Online Appendices to:

ROBUST DESIGNS FOR DOSE-RESPONSE STUDIES: MODEL AND LABELLING ROBUSTNESS

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Appendix 1: Calculations for Theorem 3

We have

$$
\begin{aligned}
\frac{d}{dt}\boldsymbol{R}^{-1}(\xi_t)_{|t=0} &= -\boldsymbol{R}^{-1}(\xi_0)\left\{\frac{d}{dt}\boldsymbol{R}(\xi_t)_{|t=0}\right\}\boldsymbol{R}^{-1}(\xi_0),\\
&= -\boldsymbol{R}^{-1}(\xi_0)\left\{\begin{array}{c}\left[\frac{d}{dt}\boldsymbol{A}(\xi_t)_{|t=0}\right]\boldsymbol{B}^{-1}(\xi_t)_{|t=0}\,\boldsymbol{A}(\xi_t)_{|t=0}\\ -\boldsymbol{A}(\xi_t)_{|t=0}\,\boldsymbol{B}^{-1}(\xi_t)_{|t=0}\left[\frac{d}{dt}\boldsymbol{B}(\xi_t)_{|t=0}\right]\boldsymbol{B}^{-1}(\xi_t)_{|t=0}\,\boldsymbol{A}(\xi_t)_{|t=0}\\ +\boldsymbol{A}(\xi_t)_{|t=0}\,\boldsymbol{B}^{-1}(\xi_t)\left[\frac{d}{dt}\boldsymbol{A}(\xi_t)_{|t=0}\right]\end{array}\right\}\boldsymbol{R}^{-1}(\xi_0)\\
&= -\boldsymbol{R}^{-1}(\xi_0)\left\{\begin{array}{c}\left[\boldsymbol{A}(\xi_1)-\boldsymbol{A}(\xi_0)\right]\boldsymbol{B}^{-1}(\xi_0)\,\boldsymbol{A}(\xi_0)\\ -\boldsymbol{A}(\xi_0)\,\boldsymbol{B}^{-1}(\xi_0)\left[\boldsymbol{B}(\xi_1)-\boldsymbol{B}(\xi_0)\right]\boldsymbol{B}^{-1}(\xi_0)\,\boldsymbol{A}(\xi_0)\\ +\boldsymbol{A}(\xi_0)\,\boldsymbol{B}^{-1}(\xi_0)\left[\boldsymbol{A}(\xi_1)-\boldsymbol{A}(\xi_0)\right]\end{array}\right\}\boldsymbol{R}^{-1}(\xi_0)\\
&= -\boldsymbol{R}^{-1}(\xi_0)\,\boldsymbol{A}(\xi_1)\,\boldsymbol{B}^{-1}(\xi_0)\,\boldsymbol{A}(\xi_0)\,\boldsymbol{R}^{-1}(\xi_0)+\boldsymbol{R}^{-1}(\xi_0)\\
&\quad +\boldsymbol{R}^{-1}(\xi_0)\,\boldsymbol{A}(\xi_0)\,\boldsymbol{B}^{-1}(\xi_0)\,\boldsymbol{B}(\xi_1)\,\boldsymbol{B}^{-1}(\xi_0)\,\boldsymbol{A}(\xi_0)\,\boldsymbol{R}^{-1}(\xi_0)-\boldsymbol{R}^{-1}(\xi_0)\\
&\quad -\boldsymbol{R}^{-1}(\xi_0)\,\boldsymbol{A}(\xi_0)\,\boldsymbol{B}^{-1}(\xi_0)\,\boldsymbol{A}(\xi_1)\,\boldsymbol{R}^{-1}(\xi_0)+\boldsymbol{R}^{-1}(\xi_0)\\
&= -\boldsymbol{R}^{-1}(\xi_0)\,\boldsymbol{A}(\xi_1)\,\boldsymbol{A}^{-1}(\xi_0)+\boldsymbol{R}^{-1}(\xi_0)\\
&\quad +\boldsymbol{A}^{-1}(\xi_0)\,\boldsymbol{A}(\xi_1)\,\boldsymbol{R}^{-1}(\xi_0)-\boldsymbol{A}^{-1}(\xi_0)\,\boldsymbol{A}(\xi_1)\,\boldsymbol{A}^{-1}(\xi_0),
\end{aligned}
$$

whence

$$
\frac{d}{dt}tr\boldsymbol{R}^{-1}(\xi_t)_{|t=0} = tr\boldsymbol{R}^{-1}(\xi_0) - tr\left\{2\boldsymbol{R}^{-1}(\xi_0)\,\boldsymbol{A}(\xi_1)\,\boldsymbol{A}^{-1}(\xi_0)-\boldsymbol{A}^{-1}(\xi_0)\,\boldsymbol{A}(\xi_1)\,\boldsymbol{A}^{-1}(\xi_0)\right\}
$$

