Published in final edited form as:

Phys Med Biol. 2016 May 21; 61(10): 3885–3902. doi:10.1088/0031-9155/61/10/3885.

An imaging-based computational model for simulating angiogenesis and tumour oxygenation dynamics

Vikram Adhikarla^{1,2} and Robert Jeraj^{3,4,5}

¹Department of Physics, University of Wisconsin, Madison, WI, USA

²Department of Radiology and Imaging Sciences, Emory University, Atlanta, GA, USA

³Department of Medical Physics, University of Wisconsin, Madison, WI, USA

⁴Department of Human Oncology, University of Wisconsin, Madison, WI, USA

⁵University of Ljubljana, Ljubljana, Slovenia

Abstract

Tumour growth, angiogenesis and oxygenation vary substantially among tumours and significantly impact their treatment outcome. Imaging provides a unique means of investigating these tumour-specific characteristics. Here we propose a computational model to simulate tumour-specific oxygenation changes based on the molecular imaging data. Tumour oxygenation in the model is reflected by the perfused vessel density. Tumour growth depends on its doubling time (T_d) and the imaged proliferation. Perfused vessel density recruitment rate depends on the perfused vessel density around the tumour ($sMVD_{tissue}$) and the maximum VEGF concentration for complete vessel dysfunctionality ($VEGF_{max}$). The model parameters were benchmarked to reproduce the dynamics of tumour oxygenation over its entire lifecycle, which is the most challenging test. Tumour oxygenation dynamics were quantified using the peak pO_2 (pO_{2peak}) and the time to peak pO_2 (t_{peak}). Sensitivity of tumour oxygenation to model parameters was assessed by changing each parameter by 20%. t_{peak} was found to be more sensitive to tumour cell line related doubling time (~30%) as compared to tissue vasculature density (~10%). On the other hand, pO_{2peak} was found to be similarly influenced by the above tumour- and vasculature-associated parameters (~30–40%). Interestingly, both pO_{2peak} and t_{peak} were only marginally affected by $VEGF_{max}$ (~5%). The development of a poorly oxygenated (hypoxic) core with tumour growth increased VEGF accumulation, thus disrupting the vessel perfusion as well as further increasing hypoxia with time. The model with its benchmarked parameters, is applied to hypoxia imaging data obtained using a [⁶⁴Cu]Cu-ATSM PET scan of a mouse tumour and the temporal development of the vasculature and hypoxia maps are shown. The work underscores the importance of using tumour-specific input for analysing tumour evolution. An extended model incorporating therapeutic effects can serve as a powerful tool for analysing tumour response to anti-angiogenic therapies.

Keywords

computational model; vasculature; angiogenesis; imaging-based modelling; tumour hypoxia; tumour growth; anti-angiogenic therapy

1. Introduction

The network of blood vessels in the human body carries the important task of delivering oxygen and nutrient supply as well as removal of cell waste. Similarly, the growth and development of a tumour is also dependent on this vasculature (Folkman 1976).

Angiogenesis, or the process of recruitment of new vessels from older ones, is critical to satiate the ever increasing demands of the tumour. Unlike vasculature in normal tissues, tumour vasculature is highly abnormal, immature, leaky and inefficient (Nagy *et al* 2009). This dysfunctional vasculature results in hypoxia, which can lead to both necrosis and an increase in tumour malignant potential (Vaupel and Harrison 2004). The abnormalities are a result of the haphazard regulation of numerous angiogenic processes which are tightly controlled in normal vessel growth (Carmeliet and Jain 2000). Understanding the biology and the timing behind these processes in a systematic manner is essential for designing treatment regimens for tumour eradication.

Tumour angiogenesis involves a cascade of complex signalling pathways. Tumour growth results in reduced vessel density and subsequently increased hypoxia. Hypoxic tumour cells secrete tumour angiogenic factors (TAFs) tilting the balance between the pro- and anti-angiogenic factors in the microenvironment towards increased pro-angiogenic factor concentration. The TAFs result in increased vessel permeability (Brown *et al* 1997) and angiogenesis. Vessel networking within the neovasculature establishes blood flow, decreases hypoxia and facilitates vessel maturation. A more detailed description and information on multiple modes of vasculature recruitment can be found in the literature (Pawelek and Knierim 1989, Carmeliet and Jain 2000, Bergers and Benjamin 2003, Karamysheva 2008). Typically the tumour is hypoxic as the perfused vasculature recruitment rate is unable to keep up with the tumour growth rate (Vaupel 1977). Thus the tumour has a high concentration of TAFs and its vasculature is leaky.

The biology of the angiogenic processes has been of interest to both experimentalists as well as computational researchers working on angiogenesis. Laboratory experiments and simulations complement each other to advance the science behind these processes (Sanga *et al* 2006). While laboratory experiments give researchers the much needed data and validations, computational models give researchers the fidelity to perform a variety of *in silico* experiments which would otherwise be highly expensive and time consuming to be carried out in a laboratory. *In silico* experiments also have the potential to give experimental researchers avenues to pursue in the laboratory (Jain *et al* 2007). To this end a number of models addressing different aspects of tumour growth and angiogenesis have been proposed.

Computational models of angiogenesis are typically categorized as discrete cellular level models, continuum models or hybrid models. Discrete models simulate cellular interactions at the microscopic scale demonstrating their capability to generate tree-like vascular

structures. Examples of techniques used in discrete models for vasculature generation include cellular automation, fractals, cellular potts etc algorithms (Stokes *et al* 1991, Bauer *et al* 2007). Continuum models take a different approach by focussing on the macroscopic tumour and vasculature dynamics typically based on the foundation of reaction-diffusion equations (Orme and Chaplain 1996, Levine *et al* 2001, Hogue *et al* 2006) demonstrating their dynamics over a much bigger spatial scale. Hybrid models incorporate both of these characteristics by using continuum models to simulate the broad spatial dynamics and discrete models to explicitly simulate vasculature (Plank and Sleeman 2003, Sun *et al* 2005, Milde *et al* 2008). These models include phenomenon such as random motility, chemotaxis, haptotaxis, cellular adhesion, proliferation and branching. Several vasculature models focus on the incorporation of flow (Gödde and Kurz 2001, Alarcón *et al* 2005, Bartha and Rieger 2006, McDougall *et al* 2006, Welter *et al* 2008, Liu *et al* 2011) and vasculature maturity (Arakelyan *et al* 2005, Cai *et al* 2011, Gevertz 2011, Perfahl *et al* 2011). An in-depth review of vasculature models can be found in literature (Mantzaris *et al* 2004, Scianna *et al* 2013).

