Lodz University of Technology

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

Master of Engineering Thesis

Title in english

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Łódź, 2018

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Abstract

Tresc

Technical University of Łódź
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Praca dyplomowa magisterska

Title in polish

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.

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. 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.

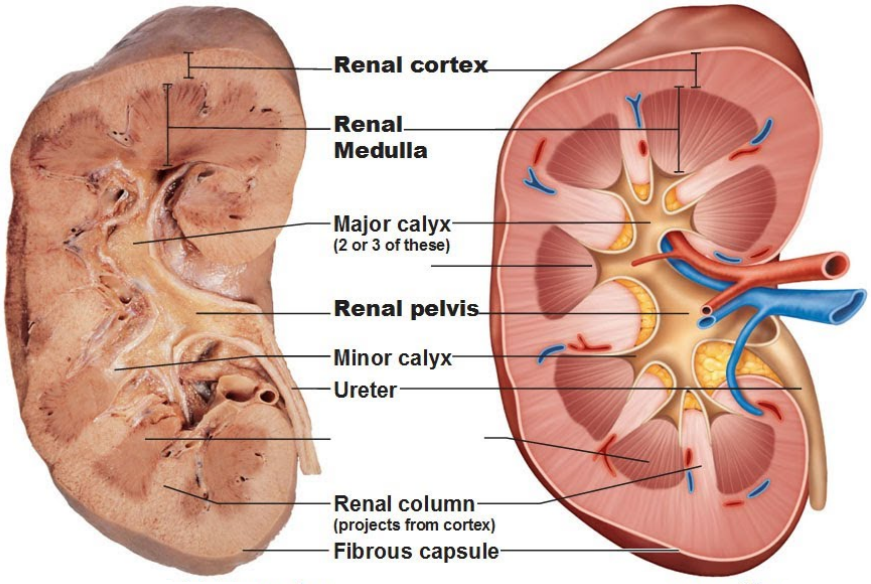


Figure 2.1. The structure of the kidney [1].

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.

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.

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. 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 controll the amount of water conserved and eliminated in the urine so that the amount of body water remains on the stable level [6].

