A quantification of iodine contrast in mammography spectral X-ray imaging with a 300 µm-Si photon-counting pixel detector

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# Table of contents

1 Introduction
   1.1 Outline .......................................................... 2

2 From grayscale X-ray to spectral X-ray
   2.1 X-ray imaging ...................................................... 3
      2.1.1 X-ray interactions in materials ......................... 3
      2.1.2 X-rays ....................................................... 4
      2.1.3 X-ray generation .......................................... 5
      2.1.4 X-ray dose ................................................ 7
      2.1.5 Spectrum filters .......................................... 8
      2.1.6 X-ray detection .......................................... 8
   2.2 X-ray image ..................................................... 10
      2.2.1 Regular imaging .......................................... 11
      2.2.2 K-edge Subtraction imaging ............................ 11
      2.2.3 Spectral imaging ........................................ 13
      2.2.4 Mammography ............................................ 15
      2.2.5 Computed Tomography .................................... 17
   2.3 X-ray system modelling ....................................... 18
      2.3.1 Incoming spectrum ....................................... 18
      2.3.2 Sample and detector ..................................... 21

3 Medipix family ...................................................... 23
   3.1 Medipix devices ................................................ 23
      3.1.1 Timepix ..................................................... 25
      3.1.2 Medipix3RX ................................................ 26
   3.2 Timepix ToT calibration ....................................... 28

4 Experiments Timepix ............................................... 31
   4.1 Contrast imaging ............................................... 31
      4.1.1 Syringes with Betadine ................................ 31
      4.1.2 Mammography sample with Ultravist ................. 41
   4.2 PCD versus state of the art mammography .................. 51

5 Conclusion .......................................................... 53

6 Discussion .......................................................... 54

7 Acknowledgement ................................................... 56
   7.1 Dankwoord ....................................................... 56

8 Summary ............................................................. 57
   8.1 Samenvatting .................................................... 57
1 Introduction

X-ray mammography is an important part of the breast cancer diagnosis chain. A lot of mammography examinations are done preventatively. Recent developments within the field of digital mammography (DM) provide more accurate diagnosis of breast cancer, compared with analogue mammograms. DM plays an increasing role in diagnosis of early stage breast tumours.

To diagnose early stage tumours, the visibility of tumour-like materials inside the breast is important. Due to the small X-ray absorption differences between tumour tissue and glandular tissue, the detectability of tumour cells is limited. On top of that the malignant tissue, especially in an early stage of cancer, can be very subtle and may be obscured by the normal glandular tissue. In this case an improvement between the contrast of the malignant tissue and normal tissue is desirable. This is achieved by intravenous injections (IV) of iodinated contrast agents. This methodology is called contrast enhanced digital mammography (CEDM).

CEDM is very useful since it has been shown that the growth of breast cancer can be indicated by a relative large amount of blood vessels in an area. Those vessels are created by the body to supply the tumour with oxygen and nutrients that are required for its further development. This new microvessels are highlighted by contrast agents. Contrast agents thus enhance contrast in the region surrounding the tumour. Over time a few techniques have been proposed and developed to make use of CEDM. The core task is to make iodine distinguishable from all surrounding tissues, so that a tumourous region is highlighted. Spectral X-ray information is a promising factor in highlighting contrast agents.

Unfortunately, traditional and clinical X-ray setups only collect information on X-ray intensity-loss, which results in a single attenuation map. In this measurements a lot of spectral (energy) information of X-rays is lost, while the attenuation in matter highly depends on X-ray energy. Recent developments in X-ray systems featuring energy selective X-ray photon-counting detection have resulted in a new (spectral) sense organ in the field of X-ray imaging. One technique that the developments have brought is an imaging procedure called K-edge subtraction mammography (KESM). In this procedure the K-edge of iodine is used to extract spectral information from the sample that contains iodine.

K-edge imaging uses the discontinuity in the X-ray attenuation of materials that comes from photons that are absorbed by freeing electrons in the lowest-energy shell of a material. This occurs for photons that have an equal or greater amount of energy than the binding energy of the so called K-shell electrons. Elements that have their K-edge within the X-ray energy spectrum that is released by the X-ray source, can in principal be used as K-edge contrast medium. It should be noted that any contrast medium should be tested extensively before being used on patients, since a lot of materials can be toxic. Much of this research is already done by Yeh et al.

The aim of this work is to test whether spectral sensitivity in the sensor will enhance contrast in contrast enhanced digital mammography examinations. This is tested by fitting a model of the X-ray source and detector system with data. This data is gathered by a 2x2 cm², 300µm-Si thick sensitive layer in combination with a Timepix chip. Both fitting and (spectral) KESM procedures are used to determine the minimum concentration of iodine that is needed to get a sufficiently high contrast between iodine and the rest of the materials within the sample. This is quantified by the so called Contrast to Noise Ratio (CNR). A CNR of 5 is, according to Rose, the minimum contrast that is needed between pixels to be able to distinguish them from each other. The absorbed radiation dose in the breast, Mean Glandular Dose (MGD), is also taken into account. The conventional parameter of CNR normalised by MGD is used to determine the contrast-dose-quality. The resulting concentration limits of iodine are compared to the limits of state-of-the-art clinical CEDM examinations.

1.1 Outline

This thesis is composed of four different parts. The first part explains what X-rays are and how they are produced and can be detected. The second part addresses photon counting detectors and especially highlights some spectral features of them. That detectors are used for CEDM related experiments which are elaborated and analysed in the third part. The results that come out of this analysis are compared with state-of-the art CEDM techniques in the fourth part.

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1 Some spectral information is kept due to beam hardening effects, which contain spectral information
2 From grayscale X-ray to spectral X-ray

2.1 X-ray imaging

2.1.1 X-ray interactions in materials

In the field of X-ray physics one is interested in the absorption of X-rays within materials. The absorption of X-rays is described by the material dependent mass attenuation coefficient. The (mass) attenuation coefficient, \( \mu \), encompasses three interaction processes in the energy range which is relevant for medical examinations. Those processes are: Photoelectric Effect, Compton Effect and coherent scattering. However, for mammography purposes the Photoelectric Effect is most dominant. All processes are summarised in figure [1].

**Photoelectric Effect and K-edge** The Photoelectric Effect takes place when the energy of an incoming X-ray photon is absorbed for ejecting an electron out of its shell\(^2\). The resulting vacancy can be filled by an electron from a higher shell. The energy difference that this electron loses for going into a lower (potential energy) shell is transferred into an X-ray photon. The (photo)electron that is ejected by the incoming X-ray is able to ionise neighbouring atoms. In the case of an incoming X-ray having an equal or slightly higher energy than the atom’s K-shell binding energy, the probability of knocking out a K-shell electron is maximal. This results in an increase of X-ray attenuation at the K-absorption energy (K-edge). Neglecting K-edges, the photoelectric part of the attenuation coefficient is described by (7)

\[
\mu_p \propto \frac{Z^4}{E^3},
\]

where \( E \) is the energy of the incoming X-ray photon that hits a material with atomic number \( Z \). The photoelectric effect is dominant in creating contrast between materials. This is due to the \( Z^4 \) dependence of \( \mu_p \).

![Illustrative summary of x-ray interactions](image)

**Figure 1: Illustrative summary of x-ray interactions** [3].

**Compton Effect** The Compton Effect occurs when an incoming X-ray hits an atom’s bound electron. The photon scatters off in another direction. The resulting photon can travel towards the X-ray tube, towards the detector or it scatters again with another bound electron within (another) atom. The Compton attenuation has a certain \( Z \) and \( E \) dependence. However, in the energy range that is relevant for clinical X-ray examinations the Compton part of the attenuation coefficient can be assumed to be independent of \( Z \) and \( E \). The most dominant factor in the Compton cross section is the scattering angle \( \theta \) between the incoming and outgoing photon. The differential Compton cross section is given by,

\[
\frac{d\sigma_{ce}}{d\Omega} = \frac{Z}{(1 + \epsilon(1 - \cos \theta))^2} \left[ 1 + \cos \theta + \frac{\epsilon^2(1 - \cos \theta)^2}{1 + \epsilon(1 - \cos \theta)} \right],
\]

where \( \epsilon \) and \( Z \) are constants that do not have the same value. It should be noted that \( \mu_{ce} \propto \sigma_{ce} \).

---

\(^2\)The shell is defined here as what is known as the electron shell (K, L, M and so on).
Coherent scattering  The third interaction, coherent scattering\(^3\) occurs at low energies. The X-ray photon has not enough energy to ionise an atom and is only transferred in another direction. The coherent part of the attenuation coefficient comes with the following relation (7),

\[ \mu_{cs} \propto \frac{Z^2}{E^{1.9}}. \]  

2.1.2 X-rays

In the previous subsection all important X-ray interactions are introduced. In clinical mammography the photoelectric effect is dominant. All processes in this thesis are therefore assumed to be photoelectric, unless otherwise specified. On top of that the photoelectric effect enhances contrast in X-ray images, while Compton and coherent scattering blur the X-ray image. In X-ray imaging users are able to perform non-invasive studies inside objects. An X-ray image is a flat (2D) representation of an object obtained by imaging absorption of X-rays in materials. To do X-ray imaging, X-ray (photons) are needed. An energy band between 100 eV-140 keV within the electromagnetic spectrum is ascribed to those X-ray photons. As stated in the previous subsection, every material has a characteristic absorption of X-ray photons. This is described by the mass attenuation coefficient (\(\mu\)). The X-ray intensity (number of photons) follows the Lambert-Beer law. In case of a homogeneous object (constant \(\mu\)) of length \(l\) and X-ray photons with a constant energy (monochromatic beam) the photon intensity is described by

\[ I(E) = I_0(E,l) \cdot e^{-\mu(E)l}, \]  

where \(I_0\) is the initial X-ray intensity\(^4\) (number of photons). The quantity \(\frac{I(E)}{I_0(E)}\) is called the Radon transform and is a quantity which is commonly used in the field of X-ray imaging and CT, see subsection 2.2.5. Since most objects are far from homogeneous and X-ray tubes hardly produce monochromatic X-ray beams (except from e.g. synchrotrons), equation (4) changes to

\[ I_{x,y,z}(E_i) = \int_{E_i} I_0(E) \cdot e^{-\int x,y \mu(E,x,y,z) d z} dE, \]  

where \(E_i\) correspond to a certain energy and \((x,y)\) refers to the position in space (mostly in the detection plane). This is shown in figure (2).

**Figure 2:** Schematic drawing of a three-component sample that is illuminated by X-ray photons with different energies of \(E_i\). Equation (5) describes the green arrow at every position on the z-axis.

This poly-chromatic beam and non-homogeneous object makes equation (5) a general expression for X-ray intensity. In this situation every position in space has its own specific X-ray attenuation. In fact the total attenuation is built up by different materials that come in different concentrations and densities. In this thesis a maximum of three different materials is assumed. In this case equation (5) can be rewritten to

\[ I_{x,y}(E_i) = \int_{E_i} I_0(E) \cdot e^{-\mu_A(E) \cdot t_A + \mu_B(E) \cdot t_B + \mu_C(E) \cdot t_C} dE, \]  

where A, B and C are the materials that are used and t correspond to material thickness. See also figure (3).

\(^3\)Coherent scattering is known as Rayleigh scattering.

\(^4\)The initial X-ray intensity is often referred as Open Beam (OB) measurement.
It is also possible to introduce material densities in equations 4, 5 and 6. The $\mu$ factors are then described by $\frac{\mu}{\rho}$, where $\mu$ is the energy-dependent attenuation coefficient and $\rho$ the material density. The values for attenuation coefficients that are used in this thesis are extracted from the XCOM tables on NIST. Those tables are imported via the XrayDB and xraylib library for python. The material densities are kept constant and are extracted from the periodictable library. For compounds the density value that is available on wikipedia is used. If this value is not available, the density is entered manually.

2.1.3 X-ray generation

For the generation of X-ray beams an X-ray tube can be used, see figure 4. At Nikhef a Hamatsu Microfocus X-RAY source with an maximum photon energy of 90 keV is available. The production of X-ray photons starts with energetic electrons striking a target material. In most (clinical) X-ray tubes tungsten is used as target material. In mammography also molybdenum (Mo) and rhodium (Rh) are often used as target materials. In this thesis a tungsten target is assumed to be the standard.

A high current through the metallic cathode (filament) leads to the thermal emission of electrons. An external tube voltage accelerates the electrons towards the target anode. The interaction with the target results in the emission of X-rays.

X-ray emission  Tungsten emits X-rays in two different ways: bremsstrahlung and characteristic emission. Bremsstrahlung is explained in figure 5a. Bremsstrahlung corresponds to the loss of energy of an incoming electron which is deflected due to the presence of a positive (atom) core. This process result in a continuous X-ray energy spectrum. The emission of characteristic X-rays is explained in figure 5b. If the energy of an incoming electron (1) is sufficiently high it can eject an (inner) orbital electron (2) out of its orbit. The vacancy (3) will be filled up by a higher orbital electron, which results in the emission of X-ray photons (4) with a characteristic energy. Those photons can for example be used for monochromatic X-ray setups. The two processes of bremsstrahlung and characteristic X-rays result in a specific X-ray tube output. This is shown in figure 6.

$^5$Those materials produce Characteristic X-rays with energies near the optimum energy for mammography. This makes them very likely to be used in traditional mammography setups.

$^6$The energy of the electron should be high enough to overcome the ionisation energy of the atom.

$^7$It should be noted that the energy of the incoming electron could be high enough to eject more than one orbital electron.
The spectrum shown in figure 5 depends on a lot of factors. Numerous parameters are modelled in a publication by Hernández and Fernández. This model is implemented in a python toolbox called xpecgen. This toolbox is used to simulate X-ray tubes and subsequently for modelling purposes. In this thesis the toolbox is used to reconstruct samples that contain iodine. See also subsection 2.3.1.

**X-ray tube settings**  The operation of the tube is driven by two parameters. The peak kilovoltage given in kVp and the current typically in µA. The value of kVp corresponds to the maximum photon energy in keV. Increasing the kVp broadens the spectrum. Increasing the current results in an increase of photon-flux. This is visualised in figures 7a and 7b.
2.1.4 X-ray dose

As shown in the previous subsection, the X-ray tube produces a certain amount of photons distributed over an energy-dependent spectrum. The integrated amount of energy can be expressed in an X-ray dose. In this thesis the dose is quantified by the Entrance Surface (or Skin) Dose (ESD) \(15\). The ESD is the amount of energy per mass unit (kg) that enters a material. ESD is also known as incident air KERMA. The ESD in milliGray (mGy) for the X-ray tube that is used in this research is described by,

\[
ESD = 2.92 \cdot 10^{-4} \cdot \left(\frac{kVp}{90}\right)^2 \cdot \left(\frac{FDD}{FSD}\right)^2 \cdot \left(\frac{I}{89}\right) \cdot t, \tag{7}
\]

where kVp and I correspond to tube settings of peak-kilovoltage and current (in \(\mu \text{A}\)) respectively. Parameters FDD and FSD (in cm) are defined in figure 8 and t is equal to the total acquisition time in seconds. In this model the possible scatter of photons at the surface of the sample is ignored. The factor of \(2.92 \cdot 10^{-4}\) is experimentally determined and differs per X-ray tube. The value is calculated during a safety check at the manufacturer of the tube.

\[F_d \propto I_0(1 - e^{-\mu \cdot t}). \tag{8}\]

Another measure to quantify the absorption of materials is the Half Value Layer (HVL). HVL is defined as the material thickness where 50% of photons are absorbed. In other words \(e^{-\mu \cdot HVL} = \frac{1}{2}\) and thus \(HVL = \ln(0.5) \mu\). From equation 8 it can be shown that thick samples/patients absorb more photons and are thus exposed to a higher dose. On top of that the relations in equations 7 and 8 show that low energy X-ray photons result in a higher attenuation in materials. In mammography examinations both relations are reasons to compress the breast and make use of spectrum filters to reduce the administered dose. The effect of spectrum filters is explained in paragraph 2.1.5.

**Dose modelling in mammography** In mammography a model for calculating the amount of exposed X-ray dose is called the Mean Glandular Dose (MGD) \(9\), which is described by

\[
MGD = K \cdot g \cdot c \cdot s. \tag{9}
\]

\(K\) is here defined as the incoming ESD without keeping in mind (Compton)backscatter. ESD is given by equation 7 and is not MGD-model dependent. The values of \(g, c\) and \(s\) are unitless and depend on different model parameters. The factor \(g\) corrects for the amount of energy absorbed in the breast \(^8\) \(c\) for the breast composition and \(s\) the X-ray anode/filter that is used during examination. The values of \(g, c\) and \(s\) are caught in the MGD model and are tabulated in Dance and Sechopoulos \(16\). In this thesis the tabulated version of the MGD-model is used as standard. 

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\(^8\)KERMA is described by Kinetic Energy Released per unit Mass.

\(^9\)Mean Glandular Dose is often referred as Average Glandular Dose (AGD).

\(^10\)This absorbed energy depends on HVL. Both HVL and breast thickness result in a correction factor for \(g\).
(a) Simulation of tube output with a tungsten anode \((14)\). On the x-axis: X-ray energy in keV, on the y-axis an arbitrary quantity that visualises the X-ray photon intensity.

(b) Simulation of tube output corrected with 1mm Al filter, calculated with equation \((10)\) \((14)\). On the x-axis: X-ray energy in keV, on the y-axis an arbitrary quantity that visualises the X-ray photon intensity.

