Non-invasive assessment of renal function by dynamic imaging

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Non-invasive Assessment of Renal Function by Dynamic Imaging

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A thesis submitted to Nanyang Technological University in the fulfillment of the
requirement for the degree of Doctor of Philosophy

2007

Statement of Originality

I hereby certify that the work embodied in this thesis is the results of original research done by me and has not been submitted for a higher degree to any other universities or institutes.

Date

Zhang Lei

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Summary

Kidneys are important but vulnerable organs in the human body. In this thesis, the thesis focuses on the study of assessing renal function by dynamic imaging.

Dynamic renal scintigraphy is a well-established imaging technique for renal-function evaluation. To analyze the scintigraphic images by parametric deconvolution (also termed as model fitting), some models of renal impulse retention function (IRF) were proposed and improved. A novel biphasic model-fitting approach based on renal physiology was proposed as well. With the improved IRF model (termed as Fine's model with vascular delay) and biphasic fitting approach, renal vascular and parenchyma parameters can be simultaneously and reliably identified. Many of these parameters are indicative of some renal pathologies and functional status.

Dynamic contrast-enhanced magnetic resonance imaging (DCE MRI) has emerged in recent years as a promising tool for functional renography, because of the more detailed morphologic information provided and no use of radioactive tracer. Quantitative analysis of dynamic MRI images requires accurate estimation of contrast-medium concentration from the images. For a commonly-used MR sequence, properly selecting some image-acquisition parameters, such as flip angle, helps improve the accuracy of estimated concentration. A numerical optimization method was proposed to find the optimal flip-angle values, and an optimal image-acquisition protocol was finally determined. Moreover, some features observed in the optimal numerical solution were proved mathematically, and an analytical expression was derived.

Finally, model fitting using Fine's model with vascular delay was applied to analyze kidney data collected by DCE MRI. Most parameter estimates were generally in

agreement with their respective reference values in literature. Absolute quantification of renal perfusion-related parameters from DCE MRI requires further increase of temporal resolution in imaging, and more accurate determination of relaxivity in human renal parenchyma. As a comparison, a conventional analysis method was applied for the same set of data. Model fitting and the conventional method provided comparable renal perfusion parameter estimates, and comparable filtration-function parameters as well. The additional parameters by model fitting can be regarded as an advantage.

In conclusion, biphasic model fitting using Fine's model with vascular delay is capable of identifying multiple clinically-useful parameters from renal scintigraphic data. For DCE MRI data, model fitting using the improved model performs similarly to a conventional approach in identifying renal filtration and perfusion parameters. DCE MRI combined with model fitting has the potential to provide reliable renal functional information for clinical use. Finally, recommendations for future work are suggested for improving the role of dynamic imaging in non-invasive assessment of renal function.

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List of Abbreviations and Symbols

AUC	Area under curve
CLSR	Constrained least-squares restoration
CM	Correlation matrix
Cr ⁵¹ -EDTA	Ethylenediaminetetraacetic acid labeled with Chromium 51
CT	Computed tomography
CT-KUB	Computed tomography of kidneys, ureters and bladder
CV	Coefficient of variance
DCE MRI	Dynamic contrast-enhanced magnetic resonance imaging
DTPA	Diethylene triamine pentaacetic acid
FLASH	Spoiled fast low angle shot
FOV	Field of view
GA	Genetic algorithm
Gd	Gadolinium
GFR	Glomerular filtration rate
G.func	Good function
G.perf	Good perfusion
IR	Inversion recovery
IRF	Impulse retention function
IVU	Intravenous urography
K/A	Kidney-aorta ratio
LV	Left ventricle
MAG3	Mercaptoacetylglycine
MinTT _b	Minimal vascular transit time
MinTT _p	Minimal parenchymal transit time
MR	Magnetic resonance
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging

MTT _b	Vascular mean transit time
MTT _p	Parenchyma mean transit time
NF	T_1 noise factor
NMR	Nuclear magnetic resonance
Obs.	Obstruction
PCL	Piecewise continuous linear
P.func	Poor function
PI	Perfusion index
RF	Radiofrequency
ROI	Region of interest
RVH	Renovascular hypertension
SD	Standard deviation
SNF	Summed version of T_1 noise factor
SNR	Signal-noise ratio
SPGR	Spoiled gradient recalled echo
SR	Saturation recovery
SSFP	Steady-state free precession
SSR	Sum of squared residue
SVD	Singular value decomposition
Tc ^{99m}	Technetium-99m
TAC	Time-activity curve
TTP	Time to peak
TTS	Transit time spectrum
α	Flip angle
B_0	Magnitude of external magnetic field
$\vec{B}_0$	External magnetic field
$\vec{B}_1$	Weak magnetic field induced by radio-frequency pulse
C	Tracer concentration

cm	Centimeter
E	Extraction rate
f	Filtration fraction
F	Renal blood flow
H	Cumulative outflow function of whole renal system
h_b	Cumulative outflow due to the vascular phase
Hct	Hematocrit
h_p	Cumulative outflow due to the parenchymal phase
I	Input curve
K	Kidney retention curve
L	Liter
M_0	Equilibrium magnetization
min	Minute
ml	Milliliter
mm	Millimeter
mM	Milli-mole per liter, a unit of concentration
ms	Millisecond
M_0	Equilibrium magnetization
$\vec{M}$	Bulk magnetization vector
MBq	Megabecquerel, unit of radioactivity
N_{acq}	Number of signal averages
N_{enc}	Number of encoding (for coverage of k space)
nm	Nanometer
P	Parenchyma-parameter set $\{f, MinTT_p, MTT_p\}$
r	Relaxivity
R	Impulse retention function
R_1	Relaxation rate
R_1^0	Pre-contrast relaxation rate
R_1^c	Post-contrast relaxation rate

R_{Norm}	Normal impulse retention function
R_{RVH}	Renovascular-hypertension impulse retention function
R_{Obs}	Obstructive impulse retention function
R_{PCL}	Piecewise-continuous linear model
R_{Fine}	Fine's model
$R_{\text{Fine,d}}$	Fine's model with vascular delay
s	Second, unit of time
S	Signal intensity
S_{Ern}	Signal intensity at Ernst angle
t	Time
T	Tesla
T_1	Longitudinal relaxation time
T_1^0	Longitudinal relaxation time without contrast
T_1^c	Longitudinal relaxation time with contrast
T_2	Transverse relaxation time
T_{acq}	Acquisition time for one image
TI	Inversion time
T_R	Repetition time
T_E	Echo time
V	Vascular-parameter set $\{F, \text{MinTT}_b, \text{MTT}_b\}$
$\vec{\mu}$	Magnetic moment
ω_0	Larmor frequency
ω_{rf}	Rotation frequency of $\vec{B}_1$
γ	Gyromagnetic ratio

Chapter 1

Introduction

1.1 Motivation

The kidneys are important organs in the human body. The main function of the kidneys is to remove end products of metabolism and excess fluids from blood. The kidneys also play an important role in maintaining acid-base balance and producing several hormones [1]. For example, one hormone produced by kidney stimulates the production of red blood cells, while others help regulate blood pressure or calcium metabolism. Normal function of the kidneys is very important for the overall physical well-being of the human body. However, because of the vulnerability of the kidneys, kidney diseases have developed into a new and worldwide threat. According to National Kidney Foundation of United States, more than 20 million people in the United States (~12%) suffer from chronic kidney diseases. In Singapore, about 500 patients are diagnosed as end-stage kidney failure every year [2]. Around the world, more than 1 million people are living on renal dialysis [3]. The incidence and prevalence of kidney failure have doubled in the last 15 years and are expected to continue to increase [3].

The cause of kidney diseases, especially the chronic ones, is complicated. Non-healthy diet [4], obesity [5] and smoking [6] [7] [8] may increase the occurrence of kidney diseases. Current clinical studies have also indicated that diabetes and hypertension are among the pathologic causes [9] [10] [11]. Moreover, a fraction of newborn babies suffer from congenital kidney diseases, such as primary defects in renal parenchyma and hydronephrosis. Nearly all kidney diseases are accompanied with damage of the functional unit of the kidney, the nephron, which performs filtration of blood. Each normal kidney of human contains about 1 million nephrons from birth, and new ones do not form if some are injured [1]. Once some of the nephrons are damaged, the remaining ones will adapt to handle a larger-than-normal filtration load (up to 4 times of normal load), which may initiate the progression of kidney function loss without significant signs and finally result in kidney failure [1]. Increasing evidence shows that timely detection and treatment at an early stage can prevent or delay the progressive functional loss [12]. Hence, it is desirable to assess renal function timely and reliably, especially for those patients with diabetes or hypertension.

1.2 Brief Background

1.2.1 Non-imaging Approaches

Generally speaking, the approaches for assessing renal function can be classified into two groups: plasma-clearance techniques and dynamic imaging methods. Clearance techniques involve intravenous injection or infusion of a physiologically-inert substance, which is normally eliminated by kidneys, and subsequent measurement of its clearance

rate from blood plasma. The clearance rate of this substance can indicate the overall functional status of the two kidneys. Representative examples are inulin clearance technique [13] and Cr^{51} -EDTA clearance technique [14] [15] [16]. Inulin clearance technique usually requires continuous intravenous infusion and urine collection, to determine the clearance rate. For some patients with renal obstruction or incomplete-emptying problem, bladder catheterization (insertion of a catheter into a patient's bladder, to drain urine out of bladder) may be necessary. Single-injection Cr^{51} -EDTA clearance technique requires serial blood samplings to monitor the residue concentration in blood. Conventionally, the interval between adjacent blood samplings is several minutes, and the whole examination may take 3~4 hours [17]. To reduce the inconvenience caused for patients, single-sampling technique, which requires only one blood sampling, has been proposed [18] [19], but systematic errors may occur for some very low or high clearance rates [20] [21]. Moreover, no matter for single or multiple-sampling techniques, the time points for blood sampling are chosen empirically, which may cause some indeterminacy.

1.2.2 Dynamic Renal Imaging

Dynamic renal imaging, also termed as dynamic renography, primarily aims to assess renal function non-invasively. Similar to the plasma-clearance techniques, a physiologically-inert substance, called a tracer, is injected intravenously prior to renal imaging, while the difference is that an external imaging device, rather than blood sampling, is used in dynamic renal imaging. Using an imaging device, sequential images with kidneys in the field of view are recorded, within a time interval. Via the dynamic imaging, tracer retention within kidney region of interest (ROI) is monitored as a function of time. Renal uptake and excretion of the tracer can thus be studied by analyzing these

dynamic images, revealing useful information on renal function and possible pathologies. Compared with the plasma-clearance techniques, dynamic renal imaging is more efficient and versatile. Normally, such an imaging examination takes only about 30 minutes. With imaging, function of a single kidney can be evaluated, and useful information can be provided for some unilateral-kidney diseases, such as renal cell carcinoma (one kind of cancer) and renal obstruction [22] [23] [24] [25]. Moreover, morphologic information of urinary system (kidneys, ureters and bladder) can be obtained from the images.

Dynamic renography can be implemented by various imaging modalities, such as renal scintigraphy and magnetic resonance imaging (MRI). Among these modalities, dynamic renal scintigraphy is the most commonly used and also the most well-established one till now [26]. As compared with other modalities, dynamic renal scintigraphy offers images of high temporal resolution, which is important for functional imaging. Besides, the low-cost feature makes renal scintigraphy widely adopted for routine clinical use. Dynamic contrast-enhanced magnetic resonance imaging (DCE MRI) for dynamic renography has attracted much attention in recent years [27] [28]. The temporal resolution of DCE MRI has been increased substantially as a result of the advance in MR hardware and the appearance of various fast MR sequences. Compared with renal scintigraphy, DCE MRI does not employ radioactive tracer, and offers images of much higher spatial resolution. MR images of high spatial resolution provide more detailed morphologic information. In some situations, morphologic features alone, such as kidney enlargement and renal pelvis (the inner cavity for collecting urine) enlargement, can be indicative of some renal

diseases [29] [30]. Combination of both functional and morphologic information of kidney improves the confidence of medical doctors in making a diagnosis.

1.2.3 Analysis of Dynamic Images

Many approaches have been proposed for analyzing dynamic renal scintigraphic images. For the analysis, a renogram is first generated from the dynamic scintigraphic images. A region of interest (ROI) is defined over renal parenchyma or the whole kidney in every image, and summing up or averaging intra-ROI pixel values (proportional to tracer concentration) results in tracer residue within the ROI at the corresponding time. The resultant retention-vs.-time curve is termed as a renogram. As we can see, a renogram describes the tracer retention in kidney as time goes on. Compared with the large data set of dynamic images, renogram characterizes the uptake and excretion of tracer by a kidney, in a much conciser form.

Analysis of renogram has been the main approach for extracting information from dynamic renal scintigraphic images since 1970's [31] [32] [33]. Some conventional methods identify some simple parameters, such as the area-under-curve parameters [34], from renogram alone. Because renogram contains information on both the kidney and its arterial input, the identified parameters, which are ideally indicative of renal function, will be inevitably affected by the arterial input. This potential problem makes it difficult to compare parameter estimates between different patients or even different studies of the same patient. For this reason, most investigators prefer to include an input curve in analyzing renogram, with the aim of eliminating arterial-input information from the estimated parameters. A representative example is deconvolution analysis, by which renal

impulse retention function (IRF) is obtained. The parameters identified from renal IRF include perfusion indices [35] [36] and various transit times [37]. Many parameters thus estimated have been shown to be indicative of various renal pathologic conditions [38].

Compared with renal scintigraphy, it is more complicated to generate a renogram from dynamic images of DCE MRI. Different from renal scintigraphy, the intensity of MR signal (S) depends on several parameters, and the relationship between S and tracer concentration (C) or mass is nonlinear for most MR sequences. Hence, to generate renogram, it is necessary to first construct reliable tracer- C maps according to MR images. For some MR sequences usually used for dynamic imaging, such as spoiled gradient recalled echo (SPGR), it is challenging work to reliably estimate tracer concentration from dynamic MR images.

1.3 Objectives

The primary objective of this thesis is to maximally extract reliable and clinically-useful information from dynamic renographic images (both renal scintigraphy and DCE MRI), for renal functional assessment and pathologic diagnosis. There are at least 2 aspects that we can endeavor to improve: (1) quantitative analysis of renogram (based on renal scintigraphy); (2) reliable quantification of tracer concentration from DCE-MR images, and then verification of the feasibility of DCE MRI in non-invasive assessment of renal function.

In this thesis, we focus on the quantitative analysis of renogram using parametric deconvolution (also termed as model fitting). In parametric deconvolution, parameters of renal IRF model are adjusted to fit the convolution of input curve and renal IRF to the measured renogram. The advantage of parametric deconvolution over non-parametric approach lie in the fact that the noise-sensitive problem associated with deconvolution is circumvented, and physiologic parameters can be identified directly. Besides, one can design appropriate renal IRF models, for different applications. The following issues need to be addressed.

- It would be desirable that renal IRF models of different complexities are available for use in different situations. In some situations when renogram is of low temporal resolution or the parameters to be identified are stable, a simple model would be enough; when facing renogram of high temporal resolution or high signal-noise ratio, a more composite IRF model would be necessary to extract more useful information.
- The performance of model-fitting methods affects the accuracy of identified parameter estimates. As observed in a preliminary study, conventional model fitting does not perform very well in analyzing scintigraphic renograms obtained by common protocols. To maximally and reliably extract useful information from renogram, a new model-fitting method should be designed.

Quantitative renal study using DCE MRI requires first converting dynamic MR image to dynamic concentration maps. For one routinely-used MRI sequence, SPGR, it has been found that selecting flip angles (a parameter for MR acquisition) properly in acquisition of pre- and post-contrast images has the effect of minimizing the noise propagation from

MR signal to longitudinal relaxation time (T_1), and thus to concentration (C) (as will be introduced in Chapter 2, C is related to difference of pre- and post-contrast T_1).

- A method for flip-angle optimization is needed to select appropriate flip angles for acquiring pre- and post-contrast images. It would be desirable that the method is flexible enough in producing flip angles appropriate for imaging various tissues of interest.
- In previous studies, some interesting phenomena were observed in numerical flip-angle optimization. Mathematical proof for these phenomena may gain us deeper understanding on the mechanism of noise propagation from MR signal to concentration.

With a reliable renogram generated from DCE-MR images, it would be necessary to verify the feasibility of DCE MRI for renal functional assessment, by analyzing its renogram using methods previously proposed based on renal scintigraphy.

1.4 Major Contributions

The major contributions of this thesis are listed as follows:

- A simple model for renal IRF, named as piecewise continuous linear model, was proposed. This model is useful in rapid determination of parenchyma mean transit time, which shows great value in diagnosis of renal obstruction and renovascular hypertension. A previous nonlinear model of renal IRF was improved, with the aim of characterizing the renal vascular phase more realistically. The vascular parameters thus identified are indicative of various renovascular pathologies.

- A novel model-fitting method was proposed to deal with dynamic scintigraphic images of non-uniform time interval. Using the fitting method and the improved IRF model above-mentioned, renal vascular and parenchyma parameters can be simultaneously identified. The vascular parameters thus estimated were shown to be more accurate than those by previous methods.
- For renography using DCE-MRI SPGR, a numerical method for flip-angle optimization was proposed. The method can be applied to DCE-MR SPGR imaging of all organs or tumors, not simply MR renography. In this thesis, its greater potential in MR imaging of breast tumor is shown. Some interesting properties observed in numerical flip-angle optimization were proved mathematically. With the assistance of some of the properties, the analytic expression for the optimal flip angles was derived for the first time. Based on the analytic expression, one set of flip angles was proposed for image acquisition, for more balanced estimation accuracy across a T_1 range.
- DCE-MRI kidney data were analyzed by model fitting using the improved IRF model. The various parameters identified were generally in agreement with their respective reference values in literature. This validated the feasibility of DCE MRI and complex model fitting for renal functional evaluation.

1.5 Organization of the Thesis

The rest of the thesis is organized into the additional 7 chapters. Chapter 2 gives background knowledge on kidney, renal scintigraphy and DCE MRI, after which is the literature review on the methods for renogram analysis and flip-angle optimization.

Chapter 3 presents the proposed and improved models for renal IRF. Chapter 4 describes a novel model-fitting method: biphasic model fitting. In Monte Carlo simulations and patient studies, the proposed method was compared with conventional model fitting and previous indices. Chapter 5 presents a numerical flip-angle optimization method and its validation by Monte Carlo simulation. Chapter 6 presents mathematical proof for some interesting properties of numerical solution for optimal flip angles, and further derives an analytic solution for optimal flip angle. One set of flip angles was proposed for estimating T_1 within a range with more balanced accuracy. Chapter 7 illustrates quantitative analysis of DCE-MRI kidney data. A comparison was made between model fitting and a conventional approach. Chapter 8 concludes the thesis, and recommendations for future work are highlighted.

Chapter 2

Background and Literature Review

2.1 Background

In this section, background knowledge on the kidneys and two dynamic imaging techniques: renal scintigraphy and DCE MRI is presented. Brief introduction of kidney will mainly focus on blood perfusion and filtration within kidney, which is the physiologic basis for modelling. With regard to the two imaging techniques, emphasis will be put on how the images are formed, and how the image intensity relates to tracer concentration. For quantitative analysis of organ function using tracer kinetic techniques, quantification of tracer concentration from the dynamic images is an important prelude.

2.1.1 Renal Anatomy and Physiology

1. Location and Structure

The two kidneys are located on different sides of the vertebral column, high in the abdominal cavity: from the level of twelfth thoracic (the middle segment of the vertebral

column) to the third lumbar vertebrae (under the thoracic vertebrae). The right kidney is usually lower than the left one, because large space in the right side of abdominal cavity is occupied by liver, which is over the right kidney. Each kidney is bean-shaped, and for an adult, is about 11cm long, 6cm wide and 5cm thick.

Tissue part of each kidney (Figure 2-1), termed as renal parenchyma, is generally divided into 2 layers: medulla and cortex. Renal cortex, the outer layer, is where the filtration of blood occurs. Surrounded by renal cortex, renal medulla contains 8~15 renal pyramids (conical structure), which are separated from each other by renal columns. The indented surface (on the medulla side) of each kidney is penetrated by renal artery, renal vein and ureter. Renal artery and vein transport blood in and out of kidney, respectively, and ureter carries urine (filtrate from blood) out into the bladder [1].

2. Vascular Distribution

Kidney receives blood from renal artery, an immediate branch from abdominal aorta. Through renal artery, each kidney receives 10-12% of the cardiac output (5000~6000 ml/min for adult). Hence, blood flow through renal artery is about 600 ml/min [1].

Renal arterial blood is distributed to renal cortex through a well-organized multi-branch vascular capillary network. Renal artery divides into several segmental arteries. Interlobar arteries, which are branches of segmental artery, go through the renal columns. At the end of renal column, the interlobar arteries arch along the border between the renal medulla and cortex, and here they are known as the arcuate arteries. Branches of the

arcuate arteries, called interlobular arteries, penetrate into the renal cortex, and give off the final branches called afferent arterioles. Through an afferent arteriole, blood enters a nephron, the filtration unit of kidney which is located in the renal cortex.

Figure 2-1 Frontal section of kidney across a medial plane

3. Blood Filtration, Re-absorption and Secretion

Every kidney has about 1 million nephrons, each of which is fed by an afferent arteriole. A schematic diagram of a nephron is shown in Figure 2-2. Afferent arteriole divides into a tangled, ball-shaped capillary network called the glomerulus. The glomerulus is

surrounded by glomerular capsule (also called Bowman's capsule). As blood in afferent arteriole enters the glomerulus, a fraction of blood plasma, which contains water, some nutrient and waste products, is filtered into glomerular capsule (*filtration process*), while the remainder goes through the efferent arteriole (out of glomerular capsule) and into peri-tubular capillaries. Now there are two parallel pathways: the tubule extended from glomerular capsule, and peri-tubular capillaries entwining the tubule. As the filtered fluid flows along the tubule, most water and useful solutes are re-absorbed by the tubule cells and returned to the blood in the peri-tubular capillaries (*re-absorption process*). On the other hand, as blood flows along peri-tubular capillaries, some unfiltered wastes are secreted from the blood and into the tubule (*secretion process*). After re-absorption and secretion between tubule and peri-tubular capillaries, the 'clean' blood flows through various kinds of vein, and finally exits kidney via renal vein. Urine containing waste takes a much longer time to flow down through collecting duct, renal pelvis and finally ureter. Blood filtration, re-absorption and secretion are the main processes of nephrons. By these processes, kidneys clear harmful substances out of blood, while keeping nutrient and most of water.

Glomerular filtration is a very important aspect of renal function. More details on glomerular filtration will be given as follows. The filtration membrane is formed by endothelial cells of glomerular capillaries and podocytes that encircle the capillaries. Through this membrane, the substances with diameter less than 7 nm (plasma and some solutes) are permitted to be filtered into glomerular capsule, while blood cells (diameter: 6000~20000 nm), platelets (diameter: 2000~3000 nm) and proteins in blood (diameter $\geq$

7.1 nm) remain unfiltered. Impairment of filtration membranes may lead to appearance of blood cells or proteins in urine, which is clinically termed as hematuria and glomerular proteinuria, respectively. Glomerular filtration rate (GFR), the volume of filtrate into glomerular capsule per unit of time, is controlled by the pressure difference between the two sides of the membrane (net pressure that promotes filtration). In a normal kidney, the net pressure is about 10 mmHg. Many factors, such as severe blood loss, renal artery stenosis, or afferent-arteriole vasoconstriction stimulated by neural regulation, can cause the fluctuation of net filtration pressure, and thereby GFR. In clinical practice, GFR is regarded as the main index of renal function.

Figure 2-2 The functional unit of kidney: nephron. Some water and waste products are filtered from glomerulus into glomerular capsule, while the remainder flows into peritubular capillary. Re-absorption and secretion occur between tubule and peritubular capillary, to retrieve filtered water into blood and remove unfiltered waste out of blood.

2.1.2 Renal Scintigraphy

Renal scintigraphy, also termed as radioisotope or radionuclide renography, was first introduced by Taplin et al [39] in 1956. Over the last 50 years, renal scintigraphy has

developed constantly and, because of its simplicity and reliability, has been adopted as the main tool for non-invasive evaluation of renal function. Although a more advanced imaging technique, such as MRI, provides more detailed morphologic information, the major role of renal scintigraphy for functional evaluation has not been fully replaced.

1. Imaging Mechanism

As a nuclear medicine imaging technique, renal scintigraphy forms images based on the emission of gamma radiation from a radiopharmaceutical, which is usually administered intravenously. The radiopharmaceutical is some compound that is labelled with radionuclide (an atom with unstable nucleus), and is excreted by the kidneys. The most common radionuclide used for renal scintigraphy is technetium-99m ($\text{Tc}^{99\text{m}}$, 'm' denotes metastable state). The decay of $\text{Tc}^{99\text{m}}$ to lower-energy Tc^{99} is accompanied with the emission of gamma ray. With an imaging device, called gamma camera, positioned behind the patient, some of emitted gamma rays are detected and counted.

Gamma camera (Figure 2-3) usually has two components: collimator and crystal scintillator. For a cluster of $\text{Tc}^{99\text{m}}$ -labelled radiopharmaceutical within body, gamma rays are emitted in all directions. Only those rays emitted perpendicularly to gamma camera manage to go through the entries of collimator. Each entry corresponds to a pixel in image. The gamma rays reaching crystal scintillator from an entry are counted for a predefined time interval. The count number is proportional to the image intensity of the corresponding pixel in the formed image. Because of the imaging mechanism, any $\text{Tc}^{99\text{m}}$ 'facing' the collimator entry may contribute to the count number, while its distance to

gamma camera does not matter. Hence, renal scintigraphy is a 2-dimensional imaging technique, by projecting 3D objects into 2D image.