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The final trace is

$$\begin{aligned}
& tr\left\{2\boldsymbol{R}^{-1}(\xi_0)\,\boldsymbol{A}(\xi_1)\,\boldsymbol{A}^{-1}(\xi_0) - \boldsymbol{A}^{-1}(\xi_0)\,\boldsymbol{B}(\xi_1)\,\boldsymbol{A}^{-1}(\xi_0)\right\} \\
= & \sum_{i=1}^{N} \xi_{1,i}\left[tr\left\{\alpha_i 2\boldsymbol{R}^{-1}(\xi_0)\,\boldsymbol{q}_i\boldsymbol{q}_i'\boldsymbol{A}^{-1}(\xi_0) - w_i\alpha_i\boldsymbol{A}^{-1}(\xi_0)\,\boldsymbol{q}_i\boldsymbol{q}_i'\boldsymbol{A}^{-1}(\xi_0)\right\}\right] \\
= & \sum_{i=1}^{N} \xi_{1,i}\left[2\alpha_i\boldsymbol{q}_i'\boldsymbol{A}^{-1}(\xi_0)\,\boldsymbol{R}^{-1}(\xi_0)\,\boldsymbol{q}_i - w_i\alpha_i\boldsymbol{q}_i'\boldsymbol{A}^{-1}(\xi_0)\,\boldsymbol{A}^{-1}(\xi_0)\,\boldsymbol{q}_i\right] \\
= & \sum_{i=1}^{N} \xi_{1,i}\left\{2\boldsymbol{D}_\alpha\mathbf{Q}_1\boldsymbol{A}^{-1}(\xi_0)\,\boldsymbol{R}^{-1}(\xi_0)\,\mathbf{Q}_1' - \boldsymbol{D}_w\boldsymbol{D}_\alpha\mathbf{Q}_1\boldsymbol{A}^{-1}(\xi_0)\,\boldsymbol{A}^{-1}(\xi_0)\,\mathbf{Q}_1'\right\}_{ii}.
\end{aligned}$$

Thus

$$\frac{d}{dt}tr\boldsymbol{R}^{-1}(\xi_t)_{|_{t=0}} = tr\boldsymbol{R}^{-1}(\xi_0) - \sum_{i=1}^{N}\xi_{1,i}\left\{2\boldsymbol{D}_\alpha\mathbf{Q}_1\boldsymbol{A}^{-1}(\xi_0)\,\boldsymbol{R}^{-1}(\xi_0)\,\mathbf{Q}_1' - \boldsymbol{D}_w\boldsymbol{D}_\alpha\mathbf{Q}_1\boldsymbol{A}^{-2}(\xi_0)\,\mathbf{Q}_1'\right\}_{ii}.$$

With $\boldsymbol{P}(\xi_t) = \boldsymbol{A}^{-1}(\xi_t)\,\boldsymbol{S}(\xi_t) : d \times N - d$, we have $\boldsymbol{U}_*(\xi_t) = \boldsymbol{P}'(\xi_t)\,\boldsymbol{P}(\xi_t)$, with

