ANALYSIS OF MATHEMATICAL MODEL FOR THE PHARMACOKINETIC PROCESS OF [^{18}F]-2FLOURO-DEOXYGLUCOSE

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Dedication

For the Memory of My Father (Fikadu Gerba)

Abstract

Parametric imaging is a compartmental approach that processes nuclear imaging data to estimate the spatial distribution of the kinetic parameters governing tracer flow. The aim of this thesis is to analyzed the Mathematical model for the pharmacokinetic process of radiopharmaceutic in the tissue, using Laplace transform method. When the tracer is administered intravenously absorption is complete and it is available in the bloodstream to be distributed throughout the whole body in all tissues and fluids, then eliminated. This kinetic mathematical model define a relation ship between the concentration of the radioactive tracer in a given tissue and the concentration of radioactive tracer in the plasma. This analysis of compartmental model is described by a system of two differential equations, where each equation represents the sum of all the transfer rates to and from a specific compartments. The transport of [^{18}F] FDG across the arterial blood is very fast in the first ten minutes and then decreases slowly. The thesis show actual uptake of [^{18}F]FDG in arterial tissue. The model is stable, positive and well posed. We have introduced a quantitative analysis method that provides a direct estimate of the metabolic rate of [^{18}F]FDG in arterial tissue.
Key words: Derivative, Laplace transform, Heaviside function,[^{18}F]FDG.

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Abbreviation

- FDG Flouro-deoxy glucose
- COPD Chronic obstructive pulmonary disease
- PET possitron emmision tomography
- (iv) intravascular
- (ev) extra-vascular
- LTI linear time-invariant
- ODE ordinary deferential equation
- INAC International nuclear atlantic conference
- CM Compartmental modeling
- IRF impulse response function
- SA spectral analysis.

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Chapter 1

Introduction

1.1 Background of the study

Positron emission tomography (PET) is a functional imaging technique that measures the local concentration of an exogenous tracer molecule in the target tissue. The power of PET lies in its molecular specificity. By using a particular radiotracer molecule, one can monitor the interaction of that molecule with the bodys physiological processes. For example, blood flow can be measured by using radioactive water as a tracer; metabolism can be measured with radioactive glucose (FDG)[15].

FDG is a glucose analog that is transported from the blood into cells by glucose transporters. Once in the cell, FDG is phosphorylated by hexokinase to form FDG-6-phosphate. Further metabolism of FDG-6-phosphate is limited and FDG-6-phosphate is essentially trapped in the cell. Although certain cells have phosphatases that dephosphorylate FDG-6-phosphate allowing washout, this is very limited over the imaging time period.

In general, patients are asked to fast for 4 - 6 hours prior to the administration of [^{18} F]FDG. Normally, diabetic patients are asked to fast for 4 hours while non-diabetic patients are asked to fast for 6 hours. Oral hydration prior to and following the study is encouraged. Exercise should be avoided for 24 hours prior to the study. If intravenous contrast material is used, patients should be screened for a history of iodinated contrast material allergy, use of metformin for the treatment of diabetes mellitus and renal disease.

The blood glucose level should be checked before [^{18}F]-FDG administration. For brain imaging, the patient should be in a quiet and dimly lit room from the time of radiopharmaceutical administration through the uptake time[27].The first human administration of [^{18}F]FDG occurred in 1976 in normal volunteers. The radiation dose to the patient for [^{18}F]FDG PET is based on the combination of the radiation dose from the radiopharmaceutical and from the CT portion of the study.

The use of the positron emitting glucose analogue [^{18}F] 2-fluorodeoxyglucose ([^{18}F]FDG) together with positron emission tomography (PET) makes it possible to image regional metabolism in the brain and in other organs,such as heart, muscle and liver. Dynamic PET data, analyzed with mathematical models of [^{18}F]FDG kinetics, allow the estimation of tissue fractional uptake of [^{18}F]FDG. The regional metabolic rate of glucose, by using the so-called lumped constant (LC), a scale factor between glucose and [^{18}F]FDG metabolism.^{18}F is radionuclide with half-life of 109.7 minutes. Normally only a single macroscopic parameter, i.e., [^{18}F]FDG is calculated. However, most of the models also have the potential to provide

a much more intimate picture of the system, e.g., degree of tissue heterogeneity and rate constants of blood-tissue exchange. Recently, the model by Sokoloff et al. [25] has been used to evaluate microscopic parameters in muscle, heart and liver in various pathophysiological conditions.

Comparison of models of [^{18}F]FDG kinetics is, however, lacking, the only available study being that of Lammertsma et al [8] from 1987, where two-compartmental models, the Sokoloff et al and the Phelps et al and the Patlak graphical method were investigated for brain data only. In recent years, new models have been proposed, notably the Schmidt et al.

In PET, the images are composite of various superimposed signals, only one of which is of interest. The desired signal may describe the amount of tracer trapped at the site of metabolism or tracer bound to a particular receptor[30].

In order to isolate the desired component of the signal (think of an image composed of layers), we must use a mathematical model relating the dynamics of the tracer molecule and all its possible states to the resultant PET image. Each of these states is known in the language of kinetic modeling as a compartment. For example, in a receptor-imaging study, the set of molecules that are bound to the target receptor can constitute one compartment. Each compartment is characterized by the concentration of the tracer within it as a function of time. These concentrations are related through sets of ordinary differential equations, which express the balance between the mass entering and exiting each compartment. By solving these simultaneous equations, we are able to determine the quantities of interest[7].

When modelling the system we will obtain relationships between variables, many of which will be related through derivatives. Even in a simple system with a mass, tracer and compartment there are many variables which can be identified, for example the parameter of compartments and its concentration and rate of flow of tracer from one compartment to another. A choice of variables that completely describe the system is an important task in systems analysis. These variables are then called the state variables. These can be related to each other and the system inputs through a system of first-order differential equations which are found by using scientific laws and biological principles to model the system[8].

Kinetic models for PET typically derive from the one, two, or three compartment model in which a directly measured blood curve (concentration of radiotracer in the blood as a function of time) serves as the models input function. The coefficients of the differential equations in the model are taken to be constants that are reflective of inherent kinetic properties of the particular tracer molecule in the system. By formally comparing the output of the model to the experimentally obtained PET data, one can estimate values for these kinetic parameters and thus extract information about binding, delivery or any hypothesized process as distinct from all other processes contributing to the PET signal[2].

Compartmental modeling is used to describe systems that vary in time but not in space. Thus, the assumptions of compartmental modeling are the well-mixed, there are no spatial concentration gradients in the area being sampled and whatever radio active species contribute to the emanating radioactive signal are in uniform concentration and can be characterized as being in unique states. Each of these states is assigned a compartment, which is described by a single ordinary differential equation.

Any system requires an input to drive it. We typically consider the input to the system to be the measured radioactive concentration in the blood supply as a function of time. Although the blood supply is a compartment in the physical sense, it is not a compartment of the model in the mathematical sense. Because it is measured rather than solved for.

However, the input concentration is often depicted as a circle in graphical representations of kinetic models[23].

Compartmental models often arise in the course of describing the kinetics of a tracer injected into a physiological system. In tracer studies, we make certain assumptions about the behavior of the tracer molecule, often radioactive, but sometimes labeled with a flourochrome or other detectable marker[25].
The key assumptions that must be satisfied are as follows.

1. The amount of tracer injected is a trace amount; that causes no change in the physiology of the organism.

   Example 1.1. *The tracers are often drugs, but when injected as tracers they must cause no drug effects.*

2. The tracer is in steady state with the endogenous molecule that the tracer seeks to emulate. In PET, we often talk about freely diffusible tracers.

3. There are no isotope effects. That is, the act of labeling the tracer molecule with a radionuclide does not alter its properties.

Compartment is considered as a unit of volume, where tracer appears to occupy after tracer has been absorbed [22]. Compartments should not be understood as a physical volume, but rather as a well-mixed space where the tracer is uniformly distributed; thus a system that reaches equilibrium at different time points will be described with a multi-compartmental model.

