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QIN: Quantitative Assessment of Dynamic PET Imaging Data in Cancer Imaging

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Abstract

Purpose—Clinical imaging in PET is often performed using single time point estimates of tracer uptake or static imaging that provides a spatial map of regional tracer concentration. However, dynamic tracer imaging can provide considerably more information about in vivo biology by delineating both the temporal and spatial pattern of tracer uptake. In addition several potential sources of error that occur in static imaging can be mitigated. This review focuses of the application of dynamic PET imaging to measuring regional cancer biologic features and especially in using dynamic PET imaging for quantitative therapeutic response monitoring in cancer clinical trials. Dynamic PET imaging output parameters, particularly transport (flow) and overall metabolic rate, have provided imaging endpoints for clinical trials at single center institutions for years. However dynamic imaging poses many challenges for multi-center clinical trial implementations from cross-center calibration to the inadequacy of a common informatics infrastructure. Underlying principles and methodology of PET dynamic imaging are first reviewed, followed by an examination of current approaches to dynamic PET image analysis with a specific case example of dynamic FLT imaging to illustrate the approach.

Keywords

Dynamic PET/CT; compartmental modeling; parametric imaging; multi-center clinical trials

Introduction

“The promise of PET is as a quantitative measurement device for in vivo assessment of biochemical metabolism”

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Currently, PET imaging for metabolic assessment of cancer is in wide clinical use with static, largely qualitative ^{18}F -fluorodeoxyglucose (FDG) imaging to estimate energy consumption in tumors. However, in the early years of PET imaging, dynamic acquisitions were predominant, and now are experiencing resurgence in interest for several reasons. These include the extraction of multiple biological assessments with a single tracer injection, the reduction of variability through compartmental modeling, and interest in using PET as a tool for measuring *in vivo* cancer biology in addition to its use as a clinical imaging assay for cancer.

Radiotracer imaging has its roots in the basic biochemistry of reaction rates of substrates with specificity for enzymes or receptors indicating a particular biological process. In the case of metabolic pathways, enzymatic reactions along a pathway are assumed to be at equilibrium during the PET scan, and the injected tracer can be used to assess the rate of ongoing metabolism along that metabolic route. Two reasons this can be accomplished is that the acquisition of counts in a PET scanner derived from positron annihilation events is a linear quantitative phenomenon, and the radiotracer concentration is well below physiological levels. Under these circumstances, the rate of metabolic events, or kinetics, can be inferred directly from the dynamic imaging sequence, and first order rate constant or Michaelis-Menten kinetics applies to tracer metabolism, similar to spectrophotometric assessment of substrate degradation in the biochemistry lab.

The dynamic PET imaging process can be considered as a spatial integration of the tracer of interest in a region. The radiotracer can be distributed between several biochemical processes at the same location, so that the PET image at each time point is a weighted average of these signals. In addition, the basic radioactivity concentration measure by the PET scanner is both noisy and biased. Acquisition of the time-varying radioactivity concentration at each spatial location can provide *both* the true amount of radiotracer in each biochemical state at each location, as well as the biochemical rates at each location.

To determine metabolic rates from the PET scanner, data must be collected at multiple times after substrate administration at a time resolution on the scale of the rate of biochemical reaction of the radiotracer. Unlike controlled *in vitro* laboratory investigations, *in vivo* dynamic imaging of radiotracer biochemistry adds the complexity of transit through systemic vasculature into the imaging field. To separate transport effects from the metabolic rate of tracer metabolism, a mathematical model of tracer kinetics from blood into tissues is applied to the dynamically acquired PET data. The kinetic model of PET tracer activity estimates biologically relevant parameters, such as vascular transport and cellular metabolism, and require a determination of the blood activity concentration over time as an input function to the model. The input function characterizes the delivery and availability of the tracer to the tissue of interest. Model formulation and kinetic analysis therefore involve a compromise between a complete mathematical description of tracer biochemical kinetics and the practical limitations associated with patient imaging. We review some of the important components required to for PET imaging acquisition and quantitative analysis in order to be able to perform these kinetic measurements.

Dynamic PET Imaging Protocols

In dynamic PET scanning (Figure 1), the patient is positioned in the scanner and immobilized to restrict movement, after which catheter lines are placed in the patient. These lines provide not only vascular access for delivery of the tracer, but also provide for periodic blood sampling during the scan to assess radioactive delivery to the tissues. Several centers have automated blood sampling devices coordinated with the PET scanner, but non-invasive

methods using image segmentation of the dynamic sequence for input function recovery are gaining prominence and offer a considerably more practical alternative for patient imaging.

For repeatability, safety and accuracy the radiotracer is injected intravenously using a syringe pump or similar device to provide a known infusion schedule. A consistent infusion schedule of radiotracer delivery minimizes the errors of the blood time activity curve acquired from either blood samples or image based segmentation techniques.

