15th International Symposium on Computer Methods in Biomechanics and Biomedical Engineering
and
3rd Conference on Imaging and Visualization
CMBBE 2018
P. R. Fernandes and J. M. Tavares (Editors)

IMAGE-DERIVED CAROTID ARTERIAL INPUT FUCTION AS AN INVERSE PROBLEM IN KINETIC MODELING OF [18F]2-FLUORO-2 DEOXY-D-GLUCOSE(FDG) IN ALZHEIMER'S DISEASE

Eliete B. Hauser*, Gianina T. Venturin†, Samuel Greggio†, Wyllians V. Borelli†, Jaderson C. Costa†

*Brain Institute of Rio Grande do Sul (BraIns)/School of Sciences, PUCRS
Av. Ipiranga, 6681 - Building 12 Zip Code:90619-900 City:Porto Alegre - RS - Brazil
eliete@pucrs.br

†Brain Institute of Rio Grande do Sul (BraIns), PUCRS
Av. Ipiranga, 6690 - Building 63 Zip Code:90610-000 City:Porto Alegre - RS - Brazil
gianina.venturin@pucrs.br

Keywords: Carotid Arterial Input Function, Kinetic Modelling, Laplace Transform, Positron Emission Tomography(PET).

Abstract: *A two-tissue reversible compartment model is solved by Laplace transform method for kinetic modeling of [18F]2-fluor-2deoxy-D-glucose(FDG), in order to quantify amyloid in Positron Emission Tomography(PET) image. A reverse engineer technic is applied to determine the input function(Ca(t)), that represents the time-course of tracer concentration arterial blood. Ca(t) is obtained by non-linear regression, and, noninvasively from the time–activity curve in a carotid volume of interest(VOI). After calculating a convolution integral, the analytical solution is completely described.*

1. INTRODUCTION

The image-derived arterial input function (IDAIF) provides data that are similar to arterial blood input methods and can be used to noninvasively quantify the metabolic rate for glucose in dynamic brain [18F] 2-fluor-2deoxy-D-glucose(FDG) in positron emission tomography (PET) studies, according to previous studies [2, 5, 16, 24].

The aim of this study is to compute the IDAIF by non-linear regression from the time–activity curve in a carotid volume of interest(VOI), in FDG PET dynamic brain studies. The IDAIF must be chosen in order to solve the exact form of the system of two differential equations to describe the dynamic behavior of the FDG tracer in brain dynamic PET studies.

FDG is a glucose analogue used to evaluate brain's metabolic activity in vivo through positron emission tomography with computed tomography (PET/CT). The irreversible two-compartment model for FDG is used for description of this tracer, which is first entering a free compartment, C1, and is then metabolized irreversibly in the second compartment C2 [9, 8]. In order to determine the parameters of the model, information on the tracer delivery is needed

in the form of the input function that represents the time-course of tracer concentration in the arterial blood or plasma. We use the Heaviside function to represent the IDAIF, because the transport of FDG across the arterial blood is very fast in the first few minutes and then slowly decreases. The Laplace transform method determines the analytical solution for the FDG two-tissue irreversible compartment model, with only approach is the IDAIF.

Older adults with exceptional memory ability are coined Superagers [6]. Their preserved cognitive capacities with aging may help uncover neuromechanisms of dementia. These individuals showed whole-brain volume similar to middle-aged individuals and some areas thicker than usual agers [6, 19, 18]. Intriguingly, they also exhibited decreased atrophy rate when compared to normal older adults [3]. To our knowledge, their brain functional integrity is yet to be uncovered.

Data used in this work was obtained from the Superagers project at the Instituto do Cérebro (InsCer/BraIns) at Pontifical Catholic University of Rio Grande do Sul (PUCRS) on a healthy 51-year-old, community-dwelling woman underwent FDG PET/CT imaging.

2. THE PROPOSED METHOD FOR TWO-TISSUE IRREVERSIBLE COMPARTMENT MODEL

The mathematical model for the FDG irreversible two compartment model is expressed by the system of two differential equations:

$$\begin{aligned} \frac{d}{dt}C_1(t) &= K_1\, C_a(t) - (\, k_2 + k_3\,)\, C_1(t) \\ \frac{d}{dt}C_2(t) &= k_3\; C_1(t) \\ C_1(0) &= 0\,, C_2(0) = 0\,, C_a(0) = 0, \end{aligned} \tag{1}$$

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 are positives proportionality rates describing, respectively, the tracer influx into and the tracer outflow from the compartment(transport constants).

