LAPLACE TRANSFORM METHOD FOR 11C-PIB TWO-TISSUE REVERSIBLE COMPARTMENT MODEL WITH IMAGE-DERIVED ARTERIAL INPUT FUNCTION

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Abstract. *Positron Emission Tomography (PET) has been of utmost importance for helping the diagnostics of neurodegenerative diseases, such as Alzheimer's disease(AD). Radiolabeled drugs help quantifying the amount of deposition of beta-amyloid in the brain which can be a strong indication for AD. In this work, using data coming from an experiment at the Brain Institute with Pittsburgh Compound-B (11C-PIB) as a marker, we propose a two-tissue reversible compartment model as a mathematical modeling in the quantitative analysis of the 11C-PIB. Laplace Transform is applied to solve the corresponding system of differential equations for*

each compartment. Using as a reference region the cerebellum, known to be amyloid free, we obtained an analytical solution for the Image Derived Input Function (IDAIF) as well as for the concentration of beta-amyloid in each compartment. Our results corroborate what has been seen in the literature.

Keywords: *Laplace Transform, Image-Derived Arterial Input Function, Alzheimer Disease, Pittsburgh Compound-B (11C-PIB)*

1 INTRODUCTION

Mathematical modeling has been of great help in studying the dynamics of several real class problems in many areas of expertise such as Physics, Engineering, Biology among many others (Mao, 2007). In pharmacokinetics, mathematical modeling has been also playing an important role when compartmental models are used to determine the dynamics of radiotracers (Hauser et al., 2015, Hauser, 2013). An important part of this process is to determine the arterial input function which is a quantitative measure of the amount of radiotracer in the blood stream. In this work, in particular, we compute what is called an image-derived arterial input function (IDAIF). The IDAIF is obtained by means of a Time Activity Curve (TAC) on a reference region in the brain (more specifically the cerebellum (Su et al., 2015)) whose data are obtained during an imaging scan, for example the micro Positron Emission Tomography (μPET). The reason for using the cerebellum as the reference region is because this region is known to be amyloid free. The presence of amyloid in the brain can be determined using radiotracers such as Pittsburgh Compound-B $[^{11}C]PIB$ (Klunk et al., 2004), among others. In the case of $[^{11}C]PIB$, the amount of amyloid plaques is estimated by considering how long it takes for the tracer to leave a given region when compared to the reference region. The faster it leaves the region the lesser amyloid plaques. In other words, the smaller the chance for the patient to be amyloid positive.

In the sequence, we use a differential equation to compute an IDAIF and then a system of two differential equations solved using Laplace transform to determine the dynamics of the radiotracer.

The transport of across the arterial blood is very fast in the first minutes and then decreases slowly. We use the Delta de Dirac and Heaviside step functions 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 reversible compartment model is obtained.

Data used in this work was obtained from an experiment with $[^{11}C]PIB$ at Instituto do Cérebro (InsCer/BraIns) at Pontifical Catholic University of Rio Grande do Sul (PUCRS) on a healthy mouse. The μPET studies is highly applicable in the development of new drugs and cell therapy, elucidation of pathophysiological mechanisms of neurological diseases and is a valuable tool for studying animal models of human disease(like cancer).

2 IMAGE-DERIVED ARTERIAL INPUT FUNCTION

The Image-Derived Arterial Input Function (IDAIF) is obtained from a Time Activity Curve (TAC) using the cerebellum (known to be amyloid free) as a reference region (Su et al., 2015). The IDAIF was quantifyed through the dynamics of $[^{11}C]PIB$ tracer which follows a known pattern. Other ways of determining the arterial input function can be seen in Vriens et al., 2009, Zaidi, 2006, La Forest et al., 2006.

The dynamics of the radiotracer on the reference region is governed by the differential equation (Su et al., 2015)

$$\frac{dC_r}{dt} = K_1^{'} C_a(t) - k_2^{'} C_r(t) \tag{1}$$

where $C_a(t)$ is the concentration of the radiotracer in the arterial blood, $C_r(t)$ is the concentration of the radiotracer in the reference region and ${K_1}' > 0$ and ${k_2}' > 0$ are proportionality rates describing, respectively, the tracer influx into and the tracer outflow from the reference tissue.

In this case, $C_r(t)$ will be approximated by means of nonlinear regression of the data obtained from a TAC curve on a Positron Emission Tomography(PET) image, as exemplified in Figure1 and Figure 2,(in this work we use the Biomedical Image Quantification software PMOD).