The study of movement of drug in the body is called pharmacokinetics. The science of pharmacokinetics uses mathematical equations to describe the movement of the drug through the body[9]. Nuclear Medicine analyzes dynamic data of functional processes related to a specific metabolic activity. Nuclear medicine imaging data are acquired by means of devices that detect the product of the decay of radioisotopes in a radioactive tracer, which is bound to molecules with known biological properties and diffused in the living organism. PET is the most modern nuclear medicine modality and FDGPET is the PET modality in which the radiopharmaceutical [^{18}F]-2fluoro-deoxyglucose is used as a tracer to evaluate glucose metabolism[4].

[^{18}F] FDG-PET dynamic images of tracer distribution, obtained from the measured radioactivity by applying an appropriate reconstruction algorithm, a reliable estimate of the functional behavior of glucose into tissues. Therefore, FDGPET experiments allow clinicians to detect and stage diseases related to the pathological glucose consumption, such as cancer or diabetes [3, 5, 13].

In order to relate the time-evolving tracer bio-distribution to the underlying functional process of interest, the application of mathematical model is necessary. It can be seen as an input or output transform, where the inputs are represented by the PET measurements acquired during the study and the measurements of radioactive concentration in plasma, while the output is represented by a set of parameter describing the tracer kinetics.

Compartmental analysis identifies different functional compartments in the physiological system of interest, each one associated with a specific metabolic state of the tracer. The tracer typically is injected into the blood and the tracer concentration in the blood is mathematically modeled by the so-called input function (IF) of the compartmental system. The

time dependent concentrations of tracer in each compartment constitute the state variables of the model and can be determined from PET data[14].

The time evolution of the state variables, i.e. the kinetics of the system, is here modeled by a linear system of ordinary differential equations (ODE) with constant coefficients, expressing the conservation of tracer during the flow between compartments. The coefficients define the input/output rate of tracer for each compartment and represent the physiological parameters describing the metabolism of the system. The forward problem is constructed by assuming that the tracer coefficients are known. The illustrative diagram of two tissue compartmental model is the following:

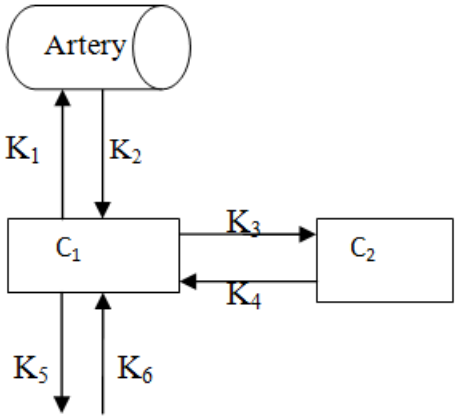

Fig 1.1 General representation of two tissue reversible compartment model

The symbols in this diagram have the following meanings:

- C_1 is concentration of compartment one.
- C_2 is concentration of compartment two.
- K_2 is the rate flow of tracer substance from artery to compartment one.
- K_1 is the rate flow of tracer substance from compartment one to artery.
- K_3 is the rate flow of tracer substance from compartment one to compartment two.
- K_4 is the rate flow of tracer substance from compartment two to compartment one.
- K_5, is rate flow of tracer from compartment one to unbinding compartment.
- K_6 is rate flow of tracer from unbinding compartment to compartment one.

To represent the flow model of tracer from one compartment to other in figure (1.1) above we use system of differential equations, where each equation corresponds to the sum of all the transfer of tracer of specific compartments.

In Figure (1.1) above if the number of compartments are N, then the concentration of tracer in compartment i is the difference between the constant rate to compartment i times the concentration of source compartment j and the constant rate from compartment i times concentration in compartment i. It is described by the following equation.

$$\frac{d}{dt}C_i = \sum_{j=1, j\neq i}^{N} [K_{ij}C_j - K_{ji}C_i] \tag{1.1}$$

where:

- $\frac{dC_i(t)}{dt}$ is concentration in i^{th} compartment.
- K_{ij} is the transfer rate from compartment j to compartment i.
- K_{ji} is the transfer rate from compartment i to compartment j.
- C_j and C_i are compartment j and i respectively.

In this analysis, kinetic parameter describing the tracer exchange to the target compartment i from the source compartment j. The kinetic parameters also known as rate constants or exchange coefficients are real positive numbers and the plus or minus signs against them characterize incoming and outgoing fluxes, respectively.

Pharmacokinetic modeling in general involves the development of a model that can quantitatively describe the pharmacokinetic behavior of the tracer in the body. In compartmental modeling, the body is described by one or more interconnected compartments depending on the rate of the tracer distribution to the different parts of the body. The number of compartments in the model depends on the rate of drug distribution to the different parts of the body. Each of the compartments has its own volume of distribution and the inter-compartmental clearances that govern the tracer distribution and transfer between these compartments. The model includes an input function that describes the tracer entry to the systemic circulation. The order of the elimination process and the compartment where the elimination process takes place are included in the model [10].

Compartmental pharmacokinetic mathematical models differ in the number of compartments; the compartment(s) where tracer elimination occurs and the arrangement of these compartments. The number of compartments in the model depends on the rate of drug distribution to the different parts of the body. If the drug in the systemic circulation is distributed rapidly to all parts of the body, the body behaves as a single compartment and the tracer pharmacokinetic behavior can be described by one-compartment pharmacokinetic mathematical model, while if the tracer is distributed rapidly to some tissues and organs and slowly to other tissues and organs, the two-compartment pharmacokinetic mathematicalmodel can be used to describe the pharmacokinetic behavior of the tracer in this case. On the contrary, when the tracer is distributed to the different parts of the body at three distinguished rates, for example rapid, slow, and very slow, the three-compartment pharmacokinetic mathematical model can be used to describe this pharmacokinetic behavior. The pharmacokinetic behavior of most tracer can be described by one, two, or three compartment mathematical model for pharmacokinetic process; however, models with more compartments can be used if the obtained data can support these complicated models[5].

The tissue homogeneity model,therefore describes tissue in terms of two compartments, one intra-vascular space(iv) and one extra vascular space(ev), is solved by Laplace transform of coupled ordinary differential equations, by assuming a functional form for the arterial input function (AIF) or by fitting to an experimentally determined AIF, this function is introduced into the solution as a boundary condition describing the time dependent input to

the capillary. The solution to the tissue homogeneity model equations in Laplace space are numerically inverted to obtain the concentration of tracer in the extra vascular space as a function of time and in the intravascular space as a function of both position and time [17].

1.2 Statement of proplem

The physiological system of dynamic processes in the tissue of interest is decomposed into a number of compartments, which interact each other. The ability to extract reliable quantitative information from FDG-PET data is great importance and much work has been done in this area using compartmental pharmacokinetic mathematical model. Such approaches typically involve assuming a functional form for the arterial input function (AIF), such as bi-exponential[30]. Once the connections or paths that the tracer can take between compartments have been specified, the mass balances on each compartment can be written in the form of ordinary differential equations. One differential equation must be specified for each unknown quantity. If the concentration of tracer in the plasma is known, it is not a compartment but its (time-varying) concentration does factor into the mass balances of the compartments. The differential equations of the model are written to describe influx and efflux of each compartments.

The tracer concentration in the tissues is given by the convolution of the tissue impulse response with the arterial input function. In order to simplify the mathematics a bi-exponential form is used for the AIF[29]. Inside a compartment the tracer is considered to be distributed uniformly. There is no diffusion or other barrier inside the compartment. Therefore, this research work will try to address the following basic questions:

- How to find concentration of [^{18}F]FDG in each compartment analytically?
- How to find the equilibrium point, invariant region and positivity of the mathematical models of [^{18}F]FDG and its transmission between two compartments?
- How to estimate all the pharmacokinetic parameters of the two-compartment mathematical model for pharmacokinetic process from plasma concentrations obtained after a single intra-vascular administration?

1.3 Objective of the study

1.3.1 General objective

The main objective of this study is analyze the mathematical model for the pharmacokinetic processes of [^{18}F]-2fluoro-deoxy glucose.