Figure 2-3 Gamma-ray detection by gamma camera with parallel-hole collimator. Only gamma rays perpendicularly emitted to collimator reach crystal scintillator. Gamma rays arrived through every entry of collimator are counted for a predefined time interval. The count number is proportional to the intensity of the corresponding pixel of the formed image.

One important feature of renal scintigraphy is that the intensity (S) of scintigraphic image is proportional to the quantity of the radiopharmaceutical at the corresponding location. This feature is explained briefly as follows. According to the principle of radioactive decay, the emission of gamma ray from a single radioactive nucleus, or decay, is random, i.e. its occurrence is equally likely at any time. Therefore, for a cluster of radioactive nuclei, the number of decay within a short time interval (dN/dt , termed as activity) is proportional to the number of the nuclei (N). The proportionality constant in between is called decay constant. That is to say, the following relation is valid, $S \propto \frac{dN}{dt} \propto N$.

As will be introduced in later sections, this feature makes quantitative analysis of scintigraphic images very convenient.

The commonly used $\text{Tc}^{99\text{m}}$ -labeled tracers for renal scintigraphy include $\text{Tc}^{99\text{m}}$ -diethylenetriamine pentaacetic acid ($\text{Tc}^{99\text{m}}$ -DTPA) [37] [40] [41] and $\text{Tc}^{99\text{m}}$ -mercaptoacetyltriglycine ($\text{Tc}^{99\text{m}}$ -MAG3) [42] [43]. These two tracers are for evaluating different aspects of renal function. Recall that nephrons clear the blood by three processes: glomerular filtration, tubular re-absorption and secretion. $\text{Tc}^{99\text{m}}$ -DTPA is cleared through glomerular filtration. In every single pass, 20% of blood plasma with $\text{Tc}^{99\text{m}}$ -DTPA is filtered in a normal kidney. Because $\text{Tc}^{99\text{m}}$ -DTPA is not re-absorbed or secreted [44], it is one of the most commonly used tracers for evaluating renal filtration function. Note that 5% of $\text{Tc}^{99\text{m}}$ -DTPA is bound to protein in blood, thus underestimating GFR slightly. $\text{Tc}^{99\text{m}}$ -MAG3, which is highly protein-bound, is excreted by active transport through tubular secretion [45] [46].

2. An Established Protocol

In image acquisition, the patient is usually supine and the gamma camera is underneath his/her back. The following established protocol for imaging is usually used for $\text{Tc}^{99\text{m}}$ -DTPA study [47]. Before tracer injection, a tourniquet is applied to one arm of the patient. $\text{Tc}^{99\text{m}}$ -DTPA at a dose of 500 MBq (volume 0.5~1 ml) is injected manually as a bolus into a vein located at the forearm. Immediately after tracer injection is a 20ml saline flush, during which the tourniquet is released and the arm is lifted to ensure a compact bolus into the heart. The injection and saline flush process is done by a well-trained operator,

which takes a time of 5-10 s. The imaging began immediately after the injection of $\text{Tc}^{99\text{m}}$ -DTPA by a gamma camera at 1 second per frame for the initial 1 minute, followed by 10-second frames for 15 minutes. Every image is recorded in a 128×128 matrix, and both kidneys and heart are included. The initial 1s-interval frames are acquired for studying blood perfusion, also called perfusion imaging or first-pass study. Example of dynamic images is shown in Figure 2-4, together with a contour of kidney.

Figure 2-4 Dynamic renal scintigraphic images. The images are recorded sequentially as time goes on. For its analysis, contour of every kidney (the green line) is usually drawn in the images to define a kidney region of interest (ROI).

3. Post-processing

Dynamic images acquired in renal scintigraphy are usually analyzed by region-of-interest (ROI) approach. ROI is defined on whole kidney or renal parenchyma. In every image,

intensities of pixels within the ROI are summed up to be the tracer retention within kidney at the time of acquiring the image. From a whole set of dynamic images, a tracer retention vs. time curve can be generated, which is usually called a renogram. An example of a renogram is shown in Figure 2-5. Conventionally, a renogram is described with 3 phases [48]: vascular phase, secretory phase, and excretory phase. The vascular phase is the initial sharp peak in the 10s-interval renogram. In the initial short period, the tracer bolus enters kidney and is taken up by kidney. The secretory phase (1-3 minutes) reflects tracer passage and accumulation in tubules and collecting duct. In the 10s-interval renogram, secretory phase is represented by the increasing part before the main peak. After about 3 minutes is the excretory phase, during which the filtered tracer in urine begins to exit from renal pelvis and the renogram decreases. The analysis of renogram reveals information on the status of kidney.

Figure 2-5 A typical renogram of 10s-interval. Every data point represents the tracer residue within kidney or parenchyma at the associated frame or time.

2.1.3 Magnetic Resonance Imaging (MRI)

MRI is based on the well-known nuclear magnetic resonance (NMR) phenomenon, first observed independently by Felix Bloch [49] and Edward Purcell in 1946. In 1973, Paul Lauterbur produced the first MR images by spatially encoding the NMR signals [50]. From the crude beginning, the development of clinical MRI has been tremendously rapid. By 1980's, improvements in MR hardware and software had resulted in whole body imaging systems that were capable of producing high contrast images with spatial resolution of less than 1 mm.

1. NMR Phenomenon

Physically, any nuclei with odd atomic number, such as ^1H , ^{13}C and ^{19}F , can produce NMR phenomenon. For clinical imaging, ^1H nucleus, i.e. proton, is of interest uniquely because of its natural abundance in human body. In the following, the description will be limited to proton NMR.

Hydrogen atom, which has odd atomic number, possesses an angular momentum, often called spin. Like any spinning charged object, spinning of a charged nucleus induces a magnetic field with an axis coincident with the axis of spin, called magnetic moment ($\vec{\mu}$) (Figure 2-6). Due to thermal random motion, the magnetic moment orients in random direction in the absence of an external magnetic field. Macroscopically, for an object with a large number of protons, bulk magnetization vector $\vec{M}$, which is the vector sum of all the proton magnetic moments, is zero. In the presence of external magnetic field ($\vec{B}_0$, assuming it is in z direction of the stationary xyz frame), these random-oriented magnetic

moments tend to assume 2 discrete orientations or states, spin-up state and spin-down state. As there is an excess of a very small fraction of spins in the lower-energy state, a non-zero $\vec{M}$ comes into being. The magnitude of $\vec{M}$ is mainly dependent on 2 parameters: the external magnetic field strength B_0 and the temperature of spin system. For $B_0=1$ tesla, and at room temperature (300 Kelvin), the fraction of excess low-energy-state spins is about 3/1000000. In other words, only 3 out of 1 million spins are activated in such conditions [55].

Although, in presence of $\vec{B}_0$, the macroscopic $\vec{M}$ is aligned to $\vec{B}_0$, the alignment of every magnetic moment $\vec{\mu}$ with $\vec{B}_0$ is non-perfect (Figure 2-6), thus forming a cone-shaped rotation analogous to the rotation of a top in the presence of the gravitational field. The rotation is called Larmor precession, and the angular frequency is called Larmor frequency. Larmor frequency, ω_0 , is solely determined by the external magnetic field strength,

$$\omega_0 = \gamma B_0 \quad (2.1)$$

where γ is known as gyromagnetic ratio. This relation is the basis for MR image reconstruction using frequency encoding. In summary, in an external magnetic field, an ensemble of magnetic moments align to produce a non-zero bulk magnetization M_0 in the direction of B_0 , and the magnetic moments precess with the same frequency (because of the same B_0) but random phases.

Figure 2-6 Precession of a proton spin about an external magnetic field B_0

For the magnetization $\vec{M}$ to be detected, radiofrequency (RF) pulse is applied. RF pulse is essentially a short-lived weak magnetic field ($\vec{B}_1$) applied within x - y plane, thus perpendicular to $\vec{B}_0$. $\vec{B}_1$ can be understood as orienting along one specific direction (say, x -axis) with oscillating strength, or as rotating within x - y plane with constant strength. These two forms are same in essence, but the latter makes further discussion in a rotating frame more convenient. When rotation frequency of $\vec{B}_1$, ω_{rf} , equals to the Larmor frequency ω_0 , the magnetic vectors with random phases will establish a state of phase coherence, i.e. resonance. In laboratory reference frame, the approach to such resonance appears complex. Following convention, a rotating reference frame x' - y' - z' is defined, which rotates about z axis with angular frequency of ω_{rf} . In the rotating frame, $\vec{B}_1$ is stationary. Without loss of generality, we assume that $\vec{B}_1$ points along x' axis. In the

condition that $\omega_{rf} = \omega_0$, all magnetic vectors (thus M_0) ‘look’ stationary in the rotating frame as well. Analogous to the precession of $\vec{\mu}$ with $\vec{B}_0$, the application of B_1 results in a precession of the magnetization M_0 about x' axis with a frequency of $\omega_1 = \gamma B_1$, creating a measurable transverse component $\vec{M}_{x'y'}$ (Figure 2-7). Viewing from the laboratory frame, $\vec{M}_{x'y'}$ is a rotating magnetization (around z axis), and can be detected by MR detection coil according to Faraday law of electromagnetic induction. An important parameter associated with the flip of $\vec{M}$ is flip angle. The flip angle α is defined as the smaller angle between $\vec{M}$ and z' axis. In the case of a rectangular pulse (constant B_1 strength),

$$\alpha = \omega_1 t_p \quad (2.2)$$

where t_p is the pulse duration. The associated RF pulse is usually named as ‘ α pulse’. Flip angle is one of the only few parameters that can be freely selected by operators. As we will see in later chapters, the proper selection of α in acquiring image with some MR sequences is important for some further image analysis [51].

2. Magnetization Relaxation

In the previous section, we described the tip of magnetization away from z direction by RF pulse (the excitation process). After removal of B_1 , the bulk magnetization will return to its original equilibrium state: a recovery of the longitudinal (z direction) magnetization and destruction of the transverse (x - y plane) magnetization. This is called the relaxation process. Note that, although ignored in short-lived excitation process, relaxation is actually in progress all the time.

Figure 2-7 Motion of the bulk magnetization vector in the presence of a rotating RF field as observed in the RF-rotating frame

The longitudinal and transverse relaxations proceed independently, and can be described quantitatively by a simpler form of Bloch equation [49] [52] [53] [54], which is used for describing time-dependence of magnetization in the presence of an external magnetic field. The simpler form of Bloch equation for relaxation in the Larmor-rotating frame is as follows,

$$\begin{cases} \frac{dM_{z'}}{dt} = -\frac{M_{z'} - M_z^0}{T_1} \\ \frac{dM_{x'y'}}{dt} = -\frac{M_{x'y'}}{T_2} \end{cases} \quad (2.3)$$

where T_1 and T_2 are known as spin-lattice relaxation time and spin-spin relaxation time respectively, and M_z^0 is the longitudinal magnetization at thermal equilibrium, which is proportional to proton density. T_1 , T_2 and M_z^0 are important intrinsic parameters of tissue.

As we will see in later sections, these intrinsic parameters and some extrinsic parameters (such as flip angle) mutually determine the amplitude of the detected MR signals.

3. MR Signal Localization

In this section, the signal localization for image reconstruction will be briefly described. The excitation of measurable transverse magnetization in an object immersed in a spatially constant B_0 has been introduced. In such case, the signal after a pulse excitation is a sum of signals from all parts in the object because of their same resonance frequency. For acquiring an ‘image’, the sources of the signal have to be localized. Utilizing the fact that the resonance frequency is determined by the strength of external magnetic field, gradient fields are employed to excite a region of interest selectively. After excitation by selective or nonselective pulses, spatial information can be encoded into the signal during the free precession period. The signal can be frequency-encoded or phase-encoded, which are achieved by application of magnetic gradients. By repetitive excitation and encoding each signal properly, frequency space (more usually termed as k -space by many MRI physicists) can be covered with various sampling trajectories. These samples in frequency domain are then converted to MR image by inverse Fourier transform [55].

4. Typical MR Sequences

According to previous discussion, MR image intensity is a function of many intrinsic parameters, such as proton density, spin-lattice relaxation time (T_1), spin-spin relaxation time (T_2), and so on. These parameters are associated with different characteristics of tissues. The versatility of MRI lies in that various MR sequences can be designed to

produce MR images with weighting of some specific intrinsic parameters. The most commonly-used MR sequences include saturation recovery (SR), inversion recovery (IR), spoiled gradient-recalled echo (SPGR), steady-state free precession (SSFP), etc. In the following, only SR and SPGR, which will be used in later chapters, are briefly introduced.

The basic SR consists of a series of equal-spaced 90° pulses, and the time interval between successive pulses is called repetition time (T_R). For $T_R \gg T_2$, the decay of transverse magnetization is complete before the application of next 90° pulse, according to Equation (2.3). Under this condition, we need only to consider the relaxation of longitudinal magnetization,

$$\frac{dM_{z'}}{dt} = \frac{M_z^0 - M_{z'}}{T_1}. \quad (2.4)$$

According to Equation (2.4), $M_{z'}$ value by the time next pulse applies, reaches a steady state (Figure 2-8),

$$M_{z'} = M_z^0 [1 - \exp(-T_R / T_1)]. \quad (2.5)$$

After 90° -pulse flip, this signal can be measured by detection coil.

Compared with some fast imaging sequences, SR is time consuming, because 90° pulses are applied and after each pulse it takes a long T_R for transverse magnetization to decay completely. For example, given $T_R = 1\text{s}$, about 4 min is needed for acquiring a 256×256 SR image. This long acquisition time is not appropriate for dynamic imaging, because some physiologic processes may take place in a few seconds. However, SR sequence

produces MR images of high signal-noise ratio. T_1 maps calculated from SR images are usually regarded as the reference for validating results from fast imaging.

Figure 2-8 The longitudinal relaxation curve of saturation recovery (SR)

Currently, fast imaging is one of the most active areas of MRI research. For MRI, the total image acquisition time (T_{acq}) can be calculated as follows,

$$T_{acq} = N_{acq} \cdot N_{enc} \cdot T_R \quad (2.6)$$

where N_{acq} is the number of signal averages, N_{enc} is the number of encoding (for coverage of k -space) and T_R is the time interval between two consecutive excitations. T_{acq} can be shortened by reducing N_{acq} , N_{enc} , and T_R , individually or simultaneously. Since reducing N_{acq} directly leads to a loss of signal-noise ratio, fast imaging techniques are usually accomplished by reducing the other 2 parameters. For example, echo-planar imaging [56], an ultra high-speed technique, collects all encoding lines after a single excitation pulse ($N_{enc} = 1$), by employing time-varying gradients; burst imaging [57] utilizes multi-echo method to cover k -space in a single cycle. In the following section, one widely-used fast-imaging sequence by reducing T_R will be briefly introduced.

Spoiled gradient recalled echo (SPGR) is one of the most widely used fast imaging sequences that employ short T_R . The sequence diagram of SPGR is shown in Figure 2-9. In SPGR imaging, RF pulses of small flip angle are applied (for this reason, it is also termed as spoiled fast low angle shot (FLASH) [58]), accompanied with relaxation of short T_R . Because such T_R may not be long enough for complete decay of transverse magnetization, a spoiler gradient pulse is usually applied to destroy the transverse residual. The amplitude of the spoiled gradient is varied from one excitation to another in order to avoid coherent buildup of the transverse magnetization. Similar to SR, a steady state can also be reached in SPGR. The steady-state signal expressed in the rotating frame can be given as follows [55],

$$M_{x'y'}^{SS} = \frac{M_z^0 [1 - \exp(-T_R/T_1)] \sin \alpha}{1 - \exp(-T_R/T_1) \cos \alpha}. \quad (2.7)$$

Figure 2-9 Two-dimensional SPGR sequence. The slice-selective excitation is accomplished by the application of the z-direction gradient at the same time of pulse. The later minus gradient with a half-time duration is for post-excitation rephasing. Gradients along y direction are for phase encoding, and that along x-direction for acquiring gradient echo signal. Later, gradient spoiler is applied along z-direction.

5. DCE MRI

DCE MRI is performed with intravenous injection of some paramagnetic agent prior to or during the repetitive acquisition of MR images. The effect of paramagnetic agents (such as Gadolinium, Gd) is to shorten T_1 of the surrounding water protons [59]. For the widely used agent Gd-DTPA, the shortening of T_1 can be described by the following formula,

$$\frac{1}{T_1^c} = \frac{1}{T_1^0} + r \cdot C \quad (2.8)$$

where T_1^c is T_1 in the presence of Gd (post-contrast), T_1^0 is the T_1 without Gd, r is a constant called relaxivity, and C is concentration of Gd. In T_1 -weighted MR sequences, the shortening of T_1 directly leads to MR signal enhancement. Generally, this signal enhancement has two applications: (1) for differentiation of normal and diseased tissue by enhanced contrast in between; (2) for assessment of organ function or blood perfusion using tracer-kinetic techniques. The latter application has been successful in many areas, such as tumor imaging [60] [61], MR angiography [62], and myocardial perfusion [63]. For evaluating organ function or blood perfusion, temporal resolution of DCE-MRI is crucial. That is why the fast-imaging MR sequences are used for DCE-MRI.

2.2 Literature Review

This thesis focuses on 2 aspects of research on renal-function assessment by dynamic imaging: renogram analysis by parametric deconvolution and DCE MRI for dynamic renography. Literature review was carried out in these two aspects accordingly. Firstly, some approaches that were proposed for analyzing renogram generated from scintigraphic images are reviewed. Secondly, DCE-MRI shows great potential as a

valuable tool for renography. Its satisfactory application requires a few issues to be addressed, one of which is the reliable quantification of tracer concentration from MR images. The flip-angle optimization, which was believed to be helpful for the issue, will be reviewed.

2.2.1 Renogram Analysis

In the context of renal scintigraphy, renogram is more commonly termed as renal time-activity curve (TAC). According to the image-acquisition protocol previously described, 60 frames of 1s interval are recorded in the initial 1 minute. These frames are for vascular perfusion study. Some perfusion parameters can be identified from the 1s-interval TAC, and are useful for assessing transplanted kidney and renal vascular diseases. For evaluating renal function, these frames are summed into 6 10s-interval frames, and followed by the latter 10s-interval frames. In the following, some methods for analyzing the 10s-interval renogram (Figure 2-5) will be introduced.

Renogram can be analyzed in a fashion by merely inspecting the renogram and producing conceptually simple parameters. These parameters include area-under-curve (AUC) at 1-2 minutes, time to peak of renogram (TTP), etc [64] [65] [66] [67] [68]. Derivation of the parameters is simple. However, the problem is that these parameters are input-dependent, which may prevent reliable comparison between results from different patients. More recently, deconvolution and Patlak plot (or Patlak-Rutland plot), which aim to eliminate information of arterial input from renogram, were applied to renogram analysis [31] [69] [70] [71]. The implementation of deconvolution or Patlak plot requires an input

concentration curve ($I(t)$), which is usually obtained from a left-ventricle ROI in scintigraphic images. Comparison study between the above-mentioned simple parameters and deconvolution method was carried out by Sutton and Kemp in 1993 [72], while that between deconvolution and Patlak plot was by Fleming and Kemp in 1999 [73].

1. Patlak Plot

Patlak plot was initially proposed by Patlak to evaluate blood-to-brain transfer rates [70], and was later applied to analyze renogram [71]. The theory underlying the method is briefly described as follows. Blood with tracer flows into kidney, and a fraction of tracer is filtered into tubules. It takes some time for the filtered tracer to begin to leave from tubular pathway. Before any tracer exits from tubular pathway, the filtered tracer accumulates in it. That is to say, the tubular pathway acts as an integrator of the arterial input, $I(t)$. As the flow in vascular pathway is very rapid, the tracer content in it is approximately proportional to blood input $I(t)$. Hence, renal TAC, $K(t)$, relates to input TAC, $I(t)$, by

$$K(t) = aI(t) + b \int_0^t I(\tau) d\tau. \quad (2.9)$$

Dividing both sides of Eq (2.9) by $I(t)$, we get

$$\frac{K(t)}{I(t)} = a + b \frac{\int_0^t I(\tau) d\tau}{I(t)} \quad (2.10)$$

In practice, $K(t)$ and $I(t)$ are measured discretely, and are contaminated by measurement noise, so that the plot of $K(t)/I(t)$ against $\int_0^t I(\tau) d\tau / I(t)$ gives some discrete points, not a straight line. By linear regression, y-intercept a and gradient b of the line can be

determined from the noisy data. A schematic diagram is illustrated in Figure 2-10. Constant b is proportional to glomerular filtration rate, and a is related to the volume of vascular compartment. After an initial period of about 2 minutes, filtered tracer in tubules begins to flow out of kidney, and the linear relation does not exist anymore. Hence, for implementation, intervention from the operator is required to determine the time window, within which noisy data be used for the linear regression.

Figure 2-10 Patlak/Rutland plot

2. Deconvolution

Renogram is not the simplest form that represents the renal handling of tracer [31] [74]. By assuming that kidney is a linear and stationary system, a kidney can be fully characterized by its impulse response function. As the tracer residue at different time instances is measured in renal scintigraphy, the impulse response function is actually an

impulse residue (or retention) function ($R(t)$). The relation of $I(t)$, $K(t)$ and $R(t)$ can be expressed by the following convolution [75] [76],

$$K(t) = F \int_0^t I(t - \tau) \cdot R(\tau) d\tau \quad (2.11)$$

where F is renal blood flow. Some investigators prefer to combine F and $R(t)$ together, thereby resulting in ‘flow-weighted R ’. The derivation of $R(t)$ from the above convolution is the so-called deconvolution. Deconvolution techniques applied for renogram analysis are briefly reviewed as follows.

(1) Matrix method

Matrix method is one of the deconvolution techniques that were first applied for renogram analysis [31] [74]. Nowadays matrix method is still favored by many coworkers, because of its simplicity and easy implementation [37] [41] [77] [78]. TACs $K(t)$ and $I(t)$ are generated from dynamic images with time interval Δt , so the above convolution (Eq. (2.11)) can be written in the following summation,

$$K(i) = F \sum_{j=1}^i I(i - j + 1) \cdot R(j) \cdot \Delta t \quad (2.12)$$

The matrix form of Eq. (2.12) is as follows,

$$\begin{pmatrix} K(1) \\ K(2) \\ K(3) \\ \vdots \\ \vdots \end{pmatrix} = F \begin{pmatrix} I(1) & 0 & 0 & \bullet & \bullet \\ I(2) & I(1) & 0 & \bullet & \bullet \\ I(3) & I(2) & I(1) & \bullet & \bullet \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ \vdots & \vdots & \vdots & \vdots & \vdots \end{pmatrix} \begin{pmatrix} R(1) \\ R(2) \\ R(3) \\ \vdots \\ \vdots \end{pmatrix} \Delta t \quad (2.13)$$

The matrix containing I is triangular, so R can be determined step by step, starting from $R(1)$. More specifically,

$$R(i) = \frac{1}{I(1)} \left[\frac{K(i)}{\Delta t \cdot F} - \sum_{j=1}^{i-1} I(i-j+1) \cdot R(j) \right]. \quad (2.14)$$

Because of this approach for calculating R , the noise in K and I is propagated and accumulated through the entire solution. This is the reason why some investigators state that matrix method is susceptible or sensitive to noise. The noise-sensitive problem is more pronounced when matrix method is applied to analyze poorly-functioning kidneys [33]. Because of lower tracer uptake, renal TAC of such case is lower than that of normal case, and thus has lower signal-to-noise ratio.

(2) Transform Methods

This class of methods includes Laplace-transform method [69] [75] and Fourier-transform method [79]. By the convolution theorem, Laplace transform turns the complicated convolution into simple multiplication. Taking Laplace transform for both sides of Equation (2.11), we get

$$K(s) = F \cdot I(s) \cdot R(s), \quad (2.15)$$

where $K(s)$, $I(s)$ and $R(s)$ are the Laplace transforms of $K(t)$, $I(t)$ and $R(t)$, respectively.

Dividing $F \cdot I(s)$ at both sides, we get

$$R(s) = \frac{K(s)}{F \cdot I(s)}. \quad (2.16)$$

By approximating $I(t)$ as a bi-exponential [69] or tri-exponential function [75], the implementation of Eq. (2.16) can be quite easy, although modern computers are able to implement it efficiently even without the approximation. Besides, transform methods offer a straightforward way to de-noise K and I , with the aim of reducing meaningless

oscillation in resulted $R(t)$. The high-frequency components in $K(s)$ and $I(s)$ (or Fourier transform of them) can be regarded as noise contribution. Discarding off the noise components has the same effect as denoising K and I in time domain [80]. However, there are a few practical difficulties in implementing this denoising technique [81] [82], especially in the situation that the signal itself contains some high-frequency components.

(3) Constrained Least-Squares Restoration (CLSR)

One problem central to deconvolution analysis of renogram is that noise in renogram and input curve leads to unstable solutions, and as renal function becomes poorer, the instability becomes more pronounced. Hence, it is necessary to decide whether renal function is good enough to allow deconvolution analysis (by matrix or transform methods). In 1992, Sutton and Kempf [83] proposed a deconvolution method, constrained least-squares restoration (CLSR), to circumvent such a decision. An estimate of $R(f)$ (Fourier transform of $R(t)$) is given as follows,

$$F \cdot \hat{R}(f) = \frac{I^*(f)}{I^2(f) + \Gamma \cdot P(f)} K(f), \quad (2.17)$$

where $I(f)$, $K(f)$, $\hat{R}(f)$ and $P(f)$ are Fourier transforms of $I(t)$, $K(t)$, $\hat{R}(t)$ (an estimate of $R(t)$) and $P(t)$ (a second-difference operator $[1, -2, 1, 0, \dots, 0]$, as a measure of smoothness constraint) respectively, and the asterisk represents the complex conjugation operator. Each value of Γ yields a $\hat{R}(t)$, and the problem becomes one of adjusting Γ

until $\sum_{i=1}^N \left[K(i) - F \sum_{j=1}^i I(i-j+1) \cdot \hat{R}(j) \cdot \Delta t \right]^2$ is smaller than a tolerance limit. We note that

no filtering of $K(t)$ and $I(t)$ is required for its implementation. It seems that CLSR has not

been taken up by many workers [33], probably because its mathematical complexity did not bring enough desirable benefit.

