Quantitative analysis of dynamic contrast enhanced medical images with tracer kinetics models for In Vivo assessment of tumor physiology

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**Quantitative Analysis of Dynamic Contrast
Enhanced Medical Images with Tracer Kinetics
Models for *In Vivo* Assessment of Tumor
Physiology**

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School of Electrical and Electronic Engineering

A thesis submitted to the Nanyang Technological University
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Summary

Physiological parameters associated with blood perfusion, such as blood flow, blood volume, vascular transit times and blood vessel leakiness, can potentially provide diagnostic and prognostic information about the pathological tissue. These microcirculatory parameters can be extracted from dynamic contrast enhanced (DCE) images. Recent developments in imaging technologies have allowed significant improvements in both the spatial and temporal resolutions of DCE imaging datasets. For quantitative analysis of such datasets, more realistic models of tissue microcirculation can be developed.

In this study, distributed-parameter (DP) tracer kinetics models were developed and applied to clinical DCE X-ray Computed Tomography data for various tumors. A multiple-compartment, mammillary DP model that accounts for more than one kinetically distinct compartment within the tissue interstitial, was developed. This model has been further enhanced by including the distribution of capillary transit times to account for different capillary lengths in the tissue. These models were tested using clinical DCE images to study their applicability in the clinical setting. A comparative study of distributed- and lumped-parameter compartmental models was performed. The lumped-parameter model yielded different parameter values as compared to the DP model on the same dataset. An adiabatic approximation to the DP model resulted in parameter estimations that were very close to those obtained with the DP model.

New directions for further research to achieve better quantitative analysis of DCE images and some issues that might have been more appropriately resolved are discussed.

This work demonstrates that the more realistic DP models can be practically applied for analysis of tumor DCE imaging data, and encourages the use of such models on clinical DCE imaging datasets. Our efforts have received special recognition in the journal *Radiology* [1] and attracted some interest from international researchers in the DCE imaging community. There is also ongoing collaboration with researchers in Germany to apply and validate the DP models on other types of tumors.

Abbreviations

ASL	arterial spin labeling
ASM	active snake model
ATH	adiabatic approximation to the tissue homogeneity model
BBB	blood brain barrier
CC	conventional compartmental
CC ₂	2-compartment, conventional compartmental
CDP ₃	3-compartment, catenary, distributed-parameter
CT	X-ray computed tomography
DCATH	distributed-capillary ATH
DCDP ₂	2-compartment, distributed-capillary, distributed-parameter
DCE	dynamic contrast enhanced
DP	distributed-parameter
DP ₂	2-compartment, distributed-parameter
DSC	dynamic susceptibility contrast
EES	extravascular extracellular space, or interstitial space
GK	general kinetic
GM	grey matter of the brain
ICA	independent component analysis
IVPS	intravascular plasma space
LDA	linear discriminant analysis
MCC ₃	3-compartment mammillary conventional compartmental
MCC ₄	4-compartment mammillary conventional compartmental
MDP _n	<i>n</i> -compartment, mammillary, distributed-parameter

MR	magnetic resonance
MRI	magnetic resonance imaging
PCA	principal component analysis
PET	positron emission tomography
Pixel	picture element
PVA	partial volume averaging
RF	radio frequency
ROI	region of interest
SPECT	single photon emission computed tomography
SVD	singular value decomposition
SVM	support vector machine
T1	spin-lattice relaxation time
T2	spin-spin relaxation time
T2*	spin-spin relaxation time (with inhomogeneity effects)
VOI	volume of interest
Voxel	volume element
WM	white matter of the brain

Symbols

$\otimes$		Convolution operator
A_i	(cm ²)	Cross sectional area of compartment i
α		Statistical significant level
b		Transfer coefficient
c		y-intercept of regression line
$C_i(t, z)$	(mmol mL ⁻¹)	Concentration of tracer in compartment i at time t and distance z from the arterial end
$C_a(t)$	(mmol mL ⁻¹)	Concentration of tracer over time in the arterial blood
C_i	(mmol mL ⁻¹)	Concentration of tracer over time in compartment i
$C_{\text{tiss}}(t)$	(mmol mL ⁻¹)	Concentration of tracer over time in the tissue VOI
$C_{\text{tiss}}^{\text{expt}}(t)$	(mmol mL ⁻¹)	Concentration of tracer over time in the tissue VOI, measured from experiment
$C_{\text{tiss}}^{\text{model}}(t)$	(mmol mL ⁻¹)	Concentration of tracer over time in the tissue VOI, estimated by a tracer kinetic model
$C_v(t)$	(mmol mL ⁻¹)	Concentration of tracer over time in the outflowing blood from the VOI
χ^2		Chi-squared statistic
χ_n		Arbitrary expression, $t_1 \sum_{i=2}^n k_{i1}$
$\delta_t(t)$		Dirac delta function that represents an unit impulse when $t = 0$

$\delta_z(z)$		Dirac delta function that represents an unit impulse at the arterial end of the capillary, at $z = 0$
E		First pass extraction ratio of tracer into EES from IVPS, or the fractional amount of incoming impulse of tracer that remained in the compartmental system
$f(\chi_1^2, \chi_2^2)$		A F-distribution statistic
$f_n(s)$	(cm^{-1})	Arbitrary expression, $\frac{v_1 s}{\rho F_p L} \left(1 + \sum_{i=2}^n \frac{k_{i1}}{s + k_{1i}} \right)$
fBV		Fractional blood volume
F	($\text{mL g}^{-1} \text{min}^{-1}$)	Blood perfusion
F_p	($\text{mL g}^{-1} \text{min}^{-1}$)	Blood plasma perfusion
ϕ		Number of DCE images
$g(t_1)$		A suitable probability distribution function for capillary transit time distribution
$g_i(s)$		Arbitrary expression, $\begin{cases} 1 & i = 1 \\ \frac{A_1}{A_i} \frac{k_{i1}}{s + k_{1i}} & i = 2 \dots n \end{cases}$
γ		Ratio of PS / F_p
$\gamma(s)$	(min^{-1})	Arbitrary expression, $s - \frac{k_{21}s}{s + k_{12}}$
Hct		Hematocrit ratio
$I_0(\cdot)$		The zeroth-order modified Bessel function of the first kind
$I_1(\cdot)$		The first-order modified Bessel function of the first kind
$J(\cdot, \cdot)$		The J function
k_{adb}	(min^{-1})	Adiabatic version of the rate constant k_{12}
k_{ep}	(min^{-1})	Rate constant in generalized kinetic models, from EES into IVPS
k_i	(min^{-1})	Arbitrary expression, $t_1 k_{1i} k_{i1}$

k_{i1}	(min ⁻¹)	Rate constants for tracer flowing into the compartment i ($i=2,...,n$) in EES from IVPS for n -compartment mammillary models, where
		$k_{i1} = \frac{K_{i1}}{v_1}$
k_{1i}	(min ⁻¹)	Rate constants for tracer flowing into IVPS from compartment i ($i=2,...,n$) in EES for n -compartment mammillary models, where
		$k_{1i} = \frac{K_{1i}}{v_i}$
K_{i1}	(min ⁻¹)	Transfer constants for tracer flowing into the compartment i ($i=2,...,n$) in EES from IVPS, where $K_{j1} = \lambda \sum_{j=2, j \neq i}^n K_{1j}$
K_{1i}	(min ⁻¹)	Transfer constants for tracer flowing from the compartment i ($i=2,...,n$) in EES into IVPS
K^{trans}	(min ⁻¹)	Transfer constant in generalized kinetic models, from IVPS into EES
L	(cm)	Average length of capillaries from the arterial to the venous end
$\mathcal{L}_t(\cdot)(s)$		Laplace transform from t to s
$\mathcal{L}_z(\cdot)(p)$		Laplace transform from z to p
λ_{1i}		Equilibrium partition coefficient of tracer between compartment 1 and compartment i ($i=2,...,n$)
m		Gradient of regression line
MTT	(min)	Mean transit time in tissue VOI
μ	(min)	Vascular mean transit time
$\mathbf{p}$		Array of the corresponding parameter in a tracer kinetic model impulse residue function
p	(cm ⁻¹)	Laplace transformed variable of z
P	(cm ² min ⁻¹)	Permeability coefficient of the vessel wall with respect to the contrast agent
PS	(mL g ⁻¹ min ⁻¹)	Permeability-surface area product, $PS = P \times S / \rho$
r		Ratio of Hct in small vessel over larger vessel.

r^2		Coefficient of determination
$R(t)$		Impulse residue function over time
$R_{\text{model}}(t, \mathbf{p})$		Analytical expression for the impulse residue function over time of a model, with parameters contained in the array $\mathbf{p}$
s	(min^{-1})	Laplace transformed variable of t
S	(cm^2)	Surface area of the vessel wall in the tissue VOI
σ	(min)	Standard deviation of the vascular transit time
t	(min)	Time measured from the time bolus first arrived
t_1	(min)	Vascular mean transit time
$t_{1,i}$	(min)	Vascular transit time through a particular capillaries pathway
t_k	(min)	Time between the first and the k^{th} image acquisitions
t_{min}	(min)	Minimum transit time
$u(t)$		Heaviside unit step function
v_1		Fractional tracer distribution volume in IVPS respectively
v_i		Fractional tracer distribution volume in compartment i ($i=2, \dots, n$) in EES
v_e		Fractional tracer distribution volume in EES, where $v_e = \sum_{i=2}^n v_i$
V	(mL)	Distribution volume of tracer in the tissue VOI
V_i	(mL)	Distribution volume of tracer in compartment i
ξ		Ratio of z / L
z	(cm)	Distance from the arterial end along compartment 1 in the tissue VOI

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Chapter 1

Introduction

1.1 Motivation

Cancer¹ is one of the most common causes of death in developed countries, and has been the top principal cause of death and the second most common reason for hospitalization in Singapore [2]. In the fight against cancer, there are three areas worthy of research attention, namely, early detection, treatment monitoring, and improved understanding of the physiological basis of cancer.

It has long been known that an abnormal vasculature is an integral feature of tumors [3]. Growth of tumor size beyond a millimeter in diameter requires vascular in-growth. The process of angiogenesis² in normal tissues is well-organized, while in a tumor the angiogenesis is more chaotic. The major characteristics of tumor vasculature include:

- (a) spatial heterogeneity and chaotic structure, arteriovenous shunting;

¹ Uncontrolled, abnormal growth of cells.

² The process of vascularisation of a tissue involving the development of new capillary blood vessels.

- (b) poorly formed, fragile vessels with high permeability to macromolecules;
- (c) high vascular tortuosity³ and vasodilatation⁴;
- (d) intermittent or unstable flow and areas of spontaneous haemorrhage⁵;
- (e) areas of low vascular density mixed with regions of high angiogenic activity.

Microcirculation within tumors plays an important role [4] both in the identification of tumor tissue and the evaluation of tumor response to cytotoxic treatment such as chemotherapy, immunotherapy or radiation therapy. A reliable and convenient method for assessment of tumor microcirculatory parameters, before and during the course of cancer therapy, may therefore be used to predict which patients are likely to fail therapy, and further, to help to optimize the therapy schedule for individual patients. To be useful, such a method must describe the microcirculation within tumors by using physiological parameters that can reflect the clinically relevant characteristics of tumor vasculature.

Obviously, routine assessment of cancer patient's condition has to be performed *in vivo*⁶, and preferably should also be non-invasive or only minimally invasive. Although most medical imaging techniques are non-invasive and minimally invasive where contrast materials are used, they are sometimes inadequate to differentiate between the functional state of tumor and normal tissues since these tissues have similar composition. Medical imaging techniques that specifically focus on functional state of tissue, such as dynamic contrast enhanced (DCE)

³ Frequent bends in different directions.

⁴ A state of increased caliber of the blood vessels.

⁵ The escape of blood from the vessels.

⁶ Within the living body.

studies using X-ray computed tomography (CT) or magnetic resonance imaging (MRI), have the following strengths [5]:

- (a) improved disease detection since functional changes in tissue occur before structural changes are apparent;
- (b) identification of pathologies⁷ that are otherwise undetectable by structural imaging;
- (c) ability to demonstrate response to treatment before structural changes can be detected.

Several currently available imaging modalities can generate DCE images, provided that appropriate contrast agents are used. Various radiopharmaceuticals as contrast agents are used in nuclear medicine imaging; for example, the gamma camera produces planar DCE images, the Single Photon Emission Computed Tomography (SPECT) and the Positron Emission Tomography (PET) techniques generate cross-sectional DCE images. These modalities are commonly known as functional imaging rather than DCE imaging because the use of radiopharmaceuticals is necessary rather than optional to produce image data. By using iodinated solution as the contrast agent, X-Ray Computed Tomography (CT) is capable of generating cross-sectional DCE images. A paramagnetic material can be used as the contrast agent in Magnetic Resonance Imaging (MRI) technique to generate cross-sectional DCE images. In addition, active research is being conducted into new and better methods to create DCE images, such as the use of arterial spin labeled (ASL) blood as the contrast agent in MRI.

⁷ The branch of medicine concerned with disease, especially its structure and its functional effects on the body.

The hardware technology of medical imaging devices has been making significant advancements in recent years [6]-[8]. Vacuum tubes in gamma cameras have been replaced by solid-state detectors [9], [10] digitized signals acquisition technology has improved drastically, leading to better quality of images. These advances benefit in particular the SPECT and PET images that are generated by gamma camera [11], [12]. A combined PET/CT machine [13] built by merging PET and CT devices can produce images with good functional and anatomical features. CT machines with multi-slice detectors [14], [15] have replaced systems with only single slice acquisition capabilities, thus allowing higher speed and more coverage per acquisition, allowing creation of image sets that cover many thin slices in a single scan. MRI machines have advanced from 1 Tesla to 3 Tesla for human examinations [16] and up to 14 Tesla for experimental studies of animals [17]. MRI machine operating at higher magnetic field can produce stronger signal and therefore allow generation of images with better resolution and accuracy. Essentially, we can expect greater availability of DCE images as hardware capability to produce images with increasing spatial and temporal resolution grows. As a result, the need for better methods to study them will also increase.

DCE images record the behavior of contrast agent passing through the tissue; analysis of such data has the potential to provide us with values of functional and physiological parameters that facilitate the understanding of the status of studied tissue. Five clinically relevant parameters have been identified:

- (a) Blood perfusion or capillary flow: The delivery of oxygen and other nutrients to a tissue is dependent upon it. Blood supply may be characterized in 'absolute' units, mL/min, that describe the volume of

blood passing through a large artery supplying the organ, or alternatively as perfusion, which characterizes flow in capillaries per unit tissue mass, mL/g/min. High perfusion values may be due to a high flow or large volume of capillary bed.

- (b) Blood Volume: This is defined as the volume of distribution spaces of the contrast agent within the tissue. It is usually measured as a fractional volume and has no unit. Strictly speaking, this definition is correct only if the contrast agent does not penetrate the capillary walls and enter into interstitial space.
- (c) Mean Transit Time: It is the average of time spent by contrast agent within the tissue.
- (d) Permeability-surface area product: It characterizes the leakage of the vessel walls as the contrast agent penetrates across the vessel walls into the interstitial spaces of tissue, and has the same unit as perfusion.
- (e) Extraction fraction: It is the fraction of a bolus of contrast agent that leaked into interstitial space of tissue during a single pass of bolus through the capillary bed of tissue. Extraction fraction and permeability values depend on both the type of contrast agent and the permeability of the blood vessels.

Tumor angiogenesis is a complex process important to the growth of cancer cells, and is different from angiogenesis in normal tissue [3]. Tumor tissue has higher perfusion because it has high vessel density due to increased demand for more oxygen and nutrients caused by rapid growth. Correspondingly, tumor tissue has higher fractional blood volume. Mean transit time helps to differentiate highly perfused tumor tissue from normal tissue that has a larger blood vessel passing

through it. The vascular mean transit time for the latter shall be significantly shorter than the former. Values of permeability-surface area product and extraction ratio are higher in tumors due to poorly formed, fragile, and leaky vessels commonly present in tumor tissues.

A better understanding of microcirculation characteristics of the tumor is beneficial to the development of diagnosis and treatment methods, as well as monitoring of tumor response during treatment process. Thus, DCE images contain useful information that, if used efficiently, could improve the outcome of cancer therapy. A number of readily available medical imaging technologies can produce DCE images today. In addition, during the past few years, there were significant advances in medical imaging, for example, the temporal resolution or the time interval between consecutive images of DCE acquisitions has improved from tens of seconds to sub-second range.

However, DCE images are commonly analyzed by methods that were designed for low temporal and spatial resolution data such as PET images acquired at 10 s intervals and 5 mm² pixels. At temporal resolution of 1 to 2 s, modern DCE data capture the rapid tracer concentration increase in the arterial blood during the first few seconds. Early analysis methods do not account for this newly available data. Higher spatial resolution implies higher signal accuracy. Early analysis methods might not fully utilize this improved accuracy. Furthermore, patients who need to have DCE imaging studies performed would have to bear either the radiation risks from imaging devices such as gamma camera, SPECT, PET or CT, or the high cost of MR scans. This thesis addresses the need to develop new methods that can take

advantage of the high spatial and temporal resolution of currently available DCE images to assess tumor state.

1.2 Objectives

In recent years, there have been significant technological improvements in imaging devices that are capable of generating DCE images. Modern imaging systems are providing better quality DCE images than those available even a few years ago. However, the methods of DCE images analysis in common use today are still similar to those that have been employed at the time when the first gamma camera was introduced more than half a century ago. The existing methods use both qualitative and quantitative approaches. The quantitative approaches employ tracer kinetics methods and simple models. The overall goal of this thesis is to enhance the quality of analysis of DCE images obtainable from modern medical imaging devices. To fulfill this goal, the following tasks have been identified:

- (a) Enhance the existing two-compartment, distributed-parameter model to include more than one mamillary⁸ extravascular compartments. The heterogeneity of tumor tissue prompted a further refinement to the model by dividing the extravascular space into at least two regions in different physiological states (such as viable and necrotic tissues).
- (b) Encourage the use of distributed-parameter models, which are computationally more complex than compartmental models commonly used thus far. The assumption of homogeneity of tracer concentration in

⁸ The word ‘mamillary’ used in this thesis is in the context of compartmental modeling, and does not refer to the breast. It refers to arrangements of compartments where a central compartment may exchange tracers with multiple compartments.

narrow intravascular space in compartmental models might not be applicable to DCE images acquired with higher temporal resolution since effects of spatial-distribution of tracer concentrations might become apparent in such images.

- (c) Account for the distribution of capillary lengths to enhance the distributed-parameter models. In a realistic analysis of data, differences in capillary length should be accounted for in a model.

1.3 Major Contributions of the Thesis

Consistent with the stated goal, two new, more realistic tracer kinetics models were developed, implemented and applied for the analysis of DCE CT images of cerebral tumors. The major contributions to this project, included in this thesis, are the following:

- (a) A multiple-compartment, mammillary, distributed-parameter model was developed. It was applied to a prostate cancer study case to illustrate the existence of two kinetically different compartments within the tumor interstitial space. Results were published in the IEEE Transactions on Biomedical Engineering [18].
- (b) A comparative study to explore the similarities and differences of three tracer kinetics models: a distributed-parameter model, a conventional compartmental model and an adiabatic approximation to the distributed-parameter model. Intracranial meningioma DCE CT data had been analyzed using these three models. For DCE CT data acquired at 1 s time interval, the conventional compartmental model generates quantitatively

different estimates from the distributed-parameter model. Results were published in the Radiology Journal [19].

- (c) The inclusion of a capillary transit time distribution in the mammillary distributed-parameter model. Simulation studies and application of the model to clinical DCE CT data of cerebral tumors were performed. By estimating the variance of capillary transit time, the model shows that tumor vasculature exhibits a higher degree of variability than normal tissues. Results were published in the NeuroImage Journal [20].

This work illustrates the feasibility of employing distributed-parameter models for the analysis of high temporal resolution DCE CT data and to estimate several microcirculatory parameters that are potentially of clinical interest for tumor diagnosis.

1.4 Organization of the Thesis

This thesis is organized as follows:

Chapter 2 gives an overview of the technologies and analysis methods used in DCE imaging studies. Common medical imaging modalities that can generate DCE images are described. Analysis methods found in the literature were grouped into the qualitative and quantitative approaches. Quantitative methods that use tracer kinetics models are discussed.

Chapter 3 describes the materials and methods used in this work.

Chapter 4 presents the solution for the multiple-compartment, mammillary, distributed-parameter model. Models with 2, 3, and 4 compartments were applied on a prostate study case to illustrate the application of the model.

Chapter 5 compares the distributed-parameter model with a lumped-parameter model and an adiabatic approximation to the distributed-parameter model. Intracranial meningioma data have been analyzed using these three models.

Chapter 6 presents an approach to incorporate a capillary distribution with the mammillary distributed-parameter model. Intracranial metastasis data have been analyzed using this model.

Chapter 7 concludes the thesis and provides suggestions for further research.

Appendix A presents the calibration data of the slip-ring, helical CT scanner (HiSpeed; General Electric Medical Systems), that was used to acquire the DCE CT data used in this work.

Appendix B summarizes the solutions of the two-compartment lumped-parameter model and the adiabatic tissue homogeneity model, which are used in Chapter 5.

