KINETIC MODELING IN POSITRON EMISSION TOMOGRAPHY (PET)

LANA KRALJ

Faculty of Mathematics and Physics
University of Ljubljana

This article firstly introduces Positron Emission Tomography (PET) as a functional and molecular imaging technique and describes main physical principles on which PET imaging works. Then, it focuses on kinetic modeling in PET. The purpose of kinetic modeling in PET is a description of radioactive tracer tissue uptake kinetics in mathematical terms. Assuming we have a mathematical model, an input function which provides the tracer concentration in blood as a function of time, and dynamic PET data which provide the tracer concentration in a tissue as a function of time, the kinetic parameters of a proposed model can be estimated. Kinetic parameters have relevant physiological interpretation, i.e provide the quantitative information about physiological processes that take place in an observed tissue or organ. Therefore, this article also introduces compartment models which are most often used method for describing the radioactive tracers tissue uptake, the concept of input function, and explaines the estimation of kinetic parameters.

KINETIČNO MODELIRANJE V POZITRONSKI EMISIJSKI TOMOGRAFIJI (PET)

Članek najprej predstavi Pozitronsko Emisijsko Tomografijo (PET) kot funkcionalno in molekularno tehniko slikanja ter glavne fizikalne principe delovanja PET slikanja. Nato se osredotoči na kinetično modeliranje pri PET-u. Namen kinetičnega modeliranja pri PET-u je opis kinetike privzema radioaktivnega sledila v tkivih z matematičnimi termini. Če imamo na voljo matematičen model, vhodno funkcijo, ki vsebuje podatke o koncentraciji radioaktivnega sledila v krvi v odvisnosti od časa, in dinamične PET meritve, ki vsebujejo informacijo o koncentraciji radioaktivnega sledila v tkivu kot funkcijo časa, lahko ocenimo kinetične parametre predlaganega modela. Kinetični parametri nosijo relevantno fiziološko interpretacijo. Le ti zagotovijo kvantitativno informacijo o fizioloških procesih v določenem tkivu ali organu. Članek predstavi tudi razdelčne modele, ki se najpogosteje uporabljajo za opis privzema radioaktivnih sledil v tkivih, razloži koncept vhodne funkcije in pojasni ocenjevanje kinetičnih parametrov.

1. Introduction

Positron emission tomography - PET is a non invasive functional and molecular imaging technique used to map biological and physiological processes in the body. Most common targets of functional imaging are oxygen, glucose, lactate metabolisms, cellular growth, perfusion, neurotransmitter systems, organs and tissues. PET is used both in medical purposes in clinical oncology, neurology and cardiology and in research where it has become important in the fields of drug development and gene therapy.

Kinetic models are important tools in the research field of PET developed for descriptions of the kinetics of radiopharmaceutical tissue uptake in mathematical terms. They are useful because they lead to better understanding of the body's physiological processes which enables gathering information about the body.

2. Physical principles of PET

PET imaging technique is based on the detection of pairs of gamma rays emitted by a positron emitting radionuclide. The short lived radionuclide is delivered into the body via tracer - a radionuclide labelled molecule. When radionuclide emits a positron in the body, it undergoes annihilation with nearby electrons. That results in the release of two coincident gamma rays detected by the system. The resulting data is used to reveal the spatial distribution of the tracer in the body.

2.1 Tracers and radionuclides

Tracer is a biologically active molecule introduced into the body intravenously in nanomolar or picomolar quantities. The interaction of tracer molecule with the body's physiological processes is monitored. PET techology enables tracing the biological pathway of any PET isotope radiolabled molecule. Therefore, tracer molecules are tagged with positron-emitting radionuclides with half-lives long enough to provide optimal use of imaging photons while at the same time short enough to keep patient radiation dose as low as possible (most commonly used radionuclides are ^{18}F with half-life 109.8 min, ^{15}O with half-life 2 min, ^{11}C with half-life 20 min, and ^{13}N with half-life 10 min). Some tracers are toxic, but PET imaging uses such small tracer concentrations, that their toxicity does not represent a problem.

