Modelling and simulation of dynamic contrast-enhanced MRI of abdominal tumours

A thesis submitted to the University of Manchester for the degree of Doctor of Philosophy in the Faculty of Medical and Human Sciences

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Abstract

Dynamic contrast-enhanced (DCE) time series analysis techniques are hard to fully validate quantitatively as ground truth microvascular parameters are difficult to obtain from patient data. This thesis presents a software application for generating synthetic image data from known ground truth tracer kinetic model parameters. As an object oriented design has been employed to maximise flexibility and extensibility, the application can be extended to include different vascular input functions, tracer kinetic models and imaging modalities. Data sets can be generated for different anatomical and motion descriptions as well as different ground truth parameters. The application has been used to generate a synthetic DCE-MRI time series of a liver tumour with non-linear motion of the abdominal organs due to breathing.

The utility of the synthetic data has been demonstrated in several applications: in the development of an Akaike model selection technique for assessing the spatially varying characteristics of liver tumours; the robustness of model fitting and model selection to noise, partial volume effects and breathing motion in liver tumours; and the benefit of using model-driven registration to compensate for breathing motion.

When applied to synthetic data with appropriate noise levels, the Akaike model selection technique can distinguish between the single-input extended Kety model for tumour and the dual-input Materne model for liver, and is robust to motion. A significant difference between median Akaike probability value ($P \leq 0.01$) in tumour and liver regions is also seen in 5/6 acquired data sets, with the extended Kety model selected for tumour. Knowledge of the ground truth distribution for the synthetic data was used to demonstrate that, whilst median $K^{\text{trans}}$ does not change significantly ($P \leq 0.01$) due to breathing motion, model-driven registration restored the structure of the $K^{\text{trans}}$ histogram and so could be beneficial to tumour heterogeneity assessments.
Declaration

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Thanks to James. Thanks to Mum. And I hope that I have undertaken this research with the respect and integrity, as well as the perspective and enthusiasm that my Dad would have been proud of.
Publications

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Conference


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Chapter 1

Introduction

The growth of a tumour is known to be largely dependent on its ability to recruit a blood supply from the established vasculature within the host tissue [1]. As the cells of the tumour divide, causing the tumour to grow, conditions within the tumour microenviroment, such as hypoxia, hypoglycaemia and acidity, trigger angiogenesis - the formation of new blood vessels. If the tumour was unable to develop a blood supply, its growth would be limited by the capacity of diffusion from the nearest host tissue vessels to supply nutrients and oxygen and remove waste products from the tumour cells. The process of angiogenesis and the tumour vasculature itself have become targets for novel anti-cancer therapeutics. If the drugs can prevent the formation of new vessels or destroy existing tumour vessels, then tumour growth could potentially be halted. For example, the anti-angiogenic drug bevacizumab aims to prevent the action of the cytokine vascular endothelial growth factor which promotes growth of the vascular endothelium and increases the permeability of the vascular walls [2].

Potential new anti-cancer compounds are tested in the well-established clinical trial process that evaluates the safety and efficacy of the drug for human use. For anti-angiogenic drugs, which are not necessarily expected to cause a reduction in tumour size, the commonly used RECIST criteria are unlikely to be an appropriate biomarker of drug efficacy. Assessing tumour size also cannot confirm the mode of action of the drug - for example, does bevacizumab affect the permeability of the vasculature or does it impede tumour growth by some other possibly unexpected mechanism? Clinical trials of anti-angiogenic therapeutics therefore required new biomarkers that
would allow the potential changes in microvascular characteristics caused by the drug to be estimated. Histology could potentially provide this information, however biopsy is an invasive technique. Therefore, it is not always suitable (depending on the location of the tumour) for the repeated measurements typically performed at different stages during the clinical trial to establish the time course of the drug effect. Biopsies are also effectively point measurements and so they cannot provide information on tumour heterogeneity and may miss the most active tumour regions.

Dynamic contrast-enhanced (DCE)-magnetic resonance imaging (MRI) - in combination with tracer kinetic model fitting - has provided biomarkers for anti-angiogenic drugs that are relevant to the mode of action, minimally invasive and, as only non-ionising radiation is involved, can be measured at repeated time points without causing additional patient safety concerns. An image volume is acquired at each time point in the DCE imaging performed at each visit and multiple visits are often used to monitor the time course of the drug effect. For DCE-computed tomography (CT) this can result in a substantial radiation dose to the patient, but this is not a concern for DCE-MRI. Fitting a tracer kinetic model to the time course data derived from DCE-MRI allows parameters that reflect the underlying tumour physiology to be estimated. For example, fitting the extended Kety model [3] and estimating $K^{\text{trans}}$, which is a transfer constant that is influenced by the permeability of the blood vessels, allows the expected biological action of bevacizumab to be confirmed or otherwise [2].

Tracer kinetic models have been formulated for, and applied to, tissues with different underlying physiology, for example tumour [4, 3], liver [5], kidney [6] and lung [7]. The differing characteristics of healthy liver and liver tumour tissue suggest that a different model may be required to adequately describe the time course data for each tissue type. For example, the liver has a dual blood supply from the hepatic artery and the hepatic portal vein whilst tumours within the liver have been shown to recruit a predominantly arterial blood supply [8]. It may therefore be possible to investigate the spatially varying microvascular characteristics of livers with metastatic disease by using model selection to determine which of two candidate models better describes the time course data of each voxel. The candidate models would be a model that is relevant for tumour and a model that describes non-tumorous liver tissue. Such a technique could have potential application to early detection of metastases, monitoring of drug effect or natural history and provide information about tumour extent and invasion.
A typical DCE-MRI acquisition takes approximately 5 - 10 minutes to capture the accumulation and wash out of contrast agent within the tumour. Microvascular parameters can be estimated for each voxel and then a mean or median value calculated for the tumour region and monitored during the drug trial. Any tumour located within the liver will be subject to respiratory motion which may cause displacement and deformation of the tissues. This is likely to disrupt the time course data and may adversely affect the accuracy and precision of the estimated model parameters.

Registration algorithms could be used to re-align the time series images. However, developing registration algorithms for DCE-MRI is challenging as the features within the images change during the time series in accordance with the concentration of contrast agent in each voxel. The liver presents further difficulties for registration as it is likely to undergo a complex set of deformations during the respiratory cycle due to the motion of the diaphragm, its contact with other abdominal organs and the limited space within the body. Using acquired data sets, it is difficult to establish whether a registration has been of benefit, or even whether model fitting is robust to motion and registration is not required, as ground truth values for the model parameters are not known. Synthetic data can be invaluable for providing test sets with which to quantitatively evaluate model fitting and registration, and have previously been used to assess registration algorithms for DCE-MRI in liver and breast tumours [9, 10, 11, 12].

The work performed in this research aims to produce synthetic data for DCE-MRI of liver metastases that will be based on physiological models of tracer kinetics and that will have quasi-realistic anatomy and motion characteristics. These data can be used for quantitative evaluations of model fitting, model selection and registration methods. This research also aims to generate the software phantoms using techniques which have wider application, in particular to other time series imaging techniques such as single positron emission CT, positron emission tomography (PET), ultrasound and CT, and which may also find great value during the emergence of multi-modality imaging techniques, such as PET-MR. Therefore, rather than building each test set individually, we have built a software phantom generator application that has a flexible design which should facilitate its extension to multiple imaging scenarios including different anatomical regions.

This thesis presents synthetic data for DCE-MRI of liver tumours and demonstrates its utility in the validation of DCE-MRI analysis techniques and also in the develop-
ment of a novel method of assessing the spatially varying microvascular characteristics of livers with metastatic disease. The synthetic data includes emulation of abdominal organ motion due to respiration based on a biomechanical model, allowing the potential benefits of registration to be investigated.

1.1 Aims and objectives

- To develop a software phantom generator that produces synthetic images with quasi-realistic anatomy from known ground truth based on MR physics and tracer kinetic models to allow DCE-MRI time series analysis techniques to be assessed.

- To develop a module that incorporates motion emulation into the synthetic data, in particular the deformations and displacements associated with respiration.

- To design the software phantom generator and motion emulator applications so that they can be extended to include different imaging modalities, and different anatomical, physiological and motion descriptions.

- To develop and evaluate a model selection technique for livers with metastatic disease, including the fitting of a dual-input model which requires a portal input function.

- To use the phantoms generated with the above applications to quantitatively assess the robustness of model fitting and model selection to partial volume effects (PVEs), noise and motion.

- To use the phantoms generated with the above applications to quantitatively assess the benefits of performing a model-driven registration, prior to model fitting and selection.

1.2 Thesis overview

In Chapter 2, we introduce tracer kinetic modelling and model selection for livers with metastatic disease, starting with an overview of physiology in the healthy and
diseased liver. The acquisition of DCE-MRI data for tracer kinetic modeling is then described, including an overview of MR theory. We then discuss motion problems for abdominal DCE-MRI along with methods for their correction using image registration. Lastly, we review published software phantoms that are relevant to this thesis along with possible methods of emulating motion of the abdominal organs mostly due to respiration.

In Chapter 3 and Chapter 4, we present the phantom generator and motion emulator applications and demonstrate the function of each of the modules from which these applications are built. We then show a DCE-MRI synthetic data set that is generated from ground truth data based on acquired data sets, and that includes motion emulation (also based on acquired data).

In Chapter 5, we introduce a model selection technique for assessing the spatially varying characteristics of livers with metastatic disease, including a novel method of estimating the portal input function for fitting a dual input model for the liver. We then demonstrate the validity of the technique using synthetic data and further evaluate it using 6 acquired data sets. The accuracy and precision of model fitting (from which the microvascular characteristic $K^{\text{trans}}$ is estimated and upon which model selection is based) is also assessed using synthetic data along with the robustness of model fitting and model selection to noise, PVEs and input function offset.

In Chapter 6 we assess the robustness of $K^{\text{trans}}$ estimation and model selection to motion, along with the benefit of applying a registration algorithm, using a generated liver phantom with motion emulation and acquired data. Lastly, in Chapter 7 we present the conclusions, discussion and possible further work.

### 1.3 Contributions to this thesis

Unless otherwise stated, the work presented in this thesis was performed by the author.

#### 1.3.1 Contributions from the author

The major contributions from the author were:
• The design and implementation of the PhantomGenerator and MotionEmulator software applications for generating synthetic image data sets with motion emulation.

• The generation of synthetic data including a DCE-MRI data set of a liver tumour with breathing motion emulation.

• The development and evaluation of a novel method for estimating the hepatic portal input function from knowledge of the arterial input function.

• The development and evaluation of a novel model selection technique for investigating the spatially varying microvascular characteristics of livers with metastatic disease using acquired and synthetic data.

• The quantitative assessment of the robustness of model selection and \( K^{\text{trans}} \) estimation to noise, vascular input function offset, PVEs and motion using synthetic data.

• The quantitative evaluation of the benefits of a DCE-MRI registration technique, using synthetic and acquired data, for model selection and \( K^{\text{trans}} \) estimation.

1.3.2 Contributions from others

In Chapter 3, the software module used to read, write and store ANALYZE images was written by Angela Caunce.

In Chapter 4, the displacement maps, which were used to emulate breathing motion, were provided by Kristy Brock and the acquired breathing trace was provided by Alex Morgan. The motion emulation application uses the \texttt{vq3d} library, written locally by Tim Cootes and members of his research group.

In Chapter 5 the model fitting and selection code was provided by Jo Naish and adapted to fit the Materne model for the liver by the author. The input functions for the portal input function estimation method and evaluation were provided by Vivian Lee, Pari Pandharipande, Henry Rusinek and Tong San Koh.

The registration software used in Chapter 6 was developed by Gio Buoanaccorsi, Angela Caunce and Geoff Parker. The software application used for registration was
written by Angela Caunce and the data sets were registered by Gio Buonaccorsi (to match the procedure that is performed for clinical trials).

All the volumes of interest for the patient data within this thesis were drawn by Yvonne Watson, an experienced research radiographer.

The acquired data analysed retrospectively within this thesis were part of two clinical trials within this institute for which Gordon Jayson was the principal investigator. Caleb Roberts was responsible for quality control of this data and Sue Cheung for arterial input function extraction.
Chapter 2

Background, theory and methods

2.1 Introduction

In this thesis we are interested in generating synthetic data for quantitative assessment of dynamic contrast-enhanced (DCE) tracer kinetic modelling based analyses. In particular we address the sensitivity of DCE-magnetic resonance imaging (MRI) parameterisation to motion in liver tumours and the benefits of performing registration. We are also interested in evaluating a novel model selection technique which could provide information about the spatially varying characteristics of livers with metastatic disease. We therefore begin this chapter, in Section 2.2, with a description of the physiology of the liver and of liver tumours which, whilst the software phantom generator has been developed to have much broader utility, is the specific application area addressed in this thesis. An understanding of the vascular structure of the liver and of liver tumours then allows us to discuss the tracer kinetic models that are appropriate for describing these tissues in Section 2.3. We introduce the challenge of measuring vascular input functions in Section 2.3.2, and then, in Section 2.3.3 describe the model selection technique.

In Section 2.4, we describe how DCE-MRI can be used to provide data suitable for model fitting, therefore allowing us to probe the micro-vascular characteristics of the tissues of interest. This section includes a brief overview of the classical interpretation of MR imaging (including the effects of contrast agents), a description of the spoiled gradient echo (SPGR) pulse sequence, which was used within the research presented in this thesis, and of the data acquisition and analysis protocols used.
Having discussed the theory and methods required for using DCE-MRI in combination with tracer kinetic model fitting for probing the microvascular characteristics of the diseased liver, we then introduce the issue of liver motion during acquisition of the DCE-MRI time series, which is mostly due to breathing (Section 2.5). We discuss the nature of this motion, and the potential for using registration for re-aligning the DCE-MRI time series images. We have included a brief overview of registration methods, and have focused on the model-driven registration technique [9] that we have assessed in this thesis.

Lastly, in Section 2.6, we review published methods of generating synthetic data for assessment of registration and analysis techniques. In particular, we discuss synthetic data for DCE-MRI post-acquisition processing techniques. We include a review of the techniques used for emulating breathing motion in the liver and focus on the multi-organ finite element modelling developed by Brock et al. [13] used to emulate motion within this thesis.

### 2.2 Vasculature in the healthy and diseased liver

#### 2.2.1 Liver anatomy, physiology and histology

The liver is the largest visceral organ and the largest gland in the body [14]. It weighs approximately 1.5 kg on average in adults and is situated anteriorly in the upper abdominal cavity directly below the diaphragm with the majority of its mass in the right hypochondriac and epigastric regions as shown in Figure 2.1. Anatomically, the liver is divided into 4 lobes. The right and left lobes are separated by the falciform ligament on the anterior of the liver and on the posterior surface the caudate and quadrate lobes are separated by the channel of the inferior vena cava.

The liver has a multitude of functions that are involved in moderating the contents of the blood and processing the products of digestion. Examples include the modification of toxins for their removal from the blood system; the production of bile; amino acid synthesis; and glycogen and vitamin storage. The liver receives venous blood directly from the splanchnic circulation, which includes the stomach, spleen, pancreas and small and large intestines, allowing absorbed compounds to be processed by the liver before the blood returns to the heart and is pumped to the rest of the body.
Chapter 2. Background, theory and methods

Figure 2.1: Position of the liver

and the brain. The venous blood from the digestive system is delivered to the liver through the hepatic portal vein and is in addition to the oxygenated blood supplied via the hepatic artery, see Figure 2.2.

Figure 2.2: Blood supply to the liver

The hepatic artery branches from the coeliac trunk which attaches to the aorta. It enters the liver, along with the portal vein, at the porta hepatis (located on the posterior surface of the liver) and bifurcates into the left and right hepatic arteries. The hepatic portal vein receives venous blood from the gastric, splenic, superior mesenteric and inferior mesentric veins. It typically crosses the aorta anteriorly near the junction with the coeliac trunk and follows a similar path and bifurcates in a similar manner to the hepatic artery.
Chapter 2. Background, theory and methods

The hepatic artery supplies approximately 25% of the blood to the liver and meets about 50% of its oxygen needs [15]. The remaining 75% of blood and 50% of oxygen are supplied by the hepatic portal vein. However, the percentage provided by each of the supplies is known to change with exercise, fasting, time of day, caffeine intake and disease [16, 17, 18, 19]. The hepatic artery compensates for changes in flow in the portal vein, ensuring that the liver has an adequate blood supply even when flow through the splanchnic circulation is low [15]. The amount of blood in the splanchnic circulation increases due to postprandial hyperemia in the digestive tract and decreases as the digestive tract empties. The pressure in a terminal portal venule is 50 mm H$_2$O compared to a value of 300 – 400 mm H$_2$O in a terminal hepatic arteriole [15].

Histologically, the liver is a homogeneous structure that is composed of approximately 100,000 liver lobules [14]. These are the functional units of the liver that are roughly hexagonal in shape and are just visible to the human eye. The lobules contain columns of hepatocytes, the liver’s functional cells, which radiate out from the centre of the lobule (see Figure 2.3). Blood from branches of the hepatic artery and portal vein enter the lobules at the portal triads and mix within the sinusoids. These are the smallest blood vessels within the liver and have a discontinuous basement membrane and an epithelium lining that contains many fenestrations. The highly leaky structure of the sinusoids encourages the extravasation of the blood plasma and its contents so that they can be processed by the hepatocytes and other cells such as Kupffer cells. The blood from the sinusoids drains into the central vein in each lobule, which joins one of the varying number of hepatic veins that transport the blood directly to the inferior vena cava at a point just below the diaphragm.

2.2.2 Liver tumours

A liver tumour will have a different histological structure to healthy liver tissue and may also have different blood supply characteristics. Matsui [20] used computed tomography (CT) during arterial portography and hepatic arteriography, along with histology from biopsy, to investigate how the blood supply to a lesion changed as it developed from a regenerative nodule into a malignant poorly differentiated hepatocellular carcinoma in humans. As the lesion progresses through the multi-stage carcinogenic process the volume of blood from both the established portal and arterial supplies decreases whilst the amount of blood supplied from newly formed arterial
vasculature increases. Liu [8] demonstrated a similar step-wise effect that had a statistically significant correlation with mean tumour diameter using in vivo fluorescent microscopy in the growth of murine colonic hepatic metastases.

The formation of new arterial vasculature (angiogenesis) is triggered by metabolic stress such as hypoxia, hypoglycaemia and acidity [1]. These conditions occur when a tumour reaches a size where the cells no longer receive oxygen from the existing vasculature as the diffusion limit of oxygen (100 – 200 µm) has been reached. Production of pro-angiogenic agents, such as the cytokine vascular endothelial growth factor (VEGF), are then up-regulated by the tumour cells. VEGF promotes the growth of the vascular endothelium and also increases the permeability of existing endothelial walls.

The characteristics of the vasculature created under stress are distinct from those in well-established networks within non-pathological tissue [21]. The lumen can be irregularly shaped or collapsed and the length of the capillary can be distorted and bent. The vessel walls are fenestrated and have a mosaic pattern with tumour cells patched to normal endothelial cells. The basement membrane is commonly discontinuous or absent. This results in leaky vessel walls and, in combination with the action of VEGF and the normal hydrostatic blood pressure, produces an increased movement of small to medium sized molecules across the endothelium where the necessary partial pressure differential exists.

Figure 2.3: Structure of a liver lobule
The erratic architecture of the vasculature and the restriction of the lymphatic vessels can result in acidic and hypoxic regions that encourage angiogenesis and select for malignant cells that have lost their apoptotic ability \cite{1}. Eventually this process can lead to tumour regions that are necrotic or quiescent and regions in which pathological angiogenesis, with the associated leaky blood vessel walls, is prolific. For example, a hypo-perfused tumour core and a well-perfused outer rim may be seen.

The presence of liver metastases has been found to have a global effect on the blood supply to the liver, reducing the blood flow within the hepatic portal vein \cite{17} \cite{22}. Leen \cite{17} suggests that this may be due to the production of vasoactive agents (by either the metastases or the host tissue) that increase the resistance within the vasculature of the gastro-intestinal (GI) tract.

Among cancer therapies, two classes of therapeutic agents exist that target the vasculature of a tumour \cite{23}. Anti-vascular agents target the established vessels and can cause the death of cells within the existing tumour. Anti-angiogenic agents, such as VEGF inhibitors, can prevent the growth of further tumour cells that are outside the limits of diffusion processes from the nearest blood vessels.

### 2.3 Modelling tumour and liver vasculature

Microvascular characteristics such as blood flow, blood volume, capillary density and endothelial permeability, as well as tissue characteristics such as cell density, are all potential indicators of pathology. Therefore, estimates of these parameters can provide useful information about the physiological status of a tumour. For example, they can be used to monitor the effect of anti-angiogenic drugs that target the tumour microvasculature \cite{2}. These underlying physiological parameters can be estimated by fitting a tracer kinetic model to contrast agent concentration curves. The models can be fitted to image data on a per voxel basis to give parameter maps and summary statistics.

Biopsy, along with histological techniques, can be used for measuring microvascular characteristics. However, biopsy is an invasive technique and therefore (depending on the location of the tumour) not suitable for multiple serial visits. Biopsy is also a “point” measurement technique and in a heterogeneous tumour it may fail to sample the most relevant tissues. DCE imaging does not suffer from these limitations as it is
minimally invasive so can be repeated at multiple visits for monitoring purposes, and information about the full tumour volume and heterogeneity can be obtained from parameter maps.

DCE imaging involves the injection of a contrast agent or tracer into the patient’s blood system. The accumulation and wash out of the tracer in the tissue of interest is then captured by acquiring a time series of images. Contrast agent concentration curves can be derived from the time series and a tracer kinetic model fitted to estimate the physiological parameters of interest, for example endothelial permeability.

In Section 2.3.1 we introduce tracer kinetic modelling and describe in detail a model that is relevant to the liver (the Materne model [5]) and a model that is appropriate for liver tumours (the extended Kety model [3]). We then discuss the measurement of the vascular input functions required for these models (Section 2.3.2) and lastly introduce a model selection method (Section 2.3.3) based on the Akaike information criterion (AIC) [24]. Model selection between two physiologically plausible candidate models, one that represents liver tissue and one that represents tumour tissue, on a per voxel basis could potentially indicate whether the tissue within each voxel is more likely to be tumour or liver. This could have potential application to areas such as tumour localisation, detection of early signs of metastases, tumour infiltration assessment, and monitoring drug efficacy.

### 2.3.1 Tracer kinetic models

Tracer kinetic models are simplified mathematical descriptions of changes in contrast agent concentration in a tissue due to movement of the tracer between the different tissue compartments. The models include parameters that reflect tissue characteristics such as the volume of the extravascular-extracellular space (EES) and microvascular characteristics such as capillary permeability. It is common practice to fit the models to contrast agent time course data using standard optimisation routines (such as the Nelder-Mead simplex [25]) which vary the free parameters of the model until a measure of discrepancy between the model and the data, such as sum of squared errors (SSE), is minimised. The models require a vascular input function which describes the time varying concentration of the tracer in the blood plasma of a feeding artery. This is affected by factors such as the injection protocol and potentially the patient’s cardio-vascular condition [26].
Numerous tracer kinetic models have been, and continue to be, developed [27, 5, 3]. When selecting a model for a specific study, it is important to ensure that the model reflects the underlying physiology so that the parameters are relevant and changes connected to the expected study effect (caused by a drug or natural progression, for example) can be investigated. For example, models have been developed to reflect the contrast agent kinetics in tumours [28, 4, 3], the kidney [6] and the liver [27, 5]. However, the information contained in the DCE-MRI data is limited due to factors such as noise, temporal and spatial resolution restrictions, dynamic series acquisition time, motion artifacts and the various confounds of vascular input function measurements [29, 30, 31]. Therefore, there may not be enough accessible information within DCE-MRI time series data to support the use of more detailed models that better represent the underlying physiology.

Applying an overly complex model to noisy data may result in over-fitting to noise leading to inaccurate parameter estimates and the consequent loss of sensitivity of the model parameters to underlying physiological changes. To ensure a stable model fitting process that avoids parameter redundancy, reduces the likelihood of finding local minima and remains sensitive to physiological changes, relatively simple models can be used where compound parameters are used to describe the tissue characteristics. For example, the extended Kety model combines capillary permeability-surface area product and blood flow terms within the transfer co-efficient $K_{\text{trans}}$, whereas the adiabatic approximation to the tissue homogeneity model (AATH) model [4] has separate terms for both of these parameters.

Within this work we are interested in probing the micro-vasculature of liver tissue and tumours situated in the liver. As described in Section 2.2, these two tissues have differing vasculature and tissue characteristics so a separate tracer kinetic model may be required for each tissue type. The extended Kety model, shown in Equation (2.1) and Figure 2.4(b), has been selected to describe tumour tissue and has been widely applied to DCE-MRI data of tumours [32]. This model has two compartments separated by a semi-permeable membrane to represent separation of the vascular space from the EES by the capillary endothelium, and one input (the arterial plasma concentration of tracer), so in this case we assume that the tumour has a predominantly arterial blood supply with negligible portal contribution.

$$C_t(t) = v_p C_p(t - \tau_a) + K_{\text{trans}} \int_0^t C_p(t' - \tau_a) \exp \left[ \frac{-K_{\text{trans}}(t - t')}{v_e} \right] dt' \quad (2.1)$$
where \( C_t \) is the measured concentration of contrast agent within the tissue and \( C_p \) is the measured contrast agent concentration within the blood plasma, known as the arterial input function (AIF). The four free parameters are \( v_p \), the fractional blood plasma volume; \( v_e \), the fractional volume of the EES; \( K^{\text{trans}} \), transfer coefficient between the intravascular space and the EES; and \( \tau_a \), the delay time between detection of contrast agent in the artery selected for \( C_p \) estimation and the contrast agent reaching the tissue.

\[
v_t = v_e + v_b + v_i = 1, \tag{2.2}
\]

where \( v_t \) is the tissue volume, \( v_i \) is the fractional intracellular volume and \( v_b \) is the fractional volume of the blood.

\[
v_p = (1 - hct)v_b, \tag{2.3}
\]

where \( hct \) is the haematocrit for which a value of approximately 0.4 is often assumed [33].

**Figure 2.4:** Schematic diagrams of the Materne, Equation (2.4), and extended Kety, Equation (2.1), models. The underlined quantities are the free parameters within the model fitting.

The extended Kety model, published by Tofts et al. [34, 3] mirrors work by Kety which approximates the movement of the contrast agent from the intra-vascular space to the EES by a simple rate equation that describes diffusive flux across a semi-permeable
membrane [35]. The two compartments (the intra-vascular space and EES) are assumed to have bulk tissue characteristics with the contrast agent instantaneously well mixed within them. The model is formulated for contrast agents, such as gadolinium chelates, that do not enter the intracellular environment and therefore no representation of this volume is required [33]. The first term in Equation (2.1) represents the contribution from the intra-vascular compartment and the second term in Equation (2.1) represents the concentration of the contrast agent in the EES as a function of time.

The Materne model (Equation (2.4) and Figure 2.4(a)), developed for modelling liver tissue, has a dual input to account for the blood supply from the hepatic portal vein as well as the hepatic artery. In comparison to the extended Kety model it only has one compartment as it assumes that the contrast agent, on reaching the sinusoids, instantly mixes with the EES. This is an acceptable assumption when considering the leaky nature of the sinusoids and the limited temporal resolution and contrast-to-noise ratio in DCE-MRI data. For example, Koh [27] applied a two-compartment dual-input model to DCE-MRI data from livers with metastatic disease and reported that the surrounding non-tumorous liver tissue was effectively one compartment, unlike the hepatic metastases which contained two compartments.

Five parameters are estimated for the Materne model: the arterial flow rate constant, \( k_{1a} \); a portal flow rate constant, \( k_{1hpv} \), which we introduce as part of the portal input function (PIF) estimation method outlined below; the outflow rate constant, \( k_2 \); a PIF offset time, \( \tau_{pif} \); and an AIF offset time, \( \tau_{aif} \).

\[
C_t(t) = \int_0^t \left[ k_{1a}C_p(t' - \tau_{aif}) + k_{1hpv}C_{hpv}(t' - \tau_{pif}) \right] e^{-(t-t')k_2} dt'
\]

(2.4)

where \( C_p \) and \( C_{hpv} \) are the concentrations of contrast agent in the blood plasma for the AIF and PIF, respectively. As for the extended Kety model, the contrast agent does not enter the cells. Other contrast agents, such as gadoxetic acid (Gd-EOB-DTPA), are taken up by the hepatocytes which then necessitates the use of different models which account for the intra-cellular compartment.

Other more physiologically realistic models exist for the tumour including the two compartment exchange model [28] and the AATH model [4] which separate blood flow and permeability-surface area product. Koh et al. [27] developed a two-compartment dual-input distributed parameter model for use in liver tumours. Orton et al. [36]
modified the extended Kety model and the simplified Kety model [37] to include a portal input function for use in liver tumours. The results from both authors suggest that there may be a non-negligible contribution from the portal vein even in larger liver metastases. However, the accuracy of these results are dependent on accurate estimation of the PIF which can be problematic (see Section 2.3.2). In this thesis we have chosen the extended Kety model for the tumour as it has a single arterial supply which models the physiology described by Liu et al. [8] for established liver metastases. It is also a relatively simple model that is likely to have adequate accuracy and precision when fitted to data acquired using the acquisition protocol employed in this work (see Section 5.3.3) and has established use in tumours [32].

2.3.2 Vascular input functions

Both the extended Kety and Materne models require an AIF, and in addition to this a PIF is also required for the Materne model. Ideally, localised input functions for each voxel would be used. However, obtaining a signal intensity from a small vessel is not possible due to spatial resolution restrictions. Therefore, the signal intensity time course from a larger feeding vessel is often used as a proxy for deriving the local input. For abdominal DCE-MRI, voxels in the centre of the aorta are often used to avoid partial volume effects (PVEs). The contrast agent within the aorta will not have experienced the same degree of temporal dispersion as a local input vessel [38], but because the input function is derived from acquired data it is likely be specific to each patient’s cardio-vascular condition [26]. A delay time can be introduced within the model (for example $\tau_a$ in Equation (2.1)) to allow for time between signal measurement in the aorta, for example, and the contrast agent reaching the voxel of interest in the liver.

Parker et al. [39] developed an automated method of detecting suitable voxels for AIF measurement in abdominal DCE-MRI. The method identifies voxels that have a peak contrast agent concentration within 20 seconds of the injection and, from these voxels, those that have the top 5% peak concentrations are selected. This algorithm aims to identify the first pass peak in the centre of a major artery and therefore avoid PVEs. This method was validated in the generation of a population AIF [40].

Accurate estimation of the concentration time course in the AIF requires a known relationship between signal intensity and contrast agent concentration (usually achieved
via $T_1$ measurement). If the signal intensity time course is affected by artifacts such as inflow and $B_1$ inhomogeneities [31], the relationship to contrast agent will no longer hold. It is therefore important to minimise the effects of such artifacts in AIF quantification. In axial imaging this can be achieved by selecting a slice for AIF measurement that is distal to the inflowing blood to ensure that steady-state of the magnetisation has been reached (see Section 2.4.2) whilst avoiding slices near the edge of the image that are vulnerable to $B_1$ inhomogeneities.

If deriving a reliable AIF from direct measurements is not possible an assumed functional form derived to match the expected shape of the AIF can be used. Tofts and Kermode [34] used a bi-exponential function that is based on measurements from blood samples [41]. However, the temporal resolution of these samples is relatively low and important features of the AIF are not present [33]. Parker et al. [40] developed a higher temporal resolution parameterised form of a population average which was derived from DCE-MRI image data. This AIF representation is a functional form that closely follows the empirical data rather than a mathematical model based on the behavior of the system. It displays characteristic AIF features such as the ‘first pass peak’ seen when the contrast agent bolus first passes through the artery and the ‘recirculation peak’ seen as the bolus returns for the second time. Horsfield et al. [42] and Orton et al. [43] have also developed functional forms for the AIF. The functional form developed by Horsfield was based on physiological models of blood circulation, whereas the raised cosine used by Orton provided a mathematical form that allowed the tissue contrast agent uptake curve to be calculated analytically thereby increasing the computational speed of model fitting applications.

Measurement of the signal intensity time course in the portal vein introduces further difficulties. First, the portal vein runs laterally across the body so diaphragm motion may cause it to move substantially during the acquisition of the image time series (which typically have a duration of 5-10 minutes). Second, the cross-sectional area of the portal vein is smaller than that of the aorta, so it is more prone to partial volume effects, in particular because it follows an adjacent path to the hepatic artery and so can be contaminated by the strong arterial signal intensity time course. Third, a suitable portion of the portal vein may not be present within the field of view of a DCE-MRI time series focusing on a specific liver lesion [37], which in some cases has resulted in data sets being rejected from a study [44]. These problems do not hold for AIF estimation from the aorta when studying the liver in an axial plane.
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For the PIF a functional form does not yet exist. Orton et al. [45] developed a method for estimating a global dispersion term for the liver, directly from the tissue uptake curve, to apply to a raised cosine representation of a population AIF [40] to give a PIF. This method assumes that the wash out of the PIF will match that of the AIF and so the dispersion term is only applied to the parameters of the raised cosine that describe the first pass peak. The leakage of contrast agent within the GI tract is also assumed to be negligible. Whilst estimating a dispersion term for each patient can account for the potential variability in dispersion caused by the anatomy of the splanchnic circulation differing between patients, a raised cosine may not be an adequate representation of the AIF and PIF for providing accurate parameter estimates.

Monk et al. [46] developed a method of predicting the PIF from the arterial time activity curve for positron emission tomography (PET) tracers in pigs. Both arterial and portal time activity curves were measured using blood sampling with an initial temporal resolution of 5 s. A mathematical form for the impulse response function (IRF) that relates the PIF to the AIF was fitted to the data. The mean and standard deviation of the transit time of the tracers through the splanchnic circulation were derived from the free parameters of the IRF. This method was applied to 13 pigs for two radio-pharmaceuticals and the mean transit times compared with those reported in the literature for humans to demonstrate that this method is suitable for human PET studies.

Winterdahl et al. [47] applied the work by Monk to further porcine data sets using 5 PET tracers including $^{15}$O-Carbon monoxide, which is purely intravascular as it binds to the erythocytes, and freely diffusible $^{15}$O-water. Using estimated mean splanchnic transit times they estimated the PIF from the AIF measured in the femoral artery. The estimated PIF was compared with measured data from blood sampling in the portal vein. Using mean transit times to for each tracer to estimate the PIF gave good, but not exact agreement with the measured data. Again, Winterdahl compared the mean transit times and also measured blood flow rates to literature values to demonstrate that this method could be applied to human data. It is interesting to note that for the intravascular tracer, $^{15}$O-Carbon monoxide, the measured time activity curve for the portal vein presented for one animal is similar in height and form to the curve for the femoral artery. In comparison, the time course for the freely diffusible tracer, $^{15}$O-water, does not have a first pass peak or reach concentration levels above the washout slope of the AIF. This difference is due to the greater
distribution volume available to $[^{15}\text{O}]-\text{water}$ as it passes through the gut.

We address the issue of providing a PIF for DCE-MRI of humans with gadolinium based contrasts within Section 5.2.

### 2.3.3 Model selection

Model selection allows us to propose, from a number of candidate models, which model best represents the given data. Model selection using the Akaike information criterion (AIC) has previously been applied to DCE-MRI lung tumour data by Naish [48], brain lesion data by Sourbron [49], and to synthetic tissue curves representative of tumour by Brix [50]. The F-test is an alternative criterion for model selection and has been applied to DCE-MRI data by Donaldson et al. [51]. However, it requires the two candidate models to be nested and is therefore not a valid method for selecting between the Materne model and the Extended Kety model.