The acquisition timing protocol of these PET emission scans depends on the half-life of the nuclide, the kinetics of the tracer, the biological distribution and the analysis model for quantitation. In general, the blood and tissue concentration of radiotracer will be changing most rapidly early after injection; therefore most dynamic PET imaging sequences have finer time sampling early after injection and wider time bins at later time points. For example, a typical time sequence for a 60 minute dynamic FDG PET study for tumor kinetics using a one-minute infusion time is 15×5 sec, 5×15 sec, 5×30 sec, 4×1 min, 4×3 min and 9×5 min time frames.

In principal, since nuclear emissions occur at random intervals on an infinitesimally short time scale, time sampling for dynamic PET can be quite fine. In practice, time sampling is limited by coincidence photon event counting statistics, since short time bins lead to low counts, and therefore high noise images. For radioisotopes other than very short half-life tracer such as ^{15}O ($T_{1/2} \sim 2$ minutes), time bins are practically limited to times of 5–10 seconds or longer. For some systems, the time bins must be specified prior to image acquisition and are collected as a series of discrete images. Other imaging systems may offer “list-mode” collection, where each photon pair detection event is recorded with a time stamp, and time binning of image data may be performed retrospectively.

Static vs Dynamic Imaging

Dynamic FDG PET imaging procedures can be simplified by acquiring image data over a single time frame (static imaging) to approximate tracer metabolic assessment using the complete dynamic sequence. These static imaging protocols offer clinical applicability, and typically the relative tracer uptake is of interest (e.g., cancer diagnosis or staging with FDG). In this case the relative tracer uptake is characterized as the Standardized Uptake Value (SUV), where the measured (and decay-corrected) tracer uptake in MBq/ml from the PET image is normalized by the amount of injected activity and the distribution volume within the patient. Typically patient weight (or lean body mass) is used as a surrogate for the distribution volume within the patient. Dynamic imaging, however, provides some advantages over static imaging; 1) the dynamic process of tracer uptake and retention can be better assessed through a time series of images, and 2) static imaging may impose a bias by arbitrarily choosing a single time frame to represent overall tracer metabolism. However, depending on the desired information and the questions being asked, a single static image may provide enough information within acceptable error limits. Details of the errors associated with static SUV images have been well documented. The compromise between PET image protocol complexity and the quantity of data collected depends on the disease, metabolism of the radiotracer, the level of significance in a population of patients with similar disease, and the desired endpoints of patient assessment. Static scanning parameters, such as scan start and duration, are usually fixed for an imaging protocol as variations can significantly alter uptake patterns and lead to erroneous conclusions about the imaging study. Generally, new PET radiopharmaceutical studies should begin by collecting as much data as possible, in order to design simpler, more clinically feasible protocols based upon a thorough understanding of tracer kinetics and the relationship to the disease process under study.

Blood Sampling

Quantitative dynamic PET studies require blood samples for 1) determining radiotracer blood clearance, 2) specific biological assays, such as measuring glucose concentration for FDG studies, and 3) determining radiotracer metabolites. To assess blood radioactivity, a sample is collected by vascular access and counted in an external counting system, such as a well counter (Figure 2A). The external counting system must be calibrated with the tomograph in order to relate the resulting activity information to the PET image data. Typically a phantom with known activity measured using a dose calibrator, with several aliquots from the phantom counted in a well counter, is imaged in the PET scanner. The values obtained from the PET images, the well counter and the dose calibrator provide the calculation of standard units of activity concentration, such as MBq/cc.

Measuring the patient blood activity concentration during the imaging study gives a direct measure of tracer clearance and availability for tissue uptake. For high first pass extraction radiotracers (e.g., $H_2^{15}O$), sampling arterial blood provides the best measure of radiotracer availability to the tissue and is essential in the initial evaluation of radiopharmaceuticals. Typically, about 20–30 arterial blood samples are acquired for routine modeling of a dynamic PET scan following a 1 minute infusion of the radiotracer. The resulting arterial blood-time activity curve (AIF) is used in compartmental modeling analysis of the dynamic PET data to extract biologically important parameters such as transport and metabolic flux.

However, arterial blood sampling is invasive, time consuming and difficult to justify for routine clinical imaging. An alternative to detailed blood sampling is the use of a standardized, population-based blood clearance curve. The shapes of the arterial blood clearance curves are quite similar for most patients with a comparable injection protocol (e.g., 1 min infusion) for a given radiotracer (Figure 2B). A common method to combine sampled arterial blood curves from many patients is by averaging them and scaling the resulting population curve for each patient with one or two blood samples. Olshen proposed a statistical method of combining the measured arterial blood data from patients as a time and dispersion-adjusted population curve followed by a deconvolution procedure to create the population arterial blood curve template. The population template scaled by a late venous sample produces an individual patient AIF for the input function to compartmental modeling. The population based input function can reduce blood sampling and incur modest error (7–10%) in estimating FDG metabolic rate.

When arterial blood sampling is not practical for dynamic PET scans of cancer patients for studies without a population template, other methods are employed to determine the blood clearance curve. Image-based blood time activity curves may be derived from a manual region of interest (ROI) placed over a cardiac chamber or the aorta to acquire a time course of tracer blood concentration, which has the advantage of providing the arterial curve without blood sampling. To account for some of the effects of partial volume and spillover, the image-derived AIF may require further refinement.

