STATISTICAL MODELING AND APPLICATIONS OF PARTICLE SWARM OPTIMIZATION

Seongho Kim, Ph.D

Biostatistics Core, Karmanos Cancer Institute

Department of Oncology, School of Medicine

Wayne State University, Detroit, MI

Outline

- Pharmacokinetics (PK) analysis
  - Global optimization
  - Identifiability
- Two-stage single-arm phase 2 clinical trial designs
  - Simon's two-stage and Lin and Shih's adaptive designs
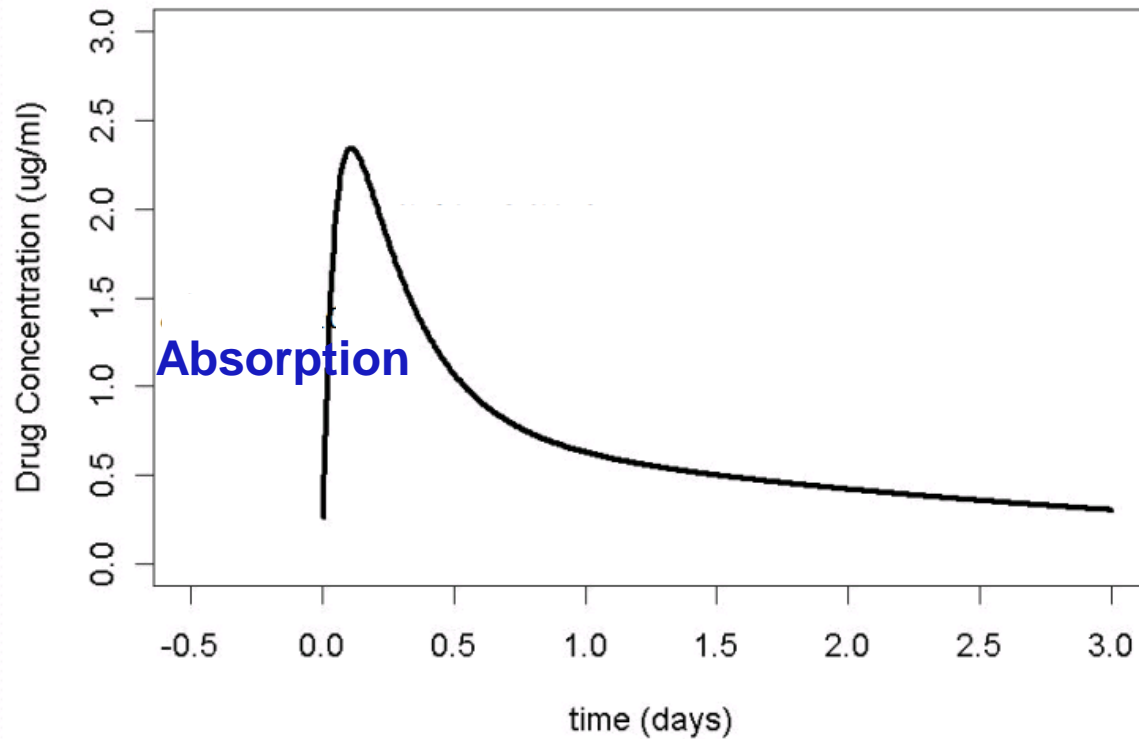 - Adaptive designs with three target response rates