Appendix C presents an approach for efficient calculation of the distributed-parameter model with capillary distribution.

Chapter 2

Overview of Dynamic Contrast Enhanced Imaging Studies

2.1 Introduction

Dynamic Contrast Enhanced (DCE) imaging has gained widespread interest as a method for *in vivo* assessment of tissue hemodynamics, which can potentially provide physiological or functional information for diagnostic purposes [3], [4], [21]-[36]. DCE images must be post-processed to extract information that describes microcirculation within the tissue. Section 2.2 provides an overview of the features and requirements of a DCE imaging experiment. Section 2.3 reviews some of the existing methods and models commonly employed for the analysis of DCE images. Section 2.4 explains the need to improve on the analysis of DCE images with the recent advances in imaging technologies, and the aims for undertaking this research project.

2.2 Acquisition of DCE Images

2.2.1 Imaging Modalities for DCE Studies

X-ray Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) are common clinical imaging modalities that can be used for DCE imaging studies. In the literature, DCE imaging is also referred to as ‘perfusion imaging’ or ‘functional imaging’, which depicts the purpose of the technique.

2.2.1.1 X-ray computed tomography (CT)

The first practical CT instrument was developed in 1971 by Hounsfield [37]. Two decades ago, Axel proposed the use of CT for DCE imaging studies [38]. However, it was only about a decade later, with the advent of the spiral CT systems in the 1990s, that DCE studies were more widely performed [39].

Fundamentally, CT creates a 2-dimensional image that represents a 3-dimensional slice of tissue within a living organism. X-rays penetrate the tissue and reach the opposite side of the emitter, where detectors measure the attenuation caused by the tissue. The X-ray attenuation is assumed to be proportional to tissue radiodensity, and the total attenuation measured can be expressed as a sum of tissue radiodensities along the X-ray path. The X-ray emitter rotates around the tissue to collect sufficient attenuation data for the reconstruction of an image, by solving for individual voxel radiodensities. Thus, pixel values on a CT image represent tissue voxel radiodensities, which can be expressed in Hounsfield unit (Hu). As defined by Hounsfield, the radiodensities of distilled water and air are 0 Hu and -1000 Hu,

respectively. The method of Filtered Back-Projection is commonly used for reconstructing CT images.

A major strength of CT is its widespread availability and cost advantage. The high spatial resolution (about 0.2 mm^2 in our dataset) allows arterial vessels to be recognizable in the DCE images, which is beneficial to quantitative analyses of DCE data (see (2.3)). A major disadvantage is the use of ionizing radiation, i.e. X-rays. For DCE CT imaging, lower voltage CT protocols are recommended, for example 80 kVp as compared to 120 kVp for a regular diagnostic scan [40], [41]. Wintermark *et al.* [41] found that 80-kVp acquisition of DCE CT studies lowers the radiation dose by a factor of 2.8 as compared with 120 kVp (291 mGy at 80 kVp and 806 mGy at 120 kVp). Thus, the overall effective dose required for a DCE CT study can be kept at levels close to that required for a routine whole brain CT scan.

2.2.1.2 Magnetic resonance imaging (MRI)

The first commercial MRI scanners appeared about a decade after Lauterbur published the first MRI results in 1970s [42]. MRI technology has been advancing both in hardware and software, achieving higher spatial resolution, shorter imaging time, and better signal-to-noise ratio (SNR). DCE MRI images were initially used in the 1990s to study diseased conditions of the brain, resulting in the disruption of the blood-brain barrier⁹ (BBB).

⁹ The blood-brain barrier is composed of endothelial cells packed tightly in the brain capillaries that more effectively restrict passage of substances from the bloodstream than do endothelial cells in capillaries elsewhere in the body.

MRI [43] is fundamentally different from CT although both allow visualization of a 3-dimensional slice of tissue on a 2-dimensional image. The main signal sources in MRI are the hydrogen nuclei, found abundantly in both fat and water molecules present in the tissue. These protons are perturbed by specific radiofrequency (RF) pulses, in the presence of a strong magnetic field. When the perturbed protons relax, they again emit RF signals in all directions. By preparing a tissue slice such that the RF signal emitted from different voxel locations are encoded in both the phase and frequency, the received RF signal can then be decoded using Fourier Transform, to derive a map of signal magnitudes corresponding to the voxel locations in the slice.

MRI offers great flexibility to obtain a number of different types of images by varying the MR sequences. These sequences represent various ways of preparing and sending RF impulses to the tissue slice, and the various post-processing methods for the RF signal received. Two common types of MRI images are the T1-weighted and T2*-weighted images, corresponding to the spin-lattice (T1) and spin-spin (T2*) relaxation times, respectively, of the tissue imaged.

MR images can have spatial resolution comparable to CT images, and allow large arterial vessels to be recognizable on the MR image. However, the relationship between the pixel signal enhancement and the concentration of contrast agent is nonlinear, and this raises concerns on the suitability of quantitative analysis by DCE MRI. The main attractiveness of MRI is that it is considered safe, since ionizing radiation is not involved. ASL-MRI could be a promising DCE imaging modality as it is truly non-invasive, and does not require external substance to be

injected as contrast agent, which may affect the physiological behavior of the studied tissue.

2.2.2 Contrast Agents

Clinically approved contrast agents are often used for better differentiation and visualization of tissues in medical imaging. These contrast agents are usually injected intravenously at an arm. A set of DCE images is a series of images that records the amount of contrast agent at the same tissue location, for successive time instances. In DCE imaging, the contrast agent acts like a tracer of blood flow, and by monitoring the residual amount of tracer within the tissue of interest, one attempts to derive information on the hemodynamics of the tissue.

Iodinated compounds used as contrast agents for CT imaging, have higher radiodensity than normal tissue, and the presence such compounds in the tissue increases the pixel values in a CT image. This increase in pixel value is linearly proportional to the concentration of the contrast agent, within a wide range of contrast agent concentration [44], and can be validated by performing CT calibration experiments.

The contrast agents used in DCE MRI studies are paramagnetic substances (usually gadolinium compounds) that can result in the shortening of T1 and T2* of the perfused tissue. This selectively affects the signal strength for various regions within the T1-weighted and T2*-weighted images. Two different terms, DCE-MRI and DSC-MRI (Dynamic Susceptibility Contrast enhanced), refer to DCE images obtained by the T1-weighted and T2*-weighted MR imaging sequences, respectively.

Both the iodinated and gadolinium contrast agents, respectively used in DCE CT and MRI, have similar molecular sizes and the tracer kinetics of these two compounds are functionally similar. Both contrast agents may diffuse from the blood plasma within the capillaries into the tissue interstitial, but not into the cells in the tissue. Therefore, the distribution space for these two contrast agents include the intravascular plasma space (IVPS) and the interstitial or extravascular, extracellular space (EES). The IVPS is the space within the blood vessel, excluding the internal space of blood cells. The EES is the space outside the blood vessels excluding the internal space of tissue cells.

2.3 Methods for Analysis of DCE Images

2.3.1 Qualitative Approaches

2.3.1.1 Graphical methods

A plot of pixel values against time can be obtained by identifying a group of one or more pixels that specify a region of interest (ROI) within the images or a volume of interest (VOI) of the tissue. Such plots illustrate the behavior of the contrast agent as it passes through the tissue. The analysis of DCE images thus reduces to analysis of each of these curves. Descriptive parameters that characterize the curve, such as peak value, bolus arrival time, time to peak, initial rising slope and half maximum full width can be determined. These parameters can provide some level of appreciation of the physiological differences among tissue voxels.

2.3.1.2 Feature classification methods

By treating a series of ϕ DCE images as a single image in which each pixel contains a set of ϕ features, one can perform image segmentation by feature-classification methods. Typical methods includes Principal Component Analysis (PCA), Linear Discriminant Analysis (LDA), Independent Component Analysis (ICA), Active Snake Model (ASM) and Support Vector Machine (SVM). Although the segmented regions do contain physiological rather than anatomical information, the actual physiological condition of these regions is usually not known.

2.3.2 Quantitative Approaches

An important reason for performing DCE imaging is to achieve quantitative description of the tissue physiology. The typical behavior of the contrast agent, as it follows the flow of blood into and out of a tissue volume, is described here. Physiologically based mathematical relations of time-concentration curves are formulated to describe the transit behavior of the contrast agent.

Figure 2.1 shows a schematic illustration of the tissue vasculature. In this discussion we will only consider extracellular contrast agents that cannot enter into cells and distribute only in the IVPS and EES spaces within the tissue VOI. Blood carrying the injected contrast agent enters at the arterial end and exits from the venous end at the same volumetric flow rate. During the passage through the tissue, contrast agent might diffuse from the IVPS into the EES, which is called an

influx. Over time, contrast agent in the EES will diffuse back from the EES into the IVPS, which is called an efflux, or back flux.

Figure 2.1 A schematic illustration of the vasculature within a tissue region. Solid lines represent blood vessels. The dotted-line box represents a cross-sectional view of the tissue volume of interest. The dots represent the cells (not to scale). The arrows indicate the direction of blood flow.

From the system theory perspective, each tissue VOI can be viewed as a transport system, with the input signal $Input(t)$ being the amount of contrast agent entering the system and the output signal $Output(t)$ as the amount remaining¹⁰ in the system, at a given time t . For contrast agents that follow¹¹ Fick's mass conservation law, and assuming that the tissue physiological state remains constant during the acquisition of the DCE images, each tissue VOI is a linear, time-invariant system. The relation between the input and output signal of a linear, time-invariant system can be described by the convolution relation,

$$Output(t) = Input(t) \otimes R(t), \quad (2.1)$$

¹⁰ One must not confuse the output signal with the outflow of contrast agent from the tissue VOI.

¹¹ Discussion of cases for contrast agents that do not follow Fick's law or are involved with metabolism is beyond the scope of this thesis.

where t is the time measured from the first appearance of contrast agent at the tissue arterial supply end, $\otimes$ is the convolution operator and $R(t)$ is the impulse response function [or the impulse residue function, since the output signal reflects the remaining or residual contrast agent in the tissue VOI]. The impulse residue function $R(t)$ denotes the fraction of an impulse of contrast agent remaining in the tissue VOI since its arrival.

One may consider the incoming bolus of tracer¹² as a sequence of impulses entering the tissue region, and the total amount of tracer remaining in the tissue region at a given time is hence the superposition of the corresponding residue functions of the incoming impulses, which can be represented using a convolution integral.

Therefore, $R(t)$ depends on the characteristics of each tissue VOI and the tracer used. $R(t)$ contains information related to each tissue VOI, such as the structure of the capillary network, length and size of capillaries, amount and rate of tracer and blood passing through it, how much tracer and blood went out of the vascular vessel, and etc. Quantitative analysis of DCE data aims to uncover these information from $R(t)$.

From the system theory point of view, the $Output(t)$ can be treated as the remaining tracer quantity,

$$Output(t) = C_{tiss}(t) V, \quad (2.2)$$

¹² The term ‘tracer’ will be used hereafter in place of contrast agent.

where $C_{\text{tiss}}(t)$ (mmol mL^{-1}) is the tracer concentration in the tissue VOI and V (typically specified in mL) is the volume of the tissue VOI. $\text{Input}(t)$, which is the amount of tracer entering the tissue VOI from incoming arterial vessels, can be expressed as the product of tracer concentration in the IVPS and the volume of blood plasma entering the tissue VOI per unit time,

$$\text{Input}(t) = \frac{C_a(t)}{(1-Hct)} (1-r Hct) \rho F V, \quad (2.3)$$

where $C_a(t)$ (mmol mL^{-1}) is the tracer concentration in arterial blood entering the VOI, Hct is the hematocrit¹³ ratio in large vessel and r is the ratio of the hematocrit ratios in small vessel over large vessel [45]-[47]. F (typically expressed in mL/g/min) is the blood perfusion while ρF (min^{-1}) is the fractional volume of blood entering the tissue VOI per unit time, where ρ (g/mL) is the tissue density. Inclusion of Hct (typically about 0.4) in the first term is to convert the input $C_a(t)$ to tracer concentration in plasma, because $C_a(t)$ is usually sampled at a major artery visible on the DCE image, which therefore refers to tracer concentration in whole blood (plasma and blood cells) in the artery. Inclusion of r (typically about 0.8) and Hct in the second term is to convert the blood perfusion, F , into plasma perfusion at the tissue capillaries as the former is the usual definition of the term ‘perfusion’.

From (2.1) one obtains

$$C_{\text{tiss}}(t) = \frac{(1-r Hct)}{(1-Hct)} \rho F C_a(t) \otimes R(t). \quad (2.4)$$

Therefore, for quantitative analysis, the image pixel values need to be converted into values that are linearly proportional to tracer concentration. Then, with the

¹³ Whole blood consists of both plasma and blood cells. Hematocrit ratio is the fraction of whole blood that is occupied by blood cells.

time-concentration curves $C_a(t)$ and $C_{tiss}(t)$ obtained from the DCE images, (2.4) can be solved by a deconvolution process to retrieve the product of blood perfusion F and the impulse residue function, $R(t)$. Blood perfusion indicates if the tissue was being supplied by sufficient amount of blood. The area under the $R(t)$ curve is equal to the mean transit time [48], [49], MTT (min), of tracer through the tissue. From the values of MTT one can tell if the tracer traversed the tissue quickly through the blood vessels or if it was retained in the tissue VOI, most likely due to leakage from the vessels into EES. According to the Central Volume Principle [48], [49], the vasculature can be approximated as a single ‘central’ vascular space, such that the product of the constant volumetric flow rate and mean transit time yields the volume of central vascular space. Thus, the product $F \times MTT$ is equal to the fractional blood volume fBV in the tissue VOI. If there is no leakage of tracer from the blood vessels into EES, fBV is equal to the fractional vascular volume, and MTT is equal to the fractional vascular mean transit time.

Two major approaches in solving the convolution equation (2.4) are:

- (a) Numerical deconvolution methods;
- (b) Tracer kinetic modeling methods that account for convective transport (blood flow) and blood tissue exchange (capillary permeability).

2.3.2.1 Numerical deconvolution

In practice $C_a(t)$ and $C_{tiss}(t)$ are usually sampled at discrete intervals of Δt . In such a case, (2.4) can be rewritten in a matrix form,

$$\begin{pmatrix} C_{\text{tiss}}(0) \\ C_{\text{tiss}}(\Delta t) \\ \vdots \\ C_{\text{tiss}}((n-1)\Delta t) \end{pmatrix} = \begin{pmatrix} C_a(0) & 0 & \cdots & 0 \\ C_a(\Delta t) & C_a(0) & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ C_a((n-1)\Delta t) & C_a((n-2)\Delta t) & \cdots & C_a(0) \end{pmatrix} \times \begin{pmatrix} R(0) \\ R(1) \\ \vdots \\ R(n-1) \end{pmatrix} \Delta t F. \quad (2.5)^{14}$$

The product $FR(t)$ can be computed by multiplying both sides of (2.5) by the inverse of the C_a matrix. Thus, numerical deconvolution methods yield a discrete curve for this product. Since $R(t)$ by definition, must be equal to one (unity) at the first instance when an impulse of tracer arrives and has to be a decreasing function, the first, or the maximum value of the $FR(t)$ discrete curve can be used to estimate F [50]. Furthermore, fBV can be calculated from the area under this curve. Finally, the MTT can be calculated from the ratio fBV / F , by the Central Volume Principle.

The matrix method is the most widely used numerical deconvolution technique [51]. It is simple to understand and implement on a computer [51], [52]. Numerical deconvolution has the advantage of not requiring *a priori* knowledge or assumptions regarding the features of the tissue impulse residue function. Unfortunately, it is extremely sensitive to noise in the data. Regularized Singular Value Decomposition (SVD) is a common algebraic approach to minimize the effects of noise, by minimizing the residual vector norm [53]. To handle the noise, some constraints such as enforcing $R(t)$ to be non-negative, less than 1 and having non-positive gradient, can be incorporated to improve the results [51].

¹⁴ The constant term in (2.4) was set to unity.

Numerical deconvolution methods are fast and quantitative, although they are not significantly faster than many qualitative methods and produce less quantitative information than tracer kinetic modeling.

2.3.2.2 Tracer kinetic modeling

The numerical deconvolution methods are limited by the amount and quality of information extractable from the discrete curve representation of the impulse residue function. Tracer kinetic modeling approaches attempt to describe the physical transport and diffusion processes within the tissue VOI.

Tracer kinetic modeling solves (2.4) by performing the following steps:

- (a) Define the model specifications for the tracer behavior by treating different diffusion spaces of the tracer as separate compartments, to describe with appropriate assumptions tracer kinetics in the tissue VOI.
- (b) Derive the impulse residue function, $R_{\text{model}}(t, \mathbf{p})$, based on model specifications, where array $\mathbf{p}$ contains the corresponding model parameters. The result is an analytical expression in terms of parameters used within the model;
- (c) Determine the best set of parameters, F and $\mathbf{p}$, in the expression $FR_{\text{model}}(t, \mathbf{p})$ that will produce the best agreement with the measured $C_a(t)$ and $C_{\text{tiss}}(t)$ curves, according to (2.4).

The first two steps represent the main effort in tracer kinetic analysis. Different model assumptions, or different derivations of the analytical expression could lead to different realizations of $R_{\text{model}}(t, \mathbf{p})$. The third step usually involves some

standard optimization, or curve fitting routines to achieve a best fit between the experimentally measured and the calculated $C_{\text{tiss}}(t)$. The modeled impulse residue function $R_{\text{model}}(t, \mathbf{p})$, being an analytical expression containing an extended physiological parameters set, may now provide additional information, instead of only F , MTT and fBV as is the case of numerical deconvolution.

From the analysis of the schematic diagram shown in Figure 2.1, one recognizes that there are at least three features worthy of inclusion in a useful tracer kinetic model. The first is the diffusion of the tracer through the wall of capillaries between IVPS and EES. The second is the distribution of tracer along capillaries. The third is the distribution of transit times to traverse the mesh of capillaries in the tissue VOI. However, in practice, the application of models with more features is limited by the quality of experimental data.

2.3.2.2.1 Some existing tracer kinetic models

This section reviews a few existing models that are commonly used in the literature. The following review is not meant to be exhaustive, but it serves to provide an appreciation of the trend of developments in tracer kinetic modeling.

By convention, in a tissue VOI system as illustrated in Figure 2.2, the IVPS is labeled as compartment 1 and the EES is labeled as compartment 2. Tracer concentration in compartment i is expressed as $C_i(t)$. Tracer enters and exits the IVPS at a constant perfusion rate. At each moment in time, tracer quantity in IVPS and EES changes, due to tracer diffusing between the IVPS and EES. This change in tracer quantity depends on the transfer constants. The transfer constant K_{ji}

(min^{-1}) is defined as the fractional volume of tracer in the tissue VOI volume that moves from compartment i to compartment j per unit time.

Figure 2.2 The block diagram of a typical representation of the tissue VOI as the IVPS and EES compartments. The outlined-arrows refer to the blood perfusion. The dotted-line box represents the tissue VOI. The tracer diffusion process is represented by transfer constants K_{21} and K_{12} .

2.3.2.2.1.1 Kety's single-compartment model

Kety's model [54] was first designed about 50 years ago for freely diffusible tracer (e.g. an inert gas being breathed in). It is commonly referred to as a single-compartment model. Tracer concentration gradient is assumed to be zero within the compartment, or instant mixing of tracer within the compartment is assumed.

When applying this model in the context of a tissue VOI, this means that the concentration of tracer in the IVPS is in diffusion equilibrium with the concentration in the EES at all times, and therefore these two spaces may be perceived to have 'merged' together as the only compartment in the tissue VOI with a single tracer concentration across the entire VOI (Figure 2.3).

Figure 2.3 The block diagram representation of the Kety's model. For consistency with other models mentioned here, we labeled the 'merged' compartment as compartment 2 and use K_{02} for the transfer constant out of the compartment, where compartment 0 is the space outside the tissue VOI.

Kety's model is described by the rate of tracer washout from the 'merged' compartment after an impulse of tracer enters at $t = 0$,

$$V_2 \frac{dC_2(t)}{dt} = -V K_{02} C_2(t), \quad C_2(0) = 1, \quad (2.6)$$

where V_2 (mL) is the volume of compartment 2 (IVPS+EES), $C_2(t)$ is the tracer concentration in compartment 2. By solving this equation, we find out that the impulse residue function is a single exponential decay function describing the rate of tracer washout from the tissue VOI,

$$R_{\text{Kety}}(t, k_{02}) = \exp(-k_{02} t), \quad (2.7)$$

where, $k_{ji} = K_{ji} / v_i$, and $v_i = V_i / V$. k_{ji} (min^{-1}) is called the rate constant defined as the fractional volume of tracer within compartment i that moves from compartment i to compartment j per unit time, which differs slightly from the definition of transfer constant K_{ji} . v_i is the fractional volume of compartment i within the tissue VOI volume.

By comparing Figure 2.2 and Figure 2.3, it is clear that the Kety's model does not provide any information about the K_{21} or K_{12} , as they are masked by the model

assumptions. Thus, this model does not provide information about the leakiness of capillary walls.

