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TOPICAL REVIEW

Monte Carlo role in radiobiological modelling of radiotherapy outcomes

Issam El Naqa, Piotr Pater and Jan Seuntjens

Department of Oncology, Medical Physics Unit, Montreal, QC, Canada

E-mail: issam.elnaqa@mcgill.ca

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Abstract

Radiobiological models are essential components of modern radiotherapy. They are increasingly applied to optimize and evaluate the quality of different treatment planning modalities. They are frequently used in designing new radiotherapy clinical trials by estimating the expected therapeutic ratio of new protocols. In radiobiology, the therapeutic ratio is estimated from the expected gain in tumour control probability (TCP) to the risk of normal tissue complication probability (NTCP). However, estimates of TCP/NTCP are currently based on the deterministic and simplistic linear-quadratic formalism with limited prediction power when applied prospectively. Given the complex and stochastic nature of the physical, chemical and biological interactions associated with spatial and temporal radiation induced effects in living tissues, it is conjectured that methods based on Monte Carlo (MC) analysis may provide better estimates of TCP/NTCP for radiotherapy treatment planning and trial design. Indeed, over the past few decades, methods based on MC have demonstrated superior performance for accurate simulation of radiation transport, tumour growth and particle track structures; however, successful application of modelling radiobiological response and outcomes in radiotherapy is still hampered with several challenges. In this review, we provide an overview of some of the main techniques used in radiobiological modelling for radiotherapy, with focus on the MC role as a promising computational vehicle. We highlight the current challenges, issues and future potentials of the MC approach towards a comprehensive systems-based framework in radiobiological modelling for radiotherapy.

(Some figures may appear in colour only in the online journal)

1. Introduction

Recent years have witnessed burgeoning interest in using radiobiological models to rank radiation therapy patient treatment plans in order to identify the 'optimal' plan or at least

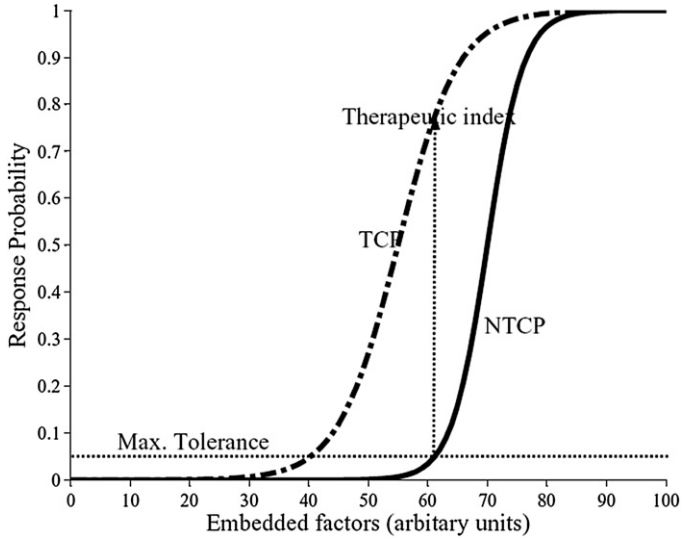

Figure 1. Sigmoidally shaped response curves (for TCP and NTCP) are constructed as a function of a linear weighting of various factors, for a given dose distribution, which may include multiple dose–volume metrics as well as clinical factors. The units of the *x*-axis may be thought of as 'equivalent dose' units. Reproduced with permission from El Naqa *et al* 2006a *Int. J. Radiat. Oncol. Biol. Phys.* **64** 1275–86. Copyright 2006 Elsevier Inc.

personalize the patient's plan (Brahme 1999, Deasy *et al* 2002, Li 2011). This interest has been driven by technological advances in 3D treatment planning and intensity modulated radiotherapy (IMRT) that have allowed the delivery of very complex shaped dose distributions almost unimaginable a decade ago. Nevertheless, these technological advances did not translate into similar significant improvements in cancer patient survival rates (Begg *et al* 2011, Fraass and Moran 2012). By part, this has been hampered by a lack of current radiobiological model's ability to predict accurately, at the time of treatment planning, the individual outcomes associated with such complex dose distributions and delivery time sequences. It is believed that accurate prediction of treatment outcomes would provide clinicians with better tools for informed decision-making about designing more effective treatment plans that are tailored to maximize benefit and reduce side effects for individual patients (Halperin *et al* 2008).

Radiotherapy outcomes are usually characterized by two metrics: the tumour control probability (TCP) and the normal tissues complication probability (NTCP) of surrounding normal tissues (Steel 2002, Webb 2001). TCP/NTCP models could be used during the consultation period as a guide for ranking treatment options (Armstrong *et al* 2005, Weinstein *et al* 2001). Alternatively, these models could be included in an objective function, and the optimization problem driving the actual patient's treatment plan can be formulated in terms relevant to maximizing tumour eradication benefit and minimizing complication risk (Moiseenko *et al* 2004, Brahme 1999) as shown in figure 1.

Several radiobiological models for radiotherapy have been proposed in the literature. The linear-quadratic model (LQ) is the most frequently used model for including the effects of repair between treatment fractions. The LQ model is based on clonogenic cell survival curves and is parameterized by the radiosensitivity ratio (α/β). It is thought that it quantifies the effects of both unrepairable damage and repairable damage susceptible to misrepair after tumour sterilization by radiation (Hall and Giaccia 2006). Several variations of this model have been proposed including a Poisson-based (Goitein 1987) and a birth–death model (Zaider

and Minerbo 2000). Phenomenological models such as the equivalent uniform dose (EUD) proposed by Niemierko are also applied (Niemierko 1999). The EUD model is characterized by a single exponent parameter '*a*' that controls volume effect. These models and their variations use information only about the dose distribution and fractionation. However, it is well known that radiotherapy outcomes may also be affected by multiple clinical and biological prognostic factors such as stage, volume, tumour hypoxia, etc (Choi *et al* 2001, Fu *et al* 1999). Therefore, approaches that utilize data-driven models, in which dose–volume metrics are combined with other patient or disease based prognostic factors have been proposed (Blanco *et al* 2005, Bradley *et al* 2004b, Marks 2002, Hope *et al* 2005, Tucker *et al* 2004). In a standard modelling exercise, model parameters could be chosen using traditional statistical techniques to define the abscissa of a logistic regression function, for instance (Blanco *et al* 2005, Bradley *et al* 2004a, Levegrun *et al* 2001, Marks 2002, El Naqa *et al* 2006b, Hope *et al* 2006). These methods though useful, are incapable of handling potentially complex physical and biological interactions, manifested as important nonlinear relationships between combinations of variables and resulting outcomes, thus limiting their predictive power and applicability in clinical practice. Other methods based on nonlinear artificial intelligence and machine-learning techniques have been applied to confer cross-variable interactions. Artificial intelligence techniques (e.g. neural networks and decision trees), which are able to emulate human intelligence by learning the surrounding environment from the given input data, have also been utilized for their ability to detect nonlinear patterns in the data. In particular, neural networks were extensively investigated to model post-radiation treatment outcomes for cases of lung injury (Su *et al* 2005, Munley *et al* 1999) and biochemical failure and rectal bleeding in prostate cancer (Gulliford *et al* 2004). However, in a recent work, we have demonstrated that kernel-based machine learning methods can provide superior performance for modelling NTCP (El Naqa *et al* 2009) and TCP (El Naqa *et al* 2010). Nevertheless, such methods in their current state do not provide mechanistic understanding of radiation interaction with living tissue relying on population averaged selected information, rather than first physical, chemical and biological principles.