The AIC [24, 52] was developed for use in information theory and balances the sum of squared errors (SSE), a measure of fit of the estimated model curve to the data, against the number of free parameters within each model. In this way, it works on the principle of parsimony requiring additional parameters to be justified by a substantial decrease in the SSE. As we have 75 time-points within the data acquisition protocol used for this research, we have used the corrected AIC ($AIC_c$) (Equation (2.5)) which accounts for small sample sizes and is recommended where $N/K \leq 40$ [52].

$$AIC_c = N \ln \left( \frac{\text{SSE}}{N} \right) + 2K + \frac{2K(K + 1)}{N - K - 1}, \quad (2.5)$$

where $K$ is the number of free parameters plus 1 (to account for the SSE, which is calculated using the estimated data) and $N$ is the number of time points.

From the $AIC_c$ for each model, the Akaike probability [52] can be calculated to compare the two models (Equation (2.6)).

$$p = \frac{\exp^{-0.5\Delta}}{1 + \exp^{-0.5\Delta}}, \quad (2.6)$$

where $\Delta$ is $AIC_c$ for the model with the greater number of free parameters minus $AIC_c$ for the second model. Probabilities above 0.5 indicate that the model with the
higher number of free parameters is likely to give a better description of the data and values below 0.5 indicate the second model better describes the data.

We have used the AIC\textsubscript{c} to assess whether the Materne model or extended Kety model better describes the data for each voxel within the liver (see Section 2.3). As the Materne model (Equation (2.4)) has 5 free parameters in comparison to 4 free parameters for the extended Kety model (Equation (2.1)), an Akaike probability value of greater than 0.5 in a voxel indicates that the more complex Materne model is a better description of the data, and an Akaike probability value of less than 0.5 indicates that the extended Kety model is a better description. If the Materne model is selected for a voxel it suggests that the tissue within that voxel is liver tissue with a dual blood supply and sinusoids (see Section 2.2.1). However, if the extended Kety model is selected it suggests that the tissue is tumour containing capillaries that have predominantly an arterial blood supply (see Section 2.2.2).

2.4 DCE-MRI for probing microvascular structure

In the previous section we introduced tracer kinetic modelling and described in detail the extended Kety model and the Materne model which can be used to probe the microvasculature of tumour and liver tissues respectively. Tracer concentration time curves for model fitting can be derived from DCE-MRI, DCE-CT, PET, single photon emission computed tomography (SPECT) or ultrasound. MRI provides good anatomical coverage, adequate spatial resolution and quantitative results without the risk of ionising radiation and is therefore often used in clinical trials protocols.

In this section we introduce DCE-MRI starting with a brief overview of the classical interpretation of MRI including how the magnetic resonance (MR) signal is produced and how it is affected by contrast agent. We describe a pulse sequence that is advantageous for DCE-MRI and how the signal intensity values from this sequence can be converted to contrast agent concentration time courses for tracer kinetic model fitting. We also list the acquisition parameters used for acquiring data and generating synthetic data within this thesis and describe the model fitting analysis procedure.
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2.4.1 Relaxation times

Water is a major constituent of the body and accounts for up to two-thirds of total body weight [14]. The hydrogen atoms in free (i.e. unbound) water contain an individual proton which has a positive charge and the quantum characteristic of spin, giving the proton a magnetic moment. The magnetic moment of the protons precesses around the static magnetic field of the MR scanner, \( B_0 \), resulting in a net tissue magnetisation with a positive longitudinal component lying in the same direction as \( B_0 \) as more protons occupy the lower energy state in which their magnetic fields are aligned with the external field [53], see Figure 2.5(a). The net transverse component is zero as the magnetic moments of the individual protons precess with a random distribution around the direction of \( B_0 \) and the magnetic components perpendicular to the external field therefore cancel. Without the external magnetic field, thermal energy prevents the protons from aligning and no net magnetisation is seen.

\[
\begin{align*}
\omega_0 &= \gamma B_0, \\
\end{align*}
\] (2.7)

The Larmor equation (2.7) describes the angular frequency, \( \omega_0 \), with which the nuclear magnetisation vector of an element will precess under the influence of a magnetic field \( B_0 \).
were $\gamma$ is the gyromagnetic ratio and is specific to each element. For $^1\text{H}$ $\gamma/2\pi = 42.58$ MHz/T.

The application of an RF pulse, with a frequency equal to $\omega_0$, causes more protons to align in the higher energy state antiparallel to $B_0$ resulting in a decrease in the net longitudinal magnetisation. Classically, the RF pulse is described as the application of an oscillating magnetic field, $B_1$, perpendicular to $B_0$. The magnetic moment of the individual protons start to precess around $B_1$ causing the net magnetisation vector to tip towards the transverse plane (see Figure 2.5(b)), giving an increase in the net transverse magnetisation. The amount by which the net magnetisation is rotated by the RF pulse from its original position is described by the flip angle; a 90° pulse tips the full equilibrium longitudinal magnetisation into the transverse plane (see Figure 2.5(c)).

The rotation of the magnetic moments of the individual protons towards the transverse plane produces phase coherence of their precession about $B_0$. The resultant net magnetisation vector rotates in the transverse plane around $B_0$ generating an oscillating magnetic field which can be detected by an RF coil as the MR signal.

After the RF pulse, the longitudinal and transverse magnetisation components return to their equilibrium state via two independent processes. The longitudinal magnetisation, which is diminished by the RF pulse, grows as energy is released into the local tissue lattice and the magnetic moments of the protons re-align with $B_0$. The rate at which this occurs depends on the overlap between the Larmor frequency and the natural frequencies within the molecules and structures of the lattice. Spin-lattice relaxation is characterised by the $T_1$ parameter, which is the time constant of the exponential recovery process. It is the time taken for approximately 63% of the longitudinal magnetisation to recover following the RF pulse.

$T_2$ is the corresponding time constant for the exponential decay of the transverse magnetisation. It is the time taken for the transverse magnetisation to drop to approximately 37% of the value resulting from the application of the RF pulse. Reduction in transverse magnetisation is caused by each proton experiencing the fluctuating magnetic fields of other nearby molecules resulting in changes in precessional frequency and the loss of phase coherence. This is known as spin-spin interaction. Magnetic inhomogeneities extrinsic to the tissues also exist, for example $B_0$ imperfections or susceptibility effects caused by tissue air interfaces. These accelerate the dephasing of the transverse magnetisation to its equilibrium state and, combined with the effect
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of the intrinsic magnetic characteristics, are described by the $T_2^*$ constant.

In general, spin-spin relaxation occurs at a much faster rate than spin-lattice relaxation: $T_1 > T_2 > T_2^*$ [54]. It is possible to create images that are dominated by any of the $T_1$, $T_2$, $T_2^*$ relaxation properties of the tissues or by the proton density by using the appropriate pulse sequence and pulse sequence parameters.

2.4.1.1 The effects of contrast agents in MR imaging

Gadolinium is an example of a paramagnetic chemical element that, particularly in its ionic state, affects the MR signal. It is combined with a chelating agent, for example DTPA-BMA for gadodiamide (Omniscan, GE Healthcare), to reduce its toxicity to a level that is considered to be acceptably low. However, its use is not advised for patients that have moderate to severe renal disease as there is strong evidence of a link between the use of some gadolinium chelates and nephrogenic systemic fibrosis for these patients [55]. Gadolinium based contrast agents have a low molecular weight and can enter the EES space through the endothelial lining of the blood vessel walls, except in the brain where the blood-brain barrier does not allow passage [23]. This makes it an ideal agent for investigating the microscopic characteristics of tumour vasculature, such as the permeability of the endothelium, and tissue characteristics, such as the volume of the EES.

MR contrast agents, such as gadolinium chelates, do not affect the MR signal directly [53]. Instead, the unpaired electrons in the gadolinium ion lead to dipole-dipole interactions which increase the longitudinal relaxation rate leading to a reduction in $T_1$ as predicted by Equation (2.8) [53].

$$T_1 = \frac{T_{10}}{1 + C_t T_{10} r_1}$$

(2.8)

where $T_{10}$ is the pre-contrast $T_1$ value, $T_1$ is the post-contrast $T_1$ value, $C_t$ is the contrast agent concentration in the tissue, and $r_1$ is the relaxivity of the contrast agent with units of mM$^{-1}$s$^{-1}$.

Due to the decrease in $T_1$ caused by gadolinium, the longitudinal magnetisation will, at a given time after the RF pulse and prior to reaching equilibrium, be greater in a tissue containing gadolinium than in the same tissue without the contrast agent. This leads to an increase in the MR signal in voxels were gadolinium is present in
T$_1$-weighted acquisitions.

Gadolinium is also used as a contrast agent within dynamic series of T$_2$ and T$_2^*$ weighted images (dynamic susceptibility contrast-enhanced (DSC)-MRI). The presence of gadolinium leads to a reduced signal intensity in T$_2$ or T$_2^*$ weighted images as the susceptibility-induced field gradients lead to dephasing of the MR signal. As this effect is greater where gadolinium is compartmentalised, DSC-MRI is often used for the brain where the blood brain barrier prevents extravasation of the contrast agent.

For characterising liver tumours, T$_1$-weighted imaging is advantageous as it does not rely on the contrast agent being compartmentalised within the vasculature to produce the necessary contrast, as is the case for DSC imaging. The signal intensity time courses from DCE imaging can be converted to contrast agent curves that allow tracer kinetic models such as the Materne model and extended Kety model to be fitted giving quantitative estimates of microvascular and tissue parameters.

### 2.4.2 Spoiled Gradient Echo pulse sequence

For quantitative assessment of the accumulation and wash-out of contrast agent in a tumour via tracer kinetic modelling, a time series of image volumes is required. The image acquisition sequence chosen must allow for collection of data with a high enough temporal resolution to accurately estimate the parameters of the selected tracer kinetic model. For example, inadequate temporal resolution leads to mis-sampling of the contrast agent concentration peak within the AIF and the tissue curve resulting in imprecise estimates of $v_p$ within the extended Kety model [30].

The length of acquisition time is also important for estimating parameters such as $v_e$ in the extended Kety model, as $v_e$ is influenced by the wash out of the contrast agent from the tissue over several minutes [56].

Temporal resolution is proportional to the time to repeat (TR) of the pulse sequence [54]. The TR is the time between the RF pulses used to excite the tissue samples and build an image of the volume of interest, see Figure 2.6. This time interval is limited by the requirements and characteristics of the various components that constitute the pulse sequence, such as the magnetic gradients that spatially encode the MR signal enabling image formation. The temporal resolution is balanced against a number of other image quality factors, such as spatial resolution, in order...
to retain adequate definition of the features of interest and information about how these change with time.

![Pulse sequence diagram for the SPGR pulse sequence](image)

**Figure 2.6:** Pulse sequence diagram for the SPGR pulse sequence. The x-axis represents time. Gss is the slice selecting gradient, Gpe are the phase encoding gradients and Gfe is the frequency encoding gradient.

Spoiled gradient echo imaging (using pulse sequences such as SPGR (GE Healthcare), FLASH (Siemens) and \(T_1\)-FFE (Philips), and which will be referred to generically as SPGR from hereon) involves building up a steady state of longitudinal magnetisation where the amount of magnetisation flipped into the transverse plane is the same at each RF pulse [57]. If full relaxation to the equilibrium value is prevented by using a short TR and a large enough flip angle is selected, the amount of longitudinal magnetisation available at subsequent pulses will be dependent on the \(T_1\) constant of the tissue. The longitudinal magnetisation is converted to transverse magnetisation by the RF pulse to produce the MR signal. Therefore, the MR images will have contrast differences that are predominantly dependent on the \(T_1\) values of the tissues, assuming that an appropriately short echo time (TE) is used.

Spin-echo imaging is an alternative imaging technique which includes an additional 180° RF pulse to rephase the magnetic moments of the protons and produce the MR signal [58], rather than the magnetic gradients used in SPGR imaging. However,
the application of the 180° pulse requires additional time and so SPGR imaging is preferred as a shorter minimum TR can be achieved. If TR is short in comparison to the $T_1$ of the tissues then low flip angles can be used. This further reduces the time required for a specific amount of longitudinal magnetisation to recover and low flip angles are adequate to provide a strong $T_1$ weighting.

Short TRs can also cause the growth of a residual transverse magnetisation component [58] as there is not enough time for complete dephasing of the proton magnetic moments. Spoiling any remaining transverse magnetisation within each TR, by applying spoiler gradients (see Figure 2.6) that cause dephasing of the proton magnetic moments, reduces contamination of the images due to any $T_2$ and $T_2^*$ effects or artifacts. RF spoiling is often used in combination with gradient spoiling to further reduce these artifacts. RF spoiling involves using a different phase offset for the RF pulse in each TR. This results in the net magnetisation vector rotating towards a different position on the x-y plane and prevents phase coherence from building up over successive RF excitations.

The pulse sequence diagram for the SPGR sequence is shown in Figure 2.6. Three sets of gradients are used for image formation. The slice selection gradient (Gss) allows one slice to be stimulated by the RF pulse. The phase encoding (Gpe) and frequency encoding (Gfe) gradients spatially encode the MR signal from the selected slice. The signal induced in the receiver coil is sampled and stored in k-space (2D spatial frequency domain). It is then Fourier transformed to produce the image. Multiple different phase encoding gradients are required to sample all the spatial frequencies in the phase encoding direction, therefore multiple TRs are required to build the image. The elongation of the frequency encoding gradient refocuses the magnetic moments of the protons to produce the signal. It can also act as a spoiler gradient, to dephase the magnetic moments once the signal has decayed. Spoiler gradients can also be applied in the slice selection and phase encoding directions [57].

In summary, SPGR imaging with low flip angles is a suitable pulse sequence for DCE-MRI as it provides rapid data acquisition whilst maintaining adequate signal to noise ratio (SNR) and contrast definition. As SPGR is rapid it is possible to acquire 3D images with good temporal resolution and volume coverage (usually enough to include an entire tumour) and adequate spatial resolution. SPGR sequences are also very widely available as standard MRI protocols from all manufacturers. It is therefore possible to construct an SPGR protocol that can run at multiple centres.
without having to programme scanners (which often is not possible). Finally, SPGR methods, via the variable flip angle (VFA) method [59], allow \( T_1 \) to be estimated. It is not the most accurate or precise approach to \( T_1 \) measurement available (for example, inversion recovery is more accurate but requires a longer acquisition time), but when the other advantages are considered it is a good pragmatic choice.

The signal produced by the SPGR pulse sequence [57] is described by Equation (2.9). It is a closed form solution to the Bloch equations which describe the behaviour of the three spatial magnetic moment components [54]. It is only valid when enough RF pulses have been transmitted for the longitudinal magnetisation to reach a steady state.

\[
S_\theta = S_0 \left( \frac{\sin \theta \left( 1 - e^{-TR/T_1} \right) e^{-TE/T_2}}{1 - \cos \theta e^{-TR/T_1}} \right)
\]

(2.9)

where \( S_\theta \) is the signal assuming perfect spoiling, \( \theta \) is the flip angle, and \( S_0 \) accounts for the magnetisation of each tissue at equilibrium and any scanner dependent variables. TE is assumed to be much smaller than \( T_2^* \), therefore \( e^{-TE/T_2^*} \) is approximated to 1 to give

\[
S_\theta = S_0 \left( \frac{\sin \theta \left( 1 - e^{-TR/T_1} \right)}{1 - \cos \theta e^{-TR/T_1}} \right)
\]

(2.10)

2.5 Motion problems and correction in abdominal time series

As described in the previous section, a typical DCE-MRI imaging protocol in our centre lasts for approximately 7 minutes. If the tumour under investigation lies in the abdomen it will be subject to physiological motion, in particular breathing, as well as any gross motion of the patient. This movement changes the tissue-to-voxel mapping among the images of the DCE-MRI time series [60] which could affect the accuracy and precision of the parameters estimated using tracer kinetic model fitting (described in Section 2.3).

In this section, we describe the motion seen in liver tumours caused mostly by breathing. There are a number of strategies that have been used to address the problems caused by motion in DCE-MRI such as navigator acquisitions, breath-hold techniques [37] and registration. In this chapter we give a brief overview of registration techniques and in particular describe the model-driven registration developed by
Buonaccorsi et al. [9] for free-breathing DCE-MRI abdominal imaging. We are concerned with the re-alignment of the time-series images, rather than any intra-frame degradation, such as ghosting, caused by motion during the acquisition of each image volume.

2.5.1 Motion of the liver and liver tumours due to breathing

The main muscles of breathing are the diaphragm and the intercostal muscles [14]. The diaphragm is a dome-like structure that separates the thoracic and abdominal cavities. It flattens as it contracts during inhalation, increasing the volume of the thoracic cavity. The intercostal muscles also contract during inhalation pulling the ribs up and out. The increase in lung volume leads to lower than atmospheric pressure within the lungs which draws air in and allows the exchange of gas across the surface of the alveoli. During exhalation, the muscles relax and the lung volume reduces with a corresponding increase in pressure that forces air out. Accessory respiratory muscles, such as those in the neck, shoulder and abdomen, are also used depending on the level of activity. A respiratory rate of between 12 to 18 breaths per minute is seen in adults during rest.

Rohlfing et al. [61] acquired 10 MRI images of the liver during the respiratory cycle for 4 healthy male volunteers (axial slices with a spatial resolution of 1.56 mm x 1.56 mm x 5 mm, and a 1 mm slice gap). To model motion during the respiratory cycle 3D deformation maps were generated by registering each of the images to the end-exhale image using a non-rigid transformation with an initial rigid registration step. Deformations ranging from 12 to 26 mm in the cranio-caudal direction, 1 to 12 mm in the anterior-posterior direction and 1 and 3 mm in the lateral direction, and with rotations less than 1.5 degrees were found. The greatest displacement for each patient was seen in the cranio-caudal direction. A maximum non-rigid deformation of 34 mm with an average of 10 mm was reported and found generally to be greater towards the superior-posterior portion of the liver.

Brock et al. [62] used finite element methods with an elastic deformation model to generate displacement maps from end-exhale and end-inhale CT liver data and reported displacements for 1 patient (voxel dimensions not given). They found the largest displacement to be in the cranio-caudal direction with a displacement of 24 mm in the superior region of the liver and 10 mm in the inferior region demonstrating
non-linear nature of the deformations. These displacements are comparable with those reported by Rohlfing [61]. Brock et al. also noted that the top of the liver flattens during inhale as the width increases in the medial and lateral directions and that a 0.93% reduction in volume was seen.

Further work by Brock et al. [63] extended the biomechanical model and applied it to end-exhale and end-inhale CT scans (voxel size 0.8 mm x 0.8 mm x 3 mm) in 5 liver cancer patients. Relating diaphragm to tumour centre of mass displacements, they found a maximum difference of 10 mm in the cranio-caudal direction with the diaphragm motion both underestimating and overestimating tumour centre of mass motion in different patients and tumours. The superior surface of the liver is in contact with the diaphragm and is likely to move in conjunction with it, so the discrepancy between diaphragm and tumour displacements again implies non-linear motion of the liver.

Applying the same biomechanical model to end-inhale and end-exhale MRI images (inplane voxel size of 1.32 to 1.72 mm, slice thickness 4 to 5 mm) in healthy volunteers, Brock et al. [13] found that across the liver for all patients, motion ranged from -31.5 to +7.8 mm in a caudal direction, -6.5 to +22.3 mm anteriorly, and -14.2 to +12.5 mm to the right. Motion in a superior direction, as indicated by a +7.8 mm displacement, is unexpected as the diaphragm, and so the liver, is expected to move in an inferior direction. The authors do not suggest any possible reasons for this (their aim was to develop a registration technique rather than characterise breathing motion). The registration was validated against landmark features and an average error of 10 mm was found. The displacement values reported are larger than those found by Rohlfing [61] which may be due to differing registration techniques or different spatial resolutions. Also, breath-hold imaging was used by Brock compared to free-breathing in the study by Rohlfing. Breath-hold may result in a greater expansion of the lungs than during free breathing even if volunteers are asked to remain within their normal resting breathing range.

Buonaccorsi et al. [9] reported liver tumour displacements for one data set, assessed to have moderate to severe motion, to demonstrate that the displacements applied by a novel registration method were physically plausible. The displacements were estimated from applying model driven registration (described in Section 2.5.2.1) to DCE-MRI datasets with a temporal resolution of 4.97 s and voxel dimensions of 2.93 mm x 2.93 mm x 4 mm acquired with free breathing. This work was performed at our
centre using the same protocol as used for the research presented within this thesis. A maximum absolute displacement of 6.90 mm was seen in the cranio-caudal direction, 3.35 mm in the anterior-posterior direction and 1.52 mm in the lateral direction. The displacement in the cranio-caudal direction is less than the range reported by Rohlfing [61]. This discrepancy may be due in part to different temporal and spatial resolutions and registration techniques. For example, Buonaccorsi et al. apply rigid transformations only and these may not fully correct for motion. Additionally, the displacements reported by Buonaccorsi et al. are from a patient with liver metastases enrolled on a clinical trial as the standard treatments were no longer effective. This patient is therefore likely to have been affected by the presence of long term disease and this could impact on their breathing range. There could also be a difference in tissue compliance due to the presence of lesions.

In summary, these results suggest that the largest component of liver motion is likely to be in the cranio-caudal direction and that the motion of the liver is non-linear with greater displacements seen in the superior portion of the liver which is in contact with the diaphragm. The motion seen in a tumour is therefore likely to depend on its position within the liver. Caunce et al. [64] (see Section 2.5.2.1) extended the work by Buonaccorsi [9] to include non-linear deformations and found that the additional benefit gained was much smaller than the benefit of performing rigid registration alone. The authors therefore suggest that breathing motion predominantly displaces liver metastases rather than causing rotation or deformation. This may be due to the higher rigidity of the tumour in comparison to the surrounding liver tissue [65], but it could also be because the transforms used could not mimic the physiological motion present in that region. Noterdaeme et al. [66] found a significant non-rigid motion component around the tumour rim in liver tumours. Again this could be a reflection of the nature of the deformation in that area or an artifact of the registration algorithm used.

2.5.2 Image registration

Registration algorithms aim to align a (movable) floating image to a “fixed” reference image by calculating the transformation required to optimise a measure of similarity between the two images [67]. An iterative approach is used to adjust the transformation until the similarity measure is optimised to within a given tolerance level.
Similarity measures have been developed for both intramodality and intermodality imaging [67]. Sum of squared differences (SSD) and correlation coefficient (CC) are primarily suitable for intramodality registration where the intensity values of each tissue are assumed to be the same (SSD) or have a linear relationship (CC) between images. In inter-modality imaging this may not be the case. For example, on MRI images fluid may appear bright but may be dark on CT images, whereas bone may have high signal intensity on images from both modalities. For intermodality registration, some similarity measures have been developed from information theory with normalised mutual information (NMI) [68] often employed.

In DCE-MRI time series images there is a changing relationship between tissue intensities during the time series due to the time dependent concentration levels of the contrast agent. Therefore, intermodality similarity measures are more appropriate for either registering each image to a selected reference image from the time series or a mean time series image volume. However, unfeasible deformations can still occur as features appear and disappear during the time series. For example, Tanner et al. [69] found that large changes in tumour size were produced by a non-linear registration technique based on B-splines used to register DCE-MRI breast images. They imposed a volume preserving constraint to prevent implausible volume changes of the tumour and used a combination of NMI and CC as a similarity measure.

One method of accounting for the changing features within DCE-MRI data is to generate a motion-free synthetic time series with contrast enhancement to which the acquired data can be registered. For example, Buonaccorsi et al. [9] generated motion free time series using a tracer kinetic model for registering free breathing acquisitions (described in Section 2.5.2.1). Melbourne et al. [70] used principal component analysis of time series to produce synthetic reference data without motion caused by inconsistent diaphragm position during breath-hold acquisitions. Using a tracer kinetic model to generate the synthetic data imposes a contrast agent concentration time course which may not be a good approximation to the data and which may therefore affect the accuracy of the registration algorithm. However, using principal component analysis may not be suitable for free-breathing where the motion components may be more complex than those seen for breath-hold. Despite their limitations, both these methods have been shown to be capable of accounting for signal intensity changes due to contrast agent when registering DCE-MRI data.

Another technique is the inclusion of a term that accounts for contrast agent uptake in
the model used within the registration algorithm. For example Martel et al. [71] used a non-rigid optical flow algorithm with an additional term to account for changing signal intensity due to contrast uptake in breast MRI.

A further approach is to register each image to the previous image in the time series on the assumption that the contrast agent concentration changes between temporally adjacent images are unlikely to be large. This is likely to be an acceptable assumption, except around the arrival of contrast agent where bolus injection is used. Noterdaeme [66] and Rajaraman [11] used this method for registering breath-hold DCE-MRI of liver tumours. Using breath-hold can limit the temporal resolution and potentially result in the loss of the first pass peak in the tissue uptake curve. This could be advantageous to registration methods that assume small changes in contrast between adjacent time series images. However, this assumption may not hold for higher temporal resolution free-breathing acquisitions but lower temporal resolution breath-hold time series may not provide adequate information for accurate and precise tracer kinetic modelling.

Registration techniques can be categorised by the nature of the transform applied to align the images. Rigid registration has six degrees of freedom from rotation around the three axes and translation in the three planes. Affine registration is an extension of rigid registration that also includes shearing and scaling giving 12 degrees of freedom. However, rigid or affine registration cannot accurately reflect the types of non-linear deformations seen in liver tissues due to the motion of the diaphragm, as described in Section 2.5.1. Instead, these deformations may be more appropriately registered using non-linear transformations such as spline-based, elastic or fluid deformations [72].

Spline based transformations use an underlying mesh of control points which are displaced to optimise the chosen similarity measure. Rohlfing et al. [61] used free-form transformations based on B-splines to investigate the motion of the liver during the respiratory cycle. Elastic and fluid registrations model tissue deformations as the distortion of an elastic material or as fluid movement respectively. The deformation between the images is estimated by solving the system partial differential equations used to model the behaviour of the tissue. Rajaraman [11] and Melbourne [70] used elastic and fluid registration schemes respectively to register DCE-MRI liver data. Brock et al. [13] used finite element modelling (FEM) with a linear elastic model to register end-inhale and end-exhale abdominal CT images. We discuss this registration in more detail in Section 2.6.4.
Non-linear registration often involves an initial rigid registration step [66, 11] which may prevent the non-linear registration step from making large non-physiological deformations. This may be of particular benefit where there are changing intensity patterns due to contrast agent uptake.

This research aims to generate synthetic data for assessing the benefits of registration for DCE-MRI parameterisation rather than develop novel registrations methods. Whilst the synthetic data could be used to compare a number of the different registration methodologies discussed above, this thesis aims to demonstrate the utility of the synthetic data (Chapter 6) by focusing on assessment of the model driven registration described below (Section 2.5.2.1). The model driven registration algorithm has been developed for a free breathing DCE-MRI acquisition protocol. This protocol has been used for tracer kinetic model analysis within clinical trials of anti-angiogenic drugs and is therefore also relevant for model selection (see Chapter 5).

### 2.5.2.1 Model driven registration for DCE-MRI

In this section we describe the model driven registration algorithm developed by Buonaccorsi et al. [9] that provides reference images that account for changing features within the images of the time series due to time dependent contrast agent enhancement.

The registration process first involves fitting the extended Kety model, Equation (2.1), on a per voxel basis with an AIF derived from the time series data via an automated procedure [39] or using a population average AIF [40]. Synthetic time series image volumes are then generated from the estimated model parameters by using the extended Kety model to calculate contrast agent uptake curves which are then converted to signal intensity time courses using Equation (2.8) and the SPGR pulse sequence equation (Equation (2.10)) and the estimated $T_1(0)$ and $S_0$ values. Each of the acquired image volumes is then registered to the equivalent image in the synthetic time series. Translation only registration was performed and normalised CC used as a similarity measure within the tumour volume of interest (VOI) only. Model fitting was then applied to the registered time series and a registered synthetic intensity time-series created. 10 iterations of generating synthetic reference data sets and registration to this data were performed and the data set with the lowest model fitting SSE selected as the optimum.
The registration was originally assessed using synthetic DCE-MRI time series images with simple nested cuboidal structure, to represent tumour core and rim, and a sinusoidal motion pattern [9]. An improvement in the accuracy of the estimated model parameters was seen. The registration was also applied to acquired data sets of 10 patients with hepatic metastases (13 lesions in total) and a reduction in a visually assessed motion score was seen. However, a consistent improvement in the reproducibility of median estimated parameters in the tumour VOIs between two pre-treatment baseline visits was not seen. Inspection of the parameter maps revealed areas of improved definition around the enhancing rim of the tumour. Therefore, the authors suggest that the registration may have a beneficial effect on the fine spatial detail of DCE-MRI parameterisations within each tumour but that this benefit is lost when median values that do not encompass heterogeneity are used. Further work by Buonaccorsi [73] found that this registration technique did have a beneficial effect when performing data-driven tumour sub-segmentation, a technique that investigates the heterogeneous nature of tumours.

Caunce et al. [64] extended the registration to include affine and non-linear transforms and assessed the registration on the same data sets as used by Buonaccorsi [73]. The benefit gained from increasing the complexity of the transforms was small compared to the initial gain from translation only registration, and registration failures were also more common. The authors suggest that the results imply that breathing motion mainly causes displacement of the liver tumours with little deformation or rotation. The effect on estimated model parameters was not investigated.

The validation of the original translation only registration by Buonaccorsi [9] using synthetic data demonstrates that the registration algorithm has been correctly implemented as both the registration algorithm and the synthetic data use translation only deformations. However, it does not test the robustness of the registration as the synthetic data does not replicate the more complex deformations and irregular motion patterns that may occur due to breathing (see Section 2.5.1). Also, the time courses for the tissue surrounding the tumour are not generated with a model that emulates liver tissue, for example a dual-input model (see Section 2.3.1). As motion will cause the time courses within the tumour to be corrupted by the contrast agent concentration curves in the surrounding tissue, a physiologically relevant model for liver is required to assess the application of the registration algorithm to tumours in the liver. The synthetic data also has a simplified geometry which does not aim to be representative of true anatomy. It lacks other features, such as liver vasculature and
major blood vessels, that are potentially relevant to registration methods and which are required for assessing time series analysis techniques. It is these inadequacies that motivates the development of the synthetic data generation methods presented in this thesis.

2.6 Software phantoms for assessing analysis techniques

2.6.1 Registration validation techniques

The predominant motivation for using synthetic data to assess DCE-MRI post-acquisition processing techniques such as tracer kinetic model fitting and registration is that it provides ground truth for the model parameters. It is not possible to derive ground truth values for acquired patient data, although biopsy and histology may provide an indication of whether the imaging results reflect the underlying structure and function. Individually, acquired data with histology, synthetic data or hardware phantoms cannot be used to fully explore post-acquisition processing techniques. Therefore, using multiple validation techniques is important with synthetic data fulfilling the essential role of providing ground truth. Software phantoms can also allow generation of multiple data sets for different imaging scenarios (such as temporal resolution or slice thickness [74]), anatomical variations [75] and disease states [76].

Registration techniques that correct for breathing motion have been quantitatively assessed by measuring the offset of anatomical landmarks between registered end-inhale and end-exhale images. Example landmarks used for the liver are vessel bifurcations [77], centre lines of portal veins and the inferior vena cava [61] and the liver surface [61]. Alternatively, the displacement of each voxel can be compared against a ground truth deformation map used to emulate motion in a synthetic data set [71, 12]. However, these techniques are not adequate where tracer kinetic modelling is applied as they do not measure the effect of registration on the accuracy or precision of the model parameters, and the assumption that registration success will benefit the final outcome measure may not be true. As noted by Martel [71], this assumption is particularly doubtful in tissue regions where there are no clear landmarks with which to
judge registration success and the motion has a significant non-rigid component.

Generating synthetic data using ground truth model parameters with a physically plausible motion pattern can address this inadequacy. However, synthetic data has limitations. It is unlikely to have the full level of anatomical complexity seen in acquired images or fully emulate the complex nature of motion seen in abdominal organs as they slide over each other and deform non-rigidly during the breathing cycle. In software phantoms, tissues are often modelled as homogeneous in terms of ground truth values [74] and biomechanical properties for motion emulation [62], ignoring the natural variations that exist. It is also difficult to model, and therefore simulate, the interactions between MRI hardware, pulse sequence parameters and patient dependent factors such as size, motion and thermal noise. Hardware phantoms may have the potential to fill such gaps. However, given the complexity of physiological motion, anatomical description and tissue characteristics it is currently not feasible to produce a hardware phantom that provides ground truth for DCE-MRI tracer kinetic model fitting parameters.

### 2.6.2 Synthetic data for assessing DCE-MRI registration techniques

For testing the robustness of DCE-MRI model fitting algorithms to breathing motion and the benefit of using a registration algorithm, the synthetic data must emulate multiple aspects of acquired images. For example, the time series images require signal intensity time courses that change with contrast enhancement, each image needs a geometrical definition preferably including PVEs and throughout the time series motion and noise emulation are required.

Schnabel [78] and Martel [71] generated synthetic data with motion emulation for contrast enhanced imaging of the breast by applying deformation maps to acquired images. This method produces synthetic images with natural variations of physiology within the tissues and the anatomical complexity is that of acquired images. However, the ground truth for model parameters can not be provided in this way. Different motion patterns can be applied to each data set, but simulating variations in anatomy and disease depends on acquiring further patient data.

Rather than using signal intensity values from acquired images, the relevant pulse se-
Chapter 2. Background, theory and methods

A sequence equation and tracer kinetic model can be used to generate signal intensity time course data from ground truth values. Buonaccorsi [79], Melbourne [10] and Rajaraman [11] used this method for generating synthetic DCE-MRI liver data. However, only Melbourne used a dual input model for the liver. Different input function representations can be used as input to the tracer kinetic model. For example, Rajaraman used a bi-exponential functional AIF form described by Tofts and Kermode [34], Melbourne used raised cosine functions for the AIF and PIF [43] and Buonaccorsi used a functional form of a population averaged AIF developed by Parker et al. [40]. The functional form developed by Parker is based on higher resolution data than that described by Tofts and so is likely to be more appropriate for higher resolution simulations. The raised cosine described by Orton has a simplified form from that seen in acquired data and will therefore not give as accurate a representation of the time courses observed in acquired data.

Generating synthetic data using mathematical models requires ground truth for the model parameters. Rajaraman used ground truth values for the extended Kety model and MRI parameters from analysis of acquired data sets and published literature values. Tissue heterogeneity was emulated by assuming a normal distribution with a standard deviation of 5% of the mean. The distribution for each parameter was sampled for each voxel as each parameter was assumed to be independent. Using models with greater physiological complexity are likely to generate time courses that are more representative of acquired data, for example Mescam [76] used a 5 compartment distributed model for the liver. However, gaining ground truth for a more complex model is in itself is a challenge (see Section 2.3.1).

Noise can be included in the synthetic data generation process by converting the image to k-space and adding Gaussian noise to the real and imaginary parts [11]. Alternatively, zero mean Gaussian noise can be added to the generated signal intensities [79]. Whilst adding Gaussian noise to k-space data will produce a more accurate noise distribution, the latter method is a good first approximation to the Rician noise distribution for magnitude images [80] and is simpler to implement.

Different levels of anatomical complexity have been used for synthetic data generation from the simple nested cuboidal structure used to represent tumour rim and core by Buonaccorsi [79] to the tissue masks based on high spatial resolution photographic images from the visible human project used by Rajaraman [11]. Using high resolution data implicitly gives emulation of PVEs when the data is downsampled to
a typical resolution for DCE-MRI. An alternative approach to emulating PVEs was used by Collins et al. [74] for generating synthetic brain images. Fuzzy masks, which describe the percentage of tissue type contained in each voxel, were generated from the segmentation of acquired $T_1$, $T_2$ and proton density MR images, MR angiography and CT images for one subject. Whilst using tissue masks gives an anatomical description with a structure which reflects acquired images, new data sets are required for different variations in anatomy seen in the population. A hybrid approach was employed by Segars [75] who used surfaces based on the visible human project data set and allowed those surfaces to be altered using population data for external body measurements, such as chest width, providing the ability to generate data sets with anatomical variations without the need for further image acquisitions. The anatomical phantom has been used to generate CT, PET and SPECT data sets. However, it may be possible to generate implausible anatomical configurations and the synthetic data produced does not yet include emulation of disease.

