

ŁODZ UNIVERSITY OF TECHNOLOGY

FACULTY OF ELECTRICAL, ELECTRONIC,
COMPUTER AND CONTROL ENGINEERING
INSTITUTE OF ELECTRONICS

MASTER OF ENGINEERING THESIS

**Numerical Assessment of Kidney Function from
DCE-MRI**

Katarzyna Sprawka

Student's number: 213407

Supervisor:

Prof. hab. dr inż. Andrzej Materka

Auxiliary supervisor:

Dr inż. Marek Kociński

Łódź, 2018

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Abstract

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TECHNICAL UNIVERSITY OF ŁÓDŹ
WYDZIAŁ ELEKTROTECHNIKI, ELEKTRONIKI, INFORMATYKI I AUTOMATYKI

Katarzyna Sprawka

PRACA DYPLOMOWA MAGISTERSKA

**Numeryczna ocena funkcjonowania nerek na podstawie obrazów
DCE-MRI**

Łódź, 2012

Supervisor: Prof. hab. dr inż. Andrzej Materka
Auxiliary supervisor: Dr inż. Marek Kociński

Streszczenie

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Abbreviations

AIF	Arterial Input Function
CA	Contrast Agent
CNN	Convolutional Neural Network
DCE-MRI	Dynamic Contrast Enhanced Magnetic Resonance Imaging
FID	Free Induction Decay
Gd	Gadolinium
Gd-DOTA	Gadoteric Acid
GFR	Glomerural Filtration Rate
Hct	Hematocrit
PC	Principal Component
PCA	Principal Component Analysis
PK (models/modelling)	Pharmacokinetic (models/modelling)
RF	Radio Frequency
ROI	Region of Interest
SCr	Serum-creatinine
SD	Standard Deviation

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Introduction

ACCORDING TO THE BELIEFS OF ANCIENT HEBREWS, the kidneys are the seat of the human soul and consciousness. They were also associated with the feeling of the fear and sadness[1]. Today, more mundane, but not less important tasks are being assigned to them.

Kidneys, although often underestimated, are the fundamental organs of human body and their working mechanism is extremely complex. Their essential task is to remove wastes from the organism but their functionality is much wider. They are also involved in maintaining acid-based balance, regulating the blood pressure and are major endocrine organs, which secret three important hormones: erythropoietin, calcitriol and renin [2]. In short terms, they maintain whole body homoeostasis, which is essential for overall health of the organism.

Gradually progressing loss of kidney function known as a chronic kidney disease is a growing world-wide problem. As much as 8–16% of whole population suffers from this condition [3]. It significantly decreases comfort of life and in extreme cases leads to death. What is more, it was shown that renal diseases are risk factor for development of cardiovascular diseases [4]. Because of the fact that symptoms don't resemble renal failure, approximately 90% of the ill are unconscious of it until late stages [5]. That is why there is the demand for methods, which enable fast and accurate measurement of renal function required for all of three: prevention, monitoring and therapy.

The metrics of level of kidney function is glomerular filtration rate (GFR) [6]. Good performance of the several important functions of the kidney are dependent on the GFR value. Not only does it allow for assessment how well our kidneys are working, but also it can determine the stage of kidney disease. The gold standard of GFR measurement incorporates injection of the exogenous marker that is freely filtered by the kidney, and that does not undergo metabolism, tubular secretion or absorption. An example of such a marker can be insulin. However, in clinical practice usually the endogenous marker is used such a creatinine or urea and GFR is estimated applying robust algorithms [7]. Although chemical methods allow for accurate GFR estimation, they are not very practical in clinical use. Not only are they time-consuming and expensive but also they can be cumbersome. What is more they provide information about combined GFR value and cannot be used for single kidney function assessment. Thus other methods are desired [8].

An innovative approach in estimating renal function is performing dynamic contrast-enhanced magnetic resonance (DCE-MRI), which provides time-varying images of the abdominal. The analysis of the obtained time-intensity changes as a function of time provides important information about renal performance [8, 9]. Traditionally, this evaluation is performed by experienced observer, although this method is very subjective and strongly depends on the experience of the expert. Other technique involves fitting tissue intensity changes to pharmacokinetic models, which allows quantification of renal function [9]. Even though this strategy is gaining more and more supporters, most of the methods still require interference of the human at some stage, which makes them vulnerable to human factors.

The works included in this thesis are the part of the bigger project, which aims to develop entirely data-driven method of GFR estimation directly from DCE-MRI, which would be fast and efficient and accurate enough to be used in clinical applications.

Chapter 1

Aims and scope of the work

To be done

Chapter 2

The blood filter

There is no life without metabolizing, and metabolism always produces variety of waste products, which accumulated in the tissues are toxic to the organism. Some of them are removed from the body by respiratory tracts, others through digestive system and some of them are extracted through the sweat glands. However, there is no doubt that the urinary system plays the major role in waste extraction [2, 10].

The main organs of the urinary system are the kidneys. It is them, which perform the filtering function. The remaining ones, ureters, urinary bladder, and urethra, form the urinary tracts and are responsible only for transforming and storing the urine [2]. In this chapter the anatomy and physiology of the kidneys will be briefly introduced.

2.1 Structure of the kidney

The kidneys are bean-shaped, usually paired structures located at the back of the abdominal cavity in the retroperitoneal space. They lie on at the level of vertebrae T12 to L3. The right kidney is slightly lower than the left one, because of the close

proximity to the liver [2, 10].

The average healthy adult kidney weights around 150 g, is 11 cm long, 6 cm wide and 3 cm thick [2, 11]. As mentioned before, humans usually have two kidneys, however not always. Some people are born with only one of them. In such case, the present kidney is as heavy and big as the two kidneys together would be. In most cases it doesn't affect normal live [12].

The kidneys are surrounded and protected by three types of connective tissue, from the outer part: (1) *renal fascia* anchoring the kidneys and the neighbouring organs to the abdominal wall; (2) *adipose capsule*, which is a layer of fat tissue holding the kidney in place; (3) *renal capsule*, made of fibrous tissue, firmly enclosing the organ and protecting it from traumas and infections [2, 10]. In the medial concave surface, there is a slit called *hilum*, which is the place where the renal artery enters and the renal vein and the ureter leave the kidney. The hilum extends into the *renal sinus*, which is a large cavity occupied by blood and lymphatic vessels, nerves, urine-collecting structures and adipose tissue [10].

The renal parenchyma is divided into two major parts: (1) the outer 1 cm thick portion of the kidney, *renal cortex* (2) the inner *renal medulla* [2, 10]. The cortex projects into the kidney forming *renal columns*, which divide the medulla into 10-14 *renal pyramids*. Each of them has a characteristic shape of a cone with the wide base facing the cortex and the tip attached to the sinus called *renal papilla*. The papilla of each pyramid points towards the *minor calyx* collecting its urine. Few of them converge into the *major calyx*, whereas the all latter ones form the funnel-shaped basin, the *renal pelvis*, which is the extension of the *ureter* transforming the urine to the bladder [2, 10, 13]. The gross anatomy of the kidney is illustrated in Figure 2.1.

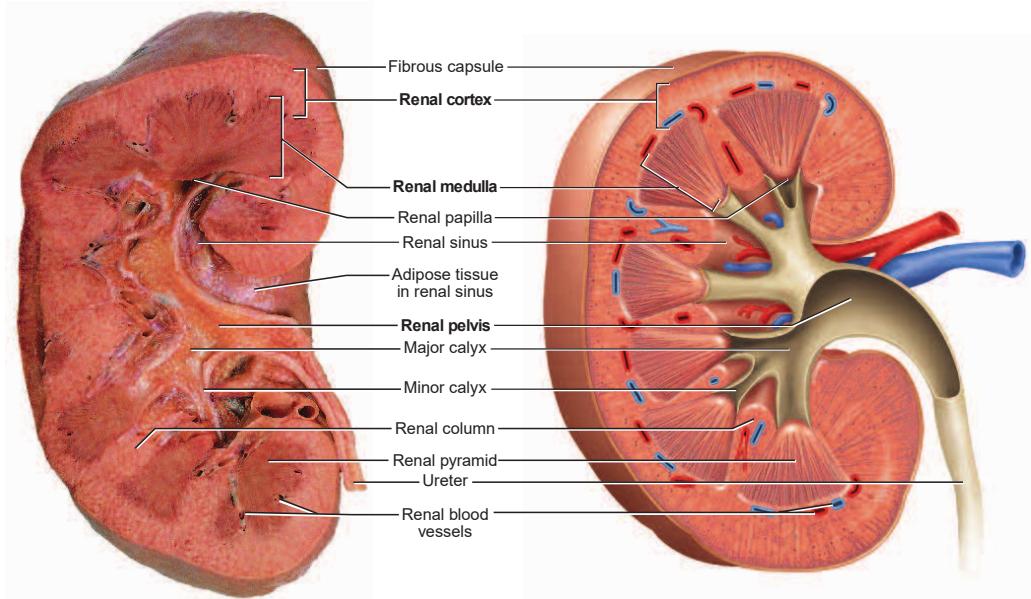


Figure 2.1. Gross anatomy of the kidney [2].

2.1.1 The nephron

As it is with most of the aspects of the human anatomy, the most interesting features of the kidney are invisible with naked-eye. The basic microscopic functional units of the kidney are nephrons. Above million of them enables the kidney to perform its functions [10]. Each of them is a tiny coiled tube, called the *renal tubule*, with a bulb at the end, the *renal corpuscle*, and extends through both the cortex and the medulla [2].

The renal corpuscle is composed of the two-layered *glomerular (Bowman) capsule* enclosing the *glomelurus*, which is a cluster of capillaries. The renal tubule is a duct leading from the glomelural capsule to the pyramid papilla. It can be divided into several regions, subsequently from the glomerular corpuscle: (1) the *proximal convoluted tubule* (PCT); (2) the *nephron loop (loop of Henle)*, which consists of the *descending and ascending limbs*; (3) the *distal convoluted tubule* (DCT); (4) the *collecting duct*.

duct receiving the fluids from the DCTs of few nephrons. Multiple of them merge and form papillary ducts, which lead to the minor calyx. Each of the segment has a distinct cellular appearance and function [2, 10, 13].

Every functional unit of the kidney is supplied with the blood by a small blood vessel called the *afferent arteriole*, whereas the *efferent arteriole* takes it back. The blood leaving the nephron, flows into a network of *peritubular capillaries* surrounding the renal tubule [2, 10] The particular parts of the nephron are depicted in Figure 2.2.

2.2 Functions of the kidney

Despite the fact that the key function of the kidneys is purifying the blood, the other ones are equally important. Kidneys are responsible for maintaining the homeostasis of the whole body due to which, all organs can work in an optimal environment. It is crucial for a proper functioning of whole organism [13]. One can conclude that the role of kidneys is enormously important. Indeed, the kidneys are involved in the following processes:

Blood filtering. The kidneys filter the blood from metabolic waste, excessive amounts of salts, toxins and then excrete unwanted substances in the urine [2, 10, 13].

Osmoregulation. For a proper functioning of the organism, the concentration of the salts in the body has to remain relatively the same. The kidneys influence this concentration by controlling the amount of water and solutes excreted from the organism [14].

