Acta Univ. Palacki. Olomuc., Fac. rer. nat.,
Mathematica **48** (2009) 171–188

Suitability of Linearization of Nonlinear Problems not only in Biology and Medicine*

Jana VRBKOVÁ

Department of Mathematical Analysis and Applications of Mathematics
Faculty of Science, Palacký University
tř. 17. listopadu 12, 771 46 Olomouc, Czech Republic
e-mail: vrbkova@inf.upol.cz

(Received January 30, 2009)

Abstract

Biology and medicine are not the only fields that present problems unsolvable through a linear models approach. One way to overcome this obstacle is to use nonlinear methods, even though these are not as thoroughly explored. Another possibility is to linearize and transform the originally nonlinear task to make it accessible to linear methods. In this aricle I investigate an easy and quick criterion to verify suitability of linearization of nonlinear problems via Taylor series expansion so that linear models with type II constraints could be used.

Key words: Linear models with constraints, compartmental analysis, nonlinear models, linearization via a Taylor series.

2000 Mathematics Subject Classification: 62J05

1 Used symbols

$h(\mathbf{A})$	rank of the matrix $\mathbf{A}$
$\mathbf{M_A}$	a matrix $\mathbf{M_A} = \mathbf{I} - \mathbf{P_A}$
$\mathbf{P_A}$	a projector on the space $\mathcal{M}(\mathbf{A})$ in Euclidean norm
$\mathcal{M}(\mathbf{A})$	range space of the matrix $\mathbf{A}$
$\mathbb{R}^k$	k-dimensional linear vector space
$\chi^2_f(0; 1-\alpha)$	$(1-\alpha)$-quantile of the random variable with $\chi^2_f(0)$ distribution
$\mathbf{X}^-$	generalized inverse of the matrix $\mathbf{X}$
$\mathbf{X}^+$	Moore-Penrose g-inverse of the matrix $\mathbf{X}$
$(\mathbf{X})^-_{m(\mathbf{\Sigma})}$	minimum $\mathbf{\Sigma}$-norm (seminorm) g-inverse of the matrix $\mathbf{X}$

*Supported by the Council of the Czech Government MSM 6 198 959 214.

2 Linearization via a Taylor series

Let us consider a general nonlinear model

$$\mathbf{Y} \sim_n (\mathbf{f}(\boldsymbol{\beta}_1), \boldsymbol{\Sigma}), \quad \boldsymbol{\beta}_1 \in \mathbb{R}^{k_1}, \quad \boldsymbol{\beta}_2 \in \mathbb{R}^{k_2},$$

where the parameter $\boldsymbol{\beta}_2$ occurs only in a constraint $\mathbf{g}(\boldsymbol{\beta}_1, \boldsymbol{\beta}_2) = \mathbf{0}$, the function

$$\mathbf{f} : \mathcal{V} \to \mathbb{R}^n, \quad \mathcal{V} = \left\{ \begin{pmatrix} \boldsymbol{\beta_1} \\ \boldsymbol{\beta_2} \end{pmatrix} : \mathbf{g}(\boldsymbol{\beta_1}, \boldsymbol{\beta_2}) = \mathbf{0} \right\},$$

has continuous second derivatives, and $\mathbf{g}(\cdot)$ is a q-dimensional function with continuous second derivatives.

If we know approximate values $\boldsymbol{\beta}_1^0$, $\boldsymbol{\beta}_2^0$ of the parameters $\boldsymbol{\beta}_1$, $\boldsymbol{\beta}_2$ we can linearize functions $\mathbf{f}(\cdot)$ and $\mathbf{g}(\cdot)$ via Taylor series

$$\mathbf{f}(\boldsymbol{\beta}_1) = \mathbf{f}\left(\boldsymbol{\beta}_1^0\right) + \mathbf{F}\left(\boldsymbol{\beta}_1^0\right)\delta\boldsymbol{\beta_1} + \frac{1}{2}\boldsymbol{\kappa}(\delta\boldsymbol{\beta}_1) + \ldots,$$

where

$$\mathbf{F}\left(\boldsymbol{\beta}_1^0\right) = \partial\mathbf{f}(\boldsymbol{\beta}_1)/\partial\boldsymbol{\beta}_1'|_{\boldsymbol{\beta}_1=\boldsymbol{\beta}_1^0}, \quad \boldsymbol{\kappa}(\delta\boldsymbol{\beta}_1) = (\delta\boldsymbol{\beta}_1'\mathbf{F}_1\delta\boldsymbol{\beta}_1, , \ldots, \delta\boldsymbol{\beta}_1'\mathbf{F}_n\delta\boldsymbol{\beta}_1)',$$

$$\mathbf{F}_i = \partial^2 f_i(\boldsymbol{\beta}_1)/\partial\boldsymbol{\beta}_1\partial\boldsymbol{\beta}_1'|_{\boldsymbol{\beta}_1=\boldsymbol{\beta}_1^0}, \quad i = 1, \ldots, n,$$

and

$$\mathbf{g}(\boldsymbol{\beta}_1, \boldsymbol{\beta}_2) = \mathbf{b} + \mathbf{B}_1\delta\boldsymbol{\beta}_1 + \mathbf{B}_2\delta\boldsymbol{\beta}_2 + \frac{1}{2}\boldsymbol{\omega}(\delta\boldsymbol{\beta}_1, \delta\boldsymbol{\beta}_2) + \ldots,$$

where

$$\mathbf{b} = \mathbf{g}(\boldsymbol{\beta}_1^0, \boldsymbol{\beta}_2^0), \qquad \mathbf{B}_1 = \left.\frac{\partial\mathbf{g}(\boldsymbol{\beta}_1, \boldsymbol{\beta}_2)}{\partial\boldsymbol{\beta}_1}\right|_{\substack{\boldsymbol{\beta}_1=\boldsymbol{\beta}_1^0 \\ \boldsymbol{\beta}_2=\boldsymbol{\beta}_2^0}}, \qquad \mathbf{B}_2 = \left.\frac{\partial\mathbf{g}(\boldsymbol{\beta}_1, \boldsymbol{\beta}_2)}{\partial\boldsymbol{\beta}_2}\right|_{\substack{\boldsymbol{\beta}_1=\boldsymbol{\beta}_1^0 \\ \boldsymbol{\beta}_2=\boldsymbol{\beta}_2^0}}$$

and

$$\{\boldsymbol{\omega}(\delta\boldsymbol{\beta}_1, \delta\boldsymbol{\beta}_2)\}_i = (\delta\boldsymbol{\beta}_1', \delta\boldsymbol{\beta}_2')\begin{pmatrix} \mathbf{A}, & \mathbf{B} \\ \mathbf{B}', & \mathbf{D} \end{pmatrix}\begin{pmatrix} \delta\boldsymbol{\beta}_1 \\ \delta\boldsymbol{\beta}_2 \end{pmatrix},$$

$$\mathbf{A} = \partial^2 g_i(\boldsymbol{\beta}_1, \boldsymbol{\beta}_2)/\partial\boldsymbol{\beta}_1\partial\boldsymbol{\beta}_1'\Big|_{\boldsymbol{\beta}_1=\boldsymbol{\beta}_1^0, \boldsymbol{\beta}_2=\boldsymbol{\beta}_2^0},$$

$$\mathbf{B} = \partial^2 g_i(\boldsymbol{\beta}_1, \boldsymbol{\beta}_2)/\partial\boldsymbol{\beta}_1\partial\boldsymbol{\beta}_2'\Big|_{\boldsymbol{\beta}_1=\boldsymbol{\beta}_1^0, \boldsymbol{\beta}_2=\boldsymbol{\beta}_2^0},$$

$$\mathbf{D} = \partial^2 g_i(\boldsymbol{\beta}_1, \boldsymbol{\beta}_2)/\partial\boldsymbol{\beta}_2\partial\boldsymbol{\beta}_2'\Big|_{\boldsymbol{\beta}_1=\boldsymbol{\beta}_1^0, \boldsymbol{\beta}_2=\boldsymbol{\beta}_2^0},$$

$i = 1, \ldots, q$, $\delta\boldsymbol{\beta}_1 = \boldsymbol{\beta}_1 - \boldsymbol{\beta}_1^0$, $\delta\boldsymbol{\beta}_2 = \boldsymbol{\beta}_2 - \boldsymbol{\beta}_1^0$.

After ommitting terms of the second and higher orders we get a linearized model

$$\mathbf{Y} - \mathbf{f}\left(\boldsymbol{\beta}_1^0\right) \sim_n (\mathbf{F}\left(\boldsymbol{\beta}_1^0\right)\delta\boldsymbol{\beta}_1, \boldsymbol{\Sigma}), \begin{pmatrix} \delta\boldsymbol{\beta}_1 \\ \delta\boldsymbol{\beta}_2 \end{pmatrix} \in \left\{ \begin{pmatrix} \mathbf{u} \\ \mathbf{v} \end{pmatrix} : \mathbf{b} + \mathbf{B}_1\mathbf{u} + \mathbf{B}_2\mathbf{v} = \mathbf{0} \right\}.$$

If $h\left(\mathbf{F}\left(\boldsymbol{\beta}_1^0\right)\right) = k_1 < n$, $h\left(\mathbf{B}_1, \mathbf{B}_2\right) = q < k_1 + k_2$, $h\left(\mathbf{B}_2\right) = k_2 < q$, and $\boldsymbol{\Sigma}$ is a positive definite matrix we say that the model is regular. It is a linear model with type II constraints.

Let us denote shortly $\mathbf{f}_0 = \mathbf{f}\left(\boldsymbol{\beta}_1^0\right)$, $\mathbf{F} = \mathbf{F}\left(\boldsymbol{\beta}_1^0\right)$.