Tracer may be radiolabeled version of compounds normally used by the body. An example is water labeled with ^{15}O, [^{15}O]H_2O - radiowater.
Alternatively, the analogues of the natural compounds can also be used as tracers. Analogues are similar to natural compounds to which they are related, but have somewhat different biological pathways. Because of that, carefully chosen analog can simplify the modeling as original compounds can have very complex biochemical pathways which means that the models related to them will often be too complex. An example for this is tracer often used for measuring metabolic activity, [^{18}F]FDG. Chemically, [^{18}F]FDG is radiolabeled 2-deoxyglucose. Deoxyglucose and glucose enter cells by the same mechanism, but 2-deoxyglucose doesn't undergo usual glucoses metabolic pathway called glycolysis and because of that the product of its phosphorylation will be trapped intracellulary. Trapping of FDG in cells by phosphorylation is proportional to the metabollic rate of true glucose, but the inability of FDG glycolisis makes the intermediate product detectable by PET imaging.
Another advantage of [^{18}F] FDG is a suitable half-life which matches technical requirements of imaging, ($t_{1/2,[^{18}F]} = 109.8$ min).
Finally, unique compounds that do not naturally occur in the body, such as radiolabeled drugs, can also be used as tracers (for example, an [^{18}F] Fluoromisonidazole or [^{18}F] FMISO, which is a [^{18}F] labelled 2-nitroimidazole derivative[1] [1], and copper labelled Cu(II)-diacetyl-bis (N^4-methylthiosemicarbazone) or CuATSM[2] [2] used for hypoxia imaging).

2.2 Electron positron annihilation

Radioisotope undergoes positron emission decay. $\beta+$ decay is a subtype of beta decay, in which a proton inside a radionuclide nucleus is converted into a neutron while emiting a positron which is an antiparticle of the electron with opposite charge and equal mass, and an electron neutrino (ν_e). The process is described by relation (1):

$$p^+ \rightarrow n + \beta^+ + \nu_e. \tag{1}$$

The emitted positron decelerates in a tissue to a point where it can interact with nearby electron. The encounter results with the annihilation of both particles. Particle masses are in most cases converted in the annihilation process to two annihilation gamma rays moving in two opposite directions with an energy of around 511 keV each.

[1] Hypoxia is a state of low oxygen concentration in tissues. In tumours, hypoxia has emerged as an important factor promoting tumour progression and resistance to radiotherapy and chemotherapy. FMISO is used as a tracer for hypoxia imaging. Most of compounds used for hypoxia imaging with PET contain a 2-nitroimidazole structure, because 2-nitroimidazole derivatives are reduced and specifically accumulated in hypoxic areas. It is believed that FMISO accumulates in hypoxic cells via covalent binding with macromolecules after reduction of its nitro group [1].

[2] As discussed in [2], copper labelled Cu(ATSM) molecule is a lipophilic molecule that can easily diffuse from blood into the cell. Within the cell, it is reduced from copper(II) to copper(I) and then trapped in the hypoxic tissues but not in the normal tissues.

2.3 Detection

The main purpose of PET detectors is the detection of coincidental gamma rays from the tissue. PET detectors are positioned in a circle around the patient, so that they can detect as much pairs of gamma rays as possible.

Detectors detect annihilation when they detect gamma rays that arrive in pairs on the opposite sides of detector ring. Normally, a time window for detection of photons that originate from the same annihilation event is imposed on time difference between interaction of photons on each side of the detector ring. Such window should account for the difference in traveling distance of both photons, which, comparable to body dimensions of 20 cm, equates to a few ns. PET detectors should ideally detect only those coincidence events that originate as a result of positron annihilation along the line between the two parallel opposite detectors, but as they consist of scintillators, which are crystals (typically bismuth germanate ($Bi_4Ge_3O_{12}$ or BGO [3]) or cerium-doped lutetium oxyorthosilicate (Lu_2SiO_5[Ce] or LSO [3]) with decay time (the time duration required by a scintillator to emit photoelectron), their timing precision is limited. Traditionally, coincidence events were accepted within a finite interval 4 to 12 ns [4], however the new generations of PET scanners are capable of resolving events just few hundreds of picoseconds apart (500 – 700 ps) [5]. The place where annihilation took place is localized along the line of response, or LOR. LOR is a line in space connecting the two detectors along which the positron emission occurres. It is defined by the coincident observation of two 511 keV photons.

2.4 Image reconstruction and PET image data

In the simplest case of a single ring, detected interactions are limited to a single plane. Every planar LOR can be described by two coordinates, s which describes the distance from the center, and ϕ, an angle from the y axis. Line integration along all planar LORs at fixed direction ϕ forms a projection $p(s, \phi)$. As we can see on Figure 1, projections are further organized into sinograms.