We apply the Laplace transform with respect to t in (1), denoting

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

and

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

We obtain, with $C_1(0) = 0$ and $C_2(0) = 0$, an algebric system:

$$\begin{aligned} (\, s + k_2 + k_3 \,)\, \overline{C}_1(s) \;&=\; K_1\, \overline{C}_a(s) \\ -\, k_3\, \overline{C}_1(s) \;+\; s\; \overline{C}_2(s) \;&=\; 0\,. \end{aligned} \tag{2}$$

Now we apply the inverse Laplace transform to equation (2)

$$C_i(t) = \; \pounds^{-1} \left\{ \overline{C}_i(s) \right\} \,.$$

Therefore, we obtain

$$\begin{aligned} C_1(t) &= \; \pounds^{-1} \left\{ \frac{K_1\, \overline{C}_a(s)}{(\, s + k_2 + k_3 \,)} \right\} \\ C_2(t) &= \; \pounds^{-1} \left\{ \frac{k_3\, \overline{C}_1(s)}{s} \right\} . \end{aligned} \tag{3}$$

Then,

$$\begin{aligned} C_1(t) &= \;\; K_1\, \pounds^{-1} \left\{ \frac{1}{(\, s + k_2 + k_3 \,)} \right\} \,*\, \pounds^{-1} \left\{ \overline{C}_a(s) \right\} \\ C_2(t) &= \; k_3 \,*\, \pounds^{-1} \left\{ \overline{C}_1(s) \right\} \,, \end{aligned} \tag{4}$$

where $*$ denotes the convolution operation.

The representation (4) implies that

$$\begin{aligned} C_1(t) &= \; K_1\, e^{-(\, k_2 + k_3 \,)\, t} \,*\, C_a(t) \;=\; K_1 \int_0^t e^{-(\, k_2 + k_3 \,)\, (t-u)}\; C_a(u)\, du \\ C_2(t) \;&=\; k_3 \,*\, C_1(t) \;=\; k_3 \int_0^t C_1(u)\, du \;. \end{aligned} \tag{5}$$

Then, with $\lambda \;=\; k_2 + k_3 \;>\; 0$, the analytical solution of the irreversible two compartment model for FDG (1) is

$$\begin{aligned} C_1(t) &= \; K_1\, e^{-\lambda\, t} \int_0^t e^{\lambda\, u}\; C_a(u)\, du \\ C_2(t) \;&=\; k_3 \int_0^t C_1(u)\, du \;. \end{aligned} \tag{6}$$

It is important now to choose a suitable model to represent the the input function $C_a(t)$, which makes it possible to calculate the integral

$$I \;=\; \int_0^t e^{\lambda\, u}\; K_1\, C_a(u)\, du \,. \tag{7}$$

3. CAROTIDS IMAGE-DERIVED ARTERIAL INPUT FUNCTION (IDAIF)

The dynamics of the radiotracer in a reference region is governed by the differential equation [20, 7]

$$\begin{aligned} \frac{dC_r}{dt} &= K_1^{'} C_a(t) - k_2^{'} C_r(t) \\ C_r(0) &= 0 \end{aligned} \tag{8}$$

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.

Then, $C_a(t)$, the IDAIF,is given by

$$C_a(t) = \frac{1}{K_1^{'}} \frac{dC_r}{dt} + \frac{k_2^{'}}{K_1^{'}} C_r(t) \tag{9}$$

The effective dose injected can be calculated as:

$$C_a(0) = C_a^i e^{-\frac{ln2}{t_{1/2}}(t_0 - t_i)} - C_a^e e^{-\frac{ln2}{t_{1/2}}(t_e - t_0)} \tag{10}$$

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.

