LAPLACE TRANSFORM IN TRACER KINETIC MODELING

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ABSTRACT

The main objective this paper is to quantify the pharmacokinetic processes: absorption, distribution and elimination of radiopharmaceutical (tracer), using Laplace transform method. When the drug is administered intravenously absorption is complete and is available in the bloodstream to be distributed throughout the whole body in all tissues and fluids, and to be eliminated. Mathematical modeling seeks to describe the processes of distribution and elimination through compartments, where distinct pools of tracer (spatial location or chemical state) are assigned to different compartments. A compartment model is described by a system of differential equations, where each equation represents the sum of all the transfer rates to and from a specific compartment. In this work a two-tissue irreversible compartment model is used for description of tracer, \[^{18}F\]2-fluor-2deoxy-D-glucose. 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. We estimate the arterial input function in two stages and apply the Levenberg-Marquardt Method to solve nonlinear regressions. The transport of FDG across arterial blood is very fast in the first ten minutes and then decreases slowly. We use the Heaviside function to represent this situation and this is the main contribution of this study. We apply the Laplace transform and the analytical solution for two-tissue irreversible compartment model is obtained. The only approach is to determine the arterial input function.

1. INTRODUCTION

Positron Emission Tomography (PET) is a functional imaging technology that visualizes physiological changes through the administration of radiopharmaceutical molecular tracers into living systems.

Compartment model is an important kinetic modeling technique used for quantification of PET. A compartment model is described by a system of differential equations, where each equation represents the sum of all the transfer rates to and from a specific compartment. In this work we describe the glucose metabolism using the irreversible FDG-model. The irreversible two compartment model for FDG is used for description of tracer, \[^{18}F\]2-fluor-2deoxy-D-glucose, which is first entering a free compartment, C1, and is then metabolized irreversibly in the second compartment C2.

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, [5].
Quantitative Positron Emission Tomography studies often require that input function be measured.[4, 6].

We estimate the arterial input function in two stages and apply the Levenberg-Marquardt Method to solve nonlinear regressions. The transport of FDG across arterial blood is very fast in the first ten minutes and then decreases slowly. We use the Heaviside function to represent this situation and this is the main contribution of this study.

Physiological or biochemical systems are described using models of compartments in which a tracer is distributed between compartments, which represent regions separate space (for example, the vascular space, interstitial intracellular) or different chemical stages.

Rate transferring from one compartment to another is proportional to concentration in the compartment of origin.

Mathematical modeling seeks to describe the processes of distribution and elimination through compartments, where distinct pools of tracer (spatial location or chemical state) are assigned to different compartments.

A compartment model is described by a system of differential equations, where each equation corresponds to the sum of all the transfer rates and a specific compartment

\[
\frac{d}{dt}C_i(t) = \sum_{j=1, j\neq i}^{N} [K_{ij}C_j(t) - K_{ji}C_i(t)]
\]

where \(C_i(t)\) is the concentration of radioactive tracer in compartment \(i\), \(N\) is the number of sections of the model is the rate constant for transfer from compartment \(j\) to compartment \(i\).

Models Compartments can be reversible or irreversible. Irreversible models are those containing at least one compartment which has no outlet.

2. TWO-TISSUE IRREVERSIBLE COMPARTMENT MODEL

The glucose metabolism is investigated using the irreversible FDG-model, which was developed for description of the tracer \([^{18}F]2\)-fluor-2-deoxy-D-glucose, [3]. The irreversible two compartment model for a FDG is illustrated in Figure 1 and is used for description of tracer, which is first entering a free compartment, \(C1\), and is then metabolized irreversibly in the second compartment \(C2\).

The mathematical model for the problem is expressed by the system of two differential equations:
Figure 1: FDG model.

\[
\begin{align*}
\frac{d}{dt}C_1(t) &= K_1 C_a(t) - (k2 + k3) C_1(t) \\
\frac{d}{dt}C_2(t) &= k3 C_1(t)
\end{align*}
\]  

(2)

The tracer concentration in arterial blood \( C_a(t) \), the input function depends on the time \( t \), is a known quantity.