2.3.2.2.1.2 Renkin-Crone's model

If blood flow were so high that a fraction of incoming tracer had already passed through the tissue VOI before diffusion equilibrium had been reached, then Kety's model will describe only the remaining tracer. Renkin [55] first introduced an extraction fraction E to account for the fractional amount of incoming impulse of tracer that remained in the tissue VOI. Thus, the initial value in (2.6) is set to E , $C_2(0) = E$, and modified Kety's model [55], [56] impulse residue function became

$$R_{\text{Renkin-Crone}}(t, k_{02}) = E \exp(-k_{02} t) . \quad (2.8)$$

The undesirable side effect of such an approach is that only the product EF in (2.4) can be estimated since we do not know E .

2.3.2.2.1.3 Generalized kinetic model

The generalized kinetic model (GK) (Figure 2.4) [57] is a two-compartment model that ignores the tracer concentration in IVPS, $C_1(t)$. The contribution of intravascular tracer to the MRI signal remains a problem. As explained by Tofts *et al.* [57], $C_1(t)$ might not be visible in images produced by some DCE-MRI acquisition sequences, thus making its contribution negligible. For this reason, Figure 2.4 differs from Figure 2.2 by the region of the tissue VOI (dotted-line box).

This exclusion of tracer concentration in IVPS means that $C_2(t) = C_{\text{tiss}}(t) / v_2$. The change in concentration in the tissue VOI is described by

$$\frac{dC_{\text{tiss}}(t)}{dt} = K^{\text{trans}} C_1(t) - k_{\text{ep}} C_{\text{tiss}}(t) , \quad (2.9)$$

where $K^{\text{trans}} = K_{21}$, $k_{\text{ep}} = k_{12} = K_{12} / v_2$. Letters ‘p’ and ‘e’ were used in the literatures to represent the plasma space (IVPS) and the EES, and the order of ‘ep’ in the rate constant k_{ep} refers to tracer diffusion from EES to IVPS. Solving (2.9) gives

$$C_{\text{tiss}}(t) = C_1(t) \otimes (K^{\text{trans}} \exp(-k_{\text{ep}} t)) . \quad (2.10)$$

By comparing with (2.4), since $C_1(t) = C_a(t) / (1 - \text{Hct})$ we get

$$K^{\text{trans}} \exp(-k_{\text{ep}} t) = (1 - r \text{Hct}) F R_{\text{GK}}(t, k_{\text{ep}}) . \quad (2.11)$$

Figure 2.4 The block diagram representation of the generalized kinetic model.

For a freely diffusible tracer as in Kety’s model, the amount of incoming tracer is fully dependent on the perfusion F . Thus, $K^{\text{trans}} = (1 - r \text{Hct}) F$ and $R_{\text{GK}}(t, k_{\text{ep}}) = R_{\text{Kety}}(t, k_{02})$ and $k_{02} = k_{\text{ep}}$. In general, if only a constant fraction of incoming tracer is entering the tissue VOI, using the extraction fraction E as this fraction throughout the imaging process, $K^{\text{trans}} = (1 - r \text{Hct}) F E$ and thus $R_{\text{GK}}(t, k_{\text{ep}}) = R_{\text{Renkin-Crone}}(t, k_{02})$ and $k_{02} = k_{\text{ep}}$.

As a two-compartment model, the GK model describes the diffusion between the two compartments. With the exclusion of $C_1(t)$, $R_{GK}(t, k_{ep})$ becomes equivalent to a single-compartment model.

2.3.2.2.1.4 Two-compartment conventional compartmental model

Clearly, two-compartment models are better than single-compartment models since the tissue VOI consists of at least two tracer distribution spaces, the IVPS and EES. The GK model is a special case where $C_1(t)$ could be justifiably ignored. Larson *et al.* [58] have shown that the extraction ratio is not constant due to the back flux of tracer from EES into the IVPS, thus reducing the net amount of tracer being transferred from IVPS to EES over time. Thus, in the above models, the constant initial extraction fraction, $E(0)$ is only an estimate for the actual time-varying extraction ratio $E(t)$ [57], [58].

Two-compartment models are needed when the measured $C_{tiss}(t)$ has significant contributions from both $C_1(t)$ and $C_2(t)$ [57], which is the case for DCE CT data. The two-compartment, conventional compartmental (CC₂) model assumes that the IVPS and EES are homogeneous compartments (Figure 2.2). Typically, a pair of differential equations for the two interacting compartments can be written as

$$v_1 \frac{dC_1(t)}{dt} = -\rho (1 - r Hct) F C_1(t) - K_{21} C_1(t) + K_{12} C_2(t) + \frac{\delta_t(t)}{V}, \quad (2.12a)$$

$$v_2 \frac{dC_2(t)}{dt} = -K_{12} C_2(t) + K_{21} C_1(t), \quad (2.12b)$$

where v_1 and v_2 are the fractional IVPS and EES volumes respectively, the Dirac delta function $\delta_t(t)$ represents the unit impulse input into the IVPS at $t = 0$. The first term of (2.12a) represents the tracer leaving through the outflow of blood plasma

in venous vessels. The second and third terms of (2.12a) and the two terms in (2.12b) represent tracer diffusion between compartments 1 and 2. Since in the GK model, $C_2(t) = C_{\text{tiss}}(t) / v_2$ due to the exclusion of $C_1(t)$, left hand side and the last term of (2.9) can also be expressed as in (2.12b) by substituting $C_{\text{tiss}}(t) = v_2 C_2(t)$.

The solution for the impulse residue function of the two-compartment model is [59]:

$$R_{\text{CC}}(t, t_1, k_{21}, k_{12}) = A \exp(s_1 t) + (1 - A) \exp(s_2 t) , \quad (2.13)$$

which is a bi-exponential function where t_1 (min) is the vascular mean transit time,

$$s_1, s_2 = \frac{1}{2} \left[- \left(k_{21} + k_{12} + \frac{1}{t_1} \right) \pm \sqrt{\left(k_{21} + k_{12} + \frac{1}{t_1} \right)^2 - 4 \frac{k_{12}}{t_1}} \right] , \quad (2.14a)$$

$$A = \frac{s_1 + k_{21} + k_{12}}{s_1 - s_2} . \quad (2.14b)$$

By considering only the leakiness of blood vessels, which is the physical wall separating the IVPS and EES, the transfer constants K_{ji} can also be described as the product of permeability coefficient P ($\text{cm}^2 \text{min}^{-1}$), which is the fractional volume in tissue VOI passing through the wall per unit area per unit time, and surface-area of the wall S (cm^2). In general, K_{21} and K_{12} differ according to the partition coefficient λ_{12} between IVPS and EES such that

$$\lambda_{12} K_{12} = K_{21} = \rho PS . \quad (2.15)$$

where it is very often to assume $\lambda_{12} = 1$. It should be noted that transfer constants are kinetic parameters measuring the actual volumetric flow rate through the vessel wall, whereas PS is a physical measurement of the maximally allowed volumetric flow rate of the tracer through the vessel wall.

2.3.2.2.1.5 Multiple-compartment mammillary CC model

Ludemann *et al.* [23] have devised a three-compartment, mammillary CC model (MCC_3), with two EES compartments in direct exchange with one IVPS compartment. They believed that the two distinct EES compartments with different rate constants, could account for the filling of viable and necrotic tissues within a tumor. In other words, the tissue VOI (dotted-line box in Figure 2.1) is assumed to consist of viable and necrotic tissues, which are represented by two EES compartments. They applied the MCC_3 model on DCE MRI datasets of cerebral gliomas and derived fractional volume maps which showed a correspondence with World Health Organization grading in 83% of the cases.

Port *et al.* [60] have also devised a four-compartment mammillary CC model (MCC_4), with three EES compartments in direct exchange with one IVPS compartment, for analysis of DCE MRI data of breast tumors. They found that kinetic heterogeneity (i.e two or more distinct EES compartments) was present in 85% of the carcinomas. However, explicit solution of $R(t)$ to the MCC_4 model was not given and a commercial software was employed to solve the differential equations and derive the parameter estimates.

2.3.2.2.1.6 Tissue homogeneity model

A number of researchers [57], [58], [61]-[63] recognized the limitations of the conventional compartmental models and had proposed more realistic models. The conventional compartmental models include blood exchange between IVPS and EES, but not the convective transport along the vessel. Next, we review some work on a better model that takes into account both convective transport in the IVPS and

blood tissue exchange between the IVPS and EES. This model is defined with following assumptions:

- (a) Different regions of the EES or tissue parenchyma have the same tracer concentration, i.e. one assumes the parenchymal tissue to be homogeneous;
- (b) Tracer concentration within the blood vessel is defined as a function of time and distance along the vessel's path;
- (c) Tracer concentration is assumed to be independent of the radial distance within the blood vessel.

Figure 2.5 The block diagram of a tissue homogeneity model. Concentration of tracer in IVPS is expressed in terms of both time, and distance from the arterial end.

Since only the EES or tissue parenchyma is assumed to have homogeneous concentration, some literature [62], [63] refers to it as the tissue homogeneity (TH) model. Figure 2.5 illustrates this model. The rate of change of tracer concentration in compartment 1 and 2 are

$$\begin{aligned}
 v_1 \frac{\partial}{\partial t} C_1(t, z) dz = & -\rho(1 - r Hct) F L \frac{\partial}{\partial z} C_1(t, z) dz - K_{21} C_1(t, z) dz \\
 & + K_{12} C_2(t, z) dz + \frac{L}{V} \delta_1(t) \delta_z(z) dz,
 \end{aligned} \tag{2.16a}$$

$$v_2 \frac{\partial}{\partial t} C_2(t, z) dz = -K_{12} C_2(t, z) dz + K_{21} C_1(t, z) dz , \quad (2.16b)$$

where z (cm) is the distance from the arterial end, L (cm) is the average length of the capillaries and the Dirac delta functions in time and space domains, $\delta_t(t)\delta_z(z)$ together represent the unit impulse input into the IVPS at time $t = 0$ min and position $z = 0$ cm.

Johnson and Wilson [61] were first to solve (2.16) for modeling of blood tissue exchange. They found out that tracer concentrations in the two compartments, in the complex domain, can be described by equations

$$\overline{\overline{C_1(s, z)}} = \frac{1}{s} \exp(-(\gamma + s)) \xi + \frac{(1 - \exp(-(\gamma + s)))(1 - \exp(-(\gamma + s)) \xi)}{s (P(s) - \exp(-(\gamma + s)))} , \quad (2.17a)$$

$$\overline{\overline{C_2(s)}} = \frac{(\gamma + s)(1 - \exp(-(\gamma + s)))}{\gamma s (P(s) - \exp(-(\gamma + s)))} , \quad (2.17b)$$

where $\overline{\overline{C_1(s, p)}} = \mathcal{L}_t(\mathcal{L}_z(C_1(t, z))(p))(s)$, $\overline{\overline{C_2(s)}} = \mathcal{L}_t(C_2(t))(s)$ denotes the Laplace transforms and s is the Laplace transform of t , $\gamma = PS / F$, $\xi = z / L$,

$$P(s) = \left(\frac{K}{\gamma^2} \right) s^3 + \left(\frac{(2K+1)}{\gamma} \right) s^2 + (K+1)s + 1 , \quad (2.18)$$

and $K = v_2 / v_1$. However, their asymptotic solution in time domain is not available in closed form as they expanded the denominator into an infinite series before performing the inverse Laplace transformation. Thus, in practice, only the truncated solutions could be used.

2.3.2.2.1.7 Multiple-compartment catenary distributed-parameter model

Larson *et al.* [58] did a comparative study of distributed-parameter and lumped-parameter models, and derived a solution for the impulse residue function of the

TH model. Although they referred to the TH model as a two-compartment distributed-parameter (DP_2) model, they explained that it is in fact a hybrid, involving a combination of lumped and distributed-parameter assumptions, respectively, in the EES and IVPS.

Figure 2.6 The block diagram of the CDP_3 model. The gray boundary between compartments 2 and 3 is not a physical boundary.

Larson *et al.* [58] further derived the impulse residue function for a three-compartment, catenary distributed-parameter (CDP_3) model, with the EES divided into two sub-compartments (Figure 2.6), i.e the first surrounding the IVPS and second surrounding the first. In the following, we shall follow Larson *et al.* to refer to such models as ‘distributed-parameter’, and we recognize that only the IVPS is a distributed-parameter space, while the EES may involve one or more lumped compartments. Closed-form impulse residue functions of the DP_2 and CDP_3 models in time domain are [58]:

$$R_{DP_2}(t, t_1, k_{21}, k_{12}) = u(t) - \left\{ u(T) \left[\frac{1 - J(T, \chi) + \exp(-\chi) \exp(-k_{12} T) I_0(2\sqrt{\kappa T})}{\exp(-\chi) \exp(-k_{12} T) I_0(2\sqrt{\kappa T})} \right] \right\}_{T=t-t_1}, \quad (2.19a)$$

$$R_{\text{CDP3}}(t, t_1, k_{21}, k_{12}, k_{32}, k_{23}) = u(t) - \exp(-\chi) u(t - t_1) \left\{ 1 + \sum_{i=1}^2 \left[\int_0^T \exp(-\beta_i \tau) y_i(\tau) d\tau \right] + \int_0^T [\exp(-\beta_1 \tau) y_1(\tau)] \otimes [\exp(-\beta_2 \tau) y_2(\tau)] d\tau \right\}_{T=t-t_1}, \quad (2.19b)$$

where $u(t)$ is the Heaviside unit step function, J is the J function (2.20a), I_0 is the zeroth-order modified Bessel function of the first kind,

$$J(w, y) = 1 - \exp(-y) \int_0^w \exp(-r) I_0(2\sqrt{yr}) dr, \quad (2.20a)$$

$$\chi = k_{21} t_1, \quad (2.20b)$$

$$\kappa = k_{21} k_{12} t_1, \quad (2.20c)$$

$$\beta_1, \beta_2 = \frac{1}{2} \left((k_{12} + k_{32} + k_{23}) \pm \sqrt{(k_{12} + k_{32} + k_{23})^2 - 4 k_{12} k_{23}} \right), \quad (2.20d)$$

$$y_i(t) = \sqrt{\frac{B_i}{t}} I_1(2\sqrt{B_i t}), \quad i = 1, 2, \quad (2.20e)$$

$$B_1 = \frac{k_2 (\beta_1 - k_{23})}{(\beta_1 - \beta_2)}, \quad (2.20f)$$

$$B_2 = \frac{k_2 (k_{23} - \beta_2)}{(\beta_1 - \beta_2)}. \quad (2.20g)$$

However, these solutions have been found to be difficult to implement in practice [64].

2.3.2.2.1.8 Adiabatic approximation to the TH model

A relatively simple model has recently been introduced by St. Lawrence and Lee [62], which is an adiabatic approximation to the tissue homogeneity (ATH) model. The ATH model assumes that the change in tracer concentration with time is slow in the parenchymal tissue compared to concentration changes in the blood vessel. Therefore, it can be assumed to remain constant during small time intervals. With

these assumptions, they derived a closed-form solution in the time domain; its impulse residue function is equal to

$$R_{\text{ATH}}(t, t_1, E, F_p, v_e) = \begin{cases} 1 & 0 < t \leq t_1 \\ E \exp\left(-\frac{E F_p}{v_e}(t - t_1)\right) & t > t_1 \end{cases}, \quad (2.21)$$

where $v_e = v_2$, $F_p = (1 - r Hct) F$ which is the plasma perfusion.

We note that only for time $t > t_1$, $R_{\text{ATH}}(t, t_1, E, F_p, v_e)$ is different from (2.19a) for the DP₂ model. In fact, for time $t > t_1$, $R_{\text{ATH}}(t, t_1, E, F_p, v_e)$ is equivalent to a case of the GK model, $R_{\text{Renkin-Crone}}(t, k_{02})$ (see Section 2.3.2.2.1.3). If one defines $K^{\text{trans}} = (1 - r Hct) F E = E F_p$ and assumes $K_{12} = K_{21}$ (i.e. no preference of diffusion direction), then $k_{02} = k_{12} = K_{12} / v_e = K_{21} / v_e = K^{\text{trans}} / v_e = E F_p / v_e$. Thus, functionally, the ATH model can be viewed as a rectangular shaped $R(t)$ for $t \leq t_1$ followed by $R_{\text{Renkin-Crone}}(t - t_1, E F_p / v_e)$ for $t > t_1$

$$R_{\text{ATH}}(t, t_1, E, F_p, v_e) = \begin{cases} 1 & 0 < t \leq t_1 \\ R_{\text{Renkin-Crone}}(t - t_1, E F_p / v_e) & t > t_1 \end{cases}. \quad (2.22)$$

In other words, the effect of the adiabatic approximation is the same as ignoring contribution of tracer concentration in the IVPS to the concentration in the tissue VOI after time t_1 . Thus, the main added value by the DP₂ model, namely, the distribution of tracer concentration in IVPS, is removed by the adiabatic approximation for $t > t_1$, and the DP₂ model reduces to a GK model after time t_1 . Nevertheless, unlike the GK model, F and E are separately identifiable from the ATH model.

2.3.2.2.1.9 Distributed-capillary ATH model

In the TH, DP₂ and ATH models, (2.19a) and (2.22) depict discontinuous functions at t_1 . Johnson and Wilson have proposed to use the DP₂ model to model a single capillary exchange [61]. In their model, t_1 is the transit time through compartment 1 because they assume bolus flow in a single capillary, where segments of plasma are assumed to be trapped between successive blood cells. Since there are numerous capillaries in the real tissue, and compartment 1 represents their combined IVPS, t_1 is the average of all the different actual transit times in different capillaries (Figure 2.1), which are lumped into a single IVPS (Figure 2.2 and Figure 2.5).

More recently, Koh *et al.* [63] included the capillary transit time distribution into the ATH (DCATH) model. The DCATH model takes into account the functional distribution of blood vessels in tissue, with each vessel behaving according to the ATH model. The standard deviation, σ , of the transit times is the additional parameter derivable from the DCATH model. The DCATH model impulse residue function is equal to

$$R_{\text{DCATH}}(t, t_1, E, F_p, v_e, \sigma) = 1 - \int_0^t g(\tau, t_1, \sigma) d\tau + E \exp\left(-\frac{E F_p}{v_e} t\right) \int_0^t g(\tau, t_1, \sigma) \exp\left(\frac{E F_p}{v_e} \tau\right) d\tau, \quad (2.23)$$

where $g(t, t_1, \sigma)$ is a suitable probability distribution function that models the capillary distribution. They have studied a modified normal distribution and an asymmetric distribution.

2.4 Concluding remarks

Recently, DCE imaging is becoming more popular with the technology advancements in CT and MRI. Existing methods for DCE image analysis have been adapted mostly from the earlier, functional imaging methods used in nuclear medicine. A survey of developments in medical imaging technologies shows a steady trend towards increased quality of medical images. For example, the advanced multi-detector CT machines now have up to 16 or more detectors, and up to 8 Tesla MRI machines are available. Current imaging technologies are producing DCE images with better spatial and temporal resolution than those available just a few years ago. These high quality images reveal the limitations of current methods of data analysis. Clinicians and researchers are looking for better analysis methods.

Many recent published papers are seeking quantitative information from the DCE images from CT and MRI. To achieve this goal, the generalized kinetic model (Section 2.3.2.2.1.3) and conventional compartmental models (Section 2.3.2.2.1.4) are commonly used, although there are more realistic models (Sections 2.3.2.2.1.5 to 2.3.2.2.1.9) that can better represent the tissue being studied. We also noted that the low quality of early DCE images and the computational complexities of distributed-parameter models have discouraged the application of the distributed-parameter models, even though they admittedly are more realistic.

Against this background, this research project aims to fill such needs by:

- (a) Developing and implementing models more suitable for analysis of high quality DCE images;
- (b) Verifying the performance of these models;
- (c) Improving the efficiency of applications of such models.

Chapter 3

Materials and Methods

3.1 Materials

This section describes the acquisition protocols of the DCE CT datasets used in Chapters 4, 5 and 6. A major concern for DCE CT is the additional radiation exposure. Only a limited number of patient study cases were carried out, with approval from the institutional ethics committee, and with informed, written consent from the patients. For DCE CT, appropriate measures should be taken to keep the radiation burden within clinically acceptable range. Apart from reducing and limiting the number of scans, lower voltage CT protocols are also recommended for DCE CT studies [41], [46]. Using a low voltage (80 kVp) protocol, Nabavi *et al.* [46] have checked that the overall effective dose equivalent for a DCE CT study (~ 2.0 mSv) can be kept lower than those of perfusion studies performed using PET or SPECT.

3.1.1 Intracranial Meningioma and Metastases

Written consent was obtained from 6 patients (2 female and 4 male, age 59.3 ± 9.27 years) with intracranial meningioma and 5 patients (all male, age 66.4 ± 10.31 years) with cerebral tumors (metastasis). All patients were included in a clinical study to evaluate the feasibility of using DCE CT for assessment of cerebral perfusion in intracranial lesions. Final diagnosis was achieved by histological examination and follow-up imaging. The observed metastases were from bronchogenic carcinoma and there was no evidence of hemorrhage in the lesions studied. The study was approved by the local ethics committee for the National Neuroscience Institute, Singapore, and none of the patients suffered any direct complication related to this study.