Maintainance of water balance. The kidneys control the amount of water conserved and eliminated in the urine so that the amount of body water remains on the stable level [15].

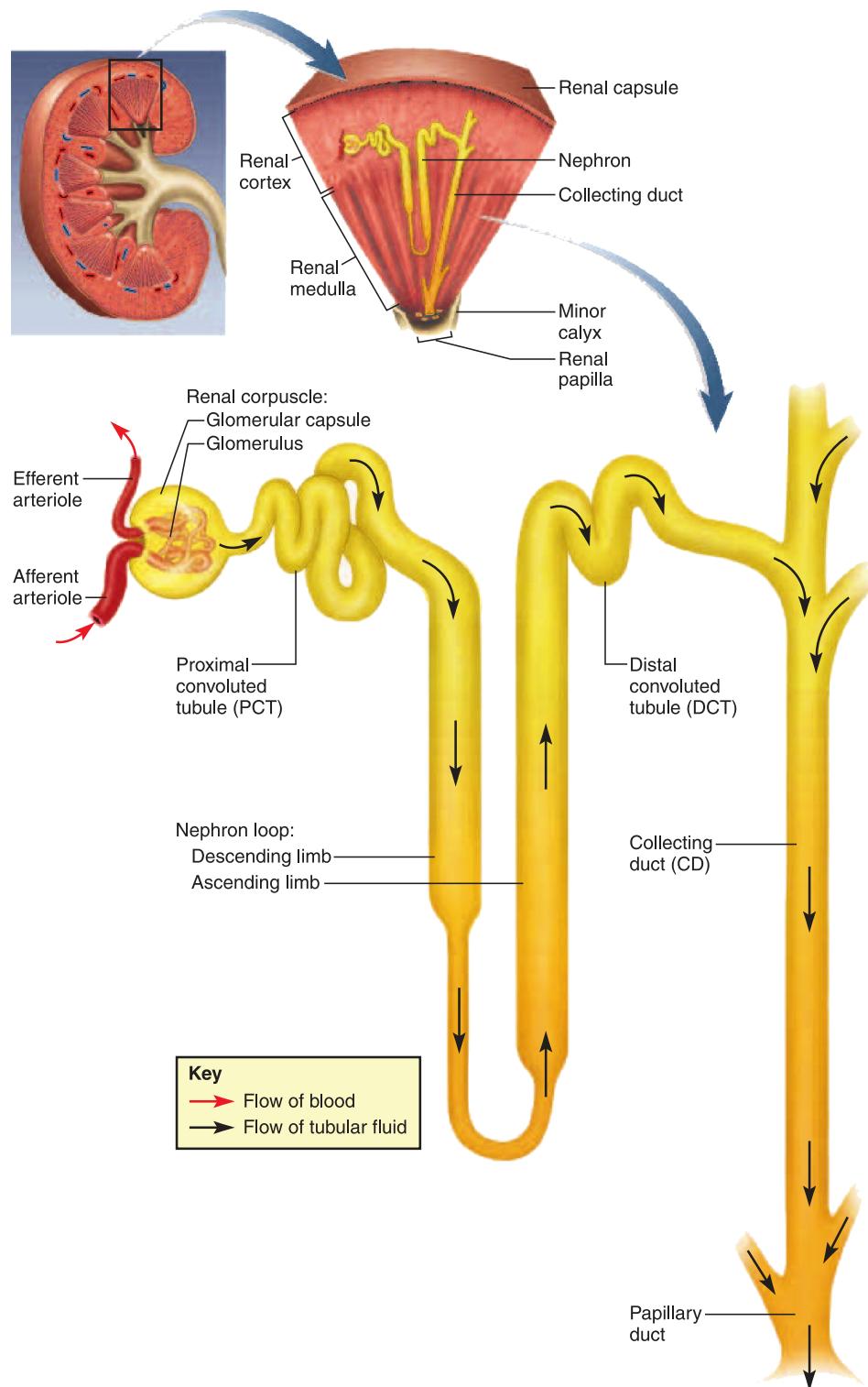


Figure 2.2. The structure of the nephron [2].

Blood pressure regulation. Maintaining the normal blood pressure is achieved in two ways: (1) if the blood pressure drops, the kidneys release the enzyme *renin*, which activates the blood protein *angiotensin*, making the blood vessels to constrict. What is more, angiotensin triggers the mechanism which increases the absorption of water and sodium, which in turn increase the blood volume; (2) by regulating the amount of water, which was mentioned before [16].

Maintainance of the acid-base balance. The food contained in our diet can acidify or alkalize the organism. If the pH level is out of the tolerable boundaries, enzymes and proteins break down, which in extreme cases can lead to death. Kidneys in collaboration with the lungs are responsible for maintaining healthy pH of the body fluids. While the lungs' task is to regulate carbon dioxide (CO_2) concentration, the kidney acts by reabsorbing or regenerating bicarbonate (HCO_3^-) from the urine and excreting hydrogen ions and fixed acids into the urine [17].

Red blood cell production. If the level of oxygen in the tissues is insufficient, the kidneys release *erythropoietin*, the hormon stimulating the bone narrow to red blood cells production [18].

Keeping the bones strong. The kidneys, together with the liver, synthesize the active form of vitamin D called *calcitriol* (1,25-dihydroxycholecalciferol) enabling the body to absorb calcium and phosphorus, which are the crucial minerals for strengthening the bones [19].

Prevent the hunger. In the situation of extreme starvation, the kidneys can synthesize glucose from non-carbohydrate carbon substrates, breaking down other molecules. This phenomena is known as *gluconeogenesis* [20].

2.2.1 Urine formation

Everyday, our kidney filter as much as 200 litres of fluid which is 60 times volume of blood in the body, and excrete 1.5 litres of urine [2]. These enormous amounts are a result of complex process involving numerous exchanges between a nephron and the blood stream. The process of the urine formation can be divided into 4 stages:

1. **Glomerular filtration.** When the blood enters the glomerulus through the afferent arteriole, the first step begins. Sievelike walls of the glomerular capillaries pass every molecule smaller than 3 nm to the glomerular capsule. These molecules include the water and some solutes as glucose, electrolytes, fatty acids, nitrogenous wastes, amino acids and vitamins. On the other hand, they are impermeable to the larger components such as protein molecules and blood cells. The diameter of the afferent arteriole is larger than that of efferent one, which gives the capillaries a large inlet and a small outlet. This in turn causes the pressure in the glomerulus to be much higher than elsewhere in the organism. Because the high pressure overrides the reabsorption, the movement of the particles occurs. This movement of the components, from the blood into the Bowman's capsule is known as *glomerular filtration* and the fluid in the glomerular capsule, *glomerular filtrate* [2, 10].
2. **Tubular reabsorption.** The filtrate passing through the renal tubule apart from wastes, contains also water and many other useful substances such as ions and nutrients, which is a huge loss to the organism. Thus, they are being regained and returned to the bloodstream during the *tubular reabsorption*. The movement is not direct but involves also extracellular fluids and is obtained through the *diffusion, osmosis and active transport* [10].
3. **Tubular secretion.** At this stage the final adjustment of the content of the urine is made. Wastes, toxins and unnecessary substances are passed from the

blood to the renal tubule. What is of great importance, in this process also the hydrogen and bicarbonate ions can be removed in order to regulate the acid-base balance of the body [10].

4. **Urine condensation.** When the filtrate enters the collecting duct, it becomes the urine. In order to prevent the water loss and keep the fluid balance of the body, during the last step, the water is returned to the tissue fluid and the bloodstream, which makes the urine more and more concentrated [2].

Urine formulated in such a way is then extracted from the organism. The above stages are summarized in Figure 2.3.

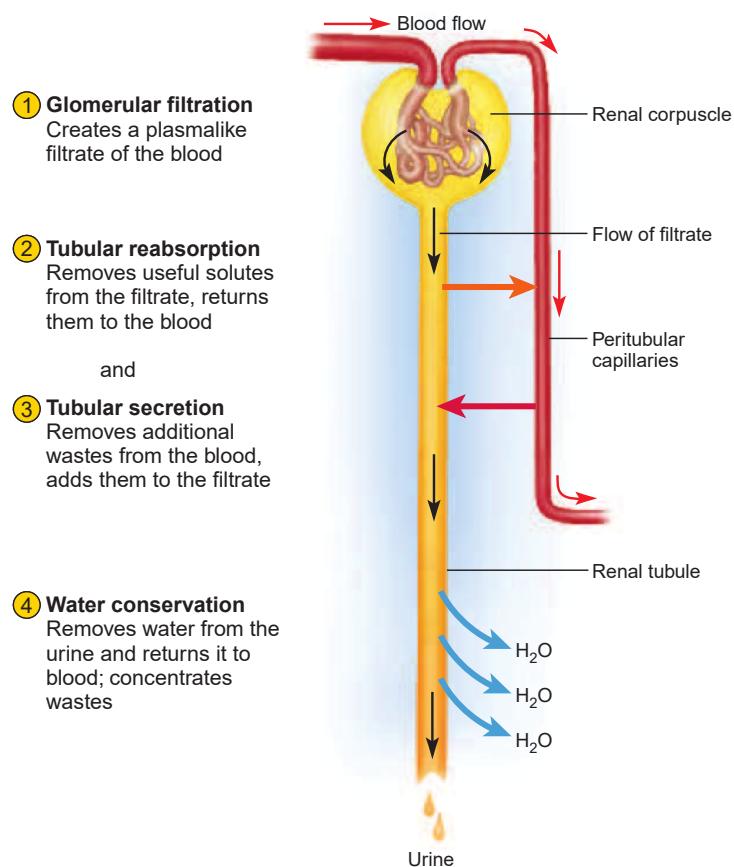


Figure 2.3. Process of the urine formation [2].

2.2.2 Glomerular filtration rate

Glomerular filtration rate (GFR) is a volume of fluid filtered during glomerular filtration from the renal glomerular capillaries into the Bowman's capsule per unit time by two kidneys combined and its unit is mL/min [21]. After standardisation, which is recalculation for standard *body surface area* (BSA), GFR is expressed in mL/min/1.73 m² [2].

The GFR in healthy adult kidneys is equal approximately 90–130 mL/min/1.73 m² [22]. Lower at birth, it approaches its adult value at the age two and maintains its level till the age of forty, when it starts decreasing again [23]. Appropriate GFR determines performance of several basic functions of the kidney. Neither too low, nor too high GFR is healthy to the organism [2].

In clinical practice, GFR is an approximate estimator of the number of active nephrons and is considered as a unit of level of kidney function. What is of great importance, GFR can also determine the stage of chronic kidney disease [6]. GFR between 60–120 mL/min/1.73 m² is considered normal, healthy value, below 60 mL/min/1.73 m² indicates definite kidney disease, while the number under 15 mL/min/1.73 m² is associated with renal failure [24]. The reference values of GFR are shown in Figure 2.4.

