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A mathematical approach towards simulating a realistic tissue activity curve of ^{64}Cu-ATSM for the purpose of sub-target volume delineation in radiotherapy

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ABSTRACT

One unique feature of positron emission tomography (PET) is that it allows measurements of regional tracer concentration in hypoxic tumour-bearing tissue, supporting the need for accurate radiotherapy treatment planning. Generally the data are taken over multiple time frames, in the form of tissue activity curves (TACs), providing an indication of the presence of hypoxia, the degree of oxygen perfusion, vascular geometry and hypoxia fraction. In order to understand such a complicated phenomenon a number of theoretical studies have attempted to describe tracer uptake in tissue cells. More recently, a novel computerized reaction diffusion equation method developed by Kelly and Brady has allowed simulation of the realistic TACs of ^{18}F-FMISO, with representation of physiological oxygen heterogeneity and tracer kinetics. We present a refinement to the work of Kelly and Brady, with a particular interest in simulating TACs of the most promising hypoxia selective tracer, ^{64}Cu-ATSM, demonstrating its potential role in tumour sub-volume delineation for radiotherapy treatment planning. Simulation results have demonstrated the high contrast of imaging using ATSM, with a tumour to blood ratio ranging 2.24–4.1. Similarly, results of tumour sub-volumes generated using three different thresholding methods were all well correlated.

1. Introduction

Today it is well appreciated that hypoxia plays a significant role in tumour resistance to radiotherapy treatment, chemotherapy treatment [1] and also of surgery [2], this being attributed to the effect of oxygen. Ideally, the presence of oxygen is required to repair the induced damage to DNA by radiation. It appears also that oxygen plays a major role in increasing the damage produced by radiation [2]. An adequate level of oxygenation, approximately 25–30 mmHg, would significantly increase the effective half-life of the toxic free radicals, thus causing further damage to the cell components. This in turn, explains the poor local control and quality of life sometimes experienced by survivors of squamous cell carcinoma of head and neck and cervix cancer, where $pO_2 < 10$ mmHg [3].

One unique feature of positron emission tomography (PET) imaging is that it allows measurements of regional tracer concentration in tissue and different body organs, quantitatively and non-invasively. The objective of such procedure is, in general, to find a set of features which have both inter- and intra-variance in hypoxic tumour-bearing tissue. To-date possibly the most well-indicated alternative to ^{18}F-FMISO as a hypoxic reagent is ^{64}Cu-ATSM [4].

Determining the relationship between the regional tracer concentration in tissue, in the form of tissue activity curves (TACs), shape and the underlying tumour physiology is of fundamental importance, as knowledge of the tumour environment may help determine the most likely course of a response. Standard techniques such as conventional compartment models are limited as they assume that each compartment is a mathematical abstraction, independent of its location. Thus, the diffusible tracer is likely to be homogeneous across the vasculature, which is far from reality, as argued by Ref. [5]. Kelly and Brady have developed a novel computerized reaction diffusion method [5] to simulate realistic TACs of ^{18}F-FMISO, with representation of vasculature architecture and tracer kinetics. Here, we present a refinement to that work, showing a particular interest towards simulating the TACs of ^{64}Cu-ATSM. Furthermore, we attempt to demonstrate the potential use of ^{64}Cu-ATSM in radiation therapy treatment planning as an indicator of tumour hypoxic regions. In this work all simulations have been coded in 2D, for a vasculature size of 4 mm^2, using Matlab 2007b and finite difference methods.

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2. The reaction diffusion model

In this work we simulate realistic TACs of ^{64}Cu-ATSM, with representation of the complexity of vascular architecture, tracer diffusivity, tracer binding rate, transvascular permeability and blood vessel densities. Thus, the reaction diffusion model simulating ^{64}Cu-ATSM heterogeneity in 2D can be described as:

$$\frac{\partial Tr(x,y,t)}{\partial t} = D_{Tr}\nabla^2 Tr - k_{on}Tr + \frac{P_m S}{V}(Tr_{plasma} - Tr_{tissue})R, \quad (1)$$

where Tr is the concentration of the tracer (^{64}Cu-ATSM) in tissue cells, in μCi/ml, D_{Tr} is the diffusion coefficient of tracer in $mm^2\,s^{-1}$, k_{on} is the binding rate of ATSM in s^{-1}, Tr_{plasma} is the concentration of tracer in the plasma in μCi/ml, P_m is the permeability of the vessel to the tracer in $mm\,s^{-1}$, S/V is the surface area to blood vessel volume in mm^{-1} and R is the proportion of vessels covering the vasculature.

The location of blood vessels in the plane (i.e. the vascular map) is described by the function $R(x)$. Blood vessels are randomly distributed in the imaging plane on a fixed equally spaced Cartesian mesh known as the vascular mesh. The grid points on the vascular mesh will be designated so that where there is a vessel the value on the mesh will be 'one' and where there is no vessel the value will be zero, using a probability mass function $\tilde{R}_{i,j}$ defined on the basis of individual probability, p. Thus, the grid points are:

$$x_{i,j} = \begin{cases} 1 & \text{if } R_{i,j} = 1 = p \\ 0 & \text{if } R_{i,j} = 0 = 1 - p \end{cases}, \quad (2)$$

Table 1
Baseline parameters applied in the model for the reagent ^{64}Cu-ATSM.

