Sequential designs for Individualized dosing algorithms

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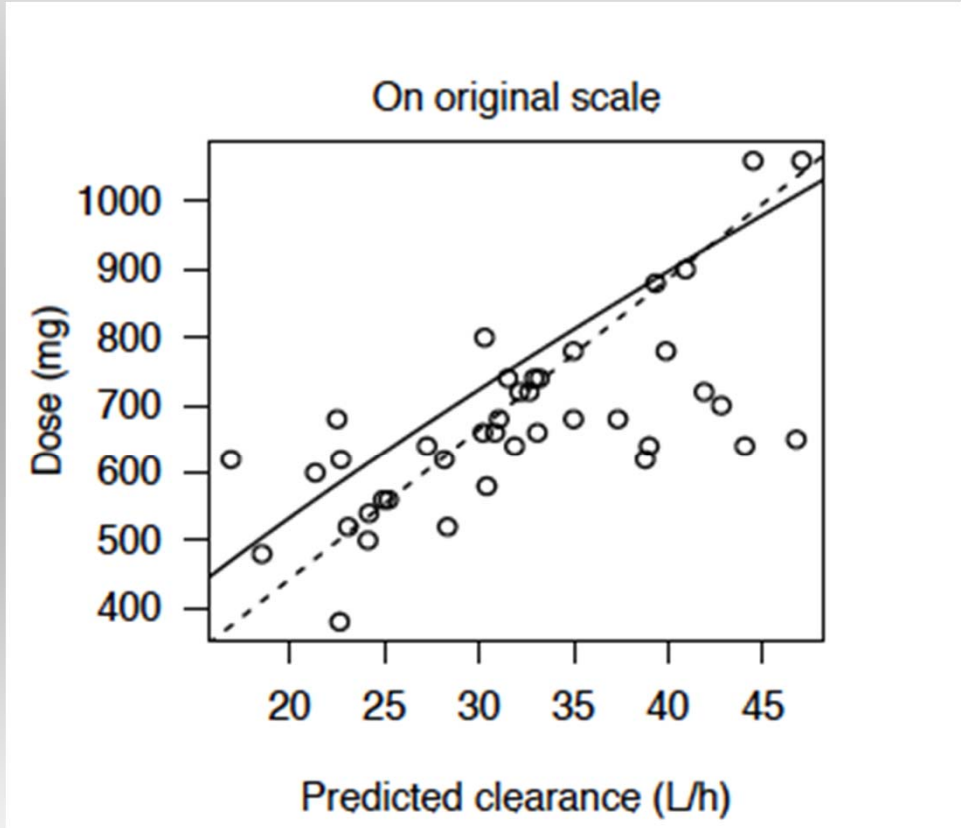
Mao, Cheung (2016+). Sequential designs for individualized dosing in phase I cancer clinical trials. Contemporary Clinical Trials. In press.

Agenda

- Data, design objective & least squares recursion
- **Eigenvalue condition (EVC)**
- **Method: Least squares recursion with EVC**
- Simulation study
- Discussion

