Evaluation of Methods for Obtaining an Image Derived Input Function from Dynamic PET-images

Utvärdering av metoder för att erhålla en bildbaserad input-funktion från dynamiska PET-bilder

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Dynamic PET is a technique to follow the uptake kinetics of radioactive labelled molecules in the human body. The kinetic behaviour may be analysed to acquire parameters, such as perfusion of blood to tissue, with the knowledge of the blood activity time curve (also called input function). This is usually measured by continuous sampling by letting the blood flow through a detector but this is both burdensome and not without risk to the patient [5]. Instead, an alternative method would be to determine the input function from the PET-images and thus get an image derived input function (IDIF).

In this master thesis evaluation of analytical models, tested on both experimental sampled data of a phantom and on data from actual patients, were used to determine the IDIF from small blood vessels. A phantom was built from plastic tubes and plexiglass to test and evaluate different methods.

In order to get a correct IDIF one needs to correct for partial volume effect (PVE) which in small volumes of interest (VOI) gives apparent lower activity than reality. The correction can be done in a few different ways but this paper focuses on multi-target correction (MTC) which uses two or more VOIs to obtain the true activity value [2]. The method was evaluated using data from phantom measurements where the activity was known and could be used as a reference. The phantom was constructed using ten tubes of different dimensions, a plexiglass holder and a plastic box.

The result from the PVE correction turned out to be highly dependent on accurately knowing the diameter. However, when the diameter of the VOI matched the diameter of the tube the error of activity was, on average, less than 6.1 % (less than 4.9 % for tubes larger than 6 mm in diameter) when evaluating the measured phantom data without added background. Also, varying backgrounds were added creating different contrasts between the tubes and background. When adding background the noise in the image is increased and the results from the PVCs, when using the most accurate diameter, were less accurate with a total average activity error of 17.9 % (11.1 % for diameters larger than 6 mm and 22.4 % for diameters smaller than 6 mm).

As a conclusion, the size of the blood vessel needs to be accurately known in order for the PVC to give the most accurate result. Also using vessels larger than 6 mm is beneficial.
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<th>Description</th>
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<td>CT</td>
<td>Computed Tomography</td>
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<tr>
<td>CBF</td>
<td>Cerebral Blood Flow</td>
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<td>FWHM</td>
<td>Full Width at Half Maximum</td>
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<td>IDIF</td>
<td>Image Derived Input Function</td>
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<td>IF</td>
<td>Input Function</td>
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<td>LOR</td>
<td>Line of Response</td>
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<td>MR</td>
<td>Magnetic Resonance (short for MRI)</td>
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<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
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<tr>
<td>H$_2^{15}$O</td>
<td>$^{15}$O-labelled water</td>
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<td>PET</td>
<td>Positron Emission Tomography</td>
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<td>RC</td>
<td>Recovery Coefficient</td>
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<td>Partial Volume Correction</td>
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<td>PSF</td>
<td>Point Spread Function</td>
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<td>PTAC</td>
<td>Plasma Time Activity Curve</td>
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<td>TAC</td>
<td>Time Activity Curve</td>
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<td>TTAC</td>
<td>Tissue Time Activity Curve</td>
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<td>VOI</td>
<td>Volume of Interest</td>
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\(\beta^+\)  Positron

\(\gamma\)  Photon

\(\lambda\)  Radioactive decay constant

\(\dot{A}\)  Measured activity (kBq)

\(A\)  Known activity (kBq)

\(C_p\)  Concentration of activity in plasma (kBq·ml\(^{-1}\))

\(C_t\)  Concentration of activity in tissue (kBq·ml\(^{-1}\))

\(C_x\)  Concentration of activity in tissue or process (kBq·ml\(^{-1}\))

\(e^-\)  Electron

\(k\)  Fractional transfer rate (kBq·s\(^{-1}\))

\(K_i\)  Influx rate constant (kBq·s\(^{-1}\))

\(m_{tb}\)  Spill over coefficient from tissue to blood vessel

\(rc\)  Recovery coefficient

\(F\)  Blood flow per unit mass of tissue (ml·min\(^{-1}\)·100 ml\(^{-1}\) or min\(^{-1}\))

\(V_d\)  Volume of distribution of water
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1 Introduction

1.1 Background

Using Positron Emission Tomography (PET) as an imaging technique for diagnosis of different diseases has become more common the last few years. In order to calculate certain parameters, such as perfusion, with dynamic PET-images in water studies you need to know the activity in the blood plasma, the so called input function. This is usually measured by letting the blood flow through a detector by continuous arterial sampling. However, this is both burdensome and not without risk to the patient [5]. An alternative method would be to measure the input function from the PET-images and hence get an image derived input function (IDIF).

This thesis will focus on determining and evaluate the IDIF from PET-images acquired during water perfusion studies of the brain with the goal to implement the method clinically at University Hospital of Umeå.

1.2 Purpose and Goal

The purpose of this thesis is to calculate and evaluate the input function from dynamic PET-images. This would provide a more safe and easier procedure during examination with water perfusion.

