Preface

This book provides a unique and comprehensive overview of state-of-the-art understanding of the molecular and nanoscale processes that play important roles in ion-beam cancer therapy. It covers experimental design and methodology, and reviews the theoretical understanding of the processes involved. It offers the reader an opportunity to learn from a coherent approach about the physics, chemistry and biology relevant to ion-beam cancer therapy, a growing field of important medical application worldwide. The book describes phenomena occurring on different time, spatial and energy scales relevant to the radiation damage of biological targets and ion-beam cancer therapy from the molecular (nano) scale up to the macroscopic level. It illustrates how ion-beam therapy offers the possibility of excellent dose localization for treatment of malignant tumours, minimizing radiation damage in normal tissue whilst maximizing cell-killing within the tumour, offering a significant development in cancer therapy. The full potential of such therapy can only be realized through the understanding of the physical, chemical and biological mechanisms, on a range of time and space scales that lead to cell death under ion irradiation. This book describes how the recently developed multiscale approach, unifying all the experimental and theoretical expertise available in the field, leads to greater insight at the nanoscopic and molecular level into radiation damage of biological targets induced by ion impact. The book is intended for the master and Ph.D. students and specialists in the areas of physics, chemistry, biology and medicine related to ion-beam therapy, radiation protection, biophysics, radiation nanophysics and chemistry, atomic and molecular physics, condensed matter physics, and the physics of interaction of charged particles with matter. The most important features and benefits of the book are in the systematic description of the inclusive multiscale approach for the description of complex and highly interdisciplinary processes behind the ion-beam cancer therapy and its key components. This theoretical approach, being stretched from the atomistic level up to the biological scale, is demonstrated to be in the excellent agreement with experimental observations.

Ion-beam cancer therapy (IBCT, or hadron therapy) represents an effective method for providing high-dose delivery into tumours, thereby maximizing the probability of killing the cancer cells whilst simultaneously minimizing the

radiation damage to surrounding healthy tissue [1–3]. Despite its high cost, proton-beam therapy is widely spread around the world with over 65 operational centres[1]. In ten European and Asian centres, patients are irradiated with carbon ions. Nonetheless, the full potential of these therapies can only be realized by achieving a better understanding of physical, chemical and biological mechanisms, over a range of time and space scales, that lead to cell inactivation under ion radiation.

The damaging effect of ionizing radiation has been known for many years. It has been commonly accepted that high-energy tracks formed by α, β, and γ radiation and atomic ions ionize cell components along the track, thereby leading to various dissociation channels and to the formation of damaging radicals. This has led to intensive research on the study of the mechanisms for the formation of such radicals and the fragmentation pattern of biomolecules by photons, electrons and ions. Such fundamental data underpins the study of radiation protection and the development of biomedical uses of different radiation, generally called radiotherapy, for treatment, of tumoural diseases in particular. The next generation of radiotherapy may be based on hadron therapy [4] and in particular ion-beam therapy. To date the development of ion-beam therapy has been based on empirical rather than phenomenological or *ab initio* scientific methods [5]. The emergence of the "RADAM" [5] and then "NanoIBCT" [6] communities has played an important role in attracting physicists, chemists and biologists into the field to tackle a plethora of scientific questions raised by the technological advances in this field.

The majority of biological effects of ion beams are associated with the process of ionization of the medium by traversing ions. It is commonly accepted that secondary electrons, ejected by ionization, are mainly responsible for DNA damage, either breaking the DNA strands directly, or reacting with molecules of tissue, producing free radicals and other reactive species. Macroscopically, the advantages of using ion beams compared to photons are related to the presence of a Bragg peak in the depth–dose distribution, where the production of secondary electrons is maximized. This localizes irradiation effects deep in tissue thus increasing the treatment efficiency and reducing side effects by sparing neighbouring healthy tissue. However, the mechanisms involved in radiation damage at the nanoscale and molecular level are still a subject of fundamental multidisciplinary research.