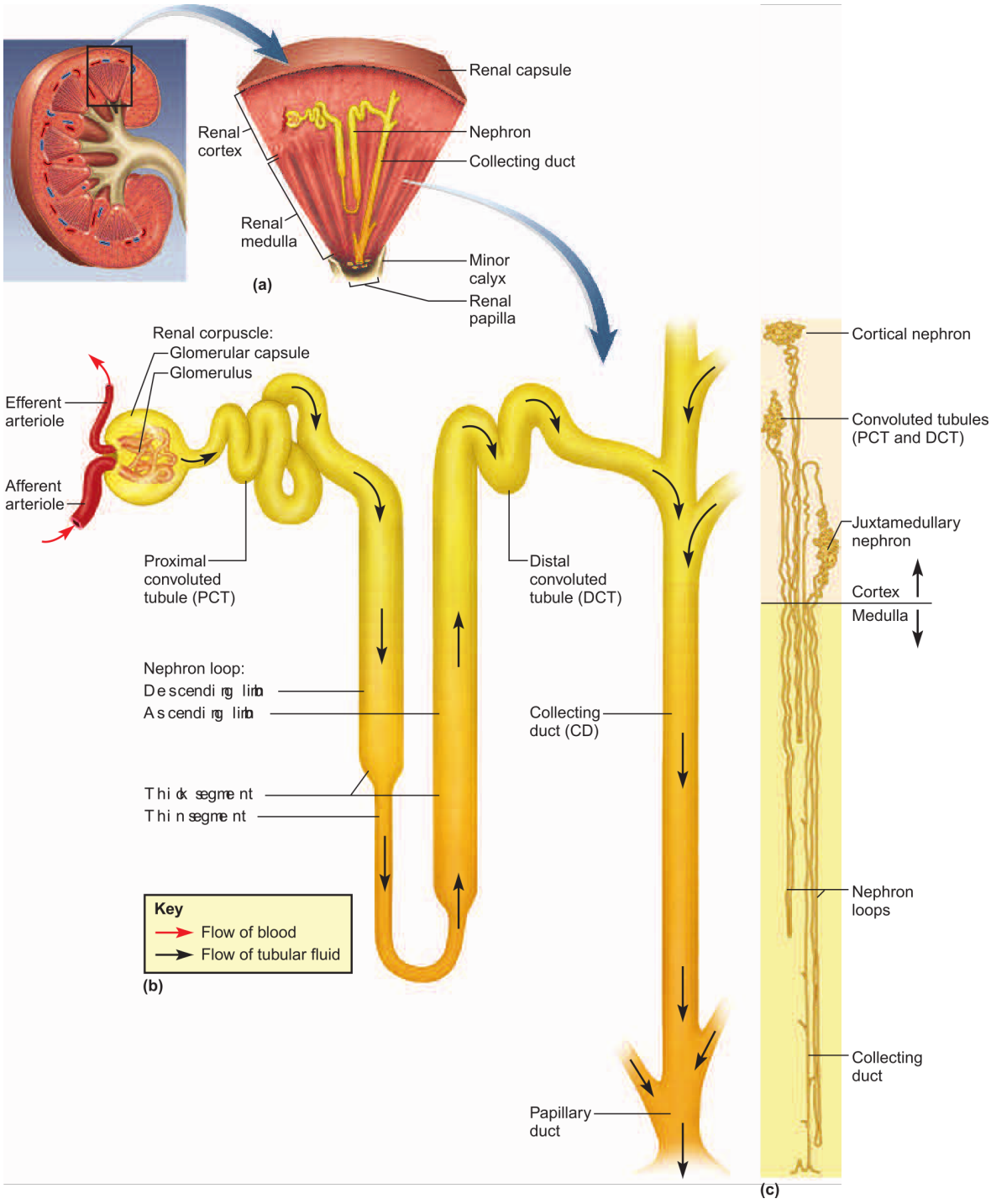


Figure 2.2. The structure of the kidney [1].

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 increasing 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 breakind down the other molecules. This phenomena is known as *gluconeogenesis* [11].

Hormones degradation. The kidneys takes 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 fluidis 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.

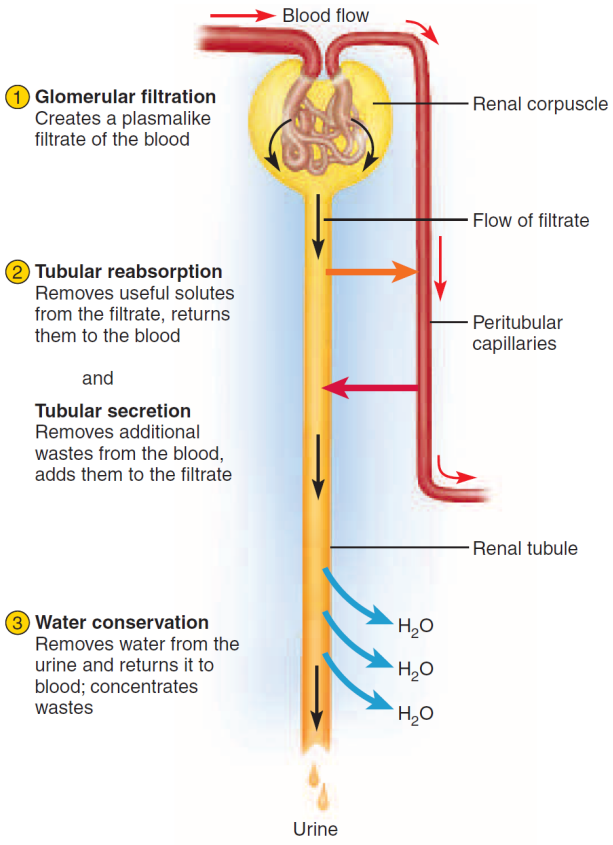


Figure 2.3. urine formation [1].

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 $\mathrm{mL/min/1.73\,m^2}$.

The GFR in healthy adult kidneys is equal approximately 90–130 $\mathrm{mL/min/1.73\,m^2}$ [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.