The goal of this work is to calculate and evaluate published algorithms used to obtain the image derived input function from dynamic PET-images for water perfusion studies.
2 Theory

2.1 Positron Emission Tomography (PET)

PET is a medical imaging technique that is considered a functional technique opposite to x-ray or MRI that are structural techniques. This means that in PET-scans you visualize physiological or biochemical processes, instead of anatomic structures. This is done by measuring and localizing labelled molecules with a biological function. The PET-scanner is usually combined with a CT or MRI to get the anatomical structure in the same scanning section. [4]

![PET/MR scanner at University Hospital of Umeå.](http://www.cancerforskningsfond-umea.lions.se/)

**Figure 1:** A PET/MR scanner at University Hospital of Umeå. (Source: Lions Cancerforskningsfond, http://www.cancerforskningsfond-umea.lions.se/)

In PET a so called tracer is injected into the patient. The tracer consists of a substance that has the same properties of the biochemical process of interest and labelled with a radioactive positron emitting isotope. The most common positron emitting isotopes are $^{18}$F, $^{11}$C and $^{15}$O. The isotopes are produced on demand in a cyclotron because the isotopes have short half life. In this thesis we will focus on water perfusion using $^{15}$O-labelled water ($\text{H}_2^{15}\text{O}$). [4] The radionuclide $^{15}$O-water is used when examining perfusion of water in the brain. The nuclide $^{15}$O has a half-life of 2.07 minutes and is incorporated into the water molecule through a chemical process.
A PET-scanner consists of thousands of detectors forming a ring that detects two opposing 511 keV photons from positron annihilation (see figure 2). If two photons are detected on opposite sides of the body within a very short time it is assumed that somewhere along the line between the detectors an annihilation event has taken place. The line is called a line of response (LOR) and by calculating the crossing of all the LORs the location of the radiation source can be determined [8]. By determining the locations of radiation sources a 3D image of the distribution in the patient can be achieved (see figure 3). In some cases a dynamic sequence of PET images are requested in which the images are acquired at different times after injection of tracer to the patient. An example of this can be seen in figure 4.
The two photons that are detected within a short time (typically 5-15 ns) and within an energy window (typically 350-650 keV) are called coincidences. Besides the true coincidence a number of other coincidences will occur during a PET scan. In figure 5 the different cases are depicted. Scatter coincidence (B) occurs when one of the photons from the annihilation is deflected due to scattering within the body of the patient. A random coincidence (C) occurs when two annihilation photons, or two single photons, from two different decay event is detected within the time window. Lastly, one or both of the annihilation photons is attenuated within the body and will hence not be considered as a coincidence (D). [8]
Figure 5: Graphical view over the different coincidences that will occur during a PET scan. The cases are described in the section above.
2.2 Compartmental Modelling

The compartment model is a way of describing the dynamic process that the tracer follows in the body. Each compartment can be describing either a physical or a chemical process.

![Diagram of compartment model](image)

**Figure 6:** An example of a compartment model where $C_p(t)$ is the amount of tracer in the plasma, $C_1(t)$ represent the amount of activity in different tissues or processes and $k_x$ are the fractional transfer rates describing how the tracer is transported.

An example is shown in figure 6 where $C_p(t)$ is the amount of tracer in the plasma, from where the tracer usually is transported, $C_1(t)$ represent different tissues or processes which to and from the tracer is flowing according to fractional transfer rates $k_x$. The fractional transfer rates can be approximated to be linear if the system is in steady state and is time invariant over the study time [4].

![Diagram of compartment model](image)

**Figure 7:** An example of a compartment model describing water perfusion in the brain where $F$ is the blood flow per unit mass of tissue and $V_d$ is the volume of distribution.

In our case, with water perfusion in the brain, the compartment model can be described according to figure 7. In this case $C_p(t)$ is the amount of $^{15}$O-water in the arterial plasma, $C_1(t)$ is the tracer concentration in the tissue of the brain, and $K_1$ and $k_2$ are first-order kinetic rate constants. The blood flow can thus be quantified by assuming that $K_1 = F$ and $k_2 = F/V_d$, where $F$ is the blood flow per unit mass of tissue and $V_d$ is the volume of distribution.

![Diagram of compartment model](image)

**Figure 8:** An example of a compartment model describing water perfusion in the brain.
The compartments can be described by two curves; a plasma time activity curve (PTAC) and a tissue time activity curve (TTAC) (see figure 8). The PTAC is used as the input function (IF) in this compartment model. [4]

![Time Activity Curves](image)

**Figure 9:** Example of TACs during perfusion from blood vessel to tissue. The blood vessel curve is the input function.

Figure 9 shows typical TACs (time activity curves) for blood vessel and tissue during perfusion examination of a patient. The blood vessel curve is the so called input function when determining the perfusion parameter.

### 2.3 Aorta and Carotid Vessels

The carotid vessels are important components in perfusion studies of the brain. The carotid arteries are the arteries that supply oxygenated blood to the head and neck. Figure 10 shows a schematic image of the carotid artery and its main branches. The curve right before the brain, marked with an arrow, is where the in the dynamic PET images the IDIF will be determined and evaluated.

The carotid arteries go on either side of the neck and up to the head to supply the head and neck with oxygenated blood. They are typically 3-5 mm in diameter in the upper parts of the vessel that are closest to the brain.

The aorta is the main artery in the human body and works as a reference in this thesis when evaluating methods on the carotids. It origins from the left ventricle of the heart and goes down to the abdomen where it splits into smaller arteries. The size of the aorta varies from person to person and also depending on where in the body it is measured. Typically it is 20-30 mm in diameter with a 1-3 mm wall thickness.
Figure 11 shows an example of PET images of the carotids and aorta respectively.

**Figure 10:** The common carotid artery and its main branches. The arrow shows where evaluations are made in this paper.

**Figure 11:** PET image of the carotid arteries (left) and of the aorta (right).
2.4 Partial Volume Effect (PVE)

The partial volume effect (PVE) can in general be defined as the loss in apparent activity in the image that occurs because of the limited resolution in the imaging system. In emission tomography the spatial resolution is mainly affected by the range of the positrons (i.e. how far the positrons propagates before annihilation takes place) and the angle between the detected photons not being exactly 180 degrees every time (see figure 2).