In 2010–2014, the European Concerted Research Action, COST Action MP1002: "Nano-scale insights in ion beam cancer therapy (Nano-IBCT)" was devoted to acquiring a deeper understanding of radiation-induced damage with ions on the nanoscopic and molecular level [6]. This endeavour clustered around the multiscale approach to the physics of radiation damage with ions [1, 7], designed to achieve a quantitative understanding of the physical, chemical and biological effects that take place on a wide range of spatial, temporal and energy scales. The COST Action combined European experimental and theoretical expertise in several topics including nuclear reactions and electromagnetic processes during the propagation of

[1]As of May 2016 [4].

ion beams in tissue, primary ionization in the medium (water and biological molecules), direct damage and production of secondary species (secondary electrons, radicals, holes), propagation of secondary species and their interaction with DNA, and radiobiological scale effects.

Action was formally launched in December 2010 and since then has brought together more than 300 experts from different disciplines (physics, chemistry, biology, etc.) drawn from more than fifty different institutions including hadron therapy centres and medical institutions. The Action also engaged with colleagues working in countries outside the EU, including Canada, Australia, Japan, India, China and the USA. Two-thirds of those participating were early-career researches and a quarter were postgraduate students half of which were young female researchers. The Action also supported more than 100 short-term scientific missions between different institutions and countries, which resulted in more than 200 publications in high-impact journals. Within the framework of the COST Action Nano-IBCT three major conferences (held in Caen, France October 2011, Sopot, Poland May 2013 and Boppard, Germany 2013, see conference photos in Figs. 1–3) and 12 workshops were organized. These conferences provided the opportunity to review the progress in the field of radiation damage to biomolecular systems and how such knowledge can be applied to the development of new cancer therapies. For further details, see the Action's website [6], the special issue of the Journal of Physics: Conference Series [8], and the topical issues of the European Physical Journal D: Atomic, Molecular, Optical and Plasma Physics [9, 10].

The main objective of the Action was to address the basic scientific questions which underpin the nanoscopic and molecular mechanisms associated with ion-beam cancer therapy. In particular, the following goals were pursued:

- Understanding the unique features of ion irradiation on the molecular level, e.g. site and bond selectivity, clustered damage, local temperature and chemical effects. Some of the open questions are related to the ratio of direct/indirect damage, the mechanisms leading to double strand break (single- or multiple electron-induced fragmentation) and the elucidation of possible lethal effects that are not present during photon irradiation.
- To establish comprehensive databases of recommended values for all the major processes involved in IBCT: ion and electron interaction cross sections, energy loss in biologically relevant systems, etc. This objective implies an important experimental and theoretical effort to determine differential and integral cross sections, both elastic and inelastic, for low incident energies.
- To yield a quantitative prediction of dose distribution and molecular damage generated by the passage of ions through cells, for example determining the rate and type of DNA single and double strand breaks, as well as complex damage sites.
- To develop a multiscale approach for the quantitative analysis of radiobiological effects and therapy planning, tested at different levels with experiments; also including reliable estimates of the relative biological effectiveness (RBE) for different ions.

Fig. 1 Conference photo, 1st Nano-IBCT Conference, 2–6 October, 2011, Caen, France

Fig. 2 Conference photo, 2nd Nano-IBCT Conference, 20–24 May, 2013, Sopot, Poland

Fig. 3 Conference photo, 3rd Nano-IBCT Conference, 27–31 October, 2014, Boppard, Germany

- To develop a new low-energy particle track simulation method based on the distribution functions derived from evaluated experimental and theoretical cross sectional data and energy loss providing information on energy distribution and induced damage at the molecular level.

The COST Action was organized through five Working Groups (WGs) each dedicated to a specific topic. WG1: Ion propagation, WG2: Primary ionization in the medium, direct damage and production of secondary species, WG3: Propagation of secondary species, WG4: Electron attack on DNA, WG5: Radiobiological scale effects. These working groups form the pillars upon which the research plan for a multiscale approach to the physics of ion-beam cancer therapy was based [1].

This book summarizes the main research achievements of the COST Action Nano-IBCT. It provides a comprehensive overview of state-of-the-art understanding of the molecular and nanoscale processes that play significant role in ion-beam cancer therapy. It covers experimental design and methodology, and reviews the theoretical understanding of the processes involved. It is based on the reviews written by the teams of experts devoted to the essential aspects of the multiscale scenario of the complex cascade of physical, chemical and biological processes involved into the ion-beam cancer therapy [1]. The topics of the reviews and their interrelationship arise naturally from the action aims, its research and organizational structure, as well as from the follow-up research developments.