For emulating DCE-MRI of liver tumours, vascular structure within the liver and the inclusion of one or more tumours are required. Again these could be provided by masks based on acquired data, or by insertion of a synthetic tumour. For example Rajaraman [11] used an ellipsoid shape and Melbourne [10] used rough spheres, with deviations in the radius, which are nested to represent tumour rim and core.

Alternatively, the growth of the tumour and the vascular structure could be modelled. For example, Mescam et al. [76] used the model developed by Kretowski et al. [81] for generating synthetic DCE-MRI data sets of the multi-step carcinogenic process of primary liver tumours. The model includes the growth of three vascular trees (arterial, portal and venous) and tissue units whose function is described using a tracer kinetic model. Tumour growth is emulated by allowing the class of the tissue units, and therefore the tracer kinetic model parameters, to change to reflect each disease stage. New tissue units can also appear to emulate the multiplication of tumour cells. Within the model the new tissue units result in further growth of the vasculature in that region. This model requires a large number of ground truth parameters and heuristics to guide the growth of the tumour and vasculature and for the mathematical models used in the signal generation process. Ensuring that the choice of these parameters results in synthetic data that is representative of acquired time-series may in itself be a challenging problem.


2.6.3 Motion emulation

Motion corruption due to breathing has been emulated with varying degrees of complexity. Buonaccorsi et al. [79] applied a sinusoidal rigid transformation to their nested cuboid tumour phantom to validate the model driven registration [9] described in Section 2.5.2.1. The simple nature of the geometry allowed the authors to easily demonstrate the effectiveness of the technique visually, and the application of translation only sinusoidal breathing motion showed that the registration algorithm (which was also translation only) worked as expected.

Rajaraman et al. [11] developed a synthetic phantom for sequential breath-hold liver DCE-MRI based on tissue masks from the visible human project. Motion was emulated using a polynomial deformation to give a smooth non-rigid displacement field. A polynomial degree between 0.95 and 1.05 was randomly sampled to emulate inconsistent diaphragm position during each end-exhale breath-hold. Melbourne [10] also emulated a sequential breath-hold liver DCE-MRI series with the anatomical description from segmented MR images. The deformation used was based on a linear elastic model with placement of a time varying force at the diaphragm. The force was scaled according to an asymmetrical spline based breathing trace where the spline nodes were varied in each cycle according to a Gaussian distribution. Deformation of the inserted near-spherical tumour was limited to rigid transformations to ensure volume preservation. Segars et al. [75] emulated motion in the liver for synthetic CT images using rigid displacements applied to control points on a surface model. The displacements were estimated from 20 CT datasets with 10 points in each respiratory cycle. Within their phantom generation process respiratory motion parameters, such as the respiratory period and range of cranio-caudal motion, can be altered to generate different synthetic data sets.

Lujan et al. [82] generated a probability density function that described liver tumour motion due to breathing for calculating radiotherapy dose distributions. A mathematical model was fitted to fluoroscopic data of diaphragm position and assumed a periodic breathing cycle with a fixed amplitude. The model produced was asymmetrical with more time spent during exhale than inhale and it flattened around the maximum exhale position (the diaphragm became near to stationary). When simulating treatment using this breathing model, they also assumed that motion of the liver was rigid, only occurred in the superior-inferior plane, and was well correlated with diaphragm motion. Simulations were performed by moving the beams within
the treatment planning system in the opposite direction to motion of the organs, rather than generating synthetic images. Whilst this work is built upon a number of assumptions that may not hold, the mathematical model of the breathing cycle may provide a useful method for simulating organ motion, especially if it can be combined with natural variations in the period and amplitude of the breathing cycle that occur during imaging acquisition.

None of these motion techniques fully capture the non-rigid motion of each of the abdominal organs during the breathing cycle. Schnabel [78] used a biomechanical model to emulate motion in DCE-MRI of the breast. The tissues were segmented into fat, fibro-glandular tissue and tumour. Elastic properties were assigned to each of these tissue types and an additional skin class. A displacement force was then applied to the model and FEM used to estimated the deformation field. This gives non-linear displacements that are likely to replicate more closely the actual deformations. The simulated displacements are also of a greater level of complexity than the registration algorithms tested using synthetic data generated with this technique [71, 78]. This is important for giving the registration algorithms a challenge that more closely replicates that of acquired data.

2.6.4 Multi-organ finite element modelling for emulating liver motion

We wish to produce synthetic data sets with plausible deformations of the complex motion of the abdominal organs, including a liver tumour, due to breathing. The synthetic data can then be used to assess the robustness of model fitting and selection to motion and the benefit of using registration. If the deformation patterns used to generate the synthetic data are less complex than those seen in acquired data and also than those applied in the registration method, only the correctness of the software implementation and algorithm has been tested, rather than a full assessment of accuracy, precision and robustness for the relevant application area.

As mentioned previously, Schnabel et al. [12] used biomechanical modelling to generate synthetic data with plausible deformations in the breast for quantitative validation of a registration algorithm. Brock et al. [13] developed a finite element model-based multi-organ deformable image registration technique, which they applied to liver tumours, and it is the dense displacement maps produced from this technique that we
have used to emulate motion within this thesis.

The registration technique developed by Brock was originally assessed on MR images of 5 healthy volunteers [13] and was then applied to contrast enhanced CT images of 5 patients with liver tumours [63]. End-inhale and end-exhale breath-hold images were acquired in both cases. Organ masks were defined manually for the liver, spleen, stomach, kidneys and the external body surface. From these masks, triangular mesh surface representations of each organ were generated and input to the FEM application (HyperMesh, Hyperworks 7.0). The FEM application then generated a 3D four node tetrahedral volume mesh for each organ. An additional internal body mesh was generated by subtracting the meshes for all the defined organs from the external body mesh. Mesh nodes on the surface of the organs were defined to be common to the organ and the interior body mesh.

A linear elastic material model was used for all the organs. Literature values were originally used for the material properties of each organ and the organs were assumed to be homogeneous. The literature values were refined using the data from healthy volunteers to give greater registration accuracy (although there were no tumours in these cases). The material properties used for registering the liver tumour data are shown in Table 2.1. Note that the Young’s modulus of tumour is 10 times greater than that of liver to reflect the higher rigidity of tumour tissue.

Boundary conditions for the FEM were determined by using a guided surface projection method where the nodes of the tetrahedral volume mesh of the end-exhale organs were matched to the surface representation of the end-inhale organs (performed using HyperMorph, available in HyperMesh). The vectors that describe the displacement of the nodes (on the exhale organ) required to achieve this match form the boundary conditions for the finite element model. Boundary conditions were only determined for liver, external body surface and spleen as these organs were easier to segment. Therefore, within the finite element analysis, only these three tissues are explicitly

<table>
<thead>
<tr>
<th></th>
<th>Poisson’s ratio</th>
<th>Young’s modulus (kPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>0.450</td>
<td>7.8</td>
</tr>
<tr>
<td>Liver tumour</td>
<td>0.450</td>
<td>78</td>
</tr>
<tr>
<td>Spleen</td>
<td>0.499</td>
<td>50</td>
</tr>
<tr>
<td>Stomach</td>
<td>0.499</td>
<td>500</td>
</tr>
<tr>
<td>Kidneys</td>
<td>0.499</td>
<td>24</td>
</tr>
<tr>
<td>Body</td>
<td>0.400</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Table 2.1: Linear elastic material properties from [63].
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deformed and all others are deformed implicitly.

A finite element analysis application (ABAQUS 6.4, Inc, Providence RI) was then used to generate and solve the differential equations for the finite element model. A dense displacement map that describes the distance each voxel in the end-exhale image is displaced to approximate the end-inhale image is produced for each of the three axes.

The accuracy of the registration technique was measured by assessing the difference in position of vessel bifurcations within the liver between the warped exhale image and the inhale image of 5 healthy volunteers [13] (inplane voxel size of 1.32 to 1.72 mm, slice thickness 4 to 5 mm). An average absolute difference of 1.2 mm in the lateral direction, 1.7 cm in the anterior-posterior direction and 1.4 cm in the cranio-caudal direction was found. These differences are comparable to the voxel size. The accuracy of the registration algorithm will be affected by the accuracy of the assigned biomechanical properties and by assuming that the liver is a homogeneous structure, which does not account for the presence of blood and bile vessels that may affect the biomechanical properties and the separate lobes that may slide against each other. However, even if full accuracy is not achieved, this is likely to be a good method for emulating plausible liver motion due to breathing including non-rigid deformations.

2.7 Summary

In this chapter we have described the theory and methods involved in probing the microvascular characteristics of liver with metastatic disease using DCE-MRI and tracer kinetic model fitting. Included was a description of a model selection technique for distinguishing between tumorous and non-tumorous tissue within the liver. We have discussed the motion of the liver due to breathing that will occur during acquisition of the DCE-MRI time series and reviewed registration methods that are relevant to DCE-MRI in liver tumours. Following from this we have introduced published methods of generating synthetic data for assessing modelling techniques and registration.

In the next chapter we introduce the software phantom generator that we have developed for generating DCE-MRI synthetic data. Whilst we have focused on DCE-MRI of liver tumours within this chapter, the software phantom generator has much
broader application as it can be extended both to other anatomical areas and to other imaging modalities. The flexibility of the phantom generator extends the relevance of this thesis beyond DCE-MRI of liver tumours. However, focusing on this application (including the development of a model selection technique for assessing the microvascular characteristics in livers with metastatic disease) demonstrates the utility of the phantom generator for validating analysis techniques that have potential to be involved in the clinical trial pipeline.
Chapter 3

Software phantom generator

3.1 Introduction

In Chapter 2 we described how DCE-MRI with tracer kinetic model fitting can be used to probe the microvascular characteristics of tumours. Assessing the robustness of this technique to noise and motion is difficult to achieve using acquired data sets as ground truth values are unknown. Therefore, in Section 2.6 we introduced the use of software phantoms to provide ground truth for assessing post acquisition processing algorithms.

In this chapter, we introduce the methodology and design used to produce the PhantomGenerator, a software application for producing synthetic data sets for DCE-MRI of abdominal tumours. For maximum utility, the design of the is extensible to other imaging scenarios, for example a different modality such as computed tomography (CT), or a different anatomy and imaging technique such as oxygen-enhanced imaging of the lung. As the PhantomGenerator can produce multiple synthetic data sets, it is possible to test analysis techniques with a wide range of ground truth values or motion characteristics.

In Section 3.2, we present the software development methodology used. It is important that well-established software development principles are used to ensure that the correct output is produced, otherwise the use of the generated synthetic data sets as standards with which to assess analysis techniques is undermined. For example, using a version control system for the code, logging statements and unit testing allows early
detection and efficient resolution of software bugs (Section 3.2.1). Also, producing a modular design by following object-oriented design principles facilitates unit testing and prevents the addition of software bugs (see Section 3.2.2).

As we require the PhantomGenerator to be extensible to different imaging scenarios, it is important to produce a clear, easily understandable software design in which any software components that are likely to have multiple options (e.g. imaging modality) have been identified. This allows new scenarios to be accommodated without compromising the integrity of the application’s structure, and therefore the correctness of its output.

An overview of the design of the PhantomGenerator is presented in Section 3.4 along with example output from each of the packages is shown alongside its design. Then, in Section 3.5, we present a synthetic DCE-MRI data set based on acquired data giving it characteristics similar to those seen in acquired data sets. The synthetic data set presented does not yet include motion emulation as this is described in Chapter 4.

### 3.2 Software development methodology

It is important to use established software development principles to ensure that all the required functionality is present and that the correct results are produced. This is of particular relevance to the PhantomGenerator as the generated data may be used to determine whether a processing algorithm will be included in a clinical trial. It is therefore important to have confidence in the provenance of the synthetic data.

The software development process includes documenting the tools, procedures, and guidelines used for design, implementation, testing and validating that the requirements have been met. The software tools and procedures are detailed in Section 3.2.1.

We have selected an object-oriented programming paradigm for the PhantomGenerator as it aids good software practices and the development of flexible and extensible software applications. This paradigm and its advantages are explained in Section 3.2.2. This paradigm was also used by Kwan et al. [83] for developing an MRI simulator.
3.2.1 Software development tools and procedures

Universal modeling language [84] was used to document the design and published design patterns [85] were used where possible. The initial design was reviewed formally by two experienced software engineers with knowledge of DCE-MRI (Gio Buonaccorsi and Angela Caunce). Following from this, additions were reviewed at regular meetings and appropriate changes could then be made after review.

The code was written in C++, which contains programming constructs that support but do not enforce object-oriented programming. It was compiled for SUSE Linux using g++ version 4.1.0 with the compiler optimisation level was set to zero (no optimisations are performed at this level). Smart pointers from the Boost library were used for memory management [86]. This is considered good practice as it reduces memory leaks which is an important factor when producing a reliable application [87]. Output logging statements were written using the log4cxx logging library from Apache [88]. These provide an excellent debugging aid where the level of information output can be changed without the need for recompilation. User input via a configuration file or the command line was implemented using the Boost "program_options" library [89]. Other established libraries were used wherever possible, for example the Boost "FileSystem" library [89]. Eclipse was selected for the Integrated Developer Environment [90].

The code (along with unit tests) was written by the author. A code review [87] was then performed by Gio Buonaccorsi to aim to ensure the correct implementation of the following areas:

- The implementation of the spoiled gradient echo (SPGR) pulse sequence to ensure it replicates Equation 14.8 in [57].
- The implementation of the extended Kety model to ensure it replicates Equation 15 in [3].
- The implementation of the population averaged arterial input function (AIF) to ensure it replicates Equation 1 with the parameter values given in Table 1 in [40].
- The design to check that a new tracer kinetic model, pulse sequence and input function definition can be easily added.
Unit testing was implemented using the CppUnit library [91]. The tests were written alongside the application code to ensure the correct output was produced as the application developed. The reference data came from two sources: a prototype software phantom generator written by Buonaccorsi et al. [79] and independent implementations of the functions written in Matlab. The unit tests were used for regression testing to ensure that the application remained stable during its development.

Concurrent version system (CVS) was used to version control the code base [92]. This allows versions to be tagged during development and roll back or comparisons in the case of bugs appearing. It also provides a good backup system.

Validation of the PhantomGenerator was performed by using generated synthetic data to characterise the optimisation algorithms within two independently written DCE analysis software applications: Manchester dynamic modelling application (MaDyM), written by Geoff Parker and Gio Buonaccorsi; and a Matlab DCE model fitting application, written by Jo Naish. Both these applications have been well-used, their results have been presented in peer reviewed publications and reported as part of drug trials, for example [2, 48]. The parameter values estimated by these applications were found to be good approximations to the ground truth used to generate the synthetic data [93]. Whilst this may seem circular, if there was not good agreement to the ground truth there would be doubt as to whether the model fitting applications or the PhantomGenerator were implemented correctly. As close approximation to the ground truth was seen this gives confidence correctness of the PhantomGenerator.

### 3.2.2 Advantages of the object-oriented software paradigm

In object-oriented design and programming [94, 95, 96], the code is grouped into modules, known as classes, that generally represent real world objects. Each class encapsulates its associated data, which are known as member variables, and can itself include class objects. In general, it is good practice for a class to prevent direct access and modification of its data. Instead member functions that control interrogation and manipulation of the data are provided. Data encapsulation allows the format in which the data is stored to be changed without any alteration to the way that the member functions are called from code external to the class, therefore limiting the effects of data representation changes to within the relevant module. To construct an application with the required functionality, objects of the relevant classes are
instatiated which results in memory allocation for the data and initialisation of the member variables when the code is executed. When each object has been instantiated, the member functions can be called on that object.

When designing an object-oriented application, it is important to isolate any elements that are likely to be subject to change or that may have different options. For components that are likely to have different options, an interface can be used to enforce the functions that must be implemented by the class for each option. The interface itself does not have any data or function implementations. Alternatively, an abstract class can be used where some functionality or data will be common to some of the options. An abstract class only includes implementations for common functionality and (as for an interface class) enforces the functions that must be implemented by the classes for each option. For example, within the PhantomGenerator we have written a tracer kinetic model interface and all tracer kinetic model classes must implement a function called the calculates contrast agent concentration for a given time (see Section A.1.1). It is then possible to program to the interface, rather than to a particular class, and the object of the correct class can be determined at run time (rather than compile time), depending on the user’s input.

Another design practice that aids data encapsulation and flexibility is composition, where an object is held as a member variable of a class. If an object is a member variable of a class, the containing class can limit access to the functions that manipulate that object. It also allows the interface of the member variable object to be changed without affecting code that uses the containing class. Composition often reflects the structure of real world objects, therefore leading to a design that can be understood intuitively. For example, in the PhantomGenerator the class which represents a tissue type contains an object which represents a tracer kinetic model, which itself contains an object that represents a vascular input function. Therefore, the type of vascular input function or the interface of the vascular input function class could be changed without any alterations to the class that represents a tissue.

The modular design of object-oriented applications and the practice of programming to interfaces leads to flexible and easily extensible software applications. For example, it is easy to switch one tracer kinetic model class for another as the interface for all the classes is the same and a new tracer kinetic model class can be added by realising this interface (see Section A.1.1). This helps ensure that, as the application is extended to new scenarios, the functionality does not outgrow the design leaving the
implementation muddled and more prone to software bugs. The modular structure also helps ensure that the correct output is produced as each class can be unit tested. Unit tests are modules of code that call the member functions of generally one class to test that the expected outcome of executing those functions has been produced. The unit tests can then form a battery of regression tests. These are a group of tests that are run regularly during development to prevent the deterioration of the code base as new functionality is added, hence increasing the reliability of the software.

### 3.3 Requirements

For a formal software project, requirements are typically collected from the intended users before the design and implementation phases of the project. Validation testing then ensures that the application has fulfilled the requirements, indicating that the application is likely to meet the users’ needs. Within this research, detailed requirements were not formally collected as the requirements remained flexible to the needs of the researcher during the project. However, the high level requirements that became apparent during the project have been listed below.

The components that are required to be flexible at run time and extensible within the PhantomGenerator are listed in Table 3.1 along with the options that were implemented. Extension of the PhantomGenerator to other scenarios may be achieved by implementing new models or modalities other than those listed. The required inputs that can be specified by the user at run-time are listed in Table 3.2. A further requirement for the application is to output enough information to identify all the inputs and so allow the synthetic data to be regenerated was implemented.

<table>
<thead>
<tr>
<th>Flexible component</th>
<th>Implemented options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular input function</td>
<td>The population averaged DCE-MRI AIF [40], bi-exponential AIF [41], a text file describing a patient specific AIF or a portal input function</td>
</tr>
<tr>
<td>Pulse sequence</td>
<td>The SPGR and inversion recovery pulse sequences</td>
</tr>
<tr>
<td>Imaging modality</td>
<td>MRI</td>
</tr>
<tr>
<td>Noise</td>
<td>Gaussian noise</td>
</tr>
</tbody>
</table>

**Table 3.1:** Flexible and extensible components within the PhantomGenerator
### Component Parameters

<table>
<thead>
<tr>
<th>Component</th>
<th>Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular input function</td>
<td>Delay time and haematocrit</td>
</tr>
<tr>
<td>Tracer kinetic model</td>
<td>Ground truth parameters</td>
</tr>
<tr>
<td>Tissue</td>
<td>MR properties such as $T_1$</td>
</tr>
<tr>
<td>Pulse sequence</td>
<td>Acquisition parameters such as TR and flip angle.</td>
</tr>
<tr>
<td>Contrast agent</td>
<td>Relaxivity and pre-bolus time</td>
</tr>
<tr>
<td>Anatomy</td>
<td>Anatomical and motion description</td>
</tr>
<tr>
<td>Image time series</td>
<td>Time series parameters (such as temporal resolution), noise level, and voxel size</td>
</tr>
</tbody>
</table>

Table 3.2: Required input parameters for the PhantomGenerator

### 3.4 Software phantom generator design and output

The PhantomGenerator contains five packages as shown in (see Figure 3.1). The Physiology, SignalGeneration, and ImageGeneration packages contain the core functionality for generating an image. The TimeSeries package allows an image for each time point to be generated. Kwan et al. [83] also produced a design, used for the BrainWeb simulations [97], where the signal generation mechanism was separated from the image production module.

A flow diagram of the process for generating a synthetic DCE-MRI image within the PhantomGenerator is shown in Figure 3.2. The Physiology package generates the contrast agent concentration, $C_t$, for each tissue at each time point using the selected
Chapter 3. Software phantom generator

tracer kinetic model and vascular input functions. The SignalGeneration package then uses the value of $C_t$ to calculate the signal intensity for each tissue. It is possible to adapt the SignalGeneration package for other imaging modalities, such as CT. Neither the Physiology nor the SignalGeneration package have any knowledge of the anatomy being emulated and calculate their outputs on a per tissue type basis only. The anatomical definition is the responsibility of the ImageGeneration package which maps the signal intensities for each tissue into the image volume whilst remaining blind to the mechanism by which the signal intensity values were generated.

Figure 3.2: Flow diagram showing the main packages in the PhantomGenerator for a DCE-MRI scenario.

The required anatomy is specified by the user by using masks for each tissue or organ and partial volume effects (PVEs) are represented using intermediate values between 0 (no tissue in the voxel) and 1 (voxel only contains that tissue). Tracer kinetic parameter maps can also be used as input to the PhantomGenerator. Motion is emulated by providing a mask for each tissue at each time point. (The generation
of a time series of masks that include realistic motion characteristics is described in Chapter 4.) The ImageGeneration package can also downsample the images to the required resolution and add noise.

The TimeSeries package is then used to generate image volumes at each time point and provides the acquisition time to the Physiology package for calculating the contrast agent concentration and to the ImageGeneration package for recording the time in the output files.

Figure 3.3 shows an overview of the modules in the PhantomGenerator. The presented structure allows the requirements for run time flexibility and extensibility documented in Table 3.1 to be met. For example, multiple tracer kinetic models can be implemented and the tracer kinetic model for each tissue type can be specified by the user. Further tracer kinetic models can be added to simulate different physiological characteristics. Also, any number of tissue modules can be created to describe the anatomy specified by the user. As described earlier, signal production modules for alternative modalities, such as CT, can be implemented.

The PhantomGenerator also includes the GeneratorConfiguration package which reads user input in the form of a configuration file and the command line. It instantiates and configures the required objects for each of the packages for the imaging scenario defined by the user input, for example by instantiating the specified tracer kinetic model for each tissue and the specified pulse sequence. The GeneratorConfiguration package relies heavily on the configuration components that are present within each of the three main packages. All the configuration classes are easily extensible. Therefore the addition of any new options, for example input functions, only requires the implementation of a new class for that option and minimum alteration to the relevant configuration component.

The detailed designs for each of the packages are documented in Appendix A.1 and outputs of the PhantomGenerator modules are demonstrated in Sections 3.4.1 - 3.4.4.

3.4.1 Output of the Physiology package

Input functions generated by the Physiology package are shown in Figure 3.4 for modules implementing a population averaged AIF [98] and a bi-exponential AIF [41] with a for a contrast agent dose of 0.1 mmol/kg. Figure 3.4 also shows the
Figure 3.3: An overview of the modules in the PhantomGenerator for a DCE-MRI scenario. The Physiology package is shown in red, the SignalGeneration package in green, the ImageGeneration package in blue and the TimeSeries package in black. The modules with dotted borders are options that are flexible at run time options and that are extensible within the design. The arrows point in the direction of information requests. For example, the pulse sequence module requests the dynamic $T_1$ value from each tissue module.
output of a module that contains input function data read a text file. In this case it contains a portal input function (PIF) estimated from the population-averaged AIF (as described in Section 5.2).

![Plasma curves produced by the Physiology package.](image)

**Figure 3.4:** Plasma curves produced by the Physiology package.

Contrast agent concentration curves for tumour core, tumour rim and liver tissue are shown in Figure 3.5. The extended Kety model has been used to generate the tumour core and rim and the Materne model has been used for the liver. Note that the integrals within all three models are approximated using the trapezoid rule and that a step size of 1 s is used for this approximation regardless of the temporal resolution of the time series. The ground truth values for the model parameters are derived from acquired DCE-MRI data sets of patients with liver metastases (see Table 3.3 and Table 3.4 in Section 3.5). The output shown in Figure 3.5(a) uses the population averaged AIF, with a PIF estimated from this AIF for the liver (see Section 5.2). Figure 3.5(b) shows output generated with the bi-exponential AIF.

### 3.4.2 Output from the SignalGeneration package

Figure 3.6 shows the output produced from the modules that represent a tissue type (which implement Equation (2.8)) for the same tissues used to demonstrate the output of the PhysiologicalCharacteristics package (see Figure 3.5). The ground truth pre-contrast $T_1$ values are shown in Table 3.3 and Table 3.5 and a contrast agent $T_1$ relaxivity of $4.5 \text{ s}^{-1} \text{ mM}^{-1}$ for gadolinium was used. The dynamic $T_1$ time courses using both the population-averaged and bi-exponential AIF are shown.
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Figure 3.5: Tissue curves produced by the Physiology package for the tumour rim, tumour core and liver.

Figure 3.6: Dynamic $T_1$ curves produced by the tissue module in the SignalGeneration package for the tumour rim, tumour core and liver. (a) uses the population-averaged AIF and (b) uses the bi-exponential AIF.
Figure 3.7 shows the signal intensity curves generated by the module that represents the SPGR pulse sequence by converting the dynamic $T_1$ values from the tissue module using $S_0$ ground truth values (see Table 3.3 and Table 3.5) as described in Equation (2.10). A flip angle of 20° and time to repeat (TR) of 4 ms were used to match the pulse sequence parameters used for acquired data (see Table 5.6).

![Signal intensity curves generated by the module representing the SPGR pulse sequence.](image)

**Figure 3.7:** Signal intensity time courses produced by the SignalGeneration package for the tumour rim, tumour core and liver. (a) uses the population-averages AIF and (b) uses the bi-exponential AIF.

### 3.4.3 Output from the ImageGeneration package

The output of the ImageGeneration package is demonstrated in the output of the time series package (Figure 3.9) and in the output of the PhantomGenerator (Figure 3.11) as each image in the time series is generated using the ImageGeneration package. Figure 3.9 presents output generated using parameter maps, and Figure 3.11 presents output generated from organ masks defined on acquired data sets.

Figure 3.8 demonstrates the downsampling, noise and PVEs emulation capabilities provided by the ImageGeneration package. The images have been generated with the masks from the University Health Network, Toronto (UHN) data set (Section 4.5.2.1) and are pre-contrast images with ground truth $T_1$ and $S_0$ values from Table 3.3 and Table 3.5. The input organ masks are binary images but have been warped for motion emulation (discussed in Chapter 4), therefore PVEs can be seen in Figure 3.8(b). Greater PVEs are noticeable when comparing Figure 3.8(b) with the downsampled...
equivalent slice in Figure 3.8(c).

![Figure 3.8](image)

**Figure 3.8**: Output of the ImageGeneration package demonstrating downsampling and the addition of noise. (a) is the original CT image. (b) is a pre-contrast noise free image (slice 12) with a voxel size of 0.98 × 0.98 × 2.5 mm³. (c) is a pre-contrast noise free image generated with the same organ masks as (b) but downsampled to a voxel size of 2.93×2.93×4 mm³. (d) is the same image as in (c) but with zero mean Gaussian noise with a standard deviation that gives an SNR of approximately 7 in liver tissue added. Note that (a) may not be an exact slice match as the MR images have been warped by motion.

### 3.4.4 Output from the TimeSeries package

To demonstrate the output of the TimeSeries package, we have presented synthetic data that, with the addition of noise, has been used to test the accuracy and precision.
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of $T_1$ estimation and model fitting algorithms [93]. Rather than having an anatomical geometry, the synthetic data is produced from ground truth parameter maps where the parameter values vary in even steps along the image volume axes. This allows the algorithms to be assessed with multiple different combinations of ground truth values.

Figure 3.9 shows a noise free synthetic DCE-MRI time series generated using the protocol detailed in Table 5.6 for the SPGR pulse sequence. In (a) $v_e$ varies along the y-axis, $v_p$ varies along the x-axis and a constant $K^{\text{trans}}$ value has been used. In (b) $v_e$ again varies on the y-axis but $v_p$ has been kept constant and $K^{\text{trans}}$ varies along the x-axis. For a fixed $K^{\text{trans}}$ value (see Figure 3.9(a)), $v_p$ has a greater effect on the signal intensity around the arrival of the AIF peak (time point 9) while $v_e$ has a lesser influence (the signal intensity varies along the x but not the y-axis). However, this reverses in the later time points, where $v_p$ has little influence. Where $v_p$ has a fixed value (see Figure 3.9(b)), $K^{\text{trans}}$ can be seen to have an influence in the early part of the time series where variation along the x-axis can be seen (post-contrast arrival). However, this is reduces at the later time points.

Output of the TimeSeries package using organ masks as input is shown in Section 3.5.

3.5 Generating a synthetic DCE-MRI time series based on acquired data

The PhantomGenerator was used to generate a synthetic DCE-MRI time series using organ masks from the UHN data set (contrast-enhanced CT end-exhale image) described in Section 2.6.4 and Section 4.5.2.1 as input. The input masks have a voxel size of $0.98 \times 0.98 \times 2.5 \text{ mm}^3$. Therefore, the output images have been downsampled to a voxel size of $2.93 \times 2.93 \times 4 \text{ mm}^3$ to match the acquisition protocol used for the acquired DCE-MRI data analyzed in Chapter 5 (see Table 5.6). The other acquisition parameters detailed in Table 5.6 have also been used to generate the synthetic data.

Estimation of ground truth parameters is described in Section 3.5.1 and the generated time series is presented in Section 3.5.2.
Figure 3.9: Synthetic time series generated using parameter maps. The acquisition time is shown above each image with the time point number in brackets. (a) shows the images produced for a fixed $K_{\text{trans}}$ and (b) shows the images produced for a fixed $v_p$. The images have a matrix size of 20 by 20 and therefore the parameter values vary between the ranges given in 19 even steps.
3.5.1 Ground truth parameter values

The ground truth values for each organ (see Table 3.3, Table 3.4, and Table 3.5) were derived from the DCE-MRI data sets of liver metastases described in Chapter 5. All the organs are described by the extended Kety model except for the liver, where the Materne model is used. Volumes of interest (VOIs) were drawn for each of the organs by an experienced research radiographer (Yvonne Watson).

For estimating ground truth values, the kidney region includes both cortex and medulla and the bone region has been defined in bone marrow in spine vertebrae as these VOIs gave large enough numbers of voxels for estimating median values. The kidney mask used to generate the synthetic data contains the same tissues used for ground truth estimation (both cortex and medulla). However the bone mask used to generate the synthetic data also includes multiple different parts of the skeleton such cortical bone in the vertebrae and the ribs. Using a single ground truth value for the kidney region and a value based on bone marrow for all bone tissue will not produce accurate representations for these tissues in the generated synthetic data. However, the PhantomGenerator allows specific input for these regions to be used if required. As these regions are unlikely to affect the performance of analysis or registration techniques which focus on the tumour region, refinement of the input for the kidneys and bone has not been addressed. The estimated ground truth values should still result in synthetic images that have a visual appearance which, overall, is a close approximation to acquired data (see Section 4.6). Any organ masks for the digestive system (e.g. stomach and bowels) are modeled as air.

Median values for each VOI for each patient were calculated from the parameter maps derived from model fitting (see Section 5.3.1). Mean values across the six patient data sets for each organ were then used. For the aorta the $T_1$ value appeared to be low (990 ms) compared to values reported in the literature, possibly due to partial volume effects and inflow effects. Therefore, this value was replaced with a value of 1441 ms from Stanitz et al. [99].

The $S_0$ value includes the proton density of the tissue and also scanner dependent variables such as the scanner gain. As the scanner gain changes on a per acquisition basis, $S_0$ is a relative quantity (comparisons between $S_0$ values of different tissues are not valid for across multiple acquisitions or patients). Therefore the $S_0$ values from one patient have been selected, rather than calculating a mean across the patient.
### Chapter 3. Software phantom generator

$K^{\text{trans}}(\text{min}^{-1})$ $v_p$ $v_e$ $\tau_{aif}(\text{min})$ $T_1(\text{ms})$ $S_0$ number of voxels

<table>
<thead>
<tr>
<th>bone</th>
<th>0.19</th>
<th>0.0053</th>
<th>0.19</th>
<th>0.11</th>
<th>391</th>
<th>6717.58</th>
<th>299.5</th>
</tr>
</thead>
<tbody>
<tr>
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<td>(0.0052)</td>
<td>(0.078)</td>
<td>(0.038)</td>
<td>(122.5)</td>
<td>(113.2)</td>
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</tr>
<tr>
<td>kidney</td>
<td>0.52</td>
<td>0.1</td>
<td>0.91</td>
<td>0.091</td>
<td>867.2</td>
<td>10155.1</td>
<td>278.7</td>
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<tr>
<td></td>
<td>(0.079)</td>
<td>(0.043)</td>
<td>(0.13)</td>
<td>(0.025)</td>
<td>(155)</td>
<td>(132.1)</td>
<td></td>
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<tr>
<td>cord</td>
<td>0.0088</td>
<td>0.0012</td>
<td>0.019</td>
<td>0.1</td>
<td>880.4</td>
<td>8475.69</td>
<td>37.17</td>
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<tr>
<td></td>
<td>(0.013)</td>
<td>(0.0015)</td>
<td>(0.023)</td>
<td>(0.07)</td>
<td>(182.1)</td>
<td>(14.36)</td>
<td></td>
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<tr>
<td>spleen</td>
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<td>0.038</td>
<td>0.38</td>
<td>0.082</td>
<td>981.9</td>
<td>9019.77</td>
<td>485.5</td>
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<tr>
<td></td>
<td>(0.53)</td>
<td>(0.035)</td>
<td>(0.086)</td>
<td>(0.022)</td>
<td>(249.4)</td>
<td>(112.1)</td>
<td></td>
</tr>
<tr>
<td>fat</td>
<td>0.039</td>
<td>0.0053</td>
<td>0.12</td>
<td>0.076</td>
<td>205.4</td>
<td>10019.4</td>
<td>455</td>
</tr>
<tr>
<td></td>
<td>(0.036)</td>
<td>(0.0045)</td>
<td>(0.1)</td>
<td>(0.086)</td>
<td>(32.88)</td>
<td>(270.5)</td>
<td></td>
</tr>
<tr>
<td>muscle</td>
<td>0.053</td>
<td>0.0049</td>
<td>0.19</td>
<td>0.12</td>
<td>692</td>
<td>8157.2</td>
<td>359.3</td>
</tr>
<tr>
<td></td>
<td>(0.034)</td>
<td>(0.0052)</td>
<td>(0.057)</td>
<td>(0.063)</td>
<td>(57.15)</td>
<td>(106.5)</td>
<td></td>
</tr>
<tr>
<td>tumour core</td>
<td>0.18</td>
<td>0.015</td>
<td>0.26</td>
<td>0.12</td>
<td>1083</td>
<td>10871.1</td>
<td>140.3</td>
</tr>
<tr>
<td></td>
<td>(0.069)</td>
<td>(0.014)</td>
<td>(0.082)</td>
<td>(0.018)</td>
<td>(147.5)</td>
<td>(46.42)</td>
<td></td>
</tr>
<tr>
<td>tumour rim</td>
<td>0.36</td>
<td>0.01</td>
<td>0.3</td>
<td>0.13</td>
<td>821.5</td>
<td>10500.1</td>
<td>140</td>
</tr>
<tr>
<td></td>
<td>(0.11)</td>
<td>(0.17)</td>
<td>(0.059)</td>
<td>(0.015)</td>
<td>(180)</td>
<td>(46.21)</td>
<td></td>
</tr>
<tr>
<td>liver</td>
<td>0.57</td>
<td>&lt; 0.001</td>
<td>0.33</td>
<td>0.18</td>
<td>672</td>
<td>9249.94</td>
<td>331</td>
</tr>
<tr>
<td></td>
<td>(0.25)</td>
<td>(&lt; 0.001)</td>
<td>(0.14)</td>
<td>(0.1)</td>
<td>(200)</td>
<td>(116.5)</td>
<td></td>
</tr>
<tr>
<td>aorta</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>989.5</td>
<td>11898.5</td>
<td>54.83</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>(252.2)</td>
<td>(19.8)</td>
<td></td>
</tr>
</tbody>
</table>

**Table 3.3:** Ground truth values for the organs described using the extended Kety model, estimated from the 6 acquired data sets analysed in Chapter 5. Estimated values for the liver are also shown for information even though the liver is simulated using the Matern model. The mean value for the 6 patient data sets is shown with the standard deviation in brackets. The bone corresponds to marrow and the kidney region includes both cortex and medulla. The $S_0$ values are the median values from Patient 5 as $S_0$ is visit dependent.

