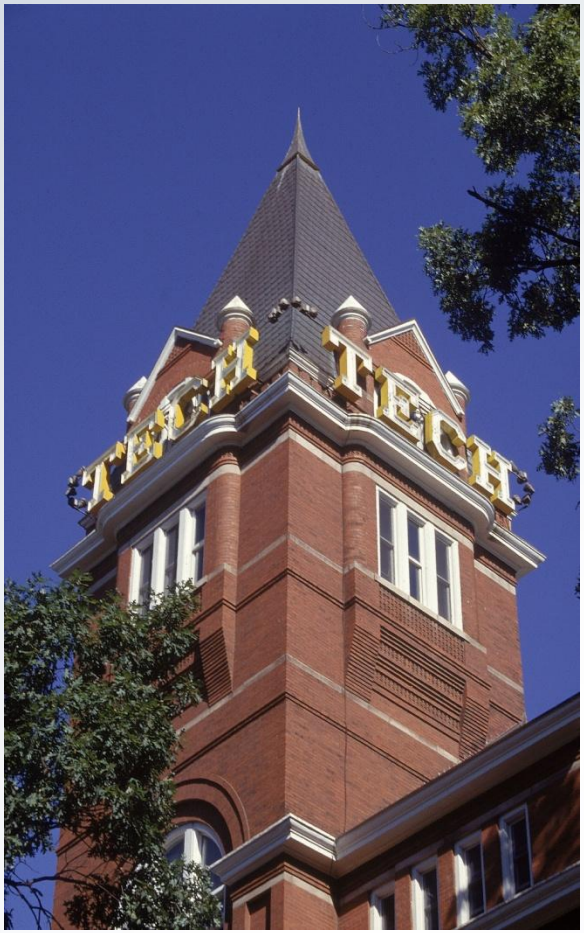


Track-Structure Based Radiobiological Modeling for Estimating Radiation Quality

C-K Chris Wang, Ph.D., P.E.

Professor

Nuclear & Radiological Engineering &
Medical Physics Program
Woodruff School of Mechanical Engineering
Georgia Institute of Technology

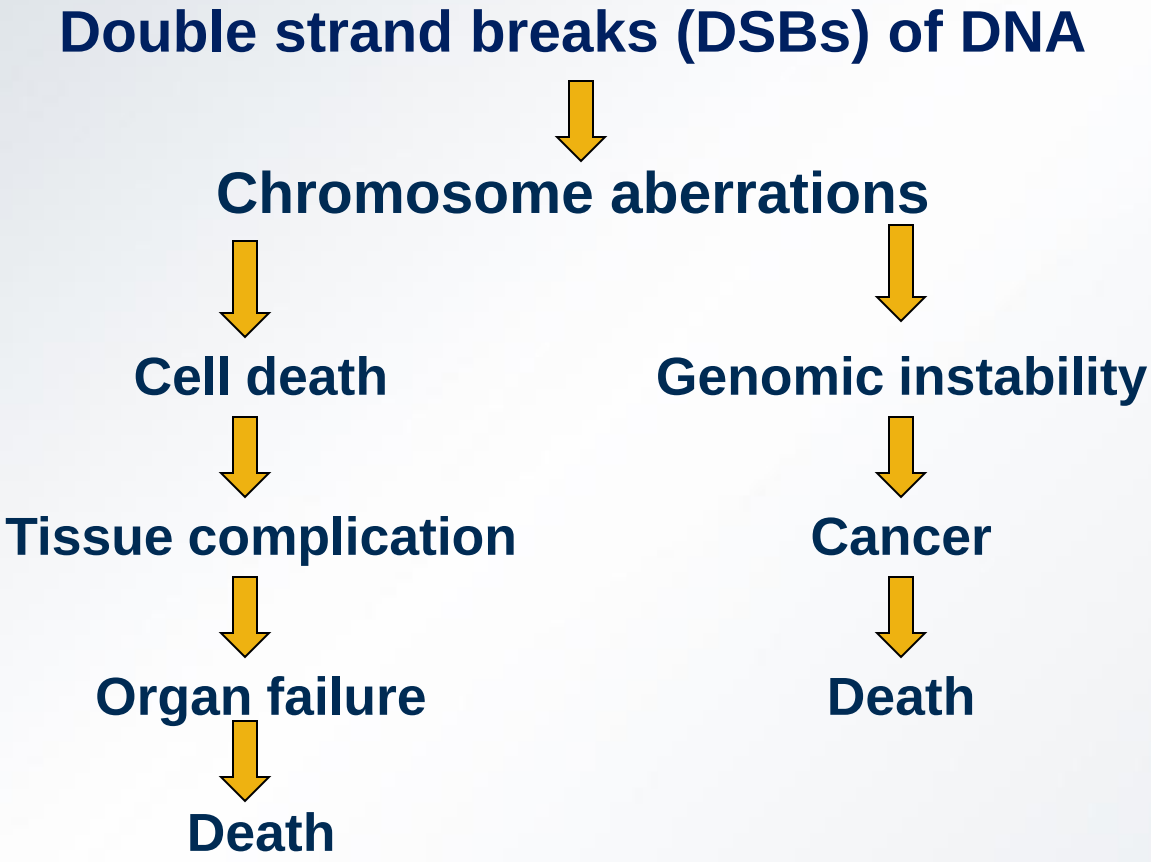
Applications of radiobiological modeling

- **Radiotherapy**
  - To assess the biologically equivalent doses delivered by two different schemes or by two different radiation types.
- **Radiation protection**
  - To assess the weighting factor (or quality factor) of a high-LET radiation or of the same radiation but with different dose rates (or dose-rate factor).

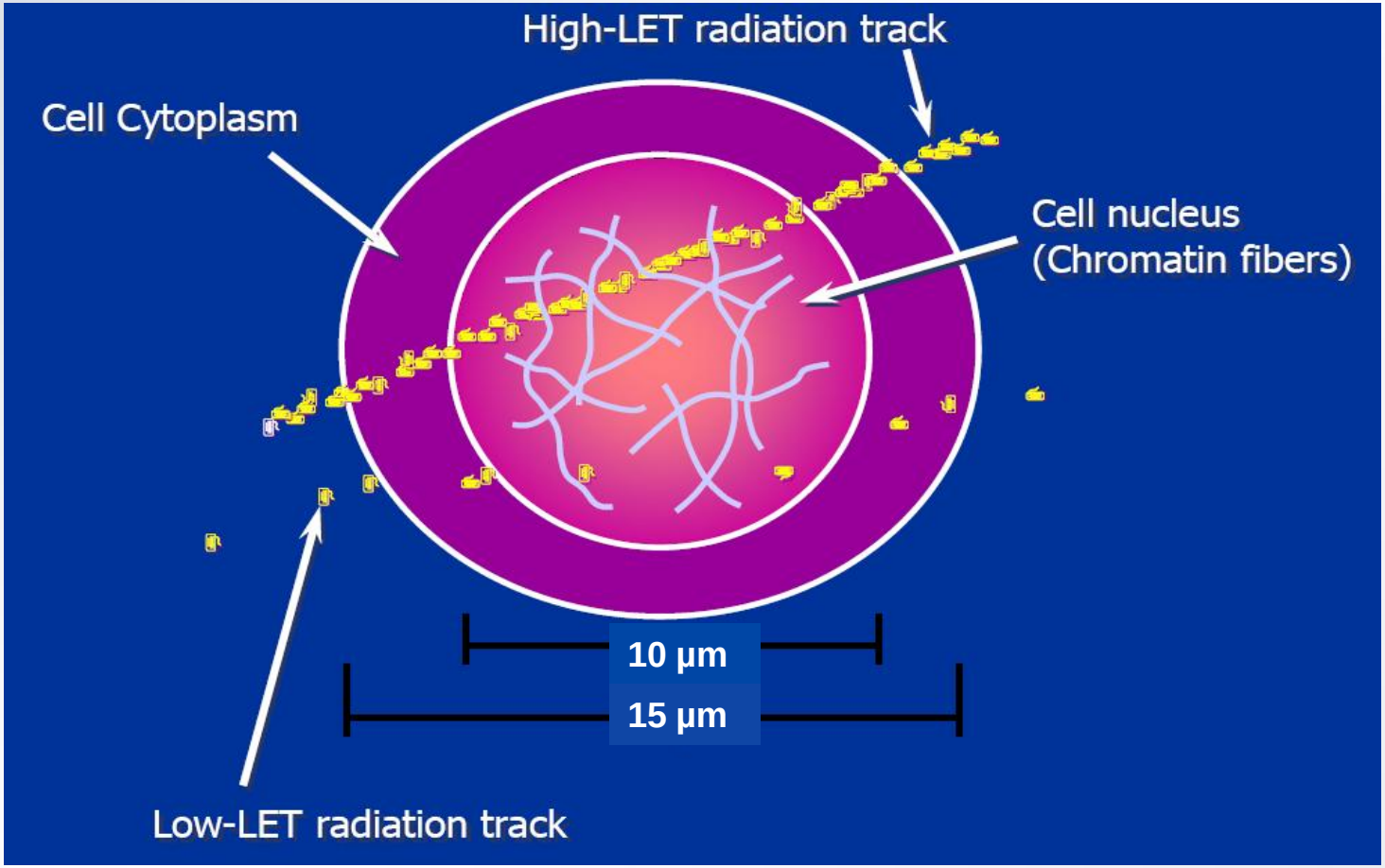
Important radiobiological effects

- Dose rate effect of low-LET radiation
- RBE of high-LET radiation
- Oxygen enhancement effect of Low-LET radiation
- Non-targeted effects (e.g. the bystander effect)

Biological endpoints associated with DNA damage



Tracks of high- and low-LET radiations



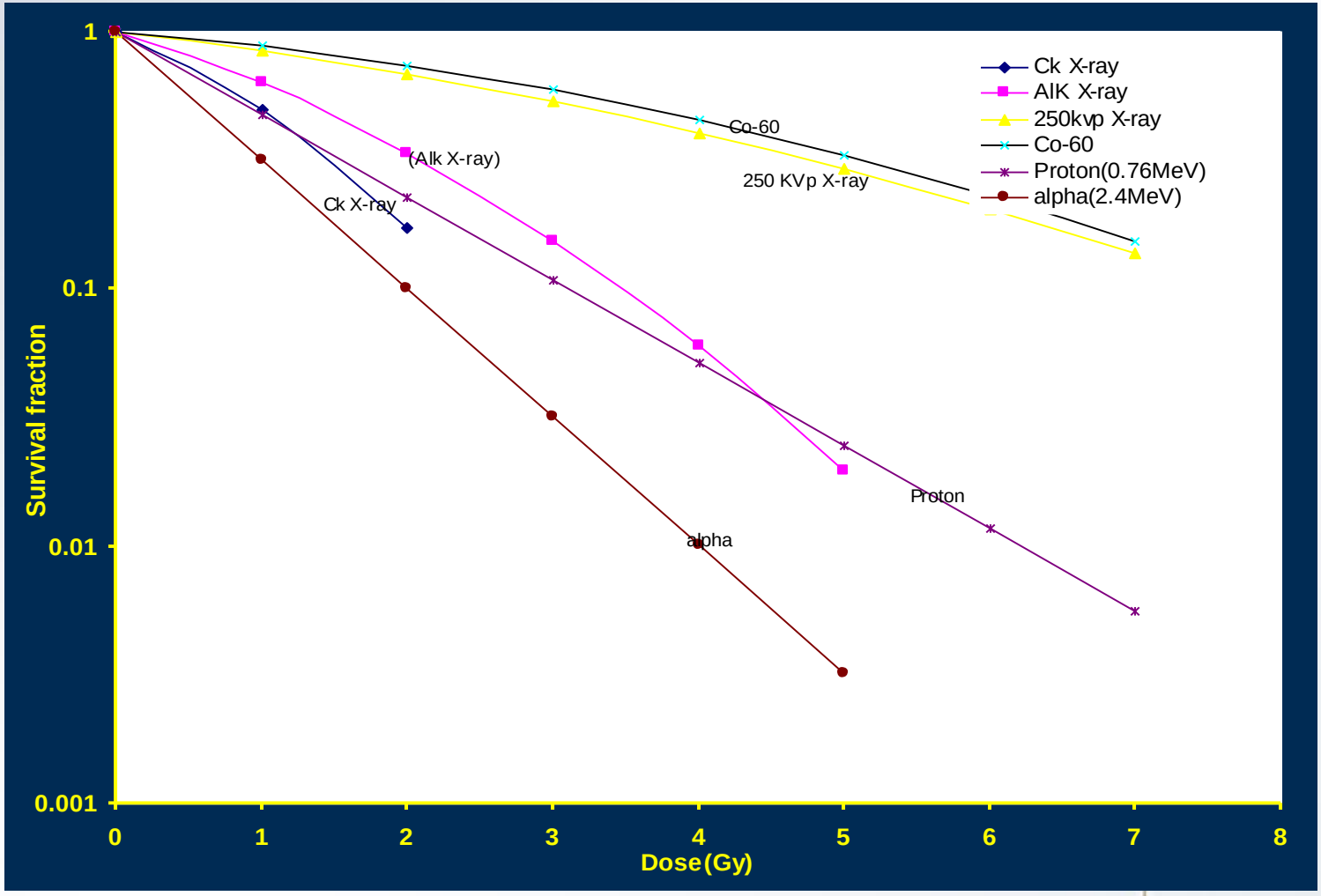
Relative biological effectiveness (RBE)

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

$$\mathrm{RBE}_{\mathrm{x}} = \frac{D_{\gamma}}{D_{\mathrm{x}}}$$

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_{x} is the absorbed dose for the test radiation to produce the same biological effect.