Although, tumour models such as the ones mentioned above can simulate hypothetical tumour and vasculature behaviour, it is not possible to predict the dynamics of individual tumours. This is due to the inherent complexity of these growth dynamics which depend on the microenvironment as well as the characteristics of the particular tumour in question. The heterogeneity of its growth and response to therapy also hampers the treatment of cancer (Michor and Polyak 2010). Imaging provides a unique opportunity to gain knowledge about the tumour condition. Based on imaging data short term predictions about its growth and development can also be made. Imaging techniques such as computed tomography (CT), positron emission tomography (PET), magnetic resonance imaging (MRI) and ultrasound are non-invasive and are routinely used in the clinics. PET and MRI are capable of providing functional as well as molecular information about the tumour microenvironment. Examples include perfusion, blood volume, permeability, angiogenesis, oxygenation levels, and cell proliferation (Matsumoto *et al* 2009, Michalski and Chen 2011, Stephen *et al* 2012, Buscombe and Wong 2013).

Acknowledging the power of imaging, modelling of tumour and vasculature based on imaging data has been steadily gaining importance. Swanson and colleagues developed a model describing the invasion patterns of gliomas using MRI images (Swanson *et al* 2000, 2003, Jbabdi *et al* 2005). This model has since been enhanced to investigate how the proliferation and dispersal of glioma cells can affect tumour malignancy (Swanson *et al* 2011). Recently, the model was applied incorporating the effects of hypoxia-mediated radiation resistance to predict therapeutic outcome (Rockne *et al* 2015). Yankeelov *et al* (2010) proposed a methodology to incorporate PET, MRI and SPECT imaging data into a reaction-diffusion based mathematical model though explicit imaging data was not used. In a different work (Yankeelov *et al* 2013) they used MRI and FDG imaging data to simulate tumour growth and the evolution of its glucose concentration with time. Titz and Jeraj (2008) proposed a PET imaging-based model to simulate the effect of radiotherapy on tumour growth and subsequently advanced the model to simulate response to anti-angiogenic therapy based on hypoxia and proliferation data (Titz *et al* 2012) although the explicit modelling of vasculature dynamics was not proposed. Explicit modelling of

imaging-based vasculature growth is important to further advance our understanding of anti-angiogenic therapies and why and how they fail.

Here we propose an imaging-based model simulating the temporal changes in tumour vasculature and its related tumour oxygenation based on molecular imaging data. The model uses the hypoxia PET imaging data to characterize tumour oxygenation status and proliferation PET imaging data to characterize tumour growth. We build upon a previous work where a stochastic model for the simulation of the vasculature based on a hypoxia PET scan was proposed (Adhikarla and Jeraj 2012). The current work extends the model to incorporate tumour growth and angiogenesis based on the molecular imaging as well as literature-based experimental data. The model is benchmarked to reproduce the observed temporal dynamics of tumour oxygenation in a xenografted mice tumour. The effects of model parameters on tumour oxygenation were analysed and the benchmarked parameters were then applied to preclinical imaging data.

2. Description of the model

2.1. Model workflow

To simulate the growth of tumour vasculature over time, the model uses imaging inputs related to tumour oxygenation and tumour proliferation. Figure 1 demonstrates the model workflow.

2.1.1. Calculation of perfused vessel density (Step I).—Tumour oxygenation map is derived from its hypoxia map using a functional relationship as described in earlier works (Lewis *et al* 1999, Titz and Jeraj 2008, Adhikarla and Jeraj 2012). A previous work (Adhikarla and Jeraj 2012) quantified the amount of vasculature present in the microenvironment based on its oxygen tension with higher vessel density reflecting higher oxygen tension (equation (1)).

$$pO_2 = 60 \frac{sMVD^{1.95}}{sMVD^{1.95} + 0.015^{1.95}} \text{mmHg} \quad (1)$$

The simulated microvessel density (sMVD) used as a model parameter reflects the percentage of the tissue volume occupied by the capillaries. Thus given the hypoxia imaging data, the microvessel density of each voxel could be obtained.

2.1.2. Calculation of non-perfused vessel density.—At the start of the simulation all the vessels are assumed to be perfused. Alternately, estimates of the non-perfused vessel density could be obtained from additional imaging; such as measurement of tumour blood volume using dynamic PET or MR imaging data.

2.1.3. Tumour angiogenic factor concentration (Step II).—Hypoxic tumour cells secrete angiogenic factors which diffuse in the micro-environment to initiate the process of vascular recruitment. The concentration of the angiogenic factor in the tumour micro-

environment can be calculated by numerically solving its diffusion equation (equation (2)). Data on vascular endothelial growth factor (VEGF) which is one of the prime angiogenic factors has been used.

$$\frac{dc_{\text{VEGF}}}{dt} = D_{\text{VEGF}} \nabla^2 c_{\text{VEGF}} - \lambda_{\text{VEGF}} c_{\text{VEGF}} - Q_{\text{VEGF}} + S_{\text{VEGF}} \quad (2)$$

Where c_{VEGF} is the VEGF concentration, D_{VEGF} is the diffusion coefficient of VEGF in the tissue, λ_{VEGF} is the decay rate of VEGF in tissue, Q_{VEGF} is the VEGF consumption rate and S_{VEGF} is the VEGF secretion rate. Details regarding the implementation of the diffusion equation and the calculation of c_{VEGF} at the voxel level are presented in the supplementary material section (stacks.iop.org/PMB/61/3885/mmedia).

Increased hypoxia results in increased secretion of the angiogenic factors. Work done by Leith and Michelson (1995) on HCT-8 and Clone-A cells *in vitro* has been used to quantify this relationship (supplementary material) between the secretion rate of VEGF and the tumour oxygen tension. Unless explicitly stated, the secretion rate characteristics of VEGF by the HCT-8 cell line have been used in the presented work.

2.1.4. Change in total vessel density (Step III).—The growth rate of vasculature depends on the amount of angiogenic factor in the tumour microenvironment. Higher concentration of the angiogenic factor results in increased vessel growth. The amount of vessel growth depends specifically on the particular angiogenic factor. The total vessel density ($\text{sMVD}_{\text{total}}$) after time t_{sim} can be calculated as:

$$\text{sMVD}_{\text{total}}(t + \Delta t_{\text{sim}}) = \text{VGR}(c_{\text{VEGF}}, \Delta t_{\text{sim}}) \times \text{sMVD}_{\text{total}}(t) \quad (3)$$

Where VGR is the vasculature growth ratio reflecting the growth rate of the vasculature and is directly dependant on the concentration of VEGF and is calculated (supplementary material) based on the study by Ferrara and Henzel (1989).