$$\begin{aligned}
& \frac{d}{dt}\boldsymbol{b}'\left[\frac{d}{dt}\boldsymbol{U}_*(\xi_t)_{|_{t=0}}\right]\boldsymbol{b} \\
= & 2\boldsymbol{b}'\boldsymbol{P}'(\xi_0)\left[\frac{d}{dt}\boldsymbol{P}(\xi_t)_{|_{t=0}}\right]\boldsymbol{b} \\
= & 2\boldsymbol{b}'\boldsymbol{P}'(\xi_0)\left[\frac{d}{dt}\boldsymbol{A}^{-1}(\xi_t)_{|_{t=0}}\boldsymbol{S}(\xi_0) + \boldsymbol{A}^{-1}(\xi_0)\,\frac{d}{dt}\boldsymbol{S}(\xi_t)\right]\boldsymbol{b} \\
= & 2\boldsymbol{b}'\boldsymbol{P}'(\xi_0)\left[-\left\{\boldsymbol{A}^{-1}(\xi_0)\,(\boldsymbol{A}(\xi_1) - \boldsymbol{A}(\xi_0))\,\boldsymbol{A}^{-1}(\xi_0)\right\}\boldsymbol{S}(\xi_0) + \boldsymbol{A}^{-1}(\xi_0)\,(\boldsymbol{S}(\xi_1) - \boldsymbol{S}(\xi_0))\right]\boldsymbol{b} \\
= & 2\boldsymbol{b}'\boldsymbol{P}'(\xi_0)\,\boldsymbol{A}^{-1}(\xi_0)\,\{\boldsymbol{S}(\xi_1) - \boldsymbol{A}(\xi_1)\,\boldsymbol{P}(\xi_0)\}\,\boldsymbol{b} \\
= & 2\sum_{i=1}^{N}\xi_{1,i}\left\{\boldsymbol{b}'\boldsymbol{P}'(\xi_0)\,\boldsymbol{A}^{-1}(\xi_0)\,\boldsymbol{q}_i\boldsymbol{e}_i'\boldsymbol{D}_\alpha\mathbf{Q}_2\boldsymbol{b} - \alpha_i\boldsymbol{b}'\boldsymbol{P}'(\xi_0)\,\boldsymbol{A}^{-1}(\xi_0)\,\boldsymbol{q}_i\boldsymbol{q}_i'\boldsymbol{P}(\xi_0)\,\boldsymbol{b}\right\} \\
= & 2\sum_{i=1}^{N}\xi_{1,i}\left\{\boldsymbol{e}_i'\boldsymbol{D}_\alpha\mathbf{Q}_2\boldsymbol{b}\boldsymbol{b}'\boldsymbol{P}'(\xi_0)\,\boldsymbol{A}^{-1}(\xi_0)\,\boldsymbol{q}_i - \alpha_i\boldsymbol{q}_i'\boldsymbol{P}(\xi_0)\,\boldsymbol{b}\boldsymbol{b}'\boldsymbol{P}'(\xi_0)\,\boldsymbol{A}^{-1}(\xi_0)\,\boldsymbol{q}_i\right\} \\
= & 2\sum_{i=1}^{N}\xi_{1,i}\left\{\boldsymbol{D}_\alpha\mathbf{Q}_2\boldsymbol{b}\boldsymbol{b}'\boldsymbol{P}'(\xi_0)\,\boldsymbol{A}^{-1}(\xi_0)\,\mathbf{Q}_1' - \boldsymbol{D}_\alpha\mathbf{Q}_1\boldsymbol{P}(\xi_0)\,\boldsymbol{b}\boldsymbol{b}'\boldsymbol{P}'(\xi_0)\,\boldsymbol{A}^{-1}(\xi_0)\,\mathbf{Q}_1'\right\}_{ii} \\
= & 2\sum_{i=1}^{N}\xi_{1,i}\left\{\boldsymbol{D}_\alpha\left[\mathbf{Q}_2 - \mathbf{Q}_1\boldsymbol{A}^{-1}(\xi_0)\,\boldsymbol{S}(\xi_0)\right]\boldsymbol{b}\boldsymbol{b}'\boldsymbol{S}'(\xi_0)\,\boldsymbol{A}^{-2}(\xi_0)\,\mathbf{Q}_1'\right\}_{ii}.
\end{aligned}$$

By Theorem 1 of Magnus (1985), $\lambda(\xi_t)$ is differentiable, with

$$
\begin{aligned}
\frac{d}{dt}\lambda(\xi_t)_{|_{t=0}} &= z'(\xi_0)\left[\frac{d}{dt}\boldsymbol{U}(\xi_t)\right]_{|_{t=0}} z(\xi_0) \\
&= 2z'(\xi_0)\left\{\begin{array}{c} \left[\frac{d}{dt}\boldsymbol{A}^{-1}(\xi_t)_{|_{t=0}}\right]\boldsymbol{Q}_1'\boldsymbol{D}_{\xi_t}^2\boldsymbol{D}_\alpha^2\mathbf{Q}_1\boldsymbol{A}^{-1}(\xi_t)_{|_{t=0}} \\ +\boldsymbol{A}^{-1}(\xi_t)_{|_{t=0}}\left[\frac{d}{dt}\boldsymbol{Q}_1'\boldsymbol{D}_{\xi_t}\boldsymbol{D}_\alpha\right]\boldsymbol{D}_\alpha\boldsymbol{D}_\xi\mathbf{Q}_1\boldsymbol{A}^{-1}(\xi_t)_{|_{t=0}} \end{array}\right\} z(\xi_0) \\
&= 2z'(\xi_0)\left\{\begin{array}{c} -\boldsymbol{A}^{-1}(\xi_0)\left[\boldsymbol{A}(\xi_1)-\boldsymbol{A}(\xi_0)\right]\boldsymbol{A}^{-1}(\xi_0)\boldsymbol{Q}_1'\boldsymbol{D}_{\xi_0}^2\boldsymbol{D}_\alpha^2\mathbf{Q}_1\boldsymbol{A}^{-1}(\xi_0) \\ +\boldsymbol{A}^{-1}(\xi_0)\boldsymbol{Q}_1'\left[\boldsymbol{D}_{\xi_1}-\boldsymbol{D}_{\xi_0}\right]\boldsymbol{D}_\alpha^2\boldsymbol{D}_{\xi_0}\mathbf{Q}_1\boldsymbol{A}^{-1}(\xi_0) \end{array}\right\} z(\xi_0) \\
&= 2z'(\xi_0)\left\{\begin{array}{c} -\boldsymbol{A}^{-1}(\xi_0)\boldsymbol{A}(\xi_1)\boldsymbol{A}^{-1}(\xi_0)\boldsymbol{Q}_1'\boldsymbol{D}_{\xi_0}^2\boldsymbol{D}_\alpha^2\mathbf{Q}_1\boldsymbol{A}^{-1}(\xi_0) \\ +\boldsymbol{A}^{-1}(\xi_0)\boldsymbol{Q}_1'\boldsymbol{D}_{\xi_0}^2\boldsymbol{D}_\alpha^2\mathbf{Q}_1\boldsymbol{A}^{-1}(\xi_0) \\ +\boldsymbol{A}^{-1}(\xi_0)\boldsymbol{Q}_1'\boldsymbol{D}_{\xi_1}\boldsymbol{D}_\alpha^2\boldsymbol{D}_{\xi_0}\mathbf{Q}_1\boldsymbol{A}^{-1}(\xi_0) \\ -\boldsymbol{A}^{-1}(\xi_0)\boldsymbol{Q}_1'\boldsymbol{D}_{\xi_0}\boldsymbol{D}_\alpha^2\boldsymbol{D}_{\xi_0}\mathbf{Q}_1\boldsymbol{A}^{-1}(\xi_0) \end{array}\right\} z(\xi_0) \\
&= -2z'(\xi_0)\left\{\begin{array}{c} \boldsymbol{A}^{-1}(\xi_0)\boldsymbol{A}(\xi_1)\boldsymbol{A}^{-1}(\xi_0)\boldsymbol{Q}_1'\boldsymbol{D}_{\xi_0}^2\boldsymbol{D}_\alpha^2\mathbf{Q}_1\boldsymbol{A}^{-1}(\xi_0) \\ -\boldsymbol{A}^{-1}(\xi_0)\boldsymbol{Q}_1'\boldsymbol{D}_{\xi_1}\boldsymbol{D}_\alpha^2\boldsymbol{D}_{\xi_0}\mathbf{Q}_1\boldsymbol{A}^{-1}(\xi_0) \end{array}\right\} z(\xi_0)
\end{aligned}
$$