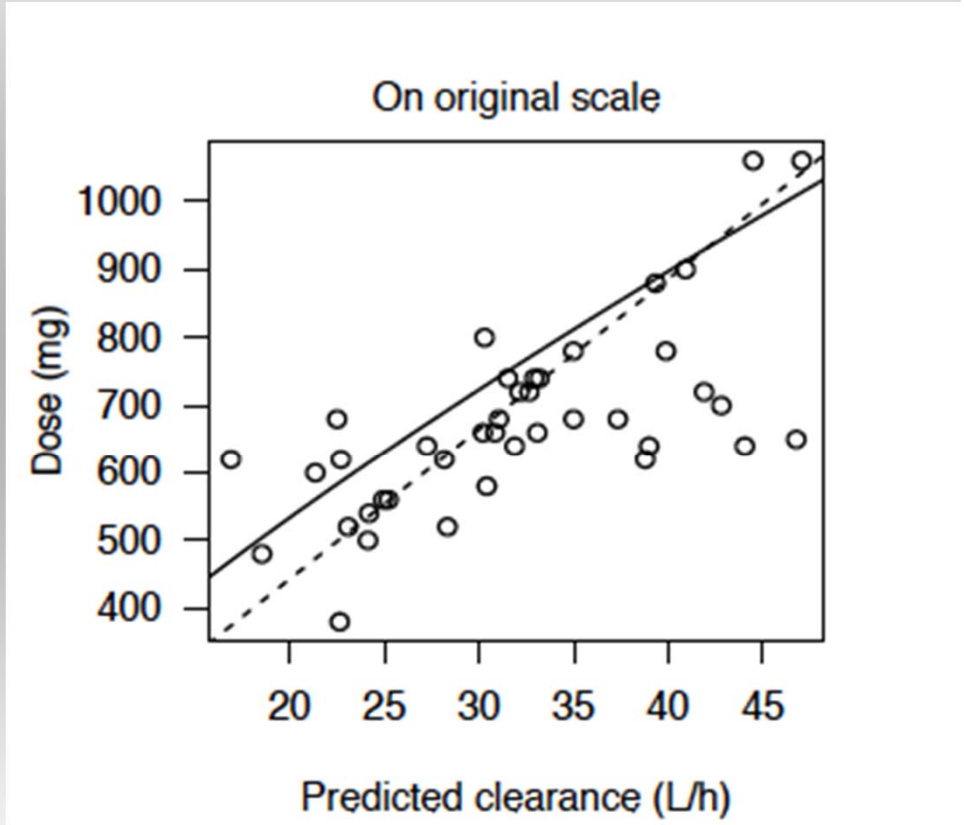
Data

- *Irinotecan*
- *BSA formula (n = 20)*
  - *X = log(350) + log(BSA)*
- *Dosing Equation (n = 20)*
  - *Target AUC at 22.157 micrograms h/ml*
  - *Dotted line*



Objectives

- *Estimate a dosing algorithm (solid line)*
- *Treat study subjects close to their targets*



Defining the problem

- Y = log(AUC); X = log(Dose); Z = log(Biomarker)

$$Y = \alpha + \beta X + \gamma Z + \epsilon, \quad \beta > 0, \ \gamma \leq 0,$$

