COVARIANCE OF KINETIC PARAMETER ESTIMATORS BASED ON TIME ACTIVITY CURVE RECONSTRUCTIONS: PRELIMINARY STUDY ON 1D DYNAMIC IMAGING

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ABSTRACT

We provide approximate expressions for the covariance matrix of kinetic parameter estimators based on time activity curve (TAC) reconstructions when TACs are modeled as a linear combination of temporal basis functions such as B-splines. The approximations are useful tools for assessing and optimizing the basis functions for TACs and the temporal bins for data in terms of computation and efficiency. In this paper we analyze a 1D temporal problem for simplicity, and we consider a scenario where TACs are reconstructed by penalized-likelihood (PL) estimation incorporating temporal regularization, and kinetic parameters are obtained by maximum likelihood (ML) estimation. We derive approximate formulas for the covariance of the kinetic parameter estimators using 1) the mean and variance approximations for PL estimators in (Fessler, 1996) and 2) Cramér-Rao bounds. The approximations apply to list-mode data as well as bin-mode data.

1. INTRODUCTION

A primary application of dynamic PET or SPECT imaging is to quantify parameters of *nonlinear* tracer kinetic models or compartmental models representing specific physiological processes. The goal is to estimate the kinetic parameters for each region of interest (ROI) or voxel. Kinetic parameters are conventionally estimated as follows [1]: a series of images are reconstructed frame-by-frame, ROIs are identified and then kinetic parameters are obtained by fitting a compartmental model (with a measured or estimated input function) to spatially averaged image values for each ROI.

Recently have spatiotemporal reconstruction methods been proposed to reconstruct time activity curves (TACs) by modeling each TAC as a *linear* combination of cubic B-splines [2]. Also, TAC reconstructions for each ROI obtained using B-spline temporal basis functions have been used to estimate kinetic parameters [3]. The performance, such as bias and variance, of the kinetic parameter estimators is affected by the choice of temporal basis functions for TACs (*e.g.*, the order of B-splines [3] and their knot locations). Although the effects of basis functions on TAC reconstructions have been studied in [4, 5], the effects on kinetic parameter estimators have little been analyzed.

In this paper we provide analytical approximate expressions for the covariance of kinetic parameter estimators in a simple 1D temporal "imaging" case. We do not analyze bias since we estimate the kinetic parameters from TAC reconstructions by (asymptotically) *unbiased* maximum likelihood (ML) estimators as opposed to widely-used (data-weighted) least squares estimators. The approximation formulas are very useful tools since they enable one to assess and optimize temporal basis functions in terms of complexity and variance without exhaustive simulations.

Our approximations apply to list-mode data as well as (temporal) bin-mode data. List-mode acquisitions are more attractive than conventional frame-by-frame scans since all temporal information is contained in the event list. Our expressions can be used to compute how much information is lost through temporal binning compared to list-mode data, and they also show the effects of temporal regularization in TAC reconstruction.

2. PROBLEM

To focus on temporal aspects rather than interactions with spatial distributions, we consider a single-voxel or single-ROI object, containing a radiotracer, and a single detector unit, recording list-mode data, that is, the arrival times of detected photons, or temporal bin-mode data. The model is not an unrealistically simple one; for example, in planar dynamic imaging, one could take a ROI and investigate the (average or dominant) dynamic tracer behavior using corresponding data. The goal is to estimate tracer kinetic parameters governing dynamic activity changes.

The photon emissions in the object can be modeled as an inhomogeneous Poisson process whose rate function $\eta(t;\boldsymbol{\theta})$ corresponds to a TAC parameterized by kinetic parameters $\boldsymbol{\theta} = [\theta_1 \ldots \theta_p]'$ where $'$ denotes vector and matrix transpose [2]. Suppose $\{\tau_k\}_{k=1}^K$ denotes list-mode data, that is,

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event arrival times. Then the log-likelihood of $\boldsymbol{\theta}$ given the list-mode data is [6, p. 57]

$$L(\boldsymbol{\theta}, \{\tau_k\}_{k=1}^K) = \sum_{k=1}^{K} \log\{\alpha(\eta(\tau_k;\boldsymbol{\theta}) + r(\tau_k))\} - \int_0^T \alpha(\eta(t;\boldsymbol{\theta}) + r(t))dt$$

where $r(t)$ is the rate function of the background process such as scatters and randoms, T denotes the total scan time, and α denotes a constant factor proportional to a radioisotope dosage. Although the background process $r(t)$ can be a function of α, we neglect the dependence for simplicity. One can obtain the Fisher information matrix $\boldsymbol{I}_{\boldsymbol{\tau}}(\boldsymbol{\theta})$ as [6, p. 81]

$$[\boldsymbol{I}_{\boldsymbol{\tau}}(\boldsymbol{\theta})]_{ij} = \alpha \int_0^T \frac{\partial\eta(t;\boldsymbol{\theta})}{\partial\theta_i} \frac{\partial\eta(t;\boldsymbol{\theta})}{\partial\theta_j} \frac{1}{\eta(t;\boldsymbol{\theta}) + r(t)} dt.$$

