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Accelerating the Possibilities

Optimal Design of Experiments for Delayed Responses in Clinical Trials

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OUTLINE

1. Adaptive Dose Ranging Studies
2. Longitudinal Models
3. Conclusion

Dose-Ranging Studies: Objectives

Detecting DR	• evaluate if there is evidence of activity associated with the drug, represented by a change in clinical response resulting from a change in dose (PoC);
Identifying clinical relevance	• if PoC is established, determine if a pre-defined *clinically relevant* response (compared to the placebo response) can be obtained within the observed dose range;
Selecting a target dose	• when the previous goal is met, select the dose to be brought into the confirmatory phase, the so-called *target dose*;
Estimating the dose response	• finally, estimate the dose-response profile within the observed dose range.

Motivating Example

- Doses:
  - 9 doses: {0,1,2,3,4,5,6,7,8}
- Primary Endpoint:
  - change from baseline in pain score at W12
- Clinically meaningful difference: –1.3
- Variance: 4.5
- Total Sample Size: 250 subjects
- Enrollment: uniform over 52 Weeks
- Randomize the first 50 subjects to a subset of doses: {0,2,4,6,8}
- IA after every 50 subjects enrolled

Optimal Design of Experiment

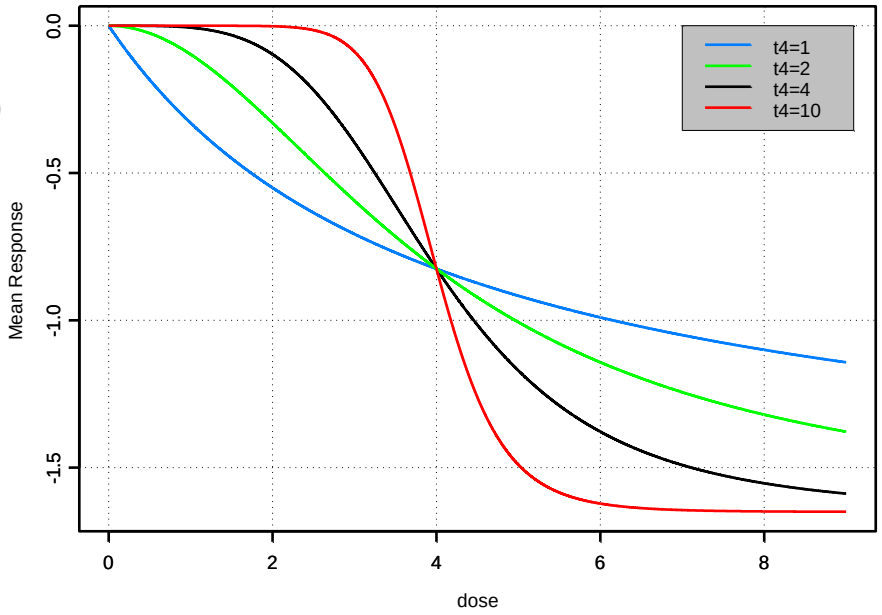
- Optimal design of experiment provides a powerful framework
  - to formulate the objective(s) of a dose ranging study
    - flexible model (as a function of dose) for the mean of the primary endpoint
    - the objective function to be optimized
  - and to find the solution (the design)
    - the set of doses and the corresponding randomization probabilities
- **Estimating the dose response:** *D-optimal design* that minimizes the volume of the ellipsoidal confidence region for the unknown parameters
- **Selecting the target dose:** *c-optimal design* that minimizes the variance of the estimate of MED

Primary Efficacy Endpoint

- Sigmoid Emax model (4 parameter logistic)

