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TRACER KINETIC MODELING OF TUMOR MICROCIRCULATION

SHI WEN

School of Electrical and Electronic Engineering

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Abstract

This thesis focuses on the investigation of Dynamic Contrast-Enhanced (DCE) based parametric assessment methods for tumor characterization, diagnosis and prognosis.

In the recent few decades, extensive studies have been done on parametric assessments of tumor microcirculation characteristics. The introduction of DCE technique further enables the determination of relevant tumor microcirculation parameters, such as blood flow, blood volume, and capillary permeability. Early empirical model-free methods using DCE imaging are fast and simple in parameter assessment but their theoretical ground is insufficient. To model tracer concentration-time curves in a more systematic way, tracer kinetic models have been developed. However, practical applications of existing models are constrained by imprecise mathematical representation, unreliable parameter estimation, and high computational complexity. To address these issues, the research reported in this study proposes novel solutions using theoretical, numerical, and experimental techniques.

Firstly, an Infinite-Pathways Distributed Parameter (IPDP) model was developed. It originates from the multiple-pathway model by Bassingthwaite *et al.* and inherits the advantage of blood flow variability assessment. Through reconstructing the mathematical representation of the vasculature network, the IPDP model eliminates the

discontinuities and normalization errors in multiple-pathway model, and at the same time relieves the dependency on hardware performance. The reconstruction of mathematical representation also enables *in vivo* assessment of blood flow distribution with DCE imaging. The IPDP model was assessed by applying on patient data with cerebral tumors. Estimation results clearly show the properties of capillary-tissue units and distinguish tumor tissues from normal tissues effectively.

Secondly, a study using the proposed IPDP model was made to evaluate the performance of empirical model-free methods. The results obtained show that the accuracy of empirical methods is condition-dependent and some conditions may be difficult to meet in practice. The results also suggest that the peak enhancement metrics are not linearly related to any intrinsic tissue parameters.

Thirdly, an improvement was made on the reliability of parameter estimation using the IPDP model. Studies have shown that the model-fitting process is sometimes trapped in a local minimum that is far from the global minimum, and it generates undesired results. A dual-phase model-fitting method was proposed to drive the model-fitting process towards global minimum for tracer enhancement curves with a washout pattern. Numerical results show that the coefficient of variation using the proposed approach can be reduced by up to 83% and the estimation bias is also alleviated in general. The proposed approach is applicable in blood flow dominated cases and could be implemented in existing tracer kinetic models for more accurate and stable parameter extraction.

Finally, an attempt was made to reduce the computational complexity of the IPDP model. Specifically, a simplified Infinite-Pathway Conventional Compartmental (IPCC) model was developed by incorporating a conventional two-compartment model into

each of the multiple pathways. The IPCC model was used to generate perfusion parameter maps for three DCE computed tomography patient cases to study its clinical applicability. The simplified IPCC model takes approximately 0.1s to generate an impulse response function compared to the 81s processing time by the original multiple-pathway software. Results also show that the simplified IPCC model has better fitting performance than the standard two-compartment model in most cases.

In summary, the research conducted has led to the proposal of advanced tracer kinetic models. IPDP model improves the mathematic representation of the existing multiple-pathway kinetic models. Using the IPDP model, an in-depth study has been conducted on the performance and physiological implications of existing empirical model-free methods. Furthermore, the dual-phase model-fitting method and the IPCC model were proposed to reduce the coefficient of variations, estimation bias, and computational complexity of the IPDP model. The work reported in this thesis has offered desirable tracer kinetic models, modeling approach and algorithm for the characterization and diagnosis of cerebral tumor.

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List of Abbreviations

AIC	Akaike Information Criterion
AIF	Arterial Input Function
BBB	Blood-Brain Barrier
cAIC	Corrected Akaike Information Criterion
CC	Conventional Compartmental
CC2	Conventional two-Compartment
CT	Computed Tomography
CV	Coefficient of Variation
DCE	Dynamic Contrast-Enhanced
DP	Distributed Parameter
DP2	Two-compartment Distributed Parameter
DP3	Three-compartment Distributed Parameter
EES	Extravascular Extracellular Space
EGK	Extended Generalized Kinetics
GK	Generalized Kinetics

GM	Generating Model
IAUC	Initial Area Under Curve
IPCC	Infinite-Pathway Conventional Compartmental
IPDP	Infinite-Pathways Distributed Parameter
IVPS	Intravascular Plasma Space
M1	Model 1
M2	Model 2
M3	Model 3
MMID4	Multiple path, Multiple tracer, Indicator Dilution, 4 region
MRI	Magnetic Resonance Imaging
MTT	Mean Transit Time
PET	Positron Emission Tomography
RD	Relative Dispersion
ROI	Regions of Interest
SD	Standard Deviation
SNR	Signal-to-noise Ratio
SSR	Sum of Squared Residuals
TTP	Time-to-peak

Chapter 1

Introduction

1.1 Background

Cancer has been among the principal causes of death for many years [1]. It is also the second most common reason for hospitalization in Singapore [2]. In the recent few decades, extensive studies have been conducted on microcirculation systems for tumor characterization and diagnosis, in both academic institutions and commercial companies [3-9]. Such studies rely on the observation of microvascular transport utilizing intravascularly injected tracer. Traditional arterial-venous sampling experiments [6, 10, 11] have been used for observing tracer outflow to look into the characteristics of tumor microcirculation. They involve the injection of one or more tracers into the arterial at an organ/tissue inlet and sampling from the venous at the organ/tissue outlet. This approach is invasive and the experimental results are obtained *ex-vivo*. The more advanced functional oncology imaging techniques for observing the traverse of tracer have been developed in recent years. As opposed to the arterial-

venous sampling experiment, the functional oncology imaging techniques can monitor physiological activities within the tissue/organ noninvasively by recording the traverse of the tracer and deriving *in-vivo* information on blood flow and tissue microcirculation.

1.1.1 Tumor and Anti-angiogenic Therapy

Tumor growth, proliferation, and metastatic spread are known to be dependent on abnormal angiogenesis. Angiogenesis in tumor can result in an increased number of blood vessels for supply of oxygen, nutrients, and survival factors that benefit tumor cells. The rapidly developed blood vessels are usually irregularly formed with leaky capillary walls and randomly distributed branches. This enables tumor expansion, local invasion, and dissemination [12]. In the absence of vascular support, tumors may become necrotic or even apoptotic [13]. Therefore, assessment of tumor angiogenesis is valuable in selecting patients with early tumor stages for aggressive therapy [14].

The most new and effective cancer therapeutic drugs nowadays are anti-angiogenic drugs. The treatments of tumor/cancer have been developing all through the time. Traditional treatments include surgery, chemotherapy, and radiotherapy. These treatments kill both tumor and normal tissues at the same time. The targeted therapy using anti-angiogenic drugs, as the most newly developed technique, attempts to target the tumor vasculature by limiting the tumor angiogenesis. Cancerous tissues can be killed by this new treatment technique due to the lack of nutrition and oxygen supply while the harm to normal tissues is minimized. Yet every method has its limitation. The drugs used for targeted therapy may lead to cancer resistance to some patients.

A crucial aspect in the administration of these drugs is timeliness. When the drug takes effect, the tumor size may remain same for the initial few weeks. Also, for patients who do not respond positively to such treatment, it is important to detect poor response early and switch to other forms of treatment. Therefore, the monitoring of changes in tumor microcirculation is more timely and reliable than the monitoring of structural changes in tumor size and shape. Microvasculature characteristics are essential biomarker for illness progress and treatment effect, especially for tumor lesion with rapid angiogenesis. Dynamic Contrast-Enhanced (DCE) imaging reveals potential effects of anti-angiogenic drugs on various aspects by analyzing a series of rapidly acquired DCE imaging data with a post-processing method. A set of hemodynamic parameters are therefore obtained to provide physiological information about the dynamics of the tracer perfusion pertaining to tissue microcirculation, such as blood flow rate, vascular volume, interstitial volume, capillary permeability, etc. As tumors rely on increased blood supply for growth and propagation, these parameters are clinically useful in both diagnosis and prognosis of cancer.

1.1.2 DCE Imaging and Tracer Kinetic Modeling

By applying DCE imaging and the post-processing, early changes in the tumor vasculature and blood flow can be detected for drug administration instead of waiting for tumor size change. The technique of DCE imaging involves the injection of a clinically approved contrast agent (tracer) followed by sequential imaging to monitor the passage of the tracer within the tumor with respect to time [15]. The traversal of the tracer within the tumor gives information on the tumor micro-vessels, and such information can be captured by sampling the tumor tracer concentration-time curves from the DCE imaging data.

Cancer or tumor tissues are well known for the rapid growth [16] and thus processing time is crucial for patients suffering from such diseases. It is vital to obtain an optimal post-processing method for the DCE image analysis which can satisfy the requirements of being accurate, precise, and fast simultaneously. Early assessment methods adopted the empirical model-free approaches based on tissue enhancement curve indexes [17, 18]. These approaches are fast and relative easy to implement but are lack of theoretical basis and physiological implications. More recently, model based quantitative analysis of DCE imaging data were performed by mathematical modeling of tumor concentration-time curves. Estimations of physiological parameters relevant to the tumor vasculature were obtained accordingly.

1.2 Research Objectives

DCE imaging can monitor the traversal of tracer in human tissues and provide information on blood flow and tissue microcirculation. This thesis is concerned with the analysis of DCE imaging data for microcirculation system characterization and tumor diagnosis. The focus of the analysis is on quantitative modeling and parametric assessment of tumor and cancerous tissues. Specifically, there are three research objectives for the thesis:

1. The first objective is to develop an advanced tracer kinetic model for tumor modeling and characteristic. Compared to normal tissues, tumor microvasculature is tortuous with proliferating blood vessels and random branching, which results in a higher variability of blood flow through the microvessels within the tumor. It is therefore useful to develop a tracer kinetic model to quantify the variability of blood

flow distribution. A multiple-pathway model that incorporates blood flow heterogeneity into the model was devised by Bassingthwaite *et al.* [10]. However, a direct application of this model for analyzing DCE imaging data entails computational issues of discontinuity and normalization errors. This thesis aims to propose a feasible solution to address these issues.

2. The second objective is to thoroughly evaluate the performance of the empirical model-free measurements of DCE data, through both mathematical derivations and simulations. Empirical model-free measures of tissue enhancement are commonly adopted in parametric studies of DCE data with respect to tumor characteristics, treatment outcomes, etc. However, despite their frequent usage, the physiological basis and interpretation of these tissue enhancement metrics are unclear. This thesis aims to figure out their physiological implications as well as the dynamics that can affect their applicability based on the tracer kinetic modeling.
3. The third objective is to develop an algorithm with high precision and efficiency for the tracer kinetic modeling/simulation and applications. Tracer kinetic models with more physiological realistic assumptions are more likely to entitle higher computational complexity. Meanwhile the model-fitting process sometimes gives undesired estimates by being trapped in a local minimum that is far from the global minimum. To enhance the computation efficiency and parametric estimation reliability of the proposed model, two aspects in model's structure and model-fitting process will be considered for the model's modifications.

1.3 Original Contributions

Tracer kinetic models of blood flow commonly employed in the literature are linear compartmental models, which assume an average blood flow in the tumor vasculature. However, these models do not adequately describe heterogeneity of blood flow in a tumor, which may result in the broadening of the blood flow distribution and provide additional information on the angiogenic potential of the tumor. The multiple-pathway approach developed by Bassingthwaighe *et al.* has been recognized as one of the most advanced models of blood flow. In Bassingthwaighe's model, tissue vasculature was modeled as a discrete number of pathways, with the total number of pathways restricted by computer memory and processing time. In this study, an Infinite-Pathway Distributed Parameter (IPDP) model was proposed to reconstruct the blood flow heterogeneity within vasculature network with the incorporation of an infinite number of pathways. Such reconstructed mathematical representation enabled *in vivo* assessment of tumor blood flow variability by DCE imaging by solving three potential drawbacks during the implementation of the original multiple-pathway model: (1) the occurrence of multiple discontinuities in the impulse residue response function is eliminated; (2) the normalization error caused by a discrete number of pathways is diminished; and (3) the total number of pathways is no longer restricted by computer memory and processing time. Comparing to conventional compartmental models or distributed parameter models, the IPDP model enables the estimation of one additional property of tumor, the distribution of blood flows within microvasculature. Clinical application of the proposed model was also assessed by applying on clinical DCE Computed Tomography (CT) datasets. More randomness of tracer fraction remaining in tumor was shown than that in normal tissue according to the

fitting results. Estimation results clearly reveal properties of capillary-tissue units and distinguish tumor tissues from normal tissues. (*Chapter 3: Infinite-Pathway Distributed Parameter Model*)

The proposed IPDP model was used to provide insights on the physiological meaning and applicability of empirical indices and methods that are commonly applied clinically for DCE imaging data. The physiological conditions of the tissue that can affect the accuracy of the empirical indices were analyzed through both mathematical derivation and computer simulation. Investigations were conducted to observe curve change trends due to the change of parameters. The accuracy of the maximal slope method is found to be affected by a high blood flow or a low vascular volume. Curve peak indexes of the tissue enhancement curve are revealed to be not linearly related to intrinsic tissue parameters. An alternative and simpler estimate of the total tracer distribution volume is suggested for a quick estimation of tissue vascular volume. These findings are instructive to the use of the empirical model-free methods. (*Chapter 4: Analysis of Empirical Tissue Enhancement Measurements*)

The model-fitting process using tracer kinetic models, including the IPDP model, usually has uncertainty of the estimation results for being trapped in a local minimum that is far from the global minimum. Extra repeated fittings with multiple initial guesses [19-21] are therefore needed to circumvent such local minima, which make the post-processing time-consuming. A model-fitting approach with dual phases was proposed in this thesis to address this problem. In particular, the method involves the development of a model-fitting approach with dual phases. The first phase employed partial Sum of Squared Residuals (SSR) during optimization, which drives the model-fitting process towards global minimum and can achieve more reliable individual parameter estimation. The

particular parameter estimated in the first phase was adopted to constrain the fitting boundaries of the second phase of model-fitting. Monte Carlo experiments were designed and conducted to compare the proposed approach with the conventional fitting method on cerebral tissues. Numerical results show that the Coefficient of Variation (CV) of parameter estimation using the proposed approach can be reduced by up to 83%. The reliability of parameter estimation is subsequently improved. Furthermore, the proposed approach reduces excessive computation consumptions by achieving more reliable estimation with less fitting repetitions. The proposed dual-phase model-fitting approach can potentially reduce misdiagnosis of cerebral tumor and speed up DCE analysis with a high precision. (*Chapter 5: Dual-Phase Model-Fitting Approach*)

To reduce the modeling processing time for better clinical applicability, this study has further investigated the possibility of incorporating simplified compartmental models into each pathway of the IPDP model. A simplified Infinite-Pathway Conventional Compartmental (IPCC) model was developed by modifying a conventional two-compartment model instead of the distributed parameter model within each pathway. The simplified IPCC model was used to generate perfusion parameter maps for patient cases to evaluate its clinical applicability. Monte Carlo experiments were performed to study the possibility of reducing the number of model parameters under various noise and tissue conditions. The IPCC model is shown to be better applicable in most practical situations (where SNRs of DCE data are at a moderate or high level) than the standard conventional compartmental model. The present simplified model takes about 0.1s to generate an impulse residual response function which is much shorter than the 81s needed for the original multiple-pathway software. (*Chapter 6: A Simplified Multiple-pathway Tracer Kinetic Model*)

1.4 Organization of Thesis

This thesis shows how an advanced tracer kinetic model can help clinicians and researchers to understand the performance characteristics of the tumor microcirculation system. The organization of this thesis is illustrated in **Figure 1-1** and described as follows.

Chapter 1 presents a brief introduction to the background and the objectives of this research. Chapter 2 gives a detailed literature review on functional imaging in oncology, the basics of physiological background of tumor and cancerous tissues, and parametric studies for tumor characterization and diagnosis using DCE techniques. Existing methods to assess tumor characteristic were introduced and summarized for an overall understanding.

In Chapter 3, a widely recognized multiple-pathway model developed by Bassingthwaighe *et al.* was firstly introduced. Then an Infinite-Pathway Distributed Parameter (IPDP) model was proposed to reconstruct the mathematical representation of blood flow heterogeneity within vasculature network. The advantages of the proposed IPDP model were evaluated and compared with Bassingthwaighe's model. Thirdly, the proposed model was implemented on actual DCE CT data of brain tumors to study its clinical applicability.

Chapter 4 focuses on the capability of the proposed IPDP model to give interpretations of the empirical model-free methods in describing microcirculation characteristics. The theoretical foundations of these methods were thereafter highlighted. Both analytical and experimental studies on the empirical methods were

carried out. At last, computer simulations with the use of the IPDP model were conducted to reveal practical applicability of these empirical methods.

Figure 1-1 Chapter organization in the present thesis.

Chapter 5 and 6 focus on the estimation reliability and computation efficiency of the IPDP model. In particular, Chapter 5 extends the IPDP model to a modification on the model-fitting process. Current conventional model-fitting method was reviewed, including its limitations in practical estimation. A dual-phase model-fitting method to apply the tracer kinetic models was proposed. The design and construction of the dual-phase model-fitting approach was illustrated in details. Monte-Carlo experiments were applied to this approach to assess its performance under various circumstances.

Chapter 6 extends the IPDP model to a modification on model structure. An Infinite-Pathway Conventional Compartmental (IPCC) was developed to reduce the computation complexity of the IPDP model. The IPCC model was applied on three patient DCE CT cases with cerebral tumors to study its clinical applicability.

Finally, Chapter 7 summarizes research work and main conclusions of this thesis, as well as recommendations for future work.

Chapter 2

Literature Review

2.1 Functional Imaging in Oncology

In recent years, medical imaging has been increasingly shifted from purely structural imaging to functional imaging. This is because of the need to assess how well the organ/tissue is functioning through imaging apart from obtaining structural information such as size and shape of an organ/tissue. As the function of an organ/tissue is closely related to its vascular characteristics, functional imaging techniques allow for the assessment of physiological parameters pertaining to vascular characteristics. It is well-established that tumor blood flow is markedly different from that of normal tissues. The aggressive tumor has an increased number of blood vessels (denser vasculature) that are more tortuous, leaky and randomly distributed. Tumors rely on these changes in their vasculature for growth and progression. Thus, a potentially useful application of functional imaging in oncology is to quantify (i.e. derive measures for) such vascular changes for tumor characterization, diagnosis and prognosis.

Functional oncologic imaging has been performed using dynamic contrast-enhanced (DCE) imaging modalities such as Computed Tomography (CT), Magnetic Resonance Imaging (MRI), and the Positron Emission Tomography (PET) [22-25]. These techniques require the injection of a tracer (or contrast agent) rapidly (“bolus”). Sequential imaging is thereafter repeatedly performed to observe its influx. The traversal of the tracer within tissue is thus monitored with respect to time and the information on blood flow is consequently achieved. Technically, such methods are also called dynamic imaging techniques, i.e. dynamic PET, DCE CT or DCE MRI. Other common names include functional CT/MRI and perfusion CT/MRI. The correlation of angiogenesis with tumor has been proven in many studies [14, 26, 27]. The DCE techniques measure capillary hemodynamics, which in turn reflect angiogenesis.

The first *in vivo* image of tumor angiogenesis was achieved in 1939 [28]. Each imaging modality has its strengths and weaknesses. The PET tracer can be tailor-made with specific chemistry to target a wide range of vascular and cellular function. However, the PET image suffers from poor spatial resolution and low signal-to-noise levels. DCE CT offers a better temporal and spatial resolution than PET and DCE MRI but it involves the use of ionizing radiation. Although DCE MRI can generate sufficiently good image quality, blood flow quantification by MRI requires additional careful design of acquisition protocols for signal calibration and to reduce imaging artifacts.

In the following literature review of oncological functional imaging, the common acquisition procedure of the DCE imaging data is described. Meanwhile the various computational analysis and processing methods applicable for DCE CT/MRI are also summarized.