Chapter "Multiscale Physics of Ion-Beam Cancer Therapy" by E. Surdutovich and A.V. Solov'yov is the most comprehensive review of the multiscale approach to the physics of radiation damage with ions. The approach allows one to predict survival probabilities for cells irradiated with ions based on the series of phenomena that take place on a variety of scales in time, space, and energy. The scenario of biodamage starting from ion entering tissue is the basis for an analytic synthesis of microscopic effects that comprise the macroscopic coefficients of the linear-quadratic model describing survival probabilities. The latter are calculated for both aerobic and hypoxic conditions at a variety of linear energy transfers. The oxygen enhancement ratio is obtained as a byproduct of these calculations. The calculated survival curves are compared with experiments on different cell lines and ready for medical applications.

Chapter "Propagation of Swift Protons in Liquid Water and Generation of Secondary Electrons in Biomaterials" by P. de Vera, R. Garcia-Molina, and I. Abril introduces a proper description of the propagation of a swift proton beam through biomaterials, accounting for the energy deposited as well as the geometrical evolution of the beam as a function of the target depth and nature, that is a crucial issue in proton therapy. For this purpose, simulation is a very adequate tool, since the most relevant interactions that take place between the projectile and the target constituents (electrons and nuclei) can be conveniently accounted for in a controlled manner. For this purpose, in this chapter an overview and relevant results for hadron therapy are presented which were obtained using the code SEICS (Simulation of Energetic Ions and Clusters through Solids). This approach

combines Monte Carlo and molecular dynamics, to follow in detail the motion and energy deposition of swift protons through targets of hadron therapeutic interest, mainly liquid water. The main interactions considered in our study are of elastic nature (affecting mainly the projectiles direction) and inelastic processes (leading to either nuclear reactions or electronic energy loss). The performance of the code, as well as the quality of its main input, namely the stopping force for proton beams in liquid water (which is the main tissue constituent), are benchmarked by comparing the results of the simulations with available experimental proton energy spectra as a function of the detection angle after traversing a micrometric water jet. The excellent agreement with experiments validates the SEICS code, which can be used then to study several problems of interest for proton therapy, including the calculation of depth−dose curves and lateral dose profiles, the energy evolution of the proton beam along the target, as well as the production of secondary electrons at the Bragg peak in relevant biomaterials.

Chapter "Monte Carlo-Based Modeling of Secondary Particle Tracks Generated by Intermediate- and Low-energy Protons in Water" by A. Verkhovtsev, P. Arce, A. Munoz, F. Blanco, and G. Garcia gives an overview of recent developments in the Monte Carlo-based modelling of the interaction of ionizing radiation with biologically relevant systems. Several track structure codes, such as Geant (GEometry ANd Tracking), Geant4-DNA and LEPTS (Low-Energy Particle Track Simulation), are described. Main features, areas of application and current limitations of each tool are discussed. A special attention is focused on the energy range covered by primary and secondary charged particles and on the type of interactions included in the simulation. A recent development of LEPTS is presented, aimed at the simulation of full slowing down of protons in water together with all molecular processes involving particles. The utilized approach allows one to study radiation effects on the nanoscale in terms of the number and the type of induced molecular processes. Development of new tools for the simulation of biologically relevant materials opens the way for a more realistic, physically meaningful description of radiation damage in living tissue.

Chapter "Ion Collisions with Biomolecules and Biomolecular Clusters" by P. Rousseau and B.A. Huber describes the recent progress which has been made in experimental studies of ion collisions with biomolecular systems, either in form of isolated biomolecules in the gas phase or as clusters containing up to several tens of biomolecules. Most of the work has been performed with projectiles which play an important role in ion beam cancer therapy applications as protons or multiply charged ions of carbon and oxygen. The biomolecular targets are characterized by an increasing complexity and include water molecules, nucleobases, nucleosides and nucleotides, as well as amino acids and protein segments. Other complex targets are heterogeneous clusters containing biomolecular systems which are embedded in a water environment. After an introduction to ion–molecule collisions using C60 fullerene as a model system, ionization and charge transfer processes as well as ion-induced fragmentation studies are reviewed. Finally the effect of the environment considering clusters of biomolecules including hydrated systems is discussed.

