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Science vs. technology in radiation therapy from X-rays to ions

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In general, science and technology march in their ways, sometimes starting at different times and developing at different paces. Radiation therapy as an application of ionizing radiation to treat tumors by inactivating cells is a good example of this notion. Brachytherapy, a cancer treatment performed by placing a radioactive source in the direct vicinity of the tumor, was independently suggested by Curie and Bell (Gupta 1995) within 5 years of the discovery of radioactivity by Becquerel in 1896. This happened well before the radioactivity and the propagation of different types of projectiles in tissue were understood. Then, the development of science helped to better select the isotopes and their dosage to improve brachytherapy.

Treatments of tumors with X-rays started at the end of the 1890s, soon after the discovery of X-rays by Roentgen in 1895. One of the pioneering works on radiation damage was done in 1930s (Timofeeff-Ressovsky et al. 1935), but the first theory of biodamage with X-rays was suggested by Lea (1955) who in 1955 had very little idea about DNA, not even speaking about the types of lesions. Nevertheless, by the end of 1990s, the radiation damage due to exposure to X-rays was understood in detail (Hall and Giaccia 2012). Current improvements and modifications to photon therapy, such as FLASH therapy (Montay-Gruel et al. 2018), arise from biological rather than physical or chemical properties.

Hadron therapy is developing through similar stages. Proton therapy was first suggested in 1946 by Wilson and the first cancer treatment took place in 1954. Therapy was developed in different experimental facilities until the first clinical center was built in 1990 in Loma Linda, CA. The understanding of differences between radiation damage with ions and X-rays from the theoretical point of view (besides the advantages of depth dose curves such as the Bragg peak that has been known much earlier (Ma and Lomax 2012) is present in the paper of Butts and Katz (1967), which became a seminal paper of Katz's theory. In that paper, the idea of targeting of bacteria with δ-electrons was considered and the concept of radial dose (the distribution of dose as a function of distance from ion's path) was emphasized.

However, the treatment planning developed in 1990s is based on microdosimetry (Rossi and Zaider 1996) and on models that were derived from the assessments of radiation damage done with X-rays. For instance, the modified microdosimetric-kinetic model (Kase et al. 2006), which is one of the pillars of contemporary treatment planning, is a modification of the microdosimetric-kinetic model (Hawkins 1996) that was derived

from previous models obtaining cell survival curves (dependence of probability of cell survival on dose) for "any" value of the linear energy transfer (LET). This model, being mathematically sound, is based on microdosimetry and takes into account a mathematical model for enzymatic repair.

The local effect model (LEM) (Scholz and Kraft 1996) appeared as a hybrid that has a radial dose as one of the components, but the probability of lethal damage is obtained from the X-ray survival curves. This model has undergone several modifications, the LEM IV (Friedrich et al. 2012) being considerably different from the first three (Bueve 2017). In spite of significant empirically established improvements of LEM IV with respect to LEM I, the latter is still being used in clinical treatment planning.

Since 2009, the multiscale approach (MSA) to the physics of ion-beam therapy has been developed (Solov'yov et al. 2009; Surdutovich and Solov'yov 2014; Solov'yov 2017). This approach set the goal of building a comprehensive scenario of radiation damage with ions including all relevant physical, chemical and biological effects. MSA elaborated the targeting aspects of Katz's theory considering the energy deposition by secondary electrons and formation of reactive species. Then, the physical stage of the scenario was reconsidered. First, the effect of low-energy electrons whose action was discovered by Sanche and his group (2005) was taken into account. In addition to the direct damage done by secondary electrons, ion-induced shock waves were predicted. This prediction is based on the idea that the pressure inside a nm-size region around ion paths can develop faster than the energy could be transferred away from that region. The ion-induced shock waves can substantially affect the initial conditions for the chemical stage of the scenario.

This series contains three reviews and one research paper. The main paper that has nearly the same title as the series, "Multiscale modelling for cancer radiotherapies" (Surdutovich and Solov'yov 2019), is a general review of the MSA. The review by de Vera et al. (2019) is devoted to ion-induced shock waves in the context of ion-beam therapy. The review by Baldacchino et al. (2019) is devoted to the chemical stage of the radiation damage scenario. Finally, the research paper by Verkhovtsev et al. (2019) presents a new analysis of survival curves predicted by the MSA for healthy tissue cells, which is a continuation of previous research (Surdutovich and Solov'yov 2014; Verkhovtsev et al. 2016). It also contains the MSA treatment of the relative biological effectiveness including the overkill effect that appears there naturally, without any special modifications.

What is the right path to the future of optimization and planning of ion-beam therapy? Being biased as the authors of the multiscale approach, we believe that the MSA, based on a solid theoretical ground and inclusive with respect to physical, chemical and biological aspects, can be a part of this future. Certainly, the track structure community (Goodhead et al. 1993; Deingfelder 2006; Friedland et al. 2017; Nikjoo et al. 1998, 2006; Liamsuwan and Nikjoo 2013; Frese et al. 2012; Stewart 2015; McNamara et al. 2017) simulating the scenario of radiation damage and going through physical, chemical, and biological stages also aim at constructing a scientific approach to treatment planning. Do their Monte Carlo simulations include "everything" they have to include to cover the relevant science? Time will give the answer to the above question, but now we hope that more people ask what science is included in the current clinical protocols and how to improve them.

Authors' contributions
ES and AVS discussed the editorial, ES drafted the manuscript. Both authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

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