2.1.1 Acquisition of DCE Imaging Data

Many clinical techniques can be used to experimentally characterise tumor microcirculation structure and function. For the purposes of tumor detection and angiogenesis evaluation, DCE MRI is generally superior comparing to other imaging techniques mainly because it avoids ionizing radiation and provides good spatial resolution. Yet DCE CT is more widely available, faster, and less expensive. In this research work, our consideration for the choice of imaging modality for functional oncologic imaging includes two important factors related to practicality: (1) availability of the scanner and (2) cost of scanning. Currently in Singapore, PET is only available in two hospitals, while CT and MRI are commonly available in all hospitals. The cost of a CT or MRI examination is only a fraction (typically one-tenth to one-fifth) of that of a PET scan. Thus, functional oncologic imaging based on CT and MRI can be made more widely available and affordable to patients.

The MRI signal is generated from the effect of strong magnetic fields and non-ionizing radiation in the radio-frequency band onto local tissue water. MRI performs better in imaging soft tissues than in bone tissues, while CT is superior at visualizing the lungs and other organs in the chest cavity. Different contrast settings (such as T1-, T2-, T2*-weighted MRI) will highlight different types of tissue. However, MRI is usually contraindicated if the patient has any type of metallic implants such as cardiac pacemakers, cochlear implants, deep brain stimulators, etc. These metallic devices may malfunction or heat up during a scan. Thus for patients having them, CT scanning is more preferred.

Table 2-1 A typical set of DCE CT scanning images on brain tumor.

Time point #1-8: Before tracer arrival*	#1	#3	#5	#7

	#9	#11	#13	#15

	#16	#18	#20	#22
Time point #9-15: Tracers get into cerebral vessels
	#24	#27	#30	#32

	#36	#40	#45	#50

Time point #16-22: Tracers leak into tumor via vessels developed within tumor				
Time point #23-32: Most tracers flow out				
Time point #33-50: Slowly washout of tracers remaining within tumor				

* The bright point is the sagittal sinus.

An example of a DCE CT dataset with a brain tumor is shown in **Table 2-1**. The DCE imaging using CT (aka CT Perfusion) generates a sequence of images (50 images) at the same location taken in a given time interval. The image voxel in vessels is usually used as sampled arterial input for further modeling analysis. The voxel in tumor can be fitted to mathematical models of tracer concentration change along with time to quantify capillary properties. The physiological parameters describing capillary changes are achieved voxel by voxel.

Image acquisition modalities have gone through rapid development during the last decades, which invoked the research in medical image computing. Computational analysis of images was paid particular attention to. The main goal of this field is to obtain important clinically pertinent information from medical images [29] and to further develop computational methods to solve problems pertaining to biomedical research and clinical care. Comparing to common images, information used for medical image processing comes not only from the images themselves, but also from *priori* knowledge in imaging environment or biomechanical behavior of certain structure [30]. The methods developed are fundamental tools in medical physics, which can be broadly grouped into multiple categories: image segmentation, image registration, and image-based physiological modeling, to name a few.

2.1.2 Image Segmentation

In DCE CT and MRI, the injected tracer serves as a contrast medium which enhances the appearance of the blood vessels as the tracer passes through the vessels and increases tumor contrast against the background tissue. Thus, DCE CT/MRI is often used clinically to improve tumor delineation. With the improved tumor-tissue contrast,

automated tumor segmentation algorithms are more likely to be successful on the DCE imaging data than conventional unenhanced images.

Traditional segmentation methods based on thresholding [30-33], region-growing [34-36], and watershed [37, 38] algorithms are likely to be applicable on DCE imaging data. These methods rely on the stipulation of threshold parameters that are dependent on the image quality, such as signal intensity, noise level and noise characteristics. More advanced pattern recognition techniques based on supervised [39, 40] and unsupervised [41, 42] clustering algorithms have been previously used for segmentation of anatomical cardiac and brain images [30]. Also, segmentation based on deformable models has been widely applied for both CT and MR images of various anatomical regions [43-45]. These segmentation methods should be applicable for DCE CT/MR images and it would be of interest to compare their performance on the basis of the enhanced tumor-tissue contrast of DCE imaging data.

Automated and semi-automated tumor segmentation can be incorporated as a pre-processing step in a larger medical software system, for purposes such as tumor volume measurement, radiation treatment planning, computer-integrated surgery etc. Currently, a generic segmentation method that works for all tumors and on both CT and MR images has not been reported. Most methods can work only on specific tumor types, or certain anatomical regions of the body. Image quality of CT and MRI scanners can vary considerably depending on the parameter settings of the machines in each hospital. The problem of tumor segmentation can be further complicated by the fact that the boundaries of most tumors at an early stage are inherently unclear, even to the experienced human eye.

2.1.3 Image Registration

As illustrated in **Table 2-1**, DCE imaging data are acquired at various time points within which the patient can move, resulting in the misalignment of anatomical features. Image registration is the transformation of two or more images into a common frame of reference [46]. Major steps of image registration consist of feature detection, feature matching, mapping function estimation, and image resampling and transformation [47].

Feature-based feature detection method is commonly employed for the images with rich details (forests, rivers, roads, etc). For medical images that lack distinct and easily detectable objects, area-based methods (such as the cross-correlation method and its modifications) are often recommended for the feature detection and feature matching steps. Once feature correspondence has been recognized and ascertained, a mapping function is constructed which specifies the transformation between the reference and misaligned image [15]. The choice of mapping function should correspond to the method of image acquisition, the assumed geometric deformation of the images, as well as the required registration accuracy [47]. Mapping functions can be classified as global models and local mapping functions according to the amount of image data used [47, 48]. Mappings by radial basis functions [49-51] are global mapping methods that can handle local geometric distortions well. Goshtasby's weighted least square and weighted mean methods [52] are examples of local image registration methods. In the implementation of mapping functions, image transformation can be accomplished by the forward or backward approach [15]. The

backward approach uses the inverse of the estimated mapping functions to generate registered images, and is more frequently used due to output quality.

Clinical applicability of image registration can vary considerably under different situations. In regions of the body where movement is inevitable, such as the heart and lungs, appropriate image registration would be a crucial step for subsequent accurate analysis of DCE imaging data. In adverse situations of trauma and pain, movements in patients can be drastic and erratic, resulting in substantial changes in the shape and sizes of anatomical features and organs on the images. Sometimes, uncontrollable patient movements can simply be due to old age. Large variations in information content in such images would render most registration methods impractical. At another extreme, in regions of the body where movement can be restrained within a reasonably short period of time during imaging (such as the head and limbs), image registration may not be required at all.

2.1.4 Image-based Physiological Modeling

DCE imaging is effective in providing microvascular information of tumor or cancer tissue and monitoring the therapeutic outcomes. Tracer concentration-time curves of the tissue can be obtained from the DCE imaging data and evaluated using tracer kinetic models. Physiological parameters associated with the tissue microvasculature are accordingly derived [4]. Such parameters include but not limited to plasma blood flow rate F which gives the volume of blood plasma passing through per unit tissue per unit time, permeability-surface area product PS of the capillaries in the Regions of Interest (ROI), fractional blood volume v_p and fractional interstitial space (i.e., EES) volume v_e , etc [53]. These related physiology parameters of microcirculation system

possess crucial position in the diagnosis and stage judgment of tumor and cancer. Generally, the concentration-time curves measured by DCE imaging can be mathematically detailed by a convolution of an Arterial Input Function (AIF) with an impulse response function. The impulse response function, either impulse outflow response or impulse residue response, reveals all the information existed in the ROI tissue microcirculation [53].

2.2 Physiological Background of Tumor and Cancerous Tissues

2.2.1 Microcirculation System

Generally, every organism organ and tissue is supplied by an aorta for blood input. Blood circulation through the capillary vasculature network enables the exchange of nutrients and waste. After the substance exchange, blood then flows out through a main vein. The capillary network can be subdivided into similar units of blood circulation composed by a secondary artery, a secondary capillary vasculature network and a secondary venule. The most basic unit of blood circulation is regarded as microcirculation system as shown in **Figure 2-1**. The microcirculation system has four main characteristic parameters: blood flow, plasma volume, intercellular fluid volume, and capillary wall permeability.

The contrast agents commonly employed in clinical DCE CT and DCE MRI are easily diffusible [54] and are usually extravascular and extracellular tracers, so that they can diffuse from the vascular plasma space into the extravascular-extracellular space

but cannot get access into any cells [55]. The distribution spaces of these contrast agents are referred to as the Intravascular Plasma Space (IVPS) and the Extravascular Extracellular Space (EES) [56]. This microcirculation system is assumed to the bottom vasculature within a ROI, “which can be a voxel or a cluster of voxels on the DCE CT/MRI image” [56]. The tissue space that is not accessible by the contrast agents can be referred to as intracellular space [57]. The fractional volume of each space is usually described as a ratio of the whole tissue volume V_{tiss} , such that

$$v_p + v_e + v_c = 1, \quad (2.1a)$$

where v_p , v_e , and v_c respectively denote the fractional volumes of the IVPS, the EES and the intracellular space. The fractional volume for the whole blood (including blood cells) is given by

$$v_b = \frac{v_p}{(1-H_{SV})}, \quad (2.1b)$$

where H_{SV} denotes the small vessel hematocrit.

Figure 2-1 Illustration of the microcirculation system

2.2.2 Angiogenesis in Tumor and Cancerous Tissues

Tumor tissue, as we know, behaves differently from normal tissue morphologically and functionally. The structural differences between normal tissue and tumor tissue are the amount of capillaries and the leaky extent of the capillary walls. **Table 2-2** shows the differences between them, as well as the resulting changes in physiological parameters of the microcirculation system.

In normal tissues, an artery would branch into several tiers of arterioles and finally into permeable micro-vessels (capillaries) for exchange of nutrients and wastes. The size of normal tissue would be limited by the growth limiting factor. However, tumors or cancerous tissues would strive for more nutrients by getting more blood to flow through it. So the capillaries in tumors proliferate with irregular branching, generating a big vascular network, which can result in a larger blood flow F and higher fractional plasma volume v_p . Another major difference between them occurs on the capillary walls. Normal capillary walls do appear to be discontinuous for the purpose of substance exchange. But the rapidly proliferated capillaries in tumors suffer from incompletely developed endothelial walls. Thus the capillary permeability PS of tumor is higher than that in normal tissue [58]. It was noted that these features of the tumor microvasculature structure can be reflected as an increase in blood flow, plasma volume and capillary permeability. The volume of tumor cells is theoretically increasing, while the speed of the proliferating of tumor cells is depended on specific cases. Therefore, the change of fractional EES volume v_e needs to be determined according to the type of cancer. Moreover, the irregular branching of blood vessels theoretically results in a wider dispersion (i.e. increased variability) in blood flow

distribution. However, this distinct characteristic of tumor microcirculation is not taken into account by the tracer kinetic models commonly used [58].

Table 2-2 Structural differences between normal tissue and tumor tissue, where F is the blood flow rate, PS is the permeability surface-area product, v_p is the fractional IVPS volume, and v_e is the fractional EES volume.

		Normal Tissue	Tumor Tissue
Structural Differences	Capillary Network	<p>Capillary network</p> <p>Artery</p> <p>Vein</p> <p>Capillary-tissue exchange unit</p>	<p>Capillary network</p> <p>Artery</p> <p>Vein</p>
	Capillary Walls	<p>PS</p> <p>F</p>	<p>PS</p> <p>F</p>
Theoretical Parameter Changes	F	Normal	Higher ($\uparrow$)
	PS	Normal	Larger ($\uparrow$)
	v_p	Normal	Increased ($\uparrow$)
	v_e	Normal	May be increased or decreased, depending on particular situation ($\uparrow$ or $\downarrow$)

2.2.3 Capillary-Tissue Exchange Unit

After the bolus injection of tracers at the organ/tissue inlet, the tracers move along with plasma flow to get into the capillary. The substance exchange of nutrition and oxygen happens within the capillary-tissue exchange unit. The extravascular and extracellular tracers adopted in this study are commonly low-molecular-weight gadolinium-based tracers. Tracers can pass through the capillary walls and travel between the IVPS and the EES but they do not have access into tissue cells nor blood cells.

Figure 2-2 An illustration of the capillary-tissue exchange unit. The red dots within illustrated IVPS and yellow dots within the illustrated EES represent blood cells and tissue cells, respectively

As depicted in **Figure 2-2**, a constant plasma flow F is supplying the capillary-tissue exchange unit. Indicating the tracer concentration in tissue $C_{tiss}(t)$ and feeding artery $C_A(t)$ as functions of time t , their relationship is defined by a convolution integral

$$C_{tiss}(t) = F \frac{C_A(t)}{(1-H_{LV})} \otimes R(t) = \frac{F}{(1-H_{LV})} \int_0^t C_A(t-\tau) R(\tau) d\tau, \quad (2.2a)$$

where F and $H_{LV}(t)$ are tissue parameters which denote blood flow and fractional hematocrit in large vessels, respectively (see Chapter 3 for details). As the tissue derives its blood supply from an artery, the input function $C_A(t)$ can be sampled from a major feeding artery visible on the DCE imaging data and is commonly called the Arterial Input Function (AIF). The impulse residue response $R(t)$ denotes the portion of tracer staying within the tissue following an impulse tracer input.

The tracer mass in the system m_{tiss} can be described by multiplying convolution equation Eq. (2.2a) by the total tissue volume V_{tiss} :

$$m_{tiss}(t) = V_{tiss} C_{tiss}(t) = f_p \frac{C_A(t)}{(1-H_{LV})} \otimes R(t), \quad (2.2b)$$

where f_p accounts for the plasma flow.

2.2.3.1 Tissue Impulse Response

The concept of a system's impulse response is generally adopted in systems theory [59]. Assume a tracer experiment with a unit impulse input (a known amount of tracer) injected at the arterial inlet as depicted in **Figure 2-3**. The injected tracer emerges from the venous outlet as a postponed and expanded version of the impulse input. $h(t)$ is referred to as the impulse outflow response of the system. The cumulative tracer output can be given by the integral $\int_0^t h(\tau) d\tau$. Assuming the conservation of tracer mass throughout the experiment and the eventually cleared out state of all tracers, the area under $h(t)$ should be unity [56].

Figure 2-3 Two approaches to observe a tracer experiment, and their corresponding function forms of impulse responses. [56].

An alternative way to observe the tracer experiment is to monitor the portion of tracer staying in the system, i.e. the impulse residue response $R(t)$. Three features of $R(t)$ are observed: (i) $R(t)$ is zero before the tracer impulse input and $R(t) = 1$ upon the arrival of the tracer impulse; (ii) $R(t)$ is a positive non-increasing function; and (iii) $R(t)$ approaches zero gradually as time passes [6, 10, 11, 56]. The correlation between $R(t)$ and $h(t)$ can be explained by

$$R(t) = 1 - \int_0^t h(\tau) d\tau. \quad (2.3)$$

It is readily recognized that $h(t)$ and $R(t)$ are used to evaluate arterial-venous sampling experiment data and DCE imaging data, respectively.

From a statistical viewpoint, $h(t)$ suggests a certain probability of the tracer taking a transit time t to pass through the system. As a result, $h(t)$ describes the transit time distribution [6, 10, 11]. The tracer Mean Transit Time (MTT) is thus given by

$$\text{MTT} = \int_0^{\infty} t h(t) dt = \int_0^{\infty} R(t) dt . \quad (2.4)$$

2.2.3.2 Convolution

A direct impulse input of tracer into a tissue ROI is not practical and a measured $C_A(t)$ from the organ inlet is often considered. To understand the convolution calculation in Eq. (2.2a), $C_A(t)$ was approximated as a series of tracer impulses with a regular time interval Δt as depicted in **Figure 2-4** [56]. Since the plasma flow f_p supplying the system is delivering tracer into the tissue, the approximate amount of tracer in each impulse input at time t is given by $f_p \frac{C_A(t)}{1-H_{LV}} \Delta t$.

A clinical DCE CT/MRI examination usually takes only a few minutes with the patient lying down for the scanning. Within this short period of time, it is reasonable to assume that the imaged organ/tissue does not undergo major changes/deterioration and behaves consistently with respect to blood flow. The traversal of tracer within the microcirculation system can then be modeled as a linear stationary (time-invariant) system. Under such assumptions, the calculation of net impulse residual within the microcirculation system is described in **Figure 2-4**. For instance, at $t=2\Delta t$, the total tracer mass staying in the system is calculated by

$$m_{\text{tiss}}(2) \cong \frac{f_p}{(1-H_{LV})} [C_A(2)R(0) + C_A(1)R(1) + C_A(0)R(2)] \Delta t . \quad (2.5a)$$

Here, the integers within the brackets are used to denote time (i.e. an integer i within the brackets indicate $t = i\Delta t$). The summation of these three terms can be written by adding the three terms sequentially from left to right or from the reverse direction. For any subsequent time t , the net residual mass of tracer is given by

$$m_{\text{tiss}}(t) \cong \frac{f_p}{(1-H_{\text{LV}})} \sum_{\tau=0}^t C_A(t-\tau)R(\tau)\Delta t = \frac{f_p}{(1-H_{\text{LV}})} \sum_{\tau=0}^t C_A(\tau)R(t-\tau)\Delta t, \quad (2.5b)$$

and as $\Delta t \rightarrow 0$,

$$m_{\text{tiss}}(t) = \frac{f_p}{(1-H_{\text{LV}})} \int_0^t C_A(t-\tau)R(\tau) d\tau = \frac{f_p}{(1-H_{\text{LV}})} \int_0^t C_A(\tau)R(t-\tau) d\tau. \quad (2.5c)$$

Therefore, under the assumption of linear stationary system, the tracer concentration of tissue in time domain $C_{\text{tiss}}(t)$ can be given by the convolution of $FR(t)$ and the tracer arterial input $C_A(t)$. In other words, the structural information within $R(t)$ can be derived from the sampled concentration-time curves from the images [56].

“The concepts of impulse response functions and convolution relating to a linear stationary system are applicable to both intravascular and extravascular tracers” [56]. In the case of DCE imaging for brain tissues where the tracer stays only inside the IVPS because of an intact Blood-Brain Barrier (BBB), the plasma volume within IVPS can be deduce by the central volume principle [6, 11, 60, 61] as

$$\begin{aligned} v_p = F \cdot \text{MTT} &= \frac{F \int_0^\infty R(t) dt \int_0^\infty C_A(t) dt}{\int_0^\infty C_A(t) dt} = \frac{F \int_0^\infty C_A(t) \otimes R(t) dt}{\int_0^\infty C_A(t) dt} \\ &= (1-H_{\text{LV}}) \frac{\int_0^\infty C_{\text{tiss}}(t) dt}{\int_0^\infty C_A(t) dt}. \end{aligned} \quad (2.6a)$$

Figure 2-4 Illustration to the concept of convolution. The residue response $R(t)$ to impulse inputs at $t=0$, $1\Delta t$, and $2\Delta t$, are respectively shown in plots (i), (ii) and (iii).

Therefore, in Dynamic Susceptibility Contrast MRI, the cerebral (whole) blood volume given by Eqs. (2.1b) and (2.6a) can be expressed as

$$v_b = \frac{v_p}{(1-H_{sv})} = \frac{(1-H_{LV})}{(1-H_{sv})} \frac{\int_0^\infty C_{tiss}(t) dt}{\int_0^\infty C_A(t) dt} = F_b \cdot MTT, \quad (2.6b)$$

where F_b denotes brain blood flow rate. In cerebral tumors with the existence of BBB, the estimation of blood volume needs appropriate techniques to correct the first-pass leakage [62].

2.3 Parametric Studies for Tumor Characterization and Diagnosis

2.3.1 Empirical Curve Index Analysis of Tracer Data

The analysis of DCE imaging data can be conducted with the use of tracer kinetic models to quantitatively estimate the physiological parameters relating to tissue microcirculation. However, the data-fitting process during such quantification analysis is usually complicated. Simple empirical methods are more desired for DCE imaging data estimation. Curve index of tissue enhancement such as the maximum slope, peak enhancement and area under curve, are commonly employed in exploratory studies of possible DCE MRI correlation with cancer treatment response [17, 18, 63-65]. In the commercial software currently been applied clinical, these curve index based methods of the early years is still in use [66].

However, despite the frequent usage of these empirical tissue enhancement curve index, their physiological basis and theoretical interpretation stay unclear. Some index are simply observed from the CT or MRI imaging datasets [67] to derive physiological parameters. Many of such derivation were actually accumulated by clinical experiences with limit mathematical rationality. Moreover, the assumptions used in these empirical methods need to be investigated for their justifiability.

