Lodz University of Technology

Faculty of Electrical, Electronic,
Computer and Control Engineering
Institute of Electronics

Master of Engineering Thesis

Numerical Assessment of Kidney Structure and Function from DCE-MRI Images

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Abstract

Tresc

Technical University of Łódź
Wydział Elektrotechniki, Elektroniki, Informatyki i Automatyki

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Praca dyplomowa magisterska

Numeryczna ocena budowy i funkcjonowania nerek na podstawie obrazów DCE-MRI

Łódź, 2012

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Streszczenie

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Acknowledgements

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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 trucks, others through digestive system and some of them are extracted through the sweat gland. However, there is no doubt that the urinary system plays the major role in waste extraction [1, 2].

The main organs of the urinary system are the kidneys. It is them, who perform the filtering function. The remaining ones, ureters, urinary bladder, and urethra, form the urinary tracks and are responsible only for transforming and storing the urine [1]. 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 presence~~

of the liver [1, 2].

The average healthy adult kidney weights around 150 g, is 11 cm long, 6 cm wide and 3 cm thick [1, 3]. 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.

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

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* [1, 2]. 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 cone with wide base facing the cortex and the tip attached to the sinus called *renal papilla*. The papilla of ~~the~~ 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 [1, 2, 4]. The gross anatomy of the kidney is illustrated on the Figure 2.1.

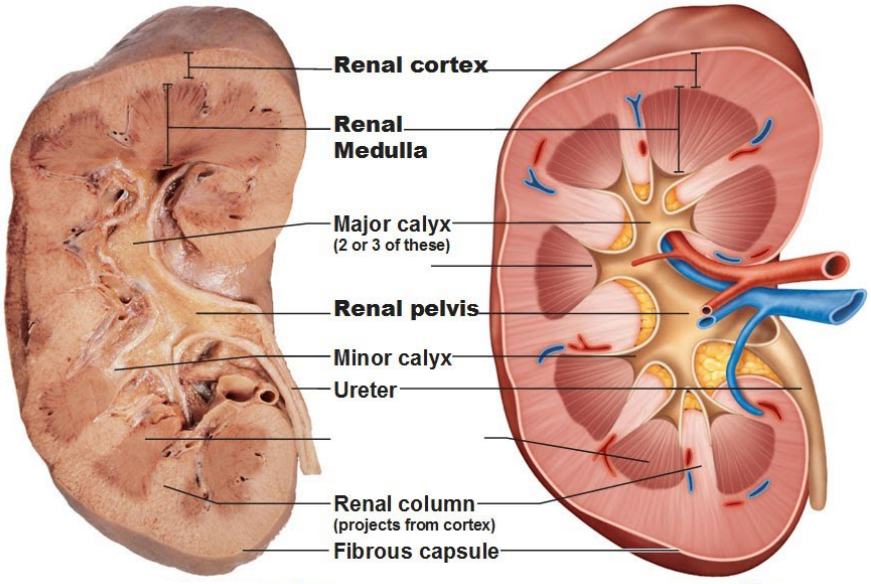


Figure 2.1. Gross anatomy of the kidney [1].

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 nephrones. Above million of them enables the kidney to perform its functions [2]. Each of them is a tiny coiled tube, the *renal tubule*, with a bulb at the end, the *renal corpuscle*, and extends through both the cortex and the medulla [1].

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* 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 ~~individual~~ cellular appearance and function [1, 2, 4]

Every functional unit of the kidney is supplied with the blood by the small blood vessel called *the* ~~*proximal convoluted tubule*~~ whereas the *efferent arteriole* takes it back. The blood leaving the nephron, flows into a network of *peritubular capillaries* surrounding the renal tubule [1, 2] The particular parts of the nephron are depicted on the Figure 2.2.

2.2 Functions of the kidney

Despite ~~of~~ the fact that the key function of the kidneys is purifying the blood, the other ones are equally important. Kidneys are responsible for maintaining homeostasis of all body due to which, all organs can work in optimal environment. It is crucial for proper functioning of whole organism [4]. One can conclude that the role of kidneys is enormously important. The kidneys are involved in the following processes:

Blood filtering. The kidneys filter the blood from metabolic waste, excess salt ~~and toxins~~ and then excrete unwanted substances in the urine [1, 2, 4].

Osmoregulation. For proper functioning of the organism, the concentration of the salts in the body has to remain relatively the same. The kidneys~~,~~ influence this concentration ~~which~~ by controlling the amount of water and solutes excrected from the organism [5].