<table>
<thead>
<tr>
<th>$k_{1a}(\text{min}^{-1})$</th>
<th>$k_{1b_pv}(\text{min}^{-1})$</th>
<th>$k_2(\text{min}^{-1})$</th>
<th>$\tau_{aif}(\text{min})$</th>
<th>$\tau_{pif}(\text{min})$</th>
<th>number of voxels</th>
</tr>
</thead>
<tbody>
<tr>
<td>liver</td>
<td>0.61</td>
<td>0.31</td>
<td>2.9</td>
<td>0.12</td>
<td>0.33</td>
</tr>
<tr>
<td></td>
<td>(0.35)</td>
<td>(0.43)</td>
<td>(1.3)</td>
<td>(0.07)</td>
<td>(0.09)</td>
</tr>
</tbody>
</table>

**Table 3.4:** Ground truth for the liver described using the Matern model. The mean value for the 6 patient data sets is shown with the standard deviation in brackets.

<table>
<thead>
<tr>
<th>$T_1(\text{ms})$</th>
<th>$S_0$</th>
<th>number of voxels</th>
</tr>
</thead>
<tbody>
<tr>
<td>liver</td>
<td>672</td>
<td>9249.94</td>
</tr>
<tr>
<td></td>
<td>(200)</td>
<td>(116.5)</td>
</tr>
</tbody>
</table>

**Table 3.5:** Ground truth for the liver MRI parameters. The mean value for the 6 patient data sets is shown with the standard deviation in brackets. The $S_0$ value is the median value from patient 5 as $S_0$ is visit dependent.
As separate ground truth values were required for tumour core and rim regions, the median $IAUC_{60}$ was calculated for each tumour and used to sub-segment each VOI. Voxels with values lower than the median were labelled as core. This, on the whole, gave spatially contiguous regions that were classified as core and rim, see Figure 3.10.

A functional form of a population AIF [40] was used as input to the both the Kety and Materne model. For the Materne model a PIF is also required and was estimated from the population AIF using the method described in Section 5.2. Contrast agent concentration values from the AIF are calculated using an implementation of the functional form. The PIF is input to the PhantomGenerator as a text file containing the contrast agent concentration values in the plasma at the required temporal resolution (4.97 s to match the temporal resolution of the acquired data sets analysed, see Table 5.6). When the delay ($\tau_{pif}$, see Table 3.4) is applied to the PIF, linear interpolation is used to calculate the plasma concentration at intermediate points.

The vasculature does not require a tracer kinetic model. Contrast agent concentration in plasma ($C_p$) is converted to concentration in whole blood ($C_b$) by accounting for the haematocrit using Equation (2.3). $C_b$ is then converted to signal intensity using Equation (2.8) and Equation (2.10). For the vena cava the portal input function was used, rather than the AIF, as it provides a closer representation to the multiple delays and dispersions that occur as the initial bolus of contrast agent passes through multiple tissue beds before reaching the vena cava via the venous return system from each organ. A pre-bolus time of 29.82 s was used with an offset of 0 (no delay between injection and the arrival of the contrast agent concentration) for the aorta and liver vasculature. For the vena-cava an offset of 0.12 min was used as this equals the delay in the liver and this gave a visual appearance that was close to that of acquired data.

### 3.5.1.1 Noise assessment

A noise assessment was performed to estimate an appropriate noise level to apply to the synthetic data. VOIs were drawn by an experienced research radiographer (Yvonne Watson) for liver and para-spinal muscle regions on the 6 acquired DCE-MRI data sets of liver metastases described in Chapter 5.

For each voxel within the VOIs the mean and standard deviation of signal intensity
Figure 3.10: Axial slices through the analysed tumour VOI in each of the six patient data sets. The slice number is shown above each image with lower numbers corresponding to the inferior slices (only a section of the image around the tumour is shown). Voxels with an $IAUC_{60}$ value lower than the median are labelled as core (shown in green). Voxels with an $IAUC_{60}$ value higher than the median are labelled as rim (shown in red).
values was calculated across the pre-contrast time points (not including the first time point as steady-state may not yet have been reached). The number of pre-contrast time points used ranged between 5 and 7 with a median of 6.5. The SNR for each voxel is then calculated as \( \text{SNR} = \frac{\text{mean}}{\text{standard deviation}} \). For each VOI the mean SNR across the voxels is calculated, followed by the mean across the patients. The mean SNR for the liver VOIs ranges from 5.60 to 11.86 with a mean of 8.80 across the patients. The mean SNR for the muscle VOIs ranges from 3.80 to 20.60 with a mean of 12.59. The mean standard deviation in the muscle is less than in the liver in all patients with a mean decrease of 61%. As the muscle VOI was located in para-spinal muscle and the patients are supine the difference in standard deviation between the muscle and the liver could be partly attributed to the liver being affected more by motion than the muscle.

### 3.5.2 PhantomGenerator output

A generated synthetic DCE-MRI time series (using the SPGR pulse sequence) is presented in Figure 3.11. The ground truth parameters are documented in Table 3.3, Table 3.4 and Table 3.5. The acquisition parameters are listed in Table 5.6, except a flip angle of 30° was used. Zero mean Gaussian noise with a standard deviation that gives an SNR of approximately 7 in liver tissue was used.

The contrast agent can be clearly seen in the aorta and liver vasculature on the 8th time point. The spleen starts to brighten on the 9th time point when the contrast agent also enters the inferior vena cava, but at a much lower rate than in the aorta as this is being modelled using a PIF estimated from the population average AIF (see Section 4.6). The signal intensity in the liver starts to increase by the 10th time point reaching a peak around the 12th time point. The tumour core can be clearly distinguished from the liver in time point 11, but the tumour rim is less easy to see. The tumour core and rim and liver follow the signal intensity curves shown in Figure 3.7(a).

To demonstrate the flexibility of the PhantomGenerator, we have also generated images for the same anatomy as shown in Figure 3.11 but with the inversion recovery pulse sequence (see Equation (3.1) [100]) often used for \( T_1 \) estimation. (Equation
Figure 3.11: Slice 9 from a synthetic time series generated using organ masks based on an acquired CT data set. The acquisition time is shown above each image with the time point number in brackets. The signal intensity is relative and comparable across all time points. The numbered arrows label the tissues as follows: 1) aorta, 2) fat, 3) spleen, 4) liver, 5) inferior vena-cava, 6) tumour core, 7) muscle, 8) stomach and 9) bone.
(3.1) assumes that \( TE \ll T_2 \).

\[
S_{TI} = S_0 \left( 1 - 2e^{-T_I/T_1} + e^{-TR/T_1} \right)
\]  

(3.1)

This flexibility is provided by the PulseSequence interface in the SignalGenerator package (see Figure A.4). Figure 3.12 shows slice 9 from 5 images generated with different inversion times ranging from 50 to 5000 ms. A TR of 5500 ms and a noise standard deviation of 400 were used to generate the images. Figure 3.12(f) shows the \( T_1 \) map estimated from the generated inversion recovery images. The mean \( T_1 \) value in the liver VOI (see Figure 6.7) is 676 ms, which is a close approximation to the ground truth value of 672 ms (see Table 3.5). The mean \( T_1 \) values in the tumour VOI is 909 ms, which lies between the ground truth values for the tumour rim and core of 822 and 1083 ms respectively (see Table 3.3).

![Image](image_url)

**Figure 3.12:** Figures (a) - (e) are images generated using the inversion recovery pulse sequence (Slice 9 is shown). The anatomy is based on the same masks used to generate the SPGR images in Figure 3.11. The inversion time is shown below each image. The colour-bar in (e) (Signal Intensity) applies to figures (a)-(e). Figure (f) shows the \( T_1 \) values estimated using images (a) - (e).

Figure 3.13 shows fitted inversion recovery curves to single voxel signal intensity
values for the tumour rim and core and liver with estimated $T_1$ values of 851 ms for tumour rim, 1078 ms for core and 671 ms for liver. The difference to the ground truth values of 822 ms, 1083 ms, and 672 ms (see Table 3.3) respectively can be accounted for by noise and also possibly by PVEs for the tumour core and rim.

![Fitted curves for the inversion recovery signal intensity values for a voxel in (a) tumour core, (b) tumour rim, and (c) liver. The ground truth (noise free) curve is shown alongside the fitted curve and the generated signal intensity values.](image)

**Figure 3.13:** Fitted curves for the inversion recovery signal intensity values for a voxel in (a) tumour core, (b) tumour rim, and (c) liver. The ground truth (noise free) curve is shown alongside the fitted curve and the generated signal intensity values.

### 3.6 Summary

In this chapter we have described the design of the PhantomGenerator. It consists of four packages (Physiology, SignalGeneration, ImageGeneration, and Time-Series) that are used to generate the synthetic images and the PhantomConfiguration package that is responsible for reading in the configuration file and command line and configuring the PhantomGenerator for the user specified imaging scenario. The flexibility and extensibility of the design has been highlighted to demonstrate that the software can be easily extended to other imaging scenarios. For example, a CT SignalGeneration package could be implemented or an additional tracer kinetic model that describes the kidneys including extraction into the tubules [6] could easily be added.

Output of each of the software modules has been presented to demonstrate the current available implementations and the capability of the phantom to easily switch between these implementations. For example, contrast agent concentration curves are produced for the extended Kety model and the Materne model with both a pop-
ulation and a bi-exponential AIF. Finally, we presented a synthetic DCE-MRI time series with realistic anatomy based on segmentation of a CT data set and ground truth values derived from acquired data. To further demonstrate the flexibility of the PhantomGenerator we presented images generated with the same anatomy but using the inversion recovery rather than the SPGR pulse sequence.

We have also described the software development methodology used for designing, implementing and testing the PhantomGenerator. Using such a methodology is important for giving confidence that the algorithms used to generate the synthetic data are implemented correctly and also to ensure that the design and implementation can be easily extended without affecting the quality of the code base.

Motion emulation is required to produce synthetic data that can be used to assess registration algorithms and also to test the robustness of tracer kinetic model fitting in tissues subject to respiratory motion, for example. The PhantomGenerator has been designed so that a changing anatomical definition can be read in for each time point and in Chapter 4 we describe the MotionEmulator, an application which produces tissue masks for each time point which can be used as input to the PhantomGenerator. The MotionEmulator and PhantomGenerator applications are then combined to produce a synthetic DCE-MRI data set with realistic anatomy and motion which we then compare with an acquired DCE-MRI data set.
Chapter 4

Emulating motion

4.1 Introduction

In Chapter 3 we described the design and development of the software phantom generator (PhantomGenerator) and demonstrated how the PhantomGenerator can be used to produce synthetic time series images from ground truth model parameters. We presented a synthetic DCE-MRI liver tumour data set with quasi-realistic anatomy and ground truth values derived from acquired data. In Chapter 3 we emulated static tissue structures but in reality breathing and other physiological sources of motion cause abdominal organs to move, altering the tissue-to-voxel mappings for images at different time points in the DCE data. This chapter describes the addition of organ motion, which is required to test the robustness of DCE-MRI time series analysis techniques. In later chapters we evaluate the effects of motion on model fitting and model selection, and assess the possible benefits of image registration (Chapter 6). As with the PhantomGenerator, the motion emulation techniques can also be used to generate synthetic data sets for other modalities, such as DCE-computed tomography (CT) and oxygen-enhanced MRI which may also be subject to motion.

Possible methods for characterising motion were discussed in Section 2.6.3. The displacement maps from multi-organ finite element modelling (FEM) [63] provide a description of breathing motion that includes non-linear organ deformations and that is sufficiently complex to mimic most effects of respiratory motion. Displacement maps and organ masks from this method for one patient data set (referred to as the University Health Network, Toronto (UHN) data set) have been used as the
input to the motion emulator application (MotionEmulator). However, any set of displacement maps and masks could be used to give a number of different anatomical and motion representations.

The motion emulation module has been written as a separate software application to the PhantomGenerator to simplify the number of input parameters and to allow the PhantomGenerator to be run multiple times for the same motion parameters. The output of the MotionEmulator is a mask for every organ at every time point that can then be read in by the PhantomGenerator.

In this Chapter we describe how dense displacement fields are applied to organ masks (Section 4.2) and how displacements at intermediate points in the breathing cycle are calculated using an acquired respiratory trace (Section 4.3). We demonstrate the function of the MotionEmulator firstly through simple examples (Section 4.5.1) and then by using organ masks and displacements from the UHN data set and an acquired respiratory trace (Section 4.5.2). Lastly, we describe how the MotionEmulator is combined with the PhantomGenerator to generate a synthetic DCE-MRI data set with motion emulation using the UHN masks and displacement maps (Section 4.6). We then compare the generated time series to an acquired data set.

4.1.1 Acknowledgements

This chapter incorporates data provided by other researchers and uses standard algorithms from a locally written software library.

Thanks to Kristy Brock for the organ masks based on acquired contrast-enhanced CT data, the associated displacement maps and the end-inhale and end-exhale contrast-enhanced CT images (the UHN data set). Thanks also to Alex Morgan for the MRI lung imaging data including the respiratory trace and the identification of the maximum inhale and exhale images within the time series. Lastly, thanks to Tim Cootes for the use and explanation of the \texttt{vq3d} library used for applying the displacement maps (see Appendix C).
4.2 Applying the displacement maps

A dense displacement map for each of the x, y, and z directions, produced using the multi-organ FEM based registration described in Section 2.6.4, was provided by Kristy Brock. The displacement maps describe the deformation required to transform the end-exhale image to match the end-inhale image, where both images were acquired during breath-hold. For example, each voxel within the z displacement map contains the distance through which that voxel was moved in the cranio-caudal direction between end-exhale and end-inhale (see Figure 4.1). The displacement maps have a matrix size of 512 x 512 x 120 and voxel dimensions of 0.98 mm x 0.98 mm x 2.5 mm.

![Figure 4.1: Slice 82 through the displacement map for (a) the x direction (left-right), (b) the y direction (anterior-posterior) and (c) the z direction (cranio-caudal) and (d) the contrast-enhanced CT image at end-exhale for the same slice. A positive displacement represents movement to the right, anterior and upward in the x, y and x directions respectively (displacements are in cm). The slices are presented according to radiological convention.](image)

The purpose of the MotionEmulator is to generate simulated images at sampled
Chapter 4. Emulating motion

time points throughout the full breathing cycle. This is achieved by applying the
displacement maps (scaled at each time point by a displacement fraction as described
in Section 4.3) to a set of organ masks defined on the end-exhale image and generating
warped masks for each time point of the dynamic series. The displacement maps could
be applied directly to the end-exhale organ masks to give the end-inhale masks (the
forward transform). However, this could lead to two scenarios where the value in a
voxel in the warped mask would be unknown, see Figure 4.2(a). Firstly, two voxels
from the source image (end-exhale) could be displaced to the same voxel within the
destination image (end-inhale). Secondly, a destination voxel may not receive content
from any of the source voxels. To avoid these two cases, the inverse transform is used.
In this case, a displacement vector points to the centre of every voxel in the destination
image, see Figure 4.2(b). If the start of the vector is located between the centre of
two voxels in the source image, linear interpolation between the voxels in the source
image is used to determine the value in the destination voxel.

![Forward transform](image1)
![Inverse transform](image2)

**Figure 4.2:** (a) Problems encountered when using the forward transform: voxels without
any information content are shown as white on the destination image and voxels with
information from a number of source voxels are shown in dark red. (b) Using the inverse
transform avoids these issues.

The inverse transform is estimated using a regular tetrahedral mesh resulting in a
piecewise affine transform computed using barycentric co-ordinates (see Section C.1)
and then applied to the end-exhale input masks as described in Appendix C. The
bodywise centred cubic (BCC) grid used to generate the tetrahedral mesh (see Ap-
pendix C) is defined to cover the full image volume, but with a half voxel gap at all
edges. The generated inhale masks are then cropped to remove any edge effects from
warping due to the boundaries of the mesh sitting within the image (rather than fully
filling it) and due to the transform requiring information from outside of the image,
see Figure 4.3. The amount of cropping required can be assessed by applying the full displacement and visually checking the warped images as shown in Figure 4.3.

Figure 4.3: Edge effects from applying the full displacement maps to the liver mask. A tetrahedral mesh from a BCC mesh of 119 x 119 x 69 nodes was used. Slice 26 is the most inferior slice and the displacements are in an inferior direction. Slices 32 - 35 are not shown as they only contain zeros. Slice 26 is free from edge effects and slices below this are therefore not shown.

Approximating the inverse transform may result in displacements that are not exact. However, using the forward transform would also require approximations due to the problems described above. As we aim to create synthetic data which includes motion that is sufficiently complex to test analysis techniques, an exact match to the displacement maps is not necessary. Instead, the estimated displacements should result in deformations which approximate the effect of respiratory motion seen in acquired data sets.
4.3 Breathing cycle

The position in the breathing cycle at which each image in a time series is acquired may fall at an intermediate point between end-inhale and end-exhale, see Figure 4.4. As the displacement maps only describe the displacement between the end points of the respiratory cycle, a mathematical description of a breathing cycle is required to calculate the fraction of the full displacement to apply at each time point. We have used a respiratory trace (provided by Alex Morgan) that was recorded during free breathing MRI lung imaging using respiratory bellows to inform this mathematical function. Respiratory bellows is an air pillow that is strapped to the patient’s chest during the MRI scan. The pressure changes in the pillow are recorded every 0.002 seconds. The respiratory trace used is shown in Figure 4.5. The general physical characteristics of the UHN patient were assessed from the CT images and an attempt to find a matching lung MRI data set was made (see Figure 4.6) to gain a relevant respiratory trace.

![Figure 4.4](image.png)

**Figure 4.4:** Acquisition time points (red circles) with a temporal resolution of 4.97 s placed on a simplified sinusoidal breathing pattern with a rate of 15 breaths per minute.

The acquisition period of the respiratory trace is shorter than a typical DCE-MRI time series. To extend the trace it was truncated to a point that matched the starting position, allowing it to be looped. The truncation point is shown with a red circle in Figure 4.5.

The UHN patient data was collected using breath-hold at end-inhale and end-exhale. Whilst the patients were asked to remain within their normal at-rest breathing range, the excursions are likely to be greater than those seen when free-breathing. The displacements were therefore scaled to the excursion range seen in the free breathing MRI data.
Chapter 4. Emulating motion

To calculate the scaling value, the excursion of the top of the right hemi-diaphragm between end-exhale and end-inhale was measured on both the UHN data and the MRI lung imaging data set, see Figure 4.6. The end-exhale and end-inhale images from the MR data set were selected (by Alex Morgan) by identifying the images with the maximum and minimum positions of the centre of the right hemi-diaphragm from all the images in the data set (acquired throughout a number of breathing cycles during free-breathing). The MRI data set only consisted of one coronal slice. Therefore, the corresponding coronal slice (slice 256 of 512) on the CT data set was identified by an experienced research radiographer (Yvonne Watson). An excursion of 20 mm was measured for the UHN CT data and 17.5 mm for the MRI data, giving a scaling factor of 0.875 to be applied to the displacements.

An offset was also applied so that the displacements were not anchored to the maximum exhale position, which is unlikely to be seen in free-breathing. This offset was calculated using the reserve volumes from Martini et al. [14]. The inspiratory reserve volume is the amount of air that can be further voluntarily inhaled after the end-inhale point is reached during quiet breathing and the expiratory reserve volume is the equivalent amount of air that can be expelled after the end-exhale point. For a female, the average reserve inhale and exhale volumes are 1900 and 700 ml respectively. Therefore, the exhale reserve is a fraction of 0.27 of the total reserve. The displacements are being scaled to 0.875 of their full value to match the excursions seen in free breathing, leaving 0.125 of the displacement value between the end-inhale and end-exhale points of the free breathing cycle and the full displacement. As the expiratory reserve volume is 0.27 of the full reserve volume, 0.27 of the remaining 0.125 of the displacement value (0.034) was taken as the displacement between the

Figure 4.5: Respiratory trace acquired using respiratory bellows during MRI lung imaging. The black circle indicates the starting point and the red circle indicates the truncation point used to allow the trace to be looped.
Figure 4.6: Measurement of the right hemi-diaphragm displacement between end-inhale and end-exhale on equivalent slices on the MRI and CT images. The red line indicates the position at end-exhale and the green line indicates the position at end-inhale.
free breathing end-exhale point and the full displacement, see Figure 4.7.

Figure 4.7: The normalised acquired respiratory trace, which has been offset by 0.034 from the maximum exhale position and scaled to 0.875 of the full displacement. The red and green dotted lines indicates the 0.034 minimum displacement fraction and the 0.909 maximum displacement fraction that prevent full displacement being reached. The red stars indicate the position of image acquisitions with a 4.97 s temporal resolution.

For each time point, the offset and scaled respiratory trace was used to determine the fraction of the displacement map to apply. This gives a non-linear relationship between the magnitude of the displacement and time. However the direction of the displacement vector for each voxel is constant during inhale and reverses for exhale, see Figure 4.8(a). Whilst this may not exactly match the motion of organs due to breathing (Figure 4.8), we do not have data for intermediate time points in the breathing cycle and this method will still result in a varying tissue-to-voxel mapping that will provide a relevant test to analysis techniques.

4.4 Software development process

The MotionEmulator was developed under the same processes as described in Section 3.2. The design of the MotionEmulator is described in Section A.2.

The \texttt{vq3d} library (see Appendix C), which is based on the open-source \texttt{VXL} libraries, was developed locally by Tim Cootes and members of his research group and was unit tested by the developers. Along with the unit testing of the MotionEmulator this gives adequate confidence in the correctness of these libraries. Output using
Figure 4.8: Schematic representations of constant and non-linear voxel displacement direction between end-inhale and end-exhale. The red box is the voxel position at end-exhale and the green box is the voxel position at end-inhale. The voxel is moved towards the front of the body in a caudal direction. The MotionGenerator assumes constant displacement direction as shown (a). (b) - (d) show possible non-linear motion patterns.
simple examples is shown in Section 4.5.1 to demonstrate the correct functioning of the MotionEmulator.

4.5 MotionEmulator output

4.5.1 Simple examples

A simple input mask and displacement maps were created to demonstrate the functionality of the MotionEmulator. Figure 4.9 shows an input mask warped by various displacement maps. The BCC grid used to generate the tetrahedral mesh required to apply the warp (see Appendix C) had 10 nodes in the x and y directions.

![Figure 4.9](image)

Figure 4.9: (a) shows the input mask. (b) is the warped mask with uniform x and y displacement maps of 2 voxels. (c) is the warped mask with uniform x and y displacement maps of 1.5 voxels. (d) shows the warped mask from applying the displacement map shown in (e) in both x and y directions. (e) is a displacement map with a uniform gradient of 1.8 to 9.45 voxels in the region of the mask. In (b) - (d) the original mask is shown as a red overlay.
The displacement field shown in Figure 4.9 (e) was used with a sinusoidal breathing pattern (Figure 4.10) to produce warped masks every 12 seconds for a breathing rate of 1 breath per minute. Time points 1 to 12 are shown in Figure 4.11. The expected warped images are produced for all the examples shown in Figure 4.9 and Figure 4.10.

Figure 4.10: Sinusoidal breathing pattern with a breathing rate of 1 breath per minute and acquisition time points every 12 seconds.

4.5.2 Input derived from acquired data set

The masks (provided by Kristy Brock), defined on the contrast-enhanced CT end-exhale data set, and the associated displacement maps were used as input to the MotionEmulator along with the acquired respiratory trace shown in Figure 4.7, Section 4.3 (provided by Alex Morgan). Using these inputs the MotionEmulator generated a mask for every time point for every organ. From these masks the PhantomGenerator can be used to generate a synthetic DCE-MRI time series with quasi-realistic anatomy and motion of the abdominal organs during breathing that are complex enough to allow subjective comparison to an acquired data set, and to give a relevant test to a registration algorithm (Chapter 6).

4.5.2.1 Masks and displacement maps

The following organ masks from the UHN data set are likely to be present in a typical field of view used for imaging the liver tumour that is present in this data set: bowel, duodenum, external body mask, left kidney, liver, oesophagus, right kidney, spinal
Figure 4.11: Warped masks produced using the sinusoidal breathing pattern in Figure 4.10 with the original (unwarped) mask as a red overlay. The displacement map shown in Figure 4.9(e) was used for the x and y displacements. The displacement fraction is shown above each image.
cord, spleen, stomach, tumour.

Masks for bone, muscle, liver vasculature, aorta and vena cava were not defined as part of the FEM process. Adding the bone and muscle masks gave the synthetic data more apparent realism and allowed for easier subjective comparison to acquired data. Enhancement of the major blood vessels is a noticeable feature of DCE-MRI time series (the smaller vessels are not easy to identify due to partial volume effects (PVEs)) and they can also provide important information for registration algorithms. It would also be an essential requirement if testing an automated AIF extraction procedure (for example, the method developed by Parker et al. [39]).

The additional masks were created by thresholding the contrast-enhanced end-exhale CT images. Erosion then dilation operations were applied to the liver vasculature mask to remove stray voxels that were likely to be due to noise. The erosion and dilation was performed on each slice using the `imdilate` and `imerode` Matlab functions with a $3 \times 3$ rectangular kernel created using the `strel` function. Using thresholding to generate the muscle mask from CT data did not exclusively identify muscle tissue. However, using the generated ‘musclePlus’ mask results in synthetic data that more closely match the appearance of acquired images. Example slices of the bone, musclePlus and liver vasculature masks are shown in Figure 4.12.

![Figure 4.12: Example slice (84) through (a) the bone, (b) the musclePlus, and (c) liver vasculature masks. In (c) the liver is shown in white, the liver vasculature in green, the aorta in red, and the inferior vena cava in turquoise.](image)

As the additional masks were not defined for the FEM modelling, the displacement maps do not include displacement vectors specifically associated with their motion during the breathing cycle. The vasculature within the liver is assumed to move...
as part of the liver, and is therefore warped by the displacement maps in the same manner as the other organs. However, the vena cava and aorta are assumed to be stationary. (In the acquired data shown in Figure 4.23 the aorta appears to remain in the same position. However, the vena cava is not always easily identifiable due to the similarity of its signal intensity to the liver and the noise within the images.) To keep the aorta and vena cava stationary in the synthetic data the same displacement fraction was used for every time point. A displacement fraction of 0.47 was selected as this corresponds to the midway point of the scaled and offset respiratory trace which ranges between 0.034 and 0.909 of the full displacements (see Section 4.3).

If a moving mask overlaps a stationary mask the fraction of each tissue in the voxel is determined by the priority value assigned to each tissue (input to the PhantomGenerator in the config file). The priority values for the tissues are shown in Table 4.1. Higher priorities are allocated the fraction of a voxel defined by their mask. For example, if liver tissue moves into a voxel containing aorta and the fractions add to a value greater than one, the fraction of aorta will remain unchanged, and the fraction of liver tissue will be reduced so that the summed fractions of the two tissues equals one. (See Section A.1.3 for more details.)

The bone and musclePlus masks lie in the internal body mesh used for the FEM and were allowed to move as defined by the displacement maps. This clearly does not provide an accurate representation of their motion, however the images produced are adequate for the purpose of assessing a registration focused on the liver tumour and for subjective visual evaluation by comparison to an acquired data set.

Separate masks for tumour core and rim regions were defined for generating the DCE-MRI synthetic data. Whilst tumour structure is likely to have a higher degree of heterogeneity, these two regions, which have distinct vascular characteristics, are often seen on images. The tumour volume of interest (VOI) defined for the FEM

<table>
<thead>
<tr>
<th>Priority</th>
<th>Mask</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>fat</td>
</tr>
<tr>
<td>1</td>
<td>musclePlus</td>
</tr>
<tr>
<td>2</td>
<td>liver, spleen, kidney, spinal cord, bowel, duodenum, oesophagus, stomach, bone</td>
</tr>
<tr>
<td>3</td>
<td>tumour rim</td>
</tr>
<tr>
<td>4</td>
<td>tumour core, aorta, vena cava, liver vasculature</td>
</tr>
</tbody>
</table>

Table 4.1: Priority values for organ masks.
covered an area of voxels that were darker than liver tissue on the contrast-enhanced CT image (see Figure 4.13). However, surrounding this hypointense region is a ring of tissue that appears brighter than other areas of the liver. The increased intensity in this region could be caused by leakage of contrast agent from erratically formed vasculature in the outwardly growing fraction of the tumour where angiogenesis is most active (see Section 2.2). It may therefore correspond to the tumour rim region, although it could also be due to abnormal vasculature around the tumour. In either case the vasculature in this region may form the target for anti-angiogenic drugs and is therefore an important region to model.

An experienced research radiographer (Yvonne Watson) defined a tumour VOI on the end-exhale contrast-enhanced CT image, remaining blinded to the region drawn for FEM. This new region included the surrounding hyper-intense region. Therefore, the tumour VOI from the FEM was used to define tumour core, and the difference between this VOI and the second larger region was used to represent tumour rim (see Figure 4.13). Again, whilst the defined regions are unlikely to exactly represent the underlying histology, the generated images will provide adequate test cases for post-acquisition algorithms.

(a) Contrast-enhanced CT  (b) Core VOI  (c) Rim VOI

**Figure 4.13:** (a) shows a slice through the end-exhale contrast-enhanced exhale CT image. (b) shows the tumour VOI defined for the FEM in red. Note that the VOI in (b) corresponds to a hypointense area in the liver in (a). (c) shows the tumour rim VOI in red. Note that the VOI in (c) includes the hyperintense region that surrounds the FEM tumour VOI.

The tumour core area has been explicitly modelled within the FEM process and is assumed to be much more rigid than liver tissue with a Young’s modulus of 78 kPa compared with a value of 7.8 kPa for the liver mesh [63]. However, the tumour rim lies within the displacements defined for the liver. This assumption is acceptable as
this region may be a growing area of the tumour which has not yet progressed to have the same physiological characteristics that give the core its increased rigidity.

An example slice through the displacement maps is shown in Figure 4.1. Histograms of the displacements in the tumour core and rim regions and the liver region are shown in Figure 4.14. Median and interquartile ranges are shown in Table 4.2. Note that the displacements have been scaled by a factor of 0.875 to match the maximum displacements seen during free breathing (see Section 4.3).

The displacements are similar in amplitude to those reported by Rohlfing [61], but in the cranio-caudal direction are greater than for the case reported by Buonaccorsi [9] which uses the same acquisition protocol and is the same disease group as is being emulated in the synthetic data, see Section 2.5.1. As noted in Section 2.5.1, this may be due to the registration algorithm being unable to fully replicate the actual deformations. It should also be noted that a variation in breathing displacements is seen between patients [61] and it may be possible for the presence of multiple tumours or a single large tumour to impede the motion of the diaphragm, so an exact match between different data sets is not expected. The displacement maps in the UHN data set are from a patient with a liver tumour and have been scaled for free-breathing and so provide data for generating synthetic images with plausible deformations.

<table>
<thead>
<tr>
<th></th>
<th>liver</th>
<th>rim</th>
<th>core</th>
</tr>
</thead>
<tbody>
<tr>
<td>x</td>
<td>0.01</td>
<td>-0.09</td>
<td>-0.06</td>
</tr>
<tr>
<td>y</td>
<td>0.39</td>
<td>0.21</td>
<td>0.19</td>
</tr>
<tr>
<td>z</td>
<td>1.19</td>
<td>1.17</td>
<td>1.17</td>
</tr>
<tr>
<td>median (cm)</td>
<td>0.15</td>
<td>0.08</td>
<td>0.04</td>
</tr>
<tr>
<td>interquartile range (cm)</td>
<td>0.08</td>
<td>0.09</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Table 4.2: Displacement values for tumour and liver regions.

4.5.2.2 Memory restrictions (practical considerations)

Approximating the inverse transform initially caused the MotionEmulator application to fail as more memory was requested than was available. This problem was overcome by cropping the displacement maps (the input exhale masks were also cropped to match); optimising the code to reuse already allocated memory when approximating the displacements in each of the x, y and z planes; and running the application on a 64 bit machine so that more memory was available.
Figure 4.14: Histograms of (a) liver, (b) tumour rim and (c) tumour core displacements for the x, y, and z directions between end-exhale and end-inhale. The displacements have been scaled by a factor of 0.9 to match maximum displacement seen during free breathing.
The masks and displacement maps were cropped to 280 x 260 x 35 from an original size of 512 x 512 x 120, with a starting position of the cropped image at voxel 120, 170, 65. A tetrahedral mesh from a BCC grid with 119 x 119 x 69 nodes was used (see Appendix C).

4.5.2.3 Output

Warped masks were produced at 75 time points with a 4.97 s temporal resolution. The displacement fractions, sampled from the acquired respiratory trace, for the time points are shown in Figure 4.15. The section of the respiratory trace shown in Figure 4.16 demonstrates that more time is spent around the end-exhale point than the end-inhale point. Therefore, a larger proportion of time points have lower displacement fractions, as seen in Figure 4.15(a).

![Figure 4.15](image.png)

**Figure 4.15:** Displacement fraction generated from the scaled and offset acquired respiratory trace, shown in (a) as a histogram and (b) for each time point.

![Figure 4.16](image.png)

**Figure 4.16:** A section of the acquired breathing trace demonstrating the increased time spent around the maximum exhale point in comparison to the maximum inhale point.
Images from the 9th to 12th time points are shown in Figure 4.17 for the tumour core and Figure 4.18 for the liver. Note that the warping produces PVEs at the mask edges.

\textbf{Figure 4.17:} (a) - (d) show warped tumour masks (slice 13) from the 9th to 12th time points, corresponding to displacement fractions of 0.75, 0.06, 0.88, and 0.39.

\textbf{Figure 4.18:} (a) - (d) show warped liver masks (slice 13) from the 9th to 12th time points, corresponding to displacement fractions of 0.75, 0.06, 0.88, and 0.39.

\section*{4.6 A synthetic DCE-MRI data set with motion emulation}

To generate DCE-MRI synthetic data with motion requires both the MotionEmulator and PhantomGenerator applications. The process used for generating the synthetic data is shown in Figure 4.19.
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**Figure 4.19:** Process for generating synthetic DCE-MRI data with motion emulation
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The MotionEmulator warped the organ masks (defined on the end-exhale contrast enhanced CT image in the UHN data set) for each organ, using the associated displacement maps and the acquired breathing cycle trace, to generate a mask for each organ at each time point. The input masks were cropped to avoid memory allocation issues and the output masks were also cropped to remove edge effects from warping. Example masks produced by the MotionEmulator for the tumour and liver are shown in Figure 4.17 and Figure 4.18.

The time series of masks generated by the MotionEmulator formed the input to the PhantomGenerator along with the ground truth values for the tracer kinetic model parameters and MRI properties for each tissue (see Chapter 3.4). The signal intensity time courses were generated using imaging protocol acquisition parameters documented in Table 5.6, but with a flip angle of 30° for the dynamic series. The PhantomGenerator downsampled the generated images, as described in Section A.1.3, to give the required voxel dimensions as the CT data on which the organ masks were defined have a higher resolution (0.98 mm x 0.98 mm x 2.5 mm voxel size) than that required for the synthetic DCE-MRI data (2.93 mm x 2.93 mm x 4 mm). Zero mean Gaussian noise with a signal to noise ratio of approximately 7 in pre-contrast liver tissue (which is within the range measured on acquired data sets, see Section 3.5.1.1) was then added to the images. All the slices from time point 12 (post-contrast) are shown in Figure 4.20 with a multiplanar reconstruction in Figure 4.21.