Lemma 2.1 *The best linear unbiased estimators (BLUE) of the parameters $\delta\boldsymbol{\beta}_1$, $\delta\boldsymbol{\beta}_2$ in the regular linearized model*

$$\mathbf{Y} - \mathbf{f}_0 \sim_n (\mathbf{F}\delta\boldsymbol{\beta}_1, \boldsymbol{\Sigma}), \quad \mathbf{b} + \mathbf{B}_1\delta\boldsymbol{\beta}_1 + \mathbf{B}_2\delta\boldsymbol{\beta}_2 = \mathbf{0},$$

are

$$\widehat{\widehat{\delta\boldsymbol{\beta}_1}} = \widehat{\delta\boldsymbol{\beta}_1} - \mathbf{C}^{-1}\mathbf{B}_1'\left(\mathbf{M}_{\mathbf{B_2}}\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1'\mathbf{M}_{\mathbf{B_2}}\right)^+\left(\mathbf{b} + \mathbf{B}_1\widehat{\delta\boldsymbol{\beta}_1}\right), \tag{1}$$

$$\widehat{\widehat{\delta\boldsymbol{\beta}_2}} = -\left[(\mathbf{B}_2')^-_{m(\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1')}\right]'\left(\mathbf{b} + \mathbf{B}_1\widehat{\delta\boldsymbol{\beta}_1}\right), \tag{2}$$

and their variance matrices are

$$\operatorname{var}\left(\widehat{\widehat{\delta\boldsymbol{\beta}_1}}\right) = \left(\mathbf{M}_{\mathbf{B}_1'\mathbf{M}_{\mathbf{B_2}}}\mathbf{C}\mathbf{M}_{\mathbf{B}_1'\mathbf{M}_{\mathbf{B_2}}}\right)^+, \tag{3}$$

$$\operatorname{var}\left(\widehat{\widehat{\delta\boldsymbol{\beta}_2}}\right) = \left[\mathbf{B}_2'\left(\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1' + \mathbf{B}_2\mathbf{B}_2'\right)^{-1}\mathbf{B}_2\right]^{-1} - \mathbf{I}, \tag{4}$$

where $\widehat{\delta\boldsymbol{\beta}_1} = \mathbf{C}^{-1}\mathbf{F}'\boldsymbol{\Sigma}^{-1}(\mathbf{Y} - \mathbf{f}_0)$ *and* $\mathbf{C} = \mathbf{F}'\boldsymbol{\Sigma}^{-1}\mathbf{F}$.

Proof First we find a constrained extreme of the function

$$(\mathbf{Y} - \mathbf{f}_0 - \mathbf{F}\delta\boldsymbol{\beta}_1)'\,\boldsymbol{\Sigma}^{-1}\,(\mathbf{Y} - \mathbf{f}_0 - \mathbf{F}\delta\boldsymbol{\beta}_1)$$

with a constraint $\mathbf{b} + \mathbf{B}_1\delta\boldsymbol{\beta}_1 + \mathbf{B}_2\delta\boldsymbol{\beta}_2 = \mathbf{0}$. Derivatives of the Lagrange function

$$\Phi\left(\delta\boldsymbol{\beta}_1, \delta\boldsymbol{\beta}_2\right) = (\mathbf{Y} - \mathbf{f}_0 - \mathbf{F}\delta\boldsymbol{\beta}_1)'\,\boldsymbol{\Sigma}^{-1}(\mathbf{Y} - \mathbf{f}_0 - \mathbf{F}\delta\boldsymbol{\beta}_1) - 2\boldsymbol{\lambda}'(\mathbf{b} + \mathbf{B}_1\delta\boldsymbol{\beta}_1 + \mathbf{B}_2\delta\boldsymbol{\beta}_2)$$

are

$$\begin{aligned}
\frac{\partial\Phi\left(\delta\boldsymbol{\beta}_1, \delta\boldsymbol{\beta}_2\right)}{\partial\delta\boldsymbol{\beta}_1} &= -2\mathbf{F}'\boldsymbol{\Sigma}^{-1}\left(\mathbf{Y} - \mathbf{f}_0\right) + 2\mathbf{F}'\boldsymbol{\Sigma}^{-1}\mathbf{F}\delta\boldsymbol{\beta}_1 - 2\mathbf{B}_1'\boldsymbol{\lambda}, \\
\frac{\partial\Phi\left(\delta\boldsymbol{\beta}_1, \delta\boldsymbol{\beta}_2\right)}{\partial\delta\boldsymbol{\beta}_1} &= -2\mathbf{B}_2'\boldsymbol{\lambda}.
\end{aligned}$$

We put both derivatives equal to a null vector and solve the ensuing system of equations. By first calculating an estimator of $\delta\boldsymbol{\beta}_1$ from the first equation for the model without constraints, i.e. for $\boldsymbol{\lambda} = \mathbf{0}$, we obtain

$$\widehat{\delta\boldsymbol{\beta}_1} = \mathbf{C}^{-1}\mathbf{F}'\boldsymbol{\Sigma}^{-1}(\mathbf{Y} - \mathbf{f}_0),$$

where $\mathbf{C} = \mathbf{F}'\boldsymbol{\Sigma}^{-1}\mathbf{F}$, and therefore $\widehat{\widehat{\delta\boldsymbol{\beta}_1}} = \widehat{\delta\boldsymbol{\beta}_1} + \mathbf{C}^{-1}\mathbf{B}_1'\boldsymbol{\lambda}$. After substituting in the model the constraints $\mathbf{b} + \mathbf{B}_1\delta\boldsymbol{\beta}_1 + \mathbf{B}_2\delta\boldsymbol{\beta}_2 = \mathbf{0}$ we solve, together with the second equation, a system

$$\begin{pmatrix} \mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1', & \mathbf{B}_2 \\ \mathbf{B}_2', & \mathbf{0} \end{pmatrix}\begin{pmatrix} \boldsymbol{\lambda} \\ \widehat{\widehat{\delta\boldsymbol{\beta}_2}} \end{pmatrix} = \begin{pmatrix} -\left(\mathbf{b} + \mathbf{B}_1\widehat{\delta\boldsymbol{\beta}_1}\right) \\ \mathbf{0} \end{pmatrix}.$$

Using the Pandora-box matrix ([2, Lemma A.7.23]) in its special form ([2, Lemma A.7.24]) we obtain a solution

$$\begin{pmatrix} \boldsymbol{\lambda} \\ \widehat{\widehat{\delta\boldsymbol{\beta}}}_2 \end{pmatrix} = \begin{pmatrix} \boxed{1} & \boxed{2} \\ \boxed{3} & \boxed{4} \end{pmatrix} \begin{pmatrix} -\left(\mathbf{b} + \mathbf{B}_1\widehat{\delta\boldsymbol{\beta}_1}\right) \\ \mathbf{0} \end{pmatrix},$$

where

$$\begin{aligned}
\boxed{1} &= \left(\mathbf{M}_{\mathbf{B_2}}\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1'\mathbf{M}_{\mathbf{B_2}}\right)^+, \\
\boxed{2} &= (\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1' + \mathbf{B}_2\mathbf{B}_2')^-\mathbf{B}_2\left[\mathbf{B}_2'(\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1' + \mathbf{B}_2\mathbf{B}_2')^-\mathbf{B}_2\right]^-, \\
\boxed{3} &= \boxed{2}', \\
\boxed{4} &= \left[\mathbf{B}_2'(\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1' + \mathbf{B}_2\mathbf{B}_2')^-\mathbf{B}_2\right]^- - \mathbf{I},
\end{aligned}$$

and since ([2, Lemma A.7.9])

$$(\mathbf{B}_2')^-_{m(\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1')} = (\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1' + \mathbf{B}_2\mathbf{B}_2')^-\mathbf{B}_2\left[\mathbf{B}_2'(\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1' + \mathbf{B}_2\mathbf{B}_2')^-\mathbf{B}_2\right]^-$$

we can write

$$\begin{aligned}
\boldsymbol{\lambda} &= -\left(\mathbf{M}_{\mathbf{B_2}}\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1'\mathbf{M}_{\mathbf{B_2}}\right)^+\left(\mathbf{b} + \mathbf{B}_1\widehat{\delta\boldsymbol{\beta}_1}\right), \\
\widehat{\widehat{\delta\boldsymbol{\beta}}}_2 &= -\left[(\mathbf{B}_2')^-_{m(\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1')}\right]'\left(\mathbf{b} + \mathbf{B}_1\widehat{\delta\boldsymbol{\beta}_1}\right), \\
\widehat{\widehat{\delta\boldsymbol{\beta}}}_1 &= \widehat{\delta\boldsymbol{\beta}_1} + \mathbf{C}^{-1}\mathbf{B}_1'\boldsymbol{\lambda} = \widehat{\delta\boldsymbol{\beta}_1} - \mathbf{C}^{-1}\mathbf{B}_1'\left(\mathbf{M}_{\mathbf{B_2}}\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1'\mathbf{M}_{\mathbf{B_2}}\right)^+\left(\mathbf{b} + \mathbf{B}_1\widehat{\delta\boldsymbol{\beta}_1}\right).
\end{aligned}$$

Variance matrices can be obtained as

$$\begin{aligned}
\operatorname{var}\left[\begin{pmatrix} \widehat{\widehat{\delta\boldsymbol{\beta}}}_1 \\ \widehat{\widehat{\delta\boldsymbol{\beta}}}_2 \end{pmatrix}\right] &= \begin{pmatrix} \mathbf{I} - \mathbf{C}^{-1}\mathbf{B}_1'\left(\mathbf{M}_{\mathbf{B_2}}\mathbf{B_1}\mathbf{C}^{-1}\mathbf{B}_1'\mathbf{M}_{\mathbf{B_2}}\right)^+\mathbf{B}_1 \\ -\left[(\mathbf{B}_2')^-_{m(\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1')}\right]'\mathbf{B}_1 \end{pmatrix} \operatorname{var}(\widehat{\delta\boldsymbol{\beta}_1}) \times \\
&\times \left(\mathbf{I} - \mathbf{B}_1'\left(\mathbf{M}_{\mathbf{B_2}}\mathbf{B_1}\mathbf{C}^{-1}\mathbf{B}_1'\mathbf{M}_{\mathbf{B_2}}\right)^+\mathbf{B}_1\mathbf{C}^{-1}, -\mathbf{B}_1'(\mathbf{B}_2')^-_{m(\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1')}\right).
\end{aligned}$$

