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Likelihood Contour Method for the Calculation of Asymptotic Upper Confidence Limits on the Risk Function for Quantitative Responses

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Abstract. This paper develops a computationally and analytically convenient form of the profile likelihood method for obtaining one-sided confidence limits on scalar-valued functions $\varphi = \varphi(\boldsymbol{\psi})$ of the parameters $\boldsymbol{\psi}$ in a multiparameter statistical model. We refer to this formulation as the likelihood contour method (LCM). In general, the LCM procedure requires iterative solution of a system of nonlinear equations and good starting values are critical since the equations have at least two solutions corresponding to the upper and lower confidence limits. We replace the LCM equations by the lowest order terms in their asymptotic expansions. The resulting equations can be solved explicitly and have exactly two solutions which are used as starting values for obtaining the respective confidence limits from the LCM equations.

The remainder of the paper specializes to the problem of obtaining upper confidence limits for the risk function in a dose-response model in which responses are normally distributed. Because of normality, considerable analytic simplification is possible and solution of the LCM equations reduces to an easy one-dimensional root finding problem. Simulation is used to study the small-sample coverage of the resulting confidence limits.

Keywords: Asymptotic normality; Benchmark dose; Dose-response models; Likelihood ratio; Profile likelihood.

1 Introduction

A model-based approach to the development of risk assessment methodology is an appealing alternative to the NOAEL/LOAEL approach (Chen and Gaylor, 1992; Crump,

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1984; Stiteler and Durkin, 1990). For quantitative responses, however, it is usually not apparent how a given response value should be dichotomized into "adverse" or "not adverse." One solution (Chen and Gaylor, 1992; Crump, 1995; Gaylor and Slikker, 1990, 1994; Glowa, 1991; Kodell and West, 1993; West and Kodell, 1993) involves a so-called abnormal point—a response value that lies in the direction of adversity but is sufficiently far from the control mean that its occurrence in unexposed subjects would be considered unusual. Chen and Gaylor (1992) consider the case where the abnormal point is directly specified and is a known parameter of the problem. Kodell and West take the abnormal point to be a specified number of standard deviations from the (unknown) control mean; the abnormal point is thereby an unknown parameter of the problem. In the present paper, the abnormal point is defined to be a specified percentile of the control distribution. For example, when the direction of adversity is toward smaller responses, the abnormal point might be taken as the 5^{th} percentile of the control distribution. For normal distributions, the percentile definition of abnormal point is equivalent to that of Kodell and West; for more general distributions, the percentile definition has the advantage that it transforms in the same way as the response variable under nonlinear transformations of the response.

For a specified exposure level, the risk is the probability of an adverse response. Accordingly, the risk is a tail area of the response distribution for the given dose level (see Figure 1). When parametric models are specified for the response distributions, then a parametric expression can be derived for the risk as a function of the dose, which determines the ordinate of the dose-response curve.

Based on these ideas, the modeling and risk analysis for quantitative responses is carried out in the following steps:

1. First a parametric family $F(y;\Theta)$ of distribution functions is selected for a continuous response y. The distributional parameters Θ are then modeled as a function,

$$\Theta = \Theta(d, \boldsymbol{\psi}),$$

of the dose d and some unknown parameters $\boldsymbol{\psi}$. The distribution of $Y(d)$ can then be written as

$$F_d(y) = F(y, \Theta(d, \boldsymbol{\psi})).$$

2. Let τ be the abnormal point and α_τ the associated control risk. In our approach, α_τ is specified by the investigator and then τ is determined by the equation

$$\alpha_\tau = F_0(\tau) = F(\tau, \Theta(0, \boldsymbol{\psi})). \tag{1}$$

Note that τ is unknown because $\boldsymbol{\psi}$ is unknown. For a given dose level d, the total risk function is

$$R(d) = F_d(\tau) = F(\tau, \Theta(d, \boldsymbol{\psi})).$$

Equation (1) can be used to eliminate τ so that the risk function is parametrized by $\boldsymbol{\psi}$, i.e., $R(d) = R(d; \boldsymbol{\psi})$. The excess or additional risk is defined as $\pi(d) = R(d) - \alpha_\tau$. Since α_τ is a known constant, one can equivalently work with either $\pi(d)$ or $R(d)$. We

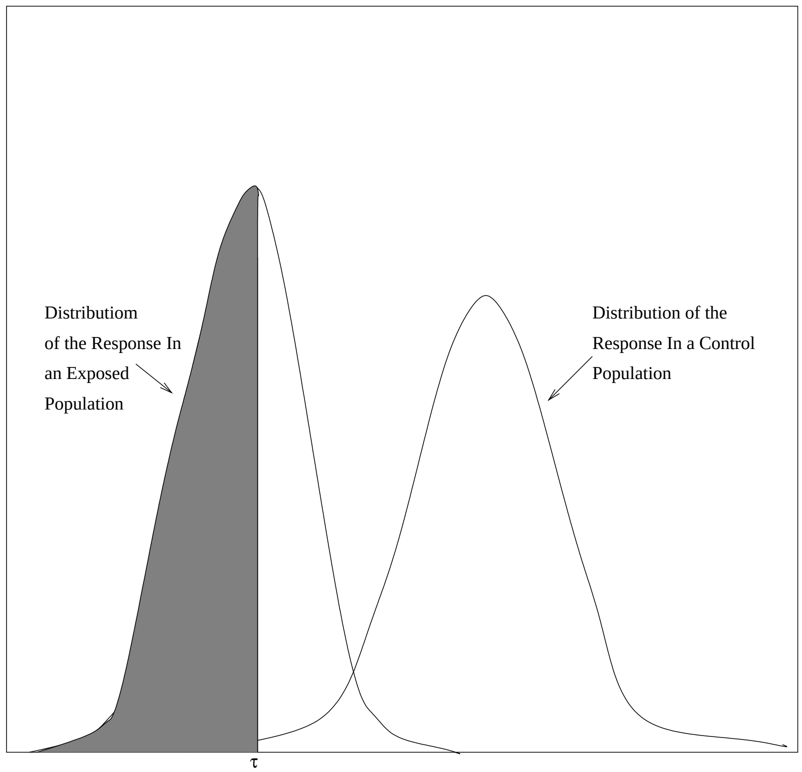

Figure 1: Schematic diagram for defining the abnormal point and corresponding risks. The abnormal point τ is a specified quantile of the control population. The shaded tail area of the response distribution for an exposed population represents the risk for that population. The risk for the control population is the background risk and is denoted by α_τ. In the approach described here, the value of α_τ is specified by the investigator and is therefore a known specification parameter. This is different from conventional dose response analysis where the background risk is generally unknown. In the present paper, it is the abnormal point τ which is unknown.

generally use $R(d)$. The equations in this step apply when the direction of adversity is to the left; the equations have to be modified appropriately if the direction of adversity is to the right.