Survival curves of V-79 cells irradiated with radiations of various LETs



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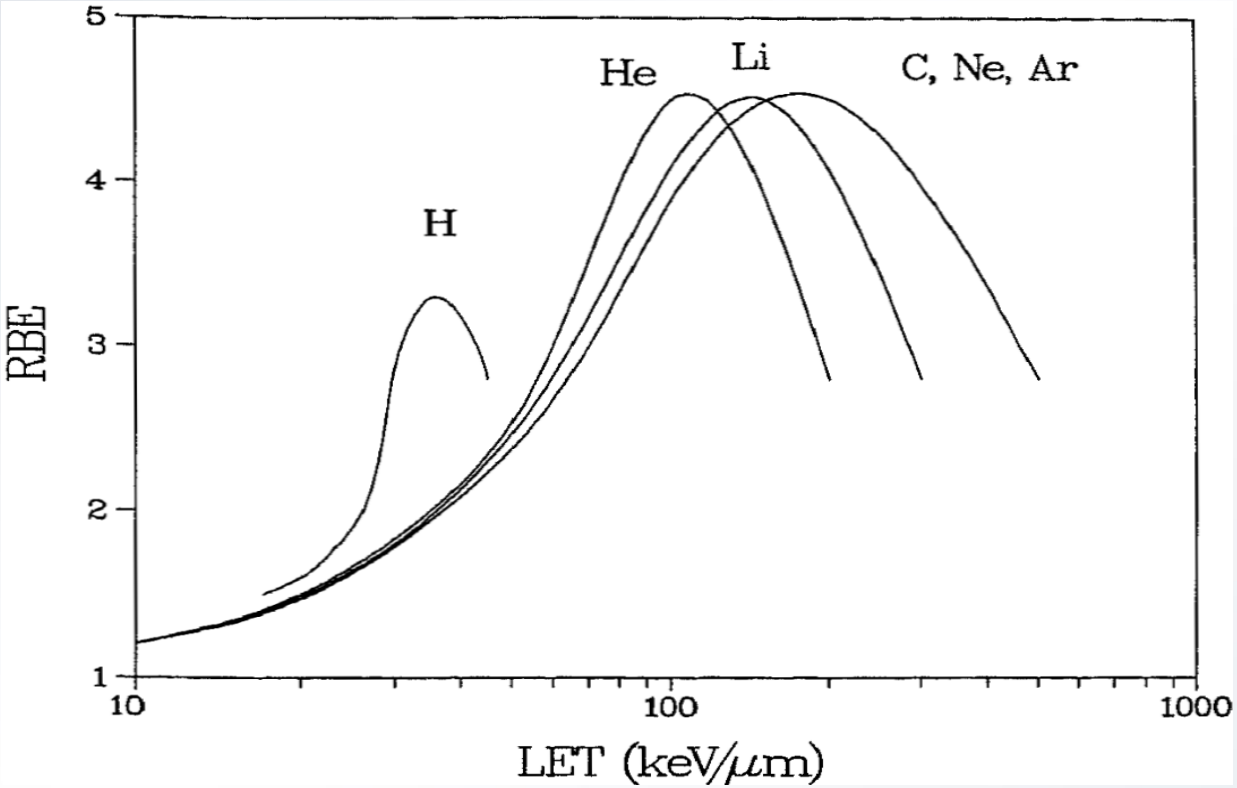
RBE vs LET

- **RBE varies not only with LET but also with the particle type**



Models describing the shape of cell survival curves

- Single-target model (1940's)
- Multi-target model (1950's)
- Linear-quadratic model (1960's)

The single-target model
(used in the early years and is considered obsolete today)

- **Assumption: There is one essential target inside a cell. The cell is inactivated if the essential target has received one or more "hit" of the radiation.**
- **Assuming that $\overline{m}$ is the average number of hits received by a cell in an irradiation experiment, then the survival fraction (SF) would be the fraction that receives no hit at all. According to Poisson statistics,**

$$SF = P_0 = e^{-\overline{m}} = e^{-\alpha D}$$

- **This model fits well only for the survival curves of high-LET radiation.**

The multi-target model
(widely used in the early years and still has some merit today)

- **Assumption: There are n essential targets in a cell. The cell is inactivated if each of the n targets has received one or more "hit" of the radiation.**
- **The probability of a target that has received at least one hit:** $1-e^{-\overline{m}}$
- **The probability of all n targets each has received at least one hit:** $(1-e^{-\overline{m}})^n$
- **The survival fraction is therefore:**

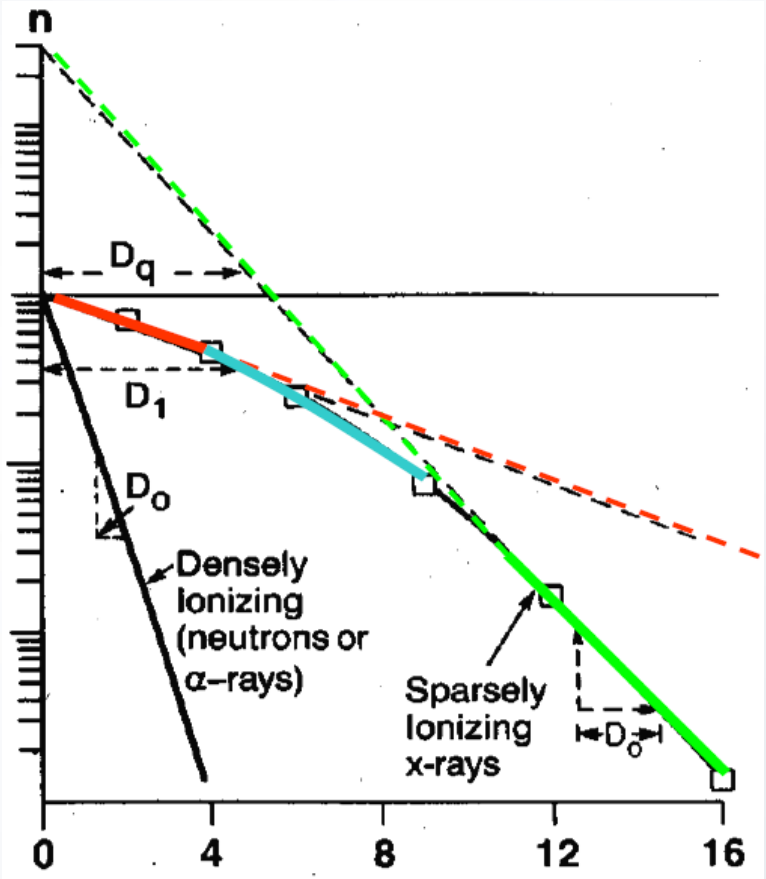
$$SF = 1-(1-e^{-\overline{m}})^n = 1-(1-ne^{-\overline{m}} + ... \pm e^{-n\overline{m}})$$

Since $\overline{m} = \alpha D$ **, at high doses the terms following** $ne^{-\overline{m}}$ **can be ignored. This leads to:**

$$SF \cong ne^{-\overline{m}} = ne^{-\alpha D}$$

The multi-target model
(widely used in the early years and still has some merit today)

- D_1, initial slope resulting from single-event killing.
- D_0, final slope resulting from multiple-event killing.
- Dq or n, quantity describing the size/width of the shoulder of the curve.



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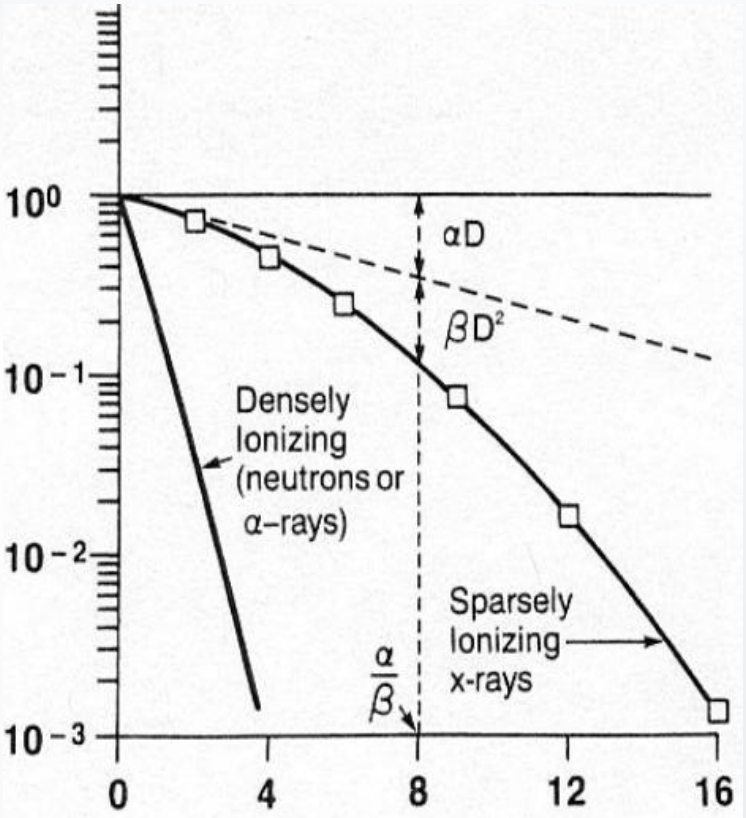
The linear-quadratic model
(Current model of choice to describe cell survival curves)

- **Repair-Misrepair Model (Tobias et. Al., 1980)**
- **Molecular Theory of Radiation Action (Chadwick & Leenhouts, 1981)**
- **Lethal-Potentially Lethal Model (Curtis, 1986)**
- **Dual Radiation Action Theory (Rossi & Kellerer, 1978)**

$$SF = e^{-\overline{m}} = e^{-(\alpha D + \beta D^2)}$$

- **Linear and quadratic components of cell killing are equal when:**

$$\alpha D = \beta D^2 \quad \Rightarrow \quad D = \alpha / \beta$$



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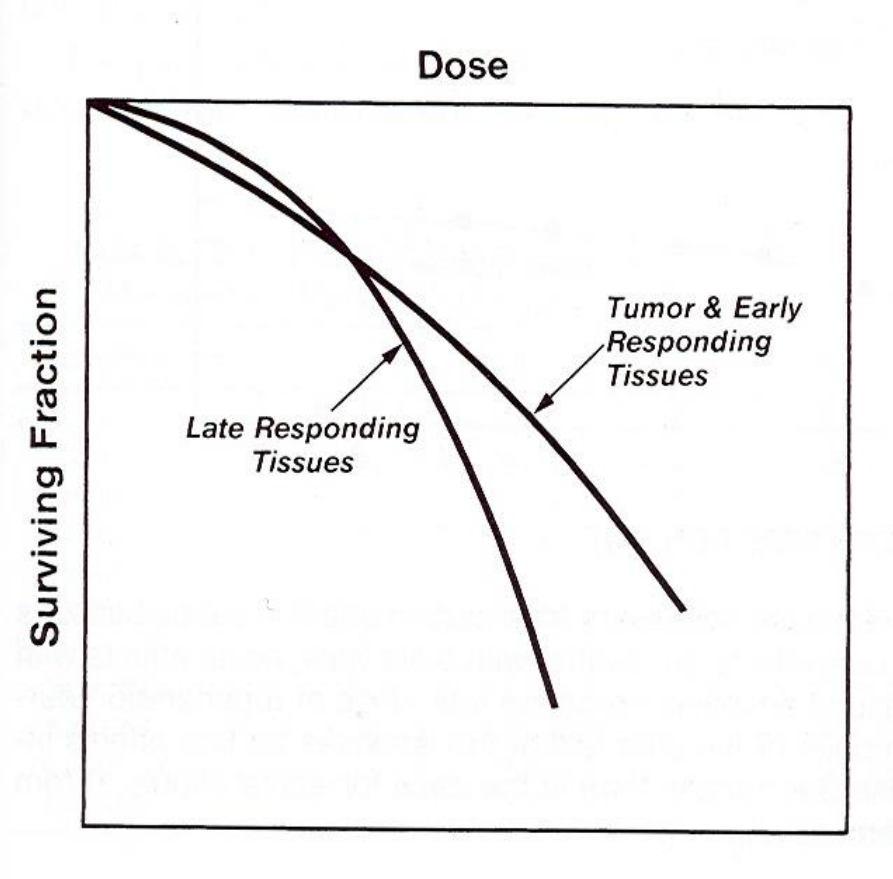
Survival curves of low-LET irradiation of cells of different DNA repair capacities