Monte Carlo (MC) techniques have witnessed increased use in radiation therapy with applications in treatment source modelling, imaging process simulations, and patient dose calculations for treatment planning or simply to get a more optimal estimate of the delivered dose. This increased impact has come about as the result of extensive research on algorithms and calculation acceleration techniques including electron transport modelling, multiple scattering theories and boundary crossing algorithms (Seuntjens and Rogers 2009). Currently, MC techniques are considered the *de facto* gold standard when it comes to dose calculation in radiotherapy.

However, despite decades of MC work in radiobiology and noted success in event-by-event particle tracking, estimation of microdosimetric quantities, and biological endpoints (e.g. DNA double-strand breaks (DSBs), mutations, chromosomal aberrations, tumour growth, etc), it did not evolve into more widespread application in developing predictive NTCP/TCP models to guide clinical radiotherapy practice. This is in contrast to the impact that macroscopic MC radiation transport simulation has had on a variety of applications in radiation therapy.

In this review, we focus on the application of MC simulations in radiobiological modelling for radiotherapy outcomes prediction, from first principles. Towards this goal, we present a brief background on radiotherapy outcomes and MC simulations. This is followed by current MC applications and its expanding role in outcomes modelling of radiotherapy response. We highlight the current challenges, including increased computing demand, and the potential future opportunities of MC approaches for modelling of radiobiological response and radiotherapy treatment outcomes.

2. Background

2.1. Monte Carlo methods in radiotherapy dosimetry

Monte Carlo methods represent a wide class of numerical computer simulation techniques that utilizes statistical resampling to solve complex systems that are not easily tractable analytically. It was originally developed by a group of radiation physicists during the Manhattan nuclear project (Eckhardt 1987). Since its inception, MC methods were successfully applied in many diverse disciplines ranging from quantum physics, electrical and telecommunication engineering, computational biology, weather forecasting, to even computer board games (Bouzy and Helmstetter 2003). The current applications of MC dosimetry methods to radiation therapy could be broadly divided into two areas of macrodosimetry and micro (nano)-dosimetry.

2.1.1. Macrodosimetry. This area of MC dosimetry application is mainly related to scoring radiation dose in larger volumes (millimetres). In a recent review marking the 50th anniversary of MC applications in medical physics, Rogers (2006 presented an elegant historical overview of the journey of developing MC codes for radiation macrodosimetry techniques for electron–photon transport simulations starting by the seminal work of Martin Berger at the National Bureau of Standards on condensed history techniques and the development of the ETRAN code, then through the Erice Summer School on MC in 1987 and discussed the broad range of codes available such as EGS4, PENELOPE, MCNP, GEANT4 with special emphasis on the EGS4/EGSnrc code system (Rogers 2006). The widespread use of these codes and adaptation by commercial vendors in the clinical arena have motivated the AAPM task group report TG-105 on 'Issues associated with clinical implementation of Monte Carlo-based photon and electron external beam treatment planning.' The report provides pedagogical review on the use of MC simulations in radiotherapy planning and discusses the salient issues associated with clinical implementation and experimental verification of MC dose algorithms. It also provides a framework for commissioning and routine quality assurance of MC-based treatment planning systems (MCTP) (Chetty *et al* 2007). An overview of the latest developments in MCTP is found in Spezi and Lewis (2008.

2.1.2. Microdosimetry or nanodosimetry. This area of MC simulation is mainly related to scoring dose in very small areas at the cellular, sub-cellular or molecular level known collectively as MC radiation track-structure codes. These track-structure codes have been developed to estimate the molecular spectrum of clustered damage in DNA and subsequent processes of damage repair. They provide knowledge about the detailed clustering of individual energy depositions by atomic ionizations and excitations along the track of ionizing particles and subsequent free radical diffusion and interaction with DNA atoms (Nikjoo *et al* 1998, 2006). Unlike their macrodosimetry counterparts, these microdosimetry MC codes can also deal with electrons and light ions at low energies and very short distances. At such low energies and small dimensions, event-by-event tracking is applied without resorting to condensed history techniques leading to longer simulation times. An inherent assumption in these codes is that the structure of the tracks of charged particle is intimately involved in determining the observed biological effect in a proportional manner to its linear energy transfer (LET). Examples of such codes include PARTRAC (Paretzke *et al* 1991), KURBUC (Uehara *et al* 1993a), MCDS (Semenenko and Stewart 2004), etc. Microdosimetric quantities such as lineal energy distributions or cluster analyses extracted from the scored low-energy ionizations and excitations shed light on the proximity of events and relate to the direct

effects of ionizing radiation on matter. These types of codes have witnessed application in different areas including: space radiation, shielding, radiation protection, radiotherapy, biophysical modelling, radiation biology, radioactive beam, high-energy physics, solid state physics, nuclear physics, accelerator-driven systems, neutron optics and spallation of neutron sources (Nikjoo *et al* 1998, 2006). Nevertheless, their application in radiobiological modelling of radiotherapy outcomes did not extend to the level that would be clinically useful for predicting radiotherapy response or for designing clinical oncology trials, for instance. This is an important intermediary area between macro- and microdosimetry that involves applications of MC in tumour growth modelling and response to radiotherapy as discussed below.

2.2. Radiobiological modelling in radiotherapy

As mentioned earlier, radiotherapy outcomes are usually characterized by TCP and the surrounding NTCP metrics (Steel 2002, Webb 2001). The methods currently used for building predictive TCP/NTCP treatment outcome models could be divided into analytical and multi-metric based approaches. However, before divulging into the details of outcomes modelling, it would be pedagogically necessary to provide a brief review of the basic relevant radiation effects and radiobiological principles.

2.2.1. Radiobiology of radiotherapy response. Classical radiobiology has been defined by 'The Four Rs' (cellular damage repair, cell-cycle redistribution, reoxygenation and cellular repopulation/division over a course of radiotherapy) (Hall and Giaccia 2006). It is believed that radiation-induced cellular lethality is primarily caused by DNA damage in targeted cells. Two types of cell death have been linked to radiation: apoptosis and post-mitotic cell death. However, tumour cell radiosensitivity is controlled via many factors (known and unknown) related to tumour DNA repair efficiency (e.g. homologous recombination or nonhomologous endjoining), cell cycle control, oxygen concentration and the radiation dose rate (Hall and Giaccia 2006, Lehnert 2008, Joiner and van der Kogel 2009).

The seminal work of Fertil and Malaise has shown that the survival of cell lines given small doses of radiation *in-vitro* correlates well with perceived ability to cure corresponding human tumours (Fertil and Malaise 1985). The preferred technique for deriving radiosensitivity data from biopsies was to allow plated cells to grow *in vitro* which were then irradiated, typically to doses similar to the single fraction doses given in conventional radiotherapy (2 Gy), and then measuring the rate of survival (SF2). Other relevant markers of radiobiology response include the potential doubling time of the cells (T_{pot}) and the gamma factor (γ), which represents the slope of the survival curve at 50% rate (Choi *et al* 2001). These concepts comprise the basis for analytical (mechanistic) outcomes modelling techniques in radiotherapy as discussed below.