We apply the Laplace transform with respect to \( t \) in Eq. (2), denoting \( \mathcal{L}\{C_i(t)\} = \mathcal{C}_i(s) \) and \( \mathcal{L}\left\{ \frac{dC_k(t)}{dt}\right\} = s \mathcal{C}_k(s) - C_k(0) \).

We obtain, with \( C_1(0) = 0 \) and \( C_2(0) = 0 \), an algebraic system of 2 equations:

\[
\begin{align*}
(s + k2 + k3) \mathcal{C}_1(s) &= K_1 \mathcal{C}_a(s) \\
-k3 \mathcal{C}_1(s) + s \mathcal{C}_2(s) &= 0
\end{align*}
\]  

(3)

Now we apply the inverse Laplace transform to Eq. (3), \( C_i(t) = \mathcal{L}^{-1}\{\mathcal{C}_i(s)\} \) and we consider * to denote the convolution operation.

Therefore, we obtain

\[
\begin{align*}
C_1(t) &= \mathcal{L}^{-1}\left\{ \frac{K_1 \mathcal{C}_a(s)}{s + k2 + k3} \right\} = K_1 \mathcal{L}^{-1}\left\{ \frac{1}{s + k2 + k3} \right\} \ast \mathcal{L}^{-1}\{\mathcal{C}_a(s)\} \\
C_2(t) &= \mathcal{L}^{-1}\left\{ \frac{k3 \mathcal{C}_1(s)}{s} \right\} = k3 \ast \mathcal{L}^{-1}\{\mathcal{C}_1(s)\}
\end{align*}
\]  

(4)

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Then, the analytical solution is

\[ C_1(t) = K_1 e^{(k_2 + k_3)t} \ast C_a(t) = K_1 \int_0^t e^{(k_2 + k_3)(t-u)} C_a(u) \, du \]

\[ C_2(t) = k_3 \ast C_1(t) = k_3 \int_0^t C_1(u) \, du. \]  

(5)

3. ARTERIAL INPUT FUNCTION

The transport of FDG across arterial blood is very fast in the first ten minutes and then decreases slowly.

We estimate the arterial input function in two stages and apply the Levenberg-Marquardt Method to solve nonlinear regressions.

We denote \( C_f(t), t \in (a, b), C_s(t), t \in (b, c) \), nonlinear functions determined by Levenberg Marquardt method.

Considering \( H(t) \) as the Heaviside function, the input function is defined as

\[ C_a(t) = \left[ H(t-a) - H(T-b) \right] C_f(t) + \left[ H(t-b) - H(T-c) \right] C_s(t). \]  

(6)

4. NUMERICAL RESULTS AND FINAL CONSIDERATIONS

We use the experimental results presented by [3]. Considering \( k_1 = 0.4, k_2 = 0.2 \) and \( k_3 = 0.05 \), we obtain the analytical solution of the system (2).

We write the input function as:

\[ C_a(t) = \left[ H(t) - H(T-10) \right] C_f(t) + \left[ H(t-10) - H(T-60) \right] C_s(t). \]  

(7)

The arterial input function for the fast stage stage, \( C_f(t) \), obtained using the Levenberg-Marquardt Method is

In. Eq.(7),

\[ C_f(t) = \frac{0.51t + 0.005}{0.21t^2 - 0.43t + 1}. \]  

(8)

represented in Fig. 2.
And, in Eq. (7), the arterial input function for the slow stage, $C_s(t)$, obtained using the Levenberg-Marquardt Method is

$$C_s(t) = \frac{(4.96 \times 10^9) t + 27.86}{(4.36 \times 10^7) t^2 - (4.29 \times 10^{10}) t + 1}, \quad (9)$$

illustrated in Fig. 3.

In Fig. 4, we present the input function $C_a(t)$.

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The input function $C_a(t)$ and the response curves, $C_1(t)$ and $C_2(t)$, with transport constants $K1 = 0.4$, $k2 = 0.2$, $k3 = 0.05$, are represented in Fig. 5.

The analytical solution, $C_1(t)$ and $C_2(t)$, for two-tissue irreversible compartment model was obtained. The only approach is to determinate de arterial input function $C_a(t)$.

The implementation and testing of these ideas must await future work in preclinical medical research(MicroPET/CT).
REFERENCES