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PhD Thesis

*Simulation Studies on X-Ray imaging of Brain Parenchyma and Tumours*

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Εξομοίωση Νεοπλασιών Εγκεφάλου για Απεικονιστικά Συστήματα Ακτίνων X

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Περίληψη

Η αξονική τομογραφία (AT) είναι μια απεικονιστική μέθοδος ακτίνων χ η οποία παρότι παρέχει πολλά πλεονεκτήματα, υπολείπεται της ικανότητας να απεικονίσει τους μαλακούς ιστούς στο εγκεφαλικό παρέχωμα καθώς και τις νεοπλασίες όταν αυτές βρίσκονται σε πρώιμα στάδια. Σκοπός της παρούσας έρευνας είναι να διερευνηθεί αν θα μπορούσε η AT να χρησιμοποιηθεί για την απεικόνιση των μαλακών ιστών του εγκεφάλου, καθώς κάτι τέτοιο θα προσέφερε ένα πολύ ισχυρό εργαλείο στους γιατρούς για την καθημερινή κλινική πράξη.

Η AT λόγω του χαμηλού της κόστους, της μεγάλης της ταχύτητας και της ικανότητας της να απεικονίζει ταυτόχρονα σκληρό και μαλακό ιστό, είναι μία από τις πιο συχνά χρησιμοποιούμενες απεικονιστικές μεθόδους στα έκτακτα περιστάτικα. Δίνοντας στην AT την δυνατότητα να παράγει εικόνες στις οποίες διαχωρίζονται οι ιστοί του εγκεφαλικού παρεχώματος, και κατά συνέπεια των νεοπλασιών πρώιμου σταδίου, θα αυξάνονταν πολύ οι πιθανότητες να ανιχνεύσουν ασθένειες οι οποίες έμεχρι στιγμής ανιχνεύονταν μόνο με χρήση Μαγνητικής Τομογραφίας (MT), όπως απομειωτικές ασθένειες, άνοια, εγκεφαλικές αγγειακές νόσου, μολυσματικές ασθένειες, επιληψία, καθώς και νεοπλασίες του εγκεφάλου σε πρώιμο στάδιο. Έχουν αναφερθεί πολλές περιπτώσεις όπου την απεικόνιση του εγκεφάλου (όπως νεοπλασίες) διαγνώστηκαν από AT τα οποία γίνονταν για τελείως διαφορετικούς λόγους (π.χ. τροχαία ατύχημα). Μια ανεπτυγμένη τεχνική AT απεικόνισης του εγκεφάλου θα μπορούσε να οδηγεί σε πολύ καλύτερη παρακολούθηση και εντοπισμό παθολογιών του κεντρικού νευρικού συστήματος (ΚΝΣ).

Βασικός στόχος της παρούσας έρευνας, είναι να γίνει εφικτή η διάκριση της λευκής από της φαία ουσία του εγκεφάλου με χρήση AT. Κάτι τέτοιο θα επιτέρπετε την ανίχνευση πόλων παθολογιών, όπως μείωσε το κενό μεταξύ AT και MT και αποτελεί την βασική συνθήκη η οποία θα οδηγήσει στην απεικόνιση των νεοπλασιών πρώιμου στάδιου.

Η παρούσα έρευνα διενεργήθηκε με την χρήση προσομοιωμένων όσο και πραγματικών δεδομένων από AT διπλής ενέργειας. Ένας προσομοιωτής απεικόνισης με ακτίνες χ που έχει αναπτυχθεί από την ομάδα χρησιμοποιήθηκε για να παρατηρούν οι προσομοιωμένες προβολικές ακτίνογραφείς.

Για να διεξαχθεί η έρευνα ήταν απαραίτητη η χρήση ενός μοντέλου του εγκεφάλου το όποιο και μεταβλήθηκε ούτως ώστε να μπορεί να χρησιμοποιηθεί για προσομοίωση απεικόνισης με ακτίνες χ. Σε δεύτερη φάση, ένας όγκος μικρού μεγέθους τοποθετήθηκε στο μοντέλο αυτό με σκοπό την διερεύνηση της απεικόνισης των νεοπλασιών πρώιμου σταδίου. Για την επίπεδη παρέμβαση της απεικόνισης του παρεχώματος δοκιμαστήκαν πολλές τεχνικές Διπλής Ενέργειας (ΔΕ) και τελικά αποφασίστηκε να χρησιμοποιηθεί μια μη γραμμική τεχνική για τον συνδυασμό των εικόνων από τις δύο
διαφορετικές ενέργειες. Η επιλεγμένη τεχνική ΔΕ τελικά κατάφερε να παράγει αντίθεση μεταξύ των ιστών του εγκεφαλικού παρεγχύματος ακόμα και στην περίπτωση των πραγματικών δεδομένων.

Λόγω του περάστου αριθμού των εικόνων που παρήχθησαν κατά την διάρκεια της έρευνας, έγινε επιπλοκική η ανάγκη ενός Δείκτη Ποιότητας Εικόνας (ΔΠΕ) ο οποίος θα ήταν σε θέση να ανιχνεύσει με ακρίβεια τις εικόνες με τα καλύτερα αποτελέσματα. Για τον λόγο αυτό ανεπαρκήθηκε ένας ΔΠΕ ο οποίος βασιζόμενος στην γραμμικά προφίλ των εικόνων, μπορούσε να προσφέρει πολύ καλά αποτελέσματα και να επιλέγει με ακρίβεια τις καλύτερες από αυτές.

Τέλος προτείνεται μια βελτίωση του αλγορίθμου ΔΕ, η οποία βασίζεται στην επίλυση της αντίστροφης συνάρτησης αντίθεσης μεταξύ εικονοστοιχείων και προσπαθεί μέσω μαθηματικών μοντέλων βελτιστοποίησης να βρει τα τοπικά ελάχιστα της συνάρτησης αυτής.
Abstract

Computed Tomography (CT) is an imaging modality with many advantages but is lacking of the ability to image the tissues in the parenchyma of the brain and brain tumours in early stages. Aim of the presented research is to investigate whether CT could be used to image the soft tissue of the brain since this would provide an extremely powerful tool in the hand of the clinicians.

CT due to its low cost, high speed and ability to image simultaneously hard and soft tissue is a very often used imaging modality especially in emergency cases. Enabling CT to differentiate brain parenchyma, and thus also brain tumours in early stage, would greatly increase the chances of detection of many pathologies that are now imaged only with MRI such as demyelinating diseases, dementia, cerebrovascular disease, infectious diseases epilepsy, and brain tumours in early stage. There are many cases reported that brain pathologies (e.g. tumours) have been diagnosed from CT scans performed for completely different reasons. An advanced Brain CT Imaging technique could lead in much better monitoring of Central Nervous System (CNS) pathologies.

Main aim is to differentiate gray from white matter with X-ray imaging, since it will allow many pathologies to be detected, close the gap with MRI and is a condition that will lead to the visualization of tumours in early stages.

An investigation was carried out using simulated and real data in order to test the feasibility of using Dual Energy CT for imaging brain soft tissue. An in-house developed X-ray Imaging Simulator was used for the production of the simulated x-ray images.

In order to perform the investigation a brain model had to be used and altered in order to be applicable in x-ray simulations. As a second step small brain tumours were inserted in the created model in order to test the imaging of early stage brain tumours. Many different DE techniques were used and it was decided to use a non-linear decomposition dual energy technique for blending the images from different energies. The DE algorithm truly managed to produce contrast between brain parenchyma tissues in all a cases used even in real data.

Due to the great number of images created for all different settings and cases tests, the need of a good and reliable Figure Of Merit (FOM) came up, thus an in home FOM ware developed based on line profiles which had very good results and great ability of detecting the best images.

Additionally an optimization of the DE decomposition algorithm is proposed, based on solving inversely the problem of contrast between pixels and trying to find the local minima of the functions that relates them.
Chapter 1 Introduction

The Brain

The human brain is the most complex and magnificent part of the human body. It’s a mysterious 1.5 kg organ that receives and interprets information of the outside world and controls all necessary body functions [2]. Our brain gives us our awareness of ourselves and of our surrounding environment, constantly processing a stream of sensory data [7]. Brain is controlling our muscles, the secretion of the glands, breathing and internal temperature. Every creative thought, feeling, is done by the brain. It is so complicated that still scientists are continually endeavouring to learn and understand exactly how it works.

General information

The human brain has in general the same structure like the brain of other mammals, with the main difference that has way more developed cerebral cortex of all. In terms of absolute size human has smaller brain than big mammals such as whales and elephants as it can be seen in Figure 1. Based on the encephalization quotient, which is a measure of relative brain size calculated as the ratio between actual brain mass and predicted mass of an animal of given size hypothesised by estimation of the intelligence of the animal [4], human brain is twice the size of the bottlenose dolphin and three time larger than a chimpanzee as it shown in Table 1. Main part of the expansion is done at the visual cortex and cerebral cortex, especially in the frontal lobes responsible for executive function as self-control, reasoning and abstract thought.

Cerebral cortex is folded in a way that increase the amount of surface that fit in the available volume. The folds pattern is similar, with variations, across individuals. The cortex is divided into four “lobes”: the frontal lobe, the parietal lobe, the temporal lobe, and the occipital lobe although other classification system exist. The left and right side of the cortex are similar in shape and most cortical areas are replicated on both sided. Due to its importance, brain is protected by the bones of the skull, is suspended in the CerebroSpinal Fluid (CSF), and it is also isolated from the bloodstream by the Blood-Brain Barrier (BBB) [8].
The adult human brain weights approximately 1.5 kg [9] with a volume of about 1130 cm³ in women and 1260 cm³ in men. It is composed of neurons, glial cells, and blood vessels. Using array tomography, it has been calculated of the order of \(10^{11}\) in the brain and equal number of non-neuronal cells the glia [10].

**Table 1 - Brain weight, encephalization quotient and number of neurons.** Table originally published on [4]

<table>
<thead>
<tr>
<th>Animal taxa</th>
<th>Brain weight (in g)²</th>
<th>Encephalization quotient/³</th>
<th>Number of cortical neurons (in millions)²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whales</td>
<td>2600–9000</td>
<td>1.8</td>
<td>10 500</td>
</tr>
<tr>
<td>False killer whale</td>
<td>3650</td>
<td></td>
<td>10 500</td>
</tr>
<tr>
<td>African elephant</td>
<td>4200</td>
<td>1.3</td>
<td>11 000</td>
</tr>
<tr>
<td>Man</td>
<td>1250–1450⁴</td>
<td>7.4–7.8</td>
<td>11 500</td>
</tr>
<tr>
<td>Bottlenose dolphin</td>
<td>1350</td>
<td>5.3</td>
<td>5800</td>
</tr>
<tr>
<td>Walrus</td>
<td>1130</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>Camel</td>
<td>762</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>Ox</td>
<td>490</td>
<td>0.9</td>
<td>1200</td>
</tr>
<tr>
<td>Horse</td>
<td>510</td>
<td>0.9</td>
<td>1200</td>
</tr>
<tr>
<td>Gorilla</td>
<td>430⁶–570</td>
<td>1.5–1.8</td>
<td>4300</td>
</tr>
<tr>
<td>Chimpanzee</td>
<td>580–630⁶</td>
<td>2.2–2.5</td>
<td>6300</td>
</tr>
<tr>
<td>Lion</td>
<td>260</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Sheep</td>
<td>140</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Rhesus monkey</td>
<td>88</td>
<td>2.1</td>
<td>480</td>
</tr>
<tr>
<td>Giraffe</td>
<td>86–105</td>
<td>1.0–2.7</td>
<td></td>
</tr>
<tr>
<td>Capuchin monkey</td>
<td>26–40</td>
<td>2.4–4.8</td>
<td></td>
</tr>
<tr>
<td>White-fronted capuchin</td>
<td>57</td>
<td>4.8</td>
<td>610</td>
</tr>
<tr>
<td>Dog</td>
<td>64</td>
<td>1.2</td>
<td>180</td>
</tr>
<tr>
<td>Fox</td>
<td>53</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>Cat</td>
<td>25</td>
<td>1.0</td>
<td>390</td>
</tr>
<tr>
<td>Squirrel monkey</td>
<td>23</td>
<td>2.3</td>
<td>480</td>
</tr>
<tr>
<td>Rabbit</td>
<td>11</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>Marmoset</td>
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<td>1.7</td>
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<tr>
<td>Squirrel</td>
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<td>1.1</td>
<td></td>
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<td>0.3</td>
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</tr>
<tr>
<td>Rat</td>
<td>2</td>
<td>0.4</td>
<td>15</td>
</tr>
<tr>
<td>Mouse</td>
<td>0.3</td>
<td>0.5</td>
<td>4</td>
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</table>
Brain is part of the nervous system. The nervous system is divided into central and peripheral systems. The brain and the dorsal spinal cord compose the Central Nervous System (CNS). The Peripheral Nervous System (PNS) is consisted of the spinal nerves that branch from the spinal cord, the cranial nerves that branch from the brain and the ganglia that are outside of the CNS Figure 2. Main function of the PNS is to connect the CNS with the limbs and organs serving as a communication system that transmits information back and forth between brain and extremities [11]. The PNS, in contradiction with CNS, is generally not protected by bone structures such as skull or vertebra or by the BBB which means that it is exposed to toxins and mechanical injuries. The PNS is divided into the Somatic Nervous System (SoNS) and Autonomic Nervous System (ANS) [12]. The SoNS is associated with the voluntary control of body movements and it consists of afferent nerves or sensory neurons which relay sensation to the CNS by detecting external stimuli and the efferent nerves or motor neurons that are responsible for the muscle stimulation and include also all the non-sensory neurons connected to muscles and skin Figure 3. The ANS is the control system over the function of the internal organs and its largely operating below the level of consciousness [13]. The functions of the ANS include influencing hear rate, digestion, breathing, salivation, perspiration, dilation of pupils, urination, sexual arousal etc.
Cells of the brain can be distinguished into two groups: neurons and neuroglia.

Neurons

Neurons, or nerve cells, are the cells that enable all the communication and processing within the brain. The sensory neurons, as mentioned before, deliver the information about the condition of body and its surrounding. Then the integration and processing of the information is done by the interneurons from which most of the gray matter is made of. Interneurons send signals to motor neurons, which carry them to the muscles and glands.

Neuron is the core component of the nervous system. It is an electrically excitable cell that processes and transmits information using electrical and chemical signals. These signals between neurons occur via synapses, specialized connections with other cells. Neurons can connect to each other to form neural networks. A typical neuron is divided into three parts: the soma or cell body, the dendrites, and the axon Figure 4. The cell body (soma) is where most of a neuron's organelles are located. Dendrites are thin structures that come from the cell body, extending for hundreds of μm and branching multiple times, getting thinner with each branching, and forming the complex "dendritic tree". The axons is a special cellular extension that begins from the body from the axon hillock and may have length of 1 meter in humans, it can be covered with myelin sheath. Although multiple dendrites can rise from neuron's body there is never more than one axon. On the other hand the axon may have hundreds of branches before its end. At the synapses in general, signals are sent from one neuron through the axon to another's dendrite. There are many exceptions to these general characteristic such as: neurons without dendrites, neurons without axon, synapses connecting an axon to another axon or a dendrite to another dendrite, etc.
Synapse is the structure that permits the signal to pass from one neuron to another. In the synapse, the plasma membrane of the neuron the signal originates (presynaptic neuron) comes very close to the membrane of the cell that the signal will be transmitted to (postsynaptic cell). Both areas of the presynaptic and postsynaptic cells, have array of molecular machinery that allow the transmission Figure 5. There are 2 main types of synapses:

**Chemical synapses**, where the electrical signal when reaches the presynaptic site of the cell is converted, with the activation of voltage gated calcium channels, into a chemical release of neurotransmitters which bind to the special receptors on the plasma membrane of the postsynaptic cell. The bound neurotransmitter provoke an electrical response or a secondary messaging pathway that could excite or inhibit the postsynaptic neuron.

**Electrical synapses**, where the pre and post synaptic cells’ membranes are connected with special “gap junction” channels that have the ability to pass electric current, enabling the voltage changes of the presynaptic cell to produce voltage changes at the postsynaptic cell [14].

Neurons are electrically excitable, maintaining voltage gradients across their membranes by means of metabolically driven ion pumps. These pumps combine with ion channels that are embedded in the membrane to generate ions concentration changes between intracellular and extracellular space. These ions sodium, potassium, chloride, and calcium. The changes in the cross-membrane voltage define the function of special channels on the membrane of the cell that are voltage-dependent. If the voltage changes are higher from a threshold, an all-or-none electrochemical pulse in generated called an action potential (Figure 6). This pulse travels rapidly along the cell's axon, and activates synaptic connections with other cells when it arrives in the presynaptic site.
Neuroglia, or else glial cells, are the supporting non-neuronal cells of the nervous system. Their function is mainly to protect the neurons by maintaining homeostasis, forming myelin and supporting the neurons of the CNS and PNS [15]. The glial cells are most commonly involved in brain tumours. Currently four main functions of the glial cells have been identified:

1. To support and hold neurons in place
2. Supply oxygen and nutrients to neurons
3. Insulate one neurons from each other
4. Remove dead neuron and destroy pathogens

In the CNS the following types of glial cells exist:

A. **Microglia**, which act like white blood cells, are specialized macrophages that perform phagocytosis and protect CNS neurons by attacking and destroying pathogens that invades the brain and spinal cord.

B. **Macrogia**, which are separated into 4 categories:

1. **Astrocytes (or astroglia)**, are the greater in number macroglial cell in the CNS [16], anchor neurons to the blood supply, and prevent chemicals and pathogens to enter the brain from the capillaries. They regulate the external environment of neurons, recycle neurotransmitter that are released at the synapses. It is believed that astrocytes form the predominant building blocks of the BBB. The activity of the astrocytes has been linked to blood flow in the brain and it is what we are measuring in function Magnetic Resonance Imaging (fMRI) [17].

2. **Oligodendrocytes**, are the cells that coat the axons of the CNS cells by wrapping around them their membrane, forming an insulation layer called myelin stealth. This insulation allows myelinated axons to transmit nerve signal much faster than unmyelinated axons, thus accelerating the communication speed of the cells within the brain [18].

3. **Ependymal cells (or ependymocytes)**, line the capillaries of the choroid plexuses, the spinal cord and the ventricular system of the brain. They are responsible from the creation and secretion of the cerebrospinal fluid (CSF) and help at is circulation. Additionally they create the blood CSF barrier, and thought to be the neural stem cells [16].

4. **Radial glia**, are cells that come from the neuroepithelial cells after the beginning of neurogenesis. In a developing nervous system act as neuronal progenitors and as scaffold. In the mature brain are retained in the cerebellum and retina, where they regulate the synaptic plasticity or participate in the bidirectional communication with the neurons respectively.
In the PNS the following types of glial cells exist:

**Macroglia**, which are separated into:

1. **Schwann cells**, that have similar function as the oligodendrocyte, by providing myelin shield to the axons of the PNS. Additionally they can perform phagocytosis and clear the debris allowing regrowth of PNS neurons [19].

2. **Satellite cells**, that surround neurons of the sensory, sympathetic and parasympathetic ganglia. Like astrocyte, they help regulate the external chemical environment.

3. **Enteric glial cells**, are cells in the intrinsic ganglia of the digestive system. The play many roles in the enteric system such as homeostasis and muscular digestive processes.

**Brain Tissues**

The tissues of the brain can be divided into two major classes the gray and the white matter.

**Gray Matter** (or grey matter), in one of the major components of the CNS. It is consisting of the neuronal cell bodies, dendrite and myelinated or unmyelinated axons, glial cells and capillaries. The main distinction of the white matter is the fact that it contains most of the brains cell bodies and just a few myelinated axons. Gray matter regions are the regions that connection of the distant parts of the brain is done and were processing of information takes place. The gray matter regions are involved in the muscle control, sensory perception, memories, emotions, speech, decision making and self-control. From the 20% of the total oxygen taken by the body that goes to brain, the 95% of it goes specifically to the gray matter [20].

Gray matter is present in the brain, brainstem, cerebellum (Figure 7) and throughout the spinal cord. It is distributed in the surface of the cerebral hemispheres and the cerebellar cortex but also in the depths of the cerebrum such as thalamus, hypothalamus, subthalamus, basal ganglia and others. It also exists in the deep cerebellar nuclei.
The clinical significance of the gray matter is very big. There have been found positive correlations between gray matter volume and measurements of semantic and short term memory in elderly people, which suggest that cognitive functions that are well preserved with ageing is connecting with the variability of gray matter volume [21]. Structural differences in the gray matter have also associated with psychiatric disorders.

**White matter**, is made mostly of myelinated neurons which connect the different regions of the gray matter to each other and to the rest of the body. In that way white matter is the information highway of the brain. Using the analogy of a computer network, the grey matter is the actual computers, whereas the white matter is the network cables connecting the computers together. It is composed of bundles of myelinated nerve cells axons that connect the different areas of gray matter. It forms the bulk of the brain’s deep parts (Figure 7) and the superficial of the spinal cord. The white colour derived from the myelin (which is a fatty substance) surrounding the nerve axons.

Males have more white matter than females in length of myelinated axons and volume. It has been calculated that at the age of 20 the total length of myelinated axons is 176.000 km in men and 149.000 km in women but there is a decline in the total length with age at a rate of 10% per decade mainly due to loss of thinner fibers, resulting in the age of 80 of a mean total length of 97.200 km from males and 82.000 km for females [22].
As it is easily guessed the clinical significance of the white matter is very big, the destruction of myelin shield around the axons due to inflammation is one of the most common diseases called Multiple Sclerosis. White matter changes called amyloid plaques are associated with Alzheimer's disease and many other neurodegenerative diseases. In case of white matter injuries, such as axonal shearing, there may be regenerations thus may be reversible. Another change in the white matter connected with age is leukoaraiosis, which is a rarefaction of the white matter caused by loss of myelin, axonal loss, and a breakdown of the BBB.

From the significant role and the highly clinical significance of white and gray matter, it is more than obvious why imaging such tissues provides great tools in the hands of medical practitioners.

The skull

The purpose of the skull is to keep the brain inside a bony cage that protects it from injury. The human skull is made from 8 bones fused together. These bones include the frontal, parietal (2), temporal (2), sphenoid, occipital and ethmoid (Figure 10). The face is formed from 14 paired bones including the maxilla, zygoma, nasal, palatine, lacrimal, inferior nasal conchae, mandible, and vomer [2]. Adult skull is consisted of two parts of different embryological origin, the neurocranium and the viscerocranium. The neurocranium (or braincase) is a protective cranial vault that surrounds the brain and brainstem. The viscerocranium (also splanchnocranium or facial skeleton) is formed by the bones supporting the face [23]. Inside there are three different areas: anterior fossa, middle fossa, and posterior fossa as shown in Figure 9. Location of tumour is often denoted by the names of these areas, e.g., middle fossa meningioma. All the arteries, veins and nerves exit the base of the skull through openings, called foramina. The main opening in the base of the skull is the foramen magnum from where spinal cord exits.
Anatomy of the Brain

There are many different ways of dividing anatomically the brain the most commonly used one is to divide brain into three main regions based on the embryonic development. Like in all vertebrates the human brain develops from three embryonic regions shown in Figure 11 and Figure 12:

The forebrain (or prosencephalon), from which the cerebrum, thalamus, hypothalamus and pineal gland are created.

The midbrain (of mesencephalon), which is locate near the very centre of the brain, and is composed by a portion of the brainstem. In contrast with the other two regions, the prosencephalon and rhombencephalon, the mesencephalon remains undivided for the remainder of neural development. It doesn’t split into other brain areas like the prosencephalon, which divides into telencephalon and diencephalon.

The hindbrain (or rhombencephalon), is made of the remaining of the stem, cerebellum and the pons.

From these three embryonic regions by the fifth week of embryonic development five brain regions have formed. As shown in Figure 12, the regions are telencephalon, diencephalon that comes from forebrain, mesencephalon created by the midbrain and the metencephalon and myelencephalon coming from differentiation of hindbrain. At a fully developed stage the most profound changes happen to the forebrain (telencephalon) which gives rise to the cerebrum that comprises the cerebral cortex,
white mater and the basal nuclei. Diencephalon comprises thalamus, hypothalamus and epithalamus, the mesencephalon comprises the midbrain, the metencephalon comprises ponds and cerebellum, while myelencephalon comprises the medulla oblongata.

**Hindbrain (Rhombencephalon)**

**Brainstem**

The brain stem connects the cerebrum and cerebellum with the spinal cord. This is a very important part of the brain, even though it's small. Any nerve fibbers that are sent to the rest of the body from the brain must move through the brain stem. Many of the most critical function for survival are done here such as breathing, hear rate, body temperature, wake and sleep cycles, sneezing, coughing, swallowing, and vomiting. 10 of the 12 cranial nerves (3-12) are beginning from here.

The brain stem is made of the midbrain (mesencephalon), pons (part of the metencephalon), and medulla oblongata (myelencephalon) (Figure 13).

**Midbrain**, is a structure made of gray and white mature (circular formation) which is found in all region of brainstem. This formation controls the tone of the muscles and is the “switch” between consciousness and sleep.