2.2.2. Analytical methods. These are methods generally based on simplified biophysical understanding of irradiation effects mainly from in vitro assays. The LQ model is the most frequently used model for including the effects of irradiation damage and repair between dose fractions. The LQ model is based on cell survival fraction (SF) analysis and is parameterized by the radiosensitivity ratio (α/β):

$$\mathrm{SF} = \exp(-(\alpha + \beta * d) * D + \ln 2 * t/T_{\mathrm{pot}}), \tag{1}$$

where d is the fraction size, D is the total delivered dose, t is the difference between the total treatment time (T) and the lag period before accelerated clonogen repopulation begins (T_K), and T_{pot} is the potential doubling time of the cells. The ratio $\ln 2/T_{\mathrm{pot}}$ is referred to as the repopulation parameter. It is thought that the LQ models can quantify the effects of both

unrepairable damage and repairable damage susceptible to misrepair after tumour sterilization by radiation as mentioned earlier (Hall and Giaccia 2006). Several variations of this model have been proposed including a Poisson-based (Goitein 1987), extension to inhomogeneities in dose and clonogenic cell density (Webb and Nahum 1993), and a birth–death model (Zaider and Minerbo 2000). Among the most commonly used LQ-based TCP models (Hall 1994) is

$$\mathrm{TCP} = \exp(-N\exp(-((\alpha + \beta * d) * D + \ln 2 * t/T_{\mathrm{pot}})), \tag{2}$$

where N is the number of cells. On the other hand, the most commonly used NTCP model is the Lyman–Kutcher–Burman (LKB) model (Lyman 1985, Kutcher and Burman 1989), which could be written as

$$\mathrm{NTCP}(D, D_{50}, m) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} \exp(-u^2/2)\,\mathrm{d}u, \tag{3}$$

where

$$t = \frac{D - D_{50}}{mD_{50}},$$

D_{50} is the position of the 50% probability dose point and m is a parameter to control the slope of the dose response. Note that D_{50} could be expressed as a function of the partial organ volume (V):

$$D_{50}(V) = D_{50}(1)/V^n, \tag{4}$$

where $D_{50}(1)$ is D_{50} for the whole volume and n is a volume dependence parameter. Another commonly used NTCP model is the critical volume (CV) model (Niemierko and Goitein 1993, Stavrev *et al* 2001), which is based on the idea that organs are composed of functional subunits (FSUs), which are arranged in serial or parallel architectures:

$$\mathrm{NTCP}(\bar{\mu}_d, \mu_{cr}, \sigma) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} \exp(-u^2/2)\,\mathrm{d}u, \tag{5}$$

where

$$t = \frac{-\ln(-\ln\bar{\mu}_d) - \ln(-\ln\mu_{cr})}{\sigma},$$

$\bar{\mu}_d$ is the mean relative damaged volume, μ_{cr} is the critical fraction of FSUs, and σ accounts for the inter-patient variability.

An alternative approach to the above formalism is based on the concept of EUD or generalized EUD (gEUD), which is given by

$$\mathrm{gEUD} = \left(\sum_i v_i D_i^a\right)^{1/a}, \tag{6}$$

where vi is the fractional organ volume receiving a dose D_i and a is a tissue-specific parameter that describes the volume effect. To account for the effects of cold spots on TCP, the tumour is represented by a negative a (<-10). In the case of NTCP, the parameter choice depends on the functional subunit organization; for serial-organ complications, a large a (>10) is selected; for parallel-organs complications, $a \sim 1$ (mean dose equivalent).

2.2.3. Multi-metric models. These are phenomenological models and depend on parameters available from the collected clinical and dosimetric data (i.e. data driven). In these data-driven models (Deasy and El Naqa 2008), dose–volume metrics are combined with other patient or disease based prognostic factors (stage, histology, site, volume, tumour hypoxia, etc (Choi *et al* 2001, Fu *et al* 1999). These methods could be applied to TCP or NTCP modelling; however, they have been more widely applied to normal tissue toxicity (Blanco *et al* 2005, Bradley

et al 2004b, Marks 2002, Hope *et al* 2005, Tucker *et al* 2004, Bradley *et al* 2007, Huang *et al* 2012, 2011). The results of this type of approach are not expressed in closed form as above but instead, the model parameters are chosen in a stepwise fashion to define the abscissa of a regression model (cf figure 1).

Many of these presented analytical/multi-metric methods require dedicated software tools for implementation. As examples of such software tools in the literature are BIOPLAN and DREES. BIOPLAN uses several analytical models for evaluation of radiotherapy treatment plans (Sanchez-Nieto and Nahum 2000), while DREES is an open-source software package developed by our group for dose response modelling using analytical and multi-metric methods (El Naqa *et al* 2006c).

More recently, artificial intelligence and machine learning methods have been proposed for radiotherapy outcome modelling (El Naqa 2012). For instance, neural networks were used to model post-radiation treatment outcomes for cases of lung injury (Su *et al* 2005) and prostate cancer (Gulliford *et al* 2004). We have demonstrated that machine learning techniques based on kernel mapping methods could be used to model TCP and NTCP with superior performance to the state-of-the art (El Naqa *et al* 2009, 2010). These methods can inherently account for complex nonlinear radiobiological interactions and provide excellent fit to out-of-sample data. However, one of the main challenges of this framework is the selection of the most relevant variables to include within the model and the ability to interpret the data mechanistically, where numerical techniques like Monte Carlo might be able to help. For instance, MC methods have been recently applied for modelling tumour growth (Tuckwell *et al* 2008) and cell response to irradiation (McMahon *et al* 2012) as discussed below. Interestingly, MC-based methods are also indirectly used for training many of such machine learning algorithms. For instance, a TCP model of tumour local control in lung cancer was developed by combining dosimetric physical variables and biological factors extracted from patients' blood sera (Oh *et al* 2011). In order to account for the hierarchical relationship between the different physical and biological variables in the TCP model, a graphical Bayesian network approach was utilized (Oh *et al* 2011). The structure and the parameters of the developed Bayesian network for TCP modelling were estimated using a modified Markov Chain Monte Carlo (MCMC) algorithm.

3. Monte Carlo techniques for radiobiological modelling in radiotherapy

3.1. MC in radiation therapy plan evaluation, radiobiological indices, uncertainties and parameters

For application of radiobiological models discussed in section 2.2 in radiotherapy, MC techniques have played a central role in determining uncertainties in extracted information from treatment planning systems such as radiobiological parameters, dose–volume metrics, set-up and margin uncertainties, or the effect of uncertainties in the dose distributions on radiobiological indices (e.g. Webb and Nahum 1993, Zagars *et al* 1987). This area of application of Monte Carlo simulation to radiation biological modelling is quite broad with a wide variety of applications. Therefore, in this review we limit ourselves to providing a few representative examples and refer interested reader to cited literature for further details.

In the case of analytical radiobiological models, Warkentin *et al* (2005 evaluated a 'population' TCP model in terms of its ability to provide reliable biologic model parameter estimates (Warkentin *et al* 2005). MC techniques based on preset values for the various radiobiological models were used to generate pseudo datasets to which fits of the population TCP model were made. It was shown based on this study that there exists a significant correlation between the level of population heterogeneity and the estimated α/β parameter.

Their results implied that fits to clinical data might not be able to distinguish between tumours exhibiting a high degree of heterogeneity and a strong beta-mechanism and those containing little heterogeneity and having a weak beta-mechanism. Booth and Zavgorodni (2001 investigated the relative importance of three uncertainties, i.e. spatially uniform dose uncertainty, spatially non-uniform dose uncertainty, and inter-patient cell sensitivity heterogeneity, on the delivered dose and TCP distribution following a typical course of fractionated external beam radiotherapy (Booth and Zavgorodni 2001). MC techniques were used for the simulation of a population of patients, and distributions of dose across the patient population were used to calculate dose and TCP related parameters with each of the three individual types of uncertainties. The calculations show that the dose errors in the tumour volume are dominated by the spatially uniform component of dose uncertainty, an observation that could be related to machine-specific parameters, such as linear accelerator calibration.