Maintainance of water balance. The kidneys control~~l~~ the amount of water conserved and eliminated in the urine so that the amount of body water remains on the stable level [6].

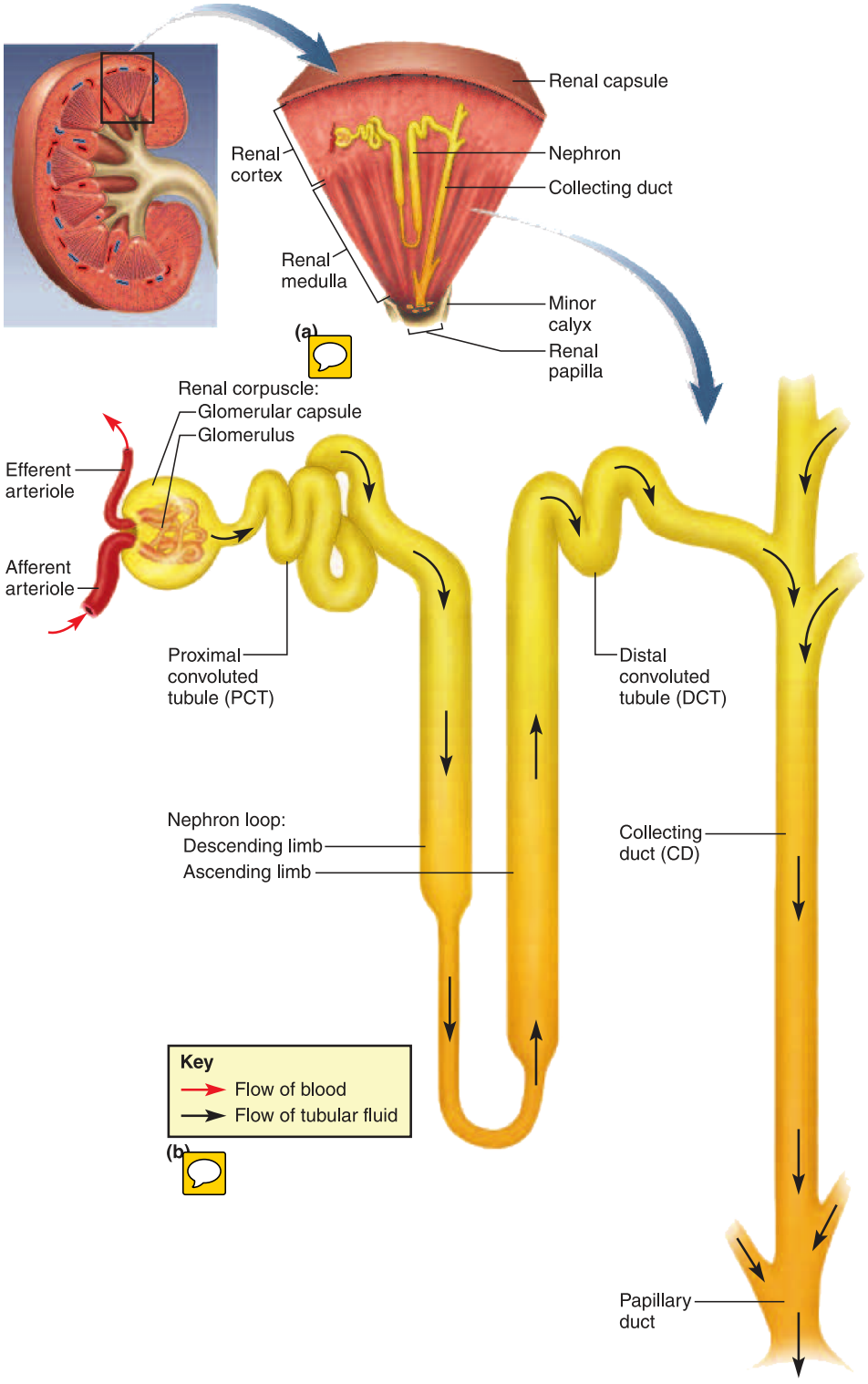


Figure 2.2. The structure of the nephron [1].

