Quantitative Methods for Tumor Imaging with Dynamic PET

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Front cover: Illustration created by the author, depicting the annihilation of a positron and an electron
For My Sister
Abstract

There is always a need and drive to improve modern cancer care. Dynamic positron emission tomography (PET) offers the advantage of \textit{in vivo} functional imaging, combined with the ability to follow the physiological processes over time. In addition, by applying tracer kinetic modeling to the dynamic PET data, thus estimating pharmacokinetic parameters associated to e.g. glucose metabolism, cell proliferation etc., more information about the tissue’s underlying biology and physiology can be determined. This supplementary information can potentially be a considerable aid when it comes to the segmentation, diagnosis, staging, treatment planning, early treatment response monitoring and follow-up of cancerous tumors.

We have found it feasible to use kinetic parameters for semi-automatic tumor segmentation, and found parametric images to have higher contrast compared to static PET uptake images. There are however many possible sources of errors and uncertainties in kinetic parameters obtained through compartment modeling of dynamic PET data. The variation in the number of detected photons caused by the random nature of radioactive decay is of course always a major source. Other sources may include: the choice of an appropriate model that is suitable for the radiotracer in question, the camera detectors and electronics, image acquisition protocol, image reconstruction algorithm with corrections (attenuation, random and scattered coincidences, detector uniformity, decay) and so on. We have found the early frame sampling scheme in dynamic PET to affect the bias and uncertainty in calculated kinetic parameters, and that scatter corrections are necessary for most but not all parameter estimates. Furthermore, analytical image reconstruction algorithms seem more suited for compartment modeling applications compared to iterative algorithms.

This thesis and included papers show potential applications and tools for quantitative pharmacokinetic parameters in oncology, and help understand errors and uncertainties associated with them. The aim is to contribute to the long-term goal of enabling the use of dynamic PET and pharmacokinetic parameters for improvements of today’s cancer care.
Sammanfattning

Det finns alltid ett behov och en strävan att förbättra dagens cancervård. Dynamisk positronemissionstomografi (PET) medför fördelen av in vivo funktionell avbilning, kombinerad med möjligheten att följa fysiologiska processer över tiden. Genom att därtill tillämpa kinetisk modellering på det dynamiska PET-datat, och därigenom skatta farmakokinetiska parametrar associerade till glukosmetabolism, cellproliferation etc., kan ytterligare information om vävnadens underliggande biologi och fysiologi bestämmas. Denna kompletterande information kan potentiellt vara till stor nytta för segmentering, diagnos, stadieindelning, behandlingsplanering, monitorering av tidig behandlingsrespons samt uppföljning av cancertumörer.

Vi fann det möjligt att använda kinetiska parametrar för semi-automatisk tumörsegmentering, och fann även att parametriska bilder hade högre kontrast jämfört med upptagsbilder från statisk PET. Det finns dock många möjliga källor till osäkerheter och fel i kinetiska parametrar som beräknats genom compartment-modellering av dynamisk PET. En av de största källorna är det radioaktiva sönderfallets slumpmässiga natur som orsakar variationer i antalet detekterade fotoner. Andra källor inkluderar valet av compartment-modell som är lämplig för den aktuella radiotracern, PET-kamerans detektorer och elektronik, bildtagningsprotokoll, bildrekonstruktionsalgoritmer och tillhörande korrekteringsmedel, inklusive attenuering, slumpmässig och spridd strålning, detektorernas likformighet, sönderfall och så vidare. Vi fann att tidssamplingsschemat för tidiga bilder i dynamisk PET påverkar både fel och osäkerhet i beräknade kinetiska parametrar, och att bildkorrekteringsmedel för spridd strålning är nödvändigt för de flesta men inte alla parametrar. Utöver detta verkar analytiska bildrekonstruktionsalgoritmer vara bättre lämpade för tillämpningar som innefattar compartment-modellering i jämförelse med iterativa algoritmer.

Denna avhandling med inkluderade artiklar visar möjliga tillämpningar och verktyg för kvantitativa kinetiska parametrar inom onkologiområdet. Den bidrar också till förståelsen av fel och osäkerheter associerade till dem. Syftet är att bidra till det långsiktiga målet att möjliggöra användandet av dynamisk PET och farmakokinetiska parametrar för att förbättra dagens cancervård.
Acknowledgments

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My supervisor Anne Larsson Strömvall, who’ve always taken the time to discuss ideas and constantly kept a positive attitude even during difficulties. Thank you for guiding me through the jungle that is being a graduate student!

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My sister Josefin, my mom Astrid and my dad David for always, and I mean ALWAYS, supporting me and being there for me no matter what... and for being crazily and disproportionately proud of me!

Finally, I would like to thank the Swedish Cancer Society and the Cancer Research Foundation at Umeå University for your generous contributions that have made this work possible.
List of Original Papers

Paper I
Semi-Automatic Tumour Segmentation by Selective Navigation in a Three-Parameter Volume, Obtained by Voxel-Wise Kinetic Modelling of $^{11}$C-acetate
I. Häggström, L. Johansson, A. Larsson, N. Östlund, J. Sörensen and M. Karlsson

Paper II
Compartment Modeling of Dynamic Brain PET – The Impact of Scatter Corrections on Parameter Errors
I. Häggström, C. R. Schmidtlein, M. Karlsson and A. Larsson
Medical Physics 41(11), pp. 111907-1-9 (2014)

Paper III
A Monte Carlo Study of the Dependence of Early Frame Sampling on Uncertainty and Bias in Pharmacokinetic Parameters from Dynamic PET

Paper IV
PETSTEP: Generation of Synthetic PET Lesions for Fast Evaluation of Segmentation
## Abbreviations and Nomenclature

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>%ID/g</td>
<td>Percent injected dose per gram of tissue</td>
</tr>
<tr>
<td>2D</td>
<td>Two-dimensional</td>
</tr>
<tr>
<td>3D</td>
<td>Three-dimensional</td>
</tr>
<tr>
<td>3DRP</td>
<td>3D filtered back-projection with reprojection</td>
</tr>
<tr>
<td>4D</td>
<td>Four-dimensional (3D plus time-dimension)</td>
</tr>
<tr>
<td>AIF</td>
<td>Arterial input function</td>
</tr>
<tr>
<td>APD</td>
<td>Avalanche photodiode</td>
</tr>
<tr>
<td>BaF$_2$</td>
<td>Barium fluoride</td>
</tr>
<tr>
<td>BGO</td>
<td>Bismuth germanate</td>
</tr>
<tr>
<td>B$_p$</td>
<td>Binding potential (unitless)</td>
</tr>
<tr>
<td>CBF</td>
<td>Cerebral blood flow (ml min$^{-1}$)</td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>CT</td>
<td>X-ray computed tomography</td>
</tr>
<tr>
<td>DCE-MRI</td>
<td>Dynamic contrast enhanced magnetic resonance imaging</td>
</tr>
<tr>
<td>EORTC</td>
<td>European Organization for Research and Treatment of Cancer</td>
</tr>
<tr>
<td>FBP</td>
<td>Filtered back-projection</td>
</tr>
<tr>
<td>FDG</td>
<td>2-deoxy-2-$^{(18}F$)fluoro-D-glucose</td>
</tr>
<tr>
<td>FLT</td>
<td>3’-deoxy-3’-$^{(18}F$)fluorothymidine</td>
</tr>
<tr>
<td>FOV</td>
<td>Field of view</td>
</tr>
<tr>
<td>FWHM</td>
<td>Full width at half maximum</td>
</tr>
<tr>
<td>GATE</td>
<td>GEANT4 Application for Tomographic Emission</td>
</tr>
<tr>
<td>GE DLS</td>
<td>General Electric Discovery LS</td>
</tr>
<tr>
<td>GSO</td>
<td>Cerium-doped gadolinium oxyorthosilicate</td>
</tr>
<tr>
<td>LC</td>
<td>Lumped constant (unitless)</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
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</tr>
<tr>
<td>LOR</td>
<td>Line of response</td>
</tr>
<tr>
<td>LSO</td>
<td>Cerium-doped lutentium oxyorthosilicate</td>
</tr>
<tr>
<td>LYSO</td>
<td>Cerium-doped lutentium yttrium oxyorthosilicate</td>
</tr>
<tr>
<td>MBF</td>
<td>Myocardial blood flow (ml min(^{-1}) g(^{-1}))</td>
</tr>
<tr>
<td>MC</td>
<td>Monte Carlo</td>
</tr>
<tr>
<td>ML-EM</td>
<td>Maximum likelihood expectation maximization</td>
</tr>
<tr>
<td>MR</td>
<td>Magnetic resonance</td>
</tr>
<tr>
<td>MR(_{\text{glu}})</td>
<td>Metabolic rate of glucose (µmol min(^{-1}) g(^{-1}))</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>Na(Tl)</td>
<td>Thallium-doped sodium iodide</td>
</tr>
<tr>
<td>NLS</td>
<td>Non-linear least squares</td>
</tr>
<tr>
<td>OSEM</td>
<td>Ordered subset expectation maximization</td>
</tr>
<tr>
<td>PERCIST</td>
<td>PET Response Criteria in Solid Tumors</td>
</tr>
<tr>
<td>PET</td>
<td>Positron emission tomography</td>
</tr>
<tr>
<td>PETSTEP</td>
<td>Positron Emission Tomography Simulator of Tracers via Emission Projection</td>
</tr>
<tr>
<td>PFS</td>
<td>Progression-free survival</td>
</tr>
<tr>
<td>PMT</td>
<td>Photo-multiplier tube</td>
</tr>
<tr>
<td>PSF</td>
<td>Point spread function</td>
</tr>
<tr>
<td>PTF</td>
<td>Perfusible tissue fraction (g ml(^{-1}))</td>
</tr>
<tr>
<td>PVE</td>
<td>Partial volume effect</td>
</tr>
<tr>
<td>RC</td>
<td>Recovery coefficient</td>
</tr>
<tr>
<td>RECIST</td>
<td>Response Evaluation Criteria in Solid Tumors</td>
</tr>
<tr>
<td>ROI</td>
<td>Region of interest</td>
</tr>
<tr>
<td>RSS</td>
<td>Residual sum of squares</td>
</tr>
<tr>
<td>SC</td>
<td>Scatter correction</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
</tbody>
</table>
**SiPM**  
Silicon photo-multiplier

**SNR**  
Signal to noise ratio

**SPECT**  
Single photon emission computed tomography

**SSS**  
Single scatter simulation

**STIR**  
Software for Tomographic Image Reconstruction

**SUV**  
Standardized uptake value

**TAC**  
Time-activity curve

**TOF**  
Time of flight

**TTAC**  
Tissue time-activity curve

**WHO**  
World Health Organization

**WNLS**  
Weighted non-linear least squares

**WRSS**  
Weighted residual sum of squares

**YSO**  
Cerium-doped yttrium oxyorthosilicate

\[ C_a \]  
Tracer activity concentration in arterial blood plasma (kBq/ml)

\[ C_{F+NS} \]  
Activity concentration of free + non-specific (=non-displaceable) tracer in tissue (kBq/ml)

\[ C_{F+NS+S} \]  
Total tracer activity concentration in tissue (free + non-specific + specifically bound) (kBq/ml)

\[ C_{PET} \]  
Apparent tracer activity concentration in a PET image voxel or ROI (kBq/ml)

\[ c_{p,glu} \]  
Plasma glucose concentration (µmol ml\(^{-1}\))

\[ C_s \]  
Activity concentration of specifically bound tracer in tissue (kBq/ml)

\[ K_1 \]  
Tracer uptake rate from blood to tissue (ml g\(^{-1}\) min\(^{-1}\))

\[ k_2 \]  
Tracer clearance rate from tissue to blood (min\(^{-1}\))
$k_3$ Exchange rate from non-displaceable to specifically bound tracer in tissue (min$^{-1}$)

$k_4$ Exchange rate from specifically bound to non-displaceable tracer in tissue (min$^{-1}$)

$K_i$ Influx rate constant, metabolic flux constant (ml g$^{-1}$ min$^{-1}$)

$V_a$ Fraction of arterial blood in tissue (ml g$^{-1}$)

$V_d, V_0$ Volume of distribution. The volume of blood that would contain the same amount of tracer as 1 ml (1 g) of tissue (ml g$^{-1}$).
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Introduction

The need and usefulness for non-invasive technologies that enable imaging of injuries and disease in vivo are irrefutable in modern health care. X-ray computed tomography (CT) and magnetic resonance imaging (MRI) are cornerstones in anatomical imaging, whereas positron emission tomography (PET) and single photon emission computed tomography (SPECT) are the workhorses in functional imaging.

1.1 Cancer

One of the endemic diseases of today is cancer, being the second leading cause of death in the European Union member states (after circulatory system diseases), according to the most recent numbers from OECD [1]. In the European Union, cancer accounted for 28% of all deaths in 2010, with lung cancer claiming the most lives. An estimated 2.4 million new cases of cancer were diagnosed in 2008, and the estimated risk of getting cancer before the age of 75 is around one in four. As the population ages however, this risk is expected to increase. Globally, in 2030 the number of new cancer diagnoses is estimated to reach 21.4 million, with 13.2 million cancer deaths during the same year [2].

In Sweden, 525 women and 655 men per 100 000 were diagnosed with cancer
in 2011 [2]. In addition, 21 685 people died from cancer in 2011, with the most deadly cancer type being lung cancer (17% of cancer deaths for both sexes). The most common cancer is breast cancer in women (30% of cancer incidence, 14% of cancer deaths) and prostate cancer in men (32% of cancer incidence, 21% of cancer deaths), followed by skin cancer (9% of cancer incidence in women and 11% in men), colon cancer (8% of cancer incidence in women and 7% in men), and lung cancer (7% of cancer incidence in both women and men) [2].

As will be discussed in more detail in Chapter 2, there are potentially major benefits associated with quantitative PET imaging in the screening, diagnosis, staging, prognosis, treatment planning, treatment monitoring and follow-up of cancerous tumors. Going one step further, tumor biology and physiology may be even better represented with dynamic PET and kinetic modeling, thus enabling further improvements in cancer care.

1.2 General aims

The long-term aim of the works presented in this thesis is to contribute to the end goal of using kinetic PET parameters in the clinic for improved tumor treatment and treatment follow-up. More specifically, to contribute to the understanding of errors and uncertainties associated with the kinetic parameters, and in doing so increase their clinical relevance and usefulness. We also wanted to show ways that kinetic parameters can in fact be of use in the clinic, by investigating the feasibility of tumor segmentation based on parametric images. Finally, advances in cancer care requires effective evaluation and development of new methods to improve PET image acquisition protocols, quality, post-processing, analysis and so on. Since computer simulations are a central part of this, we wanted to develop a fast and easy PET simulator to be useful for these purposes.
PET is a quantitative imaging technique. In short, that implies that the voxel values of a PET image are calibrated to represent units of radiotracer concentration. The signal measured by the camera can thus be appropriately corrected and scaled, and the subsequent image voxel intensities can be interpreted directly as the distribution of tracer in the body.

The works presented in this thesis are focused on applications and potential benefits in the field of oncology, and on that account this chapter is dedicated thereto. Most publications referenced in the following sections use pharmacokinetic parameters. Kinetic modeling of dynamic PET data produces kinetic model parameters, associated to physiological processes in the body. The reader is referred to Chapter 5 and the list of Abbreviations and Nomenclature for a review of what each individual parameter represents.

2.1 Benefits in tumor imaging

PET images are predominantly evaluated by visual inspection, i.e. qualitatively, compared to assessment based on quantitative measures [3–6], and
commonly also semi-quantitatively by the standardized uptake value (SUV, see Section 3.10). There are however some major benefits arising from using a truly quantitative technique. For one, the image voxel values reflect the true underlying physiology of the region looked at since the voxel intensities represent the amount of tracer uptake in that region. Secondly, by using tracer kinetic modeling techniques (see Chapter 5), one can follow the distribution of tracer over time and from that quantify new physiological parameters of interest, other than simply the static tracer uptake [7, 8]. This enables quantitative measures of e.g. metabolic and specific binding rates.

Furthermore, as properly corrected PET images directly reflect the tracer concentration, they are thus less sensitive to individual hospital, camera system and operator biases. This greatly improves the ability to do comparative and multicenter studies.

