TFY4315 Biophysics of Ionizing Radiation
Exam 2018: Suggested Solutions

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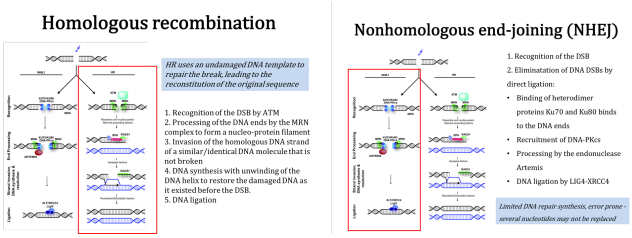
Problem 1 - DNA damage and repair

(a) A = nucleosomes, B = chromatin, C = DNA double strand, D = chromosomes

(b) Approximately 1000 SSBs, 40 DSBs, 1000 altered bases



(c)

NHEJ versus HR

- NHEJ:
  - Repairs most DSBs (about 80%)
  - Important for radiosensitivity
  - Error prone
  - All parts of the cell cycle
  - Similar in all cell types
- HR:
  - Repairs fewer DSBs (about 20%)
  - Important for radiosensitivity
  - Error free
  - S and G2 phase
  - Responsible for change in sensitivity in the cell cycle
  - Varies more between cell lines
  - Defects common in cancer

(d)

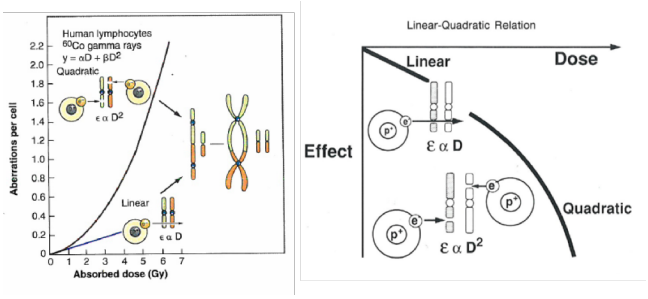
(e) Each aberration is a consequence of the interactions of two separate breaks in the chromatid. The linear component:

- has a probability proportional to the dose, D
- the breaks result from a single charged particle
- is most probable at low doses

The quadratic component:

- has a probability proportional to D^2
- the breaks result from different charged particles
- is most probable at higher doses

The linear quadratic relationship characteristic of the induction of chromosomal abberations is carried over to the cell survival curve.



Problem 2 - Models of cell survival

(a) In the multitarget model we assume that a cell dies only when multiple targets are all hit. The probability of missing a target inside the cell is given by the probability $P(0) = e^{-a}$, where a is proportional to the dose, i.e. $1 - P(0) = e^{-D/D_0}$

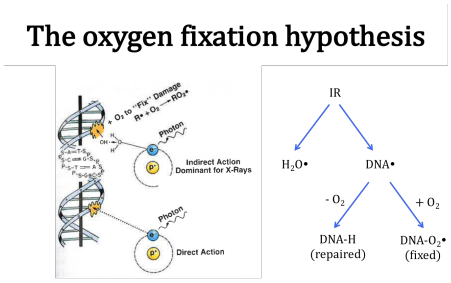
Then, the probability of at least one hit will be $P(0) = 1 - e^{-D/D_0}$

If there are multiple targets, n, where all must be hit to kill a cell, then the probability of hitting all of them at least once is $(1 - e^{-D/D_0})^n$

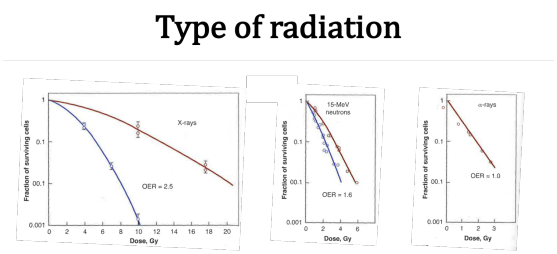
Then, the probablity of NOT hitting all of them at least once, i.e. the probability of surviving, is $S(D) = 1 - (1 - e^{-D/D_0})^n$

(b) The multitarget model is wrong for low doses as it predicts a flat response. This is not found experimentally. The LQ model provides a better model for the low doses.

(c) Exposure of cells to ionizing radiation generates free radicals that reacts directly with the DNA or indirectly through first reacting with water (H2O) molecules. A radical is an atom with unpaired valence electrons (and is highly chemically reactive). If no oxygen is present the damage can be repaired to its original state (DNA-H), but in the presence of molecular oxygen a peroxy radical is formed (DNA-O2-radical), fixing damage into a permanent irrepairable state. Means that we will have strand breaks in DNA and cell death.