An image-based method for acquiring blood clearance curve gaining prominence is to apply segmentation algorithms to the dynamic PET image sequence (Figure 2C). The automated, objective methods result in an extracted blood TAC curve that has a similar profile to the arterial blood clearance curve for a tracer with a common infusion schedule. The advantages of the segmentation methods are that 1) manual construction of a tissue region is not required and 2) both the shape and scale of the blood curve are individually derived for each patient. Many methods for image derived input functions (IDIF) require correction for partial volume and spillover effects from adjacent tissue with active uptake. Multivariate statistical methods including principal components, factor analysis, clustering and

segmentation play a key in most IDIF strategies. A particular Bayesian scheme for IDIF has been developed and validated for use with dynamic PET-FDG data in our group. In this approach a 4-dimensional (4D) segmentation procedure is used to focus the IDIF extraction on regions with significant blood signal information. In these areas a voxel-level model is used to address spillover and recovery issues that arise in consideration of the PET-measured time-course data extracted from a blood region. Adaptation of the method for various radiotracers (FDG, ^{11}C -1-glucose, H_2^{15}O , 3'-deoxy-3'- ^{18}F -fluorothymidine (^{18}F -FLT), ^{18}F -16 α -fluoroestradiol (FES), ^{11}C -acetate, ^{11}C -thymidine (^{11}C -TdR), ^{11}C -verapamil,) will soon be available as open-source software accessible to users of R, and is also being explored in the context of DCE-MRI studies.

Radiotracer Metabolites

The radioactivity measured in blood samples is usually assumed to be identical to the injected imaging agent. Radiotracers such as FDG have minimal metabolic degradation prior to clearance from the blood, but for many others, such as ^{11}C -TdR, ^{18}F -FLT, and ^{11}C -acetate, metabolism shortly following radiotracer injection produces high levels of circulating metabolites. Biochemical breakdown of the imaging agent (^{11}C -TdR, ^{11}C -acetate) or conjugation (^{18}F -FLT, ^{18}F -FES) can result in labeled metabolites in the blood circulation during the dynamic imaging study. Tissues may or may not take up labeled metabolites and may therefore confound quantitative image analysis. Independent assays of blood precursor and metabolite level scan determine the activity profile of labeled blood components. Model input functions of not only the intact radiotracer, but also labeled metabolites are required for accurate quantitative modeling analysis. Some metabolites (e.g., FLT-glucuronide) have little access to tissues outside the vascular space can simply be subtracted from the blood clearance curve to provide a better AIF for the compartmental model. Other metabolites, for example ^{11}C -CO₂ from ^{11}C -TdR, may have considerable access to tissues and will need to be included in the compartmental model to obtain accurate estimates of the kinetics of the injected radiotracer.

While the intact radiopharmaceutical targets a particular biologic process, the labeled metabolites may have a non-specific distribution in tissue or may even target a different metabolic process. In this latter case, kinetic models that assume uniform behavior of all labeled species will be incorrect and subject to unpredictable errors in parameter estimation. Circulating labeled metabolites represent a potentially significant source of error if ignored.

Data Extraction for Dynamic PET Imaging

Dynamic image reconstruction is similar, if not in some cases, identical to standard clinical static image reconstruction with just a few differences. A benefit of dynamic imaging is that a subset of the dynamic sequence summed over time or SUV images can be reconstructed at precise and specific times after injection for an uptake period that reflects the biochemistry of the tracer. For example, 5–20 minute summed SUV image for ^{11}C -acetate in glioma patients reflects rapid transport and metabolism, while a longer uptake period for FDG allows greater signal enhancement for imaging energy metabolism. For dynamic PET imaging, the uptake period for the summed image can be repeated precisely for each patient reducing the variability common with static clinical FDG SUV scans that are often acquired at variable times after tracer injection.

Region of interest (ROI) or volume-of-interest (VOI) placement is potentially a large source of error in analyzing dynamic PET image data due to subjective region placement, size and inadequate partial volume correction. An assortment of ROI construction methods have been applied to dynamic PET data and include manually drawing regions, applying isocontours at

some threshold level (e.g., 25%, 50%, 75% of the maximum tumor level) with and without background adjustment and using fixed size VOIs (e.g., 1.2 cm diameter sphere centered on the hottest pixel). As a general principal in cancer cell biology, defining a region on the hottest portion of uptake likely characterizes the most aggressive aspects of the tumor and is gaining favor as a "peak" tumor VOI.

Manual VOI construction possesses obvious bias and subjectivity, but threshold-based methods are marginally better since selection of both a threshold and a background region are subjective. Size of the VOI is important due to the count statistics of the extracted data, and threshold VOIs for low uptake tumors may expand to include cold regions. In an effort to recover consistent data from multi-center clinical trials examining response assessment of tumors, the PERCIST 1.0 guidelines has suggested the concept of a peak PET volume as a sphere of approximately 1.2 cm centered over the hottest region of the tumor that includes the hottest pixel. PERCIST 1.0 is a starting point, and dynamic imaging may require a larger region for quantitative assessment of kinetic parameters.