Blood pressure regulation. Maintaining ~~appropriate~~ blood pressure is achieved in ~~2~~ ways: (1) if the blood pressure drops, the kidneys release the enzyme *renin*, which activates ~~a~~ blood protein *angiotensin* making the blood vessels to constrict. What is more, angiotensin triggers the mechanism which increases the absorption of water and sodium increasin~~g~~ blood volume (2) regulating the amount of water, which was mentioned before [7].

Maintainance of the acid-base balance. The food conteained in our diet can acidify ~~or neutralize~~ the organism. If the pH is ~~outside~~ the tolereable 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 urine and excreting hydrogen ions and fixed acids into it [8].

Red blood cell production. If the level of oxygen in the tissue is insufficient, the kidneys release *erythroprotein*, the hormon stimulating the bone narrow to ~~red blood cells production~~ [9].

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, crucial ~~minerals~~ for strengthening the bones [10].

Prevent the hunger. In the situation of extreme starvation, the kidneys can synthesize glucose from non-carbohydrate carbon substrates breakin~~d~~ down ~~the~~ other molecules. This phenomena is known as *gluconeogenesis* [11].

Hormones degradation. The kidneys take~~s~~ part in degradation of hormones such as *parathyroid hormone* ~~or *insulin*~~ [12].

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. 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 glomerulal 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 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 ~~can occur.~~ This movement of mentioned components ~~under pressure,~~ from the blood into the capsule is known as *glomerural filtration* and the fluid in the glomerulal capsule, *glomerular filtrate.*

2. **Tubular reabsorption.** The filtrate passing through the renal tubule apart from wastes, contains 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 fluid~~s~~ and is obtained through the *diffusion*, *osmosis* and *active transport*.

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.

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 ~~and~~ the urine ~~becomes~~ more and more concentrated.

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

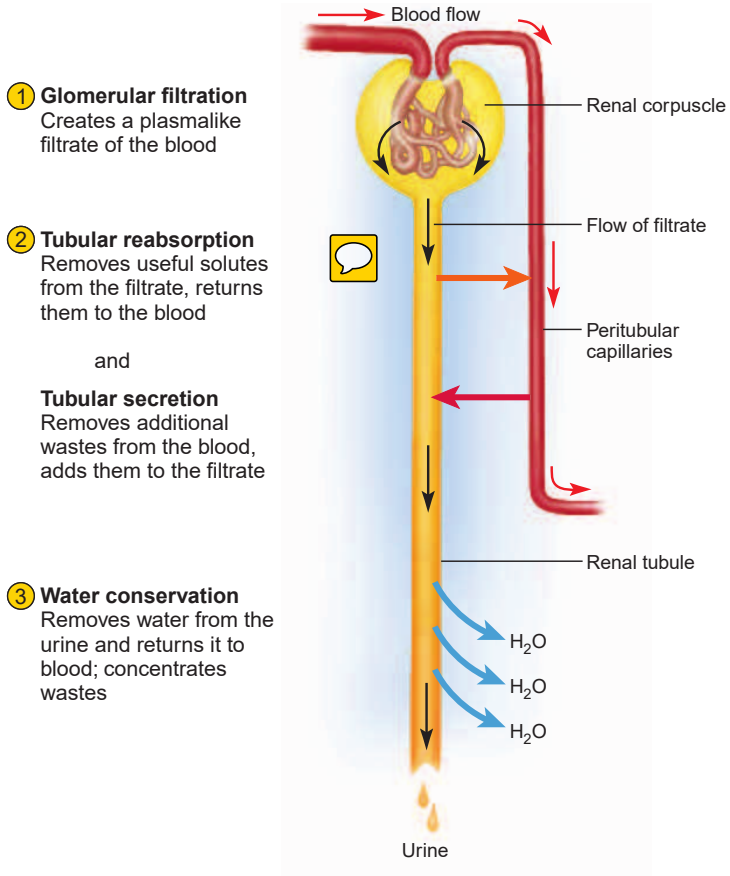


Figure 2.3. Process of the urine formation [1].

2.2.2 Glomerular filtration rate

Glomerural filtration rate (GFR) is volume of fluid filtered during glomelural filtartion from the renal glomerular capillaries into the Bowman's capsule per unit time by two kidneys combined and its unit is mL/min [13]. After standardisation, which is recalculation for standard body surface area (BSA), GFR is expressed in mL/min/1.73 m^2 [1].

The GFR in healthy adult kidneys is equal approximately 90–130 mL/min/1.73 m^2 [14]. Lower at birth, it approaches its adult value at the age two and maintains its level till the age of fourty, when it starts decreasing again [15]. Appropriate GFR determines performance of several basic functions of the kidney. Neither too low, nor too high GFR is healthy to the organism [1].