2.3.2 Deconvolution Analysis of Tracer Data

By assuming the traversal of tracer within the microcirculation system during clinical DCE scanning as a linear stationary system, such a system can be characterized by its impulse response. In particular, the impulse residue response function which describes the fraction of tracer remaining in the system is paid particular attention to. This is because DCE imaging captures information on the amount of tracer remaining within the tissue, in the form of a tracer concentration-time curve sampled from the tissue region on the DCE imaging data. Following the theory of linear stationary systems, the tissue tracer concentration-time curve $C_{tiss}(t)$ is modeled as the convolution of its impulse residue response $R(t)$ with an AIF input $C_A(t)$ as described in Eq. (2.2a).

Differences in blood flow characteristics in the tumor and normal tissues can be showed in their corresponding $R(t)$. The process of deducing $R(t)$, given $C_{tiss}(t)$ and $C_A(t)$, is called deconvolution. The methods of deconvolution for the analysis of DCE imaging data can be broadly categorized as model-fitting methods and numerical approaches.

The model-fitting approach assumes a mathematical functional form for the impulse residue function $R(t)$ [56], which can be derived by considering the passage (kinetics) of tracer within the microcirculation system as the interaction of linear compartments. Therefore, such mathematical models are also called tracer kinetic models. When appropriately formulated, parameters in the model impulse residue function $R(t)$ should describe physiologically meaningful quantities. The convolution of the model impulse residue function $R(t)$ with the

sampled arterial input $C_A(t)$ generates a model tracer concentration-time curve $C_{\text{tiss,model}}(t)$ by Eq. (2.2a), which is fitted against the actual tissue concentration-time curve $C_{\text{tiss,data}}(t)$ by adjusting the model parameters. This model-constrained fitting process can be described as the minimization of the ‘goodness-of-fit’ between $C_{\text{tiss,model}}(t)$ and $C_{\text{tiss,data}}(t)$ to find a vector $\mathbf{p}$ that gives a local minimum to the cost scalar function:

$$SSR(\mathbf{p}) = \min_{\mathbf{p}} \sum_j \left| C_{\text{tiss,model}}(j, \mathbf{p}) - C_{\text{tiss,data}}(j) \right|^2, \quad (2.7)$$

where j represents the j^{th} concentration sample point along time-axis, and $\mathbf{p}$ is a vector of the adjustable optimization elements. SSR stands for Sum of Squared Residuals, which is a commonly used cost scalar measurement for the “goodness-of-fit”. The parameter values that give the best goodness-of-fit (i.e., smallest SSR) to $C_{\text{tiss,data}}(t)$ are accepted as the parameters estimated.

The numerical deconvolution approach, on the other hand, attempts to compute $R(t)$ by algebraically inverting Eq. (2.2a) or by Fourier transform [68-71]. Regularizations are usually applied to the implementations of numerical deconvolution for stable and reasonable solutions [60]. Unlike model-fitting approach where physiological parameters can be completely deduced, numerical deconvolution can only generate estimates of $R(t)$ at the sampled time points [56], and further interpretation of $R(t)$ is required in order to derive physiological parameters.

2.3.3 Compartmental Tracer Kinetic Models

Tracer kinetic models of tissue structure aim at providing quantitative parameters to characterize physiological state of microcirculation [72, 73]. The general theory for tracer kinetic mechanism is the foundation to understand all the tracer kinetic models [73, 74]. The basic concepts were summarized in a recent review paper [5].

An immense number of tracer kinetic models were developed in early 1990s [3, 8, 75] to quantitatively assess dynamic enhanced data as a measurement way of BBB permeability. Tofts *et al.* proposed a standardization of quantities measured and their respective symbols to describe the dynamic behavior of contrast agents [76] and most of them are widely accepted and followed. In the early models of Brix, Larrson, Tofts and Kermode and the subsequent followers, a transfer constant k^{trans} has been used for many years as a combination of F and PS [72, 76]. The Generalized Kinetics (GK) model quantifies the tissue transfer constant k^{trans} and the fractional EES volume v_e [76]. But the GK model is suitable for single-compartmental modeling due to its oversimplified structure. Tofts also proposed an extended GK (EGK) model [77], which improved GK model by further considering the effect of the volume of vascular v_p . EGK model could be sorted to a two-compartmental model which is more structurally practical, but the exchange and diffusion of tracer within the IVPS was not taken into account. According to the GK and the EGK model, k^{trans} has been used to reflect a complex combination effect of blood flow and vascular permeability [72, 76]. GK model was indicated to be accurate only with weakly vascularized tissue and EGK model to be additionally accurate with highly vascularized tissue [72]. Yet they both reflect the compromise effect of more than one parameter and lead to a

misinterpretation of the parameters [72]. The lack of separation of PS from F is a crucial limitation of those early models. The need to separate them has been recognized in related fields such as nuclear medicine and physiology [5, 78]. As vascular targeting drugs may result in different pharmacodynamics effects on tumor blood flow and vascular permeability, separate estimation of them can be potentially useful [79].

A number of models that facilitate separated measurement of F and PS have been developed and applied in DCE imaging techniques [7, 54, 80-83]. For example, the Distributed Parameter (DP) model and the Conventional Compartmental (CC) model both facilitated the separate measurement of F and PS [54, 66, 79], and models EES and IVPS as a compartment with fractional volumes v_e and v_p , respectively [7, 80, 84]. In spite of this, both CC model and DP model assumes a single pathway for the blood flow which did not account for the massively branched capillaries in tumor. A multiple pathway model featuring blood flow heterogeneity [10] had been proposed to deliver more physiologically realistic details of tumor microvasculature. The capillary-tissue exchange unit within each pathway of the multiple pathway approach consists of a single-pathway tracer kinetic model.

2.3.3.1 Classification of Compartmental Models

Compartments are often used to distinguish the tracer distribution spaces in the tissue [56] when building tracer kinetic models to analyze DCE-derived microcirculation parameters. Linear compartmental structure is most commonly employed. Linear compartments are not only suitable to describe models with single compartment. The nature of interconnection of multi-compartment models can also be solved by linear

compartmental models. Multi-compartment models are broadly classified into two categories according to the arrangement of the compartments: catenary model where all compartments are connected next to each other and lined up in a chain, and mammillary model where a central compartment is surrounded by and connected to peripheral compartments.

Figure 2-5 gives an illustration of the two linear compartmental model arrangements. In catenary models as shown in **Figure 2-5(a)**, each compartment can conduct substance exchange with adjacent compartments and thereby forms a connected chain. In mammillary models as shown in **Figure 2-5(b)**, the central compartment can have substance exchange with several peripheral compartments simultaneously. A combination of these two compartment arrangements forms a more complicated multi-compartment model commonly encountered in practice.

An alternative way to classify compartmental models respects to the description of the $R(t)$ for each compartment. Lumped-parameter model assumes well-mixed compartments where the tracer movement is sufficiently fast and even, leading to a spatially uniform concentration within the volume of diffusion [5]. Under such assumption, the tracer concentration becomes merely a function of time. The GK model [76] and standard (Conventional) two-Compartment (CC2) model [80, 85-88] are lumped-parameter models commonly adopted for model-fitting analysis of DCE imaging data.

Different from lumped-parameter models which assume immediately balanced tracer concentration within the compartments, the distributed-parameter (DP) models describe the tracer concentration gradient distribution along the compartment length. The resulting curves generated using DP model is therefore related to both time and

space. DP model was first described by the Krogh model [89] for the measurement of physiological parameters. A two-compartment DP model (DP2) with both IVPS and EES as a compartment was proposed, with symmetric exchange across the barriers of the two compartments [7, 72, 84, 90]. The model was fully expressed by four parameters (v_p , v_e , F and PS) in a stationary state. The radial diffusion is often considered to be negligible because of the small diameter of capillary tubes within capillary-tissue units. Yet an axial-diffusion equilibration between inflow and outflow is not nearly sufficient to obtain [10], especially within long capillaries. The adiabatic homogeneity model [91, 92] adopted an elegant simplification which leads to a dramatic reduction in computational time in approximating a DP2 model. Multiple-compartment DP models have also been devised previously [93, 94] but are less commonly used, possibly due to mathematical complexity. Some models commonly denoted as multi-compartmental DP models may be a compound of distributed- and lumped- parameter assumptions in different spaces [95].

Figure 2-5 Compartmental model arrangements with (a) catenary model and (b) mammillary model. Each block represents a compartment.

2.3.3.2 Performance of Compartmental Models

According to some comprehensive comparisons [23, 76], DP model gives more thoroughly exploration to various kinetic parameters. In spite of the practical significance of DP model, CC model is more widely used due to its simple structure and lower computation complexity.

Although a typical tissue voxel on a perfusion image often consists of a vascular network [58], tracer kinetic models discussed before are all based on single capillary. Such single-pathway approach only describes the average of blood flow rather than accounting for the blood flow heterogeneity through the tissue vasculature [4]. Yet in a more generalized situation, the organ or tissue should be characterized by a capillary network with interconnected microvascular [96]. The inlet blood flow to the organ or tissue should be divided unequally into the capillaries in a non-uniform way. To more properly describe the tumor vasculature network, “it is of interest to devise tracer kinetic models capable of accounting for the distribution (and dispersion) of blood flow” [4].

Bassingthwaighte and Goresky have come up with the concept of spatial heterogeneity of flow in 1984 [10]. The core concept of Bassingthwaighte’s whole organ model [10] is multiple pathway capillaries and heterogeneity of blood flow. The whole organ model has been developed for a long time and is pioneering in approaching the real physiological situation. The neglect of blood flow heterogeneity may result in an underestimation of blood flow [97, 98]. The devised multiple-pathway model is designed for arterial-venous sampling experiments and is capable of accounting for the blood flow heterogeneity [58]. In the context of anti-angiogenic

drug assessment by DCE imaging, a potentially useful application of such a model would be its ability to monitor and quantitatively assess changes in the distribution of tumor blood vessels in response to treatment. Although many researches thereafter have referred to it, little has employed it. Maybe because the physical system is so complex that even with straightforward thoughts it would eventually led to intricate and time-consuming computation. The MMID4 (Multiple path, Multiple tracer, Indicator Dilution, 4 region model) software developed by Washington University incorporated the multiple-pathway model. Brix *et al.* [99, 100] have employed this software for a comparison study of tracer kinetic methods.

2.4 Clinical Relevance and Issues

The process of generating new blood vessels in tumors is called angiogenesis. Unlike chemotherapy which affects both normal and cancer cells, new cancer therapeutic drugs attempt to target the tumor vasculature by targeting angiogenesis, thereby limiting nutrient supply to the tumor. Such anti-angiogenic and anti-vascular drugs have recently shown considerable effect for cancer management in clinical trials.

An important aspect in the administration of these novel drugs is the timely assessment of their anti-vascular effects. The conventional imaging approach of detecting tumor size change is no longer relevant because the tumor size may remain static for the initial few weeks even when the drug is effective in shutting down blood vessels. There is a need for a functional imaging technique to tell early changes of the tumor vasculature and blood flow. Timeliness can often translate to patient survival in cancer treatment. Therefore waiting for size change might not be a good option. Also,

it is known that there are patients who do not respond positively to anti-angiogenic treatment. In such cases, it is important to detect poor response early and switch to other forms of treatment.

DCE imaging using CT or MRI can fulfill this immediate need in functional oncology imaging. A tracer kinetic model which can account for more physiologically realistic details of the tumor vasculature is needed in order to reveal potential effects of anti-angiogenic drugs on various aspects of tumor microcirculation.

Chapter 3

Infinite-Pathway Distributed Parameter Model

3.1 Introduction

Tracer kinetic models commonly employed for the analysis of perfusion images are single pathway linear compartmental models, which assume an averaged blood flow in the tumor vasculature network. However, these models might not adequately describe heterogeneity of blood flow in a tumor because they neglect the dispersion of blood vessels and the resulting blood flow heterogeneity. This is important because the aggressive tumor has an increased number of blood vessels that are tortuous, leaky and randomly distributed. These aspects of the tumor vasculature results in the broadening of the blood flow distribution, and provide additional information on the “aggressiveness” (angiogenic potential) of the tumor.

As a first step in exploring blood flow heterogeneity modeling, the whole organ multiple-pathway approach developed by Bassingthwaite *et al.* [10] was studied. Although this multiple-pathway approach is recognized as one of the most advanced models of blood flow, direct application of it for analysis of DCE imaging data results in some computational issues [4]. In Chapter 3, these issues associated with a discrete number of pathways were investigated and discussed. A feasible solution was proposed based on the formulation of infinite pathways in the impulse residue function.

3.2 Two-compartment Distributed Parameter Model

The symmetrical cylinder two-compartment Distributed Parameter (DP2) model and catenary three-compartment DP (DP3) model were introduced in [10, 94, 101]. These models provided impulse response functions for arterial-venous sampling experiments.

Figure 3-1 Structural illustration of the DP2 model

Figure 3-1 gives a structural illustration of the DP2 model, wherein the gradient of tracer concentration within each tracer distribution space is assumed to be distributed only along the axial direction (z-axis), and the radial (perpendicular to the z-axis direction) tracer concentration are assumed to be consistent. “Consistent” here means the tracer have uniformed concentration in the radial direction of capillaries, which is in contrast with the gradient tracer concentration in the axial direction. Therefore, the DP2 model has combined the assumptions of lumped-parameter models and distributed-parameter models. The vascular can be simplified as a typical aisle with its diameter or radius to be a constant. The length is known as L . The plasma flows into the vascular from one end of the aisle and flows out from the other end.

Assuming that the radial gradient of tracer concentration is omitted, the tracer concentration merely changes along the z axis. Such assumption is reasonable because (1) for the IVPS, the radial dimension of capillaries is much less than its length; and (2) for the EES, considering the capillaries within the vasculature network are adjacent [56], the relatively short radial path leads to a fast distribution of tracers and subsequently tracer concentration equilibrium is achieved [10, 94]. Thus Larson *et al.* pointed out that DP2 model is in fact a hybrid model which combines the assumptions of DP model and CC model in the capillary axial and radial directions, respectively [94].

The impulse residual response of the DP2 model is composed of two physiological processes:

$$R_{DP2}(t) = R_P(t) + R_{isf}(t - t_P) . \quad (3.1)$$

in which,

$$R_p(t) = u(t) - u(t - t_p) , \quad (3.2a)$$

and,

$$R_{isf}(t) = u(t) \left\{ 1 - \exp\left(-\frac{PS}{F}\right) \left[1 + \int_0^t \exp\left(-\frac{PS}{v_e} \tau\right) \sqrt{\frac{PS}{v_e} \frac{PS}{F} \frac{1}{\tau}} I_1\left(2\sqrt{\frac{PS}{v_e} \frac{PS}{F} \tau}\right) d\tau \right] \right\}. \quad (3.2b)$$

$R_p(t)$ and $R_{isf}(t)$ represent the phase of tracer getting into the tissue and the phase of tracer traversing at the reverse direction, respectively. $u(t)$ denotes the unit step function of Heaviside, and I_1 denotes the modified Bessel function. According to the central volume principle, the mean transit time for $R_p(t)$ and $R_{isf}(t)$ are $t_p = V_p / F_p$ and $t_{isf} = V_{isf} / F_p$.

This DP2 model has four independent parameters: F , PS , v_p , and v_e . When $PS = 0$, the DP2 model is equivalent to a single-compartment DP model. $R_{DP1}(t)$ can be represented by $R_p(t)$ alone.

3.3 Bassingthwaighe's Multiple-pathway Method

3.3.1 Vasculature Network

To account for the blood flow heterogeneity, Bassingthwaighe *et al.* previously proposed a formation of multiple pathways of the vasculature network. Such construction accounts for a distribution of blood flow for the analysis of arterial-venous sampling experiments [10]. The arterial-venous sampling experiments involve the injection and sequentially sampling from the organ/tissue which is invasive and the

experimental results obtained are *ex-vivo*. It is of interest to apply the Bassingthwaight's multiple-pathway model onto DCE imaging data to achieve *in-vivo* information of the ROI.

As shown by the illustration of the original multiple-pathway model in **Figure 3-2**, the microvasculature has a network of N parallel pathways. Each pathway is composed of three component structures: an arteriole, a capillary-tissue exchange unit (**Figure 2-2**), and a venule [4]. The respective impulse outflow response $h(t)$ for each component will be detailed in Section 3.3.3. Substance exchange only happens in the component of capillary-tissue exchange unit. The MMID4 software [102] adopted a DP model for the capillary-tissue exchange unit within each pathway. But the number of pathways is limited (up to 30) due to memory constraints of the hardware.

Figure 3-2 Illustration of the vasculature network constructed in Bassingthwaight's multiple-pathway model.

3.3.2 Distribution of Blood Flow

The blood flow distribution of this vasculature network is governed by a probability density function with respect to relative flows $w(f)$. The relative flow f_i in the i^{th} pathway is specified $f_i = F_i/F$, where F_i denotes the blood flow in the i^{th} pathway and F represents the average blood flow of this entire multiple-pathway vasculature network [10, 96].

Assume the i^{th} pathway has a width of $\Delta f_i, (i=1, \dots, N)$, the general expression of flow distribution would be [10]

$$\begin{aligned}\Delta f_1 &= f_2 - f_1 \\ \Delta f_i &= \frac{f_{i-1} + f_{i+1}}{2}, i = 2, \dots, N-1. \\ \Delta f_N &= f_N - f_{N-1}\end{aligned}\tag{3.3}$$

The mean relative flow of this hypothetical network is normalized, i.e.

$$\sum_1^N \Delta f_i w(f_i) f_i = 1. \tag{3.4}$$

The distribution of relative flow $w(f)$ can be described by 2 additional parameters, the Relative Dispersion (RD) and the *skewness*. RD defines the degree of variability in blood flow (i.e. the width of the flow distribution function $w(f)$) and *skewness* reflects the degree of asymmetry in $w(f)$ [58], as shown in **Figure 3-3**. The standard deviation (dispersion) of blood flow can be derived by $\sigma=RD \cdot F$ [4]. **Figure 3-4** gives an example of $w(f)$ described by a random walk distribution function.

Figure 3-3 Effects of RD and $skewness$ on the shape of $w(f)$.

Function Generator fgen_1

Domain	f
Function	RandomWalk

area	1
tMean	1
RD	.5
skewn	1.6
frPeak	1E-6
timeToRepeat	0

Figure 3-4 Example of a $w(f)$ described by a random walk distribution [4].

3.3.3 Tissue Impulse Response

The impulse outflow response of the capillary-tissue exchange unit in each parallel pathway is described by a DP2 model given by [4, 10]:

$$h_{cap,f_i}(t) = u(t - t_{cap}) \exp\left(-\frac{PS}{f_i F}\right) \times \left[\delta(t - t_{cap}) + \exp\left(-\frac{PS}{v_e}(t - t_{cap})\right) \sqrt{\frac{PS}{v_e} \frac{PS}{f_i F} \frac{1}{t - t_{cap}}} I_1\left(2\sqrt{\frac{PS}{v_e} \frac{PS}{f_i F} (t - t_{cap})}\right) \right] \quad (3.5a)$$

where t_{cap} is the tracer transit time through capillary in the corresponding pathway, which is related to its plasma flow rate $f_i F$ and its fractional volume v_p by $t_{cap} = v_p / f_i F$, and $\delta(t)$ is the Dirac delta function. The microvasculature parameters PS , v_e and v_p are assumed to be the same in all pathways of the system, while t_{cap} changes with respect to the flow rate $f_i F$ of each pathway. Since there is no substance exchange in arteriole and venule, these two component structures only serve as conductive delays of their inputs. Their respective impulse outflow responses in the i^{th} pathway are given by

$$h_{art,f_i}(t) = \delta(t - t_{art}) \quad (3.5b)$$

and

$$h_{ven,f_i}(t) = \delta(t - t_{ven}) , \quad (3.5c)$$

respectively. Here, t_{art} and t_{ven} are the corresponding tracer transit times for arteriole and venule, which are affected by their respective fractional volumes by $t_{art} = v_{art} / f_i F$ and $t_{ven} = v_{ven} / f_i F$. The parameters v_{art} and v_{ven} are again assumed to be the same in the system, while t_{art} and t_{ven} varies with respect to the flow rate $f_i F$ of each pathway. The fractional intravascular volume within IVPS is given by $v_p = v_{art} + v_{cap} + v_{ven}$. The

volume ratio in human tissues for the three component structures arterioles, capillaries, and venules is typically 15:30:55 [99, 100]. Accordingly, the values for v_{art} , v_{cap} and v_{ven} can be deduced once v_p is identified.

