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1.20

Consider a nonlinear mixed-effects model for drug concentration Y_{ij} in subject $i = 1, \ldots, n$ at measurement times t_{ij}, $j = 1, \ldots, J$. Here the concentration or log-concentration is given from the random effects model

$$Y_{ij} = \frac{V_{\max,i}\, t_{ij}}{K_{m,i} + t_{ij}} + \varepsilon_{ij} \text{ with } \varepsilon_{ij} \sim \mathcal{N}(0, \sigma_\varepsilon^2).$$

The subject-specific parameters have random effects given by

$$V_{\max,i} = V_{\max} + b_{1i} \text{ and } K_{m,i} = K_m + b_{2i},$$

with subject-specific random effect vector $(b_{1i}, b_{2i})^\top \sim \mathcal{N}_2(\mathbf{0}, \mathbf{D})$, where $\mathbf{D} = \begin{pmatrix} \sigma_{b1}^2 & \sigma_{b12} \\ \sigma_{b12} & \sigma_{b2}^2 \end{pmatrix}$ is the random-effects covariance matrix. Suppose we are interested in the clearance ratio

$$\psi = g(\boldsymbol{\theta}) = \frac{V_{\max}}{K_m}$$

where $\boldsymbol{\theta} = (V_{\max}, K_m)^\top$. Assume estimators $\widehat{V}_{\max}$ and $\widehat{K}_m$ are asymptotically normal:

$$\sqrt{n}\begin{pmatrix} \widehat{V}_{\max} - V_{\max} \\ \widehat{K}_m - K_m \end{pmatrix} \xrightarrow{d} \mathcal{N}_2(\mathbf{0}, \boldsymbol{\Sigma}),$$

where $\boldsymbol{\Sigma}$ is the covariance matrix of the fixed-effect estimates. Carry out the following:

Compute the gradient $\nabla g(\boldsymbol{\theta})$ for

$$g(V_{\max}, K_m) = \frac{V_{\max}}{K_m}.$$

$$\nabla g(\boldsymbol{\theta}) = \begin{pmatrix} \frac{\partial g}{\partial V_{\max}} \\ \frac{\partial g}{\partial K_m} \end{pmatrix}, \quad \text{where}$$

$$\begin{aligned}\frac{\partial g}{\partial V_{\max}} &= \frac{\partial}{\partial V_{\max}}\left(\frac{V_{\max}}{K_m}\right) \\ &= \frac{1}{K_m}\cdot\frac{\partial V_{\max}}{\partial V_{\max}} \\ &= \frac{1}{K_m}\end{aligned}$$

$$\begin{aligned}\frac{\partial g}{\partial K_m} &= \frac{\partial}{\partial K_m}\left(V_{\max}K_m^{-1}\right) \\ &= V_{\max}(-1)K_m^{-2} \\ &= -\frac{V_{\max}}{K_m^2}\end{aligned}$$

$$\implies \nabla g(\boldsymbol{\theta}) = \begin{pmatrix}\frac{1}{K_m} \\ -\frac{V_{\max}}{K_m^2}\end{pmatrix}$$

Apply the delta method to derive the asymptotic variance of $\widehat{\psi} = \widehat{V}_{\max}/\widehat{K}_m$.

$$\begin{aligned}\mathbf{C} = \nabla g(\boldsymbol{\theta}) &= \begin{pmatrix}\frac{1}{K_m} \\ -\frac{V_{\max}}{K_m^2}\end{pmatrix} \\ \mathrm{Var}(\sqrt{n}(\widehat{\psi}-\psi)) &\approx \mathbf{C}^\top\boldsymbol{\Sigma}\mathbf{C} \\ &= \begin{pmatrix}\frac{1}{K_m} & -\frac{V_{\max}}{K_m^2}\end{pmatrix}\begin{pmatrix}\sigma^2_{V_{\max}} & \sigma_{V_{\max},K_m} \\ \sigma_{V_{\max},K_m} & \sigma^2_{K_m}\end{pmatrix}\begin{pmatrix}\frac{1}{K_m} \\ -\frac{V_{\max}}{K_m^2}\end{pmatrix} \\ &= \frac{1}{K_m^2}\sigma^2_{V_{\max}} - 2\frac{V_{\max}}{K_m^3}\sigma_{V_{\max},K_m} + \frac{V_{\max}^2}{K_m^4}\sigma^2_{K_m} \\ \implies \mathrm{Var}(\hat{\psi}) &\approx \frac{1}{n}\left(\frac{1}{K_m^2}\sigma^2_{V_{\max}} - 2\frac{V_{\max}}{K_m^3}\sigma_{V_{\max},K_m} + \frac{V_{\max}^2}{K_m^4}\sigma^2_{K_m}\right)\end{aligned}$$

Discuss how the variance of $\widehat{\psi}$ changes if K_m is small versus large. (Hint: check the gradient components carefully.)

The asymptotic variance of $\widehat{\psi}$ is proportional to the quadratic form $\mathbf{C}^\top\boldsymbol{\Sigma}\mathbf{C}$, where

$$\mathbf{C} = \nabla g(\boldsymbol{\theta}) = \begin{pmatrix}1/K_m \\ -V_{\max}/K_m^2\end{pmatrix}.$$

When K_m approaches zero, the gradient components, particularly the term $\propto 1/K_m^2$, become extremely large. Since the variance involves terms weighted by the square of these components (up to $1/K_m^4$), the variance of $\widehat{\psi}$ explodes, indicating high instability and sensitivity to small estimation errors in K_m. Conversely, when K_m is large, both gradient components rapidly decay to zero. As the weights for the fixed-effect variances diminish (up to $1/K_m^4$), the asymptotic variance of $\widehat{\psi}$ becomes very small, allowing for a precise estimate because the ratio $V_{\max}/K_m$ is locally flatter.