Chapter "Dissociative Electron Attachment to Biomolecules" by I. Bald, R. Curik, J. Kopyra, and M. Tarana discusses the biomolecular damage caused by reactions induced by low-energy electrons (<20 eV). In this energy regime electrons can efficiently decompose molecules such as DNA or DNA building blocks by Dissociative Electron Attachment (DEA). Experiments on single DNA building blocks have been performed in the gas phase revealing that DEA can proceed with remarkable site selectivity. Low-energy electron-induced DNA strand breakage is typically investigated using plasmid DNA in the condensed phase. Very recently, a pronounced dependence of electron-induced DNA strand breakage on the nucleotide sequence was found using different experimental approaches suggesting that at least part of the observed strand breaks are due to initial electron attachment to the nucleobases. Currently, a strong research focus is on the fundamental understanding of DEA to therapeutically administered radiosensitizers. In the near future DEA to novel potential radiosensitizers will be explored, and the electron-induced damage of biomolecules within complex environments has to be investigated. Considerable attention has been paid to the theoretical research of the DEA in the context of the DNA damage. With respect to this, the theoretical part of the chapter reviews all the computational approaches that have been used to study DEA to biomolecules over the last decade. These approaches are divided into two classes. The first class consists of electronic structure methods studying the transient negative ions formed by electrons captured by the neutral building blocks of the DNA. Approaches dealing with the complicated nuclear dynamics of the DEA to biomolecules form the second class explored in this chapter.

Chapter "Photoprocesses with Biomolecules in the Gas Phase" by P. Bolognesi and L. Avaldi reviews the basic processes in molecules of biological interest induced by the absorption of VUV and soft X-rays. The study of excitation, ionization and dissociation in the gas phase on the one hand provides detailed information on the electronic structure and geometry that determine the functioning of these molecules in macroscopic systems and, on the other hand, sheds light on the microscopic effects of radiation damage in living cells.

Chapter "Irradiation-Induced Processes with Atomic Clusters and Nanoparticles" by A. Verkhovtsev, A.V. Korol, and A.V. Solov'yov gives an overview of theoretical and computational studies of physical phenomena manifesting themselves in photon, electron and ion collisions with atomic clusters and nanoparticles (NPs). The emphasis is made on ion and electron scattering as well as photoabsorption of metal NPs which are of current interest in application in cancer treatments with ionizing radiation. Although the number of reports on dose enhancement and radio sensitization due to metal NPs has been rapidly increasing during the past years, physical mechanisms of enhanced production of secondary electrons and reactive species due to sensitizing NPs are still a debated issue and require thorough investigation. In this chapter the essential role of collective electron excitations in the formation of electron emission spectra of metal clusters and NPs is elucidated. These effects appear also in other types of nanoscale systems, such as carbon-based NPs. A number of recent Monte Carlo-based studies devoted to the investigation of

radiosensitization and dose enhancement effects for proton irradiation combined with metal NPs are also briefly discussed.

Chapter "On the Quantum Description of Irradiation Dynamics in Systems of Biological Relevance" by P.M. Dinh, L. Bouessel du Bourg, C.-Z. Gao, Bin Gu, L. Lacombe, M. McAllister, M. Smyth, G. Tribello, M. Vincendon, J. Kohanoff, P.-G. Reinhard, L. Sanche, and E. Suraud discusses the two main products of ionizing radiation in biological tissues, namely electrons and radicals. Numerous secondary electrons are generated by ionization in the molecules in the vicinity of DNA and are produced with a mean energy about 10 eV. These low-energy electrons can lead to DNA strand breaks via dissociative electron attachment and other mechanisms. The modelling of these phenomena requires, on the one hand, an explicit quantum description of the electrons of the target molecule (typically, a subunit of a DNA strand), and on the other hand, a realistic account of the DNA environment. This chapter reviews theoretical and computational approaches that have allowed studies of electron dynamics (excitation, ionization, transport and localization) in systems of biological interest.