Figure 9: Two simulations of an unfiltered and filtered X-ray spectrum respectively.

are approved by the the Dutch reference centre of screening (LRCB). The use of a dose-model requires information about breast thickness, composition and chemical characteristics of breast-tissue(s). In mammography the breast is always compressed, which results in thicknesses that vary between 5-117mm \((16)\). On top of that four tissue-types are relevant in mammography dosimetry: skin, adipose, glandular and muscle-tissue. An important parameter in the MGD-model is the glandularity, which is in fact the (relative) amount of glandular tissue in the breast \((16)\). The lower the glandularity, the higher the dose. The average breast has a glandularity of approximately 50\% \((16)\). The glandularity is caught in the parameter of \(g\) in equation \((9)\).

2.1.5 Spectrum filters

Adding filters in the X-ray system has different purposes. One reason is to reduce the overall X-ray dose, another reason is to filter out photons with specific energies. For some examinations it is needed to gather more photon-statistics in specific energy ranges. This can be achieved by making use of a filter. A filter transforms an incoming spectrum like

\[
S(E) \propto TS(E) \cdot e^{-\mu_{\text{filter}}(Z,E) \cdot t_{\text{filter}}},
\]

where \(S(E)\) represents the X-ray spectrum after the filter, \(TS(E)\) is equal to the spectrum from the tube and both \(\mu_{\text{filter}}(Z,E)\) and \(t_{\text{filter}}\) are filter characteristics. The photoelectric Z and E dependence of \(\mu_{\text{filter}}(Z,E)\) can be extracted from equation \((1)\). Lets take for example aluminium (Al), a material that is often used as X-ray filter. For a given tube, \(TS(E)\) is visualised in figure 9a. Adding a layer of 1mm Al results in a transformation of \(TS(E)\) with a factor of \(e^{-\mu_{\text{Al}}(13, E) \cdot 0.1}\), which is shown in figure 9b.

Aluminium attenuates the low energy part of the spectrum more compared to the high part of the spectrum. Actually, most materials do this. This is what also can be concluded from equation \((1)\). Aluminium is used because it is considered as a standard in clinical X-ray physics. For clinical examinations higher energies are relevant, so low energy photons only contribute to X-ray dose and does not enhance contrast between relevant materials. On top of that most low energy photons will not reach the other side of the sample (or patient). However, mammography filters such as molybdenum are used to filter out high energy photons. In this case the low energy photons are energetic enough to penetrate the breast and deliver high enough contrasts, which makes the high energy part of the X-ray spectrum unnecessary. Concluding, spectrum filters are meant to shape X-ray spectra in such a way that sufficient contrast is reached in combination with a reduced amount of dose.

2.1.6 X-ray detection

Equation \((5)\) indirectly states that if it is known how the mass attenuation coefficient is distributed within the object, it should be possible to calculate material thickness and reconstruct how the object looks from the inside. The most\(^\text{11}\)

\(^\text{11}\)Those high energy photons have energies in the order of 25-110 keV.
common methods of how X-rays can be detected are film detection, scintillation detection and semiconductor pixel detection. Those methods are shortly discussed in the next paragraphs.

**Film detection**  X-ray films are often covered by an emulsion (layer) of AgBr or AgCl (silver halide). When this emulsion is exposed to X-ray light, the Br\(^-\) or Cl\(^-\) ions are freed. This change in the emulsion produces a hidden image. This image can be developed in a chemical solution (developer). Parts that have been exposed to X-rays develop faster then parts that have not. This results in the X-ray image. This film emulsion methodology is not suitable for modern medical examination due to its limited dynamic range (17).

**Scintillation detection**  When pixels of scintillation detectors are hit by X-rays, they produce light. All pixels contain a photo-diode that generates a current that is proportional to the amount of light that comes from the scintillator material. This number is directly related to the amount of absorbed energy that is released by the X-ray photons. The image that appears thus represent an energy integral of all photons that hit the detector. The currents that come from the photo-diodes are amplified and readout by electronics. The output is the X-ray image. See figure 10 for a thorax image taken with a scintillation-FPD for a clinical pneumothorax examination of the author’s lungs.

![Figure 10: Thorax X-ray image of the author taken with a scintillation-FPD at the Waterlandziekenhuis in Purmerend. On the right hand side the spine is visible. The pneumothorax is visible on the left hand side, where only - low attenuated - air (black) is located.](image)

**Semiconductor pixel detection**  A semiconductor pixel detector (SPD) is assembled by a semiconductor diode, which is depleted by a bias voltage on its electrodes. Charge carriers are liberated when a particle enters the sensor. The charge is transferred to the readout due to the presence of the bias voltage. This effect is schematically drawn in figure 11. The (particle) physics of this process is described in subsection 3.1. The combination of a depleted semiconductor detector and readout electronics is called a hybrid pixel detector (HPD) (17). In this case one part consist of a sensor which involves a sensitive layer (Si, GaAs, CdTe etc.) and a thin layer of aluminium. The other part is the chip and contains the per-pixel readout system for the sensor. Both parts are connected via bump-bonds. Due to the possibility to choose between sensitive layer materials, it is possible to pick a material that increase/decrease signals in an energy-region of interest/disinterest. This is due to the energy-dependent attenuation/absorption of materials, see figure 12. A schematic drawing of the HPD is shown in figure 13. Recently developed experimental systems in the field of HPDs are the Medipix and TimePix chips, established by the Medipix collaboration(s). In subsections 3.1.1 and 3.1.2 those devices are further elaborated. In this thesis the focus will be on the use of those chip systems and their spectral capabilities.

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12 Scintillation detectors are often Flat Panel Detectors (FPD) that consist of gadolinium sulfoxylate as scintillation material.
13 The charge carriers are released via e.g. photoelectric processes.
Figure 11: An incoming particle creates electron-hole pairs, which are further transferred due to the applied bias voltage. The electrons or holes make contact with the electronic contacts of the readout. The signal subsequently gets amplified, discriminated with a threshold value and counted (or not). This is further elaborated in subsection 3.1.

Figure 12: Absorption efficiency of different sensitive layer materials/thicknesses as function of photon energy.

Figure 13: The hybrid pixel detector consisting of two separate layers connected via bump-bonding (Nikhef/CERN).

2.2 X-ray image

In this subsection several imaging techniques and methods will be elaborated. Those different methods are used for numerous X-ray applications within medicine, safety and material recognition.
2.2.1 Regular imaging

A regular X-ray image is the direct intensity visualisation of equation 5. It is a distribution-map of photons (or their energy integral) over the imaging area in the detector plane. Regular X-ray images are mostly represented in grayscale. This grayscale commonly has gray-values of 12 bits and thus between 0-4095. Areas where more photons are detected have gray-values close to zero (black), while less photons are represented by higher gray-values (white). Look for example at figure 10 where air (low $\mu$) is represented in black and bone (high $\mu$) is represented in white. Those differences between gray-values make it possible to discriminate between different absorption-strengths and materials in a sample. This is often quantified with Signal-to-Noise-ratio (SNR, equation 11a), Contrast-to-Noise-ratio (CNR, equation 11b) and visibility (equation 11c). In medical imaging the administered dose is also a parameter of importance. In this case both SNR and CNR are weighted by the administered dose, see equations 11d and 11e. All quantification are described by

$$SNR = \frac{S}{\sigma_S}$$ \hspace{1cm} (11a)

$$CNR = \frac{S - B}{\sigma_B}$$ \hspace{1cm} (11b)

$$\nu = CNR \cdot \sqrt{N_{pixels}}$$ \hspace{1cm} (11c)

$$SNRD = \frac{SNR}{\sqrt{dose}}$$ \hspace{1cm} (11d)

$$CNRD = \frac{CNR}{\sqrt{dose}}$$ \hspace{1cm} (11e)

where $S$ is the signal of interest, $B$ the background where the signal should be compared to, $N_{pixels}$ the number of pixels that are included in the relevant part of the image and dose a quantification that comes out a dose-calculation. Both $S$ and $B$ can be photon-intensities or energy integrals, but can also represent attenuation coefficients or material thicknesses. In the latter case pixels within the Region-Of-Interest (ROI) are averaged. Their standard-deviation is used to determine both $\sigma_S$ and $\sigma_B$. A CNR of $5$ seems to be the minimum where both the eye and the computer can distinguish the signal from the background. However, some publications take a CNR of $3$ as absolute minimum. Both SNR and CNR are influenced by the square-root of the area or volume included in the ROI, $\sqrt{2}$ times the pixel size, $\sqrt{dose}$ and also the spectrum-shape.

2.2.2 K-edge Subtraction imaging

The idea of K-edge imaging was invented by Jacobson in 1953 and is applied for clinical purposes right now. The K-edge itself is already introduced in subsection 2.1.1. The K-edge Subtraction (KES) method can be introduced with equation 6, where an object consist of three different materials. For the moment the number of materials is restricted to two (A and B). The attenuation of materials A and B are schematically drawn in figure 14. Material A has a K-edge somewhere in the energy-range of the attenuation plot. In KES, two X-ray images are gathered with X-ray (beam) energies just above and below the K-edge absorption energy. Afterwards those images get (logarithmically) subtracted on a per pixel basis ($\ln(I_0) - \ln(I)$), which result in an image where material A is highlighted. Because the attenuation of material B decrease as function of energy around the K-edge of material A, the KES method removes material B from the regular X-ray image. The resulting image is called the KES-image. In medical imaging the highlighted material is often a contrast medium, see figure 15.

KES applications K-edge imaging comes with numerous applications such as the reconstruction of multiple contrast media and detection of calcification in plaque. The amount of coronary calcium is an indicator of future heart problems and is useful in making lifestyle changes. K-edge imaging provides tools for that due to its capabilities of recognising calcium (via for example iodine). In this case iodine guide the radiologist to a region of interest (ROI). In this ROI the KES-methodology is applied, to quantify the amount of calcium/calcification. Another application can be in the field of mammography, where early-stage tumours can be highlighted due to the presence of iodine in the (micro)vessels that supply the tumour with nutrients. Clinical KES methodologies can distinguish two (mixes of) materials - contrast and background at once.

---

14The photon intensity $I$ per unit area is a Poisson-process, the noise is described by $\sqrt{I}$.

15The ROI is an area or volume that is expected to be interesting. One can determine a ROI for $S$, but also for $B$.

16The background (mix of) materials may not contain K-edge discontinuities in its X-ray spectrum within the for the signal relevant energy range.
Figure 14: Schematic drawing of two different materials and their attenuation coefficients.

Figure 15: In K-edge subtraction imaging (KES), two simultaneous CT images are acquired using two x-ray beams at two different energies above and below the K-edge of Xe. Absolute quantity of the contrast agent is determined directly on any given point of a lung CT image after subtracting these two images on a logarithmic scale \(^{26}\). CT imaging is shortly discussed in subsection 2.2.5.

KES algorithm  

Let's again assume that there are two materials in a sample: A and B. Material A has a K-edge in the relevant energy range, and material B does not. In the end the thicknesses of both materials should be distinguished. The densities of both A and B are assumed to be constant again. See Baldelli et al. \(^{3}\) for varying densities. For this situation the physics for the low \((E_L)\) and high \((E_H)\) energy is described by

\[
I(E_L, E_H) = I_0(E_L, E_H) \cdot e^{-\mu_A(E_L, E_H) \cdot t_A + \mu_B(E_L, E_H) \cdot t_B},
\]

where \(t_A\) and \(t_B\) correspond to the materials thicknesses. Both \(I(E_L, E_H)\) and \(I_0(E_L, E_H)\) are measured\(^{17}\). Rewriting in terms of \(\mu\) and \(t\) gives the Radon transform,

\[
\ln \frac{I_0}{I}(E_L, E_H) = \mu_A(E_L, E_H) \cdot t_A + \mu_B(E_L, E_H) \cdot t_B.
\]

In this situation the values of \(\mu_A\) and \(\mu_B\) are known, so the thicknesses can be solved. This per-pixel calculation results in two separate images for both material A and B,

\[
t_A = \frac{\mu_B(E_L) \cdot \ln(u) - \mu_B(E_H) \cdot \ln(s)}{\mu_B(E_L) \cdot \mu_A(E_H) - \mu_A(E_L) \cdot \mu_B(E_H)} \quad (14a)
\]

\(^{17}\)The measurement of \(I_0(E_L, E_H)\) is an so-called open-beam measurement.
where $s$ correspond to $\frac{I_0}{I}$ ($E_L$) and $u$ to $\frac{I_0}{I}$ ($E_H$). Multiple pixels can be selected (in e.g. a ROI) to increase contrast, but decrease spatial resolution. This multiple-pixel methodology is used in this thesis to determine material thicknesses in mammography-like samples.

### 2.2.3 Spectral imaging

The possibilities of KES methodology resulted in developments in the field of X-ray imaging. Conventional systems only focus on measuring the total amount of absorbed photon energy (energy-integral). Because the energy-information is integrated and can not be separated anymore, spectral information is lost (4). As may be concluded from equation 5 and figure 14 the attenuation process of X-ray depends on photon energy and sample composition. In the next paragraphs it is explained how some methods extract spectral information from the X-ray system. In this thesis it is finally examined if this can be used to determine the material thicknesses in a sample.

#### Dual-energy imaging

In Dual-Energy (DE) imaging two primer methods are conventional: dual-kVp and dual-source imaging. Those methods are currently applied in clinical systems (4). In the dual-kVp method two different measurements are taken after each other. In both measurements the kVp-settings differ. Two different X-ray spectra are the result. One of the problems that appear is that there is a (small) time-difference between the two measurement. In dynamical/moving samples, this can be a problem. An alternative is the dual-source imaging method, which makes use of two different X-ray tubes operating at different kVp settings. Those measurements are taken at the same moment. For this reason dual-source imaging is more used in clinical systems (4, 27). There are even experiments that test the feasibility of triple-energy imaging (28). It should be noted that in dual-energy measurements, the acquisition time is lowered with respect to a single shot acquisition. This overcomes the increase of administered dose to a patient. An alternative way of thinking is optimising the detection part of X-ray examinations. Progress in the detectability of X-rays resulted in photon-counting detectors, as introduced in subsection 2.1.6 and further discussed in section 3.

To state it in a simple way: each photon gets counted and can be binned in an energy window. Those photons are binned by discriminating between photon energy and (pre)defined energy thresholds. The more thresholds that are available, the more energy bins can be chosen, which results in a higher amount of (contrast) materials that can be distinguished due to their K-edge. This makes energy-discrimination in DE imaging more feasible. An application of the KES algorithm is very common in this case, see figure 16.

#### Spectral K-edge Subtraction imaging

As an extension of DE imaging method, a method where numerous different monochromatic X-ray energy beams are used to image an object is conceived. This spectral imaging method should
be effective in samples that contain materials with K-edges. In this case the spectral imaging method is called Spectral K-edge Subtraction imaging (Spectral KES imaging) (22). Another option is making use of an energy-sensitive (pixel) detector, which accurately measures an incoming per-pixel X-ray spectrum. Due to progress in the field of semiconductor pixel detectors this is possible, see section 3. Spectral KES is already tested with small animals with synchrotron X-ray radiation (22). According to simulations in Zhu et al. (22) the optimal energy-band regarding SNR/CNR has a width between 0.252-0.270 keV. Above 0.5 keV the performances are equal (22). The spectral KES methodology simplifies to the KES methodology when the number of (energy)bins is reduced to two.

**Spectral KES algorithm** In spectral KES the sample may consist of two-components, a contrast (C) component and a matrix (M) component. Just as in the KES-algorithm, both the contrast and matrix thicknesses can be calculated in the end. The densities of both M and C are assumed to be constant again. See Zhu et al. (22) for varying densities. The photon intensity as function of energy is given by

$$I(E_i) = I_0(E_i) \cdot e^{-\mu_C(E_i) \cdot t_C + \mu_M(E_i) \cdot t_M},$$

where i is the index of the energy bin. The value of i can vary between 1 and the maximum number of energy bins. Rewriting in terms of $\mu$ and $t$ gives

$$\ln \frac{I_0}{I}(E_i) = \mu_C(E_i) \cdot t_C + \mu_M(E_i) \cdot t_M = r_i,$$

with $r_i$ the so called radon transform that was introduced in subsection 2.1.2 (9, 22). The per-pixel calculation (least-squares fit) results in two separate images for both C and M,

$$t_C = \frac{\bar{\mu}_{MM} \cdot \sum_i (\mu_C r_i) - \bar{\mu}_{CM} \cdot \sum_i (\mu_M r_i)}{n \cdot (\bar{\mu}_{CC} \cdot \bar{\mu}_{MM} - \bar{\mu}_{CM}^2)}$$

(17a)

$$t_M = \frac{\bar{\mu}_{CC} \cdot \sum_i (\mu_M r_i) - \bar{\mu}_{CM} \cdot \sum_i (\mu_C r_i)}{n \cdot (\bar{\mu}_{CC} \cdot \bar{\mu}_{MM} - \bar{\mu}_{CM}^2)}$$

(17b)

$$\bar{\mu}_{CC} = \frac{1}{n} \sum_i \mu_{Ci}^2$$

(17c)

$$\bar{\mu}_{MM} = \frac{1}{n} \sum_i \mu_{Mi}^2$$

(17d)

$$\bar{\mu}_{CM} = \frac{1}{n} \sum_i (\mu_{Ci} \cdot \mu_{Mi})$$

(17e)

When $n = 2$, equations 17a and 17b simplify to equations 14a and 14b respectively. In this case spectral KES methodology changes to KES methodology (22). When energy-discrimination is possible the spectral KES methodology is applied as visualised in figure 17.

The spectral-KES algorithm has not yet been developed for a three- or n-component system. This makes the model in the current stage only applicable for a single contrast material and background material (18). However, it is a very promising methodology for the near future (22).