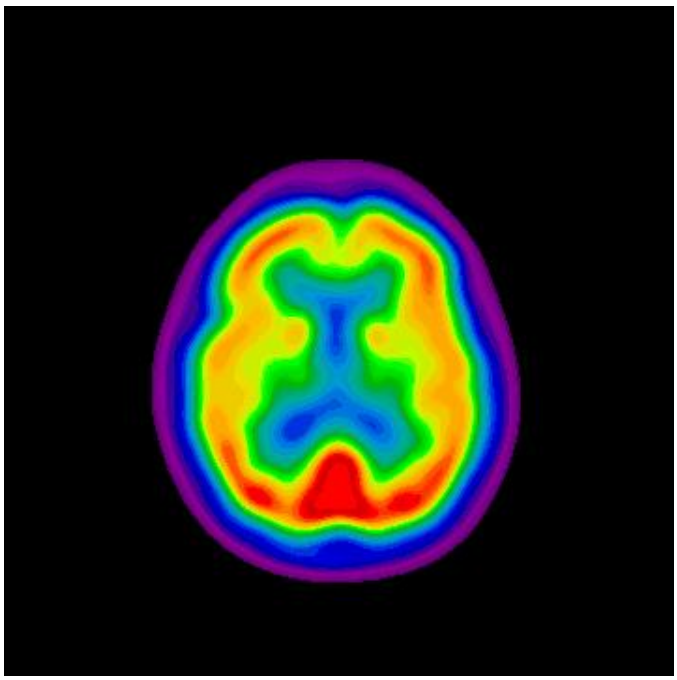

Figure 1. Healthy Brain - FDG PET: axial orientation.

We need to consider that the transport of FDG across de arterial blood is very fast in the first few minutes and then decreases slowly. We estimate the arterial input function in three stages

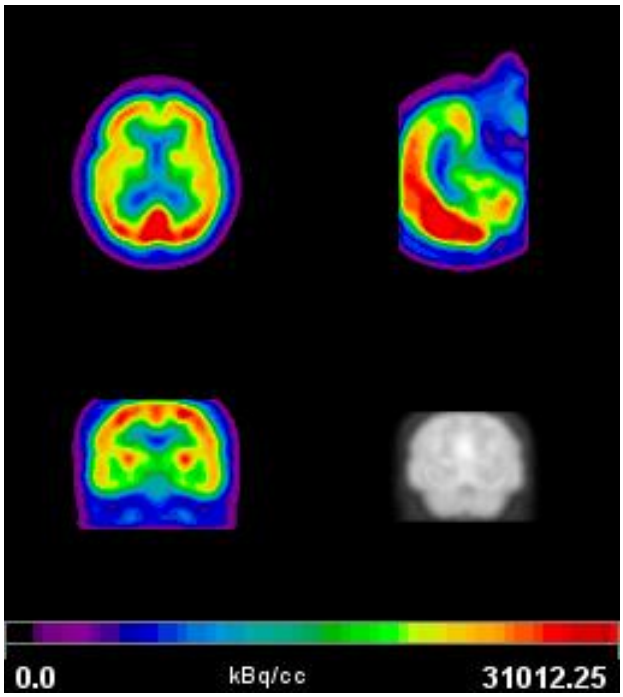

Figure 2. FDG PET: axial, coronal and sagittal orientation.

and solve nonlinear regressions. First we 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

$$C_r(t) = (H(t-t_0) - H(t-t_1))C_{rf}(t) + (H(t-t_1) - H(t-t_2))C_{rI}(t) + H(t-t_2)C_{rs}(t),$$

where $C_{rf}(t)$, $C_{rI}(t)$ and $C_{rs}(t)$ are the concentration of the radiotracer on the reference region, respectively, for the fast, intermediate and slow stage. $H(t)$ is the Heaviside function defined by

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

$$H(t-a) - H(t-b) = \begin{cases} 0, t < a \ and \ t \geq b, \\ 1, a \leq t < b. \end{cases} \tag{12}$$

4. NUMERICAL RESULTS

A 51-year-old, community-dwelling woman underwent PET/CT imaging with Fluorodeoxiglucose (FDG), Figure 1 and Figure 2.The calibrated dose in Syringe was 284160kBqcc and the remainning dose was 39035kBcc. Her Mini-Mental State Examination score was 28, she scored 13 words in a delayed-recall memory (Rey Auditory-Verbal Learning Test) and had normal fluency and working memory abilities, according to her age and education. Her clinical evaluation

was normal and lacked any history or structural evidence of neurological or psychiatric disease or use any type of medication.