It is beyond the scope of this report to discuss errors associated with dynamic PET imaging, however a number of factors may affect the accuracy of data analysis from dynamic PET imaging studies. The following items can impact estimated model parameters in dynamic PET imaging.

1. Dynamic frame timing relative to tracer metabolism: Coarse time sampling of PET data can bias estimated model parameters; Conversely, short time frames with limited counting statistics increases noise, which can also bias model parameter estimates.
2. Image reconstruction parameters: Increased image smoothing will reduce noise but increase bias for objects < 3 cm in diameter.
3. Injected activity: too little activity increases image noise especially for short time bins.
4. Lesion size and heterogeneity relative to ROI assessment: partial volume effects add considerably when the lesion size approaches the resolution of the PET scanner and for object < 3 cm in diameter; a larger ROI over a homogeneous tissue sample will have lower measurement error.
5. Assay data (e.g., blood glucose concentration): variability in blood assay data may increase error of metabolic rate assessment.
6. Measured blood activity (arterial): external counting systems may add error to overall kinetic image analysis; venous blood samples may have different tracer concentrations than arterial blood at early time points.
7. Metabolite assay activity (FLT, TdR, acetate, verapamil): assaying samples may add errors in the assessment of tracer blood metabolites manifesting the error in the AIF resulting in parameter value error.
8. Input function: blood sampling versus an image based AIF, which may be contaminated with spillover from other tissues and have partial volume effects.
9. Model selection: selecting an inappropriate model for the tracer kinetic pattern of uptake.
10. Model starting conditions and parameter ranges: inappropriate model parameters or optimization ranges can hinder curve fits and restrict parameter results.

11. Fixed variables: subjectively selecting fixed parameter values for model parameters that may be inappropriate for the biology.
12. Weighting parameters: tissue TAC for model fits based on Poisson statistics for PET.

Dynamic Modeling Considerations

Formulating a biochemical model of radiotracer metabolism is usually the first step in developing an approach for analysis of dynamic PET imaging data. The physiological biochemistry of the metabolic pathway of the tracer is assumed to be at equilibrium during the PET scan, however the uptake patterns and clearance of the radiopharmaceutical are dynamic and complex. Compartmental modeling offers a method to extract biologically meaningful parameters from large amounts of PET data, and is based on a few key steps of transport from the vasculature into cells and radiotracer metabolism along a biochemical pathway. For small-molecule radiopharmaceuticals, transport is primarily limited by blood flow into the tissue. In some cases like FLT or TdR, the blood-brain barrier (BBB) provides a significant impediment for the trans-capillary transport of molecules into brain. In brain tumor imaging both tumor and treatment can damage the blood-brain barrier and increase apparent capillary permeability. Compartmental modeling of dynamic PET image data can separate the effects of enhanced tracer delivery due to BBB damage from increased retention of tracer due to metabolic fixation through the biochemical pathway under study.

Understanding the steps in a targeted biochemical pathway is critical for interpretation of dynamic PET imaging data. Typically, the targeted pathway in active tumor metabolism results in retention of the tracer and consequently signal enhancement in PET emission images. In an example from the glucose metabolic pathway, high glycolysis in a tumor may be exhibited as high rates of phosphorylation of FDG by hexokinase (the first step in glycolysis) resulting in increased tracer trapping. Similarly, FLT becomes phosphorylated by thymidine kinase I in the DNA salvage pathway to FLT-monophosphate (FLT-MP), which is retained in the cell. The rate-limiting reaction of the target pathway will most strongly influence retention of the tracer. Hence, in formulating the model, estimates of tracer flux through the pathway will reflect the flux through the rate-limiting step. In the DNA synthetic pathway, the rate-limiting step in imaging ^{18}F -FLT is mono-phosphorylation to FLT-MP along the salvage pathway to DNA. Thus, ^{18}F -FLT dynamic imaging provides an indication of the rate of DNA synthesis by measuring the rate of FLT phosphorylation along the salvage pathway into newly formed DNA.

A Model Example: FLT Dynamic Imaging

From the prior example, consider the biochemical pathway of FLT (Figure 3A). FLT tracks the salvage pathway to the formation of DNA, where the rate limiting step is phosphorylation resulting in a compound, FLT-MP that is retained in the cell either by direct trapping or further phosphorylation to FLT di and triphosphate (FLT-DP, FLT-TP). There is a slow de-phosphorylation rate of FLT-MP by deoxynucleotidase (dNT) back to FLT. FLT can be conjugated in the liver producing a metabolite (FLT-glucuronide) that circulates in blood (Figure 3B), but is not able to cross the vascular endothelial layer into cells. The compartmental model of FLT biochemical metabolism using a radioactive form, ^{18}F -FLT (Figure 3C), relies on the plasma activity concentration as an input function to the kinetic model and tissue time activity curves usually extracted from VOIs applied to the dynamic image data (Figure 4). Plasma ^{18}F -FLT, Cp FLT, activity is typically in units of MBq/cc and reflects the activity in the vasculature that is available for tissue uptake. The tracer activity in tissue compartments for ^{18}F -FLT, the exchangeable compartment (Qe) and the trapped

compartment of phosphorylated FLT (Q_m) are considered as tissue contents in units of MBq/g for the radiolabeled compound.