**Application** Both KES and spectral KES are used in contrast enhanced (clinical) examinations. Per-pixel analysis of material thicknesses result in the possibility to determine material concentrations in a sample. Lets assume three overlapping materials with experimentally-determined thicknesses, see figure 3. In this case the volume of material A is $V_A = t_A \cdot \pi \cdot r^2$, where r is the radius of disk A, B and C. The concentration of A is then given by,

$$C_A = \frac{\rho_A \cdot V_A}{V_A + V_B + V_C}.$$  

(18)

In this case the terms of $\pi \cdot r^2$ are equal for every disk, so 18 simplifies to

$$C_A = \frac{\rho_A \cdot t_A}{t_A + t_B + t_C}.$$  

(19)

---

18This background material may consist of a mix of different tissues, as long as the total attenuation coefficient is known.
Figure 17: Spectral KES algorithm methodology visualised. Two components C and M and a K-edge in the attenuation of C. Having n energy-discriminators that result in spectral information before and after the K-edge. The energy bins contain $\ln\left(\frac{I_0}{I}\right)$ for the detected spectra. In green the lines that correspond to attenuation of material(s) M, in red the lines that correspond to attenuation of material C.

With this model it is possible to convert material thickness into a (per-pixel) concentration. To convert this to molecular/material spectral imaging lets assume that every pixel as a value for R, G and B (RGB). Every value for R, G and B could be weighted by material concentration, which results in a map of material-weighted images.

### 2.2.4 Mammography

In the field of mammography breasts are imaged with relatively low dose\textsuperscript{19}. It has the aim to detect tumours in an early stage. A mammography examination is called a mammogram. This mammogram is often assessed by radiologists and/or oncologist. The aim for higher quality mammograms resulted in the development of digital mammography. Digital mammography opens doors for imaging techniques such as dual-energy imaging and spectral KES. The increasing use of digital mammography scans has a lot of benefits for the examination of dense breasts (1, 3). To further increase the detectability of breast cancer, the use of intravenous injected iodinated contrast agents have increased over the last few years. This technique is called Contrast-enhanced digital mammography (CEDM) (29). However, CEDM is not yet clinically used for preventive examinations due to the side effects of injecting iodine. For high-risk patients this side effects are taken for granted (2). The methodology of Double CEDM (DCEDM), where two contrast materials are injected, is currently under development. In this case one contrast materials enters the tumour while the other highlights the (micro)vessel network that feeds the tumour (1). This methodology is beyond the scope of this thesis.

Temporal subtraction mammography Since the method temporal subtraction mammography (TSM) is not further elaborated in this thesis, the most simple situation is assumed: a flat breast with thickness T, uniform distribution of iodine with thickness t, no scattering and monochromatic beams. However, TSM seems to be very successful. In this method two images are taken with the same incoming open-beam ($I_0$) spectrum. The first image is taken without the injection of contrast material, while before the second image is taken the contrast agent is administered. In those situation the system is described by

\begin{align}
I(x, y)_{\text{before}} &= I_0(x, y) \cdot e^{-\mu \cdot T} \quad (20a) \\
I(x, y)_{\text{after}} &= I_0(x, y) \cdot e^{-\mu(T-t) - \mu \cdot t} \quad (20b)
\end{align}

Taking the logarithmic subtraction of before-after gives $(\mu_I - \mu)t$, which is linear in t and thus iodine concentration (3). An example of TSM is shown in figure 18 by Jong et al. (30). TSM is not used in experiments in this thesis, because the methodology only accepts static samples. This is not a realistic condition in clinical mammography. On top of that the X-ray research at Nikhef/CWI is focused on ‘real time’ X-ray imaging. This is also not possible with TSM.

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\textsuperscript{19}The relatively low dose is achieved by lowering the kVp settings and make use of specific anode/filter combinations.
Figure 18: Temporal contrast-enhanced mammography images. (a) shows a craniocaudal digitised screen-film mammogram obtained in a patient with infiltrating ductal carcinoma, which is the most common type of breast cancer. (b) shows a craniocaudal contrast-enhanced digital subtraction image obtained 1 minute after the start of contrast medium injection and shows a small nodule with rim enhancement of the entire mass (arrow). (c) shows subtraction image obtained 10 minutes after start of contrast medium injection and shows washout of contrast medium. Note that only a single breast can be obtained in one view and that in this specific case, the breast needed to be compressed for 10 minutes (31).

K-edge Subtraction Mammography  As stated in subsection 2.1.4 a breast consists of glandular, adipose and muscle tissue. When iodine is injected, the breast consist of four types of material. In K-edge subtraction mammography (KESM) two energy bins, $E_L$ and $E_H$, are selected. Those energy bins result in two different images. With those two images it is not directly possible to calculate the thicknesses of four materials. For this reason the breast is often modelled by a slab of polymethylmethacrylate (PMMA)\(^{20}\), fat and water (3). Since KESM only allows two-component systems, the background tissue is assumed to consist of only water or PMMA. The rest of the materials are either included, but kept constant in thickness. In this case equation 14 can be filled in. In principle it is thus possible to add other components, but their corresponding thickness could not be calculated from the KES algorithm. From those materials the thickness should be supplied to the modelling software. See figure 19 for an example of a KESM examination (31).

Figure 19: 55-year-old woman with normal breast tissue. CEDM imaging: low-energy image (a), high-energy image (b), and subtracted image (c), by Daniaux et al. (31).

The limitation here is that overlapping structures may obscure the contrast of iodine, because the system consists of more than two components. This introduces errors in the thickness calculations, which makes this methodology less useful for dense breasts\(^21\).

Spectral K-edge Subtraction Mammography  Just as for KES, spectral KES can be applied in mammography (spectral KESM). Since the spectral KESM algorithm is only tested for the two-component system, it is not yet clear if it will work for the three- or more component systems. See equation 17. In CEDM the contrast thickness ($C$) is equal to the thickness of iodine and the matrix thickness ($M$) is equal to the calculated thickness of water or PMMA. A three component mammography system is successfully investigated with a triple-energy beam research by Han (2).

Fitting Mammography  A methodology which is exclusively introduced in this thesis is fitting mammography. The fitting procedure described in subsection 2.3.3 makes use of the continuous spectrum that is gathered with the de-

\(^{20}\)PMMA is also known by trade names such as Plexiglas and Perspex.

\(^{21}\)A 1 mm error on a dense breast is substantial, while a 1mm thickness variation is negligible for others.
tector. It allows n-component systems, which makes it suitable for more complicated/realistic samples or even for mammography examinations on patients.

2.2.5 Computed Tomography

In normal X-ray images 2D projections of a 3D object are acquired. As structures overlap, this may obscure structures in the object. There is no three-dimensional information available in an X-ray image. In the field of Computed Tomography (CT) 3D information is reconstructed by taking many images at different angles. Since every position in space inside the object has an unique absorption of X-rays, this is in fact what should be reconstructed if the object needs to be fully understood. For this 3D reconstruction several algorithms may be used (9). Those algorithms can also be applied on spectral imaging (32). There are special spectral reconstruction algorithms, but another way of doing spectral reconstruction is making use of algorithms that are used for 2D images (such as spectral KES) and put this information into an classical reconstruction method, see figure 20.

![Figure 20: Coloured CT slice of the spectral phantom obtained using an in-house material decomposition algorithm. From the top going clockwise is air, water, canola oil, calcium chloride, an iodine complex, a gadolinium complex and a contrast agent containing gold nano-particles. The gadolinium complex was not included in the decomposition due to a construction error in the spectral phantom, by Walsh et al. (33) This image is taken with a Medipix3.1 device.](image)

The spectral 3D information that can be extracted may result in a lot of new applications in X-ray physics. One of them is the development of new contrast agents, investigated by Yeh et al. (5).
2.3 X-ray system modelling

In this section it is explained how the X-ray system is modelled in this thesis. The X-ray system in this model is described by the following equation,

\[ I_M(E_i) = \left( e^{-\int E_i \mu(E) \, dx \, dE} \right) \cdot \left( 1 - e^{-\mu_{sl}(E_i) \cdot x_{sl}} \right) \cdot I_{0M}(E_i), \]  

(21)

where the first term correspond to the X-ray absorption between the X-ray tube and detector plane/pixel, the second to the absorbed amount of photons in the sensitive layer and the last term correspond to the incoming X-ray spectrum produced by the X-ray tube in combination with a spectrum filter. This equation can thus be simplified in a more straightforward form,

\[ M = XA \times SL \times G, \]  

(22)

where M is the model, XA is described by X-ray absorption, SL represents the absorption within the sensitive layer of a semiconductor detector and G corresponds to the generation of X-rays in the X-ray tube. All terms can be modelled and are in the end compared to the real data. The situation where both data and model are alike seems to provide information of attenuation distribution and material thickness. This is done in a fitting procedure, which is best explained by the following expression

\[ \ln \left( \frac{I_{0M}(E_i)}{I_M(E_i)} \right)_{\text{FIT}} \rightarrow \ln \left( \frac{I_{0D}(E_i)}{I_D(E_i)} \right) = \int_x \mu(E_i) \, dt \approx \mu_A(E_i) \cdot t_A + \mu_B(E_i) \cdot t_B + \ldots + \mu_N(E_i) \cdot t_N, \]  

(23)

where the term on the left-hand side corresponds to the model and the middle-term is equal to the data-acquisition. The only parameter that varies in the fit is \( I_{sl}(E_i) \), this is done by varying and optimising material thicknesses in the model. \( I_{0M}(E_i) \), often referred as the open beam spectrum, is predefined because it only depends on X-ray tube settings and the used filter/thickness. On the right-hand side the attenuation (known) and thickness (unknown) for all materials are calculated. From this methodology the (fitted) material thicknesses of all materials in the model can thus be extracted.

2.3.1 Incoming spectrum

The incoming spectrum is defined as the spectrum that reaches the sample. Before reaching the sample the X-rays have to pass trough a tube output window of Beryllium (Be) and trough a spectrum filter. The spectrum that enters the Be window is the spectrum that comes from the anode in the tube, see subsection 2.1.3. The tungsten (W) anode is simulated by Hernández and Fernández (14). The spectrum is determined by the kVp-setting and tube-angle, while the Be window is the spectrum that comes from the anode in the tube, see subsection 2.1.3. The tungsten (W) anode have to pass trough a tube output window of Beryllium (Be) and trough a spectrum filter. The spectrum that enters the tube-current only scales the magnitude of the spectrum up or down. This kVp and angle effects are illustrated in figures 21a and 21b. The beam angle is tube dependent. For the tube that is used in the experiments in this thesis an focusing angle of 39 degrees is determined. The resulting X-ray beam can be filtered, as explained in section 2.1.5. The effect of different filters and thicknesses are visualised in figures 21c and 21d. In all experiments and visualisations in this thesis a spectrum filter of 1mm aluminium is used, unless otherwise indicated. This situation is simulated in the green spectrum in figure 21c.

2.3.2 Sample and detector

In the experiments that are done semiconductor pixel detectors are used, see subsection 2.1.6 and section 3 for further elaboration of those type of detectors. Those detectors make use of sensitive layers (sensors), which absorb X-ray photons. The absorption curves of different sensitive layer materials are shown in figure 12. The spectrum that is generated in the X-ray tube is transformed into an absorbed spectrum due to the presence of the sensitive-layer. This transformation is taken into account for modelling the detector system. In reality there are several detector-dependent features that also influence the measured spectrum, such as energy resolution. Those features are included in a model by Marinho and Akiba (34). An example of the sensitive layer model is shown in figure 22. The spectrum in the figure on the right hand side is the spectrum that is actually measured by the sensitive layer. It should be noted that in this model all types of X-ray attenuation (photoelectric, Compton and coherent scattering) can be calculated separately. However, in the figures and calculations for this thesis only the photoelectric effect is taken into account. All values for material density and

\[ \mu_{sl}(E_i) \] and \( x_{sl} \) represent the attenuation and thickness of the sensitive layer.
(a) kVp setting of 70 keV, beam angle of **39 degrees** at a distance of 100 cm in blue. kVp setting of 70 keV, beam angle of **10 degrees** at a distance of 100 cm in green. The beam is unfiltered.

(b) kVp setting of 100 keV, beam angle of 39 degrees at a distance of **100 cm** in blue. kVp setting of 100 keV, beam angle of 39 degrees at a distance of **10 cm** in green. The beam is unfiltered. The characteristic X-rays from tungsten are visible around 60 keV

(c) kVp setting of 70 keV, beam angle of 39 degrees at a distance of 100 cm with a **100µm Al** filter in blue. kVp setting of 70 keV, beam angle of 39 degrees at a distance of 100 cm with a **1000µm Al** filter in green.

(d) kVp setting of 70 keV, beam angle of 39 degrees at a distance of 100 cm with a **100µm Al** filter in blue. kVp setting of 70 keV, beam angle of 39 degrees at a distance of 100 cm with a **10 µm Cu** filter in green.

**Figure 21:** Visualisation of the effect of different X-ray setup settings and spectrum filters. Every spectrum integral is normalised to 1.
attenuation are gathered from databases as NIST and a SQL database (XRayDB in python) that uses tables from Elam et al. (35).

Figure 22: Transformation of tube spectrum to detector spectrum with a Si sensitive layer of 300µm thickness.

The spectrum in figure 22b is often referred as the open beam spectrum and is in fact the curve of $I_{OM}(E)$ from equation 23. The materials between the spectrum filter and sensitive layer are defined as the sample. The sum of its attenuation makes another transformation of the spectrum in figure 22b. This transformation is illustrated in figure 23. The full transformation is described by equation 21.

Figure 23: (a) Modelling of open beam spectrum (blue) and 1 cm of water (green). (b) Modelling of open beam spectrum (blue), 1 cm of water (green) and 0.001 cm of iodine (red). The increased absorption for energies above the K-edge binding energy is clearly visible at 33 keV.

To convert the graphs in figure 23 into terms of attenuation sum (attenuation coefficient times thickness) and thus indirectly with concentration, the blue and green (or red) lines should be logarithmically subtracted. This is what can be concluded from equation 23. In the case of figure 23, this results in what is shown in figure 24. Figure 24b is basically what is shown in figure 14. The graph directly corresponds to both attenuation and material thickness. If the material and its attenuation curve is known, the thickness can be solved.

If the material thickness is known, a concentration can be calculated following equation 19. The thicknesses can be calculated from K-edge methodologies, but can also be calculated in fitting procedures as in equation 23.
2.3.3 Fitting procedure

The fitting procedure to calculate material concentrations needs some user input. This input should contain information of

- sensitive layer material and thickness
- materials in the sample
- material density for some compounds
- region of interest (ROI)
- initial guess of material thicknesses

where after the fitting procedure can start. It takes approximately up to one minute to do a solid $\chi^2$ fit in python with a library by Newville et al. (36). The fit is performed by assuming a model, which is provided in equation 23.

First some pixels in the ROI in the 2D image are selected. In the case of a tube filled with iodine, one can select a group of pixels that definitely must contain iodine. For those pixels both $I_{OM}$ and $I_M$ are averaged over every energy bin. Secondly the model is fitted over the logarithmic subtraction of $I_M$ and $I_{OM}$. Since $I_{OM}$ is constant for a certain sensitive layer material/thickness and incoming tube spectrum, the only parameter that varies is $I_M$. This is actually the part where the material thickness can be modified. The material thickness(es) are tuned in such a way that the residuals between the model and data is minimised and thus where $\chi^2$ is minimal. This fit procedure is done by a python library called lmfit. Fitting the residuals takes into account weighting factors of $1/\text{error}$, where the error is calculated based on Poisson counting statistics only. An example of a fitting-procedure result is shown in 25. The quality of a fit is quantified with $\chi^2$. For every energy bin $\chi^2$ is described by

$$\chi^2_{\text{bin}} = \frac{(\text{data} - \text{model})^2}{(\sqrt{\text{model}})^2}.$$  

(24)

All $\chi^2$ values are determined and finally all values are summed. This results in the total $\chi^2$ of the spectrum. The lower this value, the better the model fits the data. The minimum $\chi^2$ is determined based on an algorithm called the Levenberg-Marquardt Method (37). In this model every parameter gets updated every iteration at once. If the $\chi^2$ improves, the algorithm iterates again with smaller changes of the parameters. This is repeated until the minimum $\chi^2$ is determined. Besides, it should be noted that the model does not yet include the energy resolution of the system, which is a feature of the detector introduced in subsection 3.1. This increases the values for $\chi^2$. Finally the resulting thicknesses are used to do a concentration calculation based on equation 19. This methodology can be used for concentration determination in samples where all materials inside the sample are known. At this stage it is not yet suitable for per-pixel imaging due to lack of per-pixel statistics and the time-consuming fitting procedure.
This should be optimised by using fast-readout systems as used in the Medipix3RX system \cite{17}. For those reasons the production of 2D spectral images is gathered with methodologies such as KES and spectral KES, described in subsection 2.2.3.
3 Medipix family

In this section the particle detectors that are relevant for X-ray detection are elaborated. The focus will be on Medipix devices, which are hybrid pixel detectors (HPD). The basics of HPDs are already described in subsection 2.1.6. The Medipix collaboration developed a few HPDs. After the introduction of the Medipix1 chip the collaboration chronologically developed the Medipix2, Timepix, Medipix2MXR, Timepix, Medipix3, Medipix3RX and Timepix3 chips. The last two are now in development. In the experiments in this thesis the Timepix is used.

3.1 Medipix devices

Medipix devices are direct converting photon counting HPDs. A single chip consist of 256x256 pixels that have a pixel pitch of 55 \( \mu \text{m} \). The total chip area adds up to approximately 1.982 cm\(^2\). The sensor and ASIC are connected via bump-bonds which are made of Ag/Sn or Pb/Sn (7). The block diagram of a MPX2 pixel is given in figure 26.