$$
\begin{aligned}
&= -2\boldsymbol{c}'(\xi_0)\left\{\boldsymbol{A}(\xi_1)\boldsymbol{A}^{-1}(\xi_0)\boldsymbol{Q}_1'\boldsymbol{D}_{\xi_0}^2\boldsymbol{D}_\alpha^2\mathbf{Q}_1-\boldsymbol{Q}_1'\boldsymbol{D}_{\xi_1}\boldsymbol{D}_\alpha^2\boldsymbol{D}_{\xi_0}\mathbf{Q}_1\right\}\boldsymbol{c}(\xi_0) \\
&= -2\sum_{i=1}^N \xi_{1,i}\boldsymbol{c}'(\xi)\left\{\alpha_i\boldsymbol{q}_i\cdot\boldsymbol{q}_i'\boldsymbol{A}^{-1}(\xi_0)\boldsymbol{Q}_1'\boldsymbol{D}_{\xi_0}^2\boldsymbol{D}_\alpha^2\mathbf{Q}_1-\alpha_i^2\boldsymbol{Q}_1'\boldsymbol{e}_i\cdot\boldsymbol{e}_i'\boldsymbol{D}_{\xi_0}\mathbf{Q}_1\right\}\boldsymbol{c}(\xi) \\
&= -\sum_{i=1}^N \xi_{1,i}\left\{\begin{array}{c} \alpha_i\boldsymbol{q}_i'\boldsymbol{A}^{-1}(\xi_0)\boldsymbol{Q}_1'\boldsymbol{D}_{\xi_0}^2\boldsymbol{D}_\alpha^2\mathbf{Q}_1\cdot 2\boldsymbol{c}(\xi)\boldsymbol{c}'(\xi)\cdot\boldsymbol{q}_i \\ -\alpha_i^2\boldsymbol{e}_i'\boldsymbol{D}_{\xi_0}\mathbf{Q}_1\cdot 2\boldsymbol{c}(\xi)\boldsymbol{c}'(\xi)\cdot\boldsymbol{Q}_1'\boldsymbol{e}_i \end{array}\right\} \\
&= -\sum_{i=1}^N \xi_{1,i}\left\{\boldsymbol{D}_\alpha\mathbf{Q}_1\boldsymbol{A}^{-1}(\xi_0)\boldsymbol{Q}_1'\boldsymbol{D}_{\xi_0}^2\boldsymbol{D}_\alpha^2\mathbf{Q}_1\boldsymbol{C}(\xi_0)\boldsymbol{Q}_1'-\boldsymbol{D}_\alpha^2\boldsymbol{D}_{\xi_0}\mathbf{Q}_1\boldsymbol{C}(\xi_0)\boldsymbol{Q}_1'\right\}_{ii} \\
&= -\sum_{i=1}^N \xi_{1,i}\left\{\boldsymbol{D}_\alpha\mathbf{Q}_1\boldsymbol{U}(\xi_0)\boldsymbol{A}(\xi_0)\boldsymbol{C}(\xi_0)\boldsymbol{Q}_1'-\boldsymbol{D}_\alpha^2\boldsymbol{D}_{\xi_0}\mathbf{Q}_1\boldsymbol{C}(\xi_0)\boldsymbol{Q}_1'\right\}_{ii}.
\end{aligned}
$$