In clinical practice, GFR is an approximate estimator of the number of active nephrons and is concidered as a unit of level of kidney function [16]. What is of great importance, GFR can determine the stage of chronic kidney disease. GFR between 60–120 mL/min/1.73 m^2 is considered normal, healthy ~~oneValue~~ below 60 mL/min/1.73 m^2 indicates definite kidney desease, while ~~GFR~~ under 60 mL/min/1.73 m^2 is associated with renal failure [17]. The reference values of GFR are shown ~~on~~ Figure 2.4.

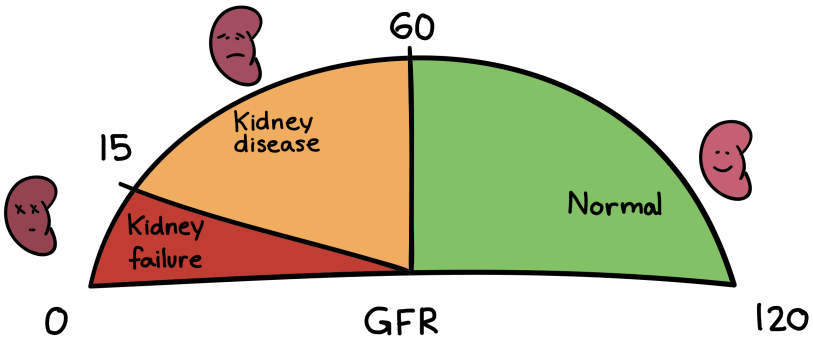


Figure 2.4. GFR reference values[18].

~~Because~~ of the fact that the concentration of the 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 volume of blood plasma from which a particular waste is completely removed in a unit time [1] This dependency is ~~shown by formula 2.1.~~

$$\begin{array}{rl} & glomerular\ filtartion of the waste \\ - & tubular\ reabsorptio\sout{i}n(x) \\ + & tubular\ secretion(x) \\ \hline & renal\ clereance \end{array} \tag{2.1}$$

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 ~~does~~ not ~~exist any~~ single solute appearing in urine and naturally produced by the body, which doesn't undergo the tubular secretion or reabsorbtion to some degree [19].

However, there appear a substance in the nature witch accomplishes the above conditions, namely insulin. One method of accurate measurement of glomelural filtration rate incorporates injecting insulin and subsequently measuring the rate of urine output and the concentrations of inulin in the blood and urine. For inulin, GFR is equal to the renal clearance [1, 19].

Even though~~t~~ this method is considered the gold standard in GFR measurement, ~~because of~~ its limitations~~,~~ it is not a clinical routine if very accurate measurements are not required. This special cases include transplant donors or scientific research [16]. Other, more frequently used techniques involve using endogenous markers such a creatinine and estimating GFR applying validated algoritms [19].

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 [20]. 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 visual representations of human interior as well as tissues and organs processes thus functionality much facilitated medical diagnosis and prognosis. Some imaging techniques has 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).

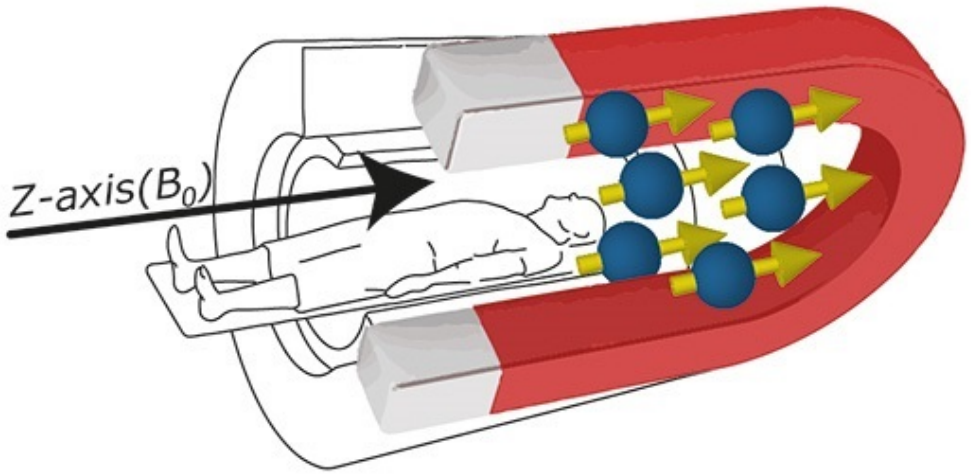


Figure 3.1. Hydrogen atoms located in a human body placed in the strong magnetic field, ~~B_0~~, generated by the MRI scanner, align to the direction of that field [25].