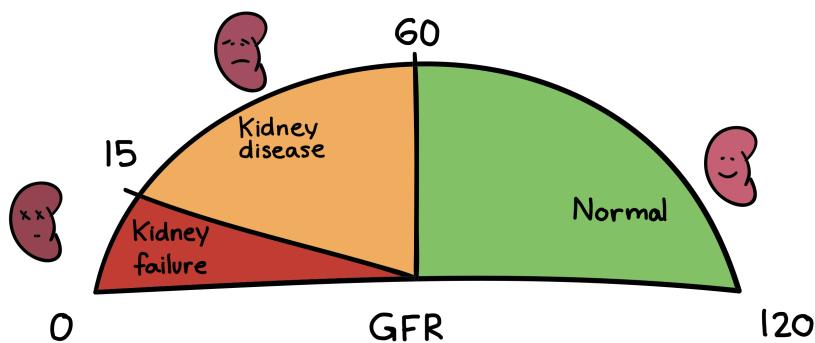


Figure 2.4. GFR reference values [25].

Due to the fact that the concentration of the particular substance in the blood and the urine is influenced not only by glomerular filtration, but also by tubular reabsorption and secretion, GFR cannot be measured directly by comparing the urine and blood concentrations. In such a way one would rather obtain *renal clearance*, which is a volume of blood plasma from which a particular waste is completely removed in a unit time [2] This dependency is expressed as follows:

$$\frac{\text{glomerular filtration of the waste}}{\text{---} \quad \text{tubular reabsorption of the waste} \\ + \quad \text{tubular secretion of the waste}} = \text{renal clearance} \quad (2.1)$$

For that reason, GFR measurement requires a substance that is neither secreted nor reabsorbed by the nephrons, which implies that its entire amount in the urine is passed there by glomerular filtration. Unfortunately, there is no single solute appearing in urine and naturally produced by the body, which doesn't undergo the tubular secretion or reabsorption to some degree [7].

However, in the nature there appear a substance which accomplishes the above conditions, namely insulin. One method of accurate measurement of glomerular filtration rate incorporates injecting insulin and subsequently measuring the rate of urine output and the concentrations of insulin in the blood and urine. For insulin, the GFR is equal to the renal clearance [2, 7].

Even though this method is considered the gold standard in the GFR measurement, due to its limitations it is not a clinical routine if very accurate measurements are not required. This special cases include transplant donors or scientific research [6]. Other, more frequently used techniques involve using endogenous markers such as *creatinine* and estimating GFR by applying validated algorithms [7].

Chapter 3

Dynamic contrast enhanced MRI

Medical Imaging started with the development of X-rays by Wilhelm Röntgen in 1895, for which he received a Nobel Price [26]. An enormous progress has been done since that time and numerous different imaging methods were developed, which found various applications in a medical field. Possibility of creating the visual representations of human interior as well as the processes occurring in tissues and organs, and thus their functionality, much facilitated medical diagnosis and prognosis. Some imaging techniques have became an integral part of clinical care (i.e computer tomography, magnetic resonance imaging, positron emission tomography), whereas there exist one, which still needs to prove its utility.

In this chapter the imaging technique, which is DCE-MRI will be introduced and its mechanism of imaging will be presented.

3.1 Fundamentals of MRI

In order to understand the mechanism of acquiring DCE-MRI sequences, it is inevitable to introduce the principle of operation of *Magnetic Resonance Imaging* (MRI).

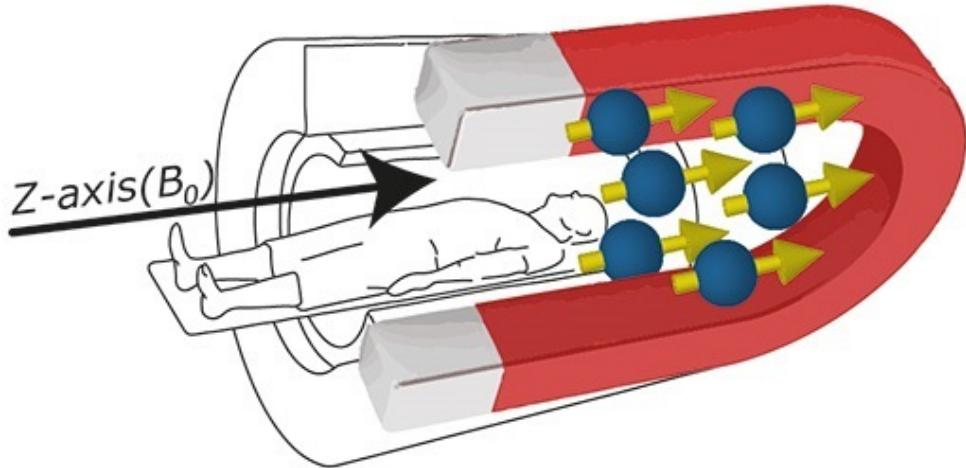


Figure 3.1. Hydrogen atoms located in a human body placed in the strong magnetic field (B_0), generated by the MRI scanner, align to the direction of that field [31].

MRI is an imaging technique based on the phenomena of induced nuclear magnetism in the patient. Every molecule possessing a nuclei with an odd number of protons or neutrons have a spin, implying a weak though observable randomly oriented nuclear magnetic moment. These particles include for example ^1H , ^{13}C , ^{31}P , ^{23}Na , ^{19}F [28, 29]. If placed in a strong static magnetic field, these moments strongly tend to align parallel to the external field. Some of them will align antiparallel to the field, however there will always be an excess of these directed towards the direction of the field, as this state is more energetically stable. The resulting net magnetic moment, M_0 , will be directed with the external field [30].

Magnetic resonance imaging explicit the fact that the human body in 80% consists of water. During the MRI examination, the object is placed in the scanner producing strong magnetic field, which causes the hydrogen atoms to align in the direction of the field, pointing towards the head of the object as shown in Figure 3.1 [30].

In addition, atoms have an angular momentum making them precess about the magnetic field direction with a frequency ω_0 , called the *Larmor frequency*, which is

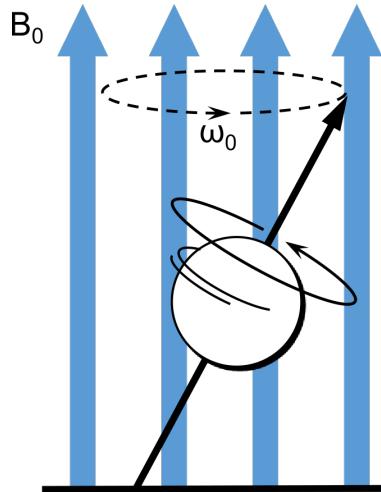


Figure 3.2. Hydrogen atom placed in a strong magnetic field B_0 precesses about the direction of that field with the frequency ω_0 .

proportional to the field:

$$\omega_0 = \gamma B_0, \quad (3.1)$$

where γ is the nuclei specific constant *gyromagnetic ratio* (for hydrogen equal to 42.6 MHz/T) and B_0 is the strength of the external magnetic field [28, 30]. This precessional motion is shown in Figure 3.2.

Further, when the radio-frequency (RF) pulse equal to the Larmor frequency is applied perpendicularly to the magnetic field, the resonance occurs. The atoms absorb the energy, transits to the higher energy state and flip to the other position. When the RF transmission is stopped, the atoms return to their equilibrium state (realign to the field B_0) releasing the energy as a radiation signal, referred to as *free-induction decay* (FID) response signal, which is picked by MRI receiver. This return to equilibrium is called *relaxation*. The relaxation time as well as the amount of the energy released strongly depends on the magnetic properties of the tissue, which means that every tissue generates different response signal. The dedicated software analyses and processes obtained signal, which is a combination of numerous

response signals from all excited atoms and generates the image [28, 30].

During the MRI examination, the strength of the magnetic field produced by the scanner varies along the body, so that the Larmor frequency is different for different regions. By changing frequency of emitted RF, the appropriate part can be imagined.

The typical MRI scanner consists of:

1. **The main field magnets**, which produces strong, uniform magnetic field polarizing the sample [28]. Typical strength of the field of a clinical MRI scanner ranges between 0.2–1.5 T, whereas research systems reaches values even up to 21 T for animal models [29, 32].
2. **Shim coils**. In clinical practice, the main field magnets never produce perfectly uniform field so the shim coils adjusting its homogeneity have to be used [28].
3. **Gradient coils** producing three secondary gradient magnetic fields in each of the x -, y - and z - direction. In this way, the resonance frequency of protons varies as a function of position, which enables encoding the spatial position and imaging of thin anatomic slices [33].
4. **RF system**, task of which is to excite the hydrogen atoms and to receive their FID response signal [28]
5. **The processing unit of high performance** controlling the system and processing the received combination of response signals [28].

3.1.1 T_1 - and T_2 -weighted images

Although, there are few approaches of obtaining the contrast between different tissues in an image, utilizing different tissue properties, most widely used in clinical applications are these based on the relaxation of the magnetization. However, there

are two kinds of relaxation, and thus two mechanisms of creating the MRI image can be distinguished [28].

T_1 -weighted images exploits spin-lattice relaxation, characterised by the time T_1 , which describes the time required by excited atoms to return to the equilibrium state after it was altered by the RF pulse. This mechanism is shown in Figure 3.3a. Sometimes the acquiring of T_1 -weighted sequence is preceded by the injection of *gadolinium*, paramagnetic contrast agent (CA), which shortens time T_1 and appears very bright on the image. This property is especially useful while visualising vascular structures or brain tumours and abscesses blocking a blood supply [28, 29].

T_2 -weighted images are based on spin-to-spin relaxation, described by the T_2 indicating the time required by the nuclei response signal to decay after it has been created [28, 29]. T_2 contrast is presented in Figure 3.3b.