This gives the required result, with $\boldsymbol{C}(\xi_0)=2\boldsymbol{c}(\xi)\boldsymbol{c}'(\xi)$ and

$$
\begin{aligned}
\boldsymbol{T}^{(0)}(\boldsymbol{\xi},\boldsymbol{\theta}_0) &= \left[2\boldsymbol{D}_\alpha\mathbf{Q}_1\boldsymbol{A}^{-1}(\xi_0)\boldsymbol{R}^{-1}(\xi_0)\mathbf{Q}_1'-\boldsymbol{D}_w\boldsymbol{D}_\alpha\mathbf{Q}_1\boldsymbol{A}^{-2}(\xi_0)\mathbf{Q}_1'\right] \\
\boldsymbol{T}^{(1)}(\boldsymbol{\xi},\boldsymbol{\theta}_0) &= \left[\boldsymbol{D}_\alpha\mathbf{Q}_1\boldsymbol{U}(\xi_0)\boldsymbol{A}(\xi_0)\boldsymbol{C}(\xi_0)\boldsymbol{Q}_1'-\boldsymbol{D}_\alpha^2\boldsymbol{D}_{\xi_0}\mathbf{Q}_1\boldsymbol{C}(\xi_0)\boldsymbol{Q}_1'\right], \\
\boldsymbol{T}^{(2)}(\boldsymbol{\xi};\boldsymbol{\theta}) &= \left[2\boldsymbol{D}_\alpha(\boldsymbol{\theta})\left\{\mathbf{Q}_1\boldsymbol{A}^{-1}(\xi;\boldsymbol{\theta})\boldsymbol{S}(\xi;\boldsymbol{\theta}_0)-\mathbf{Q}_2\right\}\boldsymbol{b}(\boldsymbol{\theta})\boldsymbol{b}'(\boldsymbol{\theta})\boldsymbol{S}'(\xi;\boldsymbol{\theta}_0)\boldsymbol{A}^{-2}(\xi;\boldsymbol{\theta}_0)\mathbf{Q}_1'\right].
\end{aligned}
$$

We have

$$
\begin{aligned}
tr\boldsymbol{D}_{\xi_0}\boldsymbol{T}^{(0)}(\boldsymbol{\xi}_0) &= tr\left[2\boldsymbol{D}_{\xi_0}\boldsymbol{D}_{\alpha}\mathbf{Q}_1\boldsymbol{A}^{-1}(\xi_0)\,\boldsymbol{R}^{-1}(\xi_0)\,\mathbf{Q}_1' - \boldsymbol{D}_{\xi_0}\boldsymbol{D}_{w}\boldsymbol{D}_{\alpha}\mathbf{Q}_1\boldsymbol{A}^{-2}(\xi_0)\,\mathbf{Q}_1'\right] \\
&= tr\left[2\boldsymbol{R}^{-1}(\xi_0) - \boldsymbol{A}^{-1}(\xi_0)\,\boldsymbol{B}(\xi_0)\,\boldsymbol{A}^{-1}(\xi_0)\right] \\
&= tr\boldsymbol{R}^{-1}(\xi_0)\,; \\
tr\boldsymbol{D}_{\xi_0}\boldsymbol{T}^{(1)}(\boldsymbol{\xi}_0) &= tr\left[\boldsymbol{D}_{\xi_0}\boldsymbol{D}_{\alpha}\mathbf{Q}_1\boldsymbol{U}(\xi_0)\,\boldsymbol{A}(\xi_0)\,\boldsymbol{C}(\xi_0)\,\boldsymbol{Q}_1' - \boldsymbol{D}_{\xi_0}\boldsymbol{D}_{\alpha}^2\boldsymbol{D}_{\xi_0}\mathbf{Q}_1\boldsymbol{C}(\xi_0)\,\boldsymbol{Q}_1'\right] \\
&= tr\left[\boldsymbol{A}(\xi_0)\,\boldsymbol{U}(\xi_0)\,\boldsymbol{A}(\xi_0)\,\boldsymbol{C}(\xi_0) - \boldsymbol{A}(\xi_0)\,\boldsymbol{U}(\xi_0)\,\boldsymbol{A}(\xi_0)\,\boldsymbol{C}(\xi_0)\right] \\
&= 0; \\
tr\boldsymbol{D}_{\xi_0}\boldsymbol{T}^{(2)}(\boldsymbol{\xi}_0) &= tr\left[2\boldsymbol{D}_{\xi_0}\boldsymbol{D}_{\alpha}(\boldsymbol{\theta})\left\{\mathbf{Q}_1\boldsymbol{A}^{-1}(\xi;\boldsymbol{\theta})\,\boldsymbol{S}(\xi;\boldsymbol{\theta}_0) - \mathbf{Q}_2\right\}\boldsymbol{b}(\boldsymbol{\theta})\,\boldsymbol{b}'(\boldsymbol{\theta})\,\boldsymbol{S}'(\xi;\boldsymbol{\theta}_0)\,\boldsymbol{A}^{-2}(\xi;\boldsymbol{\theta}_0)\,\mathbf{Q}_1'\right] \\
&= tr\left[\begin{array}{c} 2\boldsymbol{A}^{-1}(\xi;\boldsymbol{\theta}_0)\,\mathbf{Q}_1'\boldsymbol{D}_{\xi_0}\boldsymbol{D}_{\alpha}(\boldsymbol{\theta})\left\{\mathbf{Q}_1\boldsymbol{A}^{-1}(\xi;\boldsymbol{\theta})\,\boldsymbol{S}(\xi;\boldsymbol{\theta}_0) - \mathbf{Q}_2\right\}\cdot \\ \boldsymbol{b}(\boldsymbol{\theta})\,\boldsymbol{b}'(\boldsymbol{\theta})\,\boldsymbol{S}'(\xi;\boldsymbol{\theta}_0)\,\boldsymbol{A}^{-1}(\xi;\boldsymbol{\theta}_0) \end{array}\right] \\
&= tr\left[2\boldsymbol{A}^{-1}(\xi;\boldsymbol{\theta})\left\{\boldsymbol{S}(\xi;\boldsymbol{\theta}_0) - \boldsymbol{S}(\xi;\boldsymbol{\theta}_0)\right\}\cdot\boldsymbol{b}(\boldsymbol{\theta})\,\boldsymbol{b}'(\boldsymbol{\theta})\,\boldsymbol{S}'(\xi;\boldsymbol{\theta}_0)\,\boldsymbol{A}^{-1}(\xi;\boldsymbol{\theta}_0)\right] \\
&= 0.
\end{aligned}
$$