(4) Model Fitting: a Parametric Deconvolution

In recent years, model fitting for deconvolution has been applied for renogram analysis [38] [84] [85]. Different from deconvolution methods introduced previously, model fitting provides some clinically-useful parameters directly, and does not suffer from the noise-sensitive problem [38]. Besides, the flexibility of model fitting lies in that various models for renal impulse residue function can be designed for its implementation.

With K and I contaminated by measurement noise, the convolution in Eq. (2.11) can be written as

$$K(i) = F \sum_{j=1}^i I(i-j+1) \cdot R(j, p) \cdot \Delta t + \sigma(i), \quad (2.18)$$

where σ is the error component. The inclusion of the error component σ is necessary, because $K(i)$ and $I(i)$ ($i = 1, \dots, N$) suffer from measurement noise (Poisson noise [33] [86]) while R is an ‘ideal’ model with only one set of adjustable parameters p . As $K(i)$ and $I(i)$ ($i = 1, \dots, N$) are measured independently and from different ROIs, the error component σ is zero-mean. Under this condition, the deconvolution problem can be solved by finding appropriate parameters of R , such that the sum of squared residue (SSR) is minimized,

$$SSR = \sum_{i=1}^N \left[K(i) - F \sum_{j=1}^i I(i-j+1) \cdot R(j) \cdot \Delta t \right]^2. \quad (2.19)$$

This approach is also known as prediction-error identification method (PEM, Ljung in 1987) [87], and was applied for analyzing renogram by Fine et al (1994) [38]. Model fitting is different from CLSR in that the ‘constraint’ employed in model fitting is a physiologic model and the parameters of the model usually have physiologic meaning.

3. Models of Renal Impulse Retention Function

In this section, the modeling of renal impulse retention function will be reviewed. We mentioned in previous section that renal R models are necessary for model-fitting analysis of renogram. However, we note in literature that, before the utility of model fitting was recognized in analyzing renogram, some renal R models already existed and were used for other purposes.

One prominent feature of some renal R models in the early stage is that they only contain parenchyma component [88] [89] [(as will be shown in the following, a more realistic model contains both vascular and parenchyma components). These one-component models were usually used to post-analyze the oscillated renal R obtained in non-parametric deconvolution. In 1980’s or early 1990’s, non-parametric deconvolution such as matrix method and transform methods was used for renogram analysis. The resultant renal R is oscillated and may show an initial rapid vascular down-slope. For assessment of renal parenchyma function, the one-component R model is used to fit to the oscillated R , thus eliminating the vascular component and extracting renal parenchyma parameters. One representative parameter is parenchyma mean transit time [37] [80]. The other possible application of these models is for simulation study. By convolving a renal R

model with a blood input curve, simulated renal curves can be constructed for study purpose [89].

The popularity of one-component (parenchyma) model did not prevent the exploration of the more realistic shape of renal R . The theoretical existence of a vascular component in renal R is definite. As indicated by Reeve and Crawley in 1974 [90], renal R contains information about vascular transit in addition to renal tubular transit. In renal scintigraphy, such vascular information is obtained by acquiring initial rapid images of short interval (1-2s), and then analyzing them by extracting some parameters such as kidney/aorta ratio (K/A) [35] and perfusion index (PI) [36].

A renal R model, containing both vascular and parenchyma components, was proposed by Fine et al [38] in 1994. In this model, the impulse response functions of vascular and parenchyma pathways are described by gamma density function. Renal impulse retention function R thus constructed contains parameters such as renal blood flow (F), filtration fraction (f), vascular mean transit time (MTT_b), MTT_p , etc. Simultaneous estimation of both vascular and parenchyma parameters provides us the information on both renal perfusion and function. Moreover, analysis of these parameters may reveal some causes initiating the loss of renal function [91]. Unfortunately, Fine's model has not been fully adopted by current investigators, due to the shortage of an appropriate model fitting method that identifies these parameters reliably.

2.2.2 DCE-MRI for Renography

The advent of fast MR imaging techniques has made it possible to evaluate renal function by dynamic MRI. DCE-MRI does not use ionizing radiation, and more importantly, has the capability of combining both functional information and high-resolution images of kidney for diagnostic or prognostic purposes [92]. DCE-MRI has shown its advantage over renal scintigraphy, in diagnosing hydronephrosis and upper urinary tract obstruction. The urinary tract obstruction can be detected directly from the high-resolution MR images [93] [94].

To generate renogram from dynamic MR images, it is necessary to estimate tracer retention in renal parenchyma ROI of the images. In most of previously reviewed methods that were applied for analyzing renogram from DCE MR renography [94] [95] [96], MR signal-intensity enhancement (ΔS) was assumed to be proportional to tracer concentration in the region of interest, and was used for generating a renogram. However, it is well known that MR S or ΔS for most pulse sequences is not linear with C [97]. Preliminary animal studies were carried out, in which C -based renograms were analyzed for renal perfusion and function assessment [98] [99].

It was realized that quantification of tracer concentration (C) from DCE-MR images, i.e. C mapping, is an important issue concerned by not only the investigators in the area of MR renography, but also those in the whole area of functional MRI. Its most important applications include tumor detection and tumor-microcirculation assessment [100] [101]

[102] [103]. Because of the linear relation between tracer concentration and Gd-induced $1/T_1$ change, estimation of T_1 from MR signals becomes the focus of researchers.

In 1987, Wang et al discussed how to optimize flip angles in SPGR imaging for accurate estimation of T_1 maps [51]. In their study, a model was proposed for the propagation of SPGR signal noise to the calculated T_1 . In case of constrained temporal resolution, flip angle is the only adjustable parameter of the model. Numerical minimization of the noise-propagation model results in optimal flip angles for estimating a single T_1 value. Wang's work laid a good basis for further study. Application in cerebral MR imaging was illustrated.

In 1996, Brookes et al [104] managed to apply Wang's method in SPGR imaging of breast, for detection and characterization of breast tumors. One set of flip angles was numerically selected for optimal estimation of a range of T_1 (including that of normal tissue and breast tumors) encountered in typical breast images. In 2003 and 2004, Deoni et al [105] [106] applied a similar method in high-speed acquisition of cerebral MR images. In phantom experiment and in vivo measurement, the error of the estimated T_1 was found to be only 7%. Besides, their studies illustrated the excellent capability of DCE MRI for morphologic imaging.

2.3 Concluding Remarks

Non-invasive assessment of renal function has mainly depended on the analysis of renograms obtained by renal scintigraphy. Many methods for analyzing renogram have been proposed, among which model fitting is of great potential. Model fitting is capable of directly identifying many clinically-useful parameters indicative of renal perfusion, function and some renal pathology, such as urinary obstruction and renovascular hypertension. DCE-MRI for functional renography has attracted attention in the last 3~5 years. Functional analysis combined with the detailed morphologic information could potentially provide more information for more confident diagnostic decision. However, to extract a reliable concentration-based renogram from DCE-MR images remains to be an important task we have to deal with.

Chapter 3

Models for Renal Impulse Retention

Function

3.1 Introduction

A physiologic model is useful in quantitative characterization of a physiologic process by using dynamic imaging. The model reflects our understanding of the associated physiologic process, and conversely its application in real patient data possibly gains new insights and deepens such understanding. The model is usually controlled and constrained by one set of parameters. Ideally, the parameters carry insightful physiological meaning, and are sensitive to any degeneration in some physiologic aspects. For real data of various statuses (normal or pathologic), the model parameters are identified and interpreted. The parameter values corresponding to these statuses can be determined as reference values for future diagnostic use.

Some considerations should be taken into account in designing or applying a physiologic model for data analysis. The first consideration is the complexity of the process of interest. Sometimes, only one specific aspect of a physiologic process is of interest, so a simple but reliable model would be desirable. One example is Patlak plot for estimating GFR [71]. However, in other situations where a complex process needs to be characterized, a composite model would have to be considered. The second consideration is the quality of the data, such as temporal/spatial resolutions and signal-to-noise ratio (SNR). The information of a physiologic process is contained in dynamic images. Temporal/spatial resolutions and SNR of the images determine how much information can be reliably extracted. For data of high quality, analysis employing a simple model usually neglects some potentially useful information, while an elegant model may extract the information appropriately; for data of low quality, such elegant model would possibly produce meaningless and misleading parameter estimates. Hence, models of proper complexity have to be chosen carefully according to the complexity of the process of interest, and the quality of dynamic imaging data.

This chapter will focus on the modeling of renal impulse retention function (IRF), for analyzing dynamic images that are acquired after tracer injection. Before that, it is necessary for us to briefly review the transit of tracer (DTPA) within kidney. Blood with tracer (^{99m}Tc -DTPA in renal scintigraphy) enters kidney via renal artery. Renal artery is ultimately divided into about 1 million mini-branches, afferent arterioles, with every one of them feeding one nephron. By glomerular filtration, 20% of blood plasma with DTPA is filtered into tubules. Although most of the filtered plasma is reabsorbed back, the

filtered tracer is excreted through tubules into renal pelvis. A schematic diagram of the transit pathways is illustrated in Figure 3-1. There are 2 multiple-pathway networks for tracer to flow through: vascular and tubular. These two networks share the same former part, which is from renal artery to all afferent arterioles, but split after that. The tubular pathways are longer and have much less flow pressure than vascular pathways, so it takes much longer time for tracer to go through tubular pathways.

Figure 3-1 Intra-renal multi-pathway networks. The vascular and tubular pathways share the same former part: from renal artery to afferent arterioles. DTPA in every afferent arteriole splits into an efferent arteriole and a tubule.

Renal IRF is defined as the tracer residue within the kidney ROI (i.e. the above networks) after a unit-impulse input of tracer from renal artery, as a function of time. Hence, renal IRF is a non-increasing function, starting from 1 at time zero. As introduced previously, the transit of tracer through vascular pathways is much more rapid than that in tubular pathways, so renal IRF shows an initial decrease (tracer excretion from vascular

pathways) and a later decrease (tracer excretion from tubular pathways) after a plateau. For a normal kidney, the vascular phase is typically of the order of ~10-30s, but it could be prolonged in pathologic conditions such as renal arterial stenosis and renovascular hypertension, and for some transplant patients. The parenchymal process is reflected by the plateau followed by a gradual loss of tracer given by the renal-tubular transit times. The parenchymal process is typically about 100-200s in normal kidneys, and it could be significantly prolonged in obstructive uropathy.

3.2 A Previous Renal IRF Model

A model of renal IRF was proposed by Fine et al [38], with account of both the vascular and parenchymal processes of the kidney. In this model, the transit time spectra (TTS) of both the vascular and tubular processes are modeled by the same mathematical function. Before reviewing the mathematical expression of the model, the relation between TTS and IRF is first explained. Transit time is the time for a tracer molecule to transit from the entry to the exit of a pathway. For a unit of tracer input into multi-pathway system, the transit times for different tracer molecules may be different, because the molecules tend to disperse in plasma and also they may transit in pathways of different lengths. TTS is the frequency spectrum (or probability density function) of transit times [38] [80] [107]. Apparently, it is inherently the impulse output function, which has unit under-curve area (Figure 3-2). The integration of impulse output function results in accumulative output, which initiates from 0 and ends at 1 (whole unit of tracer is output). The IRF can be calculated by one minus accumulative output (Figure 3-2).

Figure 3-2 Relation of transit time spectrum (TTS) and impulse retention function (IRF)

As renal vascular and tubular pathways can both be regarded as length-distributed capillary systems (Figure 3-1), their TTS were modeled by gamma distribution function, respectively [38] [108]. The TTS of the whole renal system, including both vascular and tubular pathways, can be given as the following weighted sum,

$$H(t) = (1-f) \cdot \frac{t}{\tau_b^2} \cdot \exp\left(-\frac{t}{\tau_b}\right) + f \cdot \delta(t - \tau_t) \otimes \left[\frac{t}{\tau_c^2} \cdot \exp\left(-\frac{t}{\tau_c}\right) \right], \quad (3.1)$$

and the resulting impulse retention function can be thereby given by

$$\begin{aligned}
R_{Fine}(t) &= 1 - \int_0^t H(\tau) d\tau \\
&= 1 - (1-f) \left[1 - \left(\frac{t}{\tau_b} + 1 \right) \exp\left(-\frac{t}{\tau_b} \right) \right] \\
&\quad - u(t-\tau_t) f \left[1 - \left(\frac{t-\tau_t}{\tau_c} + 1 \right) \exp\left(-\frac{t-\tau_t}{\tau_c} \right) \right]
\end{aligned} \tag{3.2}$$

f is the extraction fraction which denotes the fraction of tracer extracted through the glomerulus. τ_b is the blood transit time constant and $u(t)$ is the Heaviside unit step function. τ_c is the overall dispersion parameter for the tubular processes, denoting the summed effect of the spread of tubule lengths, spread of collecting ducts and mixing in the calyces. τ_t specifies the width of the plateau and denotes the net delay time due to delays in the tubules and collecting ducts. τ_t thus corresponds to the minimum parenchymal transit time (MinTT_p) taken by tracer to flow through the shortest nephron and collecting duct. The vascular and parenchymal mean transit times can be respectively given by $MTT_b = 2\tau_b$ and $MTT_p = \tau_t + 2\tau_c$ [38]. In later sections, this model will be termed as Fine's model (Figure 3-3).

Figure 3-3 Schematic diagram of the renal impulse retention function $R(t)$, scaled by the renal plasma flow, F . The first downslope of $FR(t)$ which represents the vascular phase, starts from an initial value of F and the mean duration is the vascular mean transit time, MTT_b . The parenchymal tubular phase includes the plateau, (with height E given by the extraction rate, and width corresponding to the minimum parenchymal transit time $MinTT_p$) and the second downslope process of mean duration given by the parenchymal transit time, MTT_p .

3.3 Piecewise-Continuous Linear (PCL) Model

3.3.1 Motivation

As reviewed in Chapter 2, deconvolution approaches for analyzing renal TAC can be broadly classified as non-parametric and parametric. Non-parametric methods usually involve numerical deconvolution techniques, such as matrix method and transform methods, to obtain the IRF. However, it is recognized that the process of deconvolution is

very sensitive to the presence of noise [33], and that its usefulness could be limited for noisy scintigraphic data. Also, after deconvolution of the IRF, further analysis is required to obtain the transit time parameters. For example, Rottman et al [37] have used piecewise continuous line segments to fit the deconvolved IRF, so as to infer the parenchyma mean transit time. On the other hand, parametric methods avoid the process of numerical deconvolution by fitting the renogram using the convolution of the left-ventricle (LV) TAC and a model function of the IRF. Parameters of the model function are adjusted to achieve the best fit. Fine et al [38] have proposed such a model and the transit time parameters can be obtained after the model fitting.

In this work, the idea of Rottman et al [37] is adopted to model the renal IRF as a piecewise-continuous linear (PCL) function, but instead of fitting it to the deconvolved IRF, it is implemented as a model function of the IRF to convolve with the LV TAC for direct parametric fitting of the renogram, hence avoiding the process of numerical deconvolution.

3.3.2 Materials and Method

A schematic diagram of the typical renal IRF is shown in Figure 3-4, together with the PCL model. For a typical human kidney, processes, reflected by the downslopes in the renal IRF, take place within 20-120s [38]. Since renal scintigraphic images are collected every 10s, there are at most about 12 points (3 or 4 points in most cases) to describe the downslope processes. Considering this and the fact that the TACs are usually quite noisy, it might be difficult to fit non-linear segments, as in Fine's model, to the downslopes, and

linear segments have been used instead. The PCL model for the renal IRF can be described by simple geometric parameters

$$R_{PCL}(t) = \begin{cases} -\frac{a-b}{c}t + a & 0 \leq t \leq c \\ b & c < t \leq d \\ -\frac{b}{e-d}t + \frac{be}{e-d} & d < t \leq e \end{cases} \quad (3.3)$$

Following the conventions used by Fine et al (in section 3.2), a denotes the initial point of the renal IRF and b corresponds to the height of the plateau in the renal IRF, and both a and b are associated with units of inverse time, s^{-1} . The parameters c , d and e denote the maximum vascular transit time, minimum parenchyma transit time and maximum parenchyma transit time, respectively, and have units of time, s . The parenchyma mean transit time (MTT_p) and the extraction fraction (f), which are important for renal-function evaluation and diagnosis of renal obstructive and renovascular pathologies [37] [38] [41] [43], can be easily calculated from the geometric parameters, with $MTT_p = (d+e)/2$ and $f = b/a$. The present PCL model is much simpler than Fine's model, and can be easily implemented for parametric fitting.

To illustrate the applicability of the PCL model, a patient study including 12 kidneys with various functional statuses was carried out. Parametric fitting was performed using both PCL model and Fine's model. The Levenberg-Marquardt algorithm [109] was used for minimization of the sum of squared residuals (SSR), which is a measure of the goodness-of-fit, with a smaller SSR indicating a better fit. The correlation between parameter estimates by the different models was studied using linear regression and correlation plot.

A unit slope (s) and zero y-intercept (c) in correlation plot would indicate the correspondence of the parameter estimates concerned.

Figure 3-4 A schematic diagram of the typical renal IRF (dashed line) and the PCL model (solid line).

3.3.3 Results and Discussion

Parameter estimates (MTT_p and f) by two models (PCL and Fine's model) are tabulated in Table 3-1, and the correlation plots are shown in Figure 3-5. Correlation between MTT_p estimates (Figure 3-5 (a)) is fairly good, with correlation coefficient $r^2=0.979$. However, the slope of their regression line is 0.84, which is slightly lower than 1. As observed in Figure 3-5, this low slope was obviously caused by the two cases with long MTT_p , i.e., case 2 and 3 in Table 3-1. For these two cases, the differences in MTT_p estimates by the different models are large, and this large difference can possibly be attributed to the fact that parenchyma transit times of these two cases are longer than the whole imaging time. In such situation, the latter part of renal IRF can not be determined

accurately, so that the estimated MTT_p is not accurate, no matter for PCL or Fine's model. For filtration fraction f , the correlation plot (Figure 3-5 (b)) indicates excellent correspondence between estimates by PCL and those by Fine's model, with $r^2=0.910$ and $s=0.94$. As we can see, although PCL model simplifies the complex nonlinear process into more flexible and simpler line-segments, it can still supply estimates for MTT_p and f that are in good agreement with those obtained from Fine's model for most kidney cases in the study.

To further illustrate the implementation of the PCL model and to compare with Fine's model, we presented curve-fitting result and renal IRF for two representative case studies: a normal kidney (case 1, Figure 3-6) and an obstructive kidney (case 2, Figure 3-7). It would be also interesting to compare model fitting using the models with non-parametric deconvolution. Hence, non-parametric deconvolution was applied for these two cases using the Singular Value Decomposition (SVD) method [110], and the deconvolved IRFs are shown together with the model-fitting IRFs in Figure 3-6 (b) and Figure 3-7 (b).

For the normal-kidney case, the SSR for both the PCL and Fine's models are almost the same, and the resulting parameter estimates for MTT_p and f are also similar (case 1 in Table 3-1). However, it is noted that, in Figure 3-6 (b), the resulting renal IRFs do differ in the parenchyma minimum transit time and the plateau height. This is likely due to the linear approximations of the present PCL model on the downslope processes which are, strictly speaking, not linear in nature. Also, in this case study, it is noted that these differences are not too severe to result in significant deviation of the estimates of MTT_p

and f . For the diseased-kidney case, the PCL model is able to achieve a slightly better SSR than Fine's model, and both models give significantly larger MTT_p estimates and smaller f estimates, which is consistent with the condition of the diseased kidney. For both cases, it is noted that the IRFs obtained using the PCL model can correctly reflect the physiologic status of the kidneys, and the parameter estimates compare well with Fine's model. It is also noted that the trends and features of the deconvolved IRFs are well described by the PCL model through the present parametric fitting method, albeit the fact that they are obtained using two different approaches.

Figure 3-5 Correlation plots and linear regression for MTT_p (a) and f (b) by different models, Fine's and PCL. s and c are the slope and y-intercept of the regression line (dot-dash line), respectively, and r^2 is the correlation coefficient. The solid line is identity line.

Figure 3-6 Normal kidney study case. (a) The kidney TAC (circles) is fitted using the PCL model (dotted line) and Fine's model (dashed line). The SSR for PCL model and Fine's model are 30 and 30, respectively. (b) The corresponding renal IRFs obtained by the PCL model (dotted line), Fine's model (dashed line), and by deconvolution using SVD (circles).

Figure 3-7 Diseased kidney study case. (a) The kidney TAC (circles) is fitted using the PCL model (dotted line) and Fine's model (dashed line). The SSR for PCL model and Fine's model are 59 and 71, respectively. (b) The corresponding renal IRFs obtained by the PCL model (dotted line), Fine's model (dashed line), and by deconvolution using SVD (circles).

Table 3-1 Comparison of PCL and Fine's model in estimating MTT_p and f for 12 kidney cases.

Case	MTT_p (s)		f (%)	
	PCL	Fine	PCL	Fine
1	213	213	18.0	17.0
2	850	1088	10.0	10.0
3	988	1033	13.4	13.4
4	162	177	8.8	10.1
5	127	128	15.8	12.1
6	184	189	26.7	26.9
7	214	221	8.6	8.4
8	293	300	9.8	7.1
9	227	235	9.3	9.1
10	201	216	12.2	11.7
11	316	320	14.6	11.2
12	187	214	12.9	13.1

3.3.4 Concluding Remarks

Despite its simplicity, it was found that the PCL model could give parameter (MTT_p and f) estimates that are in good agreement with a more elaborate model, in the patient study. Further comparison of the resultant renal IRFs by the two models shows that there are some small differences between these two renal IRF, which is likely due to the linear approximations of the present PCL model on the downslope processes, but they are not too severe to result in significant deviation of the estimates of MTT_p and f . Computation of the PCL model result takes less than half the time of the Fine's model. Hence a clear advantage of the PCL model is its ease and efficiency of calculation.

3.4 Inclusion of Vascular Delay

PCL model, which is essentially a linear version of previous Fine's model, was proposed for more efficient identification of MTT_p and f from 10s-interval TACs. Both PCL and Fine's model assume that, immediately after the unit-impulse input, tracer begins to flow out from vascular pathway. That is to say, at least one vascular pathway is so short that can be regarded as with 'zero' length, and thus there is no vascular delay (minimum vascular transit time, $MinTT_b$) in the models. This assumption seems to be valid when the models are applied for analyzing 10s-interval renograms. In the following, the indispensability of such vascular delay in some situations will be demonstrated, and then Fine's model with vascular delay will be presented.

Theoretically, vascular delay for renal IRF does exist. As introduced in section 3.1, blood plasma with tracer transits in and out of kidney, through two similar length-distributed capillary systems: vascular and tubular. Every single vascular pathway is composed of a series of arteries, arterioles and veins. Although, because of higher pressure, transit in such vascular pathway is much faster than that in tubular pathway, the vascular transit time can not to be zero, even for the shortest one. Blood flow measurement by Blaufox et al [111] showed that it takes at least 5s for tracer to go through renal vascular capillary, which means the vascular delay is about 5s. With CT imaging, Lee [75] provided an estimate for vascular delay of 4~10s. Analogous to the minimum parenchymal transit time ($MinTT_p$), one could also define a minimum vascular transit time $MinTT_b$, to denote a finite time taken by the tracer to traverse the shortest vascular path. In deconvolution

analysis of 10s-interval TACs, MinTT_b of a few seconds can not be reliably identified, because of the long time interval.

Besides the 10s-interval image frames, protocols of renal scintigraphy in most centers allows collection of 1s-interval frames in the initial 1 or 2 min for perfusion study. Dynamic images of such temporal resolution can potentially be used for studying the rapid vascular process and identifying MinTT_b . For analyzing these images by model fitting approach, a vascular delay is incorporated in Fine's model for future use. The symbols and notations used in the improved model are summarized in Table 3-2.

Table 3-2 The symbols for the various parameters used in this work

Symbol	Parameter	Units	Corresponding parameters in	
			$R_{\text{Fine}}(t)$	$R_{\text{Fine},d}(t)$
F	Renal plasma flow	ml/min/100ml		
MinTT_b	Minimum vascular transit time	s		τ_v
MTT_b	Mean vascular transit time	s	$2\tau_b$	$\tau_v+2\tau_b$
f	Extraction fraction	%		
E	Extraction rate	ml/min/100ml	$E = fF/100$	$E = fF/100$
MinTT_p	Minimum parenchyma transit time	s	τ_t	τ_t
MTT_p	Mean parenchyma transit time	s	$\tau_t+2\tau_c$	$\tau_t+2\tau_c$

In Fine's model, MinTT_b can be incorporated in the model in a consistent manner as MinTT_p (Eq. 3.2), to give

$$R_{\text{Fine},d}(t) = 1 - h_b(t) - h_p(t) , \quad (3.4a)$$

where

$$h_b(t) = u(t - \tau_v)(1 - f) \left[1 - \left(\frac{t - \tau_v}{\tau_b} + 1 \right) \exp \left(- \frac{t - \tau_v}{\tau_b} \right) \right] \quad (3.4b)$$

and

$$h_p(t) = u(t - \tau_t)f \left[1 - \left(\frac{t - \tau_t}{\tau_c} + 1 \right) \exp \left(- \frac{t - \tau_t}{\tau_c} \right) \right] . \quad (3.4c)$$

Here, $h_b(t)$ denotes the cumulative outflow due to the vascular phase, which takes effect after a time τ_v , corresponding to the minimum vascular transit time, MinTT_b . For $0 < t < \text{MinTT}_b$, as all the tracer in the injected bolus is still within the kidney, $R_{d,Fine}(t)$ remains constant (unity), exhibiting a short plateau for the vascular phase. The vascular mean transit time is then given by $\text{MTT}_b = \tau_v + 2\tau_b$. Similarly, $h_p(t)$ denotes the cumulative outflow due to the parenchymal phase, and its associated parameters are the same as the original Fine's model. Hereafter, we shall refer to Eq. (3.4) as the Fine's model with vascular delay.