A slip-ring, helical CT scanner (HiSpeed; General Electric Medical Systems) that is capable for cine mode scanning was used. The dynamic CT images were obtained for a single slice positioned at the level of the largest lesion identified on non-contrast CT scans. 50 contrast enhanced images were acquired with a scanning time of 1 s per image and with the intravenous injection of 50 mL of non-ionic iodinated contrast medium, iohexol, with an iodine concentration of 300 mg/mL (Omnipaque; Nycomed, Oslo, Norway) and at a rate of 4 mL/s, using a power injector. Acquisition parameters for the CT scans were 80 kVp, 190 mAs, 512 by 512 matrix, field of view of 20-25 cm for the meningioma cases and 20-22 cm for the metastasis cases. For all cases, the slice thickness was 10 mm, except for one meningioma case (5 mm).

3.1.2 Prostate Tumor

One prostate DCE CT dataset was used. This dataset was previously acquired in the Princess Margaret Hospital, with institutional ethics approval and patient written consent. A slip-ring, helical CT scanner (HiSpeed; General Electric Medical Systems, Milwaukee, WI) was used. At the start of dynamic scans non-ionic iodinated contrast medium, Iopamidol (Isovue 300; Squibb Canada Inc., Montreal, PQ, Canada), was injected intravenously at a rate of 3.5–4.5 mL/s, and at a dosage of 1.5 mL/kg of patient body weight. Dynamic scans were performed in the first 120 s with a scan time of 1 s per image, 120 kVp, 100 mAs, 512 by 512 matrix, field of view of 22 cm, and with a slice thickness of 10 mm; followed by 12 scans with the same scan parameters and an interscan delay of 9 s.

3.2 Data Processing

The DCE CT images were processed offline on a Pentium IV personal computer. This section describes the various steps involved in the processing of these DCE CT images. An overview of the procedure is shown in Figure 3.1.

3.2.1 Realignment

To correct for in-plane patient movements, the images were registered by affine transformations (SPM software package; University College, London, UK) to the first image, which acts as a template. Images with artifacts due to through-plane movements and CT related problems, such as beam hardening, were not corrected. Nevertheless, we did not notice serious artifacts of this kind in the datasets.

1. Realign DCE CT images.
 - a. Correct for in-plane motions by registering images to the first image by affine transformation.
2. Define regions of interest.
 - a. Define arterial ROI.
 - b. Define venous ROI in brain images where arteries are small.
 - c. Define tissue ROI.
3. Extract concentration-time curves.
 - a. Extract a concentration-time curve, $C(t)$, from each ROI.
 - b. Adjust the arterial concentration-time curve, $C_a(t)$, according to the venous concentration-time curve, $C_v(t)$, if necessary.
4. Estimate parameters of tracer kinetic model.
 - a. Construct a $FR_{\text{model}}(t, \mathbf{p})$ curve at the same time points as $C_a(t)$ using pre-defined initial values for F and an array of parameters, $\mathbf{p}$, of a tracer kinetic model.
 - b. Construct a tissue concentration-time curve, $C_{\text{tiss}}(t)$, by convolving $C_a(t)$ and $FR_{\text{model}}(t, \mathbf{p})$.
 - c. Adjust values of F and $\mathbf{p}$, and repeat steps (a) and (b) to minimize the difference between the experimental and predicted $C_{\text{tiss}}(t)$ curves.

Figure 3.1 Procedure for analysis of DCE CT data by parametric fitting using a tracer kinetic model.

3.2.2 Estimation of Tracer concentration from CT numbers

A calibration experiment was performed to validate the linear relationship between CT number and tracer concentration, on the CT machine used to acquire the brain DCE CT images. The phantom used in the calibration experiment consists of containers with various tracer concentrations (data and results shown in Appendix A). Based on this linear relationship, the tracer concentration curve for a tissue voxel can be estimated by considering the difference in CT numbers between the post- and pre-contrast images, at the voxel location.

3.2.3 Correction of PVA for $C_a(t)$

In the brain DCE CT images, often an artery may not fully occupy an entire voxel (along the slice thickness axis) of the CT image, and the effect of partial volume averaging (PVA) could result in a smaller value of $C_a(t)$. To reduce the effect of PVA, one approach is to sample a venous concentration curve $C_v(t)$ to correct for the height of the underestimated $C_a(t)$ curve [65]. Veins are usually larger in diameter than arteries, and are less affected by PVA. Also, veins that are oriented perpendicularly to the plane of the image, could more likely occupy a full voxel along the slice thickness axis. As explained by Axel [38], although $C_a(t)$ and $C_v(t)$ may be associated with different profiles, they should theoretically have the same area under the curve, according to the principle of the conservation of tracer mass. Thus, a sampled $C_a(t)$ can be corrected for PVA by multiplying it with the ratio of the areas under $C_v(t)$ and $C_a(t)$.

A potential drawback of this approach is the possibility that $C_v(t)$ itself might also be affected by PVA. However, if the area under $C_v(t)$ is larger than that of the sampled $C_a(t)$, the scaling of the area of $C_a(t)$ should still be performed. The resulting ‘corrected’ $C_a(t)$ might be under-estimated, but it would be closer to its actual value than the sampled $C_a(t)$. In such cases, the approach described could provide a lower estimate of the actual $C_a(t)$, while the estimate would be good if the sampled $C_v(t)$ was not affected by PVA.

3.2.4 Deconvolution by Model Fitting

The operational equation for analysis of DCE imaging data can be given by the convolution integral

$$C_{\text{tiss}}^{\text{model}}(t, F, C_a(t), \mathbf{p}) = F C_a(t) \otimes R_{\text{model}}(t, \mathbf{p}) = C_a(t) \otimes FR_{\text{model}}(t, \mathbf{p}), \quad (3.1)$$

where $R_{\text{model}}(t, \mathbf{p})$ is the impulse residue function, with model parameters $\mathbf{p}$. The approach of obtaining $FR_{\text{model}}(t, \mathbf{p})$, by fitting against experimental data, is sometimes called parametric fitting or parametric deconvolution.

Assuming physiological values of F and $\mathbf{p}$ as the initial values for $FR_{\text{model}}(t, \mathbf{p})$, a model $C_{\text{tiss}}(t)$ curve can be obtained by convolving the sampled $C_a(t)$ with $FR_{\text{model}}(t, \mathbf{p})$, as in (3.1). The model $C_{\text{tiss}}(t)$ curve is compared with the experimental $C_{\text{tiss}}(t)$ curve extracted from the DCE images, and the difference between two curves can be given by the sum of squared residues. A search engine (optimization algorithm) is employed to systematically try out different values of F and $\mathbf{p}$ (within physiological ranges), to minimize the difference between model and experimental $C_{\text{tiss}}(t)$ curves, i.e to obtain the least-squares fit. In this project, a constrained nonlinear optimization algorithm (MatlabTM, fmincon) was used as the search engine to drive the fitting process.

3.2.5 Parameter Maps

In a set of DCE images, each voxel location can be treated as a ROI from which an experimental $C_{\text{tiss}}(t)$ curve can be extracted, and the corresponding F and $\mathbf{p}$ estimates derived by model fitting. Although such voxel-by-voxel calculation can be performed to obtain parameter maps of higher spatial resolution, it is rather time-consuming and the $C_{\text{tiss}}(t)$ curves obtained from single voxel ROIs have higher noise levels, which could affect the accuracy of parameter estimates. Averaging among the 2-by-2 voxel blocks reduces inherent noise and was found to be a good compromise between resolution and speed. For brain DCE CT data, the

SNR associated with $C_{\text{tiss}}(t)$ curves derived from single voxels containing the tumor, GM and WM were about 20, 14 and 7, respectively. The SNR was estimated by calculating the maximum increase during bolus passage, divided by the standard deviation of noise relative to pre-bolus baseline intensity [66]. The differences in SNR for the various tissue types are primarily due to the differences in contrast-related signal enhancement, and hence signal strengths, in the various tissues. The respective SNRs for tumor, GM and WM, typically improve to about 23, 18, and 9, by averaging 2-by-2 voxel blocks, which allow higher confidence on the various parameters to be estimated by tracer kinetic models.

In each parameter map, different shades of colors were used to represent a range of values for the particular parameter. Typically, the color red, which gives the impression of ‘hot’, was used to indicate high values for the parameter, and blue was used to indicate low values.

3.3 Analysis Methods

3.3.1 Goodness-of-Fit Comparison

The “goodness-of-fit” between model and data can be given by the Chi-squared statistic, χ^2

$$\chi^2 = \sum_{k=1}^{\phi} \frac{(C_{\text{tiss}}^{\text{expt}}(t_k) - C_{\text{tiss}}^{\text{model}}(t_k))^2}{\text{var}_k}, \quad (3.2)$$

where t_k is the time between the first and the k^{th} image acquisitions, and var_k is the noise variance in the experimental data. As the χ^2 statistic gives the sum of squares

of deviation between the experimental data and model fittings, a larger χ^2 value thus corresponds to a larger discrepancy between data and model fitting.

3.3.1.1 Comparing models of different complexities

A test statistic to compare the goodness-of-fit of a more complex model (χ_c^2) with that of a less complex (reduced) model (χ_r^2), can be given by

$$f(\chi_r^2, \chi_c^2) = \frac{\chi_r^2 - \chi_c^2}{df_r - df_c} / \frac{\chi_c^2}{df_c}, \quad (3.3)$$

which follows the F-distribution [67]. The degrees of freedom df_r and df_c are those associated with the reduced and complex models, respectively.

Since $\chi_r^2 \geq \chi_c^2$, we may implement a one-tailed F-test at significance level $\alpha = 0.05$. If χ_c^2 is not much less than χ_r^2 , then the complex model does not account for much more of the variability of the experimental data than does the reduced model, in which case the data suggest that the reduced model is adequate. Correspondingly, large values of $f(\chi_r^2, \chi_c^2)$ would justify the more complex model. Hence, the decision rule is: if $f(\chi_r^2, \chi_c^2) \leq f_{\alpha, df_r - df_c, df_c}$, reduced model is adequate, else complex model is justifiable, where $f_{\alpha, df_r - df_c, df_c}$ is the $(1-\alpha)$ quantile of the F-distribution with degrees of freedom, $df_r - df_c$ and df_c .

3.3.1.2 Comparing models of same complexity

A test statistic to compare the goodness-of-fit of two models, χ_1^2, χ_2^2 where $\chi_1^2 > \chi_2^2$ and the models have the equal number of parameters, can be given by

$$f(\chi_1^2, \chi_2^2) = \frac{\chi_1^2}{\chi_2^2}, \quad (3.4)$$

which follows the F-distribution [67]. A one-tailed F-test can be implemented, such that if $f(\chi_1^2, \chi_2^2) \geq f_{\alpha, df_1, df_2}$, then model 2 fits better than model 1 at the 95% confidence level ($\alpha = 0.05$).

3.3.2 Monte Carlo Simulation Experiments

The Monte Carlo simulation approach was used to study the changes in precision of model parameters, under varying noise conditions. Using (3.1), a simulated $C_{\text{tiss}}(t)$ curve for a particular tissue type can be generated using known values of F and $\mathbf{p}$ for the tissue (found in the literature), and convolving the resulting $FR_{\text{model}}(t, \mathbf{p})$ curve with an actual $C_a(t)$ curve. Random (Gaussian) noise was added to simulate noisy $C_{\text{tiss}}(t)$ curves associated with various degrees of noise, or signal-to-noise ratios (SNRs), where SNR is taken to be the ratio of the maximum value of $C_{\text{tiss}}(t)$ (before noise was added) and the standard deviation of noise [62], [66], [68]. For each SNR and tissue type, a set of 1000 noisy $C_{\text{tiss}}(t)$ curves were generated and fitted using a constrained nonlinear optimization algorithm (MatlabTM, fmincon), to derive the mean (m_i) and standard deviation (sd_i) estimates for each of the model parameters. The coefficient of variation for each parameter can be given by $CV_i = sd_i/m_i$, which gives an indication of the level of uncertainty (or error) associated with the estimation of the parameter.

Chapter 4

A Mammillary n -Compartment Distributed-Parameter (MDP $_n$) Model

Multi-compartment models can be broadly classified as 1) catenary, where compartments are connected in a linear array with each compartment communicating with its closest neighbor, and 2) mammillary, where a central compartment exchanges with one or more peripheral compartments simultaneously while no exchange occurs between peripheral compartments [69]. The mammillary topology has been employed in pharmacokinetic and tracer-kinetic studies, where organs or tissues represented by peripheral compartments are connected in parallel to the vascular space represented by the central compartment [69, 70]. Recent studies by Ludemann *et al.* [23] and Port *et al.* [60] using mammillary, lumped-compartment models have indicated that tumor tissues can demonstrate significant kinetic heterogeneity, i.e. two or more interstitial compartments with different rate constants in exchange with the vascular compartment, in a given ROI within the tumor. It has been hypothesized that a fast exchange component can be identified to describe the filling of viable tissue within the ROI, and a slow extravasation

constant describes the exchange with an additional interstitial compartment, such as necrotic tissue [23], [60]. Port *et al.* [60] further suggested that a tracer kinetic model for potentially malignant tumors should allow for tissue kinetic heterogeneity.

In view of the above, it would be of interest to devise a mammillary multiple-compartment distributed-parameter model to describe kinetic heterogeneity in tumors. In the following, a generalized solution is presented for the impulse residue function, $R_{MDP_n}(t, \mathbf{p})$, of a Mammillary, n -Compartment Distributed-Parameter (MDP $_n$) model. To study its feasibility as a potential model for DCE imaging, it is applied with increasing complexity to a prostate case study, and statistical tests are implemented to determine the number of kinetically distinct compartments. The model is also used to infer the possible pathophysiological basis of contrast enhancement descriptors commonly used for predictive and differential diagnosis of tumors.

4.1 The MDP $_n$ Model

The proposed n -compartment model consists of a vascular distributed-parameter compartment in direct exchange with a number $(n-1)$ of homogeneous interstitial compartments as shown in Figure 4.1. This hypothetical capillary-tissue model can be assumed to represent an average of the underlying vasculature [48], [49], [62] given by a region of interest (ROI), which can be a voxel or a cluster of voxels in DCE imaging. The model assumes instantaneous diffusion in the extravascular extracellular space (EES) and along the radial direction of the capillary in the

intravascular plasma space (IVPS). The central vascular compartment is labeled with index $i=1$, while $i=2, \dots, n$ denote the peripheral interstitial compartments. The time variable measured from the time the tracer enter the ROI is t and the distance variable measured from the arterial end of the capillary along the axial direction is z .

Figure 4.1 Schematic diagram of the capillary-tissue unit for the n -compartment mammillary distributed-parameter model. A_i is the cross-sectional area of compartment i , and L is the average length of capillaries.

4.1.1 Impulse Residue Function of the MDP $_n$ model

Here, the DP $_2$ model, which was derived by Johnson and Wilson [61], and Larson *et al.* [58] (see Chapter 2 Sections 2.3.2.2.1.6-7), is extended to include $n-1$ compartments in the EES, where $n>1$. Consider the conservation of tracer for the elemental volume at a particular value of z in compartment 1:

The change in the amount of tracer at time $t =$

- (Net outflow along the axial direction)
- (Outflow into compartments 2 to n)

+ (Inflow from compartments 2 to n)

+ (Initial Unit Impulse).

For the i -th compartment ($i=2,\dots,n$):

The change in the amount of tracer at time $t =$

- (Outflow into compartment 1 of cross section at z)

+ (Inflow from compartments 1 of cross section at z).

Thus, the partial differential equations can be written as

$$A_1 \frac{\partial}{\partial t} C_1(t, z) dz = -\rho F_p V \frac{\partial}{\partial z} C_1(t, z) dz - \sum_{i=2}^n V K_{i1} C_1(t, z) \frac{dz}{L} + \sum_{i=2}^n V K_{i1} C_i(t, z) \frac{dz}{L} + \delta_t(t-0) \delta_z(z-0) dz, \quad (4.1a)$$

$$A_i \frac{\partial}{\partial t} C_i(t, z) dz = -V K_{i1} C_i(t, z) \frac{dz}{L} + V K_{i1} C_1(t, z) \frac{dz}{L}, \quad (i = 2, \dots, n), \quad (4.1b)$$

subject to the following initial and boundary conditions:

$$C_1(t=0, z) = C_1(t, z=0) = C_i(t=0) = 0, \quad (i = 2, \dots, n). \quad (4.1c)$$

The expression $\delta_t(t-0)\delta_z(z-0)$ in (4.1a) denotes the initial idealized impulse excitation of a unit source [58] at the arterial end of the capillary in the ROI.

Expressing (4.1) in the standardized units and symbols recommended for kinetic parameters derived from DCE imaging [57], we have ¹⁵

$$v_1 \frac{\partial}{\partial t} C_1 + \rho F_p L \frac{\partial}{\partial z} C_1 + \sum_{i=2}^n v_1 k_{i1} C_1 - \sum_{i=2}^n v_i k_{i1} C_i = \frac{\delta_t(t-0)\delta_z(z-0)L}{V}, \quad (4.2a)$$

¹⁵ Variables t and z for C_i are excluded for simplicity.

$$v_i \frac{\partial}{\partial t} C_i + v_i k_{li} C_i - v_1 k_{il} C_1 = 0 \quad (i = 2, \dots, n) . \quad (4.2b)$$

Applying Laplace Transforms from t & z to s & p respectively, we have ¹⁶

$$v_1 s \overline{\overline{C_1}} + \rho F_p L p \overline{\overline{C_1}} + \sum_{i=2}^n v_i k_{il} \overline{\overline{C_1}} - \sum_{i=2}^n v_i k_{li} \overline{\overline{C_i}} = \frac{L}{V} , \quad (4.3a)$$

$$v_i s \overline{\overline{C_i}} + v_i k_{li} \overline{\overline{C_i}} - v_1 k_{il} \overline{\overline{C_1}} = 0 \quad (i = 2, \dots, n) , \quad (4.3b)$$

where $\overline{\overline{C_i}}(s, p) = \mathcal{L}_t \{ \mathcal{L}_z [C_i(t, z)](p) \}(s)$ denotes the Laplace transforms.

Solving for $\overline{\overline{C_i}}$ in the simultaneous equations (4.3), we have

$$\overline{\overline{C_1}}(s, p) = \frac{1}{\rho F_p (p + f_n(s)) V} , \quad (4.4a)$$

$$\overline{\overline{C_i}}(s, p) = \frac{A_i}{A_i} \frac{k_{il}}{s + k_{li}} \frac{1}{\rho F_p (p + f_n(s)) V} \quad (i = 2, \dots, n) , \quad (4.4b)$$

where $f_n(s)$ is defined as

$$f_n(s) = \frac{v_1 s}{\rho F_p L} \left(1 + \sum_{i=2}^n \frac{k_{il}}{s + k_{li}} \right) . \quad (4.5)$$

Since $R_{\text{MDPn}}(t, \mathbf{p}) = \sum_{i=1}^n A_i \int_0^L C_i(z, t) dz$, we rewrite $\overline{\overline{C_i}}(s, p)$ as

$$\overline{\overline{C_i}}(s, p) = g_i(s) \frac{1}{\rho F_p (p + f_n(s)) V} \quad (i = 1, \dots, n) , \quad (4.6)$$

where $g_i(s)$ is defined as

$$g_i(s) = \begin{cases} 1 & i = 1 \\ \frac{A_i}{A_i} \frac{k_{il}}{s + k_{li}} & i = 2, \dots, n \end{cases} , \quad (4.7)$$

so that $R_{\text{MDPn}}(t, \mathbf{p})$ can be expressed as

¹⁶ Laplace Transform variables s and p for C_i are excluded for simplicity.

$$R_{\text{MDPn}}(t, \mathbf{p}) = \mathcal{L}_t^{-1} \left(\mathcal{L}_z^{-1} \left(\sum_{i=1}^n \frac{A_i \overline{C_i(s, p)}}{p} \right)_{z=L} \right). \quad (4.8)$$

Substituting (4.6) into (4.8), we arrive at

$$R_{\text{MDPn}}(t, \mathbf{p}) = \mathcal{L}_t^{-1} \left(\frac{1}{s} \right) - \mathcal{L}_t^{-1} \left(\frac{1}{s} \exp(-L f_n(s)) \right), \quad (4.9)$$

where $L f_n(s)$ is expressed as

$$L f_n(s) = \frac{v_1}{\rho F_p} \left(s + \sum_{i=2}^n k_{i1} - \sum_{i=2}^n \frac{k_{1i} k_{li}}{s + k_{1i}} \right). \quad (4.10)$$

We note that $t_1 = \frac{v_1}{\rho F_p}$, and letting $\chi_n = t_1 \sum_{i=2}^n k_{i1}$ and $k_i = t_1 k_{1i} k_{li}$, $L f_n(s)$ can be

expressed as

$$L f_n(s) = t_1 s + \chi_n - \sum_{i=2}^n \frac{k_i}{s + k_{1i}}. \quad (4.11)$$

By substituting (4.11) into (4.9), we arrive at

$$R_{\text{MDPn}}(t, \mathbf{p}) = u(t) - \exp(-\chi_n) u(t - t_1) \int_0^{t-t_1} y_2(\tau) \otimes \dots \otimes y_i(\tau) \otimes \dots \otimes y_n(\tau) d\tau, \quad (4.12)$$

where $\otimes$ denotes the convolution operator, $u(t)$ is the Heaviside unit step function and ¹⁷

$$y_i(\tau) = \exp(-k_{1i} \tau) \delta_i(\tau) + \exp(-k_{1i} \tau) \sqrt{\frac{k_i}{\tau}} I_1(2 \sqrt{k_i \tau}) \quad (i = 2, \dots, n), \quad (4.13)$$

where I_1 is the modified Bessel function. The parameters contains in $\mathbf{p}$ are t_1 , k_{i1} , k_{1i} for $i=2 \dots n$.