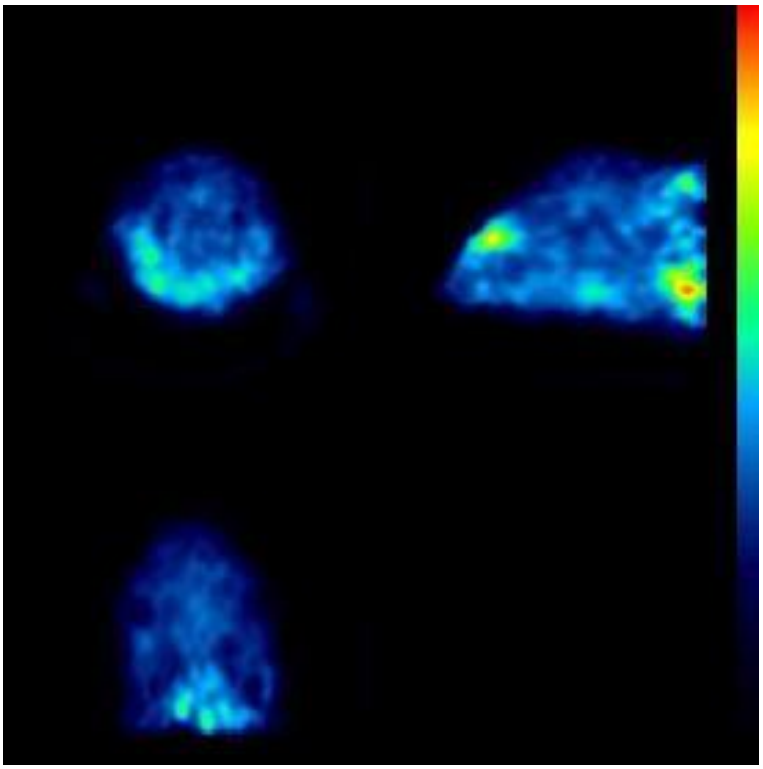

Figure 1: Mouse μPET image.

After this, deriving $C_r(t)$ and substituting in equation (1), we obtain $C_a(t)$ which is the IDAIF, given by

$$C_a(t) = \frac{1}{K_1'}\frac{dC_r}{dt} + \frac{k_2'}{K_1'}C_r(t) \tag{2}$$

According to Nelissen et el.(2012), the effective dose injected can be calculated as:

$$C_a(0) = C_a^i e^{-\frac{ln2}{t_{1/2}}(t_0 - t_i)} - C_a^e e^{-\frac{ln2}{t_{1/2}}(t_e - t_0)} \tag{3}$$

where C_a^i is the dose measured before injection at time t_i, C_a^e is the residual dose after injection measured at time t_e, and $t_{1/2}$ is the half-time of the tracer.

3 LAPLACE TRANSFORM METHOD FOR TWO-TISSUE REVERSIBLE COMPARTMENT MODEL

We consider a two-compartment model for the dynamics of $[^{11}C]PIB$ (Khalil, 2011, Su et al., 2015). The mathematical model for the problem is expressed by the system of two

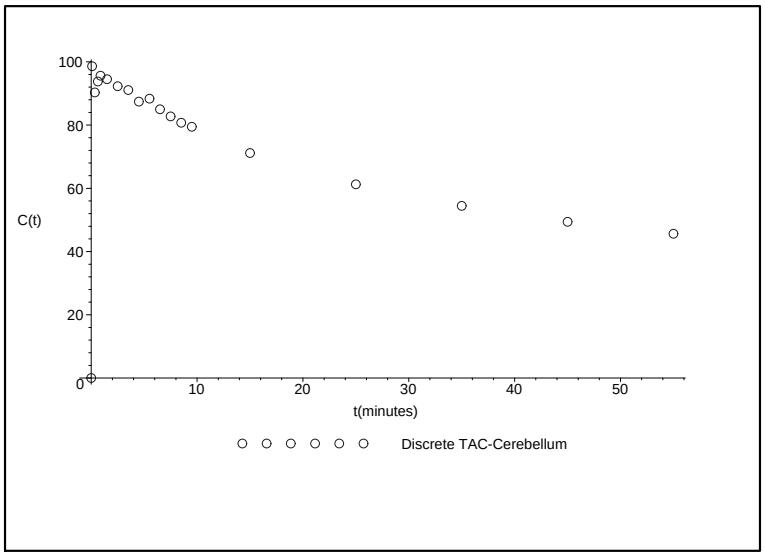

Figure 2: Discrete TAC-Cerebellum.

differential equations:

$$\begin{cases} \dfrac{dC_1}{dt} = K_1\, C_a(t) - (\, k_2 + k_3\,)\, C_1(t) + k_4\, C_2(t) \\ \\ \dfrac{dC_2}{dt} = k_3\, C_1(t) - k_4\, C_2(t) \\ \\ C_1(t) = 0\,,\ C_2(t) = 0. \end{cases} \tag{4}$$

where $C_a(t)$ is IDAIF considered to be known, $C_1(t)$ and $C_2(t)$ are, respectively, the concentration within the nondisplaceable and displaceable compartments and K_1, and k_2, k_3, k_4 are kinetic rate constants which have to be determined.

