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A radiobiological model of radiotherapy response and its correlation with prognostic imaging variables

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Abstract

Radiobiological models of tumour control probability (TCP) can be personalized using imaging data. We propose an extension to a voxel-level radiobiological TCP model in order to describe patient-specific differences and intra-tumour heterogeneity. In the proposed model, tumour shrinkage is described by means of a novel kinetic Monte Carlo method for inter-voxel cell migration and tumour deformation. The model captures the spatiotemporal evolution of the tumour at the voxel level, and is designed to take imaging data as input. To test the performance of the model, three image-derived variables found to be predictive of outcome in the literature have been identified and calculated using the model's own parameters. Simulating multiple tumours with different initial conditions makes it possible to perform an *in silico* study of the correlation of these variables with the dose for 50% tumour control (TCD₅₀) calculated by the model. We find that the three simulated variables correlate with the calculated TCD₅₀. In addition, we find that different variables have different levels of sensitivity to the spatial distribution of hypoxia within the tumour, as well as to the dynamics of the migration mechanism. Finally, based on our results, we observe that an adequate combination of the variables may potentially result in higher predictive power.

Keywords

radiobiology; TCP; imaging; mechanistic models

1. Introduction

The personalization of radiotherapy (RT) treatments requires a comprehensive understanding of the radiobiology of tumours. Computational simulations provide a powerful, safe, flexible and inexpensive ground to test different radiobiological models and treatment strategies. In addition, a large number of *in silico* tumour radiobiology models have been developed in the past few decades (Marcu et al. 2012; Sanga et al. 2007). However, it remains a challenge to find a compromise between (i) the need for highly complex and specific models defined at the microscopic level, (ii) the use of patient-specific parameters that can be extracted from data that are widely available in the clinic, and (iii) implementation through a mathematical framework that is simple enough to be run and validated on very large patient cohorts.

Traditionally, macroscopic models of radiotherapy-induced cell kill for doses of around 2 Gy per fraction have been built upon the linear quadratic (LQ) model (Fowler 1989), with additional corrections for radioresistance due to hypoxia (Buffa et al. 2001) or tumour growth kinetics (O'Donogue 2009). The formalism can also be adapted to the specific characteristics of a disease, such as glioblastoma, for which several mechanisms have been proposed to describe the dynamical equilibrium between cancer stem cells and differentiated cancer cells (Leder et al. 2014; Yu et al. 2015).

Recently, a model also inspired by the LQ model introduced a further level of complexity with respect to classical models by focusing on tumour voxels or *tumourlets*, rather than the whole tumour (Jeong et al. 2013; Jeong and Deasy 2014; Robinson et al. 2015). Population equations are applied to describe key processes such as proliferation and cell loss, and within each tumourlet cells are classified according to nutrient availability in order to explain the interplay between proliferation and hypoxia. However, these models stop short of addressing differences between patients.

Some models include microscopic descriptions of tumour biology by simulating individual cells and their interactions (Harting et al. 2007; Starnatakos et al. 2001). These models are limited by computer memory, which restricts the size of the simulations to the order of millimeters. Multiscale models have been successful in merging a macroscopic description of treatment response with a sophisticated model of the underlying biological processes at different spatial scales (Dionysiou et al. 2004; Dionysiou et al. 2006; Sanga et al. 2007). In general, however, it is still hard to tune these models to clinical data that may be obtained routinely, such as molecular imaging; and they require advanced computational resources.

There is a growing interest in multiscale models that can be personalized to each patient by using imaging data (Marcu et al. 2015). Such models have used multi-parametric magnetic imaging resonance (MRI) data (Casares-Magaz et al. 2016), or positron emission tomography (PET) data, with different radiotracers and sometimes combined with computed tomography (CT) (Jennings et al. 2015; Titz and Jeraj 2008). To be fully validated, predictions need to be checked with imaging data at multiple points in time. This requires an adequate description of tumour shrinkage, to which there are no easy solutions. Some models have incorporated geometric algorithms (Stamatakos et al. 2002), conformal shrinkage models via the centre of mass algorithm (Antipas et al. 2004), or random exchanges of cells between voxels (Espinoza et al. 2015), whereas others ignore shrinkage (Jeong et al. 2013; Titz and Jeraj 2008).