Since $\operatorname{var}(\widehat{\delta\boldsymbol{\beta}_1}) = \mathbf{C}^{-1}$ and using [2, Lemmas A.8.4 and A.8.5]

$$\begin{aligned}
\operatorname{var}\left(\widehat{\widehat{\delta\boldsymbol{\beta}}}_1\right) &= \left[\mathbf{I} - \mathbf{C}^{-1}\mathbf{B}_1'\left(\mathbf{M}_{\mathbf{B_2}}\mathbf{B_1}\mathbf{C}^{-1}\mathbf{B}_1'\mathbf{M}_{\mathbf{B_2}}\right)^+\mathbf{B}_1\right]\mathbf{C}^{-1} \\
&\quad \times \left[\mathbf{I} - \mathbf{B}_1'\left(\mathbf{M}_{\mathbf{B_2}}\mathbf{B_1}\mathbf{C}^{-1}\mathbf{B}_1'\mathbf{M}_{\mathbf{B_2}}\right)^+\mathbf{B}_1\mathbf{C}^{-1}\right] \\
&= \mathbf{C}^{-1} - 2\mathbf{C}^{-1}\mathbf{B}_1'\left(\mathbf{M}_{\mathbf{B_2}}\mathbf{B_1}\mathbf{C}^{-1}\mathbf{B}_1'\mathbf{M}_{\mathbf{B_2}}\right)^+\mathbf{B}_1\mathbf{C}^{-1} + \mathbf{C}^{-1}\mathbf{B}_1' \\
&\quad \times \left(\mathbf{M}_{\mathbf{B_2}}\mathbf{B_1}\mathbf{C}^{-1}\mathbf{B}_1'\mathbf{M}_{\mathbf{B_2}}\right)^+\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1'\left(\mathbf{M}_{\mathbf{B_2}}\mathbf{B_1}\mathbf{C}^{-1}\mathbf{B}_1'\mathbf{M}_{\mathbf{B_2}}\right)^+\mathbf{B}_1\mathbf{C}^{-1} \\
&= \mathbf{C}^{-1} - \mathbf{C}^{-1}\mathbf{B}_1'\left(\mathbf{M}_{\mathbf{B_2}}\mathbf{B_1}\mathbf{C}^{-1}\mathbf{B}_1'\mathbf{M}_{\mathbf{B_2}}\right)^+\mathbf{B}_1\mathbf{C}^{-1} \\
&= \mathbf{C}^{-1} - \mathbf{C}^{-1}\mathbf{B}_1'\mathbf{M}_{\mathbf{B_2}}\left(\mathbf{M}_{\mathbf{B_2}}\mathbf{B_1}\mathbf{C}^{-1}\mathbf{B}_1'\mathbf{M}_{\mathbf{B_2}}\right)^+\mathbf{M}_{\mathbf{B_2}}\mathbf{B}_1\mathbf{C}^{-1} \\
&= \left(\mathbf{M}_{\mathbf{B_1'M_{B_2}}}\mathbf{C}\mathbf{M}_{\mathbf{B_1'M_{B_2}}}\right)^+,
\end{aligned}$$

and similarly, when we denote $\mathbf{H} = \mathbf{B}_2' \left(\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1' + \mathbf{B}_2\mathbf{B}_2'\right)^{-} \mathbf{B}_2$,

$$\begin{aligned}
&\operatorname{var}\left(\widehat{\widehat{\boldsymbol{\delta\beta}_2}}\right) = \left[(\mathbf{B}_2')^{-}_{m(\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1')}\right]' \mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1'(\mathbf{B}_2')^{-}_{m(\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1')} \\
&= \mathbf{H}^{-}\mathbf{B}_2' \left(\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1' + \mathbf{B}_2\mathbf{B}_2'\right)^{-1} \mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1' \left(\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1' + \mathbf{B}_2\mathbf{B}_2'\right)^{-1} \mathbf{B}_2\mathbf{H}^{-} \\
&= \mathbf{H}^{-}\mathbf{B}_2' \left(\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1' + \mathbf{B}_2\mathbf{B}_2'\right)^{-1} \left(\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1' + \mathbf{B}_2\mathbf{B}_2' - \mathbf{B}_2\mathbf{B}_2'\right) \\
&\quad \times \left(\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1' + \mathbf{B}_2\mathbf{B}_2'\right)^{-1} \mathbf{B}_2\mathbf{H}^{-} \\
&= \mathbf{H}^{-1}\mathbf{H}\mathbf{H}^{-1} - \mathbf{H}^{-1}\mathbf{H}\mathbf{H}\mathbf{H}^{-1} \\
&= \left[\mathbf{B}_2' \left(\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1' + \mathbf{B}_2\mathbf{B}_2'\right)^{-1} \mathbf{B}_2\right]^{-1} - \mathbf{I},
\end{aligned}$$

because the matrix $\left(\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1' + \mathbf{B}_2\mathbf{B}_2'\right)$ can be expressed as multiplication of regular matrices (due to a model regularity)

$$\mathbf{B_1}\mathbf{C}^{-1}\mathbf{B_1'} + \mathbf{B_2}\mathbf{B_2'} = (\mathbf{B_1}, \mathbf{B_2}) \begin{pmatrix} \mathbf{C}^{-1} & ,\mathbf{0} \\ \mathbf{0} & ,\mathbf{I} \end{pmatrix} \begin{pmatrix} \mathbf{B_1'} \\ \mathbf{B_2'} \end{pmatrix},$$

and since we can use common inverse matrices instead of g-inverse matrices $\left(\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1' + \mathbf{B}_2\mathbf{B}_2'\right)^{-}$ and $\left[\mathbf{B}_2' \left(\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1' + \mathbf{B}_2\mathbf{B}_2'\right)^{-} \mathbf{B}_2\right]^{-}$. □

Remark 2.1 Since (see [2, Lemmas A.7.24 and A.7.9])

$$\begin{aligned}
\left(\mathbf{M_{B_2}}\mathbf{B_1}\mathbf{C}^{-1}\mathbf{B}_1'\mathbf{M_{B_2}}\right)^{+} &= \left(\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1' + \mathbf{B}_2\mathbf{B}_2'\right)^{-1} - \left(\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1' + \mathbf{B}_2\mathbf{B}_2'\right)^{-1} \\
&\times \mathbf{B}_2 \left[\mathbf{B}_2' \left(\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1' + \mathbf{B}_2\mathbf{B}_2'\right)^{-1} \mathbf{B}_2\right]^{-1} \mathbf{B}_2' \left(\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1' + \mathbf{B}_2\mathbf{B}_2'\right)^{-1},
\end{aligned}$$

and

$$(\mathbf{B}_2')^{-}_{m(\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1')} = (\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1' + \mathbf{B}_2\mathbf{B}_2')^{-1}\mathbf{B}_2 \left[\mathbf{B}_2'(\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1' + \mathbf{B}_2\mathbf{B}_2')^{-1}\mathbf{B}_2\right]^{-1},$$

the estimators of $\delta\boldsymbol{\beta}_1$ and $\delta\boldsymbol{\beta}_2$ in (1) and (2) can be expressed in equivalent forms without generalized inverse matrices

$$\widehat{\widehat{\delta\boldsymbol{\beta}_1}} = \widehat{\delta\boldsymbol{\beta}_1} - \mathbf{C}^{-1}\mathbf{B}_1' \left[\mathbf{T} - \mathbf{T}\mathbf{B}_2 \left(\mathbf{B}_2'\mathbf{T}\mathbf{B}_2\right)^{-1} \mathbf{B}_1'\mathbf{T}\right] \left(\mathbf{b} + \mathbf{B}_1\widehat{\delta\boldsymbol{\beta}_1}\right), \tag{5}$$

$$\widehat{\widehat{\delta\boldsymbol{\beta}_2}} = -\left(\mathbf{B}_2'\mathbf{T}\mathbf{B}_2\right)^{-1} \mathbf{B}_2'\mathbf{T} \left(\mathbf{b} + \mathbf{B}_1\widehat{\delta\boldsymbol{\beta}_1}\right), \tag{6}$$

where $\mathbf{T} = \left(\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1' + \mathbf{B}_2\mathbf{B}_2'\right)^{-1}$.

Now we turn back to the model with quadratic terms and explore the properties (1)–(4) of the estimators.

Lemma 2.2 *If*

$$\mathbf{Y} - \mathbf{f}_0 \sim_n (\mathbf{F}\delta\boldsymbol{\beta}_1 + \frac{1}{2}\boldsymbol{\kappa}(\delta\boldsymbol{\beta}_1), \boldsymbol{\Sigma}), \quad \mathbf{b} + \mathbf{B}_1\delta\boldsymbol{\beta}_1 + \mathbf{B}_2\delta\boldsymbol{\beta}_2 + \frac{1}{2}\boldsymbol{\omega}\left(\delta\boldsymbol{\beta}_1, \delta\boldsymbol{\beta}_2\right) = \mathbf{0}, \tag{7}$$

then biases of the estimators (1) and (2) are

$$\begin{aligned}
\boldsymbol{b}_1 &= E\left(\widehat{\widehat{\delta\boldsymbol{\beta}_1}}\right) - \delta\boldsymbol{\beta}_1 = \frac{1}{2}\mathbf{C}^{-1}\mathbf{B}_1'\left[\mathbf{M}_{\mathbf{B_2}}\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1'\mathbf{M}_{\mathbf{B_2}}\right]^{+}\boldsymbol{\omega}\left(\delta\boldsymbol{\beta}_1,\delta\boldsymbol{\beta}_2\right)\\
&\quad+\frac{1}{2}\left[\mathbf{M}_{\mathbf{B}_1'\mathbf{M}_{\mathbf{B_2}}}\mathbf{C}\mathbf{M}_{\mathbf{B}_1'\mathbf{M}_{\mathbf{B_2}}}\right]^{+}\mathbf{F}'\boldsymbol{\Sigma}^{-1}\boldsymbol{\kappa}(\delta\boldsymbol{\beta}_1),\\
\boldsymbol{b}_2 &= E\left(\widehat{\widehat{\delta\boldsymbol{\beta}_2}}\right) - \delta\boldsymbol{\beta}_2\\
&= \frac{1}{2}\left[(\mathbf{B}_2')^{-}_{m(\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1')}\right]'\left(\boldsymbol{\omega}\left(\delta\boldsymbol{\beta}_1,\delta\boldsymbol{\beta}_2\right)-\mathbf{B}_1\mathbf{C}^{-1}\mathbf{F}'\boldsymbol{\Sigma}^{-1}\boldsymbol{\kappa}(\delta\boldsymbol{\beta}_1)\right),
\end{aligned}$$

where $\mathbf{C}=\mathbf{F}'\boldsymbol{\Sigma}^{-1}\mathbf{F}$*.*

Proof By [2, Lemmas A.7.24 and A.8.4] and due to $\mathbf{M}_{\mathbf{B_2}}\mathbf{B_2}=\mathbf{0}$, we can write