1.3.2 Specific objectives

The specific objectives of the study are:

- To analyze the positivity, invariant region and stability of the model.

- To analyze the analytic solution of arterial input function of glucose concentration with time.
- Analyze the effect of changing one or more of the pharmacokinetic parameters on the plasma concentration-time profile and the tracer distribution between the central and the peripheral compartments after administration of tracer that follow the two-compartment mathematical model for pharmacokinetic process.

1.4 Significant of the study

The significant of this thesis are

- Increase knowledge how to show the positivity, invariant region and stability of the model.
- Improve our understanding of the glucose kinetics in the artery after [^{18}F]FDG is administered intravenously.
- Describe the plasma concentration-time profile after a single intra-vascular and oral administration, during constant rate intra-vascular infusion and administration of tracer that follow two-compartment mathematical model for pharmacokinetic process.

1.5 Delimitation of the study

This thesis was mainly analyze the mathematical model for pharmacokinetic process of [^{18}F]2-flourdeoxyglucose. In addition we analyzed positivity of the model, invariant-region and stability of the model. The method we used were Laplace transform function, derivative and Heaviside function. we did not use Levenberg-Marquardit algorithm. Because it need experiment and knowledge of healthy science.

Chapter 2

Review of Literature

The standard approach for the quantification of dynamic PET studies are represented by compartmental modeling . This approach is based on a first-order differential description of the main physiological processes in which the tracer is involved. Compartmental modeling (CM) requires the full mathematical description of the system under investigation and a complete definition of the model structure, including the type and direction of the tracer exchanges between compartments[17].

CM is the only method that can provide a detailed understanding of the physiological system. Hence it is usually adopted as a tool for the investigation of novel tracers only when the compartmental structure describing the underlying system has been characterized. Compartmental model for dynamic PET studies are generally based on a linear time-invariant (LTI) description of the system [13].

Therefore the output of these models can always be represented as the convolution product between the input of the system and its impulse response function (IRF). This condition is always true, irrespective of any nonlinearity between the model output and its parameters."Bayesian" estimation is that "the tracer concentration in the tissues is given by the convolution of tissue impulse response with the arterial input function. But [^{18}F]FDG is analog labeled with the positron emitter ^{18}F and is used as a radiopharmaceutical to investigate tissue metabolism by PET and define PET as functional imaging technology that allows studying physiological and molecular changes through the administration of radiopharmaceutical tracers into living systems. Therefore in this thesis define the relation ship between them by using system of ode and analyze the model[18].

When radio labeled drug, such as [^{18}F]FDG is administered intravenously, the absorption is complete, the compound becomes available in the blood stream to be distributed throughout the whole body in all tissues and fluids; after that it is eliminated. This property is described by compartmental mathematical model [11].

Maria Doyle,Lauren Eskew and Taylor Ruggiero are assumed the bolus is intravenously administered and the bolus is well mixed instantly after being administered. In reality, there is a short time lag from the point the drug is introduced in the body until it is fully mixed in the system. They also assumed that the compartment volumes and reaction rates are constant and the flow of drug travels from the central compartment to the peripheral; there is no diffusion from the peripheral to the central and also the tracer is degraded constantly in the blood and tissue, all patients have similar reactions to the tracer and there is no renal clearance[10].

Spectral analysis (SA) allows the quantification of dynamic data. Among the different approaches for the quantification of PET data, SA is based on the linear solution of the Laplace transform, whereas the measured tissue time-activity curves of a radiotracer are used to calculate the input response function of the tissue. Physiological or biochemical systems are described using models of compartments in which a tracer is distributed between compartments.

Patlak approach using a data set comprising [^{18}F]FDG PET scans from COPD subjects with elevated circulating inflammatory markers (fibrinogen), a recently qualified and mortality in COPD and matched healthy never smokes (HV)[24]. The measured radioactivity concentration in a region of the lung can be expressed as the sum of three terms that reflect blood, tissue and air:

$$C_M(t) = V_B C_B(t) + (1 - V_B - V_A) C_T(t, k_1, k_2, k_3, C_B) + V_A C_A(t)$$

where $C_M(t)$ is the measured radioactivity concentration, $C_B(t)$ is the radioactivity concentration in blood,$C_T(t)$ is the radioactivity concentration in tissue, $C_A(t)$ is the radioactivity concentration in air,V_A is the fractional air volume in the ROI, V_B is the fractional blood volume in the ROI, and k_1, k_2, k_3 are the compartmental models micro parameters. For radio tracers administered intra venously such as [^{18} F]FDG, the radioactivity concentration in air ($C_A(t)$) can be considered negligible and so the third term is zero[25]. The kinetics of [^{18}F]FDG in tissue have been shown to be well described in human by an irreversible two tissue compartmental model with the metabolic rate constant.

$$K_i = \frac{K_1 K_3}{K_2 + K_3}$$

The irreversible two-tissue compartment model for [^{18}F]FDG is used for description of this tracer, which is first entering a free compartment C_1 and is then metabolized irreversibly in the second compartment C_2; the arterial input function is divide in to two stages. We used Heaviside function to represent this situation and solve by Laplace transform. This is one of the contribution of this study. We applied the Laplace transform and analyze the solution for two-tissue irreversible compartment model. In order to determine the parameters of model information on a tracer delivery is needed in the form of an input function that represents the time course of tracer concentration in the arterial blood or plasma [3, 7].

From mass balance equation interacting compartments where an outlet of one compartment is connected to the inlet of another is referred to as a multi-compartment model [22]. The tissue concentration is then given by

$$\sum_{j=1}^{n} V_j C_j(t)$$

Where V_j is the fractional or relative volume corresponding to the j^{th}compartment in (ml/ml or dimensionless) and

$$\sum_{j=1}^{n} V_j \leq 1$$

The concentration $C_j(t)$ is defined as the amount of indicator in the compartment j divided by the volume that the tracer occupies, the so-called volume of distribution. The conservation

of indicator mass implies that no indicator is created or destroyed inside the tissue. In that case, the change of total amount of indicator inside the tissue sample can be expressed by the difference of the amount entering and the amount leaving the system. The pathways for indicator exchange of a compartment are described in terms of the amount of indicator transported through inlet and outlet of a compartment. Applying a mass balance equation for each compartment of a system:

$$\frac{dM_j(t)}{dt} = \sum_{i\varepsilon Inlets} \frac{\partial M_i(t)}{\partial t} - \sum_{i\varepsilon outlet} \frac{\partial M_o(t)}{\partial t}$$

they used the general physical mass balance equation. In this case$M$ is a function of time and hence the total derivative of M equals the partial derivative of M. Subsequently, the mass balance equation normalized to the tissue volume V_t has the form:

$$V_j \frac{dC_j(t)}{dt} = \sum_{i\varepsilon inlets} J_i(t) - \sum_{o\varepsilon outlets} J_o(t)$$

It follows from the conservation of indicator mass that the transport of indicator from a compartment i to a compartment j per unit time is equal to the portion of indicator leaving the compartment i. This leads to

$$\frac{\partial M_{ij}(t)}{\partial t} = KM_i$$

Modeling how pollutants move through an environment is important in the prediction of harmful effects, as well as the formulation of environmental policies and regulations. The simplest situation has a single source of pollution that contaminates a well-defined habitat, such as a lake. To build a model of this system, we picture the lake as a compartment; pollutants in the water flow into and out of the compartment. The rates of flow determine the amount of build-up or dissipation of pollutants. It is useful to represent this conceptual model with a compartment diagram, where a box represents a compartment and an arrow represents a flow rate[33]. Here is a compartment diagram for a simple model of lake pollution:

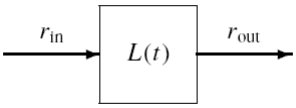

Fig 2.1

The amount of pollutant in the lake at time t is $L(t)$, while r_{in} is the rate of flow of pollutant into the lake and r_{out} is the rate of flow of pollutant out of the lake. To obtain the equation for the rate of change of the amount of pollutant in the lake, we apply the balance law: the net rate of change of the amount of a substance in a compartment is the difference between the rate of flow into the compartment and the rate of flow out of the compartment:

$$\frac{dL}{dt} = r_{in} - r_{out}$$

Medications that relieve the symptoms of high fever often contain an antihistamine and a decongestant bundled into a single capsule. The capsule dissolves in the gastrointestinal