PVE corresponds to so called spill-in and spill-out effects which means that detected coincidences, called counts, are spilling over between different image regions due to the limited spatial resolution of the PET imaging system. The spatial resolution can be characterized by the point-spread function (PSF) which corresponds to the image measured from a point source. In theory, the cross section of the PSF signal would be a delta function, but because low spatial resolution the function is "smoothed out" (see figure 12). Spill-in refers to when counts surrounding the VOI is spilling over to the VOI and spill-out refers to counts from the VOI spilling over to the surrounding. Thus PVE imply that a voxel in the image can contain a mixed signal from more than one tissue type [5]. In PET scanners the resolution is usually corresponding to an FWHM (full width at half maximum, see example in figure 12) of 3-4 mm. The smaller vessels in the head, the carotids, are usually 3-5 mm in diameter which means that there are large PVEs that are needed to be corrected for. An example of TACs during a brain examination is shown in figure 13, where the large difference in activity can be seen between the carotid and the aorta because PVE is larger in the carotids.

![Point-spread function (PSF)](image)

Figure 12: Point-spread function (PSF).
Figure 13: Example of measured TACs during perfusion from blood vessel to tissue. The concentration in the two vessels are the same, but because of PVE, they appear different.

Partial Volume Correction Techniques

Partial volume correction (PVC) can be performed pixelwise or on VOIs in the image [2]. The interfaces between blood and tissue need to be accurately known and the image resolution in x-, y-, and z-direction has to be known in order to implement the methods. For all PVC described in this section a partial volume effect (PVE) map needs to be created. The PVE-map describes how a homogeneous activity would be imaged if it was measured with the known image resolution, i.e. it is a binary map convolved with the PSF, where the binary map means that the voxels within the VOI of activity is set to one and that the background voxels are set to zero. The PVE-map is then used to determine the recovery coefficient (RC). The figure below shows example of PVE-maps used on patient data.
The RC is determined by averaging the pixels of the PVE-map inside each VOI. An extended description of RCs can be found in section 2.5. Using the RCs, the method can be extended to calculate the crosstalk between all VOIs which is called the geometric-transfer matrix (GTM). The GTM is related to the measured VOI values through a matrix equation which can be solved for the true VOI values. [2]

Another way of restoring the image is using a voxel based PVC method described by Erlandsson et al in their review article [3]. In this method, called Multi-target correction (MTC), a binary map of the region we want to examine, e.g. the artery, is convolved with the system PSF to generate an image of RCs for each voxel. Then PVC can be performed by subtract spill-in from all regions and dividing the original PET image with the obtained PVE-map. One can also perform this method with several regions and alternate between which is set to one and evaluate the RCs from that (also described by Erlandsson et al. [3]).

2.5 Recovery Coefficients Calculation

One of the most simple ways to correct for PVE is to use recovery coefficients, as described in the previous section, and use it to add missing signal to the image. There are a few ways to describe the RCs one being by the following formula:

$$RC = \frac{\tilde{A} - \tilde{A}_b}{A - A_b}$$ (1)

where $\tilde{A}$ and $\tilde{A}_b$ are the measured activities in the geometry and the background respectively, and $A$ and $A_b$ are the known activities in the geometry and background respectively. [7]

An other way to describe the RC is with the assumption that the measurement of the total radioactivity in the blood plasma, $c_p$, in the carotid is a linear combination of the true radioactivity from the blood vessel and the radioactivity from the surrounding tissues. This can be written as

$$c_p(t) = rc \cdot c_p^{true}(t) + m_{tb} \cdot c_j(t)$$ (2)

where $c_p^{true}$ is the true, spill-over free, radioactivity in the blood, $c_j$ is the radioactivity in the surrounding tissue, $rc$ is the recovery coefficient and $m_{tb}$ is the spill-over coefficient from tissue to the blood vessel.
In this work the recovery coefficient is determined by convolving a binary map with the system PSF to generate a PVE-map and averaging the pixels inside the VOI [2].

2.6 Image-Derived Input Function

In order to calculate certain parameters, such as perfusion, with dynamic PET-images in water studies you need to know the activity in the blood plasma, the so called input function (IF). In figure 8 the PTAC curve represents the IF. Usually this is done by arterial blood samples. However, this is both burdensome and not without risk to the patient [5]. An alternative method would be to measure the input function from the PET-images and hence get an image derived input function (IDIF).

3 Method

3.1 PET/CT Camera

In this project the Discovery PET/CT 690 from GE Healthcare (WI, USA) will be used. It combines the PET camera with a CT scanning system which makes it possible to do both PET and CT images during the same examination.

Figure 15: Discovery PET/CT 690 from GE Healthcare used at the Nuclear Medicine Department at the University Hospital of Umeå.
3.2 MATLAB and imlook4d

As a part of this work, calculations and evaluations were made with the software MATLAB, version R2015a, from MathWorks [6]. MATLAB is a matrix based programming language optimized for solving engineering and scientific problems. It can be combined with add-on toolboxes to get a wide range of applications.

Dicom Port [1] provides a free research tool called imlook4d that are compatible with MATLAB. With imlook4d medical images can be analysed in 4D by importing DICOM files. It comes with several pre-made scripts and it is possible to create custom scripts as well.