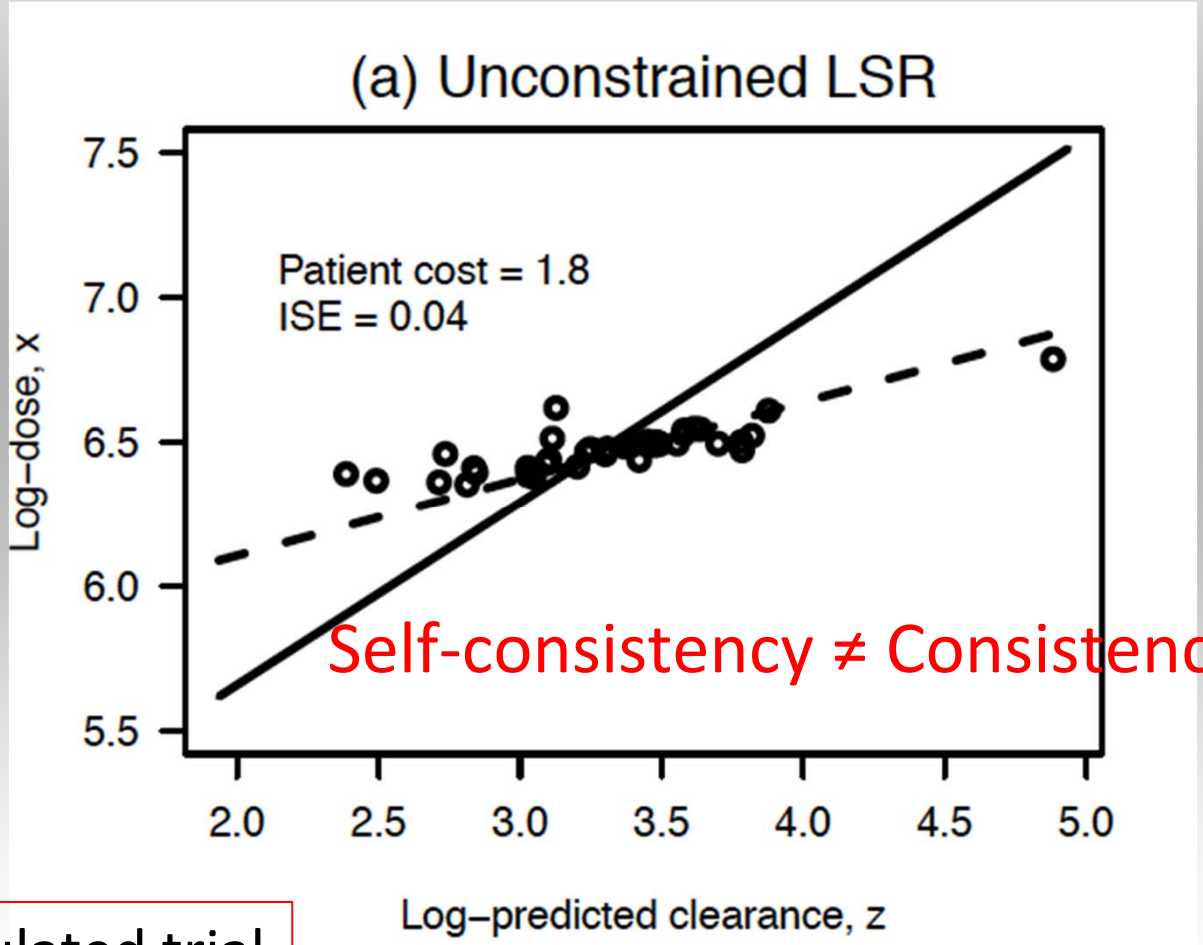
The trial objective is, for each subject with z_i, to determine a dose x_i such that $E(Y|X = x_i, Z = z_i) = t_0$, i.e. to estimate the patient-specific dosing function:

$$\theta(z) = \frac{t_0 - \alpha - \gamma z}{\beta}, \quad \textit{for any given } z \in I_Z. \qquad (3)$$

Least Squares Recursion (LSR)

$$\begin{aligned} \hat{\theta}_i(z) &= \frac{t_0 - \hat{\alpha}_i - \hat{\gamma}_i z}{\hat{\beta}_i}, \\ x_{i+1} &= \min\left\{ \max\left\{ \hat{\theta}_i(z_{i+1}), x_{min} \right\}, x_{max} \right\}, \end{aligned} \tag{4}$$

Least Squares Recursion (LSR)