Chapter "Multiscale Modelling of Molecular Processes for Biomedical and Nanotechnology Applications with MBN Explorer" by A.V. Solov'yov introduces MesoBioNano Explorer (MBN Explorer), a software package for the advanced multiscale simulations of complex molecular structure and dynamics and highlights some of its biomedical and nanotechnology applications. MBN Explorer has many unique features, a wide range of applications in Physics, Chemistry, Biology, Material Science, and in related Industries. It is suitable for classical molecular dynamics, Monte Carlo and relativistic dynamics simulations of a large range of molecular systems of different kind, such as nano- and biological systems, nanostructured materials, composite/hybrid materials, gases, liquids, solids and various interfaces, with the sizes ranging from atomic to mesoscopic. MBN Explorer can be exploited together with MBN Studio, a specially developed graphical user interface, visualizer, and analytic toolkit.

Chapter "Thermo-Mechanical Damage of Biomolecules Under Ion-Beam Radiation" by P. de Vera, N.J. Mason, E. Surdutovich, and A.V. Solov'yov reviews the recent studies of new pathways of the ion-induced radiation damage. The prediction of the relative biological effectiveness of ion beams requires the quantification of all the biomolecular damage processes involved in the interaction of energetic ions with biological media. Traditionally, the damage pathways have been classified as direct or indirect, the former being related to the direct action of the secondary electrons produced along the ion path with DNA molecules, while the latter are referred to the damage produced by the other chemical species generated, mainly free radicals. However, the development over the last years of the multiscale approach to ion-beam cancer therapy has revealed the contribution of a new damage mechanism, not present in conventional therapy with photons or electrons: the thermo-mechanical DNA damage arising from the development of shock waves on the nanometer scale around the swift ion path. The present chapter explains the theoretical framework in which this effect is predicted and reviews the

work performed over the last years to try to understand the role of this damage pathway in the mechanisms of ion-beam cancer therapy.

Chapter "Predictive Assessment of Biological Damage Due to Ion Beams" by A. Verkhovtsev, E. Surdutovich, and A.V. Solov'yov presents recent achievements in validation of the Multiscale Approach (MSA) to the physics of radiation damage with ions. An analytical recipe for the assessment of biological damage, developed using the phenomenon-based MSA, has been applied to numerous experiments, where survival curves were obtained for different cells and irradiation conditions. Contrary to other, in essence empirical methods for evaluation of macroscopic effects of ionizing radiation, the MSA predicts the biodamage based on the physical effects related to ionization of the medium, transport of secondary particles, chemical interactions, thermo-mechanical pathways of biodamage, and heuristic biological criteria for cell survival. An extensive comparison with experimental data for cell survival probability demonstrates the validity of the MSA to predict the macroscopic effects of ionizing radiation through an understanding of biological damage at the nanoscale. The analysis performed allows us to conclude that the biodamage can be accurately predicted in both aerobic and hypoxic conditions. Therefore, we anticipate this method to give great impetus to the practical improvement of ion-beam cancer therapy and the development of more efficient treatment protocols.

Chapter "New Research in Ionizing Radiation and Nanoparticles: The ARGENT Project" by M. Bolsa Ferruz, V. Ivošev, K. Haume, L. Ellis-Gibbings, A. Traore, V. Thakare, S. Rosa, P. de Vera, V.-L. Tran, A. Mika, D. Boscolo, S. Grellet, A. Verkhovtsev, B.A. Huber, K.T. Butterworth, K.M. Prise, F.J. Currell, N.J. Mason, J. Golding, E. Scifoni, G. Garcia, F. Boschetti, F. Lux, O. Tillement, C. Louis, K. Stokbro, A.V. Solov'yov, and S. Lacombe gives an overview of ARGENT (Advanced Radiotherapy, Generated by Exploiting Nanoprocesses and Technologies), an ongoing international Initial Training Network project, supported by the European Commission. The project, bringing together world-leading researchers in physics, medical physics, chemistry, and biology, aims to train 13 early-stage researchers whose research activities are linked to understanding and exploiting the nanoscale processes that drive physical, chemical and biological effects induced by ionizing radiation in the presence of radiosensitizing nanoparticles. This research is at the forefront of current practices and involves many experts from the respective scientific disciplines. In this chapter, the research topics covered by the ARGENT project are briefly reviewed.