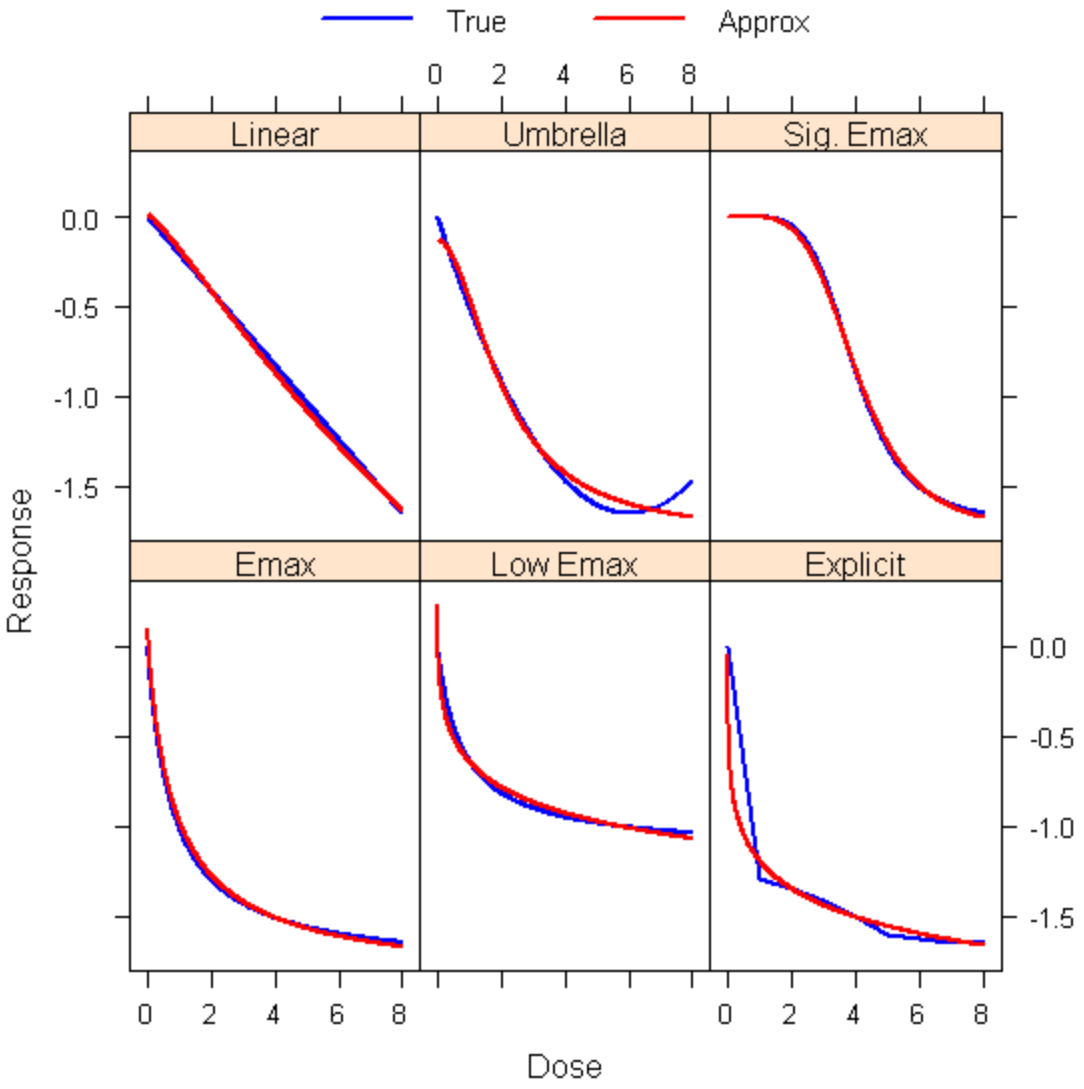
$$f(d,\theta) = \theta_1 + (\theta_2 - \theta_1)\frac{d^{\theta_4}}{d^{\theta_4} + \theta_3^{\theta_4}},$$

θ_1 the minimum mean response,
θ_2 the maximum mean response,
θ_3 ED_{50},
θ_4 the slope parameter.