$$\begin{aligned}
&E\left(\widehat{\widehat{\delta\boldsymbol{\beta}_1}}\right) = E\left(\widehat{\delta\boldsymbol{\beta}_1}-\mathbf{C}^{-1}\mathbf{B}_1'\left[\mathbf{M}_{\mathbf{B_2}}\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1'\mathbf{M}_{\mathbf{B_2}}\right]^{+}\left[\mathbf{b}+\mathbf{B}_1\widehat{\delta\boldsymbol{\beta}_1}\right]\right)\\
&= -\mathbf{C}^{-1}\mathbf{B}_1'\left[\mathbf{M}_{\mathbf{B_2}}\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1'\mathbf{M}_{\mathbf{B_2}}\right]^{+}\mathbf{b}\\
&\quad+\left[\mathbf{I}-\mathbf{C}^{-1}\mathbf{B}_1'\left[\mathbf{M}_{\mathbf{B_2}}\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1'\mathbf{M}_{\mathbf{B_2}}\right]^{+}\mathbf{B}_1\right]E\left(\widehat{\delta\boldsymbol{\beta}_1}\right)\\
&= -\mathbf{C}^{-1}\mathbf{B}_1'\left[\mathbf{M}_{\mathbf{B_2}}\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1'\mathbf{M}_{\mathbf{B_2}}\right]^{+}\mathbf{b}\\
&\quad+\left[\mathbf{I}-\mathbf{C}^{-1}\mathbf{B}_1'\left[\mathbf{M}_{\mathbf{B_2}}\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1'\mathbf{M}_{\mathbf{B_2}}\right]^{+}\mathbf{B}_1\right]\mathbf{C}^{-1}\mathbf{F}'\boldsymbol{\Sigma}^{-1}\left(\mathbf{F}\delta\boldsymbol{\beta}_1+\frac{1}{2}\boldsymbol{\kappa}(\delta\boldsymbol{\beta}_1)\right)\\
&= \delta\boldsymbol{\beta}_1-\mathbf{C}^{-1}\mathbf{B}_1'\left[\mathbf{M}_{\mathbf{B_2}}\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1'\mathbf{M}_{\mathbf{B_2}}\right]^{+}\left(\mathbf{b}+\mathbf{B}_1\delta\boldsymbol{\beta}_1\right)\\
&\quad+\frac{1}{2}\left[\mathbf{I}-\mathbf{C}^{-1}\mathbf{B}_1'\left[\mathbf{M}_{\mathbf{B_2}}\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1'\mathbf{M}_{\mathbf{B_2}}\right]^{+}\mathbf{B}_1\right]\mathbf{C}^{-1}\mathbf{F}'\boldsymbol{\Sigma}^{-1}\boldsymbol{\kappa}(\delta\boldsymbol{\beta}_1)\\
&= \delta\boldsymbol{\beta}_1+\mathbf{C}^{-1}\mathbf{B}_1'\mathbf{M}_{\mathbf{B_2}}\left[\mathbf{M}_{\mathbf{B_2}}\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1'\mathbf{M}_{\mathbf{B_2}}\right]^{+}\mathbf{M}_{\mathbf{B_2}}\left(\mathbf{B}_2\delta\boldsymbol{\beta}_2+\frac{1}{2}\boldsymbol{\omega}\left(\delta\boldsymbol{\beta}_1,\delta\boldsymbol{\beta}_2\right)\right)\\
&\quad+\frac{1}{2}\left[\mathbf{C}^{-1}-\mathbf{C}^{-1}\mathbf{B}_1'\mathbf{M}_{\mathbf{B_2}}\left[\mathbf{M}_{\mathbf{B_2}}\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1'\mathbf{M}_{\mathbf{B_2}}\right]^{+}\mathbf{M}_{\mathbf{B_2}}\mathbf{B}_1\mathbf{C}^{-1}\right]\mathbf{F}'\boldsymbol{\Sigma}^{-1}\boldsymbol{\kappa}(\delta\boldsymbol{\beta}_1)\\
&= \delta\boldsymbol{\beta}_1+\frac{1}{2}\mathbf{C}^{-1}\mathbf{B}_1'\left[\mathbf{M}_{\mathbf{B_2}}\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1'\mathbf{M}_{\mathbf{B_2}}\right]^{+}\boldsymbol{\omega}\left(\delta\boldsymbol{\beta}_1,\delta\boldsymbol{\beta}_2\right)\\
&\quad+\frac{1}{2}\left[\mathbf{M}_{\mathbf{B}_1'\mathbf{M}_{\mathbf{B_2}}}\mathbf{C}\mathbf{M}_{\mathbf{B}_1'\mathbf{M}_{\mathbf{B_2}}}\right]^{+}\mathbf{F}'\boldsymbol{\Sigma}^{-1}\boldsymbol{\kappa}(\delta\boldsymbol{\beta}_1).
\end{aligned}$$

Then

$$\begin{aligned}
\boldsymbol{b}_1 &= E\left(\widehat{\widehat{\delta\boldsymbol{\beta}_1}}\right) - \delta\boldsymbol{\beta}_1 = \frac{1}{2}\mathbf{C}^{-1}\mathbf{B}_1'\left[\mathbf{M}_{\mathbf{B_2}}\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1'\mathbf{M}_{\mathbf{B_2}}\right]^{+}\boldsymbol{\omega}\left(\delta\boldsymbol{\beta}_1,\delta\boldsymbol{\beta}_2\right)\\
&\quad+\frac{1}{2}\left[\mathbf{M}_{\mathbf{B}_1'\mathbf{M}_{\mathbf{B_2}}}\mathbf{C}\mathbf{M}_{\mathbf{B}_1'\mathbf{M}_{\mathbf{B_2}}}\right]^{+}\mathbf{F}'\boldsymbol{\Sigma}^{-1}\boldsymbol{\kappa}(\delta\boldsymbol{\beta}_1).
\end{aligned}$$

Similarly by [2, Lemma A.7.20] and due to

$$\left[(\mathbf{B}_2')^{-}_{m(\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1')}\right]'\mathbf{B}_2=\mathbf{I}$$

we obtain

$$
\begin{aligned}
E\left(\widehat{\widehat{\delta\boldsymbol{\beta}_2}}\right) &= E\left(-\left[(\mathbf{B}_2')^-_{m(\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1')}\right]'\left(\mathbf{b}+\mathbf{B}_1\widehat{\delta\boldsymbol{\beta}_1}\right)\right) \\
&= -\left[(\mathbf{B}_2')^-_{m(\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1')}\right]'\mathbf{b} - \left[(\mathbf{B}_2')^-_{m(\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1')}\right]'\mathbf{B}_1\mathbf{C}^{-1}\mathbf{F}'\boldsymbol{\Sigma}^{-1}E\left(\mathbf{Y}-\mathbf{f}_0\right) \\
&= -\left[(\mathbf{B}_2')^-_{m(\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1')}\right]'\mathbf{b} - \left[(\mathbf{B}_2')^-_{m(\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1')}\right]' \\
&\quad \times \mathbf{B}_1\mathbf{C}^{-1}\mathbf{F}'\boldsymbol{\Sigma}^{-1}\left(\mathbf{F}\delta\boldsymbol{\beta}_1+\frac{1}{2}\boldsymbol{\kappa}(\delta\boldsymbol{\beta}_1)\right) \\
&= -\left[(\mathbf{B}_2')^-_{m(\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1')}\right]'(\mathbf{b}+\mathbf{B}_1\delta\boldsymbol{\beta}_1) - \frac{1}{2}\left[(\mathbf{B}_2')^-_{m(\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1')}\right]' \\
&\quad \times \mathbf{B}_1\mathbf{C}^{-1}\mathbf{F}'\boldsymbol{\Sigma}^{-1}\boldsymbol{\kappa}(\delta\boldsymbol{\beta}_1) \\
&= \left[(\mathbf{B}_2')^-_{m(\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1')}\right]'\left(\mathbf{B}_2\delta\boldsymbol{\beta}_2+\frac{1}{2}\boldsymbol{\omega}\left(\delta\boldsymbol{\beta}_1,\delta\boldsymbol{\beta}_2\right)\right) \\
&\quad - \frac{1}{2}\left[(\mathbf{B}_2')^-_{m(\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1')}\right]'\mathbf{B}_1\mathbf{C}^{-1}\mathbf{F}'\boldsymbol{\Sigma}^{-1}\boldsymbol{\kappa}(\delta\boldsymbol{\beta}_1) \\
&= \delta\boldsymbol{\beta}_2 + \frac{1}{2}\left[(\mathbf{B}_2')^-_{m(\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1')}\right]'\left[\boldsymbol{\omega}\left(\delta\boldsymbol{\beta}_1,\delta\boldsymbol{\beta}_2\right)-\mathbf{B}_1\mathbf{C}^{-1}\mathbf{F}'\boldsymbol{\Sigma}^{-1}\boldsymbol{\kappa}(\delta\boldsymbol{\beta}_1)\right],
\end{aligned}
$$

and therefore

$$
\begin{aligned}
\boldsymbol{b}_2 &= E\left(\widehat{\widehat{\delta\boldsymbol{\beta}_2}}\right) - \delta\boldsymbol{\beta}_2 \\
&= \frac{1}{2}\left[(\mathbf{B}_2')^-_{m(\mathbf{B}_1\mathbf{C}^{-1}\mathbf{B}_1')}\right]'\left[\boldsymbol{\omega}\left(\delta\boldsymbol{\beta}_1,\delta\boldsymbol{\beta}_2\right)-\mathbf{B}_1\mathbf{C}^{-1}\mathbf{F}'\boldsymbol{\Sigma}^{-1}\boldsymbol{\kappa}(\delta\boldsymbol{\beta}_1)\right]. \qquad \square
\end{aligned}
$$

3 Measures of nonlinearity and areas of linearization

In this section we suppose the observation vector to be normally distributed. Bias of an estimator of $\delta\boldsymbol{\beta}_2$ can be split into components, i.e.

$$\boldsymbol{b}_2 = E\left(\widehat{\widehat{\delta\boldsymbol{\beta}_2}}\right) - \delta\boldsymbol{\beta}_2 = \boldsymbol{b}_{2,0} + \boldsymbol{b}_{2,1},$$

where

$$\boldsymbol{b}_{2,0} \in \mathcal{M}\left(\mathrm{var}(\widehat{\widehat{\delta\boldsymbol{\beta}_2}})\right) \quad \text{and} \quad \boldsymbol{b}_{2,1} \in \mathcal{M}\left(\mathbf{M}_{\mathrm{var}(\widehat{\widehat{\delta\boldsymbol{\beta}_2}})}\right),$$

as can be seen in Fig. 1.

