Applied Radiation and Isotopes 83 (2014) 100–104

Contents lists available at ScienceDirect

Applied Radiation and Isotopes

journal homepage: www.elsevier.com/locate/apradiso

# Multiscale physics of ion-induced radiation damage

Eugene Surdutovich [a], A.V. Solov'yov [b,*]

[a] Physics Department, Oakland University, Rochester, MI 48309, USA
[b] Frankfurt Institute for Advanced Studies, Frankfurt am Main, Germany

## HIGHLIGHTS

- ► The interdisciplinary science of IBCT relates biodamage with physical parameters.
- ► The multiscale approach is designed for understanding the mechanisms of biodamage.
- ► Distributions of damage complexity and dose lead to alternative survival curves.
- ► Thermomechanical mechanism of radiation damage with ions has to be accounted for.
- ► Studying of germane effects is the key to the quantitative assessment of biodamage.

## ARTICLE INFO

Available online 7 February 2013

*Keywords:*
Radiation damage
Ion-beam therapy
DNA damage
Multiscale approach
Complex DNA damage
Thermomechanical DNA damage

## ABSTRACT

This is a review of a multiscale approach to the physics of ion-beam cancer therapy, an approach suggested in order to understand the interplay of a large number of phenomena involved in the radiation damage scenario occurring on a range of temporal, spatial, and energy scales. We describe different effects that take place on different scales and play major roles in the scenario of interaction of ions with tissue. The understanding of these effects allows an assessment of relative biological effectiveness that relates the physical quantities, such as dose, to the biological values, such as the probability of cell survival.

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## 1. Introduction

The scientific interest in obtaining a deeper understanding of radiation damage is motivated by the development of ion-beam cancer therapy and other applications of ions interacting with biological targets. A number of important scientific questions, especially related to DNA damage assessment on the molecular level, have not yet been resolved. Therefore, recently this field has attracted much attention from the scientific community (Surdutovich, 2012; Schardt et al., 2010; Kumar and Sevilla, 2010; Solov'yov et al., 2009). There are a series of conferences devoted to these subjects, such as RADAM (Baccarelli et al., 2010) and later Nano-IBCT (http://nano-ibct.sciencesconf.org/). The latter became possible due to the support of the European framework for Cooperation in Science and Technology (COST). The COST Action, "Nano-scale insights in ion beam cancer therapy (Nano-IBCT)" (http://fias.uni-frankfurt.de/nano-ibct/) was approved in 2010. Among these studies is the multiscale approach to the assessment of radiation damage induced by irradiation with ions. It is aimed at a phenomenon-based quantitative understanding of the scenario from the incidence of an energetic ion on tissue to the cell death. This method combines many spatial, temporal, and energy scales, and is therefore a truly multiscale approach. The variety of these scales and corresponding disciplines is presented in Fig. 1.

The understanding and assessment of radiation damage due to ionizing radiation are at the focus of radiation biophysics, which has a wide scope of important applications from radiation protection to radiation therapy. The standard scope of radiation biophysics spans from the interaction of ionizing projectiles with matter, radiation chemistry that includes interactions of radiation and secondary particles with water and biomolecules, to the analysis of models of cell survival (Alpen, 1998; Lehnert, 2008; Hall and Giaccia, 2012).

One way to address the problem of biological damage starts from the analysis of so-called survival curves. The survival curve is a relation between the logarithm of cell-survival fraction and the deposited dose. These curves can be obtained experimentally and they differ for different species, cells, radiation modality, etc. Nevertheless, the main feature of these curves is that they are approximately parabolic, i.e.,

$$-\ln S/S_0 = \alpha D + \beta D^2, \quad (1)$$

where $S/S_0$ is the normalized cell survival, $D$ is the dose, and $\alpha$ and $\beta$ are coefficients. If the dose distribution is uniform, as when

* Corresponding author. Tel.: +49 6979847507.
*E-mail address:* solovyov@fias.uni-frankfurt.de (A.V. Solov'yov).

0969-8043/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.apradiso.2013.01.035

