# PhD thesis abstract

論文題目　Methods to reduce the bias and enhance the contrast of receptor density in positron emission tomography imaging


ふりがな　パウルス　カプンジャ　シグウェダ
氏　名　Paulus　Kapundja　SHIGWEDHA

専　攻　電気・電子工学専攻

指導教授　福岡 豊 教授


2020年 11月


工学院大学大学院

# 1 Introduction

Positron emission tomography (PET) is a physiological imaging technique in nuclear medicine. In a PET study, a beta-plus radioactive substance referred to as a radiotracer is administered *in vivo*. By imaging the emitted $\gamma$-rays, a time sequence of the radiotracer concentration *in vivo* (tissue time-activity curves (tTACs)) can be constructed. These data can then be used to study the kinetics of the radiotracer *in vivo*.

Logan graphical analysis (LGA) can be thought of as a linearization technique for PET data. LGA transforms PET tTAC data into a linear relationship. Physiological quantities such as distribution volume ($DV$), distribution volume ratio ($DVR$) and the non-displaceable binding potential ($BP_{ND}$) can then be obtained from the slope of the LGA. LGA is computationally efficient, in that it is easy to implement and fast to compute. The LGA slope can be estimated by the ordinary least-squares (OLS). The issue with LGA is that the estimated slope is underestimated. The underestimation is due to that both the LGA variables are contaminated with a correlated noise, but OLS only accounts for the noise in the response variable. This underestimation has been observed to increase with both the slope and noise.

A variety of methods have been proposed to address the bias problem. However, these methods have been found to either only slightly reduce the bias or reduce the bias whilst causing variations in the estimates. This necessitates the need for further studies. This study aims to establish a method to reduce the bias in the estimates of $BP_{ND}$ and improve the contrast of the resulting parametric images. It has been demonstrated that the regression method used to estimate the Logan slope influences the resulting bias. On this basis, this study employs an alternative linear regression method referred to as least-squares cubic (LSC) to estimate the LGA slope. LSC minimizes the squared residuals in both the predictor and response variables, and incorporates the correlation of errors in these variables. To further improve the LSC estimates, LSC is for the first time combined with tTACs denoising techniques, principal component analysis (PCA) and correlated component analysis (CorrCA).

# 2 Positron emission tomography, compartmental model and the Logan graphical analysis

## 2.1 Positron emission tomography

PET is used to asses physiological functioning of a biological system by monitoring the interaction of the administered radiotracer with biochemical processes such as glucose metabolism. PET is based on the fundamentals of nuclear disintegration. The administered radiotracer consists of a beta-emitting radionuclide and a biological-active molecule. This gives a biological radioactive compound, which is made to have an affinity to a specific region of interest (ROI). Upon administration, the raditracer will eventually accumulate in the ROI. The radionuclide incorporated within the raditracer will then undergo beta-decay while in the ROI. Imaging the $\gamma$-rays emitted from the positron-electron annihilation will give tTACs of the radiotracer concentration in the ROI. Using the recorded tTACs, quantitative analysis of the radiotracer kinetics can be performed using methods such as the LGA.

## 2.2 Compartmental model and the Logan graphical analysis

Compartmental model is a method used to describe the kinetics of a radiotracer *in vivo* via a set of differential equations. In compartmental model, we assume discrete physiological regions in which the radiotracer is concentrated in the ROI. These physiological regions are referred to as compartments. The differential equations then describe the rate of change in the concentration

of the radiotracer in the compartments.

The LGA is derived from the differential equations of the compartmental model, giving a linear relationship of which the slope is a physiologically interpretable quantity. Mathematically, the LGA can be expressed as below,

$$\frac{\int_0^t C(u)\,du}{C(t)} = DV\frac{\int_0^t C_P(u)\,du}{C(t)} + \text{int}, \tag{1}$$

where $C(t)$ and $C_p(t)$ denote the radioactivity in the target tissue (ROI) and blood plasma, respectively. At equilibrium, (1) becomes a linear relationship, and the slope ($DV$) can be estimated using linear regression. $DV$ can be interpreted as the equilibrium ratio of the radiotracer concentration in ROI tissues to that in plasma. Equilibrium is achieved when there is no more irreversible uptake of the radiotracer between the compartments. The radiotracer concentration in the compartments becomes constant, meaning that the flow of the radiotracer into and out of a given compartment is the same. At this point, all radiotracer flow is due to reversible uptakes, and all tissue compartments and the arterial plasma compartment are at equilibrium with each other.