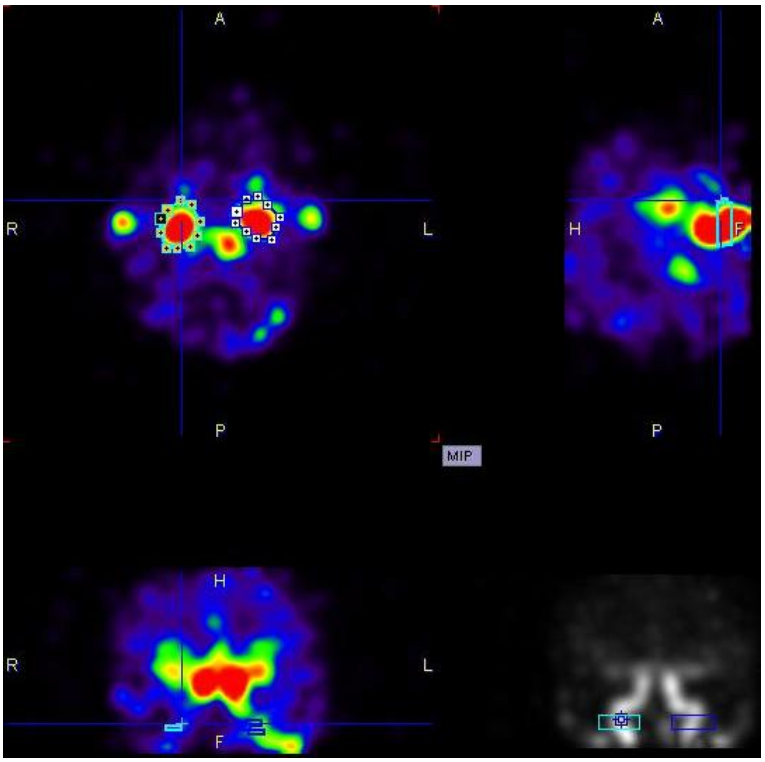

Figure 3. Left and right carotid arteries identified on the fifth frame on the positron emission tomographic(PET).

We manually define Volumes-of-Interest (VOIs), illustrated in Figure 3 and Figure 4, using PMOD, a biomedical image quantification software. VOIs are built from planar polygons called contours (CTR), with axial orientation. Use the mouse wheel, or the slices slider, to scroll to the axial three slices , and outline the right carotid there similarly. The R carotid VOI now consists of 3 ROIs, each containing 1 CTR. For those VOIs,over which the left and right carotid arteries where clearly visible, is defined discrete time activity curves(TACs) and is generated the average TAC. Afther this we apply regression techniques, [1], and we obtain:

- whit correlation coefficient 0.99, the linear as the best model for $C_{rf}(t)$:

$$C_{rf}(t) = 1022.51 * t\,;$$

- whit correlation coefficient 0.98 ,the saturation growth-rate model as the best model for $C_{rI}(t)$:

$$C_{rI}(t) = \frac{7612.38\,t}{-25.10 + t}\,;$$

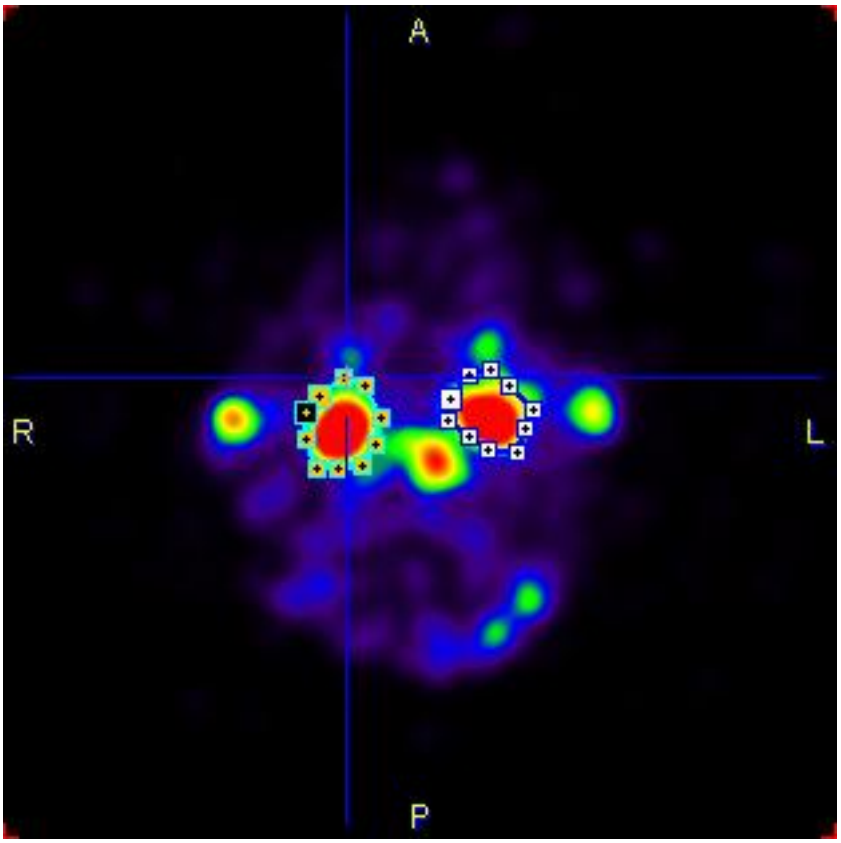

Figure 4. Left and right carotid arteries volumes of interest(VOI) defined manually.

- whit correlation coefficient 0.95, the saturation growth-rate model as the best model for $C_{rs}(t)$:

$$C_{rs}(t) = \frac{8113.45\,t}{-24.84 + t}\,.$$

We 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

$$C_r(t) = (H(t{-}.0005){-}H(t{-}32.5))C_{rf}(t) + (H(t{-}32.5){-}H(t{-}85))C_{rI}(t) + H(t{-}85)C_{rs}(t),$$

where $C_{rf}(t)$, $C_{rI}(t)$ and $C_{rs}(t)$ 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.(11).

The Carotid fitted, TAC $C_r(t)$, is shown in In Figure 5 and the IDAIF $C_a(t)$ in Figure 6, obtained using MAPLE to solve equation (9).

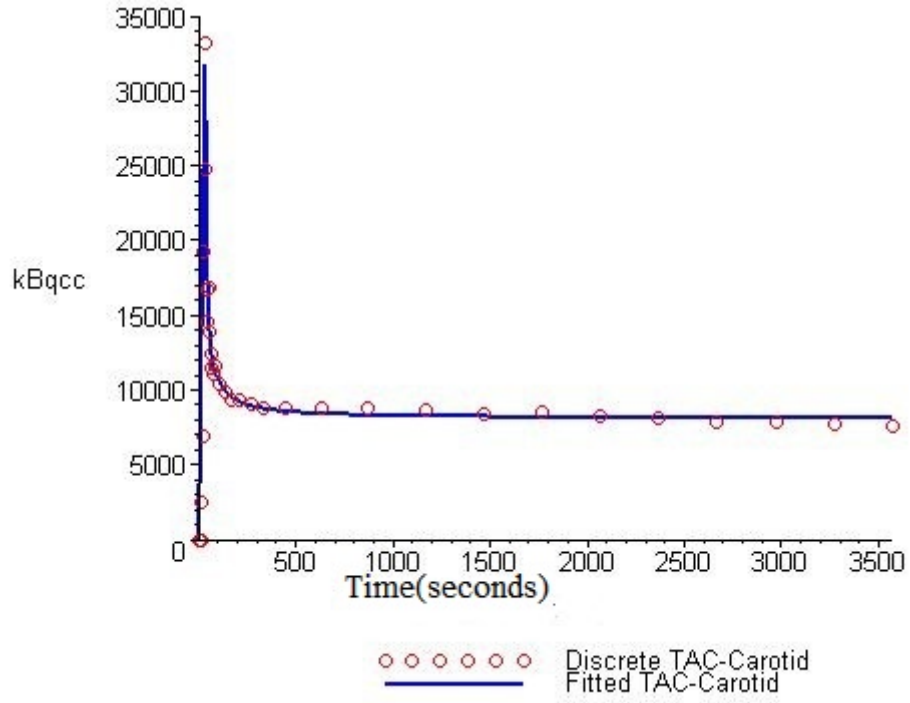

Figure 5. Discrete and Fitted Carotid Time Active Curve.