On the other hand, a frequent problem using the multi-metric radiobiological approaches is that the data extracted from dose distributions are in a context where no account for tissue heterogeneity was made during the planning of the radiation therapy. This may impact the accuracy of the derived dose–volume or dose–biological parameter metrics, and hence the parameters that are extracted from the models. Therefore, in retrospective contexts, to account for heterogeneity correction, the dose distributions are recalculated retrospectively using MC algorithms. For instance, Lindsay *et al* used the VMC++ MC code for dose recalculation. To specify proper beam weights and wedges, the beams were broken into beamlets and mathematical optimization was used to match the archived water-based dose distributions. The derived beam weights and wedge effects were then applied to MC beamlets regenerated based on the patient computed tomography (CT) densities. The method was compared with other heterogeneity correction methods (Lindsay *et al* 2007). The study found that the average absolute percent difference between heterogeneity-corrected MC and water-based treatment plans increased to $3.1 \pm 0.9\%$. Comparison of maximum lung doses showed that the average MC heterogeneity-corrected values were 5.3 ± 2.8 Gy less than the treatment plan with heterogeneity-corrected values using analytical methods. This approach was also recently applied for modelling TCP in lung cancer (El Naqa *et al* 2010). In another study, Stroian *et al* have shown that MC dose distributions can correlate much better with the probability of radiation-induced fibrosis than would the CadPlan dose distributions, which were pencil beam-based with no heterogeneity corrections (Stroian *et al* 2008). A rather different site than lung, Stathakis *et al* used MC dose recalculation to evaluate the risk of secondary malignancies undergoing IMRT for prostate cancer patients (Stathakis *et al* 2007).

Another interesting MC application is the effect of set-up errors and margins in treatment planning. Ploquin (2006 compared the effect of set-up error and uncertainty on radiation therapy treatment plans for head and neck cancer using IMRT and 3D-CRT (Ploquin 2006). MC generated set-up errors and uncertainty were performed in three orthogonal directions for 840 simulated courses of treatment for each plan. A probability approach was used to compare the sensitivities of the IMRT and the 3D-CRT plans to set-up error and uncertainty in terms of EUD to the targets and to the organs-at-risk (OARs). Based on the EUD analysis, the targets and OARs showed considerably greater sensitivity to set-up errors with the IMRT plan than with the 3D-CRT plan. Specifically, For the IMRT plan, target EUDs were reduced by 4%, 7.5% and 10% for 2 mm, 4 mm and 6 mm set-up errors, respectively.

3.2. MC modelling of radiotherapy response

The ability of MC methods to accommodate a hierarchy of models reaching from global description of birth–death processes to very specific features of intracellular dynamics have

led to their early application in tumour growth modelling (Drasdo *et al* 1995, Drasdo 1998). Specifically, they have been applied as part of discrete cell-based models such as cellular automata to reproduce the Gompertz law of cancer growth. This is in contrast to continuum models, which consider classical interactions between cell density and chemical species that provide nutrients or influence cell cycle events of tumour progression using reaction-diffusion-convection equations as learnt from spheroids, for instance (Casciari *et al* 1992). Interested reader in mathematical models of tumour growth is refereed to Roose *et al* (2007, Wodarz and Komarova (2008.

Application of MC in radiotherapy TCP and NTCP modelling covers a wide area. MC was used to study how inter-patient differences can affect the TCP (Guirado and Ruiz de Almodovar 2003). In this study, a radiosensitivity value x was drawn from a lognormal distribution and values for parameters D_{50} and γ are randomly sampled from a normal distribution. Borkenstein *et al* developed an MC-based tumour growth and response model to radiation in which each tumour cell is assigned a set of radiobiological parameters, and the status of each cell is checked in discrete intervals. Tumour proliferation is governed by individual cell cycle times, growth fraction, cell apoptotic capacity and cell angiogenesis. The response to radiation is determined by the radiosensitivity parameters and oxygenation status (Borkenstein *et al* 2004). Stamatakos *et al* investigated the effect of clonogenic cell density on radiotherapy response of glioblastoma multiforme (GBM). Their MC predictions were comparable to clinical trial experience (Stamatakos *et al* 2006). Partridge presented a cellular MC model to describe radiation damage and repair in normal epithelial tissues. The results were consistent with both the rate of induction of irreparable DNA lesions and the clinically observed acute oral and pharyngeal mucosal reactions to radiotherapy (Partridge 2008). Most recently, McMahon *et al* presented an MC model of cellular radiation response to spatially modulated fields that incorporated damage from both direct radiation and intercellular communication including bystander signalling (McMahon *et al* 2012). The simulations seemed to reproduce cell survival following modulated radiation exposures and interestingly suggesting that the bystander effect is responsible for a significant portion of cell killing in uniformly irradiated cells in contrast with traditional radiobiological models.

The different *R*s (Hall and Giaccia 2006) of radiotherapy received considerable MC modelling attention. Incorporation of tumour hypoxia in growth models of head and neck squamous cell carcinoma has been developed using MC methods (Tuckwell *et al* 2008). Hypoxia is implemented by random assignment of partial oxygen pressure values to individual tumour cells based on *in vivo* Eppendorf probe experimental data. Repopulation acceleration due to loss of asymmetry of stem cell division seemed to reshape the survival curve with a 'growth' shoulder (Marcu *et al* 2004). The effects of both hypoxia and accelerated repopulation have been incorporated for head and neck cancers (Harriss-Phillips *et al* 2011).

3.3. Particle track structure codes for radiation-induced damage

Monte Carlo methods have been extensively used to estimate the molecular spectrum of damage in clustered and not-clustered DNA lesions (Gbp^{-1} Gy^{-1}) (Goodhead 1994, Ward 1994, Cucinotta *et al* 2000, Nikjoo *et al* 2001, Watanabe and Nikjoo 2002, Semenenko *et al* 2003, Allison *et al* 2006, etc). The temporal and spatial evolution of the resulting effects of the deposition of energy from ionizing radiation can be divided into three phases: physical, chemical and biological following tentatively the time scale of figure 2.

The different available particle track structure MC codes aim to emulate these phases to varying extents. However, a main limitation of the majority of radiation transport and early track structure codes is the sole focus on the physical events (ionization, excitations

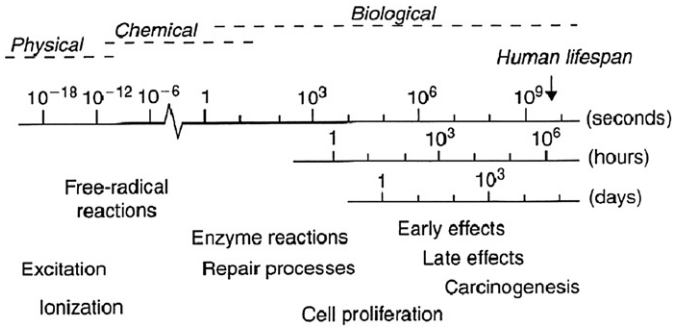

Figure 2. The different phases involved in radiation-induced effect in living tissue. Reproduced with permission from Joiner and van der Kogel 2009, copyright 2009 Hodder Education.

Table 1. Different models for the elastic, excitation and ionization cross-sections for electrons of several Monte Carlo particle track structure codes.