Image of an object needs to be reconstructed from its projections, which means that data from the sinogram need to be reconstructed back to the x-y space. This can be done by the reconstruction method backprojection. An image consists of 2D pixel matrix. Pixels are described by x-y coordinates, while sinograms are described by s and ϕ coordinates. For every point (x, y) that lies on the line described by s and ϕ, the following relation holds:

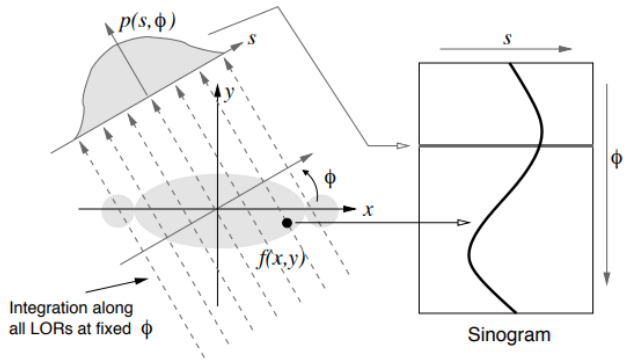

Figure 1. Projection (left) and sinogram (right) illustration. Planar line of response (LOR) is a line in space connecting the two detectors along which the positron emission occurres. Every planar LOR is described by coordinates s and ϕ. Line integration along all planar LORs at fixed direction ϕ forms a projection $p(s, \phi)$. Projections are organized into sinograms which are a visual representation of the raw data. The data are collected along planar LORs through a two-dimensional object described by $f(x, y)$ [6].

$$s = x \cos \phi + y \sin \phi. \tag{2}$$

The idea is to run projections back through the image at the angle it was acquired to obtain an approximation to the original. By running all projections back, an image is reconstructed. This means that the data about coincidence events from the sinogram are projected on the pixels which lie

along particular planar LOR, so backprojection represents the sum of all rays which pass through a point (x, y) or (s, ϕ), as illustrated in Figure 2. Such backprojection clearly overestimates the activity as all potential source pixels are counted for each event. Through filtered back-projection (FBP) this over-counting is compensated to provide realistic reconstruction of tracer distribution.

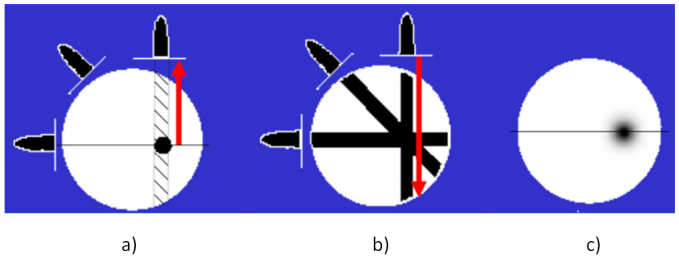

Figure 2. Illustration of reconstruction method backprojection. a) Measure = projection of object at various incidence angles. b) Backprojection = spreading of projections on image. c) Backprojection of large number of projections [7].

PET measures radioactivity concentrations which gives information about radiotracer distribution. Concentractions are usually measured in units nanocuries per mililiter (nCi/mL), becquerels per voxel, (Bq/vox) or becquerels per mililiter (Bq/mL). Typically, 10^{12} decay events need to happen in order to obtain an image with acceptable quality (activity injected into the patient via tracer is of the order of hundreds of MBq, and waiting period before measurements is small compared to the physical half-life). These measurements are reconstructed into cross-sectional images, as explained above. Static PET images contain only one time frame and therefore provide information about spatial distribution of tracer concentration. Dynamic PET images, obtained as static image sequences, provide both information about spatial and temporal distribution of tracer uptake. As kinetic modeling requires capture of time series, only dynamic PET images are used in kinetic analysis.

3. Kinetic modeling in PET

In physics, kinetics is defined as the study of motion and its causes [8]. Similarly, kinetics of radioactive tracer refers to the study of time course of the tracer absorption, distribution, metabolism, and excretion [9]. Each radiotracer is characterized by its particular kinetic behavior in the human body.

The purpose of kinetic modeling in PET is the description of the kinetics of radioactive tracer tissue uptake in order to gather quantitative information about the processes in the body [10]. Kinetic modeling in PET has applications in oncology, cardiology, in the research field of drug development and in the study of the neurochemistry of the brain.