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 $\mathrm{mL/min/1.73\,m^2}$ is considered normal, healthy oneValue below 60 $\mathrm{mL/min/1.73\,m^2}$ indicates definite kidney desease, while GFR under 60 $\mathrm{mL/min/1.73\,m^2}$ is associated with renal failure. The reference values of GFR are shown on Figure 2.4.

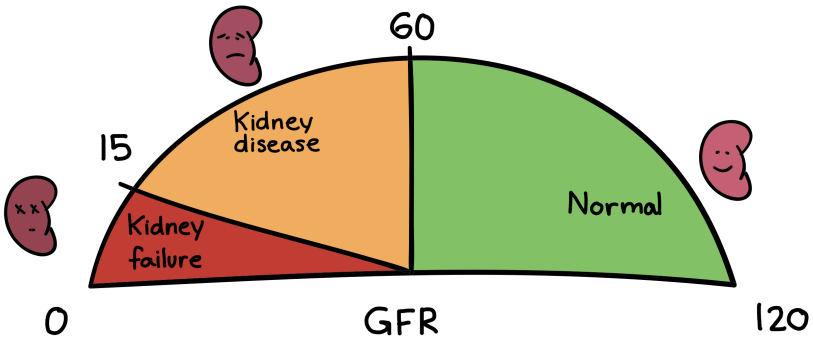


Figure 2.4. GFR reference values[**?**].

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. This dependency is shown by formula 2.1.

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

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.

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.

Even thought 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 [17].

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 [18]. 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).

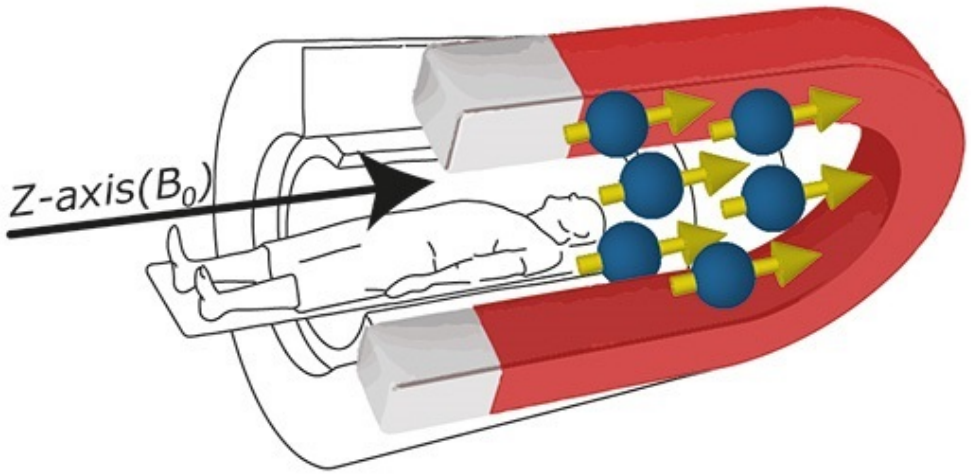


Figure 3.1. Hydrogen atoms located in a human body placed in the strong magnetic field, B_0, generated by the MRI scanner, align to the direction of that field [**?**].

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 [20]. 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.

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.

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

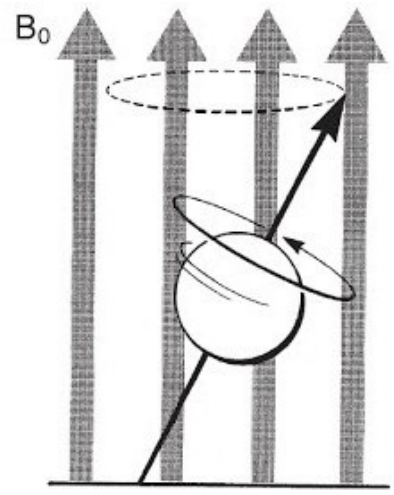


Figure 3.2. Hydrogen atom placed in a strong magnetic field B_0 precesses about the direction of that field with the frequency ω_0 [**?**].

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. 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.

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. Typical strength of the field of a clinical MRI scanner ranges between 0.2–3.0 T, whereas research systems reaches values even up to 7.4 T for Human and 21 T for animal models.