The inverse of $\boldsymbol{I}_{\boldsymbol{\tau}}(\boldsymbol{\theta})$ can serve as an approximation to the baseline covariance of the direct estimator of $\boldsymbol{\theta}$ (without TAC reconstruction) based on list-mode data. However, in cases where the kinetic model is under development, it can be preferable to first estimate a TAC, and then fit various kinetic models to it.

Next, we describe the procedure of TAC reconstruction using temporal basis functions followed by kinetic parameter estimation.

2.1. TAC Reconstruction

We model the rate function as a linear combination of temporal basis functions $\{B_l(t)\}_{l=1}^L$, which for example can be B-splines, as

$$\eta(t) \cong \sum_{l=1}^{L} w_l B_l(t),$$

and we reconstruct the coefficients by penalized-likelihood (PL) estimation.

For simplicity we consider temporal bin-mode data $\boldsymbol{y} = [y_1 \dots y_N]'$ where y_n is the number of events detected in the nth temporal bin (note $N \geq L$ or possibly $N \gg L$); the list-mode data is a limiting case where $N \to \infty$ and the bin widths approach zero [4]. The bin-mode data $\boldsymbol{y}$ are independent Poisson random variables, and the mean of each element is given by

$$\bar{y}_n(\boldsymbol{\theta}) \triangleq E[y_n] = \alpha p_n(\boldsymbol{\theta}) \quad (1)$$

$$p_n(\boldsymbol{\theta}) = \int_{t_{n-1}}^{t_n} \eta(t;\boldsymbol{\theta})dt + r_n \quad (2)$$

where t_{n-1} and t_n are the end points of the nth temporal bin, and r_n represents background contributions. The log-likelihood of $\boldsymbol{w}$ given $\boldsymbol{y}$ can be obtained, ignoring constants independent of $\boldsymbol{w}$, as

$$L(\boldsymbol{w}, \boldsymbol{y}) = \sum_{n=1}^{N} \{y_n \log(\alpha\tilde{p}_n(\boldsymbol{w})) - \alpha\tilde{p}_n(\boldsymbol{w})\}$$

where

$$\tilde{p}_n(\boldsymbol{w}) = [\boldsymbol{B}\boldsymbol{w}]_n + r_n.$$

The $N \times L$ matrix $\boldsymbol{B}$ has the $(n,\ l)$th entry as

$$b_{nl} = \int_{t_{n-1}}^{t_n} B_l(t)dt.$$

We assume that the $\{r_n\}$ are known (see [2] for methods of estimating randoms and scatters).

A PL estimate of $\boldsymbol{w}$ is obtained finding the following maximizer:

$$\hat{\boldsymbol{w}}(\boldsymbol{y}) = \arg\max_{\boldsymbol{w}\in\mathcal{W}} \Phi(\boldsymbol{w}, \boldsymbol{y}) \quad (3)$$

where

$$\Phi(\boldsymbol{w}, \boldsymbol{y}) = L(\boldsymbol{w}, \boldsymbol{y}) - \frac{\beta}{2}\boldsymbol{w}'\boldsymbol{R}\boldsymbol{w} \quad (4)$$

and

$$\mathcal{W} = \left\{\boldsymbol{w} : \sum_{l=1}^{L} w_l B_l(t) \geq 0,\ \forall t \in [0, T]\right\}. \quad (5)$$

The last term in (4) represents a roughness penalty encouraging temporal smoothness [2, 4], $\boldsymbol{R}$ is some symmetric nonnegative definite matrix (*e.g.*, see [7] for an uniform quadratic penalty), and β is a regularization parameter. The set in (5) represents the nonnegativity constraint on reconstructed TACs, $\hat{\eta}(t) = \sum_{l=1}^{L} \hat{w}_l B_l(t)$.