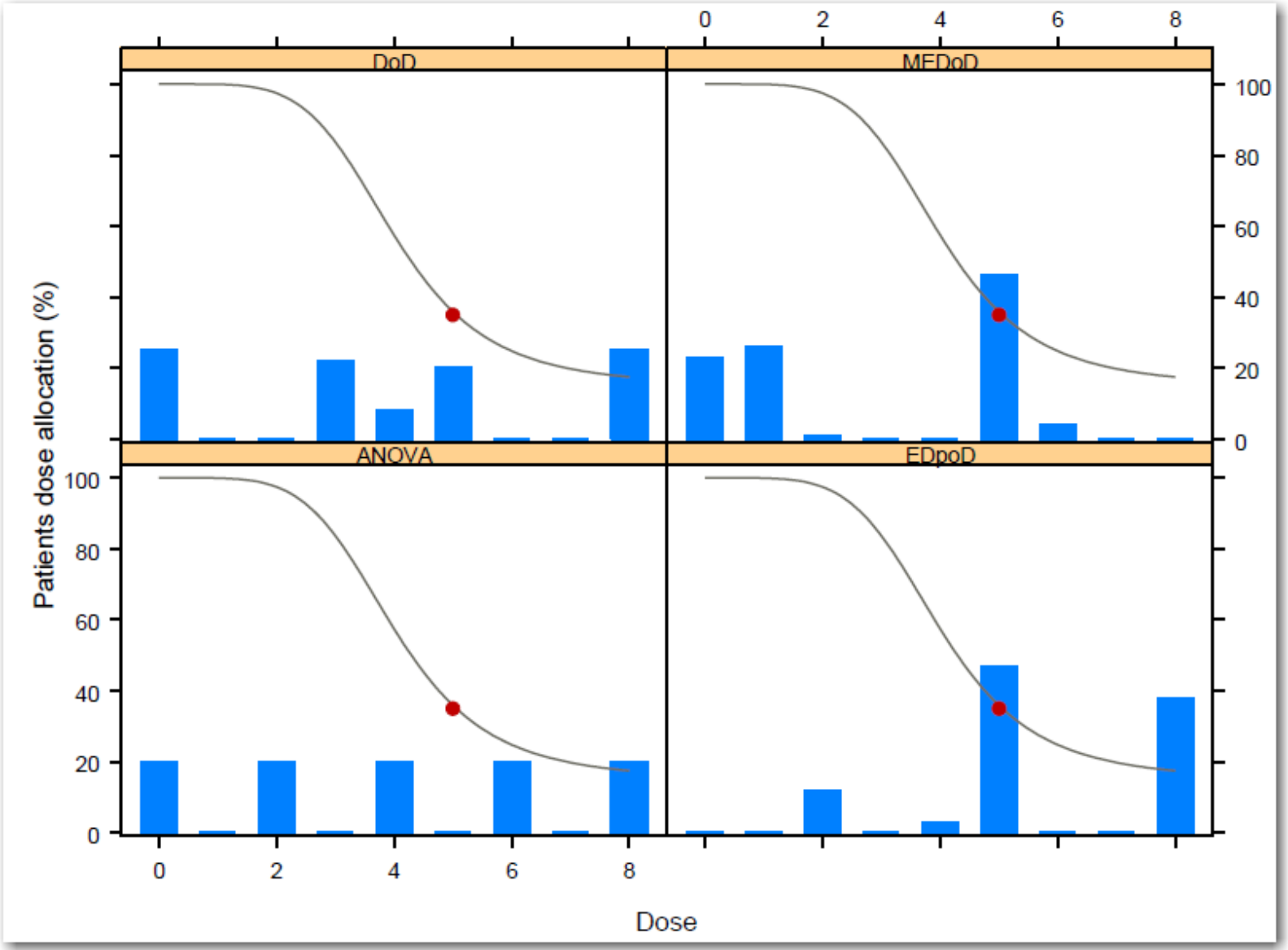


Dragalin, Hsuan, Padmanabhan. **Adaptive Designs for Dose-Finding Based on Sigmoid Emax Model.** *J. Biopharmaceutical Statistics.* 2007, 17: 1051-1070

Sigmoid Emax Fit



D- and c-Optimal Designs



D-optimal Design

MED-optimal Design

ED_{80}-optimal Design

Motivating Example

- $SigE_{max}$ as design working model
- Repeated Measures:
  - No Longitudinal Model: W12
  - 2 RM: W4, W12
  - 3 RM: W4, W8, W12
  - 6 RM: W2, W4, W6, W8, W10, W12