(GI) tract and the contents move through the intestinal walls and into the bloodstream at rates proportional to the amounts of each medication in the tract. The kidneys clear medications from the bloodstream at rates proportional to the amounts in the blood[32]. Here is a compartment diagram for this system:

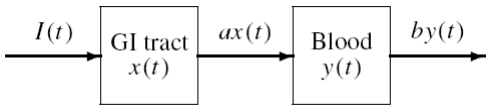

Fig 2.2

The symbols in this diagram have the following meanings:

- I(t): The rate at which the dissolving capsule releases a medication (for example, a decongestant) into the GI tract
- x(t): The amount of medication in the GI tract at time t
- ax(t): The clearance rate of the medication from the GI tract, which equals the entrance rate into the blood (a is a positive rate constant)
- y(t): The amount of medication in the blood at time t
- by(t): The clearance rate of the medication from the blood (b is a positive rate constant)

Applying the balance law to each compartment, we have a system of first- order linear ODEs:

$$\dot{x} = I - ax$$
$$\dot{y} = ax - by$$

If we know I(t), the rate constants a and b, and the initial amounts $x(0)$ and $y(0)$ of medication in the GI tract and the bloodstream, we can use ODE Architect to track the flow of the medication through the body. From a pharmacological point of view, the goal is to get the medication levels in the blood into the effective (but safe) zone as quickly as possible and then to keep them there until the patient recovers.

There are two kinds of medication-release mechanisms: continuous and on-off. In the first kind, the medication is released continuously at an approximately constant rate, so $I(t)$ is a positive constant. In the on-off case, each capsule releases the medication at a constant rate over a brief span of time and then the process repeats when the next capsule is taken. In this case we model $I(t)$ by a square wave[33].

Chapter 3

Mathematical Preliminaries

This unit provides the basic mathematical theories, concepts and methodologies required, in the analysis and understanding of the results presented in subsequent chapters.

3.1 Ordinary differential equations(ODE)

Consider the system of differential equation below,

$$\dot{x} = f(x,t), x(0) = x_0 \tag{3.1}$$

Here $f : U\text{x}R^+ \to R^n$ with $x \in U \subset R^n, t \in R^+, n \in \mathbb{N}$, and U open in R^n. The over dot in (3.1) represents the derivative with respect to time $(\frac{d}{dt})$ and (3.1) is referred to as an ordinary differential equation.

Definition 3.1. *[31] Ordinary differential equations(ODE) are equations which involves only one independent variable and derivatives of function with respect to this independent variable.*
Lets see some examples:

1. *ODE for unknown function, u, is* $\ddot{u} = u$.
2. *Equivalently, we can write the ODE as* $\frac{d^2u}{dt^2} - u = 0$.
3. *Another ODE is:* $\frac{dy}{dx} + y = sin(x)$

Definition 3.2. *A linear ordinary differential equation of order n is an equation of the form*

$$a_o(t)\frac{d^n y}{dt^n} + a_1(t)\frac{d^{n-1}y}{dt^{n-1}} + a_2(t)\frac{d^{n-3}y}{dt^{n-3}} + \ldots + a_n(t)y = f(t) \tag{3.2}$$

Where $a_o(t), a_2(t), a_3(t), \ldots, a_n(t)$ *are assumed continues real function on real interval* $0 \leq x \leq 1$ *and* $a_o(t)$ *is not identically zero.*
If $f(t) = o$*, from(3.2), then it is homogeneous ODE.*

Definition 3.3. *An ODE operator, L, is linear if it can be written as a linear combination of the unknown function, u and its derivatives. A linear ODE operator L, of order n can always be expressed as*

$$L(u) = \sum_{j=1}^{n} a_j(x)u^j$$

where u denotes the unknown function, and u^j denotes the j^{th} derivative of u, where $u^0 = u$. The coefficient functions $a_j(x)$ are specifically given by the ODE. A linear ODE operator L has constant coefficients if and only if each of the functions $a_j(x)$ is a constant function.

3.2 Laplace Transform

Differential equations arise naturally in many problems encountered when modeling physical phenomena. To begin our study of this subject, we introduce two fundamental examples that demonstrate the central role that differential equations play in our world.

Definition 3.4. *Let $f(t)$ be given for $t > 0$, and suppose that f is piecewise continuous function. Then the Laplace transform of f, is defined by*

$$\mathcal{L}\{f(t)\} = F(s) = \int_0^\infty e^{-st} f(t)dt. \tag{3.3}$$

Theorem 3.1. *If $\mathcal{L}\{f(t)\} = F(s)$ and $\mathcal{L}\{g(t)\} = G(s)$ then for any constants a and b,*

$$\mathcal{L}\{af(t) + bg(t)\} = aF(s) + bG(s)$$

Proof. By definition

$$\begin{aligned} \mathcal{L}\{af(t) + bg(t)\} &= \int_0^\infty e^{-st}[af(t) + bg(t)]dt \\ &= a\int_0^\infty e^{-st} f(tdt) + b\int_0^\infty e^{-st} g(t)dt \\ \mathcal{L}[af(t) + bg(t)] &= a\mathcal{L}\{f(t)\} + b\{g(t)\} \end{aligned}$$

□

Definition 3.5. *A function f is said to be piecewise continuous on an interval $\alpha \le t \le \beta$, if the interval can be partitioned by a finite number of points $\alpha = t < t_1 < t_2 \ldots < t_n = \beta$ so that*

- *f is continuous on each open subinterval $t_{i-1} < t < t_i$.*
- *f approaches a finite limit as the endpoints of each subinterval are approached from within the subinterval.*

Definition 3.6. *(Lerchs cancellation law)*
Let $y(t)$ and $f(t)$ be integrable over interval $[o, \infty)$, and if

$$\int_0^\infty y(t)e^{-st}dt = \int_0^\infty f(t)e^{-st}dt; \qquad then \qquad y(t) = f(t)$$

or

$$\mathcal{L}\{y(t)\} = \mathcal{L}\{f(t)\}, \qquad then \qquad y(t) = f(t)$$

In differential equation applications, $y(t)$ is the sought-after(wanted) unknown while $f(t)$ is an explicit expression taken from integral tables.

Definition 3.7. *(convergence or existence of integral).Let f be a function and M is any real number. Then f is integrable if $|f(t)| < Me^{-at}, \quad a + Re(s) > 0; \quad$ so that $e^{-[a+Re(s)t]}$ is finite, as $t \longrightarrow \infty$.*

The Laplace transform is an integral transform where a function f(t) with living in the time domain is transformed by the Laplace transform into the complex domain. The advantage of this transformation is that solving the differential equation in the time domain corresponds to simple algebraic operations in the complex [21] . The solution can then be transformed back into the time domain, by the following Laplace transforms:

Theorem 3.2. *suppose that*

- *f is piecewise continuous on the interval $0 \leq t \leq A$ for any positiveA.*
- *$|f(t)| \leq ke^{at}$ when $t \geq M$. In this inequality k, a,and M are real constants, k and M necessarily positive.*

Then the Laplace transform of $f(t) = F(s)$

Proof. To establish this theorem it is necessary to show only that the following integral converges for $s > a$; Split the improper integral into two parts as

$$\int_0^\infty e^{-st} f(t)dt = \int_0^M e^{-st} f(t)dt + \int_M^\infty e^{-st} f(t)dt \tag{3.4}$$

The first integral on the right side of equation(3.4) exists; hence the existence of $F(s)$ depends on the convergence of the second integral; for
$t \geq M; |e^{-st} f(t)| \leq ke^{-st}e^{at} = ke^{(a-s)t}$ therefore $\int_M^\infty e^{(a-s)t}dt$ is convergent. □