In order to solve the system of equations in Eq. (4), we choose to apply the Laplace transform with respect to t denoting by

$$\pounds\,\{\, C_i(t)\} = \overline{C}_i(s) = \int_0^\infty e^{-st}\, C_i(t)\, dt$$

and

$$\pounds\left\{\frac{d\, C_k(t)}{dt}\right\} = s\, \overline{C}_i(s) - C_i(0)\,.$$

Applying the initial conditions $C_1(0) = 0$ and $C_2(0) = 0$, an algebric system for $\overline{C}_1(s)$ and $\overline{C}_2(s)$ is determined:

$$\begin{cases} (\, s + k_2 + k_3\,)\, \overline{C}_1(s) - k_4\, \overline{C}_2(s) = K_1\, \overline{C}_a(s) \\ \\ -\, k_3\, \overline{C}_1(s) + (s + k_4)\, \overline{C}_2(s) = 0 \end{cases} . \tag{5}$$

which in matrix form is written as

$$\begin{bmatrix} s+k_2+k_3 & -k_4 \\ \\ -k_3 & s+k_4 \end{bmatrix} \begin{bmatrix} \overline{C}_1(s) \\ \\ \overline{C}_2(s) \end{bmatrix} = \begin{bmatrix} K_1\,\overline{C}_a(s) \\ \\ 0 \end{bmatrix}. \tag{6}$$

The solution of the system (6) is

$$\begin{bmatrix} \overline{C}_1(s) \\ \\ \overline{C}_2(s) \end{bmatrix} = \begin{bmatrix} \dfrac{s+k_4}{s^2+(k_2+k_3+k_4)s+k_2k_4} & \dfrac{k_4}{s^2+(k_2+k_3+k_4)s+k_2k_4} \\ \\ \dfrac{k_3}{s^2+(k_2+k_3+k_4)s+k_2k_4} & \dfrac{s+k_2+k_3}{s^2+(k_2+k_3+k_4)s+k_2k_4} \end{bmatrix} \begin{bmatrix} K_1\,\overline{C}_a(s) \\ \\ 0 \end{bmatrix}.$$

Therefore,

$$\begin{aligned} \overline{C}_1(s) &= \frac{(s+k_4)\,K_1\,\overline{C}_a(s)}{s^2+(k_2+k_3+k_4)s+k_2k_4} \\ \\ \overline{C}_2(s) &= \frac{k_3\,K_1\,\overline{C}_a(s)}{s^2+(k_2+k_3+k_4)s+k_2k_4} \end{aligned} \tag{7}$$

In order to determine $C_i(t)$, $i = 1, 2$, we apply the inverse Laplace transform to Eq. (7). The result is

$$\begin{aligned} C_1(t) &= \mathcal{L}^{-1}\left\{ \frac{(s+k_4)\,K_1\,\overline{C}_a(s)}{s^2+(k_2+k_3+k_4)s+k_2k_4} \right\} \\ \\ C_2(t) &= \mathcal{L}^{-1}\left\{ \frac{k_3\,K_1\,\overline{C}_a(s)}{s^2+(k_2+k_3+k_4)s+k_2k_4} \right\}. \end{aligned} \tag{8}$$

Denoting $*$ as the convolution operation, Eq. (8) can be written as

$$\begin{aligned} C_1(t) =, \mathcal{L}^{-1}\left\{ \frac{(s+k_4)}{s^2+(k_2+k_3+k_4)s+k_2k_4} \right\} * \; K_1\; C_a(t) \\ \\ C_2(t) = \mathcal{L}^{-1}\left\{ \frac{k_3}{s^2+(k_2+k_3+k_4)s+k_2k_4} \right\} * \; K_1\; C_a(t)\,. \end{aligned} \tag{9}$$

Equation (9) is the analytical solution of the reversible two-compartment model for $[^{11}C]PIB$, Eq. (4). Notice that the inverse Laplace transforms are simply linear combinations of exponential functions with the exponents depending on k_2, k_3 and k_4.