2.1.5. Change in perfused vessel density (Step IV).—Vessel functionality depends on the growth of vessels, their subsequent networking with each other and the establishment of blood flow thereafter. Tumour blood vessels are however leaky, tortuous and of uneven diameter. Notably, VEGF was discovered initially as the vasculature permeability factor (VPF). This abnormal vasculature leads to erratic and reduced blood flow with tumour growth (Nagy *et al* 2009). Given these characteristics of tumour vessels, the following assumptions have been made to derive equation (4) for the generation of perfused vasculature:

- a. Vessels with blood flow will originate from vessels that are already perfused.
- b. Increased VEGF concentration will increase the permeability and hence reduce the flow downstream (Brown *et al* 1997).

$$\Delta sMVD_{\text{perf}} = \text{PRC} \times \log\left(\frac{\text{VEGF}_{\text{max}}}{c_{\text{VEGF}}}\right) \times sMVD_{\text{perf}} \times \Delta t_{\text{sim}} \quad (4)$$

The amount of perfused vasculature recruited in a simulation time-step (t_{sim}) is limited by the total amount of vasculature recruited in that time-step. To evaluate vasculature perfusion, a vessel perfusion index (VPI) reflecting the percentage of perfused vasculature is defined.

$$\text{VPI} = \frac{sMVD_{\text{perf}}}{sMVD_{\text{total}}} \quad (5)$$

2.1.6. Tumour growth (Step V).—Changes in vessel density are governed by vascular as well as tumour growth rate. The growth rate of the tumour is determined by the doubling time of the particular tumour cell line in question. Titz and Jeraj (2008) simulated the growth in the number of tumour cells based on tumour proliferation map, which is the same as used in this work.

2.2. Model mechanics

2.2.1. Simulation of vasculature.—The simulation of vasculature structure based on tumour oxygenation has been previously described (Titz and Jeraj 2008, Adhikarla and Jeraj 2012). Briefly, all vessels are simulated as cylindrical elements of equal lengths and diameters and are assumed to have equal oxygen concentration within them. Further details regarding the simulation of vessels are provided in the supplementary materials and the previous publication (Adhikarla and Jeraj 2012).

2.2.2. Voxel coupling.—Tumours remain avascular till they attain a diameter of about 1–2 mm (Bergers and Benjamin 2003). After this stage they recruit vasculature from the feeding vessels which emerge from the existing vasculature and branch out to form a very dense network of vessels by the time they reach the tumour (Muthukkaruppan *et al* 1982). To simulate this phenomenon of vasculature recruitment from outside the tumour, the following method is employed. The tissue directly adjacent the tumour is kept at a constant vessel density of $sMVD_{\text{tissue}}$ which is a model parameter. Folkman (1976) found the maximum velocity of vessel growth from the surrounding tissue to be 1 mm d^{-1} . Hence within a simulation time-step of t_{sim} days each voxel of the tumour is assumed capable of recruiting vasculature from a distance of $d = t_{\text{sim}} * 1 \text{ mm}$. To incorporate this recruitment capability, the total and perfused vessel density recruited within a particular voxel is calculated as the average values of $sMVD_{\text{total}}$ and $sMVD_{\text{perf}}$ calculated within a cube of side $2d$ centred on that voxel.

2.2.3. Tumour growth.—The tumour is considered to have uniform cellular density. Since all the voxels are equi-volumetric, each voxel of the tumour is assumed to contain N tumour cells. The growth rate of tumour is determined by the doubling time of the particular

cell line. Given this doubling time and the voxel growth fraction, the change in the number of tumour cells in a simulation time-step within the voxel can be calculated. A change in the number of tumour cells determines the change in volume of the voxel. Details on the algorithm employed to simulate changes in the simulation matrix are provided in the supplementary material. Volumetric increase of a particular voxel cuts down the corresponding vessel density of the voxel by the same factor.

2.2.4. Simulation procedure.—To simulate vasculature dynamics *in silico*, a spherical tumour is padded with tissue with a uniform vessel density of $sMVD_{tissue}$. The avascular tumour is then allowed to grow as previously explained. Once the tumour reaches the diameter of 2 mm, the angiogenic switch is switched ‘on’ and vessel recruitment begins. The VEGF concentration for each voxel is calculated as mentioned in section 2.1. The voxel coupled new total and perfused vessel densities are calculated using equations (3) and (4) while also taking the volumetric change of the tumour voxel into account. Voxel specific oxygen tensions of the expanded tumour are recalculated and the non-tumour tissue is reinitialized to $sMVD_{tissue}$ again. For a given simulation, $sMVD_{tissue}$ is assumed to be constant and the vessel perfusion outside the tumour is assumed to be 100%. Once the new vessel density map is calculated, the vasculature is again simulated as determined by the regional vessel density. Table 1 includes the parameters used for vasculature simulation.

3. Materials and methods

3.1. Benchmarking model parameters.

The dynamics of tumour oxygenation is the result of the interplay between the vasculature and tumour growth. Nöth *et al* (2004) evaluated the dynamics of tumour oxygenation in a xenografted mouse tumour over its entire lifecycle using ^{19}F -MRI by studying the longitudinal relaxation rate ($1/T_1$) of perfluorocarbon that was injected along with tumour cells. Since the reproduction of vasculature dynamics over the entire tumour growth lifecycle is the most challenging test, this experiment was chosen as the benchmark experiment. The model was applied to reproduce these trends of a growing tumour by tuning the following parameters: $sMVD_{tissue}$, PRC and $VEGF_{max}$.

In order to reproduce experimental results, tumour was simulated as a volume with uniform vessel density (reflecting pO_2) on a Euclidian computational matrix. Initial tumour volume depended on the experimentally observed doubling time and the timing when the angiogenic switch is ‘on’ (diameter 2 mm). The timing of this switch (angiogenic switch ‘on’) was taken as the time when the pO_2 of the experimental tumour was at the minimum. The voxel resolution of the matrix (112 μm) was chosen such that a significant initial volume could be assigned to the tumour on the computational matrix, as well as to accommodate its volumetric growth for the required number of days.

3.2. Sensitivity study

To characterize the impact of the model parameters on the tumour oxygenation, a sensitivity study of the model parameters was performed by varying each parameter individually by

$\pm 20\%$. The changes in peak tumour pO_2 (pO_{2peak}) and the time to peak tumour pO_2 (t_{peak}) were quantitatively evaluated. These parameters include:

Variation in tumour-associated parameters: T_d and cell line.

Variation in vasculature-associated parameters: PRC, $sMVD_{tissue}$ and $VEGF_{max}$.

3.3. Microenvironmental characteristics

Tumour-vasculature growth impacts a variety of microenvironmental characteristics that are important indicators of the tumour condition. Mean oxygenation and perfusion values mask the spatial variation of these characteristics. Extremely hypoxic and underperfused regions might increase tumour aggressiveness or might hamper drug delivery. Spatio-temporal quantification of the vessel perfusion index (VPI), VEGF concentration as well as tumour pO_2 has been done and shown.