The aim of the present study is to develop a robust and personalizable tumour control probability (TCP) model that captures the most important voxel-level radiobiological processes, describes the process of tumour shrinkage, and can be cross-checked against longitudinal molecular imaging, while adding only minimal complexity with respect to the classical radiobiological models. This is the main difference with respect to multiscale models, which provides an advantage in terms of transparency and computational cost. The model we propose has the following characteristics:

- i. Starting from a previous single-voxel TCP model (Jeong et al. 2013), the model introduces new elements to describe patient-specific differences and intra-tumour heterogeneity.
- ii. The model incorporates a new, robust method based on kinetic Monte Carlo to simulate tumour shrinkage through cell migration and tumour deformation that respects time scales and can therefore be tuned to measurements.
- iii. The model is solved in discrete time steps, which allows for a simple simulation of non-standard fractionation schemes.
- iv. The model describes the spatiotemporal evolution of the tumour at a voxel level, and is designed to take imaging data as input.

The main goal of this extension is therefore not to improve the overall performance of the previous model, but to be able to personalize the prediction to each patient by using imaging data.

To illustrate the new concepts, several imaging-based variables found to be predictive of treatment outcome in the literature are studied using *in silico* tumours with different ranges of hypoxia. The imaging variables are re-defined in terms of model parameters, and correlated with tumour control doses. Different assumptions about tumour shrinking mechanisms are tested and the results are compared. These are the first steps towards using the model in conjunction with longitudinal patient imaging data to obtain personalized tumour control probabilities.

2. Materials and methods

Figure 1 summarizes the key processes that take place during the simulation. We will first explain the main aspects of the baseline model (steps 1–2 in Figure 1), and then discuss the new elements and techniques introduced in this paper (step 3 in Figure 1).

2.1. Single-voxel TCP model

Within the model, tumours are assumed to be composed of small, PET-voxel-size *tumourlets* ($4 \times 4 \times 4 \text{ mm}^3$)[‡]. Cells can be in one of three states, according to their access to oxygen and glucose. This classification also dictates their metabolic activity and radiosensitivity.

Proliferative cells have access to all nutrients and are thus able to divide normally; intermediately hypoxic cells have access to glucose, but not oxygen, and therefore do not divide; extremely hypoxic cells have no access to oxygen nor glucose, and are in a quiescent or dying state. Intermediately and extremely hypoxic cells, both of which are deprived of oxygen, have increased radioresistance. These three classes are seen mathematically as fixed-size compartments[§] which fill up successively: cells prefer to be in the proliferative compartment, otherwise in the intermediate compartment, and finally in the extremely

[‡]The size of a PET voxel defines the smallest unit of metabolic information we can get from the image, and therefore the smallest scale that is relevant to the model.

[§]The underlying assumption being constant perfusion over the course of RT.

hypoxic compartment. Table 1 contains a summary of the characteristics of each cell compartment.

Cells are not simulated individually. Instead, the processes of proliferation, cell loss and cell kill are captured by probabilistic radiobiological equations that describe population averages. Cells damaged by RT become doomed (as calculated by the linear-quadratic model (Brenner et al. 1998) with a compartment-specific radiosensitivity), and die when they get to the proliferative compartment and attempt mitosis. As cells die and space becomes available in more nutrient-rich compartments, there is a ‘reclassification’ of cells which results in the reoxygenation of the tumourlet.

This model has been used to describe fraction size effects, reoxygenation, the relationship between FDG-avidity and tumour radioresistance, among others (Jeong et al. 2013; Jeong and Deasy 2014; Robinson et al. 2015). In all cases, the studies assume inter- and intra-tumour homogeneity: only one voxel with a standard hypoxia level is simulated, and the result is extrapolated in three dimensions. This paper presents a natural extension of the model to account for intra-tumour variability due to heterogeneous oxygen/glucose supply.

2.2. Multi-voxel TCP model: Kinetic Monte Carlo

2.2.1. Heterogeneity and stroma—Tumours tend to have heterogeneous vasculature, and the resulting low perfusion regions develop significant levels of hypoxia (Gillies et al. 1999). Within the context of the TCP model described in Section 2.1, blood flow translates into a particular configuration of cell compartment sizes: for example, a well-perfused tumourlet has a large P compartment, while a poorly perfused one has larger I and H compartments. A heterogeneous tumour is then represented by the combination of multiple tumourlets with different P , I and H compartment sizes. The model makes the assumption that the vasculature does not change significantly during treatment, so compartment sizes remain constant in time (Jeong et al. 2013).