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.

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 [21].

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

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

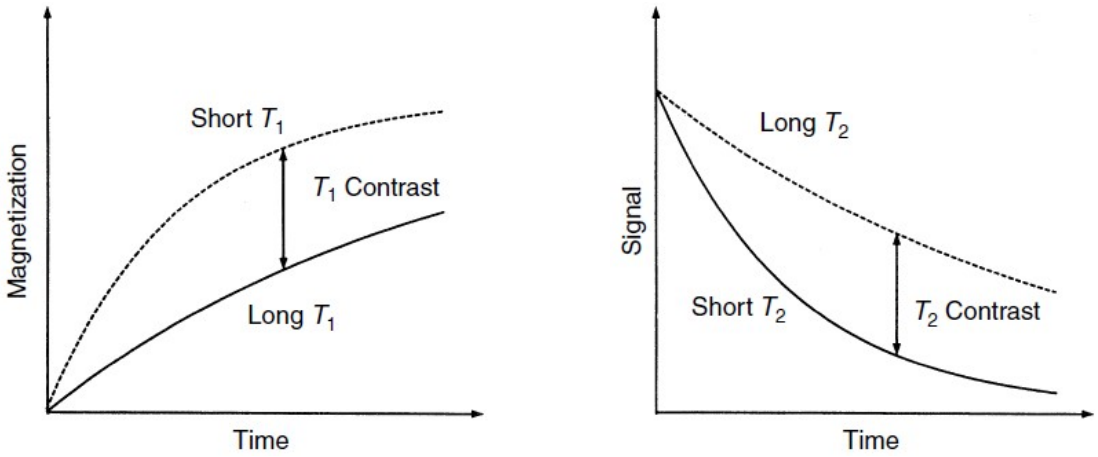
3.1.1 T_1 and T_2 weighted images

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.

***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.

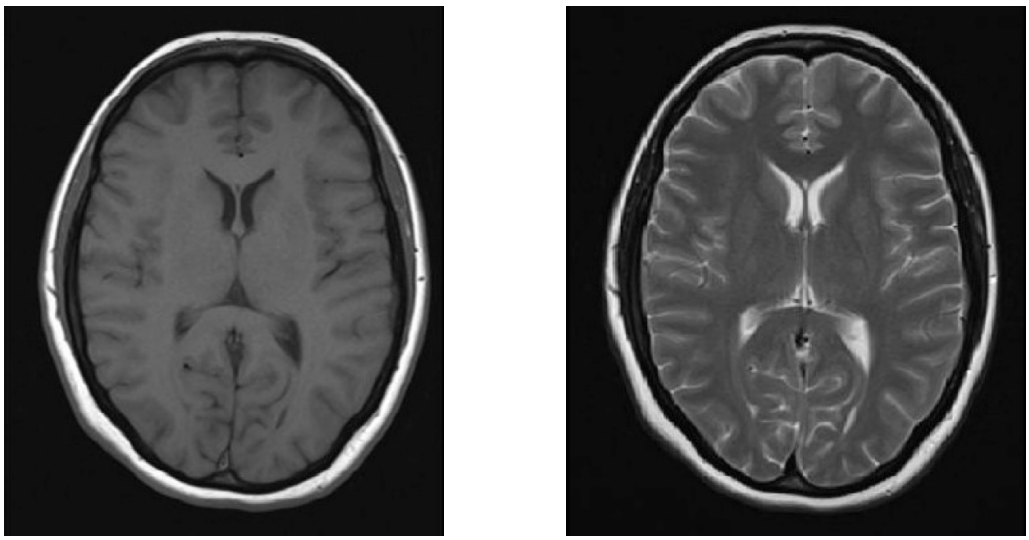
***T_2* weighted images** are based on spin-to-spin relaxation, described by the T_2 indicating the time required by the nuclei response signal to decay after it has been created. T_2 contrast is presented in Figure 3.3b.



(a) T1 plot.

(b) T2 plot.

Figure 3.3. plots [20].



(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.

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.

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 [22]. 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 [23].