3.3 Distinguish the Carotid Arteries

There are a few ways to distinguish the carotid arteries using imaging modalities. In this thesis the most intuitive would be to use the dynamic PET images to find them. Other ways would be to use computer tomography (CT) or magnetic resonance imaging (MRI), with or without contrast. The most intuitive method would be to use CT since it is the modality most commonly combined with PET.

When using dynamic PET to distinguish the carotids the early time frames were utilized.

3.4 Evaluating Threshold for Drawing VOIs in PET images

When performing PVE correction, it is necessary to accurately know the VOI. Therefore, a method of determine and drawing the VOI from dynamic PET images has been tested and evaluated in this section. To do so, a phantom was needed to ensure that the diameters were known and could be used as references.

Phantom

To generate data for analysis, a phantom was constructed and scanned in the PET-scanner. The phantom consists of ten tubes of different dimensions to simulate blood vessels of different sizes. The tubes were mounted in a special constructed plexiglass holder and positioned in a water filled plastic box.
**Figure 16:** A simple drawing of the plexiglass holder with holes for the tubes (left) and the whole phantom (right).

**Figure 17:** The plexiglass holder with tubes filled $^{18}$F-FDG and water and sealed with plastic from plastic gloves and elastic bands.

The phantom consists of a plastic box, with the dimensions 34 cm x 25 cm x 16 cm, a plexiglass holder and tubes of different dimensions (see the drawing in figure 16 and the picture in figure 17). The plexiglass holder is removable from the box in order to fill the tubes with activity. Tube mounting holes were drilled in the plexiglass glass with a depth of about 2 cm and about 2 cm apart. The tubes were mounted to the plexiglass holes and sealed with silicone. The tubes were filled with equal activity concentration from the same solution and sealed with plastic material from plastic gloves and elastic bands.
Measuring Tube Inner Diameter

The sizes of the tubes in the phantom were measured by weighing the empty and water filled tubes. The difference in grams could then correspond to the volume of the tube, since the density of water is 1 g/cm$^3$, i.e. 1 g difference in water corresponds to 1 cm$^3$ inner volume of the tube. By knowing the length $l$ of the tube the diameter $d$ could be determined by the following formula

$$d = 2 \left( \frac{V}{l \pi} \right)^{1/2}$$

where $V$ is the volume of the tube.

The resulting diameters of the tubes can be seen in table 1. The tubes were numbered from 1 to 10 according to figure 16.

<table>
<thead>
<tr>
<th>Tube #</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
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<tr>
<td>Inner diameter (mm)</td>
<td>18.8</td>
<td>13.0</td>
<td>9.1</td>
<td>5.3</td>
<td>7.8</td>
<td>5.2</td>
<td>4.4</td>
<td>4.4</td>
<td>3.3</td>
<td>3.2</td>
</tr>
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Experimental Set-Up and Execution

The mounted tubes were filled with 42.9 kBq/g of $^{18}$F-FDG at time 15:31, sealed and then placed in the box. The box was then filled with water to resemble the surrounding tissue in a patient. The phantom was placed inside the PET/CT camera so that the tubes were centred approximately at the isocenter. The scan was divided into time frames of 1, 2, 4, 8 and 16 minutes, for a total of 31 minutes.

A second scan was performed on the box, without the holder and the tubes, to get a background measurement. Water was added to reach the same level as the previous measurement. The background was filled with approximately 9.7 MBq/l $^{18}$F-FDG at 17:14 and scanned during a considerably long time, letting the activity go down to almost zero.

Since the tube walls do not contain any activity there will be a signal drop at where they are located, as described in figure 18. This is something that should be avoided which can be done by measuring the background separately and adding the image to the image of only the tubes. By adding the background measurement to the phantom measurement afterwards you get different contrast between the tubes and the background and you remove the effect from not having any activity in the tube walls.
Figure 18: Example of how the walls affect the signal when background is added and how it can be avoided. Graph A shows an ideal signal from the cross section of a tube with an inner diameter of 2 units and where the wall (with a thickness of 1 unit) would be. If a background signal would be added by adding activity to the water surrounding the tubes it would look like graph B. Since there in this case is no activity where the wall is located, there would be a signal drop. If instead the background is added by measuring the tubes and the background individually and the images is added together afterwards, this would be avoided and we get a signal looking like graph C.

The background was measured using $^{18}$F as isotope in the settings while measuring the whole phantom the isotope was set as $^{15}$O. Since these isotopes have significantly different half lives, this means that for the same measurement time, the activity differ between the tubes and the background. When taking the ratio between the intensity of the tubes and the intensity of the background ($I_{\text{tube}}/I_{\text{background}}$, where $I$ represents the intensity) there will be different contrast at the different time frames since the measured time was different for each time frame. The tube will have approximately the same intensity throughout all time
intervals, while the background intensity will increase for longer measurement time, i.e. at the later time frames.

3.5 Patient Data

In order to evaluate the methods of determining and evaluating the IDIF patient data were used. Two patients had gone through a PET brain examination using O\textsuperscript{15}-water and also had images taken of the thorax so that the aorta could be used as a reference.

4 Results

4.1 Size Determination from PET Images

The tube diameters of the phantom were measured in the PET images and the result can be seen in figure 19. In this case the VOI used to measure the size were determined in one frame by using 40 %, 50 %, 60 % and 70 % threshold levels, relative the maximum value. Number of pixels in x and y direction inside the VOI were converted into mm using the known voxel size and imlook4d [1] for MATLAB. The difference between the size measured in the PET and the actual size were calculated and the results are presented in figure 19.