3.1 ILLUSTRATIVE EXAMPLE

As an example of the two compartment model described above, we will apply the above results to describe the activity on the cerebellum and cortex in μPET imaging of a healthy mouse. Data was obtained from the first experiment performed at InsCer(BraIns) using $[^{11}C]PIB$. Figure1 and Figure 2 show, respectively, the image and the corresponding data extracted from it using PMOD, a Biomedical Image Quantification software. The final aim is to be able to quantify the amount of β amyloid on a given brain region of a mouse/patient in a μPET/PET scan(Kiessling et al., 2011, Basu et al., 2011).

First, let's define the Heaviside step function $H(t)$ and the Dirac Delta function $\delta(t)$:

$$H(t-a) = \begin{cases} 0, t < a, \\ 1, t \geq a. \end{cases} \tag{10}$$

$$H(t-a) - H(t-b) = \begin{cases} 0, t < a \ and \ t \geq b, \\ 1, a \leq t < b. \end{cases} \tag{11}$$

$$\delta(t-a) = \begin{cases} 0, \ t \neq a, \\ \infty, \ t = a. \end{cases} \tag{12}$$

From the data extracted from the μPET image, linear and nonlinear regression (Arnold,2015, Battes et al., 1988, Cunnigham, 1993) was used to find the best fitting for the given data of the region of reference (cerebellum)(as seen in figure 3).

$$C_r(t) = 1183.569\, t \left[H(t - 0.5 \times 10^{-5}) - H(t - 5/60) \right]$$

$$+ \left[H(t - 5/60) - H(t - 60) \right] 94.451 e^{-0.0152\, t}.$$

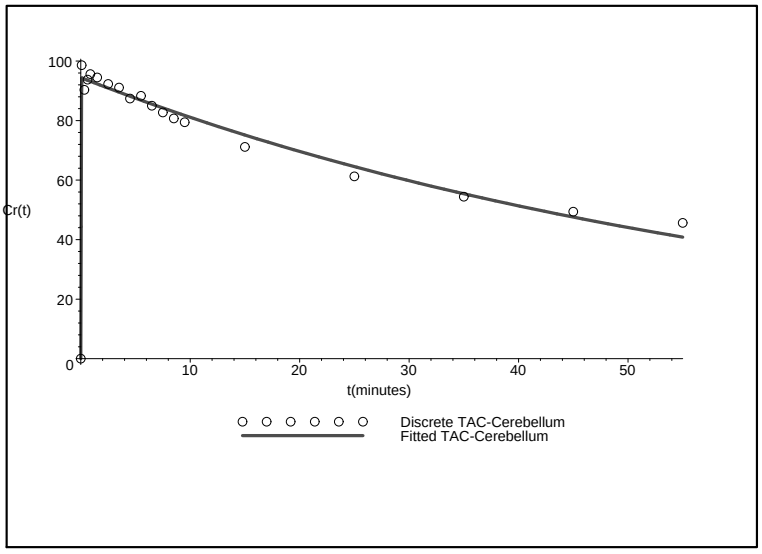

Figure 3: $C_r(t)$: Fitted TAC-Cerebellum

Afterwards, the IDAIF was computed, as described in section 1.2, with rate constants $K_1' =$

0.08 and $k_2{}' = 0.2$ using a symbolic and algebraic computational software (Maple) and Eq. (1), as

$$\begin{aligned} C_a(t) \;=\; & 14794.617\, t\,[\,\delta(t-0.5\times 10^{-5}) - \delta(t-5/60)\,] \\ & +2958.923\, t\,[H(t-0.5\times 10^{-5}) - H(t-5/60)] \\ & +14794.617[\,H(t-0.5\times 10^{-5}) - H(t-5/60)\,] \\ & +1180.648\, e^{-0.0152t}\delta(t-5/60) \;+ 218.137\, e^{-0.0152t} H(t-5/60)\,. \end{aligned} \tag{13}$$

The IDAIF obtained in equation (13) is shown in figure 4, along with $C_r(t)$.