3.4. Model application

The model was applied to imaging data obtained from imaging a TRAMP mouse tumour. Mice were injected with $[^{64}Cu]Cu$ -ATSM radiotracer and a PET scan was acquired, the duration of which was 60 min. Average uptake over this scan period was used as a surrogate of hypoxia distribution. Further scan details have been described elsewhere (Adhikarla and Jeraj 2012). The original PET data was then resampled to the desired simulation resolution chosen based on the feasibility of the computational calculations involved. Using an empirical relationship between Cu-ATSM SUV and tumour pO_2 (Lewis *et al* 1999), the hypoxia scan was then converted to a map of tumour pO_2 as has been shown earlier (Titz and Jeraj 2008, Adhikarla and Jeraj 2012). The doubling time of the TRAMP cell line was assumed to be of the same for each voxel.

To simulate tumour oxygenation dynamics, the following two vasculature parameters were tuned from the theoretical simulation case: perfusion rate constant (PRC) and the $sMVD_{tissue}$. For this purpose, the pO_2 at the tumour edge was assumed constant and the rate of change in the mean tumour oxygenation compared to the theoretical case, was normalized by the doubling time ratio of the imaged TRAMP and the xenograft tumours.

4. Results

4.1. Benchmarking model parameters

Figure 2 shows the oxygenation trends observed in the xenograft tumours (Nöth *et al* 2004); with an initial decrease in tumour oxygenation followed by a sharp rise and eventually followed by a slow decrease in oxygen tension. The model parameters (PRC, $sMVD_{tissue}$, $VEGF_{max}$) were tuned to reproduce these trends. The initial decrease in tumour pO_2 reflects tumour growth without vasculature recruitment. The sharp rise and eventual decrease in tumour pO_2 results from vasculature recruitment from surrounding tissue and the tumour growth rate outpacing the vasculature recruitment rate respectively. Variations between the simulated and the observed curve can be explained on the basis of variation in the doubling time of the tumour from its average value.

4.2. Sensitivity study

4.2.1. Variation in tumour-associated characteristics.—Tumour doubling time demonstrated the most significant impact on the time to peak pO_2 (t_{peak}) and the peak value of pO_2 (pO_{2peak}). 20% reduction in tumour doubling time reduces t_{peak} and pO_{2peak} by 27% and 31% respectively. An increase in doubling time demonstrates exactly opposite characteristics with reduced slope after the peak demonstrating the reduced rate at which hypoxia develops in the tumour. The tumour is thus significantly oxygenated even by day 26 (figure S2(a)). An increase of 20% in the doubling time increases t_{peak} by 34% and pO_{2peak} by 37%. Slower growing tumour also results in a delayed timing for the angiogenic switch. Tumour cell line impacts its pO_2 via the secretion rate of the angiogenic factors. Clone A cells secrete more VEGF (figure S1(a)) than the HCT-8 cells. This significantly hampers the recruitment of perfused vessels leading to 16% reduction in the t_{peak} and 37% reduction in pO_{2peak} .

4.2.2. Variation in the vasculature-associated characteristics.—Among the vasculature-associated parameters, the tissue vessel density ($sMVD_{tissue}$) had the biggest effect while $VEGF_{max}$ had the least effect on the tumour oxygenation. An increase in the pO_2 of the surrounding tissue leads to an increase in the tumour pO_2 due to the availability of increased number of perfused vessels from which the tumour can recruit its blood flow. While a 20% decrease in $sMVD_{tissue}$ results in 10% decrease in t_{peak} and 32% decrease in the pO_{2peak} , a 20% increase results in 8% increase in t_{peak} and 36% increase in pO_{2peak} . The effect of $VEGF_{max}$ on both t_{peak} and pO_{2peak} was about 5%. A 20% decrease in $VEGF_{max}$ decreases t_{peak} by 1% and pO_{2peak} by 6%. Corresponding 20% increase in $VEGF_{max}$ increases t_{peak} by 3% and pO_{2peak} by 4%.

The impact of PRC on tumour oxygenation was comparable to $sMVD_{tissue}$ with a 20% decrease in PRC decreasing t_{peak} by 14% and pO_{2peak} by 31%. A 20% increase in PRC increased t_{peak} by 3% and pO_{2peak} by 30%.

Figure 3 summarizes the results of the sensitivity study of model parameters. In general the changes in the peak values of the pO_2 are much greater than the changes in the timing of the peak pO_2 . The timing of the peak pO_2 (figure 3(a)) is influenced more by the tumour-associated parameters rather than vasculature-associated parameters. In contrast the value of peak tumour oxygenation (figure 3(b)) was similarly influenced by both tumour- and vasculature-associated parameters.

4.3. Microenvironmental characteristics

Figure 4(a) shows the temporal changes in the percentage of vessels perfused (VPI). At the time when the vessels are first recruited (day 3), the growth rate of vasculature ($sMVD_{total}$) is higher than the recruitment rate of perfused vasculature ($sMVD_{perf}$) due to higher VEGF concentration. This results in a sharp decrease in the vessel perfusion index corresponding to the sharp increase in pO_2 . The decrease in VEGF due to this vasculature recruitment results in a lower vasculature growth rate (of $sMVD_{total}$) in comparison to the perfused vasculature ($sMVD_{perf}$) growth rate. Hence there is an increase in the VPI. However, as the tumour grows, the VEGF concentration inside the tumour starts accumulating due to sheer volume

of the tumour (figure 4(b)). This results in increased total vasculature recruitment and a corresponding decrease in the recruitment of the perfused vessels.

Line profiles across the tumour quantitatively evaluating the values of voxel pO_2 and vessel perfusion index (VPI) are shown in figures 5(a) and (b) respectively. The decrease of both pO_2 and VPI towards the centre of the tumour can be seen.

4.4. Application to imaging data

4.4.1. Visualization of the tumour and vasculature growth.—Figure 6 demonstrates the application of the model to [^{64}Cu]Cu-ATSM PET imaging data from which the oxygen map was generated. Increased hypoxia and tumour volume can be readily seen with tumour growth. Similar results can be seen from the cross-sectional views across the tumour. Decreased vessel density can be seen in areas of low oxygen tension although the total number of vessels increases with time due to vasculature growth. Comparison of the vasculature-simulated hypoxia maps (figures 6(d)–(f)) and these hypoxia maps at the PET resolution (figures 6(g) – (i)) shows how significant local hypoxia clusters needs to be present for it to be localized well on the PET resolution scale.

