RBE) values for proton beam therapy. *Int J Radiat Oncol Biol Phys.* **53**(2), 407-421 (2002)

Potential explanation for RBE < 1





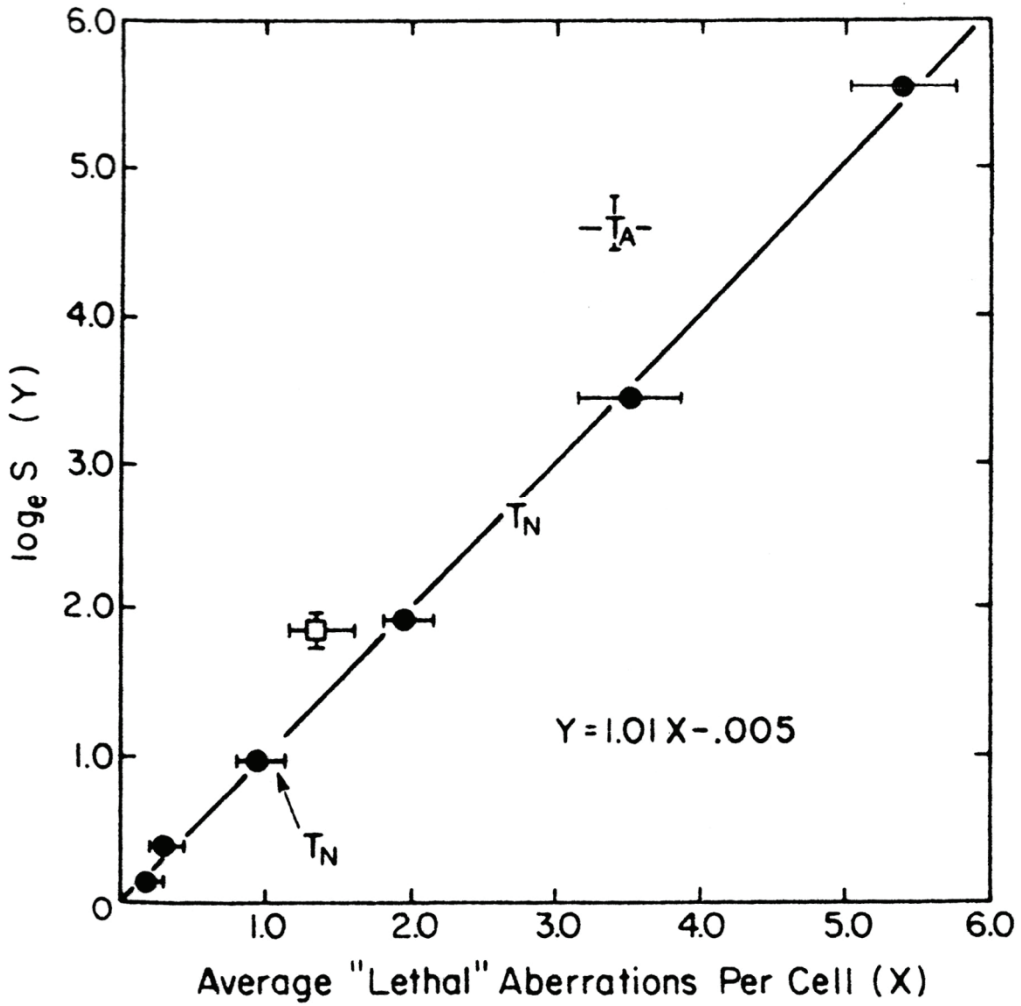
$\alpha_\gamma = 0.1\ \text{Gy}^{-1}$ $\quad$ $\alpha_p = 0.25\ \text{Gy}^{-1}$

$(\alpha/\beta)_\gamma = 1.5\ \text{Gy}$ $\quad$ $(\alpha/\beta)_p = 100\ \text{Gy}$

Is proton RBE constant?

- *Any* RBE in range from 0.8 to 1.5 consistent with available experimental data
- RBE = 1.1 unlikely to be useful (accurate) for
  - Comparing the efficacy of photon vs proton treatments
  - Guiding the selection of appropriate prescription dose and tolerance doses for normal tissues
- Constant RBE *inconsistent* with widely accepted biophysical mechanisms underpinning clonogenic survival, tumor control, …

-ln*S* vs Aberrations (= ***processed*** DSB)

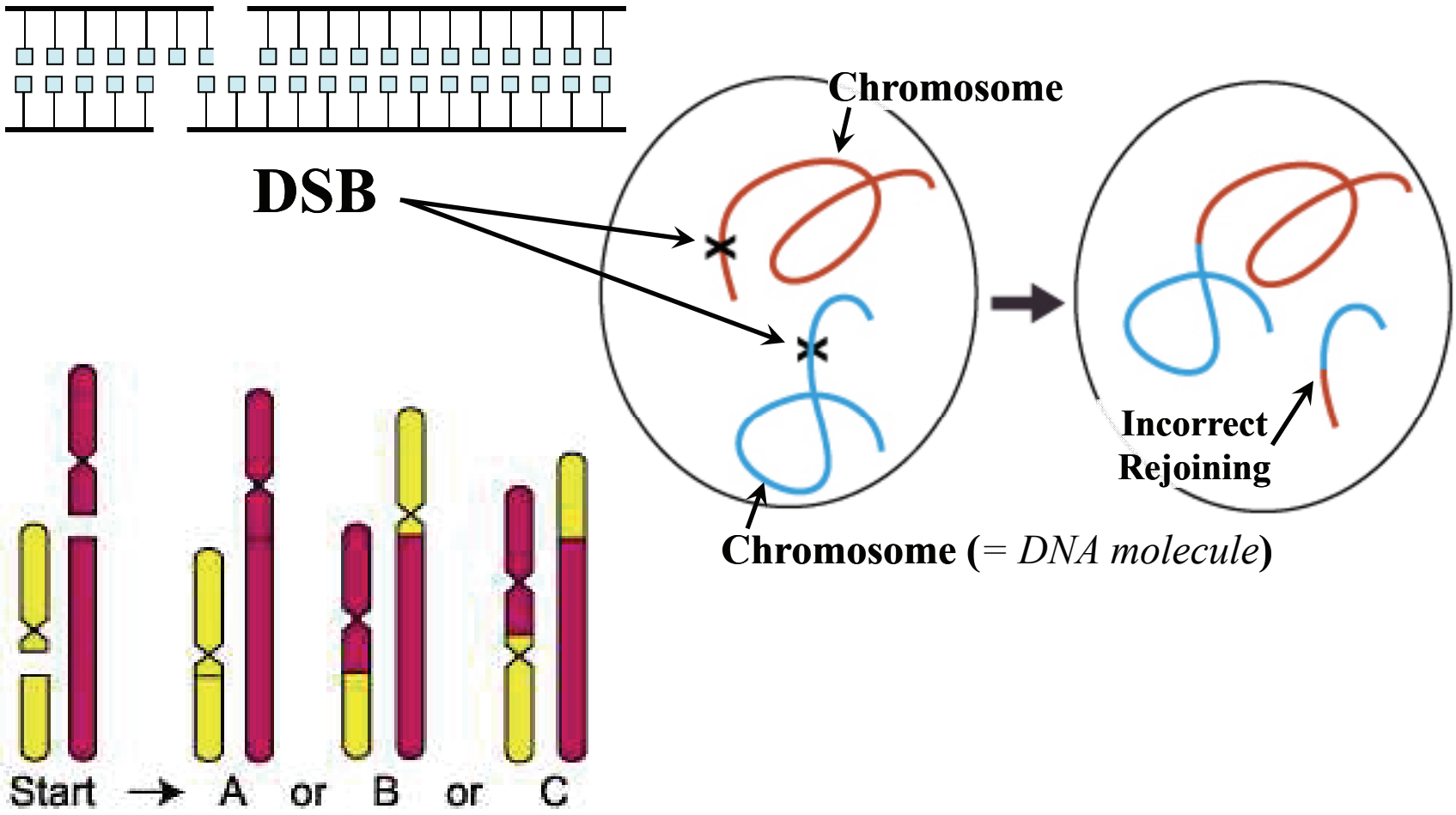


Source: Cornforth and Bedford, *Rad. Res.*, **111**, p 385-405 (1987).