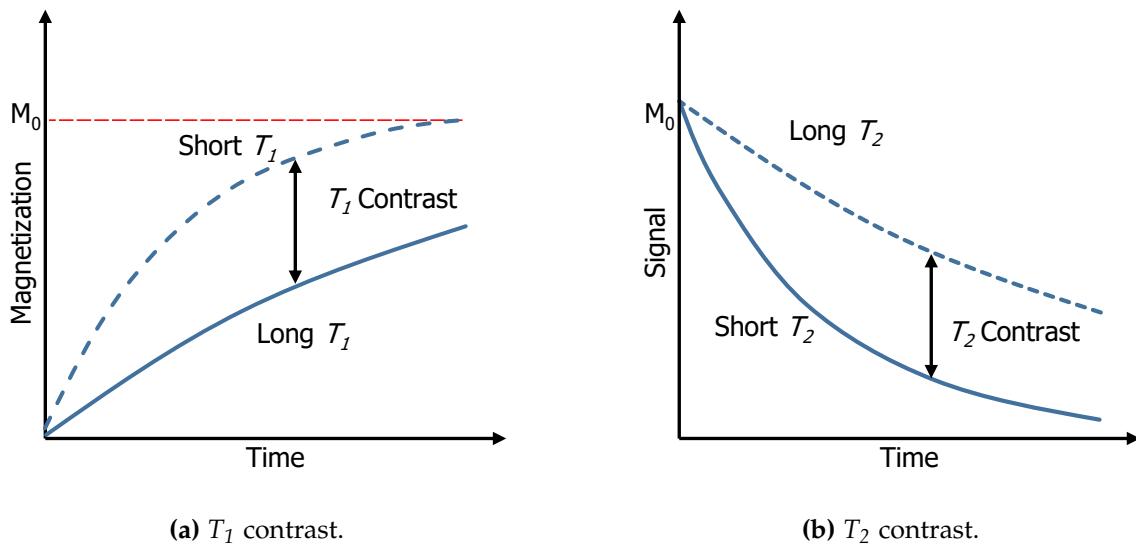
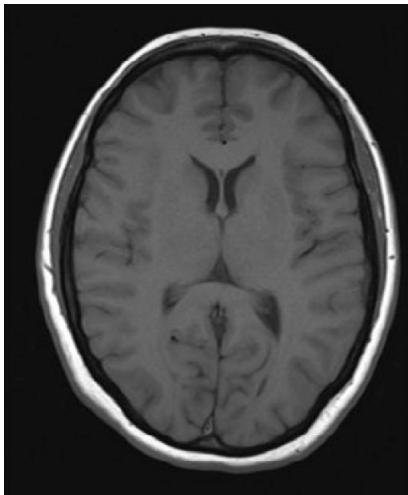
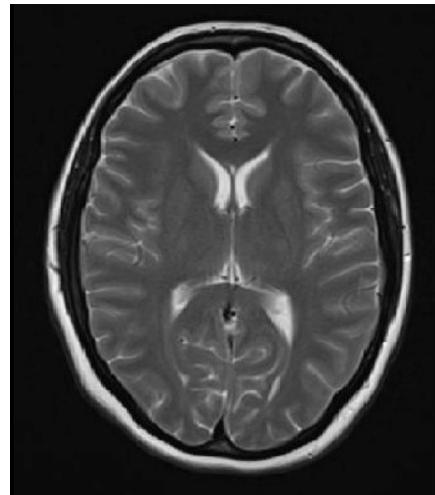


Figure 3.3. T_1 and T_2 contrast mechanisms [28].



(a) T_1 -weighted image of a brain.



(b) T_2 -weighted image of a brain.

Figure 3.4. Example MRI image of a brain of a healthy volunteer demonstrating T_1 and T_2 contrast [34].

Examples of the images acquired using described above two basic mechanisms are shown in Figure 3.4a-b. The figure presents identical axial section of a healthy person's brain. In the T_1 weighted image, one can notice ring of subcutaneous fat, which is bright due to its short spin-lattice relaxation time. Gray matter has longer T_1 than white matter, so it appears darker. In the second picture, utilizing the T_2 difference between tissues, cerebrospinal fluid in the ventricles appears very bright due to its long T_2 . T_2 of the white matter is shorter than those of gray matter, which makes the latter one brighter. T_1 and T_2 weighted images are only two of the few contrast mechanisms used in MRI and the choice of appropriate one strongly depends on the application and the region of interest under examination [28].

Currently MRI is one of the most widely used medical imaging techniques applied to all parts of a body. It allows to create the detailed anatomical images in axial, sagittal, coronal or even oblique plane. During the MRI examination subsequent thin 2D *slices* along chosen axis are produced, which makes it a tomographic

imaging method. As a result, during imaging sequence, a large dataset is acquired, from which any anatomical section can be reconstructed or a 3D model of a region of interest can be assembled [30]. Another advantage of MRI is not using any harmful ionizing radiation.

The clinical applications of MRI include diagnosis of blood vessel damages, multiple sclerosis, brain injuries, spinal cord injuries, brain strokes, blocked blood vessels, heart diseases, damages caused by a heart attack, bone infections, different kind of tumors and cancers and many more [35].

3.2 DCE-MRI

Dynamic contrast enhanced magnetic resonance imaging boils down to the acquisition of multiple MRI scans, with addition of one significant component—the time domain [36]. During the examination a contrast agent is injected in the peripheral vein into the bloodstream and the T_1 -weighted images are acquired with fast imaging technique. The passage of the tracer through the target tissue results in changes in signal intensities over the time. The kinetics of the CA, so its temporal and spatial distribution is strongly dependent on the physiological parameters such as tissue perfusion, volume of the extravascular and extracellular space and vessel permeability, and thus the analysis of so obtained intensity changes as a function of time, $S(t)$, provides important functional information [8, 9]. As an example, malignant tumours show faster and higher levels of enhancement than normally functioning tissue, which is associated with tumour's increased vascularity and higher endothelial permeability to the CA [36].

3.2.1 DCE-MRI analysis

There are many methods of time-courses analysis obtained during DCE-MRI. In general, they can be divided into qualitative, semi-quantitative and quantitative ones [37]. All methods can be applied voxel-wise or to the whole Region of Interest (ROI), where the average time-intensity curve is produced from the voxels values within the ROI [9].

3.2.1.1 Qualitative analysis

In traditional approach, the evaluation of the time-intensity curves is performed by experienced observer via subjective visual inspection, who's task is to classify the curve to one of the three predefined enhancement patterns. These three templates are shown in Figure 3.5.

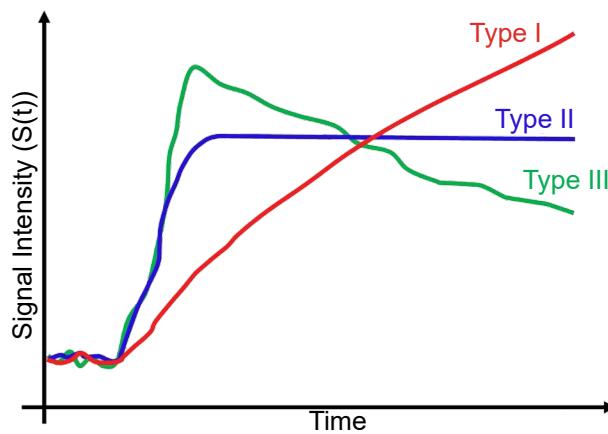


Figure 3.5. Different DCE-MRI enhancement patterns [9].

Type I defines a shape characterized by the gradual increase of the signal intensity during the whole acquisition time. In type II, after the initial peak, the plateau occurs—the curve remains relatively constant. Type III is associated with the decrease in signal intensity after the peak signal intensity [37]. In this way, i.e. the tumour can be distinguished from the healthy tissue.

Although the qualitative analysis is a very convenient one as it does not require any additional data and calculation, its major disadvantage is not delivering any quantitative parameters and being fully dependent on the observer's experience.

3.2.1.2 Semi-quantitative analysis

The semi-quantitative analysis incorporates calculation of parameters directly from the time-intensity curve characterizing its shape [9, 37]. Several examples of the parameters include *onset time* (T_o), *maximum signal intensity* (S_m), *peak enhancement* (ΔS), *time to peak* (T_p), *wash-in slope*, *wash out slope*, *average plateau*, *area under the curve* (AUC) or *initial uptake area under the curve* (IAUC) [9]. Listed parameters are depicted in Figure 3.6.

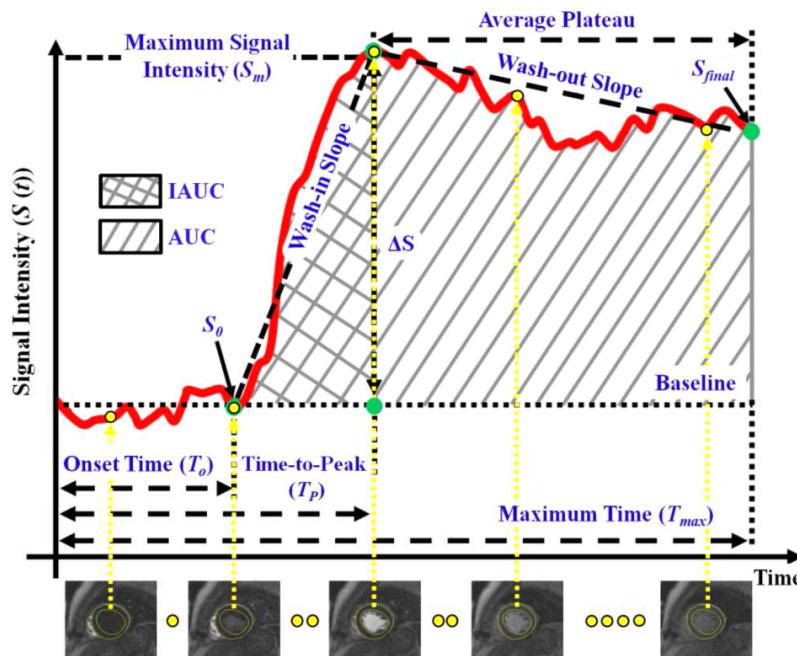


Figure 3.6. An example of the time-intensity curve, $S(t)$, with depicted metrics explored in semi-quantitative DCE-MRI analysis. Note that S_0 is the signal intensity before CA arrival whereas S_{final} is the intensity registered in the last temporal point at the end of the experiment T_{max} [9].

As in the case of previous method, the ease of the calculations performed directly from the curve is its biggest advantage. However obtained empirical parameters in some way correlate with tissue physiology, i.e. increased vascular density or permeability usually increases the wash-in slope, AUC, and peak enhancement, in the same time decreasing the time to peak, it is difficult to relate them directly to some particular physiological quantities [37].

3.2.1.3 Quantitative analysis

Quantitative assessment of the $S(t)$ curve is surely the most sophisticated one. It involves fitting one of the several quantitative mathematical models, which describes the pharmacokinetics of the contrast agent to the concentration-time curve of the target tissue. Not only does this type of analysis require acquisition of the intensity-time curve of the feeding blood vessel next to that of the target tissue but also one has to convert obtained curves into CA concentration-time curves. In reward, some physiologically interpretable kinetic parameters of the tissue are estimated [36, 37]. The issue of the pharmacokinetic modelling in details is described in Chapter 4.

3.2.2 DCE-MRI applications

Even though not present in clinical routine yet, over the last two decades DCE-MRI has been widely explored in clinical studies. There is no doubt that obtaining important functional information next to the anatomical one in a single imaging session is one of the biggest advantage of Dynamic Contrast Enhanced MRI. It has shown to have great potential in early detection of breast cancer, providing higher sensitivity than classical mammography, as well as detection of small lesions, which classical MRI is not capable to. What is more, it showed promising results in accurate localisation of prostate cancer. Further DCE-MRI was found to be reliable technique

of monitoring tumour responses for treatment (changes in vascular support). DCE-MRI also showed its effectiveness in accurate detection of renal rejection. Last but not least, what is of great importance for this project, from the DCE-MRI images, important physiological parameters of the tissue, such as GFR of the kidney can be estimated [9].

The mentioned findings, which are only a drop in the ocean of researches, suggest that DCE-MRI is a relevant non-invasive imaging technique, which can be a part of clinical care used in a really wide range of applications.

Chapter 4

Pharmacokinetic modelling

The ideal output obtained from DCE-MRI analysis would be some reliable quantitative physiological parameters of the tissue under examination. Numerical results, however, always call for some mathematical description of the system under examination.

The time-dependent distribution and deposition of a substance in a living system can be described by Pharmacokinetic (PK) models [38]. First attempts of depicting the organism by a set of components were performed by Torsten Teorell in 1937. He then created a model of whole body shown in Figure 4.1 and decribed the processes inside by a set of differential equations in the same time presenting their solutions [39]. Teorell is now considered a father of *Pharmacokinetic* (PK) modelling.