Theorem 3.3. *Suppose that f is continuous and $\dot{f}$ is piecewise continuous on any interval $0 \leq t \leq A$. Suppose further that there exist constants k, a and M such that $|f(t)| \leq ke^{at}$for $t \geq M$. Then $\mathcal{L}\{\dot{f}(t)\}$ exists for $s > a$ and moreover $\mathcal{L}\{\dot{f}(t)\} = s\mathcal{L}\{f(t)\} - f(0)$*

Proof. By definition of Laplace transform

$$\begin{aligned} \mathcal{L}\{\dot{f}\}(s) &= \int_0^\infty \dot{f}e^{st}dt \\ &= f(t)e^{-st}|_0^\infty + s\int_0^\infty f(t)e^{-st}dt \\ &= s\mathcal{L}\{f\}(s) - f(0) \end{aligned}$$

□

Theorem 3.4. *If $F(s) = \mathcal{L}\{f(t)\}$ exists for $s > a \geq 0$, and if c is a positive constant, then $\mathcal{L}\{u_c(t)f(t-c)\} = e^{cs}\mathcal{L}\{f(t)\} = e^{-cs}F(s), s > a.$*

Proof. It is sufficient to compute the Laplace transform of $U_c(t)f(t-c)$

$$\begin{aligned}
\mathcal{L}\{u_c(t)f(t-c)\} &= \int_0^\infty e^{-st}u_c(t)f(t-c)dt \\
&= \int_0^\infty e^{-st}f(t-c)dt \qquad \text{let } \xi = t-c, \text{ we have} \\
\mathcal{L}\{u_c(t)f(t-c)\} &= \int_0^\infty e^{-(\xi+c)s}f(\xi)d\xi \\
&= e^{-cs}\int_0^\infty e^{-(\xi s)}f(\xi)d\xi \\
&= e^{-cs}F(s)
\end{aligned}$$

□

Theorem 3.5. *(Exponential function)*
let t be time, a is any real number and s is any complex number, then $\mathcal{L}\{e^{at}\} = \frac{1}{s-a}$; where $a \in \mathbb{R}$ and $a \neq s$

Proof. Apply the inverse Laplace Transform to the exponential functions given

$$\begin{aligned}
\mathcal{L}\{e^{at}\}(s) &= \int_0^\infty e^{at}e^{-st}dt = \int_0^\infty (e^{(a-s)t}dt \\
&= \frac{1}{a-s}e^{(a-s)t}|_0^\infty \\
&= \frac{1}{s-a} \qquad \text{where } a \in \mathbb{R} \text{ and } a \neq s
\end{aligned}$$

, □

Theorem 3.6. *(Bi-exponential function)*
The bi-exponential functions in domain of image is given by

$$\mathcal{L}\{\frac{e^{-\alpha t}-e^{-\beta t}}{\beta-\alpha}\}(s) = \frac{1}{(s+\beta)(s+\alpha)}; \textit{where} \quad \beta, \alpha \in \mathbb{R}$$

Proof. solution of the Laplace transform of the bi-exponential function given as

$$\begin{aligned}
\mathcal{L}\{\frac{e^{-\alpha t}-e^{-\beta t}}{\beta-\alpha}\}(s) &= \int_0^\infty \frac{e^{-(s+\alpha)t}}{\beta-\alpha}dt - \int_0^\infty \frac{e^{-(s+\beta)t}}{\beta-\alpha}dt \\
&= \frac{1}{\beta-\alpha}\left[\left(-\frac{e^{-(s+\alpha)t}}{s+\alpha}|_0^\infty\right) + \left(\frac{e^{-(s+\beta)t}}{s+\beta}|_0^\infty\right)\right] \\
&= \frac{1}{(s+\alpha)(s+\beta)}
\end{aligned}$$

□

Theorem 3.7. *Let$f(t) = t^n$ and $n\varepsilon\mathbb{N}$, then $\mathcal{L}\{f(t)\} = \mathcal{L}\{t^n\} = \frac{n!}{s^{1+n}}$*

Proof.

$$\begin{aligned}
\mathcal{L}\{t^n\}(s) &= \int_0^\infty e^{-st}t^n dt; \qquad \text{where} \quad st = u \\
&= \int_0^\infty e^{-u}\left(\frac{u}{s}\right)^n \frac{du}{s} \\
&= \frac{n}{s^{n+1}}\int_0^\infty e^{-u}U^{n-1}du \\
&= \frac{n(n-1)}{s^{n+1}}\int_0^\infty e^{-u}U^{n-2}du\ldots \\
&= \frac{n!}{s^{1+n}}
\end{aligned}$$

□

Definition 3.8. *Considering H(t) as the Heaviside function(the unit step function),then H(t) is given as. The Heaviside unit function, also called the unit step function, is defined as*

$$H(t) = \begin{cases} 1 & when \qquad t \geq 0, \\ 0 & when \qquad t < 0. \end{cases}$$

$$H(t-a) = \begin{cases} 1 & when \qquad t \geq a, \\ 0 & when \qquad t < a. \end{cases}$$

$$H(t-a) - H(t-b) = \begin{cases} 1 & when \qquad a \leq t < b, \\ 0 & when \qquad t < a \ and \ t \geq b. \end{cases}$$

where t is the time variable and $t = a$ or $t = b$ denotes time at which a step change has been occured. Another step function is, which can be represented as follows

$$\begin{aligned}
\sigma(t) &= \sigma_0 H(t) + \Delta\sigma_1 H(t-\Theta_1) + \Delta\sigma_2 H(t-\Theta_2) + \ldots \\
\sigma(t) &= \sum_i^n \Delta\sigma_i H(t-\Theta_i)
\end{aligned}$$

Heaviside functions have been used in order to generate vertical lines. Besides the Heaviside unit function the Dirac delta function, also called the unit impulse function, plays a central role in creep mechanics and defined according to

$$\delta(t-a) = \begin{cases} 0 & \text{for } t \neq a, \\ \infty & \text{for } t = a. \end{cases}$$

3.2.1 Unit impulse dirac delta function

The impulse function, or delta function, is a mathematical representation of a kick. It is an idealized kick that lasts for no time at all and has energy of exactly one. The delta function, $\delta(t)$, is an example of a generalized function. A generalized function can be defined in terms of a sequence of functions. One way of defining it is as the limit of a rectangular pulse function, with area one square unit, as it halves in width and doubles in height. Although the height of the pulse is tending to infinity, the area of the pulse remains one square unit. Two important properties of the delta function are

$$\delta(t-a) = 0 \qquad \text{for} \qquad t \neq a, \tag{3.5}$$

$$\int_{-\infty}^{\infty} \delta(t)dt = 1 \tag{3.6}$$

The second property expresses the fact that the area enclosed by the delta function is 1 square unit. The unit step function, u(t), has no derivative at $t = 0$. Because of the sharp edges present in its graph and its jump discontinuity it is impossible to define a single tangent at that point. However, if we also consider the unit step function as a generalized function (by taking the limit of nice smooth, continuous curves as they approach the shape of the unit step function), we are able to define its derivative, which turns out to be the delta function. This gives the third definition

$$\frac{du}{dt} = \delta(t)$$

where u is the unit step function, t is time and $\delta(t)$ is dirac delta function.

The unit impulse (dirac delta) function or δ function has in the Laplace domain is given by

$$\mathcal{L}\{\delta(t)\} = 1$$

proof
From the shifting property of the delta function follows

$$\mathcal{L}\{\delta\}(s) = \int_0^{\infty} \delta(t)e^{-st}dt = e^0 = 1$$

Theorem 3.8.
$\mathcal{L}\{1\} = \frac{1}{s}$

Proof.

$$\begin{aligned}
\mathcal{L}\{1\} &= \int_0^{\infty} e^{-st}dt \\
&= -\left(\frac{e^{-st}}{s}|_0^{\infty}\right) \\
&= -\left(0 - \frac{e^{-s(0)}}{s}\right) \\
&= -\left(0 - \frac{1}{s}\right) = \frac{1}{s}
\end{aligned}$$

□

Chapter 4

Model formulation and analysis

4.1 Model assumption

Arterial Input Function(AIF), denoted C_a, is needed for the kinetic analysis. The most accurate way to obtain the radioactive concentration in the blood is by frequent arterial blood sampling of the patient. This may cause discomfort and can at the worst carries some risks for the patient. It also means a slightly higher risk for the personnel handling the radioactive blood samples. A noninvasive way to obtain the blood curve is by the image derived input function. This method needs to have a sufficiently large vascular structure, such as the left ventricle or a major artery visible in the images. A ROI is drawn manually over the vascular region to derive the blood activity[34].