- **Tumor & early Responding tissues:**

  $\alpha/\beta \approx 10$Gy

- **Late Responding tissues:**

  $\alpha/\beta \approx 2$Gy

The microdosimetry interpretation of the target model
(A stochastic approach developed during 1970's-80's)

- **Specific energy:** $z = \dfrac{\varepsilon}{m}$
- **Single-event specific energy:** $z_1 = \dfrac{\varepsilon_1}{m}$
- **Absorbed dose:** $D = \lim_{m \to 0} \bar{z} = \dfrac{d\bar{\varepsilon}}{dm}$, where $\bar{z} = \int_0^{z_{\max}} z\, f(z)\, dz$
- **Average no. of "hits" in the target:** $\bar{n} = \dfrac{D}{\bar{z}_1}$, where $\bar{z}_1 = \int_0^{(z_1)_{\max}} z_1\, f(z_1)\, dz_1$

$f(z)$ and $f(z_1)$ are probability density functions

$$f_0(z) = \delta(z)$$
$$f_1(z) = f_1(z)$$
$$f_2(z) = \int_0^z f_1(z') f_1(z - z')\, dz'$$
$$\bullet$$
$$\bullet$$
$$f_n(z) = \int_0^z f_{n-1}(z') f_1(z - z')\, dz'$$

$$f(z) = \sum_{n=0}^{\infty} P_n f_n(z), \quad \text{where } P_n = \frac{\bar{n}^n e^{-\bar{n}}}{n!}$$
$$= e^{-\bar{n}} \delta(z) + e^{-\bar{n}} \sum_{n=0}^{\infty} \frac{1}{n!} \bar{n}^n f_n(z)$$
$$= e^{-D/\bar{z}_1} \delta(z) + e^{-D/\bar{z}_1} \sum_{n=0}^{\infty} \frac{1}{n!} \left(\frac{D}{\bar{z}_1}\right)^n f_n(z)$$
$$\cong (1 - D/\bar{z}_1)\delta(z) + \frac{D}{\bar{z}_1} f_1(z) \quad \text{if } D << \bar{z}_1$$

The microdosimetry examples

Example (1): Annual lung alpha dose of 1.0 mGy:

$$D = (1.0\times10^{-3})\left(\frac{\text{J}}{\text{kg}}\right)\times 6.24\times10^{12}\left(\frac{\text{MeV}}{\text{J}}\right) \cong 6.24\times10^{9}\ \frac{\text{MeV}}{\text{kg}}$$

Assuming the cell nucleus of 10-μm-dia is the target

$$\bar{n} = \frac{D}{\bar{z}_1} = \left(\frac{6.24\times10^{9}\ \frac{\text{MeV}}{\text{kg}}}{0.667\ \frac{\text{MeV}}{\text{track}}}\right)\left(5.23\times10^{-13}\ \frac{\text{kg}}{\text{nucleus}}\right) \cong 0.005\ \frac{\text{tracks}}{\text{nucleus}}$$

$$\bar{z}_1 = \frac{\bar{\varepsilon}_1}{m},\ \text{where}\ \bar{\varepsilon}_1 = \left(\overline{\frac{dE}{dx}}\right)\bar{\ell} = \frac{100\ \text{keV}}{\mu\text{m}}(6.67\ \mu\text{m}) = 667\ \text{keV}$$

As such,

$$f(z) \cong 0.995\delta(z) + 0.005\, f_1(z)$$

i.e. 99.5% of cells receives no hit at all, and 0.5% receives exactly one hit. For those receiving exactly one hit, the average hit size is 0.667 MeV corresponding to $\bar{z}_1 = 0.2$ Gy.

The microdosimetry examples

Example (2): Annual gamma-ray dose of 1.0 mGy:

$$D = \left(1.0\times10^{-3}\right)\left(\frac{\text{J}}{\text{kg}}\right)\times 6.24\times10^{12}\left(\frac{\text{MeV}}{\text{J}}\right) \cong 6.24\times10^{9}\ \frac{\text{MeV}}{\text{kg}}$$

$$\bar{n} = \frac{D}{\bar{z}_1} = \left(\frac{6.24\times10^{9}\ \frac{\text{MeV}}{\text{kg}}}{0.00167\ \frac{\text{MeV}}{\text{track}}}\right)\left(5.23\times10^{-13}\ \frac{\text{kg}}{\text{nucleus}}\right) \cong 2\ \frac{\text{tracks}}{\text{nucleus}}$$

$$\bar{z}_1 = \frac{\bar{\varepsilon}_1}{m},\ \textit{where}\ \bar{\varepsilon}_1 = \left(\overline{\frac{dE}{dx}}\right)\bar{\ell} = \frac{0.25\,keV}{\mu m}(6.67\ \mu m) = 1.67\,keV$$

As such,

$$P(0) = e^{-2} = 0.135$$

$$P(1) = 2e^{-2} = 0.27$$

$$P(2) = \left(\frac{1}{2}\right)2^2 e^{-2} = 0.27$$

$$P(3) = \left(\frac{1}{3!}\right)2^3 e^{-2} = 0.18$$

i.e. 13.5% receives no hit, 27% receives exactly one hit, 27% receives exactly two hits, 18% receive exactly three hits, …. etc., and the average hit size is 1.67 keV corresponding to $\bar{z}_1 = 0.5\,\text{mGy}$.

The microdosimetry examples

Example (1): Annual lung alpha dose of 1.0 mGy:

99.5% of cells receives no hit at all, and **0.5%** receives exactly one hit. For those receiving exactly one hit, the average hit size is 0.667 MeV corresponding to $\bar{z}_1 = 0.2\,\mathrm{Gy}.$

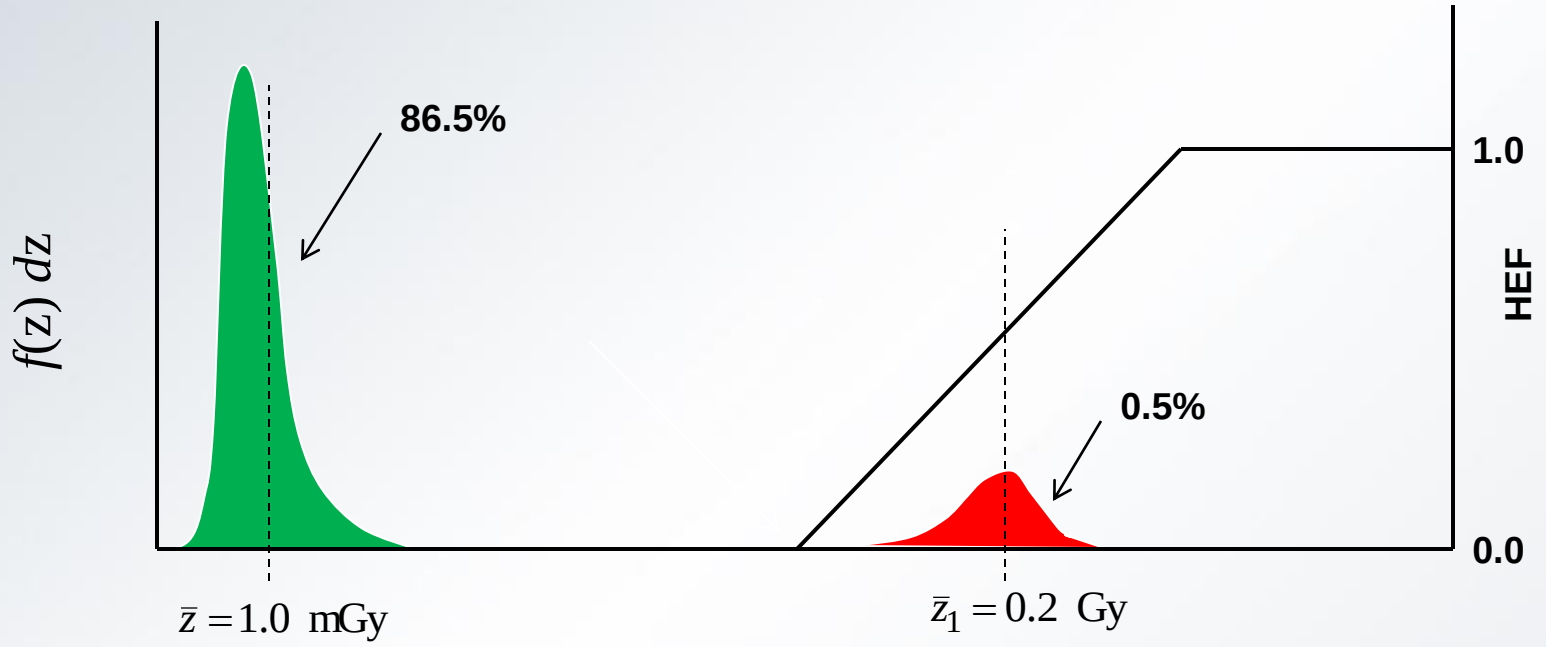
Example (2): Annual gamma-ray dose of 1.0 mGy:

13.5% receives no hit, and **86.5%** receives at least one hit, and the average size of a hit is 1.67 keV corresponding to $\bar{z}_1 = 0.5\,\mathrm{mGy}.$

How should one correlate the above results to the observed biological effects?

Ans: To use: (1) The hit-size effectiveness function (HEF)
(2) The local effect model (LEM)

The microdosimetry examples
(The HEF interpretation of cell survival fraction)



Survival fraction: $1.0 - \int_0^{z_{max}} f(z)H(z)\,dz \cong 1.0 - 0.0025 = 0.9975$ for alpha

$= 1.0 - 0.0 = 1.0$ for gamma - ray

The microdosimetry examples
(The interpretation of survival fraction based on the LEM)

It assumes that there exists a lethal-event density v, which is solely a function of the absorbed dose $D(\hat{r})$ inside a cell nucleus and is independent of the radiation type. As such, the number of lethal events in a cell nucleus caused by a high-LET ion can be obtained by integrating the lethal-event density over the nuclear volume.

$$\bar{N}_{ion} = \int v_{ion}\,(D(\hat{r}))\, dV_{nucleus}$$

where $v_{ion}(D(\vec{r}))$ is the lethal-event density which can be obtained from the low-LET cell survival curves:

$$v_{ion}(D) = v_X(D) = \frac{\bar{N}_X(D)}{V_{nucleus}} = \frac{-\ln S_X(D)}{V_{nucleus}}$$

Because $e^{-\bar{N}_X} = S_X$

and $-\ln S_X = \alpha D + \beta D^2$

Finally, $S_{ion} = e^{-\bar{N}_{ion}}$

An inherent assumption: the sensitive subnuclear targets are uniformly distributed inside the entire nuclear volume.

