A Nanodosimetry-Based L-Q Model of Cell Survival in Support of Cf-252 Neutron Brachytherapy

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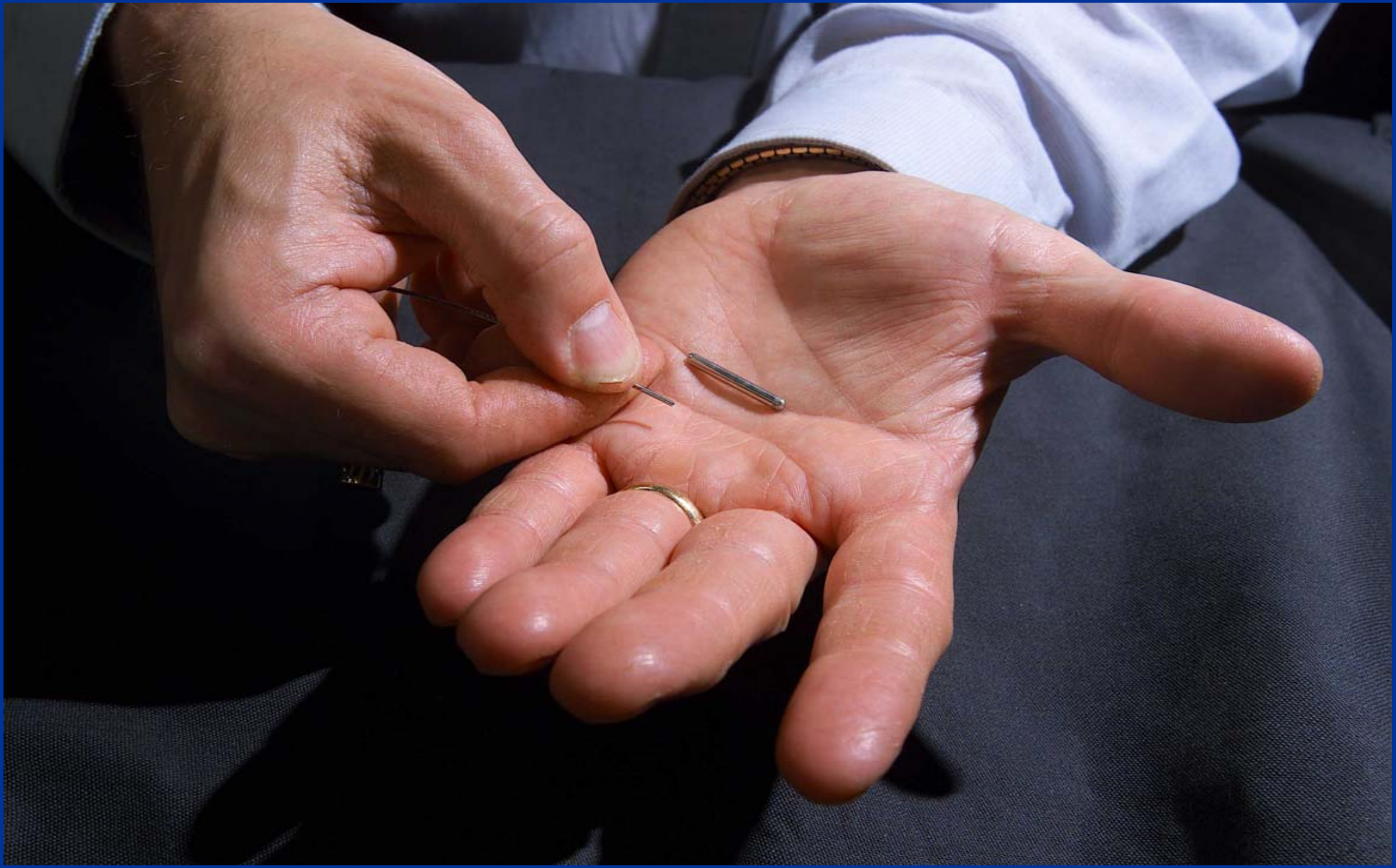
Clinical Trials of ^{252}Cf-Based NBT

- Since 1975, more than 5,000 patients have been treated in the US, Russia, Czech, and Lithuania.
- Since 1998, more than 4000 patients have been treated in China using the large Russian sources.
- Major cancers treated include gynecological tumors, head and neck tumors, rectal tumors, and sarcomas.

New Cf-252 Brachytherapy Sources



The *RBE* Issues for a Mixed n+γ Field

- $D(Gy\text{-}eq) = D_n \bullet RBE_n + D_\gamma$

  $RBE_n = ?$

- Is there a synergistic effect due to the interactions between n and γ lesions ?

Relative Biological Effectiveness (RBE)

- Generally, the RBE of a radiation is obtained by the following equations:

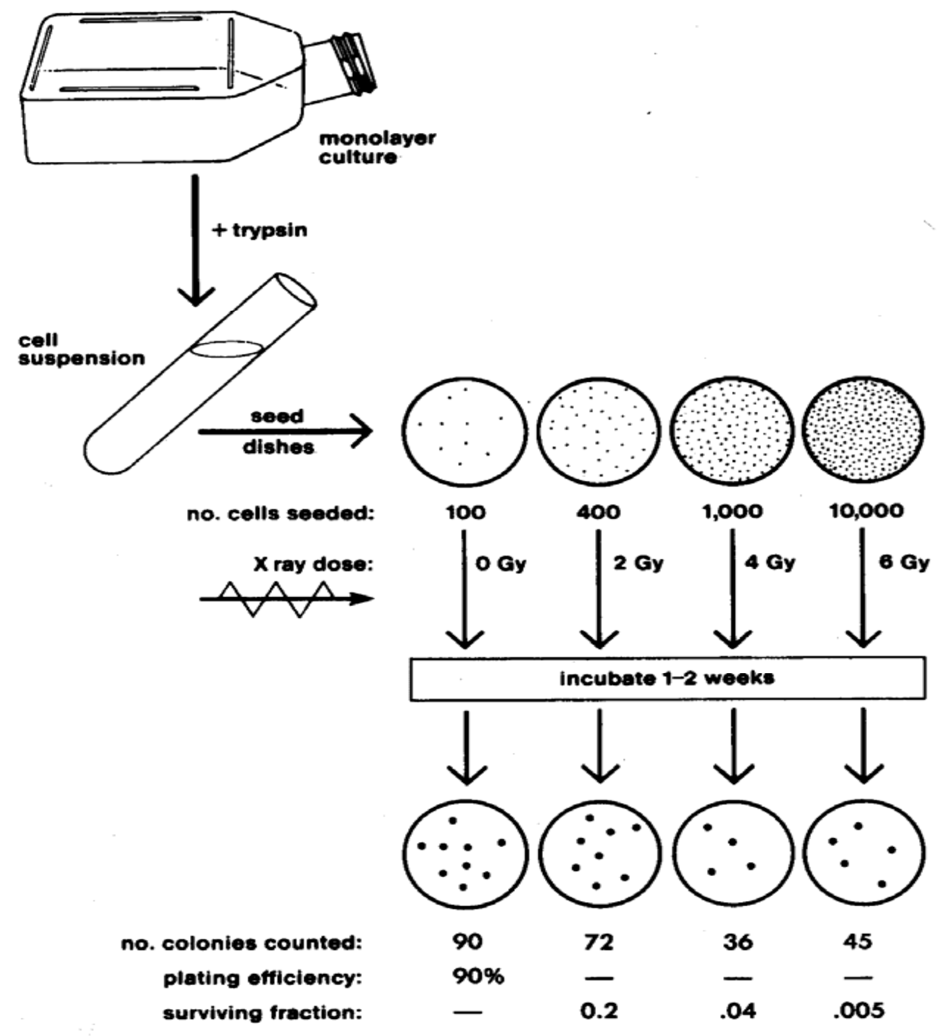
$$RBE_n = \frac{D_\gamma}{D_n}$$

where D_γ is the absorbed dose from the standard radiation (the ^{60}Co γ-ray or 250 kVp X-ray) to produce a given biological effect; D_n is the absorbed dose for the test radiation (i.e. neutron in this case) to produce the same biological effect.

