Locally optimal designs for errors-in-variables models

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Errors-in-variables (EIV) models

- Regression models where covariates cannot be observed exactly. Let $\boldsymbol{X}$ be the true variable and $\boldsymbol{W}$ be the observed variable.
  - underlying model: $\boldsymbol{Y} \mid \boldsymbol{X}$, observe $\boldsymbol{W}$ instead of $\boldsymbol{X}$
  - error model: $\boldsymbol{X} \mid \boldsymbol{W}$ or $\boldsymbol{W} \mid \boldsymbol{X}$
- Estimate model parameters of $\boldsymbol{Y} \mid \boldsymbol{X}$ by fitting $\boldsymbol{Y} \mid \boldsymbol{W}$

Taxonomy of EIV models

- True variable $\boldsymbol{X}$
  - functional models: $\boldsymbol{X}$'s are fixed constants
  - structural models: $\boldsymbol{X}$'s are random variables

- Error model structure
  - classical error model: specify $\boldsymbol{W} \mid \boldsymbol{X}, \quad \varepsilon \perp\!\!\!\perp \boldsymbol{X}$

  $\hookrightarrow$ additive error: $\boldsymbol{W} = \boldsymbol{X} + \varepsilon$.
  - Berkson error model: specify $\boldsymbol{X} \mid \boldsymbol{W}, \quad \varepsilon \perp\!\!\!\perp \boldsymbol{W}$

  $\hookrightarrow$ additive error: $\boldsymbol{X} = \boldsymbol{W} + \varepsilon$.

Choice of EIV model

- **Functional vs Structural model**:
  - Use a structural model for a random sample from a population.
  - Functional model is more attractive since it makes no assumptions on the distribution of $\boldsymbol{X}$ and avoids robustness issues due to misspecification of the distribution.

Choice of EIV model

- **Classical errors**:
  - Unable to determine the $\boldsymbol{X}$'s due to errors in measurement.
  - Include sampling and instrument errors.
  - For example,
    $\boldsymbol{X}$ = true intensity of X-ray beam, $\boldsymbol{W}$ =observed intensity,
    ε=instrument recording error $\Rightarrow \varepsilon \perp\!\!\!\perp \boldsymbol{X}$.

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Choice of EIV model

- **Berkson errors**:
  - Error in setting the $\boldsymbol{X}$'s and error in measurement is zero.
  - Include errors in application and/or errors due to physical phenomena.
  - For example,
    $\boldsymbol{X}$ = true amount of water absorbed by a plant,
    $\boldsymbol{W}$ =amount of water applied (set by a valve),
    ε=random fluctuations of pressure and/or absorption process
    $\Rightarrow \varepsilon \not\perp \boldsymbol{X}$.

Effects of errors in covariates

- Result in biased parameter estimates. Effects depend on the underlying model, the error model structure and the distribution of the errors.

- Simple linear regression model with classical additive errors: slope estimate is biased towards zero.
  $\hookrightarrow$ Attenuation to the null

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Underlying and error model

- Nonlinear functional underlying model:

$$Y_{ij} = m(\boldsymbol{x}_i, \theta) + \eta_{ij}, \qquad i = 1, \ldots, n, \;\; j = 1, \ldots, r_i$$

where $\theta = (\theta_0, \ldots, \theta_p)^T$ is the parameter vector, η_{ij} is the response error and $\boldsymbol{x}_i = (x_{i1}, x_{i2}, \ldots, x_{iq})^T \in \mathcal{X} \subset \mathbb{R}^q$ are fixed constants.