Code	Elastic scattering	Excitation	Ionization	Energy range
KURBUC (Uehara *et al* 1993b)	Screened Rutherford	Empirical formula derived from the Fano plot (Berger and Wang 1988)	Seltzer's formula (Seltzer 1988)	10 eV–10 MeV
PARTRAC (Friedland *et al* 2011a, Alloni *et al* 2012, Dingfelder *et al* 1999)	ELAST database of NIST (Berger *et al* 1993)	Complex di-electric formalism (Dingfelder *et al* 1999)		10 eV – 10 MeV
NOREC (Semenenko *et al* 2003, Ritchie *et al* 1991)	ELAST database of NIST (Berger *et al* 1993) and OREC elastic angular distributions	Complex di-electric formalism (Ritchie*et al* 1991)		7.4 eV–1 MeV
GEANT4-DNA (Agostinelli *et al* 2003, Incerti *et al* 2010)	Screened Rutherford (Champion *et al* 2009, Emfietzoglou *et al* 2000)	Semi-empirical based on complex di-electric formalism and binary encounter (Emfietzoglou *et al* 2003)		2 eV–1 MeV

and scattering) and limited tracking of subsequent chemical and biological-induced effects. However, some prominent codes have gone beyond this point into including chemical and pre-chemical tracks. The chemical phase involves the generation of free radicals through water radiolysis that will subsequently interact with the medium. Nevertheless, and unfortunately, most codes to date stop short of tracking the events of the most complex phase and actually the most relevant to radiobiological response, which is the biological phase. A summary review of many current MC particle track structure codes is given by Nikjoo *et al* (2006) using the KURBUC code as an example. For demonstration purposes of the current state-of-the-art in the field of particle track structure and illustration of these phases, we opt in our review to select few representative cases as discussed below, with special focus on GEANT4-DNA because of its broad spectrum and open-access availability to the community. Moreover, a summary of the different models used for elastic, excitation and ionization cross-sections of electrons in these codes is provided in table 1 for easy comparison by the reader.

While different particle track structure codes have different implementations, its worth mentioning that they require understandingly more processing time than particle transport MC codes. The fact that all particle interactions are explicitly simulated, without relying on condensed history or multiple scattering approximations, also limits the dimensions of the volume in which simulations can be run to the micrometre scale with current computational processing architectures. As an example, the complete simulation of a single 1 MeV electron slowing down to 10 eV in a 30 cm^3 water phantom using GEANT4-DNA processes and following all secondary electrons takes approximately 175 s if using GEANT4-DNA processes, while it takes 0.25 s if one is using GEANT4 low energy Livermore processes (simulations were carried using GEANT4.9.5 on a Linux Virtual Machine running on a 2.2 GHz Intel Core i7). Although an explicit time-comparison is difficult to achieve as it depends on the geometry, the simulation goal, and desired uncertainty, code implementation, the activated physical process, and the tracking energy limits, it is safe to say that particle track structure codes can carry a significant simulation time burden and that hardware and software advances are still needed for real-time realization. Moreover, when particle track structure codes are used to simulate radiation interaction with DNA, typically a post-processing of the simulated track data is performed to obtain relevant DNA damage values. Many approaches of analysis are available in the literature, such as K-means clustering (Michalik 1993, Verhaegen and Reniers 2004), density-based spatial clustering of applications with noise (DBSCAN) clustering (Francis *et al* 2011), or dedicated efficient algorithms to capture the major trends in the DNA damage spectrum (e.g. multiply damaged sites) predicted using detailed track structure simulation (Semenenko and Stewart 2004, Stewart *et al* 2011).

3.3.1. KURBUC. This code was developed for water vapour medium with energies between 10 eV and 10 MeV (Uehara *et al* 1993a). The code can handle light ions such as protons (1 keV–1 MeV) and alpha particles (1 keV–8 MeV). The code also provides information on the formation of ionized (H_2O^+), excited (H_2O^*) water molecules and hydration of sub-excitation electrons (electrons with energy not sufficient for excitation of water molecules). In addition, it provides the resulting radical species from water radiolysis in the chemical stage using CHEMKURBUC up to a period of 1 μs after the physical phase. This is where Brownian diffusion in aqueous solution and reactions among the reactive chemical species take place until track reaction kinetics comes to rest within 1 μs period. This could be attributed to the attenuated local concentrations of the radiolytic products. Most recently, biological phase tracking is being developed, where a kinetic model of single-strand annealing for DNA repair of DSBs has been added (Taleei *et al* 2011).

3.3.2. NOREC. This code is a modification of the original OREC (Oak Ridge electron transport code) with an updated electron elastic scattering cross-sections (Semenenko *et al* 2003). The code can calculate a detailed event-by-event transport of a primary electron and all of its secondaries in liquid water over a range of energies from 7.4 eV to 1 MeV. The chemical track remained similar to the original OREC implementation as in KURBUC (Turner *et al* 1983). The biological phase simulation is unavailable yet.

3.3.3. PARTRAC. The code was originally developed for track structure of electrons (Paretzke *et al* 1991, Dingfelder *et al* 1999). Currently, the code can handle photon and ion tracks, heterogeneous targets and modelling of radiation-induced damage to DNA. Energy ranges are available for photons (soft x-rays to energetic gamma rays), electrons (10 eV–10 MeV), protons and helium nuclei (1 keV–1 GeV) and heavier ions (1 MeV/u–1 GeV/u).

An updated version of the code also includes cross-sections for electrons, and light ions in liquid water (Dingfelder *et al* 2008). The physical track is simulated to a time scale of 1 fs. The subsequent chemical track includes the formation of diverse chemical species similar to KURBUC and NOREC, but this process has been updated and improved to extend the interaction datasets for heavier ions (Kreipl *et al* 2009). Most recently, a DNA double-strand break (DSB) repair module via the non-homologous end-joining (NHEJ) has been added (Friedland *et al* 2010, 2011b) making it among the most developed code in this regard to date.

3.3.4. GEANT4-DNA. GEANT4-DNA is an open-source simulation toolkit that aims to extend macroscopic GEANT4 to model the effects of radiation on biological systems at cellular and DNA levels (Agostinelli *et al* 2003, Allison *et al* 2006). In the following we discuss, GEANT4-DNA in more details because of its open source nature availability for future development.

The GEANT4-DNA code is actively being extended with the objective of including physical, chemical and biological models in order to simulate cellular and subcellular damage induced by ionizing radiation. It has successfully incorporated a new set of electromagnetic processess and is currently able to track particles in liquid water, low energy electrons (2 eV–1 MeV), protons (10 eV–100 MeV), alpha particles (1 keV–400 MeV), as well as light atoms (H, He, C, O, N, Fe) and ions as shown in figure 3.

The GEANT4-DNA processes can simulate explicitely every interaction. As an example, figure 4 shows two 1 keV electrons that are incident on a slab of liquid water. The left electron track was simulated using standard low energy processess (G4e-MultipleScattering, G4e-Ionization) while the right track was followed with GEANT4-DNA processes (G4DNA-Elastic, G4DNA-Excitation, G4DNA-Ionization, G4DNA-Attachment, G4DNA-VibExcitation).

A summary of the importance of the different interactions is plotted in figure 5. From figures 4 and 5, it is obvious that condensed history techniques are inapropriate for resolving resulting events at very low energies and dimensions. The models used in GEANT4-DNA are based on semi-empirical models and on the plane-wave Born approximation (Villagrasa *et al* 2011) and were verified and compared with experimental data (Incerti *et al* 2010).

GEANT4 allows the creation of detailed DNA and cellular geometries through its Detector Construction class, as was recently demonstrated (Bernal *et al* 2011). They modelled a B-DNA arrangement of 30 nm chromatin fibres totalling 5.4×10^8 base pairs irradiated by protons and alpha particles of different energies as shown in figure 6. Notably, they found that the number of DNA SSB seemed independent of the incident particles linear energy transfer (LET), whereas DSB were relatively more frequent as the LET increased. In these simulations, SSBs were counted when an event with transferred energy higher than 8.3 eV occurred inside one of the 10.8×10^8 target volumes representing the phosphodiester covalent bond groups. A DSB was counted if two SSBs were found to be closer than ten base pairs (bp) apart while lying on opposite strands of the B-DNA model.

