COMPUTATION OF VARIANCE IN COMPARTMENT MODEL PARAMETER ESTIMATES FROM DYNAMIC PET DATA

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ABSTRACT

This paper investigates the validity of the analytical framework for bias and variance in kinetic parameter estimations. Analytical computation of bias and variance is compared against Monte Carlo simulations for two different compartment models at different noise levels. Difference between the estimated and measured variance increases with the level of noise and complexity of the compartment model. The standard deviation of the computed variance also increases with the increasing noise-level and model complexity. The difference between the estimated (from the formulation) and measured variance (from Monte Carlo simulations) is less than 1.5% for 1-tissue (1T) compartment model and less than 15% for 2-tissue (2T) compartment model at all noise levels. In addition, the standard deviation in the computed variance is less than 1% for 1T compartment model and less than 10% for 2T compartment model at all noise levels. These results indicate that the proposed framework for the variance in the kinetic parameter estimations can be used for 1-T and 2-T compartment models even in the existence of high noise.

Index Terms— dynamic PET imaging, compartment models, kinetic parameter estimation

1. INTRODUCTION

In compartment models, physically or chemically distinct states of the tracer are used as separate compartments. The tracer exchange between these compartments are modelled using exchange rate coefficients. These coefficients are the parameters of the compartment model, and these parameters are generally referred as kinetic parameters. The tracer dynamics between the compartments are formulated using first order differential equations (ODE) whose coefficients are the kinetic parameters. Kinetic parameters are estimated from the measured time-activity curves (TAC). The TACs are extracted from the reconstructed emission images. The kinetic parameters that can predict the measured TAC are selected as the model parameter estimates. There are different methods for the kinetic parameter estimation [1].

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The accuracy and reliability of the estimated kinetic parameters are very important. Fessler showed that it is possible to approximate the bias and variance with implicit estimator functions, and applied this idea to conventional tomographic reconstruction [2]. In addition, effect of spatial regularization on bias and variance is investigated. Later, the same idea was extended to region-of-interest (ROI) analysis of emission tomography (PET and SPECT) by Qi et al [3]. The effect of penalized maximum likelihood (PML) reconstruction on bias and variance of ROI analysis was investigated [4]. The same formulation was then adapted for dynamic PET reconstruction and effects of bias and variance on ROI analysis of dynamic PET was investigated with different amounts of spatial regularization (or penalization for spatial variance) [5].

The bias and variance computation of kinetic parameter estimations was introduced by Wang et al. [5], and it was validated by other studies [6]. In [5], the bias and variance computations for the kinetic parameter estimations were validated on a single noise level and a single compartment model. The primary focus was the effects of spatial regularization in the emission image reconstruction on the bias and variance of kinetic parameter estimations. In [6], the bias and variance of estimated parameters were investigated at different noise levels. However, the range of noise was quite low, and the regular (physiologically important) kinetic parameters were not used.

2. COMPARTMENT MODELS

In this paper, two different compartment models (shown in Figs. 1 and 2) are investigated. These models are commonly used, and they can model many of the tracers. The models are generally named using the number of compartments within tissue (which excludes the plasma compartment) such as N-tissue compartment model.

2.1. One-Tissue Compartment Model

One-tissue compartment model is the simplest model. In 1-tissue (1T) compartment model, there is only one compartment other than the plasma compartment. Therefore, it can model tracers, that has a single chemical state inside the tissue

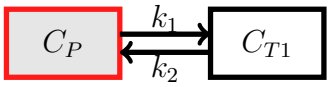


Fig. 1. 1-tissue compartment model with 2 kinetic parameters.