- Classical error model:

$$\boldsymbol{W}_{ij} = \boldsymbol{x}_i + \varepsilon_{ij}.$$

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- Classical error model:

$$\boldsymbol{W}_{ij} = \boldsymbol{x}_i + \varepsilon_{ij}.$$

Assumptions

1. $m(\boldsymbol{x}_i, \theta)$ is continuous with continuous first and second order derivatives wrt both $\boldsymbol{x}_i$ and θ
2. $(\eta_{ij}, \varepsilon_{ij})^T \overset{iid}{\sim} N(\mathbf{0}, \Sigma_{\eta\varepsilon})$, where $\Sigma_{\eta\varepsilon}$ is a fixed positive definite matrix
3. For all $\zeta > 0$, there exists a constant $\delta_\zeta > 0$ such that

$$\frac{1}{n}\sum_{i=1}^{n}\sum_{j=1}^{r_i} \inf (Y_{ij} - m(\boldsymbol{x}_i, \theta), \boldsymbol{W}_{ij} - \boldsymbol{x}_i)\Sigma_{\eta\epsilon}^{-k}(Y_{ij} - m(\boldsymbol{x}_i, \theta), \boldsymbol{W}_{ij} - \boldsymbol{x}_i)^T > \delta_\zeta,$$

$\forall\ \theta$ satisfying $|\theta - \theta_{\text{true}}| > \zeta$, $k = 0, 1$

Estimation

- Fuller (1987) fixes $r_i = 1$ and finds the limiting properties of $\hat{\theta}_{ML}$ as the error variances become small.
- For

$$\lim_{r_i \to \infty} \frac{r_i}{r} = \omega_i > 0, \qquad i = 1, \ldots, n,$$

where $r = \sum_{i=1}^{n} r_i$ and an approximate design

$$\xi = \begin{Bmatrix} \boldsymbol{x}_1 & \ldots & \boldsymbol{x}_n \\ \omega_1 & \ldots & \omega_n \end{Bmatrix},$$

the asymptotic properties of $\hat{\theta}_{ML}$ and $\hat{\theta}_{LS}$ as $r \to \infty$ are derived.

Maximum likelihood estimation

As $r \to \infty$

$$\sqrt{r}(\hat{\theta}_{ML} - \theta_{\text{true}}) \xrightarrow{\mathcal{L}} N(\mathbf{0}, M_{ML}^{-1}(\xi, \theta)),$$

where $\xrightarrow{\mathcal{L}}$ denotes convergence in distribution and

$$M_{ML}(\xi, \theta) = \sum_{i=1}^{n} \frac{\omega_i}{\sigma_1(\boldsymbol{x}_i, \theta)} \left(\frac{\partial m(\boldsymbol{x}_i, \theta)}{\partial \theta} \right)^T \left(\frac{\partial m(\boldsymbol{x}_i, \theta)}{\partial \theta} \right)$$

$$\sigma_1(\boldsymbol{x}_i, \theta) = \left(1, \frac{\partial m(\boldsymbol{x}_i, \theta)}{\partial \boldsymbol{x}_i} \right) \Sigma_{\eta\varepsilon} \left(1, \frac{\partial m(\boldsymbol{x}_i, \theta)}{\partial \boldsymbol{x}_i} \right)^T$$

Least squares estimation

As $r \to \infty$

$$\sqrt{r}(\hat{\theta}_{LS} - \theta_{\text{true}}) \xrightarrow{\mathcal{L}} N(\mathbf{0}, M_{LS}^{-1}(\xi,\theta)),$$

where $\xrightarrow{\mathcal{L}}$ denotes convergence in distribution and

$$M_{LS}(\xi,\theta) = D_0(\xi,\theta) D_1^{-1}(\xi,\theta) D_0(\xi,\theta).$$

$$D_0(\xi,\theta) = \sum_{i=1}^{n} \frac{\omega_i}{\sigma_0(\boldsymbol{x}_i,\theta)} \left(\frac{\partial m(\boldsymbol{x}_i,\theta)}{\partial\theta}\right)^T \left(\frac{\partial m(\boldsymbol{x}_i,\theta)}{\partial\theta}\right)$$

