Web-based Supplementary Materials for Modeling of Hormone Secretion-Generating Mechanisms With Splines: A Pseudo-Likelihood Approach

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Web Appendix A

Since α_i is independent of N_i, we have

$$\mathrm{E}(y(t)) = \gamma + \alpha \mathrm{E} \int_{-\infty}^{\infty} p(t-x) dN_i(x) = \gamma + \alpha \int_{-\infty}^{\infty} p(t-x) h(x) dx.$$

Let $A(t)$ be the unique compensator for $N_i(t)$ in the extended Doob-Meyer Decomposition theorem (Theorem 2.2.3 of Fleming & Harrington (1991)). Then $\mathrm{E}(A(t)) = \mathrm{E}(N_i(t)) = \int_{-\infty}^{t} h(x)dx$ and $M(t) = N_i(t) - A(t)$ is a martingale with predictable quadratic variation $< M, M > \; = A$. From Theorem 2.4.4 of Fleming & Harrington (1991),

$$\begin{aligned}
& \mathrm{E} \int_{-\infty}^{\infty} p(s-x) dM(x) \int_{-\infty}^{\infty} p(t-x) dM(x) \\
= \; & \mathrm{E} \int_{-\infty}^{\infty} p(s-x) p(t-x) d < M, M > (x) \\
= \; & \mathrm{E} \int_{-\infty}^{\infty} p(s-x) p(t-x) dA(x) \\
= \; & \int_{-\infty}^{\infty} p(s-x) p(t-x) h(x) dx.
\end{aligned}$$

Also,

$$
\begin{aligned}
& \operatorname{Cov}\left(\alpha_i \int_{-\infty}^{\infty} p(s-x) dN_i(x), \alpha_i \int_{-\infty}^{\infty} p(t-x) dN_i(x)\right) \\
= \; & \mathrm{E}\left(\alpha_i \int_{-\infty}^{\infty} p(s-x) dN_i(x) - \alpha \int_{-\infty}^{\infty} p(s-x) h(x) dx\right) \\
& \left(\alpha_i \int_{-\infty}^{\infty} p(t-x) dN_i(x) - \alpha \int_{-\infty}^{\infty} p(t-x) h(x) dx\right) \\
= \; & \mathrm{E}\left(\alpha_i \int_{-\infty}^{\infty} p(s-x) dM(x) + (\alpha_i - \alpha) \int_{-\infty}^{\infty} p(s-x) h(x) dx\right) \\
& \left(\alpha_i \int_{-\infty}^{\infty} p(t-x) dM(x) + (\alpha_i - \alpha) \int_{-\infty}^{\infty} p(t-x) h(x) dx\right) \\
= \; & (\alpha^2 + \sigma_\alpha^2) \int_{-\infty}^{\infty} p(s-x) p(t-x) h(x) dx + \sigma_\alpha^2 \left(\int_{-\infty}^{\infty} p(s-x) h(x) dx\right) \left(\int_{-\infty}^{\infty} p(t-x) h(x) dx\right).
\end{aligned}
$$

Therefore,

$$
\begin{aligned}
& \operatorname{Cov}(y(s), y(t)) \\
= \; & \sigma_\gamma^2 + (\alpha^2 + \sigma_\alpha^2) \int_{-\infty}^{\infty} p(s-x) p(t-x) h(x) dx \\
& + \sigma_\alpha^2 \left(\int_{-\infty}^{\infty} p(s-x) h(x) dx\right) \left(\int_{-\infty}^{\infty} p(t-x) h(x) dx\right) + \sigma^2 I(s=t).
\end{aligned}
$$

Web Appendix B

We show the derivation for the mean only. The derivation for the covariance is similar. The mean formula is a direct result of the following equation.