3. At each dose level d, an upper confidence limit (UCL) on the risk $R(d)$ is constructed. These calculations yield a pointwise upper confidence curve $\widehat{R}_u(d)$ on the risk function. The confidence limit calculations are often based either upon the asymptotic normality of the maximum likelihood estimates of the parameters in the model or upon the asymptotic distribution of the likelihood ratio (LR) statistic (Rao, 1947; Crump and Howe, 1983). The LR method appears to provide more reliable coverage when responses are not normally distributed (Banga, Patil, and Taillie, 2001a). For normally distributed responses, the simulations in the present paper indicate that the MLE-based coverage is effectively indistinguishable from the LR-based coverages.

4. Letting α_1 be any given risk level ($\alpha_\tau < \alpha_1 < 1$), the solution of the equation $R(d) = \alpha_1$ is the effective dose associated with the risk $\alpha_1 - \alpha_\tau$ and is denoted by $\eta = \mathrm{ED}_{\alpha_1}$. For given α_1, the effective dose is a scalar function of the parameters in the model, i.e., $\eta = \eta(\boldsymbol{\psi})$. The benchmark dose (BMD) is defined to be a lower confidence limit (LCL) on the effective dose and is denoted by BMD_{α_1}.

The present paper develops a computationally and analytically convenient form of the profile likelihood method (Lindsey, 1996, chaps. 3 and 5) for obtaining confidence limits on scalar-valued functions $\varphi = \varphi(\boldsymbol{\psi})$ of the parameters $\boldsymbol{\psi}$ in a multiparameter statistical model. We refer to this formulation as the likelihood contour method (LCM). The risk $\varphi = R(d; \boldsymbol{\psi})$ in step (3) and the effective dose $\varphi = \mathrm{ED}_{\alpha_1}$ in step (4) are examples of scalar parameters for which the LCM can be used to calculate one-sided confidence limits. In general, the LCM requires iterative solution of a system of nonlinear equations and good starting values are critical since the equations have at least two solutions corresponding to the upper and lower confidence limits. For starting values, we replace the LCM equations by the lowest order terms in their asymptotic expansions. The resulting equations can be solved explicitly and have exactly two solutions which are used as starting values for the respective confidence limits.

The remainder of this paper specializes to the problem of obtaining UCLs for the risk function (step 3, above) when responses are normally distributed. Because of normality, considerable analytic simplification is possible and solution of the LCM equations reduces to an easy one-dimensional root finding problem.

Banga, Patil, and Taillie (2000) examined the sensitivity of these normal theory formulas to model misspecification and found that the normal-theory-based UCLs on the risk gave very poor coverage when responses followed skew distributions such as the gamma, reciprocal gamma, or lognormal. Applying the log transform to the gamma and reciprocal gamma data before applying the normal theory formulas resulted in only slightly improved coverage. Accordingly, Banga, Patil, and Taillie (2001a) developed and assessed the LCM approach for the gamma and reciprocal gamma distributions and found that coverage is quite good for these distributions. Finally, Banga, Patil, and Taillie (2001b) applied the LCM approach for direct determination of benchmark dose levels (step 4, above) and showed that this was equivalent to (but computationally simpler than) inverting the LR-based UCLs on the risk function.

2 LR-Based Confidence Limits on Scalar Parameters

Consider a statistical model parametrized by a q-dimensional vector of parameters $\boldsymbol{\psi} = (\psi_1, \cdots, \psi_q)^t$. Our interest lies in obtaining one-sided confidence limits on a scalar-valued function

$$\varphi = \varphi(\boldsymbol{\psi})$$

of the parameters. Let

- $L(\boldsymbol{\psi})$ be the likelihood function for the model,
- $l(\boldsymbol{\psi}) = -\log L(\boldsymbol{\psi})$, and
- $\mathcal{D}(\boldsymbol{\psi}) = 2(l(\boldsymbol{\psi}) - l(\hat{\boldsymbol{\psi}})) = -2\log\left(\frac{L(\boldsymbol{\psi})}{L(\hat{\boldsymbol{\psi}})}\right)$, where $\hat{\boldsymbol{\psi}}$ is the MLE of $\boldsymbol{\psi}$.

If $\tilde{\boldsymbol{\psi}}$ is the MLE of $\boldsymbol{\psi}$ under some null hypothesis (sub-model), then $\mathcal{D}(\tilde{\boldsymbol{\psi}})$ is the likelihood ratio test statistic. A well known consequence of the duality between confidence limits and hypothesis testing is that an asymptotic $100(1-\alpha)$ percent one-sided UCL for φ is the maximum φ_u of $\varphi(\boldsymbol{\psi})$ subject to $\mathcal{D}(\boldsymbol{\psi}) = \chi^2_{1,1-2\alpha}$. Similarly, an asymptotic $100(1-\alpha)$ percent one-sided LCL for φ is the minimum φ_l of $\varphi(\boldsymbol{\psi})$ subject to $\mathcal{D}(\boldsymbol{\psi}) = \chi^2_{1,1-2\alpha}$ (see Figure 2). As indicated in Figure 2, the task of finding one-sided confidence limits on φ has a simple geometric interpretation. The extrema occur where the parameter contours $\varphi = c$ are tangent to the deviance contour $\mathcal{D}(\boldsymbol{\psi}) = \chi^2_{1,1-2\alpha}$. Equivalently, this amounts to finding a scalar c such that the vector perpendicular to the contour $\varphi = c$ is parallel to the vector perpendicular to the contour $\mathcal{D}(\boldsymbol{\psi}) = \chi^2_{1,1-2\alpha}$. This is essentially the geometrical interpretation of the Lagrange multiplier method for the problem of optimizing $\varphi(\boldsymbol{\psi})$ subject to the constraint $\mathcal{D}(\boldsymbol{\psi}) = \chi^2_{1,1-2\alpha}$.