During the last decade, quantitative PET imaging has strengthened its role in cancer care as an in vivo biomarker with prospects in screening, prediction, staging and treatment response monitoring of cancer [9–15]. Knowledge of molecular characteristics of a patient’s tumor can potentially enable a safer, more effective targeted therapy. In turn, this leads to more powerful means of prediction and monitoring of treatment response [11]. Since the introduction of PET in cancer care (mainly using the tracer 2-deoxy-2-(\(^{18}\)F)fluoro-D-glucose [\(^{18}\)F-FDG]), it has been shown to improve the accuracy of detection and staging of several cancers [16]. By including PET data in the work-ups, up to 40% of patients have had their treatment plan changed due to an upstage or downstage of the cancer [16]. In upstaged cancers, unsuspected metastases are detected by PET but not by the conventional imaging modalities, and in the downstaged cases, structural diagnosis found on conventional work-ups have been identified as benign rather than malignant with PET [16].

The American National Cancer Institute (NCI)\(^{a}\) has long recognized the importance of quantitative imaging, and in 2008 the Quantitative Imaging Network (QIN)\(^{b}\) was founded. It was designed to promote quantitative imag-

\(^{a}\) NCI: http://www.cancer.gov

\(^{b}\) QIN: http://imaging.cancer.gov/programsandresources/specializedinitiatives/qin
2.1 Benefits in tumor imaging

Methods to assess tumor response to treatment, and ultimately facilitate clinical decision making [11, 14].

2.1.1 Tumor segmentation

Tumor volumes in PET images are typically separated (delineated) from the surrounding tissue, a process called *segmentation*, using the voxel grayscale value or SUV. There are several methodologies for creating a segmented tumor volume, including [8, 17]

- **Thresholding.** A percentage of the mean or maximum voxel value is set as the threshold and voxels are either included (above threshold) or excluded (below threshold) from the delineated volume, based on their intensity. The threshold can also incorporate the difference between the hot lesion and background intensity. A typical threshold is 50% of the maximum SUV.

- **Adaptive thresholding.** Based on the mean SUV plus a constant. Starting with an initial guess of the percentage, the threshold value and mean SUV are updated by regression until convergence is reached.

- **Region growing.** A single or a set of voxels is set as the starting seed, and a connected region is grown from that (based on a voxel threshold value) until no more voxels can be added to the region.

- **Deconvolution.** The image of the tumor is considered a convolution between the true tumor region and the camera system’s point spread function (PSF).

- **Gradient-based methods.** The gradients (change in voxel values) are used to characterize tumor contours and enables edge detection.

- **Classifiers.** Different tissue classes (e.g. white matter, gray matter etc.) have predetermined features (e.g. voxel intensities, region textures, voxel gradients), determined by a training set. During the segmentation process, the image regions are labeled with their respective class based on a pattern recognition algorithm.

- **Clustering.** Essentially the same as classifiers, but without the use of a training set.
**Statistical methods.** These methods use spatial correlations between voxels.

Obviously, there are numerous delineation methods, including versions of the above mentioned ones. There is clearly no clear consensus or generally accepted method for tumor segmentation using PET today [8, 17].

In paper I, we investigated the potential for semi-automatic tumor segmentation based on 2-tissue model parameters from $^{11}$C-acetate, and found that parametric images, especially of the parameter denoted $K_1$, had better contrast and offered additional information compared to the normal PET uptake image. It was possible to delineate tumor tissue based on kinetic parameters, and the method could be simplified from three parameters to two by principal component analysis.

Furthermore, the findings of Cheebsumon et al. [18] showed that semi-automatic delineation of lung and gastrointestinal tumors based on kinetic modeling of dynamic $^{18}$F-FDG PET produced smaller regions of interest (ROIs) with less outliers compared to delineation based on static SUV images. The differences were largest for fixed SUV thresholds, but decreased for algorithms taking the background or local contrast or both into account, confirming that SUV-based delineation methods are sensitive to signal to background ratios. Visser et al. [19] arrived at the same conclusion. The authors delineated tumors on parametric images of the metabolic rate of glucose ($MR_{glu}$, proportional to $K_i$) from Patlak analysis of dynamic $^{18}$F-FDG scans, and compared the resulting ROIs from those based on SUV images from static scans. The parametric image ROIs were 33% smaller than the SUV ROIs. This study also confirmed that the parametric image contrast was considerably better (higher tumor to background ratio) compared to the SUV images.

Dimitrakopoulou-Strauss et al. [20] concluded that the true-negative rate of detection (specificity) of soft-tissue sarcomas was low when using only static $^{18}$F-FDG SUV, whereas using full 2-tissue compartment model kinetic parameters provided superior information for tumor discrimination and resulted in a higher specificity. Only full kinetic analysis allowed effective differentiation between tumors according to the histological grading.

Quantification of tumor hypoxia is one area that is particularly benefited by
pharmacokinetic modeling and parametric imaging, since hypoxic regions are hard to visualize directly by hypoxic-specific tracers due to typically low uptake and high noise PET images [21]. Additionally, hypoxic regions are commonly very heterogeneous since they are associated with individual vessels, further encouraging the use of voxel-wise parametric images over ROI analyses [21]. Cheng et al. [21] proposed a method for delineation of hypoxic regions in mice with squamous cell carcinomas, using $^{18}$F-FMISO PET and parametric Patlak slope ($K_i$) images. The authors concluded that the obtained hypoxia volumes correlated very well with those derived from immunohistochemistry, and promoted the use of parametric images for hypoxia delineation. In another $^{18}$F-FMISO squamous cell carcinoma mouse study by Shi et al. [22], the conclusion was that 2-tissue compartment model parameters ($k_3$) showed the largest correlation to histology.

### 2.1.2 Monitoring tumor response to treatment

The treatment regime for cancerous tumors varies depending on stage and type of cancer, tumor location, and patient condition. Chemotherapy (administration of anticancer drugs), radiotherapy (irradiation of tumor in order to kill cancer cells), and resection (surgical removal of tumor) are part of the cancer treatment arsenal. Tumor treatment response is a central part in cancer care, but it is not well understood. Some patients benefit greatly from a specific treatment regimen whilst others do not, despite apparently equivalent disease and clinical characteristics [23]. Tumors are crudely classified as responding or non-responding due to our limited understanding of the underlying tumor biology, and the significant differences between treatment outcome makes monitoring of tumor treatment response a crucial part of modern clinical oncology [23].

An earlier and more effective means of determining tumor response versus non-response would aid the patient directly by enabling personalized therapy that is subject to beneficial alterations early on during treatment. Wearisome and lengthy treatments with serious, adverse side effects could possibly be avoided or interrupted if they are deemed ineffective and thus unnecessary. This would save the patient a great deal of discomfort, stress and pain. In addi-
tion, it could potentially also increase the quality and extent of the patients life by not wasting valuable time on ineffective treatments, and instead administer the “right”, most effective treatment with little delay. Furthermore, cutting ineffective treatments at an early stage would benefit society as it would reduce the cost of cancer care [23]. Additionally, early response monitoring is crucial in the development of new anticancer drugs to determine their efficacy, thus enabling a faster, more cost-effective and productive drug advancement, hence boosting future cancer care [23–25].

Conventionally, tumor treatment response is evaluated by assessing tumor size by the contrast enhancement on CT or magnetic resonance (MR) images [3, 15, 23, 26–28]. The response is commonly measured by the World Health Organization (WHO) criteria, the Response Evaluation Criteria in Solid Tumors (RECIST) and the updated RECIST 1.1 criteria [3, 5, 15, 27–29]. Both RECIST and the WHO criteria define if tumors improve (respond), stay the same (stabilize) or worsen (progress) as a result of treatment. The response can further be divided into complete or partial response. The tumor lesion size at baseline (before treatment onset) is used as a comparison to the tumor size during and after treatment has ended. The size is commonly determined by CT or MRI scans. Depending on the percentage decrease or increase in lesion size some weeks after treatment onset, the tumor status is determined.

There are several limits to an anatomic, tumor size approach however, one being the general heterogeneity of tumor tissue. Tumor lesions are generally infiltrative, irregular and influenced by hypoxia, causing an ROI in a tumor to contain a mixture of viable tumor, normal healthy tissue, blood vessels and necrotic tissue, as depicted in Figure 2.1. These different tissues all respond differently to treatment. Metabolically active tumor often constitute only part of the entire, anatomical tumor. It is this sub-portion of the anatomical tumor mass that is most useful as a prognostic indicator [4].

Moreover, the shrinkage of the gross tumor size is often a delayed measure compared to metabolic changes, yielding observable results several weeks or even months after treatment onset [5, 12, 23, 26–28, 30]. PET has been shown to enable earlier monitoring and more rapid tumor response assessment, thus enabling the prediction of patient outcome already after the first or second cycle
2.1 Benefits in tumor imaging

Figure 2.1. Heterogeneous and infiltrative tumor tissue. Despite a non-visible change in anatomical size (determined by anatomical CT or MRI) as a result of treatment, the tumor may still respond well to the treatment.

of chemotherapy or even within a few days after treatment onset [5, 23, 25, 31].

In addition, for many tumor types (e.g. lymphomas, sarcoma, hepatomas, mesothelioma, and gastrointestinal stromal tumors), the change in tumor size as a result of treatment is often minimal, despite effective treatment [3, 25]. Furthermore, molecularly targeted anti-cancer drugs often result in a slowing or halt of tumor growth, rather than a shrinkage of the tumor volume [29].

Another major drawback with the anatomical approach is the difficulty to separate residual, active tumor from necrotic or fibrotic (scar) tissue [7, 13, 23, 25, 26]. Tumors responding well to treatment may still be classified as non-responding due to the visible mass still showing up on CT and MR images (Figure 2.1).
Obviously, the mere size of the tumor is not a direct measure of its viability since it lacks details about the molecular and physiological aspects of the tumor, and thus does not provide enough information about the tumor proliferation activity and metabolism on a cellular level [15, 25, 26, 30, 32].

Due to the limitations in only considering tumor size as a metric, the WHO and RECIST criteria are sometimes considered inadequate when it comes to assessing tumor response to treatment [3, 24]. Wahl et al. [3] proposed an updated alternative to the WHO, RECIST and RECIST 1.1 tumor response criteria called the PET Response Criteria in Solid Tumors (PERCIST), where $^{18}$F-FDG uptake (SUV) is included as a metric. The authors screened approximately 3 000 relevant articles, and found that measuring treatment response based on anatomical changes alone is limited, why the inclusion of functional $^{18}$F-FDG PET data appears especially valuable. In particular, $^{18}$F-FDG PET has proved extremely capable of detecting viable tumor tissue, i.e. lack of response to treatment, and is thus a test with a high specificity for response [23]. PERCIST is today generally accepted as the standard protocol for solid tumor response evaluation using $^{18}$F-FDG PET [4]. Young et al. [31] compiled recommendations for tumor treatment response assessment on behalf of the European Organization for Research and Treatment of Cancer (EORTC). The EORTC criteria also incorporates $^{18}$F-FDG PET, and uses changes in SUV as a metric for assessing tumor response. Worth noting however is that the task group also found MR$_{glu}$ to effectively predict tumor response.

In addition to the anatomical criteria, tumor response can also be evaluated by histopathological samples, i.e. biopsies of the tumor, where the response is defined as the percentage of active tumor relative to therapy-induced fibrosis [27]. However, this approach is very sensitive to the heterogeneity of the tumor tissue, since a small tissue sample is not fully representative of an entire tumor. Full tumor resection would be required for a truly valid response evaluation [27]. Moreover, biopsies are invasive and demand considerable lab work.

A number of studies have looked at the use of PET imaging biomarkers for evaluation of cancerous tumors. In the 2009 review by Weber [23], he noted that studies evaluating $^{18}$F-FDG PET for treatment response monitoring over
the past 20 years have observed that compared to CT, $^{18}$F-FDG PET is more accurate in differentiating viable tumor from treatment induced necrosis and fibrosis. In essence that means that despite residual tumor masses appearing on the CT, $^{18}$F-FDG PET can identify patients as having a successful treatment response.

PET has been shown to be useful for the purpose of tumor imaging and treatment response monitoring of numerous cancers, including gliomas [32–39], head and neck cancers [38], breast cancer [40] and breast cancer bone metastases [41], pheochromocytomas and paragangliomas [42], non-Hodgkin’s lymphoma [43], CNS lymphoma [44], germ cell tumors [45], soft tissue sarcomas [20], colorectal carcinoma [46], non-small cell lung carcinoma [19] and lung and gastrointestinal cancer [18].

Jacobs et al. [33] found that glioma tumor volumes defined by 3’-deoxy-3’-(18F)fluorothymidine ($^{18}$F-FLT) and $^{11}$C-methionine were significantly larger compared to volumes defined by conventional contrast enhanced MRI. Harris et al. [47] studied glioma brain tumor treatment with bevacizumab, and found that changes in parametric images from $^{18}$F-DOPA and $^{18}$F-FLT were both correlated with progression-free survival (PFS), and $^{18}$F-DOPA also with overall survival. Compared to T1- and T2-weighted MRI, changes in PET uptake was a better predictor of PFS. The study by Schwarzenberg et al. [48] also showed that changes in $^{18}$F-FLT SUV was highly correlated with PFS and concluded that $^{18}$F-FLT PET seemed a better predictor than standard MRI for early treatment response in patients with gliomas.

In the head and neck cancer study by Kishino et al. [38], based on their own findings and those of others, the authors concluded that $^{18}$F-FLT is an early predictor of treatment response, even more so than other imaging modalities including $^{18}$F-FDG PET. Significant changes in $^{18}$F-FLT uptake was seen already at the first imaging occasion at 4 weeks after treatment onset.

$^{18}$F-FDG imaging was proved to be superior to conventional SPECT, CT and MRI for detecting metastases from pheochromocytomas and paragangliomas, according to the study by Timmers et al. [42]. The authors also found $^{18}$F-FDG PET to provide a high specificity and enable functional characterization of the disease.
Herrmann et al. [43] concluded that $^{18}$F-FLT yielded an early response after only 2 days after chemotherapy of non-Hodgkin’s lymphoma, and patients with partial or complete response could be separated.

In a study with breast cancer patients, Pio et al. [40] found that changes in $^{18}$F-FLT uptake already after the first course of chemotherapy correlated with late response markers.

Although only a selection of papers are referenced in this chapter, there is an abundance of papers showing the benefit of PET in the realm of treatment response monitoring of numerous types of cancers, mostly with $^{18}$F-FDG but many other tracers as well. Another note is that most studies comparing CT and MRI to PET use conventional anatomical CT and MR imaging protocols and sequences. MRI especially does however have the possibility for functional and dynamic imaging (dynamic contrast enhanced MRI, DCE-MRI).

**Dynamic PET and parametric imaging**

Ideally, PET images should reflect real, biologically interpretable parameters as opposed to plain activity distribution. Consequently, PET may not reach its full potential before PET scans can be interpreted in terms of parametric images [4].

The dynamic process of tracer kinetics (uptake, clearance) is best evaluated by observing the time course of the tracer distribution in the body, yielding better information about the tumor biology [4, 6, 49]. This minimizes any bias introduced by choosing only a single time frame, however long, to describe the total tracer metabolism. For example, dynamic PET followed by kinetic modeling may provide a more quantitative, sensitive and detailed measure of treatment response compared to semi-quantitative measures, such as the SUV or percent injected dose per gram (%ID/g) in static imaging [8, 50]. A schematic view of a dynamic PET scan, followed by compartment modeling is seen in Figure 2.2.

It has been shown that the assessment of treatment response or drug efficacy can differ if it is based on simplified SUV-based methods compared to full kinetic analysis [50]. Simplified SUV measures offer some advantages, the major ones being simple with no need for blood sampling. However, they
2.1 Benefits in tumor imaging

Figure 2.2. Schematic figure of a dynamic PET scan, followed by compartment modeling. The arterial blood TAC, known as the arterial input function, can be obtained by arterial blood sampling, image derived or estimated by population based methods. TAC = time-activity curve.

are crude and difficult to use as comparative measures (both for follow-up of the same patient, or for comparing different patients, hospitals and so on), due to the high level of variability owing to ROI setting, time after injection, reconstruction method, normalization parameter (body weight, body area etc.), poor image quality etc. [27, 31, 51]. Note however that treatment response monitoring is usually more reliable than applications using direct SUV values,
since it typically incorporates SUV ratios where many factors (almost) cancel out during calculation [51].