For $t < \tau_t$, $R_{Fine,d}(t)$ is only characterized by the first two terms, i.e

$$R_{Fine,d}(t) = 1 - h_b(t), \quad t < \tau_t \quad (3.5)$$

since $h_p(t) = 0$ and there is no tracer outflow due to parenchymal phase. It is noted that $R_{Fine,d}$ in Eq. (3.5) contains only renal vascular parameters. This feature is due to the fact that vascular transit is much rapider than parenchyma transit, and will be very useful for parameter identification, as in Chapter 4.

The application of $R_{Fine,d}$ will be in the next chapter. Vascular phase of renal R can not be determined reliably with conventional model fitting of the 10s-interval renogram, even if

Fine's model with vascular delay is employed. In next chapter, a novel model fitting method is proposed, which is able to process the 1s-interval and 10s-interval frames simultaneously. Utilizing the new fitting method and $R_{Fine,d}$, renal vascular parameters such as MTT_b and $MinTT_b$ can be reliably identified.

3.5 Concluding Remarks

In this chapter, principles of physiologic modeling and a previous model for renal IRF, Fine's model were first reviewed. A piecewise linear continuous model was proposed by simplifying the nonlinear down-slopes in typical renal IRF model as linear segments. Compared with Fine's model, the simpler PCL model is more efficient and able to identify important parameters such as MTT_p and f with comparable accuracy. On the other hand, vascular delay was incorporated into Fine's model, with the aim of characterizing renal vascular phase more realistically. Fine's model with vascular delay is potentially useful in reliably extracting information of renal vascular phase from dynamic images. In next chapter, Fine's model with vascular delay will be applied with the aid of proper model fitting approach.

Chapter 4

Biphasic Model Fitting

4.1 Introduction

Renal scintigraphy and its post-processing were briefly reviewed. Dynamic renal scintigraphy is a well-established imaging technique in nuclear medicine, commonly used for the diagnosis of renovascular and obstructive diseases ([41], [48], [112], [113], [114], [115], [116], [117], [118]), evaluation of bilateral renal function ([31]), and postoperative follow-up of kidney transplantation ([40], [119], [120]). It involves the intravenous injection of a radiopharmaceutical tracer (such as ^{99m}Tc -DTPA), and subsequent temporal imaging using a gamma camera. The imaging protocol typically involves two sequences. An initial rapid sequence of images is acquired with a short time interval ($\sim 1\text{s}$) for a duration of about 1 min (this is sometimes called perfusion imaging ([48], [117])), followed by a second imaging sequence of a longer time interval ($\sim 10\text{s}$) for the next 20-30 min. The time-activity curves (TACs) associated with the arterial input and kidneys, can be respectively derived from regions-of-interest (ROIs) defined over the left ventricle

(LV) and the kidneys, in the dynamic images. Clinically useful parameters associated with renal function can be obtained by analyzing these TACs.

Conventionally, the assessment of renal parenchymal function and renal blood flow (perfusion), tend to proceed separately, with different methodologies for analysis of the TACs. The former usually employs the approach of non-parametric deconvolution to estimate the parenchymal mean transit time (MTT_p) ([33], [37], [38], [73], [83], [85], [121]), which can provide diagnostic information for diseases such as obstructive uropathy ([85], [116], [122]) and renovascular hypertension (RVH) ([37], [41], [112], [113], [114], [118]). However, the assessment of renal blood flow typically involves the calculation of empirical parameters, such as the kidney-aorta ratio (K/A) ([123]). The vascular flow parameters are estimated using the initial perfusion imaging sequence with a short time interval, while the estimation of MTT_p using deconvolution analysis usually involves the combined TACs of both short and long temporal imaging sequences. To combine the TAC data from the two imaging sequences of different time intervals, the initial 1s-interval data are summed to obtain data of a longer time interval (10s), before appending the rest of the 10s-interval data.

Recent studies have shown the possibility of simultaneous estimation of both vascular and parenchymal parameters by the approach of model fitting ([38], [85]), also known as parametric deconvolution. A model of the renal impulse retention function (IRF) is first constructed or assumed, with parameters associated with the physiological processes of interest. Modeling of renal IRF was introduced in Chapter 3. The renal TAC ($K(t)$) can be

related to the input TAC ($I(t)$) and $R(t)$, by a convolution integral as in Eq (2.11) [75]. $K(t)$ is then optimally fitted to the sampled renal TAC, by adjusting the model parameters. The values of the parameters that give the best fit, are taken as the parameter estimates. For example, Fine's model [38] allows the estimation of blood flow (F), vascular mean transit time (MTT_b), extraction fraction (f), and MTT_p . In Eq. (2.11), since $K(t)$ and $I(t)$ can be obtained from the scintigraphic images, the quantity $F \cdot R(t)$ thus encompasses the unknown parameters that must be estimated by model fitting.

However, as the approach of model fitting uses the entire arterial and renal TACs at 10s interval, the estimated vascular parameters obtained may not be as accurate as the parenchymal parameters. This is because for a time interval of 10s, the more rapid vascular phase (~ 10 -30s) is only represented by the initial few (~ 1 -3) points on the $R(t)$ function, which may not adequately capture the essential features of the vascular phase. Estimation of the vascular parameters, based on a few points of $R(t)$, hence suffers from greater errors as compared with the parameters associated with the parenchymal phase, which is represented by more points on the $R(t)$ curve.

In the following, a biphasic model fitting approach is proposed, which yields both the vascular and parenchymal parameters, but with the aim to improve on the estimation of the vascular parameters. Fine's model with vascular delay ($R_{\text{Fine,d}}$), which was presented in Chapter 3, is employed for model fitting. Monte Carlo simulation experiments were performed to study the confidence of the parameter estimates obtained from the proposed biphasic approach, and to demonstrate the strength of biphasic model fitting using $R_{\text{Fine,d}}$

in identifying renal vascular parameters. The proposed approach is also applied to patient study cases, to study its applicability in the diagnosis of several renal diseases.

4.2 Materials and Method

4.2.1 Biphasic Model Fitting

The proposed biphasic model fitting approach attempts to maximally utilize the information content in the two imaging sequences (1s- and 10s-intervals), by first fitting the vascular parameters of the model using only data derived from the short interval imaging sequence, before combining both short and long interval data to estimate the parenchymal parameters. The rationale for the biphasic fitting approach can be explained as follows. As the vascular phase takes place earlier than the parenchymal phase, the initial portion of the short-interval data points in the renal TAC is largely dominated by the vascular process. For the initial time period of about 40s, corresponding to $t < \text{MinTT}_p$, there is no tracer outflow through the tubular pathways, hence any tracer outflow within the initial period can be attributed to vascular transport, and the vascular parameters can be more accurately estimated by fitting these initial data points, without considering the parenchymal parameters. Once the vascular parameters are estimated, they are kept constant while the parenchymal parameters are estimated using the entire TAC (combining both short and long interval data).

When applying the biphasic fitting approach with the Fine's model with vascular delay (Eq. 3.4), the first vascular fitting phase does not involve $h_p(t)$ (Eq. 3.5), and the vascular

parameters that can be estimated in the first fitting phase are F , MinTT_b and MTT_b . Although the extraction fraction f is also included in $h_b(t)$, it can be more accurately determined in the second parenchymal phase fitting when a longer data sequence is included. Therefore, in the first fitting phase, f is treated as a dummy parameter and its estimated value discarded. In the second parenchymal fitting phase, the entire expression for $R_{\text{Fine},d}(t)$ (Eq. 3.4) is used, but with the values for F , MinTT_b and MTT_b fixed (at the values obtained in the first fitting phase), and the parenchymal parameters that are adjusted for fitting are f , MinTT_p and MTT_p . A block diagram of the biphasic model fitting approach is shown in Figure 4-1.

Figure 4-1 A block diagram illustration of the proposed biphasic parameter estimation approach. Let V and P respectively denote the sets of vascular and parenchymal parameters. In Fine's model with vascular delay, $V = \{F, \text{MinTT}_b, \text{MTT}_b\}$, and $P = \{f, \text{MinTT}_p, \text{MTT}_p\}$. In the first vascular fitting phase, the parameters in V are varied to achieve the best fit, and the parameter estimates $\hat{V}$ are obtained. In the second parenchymal fitting phase, which involves the combined TACs with 10 s interval, parameters in V are fixed at $\hat{V}$, and the parameters in P are varied to obtain the estimates $\hat{P}$.

To better appreciate the advantages of fitting the vascular process using the initial short interval data, it is instructive to illustrate some of the possible artifacts that could arise due to the summing of 1s-interval data to obtain data of 10s interval. In Figure 4-2, the initial portion of a renal TAC and LV TAC with 1s intervals are shown, together with the

corresponding 10s-interval TACs obtained by summing every ten points. Due to the summation of 1s-interval data and the discrete positioning of the resulting 10s-interval points, the peak positions of the 10s-interval TACs may not correspond with those of the original 1s-interval data. Hence, the values of F estimated from the two datasets could differ slightly, since the values of the 10s-interval TAC are not exactly 10 times that of the 1s-interval TAC. These artifacts due to the summation of 1s-interval data, could also result in discrepancies in the estimation of the other vascular parameters. One may view the summing (or averaging) of short-interval data points to obtain one point of a longer time interval, as a loss of information. In this sense, the first vascular fitting phase attempts to optimally utilize the information in the short-interval perfusion imaging sequence to estimate the vascular parameters.

Figure 4-2 The initial portions of an input (LV) TAC (a) and renal TAC (b) are shown with time intervals of 1s (circles) and 10s (squares).

4.2.2 Monte Carlo Simulation Studies

The Monte Carlo simulation was carried out with 3 objectives: (1) to evaluate the accuracy and consistency of the biphasic fitting method using Fine's model with vascular delay in the estimation of the various model parameters; (2) to demonstrate the advantage of biphasic fitting over conventional fitting method; (3) and to illustrate the benefit of including vascular delay in renal IRF model.

The input TAC used in the simulation was obtained from the left ventricle of one patient study (1s/frame for the first 60 frames, followed by 10s/frame for the next 150 frames) as shown in Figure 4-2(a). Using Eq. (2.11), simulated renal TACs ($K(t)$) were generated by convolution of the model $R(t)$ (Eq. (3.4)) with the input TAC. Examples of such simulated $R(t)$ s and $K(t)$ s are shown in Figure 4-3. The parameter values for MinTT_b , f , MinTT_p , MTT_p are chosen to reflect normal and pathologic (renovascular hypertension (RVH) or obstruction (Obs)) conditions [38] [41] [112] [115] [124]. There are few references in literature on the values of F and MTT_b for the various conditions, and the typical values encountered in clinical studies have been used. These values are shown in Table 4-1.

Poisson noise was added to the simulated renal TAC, before employing the biphasic approach to estimate the model parameters. For a signal corrupted by Poisson noise, the signal-to-noise ratio (SNR) for each signal point can be given by the ratio of its value and the standard deviation of the Poisson noise [125]. The mean of the SNRs associated with

all data points provides an estimate of the degree of Poisson noise introduced. In this study, a mean SNR of ~ 10 was used to simulate the noisy 1s-interval renal TACs. The 10s-interval TAC is typically associated with a better SNR than the 1s-TAC (as the gamma camera was exposed for a longer period of time) and a mean SNR of ~ 30 was used. These noise levels are typical of TACs obtained clinically.

Figure 4-3 Examples of normal (R_{Norm}) and RVH (R_{RVH}) impulse retention functions constructed using Fine's model with vascular delay (a), and the corresponding noisy renal TACs (b) used in the simulation studies. The inset in (a) shows the corresponding $R(t)$ s with 1s intervals.

Table 4-1 Values of the various parameters assumed for the simulation of $R(t)$ associated with different pathologies: R_{Norm} (Normal), R_{RVH} (Renovascular hypertension), and R_{Obs} (Obstruction.)

	F (ml/min/100ml)	MinTT _b (s)	MTT _b (s)	f (%)	MinTT _p (s)	MTT _p (s)
R_{Norm}	229	5	9	20	90	150
R_{RVH}	120	5	12	14	90	200
R_{Obs}	150	5	10	20	90	370

For each simulated kidney condition, 1000 noisy renal TACs were generated and fitted, using various model fitting schemes (I: conventional model fitting (Fine's model with vascular delay), II: biphasic approach (Fine's model), and III: biphasic approach (Fine's model with vascular delay)), respectively. The fitting process was driven by Levenberg-Marquardt optimization (MatlabTM), in which sum of squared residue between noisy simulated K and model-predicted K is minimized. The mean and standard deviation (SD) of each parameter estimate obtained for the 1000 simulation runs, indicate its accuracy and consistency, respectively. The potential bias in the estimation of each parameter can be given by the absolute difference between its mean and actual value. The coefficient of variation for a parameter can be given by $CV = SD/\text{mean}$, which gives a measure of the level of uncertainty associated with the estimation of the parameter. For a robust estimation scheme, it would be desirable for both the bias and CV to be small.

4.2.3 Patient Studies

The renal scintigraphic studies were performed with the patients supine, and with the intravenous administration of 500MBq ^{99m}Tc -DTPA. Image frames were acquired at 1s intervals for the first minute and at 10s intervals for the following 25 minutes, with each frame recorded in a 128×128 matrix. The kidneys and heart were included within the field of view. As shown in Figure 4-4, the renal TAC, $K(t)$, was derived from a ROI manually drawn over the renal cortex, and the input TAC, $I(t)$, was obtained from a LV ROI. All TACs were normalized by the respective areas of their ROIs. Background-correction was performed by subtracting from $K(t)$, the average activity values of a region below the kidney ROI.

Figure 4-4 Regions of interest (ROIs) manually drawn over the left ventricle (LV) and renal cortexes to obtain the input ($I(t)$) and renal ($K(t)$) TACs. Background activities were estimated by ROIs below the kidneys, and subtracted from the respective renal TACs.

A total of 14 kidney cases were analyzed, with normal and various pathologic conditions. Final diagnosis of the cases with renovascular hypertension (RVH) was achieved by magnetic resonance angiography (MRA), and that of the obstructive ones by intravenous urography (IVU) or computed tomography of kidneys, ureters and bladder (CT-KUB), depending on the clinical suspicion. For two of the cases suspected of RVH, captopril studies were also performed, after oral administration of captopril and the data were acquired under the same conditions as the baseline studies.

The proposed biphasic model fitting method was applied using Fine's model with vascular delay, for the analysis of the patient study cases. For comparison, conventional model fitting with the original Fine's model (i.e. without vascular delay) was also applied on the patient cases. To compare with other perfusion measures, an aorta ROI was also

drawn to derive an area-normalized aorta TAC ($A(t)$) for each patient case. K/A was calculated as the ratio of the maximal slopes on the rising portions of the renal and $A(t)$, with 1s time intervals [123]. A perfusion index (PI) often used with dynamic computed tomography for the measurement of organ perfusion [126], can be given by

$$PI = \frac{\frac{d}{dt} K(t)}{A(t)} \Big|_{t=t_p}, \quad (4.1)$$

where t_p is the time-to-peak of $A(t)$. The possible correlation and association between these perfusion measures with those obtained by conventional and biphasic model fitting, can be studied using linear regression analysis and the correlation plot. A unit slope (m) and zero y-intercept (c) in the correlation plot would indicate quantitative correspondence of the two parameters.

4.3 Results and Discussion

Monte Carlo Simulation Studies

Results of the Monte Carlo simulation are tabulated in Table 4-2. The biases of the various parameter estimates by scheme III (the biphasic approach using Fine's model with vascular delay) are small, deviating not more than 5% from their actual values. The biases of both vascular (F and MTT_b) and parenchymal parameters (f , $MinTT_p$ and MTT_p) are markedly smaller than those by conventional approaches. The percentage CV values for all the parameter estimates by the biphasic approach are generally acceptable, ranging from 2-13%, except for $MinTT_b$. As the actual values assumed for $MinTT_b$ are small, slight deviations from these values would result in significant percentage changes. However, it is noted that the variations in $MinTT_b$ did not affect MTT_b significantly, and

the CV values for MTT_b by the proposed method are not more than 8%. These results suggest that the proposed biphasic estimation scheme is reasonably stable under typical noise conditions associated with TACs obtained clinically.

In Table 4-2, results of scheme I (conventional fitting using $R_{Fine,d}$) show that F of various simulated cases are markedly overestimated, as compared with the actual values and the estimates by scheme III. The overestimation of F is probably due to the fact that, in summation of 1s-interval frames to 10s ones, LV TAC is lowered by a larger extent than that of renal TAC, as observed in Figure 4-2. Accordingly, filtration fraction f is underestimated, as the parenchyma plateau (excretion rate, E) can be reliably identified ($f = 100 \cdot E/F$) and the overestimation of F directly leads to the underestimation of f . The deviation of vascular transit times from their respective actual value is also obvious, but the SD is low because of higher signal-to-noise ratio of 10s-interval data. Compared with conventional model fitting, biphasic model fitting contributes to improve the accuracy of vascular parameters for two reasons. Firstly, with biphasic fitting, 1s-interval TACs can be analyzed directly without being summed as 10s-interval one, as in conventional fitting, thereby avoiding loss of vascular information. Secondly, estimation of vascular parameters mainly relies on the fitting of the initial short segment (the first minute) of renal TAC. In conventional fitting, the whole renal TAC is fitted by minimizing an overall SSR, and the fitting of the initial short segment may be sacrificed more or less to achieve a 'global' best fitting. In contrast, through fitting the initial short segment separately, biphasic model fitting avoids the problem.

Table 4-2 Results of Monte Carlo simulations on the precision of the various parameter estimates obtained by conventional model fitting using Fine's model with vascular delay ('I'), and biphasic approach using both Fine's model ('II') and that with vascular delay ('III'). Each entry represents the mean $\pm$ SD of 1000 simulation runs. The values in the brackets are the respective percentage CV.

Method	F (ml/min/100ml)	f (%)					
		MintT _b (s)	MTT _b (s)	f (%)	MintT _p (s)	MTT _p (s)	
R_{Norm}	I	341±7 (2.2)	7.1±0.1 (1.6)	9.1±0.1 (0.8)	11.6±0.4 (3.0)	104±3 (3.4)	158±2 (1.0)
	II	269±9 (3.5)	0	8.3±0.5 (6.5)	15.7±0.5 (3.4)	100±4 (4.5)	157±2 (1.1)
	III	226±8 (3.6)	5.1±1.3 (25.0)	9.0±0.4 (4.8)	19.9±1.5 (7.5)	92±8 (8.7)	152±4 (2.6)
R_{Env}	I	199±5 (2.7)	7.6±0.1 (1.2)	9.4±0.1 (0.7)	8.1±0.4 (4.4)	95±8 (8.6)	205±4 (1.9)
	II	136±5 (4.0)	0	12.3±1.1 (8.8)	10.9±0.6 (5.2)	112±12 (10.9)	215±7 (3.2)
	III	120±6 (4.7)	5.0±1.7 (34.5)	12.0±0.9 (7.4)	14.1±1.3 (9.1)	89±15 (17.1)	201±9 (4.3)
R_{Obs}	I	223±7 (2.9)	7.8±0.1 (0.8)	9.4±0.1 (0.6)	12.6±0.4 (3.4)	112±7 (6.0)	387±3 (0.9)
	II	173±7 (3.9)	0	9.6±0.8 (8.6)	16.4±0.6 (3.4)	109±9 (8.2)	385±5 (1.4)
	III	149±6 (4.2)	5.0±1.4 (27.4)	10.0±0.6 (5.9)	19.9±1.1 (5.6)	93±13 (13.7)	374±8 (2.1)

For analyzing 1s-interval data by biphasic fitting method, the vascular delay in the renal IRF model is necessary. According to results of scheme II (biphasic fitting using Fine's model) in Table 4-2, missing of vascular delay leads to overestimation of renal blood flow, F , and underestimation of filtration fraction, f . The reason for overestimation of F here is different from that in results of scheme I, as described above. Without vascular delay, the IRF decreases immediately after time 0. In fitting the renal TAC by convolution of LV TAC and F -scaled IRF (without vascular delay), the initial height of F -scaled IRF, i.e. F , has to be set at a value higher than the actual one, to compensate the absence of a vascular plateau.

Study of inter-parameter correlations helps us better appreciate the advantage of biphasic fitting. The correlation matrix (denoted as 'CM') of the parameters estimates in R_{Norm} by the biphasic method (Fine's model with vascular delay) is presented in Table 4-3. Of all the off-diagonal elements, CM(1:3, 4:6) correspond to the correlations between vascular (F , MinTT_b and MTT_b) and parenchyma (f , MinTT_p and MTT_p) parameters, which are of most interest. The majority of these elements are not more than 0.35, indicating little correlation between the associated parameters. The elements larger than 0.70 include those related to MinTT_b and that between F and f . The existence of these correlations can be explained by the fact that the vascular parameters determined in the first fitting are used for calculations in the second fitting of the biphasic method, thus influence the optimization of parenchyma parameters. As observed in Table 4-2, the accuracy of the parenchymal parameters is still satisfactory, implying that the above-mentioned influence is negligible. On the other hand, the possible influence from parenchymal parameters to

the estimation of the vascular ones is successfully avoided in the proposed method, through fixing the vascular ones in the second fitting.

Table 4-3 The correlation matrix of the 6 parameters (F , MinTT_b , MTT_b , f , MinTT_p and MTT_p) of R_{Norm} , estimated by the proposed method (Table 4-2).

F	MinTT_b	MTT_b	f	MinTT_p	MTT_p	
1.00	-0.61	-0.55	-0.72	0.30	0.31	F
	1.00	0.12	0.87	-0.70	-0.75	MinTT_b
		1.00	-0.00	0.32	0.35	MTT_b
			1.00	-0.82	-0.87	f
				1.00	0.92	MinTT_p
					1.00	MTT_p

Patient Studies- consistency between estimated parameters and pathology

The estimated parameters for the 14 kidney study cases, using the proposed biphasic fitting approach and Fine's model with vascular delay, are shown in Table 4-4. For the 6 normal kidneys, the average ($\pm\text{SD}$) values of f , MinTT_b , MTT_b , and MTT_p were found to be 14.8 ± 1.0 %, 3.4 ± 0.8 s, 8.5 ± 1.6 s, and 187 ± 22 s, respectively. These values are in agreement with those reported in the literature [31] [37] [38] [112] [119] [124]. For the normal kidneys, the average values for F and E obtained using the biphasic approach were respectively, 229 ± 47 ml/min/100ml and 33.6 ± 5.7 ml/min/100ml. These values are in good agreement with those obtained using dynamic computed tomography ($F=250\pm70$

ml/min/100ml) [127] and magnetic resonance imaging ($F=235\pm49$ ml/min/100ml, $E=40\pm20$ ml/min/100ml) [128].

Table 4-4 Results of patient study cases obtained using the proposed biphasic estimation scheme. The abbreviations used are: RVH: renovascular hypertension; Obs.: obstruction; G.perf: good perfusion; P.func: poor function; G.func: good function.

Case	F (ml/min/100ml)	MinTT _b (s)	MTT _b (s)	f (%)	E (ml/min/100ml)	MinTT _p (s)	MTT _p (s)	Diagnosis
1	216	2.8	10.0	15.2	33.0	191	221	Normal
2	180	3.0	10.0	16.6	30.0	166	200	Normal
3	264	4.6	6.5	14.1	47.2	142	165	Normal
4	306	4.2	6.6	14.1	43.2	141	161	Normal
5	216	3.0	8.4	13.9	30.0	111	186	Normal
6	192	2.6	9.5	14.7	28.2	161	186	Normal
Ave $\pm$ SD	229 $\pm$ 47	3.4 $\pm$ 0.8	8.5 $\pm$ 1.6	14.8 $\pm$ 1.0	33.6 $\pm$ 5.7	152 $\pm$ 27	187 $\pm$ 22	
7	114	3.2	14.1	8.3	9.6	293	357	RVH
8	120	3.3	10.0	20.0	24.0	97	132	RVH
9	132	6.1	13.1	16.6	22.2	115	180	No RVH
	162	0.8	9.4	15.2	24.6	102	132	
9	182	3.4	9.9	14.3	25.8	123	146	No RVH
10	90	2.4	13.2	16.8	15.0	14	1330	Obs.
11	150	2.6	5.7	18.2	27.6	262	1088	Obs.
12	204	2.0	12.4	16.9	34.2	145	470	Partial Obs
Ave $\pm$ SD	148 $\pm$ 57	2.3 $\pm$ 0.3	10.4 $\pm$ 4.1	17.3 $\pm$ 0.8	25.6 $\pm$ 9.8	140 $\pm$ 124	963 $\pm$ 443	
13	126	2.7	17.2	1.8	2.4	0	857	Transplant, G.perf & P.func
14	114	10.0	14.2	24.4	27.6	50	182	Transplant, G.perf & G.func

^a Parameters on the row are from captopril scintigraphy.