Mathematical models describe the transition of the tracer from the blood into the tissue, and blood measurements give the information about tracer concentration in the blood as a function of time. Assuming that we have a model and blood measurements, the tracer concentration in the tissue as a function of time can be mathematically predicted.

Kinetic analysis is an inverse problem. If blood measurements and dynamic PET data which carry the information about tissue activity are known, kinetic parameters of a proposed model describing the dynamic process can be estimated.

Model's kinetic parameters are reflective of the kinetic properties of the particular tissue. The goal is to find values for kinetic parameters that, when inserted into the predicted model equations, will produce the best fit to the tissue measurements, i.e. will assure that the model describes the real tissue behavior as well as possible. A good understanding of the relationship between tissue measurements and a model is essential because a good model provides a mathematical description that

predicts the tracer's physiology and biochemistry within the limitations of available instrumentation [11].

3.1 Types of models

Non-compartment models don't explicitly describe all of the specific steps that a tracer molecule could possibly enter.

Distributed models are focused on a precise description of the possible physical locations of the tracer, but, unlike compartment models, they don't assume physiological domains and associated barriers of molecular transport. They are useful when describing processes such as diffusion where concentration gradients have an important role.

Compartment models are somewhere between non-compartment and distributed models by complexity. In this article compartment models will be presented in more detail, as compartment modeling is the most commonly used method for describing the uptake of radioactive tracers in tissue [11].

3.2 Compartment modeling and compartments

In most cases, compartment models are linear since they assume a negligible interference between the tracer and the system. Therefore, in linear compartment models, the transition rates between compartments are independent of the tracer concentration. Linear compartment kinetic models for PET are constructed from a fixed number of compartments which are assumed to interact with each other through linear transition rate constants $k_{ij} = k_{ji}$ (usually, it is assumed that the transition is proportional to the concentration (linear transition kinetics) and defined by constants k_{ij}), as illustrated in Figure 3. Constants k_{ij} are assumed to be positive because they carry the quantitative information about physiological processes which are positive by definition (they indicate the fraction of mass transferred per unit time). The asumption of compartment modeling is that all molecules are evenly distributed in compartments. Each compartment is a functional unit assigned with spatial location (for example, extracellular or intracellular space) or chemical state of a particular tracer. For example, labelled FDG molecules inside brain cells form a compartment. But, FDG itself is not a compartment, nor is a brain cell.

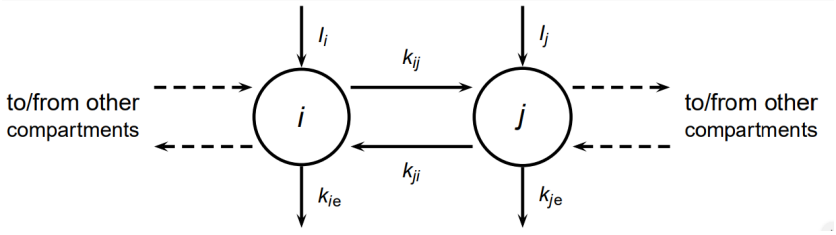

Figure 3. General n compartment linear model. Rate parameters k_{ji} and k_{ij} describe all the transfers from one compartment to other compartments while k_{ie} and k_{je} describe transfers from compartments i and j to the environment. I_i and I_j represent input functions for compartments i and j [12].

The general n compartment linear model is described by Eq. (3):

$$\begin{aligned} \dot{C}(t) &= AI(t) + KC(t) \\ C(0) &= C_0 \end{aligned} \tag{3}$$

In Eq. (3), $C(t)$ is a column vector of concentrations in the compartments, $I(t)$ is a column vector of input functions, A is a matrix of influx rate parameters from each input to each compartment, and K is a matrix that consists of rate parameters k_{ij}, which describe transfer from the compartment i

to the compartment j when $i \neq j$. The elements of A and K are assumed to be time-independent during the imaging period. The k_{ii}, described by Eq. (4), is given as sum of the terms k_{ji}, which describe all the transfers from the compartment j to other compartments, and k_{ie}, which describes transfer from the compartment i to the environment.

$$k_{ii} = -(k_{ie} + \sum_{j=1, j\neq i}^{n} k_{ji}) \tag{4}$$

The goal of kinetic analysis is to find the model values for the rate parameters k_{ij} that give the best fit to the tissue measurements when inserted into the model equations which are obtained as the solutions of the system (3) dependent on the number of compartments. An example of a solution and parameter estimation is given in subsections 3.2.3 Two-tissue compartment model and 3.2.4 Parameter estimation on the example of the two-tissue compartment model.