In figure 19 one can see that for larger tubes (5 mm - 19 mm) a threshold of 40 % or 50 % of maximum activity was preferred and for smaller tubes (3 mm - 4 mm) a threshold of 60 % or 70 % was more accurate. For all tube sizes the errors ranged from 1.54 % to 24.24 % when using the best suited threshold, and the median error was about 4 %.

When using a threshold uptake value, instead of percentage, the lowest error was achieved for varying values between 50 000 and 200 000. For diameters between 3.3 mm and 13.0 mm a threshold of 100 000 was most suitable. In this case, when using the most suitable threshold for each size, the error ranged from 0.77 % to 30.30 % where the median error was about 6 %.

The errors for each tube and threshold can be seen in table 5 and table 6 in appendix A.2.
Figure 19: Top figure: The result of determine the sizes of the tubes in the phantom. When determine the size from the PET images a threshold was used to create the VOI. The threshold was set to 40%, 50%, 60% and 70% of the maximum value in the selected VOI. Bottom figure: The error for each tube size measured in the PET image using percentage as a threshold.
Figure 20: Top figure: The result of determining the sizes of the tubes in the phantom. When determining the size from the PET images, a threshold was used to create the VOI. The threshold was set to an uptake value of 50,000, 100,000, 150,000, and 200,000. Bottom figure: The error of each tube size measured in the PET image using pixel value as a threshold.
4.2 Partial Volume Correction (PVC)

As a first approach the results from the phantom was used without added background to examine size determination and PVE corrections.

PVC and activity estimation from the phantom

Using VOIs of correct diameter and performing PVC (according to section 2.4) the activities in each tube were determined and compared to the known activity of the largest tube which should be corresponding to the true activity. The activity in each tube was measured by taking the mean of the pixel values within within the VOI. The result can be seen in figure 21 where the blue circles represent the activity after correcting for PVE and the red diamonds are without any correction. From the graph one can see that the PVE correction gave, as expected, less error in activity compared to the true activity. The difference is even more apparent for smaller diameters.

![Graph showing difference in activity before and after PVC correction.](image)

**Figure 21:** The difference in percentage between known activity and activity measured in each tube. The red diamonds are measured before PVC and the blue circles are measured after PVC.

PVC and Size

The next thing to consider was how much the size of the VOI affected the result when correcting for PVE. This was examined by using the phantom images and creating VOIs
of three different dimensions, one matching the actual diameter of the tube, one with 10% larger diameter and one with 10% smaller diameter, for each of the tubes. The difference between the actual activity and the measured concentration after PVC was plotted against tube diameter and is shown in figure 22. As can be seen in the figure the activity measured in each tube is highly dependent on tube size. For the smallest tubes, with a diameter smaller than 6 mm, the VOI size that gave the best result varied, although the VOIs matching the tube diameters were still within reasonable values. A reason for this is explained in the discussion on page 26.

![Graph showing difference in actual activity and measured activity after PVC](Figure 22: PVC performed with three different VOI diameters for each tube: one matching the actual diameter of the tube, one with 10% larger diameter and one with 10% smaller diameter.)

### 4.3 Contrast Evaluation

In order to get results applicable in real circumstances the contrast between the tubes and the background in the phantom should match the contrast between the carotid arteries and the background in patient data. To take this into account the contrast in patient data was determined and applied on the phantom evaluation.

**Determined Values from Patient Data**

By measuring the activities in four patient images with different approaches values for the most common contrasts between vessel and surrounding tissues are obtained. The mean
contrast value was 11.58 and the contrast varied between 5.64 and 25.50. From this results the proceeding measurements on the phantom are performed with contrast values between approximately 5 and 25 to get as close to the reality as possible.

**Evaluation of Measured Data**

The background was measured using $^{18}$F as isotope in the settings while measuring the whole phantom the isotope was set as $^{15}$O. Since these isotopes have significantly different half lives, this means that for the same measurement time, the activity differ between the tubes and the background. Since each time frame had different acquisition times, they could be used to acquire ratios between background and tubes. However, by doing this, the noise is not reduced. The contrast at the respectively time frame were 2.39, 2.57, 4.05, 9.08, 46.91 and 911.88 (see figure 23), where the last two are not represented in the figure, nor taken into consideration because they are not relevant when looking at real cases.

![Contrast ratio between background and tubes at different time frames](image)

**Figure 23:** Contrast between tubes and background in the phantom at different time frames. Tube intensity was measured in the largest tube.

The activity in each tube were determined using PVC in each time frame resulting in slightly varying results which are presented in figure 24. As can be seen in the bottom figure and in table 2, the error did not differ much between different contrast values. The median error of measured intensity varied between 4.08 % and 6.62 % for the contrast values, as can be seen in table 2.
Table 2: Median error for each contrast value.

<table>
<thead>
<tr>
<th>Contrast value</th>
<th>Median error (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.37</td>
<td>4.08</td>
</tr>
<tr>
<td>2.57</td>
<td>6.62</td>
</tr>
<tr>
<td>4.05</td>
<td>5.66</td>
</tr>
<tr>
<td>9.08</td>
<td>4.61</td>
</tr>
</tbody>
</table>

Figure 24: Top graph: Activity intensities for each tube and contrast value after performing PVC. Bottom graph: Error in activity intensity for each tube and contrast value.
4.4 Evaluating Methods on Patient Data

The method of performing PVC to get a correct input function was tested on patient data. The TAC of the carotid arteries, representing the IF, for both patients was plotted with and without PVC (see figures 25 and 26). The carotids were measured using a VOI with 5 mm in diameter in the top of the arteries (shown with an arrow in figure 10). The aorta was used as a reference for both patients. The maximum value and integral values for the input functions for both patients are listed in table 3. As can be seen in both figures and the table, the input function is improved after performing PVC.