$$D_1(\xi,\theta) = \sum_{i=1}^{n} \omega_i \frac{\sigma_1(\boldsymbol{x}_i,\theta)}{\sigma_0(\boldsymbol{x}_i,\theta)} \left(\frac{\partial m(\boldsymbol{x}_i,\theta)}{\partial\theta}\right)^T \left(\frac{\partial m(\boldsymbol{x}_i,\theta)}{\partial\theta}\right)$$

$$\sigma_k(\boldsymbol{x}_i,\theta) = \left(1, \frac{\partial m(\boldsymbol{x}_i,\theta)}{\partial \boldsymbol{x}_i}\right) [\Sigma_{\eta\varepsilon}]^k \left(1, \frac{\partial m(\boldsymbol{x}_i,\theta)}{\partial \boldsymbol{x}_i}\right)^T, \qquad k = 0, 1$$

σ_0 and σ_1 functions

- $Y = \theta_0 + \theta_1 x + \eta$
  $W = x + \varepsilon$,

  with $(\eta, \varepsilon)^T \sim N(\mathbf{0}, \Sigma_{\eta\varepsilon})$ and $\Sigma_{\eta\varepsilon} = \begin{pmatrix} \sigma_\eta^2 & 0 \\ 0 & \sigma_\varepsilon^2 \end{pmatrix}$

- $\sigma_0(x,\theta) = \left(1, \frac{\partial m(\mathbf{x},\theta)}{\partial \mathbf{x}}\right)\left(1, \frac{\partial m(\mathbf{x},\theta)}{\partial \mathbf{x}}\right)^T = (1, \theta_1)(1, \theta_1)^T$
  $\sigma_1(x,\theta) = \left(1, \frac{\partial m(\mathbf{x},\theta)}{\partial \mathbf{x}}\right)\Sigma_{\eta\varepsilon}\left(1, \frac{\partial m(\mathbf{x},\theta)}{\partial \mathbf{x}}\right)^T = \sigma_\eta^2 + \theta_1^2\sigma_\varepsilon^2$

- Substituting W for x

$$Y = \theta_0 + \theta_1 W - \theta_1\varepsilon + \eta = \theta_0 + \theta_1 W + \eta^*,$$

  where $\eta^* \sim N(0, \sigma_\eta^2 + \theta_1^2\sigma_\varepsilon^2)$

σ_0 and σ_1 functions

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  $W = x + \varepsilon$,
  with $(\eta, \varepsilon)^T \sim N(\mathbf{0}, \Sigma_{\eta\varepsilon})$ and $\Sigma_{\eta\varepsilon} = \begin{pmatrix} \sigma_\eta^2 & 0 \\ 0 & \sigma_\varepsilon^2 \end{pmatrix}$

- $\sigma_0(x, \theta) = \left(1, \frac{\partial m(\boldsymbol{x},\theta)}{\partial \boldsymbol{x}}\right) \left(1, \frac{\partial m(\boldsymbol{x},\theta)}{\partial \boldsymbol{x}}\right)^T = (1, \theta_1)\,(1, \theta_1)^T$
  $\sigma_1(x, \theta) = \left(1, \frac{\partial m(\boldsymbol{x},\theta)}{\partial \boldsymbol{x}}\right) \Sigma_{\eta\varepsilon} \left(1, \frac{\partial m(\boldsymbol{x},\theta)}{\partial \boldsymbol{x}}\right)^T = \sigma_\eta^2 + \theta_1^2 \sigma_\varepsilon^2$

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D-optimality for MLE

General Equivalence Theorem

A design $\xi^*_{\vec{\theta}}$ is locally *D*-optimal for maximum likelihood estimation in any functional nonlinear model with classical additive errors if and only if the inequality

$$d_{ML}(\boldsymbol{x}, \xi^*_\theta, \theta) = \left(\frac{\partial m(\boldsymbol{x}, \theta)}{\partial \theta}\right)^T M_{ML}^{-1}(\xi^*_\theta, \theta)\left(\frac{\partial m(\boldsymbol{x}, \theta)}{\partial \theta}\right) - (p+1)\sigma_1(\boldsymbol{x}, \theta) \leq 0,$$

holds for all $\boldsymbol{x} \in \mathcal{X}$ with equality at the support points of ξ^*_θ .