In PET, scanners provide measurements of radioactivity levels in a specific region, or pixel. If the tracer enters and leaves the organ via the blood, the tracer kinetics in other body regions need not be considered to evaluate the physiological traits of the organ of interest. In this way, each region or pixel can be analyzed independently [11] which means that modeling can be performed on the regional or pixel basis. When dealing with the data from the regions, tissue inhomogenity can create problems. The spatial resolution of the current PET scanners is around 5 mm full width at half maximum (FWHM). The minimum object size for accurate quantification is 2 FWHM, which leads to some problems with tissue homogenity assumption. However, simple compartment models have been shown to be adequate for the descriptions of PET imaging data [10]. On the other hand, in modeling on the pixel basis, image noise will represent greater problem. If collected data are adequate (if inhomogenities and noise are not too big), kinetic parameters averaged on region or pixel basis can be obtained by kinetic analysis.

3.2.1 Input function

Any system requires an input. In PET kinetic models, the model's input function is usually directly measured arterial blood curve - a concentraction of tracer in the arterial blood as a function of time. It is obtained from the blood sampling.

Typical plasma input function is shown in Figure 4. Black curve represents plasma concentration, and red curve metabolite corrected input function. After entering the body, tracers form radioactive metabolites that can't be distincted from parent tracer. Metabolites are also labeled and therefore detected which creates a problem because only the concentration of parent tracer can be used as input function in kinetic analysis. Because of that, input function needs to be metabolite corrected. Parent tracer can be separated from metabolites for example by taking blood samples at different time points and analyzing them with high-performance liquid chromatography (HPLC)[3]. HPLC separates parent tracer from metabolites based on different retention times in a column[4] [14]. After that, each plasma concentration needs to be multiplied by the parent tracer fraction at each sample time point. As a result the curve of parent radiotracer concentration in plasma is obtained. Also, on Figure 4 typical time dependence of plasma input function (black curve) and metabolite corrected input function (red curve) can be noticed. Both functions increase sharply with time at

[3]High-performance liquid chromatography (HPLC) is a technique used to separate and quantify each component in a mixture of molecules encountered in chemical and biological systems. In HPLC, a pressurized liquid solvent containing the sample mixture is passed through a column filled with adsorbent material. Each component in the sample interacts slightly differently with the adsorbent material. This leads to the separation of the components as they flow out of the column at different times [13].

[4]Retention time is time taken for a solute to pass through a chromatography column filled with adsorbent material.

the beginning, which is because of the initial tracer bolus infusion in the blood. After reaching peak (typically 1 min after tracer injection, when tracer mixes well with plasma), functions start to decrease because of the redistribution of the tracer from organs back to the circulation.

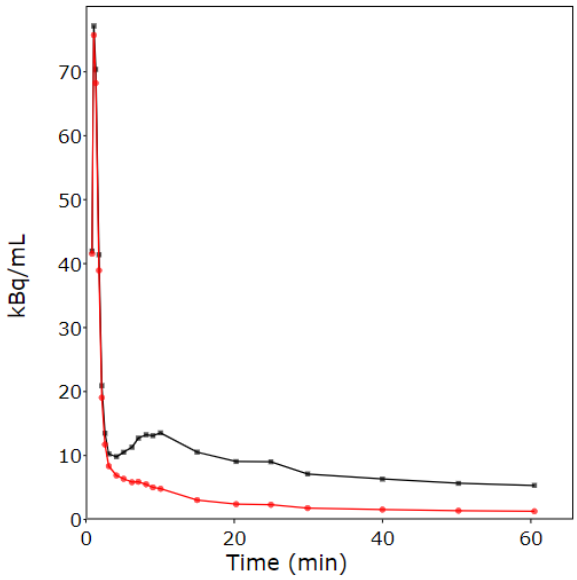

Figure 4. Example of typical input function from study where $[^{11}C]$ - Flumazenile was used as a tracer [15]. Black dots represent measurements of tracer concentration in plasma. Red dots represent metabolite corrected input function. Each plasma concentration (black) must be multiplied by the parent tracer fraction at each sample time point. That way, the curve of parent tracer concentration in plasma (red) is obtained.