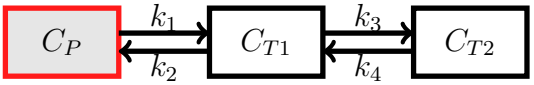


Fig. 2. 2-tissue compartment model with 4 kinetic parameters.

and no interactions other than the plasma. Typically, blood flow measurements using water labelled with ^{15}O isotope ($[^{15}O] - H_2O$) can be modelled using 1-tissue compartment model, as water can only move from the plasma to tissue and back with no further chemical states or interactions. One-tissue compartment model is shown in Fig. 1. The tracer dynamics of 1-tissue compartment model can be described as:

$$\frac{d}{dt}C_{T1}(t) = k_1 C_P(t) - k_2 C_{T1}(t) \; . \tag{1}$$

2.2. Two-Tissue Compartment Model

For more complicated physiological processes, 2-tissue compartment model can be used. In this model, there are two compartments that represent the tracer inside the tissue (shown in Fig. 2). Therefore, this model can be used for tracers that have two distinct chemical states within the tissue. The 2-tissue compartment model can be used for the most commonly used tracer in PET imaging, 2-deoxy-2-(18F)fluoro-D-glucose (FDG). This tracer is basically glucose labelled using ^{18}F, and commonly used in oncology imaging.

The ODEs that describe the tracer dynamics for this model are:

$$\frac{d}{dt}C_{T1}(t) = k_1 C_P(t) - (k_2 + k_3)C_{T1}(t) + k_4 C_{T2}(t) \tag{2}$$

$$\frac{d}{dt}C_{T2}(t) = k_3 C_{T1}(t) - k_4 C_{T2}(t) \; . \tag{3}$$

2.3. Kinetic Parameter Estimation

The activity measured from PET originates partially from the plasma compartment and from the compartments within the tissue:

$$C_{total}(t) = f_v C_P(t) + (1 - f_v)\left\{\sum_{i=1}^{N} C_{Ti}(t)\right\} S_A e^{-\lambda t} \; . \tag{4}$$

In this equation, f_v denotes the fraction of plasma within the tissue, S_A denotes the initial specific activity of the tracer (ie. efficiency of radioactive labelling), and λ denotes the decay constant for the radioactive isotope.

Lets denote the kinetic parameters of the compartment model using $\theta = [k_1, k_2, \cdots, k_p]$ ($\theta \in \mathbb{R}^p$). Furthermore, let $f(\theta, t)$ denote the forward model that models $C_{total}(t)$ with given θ and t. In practice, the TAC measurements are made at discrete times. Let $\mathbf{x} = [x_1, x_2, \cdots, x_K]$ denote the vector of TAC measurements that are taken at K discrete times at $\mathbf{t} = (t_1, t_2, \cdots, t_K)$, ie. $x_k = C_{total}(t_k)$.

Although there are many kinetic parameter estimation technique in the literature, the most commonly used method is to find the set of kinetic parameters that minimizes the weighted squared error between the measurements ($\mathbf{x}$) and the model output $f(\theta, \mathbf{t}) = [f(\theta, t_1), f(\theta, t_2), \cdots, f(\theta, t_K)]$. In this method the kinetic parameters are estimated as:

$$\hat{\theta} = \arg\min_{\theta \geq 0} \|\mathbf{x} - f(\theta, \mathbf{t})\|^2_W \tag{5}$$

where $\hat{\theta}$ is the estimated kinetic parameter, W is the diagonal weighting matrix, $\|a\|^2_W = a^T W a$, and superscript T denotes matrix transpose.

3. COMPUTATION OF VARIANCE IN KINETIC PARAMETER ESTIMATES

The kinetic parameters of a compartment model are estimated using (5), which means there is no explicit estimator such as:

$$\hat{\theta} = h(x) \; . \tag{6}$$

In literature, it has been shown that there is no need to know $h(.)$ for the computation the bias and variance in kinetic parameter estimates [2]. In fact, the derivatives of this function with respect to TAC points are sufficient for this purpose.

3.1. Analytical Computation of Variance for Kinetic Parameter Estimates

First, computation of the estimation bias will be derived. This derivation will then be extended to computation of estimation variance.

For bias derivation, first order Taylor expansion is used for the implicit function ($h(.)$) around the correct TAC values:

$$\begin{aligned} \hat{\theta} &= h(x) \\ &\approx h(x^t) + \nabla h(x^t)(x - x^t) \end{aligned} \tag{7}$$

where x^t denotes the correct TAC values, and $\nabla h(x^t)$ denotes the value of function derivative at x^t. The higher order terms are ignored.