In the kinetic model of FLT metabolism, the parameter K_1 (cc/min/g) describes the first step of delivery of ^{18}F -FLT to the tissue, and includes the effects of tracer bulk delivery via tissue blood flow, trans-capillary transport, movement through the interstitial fluid, and transport across the cell membrane. The overall transport reflected by K_1 is considered a flow parameter, and of particular importance is the transport restriction of the BBB in FLT brain imaging. The impediment to brain uptake of FLT dominates the imaging signal. While the use of a single parameter K_1 is a significant over-simplification of the transport process, it is often the most that can be gleaned from the typical resolution of dynamic PET data. The parameter, k_2 (1/min) describes transport of ^{18}F -FLT from the exchangeable tissue compartment back to the blood. It is important to note that k_2 is dependent not only upon the absolute rate of back-transport, but also the size of the exchangeable pool, Q_e . The parameter k_3 (1/min) describes the rate-limiting biochemical reaction and therefore movement from the exchangeable compartment to the trapped compartment and is also dependent on Q_e . Dephosphorylation, which implies passage back to the exchangeable compartment, is described by k_4 (1/min). Note that in this formulation K_1 is considered a flow, and has different units than the other rate constants. The blood concentration of ^{18}F -FLT, the model input function, is measured in concentration units (for example, MBq/cc), while the tissue compartments (Q_e and Q_m) are described as tissue contents (MBq/g). The differential equations describing the behavior of the compartments of the model are given below:

$$\frac{dQ_e}{dt} = K_1 C_{pFLT} - k_2 Q_e - k_3 Q_e + k_4 Q_m \quad (1)$$

$$\frac{dQ_m}{dt} = k_3 Q_e - k_4 Q_m \quad (2)$$

$$C_t = (Q_e + Q_m + V_b C_b) \rho \quad (3)$$

The first two equations {see Eqs. (1–2)} describe the kinetics of each tissue compartment of the model, driven by the FLT blood activity clearance curve (C_{pFLT}). The third equation {see Eq. (3)} relates model compartments to the total tissue time-activity curve (C_t), which is equivalent to what is measured by dynamic PET imaging. In this equation, C_b is the total blood activity including both FLT and labeled metabolites, V_b is the fractional volume of blood per gram of tissue and ρ is the tissue density in g/cc. V_b accounts for the contribution of tracer in the blood, both due to vascular blood physically present in the imaged tissue and also due to “spillover” – counts from adjacent blood pool structures contributing to the tissue time-activity curve.

Formulation of the FLT kinetic model implies a number of assumptions. Perhaps the most important is that the native substance, thymidine (TdR), is in steady state equilibrium. This implies that the blood concentration of the native substance is stable and the flux through the biochemical pathway is constant throughout the imaging study. This is obviously not true for the injected radioactive moiety, ^{18}F -FLT, but must be true for the substance under study, TdR. A second important assumption is that FLT does not perturb the biochemical and physiological system of the DNA salvage pathway. This means that the peak chemical blood concentration of FLT should be at least 1–2 orders of magnitude less than blood levels of TdR.

Interpretation of FLT Model Parameters

Some discussion is in order on the significance of model parameters. When we examine FLT through the DNA salvage pathway where phosphorylation is the rate-limiting step, the goal of compartmental analysis is to delineate the kinetics of delivery through the pathway and specifically to estimate metabolic flux through the pathway. Flux describes the rate at which FLT leaves the blood and moves through the biochemical pathway in tissue, typically given in units $\mu\text{mol}/\text{min}/\text{g}$. Upon examining the model components, one might equate flux to k_3 , the initial phosphorylation step. However, k_3 is a rate constant that is dependent upon the pool size in the exchangeable compartment, Q_e . The flux of FLT through the pathway is given by Eq.4:

$$\text{Flux} = Q_e k_3 \quad (4)$$

The initial phosphorylation of FLT, k_3 , is dependent upon both the flux and exchangeable compartment content and not simply equal to flux. To relate flux to measurable quantities, we rely upon the methods described by Sokoloff for deoxyglucose, and for the moment, ignore the small contribution of de-phosphorylation (k_4). Under Steady state conditions for the native substance, the exchangeable compartment content, Q_e , is constant, and thus

$$\frac{dQ_e}{dt} = K_1 C_{pFLT} - k_2 Q_e - k_3 Q_e = 0 \quad (5)$$

Re-arranging terms yields

$$Q_e = \frac{C_{pFLT} K_1}{k_2 + k_3} \quad (6)$$

For the native substance, TdR, the blood concentration is constant. Referring to the constant native compound concentration as $[TdR]$ and substituting for C_{pFLT} , the flux equation now becomes

$$\text{Flux} = [TdR] \frac{K_1 k_3}{k_2 + k_3} \quad (7)$$

The fraction term describes what is often termed the flux constant, K_i , which is a macro parameter (a combination of rate parameters), that appear in the flux term as a rate constant describing the overall flow of the tracer from the blood, through the metabolic pathway and into the retained compartment Q_m :

$$\text{Flux} = [TdR] K_i, \text{ where } K_i = \frac{K_1 k_3}{k_2 + k_3} \quad (8)$$