### 2.3 Logan graphical analysis using a reference region

Arterial blood sampling to obtain $C_P(t)$ is invasive and uncomfortable for patients. It is also technically demanding and expensive, which are all undesirable. An alternative approach is to use a time-activity curve of a reference region instead of plasma's. A reference region has ignorable specific binding sites for the radiotracer and a density of nonspecific binding sites equal to that in the ROI. For the $^{11}$C-PiB PET data used in this study, the cerebellum gray matter region was used as the reference region.

The output parameter of the reference LGA is $DVR$. $DVR$ is the ratio of DV in the ROI to that in the reference region. $DVR$ can also be interpreted in terms of $BP_{ND}$, which is related to $DVR$ by, $BP_{ND} = DVR - 1$. $BP_{ND}$ compares the concentration of the administered radiotracer in receptor-rich to receptor-free regions. $BP_{ND}$ is proportional to the density of binding sites, which denotes the concentration of the target receptors in ROI. Imaging $BP_{ND}$ is therefore a direct quantification of the receptors of interest.

## 3 Reducing the bias in $BP_{ND}$ estimates using least-squares cubic linear regression

### 3.1 Least-squares cubic linear regression

LSC is an errors-in-variables regression method. LSC fully considers the errors in both the predictor and response variables, by minimizing the sum of weighted squared errors in both two variables. Furthermore, LSC also accounts for the correlation of the errors in variables. Because the LGA variables are contaminated with correlated errors, and LSC accounts for correlation of the errors in variables, LSC is expected to be an appropriate regression method to estimate the LGA slope. Under specific assumptions, LSC can be shown to reduce to either OLS or other common regression methods, hence rendering LSC to be a general solution to the linear regression problem.

The emphasis about LSC is that it takes into account three important aspects, namely, **measurement weights in both variables, errors in both variables, and correlation of**

**the errors in variables**. As such, we can then note that a regression method that does not consider either of the three above-mentioned aspects makes assumptions about them in certain ways. That is, an unweighted method assumes equal weights of ones; minimizing only the residuals of the response variable means assuming that the predictor variable is error-free and not considering the correlation of errors means assuming that the errors in the measured data are uncorrelated. This further affirm the position of LSC as a general solution and a superior alternative to OLS.

In this study, we estimated the measurement weights by the inverse square of the variables. An analysis of LSC, specifically in terms of the LGA variables, was carried out to demonstrate the appropriateness of these weight functions. The correlation of the errors was estimated by the correlation between the variables themselves.

### 3.1.1 Simulation studies

A set of PET data of a two-tissue compartmental model was simulated using a clinically measured plasma curve. The kinetic parameters used for simulations were adopted from a range of values used in previous studies. 11 noise-free tTACs corresponding to 11 $BP_{ND}$ values were formed. Statistical noise was added to these noise-free tTACs, and 1024 noisy tTACs were formed for each noise-free tTAC. The $BP_{ND}$ values were then re-estimated from the noisy tTACs by LSC, multilinear reference model 2 (MRTM2), and the conventional OLS-based LGA, and the results were compared. MRTM2 is one of the well accepted methods for reducing the bias in the $BP_{ND}$ estimates.

***Results***: The results obtained showed that the LSC-based estimates are the least biased along the entire range of $BP_{ND}$ values, with a maximum up to 12% and 28% bias difference in comparison with MRTM2 and the conventional OLS-based LGA, respectively. OLS-based estimates showed the least variations. However, LSC-based estimates showed smaller variations than the MRTM2 estimates. In total, the LSC-based estimates showed the most appealing trade-off between bias and variance in comparison to MRTM2 and OLS.