3.2.2 Parameter estimation

The least-squares estimation is a commonly used method for kinetic parameters estimation when dealing with many tissue measurements [14]. This can be observed as a minimization problem, where the goal is to minimize the optimization function given by Eq. (5):

$$\chi^2 = \sum_{i=1}^{N} w_i(\hat{C}_{\mathrm{PET},i} - C_{\mathrm{PET},i})^2, \tag{5}$$

where there are N tissue tracer concentration measurements in the region of interest obtained with PET and represented by the term $\hat{C}_{\mathrm{PET},i}$. The term $C_{\mathrm{PET},i}$ represents the model's estimation of observation $\hat{C}_{\mathrm{PET},i}$. $C_{\mathrm{PET},i}$ is equal to the specific activity in the region of interest measured by PET which is given as sum of tracer concentrations in all compartments increased for the blood activity in the vessels located in the region of interest (Eq. 7 and Figure 5 for the example of the two-tissue compartment model). w_i is the weight of the measurment i.
After defining the optimization function, the values of the model parameters that minimize it can be determined by algorithms. In most cases iterative algorithms are required because even when dealing with models which themselves are linear, their solutions are often functions that are non-linear in some of the model parameters. When using iterative algorithms, an initial guess for the parameter values is made. Parameters of interest are often positive by definition, so the solutions are constrained to a physiologically acceptable values. Then, iterative algorithms reduce the value of the optimization function at each time step, i.e they repeatedly modify the parameters until changes between iterations become negligible small.

3.2.3 Two-tissue compartment model

Compartment models will be presented on the example of the often used two-tissue compartment model which consists of three compartments connected with rate constants. It is illustrated in Figure 5 and described by the set of two first order coupled ordinary differential equations (6) which simulate the differences between the fluxes entering the compartments and the fluxes leaving the compartments.

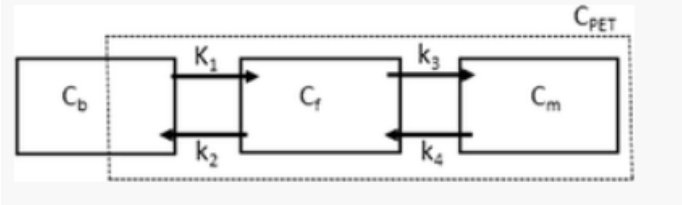

Figure 5. The two-tissue compartment model. C_b represents the tracer concentration in blood as a function of time (input function). Compartments C_f and C_m, described by the time-varying concentrations in them, represent two different compartments in the tissue. The first compartment is described by the concentration of free tracer, and the second one by the concentration of bound tracer (usually metabolites). Rate constants K_1, k_2, k_3 and k_4 model the interactions between compartments. Constant K_1 is related to perfusion, and has a unit of millilitre plasma per minute per millilitre tissue ($\mathrm{mL\,min^{-1}\,mL^{-1}}$). Accordingly, constant k_2 has a unit of millilitre of tissue per milliltre of plasma per unit time. Rate constants k_3 and k_4 have inverse time unit as they indicate the fraction of mass transferred per unit time. PET scanner measures the specific activity in the region of interest, marked with C_{PET} [15].

PET scanner measures the specific activity in the region of interest, marked with C_{PET} on the Figure 5. It is equal to the sum of the activity in both compartments increased for the blood or plasma activity in the vessels located in the region of interest (Eq. (7)):

$$C_{\mathrm{PET}}(t) = C_f(t) + C_m(t) + V_b C_b(t), \tag{6}$$

where V_b denotes the blood vessel fraction in the region of interest. By solving system (6) as discussed in [16], final expression (Eq. (8)) for $C_{\mathrm{PET}}(t)$ used for parameter estimation is obtained as following:

$$C_{\mathrm{PET}}(t) = \frac{K_1}{\alpha_2 - \alpha_1}\left((k_3 + k_4 - \alpha_1)e^{-\alpha_1 t} + (\alpha_2 - k_3 - k_4)e^{-\alpha_2 t}\right) \circledast C_b(t) + V_b C_b(t), \tag{7}$$

where the symbol $\circledast$ denotes one dimensional convolution function, and with

$$\alpha_{1,2} = \frac{\left[k_2 + k_3 + k_4 \mp \sqrt{(k_2 + k_3 + k_4)^2 - 4k_2k_4}\right]}{2}. \tag{8}$$

This model can be used to describe for example the metabolic rate of the glucose use in brain with the tracer [^{18}F]FDG. Two compartments are needed because once [^{18}F]FDG is in the tissue, it can either be transported back to the plasma or phosphorylated to [^{18}F] fluorodeoxyglucose-6-phosphate [12]. Therefore, the first compartment describes [^{18}F]FDG concentration in the observed tissue and the second one the concentration of [^{18}F] fluorodeoxyglucose-6-phosphate.