Selected images from the time series are shown in Figure 4.22. The first image shown (time point 7) is pre-contrast. In time point 8 the contrast agent arrival can be seen in the aorta and liver vasculature. In time point 10 the contrast agent has clearly reached the liver. In time point 11, the liver continues to brighten and the contrast agent can also be seen in the vena cava. The tumour core remains darker than the liver throughout the early part of the time series but in the last image of the time series (time point 75), where contrast agent has diffused into the core, it has a similar intensity to the liver.

The effects of motion are noticeable as the different features move in and out of the slice (the main direction of the motion is through-plane). For example, different parts of the liver vasculature are present on time points 8 and 9. Through-plane motion also gives the impression that a tissue is changing shape through the time series. For example, the bowel section to the left of the liver appears to change shape, as does the tumour.
Figure 4.20: Slices from a synthetic volume at time point 12 (post-contrast). The slice number is shown above each image. The purple arrows indicate the tumour rim, the green arrow indicates the tumour core, the red arrow indicates the aorta and the yellow arrow indicates the inferior vena cava.
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Figure 4.21: Multiplanar reconstruction from a synthetic volume at time point 12 showing (a) axial, (b) sagittal and (c) coronal slices. The position of the slices are shown by the red cross-hairs.

The synthetic data is compared to an acquired data set (Patient 2, see Chapter 5) in Figure 4.23. The aorta enhances at time point 8 in both the synthetic and acquired data sets. A drop in the intensity is seen within the aorta in both data sets at time point 11 followed by a rise again to time point 13. Enhancement in the vena cava can be seen in the acquired data set at time points 10 and 11 and after time point 12 it becomes indistinguishable from the liver. However, in the synthetic data set it starts to brighten at the 11th time point and remains brighter than the liver throughout the time series. The contrast agent concentration time courses in the inferior vena cava are modelled using a generated hepatic portal input function, and the disparity between the acquired and synthetic data demonstrates that this approach, as expected, is not ideal. The timing of liver enhancement and contrast agent washout are broadly similar in both data sets. The tumour core is indistinguishable from liver in the last synthetic time point but is still visible on the acquired data.

Figure 4.24 compares single voxel contrast agent time courses between the acquired and synthetic data sets. For the acquired data sets two time courses are shown for each tissue to demonstrate the variability seen. The locations of the voxels used in the acquired data set (Patient 2, see Section 5.4.2) are shown in Figure 4.24(f). The voxels for the liver and tumour in the acquired data set lie in the VOIs drawn by an experienced research radiographer (Yvonne Watson), and the locations of the aorta and vena cava voxels were verified as correct by the same radiographer. The tumour was subdivided into rim and core regions using median $IAUC_{60}$ (see Section 3.5.1).

As the ground truth for the synthetic data was derived from the median VOI values from all 6 patient data sets (see Section 3.5.1) an exact match to the time series...
Figure 4.22: Slice 9 from images at time points 7 to 24 and 75 from the synthetic DCE-MRI time series with motion emulation. The acquisition time with the time point number in brackets is shown above the image. The temporal resolution of the series is 4.97 s and the contrast agent is introduced at time point 8.
Figure 4.23: A comparison of acquired and synthetic time series. The title of each image indicates whether it is the synthetic or acquired image, the acquisition time and the time point in brackets. The acquired data set is patient 2 (see Chapter 5) and slice 13 has been used. For the synthetic data set slice 9 has been used. A tumour in each of the data sets is indicated by a red arrow on the 13th time point. The green arrow on the 10th time point indicates phase encoding artifacts.
from a single patient is not expected. However, this comparison is still of interest as it demonstrates that the synthetic data curves are plausible and highlights where differences exist. Good agreement between the acquired and synthetic data sets is seen for both voxels in the tumour rim and one of the voxels in the tumour core and the liver. The difference between synthetic and acquired time courses for one voxel in a region, whilst observing good agreement from a second voxel within the same region, results from generating synthetic data using homogeneous ground truth values. This does not replicate the variability seen in patient data.

The uniform ground truth values for each tissue in the synthetic data are also a possible cause of greater noise on the acquired time courses than for the synthetic data in the tumour core and liver. In the synthetic data, motion may cause a different part of the same tissue which has an identical time course (except for the influence of noise) to move into the voxel, which is not the case for acquired data due to the natural variability of physiological characteristics. However, the tumour rim shows similar noise levels between the synthetic and acquired data sets. In the synthetic data, the tumour rim is a narrower region than the core (see Figure 4.13) and both liver and tumour core may pass through the voxel during the time series. As the PhantomGenerator is a flexible application, it would be possible to generate data sets with greater degrees of inhomogeneity. This is discussed further in Section 4.6.1 and Section 7.2.

The acquired data for the aorta closely follows the synthetic data except for the peak where much higher values are seen in the acquired data. This may be due to in-flow effects [31], which we have not attempted to emulate. Note that this slice was not used for arterial input function (AIF) estimation and the slice used (slice 10, which is inferior to slice 13) gave times courses with peaks much closer to the synthetic data as shown on Figure 4.24(f). As discussed above, the synthetic vena cava is not expected to have a time course which matches that seen in acquired data, as the synthetic contrast agent concentration values have been generated using the portal input function (PIF).

### 4.6.1 Limitations of the synthetic data

The synthetic data set provides ground truth for assessing the model-driven registration algorithm and the effect of the registration on the subsequent model fitting
Figure 4.24: (a)-(e) compare single voxel synthetic and acquired contrast agent time courses. Slice 13 has been used for the acquired data except for the 3rd acquired series in (e), for which slice 10 (which is inferior to slice 13) is used. (f) shows the location of the voxels in the acquired data. The turquoise voxels are the tumour core, the yellow voxels are the tumour rim, the pink voxels are the liver, the red voxels are the aorta, and the blue voxels are the vena cava. The number by each voxel corresponds to the number of the acquired time course in (a)-(e).
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and model selection. The motion, derived from a FEM, is based on acquired data giving non-linear motion that is more complex than the deformations used by most registration algorithms, and therefore it provides a good test for less complex motion transforms. However, some differences can be seen between the synthetic and acquired data sets (see Figure 4.23). One of the most noticeable differences is that the acquired data set contains phase encoding artifacts noticeable as banding near the diaphragm. $B_1$ inhomogeneities, which present as a gradual variation in signal intensity across the image may also affect images, but these are not clearly visible. Other artifacts that are likely to be present in the acquired data are related to the AIF which will be affected by inflow effects [31] and saturation at high signal intensities [29].

Generating synthetic data without these artifacts allows the effect of motion on analysis of the data to be studied without their interference. However, it may be of interest to assess the influence of such artifacts on registration or model fitting, for example. Simulating $B_1$ inhomogeneities would require the input of a flip angle efficiency map to the PhantomGenerator, so a minor design change would be required. Emulating more complex phase encoding artifacts could be achieved by implementing a Bloch equation simulator [101, 102] which would require a substantial addition to the SignalGeneration package. Alternatively, converting the images to k-space and sampling from different points in the breathing cycle could produce the same effect. This would require the implementation of a further module, but would probably be less complex than integrating a Bloch equation simulator.

The number of organ masks within the synthetic data set is limited, and each mask has homogeneous ground truth values. Further organ masks can be included as input to the PhantomGenerator, for example multiple tumour sub-regions. The natural spread of ground truth parameters could be modelled for each tissue type by deriving distributions for each parameter and for each tissue from the patient data sets (see Section 3.5.1) and sampling from these distributions. Combining parameter maps that describe the natural spread of parameters within a tissue and allowing these maps to be influenced by motion may involve reassessing the design of the relevant parts of the PhantomGenerator and the MotionEmulator as well as possible alterations to the synthetic data generation pipeline.

A further level of realism could be achieved by using specialised tracer kinetic models for each organ (for example a model specific to the kidney [6]) and including a dis-
persion term within the input functions [38]. Addition of further models and input functions would be straightforward as the PhantomGenerator has been designed to facilitate such extensions. However, determining the relevant ground truth parameters for these extensions may require analysis of acquired data sets. The addition of dispersion terms to the input functions may affect the estimated model parameters [38] and so is worth considering as a future enhancement, the addition of further tracer kinetic models is unlikely to influence investigations focused on liver tumours.

Another refinement would be to include a realistic contrast agent concentration time-course for the inferior vena cava. This could be achieved using the same methodology as for PIF estimation (an impulse response function (IRF) could be generated from reference AIF and vena cava time course and this could be applied to the AIF used to generate the synthetic data). However, this was not pursued as the signal intensity changes in the vena cava are not generally of interest to DCE-MRI and will not influence the registration algorithm assessed within this research (see Section 2.5.2.1) for which the similarity measure is calculated using the tumour VOI only. This refinement would be relatively straightforward to implement if required.

For the motion emulation, only a subgroup of the organ masks was used to explicitly drive the FEM (see Section 2.6.4) and some organ masks, such as bone and aorta, were not included in the FEM. This leads to some unrealistic deformations within the synthetic images, for example the spine moves anteriorly towards the aorta and is then overwritten by the aorta in the PhantomGenerator. This could be prevented by including bone in the FEM or by also holding the bone mask static. However, as this region does not affect analysis that is focused on the liver, this refinement has not been implemented. Also, the FEM is performed between end-inhale and end-exhale with linear interpolation of the resulting displacement maps between these points. Including intermediate points may given a better representation of the motion of the abdominal organs.

Even without these possible improvements the phantom has a high degree of realism that surpasses other work in the literature for liver tumours. Possible refinements are almost limitless, especially if pathology is going to be considered, so they should be implemented in a targeted way according to the application for which the synthetic data is required.
4.7 Summary

In this chapter, we have described the function and design of the MotionEmulator application. The MotionEmulator applies dense displacement maps to organ masks by approximating the inverse transform and combines the displacement maps with an acquired respiratory trace or sinusoidal pattern to give organ motion throughout the breathing cycle. We have presented output from the MotionEmulator when using simplified input as well as organ masks defined on an acquired data set with the associated displacement maps from multi-organ FEM [63]. The MotionEmulator produces a set of organ masks for each time point in the dynamic series that can be read into the PhantomGenerator to produce DCE-MRI data with motion emulation.

We have presented a DCE-MRI synthetic data set generated from the UHN data set organ masks and associated displacement maps, an acquired breathing trace and ground truth values based on acquired data sets. As the input to the MotionEmulator is based on acquired data sets and the displacement maps are generated from FEM, this gives both quasi-realistic anatomy and motion of the abdominal organs due to breathing. Therefore, the generated data set can be used for assessing image analysis techniques, including registration and the robustness of model fitting and selection to motion (see Chapter 6).
Chapter 5

Model selection in livers with metastatic disease

5.1 Introduction

In the previous chapters we described the development of the PhantomGenerator and MotionEmulator applications which can be used to produce synthetic DCE-MRI data sets. In this chapter, we focus on two related image analysis techniques for assessing the microvascular characteristics of livers with metastatic disease: the estimation of the $K_{\text{trans}}$ parameter in the extended Kety model and model selection. We validate these methods using synthetic data generated using the PhantomGenerator and apply them to acquired data sets. $K_{\text{trans}}$ is a hybrid parameter that reflects both the permeability-surface area product of the capillary walls and also blood flow. We have focused on $K_{\text{trans}}$ as it has been observed to change due to the administration of anti-angiogenic drugs and is therefore used to assess drug effect for these therapeutics (see Section 2.2.2).

As tumours are likely to display different microvascular characteristics to healthy liver (see Section 2.2) a different tracer kinetic model may be required to give an adequate description of time course data from each of these tissue types. The dual-input single-compartment Materne model can be used to represent liver tissue with highly leaky sinusoids and two blood supplies and the extended Kety model can be used to describe tumour with capillaries supplied from an artery (see Section 2.3). We
have therefore used the Akaike model selection technique described in Section 2.3.3 to indicate on a per voxel basis whether the Materne model or extended Kety model provides a better description of the data. This technique has the potential to highlight tumour extent and invasion by identifying voxels around the periphery of the tumour where suitability of the Materne model is weakened compared to voxels further from the tumour. Model selection also has the potential to detect early signs of metastasis by monitoring for voxels where the Materne model is less able to describe the data well either in comparison to other areas of the liver or by assessment of the liver over time.

A portal input function (PIF) is required for fitting the Materne model (see Equation (2.4)). As described in Section 2.3.2, it is not always possible to accurately measure a signal intensity time course from the hepatic portal vein from acquired data sets. Therefore, in Section 5.2 we describe a technique for estimating a plausible PIF for each patient using knowledge of the arterial input function (AIF) and validate this technique by comparison with acquired portal input functions.

In Section 5.3 we use synthetic data sets generated using the PhantomGenerator to assess the model fitting and model selection techniques and the influence of partial volume effects (PVEs). In Section 5.4 we apply these techniques to six acquired liver metastases data sets. This work has been published in the Journal of Magnetic Resonance Imaging, January 2012 [103].

5.1.1 Acknowledgements

Thanks to Caleb Roberts for his role in quality control of the clinical trial data, Sue Cheung for extraction of the patient AIFs, and Yvonne Watson for the tumour VOIs. Acknowledgement is also due to Gordon Jayson (the principal investigator) for his role in collection of the clinical trial data.

Thanks to Vivian Lee, Pari Pandharipande, Henry Rusinek and Tong San Koh for providing the CT AIF and PIF data.

Lastly, thanks to Jo Naish for the model fitting application written in Matlab. This application was written to fit the extended Kety and the AATH models and to perform model selection between these two models. The application was extended by the author to fit the Materne model and perform model selection, using the corrected
AIC, between the extended Kety model and the Matern model.

5.2 Estimating the portal input function

As described in Section 2.2.1, the hepatic portal vein receives blood from the splanchnic circulation. The contrast agent bolus (AIF) will therefore travel through multiple different paths through the vasculature of the digestive tract before reaching the portal vein. The form of the contrast agent concentration time course in the portal vein can therefore be considered to be the addition of multiple parallel delayed and dispersed AIFs, and we hypothesize that it should be possible to relate the resulting PIF to the AIF using an impulse response function (IRF) as shown in Equation (5.1).

\[ PIF = AIF \ast IRF \]  

(5.1)

where \( \ast \) is the convolution operator

To estimate a portal input function, we have generated a reference IRF that relates the AIF to the PIF of a reference data set. DCE-computed tomography (CT) time courses for a single AIF and PIF from Pandharipande et al. [104] were used as a reference data set (Figure 5.1).

Figure 5.1: Reference data set used in the PIF generation process, estimated from Figure 4b of Pandharipande et al. [104]. Concentration is expressed as change in Hounsfield units (linearly related to actual concentration [105]).

Using CT reference data avoids the potential confounds of MRI data such as inflow
effects, $B_1$ inhomogeneities, and saturation of the signal intensity at high concentrations [31, 29]. We deconvolved the reference PIF from the reference AIF (using model free deconvolution) to give the reference IRF, see Figure 5.2. Model free deconvolution was performed in the frequency domain as described by Equation (5.2)

$$IRF = \mathcal{F}^{-1}(\mathcal{F}(PIF)/\mathcal{F}(AIF))$$

(5.2)

where $\mathcal{F}$ is a fast fourier transform and $\mathcal{F}^{-1}$ is an inverse fast fourier transform. These were calculated using the Matlab (MathWorks, Natick, MA) “fft” and “ifft” functions respectively.

Whilst the IRF is derived from a single data set, we have assumed it to be a good first approximation for all individuals. This assumption is discussed further within Sections 5.2.2 and 7.2.

We have defined a functional form for the IRF as described in Equation (5.3) and also shown in Figure 5.2. The time values correspond to those used for the acquisition of the input functions. To generate the functional form IRF, the reference input functions were sampled at a temporal resolution of 4.97 s prior to deconvolution to match that of the acquired data used in this thesis (see Table 5.6). The IRF was visually inspected and the last 4 time points were removed as they were affected by boundary effects and sampling. The monotonically decreasing form after the initial rise of the IRF is similar to that presented by Monk [46].

$$y = \begin{cases} 
0 & \text{for } 0 \text{ min } \leq x > 0.08 \text{ min} \\
24.16x - 2.01 & \text{for } 0.08 \text{ min } \leq x \geq 0.17 \text{ min}, \\
2.83 \exp(-10.80x) + 2.12 \exp(-1.28x) & \text{for } x \geq 0.17 \text{ min}.
\end{cases}$$

(5.3)

To estimate patient-specific PIFs the reference IRF was convolved with each patient’s AIF ($C_p(t)$) derived from acquired data [39]. (A haematocrit value of 0.42 was used to estimate contrast agent concentrations within the blood plasma ($C_p(t)$) from those in whole blood, see Equation (2.3).) Prior to generation of the IRF the reference data set was resampled at the temporal resolution of the patient’s AIF. The reference PIF was then deconvolved from the reference AIF to produce an IRF. The duration of the patient’s AIF was then matched to that of the IRF and the IRF was then convolved.
with the patient’s AIF.

As the reference data set has a shorter duration (≈ 162 s) than the DCE-MRI acquisition period for the acquired data sets analysed within this work (≈ 368 s), each patient’s AIF was shortened to match the duration of the reference IRF. The generated PIF was then extended by appending the tail of the AIF as a close correspondence is commonly seen in patient data [104, 106, 107]. Approximating the PIF washout using the AIF tail was also used by Orton [45] and Monk [46] who found that blood samples from the portal vein and aorta for positron emission tomography (PET) tracers did not differ after a given time (Section 2.3.2).

5.2.1 Evaluating the PIF estimation method

To evaluate the PIF estimation method, portal vein concentration time courses were estimated, as described above, from the measured DCE-CT AIFs published by Koh et al. [106]. The estimated PIFs were then compared with the corresponding measured PIFs from [106].

For the Materne model we define a modified flow rate constant, $k'_{1hpv}$, as

$$k'_{1hpv} = G k_{1hpv} \quad (5.4)$$

where $k_{1hpv}$ is the portal flow rate for each voxel and $G$ is the global scaling factor that is common to all liver voxels for a given DCE-MRI data set. $G$ accounts for
the degree of contrast agent leakage in the GI tract differing between the patient and reference data due to factors such as fasting status.

This gives a modified Materne model of

\[
C_t(t) = \int_0^t \left[ k_{1a} C_p(t' - \tau_{aif}) + k_{1hpu}' C_{hpu}'(t' - \tau_{pif}) \right] e^{\frac{-k_2(t-t')}{dt'}} dt' \tag{5.5}
\]

where \(C_{hpu}'\) is the estimated PIF.

When comparing the estimated and measured PIFs, we replicated the effect of \(G\) by scaling the estimated PIF to match the area under the curve of the measured PIF. This was achieved by calculating the area under the curve for the estimated and measured PIFs using the trapezoid rule after first ensuring that both included the same acquisition time after contrast agent is first seen (this point is selected by visual inspection). Scaling the estimated PIF allows us to assess whether it would give the same goodness of fit of the Materne model to measured contrast agent concentration curves as the measured PIF when model fitting. (It replicates the model fitting algorithm optimising the \(k_{1hpu}'\) parameter.)

The generated curves were also aligned temporally to the measured data. The required temporal delay could be caused by a difference in measurement position of the PIF between the reference data set used to generate the IRF and the acquired portal input patient data. Within the model fitting process this delay is incorporated within the parameter \(\tau_{pif}\), see Equation (5.5).

5.2.1.1 Results

Figure 5.3 shows measured PIFs [106] and those estimated from the corresponding AIFs. Subjectively, all the estimated curves show reasonable similarity to the acquired data.

Bland-Altman plots comparing the measured and estimated PIF concentrations at each dynamic time point are shown in Figure 5.4 and demonstrate quantitatively that there is near zero bias between the curves, although there is some evidence of overestimation of the peak concentration and underestimation of the washout, particularly in Patient B (see Figure 5.3(b)). The values for the scaling factor and temporal delay used to match the estimated PIFs to the measured data are shown in
Figure 5.3: Comparison of estimated PIFs with measured PIFs. The measured data are derived from Figures 1b - 4b of Koh at al [106]. Concentration is expressed as change in Hounsfield units (linearly related to actual concentration [106]).
Table 5.1.

![Bland-Altman plots comparing each estimated PIF with the corresponding measured PIF, expressed as change in Hounsfield units. The bottom and top dotted lines show the 95% confidence intervals and the central dotted line shows the mean difference. The y-axis plots the estimated PIF minus the measured PIF.](image)

Figure 5.4: Bland-Altman plots comparing each estimated PIF with the corresponding measured PIF, expressed as change in Hounsfield units. The bottom and top dotted lines show the 95% confidence intervals and the central dotted line shows the mean difference. The y-axis plots the estimated PIF minus the measured PIF.

5.2.2 Conclusions

Evaluation of the PIF generation technique using CT data demonstrated a good match between estimated and acquired PIFs. Although the estimated PIFs do not perfectly match those measured using CT, they are in practical terms a very good analogue, especially when the influence of measurement noise is considered. CT data are more suitable for this purpose than MRI data as the PIFs measured using CT are likely to be more accurate. If the evaluation had used MRI data, it would be unclear whether any differences were due to the method of generating the PIF or to the inaccuracies in the MRI measurement technique such as $B_1$ inhomogeneities,
Table 5.1: Scale and delay values used to match estimated and acquired PIFs.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Scale</th>
<th>Delay (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.91</td>
<td>8.33</td>
</tr>
<tr>
<td>B</td>
<td>0.92</td>
<td>9.88</td>
</tr>
<tr>
<td>C</td>
<td>1.00</td>
<td>6.12</td>
</tr>
<tr>
<td>D</td>
<td>0.87</td>
<td>10.48</td>
</tr>
</tbody>
</table>

saturation of the signal at high intensities and inflow effects [31, 29] as described in Section 2.3.2. However, the reference CT AIF and PIF data set will still be subject to motion and partial volume effects, which may affect the generated IRF and therefore the estimated PIFs. Nevertheless, given the problems with MRI data, PIF generation using an IRF derived from CT data is a potentially useful capability.

The PIF estimation method includes the scaling factor $G$, see Equation (5.4), (incorporated into the estimated $k'_{1hpe}$ parameter) that applies to all liver voxels. This scaling factor accounts for differing contrast agent concentrations, reaching the liver via the gut, that cannot be predicted directly from the AIF. Such variations could, for example, result from a difference in fasting status between the patient and the reference data set used in the PIF estimation process and also differences in the anatomy of the splanchnic circulation. Assessing spatial variations in $k'_{1hpe}$ within a patient data set is valid, but studies that intend to use absolute values of this parameter should account for the global scaling factor. Our main aim in this work was to evaluate the Akaike model selection criterion for identification of tissues with different vascular characteristics. As the Akaike information criterion (AIC) relies on the goodness of fit of the model rather than any absolute parameter value, the exact value of the scaling factor within $k'_{1hpe}$ is not a major concern. A similar issue would occur in studies that compared the absolute value of $k_{1hpe}$ derived from different visits and where exercise, caffeine and food intake were not controlled as these could all affect the portal flow and lead to the corresponding change in $k_{1hpe}$ being misinterpreted as change in disease status, for example.

Any mismatches in shape between the estimated and acquired input functions could be caused by inter-subject differences that affect portal flow such as disease burden, fasting status, exercise and time of day [17, 18, 19]. Winterdahl [47] demonstrated, using different PET tracers, that the shape and height of the PIF changed depending on the volume of distribution available within the gastro-intestinal (GI) tract to each tracer. Ideally there would be a match between the physiological status of the reference data set used to generate the PIF and the patient. We were able to
approximate the disease type as the test data [106] was taken from a similar patient
group with malignant liver lesions, but in future it would be advantageous to validate
the technique using a larger and more heterogeneous patient population. Differences
could also arise because the AIF was generated from a single reference data set which
may be atypical. Ideally the IRF would be derived from a bigger population of
patients, as this would allow for inter-individual differences and measurements to be
characterised.

A further limitation is the small number of cases used for the evaluation of the PIF
estimation technique. A comprehensive assessment would include data from patients
with a wide range of diseases as well as healthy volunteers. This would allow the
effects in the method to be properly characterised. Despite the stated limitations, this
method of IRF prediction is a promising solution to the problem of PIF measurement.
The approach taken is similar to that developed by Monk et al. [46] for PET tracers
in the pig, which was demonstrated by Winterdahl [47] to give good agreement with
PIFs measured from blood sampling when using a population mean IRF.

5.3 Validating model fitting and selection using
synthetic data

Using the PhantomGenerator, we created synthetic data sets from known ground
truth to assess the model fitting and model selection techniques at realistic noise
levels. The synthetic data were generated using the acquisition parameters shown
in Table 5.6 for both the variable flip angle technique for pre-contrast $T_1$ estimation
and the dynamic series. A pre-contrast $T_1$ value of 650 ms was used to represent
liver tissue at 1.5 T [108]. Whilst this value was measured in cirrhotic liver, it is
close to the median value of 672 ms seen for the patient data sets analysed in this
research. Also, as the models are fitted to contrast agent concentration curves rather
than signal intensity values and the accuracy of the $T_1$ estimation has been shown to
be good [93], this difference is unlikely to affect the results.

The synthetic contrast agent concentration time series were calculated using the
Materne model (Equation (2.4)), with a range of parameter values ($k_{1a}$: 0.02 to
0.9 min$^{-1}$; $k_{hpw}$: 0.4 to 0.6 min$^{-1}$; and $k_2$: 1 to 6 min$^{-1}$) that represent liver states
from healthy to high grade cirrhosis [109]. The three parameters were varied along
the three axes of the synthetic image volume in 9 even steps to give 10 different values of each parameter and 1000 different parameter combinations.

Equivalent simulations were performed with the extended Kety model as ground truth using parameter ranges derived from fitting the extended Kety model to the synthetic data generated with the Materne parameter ranges described above ($K^{\text{trans}}$: 0.001 to 1.2 $\text{min}^{-1}$; $v_p$: 0.001 to 0.1; $v_e$: 0.02 to 0.6). A population-averaged AIF [40] was used for both models with a PIF estimated for the Materne model from this AIF using the method described in Section 5.2. The AIF and portal delay times were set to zero. The maximum value of $K^{\text{trans}}$ used to generate the synthetic data is much larger than generally seen in tumour (see Table 3.3). However, when the extended Kety model was fitted to liver regions in six patient data sets median values ranging from 0.32 to 0.87 $\text{min}^{-1}$ were seen with a mean value of 0.56 $\text{min}^{-1}$ (see Table 3.3).

The signal intensity values were generated using a spoiled gradient echo (SPGR) pulse sequence (Equation 2.10), then zero mean Gaussian noise was added. Two different noise standard deviation values were used, corresponding to signal to noise ratios (SNRs) of 5 and 10 in a pre-contrast image with a flip angle of 20 degrees. The SNR of 10 reflected the random signal variations seen in the patient data sets with low levels of motion corruption. The SNR value of 5 approximately emulated the larger signal variations in the liver caused by breathing motion. Whilst breathing motion does not produce Gaussian distributed noise, the lower SNR provides a first approximation to evaluate its effects on the model selection technique (see Section 3.5.1.1).

100 data sets with different randomised noise patterns were generated for each noise level. For the generation of the VFA images, a SNR of 10 is always used, as we wished to focus on the effect of noise on model fitting to contrast agent concentration curves. A noise free data set was also generated using both models from the same ground truth data.

5.3.1 Model fitting analysis procedure

The Materne and extended Kety models describe the time dependent contrast agent concentration levels in a voxel. It is possible to perform model fitting either in the signal domain or to contrast agent concentration values. In the signal domain the noise is Gaussian distributed, which matches the noise distribution assumed by the
optimisation algorithms used for model fitting. This is not true for the concentration values due to the non-linear transformation from signal intensity using Equation (2.10). However, we converted the acquired signal intensity values at each time point to contrast agent concentrations before fitting the models for convenience and speed.

First, $T_1(0)$ (the pre-contrast $T_1$ value) was estimated using the variable flip angle (VFA) technique [59] where images at multiple flip angles were acquired with constant echo time (TE) and time to repeat (TR). (The flip angles used are shown in Table 5.6.) $T_1(0)$ for each voxel was then estimated by fitting the SPGR equation (2.10) to the signal intensity - flip angle curve. The fitting routine used was the Matlab (MathWorks, Natick, MA) function “lsqcurvefit” which implements the Levenberg-Marquardt optimisation algorithm [25]. $S_0$ was approximated for each voxel from Equation (2.10) using the estimated $T_1(0)$ value and where $S(\theta)$ is the mean signal intensity from the pre-contrast images for each voxel.

Dynamic $T_1$ values, $T_1(t)$, for each image in the time series were then calculated from Equation (5.6) [110] which is derived from considering $S_\theta(t) - S_\theta(0)$ using Equation (2.10) where $S_\theta(t)$ is the signal intensity at each acquisition time, $t$, and $S_\theta(0)$ is the mean of the measured pre-contrast signal intensity values.

$$T_1(t) = -\frac{TR}{\ln} \left( \frac{1 - (A + B)}{1 - \cos\theta (A + B)} \right)$$ (5.6)

where

$$A = \frac{(S_\theta(t) - S_\theta(0))}{(S_0 \sin\theta)}$$

$$B = \frac{(1 - E_1(0))}{(1 - \cos\theta E_1(0))}$$

$$E_1(0) = \exp^{-\frac{TR}{T_1(0)}}.$$ 

From the dynamic $T_1$ values, contrast agent concentration values ($C_t(t)$) were estimated using Equation (5.7) [53] which is Equation (2.8) rearranged.

$$C_t(t) = \frac{1}{r_1} \left( \frac{1}{T_1(t)} - \frac{1}{T_1(0)} \right)$$ (5.7)

where $r_1$ (contrast agent relaxivity) is assumed to be constant (4.5 s$^{-1}$ mM$^{-1}$ at 1.5 T for gadodiamide - Omniscan, GE Healthcare).

The extended Kety model (Equation (2.1)) and the Materne model (Equation (5.5)) were fitted on a per voxel basis. However, model fitting and subsequent analyses
are only performed on voxels with a time series that is distinguishable from the zero enhancement case as it is not possible to accurately estimate parameter values when there is inadequate contrast agent uptake for model fitting. Non-enhancing voxels were identified using model selection between a zero gradient, zero offset line model ($C_i(t) = 0$ for all $t$) and the extended Kety model. An Akaike probability (discussed in Section 2.3.3) of less than 0.5 was used to indicate that the voxel concentration time course is better described using a flat line. As the time course data includes up to ten pre-contrast time points, this suggests that no change in contrast agent concentration from baseline is occurring, therefore these voxels are labelled as non-enhancing.

The optimisation routine used for fitting the extended Kety and Materne model was Matlab’s (MathWorks, Natick, MA) “lsqcurvefit” (Levenberg-Marquardt non-linear least squares). The least squares tolerance value ($1 \times 10^{-10}$) and maximum number of iterations for the optimisation routine (1000) were matched for both models. A dual start method [111] was used to reduce the possibility of finding a local minimum. For this method, the optimisation was run twice with the parameters estimated from the first run used as start values for the second but with $v_e$ for the extended Kety model and $k_2$ for the Materne model reset to their initial values.

The start values and constraints used for the model parameter values for both optimisation runs are shown in Table 5.2 for the extended Kety model and in Table 5.3 for the Materne model. The delay time in the portal vein ($\tau_{pif}$) is constrained to be greater than the delay time for the AIF even though the PIF measurement site may be closer to the voxel of interest than the AIF measurement site. However we do not allow for $\tau_{pif} < \tau_{aif}$ because the fitting then sometimes resulted in physiologically implausible placement of the input functions (the peak of the PIF would occur before that of the AIF), possibly due to the limited temporal resolution. It is also possible that portal flow rates could be markedly slowed by the presence of disease [17] leading to a much increased portal delay time.

The AIF and PIF were input to the model fitting routines as text files that contain values of contrast agent concentration in blood plasma along with the acquisition time

<table>
<thead>
<tr>
<th>parameter</th>
<th>$K^{\text{trans}}$ min$^{-1}$</th>
<th>$v_e$</th>
<th>$v_p$</th>
<th>$\tau_a$ min</th>
</tr>
</thead>
<tbody>
<tr>
<td>start values</td>
<td>0.3</td>
<td>0.2</td>
<td>0.2</td>
<td>0.1</td>
</tr>
<tr>
<td>first bounds</td>
<td>0 to 100</td>
<td>0 to 100</td>
<td>0 to 100</td>
<td>unbound</td>
</tr>
<tr>
<td>second bounds</td>
<td>0 to 100</td>
<td>0 to 10</td>
<td>0 to 10</td>
<td>unbound</td>
</tr>
</tbody>
</table>

Table 5.2: Start values and constraints used for fitting the extended Kety model.
Table 5.3: Start values and constraints used for fitting the Materne model. $\tau_{a1}$ refers to the value approximated for $\tau_{a1f}$ during the first fitting.

for each value. If concentration values for times in between those listed were required due to the delay times, the Matlab “pchip” (piecewise cubic hermite interpolation polynomial) routine was used.

5.3.2 Box plot description

This description applies to all the box plots used to present the results within this chapter. The central red lines within the boxes are the median values and the boxes are the interquartile range. The whiskers end at the most extreme values that are not considered outliers. Outliers are values that are greater than $q_{75} + 1.5 \times iqr$ or less than $q_{25} - 1.5 \times iqr$, where $q_{25}$ and $q_{75}$ are the 25th and 75th quartile respectively and $iqr$ is the interquartile range. The whiskers would cover approximately 99% of the values if they were distributed normally. Outliers are shown as a blue cross. Where notches are present, they indicate a robust 95% confidence interval for differences among the medians.

5.3.3 Model fitting characterisation

The Materne model was fitted to the synthetic data sets generated using the same model to give estimated model parameters for each voxel. The mean estimated parameter values were then calculated for each voxel from the 100 data sets at both noise levels. For each ground truth value of one parameter, for example $k_{1a}$, there are 100 different ground truth value combinations of the other two parameters, for example $k_{1hpv}$ and $k_2$. The median values for each ground truth value of each parameter were calculated from the 100 mean estimated values (due to the 100 different parameter combinations) and compared against the known ground truth, see Figures 5.5(a) - 5.5(c). The median has been chosen as the model fitting constrains the parameters to be greater than 0, which may lead to non-normal distribution of the estimated values.
The accuracy and precision of the model fitting to the noise free data generated with the Materne model is very good, with near zero or small bias (see Table 5.4) and a low variation, see Figure 5.5. Variation is still seen for the noise free data as for each value of the specified parameter there are multiple values of the other two parameters and some parameter combinations may be harder to fit accurately. For example, a high $k_2$ (out-flow rate) will lead to small changes in contrast agent concentration and low contrast to noise ratio on the contrast agent curves to which the model is fitted. Median $k_{1a}$ is overestimated slightly at all values of $k_{1a}$ and this bias increases with increasing noise as shown in Table 5.4. Median $k_2$ has near zero bias in noise free data and an increasing overestimation with noise is seen. Median $k_{1hpv}$ has near zero bias. The precision of all the parameters decreases with increasing noise level.

<table>
<thead>
<tr>
<th>$k_{1a}$</th>
<th>% difference from ground truth</th>
<th>SNR = 10</th>
<th>SNR = 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>noise free</td>
<td>3.87</td>
<td>23.23</td>
<td>37.14</td>
</tr>
<tr>
<td>$k_{1hpv}$</td>
<td>4.46</td>
<td>-3.38</td>
<td>1.71</td>
</tr>
<tr>
<td>$k_2$</td>
<td>-0.30</td>
<td>14.97</td>
<td>27.81</td>
</tr>
</tbody>
</table>

Table 5.4: Accuracy of the Materne model fitting. The mean difference between the median estimated value and true value is calculated as a percentage of the true value across all the ground truth values for each parameter. A negative value indicates underestimation from the true value.

The corresponding validation was performed for fitting the extended Kety model to synthetic data generated with the extended Kety model, see Figure 5.6. The precision of fitting to noise free data is good and decreases with increasing noise level for all three parameters. $v_p$ shows underestimation of the median value, see Table 5.5, which is clearly present when fitting to the noise free data set. $K^{\text{trans}}$ has little bias in the noise free data and an underestimation which increases with noise. $v_e$ shows near zero bias across all the values and noise levels.