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. This particles include for example ^{1}H, ^{13}C, ^{31}P, ^{23}Na, ^{19}F [22, 23]. 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 [24].

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 the Figure 3.1 [24].

In addition, atoms have an angular momentum making them precess about the

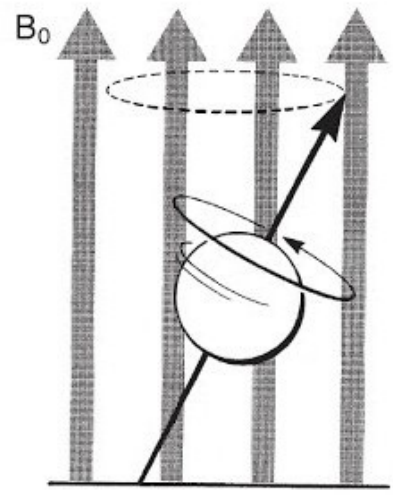


Figure 3.2. Hydrogen atom placed in a strong magnetic field B_0 precesses about the direction of that field with the frequency ω_0 [24].

magnetic field direction with a frequency ω_0, called the *Larmor frequency*, which is proportional to the field:

$$\omega_0 = \gamma B_0 \,, \tag{3.1}$$

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 [22, 24]. This preccessional motion is ~~is showed on~~ 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 ~~MRI~~ soft-

ware analyses and processes obtained signal, which is a combination of numerous response signals from all excited atoms and generates the image [22, 24].

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 [22]. 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 [23, 26].

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 [22].

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 [27].

4. **RF system**, task of which is to excite the hydrogen atoms and to receive their FID response signal [22]

5. **The ~~strong computer~~** controlling the system and processing the received combination of response signals [22].

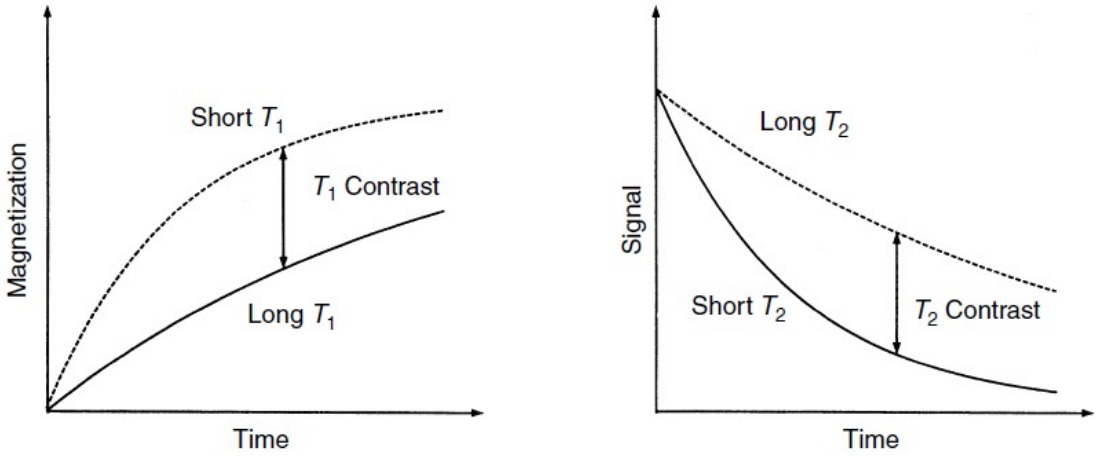
3.1.1 T_1 and T_2 weighted images

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 ~~listed~~ [22].

***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 [22, 23].

***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 [22, 23]. T_2 contrast is presented in Figure 3.3b.



(a) T1 plot. **(b)** T2 plot.

Figure 3.3. T_1 and T_2 contrast mechanisms [22].