3.2.4 Parameter estimation on the example of the two-tissue compartment model

Knowing $C_b(t)$ as input function, and $C_{\mathrm{PET}}(t)$ by dynamic PET measurements, an algorithm is used to vary the rate constants K_1, k_2, k_3, k_4 and V_b in (8) till the calculated function equates $C_{\mathrm{PET}}(t)$, thus providing the final rate constants.

An example of parameter estimation is given in Figure 6. The initial values for the rate constants were $K_1 = 0.300\,\mathrm{mL\ min^{-1}\ mL^{-1}}$, $k_2 = 0.100\,\mathrm{mL\ min^{-1}\ mL^{-1}}$, $k_3 = 0.050\,\mathrm{min^{-1}}$, $k_4 = 0.030\,\mathrm{min^{-1}}$, $V_b = 0.05$ and the fitted values $K_1 = 0.302\,\mathrm{ml\ cm^{-3}\ min^{-1}}$, $k_2 = 0.076\,\mathrm{min^{-1}}$, $k_3 = 0.010\,\mathrm{min^{-1}}$, $k_4 = 0.041\,\mathrm{min^{-1}}$, $V_b = 0.08$ [13]. The values of the final rate constants have relevant physiological interpretation. For example, perfusion-related K_1 constant carries information about observed tissue perfusion - whether it is hypoperfused or hyperperfused and some diseases (for example, dementia) are characterized exactly by tissue hypo or hyper perfusion. Also, rate constants values between healthy and sick tissues can be compared, to see how disease affects their values.

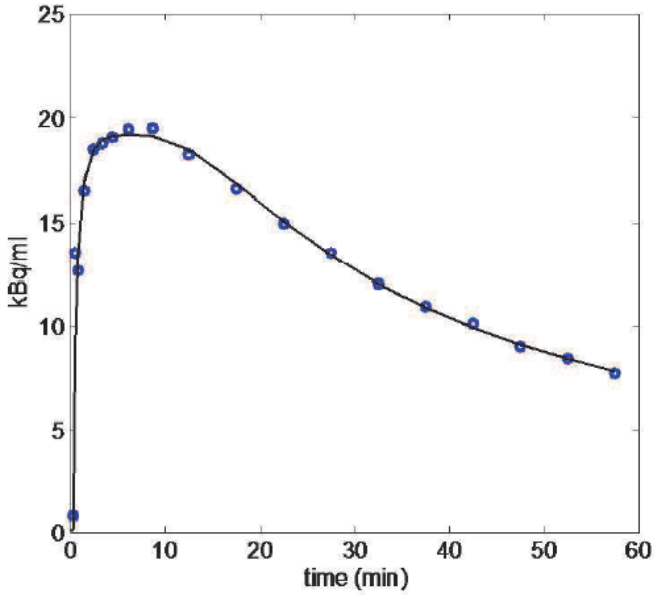

Figure 6. Activity measurements in the region of interest - right frontal region (dots) in a normal subject injected with [^{11} C] - Flumazenile as a tracer, and the corresponding fit (full line) obtained using the two-tissue compartment model [14].

3.3 Kinetic modeling pitfalls and limitations

When using kinetic modelling, the question of model selection arises. For kinetic modeling in PET, one-, two-, or three-compartment models with directly measured blood curve as the model's input function are typically used [10]. Often, a two-tissue compartment model with directly measured blood curve as input function is considered to be the gold standard model. In practice, this model is sensitive to different errors such as patient movement, errors in timing, errors in determining the input function, etc. [14]. Even thought more complex models were developed, the quality of information content of the PET data is sometimes inadequate to support them. Due to this, one must be aware that using a particular model is a great simplification of the truth and that interpretation of parameters comes with certain assumptions and conditions that must be satisfied [10].