<table>
<thead>
<tr>
<th>$K^{\text{trans}}$</th>
<th>% difference from ground truth</th>
<th>SNR = 10</th>
<th>SNR = 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>noise free</td>
<td>2.71</td>
<td>-6.24</td>
<td>-10.13</td>
</tr>
<tr>
<td>$v_p$</td>
<td>-35.01</td>
<td>-34.68</td>
<td>-28.21</td>
</tr>
<tr>
<td>$v_e$</td>
<td>3.40</td>
<td>-2.56</td>
<td>-3.39</td>
</tr>
</tbody>
</table>

Table 5.5: Accuracy of the extended Kety model fitting. The mean difference between the median estimated value and true value is calculated as a percentage of the true value across all the ground truth values for each parameter. A negative value indicates underestimation from the true value.
Figure 5.5: Comparison of mean estimated Materne model parameters with ground truth. Only 3 of the 10 ground truth values are shown for each parameter. The ground truth value is indicated by the green dotted line. The results from fitting to noise free data (nf) and data with an SNR of 10 and 5 are shown. See Section 5.3.2 for a description of the boxplot features.
Figure 5.6: Comparison of mean estimated Extended Kety model parameters with ground truth. Only 3 of the 10 ground truth values are shown for each parameter. The ground truth value is indicated by the green dotted line. The results from fitting to noise free data (nf) and data with an SNR of 10 and 5 are shown. See Section 5.3.2 for a description of the boxplot features.
5.3.4 Model selection validation

Both the Materne and extended Kety Models were fitted to all the data sets generated with both models. The Akaike probability for each voxel could then be calculated as described in Section 2.3.3. For both noise levels the mean Akaike probability value across the 100 noisy data sets for each ground truth voxel was then calculated.

The histograms in Figure 5.7 show the distribution of mean Akaike probabilities for the synthetic data sets generated with the Materne model for both noise levels. For the higher SNR of 10, 98% of the voxels have an Akaike probability above 0.5 indicating that the model selection technique is correctly choosing the more complex Materne model in the majority of voxels (see Section 2.3.3). When the SNR is reduced to 5, the percentage of voxels with a value over 0.5 drops to 64.4%. The probability maps in Figure 5.7 show that the lower Akaike probabilities occur in voxels where the portal flow is low, the arterial flow is high and the outflow is high. Figure 5.8 shows example concentration-time curves for both models fitted to the synthetic data for a high and low Akaike probability, illustrative of the selection of Materne and extended Kety models, respectively.

![Figure 5.7](image)

**Figure 5.7:** Mean Akaike probability for 100 noisy synthetic data sets generated with the Materne model. The top row corresponds to a SNR of 10 and the lower row corresponds to a SNR of 5. The leftmost plot shows a histogram of the probability values from all voxels. The three plots to the right are Akaike probability maps for three slices through the synthetic volume with differing outflow rates ($k_2$ values).
Analysis of equivalent simulations using the extended Kety model to generate the synthetic data (see Figure 5.9) gave Akaike probabilities of less than 0.5 for 98% of the voxels at an SNR of 10 (the remaining voxels had values less than 0.6) and 100% of the voxels at an SNR of 5. Those voxels with Akaike probabilities above 0.5 are generated with $K_{\text{trans}}$ values greater than 0.67 min$^{-1}$, which are unlikely to be seen in tumour (median values for the lesions analysed in this study range from 0.15 min$^{-1}$ to 0.32 min$^{-1}$) but may be seen in the liver when the incorrect model, i.e. the extended Kety model, is used (median values range from 0.29 min$^{-1}$ to 0.75 min$^{-1}$).

### 5.3.5 Assessing partial volume effects and AIF/PIF offset

Voxels on the periphery of a liver tumour are likely to contain a mixture of both tumour and liver tissue. To assess the influence of PVEs on model fitting and se-
Figure 5.9: Mean Akaike probability for 100 noisy synthetic data sets generated with the extended Kety model. The top row corresponds to a SNR of 10 and the lower row corresponds to a SNR of 5. The leftmost plot shows a histogram of the probability values from all voxels. The three plots to the right are Akaike probability maps for three slices through the synthetic volume with differing $v_e$ values.

Selection, we used the PhantomGenerator to create synthetic data sets that combine tumour rim described using the extended Kety model and liver tissue described using the Materne model in varying proportions. We have also included the assessment of the effect of varying the input function offset ($\tau_a$ within the extended Kety model, Equation (2.1), and $\tau_{aIF}$ and $\tau_{pIF}$ within the Materne model, Equation (2.4)). If the arrival of the contrast agent bolus to the voxel of interest is sampled at different time points this may affect the accuracy of model fitting and consequently the outcome of model selection.

Synthetic volumes were generated with ground truth parameters for tumour rim (see Table 3.3) and liver (see Table 3.4 and Table 3.5) derived from patient data sets as described in Section 3.5.1. Along the y-axis the fraction of tumour rim was decreased from 1 (all tumour rim) to 0 (all liver) in 10 even steps. Along the x-axis, 100 voxels with different samples from a zero mean Gaussian noise distribution with an SNR of 10 were generated for the tissue fractions specified by position on the y-axis. A separate data set was then generated for each AIF offset which was varied from 0 to 5 seconds in 5 even steps to bracket our temporal resolution of 4.97 s. The protocol used to generate images for VFA $T_1$ estimation and the dynamic series is listed in
A functional form of a population AIF [40] was used as input to both models, with the same AIF offset value applied to both models. A portal input function generated from the population AIF as described in Section 5.2 was supplied for the Materne model and was input to the PhantomGenerator as a text file of plasma concentrations and the associated acquisition times. Linear interpolation was used to calculate concentration values at intermediate times to those listed in the file. For the AIF, sampling from a functional form is more accurate as using linear interpolation risks underestimating the concentration values around the rapid rise and fall of the first pass peak. However, a functional form is not currently available for the PIF but this is not a major concern as the changes in contrast agent concentration are not as large for the PIF, see Figure 5.1 as an example. The PIF offset was calculated to be the AIF offset plus 12.6 seconds to maintain the relative delay seen in acquired data sets (Table 3.4).

5.3.5.1 Results

Model fitting and model selection were applied to each data set as described in Section 5.3.1 followed by model selection (Equation (2.6)). Figure 5.10 and Figure 5.11 show the mean estimated model parameters and Akaike probability value (calculated from the 100 noisy samples) for each combination of fraction and offset value.

When fitting the generative model to pure liver or tumour rim tissue the estimated values generally match the ground truth and $\tau_a$, $\tau_{a_{IF}}$ and $\tau_{p_{IF}}$ vary as expected with offset. When fitting the Materne model to the data sets, the results indicate that $k_{1_{a}}$, $k_{1_{hpv}}$, and $k_{2}$ are not strongly influenced by offset. When fitting the extended Kety model the results indicate that $K^{\text{trans}}$ and $v_e$ are also not strongly affected by offset, however the accuracy of $v_p$ is dependent on the offset. Voxels only containing liver tissue (generated using the Materne model) are described by the extended Kety model as high $K^{\text{trans}}$, low $v_p$, and high $v_e$ which supports the high $K^{\text{trans}}$ values observed when fitting the extended Kety model to liver volumes of interest (VOIs) in acquired data (see Section 3.3). If liver tissue is present in a voxel in a tumour VOI a higher effective $K^{\text{trans}}$ will be seen, with a mean estimated value across all the offsets of $0.36 \text{ min}^{-1}$ in pure tumour rim tissue and $0.51 \text{ min}^{-1}$ in pure liver tissue with $K^{\text{trans}}$ increasing between these values with decreasing fraction of tumour rim (see Figure 5.11(a)).
value estimated for \( v_p \) is dependent on offset and the fraction of liver tissue present.

![Graphs showing influence of PVEs and input function offset on mean estimated Materne parameters.](image)

**Figure 5.10:** The influence of PVEs and input function offset on mean estimated Materne parameters. The fraction of tumour rim and liver tissue is varied along the y-axis and input function offset is varied along the x-axis. Ground truth values for liver tissue (Materne model) are \( k_{1a} = 0.61 \text{ min}^{-1} \), \( k_{1hpv} = 0.31 \text{ min}^{-1} \) and \( k_2 = 2.9 \text{ min}^{-1} \). The tumour rim data were generated with the extended Kety model.

The influence of offset and PVEs on the model selection technique is shown in Figure 5.12. The extended Kety model is preferred where a voxel contains a fraction of \( \geq 0.3 \) of tumour rim, indicating that the model selection technique has a preference for the extended Kety model where a mixture of tissue is present. The model selection technique is dependent on offset at lower fractions for tumour rim tissue.

### 5.3.6 Conclusions

In this section we have demonstrated the utility and flexibility of the Phantom-Generator software. Specifically, we have used the PhantomGenerator to construct phantoms explicitly designed to improve our understanding of various aspects of
Chapter 5. Model selection in livers with metastatic disease

Figure 5.11: The influence of PVEs and input function offset on mean estimated extended Kety parameters. The fraction of tumour rim and liver tissue is varied along the y-axis and input function offset is varied along the x-axis. Ground truth values for tumour rim (extended Kety model) are $K_{\text{trans}} = 0.36 \text{ min}^{-1}$, $v_p = 0.01$, and $v_e = 0.3$. The liver data were generated with the Materne model.

Figure 5.12: The influence of PVEs and input function offset on Akaike probability value. The fraction of tumour rim and liver tissue is varied along the y-axis and input function offset is varied along the x-axis. (a) shows the Akaike probability value. (b) shows a threshold on 0.5 applied to the Akaike probability value. Black indicates a preference for the extended Kety model and white indicates a preference for the Materne model.
Chapter 5. **Model selection in livers with metastatic disease**

tracer kinetic model fitting and model selection in the liver in the presence of tumours. We focused on the extended Kety and Materne models, addressing the following issues:

- quantifying the accuracy and precision of parameter estimation for both models using a range of parameter values and noise levels;
- evaluating AIC model selection for data generated with both models using a range of parameter values and noise levels;
- quantifying the effects of varying partial-volume ratios and AIF/PIF offset times on the accuracy of parameter estimation for data generated with both models using fixed parameter values and noise levels that represent tumour rim and liver;
- quantifying the effects of varying partial-volume ratios and AIF/PIF offset times on AIC model selection for data generated with both models using fixed parameter values and noise levels that represent tumour rim and liver.

In general, all model parameters were estimated with adequate accuracy and precision with the sole exception that for the extended Kety model the fitting underestimated $v_p$ by a mean of $\approx 33\%$. The ability to accurately fit $v_p$ is strongly affected by the characterisation of the contrast agent bolus arrival in the tissue. The low temporal sampling means that the true contrast agent concentration peak in the tissue curve may not be captured and this is likely to lead to an underestimation in $v_p$. Whilst the synthetic data sets used for characterising the model fitting analysis were generated with zero input function offsets, the signal intensity changes around the initial arrival of the contrast agent could still be disrupted by noise. $v_p$ was also shown to be influenced by offset, unlike the other extended Kety parameters. Again this is likely to be due to the low temporal sampling.

Roberts et al. [30] investigated the effect of offset, temporal resolution and SNR on the estimated extended Kety model parameters using the adiabatic approximation to the tissue homogeneity model (AATH) model to simulate tissue curves. They found that offset affected the accuracy of $v_p$, which they attributed to mis-sampling of the tissue uptake curve and the AIF (the offset was applied to both). However, contrary to this work, they also found that $K^{\text{trans}}$ was affected. This difference may be due to Roberts et al. performing simulations at multiple noise levels and temporal resolutions...
and using a different generative model. They also applied the same offset to both the AIF and the tissue uptake curve, unlike this work where the offset is only applied to the tissue curve. When investigating the effect of noise and sampling interval, they found that error in \( v_p \) increased as SNR and temporal resolution decreased which supports our suggestions that underestimation of \( v_p \) at zero offset may also be due to noise and under sampling of the tissue uptake curves and AIF due to inadequate temporal resolution.

The precision of the estimated parameters may be worse than would typically be seen in acquired data sets if the appropriate model were fitted, due to the large range of simulated parameter values used. The range selected accounted for the estimated parameters seen when fitting the extended Kety model to liver tissue from acquired data sets and the data generated using Materne model. Therefore they included parameter values from fitting a model that is less likely to appropriately describe the data. For both models, the parameters were treated as independent and therefore parameter combinations that are unlikely to occur may be simulated. For example, a high \( k_{1hpc} \) is seen in healthy liver tissue and a high \( k_{1a} \) value is seen when cirrhosis is present [109]. However, a high \( k_{1a} \) and \( k_{1hpc} \) are unlikely to both occur in the same voxel, but this combination is included in the simulated data.

There are also likely to be ranges of simulated \( v_e \) in the extended Kety model and \( k_2 \) within the Materne model that will lead to the low changes in contrast agent concentration and therefore limited detail in the tissue curve to which the optimisation routine can fit the model. A low value of \( v_e \) means there is no extravascular-extracellular space (EES) for the contrast agent to leak into regardless of the \( K^{\text{trans}} \) value and this is likely to lead to an imprecise estimate of \( K^{\text{trans}} \). Correspondingly, if \( k_2 \) (the outflow rate) is high, the contrast agent does not remain in the tissue. Large values of \( v_e \) can also lead to reduced information in the tissue curve as the contrast concentration peak may not be seen during the acquisition period, resulting in an inaccurate estimation of \( v_e \) [56].

The investigation into the influence of PVEs demonstrated that if liver tissue is present in a voxel on the periphery of a tumour VOI it will lead to an increased apparent \( K^{\text{trans}} \) value within that voxel. If the volume of the tumour is small giving a larger surface area to volume ratio, this could lead to an overestimation of the median value [112]. This highlights the importance of accurate VOI definition as a reduction in \( K^{\text{trans}} \), due to action of an anti-angiogenic agent, could be masked by an increase
in the influence of PVEs as a tumour shrinks.

Assessment of the model selection technique using synthetic data generated with either the Materne model or the extended Kety model demonstrates that the generative model is clearly distinguishable at a SNR of 10, but less distinguishable when the SNR is halved. Uncorrected motion effects could cause unwanted variance of this order of magnitude, implying a potentially significant benefit in employing methods to reduce the impact of motion on liver DCE-MRI (for example [9, 37]). We have investigated the impact of motion and possible benefits of applying a model-driven registration algorithm [9] in Chapter 6.

In synthetic data generated with a high arterial flow, low portal flow and high outflow rate the model selection technique tends towards the extended Kety model even when the synthetic data is generated using the Materne model. Under these conditions the Materne model reduces to a form that is similar to the simple Kety Model (the extended Kety Model without the initial \( v_p \) term in Equation (2.1)). Along with the decreased SNR due to low concentration values that result from a high outflow rate this leads to the extended Kety model being preferred. Therefore, in practice the extended Kety model may be the appropriate model to fit as it is a good approximation to the system. Preference for the extended Kety model was also shown when both liver tissue and tumour tissue is present within the same voxel. The Materne model (at an SNR of 10) was not selected until 0.7 of a voxel contains liver tissue.

### 5.4 Investigating liver microvasculature using model selection

In this section we apply the model selection technique to six acquired DCE-MRI data sets containing liver metastases to evaluate whether it is an effective method of assessing spatially varying microvascular characteristics in this patient group. Using model selection to determine whether the dual-input single compartment Materne model or single input dual-compartment extended Kety model better describes the data could potentially identify which voxels have tissue and vascular properties that are more characteristic of healthy liver (the Materne model) and those which are more characteristic of tumour (extended Kety model). Therefore, we apply model selection to data sets containing liver metastases to assess whether the technique is capable of
distinguishing tumour from non-tumorous tissue. We also assess a tumour margins region which is outside but closely surrounds the tumour VOI to evaluate whether the technique could be used to investigate tumour infiltration or PVEs. In Section 5.4.1 we describe the data acquisition protocol and analysis methods, in Section 5.4.2 we document the details of the patient data and in Section 5.4.3 we show the analysis results which we then discussed in Section 5.4.4.

5.4.1 Data acquisition protocol and analysis methods

Details of the imaging protocol are shown in Table 5.6.

<table>
<thead>
<tr>
<th>TR</th>
<th>4 ms</th>
<th>temporal resolution</th>
<th>4.97 s</th>
</tr>
</thead>
<tbody>
<tr>
<td>TE</td>
<td>0.82 ms</td>
<td>Number of time-points</td>
<td>75</td>
</tr>
<tr>
<td>Flip angles used in T₁ estimation</td>
<td>2°, 10°, 30°</td>
<td>Voxel dimensions</td>
<td>2.93 mm x 2.93 mm x 4 mm (or 8 mm where a wider coverage was required)</td>
</tr>
<tr>
<td>Flip angle used for dynamic series</td>
<td>20°</td>
<td>Matrix size</td>
<td>128 x 128 x 25</td>
</tr>
</tbody>
</table>

Table 5.6: 3D-SPGR imaging protocol acquisition parameters.

The extended Kety and Materne models were fitted on a per voxel basis as described in Section 5.3.1. Akaike probability values were then calculated as described in Section 2.3.3. Validation of both the model fitting and model selection techniques using synthetic data created with the PhantomGenerator were presented in Section 5.3. For fitting the Materne model, a PIF is required. As PIFs were not available for the data sets analysed within this study (for reasons discussed on Section 2.3.2), the method described in Section 5.2 was used to estimate PIFs from each patients measured AIF.

5.4.2 Patient Data

A retrospective analysis was performed using data from patients recruited from two trials performed in our institution [113, 2]. Patients recruited to the studies had adequate hepatic and renal function. Local research ethics committee permission was granted to perform the research. To facilitate the assessment of tumour edge effects (as described towards the end of this section), we assessed the data sets acquired to find cases where a clear transition region of three voxel widths was present between
the tumour volume of interest (VOI) and non-tumour liver tissue. If voxels from another tumour VOI or the edge of the liver fell within this transition region, the data set was rejected from the analysis. This criterion led to six data sets being selected for inclusion in this thesis.

The patients were aged between 48 and 81 years. Patients 1 - 4 had metastatic colorectal cancer. Patient 5, who had metastatic ovarian cancer, had undergone previous debulking surgery followed by platinum based chemotherapy for FIGO (International Federation of Gynecology and Obstetrics) stage IIIb disease and had subsequently developed liver metastases. Patient 6, who had a metastatic small cell/neuroendocrine tumour, had not had previous treatment and had widespread liver metastases. Of the patients with metastatic colorectal cancer, patients 2 - 4 presented with hepatic metastases for initial management while patient 1 had undergone previous hemi-colectomy for a Dukes’ B tumour before developing liver metastases. This heterogeneous patient group allowed the model selection technique to be assessed on a range of metastatic disease and treatment states.

Patient 5 had a single hepatic metastasis identified in the radiological evaluations, while the other five patients had multiple hepatic metastases. Imaged metastases had diameters of at least 2 cm (large enough to guarantee sufficient voxels for analysis) ranging up to 8.2 cm.

Patients 5 and 6 were on no medication, whilst the other patients were taking medication that would not impact on imaging except for patient 3 (colorectal cancer) who was taking amlodipine for hypertension at presentation, which could alter the vascular parameters of interest in this study.

We acquired 3-D spoiled gradient echo images on a Philips 1.5 T Intera scanner for baseline $T_1$ estimation and for the dynamic time series. Gadodiamide (Omniscan, GE Healthcare) was injected as a single bolus (dose 0.1 mmol/kg) after the 5th dynamic image, at a rate of 3 mmol/s using a power injector (Spectris MR, Medrad Inc, Warrendale, PA). Further details of the imaging protocol are listed in Table 5.6. Measured AIFs [39] were available for all patients and the PIF was estimated as described in Section 5.2.

Two 3-D VOIs were manually defined on co-localised $T_1$- and $T_2$-weighted images, one for tumour and one for non-tumour liver tissue avoiding any major vessels. The liver tissue VOI was defined in the same lobe as the tumour VOI. To obtain information
about tumour margins, a third VOI was generated as follows: the tumour VOI was
dilated by three voxel widths (8.79 mm) in all directions then, separately, the tumour
VOI was dilated by one voxel width (2.93 mm) in all directions and lastly the one
voxel width dilation was subtracted from the three voxel width dilation leaving a
shell two voxels wide around the tumour, but separated from it by one voxel width
in-plane. In the slice selection direction this does not result in a contiguous gap
between the tumour VOI and the margins VOI as a slice width of 4 mm or 8 mm
was used where a wider coverage was required (patients 2 and 3). It also only results
in the addition of a maximum of 2 extra voxels in the slice selection direction where
there is a slice width of 4 mm and 1 extra voxel where there is a slice width of 8 mm.
Dilation was performed with a spherical kernel using fslmaths [114].

5.4.3 Results

To test for statistically significant differences between median Akaike probability val-
ues in the 3 VOIs for each patient, the Mann Whitney U test was used as significantly
non-normal distributions were seen (see Figure 5.13). A significance level of \( P \leq 0.01 \)
was used. No correction for multiple comparisons was applied because using \( P \leq 0.01, \)
1 in 100 comparisons are expected to give spuriously significant results. Therefore,
performing 18 comparisons gives less than a 1 in 5 chance of spurious significance
in any individual test. The same statistical testing was used for comparisons of
median \( K^{\text{trans}} \) values as again significantly non-normal distributions were seen (see
Figure 6.18).

Figure 5.13 shows box plots of Akaike probability values for the 3 VOI types (tumour,
margins and liver) for all 6 patients. Table 5.7 lists the median values and number
of voxels within each VOI. The median Akaike probabilities for the liver VOIs were
significantly higher than the tumour VOIs in 5 of the 6 cases, see Table 5.8. The same
is true for the tumour margins and tumour VOIs. For the tumour margins and liver
VOIs, 3 cases are significantly higher in the liver. The median Akaike probability
in the liver VOI is above 0.5 (selecting strongly for the Matern model) in only 2 of
the 6 patients. For the tumour VOIs all median Akaike probabilities are below 0.3,
showing strong preference for the extended Kety model.

Akaike probability parameter maps are shown in Figure 5.14 for Patients 2 and 4
alongside the \( T_2 \)-weighted images used for identifying lesions and for VOI definition.
Figure 5.13: Box plots of the Akaike probability for the three VOIs (tumour, margins, liver) within the 6 patient data sets. A higher Akaike probability suggests that the more complex model (Materne) is more likely to describe the data better than the simpler model (extended Kety). See Section 5.3.2 for a description of the box plot features.

<table>
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<td>&lt; 0.001</td>
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</tr>
</tbody>
</table>

Table 5.8: Pairwise comparisons between median tumour, margins and liver VOI Akaike probability values. The P values for each comparison, calculated using the Mann-Whitney U test, are shown. Note that for Patient 1 there is a significant difference between median values for the tumour-margins and liver regions, but the median Akaike probability value in the liver is less than that in the margins region unlike the trend seen in the other 5 patients.
The arrow indicates the location of the analysed tumour (there are multiple tumours within the slice shown for both patients). The tumours show as darker regions on the Akaike probability maps indicating lower probability values where the extended Kety model is preferred. Example tissue curves from single voxels within the tumour and liver VOIs are shown in Figure 5.15 along with the estimated PIF and measured AIFs for Patients 2 and 4.

Figure 5.14: Matching axial image slices from the Akaike probability maps (left column) and the $T_2$-weighted image (right column) used for defining the tumour VOIs. Images for Patient 2 are shown in the top row and for Patient 4 in the bottom row. An example tumour is identified by the turquoise arrow. Other tumours may be identified by generally high $T_2$-weighted signal and low Akaike probabilities.

Figure 5.16 shows the $K^\text{trans}$ values estimated in each of the three VOIs. There is a trend of increasing median $K^\text{trans}$ value from tumour, through margins to the liver.
Figure 5.15: The graphs in the left and central columns show model fits to the data points for the extended Kety model and Materne model for a voxel within the tumour VOI (left column) and liver VOI (central column). The figure in the right column shows the measured AIF and the estimated PIF. Data for Patient 2 are shown in the upper row and for Patient 4 in the bottom row.
VOI in 4 of the six patients. The median $K_{\text{trans}}$ value in the liver is in all cases significantly higher than in the tumour.

Figure 5.16: Box plots of the $K_{\text{trans}}$ for the three VOIs (tumour, margins, liver) within the 6 patient data sets. See Section 5.3.2 for a description of the box plot features.

5.4.4 Conclusions

Application of the model selection technique to three VOIs within each patient data set generally showed an increase in the Akaike probabilities as we moved from the tumour VOI, through a tumour-margin region into liver tissue. This implies a decrease in the probability that the extended Kety model is the better description of the data as we move away from the tumour. The low Akaike probabilities observed in the tumour indicate a strong preference for the extended Kety model, which is consistent with the hypothesis that malignant lesions contain capillaries rather than sinusoids and recruit blood predominantly from an arterial supply [27, 20]. In non-tumour liver tissue, the leaky sinusoids and the increased blood supply from the portal vein weaken the suitability of the extended Kety model. The tumour margin is an area where we might expect tumour infiltration and partial volume effects between tumour
and liver tissue and where, moreover, motion effects may increase partial voluming among the different tissue types, so an intermediate Akaike probability is perhaps to be expected. However, we are unaware of this phenomenon being described previously, either for the identification of subtle tumour spread or in the assessment of PVEs. Median Akaike probability values of $< 0.6$ are seen in the tumour-margin regions and we demonstrated using synthetic data (Section 5.3.5) that the extended Kety model is generally preferred where both liver tissue and tumour tissue is present in a voxel.

Although the median Akaike probability in the liver VOIs is higher than in the tumour region, the model selection technique clearly prefers the Materne model in only two out of six cases (Patients 2 and 3). While this observation could result from inaccuracies in the estimated PIF, we have demonstrated using synthetic data generated with the Materne model (Section 5.3.4) that reduced portal flow (low simulated $k_{1hpv}$ values) or low SNR due, for example, to motion corruption leads to the single input extended Kety model being preferred even though the data is generated with the Materne model. A portal flow reduction could be caused by vasoconstriction due to the presence of metastases or by fasting and exercise status [17, 18, 19], which are unknown for the patients within this study. The liver VOIs were defined in the same lobe as the tumour VOI and therefore the vascular supply to these regions may be particularly affected by the presence of a nearby tumour.

It may be possible to explain the differing Akaike probabilities in terms of the nature of each patient’s disease and their treatment. However, with small patient numbers and a heterogeneous patient population containing a number of different primary cancer types and a range of treatments it is not possible to draw any clear conclusions. Nevertheless we have shown model selection to be a promising method for assessing liver microvascular function in this population and it would be worthwhile employing this technique in the design of prospective future studies with larger patient numbers.

The model selection technique is generally capable of distinguishing between tumorous and non-tumorous tissue (a significant difference is seen in 5 out 6 patients between tumour and margins, and between tumour and liver median Akaike probability values). It therefore has potential application to delineation of lesions and to detection of early signs of malignant tumours as the vascular and tissue characteristics change from those seen in healthy tissue. It could also be used to investigate tumour infiltration by assessment of a tumour-margins region.
Median $K^{\text{trans}}$ in the tumour region is, in all data sets, less than that within the liver. This is supported by the synthetic data results where fitting the extended Kety model to data generated using the Materne model with ground truth values based on acquired data gave a higher $K^{\text{trans}}$ value (0.51 min$^{-1}$) than that generally seen in tumour (0.36 min$^{-1}$), see Section 5.3.5.1. The definition of accurate tumour VOIs within the liver is therefore important to prevent overestimation of $K^{\text{trans}}$ by limiting the inclusion of liver tissue within the tumour VOI. The model selection technique has the potential to provide an accurate method of delineating the tumour which limits the influence of PVEs on parameter estimation.

5.5 Summary

We have presented a method for assessing the disrupted microvascular characteristics of tumour-bearing livers using the Akaike information criterion to select, on a per voxel basis, whether the extended Kety model or the Materne model provides the more appropriate description of the data. Included in this process was a novel method for estimating patient-specific PIFs that allows significantly easier implementation of dual input models of liver contrast agent kinetics (Section 5.2). We have demonstrated that the results of this approach for predicting a PIF are plausible (Section 5.2.1) and that this method can be used effectively to apply the Materne tracer kinetic model to DCE-MRI data (Section 5.4.3).

The model selection technique has been assessed using both synthetic (Section 5.3.4) and patient (Section 5.4) data sets and shows promise as a method for investigating areas of disrupted microvascular characteristics in the liver. It has successfully highlighted the distinction in vascular supply and function between non-tumorous and tumour tissue within the liver in a manner consistent with known physiology. This method has potential application for lesion detection; quantitative assessment of tumour invasion; monitoring natural history and treatment effects in tumours; assessment of partial volume effects and also for investigating diffuse liver disease such as cirrhosis and fibrosis where changes in the vasculature are known to occur.

We have also assessed the accuracy and precision of model fitting (Section 5.3.3), upon which the model selection technique depends and focused on the $K^{\text{trans}}$ parameter within the extended Kety model (Section 5.3.5) which has been used for monitoring
the efficacy of anti-angiogenic drugs. The results suggest that caution should be used with the definition of the tumour VOI in the liver, particularly at smaller tumour sizes to prevent an overestimation of median $K_{\text{trans}}$.

We have demonstrated the capability of the PhantomGenerator to generate multiple synthetic data sets specifically designed for investigating various aspects of image-analysis techniques. In the next chapter we use both the PhantomGenerator and the MotionEmulator to generate synthetic data and, along with acquired data sets, investigate the influence of motion on model fitting and selection and assess the potential benefit of using a registration algorithm to align the variable flip angle and time-series images.
Chapter 6

Assessing model-driven registration

6.1 Introduction

In Section 2.5 we discussed how the motion of the abdominal organs due to breathing can lead to an inconsistent tissue-to-voxel mapping during DCE-MRI time series imaging and we considered the use of registration algorithms to re-align the time series images. In particular we described the model-driven registration algorithm developed by Buonaccorsi et al. (Section 2.5.2.1) which accounts for signal intensity changes during the time series caused by contrast agent wash in and out.

In Section 2.6 we introduced the use of software phantoms for assessing registration techniques and in Chapter 3 and Chapter 4 we presented the development of a software phantom generator for generating synthetic DCE-MRI data sets from ground truth with motion emulation. A quasi-realistic synthetic DCE-MRI data set of a liver tumour that has ground truth values, anatomy and motion patterns based on acquired data was presented in Section 4.6.

In this chapter we aim to demonstrate the utility of the generated synthetic data for quantitatively evaluating the benefits of applying model-driven registration prior to model fitting and selection. The registration algorithm is run with two types of geometric transformations: translation only and affine. In particular, we are interested in the effect of registration on $K_{\text{trans}}$ estimation within the tumour region and
on the Akaike probability values within three VOIs which represent tumour, tumour margins and liver tissue (which replicates the analysis of the acquired data sets in Chapter 5). In Section 6.3, we apply the registration algorithm to a subset of the acquired data sets presented in Chapter 5 and compare the results to those seen for synthetic data. For \( K_{\text{trans}} \) estimation, only results for the tumour region have been included. This replicates standard practice within clinical trials where \( K_{\text{trans}} \) is often used to assess the effect of an anti-angiogenic drug on the tumour and results for the host tissue are not typically included. Also, for the synthetic data the liver is generated using the Matérne model, therefore \( K_{\text{trans}} \) values are not an appropriate measure.

### 6.1.1 Registration protocol

The registration protocol was developed for analysis of clinical trial data [73]. The acquired data presented in this chapter was registered by Gio Buonaccorsi as part of this clinical trial. To ensure that the synthetic data was treated in the same manner as the acquired data, it was also registered using the same protocol by Gio Buonaccorsi. Using the same person to perform the registration was particularly important to ensure a consistent approach for evaluating the registration results (see Section 6.1.1.1).

Registration of the time series was performed using the model-driven algorithm described in Section 2.5.2.1 [9]. However, a more recent implementation of the algorithm was used, written within the research group by Angela Caunce [64] (the application was named “RegSoft”). This implementation used sum of squared differences within the tumour volume of interest (VOI) as a measure to guide the registration and the Nelder-Mead downhill simplex [25] as the optimisation algorithm.

The model-driven algorithm accounts for the changing features in the dynamic series caused by contrast agent accumulation and wash-out by using the extended Kety model to generate a template synthetic time series against which the acquired series can be registered. Whilst the registration can be an iterative process (i.e. produce parameter maps, generate the template from the parameter maps and register the acquired data to the template) only one iteration was used as there was no clear evidence for any benefit from running multiple iterations. The variable flip angle (VFA) images for \( T_1 \) estimation were registered to the first pre-contrast image of the
time series using FLIRT [115].

The time series for the acquired data sets, analysed as part of a clinical trial, were only registered using translation only registration. However, the synthetic DCE-MRI time series were registered twice, once using translation only transformations and once using affine transformations. When using affine transformations, the translation only registration is run first and the results used to initialise the translation elements of the transformation matrix for the affine registration. The translation only registration also estimates the centre of rotation, which is initialised to the centre of the tumour VOI. This estimate is again used to initialise the affine transformation. The affine registration results in a transformation matrix plus a centre of rotation parameter. These are applied to the original (un-registered) time series to give the affine registered time series. Resampling was performed with sinc interpolation, limited to a 6 by 6 neighbourhood.

6.1.1.1 Evaluating the registration results

This section describes the standard procedure used for evaluating the registration results within a protocol developed for analysis of clinical trial data [73]. The magnitude of the applied translations within the registered images and the sum of correlation coefficients across the tumour VOI between adjacent images in the time series are plotted against time. Only the tumour VOI is considered as, whilst the deformations are applied to the whole image, the optimisation measure for the registration is only calculated using voxels in the tumour VOI. If a low summed correlation coefficient or a large translation is seen for a particular time-point, the locations of the tumour in pre-registration and post-registration images are visually compared with the tumour VOI and the closer case is retained. If neither are close, the time-point is removed. Where there are numerous mis-registrations throughout the time series the tumour VOI is expanded to included other features, such as vasculature which have a strong enhancement pattern, to provide the registration algorithm with additional information.
Chapter 6. Assessing model-driven registration

6.1.2 Median value comparisons and data presentation for VOIs

Testing for significant difference between median VOI values was performed using the Mann-Whitney U test with a significance level of $P \leq 0.01$. A correction for multiple comparisons was not applied.

Box plots have been used to present measured parameters within the VOIs. Within the box plots, the red line is the median value; the top box edge is the upper quartile and the bottom edge is the lower quartile; the length of the whiskers is 1.5 times the interquartile range and the remaining data points are displayed as crosses; the notches indicate a robust 95% confidence interval for differences in the medians.

6.2 Assessing model-driven registration using synthetic data

We have used three synthetic data sets to assess the model-driven registration: the data set with motion corruption presented in Section 4.6 (‘motion corrupted’); a data set with the same ground truth and anatomical definition but without motion emulation (‘static’) shown in Section 3.5; and a static data set without noise (‘noise free’). Time series and VFA images for $T_1$ estimation were generated for each data set using the protocol described in Table 5.6, except a flip angle of 30° was used for the dynamic images. Zero mean Gaussian noise with a standard deviation that corresponds to a signal to noise ratio (SNR) of approximately 7 in liver tissue (which is within the range measured on acquired data sets, see Section 3.5.1.1) was added to the dynamic series images. For the VFA images a lower standard deviation (corresponding to an SNR of approximately 40) was used to represent the averaging of multiple images. The VFA images for the motion corrupted data set were generated at different positions in the breathing cycle.

The motion corrupted data set was registered as described in Section 6.1.1 using 3D translations only (‘translation registered’) and using 3D affine transformations (‘affine registered’). The tumour VOI described in Section 6.2.2 was used for the registration process. The registration results passed the evaluation procedure (Section 6.1.1.1) without the need for VOI dilation, removal of any images or reversion to the images
Chapter 6. Assessing model-driven registration

from the motion corrupted data set.

