PhD thesis title: Microdosimetry applied to proton radiotherapy
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Abstract:

Proton radiotherapy as a treatment for cancer is increasingly used worldwide. The main current clinical indications for proton therapy are based on the physical properties of proton beams, assuming a constant relative biological effectiveness (RBE) of 1.1 concerning x-ray radiotherapy. However, there is growing evidence of variable RBE depending on the linear energy transfer (LET) of the proton beam, which, in turn depends on the relative position along the proton track. Additionally, RBE depends on the considered endpoint and the biological properties of different cells and tissues as well as on the dose fractionation scheme. Microdosimetry is a theory that studies the patterns of energy deposition in microscopic sized volumes. By determining the local concentration of the energy imparted at such dimensions, it is possible to obtain LET and other quantities characterizing the quality of the beam from this theory. Eventually, the study of the distributions of energy imparted at this scale may lead to a better understanding of the variable RBE for proton beams, allowing for potential clinical application.

This thesis is intended to make the connection between an elementary description of proton-matter interaction in microdosimetric terms and its clinical application. First, the basics of microdosimetric quantities and their dependencies and focuses on how to produce correct microdosimetric results from Monte Carlo (MC) simulations are studied. Monoenergetic distributions for protons of energies up to 100 MeV are produced. These distributions are used to create analytical models to derive microdosimetric quantities in polyenergetic beams instead of performing dedicated MC simulations for each individual case. Results are compared to actual measurements with silicon-based microdosimeters exposed to monoenergetic proton beams. An independent formalism to calculate spectral fluences in clinical proton beams as a function of depth and lateral position in the water is provided. The combination of both formalisms allows to produce calculations of dose distributions in a treatment planning system (TPS). These results are compared to independent MC simulations with the code MCsquare and analytical calculations clinically validated from a commercial TPS, showing consistent results. Microdosimetric calculations of dose-mean lineal energy (yD), and both unrestricted and restricted dose-averaged LET can also be obtained from the combination of these formalisms. Relations between LET and lineal energy in microdosimetry are revisited, and a new equation to calculate restricted LET is proposed and tested against the previously established one. Finally, the Microdosimetric Kinetic Model (MKM) is used to calculate RBE distributions based on the physical quantities previously derived.

References to author publications included in the thesis:

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3. **Bertolet A**, Grilj V, Guardiola C, Harken AD, Cortés-Giraldo MA, Baratto-Roldán A, et al. Experimental validation of an analytical microdosimetric model based on Geant4-DNA simulations by using a silicon-based microdosimeter. Radiation Physics and Chemistry. 2020;176:109060. Available from: https://doi.org/10.1016/j.radphyschem.2020.109060
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5. **Bertolet A**, Cortés-Giraldo MA, Souris K, Cohilis M, Carabe-Fernandez A. Calculation of clinical dose distributions in proton therapy from microdosimetry. Medical Physics 2019 Oct 11;46(12):5816–23. Available from: https://doi.org/10.1002/mp.13861
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3. **Bertolet A**, Cortés-Giraldo MA, Carabe-Fernandez A. An analytical microdosimetric model for radioimmunotherapeutic alpha emitters. Radiation Research. 2020; Available from: https://meridian.allenpress.com/radiation-research/article-abstract/doi/10.1667/RADE-20-00045.1
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5. Carabe A, Karagounis I v., Huynh K, **Bertolet A**, Maity A, Dale RG. Radiobiological effectiveness difference in proton arc beams versus conventional proton and photon beams. Physics in Medicine and Biology. 2020; Available from: https://iopscience.iop.org/article/10.1088/1361-6560/ab9370