Appendix 2: Simulated comparisons

The following procedure was carried out 50 times in each of §1 – §3. The tables give the values of $\mathcal{L}_{\nu_1,\nu_2}(\xi_n;\boldsymbol{\theta}_0)$ (the minimized maximum loss) for various choices of ν_1, ν_2 together with the $\textsc{bias} = \left\| aver\boldsymbol{F}\left(\hat{\boldsymbol{\theta}} - \boldsymbol{\theta}_0\right)\right\|$ and total root-$\textsc{mse} = \left(aver\left\|\boldsymbol{F}\left(\hat{\boldsymbol{\theta}} - \boldsymbol{\theta}_0\right)\right\|^2\right)^{1/2}$, for weights w_0, w_1, w_2, w_3 respectively. We compared the logistic link $(G_0(t) = 1/(1+e^{-t}))$ to the probit $(G_0(t) = \Phi(t))$. To facilitate comparisons between the links, they were normalized to have unit variance: $G(t) = G_0(\sigma t)$. We took $n_{init} = 20$, $n_{final} = 200$. In order that the two types of error have about the same effect on $\left\|F\left(\boldsymbol{\theta}_\gamma - \boldsymbol{\theta}_0\right) + \boldsymbol{\psi}\right\|$ we took $\tau_1 = 15,\ \tau_2 = 1$.

In §1 the design points, after the first $n_{init} = 20$, were chosen at random. In §2 the values in parentheses are the averages over 50 adaptive designs, using simulated responses. The MSE values for sequential designs are based on estimates computed from the initial samples. In §3 the algorithm was run to convergence.

§1 Random designs; sequential and adaptive procedures

Table C1a. Weights $w_0(\boldsymbol{x})$.

Link↓	(ν_1,ν_2) :	$(0,0)$	$(.25,.25)$	$(.45,.45)$	$(.90,0)$	$(0,.90)$
	$\mathcal{L}_{\nu_1,\nu_2}$	489 (488)	251 (251)	52 (52)	50 (50)	53 (54)
Logistic	BIAS	27 (.43)	20 (.67)	20 (.65)	18 (.71)	16 (.61)
	$\sqrt{\text{MSE}}$	79 (1.81)	45 (1.77)	41 (1.78)	31 (1.78)	28 (1.76)
	$\mathcal{L}_{\nu_1,\nu_2}$	516 (520)	264 (262)	54 (53)	53 (53)	54 (55)
Probit	BIAS	28 (3.14)	19 (4.18)	18 (.59)	18(1.67)	18 (.51)
	$\sqrt{\text{MSE}}$	68 (18.74)	37 (26.88)	36 (1.72)	32 (11.07)	34 (1.66)

Table C1b. Weights $w_1(\boldsymbol{x})$.