The total impulse outflow response for the i^{th} pathway is composed by the individual responses from each component, as follows:

$$h_{f_i}(t) = h_{art,f_i}(t) \otimes h_{cap,f_i}(t) \otimes h_{ven,f_i}(t) . \quad (3.6)$$

The net impulse outflow response of the hypothetical vasculature network can be given by the sum of the impulse outflow responses through each pathway weighted by their respective relative flows [10]:

$$h(t) = \sum_i^N \Delta f_i w_i(f_i) f_i h_{f_i}(t) \quad (3.7)$$

3.4 Proposed IPDP Model

In Bassingthwaite's approach, a multiple-pathway DP2 model is used to simulate the whole-organ microcirculation in capillary-tissue microcirculation system. However, tissue vasculature is represented by a discrete and limited number of pathways. The total number of pathways is constrained by the hardware performance (computer memory and processing time). Another two potential drawbacks of this approach that can limit its practical implementation to DCE imaging data are: (1) occurrence of multiple discontinuities in its impulse residue response function (2) a normalization error which is not diminishing.

The given impulse outflow response in Eq. (3.7) was originally proposed for

arterial-venous sampling experiments [10]. To address the aforementioned implementation issues, an Infinite-Pathways Distributed Parameter (IPDP) model is proposed. The number of pathways in the hypothetical multiple-pathway vasculature network is reconstructed as an infinite number instead of a fixed number. Subsequently, the net impulse outflow response of the vasculature network can be written as the integration of the individual impulse outflow responses as

$$h(t) = \sum_i^N \Delta f_i w(f_i) f_i h_{f_i}(t) = \int_0^\infty w(f) f h_f(t) df, \quad (3.8)$$

where $w(f)$ is the probability density function and f is the relative flow passing through each pathway [4, 103].

Figure 3-5 Schematic diagram of the two forms of impulse response functions [4].

The two function representations of impulse responses related by Eq. (2.3) are illustrated by the schematic diagram in **Figure 3-5**. The impulse residue response $R(t)$

can be observed by DCE imaging. Therefore, for analysis of DCE imaging data, $R(t)$ is required in the model-fitting of Eq. (2.2a) [56, 104]. The corresponding $R(t)$ is given by

$$R(t) = 1 - \int_0^t h(\tau) d\tau = 1 - \int_0^t \int_0^\infty w(f) f h_f(\tau) df d\tau. \quad (3.9)$$

3.4.1 Optimization Setups

To derive microcirculation parameters of tissue ROI, the model-fitting process of the concentration-time curve $C_{tiss}(t)$ is usually repeated several times from different initials to select the best fitting result. The DCE-MRI data is often collected for a long enough scanning time so that the concentration-time curve $C_{tiss}(t)$ can include all four stages of a common tracer washout procedure as illustrated in **Figure 3-6**: growth, peak, decline, and stabilization.

The conventional model-fitting process [5, 10] is usually carried out by a constrained nonlinear multivariable optimization algorithm. The optimization finds a vector $\mathbf{p}$ that generates a local minimum to the cost function [Eq. (2.7)]. The vector $\mathbf{p}$ consists of the adjustable optimization elements which are related to the free parameters in the operational equation Eq. (3.9). The time interval of adjacent concentration sample points represents the temporal resolution. Parameters are derived through minimizing the SSR defined in Eq. (2.7) as a measure of the goodness-of-fit by adjusting the model parameters.

The dimension of the optimization problem is determined by the number of unknown parameters. The size of fitting range of each individual parameter can be reduced by appointing physical constraints. The nonlinear regression minimization in

Eq. (2.7) is specified by linear constraint matrices and their corresponding vectors, i.e., all parameters must be positive and the volume ($v_p + v_e$) must be less than 1.

Figure 3-6 Illustration of the four stages of a typical washout $C_{tiss}(t)$.

As the vector of adjustable optimization elements in the minimization function [Eq. (2.7)], $\mathbf{p}$ contains 5 elements and it is characterized by p_0 to p_5 . The first element p_0 represents the minimum transit [105] and is related to the fractional arterial volume and mean blood flow by $p_0 = v_{art}/F$. The mean blood perfusion rate F is represented by p_1 as the second optimization element. Using the central volume principle, the mean vascular transit time MTT is specified by $p_2 = MTT_v = v_p/F$ [58]. Since the volume for each of the three components of each pathway can be inferred once v_p is specified, p_0 and p_2 are considered as one optimization element. p_3 and p_4 are substance exchange rate parameters between EES and IVPS. Thus we have $p_3 = PS/v_p$ and $p_4 = PS/v_e$. The effects of *RD* and *skewness* on the shape of the flow distribution function $w(f)$ are

shown in **Figure 3-3**. Since RD in the blood flow distribution has an effect on the width of $w(f)$, the last optimization element p_5 represents RD of the IPDP model. Nevertheless, *skewness* only has a minimal effect on the $w(f)$. Therefore, *skewness* was chosen to be fixed at the nominal value of 1 in this study.

The optimization process during model-fitting employs a constrained multivariable optimization algorithm of nonlinear programming solver command '*fmincon*' in MatlabTM. The "*fmincon*" stands for "find minimum of constrained nonlinear multivariable function". When the problem is infeasible, this gradient-based algorithm attempts to minimize the maximum constraint value. The *fmincon* is implemented by interior-point algorithm, which computes the search direction with linearized Barrier problem and checks for the convergence until an optimal solution was obtained. The "linearized Barrier problem" is used in an interior method for solving nonlinear optimization problems [106]. By implementing interior-point algorithm into *fmincon* optimization algorithm, the approximating problem becomes "a sequence of equality constrained problems, which are easier to solve than the original inequality-constrained problem" [107]. To solve such approximating problem, the algorithm takes either a direct Newton step by default or a conjugate gradient step with trust region at each iteration. Two objectives in step size evaluating progress are to minimize the objective function and to minimize constraint violations. The step size is determined by decrease in Merit Function or with filter methods until objective improvement occurs. "If an attempted step does not adequately decrease the Merit Function, the algorithm discards the attempted step and attempts a new step. The output flags reflect optimization results. If either the objective function or a nonlinear constraint function returns a complex value, *NaN*, *Inf*, or an error at an iterate attempt, the algorithm declines the attempting and then attempts a different, shorter step." [107, 108]

3.4.2 Issues of Discontinuities in Implementation

Using the scripting language JSim, the impulse residue function $R(t)$ was coded following Eq. (2.3) [4]. An $R(t)$ computed for 20 pathways by the MMID4 software is presented in **Figure 3-7(a)**. As illustrated, a discrete number of N pathways causes the occurrence of N discontinuities in $R(t)$ [4]. Discontinuities in $R(t)$ with $N=1, 3$ and 10 are also presented in **Figure 3-7(b)**.

For a single pathway with $N=1$, the single discontinuity is related to the process of tracer traversal. $R(t)$ initially keeps at the value of unity for a period of time t_{cap} within which tracers are passing through the microcirculation system towards the veinule outlet after the injected bolus. During the transit time $0 < t < t_{cap}$, a fraction of the tracer may diffuse between the IVPS and the EES.

Immediately after t_{cap} , the tracer staying within IVPS exits through the veinule outlet, which results in a rapid decrease in $R(t)$ [4]. A more gradual decrease in $R(t)$ then follows, as the tracer diffuses back into the IVPS and is cleared by blood outflow [54, 70, 109]. For a multiple-pathway model with weighted sum of a finite number of N pathways, the corresponding discontinuity is repeated N times.

These discontinuities in $R(t)$ may pose difficulties in the curve-fitting of Eq. (2.2a). It has been reported that a single discontinuity in $R(t)$ can result in problems of convergence and increased parameter error during data-fitting [110, 111]. Such issues of convergence can be attributed to inaccuracies in the estimation of the convolution integral [Eq. (2.2a)] when the DCE imaging data are sampled at discrete time points [109]. Although effective correction methods have been proposed to address such

Figure 3-7 (a) MMID4 interface with the simulation of an $R(t)$ with 20 pathways (with the settings: number of spatial grids=1001, time steps of 0.1s, scanning time up to 100s. Running time: 81s) [4]. (b) Examples of the occurrence of discontinuities in $R(t)$ for $N=1, 3$ and 20.

convergence problems for $R(t)$ pertaining to a single pathway [109], the occurrence of multiple discontinuities due to multiple pathways would render such correction methods impractical.

3.4.3 Normalization Error in Implementation

A vasculature network with N pathways requires the sampling of N discrete samples of $w(f_i)$ with intervals of Δf_i . As shown in **Figure 3-8**, for N as a limited number, the discrete summation calculation in Eq. (3.4) may diverge from unity, which results in a normalization error [4]. This error is transmitted into Eq. (3.7) resulting in an $h(t)$ of which the area under it diverge from unity (as illustrated in **Figure 3-8**), and subsequently an error in $R(t)$. For different values of RD in different cases, the normalization would have unexpected deviations as the shape of $w(f_i)$ is varied along with RD during data-fitting.

Figure 3-8 Demonstration of discrete sampling resulting in a normalization error [4].

3.4.4 Solution to the Implementation Issues

Understanding that the issues of discontinuity and normalization are resulted from a limited number of pathways, an attempt was made to address these problems by reconstructing the vasculature network with an infinite number of pathways, such that impulse outflow response and the corresponding impulse residue response becomes integrals as in Eqs. (3.8) and (3.9) [4]. The integrals in Eqs. (3.8) and (3.9) can be computed numerically to an anticipated accuracy which is indicated by the user. The normalization error now converts into the computation error of integrals which can be constrained during integration [4]. The normalization error is restricted to 1.e-7 in this study.

The free parameters in the operational equations [Eqs. (3.9) and (3.5)] are F , PS , v_p , v_e , RD and $skewness$. To reduce the number of free parameters, the effects of RD and $skewness$ on the impulse residue function $R(t)$ is considered as shown in **Figure 3-9**, where F , v_p , PS and v_e are fixed at 50 mL/min/100mL, 10 mL/100mL, 40 mL/min/100mL and 20 mL/100mL, respectively. RD governs the spread in the flow distribution $w(f)$ and has a substantial effect on the width of $R(t)$. However, $skewness$ governs the degree of asymmetry in $w(f)$ and only has a negligible effect on $R(t)$. Also, previous studies and histological evidence have shown the importance of F , PS , v_p , v_e and RD in describing the tumor microenvironment, but there is a lack of conclusive evidence that the tumorous state can significantly alter the $skewness$ of the blood flow distribution. To reduce the computation complexity and the number of free parameters for fitting, $skewness$ is fixed at the nominal value of 1, as values for $skewness$ previously encountered typically range from 0.3 to 1.2 [96].

Figure 3-9 The effects of RD and $skewness$ on $R(t)$.

Figure 3-10 $R(t)$ generated by the proposed IPDP model.

Examples of $R(t)$ generated by the IPDP model are presented in **Figure 3-10** for selected parameter combinations [4]. It is observed that the discontinuities in $R(t)$ have been effectively eliminated, which should make its application to the DCE imaging data possible.

3.5 Discussion

Computer simulations were performed to investigate the possible dependence of the impulse responses on the vasculature parameters [112] in use of the proposed IPDP model. The tissue impulse response functions were analyzed for a range of physiological values of the independent parameters F , v_p , PS , v_e , RD , and *skewness* (**Table 3-1**). $C_{tiss}(t)$ and $C_v(t)$ curves were simulated corresponding to various physiological conditions.

The effect of each model parameter on $R(t)$ and $h(t)$ is shown in **Figure 3-11**. Each parameter value is changed one at a time, with the other parameters fixed at their respective baseline values (as stated in **Table 3-1**). The baseline value assumed for each parameter is typical of those of tumors [109]. To perform computer simulations to study the tissue impulse response, a realistic arterial input model $C_A(t)$ or AIF can be computer-generated using the functional form [113, 114]:

$$C_A(t) = A_B t \exp(-\mu_B t) + A_G [\exp(-\mu_G t) - \exp(-\mu_B t)], \quad (3.10)$$

where A_B , μ_B , A_G and μ_G are scaling parameters (**Table 3-1**) of $C_A(t)$. “These scaling parameters were chosen such that $C_A(t)$ peaks around 4 mM at about 6s upon bolus

arrival, which is typical of a human $C_A(t)$ after a short bolus injection of 0.1 mmol/kg Gd-DTPA [82].” [112]

Table 3-1 Values of the model parameters used in the simulation studies.

Model	Parameter	Units	Baseline Value	Tested Range
IPDP Model	F	$mL/min/100mL$	50	[20,30,50,80,120]
	v_p	%	10	[1,5,10,20,40]
	PS	$mL/min/100mL$	20	[0,10,20,40,80]
	v_e	%	10	[1,5,10,20,40]
	RD	dimensionless	0.3	[0.1,0.2,0.3,0.4,0.5]
	$skewness$	dimensionless	1	[0.1,0.6,1,1.4,1.9]
Arterial plasma input C_A	A_B	mM/min	100	
	μ_B	min^{-1}	10	
	A_G	mM	1	
	μ_G	min^{-1}	0.01

Figure 3-11 Effects of each independent parameter on $h(t)$ and $R(t)$.

It is noted that PS and v_e only have an effect on the later portion of $R(t)$ (**Figure 3-11(f)-(h)**), while RD and $skewness$ affect its middle portion (**Figure 3-11(j)-(l)**); and F and v_p affect the entire $R(t)$ curve (**Figure 3-11(b)-(d)**). The time for the first appearance of tracer outflow (initial increase of $h(t)$ from zero) is always corresponding to the time for initial decrease of $R(t)$ from unity, which is consistent with the conservation assumption of tracer mass. Since the tracer transit time passing through each pathway is different due to the different flow rates, “the first appearance of tracer at the venous exit corresponds to the minimum transit time (t_{min}) taken by tracer through the pathway with the highest flow” [112]. For a limited number of pathways, t_{min} is dependent on the number of pathways and cannot be identified as a feature of the tumor microcirculation. This problem is circumvented in the present form of integration of the IPDP model. t_{min} can now be considered as a feature of both $h(t)$ and $R(t)$, and is correlated to the other characteristics of the tumor microcirculation.

3.6 Clinical Applicability

3.6.1 Materials and Methods

To evaluate the applicability of the proposed IPDP model on clinical trials, perfusion CT data was obtained from three patients with intracranial meningioma lesions. These patients were enrolled with informed consent for the study approved by local institutional review board [4, 103]. “Dynamic CT images were acquired using a slip-ring, helical CT scanner (HiSpeed; GE Medical Systems) in cine mode for 50 seconds at a scanning time of 1s per image, on a single section at the level of the largest tumor diameter. Iodinated contrast medium (Omnipaque 300 mgI/mL) was injected at a rate of 4 mL/s using an automatic

injector, followed by saline flush. CT parameters were 80 kVp, 190 mAs, 512 by 512 matrix, 20-22 cm field of view and at 10 mm collimations.” [4]

Post-processing was performed on a personal computer with MatlabTM (MathWorks, Natick MA). The ROIs corresponding to the brain tumor and contralateral normal tissue were manually outlined. Voxels within each ROI were averaged to derive a representative tracer concentration-time $C_{tiss}(t)$ curve. Each $C_{tiss}(t)$ curve was fitted using Eq. (2.2a) along with Eqs. (3.5) and (3.9)(3.10) to derive parameters.

3.6.2 Voxel-level Application

A representative patient case is presented in **Figure 3-12** [4]. Fittings of the $C_{tiss}(t)$ curves derived from the tumor and normal tissue ROIs by the proposed IPDP model are shown and compared with the single-pathway CC2 model [115] in **Figure 3-12(b)** and **Figure 3-12(c)**. Data-fitting shows that the proposed model can better describe the ROI-averaged $C_{tiss}(t)$ curves than the CC2 model.

Parameter estimation results for each of three patients are listed in **Table 3-2**. Comparing tumor with normal tissues within individual patient cases, F , v_p and PS values are found to be consistently higher in tumors than in normal cerebral tissues, which are consistent with the current understanding of the process of neo-angiogenesis in human neoplasms. More importantly, cerebral tumors also exhibit increased variability in blood flow given by a higher standard deviation of blood flow σ (average $\sigma=11.8$ mL/min/100mL) than normal tissues (average $\sigma=4.3$ mL/min/100mL) [4, 103]. The structural information expressed by the IPDP model is distinctive. The proposed IPDP model enabled DCE based assessment of blood flow distribution for the first time, which cannot be achieved by any single-pathway model (CC, DP, TH, etc.).

Figure 3-12 (a) Tumor and normal brain tissue are respectively marked with red and blue outlines. Fittings of the ROI-averaged $C_{tiss}(t)$ curves of the tumor (b) and normal tissue (c) by the IPDP model are compared with that obtained by the single-pathway CC2 model [4].

Table 3-2 Estimated parameters of tumor/normal tissues for each of the three patients.

	Patient 1		Patient 2		Patient 3	
	Tumor	Normal	Tumor	Normal	Tumor	Normal
F (mL/min/100mL)	26.41	21.94	28.57	18.31	37.37	15.49
v_p (mL/100mL)	3.07	1.30	5.06	1.68	7.69	1.56
PS (mL/min/100mL)	15.76	3.81	65.28	0.48	24.92	1.20
RD	0.36	0.19	0.38	0.30	0.40	0.21
σ (mL/min/100mL)	9.51	4.17	10.86	5.49	14.95	3.25

In conclusion, the microcirculatory parameters derived by the IPDP model can potentially be used for differential diagnosis of tumors with DCE CT. A higher grade tumor might be associated with a higher value of standard deviation of blood flow σ , but a larger number of patients with different grades of a particular type of tumor would be required for further studies.

3.7 Chapter Summary

In the anti-angiogenic drug assessment by DCE imaging, a potential advantage of Bassingthwaite's whole-organ model with multiple-pathway approach would be its ability to quantify changes in the distribution of tumor blood vessels in response to treatment. However, this model was originally built for the analysis of arterial-venous

experiments rather than DCE imaging. Direct implementation of this model into DCE analysis results in normalization and discontinuity issues. Recognizing that such issues arise due to the discrete number of pathways, the multiple-pathway model was reconstructed to a model with infinite pathways. The Infinite-Pathways Distributed Parameter (IPDP) model was developed based on the formulation of infinite pathways in the vasculature network to enable *in vivo* assessment of tumor blood flow variability by DCE imaging. It solves the computational issues existing in the multiple-pathway modeling approach, and relieves its dependency on hardware performance. Comparing to conventional compartmental models or distributed parameter models, the proposed model inherits the advantage of the initial multiple pathway model to estimate blood flow variability, which reflects an additional property of the tumor vasculature. The *in vivo* assessment of flow variability can allow for a more complete characterization of the tumor microvasculature by DCE imaging.

Two further studies have been performed using the proposed IPDP model. (1) To study the influence of individual parameters on the impulse functions, the present IPDP model was used to generate $R(t)$ and $h(t)$ with various parameter value combinations. (2) To study its clinical applicability, the IPDP model was applied on actual perfusion data. Results show that brain tumors exhibit higher values of blood plasma flow rate, vascular volume, capillary permeability and interstitial volume than normal brain tissues. More importantly, the spread in blood flow distribution is found to be significantly higher in the tumors in concordance with a more chaotic vasculature. These initial results suggest that the proposed model can be used for differential diagnosis of tumors and it deserves further studies with more patients and tumor types.

Chapter 4

Analysis of Empirical Tissue

Enhancement Measurements

4.1 Introduction

The empirical model-free methods are frequently used in parametric studies of DCE data correspondence with tumor properties. These methods include tissue enhancement metrics of the tracer concentration-time curves such as the maximum slope method, peak enhancement method, and total tracer distribution volume method. It would be of interest to understand their physiological implications, as well as the dynamics that can affect their applicability. A comparative study of these empirical measures of tissue enhancement is also needed to assess their performance. In this chapter, the IPDP model was adopted for simulation-based evaluations of the empirical tissue enhancement measurements commonly applied in DCE analysis.