The findings of Schiepers et al. [35] showed that compartment modeling of $^{18}$F-FLT PET produced a $k_3$ parameter that could differentiate lesions that were tumor predominant and treatment change predominant in patients with glioma and brain metastases. In another glioma $^{18}$F-FLT study by Schiepers et al. [37], they found that some parameters, especially $K_i$, changed during the course of treatment and that changes were correlated to overall survival. It should be noted however that these two studies also found plain uptake values (i.e. SUV) to correlate to patient outcome. Furthermore, Wardak et al. [39] found that the ratios of $k_2$, $k_4$, as well as the volume of distribution $V_d = K_1/(k_2 + k_3)$, before and after glioma brain tumor chemotherapy treatment could predict overall patient survival for $^{18}$F-FLT. Muzi et al. [34] also looked at $^{18}$F-FLT in glioma patients, and found that the influx rate constant $K_{FLT}$ (denoted $K_i$ in this thesis) and $k_3$ successfully distinguished recurrence from radionecrosis.

Sugawara et al. [45] monitored patients with germ cell tumors using $^{18}$F-FDG PET, and compared SUVs and 2-tissue compartment model parameters before and after chemotherapy. The authors concluded that although visual inspection or SUV calculations could differentiate viable tumors from mature teratomas and necrotic/scar tissue, these metrics did not manage the finer differentiation between mature teratomas and necrotic/scar tissue. Parametric images of the influx rate constant $K$ (denoted $K_i$ in this thesis) had better contrast compared to SUV images, and parameters $K$ and $K_1$ did manage to separate teratomas from necrosis or scar.

Upon studying patients with primary central nervous system (CNS) lymphoma, Nishiyama et al. [44] found that kinetic analysis of $^{18}$F-FDG, especially with respect to $k_3$, was helpful for diagnosis and treatment response evaluation.

Doot et al. [41] concluded that kinetic parameters of the transport ($K_1$) and flux ($K_i$) of $^{18}$F-fluoride was found useful for evaluating treatment response in breast cancer bone metastases, which is hard for conventional CT and MRI techniques.

In a mouse study by Guo et al. [52], the authors found that the binding
2.1 Benefits in tumor imaging

Potential $B_p = \frac{k_3}{k_4}$ from compartment modeling of $^{18}$F-alfatide II managed to show a tumor treatment response after 3 days whereas static tracer uptake did not. Furthermore, the $^{18}$F-FDG influx rate $K_i$ also displayed statistically significant response, while static $^{18}$F-FDG uptake did not. In another mouse study by Guo et al. [53], they found that images of $B_p$ from $^{18}$F-labeled RGD peptide provided better tumor to background contrast compared to static images, and that tumor heterogeneity was more visible in parametric than static images.

Furthermore, Dimitrakopoulou-Strauss et al. [46] investigated colorectal carcinoma with $^{18}$F-FDG, and found that although SUV was quite good at predicting treatment non-response, the misclassification between partial response and stable disease was high. The results were improved when using a parameter from dynamic PET data, and the authors concluded that dynamic $^{18}$F-FDG PET is the preferred method for evaluating treatment response in metastatic colorectal cancer.

Obviously there’s potentially a huge gain from including kinetic parameters in the diagnosis, staging, treatment planning, treatment monitoring and follow-up of cancerous tumors. The reader should be aware however that despite potential benefits, full kinetic modeling for monitoring treatment response is rarely used since it requires time consuming dynamic scanning, is more complicated and less reproducible than SUV based methods [3, 26, 50, 54]. Furthermore, the limited axial FOV (~20 cm) of PET cameras makes dynamic scans of large areas difficult. All the reasons above, coupled with the requirement to know the activity concentration in arterial blood, makes kinetic modeling tricky for clinical routine, and is today thus mainly utilized for research applications [4, 5, 50]. With the advent of PET/MR (Section 3.5.1) however, image-derived arterial input functions (AIFs) are likely to be of better quality (Section 5.1.1, item “Image-based methods”) since the MR information can aid in motion correction (decrease PET image motion blurring) and partial volume correction (Section 4.3, item “partial volume effects”). Moreover, for most studies a single bed position is usually enough to image the relevant region (e.g. a single tumor).
2.2 Errors and uncertainties

Systematic errors, referred to as biases, are errors that cause the mean value of the measured entity to differ from the actual, true value, thus governing the precision of the measurement. Random errors, or uncertainties, cause repeated measurements of the same entity to differ from each other and affect the accuracy of the measurement.

The Quantitative Imaging Biomarkers Alliance (QIBA) is an initiative dating back to 2007, uniting researchers, clinicians and industry representatives with the mission to “improve the value and practicality of quantitative imaging biomarkers by reducing variability across devices, patients and time”. There have been many companion metrology publications under the QIBA initiative focused on statistical methods for evaluation of technical performance, computer algorithms, imaging procedures etc. (published in May–June 2014 in the journal Statistical Methods in Medical Research).

For a quantitative imaging technique, such as PET, it is crucial to understand but also quantify both random and systematic errors that will affect the images. Otherwise, the quantitative information is of lesser, or at worst, no practical use. To be able to use quantitative imaging biomarkers as predictors of true change in biological features (e.g. treatment response), the biomarker must reflect the true feature (e.g. size or function) in a predictable way [55]. In addition, any bias must be quantified for the relevant range of biomarker values.

An ideal quantitative biomarker will always (for the entire range of relevant values) yield an unbiased estimate of the true value [55]. In reality however, most biomarkers are less than ideal. The accuracy and precision of images and kinetic model parameter estimates from dynamic PET may be affected by a number of factors, such as [8, 27, 31, 49, 56–61]

1. Physical aspects

   (a) Radioactive decay. The primary source of noise is the inherent random nature of radioactive decay, leading to variations in the number of detected photons that make up a PET image.

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\[ \text{QIBA: } \url{http://www.rsna.org/QIBA.aspx} \]
2.2 Errors and uncertainties

(b) Measurement noise. As always, the camera detectors, electronics and recorder system contribute to the measurement noise.

2. Biology and physiology

(a) Patient size. Larger patients equates to more attenuation, more scattered coincidences and possibly more truncation artifacts that all affect the image quality.

(b) Lesion size. Partial volume effects are considerable as the lesion size approaches the scanner resolution, causing an underestimation in lesion uptake.

(c) Tumor heterogeneity. Widely heterogeneous tissue leads to large variations within the ROI (higher noise) and necrotic/fibrotic tissue results in an underestimated uptake.

(d) Assay data. E.g. blood glucose level greatly affects the uptake of $^{18}$F-FDG.

3. Image acquisition and analysis

(a) Injected activity. Low activity means poorer counting statistics and increased image noise.

(b) Time after injection. Depending on the tracer, the uptake may increase or decrease with time after injection.

(c) Frame sampling interval relative to tracer metabolism. Coarse frame sampling can introduce biases whereas short frames have limited counting statistics and thus increased noise.

(d) Image reconstruction method, settings, corrections and postfiltering. Differences in reconstruction methods (e.g. analytical vs. iterative algorithms), and corrections (attenuation, random and scattered coincidences, detector uniformity, radioactive decay) affect the resulting images. Image smoothing lowers the image noise but increases the bias for small objects.

(e) ROI definition. Generally lower average uptake for larger ROIs, and more noise in smaller ROIs.

4. Arterial input function recovery
(a) **Blood sampling of the AIF.** The timestamp, volume and activity measurement of blood samples may be flawed, and venous blood samples may have different activity concentrations from the arterial blood.

(b) **Metabolite measurement/estimation.** Needed for e.g. FLT and acetate. Faulty measurement or estimation of metabolites translates to an error in the AIF, propagating to the parameter estimation.

(c) **AIF recovery method.** Blood sampling or image-based methods may differ, and image-based AIFs may suffer from partial volume effects.

5. Kinetic model fitting

(a) **Choice of kinetic model.** Selection of an inappropriate model to represent the tracer uptake and clearance pattern causes errors in model parameter estimates.

(b) **Starting parameters and ranges for model fitting.** Improper parameter starting values and allowed ranges can hinder the curve fitting optimization.

(c) **Fixed parameters.** Fixing some of the model parameters with subjectively selected values may not reflect the true biology.

(d) **Model fitting weights.** The selection of appropriate weights for each time-activity curve (TAC) point should be based on the true uncertainty of each point (Poisson statistics, frame duration, activity concentration etc.). In reality, they have to be estimated.

PET images are notoriously known for their poor image quality compared to CT or MR images, both in terms of image resolution and noise. For simplicity, the image noise is often considered to belong to a Poisson or Gaussian distribution. Even though the decay process can be described by Poisson statistics, the actual noise in reconstructed images is in fact often not a simple Poisson or Gaussian shape, especially when non-linear iterative image reconstruction methods are used, such as ordered subset expectation maximization (OSEM) [58, 62] (see Section 4.2.1 for more details). Moreover, the noise in
OSEM images is known to be object dependent, with higher noise in regions with high uptake compared to low uptake regions [58, 60]. With all possible sources of error and uncertainty, one can conclude that the true noise characteristics in a PET image is a complex matter.

PET image noise leads to quantitative inaccuracy that can cause both bias and uncertainty in measured entities such as SUV and kinetic parameters. In the paper by Kamasak [63], he investigated both Monte Carlo (MC) simulations and an analytical framework for the computation of variance in compartment model parameters from the 1- and 2-tissue models, in relation to the level of noise in the TACs. He found that for the 1-tissue model, the relative (relative to true parameter value) standard deviation (SD) at different noise levels reached up to around 3% and 6% for $K_1$ and $k_2$, respectively. For the 2-tissue model, it reached as high as around 15%, 41%, 26%, 15%, and 23% for $K_1$, $k_2$, $k_3$, $k_4$, and $K_i$, respectively. Additionally, he found the bias to be small, within 0.2% of the true parameter values for the 1-tissue model and within 2% for the 2-tissue model. Note that these results were obtained by direct simulation of TACs with added Gaussian noise distributions and that specific causes of bias and uncertainty were not considered.

Muzi et al. [64] studied 2-tissue kinetic modeling of somatic tumors with $^{18}$F-FLT from a mathematical perspective. They used a fitted AIF based on clinical data, and from that calculated a range of response functions with added Poisson noise. The authors concluded that the flux $K_{FLT}$ (denoted $K_i$ in this thesis) and uptake rate $K_1$ are reliable with bias and standard errors $<15\%$ for a realistic noise level and range of parameter values. They also found it difficult to get reliable estimates of $k_2$ and $k_3$ independently, and overall difficult to estimate $k_4$.

Niemi et al. [57] developed a model for estimation of 2-tissue compartment model parameters and their variances from noisy and heterogeneous PET data. Their model included a Poisson term for the radioactive decay process noise and a Gaussian term for the instrument measurement noise. Furthermore, the authors assumed the model rate constants to vary randomly around some mean value to reflect tissue heterogeneity.

In a study by Cheng and Yetik [65], they investigated how errors in the AIF
propagate to the estimates of 2-tissue model parameters, based on direct TAC simulations with added Gaussian noise. The results showed that parameter $K_1$ was sensitive to AIF errors over the whole range of the dynamic acquisition, $K_1$ and $k_3$ were sensitive to errors in the early blood peak, and errors in the AIF tail affected mostly $k_3$ and $k_4$.

Most studies regarding errors and uncertainties in kinetic parameter estimates are based on assumed noise distributions of a Gaussian or Poisson shape. Although these assumptions are often “close enough” to yield decent results, they are still rather crude approximations. Some applications are best studied without too many simplifications, and thus require more sophisticated methods.

In paper II and paper III, our aim was to shed some light on possible sources of bias and uncertainty in kinetic parameters from the 2-tissue model, using full MC simulations. In the interest of the topics of these two papers, a few of the items listed as factors affecting the accuracy and precision of kinetic model parameters will be described in more detail in the following paragraphs.

2.2.1 Scattered coincidences and their correction

In paper II we looked at the effect of scattered coincidences and their correction on 2-tissue model parameter biases and uncertainties.

Cherry et al. [66] used $^{18}$F-FDG (2-tissue model) and $^{15}$O-water (1-tissue model) brain simulations, and investigated the effect of scatter on MR$_{glu}$ and the cerebral blood flow (CBF). They assumed a low frequency Gaussian distribution of scattered coincidences, and simulated TACs with added scatter profiles. The results showed that $k_2$, $k_3$, and $k_4$ were relatively insensitive to scatter, unlike $K_1$ and $K$ (denoted $K_i$ in this thesis) where the error increased linearly with the scatter fraction. They concluded that scatter correction was necessary for quantitative estimation of CBF and MR$_{glu}$.

In a $^{18}$F-FMISO animal study, Wang et al. [67] investigated the impact of attenuation and scatter corrections in tumor hypoxia-related kinetic parameters from the 2-tissue model. The authors simulated four-dimensional (4D) PET sinograms, where the scatter distribution was estimated by the single scatter simulation (SSS) algorithm. The authors found that the corrections
decreased the relative bias in $K_i$ by roughly 4 percentage points.

In a MC cardiac $^{15}$O-water PET study of quantitative myocardial blood flow (MBF) and perfusible tissue fraction (PTF), Hirano et al. \cite{68} concluded that MBF was less sensitive to scattered coincidences (and their correction), whereas corrections were essential for accurate PTF estimations. They used the conventional 1-tissue model according to $C_{PET} = PTF \cdot MBF \cdot C_a \otimes e^{-MBF \cdot t/p}$ with $p = 0.91$ (compare with Eq. (5.2)).

Based on the results of paper II, we concluded that scatter correction was necessary for most parameter estimates, however not needed (statistically significant) for $k_3$ and $K_i$ estimation. Furthermore, neither of the two scatter correction methods we used introduced any extra bias. In addition, we found a slight favor for using three-dimensional (3D) filtered back-projection with reprojection (3DRP) compared to OSEM in terms of parameter bias and uncertainty.

### 2.2.2 Frame sampling

As mentioned previously, the frame sampling is one factor affecting bias and uncertainty in kinetic parameter estimates. The focus of paper III was to investigate how the early frame sampling (frame duration) around the blood peak affects the errors in kinetic parameters from the 2-tissue model.

There are many early studies regarding optimal sampling schedule \cite{69–73}. These studies are mainly focused on sampling of blood assay data or reducing the computational time and storage space of dynamic PET images, however, rather than investigating a certain frame sampling scheme with associated errors. Raylman et al. \cite{74} investigated 1-tissue model parameters from dynamic PET cardiac imaging with the early frames sampled between 5 and 60 s. They found that the first 100 s of the dynamic acquisition have to be sampled at 5 or 10 s in order to obtain an acceptable level of bias in $K_1$ and $k_2$. In the study by Jovkar et al. \cite{75}, the authors studied schemes with the first three minutes of the acquisition sampled at combinations of 10, 30 and 60 s. They concluded that 2-tissue model parameter estimates had a decreasing uncertainty with decreasing sampling interval. These studies only looked at frame durations down to (occasionally) 5 s however, and used
simplified simulations where they directly simulated TACs with added Gaussian or Poisson noise profiles.

In paper III, we used full MC simulations of the whole PET camera, a voxelized head phantom and complete image reconstructions of early (first two minutes) frame samplings of 1, 2, 4, 6, 10, and 15 s. We found that very short early frames of 1 s yielded the largest biases and uncertainties in parameters $K_1$ and $k_2$, and concluded that such short samplings should be avoided. An early frame sampling of 6–15 s yielded overall minimal bias and uncertainty. Both parameters $k_3$ and $K_i$ were found statistically independent of sampling due to uncertainties, even though the bias was largest for the 1 s sampling for these parameters as well. Furthermore, OSEM reconstructions of short frames (low count) appeared to have spotty artifacts, not seen in 3DRP images. Additionally, OSEM yielded more uncertain parameter estimates compared to 3DRP. We also found that the choice of model fitting weight factors played a large role in which reconstruction method resulted in the best parameter estimates, since some weights favored 3DRP while another favored OSEM.