Link↓	(ν_1,ν_2) :	$(0,0)$	$(.25,.25)$	$(.45,.45)$	$(.90,0)$	$(0,.90)$
	$\mathcal{L}_{\nu_1,\nu_2}$	513 (513)	264 (261)	57 (57)	53 (53)	59 (60)
Logistic	BIAS	36 (.61)	24 (.70)	17 (.69)	18 (.68)	22 (.61)
	$\sqrt{\text{MSE}}$	79 (1.78)	47 (1.63)	32 (1.69)	39 (1.78)	48 (1.86)
	$\mathcal{L}_{\nu_1,\nu_2}$	539 (540)	277 (280)	57 (57)	56 (56)	58 (58)
Probit	BIAS	30 (.54)	20 (.57)	15 (.73)	20 (.73)	19 (.85)
	$\sqrt{\text{MSE}}$	86 (1.77)	45 (1.71)	25 (1.82)	41 (1.78)	42 (1.88)

Table C1c. Weights $w_2(\boldsymbol{x})$.

Link↓	(ν_1,ν_2) :	$(0,0)$	$(.25,.25)$	$(.45,.45)$	$(.90,0)$	$(0,.90)$
	$\mathcal{L}_{\nu_1,\nu_2}$	508 (504)	259 (257)	53 (53)	52 (52)	55 (54)
Logistic	BIAS	48 (.58)	46 (.76)	28 (.73)	30 (.71)	24 (.67)
	$\sqrt{\text{MSE}}$	122 (1.94)	97 (1.68)	70 (1.93)	65 (1.66)	51 (1.76)
	$\mathcal{L}_{\nu_1,\nu_2}$	537 (532)	273 (270)	55 (55)	54 (55)	56 (56)
Probit	BIAS	52 (.49)	15 (.72)	23 (.59)	22 (.60)	24 (.63)
	$\sqrt{\text{MSE}}$	106 (1.86)	31 (1.87)	46 (1.63)	45 (1.71)	44 (1.79)

Table C1d. Weights $w_3(\boldsymbol{x})$.

Link↓	(ν_1,ν_2) :	$(0,0)$	$(.25,.25)$	$(.45,.45)$	$(.90,0)$	$(0,.90)$
	$\mathcal{L}_{\nu_1,\nu_2}$	573	292	59	59	60
Logistic[1]	BIAS	376	900	483	260	1759
	$\sqrt{\text{MSE}}$	1470	2938	1929	986	814
	$\mathcal{L}_{\nu_1,\nu_2}$	623 (619)	318 (318)	64 (64)	63 (64)	64 (64)
Probit	BIAS	15 (.87)	179 (.95)	22 (1.02)	8 (1.33)	17 (1.07)
	$\sqrt{\text{MSE}}$	74 (3.06)	1252 (2.77)	57 (2.51)	24 (3.10)	44 (2.68)

[1] We give the sequential values only for the logistic link; the adaptive procedure too often crashed.

§2 Robust designs; sequential and adaptive procedures

Table C2a. Weights $w_0(\boldsymbol{x})$.

Link↓	(ν_1,ν_2) :	$(0,0)$	$(.25,.25)$	$(.45,.45)$	$(.90,0)$	$(0,.90)$
	$\mathcal{L}_{\nu_1,\nu_2}$	1450 (388)	3292 (193)	1490 (42)	217 (41)	380 (43)
Logistic	BIAS	38 (.66)	36 (.73)	21 (.45)	31 (.73)	58 (.72)
	$\sqrt{\text{MSE}}$	84 (1.77)	60 (1.69)	40 (1.49)	58 (1.67)	94 (1.64)
	$\mathcal{L}_{\nu_1,\nu_2}$	1246 (402)	2785 (201)	1547 (43)	243 (42)	568 (45)
Probit	BIAS	36 (.27)	21 (.66)	23 (.79)	24 (.63)	35 (.78)
	$\sqrt{\text{MSE}}$	92 (1.85)	38 (1.69)	42 (1.62)	47 (1.55)	59 (1.58)

Table C2b. Weights $w_1(\boldsymbol{x})$.

Link↓	(ν_1,ν_2) :	$(0,0)$	$(.25,.25)$	$(.45,.45)$	$(.90,0)$	$(0,.90)$
	$\mathcal{L}_{\nu_1,\nu_2}$	1485 (405)	3330 (200)	1447 (43)	287 (42)	571 (43)
Logistic	BIAS	30 (.75)	25 (.68)	29 (.49)	35 (.67)	57 (.81)
	$\sqrt{\text{MSE}}$	70 (2.21)	56 (1.70)	56 (1.62)	65 (1.87)	100 (1.66)
	$\mathcal{L}_{\nu_1,\nu_2}$	1319 (411)	3094 (205)	1898 (44)	221 (43)	676 (45)
Probit	BIAS	37 (.26)	33 (.69)	33 (.64)	24 (.52)	52 (.85)
	$\sqrt{\text{MSE}}$	83 (1.85)	68 (1.71)	65 (1.59)	41 (1.74)	95 (1.74)

Table C2c. Weights $w_2(\boldsymbol{x})$.