¹⁷ y_i here is different from Larson's CDP₃ model in Eq. (2.19b).

4.1.2 Physiological Parameters Derived from the MDP $_n$ Model

The fractional volume of the IVPS, can be expressed as

$$v_1 = t_1 \rho F_p . \quad (4.14)$$

Without using the Heaviside unit step function, (4.12) may be rewritten as

$$R_{\text{MDP}_n}(t, \mathbf{p}) = \begin{cases} 1 & 0 < t \leq t_1 \\ 1 - \exp(-\chi_n) \int_0^{t-t_1} y_2(\tau) \otimes \dots \otimes y_n(\tau) d\tau & t > t_1 \end{cases}, \quad (4.15)$$

where t before time t_1 is the vascular phase and after time t_1 is the parenchymal clearance phase.

The extraction ratio, E , which is the value of $R_{\text{MDP}_n}(t, \mathbf{p})$ in the parenchymal phase as $t \rightarrow t_1^+$, can be obtained using

$$E = 1 - \exp\left(-t_1 \sum_{i=2}^n k_{i1}\right). \quad (4.16)$$

We note that an equivalent form of (4.16),

$$E = 1 - \exp\left(-\sum_{i=2}^n \frac{K_{i1}}{\rho F_p}\right), \quad (4.17)$$

is consistent with the expression of extraction fraction derived by Renkin [55] and Crone [56],

$$E = 1 - \exp\left(-\frac{PS}{F_p}\right). \quad (4.18)$$

From (4.17) and (4.18), we may obtain PS using

$$PS = \sum_{i=2}^n \frac{K_{i1}}{\rho} = \frac{v_1}{\rho} \sum_{i=2}^n k_{i1} . \quad (4.19)$$

To derive the fractional extravascular extracellular space, v_e , which is the sum of v_i ($i=2, \dots, n$), values of K_{1i} is required. Since K_{1i} and K_{i1} generally defer by the partition coefficient of compartments involved, λ_{1i} [49], [57], [62],

$$K_{1i} = \frac{K_{i1}}{\lambda_{1i}} , \quad (4.20)$$

v_e can be expressed as

$$v_e = v_1 \sum_{i=2}^n \frac{k_{i1}}{k_{1i} \lambda_{1i}} . \quad (4.21)$$

Thus, v_e can be determined if λ_{1i} values are known or assumed. For an easily diffusible tracer, the assumption of unit partition coefficient is made in most perfusion imaging studies.

4.2 Application to a Prostate Study Case

To test whether the observed prostate tumor data supports the inclusion of additional interstitial compartments, thereby demonstrating tissue kinetic heterogeneity, we attempt to fit the tumor data set using the present MDP $_n$ model with increasing number of compartments, n . An adequate model would be one that is the simplest (i.e. smallest possible n) and whose goodness-of-fit is not significantly worse than the more complex ones. Since the MDP $_n$ model has $2n$ parameters (F , t_1 and k_{i1} , k_{1i} ($i=2, \dots, n$)), if a model includes too many compartments, the situation of over-fitting arises as several parameter

combinations could produce similar goodness-of-fit results. The MDP $_n$ model is fitted to the prostate tumor DCE CT data as described in Chapter 3 Section 3.2. To compare the “goodness-of-fit” between models in fitting the data, a one-tailed F-test was applied on their χ^2 statistic (see Chapter 3 Sections 3.3.1 and 3.3.1.1).

Figure 4.2 The tissue time-concentration curves $C_{\text{tiss}}(t)$ obtained by fitting the MDP $_n$ ($n=2,3,4$) models and their goodness-of-fit estimates are $\chi^2 = 149.5$, 130.9 and 130.9 respectively. The curves for 3 and 4 compartments are almost identical.

4.3 Results

The fitted $C_{\text{tiss}}(t)$ curves using MDP $_n$ models for $n=2,3,4$ are shown in Figure 4.2 and their corresponding impulse residue functions are shown in Figure 4.3. Values

for the various parameters obtained using $n=2, 3$ and 4 compartments are listed in Table 4.1, and compared with the parameters obtained using the ATH model.

Figure 4.3 The impulse residue functions $R_{MDP_n}(t, \mathbf{p})$ obtained by fitting the MDP $_n$ ($n=2,3,4$) models. The curves for 3 and 4 compartments are almost identical.

For this prostate case, we note the difference between MDP $_2$ and MDP $_3$, and the similarity between MDP $_3$ and MDP $_4$, from the fitted $C_{tiss}(t)$ curves, $R_{MDP_n}(t)$, and the fitted parameter values, in Figure 4.2, Figure 4.3 and Table 4.1 respectively. The respective χ^2 values obtained are 149.5, 130.9 and 130.9. To justify a more complex model over a less complex (reduced) one, $f(\chi_r^2, \chi_c^2) > f_{0.05, 2, 105} \approx 3.1$ is required. Since $f(149.5, 130.9) = 7.4 > 3.1$ and $f(130.9, 130.9) = 0 < 3.1$, MDP $_3$ model is justified over MDP $_2$ and it is also adequate when compared to MDP $_4$.

Table 4.1 Values of parameters obtained by fitting the MDP $_n$ ($n=2,3,4$) and ATH models.

Parameters	Number of Compartments			ATH
	2	3	4	
F (mL/g/min)	0.213	0.212	0.212	0.21
t_1 (min $^{-1}$)	0.717	0.688	0.688	0.698
k_{21} (min $^{-1}$)	2.183	1.854	1.853	
k_{12} (min $^{-1}$)	0.744	1.581	1.579	
k_{31} (min $^{-1}$)		0.818	0.816	
k_{13} (min $^{-1}$)		0.259	0.264	
k_{41} (min $^{-1}$)			0.000	
k_{14} (min $^{-1}$)			0.000	
E	0.80	0.84	0.84	0.73
v_1	0.15	0.15	0.15	0.143
PS (mL/g/min)	0.33	0.40	0.40	0.27
v_2	0.45	0.17	0.17	0.59
v_3		0.46	0.46	
v_4			0.00	
v_e	0.45	0.63	0.63	0.59

These statistical tests suggest that the prostate tumor dataset can be described by a model with two kinetically distinct peripheral tissue compartments in exchange with the vascular compartment, which is consistent with the recent findings of kinetic heterogeneity in tumors [23], [60]. Further investigations with more study cases should be performed to study the possible existence of kinetic heterogeneity within tumors and for quantification of the various adjustable parameters.

4.3.1 Physiological Implications of Tissue Enhancement Descriptors

Analysis of features in $C_{\text{tiss}}(t)$ curves has been a common approach used to infer functional information and to characterize and differentiate between tumors. Several enhancement parameters (or descriptors) such as the rate of enhancement, peak value and time to peak have been proposed as criterion for analysis and comparison of tissue enhancement. Although it is commonly believed that differences in the angiogenesis of tumors could be reflected by the features and

patterns of contrast enhancement, the pathophysiological basis of such features has remain uncertain.

The early tissue enhancement rate, given by the percentage increase in enhancement with time in the early post-contrast period, is commonly used as a differential diagnostic criterion. However, relating faster enhancement rates to carcinomas [71], [72] has been disputed in more recent studies [73], [74]. It is therefore desirable to have an understanding of enhancement rate from a physiological perspective for appropriate use of the technique.

Consider the vascular phase of the MDP $_n$ model when $t < t_1$,

$$\begin{aligned} C_{\text{tiss}}(t) &= F \rho \int_0^t C_a(\tau) R_{\text{MDP}_n}(t - \tau) d\tau \\ &= F \rho \int_0^t C_a(\tau) d\tau, \quad (t < t_1), \end{aligned} \quad (4.22a)$$

then tissue early enhancement rate is

$$\left. \frac{dC_{\text{tiss}}(t)}{dt} \right|_{t < t_1} = F \rho C_a(t). \quad (4.22b)$$

Equation (4.22b) describes the rate of accumulation of incoming tracer, as delivered with a perfusion rate F . The relationship between early enhancement rate and perfusion is hence subjected to the inevitable variability of the arterial input functions $C_a(t)$ between individuals and the variations in bolus injection procedures. If we assume that the variability of $C_a(t)$ can be minimized, the possible correlation of a higher enhancement rate with malignancy would suggest a higher perfusion rate for malignant lesions. However, consistency in $C_a(t)$ among patients is difficult to achieve in practice, and hence the poor specificity of the method. Another possible reason for the discrepancies could be that the

enhancement rate is sampled after t_1 , as most studies have speculated that the first few (about 2-3) minutes are desirable for studying early enhancement. If this is significantly longer than t_1 , then we expect the parenchymal phase to set in and the linear relationship of enhancement with perfusion as given by (4.22b) no longer holds.

Since t_1 is the mean vascular transit time for a distribution of capillaries in the ROI, there must be a portion of the capillaries with shorter vascular transit time than t_1 , depending on the spread of the distribution. This implies that the time for input tracer to fully accumulate within the ROI could be less than t_1 , and may be estimated by σt_1 , where σ denotes a measure of the spread of the capillary transit times. Hence, in order to accurately apply enhancement rate as a differential criterion for tumors, appropriate knowledge of the mean and distribution of capillary transit times would also be desirable.

Equation (4.22b) can also be derived using Fick's principle,

$$\frac{dC_{\text{tiss}}(t)}{dt} = F \rho [C_a(t) - C_v(t)], \quad (4.23)$$

for those times, t , before any outflow of blood occurs, i.e. venous outflow concentration, $C_v(t) = 0$, such that all tracer delivered through $C_a(t)$ till those times are accumulated within the ROI. However, this approach does not readily provide an estimate for the range of t for which it is valid.

Using the approach of Fick's principle, some investigators have suggested dividing the maximum enhancement rate by the bolus peak value of $C_a(t)$ to estimate perfusion [75]-[77],

$$F \rho = \frac{\left. \frac{dC_{\text{tiss}}(t)}{dt} \right|_{\text{max}}}{C_a(t_{\text{peak}})} . \quad (4.24)$$

Again we note that a crucial factor for the success of (4.24) is that the $C_a(t)$ reaches its peak value before σt_1 , i.e. $t_{\text{peak}} < \sigma t_1$, such that outflow can be safely assumed to be negligible, and the maximum rate of $C_{\text{tiss}}(t)$ could correspond with the maximum $C_a(t)$. In some tissues where t_1 is of the order of a few seconds, this condition might be difficult to establish in practice, as it would require a very rapid bolus injection.

It is evident from this discussion, that other descriptors for enhancement analysis such as time to peak and the peak value of the $C_{\text{tiss}}(t)$ curve, also depend on both the $C_a(t)$ and the impulse residue function. Due to the variability in the shape and strength of $C_a(t)$ among patients, it may be difficult to associate peak descriptors with any specific physiological parameter or process in general.

4.4 Conclusion

Consistent with the catenary counterparts, the generalized solution of the impulse residue function for a mammillary n -compartment distributed-parameter model is shown to exhibit the convenient property of a separable form in time domain. The present model can be applied with DCE imaging to study the physiological characteristics of tumor vasculature. As the number of distinct compartments is

indicative of tissue heterogeneity, the present model can be used to study and demonstrate possible existence of kinetic heterogeneity within tumor tissues.

Chapter 5

A Comparison Study of Distributed and Compartmental Tracer Kinetic Models

Despite the fact that DP models are more realistic in describing the kinetics of capillary-tissue transfer, CC models are more commonly used in the analysis of DCE imaging data. This is probably due to the numerical complexity of DP models, making them less efficient computationally. Nevertheless, the compelling question among researchers is whether the simplicity of the CC model is justified, or in other words, whether the parameters derived from CC and DP models differ significantly, and if so, which would be more accurate. A theoretical comparison of DP and CC models for PET receptors was recently reported by Muzic *et al.* [78]. Their theoretical study was designed to investigate how well the CC model could match the output of the DP model, and they concluded that the DP model has no advantage, given the typical temporal resolution (~ 10 s) available with PET. However, Larson *et al.* found that the DP models led to better fits than the

CC models, for high temporal resolution experimental data of penetration of radiolabeled water into the brains of rhesus monkeys [58].

Since modern CT and MRI scanners can achieve a scanning time of about 1 s or less per slice, it would be of interest to compare CC and DP models for DCE imaging performed using these modalities. However, to date, there has been lack of similar studies for DCE imaging using CT or MRI. Thus, the purpose of this study was to compare distributed and conventional compartmental kinetic models used to estimate tumor microcirculatory parameters from DCE CT data.

5.1 Materials and Methods

5.1.1 Tracer Kinetic Models

In this study, two-compartment versions of the CC_2 , ATH and DP_2 models were compared. For all three models, the transfer constants have been assumed equal to the permeability-surface area product PS , under the assumption of non-preferential diffusion of tracer between compartments [18], [62] (see Appendix B). Expressions for the impulse residue functions $R(t)$ of the CC_2 , DP_2 and ATH models are given in Appendix B, following the standardization proposed by Tofts *et al.* [57]. In the CC_2 and DP_2 models, the four fundamental kinetic parameters that can be directly obtained by parametric fitting of (3.1) with DCE imaging data, are F , t_1 , k_{12} and k_{21} . Other physiological parameters such as the fractional vascular volume v_1 , first pass extraction ratio E , permeability-surface area product PS , and the fractional volume of EES v_2 , can be derived from these fundamental kinetic parameters of the CC_2 and DP_2 models, using appropriate approximations and

assumptions (see Appendix B). In the ATH model, the four fundamental parameters that can be directly obtained from parametric fitting are F , t_1 , k_{12} and E , and parameters such as v_1 , v_2 and PS can be derived with further assumptions (see Appendix B).

5.1.2 DCE CT Images

Details of the 6 patients study cases with intracranial meningioma and the DCE CT imaging protocol used in this study are presented in Chapter 3 Section 3.1.1. The slice thickness of the DCE CT images was 10 mm and the voxel sizes for the 6 patient study cases ranged from 1.53 mm³ to 2.38 mm³.

The realignment of DCE CT images and the correction for partial volume average effects in $C_a(t)$ were performed as described in Chapter 3 Section 3.2. ROIs were manually drawn on the tumors, grey matter (GM) and white matter (WM). The sizes of ROIs for tumors, GM and WM tissues were respectively, 763±314 mm³, 925±401 mm³ and 1077±476 mm³. A $C_{tiss}(t)$ curve corresponding to each tissue ROI was extracted by averaging all voxels within the ROI at each time point. Each $C_{tiss}(t)$ was fitted using all three models.

5.1.3 Statistical Analysis

The ‘goodness-of-fit’ between model and data is given by the χ^2 statistic described in Chapter 3 Section 3.3.1. The test statistic to compare the χ^2 values of two models is described in Chapter 3 Section 3.3.1.2.

The tracer kinetic parameters for each model were estimated by the curve fitting process described in Chapter 3 Section 3.2.4. Linear regression analysis was used to analyze the correlation between the parameter estimates among the various tracer kinetic models. Since we expect the more elaborate DP₂ model to correspond more closely to physiological reality, the parameter estimates obtained using the CC₂ and ATH models were compared against those of the DP₂ model, using an approach similar to that of Muzic *et al.* [78]. The quantitative measures of interest are the coefficient of determination (r^2), P -value of correlation, gradient (m) and y-intercept (c) of the linear regression fitting. An r^2 close to unity and P -value less than 0.05 would indicate significant correlation (or association) between the parameters of the two models; and a gradient m close to unity with near zero intercept c would indicate quantitative equivalence. The one-tailed paired Student t-test was used to compare the difference of these parameters in the tumor and normal grey and white matter tissues. Significance was declared at P -value<0.05.

5.2 Results

A representative case of intracranial meningioma is shown in Figure 5.1. The meningioma typically exhibits a markedly higher concentration-time curve than the WM and GM (Figure 5.1(b)). The impulse residue function of the CC₂ model (Figure 5.1(c)) differs from those of the ATH and DP₂ models within the first few (~10) seconds, after which all the three impulse residue functions closely agree on the amount of tracer remaining in the ROI, and consistently reflect that a substantial amount of tracer leaves the ROI slowly. On the other hand, the impulse residue functions for WM (Figure 5.1(d)) and GM (Figure 5.1(e)) decrease more

rapidly, indicating that almost all the tracer has left the ROI within a short period of time (~ 3 s for ATH and DP_2 models, ~ 8 s for CC_2 model).

Figure 5.1 (a) A representative study case of intracranial meningioma. Contrast enhanced axial CT image showing the ROIs from which the respective concentration-time curves are derived. (b) The concentration-time curves for the artery (triangles), meningioma (black circles) and normal WM (white circles) and GM (grey circles) tissues. Plots show curves for F -scaled impulse residue function over time, $F \cdot R(t)$ obtained for the meningioma, WM and GM are shown in (c), (d) and (e), respectively. For each tissue type, three impulse residue functions were obtained using the three tracer kinetic models: CC_2 (dotted line), ATH (dashed line) and DP_2 (solid line). The ATH and DP_2 impulse residue functions displayed features related to the vascular and parenchyma phases that could reveal possible pathological conditions of the brain tissue.

Figure 5.1(b)-(e): see Figure 5.1 above.¹⁸

The goodness-of-fit achieved by the CC_2 and ATH models are compared against the DP_2 model in Figure 5.2. Although there are only two cases for which the DP_2 model performed significantly better (95% confidence level) than the CC_2 model, we note that the DP_2 model does consistently achieve better fittings of the datasets than the CC_2 model in most cases (Figure 5.2(a)), except for one case of GM, which was the most noisy of all GM cases. The ATH model yield very similar goodness-of-fit values as the DP_2 model (Figure 5.2(b)).

¹⁸ Abbreviations CC and DP in figures refer to CC_2 and DP_2 , respectively.

Figure 5.2 The goodness-of-fit values, χ^2 , obtained by the (a) CC₂ and (b) ATH models, plotted against those of the DP₂ model, when fitting the concentration-time curves of meningioma (black), WM (white) and GM (grey). On each plot, the dotted line indicates an equal goodness-of-fit for both models and the points above the line denote cases of which the DP₂ model gave better fittings. The circled points indicate that the DP₂ model gave significantly better fittings on the 95% confidence level. The dotted rectangular regions are magnified in the insets.¹⁹

¹⁹ Abbreviations CC and DP in figures refer to CC₂ and DP₂, respectively.

Figure 5.3 Correlation plots of the various microcirculatory parameters (a) F , (b) t_1 , (c) k_{12} , (d) k_{21} , (e) v_1 , (f) E , (g) PS and (h) v_2 . The parameters obtained using the CC₂ model (circles) and the ATH model (triangles) were plotted against the parameters of the DP₂ model (squares). Black symbols are used for meningioma, white symbols for WM and grey symbols denote GM. The dotted and dashed lines are respectively the regression lines of the CC₂ and ATH models against the DP₂ model. The linear regression equations are given beside the regression line and the coefficient of determination r^2 and P -values are stated in the legends. Excellent correspondence was found between the ATH and DP₂ models. Quantitative differences were found between the CC₂ and DP₂ models for the parameters F , t_1 , k_{21} and v_1 ((a), (b), (d) and (e)).²⁰

²⁰ Abbreviations CC and DP in figures refer to CC₂ and DP₂, respectively.

Figure 5.3(e)-(h): see Figure 5.3 above.

Results of regression analysis show excellent correspondence between the ATH and DP₂ models with r^2 and gradient (m) of regression very close to unity (except the clearance rate constant k_{12} ($r^2=0.9531$, $m=0.69$)), as well as near zero values for the intercept (c) and P -values for all parameters (Figure 5.3). The CC₂ model also exhibited good association between its parameters and those of the DP₂ model with r^2 close to unity ($0.8827 < r^2 < 0.9979$) and near zero P -values. However, quantitative differences were found between estimates of the CC₂ and DP₂ models, resulting in various m values for F ($m=1.70$), t_1 ($m=0.65$), k_{21} ($m=0.82$) and v_1 ($m=1.25$).

The parameters (k_{12} , k_{21} , E and PS) related to the extravasation of tracer into the EES, exhibit distinct separable parameter ranges between meningioma and normal (WM and GM) tissues, without overlapping values (Figure 5.3(c), (d), (f) and (g), respectively). For these extravasation parameters, the normal tissues yielded values close to zero, due to an intact blood-brain barrier (BBB), while they were substantially higher in the meningioma. The fractional vascular volume v_1 is also generally higher for meningioma than normal WM and GM tissues, except for one patient case (Figure 5.3(e)).

Table 5.1 The means $\pm$ standard deviations (SD) of microcirculatory parameters for meningioma, normal WM and normal GM tissues, obtained using the (a) CC₂, (b) ATH and (c) DP₂ models.