Three kidney study cases were related to RVH. Case 7 was diagnosed with RVH from the baseline scintigraphy study, and Case 8 was diagnosed with RVH after both baseline and captopril studies. However, Case 9 was diagnosed with ‘no RVH’ after both baseline and captopril studies. As compared with the average parameter values for the normal cases, Case 7 showed lower F (114 vs. 229 $\pm$ 47 ml/min/100ml), longer MTT_b (14.1 s vs. 8.5 $\pm$ 1.6 s), lower E (9.6 vs. 33.6 $\pm$ 5.7 ml/min/100ml), and longer MTT_p (357 s vs. 187 $\pm$ 22 s). These abnormalities in the parameters indicate that the Case 7 was in a rather advanced stage of RVH. Cases 8 and 9 were examples for which a captopril study was performed before the final diagnosis could be made, in hope that notable changes in some of the

parameter estimates, as induced by captopril, could provide further information for diagnosis. In the baseline study of Case 8, most parameters were within their respective normal ranges, except for F (120 vs. 229 ± 47 ml/min/100ml) and E (24 vs. 33.6 ± 5.7 ml/min/100ml). Changes in the parameters induced by captopril were as follows: F , MTT_b and MTT_p increased by 10%, 31% and 36%, respectively; while E decreased by 7.5%. For Case 9, the only abnormal parameter in the baseline study was E (24.6 vs. 33.6 ± 5.7 ml/min/100ml). The captopril-induced variations in the parameters were less dramatic as compared with those of Case 8. F , MTT_b and MTT_p increased by 12%, 5.3% and 11%, respectively, and E increased by 5%. These results suggested that an increase in F , with a concurrent significant increase in MTT_b and MTT_p (by about 30% or more) after captopril administration, could be indicative of RVH.

For the cases related to obstruction, the prolonged MTT_p estimates obtained by the present biphasic estimation scheme are consistent with the pathology. Cases 10 and 11 which were diagnosed with obstruction yielded significantly longer MTT_p (1330 s and 1088 s, respectively) than the normal average (187 ± 22 s). Case 12 which was diagnosed with partial obstruction also exhibited a prolonged MTT_p of 470 s as compared with the normal cases.

The two transplanted kidney cases were diagnosed with good perfusion, but Case 13 was diagnosed with poor function while Case 14 had good function. Consistent with the diagnosis, both kidneys yielded similar vascular parameter values for F (126 and 114 ml/min/100ml) and MTT_b (17.2 s and 14.2 s); but the estimated parenchymal parameter

values for MTT_p (857 s and 182 s) and E (2.4 and 27.6 ml/min/100ml) were drastically different, and are indicative of their respective functional status.

Correlation plots- comparison with established indices

To further compare the parameters obtained using the conventional and biphasic fitting schemes, correlation plots for F , MTT_b , E and MTT_p obtained using the two estimation schemes, are shown in Figure 4-5. In all the correlation plots, the subscript 1 denotes parameter estimates obtained by conventional fitting and Fine's original model, while subscript 2 denotes the estimates obtained by the present biphasic fitting approach and Fine's model with vascular delay. As expected, the correlation plots for the parenchymal parameters showed good correspondence, with $m=0.96$, $c=-0.72$ and $r^2=0.999$ for MTT_p and $m=1.00$, $c=1.49$ and $r^2=0.964$ for E . However, estimates for the vascular parameters showed little correlation, with $m=0.31$, $c=6.7$ and $r^2=0.399$ for MTT_b and $m=0.39$, $c=100.1$ and $r^2=0.386$ for F . As explained in the previous sections, these discrepancies in the vascular parameters can be attributed to the possible artifacts illustrated in Figure 4-2, and the difficulty of the conventional approach to estimate the vascular parameters based on a few initial points on the impulse retention function $R(t)$.

The correlation plots for comparing F and the K/A ratio obtained for the patient study cases, are shown in Figure 4-6. The correlation coefficients obtained for F_1 against K/A, and for F_2 against K/A, are respectively 0.442 and 0.821. The correlation plots for comparing F with PI obtained for the patient study cases, are shown in Figure 4-7. The correlation coefficients obtained for F_1 against PI, and for F_2 against PI, are respectively 0.554 and 0.884. It is clear that the F estimates obtained using the proposed biphasic

fitting scheme (i.e F_2) exhibited consistently better correlation with K/A and PI, than those obtained by conventional model fitting. In Figure 4-6 and Figure 4-7, it is also noted that, of all 4 parameters (K/A, PI, F_1 and F_2), only F_2 could differentiate normal (including nonRVH-baseline and captopril) and RVH kidney groups, as indicated by the horizontal dotted lines on the correlation plots. Further investigation on more RVH patient cases would be required to verify the usefulness of F_2 .

Figure 4-5 Correlation plots for comparison of the various parameters obtained for the patient study cases, using the conventional (subscript 1) and biphasic (subscript 2) approaches. (a) F , (b) MTT_b , (c) E , (d) MTT_p . In each plot, m and c respectively denote the slope and y-intercept of the linear regression line. r^2 is the correlation coefficient.

Figure 4-6 Correlation plots for comparison of the estimated F with K/A obtained for patient study cases. (a) Correlation between K/A and F_1 . (b) Correlation between K/A and F_2 . The symbols and notations used are the same as in Figure 4-5. The horizontal dotted line in (b) illustrates that F_2 can be used to differentiate between normal and RVH cases. Only 14 kidney cases were included in this correlation study, as the aorta TAC cannot be identified for two of the kidneys.

Figure 4-7 Correlation plots for comparison of the estimated F with PI obtained for patient study cases. (a) Correlation between PI and F_1 . (b) Correlation between PI and F_2 . The symbols and notations used are the same as Figure 4-6.

The K/A ratio has been used for the evaluation of transplant perfusion and Kirchner et al [123] found that the K/A ratio correlated with renal blood flow measured electromagnetically. The good correlation with the K/A ratio suggests that the F estimates obtained using the present biphasic estimation scheme could potentially be used for the evaluation of transplant perfusion. Additionally, the proposed biphasic approach can also simultaneously yield parenchymal parameter estimates for E and MTT_p , which are indicative of the functionality of the transplanted kidney.

Captopril renography is commonly employed as the main screening test for the diagnosis of RVH. In patients suffering from RVH, renal blood flow is decreased, usually due to renal artery stenosis, and the renin-angiotensin system is activated, resulting in the vasoconstriction of efferent arterioles. This in turn leads to the elevation of filtration pressure within the glomerulus, which could increase the filtration fraction and GFR. After the administration of captopril, renin is blocked, leading to a fall in GFR and prolonged parenchymal transit time. Hence, a captopril-induced prolonged MTT_p is commonly employed by many centers as a criterion for RVH. However, as the RVH-related pathologic changes take place originally within the vascular pathways, the vascular parameters could also be sensitive to such changes. Thus, the ability to accurately estimate the vascular parameters may potentially be useful in the diagnosis of RVH. Arteriolar vasoconstriction directly leads to the decrease in renal blood flow (F), and the administration of captopril may conversely result in the increase of F , although to a smaller extent, as in Case 8. An increase in MTT_b after captopril administration could be the combined effects of restored vascularization (i.e restored vascular pathways and

volume) and the reduction in vascular pressure due to vasodilation. The use of both vascular and parenchymal parameters could thus provide more information relevant to the diagnosis of RVH using captopril renography.

Besides its advantage of simultaneous estimation of both vascular and parenchymal parameters, the biphasic fitting approach was found to be computationally more efficient than the conventional approach. In the biphasic approach, the task of finding an optimal solution in a high-dimensional parameter space is converted to a search in two low-dimensional spaces, which reduces computation from the perspective of optimization. In the patient study cases, it was found that the time cost of implementing the biphasic approach was less than 30% that of the conventional approach.

4.4 Concluding Remarks

The biphasic model fitting approach exploits the separability of phases in the renal impulse retention function and the different temporal resolutions in the two scintigraphic imaging sequences, to optimally estimate the vascular and parenchymal parameters. Monte Carlo simulation studies indicated that the proposed biphasic approach is stable under typical noise conditions for TACs obtained clinically, and biphasic fitting using Fine's model with vascular delay provides accurate estimates for renal vascular parameters. Results of patient study cases with various renal pathologies showed that the blood flow estimates obtained by the biphasic approach correlated better with established blood flow indices (K/A and PI) than those obtained by conventional fitting. The values

of the various parameter estimates obtained using the biphasic approach were found to be indicative of and consistent with the pathologies of the kidneys. The ability to simultaneously yield both vascular and parenchymal parameter estimates accurately, could potentially be useful in the diagnosis of RVH and the evaluation of kidney transplants.

Chapter 5

Flip Angle Optimization: A Numerical Method

5.1 Introduction

In Chapters 3 and 4, renal IRF models and biphasic fitting method, for model-fitting analysis of dynamic scintigraphic images, were presented. Dynamic contrast-enhanced magnetic resonance imaging (DCE MRI), as another imaging technique appropriate for assessing renal function, provides images of high spatial resolution and does not employ radioactive tracer. Besides its usefulness in assessing organ function, DCE MRI can also be employed for tumor detection and characterization [129] [130]. The associated organs include breast, brain, liver, kidney, and so on. For example, DCE-MRI has already been validated as a promising tool in diagnosis of breast tumors [131] [132] [133]. For all these applications, i.e. organ-function assessment and tumor characterization, it is both desirable and challenging to quantify tracer (usually termed as ‘contrast medium’ in MRI) concentration from the dynamic MR images, which will be discussed in this chapter.

Because of the versatility of DCE MRI, the discussion will not be limited to DCE MRI for assessing renal function.

DCE MRI usually involves the intravenous injection of a gadolinium (Gd) contrast medium and rapid temporal imaging to monitor the changes in the MR signal as a function of time. The primary effect of Gd is the shortening of the spin-lattice relaxation time T_1 , resulting in greater signal in T_1 -weighted images. For low concentrations (C) of the contrast medium, the change in relaxation rate $R_1 (= 1/T_1)$ is proportional to C , i.e

$$R_1^c - R_1^0 \propto C \quad (5.1)$$

where R_1^c and R_1^0 are respectively, the post- and pre-contrast relaxation rates [134]. If the changes in T_1 values can be accurately measured as a function of time (t), an important task in DCE-MRI is to further deduce $C(t)$ from which physiological variables associated with tumor microcirculation or organ functionality can be estimated by tracer kinetic modeling [135].

A class of pulse sequences suitable for T_1 -weighted DCE MRI is the spoiled gradient-recalled echo (SPGR) or fast low-angle shot (FLASH) sequences, which produces relatively artifact-free images with good temporal resolution [51] [104]. The relationship between the SPGR signal S and the various imaging parameters can be given by [51] [104] [136]

$$S = \frac{M_0 [1 - \exp(-T_R / T_1)] \sin \alpha}{1 - \exp(-T_R / T_1) \cos \alpha} \quad (5.2)$$

where M_0 is the equilibrium magnetization (which accounts for the proton density and machine gain), T_R is the radiofrequency (RF) repetition time, and α denotes the RF flip

angle. Implicit in Eq. (5.2) is the assumption of $T_E \ll T_2^*$, where T_E is the echo delay time, and T_2^* is the spin-spin relaxation time. Rapid T_1 measurement can be achieved by acquiring at least two SPGR images at different RF flip angles, from which the two unknowns in Eq. (5.2) (i.e M_0 and T_1) can be calculated.

According to Eq. (5.2), signal intensity S is dependent on two parameters T_R and α that can be freely set by the operator. Selection of these two parameters may thus affect the accuracy of T_1 determined from measured signals. The relation between S and (T_R, α) is illustrated in Figure 5-1. For fixed α , long T_R corresponds to high signal intensity, which can be attributed to the more longitudinal relaxation allowed within T_R . With a same noise level, higher signal intensity means higher signal-to-noise ratio (SNR), and thus potentially more accurate T_1 . From this perspective of view, the use of long T_R in acquiring SPGR images may help improve accuracy of estimated T_1 . However, after injection of contrast medium, the rate of image acquisition, i.e. temporal resolution, has to be high enough to record detailed information for later tracer kinetic study [137]. With T_R restricted by such requirement, the selection of appropriate flip angles is the only effective approach in improving the accuracy of estimated T_1 [51] [104]. Previous studies have shown that the accuracy of the T_1 estimates using this variable flip angle method is comparable with those by conventional saturation recovery imaging [51] [136].

In the following, a method for the selection of optimal angles for both pre- and post-contrast T_1 mapping was proposed. Monte Carlo simulation studies were carried out to evaluate and compare the present approach with an existing approach.

Figure 5-1 SPGR signal (S) as a function of both flip angle (α) and T_R , with $T_1 = 500\text{ms}$ and $M_0=1$. For every α , S increases with T_R . For every T_R , as α increases, S increases, and then decreases.

5.2 Theory

5.2.1 Optimal Angles for Pre-Contrast T_1

Eq. (5.2) can be re-cast into the linear form $Y = bX + a$ [51] as:

$$\frac{S}{\sin \alpha} = \exp(-T_R / T_1) \frac{S}{\tan \alpha} + M_0 [1 - \exp(-T_R / T_1)] \quad (5.3)$$

and the problem, of choosing N optimal flip angles to most accurately determine T_1 , would correspond to the optimal placement of N points along the linear regression line, such that the error in T_1 is minimized. It is recognized that this can also be transformed into a numerical optimization problem, with an expression for the error in T_1 as the objective function to be minimized. An appropriate candidate for the objective function was previously derived [51] in the form of a noise factor (NF):

$$\begin{aligned} \text{NF} &= \left[\frac{\Delta R_1 / R_1}{\Delta S / M_0} \right] \\ &= \frac{M_0 T_1 \exp(T_R / T_1)}{T_R N [X^2 - (\bar{X})^2]} \sqrt{\sum_{i=1}^N \left[\frac{X_i - \bar{X}}{\sin \alpha_i} + \frac{Y_i - \bar{Y} - 2 \exp(-T_R / T_1)(X_i - \bar{X})}{\tan \alpha_i} \right]^2} \end{aligned} \quad (5.4)$$

where $X_i = \frac{S_i}{\tan \alpha_i}$, $Y_i = \frac{S_i}{\sin \alpha_i}$, $\bar{X} = \frac{1}{N} \sum_{i=1}^N X_i$, $\bar{Y} = \frac{1}{N} \sum_{i=1}^N Y_i$, and $\bar{X}^2 = \frac{1}{N} \sum_{i=1}^N X_i^2$ are computed from a set of N signal data $\{S_i\}$ acquired with flip angles $\{\alpha_i\}$ at a constant T_R . Eq. (5.4) describes the propagation of noise in the signal (ΔS) into the calculation of R_1 (and hence T_1) as an uncertainty ΔR_1 [51]. The contour plot of NF as a function of 2 flip angles is shown in Figure 5-2. One interesting result previously shown by Wang et al [51] was that for $N (>2)$ flip angles, the set of optimal angles that minimizes Eq. (5.4) reduces to repetitions of the two optimal angles $\{\alpha_1^{opt}, \alpha_2^{opt}\}$ corresponding to $N=2$; i.e for an even $N (=2M)$, the N optimal angles are $\{M \times \alpha_1^{opt}, M \times \alpha_2^{opt}\}$, and for odd $N (=2M+1)$, the optimal angles are $\{M \times \alpha_1^{opt}, (M+1) \times \alpha_2^{opt}\}$ [51]. Theoretical exploration of this numerical observation will be present in Chapter 6.

Figure 5-2 Contour plot of NF as a function of 2 flip angles. $T_R=10\text{ms}$, $T_1=1000\text{ms}$, $M_0=1$. Contour lines represent percentage increases (as indicated) of NF above its minimum value (at $[3.5^{\circ}, 19.5^{\circ}]$ and $[19.5^{\circ}, 3.5^{\circ}]$).

5.2.2 Optimizing for a Range of T_1

In practical MRI, a particular tissue of interest can exhibit a range of T_1 values, and there could be a few tissue types to be imaged concurrently. Although the exact T_1 values are not known before scanning, one could always specify the particular ranges of T_1 values corresponding to the various tissue types. To account for a range of T_1 values, Wang et al [51] and Brookes et al [104] have proposed similar schemes (hereby referred to as the endpoints averaging approach): (i) Find the two sets of optimal angles corresponding to the two extreme ends (i.e $T_{1,\min}$ and $T_{1,\max}$) of the T_1 range, and (ii) perform an averaging

of the two sets of angles to arrive at one final set of angles. Although the resulting set of angles may not be optimal to any particular T_1 value within the range, it serves as a compromise and could yield reasonably good precision of T_1 for the entire range.

The following objective function is proposed for a range of T_1 values given by $[T_{1,\min}, T_{1,\max}]$:

$$\text{SNF} = \int_{T_{1,\min}}^{T_{1,\max}} \text{NF}(T_1) W(T_1) dT_1 \quad (5.5)$$

which is a summed version of all T_1 noise factors within the range. The weighting function $W(T_1)$, which is normalized within the T_1 range of interest, is included to incorporate additional information for optimization. $W(T_1)$ can be selected to specify the relative frequency of occurrence (and hence the relative importance) of certain T_1 values within the range; or to incorporate user-defined preferences, such that a certain range of T_1 values corresponding to the critical tissues, can be emphasized and more accurately mapped.

As will be shown in the subsequent sections, it was found that the N (even) optimal angles obtained using Eq. (5.5) for a range of T_1 values, also exhibit the same phenomenon of repetitions of two optimal angles $\{\alpha_1^{opt}, \alpha_2^{opt}\}$; although the two optimal angles differ from those previously found [51] [104]. Hence, we shall only consider repetitions of two optimal angles for the mapping of pre-contrast T_1 values, and proceed to address the problem of the subsequent measurement of post-contrast T_1 values.

5.2.3 Optimal Angle for Post-Contrast T_1

Post-contrast changes in T_1 as a function of time, can be monitored by acquiring images at fixed intervals of time and with only one RF flip angle [104]; since only T_1 changes in Eq. (5.2) and M_0 (which is assumed unchanged after contrast injection) can be estimated from the pre-contrast images. However, the optimization problem is complicated by the fact that the range of post-contrast T_1 values also changes, and the optimal flip angle for measuring post-contrast T_1 would have to be determined over a separate T_1 range.

Suppose the set of N optimal angles $\{M \times \alpha_1^{opt}, M \times \alpha_2^{opt}\}$ (assuming even N , and $M=1,2,\dots$) for measuring pre-contrast T_1 , has been found by minimizing Eq. (5.5), the estimated error in determining the post-contrast relaxation rate R_1^c ($=1/T_1^c$) by the acquisition of another flip angle (α_3), can again be expressed as a noise factor

$$NF_C = \left[\frac{\Delta R_1^c / R_1^c}{\Delta S / M_0} \right] = M_0 T_1^c \sqrt{\frac{1}{M} \left(\frac{\partial R_1^c}{\partial S_1} \right)^2 + \frac{1}{M} \left(\frac{\partial R_1^c}{\partial S_2} \right)^2 + \left(\frac{\partial R_1^c}{\partial S_3} \right)^2} \quad (5.6)$$

where S_1 and S_2 are the respective averages of the M signals corresponding to α_1^{opt} and α_2^{opt} , and S_3 is the post-contrast signal acquired by α_3 . The partial differential terms are

$$\frac{\partial R_1^c}{\partial S_1} = \frac{S_3 \sin \alpha_3 (\cos \alpha_3 - 1)}{T_R (M_0 \sin \alpha_3 - S_3 \cos \alpha_3) (M_0 \sin \alpha_3 - S_3)} \cdot \frac{\sin \alpha_1^{opt} (\cos \alpha_1^{opt} - \cos \alpha_2^{opt}) (1 - \cos \alpha_2^{opt})}{[(S_1 / S_2) \sin \alpha_2^{opt} (\cos \alpha_1^{opt} - 1) + \sin \alpha_1^{opt} (1 - \cos \alpha_2^{opt})]^2} \quad (5.6a)$$

$$\frac{\partial R_1^c}{\partial S_2} = \frac{S_3 \sin \alpha_3 (\cos \alpha_3 - 1)}{T_R (M_0 \sin \alpha_3 - S_3 \cos \alpha_3) (M_0 \sin \alpha_3 - S_3)} \cdot \frac{(S_1 / S_2)^2 \sin \alpha_2^{opt} (\cos \alpha_1^{opt} - \cos \alpha_2^{opt}) (\cos \alpha_1^{opt} - 1)}{[(S_1 / S_2) \sin \alpha_2^{opt} (\cos \alpha_1^{opt} - 1) + \sin \alpha_1^{opt} (1 - \cos \alpha_2^{opt})]^2} \quad (5.6b)$$

$$\frac{\partial R_1^c}{\partial S_3} = \frac{M_0 \sin \alpha_3 (1 - \cos \alpha_3)}{T_R (M_0 \sin \alpha_3 - S_3 \cos \alpha_3) (M_0 \sin \alpha_3 - S_3)} \quad (5.6c)$$

Eq. (5.6) refers to a single value of T_1^c and, for a range of T_1^c given by $[T_{1,\min}^c, T_{1,\max}^c]$, the corresponding objective function may again be defined

$$\text{SNF}_C = \int_{T_{1,\min}^c}^{T_{1,\max}^c} \text{NF}_C(T_1) W_C(T_1) dT_1 \quad (5.7)$$

which is minimized to obtain α_3^{opt} . With the above proposed scheme, the set of optimal flip angles for mapping both pre- and post-contrast T_1 values can be given by $\{M \times \alpha_1^{opt}, M \times \alpha_2^{opt}, \alpha_3^{opt}\}$.

To compare two methods for optimal-angle selection in DCE MRI, the resulting error in the estimated Gd concentration C may be compared. Using Eq. (5.1), an estimate of the potential error in C can be further given by a measure of its coefficient of variation

$$\text{CV} = \frac{\Delta S}{M_0} \frac{\sqrt{(\text{NF}_C \cdot R_1^c)^2 + (\text{NF} \cdot R_1)^2}}{R_1^c - R_1} \quad (5.8)$$

where NF_C and NF are evaluated using the set of optimal angles $\{M \times \alpha_1^{opt}, M \times \alpha_2^{opt}, \alpha_3^{opt}\}$ suggested by a particular method.

5.3 Numerical Experiments

5.3.1 Simulation Parameters

Imaging of breast tumors using DCE MRI is one of the most active research areas currently [104, 130]. For this reason, the present method was applied to breast imaging

for validation. The application of the same method for imaging other organs (such as kidneys) would be similar. In DCE MRI of breast tumors, the structures of interest include normal tissues, tumors (we would like to differentiate these from the surrounding normal tissues), and a feeding artery (concentration curve of blood is required for further deconvolution analysis [135]). The ranges of T_1 and T_1^c assumed for tumors, normal tissues and blood shown in Table 5-1, are those commonly encountered in the literature [138] [139] [140] [141] for a 1.5 T MRI system. T_R values assumed for pre- and post-contrast imaging were respectively, 100 ms and 50 ms [142] [143]; and M_0 was set to unity [51] [105]. The weighting functions used in the calculation of SNF and SNF_C are shown in Figure 5-3. The relative importance in tumor, blood and normal tissue was weighted using the ratio 4:3:1, according to their respective areas under $W(T_1)$.

Figure 5-3 Weighting functions used in the calculation of SNF (solid line) and SNF_C (dash line).

Table 5-1 T_1 and T_1^c ranges assumed in this study.

	Normal Tissue	Blood	Tumor
T_1 (ms)	[200, 400]	[700, 1000]	[1000, 1500]
T_1^c (ms)	[150, 350]	[150, 250]	[500, 1300]

5.3.2 Comparison with an Existing Approach

To compare the present method with the endpoints averaging method [51] [104], the corresponding sets of optimal angles obtained by each method may be used to calculate (i) the possible errors in the estimated T_1 and T_1^c values (using Eqs. (5.5) and (5.7), respectively), and (ii) the CV of the resulting concentration estimate. To arrive at a CV value, the noise level was assumed to be $\Delta S = 0.01M_0$ [51] [105], and a pair of $\{T_1, T_1^c\}$ was randomly chosen from their respective ranges for blood and tumor (Table 5-1), with the constraint $T_1^c < T_1$, due to the T_1 -shortening effect of Gd. As each pair of $\{T_1, T_1^c\}$ indicates a concentration C value, 100 sets of $\{T_1, T_1^c\}$ were randomly generated to simulate 100 different values of C for blood and tumor, and their CV using Eq. (5.8) was evaluated.

5.3.3 Monte Carlo Simulations

For a suggested set of angles $\{M \times \alpha_1^{opt}, M \times \alpha_2^{opt}, \alpha_3^{opt}\}$, the potential error in the estimated C can also be obtained by Monte Carlo simulations. First, a pair of $\{T_1, T_1^c\}$ values (one of the 100 randomly chosen pairs) is assumed, to indicate a particular C value. Using α_1^{opt}

and α_2^{opt} , and the assumed T_1 , two ‘noiseless’ pre-contrast signals (S_1 and S_2 , respectively) can be generated by Eq. (5.2). Gaussian noise (with zero mean and standard deviation of $\Delta S = 0.01M_0$) was then added to S_1 and S_2 . For $M > 1$, the M noisy signals corresponding to the same angle were averaged. From the noisy (M averaged) S_1 and S_2 values, the pre-contrast T_1 and M_0 can be estimated ($\hat{T}_1$ and $\hat{M}_0$), which could deviate from the original (assumed) values, due to the added noise. In a similar manner, a noiseless post-contrast signal (S_3) can be generated using the assumed T_1^c and α_3^{opt} , and Gaussian noise was added. With $\hat{M}_0$ and the noisy S_3 , the post-contrast T_1^c can be estimated ($\hat{T}_1^c$), which could again differ slightly from the assumed T_1^c . The error ε in the resulting estimate of C is then proportional to $(\hat{R}_1^c - \hat{R}_1) - (R_1^c - R_1)$, with the same proportionality constant as in Eq. (5.1), and $\hat{R}_1^c$ and $\hat{R}_1$ are the corresponding relaxation rates due to $\hat{T}_1^c$ and $\hat{T}_1$, respectively. This process is repeated 1000 times for each pair of $\{T_1, T_1^c\}$ assumed, and a measure of the coefficient of variation in C obtained through these Monte Carlo simulation runs, can be given by

$$CV = \frac{\sigma}{R_1^c - R_1} \quad (5.9)$$

where σ is the standard deviation of ε .