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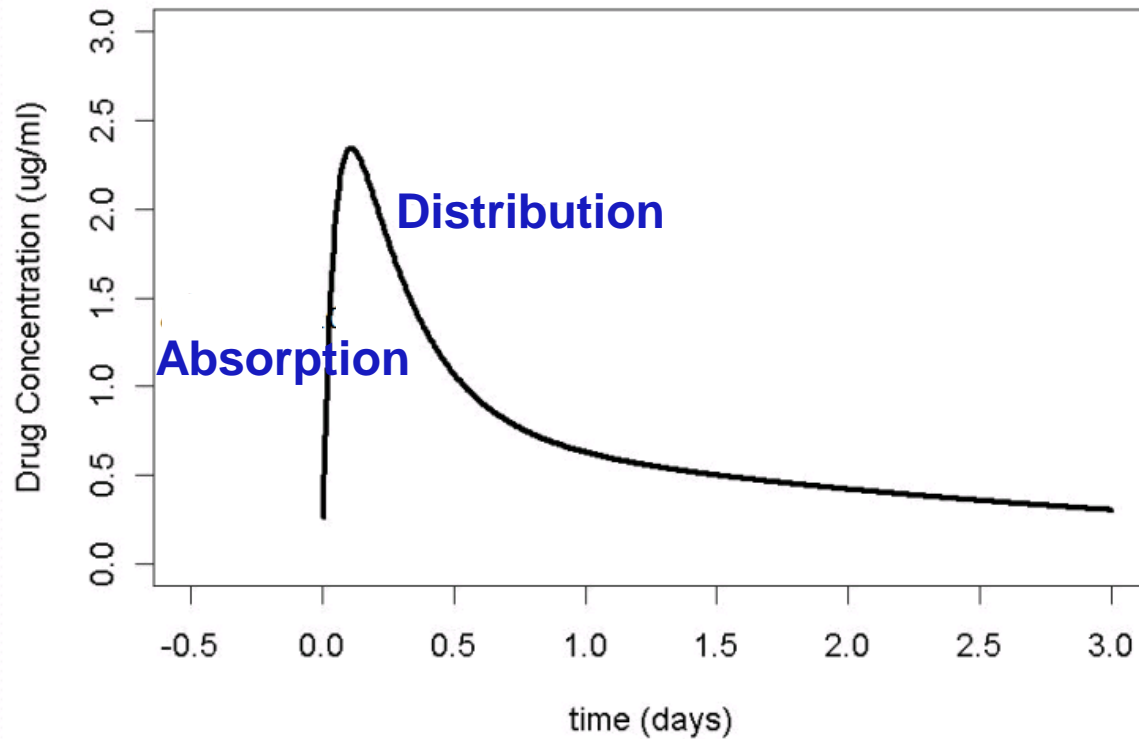 - Adaptive designs with three target response rates