(a)			
CC ₂	Meningioma	WM	GM
F (mL 100g ⁻¹ min ⁻¹)	136.61 $\pm$ 33.54	38.83 $\pm$ 15.51	58.44 $\pm$ 12.45
t_1 (sec)	4.55 $\pm$ 2.21	1.78 $\pm$ 0.44	1.82 $\pm$ 0.60
k_{12} (min ⁻¹)	2.78 $\pm$ 1.85	0.08 $\pm$ 0.06	0.24 $\pm$ 0.37
k_{21} (min ⁻¹)	4.08 $\pm$ 1.99	0.09 $\pm$ 0.15	0.11 $\pm$ 0.15
v_1	10.65 $\pm$ 7.12	1.09 $\pm$ 0.29	1.74 $\pm$ 0.64
PS (mL 100g ⁻¹ min ⁻¹)	52.40 $\pm$ 59.30	0.08 $\pm$ 0.12	0.17 $\pm$ 0.15
v_2	19.20 $\pm$ 14.74	0.78 $\pm$ 1.32	1.14 $\pm$ 1.25

(b)			
ATH	Meningioma	WM	GM
F (mL 100g ⁻¹ min ⁻¹)	72.33 $\pm$ 24.18	19.95 $\pm$ 7.23	29.69 $\pm$ 9.64
t_1 (sec)	7.00 $\pm$ 2.70	2.95 $\pm$ 0.86	3.23 $\pm$ 2.06
k_{12} (min ⁻¹)	1.89 $\pm$ 1.11	0.07 $\pm$ 0.05	0.12 $\pm$ 0.06
v_1	8.76 $\pm$ 5.56	0.93 $\pm$ 0.28	1.44 $\pm$ 0.65
E	0.44 $\pm$ 0.22	0.01 $\pm$ 0.01	0.01 $\pm$ 0.01
PS (mL 100g ⁻¹ min ⁻¹)	51.52 $\pm$ 48.86	0.12 $\pm$ 0.17	0.23 $\pm$ 0.15
v_2	20.46 $\pm$ 13.29	1.94 $\pm$ 2.55	2.40 $\pm$ 1.73

(c)			
DP ₂	Meningioma	WM	GM
F (mL 100g ⁻¹ min ⁻¹)	72.43 $\pm$ 24.20	19.93 $\pm$ 7.25	29.71 $\pm$ 9.65
t_1 (sec)	6.94 $\pm$ 2.65	2.95 $\pm$ 0.86	3.23 $\pm$ 2.06
k_{12} (min ⁻¹)	2.66 $\pm$ 1.49	0.06 $\pm$ 0.05	0.08 $\pm$ 0.04
k_{21} (min ⁻¹)	5.06 $\pm$ 2.13	0.14 $\pm$ 0.21	0.20 $\pm$ 0.23
v_1	8.69 $\pm$ 5.52	0.93 $\pm$ 0.28	1.45 $\pm$ 0.65
E	0.44 $\pm$ 0.22	0.01 $\pm$ 0.01	0.01 $\pm$ 0.01
PS (mL 100g ⁻¹ min ⁻¹)	51.18 $\pm$ 48.15	0.12 $\pm$ 0.18	0.23 $\pm$ 0.15
v_2	19.87 $\pm$ 12.61	1.94 $\pm$ 2.56	2.41 $\pm$ 1.72

For all three models, the mean values of all parameters derived from the meningiomas are clearly higher than those of the normal WM and GM (Table 5.1). For each tracer kinetic model, the paired Student t-tests reveal that the mean values of all the parameters in meningioma were significantly ($P < 0.05$) higher than those of the normal WM and GM tissues (Table 5.2).

Table 5.2 Results (P -values) of paired Student t-tests (one-tailed) at 95% confidence level for the alternative hypotheses that the parameter values are significantly greater in meningioma (M) than in WM (M>WM) and GM (M>GM), for each model. All the P -values are less than 0.05.

		F	t_1	k_{12}	k_{21}	v_1	E	PS	v_2
M>WM	CC ₂	0.000	0.007	0.002	0.000	0.004	N.A.	0.028	0.006
	ATH	0.000	0.003	0.001	0.000	N.A.	0.000	0.014	0.004
	DP ₂	0.000	0.003	0.001	0.000	0.003	0.000	0.013	0.003
M>GM	CC ₂	0.000	0.008	0.004	0.000	0.006	N.A.	0.028	0.007
	ATH	0.001	0.011	0.001	N.A.	0.005	0.000	0.014	0.004
	DP ₂	0.001	0.011	0.001	0.000	0.005	0.000	0.013	0.004

5.3 Discussion

To the best of our knowledge, this is the first application of the DP₂ model in the DCE CT studies of intracranial meningioma and brain tissues. To gauge the success of this task, we are going to compare our parameter estimates of the DP₂, ATH and CC₂ models with those reported in recent literature. Our values of F are 19.93 ± 7.25 and 19.95 ± 7.23 mL/100g/min for normal WM, obtained using the DP₂ and ATH models respectively, are in good agreement with the value of 22.9 mL/100g/min reported by Nabavi *et al.* [46]. For GM, the F values of 29.71 ± 9.65 and 29.69 ± 9.64 mL/100g/min estimated by the DP₂ and ATH models respectively, are lower than 44.3 mL/100g/min reported by Nabavi *et al.* The F values estimated using the CC₂ model are generally higher, with 38.83 ± 15.51 and 58.44 ± 12.45

mL/100g/min for WM and GM, respectively. The relatively large standard deviations for our estimates are likely due to the small sample size in this initial study.

Our t_1 values for normal WM and GM are respectively, 2.95 ± 0.86 and 3.23 ± 2.06 s, by both the DP_2 and ATH models. These are in good agreement with the values reported by Eastwood *et al.* (3.4 ± 0.6 s) [79], and Østergaard *et al.* (WM: 3.19 ± 0.93 s and GM: 2.62 ± 0.6 s) derived using their numerical deconvolution method [80]. The t_1 values presently obtained using the CC_2 model are slightly lower, with 1.78 ± 0.44 and 1.82 ± 0.60 s for WM and GM, respectively.

Our PS values for meningioma are respectively 51.18 ± 48.15 , 51.52 ± 48.86 and 52.40 ± 59.30 mL/100g/min, for the DP_2 , ATH and CC_2 models. These are comparable with the values of 57.5 to 462 mL/100g/min reported by Yeung *et al.* [81], and 14.3 ± 10.9 mL/100g/min reported by Andersen and Jensen [33] in their analysis using the CC_2 model on datasets from dynamic Gd-DTPA MRI studies of 6 patients.

The impulse residue functions $R(t)$ for ATH and DP_2 models can be described in two phases: the vascular phase and the parenchyma phase [18], [58], [62]. During the vascular phase, $R(t)$ remains constant for a period of time t_1 given by the average time needed for the tracer to traverse the IVPS. If there are highly permeable blood vessels in the tumor, or if there is disruption of the BBB, a portion of the tracer could diffuse into the EES [18], [58], [62]. The proportion of tracer that leaks into the EES can be estimated by the first-pass extraction ratio E .

After t_1 , the remaining tracer in the IVPS that is not extracted exits by out-flowing blood, resulting in a discrete drop in $R(t)$. The vascular phase is then followed by a parenchyma phase during which a more gradual decrease in $R(t)$ occur, as the extracted portion diffuses back into the IVPS and is cleared by blood outflow.

The behavior of the impulse residue function $R(t)$ obtained using the ATH or DP₂ models should differ between meningioma and normal brain tissue. Since the normal WM and GM have intact BBB, their $R(t)$ exhibits only the vascular phase, during which $R(t)$ remains constant, followed by a rapid drop to zero. However, for meningiomas with ‘leaky’ blood vessels, a portion of tracer will be extracted and the parenchyma phase would ensue. This difference in behavior of the impulse residue functions is evident in all the patient study cases, and can be observed by comparing the shapes of their impulse residue functions. On the other hand, the CC₂ model yields monotonically decreasing impulse residue functions for both the normal tissues and the meningioma, due to its strictly bi-exponential form. The difference is that in normal tissues a more rapid decay is observed compared to meningiomas.

Apart from the extravasation parameters, the ATH and DP₂ impulse residue functions can also display features related to the parenchyma phase, which reveal possible pathological conditions of the brain tissue. We note that ATH and DP₂ impulse residue functions for the meningioma also exhibit a longer vascular phase than the normal WM and GM. This suggests longer path lengths and transit times in the tumor between the feeding and draining vessels. This phenomenon may be important in neoangiogenesis, especially in primary malignant tumors, in which

denser and more irregular vasculature causes the tracer to traverse long and circuitous paths within the tumor.

The good agreement between most of the parameter estimates of the ATH model with those of the DP₂ model indicates that the adiabatic approximation is appropriate for the estimation of these parameters. The only parameter of the ATH model that deviates appreciably from the DP₂ model is the efflux rate constant k_{12} . The ATH's k_{12} is given by $k_{adb} = E F_p / v_2$ (see Appendix B). The deviation becomes more obvious as k_{12} increases. As a larger rate constant can be associated with higher vessel permeability, this indicates the potential difficulty of the adiabatic efflux rate constant to approximate the actual rate constant in the region of high permeability. This observation may be explained as follows. When vessel permeability is high, a more rapid exchange of substances between the IVPS and EES is expected, and the tracer concentration in the EES tracks more closely the concentration in the IVPS. As the adiabatic approximation assumes a much slower rate of change of tracer concentration in the EES compared with the IVPS [62], the adiabatic efflux rate constant k_{adb} might deviate from the actual rate constant. Nevertheless, a linear association between k_{adb} and the actual k_{12} was observed.

From our current datasets, the parameters of the CC₂ model could be linearly associated with those of the DP₂ model, but some of the parameters do not correspond quantitatively. The implication is that although some parameter estimates of the CC₂ model may not agree quantitatively with those of the ATH and DP₂ models, all three models could yield similar results qualitatively, in classification and correlation studies, due to good linear correlation. Generally,

based on the current goodness-of-fit results of the three models for various tissue data, we believe that both the ATH and DP₂ models can describe the DCE imaging datasets and the underlying kinetic processes, better than the CC₂ model. This is consistent with the results of Larson *et al.* [58], who found that the DP₂ model yielded better fitting than the CC₂ model on their experimental datasets.

Although only the parameters related to extravasation could produce non overlapping parameter ranges for meningioma, normal WM, and GM, the paired Student t-tests reveal that all the parameters do show significant increase for the meningioma as compared with the normal tissue. The increase in F , v_1 and t_1 would suggest a denser vasculature that is more perfused, and the increase in rate constants, E and PS indicates that the vessels are ‘leaky’. Thus, the enhancement of meningioma in DCE imaging could be caused by a combination of increased extravasation, high perfusion and dense vasculature.

Here, we should also indicate the limitations of the present study. Due to the lack of existing ‘gold standards’ [44] for *in vivo* quantification of the various blood flow parameters, the question as to which of the models could more accurately yield such parameters in situations when the parameters differ among models, can only be discussed from the standpoints of theoretical accuracy or realism in the derivation of the impulse residue models, and the comparison of model fittings for the same datasets. It is hoped that in the near future, more studies can be carried out to add statistical strength to such analysis. Also, in this study, only a single tumor type (meningioma) was studied. As it is known that meningiomas are much more ‘leaky’ than other brain tumor types, they could be more easily distinguished

from normal brain tissues, and hence the present findings may not be representative of all brain tumor types in general. Similar studies with other brain tumor types should be encouraged.

In summary, we found excellent agreement between the parameters of the ATH and DP₂ models; except for the ATH efflux rate constant, which may be underestimated as compared with the corresponding DP₂ rate constant, in the regime of high permeability. Although significant linear association is found between the parameters of the CC₂ model and the DP₂ model, some of the parameters (F , t_1 , v_1 , k_{21}) may not correspond quantitatively. The DP₂ model is not only theoretically more realistic, it was found to consistently produce better fits than the CC₂ model. Another advantage of the ATH and DP₂ models is that their impulse residue functions could reveal features linked to pathological conditions in brain tissue. Although all parameters in all three models showed significant increase for meningioma compared with the normal tissues, only the parameters related to extravasation exhibit distinct, non-overlapping ranges. These parameters may potentially be used to differentiate between normal and abnormal tissue.

Chapter 6

A Distributed-Parameter Model of Cerebral Blood-Tissue Exchange with Account of Capillary Transit Time Distribution

Regional blood flow has been shown to be markedly heterogeneous in the brain. In several pathologies of the brain, such as multiple sclerosis, ischemia and neoplasm, the normally intact blood-brain barrier (BBB) could be disturbed, resulting in the increase in tissue permeability. The ability to assess permeability and locate sites of BBB breakdown, would be a useful feature of cerebral imaging. Therefore, it is important to include the effects of capillary leakage and distribution in the physiological model used for the analysis of DCE images.

This chapter presents an approach to incorporate a capillary distribution with the MDP_n model. Monte Carlo simulation experiments were carried out to evaluate the

confidence intervals of the parameter estimates obtained by applying such a model.

The model is also applied to a few clinical cases to study its applicability to the evaluation of DCE CT images of metastatic tumors in the brain.

6.1 Theoretical model

6.1.1 A Single Capillary-Tissue Exchange Unit

For ease of explanation, a single capillary-tissue exchange unit is modeled using the DP_2 model (instead of MDP_n), in the following formulation to incorporate a capillary transit time distribution. If one strongly believes that more than two kinetically distinct compartments should exist within a particular physiological system, the incorporation of a capillary distribution with MDP_n model can be achieved in a similar fashion as the present formulation of the two-compartment version.

For convenience of reference, the impulse residue function for the DP_2 model (given in (4.12) as MDP_2) is reproduced here as

$$R_{DP_2}(t, t_1, k_{21}, k_{12}) = R_{DP_2}^v(t, t_1) + R_{DP_2}^p(t, t_1, k_{21}, k_{12}), \quad (6.1a)$$

with

$$R_{DP_2}^v(t, t_1) = u(t) - u(t - t_1), \quad (6.1b)$$

and

$$R_{DP_2}^p(t, t_1, k_{21}, k_{12}) = u(t - t_1) \left\{ 1 - \exp(-k_{21} t_1) \int_0^{t-t_1} y_2(\tau) d\tau \right\}, \quad (6.1c)$$

representing the vascular and parenchyma phases, respectively.

6.1.2 Incorporating a Capillary Distribution

The random coupling assumption is commonly used in the modeling of a capillary bed by a multi-pathway model [82], [83]. We adopt the random coupling assumption, and consider the capillary bed as consisting of a vasculature of capillary-tissue units, each described by the DP_2 model (6.1). These capillary-tissue units may differ in their physical geometries (i.e. lengths or sizes) and hence transit times, but functional properties such as transfer rates (k_{ij}) are the same for all capillary-tissue units. With this model, we note that each DP_2 capillary-tissue unit with a unique transit time t_1 can still be associated with a different extraction fraction E .

From a stochastic viewpoint, if a unit impulse of tracer is introduced in the arterial end of the capillary bed at time $t=0$, the fraction of tracer appearing at the venous end at a given time $t_{1,i}$ indicates a certain probability of tracer taking time $t_{1,i}$ to traverse the capillary bed. We may then define a probability density function for traversal times, $g(t_1)$ (or distribution of transit times) such that the fraction of emerging tracer in an infinitesimal interval dt_1 is given by $g(t_1) dt_1$. Thus $g(t_1)$ describes the relative chances that the tracer molecules would require the various possible transit times to traverse the system. This distribution of transit times is assumed to be stationary and starts from a minimum transit time $t_{\min} > 0$, to account for a finite amount of time required to traverse the shortest pathway in the vasculature [49]. As a mental construct, each value of possible transit time can be mapped into a hypothetical pathway constructed by a capillary-tissue exchange unit described by the DP_2 model.

For $g(t_1)$ to be physiologically realistic, it should be non-negative, causal (i.e. $0 \leq t_1 \leq \infty$), and normalizable. Since $g(t_1)$ describes the probability of ‘loss’ of tracer from the vasculature, in order to incorporate such a function into the formulation of the DP₂ impulse residue model, one has to consider the fate of the residual tracer from the alternative viewpoint of the probability of tracer remaining in the vasculature. It is instructive to begin with a discrete description:

$$R_{\text{DCDP}_2}(t < t_{\min}) = 1, \quad (6.2a)$$

$$R_{\text{DCDP}_2}(t = t_{1,i}, k_{21}, k_{12}) = 1 - \sum_{j=1}^i g(t_{1,j}) \Delta t_{1,j} [1 - R_{\text{DP}_2}^p(t, t_{1,j}, k_{21}, k_{12})]. \quad (6.2b)$$

Equation (6.2a) means that all input tracer remains in the vasculature before the minimum transit time $t_{\min}$. As $g(t_{1,j}) \Delta t_{1,j}$ is the probability of occurrence for pathways corresponding to the small interval of transit time $\Delta t_{1,j}$, the summation term in (6.2b) denotes the summed weighted loss of tracer due to the various pathways with transit times $t_{1,j}$ up to the i th pathway ($t_{1,i}$). The parenchyma phase of the DP₂ impulse response model $R_{\text{DP}_2}^p(t, t_{1,j}, k_{21}, k_{12})$ is associated with the index of its vascular transit time, $t_{1,j}$, to distinguish among the individual pathways. Therefore, (6.2b) describes the net retention of tracer within the vasculature up to time $t_{1,i}$.

By analogy, the continuous version of the distributed capillary DP₂ (DCDP₂) impulse residue model can be written as

$$R_{\text{DCDP}_2}(t, g(t_1), k_{21}, k_{12}) = u(t) - \int_0^t g(t_1) dt_1 + \int_0^t g(t_1) R_{\text{DP}_2}^p(t, t_1, k_{21}, k_{12}) dt_1. \quad (6.3a)$$

This expression, again can be split into two separate equations that describe a vascular phase

$$R_{\text{DCDP}_2}^v(t, g(t_1)) = u(t) - \int_0^t g(t_1) dt_1, \quad (6.3b)$$

and a parenchyma phase

$$R_{\text{DCDP}_2}^p(t, g(t_1), k_{21}, k_{12}) = \int_0^t g(t_1) \left\{ 1 - \exp(-k_{21} t_1) \int_0^{t-t_1} y_2(\tau) d\tau \right\} dt_1. \quad (6.3c)$$

The physiological significance of these phases will be further discussed later. Depending on the functional form of $g(t_1)$, the expression given in (6.3c) may not be amenable to an analytical solution, and numerical calculations involved can be intensive. An efficient approach for the numerical calculation of $R_{\text{DCDP}_2}(t, g(t_1), k_{21}, k_{12})$ is presented in the Appendix C.

The DCDP₂ model now assigns to each capillary pathway with transit time t_1 an extraction fraction given by (B.6) in Appendix B, which is a function of t_1 and k_{21} . The net extraction fraction of tracer by the vasculature would be the sum of the individual extraction fraction of each capillary pathway weighted by its probability. Hence, the net extraction fraction of the present model can be given by the weighted integral

$$E = \int_0^\infty g(t_1) [1 - \exp(-k_{21} t_1)] dt_1. \quad (6.4)$$

This integral can be formally evaluated when a distribution function for transit time $g(t_1)$ is adopted.

6.1.3 An Ansatz²¹ for Capillary Transit Time

Distribution

Examples of probability density functions that can be used to model vascular flow or transit time distributions include the lagged normal density curve [84], the random walk function [82], and the asymmetric exponential function [63], and the single-exponential [85]. As explained by Jacquez and Simon [86], [87], another useful approach for generating density functions for transit times is to consider a one-way chain of n compartments with the same transfer coefficient b . If one introduces a unit impulse into the first compartment of the linear chain of compartments, the rate of outflow from the n th compartment, i.e. the probability density function for transit time, can be expressed as

$$g(t_1, n, b) = \frac{b^n t_1^{n-1} \exp(-b t_1)}{(n-1)!}, \quad (6.5)$$

which is the density function for the Erlang or gamma distribution [86], [87]. Incidentally, this function is also commonly known as the ‘gamma variate’ in tracer kinetics studies, and is often used to model an input bolus [88].

To specify a minimum transit time $t_{\min}$ for the above transit time distribution, we may incorporate a delay:

$$g(t_1, n, b) = \frac{b^n t_1^{n-1} \exp(-b t_1)}{(n-1)!} \otimes \delta(t_1 - t_{\min}). \quad (6.6)$$

The above transit time distribution function now involves 3 parameters (n , b and $t_{\min}$), and by its definition in (6.5), n is the number of catenary compartments, which is a discrete variable. The estimation of these parameters (together with

²¹ The German word Ansatz means something like ‘basis’ or ‘starting point’. An ansatz is a guess that works. (<http://en.wikipedia.org/wiki/Ansatz>).

those in (6.3)) in a data fitting process would require a more elaborate mixed-integer optimization or searching schemes that allow the occurrences of both real and integer variables. To reduce the number of parameters and avoid mixed-integer optimization, we constrain n to the value of 2. Fine *et al.* [89] have found that gamma distribution functions with $n=2$ can give an appropriate description of the vascular and parenchyma transit times in kidneys. A previous study of prostate DCE CT imaging using of two types of transit time distributions, has shown that the values of μ and σ obtained for both types of distributions are very close to each other [63].

