Application of model-based designs in drug development

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Outline

- **Two types of problems**
  - Adaptive optimal designs for dose-response studies
  - Optimal designs for population PK/PD studies

- **Key common component in both problems:**
  - Theory/algorithms of optimal model-based designs for nonlinear models

- **Differences (for today)**
  - Dose-response: adaptive designs, require built-in estimation module
  - PK/PD: nonlinear mixed effects models
Optimal design: what we select/optimize

Dose-response studies:
- Doses
- How many doses per patient
- Number of patients enrolled

PK/PD studies:
- Location of sampling times
- No. of sampling times per patient
- Number of patients enrolled

Optimal designs:
- Optimal: with respect to precision of parameter estimates ("size" of variance-covariance matrix)
- Goal: find the most informative doses (sampling times)

Key: Fisher information matrix $\mu(x,\theta)$ of a properly defined single observational unit (individual patient)
Models

- Dose-response
  - $E_{\text{max}}$ (continuous logistic)
  - Binary logistic

- PK/PD
  - Compartmental PK (systems of ODE)
  - Various PD (systems of ODE, $E_{\text{max}}$ ...)

- Software tools: GUI-based standalone, Matlab

- Why Matlab
  - Allows for creating executable files (no license required for end-users)
  - Easy to create GUI
Optimal designs

Information matrix: \( n_i \) patients on \( x_i \) \( \Rightarrow \) \( M_N(\theta) = \sum_{i=1}^{N} n_i \mu(x_i, \theta) \)

Variance of the MLE: \( \text{Var}(\hat{\theta}) \approx M_N^{-1}(\theta) \)

\[
M(\xi, \theta) = \frac{M_N(\theta)}{N} = \sum_{i} w_i \mu(x_i, \theta) \quad \text{- normalized information, per observation}
\]

\( \xi = \{w_i, x_i\} \) - normalized design; \( w_i = n_i/N \) - weights

\[
D(\xi, \theta) = M^{-1}(\xi, \theta) \quad \text{- normalized variance-covariance matrix}
\]
Optimal designs (cont.)

Criterion of optimality \( \Psi[D(\xi, \theta)] \rightarrow \min_{\xi} \) : minimization wrt

- weights \( w_i, 0 \leq w_i \leq 1, \sum_i w_i = 1 \) (continuous designs)

- admissible \( x_i \in X \) - design region (doses/sampling sequences)

Locally D-optimal designs: \( \Psi = |D(\xi, \theta)| \)

Equivalence Theorem: Kiefer, Wolfowitz (1960), Fedorov (1972) -

Optimality criteria, ellipse \((\theta - \theta^*)^\top D^{-1} (\theta - \theta^*) \leq 1\)

\[ |D| = \lambda_1 \cdot \lambda_2 = (OA \cdot OB)^2 ; \text{area (V)} = \pi (\lambda_1 \cdot \lambda_2)^{1/2} \]

\[ E\text{-criterion: } \lambda_1 = (OA)^2 \]

\[ A\text{-criterion: } \text{tr } D = \lambda_1 + \lambda_2 = (OC)^2 = D_{11} + D_{22} \]
Adaptive optimal design for nonlinear models

- Interplay of model-based design and estimation
- Nonlinear models: *locally optimal designs*
  - **Dose-response**: for each cohort, search for “optimal” doses given current parameter estimates
    - *Box, Hunter (1965), Fedorov (1972)*

- Estimation algorithm
  - CIRLS (Combined Iteratively Reweighted Least Squares) ~ MLE
    - *Fedorov and Leonov (2004)*
Individual information matrix

Gaussian \( Y : \ E_\theta[Y|x] = \eta(x, \theta), \quad \text{Var}_\theta[Y|x] = S(x, \theta) \)

\[ \mu(x, \theta) - \text{information matrix of a single \((k\)-dimensional) sequence } x: \]

\[ \mu_{\alpha \beta}(x, \theta) = \frac{\partial \eta}{\partial \theta_\alpha} S^{-1} \frac{\partial \eta}{\partial \theta_\beta} + \frac{1}{2} \text{tr} \left[ S^{-1} \frac{\partial S}{\partial \theta_\alpha} S^{-1} \frac{\partial S}{\partial \theta_\beta} \right], \quad (2) \]

\( S = S(x, \theta), \quad \eta = \eta(x, \theta) \quad [\text{Muirhead (1982), Magnus and Neudecker (1988)}] \)
Example 1: patients with Alzheimer’s disease

Phase 2a study, endpoint - percentage decrease of a biomarker compared with baseline

Details: Leonov and Miller (2009)
Model

Measurements: \( Y_i = \eta(x_i, \gamma) + \varepsilon_i, \quad i = 1, \ldots, N \)

- \( \eta \) – response function:

\[
\eta(x, \gamma) = \frac{E_{max} x^\beta}{ED_{50}^\beta + x^\beta} = \frac{E_{max}}{1 + (ED_{50}/x)^\beta}, \quad \gamma = (E_{max}, ED_{50}, \beta)
\]