The Lagrange multiplier equations for the optimization problem are given by

$$\begin{cases} E_0 \ : \ \mathcal{D}(\boldsymbol{\psi}) = \chi^2_{1,1-2\alpha} \\ E_1, \cdots, E_q \ : \ \frac{\partial}{\partial\psi_i}\mathcal{D}(\boldsymbol{\psi}) - \lambda\frac{\partial}{\partial\psi_i}\varphi(\boldsymbol{\psi}) = 0, \qquad i = 1, \cdots, q\,, \end{cases}$$

where λ is the Lagrange multiplier. A vector representation of equations $E_1, \cdots, E_q$ is

$$\nabla\mathcal{D}(\boldsymbol{\psi}) = \lambda\nabla\varphi(\boldsymbol{\psi}).$$

The gradient $\nabla\varphi$ points in the direction of increasing φ while $\nabla\mathcal{D}$ points to the exterior of the region bounded by the $\mathcal{D}$-contours. Referring to Figure 2, this means that the solution, $\boldsymbol{\psi}^*$, which yields an upper confidence limit for $\varphi(\boldsymbol{\psi})$ is associated with a positive λ. On the other hand, when a lower confidence limit is obtained, the associated λ is negative.

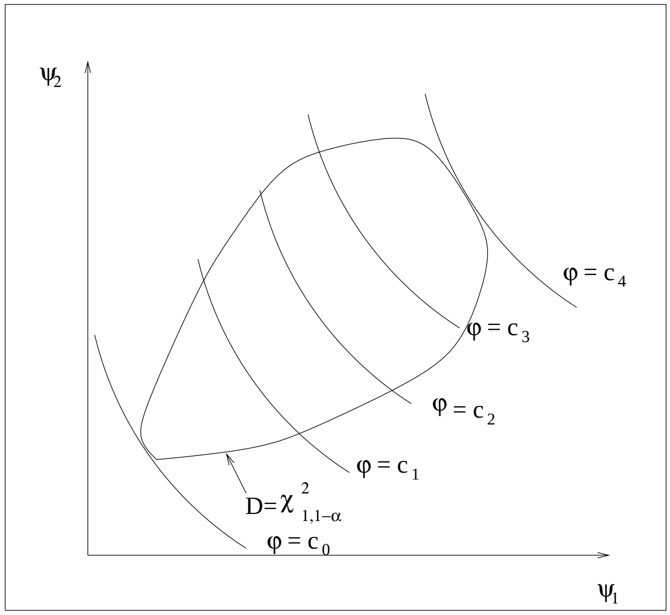

Figure 2: Two-dimensional schematic for LR-based confidence intervals for a scalar parameter φ. The constants $c_0 < c_1 < c_2 < c_3 < c_4$ label various contours of φ. A one-sided UCL for φ is $\varphi = c_4$ which is obtained by maximizing φ along the contour $\mathcal{D}(\boldsymbol{\psi}) = \chi^2_{1,1-2\alpha}$. Similarly, c_0 is an LCL for φ obtained by minimizing φ along the contour $\mathcal{D}(\boldsymbol{\psi}) = \chi^2_{1,1-2\alpha}$.

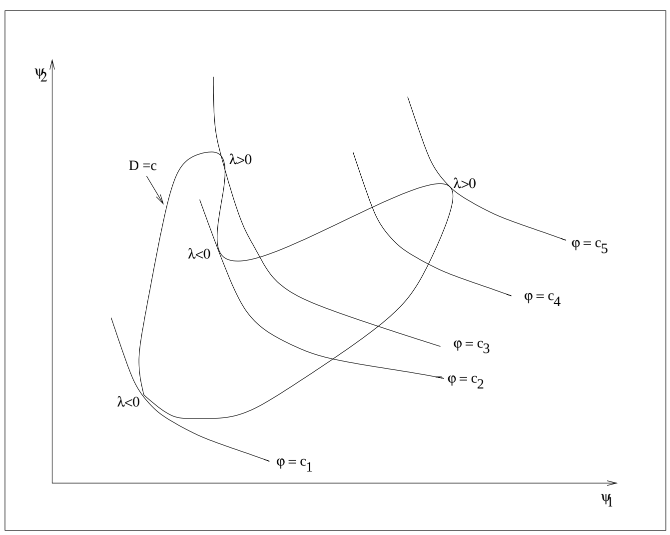

Figure 3: Two-dimensional illustration of how φ can be multimodal along a deviance contour. In this example, c_1 and c_5 are respectively the global minimum and maximum, whereas c_2 and c_3 are respectively local minimum and maximum.

Multimodality problems may be encountered along the contour $\mathcal{D}(\boldsymbol{\psi}) =$ constant even if the likelihood surface is well behaved, i.e., unimodal. See Figure 3. Good starting values are therefore needed for iterative solution of the equations.

2.1 Algorithms for solving the Lagrange equations

Consider the following augmented system of Lagrange equations:

$$\begin{cases} E_0 \; : \; \mathcal{D}(\boldsymbol{\psi}) = \chi^2_{1,1-2\alpha} \\ E_1, \cdots, E_q \; : \; \frac{\partial}{\partial \psi_i}\mathcal{D}(\boldsymbol{\psi}) - \lambda \frac{\partial}{\partial \psi_i}\varphi(\boldsymbol{\psi}) = 0, \qquad i = 1, \cdots, q \\ E_{q+1} \; : \; \varphi(\boldsymbol{\psi}) = c\,. \end{cases} \tag{2}$$

We describe two ways of solving these equations to obtain an asymptotic $100(1-\alpha)$ percent UCL for $\varphi(\boldsymbol{\psi})$. Computation of an LCL is analogous.

1. **Parameter Contour Method (PCM).** This algorithm is started by fixing a value for c. Next, the equations $E_1, \cdots, E_{q+1}$ are solved simultaneously for $(\boldsymbol{\psi}, \lambda)$ to obtain a solution $\boldsymbol{\psi}^*$. The search is constrained to the parameter contour defined by equation E_{q+1}. Note that $\mathcal{D}(\boldsymbol{\psi}^*)$ is the normed profile likelihood (Lindsey, 1996, p. 111) for the parameter φ, evaluated at $\varphi = c$. The value of c is then keep c until the solution $\boldsymbol{\psi}^*$ satisfies equation E_0. The value of c for which $\boldsymbol{\psi}^*$ satisfies E_0 is then taken to be the upper confidence limit on φ. This is essentially the algorithm described by Kodell and West (1993).