With (6.6) and $n=2$, the mean and standard deviation (dispersion) of the vascular transit times can be written as

$$\mu = t_{\min} + \frac{2}{b}, \quad (6.7a)$$

and

$$\sigma = \frac{\sqrt{2}}{b}, \quad (6.7b)$$

respectively. Using these relations, the parameters b and $t_{\min}$ can be expressed in terms of μ and σ , such that $g(t_1, 2, b)$ can also be given in terms of μ and σ , $g(t_1, \mu, \sigma)$. We also notice that within the present framework, the present DCDP₂ model (6.3) will have only one additional parameter (σ) as compared with the original DP₂ model for a capillary-tissue unit (6.1). The vascular transit time t_1 in the unit capillary-tissue DP₂ model has been averaged ('integrated out') and replaced by μ in the present model. Thus, the parameters that can be directly obtained by fitting the DCDP₂ model are F , μ , σ , k_{21} and k_{12} . The parameters v_1 and PS can again be estimated, as in the original single unit DP₂ model. With

function shown in (6.6) as the transit time distribution function and $n=2$, the extraction fraction in (6.4) can be calculated by

$$E = 1 - \left(\frac{b}{b + k_{21}} \right)^2 \exp(-k_{21}t_{\min}). \quad (6.8)$$

6.2 Materials And Methods

6.2.1 Monte Carlo Simulation Experiments

The Monte Carlo simulations used to study the changes in precision of model parameters under varying noise conditions are presented in Chapter 3 Section 3.3.2. The DCDP₂ model equations (6.3) and (6.6), and an actual $C_a(t)$ curve (Figure 6.1(a)), which was sampled with a time interval of 1 s, were used in (2.4) to generate simulated $C_{\text{tiss}}(t)$ curves. The parameter values assumed for tumor, GM and WM tissue types (listed in Table 6.1) are the median values of the 5 metastasis patients (Figure 6.2), which are also comparable with the literature [46], [90]. A set of 1000 noisy $C_{\text{tiss}}(t)$ curves were simulated for each signal-to-noise ratio (SNR) of 10 and 20.

Table 6.1 Values of the various microcirculatory parameters of the DCDP₂ model used to simulate tissues of tumor, normal grey matter (GM) and normal white matter (WM), for use in the Monte Carlo simulations.

Tissue types	F (mL/g/min)	μ (s)	σ (s)	k_{21} (min ⁻¹)	k_{12} (min ⁻¹)
Tumor	0.358	7.22	3.42	4.40	1.09
GM	0.255	4.91	0.0379	0.125	0.010
WM	0.213	3.02	0.0277	0.170	0.010

Figure 6.1 (a) The arterial input function $C_a(t)$ used in the Monte Carlo simulation experiments. The dotted line indicates the correction for the effect of recirculation. (b) Simulated impulse residue functions $R(t)$ s for tumor (solid line), normal grey matter (GM, dashed line) and normal white matter (WM, dotted line) using the parameter values listed in Table 6.1. The $R(t)$ s are scaled by their respective perfusion F values. (c) Simulated tissue concentration-time $C_{tiss}(t)$ curves for tumor (circles), normal GM (triangles) and normal WM (squares), calculated using their respective $R(t)$ s, and for a signal-to-noise ratio SNR=10. The corresponding dotted lines denote the respective $C_{tiss}(t)$ curves without added noise.

Figure 6.1(b) see Figure 6.1 above.

Figure 6.1(c) see Figure 6.1 above.

6.2.2 DCE CT Images

Details of the 5 patient study cases with cerebral metastasis and the DCE CT imaging protocol are presented in Chapter 3 Section 3.1.1. The slice thickness was 10 mm and the voxel sizes ranged from 1.53 mm^3 to 1.85 mm^3 .

The realignment of DCE CT images and the correction for partial volume average effects in $C_a(t)$ were performed as described in Chapter 3 Section 3.2. The sizes of ROIs for the arteries, tumors, GMs and WMs were respectively, $280 \pm 224 \text{ mm}^3$, $795 \pm 362 \text{ mm}^3$ and $1500 \pm 735 \text{ mm}^3$.

6.2.3 Data Processing

Curve fitting process is described in Chapter 3 Section 3.2.4. For each type of tissue, the mean and standard deviation of the various parameter values were calculated for the 5 patients. To study the differences in the various parameter

estimates obtained for tumor and normal GM and WM tissues, both the paired and unpaired t-tests (one-tail) were used to test whether parameter values in the tumor were significantly higher than those of GM and WM. Significance was declared at $P\text{-value} < 0.05$. The generation of parameter maps 2-by-2 voxel resolution is described in Chapter 3 Section 3.2.5.

6.3 Results

6.3.1 Precision of Estimated Model Parameters

The arterial input function $C_a(t)$, used in the present Monte Carlo simulation studies, is shown in Figure 6.1, together with the simulated $R(t)$ and $C_{tiss}(t)$ curves for tumor, GM and WM tissues, using the DCDP₂ model and with the parameter values listed in Table 6.1. The mean values of various parameter estimates obtained from 1000 simulation runs and the corresponding coefficients of variation (CVs) are listed in Table 6.2, for two values of signal-to-noise ratios (SNR =10 and 20). The potential biases in estimating the parameters of the DCDP₂ model are small, as can be seen by looking at the difference between the estimated mean values and ‘actual’ parameter values used in the simulation. The percentage CVs are larger for parameters whose actual values are close to zero, since a slight deviation from these small parameter values would result in a significant percentage change. These parameters include the rate constants (k_{21} and k_{12}) of the WM and GM tissues, which should be almost zero due to the intact BBB. We also note that the CV values for the parameter σ for the WM and GM are large due to the small values used in the simulation. As for the tumor, the CV for σ and the rate

constants are typically larger than the other parameters, indicating that these parameters are more sensitive to noise. For the tumor, the CV values for all parameters generally improve to a more acceptable level of about 13% or less for an SNR of 20.

Table 6.2 Results of Monte Carlo simulation study on the confidence of the various microcirculatory parameters in the DCDP₂ model, and for the different tissue types. Each entry represents the mean and percentage CV (in brackets) for 1000 simulation runs. The ‘actual’ values used in the simulation are shown in Table 6.1. The bias in each parameter estimate can be given by the difference between the mean value and the corresponding ‘actual’ parameter value.

	SNR	F (mL/g/min)	μ (s)	σ (s)	k_{21} (min ⁻¹)	k_{12} (min ⁻¹)
Tumor	10	0.360 (9.2)	7.28 (15)	3.25 (26)	4.44 (18)	1.08 (29)
	20	0.360 (4.0)	7.21 (4.9)	3.42 (5.1)	4.42 (6.4)	1.10 (13)
GM	10	0.250 (8.8)	4.85 (5.7)	0.0930 (70)	0.128 (57)	0.0170 (150)
	20	0.251 (3.7)	4.90 (1.2)	0.0650 (62)	0.128 (31)	0.0110 (78)
WM	10	0.219 (12)	3.04 (2.2)	0.0440 (137)	0.174 (49)	0.0120 (100)
	20	0.215 (7.5)	3.03 (0.7)	0.0330 (52)	0.170 (27)	0.0100 (34)

6.3.2 Parameter Estimates from clinical data

Estimates for the various microcirculatory parameter obtained by fitting $C_{\text{tiss}}(t)$ curves derived from ROIs of WM, GM and tumor for each of the 5 clinical cases, are shown in Figure 6.2. For each parameter and tissue type, the mean and standard deviation of the estimates for the 5 patients are listed in Table 6.3. The ‘average’ capillary transit time distribution for each tissue type obtained using the mean values of μ and σ for the 5 patients, is shown in Figure 6.3. The capillary transit time distributions for the tumor exhibit much wider spreads than those of the WM and GM.

Figure 6.2 The various parameter estimates for normal WM (squares), GM (triangles) and tumor (circles) obtained by fitting ROIs of 5 patients with metastatic brain tumors, using the DCDP₂ model. (a) Perfusion F (mL/g/min). (b) Mean vascular transit time μ (s). (c) Standard deviation of vascular transit time σ (s). (d) Rate constant k_{21} (min⁻¹). (e) Rate constant k_{12} (min⁻¹). (f) Fractional vascular volume v_1 . (g) Extraction fraction E . (h) Permeability-surface area product PS (mL/g/min).

Figure 6.2(e)-(h) see Figure 6.2 above

Table 6.3 The mean $\pm$ standard deviation of the various parameter estimates for normal WM, GM and tumor obtained by fitting ROIs of 5 patients with metastatic brain tumors, using the DCDP₂ model.

	WM	GM	Tumor
F (mL/g/min)	0.19 $\pm$ 0.08	0.25 $\pm$ 0.08	0.33 $\pm$ 0.07
μ (s)	3.69 $\pm$ 2.50	4.73 $\pm$ 0.63	7.17 $\pm$ 2.20
σ (s)	0.03 $\pm$ 0.01	0.07 $\pm$ 0.07	3.73 $\pm$ 2.49
k_{21} (min ⁻¹)	0.18 $\pm$ 0.16	0.18 $\pm$ 0.20	4.27 $\pm$ 1.57
k_{12} (min ⁻¹)	0.11 $\pm$ 0.13	0.11 $\pm$ 0.22	1.04 $\pm$ 0.56
v_1 (%)	0.94 $\pm$ 0.15	2.04 $\pm$ 0.79	3.97 $\pm$ 1.57
E (%)	0.93 $\pm$ 0.62	1.28 $\pm$ 1.29	35.37 $\pm$ 6.48
PS (mL/g/min)	0.002 $\pm$ 0.002	0.003 $\pm$ 0.003	0.160 $\pm$ 0.060

Figure 6.3 'Average' transit time distributions for the various tissue types, obtained using the averaged values of μ and σ for each tissue type. The time axis has been normalized such that the average value of μ corresponds to unity, for each tissue type.

Results of both the unpaired and paired t-tests, for comparison between the respective parameter estimates of tumor, GM and WM, are shown in Table 6.4. For the unpaired t-tests, which compare the respective mean parameter values of the tissue types, the tumors were found to yield significantly higher mean values as compared with WM, for all the parameters (with P -values less than 0.024 for all

parameters). Comparing the tumors with GM, the mean value of F in tumors was found to be not significantly higher than that in GM (P -value = 0.077), although the other parameters yielded significantly higher mean values in the tumor than in GM (with P -values less than 0.022). When comparing GM and WM, the mean values for all parameters in the GM were not significantly higher than those in WM (with P -values above 0.13), except for v_1 (P -value = 0.008).

For the paired t-tests, which accounts for intra-patient differences, the tumors are again found to yield significantly higher estimates for all parameters, as compared with WM (with P -values less than 0.040). When the tumors are compared with GM, all parameters were found to be significantly larger in the tumors (with P -values less than 0.042), except for μ (P -value = 0.052). Comparing GM and WM, all parameters in the GM were not significantly higher than those in WM (with P -values above 0.18), except for F and v_1 (P -value = 0.024 and 0.016, respectively).

Table 6.4 P -values of unpaired and paired t-tests (one-tailed) for comparison of the various microcirculatory parameters derived from ROIs within the tumor, GM and WM tissue regions of the 5 patients. Significance level was set at 5% (i.e. P -value < 0.05). An * indicates rejection of the corresponding hypothesis at 5% significance.

Hypothesis t-test	Tumor > WM		Tumor > GM		GM > WM	
	Unpaired	Paired	Unpaired	Paired	Unpaired	Paired
F	0.0113	0.0180	0.0766 *	0.0421	0.1294 *	0.0238
μ	0.0240	0.0397	0.0223	0.0521 *	0.1971 *	0.2401 *
σ	0.0053	0.0149	0.0056	0.0141	0.1402 *	0.1766 *
k_{21}	0.0002	0.0018	0.0002	0.0023	0.5107 *	0.5089 *
k_{12}	0.0034	0.0111	0.0043	0.0057	0.5086 *	0.5076 *
v_1	0.0013	0.0053	0.0194	0.0217	0.0079	0.0161
E	0.0000	0.0002	0.0000	0.0001	0.2995 *	0.3015 *
PS	0.0002	0.0021	0.0002	0.0020	0.2420 *	0.2673 *

Figure 6.4 Dynamic contrast enhanced CT images of patient 1. (a) Pre-contrast CT image with the various ROIs. Post-contrast CT images at (b) 10 s, (c) 20 s and (d) 30 s after arrival of contrast medium, first noticed after the eleventh image. (e) The various concentration-time curves obtained from the ROIs at an artery (filled circles), tumor (unfilled circles), GM (triangles) and WM (squares).

6.3.3 Parameter Maps

The DCE CT images of Patient 1 are shown in Figure 6.4, together with the various ROIs and enhancement curves. Two foci of metastatic deposits can be identified on the DCE images. The contrast concentration-time curve of the tumor exhibits a stronger enhancement than those of the WM and GM (Figure 6.4(e)), and remains consistently higher even as the contrast in the WM and GM washes out.

The corresponding 2-by-2 voxel parameter maps, generated using the present DCDP₂ model, are shown in Figure 6.5. These parameter maps reveal two conspicuous regions of enhancements, corresponding to the two lesions identified on the DCE images. Corresponding parameter maps for patients 2 to 5 are shown in Figures 6.6-6.9, respectively.

The demarcation is usually more obvious on the maps of the parameters associated with the extravasation (leakage) of contrast medium, namely k_{21} , E and PS . We note that the additional parameter map for σ provided by the present DCDP₂ model, which quantifies the spread in the capillary transit times, also reveal higher values in the locations of the tumor. These DCDP₂ parameter maps consist of 256x256 pixels of sizes in the range of 0.612 mm² to 0.74 mm².

6.4 Discussion

In (6.3), we show that the present DCDP₂ model can be split into two physiologic phases (vascular and parenchyma). It is interesting to note that these two phases, typical for DP impulse residue models [18], [58], [63] are also evident in the DP impulse response model for analysis of indicator dilution data [82], [91], [92]. The vascular phase, also called the intravascular response [92], represents the molecules of contrast tracer that flow directly through the capillary without ever leaving it; while the parenchyma phase refers to the ‘tail’ function that describes the return (back diffusion or backflux) of the substance from the interstitial fluid to the capillary [82].

Figure 6.5 Calculated parameter maps of patient 1, using the DCDP₂ model. (a) Perfusion F (mL/g/min). (b) Mean capillary transit time μ (s). (c) Standard deviation of capillary transit time σ (s). (d) Rate constant k_{21} (min⁻¹). (e) Rate constant k_{12} (min⁻¹). (f) Fractional vascular volume v_1 . (g) Extraction fraction E . (h) Permeability-surface area product PS (mL/g/min).

Figure 6.6 Calculated parameter maps of patient 2, using the DCDP₂ model. (a) Perfusion F (mL/g/min). (b) Mean capillary transit time μ (s). (c) Standard deviation of capillary transit time σ (s). (d) Rate constant k_{21} (min⁻¹). (e) Rate constant k_{12} (min⁻¹). (f) Fractional vascular volume v_1 . (g) Extraction fraction E . (h) Permeability-surface area product PS (mL/g/min).

Figure 6.7 Calculated parameter maps of patient 3, using the DCDP₂ model. (a) Perfusion F (mL/g/min). (b) Mean capillary transit time μ (s). (c) Standard deviation of capillary transit time σ (s). (d) Rate constant k_{21} (min⁻¹). (e) Rate constant k_{12} (min⁻¹). (f) Fractional vascular volume v_1 . (g) Extraction fraction E . (h) Permeability-surface area product PS (mL/g/min).

Figure 6.8 Calculated parameter maps of patient 4, using the DCDP₂ model. (a) Perfusion F (mL/g/min). (b) Mean capillary transit time μ (s). (c) Standard deviation of capillary transit time σ (s). (d) Rate constant k_{21} (min⁻¹). (e) Rate constant k_{12} (min⁻¹). (f) Fractional vascular volume v_1 . (g) Extraction fraction E . (h) Permeability-surface area product PS (mL/g/min).

Figure 6.9 Calculated parameter maps of patient 5, using the DCDP₂ model. (a) Perfusion F (mL/g/min). (b) Mean capillary transit time μ (s). (c) Standard deviation of capillary transit time σ (s). (d) Rate constant k_{21} (min⁻¹). (e) Rate constant k_{12} (min⁻¹). (f) Fractional vascular volume v_1 . (g) Extraction fraction E . (h) Permeability-surface area product PS (mL/g/min).

Despite the fact that the DP_2 model is physiologically realistic, the DP_2 impulse residue function typically exhibits a discrete drop, at the transition point of the two phases, which gives an estimate for the extraction fraction E [58], [62], [68]. Such a discrete drop may be reasonable for a single capillary-tissue unit, but when applying the DP_2 model to a region of interest, one would have to assume that the DP_2 capillary-tissue unit is a hypothetical, averaged model of the entire underlying vasculature. To more closely model a dense and randomly-formed vasculature (such as that associated with a malignant tumor) and allow the quantification of the degree of randomness, the discrete drop in the DP_2 model can be circumvented or smoothened, by the inclusion of the capillary distribution in the $DCDP_2$ model (Figure 6.1(b)). The incorporation of a transit time distribution is also consistent with the earlier formulation of the indicator dilution theory [48], [49], and the capillary transit time distribution has been postulated to be a characteristic function of the underlying system. Since a capillary transit time distribution can be described by its mean μ and standard deviation σ , it would be of interest to study the applicability of these parameters as possible differential descriptors of the tumor vasculature and grading.

For a very narrow capillary distribution (i.e. with a very small σ) the $DCDP_2$ model should revert back to the DP_2 model, since the $DCDP_2$ model is a distribution-weighted version of the DP_2 model. Theoretically, this may be proven by considering that the capillary distribution function $g(t_1)$ approaches a dirac delta function $\delta(t_1 - \mu)$ when σ approaches zero, and under such conditions (6.3) can then be expressed in the form

$$R_{\text{DCDP}_2}(t) = u(t) - \int_0^t \delta_t(t_1 - \mu) dt_1 + \int_0^t \delta_t(t_1 - \mu) R_{\text{DP}_2}^p(t, t_1) dt_1, \quad (6.9)$$

which reduces to (6.1) for the DP₂ model.

The mean ($\pm$ standard deviation) of estimates for F obtained for WM, GM and tumor, using the present DCDP₂ model, are 19.1 ± 8.19 , 25.3 ± 7.98 , and 33.0 ± 7.37 mL/100g/min, respectively. For WM and GM, they are comparable with the values of 22.9 and 44.3 mL/100g/min reported by Nabavi *et al.* [46], respectively. The relatively large standard deviation for the present estimates is likely due to the small sample size in this initial study. Vonken *et al.* [90] had performed perfusion MRI studies on two occasions (separated by 81 days) for a patient with glioblastoma multiforme (GBM) tumor, and the obtained F values equal to 30 ± 1 and 38 ± 5 for WM and 51 ± 3 and 55 ± 2 for the GBM tumor. These values are comparable to some of our results for cases with higher perfusion values. Our estimates for μ in normal WM, GM and tumor are equal to 3.69 ± 2.50 , 4.73 ± 0.63 , and 7.17 ± 2.20 s respectively. These values are comparable with the values obtained by Vonken *et al.* [90] (WM: 6.1 ± 0.3 , and 4.9 ± 0.5 s; GBM tumor: 8.7 ± 0.1 , and 6.7 ± 0.4), Eastwood *et al.* [79] (3.6 ± 0.8 s for regions unaffected by stroke), and Østergaard *et al.* [78] (WM: 3.19 ± 0.93 s and GM: 2.62 ± 0.6 s). Our values of v_1 for normal WM, GM and tumor are equal to 0.9 ± 0.2 , 2.0 ± 0.8 , and 4.0 ± 1.6 % respectively. These are comparable with the values of 1.26-7.76% obtained by Lüdemann *et al.* [23] for patients with gliomas of various grades. Our estimates for PS values of metastatic brain tumors are 16.01 ± 6.02 mL/100g/min, which are in agreement with those observed by Roberts *et al.* [93] on their PS maps for two patients ($PS > 10$ mL/g/min for one patient and $PS > 40$ mL/g/min for the other), using functional CT. These values are also in agreement with the values

of 14.3 ± 10.9 mL/100g/min, as reported by Andersen and Jensen [33] in their dynamic MRI studies of 6 patients with intracranial tumors.

As the normal WM and GM tissues contain an intact BBB, it is obvious that the tumors should exhibit higher values for the parameters associated with extravasation of contrast medium (i.e. k_{21} , E and PS), and our P -values obtained for these parameters are extremely low, indicating that the differences are indeed highly significant. These parameters in turn yield parameter maps that can more clearly reveal the locations of BBB disruption, and hence the existence of the tumors. This is consistent with the findings of Roberts *et al.* [93] who show that tumor conspicuity is highest on the PS map, as compared with the maps of F and v_1 . Here, we show that the parameter maps for k_{21} and E are also useful in revealing regions of BBB disruption. Although the parameters k_{21} and E of the distributed parameter model have been previously discussed and estimated [18], [58], [62], [67], the usefulness of their parametric maps in revealing the extent and locations of cerebral tumors, have not been previously illustrated.

The main advantage of the present DCDP₂ model is its ability to quantify the distribution of capillary transit times, using the parameter σ . Our results of both the paired and unpaired t-tests reveal that tumors have significantly higher values of σ than normal WM and GM tissues. An increase in σ would imply a wider spread in the spectrum of transit times taken by blood to traverse the tumor vasculature, and indicates a higher variability in the microvessel architecture of the tumor than the normal tissues. We also note that the corresponding P -values for σ are lower than those of F or μ , suggesting that σ might even be a better discriminator of tumorous

tissues than F or μ . Consistently, the parameter map for σ also reveals markedly higher values in the corresponding tumor regions, and can better reveal the extent and location of the tumors than the maps for F or μ . To the best of our knowledge, the use of the σ parameter map has not been documented in the literature to date, and this study represents a first attempt to illustrate its potential applicability to studies of cerebral tumors.