Five data sets were therefore analyzed: motion corrupted, static, noise free, translation registered and affine registered. Model fitting (Section 5.3.1) and model selection (Section 2.3.3) were applied following the same procedure as for the acquired data sets in Chapter 5. Again we focused on the three VOIs used in Chapter 5: tumour, tumour margins and liver.

6.2.1 Registration Results

Single voxel concentration time courses pre- and post-registration are shown in Figure 6.1. The post-registration time courses show less variation in the concentration values of neighbouring time points (ignoring the initial rise of the curve), which is typical of the effect of the registration seen in this data set. The reduction in spread is indicated by a decrease in sum of squared errors (SSE) for the Kety model (chosen as the Akaike probability values are less than 0.5) from 0.13 mM\(^2\) for the unregistered data set to 0.04 mM\(^2\) for translation registered and 0.03 mM\(^2\) for affine registered. The reduction for the extended Kety SSE across the tumour VOI is shown in Figure 6.2.

Figure 6.3 compares a slice through the affine registered time series to the motion corrupted time series. Note that the similarity measure for the registration algorithm is only calculated using the tumour VOI, so the alignment of features outside of this region is not expected. The image for time-point 9 (44.73 s) has been warped more than the other time series images and appears to be a mis-registration. This may be due to a lack of adequate information within the VOI for the registration algorithm. The registered images appear smoother (i.e. less variation is seen within each tissue type) than the motion corrupted data set most likely due to interpolation within the registration algorithm.

Figure 6.4 shows difference images between the motion corrupted time series and the static noise free data set and between the translation registered time series and the static noise free data set, both for the tumour VOI only. At time point 10, the motion corrupted difference image appears identical to the registered difference image indicating that no translation has been applied by the registration. At time point 13 there is similarity between the difference images and the difference values
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Figure 6.1: Single voxel concentration time courses pre- and post-registration in synthetic data. The voxel is located in the tumour core in a central slice.

Figure 6.2: Box plots of extended Kety SSE difference between post and pre registration data sets (post minus pre) for the translation only and affine registrations. A lower value indicates a better fit to the data. See Section 6.1.2 for a description of the box plot features.
Figure 6.3: Images from the motion corrupted and affine registered synthetic series for slice 9. The acquisition time for each image is shown along with the time point number in brackets.
are high, suggesting that uncorrected motion remains in the registered data sets. At time point 9 the difference values are low, suggesting that the degree of motion corruption is small at this time point. At time point 7 the registered difference image has lower values than the motion difference image indicating that the registration has resulted in closer agreement to the static data set. Residual differences due to noise on the motion corrupted and registered images even if the registration were to fully compensated.

**Figure 6.4:** Difference images for the translation registered and motion corrupted synthetic series for slice 6. Only the tumour VOI is shown. The acquisition time for each image is shown along with the time point number in brackets. The image on the left for each time point is the absolute difference between the motion corrupted image and the static noise free image. The image on the right is the absolute difference between the translation registered image and the static noise free image.
Figure 6.5 shows the signal intensity differences through the time series between the motion corrupted and static data data sets and between the translation registered and static data sets, both for the tumour VOI only. The registered data set has a lower standard deviation (17.12) than the motion corrupted data set (29.81), demonstrating that the signal intensities within the registered data set are closer to those in static data set. Again a difference due to noise would be expected.

Figure 6.5: Histogram of signal intensity differences (a) between the motion corrupted and static (noise free) images and (b) between the translation registered and static (noise free) images, both for the tumour VOI only.

Figure 6.6 compares a subset of contiguous voxels from a single row of the image through time for the 5 data sets: static, noise free, motion corrupted, translation registered and affine registered. The 28\textsuperscript{th} row from the 6\textsuperscript{th} slice has been selected as this bisects the lower portion of the tumour allowing the effects of motion, and therefore registration, to be seen as the tumour moves in and out of this region. Along the x-axes are the selected voxels from the 28\textsuperscript{th} row and along the y-axes, the voxel at each time point is shown. The time-point at which the contrast agent reaches the liver tissue can be seen as an increase in intensity (indicated by the red arrow) and from this point the darker tumour core can be clearly seen on the noise free data set (indicated by the green arrow).

In the motion corrupted data set there are higher intensity voxels in the region associated with the tumour core which show up as white bands (indicated by the blue arrow). These occur when the higher intensity liver and tumour rim tissue moves into these voxels. Within the registered data sets these brighter bands are less evident suggesting that a more consistent tissue to voxel mapping has been achieved for the
tumour core throughout the time series.

![Selected voxels](image)

**Figure 6.6:** Signal intensity time series for a subset of contiguous voxels from the 6th slice for the five synthetic data sets. The selected voxels are highlighted in red in (a). In (b) - (f) the x-axes are the selected voxels and along the y-axes, the voxel at each time point is shown. The arrival of contrast agent in liver tissue is indicated by the red arrow. The darker tumour core is indicated by the green arrow. The movement of liver tissue into voxels previously occupied by tumour core is indicated by the blue arrow.

### 6.2.2 Model fitting and selection results

Model fitting (Section 5.3.1) and selection (Section 2.3.3) of the extended Kety model and Materne model were performed in the same manner as for the acquired data sets in Chapter 5. The same three VOIs as for the acquired data sets were analyzed: tumour, tumour margins and liver (see Figure 6.7). The tumour mask used to generate the 47th time-point was downsampled to the same voxel size as the time series.
images and used for the tumour VOI during analysis as it had a displacement fraction of 0.47 which lies in the centre of the breathing displacements that range from 0.03 – 0.91 (see Section 4.3). The tumour margins VOI was generated automatically from the tumour VOI (in the same manner as for the acquired data sets) to give a shell of 2 voxel widths around the tumour but separated from it by 1 voxel width (see Section 5.4.2). The shell was then cropped so that it remained within the liver.

Figure 6.7: (a) Tumour (white), margins (yellow) and liver (red) VOIs for the synthetic data (slice 9). (b) A post-contrast image (time-point 12 at 54.67 s) from the noise-free static data set (slice 9).

Figure 6.8 shows the Akaike probability maps for slice 9 of the 5 synthetic data sets. Figure 6.9(a) shows the Akaike probability values measured in the three VOIs in a data set without motion or noise. A median value of < 0.01 for the tumour region and 1 for the margins and liver regions (see table 6.1) selects correctly for the generative model in all three VOIs. Outlying values between 0 and 1 are seen for the margins region, which are likely to be due to partial voluming between liver and tumour tissue.

The effect of noise on the Akaike probability values can be seen by comparing Figure 6.9(a) and Figure 6.9(b). The presence of noise within the fitting process now gives a median value of 0.13 for the tumour region, which still correctly selects for the extended Kety model. The median Akaike probability value for the margins and liver regions has decreased substantially to 0.52 and 0.57 respectively, tending away from

<table>
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Table 6.1: Median Akaike probability tumour values in the 5 synthetic data sets.
Figure 6.8: Akaike probability maps generated from the 5 synthetic data sets: static, noise free, motion corrupted, translation registered, affine registered. (All are slice 9.) The color bar applies to all the images. A value of 0 indicates strong selection of the extended Kety model and 1 indicates strong selection of the Materne model.
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Figure 6.9: Akaike probability box plots generated from the 5 synthetic data sets: static, noise free, motion corrupted, translation registered, affine registered. A value of 0 indicates strong selection of the extended Kety model and 1 indicates strong selection of the Matérne model. See Section 6.1.2 for a description of the box plot features.
clear selection of the Materne model. There is also an increased inter-quartile range for all three VOIs. The results for the static data set with noise are similar to those seen within the acquired data sets (see Figure 5.13) as both show a large range of values within each VOI and 5 of the 6 acquired data sets have liver regions with Akaike probability values that do not strongly select for the Materne model. This suggests that the presence of noise may be a contributing factor to these characteristics in the acquired data.

The results for the motion corrupted data set are similar to the static data set, see Figure 6.9(c) and Table 6.1, with no significant difference between the median Akaike probability values of each tissue in the motion corrupted when compared to the same tissue in the static data set (P values of 0.896, 0.050 and 0.931 for the tumour, margins and liver regions respectively). This suggests that the Akaike model selection technique is robust to motion. Both data sets show a similar trend of rising Akaike probability value as we move from the tumour, through the margins to the liver region as seen in the acquired data sets (see Figure 5.13).

The median values are significantly different for tumour to margins, tumour to liver and margins to liver comparisons within the motion corrupted data set (see Table 6.3). This significant difference is seen for the tumour to margins and tumour to liver comparison for 5 of the 6 acquired data sets and for the margins to liver comparison for 4 out of the 6 acquired data sets (Section 5.4.3). The similarities between the Akaike parameter values for the acquired and synthetic data sets suggests that the methods used to generated the synthetic data are valid and that the synthetic data provides a relevant test case for assessing analysis techniques.

The box plots of Akaike parameter values for the registered data sets are shown in (Figure 6.9(d) and Figure 6.9(e)). Assessing the margins and liver VOIs in the registered data sets may not be appropriate as the registration algorithm only aims to align the tumour. However, as we have ground truth for these regions it is still interesting to investigate the effects of the registration algorithm in these regions. The median values for all the regions in the registered data sets are significantly different to the static data sets (unlike the motion-corrupted data set). The median value for the tumour region (see Table 6.3) is lower than for the static data set and the median value for the margins and liver regions are higher, selecting more strongly for the correct generative models than in the motion corrupted or static data sets. This is probably due to the registration interpolation smoothing the images. The
smoothing reduces the noise on the time series leading to a greater reduction in SSE for the generative model than the alternative model, leading to the generative model being more strongly selected.

Figure 6.10 shows the $K^{\text{trans}}$ values for the tumour region in the 5 synthetic data sets: noise free, static, motion corrupted, translation registered and affine registered. Figure 6.10 and Table 6.2 suggest that the median value is robust to motion. The median values of motion corrupted, translation registered and affine registered data sets are not significantly different to the static data set with P values of 0.58, 0.69 and 0.83 respectively.

**Table 6.2:** Median tumour values for $K^{\text{trans}}$ in the 5 synthetic data sets.

<table>
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<tr>
<th>tumour ($\text{min}^{-1}$)</th>
<th>noise free</th>
<th>static</th>
<th>motion corrupted</th>
<th>translation</th>
<th>affine</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.35</td>
<td>0.31</td>
<td>0.29</td>
<td>0.31</td>
<td>0.31</td>
<td>0.31</td>
</tr>
</tbody>
</table>

**Figure 6.10:** $K^{\text{trans}}$ box plot for the tumour region generated from the 5 synthetic data sets: noise free (nf), static, motion corrupted, translation registered (trans), affine registered. See Section 6.1.2 for a description of the box plot features.

Histograms of $K^{\text{trans}}$ for the tumour region are shown in Figure 6.11. The tumour has two sub-regions: the core and the rim, with ground truth values of 0.18 min$^{-1}$ and 0.36 min$^{-1}$ respectively. Even for the noise-free data set a range of ground truth values are seen due to partial volume effects between the tumour, core and liver tissues. A bi-modal distribution that reflects the distinct ground truth values for the core and rim is seen in the noise free and static data sets. The bi-modal distribution is lost in the motion-corrupted data set and then restored in both translation only and affine registered data sets.

Figure 6.12 (a) - (c) show the $K^{\text{trans}}$ maps for the tumour VOI for the static noise
Table 6.3: Comparison between median tumour, margins and liver VOI Akaike probability values, using the Mann-Whitney U test. (No correction for multiple comparisons was made.)

<table>
<thead>
<tr>
<th>data set</th>
<th>tumour to margins</th>
<th>tumour to liver</th>
<th>margins to liver</th>
</tr>
</thead>
<tbody>
<tr>
<td>noise free</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>static</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>0.093</td>
</tr>
<tr>
<td>motion corrupted</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>translation</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>0.083</td>
</tr>
<tr>
<td>affine</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>0.335</td>
</tr>
</tbody>
</table>

Figure 6.11: $K_{\text{trans}}$ histograms for the tumour region generated from the 5 synthetic data sets: noise free, static, motion corrupted, translation registered, affine registered. The ground truth values for the tumour core and rim are 0.18 min$^{-1}$ and 0.36 min$^{-1}$ respectively.
free, motion corrupted and translation registered data sets for three example slices. From visual inspection, the translation registered maps appear more similar to the static noise free data set than the motion corrupted data in all three slices. For example, slice 12 has a clear rim and core pattern in the static data set that is not as obvious in the motion corrupted data set but is to some extent regained in the registered data set. The lower values in the translation registered difference map (Figure 6.12(e)) in comparison to the motion difference map (Figure 6.12(d)) indicate that after translation registration the $K_{\text{trans}}$ values are closer to the ground truth values. A residual difference would be expected, even if a perfect match to the ground truth were gained, due to the noise on the motion corrupted and translation registered data.

6.2.3 Conclusions and Discussion

Five synthetic data sets have been analysed to assess the effects of motion and the benefits of registration for model fitting and selection: noise free, static, motion corrupted, translation registered and affine registered. The ability of the Akaike model selection technique to distinguish between the tumour, margins and liver regions is robust to the motion emulated in the synthetic data set. Translation only and affine registration lead to median Akaike probability values that differ from those in the static noisy data set, but that more strongly select the correct generative model. This is likely to be due to interpolation within the registration reducing the noise on the time series therefore allowing the model selection technique to clearly identify the generative model.

There is a strong similarity between the pattern of Akaike probability values seen in the motion corrupted data synthetic data set and acquired data sets. For example, the median Akaike probability in the tumour selects for the Kety model and increasing median values are seen as we move through the margins region to the liver. There are also significant differences between the median values of the three regions and acquired and synthetic data sets. These similarities demonstrate that the methods used to generate the synthetic data are valid and that the data forms a good test set for the analysis techniques.

The results indicate that median $K_{\text{trans}}$ for the tumour region is also robust to the motion within the synthetic data. However, histograms of $K_{\text{trans}}$ for the tumour
Figure 6.12: (a), (b) and (c) show $K^{\text{trans}}$ maps for the static noise free, motion corrupted, and translation registered data sets for the tumour VOI. (d) shows the absolute difference between the motion corrupted and static noise free $K^{\text{trans}}$ maps. (e) shows the absolute difference between the translation registered and static noise free $K^{\text{trans}}$ maps. The slice number is shown above each image.
region reveal that the bi-modal distribution due to distinct ground truth values for the core and rim is lost due to motion corruption but restored by both translation-only and affine registration. These results suggest that registration is beneficial for analysis techniques that rely on tumour heterogeneity. This supports the work by Buonaccorsi et al. [73] who showed that the model-driven registration improved tumour sub-segmentation in acquired data.

These investigations demonstrate the utility of synthetic data for testing the robustness of model fitting to motion and selection and the benefit of applying the model-driven registration algorithm. For example, without knowledge of the ground truth $K^{\text{trans}}$ distribution within the tumour, it would not have been possible to determine whether the bi-modal distribution seen after registration was the recovery of the true distribution or an artifact of the registration process.

### 6.3 Applying model-driven registration to acquired data

In the previous section (Section 6.2) we assessed the model driven registration algorithm using synthetic data. We found that the registration provided limited benefit for estimated median $K^{\text{trans}}$ tumour value or for the Akaike model selection technique as we demonstrated that these methods were robust to the motion. However, we found that the registration is likely to be beneficial to measures that rely on tumour heterogeneity. In this section we apply model-driven registration to a subset of the acquired data sets presented in Chapter 5 and compare the effects of registration to those seen in the synthetic data.

#### 6.3.1 Data sets and analysis protocol

6 liver metastases patient data sets were analysed in Chapter 5. In this section, only 3 of those data sets (Patients 2, 3, and 4) are included. Patients 1 - 4 were registered as part of a clinical trial [73]. However, the registration failed for the tumour analysed for Patient 1 as the registration was unable to correct the large number of time points with large mis-alignments. Patients 5 and 6 were not part of the same clinical trial, were not registered and have therefore not been included. The registration of the time
series and VFA images was performed as described in Section 6.1.1. 3D translation only deformations were applied.

For Patients 2 and 4 the original VOI was used for registration and there was no rejection or reversion of the time series images (see Section 6.1.1.1). Whereas for Patient 3 the VOI was dilated as registration with the original VOI was evaluated to be a failure. Six images from the time series for this patient were were rejected (6, 9, 18, 45-46) and three were reverted to the original (non-registered) images.

Model fitting and selection was performed as described in Section 5.3.1 and Section 2.3.3 respectively. Analysis was focused on two regions of interest: tumour and tumour margins. The liver regions were not analysed as the registration algorithm does not aim to align the structure outside of the tumour VOI and could therefore produce unfeasible deformations in this region (as described in Section 6.1.1).

### 6.3.2 Results

Figure 6.13 compares pre- and post-registration contrast agent concentration curves for a voxel within the tumour rim and a voxel within the tumour core for Patient 2. (The core and rim regions were defined using median $IAUC_{60}$ value as described in Section 4.6.) A reduction in the spread of data can be seen for both voxels but it is more noticeable for the core voxel where the SSE for the extended Kety model reduces from 0.18 to 0.07 mM$^2$. For the rim voxel the SSE for the Materne model reduces from 0.34 to 0.31 mM$^2$. The SSE for the Materne model has been used for the rim voxel as it has an Akaike value greater than 0.5, whereas the core voxel has an Akaike probability value that selects for the extended Kety model. The degree to which the SSE changes between pre- and post-registration varies between the patient data sets (see Figure 6.14) but, as with the synthetic data set (Figure 6.2), the majority of voxels show a reduction in SSE.

Figure 6.15 shows the Akaike probability maps for Patients 2, 3, and 4 derived from pre- and post-registration data sets. The tumour region on which the registration was focused is shown by the arrow on the pre-registration Akaike probability map. Note that these patients have multiple tumours which present as dark patches in the Akaike probability maps or as lighter patches within the liver on the $T_2$-weighted images.
Figure 6.13: Single voxel concentration time courses pre- and post-registration for Patient 2 along with the estimated contrast agent curves for the extended Kety and Materne model. In (a) and (b) the voxel is located in the tumour rim in a central slice and for 6.13(c) and in 6.13(d) the voxel is located in the tumour core. The legend in (d) applies to all the figures.

Figure 6.14: Box plots of extended Kety SSE difference between pre- and post-registration data sets (post minus pre). A lower value indicates a better fit to the data. See Section 6.1.2 for a description of the box plot features.
Figure 6.15: Akaike probability maps for Patients 2, 3, and 4 derived from pre- (original) and post-registration data sets. The arrow on the pre-registration map indicates the tumour region for which the registration similarity measure was calculated. The $T_2$-weighted image is also shown.
Figure 6.16 compares pre- and post-registration Akaike probability value box plots for the tumour and margins regions. In the tumour regions a non-significant increase in the median Akaike probability value is seen post-registration in all three data sets (see Table 6.4), with a mean increase of 0.017. However, in the synthetic data set a significant decrease of approximately 0.12 is seen post-registration (translation only). In the margins regions of the patient data a non-significant increase in median Akaike probability value is seen. However, in the synthetic data this increase is significant. There is a significant difference between the median values of the tumour and margins regions in all patients in both the motion corrupted and registered data sets.

**Figure 6.16:** Akaike probability value from pre- (original) and post-registration acquired data sets for tumour and margins VOIs. See Section 6.1.2 for a description of the box plot features.

<table>
<thead>
<tr>
<th>patient</th>
<th>tumour original</th>
<th>tumour registered</th>
<th>margins original</th>
<th>margins registered</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>0.23</td>
<td>0.24</td>
<td>0.41</td>
<td>0.51</td>
</tr>
<tr>
<td>3</td>
<td>0.13</td>
<td>0.16</td>
<td>0.55</td>
<td>0.61</td>
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<tr>
<td>4</td>
<td>0.02</td>
<td>0.03</td>
<td>0.71</td>
<td>0.75</td>
</tr>
</tbody>
</table>

**Table 6.4:** Median tumour and margins values for Akaike probability value in the three patient data sets pre- and post-registration.

Figure 6.17 compares pre- and post-registration $K^{\text{trans}}$ box plots for the tumour region. There are no significant differences between the median values for the pre- and post-registration data sets, see table 6.5, with P values of 0.891, 0.545, and 0.099 for Patients 2, 3, and 4 respectively. This matches the result seen for the synthetic data.

Figure 6.18 compares $K^{\text{trans}}$ histograms of the tumour region for the original (motion-corrupted) data sets to the registered data sets. Whilst a change in the distribution
Figure 6.17: $K^{\text{trans}}$ box plots derived from pre- and post-registration acquired data sets for tumour and margins VOIs. See Section 6.1.2 for a description of the box plot features.

<table>
<thead>
<tr>
<th>patient</th>
<th>tumour original</th>
<th>tumour registered</th>
<th>margins original</th>
<th>margins registered</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>0.16</td>
<td>0.16</td>
<td>0.26</td>
<td>0.26</td>
</tr>
<tr>
<td>3</td>
<td>0.20</td>
<td>0.20</td>
<td>0.50</td>
<td>0.51</td>
</tr>
<tr>
<td>4</td>
<td>0.23</td>
<td>0.27</td>
<td>0.71</td>
<td>0.75</td>
</tr>
</tbody>
</table>

Table 6.5: Median tumour and margins values for $K^{\text{trans}}$ ($\text{min}^{-1}$) in the three patient data sets pre- and post-registration.

of $K^{\text{trans}}$ values can be seen, unlike the synthetic data where ground truth is known, it is hard to establish from these data whether applying the registration algorithm results in a distribution that is closer to the underlying ground truth.

6.3.3 Conclusions and Discussion

There is no significant difference between the median $K^{\text{trans}}$ values in the tumour VOI between pre- and post-registration data sets. This mirrors the results seen for the synthetic data set, supporting the hypothesis that median $K^{\text{trans}}$ is robust to motion. Evidence for this conclusion has also been reported by Buonaccorsi et al. [9] who found that a change in the reproducibility of median $K^{\text{trans}}$ was not seen when the model-driven registration was applied to repeated patient data acquisitions.

When comparing the median Akaike probability value between the pre- and post-registration data sets for the tumour and margins regions, no significant difference is seen. The significant difference between the tumour and margins median Akaike probability value is present both data sets. This indicates that the Akaike model selection technique is robust to motion, supporting the conclusions drawn using syn-
Figure 6.18: $K^{\text{trans}}$ tumour histograms for Patients 2, 3, and 4 derived from pre- and post-registration data sets.
thetic data. However some differences are seen between the synthetic and acquired data sets post-registration.

As noted above, in the acquired data sets the median Akaike probability values of the VOIs do not change post-registration. However, registration of the synthetic data sets gave significantly different Akaike probability values that led to the generative model being more strongly selected in all three VOIs. The models used to generate the synthetic data are the candidate models in the model selection technique, whereas the concentration time curves for the acquired data are a result of complex interacting biological and physical process for which the tracer kinetic models are only a gross approximation. The smoothing caused by interpolation in the registration algorithm leads to temporal smoothing of the contrast agent time courses. For synthetic data, this is likely to lead to a greater reduction in SSE when fitting the generative model, than when fitting the alternative model, and this results in the generative model being more strongly selected by the model selection technique. Even if the motion is not fully corrected by the registration algorithm, the homogeneous ground truth values within the synthetic data probably still allow the correct model to be identified when using the median Akaike probability value for the VOI.

It would be possible to address these issues by using more complex generative models within the PhantomGenerator and by emulating the natural variation of ground truth parameters for each organ. In fact, the PhantomGenerator has been designed to facilitate such extensions. However, gaining relevant ground truth values for more complex models requires high quality data to which the model can be confidently fitted. Including a spread of parameter values is a possible refinement that has been left for future work.

6.4 Summary

In this chapter we have used synthetic data to quantify the effect of motion on $K_{\text{trans}}$ estimation and the ability of the Akaike model selection technique to distinguish between tumorous and non-tumorous tissue within the liver. We have applied a registration algorithm to the synthetic data to quantify the benefit of performing registration prior to applying these analysis techniques. The results suggest that median $K_{\text{trans}}$ in the tumour is robust to motion, but that registration is benefi-
cial for analysis techniques that rely on heterogeneity (as shown by the histogram analysis). The Akaike model selection technique was also shown to be robust to motion. These conclusions were supported when analysis of three acquired data sets was performed and are in accordance with Buonaccorsi et al. [9] who found that the reproducibility of median $K_{\text{trans}}$ was not changed by model-driven registration and Buonaccorsi et al. [73] who reported that model-driven registration improved tumour sub-segmentation in acquired data.

Whilst there are some differences between the results for the synthetic and acquired data sets, notably the significant change in the median Akaike probability value post-registration in the synthetic data set which is not seen in the acquired data sets, on the whole the synthetic data and acquired data show similar characteristics. This demonstrates that the methods used to generate the synthetic data are valid and that the synthetic data sets are relevant test cases for assessing analysis techniques and the benefits of registration.

It would be beneficial to perform these experiments on both further synthetic and acquired patient data sets. Synthetic data could be produced with different ground truth values and breathing patterns, for example, to test where the limits of the registration are. However, this illustrative data sets clearly demonstrates the utility of synthetic data for assessing analysis techniques such as model fitting and selection and the benefit of performing registration. Quantitative assessment of the effect of registration on the final outcome measure (for example median $K_{\text{trans}}$) is possible as ground truth is known. The utility of synthetic data with known ground truth is also clearly demonstrated when considering the $K_{\text{trans}}$ histograms for the tumour VOI pre- and post-registration. In the acquired data sets it is not possible to determine whether the change in $K_{\text{trans}}$ distribution post-registration is a more accurate reflection of the physiology and heterogeneity for each tumour. Whereas the ground truth distribution of $K_{\text{trans}}$ values in a static data set is known for the synthetic data, and the restoration of this distribution as a results of registration can be clearly demonstrated.
Chapter 7

Conclusions, discussion and further work

In this thesis we have presented the flexible PhantomGenerator and MotionEmulator software applications for generating synthetic data from known ground truth with quasi realistic anatomy and motion which can then be used to validate post-acquisition image analysis techniques. We have demonstrated the utility of the PhantomGenerator by producing synthetic data that allowed us to evaluate model fitting and model selection techniques for DCE-MRI and to assess the robustness of these techniques to noise, motion and PVEs. The model selection technique itself is a novel method of investigating the microvascular characteristics of livers with metastatic disease and we have therefore further evaluated this technique with six acquired data sets. Lastly, we have used the generated synthetic data to assess a model-driven registration algorithm for re-aligning the DCE-MRI time-series images.

In this chapter we summarise the work presented within this thesis and discuss the conclusions and findings. We then consider possible future investigations that could be based on the work presented within this thesis.

7.1 Conclusions and discussion

In Chapter 3 we presented the PhantomGenerator which was developed using established software engineering and validation principles to provide a flexible modular
design and to ensure the correctness of the generated synthetic data. Object-oriented methodology [95] was employed to facilitate the extension of the PhantomGenerator to multiple imaging scenarios. For example, interfaces are used to define the functionality that input functions and tracer kinetic models should provide. Implementations of models and vascular input functions that describe the desired tissue microvascular characteristics can then be easily added by adhering to the interface definition. The same object-oriented strategy has been used to allow various pulse sequence equations to be implemented for MRI and it would also be possible to add modules for other modalities. The use of the standard object-oriented Builder and Factory design patterns ensures that the required options can be easily selected whilst retaining the extensibility and modularity of the PhantomGenerator. The modular design also allows the use of an anatomical definition that is tailored for the specified problem domain, whilst being able to use all the available signal generation capabilities and tissue characteristic descriptions.

We demonstrated the flexibility and extensibility of the PhantomGenerator by producing contrast agent concentration curves with different input functions and tracer kinetic models (Section 3.4.1) and by generating synthetic images with quasi-realistic anatomy using the inversion recovery and SPGR pulse sequences (Section 3.5.2). We also generated non-anatomical images with model parameter ranges (Section 3.4.4) that can be used for assessing the accuracy and precision of the model fitting and model selection techniques.

In Chapter 4 we presented the MotionEmulator. This application takes as input a set of end-exhale organ masks and an end-exhale to end-inhale displacement map for each axis. It outputs a set of warped masks for each time point of an image time series. Each image within the time series can occur at intermediate points between end-exhale and end-inhale in the breathing cycle, therefore a fraction of the displacement maps is applied at each time-point. The fraction is determined from a breathing trace that can either be a functional form or a text file describing an acquired breathing trace. The generated time-series of organ masks can be used as input to the PhantomGenerator to emulate image time-series with motion corruption. The MotionEmulator is a flexible application built using the same software development principles as the PhantomGenerator allowing it to be easily extended to new scenarios.

We generated a synthetic DCE-MRI time-series for a liver lesion by combining the
MotionEmulator and PhantomGenerator applications (Section 4.6). End-exhale organ masks and the associated displacement masks [63], derived from biomechanical modelling, were used as input to the MotionEmulator. (This data was provided by Kristy Brock.) An acquired breathing trace (provided by Alex Morgan) was also input to the MotionEmulator. Ground truth model and MR parameter values for each of the organs, derived from acquired data sets (Section 3.5.1), were input to the PhantomGenerator along with the warped masks output from the MotionEmulator to generate the synthetic DCE-MRI time series. We qualitatively evaluated the generated synthetic data set by visual comparison of time series images and tissue curves with an acquired data set. We demonstrated that it reflected the expected features, in particular those that would affect registration algorithms and model fitting analysis. However, some limitations were also noted (Section 4.6.1). For example, that subdividing the tumour into only two regions (core and rim) does not reflect the degree of heterogeneity seen in acquired data. Possible methods for addressing the limitations are discussed below (Section 7.2).

Synthetic DCE-MRI images of liver tumours generated using MR physics and tracer kinetic models have been previously presented [9, 10, 11], as has the use of a biomechanical model to generate post-contrast breast images [71, 12]. However, we believe that these two techniques have not previously been combined. The use of MR physics and tracer kinetic models to generate the data gives known ground truth and the biomechanical model gives a greater level of motion complexity than the synthetic DCE-MRI liver tumour data sets previously presented [9, 10, 11]. The PhantomGenerator and MotionEmulator have also been developed using well established software development principles, which may not be the case for the previously presented phantoms.

In Chapter 5 we described a model selection technique based on the Akaike information criterion [24] for investigating the spatially varying microvascular characteristics of livers with metastatic disease. The model selection technique includes fitting the dual-input Materné model [5] which requires a portal input function. Measurement of a portal input function is known to be problematic [44, 37] and we offer a solution by estimating a patient-specific PIF from the patient’s measured AIF (Section 5.2). We have shown this method to produce PIFs that are a good analogue for acquired data. The Akaike model selection technique had been previously applied to brain [49] and lung data [48] but we believe this to be its first application to the characterisation of liver metastases.
We assessed the model fitting and model selection techniques using synthetic data produced by the PhantomGenerator (Section 5.3). The model fitting analysis is required for model selection and also provides estimated parameters, such as $K^{\text{trans}}$, which reflect the underlying tumour biology and have been used to describe changes in microvascular function in studies on anti-angiogenic agents [2]. The validation of the model fitting and model selection techniques demonstrated the usefulness of the PhantomGenerator to investigate the accuracy and precision of analysis methods and their robustness to aspects such as noise and PVEs as the estimated parameters could be compared against the known ground truth. The accuracy and precision of model fitting was found to be adequate and the model selection technique was capable of distinguishing between the models at SNRs of 10 and 5.

We applied the Akaike model selection technique to six acquired data sets and analyzed three volumes of interest: tumour, tumour-margins and liver (Section 5.4). We found that the model selection technique selected for the extended Kety model [3] within the tumour region and that the suitability of the extended Kety model weakened when moving through the tumour-margins region to the liver. There was a significant difference between the median Akaike probability values for the tumour versus liver and tumour versus tumour-margins VOIs in five out of the six acquired data sets suggesting that the model selection technique is capable of distinguishing between metastases and liver tissue in a manner that supports previous knowledge of tumour and liver physiology [1, 8, 20]. This is therefore a promising technique for investigating spatially varying microvascular characteristics of livers with metastatic disease, with potential applications such as the early detection of metastases and assessment of tumour invasion.

In Chapter 6, we used the synthetic DCE-MRI data set of a liver lesion with motion emulation (presented in Chapter 4) to assess the effects of motion on $K^{\text{trans}}$ estimation and on the ability of the Akaike model selection technique to distinguish between tumour, tumour-margins and liver regions in livers with metastatic disease. We applied a model-driven registration [9] to the synthetic data set first using 3D-translation then affine transformations to assess the potential benefits of re-aligning the time series images (Section 6.2). The synthetic data indicated that median Akaike probability value of the tumour, tumour-margins and liver VOIs are robust to motion. The margins region is most (but still non-significantly) affected by motion, probably due to both tumour and liver tissue moving in and out of the voxels in the margins region during the dynamic series. In the acquired data sets (Section 6.3) we found
that the median Akaike probability value in the tumour and margins VOIs did not change significantly with registration supporting the finding that, for these data sets, model selection is robust to motion.

Similar patterns of Akaike probability value are seen in the acquired and synthetic data sets. For example, a significant difference in median Akaike probability value between tumour and liver regions is seen pre- and post- registration in both acquired and synthetic data sets. However, some post-registration differences were noted, which may be due to the homogeneous ground truth values for each tissue in the synthetic data which do not emulate the natural variability seen in the acquired data sets. The generative models for the synthetic data are also a direct match to those used in the model selection, whereas the tissue curves in the acquired data are due to complex physiological processes. Refining the PhantomGenerator to address these differences is discussed in the next section (7.2).

The median tumour $K^{\text{trans}}$ value was also found to be robust to motion using the synthetic data sets (Section 6.2), and this finding was again supported by the acquired data (Section 6.3) where the median tumour $K^{\text{trans}}$ did not change significantly after registration. The synthetic data also demonstrated that the distribution of $K^{\text{trans}}$ values within the tumour was disrupted by motion and restored by both translation-only and affine registration. Whilst it is not possible to draw general conclusions based on one synthetic data set and one registration algorithm, these results suggest that registration may be of benefit where any measures reliant on tumour heterogeneity are required. The assessment clearly demonstrates the advantages of using synthetic data for quantitative evaluation of registration methods. For example, knowledge of the ground truth $K^{\text{trans}}$ distribution allowed the benefits of registration of heterogeneity to be assessed.

By comparing the Akaike probability values and $K^{\text{trans}}$ estimates seen in acquired and synthetic data we have shown that the synthetic data is a good analogue for acquired data when validating the model fitting and model selection techniques and when assessing a model-driven registration algorithm. As the synthetic data is generated from ground truth, the phantoms produced can be used to make quantitative evaluations of the effect of algorithms that are within the post-acquisition processing pipeline on the final outcome measures - for example, does registration improve the accuracy of the model fitting technique? The flexibility of the PhantomGenerator allows the influence of various aspects of the images on the analysis techniques to be
investigated. For example, the influence of motion, noise and partial volume effects on the robustness of the model selection and fitting techniques.

To summarise, in this thesis we have presented the PhantomGenerator and MotionEmulator applications that can be used for generating synthetic time series images with motion corruption. We have demonstrated the flexibility of the applications for producing synthetic data for different imaging scenarios and have generated synthetic data for DCE-MRI of liver metastases. To demonstrate the utility of the applications, we have used the synthetic data to quantitatively evaluate model fitting and model selection techniques and the benefit of applying a model-driven registration algorithm. The PhantomGenerator and MotionEmulator allow us to address other application areas in a similarly quantitative manner and we discuss some possible areas of interest in the next section along with potential enhancements to the PhantomGenerator and MotionEmulator applications.

### 7.2 Further Work

The synthetic DCE-MRI liver data set presented in this thesis was qualitatively evaluated by visual comparison with an acquired data set (Section 4.6) and possible refinements were discussed (Section 4.6.1). Example enhancements that are relevant to model fitting, model selection and registration in livers with metastatic disease are emulation of the natural physiological variation of tissue characteristics within the liver and tumour, and inclusion of a dispersion term within the vascular input function models [38]. The natural variation of tracer kinetic and MR parameters within each tissue could be achieved by using parameter maps for each tissue that are generated from parameter distributions derived from acquired data sets. Inclusion of input function models which include dispersion terms is straightforward as the PhantomGenerator has been designed for such extensions. However, analysis of acquired data sets would be required to gain relevant ground truth for the dispersion term.