2. **Likelihood Contour Method (LCM).** This method consists of solving the equations $E_0,\ E_1, \cdots, E_q$ for $(\boldsymbol{\psi}, \lambda)$ to obtain the global maximum $\boldsymbol{\psi}^*$. The UCL $\varphi_u = c$ is then found as $c = \varphi(\boldsymbol{\psi}^*)$ from the equation E_{q+1}. In this method, the search is constrained to the likelihood contour defined by equation E_0.

The two methods are clearly equivalent. The LCM version is more convenient to program but its convergence relies heavily on the choice of starting values, particularly the starting value for λ. The PCM method, on the other hand, is a step by step procedure and does not depend so much upon the starting values. However, one will need to adjust the value of c appropriately to move toward the desired solution which depends on whether an upper or lower confidence limit is sought. Consequently, the PCM algorithm can be inconvenient to program particularly in settings such as simulation where there is a need for automatic computation.

2.2 Starting values: Asymptotic solutions of the LCM equations

Here, we obtain accurate starting values for solving the LCM equations $E_0,\ E_1, \cdots, E_q$. The idea is to approximate these equations by using the lowest order terms in their asymptotic expansions. The resulting equations can be solved explicitly. They yield exactly two solutions $(\boldsymbol{\psi}_\pm, \lambda_\pm)$ given by

$$\boldsymbol{\psi}_\pm = \hat{\boldsymbol{\psi}} + \frac{\lambda_\pm}{2} H^{-1}(\hat{\boldsymbol{\psi}}) \nabla\varphi(\hat{\boldsymbol{\psi}}) \tag{3}$$

$$\frac{\lambda_\pm}{2} = \pm \frac{\sqrt{\chi^2_{1,\,1-2\alpha}}}{\sqrt{[\nabla\varphi(\hat{\boldsymbol{\psi}})]^t H^{-1}(\hat{\boldsymbol{\psi}}) \nabla\varphi(\hat{\boldsymbol{\psi}})}}, \tag{4}$$

where $H(\boldsymbol{\psi})$ is the total negative Hessian matrix of the model. The positive sign corresponds to the UCL and the negative sign to the LCL. In these formulae, the negative Hessian matrix can be replaced by the information matrix to which it is asymptotically equivalent. The proof of the result is outlined in section 6.

The approximate solution $(\boldsymbol{\psi}_\pm, \lambda_\pm)$ can be used directly as the confidence limit if the resulting loss of accuracy is acceptable. It is typically used as starting value for iterative solution of the LCM equations; $(\boldsymbol{\psi}_\pm, \lambda_\pm)$ is usually so close to the exact solution that only a few iterations are required. In fact, it is the starting value for λ rather than for $\boldsymbol{\psi}$ that is critical. We have learned from sad experience that simply guessing a starting value for λ, even with the appropriate sign, often leads to nonconvergence or to convergence to the wrong confidence limit.

We have accumulated considerable numerical experience with the LCM equations for a variety of response distributions and have not yet encountered a situation in which the multimodality depicted in Figure 3 actually occurred. Accordingly, we cannot comment on the effectiveness of these starting values in dealing with multimodality.

Alternatively, $\varphi(\boldsymbol{\psi}_+)$ and $\varphi(\boldsymbol{\psi}_-)$ can be used as approximate upper and lower confidence limits on φ. Our simulations below and also in Banga, Patil, and Taillie (2001a,b) indicate that the resulting coverage is quite close to nominal levels as long as the sample size is greater than, say, 50. For smaller sample sizes, it is probably advisable to do a few iterations of the LCM equations.

3 Risk Analysis for the Homoscedastic Normal Model

Suppose that responses are normally distributed with a constant (but unknown) variance and with a mean whose dependence on the dose is described by a linear model. That is, let

$$Y_i \sim N(\mu_i, \sigma^2), \quad i = 1, \ldots, N$$

with

$$\mu_i = E(Y_i) = X_i\boldsymbol{\theta},$$

where X_i is the i^{th} row of the design matrix X and $\boldsymbol{\theta}$ is a p-dimensional vector whose components are unknown. Also suppose that the observations $Y_1, \ldots, Y_N$ are independent. The total sample size is

$$N = \sum_{j=1}^{g} n_j,$$

where g is the number of experimental dose groups and n_j the sample size for the j^{th} dose level d_j. For asymptotic arguments we keep $d_1, d_2, \cdots, d_g$ fixed and let $N \to \infty$ with n_j/N constant. The unknown parameters in this model are $\boldsymbol{\psi} = (\theta_0, \theta_1, \cdots, \theta_{p-1}, \sigma)^t$. Specific examples of mean functions include the straight line model with

$$\mu(d) = \theta_0 + \theta_1 d,$$

and the quadratic model with

$$\mu(d) = \theta_0 + \theta_1 d + \theta_2 d^2.$$

The quadratic model allows the risk function to be decreasing for small dose levels in case the chemical under study is beneficial for small exposure levels (Kodell and West, 1993).

Let $y(d)$ be a hypothetical response at some dose level d so that

$$y(d) \sim N(\mu(d), \sigma^2) \;\text{ and }\; \mu(d) = \mathbf{x}^t\boldsymbol{\theta},$$

where $\mathbf{x} = \mathbf{x}(d)$ depends on the dose level d. Without any loss of generality, we suppose that the direction of adversity is taken to the left so that an adverse effect is characterized by a response $y(d)$ such that $y(d) < \tau$, where τ, the abnormal point, is specified by a lower tail area of the control distribution. The probability of an adverse effect at dose level d is the total risk function given by $R(d) = \Pr(y(d) \leq \tau \,|\, d)$. Under normality, this becomes

$$R(d) = \Phi\left(\frac{\tau - \mu(d)}{\sigma}\right).$$

We are assuming that τ is unknown but that the tail area

$$\alpha_\tau = R(0) = \Phi\left(\frac{\tau - \mu(0)}{\sigma}\right)$$

is specified by the investigator and hence is known. The total risk becomes

$$R(d) = \Phi\left(z_\tau + \frac{\mu(0) - \mu(d)}{\sigma}\right) = \Phi\left(z_\tau + \frac{\mathbf{a}^t\boldsymbol{\theta}}{\sigma}\right), \tag{5}$$

where

$$z_\tau = \Phi^{-1}(\alpha_\tau) \quad \text{and} \quad \mathbf{a} = \mathbf{x}(0) - \mathbf{x}(d). \tag{6}$$

Since α_τ is known, z_τ is known and we have eliminated the need to estimate τ, the abnormal point.