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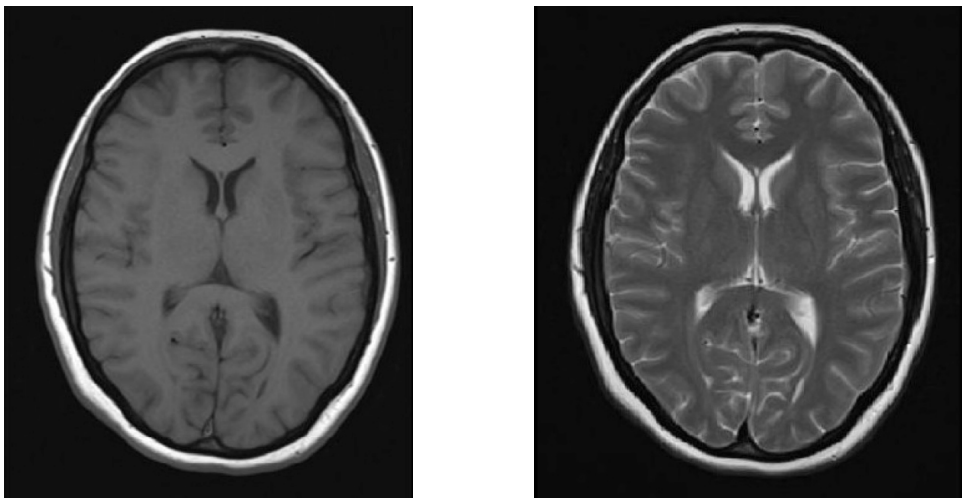

(a) T1 weighted image of a brain. **(b)** T2 weighted image of a brain.

Figure 3.4. Example MRI image of a brain of a healthy volunteer demonstrating T1 and T2 contrast [28].

Examples of the images acquired using described above two basic mechanisms are shown in Figure 3.4. The figure presents identical axial section of a healthy person's brain. In the T_1 weighted image ~~on the left hand side,~~ one can notice ~~bright~~ ring of subcutaneous fat, which is 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 that 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 [22].

Currently MRI is one of the ~~widest~~ used medical imaging techniques applied ~~in~~ all parts of a body. It ~~enables creating~~ detailed anatomical images in axial, sagittal, coronal or even oblique plane. During 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 [24]. Another advantage of MRI is not using any harmful ionizing radiation.

The clicical 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, differnet kind of tumors and cancers and many more [29].

3.2 DCE-MRI

Dynamic Contrast Enhanced Magnetic Resonance Imaging is ~~basically~~ the acquisition of multiple MRI scans, with addition of one extremely important component—the time domain [30]. During the examination a Contrast Agent (CA) is injected in the peripheral vein into the bloodstream and the T1-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 ~~is~~ 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 [31, 32]. 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 [30].

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 (1) qualitative (2) semi-quantitative (3) quantitative ones [33]. 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 [32].

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. This three *templates* are shown ~~on~~ Figure 3.5. 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 [33]. 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 [32, 33]. 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*

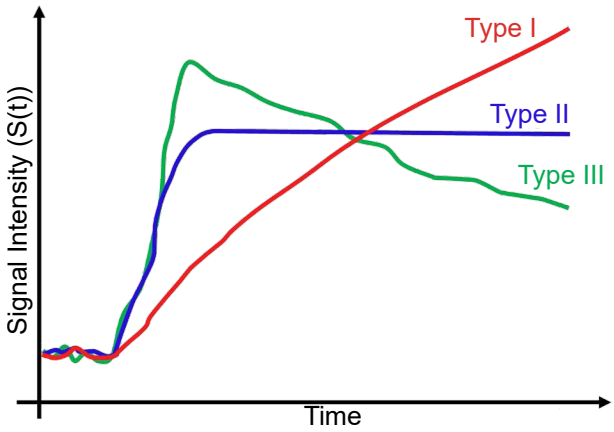

Figure 3.5. Different DCE-MRI enhacement patterns [32].

Curve (AUC) or *Initial Uptake Area Under the Curve* (IAUC) [32]. Listed parameters are depicted in Figure 3.6.

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 [33].

3.2.1.3 Quantitative analysis

Quantitative assessment of the $S(t)$ curve is surely the most sophisticated one. ~~In~~ 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 next to those 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 [30, 33].