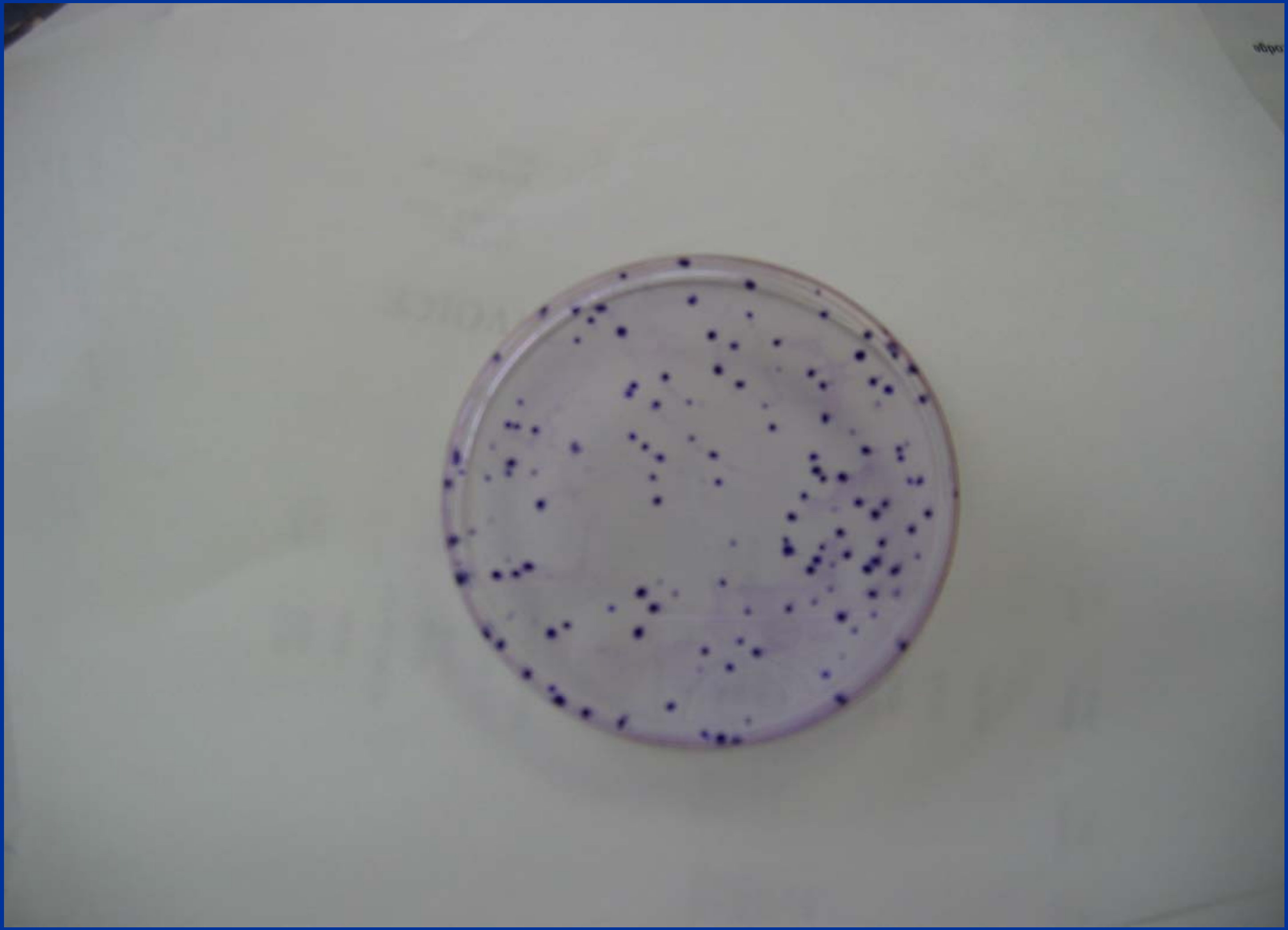
Definitions of Cell Death

- Apoptosis (or interphase death)
- Reproductive death (or mitotic death)

The Cell Culture Technique used to Generate Cell-Survival Curve



Colonies of V-79 Chinese Hamster Cells



Models of Cell Survival

- The "Target Theory", the earliest interpretive model for cell killing (Lea 1955)
- The theory of dual radiation action (Rossi 1972)
- Repair-misrepair model (Tobias 1980)
- Molecular theory of radiation action (Chadwick and Leenhouts 1981)
- The saturable repair model (Goodhead 1985)
- Lethal-potentially lethal model (Curtis 1986)

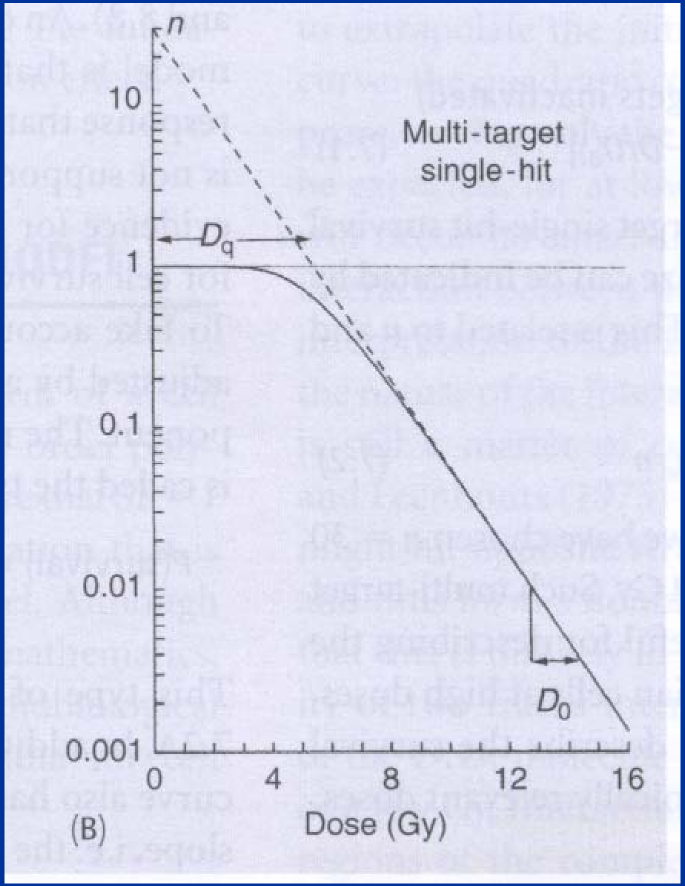
The Target Theory (Lea, 1955)

- Single-target-single-hit

$$S = e^{-kD}$$

- Multi-target-single-hit

$$S = 1 - (1 - e^{-kD})^n$$



Dual Radiation Action Theory (Kellerer & Rossi, 1972)

- Ionizing radiation leads to sublesions in the cell.
- A lesion is formed through the interaction of two sublesions.
- There is a fixed possibility that a lesion will lead to cell death.
- The interaction probability of two sublesions is dependent on the distance between them.

$$E(D) = k(\varsigma D + D^2)$$

and

$$S = e^{-E(D)} = e^{-k(\varsigma D + D^2)}$$

The Linear-Quadratic Models

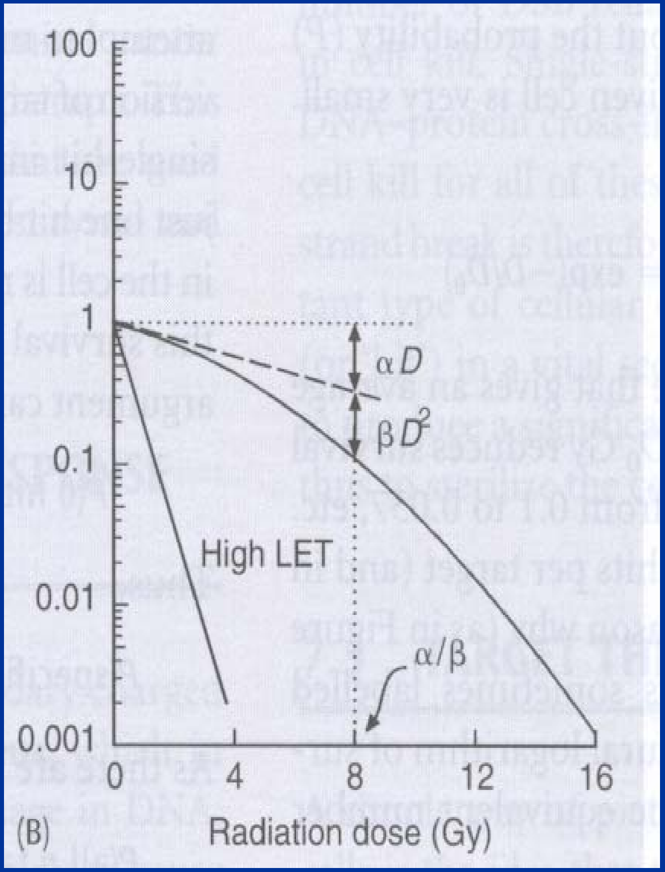
- Repair-Misrepair Model (Tobias et. Al., 1980)
- Molecular Theory of Radiation Action (Chadwick & Leenhouts, 1981)
- Lethal-Potentially Lethal Model (Curtis, 1986)

$$E(D) = \alpha D + \beta D^2$$

$$S = e^{-E(D)} = e^{-(\alpha D + \beta D^2)}$$

or

$$-\ln S = \alpha D + \beta D^2$$



The Existing Theory for a Mixed n+γ Field

- The prediction using the existing theories

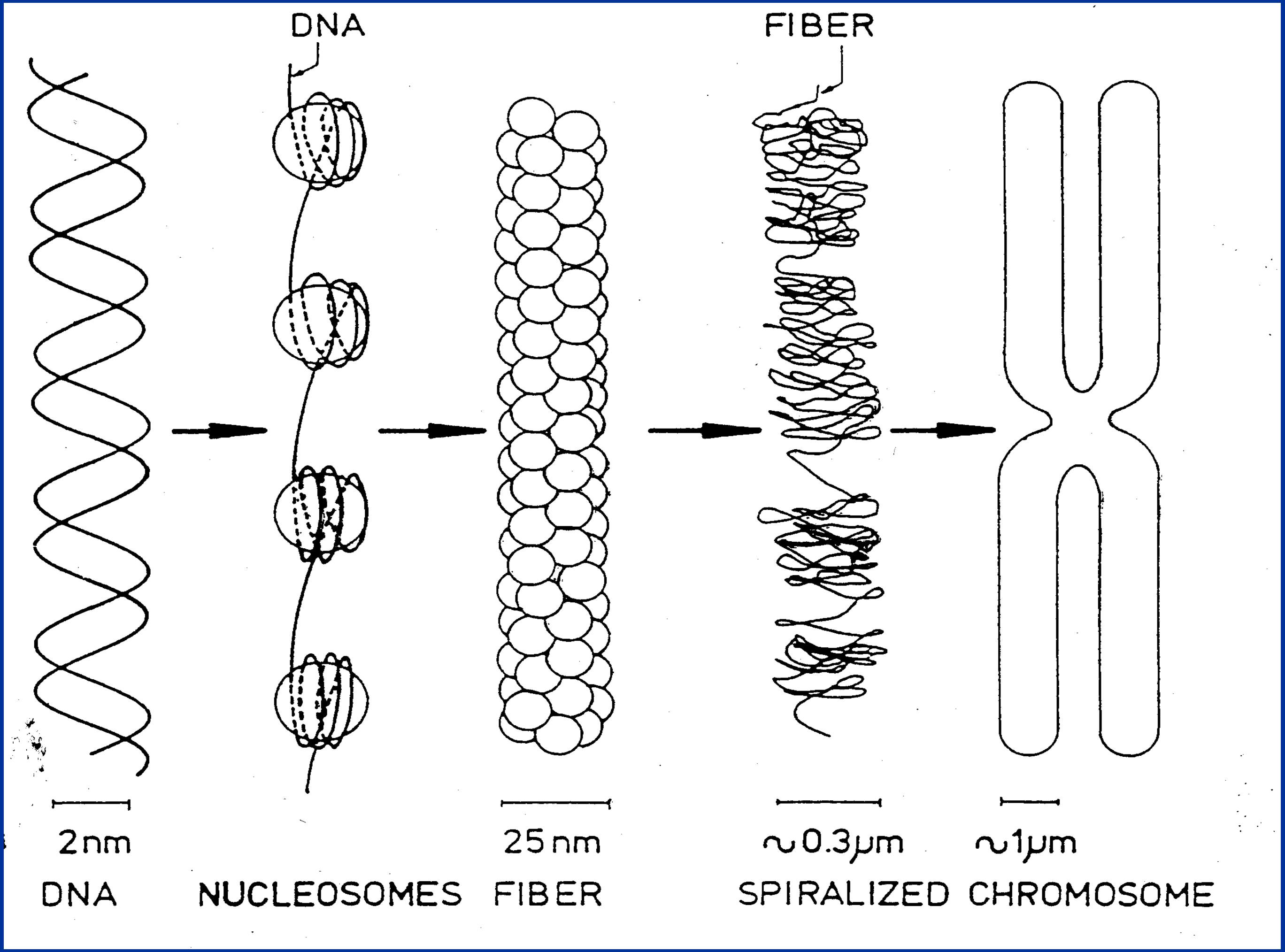
$$E_n = \alpha_n D_n + \beta_n D_n^{\ 2}$$