![Figure 26](image)

**Figure 26:** Electronic circuitry of a Medipix2 pixel cell. The analog part consists of a preamplifier and two discriminators. The digital part receives the output of the discriminators and decides in the DDL (Double Disc Logic), if the counter will be incremented. (7)

The block diagram consists of an analog and a digital part. The analog part amplifies an incoming signal and discriminates it with respect to a predefined threshold (TH). The digital block is responsible for choosing operation modes: single threshold mode (STM) and energy window mode (EWM). In STM mode all incoming particles that exceed the low threshold (THL) are counted, while in EWM all particles that exceed the THL but do not exceed the high threshold (THH) are taken into account (7).

**Physics inside a Medipix device** An X-ray photon enters the sensitive material and undergoes an interaction via photoelectric, Compton and coherent scattering. Those interactions are introduced in subsection 2.1.1. The electron that is created loses energy in the sensitive material. Subsequently, the (negative) electrons in the valence band are transferred to the conduction band. Consequently, electron-hole pairs are created in the sensitive layer. Those electrons and holes are separated because they drift to the electrodes under influence of a bias voltage (E-field). Their total charge is measured as the signal. This charge is stored - and integrated - in a capacitor. The capacitor releases the voltage, and is subsequently used in the logic-system. This results in a voltage over the discriminators. This voltage is compared with the predefined threshold voltage value (TH). If the signal is above the threshold, a particle is counted.

**Threshold equalisation** To reduce spread in pixel response a threshold equalisation is always done before doing experiments. It is needed to compensate for the pixel-to-pixel differences and threshold variations. If a threshold varies too much with respect to the average threshold on the chip, then its threshold is artificially increased or lowered. The
equalisation procedure reduces the effective threshold spread. This guarantees that all pixels will react the same under the same stimulus. Threshold values depend on three different DACs: \( T HL \) (Threshold low), \( T HS \) (Threshold spread) and \( \text{adj} \) (four-bit adjustment for every pixel).

**Energy resolution** A medipix device has a certain energy resolution, which is mostly caused by electronics. The sensor has its intrinsic resolution, but also the threshold adds a noise to the energy resolution. The contribution to the energy resolution of the sensor itself is negligibly small in the case of e.g. silicon. This can be determined by calculating the energy resolution of sensitive layers with

\[
\sigma_E = \sigma_Q \cdot W_Q \\
\sigma_Q = \sqrt{F_{sl} \cdot \frac{E_\gamma}{W_Q}} \\
\sigma_E = \sqrt{F_{sl} \cdot E_\gamma \cdot W_Q},
\]

where \( F_{sl} \) is the material-dependent Fano factor, \( E_\gamma \) the energy of the incoming photon and \( W_Q \) the ionisation energy of the sensitive material \(^{23}\). In case of silicon \((F_{Si} = 0.13 \text{ and } E_Q = 3.6 \text{ eV})\) a 40 keV photon will result in \( \sigma_E \) of 137 eV. The energy resolution \( \frac{\sigma_E}{E_\gamma} \) here is 0.34\% and decreases further for higher energy photons. In a 300\um Si Timepix system the energy resolution is in the order of 1.5 keV full width at half maximum (FWHM) for energies around 40 keV \(^9\). This corresponds to a \( \sigma_E \) of 0.64 keV. In this case \( \frac{\sigma_E}{E_\gamma} \) is 1.6\%. At this point it is proven that the sensitive layer is not fully responsible for the energy resolution. The major part of energy resolution should thus be caused by the electronics. The effect of the energy resolution on a monochromatic X-ray spectrum, is visualised in figure 27. In this thesis the energy resolution of the system, which in fact smears out photon intensities over an energy range and thus also attenuation curves, is not included in the analysis. The analysis only uses information before and after the K-edge and uses the height of the attenuation peak around the K-edge for this reason. In this case it should be able to estimate the thickness of K-edge materials without taking into account energy resolution. Because some of the spectral information is not used here, it is expected that this is not a fully clean method. This is tested in subsection 4.1.2. For this reason an improvement to include energy resolution in the methodology could be made.

\[\text{Section 3. MEDIPIX FAMILY}\]

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23The ionisation energy is the amount of energy that is needed to create charge carriers.
3.1.1 Timepix

The Timepix chip consist of a 256x256 pixel matrix and has dimensions of 16mm × 14 mm. A non-sensitive area of 2 × 14mm is used to connect the Timepix to the readout periphery via wire bonds\(^2\). It does not only allow for particle counting, but it is also able to determine the particle time of arrival (ToA) or time over threshold (ToT) per pixel. It should be noted that the Timepix module uses one threshold (THL). The operation modes ToA and ToT are visually explained in figure 29.

\(^2\)To prevent confusion: the sensitive layer and Timepix are connected via bump-bonding, while the Timepix is connected with the system readout (peripheral circuitry) via wire-bonds.

Figure 28: Visualisation of the spectral resolution when taking into account both the energy resolution and charge sharing of the medipix device.

3.1.1 Timepix

The Timepix chip consist of a 256x256 pixel matrix and has dimensions of 16mm × 14 mm. A non-sensitive area of 2 × 14mm is used to connect the Timepix to the readout periphery via wire bonds\(^2\). It does not only allow for particle counting, but it is also able to determine the particle time of arrival (ToA) or time over threshold (ToT) per pixel. It should be noted that the Timepix module uses one threshold (THL). The operation modes ToA and ToT are visually explained in figure 29.

\(^2\)To prevent confusion: the sensitive layer and Timepix are connected via bump-bonding, while the Timepix is connected with the system readout (peripheral circuitry) via wire-bonds.

Figure 28: Visualisation of the spectral resolution when taking into account both the energy resolution and charge sharing of the medipix device.

3.1.1 Timepix

The Timepix chip consist of a 256x256 pixel matrix and has dimensions of 16mm × 14 mm. A non-sensitive area of 2 × 14mm is used to connect the Timepix to the readout periphery via wire bonds\(^2\). It does not only allow for particle counting, but it is also able to determine the particle time of arrival (ToA) or time over threshold (ToT) per pixel. It should be noted that the Timepix module uses one threshold (THL). The operation modes ToA and ToT are visually explained in figure 29.

\(^2\)To prevent confusion: the sensitive layer and Timepix are connected via bump-bonding, while the Timepix is connected with the system readout (peripheral circuitry) via wire-bonds.

Figure 29: Process of two operation modes (ToA and ToT) in addition to traditional event counting mode medipix devices.
Energy calibration. There are two ways to determine a pixel (energy) spectrum. The first method makes use of a threshold scan. The Timepix has to be used in the counting mode (medipix mode). The threshold scan counts photons at different THL values. This results in the spectrum integral. The derivative of this spectrum integral is the X-ray energy spectrum per pixel. The threshold scan is often used for calibration of medipix devices. Determining the linear per-pixel response of the THL as function of energy, makes it possible to do spectral imaging. An alternative method for determining the energy spectrum is making use of the ToT operation mode of Timepix. The counted pulses (ToT values) in ToT mode are directly related to the particle’s energy. To determine how those two quantities are related a ToT-E calibration is needed. The ToT-E relation consists of a nonlinear and linear part. Their relation is proposed by Jakubek et al. (42) and follows the functions,

$$ToT(E) = a \cdot E + b - \frac{c}{E - t} \quad (26a)$$

$$E(ToT) = \frac{a \cdot t + ToT - b + \sqrt{(b + a \cdot t - ToT)^2 + 4 \cdot a \cdot c}}{2a} \quad (26b)$$

where $a$, $b$, $c$ and $t$ are factors that can be determined by fluorescence experiments. The function of equation 26a is drawn in figure 30.

Figure 30: Time over threshold dependence on particle energy. The dependence is modelled by equation 26a (42).

The parameters $a$, $b$, $c$ and $t$ will differ per pixel due to spread in the pixel response. For this reason the calibration is done on a per-pixel basis. However, it is also possible to do a relative quick calibration per chip. The analysis and methodology of a Timepix ToT-E calibration is further elaborated in subsection 3.2.

Performance. The electronic pixel noise of the Timepix is in the order of $100e^- \text{ rms}$. This corresponds, assuming an ionisation energy of 3.6 eV, to a $\sigma_{en}$ of 360 eV. After equalisation the pixel to pixel variation is $35e^- \text{ rms}$. The minimum detectable amount of charge should be in the order of $650e^- \text{ rms}$, which is in agreement with 6-8$\sigma$ from the baseline ($100e^- \text{ rms}$) (43). This corresponds to a minimum threshold of 2.7 keV, with a variation of 126 eV (9). On top of the previous parameters, the time resolution/performance of the Timepix is important for its ToA and ToT modes. The timing resolution can be determined on the basis of the clock frequency, which is 100MHz. This corresponds to a timing resolution of 10 ns. An upgrade of the Timepix (Timepix3) should bring this down to 1.6 ns (9).

3.1.2 Medipix3RX

In this subsection the most important details and features of the Medipix3RX-system are discussed. The Medipix3RX (MPX3RX) is a new generation semiconductor chip that measures and analyses incoming photons and is developed from the Medipix3 (MPX3) chip. The MPX3 was introduced to access the field of spectral imaging in HPDs. It was designed to overcome charge sharing effects to include a communication between pixels (44, 45). The MPX3RX has an area of 15.9 mm $\times$ 14.1 mm and each chip contains 256x256 pixels with a pitch of 55$\mu$m. Every pixel has a THL (low) and THH (high) setting available. The MPX3 and MPX3RX slightly differ from each other. An image of a MPX3RX chip is shown in figure 31.

There are some different system configurations and pixel operation modes where the MPX3RX can be read out. The system configuration can be set in Fine Pitch mode - which is comparable to the usual type of acquisition - and Spectroscopic mode, where a cluster of four neighbouring pixels are connected to the chip via one bump bonding. This
result in a pixel pitch of 110 $\mu$m and the availability of eight different thresholds \(^{(7)}\). In this case eight (K-edge) images can be produced at once. The pixels operate under Single Pixel Mode (SPM) or Charge Summing Mode (CSM). SPM is comparable to what is introduced as counting mode for general medipix devices. In CSM the total charge that is deposited in more than one pixel within one acquisition window is integrated and assigned to the pixel with the largest charge fraction. This is discussed in detail in the next paragraph.

**CSM Medipix3RX** The incoming particle produce a charge (of e-h pairs) within the sensitive layer. This charge is collected and integrated by an amplifier. The amplified signal is shaped by a semi Gaussian pulse shaper and is converted into a current that correspond to the incoming particle charge \(^{(7)}\). In CSM this current is sent to the system that read-out pixel clusters in CSM (four adjacent pixels). The charge is deposited in the pixel cluster corner. Every pixel in the cluster measures a signal which is a fraction of the total charge. Each fraction is copied, added and compared with the threshold(s). The pixel with the largest fraction is the pixel which get the particle count. In this case multiple charge sharing counts are avoided. This is visualised in figure \(32\).

**Energy calibration** To extract spectral information from the MPX3RX device, it should be known how threshold and energy are related. The relation should follow $E = a \cdot \text{THL} + b$, where $a$ and $b$ can be determined with fluorescence measurements \(^{(7)}\).
3.2 Timepix ToT calibration

The ToT information that is measured with Timepix is directly related to the incoming particle energy (E). The relation between ToT and E is given in equation \(26a\). The first step of the calibration is pixel equalisation. This equalisation settings should be kept for all experiments that make use of this ToT-E calibration. The calibration is done on a per-pixel basis. To do a per-pixel calibration the following steps should be taken:

- measure ToT X-ray spectrum of a known fluorescence material with a known emission spectrum;
- identify the ToT spectrum with the true spectrum;
- repeat this for every fluorescence material;
- fit equation \(26a\) through the found peaks in a ToT(E) diagram;
- determine \(a, b, c\) and \(t\);
- produce a look-up table for every energy bin that correspond to a ToT value (determine \(E(ToT)\) for each pixel).

All steps are further elaborated in this subsection.

**Measure ToT spectrum**  To measure the ToT spectrum the setup as shown in figure 33b is used. In this measurement the Timepix operates in ToT-mode. The X-ray tube was set to 60/70 kVp. In total 200,000 frames per fluorescence material are gathered with an average pixel occupancy of 1%. This is to minimise pile-up that could unfairly increase the ToT value. The low occupancy also results in a low probability of double hits to occur. Due to the photon counting statistics double hits can be ascribed to charge sharing events. Those events will be rejected from the analysis. This is further discussed in the next paragraph.

**Identify peaks**  All frames - with an occupancy around 1% - are summed to make histograms consisting ToT-values for each pixel. Pixel clusters, pixels that have neighbour-pixels that are also hit, are ignored. Those clusters probably occur due to charge sharing events. Also double hit events are deleted, because they artificially increase ToT values. Pixels containing double hit events are easily recognised by their relative high occupancy. A predefined threshold-value is set to determine whether the occupancy is high (order of a few percents). The processing of possible charge sharing events is comparable to the method that the Medipix3 uses in its CSM. Hit pixels that have neighbour-pixels that are also hit during the same acquisition are attributed to charge sharing events. The chance of having two adjacent pixel accidentally being hit is so small, that this is an acceptable assumption. After this cluster search, all possible
Figure 34: Fluorescence measurement for niobium. This measurement is used to test the calibration methodology and is not used in the final calibration. For the final calibration other elements are chosen based on their fluorescence energies.

Charge sharing and double hit events are rejected. After this per acquisition frame process is finished, all frames are used to create a histogram for each pixel. In figure 34b an example of a ToT histogram is shown. The peaks that belong to the material with characteristic emission can be found by using a peak-search algorithm in for example ROOT framework or within the scipy library of python. The position and amplitude of the found peak is subsequently fitted with a Gaussian. The resulting mean of the Gaussian is used as peak-ToT-value. The standard deviation of the Gaussian is used to weight the fit of equation 26. Both quantities of mean and standard deviation are tabulated per pixel and material. The mean ToT value now directly corresponds to the known energy fluorescence peak value of a material.

**Calibration fit and look-up table**

The abbreviations and characteristic emission absorption of the elements that are used in the fluorescence calibration are given in table 1. From this table it may be concluded that more fluorescence samples are chosen in the area of changing slope. This is due to the non-linear part that is expected according to figure 30. For this reason the fitting procedure is more accurate when those relatively low energies are included.

<table>
<thead>
<tr>
<th>Element</th>
<th>Energy (keV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cr</td>
<td>5.4</td>
</tr>
<tr>
<td>Ni</td>
<td>7.5</td>
</tr>
<tr>
<td>Zn</td>
<td>8.6</td>
</tr>
<tr>
<td>Zr</td>
<td>15.8</td>
</tr>
<tr>
<td>Pd</td>
<td>21.2</td>
</tr>
<tr>
<td>Sn</td>
<td>25.3</td>
</tr>
<tr>
<td>Nd</td>
<td>37.4</td>
</tr>
</tbody>
</table>

*Table 1: Abbreviations and characteristic emission energy of the elements that are used in the fluorescence calibration.*

When all elements went through the data-gathering and histogram production seven unique ToT-peaks and corresponding standard deviations were ascribed to every pixel. The fit works as follows: for every pixel the ToT-peaks are placed in a ToT-E graph. Every point has an error bar that depends on $\frac{1}{\sqrt{N}}$, where N is the number of counts in the ToT-histogram. Then the fit is operated based on a $\frac{1}{\text{error}}^2$ weighting. Finally the values of a, b, c and t are extracted and saved per pixel. See figure 35 for an example.

Taking equation 26 into account, a ToT → energy bin look-up table is created (0-100 keV in steps of 0.2 keV). ToT pixel histograms can now directly be converted into energy pixel histograms.
Figure 35: Pixel response gathered from fluorescence experiment including a fit of equation 26a.
4 Experiments Timepix

In this section experiments that were done with a 512x512 pixel Timepix chip are presented. Since every Timepix chip has 256x256 pixels, the detector consist of a Timepix quadboard (four chips). All data is gathered with a 300 \( \mu \text{m-Si} \) thick sensitive layer with an applied bias voltage of 100V. The measurements were taken with a threshold higher than 6\( \sigma \) of the noise level (order of 3.2 keV). The ToT clock frequency was equal to 100 MHz. Data is gathered with the at ASI developed SoPhy software. Data is saved per acquisition block\(^{25}\) in an ASCII-matrix format. Before doing (spectral) imaging with the Timepix, an energy calibration needs to be done. This process is described in subsection 3.2.

4.1 Contrast imaging

With the energy calibration ready, it is possible to do contrast imaging examinations such as (spectral) K-edge subtraction mammography. In this subsection experiments with plastic syringes and PMMA in combination with iodine are discussed.

4.1.1 Syringes with Betadine

Since spectral information is available, contrast enhanced digital mammography (CEDM) examinations are now possible with the detector system. Since iodine is often used as contrast material, determining the amount of iodine in a sample is vital for CEDM experiments. All material extraction techniques - fitting, KES, spectral KES - are used to determine the iodine concentration. Finally the results are compared.

**Sample**  In the sample four different syringes will be filled with an iodine-containing solution\(^{26}\). The sample is shown in 36.

(a) Image of the syringes filled with a iodine-containing solution. From left to right the syringes contain 6.0, 4.5, 3.0 and 0.0 ml of pure water, while the iodine-containing solution contains the amount of volume in the opposite order. It should be noted that this solution also contains water.

(b) An image of the experimental setup. In the blue box the X-ray tube is positioned. A 1000 \( \mu \text{m} \) Al filter is placed within the yellow box. The sample is in the green box and the detector system is in the red box.