**Medulla Oblongata** (or medulla), is a nervous tissue of cylindrical shape in the lower part of the brainstem and connects to the spinal cord in its lower part and to pons in the upper part [24]. In the medulla there are centres of gray matter that control involuntary body functions that contribute to homeostasis. In here the blood pressure and oxygen levels are monitored and the heart rate is regulated. It also controlling the breathing rate, vomiting, sneezing, coughing and swallowing reflexes.

**Pons**, the pons is about 2.5 cm in length and is found in top of the medulla [25], under the midbrain and anterior to the cerebellum. Combined with the cerebellum if forms the metencephalon. It is the bridges for signals from and to the cerebellum but also signals between the brain and medulla and spinal cord.
The cerebellum, which means little brain in Latin, is one of the most important regions of the brain for the motor control. It is a wrinkled, hemispherical structure of the brain located posterior to brainstem and inferior to the cerebrum (Figure 14). The outer part of the cerebellum, the cerebellar cortex, is made of tightly folded gray matter in which the proceeding is done. In the deep parts of the cortex the tree shape layer of white matter (arbor vitae) connect the cortex to the rest of brain and body. Except from its contribution to the motor control it is also involved in the cognitive functions such as attention and language, also regulating fear and pleasure response. Although cerebellum does not initiate movement, it contributes to coordination of them, precision and accurate timing [26], integrates inputs from sensory system and brain and tunes fine motor movement [27]. Additionally the cerebellum is necessary for motor learning and most notably learning to adjust to changes in sensorimotor relationships. In case of cerebellar damage, although paralysis doesn’t appear, there is a series of disorder in five movement, equilibrium, posture and motor learning [27].

Midbrain (Mesencephalon)

The midbrain is the most superior organ of the brainstem (Figure 15). It is mainly associated with motor control functions of the body such as vision, basic movements, and hearing. Additionally is plays role in the sleep/awake process, arousal and temperature regulation. Part of the midbrain called the substantia nigra plays a role in releasing dopamine-producing neurons. Degeneration of the substantia nigra leads to a loss of motor control known as Parkinson’s disease. The midbrain can be subdivided in to 2 main regions:

The tectum, which contains relay for the auditor and visual information reflexes such as pupillary reflex, accommodation reflex (focusing of distant of close objects), and startle reflexes.

The cerebral peduncles, contains nerve tracts that connect regions of the cerebrum and thalamus to the spinal cord and the substantia nigra a region of dark melanin-containing neurons that is involved in the inhibition of movement.
Forebrain (Prosencephalon)

Diencephalon

Diencephalon is made up by: thalamus, hypothalamus, and pineal glands. It is placed superior and anterior of the midbrain (Figure 16).

Thalamus, is made of a pair of oval masses of gray matter inferior to the lateral ventricles and surrounding the third ventricle (Figure 17). Sensory neurons entering the brain form relays with neurons in the thalamus that continue on to the cerebral cortex. Thus thalamus acts like the "switchboard operator" of the brain by routing sensory inputs to the correct regions of the cerebral cortex. The thalamus has an important role in learning by routing sensory information into processing and memory centres of the cerebrum [7]. The thalamus is believed to both process sensory information as well as relay it. Each of the primary sensory relay areas receives strong feedback connections from the cerebral cortex [24]. The thalamus also plays an important role in sleep and wakefulness states regulation [28].

Hypothalamus, is a region of the brain located inferior to the thalamus and superior to the pituitary gland (Figure 18). The hypothalamus is the brain’s control centre for body temperature, thirst, hunger, heart rate, blood pressure, and hormones production. It detects the condition of the body by the sensory nerves and it responses to changes by sending signals to glands, smooth muscles, and the heart to counteract these changes such as in the case of increased body temperature, where the hypothalamus stimulates sweat glands in the skin and induces the secretion of sweat. Additionally when there is lack of food or water hypothalamus sends signals to the cerebral cortex to produce the feelings of hunger and thirst [29]. It controls many other hormones, such as releasing and inhibiting hormones that are secreted into the blood to stimulate or inhibit hormone production in the anterior pituitary gland [7].
**Pineal Gland**, is a small gland located posterior to the thalamus and helps regulate the body's internal clock and circadian rhythms by secreting melatonin. It also has some role in sexual development. Light striking the retina of the eyes sends signals to inhibit the function of the pineal gland. In the dark, the pineal gland secretes melatonin, which has a sedative effect on the brain and helps to induce sleep. The pineal gland produces less melatonin as people age, resulting in difficulty sleeping during adulthood [7].

**Cerebrum**

The cerebral cortex is so large that it overshadows every other part of the brain and controls the voluntary movement and cognitive functions. It is composed from the right and left hemispheres. Each hemisphere is divided into four regions, the frontal lobe, the parietal lobe, the temporal lobe and the occipital lobe (Figure 19). The lobes are named for the skull bones that cover them. Its’ surface is a convoluted layer of gray matter known as the cerebral cortex. The cortex contains about 70% of the 100 billion nerve cells. Most of the processing of the cerebrum takes place within the cerebral cortex. The bulges of cortex are called gyri while the indentations are called sulci. The inner part of the cerebral cortex is a layer of white matter that connects the different regions of the cerebrum and the cerebrum with the rest of the body. The left and right hemispheres are connects by large band of white matter axons called corpus callosum (Figure 20).

Different regions of the cortex contain areas with different functions. The parietal lobe, for example, contains areas involved in somatosensation, hearing, language, attention, and spatial cognition. The frontal lobe controls attention, abstract thinking, behaviour, problem solving tasks, and physical reactions and personality [14]. The occipital lobe is responsible for the visual reception, visual-spatial processing, movement, and colour recognition [15]. The temporal lobe controls auditory and visual memories, language, and some hearing and speech[14].
Deep within the cerebral white matter are several regions of gray matter that make up the basal nuclei and the limbic system. The basal nuclei, including the globus pallidus, striatum, and subthalamic nucleus, work together with the substantia nigra of the midbrain to regulate and control muscle movements. Specifically, these regions help to control muscle tone, posture, and subconscious skeletal muscle. The limbic system is another group of deep gray matter regions, including the hippocampus and amygdala, which are involved in memory, survival, and emotions. The limbic system helps the body to react to emergency and highly emotional situations with fast, almost involuntary actions [7].

**Meninges**

Meninges are the membranes that envelop the central nervous system, they consist of three layers of tissue that surround the brain and the spinal cord, the dura mater, arachnoid matter and pia matter (Figure 21).

**Dura mater**, is the outer layer of the meninges, is a thick and durable membrane composed of dense fibrous tissue and the inner surface is cover by fattened cells. It forms a pocket around the brain and spinal cord to hold the cerebrospinal fluid and prevent mechanical.

**Arachnoid matter**, bellow the dura matter lays the arachnoid matter which is thinner and contains may this fibbers connecting dura to pia matter. Beneath the arachnoid mater is a fluid-filled region known as the subarachnoid space.

**Pia matter**, is the innermost layer and come directly in contact with brain’s surface and the spinal cord. It is a very thin membrane composed of fibrous tissue covered on its outer surface by a sheet of flat cells thought to be impermeable to fluid. Pia mater’s many blood vessels provide nutrients and oxygen to the nervous tissue of the brain. The pia mater help in the regulation of the flow of materials from the bloodstream and cerebrospinal fluid into nervous tissue.
Cerebrospinal Fluid (CSF) is a clear colourless fluid that exists around the brain and spinal cord. It is produced in the choroid plexus and acts as a cushion or buffer for the brain's cortex, providing a basic mechanical and immunological protection to the brain inside the skull, additionally it serves a vital function in cerebral auto regulation of cerebral blood flow. CSF fills the subarachnoid space and exerts pressure on the outside of the brain and spinal cord [30]. The pressure of the CSF acts as a stabilizer and shock absorber for the brain and spinal cord as they float within the hollow spaces of the skull and vertebrae. Inside of the brain, small CSF-filled cavities called ventricles expand under the pressure of CSF to lift and inflate the soft brain tissue (Figure 22).

CSF circulates within the ventricular system of the brain (a series of cavities filled with CSF) (Figure 23). The majority of CSF is produced from within the two lateral ventricles. The lateral ventricles both connect with the third ventricle through the foramen of Monro. The third ventricle connects with the fourth ventricle via a tube called the aqueduct of Sylvius. From the fourth ventricle, CSF flows into the subarachnoid space where it bathes and cushions the brain [2]. After circulating around the brain and spinal cord, CSF enters small structures known as arachnoid villi (finger-like extensions of the arachnoid mater that pass through the dura mater) where it is reabsorbed into the bloodstream [7].

Composition of CSF is approximately 0.3% plasma proteins, depending on sampling site [31], and it is produced at a rate of 500 ml/day. Since the subarachnoid space contains only 135 to 150 ml, CSF is drained into the blood through arachnoid resulting in CSF turning over 3.7 times a day. This continuous flow dilutes the concentration of larger, lipid-insoluble molecules that have penetrated the brain [6].
The arterial cerebral circulation is divided into anterior and posterior cerebral circulation. There are two main pairs of arteries that supply the brain: the internal carotid arteries and vertebral arteries. The internal carotid arteries supply most of the cerebrum (anterior cerebral circulation), while the vertebral supply the cerebellum, brainstem, and the underside of the cerebrum (posterior cerebral circulation) (Figure 24).

The anterior and posterior cerebral circulations are interconnected via the Circle of Willis, which provides backup circulation to the brain since if one of the major vessels becomes blocked, it is possible for blood to come across the Circle of Willis and prevent brain damage.

Although in the rest of the body the arteries and veins run together this is not the case in the brain. The venous drainage of the cerebrum is separated to superficial and deep. The superficial system is consisted of the dural venous sinuses. The most prominent vein collectors is the superior sagittal sinus. The venous sinuses collect the blood from the brain and pass it to the internal jugular veins. The deep venous drainage is primarily composed of traditional veins inside the deep structures of the brain, which join and form the vein of Galen. This vein merges with the inferior sagittal sinus.
Brain Tumours

A brain tumour (intracranial neoplasm) is a mass of unnecessary cells with abnormal growth within the brain of spine canal [32]. There are two main types of tumours:

Primary tumours, that started and tend to stay within the brain

Metastatic tumours, that begin as a malignant tumour in another part of the body and then spread to the brain.

The symptoms that are produced by the brain tumours depends on the part of the brain involved. These could be seizures, headaches, vision problem, vomiting, and even mental changes. Other symptoms may be difficulty in walking, speaking and sensation problems.[32]

Primary tumours

A tumour that starts within the brain is a primary brain tumours. Examples of primary tumours are Glioblastoma Multiform (GBM), astrocytoma, medulloblastoma and ependymoma [32]. Primary tumours can be further divided into:

Benign tumours, which are non-cancerous tumours, that grow and exert pressure on the surrounding tissues, but they rarely spread into other tissues and may recur. Main characteristics are that they are slow growing tumours with distinct borders. Cells of the benign tumours are the same appearance as the normal cells. Surgical removal itself can be an effective treatment. Never the less a benign tumour placed in a vital area can be life-threatening.

Malignant tumours, are likely to grow quickly and spread in to other brain tissue. Main characteristics are they are rapidly growing, invasive and life threatening. These tumours don’t have distinct borders due to their tendency to infiltrate nearby tissues. They also have the ability to create cells that travel through the brain. Although they are referred to as brain cancer, since primary brain tumours rarely spread outside the brain, they don’t fit the definitions of cancer. Cancer is defined by unregulated growth of cells, cells spread in the around parts of the body and interfere with normal function, and spread to distant organs.

Metastatic brain tumours

Tumours found in the brain but have started somewhere else in the body and then to the brain called metastastic brain tumours. These tumours are more common than primary brain tumours [32]. As it can be understood by the origin of this type of tumour metastatic brain tumours are by definition malignant tumours, since they have had a metastasis in the brain, and can be correctly referred to as cancer.
About 50% of the metastatic brain tumours origin from lung cancer. Other types of cancer that commonly spread to the brain are, breast cancer, melanoma, colon and kidney cancer [3, 32]. Additionally Leukaemia, lymphoma, breast cancer, and gastrointestinal cancer may spread to the leptomeninges causing leptomeningeal carcinomatosis. These tumours spread to the brain spread to the brain via the bloodstream or a magnetic-like attraction to other organs of the body [32].

**Tumour Grading by WHO**

In order for cancer to be classified the World Health Organization (WHO) has created a classification system based on the abnormality of the appearance of the cancer cell under the microscope and the speed of growth and spread of the tumours. The four following grades of tumours have been defined [3], in Table 2 a synoptic table is shown:

- **Grade I**, are low-grade tumours which are the least malignant and have long term survival. The tumour cells look more like normal cells under a microscope and grow and spread more slowly than other grade tumour cells. They rarely spread into nearby tissues. Grade I brain tumours may be cured if they are completely removed by surgery.

- **Grade II**, tumour cells grow and spread relatively slow and slower than grade III and IV. They have a slightly abnormal microscopic appearance and may spread into nearby tissue and may recur after secretion. Some tumours may evolve to a higher-grade tumour.

- **Grade III**, tumours are malignant by definition. Grade II tumour cells are reproducing abnormal cells actively, which are likely to spread and grow in the near tissues. These cells look very different from normal cells under a microscope and grow more quickly than grade I and II tumour cells. These tumours have the tendency to recur as a higher grade tumours.

- **Grade IV (high-grade)**, tumours are the most malignant tumours. The cells do not look like normal cells under a microscope, and they reproduce rapidly and can easily grow in the surrounding tissue. These tumours have the ability to form new blood vessels in order to keep a rapid growth. There may be areas of dead cells in the centre of the tumour. Grade IV tumours usually cannot be cured. Glioblastoma is the most common example.
Most of the time tumours contain several grades of cells. The highest or most malignant grade of cells determines the grade of the tumour despite of the fact that the larger part of the tumour may be of lower grade. In some cases changes can happen in a benign growth which might become malignant or a lower-grade tumour might recur as a higher-grade one.

**Causes and Risk Factors**

Causes and risk factors can be environmental (exposure to poisonous substances, diet, lack of exercise, smoking, alcohol), or genetic (born with a gene mutation, or inherit from parent, mutations can also accumulate over time.

Despite that no risk factor accounting for the majority of the brain tumours has been identified. A series of factors are studied amongst them [3]:

**Environmental factors**, which are difficult to accurately measure and long term research is need among the factors that are studied are:

- Exposure to air pollution, residential power lines, smoking (and second hand smoking), chemical from agricultural
- Working in petroleum refining production
- Smoking during pregnancy and consumption of alcohol
- Common medication such birth pills, counter pain treatments
- History of head trauma or epilepsy
- Viruses and common infections
- Consuming cured food
- Ionizing Radiation is the only that has been consistently associated with increased risk for developing brain tumours (although modern medical
X-ray modalities are of lower dose and use better focused beams than the ones decades ago.

- Cell phone radiation has not been linked with brain tumours [33], despite that WHO has classified it as possible carcinogenic.

**Genetic factors**, which refer to condition or diseases that have been inherited from the family. Only 5-10% of all cancers in actually inherited and only a few genetic syndrome are involved in brain tumours. Many types of genes are thought that are not expressing correct in brain tumours such as:

- Tumour suppressor genes
- Oncogenes
- Growth factors
- DNA repair genes
- Immune response genes and others

**Types of cancer, occurrence and severity**

According to the tissue from which the tumour arises a list with the most common tumours is shown in Table 3.

*Table 3 - Brain tumours according to tissue they arise from*

<table>
<thead>
<tr>
<th>Tissue of origin</th>
<th>Children</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Astrocytes</td>
<td>Pilocytic</td>
<td>Glioblastoma</td>
</tr>
<tr>
<td></td>
<td>Astrocytoma (PCA)</td>
<td>Multiforme (GBM)</td>
</tr>
<tr>
<td>Oligodendrocytes</td>
<td></td>
<td>Oligodendroglioma</td>
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<tr>
<td>Ependyma</td>
<td>Ependymoma</td>
<td></td>
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<tr>
<td>Neurons</td>
<td>Medulloblastoma</td>
<td></td>
</tr>
<tr>
<td>Meninges</td>
<td>Meningioma</td>
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</tbody>
</table>

According to WHO classification system the names and organizations of the brain tumours are the following:
Astrocytoma, are the tumours that arise at the astrocyte cells glial cells (Figure 25). Tumours from glial cells are also called gliomas. There are astrocytomas that grade from Grade I to Grade IV. Some of the common astrocytomas are the following:

Pilocytic Astrocytoma (grade I), represent 5-6% of all gliomas and are most common gliomas in children. They grow slowly and may form a cyst, they rarely spread. They are also curable.

Anaplastic Astrocytoma (grade III), tends to occurs more often in males and most frequently in people of 45 years old or older. They grow quickly and spread. After therapy they tend recur are grade III or IV tumours.

Brain stem gliomas (usually high grade), 10 -20% of brain tumours in children, and most often ate the age of 5 to 10 but are also rarely seen in the age 30 to 40. Vary from grade I (mainly in children) to grade II or grade III. Spread widely to the brainstem. Hard to cure.

Glioblastoma or Glioblastoma Multiforme GBM (grade IV), 17% of all primary brain tumours and 60-75% of all astrocytomas. Frequency increases with age and affect more men than women. Is found mainly in the cerebral hemispheres. They grow and spread very quickly and thus their most common symptom is to increase pressure in the brain and cause headache, nausea, vomiting and drowsiness. Symptoms may vary depending on the location of the tumour. They contain a mix of different cells such as cystic material, calcium deposits, blood vessels or mixed grade cancer cells. Additionally necrotic cells exist in the centre of the tumour. Usually they cannot be cured.

Oligodendroglial tumours, are the tumours that arise from the oligodendrocytes glial cells (Figure 26). These type of tumours are more frequently seen in young and middle age adults and most commonly in the cerebral hemisphere (mainly in the frontal lobe). Most common types of cancer are:

- **Oligodendroglioma (grade II)**, grows slowly but often spreads into nearby tissues. In some cases is curable
- **Anaplastic Oligodendroglioma (grade III)**, grows quickly and spreads in to the near tissues. Cannot be cured.
Oligoastrocytic or Mixed gliomas, mixed gliomas have more than one type of tumour cells, oligodendrocytes and astrocytes. Most common types are:

- **Oligoastrocytoma (grade II)**, slow growing tumour that can be cured.
- **Anaplastic oligoastrocytoma (grade III)**, grows quickly and spreads into nearby tissues. Worse prognosis than oligoastrocytoma (grade II).

**Ependydoma**, is a type of tumour that arises from the ependymal cells that line the ventricles in the brain and around the spinal cord. They are relatively rare tumours, 1-2% of all primary tumours and 5-6% of all gliomas. In childhood they represent 5% of brain tumours. The most common types are:

**Ependymoma (grade I or II)**, grows slowly. There are two types of grade I ependymoma: myxopapillary ependymoma and subependymoma. Grade II ependymomas grow in ventricles or in the spinal cord. Can be cured.

**Anaplastic ependymoma (grade III)**, grows quickly and spreads into nearby tissues. Has a worse prognosis than a grade I or II ependymoma.

**Medulloblastoma (grade IV)**, is a type of embryonal tumours that is always located in the cerebellum. 14% of brain tumours in children under 14 years old and 20% of brain tumours in adults. Fast growing and high grade that often spread to other parts of the CNS.

**Meningioma**, arises from the arachnoid matter of the meninges. Represents 34% of all primary brain tumours and is more frequent in middle age women. Most common types meningeal tumours are:

**Meningioma (grade I)**, the most common type of meningeal tumor. Grows slowly and it can be cured if it is completely removed by surgery.

**Meningioma (grade II and III)**, rare meningeal tumor that grows quickly and is likely to spread within the brain and spinal cord. The prognosis is worse than a grade I. Usually cannot be completely removed by surgery.

In Table 4 the complete WHO grading for the tumours of the CNS is shown [5]
Table 4 - Grading of Tumours of the CNS according to WHO, (table originally published on [5])

<table>
<thead>
<tr>
<th>Astrocytic tumours</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
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<tbody>
<tr>
<td>Subependymal giant cell astrocytoma</td>
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<tr>
<td>Pilocytic astrocytoma</td>
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<td>Pilomyxoid astrocytoma</td>
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<td>Diffuse astrocytoma</td>
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<td>Pleomorphic xanthoastrocytoma</td>
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<tr>
<td>Anaplastic astrocytoma</td>
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<tr>
<td>Glioblastoma</td>
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<td>Giant cell glioblastoma</td>
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<td>Gliosarcoma</td>
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<tr>
<td>Oligodendrogial tumours</td>
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<tr>
<td>Oligodendroglioma</td>
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<tr>
<td>Anaplastic oligo-dendroglia</td>
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<tr>
<td>Oligoastrocytic tumours</td>
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<tr>
<td>Oligoastrocytoma</td>
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<td>Anaplastic oligoastrocytoma</td>
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<tr>
<td>Ependymal tumours</td>
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<tr>
<td>Subependymoma</td>
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<tr>
<td>Myxopapillary ependymoma</td>
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<tr>
<td>Ependymoma</td>
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<td>Anaplastic ependymoma</td>
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<tr>
<td>Choroid plexus tumours</td>
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<tr>
<td>Choroid plexus papilloma</td>
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<td>Pineal parenchymal tumour of intermediate differentiation</td>
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<td>Pineoblastoma</td>
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<td>Schwannoma</td>
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<td>Malignant peripheral nerve sheath tumour (MPNST)</td>
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<td>Meningeal tumours</td>
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<td>Anaplastic / malignant meningioma</td>
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<td>Anaplastic haemangiopericytoma</td>
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<td>Haemangioblastoma</td>
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<td>Tumours of the sellar region</td>
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<td>Cranioopharynoglioma</td>
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<td>Granular cell tumour of the neurohypophysis</td>
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<td>Pituitary</td>
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<td>Spindle cell oncocytoma of the adenohypophysis</td>
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36
Brain Tumour statistics

Some statistics concerning the occurrence and brain tumours related deaths according to the American Brain Tumour Association (all presented data are published from [34]) are:

- Leading cause of cancer related deaths in children (males and females) under age 20 (leukaemia is the first).
- Second leading cause of cancer related deaths in males ages 20-39 (leukaemia is the first).
- Fifth leading cause of cancer related deaths in females ages 20-39.

Brain Tumour in numbers:

- Nearly 70,000 new cases of primary brain tumours will be diagnosed this year.
- More than 4,600 children between the ages of 0-9 will be diagnosed with a brain tumour this year.
- Brain and central nervous system tumours are the most common cancers among children ages 0-19.
- There are nearly 700,000 people in the U.S. living with a brain tumour.
- There are more than 120 types of brain tumours.

Tumour-Specific Statistics:

- Meningiomas represent 34% of all primary brain tumours, making them the most common primary brain tumour.
- Gliomas, represent 30% of all brain tumours and 80% of all malignant tumours.
- Glioblastomas represent 17% of all primary brain tumours, and 54% of all gliomas.
- Astrocytomas represent 7% of all primary brain tumours.
- Astrocytomas and glioblastomas combined represent 76% of all gliomas.
- Nerve sheath tumours represent about 9% of all primary brain tumours.
- Pituitary tumours represent 13% of all primary brain tumours.
- Lymphomas represent 2% of all primary brain tumours.
- Oligodendrogliomas represent 2% of all primary brain tumours.
- Medulloblastomas/embryonal/primitive tumours represent 1% of all primary brain tumours.
- The majority of primary tumours (34%) are located within the meninges, followed by the frontal, temporal, parietal and occipital lobes (22%).
Brain Imaging

Imaging is an extremely important tool for clinical care and researchers, and its importance is increasing through time. As the technology evolves new technique with better characteristics are emerging in an attempt to image with the highest possible detail both in spatial and temporal domain as many as possible characteristics, functions, substances or structures of the human body and most important if possibly non-invasively.

Imaging the brain or neuroimaging is a highly developing research area with great impact in every day clinical practice. A wide range of imaging technologies now provide unprecedented sensitivity to visualization of brain structure and function from the level of individual molecules to the whole brain [35]. With neuroimaging techniques researchers have the ability to study not only the structures of brain, which have been thoroughly studied, but also with the use of functional imaging techniques to evaluate the neural networks that cognitive processes take place in order to better the way that our brain works, understand diseases, diagnose them early in order to treat them more effectively.