Property	Parameter values (and reference)
Diffusion coefficient (calculated)	$5.05 \times 10^{-4}\,mm^2\,s^{-1}$ [6]
Thickness of blood vessel membrane (x)	0.2–1 μm [7]
Permeability calculated	$1.12–5.61\,mm\,s^{-1}$ [8,9]
Blood vessel radius (r)	8–10 μm [7]
Surface area to volume ratio (S/V)	$170–285\,mm^{-1}$
Micro-vessel density ($MVDs=N$)	240 vessel mm^{-2} (at tumour surface) [11]
Micro-vessel density ($MVDs=N$)	60 vessel mm^{-2} (near tumour surface) [1]
Rate of tracer binding (k_{on})	$0.0003\,s^{-1}$ [2,13]

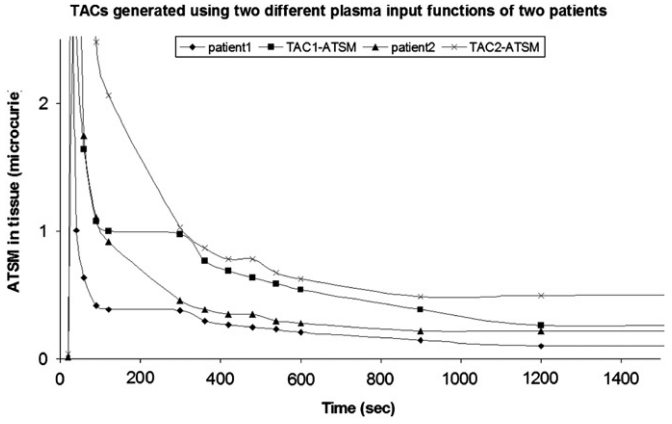

Fig. 1. Simulated TACs generated using two plasma input functions, taken from two different patients (data deindentified), where transvascular permeability was chosen to be $1.22\,mm\,s^{-1}$, and $MVDs$ approximately 121 vessel/mm^2.

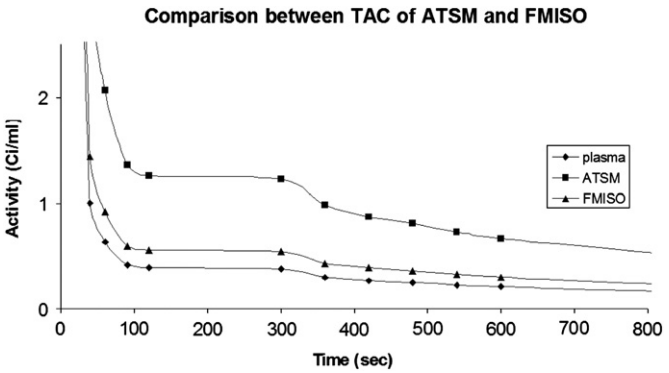

Fig. 2. Simulated TACs using the plasma input function for patient 1, with the transvascular permeability ranging 1.2–2 $mm\,s^{-1}$ and $MVDs$ approximately 121 vessel mm^{-2}.

Table 2
The influence of transvascular permeability status on tumour local contrast; measurements are presented in term of mean ± SD, $n=15$.

Permeability level (mm/s)	T/B ratio
1.22	2.6 ± 0.00
1.5	3.1 ± 0.00
1.8	3.6 ± 0.05
2.0	4.1 ± 0.01

where p is defined as:

$$p = \frac{MVDs \times \pi r^2}{M}, \quad (3)$$

with $MVDs$ the micro-vessel density (i.e. the number of vessels per unit area or volume), r the radius of blood vessel and M the spatial extent of the simulated vasculature, in this case $4\,mm^2$. The vascular map, $R(x)$, is then defined as:

$$R(x) = \sum_{i=0}^{N}\sum_{j=0}^{N} \tilde{R}_{i,j}\delta(x - x_{i,j}), \quad (4)$$

where x_i are the random locations of N blood vessels in the vasculature and δ is the Dirac delta function. Hence, $R(x)$ will be zero everywhere other than at points x_i where $\tilde{R}_{i,j} = 1$. For a good numerical approximation of $R(x)$, a sum of Gaussian functions is applied, as follows:

$$R(x) = \sum_{i=0}^{N}\sum_{j=0}^{N} \tilde{R}_{i,j} \exp\left(-\frac{|x - x_{i,j}|^2}{2\alpha^2}\right), \quad (5)$$

with $2\alpha^2$ the width of the Gaussian, giving the radius of the blood vessel ($r^2=2\alpha^2$) and $x_{i,j}$ the random locations of the capillaries (noting that they do not have to be normally distributed).

3. Results

3.1. Baseline values

All physical and biological baseline parameters applied in this work were determined from an exhaustive literature search; see Table 1 for the complete set of these baseline values.

3.2. Simulated ^{64}Cu-ATSM tissue activity curves

Simulated tissue activity curves (TACs) of ^{64}Cu-ATSM are generated using deidentified patient plasma input data [6]. Representation of simulated results using two patient data sets