One to one correlation between lethal exchanges (dicentrics and centric rings**) implies this form of damage is a major reason cells are killed by radiation**

AC 1522 normal human fibroblasts irradiated by x-rays

Breakage and Reunion Theory



R.K. Sachs and D.J. Brenner, Chromosome Aberrations Produced by Ionizing Radiation: Quantitative Studies http://web.ncbi.nlm.nih.gov/books/bv.fcgi?call=bv.View..ShowTOC&rid=mono_002

RBE for DSB induction

DSB induction is closely linked to (*but not identical to*) a major cell killing mechanism for ionizing radiation

RBE for DSB induction: dose of a reference radiation needed to produce the same # of DSB as another radiation ("*isoeffect calculation*")

$$RBE \equiv \frac{\{\text{dose of photons}\}}{\{\text{dose of proton}\}} = \frac{D_\gamma}{D_p} = \frac{\Sigma_p}{\Sigma_\gamma}$$

Σ = number of DSB Gy^{-1} $cell^{-1}$

Monte Carlo Damage Simulation (MCDS)

- MCDS successfully reproduces induction of DNA damage predicted by track structure simulations
  - Electrons (> 80 eV), protons (> 105 keV), α (> 2 MeV) up to about 1 GeV (Semenenko and Stewart 2006)
  - Photons from about 80 eV up to 1 GeV (Hsaio and Stewart 2008)
- Reasonable agreement with measured data
  - Number of SSB and DSB per Gy per cell
- Computationally efficient and freely available
  - Damage configurations for 100,000 cells exposed to 1 Gy can be simulated on 2.8 Ghz Pentium in about 1.5 minutes
  - **http://rh.healthsciences.purdue.edu/mcds/**

Y Hsiao, 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)

DSB yields – Track Structure and MCDS

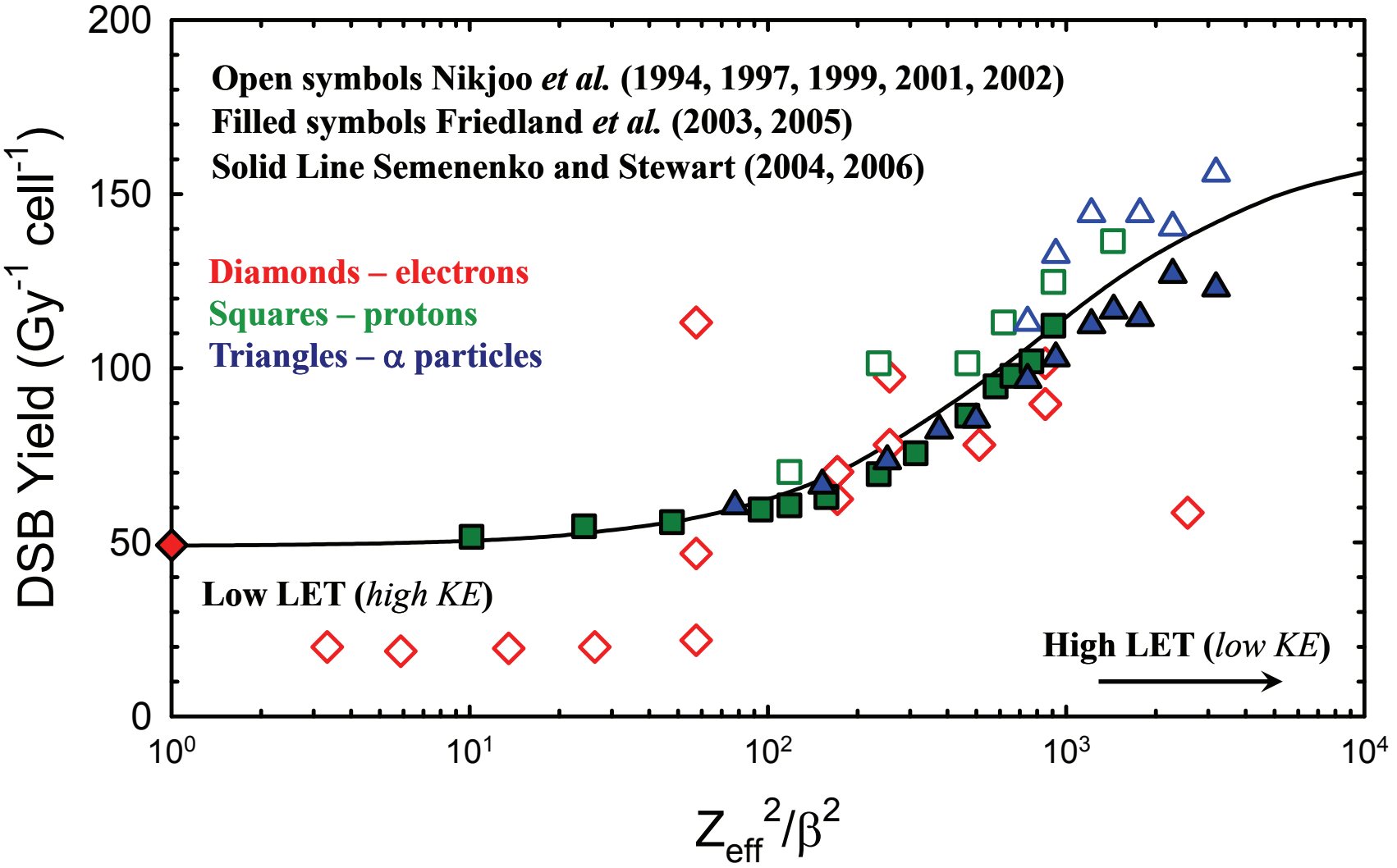
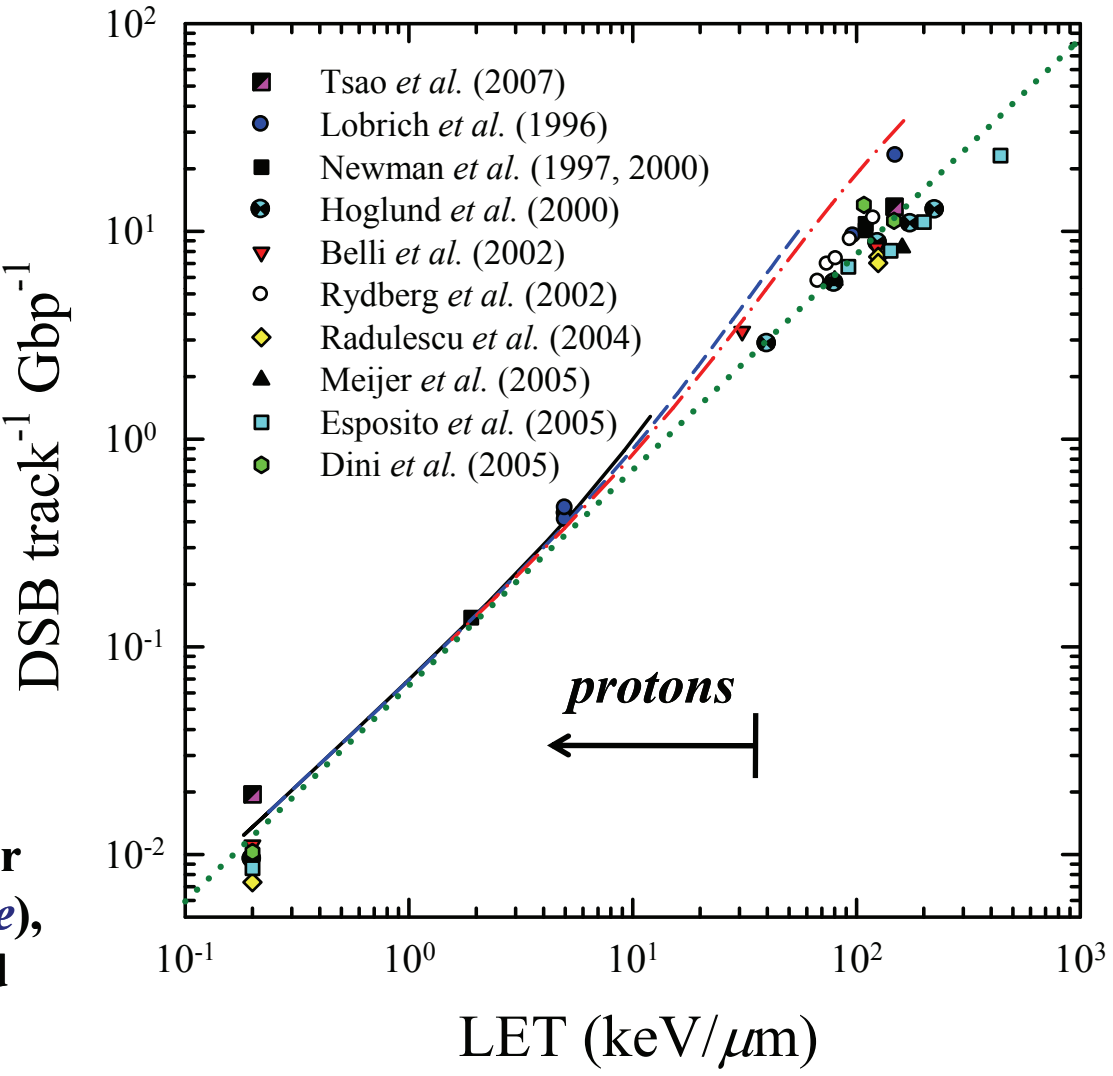