D-optimality for LSE

- $M_{LS}(\xi,\theta) = D_0(\xi,\theta)D_1^{-1}(\xi,\theta)D_0(\xi,\theta)$

Necessary Condition

Any locally *D*-optimal design $\xi^*_{\vec{\theta}}$ on $\mathcal{X}$ for least squares estimation in any functional nonlinear model with classical additive errors satisfies the inequality

$$d_{LS}(\boldsymbol{x},\xi^*_\theta,\theta) := 2d_0(\boldsymbol{x},\xi^*_\theta,\theta) - \sigma_1(\boldsymbol{x},\theta)d_1(\boldsymbol{x},\xi^*_\theta,\theta) \leq p+1,$$

for all $\boldsymbol{x} \in \mathcal{X}$ with equality at the support points of ξ^*_θ, where

$$d_k(\boldsymbol{x},\xi^*_\theta,\theta) := \left(\frac{\partial m(\boldsymbol{x},\theta)}{\partial\theta}\right)^T \frac{D_k^{-1}(\xi^*_\theta,\theta)}{\sigma_0(\boldsymbol{x},\theta)} \left(\frac{\partial m(\boldsymbol{x},\theta)}{\partial\theta}\right), \qquad k = 0,1.$$

Models

- Michaelis-Menten model: $m_1(x, \vec{\theta}) = \frac{\theta_1 x}{(\theta_2 + x)}, \quad x \in [0, x_u]$.
- Emax model: $m_2(x, \vec{\theta}) = \theta_0 + \frac{\theta_1 x}{\theta_2 + x}, \quad x \in [0, x_u]$.
- Exponential regression model: $m_3(x, \vec{\theta}) = \theta_0 + \theta_1 e^{-\theta_2 x}$, $x \in [0, x_u]$.

$\hookrightarrow$ $\theta_0 \geq 0$: effect at $x = 0$ (placebo effect)

$\hookrightarrow$ $\theta_1 > 0$: maximum achievable response for M-M and Emax models, included in the placebo effect for Exponential model.

$\hookrightarrow$ $\theta_2 > 0$: dose x producing half the maximum response for M-M and Emax models (half-saturation constant), the rate of the dose-effect for Exponential model.

Models

- $Y = m(x, \theta) + \eta$
  $W = x + \varepsilon$

- $(\eta, \varepsilon)^T \sim N(0, \Sigma_{\eta\varepsilon})$ with

$$\Sigma_{\eta\varepsilon} = \begin{pmatrix} \sigma_\eta^2 & 0 \\ 0 & \sigma_\varepsilon^2 \end{pmatrix}$$

Number of support points

MLE

For the Michaelis-Menten, Emax and exponential regression models with classical additive errors, the corresponding locally *D*-optimal designs under maximum likelihood estimation are saturated and equally weighted.

LSE

For the Michaelis-Menten, Emax and exponential regression models with classical additive errors, the corresponding locally *D*-optimal designs under least squares estimation have at most four, five and six support points respectively.

MLE - Michaelis-Menten model

The locally *D*-optimal design on $\mathcal{X} = [0, x_u]$ for MLE in the Michaelis-Menten model with classical additive errors is $\xi^*_\theta = \{x^*, x_u : 1/2, 1/2\}$, where $x^*(\neq 0)$ is the solution of the equation

$$\frac{1}{x} - \frac{1}{x_u - x} - \frac{2(\theta_2 + x)^3}{(\theta_2 + x_1)^4 + \theta_1^2\theta_2^2\varrho^2_{\varepsilon\eta}} = 0,$$

in the interval $(0, x_u)$ and $\varrho^2_{\varepsilon\eta} = \sigma^2_\varepsilon/\sigma^2_\eta$.

