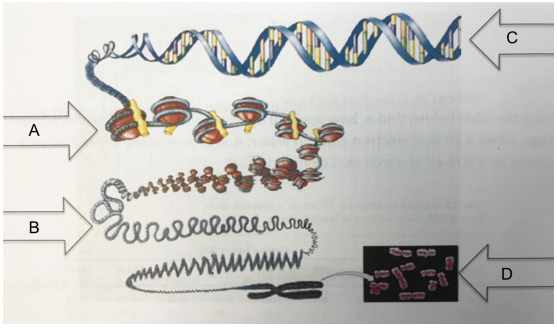
Problem 1 - DNA damage and repair

(a) Write names to the parts shown in this figure (A - D)



(b) Assume that 1 Gy of x-rays are delivered to human cells. Approximately how many single strand breaks (SSBs), double strand breaks (DSBs) and base damages are resulting from the 1 Gy dose?

(c) Name the two main types of DSB repair and describe how each of them works to repair the DSBs. Name the essential molecules involved.

(d) What are the main differences between these two types of DSB repair when it comes to frequency of repair, radiosensitivity, errors, cell cycle sensitivity and variations between cell types?

(e) A cell population is irradiated with γ-rays. Explain why the frequency of chromosomal aberrations can be seen as a linear quadratic function of the radiation dose.

Problem 2 - Models of cell survival

Cell survival models are essential tools in radiation biophysics. Most common are the target theory models and the linear quadratic model.

(a) Explain the multitarget model briefly. Derive the equation that gives the surviving fraction in the multitarget model.

(b) What is the main problem with the target theory?

(c) What is the oxygen fixation hypothesis? Illustrate and briefly describe the impact of oxygen on cell survival for three different radiation qualities: x-rays, neutrons and α particles.

(d) For clonogenic systems the α/β ratio from multi-fraction experiments can be estimated by applying the linear quadratic model. How can the α/β ratio be determined in non-clonogenic systems?

Problem 3 - Fractionated radiotherapy and biologically effective dose

The biologically effective dose (BED) can be used to compare the effect from different fractionated radiotherapy regimens on the tumor as well as on early and late responding normal tissues.

(a) Write down the expression for BED and explain each factor in the formula

(b) You are working in the radiotherapy department and responsible for telling the doctors which fractionated radiotherapy strategy to choose for a patient with head and neck cancer. These are the four treatment options you choose between:

- Conventional radiotherapy with 2 Gy/day for 5 days, totally 5 weeks
- Hyperfractionated radiotherapy with 1.2 Gy twice daily for 5 days, totally 7 weeks
- Concomitant boost where standard fractionated radiotherapy is combined with a focal boost. The standard treatment consists of 30 fractions of 1.9 Gy, once daily, 5 days/week in 6 weeks and the boost consists of 10 fractions of 1.5 Gy, once daily
- CHART strategy with 36 fractions of 1.6 Gy, 5 hours apart, 3 fractions/day for 12 days

Calculate BED for the tumor, early normal tissue and late normal tissue effect for all options. Use common α/β ratios (3 and 10 Gy). Which treatment is optimal with regards to both tumor and normal tissue effects?

(c) The BED is then modified to also include the total treatment time, T:

$$BED(D, n, T) \quad = \quad BED(D, n) - \frac{T - T_k}{\alpha T_p / \ln 2}$$

where n is the number of fractions, T_k is the kickoff time for tumor cell repopulation and T_p is the tumor population doubling time.

Let Δt be the time between fractions. Write the total treatment time as a function of n and Δt. Rewrite the expression BED(D, n, T) as a function of BED$(D, n, \Delta t)$. For BED(D, n) you can insert the same expression as in (a) when you compared the different fractionated regimens.

(d) We may optimize this result further in order to maximize the BED delivered to the tumor. Find the value of n that maximizes the BED. This value can be found without any calculations, but explain your answer.

(e) A main goal with radiotherapy optimization is to deliver as high tumor dose as possible. At the same time we must also put constraints on the maximum dose. Name at least one constraint and explain why the result found in (d) may not be acceptable in practice.

Problem 4 - Radiation protection

(a) Explain the difference between stochastic and deterministic effects on health from ionizing radiation

(b) Explain the ALARA principle

(c) An individual is exposed to radiation. Define by introducing radiation and tissue weighting factors what is meant by:

- Absorbed dose
- Equivalent dose
- Effective dose

Indicate the units used for each type of dose.

(d) What are the radiation weighting factors for

- Photons
- Electrons
- Protons
- α-particles
- Neutrons

Problem 5 - Lab and project work

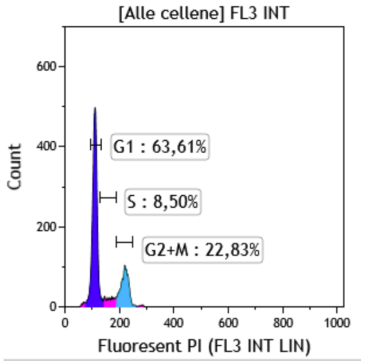
(a) List at least five different types of biologic response modifiers (also called molecularly targeted therapies) that can be combined with radiotherapy to increase the therapeutic ratio and tumor control. Describe in more detail how immunotherapy works in combination with radiotherapy. Address specifically if and how the immunotherapy + radiotherapy combination relates to one or several of the 5 R's of radiobiology.

(b) Define relative biologic effectiveness (RBE). What is RBE for protons? What is the physical explanation behind why RBE is different for protons compared to photons?

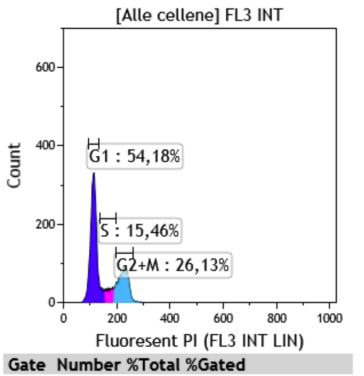
(c) Describe briefly three different approaches that can be used to target tumor hypoxia in radiotherapy

(d) The third lab included cell culture experiments and flow cytometry to learn about radiosensitivity during the cell cycle.

- Look at the DNA histogram to the left below. Explain why the S and G2+M populations are skewed to the right compared to the G1 population and why the G2+M peak is lower than the G1 peak.



Gate	Number	%Total	%Gated
All	14 592	54,98	100,00
G1	9 282	34,97	63,61
G2+M	3 332	12,55	22,83
S	1 240	4,67	8,50



Gate	Number	%Total	%Gated
All	14 797	68,32	100,00
G1	8 017	37,02	54,18
G2+M	3 866	17,85	26,13
S	2 287	10,56	15,46

- Look at the figure to the right where the cells have been analysed after receiving a radiation dose. In the lab you also found that the phase duration of G2+M increased for increasing radiation dose and that the phase duration for G1 decreased for increasing dose. Based on the figure and these findings; explain why these cell cycle changes occur after radiation.