4.2 Interpretation of Empirical Tissue Enhancement Metrics

4.2.1 Maximal Slope Method

The maximal slope method was originally proposed and employed in DCE studies [116] to assess tissue blood flow rate, by using the relation [112]

$$F_{\text{maxslope}} = \frac{\left. \frac{d}{dt} C_{\text{tiss}}(t) \right|_{\text{max}}}{C_A(t)|_{\text{max}}} . \quad (4.1a)$$

The theoretical basis of this method can be understood from the assumption of “conservation of tracer mass” which states that the amount of residual tracer in the tissue microcirculation system is given by the difference between tracer inflow and outflow:

$$C_{\text{tiss}}(t) = F \left[\int_0^t C_A(\tau) d\tau - \int_0^t C_V(\tau) d\tau \right] . \quad (4.1b)$$

Differentiating Eq. (4.1b) gives

$$\frac{d}{dt} C_{\text{tiss}}(t) = F [C_A(t) - C_V(t)] , \quad (4.1c)$$

which depicts tracer uptake rate in the tissue. The maximal slope method is built based on the assumption of a generally negligible tracer outflow (i.e. $C_V(t) \approx 0$) [116] before the peak of $C_A(t)$. Under such assumption, Eq. (4.1c) reduces to $dC_{\text{tiss}}(t)/dt \approx FC_A(t)$, such that the maximal tracer uptake rate (i.e. maximal slope of $C_{\text{tiss}}(t)$) is consistent with the maximum value of $C_A(t)$ as specified by Eq. (4.1a).

4.2.2 Peak Enhancement Method

The tracer kinetic curves performing a washout pattern is often observed in the vascular tumors with $C_{tiss}(t)$ exhibiting a peak. Some tumors exhibit washout pattern as a whole [117, 118]. The time-to-peak (TTP) refers to the time taken for $C_{tiss}(t)$ to reach its peak. Meanwhile, the maximum $C_{tiss}(t)$ concentration attained is indicated by its peak value $C_{tiss,peak}$ [17, 64, 65]. It is noted that these curve enhancement metrics of the peak location in $C_{tiss}(t)$ might not be applicable for tumors exhibiting a plateau or progressively increasing enhancement pattern [112], for these two patterns do not have an obvious peak.

4.2.3 Total Tracer Distribution Volume Method

The normalized Initial Area Under Curve (IAUC_{norm}) is achieved by computing the area under $C_{tiss}(t)$ up to a predetermined time (60-100s), and subsequently dividing this area by the corresponding area under $C_A(t)$ [119]. The physiological significance of IAUC_{norm} can be inferred by considering the integration of Eq. (2.2a) [112]:

$$\begin{aligned} \int_0^\infty C_{tiss}(t) dt &= F \int_0^\infty C_A(t) \otimes R(t) dt = F \int_0^\infty C_A(t) dt \int_0^\infty R(t) dt \\ &= F MTT \int_0^\infty C_A(t) dt = (v_p + v_e) \int_0^\infty C_A(t) dt, \end{aligned} \quad (4.2)$$

where the mean transit time $MTT = \int_0^\infty R(t) dt$ can be associated with the total tracer distribution volume ($v_p + v_e$) by the central volume principle as $(v_p + v_e) = FMTT$ [10, 104]. Thus, the ratio of the total areas under $C_{tiss}(t)$ and $C_A(t)$ gives the estimation of total tracer distribution volume ($v_p + v_e$). However, the areas under $C_{tiss}(t)$ and $C_A(t)$ can only be computed until the final DCE scan, the assessment accuracy of ($v_p + v_e$)

using $\text{IAUC}_{\text{norm}}$ has positive correlation with the duration of the DCE scanning time [112].

The Initial Area Under $C_{\text{tiss}}(t)$ Curve (IAUC) without normalization operation is usually used when the sampled $C_A(t)$ are not accurate. It is shown that IAUC is a measurement [120] which has a mixed intractable correlation with K^{trans} , v_p and v_e . Modifications to IAUC can be performed by using a reference muscle curve, and by computing IAUC over certain portions of the $C_{\text{tiss}}(t)$ curve. However, these modifications can be sensitive to changes in K^{trans} or v_e [121].

An alternative indication of the total tracer distribution volume is the ratio of the saturation values of $C_{\text{tiss}}(t)$ and $C_A(t)$, which can be assessed at the final DCE scan [112]. It was observed that $C_{\text{tiss}}(t)$ in tumors arrive at higher saturation concentration values due to either increased v_p or v_e . After a few cardiac cycles (typically about 3-4 minutes after injection), the initial bolus peak in $C_A(t)$ eventually subside and $C_A(t)$ approaches a relative steady plasma concentration level that decreases only slowly with time. As $C_A(t)$ approaches a consistent concentration value, the processes of tracer transit and capillary-tissue exchange would also approach to a steady state. For a tracer undergoing passive diffusion, the equilibrium concentration is the same in all tracer distribution spaces. However, within a tissue voxel, there is inevitably a portion of space occupied by cells that the tracer cannot diffuse into. In other words, the tissue voxel consists of both tracer accessible space and tracer inaccessible space, while the arterial voxel consists entirely of tracer accessible space. Therefore, the ratio of the net equilibrium concentration of a tissue voxel $C_{\text{tiss}}(t)$ and that of an arterial voxel $C_A(t)$ at steady state can be approximated by the sum of the fractional volumes ($v_p + v_e$).

4.3 Simulation Results and Discussion

Computer simulations were performed to study the applicability of these stated empirical tissue enhancement measurements under various tissue vasculature conditions. A realistic arterial input $C_A(t)$ was simulated using the functional form in Eq. (3.9) and the scaling parameters in **Table 3-1**.

4.3.1 Application of Maximal Slope Method

As indicated by Eq. (4.1c), the validity of the assumption of negligible venous outflow before the $C_A(t)$ peak is crucial to the effectiveness of the method. When t_{min} occurs before the peak of $C_A(t)$, the blood flow estimated with the maximal slope method ($F_{maxslope}$) would underestimate F . This can be understood by considering Eq. (2.2a), where $R(t)$ reaches unity before the first appearance of tracer at the organ/tissue outlet (i.e., before t_{min}).

Application of the maximal slope method for blood flow estimation is shown in **Figure 4-1**. “Under the conditions of high F or low v_p , both resulting in short t_{min} , F would be severely underestimated by $F_{maxslope}$ as shown in **Figure 4-1(b)** and (d), respectively. The underestimation of flow by $F_{maxslope}$ under high F and low v_p was also shown by Brix *et al.* [99] for simulation datasets with noise.” Two additional factors, namely large values of RD and *skewness*, were shown here to also be able to result in the underestimation of F by $F_{maxslope}$. The higher blood flow variability in tumors implies a larger value of RD . The applicability of $F_{maxslope}$ therefore can be limited in the vascular tumors, where both F and RD are expected to be high.

Figure 4-1 Influence of each microcirculation parameter on the assessment of blood flow by $F_{maxslope}$. The arrows on the time axes correspond to t_{min} . The green bars with circles denote the slope of $C_{tiss}(t)$ at the time when $C_A(t)$ peaks, as specified by the maximal slope method.

It is noted that changes in PS and v_e do not have influence on the accuracy of the maximal slope method (**Figure 4-1(e)-(h)**) as these parameters do not have influence on t_{min} . Their effects on the shape of $R(t)$ and $C_{tiss}(t)$ occur only after t_{min} . This suggests that the accuracy of $F_{maxslope}$ would not be affected by the large leakiness of tumor capillaries or changes of the EES volume.

Since t_{min} is a property of the microcirculation vasculature network, it is independent of the shape of $C_A(t)$. In order for $F_{maxslope}$ to be accurate, it may be proposed to use a rapid bolus input such that $C_A(t)$ can peak earlier than t_{min} . However, the use of such sudden infusion of tracer should be cautioned against as it can result in severe swelling and pain. In addition, more rapid imaging would be needed so as to adequately capture the peak of such a rapid bolus. Instead of using a rapid infusion, the technique can be modified to an ‘initial slope method’ [109] by sampling the slope of $C_{tiss}(t)$ and $C_A(t)$ at an earlier time point (instead of at the $C_A(t)$ peak). Since the initial values of $C_{tiss}(t)$ and $C_A(t)$ are lower and more easily corrupted by noise, the source of error for the initial slope would be more likely to be dependent on the quality of the perfusion data than on t_{min} of the tissue which is *a priori* unknown. “The difference in bolus arrival time between $C_A(t)$ and $C_{tiss}(t)$ can be accounted for by separately estimating the bolus arrival time for $C_A(t)$ and $C_{tiss}(t)$ using an automatic regression approach [122], which has been shown to be robust and accurate for DCE MRI [123].” [112]

4.3.2 Application of Peak Enhancement Method

Figure 4-2(a) presents a typical set of $C_A(t)$, $C_V(t)$ and $C_{tiss}(t)$ curves simulated using baseline parameter values given by **Table 3-1**. In **Figure 4-2(a)**, it is noted that TTP of

$C_{tiss}(t)$ corresponds to the intersection of $C_A(t)$ and $C_V(t)$. This is decided by the conservation of tracer mass in Eqs. (4.1b) and (4.1c). The location of the peak in $C_{tiss}(t)$ can be mathematically deduced by setting the derivative of $C_{tiss}(t)$ to zero; and setting Eq. (4.1c) to zero obtains the condition $C_A(t)=C_V(t)$, as depicted by their intersection. The implication of this observation is that the peak in $C_{tiss}(t)$ occurs when input and outflow equalize, and therefore the peak location (TTP and $C_{tiss,peak}$) would be dependent on the shape of $C_A(t)$ rather than $C_{tiss}(t)$.

To further explain this point, another two arterial inputs, a narrow bolus $C_{A,2}(t)$ and a wide bolus $C_{A,3}(t)$, were employed to simulate $C_V(t)$ and $C_{tiss}(t)$ curves in **Figure 4-2(b)** using the same baseline parameter values. It was observed that the curve peak enhancement measurements (TTP and $C_{tiss,peak}$) are indeed sensitive to changes in $C_A(t)$. As $C_A(t)$ can vary among patients with different body figures and cardiac conditions, comparisons of the peak enhancement metrics among different patients would be confused by their differences in $C_A(t)$.

Next, an attempt was made to investigate whether any of the parameters can be readily inferred from the peak enhancement method with a consistent arterial input $C_A(t)$. This would be of interest in the context of drug administration or treatment assessment, where the same patient is monitored for historical changes in microcirculation parameters before and after the medication or treatment [112]. Assuming that a consistent $C_A(t)$ can be obtained for the same patient in both examinations, the question translates to whether changes in TTP or $C_{tiss,peak}$ can be indicative of changes in any of the tissue parameters. Since a set of $C_{tiss}(t)$ curves has been generated by changing one of the tissue parameters at a time in **Figure 3-11**, the

value of each tissue parameter can be plotted against the corresponding values of TTP in the simulated $C_{tiss}(t)$ curves, as shown in **Figure 4-2(c)**.

No linear relationship between TTP and any of the tissue parameters is shown in **Figure 4-2(c)**, indicating that the change in TTP is not be linearly related with any of the tissue parameters. Similarly, **Figure 4-2(d)** shows that $C_{tiss,peak}$ cannot be linearly related to any of the tissue parameters. As TTP is a time parameter, it is also attempted to correlate TTP with the tissue mean transit time $MTT=(v_p+v_e)/F$, and the vascular mean transit time $MTT_v=v_p/F$ [10, 104]. MTT and MTT_v can be adjusted by either changing the distribution volumes or by changing F as shown in **Figure 4-2(e)**. Again, TTP cannot be linearly related with either of them.

Figure 4-2 (a) A typical set of $C_A(t)$, $C_V(t)$ and $C_{tiss}(t)$ curves. The peak of $C_{tiss}(t)$ is marked by a cross. The intersection of $C_A(t)$ and $C_V(t)$ is marked by a circle. (b) $C_V(t)$ and $C_{tiss}(t)$ curves generated by another two arterial inputs. With respect to **Figure 3-11**, each tissue parameter is plotted against TTP in (c), $C_{tiss,peak}$ in (d), and against MTT and MTT_v in (e).

4.3.3 Application of Total Tracer Distribution Volume

To demonstrate that the steady state concentrations (saturation) value of $C_{tiss}(t)$ relative to that of $C_A(t)$ approaches a ratio given by the total tracer distribution volumes (v_p+v_e), $C_{tiss}(t)$ curves were plotted for different variations of v_p and v_e totaling up to 20% and 40%, under extremes of high and low values of F and PS , as shown in **Figure 4-3(a)-(d)**.

In **Figure 4-3(a)-(b)**, PS is fixed at the baseline value of 20 mL/min/100mL, while in **Figure 4-3(c)-(d)**, F is fixed at the baseline value of 50 mL/min/100mL. C_0 indicates the final concentration of $C_A(t)$ at 10 min. Concentration levels of $0.4C_0$ and $0.2C_0$ are also marked to show the convergence of the various $C_{tiss}(t)$ curves towards those concentration levels. Based on the simulated curve plots in **Figure 4-3(a)-(d)**, comparisons of $IAUC_{norm}$ and the ratio $C_{tiss}(t)/C_A(t)$ are shown in **Figure 4-3(e)-(f)**.

Denoting the final value of $C_A(t)$ at 10 minutes by C_0 , most of the $C_{tiss}(t)$ curves approach to saturation given by $(v_p+v_e)C_0$ at the end of 10 minutes, except for the situation of low PS and high v_e [=35% in **Figure 4-3(d)**]. This is because a large EES and v_e would require a substantial amount of tracer to be extracted from the IVPS for the EES to reach a similar steady state concentration as the IVPS. However, tracer extraction into the EES depends on the capillary PS . For a low PS , tracer extraction is slow and the corresponding $C_{tiss}(t)$ approaches to its saturation state slowly.

Figure 4-3 $C_{tiss}(t)$ curves simulated using the proposed IPDP model with a high F in (a), low F in (b), high PS in (c), and low PS in (d). Based on the plots in (a)-(d), a comparison of $IAUC_{norm}$ (squares) calculated for a duration of 5 minutes and the ratio $C_{tiss}(t)/C_A(t)$ taken at 5 minutes (circles) are shown in (e). The error bar indicates ± 1 standard deviation of the estimates and the cross marks the corresponding mean value. Similarly, a comparison of $IAUC_{norm}$ calculated for a duration of 2 minutes and the ratio $C_{tiss}(t)/C_A(t)$ taken at 2 minutes are shown in (f).

Conversely, $C_{tiss}(t)$ curves with large values of v_p relative to v_e (colored black in **Figure 4-3(a)-(d)**) can approach to steady state fast, as the tracer traverses through the tissue mainly within the IVPS, with little extraction into the EES.

Considering that most DCE examinations are performed within a few minutes, the corresponding ratios of $C_{tiss}(t)$ and $C_A(t)$ at 5 minutes and 2 minutes were plotted to compare with $IAUC_{norm}$ computed for the same examination period, as shown in **Figure 4-3(e)** and **(f)**, respectively. Despite being a simpler method, the ratio of final values of $C_{tiss}(t)$ and $C_A(t)$ performed relatively well as compared with $IAUC_{norm}$. As expected, both methods meliorate with the prolonger of the DCE examination period. For an intravascular tracer, it is therefore feasible that a single DCE scan, at say 5 minutes post-contrast, is able to give a quick estimate of the total tracer distribution volumes (v_p+v_e) by simply dividing concentration in a tissue voxel by that in a vicinal major artery.

4.4 Chapter Summary

The IPDP model that accounts for the distribution of blood flows allows for more complete modeling of microcirculation characteristics. It was employed for the performance evaluation of empirical tissue enhancement methods using DCE imaging. The key findings in this chapter are:

1. The maximal slope method is able to provide accurate estimation of blood flow if the peak of the AIF occurs before any tracer outflow from the venous. The initial tracer outflow from venous can be specified by the minimum tracer transit time t_{min} . Violation of this condition would results in the underestimation

of blood flow. Parameter conditions contributing to the shortening of t_{min} include an increase in F , RD , or *skewness*, as well as a reduction in v_p .

2. The application of curve peak enhancement methods including time-to-peak TTP and peak value $C_{tiss,peak}$ should be cautioned against. These metrics are dependent on the shape of the arterial input $C_A(t)$ and cannot be linearly related to any of the tissue parameters investigated. Therefore the peak enhancement metrics should not be considered as quantitative diagnostic indicators.
3. The normalized Initial Area Under Curve (i.e., $IAUC_{norm}$) provides an estimate of the total tracer distribution volume in the tissue. The accuracy of this method improves with the duration of the DCE scanning. An alternative estimation of the total tracer distribution volume can be simply given by a quick estimate on a single DCE scan by the ratio of final saturation (steady state) values of $C_{tiss}(t)$ and $C_A(t)$ sampled a few minutes after the contrast injection.

Chapter 5

Dual-Phase Model-Fitting

Approach

Tracer kinetic modeling is a widely accepted analysis method for functional DCE imaging. However, studies have shown that parameter assessment employing tracer kinetic models might be unstable because the model-fitting process with tracer kinetic models generally brings in large uncertainty of the results. Multiple initial guesses are needed, which makes the post-processing time-consuming. This chapter proposes a dual-phase model-fitting method to address this problem, especially for the analysis of tracer enhancement kinetic curves with washout enhancement pattern. The proposed approach can reduce the occurrence of undesired local minima and drive the model-fitting process towards global minimum for the blood flow estimation.

5.1 Introduction

Current post-processing methods for parameter estimation can mainly be classified into two categories including empirical model-free measures of tissue enhancement and compartmental trace kinetic modeling methods.

It was shown in the study conducted in Chapter 4 that the accuracy of estimation using empirical tissue enhancement metrics is conditional and some conditions might be difficult to implement in practice [112]. The maximal slope method was proven to be dependent on certain assumptions that are not clinically practical. However, one underlying significance implied by this method, the impact of blood flow on the curve growth stage, is still inspiring for model-based tumor vasculature parameter assessment.

Existing tracer kinetic models has been used to quantitatively estimate tumor microcirculation, but they are not able to meet the requirements of being accurate, precise, and fast simultaneously. For example, the classical GK model [76] widely applied in clinical diagnosis was obstructed by the confounding effects of vessel permeability and blood flow [124, 125]. The CC models and DP models facilitated the separate estimation of blood flow and permeability, but did not account for the massively branched capillaries in tumor. The multiple pathway model featuring blood flow heterogeneity [10] was proposed to deliver more physiologically realistic details of tumor microvasculature. However, parameter estimation with these models might be unstable [19-21] as the model analysis involves an optimization process with model-fitting which is sometimes trapped in a local minimum that generates undesired results.

This brings in the need of repeated fitting with many initial guesses to reduce parameter estimation errors. The complex models with more precise mathematical representations or better physiologically realistic, such as the IPDP model, entail higher computation complexity. Furthermore, “when voxel-wise parameter maps are requested, the post-processing time would be substantially prolonged” [126].

In addition to existing methods, multiple studies have found that the contrast enhancement kinetic curves performing a washout pattern is often observed in the vascular tumors. Some tumors exhibit washout pattern as a whole [117, 118]. In the diagnosis of malignant tumors, washout pattern was considered with a higher sensitivity and specificity [127, 128]. For hepatic lesions, 90.5% malignant lesions and 36.8% benign lesions showed washout patterns [129]. The cerebral tumors assessed in previous clinical trials [58, 103] also exhibited washout patterns. Therefore, the characteristics of washout pattern can be integrated into model-fitting methods.

In this study, a dual-phase model-fitting approach was proposed to improve estimation precision and efficiency with the IPDP model introduced in Chapter 3. The proposed method was designed for contrast enhancement curves with washout pattern. A conditional optimization process for the model-fitting was proposed by implementing partial SSR into the IPDP model. Monte Carlo experiments were designed and conducted to assess the proposed model-fitting approach. Subsequent numerical studies of individual parameters and fitting conditions were presented. The computational efficiency of the proposed model-fitting approach was compared to that of the conventional model-fitting method.

5.2 Conventional Fitting Method

The conventional model-fitting method is commonly applied to tracer kinetic models for deriving pharmacokinetic parameters. The conventional model constrained fitting process [56] is usually performed using a constrained nonlinear multivariable optimization algorithm to find a vector $\mathbf{p}$ that gives a local minimum to the cost scalar function $SSR(\mathbf{p})$ as in Eq. (2.7). The optimization process is restarted multiple times from different initial points to circumvent the converging to an undesired local minimum that is far from the global minimum. The output flags reflect the status of the optimization search. Fitting failures with exceedingly large SSR values or negative output flags (implying no feasible solution) are excluded [58].