- $x^* = \frac{\theta_2 x_u}{2\theta_2 + x_u}$ for $\varrho^2_{\varepsilon\eta} = 0$ (Rasch (1990)).
- x^* is strictly increasing with $\varrho^2_{\varepsilon\eta} \Rightarrow x^*|_{\varrho^2_{\varepsilon\eta}>0} > x^*|_{\varrho^2_{\varepsilon\eta}=0}$.
- $x^* \to x_u/2$ as $\varrho^2_{\varepsilon\eta} \to \infty$.

MLE - Emax model

The locally *D*-optimal design on $\mathcal{X} = [0, x_u]$ for MLE in the Emax model with classical additive errors is $\xi_\theta^* = \{0, x^*, x_u : 1/3, 1/3, 1/3\}$, where $x^* (\neq 0)$ is the solution of the equation

$$\frac{1}{x} - \frac{1}{x_u - x} - \frac{2(\theta_2 + x)^3}{(\theta_2 + x_1)^4 + \theta_1^2 \theta_2^2 \varrho_{\varepsilon\eta}^2} = 0,$$

in the interval $(0, x_u)$ and $\varrho_{\varepsilon\eta}^2 = \sigma_\varepsilon^2 / \sigma_\eta^2$.

- x^* is equal to the non-trivial support point of the design for the Michaelis-Menten model.

MLE-Exponential regression model

The locally *D*-optimal design on $\mathcal{X} = [0, x_u]$ for MLE in the three-parameter exponential regression model with classical additive errors is $\xi^*_\theta = \{0, x^*, x_u : 1/3, 1/3, 1/3\}$, where $x^*(\neq 0)$ is the solution of the equation

$$\frac{1 - e^{\theta_2 x_u} + \theta_2 x_u e^{\theta_2 x_1}}{x_1 - x_u + x_u e^{\theta_2 x_1} - x_1 e^{\theta_2 x_u}} - \frac{\theta_2 e^{2\theta_2 x_1}}{e^{2\theta_2 x_1} + \theta_1^2 \theta_2^2 \varrho^2_{\varepsilon\eta}} = 0,$$

in the interval $(0, x_u)$ and $\varrho^2_{\varepsilon\eta} = \sigma^2_\varepsilon / \sigma^2_\eta$.

- $x^* = \frac{1}{\theta_2} - \frac{x_u e^{-\theta_2 x_u}}{(1 - e^{-\theta_2 x_u})}$ for $\varrho^2_{\varepsilon\eta} = 0$ (Dette et al. (2006)).
- x^* is strictly increasing with $\varrho^2_{\varepsilon\eta} \Rightarrow x^*|_{\varrho^2_{\varepsilon\eta} > 0} > x^*|_{\varrho^2_{\varepsilon\eta} = 0}$.

LSE - Saturated designs

The locally D-optimal saturated design on $\mathcal{X} = [0, x_u]$ for the Michaelis-Menten and Emax model with classical additive errors is equally supported at $\{x^*, x_u\}$ and $\{0, x^*, x_u\}$ respectively, where in both cases x^* is a solution of the equation

$$\frac{1}{x} - \frac{1}{x_u - x} - \frac{2(\theta_2 + x)^3}{(\theta_2 + x)^4 + \theta_1^2\theta_2^2\varrho_{\varepsilon\eta}^2} + \frac{2\theta_1^2\theta_2^2}{(\theta_2 + x)\left[(\theta_2 + x)^4 + \theta_1^2\theta_2^2\right]} = 0,$$

in the interval $(0, x_u)$ and $\varrho_{\varepsilon\eta}^2 = \sigma_\varepsilon^2/\sigma_\eta^2$.

- $x_{LSE}^* > x_{MLE}^*$.

LSE - Saturated designs

Under least squares estimation, the locally *D*-optimal saturated design on $\mathcal{X} = [0, x_u]$ for the three-parameter exponential regression model with classical additive errors is always supported at x_u.