During the course of RT, however, tumours undergo structural changes, which may include the formation of fibrotic stroma (Junker et al. 1997), or the enlargement of extracellular space due to apoptosis or necrosis (Kauppinen 2002). In order to account for these effects we introduce a new ‘stromal’ cell into the simulation. The simulation starts with no stromal cells within the tumour, but as the treatment progresses they invade space previously taken up by tumour cells, exerting inwards pressure on the lesion. For simplicity, we assume that there is an infinite supply of such cells surrounding the tumour. We also assume that the tumour cells’ FDG-avidity and their aggressiveness in the competition for resources are much greater than those of stromal cells. As a result, stromal cells behave within the model as inert, generic space-fillers that could also be seen as an agnostic way to quantify changes in tumour cell density.

2.2.2. Kinetic Monte Carlo—In order to fully describe changes in tumour volume, we propose a dynamic description of cell migration between neighbouring voxels, in which cells follow the directions defined by the nutrient gradients. This process is implemented via a kinetic Monte Carlo (KMC) algorithm (Bortz et al. 1975; Voter 2007).

KMC refers to a class of algorithms based on random sampling that describe the dynamical evolution of a system with multiple states; the transition from one state to another depends on a given transition rate. Kinetic Monte Carlo algorithms are widely used in condensed matter physics, chemistry and biophysics to describe processes as diverse as antibiotic translocation through proteins, the chemistry of interstellar dust grains or graphene growth (Ceccarelli et al. 2012; Cuppen et al. 2013; Lloyd-Williams et al. 2012). The type of KMC used here is commonly referred to as ‘rejection-free’ (rfKMC), and the basic ideas behind it are depicted in Figure 2a. Essentially, the algorithm selects which transition should happen next, using the transition rates as probabilities for particular interactions to occur. The most important property of KMC is that if (i) the transition rates are correct, (ii) the processes are independent and (iii) Poisson statistics apply, then one obtains the correct time scale for the whole process.

To calculate the transition rates, we assume that cell migration results in an approximately constant cell density across the tumour. Transition rates are therefore proportional to differences in cell density and are only non-zero for nearest and next-to-nearest neighbouring tumourlets. The migration process is repeated iteratively until the transitions have stabilized and the cell density has reached the nominal value within a margin of error $< 0.001\%$. As shown in Figure 2b, the simulation goes through the entire procedure on every step of the simulation, which corresponds to intervals of one hour.

The rate of cell kill is lower in hypoxic areas of the tumour, due to the oxygen enhancement ratio (OER). This results in higher cell densities, and effectively means that the transition rates also follow the gradient of nutrients in the tumour. Figure 3 shows the effective transition rate of each tumourlet laid over contour plots of the total number of cells and the number of intermediately hypoxic tumour cells. The effective transition rates point away from the region with higher concentration of intermediately hypoxic cells and towards the less dense, proliferating area of the tumour.

Note that the main advantage of rfKMC versus other random models is that it is capable of respecting the time dimension of the problem. Cell migration timescales have been ignored in this paper for simplicity, but the framework used opens the door to using data to tune the process in the future. In the meantime, one can easily obtain an approximate idea of the effects of adding in cell migration in the simulation by comparing to the results obtained when it is turned off; this defines a range of confidence around the expected true result.

2.3. Simulation

The full model proposed in this paper results from incorporating both the tumourlet heterogeneity and cell migration mechanisms described in Section 2.2 into the baseline single-voxel model explained in Section 2.1. To illustrate the properties of the model, multiple two-dimensional tumours are simulated^{||}. The tumour layers are approximately circular, with a radius of 5 tumourlets of $4 \times 4 \text{ mm}^2$, and are surrounded by stromal tissue.

^{||}Only one layer per tumour is simulated explicitly; we assume homogeneity along the third dimension for simplicity.

Each tumourlet has a different initial configuration of P , I and H cells, which is determined before the start of the simulation. The spatial distribution of the I compartment sizes is modelled according to a Gaussian function situated at the centre of the tumour. The amplitude ($I_{\max}$) determines the maximum level of hypoxia, and the standard deviation (σ_I) determine how much that value changes as a function of the radius, as illustrated in Figure 4. In these simulations, the H compartment is assumed to contain 20% of the tumour cells in all tumourlets, and the P compartment contains all the remaining cells. Once the initial configuration of the tumour has been set, the simulation of a radiotherapy treatment of daily 2 Gy fractions starts, proceeding through the stages depicted in Figure 2b.