PK models aim to characterise a physiologic system, not necessarily the whole body, by decomposing it into interacting compartments. Every of them is a homogenous, well-mixed space with the uniform tracer distribution [40]. Thus, the multicompartment system reaches the equilibrium in different time. PK models have very wide clinical application: from estimating the optimal drug dose to determining safe working environment while working with toxins [38].

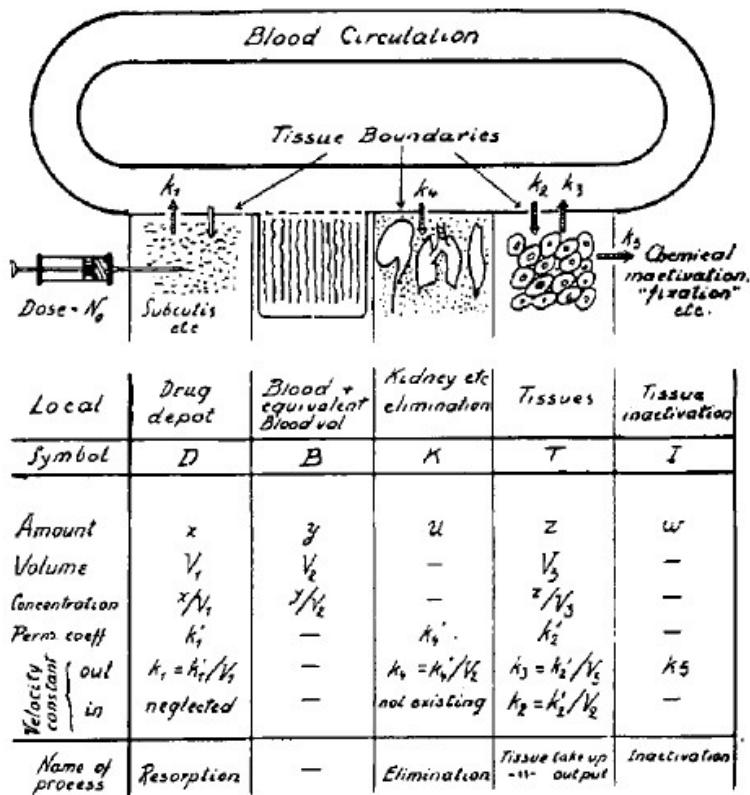


Figure 4.1. First PK model described by Teorell [?].

Given the fact that the contrast agent used in DCE-MRI examination can be considered as a substance flowing through the organism, Pharmacokinetic modelling can also be used in analysis of so obtained data. This approach, called the quantitative one, is based on fitting mathematical model to acquired tissue concentration time courses. In this way, the quantitative parameters can be assessed, which cannot be overestimated while evaluating the tissue function.

This chapter deals with the approach of PK modelling giving the brief inside in its basic principles and requirements with focus on DCE-MRI applications.

4.1 The tracer kinetic theory

The compartment PK models describe complex blood-tissue exchanges. The general tracer kinetic theory is based on mass conservation principle and PK models are formulated as mass balance equations.

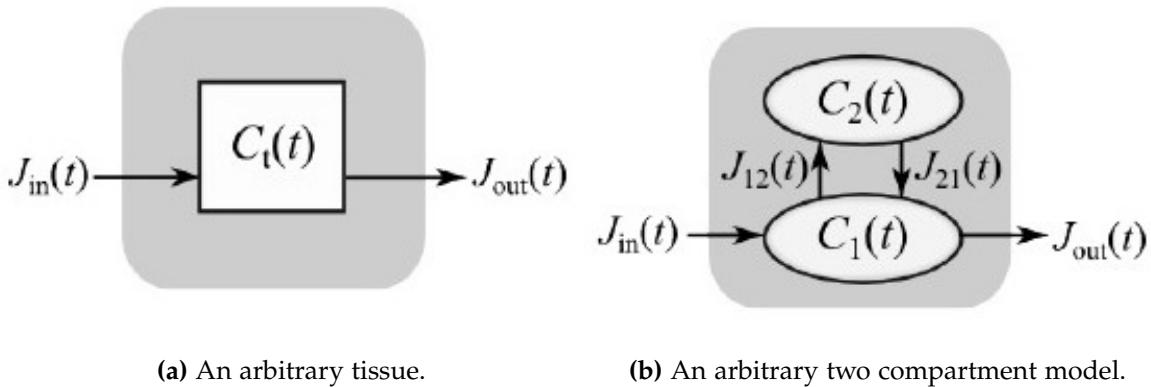


Figure 4.2. aa.

Given the tissue with at least one inlet and one outlet, see Figure 4.2a, the time-varying tracer concentration in the tissue, $C_t(t)$ can be expressed as:

$$C_t(t) = \frac{M_t(t)}{V_t}, \quad (4.1)$$

where $M_t(t)$ is the amount of tracer in the tissue (in mmol) and V_t is the volume of the tissue (mL). The *flux* (mmol/mL/min) in terms, is the amount of the tracer, which travels through an inlet or outlet per unit time. After the normalisation to the unit tissue volume the flux can be expressed as:

$$J(t) = \frac{1}{V_t} \frac{\partial M_t(t)}{\partial t} \quad (4.2)$$

Let' now consider an arbitrary multi-compartment model composed of n interacting

compartments. Then, the outlet of one compartment is in the same time the inlet of another, see Figure 4.2b. The tissue concentration in such a system is defined by:

$$C_t(t) = \sum_{j=1}^n v_j C_j(t), \quad (4.3)$$

where $v_j \leq 1$ is the *fractional volume* (dimensionless) of j th compartment and C_j is the concentration of tracer in this compartment. From the principle of the conservation of the mass it is known that no amount of the indicator is neither created nor destroyed in the tissue. Under such condition, applying the mass balance equation to the every of the compartments, the change of the total amount of substance in the compartment is given by:

$$\frac{dM_j(t)}{dt} = \sum_i^I \frac{M_i(t)}{\partial t} - \sum_o^O \frac{M_o(t)}{\partial t}, \quad (4.4)$$

where I and O are the number of inlets and outlets of the compartment respectively. After normalisation to the unit tissue volume:

$$v_j \frac{dC_j(t)}{dt} = \sum_i^I J_i(t) - \sum_o^O J_o(t), \quad (4.5)$$

The mass conservation principle implies that the amount of the substance transported from a compartment i to a compartment j per unit time is equal to the amount of the given substance leaving the i . This leads to the formula:

$$\frac{\partial M_{ij}(t)}{\partial t} = k_{ep} M_i, \quad (4.6)$$

where k_{ep} is so called *rate constant* (in min^{-1}). Again, after the normalisation to the unit tissue volume:

$$J_{ij}(t) = K_{trans} C_i(t), \quad (4.7)$$

where $K_{trans} = k_{ep}v_j$ is *transfer constant* (in ml^{-1}). K_{trans} combines both the flow and tissue permeability. Some models allow their separate estimation by differentiating the *flow F* by the *permeability surface area product, PS*.

4.1.1 Linear stationary systems

All PK models are based on two fundamental assumptions, without which solving the models' equations would not be possible: that the system is linear and stationary. Hence the response of the influx is proportional to the dose of the injected tracer.

For any linear and stationary system satisfying the initial condition $C_t(0) = 0$, which means $t = 0$ is chosen before tracer injection, the tissue concentration can be obtained by convolving the concentration of tracer input function with the Impulse Response Function (IRF) of the tissue denoted as $h(t)$ [41]:

$$C_t(t) = C_{in}(t) \otimes h(t) = \int_0^t C_{in}(\tau)h(t - \tau)d\tau \quad (4.8)$$

When the only inlet of the examined tissue is an artery, the input function corresponds to the function of plasma concentration at the entrance of the system and can be derived from so called *Arterial Input Function* (AIF), $C_{in} = C_p$. The IRF in terms can be found by applying the Laplace transform to the appropriate mass balance equations.

4.1.2 One-compartment model

For better understanding, the above theory will be explained on an example one-compartment model, which is similar to the all models used in this work. Given a one-compartment system with a single inlet and outlet and taking into consideration that all substances in the system have constant volume, it is known that

inflow have to level the outflow. On the basis of Formulas 4.5, 4.7 the mass balance equation of the system can be formulated as follows:

$$v_1 \frac{dC_1(t)}{dt} = K_{trans}(C_{in}(t) - C_1(t)), \quad (4.9)$$

where the v_1 is fractional volume of the compartment. From the Formula 4.3:

$$\frac{dC_t(t)}{dt} = K_{trans}(C_{in}(t) - C_t(t)/v_1), \quad (4.10)$$

Now, the IRF of the tissue is obtained by applying the Laplace transform to the above equation. As a result:

$$h(t) = K_{trans}e^{-k_{ep}t} \quad (4.11)$$

Finally the tracer concentration in the tissue can be expressed as:

$$C_t(t) = C_{in}(t) \otimes K_{trans}e^{-k_{ep}t} \quad (4.12)$$

The described above physical and mathematical background was shorten so that to introduce very basics and explain enough but not too much on the theory of PK models. If the reader is interested, I kindly refer to the original sources [41].

There exist numerous PK compartment models used in DCE-MRI analysis and every of them is based on different assumptions and simplifications, which are not proper in all cases. The choice of the model depends on such factors as a type of a tissue under consideration, the quality of data, the possibility of obtaining AIF and many more. One should, however, remember that no mathematical equations will ever describe the living organism accurately in 100% as there are no two samples of tissue behaving exactly in the same way. The most widely used PK models include: *Toft and Keromode* (TK), *Extended TK* (ETK), *Two-compartment Exchange* (2CXM) and *Patlak* (PM) models.

4.2 Arterial Input Function

The quantitative approaches of DCE-MRI analysis require obtaining the input function delivering the tracer to the system. From the physiological point of view, the tracer is delivered to the tissue of interest through the feeding arteries, so the input function becomes the plasma concentration, C_p in these vessels. Plasma concentration can be obtained from so called *Arterial Input Function* (AIF), which describes the changes of the tracer concentration in the feeding blood vessel. The tracer kinetics in the artery differs significantly from this of the tissue. The changes in plasma concentration are fast and sharp and it is of great importance to cover the rapid peak of the signal or else the important information about the tissue will be lost. In general there are three approaches of acquiring the AIF:

1. **Gold standard AIF** is obtained by blood sampling during DCE-MRI examination. Although its accuracy strongly depends on the frequency of collected samples, this method usually allows accurate measurement of the AIF, but is inconvenient for both the patient and the exterminator. What is more, in some cases, for example during DCE-MRI of a breast, blood collection close to the tissue of interest is impossible to perform due to the lack of big vessels in this region [9, 37].
2. **DCE-MRI AIF** is determined directly from the obtained DCE-MRI data. In this approach The time-varying signal intensity from the region containing large feeding artery is converted into the tracer concentration in this way estimating the AIF. The major limitation is that it is not always possible to cover the the desired artery in the DCE-MRI acquisition field, for example during imaging small lesions in a breast [9].
3. **Population-based AIF** is obtained by averaging the AIF of the group of subjects to be used in subsequent studies of the similar subjects. Because the need

of acquiring subject-specific AIF is eliminated, the temporal resolution of the DCE-MRI can be decreased (CA tissue kinetics is slower than in the blood) in the same time increasing the quality of the images or the spatial resolution. The biggest disadvantage of this method is possible variance between individual AIFs.