Brain imaging techniques can be divided in 3 main categories, which more or less coincide with the historical evolution of imaging:

- **Structural imaging**, which are able to image the anatomy (structure) of the brain. Most important structural imaging techniques are:
  - Computed Tomography (CT)
  - Angiography
  - Magnetic Resonance Imaging (MRI)
  - Diffusion-Tensor MRI (DTMRI)
  - Ultrasound

- **Functional imaging**, also referred to as physiological imaging techniques, which have the ability to measure the cerebral blood flow and brain metabolism thus image the areas that are functioning at different times. Most important functional imaging techniques are:
  - Positron Emission Tomography (PET)
  - Single Photon Emission Computed Tomography (SPECT)
  - Functional MRI (fMRI)
  - Magnetic Resonance Spectroscopy (MRS)
  - Electroencephalography (EEG)
  - Magnetoencephalography (MEG)
  - Functional Ultrasound Imaging (fUS)
  - Laser Doppler Ultrasound
  - Functional Near-Infrared Spectroscopy (fNIRS)
• **Molecular imaging**, which are able to image the actions of individual cells and of the molecules that compose them. Examples of molecular imaging techniques are:
  
  - Fluorescence Resonance Energy Transfer (FRET)
  - Intravital Light Microscopic technologies
  - Macroscopic Optical Scanning Techniques
  - Multi-photon Laser Microscopy
  - Optical Tomographic Imaging

Since the topic of this thesis is structural imaging, only selected of the above mention techniques will be presented shortly. A small comparison between CT and MRI is then presented in order to facilitate the understanding of the aim of the presented research.

**Structural Imaging Techniques**

**CT**

**Computed tomography (CT)** or **computerized axial tomography (CAT)**, is an X-ray imaging technique which reconstructs cross-sectional images of the body. Like all x-ray imaging techniques is based on the absorption of the x-ray beam from the tissues of human body. Analytical presentation of x-ray imaging principles and physical phenomena that take place, is given in the x-ray imaging chapter. Cross sections are reconstructed from the measurements of attenuation coefficients in the volume of the object studied.

CT data are generated using an X-ray source that rotates in a circular gantry around the patient with x-ray detectors positioned on the opposite side of the X-ray source as seen in Figure 28. There are many different types of source and detectors that can be used for at CT or cone beam CT scan which are analytically presented in the X-ray sources and detectors paragraphs. Most common detectors in medical x-ray scanner are linear detectors (x-ray sensitive elements placed in one line) of multiple line detectors in the modern multi slice systems.
As the source and detector are circling around the patient x-ray beams that have passed through the patient body are collected by the detectors from different angles. By combining raw data from a full rotation produce the sinogram is produced (Figure 29). In these data a reconstruction algorithm is applied and a reconstructed slice revealing the inner structure of the imaged object is created.

Depending on the thickness of the emitted x-ray beams different beam types are created (Figure 30), a fan beam is a very slim fan sized beam that is captured by a linear detector or a cone beam that is captured by a 2 Dimensional (2D) detector. The technique were cone beams are used with 2D detectors is called Cone Beam CT (CBCT). In CBCT projection images of the images object are created at different angles and as in the case of CT the same reconstruction algorithms can be used in order to create a reconstructed slice. CT is used in medicine as a diagnostic tool and as a guide for interventional procedures. Sometimes contrast materials such as intravenous iodinated contrast are used. This is useful to highlight structures such as blood vessels that otherwise would be difficult to delineate from their surroundings. Using contrast material can also help to obtain functional information about tissues.

Modern CT scanning can provide good images in a matter of minutes. A spiral CT scan of the head may be performed in 10–30 seconds, making it a good option for children and adults with difficulty holding still for longer periods [36]. The use of contrast dye in CT angiography provides good visualization of the vascular structures and leaks in the blood vessels [36]. Computed tomography (CT) has become the diagnostic modality of choice for head trauma due to its accuracy, reliability, safety, wide availability, and speed. Additionally it can be to assess the brain for tumours and other lesions, injuries, intracranial bleeding, structural anomalies such as hydrocephalus, infections, brain function or other conditions. It can very well depict bones, inflammations, blood existence and calcification of the brain but due to its nature it cannot depict the different tissues of brain parenchyma.
During an MRI scan a strong magnetic field is applied around the area to be imaged. This magnetic field can vary to from up to 5 or more tesla. In this technique hydrogen nucleus (a single proton) is used because of its abundance in water and fat. The hydrogen proton is spinning on its axis, like the planet earth, with a north-south pole. In this respect it behaves like a small bar magnet. Under normal circumstances, these hydrogen proton “bar magnets” spin in the body with their axes randomly aligned [37]. When the body is placed in a strong magnetic field, such as an MRI scanner, the protons' axes all line up along the direction the applied magnetic field. Energy from an oscillating magnetic field (radio wave) is temporarily applied to the patient at the appropriate resonant frequency. The excited hydrogen atoms emit a radio frequency signal which is measured by a receiver coil [38]. Receiver coils are used around the body part in question to act as aerials to improve the detection of the emitted signals. The intensity of the received signal is then plotted on a grey scale and cross sectional images are built up [37]. Multiple transmitted radiofrequency pulses can be used in sequence to emphasise particular tissues or abnormalities. A different emphasis occurs because different tissues relax at different rates when the transmitted radiofrequency pulse is switched off. The time taken for the protons to fully relax is measured in two ways. The first is the time taken for the magnetic vector to return to its resting state and the second is the time needed for the axial spin to return to its resting state. The first is called T1 relaxation, the second is called T2 relaxation [37].
Contrast agents can be used, they can be applied intravenously, orally or intra-articularly [38]. MRI is broadly used by the clinicians to image brain cancers as it is more sensitive than CT for small tumours (Figure 31) and offers better visualization of the posterior fossa. It provides very good between grey and white matter giving the ability to diagnose cerebral pathologies CNS such as demyelinating diseases, dementia, cerebrovascular disease, infectious diseases and epilepsy [39]. MRI-guided stereotactic surgery and radiosurgery is used for treatment of intracranial tumours, and other brain surgical operation conditions [40].

**Diffusion-Tensor MRI (DTMRI)**

Diffusion-tensor MRI (DTMRI) maps the diffusion process of water molecules, in biological tissues, in vivo and non-invasively. Since diffusion in tissues is not free, but reflects interactions with surround tissues such as macromolecules, fibbers, membranes, thus its diffusion can reveal microscopic details about tissue anatomy [41]. By imaging microscopic water motion in the brain tissues where this motion is facilitated along white matter tracts it can construct the images of the white matter tracts (Figure 33). DTMRI, therefore, is used to visualize white matter tracts connecting different parts of neural networks in the brain. It is used extensively in presurgical planning, such as the removal of brain tumours, to ensure that these tracts are spared during surgery. Additionally, DTMRI has been applied to the study of neurological conditions, such ADHD and other developmental disorders, that are thought to arise from problems in white matter connections [35].
**Functional Imaging**

Functional imaging techniques have the ability to measure the cerebral blood flow and brain metabolism thus image the areas that are functioning at different times. One very important parameters of all these functional techniques is their ability to discriminate between two close areas that brain activity takes place (spatial resolution) and at the same time to discriminate between two close time moment that these activities take place (temporal resolution). In Figure 34 the temporal and spatial resolution of the most important functional imaging techniques is shown. It is obvious that the desired combination is to have at the same time both high temporal and spatial resolution as in the case of the intracranial EEG (iEEG) and MEG (techniques within the yellow circle). A short presentation of the most important functional techniques will be given.

**PET**

In Positron emission tomography a three-dimensional image of functional processes in the body. A short-lived radioactive tracer isotope chemically incorporated into a biologically active molecule (most commonly fluorodeoxyglucose (FDG)) is injected in the circulation of the patient. The system detects pairs of gamma rays emitted indirectly. As the radioisotope undergoes positron emission, it emits a positron which travels in tissue for a short distance until it interacts with an electron [42]. The interaction annihilates both electron and positron, producing a pair of gamma photons moving in opposite directions. These are detected by the scintillators of the PET. With this technique 3D images of tracer concentration within the body are created. In modern PET-CT scanners, three dimensional imaging is often paired with images from a CT scanner incorporated in the same device.

**SPECT**

A SPECT scan is primarily used to view how blood flows through arteries and veins in the brain. A gamma-emitting radioisotope is injected to patient’s bloodstream and the emitted gamma rays are detected from a detector. Presence of signal indicates blood flow in the area. Projection images are acquired from different degrees thus a 3d volume of the presence of the isotope can be created.
fMRI measures brain activity by detecting associated changes in blood flow based on the fact that cerebral blood flow is an indication of neuronal activation since when an area in the brain is activated, blood flow to that region increases. The principle of fMRI is similar to MRI with the difference that it takes advantage of the change in magnetization between oxygen-rich and oxygen-poor blood. By measuring the oxygen rich and poor areas a color-coding image of the strength of activation across the brain is created (Figure 36). Although fMRI has good spatial resolution (can localize activity to within millimetres) its temporal resolution is not so good since it has a time window of a few seconds, as it can be also seen of the graph of Figure 34.

EEG / iEEG

Electroencephalography (EEG) is recording the electrical activity of the brain using electrodes placed on patient’s scalp as seen in Figure 39. EEG is a non invasive technique that measures voltage fluctuations produced from ionic current flows that is created by the ion that are pumped in the surface of the neural cells due to the polarization and delpolarixation procedures. This signal is gathered from the electrodes placed on the head of the patient and the activation of the areas are recorded within the neurons of the brain are activated. EEG activity shows oscillations at a variety of frequencies. Several of these oscillations have characteristic frequency ranges and are associated with different states of brain functioning (e.g., waking and the various sleep stages). These oscillations represent synchronized activity over a network of neurons (Figure 36). As it can be seen in the graph of Figure 34 EEG has very good temporal resolution but low spatial due to the fact that the signal
from the neuron is detected over the skull of the patient thus distributed in a much larger area. Solution to this problem was given with the intracranial EEG. In this technique the electrodes are placed in brain surface thus dramatically increasing the spatial resolution of the technique. An obvious disadvantage of this technique is the fact that surgical operation has to be performed and electrodes have to be placed on patient’s brain surface as shown in Figure 38.

**MEG**

MEG maps brain activity by recording magnetic fields produced by electrical currents occurring naturally in the brain, using very sensitive magnetometers (most common are the arrays of superconducting quantum interference (SQUIDs). EEG and MEG signals originate from the same neurophysiological processes but main difference is that magnetic fields are less distorted by the skull and skin than electric fields thus MEG has better spatial resolution of the MEG as seen in the graph of Figure 34. On the other hand due the principal upon which the MEEG is based while EEG detects activity both in the sulci and at the top of the cortical gyri, MEG is most sensitive to activity in sulci. EEG is, therefore able to record activity in more areas of the brain. Additionally activity that is visible in MEG is localized with more accuracy resulting in better spatial resolution.
In Figure 41 a typical CT scan of the brain (image on the left) and a typical MRI scan (image on the right) is shown. From comparing these images the obvious advantage of MRI arises and explains the reason why MRI is the main modality used for brain imaging. As it can be seen the MRI can image the soft tissues of the brain parenchyma with much greater contrast than the CT. The white and gray matter can be clearly differentiated in the MRI image while in the CT there are not visible at all. This consists the main advantage of MRI versus the CT. Due to this MRI is broadly used by the clinicians to image brain cancers as it is more sensitive than CT for small tumours (Figure 31) and offers better visualization of the posterior fossa. It provides very good between grey and white matter giving the ability to diagnose several pathologies CNS such as demyelinating diseases, dementia, cerebrovascular disease, infectious diseases and epilepsy [39].

But MRI does not provided superior image than CT in all cases of tumours. A series of examples were CT is providing very useful information that could not be provided by MRI are presented.

Fat has a low density on CT (~100HU). On MR, fat has a high signal intensity on both T1- and T2. Some tumours can have a high density on CT and thus imaged better. This is typically seen in lymphoma colloid cyst (medulloblastoma) [43].
One advantage of CT over MRI is in the evaluation of intracerebral calcifications. Calcifications are seen in many CNS tumours. On the left are images of a tumour with a small calcification. The calcification is not appreciated on the MR images, but is easily seen on CT. These calcification and the extension of the tumour to the cortex are very typical for an Oligodendroglioma.

On the left are images of a patient with progressive visual loss. On the coronal and sagittal MRI there is a large mass centered around the sella with a broad dural base. This patient was booked for decompression. Only after the CT was performed, was it appreciated how densely calcified this tumour is. It would be impossible to operate this tumour and preserve the patient's vision [43].

Additionally CT scans are very often used in emergency situations due to its much greater speed and lower cost when haemorrhage, stroke, or traumatic brain injury are suspected [44]. It is especially useful in emergency trauma situations, showing any abnormalities in brain structure including brain swelling, or bleeding arising from ruptured aneurysms, hemorrhagic stroke (a ruptured blood vessel), and head injury from car accidents or other types of trauma [35].

One main advantage of MRI is that it doesn’t use ionising radiation in order to operate thus no dose is given to the patient. On the other hand CT exerts an effective radiation dose from 2 to 10 mSv, which is about the same as the average person receives from background radiation in 3 to 5 years [45].

Other major advantages of CT are the facts that is cost about half the price than MRI, it is much faster since a full CT scan is completed within 5 minutes with actual scan time usually less than 30 seconds while depending on what is has to be imaged the scan may be quick (10-15 minutes) or may take a long time (2 hours). Finally, although MRI is much superior in imaging soft tissue it is less detailed on bony structures while CT provides good details about bony structures and is able to image bone, soft tissue and blood vessels all at the same time [45].
Need of Advance Brain Imaging in CT

From the presented data it can be clearly seen that CT although has many advantages as an imaging modality, in the case of brain imaging is lacking of ability to image the tissues in the parenchyma of the brain and brain tumours in early stages. Aim of the presented research is to enable CT to image the soft tissue of the brain since this would provide an extremely powerful tool in the hand of the clinicians witch will combine the advantages of CT with the ability to image soft tissue.

As it has been presented CT due its low cost, high speed and ability to image simultaneously hard and soft tissue is a very often used imaging modality especially in emergency cases. Enabling CT to differentiate brain parenchyma, and thus also tumours in early stage, would greatly increase the chances of detection of many pathologies that are now imaged only with MRI such as CNS such as demyelinating diseases, dementia, cerebrovascular disease, infectious diseases and epilepsy [39], and brain tumours in early stage. There are many cases reported that brain pathologies (e.g. tumours) have been diagnosed from CT scans performed for completely different reasons. An advanced Brain CT Imaging technique could lead in much better monitoring of CNS pathologies.

Main aim of the presented research is to differentiate gray from white matter with X-ray imaging, since it will allow many pathologies to be detected, close the gap with MRI and is a condition that will lead to the visualization of cancer in early stages.
Chapter 2 X-Ray Imaging

Introduction

Short History

From the early 1879 many scientists were interested in the new discovered radiant matter (Cathode rays) by Sir William Crookes. Some of them may have witnessed X-rays normally produced by the Crookes tubes without knowing the existence of it due to destroying photographic plates in their work rooms. Also Prof. Herbert Jackson also noticed in London this effect accidentally, no one of the researchers spend much attention on it except Wilhelm Conrad Röntgen. While working on a Crookes tube in the evening of November 8, 1895, a plate of Barium Platino-Cyanide (fluorescent crystals) on a table six feet away in his workroom glowed when he activated the tube. Even after covering the tube with black cardboard it kept glowing. Röntgen named this strange phenomena X-Rays. In the next experiments he used a photographic plate and made his first X-Ray picture, the hand of his wife Anna Bertha [46].

The discovery was announced by Röntgen on December 28, 1895 [47], with a report titled “On a New Kind of Rays”, including the first x-ray image in history of Roentgen's wife hand that was take with an exposure of more than 30 minutes (Figure 45). These rays were generated when high energy electrons were suddenly stopped by striking a metal target inside a vacuum tube – the X-ray tube. It was subsequently shown that X-rays are an electromagnetic radiation, just like light, heat and radiowaves [48]. The new invention immediately proved its usefulness as a diagnostic and therapeutic tool in medicine since physicians good have for the first time an inside look of patients body non-invasively. Since the x-rays played a crucial role in science and industry. X-rays have played a key role in the research of quantum mechanics, crystallography and cosmology. Most significant contribution of x-rays has been in medicine since disciplines have been developed such as radiobiology, diagnostic radiology, radiotherapy and radiation protection.
**Basic properties**

X-rays is a form of electromagnetic radiation with a wavelength shorter than those of UV rays and typically longer than those of gamma rays (Figure 46). In many languages, X-radiation is referred to with terms meaning Röntgen radiation, after Wilhelm Röntgen.

![Figure 46 - The electromagnetic Spectrum](image)

The wavelength lambda (λ) of electromagnetic radiation is expressed in m, cm, mm, micrometer (μm), nanometer (nm) and Ångstrom (1 Å = 0.1 nm).

X-rays have the following properties:

- Invisibility; they cannot be perceived by the senses
- Travel in straight lines and at the speed of light
- They cannot be deflected by means of a lens or prism, although their path can be bent (diffracted) by a crystalline grid
- They can pass through matter and are partly absorbed in transmission.
- They are ionising, that is, they liberate electrons in matter
- They can impair or destroy living cells

Radiation hardness (beam quality) depends on wavelength. Radiation is called hard when its wavelength is small and soft when its wavelength is long. The beam quality is related to a tube voltage (kV) range, or keV for isotopes [48].

The first two columns of Table 6 below indicate the relationship hardness/tube voltage range. The third column gives the related qualification of the radiation effect,
i.e. half-value thickness (HVT), (the thickness of a particular material necessary to reduce the intensity of a monochromatic beam by half, depends on the hardness of the radiation).

Table 6 - Values of radiation hardness against tube voltage

<table>
<thead>
<tr>
<th>Radiation quality</th>
<th>Tube voltage</th>
<th>Global half-value thickness for steel (mm)</th>
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<tbody>
<tr>
<td>Very soft</td>
<td>Less than 20 kV</td>
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<tr>
<td>Soft</td>
<td>20 – 60 kV</td>
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<tr>
<td>Fairly soft</td>
<td>60 – 150 kV</td>
<td>0.5 – 2</td>
</tr>
<tr>
<td>Hard</td>
<td>150 – 300 kV</td>
<td>2 – 7</td>
</tr>
<tr>
<td>Very hard</td>
<td>300 – 3000 kV</td>
<td>7 – 20</td>
</tr>
<tr>
<td>Ultra hard</td>
<td>meer dan 3000 kV</td>
<td>&gt; 20</td>
</tr>
</tbody>
</table>
X-ray production

X-rays are produced generally by either x-ray tubes or synchrotron radiation. In an x-ray tube, x-rays are generated when a focused electron beam accelerated across a high voltage field bombards a stationary or rotating solid target. As electrons collide with atoms in the target and slow down, a continuous spectrum of x-rays are emitted, which are termed Bremsstrahlung radiation. The high energy electrons also eject inner shell electrons in atoms through the ionization process. When a free electron fills the shell, a x-ray photon with energy characteristic of the target material is emitted. Common targets used in x-ray tubes include Cu and Mo. In recent years synchrotron facilities have become widely used as preferred sources for x-ray diffraction measurements. Synchrotron radiation is emitted by electrons or positrons travelling at near light speed in a circular storage ring. These powerful sources, which are thousands to millions of times more intense than laboratory x-ray tubes, have become indispensable tools for a wide range of structural investigations and brought advances in numerous fields of science and technology.

X-rays result from the conversion of the kinetic energy attained by electrons accelerated under a potential difference (the magnitude of which is termed voltage with units of volts (V)) into electromagnetic radiation, as a result of collisional and radiative interactions. An x-ray tube and x-ray generator are the necessary components for x-ray production and control. The x-ray tube provides the proper environment and components to produce x-rays, whereas the x-ray generator provides the source of electrical voltage and user controls to energize the x-ray tube. [49]Basic components of an x-ray system are illustrated in Figure 47.

X-Ray Generator

X-ray generators supply the electrical power to the x-ray tube and provide selection of the technique parameters. Control of x-ray energy and quantity is attained through adjustments of the voltage potential in kilovolts (kV), the x-ray tube current in mill amperes (mA), and the exposure time in seconds (s), which are user-adjusted at the x-ray generator console.

![Figure 47 - Schematic of an X-Ray system](image-url)
X-Ray Tube

In Figure 48 is depicted an early English tube that has a length of about 50 cm with a simple tiny rod cathode and a heavy metal anode. The blue glass seals and platinum connections indicate a production date late 1800, so it is possibly an experimental tube from the time that the X-Rays were invented. [46]

![Figure 48 - Early English tube with a simple tiny rod cathode and a heavy metal anode.](image)

**Basic Principle**

The X-ray tube (Figure 49) consists of a glass or ceramic envelope containing a positive electrode (the anode) and a negative electrode (the cathode) evacuated to an ultra high vacuum \([10^{-9} \text{ hPa}]\). Depending on the material of the envelope a first separation of tube types is created which will be analysed later.

The cathode comprises a filament that generates electrons. Under the effect of the electrical voltage set up between the anode and the cathode (the tube voltage) the electrons from the cathode are attracted to the anode, which accelerates their speed. This stream of electrons is concentrated into a beam by a “cylinder” or “focusing cup” (Figure 50). When the accelerated electrons collide with a target on the anode, part of their energy is converted to X-radiation.

X-rays result from the conversion of the kinetic energy attained by the accelerated electrons into electromagnetic radiation, as a result of collisional and radiative interactions.

To produce x-rays, a specific sequence of events is required which can be grouped in 3 steps.
1st step of X-ray generation

The first step for x-ray production requires free electrons to be available in the evacuated environment of the x-ray tube which are produced the cathode filament in the focusing up. The material that is mostly used for the filament is thoriated tungsten wire. Tungsten is used due to its high melting point (3410 °C) and it does not vaporize easily. Other materials used are rhenium (3170 °C) and molybdenum (2620 °C) [50].

2nd step of X-ray generation

The second step involves the application of a high voltage supplied by the x-ray generator to the cathode and anode. Upon activation, electrons are immediately accelerated to the electrically positive anode along a path determined by the filament and focusing cup geometry. Continuous electron emission continues from the filament surface at a rate dependent on the filament temperature (i.e., the filament current) during the exposure. Tube current, defined as the number of electrons traveling between the electrodes, is expressed in milliampere (mA) units, where 1 A is equal to 6.24 x 10¹⁸ electrons/s and 1 mA = 6.24 x 10¹⁵ electrons/s.

Each electron attains a kinetic energy (in keV) equal to the applied tube voltage. Thus, the tube voltage (kV), tube current (mA), and exposure duration (s) are user-selectable parameters for x-ray production. Often, the combination of tube current and exposure time in milliampere-seconds (mAs) is provided as part of the technique or protocol.

3rd step of X-ray generation

Step 3 of the x-ray production, occurs when the highly energetic electrons interact with the x-ray tube anode (also known as the target). The target is generally made of tungsten. Not only because it has a high atomic number (W, Z= 74), but also because of its high melting point (approx. 3400°C). A tungsten anode can handle substantial heat deposition without cracking or pitting of its surface. Other materials used are molybdenum (Mo, Z=42) and rhodium (Rh, Z=45). It is essential to use a material with a high melting point because of the substantial amount of heat dissipated as the electron-“bombardment” is concentrated (focused) on a very small surface.

In rare (0.5% or 5/1,000) events, an electron comes in close proximity to the nucleus of a target atom and experiences attractive forces due to the positive charge.
of the protons in the nucleus. This combined positive charge decelerates and changes direction of the electron, the magnitude of which strongly depends on the impact parameter distance. Kinetic energy lost is converted to electromagnetic radiation with equivalent energy in a process known as bremsstrahlung (a German term meaning “braking radiation”), as shown in Figure 51. Closer interactions with the nucleus cause a greater deceleration and result in higher x-ray photon energy, but the probability decreases as the interaction distance decreases. In extremely rare instances, the incident electron gives up all of its kinetic energy when stopped by the nucleus, producing the maximum x-ray energy possible. The output is a continuous spectrum of x-ray energies with maximum x-ray energy (in keV) determined by the peak potential difference (in kVp). A larger number of low energy x-rays are produced in the output spectrum, simply due to the lower probability of interaction closer to the nucleus (dartboard analogy). Lower energy x-rays are more easily attenuated (filtered) from the beam exiting the x-ray tube port, and the measured spectrum peaks at intermediate energy and goes back to zero at the lowest x-ray energies, as shown in Figure 52 for several spectra produced with different acceleration voltages. The average x-ray energy in a typical x-ray spectrum is about one-third to one-half peak energy, dependent on the amount of filtration placed in the beam.

Another possible interaction of incident electrons with the target is the removal of inner shell electrons from the tungsten atom. For tungsten, binding energies of the K, L, and M shells are 69.5, 11.5, and 2.5 keV, respectively. A highly energetic incident electron can interact with and remove a K-shell electron and eject it. Because the atom is now energetically unstable, electrons from adjacent (the L shell) will readily transition and fill the K-shell vacancy, as shown in Figure 51, event number 4, depicting the creation of characteristic radiation. As a result, a discrete energy x-ray photon is created with energy equal to the difference in binding energies. For instance, an L-to-
K electron transition produces a characteristic x-ray of 69.5–11.5 =57.0 keV. Since each element has different electron binding energies, the emitted x-ray energies are characteristic of the element. These characteristic x-rays generate the monoenergetic spikes added to the continuous spectrum, as seen in Figure 52.

**The Anode**

Since only a part of approximately 1% of the kinetic energy of the electrons is converted into X-radiation and the remainder is transformed into heat it is crucial to use a material with high melting point because of the substantial amount of heat dissipated as the electron-“bombardment” is concentrated (focused) on a very small surface. As it was mentioned previously the target is generally made of tungsten. Not only because it has a high atomic number (W, Z= 74), but also because of its high melting point (approx. 3400°C).