Investigations

- Compare *D*-optimal designs with error in the covariate for MLE and LSE.
- Compare *D*-optimal designs with and without error in the covariate.
- Sensitivity of *D*-optimal designs assuming error in the covariate under misspecifications of the parameter values.
- Non-Saturated *D*-optimal designs assuming error in the covariate for LSE.

Mihara et al. (2000)

- Model the velocity of a biochemical reaction (CSD plus pyruvate), Y, to the concentration of a substrate (L-cysteine sulfinate), X, using the Michaelis-Menten model.
- $\mathcal{X} = [0, 80]$, $(\theta_1, \theta_2) = (16, 3.5)$.
- Errors in measurement of X due to instrument recording errors.

Mihara et al. (2000)

$\varrho^2_{\varepsilon\eta} = \sigma^2_\varepsilon / \sigma^2_\eta$	x^*_{MLE}	x^*_{LSE}
4/1	8.49	9.47
2/1	7.15	8.40
1/1	6.04	7.57
1/2	5.16	6.98
1/4	4.49	6.59

- $x^*_{LSE} > x^*_{MLE}$ for all $\varrho^2_{\varepsilon\eta} \geq 0$.
- x^* increases with $\varrho^2_{\varepsilon\eta}$.

Mihara et al. (2000)

- $\xi = \{3.22, 80; 1/2, 1/2\}$ for $\varrho^2_{\varepsilon\eta} = 0$.

$\varrho^2_{\varepsilon\eta} = \sigma^2_\varepsilon / \sigma^2_\eta$	$eff_{MLE}(\%)$	$eff_{LSE}(\%)$
4/1	61	41
2/1	72	49
1/1	82	58
1/2	90	66
1/4	96	73

- $eff_{MLE} > 90\%$ only for $\varrho^2_{\varepsilon\eta} < 1$.
- Even if σ^2_ε, the *D*-optimal design assuming no error in the covariate might not be efficient.

Frisillo and Stewart (1980)

- Study the wave velocity of ultrasonic signals (Y) against the percent gas saturation in a brine solution (X). Determine the percentage of gas-brine saturation using an X-ray absorption technique where the X-ray beam intensity is measured.
- Errors in measurement of the true intensity and so of X are due to instrument recording errors.
- $\mathcal{X} = [0, 35]$ due to the absorption technique used.
- We fit the three-parameter exponential regression model assuming $\sigma_\varepsilon^2 = \sigma_\eta^2 = \sigma^2$
  $\Rightarrow (\theta_0, \theta_1, \theta_2, \sigma^2) = (1210, 66.07, 0.0696, 5.68)$.

Frisillo and Stewart (1980)

- $\xi_1^* = \{0, 17.23, 35; 1/3, 1/3, 1/3\}$, for MLE
  $\xi_2^* = \{1.25, 21.54, 35; 1/3, 1/3, 1/3\}$, for LSE

	$\pm 10\%$		$\pm 30\%$	
$\theta_1, \theta_2, \sigma^2$	ξ_1^*	ξ_2^*	ξ_1^*	ξ_2^*
$+++$	100	98.9	99.9	92.7
$++-$	100	98.9	99.9	92.7
$+-+$	100	99.5	99.8	98.1
$-++$	99.9	99.5	98.5	95.7
$+--$	100	99.5	99.9	98.1
$-+-$	99.9	99.5	98.5	95.7
$--+$	100	99.1	99.8	95.6
$---$	100	99.1	99.8	95.6

Optimal designs for LSE

- Numerical search for non-saturated designs showed that in both examples the locally *D*-optimal saturated designs are globally optimal.

Summary

- Approximate design theory for nonlinear functional models with classical additive errors is developed for MLE and LSE.
- Provide analytical characterisations of the locally *D*-optimal designs for widely used nonlinear models.
- Show that the *D*-optimal design assuming no error in the covariate is not necessarily efficient even if σ_ε^2 is small.
- For the data examples considered, the saturated designs for both estimation methods are globally optimal and robust to misspecifications of the parameters up to 30%.

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