Computation of Variance in Compartment Model Parameter Estimates from Dynamic PET Data

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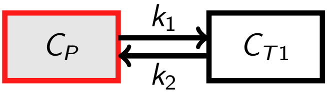
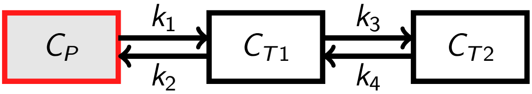
Dynamic PET and Compartment Models

- 1 tissue compartment model



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

- 2 tissue compartment model



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

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

Kinetic Parameter Estimation

- Activity measured from PET

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

f_v - fraction of plasma within the tissue,
S_A - initial specific activity of the tracer
λ - decay constant for the radioactive isotope.

- Nonlinear least squares is used to estimate kinetic parameters

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

$\theta = [k_1, k_2, \cdots, k_p]$ ($\theta \in \mathbb{R}^p$) - kinetic parameters
$f(\theta, t)$ - forward model
$\mathbf{x} = [x_1, x_2, \cdots, x_K]$ - TAC measurements ($x_k = C_{total}(t_k)$).

Computation of Variance in Kinetic Parameter Estimates

- Assume an implicit estimator

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

- First order Taylor expansion is used for the implicit function ($h(.)$) around correct TAC values:

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

  x^t - correct TAC values
  $\nabla h(x^t)$ - value of function derivative at x^t.

- Expected value of both sides

$$b_\theta \approx \nabla h(x^t) b_x \tag{8}$$

  b_x - bias in the TAC
  b_θ - bias in the kinetic parameter estimates.

Computation of Variance in Kinetic Parameter Estimates

- Covariance of the kinetic parameter estimates (Cov_x) can be computed as:

$$Cov_\theta \approx \nabla h(x^t) \mathrm{Cov}_x \nabla h(x^t)^T \ . \tag{9}$$

  where denotes the covariance matrix of the measured TAC.

- Derivative of Implicit Function ($\nabla h(.)$)

$$\nabla h(x^t) = (S^T W S)^{-1} S^T W^T \ , \tag{10}$$

  where S is the sensitivity matrix defined as:

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

Validation Experiments

- Variance obtained from Monte Carlo simulations are compared to the analytically computed values
- Comkat software library (version 3.2) is used
- Kinetic parameters used in the 1T and 2T compartment models

	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

- Total 110 min. of data is divided into 28 time frames: 4 $\times$ 0.5 min., 4 $\times$ 2 min., and 20 $\times$ 5 min.
- Gaussian noise is added to correct TAC. $\sigma = [\sigma_1, \sigma_2, \cdots, \sigma_K]$:
  $\sigma_k = \beta\sqrt{x_k/\Delta t_k}$, σ_k - standard deviation of noise
  β - noise level

Validation Experiments

- 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 ($\beta < 0.5$): region-of-interest (ROI) analysis where TACs of pixels within a uniform tissue are averaged
  - medium-level noise ($0.5 \leq \beta < 1.1$): pixel-level TAC is used to estimate the kinetic parameters
  - high-level noise ($1.1 \leq \beta$): 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.

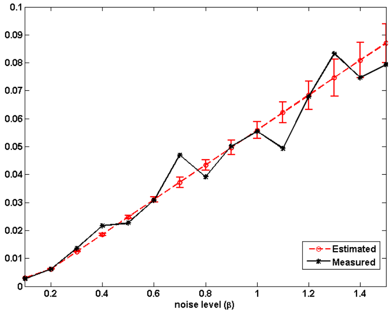
Performance metrics

- Ratio of standard deviation to true kinetic parameter for Monte Carlo simulations

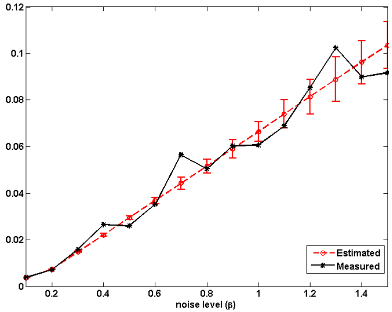
$$\xi_{k_p}^{MC} = \frac{\sqrt{\frac{1}{N-1}\sum_{i=1}^{N}(k_p^{(i)} - \overline{k_p})^2}}{k_p^t} , \tag{11}$$

  $\overline{k_p}$ - 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 $\xi_{k_p}^{(i)} = \sigma_{k_p}^{(i)} / k_p^t$,
  $\sigma_{k_p}^{(i)}$ - 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.

Covariance for 1T Compartment Model

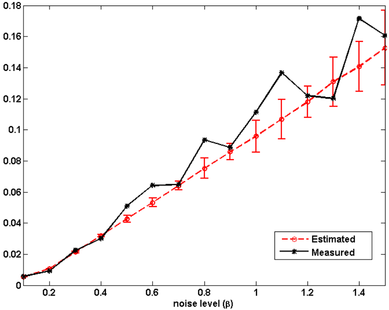


(a) k_1

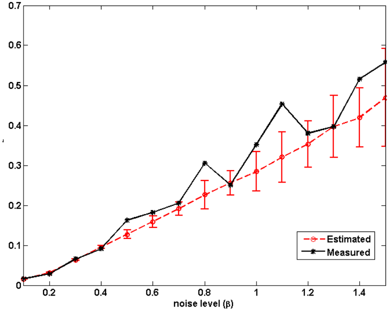


(b) k_2

Covariance for 2T Compartment Model

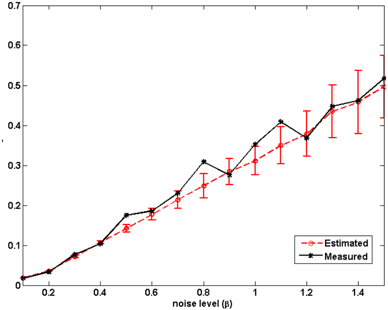


(a) k_1

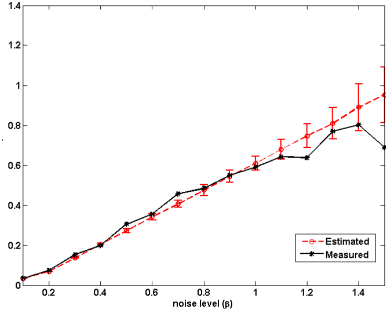


(b) k_2

Covariance for 2T Compartment Model



(c) k_3



(d) k_4

Conclusions

- Difference between Monte Carlo variance and analytical variance increases with the level of noise.
- Standard deviation of analytical variance increases with noise-level.
- Difference between Monte Carlo and analytical variance is higher for 2T compartment model compared to 1T compartment model.
- Difference between Monte Carlo and analytical variance 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.
- Standard deviation of analytical variance is less than 1% for 1T compartment model and less than 10% for 2T compartment model at all noise levels.
- 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.