- Variance models (with additive and multiplicative components)
  - \( S = \text{Var} \varepsilon_i = \sigma^2_A + \sigma^2_M \eta_i, \quad \eta_i = \eta(x_i, \gamma) \) increases with dose
  - \( S = \sigma^2_A + \sigma^2_M \eta_i (E_{max} - \eta_i) \) largest in the middle at \( ED_{50} \)
  - \( \theta = (E_{max}, ED_{50}, \beta; \sigma^2_A, \sigma^2_M) \): vector of parameters

- Goal: find dose \( ED_{90} \) which attains 90% of max response

\[
\frac{E_{max}}{1 + (ED_{50}/x)^\beta} = 0.9 E_{max} \quad \Rightarrow \quad ED_{90} = ED_{50} 9^{1/\beta}
\]

\( \text{Var}(ED_{90}) \rightarrow c\text{-optimality} \)
Practical constraints

- Safety is a priority: FTIH study
  - Small cohort sizes, always include placebo (2 per cohort)
  - Starting doses: “non-pharmacologically active”
- Doses: constrained dose-escalation
  - *Cohort-dependent design region* (upper limit)
  - Maximal increase for the next cohort:
    - 10-fold while dose has “small” effect
    - 5-fold once a PD effect is observed
  - Same dose for all patients in a cohort (or not)
- Standard design as an alternative
  - Dose escalation with evenly spaced doses
- Initial stage (starting fixed doses): can NOT be too small
Ex.1: Matlab-based stand-alone tool
Multiple simulations: selected doses (1000 runs)

First four cohorts: forced escalation

- Adaptation: cohort 8 - “cluster” weights close to optimal (0.3, 0.3, 0.4)
D-efficiency: 58 patients total, 8 cohorts

\[
E f f_D(\xi, \theta) = \left[ \frac{|M^{-1}(\xi^*, \theta)|}{|M^{-1}(\xi, \theta)|} \right]^{1/m}, \quad \xi^* \text{ - locally D-optimal}
\]

Comparison “adaptive vs locally optimal” is unfair: adaptive designs have many patients on placebo (16 total, two in each cohort) and low doses (18 total)

Much fairer comparison: with composite design

- \( \xi_0 = \{16 \text{ on placebo, 18 on low doses}\} \) – as adaptive
- Remaining 24 patients: allocated wrt composite D-optimality

\[
\xi^*_\delta = \arg \min_\xi \left| \delta M_{34}(\xi_0, \theta) + (1 - \delta) M_{24}(\xi, \theta) \right|^{-1}, \quad \delta = 34/58
\]

\[
Eff_{F, \xi^*_\delta} = 0.770, \quad \text{mean}(Eff_{A, \xi^*_\delta}) = 0.893
\]

Estimates of target dose $\text{ED}_{90}$

- Key output: histograms
- Designs are naturally “ranked”
Example 2: binary logistic model

- Phase 2 study: binary endpoint
- Model: binary logistic, with lower/upper bounds
- Additions:
  - Discreet or continuous design region
  - Composite optimal design as an option
  - Empirical confidence intervals

\[
y_{ij} = \begin{cases} 
1 \text{ (response) }, & \text{with prob. } \gamma_0 + (\gamma_1 - \gamma_0)p_i, \ j = 1, 2, \ldots, n_i \\
0 \text{ (no response) }, & \text{with prob. } 1 - [\gamma_0 + (\gamma_1 - \gamma_0)p_i], 
\end{cases}
\]

\[
p_i = P\{\text{response} \mid \text{dose } x_i, \ \theta\} = \frac{e^{\theta_0 + \theta_1 x_i}}{1 + e^{\theta_0 + \theta_1 x_i}}
\]

*Wetherill (1963)*
Example 2: simulation tool
Confidence intervals: parameters and $ED_p$

- **Red:** true value
- **Green:** median
- **Pink:** 80% CI
- **Black:** 90% CI

**Adaptation:**
Quality of estimation improves with additional cohorts
Phase 2a study: CV indication
Model: four-parameter continuous logistic

Additions:
- Cut-off values at the top (safety, high doses) and bottom (efficacy, low doses)
- *Enrollment buffers:* estimation/design for the next cohort may be performed before all data are collected from the current cohort

\[ \eta = E_0 + \frac{E_{\text{max}} - E_0}{1 + (ED_{50}/x)\beta} \]
Example 3: simulation tool
Optimal design for population PK/PD models

- PODE Workshop created in 2006
  
  **Population Optimum Design of Experiments**
  
  - Theory of optimal experimental design for nonlinear mixed effects models and its applications in drug development

- Discussion of population optimal design software started in 2007, continued in 2008-2011 (last week). Tools available:
  
  - PFIM (developed in INSERM, Université Paris 7, France)
  - PkStaMp (GlaxoSmithKline, Collegeville, U.S.A.)
  - PopDes (CAPKR, University of Manchester, UK)
  - PopED (Uppsala University, Sweden)
  - WinPOPT (University of Otago, New Zealand)

- Information matrix of individual sampling sequences:

  identical for all tools under the same assumptions
Typical model for PK/PD: mixed effects