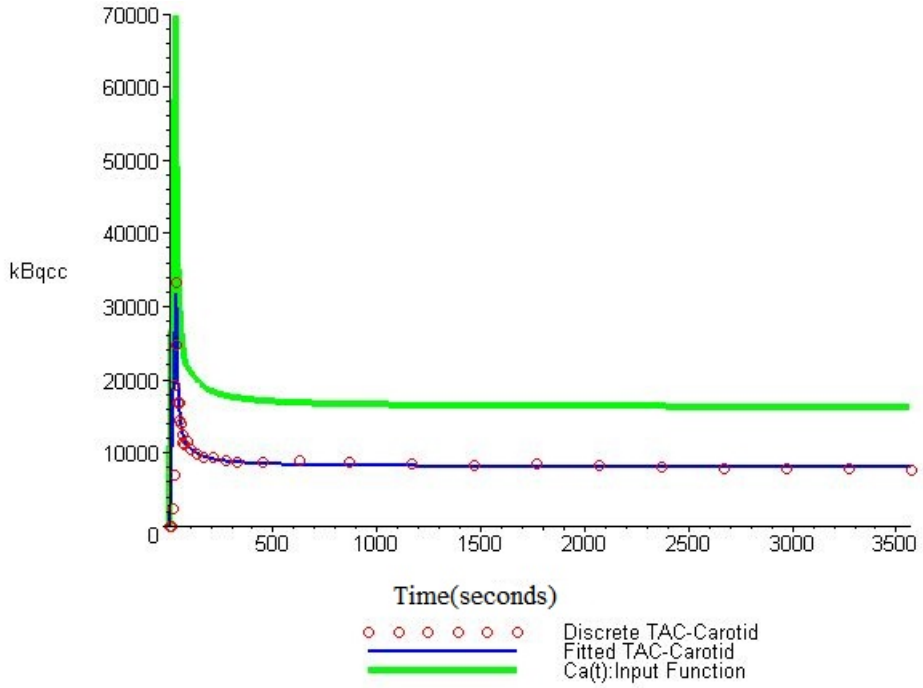

Figure 6. Discrete and Fitted Carotid Time Active Curve and The Input Function.

5. FINAL CONSIDERATIONS AND FUTURE WORKS

This study describe a non-invasive method of estimation of the input function in the FDG positron emission tomography(PET) dynamic brain. The main contribution is that we used the Heaviside function to represent the image derived carotid arterial input function as piecewise function which allows you to calculate the exact solution of the two-tissue reversible compartment model. The only approach is to determinate the arterial input function.

As future work,in thirty older adults of the BraIns superagers project, we would like: to apply this carotid IDAIF results in PET imaging in the diagnosis of Alzheimer's disease; to compare with data from a PET image scan to determine the dynamics of the radiotracer $[^{11}C]PIB$ using cerebellum IDAIF; to quantify amyloid with Laplace transform applied a two-tissue reversible compartment model.

References

[1] D. M. Bates, D. G.Watts *Nonlinear Regression and Its Applications*. Wiley, 1988.

[2] K. Chen et al. Noninvasive Quantification of the Cerebral Metabolic Rate for Glucose Using Positron Emission Tomography, 18F-Fluoro-2-Deoxyglucose, the Patlak Method, and an Image-Derived Input Function. *Journal of Cerebral Blood Flow and Metabolism* **18**, 716–723, 1998.

[3] A.H. Cook. Rates of Cortical Atrophy in Adults 80 Years and Older With Superior vs Average Episodic Memory. *JAMA*, **317**(13),1373–1375, 2017.

[4] V. J. Cunningham,T. Jones. Spectral analysis of dynamic PET studies. *J Cereb Blood Flow Metab*. **13**, 15–23, 1993.

[5] P. Z. Fregonara et al. Comparison of eight methods for the estimation of the image-derived input function in dynamic [18F]-FDG PET human brain studies. *Journal of Cerebral Blood Flow Metabolism*. **29**, 1825–1835, 2009.