Compartmental models described in terms of a set of ordinary differential equations (ODE) with constant coefficients. By convention, in the nuclear medicine literature, the first compartment is the concentration of the tracer in the blood or plasma pool. To be exact, the concentration in artery is not a compartment of the model. The concentration of tracer in the artery is a measured quantity and applied to the compartmental model as a known input function to drive the system.

When modeling the system we will obtain relationships between variables, many of which will be related through derivatives. In this thesis there are variables which can be identified, the glucose concentration in each compartments and parameters of the model.These variables are then called the state variables. These can be related to each other and the system inputs through a system of first-order differential equations which are found by using scientific law to model the system. The system output, which is some quantity that we wish to compare with the response of a real system, can then be calculated from the values of the state variables.

The glucose metabolism is investigated using the irreversible [^{18}F]FDG model, which was developed for description of the tracer [^{18}F]FDG. The irreversible two compartment model for FDG and used for description of the tracer, which inter in a free compartment and then metabolized irreversibly in the second compartment and unbinding compartment. In order to determine the parameters of the model, it is necessary to have information about the tracer delivery in the form of an input function representing the time-course of tracer concentration in arterial blood or plasma.

The following diagram is irreversible two tissue compartmental model to show the relation ship between parameters and direction of the flow of the tracer.

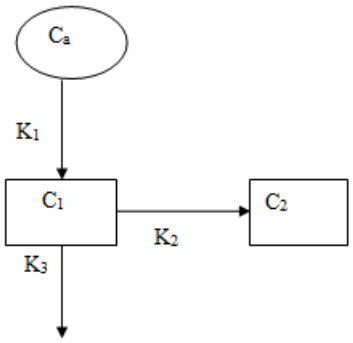

Fig 4.1 Irreversible two-tissue compartment model.

where

- C_a is measured concentration of tracer in the artery.
- C_1 is concentration of the tracer in compartment one.
- C_2 concentration of the tracer in the second compartment.
- K_1, K_2 and K_3 are rate flow of [^{18}F]FDG concentration.
- arrow show the direction of flow of tracer.
- The rectangles represent compartments.

Where C_a, K_1, K_2, and K_3 are known positive quantities and at $t = 0, C_a = 0$.

Compartmental model with more than four parameters are difficult to analyze its reliable result. Because as the number of compartment increase the numbers of parameters also increases. For example if we consider three compartment there are six parameters; there fore a compartmental model with more than two compartments are usually convert to two or one compartmental model and analyze.

4.2 The model Formulation

From irreversible[^{18}F]FDG model Figure(4.1); the tracer concentration in the tissue is given by the following system of differential equations.

$$\begin{aligned} \frac{d}{dt}C_1(t) &= K_1C_a(t) - (K_2 + K_3)C_1(t) \\ \frac{d}{dt}C_2(t) &= K_2C_1(t) \end{aligned} \tag{4.1}$$

whith $C_a(0), C_1(0)$ and $C_2(0)$, at $t = 0$
Equation(4.1) is the governing equation or mathematical model of arterial in put function of irreversible two tissue compartmental model.
Where,

- K_1 rate constant flow of tracer from C_a to C_1
- K_2 rate constant flow from C_1 to C_2
- K_3 rate constant flow from C_1 to plasma.
- $\frac{dC_1}{dt}$ is rate of change of tracer concentration in compartment(C_1).
- $\frac{dC_2}{dt}$ is rate of change of tracer concentration in compartment(C_2).

4.2.1 Basic properties of the model

The basic properties of the mathematical model (4.1) have studied. These are the invariant region, stability of the equilibrium points and positivity of solutions.

Positivity of solutions

Theorem 4.1. *For the mathematical model (4.1) with initial conditions $C_a(0), C_1(0)$ and $C_2(0)$, the model is meaning full if variables and parameters are positive, $\forall t \geq 0$. Because the variables and parameter are concentration and its transform.*

Proof. We need to show that all these state variables must remain nonnegative for $\forall t \geq 0$. K_1, K_2, K_3 are constant positive parameters.
from the first equation of the mathematical model (4.1) we have,

$$\begin{aligned} \frac{d}{dt}C_1(t) &= K_1C_a(t) - (K_2+K_3)C_1(t) \\ \frac{d}{dt}C_1(t) &+ (K_2+K_3)C_1(t) = K_1C_a(t) \\ \frac{d}{dt}C_1(t)e^{(K_2+K_3)t} &= K_1C_a(t)e^{(K_2+K_3)t} \end{aligned} \tag{4.2}$$

$C_a(t)$ is measured input tracer at time t is known constant, then by integrating both side of equation(4.2) we get,

$$\begin{aligned} C_1(t)e^{(K_2+K_3)t} &= K_1C_a(t)\int_0^t e^{(K_2+K_3)t}dt \\ C_1(t)e^{(K_2+K_3)t} &= \frac{K_1C_a(t)}{K_2+K_3}e^{(K_2+K_3)t}|_0^t \\ C_1(t)e^{(K_2+K_3)t} &= \frac{K_1C_a(t)}{K_2+K_3}e^{(K_2+K_3)t} - \frac{C_a(0)}{K_2+K_3}e^{(K_2+K_3)(0)}) \qquad \text{but } C_a(0)=0 \\ C_1(t)e^{(K_2+K_3)t} &= \frac{K_1C_a(t)}{K_2+K_3}e^{(K_2+K_3)t} \qquad (4.3) \\ C_1(t) &= \frac{K_1C_a(t)}{K_2+K_3} \qquad (4.4) \end{aligned}$$

the value of $e \approx 2.718$, then $e^{(K_2+K_3)t} \geq 1$ always and $C_a(t) \geq 0$, therefore $C_1(t) \geq 0$
From second equation of mathematical model (4.1) we have

$$\begin{aligned}
\frac{d}{dt}C_2(t) &= K_2 C_1(t) \\
C_2(t) &= K_2 \int_0^t C_1(t)dt, \qquad But C_1(t) = \frac{K_1 C_a(t)}{K_2 + K_3} \\
&= K_2 \int_0^t \frac{K_1 C_a(t)}{K_2 + K_3} dt \\
&= \frac{K_1 K_2 C_a(t)}{K_2 + K_3} \int_0^t dt \\
&= \frac{K_2 K_1 C_a(t)}{(K_2 + K_3)} t|_0^t \\
C_2(t) &= \frac{K_2 K_1 C_a(t)}{(K_2 + K_3)} t \geq 0 \qquad (4.5)
\end{aligned}$$

then $\quad C_2(t) \geq 0$

□

This show that if the parameter are positive, then all the variables of this mathematical model are positive. Hence the proof of positivity of the mathematical model (4.1).

Equilibrium point

In this subsection, we analyze the existence of equilibrium point of the system of equation (4.1) and its local stability. In the case of exchange between compartments in a pharmacokinetic model, a condition of equilibrium can theoretically be defined as having been reached when the rate of change of the concentration in the compartments is zero. The conditions for equilibrium can also be defined mathematically by setting the rate of change in the differential equations describing the system to zero. However, this idealized situation is not normally encountered in PET since the system is not closed and tracer is normally being continuously lost. Different terms for equilibria between plasma and tissue activity concentrations are used. Two tissue compartmental used Pseudo-equilibrium which refer the net exchange between the plasma compartment and the tissue compartments is small but the tracer loss from the plasma compartment is not negligible. The plasma curve has a small negative slope. In this situation, the ratio of tissue to plasma concentration will be slightly higher than in the true equilibrium situation.