2.4. Variables of interest

The ultimate goal of this model is to be used in combination with functional imaging to determine the initial heterogeneity. To this end, several image-derived variables found to be predictive of outcome in the literature have been identified and calculated using the model's own parameters. Simulating multiple tumours with different initial conditions makes it possible to perform an *in silico* study of the correlation of these variables with the dose for 50% tumour control (TCD₅₀) calculated by the model. The values of TCD₅₀ are calculated by extrapolating the results from the two-dimensional simulations up to a volume of approximately 7.7 cm³. The two-dimensional result is obtained as follows,

$$\text{TCD}_{50}^{2D} = \prod_i e^{-f_{sc} S_i}, \quad (1)$$

where i spans all the simulated tumour voxels, S_i is the total number of viable cells in each voxel, and $f_{sc} = 0.01$ is the expected fraction of stem-like cells (Hemmings et al. 2010; Jeong et al. 2013).

Fractional change in FDG SUV (δFDG): The relative change of FDG uptake measured during radiotherapy has been repeatedly found to be predictive of outcome for non small-cell lung cancer patients (Baardwijk et al. 2007; Edet-Sanson et al. 2012; Elmpt et al. 2012; Erdi et al. 2000; Giovacchini et al. 2009; Kong et al. 2007; Massaccesi et al. 2012). In our model, FDG uptake is assumed to be proportional to the number of proliferative and intermediately hypoxic tumour cells, with the latter taking up 50% more FDG per cell. This assumption is based on the observation that (i) hypoxic tumour cells enhance glycolysis to compensate for the lack of oxygen to produce energy, (ii) FDG-avid tumours tend to correlate with increased local failure (Ghooshkhaneh et al. 2014; Wang et al. 2013; Xie et al. 2011), and (iii) for the baseline TCP model, the best correspondence between FDG uptake and TCD₅₀ is obtained when one assumes that cells in the I compartment have enhanced FDG-avidity (Jeong and Deasy 2014). In this paper we study the relative fractional change in maximum FDG uptake observed 30 days after the start of treatment, $\delta\text{FDG} = \text{FDG}_{30}/\text{FDG}_1$.

Lower percentiles of perfusion histograms ($f_P^{(10\%)}$): Several dynamic contrast enhanced perfusion MRI (DCE MRI) studies performed on a cohort of cervical patients receiving

radiation and chemotherapy have highlighted the predictive power of DCE parameters obtained early during treatment (Mayr et al. 2010, 2012; Yuh et al. 2009). In particular, poorly-perfused tumour subregions (represented by low-DCE pixels) were quantified by the lower percentiles of the DCE-MRI signal intensity histograms. We define a corresponding variable within the model by assuming that the fractional sizes of the proliferative compartments (f_P) linearly correlate with perfusion levels. From the corresponding perfusion histograms we compute the 10th lower percentile, denoted $f_P^{(10\%)}$.

Malignancy: The ‘malignancy’ of a tumour (M) was defined using a phenomenological tumour control probability model derived from a kinetic model analysis of serial dynamic [^{18}F]fluoromisonidazole (FMISO) scans (Thorwarth et al. 2007, 2005). M was defined in terms of the kinetic parameters R , which characterizes the FMISO retention, and W_P , the perfusion efficiency,

$$M_i = 1 + \exp\left(\frac{bR_i}{W_{P,i} + c}\right), \quad (2)$$

where b , c are constants determined from fitting to data. The resulting TCP equation is

$$-\ln \text{TCP}(D) = a \sum_i M_i, \quad (3)$$

where a is an additional fit parameter. We study the right hand side of the equation by defining the following functionally equivalent variable,

$$M = \sum_i 1 + \exp\left(\frac{f_{I,i} + f_{H,i}}{f_{P,i}}\right), \quad (4)$$

where we have assumed that the FMISO retention is proportional to the sizes of the intermediate and extremely hypoxic compartments of each tumourlet, and the perfusion efficiency proportional to the size of the proliferative compartment.