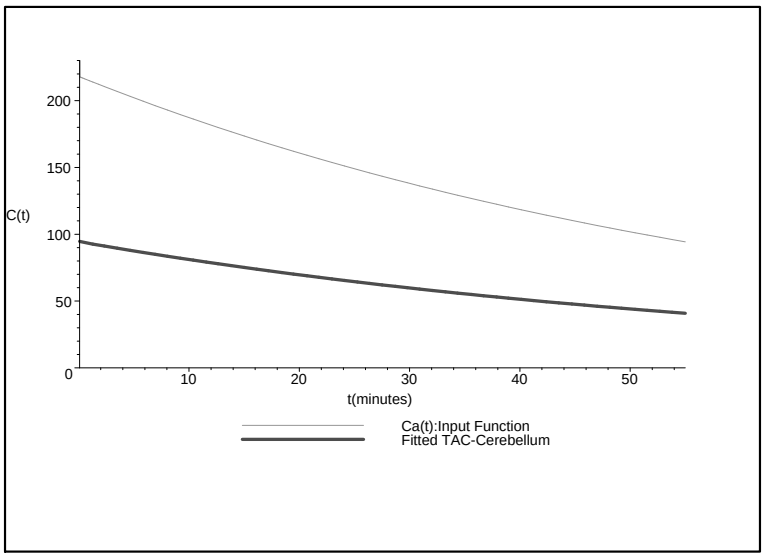

Figure 4: $C_a(t)$: IDAIF and $C_r(t)$

Finally, under the condition that $K_1/k_2 = K_1{}'/k_2{}'$, we suppose that the kinetic rate constans $K_1 = 0.1$, $k_2 = 0.25$, $k_3 = 0.1$, and $k_4 = 0.075$. Then, computing the inverse Laplace transform in equation (9) using MAPLE, the explicit expressions for the concentration within the nondisplaceable and displaceable compartments $C_1(t)$ and $C_2(t)$ can be given as:

$$\begin{aligned} C_1(t) =\; & e^{-0.2125\, t}\,(\cosh 0.1625\, t - 0.846 \sinh 0.1625\, t) \\ C_2(t) =\; & 0.6153\, e^{-0.2125\, t} \sinh 0.1625\, t\,. \end{aligned} \tag{14}$$

which is the analytical solution of the two-tissue reversible compartment model (4) and shown in figure 5. The choice of the constants is based on a relationship that they are known to satisfy (Arnold, 2016, Bates, 1988, Kiessling et al., 2011).

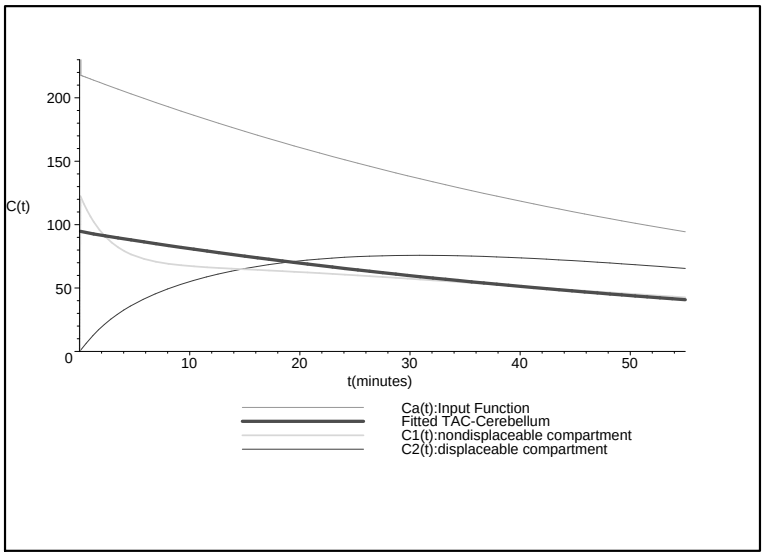

Figure 5: Solution of the two-tissue reversible compartment model in Eq.(4).

4 CONCLUSION AND FUTURE WORKS

In this work we used data from a μPET image scan to determine the dynamics of the radiotracer $[^{11}C]PIB$ on the cerebellum and cortex of a healthy mouse. Using Laplace transform we computed the solution of a set of two differential equations of a two-tissue reversible compartment model. Parameters used for the solution were theoretical and were based on Su et al.(2015), although our initial goal was to estimate these parameters through known mathematical techniques and available data.

As future work, we would like to apply these results to quantify β amyloid in PET imaging in the diagnosis of Alzheimer's disease. Differently to what was done here, we would like to approximate $C_r(t)$ by means of nonlinear regression of the data obtained from a TAC curve on a Positron Emission Tomography(PET) image, as piecewise function

$\mathbf{C}_r(t) = (H(t-t_0) - H(t-t_1))C_f(t) + (H(t-t_1) - H(t-t_2))C_I(t) + H(t-t_2)C_s(t)$, where $C_f(t)$, $C_I(t)$ and $C_s(t)$ are the concentration of the radiotracer on the reference region, respectively, for the fast, intermediate and slow stages and $H(t)$ is the Heaviside function defined in Eq.(10).

The improvement of mathematical models for the study of Alzheimer's disease is of the utmost importance, since most of the procedures today rely on invasive procedures and subjective tests. It is still a long shot before major significant results will improve the diagnosis of the disease, despite the efforts of many researchers worldwide.

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