Let a symbol $\lambda_{\max}$ denote the biggest eigenvalue of the matrix $\mathrm{var}(\widehat{\widehat{\delta\boldsymbol{\beta}_2}})$. By Theorem 9.2.1 in [3] it is easy to prove that for

$$\widehat{\widehat{\delta\boldsymbol{\beta}_2}} \sim N_{k_2}(\delta\boldsymbol{\beta}_2 + \boldsymbol{b}_2, \mathrm{var}(\widehat{\widehat{\delta\boldsymbol{\beta}_2}}))$$

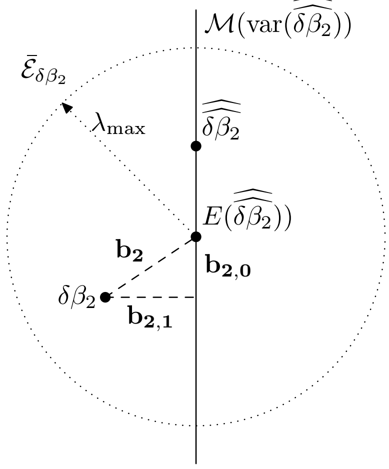

Figure 1: The components of bias.

the random variable

$$T = \left[\widehat{\delta\boldsymbol{\beta}_2} - E\left(\widehat{\delta\boldsymbol{\beta}_2}\right) + \boldsymbol{b}_{2,0}\right]' \left(\mathrm{var}(\widehat{\delta\boldsymbol{\beta}_2}) + \lambda_{\max}\mathbf{M}_{\mathrm{var}(\widehat{\delta\boldsymbol{\beta}_2})}\right)^+ \times \left[\widehat{\delta\boldsymbol{\beta}_2} - E\left(\widehat{\delta\boldsymbol{\beta}_2}\right) + \boldsymbol{b}_{2,0}\right]$$

has a noncentral χ^2 distribution with $f = h(\mathrm{var}(\widehat{\delta\boldsymbol{\beta}_2}))$ degrees of freedom and a parameter of noncentrality

$$\delta = \boldsymbol{b}'_{2,0} \left(\mathrm{var}(\widehat{\delta\boldsymbol{\beta}_2}) + \lambda_{\max}\mathbf{M}_{\mathrm{var}(\widehat{\delta\boldsymbol{\beta}_2})}\right)^+ \boldsymbol{b}_{2,0}. \tag{8}$$

A random variable

$$\bar{T} = \left(\delta\boldsymbol{\beta}_2 - \widehat{\delta\boldsymbol{\beta}_2}\right)' \left(\mathrm{var}(\widehat{\delta\boldsymbol{\beta}_2}) + \lambda_{\max}\mathbf{M}_{\mathrm{var}(\widehat{\delta\boldsymbol{\beta}_2})}\right)^+ \left(\delta\boldsymbol{\beta}_2 - \widehat{\delta\boldsymbol{\beta}_2}\right)$$

can be then rewritten in the form

$$\bar{T} = T + \frac{\boldsymbol{b}'_{2,1}\boldsymbol{b}_{2,1}}{\lambda_{\max}},$$

because by [2, Lemmas A.7.22 and A.7.2] it holds that

$$\left[\mathrm{var}(\widehat{\delta\boldsymbol{\beta}_2}) + \lambda_{\max}\mathbf{M}_{\mathrm{var}(\widehat{\delta\boldsymbol{\beta}_2})}\right]^+ = \left[\mathrm{var}(\widehat{\delta\boldsymbol{\beta}_2})\right]^+ + \frac{1}{\lambda_{\max}}\mathbf{M}_{\mathrm{var}(\widehat{\delta\boldsymbol{\beta}_2})}$$

and

$$\boldsymbol{b}'_{2,1}\left[\mathrm{var}(\widehat{\delta\boldsymbol{\beta}_2})\right]^+ \boldsymbol{b}_{2,1} = \mathbf{0}.$$

This consideration leads us to a modified confidence ellipsoid for the parameter $\delta\boldsymbol{\beta}_2$.

Definition 3.1 A modified confidence ellipsoid for the parameter $\delta\boldsymbol{\beta}_2$ in the model (7) is defined as

$$\bar{\mathcal{E}}_{\delta\boldsymbol{\beta}_2} = \left\{ \boldsymbol{u} \in \mathbb{R}^{k_2} \colon \left(\boldsymbol{u} - \widehat{\widehat{\delta\boldsymbol{\beta}_2}} \right)' \left\{ \left[\mathrm{var}(\widehat{\widehat{\delta\boldsymbol{\beta}_2}}) \right]^+ + \frac{1}{\lambda_{\max}} \mathbf{M}_{\mathrm{var}(\widehat{\widehat{\delta\boldsymbol{\beta}_2}})} \right\} \left(\boldsymbol{u} - \widehat{\widehat{\delta\boldsymbol{\beta}_2}} \right) \right.$$
$$\left. \leq \chi^2_f(0; 1-\alpha) \right\},$$

where $f = h(\mathrm{var}(\widehat{\widehat{\delta\boldsymbol{\beta}_2}}))$.

As a certain analogy of the Bates-Wats measure of curvature, a measure of nonlinearity for a confidence ellipsoid for the parameter $\delta\boldsymbol{\beta}_2$ can be defined.

Definition 3.2 For a linear model with type II constraints in the form (7), we define a measure of nonlinearity of confidence ellipsoid for the parameter $\delta\boldsymbol{\beta}_2$ as

$$\mathcal{C}^{II}_{ell,\delta\boldsymbol{\beta}_2} = \sup \left\{ \frac{\sqrt{\boldsymbol{b}_2' \left\{ \left[\mathrm{var}(\widehat{\widehat{\delta\boldsymbol{\beta}_2}}) \right]^+ + \frac{1}{\lambda_{\max}} \mathbf{M}_{\mathrm{var}(\widehat{\widehat{\delta\boldsymbol{\beta}_2}})} \right\} \boldsymbol{b}_2}}{\delta\boldsymbol{s}'\mathbf{K}_1' \left\{ \left[\mathrm{var}(\widehat{\widehat{\delta\boldsymbol{\beta}_1}}) \right]^+ + \frac{1}{\kappa_{\max}} \mathbf{M}_{\mathrm{var}(\widehat{\widehat{\delta\boldsymbol{\beta}_1}})} \right\} \mathbf{K}_1 \delta\boldsymbol{s}} \colon \delta\boldsymbol{s} \in \mathbb{R}^{k_1+k_2-q} \right\}, \tag{9}$$

where $\kappa_{\max}$ is the biggest eigenvalue of the matrix $\mathrm{var}(\widehat{\widehat{\delta\boldsymbol{\beta}_1}})$ and $\mathbf{K}_1$ is a matrix of type $k_1 \times (k_1 + k_2 - q)$ satisfying $\mathcal{M}(\mathbf{K}_1) = \mathcal{M}(\mathbf{M}_{\mathbf{B}_1'\mathbf{M}_{\mathbf{B}_2}})$.

It is obvious that

$$\mathcal{P}\left\{ \bar{T} \leq \chi^2_f(0; 1-\alpha) \right\} = \mathcal{P}\left\{ \chi^2_f(\delta) + \frac{\boldsymbol{b}_{2,1}'\boldsymbol{b}_{2,1}}{\lambda_{\max}} \leq \chi^2_f(0; 1-\alpha) \right\}$$

and certainly such $\delta_0 > 0$ exists which satisfies the equality

$$\mathcal{P}\left\{ \chi^2_f(\delta_0) + \delta_0 \leq \chi^2_f(0; 1-\alpha) \right\} = 1 - \alpha - \epsilon \tag{10}$$

for a sufficiently small $\epsilon > 0$. Now we define an area of linearization of the parameter $\delta\boldsymbol{\beta}_2$ for this δ_0.

Definition 3.3 An area of linearization of the parameter $\delta\boldsymbol{\beta}_2$ for the model (7) is

$$\mathcal{L}_{\delta\boldsymbol{\beta}_2} = \left\{ \mathbf{K}_1\delta\boldsymbol{s} \colon \delta\boldsymbol{s}'\mathbf{K}_1' \left\{ \left[\mathrm{var}(\widehat{\widehat{\delta\boldsymbol{\beta}_1}}) \right]^+ + \frac{1}{\kappa_{\max}} \mathbf{M}_{\mathrm{var}(\widehat{\widehat{\delta\boldsymbol{\beta}_1}})} \right\} \mathbf{K}_1\delta\boldsymbol{s} \leq \frac{\sqrt{\delta_0}}{\mathcal{C}^{II}_{ell,\delta\boldsymbol{\beta}_2}}, \right.$$
$$\left. \delta\boldsymbol{s} \in \mathbb{R}^{k_1+k_2-q} \right\},$$

where the matrix $\mathbf{K}_1$ has properties mentioned in Definition 3.2.

Lemma 3.1 *If* $\mathbf{K}_1\delta\boldsymbol{s} \in \mathcal{L}_{\delta\boldsymbol{\beta}_2}$, *then*

$$\mathcal{P}\left\{\delta\boldsymbol{\beta}_2 \in \bar{\mathcal{E}}_{\delta\boldsymbol{\beta}_2}\right\} \geq 1-\alpha-\epsilon.$$

Proof By the definition of $\mathcal{L}_{\delta\boldsymbol{\beta}_2}$ and $C^{II}_{ell,\delta\boldsymbol{\beta}_2}$, we can write

$$\sqrt{\boldsymbol{b}_2'\left\{\left[\mathrm{var}(\widehat{\widehat{\delta\boldsymbol{\beta}_2}})\right]^+ + \frac{1}{\lambda_{\max}}\mathbf{M}_{\mathrm{var}(\widehat{\widehat{\delta\boldsymbol{\beta}_2}})}\right\}\boldsymbol{b}_2}$$
$$\leq \mathcal{C}^{II}_{ell,\delta\boldsymbol{\beta}_2}\delta\boldsymbol{s}'\mathbf{K}_1'\left\{\left[\mathrm{var}(\widehat{\widehat{\delta\boldsymbol{\beta}_1}})\right]^+ + \frac{1}{\kappa_{\max}}\mathbf{M}_{\mathrm{var}(\widehat{\widehat{\delta\boldsymbol{\beta}_1}})}\right\}\mathbf{K}_1\delta\boldsymbol{s} \leq \sqrt{\delta_0}.$$

Since, with respect to $\mathbf{M}_{\mathrm{var}(\widehat{\widehat{\delta\boldsymbol{\beta}_2}})}\boldsymbol{b}_{2,0} = \mathbf{0}$,

$$\mathcal{P}\left\{\delta\boldsymbol{\beta}_2 \in \bar{\mathcal{E}}_{\delta\boldsymbol{\beta}_2}\right\} = \mathcal{P}\left\{\bar{T} \leq \chi^2_f(0;1-\alpha)\right\} = \mathcal{P}\left\{\chi^2_f(\delta) + \frac{\boldsymbol{b}_{2,1}'\boldsymbol{b}_{2,1}}{\lambda_{\max}} \leq \chi^2_f(0;1-\alpha)\right\}$$
$$\geq \mathcal{P}\left\{\chi^2_f(\delta_0) + \delta_0 \leq \chi^2_f(0;1-\alpha)\right\} = 1-\alpha-\epsilon. \qquad \square$$

Because the parameter $\delta\boldsymbol{\beta}_2$ is a function of the parameter $\delta\boldsymbol{\beta}_1$ we must, in order to verify of the property $\delta\boldsymbol{\beta}_1 \approx \mathbf{K}_1\delta\boldsymbol{s} \in \mathcal{L}_{\delta\boldsymbol{\beta}_2}$, construct also a modified confidence ellipsoid for the parameter $\delta\boldsymbol{\beta}_1$.