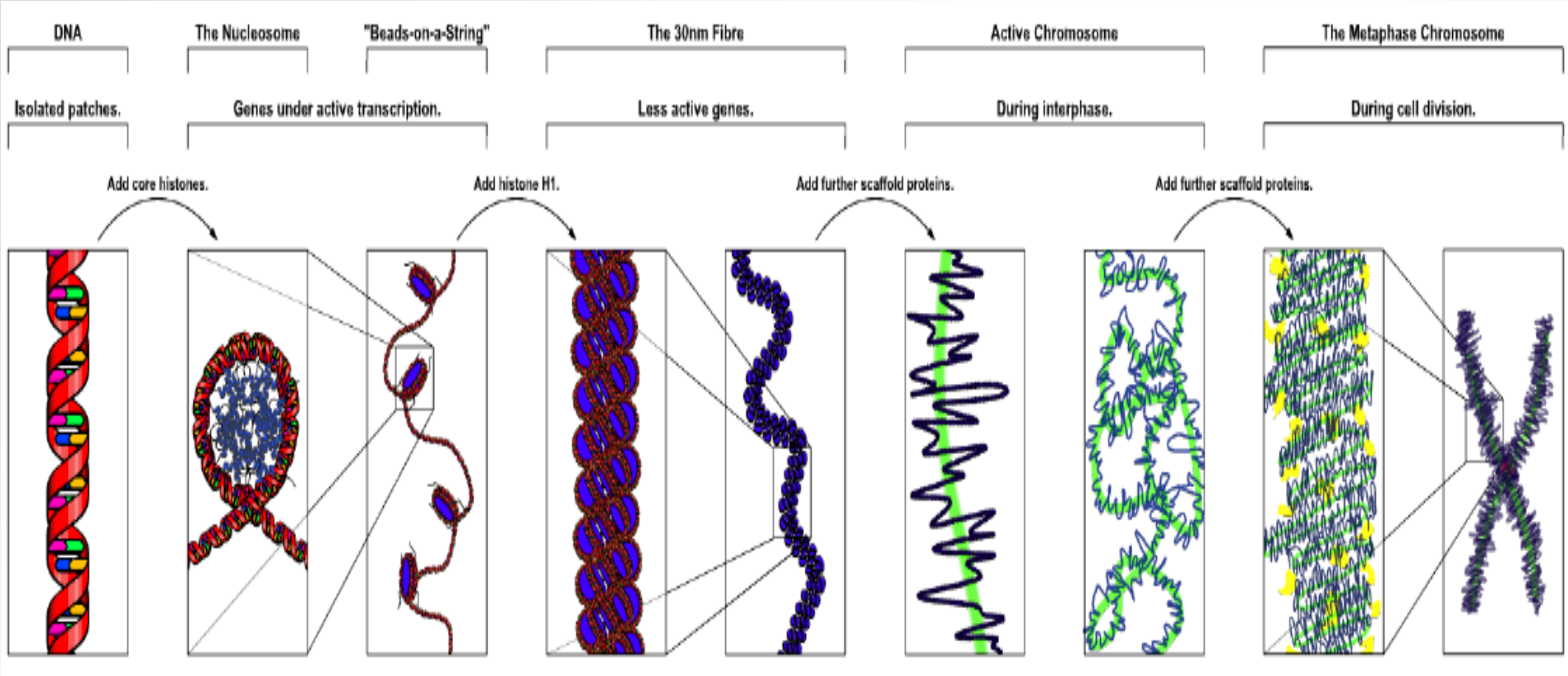
Three issues in the microdosimetry approach

1) The assumption of cell nucleus as the target.

2) The use of the average quantities, $\overline{\left(\frac{dE}{dx}\right)}$ and $\bar{\ell}$, to obtain $\bar{Z}_1$, which then is used to assess the damage to the cell.

3) The sensitive subnuclear structures are not defined. As such, there is no clear way to convert “hit size" (a physical quantity) to a real biological endpoint.

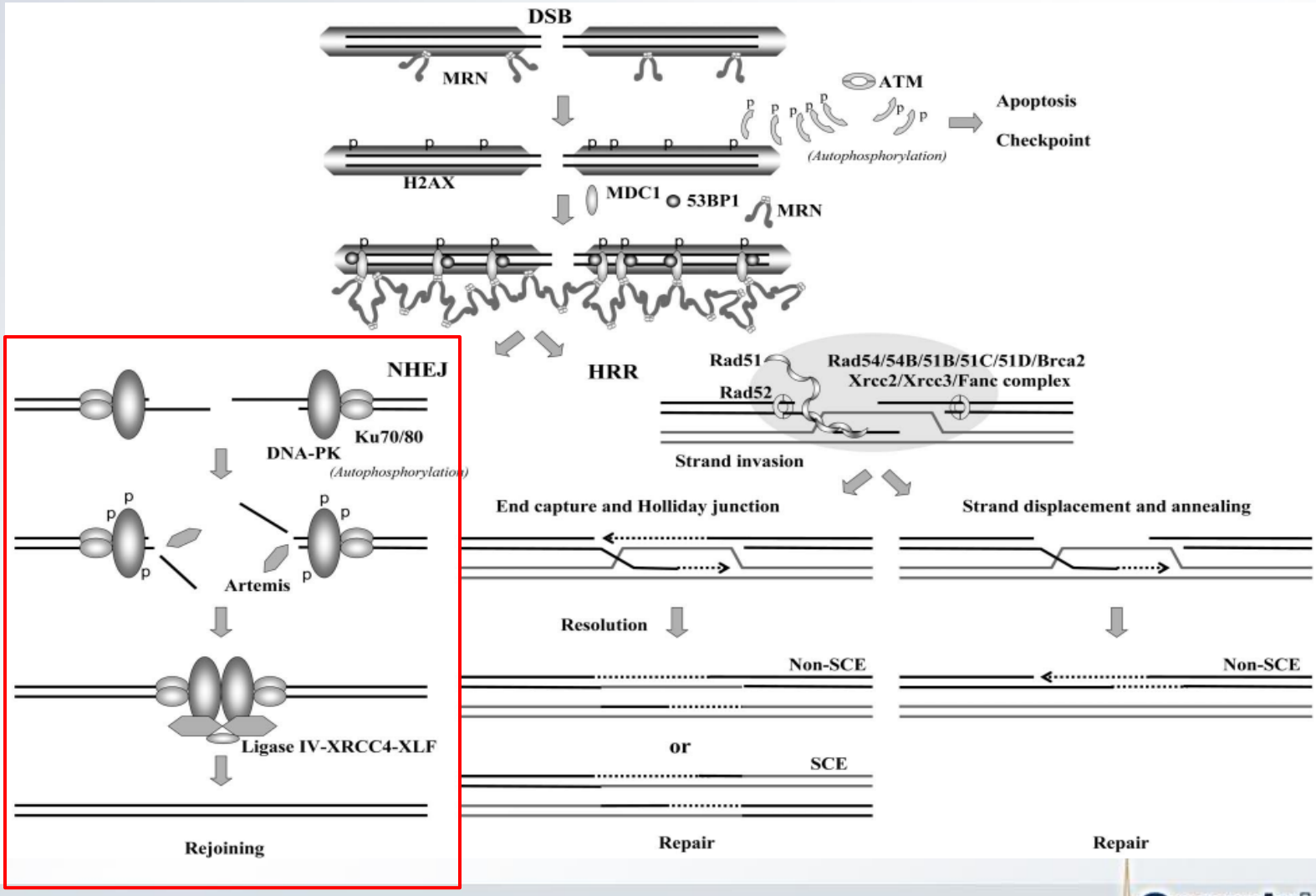
Subcellular targets and structures



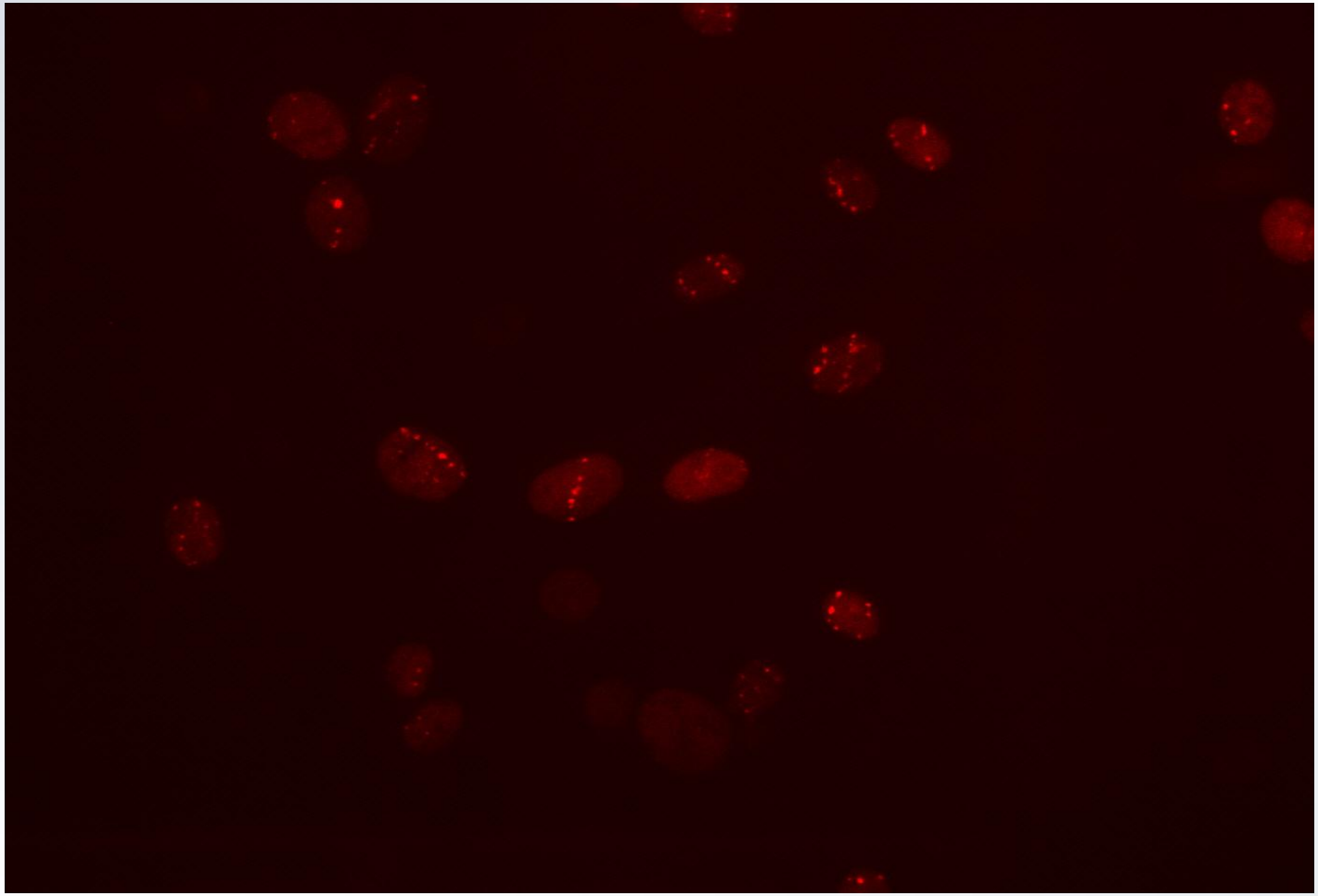
Relevant radiation signatures
(Characteristics of DNA damage as a function of LET)

- The total yield of DSBs (including both sDSB and 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.
- A mammalian cell's ability to repair a DSB becomes increasingly inhibited as the complexity of a DSB increases.
- The high yield of short (kilobase-sized) DNA fragments is a trait of high-LET radiation.
- LET-dependence is found for the yield ratio of intra-arm to inter-arm chromosomal changes (interstitial deletions/centric rings = G-ratio) and for the yield ratio of intra-arm to interchromosomal exchanges (interstitial deletions/dicentrics = H-ratio).