Two major anode designs include a simple, fixed geometry or a more elaborate, rotating configuration as shown Figure 53 and Figure 54. The simplest type of x-ray tube has a stationary anode. It consist of a tungsten insert embedded in a copper block. The copper serves a dual role: it supports the tungsten target, and it removes heat efficiently from the tungsten target. The drawback is that the small target area limits the heat dissipation rate and consequently limits the maximum tube current and thus the x-ray flux.

The most widely used anode, especially in medical imaging systems is the rotating anode, it is constructed by the target material (in this case tungsten) positioned in a track (focal track), and molybdenum is surrounding the target area which except from supporting the target material it also assists in the dissipation of the heat. The molybdenum disk is then mounted on a graphite layer which also assists in dissipating the heat. The advantages of the rotating anode is that it provides greater target area and greater heat dissipation. It provides the ability to attain greater exposure load [51]. Except from tungsten and 10% rhenium + 90% tungsten alloys are used along with new anode materials with higher heat storage capacity have been tested such as:

- Rhenium + tungsten (+ titanium + zirconium + molybdenum)
- (Rhenium + tungsten) + (Molybdenum) + graphite
- (Rhenium + tungsten) + CVD Graphite base
Cooling the anode

The heat which accompanies the production of X-radiation is quite considerable, so that the anode has to be cooled. This can be done in a variety of ways:

- by natural radiation
- by convection
- by forced circulation of liquid or gas
- by conduction

Build-up of heat energy is the major limit to instantaneous x-ray production and x-ray tube longevity (the latter by focal track scarring or rotor-bearing failure). Continuous x-ray production depends on heat dissipation by the anode assembly and tube housing.

The focal spot

The area of the target which is struck by the electrons (Figure 55) is called the focal spot or “the focus”. It is essential that this area is sufficiently large to avoid local overheating, which might damage the anode.

From the radiographic point of view, however, the focus has to be as small as possible in order to achieve maximum sharpness in the radiographic image. Effective focal spot size is the projections of the focal spot on a surface perpendicular to the axis of the beam of X-rays (number 3 in Figure 55).

The effective focus size has to be as small as possible in order to avoid geometric distortion (blurriness) and achieve maximum sharpness in the radiographic image. The effect of focus size in radiographic image is shown in Figure 56.

Collimator

Collimators adjust the size and shape of the x-ray field emerging from the tube port. The typical collimator assembly is attached to the tube housing at the tube port. A collimator assembly, is constructed with movable lead shutters, is situated adjacent to the x-ray tube output port to define the x-ray beam shape.
Synchrotron radiation

Synchrotrons are circular (ring shaped) construction that are able to produce very bright (high intensity) and very wide range of electromagnetic radiation. The basic principle of operation is the acceleration of electron in a ring shaped vacuum tube, using electromagnetic field. The high speed electron beam is forced to change direction using magnets thus the electrons are emitting electromagnetic radiation. A schematic of a synchrotron can be seen in Figure 57. Electrons are entering to the ring already accelerated using a linear accelerator, once inside the synchrotrons they can be further accelerated (thus acquiring more energy) by the application of radio frequency electric fields. At certain points (where the rings has to turn) a bending magnet is placed. Bending magnets force the electrons to change their direction and as a result they emit electromagnetic radiation. This however is not the only way that electromagnetic radiation is generated in a synchrotron facility, new generation synchrotrons use undulators which are able to produce much brighter x-ray beams than bending magnets. In an undulator there are a series of dipole magnets placed in determined distance ($\lambda$) in arrays. When the electrons are passing through this high alternating magnetic field are force to oscillate and thus they are emitting x-ray radiation. The beam resulting from an undulator is highly polarized and it can be controlled depending on the magnet structure, from linear to circular (Figure 58).

Synchrotrons can produce a very broad energy range from infrared to hard x-rays. The main advantage of synchrotrons is that they can produce very "high quality" beams in terms of: very high intensity (bright sources), many order of magnitude greater than convention x-ray sources, very board and continuous spectrums (and monochromatic beams), highly collimated beams and highly polarized beams.

Figure 57 - Schematic view of a Synchrotron Radiation [apo anthi (Mobillo and Balerna 2003)]

Figure 58 - Undulator and resulting x-ray polarization
When a x-ray photon interacts with an atom in the absorption process, part of its energy is converted into kinetic energy of high-speed charge particles (electrons or positrons), and another part may be radiated from the absorber as scattered x-ray, this is the absorption process. The scattered x-ray has different energy and direction of propagation, depending on the interaction type. In general there three possible case when a X-ray beam enter an object as seen in figure, to penetrate the object without interacting, to be completely absorbed and deposit its energy or to interact with the matter in a way that is deposited part of its energy and get scattered (deflected) from its original direction) [52].

There are four x-ray matter interaction processes:

1. Coherent scattering, will be analytically presented later.
2. Compton scattering, will be analytically presented later.
3. Photoelectric absorption, will be analytically presented later.
4. Pair production process, in this interaction the incoming x-ray photon interacts with the nucleus in such a manner that its energy is converted into matter. The interaction produces a pair of particles, an electron and a positively charged positron. These two particles have the same mass, each equivalent to a rest mass energy of 0.51 MeV. This interaction can occur only with photons with energies greater than 1.02 MeV and is not encountered in diagnostic imaging, thus is will not be analytically presented.

The three last interactions produce high energy electrons and positrons and thus constitute energy transport and dose deposition in the absorber (human body in case of medical imaging) [53].

Each of the interaction process has different probabilities to occur depending on the photon energy and atomic number of the absorber. In Error! Reference source not found. a graph depicting the probability of each process is shown.
Photon interactions

Coherent scattering has higher probability at low photon energies in material with high atomic number, it is generally not significant in most diagnostic imaging procedures [53].

There are three main steps in coherent scatter.

1. An incoming x-ray photon with low energy, less than 10 keV, interacts with an outer orbital bound atomic electron thus enabling the atom as a whole to take up the recoil.

2. Due to the great mass of the atom the interaction take place in the electrostatic field of the electron and the electric vector of the incoming photon [53]. The tightly bound electron absorbs all the energy of the photon. The incoming x-ray photon no longer exists after transferring its energy and as a result the electron is excited.

3. The exited electron gives off the excess energy and thus releasing an electromagnetic waves (x-ray photon) of the same energy and frequency as the incoming one but in any possible direction resulting being different than the one of the original incoming x-ray photon. This is the only interaction within the matter in which no energy is deposited in the scattering medium and no ionization occurs.
Compton Scattering

Compton scattering is the most dominant interaction mechanism in tissues. In Compton scattering only a portion of the energy of the photon is absorbed while the photon is deflected from its initial direction. There are three main steps in Compton scatter.

1. An incoming x-ray photon of higher energy, thus shorter wavelength, that binding energy of the electrons in the atoms becomes less significant [53], interacts with an outer orbital electron. Due to the shorter wavelength, coherence between different scattering centres is lost.

2. When the binding energy is sufficiently smaller than the photon, the recoil energy is taken by an individual photon [53]. The incoming photon knocks the orbital electron out of its orbit (becoming a recoil electron). The recoil electron loses energy as heat or creates bremsstrahlung radiation within the object being imaged [53]. The energy transferred to the electron can vary from zero to a large fraction of incoming photon's energy [4].

3. The x-ray photon is deflected in a different direction with less energy (determined by subtracting the binding energy of the orbital electron). The higher the energy of the incoming x-ray photon, the smaller the angle of deflection (meaning that the x-ray photon will continue closer to its original path).

The energy of the scattered photon is given by the equation:

\[ h\nu_{sc,ph} = h\nu_{ph} \frac{1}{1 + \alpha(1 - \cos \theta)} \]

while the energy of the Compton electron is given by the equation:

\[ E_{el} = h\nu_{ph} \frac{\alpha(1 - \cos \theta)}{1 + \alpha(1 - \cos \theta)} \]

Where \( h\nu_{sc,ph} \) and \( h\nu_{ph} \) is the energy of the scattered and incoming photon respectively, \( \theta \) is the angle of the scattered photon and \( \alpha = \frac{hv_{ph}}{m_0 c^2} \), \( m_0 c^2 \) is the rest energy of the electron.

The probability of Compton scattering is independent of the atomic number, inversely proportional to the energy of the photon and directly proportional to the number of electron per
gram (lightest to heaviest elements have only 20% difference). For low-energy photons, when the scattering interaction takes place, little energy is transferred to the patient.

**Photoelectric Absorption**

The photoelectric process occurs when a photon collides with an atom, resulting in the full photon’s absorption and the ejection of a bound electron. There are three main steps in photoelectric effect.

1. A high energy incoming x-ray photon knocks out an orbital electron (diagrams show K shell electron being knocked out). The interaction takes place in the inner orbits of the atom. The energy of the x-ray photon must be equal to or greater than the binding energy of the orbital electron.

2. The electron knocked out of its orbit is called a photoelectron. The electron is ejected from the atom by this energy and begins to travel in the surrounding matter. The electron quickly loses its energy and moves only a short distance. This loss of energy is translated as a dose deposit in the matter thus the photon's energy is, therefore, deposited in the matter. The energy of the photoelectron is given by the equation:

\[ E_{el} = h\nu_{ph} - E_{bind} \]

Where \( E_{el} \) is the energy of the photoelectron, \( h\nu_{ph} \) is the energy of the incoming photon and \( E_{bind} \) is the binding energy of the electron in its original cell.

3. Due to the ejection of the photoelectron the atom is excited with an empty orbital electron. The electrons from other orbitals will jump the shells (i.e. L shell to K shell or M shell to K shell, etc.) and produce fluorescent photons of characteristic energy. This cascade of electrons continues until the atom has filled all its empty shells. Fluorescence, in general, is a process in which some of the energy of a photon is used to create a second photon of less energy. This process sometimes converts x-rays into light photons. Whether the fluorescent radiation is in the form of light or x-ray depends on the binding energy levels in the absorbing material [52].

The photoelectric effect is dominant interaction in relatively low energies and in materials with high atomic number. The probability of is given roughly by the equation:
\[
\tau \propto \frac{Z^n}{(hv)^3}
\]

Where \(\tau\) is the probability of photoelectric effect, \(Z\) is the atomic number of the matter, \(n\) is a exponential variable (varies between 3 and 4 for gamma rays).

**Attenuation coefficients**

As a photon travels through matter, we cannot precisely predict how far it will travel before it interacts or what interaction will undergo. In clinical applications we are generally not concerned about what will happen to an individual photon but with the overall interaction of the photon beam. In particular we are interested in the overall rate of interaction through the tissue since this will show us the dose that will be deposited to the patient and also define the quality of the resulting image.

**Linear attenuation coefficient**

The probability of a photon to travel a given distance \(x\) in absorber without interacting is the product of the probabilities of survival for each particular type of interaction. The probability of traveling a thickness \(x\) of absorber without a Compton collision is \(e^{-\Sigma_{\text{comp}}x}\), where \(\Sigma_{\text{comp}}\) is the total linear attenuation coefficient (probability) of Compton effect.

In Figure 66 an illustration of the linear attenuation coefficient if done in order to be better understood. A photon beam consisted of 100 photons encounters a slice of material that is 1 unit thick. Some of the photons interact with the material, and some pass on through. The interactions, can be any of the afore mentioned interactions and as a result absorb or deflect some of the photons from the beam in a process known as attenuation. The linear attenuation coefficient \(\mu\) is the fraction of photons interacting per 1-unit thickness of the material. In the example of Figure 66 this fraction that interacts in the 1-cm thickness is 0.1, or 10%, and the value of the linear attenuation coefficient is 0.1/cm.

In terms of intensity \((I)\) linear attenuation coefficient is equal to:

\[
I = I_0 e^{\mu_{\text{comp}}} e^{\mu_{\text{photo}}} e^{\mu_{\text{coh}}} e^{\mu_{\text{pp}}}
\]
Where \( I_0 \) is the initial intensity of the x-ray beam, \( \mu_{\text{comp}} \) is the attenuation due to Compton effect, \( \mu_{\text{comp}} \) due to photoelectric effect, \( \mu_{\text{coh}} \) due to coherent absorption and \( \mu_{\text{pp}} \) due to pair production. \( \mu \) has dimensions of cm\(^{-1}\).

In terms of incident (\( N_0 \)) and transmitted photos (\( N \)) linear attenuation coefficient is equal to:

\[
N = N_0 e^{\mu_{\text{comp}}} e^{\mu_{\text{photo}}} e^{\mu_{\text{coh}}} e^{\mu_{\text{pp}}}
\]

The relation between intensity and number of photon is given by:

\[
\text{Intensity} = \text{photon energy} \times \text{flux}
\]

\[
\text{flux} = \frac{\text{photons}}{\text{cm}^2 \text{sec}}
\]

Thus:

\[
\text{Intensity} = \frac{h v \times \#\text{photons}}{\text{Area} \times \text{Time}} = \frac{\text{MeV}}{\text{cm}^2 \text{sec}}
\]

In Figure 67 the total and the partial interaction coefficients for a low Z (water) and high Z (gold) materials is shown.

As it can be seen from Figure 67 at very low energies absorption by photoelectric effect predominates decreasing rapidly with increasing the energy. As it decreases, absorption by Compton Effect becomes more important until energies slightly less than 1 MeV almost all the absorption is by Compton Effect. At energies about 1 MeV absorption pair production starts and continues to increase, while the other effects decrease [53].
Mass attenuation coefficient

The linear attenuation coefficient is dependent on the density of the material. This dependence can be overcome by normalizing the linear attenuation coefficient for the density. This normalization term is called mass attenuation coefficient, $\mu_m$ [53]. In Figure 68 two pieces of material with different thicknesses and densities but the same area mass are compared. Since both attenuate the same fraction of photons, the mass attenuation coefficient is the same for the two materials even though they do not have the same linear attenuation coefficient values.

Relationship between mass attenuation and linear attenuation coefficient is:

$$\mu_m \left( \frac{cm^2}{g\cdot cm} \right) = \frac{\mu_{lin} \left( cm^{-1} \right)}{\rho \left( \frac{g}{cm^3} \right)}$$
X-Ray detectors

In order for an x-ray image to be created the x-ray beams that have passed through the imaged object (or human body in case of medical imaging) have to be captured. In the beginning of X-ray imaging, and still in use until now in many clinical application, radiation sensitive films were used, placed on the opposite side of the x-ray source in order to interact with the x-ray beam and create the x-ray image. Since then digital detectors have replaced screen-film radiography in many medical applications. Aim of the digital detectors is to translate the absorbed x-ray energy into electrical charges, which can then be recorded and quantified in gray scale representing the amount of x-ray photons (energy) was absorbed.

Computed Radiography (CR)

First digital x-ray images were created using a phosphor cassette plates in 1980 [54]. After that another solution was with the Computed Radiography (CR) systems. In CR a phosphor plate were used that were exposed to x-ray radiation. The molecules of phosphor after interacting with the x-ray where excited. Number of elevating electrons is proportional to the amount of radiant energy absorbed. This is creating a latent image in the phosphor plate, the plates were then stimulated using a laser beam which excited further the electrons making them to return in their ground state emitting a 300-500nm (blue) light which was then captured and recorded. After reading the plate visible light was used to erase the plate and prepare it to be reused.

Direct Radiography (DR)

In Direct Radiography (DR) the detector translates the incoming x-ray beam into electrical signals without the use intermediate storage or latent image. The term DR system, frequently used in medical imaging systems, must not be confused with digital radiography since digital radiography includes bot CR and DR systems. There are 2 main categories of DR detectors based on the method by which they convert the x-ray beam into electrical charge.

- Indirect Conversion, where the incident c-ray beam is converted to visible light using a scintillator and then to electrical charge.
- Direct Conversion, where the incident x-ray beam is directly converted into electrical charge.
A graphical representation of the basic principles of operation of direct and indirect systems is given in Figure 70. In this case TFT arrays are used in order to read the electrical charges other techniques can be used for this purpose as it will be presented.

**Indirect Conversion**

There are 2 major types of indirect detectors based the technology used for reading the visible photons created by the scintillation, the CCD and TFT detectors. In both types the principle is the same, x-ray photons interact with the scintillator, most commonly cesium iodide CsI or phosphor Gd2O2S, they are converted into visible photons and the photons are recorder and converted into electric signals.

CsI has advantages due to its absorption characteristics and the ability to be grown in to dense needle like crystals (5-10 μm in diameter) [55] opposed to the dispersed powder phosphor the fluorescent light generated by X-ray absorption can be guided fiber-optically to the photodetector array without much lateral dispersion, and thus higher spatial resolution of the detector. The packing density of scintillation sites in CsI is also high due to its crystalline structure, while on the other hand powder layers consists of only about 60% phosphor and 40% binder. As a result the absorption efficiency of structured CsI is about four times higher than that of a powder phosphor.
Charge-Coupled Devices (CCD) are light sensitive detectors made by an array of coupled capacitors. Each photo detector generates an electric charge that is proportional to the amount of light striking it, and this charge is stored until it is read-out by the switching control circuit. In order to create a detector a series of the CCD chip are combined to increase the detection area. The CCD systems can be either lens-coupled or slot-scan. In the lens couples CCD system a large number of CCD are combined into an array similar to flat-panel detectors. Then optical lenses are used to reduce the lateral dispersion of the visible light and focus it on the detectors (Figure 72). A drawback of this design is that the photons reaching the detector is lower and thus the signal to noise relation is decreasing.

Slot-scan CCD systems were the x-ray beam after its generation in the source is collimated using plated of led in very thin fan beams. The patients are scanned with the beam, as presented in the previous chapter, and the slot detector is opposite of the source collecting the fan beam. This setup of thin fan beam and slam slot detectors reduces the noise due to scattering in the image, and as a result a lower noise image is created [55]. The needed exposure is about 20 msec and the time to read the data (read out) is about 1.3 seconds readout process takes about 1.3 seconds [54].
Flat Panel (TFT) Indirect Detectors

In the Flat Panel Detector (FPD) the visible light from the scintillator layer, as presented earlier, are recorded by array of photodiodes from amorphous silicon and converted to electrical charges which are then read by a TFT array. Each sensor element consists of a photodiode and a TFT both of which are made of amorphous silicon on a single glass substrate. The TFT/photodiode matrix is normally scanned progressively, one line at a time from top to bottom. A major advantage of the TFT is that the speed is very high resulting in a real time process.

The combination of CsI (very good absorption of X-rays) and a-Si (good conversion of visible photons to charge carriers) provide FPDs with high Detective Quantum Efficiency DQE. A high DQE means images can be acquired with either superior quality or the same quality at a lower dose.

Direct Conversion

In direct conversion the x-ray photons are converted directly to electrical charges. This is done using photoconducting materials such as amorphous selenium, lead iodide, lead oxide, thallium bromide, and gadolinium compound [3]. In order for the photoconductor to operate a voltage of 5,000 V has to be applied. This is done using a surface electrode, so that the charge produced can be attracted to the pixel electrodes. The lack of the intermediate scintillation layer (in comparison with an indirect FPD) leads to the fact that direct FPDs exhibit exceptional spatial resolution and DQE [5].

There are many parameters in order to compare between detectors and measure its efficiency and quality. The most important ones are listed and shortly explained below.
- **Pixel size**, is the size of the pixel of the detector, as smaller is the pixel size, the higher the resolution and the more crisp the image will be.

- **Spatial resolution**, is the ability of the detector to discriminate two object that are very close as to different entities.

- **Dynamic range**, is a measure of the signal response of a detector that is exposed to x-rays [6]. It describes the range of the x-ray beams that the detector can receive and record. Higher and linear dynamic range (which a characteristic of digital detectors) allow better appearance of structures that have close attenuation coefficient and the same time materials with great difference in their attenuation coefficient in one image.

- **Modulation Transfer Function (MTF)**, is the capacity of the detector to transfer the modulation of the input signal at a given spatial frequency to its output [56]. In other words I the ability of the detector to convert the contrast of the tissue in the equal gray scale contrast in the image. MTF is a useful measure of true or effective resolution, since it accounts for the amount of blur and contrast over a range of spatial frequencies [54].

- **Detective Quantum Efficiency (DQE)**, Dynamic range is a measure of the signal response of a detector that is exposed to x-rays [56]. It is the ability of the detector to translate the incident energy into electrical signal. Show the amount of energy that has been captured and translated in to electric signal to the total energy that reached the detector. A detector high with DQE can produce high quality images with less dose.
Radiation dose and units

Radiation Units

Until 1978 the “International Commission of Radiation Units and Measurements” (ICRU) used the conventional radiation units of roentgen (R), rad (rd), and curie (Ci). Since 1978 the ICRU has recommended the use of the international system units (SI) with special new units as shown in Error! Reference source not found.

Table 7 - Relationships of new and old units

<table>
<thead>
<tr>
<th>Designation of quantity</th>
<th>SI-units</th>
<th>Formerly used</th>
<th>Conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activity (A)</td>
<td>Becquerel (Bq)</td>
<td>1/s⁺</td>
<td>Curie (Ci)</td>
</tr>
<tr>
<td>Ionization dose rate</td>
<td>Coulomb (C)</td>
<td>C/kg</td>
<td>Röntgen (R)</td>
</tr>
<tr>
<td>Ionization dose</td>
<td>Coulomb (C)</td>
<td>C/kg.s or A/kg</td>
<td>R/s</td>
</tr>
<tr>
<td>Absorbed energy dose (D)</td>
<td>Gray (Gy)</td>
<td>J/kg</td>
<td>Rad</td>
</tr>
<tr>
<td>Equivalent dose (H)</td>
<td>Sievert (Sv)</td>
<td>J/kg</td>
<td>Rem</td>
</tr>
</tbody>
</table>

Table: Overview of new and old units
* disintegrations per second
** RBE = Relative Biological Effect

Figure 76 shows how energy is transferred from a photon beam to medium. First, a photon interacts with an atom creating one or more free moving electrons (point a). The free moving electrons transfer their energy to the medium though excitation and ionisation (point b). At this point we have photon energy given to the electron in the form of kinetic energy. This kinetic energy is in turn pass is the medium through small collision that the electrons performs along his path in the medium. The transfer of energy at (a) is called kerma and along (b) is called absorbed dose. The possible interaction are shown in Figure 76 are: photon hv' is scattered from (a), hv'' is bremsstrahlung resulting from a collision between the electron and nucleus. The δ ray is another electron track resulting from a relatively violent electron-electron collision.
**Kerma**

The quality kerma (K) has been introduced by the ICRU:

\[
K = \frac{d E}{dm} \left[ \frac{\text{energy}}{\text{mass}} \right]
\]

\(d E\) is the average kinetic energy transferred from photons to electrons in a volume element with mass in gm. The units of kerma are joules/kg.

For a monoenergetic beam of photons with energy \(h \nu\) and photon fluence \(\Phi\), the kerma is:

\[
K = \Phi \times \left( \frac{\mu}{\rho} \right) \times \bar{E}_{tr}
\]

\((\mu/\rho)\) mass attenuation coefficient of the medium.

In case of a spectrum of photon beam the kerma is given by

\[
K = \int_0^{h \nu_{\text{max}}} \frac{d \Phi(h \nu)}{d h \nu} \times \left( \frac{\mu(h \nu)}{\rho} \right) \times \bar{E}(h \nu)_{tr} \, d h \nu
\]

**Radioactivity**

The activity of a radioactive source of radiation (isotope) is equal to the number of disintegrations per second. The SI-unit is the Becquerel (Bq) and is equal to 1 disintegration per second. The Becquerel is too small a unit to be used in industrial radiography. Source strengths are, therefore, quoted in Giga Becquerel (GBq). 1 Curie = 37 GBq.

**Ionisation dose rate**

The output of an X-ray set or isotope per unit of time is generally quoted at one metre distance from the source, and designated in C/kg.s.
**Ionisation dose**

The ionising effect of radiation in one kilogram of dry air is used to define the ionisation dose. The dose of radiation delivered is equal to the ionisation dose rate multiplied by the amount of time during which radiation takes place.

The designation used is C.kg.

The output of an X-ray set, however, is quoted in Sievert per hour, measured at 1 metre distance.

**Absorbed energy dose**

The radiation energy that is absorbed is expressed in Joules per kilogram (J/kg). The SI-unit is called Gray (Gy) whereby 1 J/kg = 1 Gy. It is the mean energy exerted (ε) per unit mass (of any material) to an infinitesimal volume:

\[
D = \lim_{V \to 0} \frac{\varepsilon}{\rho V}
\]

where \( \rho \) is the density of the medium in volume \( V \).

**Equivalent dose (man dose)**

The Sievert (Sv) is the SI-unit for the biological effect of ionising radiation upon man. It corresponds with the product of the absorbed energy dose gray (Gy) with a factor that has been experimentally determined and that indicates the relative biological effect (RBE) of the ionising radiation. For X-ray this factor is equal to one, so that the Sievert is equal to the Gray.
CT Imaging

CT Principles

The main principles of operation and x-ray physics behind CT imaging have already been presented in chapter 1. A more detailed explanation of the CT scanning procedure will be presented here by presenting the evolution of CT scanners.