5.4 Results and Discussion

The sets of N optimal flip angles for pre-contrast imaging, obtained by minimizing Eq. (5.5) (using ‘fmincon’ for minimization, ‘quad’ for numerical integration (MatlabTM)), are shown in Table 5-2. Interestingly, the repetition of two angles (i.e. $M \times \alpha_1^{opt}$ (10.7°))

and $M \times \alpha_2^{opt}$ (58.2°) occurs when N is even ($= 2M$), and this phenomenon is observed for different values of T_R and $W(T_1)$ functions used, although different values of α_1^{opt} and α_2^{opt} can be obtained. The corresponding SNF decreases by a factor of $1/\sqrt{M}$ as M increases, in agreement with the findings of Wang et al. [51] for the minimization of NF. This is a convenient feature for practical DCE MRI, since (i) the pre-contrast imaging protocol with only two repeating flip angles (α_1^{opt} and α_2^{opt}) instead of N different angles may be set; (ii) the calculation of pre-contrast T_1 can be simply performed by averaging the signals (S_1 or S_2) corresponding to each flip angle, and solving T_1 and M_0 using the averaged S_1 and S_2 values; instead of a linear regression process if N different angles were used (Eq. (5.3)) and (iii) the optimization of post-contrast angle α_3 becomes more efficient as the number of partial differential terms is limited to 3 (Eq. (5.6)).

Table 5-2 The optimal flip angles obtained by the proposed method, for pre-contrast imaging with $T_R = 100$ ms. For N even ($= 2M$), the set of optimal angles can be given in repetitions, by $\{5 \times 10.4^\circ, 5 \times 56.8^\circ\}$.

N	Pre-contrast angles	SNF	Normalized SNF
2	$[1 \times 10.7^\circ, 1 \times 58.2^\circ]$	13.0	1
3	$[1 \times 11.6^\circ, 2 \times 63.4^\circ]$ or $[2 \times 9.65^\circ, 1 \times 54.2^\circ]$	11.1	0.85
4	$[2 \times 10.7^\circ, 2 \times 58.2^\circ]$	9.2	$0.71 (\approx 1/\sqrt{2})$
5	$[2 \times 11.3^\circ, 3 \times 61.1^\circ]$ or $[3 \times 10.1^\circ, 2 \times 55.7^\circ]$	8.3	0.64
6	$[3 \times 10.7^\circ, 3 \times 58.2^\circ]$	7.5	$0.58 (\approx 1/\sqrt{3})$
7	$[3 \times 11.1^\circ, 4 \times 60.2^\circ]$ or $[4 \times 10.3^\circ, 3 \times 56.4^\circ]$	7.0	0.54
8	$[4 \times 10.7^\circ, 4 \times 58.2^\circ]$	6.5	$0.50 (\approx 1/\sqrt{4})$
9	$[4 \times 11.0^\circ, 5 \times 59.8^\circ]$ or $[5 \times 10.4^\circ, 4 \times 56.8^\circ]$	6.2	0.48
10	$[5 \times 10.7^\circ, 5 \times 58.2^\circ]$	5.8	$0.45 (\approx 1/\sqrt{5})$

Table 5-3 The optimal flip angles obtained by the proposed method, for post-contrast imaging with $T_R = 50$ ms, and various values of M .

M	Post-contrast angles	SNF _C	Normalized SNF _C
1	57.5°	13.5	1
2	52.1°	11.2	0.83
3	49.6°	10.3	0.76
4	48.2°	9.7	0.72
5	47.2°	9.4	0.70

Table 5-3 shows the various values of α_3^{opt} obtained using the present approach, when M is increased from 1 to 5. Increasing the value of M improves the estimation of both T_1 and M_0 , and hence reduces the error propagated into the subsequent estimation of T_1^c . For $M = 1$ and 5, the corresponding sets of optimal angles for pre- and post-contrast imaging are respectively, $\{10.7^\circ, 58.2^\circ, 57.5^\circ\}$ and $\{5 \times 10.7^\circ, 5 \times 58.2^\circ, 47.2^\circ\}$. Using the endpoints averaging method [7], the set of optimal angles for pre- and post-contrast imaging was found to be $\{15.9^\circ, 73.9^\circ, 70.4^\circ\}$. As repetitions (M) for pre-contrast angles was not considered in the endpoints averaging method [104] for the estimation of T_1^c , we may simply repeat the two pre-contrast optimal angles, for the case of $M = 5$, i.e $\{5 \times 15.9^\circ, 5 \times 73.9^\circ, 70.4^\circ\}$.

The potential errors in the estimated T_1 and T_1^c by the proposed method and the endpoints averaging method, are shown in Figure 5-4 for $M = 1$. In Figure 5-4 (a), the ranges of pre-contrast T_1 for blood and tumor are higher than that of normal tissues, and with the heavier weightings on tumor and blood, the present approach achieves smaller errors

within their corresponding T_1 ranges, by compromising the errors in the normal tissues. It is also noted that the two curves corresponding to the two methods in Figure 5-4 (a), should intersect at some intermediate T_1 value within the total T_1 range, since the endpoints averaging method averages the best angles at both extreme ends. In Figure 5-4 (a), we see that the proposed method allows the flexibility to improve on the T_1 mapping of certain critical tissues, and also distributes the errors more evenly throughout the entire T_1 range. However, in post-contrast imaging (Figure 5-4 (b)), the T_1^c range for blood and normal tissues overlap, and the proposed method could only improve on the mapping of the tumor T_1^c values.

Figure 5-4 The potential errors in T_1 and T_1^c estimated by the proposed method ($\{10.7^\circ, 58.2^\circ, 57.5^\circ\}$) (solid line) and the endpoints averaging method ($15.9^\circ, 73.9^\circ, 70.4^\circ$) (dashed line), for $M = 1$.

Figure 5-5 Correlation plot of 100 concentration CV values (calculated by Eq. 5.8) obtained using the endpoints averaging method (CV_1) with the proposed method (CV_2). (a) $M = 1$, $CV_2 = 0.67CV_1 + 0.07$, $R^2 = 0.997$. (b) $M = 5$, $CV_2 = 0.66CV_1 + 0.04$, $R^2 = 0.992$.

In Figure 5-5, the concentration CV values (Eq. (5.8)) obtained using the proposed method and the endpoints averaging method are compared, for $M = 1$ and 5. The CV values due to the proposed method are markedly lower than those by the endpoints averaging method. The slope of regression line for correlation plot is 0.67 and 0.66 for $M=1$ and $M=5$, respectively, indicating accuracy improvement of over 30% for concentration estimation. Similar CV results were also obtained by Monte Carlo simulations, as shown in Figure 5-6. Here, the paired t -test can be used to show that the CV values obtained by the proposed method are significantly ($P < 0.05$) lower than those of the endpoints averaging method (Figure 5-6). Increasing the number of pre-contrast repetitions from $M = 1$ to 5 can result in significant reduction in the errors of the estimated C .

Figure 5-6 Correlation plot of 100 concentration CV values (obtained by Monte Carlo simulations and Eq. 5.9) obtained using the endpoints averaging method (CV_1) and the proposed method (CV_2). (a) $M = 1$, $CV_2 = 0.79CV_1 + 0.04$, $R^2 = 0.997$, P -value (paired t -test) < 0.005 . (b) $M = 5$, $CV_2 = 0.69CV_1 + 0.03$, $R^2 = 0.995$, P -value (paired t -test) < 0.005 .

The present approach for flip-angle optimization can be easily implemented for imaging of kidneys. T_1 ranges of tissues of interest, such as renal cortex, renal medulla and abdominal aorta, can be predicted or assumed as in Table 5-1, while the weighting function is determined according to the relative importance of these tissues. By minimizing Eq. (5.5) and Eq. (5.7), optimal flip angles for pre- and post-imaging of kidneys can be obtained. Discrete functions were used as weighting functions, for numerical integration of NF or NF_C , in this study. Continuous weighting function can also be employed, such as T_1 histogram curve that shows occurrence frequency of every T_1 value in a T_1 map.

5.5 Concluding Remarks

The set of optimal angles derived by the present approach $\{M \times \alpha_1^{\text{opt}}, M \times \alpha_2^{\text{opt}}, \alpha_3^{\text{opt}}\}$, can be practically implemented in a clinical DCE MRI protocol, with M repetitions of the pre-contrast scans using the angles α_1^{opt} and α_2^{opt} , and subsequent post-contrast imaging with α_3^{opt} at various time points, to estimate the concentration of contrast as a function of time. Results of Monte Carlo simulations show that the present approach could significantly improve the accuracy of contrast (Gd) concentration estimates within certain tissues of interest (as stipulated by the user), as compared with the existing endpoints averaging method. It is also noted that, in implementation, the operator can flexibly adjust the relative importance of different kinds of tissues, for selecting appropriate flip angles, and various functions such as linear segments or T_1 histogram can be used as the weighting function.

Chapter 6

Optimal Flip Angles: Analytic Derivations

6.1 Introduction

Accurate mapping of spin-lattice relaxation time (T_1) is highly desirable for at least 2 reasons. First, T_1 map has the potential of providing additional information for tumor detection and localization in MR images. Second, based on T_1 -shortening effect of Gd, concentration (C) of Gd-labeled contrast medium can be estimated, and the resultant C -vs.-time curve can be further analyzed, to give some parameters for tissue-microcirculation evaluation or organ-function assessment. In Chapter 5, we discussed the numerical optimization of flip angles in acquiring dynamic MR images (using SPGR sequence), with the objective of accurate T_1 mapping. Flip angles were selected by numerically minimizing noise propagation from signal intensity to a range of T_1 (pre- and post-contrast, respectively). As a result, an optimal imaging protocol was determined as $\{M \times \alpha_1^{\text{opt}}, M \times \alpha_2^{\text{opt}}, \alpha_3^{\text{opt}}\}$.

The motivations for this further study are as follows. Previous approaches for flip-angle optimization are based on or related to numerical optimization of flip angles for accurate estimation of a single T_1 value, i.e. minimizing NF (Eq. (5.4)). It was recognized that, for optimizing a large number of flip angles (large N in Eq. (5.4)), numerical minimization of NF would be inconvenient or even time-consuming. Moreover, the accuracy of numerical solutions may sometimes depend on the performance of the optimization technique employed. For the above reasons, an analytic expression for optimal flip angles (solution of minimizing NF), which has been unknown all along, would be useful in improving the efficiency and avoiding erroneous solutions. Secondly, some interesting phenomena were observed in numerical minimization of NF [51] [105] [106]. Exploration of these phenomena may gain deeper understanding of optimal flip angles. Another motivation for further study stems from the observation that conventional flip angles for range- T_1 estimation seem unable to provide evenly-distributed (or balanced) precision level for the whole T_1 range. As observed from Figure 5-4, error propagation to higher T_1 is much greater than to lower T_1 values. The higher T_1 corresponds to tumor and pre-contrast blood pool in tumor imaging, and pre-contrast renal parenchyma (with high blood perfusion) in MR renographic images.

In this chapter, an analytic expression was derived for optimal flip angles for single T_1 , in the process of which some properties observed in numerical studies are proven and utilized. Based on the analytic solution, a new set of flip angles appropriate for a T_1 range is proposed. The proposed flip angles were compared with conventional ones both in theory and in a phantom experiment.

6.2 Theory

Numerical minimization of NF (Eq. (5.4)) results in optimal flip angles with several interesting properties [51] [105] [106]. i) For limited N (the overall number of flip angles), the optimal solution is repetitive acquisitions of MR signal (S) at only 2 different flip angles; ii) for even number $N (=2M)$, the optimal split of N for the two flip angles is $M-M$; iii) for even number N , the 2 optimal flip angles induce S of equal intensity, about 0.71 of the maximal S (Figure 6-1); iv) as M increases, the minimal NF decreases by a rate of $1/\sqrt{M}$, thus a T_1 -precision improvement of $\sqrt{M}$. According to literature review, these properties have not been proven mathematically.

6.2.1 Analytic Solution of NF-Minimization

An analytic expression of flip-angle solution that minimizes NF (Eq. (5.4)), will be derived in the following. First of all, NF in Eq. (5.4) is simplified by virtue of the property i), which will be applied without proof. Accounting for repetitive signal acquisitions at each of two flip angles, Eq. (5.4) can be written as

$$\begin{aligned} \text{NF} &= \frac{M_0}{T_1} \sqrt{\frac{1}{a} \left(\frac{\partial T_1}{\partial S_1} \right)^2 + \frac{1}{b} \left(\frac{\partial T_1}{\partial S_2} \right)^2}, \\ &= \Omega \sqrt{\frac{1}{aS_1^2} + \frac{1}{bS_2^2}}, \end{aligned} \quad (6.1)$$

where $\Omega = \frac{M_0 T_1 \sin \alpha_1 \sin \alpha_2 (\cos \alpha_1 - \cos \alpha_2)}{T_R [\sin \alpha_2 - (S_2/S_1) \sin \alpha_1] [\sin \alpha_2 \cos \alpha_1 - (S_2/S_1) \sin \alpha_1 \cos \alpha_2]}$, and a and b

are the numbers of repetitive S measurements at the two flip angles. Note that symbol b is

introduced to represent $(N-a)$ for brevity, and thus should not be treated as an independent variable. Eq. (6.1) indicates that the noise propagation to T_1 is jointly determined by two components. Each of the two components is originally induced by the signal indeterminacy at the associated angle, while affected by the selection of the other angle. The search of optimal flip angles, by minimizing NF in Eq. (6.1), is now in a 3-parameter space of $\{a, \alpha_1, \alpha_2\}$, rather than the previous N -parameter one (Eq. (5.4)).

Figure 6-1 Schematic diagram of SPGR signal curve. The signal peaks at Ernst angle (α_{Ern}) as S_{Ern} , while the two optimal angles $\hat{\alpha}_1, \hat{\alpha}_2$ are on different sides of α_{Ern} , and correspond to the same signal intensity, $\hat{S}_{1,2} = (\sqrt{2}/2)S_{\text{Ern}}$.

For every possible value of a , NF in Eq. (6.1) is a function of two parameters, $\alpha_{1,2}$, both within $(0^\circ, 180^\circ)$. Flip angles that minimize NF, denoted as $\hat{\alpha}_{1,2}$, can be obtained by solving

$$\begin{cases} \left. \frac{\partial \text{NF}}{\partial \alpha_1} \right|_a = 0 \\ \left. \frac{\partial \text{NF}}{\partial \alpha_2} \right|_a = 0 \end{cases}. \quad (6.2)$$

The existence of the solutions ($\hat{\alpha}_{1,2}$) has been verified in numerical studies, and the possibility that a boundary point of the 2-dimensional NF surface minimizes NF, can be easily excluded. Decoupling $\hat{\alpha}_1$ and $\hat{\alpha}_2$ in Eq. (6.2) is difficult, but the following relation of a and its associated $\hat{\alpha}_{1,2}$ can be derived (Appendix A),

$$\frac{a\hat{S}_1^4}{b\hat{S}_2^4} - 1 = \frac{\sin \hat{\alpha}_1 \sin \hat{\alpha}_2}{1 - \cos \hat{\alpha}_1 \cos \hat{\alpha}_2} \left(\frac{a\hat{S}_1^2}{b\hat{S}_2^2} - 1 \right) \frac{\hat{S}_1}{\hat{S}_2}, \quad (6.3)$$

where $\hat{S}_1, \hat{S}_2$ are the signals acquired with $\hat{\alpha}_1$ and $\hat{\alpha}_2$, respectively. The separability of $\hat{\alpha}_{1,2}$ and $\hat{S}_{1,2}$ in Eq. (6.3) is a convenient feature that helps further derivation. Further analysis of Eq. (6.3) in Appendix A shows that, if $a > b$ (i.e. $a > N/2$),

$$\frac{1}{b\hat{S}_2^2} > \frac{1}{a\hat{S}_1^2}, \quad (6.4)$$

which means that, of the two components in NF (Eq. (6.1)) evaluated at every a and its associated $\hat{\alpha}_{1,2}$, the one associated with more repeat of S measurement is smaller. This feature will be very useful in the following section.

Of the three parameters (a, α_1 and α_2) in NF, the optimal value of a , i.e. the optimal split of N , can be determined firstly. It will be shown that a should be the integer nearest to $N/2$, that is, $|a - b| \leq 1$. For such a values that $a - b > 1$, the following relation can be derived according to Eq. (6.4),

$$\begin{aligned}
& \left(\frac{1}{a\hat{S}_1^2} + \frac{1}{b\hat{S}_2^2} \right) - \left[\frac{1}{(a-1)\hat{S}_1^2} + \frac{1}{(b+1)\hat{S}_2^2} \right] \\
&= \frac{1}{b(b+1)\hat{S}_2^2} - \frac{1}{a(a-1)\hat{S}_1^2}, \\
&\geq \frac{1}{b+1} \left(\frac{1}{b\hat{S}_2^2} - \frac{1}{a\hat{S}_1^2} \right) > 0
\end{aligned} \tag{6.5}$$

which directly leads to the relation,

$$\text{NF}(a, \hat{\alpha}_1, \hat{\alpha}_2) > \text{NF}(a-1, \hat{\alpha}_1, \hat{\alpha}_2) \geq \text{NF}(a-1, \hat{\beta}_1, \hat{\beta}_2). \tag{6.6}$$

$\hat{\beta}_{1,2}$ in Eq. (6.6) are optimal flip angles for $[a-1, b+1]$ split of N , and may be different from $\hat{\alpha}_{1,2}$. Considering that $\text{NF}(a, \hat{\alpha}_1, \hat{\alpha}_2)$ is the minimal NF for current a , it is concluded that such a that $a-b > 1$ is not optimal (at least, N -splitting as $[a-1, b+1]$ is better than that $[a, b]$). Similarly, such a values that $a-b < -1$ are not optimal either. Hence, it has to be $|a-b| \leq 1$. More specifically, for even number $N = 2M$, $a = M$; while for odd $N=2M+1$, $a = M$ or $M+1$. According to Eq. (6.1), the equal division of N measurement opportunities has the effect of balancing the measurement errors induced at the 2 flip angles.

Previous numerical studies show that, for optimal solution $\{M \times \hat{\alpha}_1, M \times \hat{\alpha}_2\}$, $\hat{S}_1 = \hat{S}_2$ [105] [106]. This property can be readily proven by using Eq. (6.3), and plays a key role in deriving explicit expression for $\hat{\alpha}_{1,2}$. Setting $a=b=M$ (this relation is derived above) in Eq. (6.3), we obtain (after re-arranging)

$$\left(\frac{\hat{S}_1^2}{\hat{S}_2^2} - 1 \right) \left(\frac{\hat{S}_1}{\hat{S}_2} + \frac{\hat{S}_2}{\hat{S}_1} - \frac{\sin \hat{\alpha}_1 \sin \hat{\alpha}_2}{1 - \cos \hat{\alpha}_1 \cos \hat{\alpha}_2} \right) = 0. \tag{6.7}$$

The component in the second bracket of Eq. (6.7) can not be zero, because $(\hat{S}_1 / \hat{S}_2 + \hat{S}_2 / \hat{S}_1)$ is no smaller than 2, while the other part is within $(0, 1]$. Hence, it has to be $\hat{S}_1^2 / \hat{S}_2^2 - 1 = 0$. As all signals are positive, $\hat{S}_1 = \hat{S}_2$ is derived. Note that $\hat{S}_1 = \hat{S}_2$ can not be derived for odd number N .

The importance of the above-proven property ($\hat{S}_1 = \hat{S}_2$) lies in that hereafter the search of two optimal angles, $\hat{\alpha}_{1,2}$, can be converted to a search of one optimal S (Figure 6-1). Based on this thinking, NF can be further simplified as a single-parameter function for minimization. In Appendix B, it is derived that $S(\hat{\alpha}_{1,2}) = S_{Em} / \sqrt{2}$. Numerical approximate of $0.71S_{Em}$ by Deoni et al [105] is a non-exact but fairly good estimate. Accordingly, the optimal flip angles are calculated as,

$$\hat{\alpha}_{1,2} = \arccos \left[\frac{E_1 \pm \sqrt{2(1 - E_1^2)}}{2 - E_1^2} \right], \quad (6.8)$$

in which $E_1 = \exp(-T_R / T_1)$. The associated minimal NF is readily obtained as,

$$\min\{\text{NF}_{T_1}\} = \frac{T_1(1 + E_1)}{T_R \cdot E_1} \sqrt{2(1 - E_1^2) / M}. \quad (6.9)$$

Eq. (6.9) indicates that, for $2M$ angles, the precision of estimated T_1 improves over that of two-angle case by $\sqrt{M}$, which agrees well with numerical results of Wang et al [51]. All the above derivation can be extended for the analytic solutions of optimal angles for T_2 precision in steady-state free precession (SSFP). Interested readers are referred to the paper by Deoni et al [105] for such extension, and it will not be discussed in this thesis.

6.2.2 Selection of Flip Angles for a Range of T_1

In practical imaging, one typically deals with a range of T_1 values, because every S map, acquired with one set of parameters (i.e. flip angles, T_R), contains various tissues of different T_1 values. According to Eq. (6.8), optimal flip angles are different for different T_1 , and, at constant T_R , both angles decrease as the associated T_1 increases (Figure 6-2(a)). It is reasonable to determine one set of flip angles appropriate for the T_1 range, by manipulating the optimal angles of some single T_1 within the range.

Brookes et al [104] proposed an endpoint-averaging method for a range of T_1 ($[T_1^{\min}, T_1^{\max}]$), in which flip angles are optimized for $T_1^{\min}$ and $T_1^{\max}$, respectively, and the average of the two sets of flip angles is regarded as the “optimal” flip angle for the range. With the analytic expression of $\hat{\alpha}_{1,2}$ (Eq. (6.8)), numerical optimization at $T_1^{\min}$ and $T_1^{\max}$ becomes unnecessary, and the selected angles (termed as Brookes’ angles) for the T_1 range are directly written as

$$\hat{\beta}_{1,2} = \frac{1}{2} \left\{ \arccos \left[\frac{e^{-T_R/T_1^{\min}} \pm \sqrt{2(1 - e^{-2T_R/T_1^{\min}})}}{2 - e^{-2T_R/T_1^{\min}}} \right] + \arccos \left[\frac{e^{-T_R/T_1^{\max}} \pm \sqrt{2(1 - e^{-2T_R/T_1^{\max}})}}{2 - e^{-2T_R/T_1^{\max}}} \right] \right\}. \quad (6.10)$$

Compared with the conventional numerical minimization approach, the calculation of Brookes’ angles here becomes much more straightforward.

Another method is presented for selecting flip angles for estimation of a range of T_1 . This method is simpler than that by Brookes, while not compromising in performance. Here,

the optimal flip angles for the mid-value of the T_1 range ($T_1^{\text{mid}} = (T_1^{\text{min}} + T_1^{\text{max}})/2$) are chosen as the “optimal” angles for the whole range. Specifically, by substituting $T_1 = T_1^{\text{mid}}$ into Eq. (6.8), we get

$$\hat{\gamma}_{1,2} = \arccos \left[\frac{e^{-T_R/T_1^{\text{mid}}} \pm \sqrt{2}(1 - e^{-2T_R/T_1^{\text{mid}}})}{2 - e^{-2T_R/T_1^{\text{mid}}}} \right]. \quad (6.11)$$

In the following, the angles are termed as mid- T_1 angles. The mid- T_1 angles emphasize the balance of NF in T_1 range. Hence, it is expected that, in the range of T_1 , NF curve of mid- T_1 angles would be more balanced than that of Brookes’ angles. A balanced NF curve with respect to T_1 is desirable because, estimation accuracies for different T_1 within the range do not differ too much and, even if some unexpected T_1 (out of the predicted range) exists, its estimate using the proposed angles would still be satisfactory.

6.3 Theoretical Validation and Phantom Experiment

6.3.1 Theoretical Validation

The correctness of the analytic expression for optimal flip angle of single T_1 (Eq. (6.8)) was first validated. For every T_1 value within a range, optimal flip angles were calculated using numerical optimization and analytic approach (Eq. (6.8)), respectively. For the calculation, T_R was set at its minimal value for SPGR sequence of MR machine, 6.3ms. In numerical optimization, NF in Eq. (5.4) was minimized using a numerical search (‘fmincon’ of MATLABTM), in which flip angles were adjusted to achieve minimal NF. The number of flip angles was 10, i.e. $N=10$. We expected that the optimal flip angles

would be 5 repetitions of 2 different flip angles, and the minimal NF be $1/\sqrt{5}$ of that of $N=2$. The optimization was repeated for every T_1 value in the set of [300:10:1500] ms, and after every optimization, the resultant optimal angles and the minimal NF value were recorded. On the other hand, optimal flip angles and minimal NF were respectively calculated using Eq. (6.8) and Eq. (6.9), for every T_1 of the same set as above ([300:10:1500] ms). M was set to 1, i.e. $N=2$. Correspondence between the optimal flip angles obtained numerically and analytically would indicate the correctness of the analytic expression.

The mid- T_1 angles were proposed with the aim of balancing the noise propagated to the targeted T_1 range. The performance of mid- T_1 angles was compared with that of conventional ones, by comparing their NF vs. T_1 curves over a T_1 range. The flip angles for comparison include the mid- T_1 angles, uniform-distributed angles (also termed as standard angles), and previously-proposed angles (one for breast, and the other for brain). The comparison was carried out for breast and brain, separately. The T_1 ranges and the angles are tabulated in Table 6-1. For every set of flip angles, NF can be calculated for every chosen T_1 value within a T_1 range using Eq. (5.4), and finally a NF vs. T_1 curve was plotted. Low and flat NF across a T_1 range indicates high and balanced T_1 -estimation accuracy for one set of flip angles.

Table 6-1 T_1 ranges typical for brain and breast, and the respective flip angles for theoretical comparison.