5. Discussion

The developed angiogenesis model successfully reproduces the temporal changes in tumour oxygenation observed in literature. Keeping personalized therapy in mind, the model is able to simulate the growth of tumour and its vasculature using patient-specific molecular imaging data. A key advantage of the model lies in the incorporation of microscopic vasculature along with the imaging data. This provides the model the capability to bridge the gap between the microscopic and the macroscopic (PET imaging) scales and study the oxygenation transients at both scales. Sensitivity studies of the model parameters show how drastically the tumour oxygenation can vary with the cell line specific parameters such as tumour doubling time and VEGF secretion characteristics, as well as the surrounding tissue characteristics. The impact of the surrounding tissue ($sMVD_{\text{tissue}}$) has a huge effect on the fast-growing xenograft tumour. However, human tumours typically grow slower and thus the vessel density in the immediate vicinity of an imaged voxel will have a significant impact on the vasculature growth rate. This vessel density reflected by tumour hypoxia makes the imaged hypoxia map a very strong candidate for the required imaging input for the model. While $VEGF_{\text{max}}$ as a parameter had the least influence on evaluated peak tumour pO_2 , its importance increases with tumour size as the concentration of the angiogenic factor rapidly increases within the tumour due to accumulation within it.

Different trends in tumour oxygenation (figure 2) can be attributed to different stages of tumour growth. The initial decrease is attributed to the tumour expansion and a corresponding decrease in the vessel density. At this point the tumour is still in its avascular stage. The sudden increase in the pO_2 after this minimum is related to vasculature recruitment from the surrounding tissue. At a later time point the tumour surface area exposed to perfused vessels relative to its volume decreases significantly. Meanwhile the vessels inside the tumour are significantly under-perfused due to increased VEGF concentration in the microenvironment which hampers the formation of a well networked

and stable vasculature. This results in decrease in mean tumour pO_2 with time and the formation of a hypoxic core at a later stage.

Changes in tumour VEGF concentration are typically attributed to changes in its hypoxia status. In line with this assumption, figure 4(b) demonstrates VEGF concentration trends that are exactly opposite of the trends observed in tumour oxygenation (figure 2). The initial spike in VEGF concentration is small compared to the concentration when the tumour develops a hypoxic core. While the magnitude of this initial spike depends on the TAF secretion characteristics of the cell line, another factor that is of importance here is the tumour size. For a smaller tumour, with a large surface area to volume ratio, more TAF is able to diffuse into the surroundings than remain within the tumour leading to lower concentration of tumour TAF. The concentration of TAF might also be dependent on non-hypoxia related factors. Incipient angiogenesis independent of the tumour hypoxia status was observed by Hendriksen *et al* (2009). Thus owing to contributions from non-HIF-1 α mediated pathways, the amount of angiogenic factor in the tumour microenvironment might be much higher than calculated by the model.

In the presented model, vasculature endothelial growth factor (VEGF) has been used as the sole angiogenic factor in question. Different tumour cell lines secrete both different concentrations as well as different types of angiogenic factors (Hasina *et al* 2008). The site of the tumour and the endothelial cells present are also potential variables affecting the response of vasculature to the angiogenic factor in question. Work by Ferrara and Henzel (1989) from which the vasculature growth ratio in response to VEGF (figure S1(b)) has been used, demonstrates how the growth rate of endothelial cells obtained from different tissue types can vary by a factor of four. Such changes in parameters influence the tumour oxygenation values significantly. Given how critical tumour oxygenation is for therapies (Nordsmark *et al* 2001) these factors show how important it is for models to incorporate tumour-specific data. These are however parameters that can be easily incorporated into the model by considering the tissue-specific vasculature recruitment characteristics of each type of angiogenic factor separately.

Simulations addressing large amounts of data often run into computational limitations and the current work is no exception. The tumour represented by a MATLAB matrix has to be small enough to ensure the computational efficiency of the tumour growth simulations. Thus, simulation of the tumour above a certain resolution is computationally challenging. Also, a sufficient number of tumour voxels need to be initialized such that the tumour growth algorithm registers a sufficient increase in the number of voxels. The simulation resolution of the tumour matrix (typically on the order of a few hundred micro-meters) is governed by these two conditions. The vasculature matrix could be simulated at a finer resolution than the tumour matrix and was done as such. However, it still fell short of the required minimum voxel resolution 20 μm (capillary diameter is assumed to be 20 μm), which would require a more powerful computational platform.

A potential problem that can arise while using voxel coupling to simulate vasculature recruitment from neighbouring tissue relates to the presence of hypoxia at the very edge of the tumour. This hypoxia at the tumour boundary decreased due to immediate access to well

perfused vasculature from outside the tumour. This may or may not reflect the actual hypoxia progression. Such potential problems can arise either due to use of a very aggressive tumour segmentation technique or if the tumour is surrounded by some anatomical constraint like the bone. Additionally, the tumour segmentation based solely on hypoxia imaging might not reflect the actual extent of the tumour. In such cases either the segmentation approach should be rechecked and/or an imaging-based value of $\text{sMVD}_{\text{tissue}}$ should be used.

In the presented model, the effect of tumour angiogenic factor on the vasculature is twofaced. On one hand, it increases the rate at which vasculature ($\text{sMVD}_{\text{total}}$) is recruited, and on the other it increases the permeability of the vessels leading to reduction vessel perfusion ($\text{sMVD}_{\text{perf}}$). A logarithmic dependence of the perfused vessel recruitment on the microenvironmental angiogenic factor concentration has been proposed. The advantage of this formulation is that it condenses the effect of vessel immaturity on the tumour oxygenation without incorporating additional parameters. Current imaging-based models do not incorporate vessel maturation in their framework. In the simulations performed, limited growth of vasculature ($\text{sMVD}_{\text{total}}$) has not had an impact on the oxygen dynamics since the total vasculature growth rate always being greater than the perfused vasculature recruitment rate. A more in depth modelling scheme explicitly modelling vessel permeability and maturation would be required to couple the total vessel density with the perfused vessel density.

While the parameters that impact the generation of vessel structure and its density are discussed in detail in a previous work (Adhikarla and Jeraj 2012), the presented model is calibrated (by tuning PRC , VEGF_{max} and $\text{sMVD}_{\text{tissue}}$) such that the rate of decrease of mean tumour $p\text{O}_2$ depends on the cell line doubling time and the rate of $p\text{O}_2$ decrease observed by Noth and colleagues in their experiment. However, further benchmarking the model against longitudinal imaging data will lend the model capability to successfully predict spatiotemporal changes in tumour hypoxia on a case to case basis. Apart from hypoxia and proliferation PET data that determine tumour oxygenation and growth rate, additional imaging data can be used to parameterize the model. Imaging $\alpha_v\beta_3$ integrins (Haubner *et al* 2005) using [^{18}F] Galacto-RGD can provide direct input about the level of angiogenic stimulus. This can help quantify model vessel recruitment parameter PRC that might change in between tumours and cell lines. Further validation of vascular parameters PRC and VEGF_{max} and a comprehensive picture determining the amount of vasculature and its quality can be obtained by using other imaging-based metrics such as blood volume, perfusion and vessel permeability. These measures can be derived from kinetic analysis of dynamic PET imaging or MRI data.