Figure 25: TAC of carotid arteries in patient 1 using the aorta as a reference.
Figure 26: TAC of carotid arteries in patient 2 using the aorta as a reference.

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Integral value without PVC</td>
<td>$9.79 \cdot 10^6$</td>
<td>$1.29 \cdot 10^7$</td>
</tr>
<tr>
<td>Integral value with PVC</td>
<td>$1.40 \cdot 10^7$</td>
<td>$1.61 \cdot 10^7$</td>
</tr>
<tr>
<td>Reference integral value</td>
<td>$1.83 \cdot 10^7$</td>
<td>$1.31 \cdot 10^7$</td>
</tr>
<tr>
<td>Maximum value without PVC</td>
<td>$1.26 \cdot 10^5$</td>
<td>$9.71 \cdot 10^4$</td>
</tr>
<tr>
<td>Maximum value with PVC</td>
<td>$2.32 \cdot 10^5$</td>
<td>$1.90 \cdot 10^5$</td>
</tr>
<tr>
<td>Reference maximum value</td>
<td>$2.48 \cdot 10^5$</td>
<td>$2.20 \cdot 10^5$</td>
</tr>
</tbody>
</table>
5 Discussion

5.1 Choice of Method Measuring Tube Diameter

Since the smallest tubes in my phantom were only 3 mm it were difficult to measure the inner diameter accurately using a calliper. Instead, the size was measured for each tube using water as explained in section 3.4. It is easier to get an accurate measurement of the length of the tube and weigh the water using a very sensitive scale. By doing so, the largest uncertainties come from the ruler and the scale. It was easier to weigh the tube before filling it with water, and then weigh it once it was filled, than trying to remove the water from the tube to weigh it without the water. The result of the largest tubes were compared with measurements using a ruler and a calliper and they seemed reasonable. I believe the result are more accurate than if it was to be measured using only a calliper.

5.2 Determine Tube Diameter from PET Images Using Thresholds

As can be seen in figures 19 and 20 (also in tables 5 and 6 in appendix A.2) the threshold method for determining the tube diameter didn’t result in large errors the threshold that gave the most accurate result for each tube varied with tube size in a non predictable way.

For tube diameters larger than 6 mm, a threshold of 40 % of maximum intensity gave the best results. For diameters of 4 mm - 5 mm a threshold of 50 % worked best, while for the smallest tubes, 3 mm in diameter, a threshold of 70 % was preferred.

An uptake value of 100 000 as a threshold produced good results for diameters larger than 3 mm. Although, when implemented on patient data this threshold will not work as well since the uptake depends on the amount of radioactivity that have been injected. Instead, in that case, we would prefer a threshold based on the maximum, or injected, activity.

5.3 Size Dependence

As described in section 4.2 the size of the VOI used when performing PVC is highly size dependent. For diameters smaller than 6 mm it was also noticed that the VOI giving best resulting value varied. One reason for this is the uncertainty in the VOI size that is more significant for smaller sizes and thus the result is more fluctuating. An other reason is the shape of the tubes versus the shape of the VOIs. For the smaller sizes the shape of the VOI is more square than for the larger sizes, while the tubes have a circular cross section (see figure 27).
Figure 27: Drawing showing the difference in shape between the VOI and the cross section of the tube. The VOI have a tendency to become more square for smaller diameters due to the resolution while the tube has a circular cross section. If the VOI is completely square the side of the square equals the diameter of the tube, denoted $d$ in the drawing.

If the VOI is completely square and its side is the same length as the diameter of the tube the following applies:

$$A_{VOI} = d^2$$  \hspace{1cm} (4)

and

$$A_{tube} = \left( \frac{d}{2} \right)^2 \pi$$  \hspace{1cm} (5)

which results in the following relation

$$A_{tube} = \frac{\pi}{4} A_{VOI} \approx 0.7854 \cdot A_{VOI}$$  \hspace{1cm} (6)

where $A_{tube}$ and $A_{VOI}$ is the cross section area of the tube and the VOI respectively. So since the VOI isn’t the same shape, the cross section area is not the same which could lead to more difference in activity even though the diameter is the same of the VOI and the tube.

5.4 Distinguish the Carotid Arteries

There are a few ways the carotids can be distinguished using imaging modalities. The approach where it is easiest to distinguish the carotids would be with MRI with contrast agent. This would be the most accurate image of the carotids and make them easy to see and obtain the correct size of the arteries. Instead, if CT with contrast was to be used the carotids would not be as easy to distinguish as with the MRI but they would still be visible and the measured size would be accurate. However, if no contrast is used, the arteries would not be visible in the image.

In this work the optimal approach would be to use the dynamic PET images. During the first few frames, i.e. shortly after the distribution to the patient, the tracer pass through the carotids and it is possible to distinguish the them as can be seen in figure 11. However, due to the low resolution of the PET scanner it is difficult to obtain the correct size when measured in the image.

5.5 PVC on Phantom Data

The usage of partial volume correction on the phantom data gave good results, keeping the average error at 6.1%. It was expected that the larger tubes would result in more accurate activity since they are not as affected by the partial volume effect as the smaller tubes. This
could be observed when looking at figure 21, where the errors for tubes larger than 6 mm are noticeably smaller than for tubes with diameters smaller than 6 mm.

Since the PVE is more pronounced for smaller diameters, the correction affects these tubes more (reducing the error more), which is also visible in figure 21. For the tubes smaller than 6 mm, the error went from 52.2 % to 6.9 % after performing the correction. Since the carotids are approximately 5 mm in diameter it is absolutely necessary to perform PVE corrections, as we expected.