Self-consistency ≠ Consistency

A simulated trial

Eigenvalue condition

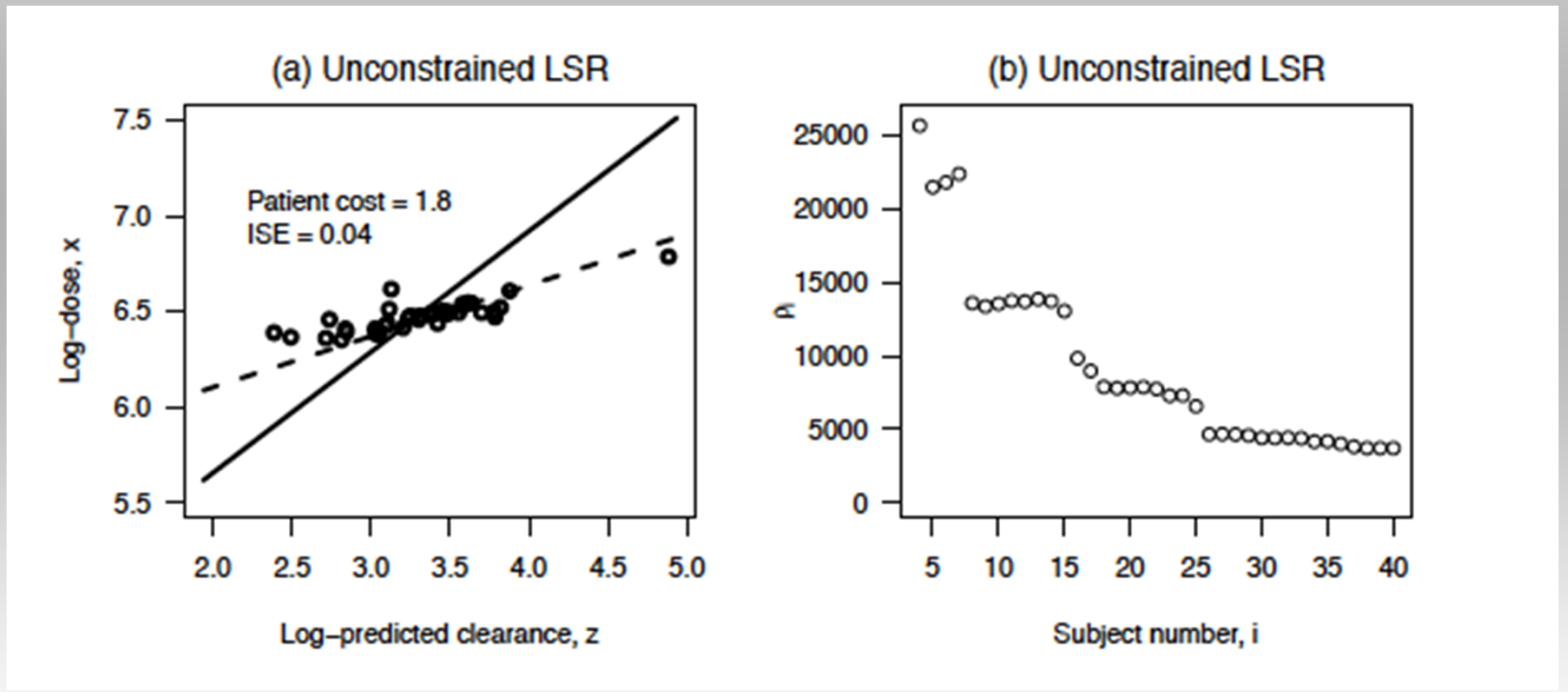
- In dose finding, we are dealing with a stochastic design matrix M_n, which requires stronger conditions for consistency than a fixed M_n. Lai and Wei (1982):

The eigenvalue condition (EVC):

$$\frac{\log \lambda_{max}(n)}{\lambda_{min}(n)} \to 0 \text{ a.s., as } n \to \infty,$$

where $\lambda_{max}(n)$ and $\lambda_{min}(n)$ are respectively the maximum and minimum eigenvalues of $M_n' M_n$.

Eigenvalue condition



LSR with EVC

$$\tilde{\theta}_n(z_{n+1}) = \arg\min_x |x - \hat{\theta}_n(z_{n+1})| \text{ subject to } \rho_{n+1}(x, z_{n+1}) \leq r_{n+1}$$

where $\rho_n(x, z) = \frac{\log \lambda_{max}(n)}{\lambda_{min}(n)}$, $r_n \to 0$

$$x_{n+1} = \max[\min\{\tilde{\theta}_n(z_{n+1}), x_{\max}\}, x_{\min}]$$

LSR with EVC

Practical Considerations

- Initial design
- Coherence
- r_n : Calibration

LSR with EVC

Practical Considerations

- Initial design
- Coherence
- r_n : Calibration

- Use conventional rule to start: e.g., BSA
- Transition to model based as long as LSE is "stable"