Definition 3.4 A modified confidence ellipsoid for the parameter $\delta\boldsymbol{\beta}_1$ in the model (7) is

$$\bar{\mathcal{E}}_{\delta\boldsymbol{\beta}_1} = \left\{\boldsymbol{u} \in \mathbb{R}^{k_1}: \left(\boldsymbol{u} - \widehat{\widehat{\delta\boldsymbol{\beta}_1}}\right)'\left\{\left[\mathrm{var}(\widehat{\widehat{\delta\boldsymbol{\beta}_1}})\right]^+ + \frac{1}{\kappa_{\max}}\mathbf{M}_{\mathrm{var}(\widehat{\widehat{\delta\boldsymbol{\beta}_1}})}\right\}\left(\boldsymbol{u} - \widehat{\widehat{\delta\boldsymbol{\beta}_1}}\right) \leq \chi^2_{f_1}(0;1-\alpha)\right\},$$

where $f_1 = h(\mathrm{var}(\widehat{\widehat{\delta\boldsymbol{\beta}_1}}))$ and $\kappa_{\max}$ is the biggest eigenvalue of the matrix $\mathrm{var}(\widehat{\widehat{\delta\boldsymbol{\beta}_1}})$.

Similarly as for $\delta\boldsymbol{\beta}_2$, it is also possible to define a measure of nonlinearity for $\delta\boldsymbol{\beta}_1$.

Definition 3.5 For the linear model (7), we define a measure of nonlinearity of a confidence ellipsoid for the parameter $\delta\boldsymbol{\beta}_1$ as

$$\mathcal{C}^{II}_{ell,\delta\boldsymbol{\beta}_1} = \sup\left\{\frac{\sqrt{\boldsymbol{b}_1'\left\{\left[\mathrm{var}(\widehat{\widehat{\delta\boldsymbol{\beta}_1}})\right]^+ + \frac{1}{\kappa_{\max}}\mathbf{M}_{\mathrm{var}(\widehat{\widehat{\delta\boldsymbol{\beta}_1}})}\right\}\boldsymbol{b}_1}}{\delta\boldsymbol{s}'\mathbf{K}_1'\left\{\left[\mathrm{var}(\widehat{\widehat{\delta\boldsymbol{\beta}_1}})\right]^+ + \frac{1}{\kappa_{\max}}\mathbf{M}_{\mathrm{var}(\widehat{\widehat{\delta\boldsymbol{\beta}_1}})}\right\}\mathbf{K}_1\delta\boldsymbol{s}} : \delta\boldsymbol{s} \in \mathbb{R}^{k_1+k_2-q}\right\}. \tag{11}$$

A sufficient condition for linearization regarding the confidence ellipsoid for the parameter $\delta\boldsymbol{\beta}_2$ is

$$\mathcal{E}_{\delta\boldsymbol{\beta}_1} \subset\subset \mathcal{L}_{\delta\boldsymbol{\beta}_2} \Rightarrow \frac{\sqrt{\delta_0}}{C^{II}_{ell,\delta\boldsymbol{\beta}_2}} \gg \chi^2_{f_1}(0; 1-\alpha), \tag{12}$$

(cf. Fig. 2).

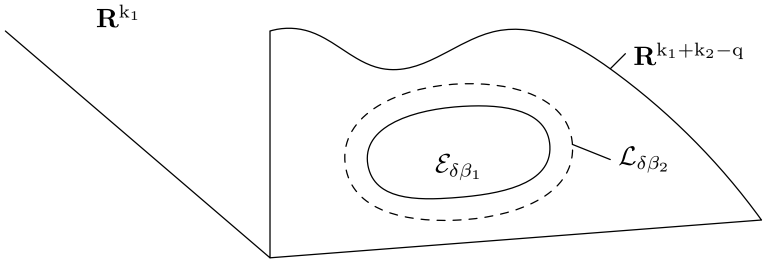

Figure 2: The confidence ellipsoid $\mathcal{E}_{\delta\boldsymbol{\beta}_1}$ and the area of linearization $\mathcal{L}_{\delta\boldsymbol{\beta}_2}$.

4 Numerical example

Tracer kinetics of liver blood flow can be described by a compartmental model (Fig. 3) and an ordinary differential equation

$$\frac{dC_L(t)}{dt} = k_{1a}C_a(t) + k_{1p}C_p(t) - k_2C_L(t). \tag{13}$$

We obtained the values of tracer concentration $C_L(t_i)$ in liver, $C_a(t_i)$ in a liver artery and $C_p(t_i)$ in a portal vein by measuring times t_i, $i = 1, 2, \dots, n$.

To the equation (13) we can add a delay, in the liver artery or in the portal vein or both. So overall, we can obtain three different equations for our compartmental model (included the one without any delay):

$$\text{(KMI)} \quad \frac{dC_L(t)}{dt} = k_{1a}C_a(t) + k_{1p}C_p(t) - k_2C_L(t),$$

$$\text{(KMII)} \quad \frac{dC_L(t)}{dt} = k_{1a}C_a(t-\tau_a) + k_{1p}C_p(t) - k_2C_L(t),$$

$$\text{(KMIII)} \quad \frac{dC_L(t)}{dt} = k_{1a}C_a(t-\tau_a) + k_{1p}C_p(t-\tau_p) - k_2C_L(t).$$

For the sake of simplicity, let us consider only the model without any delay, denoted as (KMI). A vector of observations of tracer concentrations for this model is in the form

$$\mathbf{Y} = (C_a(t_1), \dots, C_a(t_{n-1}), C_p(t_1), \dots, C_p(t_{n-1}), C_L(t_1), \dots, C_L(t_n))',$$

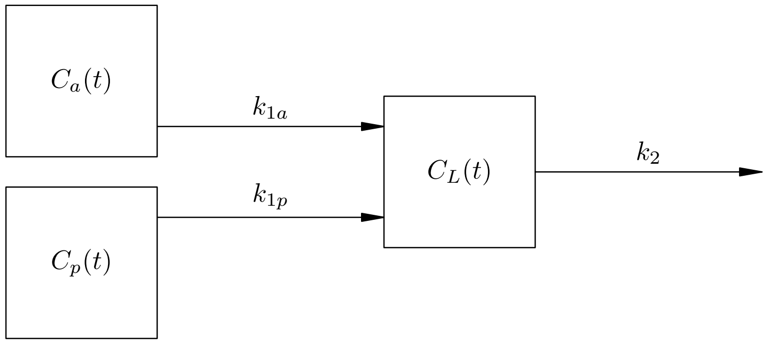

Figure 3: Dual-input one-compartmental model of blood flow in liver.

and a statistical model

$$\mathbf{Y} \sim N_{3n-2}\left(\mathbf{I}\boldsymbol{\beta_1}, \sigma^2\mathbf{I}\right), \tag{14}$$

where $\boldsymbol{\beta_1} = (\mu_1, \ldots \mu_{n-1}, \nu_1, \ldots, \nu_{n-1}, \zeta_1, \ldots, \zeta_n)'$, with constraints

$$\frac{\zeta_{i+1} - \zeta_i}{t_{i+1} - t_i} = k_{1a}\mu_i + k_{1p}\nu_i - k_2\zeta_i, \quad i = 1, 2, \ldots, n-1.$$

Let for $i = 1, 2, \ldots, n-1$

$$\mu_i = \mu_i^{(0)} + \delta\mu_i, \quad \nu_i = \nu_i^{(0)} + \delta\nu_i, \quad \zeta_i = \zeta_i^{(0)} + \delta\zeta_i,$$

then for

$$\mathbf{Z} = \mathbf{Y} - \left(\mu_1^{(0)}, \ldots \mu_{n-1}^{(0)}, \nu_1^{(0)}, \ldots, \nu_{n-1}^{(0)}, \zeta_1^{(0)}, \ldots, \zeta_n^{(0)}\right)'$$

we have a model

$$\mathbf{Z} \sim N_{3n-2}\left(\mathbf{I}\boldsymbol{\delta\beta_1}, \sigma^2\mathbf{I}\right),$$

where

$$\boldsymbol{\delta\beta_1} = (\delta\mu_1, \ldots \delta\mu_{n-1}, \delta\nu_1, \ldots, \delta\nu_{n-1}, \delta\zeta_1, \ldots, \delta\zeta_n)'.$$

Then for $k_{1a} = k_{1a}^{(0)} + \delta k_{1a}$, $k_{1p} = k_{1p}^{(0)} + \delta k_{1p}$, $k_2 = k_2^{(0)} + \delta k_2$ and

$$\boldsymbol{\beta_2} = \begin{pmatrix} k_{1a} \\ k_{1p} \\ k_2 \end{pmatrix}, \quad \boldsymbol{\delta\beta_2} = \begin{pmatrix} \delta k_{1a} \\ \delta k_{1p} \\ \delta k_2 \end{pmatrix},$$

the model constraints

$$g_i\left(\beta_1, \beta_2\right) = -k_{1a}\mu_i - k_{1p}\nu_i + \left(k_2 - \frac{1}{t_{i+1} - t_i}\right)\zeta_i + \frac{1}{t_{i+1} - t_i}\zeta_{i+1} = 0,$$

$i = 1, 2, \ldots, n-1$, can be rewritten in the form

$$g_i(\beta_1,\beta_2) = -\left(k_{1a}^{(0)} + \delta k_{1a}\right)\left(\mu_i^{(0)} + \delta\mu_i\right) - \left(k_{1p}^{(0)} + \delta k_{1p}\right)\left(\nu_i^{(0)} + \delta\nu_i\right)$$
$$+\left(k_2^{(0)} + \delta k_2 - \frac{1}{t_{i+1}-t_i}\right)\left(\zeta_i^{(0)} + \delta\zeta_i\right) + \frac{1}{t_{i+1}-t_i}\left(\zeta_{i+1}^{(0)} + \delta\zeta_{i+1}\right) = 0,$$
$$i = 1,\ldots,n-1.$$