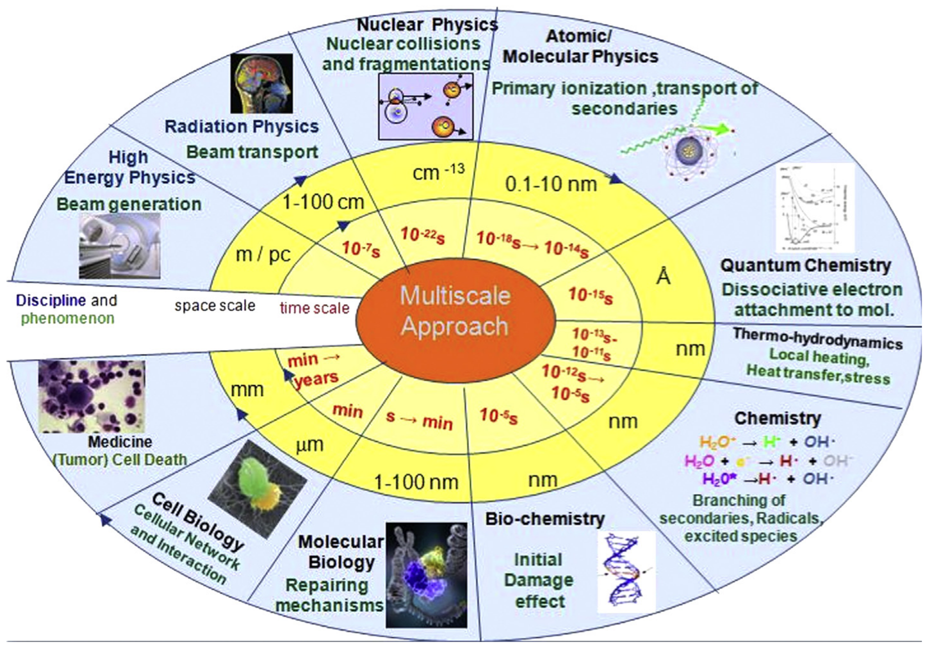


**Fig. 1.** The variety of temporal and spatial scales corresponding to different aspects and disciplines involved in the science of IBCT.

tissue is irradiated with x-rays, it is possible to find the parameters $\alpha$ and $\beta$ empirically and use them in treatment planning to determine necessary dose and optimize its delivery.

Particle projectiles change this picture. The dose distribution around each particle's path is highly nonuniform because of the number of secondary electrons released by the ionized molecules of the medium on every nm of the path. These electrons as well as holes and radicals comprise a complicated track structure with a radial distribution of the dose, while the space between different tracks is largely undisturbed. A solution to this problem was suggested by the Katz approach in which the radial dose distribution is calculated and related to the inactivation of sub-cell-nucleus targets (Butts and Katz, 1967; Katz et al., 1971; Cucinotta et al., 1999). The quality factor of radiation was introduced in order to relate the survival curve parameters to a given radiation, differentiating between track types, inactivation modes, the structural complexity of targets, etc. The eventual goal of the Katz model was to calculate the relative biological effectiveness (RBE) (Schardt et al., 2010; Alpen, 1998; Hall and Giaccia, 2012), one of the key integral characteristics of the effect of ions compared to that of photons. This ratio compares the doses of different projectiles leading to the same biological effect. Nevertheless, the biological relation of the radial dose distribution with the cell survival probability was done based on the survival curves for x-rays, without analyzing particular physical processes, i.e., the empiric coefficients $\alpha$ and $\beta$ remain central to this approach. A desire to understand on a quantitative level what is behind these parameters brought about a multiscale approach to the radiation damage with ions.

The multiscale approach was formulated in Solov'yov et al. (2009) and Surdutovich and Solov'yov (2009), where a scenario leading to DNA damage was suggested. Then, it was further elaborated as different aspects of the scenario were added in a series of works (Surdutovich et al., 2009, 2011; Scifoni et al., 2010a; Toulemonde et al., 2009; Surdutovich and Solov'yov, 2010; Yakubovich et al., 2012). Its name emphasizes the fact that important interactions involved in the scenario happen on a variety of temporal, spatial, and energy scales. Right from the beginning, the approach was formulated as phenomenon-based and was aimed at elucidating the physical, chemical, or biological effects that are important or dominating on each scale in time, space, and energy.

The multiscale approach raised questions about the nature of the effects that take place and lead to survival curves and the calculation of RBE and other macroscopic quantities, i.e. by the end of the day it should answer the question of what is behind the coefficients in Eq. (1). The main issues addressed by the multiscale approach are ion stopping in the medium, the production and transport of secondary electrons produced as a result of ionization and excitation of the medium, the interaction of secondary particles with biological molecules, the most important being DNA, the analysis of induced damage, and the evaluation of the probabilities of subsequent cell survival or death. These effects are happening on time scales ranging from $10^{-21}$ to $10^{-5}$ s, i.e., from nuclear to biochemical times. The aim of the physical part of the analysis is the calculation of the spatial distribution of primary DNA damage, including the degree of complexity of this damage.

## 2. Ion stopping and the Bragg peak

The multiscale approach started with the analysis of ion propagation in a medium. Liquid water was used as the medium because human tissues on the average consist of 75% water. These works (Surdutovich et al., 2009; Scifoni et al., 2010a) resulted in the description of the Bragg peak and the energy spectrum of secondary electrons. The Bragg peak in the stopping power of massive charged particles is obtained using a version of the Bethe–Bloch formula (Bethe, 1930; Bloch, 1933a, 1933b). This formula provides the dependence of the stopping power on the energy of the ion and practically depends on the mean excitation energy. This energy for liquid water is chosen somewhere between 70 and 80 eV (Abril et al., 2011; Pshenichnov et al., 2008). Our approach to this problem was different. We chose to use the singly differentiated (with respect to the secondary electron energy) ionization cross sections of water molecules in the medium as a physical input. These cross sections were taken from experiments (Rudd et al., 1992) with parameters tuned for liquid water (Scifoni et al., 2010a). The parameterizations were

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