3. Results

Seventy-two virtual tumours were simulated with different spatial distributions of perfusion and hypoxia, obtained by scanning uniformly over possible values for the Gaussian parameters that describe the sizes of the I compartments. Table 2 shows the exact values of the parameters scanned, as well as other simulation parameters. The simulations take the beginning of therapy as a starting point and describe the spatiotemporal evolution of the tumour under the effect of radiotherapy, as tumour cells go through the cell cycle. The impact on the results of the cell migration mechanism is evaluated by running each

simulation twice: the first one uses a fully interactive model in which voxels can exchange tumour and stromal cells, while the second one assumes that voxels are completely isolated. These two types of simulation will be referred to as 'migration' and 'non-migration', respectively.

3.1. Evolution of cell density

In the migration as well as in the non-migration simulations, the number of tumour cells per voxel (effectively, the cell density) decreases faster in well perfused areas than in hypoxic areas, as shown in Figure 5a for one of the tumour simulations. In non-migration simulations, the number of cells decreases globally in all voxels (that is, the tumour 'fades away'), so the enhancement in hypoxic regions is relatively small in effect. In migration simulations, the cell density decreases according to two opposing forces: on the one hand, the pressure exerted by stromal cells makes the tumour volume regress towards the geometric centre, while on the other, cells tend to migrate to regions with more resources. Due to the spatial symmetry of the simulations, the results are not very sensitive to this competition.

3.2. Evolution of hypoxia and stromal cells

The model naturally results in a process of tumour reoxygenation during radiotherapy. Reoxygenation is not modelled explicitly, but rather it is the result of hypoxic cells reclassifying into the proliferative compartment, where cells doomed by radiotherapy die attempting mitosis. Figure 6 shows the change in the number of cells in the hypoxic compartments as time progresses, for a migration (6a) and a non-migration (6b) simulation. By day 28, reoxygenation is complete. This process is qualitatively the same for migration and non-migration simulations.

In the migration simulations, and even more so in the non-migration ones, resistant regions correspond to initially hypoxic areas. In Figure 6, the regression of the tumour volume is indicated with a white line which corresponds to a tumour cell density of 50% of the nominal initial value.

Figure 6a shows how in migration simulations stroma cells replace tumour cells as these die and compress towards the centre of the tumour. This process does not exist in non-migration simulations, as shown in Figure 6b.

3.3. Changes in FDG uptake

The model predicts that maximum FDG uptake in each simulated tumour remains stable for a few days, after which it starts to decrease monotonically. Migration simulations prolong an initial period with the same values of maximum FDG, while in non-migration simulations the decrease starts days earlier, as seen in Figures 5b and 6. For the initial spatial configurations of hypoxia considered in our simulations, δFDG has values between approximately 0.25 and 1 in the migration case, and between approximately 0.1 and 0.75 in the non-migration case.

3.4. Predictive power of δFDG , $f_P^{(10\%)}$ and M

The values of TCD_{50} obtained for our assumed 7.7 cm^3 tumour are similar for migration and non-migration simulations, and range between 49 and 65 Gy, approximately. Figure 9 shows the three observables of interest correlated against TCD_{50} .

δFDG is positively correlated with TCD_{50} , with Spearman's correlation coefficients of $\rho_S=0.996$ and $\rho_S=0.953$ for the migration and non-migration simulations, respectively. The migration and non-migration predictions are qualitatively similar. However, the values of δFDG are consistently higher in migration simulations, and they saturate at 1, therefore losing predictive power in that region. Non-migration simulations are more scattered than migration simulations. This dispersion in TCD_{50} is explained mainly by the variation in σ_f , as shown in Figure 8a. The reason behind this dependence is discussed further in Section 4.

$f_P^{(10\%)}$ is strongly anti-correlated with TCD_{50} , with $\rho_S=-0.993$ and $\rho_S=-0.976$ for the migration and non-migration simulations, respectively. The two results are in agreement, and present little dispersion.

The malignancy M is correlated with TCD_{50} , with $\rho_S=0.981$ and $\rho_S=0.971$ for the migration and non-migration simulations, respectively. The two results are generally in agreement, although migration simulations tend to have lower TCD_{50} values, especially at high M . There is some dispersion in TCD_{50} , which increases with M . As seen in Figure 8b, the dispersion is the result of the combined effect of varying I_{max} and σ_f .

