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An Illustration of the Use of Model-Based Bootstrapping for Evaluation of Uncertainty in Kinetic Information Derived from Dynamic PET

Fengyun Gu, Qi Wu, Finbarr O'Sullivan, Jian Huang, Mark Muzi and David A. Mankoff

***Abstract*—Kinetic mapping via mixture analysis[8, 10] involves comprehensive voxel-level analysis of dynamic PET data. Bootstrapping from the fitted mixture model gives the ability to directly simulate statistical copies of the 4-D PET data, and following suitable analysis, subsequent simulations of the associated kinetic maps. This gives the ability to numerically evaluate uncertainties in inferences associated with kinetic information. We provide a simple introduction to the concept of the model-based bootstrap and an illustration of the use of the approach for kinetic mapping from dynamic PET using results from recent work in Huang et al.[4]. The illustration is from a PET flow-metabolism imaging study in a breast cancer patient. It involves separate dynamic PET imaging following injections of O-15 H2O and F-18 FDG. The bootstrapped data is created in the image domain rather than the projection domain, so there is no reconstruction requirement involved.**

***Index Terms*—Mixture models, Spatial autocorrelation, Model-based bootstrap, Standard errors, Simulation.**

I. INTRODUCTION

POSITRON emission tomography (PET) is a radio-tracer imaging technique which is widely used in the clinical management of cancer patients. When used in dynamic mode, PET has the ability to recover detailed information about the local kinetics (transport and metabolism) of the tracer's interaction with tissue. Additive mixture models have been used to map local tissue residues and associated kinetic summaries from such dynamic PET data[9, 10, 11].The modelling process involves representation of the full dynamic PET information. Thus, if the fit of the model is satisfactory, there is an opportunity to use the model to construct a scheme for simulation of statistical copies of the 4-D PET data. Using a combination of numerical simulation and analysis of physical phantom data, a comprehensive statistical model has been developed to represent the distribution and 3-D spatial autocorrelation structure of practical PET scanner data[7, 4]. These methods allow PET data simulation without recourse to the raw projection domain data. Many Bootstrap methods[5, 3] have been proposed for assessment of the statistical variation of PET data. Most of them focus on resampling list-mode and sinogram PET data. Such methods (particularly for 3-D iterative reconstructions) have limited ability to produce sufficient bootstrap samples, in excess of several hundred, to provide convincing estimates sufficient for evaluation of confidence intervals.

The basic concept of the approach is developed in section II. An illustration with data from a flow-metabolism study are described in section III. The paper concludes with discussion.

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II. METHODOLOGY

A. Model-based Bootstrapping

The bootstrap is well-developed approach to evaluation of the sampling characteristics of statistical estimators[1, 2]. The process is summarized in Fig. 1. To have a better understanding of model based bootstrap in the further analysis, we simplify to a linear model setting. We assume there is a linear relationship between a 1-d predictor variable x and response variable y. ε is a sequence of independent identically distributed(iid) random variables following a normal distribution with zero mean and standard deviation σ.

$$y = x\beta + \varepsilon,\ \varepsilon \sim N(0, \sigma^2) \tag{1}$$

Model fitting provides an estimation of β ($\hat{\beta}$) and residuals(r) as below:

$$\begin{cases} \hat{\beta} = \underset{\beta}{argmin} \sum_{i=1}^{n} (y_i - x\beta)^2 \\ r = y - x\hat{\beta} \end{cases}$$

A normal model can be used to fit residuals and estimate the noise variance σ^2.

$$\hat{\sigma}^2 = \frac{RSS(\hat{\beta})}{n-1}$$

If the linear model is appropriate, we can simulate data y based on the model fitting and diagnostics:

$$y^* = x\hat{\beta} + \varepsilon^*,\ \varepsilon \sim N(0, \hat{\sigma}^2) \tag{2}$$

Sampling distribution of bootstrap estimates can be obtained from linear modelling fitting of y^* and x. The variation of these estimates can be used to approximate the standard error/uncertainty of original estimate $\hat{\beta}$.