Currently, GEANT4-DNA offers the possibility of modelling direct damage to small biological sub-units by physically tracking particles. Recently, in version 4.9.5, a prototype for simulating the chemical phase was added and experimental validations and verifications are underway.

3.3.5. Microdosimetric quantities and relationship to DSBs. One of the main current objectives of particle track structure codes in medical physics is the calculation of

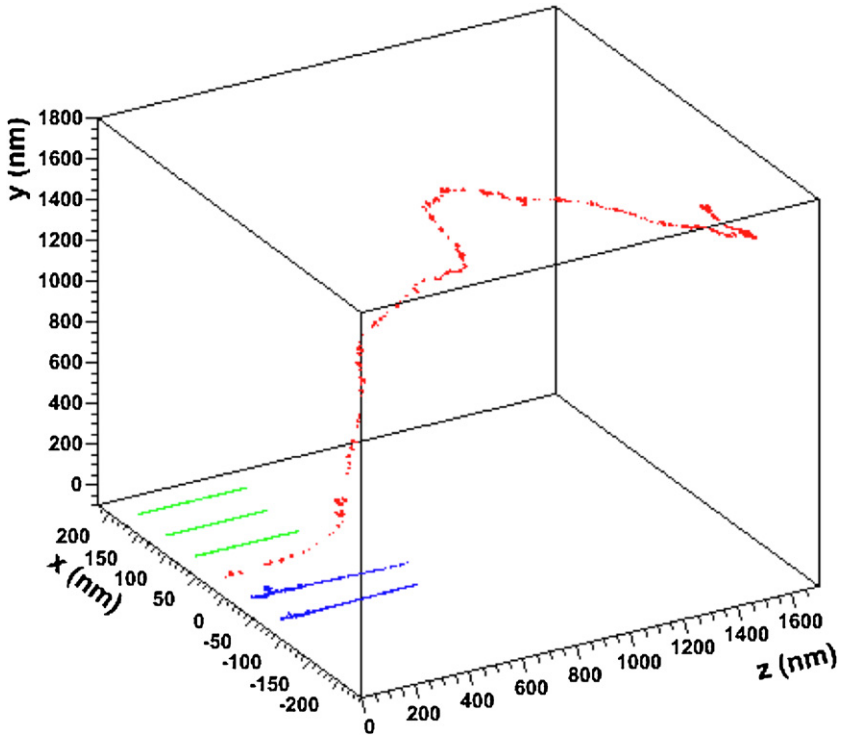

Figure 3. Comparisons of six 3D track structures obtained with GEANT4-DNA physics processes for single 10 keV incident particles in liquid water. The particles are emitted towards the positive z-direction and from different x-positions for the sake of clarity: proton ($x = -50$ nm), hydrogen ($x = -100$ nm), electron ($x = 0$), He2+ ($x = 50$ nm), He+($x = 100$ nm), helium ($x = 150$ nm) (Incerti *et al* 2010).

microdosimetric quantities with the goal to relate these quantities to measurable physical, biological or clinical endpoints. Microdosimetric, in contrast to macrodosimetric, quantities allow for a better quantification of radiation effects in a small volume of biological interest, such as volumes of shape and sizes ranging from DNA (2 nm), the nucleosome (around 10 nm), chromosome (1 μm), the cell nucleus (few μm) to a cell (10 μm). The suitability of macro- or micro-dosimetric quantities to characterize effects also depends on the fluence (i.e. on the number of particles that traverse the volume of interest for a given energy dose deposition). Away from gradients in a dose distribution, at high-absorbed dose, the dose in an extended mass is essentially the same as a small mass such as a single cell. However, at the microscopic level, energy deposition is stochastic and the absorbed dose, which by definition implies the calculation of an expectation value of the imparted energy over a large number of events, is no longer relevant. The microdosimetric fundamental quantity that describes energy absorbed on an interaction by interaction basis is denoted as *energy deposit* (ICRU 1983), ε_i, defined as the energy deposited in a single interaction, $\varepsilon_i = T_{\text{in}} - T_{\text{out}} + Q_{\Delta m}$, where T_{in} is the kinetic energy of the incident ionizing particle, T_{out} the sum of the kinetic energies of all ionizing particles leaving the interaction site, and $Q_{\Delta m}$ is the change in the rest mass energy of the atom and all the particles involved in this interaction.

Three important stochastic quantities could be derived from the quantity energy deposit: (1) the energy imparted to matter in a volume, ε, which is the summation of all the energy

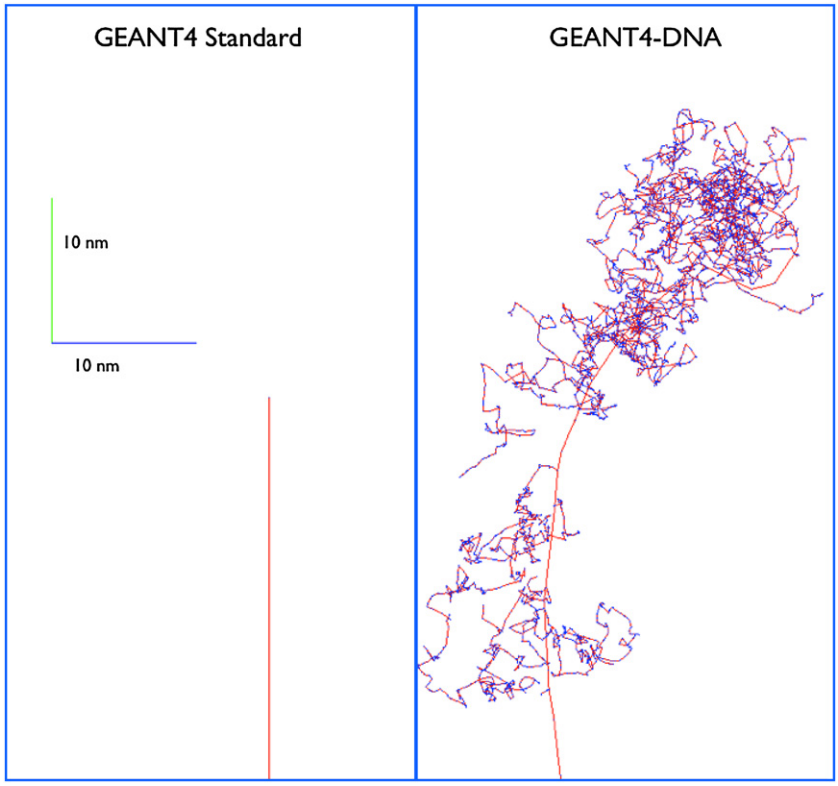

Figure 4. Two 1 keV electrons incident on slab of liquid water using: (*left*) GEANT4 standard electromagnetic processes, (*right*) GEANT4-DNA low energy processes. The standard processes kill the electron after one interaction and deposit its energy locally. The GEANT4-DNA processes explicitly simulate every interaction, elastic scattering, ionizations and excitations down to 5 eV in this simulation, where the electron energy is deposited locally.