To obtain a $100(1-\alpha)$ percent UCL on $R(d)$, it suffices to find a $100(1-\alpha)$ percent UCL, U_d, on the parameter

$$\varphi = \frac{\mathbf{a}^t\boldsymbol{\theta}}{\sigma},$$

so that $\Phi(z_\tau + U_d)$ becomes the needed $100(1-\alpha)$ percent UCL on the total risk $R(d)$. Kodell and West (1993) give an exact small-sample method using the noncentral t-distribution to obtain a UCL on the parameter φ; also see Chen and Gaylor (1992) and Sciullo, Patil and Taillie (2000a,b) in this connection.

3.1 LCM solution for homoscedastic normal model

For the homoscedastic normal model described above, the scalar parameter of interest is

$$\varphi(\boldsymbol{\psi}) = \frac{\mu(0) - \mu(d)}{\sigma} \equiv \frac{\mathbf{a}^t\boldsymbol{\theta}}{\sigma},$$

where $\mathbf{a} = \mathbf{a}(d)$ is given by equation (6) and $\boldsymbol{\psi}^t = (\boldsymbol{\theta}^t, \sigma)$. We need the following notation:

$$k = \chi^2_{1,1-2\alpha}\,, \tag{7}$$

$$\omega^2 = \mathbf{a}^t(X^tX)^{-1}\mathbf{a}\,, \tag{8}$$

where, in equation (8), we suppose that the design matrix is of full rank. Also let $\hat{\varphi}$ and $\hat{\sigma}^2$ be the likelihood estimates of φ and σ^2. These are the same as the least squares estimates except that there is no degrees of freedom correction in the denominator of $\hat{\sigma}^2$.

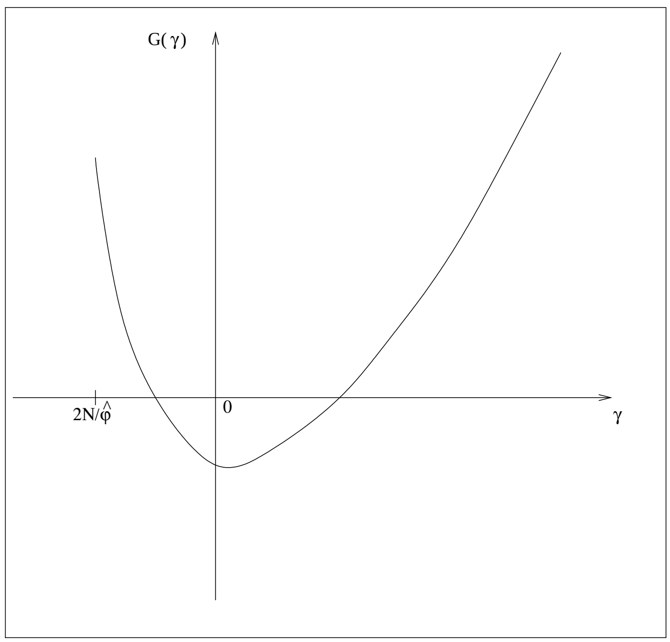

Figure 4: Sketch of the function $G(\gamma)$. The figure illustrates the case where $\hat{\varphi} < 0$.

We define an auxiliary function $G(\gamma)$ whose roots determine the LR-based confidence limits on the risk:

$$G(\gamma) \equiv \left(1 - \frac{\hat{\varphi}\gamma}{2N}\right) \log\left(1 - \frac{\hat{\varphi}\gamma}{2N}\right) - \left(1 + \frac{k}{N}\right)\left(1 - \frac{\hat{\varphi}\gamma}{2N}\right) + \frac{\gamma^2\omega^2}{4N} + 1 = 0. \tag{9}$$

The function $G(\gamma)$ has the following properties:

- $G(\gamma)$ is a convex function of γ for $-\infty < \gamma < \frac{2N}{\hat{\varphi}}$ provided $\hat{\varphi} \geq 0$, and is a convex function of γ for $\frac{2N}{\hat{\varphi}} < \gamma < +\infty$ provided $\hat{\varphi} \leq 0$. Notice that each of these two intervals where $G(\gamma)$ is defined contains the origin.

- $G(0) = -k/N < 0$.
- If $\hat{\varphi} \geq 0$ then $G(-\infty) = +\infty$ and $G\left((\frac{2N}{\hat{\varphi}})^-\right) = \frac{N\omega^2}{\hat{\varphi}^2} + 1 > 0$.
- If $\hat{\varphi} \leq 0$ then $G\left((\frac{2N}{\hat{\varphi}})^+\right) = \frac{N\omega^2}{\hat{\varphi}^2} + 1 > 0$ and $G(+\infty) = +\infty$.

It follows that the function $G(\gamma)$ has exactly two roots (see Figure 4). Furthermore, if γ_1^* is the smaller root and γ_2^* is the larger root, then $\gamma_1^* < 0 < \gamma_2^*$. The larger root yields the UCL on the risk function. In general, it can be shown that if the design matrix is of full rank then for any given sample size N and any dose level d, the LCM equations associated with the homoscedastic normal model admit exactly two solutions. These solutions correspond to the asymptotic $100(1-\alpha)$ percent upper and lower confidence limits for the risk function $R(d)$. The upper confidence limit is given by

$$\Phi\left(z_\tau + \frac{2\hat{\varphi} + \gamma^*\omega^2}{2\sqrt{1 - \gamma^*\hat{\varphi}/2N}}\right), \tag{10}$$

where γ^* is the larger root of the convex function $G(\gamma)$ and where z_τ and ω^2 are given by equations (6) and (8), respectively. The proof is very complicated and is available from authors upon request. Formula (10) is referred to as the **LREL** procedure where LR signifies "likelihood ratio" and "EL" means the solution to the exact LCM equations.

A good starting value for numerically finding the larger root of $G(\gamma)$ is

$$\gamma_a = \frac{2\sqrt{Nk}}{\sqrt{N\omega^2 + \hat{\varphi}^2/2}} - \frac{k\hat{\varphi}}{N\omega^2 + \hat{\varphi}^2/2}. \tag{11}$$

Convergence is usually achieved in fewer than five iterations for sample sizes as low as 15 observations.

Application of the **LREL** method requires the largest root of the equation $G(\gamma) = 0$. Although this one-dimensional root-finding problem is straightforward to solve numerically, we give a closed form expression for the approximate upper confidence limit on the risk that results from solving asymptotic expansions of the LCM equations as described in sub-section 2.2.