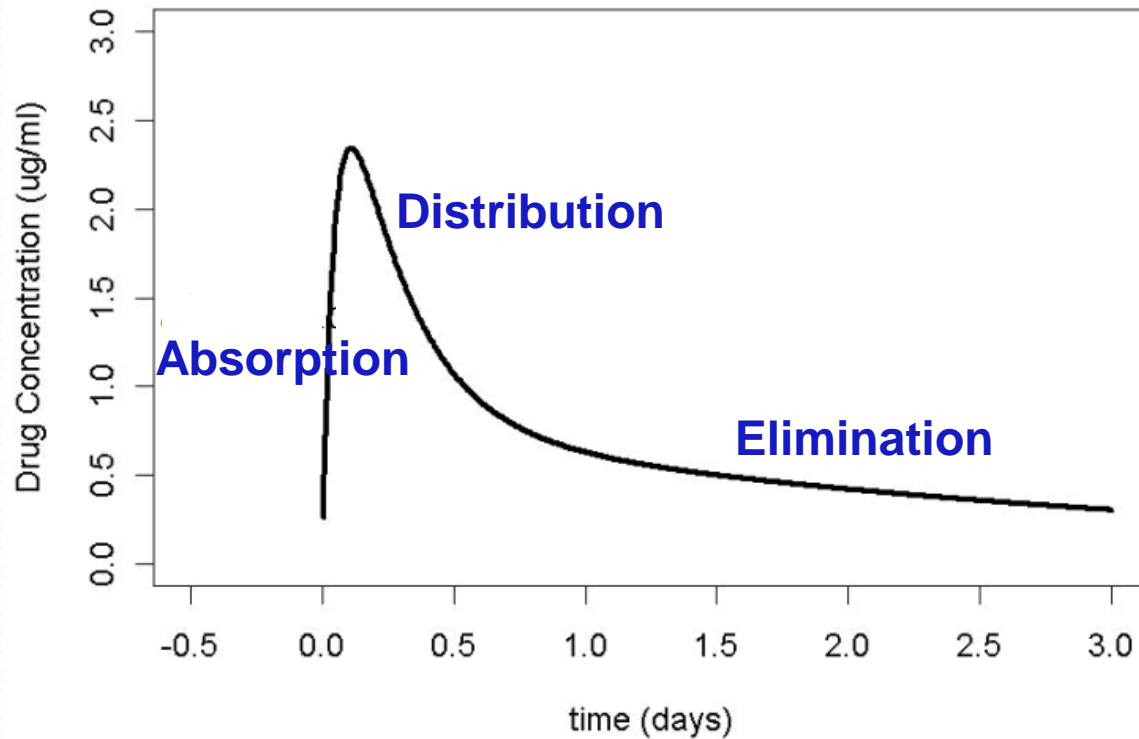
Pharmacokinetics (PK)
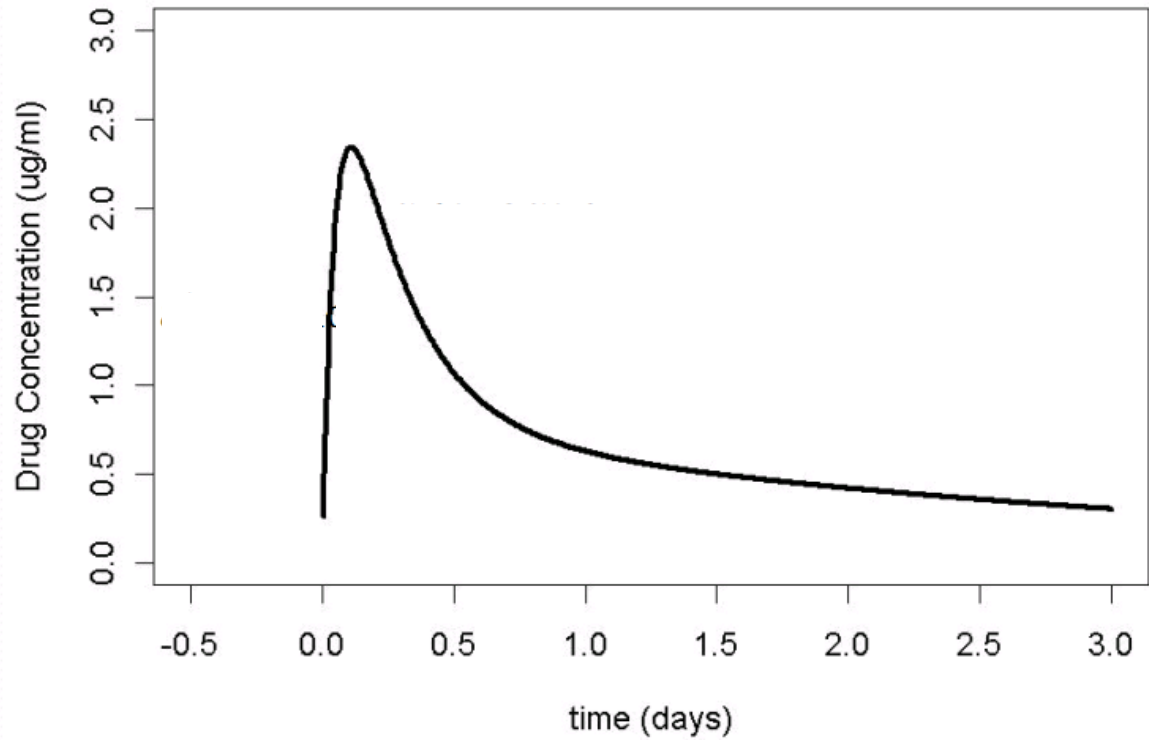
Pharmacokinetics (PK)