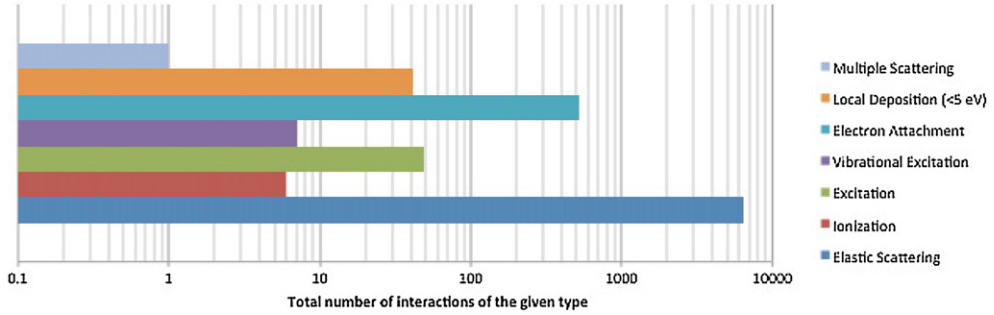

Figure 5. Total number of interactions. The electron on the *left* produced the only multiple scattering interaction. The electron on the *right* produced all the other secondary tracks and interactions.

deposits in that volume; (2) the lineal energy, which is defined as the ratio of imparted energy to the mean cord length of a volume around the interaction site, i.e. $y = \varepsilon/l$, expressed in eV nm^{-1} or keV μm^{-1}; (3) the specific energy z, expressed in Gy, which is the imparted

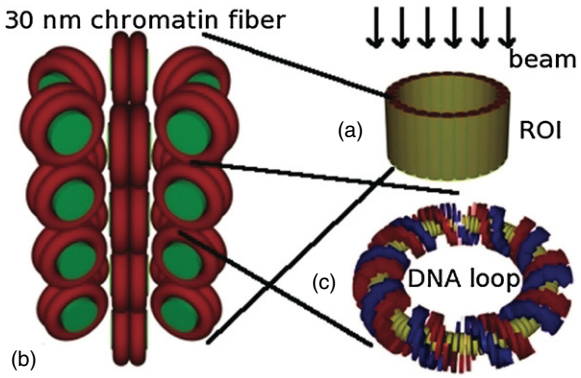

Figure 6. Geometrical features in Bernal *et al* (2011) simulations: (a) irradiation setup including 900 chromatin fibres, (b) geometrical model of the 30 nm chromatin fibre, including an arrangement of six pairs of nucleosomes (in red) wrapped around a histone (in green), and (c) one loop of the DNA molecule surrounding a histone.

energy per unit mass m. With these stochastic quantities defined, corresponding probability density functions can be associated such as the lineal energy distribution and from these, derived quantities such as the frequency mean lineal energy and the dose mean lineal energy can be obtained. This would allow measuring physical microdosimetric endpoints using tissue equivalent proportional counters, for example, and comparing these measurements to MC track structure simulations of these distributions and their corresponding average quantities for validation purposes. However, most of the microdosimetric quantities defined in ICRU (1983 do not provide information about the localization of individual interactions with respect to the target, only about mean characteristics of energy depositions or distributions in relation to virtual target volumes. Track structure MC codes, however, assuming they are accurate, do provide the detailed information on the position, proximity and the type (soft or hard ionization and excitation) of each interaction along the trajectory of the electrons slowing down or created as a result of the collision of another particle. To overcome this issue, post-processing analyses to the coordinate data can be performed to analyse the track structure. One example of such a post-processing method is the clustering method (Michalik 1993). According to this method, which is a form of K-means clustering, the types of interactions (e.g. ionizations) are grouped in spherical clusters of a given radius p. If the cluster contains j ionizations, it is said to be a cluster of order j. The clustering analysis is a simple method that helps to reconcile observed data with a crude model of ionization density in water or scaled water vapour. As an example of correlating cluster frequency with a biological endpoint, e.g., a DNA DSB, the energy dependence of the number of clusters containing at least a given number of ionizations to the energy dependence of lesion yields (measured DNA DSBs) could be compared. Figure 7 shows an example of a plot used to determine the cluster order (number of ionizations) that makes the cluster frequency consistent with both the energy dependence of the lesions as well as the absolute number of lesions. In this manner, Michalik (1993) determined that at least three ionizations in a 1 nm target are required to make the cluster analysis consistent with DSB data. For a 2 nm target, at least four ionizations are required, for a 3 nm target, at least five ionizations, and at least six ionizations for a 4 nm target. For 5 nm targets no thresholds consistent with the DSB data were found.

Verhaegen and Reniers (2004) applied the clustering analysis method to study the radiation quality effects of mammography radiation versus conventional low-LET radiation.

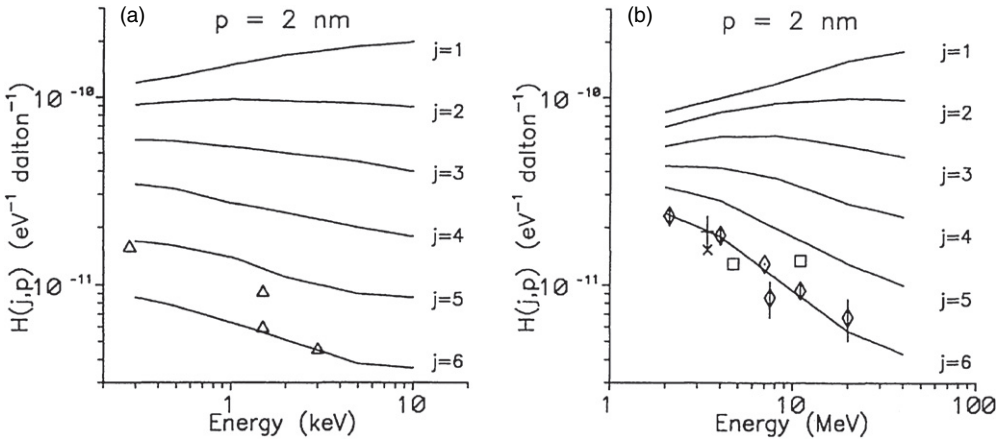

Figure 7. Energy dependence of the mean absolute frequency of clusters containing at least a threshold number of ionizations j in sites with the diameter 2 nm compared with experimental data. (a) Electrons, (b) alpha-particles. Adapted from Michalik (1993). Reproduced with permission from Michalik *et al* 1993 *Rad. Res.* **134** 265–70, Copyright 1993 by Academic Press.

Interestingly, their findings were corroborated by Bernal *et al* using the geometrical model of B-DNA presented in section 3.3.4, where they were able to predict similar radiation quality effects for mammography using explicit counting of DSBs (Bernal *et al* 2011).

4. Issues and future directions

Monte Carlo calculations are stochastic in nature and inherently contain random errors, or statistical uncertainty. These uncertainties can impact the radiobiological parameters extracted from these dose distributions. Buffa and Nahum investigated the influence of statistical uncertainties on dose–volume histograms (DVHs) and the Poisson-based TCP model (Buffa and Nahum 2000). They noticed that with MC uncertainties the TCP calculation systematically underestimates the actual TCP. This underestimation depends on the degree of heterogeneity of the radiobiological parameters over the population and decreases with increasing the biological heterogeneity. The level of uncertainty decreases inversely with the square root of the number of particles or the computational time. The level of acceptable uncertainty for clinical application has been investigated in the literature and summarized in AAPM-TG-105 (Chetty *et al* 2007). Keall *et al* discussed the effect of statistical noise on clinical acceptability of a lung treatment plan using evaluation methods such as visual examination of isodose lines on computed tomography (CT) scans and DVHs as well as calculated biological indices (Keall *et al* 2000). This approach for statistical uncertainty analysis was generalized into the evaluation of a 'cost function' that could represent any treatment plan of the suitability of the plan for the intended treatment (Kawrakow 2004). It has been determined that a statistical uncertainty of 2% or less does not significantly affect isodose lines, DVHs, or biological indices (Keall *et al* 2000, Kawrakow 2004).