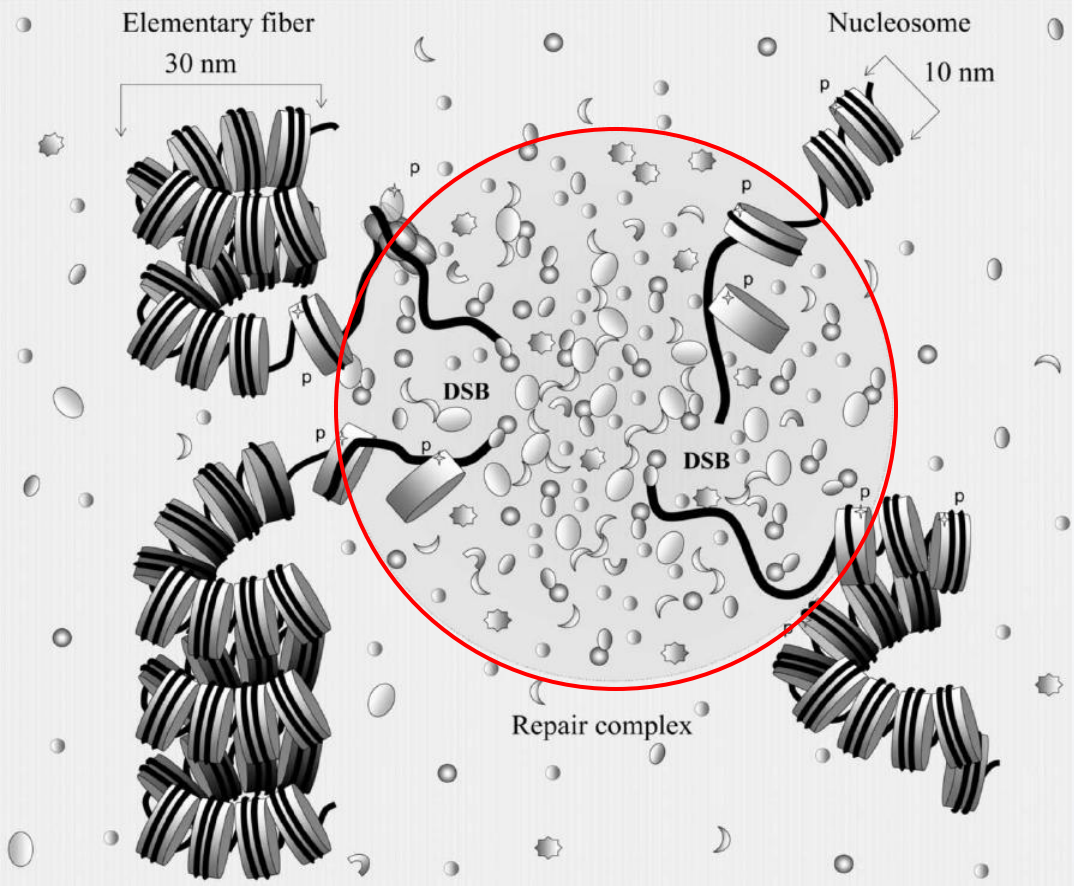
DNA structure and damage repair kinetics
(Sasaki, M.S., Int. J. Rad. Biol., 2009)



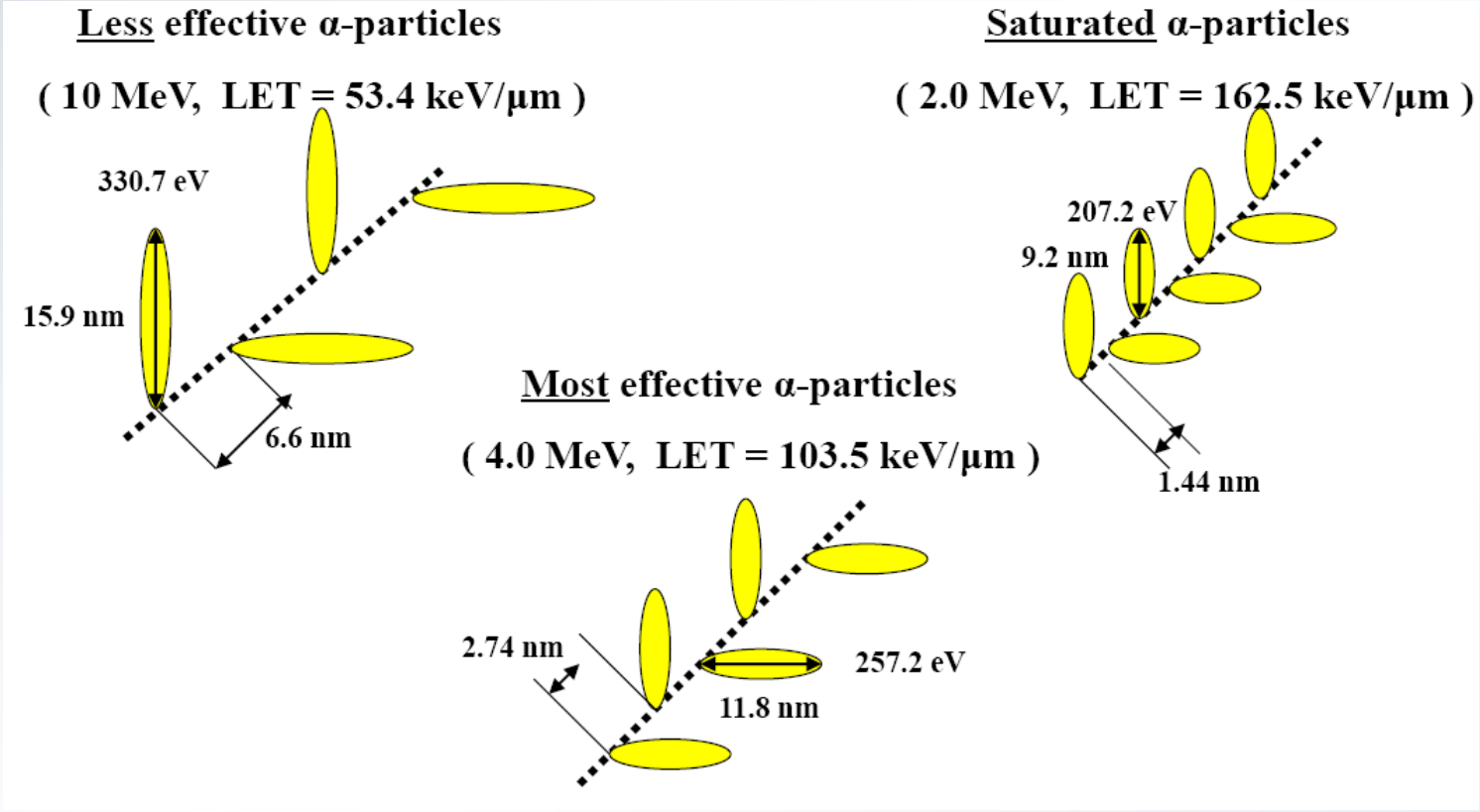
The immunofluorescent foci image of heavy ions



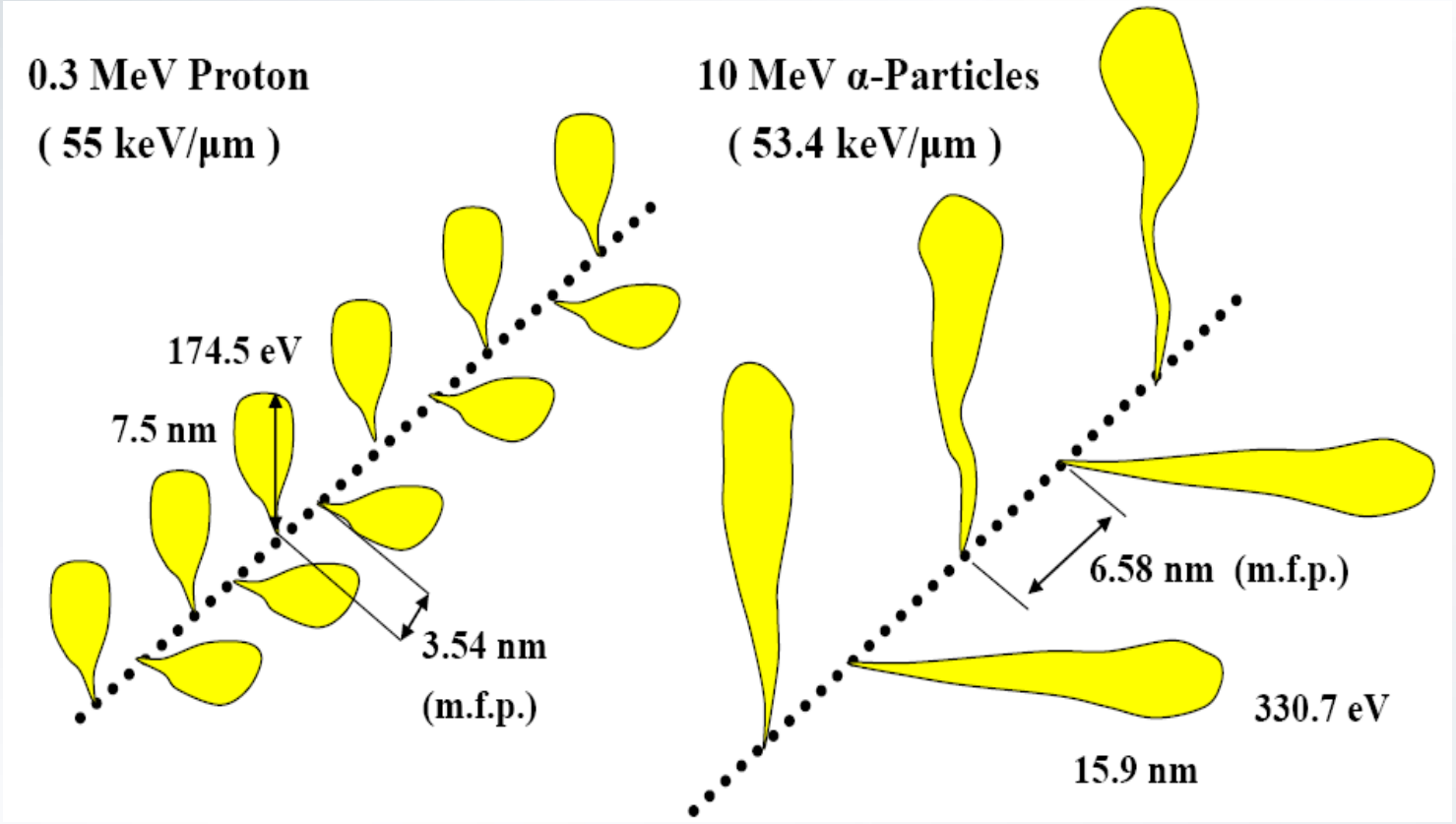
DSB repair and misjoining
(Sasaki, M.S., Int. J. Rad. Biol., 2009)



Relevant features of particle track structure
(Alpha particles with various LETs)

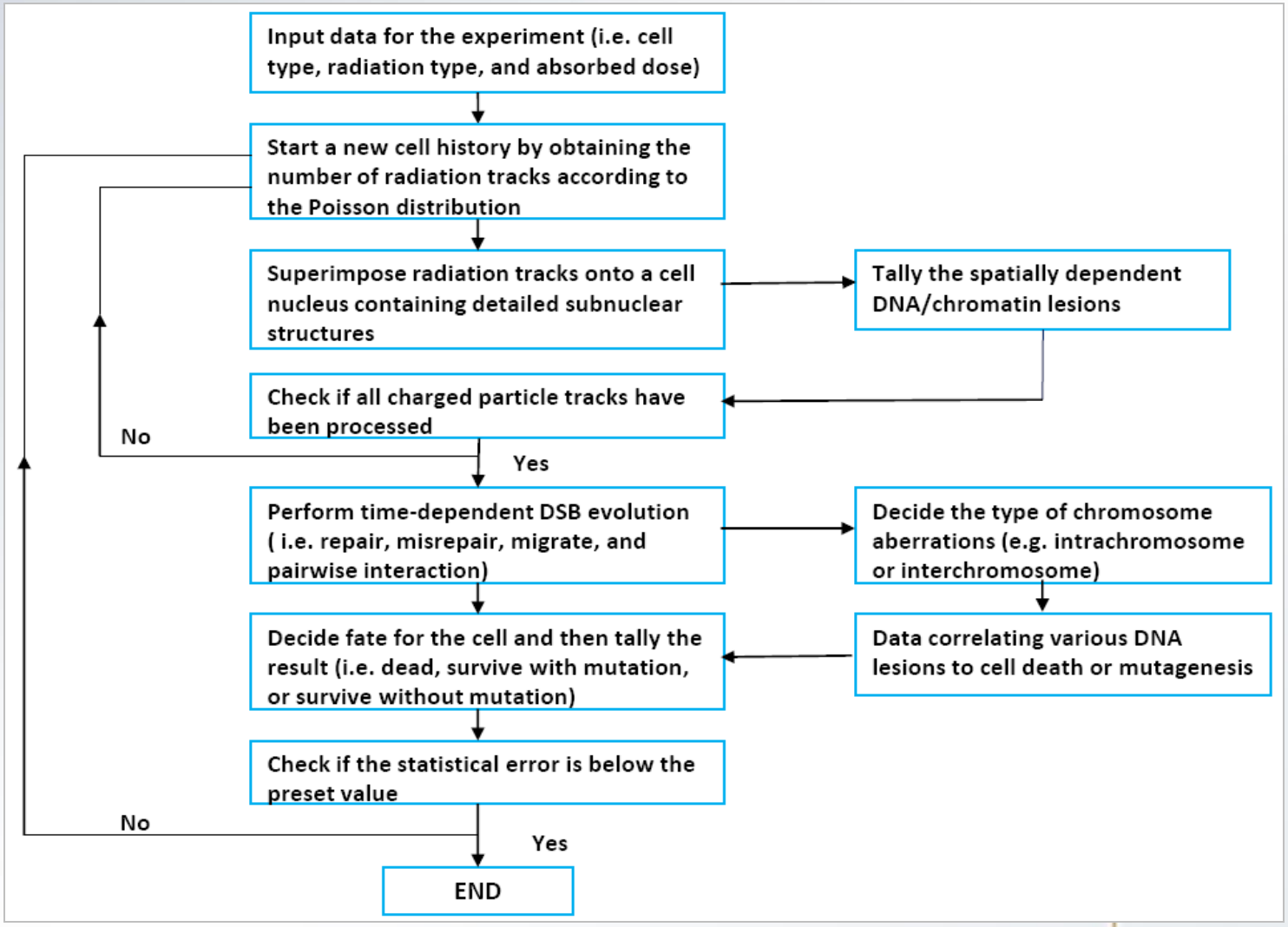


Relevant features of particle track structure
(Protons and alpha particles of the same LET)