A pseudodistribution equilibrium occurs between the two compartments following which the subsequent loss of tracer from the central compartment is slow and mainly due to elimination. This second, slower rate process, is called as the post-distributive or elimination phase. In contrast to this compartment, the concentration of tracer in the peripheral compartment first increases and reaches its max. Following peak, the tracer concentration declines which corresponds to the post-distributive phase.

Therefore the mathematical model (4.1) has equilibrium point at $(0, 0)$ only and called the tracer-free equilibrium point, which exists without any condition. This equilibrium point implies that in the absence of any tracer injection, the concentration of tracer in the tissue is negligible or no transfer among the compartment.

Local stability analysis

Here we analyzed the stability of free equilibrium point (0,0). In order to do this, we checked the sign of the eigenvalues. The Jacobian matrix of the mathematical model(4.1) is given by

$$J_{c_1,c_2} = \begin{bmatrix} f_{c_1} & f_{c_2} \\ g_{c_1} & g_{c_2} \end{bmatrix} = \begin{bmatrix} (K_2 + K_3) & 0 \\ K_2 & 0 \end{bmatrix}$$

The determinant of Jacobian J_{C_1,C_2} is given as

$$\begin{vmatrix} K_2 + K_3 & 0 \\ K_2 & 0 \end{vmatrix} = (K_2 + K_3)(0) - (K_2)(0) = 0$$

To find the eigen value of the Jacobian matrix we find the determinant of the matrix

$$\begin{vmatrix} \lambda - (K_2 + K_3) & 0 \\ K_2 & \lambda \end{vmatrix} = [\lambda - (K_2 + K_3)]\lambda = 0$$

which implies that

$$\lambda_1 = 0 \qquad \text{and} \qquad \lambda_2 = (K_2 + K_3) > 0 \tag{4.6}$$

There fore at time t=0 and $C_i(t)= 0$ is not isolated fixed point. There is either a whole body or tissue of fixed concentration.

4.2.2 The analytical solution of the model by Laplace transform

To analyze the mathematical model of (4.1) analytically we used forward Laplace transform and inverse Laplace transform as we mentioned before.
The assumption in the mathematical model are:

- Compartments are in steady state until the tracer injected in to it or
- The model is characterized by the time-varying tracer concentration in tissue.

We can solve the differential equations in mathematical model (4.1) for the concentration C_1 and C_2 interms of C_a with respect to time(t) by the following alternative way.

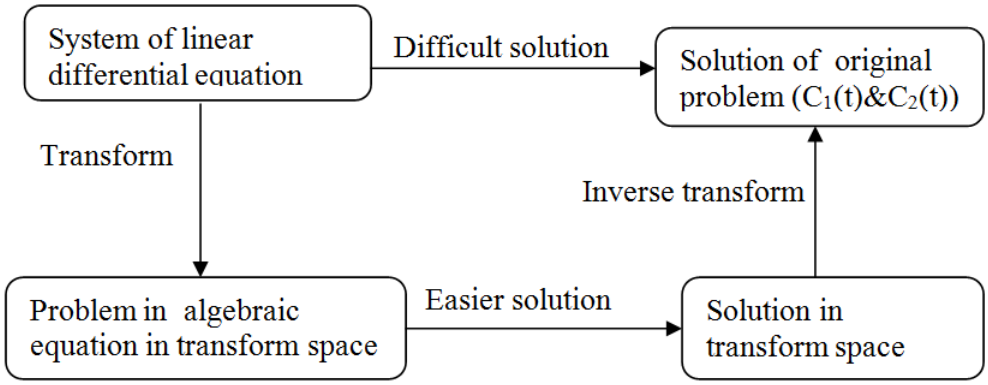

Chart 4.1 Represents alternative direction of procedure.

The tracer concentration in arterial blood ($C_a(t)$) is the in put function depends on time (t) is known quantity. Now we apply the Laplace transform in each equations of (4.1) we get

$$\begin{aligned} \mathcal{L}\{\frac{d}{dt}C_1(t)\} &= L\{K_1C_a(t) - (K_2+K_3)C_1(t)\} \\ \mathcal{L}\{\frac{d}{dt}C_2(t)\} &= \mathcal{L}\{K_2C_1(t)\} = K_2L\{C_1(t)\} \end{aligned} \tag{4.7}$$

with initial values $C_a(0) = 0, C_1(0) = 0$ and $C_2(0) = 0$, at $t = 0$. Then when we apply the Laplace transform, the algebraic equations of system (4.7) is expressed as

$$\begin{aligned} s\mathcal{L}\{C_1(t)\} - C_1(0) &= K_1\mathcal{L}\{C_a(t)\} - (K_2+K_3)\mathcal{L}\{C_1(t)\} \\ \mathcal{L}\{C_2(t)\} - C_2(0) &= K_2\mathcal{L}\{C_1(t)\} \end{aligned}$$

$$\begin{aligned} s\mathcal{L}\{C_1(t)\} + (k_2+K_3)\mathcal{L}\{C_1(t)\} &= K_1\mathcal{L}\{C_a(t)\} \\ (s+K_2+K_3)\mathcal{L}\{C_1(t)\} &= K_1\mathcal{L}\{C_a(t)\} \\ \Rightarrow \mathcal{L}\{C_1(t)\} &= \frac{K_1\mathcal{L}\{C_a(t)\}}{s+K_2+K_3} \\ \mathcal{L}\{C_2(t)\} &= K_2\mathcal{L}\{C_1(t)\} \end{aligned} \tag{4.8}$$

when we apply the inverse Laplace transform on system of equations (4.8) and simplify we get

$$\begin{aligned} C_1(t) &= \mathcal{L}^{-1}\{\frac{K_1\mathcal{L}\{C_a(t)\}}{s+K_2+K_3}\} \\ C_2(t) &= \mathcal{L}^{-1}\{\frac{K_2\mathcal{L}\{C_1(t)\}}{t}\} \end{aligned} \tag{4.9}$$

Equation(4.9) can be expressed as

$$\begin{aligned} C_1(t) &= K_1\mathcal{L}^{-1}\{\frac{1}{s+K_2+K_3}\} * \mathcal{L}^{-1}\{\frac{\mathcal{L}\{C_a(t)\}}{1}\} \\ C_2(t) &= K_2 * \mathcal{L}^{-1}\{\frac{\mathcal{L}\{C_1(t)\}}{t}\} \end{aligned} \tag{4.10}$$

$$\begin{aligned} \Rightarrow C_1(t) &= K_1e^{-(K_2+K_3)t} * C_a(t) = K_1\int_0^t e^{-(K_2+K_3)(t-u)}C_a(u)du \\ C_2(t) &= K_2 * C_1(t) = K_2\int_0^t C_1(u)e^{t-u}du \end{aligned} \tag{4.11}$$

When we use the arterial concentration (C_a) in equation (4.11) we get the following.

$$\begin{aligned} C_1(t) &= K_1e^{-(K_2+K_3)t} * C_a(t) \\ C_2(t) &= \frac{K_1K_2}{K_2+K_3}(1-e^{-(K_2+K_3)t}) * C_a(t) \end{aligned} \tag{4.12}$$

Where $*$ is convolution operation.
There fore the total signal of two-tissue irreversible compartmental model of [^{18}F]FDG is given by

$$\begin{aligned} C_T(t) &= C_1(t) + C_2(t) \\ &= (\frac{K_1K_3}{K_2+K3}e^{-(K_2+K_3)t} + \frac{K_1K_2}{K_2+K_3}) * C_a(t) \end{aligned} \tag{4.13}$$

Where $C_T(t)$ is total concentration of tissue at time t.
There fore the standard equation of total concentration can be derived by re arranging equation (4.13) and we get the following equation.

$$C_T(t) = K_i\int_0^t e^{t-u}C_a(u)du + \frac{K_3}{K_2+K_3}C_1(t) \qquad \text{where} \qquad K_i = \frac{K_1K_2}{K_2+K_3} \tag{4.14}$$

Then the analytical solution for the two tissue irreversible compartment model (4.1) is given by equation(4.14).