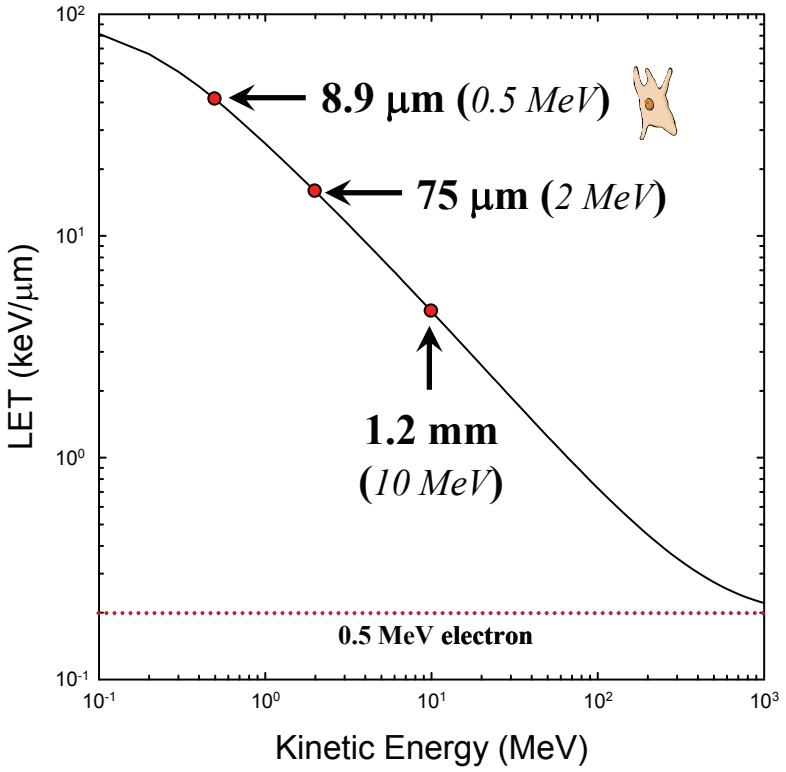
Figure adapted from V.A. Semenenko and R.D. Stewart. Fast Monte Carlo simulation of DNA damage formed by electrons and light ions. *Phys. Med. Biol.* **51**(7), 1693-1706 (2006)

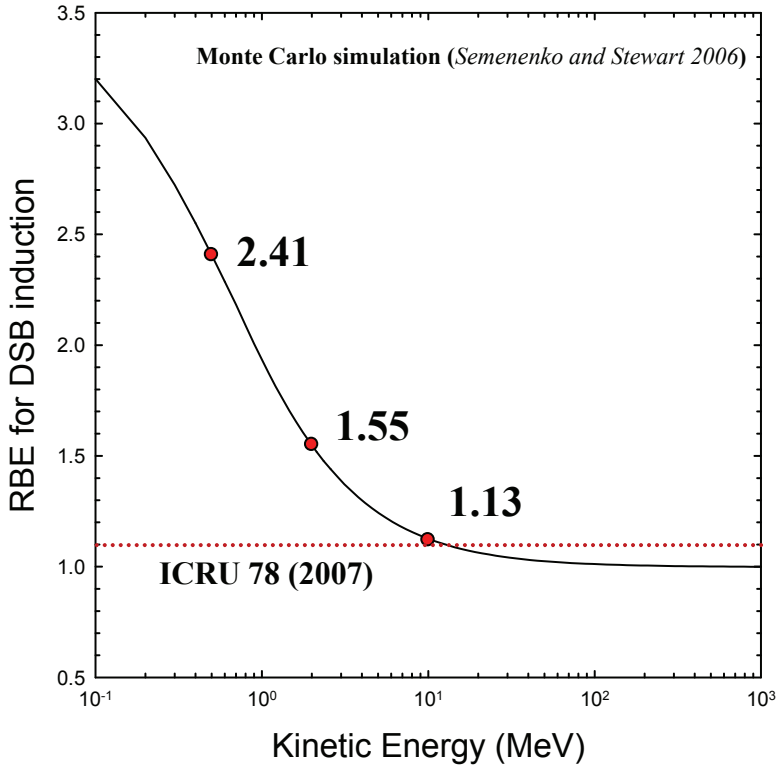
Fragmentation Analysis vs Theory (*per track*)



Lines denote damage yields for electrons (*black*), protons (*blue*), and α particles (*red*) predicted by MCDS

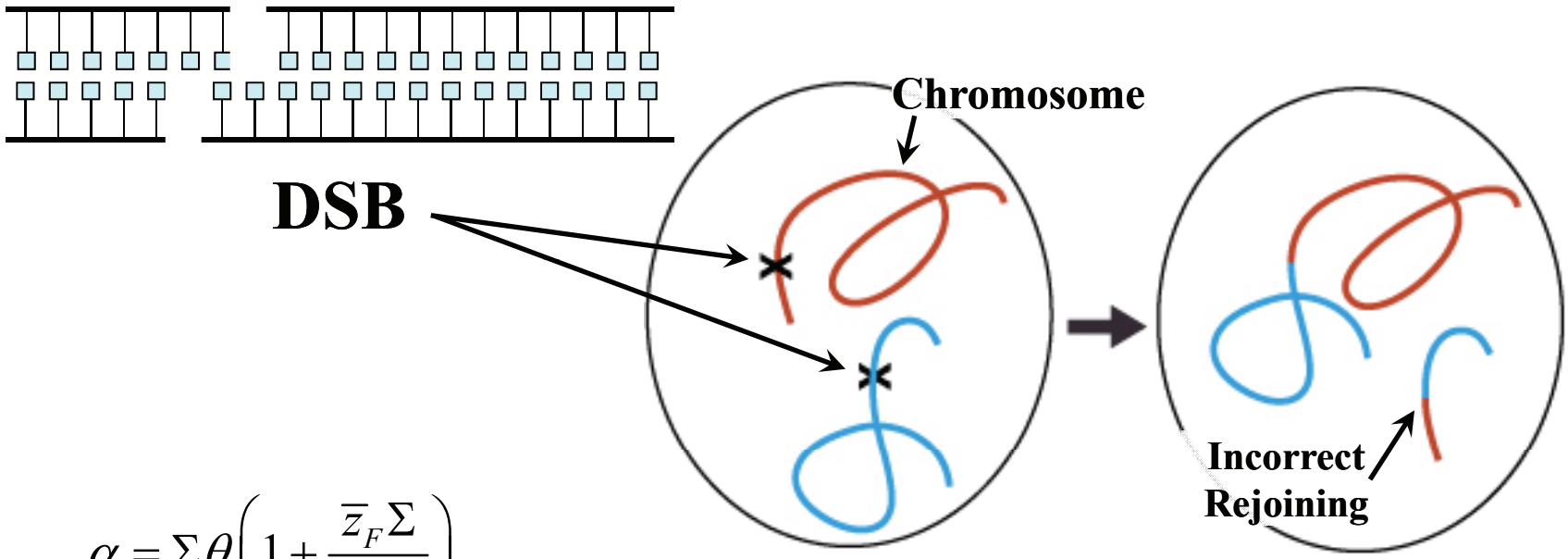
Proton RBE for DSB induction





RBE for DSB induction computed using the MCDS

Model for α and α/β (*conceptual basis*)



$$\alpha = \Sigma\theta\left(1 + \frac{\overline{z}_F \Sigma}{\theta / \kappa}\right)$$

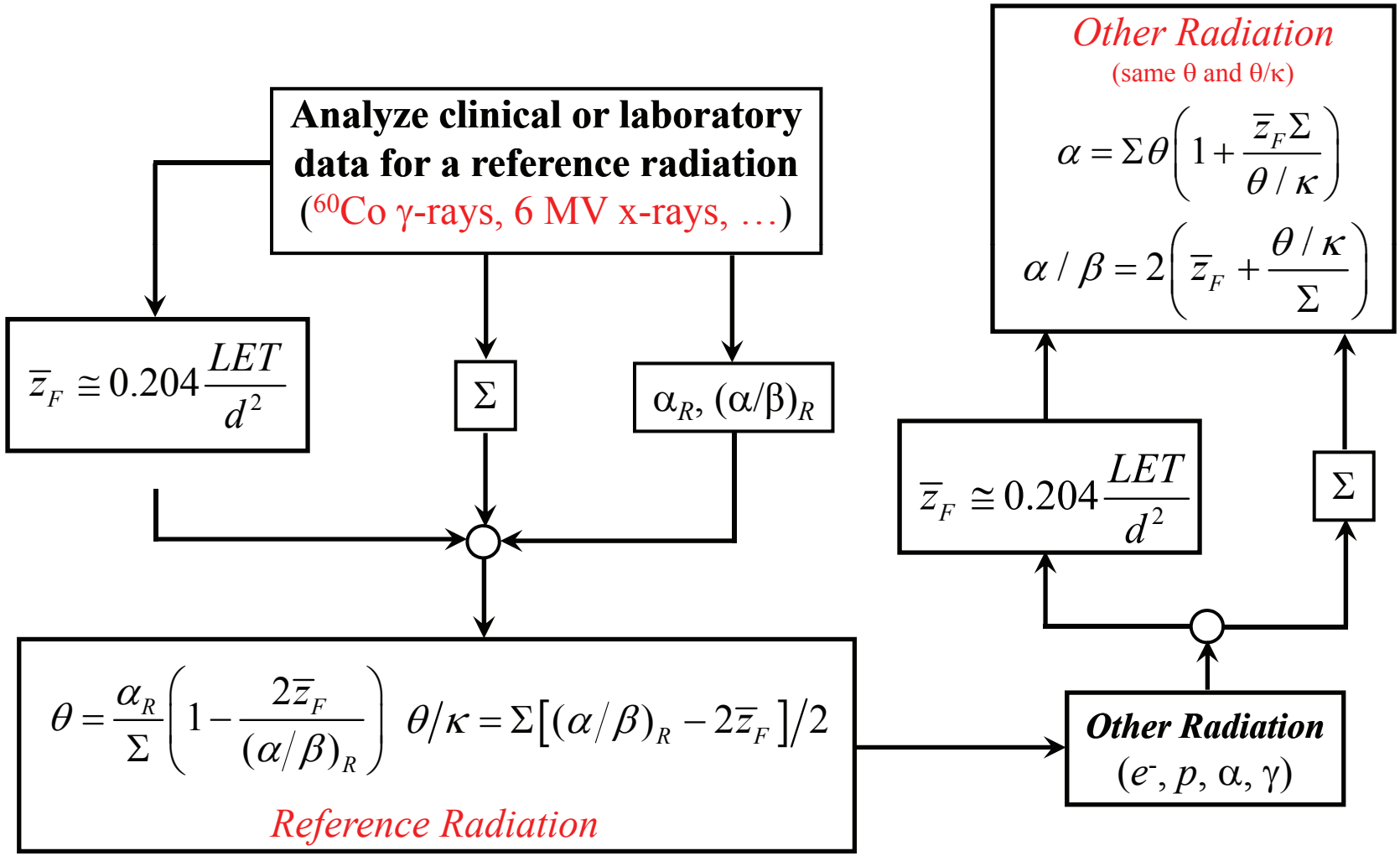
$$\alpha / \beta = 2\left(\overline{z}_F + \frac{\theta / \kappa}{\Sigma}\right)$$