$$
\begin{aligned}
& \int_{-\infty}^{\infty} p(t-x)h(x)dx \\
= & \int_{-\infty}^{t} \exp(-\beta_2(t-x))h(x)dx + \int_{t}^{\infty} \exp(-\beta_1(x-t))h(x)dx \\
= & \int_{0}^{\infty} \exp(-\beta_2 y)h(t-y)dy + \int_{0}^{\infty} \exp(-\beta_1 y)h(t+y)dy \\
= & \sum_{k=0}^{\infty} \int_{k}^{k+1} \exp(-\beta_2 y)h(t-y)dy + \sum_{k=0}^{\infty} \int_{k}^{k+1} \exp(-\beta_1 y)h(t+y)dy \\
= & \sum_{k=0}^{\infty} \int_{0}^{1} \exp(-\beta_2 (y+k))h(t-y-k)dy + \sum_{k=0}^{\infty} \int_{0}^{1} \exp(-\beta_1 (y+k))h(t+y+k)dy \\
= & \sum_{k=0}^{\infty} \exp(-\beta_2 k) \int_{0}^{1} \exp(-\beta_2 y))h(t-y)dy + \sum_{k=0}^{\infty} \exp(-\beta_1 k) \int_{0}^{1} \exp(-\beta_1 y)h(t+y)dy \\
= & \int_{0}^{1} \exp(-\beta_2 y))h(t-y)dy/(1-\exp(-\beta_2)) + \int_{0}^{1} \exp(-\beta_1 y)h(t+y)dy/(1-\exp(-\beta_1)),
\end{aligned}
$$

where we used the periodic property of h.

Web Appendix C

The minimization problem (6) in the paper is solved iteratively using the extended Gauss-Newton method in Ke & Wang (2004b). Note that $\boldsymbol{\theta}$ is fixed for the problem (6) and $\tilde{W}_i$'s are fixed at each iteration. Let

$$
\mathcal{N}_t \eta = \xi(t) = \gamma + \alpha \int_{-\infty}^{\infty} p(\boldsymbol{\beta}, t-x) \exp(\eta(x))dx,
$$

which is a non-linear functional in η. At each iteration, we approximate $\mathcal{N}_t\eta$ by its first-order Taylor expansion at previous estimate η_- (Lusternik & Sobolev 1974):

$$
\mathcal{N}_t \eta \approx \mathcal{N}_t \eta_- + \mathcal{D}_t(\eta - \eta_-),
$$

where $\mathcal{D}_t = \partial \mathcal{N}_t / \partial \eta |_{\eta=\eta_-}$ is the Fréchet differential. It is easy to check that (Debnath & Mikusinski 1999)

$$\mathcal{D}_t \eta = \alpha \int_{-\infty}^{\infty} p(\boldsymbol{\beta}, t-x) \exp(\eta_-(x)) \eta(x) dx.$$

Let $\mathcal{N}_{\mathbf{t}_i}\eta_- = (\mathcal{N}_{t_{i1}}\eta_-, \cdots, \mathcal{N}_{t_{in_i}}\eta_-)^T$, $\mathcal{D}_{\mathbf{t}_i}\eta_- = (\mathcal{D}_{t_{i1}}\eta_-, \cdots, \mathcal{D}_{t_{in_i}}\eta_-)^T$, $\mathcal{D}_{\mathbf{t}_i}\eta = (\mathcal{D}_{t_{i1}}\eta, \cdots, \mathcal{D}_{t_{in_i}}\eta)^T$, and $\tilde{\mathbf{y}}_i = \mathbf{y}_i - \mathcal{N}_{\mathbf{t}_i}\eta_- + \mathcal{D}_{\mathbf{t}_i}\eta_-$. We update η by solving

$$\min_{\eta \in W_2(per)} \left\{ \sum_{i=1}^{m} (\tilde{\mathbf{y}}_i - \mathcal{D}_{\mathbf{t}_i}\eta)^T \tilde{W}_i^{-1} (\tilde{\mathbf{y}}_i - \mathcal{D}_{\mathbf{t}_i}\eta) + N\lambda \int_0^1 (\eta''(t))^2 dt \right\}. \tag{1}$$

Since $\mathcal{D}_{t_{ij}}$'s are linear bounded functionals, the solution to (1) has the form (Wahba 1990, Wang 1998a)

$$\eta(t) = d + \sum_{i=1}^{m} \sum_{j=1}^{n_i} c_{ij} \mathcal{D}_{t_{ij}} R_1(\cdot, t), \tag{2}$$

where $R_1(s,t) = -B_4([s-t])/24$, $[s-t]$ is the fractional part of $s-t$, and $B_4(x) = x^4 - 2x^3 + x^2 - 1/30$. R_1 is the reproducing kernel for the space $W_2(per) \ominus \{1\}$. The minimization problem (1) reduces to

$$\min_{d, \mathbf{c}} \left\{ (\tilde{\mathbf{y}} - d\mathbf{z} - \Sigma \mathbf{c})^T \tilde{W}^{-1} (\tilde{\mathbf{y}} - d\mathbf{z} - \Sigma \mathbf{c}) + N\lambda \mathbf{c}^T \Sigma \mathbf{c} \right\}, \tag{3}$$