Link↓	(ν_1,ν_2) :	$(0,0)$	$(.25,.25)$	$(.45,.45)$	$(.90,0)$	$(0,.90)$
	$\mathcal{L}_{\nu_1,\nu_2}$	1691 (404)	722 (200)	171 (43)	205 (42)	165 (44)
Logistic	BIAS	44 (.55)	56 (.70)	34 (.64)	48 (.61)	42 (.64)
	$\sqrt{\text{MSE}}$	101 (1.90)	110 (1.71)	68 (1.64)	95 (1.72)	81 (1.57)
	$\mathcal{L}_{\nu_1,\nu_2}$	1375 (416)	906 (206)	235 (44)	216 (43)	231 (46)
Probit	BIAS	66 (.66)	44 (.85)	28 (.60)	28 (.52)	45 (.65)
	$\sqrt{\text{MSE}}$	199 (1.98)	88 (1.92)	50 (1.61)	48 (1.61)	81 (1.71)

Table C2d. Weights $w_3(\boldsymbol{x})$.

Link↓	(ν_1,ν_2) :	$(0,0)$	$(.25,.25)$	$(.45,.45)$	$(.90,0)$	$(0,.90)$
	$\mathcal{L}_{\nu_1,\nu_2}$	883	400	86	124	95
Logistic[1]	BIAS	348	461	751	215	271 (1.26)
	$\sqrt{\text{MSE}}$	1487	2200	2716	877	131
	$\mathcal{L}_{\nu_1,\nu_2}$	1010 (486)	414 (250)	103 (55)	111 (51)	118 (55)
Probit	BIAS	446 (.33)	6 (.80)	11 (.81)	9 (.71)	8 (.55)
	$\sqrt{\text{MSE}}$	3136 (1.97)	49 (1.89)	28 (2.20)	24 (2.08)	40 (1.86)

[1] We give the sequential values only for the logistic link; the adaptive procedure too often crashed.

§3 Robust, adaptive designs run to convergence

Table C3a. Weights $w_0(\boldsymbol{x})$.

Link↓	(ν_1,ν_2) :	$(0,0)$	$(.25,.25)$	$(.45,.45)$	$(.90,0)$	$(0,.90)$
Logistic	$\mathcal{L}_{\nu_1,\nu_2}$	382	191	40	40	40
	BIAS	.50	.43	.33	.40	.29
	$\sqrt{\text{MSE}}$	1.30	1.34	1.00	1.14	.94
Probit	$\mathcal{L}_{\nu_1,\nu_2}$	395	198	42	42	42
	BIAS	.37	.60	.27	.23	.30
	$\sqrt{\text{MSE}}$	1.33	1.47	1.07	1.03	.99

Table C3b. Weights $w_1(\boldsymbol{x})$.

Link↓	(ν_1,ν_2) :	$(0,0)$	$(.25,.25)$	$(.45,.45)$	$(.90,0)$	$(0,.90)$
Logistic	$\mathcal{L}_{\nu_1,\nu_2}$	388	196	41	41	41
	BIAS	.48	.40	.25	.32	.20
	$\sqrt{\text{MSE}}$	1.29	1.36	.92	.99	.78
Probit	$\mathcal{L}_{\nu_1,\nu_2}$	476	798	154	612	254
	BIAS	.41	.70	.32	.43	.45
	$\sqrt{\text{MSE}}$	1.19	1.50	1.10	1.11	1.02

Table C3c. Weights $w_2(\boldsymbol{x})$.

Link↓	(ν_1,ν_2) :	$(0,0)$	$(.25,.25)$	$(.45,.45)$	$(.90,0)$	$(0,.90)$
Logistic	$\mathcal{L}_{\nu_1,\nu_2}$	396	196	41	41	41
	BIAS	.70	.42	.36	.26	.28
	$\sqrt{\text{MSE}}$	1.42	1.27	.98	1.00	.92
Probit	$\mathcal{L}_{\nu_1,\nu_2}$	401	202	43	42	42
	BIAS	.30	.57	.37	.47	.29
	$\sqrt{\text{MSE}}$	1.17	1.40	1.10	1.11	.92

Table C3d. Weights $w_3(\boldsymbol{x})$.

Link↓	(ν_1,ν_2) :	$(0,0)$	$(.25,.25)$	$(.45,.45)$	$(.90,0)$	$(0,.90)$
Logistic	$\mathcal{L}_{\nu_1,\nu_2}$	Adaptive procedure too often crashed.				
	BIAS					
	$\sqrt{\text{MSE}}$					
Probit	$\mathcal{L}_{\nu_1,\nu_2}$	453	230	49	48	51
	BIAS	.38	.35	.44	.40	.46
	$\sqrt{\text{MSE}}$	1.04	1.09	1.05	1.06	1.07