The IPDP model, along with other tracer kinetic models, is usually applied on DCE imaging data by repeated conventional fitting of the impulse response function $R(t)$ to select the best fitting result. The ROI microcirculation parameters are derived according to the “best fitting” with smallest SSR value. The DCE imaging data is often collected for a long enough scanning time so that the washout enhancement curves with $C_{tiss}(t)$ exhibiting a peak can include all four stages of a common tracer washout procedure as illustrated in **Figure 3-6**: growth, peak, decline, and stabilization.

The parameter estimation generated from conventional fitting method is often disturbed by high probability of undesired local minima that are far from the global minimum. The objective functions of tracer kinetic models are generally not convex so that it is inevitably affected by the existence of many local minima [5]. Meanwhile the

“global minimum has a narrow domain of attraction, no matter how small the variance of the noise is” [19]. Therefore, the estimation procedure relies on good initial guesses. According to a recent observation [20], algorithm for the models with four parameters “fails to converge to the global minimum in about 1 out of 10 cases”. As a result, the parameter estimation has an error up to 30%-40% [20]. A strategy to find a good local minimum is to repeat the model-fitting procedure from initial points and to select the solution giving the smallest fitting SSR.

Theoretical success rate in reaching the global minimum from random initializations varies from 0% to 18% [19]. When initial sampling range is large, simulations commonly led to increased numbers of fittings that need to be rejected [20]. Yet the number of fitting repetition is still in lack of historical knowledge or *a priori* experiment to ensure an approximately global minimum. Insufficient repetition can lead to limited estimation accuracy in addition to high estimation variation, and the need of repeating the optimization from different initials reflects on the computation consumptions. It is therefore crucial to achieve more accurate hemodynamic parameter estimation with less fitting repetitions.

5.3 Proposed Dual-phase Model-fitting Approach

To reduce the estimation uncertainty from the conventional DCE-MRI image model-fitting process, a constructive idea of reconstructing the data fitting into successive phases was proposed in this study. The approach was carried out with a modified partial SSR calculation as well as a conditional optimization process during the model-

fitting. The fitting procedure was composed of two phases rather than a single one, so that more curve details can be taken into account.

5.3.1 Partial Sum of Squared Residuals Based Optimization

According to the observation from **Figure 3-11**, the influence of each independent parameter in the IPDP model on the behavior of the $C_{tiss}(t)$ curve is different. Each model parameter has an impact on particular parts of the impulse responses. Consequently, individual parameters also have an impact on particular parts of the tissue $C_{tiss}(t)$ curve. Since the model-fitting procedure was carried out by the deconvolution of Eq. (2.2a), the assumption can thus be made that particular parts of the $C_{tiss}(t)$ curve have specific impact on different parameters derived by deconvolution.

5.3.1.1 Individual Parameter Estimation

It was shown in Chapter 4 that for the empirical maximal slope method, F [**Figure 4-1 (b)**] and PS [**Figure 4-1 (f)**] have large impact on the growth stage and decline stage of the tissue enhancement curve $C_{tiss}(t)$, respectively. The other parameters v_p , v_e , and RD also have unique impacts on the $C_{tiss}(t)$ curve. This characteristic is inspired to be implemented into model-based tumor vasculature parameter assessment. Data-fitting subjected to selected curve/surface stages had been studied [130] and had been practically applied in many other research areas [131, 132].

The partial-SSR based optimization was proposed according to the aforementioned pharmacological feature. Only the SSRs for the targeted curve

stages were taken into account during the optimization. The partial-SSR was defined by:

$$SSR_{partial}(\mathbf{p}) = \min_{\mathbf{p}} \sum_{j=\alpha}^{\beta} \left| C_{tiss,model}(j, \mathbf{p}) - C_{tiss,data}(j) \right|^2, \quad (5.1)$$

where the concentration sample point j starts from the α^{th} point and ends at the β^{th} point. For a δ s time interval as the temporal resolution, the partial-SSR would be calculated from $\delta(\alpha - 1)$ s to $(\beta - 1)$ s.

To evaluate the performance of partial-SSR, all hemodynamic parameters engaged in the IPDP model were assessed for their pharmacological characteristics at each curve stage. Long and short scanning periods ranging from 179s to 499s were taken into consideration. Three typical kinds of temporal resolution with different time interval (1s, 2s, and 5s) were assessed. The assessment was based on the relative bias as $bias(p) = |(p - \bar{p})/p| \times 100\%$. The estimated result with a relative bias less than 10% was defined to be a reliable estimation. Selected results shown in **Figure 5-1** illustrate the frequency of occurrence of reliable estimations. The assumed scanning time shown in **Figure 5-1** was set up to 3 minutes within which major concentration changes are completed. The scan interval δ was set as 2s, which is a moderate temporal resolution. A total of 300 fittings were conducted with random initial guesses of each parameter corresponding to various partial-SSR fitting schemes.

Figure 5-1 Frequency of occurrence of reliable estimations from different random initial guesses. The whole curve SSR is used in (a) the conventional model-fitting method. Partial-SSR is used to fit the curve by applying to (b) growth stage (*I*), (c) peak stage (*II*), (d) decline stage (*III*), and (e) stabilization stage (*IV*).

5.3.1.2 Potential Usage of Partial-SSR

For the conventional whole curve SSR fitting method that is shown in **Figure 5-1(a)**, the fractional EES volume v_e generally performs the best with 52.67% reliable estimations, followed by the permeability surface area product PS with 48% reliable estimations. Blood flow rate F and fractional plasma volume v_p exhibit higher bias/error ratio with only 18% and 10.67% reliable estimations, respectively.

For the curve fitting using partial-SSR, all parameters reveal distinguished properties as shown in **Figure 5-1(b)-(g)**. For example, curve fitting for growth stage (*I*) can improve the estimation accuracy of F with smaller relative bias comparing to the

conventional fitting method. The frequency of reliable estimations for F is correspondingly improved from 18% [as in **Figure 5-1(a)**] to 47.5% [as shown in **Figure 5-1(b)**]. Similarly, the decline stage (*III*) fitting gives an even better PS with 68.75% reliable estimations [as shown in **Figure 5-1(d)**] comparing to 48% derived from the conventional fitting method [as in **Figure 5-1(a)**]. However, the curve peak stage (*II*) [as in **Figure 5-1(c)**] and the stabilization stage (*IV*) [as in **Figure 5-1(d)**] have weak contribution to better parameter estimations. The short time interval of the peak stage (*II*) makes it highly sensitive to noise, and the change of concentration in the stabilization stage (*IV*) is insufficient for providing independent estimation to any parameter. Several SNR values have been tried. The effects of different SNR levels to the conventional method and the proposed method have been observed to be similar. As such, the remaining part of this research will report results at a fixed SNR value.

The potential usage of partial-SSR optimization is thus revealed. By dividing a curve into certain stages, each stage of the washout enhancement curve has been found to exhibit different sensitivities to different parameters. It is reasonable to postulate that by applying only the most relevant curve stages to the SSR calculation during the optimization search, the model-fitting process can be pushed towards global minimum. Correspondingly improved estimation of a parameter can be achieved. This leads to potential individual parameter estimation with high accuracy and precision. Since all the pharmacokinetic parameters are working synergistically to produce the $C_{tiss}(t)$ curve, it has positive effect on the estimation of the rest parameters.

5.3.2 Design of Dual-phase Model-fitting Method

After the development of the partial-SSR optimization, a dual-phase model-fitting method was proposed. The first phase applies partial-SSR optimization to estimate a selected parameter θ . In the second phase, the estimated θ is incorporated into conditional optimization equation for complete parameter estimations.

The parameter θ is expected to be affected by a particular stage of $C_{tiss}(t)$ and is not sensitive to the other parts of the curve. Such particular curve stage is selected to fit the tracer kinetic model. The targeted parameter θ would be estimated with a higher accuracy because the most significant curve depicting this particular parameter has been taken into account. Unlike the conventional model-fitting which need to balance all parameters throughout the entire curve, the irrelevant curve parts are not taken into account for the targeted parameter estimation.

For a dual-phase model-fitting approach, the first phase is expected to have a targeted parameter θ with higher reliability than the conventional fitting. Theoretically, when one of the model parameters is having a reliable initial guess, the overall estimation for all parameters should be benefited to generate more reliable estimation results. Then the second phase should: (1) adopt the targeted parameter θ estimated from the first phase as the initial guess, (2) limit the fitting range of θ to a more feasible scale, (3) or add more fitting constraints to help to derive the rest hemodynamic parameters.

5.3.2.1 *Determination of successive fitting schemes*

According to the observations in Section 5.3.1, partial-SSR fitting of stage (I), stage (III) are able to give better estimation to F and PS , respectively. To build a successive fitting approach with multiple phases, the primary part of the $C_{tiss}(t)$ curve to apply partial-SSR calculation need to be selected. Accordingly the parameter to be targeted during the first phase is determined.

It is discovered from Section 5.3.1 that the curve growth stage (I) fitting gives the most reliable blood flow F estimation comparing to other fitting schemes. Meanwhile one of the adjustable optimization elements p_1 has the same value with F . The dual-phase fitting with a growth stage partial-SSR fitting followed by a conventional fitting is constructed. Experiments show that the bias obtained from this fitting scheme is lower than that from conventional fitting approach under certain conditions. Meanwhile the estimation variation of this fitting scheme is reduced to a much smaller range which will contribute to the reduction of the possible clinical false alarms or misdiagnosis of tumors.

Similarly, the fitting scheme with a curve decreasing stage (III) followed by successive conventional fitting was also assessed. The targeted parameter θ generated from curve stage (III) is the permeability PS . Unlike F , PS does not have a corresponding optimization element within p_1 to p_5 . In this case, instead of replacing initial fitting point, one more equivalent constraint derived from the first phase was added to the optimization constraints at the second phase. However, the estimation results using PS do not show significant advantages comparing to conventional fitting.

As inferred from the results of two schemes, the growth stage (*I*) partial-SSR optimization performs best when successively combined with conventional fitting. Therefore only the dual-phase fitting with a growth stage partial-SSR fitting followed by a conventional fitting was adopted for further study.

5.3.2.2 *Determination of values of α and β*

It is shown that the growth stage (*I*) has great potential to improve blood flow estimation and to further build a good dual-phase successive fitting approach. The exact start and end points for the partial-SSR calculation, i.e. values of α and β in Eq. (5.1), need to be determined. To study how the curve growth partial fitting benefits blood flow estimation, different curve intervals were testified: curve upward stage starting from 0s or starting after a few seconds of injection; upward stage ending before, after, or right at the curve peak. Each curve intervals combination was simulated 100 times to study the fitting result distribution. And each simulation has 50 repetitions. Among all combinations, the upward interval starting from the initial arrival of contrast in $C_{tiss}(t)$ and ending at the curve peak was chosen. Accordingly, α is set to 1 and β would be set case by case according to the time to curve peak.

After values of α and β were determined, the first phase of successive fitting could be performed according to partial-SSR calculation. The chosen curve growth partial fitting could acquire desirable accuracy/precision in blood flow estimation with fewer repetitions.

5.3.2.3 Conditional optimization

After the selection of successive model-fitting scheme for the first phase, the conventional fitting method with whole-curve SSR optimization is incorporated into the second phase. In the second phase, the estimated θ from the first phase will be used as the initial guess. The fitting range of θ in the second phase would also be narrowed down to a smaller but more practical sampling interval.

The blood flow F have been estimated with high precision according to the preliminary experiment results in Section 5.3.1.1. In the consideration of computation consumption and estimation precision, the blood flow F_2 in the second phase will follow the blood flow F_1 acquired at the end of the first phase optimization and be further constrained as:

$$\begin{aligned} SSR(\mathbf{p}) &= \min_{\mathbf{p}} \sum_j \left| C_{\text{tiss,model}}(j, \mathbf{p}) - C_{\text{tiss,data}}(j) \right|^2, \\ \text{s.t. } b_l p_{21} &< p_{22} < b_u p_{21} \quad (\text{or } b_l F_1 < F_2 < b_u F_1) \end{aligned} \quad (5.2)$$

in which b_l and b_u are respective multiplication factors of F_1 to constitute the lower and upper fitting boundaries of F_2 . Since the optimization element p_1 represents F , the constraint could be alternatively written as $b_l p_{11} < p_{12} < b_u p_{11}$ where p_{11} is p_1 in the first phase and p_{12} is p_1 in the second phase.

With the constrained SSR optimization, the fitting range of F was narrowed down to produce more reliable estimation based on the preliminary estimation in the first phase. Since all the tracer kinetic parameters are working synergistically to produce the $C_{\text{tiss}}(t)$ curve, the rest of model parameters would also achieve more reliable estimations and accordingly improve estimation efficiency.

5.3.3 Monte Carlo Simulation and Boundary Analysis

To maximize the performance of the proposed dual-phase model-fitting method, suitable constrained fitting boundaries in Eq. (5.2) for the second phase need to be determined. However, it is still unclear about the number of fitting repetitions needed to satisfy the accuracy/precision requirement. Since the true tissue kinetics is unlikely to be known without invasive investigation, it is difficult to evaluate the performance of model-fittings using practical DCE-MRI imaging data. Simulation is therefore the most possible way to generate assumed tissue hemodynamic data.

To have a more comprehensive study of the dual-phase model-fitting approach, Monte Carlo simulations method is adopted. It offers extra detailing with minimal approximations considering the scatter distribution and the ability to know the ground truth regarding microcirculation kinetic parameter values.

5.3.3.1 Monte Carlo Simulation Design

To evaluate each microcirculation parameter response to different fitting schemes, Monte Carlo simulations were carried out to compare the performance of individual parameter derived from IPDP model by conventional fitting method with that by the dual-phase fitting method. A total of 6 groups Monte Carlo simulations were conducted to study the precision and accuracy of the estimated model parameters. The procedure of such Monte Carlo assessments is as follows:

1. Generate a realistic arterial input $C_A(t)$ with scaling parameters to produce a $C_A(t)$ peak around 4 mM at about 6s upon bolus arrival, which is typical of a human $C_A(t)$ after a short bolus injection of 0.1 mmol/kg Gd-DTPA [82].

2. Generate smooth tissue tracer uptake curve $C_{tiss}(t)$ using the IPDP model with the above arterial input and baseline hemodynamic parameters as inputs. A typical set of cerebral tumor parameters (as dataset T1 with $F = 39.17 \text{ ml/min/100ml}$, $PS = 38.63 \text{ ml/min/100ml}$, $v_p = 5.93\%$, $v_e = 15.33\%$, $RD = 0.14$) was assumed as baseline hemodynamic parameters in this Monte Carlo experiment.
3. Add Gaussian noise with desired signal-to-noise ratio (SNR) to the simulated $C_{tiss}(t)$ curves, where SNR is taken to be the ratio of the maximum value of $C_{tiss}(t)$ (before noise is added) and the standard deviation of the noise [133]. A moderate SNR level of 50 according to other literatures and common standard was used throughout this study.
4. Use the IPDP model to fit the noisy $C_{tiss}(t)$ in step 3 with the nonlinear optimization algorithm '*fmincon*'. Because of the added noise, parameter estimates would deviate from the original (assumed) values.
 - a. For the conventional fitting, each curve was repeated 10, 20, 30, 40, or 50 times with random initial conditions within a physiological range and the fitting with the lowest SSR value was chosen.
 - b. For the dual-phase model-fitting, each curve was repeated 10 times for the first phase. Optimization element p_1 was chosen from the fitting with the lowest partial-SSR of the curve growth. p_1 from the first phase was then adopted as initial p_1 during the second phase fitting. The upper and lower fitting boundaries of p_1 were optimized according to the conditional optimization equation Eq. (5.2). Other adjustable optimization elements at the second phase are still used with random initial conditions and the same fitting boundaries as in the first phase.

5. Repeat steps (3) and (4) 100 times to derive a distribution for the estimated parameters.

To standardize with previous tracer kinetic modeling studies, comparison results were analyzed based on the coefficient of variation (CV) and the relative bias as $CV(p) = std(\hat{p})/\bar{p} \times 100\%$ and $bias(p) = |(p - \bar{p})/p| \times 100\%$. Here p represents the baseline value of the individual parameter, std is the standard deviation operation, $\bar{p}$ stands for the empirical mean value obtained from simulations. The CV provides a measure for the precision (reliability) of each parameter and relative bias provides a measure for estimation accuracy. It is clear that $CV(p)$ and $bias(p)$ make more sense than the simple average and standard deviation, since the later criteria would obscure large fluctuations in the estimation. The criteria $CV(p)$ and $bias(p)$ will be used to evaluate the estimation performance for each individual parameter.

5.3.3.2 *Preliminary Boundary Analysis*

To improve p_1 and F in the second phase, the constrained fitting range defined in Eq. (5.2) for the second phase of dual-phase fitting approach should be appropriate. If the fitting range is too narrow, there will be no searching space for optimization. If the fitting range is too broad, the advantage gained from the first phase would be insignificant. In the proposed approach, the updated fitting boundaries (i.e., b_l and b_u) for p_1 in the second phase are directly related to the optimization space of p_1 or F estimation and would subsequently affect the other parameters.

Table 5-1 shows relative bias and CV of final estimated F , where $\pm 5\%$ and $\pm 10\%$ are adopted as the constrained coefficients of the boundaries. These experimental results show that when the updated fitting range for F_2 is narrower than $\pm 10\%$ of the

estimated F_1 from the first phase, the searching range for F_2 is so small that even increasing repetition cannot further improve its final estimation. To prevent from neglecting the global minimum, the searching range should not be too narrow. Thus in the following studies, the Monte Carlo simulation groups with the second phase fitting boundaries broader than $\pm 10\%F_1$ (i.e. $b_l > 0.1$ and $b_u > 0.1$) were compared.

Table 5-1 Relative bias and CV of final estimated F .

Repetition	20	30	40	50
Relative bias with $\pm 5\%F_1$	5.25	5.07	4.92	4.94
Relative bias with $\pm 10\%F_1$	5.99	5.46	5.37	5.08
CV with $\pm 5\%F_1$	6.96	7.07	6.93	7.09
CV with $\pm 10\%F_1$	7.99	7.28	7.16	6.99

5.3.3.3 Statistical Comparison for Individual Parameters

To find the appropriate boundaries, Monte Carlo simulation applying the proposed approach was conducted with different optimization constraint coefficients b_l and b_u in the second phase. 100 simulation runs were carried out for each group, and the statistical results of individual estimated kinetic parameters in terms of the CV and relative bias were analyzed.

The baseline data to simulate the $C_{tiss}(t)$ curve was chosen from a typical brain tumor (as dataset T1 in in **Table 5-2**). Since the dual-phase fittings need 10 fitting repetitions for the first phase, the Monte Carlo experiment was started from 20 repetitions where each phase is having 10 repetitions, and was repeated up to 50

repetitions from different initial conditions. Subsequent fitting repetitions were all carried out in the second phase.

All fitting schemes of the dual-phase model-fitting method were compared together with the conventional fitting approach. The dual-phase method with $F_2 = F_1$ (i.e., b_l and b_u in the second phase to be 0%) was taken into comparison as one control group. In this Monte Carlo experiment, five groups performed the simulation with the proposed dual-phase model-fitting method with the blood flow optimization constraint coefficient b_l and b_u to be $\pm 0\%$, $\pm 10\%$, $\pm 25\%$, $\pm 50\%$, and $\pm 100\%$, respectively.

Figure 5-2(a) shows the histogram of the mean bias for respective parameters. It is observed that the relative bias of F is lower in 15 out of 20 dual-phase model-fitting schemes than that in the conventional fitting group. PS , v_p , and v_e all have the lowest bias in “dual-phase model-fitting with $\pm 50\% F_1$ boundaries”. In the dual-phase model-fittings with $\pm 0\% F_1$ or $\pm 10\% F_1$ boundaries, PS , v_p , and v_e begin with significantly higher relative bias at 20 fitting repetitions, whereas it drops quickly at 30 repetitions. **Figure 5-2(b)** shows the tendency of relative bias observed with 50 repetitions for different boundary schemes. All fitting schemes of the dual-phase model-fitting method were compared together with the conventional fitting approach. As shown, a moderate b_l and b_u value of 50% to constrain Eq. (5.2) gives the lowest mean bias.

Figure 5-2 (a) Mean relative bias of individual parameter as a measure of accuracy for (i) F , (ii) PS , (iii) v_p , and (iv) v_e . (b) Mean relative bias of the parameter estimation from 50 repetitions.

Figure 5-3 CV of individual parameters as a measure of precision for (a) F , (b) PS , (c) v_p , and (d) v_e .