4.3 Intensity to concentration conversion

As the PK models describe kinetics of the system in terms of the CA concentration in the tissue and the output of DCE-MRI examination is the signal intensity as a function of time, the conversion of the signal intensity to concentration is indispensable. As long as the relationship between CA concentration and the signal intensity is linear, and the same for both the tissue and the blood in case of acquiring AIF from DCE-MRI images, the conversion comes down to the subtracting the baseline so that the concentration before the tracer arrival is at the level of 0. This conditions are satisfied at low doses of CA.

At high doses of the CA, however, this linearity is not true anymore due to the saturation effect of the signal. Non-linearity adds one more complication to the DCE-MRI examination. In such case, in order to convert the signal intensity into the CA concentration, the pre-contrast T_1 values before the tracer injection have to be measured.

Chapter 5

Implementation

5.1 Materials and methods

5.1.1 DCE-MRI aquisition

The dataset used in this project consists of forty DCE-MRI sequences. Each of the 20 healthy, non-smoking participants underwent two MRI examination at a time interval of 7 days. A gadolinium-based CA GdDOTA (Gadoteric Acid) at a dose of 0.025 mmol/kg was administrated as a bolus injection at 3 ml/s. The data were acquired on 32 channel 1.5 T whole-body scanner (Siemens Magnetom Avanto [42]). The images covering kidneys and aorta were continuously acquired every 2.3 s for approximately 6 min in coronal-oblique plane. Each of 74 time volumes consisted of 30 slices. The aquisition matrix was 192×192 whereas the voxel size was equal to $2.2 \times 2.2 \times 3 \text{ mm}^3$. More information about aquisition of DCE-MRI data used in this project can be found in [43]. The few frames of the sample raw DCE-MRI sequence is shown in Figure 5.1.

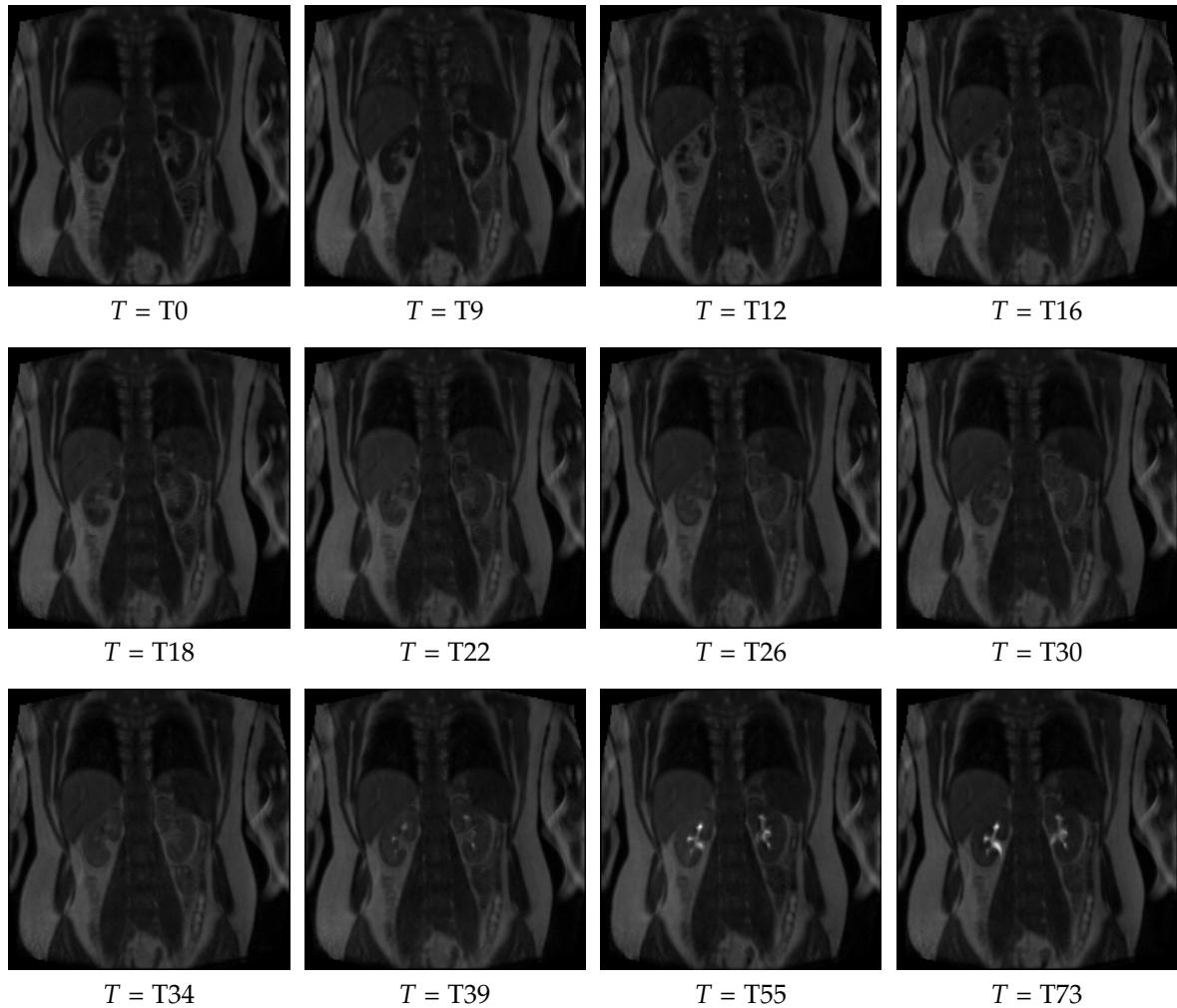


Figure 5.1. Sample DCE-MRI sequence.

5.1.2 GFR reference values

Next to the DCE-MRI examinations, the participant had their GFR assessed by two commonly used in clinical practice chemical methods: the Serum-creatinine (SCr) and iohexol GFR tests.

The clinical characteristic of the participants is included in Table 5.1

Table 5.1. Clinical characteristic of the participants. Taken from [43].

Participants	20
Gender (female/male)	16/4
Age (years)	25 (20—38)
Height [m]	1.71 ± 0.07
Weight [kg]	66.2 ± 8.7
Body mass index (BMI) [kg/m ²]	22.6 ± 2.1
Body surface area (BSA) [m ²]	
Iohexol GFR [ml/min/m ²]	103 ± 10

Values in parentheses are ranges.

Plus minus values are means ± Standard Deviations (SD).

5.1.3 Image processing and analysis

5.1.3.1 Motion correction

One of the first fundamental problem encountered during DCE-MRI analysis is misalignment of 3D volumes across time slices. This misalignment of organs is a result of the patient's respiratory motion as well as the heartbeat and bowel peristalsis and is unavoidable during examination. Studies have shown that even slight misalignment can lead to significant differences in intensity time-courses [44] and thus, motion correction of time series is essential for further analysis.

In order to remove motion artifact, all files were motion-corrected across time

points. For this purpose R programming language for statistical computing and graphics was used [45] together with the package ANTsR [46], which provides quantification tools for biomedical images. As an initial step, for every time series, the algorithm extracted 3D volumes. Each extracted volume corresponded to data obtained in one time point. Next, the average image of the temporal volumes was calculated, which was treated as a mask for image registration. Every temporal volume was then aligned to the mask and at the end they were combined back together into 4D time series.

5.1.3.2 Pelvis removal

Due to the fact that glomerular filtration takes place in renal renal parenchyma, pelvis had to be removed from further analysis.

Resulting from the physiology of the process, the three renal compartments (cortex, medulla, pelvis) can be distinguished from each other on the basis of their time courses, as shown on Figure 5.2. Depending on the compartment, the rapid enhancement of the signal occurs in different period, which makes the shapes of the time intensity curves very unique. From the 5.2 it can be seen that the biggest variation is observed between pelvis and two other renal compartments. Consequently, it can be separated by unsupervised clustering.

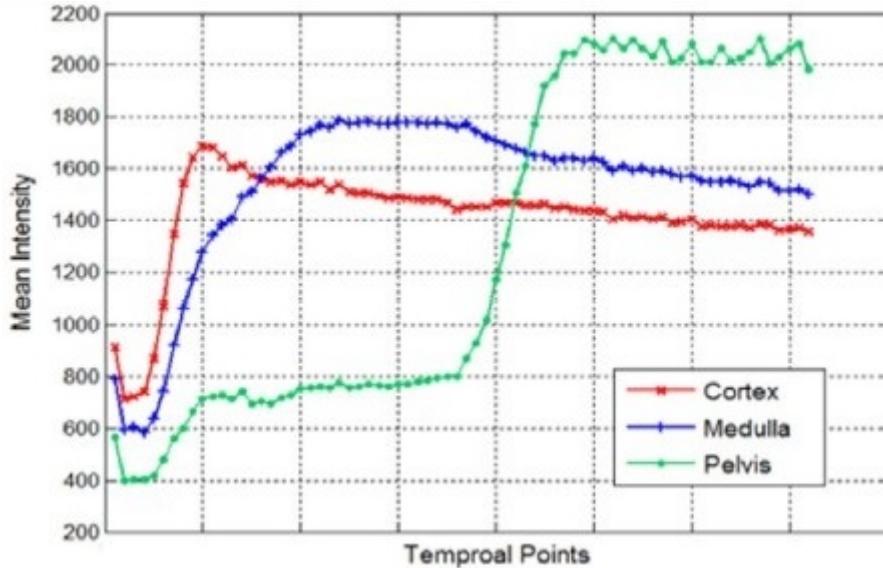


Figure 5.2. Kidney compartments timecourses [44].

First of all, every of the the voxel belonging to the label of the kidney was described by the vector of seventy-four features as follows:

$$\mathbf{v}_{ijk} = [S_{T0}, S_{T1}, \dots, S_{T72}, S_{T73}], \quad (5.1)$$

where S_{Tn} is the value of signal intensity in the time point n .

However, feature space of seventy-four dimensions is way too much for further analysis. High dimensionality of raw DCE-MRI data results in computational complexity, and thus memory and time consumption as well as numerical problems. What is more it contains a lot of noises [44]. To overcome this problems, the *Principal Component Analysis* (PCA) [47] was applied.

PCA is a statistical procedure, which transforms the number of related features into smaller set of uncorrelated variables [48]. These so called *Principal Components* (PCs) are a linear combination of the original variables [49]. As a result, after rotating the feature space, the first PC contains most variance, the last one the least and so on.

In this way the dominant patterns are extracted while the noises are reduced [47]. Further, every of the PC is characterised by a ratio of *explained variance*, which indicates the portion of the dataset's variance lying along the axis of each PC [50].