5.6 Contrast Evaluation when Adding Background

The contrast between blood vessel and background was evaluated on patient data in order to get an insight of what the contrast was in real cases. The result varied a lot, between 5.64 and 25.50, and the reason for the large variations could be the way it was measured. Different approaches were used, both with and without PVC. Another reason is that the injected amount of radioactivity varies between patients, which in turn leads to variations in contrast when measured.

When adding the background to phantom image, the difference in contrast did not affect the measured intensity. This was expected since, when measuring the activity, the background is again subtracted for the image.

5.7 PVC on Patient Data

The maximum activity were significantly improved for both patients after performing partial volume correction. For patient 1 the difference from the reference activity was lowered from 49.9 % to 6.5 %, and for patient 2 it was lowered from 55.9 % to 13.6 %. This shows that the chosen PVC method generates good results.

When measuring the input function from the carotids, a standardized VOI of 5 mm in diameter was used. The result was still good, although the carotid sizes could vary between individual patients and matching the VOI to the actual carotid size would generate even better results.

Looking at graph 25 and 26 a difference in the ”tail”, i.e. at the far right on the x-axis, between the reference and the measured input function. This difference are about 42 % and 169 % for the two patients respectively. One reason for this outcome could be that the spill-in is not corrected for properly. By drawing more, and larger, volumes of interests in the background this problem could be reduced.

5.8 Improvement of PVC Method

The PVC method could be improved in a couple of ways. As has been shown in this work, the volume of interest should match the size of the blood vessel in order to get accurate results.

In this work, the PVC used values for spatial resolution obtained in previous measurements. These values could be checked and possibly regulated to improve the results. The best alternative would be to use a PET scanner with the best possible spatial resolution.

As discussed before, the spill-in might need to be corrected for more properly by draw more,
and larger, volumes of interest in the background to use in the PVC method.

6 Conclusion

The contrast between blood vessel and background did not affect the results since the background is subtracted from the image when measuring the activity.

It was not possible to determine the tube diameters from the PET images, and since the partial volume correction is highly dependent on the size (see section 4.2) it is necessary to get a precise diameter of the carotid before the corrections are performed. This means that an alternative method should be used to determine the carotid size for individual patients. For example MRI or CT with contrast would make it possible to determine the carotid size for each patient.

Using partial volume correction significantly improved the measured activity in both the phantom and patient data. For tubes smaller than 6 mm in diameter the improvement was very pronounced, and since the carotids are approximately 5 mm in diameter, it is absolutely necessary to correct for partial volume effects, just as we expected.

Although the PVC method used in this work yielded good results, it still needs some improvements, for example, investigate the spatial resolution of the PET scanner.

6.1 Future Research

When continuing this work it would be interesting to investigate if the theory of the relation between the small square VOI and the circular tube described in section 5.3 seems reasonable.

The partial volume correction should be further improved by improving the size determination using CT or MRI.

It would also be interesting to evaluate the method on patient data when using MRI or CT with contrast to get a more accurate measurement of the carotid diameter, and still have images of the aorta as a reference.

As a next step, compartmental modelling should be incorporated in order to find the correct input function.

Finally, we want to develop and implement a way to use this clinically.
References


A Size Determination

A.1 Measured Tube Diameters Using Water

The tubes in the phantom were measured by filling them with water, weighing and calculating the diameter as described in section 3.4. The details from the measurements are presented in the table below.

Table 4 Resulting data from measuring the tube diameters using water.

<table>
<thead>
<tr>
<th>Tube #</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tube length (cm)</td>
<td>19.5</td>
<td>18.2</td>
<td>10.0</td>
<td>18.3</td>
<td>18.1</td>
<td>10.0</td>
<td>7.8</td>
<td>10.0</td>
<td>10.0</td>
<td>18.1</td>
</tr>
<tr>
<td>Weight before (g)</td>
<td>115.40</td>
<td>53.28</td>
<td>15.00</td>
<td>21.95</td>
<td>44.48</td>
<td>5.22</td>
<td>5.62</td>
<td>4.65</td>
<td>3.80</td>
<td>3.81</td>
</tr>
<tr>
<td>Weight after (g)</td>
<td>169.89</td>
<td>77.33</td>
<td>21.53</td>
<td>26.00</td>
<td>53.17</td>
<td>7.36</td>
<td>6.84</td>
<td>6.14</td>
<td>4.67</td>
<td>5.28</td>
</tr>
<tr>
<td>Difference (g)</td>
<td>54.40</td>
<td>24.05</td>
<td>6.53</td>
<td>4.05</td>
<td>8.69</td>
<td>2.14</td>
<td>1.22</td>
<td>1.49</td>
<td>0.87</td>
<td>1.47</td>
</tr>
<tr>
<td>Volume (cm$^3$)</td>
<td>54.40</td>
<td>24.05</td>
<td>6.53</td>
<td>4.05</td>
<td>8.69</td>
<td>2.14</td>
<td>1.22</td>
<td>1.49</td>
<td>0.87</td>
<td>1.47</td>
</tr>
<tr>
<td>Diameter (cm)</td>
<td>1.88</td>
<td>1.30</td>
<td>0.91</td>
<td>0.53</td>
<td>0.78</td>
<td>0.52</td>
<td>0.44</td>
<td>0.44</td>
<td>0.33</td>
<td>0.32</td>
</tr>
</tbody>
</table>
A.2 Size Determination from PET Images

Section 4.1 described how the tube diameters were determined from the dynamic PET images. In the tables below are the data to the results in graphs 19 and 20.