Figure 5-3 shows the CV of individual parameters. It is observed that for PS , v_p , and v_e to acquire a lower CV, less fitting repetitions are needed for the dual-phase model-fitting and thus the computation consumption is reduced. Dual-phase model-fitting with $\pm 25\%$ - $50\% F_1$ performs best by either getting to a lower CV sooner or obtaining the lowest CV at 20 repetitions or both. When b_l and b_u in Eq. (5.2) are set to be 0, blood flow F are constrained to have no improvement in the second phase on bias or CV as shown by “Dual-phase ($\pm 0\% F_1$)” in **Figure 5-2** and **Figure 5-3**. Subsequently the other model parameters cannot benefit from the lower bias and CV achieved from the first phase, which can be observed from “Dual-phase ($\pm 0\% F_1$)” in **Figure 5-2** and **Figure 5-3**. When b_l and b_u are set as large numbers, take 100% for example, the proposed method shows less advantage. Thus a moderate fitting range (with b_l and b_u value of 50%) to constrain Eq. (5.2) is preferred. Accordingly, comparison for conventional fitting, dual-phase fitting with $\pm 10\% F_1$, $\pm 25\% F_1$, $\pm 50\% F_1$ will be carried out in the next section.

5.3.3.4 Statistical Comparison for Different Fitting Repetitions

The above comparison showed general decrease of both bias and CV along with the increase of fitting repetitions for each parameter. Such decrease becomes less obvious with the increase in repetitions. For a more comprehensive understanding, an overall comparison for all parameters with different number of fitting repetition was carried out. **Figure 5-4(a)-(c)** shows the statistical comparison of both bias and CV of all the four parameters with repetitions of 20, 30, and 50, respectively.

From **Figure 5-4(a)**, it is observed that if the fitting repetition is limited to 20 times, the preferred fitting method is the dual-phase fitting with $b_l = 25\sim 50\%$ and $b_u = 25\sim 50\%$. Dual-phase fitting with a broader fitting boundaries (larger b_l and b_u) of F_2 tends to have larger bias and CV in F ; dual-phase fitting with a smaller b_l and b_u tends to have larger bias and CV in PS . Thus a moderate boundary would be preferred. Other than that, the sum of CV of all the four parameters has the largest value with the conventional fitting method, which proves 20 repetitions is not enough for the conventional fitting method to achieve a reliable estimation.

When the repetition number is increased to 30 as shown in **Figure 5-4(b)**, all the dual-phase fitting combinations have a significantly smaller CV than the conventional fitting method. The preferred fitting method for 30 repetitions would be the dual-phase fitting with $b_l = 25\% \sim 50\%$ and $b_u = 25\% \sim 50\%$ because of the small bias and CV.

Figure 5-4 Statistical comparison for the number of fitting repetitions limited to (a) 20, (b) 30, and (c) 50.

With a further increased fitting repetition number of 50 as shown in **Figure 5-4(c)**, CV of the conventional fitting has been reduced. Both relative bias and CV are small for all fitting schemes. It was observed that the dual-phase model-fitting with $b_l = 50\%$ and $b_u = 50\%$ still possesses superiority. Larger repetition number is required by broader fitting ranges since there is more space to search.

In conclusion, after sufficient number of fitting repetition (typically after 30), all simulation schemes tend to have relatively stable levels of bias and CV for all parameters. Smaller bias and CV of F are observed in the model-fitting with the proposed method comparing to that with the conventional fitting. The smaller bias and CV indicate better parameter precision and lower variance, which is suggesting a better model fitting [134].

5.3.4 Numerical Study and Performance Evaluation

To compare the performance of the proposed method to the conventional fitting method on cerebral tissues, typical cerebral tumor and normal microcirculation parameter values were assumed (as shown in **Table 5-2**). Another Monte Carlo experiment was conducted with 6 group datasets for each model-fitting method.

The dual-phase model-fitting method proposed in this chapter was designed for contrast enhancement curves with washout pattern. Another tissue enhancement curve type that associated with a peak, the plateau pattern, is also of interest. The plateau pattern was characterized by a relatively prominent upward slope and a final intensity 90-100% of peak grade [128]. After the upward slope, the washout speed was inversely correlated with blood flow [135]. Therefore a key difference between a

washout and a plateau is whether the blood supply is sufficient or not. Inadequate blood supply would result in a plateau or a slow washout, and adequate blood supply would lead to a fast washout pattern. Based on this consideration, in the numerical study in this section, a preliminary analysis for the feasibility of the proposed method to various tumor types was conducted.

Table 5-2 Parameter values assumed in the simulation studies.

	F (ml/min/100ml)	PS (ml/min/100ml)	v_p %	v_e %	RD dimensionless
N1	24.7	1.1	1.4	0	0.01
N2	23.9	0.8	1.1	0.1	0.01
T1	39.17	38.63	5.93	15.33	0.14
T2	42.7	33.3	7.9	32.1	0.23
T3	34.9	16.1	3.5	4.3	0.05
T4	27.7	45.8	6.6	9.6	0.1

Each group was carried out for 100 simulations using both the conventional model-fitting and the dual-phase model-fitting method to derive the estimation results, and then they are compared to the originally assumed parameter values. According to the statistical analysis demonstrated in Section 5.3.3.3 and 5.3.3.4, the fitting boundaries during the second phase of the dual-phase fitting were consistently set as $\pm 50\%F_1$. Each model-fitting simulation was subjected to 30 repetitions for a clinically feasible situation.

The dual-phase processing adopted in this chapter is subjective to good blood flow estimation in the first phase. Ideally, successful improvement on parameter estimation using this dual-phase model-fitting should happen when blood flow is higher than permeability. As shown in **Table 5-2**, the two data groups from normal brain tissue (N1 and N2) possess negligible PS and v_e due to the BBB. On the contrast, PS is higher in the brain tumor groups (T1-T4). T4 is a typical case when the delivery of tracer is compromised and PS is dominated. T1, T2, and T3 still have sufficient blood perfusion supply and thus have ample tracer delivery despite the abnormal PS . Accordingly, T4 exhibits plateau pattern on the tissue enhancement curve and other groups are characterized by the washout pattern.

Figure 5-5 demonstrates relative bias and CV estimated from the Monte Carlo experiment. According to **Figure 5-5**, when the ROI has ample blood supply and low permeability ($F \gg PS$) as in **Figure 5-5(a)** and **Figure 5-5(b)**, the dual-phase method shows apparent advantages in both bias and CV on blood perfusion F . For dataset N1 [as shown in **Figure 5-5(a)**], the CV of F is reduced from 77.17% (with conventional fitting) to 13.36% (with dual-phase model-fitting); for dataset N2 [as shown in **Figure 5-5(b)**], the CV of F is reduced from 87.49% (with conventional fitting) to 67.92% (with dual-phase model-fitting). The reduction in CV is up to 83% which could be crucial for any subsequent clinical analysis and treatment decision. The relative bias of dataset N1 and N2 are also alleviated by the proposed method. The high relative bias of PS and v_e are caused by the negligible PS and v_e in normal brain tissue, but the estimation result is still good. For the tissues within the ROI with mixed F and PS effect as datasets T1, T2, and T3 (as shown in **Figure 5-5(c)-(e)**), the dual-phase model-fitting method also shows advantages for either equal or better performance comparing to the conventional

fitting. Such advantages are not as remarkable as that in the permeability limited case, but are still convincible to be chosen. In the flow limited situation ($F \ll PS$) as in **Figure 5-5(f)**, the conventional method performs better. However, the authentic conclusion for the flow limited situation cannot be reached until more possible physical conditions are included.

The tissue enhancement curve of plateau pattern was compared with that of washout pattern. The result suggested that the proposed method is best applicable for tissues with adequate blood supply. Thus the enhancement curve with a washout pattern is better suitable for the proposed model-fitting method than that with a plateau pattern. The theoretical conclusion can be made that the dual-phase fitting method is better to be used in the blood flow dominated cases. Therefore, for patients with ample blood supply in cerebral ROI tissue, the dual-phase fitting method is recommended to be employed to improve clinical diagnose reliability and processing efficiency.

Figure 5-5 Relative bias and CV estimated from the Monte Carlo experiment for each group of parameters subjected to 30 fitting repetitions. Plots (a)-(f) each corresponds to one group of parameter values in **Table 5-2**.

5.4 Validation

To further verify the effect of the proposed dual-phase model-fitting method in practical use. A set of patient DCE CT data with meningioma was analyzed. All voxels within the ROI were averaged to derive a tracer concentration-time curve. The ROI-averaged tracer concentration-time curves for both tumor and contralateral normal brain tissue are fitted using the dual-phase fitting method based on the IPDP model, and compared with that using the conventional fitting method.

The parameter estimation variance from ~300 fittings using the two model-fitting methods are summarized in **Table 5-3**, where C stands for the conventional fitting method, and D stands for the dual-phase method. It is observed that the dual-phase

fitting produces significantly lower variance ($p < 0.05$) from model-fitting for most parameters, including the F , v_p , RD in normal tissue, and F , PS , v_p in tumor tissue. In this patient case study, the dual-phase method improved the parameter estimation in general by reducing the estimation variance of most parameters.

Table 5-3 Parameter estimation variance from the patient case study.

		F		PS		v_p		v_e		RD	
		C	D	C	D	C	D	C	D	C	D
Normal tissue	variance	1265.64	0.85	57.12	51.49	0.04	0.01	12.06	52.92	0.024	0.021
	p-value	<u>2.61E-27</u>		0.335		<u>1.09E-12</u>		0.418		<u>3.52E-4</u>	
Tumor	variance	574.55	16.54	767.89	634.05	3.14	1.44	110.88	122.36	0.031	0.032
	p-value	<u>1.55E-9</u>		<u>0.0021</u>		<u>1.61E-4</u>		0.64		0.28	

The normalized SSR from the ~300 fittings were plotted against their respective estimated blood flow F . It is observed from **Figure 5-6** (a) that with an increased SSR in a single fitting, the proposed dual-phase fitting method is still pushing the estimation outcomes toward the global minima. On the other hand, the conventional model fitting method has difficulty in converging to the global minimum for most of the cases. For the purpose of distinguishing tumor from normal tissues, the normalized SSR plotted against the estimated blood flow F using the dual-phase fittings is clearly having less interference than that using the conventional fitting as shown in **Figure 5-6** (b).

Furthermore, another advantage, which is not shown in **Figure 5-6**, is the reduction of fitting time by 27%. In addition, the dual-phase method needs fewer repetitions to arrive at the global minimum SSR and hence shorter processing time for the tracer kinetic analysis.

Figure 5-6 The normalized SSR plotted against the estimated blood flow F from each fitting. (a) Both the proposed dual-phase fitting and the conventional fitting method were applied on the normal tissue and the tumor tissue. (b) The proposed dual-phase fitting and the conventional fitting method were respectively used to classify the tumor from normal tissue with massive fitting repetitions (~ 300 fitting repetitions).

5.5 Discussion

The situation of over-fitting arises as several parameter combinations might produce approximative SSRs. To select the best fitting solely depending on SSR would have a

chance to neglect detailed features of curve. Subsequently this would result in the occurrence of large estimation errors, which is dangerous for patients. No matter how small the SSR is, the optimization might still stop at a local minimum that is far from the global minimum and the estimated parameter might possess a large bias/error. Although the proposed model-fitting approach also selects the best-fit according to SSR, the consideration of partial-SSR ensures the curve minutia to be included and forces the optimization search to stop at an approximately global minimum. Thereby the relative bias and estimation variation of the estimated parameter were alleviated. Upon that, with appropriate arrangement, the dual-phase model-fitting approach can give clinicians and doctors a more credible description of patients' status. The improvement of estimation accuracy/precision is of great clinical importance.

As for the fifth parameter in IPDP model, RD still requires hundreds of repetitions to get to the same relative bias that other parameters can get. No significant improvement was shown in the dual-phase fitting method. Therefore, in consideration of computation efficiency, only the first four parameters are analyzed in the Monte Carlo experiments. In the future, RD can be estimated independently using a separate density estimation algorithm [136].

The assumed v_p adopted in this study are less than 8%. Under such conditions, the maximal slope method underestimates blood perfusion. However, although the proposed partial-SSR optimization was inspired by the maximal slope method, it gives high accuracy and precision for parameter estimations [99, 112].

The proposed method is applied and verified on the IPDP model for boosting the process of convergence during data-fitting. Yet the convergence problem exists in many other tracer kinetic models as long as the model needs a model-fitting optimization

process for parameter estimation. This proposed dual-phase method is potentially applicable for the other models, with prior determination of the particular sensitive parameter corresponding to the curve stage. Note that the simple tracer kinetic models with more assumptions and less independent parameters rarely face the convergence problem. The proposed method can primarily benefit for the realistic models with more independent variables and higher mathematical complexities.

5.6 Chapter Summary

In this chapter, a dual-phase model-fitting approach was proposed for DCE-MRI parameters estimation. In order to enhance computational efficiency and parametric estimation reliability, an algorithm was built based on the proposed IPDP model and the dual-phase model-fitting approach.

The first phase of the proposed dual-phase model-fitting method adopted growth-stage partial-SSR optimization to achieve reliable estimation of blood flow F . The probability of reliable blood flow estimation has been increased from 18% to 47.5%. The second phase adopted the estimated F for further conditional optimization so as to estimate all other model parameters. The conditional optimization in the second phase further gives a reduction in the CV of F (up to 83%) and generally alleviated the estimation bias/error for other parameters.

Comparisons of the proposed method with the conventional fitting method were not only conducted with designed Monte Carlo experiments, but also verified using a patient case with cerebral tumor. The proposed dual-phase model-fitting approach was found to be beneficial to reduce the occurrence of undesired local minima during

optimization, and have much higher possibility to achieve an approximately global minimum. Comparison results show that the dual-phase model-fitting method can achieve more reliable parameter estimation with less fitting repetitions than the conventional model-fitting approach. The processing for DCE image analysis can consequently be speeded up.

Numerical results show that for the cerebral tissues with limited permeability or sufficient blood perfusion supply, the dual-phase model-fitting method generally gives better estimation precision than the conventional fitting method in terms of relative bias and CV of the key parameters. The proposed approach is applicable in blood flow dominated cases and could be implemented in existing tracer kinetic models for more accurate and stable parameter extraction.

Chapter 6

A Simplified Multiple-pathway

Tracer Kinetic Model

6.1 Introduction

The IPDP model enables the estimation of one additional property of tumor, i.e. the distribution of blood flows within microvasculature for diagnosis and characterization of tumors microcirculation by DCE imaging. To improve computational efficiency for better clinical applicability, this study has further investigated the possibility of incorporating simplified compartmental models into each pathway of the IPDP model. The performance of the resulting simplified model under various noise and tissue conditions was also evaluated based on the Akaike Information Criterion (AIC) approach.

6.2 Incorporation of a Simplified Compartmental Model

A simplified model of the capillary-tissue exchange unit, in replacement of the DP2 model, can be implemented into each pathway of the infinite pathway model. To apply the infinite-pathway approach for more feasible clinical analysis of DCE imaging data and allow for parametric mapping, the following modifications were proposed.

6.2.1 Modifications for Practical Implementation

The DP2 model presented in Eq. (3.5a) is mathematically complicated and requires considerable computation, which prolongs the processing time. To reduce the computation complexity, the mathematical representation of the capillary-tissue exchange unit within each pathway of the IPDP model is replaced by a standard (conventional) two-compartment (CC2) model [85, 88, 137]:

$$h_{cap,f_i}(t) = -As_1 \exp(s_1 t) - (1-A)s_2 \exp(s_2 t), \quad (6.1a)$$

where

$$\begin{aligned} \begin{pmatrix} s_1 \\ s_2 \end{pmatrix} &= \frac{1}{2} \left[- \left(\frac{PS}{v_{cap}} + \frac{PS}{v_e} + \frac{1}{t_{cap}} \right) \right. \\ &\quad \left. \pm \sqrt{\left(\frac{PS}{v_{cap}} + \frac{PS}{v_e} + \frac{1}{t_{cap}} \right)^2 - 4 \frac{PS}{v_e} \frac{1}{t_{cap}}} \right], \end{aligned} \quad (6.1b)$$

and

$$A = \frac{s_1 + \frac{PS}{v_{cap}} + \frac{PS}{v_e}}{s_1 - s_2} . \quad (6.1c)$$

The CC2 model has been previously adopted in a number of DCE imaging studies [85, 88, 137]. A schematic illustration of this model is presented in **Figure 6-1**. For the i^{th} pathway associated with a relative flow f_i , the net flow supplying the vascular compartment (i.e. IVPS) is $f_i F$. By assuming well-mixed tracer concentration with each compartment, the CC2 model gives a simpler expression for $h_{cap,fi}(t)$ (Eq. (6.1)) than the DP2 model (Eq. (3.5a)) which accounts for tracer concentration gradients within compartments. Therefore the resulting Infinite-Pathway Conventional Compartmental (IPCC) model is less computationally complex than the original IPDP model.

Figure 6-1 Illustration of the CC2 model.

As shown in **Figure 3-9**, $R(t)$ performs rather insensitive to the changes in *skewness*, which implies the possible reduction of the number of free parameters to 5 by constraining *skewness* to a fixed nominal value. The possibility of reducing model

parameters in the simplified IPCC model was further investigated by Monte Carlo experiments.

6.2.2 Monte Carlo Experiments

An attempt was made to examine whether the parameters describing blood flow heterogeneity, *RD* or *skewness*, can be excluded from curve-fitting [58]. The full IPCC model with all 6 free parameters was used as the generating model (GM) to generate $C_{tiss}(t)$ curves to imitates DCE CT imaging of 50 time points at the time interval $\Delta t = 1$ s. These $C_{tiss}(t)$ curves were fitted using three reduced versions of the IPCC model by keeping either *RD* or *skewness* fixed, or by taking both parameters away. The three reduced models (as shown in **Table 6-1**) were designed as:

1. Model 1 (M1) with *skewness* fixed at the nominal value of 1;
2. Model 2 (M2) with *RD* fixed at the nominal value of 0.3, and
3. Model 3 (M3) with both *skewness* and *RD* taken away, which is equivalent to the CC2 model with single-pathway throughout the vasculature.

Fittings by these reduced models were evaluated using the corrected AIC (cAIC) method [138] to select the best approximating model:

$$cAIC = n \ln \left(\frac{SSR}{n} \right) + 2k \left(\frac{n}{n-k-1} \right), \quad (6.2a)$$

where n is the number of sample points on the $C_{tiss}(t)$ curves and $n=50$ in this case; k =number of free parameters +1, thus $k=6$ for M1 and M2, $k=5$ for M3. Here, cAIC is used instead of AIC because $n/k < 40$ [138]. In a particular simulation run, the best model generates the smallest cAIC value [138]. The relative strength of evidence supporting model m can be given by the Akaike weight [138]:

$$w_m = \frac{\exp(-\Delta_m / 2)}{\sum_{i=1}^3 \exp(-\Delta_i / 2)}, \quad (6.2b)$$

with the Akaike distance

$$\Delta_m = \text{cAIC}_m - \text{cAIC}_{\min}, \quad (6.2c)$$

where $\text{cAIC}_{\min}$ denotes the smallest cAIC value among the models. In Eq. (6.2b), i refers to each of the three models being compared.

Table 6-1 List of parameter status and fitting ranges in the respective models.

Parameter	Model				Fitting Range
	GM	M1	M2	M3	
F (mL/min/100mL)	free	free	free	free	$(10^{-4} - 200)$
v_p (mL/100mL)	free	free	free	free	$(10^{-4} - 99)$
PS (mL/min/100mL)	free	free	free	free	$(10^{-4} - 200)$
v_e (mL/100mL)	free	free	free	free	$(10^{-4} - 99)$
RD	free	free	fixed at 0.3	non-existent	$(10^{-2} - 1)$
$skewness$	free	fixed at 1	free	non-existent	$(10^{-2} - 2)$

Two Monte Carlo experiments were performed, as detailed in **Table 6-2** [58]. The 1st Monte Carlo experiment attempted to compare the reduced models in the context of a “nominal” brain tumor ($F=50$, $v_p=10$, $PS=40$, $v_e=20$). 100 $C_{tiss}(t)$ curves were generated by GM with F , PS , v_p , and v_e fixed at their typical values for cerebral tumors. The values of RD and $skewness$ were randomly selected within their respective

physiological ranges. The 2nd Monte Carlo experiment attempted to compare the reduced models over a wider range of tissue types. 500 $C_{tiss}(t)$ curves corresponding to a wider range of microcirculatory states were generated. All the GM parameters were randomly selected from their respective physiological ranges.