	Brain	Breast
T_1 (ms)	[50, 5000]	[300, 1500]
T_R (ms)	5.0	6.3
Standard angles ($^\circ$)	[2, 4, 6, 8, 10, 12, 14, 16, 18, 20]	[3, 6, 9, 12, 15, 18, 21, 24, 27, 30]
Previous angles ($^\circ$)	[2, 3, 4, 5, 7, 9, 11, 14, 17, 22] ^a	[4, 4, 4, 4, 4, 20, 20, 20, 20, 20] ^b
Mid- T_1 angles ($^\circ$)	[2, 2, 2, 2, 2, 9, 9, 9, 9, 9]	[3, 3, 3, 3, 3, 16, 16, 16, 16, 16]

^a Deoni's angles by weighted genetic algorithm [106]; ^b 5 repeats of Brookes' angles [104].

6.3.2 Phantom Experiment

A phantom experiment was carried out to further evaluate the performance of the proposed mid- T_1 angles, and to compare it with some conventional ones. In the phantom experiment, 5 tubes (I, II, III, IV, V) were filled with Gd contrast agent of different concentrations, providing T_1 ranging from about 300 to 3000ms. All imaging was performed with 1.5T Signa Imaging Systems (General Electric) and a transmit/receive breast coil. The tubes with Gd solution were fixed at the center of the coil.

MR imaging was performed, using SPGR and inversion recovery (IR), respectively. In IR imaging, 17 IR images were acquired with $T_R = 4000$ ms, and different inversion-time (TI) values between 50 and 2300 ms, respectively. On a pixel-by-pixel basis, T_1 values were estimated using a four-parameter (M_0 , T_1 , m and n) least squares fitting, using $S_{IR} = M_0[1 - m \cdot \exp(-TI/T_1) + n \cdot \exp(-T_R/T_1)]$, and were regarded as the reference values. For SPGR sequence using various sets of flip angles, $T_R=6.3$ ms, $T_E=2.2$ ms, image 256×256 . The flip angles used were the same as those for breast in Table 6-1. Similarly, T_1 values were estimated by least squares fitting of multiple SPGR signals

using SPGR signal formula (Eq. (5.2)). In every T_1 map, a ROI of 20 by 20 pixels was positioned at the center of every tube, and the mean and standard deviation (SD) of T_1 within the ROI were calculated. The (mean $\pm$ SD) of T_1 estimates by SPGR using different flip angles (Standard, Brookes', and mid- T_1 angles) were compared with the average T_1 by IR. For T_1 estimates by SPGR, low deviation of its mean from that by IR and small coefficient of variation (CV=SD/mean) would indicate good performance of the associated flip-angle set.

Figure 6-2 (a) Optimal angles for various single T_1 over range [300, 1500] ms. (b) Minimal NF evaluated on the optimal angles for every single T_1 . Line = analytic solution, dot = numerical solution; up triangle = Brookes' angles, down triangle = mid- T_1 angles. Ten flip angles adjusted in numerical search results in 5 repeats of 2 angles, which is the same as the 2 angles from analytic solution. However, NF of the 10 (5 repeats of 2) numerically-derived angles is $1/\sqrt{5}$ of that of 2 analytically-derived angles. As T_1 increases, its optimal angles decrease. The relation is nearly linear, so that endpoint average angles falls nearly on the midpoint of the $\hat{\alpha}_1 - \hat{\alpha}_2$ line.

6.4 Results

6.4.1 Validation of the Analytic Expression

The analytic expression of optimal flip angles for a single T_1 was validated by comparing solutions by analytic approach with those by numerical approach. In numerical optimization, it was observed that the 10 optimal angles were actually 2 groups of repeated angles (5-5). Together with the analytic ones, the optimal angles are shown in Figure 6-2 (a), in which the two optimal angles were x - and y -coordinates, respectively. Obviously, the numerical and analytic solutions are identical. It is also noted that, for fixed T_R , as T_1 increases, both optimal angles decrease. In Figure 6-2 (b), the NF values of the (5-5) numerical angles are lower than the corresponding (1-1) analytic angles by a factor of about $\sqrt{5}$, which is in agreement with previous studies and $\min\{NF_{T_1}\}$ in Eq. (6.9).

Figure 6-3 NF evaluated across T_1 ranges typical for (a) brain and (b) breast. Cross = standard angles, circle = Deoni's angles by weighted GA, triangle = mid- T_1 angles, square = Brookes' angles.

6.4.2 Comparison of Various Flip Angles

NF vs. T_1 curves of various sets of flip angles are shown in Figure 6-3. For T_1 typical for brain, as shown in Figure 6-3 (a), NFs by uniformly-spaced angles and Deoni's angles both increase rapidly as T_1 value increases. Within [800, 5000] ms of this range, NF of these multiple-angle sets is much higher than that of mid- T_1 angles. The extremely high NF by mid- T_1 angles is in the range of [50, 250] ms. This range is still far lower than that of white matter (~600ms), the tissue with the lowest T_1 in brain [106] [144] [145] [146]. Hence, the overall performance of mid- T_1 angles is better than that of the above-mentioned multi-angle sets, for brain T_1 mapping. For typical T_1 range of breast, NF vs. T_1 curves of various flip angles are shown in Figure 6-3 (b). Over the whole range [300, 1500] ms, both NF of Brookes' angles and that of mid- T_1 angles are lower than that of uniformly-spaced angles. When comparing the former two, it is found that their NF curves are comparable in general, except that NF curve of mid- T_1 angles is more balanced.

Representative IR and SPGR images acquired in the phantom experiment are shown in Figure 6-4. As compared with the IR image, SPGR image contains slightly more noise. However, considering the short T_R (6.3 ms, time cost < 2s for one image) and low flip angle (3°) in SPGR imaging, the image quality is acceptable. The T_1 estimates by IR and SPGR using various flip angles are tabulated in Table 6-2. T_1 estimates by mid- T_1 angles have low coefficients of variance (CV < 6%). The deviations of these T_1 estimates from the respective values by IR are less than 7%, except for the tube I whose T_1 average deviates from the IR average for about 13%. T_1 estimates by Brookes' angles are very

near to those by mid- T_1 angles for the lower T_1 values (tube I and II). As T_1 value increases (Tube IV and V), the deviation and CV of the estimates by Brookes' angles increase accordingly. For example, in tube V, standard deviation of T_1 estimates reaches 250 ms (CV $\approx$ 10%), and deviation reaches 130 ms. Obviously, mid- T_1 angles performs better than Brooke's angles for higher T_1 within the range for breast (Tube IV) and for high T_1 out of this range (Tube V). The T_1 estimates by the uniformly-spaced angles show relatively higher CV (6%~15%) than the mid- T_1 estimates (2%~6%). The phantom results are in agreement with the previous theoretical comparison.

Figure 6-4 Phantom image examples (a) by IR (TI=1800ms, T_R =4000ms), and (b) by SPGR (T_R =6.3ms, flip angle = 3°).

Table 6-2 T_1 values calculated using IR and SPGR with various flip angles in phantom experiment. Coefficients of variation (CV) are given in brackets.

Tube	IR- T_1 (ms)	T_1 (ms) by mid- T_1 angles	T_1 (ms) by Brookes' angles	T_1 (ms) by standard angles
I	436	380 $\pm$ 8 (2%)	386 $\pm$ 9 (2%)	470 $\pm$ 50 (11%)
II	704	662 $\pm$ 15 (2%)	680 $\pm$ 20 (3%)	770 $\pm$ 50 (6%)
III	974	1040 $\pm$ 30 (3%)	1180 $\pm$ 40 (3%)	1070 $\pm$ 70 (7%)
IV	1081	1150 $\pm$ 60 (5%)	1220 $\pm$ 90 (7%)	1190 $\pm$ 80 (7%)
V	2538	2540 $\pm$ 150 (6%)	2670 $\pm$ 250 (9%)	2510 $\pm$ 380 (15%)

6.5 Discussion

It would be complex to derive analytic solution of optimal flip angles for single T_1 , through solving N partial differentiation equations of NF (Eq. (5.4)). In this study, such analytic expression was derived by proving and then utilizing some properties of optimal flip angles, which were observed by previous researchers [51] [104] [105] [106]. Utilizing these properties, the N -variable NF is finally simplified into a single-variable function. The optimal flip angles can then be easily derived from the single-variable function. The correspondence between optimal flip angles obtained analytically and numerically (Figure 6-2) verified the correctness of the derived analytic expression. However, it is noted that the analytic expression derived in this study is only valid for the even- N cases, i.e. the M - M scheme. The relation $\hat{S}_1 = \hat{S}_2$, which is critical for deriving the analytic expression, can only be achieved for even- N cases. This can be readily verified in a numerical study. Fortunately, this limitation (N is even number) of the analytic solution does not bring much hurdle for its practical use. With the analytic expression for optimal angles, numerical optimization is avoided. Moreover, those flip-angle sets for a range of T_1 , which are based on combining single- T_1 angles, are simplified to be a one-step formula (such as Eq. (6.10) for Brookes' angles and Eq. (6.11) for mid- T_1 angles).

Deeper understanding of the mechanism that determines T_1 precision has been gained. As a special linear regression problem (Eq. (5.3)), it is important to accurately determine 2 different points that are apart from each other. With limited opportunities (N) of S

acquisitions, equal measurements at the 2 flip angles is preferred for minimal error propagation to T_1 . For even-number N , the signal intensities of the 2 optimal angles are proven to be equal, probably for the aim of providing equal $\Delta S/S$ at the two points. Although the equal-signal property is not valid for odd-number N , the signal intensity of the flip angle with more repeats, as shown in Appendix A, is lower than that with less repeats, which can also be regarded as an endeavor for maintaining comparable $\Delta S/S$ for the two points.

The motivation of proposing mid- T_1 angles for the more balanced precision of a wide T_1 range can be demonstrated in Figure 6-2 (a). Characterized by Eq. (6.8), the flip-angle curve in Figure 6-2 (a) approximates a straight line for small T_R/T_1 in fast imaging. Brookes' angles, which are calculated by averaging the optimal angles of the minimal and maximal T_1 values, approximately correspond to the mid-point of the flip-angle curve. In Figure 6-2 (a), it is observed that Brookes' angles are near to optimal angles of ~ 600 ms. Hence, for the range of [300, 1500] ms, Brookes' angles would perform better in lower- T_1 end, while worse in the higher end. In contrast, choosing mid- T_1 (900ms for this case) angles may provide a more uniform precision profile for the whole T_1 range. This hypothesis was confirmed by theoretical evaluation (Figure 6-3) and phantom experiment (Table 6-2). A more uniform NF curve across a T_1 range is important in maintaining a nearly constant relative error for different T_1 estimates, and avoiding large error in estimating some unexpected high T_1 , for example, that of various kinds of tumors.

6.6 Concluding Remarks

In this study, analytic expression for optimal flip angles was derived for estimating single T_1 from multiple SPGR signals. The analytic expression makes numerical optimization unnecessary, and lays a theoretical foundation for angle optimization of ranged T_1 . Moreover, deeper understanding has been gained on the mechanism that determines T_1 precision. The proposed mid- T_1 angles are simpler than previous flip angles, while have the potential of providing more uniform relative error for different T_1 values within the expected range and even those out of the range.

Chapter 7

Model Fitting Analysis of DCE MR Renal Images

7.1 Introduction

Reliable evaluation of renal function is essential for assessing the prognosis and the therapeutic approach to functional renal diseases, and for pre-nephrectomy assessment. Conventional approaches include renal scintigraphy and laboratory measurements. In Chapters 3 and 4, renal scintigraphy, as a well-established noninvasive approach, has been extensively introduced. For extracting clinically-useful information from dynamic scintigraphic images maximally and reliably, models of renal impulse retention function were improved, and biphasic model fitting was proposed. In recent years, dynamic contrast-enhanced magnetic resonance imaging (DCE MRI) has emerged as another promising tool for assessing renal function noninvasively. The advent of fast pulse sequences has made DCE MRI appropriate as a functional imaging technique, while high spatial resolution is one advantage of MR images over scintigraphic images in renal

anatomic study. Hence, DCE MRI has the potential of combining both renal anatomic and functional information [28] [92] for more confident diagnosis.

As reviewed in Chapter 2, the application of DCE MRI for functional assessment would be more complicated than that of renal scintigraphy. For quantitative analysis, maps of contrast-agent concentration (C) should be first calculated based on MR images. However, it is well known that signal intensity of MRI (S) is usually not proportional to the concentration (C) of contrast agent. Depending on the MR sequence used, the S -to- C conversion can be achieved, either by assuming a linear relationship between S and C [147] or by utilizing the T_1 -shortening effect of Gd, i.e., $rC = 1/T_1^C - 1/T_1^0$. Constant r is termed as longitudinal relaxivity. T_1^C and T_1^0 are post- and pre-contrast longitudinal relaxation time, respectively. T_1 can be determined according to an S - T_1 calibration curve obtained in a phantom experiment [98], or be calculated according to an S - T_1 formula [51] [104] [105] [106]. In Chapter 5 and Chapter 6, the calculation of T_1 from S of SPGR according to the S - T_1 formula (Eq. 5.2), and further estimation of C utilizing the T_1 -shortening effect of Gd were discussed. With dynamic C maps, a renogram can be generated, by positioning a ROI on kidney or renal parenchyma in every C map. Whether the MR-generated renogram can be used for reliable functional assessment is an issue concerned by many researchers.

The Patlak plot, which is a simple but robust approach for renogram analysis [70] [71], has been applied for analyzing DCE MR renal images recently [147], for GFR estimation. On the other hand, model fitting, as indicated by a recent study based on renal

scintigraphy [91], has the capability of identifying multiple parameters, including GFR, renal blood flow and some transit time indices. According to the literature review, model fitting has never been applied to DCE MRI kidney data for function-assessment purpose. In this study, a patient study was carried out, to demonstrate the feasibility of DCE MRI combined with model fitting for identifying the various renal parameters, and to compare Patlak plot and model fitting in analyzing DCE MRI kidney data.

7.2 Materials and Method

7.2.1 Theoretical Comparison

Both Patlak plot and model fitting can be used to analyze renogram, thus identifying parameters indicative of renal function. In both approaches, kidney is regarded as a system with input fed from renal artery, and information of the system is extracted by eliminating dependence of renogram on arterial input. In the following, the two approaches will be briefly described, after which the theoretical relation between them is explored.

For analyzing renogram, model fitting assumes that renal system is linear and time-invariant. Renal impulse retention function (R), which is essentially the renogram after a unit-impulse input from renal artery, can be characteristic of the renal system and tracer used. The relation between measured renogram and renal R is as follows,

$$K(t) = F \int_0^t I(\tau) R(t - \tau) d\tau, \quad (7.1)$$

where K and I are renogram and input curve (obtained from left ventricle or aorta), respectively, and F is renal blood flow. K and I are contaminated by measurement errors. Parameters in R model are adjusted to minimize the sum of squared residue between the measured K and the model-predicted K (the right side of Eq. (7.1)).

Renal R determined by model fitting provides clinically-useful parameters directly. Fine et al [38] proposed an R model, which contains several parameters such as F , filtration fraction and various transit times. Recently, this model was improved by incorporating a vascular delay [91], and is termed as Fine's model with vascular delay ($R_{\text{Fine,d}}$). The formula of this model is given as follows,

$$R_{\text{Fine,d}}(t) = 1 - h_b(t) - h_p(t) \quad (7.2)$$

where

$$h_b(t) = u(t - \min TT_b)(1 - f) \left[1 - \left(2 \cdot \frac{t - \min TT_b}{MTT_b - \min TT_b} + 1 \right) \exp \left(-2 \cdot \frac{t - \min TT_b}{MTT_b - \min TT_b} \right) \right] \quad (7.2a)$$

and

$$h_p(t) = u(t - \min TT_p)f \left[1 - \left(2 \cdot \frac{t - \min TT_p}{MTT_p - \min TT_p} + 1 \right) \exp \left(-2 \cdot \frac{t - \min TT_p}{MTT_p - \min TT_p} \right) \right]. \quad (7.2b)$$

The symbols in Eq. (7.2) are listed and interpreted in Table 3-2. Another potentially useful parameter can be given by $E = fF$, which denotes the extraction rate and can serve as a measure of the glomerular filtration rate ($GFR = E(1 - Hct)$, Hct : hematocrit).

Previous applications of Patlak plot for renogram analysis are based on the assumption that, before a minimal parenchyma transit time ($\min TT_p$), there is no tracer outflow from tubular pathways. Within this period, the relation of renogram and input curve can be described by Eq. (2.9) $K(t) = a \cdot I(t) + b \cdot \int_0^t I(\tau) d\tau$ $t < \min TT_p$. Eq. (2.9) indicates that, before tracer outflow from tubular pathways, the overall tracer residue in kidney ROI is comprised of the tracer in vascular compartment and the tracer in tubular compartment, and tubular pathway can be regarded as an integrator of input. Accordingly, constant a would be a measure of the volume of renal vascular compartment, under the condition that tracer fills the vascular compartment, that is, $t > \max TT_b$, and b is actually extraction rate ($E = fF/100$), a measure of GFR. Divided by $I(t)$ at both sides, Eq (2.9) is converted

to Eq. (2.10), $\frac{K(t)}{I(t)} = a + b \cdot \frac{\int_0^t I(\tau) d\tau}{I(t)}$. With discrete measurements of $I(t)$ and $K(t)$, a and

b can be determined by linear regression.

Model fitting and Patlak plot, as introduced above, are based on different mathematical expression of renal system: one by convolution, while the other by summation and integration. It was recognized that, in an initial short period ($t < \min TT_b$), these mathematical descriptions have the same expression. Let's start from the convolution (Eq. (7.1)) using renal IRF model with vascular delay (such as $R_{\text{Fine,d}}$). Within time $t < \min TT_b$, IRF model with vascular delay remains constant (unit), so that the convolution is actually as follow,

$$K(t) = F \cdot \int_0^t I(\tau) d\tau \quad t < \min TT_b. \quad (7.3)$$

Dividing both sides of Eq. (7.3) by $I(t)$, we get

$$\frac{K(t)}{I(t)} = F \cdot \frac{\int_0^t I(\tau) d\tau}{I(t)} \quad t < \min TT_b. \quad (7.4)$$

It is noted that Eq (7.4), same as Eq (2.10), describes a linear relation between $K(t)/I(t)$ and $\int_0^t I(\tau) d\tau / I(t)$, except that the presumed y-intercept is zero. Hence, Patlak plot can be extended as follows,

$$\begin{cases} \frac{K(t)}{I(t)} = F \cdot \frac{\int_0^t I(\tau) d\tau}{I(t)} & t < \min TT_b \\ \frac{K(t)}{I(t)} = V + fF \cdot \frac{\int_0^t I(\tau) d\tau}{I(t)} & \max TT_b < t < \min TT_p \end{cases}. \quad (7.5)$$

Linear regression based on discrete points within periods of $t < \min TT_b$ and $\max TT_b < t < \min TT_p$ respectively, gives estimate of F and E ($fF/100$, measure of GFR).

Compared with the more complex IRF modeling, the above-extended Patlak plot focuses on the characterization of vascular plateau ($t < \min TT_b$) and parenchyma plateau ($\max TT_b < t < \min TT_p$) in renal IRF. These two plateaus correspond to two linear increasing segments in Patlak plot. Besides the parameters of the plateaus (F and E), model fitting provides additional parameters characteristic of the vascular/tubular downslopes in IRF, such as mean vascular/parenchyma transit time.

7.2.2 DCE MRI Acquisition and Image Analysis

The patient study was approved by the local ethics committee and all volunteers gave written informed consent. Six patients underwent DCE MRI for assessment of

angiogenesis as part of a Phase I trial. Fifteen scans with well-defined kidneys were used for analysis. MRI was performed on a whole-body Siemens 1.5 Tesla scanner ('Magnetom Avanto'). Three-dimensional spoiled gradient recalled echo (3D SPGR) sequence was performed with acquisition parameters: T_R 3.15ms, T_E 1ms, field of view (FOV) 40cm×40cm, matrix 256×256, number of slices 10, slice thickness 8mm, temporal resolution ~4s. With flip angle of 6° , the 3D SPGR imaging was repeated for 10 times to obtain 10 sets of images, followed by the other 10 sets of images using flip angle of 10° . These 20 sets of images were used to determine pre-contrast T_1 (T_1^0) and proton density (M_0) maps. Dynamic imaging was performed with the same acquisition parameters as above and flip angle of 10° continuously; overall 90 sets of images were obtained, with Gd-DTPA injected after the 10th set (this guarantees that the resultant concentration versus time curve contains at least a 10-point baseline).

Figure 7-1 Schematic diagram for DCE MRI protocol in this study. Ten sets of 3D images were acquired using flip angles 6° , and the other 10 sets using flip angle 10° . The following dynamic imaging continuously acquired 90 sets of 3D data with flip angle 10° , with Gd-DTPA injected after the 10th set.

Figure 7-2 One slice (out of 10) of 3D SPGR data, acquired at ~ 60 s after the injection of Gd-DTPA. One kidney was clearly defined, while the other one did not appear in this slice because most of the space was occupied by the liver above. In this image, renal ROI was manually drawn to include renal parenchyma, and input ROI was drawn in abdominal aorta. (b) M_0 map calculated from pre-contrast images acquired with 2 different flip angles, according to Eq. (5.3). (c) T_1^0 map obtained simultaneously with M_0 map. (d) Map of $(1/T_1^c - 1/T_1^0)$. T_1^c was converted from the SPGR image (a), according to Eq. (5.2). For the conversion, M_0 map in (b) was used. For every pixel, $(1/T_1^c - 1/T_1^0)$ is proportional to the concentration of Gd-DTPA.

Figure 7-3 Implementation of model fitting and Patlak plot for a same case example. (a) In model fitting, parameters of renal IRF model (the inset in (a)) were adjusted to minimize the sum of squared residue (SSR) between the fitting curve (convolution of aorta curve and renal IRF) and renogram (measured renal curve). (b) In Patlak plot, time windows must be chosen carefully for calculating slope of regression line. Generally, the post-Gd-injection frames, corresponding to vascular and parenchyma plateaus in renal IRF, are chosen to estimate F and GFR , respectively.

Based on the pre-contrast images of 6° and 10° (20 sets; every set contains 10 slices), T_1^0 and M_0 were calculated pixel by pixel according to Eq. (5.3), to construct T_1^0 and M_0 maps. Combined with the M_0 map, the 90 sets of dynamic images were converted to dynamic post-contrast T_1 (T_1^c) maps (Figure 7-2), according to Eq. (5.2). One slice with maximal volume of abdominal aorta was chosen, in which a proper region of interest (ROI) within aorta was drawn. For every post-contrast frame, Gd-DTPA concentration (C) within the aorta ROI was estimated as $(1/T_1^c - 1/T_1^0)/r$, where r is T_1 relaxivity ($3.75 \text{ s}^{-1}\text{mM}^{-1}$ [148] for blood). Similarly, one coronal slice across both renal pelvis and parenchyma was chosen, and ROI was defined to include renal parenchyma. T_1 relaxivity in renal parenchyma was chosen as $1.5 \text{ s}^{-1}\text{mM}^{-1}$ [149, 150]. Single-slice renogram was

generated by calculating contrast-agent mass (average concentration multiplied by slice volume) for every time point. The renogram for the whole kidney can then be estimated by multiplying the above single-slice renogram with (kidney volume/slice volume). The volume of kidney, was ~ 0.18 L according to previous studies [151], while the parenchyma volume within the chosen slice can be readily determined from that of the renal ROI. An example of renogram is shown in Figure 7-3 (a).

Model fitting using Fine's model with vascular delay ($R_{\text{Fine,d}}$) was applied for every kidney case. The fitting process was driven by Levenberg-Marquardt optimization (MatlabTM), in which sum of squared residue between the measured K and model-predicted K is minimized. For comparison, Patlak plot was applied to identify renal blood flow (F) and GFR. The implementation of these analysis methods is illustrated in Figure 7-3. Paired t-test and correlation plot were used to compare the corresponding parameters (F and GFR) by different methods. The additional parameters provided by model fitting, such as filtration fraction (f), minimal/mean vascular/parenchyma transit times, were compared with their respective reference values in literature.

7.3 Results

The parameter estimates for the kidney cases in patient study are tabulated in Table 7-1. Paired t-test showed that there is no significant difference between F estimates by model fitting using $R_{\text{Fine,d}}$ and those by Patlak plot. Similar statistical-testing result was obtained for the GFR estimates. The correlation plots for F and GFR are respectively shown in

Figure 7-4 (a) and (b). As expected, these correlation plots showed good correspondence, with slope of regression line $m=0.96$, y-intercept $c=24.8$ and correlation coefficient $R^2=0.926$ for F and $m=1.01$, $c=1.8$ and $R^2=0.915$ for GFR. Besides F and GFR, the additional parameters obtained by model fitting include f , minTT_b , MTT_b , minTT_p and MTT_p , with the average $\pm$ SD values, $15.1\pm6.5\%$, $8\pm6s$, $17\pm4s$, $61\pm39s$, and $166\pm39s$, respectively. These values are in general agreement with those reported in literature [31] [37] [38] [91] [119], which were mostly estimated based on renal scintigraphy.

Table 7-1 Parameter estimates of patient study cases by model fitting and Patlak plot.