$$\overline{z}_F \cong 0.204 \frac{LET}{d^2}$$

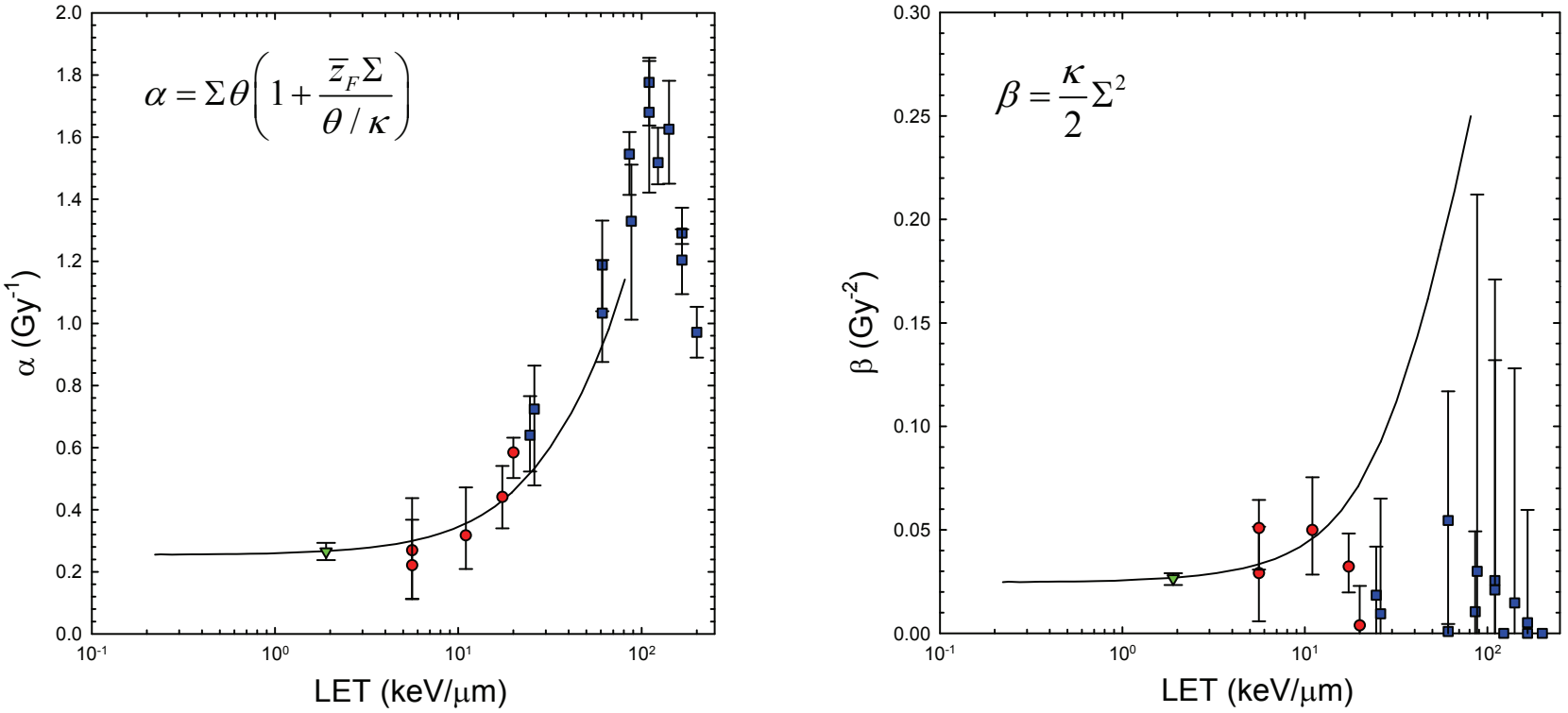
Σ = number of DSB Gy^{-1} cell^{-1} (*estimated using Monte Carlo simulations*)

θ and κ are dimensionless, cell-specific biological constants that are independent or a weak function of LET up to about 80-100 keV/μm

Radiosensitivity Parameters for Protons



Human Kidney T1 cells (*in vitro*)



Radiosensitivity parameters for human kidney cells irradiated in vitro by x-rays, $^{2}H^{1+}$ and $^{4}He^{2+}$ ions. **Filled symbols:** estimates of α and β reported by Carlson *et al.* (2008) for x-rays (filled green triangles), $^{2}H^{+}$ (filled red circles) and $^{4}He^{2+}$ (filled blue squares). Error bars denote the 95% CI. **Solid lines:** predicted LQ parameter for protons with kinetic energies between 0.1 MeV to 1 GeV ($\theta = 5.27\times10^{-3}$ and $\theta/\kappa = 249.5$). Estimate of θ and θ/κ computed from LQ parameters for x-rays with $\Sigma = 50$ DSB Gy^{-1} cell^{-1}, $\alpha = 0.265$ Gy^{-1}, $\alpha/\beta = 10$ Gy.

Carlson DJ, Stewart RD, Semenenko VA, Sandison GA, 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)

Maximum (*low dose*) RBE

When $D \ll \alpha/\beta$, $S(D) \cong \exp(-\alpha D)$ and

$$RBE = \frac{n_\gamma(\alpha/\beta)_\gamma}{2D_p}\left\{-1+\sqrt{1+\frac{4}{n_\gamma(\alpha/\beta)_\gamma}\sum_i f_i D_i\left(1+\frac{D_i}{n_p(\alpha/\beta)_i}\right)}\right\}$$

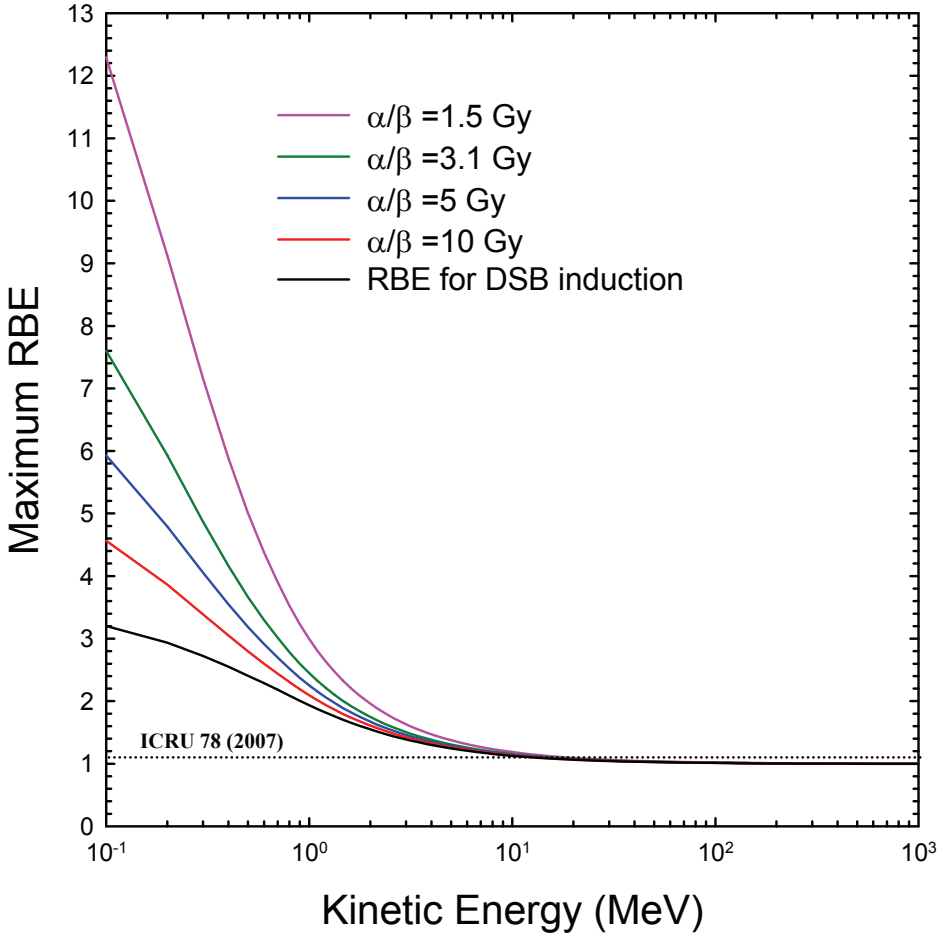
reduces to $RBE = \frac{1}{D_P}\sum_i f_i D_i$ **where**