$$E_\gamma = \alpha_\gamma D_\gamma + \beta_\gamma D_\gamma^{\ 2}$$

$$E_{n\gamma} = \alpha_n D_n + \beta_n D_n^{\ 2} + \alpha_\gamma D_\gamma + \beta_\gamma D_\gamma^{\ 2} + 2\sqrt{\beta_n \beta_\gamma} D_n D_\gamma$$

- Since $\beta_n \rightarrow 0$, there will be no synergistic effect from the interactions between neutron-induced lesions and photon-induced lesions

Subcellular Targets and Structures



Diagrams of SSB and Simple DSB (sDSB)

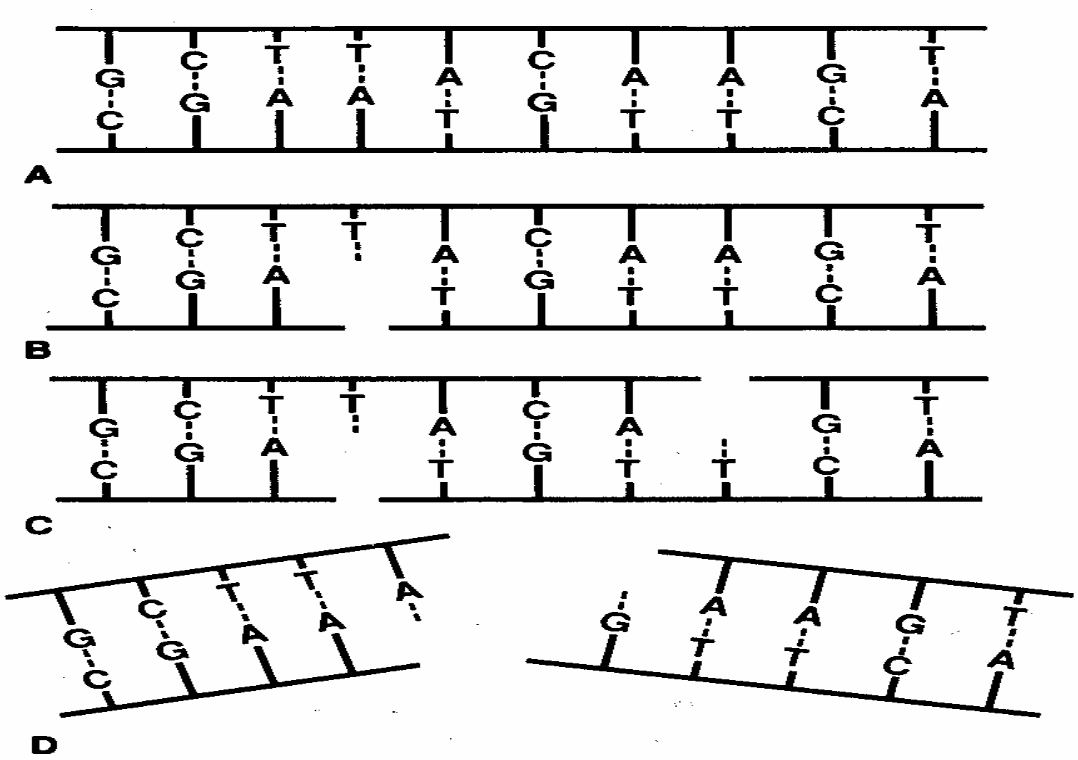
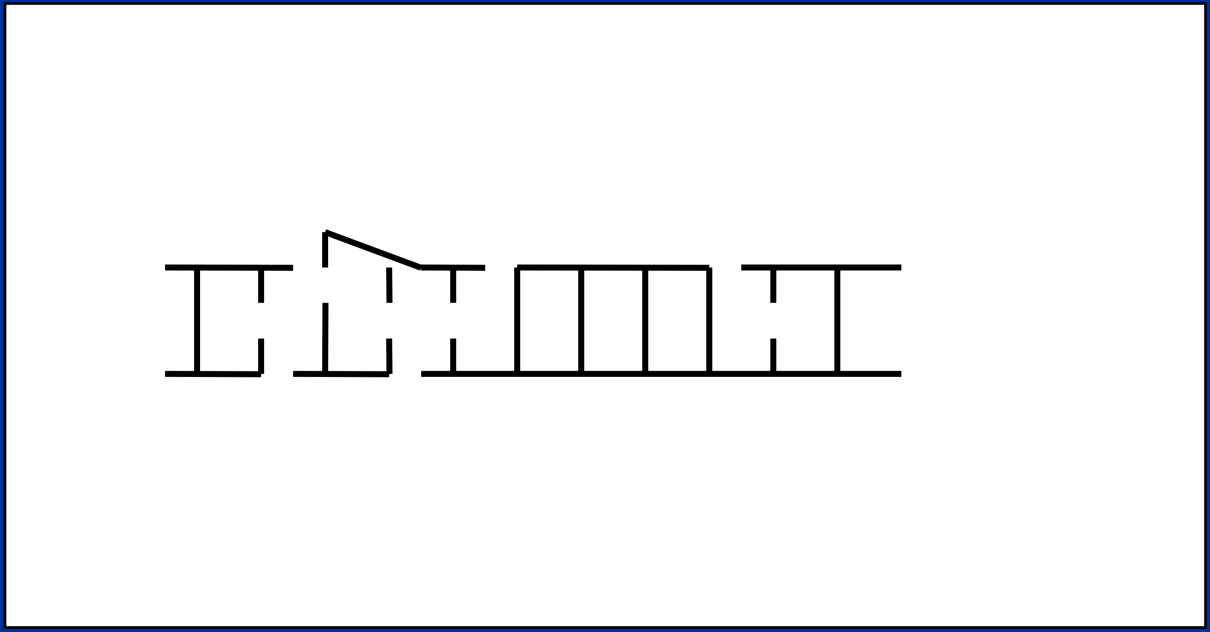
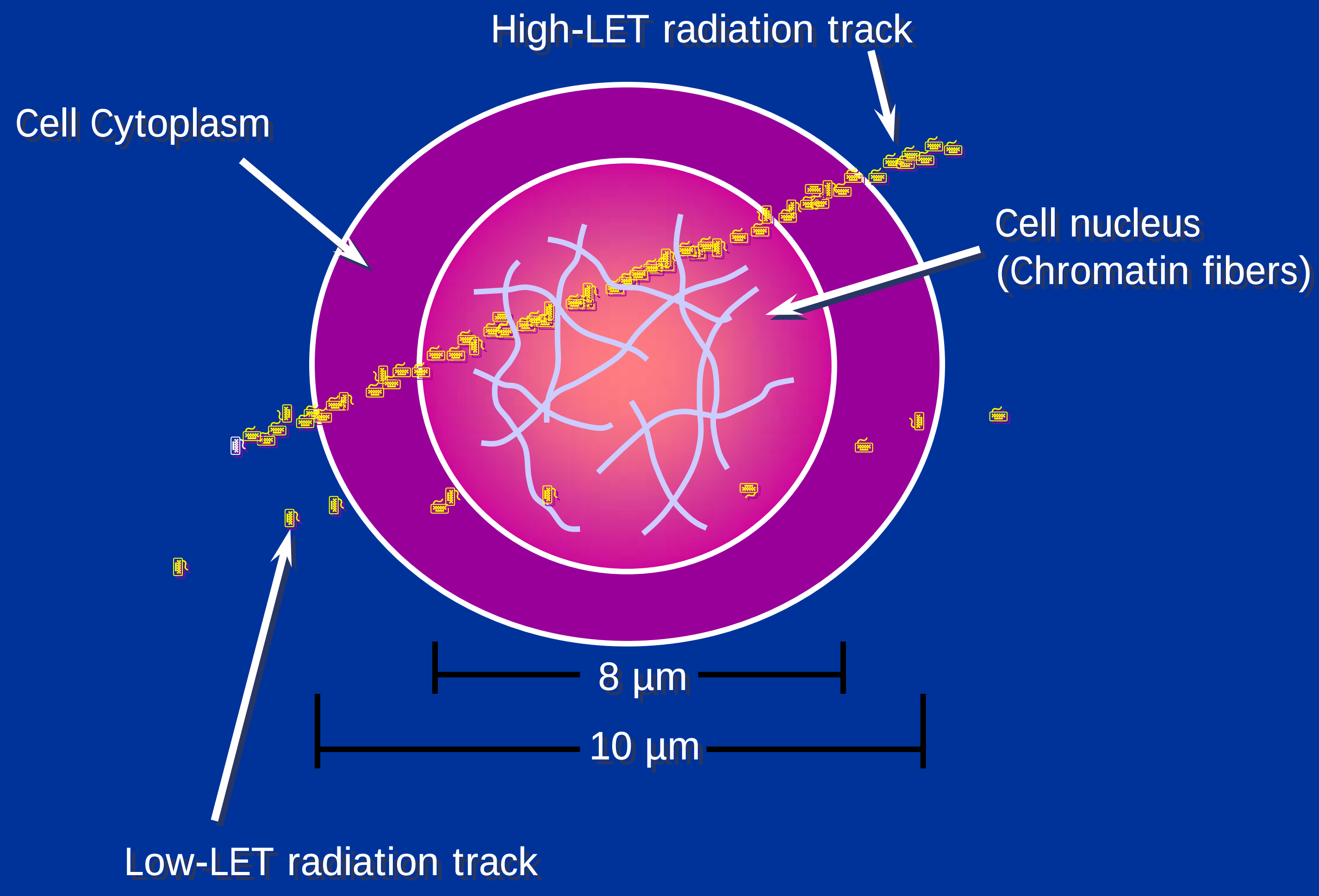