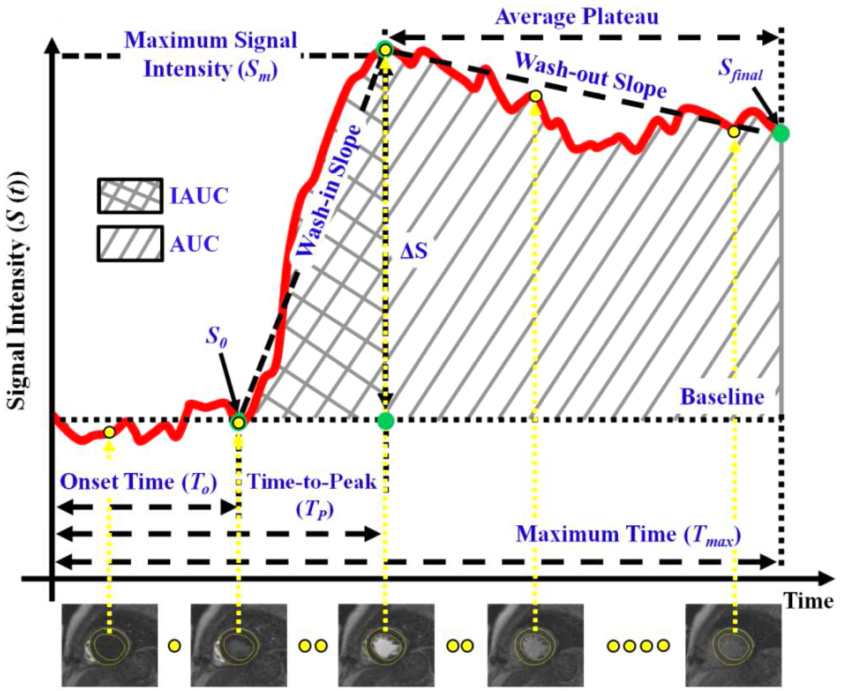

Figure 3.6. An example of the time-intensity curve, $S(t)$, with depicted metrics explored in semi-quantitative DCE-MRI analysis. Note that S_0 is the signal intensity before CA arrival whereas S_{final} is the intensity registered in the last temporal point at the end of the experiment T_{max} [32].

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 ~~is~~ widely explored in clinical studies. There is no doubt~~s~~ 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 localization 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 [32]. 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

Bibliography

[1] K. Saladin, *Anatomy & Physiology: The Unity of Form and Function*. USA: McGraw-Hill, 5th ed., 2009.

[2] K. Patton and G. Thibodeau, *The Human Body in Health & Disease*. USA: Elsevier, 7th ed., 2017.

[3] S. A. Emamian, M. B. Nielsen, J. F. Pedersen, and L. Ytte, "Kidney dimensions at sonography: correlation with age, sex, and habitus in 665 adult volunteers.," *AJR. American journal of roentgenology*, vol. 160, no. 1, pp. 83–86, 1993.

[4] B. M. Koeppen and B. A. Stanton, *Renal Physiology: Mosby Physiology Monograph Series*. USA: Elsevier-Health Sciences Division, 5th ed., 2013.

[5] P. Sturkie, "Kidneys, extrarenal salt excretion, and urine," in *Avian physiology*, pp. 359–382, Springer, 1986.

[6] E. Jéquier and F. Constant, "Water as an essential nutrient: the physiological basis of hydration," *European journal of clinical nutrition*, vol. 64, no. 2, p. 115, 2010.

[7] A. C. Guyton, T. G. Coleman, A. W. Cowley, K. W. Scheel, R. D. Manning, and R. A. Norman, "Arterial pressure regulation: overriding dominance of the kidneys in long-term regulation and in hypertension," *The American journal of medicine*, vol. 52, no. 5, pp. 584–594, 1972.

[8] L. L. Hamm, N. Nakhoul, and K. S. Hering-Smith, "Acid-base homeostasis," *Clinical Journal of the American Society of Nephrology*, vol. 10, no. 12, pp. 2232–2242, 2015.

[9] S. Donnelly, "Why is erythropoietin made in the kidney? the kidney functions as a critmeter," *American journal of kidney diseases*, vol. 38, no. 2, pp. 415–425, 2001.

[10] S. Williams, K. Malatesta, and K. Norris, "Vitamin d and chronic kidney disease," *Ethnicity & disease*, vol. 19, no. 4 Suppl 5, p. S5, 2009.

[11] E. Newsholme and W. Gevers, "Control of glycolysis and gluconeogenesis in liver and kidney cortex," in *Vitamins & Hormones*, vol. 25, pp. 1–87, Elsevier, 1967.