2.2. Kinetic Parameter Estimation

To estimate kinetic parameters $\boldsymbol{\theta}$ from $\hat{\boldsymbol{w}}$ in (3), we assume $\hat{\boldsymbol{w}}$ is Gaussian-distributed as

$$\hat{\boldsymbol{w}} \sim \mathcal{N}(\boldsymbol{\mu}_{\hat{\boldsymbol{w}}}(\boldsymbol{\theta}), \boldsymbol{K}_{\hat{\boldsymbol{w}}}(\boldsymbol{\theta})) \quad (6)$$

where $\boldsymbol{\mu}_{\hat{\boldsymbol{w}}}$ and $\boldsymbol{K}_{\hat{\boldsymbol{w}}}$ are the mean and the covariance matrix of the estimator $\hat{\boldsymbol{w}}$, respectively. The higher counts per time (or temporal bin), the more the Gaussian assumption becomes accurate. Then one can compute a ML estimate of $\boldsymbol{\theta}$ as follows:

$$\hat{\boldsymbol{\theta}}(\hat{\boldsymbol{w}}) = \arg\max_{\boldsymbol{\theta}\in\Theta} \Psi(\boldsymbol{\theta}, \hat{\boldsymbol{w}}) \quad (7)$$

where Θ is a set of feasible $\boldsymbol{\theta}$, and the log-likelihood of $\boldsymbol{\theta}$ given $\hat{\boldsymbol{w}}$ can be obtained, neglecting constants independent of $\boldsymbol{\theta}$, as

$$\Psi(\boldsymbol{\theta}, \hat{\boldsymbol{w}}) = -\frac{1}{2}(\hat{\boldsymbol{w}} - \boldsymbol{\mu}_{\hat{\boldsymbol{w}}}(\boldsymbol{\theta}))'[\boldsymbol{K}_{\hat{\boldsymbol{w}}}(\boldsymbol{\theta})]^{-1}(\hat{\boldsymbol{w}} - \boldsymbol{\mu}_{\hat{\boldsymbol{w}}}(\boldsymbol{\theta})) - \frac{1}{2}\log|\boldsymbol{K}_{\hat{\boldsymbol{w}}}(\boldsymbol{\theta})| \quad (8)$$

where $|\cdot|$ denotes determinant. Generally, the TAC estimator $\hat{\eta}(t) = \sum_{l=1}^{L} \hat{w}_l B_l(t)$ from (3) is not consistent since it can be a case that $\eta(t; \boldsymbol{\theta}^{\text{true}}) \neq \sum_{l=1}^{L} w_l B_l(t)$ for all w_l's; even in such a case, however, the ML kinetic parameter estimator $\hat{\boldsymbol{\theta}}$ in (7) can be (nearly) unbiased as shown in Sec. 4. Therefore, the inverse of the Fisher information matrix, which is shown in the next section, can serve as an approximation to the covariance of $\hat{\boldsymbol{\theta}}$.

3. COVARIANCE OF KINETIC PARAMETER ESTIMATORS

3.1. Derivation

First, we need approximate expressions for $\boldsymbol{\mu}_{\hat{\boldsymbol{w}}}$ and $\boldsymbol{K}_{\hat{\boldsymbol{w}}}$ in (6). Using a first-order Taylor approximation of $\hat{\boldsymbol{w}}(\boldsymbol{y})$ at $\bar{\boldsymbol{y}} = [\bar{y}_1 \dots \bar{y}_N]'$ in (1), the chain rule and the implicit function theorem with some reasonable assumptions [8], one can obtain the following approximations:

$$\boldsymbol{\mu}_{\hat{\boldsymbol{w}}}(\boldsymbol{\theta}) \cong \hat{\boldsymbol{w}}(\bar{\boldsymbol{y}}(\boldsymbol{\theta})) \triangleq \check{\boldsymbol{w}}(\boldsymbol{\theta}) \tag{9}$$

and

$$\begin{aligned}
&\boldsymbol{K}_{\hat{\boldsymbol{w}}}(\boldsymbol{\theta}) \\
&\cong \frac{1}{\alpha}\left[\boldsymbol{F}(\boldsymbol{\theta}) + \frac{\beta}{\alpha}\boldsymbol{R}\right]^{-1} \boldsymbol{F}(\boldsymbol{\theta}) \left[\boldsymbol{F}(\boldsymbol{\theta}) + \frac{\beta}{\alpha}\boldsymbol{R}\right]^{-1} \\
&\triangleq [\tilde{\boldsymbol{F}}(\boldsymbol{\theta})]^{-1}
\end{aligned} \tag{10}$$

where

$$\boldsymbol{F}(\boldsymbol{\theta}) = \boldsymbol{B}' \mathrm{diag}\left\{\frac{p_n(\boldsymbol{\theta})}{\tilde{p}_n^2(\check{\boldsymbol{w}}(\boldsymbol{\theta}))}\right\} \boldsymbol{B}.$$