$$f_i \equiv \frac{\alpha_i}{\alpha_\gamma} = \frac{\Sigma_i\left(1+\frac{\overline{z}_F(LET_i)\Sigma_i}{\theta/\kappa}\right)}{\Sigma_\gamma\left(1+\frac{\overline{z}_\gamma\Sigma_\gamma}{\theta/\kappa}\right)} \cong \frac{\Sigma_i}{\Sigma_\gamma}\left(1+\frac{\overline{z}_F(LET_i)\Sigma_i}{\theta/\kappa}\right) \geq \frac{\Sigma_i}{\Sigma_\gamma}$$

Σ_i (*protons*) and Σ_γ (*reference radiation*) determined using the MCDS (Semenenko and Stewart 2006, Hsaio and Stewart 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)

Maximum Proton RBE



Maximum RBE increases as α/β decreases

RBE for cell survival is *always* greater than or equal to RBE for DSB induction

1.93 to 3.00 (*1 MeV*)

1.13 to 1.18 (*10 MeV*)

1.05 to 1.10 (*25 MeV*)

< 1.01 (> *100 MeV*)

For comparison, ICRU 78 recommends an RBE = 1.1

Effective RBE in the SOBP

Proton Dose Distribution → **Equivalent Photon Dose Distribution** → **EUD_γ**

↓

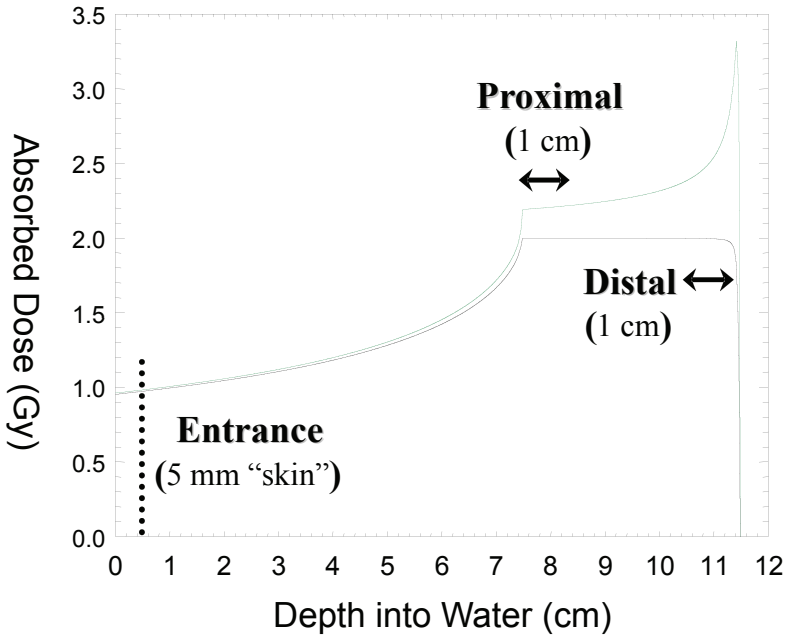
EUD_p

$$\overline{RBE} \equiv \frac{EUD_\gamma}{EUD_p}$$

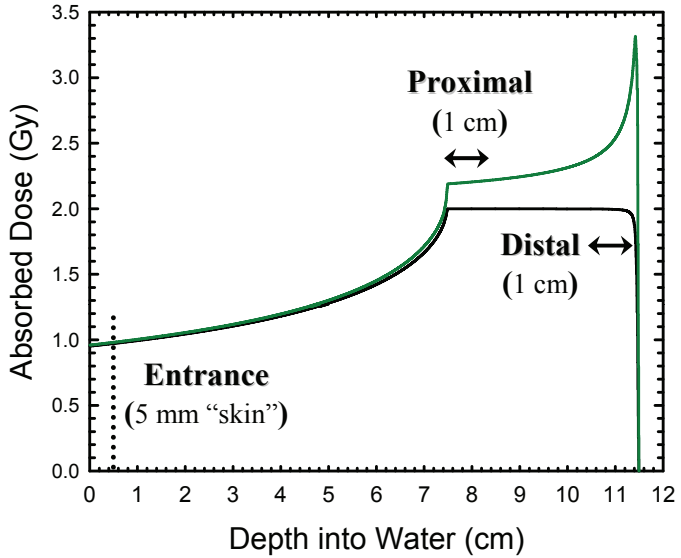
Niemierko, *Med. Phys.* **24**(1), 103-110 (1997)

125 MeV ± 0.3 MeV protons incident on water phantom

Pencil beam CSDA algorithm (NIST stopping power)



RBE in the SOBP (4 cm target, 2 Gy fraction)

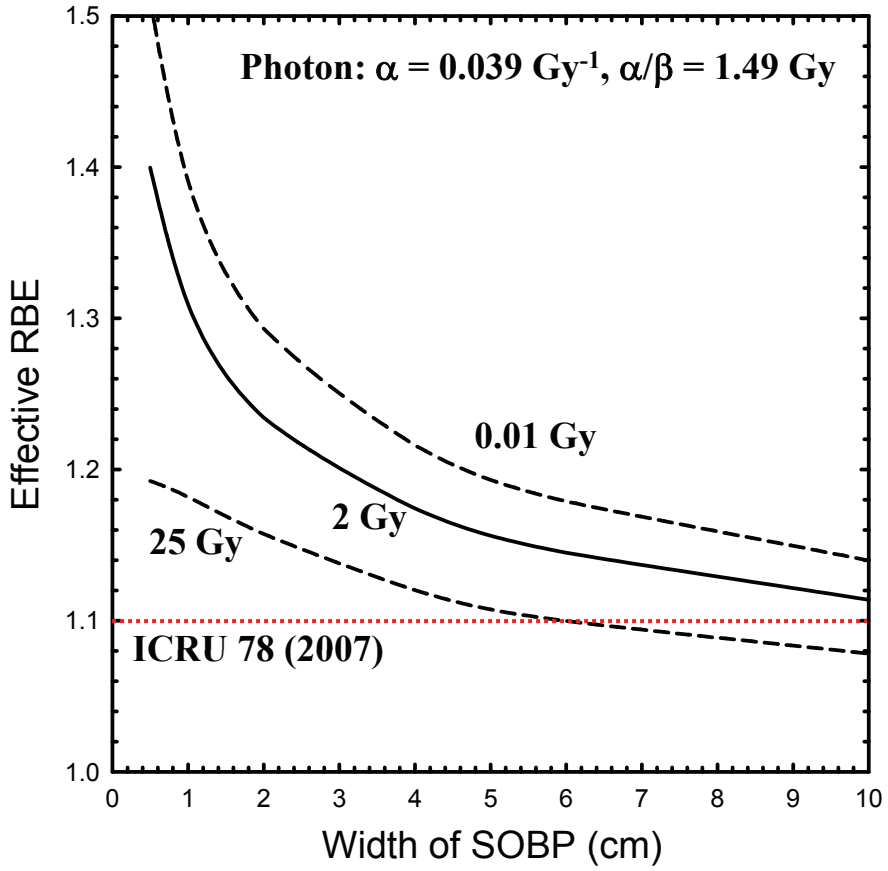


	α = 0.039 Gy^{-1}, α/β = 10 Gy		
Region	**EUD$_p$**	**EUD$_\gamma$**	**RBE**
Skin	0.96	0.97	1.00
Proximal	1.95	2.03	1.04
Middle	2.00	2.24	1.12
Distal	1.81	2.81	1.57
Target Avg.	2.00	2.24	1.12

	α = 0.039 Gy^{-1}, α/β = 1.49 Gy		
Region	**EUD$_p$**	**EUD$_\gamma$**	**RBE**
Skin	0.96	0.97	1.01
Proximal	1.95	2.06	1.06
Middle	2.00	2.34	1.17
Distal	1.81	3.27	1.83
Target Avg.	2.00	2.34	1.17

RBE increases as photon α/β decreases

Effect of Target and Fraction Size



RBE *increases* as target size *decreases*

RBE *decreases* as fraction size *increases*

Summary and Conclusions

- Entrance RBE (e.g., skin) close to 1.0
- RBE in distal edge of SOBP higher than proximal edge (1.05 $\rightarrow$ 1.8)
  - Potential for biological hot and cold spots
- Average RBE in target (1.1 to 1.5)
  - Increases as α/β decreases (*tissue and tumor specific*)
  - Increases as target size decreases
  - Increases as fraction size decreases
  - For *large fractions*, RBE < 1
  - Range comparable to experimental observations (0.8 to 1.5)

Monte Carlo Simulation of the Effects of Oxygen on Clustered DNA Lesions Formed by Ionizing Radiation

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Presented at

2008 RRS Annual Meeting (Sept 21-25, 2008**)**
Boston, MA

Stochastic Track Models
Monday September 22, 2008
2:30 to 4:30 pm

PURDUE
UNIVERSITY

School of Health Sciences
http://healthsciences.purdue.edu

Effects of oxygen on DNA damage induction

Long known that oxygen is a powerful modulator of DNA damage induction and closely related endpoints, such as clonogenic death and mutation

- Cells irradiated under reduced oxygen sustain less damage and are much more likely to survive (*factor ~ 2-4*)

Models to predict the effects of oxygen on cluster induction could be used to help test hypotheses such as

Reduced oxygen levels at the time of irradiation decreases cluster complexity (*number of DNA lesions per cluster*) and reduces the overall cluster yield per cell and per unit dose.