Oxygen molecules react with free radicals produced by ionizing radiation and give stable changes in chemical composition of DNA (oxygen "fixates" the DNA damage)



1) Low ionizing density; x-rays and γ-rays:
- broad shoulder
- significant oxygen effect
- large OER

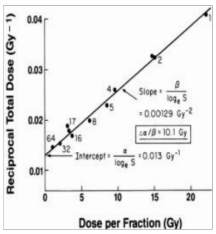
2) Intermediate ionizing density; neutrons:
- reduced shoulder
- small oxygen effect
- small OER

3) High ionizing density; low-energy α-particles:
- no shoulder
- no oxygen effect
- OER = 1

(d) See figure below. The reciprocal of the total dose is 1/nd since the total dose is D = nd. The number of fractions are shown by each point. From the values of the intercept and the slope of the best-fit line, the α and β and therefore the α/β for the dose-response curve for organ function can be determined. Intercept = α/logeS and slope = β/logeS, S = survival

Determining α/β-ratio from multi-fraction experiments in nonclonogenic systems

The total dose D divided into n fractions of dose d:



α/β is larger for early-responding tissues (10 Gy) than for late-responding tissues (3 Gy)

S is not known, but the ratio of the intercept to slope give estimate of α/β

Problem 3 - Fractionated radiotherapy and biologically effective dose

(a) Formula for BED:

$$BED = D(1 + \frac{d}{\alpha/\beta})$$

where D is the total dose, d is the fraction dose. These are related through $D = nd$, where n is the number of fractions.

(b) Conventional strategy:

$$BED_{tumor/early} = 2 \cdot 5 \cdot 5(1 + \frac{2}{10}) = 60Gy$$

$$BED_{late} = 2 \cdot 5 \cdot 5(1 + \frac{2}{3}) = 83.33Gy$$

Hyperfractionated strategy:

$$BED_{tumor/early} = 1.2 \cdot 5 \cdot 7 \cdot 2(1 + \frac{1.2}{10}) = 94.1Gy$$

$$BED_{late} = 1.2 \cdot 5 \cdot 7 \cdot 2(1 + \frac{1.2}{3}) = 117.6Gy$$

This strategy is more effective both for early and late effects. But may give intolerable normal tissue effects.

Concomitant boost:

$$BED_{tumor/early} = 1.9 \cdot 30(1 + \frac{1.9}{10}) + 1.5 \cdot 10(1 + \frac{1.5}{10}) = 67.83 + 17.25 = 85.1Gy$$

$$BED_{late} = 1.9 \cdot 30(1 + \frac{1.9}{3}) + 1.5 \cdot 10(1 + \frac{1.5}{3}) = 93.1 + 22.5 = 115.6Gy$$

This strategy is more effective than conventional therapy both for early and late effects. The strategy is almost equal for late effects, but less effective for tumor/early effects. Among the hyperfractionated therapy and the concomitant boost strategy it would therefore be better to choose the hyperfractionated treatment since it would give better tumor effect while the late effects are approximately equal.

CHART strategy:

$$BED_{tumor/early} = 1.6 \cdot 36(1 + \frac{1.6}{10}) = 66.8Gy$$

$$BED_{tumor/early} = 1.6 \cdot 36(1 + \frac{1.6}{3}) = 88.3Gy$$

The effect of this treatment is not so relevant to compare with the other strategies since this one is delivered in only 12 days and the others in 5-7 weeks. A weakness with the standard BED formula is that treatment time is not considered. CHART or hyperfractionation are good options for rapidly proliferating tumours such as head and neck cancer.

(c) Total treatment time is $T = (n-1)\Delta t$. This means that:

$$BED(D, n, T) = BED(D, n) - \frac{T - T_k}{\alpha T_p / \ln 2} = D(1 + \frac{d}{\alpha/\beta}) - \frac{(n-1)\Delta t - T_k}{\alpha T_p / \ln 2}$$

(d) The value of n that maximizes this result in $n = 1$, i.e. a single dose treatment. This is seen by looking at the two terms; the first is positive and becomes larger for smaller n (remember that $D = nd$) and the second term becomes more negative for larger n.

(e) The single dose treatment is mathematically correct in this optimization. However, it is not acceptable in practice due to normal tissue effects where the damage from a non-fractionated treatment could be excessive. Thus, to optimize we should also include at least one term that takes into account the normal tissue complication probability (NTCP).