Now one can compute the Fisher information matrix from (8) by replacing $\boldsymbol{\mu}_{\hat{\boldsymbol{w}}}$ and $\boldsymbol{K}_{\hat{\boldsymbol{w}}}$ with their approximations in (9) and (10). Some manipulation leads to our final expression for the Fisher information matrix for estimating $\boldsymbol{\theta}$ from $\hat{\boldsymbol{w}}$,

$$\begin{aligned}
\boldsymbol{I}_{\hat{\boldsymbol{w}},\mathrm{bin}}(\boldsymbol{\theta}) &= E_{\boldsymbol{\theta}}[-\nabla^2_{\boldsymbol{\theta}} \Psi(\boldsymbol{\theta}, \hat{\boldsymbol{w}})] \\
&\cong [\nabla_{\boldsymbol{\theta}} \check{\boldsymbol{w}}(\boldsymbol{\theta})]' \tilde{\boldsymbol{F}}(\boldsymbol{\theta}) \nabla_{\boldsymbol{\theta}} \check{\boldsymbol{w}}(\boldsymbol{\theta}) \\
&= \alpha [\nabla_{\boldsymbol{\theta}} \boldsymbol{p}(\boldsymbol{\theta})]' \mathrm{diag}\left\{\frac{1}{\tilde{p}_n(\check{\boldsymbol{w}}(\boldsymbol{\theta}))}\right\} \boldsymbol{B} [\boldsymbol{F}(\boldsymbol{\theta})]^{-1} \cdot \\
&\quad \boldsymbol{B}' \mathrm{diag}\left\{\frac{1}{\tilde{p}_n(\check{\boldsymbol{w}}(\boldsymbol{\theta}))}\right\} \nabla_{\boldsymbol{\theta}} \boldsymbol{p}(\boldsymbol{\theta})
\end{aligned} \tag{11}$$

where $\nabla_{\boldsymbol{\theta}} = [\frac{\partial}{\partial \theta_1} \cdots \frac{\partial}{\partial \theta_p}]$ denotes the row gradient operators, $\nabla^2_{\boldsymbol{\theta}}$ denotes the Hessian operator, and $\boldsymbol{p} = [p_1 \dots p_N]'$ is defined in (2). The information matrix $\boldsymbol{I}_{\hat{\boldsymbol{w}},\mathrm{bin}}(\boldsymbol{\theta})$ depends implicitly on temporal regularization only through $\tilde{p}_n(\check{\boldsymbol{w}}(\boldsymbol{\theta}))$ [see (3), (4) and (9)].

3.2. Information Matrix for List-Mode Data

By increasing the number of bins N to ∞ and decreasing the bin widths to 0 in (11), one can obtain the following information matrix for list-mode data:

$$\begin{aligned}
&[\boldsymbol{I}_{\hat{\boldsymbol{w}},\mathrm{list}}(\boldsymbol{\theta})]_{ij} \cong \alpha [\boldsymbol{F}(\boldsymbol{\theta})^{-1}]_{pq} \cdot \\
&\quad \sum_{p=1}^{L} \sum_{q=1}^{L} \int_0^T \frac{\partial \eta(t;\boldsymbol{\theta})}{\partial \theta_i} \frac{B_p(t)}{\sum_{l=1}^{L} \check{w}_l(\boldsymbol{\theta}) B_l(t) + r(t)} dt \cdot \\
&\quad \int_0^T \frac{\partial \eta(t;\boldsymbol{\theta})}{\partial \theta_j} \frac{B_q(t)}{\sum_{l=1}^{L} \check{w}_l(\boldsymbol{\theta}) B_l(t) + r(t)} dt
\end{aligned} \tag{12}$$

where

$$[\boldsymbol{F}(\boldsymbol{\theta})]_{ij} = \int_0^T B_i(t) B_j(t) \frac{\eta(t;\boldsymbol{\theta}) + r(t)}{\left(\sum_{l=1}^{L} \check{w}_l(\boldsymbol{\theta}) B_l(t) + r(t)\right)^2} dt.$$

If temporal basis functions are constant B-splines as

$$B_l(t) = I_{[t_{l-1},\, t_l]}(t)$$

where $I_{[t_{l-1},\, t_l]}$ is an indicator function, then the information matrix in (12) becomes

$$\boldsymbol{I}_{\hat{\boldsymbol{w}},\mathrm{list}}(\boldsymbol{\theta}) \cong \alpha [\nabla_{\boldsymbol{\theta}} \boldsymbol{p}(\boldsymbol{\theta})]' \mathrm{diag}\left\{\frac{1}{p_n(\boldsymbol{\theta})}\right\} \nabla_{\boldsymbol{\theta}} \boldsymbol{p}(\boldsymbol{\theta}). \tag{13}$$

This information matrix *is independent of temporal regularization!* One can also obtain the same result as (13) from (11) by making temporal bins agree with the constant B-spline basis functions $\{B_l(t)\}$. In this case $\boldsymbol{B}$ and $\boldsymbol{F}$ are diagonal, and the regularization-related terms $\tilde{p}_n(\check{\boldsymbol{w}}(\boldsymbol{\theta}))$ are canceled out in (11). In fact, the equality happens to hold in (13) [6, p. 81].