2.2.3 Analytical versus iterative reconstruction for kinetic modeling

In the studies by Boellaard et al. [60] and Reilhac et al. [61], the authors found that the analytical reconstruction method filtered back-projection (FBP) was more consistently accurate for dynamic PET measurements and kinetic modeling, compared to maximum likelihood expectation maximization (ML-EM)-based iterative methods. These results are strengthened by our results in both paper II and paper III, where we found OSEM images to produce more uncertain, more frame sampling dependent and often more biased kinetic parameter estimates than 3DRP images. Herranz et al. [76] investigated the quantification limits of iterative reconstruction methods in regards to kinetic parameters, and also found that for normal fitting procedures, FBP outperformed OSEM. However, when including the estimated systematic deviation from true values (bias) in the fitting procedure, OSEM images could produce as accurate kinetic parameter estimates as FBP.
Principles of PET

Positron emission tomography enables non-invasive visualization and quantification of biological and physiological processes within the body. The core of PET is the imaging of a radiolabeled tracer, injected into a patient or phantom. The radioisotope bound to the tracer molecule should be a short lived positron emitter, and isotopes of fluorine, carbon, gallium, and oxygen are commonly used. As the nuclide decays, the emitted positron recombines with an electron and they annihilate, creating two annihilation photons. The PET camera is designed to detect these photons, and by applying mathematical methods to the registered data, PET images of the uptake distribution (annihilation sites) can be obtained.

3.1 Tracers

The aim of PET is to image physiological functions of particular interest, such as metabolic processes, blood flow, transport steps, receptor binding processes etc. Examples are the glucose metabolism for tumor imaging in oncology, dopamine system functionality in neurology, and myocardial viability in cardiology to mention a few.

Depending on the desired target of the imaging, a suitable molecule is chosen as the tracer. The most commonly used PET tracer by far is the
3 Principles of PET

glucose analogue $^{18}$F-FDG, marking the uptake and metabolism of glucose in tissue [77]. Its main use is for tumor imaging in the field of oncology. Other tracers are also useful in this field, and some common PET tracers and their clinical applications are found in Table 3.1.

**Table 3.1.** Different PET tracers and their clinical applications in oncology.

<table>
<thead>
<tr>
<th>Biologic process</th>
<th>Tracer</th>
<th>Cancer</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose metabolism</td>
<td>$^{18}$F-FDG</td>
<td>Breast, Cervix, Colorectal, Esophagus, Head and neck, Lung, Lymphoma, Melanoma, Sarcoma</td>
<td>[9] [78] [79] [80] [30] [13]</td>
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<tr>
<td>Cell proliferation</td>
<td>$^{18}$F-FLT</td>
<td>Breast, Lung, Lymphoma, Rectal, Sarcoma</td>
<td>[81] [82] [83] [79] [80] [13] [84]</td>
</tr>
<tr>
<td>Lipid metabolism</td>
<td>$^{11}$C-choline</td>
<td>Brain, Breast, Lung, Prostate, Bone</td>
<td>[9] [81] [79] [85] [13]</td>
</tr>
<tr>
<td></td>
<td>$^{18}$F-choline</td>
<td>Brain, Liver, Prostate</td>
<td>[79] [85] [83] [80] [25]</td>
</tr>
<tr>
<td>Bone metabolism</td>
<td>$^{18}$F-fluoride</td>
<td>Bone</td>
<td>[83] [80]</td>
</tr>
<tr>
<td>Lipid metabolism, oxygen consumption</td>
<td>$^{11}$C-acetate</td>
<td>Liver, Prostate</td>
<td>[9] [81] [79] [13]</td>
</tr>
</tbody>
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### Table 3.1. – Continued from previous page

<table>
<thead>
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<th>Tracer</th>
<th>Cancer</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
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<td>Hypoxia</td>
<td>$^{18}$F-FMISO</td>
<td>Brain</td>
<td>[9] [81] [82]</td>
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<tr>
<td></td>
<td></td>
<td>Head and neck</td>
<td>[83] [79] [80]</td>
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<tr>
<td></td>
<td>$^{65}$Cu-ATSM</td>
<td>Cervical</td>
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<td></td>
<td></td>
<td>Lung</td>
<td>[79] [80]</td>
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<td></td>
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<td>Rectal</td>
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<tr>
<td></td>
<td>$^{18}$F-octreotide</td>
<td>Neuroendocrine</td>
<td>[9]</td>
</tr>
<tr>
<td></td>
<td>$^{68}$Ga-octreotide</td>
<td>Neuroendocrine</td>
<td>[9] [80]</td>
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<td></td>
<td></td>
<td>Thyroid</td>
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<tr>
<td></td>
<td>$^{68}$Ga-DOTATOC</td>
<td>CNS</td>
<td>[79] [80] [85]</td>
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<td>Neuroendocrine</td>
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<td>$^{68}$Ga-DOTATATE</td>
<td>Neuroendocrine</td>
<td>[79] [80]</td>
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<tr>
<td>Somatostatin receptors</td>
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<tr>
<td>Dopamine</td>
<td>$^{18}$F-FDOPA</td>
<td>Neuroendocrine</td>
<td>[81] [83] [13]</td>
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<tr>
<td>Perfusion, blood flow</td>
<td>$^{15}$O-water</td>
<td>Brain</td>
<td>[9] [80]</td>
</tr>
<tr>
<td>Amino acid transport and metabolism</td>
<td>$^{18}$F-FET</td>
<td>Brain</td>
<td>[83] [79] [80]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Head and neck</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$^{11}$C-methionine</td>
<td>Brain</td>
<td>[9] [81] [79]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CNS</td>
<td>[80] [13]</td>
</tr>
<tr>
<td></td>
<td>$^{11}$C-tyrosine</td>
<td>Brain</td>
<td>[9] [80]</td>
</tr>
<tr>
<td>Androgen</td>
<td>$^{18}$F-FDHT</td>
<td>Prostate</td>
<td>[84] [15] [85]</td>
</tr>
<tr>
<td>Estrogen</td>
<td>$^{18}$F-FES</td>
<td>Breast</td>
<td>[9] [82] [84]</td>
</tr>
<tr>
<td>HER2 growth factor</td>
<td>$^{68}$Ga-Fab2’ herceptin</td>
<td>Breast</td>
<td>[84] [15]</td>
</tr>
<tr>
<td>$\alpha_v\beta_3$ integrin binding (angiogenesis, metastasis, proliferation)</td>
<td>$^{18}$F-RGD peptides</td>
<td>Bone</td>
<td>[9] [79] [80]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Breast</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Colon</td>
<td>[85] [13]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Head and neck</td>
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<tr>
<td></td>
<td></td>
<td>Melanoma</td>
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<tr>
<td></td>
<td></td>
<td>Sarcoma</td>
<td></td>
</tr>
</tbody>
</table>

The amount of tracer injected to a patient is commonly on the order of a few pmol, and for $^{18}$F-FDG in actively metabolic tumors this leads to concentra-
3 Principles of PET

tions of around $10^{-15}–10^{-12}$ mol/liter. PET is a highly sensitive modality able to detect these tiny, non-pharmacological concentrations, enabling the observation of biological processes without disturbing or affecting them [5, 9, 13].

3.2 Positron emission

If an atomic nucleus has an excess of protons it is unstable and subject to radioactive decay. Radioactive decay is a spontaneous, random process, and the exact moment of decay of a certain nucleus cannot be predicted [86].

For large proton-rich nuclei, the main form of decay is via positron emission, where one atomic proton ($p^+$) decays into a positron ($\beta^+$), and a neutron ($n^0$) according to [7]:

$$p^+ \rightarrow n^0 + \beta^+ + \nu^0 + \text{energy}, \quad (3.1)$$

where $\nu^0$ is a neutrino, balancing the energy, momentum and angular momentum of the initial and final state. For a nuclide, this results in an unaltered mass number $A$ but a change in atomic number $Z$, meaning a conversion to a new nuclide [86]:

$$A \underbrace{Z X \rightarrow_{Z-1} A}_{Z-1} Y + \beta^+ + \nu^0 + \text{energy}. \quad (3.2)$$

Proton-rich nuclei can also decay through electron capture, which is the primary mode of decay if the energy difference between the parent and daughter nuclide is less than the combined mass-energy equivalent of an electron and a positron, $2 \times 0.511 \text{ MeV} = 1.022 \text{ MeV}$ [7].

3.2.1 Positron range

The energy released in the decay process in Eq. (3.2) is called the transition energy [86]. The mass of the parent nuclide to the left of the arrow in Eq. (3.2) will exceed the total mass of all products to the right, and the difference in mass will be converted to energy to share between the daughter products. Most of the released energy is imparted as kinetic energy to the emitted particles ($\beta^+$ and $\nu^0$) or converted to photons, and a tiny portion is transferred to the
3.3 Annihilation

Figure 3.1. A nucleus decays by emitting a positron $\beta^+$. The positron travels a short distance, while loosing its kinetic energy in collisions with atoms in the surrounding medium. Finally, it recombines (annihilates) with an electron $e^-$, forming two opposite annihilation photons $\gamma$.

daughter nucleus ($^{A}_{Z-1}Y$) as kinetic energy [86].

The created positron will be ejected from the decaying nucleus with the obtained kinetic energy. Passing through the surrounding medium (tissue), the positron will collide and interact with the atoms of the tissue, and in doing so lose its kinetic energy. After a short distance the positron will have lost all of its energy and come to a full stop, depicted in Figure 3.1. The maximum distance traveled, or maximum range, depends on the initial energy of the positron, and in body tissue it is around 2.4 mm for $^{18}$F-positrons [86, 87].

3.3 Annihilation

The positron is an elementary particle of the same mass and equal but opposite charge as the electron. An electron and a positron thus form a matter – anti-matter pair. The recombination of matter and anti-matter is referred to as an annihilation event (see Figure 3.1).

A positron emitted from a decaying nucleus is free to travel in the surrounding medium (tissue), and while doing so lose kinetic energy by collisions and interactions with tissue atoms. Eventually, usually after only a few millimeters from the decay site, the positron has lost essentially all of its energy and comes to rest. At this point, the annihilation of the positron and a nearby electron takes place and their masses are converted into energy. The result is two opposite 511 keV annihilation photons, separated by 180° [86].
3 Principles of PET

Figure 3.2. Annihilation non-collinearity as a result of the positron not being fully at rest upon recombination. The annihilation of a non-stationary electron $e^{-}$ and positron $\beta^{+}$ creates two photons $\gamma$ that are not ejected in completely opposite directions, but are separated by an angle $180^\circ \pm \alpha$.

3.3.1 Non-collinearity

The $180^\circ$ separation - referred to as back-to-back emission - between the annihilation photons is required to conserve the energy and momentum of the converted electron-positron pair [86]. However, this is valid only when the two particles are stationary. In reality, the positron may not have come to a complete stop before annihilation, and as the orbital electron is also moving, the resulting energy is slightly above 1.022 MeV. This excess causes the annihilation photons to be emitted in almost opposite directions, usually off by a small fraction of a degree, depicted in Figure 3.2. This effect is known as annihilation non-collinearity or acollinearity.

3.4 Photon attenuation

After creation in the annihilation event, the two annihilation photons travel in opposite directions. They will each pass through the patient or phantom medium, before reaching the camera detectors. Different interactions between the photon and surrounding medium take place with different probabilities depending on the properties of the medium (e.g. density) and the energy of the photons. Thus, every medium has a certain ability to stop, or attenuate, photons passing through it, and this ability is summarized in the materials linear attenuation coefficient $\mu$. For a photon passing a distance $d$ through a medium with linear attenuation coefficient $\mu$, the attenuation is described by [87]

$$N = N_0 e^{-\mu d}, \quad (3.3)$$

28
where \( N_0 \) is the initial number of photons entering the medium and \( N \) is the number that successfully passed through \((N \leq N_0)\). Typically, the attenuating medium consists of several different materials with different attenuation coefficients. For \( m \) materials, Eq. (3.3) is then adjusted according to

\[
N = N_0 e^{-\mu_1 d_2} e^{-\mu_2 d_2} \cdots e^{-\mu_m d_m} = N_0 e^{-\alpha}, \quad \text{where } \alpha = \sum_{i=1}^{m} \mu_i d_i. \quad (3.4)
\]

### 3.5 PET camera design

Historically there were dedicated PET cameras available, but virtually all modern cameras will have PET combined with an anatomical imaging modality, the most common one being CT, forming a PET/CT camera. In later years, PET/MR has also evolved as an integrated technique. The design concept is to obtain functional information from PET while complimenting with anatomical and attenuation information from the CT (or MR).

Generally, a PET camera is composed of detector blocks arranged in a circle, thus forming a cylinder of detector elements. This design is often referred to as a multi-ring design since the many detector arrays result in the camera having multiple, adjacent rings of detectors. Typically, each block contains around 8×8 crystal detectors and the total camera around 16-24 detector rings [7, 88]. The transaxial field of view (FOV) is commonly up to 70 cm in diameter and the axial FOV is usually 15–22 cm [89]. Arrays of photo-multiplier tubes (PMTs) are connected to the back of the crystals to register and amplify the detector signals. An 8×8 crystal array is typically covered by four PMTs [90]. A schematic drawing of a PET camera is depicted in Figure 3.3. A PET scan is usually performed in 15–90 minutes, depending on the tracer, part of the body to be scanned, static vs. dynamic acquisition and so on.

The detector elements are scintillation crystals, usually made from cerium-doped lutentium oxyorthosilicate (LSO), cerium-doped lutentium yttrium oxyorthosilicate (LYSO), bismuth germanate (BGO), cerium-doped yttrium oxyorthosilicate (YSO), cerium-doped gadolinium oxyorthosilicate (GSO), and the more uncommon thallium-doped sodium iodide (NaI(Tl)) or barium fluo-
Figure 3.3. Schematic view of the PET camera. The two annihilation photons $\gamma$ are detected by two opposite detector elements. The imaginary line connecting the two detectors is called the line of response. The detector signals are then processed and subsequently reconstructed into images.

ride (BaF$_2$) [7, 89]. There are other materials as well, commonly derivatives of the above mentioned crystals however. The scintillator materials should ideally combine high light output with fast timing properties and a high stopping power for 511 keV photons [89].

3.5.1 PET/CT and PET/MR

It is outside the scope of this thesis to go into much detail about the CT or MR technologies. A more extensive explanation about PET/MR is however included, due to the high interest in this new technology, and its potential in dynamic and functional imaging.

Today, almost all PET cameras are hybrid PET/CT cameras. The functional information is obtained through the PET scan, and additional anatomical information is obtained via the CT. The anatomical information supplied by
the CT is used for diagnostic purposes and for image fusions that aid the radiologist in PET image evaluation. It also provides information about the photon attenuation and hence serve as a base for attenuation correction [7, 89]. Oncology is the main indication for a PET/CT scan today, and the technique is a highly important cancer imaging modality [91].

The PET/CT technique has limitations however, mainly the poor soft-tissue contrast, the inability to perform the PET and CT study simultaneously and the extra radiation dose induced from the CT [92]. In recent years, PET/MR has also entered the stage. Here, the very high detection sensitivity of functional PET imaging is combined with the excellent soft-tissue contrast morphological (and functional) information from MRI [91, 92]. In addition, the absence of ionizing radiation coupled with the flexible scan possibilities and potential of functional imaging in MRI, makes PET/MR preferable over PET/CT in some instances [92]. The information obtained from the two modalities PET and MR is rarely redundant but instead highly complementary, making this new technique a potential gold mine when it comes to in vivo studies of pathology and biochemical processes [92]. Furthermore, PET images typically suffer from heavy motion blurring effects due to long acquisition times (relative e.g. cardiac motion and breathing). Since PET and MR can be obtained simultaneously in PET/MR, there is a great potential for utilizing the high resolution MR images for effective motion correction of the PET images [93].

Challenges with an integrated PET/MR system include [91–94]

1. PMTs are used in conventional PET detectors, and are highly sensitive to magnetic fields.

2. One major difficulty with PET/MR is the attenuation correction, since MR - contrary to CT - images are not proportional to the photon attenuation in the different tissues. The additional hardware present in the FOV, such as MR head or body coils, also have to be included in the attenuation maps.