4.3 Arterial input function

The transport of [^{18}F]FDG across the arterial blood is very fast in the first ten minutes and then decreases slowly[6]. Let we denote the fast stage by $C_f(t), t\varepsilon(a,b)$ and the slow Stage by $C_s(t), t\varepsilon(b,c)$. Then we can estimate the arterial input function by the following equation.

$$C_a(t) = [H(t-a) - H(t-b)]C_f(t) + [H(t-b) - H(t-c)]C_s(t) \tag{4.15}$$

where $H(t)$ is Heaviside function and a, b and c are non-negative real numbers.
So as we understood from review of literature we can take $a = 0$ minute, $b = 10$ minute, $c > 10$minute, let c=60minute. Then equation 4.15 can be express as

$$C_a(t) = [H(t) - H(t-10)]C_f(t) + [H(t-10) - H(t-60)]C_s(t) \tag{4.16}$$

4.3.1 Numerical Results

We use the experimental result presented in the [3], we have K_1= 0.4, K_2=0.2 and $K_3 = 0.05$. we can obtain the analytical solution of the system (4.1). Then the arterial input function for the fast stage, $C_f(t)$ is obtained using the Levenberg-Marquardt Method in equation (4.16) is,

$$C_f(t) = \frac{0.51t + 0.005}{0.21t^2 - 0.43t + 1} \tag{4.17}$$

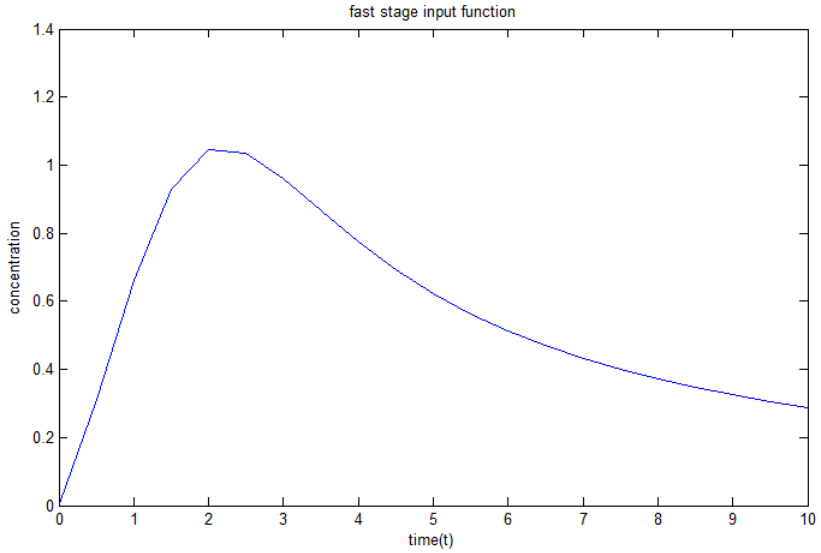

Fig.4.2 Fast face arterial input function.

Again from equation (4.16), the arterial input function for the slow stage $C_s(t)$, expressed as

$$C_s(t) = \frac{(4.96x10^9)t + 27.86}{(4.36x10^7)t^2 + (4.29x10^{10})t + 1} \tag{4.18}$$

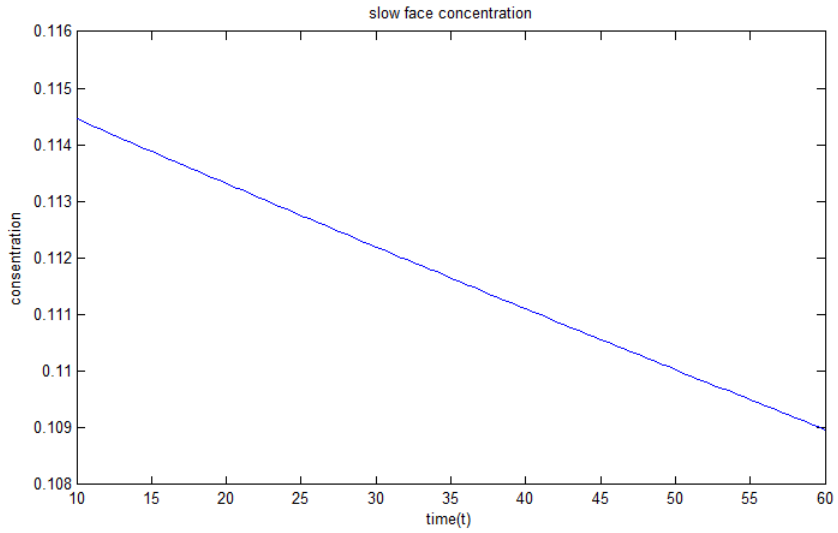

Fig.4.3 Slow face arterial input function.

which implies that

$$\begin{aligned} C_a(t) &= C_f + C_s \\ C_a(t) &= \frac{0.51t + 0.005}{0.21t^2 - 0.43t + 1} + \frac{(4.96x10^9)t + 27.86}{(4.36x10^7)t^2 + (4.29x10^{10})t + 1} \end{aligned}$$

The input function $C_a(t)$ and the response curves $C_1(t)$ and $C_2(t)$, with transport constants $K_1 = 0.4, K_2 = 0.2, K_3 = 0.05$. The analytical solution $C_1(t)$ and $C_2(t)$, for two tissue irreversible compartmental model were obtained. No absolute dose of FDG is universally employed due to differences between centers in camera sensitivity, imaging duration and uptake time. The dose employed is based on the offsetting goals of reducing the radiation exposure to the patient and minimizing the duration of imaging (i.e., timer per bed position). The dose of FDG employed is generally 0.14 0.21 mCi per kg or 5 20 mCi, with 10 mCi being the most commonly employed dose[35]

Chapter 5

Discussions and Conclusion

We analyzed the irreversible two compartmental model for [^{18}F]FDG. In the model rate of change of [^{18}F]FDG concentration in artery is depend on time, initial concentration and constant rate of change. This mathematical model is well posed and biologically meaning full. The concentration of [^{18}F]FDG in the compartment; as time increase the concentration of the tracer is decreased and the total concentration in the compartment is directly related with concentration of [^{18}F]FDG in central compartment(C_a). After fixed time, the concentration of [^{18}F]FDG administered in body was calculated analytically.

[^{18}F]FDG concentration in arterial tissue and the rate of uptake by reporting of response data by equation (4.14). This is not intended to be exclusive of other measurements, but to provide a frame work for comparison between studies and centers to facilitate assessment of this technique. So the absorption of [^{18}F]FDG is high in the firts 10 minutes and slowly decrease as time increase. In this thesis, a deterministic mathematical model for pharmacokinetic process of [^{18}F]FDG has been presented. It was showed that there exists a domain in which the model is mathematically and biologically well posed. The equilibrium(0,0) is not stable. It shows that the concentration of [^{18}F]FDG is unstable, because glucose all ways available in brain,lung and arms. The mathematical model and the analysis ot this mathematical model is show the use of [^{18}F]FDG tracer in PET camera using Laplace transform, integration and derivative.

Future work: In future I will work on the reduction of error in non linear regression. Recommendations the result of this thesis is not based on experiment,therefore for farther use and application it must await future work in medical science research(PET/CT) and will be thought still needs to be given to the broader perspective of assessing the predictive value of [^{18}F]FDG PET within clinical trials. In Ethiopia the use of [^{18}F]FDG is not practiced up to now and its factor is not yet planted.

Appendix

$>> t = 0 : 0.5 : 10;$
$>> Cf = (0.51. * t + 0.005)./(0.21. * t.^2 - 0.43 * t + 1);$
$>> plot(t, Cf);$

$>> t = 10 : 0.5 : 60;$
$>> Cs = ((4.96. * 10.^9). * t + 27.86)./((4.36. * 10.^7). * t.^2 + (4.29. * 10.^10). * t + 1);$
$>> plot(t, Cs);$

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