Also, more complex tracer kinetic models could be easily implemented within the PhantomGenerator. For example, the AATH [4] model used to generate synthetic contrast agent time courses by Roberts [30] or the MMID4 model (National Simulation Resource, Department of Bioengineering, University of Washington) used by
Buckley [116]. These are likely to give tissue uptake curves which are closer to those in acquired data. This may, for example, benefit assessment of the model selection technique as the generated tissue curves will be more complex than the candidate models, as is the case for acquired data. However, acquisition of high quality data sets may be required to gain relevant ground truth for these more complex models, which in itself may be challenging and time consuming.

Despite the noted limitations, the utility of the synthetic data for evaluating model fitting, model selection and registration has been demonstrated and it could also be used, without modification, to perform a quantitative comparison of different registration algorithms for DCE-MRI of liver tumours and to aid refinement of the model-driven registration. Further synthetic data sets for these evaluations could be produced by: sampling the breathing cycle at different time points; using different acquired respiratory traces; using the ground truth values from each of the 6 patient data sets (see Section 3.5.1) with patient specific AIFs and PIFs to create a synthetic data set for each patient; and obtaining sets of input organ masks and associated displacement maps for other patient cases. It would also be possible to generate synthetic data which could be used to assess the relative benefits of a free-breathing acquisition to the breath-hold approach [37].

The flexible nature of the PhantomGenerator and MotionEmulator lends itself to use in further investigations that include the development and quantitative evaluation of image analysis techniques. If extension of the PhantomGenerator is considered (and this is facilitated by the modular design), then validation test data sets could be produced for a wide range of imaging applications. Examples include DCE in other anatomical regions with different vascular functions, for example the kidneys; modelling arterial spin labelling MRI, PET, functional MRI, and MR elastography; and MR artifact modelling (beyond motion). The applications could also be used to provide insight into the behaviour of different MRI acquisition methods. For example, testing for contrast to noise ratio differences between different $T_1$ acquisition protocols. We discuss some examples of further application areas in detail below.

One relevant extension to the work in this thesis would be the addition of a CT signal generation module. By generating DCE-CT and DCE-MRI phantoms for the same synthetic patient, it would be possible to assess the quality of an existing inter-modality registration algorithm that has been used to determine whether extended Kety model parameters obtained with DCE-CT match those from DCE-MRI [117].
The addition of MR specific tracer kinetic models that account for water exchange [53] would also allow us to quantitatively evaluate the influence of water exchange on the comparison of the estimated model parameters between the two modalities.

Considering applications more removed from this thesis, there is also the possibility of using synthetic data to assess new MRI acquisition strategies. For example, DCE-MRI liver tumour phantoms with and without motion emulation at different temporal resolutions could be converted to k-space and the effect of motion on a method of sub-sampling k-space that is optimised for DCE-MRI could be assessed [21]. Synthetic data with motion emulation could also be used for comparing planned dose distributions for radiotherapy of liver lesions to those likely to be received when accounting for breathing motion. The work by Lujan et al. [82] assumed that liver lesions would have rigid body motion in the cranio-caudal direction only, and a phantom with greater motion complexity would allow the impact of those assumptions to be assessed.

We have demonstrated that the Akaike model selection technique is a promising method for characterising the spatial variations of microvascular characteristics in livers with metastatic disease. We believe that the method has promise for automatically distinguishing metastatic from non-tumorous tissue. It would be worthwhile undertaking a prospective study in a larger patient group where exercise, food intake and caffeine are carefully controlled and healthy volunteers are included to identify the range of Akaike probability values seen in non-diseased liver. It would then be interesting to consider other disease groups where model selection may provide useful information, such as hepatocellular carcinoma (primary liver cancer) where it may provide information on tumour extent, natural history or drug effect. It could also have application to patients with fibrosis and cirrhosis where capillarization of the sinusoids [109] could lead to a reduction in the suitability of the Materne model for the data.

It may also be worthwhile increasing the number of candidate models within the selection process to assess whether this gives additional information about the spatial variation of microvascular characteristics and whether the data quality contains adequate information to support the more complex models. Inclusion of the distributed parameter dual-input two-compartment model developed by Koh [106] and the dual-input extended Kety model used by Orton [36] may provide interesting information.

We have developed and evaluated a method for estimating a patient specific PIF, demonstrating that the generated portal input functions can provide a good analogue...
for measured data. However, the estimation method only used a single reference data set. Generating a population IRF that relates a population PIF to the AIF may prove a useful tool for other researchers in this area. It would also allow measurement of variability with this patient cohort. Collection of PIF data would ideally be performed for the relevant disease group and with controls for caffeine, exercise and food intake. Repeated measurements within the same patients would allow repeatability and the effect of PIF variation on the model selection technique to be assessed.
Acronyms

AATH  adiabatic approximation to the tissue homogeneity model.
AIC  Akaike information criterion.
AICc  corrected AIC.
AIF  arterial input function.
BCC  bodywise centred cubic.
CC  correlation coefficient.
CT  computed tomography.
CVS  concurrent version system.
DCE  dynamic contrast-enhanced.
DSC  dynamic susceptibility contrast-enhanced.
DTPA  diethylenetriamine pentaacetic acid.
EES  extravascular-extracellular space.
FEM  finite element modelling.
FFE  fast field echo.
FLASH  fast low angle shot.
Gd  gadolinium.
GI  gastro-intestinal.
IAUC initial area under the curve.

IQR interquartile range.

IRF impulse response function.

MaDyM Manchester dynamic modelling application.

MMID4 multiple indicator, multiple path, indicator dilution 4 region model.

MR magnetic resonance.

MRI magnetic resonance imaging.

NMI normalised mutual information.

PET positron emission tomography.

PIF portal input function.

PVEs partial volume effects.

RECIST response evaluation criteria in solid tumors.

RF radio frequency.

SNR signal to noise ratio.

SPECT single photon emission computed tomography.

SPGR spoiled gradient echo.

SSD sum of squared differences.

SSE sum of squared errors.

TE echo time.

TR time to repeat.

UHN University Health Network, Toronto.

UML unified modelling language.
**VEGF** vascular endothelial growth factor.

**VFA** variable flip angle.

**VOI** volume of interest.
List of symbols

\( B_0 \)  Static (time-independent) magnetic field.

\( B_1 \)  Oscillating magnetic field of the applied RF pulse.

\( C'_{hpv} \)  Estimated concentration of the contrast agent in the blood plasma of the hepatic portal vein (modified Materne model).

\( C_p \)  Concentration of the contrast agent in the blood plasma of an artery.

\( C_t \)  Concentration of the contrast agent in a tissue.

\( C_{hpv} \)  Concentration of the contrast agent in the blood plasma of the hepatic portal vein.

\( G \)  Global scaling factor for \( k_{1hpv}' \) (modified Materne model).

\( K^{\text{trans}} \)  Transfer coefficient describing the movement of the contrast agent between the intravascular space and the EES (extended Kety model).

\( S_0 \)  Magnetisation at equilibrium, accounts any scanner dependent variables.

\( T_1 \)  Time constant used to describe longitudinal relaxation.

\( T_1(0) \)  Pre-contrast \( T_1 \) value.

\( T_2 \)  Time constant used to describe transverse relaxation.

\( T_2^* \)  Time constant used to describe transverse relaxation due to intrinsic and extrinsic local magnetic field inhomogeneities.

\( IAUC_{60} \)  Initial area under the concentration time course curve for the first 60 seconds after contrast agent arrival.

\( hct \)  haematocrit.
\( \tau_a \) AIF delay time (extended Kety model).

\( \tau_{a\text{if}} \) AIF delay time (Materne model).

\( \tau_{p\text{if}} \) PIF delay time (Materne model).

\( k'_{1\text{hpv}} \) Modified portal flow rate constant (modified Materne model).

\( k_{1a} \) Arterial flow rate constant (Materne model).

\( k_{1\text{hpv}} \) Portal flow rate constant (Materne model).

\( k_2 \) Outflow rate constant (Materne model).

\( r_1 \) Longitudinal relaxivity of the contrast agent.

\( v_b \) Fractional volume of the blood.

\( v_c \) Fractional volume of the EES (extended Kety model).

\( v_p \) Fractional volume of the blood plasma (extended Kety model).
Glossary of software engineering terms

abstract class  Class in which one or more functions have no implementation. Objects of abstract classes can not be instantiated.

class  Unit of code within object oriented programming that contains data and functions associated with the data.

compilation  Process of converting the human readable source code into machine code.

composition  If class B is contained in class A via composition then class A has a member variable which is an object of class B.

constructor  Function that creates an object of that class, which includes allocating memory for the member variables.

destructor  Function that deletes an object of that class, which includes deleting the memory for the member variables.

extends  If class B extends class A, then class B inherits the member functions and variables of class A and can also include further functions and variables specific to its role.

implementation  Human readable source code.

inherits  If class A inherits from class B, then the member functions and variables in class B are also included in class A.

instantiate  If an object of a class is instantiated then memory is allocated for the member variables and the member functions can be called on that object.
**interface** Class that defines function signatures, but doesn’t contain any function implementations or member variables. An interface cannot be instantiated.

**module** Defined unit of software such as a class or a packages.

**object** Specific instance of a class. Memory is allocated for the member variables, and functions calls on the object can be made.

**object-oriented** Software engineering paradigm that describes software in terms of modules, each with their own roles and responsibilities.

**package** Collection of related classes.

**private** A private function or variable can only be accessed by the object that contains it, and not by any other object.

**public** A public function or variable can be accessed by any other object.

**realises** If class B realises interface A, it provides implementations of all the functions defined in interface A. Objects of class B can be created, whereas objects of interface A cannot.

**regression tests** A set of tests that check whether new alterations or additions to the software break the existing functionality.

**run-time** If an event occurs at run-time, it occurs during execution of the application rather than during compilation (compile-time).

**template** A pseudo-class that doesn’t specify the data type stored, but can contain functions for manipulating the data. For example an image template could store integers or floating point data types. The data type is specified in the class declaration.

**Unified Modeling Language** Diagrammatic language often used for describing object oriented design.
Appendix A

PhantomGenerator and MotionEmulator design details

A.1 PhantomGenerator

The design has been described using standard software engineering terminology for the object-orient paradigm and presented using unified modelling language (UML). A glossary of software engineering terms (pg. 196) and an explanation of the basic UML types (Appendix B) is included. A description of the UML symbols which represent the relationship between classes is included in the caption for each figure. Note that, for simplicity, constructors and destructors have not been included in the class diagrams except when demonstrating a particular design pattern. Also, only the member variables and functions that are relevant to understanding the structure and function have been included and no function arguments or return types have been shown.

A.1.1 Physiology package

The class diagrams for the Physiology package are shown in Figure A.1 and Figure A.2. The PhysiologicalCharacteristics interface provides the flexibility to represent each tissue type with a different tracer kinetic model. Classes for the extended Kety [3] and Materne [5] models have been provided and contain member
variables that store the ground truth for the model parameters. They also contain an object that extends the `InputFunction` class, and an implementation of the `getContrastAgentConcentration` function. An additional `InputFunction` object is included within the Materne model to represent the portal input.

The `PureIF` class generates contrast agent concentrations for vasculature by converting the plasma concentration from the `InputFunction` object into concentration in whole blood by accounting for the haematocrit (see Equation (2.3)).

![Class diagram for the Physiology package](image)

**Figure A.1:** Class diagram for the Physiology package. All the realisations of the `PhysiologicalCharacteristics` interface use the `Clock` class but, for clarity, only the dependency for the `ExtendedKety` class is shown. The solid open arrow indicates that the `SignalGeneration` package uses between 1 and many `PhysiologicalCharacteristics` objects. The dashed closed arrow indicates realisation of the `PhysiologicalCharacteristics` interface. The solid diamond indicates composition, for example the `ExtendedKety` model contains 1 `InputFunction` object.

The `InputFunction` abstract class allows a range of vascular input functions to be emulated, see Figure A.2. The functional form of the population-averaged [98] and bi-exponential [34] arterial input functions (AIFs) have been implemented in the `PopulationAIF` and `BiexponentialAIF` classes respectively. There is also an
AcquiredIF class that reads input function data from a text file. This class can be used for AIFs derived from acquired data and for estimated portal input functions for the Materne model (see Section 5.2). The ground truth for the offset time (for example, the $\tau_{aif}$ term in Equation (2.1)) is held by the InputFunction abstract class.

![Class diagram for the vascular input function representations. The BiexponentialAIF is dependent upon the Clock and ContrastAgent classes and the AcquiredIF class is dependent upon the Clock class but for clarity these dependencies are not shown. The dashed open arrow indicates a dependency. The solid closed arrow indicates inheritance.](image)

**Figure A.2:** Class diagram for the vascular input function representations. The BiexponentialAIF is dependent upon the Clock and ContrastAgent classes and the AcquiredIF class is dependent upon the Clock class but for clarity these dependencies are not shown. The dashed open arrow indicates a dependency. The solid closed arrow indicates inheritance.

Also included in the Physiology package are the ModelFactory and AIFFactory classes that are used for configuring the package for the requested tissue types at run time. These are discussed later in Section A.1.5. It is possible to instantiate as many PhysiologicalCharacteristics objects as required for generating each synthetic image. If masks are used to represent the anatomical definition, then one PhysiologicalCharacteristics object per mask will be instantiated. Whereas if parameter maps are used as input to the PhantomGenerator, a PhysiologicalCharacteristics object will be created for each voxel that contains data within that map. The input configuration file specifies whether the input files are parameter maps or masks.
A.1.2 SignalGeneration package

An overview of a SignalGeneration package for MRI is shown in Figure A.3. The SignalProduction interface class provides the flexibility to add implementations for imaging modalities other than MRI. The MRSignalProduction class realises the SignalProduction interface and is composed of a ContrastAgent and PulseSequence object. The array of Tissue objects is passed to the generateSignalForAllTissues function to generate the signal intensities for all the tissues at the current time point.

To allow the pulse sequence to be easily switched, the PulseSequence interface, ContrastAgent and Tissue abstract classes are provided, see Figure A.4. Extensions of these classes have been implemented to produce synthetic data for the spoiled gradient echo (SPGR) and inversion recovery pulse sequences. However, implementations for other pulse sequences could be easily added in the same manner.
Appendix A. PhantomGenerator and MotionEmulator design details

ContrastAgent
- dose
- prebolusTime
+ getDose()
+ getPrebolusTime()

MRContrastAgent
- t1Relaxivity
+ getRelaxivity()

MRTissue
- t1Zero
- sZero
+ getT1Zero()
+ getSZero()
+ getDynamicT1()

Tissue
- type
+ getType()

Physiology

PhysiologicalCharacteristics

<<Interface>>
PulseSequence
+ getSignalIntensity()

T1SpGr
- tr
- flipAngle

InversionRecovery
- tr
- ti

Figure A.4: Class diagram for MRI specific elements of the SignalGeneration package. The solid open arrow indicates that one class uses the functionality of another. For example, the MRTissue class uses 1 instance of the MRContrastAgent class. The solid closed arrow indicates inheritance and the dashed closed arrow indicates realisation of the PulseSequence interface. The solid diamond indicates composition, for example the Tissue class contains 1 PhysiologicalCharacteristics object.
Appendix A. PhantomGenerator and MotionEmulator design details

The T1SpGr and InversionRecovery classes realise the PulseSequence interface and contain the time to repeat (TR) and the flip angle or the inversion time respectively. They use the MRTissue objects to calculate the signal intensity for each tissue type in the getSignalIntensity function.

The Tissue abstract class is purely responsible for encoding the type of the tissue and could therefore be used for other MRI pulse sequences and imaging modalities. It has been extended by the MRTissue class to provide the tissue specific properties $S_0$ and $T_1(0)$ for a SPGR or inversion recovery pulse sequence.

The MRTissue class is composed of a realisation of the PhysiologicalCharacteristics interface, for example the ExtendedKety class, from which it obtains the value of $C_t$ at the current time point to calculate the current $T_1$ value in the getDynamicT1 function. Note that it is possible for each tissue object to contain a different realisation of the PhysiologicalCharacteristics interface.

The ContrastAgent abstract class is responsible for the dose and prebolus time of the contrast agent and can be used with other imaging modalities or pulse sequences. The MRContrastAgent class is an extension of the ContrastAgent class for the SPGR and inversion recovery pulse sequences and contains the $T_1$ relaxivity.

The SignalGeneration package also contains the MRTissueFactory, TissueFactory and SignalProductionBuilder classes which are used for configuring the package for the required imaging scenario. These are classes described in Section A.1.5.

A.1.3 ImageGeneration package

The class diagram for the ImageGeneration package is shown in Figure A.5. The ImageVolume class communicates with the SignalGeneration package to get the signal intensities for all the tissue types and then uses the TissueToVoxelMap to find the tissue types contained within each voxel and calculate the signal intensity for that voxel. The image is stored as an IMAGE_Analyze3D object and the functionality within this class is used by ImageVolume to write the image and downsample the image, if required. Downsampling is performed using decomposed sinc interpolation with a Blackman-Harris 4-term windowing function and a window width of 6 voxels [118]. The IMAGE_Analyze3D class was written within the research group by Angela Caunce. Using masks and parameter maps that have a resolution that is higher than
the images being emulated as input and downsampling the generated images allows realistic partial volume effects (PVEs) to be simulated (described below).

Noise can be added to the images using the `GaussianNoise` class which realises the `Noise` interface. The interface provides the flexibility for other noise distributions to be implemented. The `Gaussian` class implementation is based on the Numerical recipes in C [25] `gausdev` function and is composed of a `RandomNumberGenerator` object which is based on the Numerical recipes in C `ran1` function. The noise level can be set using either the signal to noise ratio (SNR) or standard deviation.

![Figure A.5: Class diagram of the ImageGeneration package. The solid open arrow indicates that one class uses the functionality of another. For example, the ImageVolume class uses 1 or more instances of the TissueToVoxelMap class. The dashed open arrow indicates a dependency. The dashed closed arrow indicates that the GaussianNoise class realises the Noise interface. The solid diamond indicates composition, for example the GaussianNoiseGenerator class contains 1 RandomNumberGenerator object.](image-url)
The TissuetoVoxelMap extends the Image_3D template class (which inherits from the IMAGE_Base template class written by Angela Caunce) with VoxelProportions as the template parameter, i.e. there is one VoxelProportions object for every voxel (see Figure A.6). The VoxelProportions class manages the fraction of each tissue type within a voxel using a vector object to store the TissueFractions objects, allowing PVEs to be simulated.

![Class diagram of the TissuetoVoxelMap class within the ImageGeneration package.](image)

**Figure A.6:** Class diagram of the TissuetoVoxelMap class within the ImageGeneration package. The solid closed arrow indicates inheritance. The solid diamond indicates composition, for example the VoxelProportions class contains 1 or more TissueFraction objects. The dashed box indicates the template type, that is the Image_3D object will store VoxelProportions objects for every voxel.

Tissues are added to the VoxelProportions objects using the addSameOrHigherPriorityTissue function. Each tissue is given a priority number by the user where higher priority tissues, under certain conditions, will remove lower priority tissues from a voxel. For example, the user may have a body outline mask with the lowest priority. A liver mask with a higher priority may then be added and where the liver mask indicates that a voxel is liver only, the body tissue will be overwritten. A liver tumour parameter map could then be given a higher priority than the liver. The details of how PVEs are emulated are detailed in Algorithm 1. For example, if the

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Appendix A. PhantomGenerator and MotionEmulator design details

liver mask indicates that a voxel contains 60% liver, then the amount of body tissue would be reduced to 40% in that voxel. Note that tissues must be added in order of priority with the lowest first.

Algorithm 1 Pseudocode for the addSameOrhigherPriorityTissue function in the VoxelProportions class

if no tissues present then
    add the new tissue to componentTissues
    total ← newTissue.fraction
else if tissues already present then
    if (newTissue.priority > lastTissueAdded.priority) & (newTissue.fraction == 1)
        then
            clear all componentTissues
            add the new tissue to componentTissues
            total ← 1
        else
            topPrioritySumFractions = sum of fractions of top priority tissues
            if topPrioritySumFractions ≥ 1 then
                delete all lower priority tissues
                add the new tissue to componentTissues
                total ← topPrioritySumFractions
            else
                while total + newTissue.fraction > 1 do
                    starting from lowest priority
                    remove tissues or reduce tissue fraction
                    total ← total − removedTissue.fraction
                end while
                add the new tissue to componentTissues
            end if
        end if
    end if
end if

It is possible for the total fraction of tissues in a voxel to be greater than one (for example if there are 3 tissues of the same priority with a fraction of 0.5 each). In this case, when all the tissues have been added, if the sum of all the tissue fractions is greater than 1, the fraction for each tissue is divided by the total sum.

The ImageGeneration package contains two configuration classes: TissueMapFactory and AnatomyBuilder, and the Organ abstract class which is extended by the ParameterMap and TissueMask classes. These are used to read in the masks, parameter maps, and configuration files that describe the anatomy being emulated and, if motion is being simulated, to provide a different TissuetoVoxelMap for each time
point is required. These classes are described further in Section A.1.5.

A.1.4 TimeSeries package

The design of the TimeSeries package is shown in Figure A.7. The Clock class follows
the singleton design pattern [85], therefore only one instance of the Clock object can
be created. This ensures that the current time does not have to be maintained across
a number of different classes. The image acquisition times can be set using either a
temporal resolution and number of time points or a vector object of specified time
points. The latter option allows acquisition times to be read in from a text file to
match those seen in an acquired AIF for example, or to generate a time series with
uneven temporal resolution.

The DynamicSeries class uses the AnatomyBuilder (see Section A.1.5) to get a
TissueToVoxelMap (see Section A.1.3) for each time point which allows motion to be
simulated as the mapping can change during the time series. The TissueToVoxel-
Map is passed to the ImageVolume class which is then used to generate, resample,
add noise and then write the image for each time point (resampling and noise are
optional). The DynamicSeries class is also responsible for updating the Clock object
at each time point.

A.1.5 GeneratorConfiguration package

The GeneratorConfiguration package reads in information from the command line
and the given configuration file(s) and stores any default options. From this in-
formation it co-ordinates instantiation of the objects required to emulate the given
imaging scenario. The classes that are used to create all the required objects are
split among the Physiology, SignalGeneration and ImageGeneration packages so
that they are within the same package as the objects that they are instantiating.
All of the configuration classes are described in this section. They are based on the
published Factory and Builder design patterns [85] as indicated by their name, for
example TissueFactory. The configuration classes have been designed to allow new
extensions to be added (eg a new tracer kinetic model) whilst minimising the changes
that are required within these classes. Situating the configuration classes within the
relevant packages also eases the addition of extensions.
The `GeneratorConfiguration` class reads in the configuration file and command line using the Boost `program_options` library [89] and this information is then held in a `variables_map` object from that library and can be accessed as required by each configuration class. Each of the Builder and Factory classes defines its own set of configuration file and command line options that it expects along with any default options and is responsible for checking that the input data is valid (for example that a value of \( v_e \) exists for every extended Kety tissue). For simplification of this section, the functions and member variables used for validating the input data have not been included in the class diagrams or descriptions.

An overview of the `GeneratorConfiguration` package is shown in Figure A.8. The `PhantomBuilder` class is instantiated in the `main` function and is used to generate the `Noise` and `DynamicSeries` objects. It is composed of a `SignalProductionBuilder` object which it uses to generate the `SignalProduction` object for the selected modality and an `AnatomyBuilder` which it uses to generate the `Tissue` objects. Within the `main` function the `generateTimeSeries` function (see Figure A.7) can then be called on the `DynamicSeries` object to produce the required synthetic images. The `AnatomyBuilder` is passed as an argument to this function to allow access to the `TissueToVoxelMap` for each time point.

**Figure A.7:** Class diagram of the `TimeSeries` package. The private constructor of the `Clock` class is shown to demonstrate the singleton design pattern. The solid open arrow indicates that one class uses the functionality of another. For example, the `DynamicSeries` class uses 1 instance of the `ImageVolume` class for every time point.
Appendix A. PhantomGenerator and MotionEmulator design details

**Figure A.8:** Class diagram of the GeneratorConfiguration package. The filled boxes indicate that one class instantiates an object of the class in the filled box. For example, the PhantomBuilder class instantiates 1 GaussianNoise object. The solid diamond indicates composition, for example the PhantomBuilder class contains 1 AnatomyBuilder object.

The class diagram for the AnatomyBuilder is shown in Figure A.9. It coordinates production of the TissueToVoxelMap which is part of the ImageGeneration package and describes the anatomy, and the Tissue objects which are part of the SignalGeneration package and contain any relevant tissue properties for example $T_1$ and, within an ExtendedKety object, the extended Kety model parameters. The information for generating these objects is input in the form of parameter maps, which contain both anatomical and tissue properties and organ masks co-ordinated with tissue properties in the configuration file. It is possible to use a combination of these input forms for each synthetic data set.

The TissueFactory produces TissueMask and ParameterMap objects. These are subclasses of the Organ class that are responsible for reading in data from the input tissue masks and parameter maps, and for providing iterator functionality to access the data. The Organ subclass objects are passed to the TissueMapFactory which then uses them to produce the TissueToVoxelMap. The process of reading in the parameter maps and tissue masks and producing a TissueToVoxelMap is required for every time point if motion emulation is required.

The details of the TissueFactory class are shown in Figure A.10. The MRTissueFactory class extends the TissueFactory class to produce MRTissue objects. It is composed of a ModelFactory which contains an AIF factory enabling the PhysiologicalCharacteristics and InputFunctions objects required to emulate the different tissue types to be instantiated to build each MRTissue object. All three Factory classes rely on the Parameter class for handling the input information from either
Appendix A. PhantomGenerator and MotionEmulator design details

The class diagram for the AnatomyBuilder is shown in Figure A.9. The solid open arrow indicates that one class uses the functionality of another. For example, the AnatomyBuilder class uses the TissueFactory class. The filled boxes indicate that objects of that class are being instantiated. For example the TissueFactory class instantiates 1 or more Tissue objects. The solid closed arrow indicates inheritance.

The parameter maps or the configuration file.

The class diagram for the SignalProductionBuilder is shown in Figure A.11. The MRSignalProductionBuilder extends the SignalProductionBuilder class to instantiate the ContrastAgent and PulseSequence objects from which the MRSignalProduction object is then built.

A.2 MotionEmulator

The class diagram for the motion emulation module is shown in Figure A.12. (The reader is referred to Section 3.4 and Appendix B for an explanation of the class diagrams and to pg. 196 for a glossary of object oriented terminology.) The Motion class is responsible for generating both the original and warped meshes from the displacement maps as described above in Section 4.2. The applyWarp function uses the warp_trilin function from the vq3d library (see Section 4.2) to warp a given organ mask by a given fraction of the full displacement and produce a warped mask. The RespiratoryTrace class is responsible for the acquired respiratory trace data.
Appendix A. PhantomGenerator and MotionEmulator design details

Figure A.10: Class diagram of the TissueFactory. The solid open arrow indicates that one class uses the functionality of another. For example, the ModelFactory class uses 1 or more instances of the Parameter class. The filled boxes indicate that objects of that class are being instantiated. For example the ModelFactory class instantiates 0 to multiple Materne objects. The solid closed arrow indicates inheritance. The solid diamond indicates composition, for example the MRTissueFactory class contains 1 ModelFactory object.

Figure A.11: Class diagram of the SignalProductionBuilder. The filled boxes indicate that objects of that class are being instantiated. For example the MRSignalProductionBuilder class instantiates a MRSignalProduction object. The solid closed arrow indicates inheritance.
Figure A.12: Class diagram for the MotionEmulator. The closed dashed arrow indicates that the RespiratoryTrace and Sinusoidal classes realise the TemporalPattern interface. For clarity only the major functions are shown and the function arguments are not detailed.

which is read in from a text file. An interface, TemporalPattern, is provided so that other breathing patterns can be implemented. For example, the Sinusoidal class implements a simple sinusoidal pattern that calculates the required fraction for a given breathing rate. All subclasses of TemporalPattern must implement the getWarpFractions function which calculates the displacement fraction for each time point in the dynamic series for a given temporal resolution and number of time points.

The pseudo code in Algorithm 2 describes the overall functionality of the MotionEmulator.

Algorithm 2 Pseudocode for the overall functionality of the motion emulator

if using acquired respiratory trace then
  read in text file
end if
for all organ masks do
  for all time points do
    get displacement fraction for this time point for this organ
    scale the displacement maps with the displacement fraction
    apply displacement maps to the mask for this organ
    write the warped mask
  end for
end for
Appendix B

UML Symbols

This appendix gives and explanation of the basic UML types [84] used in this thesis.

Figure B.1 shows the UML symbol that represents a class. The class name, member variables and member functions are shown in the upper, middle and lower sections respectively. Member variables and functions preceded by a plus sign are public (can be accessed by code outside the class), whereas those preceded by a minus sign are private (can only be accessed by code within the class). Function arguments and return types, as well as constructors and destructors have been omitted from the diagrams within this thesis for simplicity.

<table>
<thead>
<tr>
<th>ClassName</th>
</tr>
</thead>
<tbody>
<tr>
<td>-privateMemberVariable</td>
</tr>
<tr>
<td>-privateMemberFunction()</td>
</tr>
<tr>
<td>+publicMemberFunction()</td>
</tr>
</tbody>
</table>

Figure B.1: UML symbol that represents a class

Figure B.2 shows a class within a package. The package name is shown in the upper section. Only the class that is relevant to the part of the design that is being demonstrated is shown, although the package may contain multiple classes.

Figure B.3 shows a class with a stereotype which is documented in the upper section between the chevrons. The stereotype could indicate that the class is an interface or
Appendix B. UML Symbols

Figure B.2: UML symbol that represents a package that follows a particular design pattern, for example.

Figure B.3: UML symbol for a class with a stereotype

Figure B.4 shows the UML symbol for a template. The template type is shown in the dashed box with the template name in the upper section of the solid box. Templates are generic classes, i.e. the type of the object that they hold is not specified in the template definition, but in its declaration. For example, an Image could be a generic container for floating point or integer types. The type could also be a class.

Figure B.4: UML symbol that represents a template
Appendix C

Warping the masks: technical details

As described in Section 4.2 we need to approximate the inverse transform from the displacement maps and apply it to the end-exhale organ masks to produce the deformed images (dynamic time series images). Within the MotionEmulator (see Chapter 4), we have used the locally written vq3d library, which is based on the VXL library [119]. Three functions provide the main functionality for transforming the organ masks. vq3d_make_bcc_mesh_box creates a 3D tetrahedral mesh that will fit within the exhale mask image. vq3d_mesh_from_warp_field generates a warped version of this mesh that approximates the displacement maps. warp_trilin uses the original mesh and the warped mesh to deform the exhale mask and give an inhale mask. Within this last function the inverse transform is calculated implicitly.

The first function (vq3d_make_bcc_mesh_box) generates a 3D tetrahedral mesh created from a bodywise centred cubic (BCC) structure. To create a BCC structure, a grid of cubes is generated and a second grid of cubes is laid inside the first. The nodes (corners of the cubes) of the second grid lie at the centre of each cube within the first grid (see Figure C.1(a)). The nodes of both sets of cubes are then joined in a manner that results in 24 tetrahedra intersecting each cube in the original grid (see Figure C.1(b)). (4 tetrahedra intersect each face and there are 6 faces.) In a 2D image it would be possible to use equilateral triangles to create a tightly packed regular structure. However, for a 3D image a BCC mesh is required. The BCC grid is described by defining the position of the bottom left-hand front corner of the mesh.
on the image, then choosing the distance between the nodes and the number of nodes, all in units of voxels for each of the x, y, and z directions.

![Diagram](image1.png)

**(a)** Bodywise centered cubic grid  **(b)** Tetrahedron within a BCC grid

**Figure C.1:** (a) Shows the placement of a second mesh (blue) within the first (grey). The pink nodes lie at the centre of the cubes in the grey grid. (b) Shows the creation of a tetrahedron using the green nodes from the first grid and pink nodes from the second grid also shown on (a). The 4 faces of the tetrahedron are the two triangles outlined in red, the blue filled triangle and the grey filled triangle.

When warping the original mesh to approximate the displacement maps, the function \texttt{vq3d mesh from warp field} performs an optimisation that moves the nodes of the mesh until the sum of squared differences between the displacement maps and the approximated displacement for every voxel is minimised. The optimisation routine used is a least squares routine for linear systems [120]. The difference calculation uses every voxel within the displacement image. However, the nodes (whose positions are manipulated in the minimisation) are distributed more sparsely than one node per voxel. Each tetrahedron should contain enough voxel centres to give adequate information for the optimisation, but should be kept small enough to prevent edge effects from corrupting important areas of the warped image. Edge effects result from gaps between the tetrahedral mesh and the edge of the image. The approximated displacements for the centre of each voxel are calculated from the original and warped meshes using barycentric co-ordinates (see Section C.1).

After \texttt{vq3d mesh from warp field} has been used to produce a warped mesh, it is used along with the original mesh by \texttt{warp trilin} to warp the end-exhale mask. The inverse transform is calculated using barycentric co-ordinates as described in Section C.1 except that, for the inverse transform, the centre of every voxel in the inhale mask is mapped to a position in the exhale mask. As the transform within each tetrahedron is linear this results in a piecewise affine transform being applied to the end-exhale image.
Appendix C. Warping the masks: technical details

C.1 Barycentric co-ordinates

Barycentric co-ordinates allow the position of the centre of a voxel within an original tetrahedron to be mapped to the equivalent position within the warped tetrahedron. As an example in 2D, a triangle has three nodes with position vectors $a$, $b$, and $c$, see Figure C.2. Point $p$ (the centre of a voxel) inside this triangle exists at $p = \alpha a + \beta b + \gamma c$, where $(\alpha, \beta, \gamma)$ are the barycentric co-ordinates of point $p$ and $\alpha + \beta + \gamma = 1$. The $\alpha$, $\beta$ and $\gamma$ terms are weights on each of the nodes that result in the point $p$ being the centre of mass of the triangle and are calculated for $p$. (The triangle has no mass except for the weights on the three nodes.) If $\alpha$, $\beta$ and $\gamma$ are all $\geq 0$, then the point is inside the triangle. If any one of them is zero, then the point lies on the edge opposite the corresponding corner.

Figure C.2: Using barycentric co-ordinates to calculate the displacement of a point within a warped triangle.

When the triangle is warped the nodes are moved to the known positions $\hat{a}$, $\hat{b}$, and $\hat{c}$. $p$ has an equivalent point $\hat{p}$ within the warped triangle given by $\hat{p} = \alpha \hat{a} + \beta \hat{b} + \gamma \hat{c}$. That is, the weights on the nodes remain the same and $\hat{p}$ is placed at the centre of mass of the warped triangle given these values of $\alpha$, $\beta$ and $\gamma$. The difference between the position vectors $\hat{p} - p$ is the approximated displacement.

In Figure C.2, the barycentric co-ordinates for point $p$ are $\alpha = 0.2$, $\beta = 0.5$ and $\gamma = 0.3$. $a$, $b$ and $c$ are located at the cartesian co-ordinates $(10, 10)$, $(30, 10)$, and $(20, 50)$ respectively. The cartesian co-ordinates for $p$, $(x_p, y_p)$, are $x_p = a_x \times \alpha + b_x \times \beta + c_x \times \gamma$ and $y_p = a_y \times \alpha + b_y \times \beta + c_y \times \gamma$, where $(a_x, a_y)$ are the cartesian co-ordinates for point $a$, for example. Therefore, $p$ is located at $(23, 22)$. The barycentric co-ordinates for $\hat{p}$ are equal to those for $p$. The cartesian co-ordinates for $\hat{a}$, $\hat{b}$, and $\hat{c}$ are $(10, 10)$,
(40, 10) and (20, 70) respectively. Therefore, the cartesian co-ordinates for $\hat{p}$ are (28, 28). Giving a displacement vector of (5, 6) for $p$ when the triangle is warped.
Bibliography