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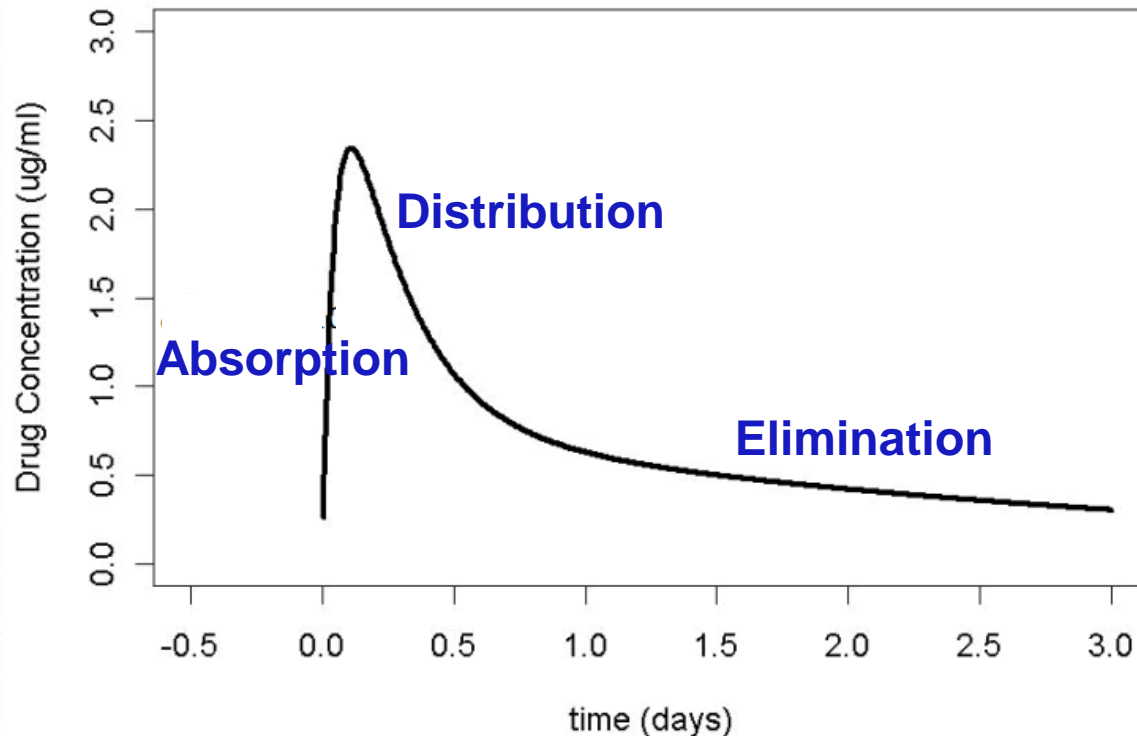
Pharmacokinetic (PK) analysis is to estimate the rates of the absorption, the distribution and the elimination (metabolism and excretion) over time of a drug and its metabolites