In the analysis of FLT model parameter error, sensitivity and accuracy, we find that the parameters that are the most well defined are transport of the tracer, K_1 , and overall metabolic flux, K_i , and are also of the most biological interest as well. In brain tumor imaging, where FLT is restricted by the BBB, both tumor and treatment can damage the BBB and increase apparent capillary permeability. Under this situation, transport effects across the BBB into compartment C_e (K_1) dominate the imaging signal, while the metabolic fixation of the tracer in Q_m (K_i) is dependent on tracer delivery. Compartmental modeling

of dynamic PET image data can separate the effects of enhanced tracer delivery due to BBB damage from increased retention of tracer due to metabolic fixation, although both processes occur at low rates. For somatic tissues, transport is not restricted and rate parameters for metabolic flux and transport are generally robust, however they can still be impacted by therapeutic treatment. Thus, K_1 can be considered a flow from blood to the exchangeable tissue compartment, while K_i can be considered a flow from blood into the trapped tissue compartment.

Alternatives to Compartmental Modeling Analysis

Simplifications of compartmental modeling have been proposed in order to determine several macro parameters without model optimization and parameter estimation. Graphical analysis applies to compounds that can be modeled as having a compartment of irreversible or nearly irreversible binding. In this case, a graphical approach can be used to estimate the flux constant, K_i , describing movement from the blood into the trapped compartment, as previously described for kinetic analysis. The technique presents a reformulation of the 2-compartment model offering a simple linear regression method to derive metabolic flux of the tracer using a blood clearance curve and a tissue time activity curve. A primary assumption for graphical analysis is that loss of tracer does not occur from the retained compartment, however when loss occurs the plot deviates from linearity making selection of the linear component difficult. These easier methods offer some advantages over non-linear model optimization, such as avoiding parameter sensitivity to noise, parameter co-variance, local minima in optimization, and dependence on model parameter starting conditions. However the trade-off is that graphical analysis only estimates the flux constant and not the individual parameters, which may be a limitation in cases such as FLT brain imaging, where it may be of interest to assess the contribution of initial transport across the BBB to that of overall metabolic flux.

A different approach from compartmental modeling that has recently been developed is the application of residue analysis to imaging studies (Figure 4). PET tracers are assumed to behave in a linear, time-invariant fashion at the local tissue level, and can be described by an impulse response function. Kinetic analysis of compartmental models, have full reliance on this impulse response assumption. Indeed, the most popular 1- and 2-compartmental models in PET can be presented as a description of the impulse response as a mixture of exponentials. The impulse response for tracer analysis precedes PET, and can be traced to the development of dilution theory where the impulse response is referred to as the tissue residue function. Nonparametric evaluation of the residue function has found use in fields outside of PET, most notably it is the basis of Ostergaard's singular value decomposition approach for evaluation of perfusion and flow in DCE-MRI studies. In a recent review by Hawe et al., there are two major benefits arising from residue analysis:

1. rapid quadratic-programming based methods for computation, free of the usual limitations of compartmental modeling, such as initialization and multiple local minima.
2. more accurate representation of data, which deviates from compartmental model assumptions of idealized vascular delivery and a description of tissue as a well-mixed homogenous solution.

Non-parametric residue analysis allows evaluation of key parameters describing vascular delivery or transport and tissue retention (Figure 4), because transit time, flow, volumes of distribution, extraction and flux are functions of the residue. Thus while these quantities may be reduced to certain parametric forms in compartmental models; they have a valid interpretation beyond the compartmental model. The linear structure of residues, allows for

easy adaptation of mixture analysis for voxel level implementation and parametric imaging, examples of which can be seen in Figure 4.

Parametric Imaging; Alternatives to regional assessment

An alternate approach to regional estimates of tracer kinetics is termed parametric imaging. The approach consists of estimating model parameters on a pixel level basis to generate images or maps of kinetic parameters. Parametric imaging reveals the heterogeneity of tumors down to the image sampling distance (typically a few mm) and avoids the inherent bias of defining tissue ROIs from summed or anatomic images. The chief limitations of parametric imaging include AIF determination and image noise. This is especially true in the approach to parametric imaging which treats each image pixel as a separate data point, generating an entire volume of pixel-wise tissue time-activity curves. A variety of procedures have been developed to allow the mapping of kinetic parameters on a voxel-level basis. The computational simplicity of graphical techniques (Patlak and Logan) makes them particularly suited to a voxel-level approach. Similar to IDIF, there is a good deal of reliance on multivariate statistical methods in parametric imaging including factor analysis, singular value decomposition, spectral analysis, principal component analysis and clustering or mixture analysis. The linear structure of residues, allows for easy adaptation of mixture analysis for voxel level implementation and parametric imaging, examples of which can be seen in Figure 4.