Anti-angiogenic drugs targeting tumour angiogenesis have faced numerous challenges owing to the complexity of angiogenesis and very few anti-angiogenic drugs have received FDA approval (Samant and Shevde 2011). Normalization of vasculature leading to efficient vascular network and better blood flow has been postulated as a consequence of anti-angiogenic drug treatment (Jain 2005). However, evidence of normalization has been controversial, its efficacy moderate and our understanding shallow (Bruce *et al* 2014). The time scales of normalization are still under investigation. The proposed model can prove to

be extremely beneficial in analyzing the maturation time frames affecting vascular perfusion. Evaluation of vessel maturation and perfusion changes to anti-angiogenic therapy and relating them to the doubling time of the tumour is a future direction of model application. Such modelling scheme might give possible hints on extrapolating the results to the timescales of human patients (order of months) and help in classifying patients who would benefit from the anti-angiogenic therapy. While modelling such therapies, it should not be forgotten that there are multiple angiogenic factors in play and the tumour might use other escape angiogenic pathways for vessel recruitment.

6. Conclusion

Incorporation of imaging data into tumour modelling is a powerful technique for studying the dynamics of tumour progression; eventually these models will find application in simulating tumour response to different therapies and for optimizing them. In the presented work, molecular imaging data related to tumour hypoxia has been used to simulate transients in tumour hypoxia and its growth. Quantification of the impact of tumour- and vasculature-associated parameters on tumour oxygenation demonstrates how cell line and imaging-based tumour-specific measures have a profound impact on tumour hypoxia. Further imaging data particularly related to angiogenesis will prove to be an important input to further the model. Simulating anti-angiogenic therapies *in silico* and analysing the reasons for their potential success or failure is a key application of the model.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The work is supported in part by the NIH grant 1R01CA136927.

References

- Adhikarla V and Jeraj R 2012 An imaging-based stochastic model for simulation of tumour vasculature *Phys. Med. Biol* 57 6103–24 [PubMed: 22971525]
- Alarcón T, Byrne H M and Maini P K 2005 A multiple scale model for tumor growth *Multiscale Model. Simul* 3 440–75
- Arakelyan L, Merbl Y and Agur Z 2005 Vessel maturation effects on tumour growth: validation of a computer model in implanted human ovarian carcinoma spheroids *Eur. J. Cancer* 41 159–67 [PubMed: 15618001]
- Bartha K and Rieger H 2006 Vascular network remodeling via vessel cooption, regression and growth in tumors *J. Theor. Biol* 241 903–18 [PubMed: 16545398]
- Bauer A, Jackson T and Jiang Y 2007 A cell-based model exhibiting branching and anastomosis during tumor-induced angiogenesis *Biophys. J* 92 3105–21 [PubMed: 17277180]
- Bergers G and Benjamin LE 2003 Tumorigenesis and the angiogenic switch *Nat. Rev. Cancer* 3 401–10 [PubMed: 12778130]
- Brown LF, Detmar M, Claffey K, Nagy JA, Feng D, Dvorak AM and Dvorak HF 1997 Vascular permeability factor/vascular endothelial growth factor: a multifunctional angiogenic cytokine *Exp. Suppl* 79 233–69 (PMID:) [PubMed: 9002222]

- Bruce JY et al. 2014 A phase I pharmacodynamic trial of sequential sunitinib with bevacizumab in patients with renal cell carcinoma and other advanced solid malignancies *Cancer Chemother. Pharmacol* 73 485–93 [PubMed: 24414551]
- Buscombe JR and Wong B 2013 PET a tool for assessing the in vivo tumour cell and its microenvironment? *Br. Med. Bull* 105 157–67 [PubMed: 23360594]
- Cai Y, Xu S, Wu J and Long Q 2011 Coupled modelling of tumour angiogenesis, tumour growth and blood perfusion *J. Theor. Biol* 279 90–101 [PubMed: 21392511]
- Carmeliet P and Jain RK 2000 Angiogenesis in cancer and other diseases *Nature* 407 249–57 [PubMed: 11001068]
- Ferrara N and Henzel WJ 1989 Pituitary follicular cells secrete a novel heparin-binding growth factor specific for vascular endothelial cells *Biochem. Biophys. Res. Commun* 161 851–8 [PubMed: 2735925]
- Foster BA, Gingrich JR, Kwon ED, Madias C and Greenberg NM 1997 Characterization of prostatic epithelial cell lines derived from transgenic adenocarcinoma of the mouse prostate (TRAMP) model *Cancer Res* 57 3325–30 [PubMed: 9269988]
- Folkman J 1976 The vascularization of tumors *Sci. Am* 234 58–64 70–3 [PubMed: 1273568]
- Gevertz JL. Computational modeling of tumor response to vascular-targeting therapies—part I: validation. *Comput. Math. Methods Med.* 2011; 2011:830515. [PubMed: 21461361]
- Gödde R and Kurz H 2001 Structural and biophysical simulation of angiogenesis and vascular remodeling *Dev. Dyn* 220 387–401 [PubMed: 11307171]
- Hasina R, Whipple ME, Martin LE, Kuo WP, Ohno-Machado L and Lingen MW 2008 Angiogenic heterogeneity in head and neck squamous cell carcinoma: biological and therapeutic implications *Lab. Invest* 88 342–53 [PubMed: 18283272]
- Haubner R. Noninvasive visualization of the activated $\alpha v \beta 3$ integrin in cancer patients by positron emission tomography and [18F]Galacto-RGD. *PLoS Med.* 2005; 2:e70. [PubMed: 15783258]
- Hendriksen EM, Span PN, Schuurin J, Peters JP, Sweep FC, van der Kogel AJ and Bussink J 2009 Angiogenesis, hypoxia and VEGF expression during tumour growth in a human xenograft tumour model *Microvasc. Res* 77 96–103 [PubMed: 19118564]
- Hogea CS, Murray BT and Sethian JA 2006 Simulating complex tumor dynamics from avascular to vascular growth using a general level-set method *J. Math. Biol* 53 86–134 [PubMed: 16791651]
- Jain R. Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy *Science* 307 58–62. 2005
- Jain RK, Tong RT and Munn LL 2007 Effect of vascular normalization by antiangiogenic therapy on interstitial hypertension, peritumor edema, and lymphatic metastasis: insights from a mathematical model *Cancer Res* 67 2729–35 [PubMed: 17363594]
- Jbabdi S, Mandonnet E, Duffau H, Capelle L, Swanson KR, Pélérini-Issac M, Guillemin R and Benali H 2005 Simulation of anisotropic growth of low-grade gliomas using diffusion tensor imaging *Magn. Reson. Med* 54 616–24 [PubMed: 16088879]
- Karamysheva AF 2008 Mechanisms of angiogenesis *Biochemistry (Mosc)* 73 751–62 [PubMed: 18707583]
- Konerding M, Malkusch W, Klapthor B, van Ackern C, Fait E, Hill S, Parkins C, Chaplin D, Presta M and Denekamp J 1999 Evidence for characteristic vascular patterns in solid tumours: quantitative studies using corrosion casts *Br. J. Cancer* 80 724–32 [PubMed: 10360650]
- Leith JT and Michelson S 1995 Secretion rates and levels of vascular endothelial growth factor in clone A or HCT-8 human colon tumour cells as a function of oxygen concentration *Cell Prolif* 28 415–30 [PubMed: 7548442]
- Less J, Skalak T, Sevcik E and Jain R 1991 Microvascular architecture in a mammary carcinoma: branching patterns and vessel dimensions *Cancer Res.* 51 265–73 [PubMed: 1988088]
- Levine HA, Sleeman BD and Nilsen-Hamilton M 2001 Mathematical modeling of the onset of capillary formation initiating angiogenesis *J. Math. Biol* 42 195–238 [PubMed: 11315313]
- Lewis J, McCarthy D, McCarthy T, Fujibayashi Y and Welch M 1999 Evaluation of ^{64}Cu -ATSM in vitro and in vivo in a hypoxic tumor model *J. Nucl. Med* 40 177–83 (PMID:) [PubMed: 9935074]