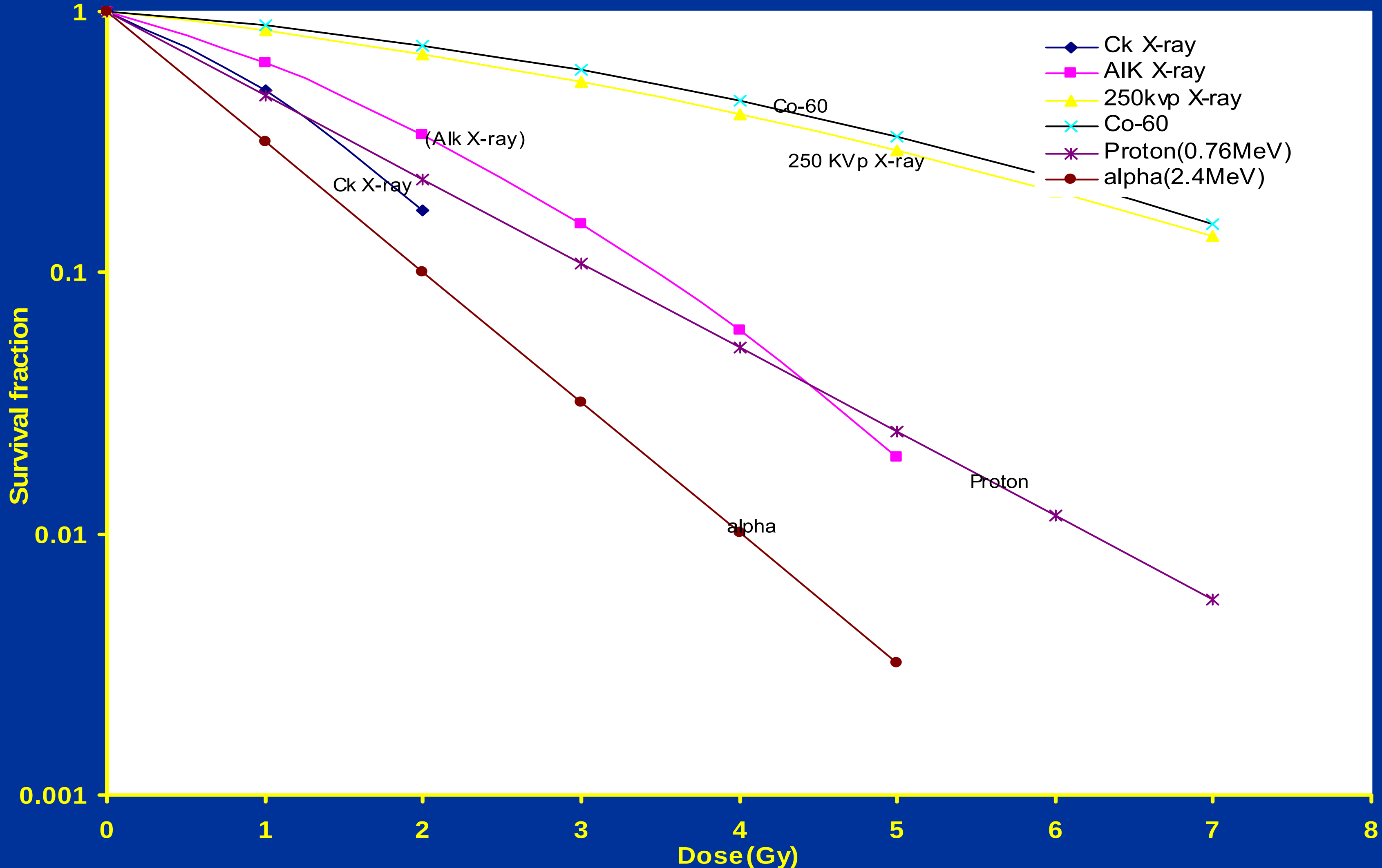
Diagram of a Complex DSB (cDSB)



Tracks of High- and Low-LET Radiations



New Survival Curves of V-79 Cells Irradiated with Radiations of Various LETs



New Data on DNA Damages and Repairs

- Both the low- and high-LET radiations can cause the DNA damages. The low-LET radiations tend to cause more SSBs and sDSBs and the high-LET radiations tend to cause more sDSBs and cDSBs.

- The total yield of DSBs (i.e. sDSB + cDSB) per unit dose does not vary greatly over a wide range of LET. The yield of cDSB per unit dose, however, proportionally increases with LET.

New Data on DNA Damages and Repairs

- The mammalian cells primarily repair a DSB by nonhomologous end joining (NHEJ) and that NHEJ becomes increasingly inhibited as the degree of damage (or complexity) of a DSB increases.

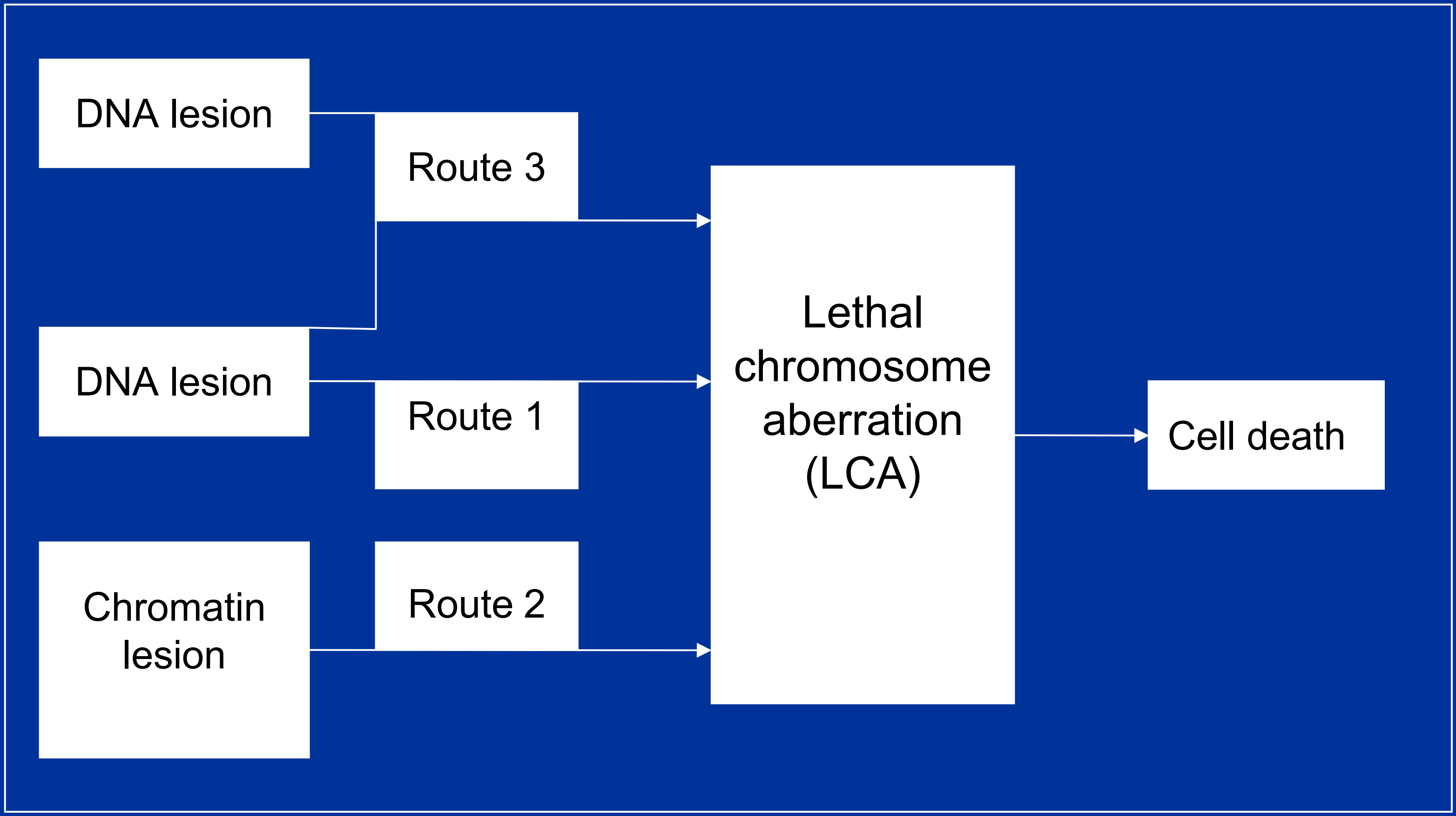
- Clusters of DNA lesion distributed over a chromatin fiber (a 25 nm target) give rise to kilobase-sized DNA fragments and that the yield of these DNA fragments per unit dose is proportional to LET of the radiation.

Key Pieces of Information Drawn from the New Data

- C_K ultrasoft X-rays were highly effective in cell killing.
- The photoelectrons produced by the C_K X-rays have an average energy of 250 eV which is deposited as a dense cluster of ionizations in the scale of 5 nanometers.
- kilobase-sized DNA fragments (a 25 nm target) is unique to high-LET radiation damage.