Chapter "Biophysics Modeling to Optimize Ion Beam Cancer Therapy" by M. Beuve discusses the ion-beam cancer therapy (IBCT) and its optimization. The optimization of treatments by IBCT relies on modelling to simulate the transport of the incident ions (and the secondary particles) into patients, and, to predict the biological effects induced by all these particles. Considering the complexity of biological systems, multiscale approaches seem necessary to build the bridge between the primary physical and chemicals events and the consequences for patients both in healthy tissues and tumours. After a brief history of IBCT in France, this chapter presents models used to estimate the probability of tumour

control by IBCT, showing the importance of predicting the survival of biological cells to complex irradiation. Then, follows a presentation and analysis of models predicting cell survival to irradiation with ions, including: the procedure developed in Japan for cancer treatments with passive beams; the microdosimetry models TDRA and MKM, and, the MMKM, a modified version of MKM used for active beam in Japan; the Katz models and the LEM, which is presently used by the European centres of therapy with carbon ions. Then, as perspectives, modelling based on nanodosimetry are addressed with a focus on the NanOx^{TM} model.

Chapter "Treatment Planning Systems and Hadron Therapy Practice in France" by L. De Marzi, A. Patriarca, A. Mazal, J.-L. Habrand describes briefly the history of particle therapy development in France and discusses the technical and clinical aspects of proton-beam treatment planning, as many similarities exist between proton and ion therapy. This chapter includes a summary of the physics and approximations used in proton dose algorithms, including the impact of accelerator and nozzle modelling, a description of conventional delivery approaches such as passive scattering or pencil beam scanning, immobilization specificities and the need for accurate imaging of patient geometry. The issues of neutron generation, risk of second cancers, and radiobiological effectiveness (RBE) of protons will also be discussed. As several of these aspects are common to proton and ion therapy, one section of this chapter will be devoted to the differences between these techniques, especially the biological effects of radiation. Finally, recent developments and perspectives in the planning process will be presented.

Concluding, the COST Action Nano-IBCT played a very important role in the foundation of a strong European Nano-IBCT community, which inherited and broadened the traditions of the initial RADAM network. Ideas that emerged during the Nano-IBCT COST Action led to many research collaborations including the establishment of the current ARGENT programme exploring nanoparticles as radiosenistizers (www.itn-argent.eu).

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References

1. E. Surdutovich, A. Solov'yov, Eur. Phys. J. D **68**, 353 (2014)
2. D. Schardt, T. Elsässer, D. Schulz-Ertner, Rev. Mod. Phys. **82**, 383 (2010)
3. M. Durante, J. Loeffler, Nat. Rev. Clin. Oncol. **7**, 37 (2010)

4. Particle therapy co-operative group. http://www.ptcog.ch/index.php/facilities-in-operation. Accessed May 2016
5. I. Baccarelli, F. Gianturco, E. Scifoni, A. Solov'yov, E. Surdutovich, Eur. Phys. J. D **60**, 1 (2010)
6. Cost action nano-ibct. http://mbnresearch.com/project-nanoibct
7. A. Solov'yov, E. Surdutovich, E. Scifoni, I. Mishustin, W. Greiner, Phys. Rev. **E79**, 011909 (2009)
8. B.A. Huber, Ch. Malot, A. Domaracka, A.V. Solov'yov, 1st Nano-IBCT Conference 2011 Radiation damage of biomolecular systems: nanoscale insights into-ion beam cancer therapy. J. Phys.: Conf. Ser. **373**, 011001 (2012)
9. M.A. Smialek, P. Limao-Vieira, N.J. Mason, A.V. Solov'yov, Radiation Damage of Biomolecular Systems: Nanoscale insights into Ion Beam Cancer Therapy. 2nd Nano-IBCT Conference. Editorial for Topical issue Nanoscale insights into Ion-Beam Cancer Therapy. Eur. Phys. J. **D68**, 312 (2014)
10. E. Surdutovich, G. Garcia, N.J. Mason, A.V. Solov'yov, Nano-scale processes behind Ion-Beam Cancer Therapy. Editorial for Topical issue Nano-scale processes behind Ion-Beam Cancer Therapy. Eur. Phys. J. **D70**, 86 (2016)

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