This is given by

$$\Phi\left(z_\tau + \hat{\varphi} + \frac{\sqrt{k}\,(N\omega^2 + \hat{\varphi}^2/2)}{\sqrt{N\omega^2 + \hat{\varphi}^2/2} - \sqrt{k/N}\,\hat{\varphi}/2}\frac{1}{\sqrt{N}}\right), \tag{12}$$

where z_τ, ω^2, and k are given by equations (6), (8), and (7), respectively.
The proof is also available from authors on request. We refer to the formula (12) as the **LRAL** procedure where "AL" signifies the solution to the approximate LCM equations in in sub-section 2.2.

3.2 MLE-based UCL on the risk for homoscedastic normal model

As mentioned earlier, a well known method for calculating confidence limits uses asymptotic normality of maximum likelihood estimators. Specifically, by writing the first-order Taylor expansion of $\varphi(\psi)$, it can be shown using the Cramer δ-theorem that $\varphi(\hat{\psi}) - \varphi(\psi)$ is asymptotically distributed as normal with mean 0 and variance given by

$$[\nabla\varphi]^t \left(E[H(\boldsymbol{\theta}, \sigma)]\right)^{-1} \nabla\varphi = \omega^2 + \varphi^2/2N.$$

A consistent estimator of the variance is obtained by replacing φ with $\hat{\varphi}$ in the above. It follows that an asymptotic $100(1-\alpha)$ percent UCL for $R(d)$ is given by

$$\Phi\left(z_\tau + \hat{\varphi} + z_{1-\alpha}\frac{1}{\sqrt{N}}\sqrt{N\omega^2 + \hat{\varphi}^2/2}\right). \tag{13}$$

This formula is referred to as the **MLE** procedure. Our simulation studies reported below have shown that this MLE-based UCL provides essentially the same coverage probability as the LREL method. On the other hand, Banga, Patil, and Taillie (2001a) have found that the MLE procedure gives very poor coverage for gamma and reciprocal gamma response distributions. The good coverage for the MLE procedure for normally distributed responses appears to be due to two very special features:

(i) We have applied the δ-method to the parameter φ and only afterwards applied the nonlinear transformation $\Phi(\cdot)$ rather than using the δ-method directly on the risk $R(d)$. This device, which effectively removes much of the nonlinearity from the problem, cannot be applied generally because the CDF for most nonnormal distributions depends inherently upon unknown shape parameters.

(ii) The MLE of the parameter φ, suitably normalized, follows a noncentral t distribution and is already close to normal unless N is quite small.

4 Simulation Study for Homoscedastic Normal model

We conduct a simulation study to evaluate and compare the performance of the LREL, LRAL, and MLE methods. Asymptotic 95 percent UCLs on the risk are calculated based on the three methods. There is a total of six experiments in this investigation, each of which is determined by the parameter σ in the models

$$y(d) = \mu(d) + \epsilon = 3 - d - 0.1d^2 + \epsilon,$$

where ϵ is generated as $N(0, \sigma^2)$ and σ is fixed at 0.25, 0.5, 1.0, 1.5, 2.0 and 4.0.

For each of these six models there are five dose groups: a control group ($d = 0$) and four treatment or experimental dose groups d_1, d_2, d_3, and d_4. The experimental dose levels are varied so that they yield the same true risk across the six experiments. With this setup, experiment-to-experiment differences can be attributed to distributional changes as the parameter σ changes in the study. The background risk in each of the six experiments is specified as $\alpha_\tau = 0.05$. In addition, each dose group is simulated with first 5 ($n_i = 5,\ N = 25$), then 10 ($n_i = 10,\ N = 50$) and finally 20 ($n_i = 20,\ N = 100$) observations. Asymptotic 95 percent UCLs in each of the 3 designs of the 6 experiments are calculated for 4000 replicates. The estimated coverage probability in each case is computed as the proportion of the 4000 simulations for which the resulting UCLs are greater than or equal to the true risk. Since the targeted coverage probability is 95 percent, the simulation error for the computed coverage has an approximate standard deviation of $\sqrt{.95(.05)/4000} = .003$ or 0.3 percentage points.

5 Summary and Discussion

Figures 5, 6 and 7 summarize our findings. The LREL and the MLE methods provide coverage probabilities which are graphically indistinguishable from each other and which are very close to the nominal 95 percent level. The LRAL procedure, on the other hand, under-covers slightly for small sample sizes but becomes more consistent with the other two methods as the sample size increases. LR-based confidence limits often provide better coverage probabilities than the MLE approach. However, this study shows that for the homoscedastic normal model the MLE method (as implemented above) is as good as the LR method.

In general, the LCM method provides a simpler fomulation of the optimization problem involved in the calculation of the LR-based confidence limits and is applicable to non-normal dose response models as well. When applied to normal dose response models, the optimization problem reduces to an easy one-dimensional root finding problem which is straight forward to solve numerically. However, for non-normal dose response models no analytic simplification is available, and as a result the numerical resolution of the equations relies heavily on the starting values. An example of such application was treated in Banga, Patil and Taillie (2001a) where the LCM method was applied to the gamma and reciprocal gamma dose response models. The starting values provided in sub-section 2.2 were proven to be effective through extensive simulation studies. In addition, when the starting values were used to directly compute the UCLs, they provided better coverage probabilities than the MLE method.

6 Appendix

We outline here the derivation of the starting values provided earlier in sub-section 2.2.

The negative log likelihood function of the model $l(\boldsymbol{\psi})$ can be asymptotically approximated by a quadratic with minimum at the MLE $\hat{\boldsymbol{\psi}}$ and curvature given by the Hessian or the Fisher information matrix. First, we write the LCM equations $E_0,\ E_1, \cdots, E_q$ in vector form as

$$\begin{aligned} \mathcal{D}(\boldsymbol{\psi}) &= \chi^2_{1,1-2\alpha} \\ \nabla\mathcal{D}(\boldsymbol{\psi}) &= \lambda\nabla\varphi(\boldsymbol{\psi})\,. \end{aligned}$$