3. Typical MR sequences cannot differentiate bone and air since neither of them provide any MR signal. Since the difference in photon attenuation between bone and air is very large, this issue has to be addressed properly for attenuation correction.
4. MR usually has a limited transaxial FOV, smaller than that of PET. This causes truncation of e.g. the patients arms in MR body images, and is a more serious problem the larger the patient is. For proper attenuation correction of the PET images however, this problem has to be taken care of.

There are different attempts to solve the listed difficulties. One solution to the magnetic field sensitivity of PMTs is the use of optical fibers to lead scintillation light outside the strong magnetic field. Completely replacing the PMTs with magnetic field insensitive avalanche photodiodes (APDs), or the faster silicon photo-multipliers (SiPMs) are however more recent developments [91, 93, 94].

There are many algorithms and methods for performing PET attenuation correction based on MR images. Without going into detail about specifics, common methods include the use of ultra-short echo time MR sequences to enable imaging of bone, or atlas-based methods where an attenuation map template is morphed to fit the actual patient [91, 93, 94].

To account for the truncated MR images, one approach is to use the body contour in PET to complete the MR images, or to measure the magnetic- and gradient field non-linearities and compensate for truncations by an optimization algorithm [93].

The difficulties associated with PET/MR are not completely solved however, and there is much ongoing research in new technical solutions, reconstruction and correction methods. There will certainly be a lot of updates and improvements in PET/MR sequences and correction algorithms during the coming years.

Oncological applications of PET/MR

There is a long and rich experience in oncology with PET/CT, and the benefits of the combined modality are irrefutable. With the coming of PET/MR, new aspects within the field are now being acknowledged more extensively.

Considering the reduced dose aspect contra PET/CT, PET/MR is a valuable alternative when low dose is especially important, in e.g. pediatric oncology or when multiple scans are performed on single patients, such as longitudinal follow-up studies or for treatment response monitoring [93, 94].
3.6 Coincidences

Furthermore, for regions of the body where high soft-tissue contrast is extra relevant, PET/MR is potentially highly beneficial. One example is the head and neck area, where MR is superior to CT when it comes to staging of the tumor extent, and evaluation of the nodal plus soft-tissue structure involvement [94]. The same goes for pelvic malignancies (prostatic, gynecological and rectal cancers), where MR is preferred over CT [94]. Other cancers include breast, soft-tissue sarcomas, and parenchymal abdominal cancer [91].

Some MRI studies are performed dynamically (e.g. DCE-MRI), allowing the imaging of e.g. tumor vascularity which is central in angiogenesis-targeted chemotherapy [94]. Tumor hypoxia is another field that might profit from dynamic PET/MR [91].

PET/MR has a great potential to aid the evaluation of tumor treatment response, not only by assessing tumor volume shrinkage but also to follow changes in relevant biomarkers [94].

3.6 Coincidences

The desired data to be recorded by the camera system are detector hits of annihilation photons traveling straight from the site of annihilation to a detector element. The time and energy of each hit is recorded by the electronics system. Two main aspects of the electronics system are the time and energy windows [7]. User settings as well as inherent electronics and detector properties determine the PET camera’s window widths. The time window is typically a few nanoseconds and the energy window around 350–650 keV [90]. The time window is set to allow both photons from the same annihilation to be registered, and is limited by the timing resolution of the scintillator detector crystals. The energy window is set to include all 511 keV photons while rejecting most photons that have undergone scattering, thus having lost much of their energy. The limited energy resolution of the detectors increases the energy window width.

Coincidences (or coincidence counts) are the essence of PET data. If two annihilation photons fall within the energy window and are detected within the time window they form a coincidence count for the imaginary line connecting the two detector elements, known as the line of response (LOR). Convention-
ally, the annihilation event is known to have happened anywhere along the LOR, not known precisely where however. The newer scintillator crystals (e.g. LYSO) have faster timing properties (increased timing resolution) than the old standards (e.g. BGO), allowing time of flight (TOF) information to be stored. A TOF PET camera uses the tiny difference in arrival time of the two coincidence photons to locate more precisely where along the LOR the annihilation event occurred (still not exactly where however).

For most annihilations, one or both photons will never hit a detector or be paired into a coincidence. Single detector hits without any detected partner are thus referred to as singles. A PET scanner will typically pair between 1% and 10% of singles into coincidences [7]. In two-dimensional (2D) PET, the rings of the camera are separated by septa that only allow coincidences within the same ring, a.k.a. direct LORs. In 3D PET however, the septa are removed or retracted allowing oblique LORs as well, thus increasing the sensitivity. In general, only around 0.5% of all annihilation photons that are emitted within the FOV are detected for 2D PET, with the number rising to roughly 3% for 3D PET [90].

The three main types of coincidences – true, scattered and random – are seen in Figure 3.4. There are also multiple coincidences where a registered photon can be paired with two or more other photons. Usually these events are discarded however. The total number of registered coincidences is referred to as the prompt coincidences, and is the sum of all true, scattered and random coincidences.

3.6.1 True coincidences

If both annihilation photons successfully reach opposite detector elements, without interacting with the patient or phantom material, and both fall within the allowed time and energy window, they form a true coincidence [7, 95]. The true coincidence countrate increases linearly with injected activity, and these counts represent good data and would ideally constitute all acquired coincidences [7, 95].
3.6 Coincidences

3.6.2 Scattered coincidences

If one or both of the detected photons making up a coincidence have undergone single or multiple scattering events, the coincidence is considered to be scattered [7, 95]. The scattering can occur both within the patient or phantom, and within the detector crystal. The scatter fraction (ratio of scattered to total coincidences) is typically around 15% for a 2D PET acquisition, but up to 50% or more for a full 3D acquisition [7]. During inelastic Compton scattering, the photon loses some of its energy and is thus redirected at an angle dependent on the initial energy of the photon. The scattered photon, even though having lost some energy, may still fall within the PET camera’s energy window. The net effect is a perceived LOR that differs from the true one where both photons travel straight. This causes an image degradation in the form of a haze that reduces image contrast, overestimates the activity inside the scattering medium and decreases quantitative accuracy [95].

The amount of scatter will vary depending on object size, attenuation, LOR acceptance angle, energy window width and the tracer distribution [7, 95]. The contribution of scattered coincidences to the total count increases with the density of the tissue and detectors, as well as the depth within the tissue. The effect is thus more prominent the larger the scattering medium is, and hence is a more serious problem for e.g. imaging of the pelvis or torso compared to the head. In addition, the image degradation is especially large for 3D as opposed to 2D PET where septa are in use [95]. Just like true coincidences,
the amount of scattered coincidences increases linearly with injected activity. The scatter to true fraction is thus independent of activity, and furthermore does not change with the time window width [95].

### 3.6.3 Random coincidences

A random coincidence is an “accidental” or “chance” coincidence where the two detected photons originate from different annihilations, and are thus uncorrelated. It is possible that two unrelated photons are registered by opposite detectors, within the allowed time (and energy) window, and thus are thought to originate from one and the same annihilation event [7, 95].

The amount of random coincidences is proportional to the square of the countrate (administered activity), meaning more possible random pairing of unrelated photons at higher countrates. In turn, this implies a higher random to true fraction at higher countrates. The number of random counts also increases with increasing width of the time- and energy windows [95].

### 3.7 Data storage

Raw PET data is acquired and stored in one of two ways [7, 86]:

1. **Sinogram-mode.** Detector hits are paired and sorted into coincidences directly, and stored in **sinograms**. The total counts recorded for one LOR at a perpendicular distance \( r \) from the camera center and at an angle \( \theta \), corresponds to the sum of all annihilation events along that line, i.e. the **line integral**. A schematic drawing is seen in Figure 3.5. The set of line integrals covering the whole camera (all possible \( r \)) is called a **projection profile**. An entire set of projection profiles around the camera, covering all angles \( \theta \), makes up the sinogram data matrix. Each time frame is recorded as a separate sinogram, implying that the frame lengths are decided pre-acquisition.

2. **List-mode.** The relevant information about each detector hit is stored in a sequential data stream called a **list-mode** data set. The detector hits may or may not have been paired as coincidences before storage, and the detector localization, time of detection and photon energy are
3.8 PET image quality

As mentioned in Chapter 2, PET images are of comparatively low quality compared to CT or MR images, both regarding spatial resolution and noise. Image degradation in the form of artifacts can appear in PET images from a number of sources [89]. The patient’s external motion as a result of coughing and twitching to name a few, as well as internal motion due to respiration,
bowl movement, cardiac movement etc., all cause image motion artifacts. In addition, CT images of large patients are typically truncated as the patients exceed the FOV, causing truncation artifacts in the attenuation corrected PET images. Metal implants also cause artifacts in the attenuation correction maps, propagating to the reconstructed PET images.

Furthermore, the PET image quality is largely dependent on reconstruction method. Analytical versus iterative reconstruction methods produce images with different noise characteristics and resolution. This will be discussed in more detail in Chapter 4.

### 3.8.1 Noise

Simply put, PET image noise is caused by the finite number of detected photons. The number of detected photons is in turn affected by the amount of injected activity, patient attenuation, scan duration, detector sensitivity and geometrical effects (solid angle subtended by the detector) [4]. Normally, in simple measurements such as planar scintigraphic imaging, the signal to noise ratio (SNR) in each image voxel is equal to $\sqrt{N}$, where $N$ is the number of recorded counts in that voxel [86]. In PET images however, the noise characteristics is more complicated since the obtained voxel values are a result of many computations involving several views (including basically all other image voxels), filtering operations, specific reconstruction algorithms and so on. The PET image SNR still depends on the total number of recorded counts, but with a more complicated relationship between individual pixels and the total counts [86].

### 3.8.2 Spatial resolution

There are several factors affecting the effective PET image spatial resolution. The major factor is usually the size of the detector elements, due to the limited solid angle coverage and inability to precisely determine the point of photon interaction within the crystal [96]. Additional factors include the positron range, annihilation non-collinearity, depth of photon penetration into detector crystals (depth of interaction), and the use of multiple crystals per PMT [4, 7, 96, 97]. Another important factor is the reconstruction method.
and postfilter used \([4, 7, 97]\). Most whole-body PET systems today have an intrinsic spatial resolution of 4–6 mm \([4, 5, 89, 97]\). However, lesions as small as 2–3 mm in size can normally be detected if the signal to background ratio is sufficiently high \([89, 97]\). The positron range and non-collinearity combine to a physical limit of the highest achievable resolution of about 2 mm for clinical PET cameras, and therefore crystals smaller than that simply would not be useful \([96]\). Modern, advanced cameras commonly utilize resolution enhancing algorithms within the iterative reconstruction methods, pushing the resolution up to around 2 mm \([17]\).

### 3.9 The partial volume effect

The partial volume effect (PVE) causes the signal measured by the PET camera (in extension the PET image voxel values), to be different from the actual, true value. The PVE is in reality the collective name of two distinct effects \([98]\). Firstly, the finite spatial resolution of the imaging system causes spillover between adjacent regions, where hotter regions spill out to colder surrounding regions (increasing the cold signal) while cold regions spill in to the hotter regions (lowering the hot signal), resulting in 3D blurring. Secondly, the limited image sampling (voxel size) does not exactly match the true contours of imaged objects, hence most voxels will contain different types of tissues and the measured voxel value will be the average of the different signals. The two effects are shown in Figure 3.6.

### 3.10 Standardized uptake value (SUV)

PET images are usually not only visually interpreted, but also quantitatively. The standardized uptake value, is a semi-quantitative measure of the tracer uptake relative to the injected activity and distribution within the patient \([7, 49]\). It doesn’t require a dynamic scan, and is thus the most commonly used measure in static PET imaging \([18, 99]\). It is commonly defined as

\[
SUV = \frac{C_{PET}}{A/W},
\]  

\(3.5\)
3 Principles of PET

![Diagram](image.png)

(a) The inherent resolution of the camera system causes a smearing of the measured activity distribution.

(b) The finite size of the reconstructed image voxels causes object edges to experience blurring.

Figure 3.6. The two aspects of the partial volume effect.

where $C_{PET}$ is the measured activity concentration in kBq/ml in an image ROI or voxel, $A$ the injected activity in MBq and $W$ the patient body weight in kg. One ml of tissue weighs approximately one gram, making the SUV a unitless measure. As the SUV is a measure of the distribution of the injected tracer, an SUV value of 1.0 corresponds to all of the injected tracer being evenly distributed in the entire body.

The SUV definition in Eq. (3.5) is the most common one, but instead of bodyweight $W$, the injected activity can also be normalized to e.g. body surface area, lean body mass or a combination of body weight and blood glucose level [99].

The %ID/g is very similar to the SUV, and under the assumption of 1 ml=1 g of tissue, it is simply equal to $C_{PET}/A$. 

40
Image reconstructions take PET raw data and produce 3D images, where each voxel is localized according to the anatomical position, and portrays the distribution of radiotracer inside the body. All reconstruction techniques assume some mathematical model to couple the measured PET sinogram data to the actual image. Thus, by inverting the mathematical model, one can reconstruct the image from the sinogram data [100].

There are two main branches of reconstruction methods: Analytical algorithms where the model can be inverted to find the image, and iterative algorithms where the model cannot be analytically inverted, and the image needs to be found iteratively [7, 86, 100]. Since it is outside the scope of this thesis, this chapter will not go into details regarding the different algorithms, but rather give a descriptive overview of them. Furthermore, 3D techniques will be focused on as 2D techniques have not been used in the works included in this thesis.

4.1 Analytical reconstruction

Analytical image reconstruction algorithms offer a direct mathematical solution of what the image looks like, given sinogram data. These algorithms simply
state that any point in the measured sinogram data matrix is the line integral (introduced in Section 3.7) over the corresponding LOR over the imaged object [7, 100]. In essence that means that the measured sinogram (projection data) is an expression of the radon transform of the original object (image), and that the image of the object can be reconstructed by taking the inverse radon transform of the sinogram [101].

Filtered back-projection is the cornerstone in tomographic 2D image reconstruction. The name stems from running a set of filtered projection profiles (sinograms) back over the image grid (back-projecting, i.e. taking the inverse radon transform), distributing the filtered profile counts over the image pixels in the projection path to obtain an estimate of the original image [86]. Due to the limited axial size of the PET camera however, there will be missing oblique line integrals and truncated projections. The 3D FBP algorithm is thus not optimal since it requires complete sampling of all projections in order not to result in severe image artifacts [88, 100]. In 3DRP, the oblique sinograms that are not measured are estimated to form a complete sampling set, thus overcoming the limitation of plain FBP [100, 102]. Normal 3D FBP is then performed on the complete data. 3DRP is considered the golden standard for analytic 3D reconstruction [88, 100, 101].

4.1.1 Rebinning methods

3D projection data can be manipulated, a.k.a. rebinned, to obtain 2D data (richer data compared to truly 2D data) consisting of only direct and no oblique LORs. This data can be reconstructed with an ordinary 2D method such as FBP. Rebinning methods speed up the reconstruction process by reducing the amount of data. The most popular algorithms include single slice rebinning (SSRB), multiple slice rebinning (MSRB), Fourier rebinning (FORE), and variations of the latter such as FOREX and FOREJ [101].

4.1.2 Pros and cons

The major advantages with analytic reconstruction algorithms is the speed and easy implementation [86]. In addition, due to the linear nature of the algorithm, the variance (noise) in the reconstructed images tends to be rather
4.2 Iterative reconstruction

**Figure 4.1.** Comparison of 3DRP and OSEM at different count statistics, from $4 \times 10^7$ true counts (1/1) down to roughly 1/500 of the counts.

uniform over the whole FOV [62, 103]. Furthermore, for linear reconstruction algorithms, the reconstructed image covariance (how individual image voxel intensities vary with the other voxels) and resolution can easily be characterized and calculated straightforwardly by the known statistical properties (Poisson) of the data and the system’s PSF [4, 7, 104].