In the case of track structure modelling, there are still several challenges related to the different physical, chemical and biological phases. Recently, Toburen (2012) summarized the physical challenges as follows: (1) uncertainties in simulating low-energy electrons (sub-1 keV), which has been recently questioned in the context of the quantum uncertainty principle (Thomson and Kawrakow 2011); (2) charge transfer and the devolvement of single electron

loss by capture cross-sections; and (3) estimation of effective charge lost by electron capture interactions. As for the simulation of the chemical phase, Toburen highlights the issue of high ionization density estimates following interactions of charged particles with water, or other descriptors of the biologic medium. For instance, the ionization density along a proton track at energies near the Bragg peak (maximum in the stopping power) leads to about one ionization per 10 Å, or about an ionization for every 2–3 molecules traversed along the path of the proton; thus ionizations are separated sufficiently that one is generally independent of another. Moreover, it is noticed that most of the microdosimetric quantities defined in ICRU (1983 do not provide information about the localization of individual interactions with respect to the target as described earlier. Therefore, a more realistic representation would involve the simulation of interactions between radiation and the DNA molecules surrounded by water molecules in crystalline form using clustering techniques, for instance. An advantage of the clustering analysis is that it can be applied to different types of events, including ionization and also, for example, the distribution of radicals. This could be applied to the radical distributions resulting from more recent Monte Carlo codes that include elements of the chemical phase. Radiation transport modelling in more realistic models of the cell and different targets within the cell is required to better link measurable biological endpoints to track structure. In addition to these issues, there are other challenges to the chemical stage, which includes radical diffusivity (random walk), damage fixation, scavenging, etc. In the case of the biological phase, the picture is even more complicated since accurate understanding of cell death processes, the presence of asynchronous cells, complex signalling pathways, epigenetic variations, are still virtually unknown. This is in addition to the computational burden associated with event-by-event particle tracking compared to macroscopic dose calculations, which limits these types of model calculations to microscopic volumes and making it orders of magnitude away from allowing the representation of a radiotherapy application to a human tumour. Nevertheless, the combination of modelling approaches with current evolution in biotechnology data may actually prove to be very useful despite these outlined challenges. As Toburen puts it 'Hopefully physicists will continue to provide the data needed to address model weaknesses and modellers will incorporate these new data as we seek to provide better tools for understanding the mechanism(s) responsible for biologic response to ionizing radiation and to reduce the uncertainties in estimating risks from new and different radiation source characteristics.'

MC techniques application for radiotherapy outcomes prediction is still in its infancy. However, successful strides have been made in modelling DSBs, tumour growth and hypoxia effect. Recently, a new kinetic model was developed to link DSB induction from MC simulations to deterministic repair models. Specifically, formulae linking the LQ model radiosensitivity parameters to DSB induction and repair explicitly were developed to account for the contribution to cell killing of unrejoinable DSBs, misrepaired and fixed DSBs (Carlson *et al* 2008).

A rather promising approach would be to follow a systems biology framework, which uses engineering inspired techniques to develop comprehensive mathematical models of complex biological systems. For instance, methods based on multi-scale analysis have been successfully applied for comprehensive modelling of tumour growth. This approach allows conducting simulations in space and time simultaneously over the different microscopic and macroscopic scales, which has been increasingly recognized as a powerful tool to refine hypotheses, focus experiments, and enable more accurate predictions of tumour behaviour (Deisboeck *et al* 2011, Zhang *et al* 2009). Recently, Friedland and colleagues stated that for better understanding of radiation action on biological systems like cellular macromolecules (e.g. DNA in its higher structures), a synergistic approach of experiments and quantitative modelling of working hypotheses would be necessary (Friedland *et al* 2008). Furthermore, patient's imaging data

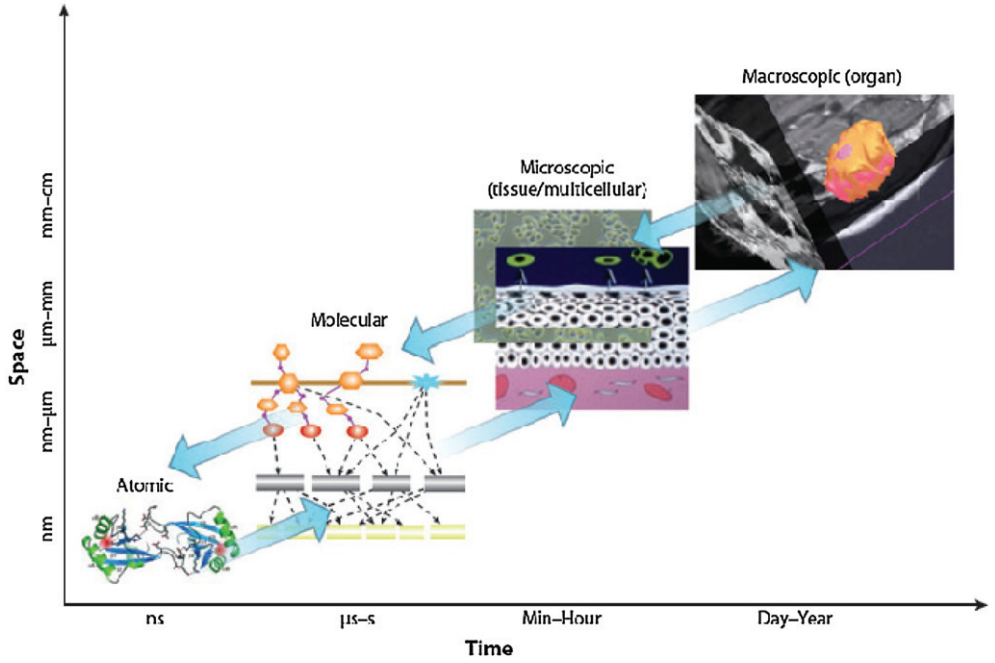

Figure 8. A depiction of multiscale-modelling framework of tissue (tumour) radiation response along the time and space axes. (a) Tumour growth model (reproduced with permission from Deisboeck *et al* (2011) *Annu. Rev. Biomed. Eng.* **13** 127–55. Copyright 2011 by Academic Press). (b) Radiation response phases.

could be used as an indispensible resource to support application of such modelling schemes *in vivo* (Stamatakos *et al* 2002, Titz and Jeraj 2008, Vaidya *et al* 2012).

In a more recent review, Wang (2010 suggested using MC methods in conjunction with the LQ model in a time-dependent bottom-up fashion to mitigate uncertainty issues with current radiobiological models in modern radiotherapy (Wang 2010). In our view, a comprehensive

multi-scale approach that can span spatial and temporal changes could be represented as depicted in figure 8, which would encompass the multi-scale parts of the tumorigenesis (atomic, molecular, tissue, organ) and the various multi-scaled radiation-induced response stages (i.e. physical, chemical and biological) over the spatial and temporal axes.

5. Conclusions

Monte Carlo techniques have been successfully applied for calculating radiotherapy dose distributions, treatment plan evaluation and uncertainty estimates, modelling tumour growth and simulating particle track structures. However, their application for radiobiological modelling of response and treatment outcomes in radiotherapy has been limited thus far. In this review, we have presented an overview of the emerging role that MC can play as a computational vehicle for radiobiological modelling in radiotherapy. We provided a brief review of TCP/NTCP modelling using analytical and multi-metrics approaches. We presented the current application of MC in radiobiological modelling in radiotherapy as a tool for estimating analytical models' uncertainties, dose recalculation in multi-metric techniques to improve dosimetric accuracy, modelling tumour growth, and its role in particle structure track simulation. We provided several demonstrative examples of these MC applications and presented the main features of some representative track structure codes highlighting their current abilities and limitations. Finally, we discussed the current challenges for MC application in radiobiological modelling in radiotherapy and presented some potential future directions based on multi-scale computing systems (ie systems radiobiology). To recapitulate, we believe that a new dawn of *in silico* radiotherapy is breaking through and MC methods are expected to be one of its main shining computational vehicles.

Acknowledgments

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