Both Monte Carlo experiments were conducted under different levels of noise. An arterial input [as shown in **Figure 6-4(a)**] obtained from one actual patient case was used in generating $C_{tiss}(t)$ curves by GM. Fitting of each simulated $C_{tiss}(t)$ curve adopted the conventional model-fitting by repeating 10 times with initial values randomly selected within respective fitting ranges.

Table 6-2 Parameter details of the two Monte Carlo experiments.

Parameter	1 st Monte Carlo Experiment (100 GM curves)	2 nd Monte Carlo Experiment (500 GM curves)	Physiological Ranges
F (mL/min/100mL)	fixed at 50	randomly selected	(10 – 100)
v_p (mL/100mL)	fixed at 10	randomly selected	(1 – 20)
PS (mL/min/100mL)	fixed at 40	randomly selected	(0.01 – 80)
v_e (mL/100mL)	fixed at 20	randomly selected	(5 – 40)
RD	randomly selected	randomly selected	(0.1 – 0.5)
<i>skewness</i>	randomly selected	randomly selected	(0.2 – 1.5)

6.2.3 Monte Carlo Experiment Results

Results of the 1st Monte Carlo experiment are presented in **Table 6-3**, and some simulation examples are shown in **Figure 6-2**. With a noise level SNR=50, among the 100 simulated $C_{tiss}(t)$ curves with different values of RD and $skewness$, M1 is able to approximate the full model (aka GM) better than M2 in 80 simulation runs (an example is shown in **Figure 6-2(a)-(b)**), by generating lower SSR and hence cAIC. The other 20 cases in which M2 ranked better than M1 corresponds to the situations when the original value of RD in the GM is close to 0.3 (an example is shown in **Figure 6-2(c)-(d)**). Since M2 has a RD fixed at 0.3 and a variable $skewness$, such situations favor the fitting of M2 over M1, especially when the actual $skewness$ in the GM is far from the value of 1. However, for a general range of values of RD and $skewness$, M1 is found to be more adaptable than M2 in approximating GM.

M3 was not selected to be the best model at SNR=50. However, it overtakes M1 at SNR=10. An example of M3 selected as the best model at SNR=20 is shown in **Figure 6-2(e)-(f)**. At a less noisy condition with moderate or higher SNR level, parameters estimated by M3 tend to deviate more from the initial parameters of GM as compared with M1 and M2. This may be caused by the different curvature in the impulse residue function $R(t)$ of M3 with that of GM [**Figure 6-2 (b), (d) and (f)**]. However, the second term of the cAIC expression [Eq.(6.2a)] has partiality to a small number of free parameters, which can offset the ranking by SSR under noisy conditions.

Figure 6-2 Examples from the 1st Monte Carlo experiment. (a)-(b) M1 selected as the best model; (c)-(d) M2 selected as the best model; (e)-(f) M3 selected as the best model. In the legends of (b), (d) and (f), the units of the values stated within brackets for GM, M1 and M2 corresponds to (F mL/min/100mL, v_p mL/100mL, PS mL/min/100mL, v_e mL/100mL, RD and $skewness$) and the units for M3 corresponds to the first four parameters.

Table 6-3 Results of the 1st Monte Carlo experiment. The frequency of each model selected as the best model is stated as a percentage over 100 simulation runs.

SNR	Model	Frequency as Best Model (%)	Δ_m median (17 th , 83 rd percentile)	w_m median (17 th , 83 rd percentile)
50	M1	80	0.000 (0.000, 0.028)	0.582 (0.495, 0.760)
	M2	20	0.672 (0.000, 2.342)	0.416 (0.236, 0.503)
	M3	0	23.147 (11.024, 36.211)	0.000 (0.000, 0.002)
20	M1	63	0.000 (0.000, 0.870)	0.463 (0.288, 0.579)
	M2	11	0.585 (0.056, 2.155)	0.372 (0.216, 0.445)
	M3	26	2.916 (0.000, 10.047)	0.107 (0.004, 0.464)
10	M1	36	1.000 (0.000, 2.419)	0.278 (0.188, 0.494)
	M2	5	1.256 (0.328, 2.452)	0.261 (0.184, 0.367)
	M3	59	0.000 (0.000, 3.016)	0.458 (0.114, 0.628)

Table 6-4 Results of the 2nd Monte Carlo experiment. The frequency of each model selected as the best model is stated as a percentage over 500 simulation runs.

SNR	Model	Frequency as Best Model (%)	Δ_m median (17 th , 83 rd percentile)	w_m median (17 th , 83 rd percentile)
50	M1	64.2	0.000 (0.000, 0.325)	0.516 (0.380, 0.666)
	M2	20.6	0.470 (0.000, 2.609)	0.416 (0.186, 0.500)
	M3	15.2	19.600 (0.771, 52.450)	0.000 (0.000, 0.265)
20	M1	49.2	0.006 (0.000, 2.182)	0.425 (0.205, 0.549)
	M2	13.2	0.633 (0.055, 2.514)	0.335 (0.185, 0.472)
	M3	37.6	1.800 (0.000, 13.549)	0.175 (0.001, 0.606)
10	M1	32.6	1.040 (0.000, 2.512)	0.276 (0.183, 0.483)
	M2	5.4	1.356 (0.239, 2.566)	0.259 (0.178, 0.396)
	M3	62.0	0.000 (0.000, 3.259)	0.464 (0.097, 0.640)

Figure 6-3 An example of a simulation run from the 2nd Monte Carlo experiment which selected M3 as the best model at SNR=50.

Results from the 2nd Monte Carlo experiment are shown in **Table 6-4**. These simulations investigate a wider range of tissue parameters. It is shown under certain conditions, M3 can be ranked as the best model at SNR=50 (an example is shown in **Figure 6-3**). A small vascular volume v_p together with a high blood flow F results in a rapid tracer transit time (MTT), such that venous outflow occurs almost immediately and the initial plateau in the $R(t)$ of GM diminishes. Such an $R(t)$ of GM can be well approximated by M3. Results in both Monte Carlo experiments are consistent with the suggestion that M1 may be generally applicable for SNR>~20, while M3 may be preferred for tissue types with high flow and small vascular volumes. Due to the development of DCE imaging techniques, the SNR level of the acquired DCE imaging data has been largely improved. Thus M1 (the reduced IPCC model with *skewness* fixed) would have major applicability over M3 (which is the CC2 model) in most practical situations.

6.3 Clinical Applicability

As reported in the work [58], “informed consent was obtained from three patients with meningioma recruited in a DCE CT study. The patients were examined using a slip-ring, helical CT scanner (HiSpeed; GE Medical Systems) with the dynamic CT images obtained on a single section at the level of the largest tumor diameter identified on non-contrast CT scans. 50 enhancement images were acquired with a scanning interval of 1s and with the intravenous injection of 50 ml of non-ionic iodinated contrast medium (Omnipaque 300 mgI/ml) at a rate of 4 mL/s. Parameters for the CT scans were 80 kVp, 190 mAs, 512×512 matrix, 20-22 cm field of view and at 10 mm collimations.”

The CT images were processed on a personal computer. A 5×5 median filter kernel was applied to the DCE CT images to reduce noise. The ROIs of tumor and contralateral normal tissues were manually drawn. The AIF for each patient was sampled from a ROI over an artery. The voxel-level $C_{tiss}(t)$ curves corresponding to tumor and normal tissue were fitted using the selected reduced IPCC model. An adjustable delay was imposed considering the difference in bolus arrival time between $C_{tiss}(t)$ and $C_A(t)$. Conventional model-fitting was performed using a by MatlabTM.

6.3.1 Patient Studies

Examples of fitting M1 to voxel-level $C_{tiss}(t)$ curves for tumor tissue and normal tissue are shown in **Figure 6-4(a)**. The corresponding impulse residual responses scaled by blood flow $FR(t)$ are shown in **Figure 6-4(b)**. As $R(t)$ is a characteristic function of the tissue microcirculation system, it reflects the differences in properties between tumor and normal tissue. It is observed that the higher values of v_p , PS , and v_e in the tumor result in a broader $R(t)$ that approaches zero slowly, while $R(t)$ for the normal tissue is narrower and approaches zero faster.

An example of parameter maps generated by the reduced IPCC model M1 is shown in **Figure 6-5(a)**. It can be observed that the tumor exhibit increased values for all parameters as compared with the normal brain tissue. Tumor delimitation is more apparent on the parameters maps corresponding to the extravasation of tracers, namely PS and v_e . Histograms of various parameters are shown in **Figure 6-5(b)** to indicate that most parameters have remarkably different distributions for the tumor and normal tissues. To discover possible association or dependency of the additional parameter RD of the infinite-pathway models on the other parameters, scatter plots of the model

parameters with RD are given in **Figure 6-5(c)**. These scatter plots prove that RD is not correlated with the other parameters for either type of tissues [58].

Figure 6-4 (a) Voxel-level fittings of the reduced IPCC model (M1) to tracer $C_{tiss}(t)$ curves. (b) Corresponding impulse residue functions scaled by the respective flows.

(a)

Figure 6-5 (a) Parameter maps of a study case (Patient 1) depicting brain tissues. ROI drawn with the red and blue outline represents for tumor tissue and contralateral normal brain tissue, respectively. (b) Histograms of the parameters sampled from these ROIs. (c) Scatter plots to investigate correlation between RD and the other parameters.

Table 6-5 Statistics (median, mean $\pm$ SD) from ROI analysis of each parameter in the tumor/normal tissues of each study case.

	Patient 1		Patient 2		Patient 3	
	Tumor	Normal	Tumor	Normal	Tumor	Normal
F (mL/min/100mL)	38.8, 41.7 $\pm$ 14.7	22.6, 29.0 $\pm$ 23.3	27.7 32.7 $\pm$ 25.5	24.7, 28.7 $\pm$ 9.9	34.9, 43.1 $\pm$ 31.8	23.9, 30.5 $\pm$ 23.0
v_p (mL/100mL)	7.0, 7.4 $\pm$ 2.8	1.4, 1.5 $\pm$ 0.5	6.6, 6.9 $\pm$ 2.0	1.4, 1.5 $\pm$ 0.7	3.5, 3.5 $\pm$ 1.4	1.1, 1.3 $\pm$ 0.7
MTT (sec)	11.0, 10.9 $\pm$ 2.5	4.2, 4.6 $\pm$ 2.7	14.8, 14.9 $\pm$ 3.8	3.9, 3.7 $\pm$ 1.9	6.6, 6.7 $\pm$ 3.2	3.4, 3.4 $\pm$ 1.8
PS (mL/min/100mL)	37.9, 42.8 $\pm$ 20.4	1.4, 2.1 $\pm$ 2.8	45.8, 55.1 $\pm$ 34.6	1.1, 2.7 $\pm$ 5.4	16.1, 18.0 $\pm$ 14.3	0.8, 1.7 $\pm$ 3.0
v_e (mL/100mL)	17.8, 21.5 $\pm$ 20.8	0.0, 2.8 $\pm$ 10.3	9.6, 19.4 $\pm$ 25.0	0.0, 2.0 $\pm$ 8.4	4.3, 5.1 $\pm$ 6.2	0.1, 2.5 $\pm$ 10.6
RD	0.03, 0.12 $\pm$ 0.20	0.01, 0.07 $\pm$ 0.15	0.1, 0.18 $\pm$ 0.23	0.01, 0.11 $\pm$ 0.19	0.05, 0.13 $\pm$ 0.22	0.01 0.09 $\pm$ 0.17

Statistics of various parameters in the tumors and normal tissues for all the three patient cases are presented in **Table 6-5**. T-tests were conducted for comparison of parameter mean values between tumor and normal tissue in each study case. The p-values obtained are less than 0.01 for all parameters, denoting that all tumor parameters are significantly different from those in the normal tissue for each patient. Tumors are found to be generally associated with higher RD , indicating that the tumor vasculature exhibit a higher degree of blood flow variability than the normal tissues.

6.3.2 Voxel-level Application and Discussion

The present IPCC model formulated $R(t)$ with the integration of an infinite number of pathways. It reduced the complexity by replacing the DP2 model with a CC2 model in the capillary-tissue exchange unit of each pathway. On a personal computer (Intel® Core™ i7 Processor), MMID4 with $N=20$ [as the example in **Figure 3-7(a)**] takes about 81s to compute while the present IPCC model takes about 0.1s to generate a corresponding $R(t)$. Application of the present simplified model for analysis of DCE imaging data becomes feasible with the substantial reduction of processing time.

The Monte Carlo simulation results in Section 6.2.3 indicate that one should be cautioned to the use of the IPCC model under noisy conditions with $SNR \sim 10$, and for tissue types with high flow and small vascular volumes. However, although normal brain tissues generally have small vascular volumes, $R(t)$ can still exhibit a plateau [as shown in **Figure 6-4(b)**] because their blood flows are not exceedingly high. It may not be well-approximated by the CC2 model [85]. Normal tissues are usually less enhanced on DCE CT with lower SNRs of ~ 10 , and the tumors are associated with higher SNRs

>~20. Parameter estimations by the IPDP/IPCC model would be associated with much less error for the tumors tissues than normal.

Parameter maps generated by M1 [as shown in **Figure 6-5(a)**] and ROI analysis (**Table 6-5**) indicated higher values for blood flow F , vascular volume v_p , vascular MTT and permeability PS in the tumors than those in the normal tissues. It is consistent with the current understanding. The leaky tumor vasculature allows the tracer to access the tumor interstitial space (i.e. EES) and gives estimations of the fractional EES volume v_e . But the surrounding normal cerebral tissues obtain near-zero values for PS and v_e [as shown in **Figure 6-5(a)**]. This does not indicate that the actual EES volume of the normal tissue is zero, but that the EES is not assessable by the tracer due to the existence of intact BBB. The mapping of these parameters can therefore more clearly reveal the location and extent of the tumor. This is consistent with the findings of Roberts *et al.* [139].

6.4 Chapter Summary

In summary, a structure modification of the IPDP model was proposed to develop a simplified Infinite-Pathway Conventional Compartmental (IPCC) model. The IPCC model has substantial advantages in processing time. The IPCC model with five free parameters (in which *skewness* kept as constant) is shown to be more applicable in most practical DCE analysis cases. The model was used to generate perfusion parameter maps for patient cases to test for its clinical applicability. The parameter maps generated using the IPCC model delivered both spatial and functional information with sufficient clarity.

Chapter 7

Conclusions and Future Work

This thesis is focused on the investigation of tracer kinetic modeling for tumor microcirculation and dynamic contrast-enhanced based parametric assessment methods for tumor characterization, diagnosis and prognosis. Theoretical, numerical, and experimental techniques have been employed in the studies. Based on the studies in this thesis, main conclusions and future work are summarized as follows.

7.1 Conclusions

An Infinite-Pathways Distributed Parameter (IPDP) tracer kinetic model was developed based on the formulation of infinite pathways in the vasculature network to enable *in vivo* assessment of tumor blood flow variability by DCE imaging. It not only solves the discontinuity and normalization error issues encountered during the implantation of the existing multiple-pathway model into DCE data analysis, but also relieves its dependency on hardware performance. Comparing to the conventional

compartmental models or distributed parameter models, the IPDP model enables the estimation of one additional property of tumor, i.e. the distribution of blood flows within microvasculature.

To serve as an advanced model with more complete characterization to tumor and with better applicability in data-fitting, the proposed IPDP model was applied in simulation studies to evaluate the performance of empirical model-free methods. Interesting results pertaining to the clinical applicability of these metrics are therefore revealed. Based on the mathematical derivations and computer simulations, some model tissue enhancement metrics (such as time-to-peak TTP and peak value $C_{tiss,peak}$) are found to be unrelated to the tumor physiological conditions and some are found to be conditionally dependent (such as the maximal slope method). The normalized Initial Area Under Curve ($IAUC_{norm}$) provides an estimation of the total tracer distribution volume in the tissue, which can be alternatively estimated by a quick estimate on a single DCE scan by the ratio of the saturation values of $C_{tiss}(t)$ and $C_A(t)$.

A dual-phase model-fitting method was proposed to improve the accuracy, precision, and efficiency of parameter estimation with the use of tracer kinetic models. In particular, partial Sum of Squared Residuals (SSR) fitting was implemented into the proposed IPDP model to reduce the occurrence of undesired local minima and to improve the possibility of achieving approximately global minimum for the blood flow estimation. Successively, a conditional optimization was adopted to further restrict the fitting boundaries of blood flow and obtain more accurate and precise estimations to the rest microcirculation parameters. Monte Carlo experiments were designed and conducted to compare the proposed approach with the conventional fitting method on cerebral tissues. An algorithm was built based on the proposed IPDP model and the

dual-phase model-fitting approach. Numerical results show that the coefficient of variation of parameter estimation using the proposed approach is reduced by up to 83%. The estimation precision and reliability is subsequently improved. Furthermore, the proposed approach reduces excessive computation consumptions by achieving better estimation with less fitting repetitions. The proposed approach is applicable in blood flow dominated cases and could be implemented in existing tracer kinetic models for more accurate and stable parameter extraction.

A further improvement of computation efficiency was proposed by simplifying the structure of IPDP model. The resulting Infinite-Pathway Conventional Compartmental (IPCC) model is more suitable for practical use due to its reduced processing time. Using this simplified model, voxel-level fitting of tissue concentration-time curves $C_{tiss}(t)$ becomes computationally feasible. Clinical parameter maps of tumor microcirculation can also be generated to provide both spatial and functional information with sufficient clarity. The IPCC model is better applicable in most practical situations (where SNRs of DCE data are at a moderate or high level) than the standard two-compartment model.

Experiment results show that the proposed IPDP and IPCC models can be applied on actual DCE CT datasets and to estimate the blood flow heterogeneity. Clinical studies using the proposed IPDP model reveal a higher variability in tumor blood flow distribution than the normal tissues. Consequently, the IPDP and IPCC models can potentially allow for a more complete characterization of the tumor vasculature based on DCE imaging.

In summary, the work reported in this thesis includes innovative tracer kinetic models, modeling approach and algorithm for the characterization and diagnosis of

cerebral tumor. Based on the proposed IPDP/IPCC model and the dual-phase model-fitting approach, an algorithm was developed with good precision and high efficiency for the tracer kinetic modeling/simulation and applications. The application of these proposed models/methods/algorithm can potentially reduce misdiagnosis of cerebral tumor and speed up DCE data analysis with a high precision.

7.2 Future Work

Further studies can be pursued in the following directions.

It is recommended to incorporate the IPDP/IPCC model with specific tissue/organ features to extend its applicability. For example, liver with dual arterial inputs requires specific model design. By incorporating the infinite-pathway model, blood flow heterogeneity for these specific organs can be estimated using DCE data.

Another potential direction of future work is to develop multiple-phase model-fitting methods based on the framework of the proposed dual-phase model-fitting method. It would be of interest to further push the optimization result towards the global minima.

One can also have a comparative assessment of the infinite-pathway model incorporating every existing single-pathway tracer kinetic models. The comparison is recommended to be focused on degrees of complexity and physiological realism, as well as interrelationship between each other. This will lead to a better utilization of the existing tracer kinetic models and more variants of existing models can be developed for special applications.

List of Publications

- [1] S. Hartono, C. H. Thng, Q. S. Ng, C. X. Yong, C. T. Yang, W. Shi, *et al.*, *High Temporal Resolution Dynamic Contrast-Enhanced MRI at 7 Tesla: A Feasibility Study with Mouse Liver Model*. 2011 Annual International Conference of the IEEE Engineering in Medicine and Biology Society. 2011. 2788-2791.
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- [3] W. Shi, T. S. Koh, C. H. Thng, L. H. D. Cheong, and C. C. T. Lim, *Accounting for blood flow heterogeneity in cerebral tumors: A perfusion CT study*. in *World Congress on Medical Physics and Biomedical Engineering*. 2012. Beijing, China: Springer Verlag.
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List of Publications

- [6] W. Shi, W. Ser, and T. S. Koh, *Multiple-Pathway Tracer Kinetic Models of Blood Flow: Issues with a discrete number of pathways*. in *13th Annual World Pharma Congress*, Boston, U.S., 2014.
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