- $\gamma$ - response parameters (rate constants)

- $\gamma_i$ - parameters of patient $i$ (sampled from population):
  
  normal, $\gamma_i \sim N(\gamma^0, \Omega)$, or log-normal ($\gamma^0$ - “typical values”)

- Data $y(x_{ij}) = \eta(x_{ij}, \gamma_i) [1 + \varepsilon_{ij}^p] + \varepsilon_{ij}^a$, $j = 1, \ldots, k_i$. (1)
  
  $\varepsilon_{ij}^a \sim N(0, \sigma_a^2)$, $\varepsilon_{ij}^p \sim N(0, \sigma_p^2)$

- Combined vector of parameters: $\theta = (\gamma^0; \Omega; \sigma_A^2, \sigma_P^2)$

Example: one-compartment model, single dose $D$ at $x = 0$,

$$\eta(x, \gamma) = \frac{Dk_a}{V(k_a - k_e)} \left( e^{-k_ex} - e^{-k_ax} \right), \quad \gamma = (k_a, k_e, V)^T$$
PkStaMp library

- **PK Sampling Times Allocation (STand-Alone Application), Matlab Platform**

- Collection of independent modules created for various projects with GSK pharmacokineticists, 2003-2011

- Last 2+ years: joint work with Dr. Alexander Aliev
  (Institute for Systems Analysis, Russian Academy of Science, Moscow)

  *Aliev et al.* (2009)
Typical screen: one-compartment, 1st order absorption
PkStaMp library: inputs

• Response parameters $\gamma$ ("typical values"/"effects", rates/clearances)

• Effects: random (fixed/given constant) $\implies$ population covariance $\Omega$

• Population distribution of $\gamma$ (normal/log-normal)

• Residual variances $\sigma_a^2, \sigma_p^2$: whether parameters or given constants

• Type of administration (1st-order absorption, bolus, continuous infusion)

• Doses: starting and repeated (if necessary), frequency, length of infusion
Selection of sampling sequences:

- Option 1: specify
  - All candidate times \((x_1, x_2, \ldots, x_K)\)
  - Number of sampling times per patient \(k \in [k_{\text{min}}, k_{\text{max}}]\)
  - Lag between samples: \(x_{i,j+1} - x_{i,j} \geq \Delta\)

- Option 2: pre-specify an arbitrary set of candidate sequences in a file
  \(\downarrow\)

Design region \(X = \{x_i = (x_{i,1}, \ldots, x_{i,k_i})\}\)
1. Michaelis-Menten:
no analytical solution
(ODE solver)

\[
\begin{align*}
\dot{f}_0(t) &= -k_a f_0(t) \\
\dot{f}_1(t) &= k_a f_0(t) - (k_{12} + k_e) f_1(t) + \frac{(V_m/V) f_1(t)}{k_m + f_1(t)/V} \\
\dot{f}_2(t) &= k_{12} f_1(t) - k_{21} f_2(t)
\end{align*}
\]

2. One-compartment PK and \(E_{\text{max}}\) PD model
(measured, in general, at different times)

\[
E = E_0 \cdot \left(1 - \frac{C_p}{IC_{50} + C_p}\right)
\]

\(k_a\): first-order absorption rate constant (h\(^{-1}\))
V/F: apparent volume of distribution (L)
CL/F: apparent systemic clearance (L/h)
\(E_0\): PD endpoint at baseline (nM/min/mL)
\(IC_{50}\): Drug X plasma concentration causing 50% inhibition of PD endpoint (ng/mL)

3. Cost-based designs: \(c(x)\) – cost of sequence \(x\) (Elfving, 1952)
Benchmark test (just completed), proposed by France Mentré: combination drug for treating chronic hepatitis C (HCV) infection

\[\begin{align*}
\dot{f}_0(t) &= -k_a f_0(t) + r(t) \\
\dot{f}_1(t) &= k_a f_0(t) - k_e f_1(t) \\
\eta_1(t) &= \frac{f_1(t)}{V_1}
\end{align*}\]

PK: parameters \((k_a, k_e, V_1)\), response \(\eta_1\) (continuous infusion term \(r(t)\))

\[\begin{align*}
\dot{g}_1(t) &= -C_2 g_1(t) - C_1 g_1(t) g_3(t) + C_3 \\
\dot{g}_2(t) &= -\delta g_2(t) + C_1 g_1(t) g_3(t) \\
\dot{g}_3(t) &= C_4 \left[1 - \frac{1}{1+(EC_{50}/\eta_1)^n}\right] g_2(t) - c g_3(t)
\end{align*}\]

\[\eta_2(t) = \log_{10} g_3(t)\]

\(g_1(t)\) - “target cells”, \(g_2(t)\) - infected cells, \(g_3(t)\) - viral particles (load)

PD: parameters \((\delta, EC_{50}, n, c)\), response \(\eta_2\)
Concluding remarks

Optimal designs

- Help in finding most informative doses (sampling times)
- Validate the quality of standard/alternative designs (optimal design as a reference/benchmark)
- Robustness of optimal designs
- May incorporate costs
References

References (cont.)