The rate and fidelity (*efficiency*) of cluster repair increases as cluster complexity decreases. Enhanced repair of clusters increases cell survival.

Chemical Basis of the Oxygen Effect

Competition between oxygen fixation and chemical repair is the prevailing hypothesis (von Sonntag 2006)

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

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

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

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

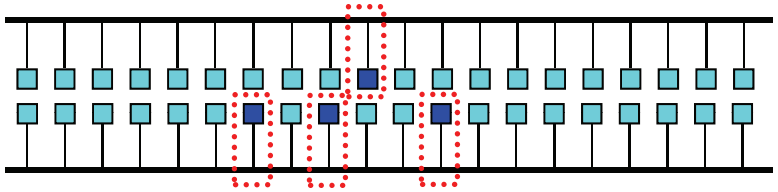
(*5*) DNA· → DNA lesion (*biochemical repair required*)

*** 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…**

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

MCDS Modification – Step 1

Use the original MCDS to simulate the location of DNA radicals



At this stage of the simulation…

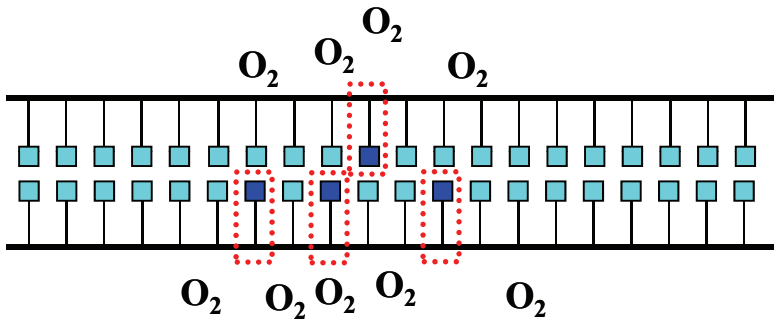
All lesions formed in the original MCDS treated as a radical that may undergo fixation or chemical repair

No distinction made between radicals formed through direct and indirect mechanisms

Preserves the ability of the MCDS to simulate lesion (*radical*) clustering effects without introducing any *additional parameters* into the modeling process.

MCDS Modification – Step 2 (*conceptual basis*)

Oxygen is uniformly distributed near the DNA and able to interact with all DNA radicals with equal probability



If *oxygen fixation* occurs (DNA· + O_2 → DNA-O_2·), radical converted to a strand break or damaged base *as in the original MCDS* – cluster yields for normoxic conditions same as original MCDS.

"Fixation" implicitly includes other processes that convert DNA radicals to a form requiring biochemical repair.

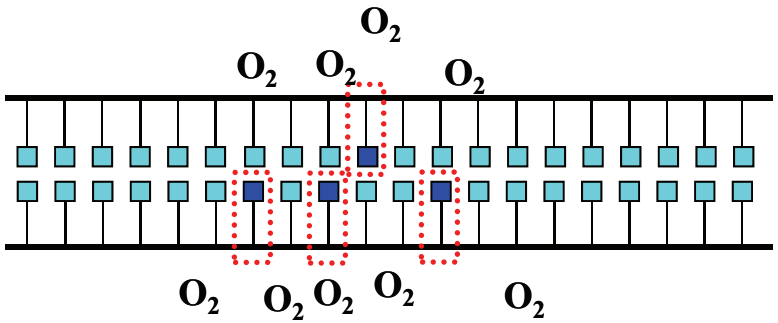
DNA· → DNA lesion (*biochemical repair*)

If *chemical repair* occurs (DNA· + RSH → DNA), DNA is restored to its original (*undamaged*) state – *lesion not created*

Chemical repair or fixation?

Define *f* as the fraction of the DNA radicals that undergo chemical repair

Fraction (1-*f*) of the DNA radicals are "fixed" by oxygen



$$f\left(\left[O_2\right]\right) = 1 - \frac{\left[O_2\right] + K}{\left[O_2\right] + M \cdot K}$$

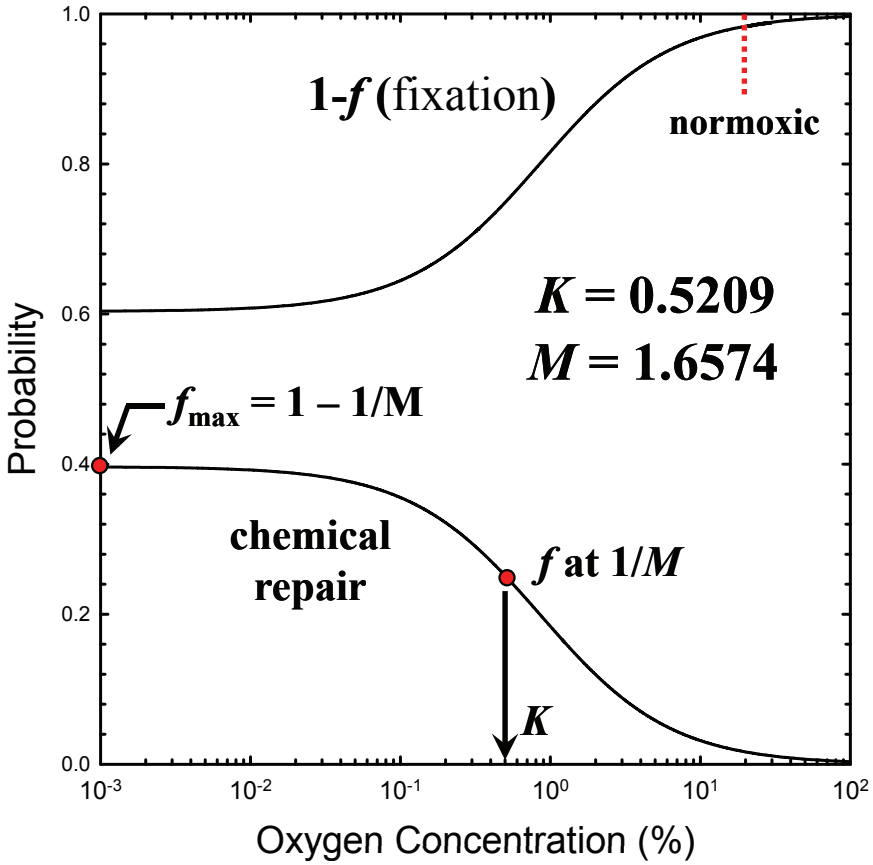
[O_2] = oxygen concentration at time of irradiation

Formula is derived from (*related to*) oxygen-effect formula of Alper and Howard-Flanders (1956)

Introduces two adjustable parameters (*M* and *K*) into the modeling process.

Alper T, Howard-Flanders P. Role of oxygen in modifying the radiosensitivity of E. coli B, *Nature* (London) **178**, 978–979 (1956).