**Table 5** Errors when determining the tube size with different threshold values. The bold values represent the lowest error of each tube.

<table>
<thead>
<tr>
<th>Size (mm)</th>
<th>Error when using a threshold of...</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>... 40 % (%)</td>
</tr>
<tr>
<td>18.8</td>
<td>5.32</td>
</tr>
<tr>
<td>13.0</td>
<td>1.54</td>
</tr>
<tr>
<td>9.1</td>
<td><strong>5.49</strong></td>
</tr>
<tr>
<td>5.3</td>
<td><strong>17.95</strong></td>
</tr>
<tr>
<td>7.8</td>
<td>43.40</td>
</tr>
<tr>
<td>5.2</td>
<td>13.46</td>
</tr>
<tr>
<td>4.4</td>
<td>27.27</td>
</tr>
<tr>
<td>4.4</td>
<td>34.09</td>
</tr>
<tr>
<td>3.3</td>
<td>69.70</td>
</tr>
<tr>
<td>3.2</td>
<td>78.13</td>
</tr>
</tbody>
</table>

**Table 6** Errors when determining the tube size with different threshold values. The bold values represent the lowest error of each tube.

<table>
<thead>
<tr>
<th>Size (mm)</th>
<th>Error when using a threshold of...</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>... 50000 (%)</td>
</tr>
<tr>
<td>18.8</td>
<td>17.02</td>
</tr>
<tr>
<td>13.0</td>
<td>16.92</td>
</tr>
<tr>
<td>9.1</td>
<td>26.37</td>
</tr>
<tr>
<td>7.8</td>
<td>23.08</td>
</tr>
<tr>
<td>5.3</td>
<td>45.28</td>
</tr>
<tr>
<td>5.2</td>
<td>23.08</td>
</tr>
<tr>
<td>4.4</td>
<td>27.27</td>
</tr>
<tr>
<td>4.4</td>
<td>43.18</td>
</tr>
<tr>
<td>3.3</td>
<td>69.70</td>
</tr>
<tr>
<td>3.2</td>
<td><strong>18.75</strong></td>
</tr>
</tbody>
</table>
B MATLAB Code

In this section the relevant MATLAB code is presented.

B.1 General PVC Code

Open the dynamic PET-image in imlook4d and draw two VOIs (in the code, VOI is replaced by ROI (region of interest), one representing the geometry of interest (e.g. the carotids) and one that will represent the background. The VOIs should not be close but not interfering with each other.

The matrix of ROI indices will be called imlook4d_ROI, and the pixel values imlook4d_Cdata. Also the ROI values are needed, which in imlook4d is called imlook4d_ROI_data.mean.

```matlab
% Start with exporting matrices and ROI values from imlook4d
Export
ROI_data_to_workspace
% Get voxelsize in mm. Can also be specified as vector vox = [ 2 2 2 ];
vox = voxel_size(imlook4d_current_handles)
% Convert known resolution in mm fwhm=[ 3.59, 3.40, 4.32], to fwhm in pixels
fwhm_pixels = pixels([ 3.59, 3.40, 4.32], vox);
% Convert from fwhm to sigma
sigma_pixels = fwhm_pixels / 2.35;
% Calculate PVE-corrected using MTC
[MGM on all ROIs with GMT-corrected true ROI values]
[C, P, TACT] = pveCorrection('MTC',imlook4d_Cdata, imlook4d_ROI, sigma_pixels);
% Display corrected matrix
imlook4d(C);
```
B.2 PVC on Desired Image

This script was used to perform PVE corrections on desired images in imlook4d. Two VOIs need to be drawn and saved as a ROI-file: the VOI of the desired geometry (e.g. the carotid) and a larger background VOI.

% This script performs PVE correction on a DICOM file of choice. Two ROIs need to be known and the ROI-files saved. The paths to the image file, the background ROI-file and to the ROI-file of the desired geometry must be entered manually.

% Open DICOM file
INPUTS = Parameters( {'Path to image file'} );
imlook4d_current_handle = Open(INPUTS{1}); % Handle to imlook4d window

% Load large ROI (background ROI)
INPUTS = Parameters( {'Path to background ROI-file'} );
Menu('Load ROI')
Menu('Export (untouched)')
ROI_large = imlook4d_ROI;

% Load small ROI (vessel ROI)
INPUTS = Parameters( {'Path to vessel ROI-file'} );
Menu('Load ROI')
Menu('Export (untouched)')
ROI_small = imlook4d_ROI;

% Combine the ROIs and add a background ROI on whole image
imlook4d_ROI = ROI_large + ROI_small + 1;
Import;

% PERFORMING PVC (see the dokument "PVE-corrections" by Jan Axelsson for more information)
% Get voxel size in mm. Can also be specified as vector vox = [ 2 2 2 ];
vox = voxel_size(imlook4d_current_handles);
% Convert known resolution in mm fwhm=[ 3.59, 3.40, 4.32], to fwhm in pixels
fwhm_pixels = pixels([ 3.59, 3.40, 4.32], vox);
% Convert from fwhm to sigma
sigma_pixels = (1/(2*sqrt(2*log(2)))).*fwhm_pixels;
% Calculate PVE-corrected using MTC
[C, P, TACT] = pveCorrection('MTC',imlook4d_Cdata, imlook4d_ROI, sigma_pixels);

% Import the PVE corrected imaget to imlook4d
imlook4d_Cdata=C;
imlook4d_ROI=ROI_small;
Import;