[6] T. M. Harrison et al. Superior memory and higher cortical volumes in unusually successful cognitive aging. *Journal of the International Neuropsychological Society*, **18**(6), 1081–1085, 2012.

[7] E. B. Hauser, G. T. Venturin, S. Greggio, E. Manica, E. R. Zimmer, J.C.C. Costa. Laplace Transform Method for 11C-PIB Two-Tissue Reversible Compartment Model with Image-Derived Arterial Input Function. *Ibero-Latin American Congress on Computational Methods in Engineering*, 1–10 ,2017.

[8] E. B. Hauser, G. T. Venturin, S. Greggio, J.C.C.Costa. Mathematical modeling to quantify the pharmacokinetic process of [18F]2-fluor-2deoxy-D-glucose (FDG). In Constanda, C. & Kirsch,A.(ed.s), *Integral Methods in Science and Engineering*, 301–308 , Birkhäuser, 2015.

[9] E. B.Hauser. Laplace Transform in Tracer Kinetic Modeling, *Meeting on Nuclear Applications (ENAN)*, 1–7,2013

[10] M. M. Khalil, *Basic Sciences of Nuclear Medicine*, Springer, 2011.

[11] R. B.Innis et al. Consensus nomenclature for in vivo imaging of reversibly binding radioligands. *Journal of Cerebral Blood Flow Metabolism*. **27**, 1533–1539, 2007.

[12] F. Kiessling, B. J. Pichler. *Small Animal Imaging*. Springer, 2011.

[13] R. A. Koeppe et al. Compartmental Analysis of [llC]Flumazenil Kinetics for the Estimation of Ligand Transport Rate and Receptor Distribution Using Positron Emission Tomography. *Journal of Cerebral Blood Flow and Metabolism*. **11**, 735–744, 1991.

[14] R. Laforest et al. Measurement of input functions in rodents: challenges and solutions. *Nuclear Medicine and Biology*. **3**,679–685, 2005.

[15] N. A. Lassen.Neuroreceptor Quantitation In Vivo by the Steady-State Principle Using Constant Infusion or Bolus Injection of Radioactive Tracers. *Journal of Cerebral Blood Flow and Metabolism*. **12**, 709–716, 1992.

[16] B. J. Lopresti et. al. Simplified quantification of Pittsburgh Compound B amyloid imaging PET studies: a comparative analysis. *J. Nucl Med*, **46**(12),1959–72, 2005.

[17] N.Nelissen, J.Warwick, P. Dupont. Kinetic Modelling in Human Brain Imaging. Chia-Hung Hsieh, eds, In *Positron Emission Tomography - Current Clinical and Research Aspects*, 56–84, 2012

[18] A. B. Rodell et al. Cerebral Blood Flow and AB-Amyloid Estimates by WARM Analysis of [11C] PiB Uptake Distinguish among and between Neurodegenerative Disorders and Aging .*Frontiers in Aging Neuroscience*, **8**, 1–11, 2017.

[19] E J. Rogalski et al. Youthful Memory Capacity in Old Brains: Anatomic and Genetic Clues from the Northwestern SuperAging Project. *Journal of Cognitive Neuroscience*,**25**(1),29–36, 2013.

[20] Y. Su et al.,. Quantitative Amiloid Imaging Using Image-Derived Arterial Input Function. *PLoS One* . **10**(4), 1–16, 2015.

[21] D. Vriens, D. et al. A Curve-Fitting Approach to Estimate the Arterial Plasma Input Function for the Assessment Of Glucose Metabolic Rate and Response to Treatment.*The Journal of Nuclear Medicine*. **50**(12), 1933–1939, 2009.

[22] S. Basu et al. Quantitative Techniques in PET-CT Imaging, *Current Medical Imaging Reviews*, **7**, 216–233, 2006.

[23] H. Zaidi. *Quantitative Analysis in Nuclear Medicine Imaging*, Springer, 2011.

[24] S. Zhou ET AL. A method for generating image-derived input function in quantitative 18F-FDG PET study based on the monotonicity of the input and output function curve, *Nuclear Medicine Communications*, **33**(4), 362–370, 2012.