Effect of O_2 on fixation and chemical repair

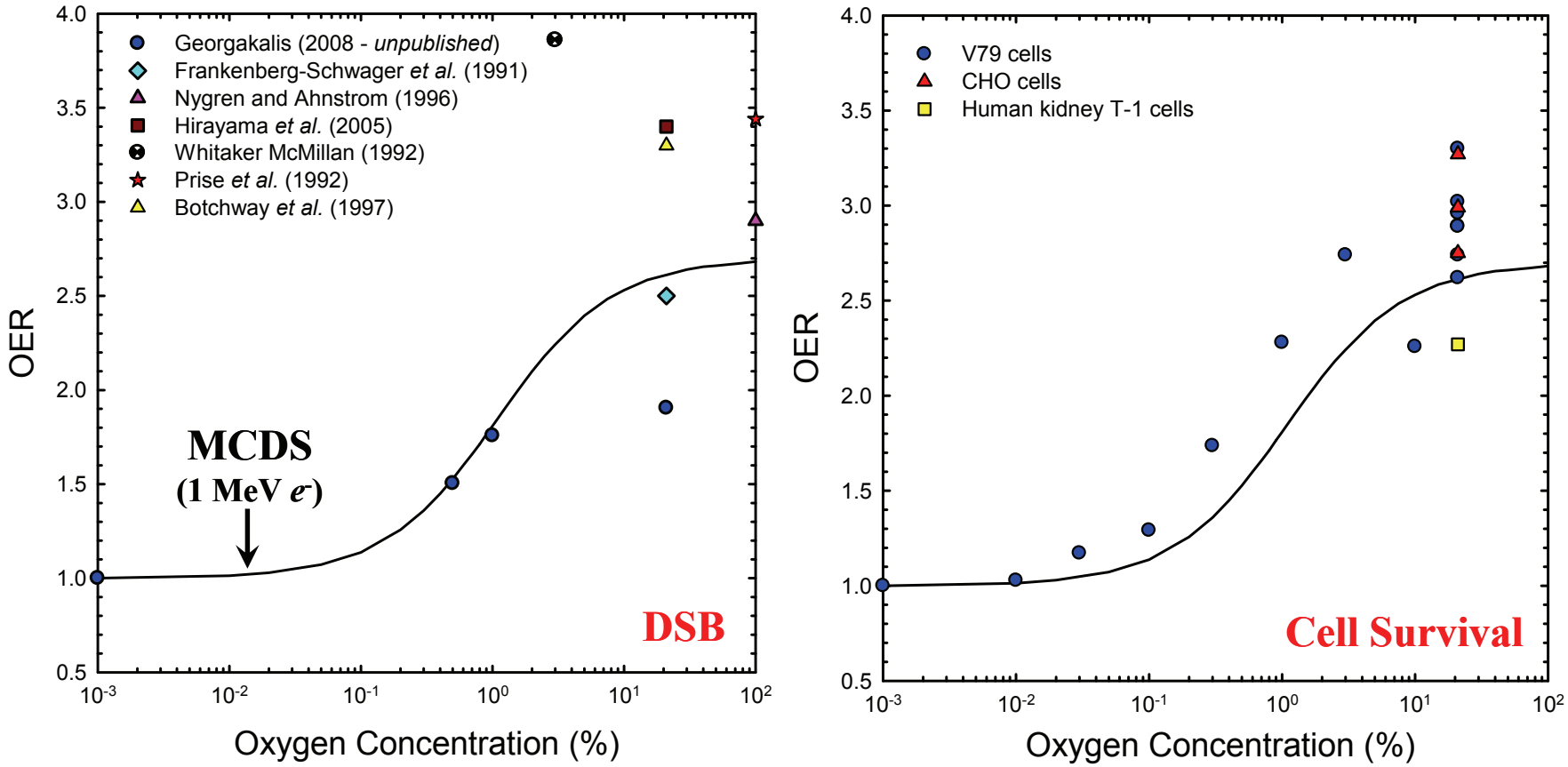


$$f\left(\left[O_2\right]\right) = 1 - \frac{\left[O_2\right] + K}{\left[O_2\right] + M \cdot K}$$

M **determines maximum fraction of radicals fixed at 0% O_2**

K **= oxygen concentration at which** ***f*** **equals 1/*M***

OER for Damage Induction (*low LET*)



Trends and estimates of OER for DSB induction and cell survival comparable to values predicted by MCDS ($K = 0.5209$, $M = 1.6574$).

Carlson DJ, Stewart RD, Semenenko VA, Effects of oxygen on intrinsic radiation sensitivity: A test of the relationship between aerobic and hypoxic linear-quadratic (LQ) model parameters. *Med Phys.* **33**(9), 3105-3115 (2006).

Interplay between oxygen and LET

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

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

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

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

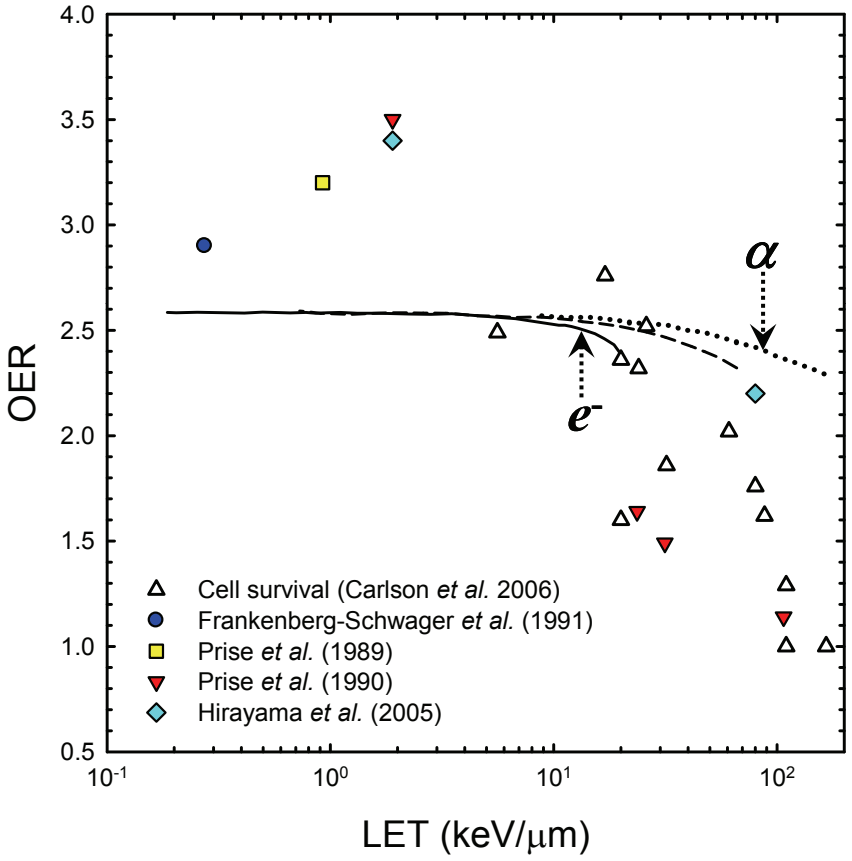
(*5*) **DNA· → DNA lesion (***biochemical repair required***)**

If ionization does not substantially alter the local cellular environment (e.g., "*oxygen-in-track hypothesis*"), might expect reactions (*3*)-(*5*) to be same for low and high LET radiation.

$$f([O_2]) = 1 - \frac{[O_2] + K}{[O_2] + M \cdot K}$$

Assume *M* and *K* are independent of radiation quality.

OER with *f* independent of LET



Model cannot easily explain the decrease in the OER as LET increases

2 MeV α
(162.5 keV/μm)
→
***f* = 39.6%**

Number of Lesions	DSB Yield (%) Anoxic	Normoxic
1	-	-
2	16.033	5.148
3	21.070	9.163
4	18.900	10.914
5	14.523	11.180
6	10.345	10.490
7	6.929	9.408
8	4.558	8.143
9	2.937	6.921
10	1.850	5.716
11	1.142	4.711
12	0.676	3.823
13	0.418	3.059
14	0.254	2.467
15	0.150	1.939
≥ 16	0.214	18.207
Avg per DSB	**4.711**	**7.859**

Possible explanation for LET effect?

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

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

(*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*)

Ionization does not substantially alter the local cellular environment (*reactions 3-5 same for low and high LET radiation*), but reaction *1* is enhanced relative to reaction *2*

$$f\left(\left[O_2\right]\right) = 1 - \frac{\left[O_2\right] + K}{\left[O_2\right] + M(l) \cdot K}$$

***K* isindependent of radiation quality and *M* becomes function of radiation quality (*convenient way to implement effect into model*)**

OER with *f* a function of radiation quality

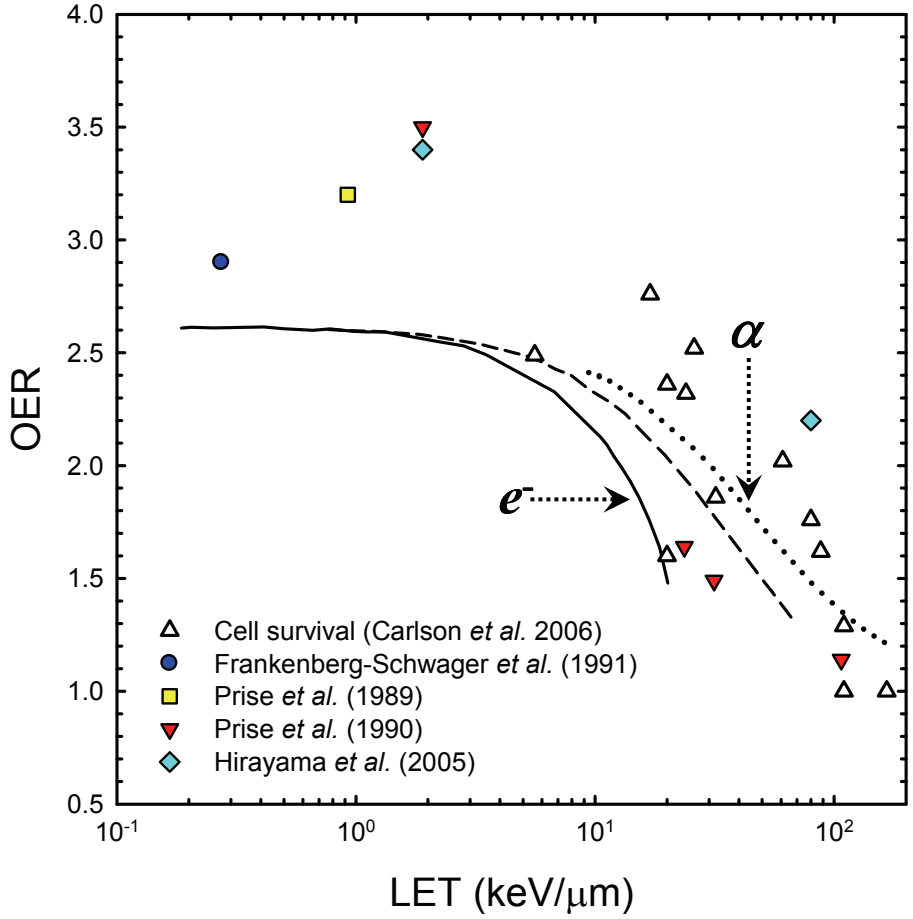
$$f\left([O_2]\right) = 1 - \frac{[O_2] + K}{[O_2] + M(l) \cdot K}$$