- **The new model must include the spatial distribution of ion clusters (i.e. the radiation track structure) and biomolecular targets at the nanometer level.**

The New Model
(Phys Med Biol, 51, 6087-98, 2006)



Premises for the New Model

- The LLs produced via the first route is linearly proportional to both the absorbed dose, *D*, and the threshold probability F_1 defined as:

$$F_1 = \int_{200\ \text{eV}}^{\infty} f(\varepsilon)\, d\varepsilon$$

where $f(\varepsilon)$ is the single-event frequency distribution of energy deposition, ε, per unit dose in a 5x5 nm tissue target, and 200 eV is the threshold energy characteristic to complex and irreparable DNA damages.

Premises for the New Model (Cont.)

- The LLs produced via the second route is linearly proportional to both the absorbed dose, *D*, and the threshold probability F_2 defined as:

$$F_2 = \int_{1\ \mathrm{keV}}^{\infty} f(\varepsilon)\, d\varepsilon$$

where $f(\varepsilon)$ is the single-event frequency distribution of energy deposition, ε, per unit dose in a 25x25 nm tissue target, and 1 keV is the threshold energy.

Premises for the New Model (Cont.)

- The NLLs are linearly proportional to both the absorbed dose, $\boldsymbol{D}$, and the threshold probability $\boldsymbol{F}_3$ defined as:

$$F_3 = \int_{100\ \text{eV}}^{1\ \text{keV}} f(\varepsilon)\, d\varepsilon$$

where $\boldsymbol{f(\varepsilon)}$ is the single-event frequency distribution of energy deposition, ε, per unit dose in a 25x25 nm tissue target, and 100 eV is the threshold energy characteristic to a repairable DNA damage.

Formula Derivation for the New Model

- The number of LCAs in a cell due to route 1:

$$(N_{LCA})_1 = r_1 F_1 D$$

- The number of LCAs in a cell due to route 2:

$$(N_{LCA})_2 = r_2 F_2 D$$

where r_1 and r_2 are the corresponding biological factors associated with routes 1 and 2, respectively.

Formula Derivation for the New Model (Cont.)

- The number of LCAs in a cell due to two-track effect can be derived from:

$$\frac{dN_{RL}}{dt} = k_3 F_3 \dot{D} - \lambda N_{RL}$$

$$N_{RL}(t) = \frac{k_3}{\lambda} F_3 \dot{D} (1 - e^{-\lambda T}) e^{-\lambda (t-T)}$$

$$\cong k_3 F_3 D e^{-\lambda t} \quad if\ T << t\ \ and\ \ \lambda T << 1$$

$$(N_{LCA})_3 = \int_0^{t'} \nu N_{RL}(t)^2 dt$$

$$= \frac{\nu k_3^2}{2\lambda} (1 - e^{-2\lambda t'}) F_3^2 D^2$$

Formula Derivation for the New Model (Cont.)

- The total number of LCAs:

$$N_{LCA} = (N_{LCA})_1 + (N_{LCA})_2 + (N_{LCA})_3$$

$$= (r_1 F_1 + r_2 F_2) D + r_3 {F_3}^2 D^2$$

i.e.

$$\alpha = r_1 F_1 + r_2 F_2$$

$$\beta = r_3 {F_3}^2$$

Validation of the New Model Using the Published Cell Survival Curves

- Since the three biological factors should be unique to each cell type and are independent of the radiation type, the consistency of the various sets of values of r_1, r_2 and r_3 obtained from cell survival curves of various radiation types should serve as a validation to the new model.
- The useful set of survival curves would be one that includes many different radiation types of the same cell line.

Validation of the New Model Using the Published Cell Survival Curves

- Eleven V-79 cell survival curves from irradiation of ultrasoft x-rays, 250 kVp x-rays, ^{60}Co γ-rays, protons and alpha particles are selected to validate the new model.
- The α and β values are obtained from curve fitting. The three physical parameters of F_1, F_2, and F_3 for the various radiation types are obtained from the published computational data.
- Any two sets of values of α, F_1, and F_2 from two different survival curves can be used to uniquely determine the values of r_1 and r_2.
- Any one of the survival curves could uniquely give a value of r_3 .

The values of α and β obtained from the published V-79 survival curves, and the calculated values of F_1, F_2, and F_3 for the various types of ionizing radiation.

Radiation type	α (Gy^{-1})	β (Gy^{-2})	F_1 (Gy^{-1})	F_2 (Gy^{-1})	F_3 (Gy^{-1})
250 kVp X-ray	0.15	0.019	1.7×10^{-7}	6.8×10^{-7}	1.9×10^{-4}
^{60}Co γ-ray	0.10	0.024	1.2×10^{-7}	1.2×10^{-7}	1.6×10^{-4}
C_K X-ray	0.50	0.19	7.0×10^{-7}	0.0	3.2×10^{-4}
Al_K X-ray	0.38	0.081	4.5×10^{-7}	1.1×10^{-5}	2.0×10^{-4}
Ti_K X-ray	0.26	0.033	3.1×10^{-7}	8.0×10^{-7}	1.9×10^{-4}
0.64-MeV proton	0.65	–	6.43×10^{-7}	1.69×10^{-5}	1.11×10^{-4}
1.41-MeV proton	0.47	0.044	3.76×10^{-7}	6.45×10^{-6}	1.79×10^{-4}
3.2-MeV proton	0.37	0.036	2.71×10^{-7}	2.30×10^{-6}	2.31×10^{-4}
2.4-MeV α-particle	1.15	–	1.08×10^{-6}	2.68×10^{-5}	2.03×10^{-5}
3.8-MeV α-particle	1.32	–	1.13×10^{-6}	3.21×10^{-5}	3.51×10^{-5}
8.0-MeV α-particle	1.05	–	8.85×10^{-7}	3.14×10^{-5}	7.06×10^{-4}

The values of r_1 and r_2 obtained from V-79 survival curves for various radiation types

Radiation type	r_1	r_2
^{60}Co γ-ray and 0.64 MeV proton	8.26E+05	7.02E+03
^{60}Co γ-ray and 2.4 MeV α-particle	8.24E+05	9.72E+03
^{60}Co γ-ray and 3.8 MeV α-particle	8.21E+05	1.22E+04
^{60}Co γ-ray and 8.0 MeV α-particle	8.23E+05	1.02E+04
250 kVp X-ray and 0.64 MeV proton	8.59E+05	5.77E+03
250 kVp X-ray and 2.4 MeV α-particle	8.47E+05	8.77E+03
250 kVp X-ray and 3.8 MeV α-particle	8.36E+05	1.17E+04
250 kVp X-ray and 8.0MeV α-particle	8.44E+05	9.66E+03
	r_1 = 8.35E+5 ± 1.7%	r_2 = 9.38E+3 ± 23%

The Values of r_3 Obtained from V-79 Survival Curves for Various Radiation Types

Radiation type	r_3
Ti_K X-ray	9.22E+05
250 kVp X-ray	5.30E+05
^{60}Co γ-ray	9.39E+05
3.2-MeV proton	6.76E+05
	$r_3 = 8.99 \pm 18\%$