4. Discussion

We have presented the extension of a previous TCP model in order to account for spatial nutrient heterogeneity and the dynamic migration of cells within the tumour during radiotherapy. The model reproduces the spatial interplay between proliferation and hypoxia, and shows that various imaging-derived variables of interest are correlated with TCD_{50} , as observed clinically. This is a novel result that crucially depends on the addition of heterogeneity to the model. This enables the direct comparison with imaging data, and the exploration of other image-based predictive variables and treatment schedules.

In terms of computational performance, a 45-day treatment for a 10×10 -voxel simulation like the ones used here (including inter-voxel migration) takes approximately 30 minutes. If the condition on the accuracy of the cell density that has to be achieved is relaxed from $< 0.001\%$ to 0.1% , the computation time is reduced to 1 minute. Preliminary studies show that a three-dimensional simulation of a tumour with 5434 voxels contained within a grid of $12 \times 22 \times 13$ (approx. 67 cm^3) takes of the order of 1 hour with a margin of error of 1% on the target cell density. Having larger voxels would average out some of the intra-tumour variability, but it would speed up the simulation. Finding the right balance between speed, intra-tumour heterogeneity and cell density constraints will therefore have to be determined by data in a subsequent study, and it is likely to be disease-dependent.

The simplifications that the baseline model makes have been discussed previously (Jeong et al. 2013). Among the most important ones is the assumption that voxels receive a constant

supply of nutrients. This is supported by the observation that the functional vascularity in human tumours remains “unchanged or improves slightly” during radiotherapy, only diminishing gradually in the later part of treatment (Park et al. 2012). The main assumptions that we introduce in the present study are related to the mechanism of cell migration, which we have tested in comparison to the more naive scenario in which tumourlets do not interact with each other. We observe that when no interaction is allowed, the tumour cell density decreases almost uniformly in most voxels (Figure 5a). If we assume that no other cells replace those that die, then this scenario would correspond to a tumour that vanishes gradually, as opposed to the shrinking tumour that is more often observed clinically. The KMC cell migration mechanism allows us to describe the exchange of cells in a controlled way, including the passage of stromal cells that fill in the space left by dead tumour cells. Although here we only study the two extreme cases (migration on and off), in follow-up studies it would also be possible to introduce a parameter to control the mobility of each class of cells. Adding such a parameter would make it possible to tune the algorithm to match observed processes within the tumour microenvironment, such as measurements of cell mobility, or other type of longitudinal pathology analyses.

Although kinetic Monte Carlo has not been used before in this context, other studies have used Monte Carlo methods to simulate cell migration, such as Little 2007. However, in their model the migration happens between large-scale ‘compartments’ corresponding to, for example, bone marrow or blood. This is therefore a body-wide migration, different to the intra-tumour dynamics that is relevant for our study. Moreover, the migration mechanism presented here relies on transition probabilities between neighbouring voxels, while the migration in Little’s study has fixed, global rates and no a-priori spatial constraints.

The changes in FDG uptake and hypoxia obtained in the simulations agree qualitatively with the concept of a tumour that reoxygenates during radiotherapy and shows decreasing FDG-avidity. To validate the results it will be necessary to compare the predictions to images taken at different times during treatment. An increase in FDG uptake in the early stages of treatment has sometimes been observed (Baardwijk et al. 2007; Rege et al. 1993). This could be due to a stress reaction from tumour cells, or infiltration by scavenging and inflammatory cells (Baert and Hermans 2006). The baseline model used for this study does not account for dynamic changes in the vasculature (including angiogenesis), which means that the tumour can neither grow in volume nor increase the FDG uptake of the pre-treatment tumour. This issue can be addressed in a follow-up study by using perfusion imaging to model changes in vascularization. Nevertheless, having a simulation of the expected change in FDG ignoring those effects may potentially still be useful as a lower bound that could help identify good responders.

Our results show significant correlations between TCD_{50} and the observables of interest, which have a semi-empirical (M) or fully data-driven (δFDG and $f_p^{(10\%)}$) origin. The ability to interpret imaging quantities in terms of a mathematical model of tumour radiobiology may help to redefine the variables in order to achieve greater prognostic power. One possibility would be to determine ranges of validity for each variable, that could for example be defined as the ranges in which TCD_{50} is approximately linearly correlated with the

parameter. Figure 9 shows that the linear regions of the three variables do not fully overlap, which suggests that combining the three could potentially result in a more predictive parameter.