### 3.1.2 Clinical $^{11}$C-PiB PET studies

Two patients, (one beta amyloid (A$\beta$)-negative and the other A$\beta$-positive), participated in this study. The two patients underwent a $^{11}$C-PiB PET scan for 70 minutes. $BP_{ND}$ parametric images of A$\beta$ deposits were then generated from the obtained PET data using the three algorithms, LSC, MRTM2, and the conventional OLS-based LGA.

***Results***: Comparisons of the obtained $BP_{ND}$ images showed that the LSC-based images have higher total $BP_{ND}$ estimates than those of OLS-based for both patients. This implies that the LSC approach has reduced the bias in the $BP_{ND}$ estimates. The images obtained by MRTM2 have the highest total $BP_{ND}$ estimates. However, for MRTM2 images, considerably higher levels of noise are observed. The noise in the MRTM2 images is consistent with the large variances observed in the simulation studies.

# 4 Tissue time-activity curves denoising techniques

## 4.1 Principal component analysis

PCA is a dimensionality reduction technique used mostly for feature extraction and noise filtering. PCA transforms variables into new sets of variables that are linear functions of the original variables. The new sets of variables are uncorrelated and are defined by sets of orthogonal

basis vectors and principal components that optimally describe the variance in the data. The principal components and the corresponding variance are respectively obtained by solving for the eigenvectors and eigenvalues of the covariance matrix of the data. The number of principal components retained to estimate the denoised data in this study was such that 95% of the variance could be realized from it. We denoted the fusion of LSC and PCA as LSC–PCA.

## 4.2 Correlated component analysis

CorrCA is a feature extraction method which operates by identifying components that are maximally correlated between repetitions in multivariate data. Specifically, CorrCA maximizes the ratio of between-repetition to within-repetition covariance. In the context of our application to PET data, our repetitions are along the slices dimension. CorrCA will therefore maximize the ratio of between-slices to within-slices covariance. This ratio is generally referred to as inter-subject correlation (ISC). Specifically in our context, it translates to inter-slice correlation.

Consider a set dynamic PET brain volume data arranged as an array of size $\mathbf{q} \times \mathbf{p} \times \mathbf{M}$, where $\mathbf{M}$ denotes the number of slices, $\mathbf{q}$ denotes the number of voxels in a slice, and $\mathbf{p}$ denotes the number of time points. CorrCA identifies directions in the $\mathbf{p}$-dimensional space along which the tTACs maximally correlate between $\mathbf{M}$ slices, with correlation measured across $\mathbf{q}$ voxels.

Let us put it in perspective in comparison to PCA applied to the same data. For the PCA case, we will represent the brain volume as a $\mathbf{R} \times \mathbf{p}$ array, where $\mathbf{R}$ is a product of $\mathbf{q}$ and $\mathbf{M}$. PCA returns a set of $\mathbf{p}$-dimensional vectors which successively capture the variance in the data in a descending order. Similarly, CorrCA returns a set $\mathbf{p}$-dimensional vectors which successively capture the ISC in a descending order. CorrCA also formulates into an eigenvalues and eigenvectors problem, from which the $\mathbf{p}$-dimensional principal vectors (correlated components) are found as the eigenvectors, and ISCs as the eigenvalues. We denoted the fusion of LSC and CorrCA as LSC–CorrCA.

Maximizing the between-slices to within-slices covariances maximizes the mean-over-variance across slices, which has been asserted to define a signal-to-noise ratio. CorrCA capitalize on the ability to simultaneously operate "within individual slices" and "across all slices", without arranging the slices in one plane. That means operating directly on the $\mathbf{q} \times \mathbf{p} \times \mathbf{M}$ array, unlike PCA which rearranges the slices side-by-side in the $\mathbf{R} \times \mathbf{p}$ array. This means that CorrCA is a dual operation, exploiting through all slices whilst also treating each slice individually. We see this as advantageous over PCA, which means CorrCA can possibly provide a better noise filter method over PCA. We therefore seek to introduce CorrCA to PET parametric imaging and assess the performance of CorrCA in comparison to PCA. For CorrCA only two correlated components were retained to denoise the tTACs.