However, care must be taken to avoid the full complexity of voxel-level rate constant optimization. The number of image counts contributing to the individual pixel's curve is small, generating noisy curves and often creating considerable inaccuracy and unpredictability in parameter estimation. A more statistically robust approach proposed by O'Sullivan is to consider the image over both time and space (4-D, 4-dimensional) and decompose the image into a limited number of functional, biological components that can be used to describe the 4-D image array. An early example is mixture analysis, where the image is segmented into a group of pixels with statistically similar time courses of biological uptake, or sub-TACs. The process yields a modest number of sub-TACS (typically 30 or less for FDG) with much better counting statistics than an individual pixel time-activity curve. Compartmental or residue analysis can be applied to each individual sub-TAC, and the final parametric image volume is formed as a linear combination of the parameter estimates for each curves contribution to the voxel using a linear combination of constants calculated in the segmentation process. Mixture analysis allows assessment of all the image data into a relatively small number of time-activity curves, yields low-noise tissue time-activity curves, and results in reliable parameter estimates providing a kinetically correct approach to image smoothing

Constraints of Clinical Research and Clinical Dynamic PET Imaging

While pre-clinical studies and early pilot human studies can be performed with sufficiently detailed protocols to allow rigorous kinetic analysis, such detail is not always possible in larger scale clinical research studies and in routine clinical practice. The reasons for this include the following: (1) many patients, particularly those with more advanced cancers, may not tolerate long procedures and may be sufficiently anemic to limit blood sampling that may be performed; (2) many patients involved in serial studies will be unwilling to return for follow-up studies if the first study was too long and/or uncomfortable; (3) long procedures times may not be practical for studies with a large number of subjects; and (4) centers primarily focused on clinical imaging may not have the expertise to perform more complex quantitative analyses. These considerations have prompted the development of simplified quantitative approaches for routine use in clinical research and in clinical

practice. Simplified approaches have best been tested for FDG PET, which has seen by far the most widespread clinical use of the PET radiopharmaceuticals. Because the simplified approaches invariably make approximations regarding the kinetic behavior of the radiopharmaceutical, they are inherently more prone to bias than full kinetic analysis. Therefore, the decision to use a simplified quantitative analysis approach always incurs some trade-off between clinical convenience and quantitative rigor. Where to adjust the imaging protocol in the balance between these competing considerations depends upon the clinical and biologic question addressed by PET imaging and the clinical research study or clinical diagnostic application for which PET is being used.

An important general principle of research involving new radiopharmaceuticals is that the approach should start with a detailed rigorous analysis, and using the results of that analysis, suggest alternate, simpler approaches. In other words, it is inappropriate for new imaging approaches to start with overly simplified quantitative approaches only to find later that sources of variability and bias that would have been apparent in more detailed studies were missed.

From the standpoint of clinical convenience, the following properties are desirable for practical, quantitative measures using dynamic PET imaging.

1. Patients prefer short imaging times, preferably one hour or less.
2. No or minimal blood sampling, including avoiding the need for multiple vascular access sites.
3. Easy to implement imaging protocol, with few details outside those required for standard static PET image acquisition.
4. Applicable to a wide variety of PET tomographs with the basic requirements of automated dynamic acquisitions and routine scanner calibration.

A general dynamic PET imaging protocol (Figure 5) would match tracer biochemistry to the duration of the imaging session and will range from a few minutes (H_2^{15}O , $^{15}\text{O}_2$), a half hour (^{11}C -verapamil, ^{11}C -acetate) to an hour (FDG, ^{18}F -FLT, ^{18}F Fluoride, FES, ^{11}C -TdR). When the patient arrives, some basic information is acquired (identity verification, weight and height, blood glucose level) before positioning and immobilization in the PET scanner. For tracers with a well-characterized blood profile such as FDG, ^{18}F -FLT and ^{11}C -acetate, a singular venous line will be sufficient for tracer delivery. The tracer is drawn into a syringe used for injection, measured for total activity and placed in an automated infusion pump, preferably shielded to limit scatter into the PET scanner. At the onset of tracer injection into the patient, a dynamic acquisition protocol is activated for the PET scanner. Injection proceeds over a fixed time period, usually 1 minute for most tracers, after which the injection syringe and line into the patient are removed and measured for residual activity. The acquisition protocol should be pre-programmed to acquire time frames of data very frequently at the onset of scanning in order to determine the shape and magnitude of the blood clearance curve of the tracer from a blood pool in the dynamic image sequence, typically beginning with 2–5 second intervals. A useful protocol for a 60 min dynamic FLT imaging session may use 15×5 sec, 5×15 sec, 5×30 sec, 4×1 min, 4×3 min and 9×5 min time frames. A 30-minute dynamic acquisition sequence, for acetate, would be identical except with fewer five-minute time frames. Following the low dose CT scan required for attenuation correction, the patient is removed from the scanner.