4. RESULTS

To assess the accuracy of the approximation for the covariance of kinetic parameter estimators given by the inverse of (11), we simulated dynamic imaging data. The simulated TAC was given by

$$\eta(t; \boldsymbol{\theta}) = \theta_2 \exp(-\theta_1 t)$$

for $t \geq 0$ to mimic the response of a one tissue compartment model, and the input function was considered an ideal impulse $\delta(t)$ for simplicity. The total scan time T was set to 15 min, and the true kinetic parameters were set as $[\theta_1, \theta_2] = [0.15, 0.7]$. The total counts were 300, and r_n corresponded to a temporally uniform field of 10% of background events. The data were acquired using 30 uniform temporal bins ($N = 30$). We used the uniform quadratic penalty with $\beta = 10$, and 10 B-spline basis functions of different orders with uniformly spaced knots for TAC reconstruction ($L = 10$). Given temporal basis functions and given (simulated) noisy data, $\hat{\boldsymbol{w}}$ was estimated by (3) with linear constraints $\boldsymbol{B}\boldsymbol{w} \geq \mathbf{0}$ as reasonable approximations to (5), and then $\hat{\boldsymbol{\theta}}$ was estimated by (7) using (9) and (10) with nonnegativity constraints $\boldsymbol{\theta} \geq \mathbf{0}$. We computed the sample mean and the sample covariance of $\hat{\boldsymbol{\theta}}$ from 200 realizations for each set of basis functions. For maximization in (3) and (7), we used separable surrogates [9], and the `fmincon` and `sqscon` functions of `Matlab`.

Table 1 shows that (7) yielded unbiased estimates, and Table 2 shows that approximate variances obtained from the inverse of (11) were reasonably close to empirical variances.

5. CONCLUSION

We derived the covariance matrix (the inverse of the Fisher information matrix) of kinetic parameter estimators based on TAC reconstructions using temporal basis functions for list-mode data as well as bin-mode data in a 1D temporal problem. We demonstrated the covariance approximation works well for simulated data. We plan to perform extensive comparison of temporal basis functions and to extend the results to the case where tomographic spatial aspects are incorporated. Future work will also include optimizing B-spline knot locations and developing computationally cheaper approximate expressions for kinetic parameter estimator covariances.

Table 1. Sample means of kinetic parameter estimators $\hat{\boldsymbol{\theta}}$

basis	parameter	true	sample mean
cubic	θ_1	0.15	0.151 ± 0.001
B-splines	θ_2	0.70	0.696 ± 0.005
quadratic	θ_1	0.15	0.150 ± 0.001
B-splines	θ_2	0.70	0.695 ± 0.005
linear	θ_1	0.15	0.150 ± 0.002
B-splines	θ_2	0.70	0.695 ± 0.007
constant	θ_1	0.15	0.150 ± 0.002
B-splines	θ_2	0.70	0.695 ± 0.007

Table 2. Comparison of predicted and empirical variances of kinetic parameter estimators $\hat{\boldsymbol{\theta}}$

basis	variance	predicted ($\times 10^{-3}$)	empirical ($\times 10^{-3}$)
cubic	$\mathrm{Var}\{\hat{\theta}_1\}$	0.263	0.236 ± 0.024
B-splines	$\mathrm{Var}\{\hat{\theta}_2\}$	4.611	4.023 ± 0.403
quadratic	$\mathrm{Var}\{\hat{\theta}_1\}$	0.263	0.234 ± 0.023
B-splines	$\mathrm{Var}\{\hat{\theta}_2\}$	4.611	4.019 ± 0.403
linear	$\mathrm{Var}\{\hat{\theta}_1\}$	0.263	0.231 ± 0.023
B-splines	$\mathrm{Var}\{\hat{\theta}_2\}$	4.611	3.992 ± 0.399
constant	$\mathrm{Var}\{\hat{\theta}_1\}$	0.266	0.235 ± 0.024
B-splines	$\mathrm{Var}\{\hat{\theta}_2\}$	4.646	4.009 ± 0.401

6. REFERENCES

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