$$SE(\hat{\beta}) \approx \sqrt{Var(\hat{\beta}^*)} \tag{3}$$

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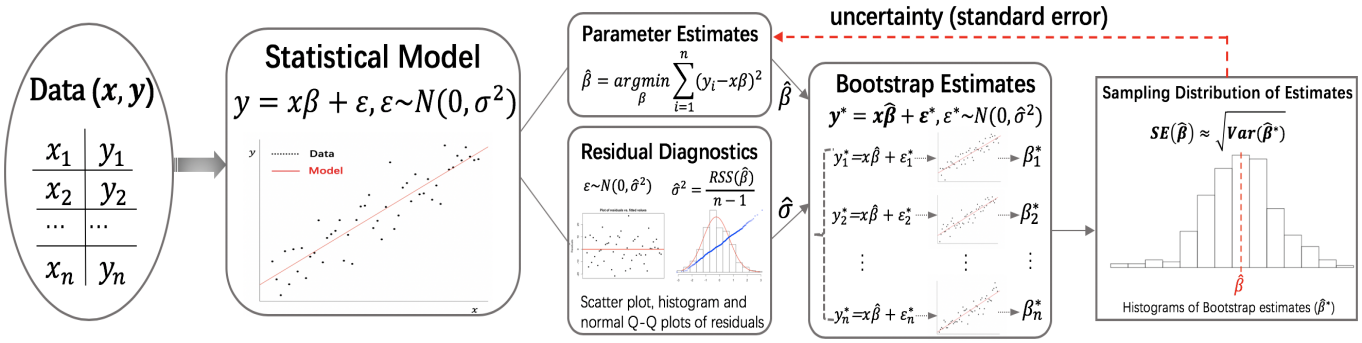


Fig. 1: Schematic summary of the Model-based Bootstrap Concept in a Simple Linear Regression Model.

B. Adaptation to Kinetic analysis of Dynamic PET

The mixture analysis process involves representation of voxel-level PET data, which can be expressed as a linear combination of several underlying time activity curves(sub-TACs).

$$z(x,t) = \alpha(x)^{'}\mu(t) + \sigma_x\sigma_t\varepsilon(x,t) \quad (4)$$

where z are the full voxel-level data, α are positive mixing coefficients, μ are sub-TACs, σ_x and σ_t represent spatial and temporal variation, $\varepsilon(x,t)$ is the measurement/modeling error process. A comprehensive statistical model for PET data, accounting for 3-D auto-covariance and distributional characteristics associated with both iterative and non-iteratively reconstructed data, has been developed in recent work by our group[7, 4]. This modelling approach has been validated using numerical simulations and physical phantom measurements.

Residuals from mixture model are defined as

$$r(x,t) = z(x,t) - \hat{\alpha}(x)^{'}\hat{\mu}(t)$$

A detailed analysis of the spatial covariance of residuals gives the opportunity to describe the standardized residuals process in terms of a stationary SAR processWe use this approach to simulate 4D data based on the mixture model:

$$z^*(x,t) = \hat{\alpha}(x)^{'}\hat{\mu}(t) + \hat{\sigma}_x\hat{\sigma}_t\varepsilon^*(x,t) \quad (5)$$

Hence, a set of bootstrap simulations of the 4-D PET data can be derived. Each dataset is analyzed using the a full mixture model process to derive maps of kinetic parameters. Analysis of the bootstrapped kinetic data provides assessments of uncertainty metabolic parameters. The process is summarized in Fig. 2.

III. ILLUSTRATIVE EXAMPLE

A series of flow-metabolism PET studies conducted in locally advanced breast cancer (LABC) patients have been reported by Mankoff et al.[6]. We consider data from this series. The patient underwent PET scanning prior to surgical resection and prior to scheduled neo-adjuvant chemotherapy. PET scanning involved dynamic imaging with O-15 H2O and F-18 FDG in the same session. Details of PET radiotracer production and dynamic imaging protocols are given in the earlier reports[11, 6]. The 4-D PET data set consists of an imaging volume with $N = 128 \times 128 \times 35$ voxels and $T = 82$ time-frames of acquisition. Arterial input functions for kinetic analysis were recovered from left-ventricle (LV) ROIs - the "gold-standard" in this setting.

The results of 350 Bootstrap realizations are shown in Fig. 3. The distribution of parametric images reports measures of the uncertainty - standard errors. The average standard error (standard deviation of the bootstrap values) by various color levels represented in the coronal scan. The bootstrap analysis can also be used to obtain direct evaluation of uncertainties in regional parameters and separation between tumor and normal breast tissue.