Limitations however include the hallmark of FBP reconstructions, i.e. disturbing *streak artifacts*, especially bothersome for images with poor counting statistics [7, 86]. These are clearly seen in Figure 4.1, comparing 3DRP and OSEM reconstructions of different count statistics. In addition, FBP reconstructions are prone to major image artifacts if the object is incompletely imaged (defected detectors, limited FOV etc.). Finally, the nature of the FBP algorithm makes it impossible to include models for the camera system detection possibilities, statistical noise properties of the measured counts, physical aspects of the acquisition including scattered radiation and limited spatial resolution etc. [86].

### 4.2 Iterative reconstruction

Iterative reconstruction algorithms are a newer concept that allow the use of more complex and realistic models compared to the plain integral model used in analytical algorithms [100]. Simply put, this approach starts with an initial
guess of the image, typically set to a uniform distribution of ones or a unit cylinder. The estimated image is then successively improved by projecting and back-projecting the measured and estimated data between sinogram and image space [7, 101]. Each new iteration yields a new estimate of the true image, based on the previous guess.

The basis of these models is the system matrix, also called the sensitivity matrix, $A$ with elements $A_{i,j}$. For a radioactive decay occurring in voxel $j$, $A_{i,j}$ defines the probability of detection of that decay in LOR $i$. The inclusion of this matrix within the iterative loop incorporates the measurement system properties, but can also include statistical features regarding the data acquisition. Statistical iterative maximum likelihood algorithms are common, and the ML-EM [105] is the most used because of its relatively simple implementation [7, 100]. Unfortunately, the convergence rate of the ML-EM algorithm is slow, however. The OSEM [106] algorithm is an accelerated version of ML-EM. Instead of updating the image estimate once per iteration after going through all LORs of the sinogram, the image is updated $M$ times per iteration using only a subset of the sinogram. The LOR data is partitioned into $M$ disjoint subsets, resulting in a convergence speed-up by approximately a factor of $M$ [7, 100].

Finally, some algorithms incorporate constraints or a priori regularization or penalization. Constraints may include positivity conditions or tissue boundary information [101]. This subgroup of iterative reconstruction algorithms is called penalized or regularized algorithms, and Bayesian maximum a posteriori (MAP) algorithms belong to this group [101].

In summary, and as stated by Fessler [107], statistical iterative reconstruction methods require five components:

1. A finite parametrization of the positron annihilation distribution, i.e. its representation as a discrete image.
2. A system matrix that relates the unknown image to the expectation of each detector measurement.
3. A statistical model for how the detector measurements vary around their expectations.
4. An objective function that is to be maximized to find the image estimate.
4.2 Iterative reconstruction

Figure 4.2. Comparison of the distribution of voxel values in hot and background regions for 3DRP and OSEM reconstructions.

5. A numerical algorithm, typically iterative, for maximizing the objective function, including the initial estimate and a stopping criterion. For the iterative algorithms, each iteration takes the estimation closer and closer to the true image, i.e. the mean voxel value approaches the true value. After some number of iterations (depending on object shape, size, activity etc.), the mean voxel value has converged according to the optimization criteria. Additional iterations will not improve the mean voxel value, but will instead only increase the image noise [8]. Thus, over-iteration is possible where the most “desirable” image solution is not obtained due to noise. In practice, the iteration loop is usually stopped after a few iterations to keep the noise level down [8].

4.2.1 Pros and cons

Compared to analytical FBP reconstructions, ML-EM and OSEM images have reduced streak artifacts and a higher SNR in low uptake regions. The decreased noise in low uptake regions may be beneficial since it makes the body contour more visible and possibly increases the detection efficiency for low-contrast lesions, e.g. brain lesions in white matter [7, 103]. Overall, the noise characteristics are generally improved for iteratively reconstructed images [8], as seen in Figure 4.1. The exception seems to be very hot lesions however, where the SNR is typically not improved, and FBP images may in fact even have a higher SNR [103, 104] (see Figure 4.2). The system matrix
employed by these algorithms allow the inclusion of the system’s PSF model (taking into account the crystal penetration, inter-crystal scatter, annihilation non-collinearity, positron range etc.) and TOF information. This results in an increase in image resolution and improved noise properties [108].

One of the major drawbacks however is that noise and resolution properties are locally dependent of the imaged object. Maximum likelihood reconstructions have a slower convergence rate for low uptake regions compared to high uptake regions. As a result, the noise in the reconstructed image is roughly proportional to the image itself, thus having more noise in hot compared to cold areas [7, 60, 62, 103]. This can cause bias in the image uptake values in high contrast regions, and image-derived AIFs are often less accurate for OSEM compared to FBP images [60]. Furthermore, OSEM algorithms typically enforce a positivity constraint, preventing the update image to contain negative uptake values. The result is a positive bias in images from low statistics data [61, 109]. This effect will thus be more prominent for dynamic PET data with shorter frames with less counts, compared to static PET (Figure 4.1).

Since the iterative reconstruction algorithms are non-linear, the statistical properties and distributions of the images cannot easily be computed directly from the measured data [4, 7]. Covariance calculations are complex, and the PSF is object dependent, leading to non-uniform spatial resolution (especially for areas with large differences in the attenuation coefficient, e.g. in the chest) depending on the size and intensity of the imaged object [7, 104]. Finally, some studies suggest that despite improved image quality, OSEM may not result in superior parametric images compared to FBP, and may in fact be inferior especially regarding image-derived AIFs and low count data [60, 61, 110].

4.3 Corrections

As discussed in Chapter 2, PET is a quantitative imaging technique. This requires all physical, instrumental, and user defined factors that may deflect the measured voxel value from the true value, to be properly corrected for. Typically, corrections are incorporated into the sensitivity matrix used in the loop for iterative reconstruction algorithms, and used as precorrections (subtraction) for analytical algorithms. The main factors that affect the quanti-
4.3 Corrections

tativeness, and thus require corrections are listed below [7, 95]. See Chapter 3 for a refresher of the concepts.

1. **Photon attenuation.** To get one coincidence count, both annihilation photons have to travel though the patient/phantom medium and reach opposite detectors. The probability for detecting a coincidence thus depends on the combined path of both photons. The photon attenuation makes photons that have to travel far through dense material be more attenuated compared to photons that travel just a short distance through the material. The net effect is that central parts of uncorrected patient or phantom images will appear to have a lower tracer uptake compared to the contour, since photons originating from the center will be more attenuated. To correct for this, a transmission image (typically based on the CT) reflecting the attenuation $\mu$ for 511 keV photons (known as the $\mu$-map) is used to calculate the attenuation (Eq. (3.3)) for each LOR [7, 95]. The LOR is then corrected by the amount it was attenuated. This is the most important correction, and the results of omitting it is seen in Figure 4.3 (first column).

2. **Scattered coincidences.** As mentioned in Section 3.6.2, scattered coincidences increase the background signal, reducing the contrast and overestimate the activity inside the scattering medium. This can be seen in Figure 4.3 (fourth column), where true+scattered coincidences are reconstructed without scatter correction. Characteristics of the distribution of scattered coincidences include [7]

- LORs outside the patient/phantom contour must be due to scatter (assuming random coincidences have been subtracted).
- The scatter distribution contains mainly low spatial frequencies and is thus broad and relatively featureless.
- The recorded coincidences’ energy spectrum below the photopeak has a large contribution from scattered coincidences.
- Scattered coincidences falling within the photopeak have undergone single scattering.

Correction techniques include [7, 95] a) tail fitting approaches where a
simple polynomial or Gaussian function is fitted to the counts outside the object (only scatter) to estimate the scatter contribution within the object. The estimated scatter is then subtracted from the measured data. b) dual or multiple energy window methods where one or more additional energy windows (below or above and possibly partly overlapping the photopeak window) are applied. The counts from these windows are assumed to contain mostly scatter and are used to estimate the scatter contribution to the counts in the main photopeak window, and subsequently correct for it. c) convolution approaches where the scatter distribution is estimated by measurements of a line or point source placed at different positions in the FOV. The scatter-corrected sinogram data is found by deconvolving (deblurring) the measured data with the scatter data. d) simulation-based methods where the $\mu$-map (photon attenuation information, typically CT-based) of the object and activity distribution (initial uncorrected image) is used to model the scatter distribution. The modeling can be done analytically or numerically (e.g. MC techniques). Analytically, the Compton interaction model is used to estimate the scatter contribution to each LOR. For MC methods, the photon interactions are tracked within the patient/phantom as well as within the detector material. A tracked photon will have a certain
probability of interaction in each voxel it traverses. Simulation-based methods are very accurate, however most complex and time consuming, and do not take into account scatter from outside the source.

In both paper II and paper III, the the simulation-based SSS algorithm implemented in STIR was used [111–113]. Briefly, the steps of the algorithm are

(a) Correct the original (uncorrected) emission image for normalization and attenuation.

(b) Reconstruct the attenuation image (if not already available as an ideal \(\mu\)-map for e.g. MC simulated data).

(c) Create a tail mask of the region outside the object that will be used for scaling the scatter estimate.

(d) Reconstruct the emission image without any scatter correction.

(e) Create a subsampled sinogram template.

(f) Reconstruct a coarse attenuation image, alternatively subsample the full attenuation image.

(g) Estimate a subsampled scatter sinogram estimate using the implemented SSS algorithm.

(h) Upsample the scatter sinogram estimate and scale it using the tail mask.

(i) Iterate (d)–(h) again, but include the estimated scatter sinogram in (d) this time.

(j) Calculate the average of the two scatter sinogram estimates to obtain a final estimate.

3. Random coincidences. Random coincidences raise the background of PET images, causing a decrease in image contrast [7, 95]. The distribution of randoms tend to be rather uniform over the FOV, thus being a more serious problem for highly attenuating areas where the ratio true to random coincidences is lower [7]. The two major correction methods are [95] a) the use of a delayed time window, e.g. delayed by 50 ns. Events with a large timing separation (the corresponding
distance traveled for a photon larger than the camera size) that are paired to coincidences must be random and cannot come from the same annihilation. b) the $2\tau$ method where the random countrate is estimated from the singles countrate of the two detectors for each LOR.

4. **Normalization.** The individual detection efficiencies of the detector pairs (LORs) differ in PET. In turn, this results in non-uniform count detection and hence non-uniform PET images. The reasons for the variations include the physical diversity of individual detectors and the location of the crystals within the camera, geometric effects (location of LOR), together with variations in the gain of the PMTs [7, 95]. Normalization is required to remove these variations. The most common way to do this is by uniform exposure of all possible LORs with a 511 keV photon source (commonly $^{68}$Ge), and then calculating normalization factors for each detector pair by dividing the acquired individual counts by the average count for all LORs [7, 95].

5. **Detector dead-time.** Each step in the detection and recording of a detector hit requires a certain amount of time. The photon absorption in the crystal and subsequent scintillation (light production), the PMT response and finally the determination of the photon’s spatial position and energy, all build up the total detector dead-time. If the detector is hit again during this time, the signals may be superimposed, causing a larger signal. Also, the detector has a reset time in which the system cannot process any further events. This makes the ratio of measured to true countrate decrease as the countrate increases. To correct for this, the measured countrate as a function of increased injected activity is precompiled into a look-up table using a reference phantom [7, 95]. Any given countrate can then be corrected using the table.

6. **Partial volume effects.** Measured voxel values will be biased depending on the image spatial resolution and voxel size, size and shape of the underlying object (e.g. tumor), contrast between neighboring tissues, and measurement method (e.g. SUV$_{\text{mean}}$ vs. SUV$_{\text{max}}$) [98]. The effect is a loss of image resolution as voxel values appear smeared. To reduce the effect of PVEs, the imaging model (blurring effects) can be included
4.4 Direct reconstruction of parametric images

in the sensitivity matrix to improve the image spatial resolution (for iterative reconstruction algorithms, e.g. OSEM) [98]. Small structures will thus not be as affected by PVEs and measured voxel values will be less biased. The simplest partial volume correction method is to pre-calculate a recovery coefficient (RC, ratio of true to measured activity) as a function of object size and contrast (based on separate phantom measurements), and multiply the measured ROI values with the corresponding RC. The RCs between several structures (not only e.g. tumor and background) can also be found by convolving the ROI masks of all structures with the system PSF. Furthermore, the reconstructed images can be viewed as a convolution between the imaging system’s PSF and the true (unblurred) image, which can be retrieved by deconvolving the measured image with the system PSF. A similar approach involves using a CT or MR image as *a posteriori* information during reconstruction to compensate the measured image for PVEs [98].

4.4 Direct reconstruction of parametric images

Typically, activity images are reconstructed from sinogram data, resulting in one 3D image per frame. Kinetic model parameters (or parametric images) are then estimated by fitting the image-derived TACs to a specific compartment model. This methodology is the typical approach, and is used for the works in this thesis. For completeness however, a small paragraph about direct parametric image reconstruction is included.

The “indirect” approach of going from raw PET data → sinograms → reconstructed images → compartment model fitting → parametric images, reduces the SNR due to having to split the sinograms into individual frames [114]. The TAC in each voxel is subject to a high level of noise, making model fitting difficult [115, 116]. Furthermore, shortcomings in reconstructed data, such as streak artifacts or high noise, propagates to the resulting parametric images [21]. There are numerous algorithms available for cutting the image reconstruction step, thus going directly from raw PET data → sinograms → compartment model fitting → parametric images. A brief history of direct
reconstruction algorithms, dating back to 1984, can be found in the 2013 review by Wang et al. [115] and a more recent summary is found in Cheng et al. [21].

Direct reconstruction can help improve the parametric image quality to have a smaller standard deviation and a higher SNR, and lower bias compared to the indirect method [21, 114, 115]. Note however that direct reconstruction methods are typically not used due to the higher level of computational complexity, difficulty in evaluating the accuracy and precision of the estimated parameters and more difficult motion correction [114, 116].

4.5 STIR

Clinical PET data is normally reconstructed via the proprietary software coming with the scanner workstation. For MC simulated data however, a scanner may not be available, or it may be difficult to convert the data to the appropriate format and import it to the scanner workstation for reconstruction. Moreover, some research may require more control over the reconstruction process than available in the vendor reconstruction algorithms.

There are a number of software packages available for external image reconstruction [101, 117]. Examples are ASPIRE\textsuperscript{a}, NiftyRec\textsuperscript{b}, FIRST [118], TIRIUS\textsuperscript{c} and PRESTO [119]. For the MC data used in paper II, paper III, and paper IV, the Software for Tomographic Image Reconstruction (STIR\textsuperscript{d}) [117] was used. STIR is an open source C++ library for PET image reconstruction and processing in research, and it contains several classes and functions for 2- and 3D PET [117]. It dates back to the European Union funded PARA-PET project (1997-1999), and has since been updated and expanded, and is today one of the most widely known and used open source reconstruction packages [117].

\begin{footnotesize}
\begin{enumerate}
\item ASPIRE: \url{http://web.eecs.umich.edu/~fessler/aspire}
\item NiftyRec: \url{http://niftyrec.scienceontheweb.net/wordpress}
\item TIRIUS: \url{http://www.pages.usherbrooke.ca/jdleroux/Tirius/TiriusHome.html}
\item STIR: \url{http://stir.sourceforge.net}
\end{enumerate}
\end{footnotesize}
Tracer Kinetic Modeling

The tracers used in PET imaging are developed to target specific physiological parameters, such as metabolism, cell proliferation, blood flow or receptor ligand binding to mention a few. The collected data from a PET scan will comprise signal from all such parameters, so that the intensity value in each PET image element depends on the complete underlying physiology of the inspected region.

If one can isolate the signal from the physiological parameter of interest, there is a potential to gain a lot of additional information. The idea behind tracer kinetic modeling techniques is to do just that, by applying suited mathematical models to the dynamic PET data and in doing so extract numerical estimates of the parameters.

5.1 Compartmental modeling

The most common way to describe the uptake and clearance of PET tracers in tissue is via the mathematical framework of compartment models [7, 120]. In these models, it is stated that each administered tracer molecule will be delivered to a single compartment, where each compartment defines a specific state of the tracer, specifically its physical location and chemical state. The tracer
Figure 5.1. The a) 1- and b) 2-tissue compartment models comprising the time course of tracer concentration in arterial blood plasma ($C_a$), free + non-specific tracer in tissue ($C_{F+NS}$), specifically bound tracer in tissue ($C_S$), and the fraction of arterial blood appearing in the tissue ($V_a$). The rate constants ($K_1$, $k_2$, $k_3$, and $k_4$) describe the rate of tracer exchange between the compartments.

molecules move between the compartments (or states) at rates determined by the model rate constants (the fraction of tracer molecules that travel from one compartment to another per time unit, usually min$^{-1}$), typically denoted $k$. The time course of the tracer concentration $C(t)$, in the different compartments are key elements of the model. The time dependence of the concentrations is implicit and will from now on be written as $C$ instead of $C(t)$.