The first modern CT scanner was developed by Godfrey Hounsfield in 1967 in his lab and after the verification of his theory the first clinical CT scanner was build and installed in 1971 at Atkinson-Morley Hospital in England [57]. In this first generation CT scanner a pencil beam was used and an x-ray detector was located on the other side of the object. The detector and source were performing a transverse scan through the imaged slice and then the tube-detector assembly were rotated at a step of 1 degree and the same scanning procedure was repeated to collect 180 different views over 180°. The scanning procedure with this generation of scanners was very slow taking minutes for one projection.

Second generation scanners, appeared in 1974, the source was emitting beams in a larger angle creating a narrow fan beam of around 10° and about 20 or more detectors were collecting the bam simultaneously. The same design of the first scanner of translation and rotation was still used. Due to the fact that the line profile collected by each detector is slightly tiled multiple parallel scanners at different angles would be captured in one translation. In the example of Figure 79 3 projection at 3 different angles could be acquired per each translation. This set-up dramatically decrease the time of scan making the slice scan time to go down to 20s. This also had a major impact on the quality of the produced image since a slice scan could be produced within a breath hold of the patient significantly reducing motion artefacts[57].
Third generation scanners appeared during 1975, in this generation the x-ray fan beam was much wider and an array of high spatial resolution detectors, able to measure the fan beam projection of the entire patient cross section were used. Since the whole cross section of the patient is measured at once no translational movement is needed thus only ration of the tube-detectors assembly around the patient is done. This tube – detector motion is referred to as rotation-rotation. With this generation the scanning time increased even more needing half a second for a slice scan. In order for the system to perform, a very high detector stability and matching response of all the elements had to be achieved. Additionally very could calibration of the detector tube assemble has to be done and to be very rigidly linked together (mechanically most of the cases). If there is a miss calibration then a ring artefact appears in the image were the line of the miss calibrated detector intersects with the rest. In this generation collimators were used in each of the detector element of the line detector in order to eliminate the scatter of the beam and thus increasing the image quality by reducing noise.

Fourth generation scanners appeared on 1976, in these scanners a ring of detectors was used. Only the tube was rotating producing a fan beam. Scanning time was further decreases with this technique. Since the detectors are stationary and any detector can measure any distance from the centre of rotation the ring artefact was eliminated with this generation. In order to achieve good resolution a huge number of detector had to be used (up to 4800) but only ¼ of them were used at any point during scanning. Additionally the dose efficiency of these scanners was low due to geometry limitation (minimum distance of tube and skin) and detector size limitation. Finally the anti scatter septa of the 3rd generation CT could not be used in these scanners. In other design of the scanners the Tube could be outside of the detector ring and a tilted slice would be captured.
In 5th generation scanners the x-ray tube is not a moving tube but a ring that circles the patient opposite to the detector ring. A flying electron beam, steered electromagnetically in order to hit the anode strips that were placed in a ring around the patient. This designed has no moving parts resulting in a very fast scanning time, of the range of 50 milliseconds per slice resulting gin 17 CT slices/second. This design was build and mainly

Disadvantage of this design is there cost and the difficult calibration procedure, higher noise level and lower spatial resolution. Still there are ideal from particular application like cardiac imaging were motion artefact greatly reduces the image on other ct designs.

Sixth generation of CT scanners appeared in 1990 and it’s mostly known Spiral or Helical CT. In this design the tube – detectors assembly are rotating and acquisition data continuously as the table of the patient is smoothly translating through the gantry. This technique produces a continuous volume set of data. With this design a 1sec/slice time allowing nowadays a full body scan in 30 sec. Due to simultaneous gantry rotation and table movement improved interpolation algorithms had to be developed in order to handle the projection data. In order the helical CT scan to be feasible a new technology of the wiring of the tube and the detector had to be used that would allow the continuous rotation of the gantry. Until this generation the after a 360° rotation the assembly had to inverse in order for the connecting cables to re-spool. This had a tremendous effect on the time of the scanning. Solution to this problem was given with slip rings, which were circular electrical conductive rings passing both the electrical energy and measured signals to busses without the need of rewinding the cables. This allowed continues rotation to occur.
Seventh generation is the new generation of CT systems, were the single rows detectors due to its profound limitation of the area that could cover, were replaced with multiple detector array. A wider collimator space is used and more the produced x-ray are used. The wider opening to the collimator creates a cone shaped beam resulting this technique to be referred to as Cone Beam CT (CBCT). Using multiple array detectors slice thickness is not determined by the collimation of the fan bean but from the detector size, additionally anti-scatter grids are used to further reduce noise in image. Now day there CBCT scanners that are using 64 or more slices. This technique greatly reduces the scanning time due to the volume that can be scanned in ton circle. This design of scanning provides multiple volumes per slice from which the final image is constructed, thus increasing its quality and averaging possible motion artefacts. Most of the Ct scanners produced nowadays use this design combined with helical CT and have reduced the scanning time of a full body scan up to 22 seconds.

**Dual Energy Imaging**

**General theory of Dual Energy Imaging**

Dual Energy (DE) x-ray imaging, is technique that was initially developed in order to eliminate the bone information form a radiograph in order for the lung parenchyma to be better imaged. Since then a series of evolution on this technique have been done in order to be able to enhance imaging of tissues, increase contrast or discriminate different tissues within the imaged volume.

Dual energy is based on the fact that, as have been presented in the previous chapters, the attenuation of x-ray beams on the same materials is strongly depended on the energy of the x-ray beams (Figure 88). Based on that fact by acquiring two identical x-ray images in terms of geometry but with different energies a correct manipulation of the data would allow us either to emphasize or to eliminate the imaging of particular tissues. There are many different algorithm available for combining the data of the different energies as also different methods of acquiring them. The most important of them will be presented here with main focus on the Dual Energy CT (DECT) systems which are also used in the presented work.
2D imaging DE acquisition techniques

A first approach for recording dual energy data was dual exposure technique. In this technique two successive acquisitions are performed using 2 different x-ray energy beams. The energy is switched by changing the voltage of the x-ray source and the used filtration. The main disadvantage of this method is the fact that it needs time for the tuning of the energy of the x-ray beam thus the object has to be static, or in case of medical imaging the patient completely still. Any movement wouldn’t allow the two images to be combined [58].

Another widely used dual energy acquisition technique is the sandwich detector technique. With this method both high and low energy data are acquired with a single exposure. This is done by putting two detectors together, other behind the other separated by a filter layer. X-ray tube, as presented before emits a spectrum (range of x-ray energies) and with this placement the first detector receives the low energy photons while the back one the high energy ones. Main advantage of this technique is that both images are taken simultaneously thus no motion artefact is present. This technique is used both in medical but and security application (x-ray line detectors used in luggage scans in airports) [58].

Dual Source CT

A first approach of DE CT was the sequential acquisition in which slice is scanned with one energy and then scanned again is the second one. This technique has slow scanning time, thus motion artefacts and contrast concentration could change between acquisitions.

There are two main techniques that allow almost simultaneous acquisition of data from both energies in CT. The Rapid voltage switching and the dual source CT.

In the rapid voltage switching, a single rotating x-ray source is used that has the ability to switch very fast between two energies (most commonly 80 and 140 kVp). The speed is up to 0.5 msec intervals during single gantry rotation. This high speed switching is combined with a very fast responding detector system, with high sampling rate from an equally fast data acquisition system. With this technique the low and high energy spectra images are acquired in very small intervals thus being almost simultaneous. Example of a commercial available scanner utilizing this technique is the GE high-definition 64-MDCT (Discovery 750 HD, GE Healthcare; Milwaukee, Wisconsin, USA). This single source CT allow a field of view (diameter of the imaged cylindrical volume) of 50 cm.
Dual Source CT (DSCT) is a relatively new technique which in order to acquire as fast as possible the two images (low and high energy) 2 x-ray sources are used positions at 90 degrees from one each other, and two corresponding detectors in the opposite of each tube. This way the patient is exposed at both energies at the same time without the need of voltage switching. The field of view of these scanners is relatively smaller than of single tube ones with a diameter of 33cm. Examples of commercial CT scanners that are applying this technique are 64-slice dual-source CT (Definition, Siemens Medical Systems; Erlangen, Germany), 128-slice dual-source CT (Definition Flash, Siemens Medical Systems) [59]. DSCT compared to Single Source (SS) DECT has better spectral separation between low and high energy. It is easier to equalize dose and noise between the low and high energy since each tube can be controlled completely independently. The dose applied is much lower and are seen as dose neutral compared with SS CT scanners.
Dual Energy Algorithms

There are various different linear and non-linear algorithms in order to combine (blend) the low and high energies together. Most widely used blending algorithms, as shown in Figure 90, also reported on [60], are: linear (simple subtraction algorithms), binary, slope, modal, normalized Gaussian, modal with 30% linear offset and normalized Gaussian with 30% linear offset. Especially the case of modal blending algorithm has been reported by various sources [60, 61] as an algorithm which provides positive results. Another DE algorithm is based on the theory of Alvarez [62], Macovski [63] and Lehmann et al. [64], and used in various other medical imaging fields such as mammography [65] or assessment of atherosclerosis [66].
This algorithm is based in the decomposition of the attenuation coefficients (\(\mu\)) of each pixel in the projection or reconstructed images of both low and high energy, into a pair of basis reference materials thus creating decomposed images of each material. These images are then fused using an non-linear equation. Depending of the fusing of the images (As seen in Figure 91) suppression of one tissue relatively to the other or cancelation of both tissues in order for a third to be visible can be achieved. This technique will be further analysed in following chapters.

**Usage of Dual Energy in the brain up to now**

Main application of DE in brain imaging is restricted in bone removal and angiography using contrast media. Other application are restricted in intracerebral haemorrhage differentiation [67], bone removal and angiography [68]. Due to the fact that the MRI is providing better discrimination of soft tissues, DE is not utilised in order to differentiate the soft tissues of the brain, since the initial trial of such technique didn't provide good results. Aim of this research is to study the possibility of image brain parenchyma with dual energy CT.

**Reconstruction techniques**

Reconstruction is the procedure applied in order to create the slice of the imaged object from the projection data acquired during the scanning. In a CT reconstructed image pixel have Hounsfield Units (HU) value which is a term of relative radio density, according to:

\[
HU = 1000 \times \frac{\mu_x - \mu_{water}}{\mu_{water}}
\]

Where \(\mu_x\) is the linear attenuation coefficient of the tissue and \(\mu_{water}\) is the linear attenuation coefficient of water at the specific energy. The pixel takes a value according to the mean attenuation of the imaged tissues on a scale from \(-1024\) to \(+3071\) for the least to the most attenuation respectively, on the Hounsfield scale. Water
is Hounsfield scale has 0 (since the numerator becomes 0), while air is $-1000$ HU, cranial bone 2000 HU or more due to its high attenuation and because of this can cause artefacts. The attenuation of metallic implants depends on atomic number for example iron steel heavily attenuates the X-rays and produces for well-known line-artefacts in the reconstructed images.

There are two major categories of reconstruction techniques, analytical and iterative reconstruction techniques.

**Analytical Reconstruction**

The most well established and on with most of the widely used techniques are based, is the Back projection technique. Its basic principle is to reverse the process of creation of projection data to an image. In Figure 93 projection of a simple object are seen from 32 different angles. The idea is that these projections are "smeared" back across the reconstructed image as it can be seen in Figure 94 in the image with number 2 on the upper right corner. The profiles from 0 and 90 degrees seen in image on the left are applied to the whole reconstructed image.

By summing all the projections in the image three reconstructed slice is created. As it is seen in Figure 94 if the number of projection used is small then the star shape artefacts appears while as the number increases the object is reconstructed more precisely. It has to be note that in this simple version of back projection, no filtering is used and thus the blurriness in the final image.

![Figure 93 - Projections of a simple object from 3 different angles](image)

![Figure 94 - Results of reconstructing using different number of projections](image)
An improvement to this method is the Filtered Back Projection (FBP). In this technique in order to increase the quality and sharpness of the final image, the projections are filtered before they are back projected. Different filters can be applied depending on the desired result, smooth filtered can be used from soft tissue imaging, or sharp filters for high resolution sharp images.

The Back projection methods used after the filtering is the same as before. In Figure 95 an example of non filtered and filtered projection is shown. The filter used in this case, and the one most widely used, is the ramp filter. The result as it can be seen is the negative areas ate the edges of the object. Once these filtered projections are smeared on the reconstruction image the resulting slice can be seen in Figure 96. As it is clearly seen the result of the FBP has eliminated the blurring effect of simple back projection algorithm. The FBP technique and its variations is the one of the most used being computationally undemanding, very little time is needed for each reconstruction.

Iterative

Iterative reconstruction techniques use iterating calculations starting from a first assumption of the result and continuously narrowing the error, calculating the final image in small steps. The most known and used of these techniques are the Algebraic Reconstruction Technique (ART), the Simultaneous Iterative Reconstruction Technique (SIRT), and the Iterative Least Squares Technique (ILST). They differ from each other in the way they perform the successive corrections ray-by-ray, pixel-by-pixel, or simultaneously correcting the entire data set, respectively. These techniques are better due to the fact that they use model of the physical properties of the scanner along with models of the X-ray matter interactions. As a result they provide images with higher resolution, less noise and artefacts and by combining modern sparse techniques even the dose can be greatly reduced. Main disadvantage of these techniques is that they are very computational demanding techniques, which due to the last year’s progress of computer sciences and available computational power, in example with use of GPU programming, their application in real practical uses is available.
Chapter 3 Materials & Methods

X-Ray Imaging Simulation

Why Simulation

The computer simulation of x-ray based systems is a very active research field and a modern way to carry out studies in diagnostic radiology and radiotherapy. Simulation of imaging is needed to assess quantitatively and qualitatively the image formation process and to assist developments of new imaging modalities, x-ray tubes, collimators, anti-scatter grids and new detectors.

Generally, two approaches are used to simulate x-rays through the matter the 1st is analytical approach, using simple relationships and approximations and the 2nd Monte Carlo and deterministic methods used to solve the transport equation.

Simulation of x-ray imaging techniques, based on the analytical approach is simply implementation of the completely deterministic Beer’s law [69]. Consequently, the computed images present no photon noise. Nevertheless, the variance of the signal associated with each pixel of the detector can be determined, which enables contrast-to noise ratio maps to be computed in order to predict quantitatively the delectability of defects in the inspected object.

More complicated models include additional model presentation for the scatter [70-72] Simulation results closer to these obtained in practice however can be achieved with the simulation of the trajectories and the interactions of each particle existing and arising in the particle shower. The particle transport is carried out by solving either numerically or analytically the Bolzmann’s transport equation. Analytically, however it can be only solved if severe restrictions are placed on several components of the equation. These limits often restrict the usefulness of the solutions obtained. To obtain physically realistic solutions to the transport equation, two types of numerical technique are used. In the first deterministic methods, the transport equation is discretized using a variety of methods and then solved directly or iteratively. The most popular approach here is the Discrete Ordinates method. The second type of techniques, Monte Carlo methods, construct a stochastic model, in which the expected value of a certain random variable is equivalent to the value of a physical quantity to be determined. The expected value is estimated by the average of many independent samples representing the random variable. Random numbers, following the distributions of the variable to be estimated, are used to construct these independent samples. There are two different ways to construct a stochastic model for Monte Carlo calculations. In the first case the physical process is stochastic and the Monte Carlo calculation involves a computational simulation of the real physical process. In the
other case, a stochastic model is constructed artificially, such as the solution of deterministic equations by Monte Carlo.

**Analytical Simulation**

The x-ray image acquisition model is based on a combination of ray tracing techniques and the x-ray attenuation law (chapter 2, subsection 2.2.5). The x-ray emitter is a point source that lies at distance SID (source to isocenter distance) from the isocenter point. The detector is geometrically presented as a rectangle with user defined dimensions, located at distance SDD (source-to-detector distance) from the x-ray source. By choosing the number and the size of the pixels (Δa), the spatial resolution of the detector can be adjusted. The transmitted intensity reaching an elementary area Δa of the detector is calculated by a line integral along the ray connecting the centre of this area with the source:

\[ I = I_0 * \exp \left( - \int \mu(x, y, z) \, dl \right) \]

where \( \mu(x, y, z) \) is the spatially dependent linear attenuation coefficient and \( I_0 \) is the intensity of radiation at the source segment that emits to the elementary area (Δa) of the detector, taken equal for all viewing angles. The object under irradiation represents combination of 3D geometrical primitives, matrixes of voxels or a complex phantom that presents a combination of them. The attenuation due to the geometrical primitives is calculated by adding the contributions of the primitives and equation 3.26 is rewritten as:

\[ I = I_0 * \exp \left( - \sum_{i} \mu_i d_i \right) \]

where \( \mu_i \) is the attenuation coefficient of the ith region; \( d_i \) is the path length through each of the regions encountered; \( n \) is the number of regions that x-ray crosses. In voxelized primitives, the exact radiological path through the phantom volume is calculated using the algorithm proposed by Siddon (1985):

\[ d = \sum_i \sum_j \sum_k l(i, j, k) * \mu(i, j, k) \]

where \( \mu(i, j, k) \) is the attenuation coefficient of the voxel through which the x-ray travels a length \( l(i, j, k) \).

Monochromatic beams from the source are considered. Ray tracing through a phantom is performed in the object coordinate system as described in the previous section. Angular projections are obtained by isocentrically rotating the source and the detector by the corresponding angle. Scatter and detector responses are not included in this analytical simulation.
Software Phantoms

There are two main types of phantoms used in imaging simulation. The Object and Voxel phantoms. Object phantom are phantoms that in order to create the final shape and structure of the modelled entity, they are using geometrical primitives which are then combined correctly and the final 3D object is created. XRaySimulotar [6] has the ability both to create and to use in order to simulate x-ray imaging object phantoms. An example of a 3D breast phantom created using the XRaySimulotaor [6] and the resulted simulated x-ray images is shown in Figure . In the case of brain modelling object phantom are not available mainly due its complex structure. Voxel phantom on the other hand are three dimensional matrices, where each element of the matrix represents a voxel in space and the value that is appointed at it represent the specific characteristic that you want to model (it could be from linear attenuation coefficient for X-ray imaging up to young modules form mechanical modelling of the behaviour of the brain under stress and strain).

In order to perform simulations for brain imaging, an accurate and reliable brain phantom had to be found. An adequate phantom of CT of x-ray correlated properties (such as tissue linear attenuation coefficient of HU units) data for the brain is not available due to the fact that CT cannot image the soft tissue parenchyma of the brain and distinguish between gray and white matter. For this reason we had to create our phantom using other available voxel phantoms of the brain which were created based on MRI and other imaging modalities data. This phantom was then modified and its data altered in order to be used for X-Ray imaging.
The phantom used in this study is based on the Digital Brain Phantom II [73]. The latter was created using 27 T1-weighted, 12 PD-weighted, 12 T2-weighted MRI scans, 1 CT scan and 1 MR Angiography from a single subject. The phantom is provided in the form of three-dimensional matrices of 10 brain tissue volumes as shown in Figure 98. Each 3D volume has dimensions of $181 \times 217 \times 181$ voxels in X, Y and Z axis respectively, with a voxel size of 1 mm in each direction. Each voxel is given a value between 0 and 255 that reflects whether the tissue in the voxel is evident (255) or not (0). For this study volumes of gray matter, white matter, skull and cerebrospinal fluid were taken into consideration.

The resulted volumes were combined into a single 3D brain phantom, using weighted summing method.
**Phantom for analytical simulation**

In order to use the brain model for x-ray imaging simulation, the voxel values had to be changed to values of x-ray linear attenuation coefficient of the tissues each voxel is composed by. X-ray attenuation coefficients of gray, white, cerebral spinal fluid (CSF) and bone tissues were calculated according to [74] for the used incident photon energies. Specifically, the elemental compositions of the skull and the cerebrospinal fluid were taken from NIST database, while the elemental composition of the gray and the white matter were defined based on real brain CT data, collected from two different clinical CT systems: Siemens Somatom Definition Flash, 80kV, 512x512 pixels, shown in Figure 99a and GE Medical Systems, 120kV, 512x512 pixels, shown in Figure 99b, as well as data found from the literature [75-77]. Table summarises the Hounsfield Units and densities for the tissues used in the simulation.

**Table 8 - HU units and Densities of the tissues used**

<table>
<thead>
<tr>
<th>Tissue</th>
<th>HU</th>
<th>Density (gcm⁻³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone</td>
<td>1527</td>
<td>1.92</td>
</tr>
<tr>
<td>CSF</td>
<td>13</td>
<td>1.01</td>
</tr>
<tr>
<td>White Matter</td>
<td>24</td>
<td>1.04</td>
</tr>
<tr>
<td>Gray Matter</td>
<td>35</td>
<td>1.04</td>
</tr>
</tbody>
</table>

Using the relationship between HU and the linear attenuation coefficient, the values of the linear attenuation coefficients of the tissues per incident energy were calculated as followed:

\[
HU = 1000 \cdot \frac{\mu_X - \mu_{\text{water}}}{\mu_{\text{water}}}
\]
Where $\mu_x$ is the linear attenuation coefficient of the tissue and $\mu_{\text{water}}$ is the linear attenuation coefficient of water at the specific energy. The resulting linear attenuation curves form the soft tissues of the brain are shown in Figure 100. As it can be seen the linear attenuation coefficients of gray and white matter (black and red line respectively) are very close to each other, therefore very difficult to differentiate in x-ray imaging.

As a second step insertion of the chemical composition of gray and white matter and calculation of all needed physical parameters for simulation was done [75]. The chemical composition was then used as an input to the XCom [74] in order to calculate the exact attenuation coefficient. As it can be seen from the graph the difference between the 2 tissues is very small with gray matter having a bit more oxygen and a bit less carbon. This similarity into their chemical composition is the reason for the same response when radiated with x-ray beam and the difficulty in achieving a contrast between them.
Chapter 4 Gray and White matter differentiation

Analytical Simulation without noise

Intro

The aim of this study was to investigate the feasibility of using dual-energy (DE) imaging in order to discriminate gray from white matter in brain CT images. Due to fact that the linear attenuation coefficients of gray and white matter are very close, the use of x-rays in imaging brain parenchyma is not preferred especially since the Magnetic Resonance Imaging (MRI) can provide excellent differentiation of these tissues. For this reason DECT in the brain has been restricted mainly in imaging anatomical changes in the brain. Potential ability of DECT to discriminate such tissues in the brain parenchyma could be a major breakthrough. Usage of CT is much higher in everyday clinical practice than MRI since it tends to be a routine examination (in case of an emergency, or accidents CT scan is very often performed). Additionally, CT is much cheaper, faster and provides higher resolution images than MRI. A potential ability of DECT to image such tissues would allow limitless advantages in clinical service.

A series of different DE algorithms have been tested and the results of the selected non-linear material decomposition algorithm are presented. An optimization study aimed to find the optimal low and high energy incident spectra for such DE applications in presented. Simulations are carried out exploiting an in-house developed software simulator to generate noiseless x-ray cone-beam images that were further combined appropriately into DECT brain images. For the purposes of simulations, we used varied imaging energies and a software voxel-based brain phantom. One hundred and eighty (180) projection images are generated within a full gantry acquisition arc of 360° for each of the incident monochromatic and polychromatic beams. DE algorithms were subsequently applied. Brain CT slices of the obtained dual energy images were generated using filtered Multiple Projection Algorithm (fMPA) (ref) [78]. Resulting images were evaluated visually and quantitatively in comparison to single energy brain CT images.
Materials & Methods

Brain Phantom

The phantom used in this study is based on the Digital Brain Phantom II [73] as it was described in the brain phantoms paragraph. For this study volumes of gray matter, white matter, skull and cerebrospinal fluid were taken into consideration. The resulted volumes were combined into a single 3D brain phantom, using weighted summing method.

Dual Energy Algorithm

A series of dual energy blending algorithms were used in order to determine which had the better results in order to be further investigated. The blending algorithms used, also reported on [60], were: linear, binary, slope, moidal, normalized Gaussian, moidal with 30% linear offset and normalized Gaussian with 30% linear offset. Especially for the case of moidal blending algorithm which was reported by various sources [60, 61] as the preferred algorithm a Graphical User Interface (GUI) was created to implement the blending function presented in [61] in order to quickly modify all the parameters of the algorithms and instantly evaluate the result, as shown in Figure 102.