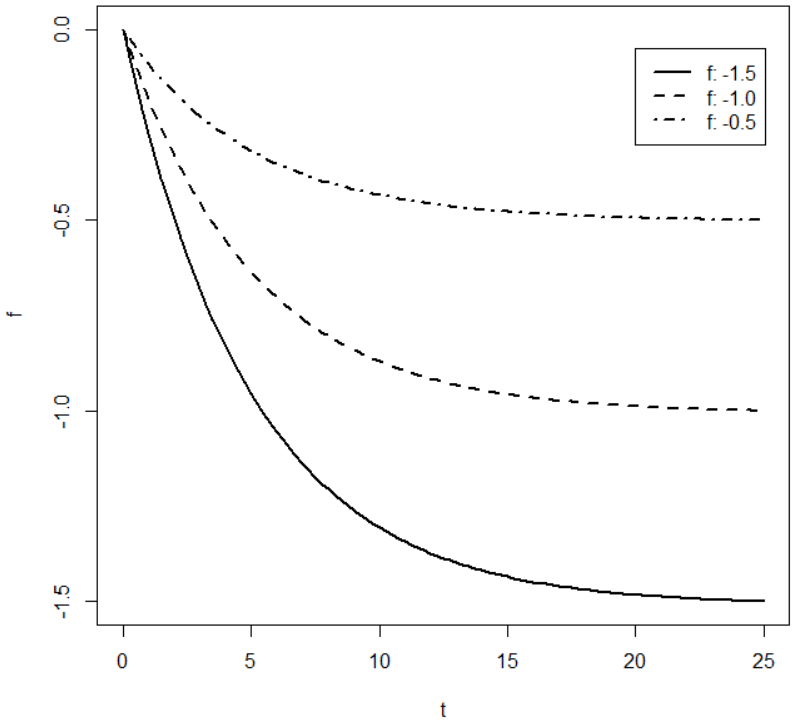
Longitudinal Model

Patient j on dose d_i can provide measurements

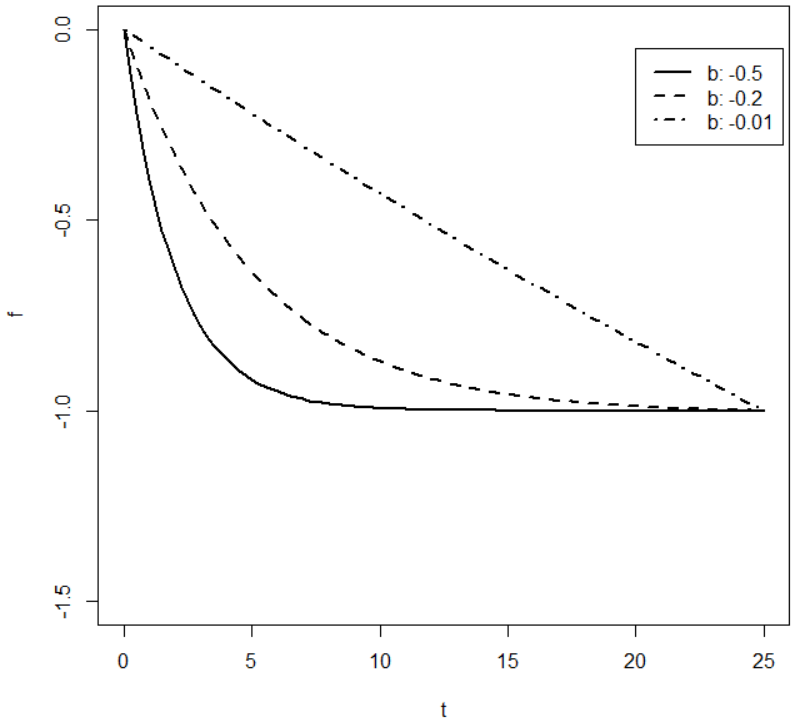
$$Y_{ijk} = (f(d_i, \theta) + s_{ij} + \varepsilon_{ijk}) \frac{1 - e^{\beta t_{jk}}}{1 - e^{\beta T}},$$

at $0 \le t_{j1} < t_{j2} < \cdots < t_{jk_j} \le T.$

Fixed β = - 0.2



Fixed $f(d,\theta)$ = - 0.2



Individual Design

An individual design ζ_K on patient level with K repeated measurements can be defined as a K-dimensional vector of time points (t_1, t_2, …, t_K)

$$\mathbf{Y}_{ij} = (Y_{ij1}, Y_{ij2}, \ldots, Y_{ijK})$$

is a multivariate normal with mean

$$\eta_i(\zeta_K, \theta, \beta) = f(d_i, \theta) * \gamma(\zeta_K, \beta)$$

and covariance

$$\mathrm{Cov}(\mathbf{Y}_{ij}) = \Sigma_i(\zeta, \beta) = \tau^2 \Gamma_K^\top \Gamma_K + \sigma^2 \mathrm{diag}\{\Gamma_K^2\},$$

where $\Gamma_K = \gamma(\zeta_K, \beta) = (\gamma_1, \gamma_2, \ldots, \gamma_K)$.

$$\gamma_k = \frac{1 - e^{\beta t_{jk}}}{1 - e^{\beta T}}$$

Individual Information Matrix

Closed-form solution for the Fisher information matrix of an individual design ζ

$$\mu_{ab}(\zeta,\vartheta) = \frac{\partial \eta(\zeta,\vartheta)}{\partial \vartheta_a}\Sigma^{-1}(\zeta,\beta)\frac{\partial \eta^{\top}(\zeta,\vartheta)}{\partial \vartheta_b} + \frac{1}{2}\mathrm{tr}\left[\Sigma^{-1}(\zeta,\beta)\frac{\partial \Sigma(\zeta,\beta)}{\partial \vartheta_a}\Sigma^{-1}(\zeta,\beta)\frac{\partial \Sigma(\zeta,\beta)}{\partial \vartheta_b}\right], \; a,b = 1,\ldots 5.$$