where $\tilde{\mathbf{y}} = (\tilde{\mathbf{y}}_1^T, \cdots, \tilde{\mathbf{y}}_m^T)^T$, $z_{ij} = \alpha \int_{-\infty}^{\infty} p(\boldsymbol{\beta}, t_{ij} - x) \exp(\eta_-(x)) dx$, $\mathbf{z}_i = (z_{i1}, \cdots, z_{in_i})^T$, $\mathbf{z} = (\mathbf{z}_1^T, \cdots, \mathbf{z}_m^T)^T$, $\Sigma_{ii'} = (\mathcal{D}_{t_{ij}} \mathcal{D}_{t_{i'j'}} R_1(\cdot, \cdot))_{j=1}^{n_i}{}_{j'=1}^{n_{j'}}$, $\Sigma = (\Sigma_{ii'})_{i,i'=1}^m$, $\mathbf{c}_i = (c_{i1}, \cdots, c_{in_i})^T$, $\mathbf{c} = (\mathbf{c}_1^T, \cdots, \mathbf{c}_m^T)^T$, and $\tilde{W} = \text{diag}(\tilde{W}_1, \cdots, \tilde{W}_m)$. Furthermore, let $\tilde{\tilde{\mathbf{y}}} = \tilde{W}^{-1/2}\tilde{\mathbf{y}}$, $\tilde{\mathbf{z}} = \tilde{W}^{-1/2}\mathbf{z}$, $\tilde{\Sigma} = \tilde{W}^{-1/2} \Sigma \tilde{W}^{-1/2}$ and $\tilde{\mathbf{c}} = \tilde{W}^{1/2}\mathbf{c}$. The minimization problem (3) reduces to

$$\min_{d, \tilde{\mathbf{c}}} \left\{ ||\tilde{\tilde{\mathbf{y}}} - d\tilde{\mathbf{z}} - \tilde{\Sigma}\tilde{\mathbf{c}}||^2 + N\lambda \tilde{\mathbf{c}}^T \tilde{\Sigma} \tilde{\mathbf{c}} \right\}, \tag{4}$$

which is computed by the R function `ssr` in the ASSIST package (Ke & Wang 2004a). We estimate the smoothing parameter λ at each iteration using the generalized cross-validation (GCV) method which minimizes

$$V(\lambda) = \frac{1/N \| (I - A(\lambda)) \tilde{\tilde{\mathbf{y}}} \|^2}{[(1/N) tr(I - A(\lambda))]^2}$$

or the generalized maximum likelihood (GML) method which minimizes

$$M(\lambda) = \frac{\tilde{\tilde{\mathbf{y}}}^T (I - A(\lambda))\tilde{\tilde{\mathbf{y}}}}{[\det^+(I - A(\lambda))]^{\frac{1}{N-1}}},$$

where $A(\lambda)$ is the hat matrix (Wahba 1990, **?**).

We now discuss how to compute $\mathcal{N}_{t_{ij}}\eta_-$, $\mathcal{D}_{t_{ij}}\eta_-$, z_{ij}, $\tilde{W}$ and

$$\mathcal{D}_{t_{ij}}\mathcal{D}_{t_{i'j'}}R_1(\cdot,\cdot) = \alpha^2 \int_{-\infty}^{\infty}\int_{-\infty}^{\infty} p(\boldsymbol{\beta}, t_{ij} - x)p(\boldsymbol{\beta}, t_{i'j'} - y)\exp(\eta_-(x) + \eta_-(y))R_1(x,y)dxdy.$$

A naive application of Gaussian quadrature to approximate involved integrals directly is computational intensive since the integrands depend on observation time points and, consequently, the approximations have to be done for every unique time point. In addition, a relatively large number of points is needed to approximate these integrals over large intervals.

Let $t_{(j)}, j = 1, \cdots, N'$, be the sequence of the ordered unique observation time points from all subjects, where N' denotes the total number of unique observation time points. After some tedious algebra (one example shown below), when the pulse shape function p is double exponential function, these integrals can be computed from integrals $\int_{t_{(j_1)}}^{t_{(j_1+1)}} \mathrm{INT}_1(x)dx$ and $\int_{t_{(j_1)}}^{t_{(j_1+1)}} \int_{t_{(j_2)}}^{t_{(j_2+1)}} \mathrm{INT}_2(x,y)dxdy$ for some integrands INT_1 and INT_2. For example, to calculate the integral in $\mathcal{N}_t\eta_-$, we use the following equation