Problem 4 - Radiation protection

(a) Deterministic effects: when you reach doses above a threshold enough cells are killed to affect organ function. The severity increases with dose. Stochastic effects: Irradiated cells survive but are modified, no threshold. The severity is independent of dose but the probability increases with dose.

(b) ALARA = As Low As Reasonably Achievable (the recommendations are all upper limits, no unneccessary exposure should be allowed, no exposure permitted without considering the benefits from that exposure and the relative risks for alternative approaches)

(c)
- Absorbed dose: energy absorbed per unit mass of tissue. A physical quantity. Unit: Gray (Gy) = J/kg.
- Equivalent dose: the same absorbed dose of different types of radiation may have different biological effects. Adjusting the absorbed dose (for each tissue/organ radiated) with a radiation weighting factor (W_R) (according to energy and type of radiation) gives the equivalent dose for biological effects. Unit: Sievert (Sv).
- Effective dose: the sum of all the weighted equivalent doses in all tissues/organs irradiated. W_T is a weighting factor for different organs according to their radiation sensitivity. Unit: Sievert. The effective dose corresponds to the whole body dose of X-rays that would have to be delivered to produce the same stochastic risk as the partial body dose that actually was delivered.

(d) Photons and electrons = 1, protons = 2, α-particles = 20, neutrons = a continuous curve as a function of neutron energy (ranging from 1-20).

Problem 5 - Lab and project work

(a) From poster - group 1. Types of biologic response modifiers: metabolic inhibitors, immunotherapy, growth factor inhibitors, anti-invasive agents (e.g. kinase inhibitors), antiangiogenic agents, DNA damage response inhibitors, survival signalling inhibitors, anti-hypoxia agents. Immunotherapy: When tumor cells die of radiation they release signalling cytokines which recruit tumor responses trying to repair the damage. Antagonists of immune molecules and immune-stimulating drugs are developed to overcome the response when the body is exposed to radiation, for example by priming the T-cells of the tumor. This can prevent repair (1st R of radiobiology) and repopulation (2nd R of radiobiology) within the tumor, as well as outside of the radiotherapy field (abscopal effect).

(b) From poster - group 2. The RBE is used to account for differences in biological effect between radiation qualities and is defined as RBE = dose of standard radiation / dose of test radiation, where standard radiation usually is orthovoltage X-rays (250 kVp). RBE of protons is 1.1 (but is being debated). The increased biological effect from protons compared to photons is due to that the linear energy transfer (LET) of protons will increase as the energy deposited to the medium increases. A higher LET means that the radiation is more densely ionizing and will produce more cell killing per Gy; i.e. is biologically more effective.

(c) From poster - group 3. Several approaches can be used to target hypoxia. Examples:

- Increasing the oxygen delivery to tumours. This may be achieved using hyperbaric oxygen chambers, breathing oxygen-rich gas to treat chronic hypoxia, or by using nicontinamide to treat acute hypoxia. A combination can be used, e.g. ARCON (Accelerated Radiotherapy, Carbogen, and Nicontinamide).
- Using chemicals that target hypoxic tissue. Hypoxic cell radiation sensitizers are typically chemicals that mimic oxygen to fix radiation damage, e.g. tirapazamine. Hypoxic cell cytotoxins are drugs that target and kill hypoxic cells directly, e.g. bioreductive prodrugs, molecular target inhibitors.
- Increasing the radiation dose. The dose may be increased for the whole tumor volume or only to a hypoxic sub-volume. This requires dose painting with IMRT/IGRT. High LET radiation like carbon ions or neutrons may also be used, as they depend less on indirect damage.

(d)
- The cells in the G1 phase have an equal amount of DNA content. In S phase the DNA is replicated, hence some cells have more DNA content than others. By the time of the G2 phase, the DNA content has doubled, hence this peak should move twice to the right at the x-axis. The G2 peak is lower than for the G1 peak as the cells spend a shorter time in G2. Cells in mitosis (M), have the same amount of DNA content as G2, and are registered simultanously.
- A decreasing phase duration of G1 and increasing phase duration of G2+M can be explained by the G1 checkpoint since cells with DNA damage is stopped from continuing through the cell cycle. The increased phase duration of G2+M can indicate inefficient DNA repair that prolongs G2 arrest. After radiation we also expect to see a greater fraction in G2+M due to accumulation of cells that cannot be repaired, i.e. that will lead to cell death (mitotic catastrophe).