Due to the unsatisfying results of the application of the mentioned blending algorithms, a non-linear material decomposition approach was chosen. The subtraction algorithm used is based on the theory of Alvarez [62], Macovski [63] and Lehmann et al. [79]. The algorithm can be applied on both projection and reconstruction images. The process followed, as depicted in Figure 103, is the decomposition of the attenuation coefficients (μ) of each pixel in the projection or reconstructed images of both low and high energy, into a pair RG and RW images of the basis materials Gray and White matter following the equations:

\[
R_G = \frac{\mu_{\text{high}}\mu_{\text{W(low)}} - \mu_{\text{W(low)}}\mu_{\text{high}}}{a} \quad (1)
\]

\[
R_W = \frac{\mu_{\text{low}}\mu_{\text{G(high)}} - \mu_{\text{G(high)}}\mu_{\text{low}}}{a} \quad (2)
\]

\[
a = \frac{\mu_{\text{W(low)}}\mu_{\text{G(high)}} - \mu_{\text{W(hi)}}\mu_{\text{G(low)}}}{\mu_{\text{W(low)}}\mu_{\text{G(high)}} - \mu_{\text{W(high)}}\mu_{\text{G(low)}}} \quad (3)
\]

Figure 102 - Simple Graphical User Interface created to evaluate moidal blending function (a) and the corresponding implemented function (b)
Subtracted image is created based on tissue cancelation as following:

\[ DE = R_G \sin(\phi) + R_W \cos(\phi) \] (4)

The parameter \( \phi \) is the Tissue Cancelation Angle (TCA) the variation of which changes the contrast/cancelation of the two basis tissues.

**Spectra**

The following beam spectra were used in simulations: (a) ten monochromatic beams with energy from 20 keV to 110 keV with an increment of 10 keV and (b) four polychromatic beams 80 kVp, 100 kVp, 120 kVp, 140 kVp, which are all available at a commercially available DECT scanner. Figure 104 depicts two of the used incident spectra at 80 kVp and 100 kVp, respectively.

**DECT Simulation.**

The energies of the monochromatic beams vary from 20 to 100 keV for low-energy and from 30 to 110 keV for the high-energy beams resulting in 81 DE combinations. Polychromatic images are obtained through a weighted fusion of monochromatic images generated for energies sampled from the corresponding energy spectrum. For each energy combination, the incident air kerma and therefore the incident photon fluence were calculated. Thereafter, the synthetic images are transformed to images that represents the number of photons absorbed in the detector. In case of monochromatic beams, a total of 729 DE combinations were produced. These combinations consist of 81 different low and high energy pairs combinations, for each
one of which nine weightings between low- and high- energy have been performed (i.e. 10/90 Low to High energy dose ratio etc). From this 729 approximately 130K projection images were simulated. In order to evaluate the decomposition algorithm for each of the 729 combination 360 different values of TCA, $\phi$ as appearing in equation 4, have been investigated resulting in a total number of approximately 260K final cancelation images of the brain.

In the particular case of polychromatic spectra, the basis materials attenuation that is used in the subtraction algorithm described, weighted attenuation coefficient was calculated for each energy at all energy spectra. Tomograms were reconstructed using the filtered Multiple Projection Algorithm [78] applied on the obtained 180 DE images.
Due to great amount of the created cancelation images a number of different Figure OfMerit (FOMs) were used in order to quantitatively evaluation the results. FOMS used and their corresponding formulas were:

\[
\text{Contrast to Noise Ratio (CNR)} = \frac{|\bar{R} - \bar{B}|}{\sigma_{\text{Back}}} \quad (5)
\]

\[
\text{Contrast Michelson} = \frac{|\bar{R} - \bar{B}|}{\bar{R} + \bar{B}} \quad (6)
\]

\[
\text{Contrast Weber} = \frac{|\bar{R} - \bar{B}|}{\bar{B}} \quad (7)
\]

\[
\text{Signal to Noise Ratio (SNR)} = \frac{\bar{R}}{\sigma_{\text{Back}}} \quad (8)
\]

Were $\bar{R}$ and $\bar{B}$ are the mean value of pixels in the Region Of Interest (ROI) (in this case gray or white matter), $\bar{B}$ is the mean value of pixels in the background (in this case gray or white matter), $\sigma_{\text{Back}}$ is the standard deviation of the background. In Figure 105 the selected regions of interest can be seen. One big region in the white matter is set as ROI and for background 4 smaller regions in the gray matter have been defined, due to the smaller area of the gray matter.
Due to the fact that none of the above mentioned FOMs could clearly differentiate between the 260K setting and the results didn’t come in accordance with visual evaluation, a new FOM was defined, based on data extracted from several line profiles taken at different regions of interests (ROI). This FOM is referred as Line Contrast (LC). Specifically, for each cancellation image, three different line profiles were drawn as shown in Figure 106. Each line profile is consisted of 3 pixel width lines an average of which is taken in order to eliminate noise. The line profiles are shifted by adding the absolute minimum value and normalized to max value in order to be objective in all energy combinations. In each line profile, 5 ROIs were set in the regions where there is a transition from white to gray matter. Within each ROI the maximum to minimum difference is calculated and stored. Then the LC is calculated by finding the maximum difference along the ROIs.

![Figure 106 - The three different line profiles that were calculate in a brain slice](image-url)
Results

Selection of proper evaluation parameter

In Figure 107 a comparison between the results of the different FOMs is shown. In each line the first three images with the higher score of for each FOM are shown, presented image are the combination of Low Energy, High Energy images and TCA that each FOM picked with higher score. As it can be seen from visual investigation the contrast on images selected using LC FOM is higher than in the ones selected using CNR or Michelson contrast. Especially in the case of Michelson contrast it is seen that the image with the higher score has the lower contrast than all images in the figure.

On Table a comparison of the best results when using each FOM are depicted. Below each image the value that the image gets using each FOM is shown. From this table the accordance of visual and FOM investigation using LC can be seen since the LC values of the 3 images depict the actual contrast seen on the images. While in the
case of CNR and Michelson Contrast the two images on the right which have inferior contrast make a higher score.

Table 9 - Comparison of the best results when using each FOM and corresponding FOM values

<table>
<thead>
<tr>
<th></th>
<th>Max LC</th>
<th>CNR</th>
<th>Michelson</th>
</tr>
</thead>
<tbody>
<tr>
<td>LC</td>
<td>0.9199</td>
<td>0.3493</td>
<td>0.2215</td>
</tr>
<tr>
<td>CNR</td>
<td>6.2873</td>
<td>9.4786</td>
<td>8.6875</td>
</tr>
<tr>
<td>Michelson</td>
<td>-1.5319</td>
<td>0.6184</td>
<td>389.3696</td>
</tr>
</tbody>
</table>

Line Contrast calculations were performed for all 729 low/high monochromatic and 6 polychromatic energy combinations, as each one consists of 360 brain DECT images obtained for all 360 TCAs. Initially, the optimal TCA per energy combination is found and thereafter a comparison between the 729 LC results in the optimal low/high energy combination that would give a maximum contrast differentiation between the tissues that belong to the brain parenchyma.

**Dual Energy Brain CT image Optimization**

Table 10 summarizes the first ten optimal low/high energy pair combinations of monochromatic beams and their corresponding optimal TCA. Greatest LC values and therefore superior image quality between gray and white matter is achieved for the energy pair 100 keV (low) / 110 keV (high), followed by the pairs 60/100 and 60/70 keV. Although the first two energy pairs may be beneficial in terms of reduced dose imparted to the brain, due to the high energy of the x-rays, it may not be technically achievable with the currently available CT scanners. The third energy pair 60 keV (low) / 70 keV (high) is therefore considered as the most feasible combination and will be used in the rest of the paper for further comparisons.
Table 10 - Combinations of low and high energies monochromatic beams that result in the top 10 LC factor

<table>
<thead>
<tr>
<th>Rank</th>
<th>Low Energy keV</th>
<th>High Energy keV</th>
<th>Line Contrast (LC)</th>
<th>Tissue Cancelation Angle (φ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
<td>110</td>
<td>0.4785</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>100</td>
<td>0.4584</td>
<td>167</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
<td>70</td>
<td>0.4469</td>
<td>101</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td>60</td>
<td>0.4283</td>
<td>155</td>
</tr>
<tr>
<td>5</td>
<td>50</td>
<td>60</td>
<td>0.4219</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
<td>90</td>
<td>0.4122</td>
<td>83</td>
</tr>
<tr>
<td>7</td>
<td>80</td>
<td>100</td>
<td>0.3948</td>
<td>254</td>
</tr>
<tr>
<td>8</td>
<td>60</td>
<td>110</td>
<td>0.3591</td>
<td>197</td>
</tr>
<tr>
<td>9</td>
<td>50</td>
<td>90</td>
<td>0.3590</td>
<td>101</td>
</tr>
<tr>
<td>10</td>
<td>70</td>
<td>90</td>
<td>0.3342</td>
<td>21</td>
</tr>
</tbody>
</table>

Similarly, Table 11 presents the results for DE brain CT images obtained from polychromatic beam pairs as the results are sorted by the highest LC value. Optimal combination is achieved for the combination 80 kVp (52 keV mean) and 100 kVp (59.5 keV mean), shown in figure 1.

As it is seen for both monochromatic and polychromatic beams, the angle at which the maximum gray white contrast is achieved varies with the energy of the low and the high energy image. In addition, as excepted, the contrast between gray and white matter is higher on brain DECT images obtained with monochromatic beams compared to images obtained with polychromatic spectra by a factor of 2.

Table 11 - Combinations of low and high energies polychromatic beams sorted according LC factor

<table>
<thead>
<tr>
<th>Rank</th>
<th>Low Energy kVp</th>
<th>High Energy kVp</th>
<th>Line Contrast Angle</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>80</td>
<td>100</td>
<td>0.2784 311</td>
</tr>
<tr>
<td>2</td>
<td>80</td>
<td>140</td>
<td>0.2384 158</td>
</tr>
<tr>
<td>3</td>
<td>80</td>
<td>120</td>
<td>0.2266 180</td>
</tr>
<tr>
<td>4</td>
<td>120</td>
<td>140</td>
<td>0.2223 312</td>
</tr>
<tr>
<td>5</td>
<td>100</td>
<td>120</td>
<td>0.1877 164</td>
</tr>
<tr>
<td>6</td>
<td>100</td>
<td>140</td>
<td>0.1774 152</td>
</tr>
</tbody>
</table>
Visual & Quantitative Evaluation

The plots of the line profiles taken across the cancelation and single monochromatic energy images are shown together with the corresponding images for the optimal energies in Figure 108. The quality of the image increases considerably in the brain DECT images where the white matter can be clearly distinguished in the brain parenchyma. In terms of Line Contrast the brain DECT image demonstrated improvement of factor of 12.6 compared with both low and high energy images.

![Figure 108 - Line profiles taken across x-ray image simulated at 100 keV; x-ray image simulated at 110 keV and dual energy image, calculated from the combination of two energies](image)

Figure 109 depicts the comparison of line profiles taken across the brain CT images obtained from the optimal DE pair (80kVp and 100 kVp) and single polychromatic energy images. Similarly to the monochromatic case, in the case of polychromatic beams the contrast of white and gray matter in the brain parenchyma is greatly increased in the brain DECT image. The LC of brain DECT image is improved with a factor of 7 compared with both low and high energy images. The improvement in this case is reduced almost half of that for monochromatic beam.
Conclusion

The simulation study demonstrated that the use of dual energy may be of great advantage for the visualization of the very small x-ray attenuation differences of soft tissues within the brain parenchyma when using brain CT modality. As it can be seen in the resulted images, although no discrimination of brain parenchyma can be done at the original low or high energy images, the gray to white matter contrast is highly increased when the non-linear dual energy algorithm is applied. Although we have to keep in mind when interpretation these result the absence of noise in the simulated images therefore, more simulation were performed in order to investigate if such a differentiation could exist with the presence of noise.

The resulting contrast using polychromatic energy beams is inferior to the monochromatic images, but this was expected and comes into agreement with theory, thus confirming the validation of the simulation procedure.

Additionally the proposed Line Contrast FoM, has proven to be much more efficient in finding the images with the higher contrast. It also provides the most consisted results in terms of visual and quantitatively agreement than all other FoMs used.
Analytical Simulation with addition of noise

Intro

In order to further investigate the feasibility of application of this DE algorithms in real data, noise had to be simulated and added to the produced ideal images. Poison noise has been added with Matlab using different number of photons from $9 \times 10^6$ to $1.977 \times 10^{11}$ in order to simulate image acquisitions with different doses. Only energies of 100 and 110 KeV are used since they were concluded to be the best energies from the previously presented ideal simulation study.

Filtering has been used to remove noise from the images, and the cases of pre filtering, post filtering or applying filter in both cases has been investigated. Additionally a number of different filters are investigated, including median filter, anisotropic diffusion filter, and sparse de-noising (KSVD) method.

Materials & Methods

Addition of noise (simulated dose)

Noise has been added in the ideal simulated images in order to investigate the behaviour of the DE technique in the presence of noise. Different levels of doses have been used in order to evaluate the effect of the dose in the resulted image quality and soft tissue differentiation.

Poison noise was added in the ideal images using different number of photons that correspond at different doses of x-ray radiation exerted to the patient. The addition of noise was done according to the following routine:

$$N = N_0 \exp(\mu(\chi))$$

Where $N_0$ is the number of the incident photons $\mu(\chi)$ is the attenuation coefficient image (matrix). Then random poison noise is added in the matrix $N$, and the image is again constructed using the follow equation:

$$\mu = \log \frac{1}{\frac{N_{\text{noise}}}{N_0}}$$

Human brain is one of the organs of the human body with the lowest tissue weighting factors which is used in order to calculate the effective dose that is deposited in the human body when exposed to x-ray radiation. As it can be seen in Figure 110, the values of the weighting factor for different organs or tissues as are set by the International Commission on Radiological Protection (ICRP) in 2007 [80] vary greatly between different organs. There tissues like bone marrow or breast tissues which are
very sensitive to radiation, and thus they have a very big weighting factor which is disproportionally to the fraction of body mass they represent. While other tissues such as brain are insensitive to radiation and are assigned with a very low weighting factor. As a result of this human brain imaging techniques vary greatly in the amount of doses used.

There is a series of publication measuring the dose applied to brain when imagine with different modalities of CT [81, 82]. Surface radiation doses for diagnostic cerebral angiography can be up to 95 Gy/cm² [26], up to 2.500 mGy for cerebral Ct perfusion studies at 140 kV-200 mA [83] or even 3967 mGy for the low dose CB Mercuray clinical system [82]. According to these data two different doses were simulated using $9.527e^{10}$ photons for the acquisition of both energy corresponding to the low dose simple CBCT CB mercuray system, and a higher dose of $1.977e^{11}$ photons resulting in surface dose applied in a diagnostic cerebral angiography according to [80]. The doses are calculated as for the scanning of both low and high energy images, thus half of the number of photons are used in each energy.

**DE techniques used**

**Material Decomposition DE**

The same subtraction algorithm used in the case of ideal simulation was used based on the theory of Alvarez [62], Macovski [63] and Lehmann et al. [79]. The process followed, as depicted in Figure 103 and described in the previous section, the attenuation coefficients ($\mu$) of each pixel in the reconstructed planes of both low and high energy are decomposed into a pair $R_G$ and $R_W$ images of the bases materials Gray and White matter following the equations:

$$R_G = [\mu(\text{high})\mu(\text{low}) - \mu(\text{low})\mu(\text{high})]/a$$  \hspace{1cm} (1)

$$R_W = [\mu(\text{low})\mu(\text{high}) - \mu(\text{high})\mu(\text{low})]/a$$  \hspace{1cm} (2)

$$a = \mu(\text{low})\mu(\text{high}) - \mu(\text{high})\mu(\text{low})$$  \hspace{1cm} (3)

Subtracted image is created based on tissue cancelation as following:

$$DE = R_G\sin(\phi) + R_W\cos(\phi)$$  \hspace{1cm} (4)

The parameter $\phi$ is the Tissue Cancelation Angle (TCA) the variation of which changes the contrast/cancelation of the two basis tissues.
In order to improve the final result of the DE algorithm in the case of presence of noise, an optimization procedure was applied. As it can be seen in Figure 111 in order to improve the final image the parts of the schematic in red boxes can be altered. As far as the filtering is concerned, it can be applied in the low and high energy images before the application of decomposition algorithm, in the final cancelation image or in both cases. The filtering steps and filters used will be presenting in the following part.

The other part that can be altered are the data decompose the images in the bases materials along with the tissues cancelation Angle applied. The idea behind this optimization was to define the best values of the basis materials (attenuation coefficient values) that should be used based on which the low and high energy images were decomposed. In fact is an application of inverse engineering, since the desired outcome is the highest possible contrast between the two tissues the best basis material are used in order to by achieve this contrast.

In order to find the best values of basis material attenuation coefficient mathematical optimization procedures were used. Mathematical optimization is a method to find numerically minimums (local or global minima) or maximums (local or global maxima) or zeros of a function (Figure 112). The function the local minima or maxima are investigated is called cost function, or objective function. By convention, the standard form of an optimization problem is stated in terms of minimization. In general, there may are several local minima, where a local minimum $x^*$ is the point for which there exists some $\delta > 0$ so that for all $x$:

$$\|x - x^*\| \leq \delta$$

So that the expression:
\[ f(x^*) \leq f(x) \]

Is valid for a region around \( x^* \) (defined by the constrains applied in the objective function) all of the function values are greater or equal to the value at that point \( x^* \). In order to solve a maximization problem the solution is relatively easy if the aims is:

\[ \max_x f(x) \]

Then the objective function has to defined as:

\[ g(x) = -f(x) \]

And minimization of \( g(x) \) has to be applied.

Application of these techniques in the case of the presented DE technique was done using the following main idea. Our aim is to increase the contrast between two different tissues. In terms of imaging this is translated as the fact that we want the values of two pixels, one of which is representing the 1\textsuperscript{st} tissue and the other the 2\textsuperscript{nd} tissue, to have the maximum possible difference, since that will be shown as big contrast on the resulting image. In order to do that, the non-linear equation used to decompose the images and cancel one tissue to the other, was calculated for 2 pixels that are assumed to depict the two different tissues (\( p_1 \) and \( p_2 \) respectively). In order to find the maximum difference the problem was set as:

\[ \text{Min}( -|p_1 - p_2|) \]

The resulting objective function that was used for the optimization solver was the following:

\[
\begin{align*}
    f &= -\left| \left( \frac{(p_{1\text{he}} \times x(3)) - (p_{1\text{le}} \times x(4))}{x(3) \times x(2) - x(4) \times x(1)} \sin(x(5)) + \frac{(p_{1\text{lw}} \times x(2)) - (p_{1\text{he}} \times x(1))}{x(3) \times x(2) - x(4) \times x(1)} \cos(x(5)) \right) \right| \\
        & \quad - \left( \frac{(p_{2\text{he}} \times x(3)) - (p_{2\text{le}} \times x(4))}{x(3) \times x(2) - x(4) \times x(1)} \sin(x(5)) + \frac{(p_{2\text{lw}} \times x(2)) - (p_{2\text{he}} \times x(1))}{x(3) \times x(2) - x(4) \times x(1)} \cos(x(5)) \right)
\end{align*}
\]

Where:

\( p_{1\text{le}} \) and \( p_{1\text{he}} \) are the values of high and low energy of the 1\textsuperscript{st} tissue
\( p_{2\text{le}} \) and \( p_{2\text{he}} \) are the values of high and low energy of the 2\textsuperscript{nd} tissue
\( x(1) \) and \( x(2) \) are the low and high energy values of the 1\textsuperscript{st} optimized basis material
\( x(3) \) and \( x(4) \) are the low and high energy values of the 2\textsuperscript{nd} optimized basis material
\( x(5) \) is the optimum tissue cancelation angle (\( \phi \))
Output of the solvers was the x() vector containing the optimum values of high and low energy for the 2 basis materials along with the optimum TCA. In order for the optimization procedure to be done, the values of the pixels (p1 and p2) that the contrast has to be achieved had to be given as input. This could be done either from theoretical knowledge of the values of the attenuation coefficient of the tissues that contrast is desired or using a graphical user interface (GUI), as seen in Figure 113, were the user could select an area or a pixel that has the desired tissues that contrast is wanted to be achieved. If an area is selected then the mean value and standard deviation of this area are calculated.

Two different optimization solver were used in Matlab in order to find the optimum values for the basis material global search and multistart algorithm. GlobalSearch and MultiStart have similar approaches to finding global or multiple minima. Both algorithms start a local solver (such as fmincon) from multiple start points. The algorithms use multiple start points to sample multiple basins of attraction [84]. The main differences between GlobalSearch and MultiStart, as they are stated in Matlab documentation are:

- GlobalSearch uses a scatter-search mechanism for generating start points. MultiStart uses uniformly distributed start points within bounds, or user-supplied start points.
- GlobalSearch analyses start points and rejects those points that are unlikely to improve the best local minimum found so far. MultiStart runs all start points (or, optionally, all start points that are feasible with respect to bounds or inequality constraints).

**Filtering and its optimization procedure**

As mentioned before in order further improve the DE algorithm output filtering can be applied in the low and high energy images before the application of decomposition algorithm, or in the final cancelation image or in both cases 3 different filters have been investigated in order to reduce the noise. The three different filters used are median filtering, Anisotropic Diffusion (AD) filtering and sparse filtering.
Median Filter

Median filtering is a nonlinear operation often used in image processing to reduce "salt and pepper" noise. A median filter is more effective than convolution when the goal is to simultaneously reduce noise and preserve edges. The main idea is to apply through the images matrix pixel by pixel replacing each pixel values with the median of the values of the neighbouring pixels within a particular windows. In the case of imaging this window can have different patterns such as an array (Figure 115) or a cross or other. It has to be noted that in the case that odd number of neighbouring pixels is used then the median is just the middle value of the sorted pixels.

Non Linear Anisotropic Diffusion Filter

The anisotropic diffusion algorithm by Perona and Malik published on 1990 [85] is the pioneering work in de-noising using partial derivatives equations (PDE).

It applies the law of diffusion on pixel intensities to smooth textures in an image. A threshold function is used to prevent diffusion to happen across edges, and therefore it preserves edges in the image. (Unlike for instance Gaussian blur filter.) This makes it very interesting if you want to remove noise, but do not want to smooth out the edges of your image, for instance if you want to use these edges to segment the image, without being perturbed by the noise.

Anisotropic diffusion or Perona–Malik diffusion, provides noise reduction without removing edges, lines or other details of the image[85] This filter produces a family of parameterized images, but each resulting image is a combination between the original image and a filter depending on the image, therefore is a non-linear transformation of the image.

\[ c(x, y) = \exp[-0.5 \left( \frac{\|Du\|}{k} \right)^2] \]

NAD filtering is based on nonlinear evolution partial differential equations \( u \), and seeks to improve images by removing noise while preserving details and even enhancing edges. \( K \) is the number of iterations. Anisotropic diffusion can be used to remove noise from digital images without blurring edges. Is ideal for removing noise but also indiscriminately blurs edges too.
There are two main variables that can be altered in the implementation of the anisotropic diffusion, as it is also used in this research. The number of the iterations, as the number increase the application of the filters smoothen further the images but with an inevitable loss of edge information. The 2nd parameter is the diffusion constant that can be altered in order to choose the height of the edges that are going to be kept or be filtered. Depending on this value different regions are include in the mask, thus you could enhance of suppress edge sharpening of smoothening.

Sparse Filtering

Finally a Sparse filtering technique was used as it was investigated and developed in our lab [86]. A filter based on sparse and redundant representations of images over learned dictionaries [87]. The aim of such representation is to provide a redundant sparse decomposition of the image through an over complete dictionary. This decomposition can be done using a greedy pursuit algorithm which finds the sparsest approximate representation of the signal given a specific dictionary. The method is also called sparse-coding. The dictionary can either be a pre-specified linear transform (i.e. the Discrete Cosine Transform) or the result of a training process that adapts its content to fit a certain set of example signals. In the latter case, the K-SVD algorithm [88] is used for dictionary training and sparse-coding of the signal is done using Orthogonal Matching Pursuit (OMP) greedy algorithm. The corrupted image is broken up into overlapping patches and the vectorized version of each patch, is sparse-coded via OMP using a user defined dictionary. Finally, the approximation of the clean image is computed and reformed by averaging the overlapping patches. The data noise is modelled by Gaussian distribution. Although noise in low-dose X-ray images is dominated by additive Poisson-distributed quanta noise, for a sufficiently large number of quanta contributing per pixel, the Poisson distribution can be approximated by a Gaussian distribution with same mean and variance.

Given an overcomplete dictionary matrix \( D \in \mathbb{R}^{n \times K} \), assumed known and fixed, with \( K \) signal-atoms for columns and a signal \( x \in \mathbb{R}^{n} \), the solution of the sparse representation of \( x \) over \( D \) is

\[
\hat{a} = \arg \min_{a} ||a||_0 \text{ subject to } Da = x \tag{1}
\]

or equivalently

\[
\hat{a} = \arg \min_{a} ||a||_0 \text{ subject to } ||Da - x||^2 \leq \epsilon \tag{2}
\]

where \( \epsilon \) is the error tolerance. In other words, \( x \) can be represented as a linear combination of just a few columns from dictionary \( D \). The vector \( a \) holds the representation coefficients of signal \( x \), and the L0 norm counts the non-zero elements (i.e. the representation coefficients) of \( a \). Except of representation error boundary \( \epsilon \), there can also be a restraint on the number of dictionary atoms that participate in the sparse representation of the signal, adding a requirement of the form \(||\hat{a}||_0 \leq L\).
To meet the noise removal problem, we consider the noisy version of x, corrupted by Additive zero-mean White Gaussian Noise n (AWGN) with standard deviation $\sigma$:

$$y = x + n.$$ 

In this case, the error $\|D_a - y\|_2^2$ is bounded by $T$, which is dictated by $\varepsilon$ and $\sigma$. The approximation of x is given by solving $x_{apr} = D\hat{a}$.