- Liu G, Qutub AA, Vempati P, Mac Gabhann F and Popel AS 2011 Module-based multiscale simulation of angiogenesis in skeletal muscle *Theor. Biol. Med. Model* 8 6 [PubMed: 21463529]
- Mantzaris NV, Webb S and Othmer HG 2004 Mathematical modeling of tumor-induced angiogenesis *J. Math. Biol* 49 111–87 [PubMed: 15293017]
- Mac Gabhann F, Ji JW and Popel AS 2007 VEGF gradients, receptor activation, and sprout guidance in resting and exercising skeletal muscle *Appl. Physiol* (1985) 102 722–34
- Matsumoto S et al. 2009 Simultaneous imaging of tumor oxygenation and microvascular permeability using Overhauser enhanced MRI *Proc. Natl Acad. Sci. USA* 106 17898–903
- McDougall SR, Anderson AR and Chaplain MA 2006 Mathematical modelling of dynamic adaptive tumour-induced angiogenesis: clinical implications and therapeutic targeting strategies *J. Theor. Biol* 241 564–89 [PubMed: 16487543]
- Michalski MH and Chen X 2011 Molecular imaging in cancer treatment *Eur. J. Nucl. Med. Mol. Imaging* 38 358–77 [PubMed: 20661557]
- Michor F and Polyak K 2010 The origins and implications of intratumor heterogeneity *Cancer Prev. Res. (Phila)* 3 1361–4 [PubMed: 20959519]
- Milde F, Bergdorf M and Koumoutsakos P 2008 A hybrid model for three-dimensional simulations of sprouting angiogenesis *Biophys. J* 95 3146–60 [PubMed: 18586846]
- Muthukkaruppan VR, Kubai L and Auerbach R 1982 Tumor-induced neovascularization in the mouse eye *J. Natl Cancer Inst* 69 699–708 (PMID:) [PubMed: 6180212]
- Nagy J, Chang S, Dvorak A and Dvorak H 2009 Why are tumour blood vessels abnormal and why is it important to know? *Br. J. Cancer* 100 865–9 [PubMed: 19240721]
- Nordmark M, Alsner J, Keller J, Nielsen O, Jensen O, Horsman M and Overgaard J 2001 Hypoxia in human soft tissue sarcomas: adverse impact on survival and no association with p53 mutations *Br. J. Cancer* 84 1070–5 [PubMed: 11308256]
- Nöth U, Rodrigues LM, Robinson SP, Jork A, Zimmermann U, Newell B and Griffiths JR 2004 In vivo determination of tumor oxygenation during growth and in response to carbogen breathing using ¹⁵C5-loaded alginate capsules as fluorine-19 magnetic resonance imaging oxygen sensors *Int. J. Radiat. Oncol. Biol. Phys* 60 909–19 [PubMed: 15465209]
- Orme ME and Chaplain MA 1996 A mathematical model of the first steps of tumour-related angiogenesis: capillary sprout formation and secondary branching *IMA J. Math. Appl. Med. Biol* 13 73–98 [PubMed: 8671581]
- Pawletz N and Knierim M 1989 Tumor-related angiogenesis *Crit. Rev. Oncol. Hematol* 9 197–242 [PubMed: 2480145]
- Perfahl H. Multiscale modelling of vascular tumour growth in 3D: the roles of domain size and boundary conditions. *PLoS One*. 2011; 6:e14790. [PubMed: 21533234]
- Plank M and Sleeman B 2003 Tumour-induced angiogenesis: a review *J. Theor. Med* 5 137–53
- Rockne RC. A patient-specific computational model of hypoxia-modulated radiation resistance in glioblastoma using 18F-FMISO-PET. *J. R. Soc. Interface*. 2015; 12:20150927. [PubMed: 26577597]
- Samant RS and Shevde LA 2011 Recent advances in anti-angiogenic therapy of cancer *Oncotarget* 2 122–34 [PubMed: 21399234]
- Sanga S, Sinek JP, Frieboes HB, Ferrari M, Fruehauf JP and Cristini V 2006 Mathematical modeling of cancer progression and response to chemotherapy *Expert Rev. Anticancer Ther* 6 1361–76 [PubMed: 17069522]
- Scianna M, Bell CG and Preziosi L 2013 A review of mathematical models for the formation of vascular networks *J. Theor. Biol* 333 174–209 [PubMed: 23684907]
- Serini G, Ambrosi D, Giraudo E, Gamba A, Preziosi L and Bussolino F 2003 Modeling the early stages of vascular network assembly *EMBO J* 22 1771–9 [PubMed: 12682010]
- Steel GG 2002 *Basic Clinical Radiobiology* (London: Arnold)
- Stephen RM, Pagel MD, Brown K, Baker AF, Meuliet EJ and Gillies RJ 2012 Monitoring the development of xenograft triple-negative breast cancer models using diffusion-weighted magnetic resonance imaging *Exp. Biol. Med.* (Maywood) 237 1273–80 [PubMed: 23239438]