Applying the theory to practice, each voxel belonging to the kidney, initially described by forty-four features was described by a number of PCs:

$$\mathbf{v}_{ijk} = [PC1, PC2, \dots, PCn] \quad (5.2)$$

The amount of PCs, n , was chosen as a minimum number of dimensions required to preserve 95% of the data's total variance so that the sum of the explained variances of n PCs was equal to at least 0.95 (usually between 4—6 PCs). The visual representation of the feature space with first three dimensions (PCs) for sample kidney is shown in Figure 5.3. Note that for better understanding, the clusters were already marked with different colors.

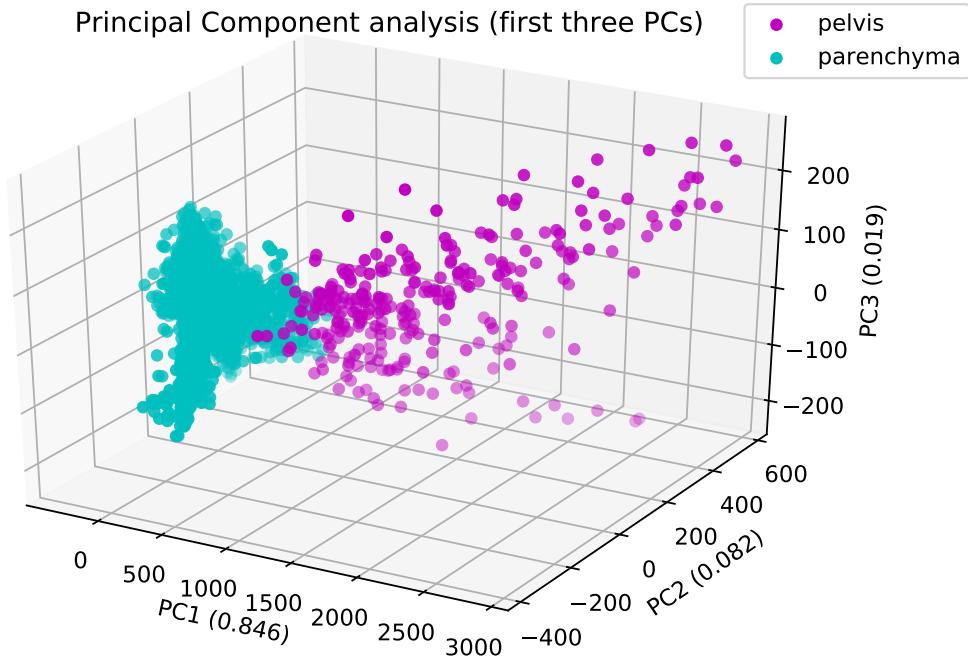


Figure 5.3. Principal Component Analysis for sample kidney. The values in brackets are the ratios of explained variance for the given PCs. Note that the number of PCs was reduced to three for visualisation purpose.

To the dimensionally reduced data, the *k-means clustering* [51] was applied in order to separate voxels into two groups: pelvis and renal parenchyma. The k-means is an unsupervised clustering algorithm aiming to divide the data into groups so that the diversity between the groups is maximised whereas the similarity within the single group is maximised.

Given a data set $X = \{\vec{x}_1 \dots \vec{x}_n\}$ in m -dimensional space (what actually corresponds to the m features of a sample) the algorithm's objective is to minimize the square error function given by:

$$J = \sum_{j=1}^k \sum_{i=1}^n (\|x_i - c_j\|)^2, \quad (5.3)$$

where $\|x_i - c_j\|$ is the Euclidean distance between a data point x_i and the cluster centre c_j of k predefined clusters. It is achieved by the steps summarised in Algorithm 1.

Algorithm 1. K-means clustering

Input : number of clusters k ,

set of points in m -dimensional space: $X = \{\vec{x}_1 \dots \vec{x}_n\}$

Output: set of cluster labels of X : $L = \{l(\vec{x}_i) | i \in \{1 \dots n\}\}$,

coordinates of cluster centroids: $(\vec{c}_1 \dots \vec{c}_k)$

```

1  $(\vec{c}_1 \dots \vec{c}_k) \leftarrow \text{RandomlyChooseCentroids}(k, X)$   $(\vec{c}_1 \dots \vec{c}_k) \in X$ 
2 repeat
3   /* assign each data point to the closest centroid on the basis of
4    Euclidean distance */  

5    $l(\vec{x}_i) \leftarrow \text{argminDistance}(\vec{x}_i, \vec{c}_j) | j \in \{1 \dots k\}$ 
6    $(\vec{c}_1 \dots \vec{c}_k) \leftarrow \text{CalculateMeanOfPointsInCluster}()$       /* recalculate centroids */
7   until none of  $(\vec{c}_1 \dots \vec{c}_k)$  changes
8 return  $L, (\vec{c}_1 \dots \vec{c}_k)$                                      /* points divided into clusters */

```

To segment the kidney, the k-means algorithm was initiated with two clusters, $k = 2$ and performed for points (kidney voxels) in ten-dimensional space (10 PCs).

Furter, for each of the identified clusters, the average time point, T_{max} in which signal intensity reaches its maximum was calculated. Following the assumption that $T_{max_pelvis} > T_{max_parenchyma}$, the cluster with greater T_{max} was marked as the pelvis and removed from the *Region of Interest* (ROI). The average time-intensity curves for two detected clusters in k-means clustering algorithm for sample kidney are presented in Figure 5.4. On can easily note the wash in phase in pelvis takes place much later than in renal parenchyma. The results of the segmentation in turn are shown in Figure 5.5.

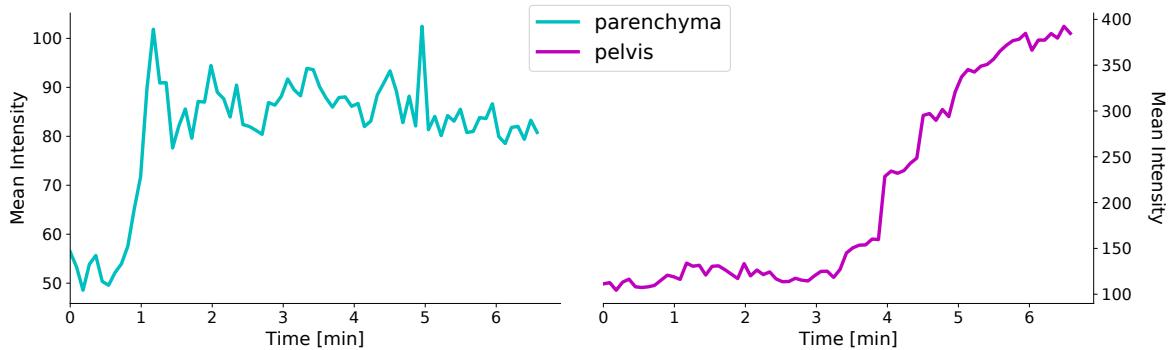
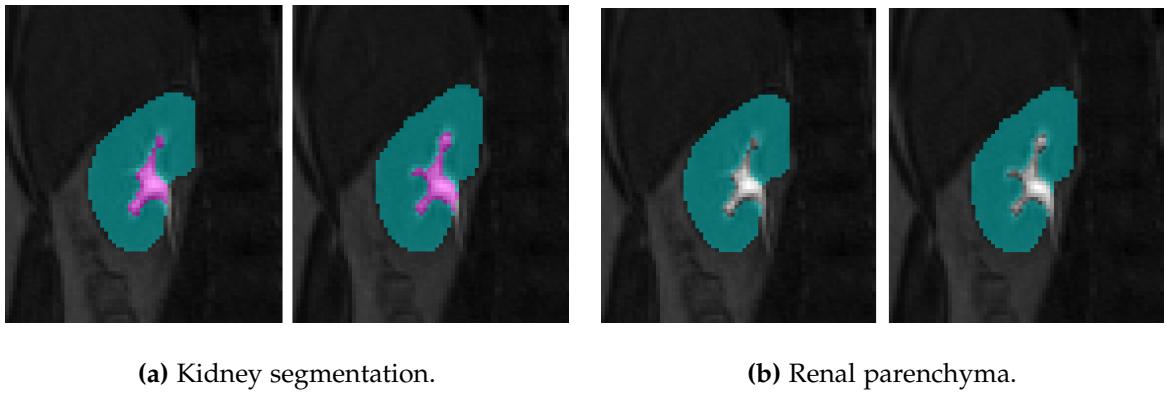


Figure 5.4. Average time courses for two clusters detected in k-means algorithm performed for sample kidney.



(a) Kidney segmentation.

(b) Renal parenchyma.

Figure 5.5. The results of the segmentation obtained with k-means clustering. Figure (a) shows two regions of sample kidney: the pelvis (cyan) and the renal parenchyma (magenta); Figure (b) presents the kidney after pelvis removal. The images were intentionally presented at Time point $T_p = 73$, when the enhancement of the pelvis is big, for better visualisation.

5.1.3.3 Concentration-time curves

Having labelled the proper ROI, the time has come for the principal part of the analysis, namely pharmacokinetic modelling. All PK models used during quantitative DCE-MRI analysis call for determining both the tissue, $C_t(t)$, and blood plasma, $C_p(t)$, concentration as a function of time. In our case, the $C_t(t)$ is the mean

concentration in renal parenchyma, whereas the $C_p(t)$, can be derived from Arterial Input Function, which is a concentration in a blood vessel feeding the kidney (aorta) [9]. Thus, they were calculated in the next steps of the project.

For each of the kidney, as well as for the aorta, the mean intensities of the voxels included in the particular labels were calculated at the each time point and the time courses were plotted. Sample time courses are shown in Figure 5.6.

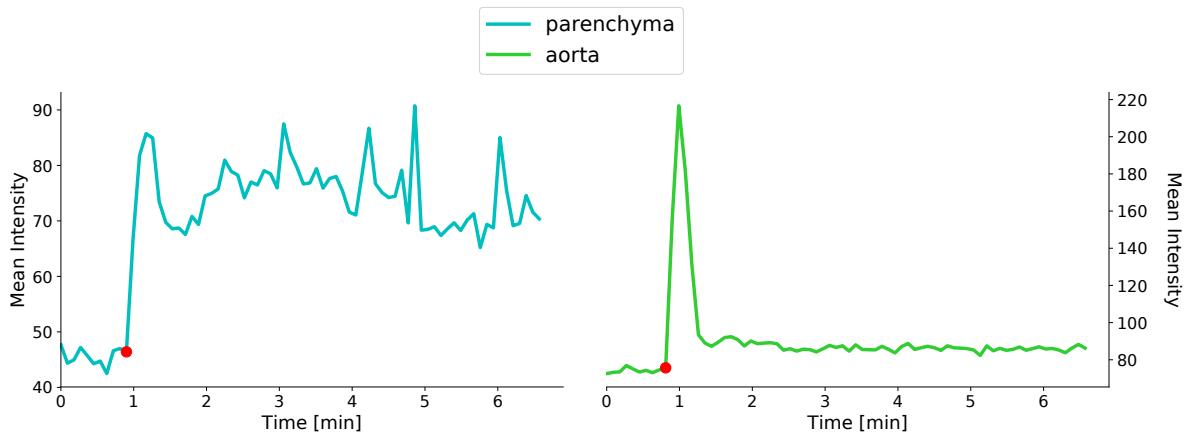


Figure 5.6. a.