**Figure 36:** Pictures of the syringe sample and setup.

The amount of pure iodine in the solution is not well-defined, since (parts of) the solution probably evaporated and the manufacturer did not clearly indicate the iodine concentration. However, the ratios of iodine concentration between the syringes are well-defined. It is assumed that every syringe contains only water and iodine. Each syringe has a width of 6.7 mm and an inner thickness of 4.7 mm. Due to the circular shapes of the syringe’s plastic, the total syringe-length that X-rays pass trough, varies. Some positions of the syringe absorbed more photons than others. This is shown in figure 37. The varying thickness can be an check for the methodologies. After all, both thicknesses of iodine and water vary both. Under the assumption that the absorption differences of the syringes is negligibly small, the concentration of both water and iodine should roughly be constant over the whole syringe.

\(^{25}\)An acquisition block is defined as acquisition time plus dead time of the system.

\(^{26}\)The solution that has been used is Povidonjood Kruidvat, containing 1% of ‘active’ iodine.
**Figure 37:** Visualisation of intersection through a syringe. Syringe-thickness plastic varies over the sample due to its circular shape. Inner part is filled with iodine-solution.

**Acquisition settings and data**  The acquisition settings of the experiment are provided in table 2. In this case the ESD (following equation 7) is equal to approximately 0.05 mGy. Using equation 9 to convert ESD into MGD results in a dose of 0.09 mGy.

<table>
<thead>
<tr>
<th>kVp (kV)</th>
<th>Occupancy(%)</th>
<th>Frames</th>
<th>Filter</th>
<th>Acquisition time (s/frame)</th>
<th>ESD (mGy)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 mm Al</td>
<td>6.0 \cdot 10^{-4}</td>
<td>0.05</td>
</tr>
</tbody>
</table>

*Table 2: Acquisition settings of syringe experiment.*

The sample is divided over four chips. In this way results can be cross-checked. The ToT spectra are converted into energy spectra with a bin-width of 0.2 keV in the range of 0-100 keV. A spectral integral is shown in figure 38. The cross in the middle of this figure appears due to multiple chips that are connected with just one sensitive layer on top. The pixels that form the cross receive signals from a larger area of sensitive material and thus count a larger number of photons \(^{(48)}\).

During the time of experiments some of the water inside the syringes evaporated, which result in air-bubbles. This does not only reduce the area that can be used for determining iodine thickness, but also has effects on the ratio between iodine/water (since the amount of water changed). The iodine-concentration may come out higher in this situation. A well-defined open beam measurement is missing for this experiment. Because the interesting part is within the syringes, the plastic of the syringe can function as open beam reference. Pixels at the edges of each syringe are selected and averaged for every syringe. The resulting spectrum is used as open beam spectrum. With this methodology the syringe attenuation spectrum is extracted from the syringe + content spectra. Both attenuation factors of water and iodine are left in this case \(^{(28)}\). A visualisation of the open beam spectrum and the spectrum of the most concentrated syringe is shown in figure 39a.

If those spectra are logarithmically subtracted, the sum of attenuation factors of iodine and water are left. This is shown in figure 39b. Around 33 keV (K-edge of iodine) the increase of attenuation is clearly visible. However, the energy resolution of the system smears out this increase. Besides, another effect occurs below 14 keV. It is expected that the lower the energy, the higher the attenuation. However, below 14 keV the attenuation suddenly decreases. This effect is described by the Compton scatter inside the sensitive layer (Si).

**Compton scatter**  The Compton effect influences the attenuation spectrum. The question is if the effect in figure 39a can be explained by Compton scatter. An X-ray photon that Compton scatters has different energies before and after collision, \(E_{\gamma 1}\) and \(E_{\gamma 2}\) respectively. The energy of the electron that is measured is thus equal to

\[
E_e = E_{\gamma 1} - E_{\gamma 2}. \tag{27}
\]

Taking the scattering angle \(\theta\) into account, the energy of the electron is described by,

\[^{(27)}\text{This is calculated with a model provided by the dutch institute LRCB.}\]
\[^{(28)}\text{It is assumed here that the other materials, such as E-numbers, do not really contribute to the spectrum shape.}\]
Figure 38: Raw image of the per-pixel spectrum integral. From top to bottom the most concentrated iodine solution is on top, while the ‘water only’ syringe is on bottom.

(a) Spectra of both open beam and most concentrated syringe. The green line correspond to the open beam/syringe spectrum, while in the blue line additionally the content (water and iodine) is included.

(b) Logarithmic subtraction of open beam data with most concentrated syringe, resulting in a plot of the attenuation sum per energy bin of 0.2 keV in energy range 5-55 keV. The decrease of attenuation starts around 12 keV, which is in agreement with the Compton effect shown in figure 41.

Figure 39: Resulting spectra for most concentrated syringe. The increase of attenuation is visibly around 33 keV (due to Iodine K-edge), but there is also an increase of attenuation in the lower energy region. This is caused by the Compton effect. An explanation is provided in the next paragraph.

\[ E_c(E_{\gamma 1}, \theta) = E_{\gamma 1} - \frac{E_{\gamma 1}}{1 + \frac{E_{\gamma 1} (1 - \cos(\theta))}{511 \text{keV}}} \]  

(28)

where \( \theta \) is the scattering angle and 511 keV the rest mass of the electron. For \( \theta = 180^\circ \), \( E_c \) reaches its maximum. In this case \( E_c \) is equal to \( E_{\gamma 1} \). The Compton and photoelectric (and total) attenuation are visualised for an open beam situation with 300\( \mu \)m Si sensitive layer in figure 40. This gives a certain probability for the Compton effect.
to occur (with respect to the photo-electric effect). The Compton spectrum that is actually measured in our detector differs from the spectrum in figure 40.

**Figure 40:** Attenuation of both photoelectric (blue) and Compton effect (green). The sum of both effects is provided in red.

The energy that is measured is equal to the energy in equation 28. In this case the Compton effect that is measured includes an angle-dependence. For every energy and angle an unique Compton spectrum can be simulated. An example is given in figure 41a. Integrating those spectra for every energy and angle gives an attenuation probability distribution of the Compton effect in the sensitive layer. It should be noted that it is assumed that the photon scatters a single time. If it scatters again, the resulting electron can have another energy with respect to the first electron. The spectrum of first order Compton scattering is provided in figure 41b. It should be remarked that the Compton effect becomes dominant in an energy range of the spectrum that is not used in the iodine-analysis. For this reason secondary (and further) scatters are not included. An alternative way of calculating the Compton spectrum (Compton edge) is via the Klein-Nashina distribution. This calculation is beyond the scope of this thesis, but is well-explained at [http://www.phys.utk.edu](http://www.phys.utk.edu). It calculates in fact the Compton distribution provided in figure 40. In the case of silicon, this distribution is already known.

**Fitting procedure** In the fitting procedure a per chip analysis is performed. On every chip pixels are selected that cover an area of iodine and water. The system settings such as kVp, intensity and materials in the sample and expected thicknesses are supplied to the software. This is done following the steps described in subsection 2.3.3. The minimum, maximum and initial thickness values are provided in table 3. The initial guesses are based on figure 37.

<table>
<thead>
<tr>
<th>Material</th>
<th>Minimum thickness (cm)</th>
<th>Maximum thickness (cm)</th>
<th>Initial thickness (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>0.3</td>
<td>0.47</td>
<td>0.46</td>
</tr>
<tr>
<td>Iodine</td>
<td>0.0030</td>
<td>0.0047</td>
<td>0.0024</td>
</tr>
</tbody>
</table>

*Table 3: Minimum, maximum and initial thickness settings in the fitting algorithm for the syringe experiment.*

The iodine initial guess is halved for every less concentrated syringe. The open beam spectrum $I_0$ is scaled to the data by a factor of $\frac{p}{p_0}$, where $p$ is the number of pixels that is selected in the data and $p_0$ is the number of pixels that is selected to form the open beam spectrum. Subsequently equation 23 is fitted, where material A is ascribed to water and material B is ascribed to iodine. The energy range between 17-53 keV is selected to fit. The lower bound is set due to the Compton effect that appears below approximately 14 keV. The lack of statistics in the higher energy range due to kVp settings and silicon transparency provides the upper bound of 53 keV. The resulting fits and their corresponding water and iodine concentrations are provided in figure 42 and table 4 respectively. The results are visualised in figure 43. In this plot the syringes are visualised and the concentration ratio between water and iodine is clarified. It becomes clear that the iodine concentration decreases per syringe, while the concentration of
Both photoelectric spectrum (blue) and Compton spectrum (green). The Compton spectrum is calculated based on the Compton spectrum in figure 40 and equation 28. $\theta = 180^\circ$.

Integrating the Compton effect over all angles provides the plot where both photoelectric and Compton effect are visualised at measured energies. The resulting spectrum should be comparable to the spectrum in figure 39a (expect the energy resolution of the detector).

Figure 41: Plots to describe the resulting spectrum of the Compton effect.

Table 4: Resulting concentrations based on equation 19. Results of the fits in figure 42 are used to determine material thickness. Errors are introduced using the $\chi^2$ fitting methodology. The Limit of Detection (LoD) is set to 3$\sigma$ of the zero measurement in syringe 1, which is equal to 2.88 mg I/ml.

<table>
<thead>
<tr>
<th>Syringe</th>
<th>mg I/ml</th>
<th>mg H$_2$O/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.18 ± 0.96</td>
<td>999.9 ± 44.6</td>
</tr>
<tr>
<td>2</td>
<td>4.39 ± 0.43</td>
<td>999.1 ± 25.2</td>
</tr>
<tr>
<td>3</td>
<td>9.31 ± 0.79</td>
<td>998.1 ± 31.2</td>
</tr>
<tr>
<td>4</td>
<td>14.9 ± 1.07</td>
<td>997.0 ± 46.1</td>
</tr>
</tbody>
</table>

Discussion fitting

The fitting procedure deals with a couple of points for discussion. One of the points is caused by the energy resolution that is not included in the model. The relation between the energy resolution and energy is not yet determined for the detector system. The lack of energy resolution in the attenuation model results in a biased fit. An increase of attenuation is visible, but is not as sharp as it should be according to the model. In fact, the increased attenuation could be smeared out over a wider energy range, which in the end results in an underestimation of iodine. In the next experiment the data around the K-edge are ignored and the shape of the spectrum before and after the K-edge determines the amount of iodine that is extracted. It seems that this works relatively better with respect to the true amount of iodine. Another error that is brought in the system is the removal of clusters due to charge sharing. It is expected that the cluster-removal is not constant as function of energy $^{29}$. Since the cluster removal is not constant over energy, another difference between the model and the data arises. In the higher energy range the model underestimates the data and thus underestimates the amount of iodine. Finally the documentation of the iodine containing solution that was insufficiently extensive. For this reason other unknown materials, besides iodine and water, may have contributed to the total attenuation. Adding more materials in the system is yet theoretically possible. However, the purpose was to extract the amount of iodine from the sample. The rest of attenuation is ascribed to water (of water equivalence).

KES

In this paragraph the analysis of the KES methodology described in subsection 2.2.3 applied on the syringes-experiment, is elaborated. In this methodology every pixel is logarithmically subtracted to an open beam reference spectrum. This open beam spectrum is selected per chip. Within each resulting pixel spectrum subtraction a lower and

---

29 This is based on a few fluorescence measurements. In the lower energy range less clusters are ignored compared to higher energies.
Figure 42: Resulting fits of fitting procedure applied on syringe experiment. The upper plots represent the difference between the model and the data. The lower plot represent the initial model, the data and fitted model.
Figure 43: Visualisation of syringes including water and iodine concentration. Error analysis is based on errors that were introduced in the fitting analysis.

higher energy bin (before and after K-edge) is selected. Each bin is integrated and subsequently averaged. The average energy in the bin is used as energy to extract attenuation information of the included materials from an attenuation database. For the syringe experiment the lower energy bin is selected in the range of 20-28 keV (to include contrast of water and forget about the Compton spectrum), while the higher energy bin included the energy range of 36-39. The energy binning is visualised in figure 44. The energies are divided in steps of 0.2 keV, which should be an optimal energy width for KES according to Zhu et al. (22). It should be noted that this choice was made by chance.

From the KES algorithm two per-chip plots can be extracted that contain per-pixel information of material thickness of both material A and B. This information is thereafter used to determine iodine and water concentrations by making use of equation 19. Since this analysis is performed on a per-pixel basis, it is also possible to determine a corresponding CNR. Two thickness plots of both water and iodine of the upper right chip are shown in figure 45. Those plots contain per-pixel information of material thickness of water and iodine respectively. In those plots the circular structure of the syringes is visible for both water and iodine. A profile plot of the y-axis should provide thickness information about both syringes and their content. Since the syringes are straight, integrat-

Figure 44: Energy bin selection for the KES methodology for most concentrated syringe.
Thickness visualisation of water on the upper-right chip. The thickness of water should be almost equal in both syringes.

Thickness visualisation of iodine on the upper-right chip. The thickness of iodine should differ per syringe.

Figure 45: Thickness plots for both water and iodine in the syringes using KES algorithm methodology.

Profile plots of water looking at two syringes. Both syringes become clearly visible and so does the shape of the syringe (circular).

Profile plots of iodine looking at two syringes. Both syringes become clearly visible and so does the shape of the syringe (circular).

Figure 46: Thickness profile plots for both water and iodine in the syringes using KES algorithm methodology.

From those results the concentrations and the corresponding CNRs can be calculated. The signal pixels (25 pixels) are selected, averaged and their standard deviation is calculated. The same is done for the background pixels. Those quantities can be calculated from equation 11. The results are shown in table 5.

Spectral KES In this paragraph the analysis of the syringes using spectral KES described in subsection 2.2.3 is elaborated. This method differs with respect to KES, because it uses every single energy bin to make a thickness calculation. In this analysis every energy bin in the range between 20 and 38 keV is used in steps of 0.2 keV per bin. For every

---

30In this experiment the integration range is defined between x = 5 and x = 250.
energy bin a corresponding attenuation factor is extracted from the NIST database that is used in the experiment analysis. The open beam spectrum fully corresponds with the spectrum that is used for KES analysis. Also the analysis is performed on a per-pixel basis and is executed per chip. The results are cross checked per chip. Finally the CNR values are calculated. Let's first introduce two thickness plots of the upper right chip, see figure 47.

(a) Thickness visualisation of water on the upper-right chip. The thickness of water should be almost equal in both syringes.

(b) Thickness visualisation of iodine on the upper-right chip. The thickness of iodine should differ per syringe.

Figure 47: Thickness plots for both water and iodine in the syringes using spectral KES algorithm methodology.

A profile plot of the y-axis should provide thickness information about the different syringes. Since the syringes are straight, integrating and averaging over the x-axis should provide a well-defined material profile thickness for every syringe within the chip window. With this information the concentration in the syringes can be calculated from equation 19. The results for the upper right chip are visualised in figure 48.

From those results the concentrations and the corresponding CNR are calculated. The signal pixels are selected in the middle of the syringe and subsequently averaged. The resulting list of numbers has a standard deviation. This standard deviation is used for CNR calculations, but is also used for error propagation. The same is done for the background pixels. Those quantities are supplied to equation 11. Their outcomes are shown in table 6.

<table>
<thead>
<tr>
<th>Syringe</th>
<th>mg I/ml</th>
<th>mg H₂O/ml</th>
<th>CNR I</th>
<th>CNR H₂O</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.2 ± 1.3</td>
<td>997.7 ± 138.2</td>
<td>1.9</td>
<td>20.9</td>
</tr>
<tr>
<td>2</td>
<td>2.7 ± 1.8</td>
<td>999.5 ± 131.0</td>
<td>2.1</td>
<td>18.4</td>
</tr>
<tr>
<td>3</td>
<td>8.1 ± 2.2</td>
<td>998.4 ± 109.0</td>
<td>5.9</td>
<td>14.7</td>
</tr>
<tr>
<td>4</td>
<td>11.9 ± 1.7</td>
<td>997.3 ± 92.4</td>
<td>10.9</td>
<td>13.2</td>
</tr>
</tbody>
</table>

Table 5: Resulting concentrations following equation 19 thickness and using results of the KES methodology. Errors are based on fluctuations in material thickness in the selected pixels.

Discussion (spectral) KES It should be noted that the numbers on the y-axes in figures 46 and 48 do not directly correspond to physical quantities. However, the absolute differences between the background and signal pixels do

---

31 In this experiment the integration range is defined between x = 5 and x = 250.
Profile plot of water looking at two syringes. Both syringes become clearly visible and so does the shape of the syringe (circular). A baseline (between $y_{100}$ and $y_{150}$) could not really be defined due to the varying open beam spectrum due to different plastic thicknesses.

Profile plot of iodine looking at two syringes. Both syringes become clearly visible and so does the shape of the syringe (circular).

Figure 48: Thickness profile plots for both water and iodine in the syringes using spectral KES algorithm methodology.

Actually correspond to physical thickness differences (in cm). Since it is assumed that the plastic in the background pixels do not carry information of water and iodine attenuation, this is an acceptable methodology. However, a separate open beam measurement makes this assumption unnecessary. Besides, it should be noted that the used energy range are very suitable to determine iodine concentration, while the concentration of water should be determined in a lower energy range. In other words, the chosen lower and upper energy bin are far from ideal for analysing water.

Summary All three methods provide promising results for both iodine and water concentrations in the syringes. For the (spectral) KES methodologies also CNRs are quantified. From this CNRs also CNRDs can be determined. In this experiment the total administered dose was equal to 0.09 mGy, which is in the dose range of mammography examinations. In this situation the CNRD at CNR = 5 is equal to $16.7 \text{ mGy}^{-1/2}$. Let's first provide a plot where the three iodine concentration determination methodologies are summarised, see figure 49 and table 7.