## 4.3 Simulation studies

Another set of simulation data of a two-tissue compartmental model was generated with the same kinetic parameters as in **Section 3.1.1**. The $BP_{ND}$ values were then estimated from the noisy tTACs by four methods, LSC–CorrCA, LSC–PCA, LSC and OLS-based LGA, and the results were compared.

***Results***: Comparison of percentage bias in the $BP_{ND}$ values estimated from the noisy tTACs showed that both LSC–CorrCA and LSC–PCA estimates have reduced the variations in the estimates, in comparison to LSC. Smaller error bars are an indication of reduced variance in the estimates. LSC–CorrCA estimates shows the smallest error bars amongst all methods,

suggesting that it gives estimations with the least variation. With this we expect parametric images obtained by LSC–CorrCA to have show the highest contrast values.

### 4.4 Clinical $^{11}$C-PiB PET studies

A cohort of 12 (11 A$\beta$-negative and 1 A$\beta$-positive) subjects was used for this analysis. The subjects underwent a 70 min $^{11}$C-PiB PET scan. $DVR$ parametric images were then generated from the PET data by LSC–CorrCA, LSC–PCA, LSC, and OLS methods. Parametric images were compared visually, and numerically in terms of the contrast between the four main gray matter cortices (frontal, temporal, occipital, and parietal) and white matter (corona radiata).

***Results***: The results obtained for contrast comparisons showed LSC–CorrCA and LSC–PCA to have improved the contrast of the parametric images. This was observed for all four gray matter regions. Visual comparison of the images obtained by the four methods are consistent with the numerical comparisons. Random sharp increases in the $DVR$ could be seen in the LSC-based images. On the other hand, images obtained by LSC–CorrCA and LSC–PCA has a rather fair distribution of the $DVR$ estimates in the displayed images.

The contrast of LSC–CorrCA images were observed to be higher than those for LSC–PCA images, as expected based on the simulation results. However, this difference was not statistically significant in terms of the calculated p-value. These findings based on the calculated contrasts are in agreement with the visuals of the displayed images, as not much of a difference could be seen between the images obtained by the two methods, LSC–CorrCA and LSC–PCA. This means that the difference in contratst was not effective enough to be reflected in the displayed $DVR$ images. We however also note that LSC–CorrCA with only two correlated components was able to achieve seemingly better or similar results with LSC–PCA with many principal components. This could be that CorrCA enables it to capture much information in a less number of components in comparison to PCA. This will require further analysis to be established as such.

## 5 Summary and future directions

In the first part of the study (Chapter 3), an alternative linear regression method, LSC, was employed to estimate the $BP_{ND}$. The results showed that LSC-based estimates are the least biased in comparison to those of MRTM2 and the OLS-based LGA. In comparison to the standard OLS-based LGA, LSC reduced the bias at a slight expense of increased variation. However, in total, LSC providied a better trade-off between bias and variability, making it a promising tool for parametric $BP_{ND}$ estimation.

Having noted the slight increased variances in the LSC estimates in comparison with OLS estimates, the second part of the study (Chapter 4) employed two tTACs denoising techniques. Both PCA and CorrCA operates by finding the most important dimensions. The results obtained demonstrate that both LSC–CorrCA and LSC–PCA methods improved the contrast of the parametric images. These are complementary approaches in which LSC mainly serve to reduce the bias, and PCA and CorrCA are employed to minimise the variations in the estimates. This then results in parametric images with minimal biases and improved contrast.

For the whole study, further studies could focus on validating the approaches in this study over a wide range of radiotracers. Studies with a larger number of subjects would also be appropriate. For LSC, a deeper look into weighting techniques could provide for improved estimates. This will also allow LSC to be a stand-alone approach, which means the data will no longer need to

be pre-treated with methods like PCA or CorrCA prior to parameter estimation by LSC. For PCA and CorrCA, further studies could be to explore the methods to determine the number of components to be retained to denoise the data. This is especially worth a while for CorrCA since it is showing the smallest variations (in simulation data) and the highest contrasts (in clinical data); the aim will be to clearly reflect these observations in the displayed parametric images.

# Contents