Of the three parameters studied, δFDG is the most sensitive to the effects of cell migration. This is expected due to the fact that it depends on the difference between two time points, and that it singles out one voxel in the calculation. This sensitivity can be exploited to tune the migration algorithm with the use of longitudinal imaging data. As mentioned above, the tuning parameter could be a new cell mobility parameter, since currently we assume that cells can move instantaneously between voxels. Alternatively, one could try to avoid this type of variable when using simulations, and rely on more robust observables that treat all voxels inclusively. The non-inclusive nature of δFDG is also the cause of the dispersion in TCD_{50} in the non-interactive case: the value of δFDG is mostly determined by the one voxel with $I_{\max}$, regardless of σ_I , while TCD_{50} depends on how hypoxic the other voxels in the tumour are as well. This makes TCD_{50} much more sensitive to σ_I than δFDG , and results in the observed dispersion.

Neither of the other two parameters ($f_p^{(10\%)}$ and M) are sensitive to cell migration. This makes them attractive candidates for studies with large patient cohorts where simulations may be costly, as our results indicate that it might be possible to simply suppress the migration step. It should be noted that because of the assumption that the spatial distribution of nutrients is constant during therapy, the calculation of $f_p^{(10\%)}$ is time-independent in our simulation. Adding time dependence to the nutrient delivery may introduce variability to $f_p^{(10\%)}$ if it is calculated at a later time point, as was done in the clinical studies (Mayr et al. 2010). We also observe that $f_p^{(10\%)}$ has a small dispersion along the TCD_{50} axis both in the interactive and non-interactive cases. This suggests that $f_p^{(10\%)}$ may behave as a surrogate of the ‘growth fraction’ parameter discussed in previous papers (Jeong et al. 2013; Jeong and Deasy 2014), which is highly correlated with tumour control.

Finally, the malignancy M is mostly insensitive to cell migration, but unlike $f_p^{(10\%)}$ it has a growing dispersion in TCD_{50} as M increases. This dispersion is explained by the heterogeneity parameters σ_I and $I_{\max}$. For example, two patients with the same TCD_{50} but with different levels of σ_I would have different M ; conversely, two patients with the same M may have different values of TCD_{50} depending on their $I_{\max}$.

5. Conclusion

In this work, a personalizable tumour control probability model that addresses intra-tumour heterogeneity was explored. The model builds upon a mathematical framework based on the conservation of chemical resources within tumour voxels, and describes the migration of cells between neighbouring voxels via a novel kinetic Monte Carlo algorithm (KMC). One of the main advantages of this method is that it is capable of respecting the timescale of the process described, and it can therefore be tuned to data. Several image-based variables found to be predictive of outcome in the literature were defined in terms of model parameters and

tested in tumour simulations with different spatial distributions of nutrients. The variables were found to be correlated with the tumour dose for 50% control (TCD₅₀). The 10th percentile of the perfusion histogram and the malignancy M were found to be robust against changes in the cell migration algorithm, unlike the changes in FDG uptake. The tumour malignancy M was found to be especially sensitive to the heterogeneity of the hypoxia distribution. In order to further tune and validate the algorithm, clinical datasets, ideally with functional images taken at multiple time points during treatment, will be required.

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Figure 1.

Schematic of the key biological processes of the model. Two neighbouring tumourlets with arbitrary compartment sizes are depicted at three different time points. Cells in the Proliferative compartment (P) are normoxic and proliferating. Cells in the Intermediately hypoxic compartment (I) are hypoxic and non-proliferating, but still metabolizing. Cells in the extremely Hypoxic compartment (H) are starving and non-proliferating. Steps 1 and 2 include processes that happen only within each tumourlet, following the method described in Jeong et al. 2013. In step 1, a fraction of the cells in each compartment gets 'doomed' due to radiation. After some of the doomed cells die after attempting mitosis, the remaining cells move to more nutrient-rich compartments in step 2. Step 3 represents the inter-tumourlet migration introduced in the present study. The figures are meant to be suggestive; the actual arrangement of various cells is highly variable.

Figure 2. Details of the simulation process

(a) Simplified schematic of the main steps of the rfKMC algorithm. The goal is to produce a succession of transitions with the right frequencies. In order to do this, the algorithm builds the cumulative sum vector of all transition rates (that is, $[r_{12}, r_{12} + r_{13}, \dots, R]$, where $R = \sum_j r_{ij}$). Then, a random number uniformly distributed between 0 and R is generated. The number will fall between two elements of the vector: this determines which transition occurs next. Because likely transitions have large transition rates, it is more likely that a random number will fall within their range. This is how the right dynamics is obtained.