Minimal blood sampling for clinical dynamic scanning may be required for certain tracers where 1) a blood activity concentration is measured to scale the image-extracted blood curve, 2) a biological measurement is needed where the tracer produces significant metabolites that must be assessed in order to interpret the imaging signal, for example ^{18}F -

FLT and ^{11}C -acetate. For a simple, clinical dynamic scan, a single blood sample may be acquired after the scan by any routine, clinical method using a 5 mL heparinized vacutainer tube, obviating the need to insert a secondary vascular access line into the patient. Under no circumstances should a blood sample be drawn from the injection line due to tracer contamination of the blood sample. A critical element in blood sampling is to record the time the blood sample was acquired relative to the administration time of the tracer. The blood sample and any metabolite assays are assessed for radioactivity concentration in a counting system that is cross-calibrated with the PET scanner yielding activity in common units of radioactivity, usually Bq/cc.

Following a simple, clinical acquisition of a dynamic PET image study, reconstructed images can be transferred to a workstation, where software analysis would begin with 4D segmentation of the image data to develop clusters of similar time-activity profiles (sub-TACs) of all the voxels in the imaging volume. With an arterial blood pool in the imaging field, one of these segmented profiles is the AIF and can be extracted and used as the blood clearance curve. During the segmentation process, the scale of the profiles are not retained; however, the measured activity concentration of the blood sample can be used to scale the image based AIF. Alternatively, a blood VOI can be manually constructed on the dynamic series by rendering each volume as a MIP (maximal image projection) for early time frames to identify a blood pool from which an AIF can be recovered. The manual method will likely be noisy and possess spillover effects from uptake in surrounding tissue.

Through residue analysis of the sub-TACs, the AIF is deconvolved with the segmented activity profiles yielding determinants of tracer transport and overall metabolic flux. Parametric maps of transport and flux are generated by a linear combination of the parameter estimates for each curves contribution to the voxel using a linear combination of constants calculated in the segmentation process. Typically, post processing of PET image data is performed by coupling software modules for segmentation, residue analysis and parametric image generation, which accepts inputs of blood activity concentration and metabolite assay information if needed, and then selecting the dynamic image data for analysis. The resulting parametric maps of transport or flux can be directly investigated for clinical assessment of the rates of tumor metabolism and offer distinct advantages over static SUV imaging for tracers like ^{18}F -FLT and ^{11}C -acetate.

With the advent of simple quantitative dynamic imaging protocols and incorporation of new analytical methods, future PET researchers and clinicians will likely be reviewing parametric images of the rates of tumor metabolism alongside crude uptake scans. A simplified dynamic PET imaging protocol can be extended to multi-center clinical trials, and potentially to routine nuclear medicine imaging.

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Dynamic PET Imaging

Patient Arrives, and is positioned in the PET scanner.

A shielded syringe pump delivers the tracer as PET scanning begins

A sequential series of PET images are collected as the tracer biologically distributes in tissues

Blood activity is determined during imaging.

Figure 1. The PET dynamic imaging protocol requires patient positioning prior to scanning, a shielded syringe pump for tracer delivery and perhaps blood sampling during dynamic imaging.

Arterial Input Function (AIF) Recovery Methods

A

Arterial Blood Sampling

“Gold Standard”, Invasive

20-30 Samples per Study

PET : γ Cross-Calibration

B

Historical Data

Scalable Templates

Camouflaged Deconvolution
Variance Representation

Scale by late Venous
Blood Sample

C

Image Based (IDIF)

Automated, Objective

Segmentation, Curve Recovery,
Spillover Adjustment

Scale by late Venous
Blood Sample

Figure 2.

Modeling dynamic (4D) PET images requires a model input function as the arterial concentration of the radiotracer (AIF) over the imaging study. Several methods have been used to recover the AIF and include (A) manual blood sampling and counting, (B) use of an historical population-based AIF and (C) segmentation of the dynamic imaging sequence to extract an AIF from the PET scans.

A. Biochemistry of FLT (Salvage Pathway)

B. Metabolites of FLT (Liver to Blood)

C. Kinetic Model of FLT Metabolism

Figure 3.

(A) Biochemical metabolism of native thymidine and FLT along the salvage pathway into DNA. (B) The conjugation of ^{18}F -FLT in the liver produces a labeled metabolite that circulates in blood but is not taken up in cells. (C) The kinetic model for ^{18}F -FLT requires two tissue compartments, and 4 rate parameters to characterize transport and metabolism.

Dynamic PET Data Analysis

Figure 4. Methods of dynamic PET image analysis using regionally extracted ROI data and full image volume parametric techniques.

Dynamic Clinical PET: Future Protocol

Automated Post-Acquisition Analysis

- **Single venous sample** (post scan, vacutainer)
- **Objective, automated image analysis** (similar to DCE-MRI Ktrans)
- **Parametric images of metabolism** for clinical review

Figure 5.

A simplified clinical dynamic PET image acquisition protocol and analysis paradigm for multi-center clinical trials.