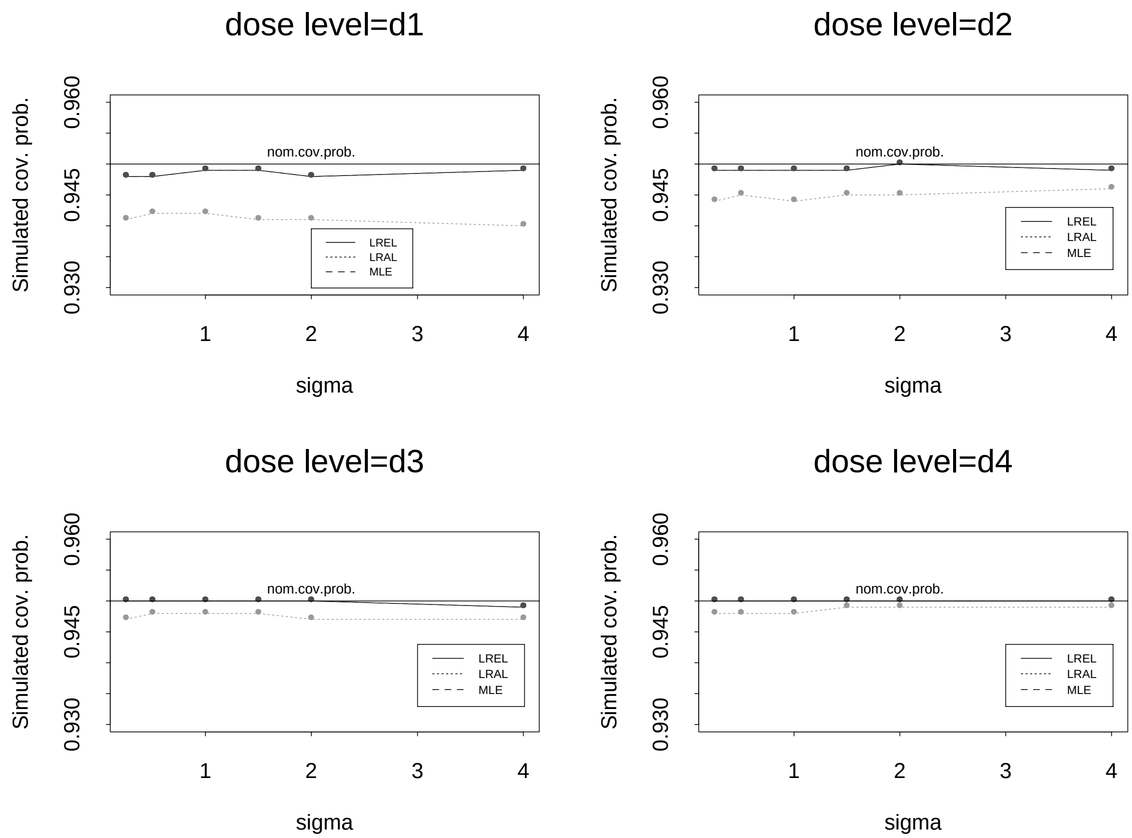

Figure 5: Simulated coverage probabilities for the normal homoscedastic model. The nominal coverage probability is 0.95. Each experimental dose group consists of **5** animals so that the total sample size is $N = \mathbf{25}$. The LREL and MLE coverage probabilities are graphically indistinguishable but not identical. Simulation error for the coverage has an approximate standard deviation of 0.3 percentage points.

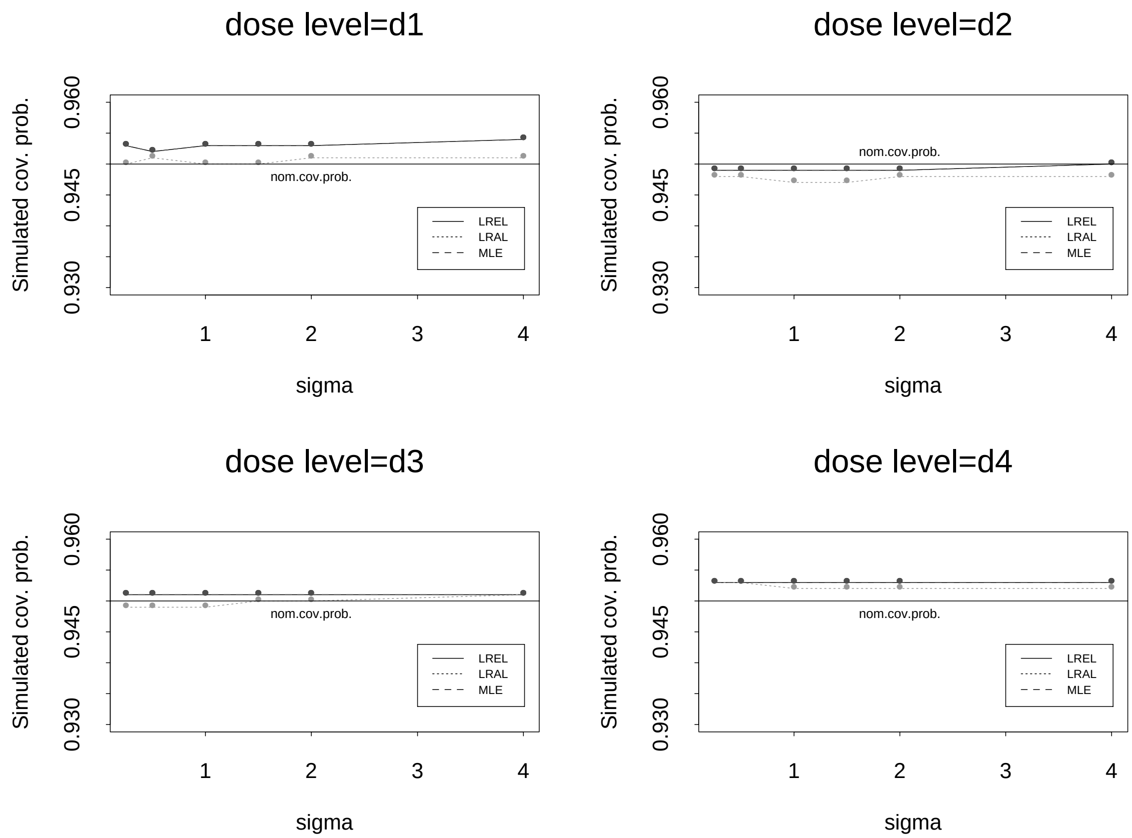

Figure 6: Simulated coverage probabilities for the normal homoscedastic model. The nominal coverage probability is 0.95. Each experimental dose group consists of **10** animals so that the total sample size is $N = \mathbf{50}$. The LREL and MLE coverage probabilities are graphically indistinguishable but not identical. Simulation error for the coverage has an approximate standard deviation of 0.3 percentage points.