<table>
<thead>
<tr>
<th>Method</th>
<th>T4 (mg I/ml)</th>
<th>T3 (mg I/ml)</th>
<th>T2 (mg I/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KES</td>
<td>11.9 ± 1.7</td>
<td>8.1 ± 2.2</td>
<td>2.7 ± 1.8</td>
</tr>
<tr>
<td>sKES</td>
<td>13.5 ± 1.5</td>
<td>8.1 ± 1.6</td>
<td>4.0 ± 1.6</td>
</tr>
<tr>
<td>Fit</td>
<td>14.9 ± 1.2</td>
<td>9.3 ± 0.8</td>
<td>4.4 ± 0.7</td>
</tr>
</tbody>
</table>

Average 13.4 ± 0.9 8.5 ± 0.9 3.7 ± 0.8

Table 7: Summary of all methodologies regarding the syringe iodine concentration determination. T4 corresponds to the syringe filled with the most concentrated iodine solution.

With those results it is also possible to determine the ratios between iodine and water, but that is not the purpose of this research. The research is focused on determining the limits of iodine concentration with CNR = 5, reached at an acceptable dose. The results for both KES and spectral KES are shown in figure 50. Considering the Rose limit the KES methodology in this experiment reached the concentration limit in the order of 7 mg I/ml. Looking at the spectral KES methodology the limit is not yet reached at 4 mg I/ml. Making use of the measures of the least concentrated syringe, it is expected that the limit of CNR = 5 will be reached in the order of 3.1 mg I/ml.
4.1.2 Mammography sample with Ultravist

Sample  After the somewhat non-exotic sample with the four syringes, a more realistic sample is prepared. This sample should make it possible to make a clear comparison with clinical mammography. It consists of three different sections with different thicknesses, which should correspond to different breast thicknesses. The material where the sample is made of (PMMA) is often used for breast modelling and mammography-like experiments. The molecular formula for PMMA is \((\text{C}_5\text{O}_2\text{H}_8)_n\). Its attenuation is comparable, with a certain conversion, to a real breast containing glandular tissue \([16]\). The sample has again four corridors that can be filled with a solution. The solution is in this case a real contrast agent: Ultravist 300. This solution contains 300 mg I/ml. The solution is diluted to adjust the iodine concentration. A schematic drawing of the sample is shown in figure 51. The OB section is created as open beam reference to measure the open beam spectrum. The number of total counts...
**Figure 51:** Mammography sample with four corridors that are filled with Ultravist solution. Sample is divided in four sections: section A (PMMA thickness of 58.5 mm), section B (PMMA thickness of 43.6 mm), section C (PMMA thickness of 27.0 mm) and section OB. The OB section is just a hole in the sample, which is to provide an open beam reference exposure. The corridors have a width of 4 mm and a height of 4 mm. 1.6 mm of the height consist of layers of glue.

is used to determine the scaling factor that is needed between the open beam reference spectrum (OB section) and separate open beam measurement. The scaling multiplied with the separate open beam spectrum is used as $I_{OD}$ spectrum. This spectrum is used in the analysis. Compared to the previous experiment the resulting open beam spectrum does correct for possible chip gradients. The left corridor is filled with the most concentrated solution (100 ml I/ml), the next corridors are filled with 10, 1 and 0 mg I/ml respectively. The corridors are square-shaped and have a height of 2.4 mm and a width of 4 mm.

**Acquisition settings and data** The acquisition settings used in the mammography experiment are shown in table 8.

<table>
<thead>
<tr>
<th>kVp (kV)</th>
<th>Occupancy(%)</th>
<th>Frames</th>
<th>Filter</th>
<th>Acquisition time (s/frame)</th>
<th>ESD (mGy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>70</td>
<td>2.5 (at 10µA)</td>
<td>$3 \cdot 10^6$</td>
<td>1mm Al</td>
<td>$1.5 \cdot 10^{-5}$</td>
<td>0.25</td>
</tr>
</tbody>
</table>

*Table 8: Acquisition settings of mammography experiment*

In this experiment the ESD (following equation 7) is equal to approximately 0.25 mGy. Using equation 9 to convert ESD into MGD, every section absorbed a different amount of dose. The amount of doses are provided in table 9.

<table>
<thead>
<tr>
<th>Sector</th>
<th>PMMA thickness (mm)</th>
<th>MGD (mGy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>58.5</td>
<td>0.26</td>
</tr>
<tr>
<td>B</td>
<td>43.6</td>
<td>0.33</td>
</tr>
<tr>
<td>C</td>
<td>27.0</td>
<td>0.42</td>
</tr>
</tbody>
</table>

*Table 9: Mean glandular dose (MGD) in different section of sample. Calculations based on publication by Dance and Sechopoulos (10), which is tabulated by LRCB.*

The sample is divided over four chips. In this way results can be cross-checked per chip. The ToT spectra are converted into energy spectra with a bin-width of 0.2 keV in the range of 0-100 keV. A spectral integral is shown in figure 38. During the time of experiments some of the water inside the corridors evaporated, which result in in an effective higher iodine concentration. Assuming that only water evaporated the new iodine concentration can be calculated by

$$con = \frac{con_0 V/V_0} = \frac{con_0 l \cdot w \cdot h / l_0 \cdot w \cdot h}{l/l_0},$$

where $con_0$ is the starting concentration, $l_0$ the length of the corridor and $l$ the height where the solution reaches after the measurement. The begin and end concentrations are provided in table 10.
Figure 52: Raw image of the per-pixel spectrum integral. From top to bottom the most concentrated iodine solution is on top, while the ‘water only’ corridor is on bottom. From left to right the thickest layer of PPMA is on the left and the thinnest on the right.

<table>
<thead>
<tr>
<th>Corridor</th>
<th>Con₀₀ (mg I/ml)</th>
<th>Con₀ (mg I/ml)</th>
<th>Con (mg I/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
<td>105.6</td>
<td>113.1</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>12.1</td>
<td>13.6</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 10: Concentrations in the corridors due to the effect of water evaporation over time. Con₀₀ is the iodine concentration after filling the corridors, Con₀ is the iodine concentration just before starting the measurement and Con is the iodine concentration after finishing the measurement.

Assuming that the evaporation speed was constant over time, the concentrations that should be determined are in the order of \(\frac{\text{Con₀} + \text{Con}_2}{2}\). For this experiment a separate open beam measurement is taken. The OB section is needed to define an open beam spectrum, which is scaled to the data spectrum. The open beam spectrum and the spectrum of the most concentrated corridor is shown in figure 53.

If those spectra are logarithmically subtracted from each other, the sum of attenuation factors of iodine, PMMA and other materials that Ultravist 300 contains are left. See figure 53b. Around 33 keV (K-edge of iodine) the increase of attenuation is clearly visible. However, the energy resolution of the system smears out this increase. Besides, another effect occurs around 15 keV. It is expected that the lower the energy, the higher the attenuation. However, below 15 keV the attenuation suddenly decreases. This effect is described by the Compton scatter inside the sensitive layer (Si).

An explanation is provided in subsection 4.1.1. All three (thickness) sections are divided into four different corridors. This results in a 4x3 matrix of concentration determinations. Those results are provided in the next paragraphs. For both KES and spectral KES methodologies also (dose normalised) CNR quantification are given.

**Fitting procedure** In this fitting procedure a per chip analysis is performed. On every chip pixels are selected, that cover an area of iodine. This is called a corridor. The system settings such as kVp, intensity, materials in the sample and expected thicknesses are supplied to the modelling software. This is done following the steps described in subsection 2.3.3. The minimum, maximum an initial thickness values are provided in table 11. The initial guesses are based on figure 51.

The iodine initial guess is multiplied with 1/10 for every less concentrated corridor. This is what is expected due to the dilution of water in the solution. Subsequently equation 23 is fitted, where material A is equal to PMMA (+ fixed amount of water) and material B to iodine. It should be noted that, except from water, other materials that Ultravist...
(a) Spectra of both open beam and most concentrated corridor.

(b) Logarithmic subtraction of open beam data with most concentrated corridor, resulting in a plot of the attenuation sum per energy bin of 0.2 keV in energy range 5-70 keV.

Figure 53: Resulting spectra for most concentrated corridor. The increase of attenuation is visibly around 33 keV (due to Iodine K-edge), but there is also a decrease of attenuation in the lower energy region. This is caused by the Compton effect.

<table>
<thead>
<tr>
<th>Material</th>
<th>Minimum thickness (cm)</th>
<th>Maximum thickness (cm)</th>
<th>Initial thickness (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>2.0</td>
<td>3.0</td>
<td>2.6</td>
</tr>
<tr>
<td>Iodine</td>
<td>0.0010</td>
<td>0.0023</td>
<td>0.0015</td>
</tr>
</tbody>
</table>

Table 11: Minimum, maximum and initial thickness settings in the fitting algorithm for the syringe experiment.

Table 12: Result of fitting methodology in section C: concentration of iodine and PMMA thickness.

<table>
<thead>
<tr>
<th>Corridor</th>
<th>Concentration I (mg I/ml)</th>
<th>Thickness PMMA (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>92.5 ± 19.2</td>
<td>21.9 ± 6.2</td>
</tr>
<tr>
<td>2</td>
<td>12.6 ± 2.6</td>
<td>23.2 ± 6.9</td>
</tr>
<tr>
<td>1</td>
<td>0.6 ± 0.1</td>
<td>29.9 ± 3.7</td>
</tr>
</tbody>
</table>

It seems that the model of PMMA, water and iodine fits well. The fit in figure 54d has the largest $\chi^2$ of 27. The value is this high, due to the lack of energy resolution in the model. Introducing the energy resolution in the model requires a lot more processing time. To find out if energy resolution in the analysis is really needed, it is tested if the introduction of energy resolution in the model changes the found amount of iodine in case of figure 54d. In this situation a linear energy resolution of 3 keV introduced. The linearity means that all energy bins have the same weight in calculating the average attenuation over the relevant energy bin. The result of including energy resolution in the model, tested on the situation of figure 54d results in figure 55. Fortunately the amount of iodine that was found in both fits are equal. This means that the bias that the lack of energy resolution in the model introduces, is negligible. In this case the model that does not include the energy resolution is preferred.

To calculate the attenuation of e.g. the 30 keV energy bin, the average attenuation of the energy bins of 28.5-31.5 keV is calculated and ascribed to the 30 keV bin.
(a) Fit of only PMMA and water corridor in section C, contains no iodine.

(b) Fit of least concentrated corridor in section C, contains 1-1.1 mg I/ml.

(c) Fit of second concentrated corridor in section C, contains 10-13.6 mg I/ml.

(d) Fit of most concentrated corridor in section C, contains 100-113.1 mg I/ml.

**Figure 54:** Resulting fits of fitting procedure applied on mammography experiment. The upper plots represent the difference between the model and the data. The lower plot represent the initial model, the data and fitted model. The fit include PMMA and iodine thickness. Water is fixed to a thickness of 2.2 mm.
In this paragraph the analysis of the KES methodology described in subsection 2.2.3 applied on the mammography-experiment, is elaborated. In this methodology every pixel is logarithmically subtracted from an open beam reference spectrum. This open beam spectrum is selected per chip. Just as for the syringe-experiment in each resulting pixel spectrum subtraction a lower and higher energy bin (before and after K-edge) is selected. Each bin is integrated and subsequently averaged. The average energy in the bin is used as energy to extract attenuation information of the included materials from an attenuation database. For the mammography experiment the lower energy bin is selected in the range of 21-29 keV to include contrast of PMMA and to make sure that the Compton spectrum does not influence the result, while the higher energy bin included the energy range of 36-39 keV. This type of binning is visualised in figure 44. The energies are divided in steps of 0.2 keV. From the KES algorithm two per-chip plots can be extracted that contain per-pixel information of material thickness for both material A and B. This information is thereafter used to determine iodine concentration and PMMA thickness. Since this analysis is performed on a per-pixel basis, it is also possible to determine a corresponding CNR. Lets first introduce two thickness plots of both PMMA and iodine of the upper right chip, see figure 56. Those plots contain per-pixel information of material thickness. In those plots the structure of the PMMA and corridors are visible. Since the difference in thickness due to the corridor in PMMA is only 2.4 mm, it is not expected that there is a lot of contrast difference between those corridor areas and PMMA (2.4 mm with respect to a thickness of approximately 2.7 cm). However, in figure 56a the corridors become clearly visible. Especially in the most concentrated corridor. This is due to the unknown materials in the Ultravist solution, such as iopromide salt. This does not match with the algorithm materials PMMA+water and iodine. The distribution of this salt gets visible due to higher solution concentration. The excess of attenuation is in this case ascribed to PMMA-thickness. Experiments showed that the attenuation of the iopromide salt is not negligible for concentrations above 8 mg I/ml.

A profile plot of the y-axis should provide thickness information of the corridors, while a profile plot of the x-axis should provide thickness information of the (PMMA) section. Since the corridors and sections are straight, integrating and averaging over both axis should provide a well-defined material profile thickness. With this y-axis profile information, the iodine concentration can be calculated from equation 19. The results for the upper right chip are visualised in figure 57.

From those results the concentrations and the corresponding CNR could be calculated. The signal pixels (25 pixels) are selected, averaged and their standard deviation is calculated. The same is done for the background pixels. Those quantities are entered in equations 11. The results of iodine concentration, CNR and PMMA thickness calculated with the KES methodology are provided in table 13.

### Spectral KES

In this paragraph the analysis of the mammography sample using spectral KES methodology described in subsection 2.2.3 is elaborated. In this analysis every energy bin in the range between 22 and 50 keV is used in steps of 0.2 keV per bin. For every energy bin a corresponding attenuation factor is extracted from the NIST database and
Master thesis W.R. Poland

Thickness visualisation of PMMA on the upper-right chip. The thickness of PMMA should be constant per section. On the left hand side the thickness of section B is visualised, while on the right hand side the thickness of section C is visualised. There is also some structure of the corridors present. This is caused by the iopromide salt in Ultravist 300.

Thickness visualisation of iodine on the upper-right chip. The thickness of iodine should differ per syringe.

Figure 56: Thickness plots for both PMMA and iodine in the sample using KES algorithm methodology.

Profile plot of PMMA looking at two sections. On the left section B, on the right section C. From figure 56a the x-profile is integrated and averaged between the range of $y = 91$ to $y = 124$.

Profile plot of iodine looking at corridors. Both corridors become visible and so does the shape of the corridor (rectangular). From figure 56b the y-profile is integrated and averaged between the range of $x = 104$ to $x = 250$.

Figure 57: Thickness profile plots for both PMMA and iodine in the syringes using KES algorithm methodology.

is used for the analysis. The open beam spectrum fully corresponds with the spectrum that is used for KES analysis. Also the analysis is performed on a per-pixel basis and is executed per chip. The results are cross checked per chip. Finally quantities such as CNR can be calculated from this. Lets first introduce two thickness plots of the upper right chip, see figure 58.

In those plots the structure of the PMMA and corridors are visible. In the PMMA plot the corridors are also visible. This is explained in the previous paragraph. A profile plot of the y-axis should provide thickness information of the corridors, while profile plot of the x-axis should provide thickness information of different PMMA sections. Since the corridors and sections are straight, integrating and averaging over the axis should provide a well-defined material profile thickness for both PMMA and iodine. The results for the upper right chip are visualised in figure 59.

From those plots the iodine concentrations and corresponding CNRs are calculated. The signal pixels (25 pixels) are selected in the middle of the corridor and are averaged. The list of pixels differ in value and thus have a standard de-
Table 13: Table that contain results of KES methodology. It contains information of PMMA thicknesses, iodine concentration and CNR.

<table>
<thead>
<tr>
<th>KES Corridor</th>
<th>Section</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Information</td>
<td>Thickness PMMA (mm)</td>
<td>45.8 ± 0.4</td>
<td>35.3 ± 0.4</td>
<td>26.2 ± 0.3</td>
</tr>
<tr>
<td>1 Iodine concentration (mg I/ml)</td>
<td>24.2 ± 8.4</td>
<td>24.9 ± 7.6</td>
<td>22.6 ± 5.5</td>
<td></td>
</tr>
<tr>
<td>1 CNR</td>
<td>7.5</td>
<td>9.0</td>
<td>12.8</td>
<td></td>
</tr>
<tr>
<td>2 Iodine concentration (mg I/ml)</td>
<td>4.6 ± 4.2</td>
<td>4.2 ± 3.9</td>
<td>3.0 ± 2.4</td>
<td></td>
</tr>
<tr>
<td>2 CNR</td>
<td>1.1</td>
<td>1.5</td>
<td>1.7</td>
<td></td>
</tr>
<tr>
<td>3 Iodine concentration (mg I/ml)</td>
<td>2.1 ± 4.3</td>
<td>2.0 ± 3.9</td>
<td>1.3 ± 2.4</td>
<td></td>
</tr>
<tr>
<td>3 CNR</td>
<td>0.2</td>
<td>0.6</td>
<td>0.8</td>
<td></td>
</tr>
</tbody>
</table>

Table 14: Table that contain results of spectral KES methodology. It contains information of PMMA thicknesses, iodine concentration and CNR.