Additional Validation Using Heavy Ion Data

RBE vs. LET

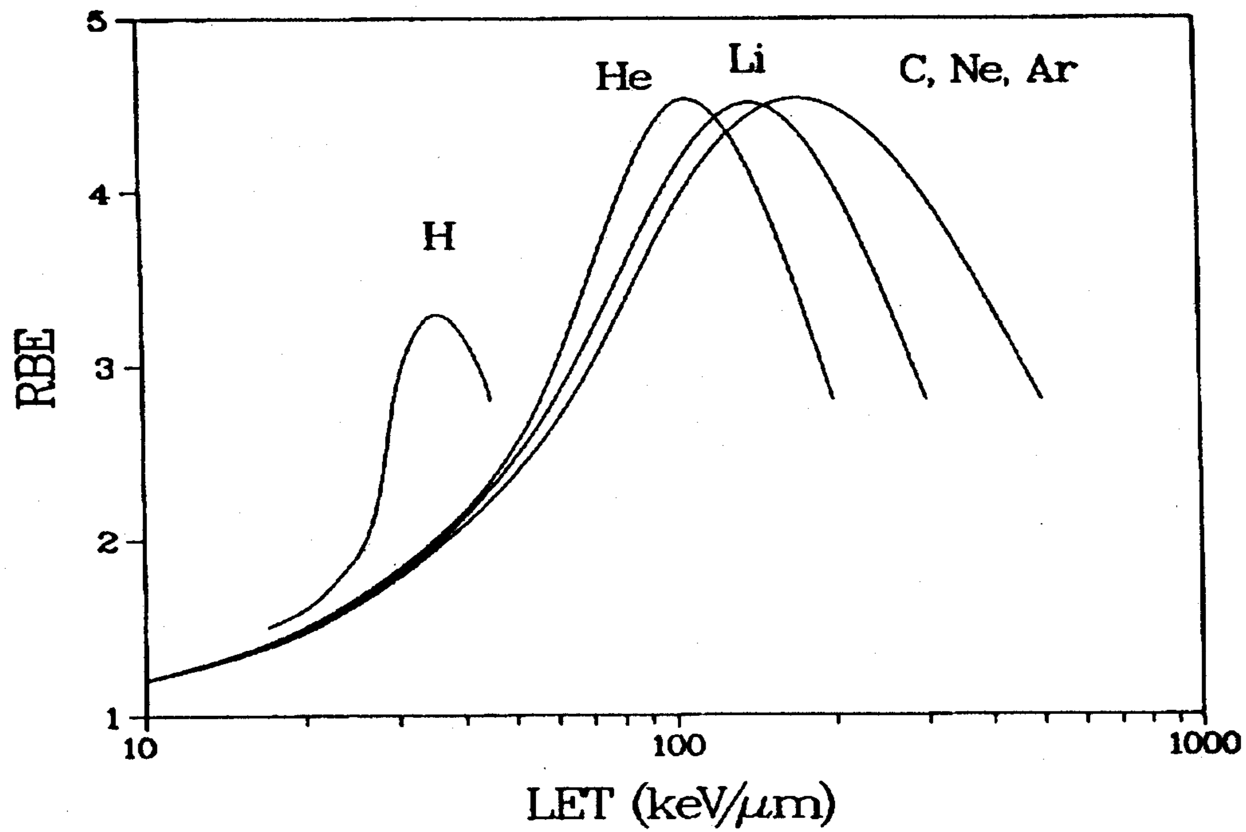
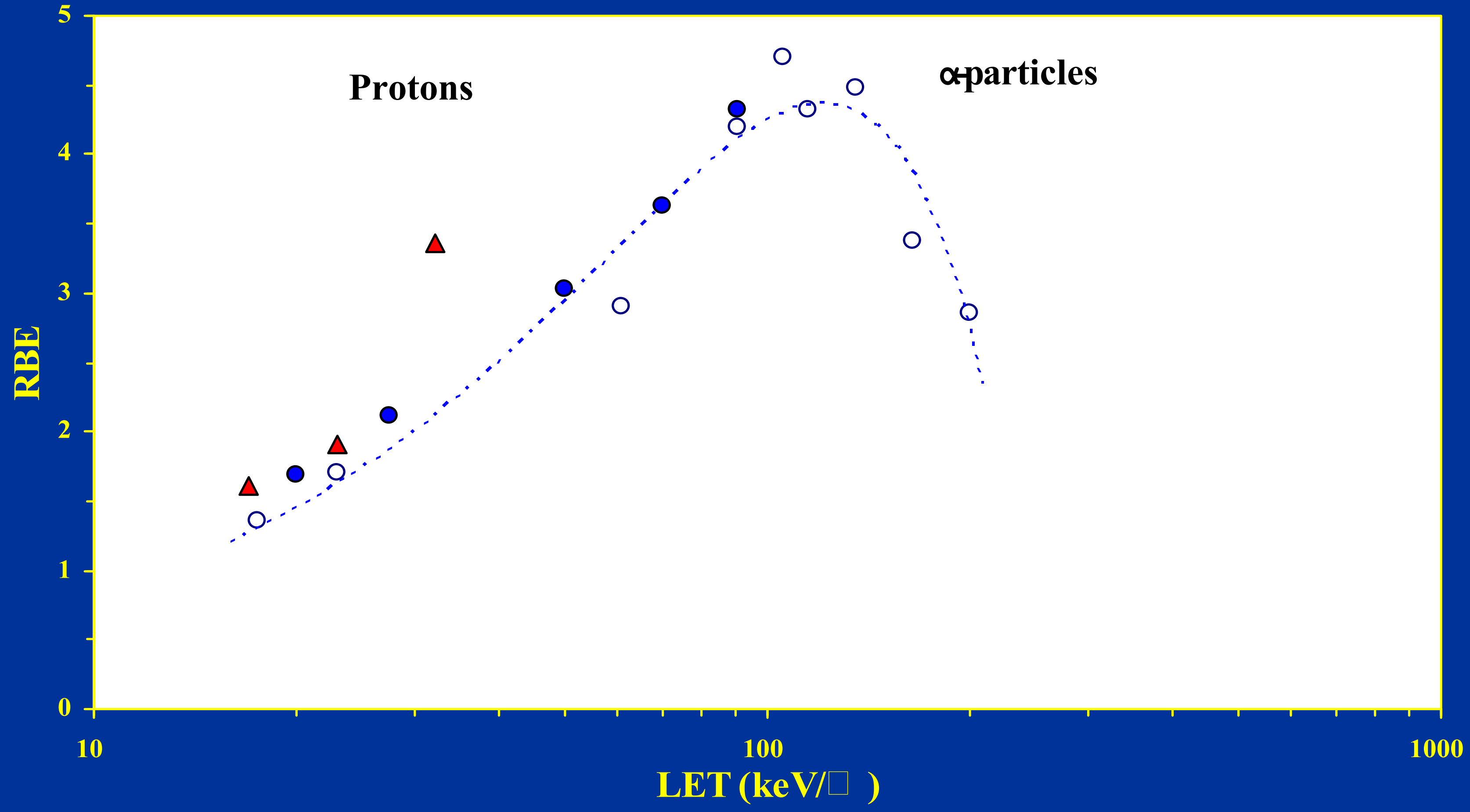
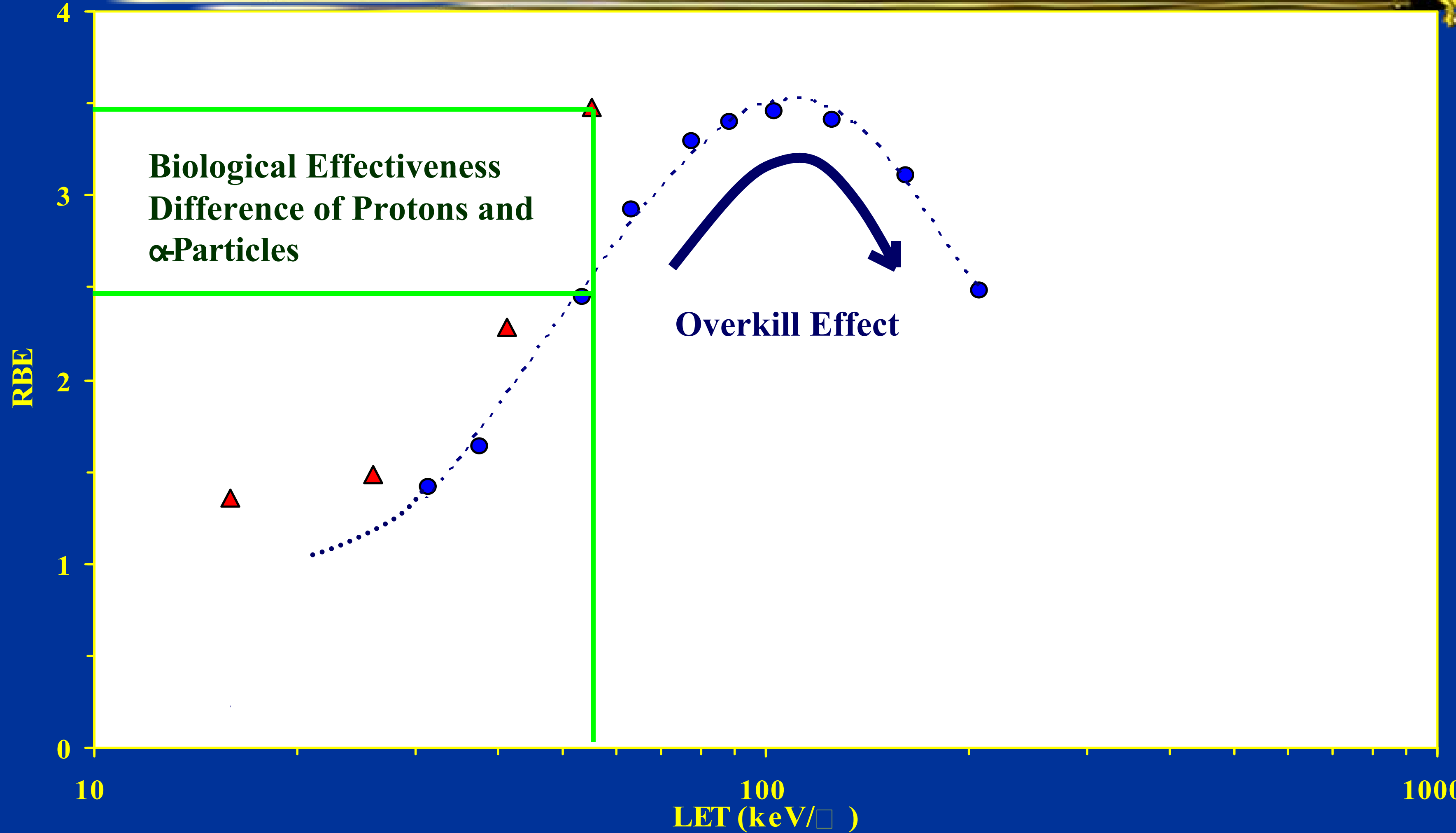


Figure 1. Schematic representatives based on experimental data on the relationship between *RBE* and LET for protons, α-particles and heavy ions.