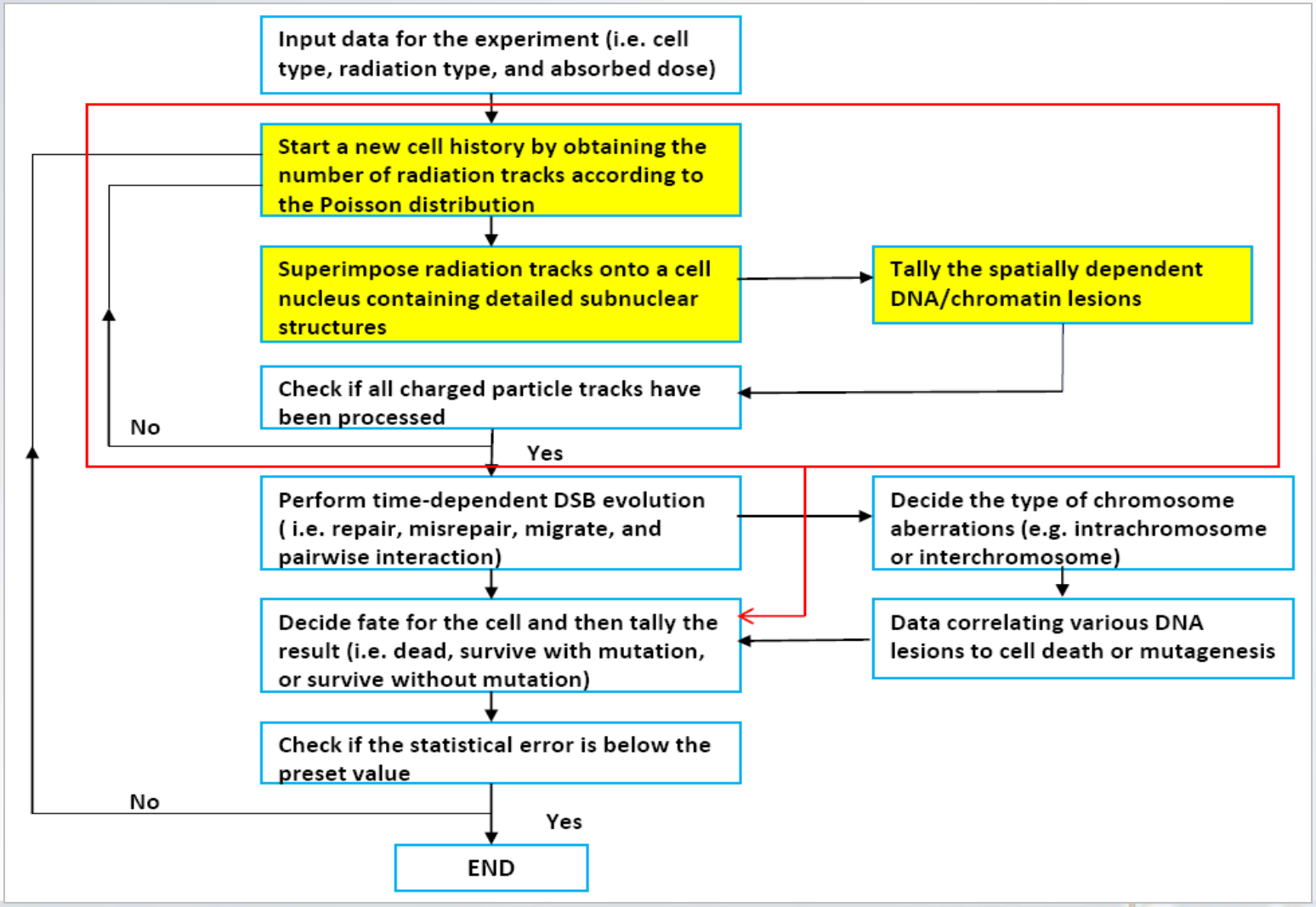


The systems biology approach of radiobiological modeling

(Wang C., Mutation Res, 704, 175-181, 2010)



Track-structure based radiobiological modeling



Random assignment of the number of particle tracks for each cell

Step 1: Calculate the mean single-event specific energy for a cell nucleus

$$\bar{z}_1 = \frac{\bar{\varepsilon}}{m}$$

where $\bar{\varepsilon}$ is the mean energy deposited by a single particle track, and m is the mass of the cell nucleus.

Step 2: For a specified absorbed dose D, calculate the corresponding average number of particle tracks

$$\bar{n} = \frac{D}{\bar{z}_1}, \text{ where } \bar{z}_1 = \frac{\bar{\varepsilon}_1}{m} \text{ and } \bar{\varepsilon}_1 = \overline{\left(\frac{dE}{dx}\right)}\bar{\ell}$$

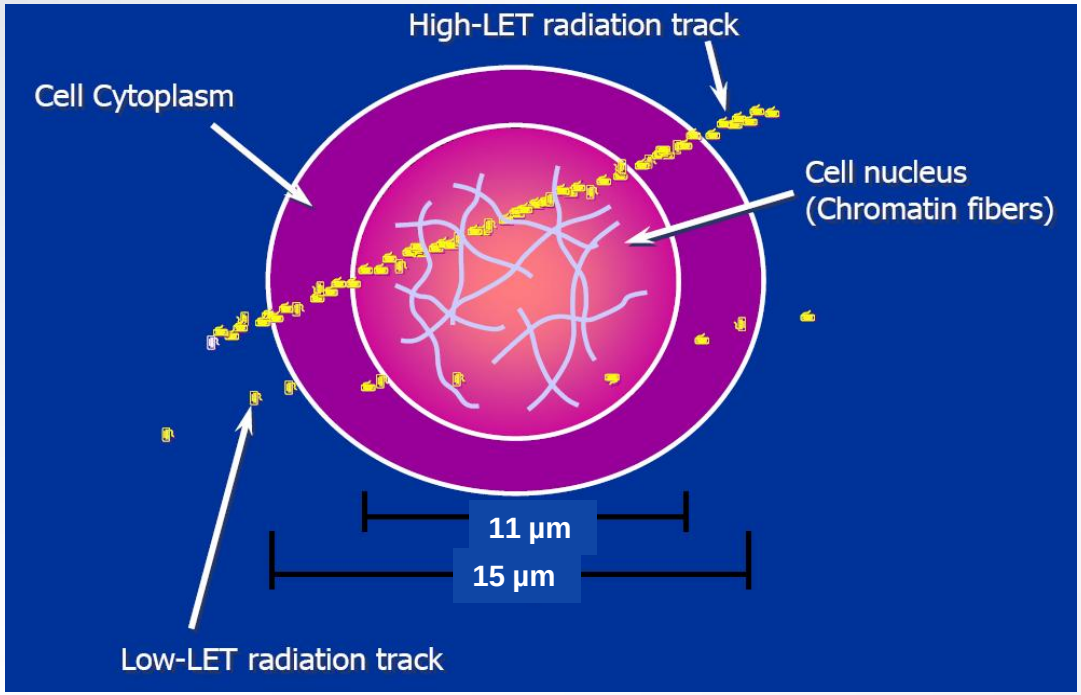
Step 3: Pick a random number, $\Re$, and apply it to the cumulative probability function F_v, which is obtained using the Poisson distribution P_n as the probability density function. That is,

$$P_n = \frac{\bar{n}^n e^{-\bar{n}}}{n!} \quad \text{and} \quad F_n = \sum_{n=0}^{n} P_n$$

If $F_n < \Re < F_{n+1}$, then $v = n$, which is the randomly assigned number of particle tracks.

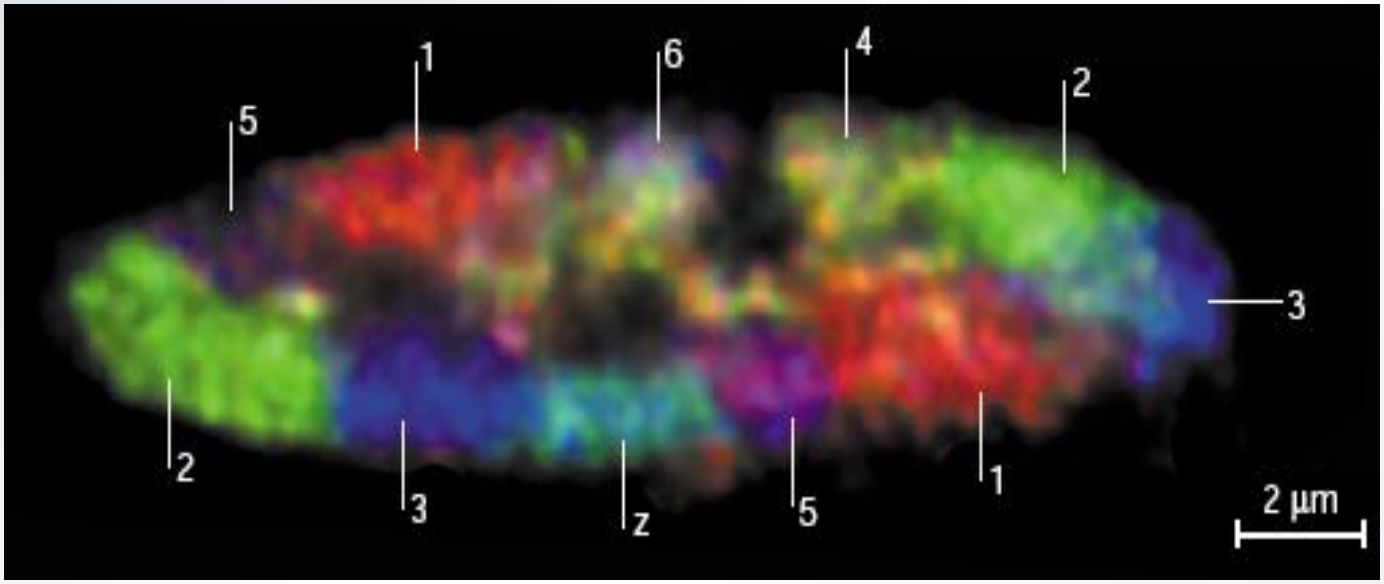
Superimpose a radiation track onto a cell nucleus containing detailed subcellular structures

- The data associated with a track structure include the positions (x, y, and z) of all the energy transfer points, the types of energy transfer (i.e. ionization or excitation), and the amount of energy transfer at each point.
- The subnuclear structures include chromosome territories (CTs), chromatin domains (CDs), interchromatin compartment (IC), and chromatin fibers.