Pharmacokinetics (PK) Goal: Therapeutic Optimization

- Achieve concentration profile attaining Efficacy and avoiding Toxicity

How much? How often? How long?: dose regimen
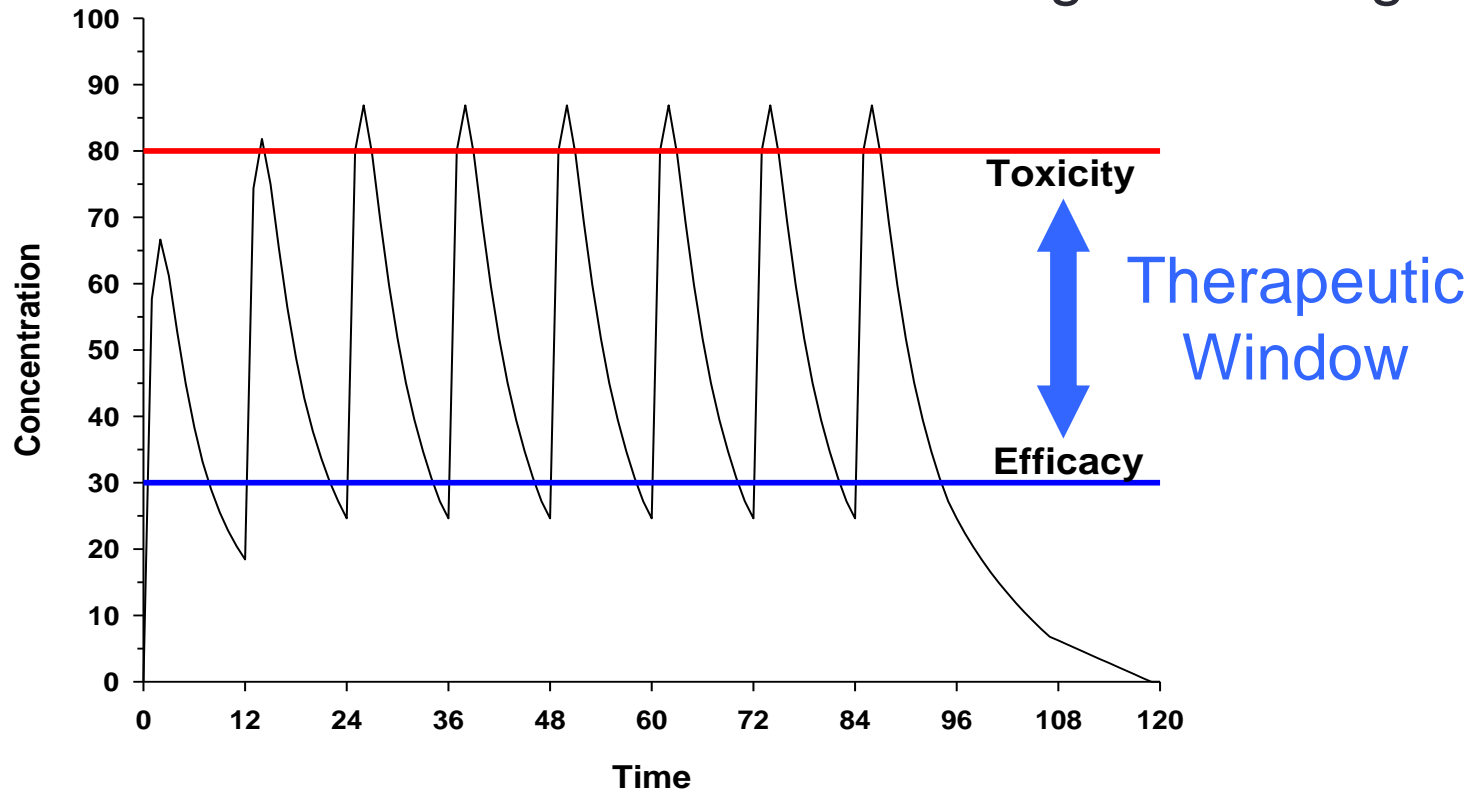
Pharmacokinetics (PK) Study
: Two-Compartment Model

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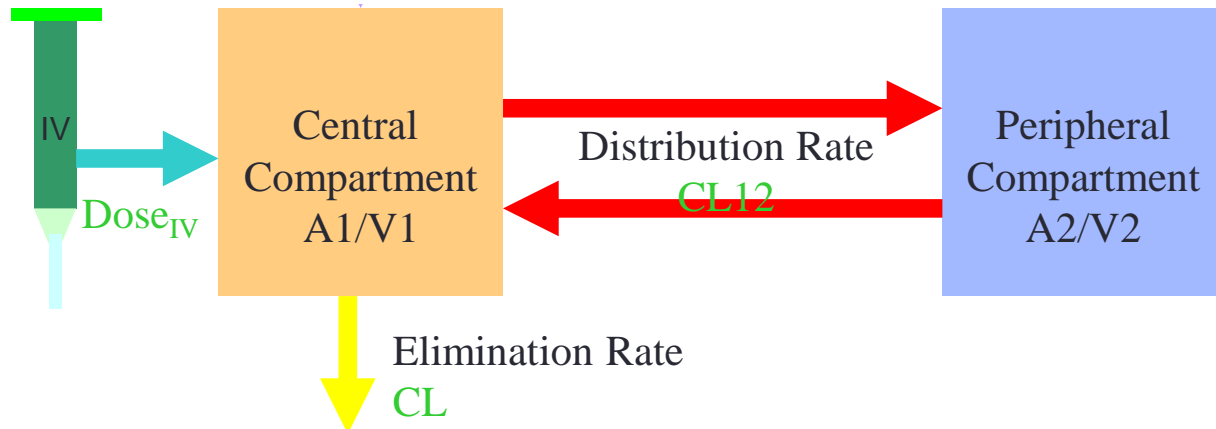
- IV model