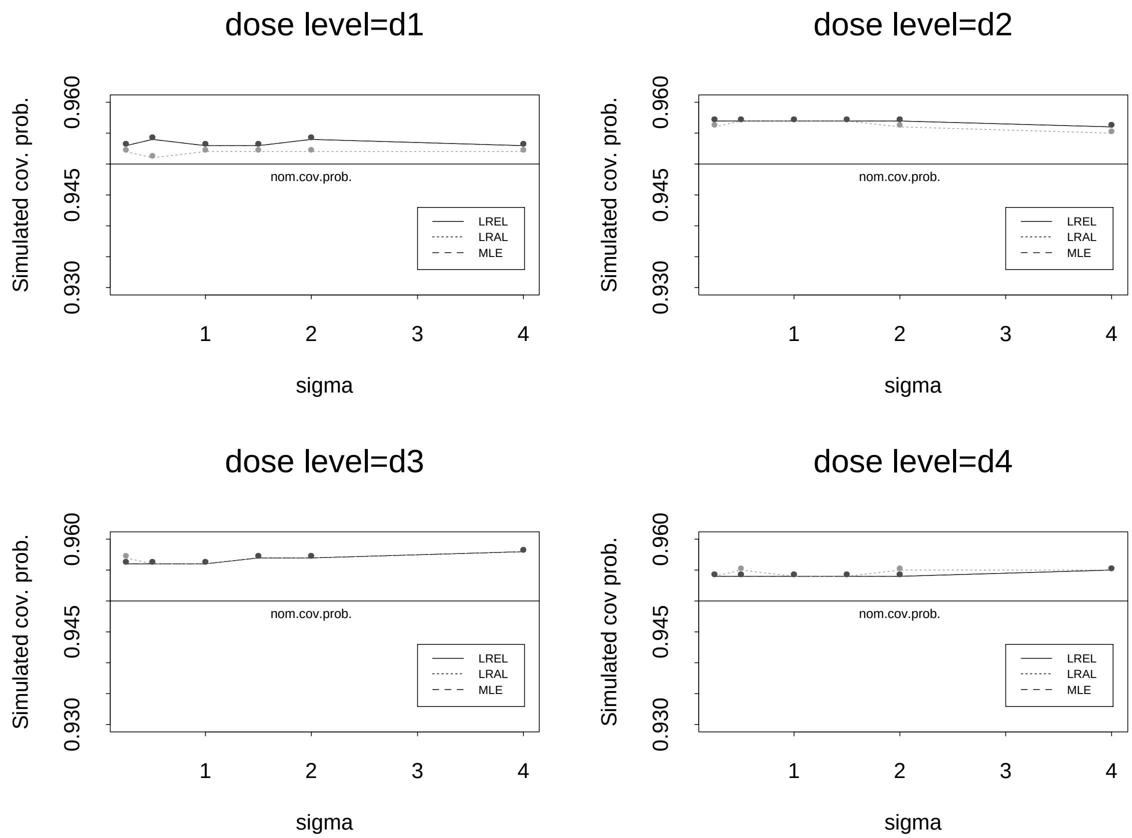

Figure 7: Simulated coverage probabilities for the normal homoscedastic model. The nominal coverage probability is 0.95. Each experimental dose group consists of **20** animals so that the total sample size is $N = \mathbf{100}$. The LREL and MLE coverage probabilities are graphically indistinguishable but not identical. Simulation error for the coverage has an approximate standard deviation of 0.3 percentage points.

With the usual regularity conditions on the likelihood, we have the following asymptotic expansions where N is the number of (independent) observations and $\hat{\boldsymbol{\psi}}$ is the MLE of $\boldsymbol{\psi}$

$$\begin{aligned} \hat{\boldsymbol{\psi}} &= \boldsymbol{\psi} + O_p(\frac{1}{\sqrt{N}}) & (14) \\ \nabla\varphi(\hat{\boldsymbol{\psi}}) &= \nabla\varphi(\boldsymbol{\psi}) + O_p(\frac{1}{\sqrt{N}})\,. & (15) \end{aligned}$$

This last equation supposes that the gradient of φ does not vanish at the true parameter value $\boldsymbol{\psi}$. Also,

$$H(\hat{\boldsymbol{\psi}}) = O_p(N) \tag{16}$$

since the total negative Hessian is the sum of N independent terms. This gives the expansions

$$\begin{aligned} \mathcal{D}(\boldsymbol{\psi}) &= 2\,\left(l(\boldsymbol{\psi}) - l(\hat{\boldsymbol{\psi}})\right) \\ &= (\boldsymbol{\psi} - \hat{\boldsymbol{\psi}})^t\, H(\hat{\boldsymbol{\psi}})\, (\boldsymbol{\psi} - \hat{\boldsymbol{\psi}}) + O_p(\frac{1}{\sqrt{N}}) & (17) \\ \nabla\mathcal{D}(\boldsymbol{\psi}) &= 2\, H(\hat{\boldsymbol{\psi}})\, (\boldsymbol{\psi} - \hat{\boldsymbol{\psi}}) + O_p(1)\,. & (18) \end{aligned}$$

The asymptotic expansions of the LCM equations are then

$$\begin{aligned} (\boldsymbol{\psi} - \hat{\boldsymbol{\psi}})^t\, H(\hat{\boldsymbol{\psi}})\, (\boldsymbol{\psi} - \hat{\boldsymbol{\psi}}) &= \chi^2_{1,\,1-2\alpha} + O_p(\frac{1}{\sqrt{N}}) & (19) \\ H(\hat{\boldsymbol{\psi}})\, (\boldsymbol{\psi} - \hat{\boldsymbol{\psi}}) &= \frac{\lambda}{2}\nabla\varphi(\hat{\boldsymbol{\psi}}) + O_p(1)\,. & (20) \end{aligned}$$

We ignore the higher order terms in these last two equations. Then, equation (20) can be solved for $\boldsymbol{\psi} - \hat{\boldsymbol{\psi}}$ to give

$$\boldsymbol{\psi} - \hat{\boldsymbol{\psi}} = \frac{\lambda}{2}\, H^{-1}(\hat{\boldsymbol{\psi}})\, \nabla\varphi(\hat{\boldsymbol{\psi}})\,, \tag{21}$$

which is formula (3). Substituting (21) into equation (19) and solving for λ gives formula (4). The solution with positive λ yields the UCL on φ and the solution with negative λ yields the LCL on φ, as pointed out above.

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