Examples of two of the simplest models, the 1- and 2-tissue compartment models, are seen in Figure 5.1. Here the consensus nomenclature for naming the compartments is used, according to Innis et al. [121] where $F$ denotes free, $NS$ non-specific, and $S$ specifically bound tracer in tissue. Free plus non-specific tracer in tissue is also known as non-displaced, ND. We used the 1-tissue model in paper I to describe the tracer exchange of $^{11}$C-acetate, and the 2-tissue model was used in paper II and paper III to describe $^{18}$F-FLT.

5.1.1 Input function

The amount of tracer in a given compartment at a given time (omitting physical decay) is governed by the rate of inflow and outflow of tracer to the
5.1 Compartmental modeling

compartments (the rate constants) and by the amount of tracer available. The tracer is injected into the blood stream and supplied to the tissue by the arterial plasma [7, 86]. The time-activity curve of tracer in the arterial blood is known as the *arterial input function* since it is considered a known input to the model rather than a result. As an input, it is commonly considered a noiseless TAC to be obtained through measurement prior to model fitting. The tissue TAC (TTAC) on the other hand is a result of the AIF combined with the model parameters, and is thus called the *response function* [86].

In order to estimate kinetic parameters from a given compartment model, one typically needs to know the AIF. There are three different approaches, depicted in Figure 5.2, to obtain this TAC [6, 8, 49]:

1. **Arterial blood sampling.** Arterial blood samples (typically 20–30) are quickly drawn from the patient at initially short timing intervals, growing longer as the PET scan progresses. The activity of the blood samples are rapidly measured by an external γ-counting system (usually

![Figure 5.2. The three different main methods to recover the AIF: (a) arterial blood sampling, (b) population-based methods, and (c) image-based methods.](image-url)
a well counter). This is the gold standard when it comes to recovering the AIF. Drawbacks with this approach is that it is invasive, time consuming, and laborious for clinical routine. Moreover, blood extraction can often be difficult in e.g. small animals (preclinical studies) or seriously ill patients that often are anemic [49, 65, 122]. Furthermore, some tracers such as \(^{18}\)F-FLT and \(^{11}\)C-acetate, quickly undergo significant metabolic degradation after injection [49, 122]. This causes radiolabeled metabolites to circulate the blood and thus contribute to the measured activity of a blood sample. However, the metabolites are often not taken up by the tissue and should hence not be included in the model AIF for parameter estimation. In order not to overestimate the AIF, the amount of metabolites has to be excluded. This is typically done by physically separating them from the blood plasma prior to activity measurement, or by estimating them by known distributions and subtract from the measured (contaminated) AIF [49]. Moreover, tracer injection at one site, followed by blood sampling from a peripheral site (typically the radial artery), does not produce the same shape AIF as that present far from the site of measurement, e.g. in the brain. The shape of the injected bolus will undergo smearing (dispersion) as it passes through the blood vessels [75, 123]. In addition, there will be a delay in the arrival time of the bolus between the blood sampling site and the imaged site of interest (e.g. brain) [123]. These effects have to be accounted for.

2. Population-based methods with scalable templates. Instead of drawing multiple arterial blood samples, the shape and height of the curve is estimated by historical data [49]. Since the AIF is often rather similar for same-category patients that are injected with the same radiotracer according to the same injection protocol, it can be standardized [8, 49, 122]. The arterial blood sample curves from many patients can thus be averaged into a single AIF template. For an individual patient, a few late blood samples is all that’s needed to properly calibrate the height of the AIF to match the current patient [49, 122]. One drawback with this approach is of course that individual characteristics are not considered, which can seriously affect the result for divergent pa-
tients. Furthermore, the peak position and height of the AIF can differ some between this approach and actual arterial blood sampling [122].

3. **Image-based methods.** If the heart or a large artery (e.g. the aorta) is in the FOV of the dynamic PET images, the AIF can be recovered from image ROIs, i.e. image-derived [49, 122]. This method is non-invasive and practically simple. However, due to the usually small size of the regions from where the AIF is derived, PVEs are considerable and have to be carefully corrected for [122]. Furthermore, for tracers that are metabolized during the scan, there is still a need to correct for labeled metabolites in the blood [122]. In addition, for the same reasoning as mentioned under “arterial blood sampling”, when using heart scans for AIF recovery and the imaged site of interest is far away (e.g. brain), one still needs to correct for the arrival time discrepancy and dispersion of the measured AIF compared to the AIF in the target of interest. Finally, AIFs derived from OSEM reconstructions may be biased (hence lead to incorrect kinetic parameter estimates), since small regions of high uptake on low background and vice versa are prone to bias in OSEM images [60].

For simplicity, the AIF is generally assumed to be the same for entire regions, e.g. the entire brain. The same AIF is thus used for model fitting of all ROIs in the region or all voxels in parametric imaging. Note that there are blind methods where the input function is not considered known, but is included in the model fitting algorithm to be estimated alongside the model parameters. Using these methods, the individual parameters can not be estimated in absolute terms however but only in relative ones. These methodologies will not be described further here however. See e.g. Cheng et al. [65] and included references for more information.

### 5.1.2 Rate equations

Leaving the realm of physiology and viewing the models with mathematical eyes, the flux of tracers between compartments is of interest. The sum of all tracer inflows minus the sum of all outflows defines the net flux into each compartment, in units of concentration $C$ per time unit (min$^{-1}$), or $\frac{dC}{dt}$. The
5 Tracer Kinetic Modeling

exception of unit is $K_1$ (ml g$^{-1}$ min$^{-1}$) which is defined as the volume of tracer taken up per gram of tissue per time unit.

For the 1-tissue compartment as shown in Figure 5.1a, the differential rate equation describing the flux into the tissue compartment, i.e. the change in concentration $C_{F+NS+S}$, is thus

$$\frac{dC_{F+NS+S}}{dt} = K_1 C_a - k_2 C_{F+NS+S}. \quad (5.1)$$

Note that no equation for the change in arterial blood concentration $C_a$ is stated. As mentioned previously in Section 5.1.1, $C_a$ is usually considered known and fixed.

When considering the 1-tissue model in Figure 5.1a, the TAC measured in a PET image, denoted $C_{1t}^{pet}$, will simply be the tissue concentration $C_{F+NS+S}$. Eq. (5.1) can be solved explicitly for $C_{F+NS+S}$, yielding [63]

$$C_{1t}^{pet} = C_{F+NS+S} = K_1 C_a \otimes e^{-k_2 t}, \quad (5.2)$$

where “$\otimes$” denotes temporal convolution.

Moving on to the the 2-tissue model depicted in Figure 5.1b, the tissue consists of two compartments, $C_{F+NS}$ and $C_S$, where $C_{F+NS}$ contains free and non-specific tracer and $C_S$ specifically bound tracer in tissue. The rate equations describing the flux of tracer concentration are

$$\frac{dC_{F+NS}}{dt} = K_1 C_a - (k_2 + k_3)C_{F+NS} + k_4 C_S, \quad (5.3)$$

$$\frac{dC_S}{dt} = k_3 C_{F+NS} - k_4 C_S.$$ 

The two tissue compartments cannot be distinguished by the PET camera, and the measured TAC, $C_{2t}^{pet}$, will be the sum of the two. The solution to the system of equations in Eq. (5.3) for $C_{2t}^{pet}$ is hence given by [124]

$$C_{2t}^{pet} = C_{F+NS} + C_S = \frac{K_1}{\alpha_1 - \alpha_2} \left\{ (\alpha_1 - k_3 - k_4)e^{-\alpha_1 t} \right. \right.$$ 

$$\left. \quad - \left( \alpha_2 - k_3 - k_4 \right)e^{-\alpha_2 t} \}\otimes C_a, \quad (5.4)$$

$58$
5.1 Compartmental modeling

where again “⊗” denotes temporal convolution and

$$\alpha_{1,2} = \frac{k_2 + k_3 + k_4 \pm \sqrt{(k_2 + k_3 + k_4)^2 - 4k_2k_4}}{2}. \quad (5.5)$$

The overall flux of tracer into the cells, known as the influx rate constant $K_i$ (ml g$^{-1}$ min$^{-1}$) or the metabolic flux constant, is a parameter that is often of clinical interest, and it is calculated as [35, 64]

$$K_i = \frac{K_1k_3}{k_2 + k_3}. \quad (5.6)$$

The glucose metabolic rate $MR_{glu}$ ($\mu$mol g$^{-1}$ min$^{-1}$) that can be used for $^{18}$F-FDG is closely related to the influx rate constant [8, 19, 31]

$$MR_{glu} = \frac{K_1k_3}{k_2 + k_3} \frac{c_{p,glu}}{LC} = K_i \frac{c_{p,glu}}{LC}, \quad (5.7)$$

where $c_{p,glu}$ (\mu mol ml$^{-1}$) is the plasma glucose concentration and $LC$ (unitless) the lumped constant defined as the ratio of extraction fraction of $^{18}$F-FDG to glucose under steady-state conditions. The glucose concentration $c_{p,glu}$ is approximately constant during a PET scan for a fasting patient, making $K_i$ and $MR_{glu}$ steadily proportional.

5.1.3 Spillover

The limited spatial resolution of the PET scanner and the finite voxel size of the reconstructed image cause the measured (image-derived) TTAC to be influenced by PVEs. Moreover, arterial blood from vessels nearby or within the volume of interest may contaminate the TTAC further. To account for these effects, a spillover term can be added, yielding [125]

$$C_{PET} = (1 - V_a)C_{pet}^{*t} + V_aC_a, \quad (5.8)$$

where $C_{PET}$ is the tissue activity concentration measured in a PET image ROI or voxel and $V_a$ (ml g$^{-1}$) is the volume of arterial blood appearing in tissue per
gram of tissue. Note that Eq. (5.8) is valid for $C_{\text{pet}}^*$ according to both the 1- and 2-tissue model, represented by Eqs. (5.2) and (5.4), respectively.

### 5.2 Model fitting and parameter estimation

As stated in the introduction of this chapter, the aim of compartment modeling is to numerically estimate the parameters composing the chosen model. The model response $C_{\text{PET}}$ does not have a closed-form solution based on the input $C_a$ and model, hence the parameters have to be estimated by applying an initial guess of their value and iterating the estimation until some stopping criteria is met. Since the dependence of response to input and model parameters is non-linear, the problem is commonly solved by applying a non-linear least squares (NLS) fitting procedure $[8, 120]$. The best estimation of the model parameters is found by minimizing the residual sum of squares (RSS) based on the difference between the measured curve ($C_{\text{PET}}$) and the response curve calculated from estimated parameters $[126–128]$

$$RSS = \sum_i (F_i - C_{\text{PET},i})^2,$$

(5.9)

where $i$ denotes the $i$th time point and $F$ is the calculated response curve.

#### 5.2.1 Weighting

The NLS fitting procedure assumes all data points to have an equal statistical uncertainty. Hence, all points are given an equal weight when fitting. For TACs there are a number of factors that can affect the reliability of each data point (i.e. ROI or voxel value of a certain frame), such as the duration of that frame, time after injection, tracer uptake and so on. To find the truly optimal estimation of the model parameters according to Eq. (5.9), this has to be considered. In dynamic PET, weighted NLS (WNLS) is thus a more suitable procedure than plain NLS $[63, 128, 129]$. Eq. (5.9) is then modified to the weighted RSS

$$WRSS = \sum_i w_i (F_i - C_{\text{PET},i})^2.$$

(5.10)
The weight should be proportional to the inverse of the variance of the TAC value, but since the true variance of a given TAC point is most often unknown, it has to be estimated. Common weights to apply to the $i^{th}$ frame are [126, 127]

$$w_i = d_i e^{-\lambda t_i}, \quad (5.11)$$

or, when including the tracer concentration

$$w_i = \frac{d_i e^{-\lambda t_i}}{TAC_i}, \quad (5.12)$$

where $d_i$ is the frame duration, $t_i$ the midtime of the frame, TAC$_i$ the TAC value of the frame, and $\lambda$ the decay constant of the radionuclide. There are a number of other weight compositions used as well. There are many studies however that advice against the use of model fitting with weighting based on noisy TAC data, such as Eq. (5.12), since it can result in poor parameter estimates [126–128].

### 5.3 Graphical analysis

There are a number of graphical approaches to transform non-linear compartment model problems into linear ones, thus simplifying the visual interpretation and mathematical regression procedure to find the relevant model parameters. Since these methods have not been used in the works included in this thesis however, they will only be presented briefly. The interested reader is referred to [7, 130, 131] for more information on the Patlak and Logan plots.

#### 5.3.1 Patlak plot

The Patlak plot is the most commonly used graphical analysis approach, and is appropriate for representations of irreversibly trapped tracers ($k_4 \approx 0$) [7]. It is widely used for e.g. $^{18}$F-FDG. Assuming the irreversible compartment and blood plasma are in equilibrium, the system can be described by the linear equation [7]
$\frac{C_{PET}(t)}{C_a(t)} = V_0 + K_i \left( \int_0^t \frac{C_a(\tau) d\tau}{C_a(t)} \right), \quad (5.13)$

where the intercept $V_0$ is the initial volume of distribution in the central compartment, and the slope $K_i$ is defined by Eq. (5.6). The intercept and slope can thus easily be found by linear regression. The glucose metabolic rate can be calculated according to Eq. (5.7) as usual.

The Logan plot is derived in a similar fashion, but for reversibly trapped tracers (mainly used in neuroreceptor studies).

### 5.4 Reference region methods

As described in Section 5.1, compartmental modeling is based on a known input function to estimate kinetic parameters from the measured tissue response function. There are however methods to avoid the need for a separately known AIF [7]. The basics for these methods is the use of a reference region, e.g. the cerebellum for neuroreceptor studies. The TAC of the relevant ROI is compared to the TAC of the reference region to deduce ratios of kinetic model parameters.
Simulations in Nuclear Medicine

Patient and even phantom PET scans are expensive and time consuming, and in many cases an extensive patient base is hard to acquire, especially for rare diseases. The collection of patient data can take months or even years before the dataset is large enough to yield sufficient statistics. Furthermore, studies with healthy volunteers is restricted due to the radiation dose associated with PET scans.

Additionally, the “ground truth” regarding the actual tracer uptake and kinetics is never completely known for clinical PET studies. Phantom studies solve part of this problem, however dynamic scans where the tracer kinetics is of interest are not fully possible, even with state-of-the-art phantoms. Advanced as they may be, phantoms can never truly represent a real patient in a clinical situation. Furthermore, the origin of each coincidence in a clinical PET dataset is unknown, hence for studies where this information is needed or e.g. to acquire truly scatter-eliminated data, real PET scans are not an option.

This is where the role of simulations come in. All properties of the patient (phantom) and kinetics are known, and the degree of complexity and detail
of the simulation can be chosen according to the specific aim of the study. Physical effects can be included or not in order to streamline the focus of the investigation. Depending on the level of intricacy, a large (even huge) number of simulations can be performed in a reasonable time.

6.1 Monte Carlo simulations

The MC method is any method consisting of computational algorithms that use repeated random samplings to describe some process, e.g. card dealing at a blackjack table or how radiation interacts with matter. It is an essential tool in the field of nuclear medicine and emission tomography where it is used to calculate radiation doses, understand and design new medical imaging systems and detectors, evaluate image reconstruction, correction and segmentation algorithms, and optimize scan protocols. MC allows realistic simulations of all processes involved in a real PET scan, from the physical decay of the positron emitting tracer nuclide, to the processing of the PET camera detector hits. The simulated, raw PET data can then be reconstructed using real scanner software or external reconstruction software (see Section 4.5). By using MC simulations, the user doesn’t have to make simplifications and assumptions regarding the blurring effects introduced by the camera system or the noise distribution in the final PET image.