$$|M'_{n0} M_{n0}| \geq 0.01$$

LSR with EVC

Practical Considerations

- Initial design
- Coherence
- r_n : Calibration

- Ethical consideration (Cheung, 2005, Biometrika)
- If the current patient has AUC lower than t_0 and the next patient has a higher clearance, do not de-escalate

$$x_{n+1} = \begin{cases} \max[\min\{\tilde{\theta}_n(z_{n+1}), x_n\}, x_{\min}] & \text{if } y_n > t_0 \text{ and } z_{n+1} \leq z_n, \\ \min[\max\{\tilde{\theta}_n(z_{n+1}), x_n\}, x_{\max}] & \text{if } y_n < t_0 \text{ and } z_{n+1} \geq z_n, \\ \max[\min\{\tilde{\theta}_n(z_{n+1}), x_{\max}\}, x_{\min}] & \text{otherwise.} \end{cases}$$

LSR with EVC

Practical Considerations

- Initial design
- Coherence
- r_n : Calibration

$$r_n = \frac{C \log n}{n^{\delta_1} (\log n)^{\delta_2}}$$

1. Iterate δ_1 and δ_2 on a relevant grid
2. Run simulation by drawing 10000 scenarios from the posterior distribution
3. Record average loss

Choose δ_1 and δ_2 with the minimum average loss

LSR with EVC

Practical Considerations

- Initial design
- Coherence
- r_n : Calibration

Integrated error in estimation of theta(z)

$$C_\kappa(\delta_1,\delta_2) = \frac{1}{10000}\sum_{j=1}^{10000}\left\{D_n^{(j)} + \kappa n \mathrm{ISE}_j\right\} := \bar{D}_n + \kappa n \overline{\mathrm{ISE}}$$