In a matrix form we can write

$$\boldsymbol{g}(\beta_1,\beta_2) = \mathbf{b} + (\mathbf{B}_1,\mathbf{B}_2)\begin{pmatrix}\boldsymbol{\delta\beta_1}\\ \boldsymbol{\delta\beta_2}\end{pmatrix} + \frac{1}{2}\begin{bmatrix}\left(\boldsymbol{\delta\beta_1}',\boldsymbol{\delta\beta_2}'\right)\frac{\partial^2 g_1(\boldsymbol{\beta_1},\boldsymbol{\beta_2})}{\partial\binom{\boldsymbol{\beta_1}}{\boldsymbol{\beta_2}}\partial(\boldsymbol{\beta_1}',\boldsymbol{\beta_2}')}\begin{pmatrix}\boldsymbol{\delta\beta_1}\\ \boldsymbol{\delta\beta_2}\end{pmatrix}\\ \vdots\\ \left(\boldsymbol{\delta\beta_1}',\boldsymbol{\delta\beta_2}'\right)\frac{\partial^2 g_{n-1}(\boldsymbol{\beta_1},\boldsymbol{\beta_2})}{\partial\binom{\boldsymbol{\beta_1}}{\boldsymbol{\beta_2}}\partial(\boldsymbol{\beta_1}',\boldsymbol{\beta_2}')}\begin{pmatrix}\boldsymbol{\delta\beta_1}\\ \boldsymbol{\delta\beta_2}\end{pmatrix}\end{bmatrix},$$

where for $\Delta t_i = t_{i+1} - t_i$, $i = 1,\ldots,n-1$,

$$b_i = -k_{1a}^{(0)}\mu_i^{(0)} - k_{1p}^{(0)}\nu_i^{(0)} + \left(k_2^{(0)} - \frac{1}{\Delta t_i}\right)\zeta_i^{(0)} + \frac{1}{\Delta t_i}\zeta_{i+1}^{(0)}, \quad i = 1,\ldots,n-1,$$

a matrix $\mathbf{B}_1$ is of type $(n-1)\times(3n-2)$ and it should be divided into three blocks

$$\mathbf{B}_1 = \left[-k_{1a}^{(0)}\mathbf{I}_{n-1}, -k_{1p}^{(0)}\mathbf{I}_{n-1}, \boxed{1}\right],$$

where

$$\boxed{1} = \begin{bmatrix} k_2^{(0)} - \frac{1}{\Delta t_1}, & \frac{1}{\Delta t_1}, & 0, & 0, & \ldots, & 0, & 0\\ 0, & k_2^{(0)} - \frac{1}{\Delta t_2}, & \frac{1}{\Delta t_2}, & 0, & \ldots, & 0, & 0\\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots\\ 0, & 0, & 0, & 0, & \ldots, & k_2^{(0)} - \frac{1}{\Delta t_{n-1}}, & \frac{1}{\Delta t_{n-1}} \end{bmatrix},$$

$$\mathbf{B}_2 = \begin{pmatrix} -\mu_1^{(0)}, & -\nu_1^{(0)}, & \zeta_1^{(0)}\\ -\mu_2^{(0)}, & -\nu_2^{(0)}, & \zeta_2^{(0)}\\ \vdots & \vdots & \vdots\\ -\mu_{n-1}^{(0)}, & -\nu_{n-1}^{(0)}, & \zeta_{n-1}^{(0)} \end{pmatrix}.$$

For $i = 1,\ldots,n-1$ the $(3n+1)\times(3n+1)$ matrix

$$\frac{\partial^2 g_i(\boldsymbol{\beta_1},\boldsymbol{\beta_2})}{\partial\begin{pmatrix}\boldsymbol{\beta_1}\\ \boldsymbol{\beta_2}\end{pmatrix}\partial\left(\boldsymbol{\beta_1}',\boldsymbol{\beta_2}'\right)}$$

has almost all elements equal to zero except for

$$\left\{\frac{\partial^2 g_i\left(\boldsymbol{\beta_1},\boldsymbol{\beta_2}\right)}{\partial\begin{pmatrix}\boldsymbol{\beta_1}\\ \boldsymbol{\beta_2}\end{pmatrix}\partial\left(\boldsymbol{\beta_1}',\boldsymbol{\beta_2}'\right)}\right\}_{3n-1,i} = -\frac{1}{2}$$

$$\left\{\frac{\partial^2 g_i\left(\boldsymbol{\beta_1},\boldsymbol{\beta_2}\right)}{\partial\begin{pmatrix}\boldsymbol{\beta_1}\\ \boldsymbol{\beta_2}\end{pmatrix}\partial\left(\boldsymbol{\beta_1}',\boldsymbol{\beta_2}'\right)}\right\}_{3n,n+i-1} = -\frac{1}{2}$$

$$\left\{\frac{\partial^2 g_i\left(\boldsymbol{\beta_1},\boldsymbol{\beta_2}\right)}{\partial\begin{pmatrix}\boldsymbol{\beta_1}\\ \boldsymbol{\beta_2}\end{pmatrix}\partial\left(\boldsymbol{\beta_1}',\boldsymbol{\beta_2}'\right)}\right\}_{3n+1,2n+i-2} = +\frac{1}{2}$$

and the corresponding symmetric elements.

Calculation of estimators of $\delta\boldsymbol{\beta}_1$ and $\delta\boldsymbol{\beta}_2$ is iterative. For initiative iteration we put

$$\mu_i^{(1)} = C_a(t_i), \quad \nu_i^{(1)} = C_p(t_i), \quad \zeta_i^{(1)} = C_L(t_i), \quad i = 1,\ldots,n-1,$$

and $k_{1a}^{(1)}$, $k_{1p}^{(1)}$, $k_2^{(1)}$ are calculated as a solution to a system

$$\mathbf{B}_2\begin{pmatrix}k_{1a}^{(1)}\\ k_{1p}^{(1)}\\ k_2^{(1)}\end{pmatrix} = \begin{pmatrix}\frac{\zeta_1^{(1)}-\zeta_2^{(1)}}{\Delta t_1}\\ \vdots\\ \frac{\zeta_{n-1}^{(1)}-\zeta_n^{(1)}}{\Delta t_{n-1}}\end{pmatrix},$$

i.e. from the model constraints for $\delta\boldsymbol{\beta}_1 = \mathbf{0}$ and $\delta\boldsymbol{\beta}_2 = \mathbf{0}$.

From (5), (6) we calculate the $(k+1)$-th iteration of estimators of $\delta\boldsymbol{\beta}_1$ and $\delta\boldsymbol{\beta}_2$, i.e. in this case

$$\begin{aligned}\delta\boldsymbol{\beta}_1^{(k+1)} &= \mathbf{Z}^{(k)} - \mathbf{B}_1'\left[\mathbf{T} - \mathbf{T}\mathbf{B}_2\left[\mathbf{B}_2'\mathbf{T}\mathbf{B}_2\right]^{-1}\mathbf{B}_2'\mathbf{T}\right]\left(\mathbf{b}^{(k)} + \mathbf{B}_1\mathbf{Z}^{(k)}\right)\\ \delta\boldsymbol{\beta}_2^{(k+1)} &= -\left[\mathbf{B}_2'\mathbf{T}\mathbf{B}_2\right]^{-1}\mathbf{B}_2'\mathbf{T}\left(\mathbf{b}^{(k)} + \mathbf{B}_1\mathbf{Z}^{(k)}\right),\end{aligned}$$

where $\mathbf{T} = (\mathbf{B}_1\mathbf{B}_1' + \mathbf{B}_2\mathbf{B}_2')^{-1}$, $\mathbf{Z}^{(k)} = \mathbf{Y} - \boldsymbol{\beta_1}^{(k)}$, and

$$\mathbf{b}^{(k)} = \mathbf{B_1}\boldsymbol{\beta_1}^{(k)} + \frac{1}{2}\begin{bmatrix}\left(\boldsymbol{\delta\beta_1}^{(k)\prime},\boldsymbol{\delta\beta_2}^{(k)\prime}\right)\frac{\partial^2 g_1\left(\boldsymbol{\beta_1}^{(k)},\boldsymbol{\beta_2}^{(k)}\right)}{\partial\binom{\boldsymbol{\beta_1}}{\boldsymbol{\beta_2}}\partial\left(\boldsymbol{\beta_1}',\boldsymbol{\beta_2}'\right)}\begin{pmatrix}\boldsymbol{\delta\beta_1}^{(k)}\\ \boldsymbol{\delta\beta_2}^{(k)}\end{pmatrix}\\ \vdots\\ \left(\boldsymbol{\delta\beta_1}^{(k)\prime},\boldsymbol{\delta\beta_2}^{(k)\prime}\right)\frac{\partial^2 g_{n-1}\left(\boldsymbol{\beta_1}^{(k)},\boldsymbol{\beta_2}^{(k)}\right)}{\partial\binom{\boldsymbol{\beta_1}}{\boldsymbol{\beta_2}}\partial\left(\boldsymbol{\beta_1}',\boldsymbol{\beta_2}'\right)}\begin{pmatrix}\boldsymbol{\delta\beta_1}^{(k)}\\ \boldsymbol{\delta\beta_2}^{(k)}\end{pmatrix}\end{bmatrix}.$$

The matrices $\mathbf{B}_1$, $\mathbf{B}_2$ are constructed with the k-th iteration of the parameters $\boldsymbol{\beta_1}$, $\boldsymbol{\beta_2}$ obtained from

$$\begin{aligned}\boldsymbol{\beta_1}^{(k)} &= \boldsymbol{\beta_1}^{(k-1)} + \boldsymbol{\delta\beta_1}^{(k)},\\ \boldsymbol{\beta_2}^{(k)} &= \boldsymbol{\beta_2}^{(k-1)} + \boldsymbol{\delta\beta_2}^{(k)}.\end{aligned}$$