There are a number of MC simulation packages available for PET or SPECT or both, including GEANT4, EGSnrc/EGS4, MCNP/MCNPX, ITS, PET-SORTEO, SIMIND, PENELOPE, FLUKA, SimSET, and GATE. Each of these packages has its own advantages, drawbacks and limitations as well as level of reliability and flexibility.

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a GEANT4: http://geant4.cern.ch
c MCNP: https://mcnp.lanl.gov
e PET-SORTEO: http://sorteo.cermep.fr/home.php
f SIMIND: http://www.msf.lu.se/forskning/the-simind-monte-carlo-program
g PENELOPE: http://www.oecd-nea.org/tools/abstract/detail/nea-1525
h FLUKA: http://www.fluka.org/fluka.php
i SimSET: http://depts.washington.edu/simset/html/simset_main.html
j GATE: http://www.opengatecollaboration.org
6.1 Monte Carlo simulations

6.1.1 GEANT4 and GATE

Originating from an international collaboration of 100 physicists and software engineers, GEANT4 [132] was developed as a MC simulation toolkit for tracking particles passing through matter. It was developed to meet the growing need for extensive, robust, accurate and complex simulations, mainly of particle detectors in disciplines such as radiation physics, space science and nuclear medicine.

The GEANT4 Application for Tomographic Emission, abbreviated GATE [133], is a well-known, free and increasingly used software, developed by the openGATE collaboration. Its development can be traced back to 2001 and historically it was dedicated to PET and SPECT, but has expanded to nowadays also include CT and radiotherapy experiments. It allows realistic simulations of emission tomography geometries and is a macro language built on the GEANT4 particle interaction libraries in order to achieve well-validated physics models with advanced geometry descriptions and powerful 3D visualization tools. For each imaging simulation (e.g. PET) with GATE, the user has to [134]

1. Define the scanner geometry.
2. Define the phantom geometry.
3. Set up the physics processes.
4. Initialize the simulation.
5. Set up the detector model.
6. Define the source(s).
7. Specify the data output format.
8. Start the acquisition.

Physics in GATE

All physical processes in GATE are based on the electromagnetic interactions as implemented in GEANT4, managing electrons, positrons, $\gamma$-rays, X-rays, optical photons, muons, hadrons and ions. The following section is a condensation of the GATE users guide [134], describing how the physical processes
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relevant for PET are implemented in GATE.

For PET simulations, positrons or, skipping directly to the annihilation event, back-to-back photons, are used as source particles. When simulating positron source particles, GATE generates positrons with initial energies in line with the proper $\beta^+$ spectra for the isotope in question (e.g. $^{18}$F). Moreover, the non-collinearity of the resulting annihilation photons is included, according to a Gaussian angular distribution in water of 0.5° full width at half maximum (FWHM). Photons undergo standard electromagnetic processes including Compton scattering and the photoelectric effect. Electron/positron processes include bremsstrahlung, ionization, annihilation as well as X- and $\delta$-ray production.

6.2 Simplified simulations

One drawback with MC simulations is the usually very high demand for computing power, time, and level of expertise of the user. Furthermore, large scale MC simulations typically require the use of medium to large computer clusters in order to accommodate the computer memory and storage needed, as well as to perform the simulations in a reasonable time. These types of resources are not available for most researchers and clinics, and the time needed for familiarizing oneself and setting up full MC simulations and running them is usually not feasible. This creates a need for faster and simpler simulation options that can be used when precise interaction details are not necessary, but can be compromised on behalf of the possibility to create large datasets on a single computer and in a practical amount of time.

In paper IV, we developed a fast and simple PET simulator called PETSTEP (Positron Emission Tomography Simulator of Tracers via Emission Projection), allowing fast generation of 3D PET data. One of its main features is the possibility to insert tumor regions into the data, making the tool especially useful for cancer applications. There are also image reconstruction options implemented, such as FBP and OSEM with or without PSF correction. There is currently ongoing work on implementing tracer kinetic modeling into PETSTEP, enabling the creation of 4D PET datasets from parametric images of a given compartment model. The user interface of PETSTEP is shown
In Figure 6.1. There are a number of approximations and simplifications implemented in PETSTEP compared to full MC simulations. For example, random and scattered coincidences are not truly traced, but are estimated. An estimation of the random counts is generated as a uniform background in sinogram space, scaled according to the user defined random fraction. The scatter distribution is estimated as a forward projection of a heavily blurred (20 cm FWHM Gaussian kernel) image of the true object. This sinogram estimate is then scaled by the user defined scatter fraction. Both of these sinogram estimates are added to the starting sinogram to simulate the additive noise of random and scattered coincidences.

Due to the simplifications implemented in PETSTEP, it is less useful for applications that require a more realistic random and scatter distributions. It is however useful for research or educational application that mainly need the features mean resolution and noise to resemble real clinical PET data. Such applications may include tumor segmentation and detection, machine learning and resident education to mention a few.

Upon comparing PETSTEP to MC simulations in GATE, we found PETSTEP to require roughly 3 min to simulate about 70 million prompt coincidences from the General Electric Discovery LS (GE DLS), whereas it
took 2750 hours for a full MC simulation in GATE. The time saved for this example thus computes to a factor of 55 000, emphasizing the usefulness of such a simulator.

### 6.3 Personal simulation and reconstruction platform

In paper II and paper III, and for validation of PETSTEP in paper IV, we used GATE and STIR for the generation and reconstruction of PET data. Matlab was used for calibrating the 4D images and doing all later image analyses. The following steps make up the basis for a complete run, from MC simulation to reconstructed images:

1. Set up the patient/phantom geometry and source in GATE.
2. Run a GATE simulation with desired acquisition settings.
3. Bin the raw list-mode data into 3D sinograms, resulting in one 3D sinogram per frame.
4. Use STIR to reconstruct each frame sinogram by OSEM or 3DRP.
   (a) 3DRP: Pre-correct sinogram for normalization\textsuperscript{k}, attenuation and possibly also scatter and random coincidences.
   (b) OSEM: Include normalization\textsuperscript{k}, attenuation and possibly also scatter and random corrections in the iterative loop.
5. Read the stack of reconstructed 3D frames into a 4D matrix in Matlab.
6. Calibrate (scale) the 4D matrix to convert the voxel values from counts to units of Bq/ml.
7. Perform all image analyses in Matlab (extraction of TACs, compartment model fitting, parameter analysis etc.)

The camera simulated in paper II, paper III and paper IV is a well validated GE DLS camera [136], depicted in Figure 6.2. The main features of the camera are 18 detection rings, each containing 672 BGO crystals of size $4 \times 8 \times 30$ mm (grand total of 12 096 crystals). The time window is $6.25 \text{ ns}$.

\textsuperscript{k} Described in [135] and in appendix B of paper IV
6.3 Personal simulation and reconstruction platform

Figure 6.2. Simplified drawing of the GE Discovery LS camera [136], as simulated in GATE.

and the energy window is 375–650 keV. The camera has a transaxial FOV of 550 mm and a 152 mm axial FOV.
Summary of Publications

The following pages gives a brief summary of the four publications included in this thesis.
Paper I

Semi-Automatic Tumour Segmentation by Selective Navigation in a Three-Parameter Volume, Obtained by Voxel-Wise Kinetic Modelling of $^{11}$C-acetate
I. Häggström, L. Johansson, A. Larsson, N. Östlund, J. Sörensen and M. Karlsson


**Background:** PET is more and more frequently used for delineation of tumor tissue, commonly done on static PET images. Kinetic parameters, obtained from compartment modeling of dynamic PET data, potentially represent the underlying tumor biology and physiology better, allowing more effective tumor image segmentation. In *paper I* we investigate the feasibility of segmenting tumor tissue on parametric images.

**Methods:** Dynamic $^{11}$C-acetate PET images of four head and neck patients were used to derive time-activity curves that were fitted to a three parameter, 1-tissue compartment model. Furthermore, a principal component (PC) analysis was performed on the fitted parameters. Tumor tissue was segmented in the three parameter-space as well as in PC-space.

**Results:** Parametric images contained information different from the standard PET uptake images. Especially parametric $K_1$ images had better image contrast. Tumor tissue was successfully segmented from normal tissue in both parameter- and PC-space. PC analysis reduced the number of parameters needed for segmentation from three to two.

**Conclusions:** Different tissues were more clearly seen in parametric images than PET images, and even more so in PC-space compared to parameter-space. Semi-automatic tumor segmentation based on kinetic parameters or PCs show great potential.
Background: Up to $\sim 40\%$ of all registered coincidences in a brain PET scan have undergone scattering, leading to a decrease in image contrast and quantitative accuracy. PET images are corrected for this, but the effect scattered coincidences and scatter corrections (SCs) have on kinetic parameters is not well investigated. In paper II we investigate the effect of these factors on bias and SD in kinetic parameters.

Methods: We performed 15 repetitions of two full MC simulations of a voxelized, dynamic head phantom with inserted tumors. All tissues were assigned realistic TACs representing the 2-tissue compartment model. Simulated data was reconstructed into images and TACs were derived from image regions of interest. True and true+scattered coincidences were reconstructed by both 3DRP and OSEM, with or without applying one of two SC schemes.

Results: Both SC methods performed well and the results did not differ from true coincidences with only attenuation correction (reference). SC was essential for most parameters since the bias increased by on average 10 percentage points when omitting it. SC was not found necessary for $k_3$ and $K_i$ however. There was a slight favor for 3DRP which produced less biased $k_3$ and $K_i$ estimates, compared to OSEM which resulted in a less biased $V_a$. Furthermore, 3DRP produced on average a 20% lower SD compared to OSEM.

Conclusions: SC is important for estimation of most kinetic parameters and both investigated SC schemes worked equally well without introducing parameter bias. 3DRP was slightly favorable over OSEM in terms of parameter biases and SDs.
A Monte Carlo Study of the Dependence of Early Frame Sampling on Uncertainty and Bias in Pharmacokinetic Parameters from Dynamic PET


**Background:** Quantification of tracer kinetics is made possible through compartment modeling of dynamic PET. The frame sampling possibly affects the error and uncertainty in kinetic parameters, and in paper III we investigate what impact the early frame sampling has on parameter bias and SD.

**Methods:** We performed $2 \times 15$ full MC simulations of a dynamic, realistic head phantom representing two setups of the 2-tissue compartment model for brain $^{18}$F-FLT. Images were reconstructed with either 3DRP or OSEM, and frames of the first two minutes were sampled at either 1, 2, 4, 6, 10, or 15 s. TACs were derived from the images and fitted to the model to obtain kinetic parameter estimates. Calculated biases and SDs were compared.

**Results:** Parameters $K_1$, $k_2$, and $V_a$ were statistically found dependent on early frame duration. Frame samplings of 6–15 s minimized bias and uncertainty, and samplings of 4–15 s were generally not significantly different. The shortest 1 s frames however yielded parameter biases larger by 34%, and uncertainties larger by 10–70%. Overall, 3DRP resulted in a smaller parameter SD by 15% compared to OSEM, and showed less frame sampling dependence. The average bias was however larger, although it was shown that the choice of model fitting weights played a large role in which reconstruction method was less biased. 3DRP images were noisier with streak artifacts, but short frame OSEM images had spotty uptake artifacts.

**Conclusions:** An early frame length of 6–15 s generally minimized parameter biases and SDs, while 1 s frames maximized them. Overall, 3DRP resulted in less sampling dependent and more accurate parameters than OSEM, despite more visually favorable OSEM images.
Paper IV

PETSTEP: Generation of Synthetic PET Lesions for Fast Evaluation of Segmentation Methods

Background: Simulated PET images are useful for oncological applications in both prognosis and therapy. MC simulations yield accurate results, but are very time consuming, require considerable amounts of computer power, and are cumbersome to implement. In paper IV our aim was to create a fast and simple PET simulator called PETSTEP (Positron Emission Tomography Simulator of Tracers via Emission Projection), allowing the generation and reconstruction of 3D PET data in a short time on a single computer.

Methods: The code is implemented in Matlab using the radon and its inverse as forward and back-projectors. CERR is used to delineate new or existing tumors on clinical data. One uniform distribution and one forward projection of the blurred object is added onto the sinogram to estimate additive noise of randoms and scatters, respectively. Reconstruction with FBP or OSEM with or without PSF correction are implemented. PETSTEP images were compared to a clinical dataset and a GATE MC simulation of the NEMA IEC phantom.

Results: The mean intensities of the PETSTEP images were within 6% and 5% for both background and hot spheres, compared to the clinical and MC images, respectively. The background FWHM of the PETSTEP images were higher compared to both clinical and MC images (33% versus 19% and 26% versus 19%). PETSTEP simulated a full 3D PET scan in ~3 min.

Conclusions: PETSTEP is fast, easy to use, and yields high quality images close to both clinical and MC data. PETSTEP shows great promise for applications in tumor detection, segmentation, machine learning and education.
Summary and Conclusions

There’s potentially a substantial gain in modern cancer care if one can include kinetic parameters from dynamic PET in the diagnosis, staging, treatment planning, treatment response monitoring and follow-up of cancerous tumors. Numerous publications have shown the benefit of including PET, compared to only using CT or MRI, especially in monitoring early response to treatment. The inclusion of static PET has proved to be very important, and pharmacokinetic parameters from dynamic PET even more so in many cases.

In paper I we investigated the potential of using pharmacokinetic parameters for tumor segmentation. Results showed that it was feasible and that parametric images had better contrast and showed additional information compared to the plain PET uptake image.

A prerequisite for pharmacokinetic parameters that are clinically useful and reliable is however knowledge about the errors and uncertainties associated with them. The goal of paper II and paper III was to investigate a couple of sources of parameter bias and uncertainty. In paper II we studied the effects of scattered radiation and scatter corrections and in paper III the effects of early frame sampling scheme. Based on the findings of paper II, we concluded that scatter correction was necessary for all parameters except $k_3$ and $K_1$, and that the scatter correction methods investigated did not introduce
additional parameter bias. In addition, reconstructions with 3DRP yielded slightly better parameter estimates compared to OSEM, in terms of parameter bias and uncertainty. In paper III we concluded that a very short early frame sampling (1 s) yielded the poorest parameter estimates, whereas a sampling of 6–15 s generally resulted in the least biased and most accurate estimates. Furthermore, $k_3$ was typically the least biased parameter.

The data used in paper II and paper III were Monte Carlo simulated. This is a highly detailed and realistic method, however laborious and time consuming. For studies that do not require such sophisticated simulations where only the basic image features are critical (mean resolution and noise), there is a need for a fast and simple simulator that allows the quick generation of large sets of 3D PET data, and enables easy tumor insertion. In paper IV, we developed a simplified simulator called PETSTEP that we believe will be highly useful for these purposes, as well as for image-based tasks such as tumor detection and segmentation, machine learning and resident education. Work is also under way to include functions for simulation of dynamic PET data based on parametric images.

It is clear that there are still many difficulties associated with full kinetic modeling in clinical routine. Practical issues regarding blood sampling and time consuming dynamic acquisitions are major hurdles, and methods for obtaining and analyzing kinetic model parameters in a reliable and repeatable fashion are much needed. One step seems to be the use of analytical image reconstruction for compartment modeling applications, since ours and other studies show that analytical algorithms (3DRP) yield more reliable parameter estimates compared to iterative algorithms (OSEM). Furthermore, the knowledge of the extent of the errors and uncertainties in parameter estimates must be taken into account when using their values for staging, prognosis, response monitoring etc. of cancerous tumors. In addition, faster and easier simulation and evaluation possibilities of dynamic PET scans enables faster methodology advances.

Despite the much simpler methodologies associated with static PET imaging compared to dynamic imaging plus kinetic modeling, it is highly likely that the potential benefits in earlier and more effective means of monitoring
treatment response will only increase in importance and relevance during coming years. There are numerous studies investigating the usefulness of kinetic parameters in several fields of oncology, including tumor segmentation, staging and treatment response monitoring. With advances in PET scanner hardware, the advent of PET/MR, new and improved indirect as well as direct reconstruction algorithms, and a better understanding of quantitative errors and uncertainties, dynamic PET and kinetic modeling will presumably be invaluable tools in future cancer care.
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