Assuming the linear relation between tracer concentration and signal intensity $S(t)$ [52], the tracer concentration can be expressed as:

$$C(t) = S(t) - S_0, \quad (5.4)$$

where S_0 is the baseline signal, which is the average signal intensity among the time before the administration of CA. In order to determine S_0 , the time point before rapid signal increase, $T_{baseline}$ had to be found as marked with red dot in Figure 5.6.

To achieve it, firstly, for the purposes of the examination of the function changes, the median filter with the *kernel size* = 5 was applied in order to smooth the signal and eliminate artificial peaks and valleys, see Figure 5.7 In next step, for every

intensity time course under analysis, its derivative was calculated. The derivative describes the instantaneous rate of change of the function. It tells how fast the output of the function (signal intensity) changes compared to the independent variable (time) [53] and seems to be a perfect solution to the problem, which comes down to the finding the most rapid signal change. Because of one's interests is detection only of the function's increases, not decreases, the points, in which the derivative is negative were neglected, $S'(t) < 0 \leftarrow 0$. So modified derivative of the sample kidney and aorta are shown in Figure 5.8.

Now, all that had to be done to find $t_{baseline}$ was to find the point, in which the derivative of the signal intensity time course reaches its maximum, $t_{baseline} = argmax S'(t)$. Having it determined, the S_0 was calculated as the mean signal intensity value from the beginning of the measurement ($t = 0$) to $t_{baseline}$. Finally, the CA concentration in the tissue and aorta were calculated according to the Formula 5.4. The results of intensity-concentration conversion for sample time curves are shown in Figure 5.9.

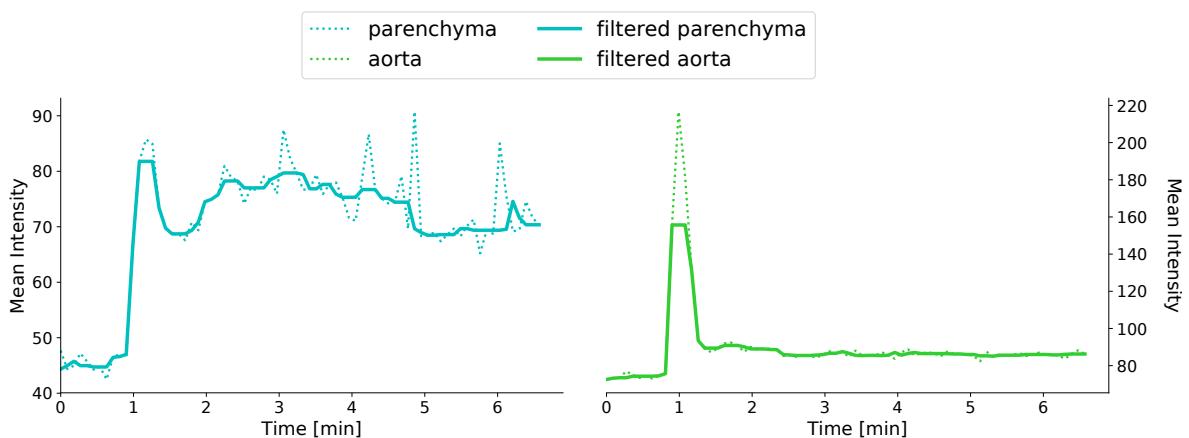


Figure 5.7

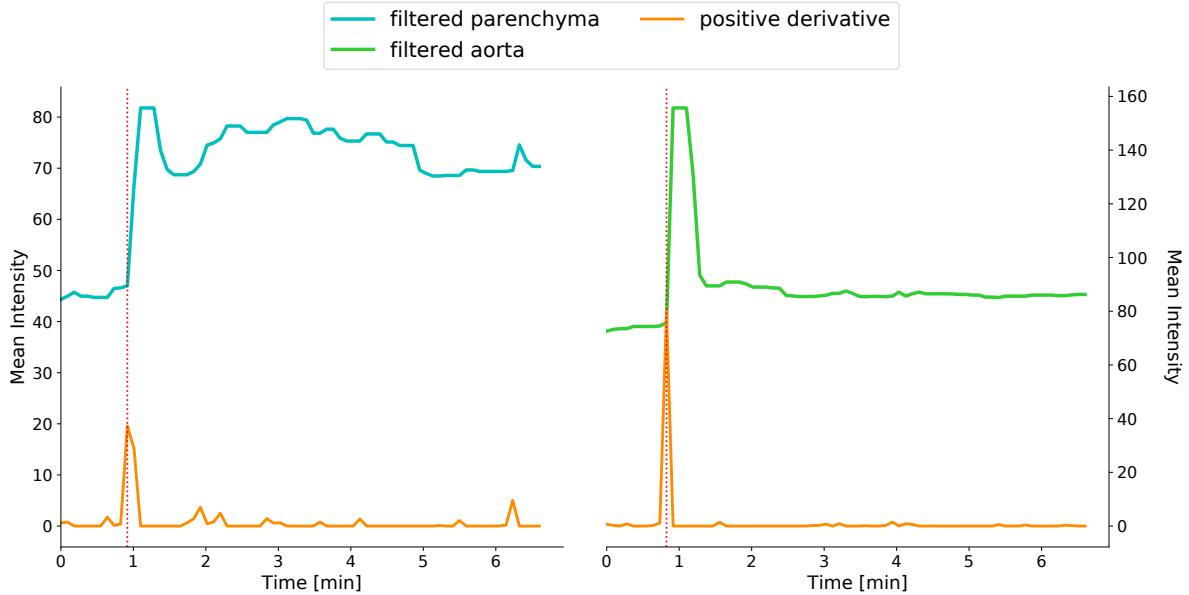


Figure 5.8. Average time courses for two clusters detected in k-means algorithm performed for sample kidney.

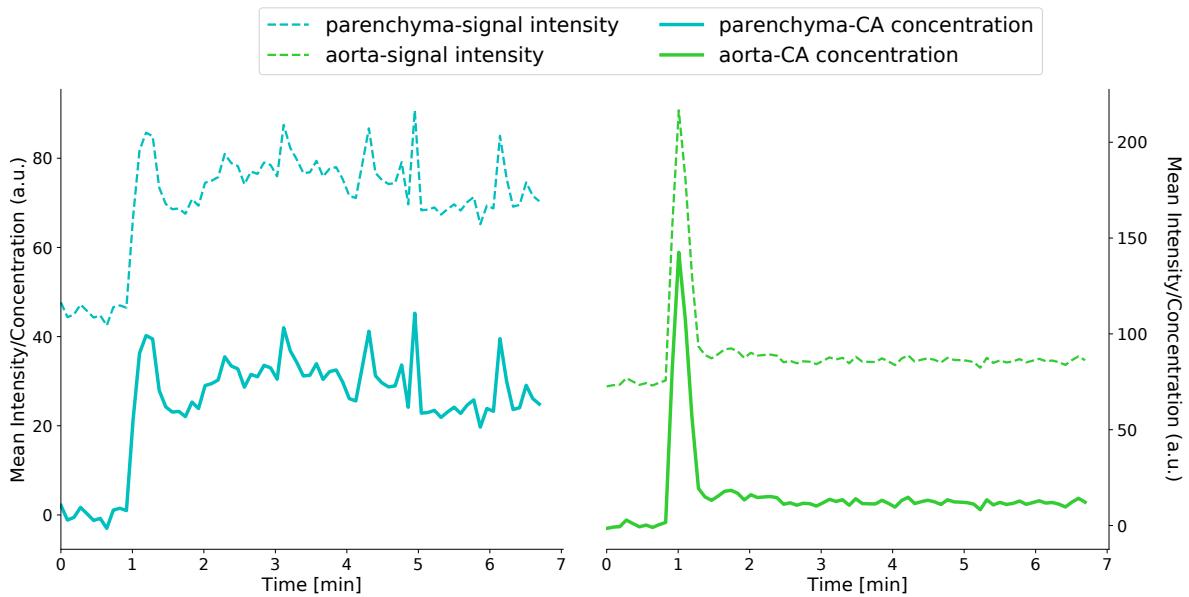


Figure 5.9. Average time courses for two clusters detected in k-means algorithm performed for sample kidney.

5.1.3.4 Pharmacokinetic modelling

Having determined the AIF and the concentration time course for the renal parenchyma, almost all components necessary for the renal quantitative evaluation were obtained. Almost, but not all. One should take into consideration the fact that AIF is the concentration of CA in the blood of the aorta, which consist of both the red blood cells and the blood plasma. All PK models, however, require the concentration only in the blood plasma. Thus the *hematocrit* (HCT) correction were performed as follows:

$$C_p = C_{AIF} / (1 - HCT), \quad (5.5)$$

where HCT is s the volume percentage of red blood cells in blood. In this study, the value was taken from the literature as an average population value and was equal to $HCT = 0.43$ [?].

Finally, the long-awaited PK modelling could have been performed. The models of choice were the Toft's model, Extended Toft's model, Patlak model and 2-Compartment Exchange model

Toft's model The two compartment Toft's model [54] assuemes the diffusion of the tracer from the blood plasma at rate specified by the transfer constant K_{trans} (min^{-1}) and returns at the rate $k_{ep} = K_{trans}/v_e$ (min^{-1}). In this model the assumption $C_t(t) = v_e C_e(t)$ is made, which means that plasma contribution is neglected. The blood plasma concentration C_p is specified by AIF. According to the Toft's model the CA concentratior is specified by the formula:

$$\frac{dC_t(t)}{dt} = K_{trans}(C_a(t) - C_t(t)/v_e) \quad (5.6)$$

$$C_t(t) = C_p \circledast K_{trans} e^{-k_{ep}t} = K_{trans} \int_0^t C_p(t') e^{-k_{ep}(t-\tau)} d\tau \quad (5.7)$$

Extended Toft's model While the Toft's model neglects intravascular contribution assuming weak vascularization of the tissue, the Extended Toft's model ?? does take it into account. The tissue concentration is described by the formula:

$$\begin{aligned} C_t(t) = & v_p C_p(t) + \\ & + K_{trans} \int_0^t C_p(t') e^{-(K_{trans}/v_e)(t-t')} dt', \end{aligned} \quad (5.8)$$

where v_p is the fractional plasma volume.

In Toft's and extended Toft's models the free parameters K_{trans} , v_e and v_p are estimated by fitting the model to obtained in DCE-MRI examinations time concentration curves.

Patlak plot Another proposed approach is the graphical one called Patlak plot [55]. Patlak plot neglects k_{ep} due to the low permeability and short examination time. As a result tissue concentration is expressed as:

$$C_t(t) = v_p C_p(t) + K_{trans} \int_0^t C_p(t') dt' \quad (5.9)$$

The above equation is the linearised as:

$$Y = K_{trans}X + v_p, \quad (5.10)$$

where $Y = C_t(t)/C_p(t)$ and $X = \int_0^t C_p(t') dt'/C_p(t)$. The free parameters K_{trans} and v_p can be then estimating by constructing a linear plot and calculating its slope and intercept respectively.

5.1.3.5 GFR estimation

5.2 Results

Chapter 6

Discussion

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