The Experimental Data of RBE vs. LET

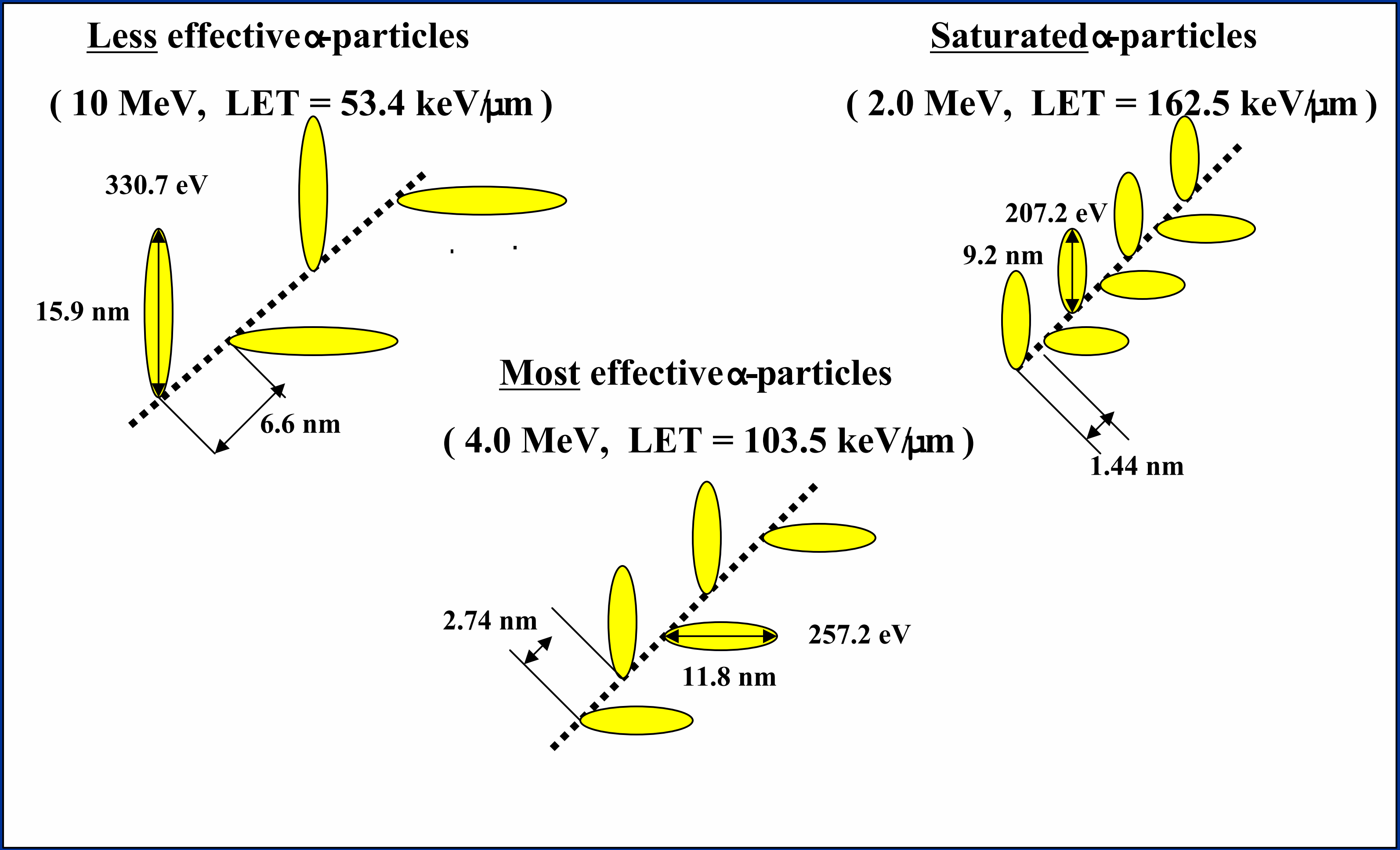


RBE vs. LET Predicted by the New Model

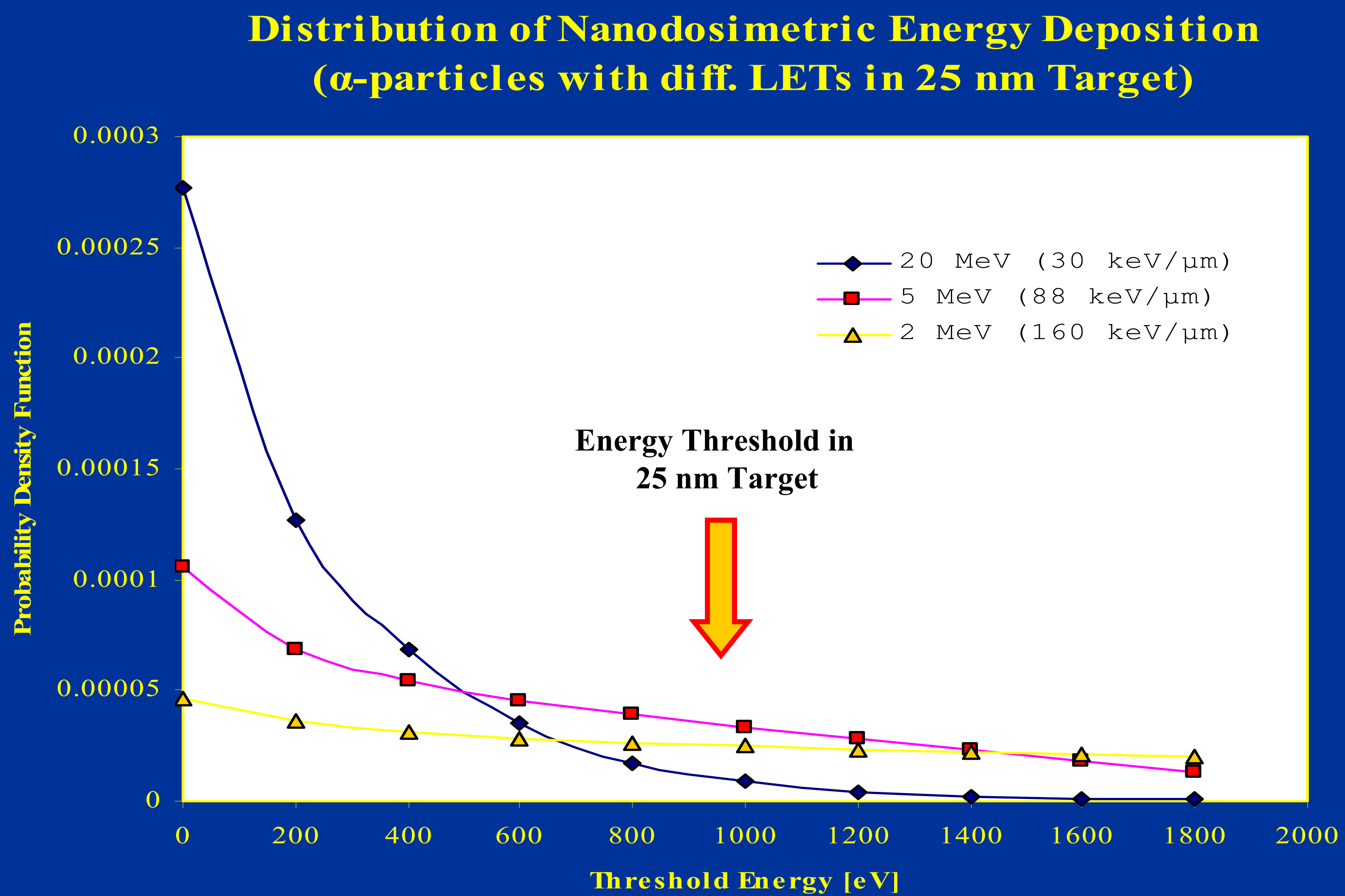


The RBE-LET relationship for V-79 cells; (▲) Protons, ( ) Alpha particles

Track Structures of Alpha Particles with Various LETs



Overkill Effect of Alpha Particles is Embedded in the Nanodosimetry Quantity F_2



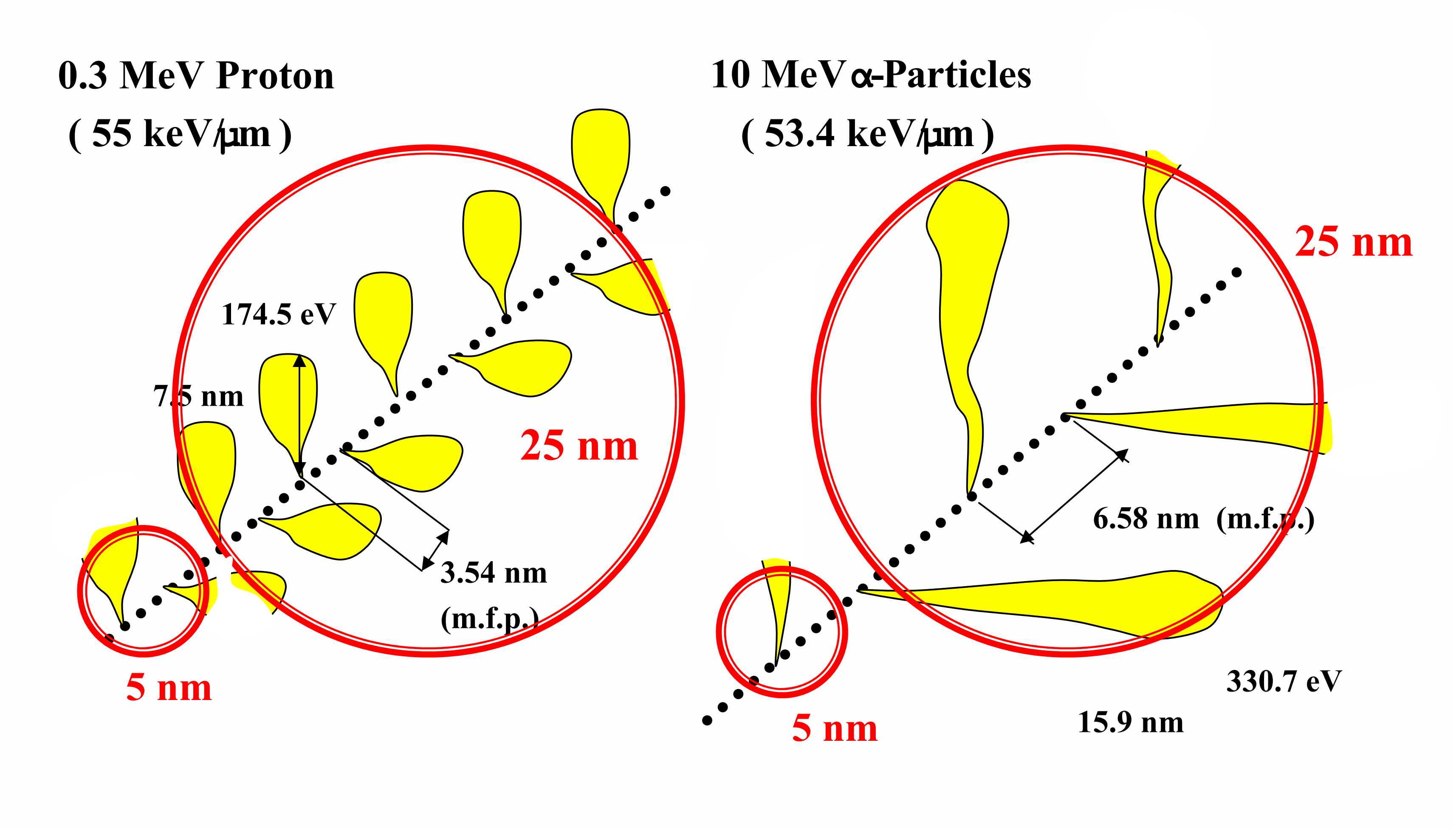
Difference of RBEs of Protons and Alpha Particles of the Same LET

- RBEs of protons and α-particles with the same LET (~54 keV/micron)