$$M(l) = M_0 - \frac{(M_0 - 1)}{1 + q / l}$$

$$\text{where } l \equiv \left(\frac{Z_{eff}}{\beta} \right)^2$$

$$Z_{eff} = Z\left[1 - \exp\left(-125\beta Z^{-2/3}\right)\right]$$

$$\beta = \sqrt{1 - \frac{1}{\left(1 + T / m_0 c^2\right)^2}}$$



$M_0 = 1.658326$, $q = 817.2638$, $K = 0.5209$

Effect of Oxygen on Cluster Complexity

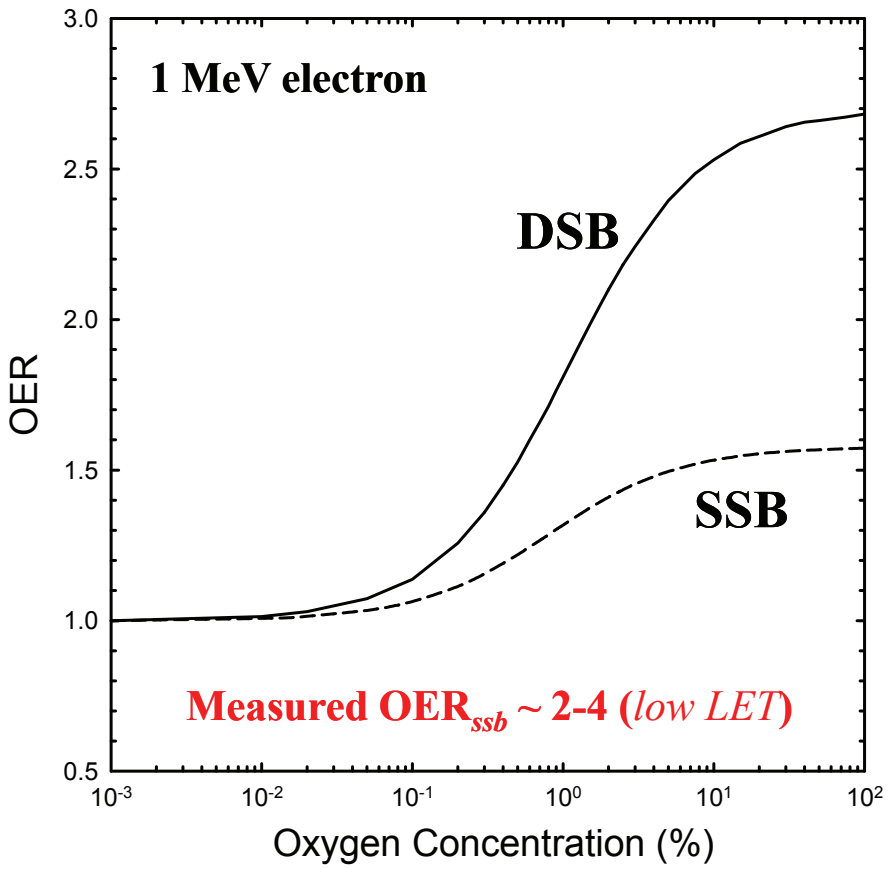
Number of Lesions	DSB Yield (%)	
	Anoxic	Normoxic
1	-	-
2	6.969	4.987
3	11.678	8.856
4	13.178	10.730
5	12.721	10.969
6	11.266	10.388
7	9.600	9.347
8	7.799	8.125
9	6.264	6.924
10	4.928	5.809
11	3.819	4.796
12	2.945	3.881
13	2.214	3.168
14	1.694	2.555
15	1.279	2.020
≥ 16	3.645	7.446
Avg per DSB	**6.856**	**7.994**
OER	**1.217**	

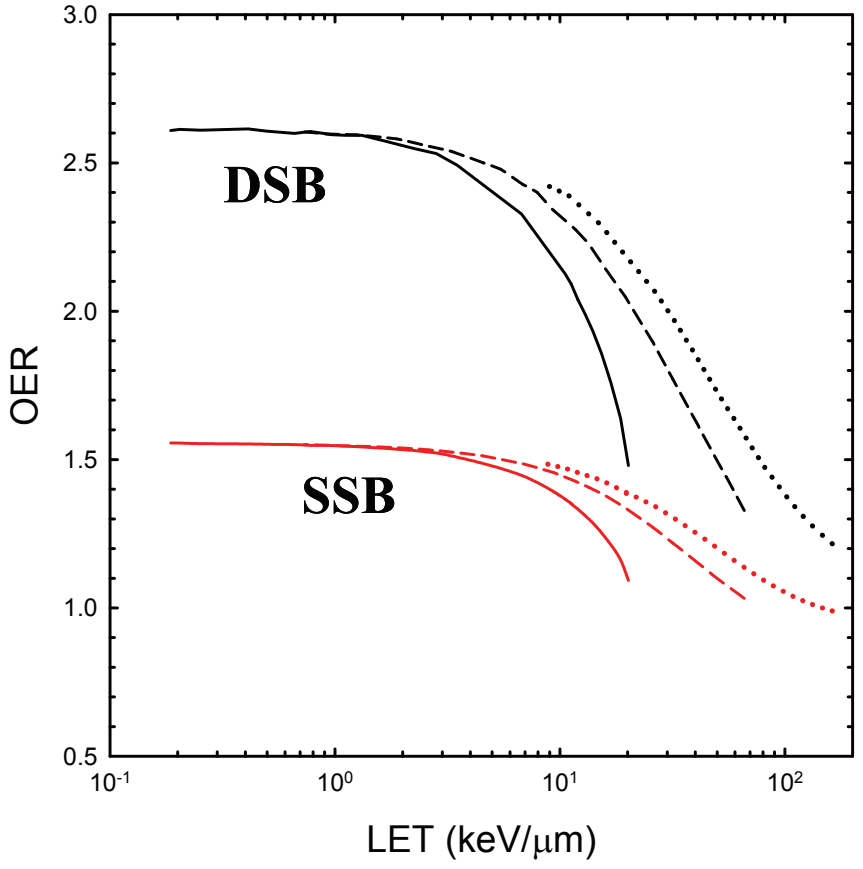
2 MeV α (162.5 keV/μm)

Number of Lesions	DSB Yield (%)	
	Anoxic	Normoxic
1	-	-
2	64.844	49.407
3	25.854	30.495
4	7.117	12.936
5	1.700	4.786
6	0.385	1.603
7	0.081	0.532
8	0.015	0.166
9	0.004	0.054
10	-	0.016
11	-	0.004
12	-	0.001
13	-	0.001
14	-	0.000
15	-	-
≥ 16	-	-
Avg per DSB	**2.473**	**2.813**
OER	**2.585**	

1 MeV e^- (0.186 keV/μm)

OER for SSB and DSB induction





$$OER_{dsb} \cong (OER_{ssb})^2 \cong M(l)^2$$

Summary

- Predicted trends in the OER for DSB induction consistent with estimates derived from measured data for DSB induction *and* cell survival (OER ~ *2 to 3*)
  - Three new parameters introduced into the modeling process to account for oxygen concentration (*M* and *K*) and to correct for the effects of radiation quality (*q*)
  - As LET increases, the probability chemical repair occurs per initial DNA radical may decrease (oxygen fixation increases and/or lesions are directly created)
- Predicted OER for SSB induction approximately equal to the square root of the OER for DSB induction (OER ~ 1.4 to 1.7)
  - Most of the measured data suggest a higher OER for SSB induction
- Average cluster complexity increases as the oxygen concentration increases
  - **1 MeV e^-** (2.5 lesions/DSB 0% O_2 and 2.8 lesions/DSB 21% O_2)
  - **2 MeV α** (6.8 lesions/DSB 0% O_2 and 8.0 lesions/DSB 21% O_2)