If it is assumed that the implicit estimator will give the correct kinetic parameters for the correct TAC, then (7) becomes:

$$\hat{\theta} - \theta^t \approx \nabla h(x^t)(x - x^t) \; . \tag{8}$$

In some models, the kinetic parameters may not be identifiable. This means that different sets of kinetic parameters give the same (or very close) TAC output. If the kinetic parameters of a model are not identifiable, (7) cannot be written as (8) as $\theta^t \neq h(x^t)$.

By taking the expected value of both sides in (7), we obtain:

$$b_\theta \approx \nabla h(x^t) b_x \tag{9}$$

where b_x and b_θ denote the bias in the TAC and bias in the kinetic parameter estimates respectively. Similarly, the covariance of the kinetic parameter estimates can be computed as:

$$Cov_\theta \approx \nabla h(x^t) \mathrm{Cov}_x \nabla h(x^t)^T \ , \tag{10}$$

where Cov_x denotes the covariance matrix of the measured TAC.

3.2. Estimation of Derivative of Implicit Function ($\nabla h(.)$)

The derivative of the implicit function $h(.)$ is required for the computation of both bias and variance. Furthermore, it is sufficient to know the derivative only at the correct TAC values. Derivation of the implicit function ($\nabla h(.)$) was derived in [2, 5] as:

$$\nabla h(x^t) = (S^T W S)^{-1} S^T W^T \ , \tag{11}$$

where S is the sensitivity matrix defined as:

$$S \triangleq \left[\frac{\partial f(\theta^t, t)}{\partial k_1}, \frac{\partial f(\theta^t, t)}{\partial k_2}, \cdots, \frac{\partial f(\theta^t, t)}{\partial k_P} \right] \ .$$

4. RESULTS FOR VALIDATION OF VARIANCE COMPUTATION

The framework for analytical computation of variance in kinetic parameter estimations is validated using Monte Carlo simulations. Comkat software library (version 3.2) is used to estimate the kinetic parameters for the compartment models [7]. [1]

Monte Carlo simulations are performed to validate the computed variance of kinetic parameter estimates. The kinetic parameters used in the 1T and 2T compartment models are listed in Table 4. Total 110 min. of data is divided into 28 time frames: 4×0.5 min., 4×2 min., and 20×5 min.

For validation of variance computation, Gaussian noise is added to the correct TAC. The standard deviation of the Gaussian noise is $\sigma = [\sigma_1, \sigma_2, \cdots, \sigma_K]$: $\sigma_k = \beta \sqrt{x_k / \Delta t_k}$, where σ_k is the standard deviation of the Gaussian noise for activity at time t_k, and β is a constant that determines the noise level [8].

[1] Comkat software library is available at http://comkat.case.edu.

Table 1. Kinetic parameter values that are used the simulations.

	1-T model	2-T model
k_1	0.1020	0.1020
k_2	0.1300	0.1300
k_3	-	0.0620
k_4	-	0.0068

Monte Carlo simulations are performed at 15 different noise levels from $\beta = 0.1$ up to $\beta = 1.5$ by increments of 0.1. The noise level can be divided into three regions: low-level noise ($\beta < 0.5$), medium-level noise ($0.5 \leq \beta < 1.1$), and high-level noise ($1.1 \leq \beta$). Low-level noise is typically obtained in region-of-interest (ROI) analysis where TACs of pixels within a uniform tissue are averaged. Medium-level noise is the case where pixel-level TAC is used to estimate the kinetic parameters. High-level noise is typically seen when low (dose) concentration of tracer is used.

For each noise level, 1000 realizations of independent and identically distributed (iid) Gaussian noise are added to the correct TAC.

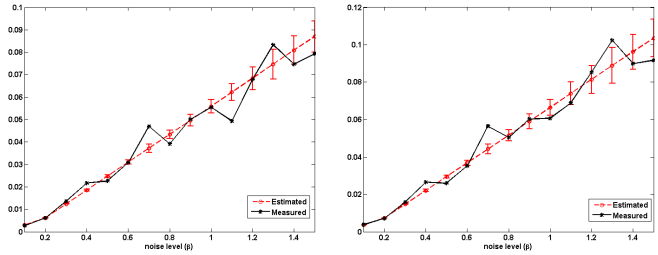
In order to compare the results of the estimated (computed) variance using the framework against the measured variance from Monte Carlo simulations, the ratio of standard deviation to the correct value of the kinetic parameter is used. The ratio of standard deviation to true kinetic parameter for Monte Carlo simulations is estimated as:

$$\xi_{k_p}^{MC} = \frac{\sqrt{\frac{1}{N-1} \sum_{i=1}^{N} (k_p^{(i)} - \overline{k_p})^2}}{k_p^t} \ , \tag{12}$$

where $\overline{k_p}$ denotes the average value for kinetic parameter k_p estimated from all noise realizations. The ratio of standard deviation to true kinetic parameters is computed for each noise realization, and the mean and standard deviation of this ratio is computed: $\xi_{k_p}^{(i)} = \sigma_{k_p}^{(i)} / k_p^t$, where $\sigma_{k_p}^{(i)}$ is the standard deviation of kinetic parameter p for noise realization i. Mean and standard deviation of ξ_{k_p} are compared to $\xi_{k_p}^{MC}$ at different noise levels.

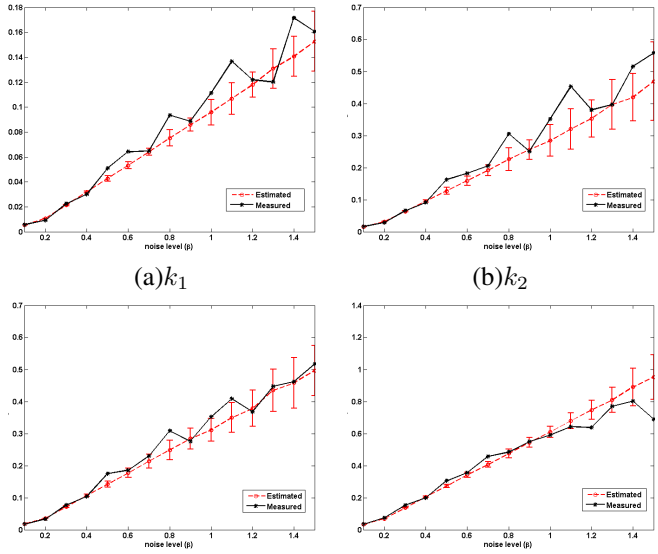
Fig. 3 illustrates the results of variance of kinetic parameter estimations measured from Monte Carlo simulations (ξ^{MC} by solid line) and estimated variance (dashed line) for 1T compartment model. In this figure, markers in the dashed line shows the mean of ξ_{k_p} ($\overline{\xi_{k_p}}$), and the vertical line around the marker shows its standard deviation ($\sigma_{\xi_{k_p}}$). Comparisons for k_1 and k_2 are shown in Fig. 3(a) and Fig. 3(b) respectively.

Fig. 4 compares the results of variance of kinetic parameter estimations measured from Monte Carlo simulations (ξ^{MC} by solid line) and estimated variance (dashed line) for 2T compartment model. Similar to 1T compartment model, the standard deviation of estimated variances increase with the level of noise. Compared to 1T compartment model, the



(a)k_1 (b)k_2

Fig. 3. The estimated and measured variances of kinetic parameters of 1T model for different noise levels β.



(a)k_1 (b)k_2

(c)k_3 (d)k_4

Fig. 4. The estimated and measured variances of kinetic parameters of 2T model for different noise levels β.

difference between the mean of the estimated variance and measured variance increase.

5. CONCLUSIONS

Analytical framework developed for the variance of the kinetic parameter estimation is validated using 1T compartment model with 2 parameters and 2T compartment model with 4 parameters on different noise levels.

Difference between the estimated (from the formulation) and measured variance (from Monte Carlo simulations) is increasing with the level of noise. Similarly, the standard deviation of the computed variance increases with the increasing noise-level. In addition, the difference between the estimated and measured variance is higher for 2T compartment model compared to 1T compartment model.

The difference between the estimated (from the formulation) and measured variance (from Monte Carlo simulations) is less than 1.5% for 1-tissue (1T) compartment model and less than 15% for 2-tissue (2T) compartment model at all noise levels. In addition, the standard deviation in the computed variance is less than 1% for 1T compartment model and less than 10% for 2T compartment model at all noise levels. These results indicate that the proposed framework for the variance in the kinetic parameter estimations can be used for 1-T and 2-T compartment models even in the existence of high noise.

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