(b) Flow chart of the full simulation process. 'Cell cycle' indicates mitosis and cell death, and 'reclassify' refers to the process in which cells move to a compartment with more nutrients if space is available. The ellipsis indicates that the flow lines corresponding to the remaining tumourlets have been omitted.

Figure 3.

Sample maps of the effective transition rates used as input to the rfKMC algorithm, overlaid on contour plots of the number of tumour cells in the *I* compartment (left) and the total number of cells (right). Red lines indicate regions of higher number of intermediately hypoxic tumour cells in the left panel, and higher total number of cells in the right panel. Each effective transition rate (i.e. each arrow) is obtained by adding vectorially all the transition rates originating from the same tumourlet and ending in its nearest and next-to-nearest neighbours.

Figure 4. Two examples of the profile distribution of I compartment sizes for two simulations with different values of σ_I and $I_{\max}$. Compartment sizes are normalized to 1.

Figure 5.

Time evolution of the transverse profile of the number of tumour cells (left) and of the maximum FDG uptake (right) of a simulated tumour with $I_{\max}=45\%$ and $\sigma_I=0.3$, both with and without cell migration. The numbers in the left panel indicate the number of days passed.

Figure 6.

Evolution of a simulated tumour with $I_{\max}=45\%$ and $\sigma_I=0.3$, with (left) and without (right) cell migration. The hypoxic core is off-centre in this particular simulation to better illustrate the properties of the simulation. Each panel contains the evolution in time of the total number of hypoxic tumour cells, the number of stromal cells, and the simulated FDG uptake. Dark blue equals zero density.

Figure 7.

Correlation of several imaging-based variables with TCD_{50} : δ FDG (left), $f_P^{(10\%)}$ (centre) and M (right). Each marker corresponds to a simulated tumour with different initial conditions of hypoxia, defined in terms of I_{max} and σ_I .

Figure 8. Correlation of (a) δ FDG and (b) M with TCD_{50} , plotted as a function of σ_I and colour-coded according to I_{max} . The simulations do not include migration.

Figure 9.

Three-dimensional scatter plot of δFDG , $f_P^{(10\%)}$ and M for the simulated tumours. Points falling in the region where δFDG is approximately linearly correlated with TCD_{50} are marked with a blue circle. Similarly, points falling in the region where $f_P^{(10\%)}$ and M are linearly correlated with TCD_{50} are marked with green squares and red crosses, respectively.

The ranges are $\delta\text{FDG} < 1$, $f_P^{(10\%) < 0.5$, and $M < 6$, and they are determined from visual inspection of the correlation plots between each of the variables and TCD_{50} .

Table 1

Cell compartments included in the model, and their main characteristics. OER stands for *oxygen enhancement ratio*. The ‘order’ refers to the compartment in which cells prefer to be, should enough space be available.

Compartment	Symbol	Oxygen	Glucose	OER	FDG-avidity	Order
Proliferative	<i>P</i>	✓	✓	1.0	1.0	1
Intermediately hypoxic	<i>I</i>	✗	✓	1.7 ^(a)	1.5 ^(b)	2
Extremely hypoxic	<i>H</i>	✗	✗	1.37 ^(c)	0	3

^(a) Approximate value, compatible with the range defined in Wenzl and Wilkens 2011.

^(b) Clavo et al. 1995; Jeong and Deasy 2014.

^(c) Chan et al. 2008. A reduced value of the OER is expected for extremely hypoxic cells due to chronic stress and the decreasing availability of homologous recombination.

Table 2

List of all the parameters used in the simulation, including those used to model nutrient heterogeneity and those belonging to the radiobiological evolution of the tumour. The values of the radiobiological parameters are taken from Jeong et al. 2013.

Parameter	Value
$I_{\max}$, Maximum I compartement size	30–70%, in steps of 5%
σ_I , standard deviation of I compartement sizes	0.1–0.8, in steps of 0.1
α	0.38
β	0.0576
Cell loss $t_{1/2}$	2 days
Lysis $t_{1/2}$	3 days
Cell cycle	2 days
Tumourlet volume	0.064 cm ³
Cell density	10 ⁹ cells/cm ³
Initial fraction of P cells in cell cycle	0.5
Surviving fraction post-mitosis	0.3