$$\begin{aligned}
& \int_{-\infty}^{\infty} p(\boldsymbol{\beta}, t-x)\exp(\eta_-(x))dx \\
= \; & \tfrac{1}{1-\exp(-\beta_2)} \int_0^1 \exp(-\beta_2 x)h_-(t-x)dx + \tfrac{1}{1-\exp(-\beta_1)} \int_0^1 \exp(-\beta_1 x)h_-(t+x)dx \\
= \; & \tfrac{1}{1-\exp(-\beta_2)} \int_0^t \exp(-\beta_2 x)h_-(t-x)dx + \tfrac{1}{1-\exp(-\beta_2)} \int_t^1 \exp(-\beta_2 x)h_-(t-x)dx \\
& + \tfrac{1}{1-\exp(-\beta_1)} \int_0^{1-t} \exp(-\beta_1 x)h_-(t+x)dx + \tfrac{1}{1-\exp(-\beta_1)} \int_{1-t}^1 \exp(-\beta_1 x)h_-(t+x)dx \\
= \; & \tfrac{1}{1-\exp(-\beta_2)} \int_0^t \exp(-\beta_2(t-y))h_-(y)dy + \tfrac{1}{1-\exp(-\beta_2)} \int_t^1 \exp(-\beta_2(1+t-y))h_-(y-1)dy \\
& + \tfrac{1}{1-\exp(-\beta_1)} \int_t^1 \exp(-\beta_1(y-t))h_-(y)dy + \tfrac{1}{1-\exp(-\beta_1)} \int_0^t \exp(-\beta_1(y-t+1))h_-(y+1)dy \\
= \; & \tfrac{exp(-\beta_2 t)}{1-\exp(-\beta_2)} \int_0^t \exp(\beta_2 y)h_-(y)dy + \tfrac{\exp(-\beta_2(1+t))}{1-\exp(-\beta_2)} \int_t^1 \exp(\beta_2 y)h_-(y)dy \\
& + \tfrac{\exp(\beta_1 t)}{1-\exp(-\beta_1)} \int_t^1 \exp(-\beta_1 y)h_-(y)dy + \tfrac{\exp(\beta_1(t-1))}{1-\exp(-\beta_1)} \int_0^t \exp(-\beta_1 y)h_-(y)dy.
\end{aligned}$$

The above derivation used results in Web Appendix B and the periodicity of the function h_-. Note that the integrands are independent of observation time points. The integrals in the last step are computed by cumulating integrals $\int_{t_{(j)}}^{t_{(j+1)}} \exp(\beta_2 y)h_-(y)dy$ and $\int_{t_{(j)}}^{t_{(j+1)}} \exp(-\beta_1 y)h_-(y)dy$, $j = 1, \cdots, N'$, which are approximated numerically by a three-point Gaussian quadrature. Integrals in $\mathcal{D}_{t_{ij}}\eta_-$, z_{ij} and $\tilde{W}$ are approximated similarly. The term $\mathcal{D}_{t_{ij}}\mathcal{D}_{t_{i'j'}}R_1(\cdot,\cdot)$ involves double integrals $\int_{t_{(j_1)}}^{t_{(j_1+1)}}\int_{t_{(j_2)}}^{t_{(j_2+1)}} \text{INT}_2(x,y)dxdy$ which are approximated by a nine-point Gaussian quadrature.

The total number of observations N is very large in our real example and simulations. Therefore, solving the minimization problem (6) is computational intensive. Note that observation time points are the same for all subjects in our real example and simulations. Therefore, n_i, t_{ij}, $\boldsymbol{\xi}_i$ and $\tilde{W}_i$ are all independent of i. To save computational time, we used average observations across subjects as the response vector. Specifically, let $\bar{\mathbf{y}} = (\sum_{i=1}^m y_{i1}/m, \cdots, \sum_{i=1}^m y_{in}/m)$. Then the minimization problem (6) in the paper reduces to

$$\min_{\eta \in W_2(per)} \left\{ (\bar{\mathbf{y}} - \boldsymbol{\xi})^T \tilde{W}^{-1} (\bar{\mathbf{y}} - \boldsymbol{\xi}) + n\lambda \int_0^1 (\eta''(t))^2 dt \right\},$$

where the subscript i in n_i, $\boldsymbol{\xi}_i$ and $\check{W}_i$ are dropped. The extended Gauss-Newton procedure discussed above was applied with $m = 1$. An alternative approach for saving computational time is to use a subset of basis functions as in Kim & Gu (2004).

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