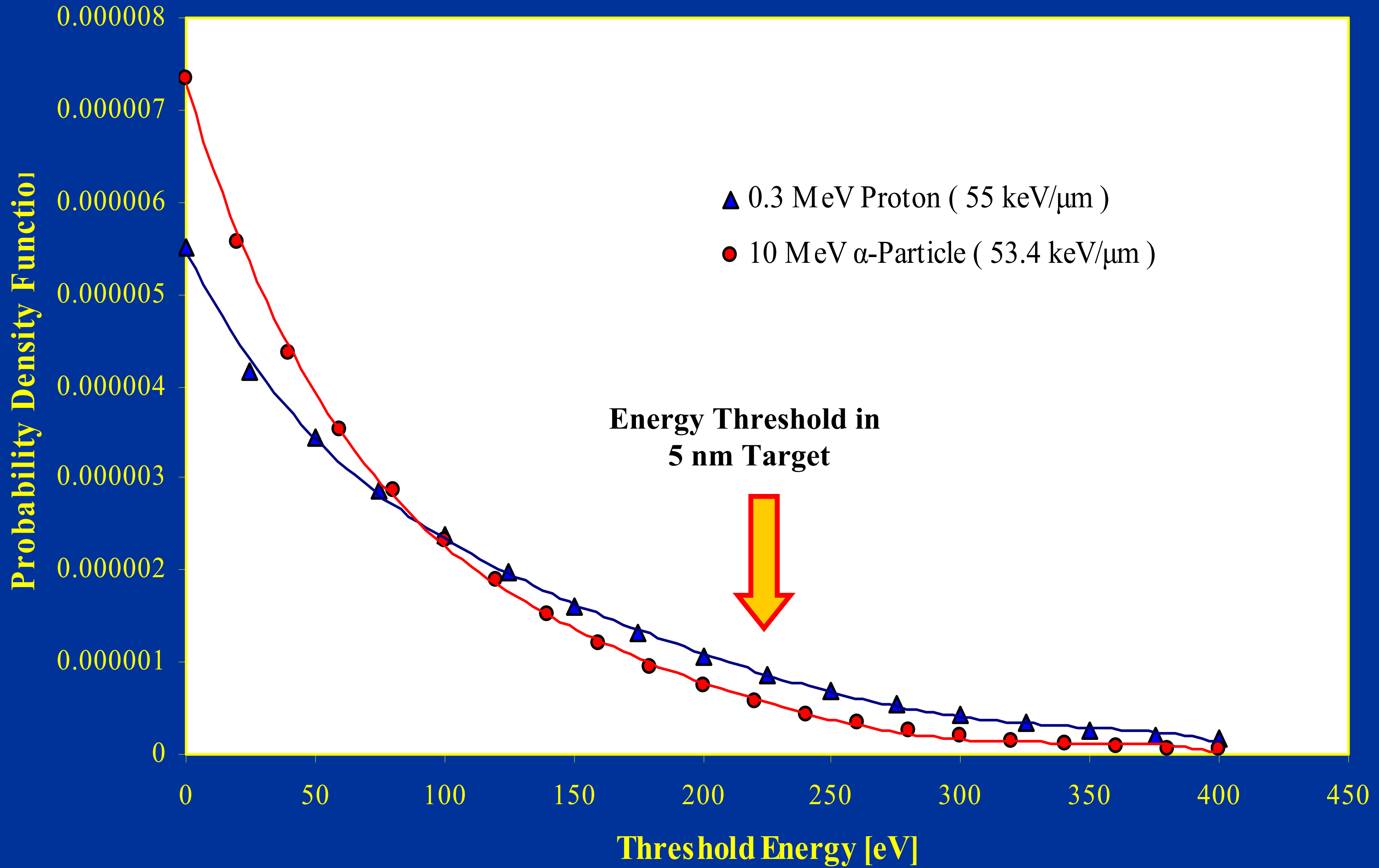
  - RBE of the 0.3 MeV proton - 3.5
  - RBE of the 10 MeV alpha particles - 2.4

➔ This difference can be explained by the differences in the track structures of protons and α-particles

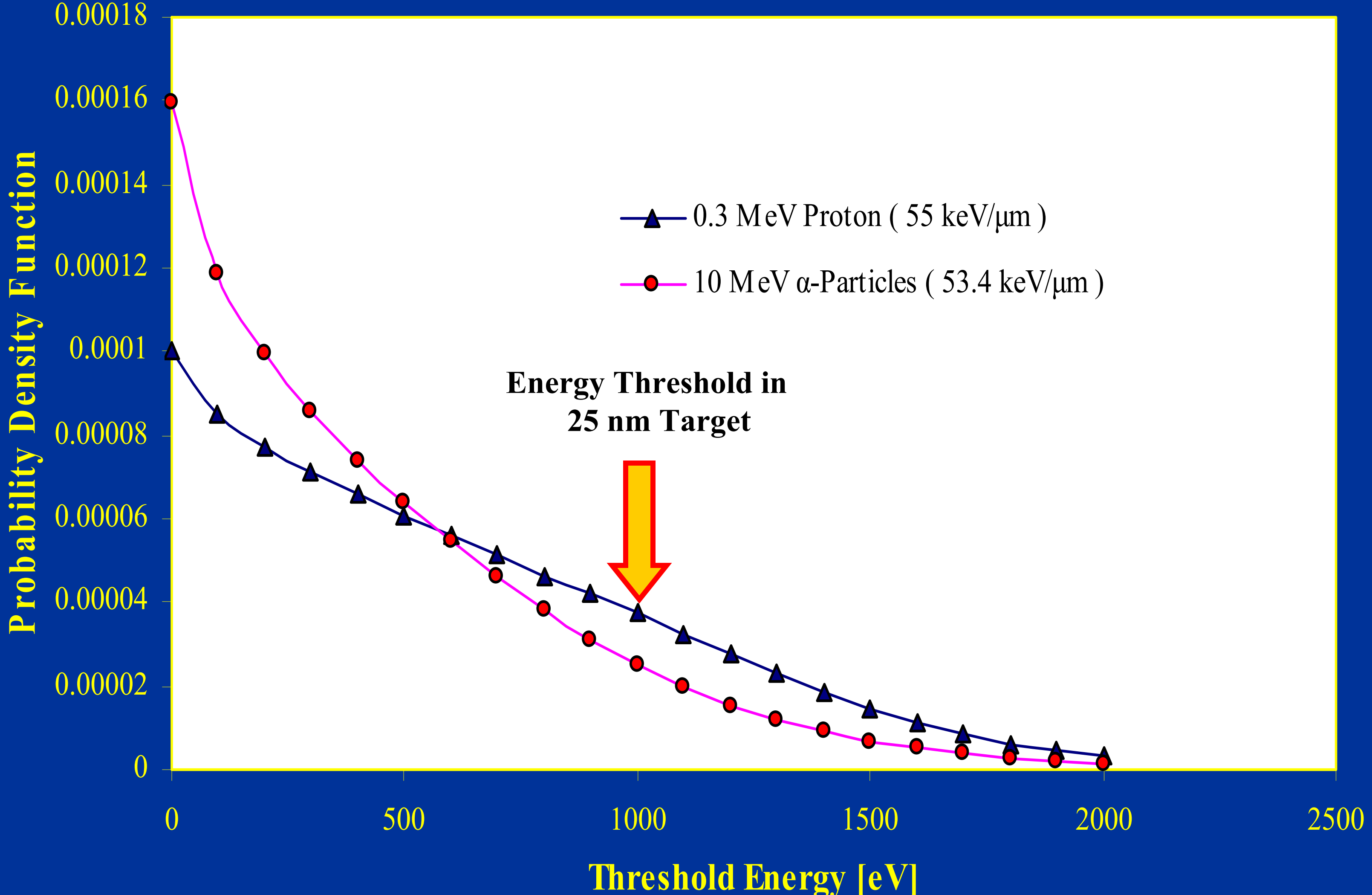
Track Structures of Protons and Alpha Particles of the Same LET



Comparison of the Energy Deposition Distributions in a 5-nm Target



Comparison of the Energy Deposition Distributions in a 25-nm Target



Application of the New Model to a Mixed n+γ Field

$$-\ln(S_{n\gamma}) = \alpha_{n\gamma} D_{n\gamma} + \beta_{n\gamma} D_{n\gamma}^{2} = \left[r_1 (F_1)_{n\gamma} + r_2 (F_2)_{n\gamma}\right] D_{n\gamma} + r_3 (F_3)_{n\gamma}^{2} D_{n\gamma}^{2}$$

where

$$D_{n\gamma} = D_n + D_\gamma$$

$$(F_1)_{n\gamma} = \frac{(F_1)_n D_n + (F_1)_\gamma D_\gamma}{D_n + D_\gamma}$$

$$(F_2)_{n\gamma} = \frac{(F_2)_n D_n + (F_2)_\gamma D_\gamma}{D_n + D_\gamma}$$

$$(F_3)_{n\gamma} = \frac{(F_3)_n D_n + (F_3)_\gamma D_\gamma}{D_n + D_\gamma}$$

Application of the New Model to a Mixed n+γ Field

$$-\ln(S_{n\gamma}) = \left[r_1(F_1)_n + r_2(F_2)_n\right]D_n + \left[r_1(F_1)_\gamma + r_2(F_2)_\gamma\right]D_\gamma +$$

$$+ r_3\left[(F_3)_n{}^2 D_n{}^2 + (F_3)_\gamma{}^2 D_\gamma{}^2 + 2(F_3)_n(F_3)_\gamma D_n D_\gamma\right]$$

$$= \alpha_n D_n + \beta_n D_n{}^2 + \alpha_\gamma D_\gamma + \beta_\gamma D_\gamma{}^2 + \beta_{n\gamma} D_n D_\gamma$$

where

$$\beta_{n\gamma} = 2\, r_3\, (F_3)_n\, (F_3)_\gamma$$

Application of the New Model to a Mixed n+γ Field

- **For a typical doses of D_n = 4 Gy and D_γ = 2 Gy in a ^{252}Cf brachytherapy treatment, the synergistic term $\beta_{n\gamma}D_nD_\gamma$ amounts to be 0.33, which translates to an additional 28% cell death.**

Conclusions

- The new nanodosimetry-based L-Q model for radiation-induced cell death has been developed.
- It has been shown that the survival curves predicted by the new model is consistent with the previously published data.
- The new model uniquely explains the RBE-vs-LET relationships for various high-LET radiations including protons and alpha particle.
- The new model can be used to estimate the synergistic effect of a mixed field of high- and low-LET radiations, and it is applicable to all mixed-LET radiation modalities for cancer treatment.