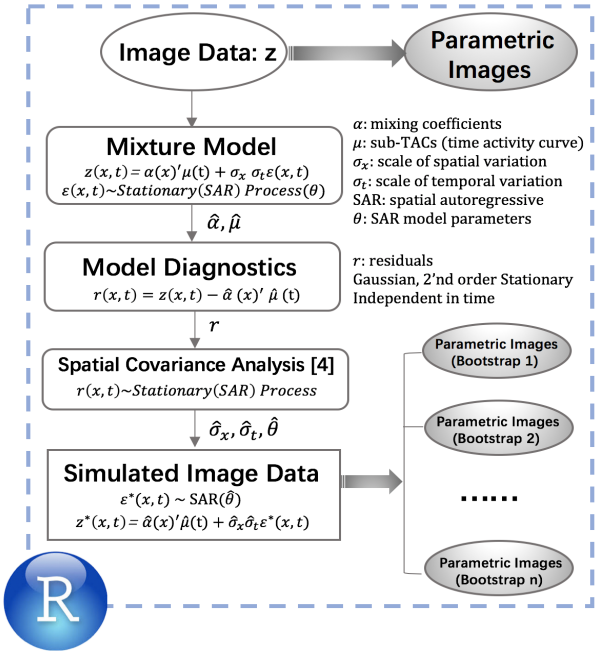


Fig. 2: Model-based Bootstrapping of Dynamic PET

IV. DISCUSSION

Comprehensive modeling of full 4-D dynamic PET data, gives the potential to construct a model-based bootstrap approach for assessment of the statistical uncertainties of computed imaging biomarkers. This approach has significant potential to practically supplement quantitative decision making based on complex PET imaging biomarkers in an individual patient. Full technical details of the approach are contained in a paper which will be submitted for publication.

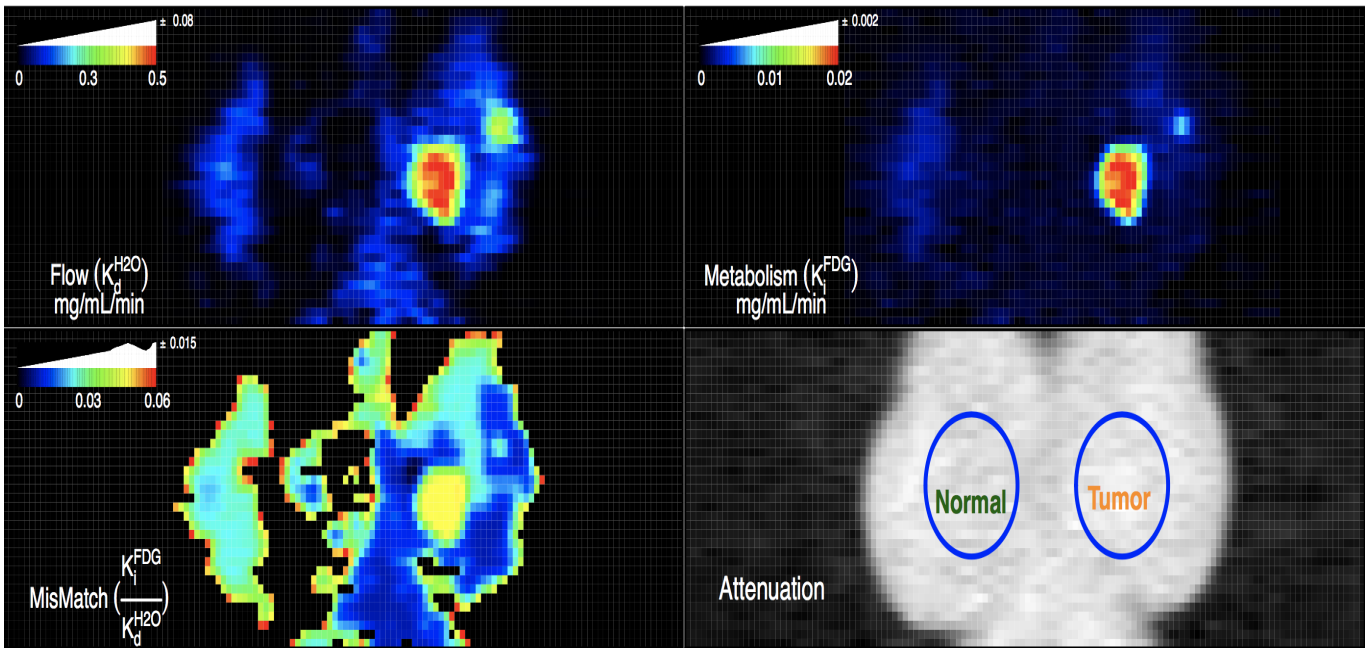


Fig. 3: Coronal views of parametric images of flow, metabolism and mismatch from the breast cancer study. The region of the tumour on the slice is indicated in Attenuation image. Color bars are augmented to present the average standard error (white profile above the color bar) for all pixels on the coronal slice with the corresponding color intensity.

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