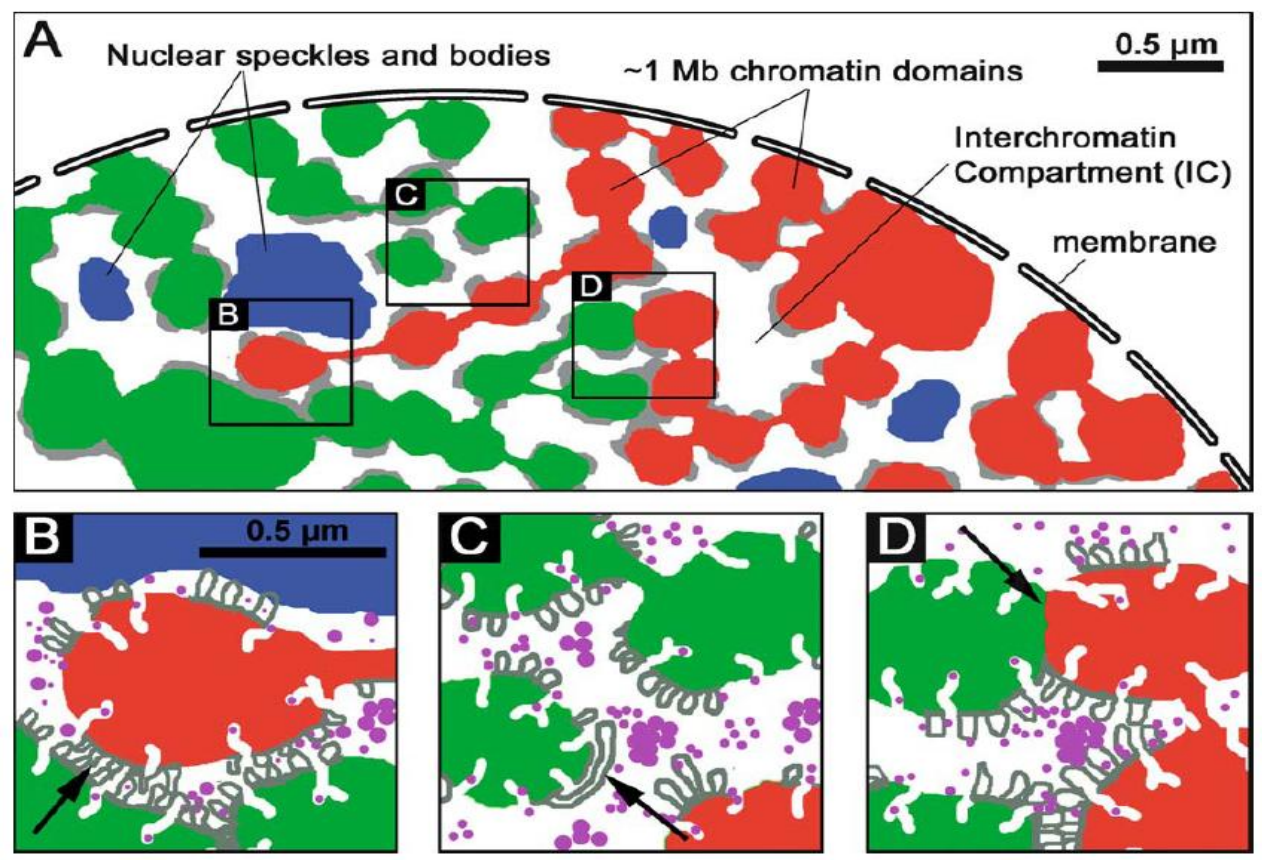
How should one model the detailed subnuclear structures?

Chromosome territories (CTs)



Mid-plane light optical section through a chicken fibroblast nucleus shows mutually exclusive chromosome territories (CTs) with homologous chromosomes seen in separate locations. **(T. Cremer and C. Cremer, Nature Reviews, 2001)**

Chromatin domains and interchromatin compartment



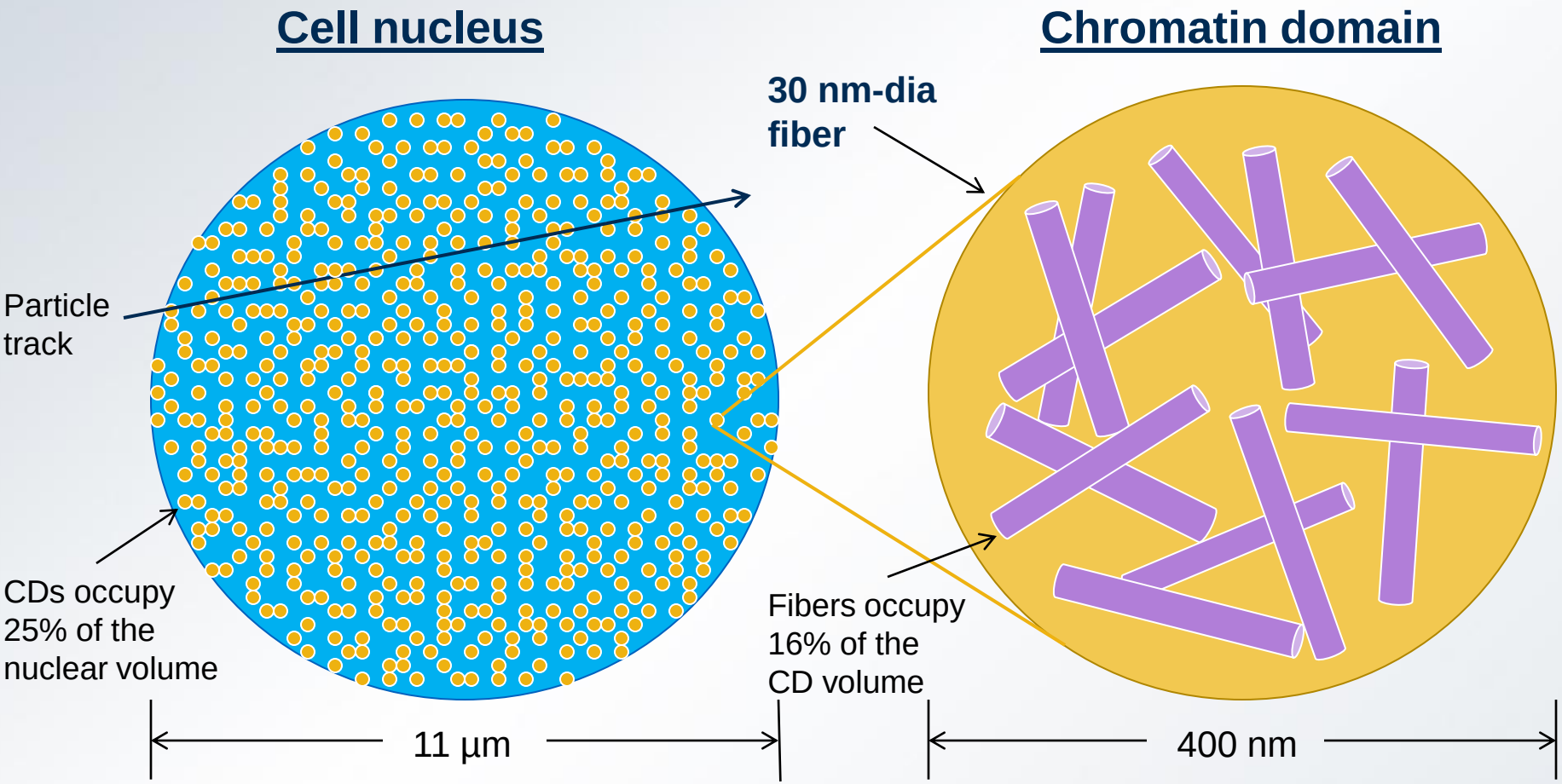
Chromatin domains and interchromatin compartment form structurally defined functionally interacting nuclear networks.
(Albiez et. al., Chromosome Research, 2006)

Modeling of subnuclear structures

- Cell nucleus is a perfect sphere with 11 μm in diameter.
- The cell nucleus is randomly and uniformly filled with 6,000 chromatin domains (CDs), of which each is a 400-nm-dia sphere containing 1 Mbps of DNA.
- The CDs occupy approximately 25% of the nuclear volume. The rest of nuclear volume is chromatin-free.
- Each CD is randomly and uniformly filled with the 30-nm-dia chromatin fibers, which occupy approximately 16% of its volume.

Approximately 96% of the nuclear volume is chromatin-free!

Modeling of subcelluler structures

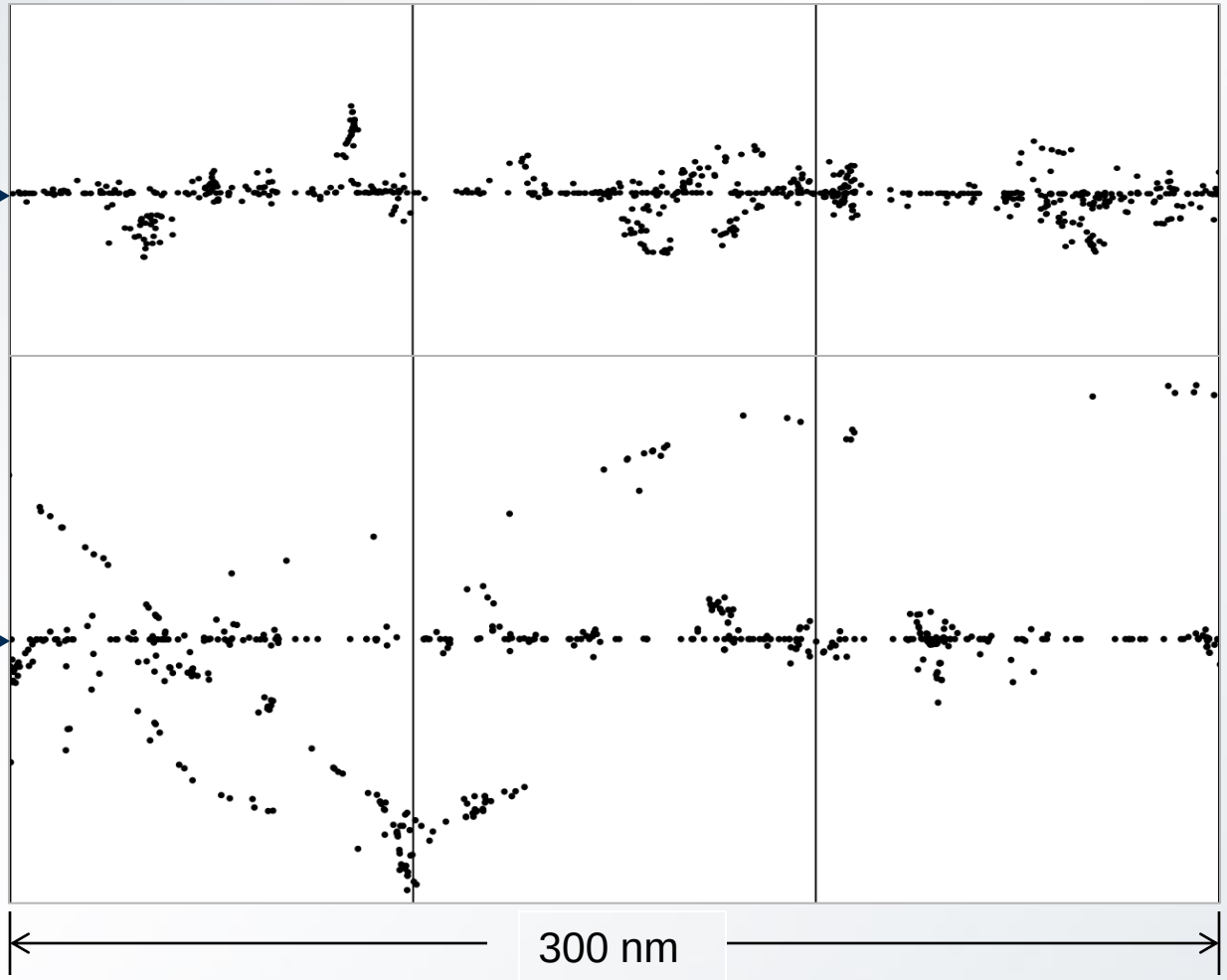


Track structures (from GEANT4-DNA) of proton and alpha particle having the same LET in water

0.7-MeV proton

$$\frac{dE}{dx} \cong 32\ keV/\mu m$$

20-MeV alpha



Each dot represents an energy transfer point, where an excitation or an ionization event occurs.

Monte Carlo procedure for generating the initial locations of chromatin-damage site along a charged particle track

Step 1: Randomly superimpose the particle track onto the 11-μm-dia spherical cell nucleus.

Step 2: Follow each energy transfer point along the particle track, and randomly decide the next "collision site" where the particle runs into a chromatin domain (CD).

Step 3: Upon entering the CD, randomly decide the next "collision site" where the particle runs into a chromatin fiber.

Step 4: Tally the energy deposited (or hit size) in the chromatin fiber.

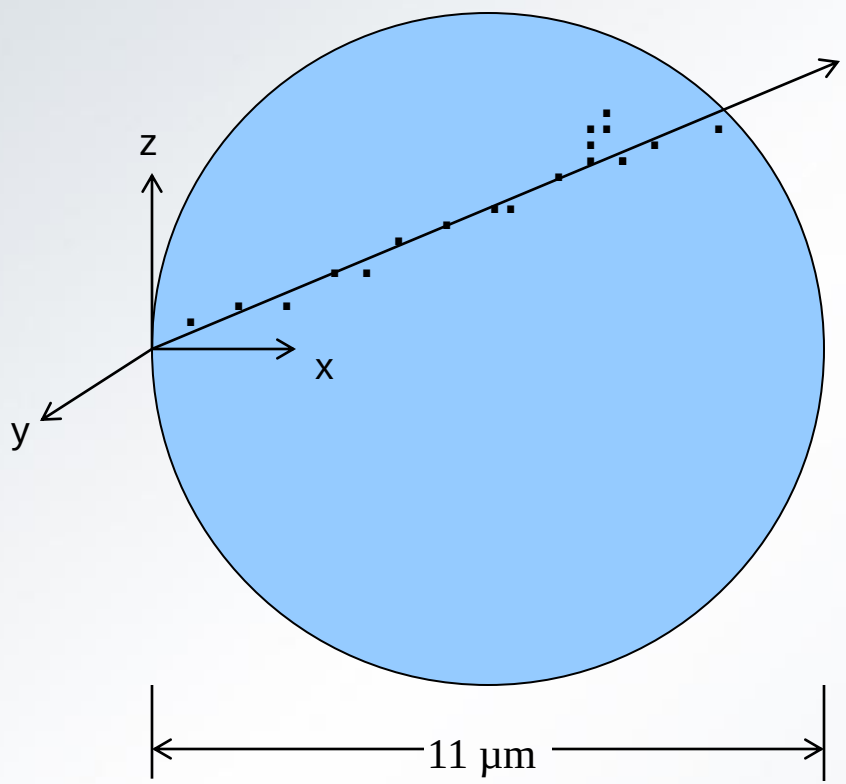
Step 5: Repeat Steps 2-4 until the particle comes out of the cell nucleus.