- Stokes CL, Lauffenburger DA and Williams SK 1991 Migration of individual microvessel endothelial cells: stochastic model and parameter measurement J. Cell Sci 99 419–30 (PMID:) [PubMed: 1885678]
- Sun S, Wheeler M, Obeyesekere M and Patrick CJ 2005 A deterministic model of growth factor-induced angiogenesis Bull. Math. Biol 67 313–37 [PubMed: 15710183]
- Swanson KR, Alvord EC and Murray JD 2000 A quantitative model for differential motility of gliomas in grey and white matter Cell Prolif 33 317–29 [PubMed: 11063134]
- Swanson KR, Bridge C, Murray JD and Alvord EC 2003 Virtual and real brain tumors: using mathematical modeling to quantify glioma growth and invasion J. Neurol. Sci 216 1–10 [PubMed: 14607296]
- Swanson KR, Rockne RC, Claridge J, Chaplain MA, Alvord EC and Anderson AR 2011 Quantifying the role of angiogenesis in malignant progression of gliomas: in silico modeling integrates imaging and histology Cancer Res 71 7366–75 [PubMed: 21900399]
- Titz B and Jeraj R 2008 An imaging-based tumour growth and treatment response model: investigating the effect of tumour oxygenation on radiation therapy response Phys. Med. Biol 53 4471–88 [PubMed: 18677042]
- Titz B, Kozak KR and Jeraj R 2012 Computational modelling of anti-angiogenic therapies based on multiparametric molecular imaging data Phys. Med. Biol 57 6079–101 [PubMed: 22972469]
- Vaupel P 1977 Hypoxia in neoplastic tissue Microvasc. Res 13 399–408 [PubMed: 327212]
- Vaupel P, Kallinowski F and Okunieff P 1989 Blood flow, oxygen and nutrient supply, and metabolic microenvironment of human tumors: a review Cancer Res 49 6449–65 [PubMed: 2684393]
- Vaupel P and Harrison L 2004 Tumor hypoxia: causative factors, compensatory mechanisms, and cellular response Oncologist 9 4–9
- Welter M, Bartha K and Rieger H 2008 Emergent vascular network inhomogeneities and resulting blood flow patterns in a growing tumor J. Theor. Biol 250 257–80 [PubMed: 17996256]
- Yankeelov TE, Atuegwu NC, Deane NG and Gore JC 2010 Modeling tumor growth and treatment response based on quantitative imaging data Integr. Biol. (Camb) 2 338–45 [PubMed: 20596581]
- Yankeelov TE, Atuegwu N, Hormuth D, Weis JA, Barnes SL, Miga MI, Rericha EC and Quaranta V 2013 Clinically relevant modeling of tumor growth and treatment response Sci. Transl. Med 5 187ps9

Figure 1.
Flowchart demonstrating the dynamics between the different model blocks.

Figure 2.

Reproducing trends in tumour oxygenation. Variations between the simulated and the observed data can be explained on the basis of variation in the tumour doubling time from its average value. Simulation parameters: $\text{PRC} = 0.05 \text{ d}^{-1}$, $\text{sMVD}_{\text{tissue}} = 3.5\%$, $\text{VEGF}_{\text{max}} = 1000 \text{ pg cm}^{-3}$.

Figure 3.

Sensitivity study of model parameters. (a) Impact on time to peak tumour pO_2 (t_{peak}). (b) Impact on peak tumour pO_2 (pO_{2peak}). Both tumour- and vasculature-associated parameters have similar impact on pO_{2peak} . Tumour-associated parameters however, have more impact on t_{peak} as compared to vasculature-associated parameters. Note: since the VEGF secretion rates of only two kinds of cell lines have been used, the box for the cell line does not represent the $\pm 20\%$ change that is typical for the other parameters.

Figure 4. Temporal changes in perfusion and angiogenic factor characteristics. (a) Vessel perfusion index. (b) Tumour angiogenic factor (VEGF) concentration.

Figure 5.

Line profiles across the tumour. The curves demonstrate the changes in (a) tumour oxygenation and (b) vessel perfusion index at different time points. The edge of the tumour is reflected in the graphs when the pO_2 is roughly 50 mmHg (reflecting $sMVD_{tissue}$) and the VPI is 100%.

Figure 6.

Volumetric and cross-sectional visualization of tumour growth and change in tumour hypoxia obtained from simulations. (a)–(c) Volumetric visualization of [^{64}Cu] Cu-ATSM hypoxia PET maps along with the simulated vasculature on day 0, 7 and 14. (d)–(f) Cross-sections of the vasculature and the simulated hypoxia maps from the vasculature on day 0, 7 and 14. (g)–(i) Cross-sections of the vasculature and the simulated hypoxia maps (resampled to PET resolution) from the vasculature on day 0, 7 and 14. An increase in tumour volume and hypoxia along with reduced vessel density is immediately visible.

Table 1.

Model parameters.

Model parameter/literature-based constant	Symbol	Value (range)	Reference/comments
Vasculature simulation parameters:			
Vascular pO_2	p_0	60 mm Hg	
Capillary radius	r_c	10 μm (2–100 μm)	(Konerding <i>et al</i> 1999)
Average vessel length	SL	Capillaries: 120 μm (diameter:length = 1:6)	(Less <i>et al</i> 1991)
Oxygen consumption rate	Q_{max}	0.5ml O_2^{-1} $100\text{g}^{-1} \text{min}^{-1}$ (0.2–4ml O_2^{-1} $100\text{g}^{-1} \text{min}^{-1}$)	(Vaupel <i>et al</i> 1989)
Minimum voxel resolution required for simulation (capillary diameter)			
Theoretical tumour simulation (base case):			
Tumour doubling time	T_d	3–4 d	(Nöth <i>et al</i> 2004)
Surrounding tissue vessel density	sMVD _{tissue}	3.5%	Variable tuned
Perfusion rate constant	PRC	0.05 d ⁻¹	Variable tuned
VEGF concentration for complete vessel dysfunctionality	VEGF _{max}	1000 pg cm ⁻³	Variable tuned
Cell density		1×10^6 cells per voxel	(Steel 2002)
VEGF diffusion coefficient	D_{VEGF}	100 $\mu\text{m}^2 \text{s}^{-1}$	(Mac Gabhann <i>et al</i> 2007)
Decay rate of VEGF	λ_{VEGF}	0.65 h ⁻¹	(Serini <i>et al</i> 2003)
Voxel resolution for tumour matrix		112 μm	
Voxel resolution for vasculature matrix		60 μm	
Application to <i>in vivo</i> data (parameters that have been altered from the base case):			
Tumour doubling time	T_d	11.3 d	(Foster <i>et al</i> 1997)
Vessel density at the tumour edge	sMVD _{tissue}	1.5%	Variable tuned
Perfusion rate constant	PRC	0.028 d ⁻¹	Variable tuned
VEGF concentration for complete vessel dysfunctionality	VEGF _{max}	1000 pg cm ⁻³	From theoretical scenario
Voxel resolution for tumour matrix		250 μm	
Voxel resolution for vasculature matrix		100 μm	