As an exact determination of the sparsest representation is an NP-hard problem, alternative methods that lead to approximate solutions have been considered [10], [11]. One such method is the greedy algorithm Orthogonal Matching Pursuit that is proven to be simple and efficient.
Results

Simple DE Decomposition Algorithm

Without Filtering

Simulations using 9.527e10 photons

In Figure 116 a comparison between the results of the different FOMs is shown. Since there has been a first analysis of the results of the FoM in the previous case of ideal simulation only the LC FoM and the CNR are used. In the case LC two different variations are shown, max LC is the maximum difference that appeared within the set of ROIs in the line profiles, while average LC is the mean values of the differences within the set of ROIs in the line profiles. In each line the first three images with the higher score of for each FOM are shown, presented image are the combination of 100 and 110 KeV images and TCA that each FOM picked with higher score. In following results basis materials values were set using theoretical values of the tissues.

![Figure 116 - Comparison between the results of the different using 9.527e10 photons, basis materials set from theoretical values without using filtering.](image)

No additional filtering has been applied in the images either before either after the application of the decomposition algorithm.
As it can be seen from visual investigation the contrast on images selected using LC FOM is higher than in the ones selected using CNR. Especially in the case of max LC the images have the higher contrast.

On Table 12 a comparison of the best results when using each FOM are depicted. Below each image the value that the image gets using each FOM is shown. From this table the accordance of visual and FOM investigation using LC can be seen since the LC values of the 3 images depict the actual contrast seen on the images. While in the case of CNR the image has inferior contrast nevertheless it has better CNR score.

<table>
<thead>
<tr>
<th></th>
<th>Max LC 1st Result</th>
<th>Average LC 1st Result</th>
<th>CNR 1st Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max LC</td>
<td>0.8419</td>
<td>0.7977</td>
<td>0.1615</td>
</tr>
<tr>
<td>Average LC</td>
<td>0.4647</td>
<td>0.5019</td>
<td>0.0924</td>
</tr>
<tr>
<td>CNR</td>
<td>3.4015</td>
<td>3.4242</td>
<td>3.6071</td>
</tr>
</tbody>
</table>

Table 12 - Comparison of the best results when using each FOM and corresponding FOM values

As it is seen from the images the presence of noise greatly deteriorates the resulting contrast. As it presented before these data were produced using theoretical values of the tissues attenuation as basis materials. Due to the presence of noise these values do not correspond in the real values of the tissues in the images thus mean values from the ROIs that were used and presented in the FoM analysis were used in order to set the values of the basis materials with which the decomposition is done. The results from this application are shown in Figure 117.

In Figure 117 in accordance with the previews figures a comparison between the results of the different FOMs is shown. No additional filtering has been applied in the images either before either after the application of the decomposition algorithm and basis materials values were set using mean values of the ROIs of the tissues.
As it can be seen from visual investigation the contrast on images selected using LC FOM is higher than in the ones selected using CNR. Especially in the case of average LC the images have the higher contrast, since it appears that average LC due to the fact that it does not rely on one high value of difference, it can better select the images with better overall contrast.

On Table 13 a comparison of the best results when using each FOM are depicted. Below each image the value that the image gets using each FOM is shown. From this table the accordance of visual and FOM investigation using LC can be seen since the LC values of the 3 images depict the actual contrast seen on the images. While in the case of CNR completely fails to detect the image with high contrast.
As it is seen from the images the presence of noise greatly deteriorates the resulting contrast. The use of mean values from the ROIs within the images produces better results. Additionally in this case the average LC seems to better detect and score images depending on their real contrast as seen from visual investigation.

<table>
<thead>
<tr>
<th></th>
<th>Max LC 1st Result</th>
<th>Average LC 1st Result</th>
<th>CNR 1st Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max LC</td>
<td>0.6139</td>
<td>0.5789</td>
<td>0.1288</td>
</tr>
<tr>
<td>Average LC</td>
<td>0.4244</td>
<td>0.4355</td>
<td>0.0403</td>
</tr>
<tr>
<td>CNR</td>
<td>1.2182</td>
<td>1.2381</td>
<td>2.2933</td>
</tr>
</tbody>
</table>

*Table 13 - Comparison of the best results when using each FOM and corresponding FOM values*
Simulations using $1.977 \times 10^{11}$ photons

In Figure 118 a comparison between the results of the different FOMs is shown. In this case the number of photons has been increased and as it can be seen the results are much better than in the previous case. In each line the first three images with the higher score of for each FOM are shown, presented image are the combination of 100 and 110 KeV images and TCA that each FOM picked with higher score. In following results basis materials values were set using theoretical values of the tissues.

On Table 14 a comparison of the best results when using each FOM are depicted. Below each image the value that the image gets using each FOM is shown. From this table the accordance of visual and FOM investigation using LC can be seen since the LC values of the 3 images depict the actual contrast seen on the images. While in the case of CNR completely fails to detect the image with high contrast.

![Figure 118 - Comparison between the results of the different using $1.977 \times 10^{11}$ photons, basis materials set from theoretical values of the tissues without using filtering.](image-url)
As it is seen from the images the increase on the number of photons used greatly increases the contrast and clear appearance of the brain parenchyma in the final images. The values of the FOMs are also higher in this case showing the correspondence of the value of LC with the visual investigation. CNR although the ROIs are very well placed cannot detect the correct images where the contrast is higher. On the other hand between the max and average LC FOM the average approach seems to produce better results.

In Figure 119 in accordance with the previews figures a comparison between the results of the different FOMs is shown. No additional filtering has been applied in the images either before either after the application of the decomposition algorithm and basis materials values were set using mean values of the ROIs of the tissues.

<table>
<thead>
<tr>
<th></th>
<th>Max LC 1st Result</th>
<th>Average LC 1st Result</th>
<th>CNR 1st Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max LC</td>
<td>0.8686</td>
<td>0.8672</td>
<td>0.1373</td>
</tr>
<tr>
<td>Average LC</td>
<td>0.4478</td>
<td>0.5122</td>
<td>0.0627</td>
</tr>
<tr>
<td>CNR</td>
<td>2.1134</td>
<td>2.2264</td>
<td>3.5449</td>
</tr>
</tbody>
</table>

Table 14 - Comparison of the best results when using each FOM and corresponding FOM values
On Table 15 a comparison of the best results when using each FOM are depicted. Below each image the value that the image gets using each FOM is shown.

**Figure 119 - Comparison between the results of the different using 1.977e11 photons, basis materials set from mean ROIs values without using filtering.**

On Table 15 a comparison of the best results when using each FOM are depicted. Below each image the value that the image gets using each FOM is shown.

**Table 15 - Comparison of the best results when using each FOM and corresponding FOM values**

<table>
<thead>
<tr>
<th>FOM</th>
<th>1st Result</th>
<th>2nd Result</th>
<th>3rd Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max LC</td>
<td>0.6508</td>
<td>0.6355</td>
<td>0.1377</td>
</tr>
<tr>
<td>Average LC</td>
<td>0.3923</td>
<td>0.4322</td>
<td>0.0597</td>
</tr>
<tr>
<td>CNR</td>
<td>2.0831</td>
<td>1.9910</td>
<td>2.5842</td>
</tr>
</tbody>
</table>
In this section a series of results will be shown that were acquired using median filter. A full investigation of the possibilities of the filter is shown. Three different cases are investigated:

- Pre-Filtering, where the median filter is applied in the images before they are set as input to decomposition algorithm
- Post-Filtering, where the filter is applied in the final cancelation image coming as an output from the decomposition algorithm
- Pre and Post Filtering, where the filter is applied in both case before and after the decomposition algorithm.

For each of these cases the use of the different values of basis material are applied as presented before:

- Theoretical values of the tissues attenuation are applied as basis materials
- Mean Values of the ROIs. These mean values, in the case were pre-filtering is applied, are calculated after the image has been filtered.

Finally the use of both different number of photons is investigated. Results are present in the same scheme as in the case of no filter application.
Simulations using $9.527 	imes 10^9$ photons

Pre-Filtering

In Figure 120 a comparison between the results of the different FOMs is shown. In each line the first three images with the higher score of for each FOM are shown, presented image are the combination of 100 and 110 KeV images and TCA that each FOM picked with higher score. In following results basis materials values were set using theoretical values of the tissues.

Pre-filtering using median filter has been applied in the images before the application of the decomposition algorithm.

![Comparison between the results of the different FOMs](image)

Figure 120 - Comparison between the results of the different using $9.527 	imes 10^9$ photons, basis materials set from theoretical values and pre-filtering with median filter.

As it is seen from the images the use of pre-filtering with median filter blurs the images contrast deteriorates and there cannot be a good separation between the boarders of the tissues (edges). Since CNR has proven to be inadequate only LC results will be shown.
In Figure 121 in accordance with the previews figures a comparison between the results of the different FOMs is shown. In this case basis materials values were set using mean values of the ROIs of the tissues as they were calculated after the application of the median filter.

Since the contrast that is achieved with this number of photons is very low using median filter pre-filtering approach no further analysis of these results. It has to be mentioned that in this case max and average LC FOMs have picked the same images as the ones with best contrast.
Post-Filtering

In Figure 122 the three better results from the post filtering approach according to LC FOMs are, shown both max and average LC have produced the same results.

Post-filtering using median filter has been applied in the final cancelation image as it came as an output from the decomposition algorithm.

![Image of results comparisons](Image)

**Figure 122 – The three best results using \(9.527 \times 10^9\) photons, basis materials set from theoretical values and post-filtering with median filter.**

As it is seen from the images the use of post-filtering with median filter produces much better results in comparison of the pre filtering approach. It is also important to notice that although the 1st image has indeed better difference between white and gray matter no other tissues can be seen, while the 2nd and 3rd results have lower contrast but also surrounding tissues are shown.

In Figure 123 in accordance with the previews figures a comparison between the results of the different LC is shown. In this case basis materials values were set using mean values of the ROIs of the tissues.

![Image of results comparisons](Image)

**Figure 123 - Comparison between the results of the different FOMs using \(9.527 \times 10^9\) photons, basis materials set from mean ROIs values and post-filtering with median filter.**
On Table 16 a comparison of the best results when using each FOM are depicted.

Table 16 - Comparison of the best results when using each FOM and corresponding FOM values

<table>
<thead>
<tr>
<th></th>
<th>Max LC 1st Result</th>
<th>Average LC 1st Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max LC</td>
<td>0.7915</td>
<td>0.7868</td>
</tr>
<tr>
<td>Average LC</td>
<td>0.4105</td>
<td>0.4321</td>
</tr>
</tbody>
</table>

As it can be seen from the images, the use of post-filtering combined with values of basis materials from the ROIs produces better results even in this low dose setup. It is also important to notice that max LC manages to find the images with the higher contrast, but average LC find images were more information of the surround tissues are kept which in some cases may have greater clinical value. Thus the both use be used depending on the application.
Simulations using $1.977\times10^{11}$ photons

Pre-Filtering

In Figure 124 a comparison between the results of the different FOMs is shown. In each line the first three images with the higher score of for each FOM are shown, presented image are the combination of 100 and 110 KeV images and TCA that each FOM picked with higher score. In following results basis materials values were set using theoretical values of the tissues.

Pre-filtering using median filter has been applied in the images before the application of the decomposition algorithm.

![Image](image_url)

*Figure 124 - Comparison between the results of the different using $1.977\times10^{11}$ photons, basis materials set from theoretical values and pre-filtering with median filter.*

As it can be seen from visual investigation the contrast on images selected using LC FOM is higher than in the ones selected using CNR. Especially in the case of max LC the images have the higher contrast.

On Table 17 a comparison of the best results when using each FOM are depicted. Below each image the value that the image gets using each FOM is shown. From this
table the accordance of visual and FOM investigation using LC can be seen since the LC values of the 3 images depict the actual contrast seen on the images. While in the case of CNR the image has inferior contrast nevertheless it has better CNR score.

As it is seen from the images the use of pre-filtering with median filter blurs the images and although contrast is maintained there cannot be a good separation between the boarders of the tissues (edges).

As it is seen from the images the use of pre-filtering with median filter blurs the images and although contrast is maintained there cannot be a good separation between the boarders of the tissues (edges).

### Table 17 - Comparison of the best results when using each FOM and corresponding FOM values

<table>
<thead>
<tr>
<th></th>
<th>Max LC 1st Result</th>
<th>Average LC 1st Result</th>
<th>CNR 1st Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max LC</td>
<td>0.9110</td>
<td>0.9110</td>
<td>0.0350</td>
</tr>
<tr>
<td>Average LC</td>
<td>0.3852</td>
<td>0.4002</td>
<td>0.0241</td>
</tr>
<tr>
<td>CNR</td>
<td>1.9957</td>
<td>1.9957</td>
<td>2.2838</td>
</tr>
</tbody>
</table>

As it is seen from the images the use of pre-filtering with median filter blurs the images and although contrast is maintained there cannot be a good separation between the boarders of the tissues (edges).

In Figure 125 in accordance with the previews figures a comparison between the results of the different FOMs is shown. In this case basis materials values were set using mean values of the ROIs of the tissues as they were calculated after the application of the median filter. Since the use of CNR has proven it not to be adequate FOM only results from LC is shown.
As it can be seen from visual investigation in this case max LC and average LC FOM have picked very similar images as the best results. This can also be seen and on Table 18 were a comparison of the best results when using each FOM are depicted. Below each image the value that the image gets using each FOM is shown. From the values of the FOMs are very close in both images.

<table>
<thead>
<tr>
<th>Max LC 1st Result</th>
<th>Average LC 1st Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max LC</td>
<td>0.7659</td>
</tr>
<tr>
<td>Average LC</td>
<td>0.4891</td>
</tr>
</tbody>
</table>

As it is seen from the images all though higher number of photons is used the application of filtering before the images are set as input on the decomposition algorithm deteriorates the quality of the image.
Post-Filtering

In Figure 126 results the three better results from the post filtering approach according to LC FOMs are, shown both max and average LC have produced the same results.

Post-filtering using median filter has been applied in the final cancelation image as it came as an output from the decomposition algorithm.

When higher dose is used the use of post-filtering with median filter produces much better results in comparison of the pre filtering approach.

In this case of higher dose the max and average LC have picked different results as better. Max LC seems to have the best discrimination ability as also seen in Table 19.

![Figure 126 - Comparison between the results of the different using 1.977e11 photons, basis materials set from mean ROIs values and post-filtering with median filter.](image)

<table>
<thead>
<tr>
<th>Max LC 1st Result</th>
<th>Average LC 1st Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max LC</td>
<td>0.9444</td>
</tr>
<tr>
<td>Average LC</td>
<td>0.4109</td>
</tr>
</tbody>
</table>

Table 19 - Comparison of the best results when using each FOM and corresponding FOM values
In Figure 127 the best 3 results are shown since when the basis materials values were set using mean values of the ROIs of the tissues, both max and average LC pick the same images as optimum.

As it can be seen from the images, the use of post-filtering combined with values of basis materials from the ROIs produces the best results.

**Pre and Post - Filtering**

When filter is applied in the both stages, before the decomposition and at the final cancelation image the resulted image is strongly affected. There is evident blurring in all cases and edges information are completely lost. This method is not providing good results even in the case of high number of photons (Figure 128)
As it was presented in the material and methods, the NAD filter has 2 main parameters that can be altered. The number of iterations that the filter will execute, and the diffusion constant that will affect the edge sharpening of blurring of the result. In this investigation the 2nd option can take 2 different value, 1 and 2 for edge sharpening and blurring result respectively.

**Simulations using 9.527e10 photons**

**Pre-Filtering**

In the following table (Table ) the results for max LC, average LC and CNR FOMs are shown for all 24 investigated combinations. The combination include 1 to 55 iterations for both edge sharpening option 1 and 2 (1 enhances edge sharpening, 2 more blurred result). The FOMs were also calculated in all cases using theoretical values for basis materials or mean value of ROIs, as presented in the previews paragraphs.

<table>
<thead>
<tr>
<th>Edge Option</th>
<th>Iterations</th>
<th>Max LC</th>
<th>Average LC</th>
<th>CNR</th>
<th>Edge Option</th>
<th>Iterations</th>
<th>Max LC</th>
<th>Average LC</th>
<th>CNR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>0.6811</td>
<td>0.3972</td>
<td>8.7013</td>
<td>1</td>
<td>1</td>
<td>0.8373</td>
<td>0.4725</td>
<td>6.2653</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>0.6997</td>
<td>0.3972</td>
<td>11.8790</td>
<td>1</td>
<td>2</td>
<td>0.8373</td>
<td>0.4725</td>
<td>11.2824</td>
</tr>
<tr>
<td>1</td>
<td>3</td>
<td>0.7610</td>
<td>0.3972</td>
<td>14.0489</td>
<td>1</td>
<td>3</td>
<td>0.7951</td>
<td>0.4661</td>
<td>14.0022</td>
</tr>
<tr>
<td>1</td>
<td>4</td>
<td>0.7669</td>
<td>0.3972</td>
<td>15.4883</td>
<td>1</td>
<td>4</td>
<td>0.7583</td>
<td>0.4578</td>
<td>15.4668</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>0.6997</td>
<td>0.3972</td>
<td>8.6930</td>
<td>2</td>
<td>1</td>
<td>0.8373</td>
<td>0.4725</td>
<td>6.8834</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>0.6997</td>
<td>0.3972</td>
<td>11.7851</td>
<td>2</td>
<td>2</td>
<td>0.7951</td>
<td>0.4661</td>
<td>11.2824</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>0.7610</td>
<td>0.3972</td>
<td>14.0489</td>
<td>2</td>
<td>3</td>
<td>0.7583</td>
<td>0.4578</td>
<td>13.9657</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>0.7669</td>
<td>0.3972</td>
<td>15.4883</td>
<td>2</td>
<td>4</td>
<td>0.7263</td>
<td>0.4504</td>
<td>15.4320</td>
</tr>
<tr>
<td>1</td>
<td>5</td>
<td>0.7181</td>
<td>0.3972</td>
<td>15.8373</td>
<td>1</td>
<td>5</td>
<td>0.6983</td>
<td>0.4418</td>
<td>16.2092</td>
</tr>
<tr>
<td>1</td>
<td>10</td>
<td>0.6997</td>
<td>0.3972</td>
<td>15.8473</td>
<td>1</td>
<td>10</td>
<td>0.6801</td>
<td>0.4304</td>
<td>17.6183</td>
</tr>
<tr>
<td>1</td>
<td>15</td>
<td>0.6995</td>
<td>0.3972</td>
<td>16.8377</td>
<td>1</td>
<td>15</td>
<td>0.6745</td>
<td>0.4184</td>
<td>19.8396</td>
</tr>
<tr>
<td>1</td>
<td>20</td>
<td>0.6915</td>
<td>0.3972</td>
<td>18.2044</td>
<td>1</td>
<td>20</td>
<td>0.6693</td>
<td>0.4075</td>
<td>22.3701</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>0.7579</td>
<td>0.3972</td>
<td>15.8045</td>
<td>2</td>
<td>5</td>
<td>0.6705</td>
<td>0.3965</td>
<td>16.1221</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>0.7380</td>
<td>0.3972</td>
<td>15.8617</td>
<td>2</td>
<td>10</td>
<td>0.6705</td>
<td>0.3965</td>
<td>17.6794</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>0.6969</td>
<td>0.3972</td>
<td>16.8417</td>
<td>2</td>
<td>15</td>
<td>0.6594</td>
<td>0.3965</td>
<td>19.8949</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>0.6766</td>
<td>0.3972</td>
<td>18.2084</td>
<td>2</td>
<td>20</td>
<td>0.6477</td>
<td>0.3858</td>
<td>22.3540</td>
</tr>
<tr>
<td>1</td>
<td>25</td>
<td>0.6750</td>
<td>0.3972</td>
<td>24.5951</td>
<td>1</td>
<td>25</td>
<td>0.6367</td>
<td>0.3760</td>
<td>31.8296</td>
</tr>
<tr>
<td>1</td>
<td>35</td>
<td>0.3871</td>
<td>0.1829</td>
<td>26.2502</td>
<td>1</td>
<td>35</td>
<td>0.6181</td>
<td>0.3647</td>
<td>33.2914</td>
</tr>
<tr>
<td>1</td>
<td>45</td>
<td>0.3871</td>
<td>0.1829</td>
<td>27.9202</td>
<td>1</td>
<td>45</td>
<td>0.5993</td>
<td>0.3537</td>
<td>34.1511</td>
</tr>
<tr>
<td>1</td>
<td>55</td>
<td>0.3675</td>
<td>0.1795</td>
<td>29.4579</td>
<td>1</td>
<td>55</td>
<td>0.5820</td>
<td>0.3436</td>
<td>34.7941</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>0.4246</td>
<td>0.1967</td>
<td>24.9413</td>
<td>2</td>
<td>25</td>
<td>0.5660</td>
<td>0.3342</td>
<td>31.7673</td>
</tr>
<tr>
<td>2</td>
<td>35</td>
<td>0.4246</td>
<td>0.1967</td>
<td>26.3125</td>
<td>2</td>
<td>35</td>
<td>0.5510</td>
<td>0.3255</td>
<td>35.1936</td>
</tr>
<tr>
<td>2</td>
<td>45</td>
<td>0.4040</td>
<td>0.1926</td>
<td>27.9202</td>
<td>2</td>
<td>45</td>
<td>0.5370</td>
<td>0.3172</td>
<td>35.0224</td>
</tr>
<tr>
<td>2</td>
<td>55</td>
<td>0.3425</td>
<td>0.1740</td>
<td>29.3812</td>
<td>2</td>
<td>55</td>
<td>0.5237</td>
<td>0.3095</td>
<td>34.6381</td>
</tr>
</tbody>
</table>

As it can be seen from the above table the highest contrast results are achieved using a number of iteration around 2-5 and values of basis materials set by mean of ROIs. Additionally we can clearly see the deterioration of image contrast when iterations are over 20, which is in agreement with the visual investigation in the following figures.
In Figure 1 results from application of NAD filter with both edge options and different number of iterations are shown. The values of basis material are theoretically set.

In Figure 1 the same results as in the previous figures are shown with differentiation that in this case the base materials values were set by mean values of

![Image of Figure 1 showing comparison between different NAD pre filtering options using 9.52e10 photons, basis materials set from theoretical.](image-url)
the ROIs. This has every big effect as it is seen in the resulted images, in which the contrast is better than in the cases of theoretical values for basis material. This also is in accordance with the FOMs. Additionally the number of iteration doesn’t affect very much result from 5 to 20 iterations after that dense blurring occurs. For this reason only result with up to 20 iteration will be presented from now on. Post filtering results will be shown for the case of higher number of photons.

Simulations using 1.977e11 photons

Pre-Filtering

In Table 21 FOMs from the application of the NAD filter in all presented combination when high number of photons is shown. As it is seen the values of all FOMs are higher than in the case of lower number of photons and again the images that were created using as basis materials values the mean of the ROIs are higher and kept for even higher number of iterations. The actual images are shown in the following figures for visual comparison of the results.

Table 21 - Highest FOMs values for all different options. 1.977e11 photons used and pre-filtering was applied.

<table>
<thead>
<tr>
<th>Edge Option</th>
<th>Iterations</th>
<th>Max LC</th>
<th>Average LC</th>
<th>CNR</th>
<th>Edge Option</th>
<th>Iterations</th>
<th>Max LC</th>
<th>Average LC</th>
<th>CNR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>0.8670</td>
<td>0.4203</td>
<td>7.9935</td>
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<td>40.2798</td>
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<td>45</td>
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<td>55</td>
<td>0.8164</td>
<td>0.3624</td>
<td>34.8089</td>
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In Figure 130 results from application of NAD pre filtering with up to 20 iterations are shown, in this case the basis materials values are set using theoretical values, as it can be seen the images have greater contrast than the ones with the lower number of photons and additionally coming in to agreement with the FOMs when the option 2...
is used for filtering the image quickly blur out even at only 5 iteration steps. Although the result when 3 iterations are performed is the best both in optical and FOMs values.

![Image of 1st Edge Option with 1, 3, 5, and 10 iterations]

![Image of 2nd Edge Option with 1, 3, 5, and 10 iterations]

**Figure 131 - Comparison between the results of the different NAD pre filtering options using 1.9e11 photons, basis materials set from mean of ROIs.**

Again in accordance with the FOM values, when basis materials are set using the ROIS then better results are occurring. As in the case of lower number of photons, also in this case a different response of the filter in the speed of blurring result on the image is seen. Although the images become more and more blurred when the number of iterations is increased, especially in case of edge option 2, the speed of blurring and deterioration of the image quality is much lower in the case were mean values from the ROIs within the image are used.
Post-filtering

In Table 22 the FOMs for the case of post-filtering using different settings for NAD filter are presented. Both cases of basis materials values from theory and means of ROIs within the image are given. Based on the conclusions from the previous analysis, iterations were set up to 20.