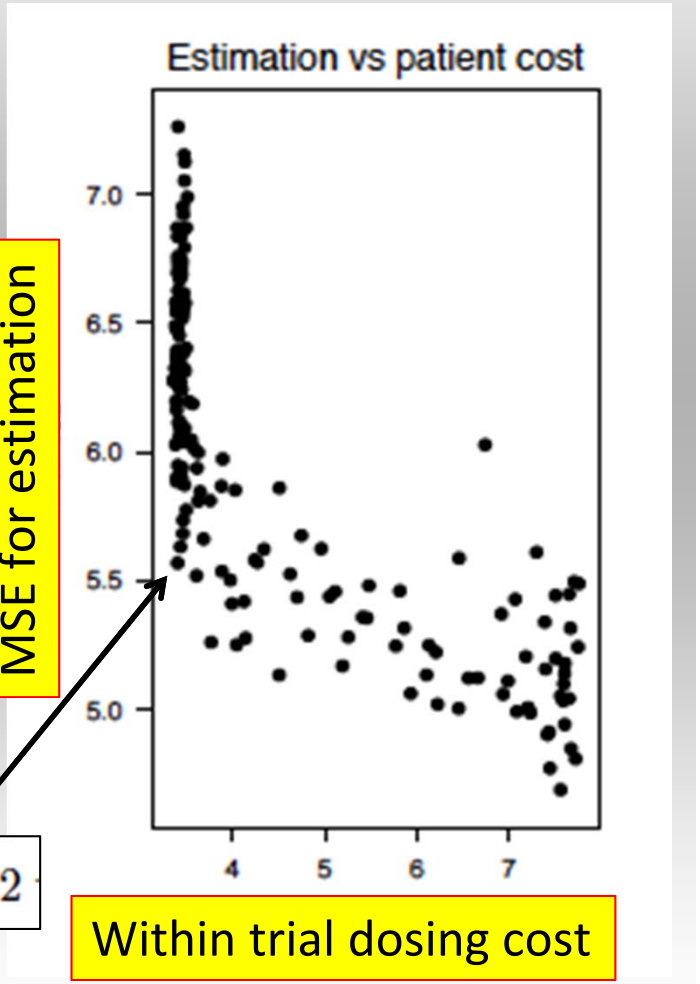
Within trial dosing cost in a trial

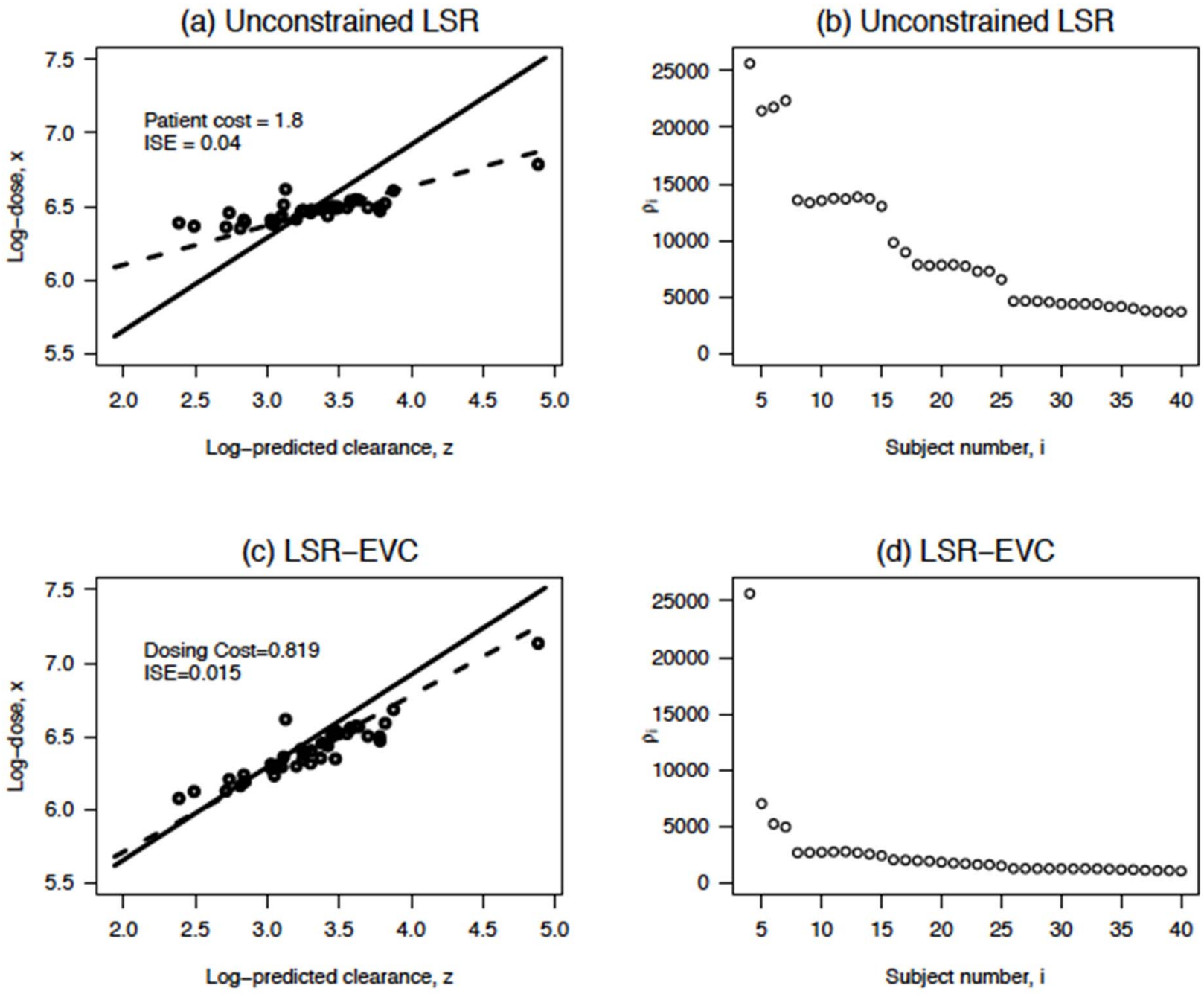
LSR with EVC

Practical Considerations

- Initial design
- Coherence
- r_n : Calibration

$$r_n = \frac{C \log n}{n^{\delta_1} (\log n)^{\delta_2}}$$

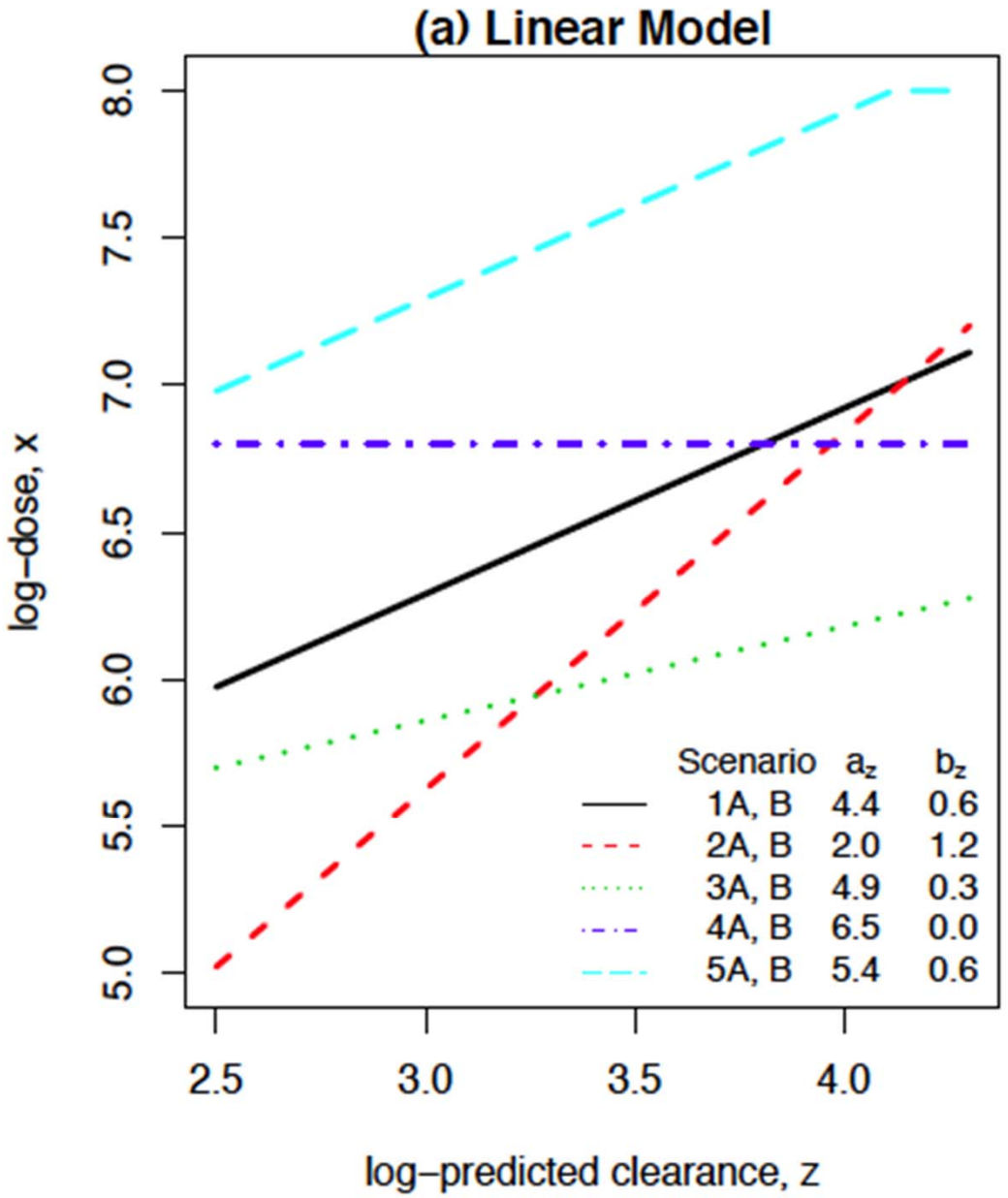



(a) Unconstrained LSR
Patient cost = 1.8
ISE = 0.04
Log−dose, x
Log−predicted clearance, z
(b) Unconstrained LSR
ρ_i
Subject number, i
(c) LSR−EVC
Dosing Cost=0.819
ISE=0.015
Log−dose, x
Log−predicted clearance, z
(d) LSR−EVC
ρ_i
Subject number, i

Simulation study

- Outcome generation:
  - $Y = g(a + bx + cz) + N(0,0.26^2)$
  - Scenarios 1-5: $g(s) = s$ for Scenarios 1-5
  - Scenarios 6-7: Nonlinear $g(s)$
  - $b = 0.68, 0.32$
- Methods: $n = 40$
  - LSR (with coherence constraint)
  - LSR-EVC
  - BSA
  - Equation formula

Simulation Scenarios



Simulation Results