Step 6: Repeat Steps 1-5 as many times as needed to obtain the "hit-size distribution" normalized for each type of particle track.

Step 7: Convert hits into chromatin damage of various degrees of severity corresponding to the hit size.

Monte Carlo procedure – Step 1a

- **Randomly superimpose the particle track (obtained from GEANT4_DNA) onto the 11-μm-dia spherical cell nucleus.**

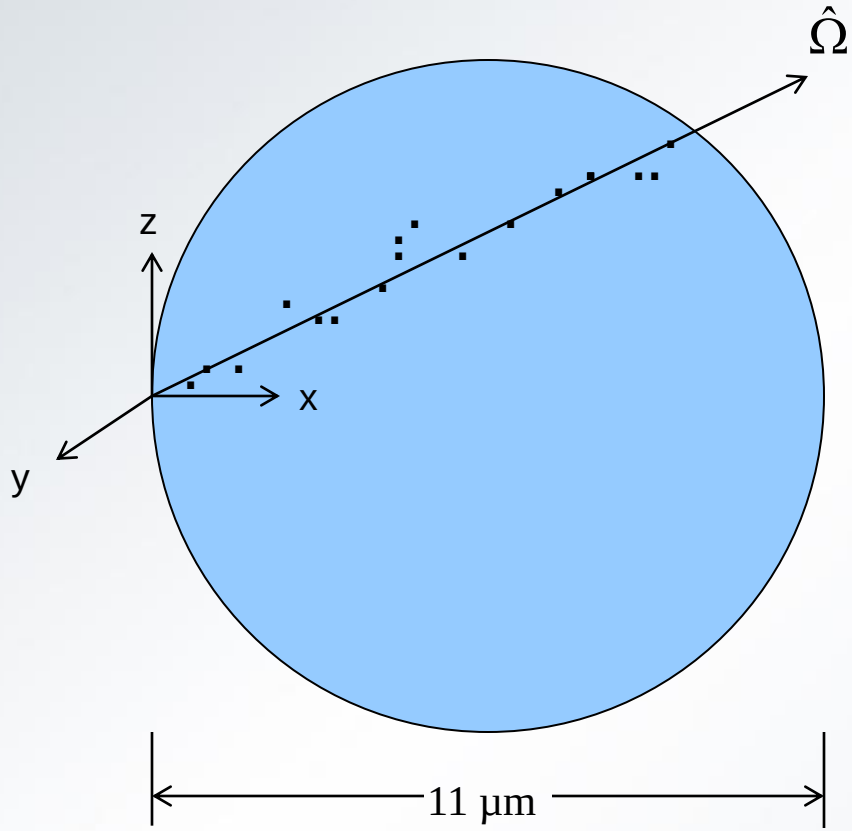


A randomly picked direction that can be determined by two random numbers:

$$\hat{\Omega} = u\hat{i} + v\hat{j} + w\hat{k}, \text{ where } u = \cos\varphi,$$
$$v = \cos\theta\sin\varphi, \; w = \sin\theta\sin\varphi,$$
$$\varphi = \cos^{-1}(1 - \Re_1), \; \theta = 2\pi\Re_2,$$
where $\Re_1$ and $\Re_2$ are two random numbers.

Monte Carlo procedure – Step 1b

- **Randomly superimpose the particle track (obtained from GEANT4_DNA) onto the 11-μm-dia spherical cell nucleus.**



To transform each energy transfer point (x,y,z) of the particle track obtained from Geant-4 to the new coordinates (x',y',z') via:

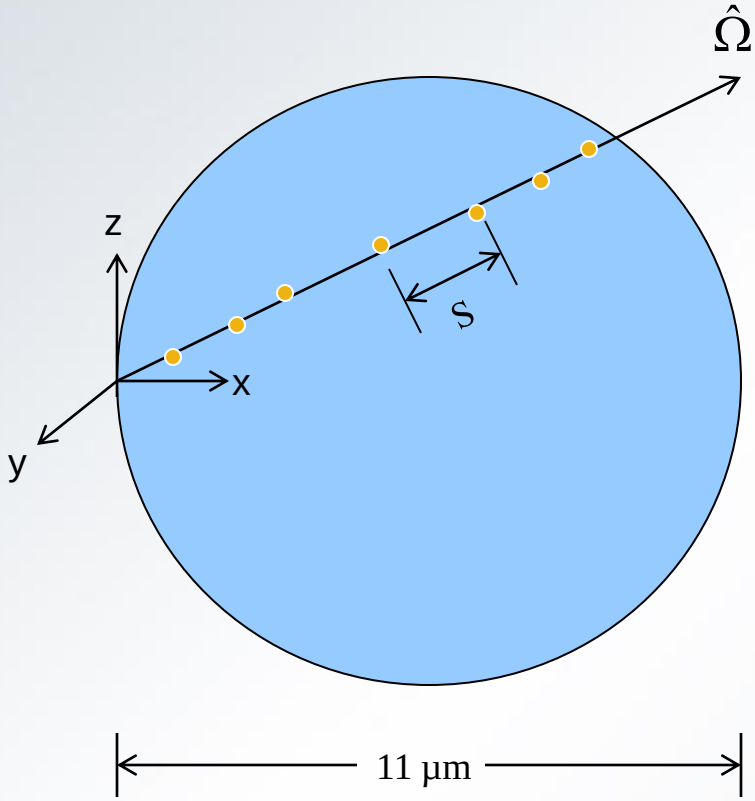
$$x' = -5.5 + \cos\varphi + z\sin\varphi$$

$$y' = y\cos\theta + z\cos\varphi\sin\theta - x\sin\varphi\sin\theta$$

$$z' = z\cos\varphi\cos\theta - y\sin\theta - x\sin\varphi\cos\theta$$

Monte Carlo procedure – Step 2

- **Follow each energy transfer point along the particle track, and randomly decide the next "collision site" where the particle runs into a chromatin domain (CD).**



$$S = \lambda \ln\left(\frac{1}{\Re}\right), \text{ where } \Re \text{ is a random number}$$

and λ is the mean free path :

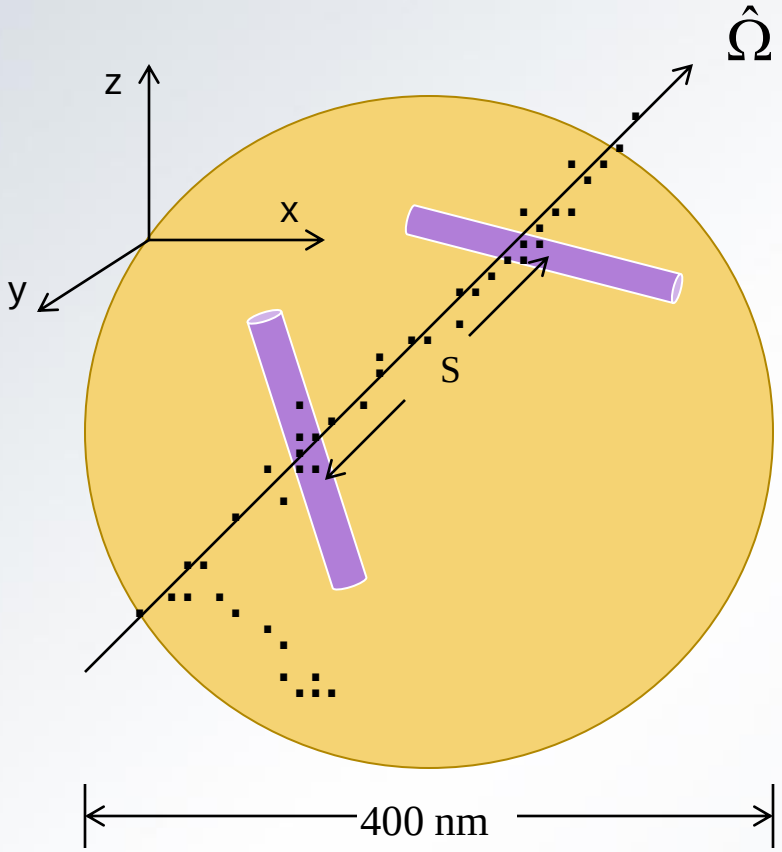
$$\lambda = \left(\frac{75}{25}\right) R_{av} = (3)\left(\frac{2}{3}\right)(400\ \text{nm}) = 800\ \text{nm}$$

Mean chord length of the CD

Since the average chord length of the nucleus is 7.33 µm, this translates to an average of ~9 hits for each track traversing a nucleus.

Monte Carlo procedure – Step 3

- **Upon entering the CD, randomly decide the next "collision site" where the particle runs into a chromatin fiber.**



$$S = \lambda \ln\left(\frac{1}{\Re}\right), \text{ where } \Re \text{ is a random number}$$

and λ is the mean free path :

$$\lambda = \left(\frac{84}{16}\right)(R_{av}) = \left(\frac{84}{16}\right)\left(\frac{5}{3}(30\text{ nm})\right)$$

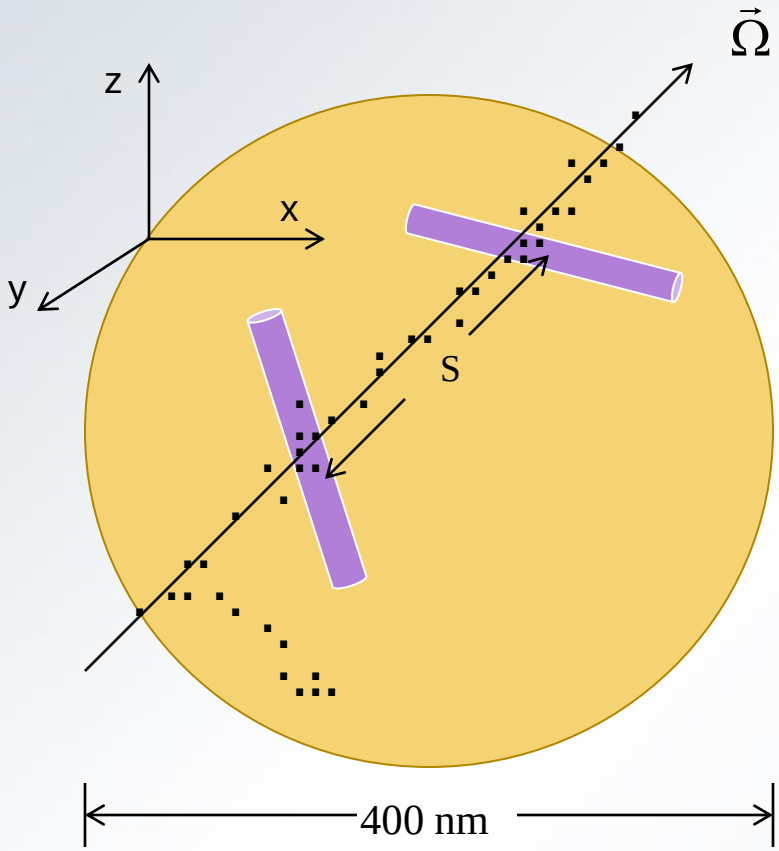
$$= 262.5\text{ nm}$$

R_{av} is the mean chord length of the chromatin fiber

Since the average chord length of a CD is 267 nm, this translates to an average of ~1 hit for each track traversing a CD.

Monte Carlo procedure – Step 4

- **Two quantities to be tallied: the position of each hit and the hit size.**



$$\overline{(\hat{r})} = \frac{\sum_{i=1}^{n} \varepsilon_i \, \hat{r}_i}{\varepsilon}, \quad \text{where} \quad \varepsilon = \sum_{i=1}^{n} \varepsilon_i$$

$$\varepsilon = \sum_{i=1}^{n} \varepsilon_i$$

Results

To be published soon!

Questions?