Estimators of covariance matrices of the final estimators $\widehat{\widehat{\boldsymbol{\delta\beta_1}}}$, $\widehat{\widehat{\boldsymbol{\delta\beta_2}}}$ are calculated from (3), (4), i.e. in this case ($\mathbf{C} = \sigma^{-2}\mathbf{I}$)

$$\begin{aligned}\widehat{\mathrm{var}(\widehat{\widehat{\boldsymbol{\delta\beta_1}}})} = \widehat{\mathrm{var}(\widehat{\widehat{\boldsymbol{\beta_1}}})} &= \widehat{\sigma^2}\left(\mathbf{M}_{\mathbf{B}_1'\mathbf{M}_{\mathbf{B_2}}}\mathbf{M}_{\mathbf{B}_1'\mathbf{M}_{\mathbf{B_2}}}\right)^+,\\ \widehat{\mathrm{var}(\widehat{\widehat{\boldsymbol{\delta\beta_2}}})} = \widehat{\mathrm{var}(\widehat{\widehat{\boldsymbol{\beta_2}}})} &= \widehat{\sigma^2}\left(\left[\mathbf{B}_2'\left(\mathbf{B}_1\mathbf{B}_1' + \mathbf{B}_2\mathbf{B}_2'\right)^{-1}\mathbf{B}_2\right]^{-1} - \mathbf{I}\right),\end{aligned}$$

where

$$\widehat{\sigma^2} = \frac{\left(\mathbf{Y} - \widehat{\widehat{\boldsymbol{\beta_1}}}\right)'\left(\mathbf{Y} - \widehat{\widehat{\boldsymbol{\beta_1}}}\right)}{n + q - (k_1 + k_2)}$$

and

$$\left(\mathbf{M}_{\mathbf{B}_1'\mathbf{M}_{\mathbf{B_2}}}\mathbf{M}_{\mathbf{B}_1'\mathbf{M}_{\mathbf{B_2}}}\right)^+ = \left(\mathbf{I} - \mathbf{B}_1\left[\mathbf{M}_{\mathbf{B_2}}\mathbf{B}_1\mathbf{B}_1'\mathbf{M}_{\mathbf{B_2}}\right]^+\mathbf{B}_1\right).$$

For data from the graphic example in [4] (values of tracer concentration in liver, artery and portal vein measures at 23 times—see Table 1 and Fig. 4), i.e. for $n = 23$, $q = n - 1 = 22$, $k_1 = 3n - 2 = 67$ and $k_2 = 3$, we get these results after 4 iterations:

$$\widehat{\widehat{\boldsymbol{\beta_2}}} = \begin{pmatrix} 0.002431475 \\ 0.009413782 \\ 0.039506253 \end{pmatrix},$$

$$\widehat{\sigma^2} = 0.001130171,$$

$$\mathrm{var}\left(\widehat{\widehat{\boldsymbol{\beta_2}}}\right) = \mathrm{var}\left(\widehat{\widehat{\boldsymbol{\delta\beta_2}}}\right)$$

$$= \begin{pmatrix} 3.238255e-07 & -6.991068e-07 & -2.103772e-06 \\ -6.991068e-07 & 3.001722e-06 & 1.255561e-05 \\ -2.103772e-06 & 1.255561e-05 & 5.826697e-05 \end{pmatrix}.$$

Among the results we were interested only in the vector of kinetics parameters $\boldsymbol{\beta_2}$, because they seem to be important for early diagnosis of substantional liver diseases.

In Fig. 5 there are discrete points of measured tracer concentration in liver and a curve of the tracer concentration in liver estimated from the model (i.e. $\zeta_1, \ldots, \zeta_n$ values).

Now we calculate the measure of nonlinearity $\mathcal{C}^{II}_{ell,\delta\boldsymbol{\beta}_2}$ by algorithm mentioned in [1] (pp. 230–231) with the value of δ_0 from (10) set at $\epsilon = 0.04$. The value of

$$\frac{\sqrt{\delta_0}}{\mathcal{C}^{II}_{ell,\delta\boldsymbol{\beta}_2}} = \frac{\sqrt{1.570312}}{0.04511495} = 27.77618$$

is compared with the value of $\chi^2_{48}(0; 0.95) = 65.17077$. From the numerical results it is obvious that the condition mentioned in (12) is not satisfied, i.e. for our data set it is not suitable to linearize the original nonlinear model and work with the estimators of kinetics coefficients obtained from the linearized model, although these estimators seem to be very accurate. If the estimated parameter $\widehat{\sigma}$ was three times lower, which might be accomplished by more accurate measurement or by measurement in shorter time intervals, the condition would be satisfied and linearization would be appropriate.

i	t_i [s]	$C_L(t_i)$ [mmol/l]	$C_a(t_i)$ [mmol/l]	$C_p(t_i)$ [mmol/l]
1	0.00	0.000	0.000	0.00
2	3.30	0.000	0.000	0.00
3	6.75	0.000	2.350	0.00
4	10.00	0.000	4.230	0.07
5	13.25	0.030	4.350	0.19
6	16.75	0.111	3.620	0.68
7	20.00	0.156	2.440	1.36
8	23.50	0.126	1.600	1.88
9	26.75	0.204	1.220	2.11
10	30.00	0.309	1.220	2.49
11	33.50	0.294	1.500	2.30
12	36.75	0.360	2.000	2.21
13	40.50	0.378	2.230	2.26
14	43.50	0.411	2.162	2.21
15	47.00	0.489	1.970	2.40
16	50.50	0.519	1.790	2.28
17	54.00	0.561	1.600	2.35
18	57.00	0.516	1.480	2.26
19	60.50	0.618	1.580	2.23
20	64.00	0.543	1.530	2.16
21	67.00	0.561	1.620	2.26
22	70.50	0.510	1.430	2.16
23	74.00	0.600	1.430	2.07

Table 1: Measured data of tracer concentration.

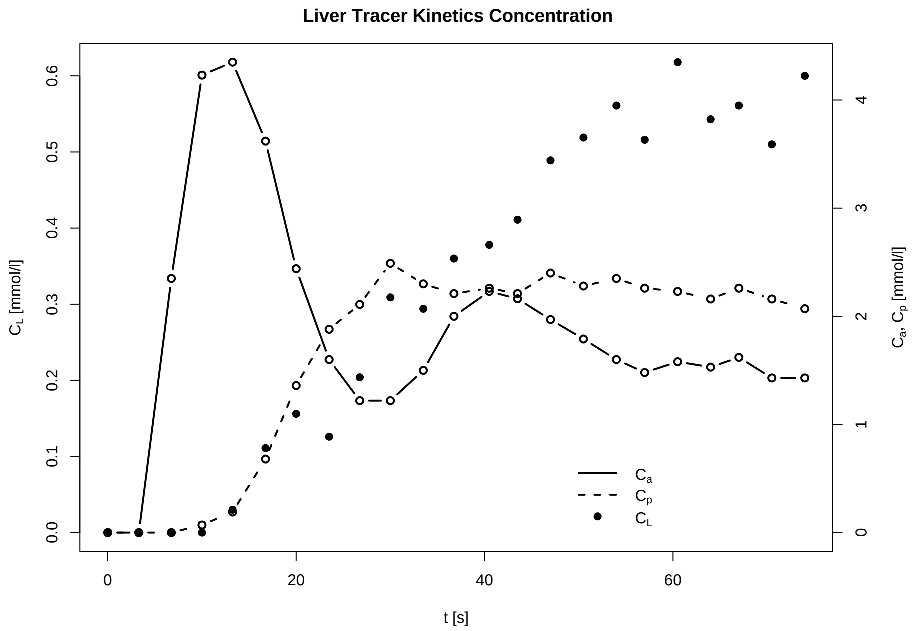

Figure 4: Curves of measured tracer concentration in a liver artery $C_a(t)$ and a portal vein $C_p(t)$ and points of measured tracer concentration in liver $C_L(t)$.

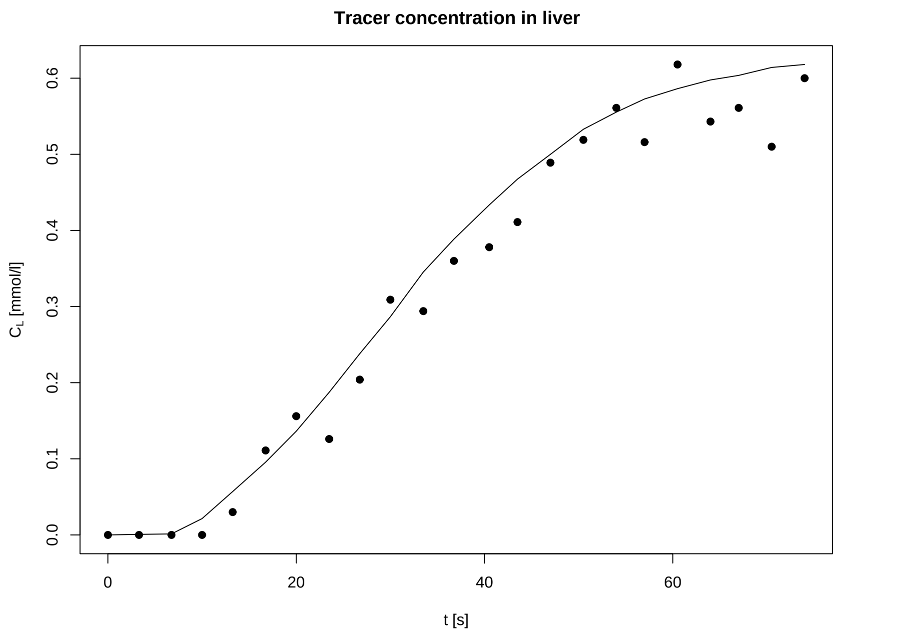

Figure 5: Measured (points) and estimated (a curve) tracer concentration in liver.

5 Conclusions

Many real-life systems are basicaly nonlinear. Particularly in biology and medicine we meet nonlinear problems very often. By treating them as linear we employ a very rough and limited approximation [5]. There are many methods that solve nonlinear problems, mostly numerical methods, but these usualy suppose accurate measurements, and they do not take into consideration inaccuracy and uncertainty inherent in biology and medicine settings (subjective examination, inter- or intraobjective variability and so on). One way out is to apply linearization of nonlinear problems, for example the above-mentioned linearization via Taylor series, to use the well-known and well-explored theory of linear models. We know how to estimate parameters and their variability in the linearized models [1]. However, we should check whether the type of problem and measured data allow for treating the nonlinear problem in this way.

The aim of this article was to find a condition which would guarantee for linear models with type II constraints that the true values of estimated parameters are covered by a modified confidence ellipsoid (with probability no less than $1 - \alpha - \epsilon$ for a preset small $\epsilon > 0$), and to verify in this manner that the usage of linearization is appropriate. As can be seen in the numerical example, this condition is not easy to satisfy, although calculated estimators (and their variances) in the linearized model look very good. When solving a nonlinear problem by linearization we should proove that the linearization is safe. In case of linear models with type II constraints a method of such verification was presented here.

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