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 [24]. During the examination a Contrast Agent (CA) is injected in the peripheral vein into the bloodstream and the T1-weighted images are acquired. The passage of the tracer through the target tissue results in changes in signal intensities over the time. The analysis of so obtained intensity changes as a function of time, $S(t)$, provides important functional information [25, 26].

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 methods [27].

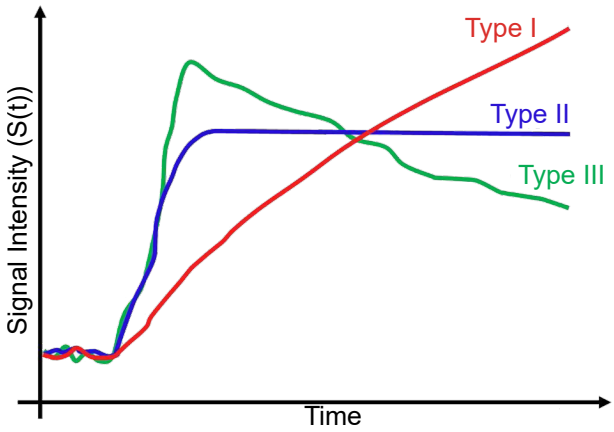


Figure 3.5. Different DCE-MRI enhacement patterns [26].

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 predefined enhancement patterns. This method do not deliver any quantitative parameters and is fully dependent on the observer's experience. The Three types of the *templates* are shown on Figure 3.5.

3.2.1.2 Semi-quantitative analysis

The semi-quantitative analysis incorporates calculation of parameters directly from the time-intensity curve characterizing its shape. 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). Listed parameters are depicted in Figure 3.6.

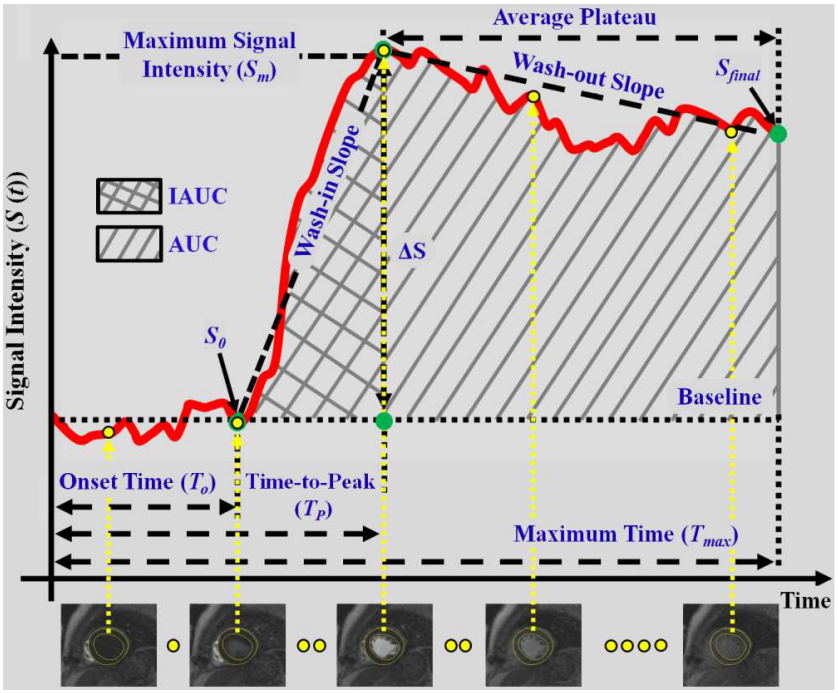


Figure 3.6. An example of the time-intensity curve, $S_(t)$, with depicted metrics explored in semi-quantitative DCE-MRI analysis. Note that S_0 is the signal intensity before CA arrival whereas S_{final} is the intensity registered in the last temporaly point at the end of the experiment; T_max depicts the duration of the experiment [26].

3.2.1.3 Quantitative analysis

3.2.2 DCE-MRI applications

There is no doubts that obtaining important both structural and functional information in a single imaging session is one of the biggest advantage of Dynamic Contrast Enhanced MRI.

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