Our findings of significantly larger values for v_1 , σ and the extravasation parameters (k_{21} , E and PS) in the tumor as compared to normal tissues, are consistent with the current understanding of the process of neo-angiogenesis in human neoplasms. Studies of human neoplasms have shown that the more angiogenic and aggressive tumors generally possess a notably higher density of randomly formed microvessels, which are immature and have increased permeability [18], [94], [95]. Hence, the pathophysiological basis for the significantly larger v_1 and σ estimates in the metastatic tumor, is the increased microvessel density and variability in the underlying neo-vasculature, typical of a malignant tumor. Higher values of the extravasation parameters in tumors are indicative of the increased permeability of the vessel walls.

It is known that the outcome of cancer therapy can depend on the tumor vascularization. The efficacy of radiotherapy is related to tissue oxygenation and hypoxic tumor regions are relatively protected against radiation damage. In tumors with extensive necrotic areas, large intercapillary distances may exist in a significant portion of the tissue which will result in reduced transport and activities of chemotherapeutic agents. On the other hand, the delivery of hyperthermia

therapy is more effective in poorly vascularized regions of the malignant tissue [96]. Thus, knowledge of blood perfusion and vascular distribution provided by the various parameter maps can be used to guide and optimize cancer therapy. Since DCE imaging can be repeated during and after a course of therapy, it may be useful in the evaluation of treatment outcome. With the development of anti-angiogenic therapeutic pharmaceuticals, the information derived from DCE imaging could serve as a valuable tool for the *in vivo* assessment and monitoring of treatment effects.

Chapter 7

Conclusions and Recommendations

7.1 Conclusions

Physiological features such as blood perfusion, blood volume, vascular transit times and blood vessel leakiness contain important information about the state of tissue. Therefore, they might prove useful in contributing to improved detection of the disease, evaluation and monitoring of the treatment effectiveness and therapy planning. Dynamic contrast enhanced (DCE) techniques allow measurements of these features non-invasively *in vivo*. In recent years, the quality of DCE imaging has been improving quickly due to technology advancements in medical imaging.

However, in a model-based quantitative analysis of DCE images, lumped parameter compartmental tracer kinetics models have been used to date by most researchers and clinicians. The need for better models to take advantage of higher quality in modern DCE images became apparent. The goal of this thesis is to address this problem by introducing more realistic tracer kinetics models.

The possible existence of both viable and necrotic tissue regions in many tumors suggests that an n -compartment mammillary distributed-parameter (MDP_n) model that considers more than one type of tissue is needed. Such a model was developed and used to analyze DCE CT data for prostate tumor. The results reveal that the tumor can be characterized by at least two groups of physiologically different tissues.

Comparative study of DP and compartmental models was performed. A two-compartment distributed-parameter model (DP_2), a conventional compartmental model and an adiabatic approximation to the DP_2 model were compared by using them to analyze intracranial meningioma DCE images. The conventional compartmental model yielded parameter values that were significantly different from those determined using distributed-parameter models. The adiabatic model was able to closely approximate the DP_2 model while being more efficient.

Many early studies of DCE images were limited to models that represented an organ with a large vessel. Tumor tissue contains many capillaries. Thus, the model was enhanced by including the distribution of capillary transit times to account for different capillary lengths in the tissue. A two-compartment distributed-capillary distributed-parameter ($DCDP_2$) model was applied to DCE data for intracranial metastasis. The model provides additional information about the heterogeneity of capillary transit times in tumor tissue.

This thesis has provided more evidence that DCE imaging might be useful as a clinical tool for diagnosis of tumors and monitoring of cancer therapy outcomes

[1]. At present, there is an ongoing collaboration with researchers in Germany to study neck tumors and stroke.

7.2 Recommendations for further research

The knowledge gathered and findings from this research have pointed to new directions for further research and revealed ancillary issues that could have been more appropriately resolved. We would like to recommend the following for further research and highlight some ancillary issues.

7.2.1 Further research directions

- (a) Development of tissue specific models. The mamillary three-compartment distributed-parameter model that included distribution of capillaries was considered promising after the presence of viable and necrotic regions in tumors was observed. However, such an approach might be inappropriate since the two regions might have different capillaries distributions. We suggest tissue-specific models that incorporate clinical knowledge in their design to allow more meaningful parameter selection and possibly simpler formulation than the general ones.

- (b) Explore possible ways to reduce the analysis time. Two main factors affecting the efficiency are the numerical calculation of the DP models and the need for optimization of data fitting in model-based approaches. Usually, the curve-fitting algorithm is a general one, independent of the type of mathematical functions and data being fitted. Considering these two

areas together could lead to the development of a more efficient computation algorithm.

- (c) Clinical studies to determine the relationship between the measured tumor physiological parameter values and the tumor grades, therapy effectiveness, and treatment outcome. Such studies should include DCE imaging of different types of tumors, performed with various imaging modalities.

7.2.2 Ancillary issues

Ancillary issues refer to issues that could affect the quality of research results, but not within the scope of model-based quantitative DCE analysis.

- (a) Effects of patient movement during the acquisition were typically corrected by applying image realignment algorithms that are mainly developed for the purpose of image registration between different imaging modalities, e.g. PET and CT. However, DCE images have additional feature due to the passage of contrast agent. On one hand, this unaccounted feature might cause errors in these image alignment algorithms, making them inappropriate. On the other hand, incorporating this feature into the alignment algorithm should improve the algorithm accuracy.
- (b) As technologies in medical imaging machines advance, continuous verification and validation tasks should be carried out to ensure that image pixel values are indeed linearly proportional to the tracer concentrations. In addition, realistic tissue phantoms might be necessary for more accurate

calibration replacing methods that rely on using tracer solutions of different concentrations.

- (c) The length of acquisition time and the number of CT acquisitions for proper analysis depends on the concentration of the tracer remaining in the tissue of interest. CT machines should include the capability to increase the time interval between images when the signal strength decreases slowly. Thus, the tracer passage can be studied for a longer period with the same number of images acquired as the current fixed time interval method, enabling better utilization of the tracer. In addition, the capability to stop scanning once the signal decreases to near pre-contrast level may avoid unnecessary radiation exposures.
- (d) It has been suggested that the hematocrit in pathological tissue, such as tumors, might be different from normal capillaries. Thus, to be able to measure the hematocrit ratios in various tissue regions correctly and, preferably, *in vivo* would be of great value.

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3. L. H. Cheong, X. Y. Wu, and T. S. Koh, "A Mammillary Distributed-Parameter Model for Dynamic Contrast Imaging of Tumor", *Eur. J. Med. Phys. (Physica Medica)*, vol. XIX, p. 65, 2003.
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Appendix A

Calibration Experiment on CT

A.1 Introduction

Quantitative analysis of DCE imaging data using tracer kinetic models requires measurements of contrast agent concentration in tissue. Theoretically, we would expect CT numbers and contrast agent concentrations have a linear relationship [44]. This experiment aims to verify the linear relationship between the CT numbers and the contrast agent concentrations.

A.2 Materials and Methods

Various amounts of contrast agent (iohexol with an iodine concentration of 300 mg/mL (Omnipaque; Nycomed, Oslo, Norway)) were mixed with pure water to obtain 20mL solutions of different contrast agent concentrations listed in Table A.1.

These were scanned at the same CT settings as in DCE scans. In addition, slice thickness were also set at 3 other values, as shown in Table A.1.

A.3 Results

Table A.1 shows the CT numbers for different contrast agent concentrations that was measured at different slice thickness settings. Figure A.1 shows 4 linear regression lines corresponding to the 4 slice thicknesses, and Table A.1 lists the linear regression attributes. Regression lines have near zero y-interceptions and gradients in a narrow range from 41.61 to 42.53 Hu/mg/mL. CT numbers measured were in small overlapping ranges for different slice thicknesses.

A.4 Discussion and Conclusion

The range of CT numbers includes 1200 Hu, while CT numbers we have encountered in our data are below 900 Hu. Thus, we can assume linear relationship between CT numbers and tracer concentrations.

If we assume materials replaced by contrast agent in tissue VOI have the same radiodensity, CT numbers and contrast agent concentration in tissue VOI should still be linearly related. However, the corresponding regression attributes may not be the same. Thus, these results do not allow us to calculate the quantity of contrast agent in tissue.

Nevertheless, if we assume materials replaced by contrast agent from arterial VOI and from tissue VOIs have the same radiodensity, the linear regression lines related to these VOIs would have the same gradient value. Thus, this gradient value will be removed in (2.4), when we expand both concentrations as products of this gradient and CT numbers from the arterial and tissue VOIs, respectively.

Table A.1. Calibration results.

Amount of Iohexol (mL)	Amount of pure water (mL)	Iodine concentration (mg/mL)	CT numbers (Hu mean±SD) measured at various slice thickness			
			1 mm	3 mm	5 mm	10 mm
0.0	20.0	0.0	-7.3±4.81	-6.63±3.74	-6.21±2.54	-3.66±2.56
0.1	19.9	1.5	61.73±8.87	61.01±8.4	58.12±9.97	54.10±9.22
0.2	19.8	3.0	140.57±8.48	133.56±14.23	135.95±13.59	130.02±13.24
0.5	19.5	7.5	319.98±8.46	325.59±8.06	327.66±7.11	331.64±4.82
1.0	19.0	15.0	681.74±6.65	686.34±4.67	689.46±5.88	693.97±2.59
1.5	18.5	22.5	942.38±16.22	955.17±31.13	943.84±21.35	957.39±25.58
2.0	18.0	30.0	1237.1±30.51	1266.14±49.61	1268.94±48.10	1255.34±36.66
Linear regression	y-intercept (Hu)		9.78	5.69	6.16	6.89
	Gradient (Hu/mg/mL)		41.61	42.53	42.45	42.40
	r^2		0.9770	0.9838	0.9799	0.9748
	P-value of correlation		<0.0001	<0.0001	<0.0001	<0.0001

Figure A.1 Error bars plots and regression lines for slice thicknesses of 1 mm (crosses, dotted-line), 3 mm (circles, dotted-dashed-line), 5 mm (squares, dashed-line), and 10 mm (triangles, solid-line).

In conclusion, our results show strong linear relationship between contrast agent concentrations and CT numbers measured by the CT machine, which was used in our DCE studies.

Appendix B

Tracer Kinetic Models Discussed in Chapter 5

In Chapter 5, each of the three tracer kinetic models (CC₂, ATH and DP₂) is a two-compartmental system which can be described by a pair of linear differential equations, with restriction that the tracer mass conserved. The CC₂ and DP₂ models differ in the formulation of the differential equations, due to different assumptions adopted. The formal solution for the impulse residue function for each model can be obtained by simultaneously solving the appropriate pair of differential equations.

The CC₂ model assumes two homogeneous compartments, and a pair of differential equations for the two interacting compartments can be written as

$$v_1 \frac{dC_1(t)}{dt} = -\rho F_p C_1(t) - K_{21} C_1(t) + K_{12} C_2(t) + \frac{\delta_t(t)}{V}, \quad (\text{B.1a})$$

$$v_2 \frac{dC_2(t)}{dt} = -K_{12} C_2(t) + K_{21} C_1(t), \quad (\text{B.1b})$$

where $\delta_t(t)$ is the unit impulse at $t = 0$, V is the voxel volume and the quantities v_1 , v_2 , ρ , C_1 and C_2 are defined in Chapter 5.

These equations form a set of linear, first order differential equations that can be solved using standard methods. The solution for the impulse residue function of the CC₂ model is

$$R_{CC}(t, t_1, k_{12}, k_{21}) = A \exp(s_1 t) + (1 - A) \exp(s_2 t) , \quad (\text{B.2})$$

which is a bi-exponential function with

$$\begin{pmatrix} s_1 \\ s_2 \end{pmatrix} = \frac{1}{2} \left[- \left(k_{21} + k_{12} + \frac{1}{t_p} \right) \pm \sqrt{\left(k_{21} + k_{12} + \frac{1}{t_1} \right)^2 - 4 \frac{k_{12}}{t_1}} \right] , \quad (\text{B.3a})$$

$$A = \frac{s_1 + k_{21} + k_{12}}{s_1 - s_2} . \quad (\text{B.3b})$$

The DP₂ model does not assume a homogeneous IVS and defines the tracer concentration within the IVS as a function of both time and position along the length, L of the capillary. However, due to the small radial dimension of a capillary, radial concentration gradients can be neglected, and concentration is assumed homogenous along the radial direction. Therefore, as pointed out by Larson *et al.* [58], the DP₂ model encompasses a hybrid combination of compartmental and distributed-parameter assumptions, with the following set of differential equations

$$\begin{aligned} v_1 \frac{\partial}{\partial t} C_1(t, z) dz = & -\rho F_p L \frac{\partial}{\partial z} C_1(t, z) dz - K_{21} C_1(t, z) dz \\ & + K_{12} C_2(t, z) dz + \frac{L}{V} \delta_t(t) \delta_z(z) dz , \end{aligned} \quad (\text{B.4a})$$

$$v_2 \frac{\partial}{\partial t} C_2(t, z) dz = -K_{12} C_2(t, z) dz + K_{21} C_1(t, z) dz , \quad (\text{B.4b})$$

where z is the distance from the arterial end and the expression $\delta_t(t)\delta_z(z)$ is the unit impulse at $t = 0$ and $z = 0$. The other terms are defined in Chapter 5.

The corresponding impulse residue function for the DP₂ model, which is (4.15) of the MDP _{n} model with $n = 2$,

$$R_{DP_2}(t, t_1, k_{12}, k_{21}) = \begin{cases} 1 & 0 < t \leq t_1 \\ 1 - \exp(-k_{21} t_1) [1 + X_2(t - t_1)] & t > t_1 \end{cases}, \quad (B.5)$$

where $X_2(t) = \int_0^t \exp(-k_{12} \tau) \sqrt{\frac{t_1 k_{12} k_{21}}{\tau}} I_1(2 \sqrt{t_1 k_{12} k_{21} \tau}) d\tau$, and I_1 is the modified Bessel function. The first pass extraction ratio for the DP₂ model can be formally evaluated to be

$$E = 1 - \exp(-k_{21} t_1). \quad (B.6)$$

For both the CC₂ and DP₂ models, the four fundamental kinetic parameters that can be directly obtained by parametric fitting of (2.4), are F , t_1 , k_{12} and k_{21} . Additional parameters of physiological significance can be deduced from the four fundamental kinetic parameters. Using the Central Volume Principle [44], we may calculate the fractional vascular volume v_1 by

$$v_1 = t_1 F_p \rho. \quad (B.7)$$

When there is no preferential extraction for the diffusible tracer (or non-selective distribution brought about by passive diffusion), the transfer constants in opposite directions may be assumed equal, i.e. $K_{i1} = K_{1i}$, which can be associated with the permeability-surface area product, PS . We may then estimate PS by

$$PS = \frac{K_{21}}{\rho} = \frac{v_1 k_{21}}{\rho}. \quad (B.8)$$

The fractional EES volume v_2 can then be estimated by

$$v_2 = \frac{K_{12}}{k_{12}} = \frac{PS \rho}{k_{12}}. \quad (B.9)$$

The ATH model has a similar formulation as the DP₂ model, but differs in the use of the adiabatic approximation when solving for the impulse residue function. The resulting solution for the impulse residue function of the ATH model is

$$R_{\text{ATH}}(t) = \begin{cases} 1 & 0 < t \leq t_1 \\ E \exp(-k_{\text{adb}}(t - t_1)) & t > t_1 \end{cases}, \quad (\text{B.10})$$

where $k_{\text{adb}} = E F_p / v_2$ is the adiabatic version of the efflux (clearance) rate constant k_{12} . $R_{\text{ATH}}(t)$ is much simpler (and hence more efficient computationally) than $R_{\text{DP2}}(t)$. The parameters that can be directly obtained by parametric fitting of (2.4), are F , t_1 , k_{adb} and E . We may again use (B.7) to estimate v_1 , and PS can be estimated using the Renkin-Crone [55], [56] equation:

$$E = 1 - \exp\left(-\frac{PS}{F_p}\right). \quad (\text{B.11})$$

Appendix C

Efficient computation methods for the DCDP₂ model

A direct calculation of (6.3) would require the evaluation of the inner integral of (6.3c) with $y_2(t)$, which contains the modified Bessel function $I_1(t)$. To the best of our knowledge, the closed-form solution of this integral with $y_2(t)$ has not been found analytically [62]. On the other hand, if we attempt first the outer integration in (6.3c), the combination of function $g(t_1)$ in (6.6) together with the modified Bessel function, further complicates the solution. In cases where analytical solutions for both integrals in (6.3) are not available, a two-dimensional numerical integration would have to be performed, which can be computationally intensive. In order to reduce the numerical calculation to a single integral, we suggest that part of the calculation be performed analytically in Laplace space. The rationale for such an approach is that the Laplace transform of the single unit DP₂ impulse residue model results in a functional form that is much simpler to work with, i.e.

$$\overline{R_{\text{DP}_2}(s, t_1)} = \frac{1}{s} - \exp(-s t_1) \exp(-k_{21} t_1) \frac{1}{s} \exp\left(\frac{k_{21} k_{12} t_1}{s + k_{12}}\right), \quad (\text{C.1})$$

where $\overline{R_{DP_2}(s, t_1)} = \mathcal{L}_t(R_{DP_2}(t, t_1))(s)$ denotes the Laplace transform of $R_{DP_2}(t, t_1)$ and s is the transform variable. Since Laplace transform is a linear operator, we may write the Laplace transform of the DP_2 impulse residue model with capillary distribution as

$$\overline{R_{DCDP_2}(s)} = \int_0^\infty g(t_1) \overline{R_{DP_2}(s, t_1)} dt_1, \quad (C.2)$$

The above integral only involves exponential functions of t_1 with the transit time distribution function $g(t_1)$. It can be solved analytically for a large class of distribution functions. Then the time domain solution $R_{DCDP_2}(t)$ for the proposed model can be found by the inverse Laplace transform of $\overline{R_{DCDP_2}(s)}$, i.e.

$$R_{DCDP_2}(t) = \mathcal{L}_t^{-1}(\overline{R_{DCDP_2}(s)}).$$

For the transit time distribution function shown in (6.6) with $n=2$, the integral in (C.2) can be readily evaluated to yield

$$\overline{R_{DCDP_2}(s)} = \frac{1}{s} - \frac{\exp(-t_{\min} \gamma(s))}{s} \left(\frac{b}{b + \gamma(s)} \right)^2, \quad (C.3)$$

where

$$\gamma(s) = s - \frac{k_{21}s}{s + k_{12}}, \quad (C.4)$$

In this case, the inverse transform of $\overline{R_{DCDP_2}(s)}$ can be evaluated by

$$R_{DCDP_2}(t) = \mathcal{L}_t^{-1}(\overline{R_{DCDP_2}(s)}) = u(t) - \mathcal{L}_t^{-1}(\exp(-t_{\min} \gamma(s))) \otimes \mathcal{L}_t^{-1}\left(\frac{1}{s} \left(\frac{b}{b + \gamma(s)}\right)^2\right) \quad (C.5)$$

with

$$\mathcal{L}_t^{-1}(\exp(-t_{\min}\gamma(s))) = u(t-t_{\min})\exp(-k_{21}t_{\min}) \times \left[\exp(-k_{12}t)\delta(t) + \exp(-k_{12}t)\sqrt{\frac{t_{\min}k_{21}k_{12}}{t}}I_1(2\sqrt{t_{\min}k_{21}k_{12}t}) \right], \quad (\text{C.6})$$

and

$$\mathcal{L}_t^{-1}\left(\frac{1}{s}\left(\frac{b}{b+\gamma(s)}\right)^2\right) = b^2[\exp(\alpha t)(A_2 + A_1t) + \exp(\beta t)(B_2 + B_1t) + C]u(t), \quad (\text{C.7a})$$

where

$$\begin{pmatrix} \alpha \\ \beta \end{pmatrix} = \frac{1}{2} \left[-(k_{21} + k_{12} + b) \pm \sqrt{(k_{21} + k_{12} + b)^2 - 4k_{12}b} \right], \quad (\text{C.7b})$$

$$A_1 = \frac{1}{\alpha} \left(\frac{\alpha + k_{12}}{\alpha - \beta} \right)^2, \quad (\text{C.7c})$$

$$B_1 = \frac{1}{\beta} \left(\frac{\beta + k_{12}}{\beta - \alpha} \right)^2, \quad (\text{C.7d})$$

$$A_2 = A_1 \left(\frac{2}{\alpha + k_{12}} - \frac{1}{s} - \frac{2}{\alpha - \beta} \right), \quad (\text{C.7e})$$

$$B_2 = B_1 \left(\frac{2}{\beta + k_{12}} - \frac{1}{s} - \frac{2}{\beta - \alpha} \right). \quad (\text{C.7f})$$

The convolution in (C.5) can be evaluated with a numerical integration. The numerical calculation of (6.3) with the double integral, takes about 21 s on a Pentium IV personal computer, while the calculation of (C.5), with one numerical integration, requires only 0.6 s (about 35 times faster). This improvement in computation efficiency greatly facilitated the use of the present model in the generation of parametric maps.