Another point is that comparing different models is complex. As suggested in [14], to compare the agreement between two different models (or a model and the gold standard), for example a Bland-Altman plot can be used[5].

Limitations can also be experimental. The most common experimental limitation is the inconvenience of obtaining directly measured plasma input function [10].

[5]In Bland-Altman plot the difference of the two model parameters is plotted against their mean. It is recommended that 95% of the data points should lie within ± two standard deviations of the mean difference in order to declare agreement between models [17],

4. Conclusion

Kinetic modeling became an important tool of functional and molecular imaging technique PET developed for describing the kinetics of radiotracer tissue uptake. With known input function, dynamic PET data and proposed model, kinetic analysis estimates kinetic parameters which describe the dynamic process in a region of interest so that parameters obtained from analysis give the best possible fit betwen proposed model and measurements.

PET kinetic modeling offers existing potential in different research fields such as gene therapy, neurotransmitter imaging and drug developmet.

5. Acknowledgement

I would like to thank my mentor doc. dr. Urban Simončič for his guidance and all the useful advice on writing this work.

REFERENCES

[1] Y. Masaki, Y. Shimizu, T. Yoshioka, Y. Tanaka, K.Nishijima, S. Zhao,..., and Y.Kuge, *The accumulation mechanism of the hypoxia imaging probe "FMISO" by imaging mass spectrometry: possible involvement of low-molecular metabolites*, Scientific Reports (2015), 2.

[2] V. Gangemi, C. Mignogna, G. Guzzi, A. Lavano, S. Bongarzone, Giuseppe L. Cascini and U. Sabatini, *Impact of [64Cu][Cu(ATSM)] PET/CT in the evaluation of hypoxia in a patient with Glioblastoma: a case report*, BMC Cancer (2019), 4.

[3] C.L.Melcher, *Scintillation Crystals for PET**, Journal of Nuclear Medicine (2000), 1051.

[4] U.Kumar, A. K. Shukla, *Positron emission tomography: An overview*, Journal of Medical Physics (2006), 13 – 21.

[5] M.N.Ullah, E.Pratiwi, J.Cheon, H.Choi and J.Y. Yeom, *Instrumentation for Time-of-Flight Positron Emission Tomography*, Nuclear Medicine and Molecular Imaging (2016), 114.

[6] A. Alessio, P. Kinahan, *PET Image Reconstruction*, Nuclear Medicine, 1 – 4.

[7] I. Lackovic, *Biomedicinska instrumentacija* [PowerPoint slides], Zagreb, Croatia: Faculty of electrical engineering and computing (2016).
Retrieved from https://www.fer.unizg.hr/download/repository/P042016MedicalImaging(2).pdf (5.3.2020)

[8] *Kinetics*. Retrieved from https://en.wikipedia.org/wiki/Kinetics (25.3.2021)

[9] A.M.Peters, *Fundamentals of tracer kinetics for radiologists*, The British journal of radiology (1998), 1116.

[10] E.D.Morris, C.J.Endres, K.C.Schmidt, B.T.Christian, R.F. Muzic Jr. and R.E.Fisher, *Kinetic modeling in Positron emission tomography*, Emission Tomography: The Fundamentals of PET and SPECT (2012), 499 – 510.

[11] R.E.Carson, *Tracer kinetic modeling in PET*, Positron Emission Tomography (2006), 127 – 179.

[12] N.D.Evans, *Compartmental Modeling: Eigenvalues, Traps and Nonlinear Models* [PowerPoint slides], University of Warwick (2014). Retrieved from https://warwick.ac.uk (12.3.2020)

[13] *High - performance liquid chromatography*. Retrieved from https://en.wikipedia.org/wiki/High-performance-liquid-chromatography (17.10.2020)

[14] P. Dupont, N.Nelissen and J. Warwick, *Kinetic modelling in human brain imaging*, Positron Emission Tomography - Current Clinical and Research Aspects (2012), 55 – 82.

[15] *Correction of plasma TAC for metabolites*.
Retrieved from http://www.turkupetcentre.net/petanalysis/inputmetabolitecorrection.html (28.2.2020)

[16] *Razdelčni in nelinearni modeli* [Lectures at subject Modelska analiza za medicinske fizike], Ljubljana, Slovenia: Fakulteta za matematiko in fiziko, 2 – 3.

[17] D.Giavarina, *Understanding Bland Altman analysis*, Biochem Med (2015), 143.