Population Design

- Consider now a population design ξ with m different doses

$$\xi = \begin{Bmatrix} x_1, & \ldots, & x_m \\ w_1, & \ldots, & w_m \end{Bmatrix}$$

- and weights $0 < w_i < 1 \text{ and } \sum w_i = 1$

- Patients on each dose may be allocated to R distinct individual designs $\zeta_1, \ldots, \zeta_R$, with relative allocation ratios $\nu_1, \ldots, \nu_R$, such that

$$\sum_{r=1}^{R} \nu_r = 1$$

- We will denote such an allocation scheme as Ξ.

Normalized Information Matrices

- The normalized information matrix for Ξ at dose x_i is

$$I_i(\Xi, \vartheta) = \sum_{r=1}^{R} v_r \mu_i(\zeta_r, \vartheta),$$

- The normalized information matrix for the ***combined*** design (ξ, Ξ) is

$$M(\xi, \Xi, \vartheta) = \sum_{i=1}^{m} w_i I_i(\Xi, \vartheta)$$

D-optimal Design

- It is rather straightforward
  - to define optimization criteria depending on the normalized information matrix
  - to construct numerical algorithms for the optimal designs, and
  - to derive their properties
- D-optimality Criterion

$$\Psi(M(\xi, \Xi, \vartheta)) = \log\det[M(\xi, \Xi, \vartheta)],$$

- Equivalence Theorem

$$\mathrm{tr}[I_i(\Xi, \vartheta) M^{-1}(\xi^*, \Xi^*, \vartheta)] \leq p$$

for all doses x_i and all individual designs Ξ

Adaptive Design Implementation

1. Start with an initial design ξ_0 with a given allocation scheme Ξ^* randomizing the initial cohort of N_0 subjects

2. At the end of Stage 1 with the "realized" allocation scheme Ξ_0, obtain estimator $\hat{\vartheta}_0$

3. Plug-in the estimator $\hat{\vartheta}_0$ in the D-optimality criterion and maximize it with respect to ξ

$$\log\det[\alpha M(\xi_0, \Xi_0, \hat{\vartheta}_0) + (1-\alpha) M(\xi, \Xi^*, \hat{\vartheta}_0)]$$

where $\alpha = N_0/(N_0+N_1)$

4. Repeat 2-3 with the next cohort of N_1 subjects

Cost-constrained Designs

- Total cost for a trial with N patients randomized according to a combined design (ξ, Ξ) is

$$C_N(\xi, \Xi) = N(c_1 + c_2 \sum_{r=1}^{R} v_r K_r)$$

  - c_1 – cost for a patient
  - c_2 – cost for a measurement at a time point

Cost-normalized information matrix

$$\tilde{M}_C(\xi, \Xi, \vartheta) = M_N(\xi, \Xi, \vartheta)/C_N(\xi, \Xi) = \sum_{i=1}^{m} w_i \sum_{r=1}^{R} \tilde{v}_r \tilde{\mu}_i(\zeta_r, \vartheta) = \sum_{i=1}^{m} w_i \tilde{I}_i(\Xi, \vartheta)$$

$$\tilde{v}_r = v_r \frac{c_1 + c_2 K_r}{C(\Xi)} \quad \text{and} \quad \tilde{\mu}_i(\zeta_r, \vartheta) = \frac{\mu_i(\zeta_r, \vartheta)}{c_1 + c_2 K_r},$$

$$C(\Xi) == c_1 + c_2 \textstyle\sum_{r=1}^{R} v_r K_r$$

Cost-constrained design

The cost-constrained D-optimal design maximizes

$$\log\det\left[M\left(\xi,\Xi,\vartheta\right)/C\left(\Xi\right)\right]$$

and

$$\mathrm{tr}\left[I_i\left(\Xi,\vartheta\right)M^{-1}\left(\xi^*,\Xi^*,\vartheta\right)\right]\leq p\frac{C\left(\Xi\right)}{C\left(\Xi^*\right)}$$

Conclusion

- Optimal design of experiment provides a powerful framework to address the complex objectives of dose-ranging studies
- Adaptive designs improve precision of target dose selection + DR estimation even in case of delayed responses
- Adaptive, model-based dose ranging methods should be routinely considered in Phase II