<table>
<thead>
<tr>
<th>Spectral KES Corridor</th>
<th>Section</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Information</td>
<td>Thickness PMMA (mm)</td>
<td>43.2 ± 0.5</td>
<td>33.1 ± 0.4</td>
<td>23.8 ± 0.4</td>
</tr>
<tr>
<td>1 Iodine concentration (mg I/ml)</td>
<td>49.9 ± 10.3</td>
<td>61.6 ± 13.8</td>
<td>65.1 ± 12.1</td>
<td></td>
</tr>
<tr>
<td>1 CNR</td>
<td>24.2</td>
<td>31.1</td>
<td>34.8</td>
<td></td>
</tr>
<tr>
<td>2 Iodine concentration (mg I/ml)</td>
<td>4.5 ± 0.9</td>
<td>6.5 ± 3.0</td>
<td>6.2 ± 2.8</td>
<td></td>
</tr>
<tr>
<td>2 CNR</td>
<td>2.4</td>
<td>3.3</td>
<td>3.3</td>
<td></td>
</tr>
<tr>
<td>3 Iodine concentration (mg I/ml)</td>
<td>1.9 ± 1.8</td>
<td>3.5 ± 3.4</td>
<td>2.3 ± 2.1</td>
<td></td>
</tr>
<tr>
<td>3 CNR</td>
<td>1.4</td>
<td>1.6</td>
<td>1.8</td>
<td></td>
</tr>
</tbody>
</table>

(a) Thickness visualisation of PMMA on the upper-right chip. The thickness of PMMA should be constant per section. On the left hand side the thickness of section B is visualised, while on the right hand side the thickness of section C is visualised. There is also some structure of the corridors present. This is due to the iopromide salt in Ultravist 300 [3].

(b) Thickness visualisation of iodine on the upper-right chip. The thickness of iodine should differ per syringe.

Figure 58: Thickness plots for both PMMA and iodine in the sample using KES algorithm methodology.
Summary  All three methods provide results of both iodine concentration and PMMA thickness in the sample. For the (spectral) KES methodologies also CNRs are quantified. From this CNRs also CNRDs can be determined, by making use of the MGD model for quantifying dose. In this experiment the total dose is every section was in the range of 0.2-0.5 mGy. In figure 60, a plot where the three iodine concentration determination methodologies are summarised is shown. The results are also provided in table 15. It should be noted that for the (spectral) KES methodologies the outcomes for section C are used.

Figure 59: Thickness profile plots for both PMMA and iodine in the corridors using the spectral KES algorithm methodology.

Figure 60: Plot that summarises the iodine concentration determination for three methodologies: fitting, KES and spectral KES. C1 corresponds to the corridor filled with the most concentrated iodine solution. In the fitting procedure all iodine containing pixels are taken into account (in all sections), while for (spectral) KES only results for section C are included. The error bars on the true amount of iodine are caused by the evaporation of water in the corridor during the measurement, see table 10.
From those results it can be concluded that the concentration of iodine that every method finds is consistently lower with respect to the true concentration. This can be explained by the absence of energy resolution in (spectral) KES methodologies. From figure 55 it is already concluded that the fitting procedure is not influenced by the energy resolution due to the possibility that some energy bins are ignored. However, in the (spectral) KES methodologies it is not possible to ignore the energy bins that are smeared out. Nevertheless, the structural offset in a specific energy range for every methodology can be determined. This can be used to scale up (or down) the measured iodine concentration. An alternative is to further develop the (spectral) KES methodologies and include the effect of energy resolution.

The research is focused on determining the limits of iodine concentration with an acceptable CNR with a specific mammography dose. This is quantified with the KES and spectral KES methodology. The results are shown in figures 61 and 62. Both plots contain results for every section in the sample.

**Figure 61: Iodine concentration as function of CNR for KES methodology in different sections. Section C in blue, section B in orange and section A in green. The Rose limit (CNR = 5) is visualised in red.**

Considering the Rose limit, the KES methodology in this experiment reached the concentration limit in the order of 8.8 mg I/ml in section C. The other sections have higher limits, due to the higher background signal from the PMMA. Looking at the spectral KES methodology the limit is reached at 9.4 mg I/ml. In section C a MGD of 0.42 mGy is administered. A CNR of 5 corresponds to a CNRD of 7.7 mGy$^{-\frac{1}{2}}$ in this case. In short: the minimum amount of iodine where the contrast can be distinguished in this experiment is approximately 9 mg I/ml. In this case the sample is exposed to 0.42 mGy and is analysed with KES techniques. Comparing the results with the syringe experiment the minimum amount of detectable iodine is a factor of $9^{\frac{1}{2}} \approx 2.9$ higher. Taking also the increased dose into account, this experiment did a factor of $\frac{9}{3.1\sqrt{0.09}} \approx 6.4$ worse. It is expected that this is caused by the lower background due to the thin plastic of the syringes.

---

**Table 15: Summary of all methodologies regarding the mammography iodine concentration determination. C1 corresponds to the corridor filled with the most concentrated iodine solution. For C1 and C2 also the difference in iodine concentration per method with respect to the true iodine concentration is provided.**

<table>
<thead>
<tr>
<th>Method</th>
<th>C1 (mg I/ml) @ % from true value</th>
<th>C2 (mg I/ml) @ % from true value</th>
<th>C3 (mg I/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KES</td>
<td>22.6 ± 5.5 @ - 80%</td>
<td>3.0 ± 2.4 @ - 78%</td>
<td>1.3 ± 2.4</td>
</tr>
<tr>
<td>sKES</td>
<td>65.1 ± 12.1 @ - 42%</td>
<td>6.2 ± 2.8 @ - 54%</td>
<td>2.3 ± 2.1</td>
</tr>
<tr>
<td>Fit</td>
<td>92.5 ± 19.2 @ - 18%</td>
<td>12.6 ± 2.6 @ - 7%</td>
<td>0.6 ± 0.1</td>
</tr>
<tr>
<td></td>
<td>Average</td>
<td>60.1 ± 7.8 @-47%</td>
<td>7.3 ± 1.5 @ -46%</td>
</tr>
</tbody>
</table>
Figure 62: Iodine concentration as function of CNR for spectral KES methodology in different sections. Section C in blue, section B in orange and section A in green. The Rose limit (CNR = 5) is visualised in red.

4.2 PCD versus state of the art mammography

In this section the results provided in section 4 are compared to state-of-the-art detector systems that are currently used for clinical (mammography) purposes. Most clinical examinations take place in hospitals and are based on the dual energy technique, which is introduced in subsection 2.2. The technique of KES can be applied here (3).

KESM

In this work the three different methodologies (fitting, KES and spectral KES) will be compared to several dual energy KES examinations. The publication which is used for comparison is Evaluation of the minimum iodine concentration for contrast-enhanced subtraction mammography which is published by Baldelli et al. (3). In this work Baldelli et al. make use of a sample that consist of PMMA spheres, animal fat and a layer with cavities which are filled with a iodine and water solution. The cavities have different dimensions (5mm and 8mm circular shaped). The same contrast agent as in the work in this thesis is used (Ultravist 300). CNR quantifications are based on signal, background and a deviation of background values within a region of interest (ROI). The amount of photons that enter the sensor scales directly with the area (A) of ROI. Considering photon statistics, \( \text{CNR} \propto \sqrt{N} \). In this case: \( \text{CNR} \propto \sqrt{A} \) (3). Since iodine concentration and CNR are linearly related (3), the minimum amount of detectable iodine scales also with \( \sqrt{A} \). The same is true for the dose (ESD, see equation 7). In this case \( \text{CNR} \propto \sqrt{\text{dose}} \). The (minimum) detectable iodine concentration thus scales with \( \sqrt{\text{dose}} \). In (3) the minimum iodine concentration for clinical KESM systems is 5.75 mg I/ml for a cavity of 5mm diameter at a MGD of 2 mGy. In both Baldelli and this thesis the ROI areas were equal to \( A_{\text{baldelli}} = \pi \cdot (2.5 \text{mm})^2 = 19.6 \text{mm}^2 \) and \( A_{\text{experiment}} = 4 \text{mm} \cdot 25 \text{pixels} \cdot 55 \mu \text{m} = 5.5 \text{mm}^2 \) respectively. Taking the same circumstances (area and dose), the minimum detectable iodine concentration in the mammography-like experiment of this thesis is equal to 2.18 mg I/ml. This result is 62.1% lower with respect to the clinical KESM system used in Baldelli et al. (3).

Spectral KESM

The spectral KESM methodology is tested in Spectral K-edge subtraction imaging, by Zhu et al. (22). As claimed in Zhu et al. (22), also from this work it seems that the spectral KESM methodology is slightly more sensitive for determining amounts of iodine compared to the KESM methodology. In Zhu et al. (22) a SNR, which is a measure that marginally differs from CNR, of 3 is chosen as absolute minimum. It claims that a SNR of 3 is reached at 0.65 mg I/ml, assuming 18.7 \( \mu \)m pixels and a dose of 4320 mGy. According to Zhu et al. (22) SNR scales with \( \sqrt{2} \) pixel size, and, as already mentioned, the square root of the dose. In the mammography experiment 55\( \mu \)m pixels are used (Timepix). The total exposed dose was 0.42 mGy. Assuming that a CNR of 3 is acceptable, the iodine concentration

\[ \text{Iodine concentration} = \frac{\text{Signal}}{\text{Background} + \text{Deviation}} \]

\[ \text{CNR} \propto \sqrt{\text{dose}} \]

\[ A_{\text{baldelli}} = \pi \cdot (2.5 \text{mm})^2 = 19.6 \text{mm}^2 \]

\[ A_{\text{experiment}} = 4 \text{mm} \cdot 25 \text{pixels} \cdot 55 \mu \text{m} = 5.5 \text{mm}^2 \]

\[ \text{SNR} \propto \sqrt{\text{dose}} \]

\[ \text{SNR} \propto \sqrt{2} \text{ pixel size} \]

\[ \text{SNR} \propto \sqrt{2} \text{ pixel size} \]

\[ \text{SNR} \propto \sqrt{2} \text{ pixel size} \]

\[ \text{SNR} \propto \sqrt{2} \text{ pixel size} \]
limit that was found in the mammography-like experiment is 5.4 mg I/ml. Converting this to the pixel size and used
dose as in Zhu et al. (22), an iodine concentration of 0.22 mg I/ml should be able to be detected. If a CNR of 5 is needed
this converts to a limit of 0.37 mg I/ml. The spectral KES methodology thus does better compared to state-of-the-art
methodologies. A summary is given in table 16.

<table>
<thead>
<tr>
<th>Method</th>
<th>Situation</th>
<th>Baldelli et al. (3)</th>
<th>Zhu et al. (22)</th>
<th>Poland</th>
<th>Optimisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>KES</td>
<td>CNR=5, dose=2mGy, pitch=19.6mm²</td>
<td>5.75 mg I/ml</td>
<td>-</td>
<td>2.18 mg I/ml</td>
<td>62.1%</td>
</tr>
<tr>
<td>sKES</td>
<td>CNR=3, dose=4320mGy, pixel=18.7µm</td>
<td>-</td>
<td>0.65 mg I/ml</td>
<td>0.22 mg I/ml</td>
<td>66.2%</td>
</tr>
</tbody>
</table>

Table 16: Summary of comparison of minimum iodine concentration between experiments in this thesis and state-of-the-art systems.

Sensitive layer A drawback of the used detection system that is used in the experiments is the type sensitive layer:
silicon. As discussed in subsection 2.1.6, Silicon is a limiting factor in the for iodine relevant energy range (order of
30 keV). This is visualised in figure 12. Since the photon absorption is relatively low around 30 keV when using a
layer of 300 µm silicon, this influences the CNR. Assuming Poisson counting statistics the CNR scales with the photon
intensity following

\[ CNR \propto \frac{1}{\sqrt{I + \frac{1}{I_0}}}, \]  

(30)

where I is the measured intensity in the data and I_0 the measured intensity in the open beam dataset (22). If another
sensitive layer is used, both I and I_0 scale up with the same percentages. In this case \( CNR \propto \frac{1}{\sqrt{f}} \), where f is the relative
increase of photon counts with respect to 300 µm Si. Comparing a sensitive layer of 300 µm of Si with 300 µm GaAs
inn the energy range of 22-50 keV results in a f of 13.4. A CNR would increase with a factor of approximately 2.6 in
this situation. This means that the iodine concentration limit can be reduced by another factor of 2.6. The simulation
of the photoelectric absorption in an open beam measurement for both Si and GaAs is shown in figure 63.

Figure 63: Visualisation of model that provides photoelectric absorption as function of energy for three different sensitive layers: 300µm GaAs (blue), 200µm Si (green) and 300µm Si (purple).
5 Conclusion

The aim of this work was to set up an iodine quantification method in mammography-like experiments with energy selective photon counting detectors. The results were in the end used for the determination of the minimum amount of iodine that is needed to deliver enough contrast in an analysed mammography image (CNR = 5). This is done by making use of three different analysis algorithms: fitting X-ray model, KES \(^{[3]}\) and spectral KES \(^{[22]}\). The limits of detectability are finally compared to (clinical) state-of-art examinations.

**Fitting**  In this method the X-ray tube, sensitive layer (part of the detector system) and photon interactions that occur between the tube and detector are modelled. It does not provide a detection limit in the sense of CNRs, but it provided information on how well the amount of iodine can be determined with respect to the true amount. For the mammography-sample experiment, the \(\chi^2\) and p-value can be calculated by comparing table 10 and 12. In this case \(\chi^2\) is 5.1 and the corresponding p-value is 0.078. This makes the fitting procedure an acceptable methodology for determining iodine concentration. Based on the residuals in the fitting plots, it can be stated that the model is an approximation of what happens in the X-ray cabinet. The model needs further optimisations to decrease the magnitude of residuals. Some optimisations are provided in the next section.

**KES**  In this methodology two bins, before and after iodine K-edge, were selected. The increase of attenuation around the K-edge provides information of the amount/thickness of iodine on a per-pixel basis. This information is subsequently used to determine the iodine concentration. In this case \(\chi^2\) is 400 and the corresponding p-value is 1.466. This value for \(\chi^2\) seems to prove that the KES methodology applied on the data is not yet suitable to determine the correct amount of iodine in a mammography sample. This is further elaborated in section 6. If it is assumed that the amount of iodine can be determined correctly a concentration limit of 8.8 mg I/ml should be achievable. This is achieved at a CNRD of 7.7 mGy\(^{-\frac{1}{2}}\).

**Spectral KES**  The spectral KES method differs in the sense that spectral KES makes use of more than two energy bins, to calculate the amount of materials inside a sample. It also makes use of K-edge information of iodine to separate materials. In this case \(\chi^2\) is 40 and the corresponding p-value is 0.82. It also becomes clear that the spectral KES methodology is not accurate enough to determine the correct amount of iodine. However, it does better compared to KES. For a further explanation see section 6. Under the assumption that the determination of iodine is fully correct, the minimum amount of iodine where the contrast can be distinguished is equal to 9.4 mg I/ml, which is in the same order as KES. The corresponding CNRD is equal to 7.7 mGy\(^{-\frac{1}{2}}\).

**State of the art comparison**  Both KES and spectral KES methodologies are compared to Baldelli et al. \(^{[3]}\) and Zhu et al. \(^{[22]}\) respectively. Those experiments provide clinical results based of a few free parameters: dose, pixel size, area. In a clinical KES system the detection limit came out on 5.75 mg I/ml \(^{[3]}\). In this situation the mammography experiment using KES would have measured a detection limit of 2.18 mg I/ml. For the spectral KES methodology the clinical limit is set on 0.65 mg I/ml, assuming that a CNR of 3 is acceptable. Taking the circumstances as in Zhu et al. \(^{[22]}\), the detection limit for the mammography-like experiment would have been 0.22 mg I/ml. Both KES and spectral KES methodology thus do better compared to clinical examinations. With that in mind a sensitive layer of 300 \(\mu\)m GaAs should have done another factor of 2.6 better compared to a 300 \(\mu\)m Si sensor. Also the use of a different anode/filter combination possibly bring another improvement of counting statistics in the iodine K-edge energy range. Future experiments thus should focus on both testing other sensitive layers and anode/filter combinations to further decrease the detection limit of iodine.
6 Discussion

In this section some general drawbacks and future improvements of the used methodologies will be discussed. Besides, every applied methodology is discussed and some specific optimisations are proposed.

Fitting The fitting procedure seems very suitable for determining the amount of iodine in a sample. However, due to limited statistics, it is not yet possible to produce per-pixel images with this methodology. Due to the lack of counting statistics in the, for iodine relevant, energy range, the fitting model does not recognise any K-edge on a single pixel spectrum (or at least very sloppily). There are two ways to increase the counting statistics: use a different (high-Z) sensitive layer and increase the X-ray dose. The latter consequently results in a degrade of CNRD due to the increased dose. When enough statistics is gathered, it is unknown which limiting factors regarding the fitting procedure play a role in determining the correct amount of iodine. It is unknown which errors the used fitting algorithm (Levenberg-Marquardt Method) introduces. At this point the fitting procedure needs some information before the analysis starts: it needs information of all materials that are in the sample and needs a well-defined estimation on how the materials are distributed. The material input can be replaced by looping over a database with materials and compounds that may be inside the sample. At first some rough fits are applied, after which the probabilities of having a material inside a sample can be calculated. With this information a second iteration can be done. Material thicknesses should be fitted here. This step should be comparable to the fitting procedure as elaborated in this thesis. If it can be quantified how many photons are needed to do a per-pixel reconstruction, the fitting procedure should be a candidate for advanced spectral material imaging.

Sensitive layer One way to increase the amount of counting statistics is making use of a different sensor material than silicon. Silicon has a relatively low absorption for high energy photons. The more high energy photons are detected in the range of iodine K-edge, the higher the CNR according to equation [30] Replacing Si with GaAs should already bring an improvement of 2.6× CNR in the energy range of 22-50 keV. Different sensitive layer constructions can be used in future experiments to determine the iodine concentration limit per sensitive layer type/thickness. Before that equation [30] can be used to do a first order estimation on how CNR improves as function of counting statistics.