[12] D. Emmanouel, M. Lindheimer, and A. Katz, "Role of the kidney in hormone metabolism and its implications in clinical medicine," *Klinische Wochenschrift*, vol. 58, no. 19, pp. 1005–1012, 1980.

[13] The Free Dictionary: medical dictionary, "Glomerular filtartion rate." [Online]. Available: https://medical-dictionary.thefreedictionary.com/glomerular+filtration+rate. [Accessed: 01-Feb-2017].

[14] H. W. Smith, *The kidney: structure and function in health and disease*, vol. 1. Oxford University Press, USA, 1951.

[15] J. R. Weinstein and S. Anderson, "The aging kidney: physiological changes," *Advances in chronic kidney disease*, vol. 17, no. 4, pp. 302–307, 2010.

[16] J. Traynor, R. Mactier, C. C. Geddes, and J. G. Fox, "How to measure renal function in clinical practice," *BMJ: British Medical Journal*, vol. 333, no. 7571, p. 733, 2006.

[17] National Kidney Foundation, "Glomerular Filtration Rate (GFR)." [Online]. Available: https://www.kidney.org/atoz/content/gfr. [Accessed: 13- Nov-2017].

[18] Khanacademy, "Renal physiology: Glomerular filtration." [Online]. Available: https://www.khanacademy.org/test-prep/mcat/organ-systems/the-renal-system/a/renal-physiology-glomerular-filtration. [Accessed: 12-Feb-2017].

[19] P. Delanaye, "How measuring glomerular filtration rate? comparison of reference methods," in *Basic Nephrology and Acute Kidney Injury*, InTech, 2012.

[20] W. C. Röntgen, "On a new kind of rays," *Science*, vol. 3, no. 59, pp. 227–231, 1896.

[21] J. D. Bronzino, *Biomedical engineering handbook*, vol. 2. CRC press, 1999.

[22] S. Conolly et al., *Biomedical engineering handbook*, ch. Magnetic Resonance Imaging. Vol. 2 of [21], 1999.

[23] V. P. Grover, J. M. Tognarelli, M. M. Crossey, I. J. Cox, S. D. Taylor-Robinson, and M. J. McPhail, "Magnetic resonance imaging: principles and techniques: lessons for clinicians," *Journal of clinical and experimental hepatology*, vol. 5, no. 3, pp. 246–255, 2015.

[24] S. C. Bushong and G. Clarke, *Magnetic resonance imaging: physical and biological principles*. Elsevier Health Sciences, 2014.

[25] Startradiology, "MRI Technique." [Online]. Available: http://www.startradiology.com/the-basics/mri-technique/. [Accessed: 12-Feb-2017].

[26] R. Sharma, S. Fulzele, K. Shetty, M. Sachdeva, and B. R. Locke, "21 tesla micro-mri of rat skin," 2008.

[27] S. Hidalgo-Tobon, "Theory of gradient coil design methods for magnetic resonance imaging," *Concepts in Magnetic Resonance Part A*, vol. 36, no. 4, pp. 223–242, 2010.

[28] St. Vincent's University Hospital. Radiology Departament, "MRI." [Online]. Available: http://www.svuhradiology.ie/diagnostic-imaging/mri/. [Accessed: 12-Feb-2017].

[29] WebMD, "What Is an MRI?." [Online]. Available: https://www.webmd.com/a-to-z-guides/what-is-an-mri#1. [Accessed: 08-Feb-2018].

[30] A. Jackson, D. L. Buckley, G. J. Parker, *et al.*, *Dynamic contrast-enhanced magnetic resonance imaging in oncology*. Springer, 2005.

[31] L. Bokacheva, H. Rusinek, J. L. Zhang, and V. S. Lee, "Assessment of renal function with dynamic contrast-enhanced MR imaging," *Magnetic resonance imaging clinics of North America*, vol. 16, no. 4, pp. 597–611, 2008.

[32] F. Khalifa, A. Soliman, A. El-Baz, M. Abou El-Ghar, T. El-Diasty, G. Gimel'farb, R. Ouseph, and A. C. Dwyer, "Models and methods for analyzing dce-mri: A review," *Medical physics*, vol. 41, no. 12, 2014.

[33] S. L. Barnes, J. G. Whisenant, M. E. Loveless, and T. E. Yankeelov, "Practical dynamic contrast enhanced mri in small animal models of cancer: data acquisition, data analysis, and interpretation," *Pharmaceutics*, vol. 4, no. 3, pp. 442–478, 2012.

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