Case	F (ml/min)		GFR (ml/min)		f (%)	minTT_b (s)	MTT_b (s)	minTT_p (s)	MTT_p (s)
	$R_{\text{Fine, d}}$	Patlak	$R_{\text{Fine, d}}$	Patlak					
1	1647	1607	75	70	7.6	2.0	11.0	50	130
2	1495	1444	90	88	10.0	5.7	8.8	62	120
3	859	937	59	47	11.4	5.4	17.6	65	153
4	1009	1043	73	87	12.1	2.0	13.3	47	182
5	1057	1388	52	59	8.2	3.5	14.2	15	139
6	860	1158	48	63	9.4	7.3	15.3	59	120
7	2108	1961	348	312	27.4	20.0	20.0	20	112
8	830	899	129	114	26	9.1	18.2	38	156
9	1952	1992	138	194	11.8	2.0	21.7	22	208
10	1652	1709	120	116	12.1	2.0	16.3	65	146
11	1100	990	97	59	14.7	2.0	19.0	26	168
12	342	295	46	38	22.4	15.0	20.0	82	197
13	699	471	90	82	21.4	14.0	20.0	82	213
14	536	649	63	61	19.6	17.6	17.6	148	215
15	454	384	34	32	12.5	12.1	20.0	131	229
Mean $\pm$ SD	1120 $\pm$ 540		96 $\pm$ 73		15.1 $\pm$ 6.5	8 $\pm$ 6	17 $\pm$ 4	61 $\pm$ 39	166 $\pm$ 39

Figure 7-4 Correlation plots for comparison of the estimated F (a) and GFR (b) for the kidney cases, using model fitting with $R_{\text{Fine,d}}$ (subscript 2) and Patlak plot (subscript 1). The dot-dash line is regression line, with m and c as the slope and y-intercept. R^2 is the correlation coefficient. The solid line is the identity line ($y=x$).

7.4 Discussion

Some issues on the post-processing of dynamic MR images before functional analysis will be first discussed. The first issue is the choice of ROI for input curve. In previous renal scintigraphy, input ROI is chosen at left ventricle, while abdominal aorta is thought to be not clear enough under noisy condition. With MR images of higher signal-to-noise ratio and spatial resolution, the whole aorta can be clearly observed and thus is appropriate to be input ROI. Renal artery branches directly from abdominal aorta, so the latter can be a better location for generating input curve, than left ventricle. However, one should be careful in determining aorta ROI, to avoid partial volume problem (i.e. inclusion of some non-aorta volume, such as abdominal cavity), especially for the coronal images as in this study. Since the relation between MR signal and tracer concentration is not linear, partial volume effect is more complex in MR images.

The second issue is related to renal parenchyma ROI that is for generating renogram. Renal parenchyma appears in multiple slices of MR data. To segment renal parenchyma, one can define 2D ROI that includes parenchyma tissue in every slice. Tracer retention in renal parenchyma can thus be calculated by summing up the retention within 2D ROI of all slices. However, it is realized that within some slices the 2D ROI may suffer from partial volume problem. Decrease in the slice thickness in imaging may partially alleviate the problem, but that would increase the acquisition time accordingly (as more slices would be required for imaging the whole kidney). Hence, in this study we would rather choose one median slice that shows a C-shaped parenchyma ROI, which guarantees that partial volume problem is avoided. As a result, renogram for one slice is obtained, and by multiplying a volume ratio, renogram for the whole parenchyma can be estimated.

As reviewed in Chapter 2, renogram generated from renal scintigraphic images is conventionally divided into 3 phases: vascular phase, secretory phase and excretory phase. In this study, the renogram was reconstructed based on SPGR-signal (S) curve. Pre- and post-contrast T_1 values are first calculated from the S 's, and concentration (C) is then estimated according to the T_1 -shortening effect of Gd. In Figure 7-3, one example of renogram thus reconstructed is presented, which is clearly composed of the above-mentioned 3 phases. The correct pattern of the renograms indicates that the scheme employed for quantifying C from S is appropriate. It is also observed that the noise level of the renogram is low enough, so that the renogram can be analyzed by model fitting. The low noise level can be attributed to the image acquisition scheme employed, i.e.

repetitive pre-contrast imaging for the same times at two separated flip angles, and then post-contrast imaging at some proper angle. With this scheme, the noise propagation from S to C is effectively suppressed.

When comparing model fitting and Patlak plot, it was found that the two approaches offered comparable F estimates, and comparable GFR estimates in the patient study. Considering their theoretical correspondence as derived in theory section, such result is not surprising. It is also interesting to compare the performances of these two approaches in processing the actual kidney data. It is noted that these two methods have their respective limitations in some situations. For Patlak plot, one has to be very careful in choosing appropriate time windows for linear regression. Sometimes, a slight deviation from the correct time window may lead to a slope value with large error. Hackstein et al [147] studied the variation of estimated GFR value when different time windows were employed for Patlak plot. For model fitting, the fitting may not be satisfactory for some cases with serious obstruction of ureter. In such cases, the accumulated urine within renal pelvis produces high pressure, which may distort the later part of renal curve. To eliminate such distortion, it may be helpful to draw a thin ROI for renal parenchyma, thus avoiding renal pelvis as much as possible. Alternatively, one can also choose to just fit the former segment of renal curve, discarding the latter distorted segment.

Except for GFR and F , the various parameters identified by model fitting are comparable to their respective reference values in literature. Previous studies using renal scintigraphy indicated these parameters are diagnostically useful for various renal pathologies, such as

renovascular hypertension, obstructive uropathy, and kidney transplant. These parameters identified from DCE MRI can be combined with the morphologic information, to achieve more confident diagnosis for some renal diseases.

However, it is noted that F and GFR identified in the patient study are higher than the reference values (about 600 and 60 ml/min respectively). There are several possible explanations. Firstly, the temporal resolution for MR image acquisition is 4s, which may not be able to capture the essential feature of aorta peak. The underestimation of input function leads to overestimation of F and GFR. The overestimation of F by rough temporal resolution was illustrated in the previous study [91]. Note that in conventional dynamic renal scintigraphy, the temporal resolution for perfusion imaging is usually 1s. Secondly, another potential source of error is the relaxivity (r). Relaxivity is necessary to convert variation of post-contrast relaxation rate ($1/T_1^c - 1/T_1^0$) to concentration C . Because in literature review there is no in vivo measurement of human renal-parenchyma relaxivity, estimates from animal experiments were used in this study. There may be possible difference between renal parenchyma relaxivities of human and animals. Further studies are required to validate the utility of the relaxivity measured from animals for reliable human quantification.

7.5 Concluding Remarks

Patlak plot and model fitting using Fine's model with vascular delay were compared theoretically and clinically. Both methods have the capability to quantify renal blood flow and glomerular filtration rate. In patients study, the two methods provided

comparable estimates for F and GFR, respectively. It is also noted that, with model fitting, additional clinically-useful parameters, such as vascular and parenchyma MTT, can be identified from DCE MRI data for more confident diagnosis of renal pathology. However, the performance of both methods depends on the availability of reliable aorta and renal parenchyma curves, which requires high temporal resolution, and accurate relaxivities (especially for renal parenchyma).

Chapter 8

Conclusions and Recommendations

8.1 Conclusions

This thesis focuses on non-invasive assessment of renal function using dynamic imaging. As a well-established imaging technique for the purpose, renal scintigraphy has been proven to have the ability of providing diagnostic information indicative of renal function and various renal pathologies. From dynamic scintigraphic images, multiple clinically-useful parameters can be identified by parametric deconvolution (model fitting). In this thesis, new models for renal impulse retention function and novel model fitting approach were proposed, for better application of model fitting in analyzing renal scintigraphic images.

- 1) A piecewise-continuous linear (PCL) model was proposed for renal impulse retention function. The model contains vascular and parenchyma components as in more complex Fine's model, but characterizes the downslopes by linear segments. Compared with Fine's model, PCL model is more efficient and is able to identify

important parameters such as MTT_p and filtration fraction with comparable accuracy. Based on Fine's model, a more realistic model was designed by incorporating a vascular delay in the vascular component. It was termed as Fine's model with vascular delay. This model has the potential to extract accurate vascular information from perfusion-imaging sequence of renal scintigraphy. The application of Fine's model with vascular delay was illustrated with the assistance of biphasic model fitting.

- 2) The biphasic model fitting approach was proposed to analyze the non-uniform-interval data of renal scintigraphy, so as to improve the estimation accuracy of renal vascular parameters. For its implementation, Fine's model with vascular delay was employed. The stability of the proposed fitting approach was validated in Monte Carlo simulation. In patient study, renal blood flow estimates obtained by the biphasic approach correlated better with established blood flow indices (K/A and PI) than those obtained by conventional fitting. The various vascular/parenchymal parameters estimated by the biphasic approach were found to be indicative of and consistent with some pathology of the kidneys.

DCE MRI has been recognized as a valuable technique for functional analysis, because of its high spatial resolution and no use of radioactive tracer. However, it is a challenging work to reliably quantify concentration of contrast medium from MR images, which is necessary for analyzing organ's function. Also, a study is required to demonstrate the feasibility of DCE MRI combined with model fitting in assessing renal function.

- 1) For spoiled gradient recalled echo sequence (SPGR), one of the most usually used sequences for DCE MRI, selecting flip angles properly for image acquisition helps suppress the propagated error to estimated T_1 and C . In this thesis, a convenient and high-performance scheme was designed for SPGR acquisition, $\{M \times \alpha_1^{\text{opt}}, M \times \alpha_2^{\text{opt}}, \alpha_3^{\text{opt}}\}$, i.e. M repetitions of the pre-contrast scans using the angles α_1^{opt} and α_2^{opt} , and subsequent post-contrast imaging with α_3^{opt} at various time points. The flip angles were obtained by numerical optimization, in which a weighting function, reflecting the relative importance of various tissues, was incorporated. Results of Monte Carlo simulations show that the present approach could significantly improve the accuracy of contrast (Gd) concentration estimates within certain tissues of interest.

- 2) In literature, numerical identification of optimal flip angles for a single T_1 is the key step of identification of optimal angles for a range of T_1 , which is usually encountered in a typical image. In this thesis, some interesting features of single- T_1 optimal angles were proved, and the analytic expression for these angles was derived. Such analytic expression makes numerical optimization unnecessary. Moreover, a new method was proposed for selecting flip angles for a range of T_1 : mid- T_1 angles. With the mid- T_1 angles, different T_1 values can be estimated with more uniform predicted error, as compared with previous angles. With this feature, even some unpredicted T_1 values (out of the predicted range) can be estimated with an error near to the predicted level.

- 3) Finally, the feasibility of DCE-MRI combined with model fitting as a tool for renal functional assessment was demonstrated. Fine's model with vascular delay was employed for the purpose. Patlak plot, which had already been applied for analyzing DCE MR data, was applied as a comparison (with model fitting). Theoretical derivation indicated that both Patlak plot and model fitting using Fine's model with vascular delay can be used to estimate F and GFR. In a patient study, the two methods provided comparable estimates for renal blood flow and GFR, respectively. With model fitting, additional clinically-useful parameters, such as vascular and parenchyma MTT, can be identified from DCE MRI data for more confident diagnosis of various renal pathologies.

8.2 Recommendations for Future Work

Quantitative evaluation of renal perfusion and function non-invasively has been an attractive goal for many researchers and medical doctors. In recent years, blood sample or urine collection is not regarded as an indispensable supplement anymore. However, much additional endeavor has to be put for fully quantitative identification of some parameters. Compared with renal scintigraphy, DCE MRI is more powerful, but seems to require more endeavor before it is developed into a reliable technique. In the following, some recommendations for further research in this area were presented.

- 1) Using biphasic model fitting and Fine's model with vascular delay, GFR and F can now be estimated non-invasively from dynamic images, with unit of 'ml/min' or 'ml/min/100ml of tissue'. It would be desirable to compare these values with those by the gold-standard techniques, which involve multiple blood samplings and urine

collection, in a large patient data set to validate the emerging value of dynamic imaging.

- 2) With biphasic fitting using complex model, renal vascular and parenchyma parameters can be simultaneously identified. The correlation between the parameters and status or diseases of kidney should be explored. A preliminary study was carried out in Chapter 4, but it is not systematic enough as only a few cases are included. With more and more patient cases, a grade system can be constructed for some renal diseases (such as obstructive uropathy, renovascular hypertension), according to the values of the related parameters. Such a system will be very helpful for the assessment of related renal diseases.
- 3) For more accurate assessment of renal function using DCE MRI, the temporal resolution (rate for image acquisition) has to be high enough. According to the studies in renal scintigraphy, a rate of 1~2 second per frame for the initial minute after tracer injection would be desirable, because such rate is able to capture the essential feature of the rapid vascular process. Protocols for image acquisition can be appropriately designed to achieve such temporal resolution.
- 4) Longitudinal (T_1) relaxivity for renal cortex or parenchyma is an important parameter for quantifying concentration of contrast medium within renal parenchyma ROI in MR images. The value of relaxivity used in the studies was measured in animal experiments by previous researchers. Until now, the possible difference between such value of human and that of animals has not been evaluated.
- 5) In MR images of high spatial resolution, finer structures can be discriminated, such as renal cortex/medulla/pelvis, and even renal columns/pyramids. It would be

desirable that functional analysis is done for these finer structures, instead of current whole renal parenchyma. Such analysis would require more complicated modeling, but reveal more detailed information of kidney.

In closing, endeavors have been put in improving analysis approaches for dynamic imaging, especially based on dynamic renal scintigraphy; all these approaches can be readily applied for DCE MRI, a more promising tool for renal functional assessment. Issues on converting MR image intensity to concentration have also been discussed. Recommendations for future work were listed for further increasing the role of dynamic imaging (especially DCE MRI) in assessment of renal function.

Author's Publications

Papers in peer-reviewed journals

1. **Jeff L. Zhang**, L. Zhang, T.S. Koh and B. Shuter. Estimation of renal scintigraphy parameters using a linear piecewise-continuous model. *Physics in Medicine Biology* 48 N167-N172, 2003.
2. **Jeff L. Zhang** and T.S. Koh. On the selection of optimal flip angles for T_1 mapping of breast tumors with dynamic contrast enhanced magnetic resonance imaging. *IEEE Transaction on Biomedical Engineering* 53 (6) 1209-1214, 2006.
3. T.S. Koh, **Jeff L. Zhang**, C.K. Ong and B. Shuter. A biphasic parameter estimation method for quantitative analysis of dynamic renal scintigraphic data. *Physics in Medicine Biology*. 51 2857-2870, 2006.
4. **Jeff L. Zhang** and T.S. Koh. Selection of flip angles for T_1 mapping using spoiled gradient-recalled echo imaging: theoretical derivation and implementation. In final preparation.
5. CH Thng, **Jeff L. Zhang**, TS Koh, H Rumpel and BC Goh. Measurement of glomerular filtration rate and renal blood flow using dynamic contrast-enhanced MRI: a comparative study of Patlak plot and model fitting method. In final preparation.

Papers presented in conferences

1. **Jeff L. Zhang**, L. Zhang, T.S. Koh and B. Shuter. A piecewise-continuous linear model for estimation of renal scintigraphy parameters. *World Congress on*

Medical Physics and Biomedical Engineering (WC2003), Sydney, Australia, Aug. 2003.

2. **Jeff L. Zhang** and T.S. Koh. Optimizing flip angles for T_1 mapping of breast tumors with dynamic contrast-enhanced magnetic resonance imaging. *World Congress on Medical Physics and Biomedical Engineering (WC2006)*, Seoul, Korean, 2006.
3. T.S. Koh and **Jeff L. Zhang**. The inclusion of capillary distribution in a tracer kinetics model. *World Congress on Medical Physics and Biomedical Engineering (WC2006)*, Seoul, Korean, 2006.
4. **Jeff L. Zhang**, C.H. Thng, T.S. Koh, H. Rumpel and B.C. Goh. Measurement of glomerular filtration rate and renal blood flow using dynamic contrast-enhanced MRI: a comparative study of Patlak plot and model fitting method. *European congress of radiology*, Vienna, Austria, 2007

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Appendix

APPENDIX A

Analogous to NF of T_1 , we define NF_{E_1} , in which $E_1 = \exp(-T_R/T_1)$. NF_{E_1} and NF have the following relation,

$$\text{NF}_{E_1} = \frac{\Delta E_1 / E_1}{\Delta S / M_0} = \frac{dE_1}{dT_1} \cdot \frac{T_1}{E_1} \cdot \frac{\Delta T_1 / T_1}{\Delta S / M_0} = \frac{T_R}{T_1} \text{NF}. \quad (\text{A1})$$

Combining Eq. (6.1) and Eq. (A1), we get

$$\text{NF}_{E_1} = \frac{\sqrt{\frac{1}{a} \left(\frac{1 - E_1 \cos \alpha_1}{\sin \alpha_1} \right)^2 + \frac{1}{b} \left(\frac{1 - E_1 \cos \alpha_2}{\sin \alpha_2} \right)^2}}{\frac{1 - E_1}{1 - E_1 \cos \alpha_1} - \frac{1 - E_1}{1 - E_1 \cos \alpha_2}}. \quad (\text{A2})$$

Taking logarithm does not affect the optimal flip angles for NF_{E_1} . Denote the logarithm of NF_{E_1} as L . Take partial derivative of L with respect to α_1 and α_2 , respectively, and setting them to 0, we get

$$\begin{cases} \frac{a(\sin \alpha_1)^4 (1 - E_1 \cos \alpha_2)}{(E_1 - \cos \alpha_1)(1 - E_1 \cos \alpha_1)^2} = \frac{\cos \alpha_2 - \cos \alpha_1}{\frac{1}{a} \left(\frac{1 - E_1 \cos \alpha_1}{\sin \alpha_1} \right)^2 + \frac{1}{b} \left(\frac{1 - E_1 \cos \alpha_2}{\sin \alpha_2} \right)^2} \\ \frac{b(\sin \alpha_2)^4 (1 - E_1 \cos \alpha_1)}{(E_1 - \cos \alpha_2)(1 - E_1 \cos \alpha_2)^2} = \frac{\cos \alpha_1 - \cos \alpha_2}{\frac{1}{a} \left(\frac{1 - E_1 \cos \alpha_1}{\sin \alpha_1} \right)^2 + \frac{1}{b} \left(\frac{1 - E_1 \cos \alpha_2}{\sin \alpha_2} \right)^2} \end{cases}. \quad (\text{A3})$$

Decoupling α_1 and α_2 in Eq. (A3) is difficult, but we manage to obtain

$$\frac{aS_1^3 \sin \alpha_1}{E_1 - \cos \alpha_1} = -\frac{bS_2^3 \sin \alpha_2}{E_1 - \cos \alpha_2}. \quad (\text{A4})$$

On the other hand, the ratio of S_1 and S_2 is

$$\frac{S_1}{S_2} = \frac{\sin \alpha_1 (1 - E_1 \cos \alpha_2)}{\sin \alpha_2 (1 - E_1 \cos \alpha_1)}. \quad (\text{A5})$$

For unequal α_1 and α_2 within $(0^\circ, 180^\circ)$, combining Eq. (A4) and Eq. (A5) (eliminate E_1) results in

$$\frac{a}{b} \frac{S_1^4}{S_2^4} - 1 = \frac{\sin \alpha_1 \sin \alpha_2}{1 - \cos \alpha_1 \cos \alpha_2} \left(\frac{a}{b} \frac{S_1^2}{S_2^2} - 1 \right) \frac{S_1}{S_2}. \quad (\text{A6})$$

Because $(\sin \alpha_1 \sin \alpha_2) / (1 - \cos \alpha_1 \cos \alpha_2) \in (0, 1)$, we derive from Eq. (A6) that

$$\begin{cases} S_1 < S_2 \text{ and } \frac{1}{b S_2^2} > \frac{1}{a S_1^2} & \text{if } a > b \\ S_2 < S_1 \text{ and } \frac{1}{a S_1^2} > \frac{1}{b S_2^2} & \text{if } b > a \end{cases}. \quad (\text{A7})$$

The case of $a = b$ will be discussed in other sections.

APPENDIX B

Substituting $\alpha_{Em} = \arccos(E_1)$ into Eq. (5.2), we get the maximal signal intensity,

$$S_{Em} = S(\alpha_{Em}) = M_0 \sqrt{\frac{1 - E_1}{1 + E_1}}. \quad (\text{B1})$$

Denote signals weaker than S_{Em} as $h S_{Em}$, where $h \in (0, 1)$. The associated flip angle can be calculated by substituting $h S_{Em}$ into Eq. (5.2). That is,

$$h M_0 \sqrt{\frac{1 - E_1}{1 + E_1}} = \frac{M_0 (1 - E_1) \sin \alpha}{1 - E_1 \cos \alpha}. \quad (\text{B2})$$

From Eq. (B2), we get

$$\tilde{\alpha}_{1,2} = \arccos \left[\frac{E_1 h^2 \pm (1 - E_1^2) \sqrt{1 - h^2}}{1 - E_1^2 + h^2 E_1^2} \right]. \quad (\text{B3})$$

As it has been proven that optimal flip angles correspond to same signal intensity, there must be one $\tilde{\alpha}_{1,2}$ pair, denoted as $\hat{\alpha}_{1,2}$, that minimizes NF_{E_1} (thus NF).

Substituting Eq. (B3) into Eq. (A2), NF_{E_1} can be expressed as a function of h ,

$$\text{NF}_{E_1} = \frac{(1 - E_1^2)}{\sqrt{2} M_0 E_1} \sqrt{\frac{1 + E_1}{M(1 - E_1)}} \frac{1}{h \sqrt{1 - h^2}}. \quad (\text{B4})$$

Taking derivative of NF_{E_1} with respect to h , and setting it to 0, we find that $h = \sqrt{2}/2$.

That is to say,

$$S(\hat{\alpha}_{1,2}) = \frac{\sqrt{2}}{2} S_{Em}. \quad (\text{B5})$$

Substituting $h = \sqrt{2}/2$ into Eq. (B3), we obtain

$$\hat{\alpha}_{1,2} = \arccos \left[\frac{E_1 \pm \sqrt{2}(1 - E_1^2)}{2 - E_1^2} \right]. \quad (\text{B6})$$

Substituting Eq. (B6) into Eq. (6.1), we get the minimal NF of $2M$ signal acqu

$$\min\{\text{NF}_{T_1}\} = \frac{T_1(1 + E_1)}{T_R E_1} \sqrt{2(1 - E_1^2)/M}. \quad (\text{B7})$$

APPENDIX C Manual segmentation of kidney in dynamic scintigraphic images

Renal scintigraphy is a 2-dimensional imaging technique with relatively low spatial resolution. Segmentation of kidney in scintigraphic images requires knowledge on the transit of the tracer in kidney. The injected tracer, such as Tc99m-DTPA, first arrives at glomeruli that reside in the outer layer of kidney - renal cortex. A fraction of tracer is filtered into renal tubules, and flows into the inner layer - renal medulla. Finally, the urine with tracer exits renal parenchyma into renal pelvis. In the dynamic images, we will expect to see that the regions corresponding to renal cortex, medulla and pelvis becomes bright sequentially, indicating the tracer's transit through them. Obviously, renal cortex and medulla may become bright in images acquired at different time points. Hence, for determining kidney region of interest (ROI), which is composed of renal cortex and renal medulla, multiple image frames need to be summed up to create a single image with sufficient counts and with both bright cortex and bright medulla. However, for kidneys of different functional status, tracer enters renal tissues (either cortex or medulla) at different times, so it is impossible to sum up dynamic images of one same time period for segmenting all kidneys. This constitutes one difficulty for automatic segmentation. Also, because of the 2-D imaging and the relatively low spatial resolution, the edge of kidney can not be defined clearly. The overlay of kidney with liver and spleen, and possible inclusion of partial renal pelvis make the situation much tougher.

In most clinical centers and research institutions, segmentation of kidneys from scintigraphic images depends on manual method. In this study, manual segmentation was

performed. The dynamic data were acquired using the following protocol: 1 frame per second for the 1st minute, then 1 frame per 10 second for the following 15 minutes. Multiple frames are summed up to one single image with bright parenchyma and much brighter pelvis. In the image, a contour was drawn using 'roiploy' in MATLAB, to include parenchyma but exclude the pelvis [152, 153]. The contour was then applied to every frame, and the intra-ROI intensities, proportional to tracer concentration, were averaged to indicate tracer retentions in renal parenchyma at the corresponding frame (i.e. time point). The retention versus time curve (also termed as time-versus-activity curve (TAC)) is analyzed for extracting information on renal function. Some researchers include renal pelvis in renal ROI. As renal pelvis becomes bright at later frames, the inclusion of it does not affect the estimation of renal vascular parameters and filtration fraction much, but will increase parenchymal mean transit time.

A simulation study was done to evaluate the effect of the variability of manual selected region of interest (ROI) for renal parenchyma to the resultant TAC. In a summed-up and cropped image from one patient data (Figure C1 (a)), ROI was determined manually as described above, and was used as the baseline contour for our simulation study below (red contour in Figure C1 (a)).

Every control point in the baseline contour was moved along the direction perpendicular to the line linking its two neighbor points. The moving distance between the new point to the old one was randomly chosen, with a limit of ± 1.5 pixels. The 3-pixel gap, which is

shown in Figure C1(a) as green dashed lines, is broad enough to account for possible variability in manual drawing by an operator. The process was repeated 100 times, to generate 100 contours. One example of the randomly generated contours is shown in Figure C1(a) as blue line. For every contour, time activity versus time curve (TAC) was extracted from the intra-ROI pixels of the dynamic data. In Figure C1(b), we plotted the TACs, with the red one as the TAC from the baseline contour, while the blue ones as the 100 randomly generated ones. At every time point, the coefficient of variance (CV) of TAC magnitude, due to variability of manual selected ROI, was calculated as the standard deviation of the 100 estimates from the randomly generated ROIs, divided by the reference value at this point from the baseline ROI. For all the time points, the CVs have an average of 2.2%, and standard deviation of 0.8%. Hence, by manually selecting ROI for renal parenchyma as in the study, about 2-3% noise was induced into the resultant TACs. In Chapter 4, simulations were carried out by introducing 10% noise into TAC, and showed that our models performed stably and the accuracy of the model parameters was satisfactory.

Figure C1. (a) In a summed-up and cropped scintigraphic image, a baseline ROI was determined (red contour); every control point in baseline contour was moved along the direction perpendicular to the straight line linking its 2 neighbor points, and the distance between the new point after movement and the old one was randomly chosen, within a limit of ± 1.5 pixel (the 3-pixel gap is shown by the 2 green contours). The blue contour is an example of the randomly generated contours. (b) The resultant TACs. Blue dots: 100 TACs from randomly-generated ROIs; red line: TAC of the baseline ROI.