Method	Scenario	$E(D_n)$	$E(\text{ISE}) \times 100$	Efficiency	Scenario	$E(D_n)$	$E(\text{ISE}) \times 100$	Efficiency
LSR	1A	2.20	1.17	1.00	1B	4.04	5.40	1.00
LSR-EVC		2.01	0.90	1.30		4.22	3.90	1.38
BSA		3.13	17.6	0.07		3.13	31.9	0.17
Equation		1.36	—	—		1.36	—	—
LSR	2A	4.36	0.88	1.00	2B	8.32	5.31	1.00
LSR-EVC		3.88	0.84	1.05		7.12	3.89	1.37
BSA		15.7	30.1	0.03		15.7	68.7	0.08
Equation		5.85	—	—		5.85	—	—

Simulation Results

LSR	3A	3.45	0.95	1.00	3B	6.81	5.40	1.00
LSR-EVC		3.12	0.89	1.07		6.06	3.85	1.10
BSA		10.4	33.4	0.03		10.4	64.6	0.08
Equation		15.9	—	—		15.9	—	—
LSR	4A	2.41	1.04	1.00	4B	4.81	5.41	1.00
LSR-EVC		2.40	0.88	1.18		4.85	3.81	1.42
BSA		4.42	24.9	0.04		4.42	42.1	0.13
Equation		12.6	—	—		12.6	—	—
LSR	5A	8.40	0.72	1.00	5B	13.3	3.18	1.00
LSR-EVC		7.88	0.72	1.00		12.1	3.13	1.02
BSA		48.2	48.7	0.01		48.2	140	0.02
Equation		43.9	—	—		43.9	—	—

Simulation Results (Non-linear Model)
Scenarios 6: E-max
Scenarios 7: Power

LSR	6A	6.25	1.59	1.00	6B	5.25	0.88	1.00
LSR-EVC		5.41	1.54	1.09		4.74	0.86	1.07
BSA		13.8	42.84	0.07		18.75	36.69	0.05
Equation		1.41	—	—		8.99	—	—
LSR	7A	5.05	1.99	1.00	7B	7.15	1.00	1.00
LSR-EVC		4.49	1.73	1.14		6.42	0.98	1.08
BSA		12.53	38.19	0.08		27.59	63.98	0.04
Equation		0.8	—	—		15.11	—	—

Discussion 1

- EVC is easy to calculate: Free of model parameters
- EV condition for consistency holds for
  - GLM (for different endpoints; Chen et al., 1999)
  - Bayes estimation (for different estimation methods)
- EVC can be applied to other dose finding problems:
  - Drug combinations $Y \sim X_1 + X_2$
  - Non-monotone dose response $Y \sim f(X)$ as long as f is specified

Discussion 2

- Design parameter: Convergence rate r_n is key

- Model robustness
  - Simulation
  - Extension from PK model

Reference

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