Energy resolution A feature in the detector system that is highly underexposed in this thesis is the energy resolution. The energy resolution, introduced in subsection [31] smears out spectral information of the X-rays that pass trough a sample. This smearing out is best visualised by the fits in figure [54]. The model has a spontaneous increase of attenuation, while in the data the attenuation jump is smeared out over a wider energy range. Since the attenuation jump is characteristic for the amount of iodine, the smearing out results in an underestimation of iodine with respect to the true amount of iodine. For this reason the fitting procedure for the mammography-like experiment is based on statistics before and after the K-edge only. If the shape of the fit before and after the K-edge matches the true data, the found iodine concentration came very close to the true concentration. In this case it seems that the peak value around 33 keV in figure [54] does not match with the true attenuation increase and thus with iodine thickness. An optimisation in the model should include the energy resolution of the detector system. However, from the resulting fit in figure [55] it can be concluded that including a linear energy resolution in the model does not change the amount of iodine that is found. If one want to include the true energy resolution in the model the ToT → Energy calibration dataset can be used. This dataset contains widths (σ) of photo-peaks of the fluorescence materials which can be compared to the true width (FWHM). With this calibration the ΔE/E could be determined as function of E. This energy bias can be implemented in the fitting model by modifying $I_{0M}$ and $I_M$ in equation [25]. The ΔE/E calibration set should be determined for every different sensitive layer. For example a Timepix detector with GaAs:Cr sensor has an energy resolution of 8% and 13% at 60 keV and 20 keV respectively [49].

Dose calculation The dose calculation in this thesis is based on a dose-scan by Marcel Vervoort and manufacturer of the tube. Equation [7] is based on this scan. It results in relatively low administered amounts of dose, compared to state-of-the-art examinations. For this reason the dose determination is cross checked with the X-ray tube model by Hernández and Fernández [14]. This model includes an incident air KERMA dose-quantification (in mGy), which is based on equation [7]. In this case it is assumed that the incident air KERMA is equal to the entrance surface dose. For an open beam measurement with no sample but a filter of 1mm Al the measured photon spectrum is determined for a single chip. This spectrum is divided trough the sensor response of 300/μm Si. This should correspond to the spectrum that reaches the sample. The resulting spectrum is integrated. This integrated spectrum represent the amount of photons in the X-ray beam. The model of Hernández and Fernández [14] is now able to calculate the corresponding incident air KERMA, given the tube settings, distance and characteristics. The amount of dose is, according to this
model, equal to 0.20 mGy. This is slightly lower compared to the determination by the manufacturer (0.25 mGy). This is because it is assumed that a filter is not used in that experiment. It thus seems that the dose as calculated in this thesis is acceptable. However, it is really recommended for further research to have more accurate measures on the incident air KERMA. It should be determined how the measured spectrum and integrated energy should be converted into conventional dose quantifications such as incident air KERMA.

**KESM** The KESM methodology is limited in the sense that it is only suitable for a two-component systems. It should be noted that in principle every tissue mix can be used in the methodology, as long as its attenuation curve is well-known. In practice, due to simplicity and the fact that the body substantially consist of water, H$_2$O is often chosen as only contributing background compound. When a third component (e.g. another contrast agent, tissue mix and blood) comes in, the methodology breaks down.

KESM makes use of limited spectral information due to the fact that only two energy bins are selected and used for material analysis. From this thesis it is also concluded that the spectral KES methodology does better compared to state-of-the-art systems. For this reason future experiments should be limited to the analysis with the fitting procedure and spectral KESM.

**Statistics** In X-ray physics Poisson counting statistics is the dominant factor in determining CNR quantifications under assumption that the model is fully accurate. In the case of KES, the determination of the noise with respect to the signal is roughly defined by $N_S = \sqrt{2N}$ (noise add quadratic due to the two energy bins). To extract a certain amount of thickness, quantified in terms of percentages $p$, $N_S < p$. In other words $N > \frac{p^2}{2}$. To extract for example a 1% step of signal only with a K-edge, already in the order of 20000 photons are needed. Taking the energy spectrum around the iodine K-edge, the mammography experiment reached far from enough statistics per pixel. However, summing pixels increases the amount of photons (N) and thus should return better results. This is what is done in the experiment’s analysis. In the order of 25-150 pixels are used to quantify the amount of iodine around the K-edge with the KES methodology. Increasing the pixel pitch thus increases the distinctive ability of the system, but decreases the (spatial) resolution.
7 Acknowledgement

7.1 Dankwoord

Voor een masterproject wellicht een tikkeltje overdreven, maar omdat deze thesis het eindproduct is van vijf jaar Natuurkundestudie wil ik toch even stilstaan bij de totstandkoming ervan. Voor wat betreft deze thesis wil ik uiteraard graag mijn begeleiders Els en Martin bedanken. Ondanks het drukke schema dat Els erop nahoudt, was zij er altijd op de juiste momenten om waar nodig bij te sturen. Dat heeft een hoop ontspanning met zich meegebracht. Daarnaast heeft Martin dagelijks zijn handen vol gehad aan de begeleiding van mijn masterproject. Een substantieel deel van het in dit verslag gepresenteerde werk is tot stand gekomen dankzij zijn intensieve begeleiding. We hebben niet alleen op het gebied van X-ray physics een hoop aan elkaar gehad, maar ook aan de pauzes hielden we altijd interessante gesprekstof en stof tot nadenken over. Verder wil ik ook graag de steun van Stergios en Michele benoemen. Het is altijd fijn om met medestudenten te overleggen en zeker in de eerste weken heb ik een hoop aan jullie advies gehad. Uiteraard moet ik ook even stilstaan bij de gezelligheid die mijn studiegenoten en vrienden Bas, Bram, Stephan en Joran hebben gebracht in de soms iets wat uitgelopen pauzes. Jullie gaven mijn (werk)dagen op het Nikhef een extra kleurtje. Ik had mij niet willen voorstellen hoe het afgelopen jaar was geweest zonder jullie bijzijn. Laat ik dan ook meteen even stil staan bij het feit dat ik het hele jaar ontzettend goed ben ondersteund door mijn collegas bij Bijlescontact en dan in het bijzonder: Bart en Werner. Zonder jullie begrip en steun had Bijlescontact mogelijk nooit bestaan of sterker: nooit zo'n mooie organisatie geweest als nu. Dankzij jullie heb ik tijdens mijn studietijd vooruit kunnen kijken op het runnen van een ontzettend mooi bedrijf. Tot slot wil ik - wellicht wel het meest - bedanken: mijn ouders. Toen ik als 12-jarige op het VMBO begon, hebben jullie continu geloofd wat ik zelf al wist: er zit meer in dan men nu denkt. Aan schooladviezen als ‘een stapje hoger lukt niet’ hadden jullie geen boodschap. Ik heb alle mogelijkheden van jullie aangeboden gekregen die nodig zijn om het school/studietraject zoals de mijne, te doorlopen. Door de drukte werd het er thuis wellicht niet altijd even gezellig op, maar weet dat jullie een ontzettend groot aandeel hebben gehad in waar ik de afgelopen jaren mee bezig ben geweest.
8 Summary

8.1 Samenvatting

Borstkankeronderzoek is ontzettend belangrijk. Het onderzoek begint bij het (preventief) opsporen van deze vorm van kanker. Het radiologisch in kaart brengen van de borst is van fundamenteel belang bij eventueel vervolgonderzoek. Een van de vooruitgangen binnen het radiologische veld van borstkanker (mammografie) is het gebruik van digitale detectoren. Borstkanker manifesteert zich als een groeiende hoeveelheid (kwaadaardig) weefsel, dat door middel van bloedtoevoer groter kan worden. Het lichaam maakt in het geval van borstkanker een adernetwerk naar de tumor aan. Omdat het om flinterdunne haarvaten gaat, zijn deze vaak lastig zichtbaar op een mammogram. Door middel van zogenaamde contrastmiddelen, waaronder jodium, kunnen deze haarvaten alsnog zichtbaar worden gemaakt. Er zijn echter een aantal bijwerkingen bij het gebruik van deze contrastmiddelen. Het gebruik ervan wordt dan ook zelden overwogen bij preventieve onderzoeken. Het doel van dit onderzoek is erop gericht om uit te zoeken of het gebruik van energie-gevoelige detectoren mogelijkheden biedt om met de spectrale informatie die X-rays met zich meedragen de benodigde hoeveelheid jodium te reduceren. Door middel van het testen van verschillende fit-algoritmes op verkregen data van deze energie-gevoelige detectoren is gebleken dat het betreffende onderzoeksveld gebruikt kan worden om verder te onderzoeken of de hoeveelheden jodium verder omlaag kunnen ten opzichte van reeds behaalde medische detectielimieten. Dit is onderzocht aan de hand van het modelleren van X-ray fysica van de X-ray buis, het fantoom en de gevoelige laag van de detector. Daarnaast is er gebruik gemaakt van spectrale K-edge subtraction methodieken. Ervan uitgaande dat een zogenaamde CNR (contrast over ruis) van 5 nodig is (6) wordt er bij een dosis van 2 mGy binnen een interessegebied van 19.6 mm² een limiet van 2.18 milligram jodium per milliliter behaald. Dit is in vergelijking met de medische limiet, 5.75 milligram jodium per milliliter door Baldelli et al. (3), reeds een optimalisatie van 62.1%. Verder onderzoek naar onder andere het gebruik van verschillende sensoren binnen het detectiesysteem moeten uitwijzen of verdere optimalisaties mogelijk zijn.
Figures

1. Illustrative summary of x-ray interactions (8) .............................................. 3
2. Schematic drawing of a three-component sample that is illuminated by X-ray photons with different energies of E
   . Equation describes the green arrow at every position on the z-axis. .................. 4
3. Schematic drawing of a sample that can be described by equation [6] ............. 5
4. Schematic drawing of an X-ray tube (auro.org) ............................................ 5
5. Two dominant processes in the production of X-rays from an X-ray tube ....... 6
6. Energy distribution of X-ray photons, including bremsstrahlung and characteristic X-rays (13) .... 6
7. Two important parameters X-ray photons and their influence on the outgoing X-ray spectrum ............. 6
8. Schematic view of the X-ray system. System consist of an X-ray tube (grey), mammography sample (orange), X-ray beam (yellow) and detector system (green). Focus to Skin Distance (FSD) and Focus to Detector Distance (FDD) are drawn. The numerical factor of in equation is extracted after an calibration where was set to FDD = 100 cm. ESD inversely squares with the distance ........................................... 7
9. Two simulations of an unfiltered and filtered X-ray spectrum respectively .... 8
10. Thorax X-ray image of the author taken with a scintillation-FPD at the Waterlandziekenhuis in Purmerend. On the right hand side the spine is visible. The pneumothorax is visible on the left hand side, where only - low attenuated - air (black) is located ...................................................... 9
11. An incoming particle creates electron-hole pairs, which are further transferred due to the applied bias voltage. The electrons or holes make contact with the electronic contacts of the readout. The signal subsequently gets amplified, discriminated with a threshold value and counted (or not). This is further elaborated in subsection 3.1. ................................................................. 10
12. Absorption efficiency of different sensitive layer materials/thicknesses as function of photon energy (10) ... 10
13. The hybrid pixel detector consisting of two separate layers connected via bump-bonding (Nikhef/CERN) ................................................................. 10
14. Schematic drawing of two different materials and their attenuation coefficients ...................................................... 12
15. In K-edge subtraction imaging (KES), two simultaneous CT images are acquired using two x-ray beams at two different energies above and below the K-edge of Xe. Absolute quantity of the contrast agent is determined directly on any given point of a lung CT image after subtracting these two images on a logarithmic scale (26). CT imaging is shortly discusses in subsection 2.2.3 ........................................... 12
16. KES algorithm methodology visualised. Two materials A and B and a K-edge in the absorption of material A. Setting four energy-discriminators and after the K-edge (binning of and ) that contain information before and after the K-edge. In the algorithm both attenuation coefficients of A and B are filled in for the average bin-energy (e.g. ). The energy bins contain for the detected spectra ........................................... 13
17. Spectral KES algorithm methodology visualised. Two components C and M and a K-edge in the attenuation of C. Having n energy-discriminators that result in spectral information before and after the K-edge. The energy bins contain for the detected spectra. In green the lines that correspond to attenuation of material(s) M, in red the lines that correspond to attenuation of material C ........................................... 15
18. Temporal contrast-enhanced mammography images. (a) shows a craniocaudal digitised screen-film mammogram obtained in a patient with infiltrating ductal carcinoma, which is the most common type of breast cancer. (b) shows a craniocaudal contrast-enhanced digital subtraction image obtained 1 minute after the start of contrast medium injection and shows a small nodule with rim enhancement of the entire mass (arrow). (c) shows subtraction image obtained 10 minutes after start of contrast medium injection and shows washout of contrast medium. Note that only a single breast can be obtained in one view and that in this specific case, the breast needed to be compressed for 10 minutes (30). ........................................... 16
19. 55-year-old woman with normal breast tissue. CEDM imaging: low-energy image (a), high-energy image (b), and subtracted image (c), by Daniaux et al. (31) ........................................... 16
20. Coloured CT slice of the spectral phantom obtained using an in-house material decomposition algorithm. From the top going clockwise is air, water, canola oil, calcium chloride, an iodine complex, a gadolinium complex and a contrast agent containing gold nano-particles. The gadolinium complex was not included in the decomposition due to a construction error in the spectral phantom, by Walsh et al. (33) This image is taken with a Medipix3.1 device ........................................... 17
21. The average and standard deviation of critical parameters ........................................... 19
22. Transformation of tube spectrum to detector spectrum with a Si sensitive layer of 300 µm thickness ........................................... 20
23. (a) Modelling of open beam spectrum (blue) and 1 cm of water (green). (b) Modelling of open beam spectrum (blue), 1 cm of water (green) and 0.001 cm of iodine (red). The increased absorption for energies above the K-edge binding energy is clearly visible at 33 keV.
On the left hand side, the picture of the Medipix3RX chip is shown. On the right hand side, the chip connection to a 300 \( \mu \text{m} \) thick Si sensor is shown. The digital part receives the output of the discriminators and decides in the DDL (Double Disc Logic), if the counter will be incremented. The dependence is modelled by equation 26a. (42). Visualisation of the spectral resolution when taking into account both the energy resolution and charge sharing of the medipix device. Time over threshold dependence on particle energy. The dependence is modelled by equation 26a. (42). Process of two operation modes (ToA and ToT) in addition to traditional event counting mode medipix devices. Logarithmic subtraction of red line with blue line in (a) result in (b). Pixel response gathered from fluorescence experiment including a fit of equation 26a. The average and standard deviation of critical parameters. Fluorescence measurement for niobium. This measurement is used to test the calibration methodology and is not used in the final calibration. For the final calibration other elements are chosen based on their fluorescence energies. Resulting spectra for most concentrated syringe. The increase of attenuation is visibly around 33 keV (due to Iodine K-edge), but there is also a decrease of attenuation in the lower energy region. This is caused by the Compton effect. An explanation is provided in the next paragraph. Attenuation of both photoelectric (blue) and Compton effect (green). The sum of both effects is provided in red. Plots to describe the resulting spectrum of the Compton effect. The average and standard deviation of critical parameters. Visualisation of syringes including water and iodine concentration. Error analysis is based on errors that were introduced in the fitting analysis. Energy bin selection for the KES methodology for most concentrated syringe. Thickness plots for both water and iodine in the syringes using KES algorithm methodology. Thickness profile plots for both water and iodine in the syringes using spectral KES algorithm methodology. Thickness profile plots for both water and iodine in the syringes using spectral KES algorithm methodology. Thickness profile plots for both water and iodine in the syringes using spectral KES algorithm methodology. Plot that summarises the iodine concentration determination for three methodologies: fitting, KES and spectral KES. T4 corresponds to the syringe filled with the most concentrated iodine solution. Iodine concentration as function of CNR for both KES (blue) and spectral KES (orange) methodologies. The Rosen limit (CNR = 5) is visualised in red. Mammography sample with four corridors that are filled with Ultravist solution. Sample is divided in four sections: section A (PMMA thickness of 58.5 mm), section B (PMMA thickness of 43.6 mm), section C (PMMA thickness of 27.0 mm) and section OB. The OB section is just a hole in the sample, which is to provide an open beam reference exposure. Thickness profile plots for both water and iodine in the syringes using spectral KES algorithm methodology. Thickness profile plots for both water and iodine in the syringes using spectral KES algorithm methodology. Thickness profile plots for both water and iodine in the syringes using spectral KES algorithm methodology. Thickness profile plots for both water and iodine in the syringes using spectral KES algorithm methodology.
Thickness profile plots for both PMMA and iodine in the syringes using KES algorithm methodology.

Thickness plots for both PMMA and iodine in the sample using KES algorithm methodology.

Thickness profile plots for both PMMA and iodine in the corridors using the spectral KES algorithm methodology.

Plot that summarises the iodine concentration determination for three methodologies: fitting, KES and spectral KES. C1 corresponds to the corridor filled with the most concentrated iodine solution. In the fitting procedure all iodine containing pixels are taken into account (in all sections), while for (spectral) KES only results for section C are included. The error bars on the true amount of iodine are caused by the evaporation of water in the corridor during the measurement, see table 10.

Iodine concentration as function of CNR for KES methodology in different sections. Section C in blue, section B in orange and section A in green. The Rose limit (CNR = 5) is visualised in red.

Iodine concentration as function of CNR for spectral KES methodology in different sections. Section C in blue, section B in orange and section A in green. The Rose limit (CNR = 5) is visualised in red.

Visualisation of model that provides photoelectric absorption as function of energy for three different sensitive layers: 300µm GaAs (blue), 200µm Si (green) and 300µm Si (purple).
References