Table 22 - Highest FOMs values for all different options. 1.977e11 photons used and post-filtering with NAD filter applied.

<table>
<thead>
<tr>
<th>Theoretical Values for Basis material</th>
<th>Mean of ROIs for values of Basis Material</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edge Option</td>
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<tr>
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</tr>
<tr>
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<td>2</td>
</tr>
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<tr>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
</tr>
</tbody>
</table>

As it can be seen in from the LC FOMs in the case of filtering using the NAD filter for post filtering the final cancelation image, the resulted contrast isn’t better than when pre-filtering is applied as in the case of median filter. The use of NAD filter for post filtering increased although it increases the contrast of the image, the maximum FOM values that are achieved are not as high as in the case of pre0filtering. Again, also in this case as in the pre-filtering, the choice of basis material values is very important for the final result. As it seen from the LC FOMs when the values of the basis materials are set using the mean of the ROIs within the images the resulting contrast is greater than in the case that theoretical data are used. This has to do with the high sensitivity of the decomposition algorithm in the basis materials, which is confirmed by the FOMs. Due to the presence of noise the values of the pixel differ from the theoretical ideal ones, thus when the basis material is set based on theory it doesn’t represent the real values within the image. On the other hand when mean values from ROIs within the image are taken better results are produce. In the following figures () the optical confirmation of these finding is shown.
Figure 132 - Comparison between the results of the different NAD post filtering options using $1.9e^{11}$ photons, basis materials set from theoretical values.
As it can be seen the resulted images come into agreement with the conclusions drawn by the LC FOMs.
Results from optimized DE with different filtering parameters

As it was described in the DE optimization part, of material and methods, in order to further increase the quality of the produced DE images in terms of contrast between white and gray tissue, a reverse engineering approach was followed. According to this, the formulas from calculating the value of two neighbouring pixels has been recalculated and the values of bases materials in order to maximise this deference are searched. The maximization is done using Matlab’s Optimization Toolbox and in particular two different algorithm the Globalsearch and Multistart. This local minima find optimization approach has to do with the starting conditions (initial values) and the constrains that are set to optimizer. The starting values are randomly selected based on user’s input and a series of iterations are performed in order to change the starting values until a local minima is reached.

From the way the optimization works it is understood that the output of the algorithm is not deterministic but is probabilistic and thus varies between successive executions of the code. For this reason a series of experiments were done in order to find the best values for the bases materials for the DE decompositions algorithm.

At the beginning both optimization algorithms were run for a set of images with noise but no constrains were set in the outputs of the functions as it can be seen in the following part of Matlab code:

```matlab
starting=[ m1_low m1_high m2_low m2_high];
problem = createOptimProblem('fmincon',...
    'objective', @(x) objecfun_new(x,m1_low,m1_high,m2_low,m2_high,a_abs),...  
    'x0',[starting , 100*rand],'
    'Aineq',[],'bineq',[],...
    'lb',[0,0,0,0,0], 'ub',[inf,inf,inf,inf,360],...
    'options',optimset('Algorithm','sqp'));
gs = GlobalSearch;
ms = MultiStart;
```

As it can be seen the lower bounds of the output (the ‘lb’ term) are set to 0 in order to ensure that the values of basis materials will be positive (negative has no physical meaning), and the upper bound (the ‘ub’ term) are set to infinite in order to let the algorithms produce any possible output.

Both algorithms were executed for 1000 times in order to statistically investigate the proposed values for basis materials. As it is seen in the Figure 134, where a histogram of an indicating results’ set is shown, the greatest percentage of the proposed optimal values for the basis materials were in a range shorter than ±10% of the mean values of the ROIs within the image. Therefore the outputs constrains on the output of the optimization procedure were set in the range of
±1% of the mean values of the ROIs within the image. The part of the Matlab’s code for setting constrains was the following:

```matlab
result_range = 0.01;
starting = [m1_low m1_high m2_low m2_high];
problem = createOptimProblem('fmincon', ...  'objective', @(x) objecfun_new(x, m1_low, m1_high, m2_low, m2_high, a_abs), ...  'x0', [10*rand(1,4), 100*rand], 'Aineq', [], 'bineq', [], ...  'lb', [(1-result_range)*m1_low, (1-result_range)*m1_high, (1-result_range)*m2_low, ...  (1-result_range)*m2_high, 0], 'ub', [(1+result_range)*m1_low, (1+result_range)*m1_high, ...  (1+result_range)*m2_low, (1+result_range)*m2_high, 360], ...  'options', optimset('Algorithm','sqp'));
gs = GlobalSearch;
ms = MultiStart;
```

As it is shown the output of the optimization procedure is restricted in ±1% of the input which was the mean values of the ROIs.

According to the optimum settings derived from the presented investigation of DE decomposition with the presence of noise results using the optimization will be shown for the following cases:

- Without Filtering
- Using Pre-filtering with median filter
- Using Pre-filtering with NAD filter

In all cases the staring values that were set as inputs in the images were mean values of ROIs within the image (filtered on non-filtered depending on the case). For each of these cases the optimization was executed values of the proposed optimum results were set as values for the basis materials. All results have simulated noise using 1.9e11 photons.

As it will be shown from the results of the optimization procedure the decomposition algorithm is extremely sensitive on the values of the basis material. Although good results are acquired using the procedure the best practice is concluded to be the use of the mean values for the ROIs within the image.
Without Filtering

The first thing that has to be noticed is the reaction of the DE algorithm in the alternation of the values of the bases materials. In Figure 135 a comparison of the plots of the max LC FOM versus the Tissue Cancelation Angles when values of bases materials are set from mean of ROIS, results of Global Search and Multistart optimization algorithms is shown.

As it is seen due to the change of the values of the bases materials the algorithm only creates contrast in very specific TCA that appears as spikes in the graphs. The resulted FOM values are good but the results using the mean values of ROIs within the images are better. In the following figure the best contrast images are shown.

Another conclusion is that the global search algorithm seems to produce better results than the multistart.
**Median Filter**

In the following figure results from the application of post filtering using median filter, which was concluded to have better results than pre-filtering are shown. In Figure 137 a comparison of the plots of the max LC FOM versus the Tissue Cancelation Angles when values of bases materials are set from mean of ROIS, results of Global Search and Multistart optimization algorithms is shown.

In this case the result of the Multi Start algorithm is much lower than of Global Search and mean of ROIs. Again although Global search produces good results they are inferior to the mean values of ROIs. The actual images are shown in the next Figure 138.
As last comparison results from the application of pre filtering using NAD filter using edge option 2 and 3 iterations are shown. In Figure 139 a comparison of the plots of the max LC FOM versus the Tissue Cancelation Angles when values of bases materials are set from mean of ROIS, results of Global Search and Multistart optimization algorithms is shown.

Figure 139 - Comparison of the plots of max LC FOM versus TCA when pre filtering with NAD filter and values of bases materials are set from mean of ROIS, results of Global Search and Multistart optimization algorithms

The same results as in the previous case are seen and with the use of NAD filter. Again the multi start algorithm produces very low results. The actual images are shown in the next figure.

Figure 140 – Resulted contrast images when pre-filtering with NAD and values of bases materials are set from mean of ROIS, results of Global Search and Multistart optimization algorithms
Chapter 5 DE images from Real Brain CT Data

Intro

In this chapter the application of the algorithm on real data will be presented. As mentioned before, during this study a series of real data have been used in order to compare with real images and also for determining the attenuation coefficients of the tissues of the brain. One of these sets of data will be used here in order to present the results that can be achieved when the decomposition is applied in combination with filtering in real brain dual energy images.

It has to be stressed that the data that are used are data coming from a simple head DE and not from a cerebral Ct perfusion studies. Thus the dose used here is way lower than in the case of cerebral Ct perfusion studies or the doses simulated in previous chapter. This has a significant result in the noise of the images which is very high.

Additionally it has to be noted that the energies to be used couldn’t be altered and were set to 80kVp for low energy and 140kVp for high energy and not the 80-100kVP setting that was found to be optimum during the simulation study.

The result of these very crucial constrains is that the available images were of low image quality and with presence of great noise. In Figure the low and high energy slices used in the rest of the investigation are shown. These are the initial images from where contrast will be tried to achieved. As it is seen there is no ability to discriminate any tissue in the brain parenchyma.

Results from gray white differentiation and from a lesion that was present in higher slices will be shown.
**Materials & Methods**

The images used were acquired from the University Hospital of Sv. Marina, Varna Bulgaria. They were acquired using a Siemens Somatom DE scanner and the spectra used were 80 and 140 kVP for low and high energy respectively.

Images were analysed using the presented decomposition algorithm using values from means of ROIs within the images and DE optimization. All images were filtered with pre-filtering, since this had proven to produce the better results. Pre filtering was the only option in this case since very low dose had been used, and slight change of the parenchyma had to be intensified in order to achieve contrast. Two different filter were used:

- Anisotropic Diffusion filter, in which as present before a number of combinations of the edge option parameter and number of iterations were investigated.
- Sparse filter, in which a number of combinations of the size of the block and size of dictionary used were also investigated.

Two ROIs have been selected the mean values of which were used as inputs for the values of bases materials. The position of the ROIs can be seen in Figure 143.

![Figure 143 - ROIs used for setting the values of bases materials](image)

Optimization DE algorithm was also used while in this case of real data results from using and not using constrains on the output were used. Only selected results from all the combinations tried and data produced will be presented in this chapter.
Results

NAD Filter

In total 16 combinations of the edge option parameter and number of iterations have been investigated:

- Edge option between the two value for edge sharpening and blurring effect
- Iterations from 1 up to 20, since the images were intensively blurred for more iterations.

In the following Figure 144 results using a small number of iterations and edge option 1 and 2 are shown.

![Figure 144 – Results of low iteration number using NAD pre filtering](image)
As it can be seen with this small number of iterations no discrimination between gray and white matter can be achieved.

In Figure 145 when the number of iterations is increased the discrimination of gray and white matter is more feasible and the overall area that is captured by white matter can be discriminated.

*Figure 145 – Results of high iteration number using NAD pre filtering*
In Figure 146 optimum results are shown when DE optimization as applied after different runs and without the use of constrains in the output. The window in the images has been changed in order to achieve better result.

As it seen using NAD pre-filtering we are able to discriminate the gray from white matter, all thought details cannot be seen, the overall area occupied by white matter is shown.
In total 20 combinations of the block size and dictionary size have been investigated:

- Block sizes of 8 and from 12 to 18 with a increment step of 2
- Dictionary sizes from 128 to 512 with an increment step of 128

The dictionary size was found to perform better at the size of 256, as also reported in [86] therefore only results using a dictionary size of 256 will be shown. In the following figures 2 selected results from each block size will be shown.

Figure 147 – Results using Sparse pre-filtering with block sizes from 8 to 12
As it seen the Sparse filter can produce smoother images and greater contrast than the NAD filter. As the block size increases the blurring is also increased starting to greatly deteriorate the image quality.

Application of sparse filtering produces more smoothed areas while preserving the edges of the areas of different matters. Thus it is better for understanding the exact area in which is tissues is.
Imaging of Lesion

As it is seen in the images produced and presented, in the upper right part of the head the white matter seems to take smaller area than in the left part of the brain. This is more evident on the images produced using sparse filtering (Figure 147 and Figure 148).

This is not an artefact, the reason for this the fact than in higher parts of the brain a lesion exits which has taken this volume. The region is also seen in the initial images as is shown in Figure 149. On the upper right part of the brain the lesion is visible in the low energy image.

The decomposition algorithm was used with sparse pre filtering. Selected results are shown in the following figures. Block sizes of 2 and 4 were used in order to better preserve the edges of the lesion. The dictionary size was set to 256.
The imaging of the lesion is greatly increased when the DE algorithm is applied. The block size greatly affect the edges of the images, since in Figure 150 were a small block size equal to 2 is used the edges are much sharper than in Figure 151 were size 4 is used. Nevertheless in both cases the contrast is greatly increased.
Chapter 6 Cancer Simulation

Intro

In order to investigate the possibility of imaging brain tumours in early stages with DE CBCT, a small ellipsoid tumour has been inserted in the 3D phantom, in the part of the white matter. As it is presented in the imaging of the brain paragraph of chapter 2, imaging of brain tumours using x-rays is limited in very particular cases. Such case are the tumours that create calcifications, where the calcifications regions are very well images with CT or in high grade tumours where the necrotic areas inside the tumour are also well depicted with brain ct.

The aims of this study is to investigate if the application of DE decomposition technique, could allow us to image brain tumours in earlier stages. As it is known early stage tumour tissues differentiate slightly from the healthy tissue, and their discrimination cannot be done even during operations were visual contact is available. For this reason imaging of low grade gliomas is difficult using x-ray since their attenuation coefficient are very close. The only way that surgeons are able to discriminate between early stage tumours that are in the outer area of the lesion and the healthy tissue in order to completely remove cancer cells during an operation, is by palpitation the tissue around the tumour since the tumours tissues if slightly less soft that healthy tissue. Use of ultrasound electrography has been proposed an investigated the last years in order to measure the elasticity (hardness) of brain tissues and guide surgeons to completely remove tumours [89-91].

An ellipsoidal tumour was inserted in the white tissue region of the brain, in the border with gray matter and imaging of that tumour is investigated, is done and presented using analytical simulation and noise free ideal images. Two different tumour grades have been simulated assuming different levels of densities and selected results are briefly presented.
Materials & Methods

Brain Phantom with Tumour

The same brain phantom used in the case of analytical simulations is used and a small ellipsoidal tumour has been inserted in the white matter area of the brain parenchyma. The tumour is not in the centre of the white matter, but is placed on the boarders with gray matter in order to better investigate the imaging of low grade gliomas and their ability to be differentiated from both white and gray matter. The position and size of the inserted lesion is shown in Figure 152. A three orthogonal view of the brain phantom is shown with the tumours highlighted in order to be better viewed.

The values of the tissues with in the phantom are the same as in the case of analytical simulation presented in chapter 3. Values of the attenuation coefficient of the tissue were set for each pixel. Calculation of these values was done using theoretical kai real data as presented before. For the case of low grade brain tumour the attenuations coefficients were set by altering the density of the tissue. This was decided based on the inputs from neurosurgeons about the difference of the hardness between healthy and tumours tissues. Since the GBM is a white matter tumour, the composition of the tissue was kept the same as of white matters (since we are in very early stage no great differentiations have happened) and only the densities were increased by 1.5% and 2.5% for 1st and 2nd grade tumours respectively. In Table 23 the HU and densities used for each tissue are listed.

<table>
<thead>
<tr>
<th>Tissue</th>
<th>HU</th>
<th>Density (gcm⁻³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone</td>
<td>1527</td>
<td>1.92</td>
</tr>
<tr>
<td>CSF</td>
<td>13</td>
<td>1.01</td>
</tr>
<tr>
<td>White Matter</td>
<td>24</td>
<td>1.04</td>
</tr>
<tr>
<td>Gray Matter</td>
<td>35</td>
<td>1.04</td>
</tr>
<tr>
<td>1st Grade Tumour</td>
<td>24</td>
<td>1.055</td>
</tr>
<tr>
<td>2nd Grade Tumour</td>
<td>24</td>
<td>1.066</td>
</tr>
</tbody>
</table>
Using the relationship between HU and the linear attenuation coefficient, the values of the linear attenuation coefficients of the tissues per incident energy were calculated as followed:

\[
HU = 1000 \times \frac{\mu_X - \mu_{\text{water}}}{\mu_{\text{water}}}
\]

The resulted linear attenuation coefficients for each tissue are listed in Table 24. Coefficients on this table are calculated for x-ray photon energy of 100keV and 110 keV.

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Attenuation at 100keV</th>
<th>Attenuation at 110keV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone</td>
<td>0.8248</td>
<td>0.8006</td>
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<tr>
<td>CSF</td>
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<td>0.1688</td>
</tr>
<tr>
<td>White Matter</td>
<td>0.1810</td>
<td>0.1757</td>
</tr>
<tr>
<td>Gray Matter</td>
<td>0.1830</td>
<td>0.1776</td>
</tr>
<tr>
<td>1st Grade Tumour</td>
<td>0.1838</td>
<td>0.1784</td>
</tr>
<tr>
<td>2nd Grade Tumour</td>
<td>0.1856</td>
<td>0.1801</td>
</tr>
</tbody>
</table>

One hundred and eighty (180) ideal projection images are generated within a full gantry acquisition arc of 360° for each of the incident monochromatic beams. DE algorithms were subsequently applied. Brain CT slices of the obtained dual energy images were generated using filtered Multiple Projection Algorithm (fMPA) [78], selected results from ideal simulation are briefly presented.
Results

1st Grade Tumour

In the following figure (Figure 153) selected results of imaging of the 1st grade tumour are shown. The optimum energy set, as found in the investigations presented in chapter 4, of 100 keV and 110 keV was used. The DE decomposition algorithm was used without the need of any filtering due to the ideal nature of the images. As it can be seen there can be a very clear differentiation of the tumour. Theoretical values of the tissues attenuation coefficient were used as values of bases materials for the decomposition.

Figure 153 – Selected results of 1st grade tumour imaging
In the Figure 154 selected results of imaging simulation of the 2nd grade tumour are shown. The optimum energy were again set to 100 keV and 110 keV. The DE decomposition algorithm was used without the need of any filtering due to the ideal nature of the images. As it can be seen there can be a very clear differentiation of the tumour. Theoretical values of the tissues attenuation coefficient were used as values of bases materials for the decomposition.

As it seen from the presented results the imaging of low grade tumours could be feasible using DE CBCT with the proposed decomposition algorithm. Future investigations will simulate the tumour imaging in present of noise using analytical and Monte Carlo simulations.
Chapter 7 General discussion and Conclusions

As presented CT has many advantages as an imaging modality but in the case of brain imaging is lacking of ability to image the tissues in the parenchyma of the brain and brain tumours in early stages. Aim of the presented research is to investigate whether CT could be used to image the soft tissue of the brain since this would provide an extremely powerful tool in the hand of the clinicians.

Main aim is to differentiate gray from white matter with X-ray imaging, since it will allow many pathologies to be detected, close the gap with MRI and is a condition that will lead to the visualization of cancer in early stages.

In order to perform this investigation a brain model had to be used and altered in order to be applicable in x-ray simulations. Additionally for the many different DE techniques used it was finally concluded that the DE decomposition technique proposed by Alvarez [62] was the ones to perform better. As is was shown from all the presented results the DE algorithm truly manage to produce contrast between brain parenchyma tissues in all a cases used even in real data.

During the investigation and mainly due to great number of images created for all different setting and cases test, the need of a good and reliable FOM came up. Many well know FOM were used but didn’t seem to have the required sensitivity and ability to pic the correct images, thus an in home FOM ware developed based on line profiles which had very good results and great ability of detecting the best images.

In order to further increase the achieved contrast with the DE decomposition algorithm an optimization of the algorithm is proposed, based on solving inversely the problem of contrast between pixels and trying to find the local minimas of the functions that relates them.

Conclusions that were made from each part of the investigation are presented.

Initial noise free investigation

Energy investigation

As a first step an noise free investigation was done in order to determine which are the optimum energies to be combined in order to achieve higher contrast. It was conclude that the optimum energies were 100 keV and 100 keV for the case of monochromatic beam and 80 and 100 kVp in the case of x-ray spectrum. The resulting contrast using polychromatic energy beams is inferior to the monochromatic images, but this was expected and comes into agreement with theory, thus confirming the validation of the simulation procedure.
**FOMs investigation**

Additionally using the noise free simulation results a thorough investigation of the FOMs was done which showed that LC FOM had the best performance since it was proven to be much more efficient in finding the images with the higher contrast. It also provided the most consisted results in terms of visual and quantitatively agreement than all other FoMs used. CNR although the ROIs were very well placed couldn’t detect the correct images where the contrast is higher. As far as comparing between the two different outputs of LC, It is important to notice that max LC manages to find the images with the higher contrast, but average LC find images were more information of the surround tissues are kept which in some cases may have greater clinical value. Thus the both use be used depending on the application.

Results from this ideal investigation were used for the rest of the research.

**Added Noise**

After concluded on the FOMs to be used and the optimum energies to be combined noise was added to the images simulating 2 different dose scenarios, a low dose and a high dose one. As it was expected when higher dose was used the resulted image contrast and quality was higher. A series of filtered user used either pre of post applied to the data and the conclusions made are the following:

**Without filtering**

As it was shown the presence of noise greatly deteriorates the resulting contrast. The use of mean values from the ROIs within the images as values for the bases materials of the decomposition algorithm produces better results.

**Median Filter**

In the case of filtering using mean filter it was shown that the use of post-filtering combined with values of basis materials from the ROIs produces better. Pre- filtering also increased the quality of the images compared to non filtered but was inferior of the post processing results. When filter is applied in the both stages, before the decomposition and at the final cancelation image the resulted image is strongly affected. There is evident blurring in all cases and edges information are completely lost. This method is not providing good results even in the case of high number of photons.
Non Linear Anisotropic Diffusion Filter

When NAD filter was used the highest contrast results are achieved using a number of iteration around 2-5 and values of basis materials set by mean of ROIs. Additionally the deterioration of image contrast when iterations are over 20 was clearly evident since after that dense blurring occurs.

In contrast with the mean filter the NAD filter had better resulted when applied before the decomposition algorithm. This was because of the nature of the filter with smoothens the values over an area without edges but at the same time keeping the edges that separates areas that are occupied from different tissues. This way the prefilled images where entered in the decomposition algorithm could produce better and more smooth result. Gain, also in this case as in the pre-filtering, the choice of basis material values is very important for the final result. When the values of the bases materials are set using the mean of the ROIs within the images after they are filtered the resulting contrast and image quality is further increased. This has to do with the high sensitivity of the decomposition algorithm in the basic materials. Due to the presence of noise the values of the pixel differ from the theoretical ideal ones, thus when the basis material is set based on theory it doesn’t represent the real values within the image. On the other hand when mean values from ROIs within the image are taken better results are produce.

DE optimization

The DE technique proved that the decomposition algorithm is extremely sensitive on the values of the basis material. Good results were acquired using the procedure the best practise is concluded to be the use of the mean values for the ROIs within the image for the case of the simulated images.

In the case of real images the decomposition technique was able to create very good result sometime even better that then mean values of the ROIs, but due to its probabilistic output many run have to be performed to achieve the result.

Between the two different solvers used for finding the minima of the functions the Global search produced better result than the multi start, mainly due to the fact that it tries multiple starting points and thus is able to find better local minima for greater areas.
Real data

The algorithm was also used in real data taken from the University Hospital of Varna. Pre filtering was applied for the same reason as presented before, and since it was proved from the simulation procedure that it produces better results. Due to the low dose and over all very high noise presence on the data, the pre filtering as done using more iterations than in the cases of simulated data. This was done in order to allow the filter to greatly smoother areas that contained the same tissue din order for them to be differentiated when the DE algorithm was applied.

Non Linear Anisotropic Diffusion Filter

After pre filtering with NAD it was seen that when the number of iterations is increased the discrimination of gray and white matter is more feasible and the overall area that is captured by white matter can be discriminated. When DE optimization was applied after different runs and without the use of constrains in the output the results were also very good.

Sparse Filtering

A sparse filter was also used in the real data and it was proven that Sparse filter can produce smoother images and greater contrast than the NAD filter. As the block size increases the blurring is also increased starting to greatly deteriorate the image quality. Application of sparse filtering produces more smoothed areas while preserving the edges of the areas of different matters. Thus it is better for understanding the exact area in which is tissues is.

Sparse pre filtering and the DE algorithm was also used to investigate the inverse in contrast of a lesion in the brain. The results was a great increase in the contras while keeping the edges of the lesion very clearly imaged.
Main contribution points of the PhD work

- Development of a novel Figure of Merit (FoM) which is based on analysis of data extracted from line profiles within the image and is referred as Line Contrast (LC). LC comes into full accordance with visual assessment, has consistent agreement with visual investigation results and overpass the traditionally used CNR, especially in the ability of detecting higher contrast images and the edge enhancement when different filters are used.
- A non-linear Dual Energy algorithm based on image decomposition has been applied in x-ray brain imaging for the first time, showing that the differentiation of gray and white matter within the brain parenchyma is feasible.
- A novel improvement of the DE algorithm is proposed.
- An automatic mathematical optimisation procedure is proposed as a new approach to further improve the results of the DE algorithm.
- The use of Sparse Filtering algorithms in x-ray brain imaging has been investigated and showed very good results, encouraging further development of these algorithms in order to be better adjusted in X-ray imaging specific applications.
- Thorough comparison of different filters in both real and simulated x-ray images has been presented, pointing out the advantages and disadvantages of each filter, along with the optimum setting and application in which each one performs better.
- The study showed that brain’s gray and white matter contrast can be actually achieved with x-ray imaging, provided that higher doses in combination with the proposed algorithm are applied.
Brain Imaging


X-ray Imaging and 3D Modeling


Ultrasound Imaging


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