Pharmacokinetics (PK) Study : Two-Compartment Model

- IV model

$$\frac{dA_1}{dt} = -CL \times \frac{A_1}{V_1} + CL_{12} \times (\frac{A_2}{V_2} - \frac{A_1}{V_1})$$

$$\frac{dA_2}{dt} = CL_{12} \times (-\frac{A_2}{V_2} + \frac{A_1}{V_1})$$
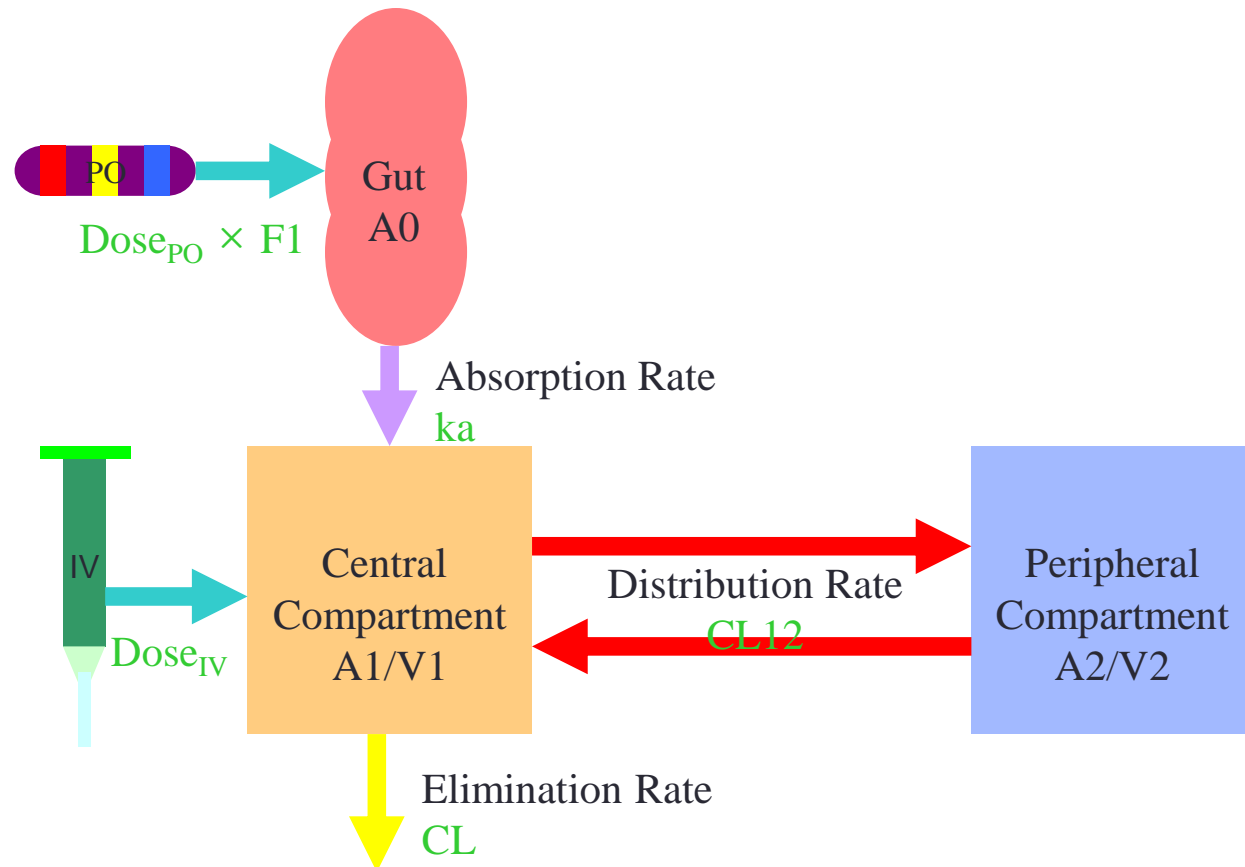
$$[A_1(t), A_2(t)]\,|_{t=0} = (Dose, 0)$$

A_1: Amount of drug in central compartment
A_2: Amount of drug in peripheral compartment

V_1: Volume of distribution in the central compartment
V_2: Volume of distribution in the peripheral compartment

CL: Clearance
CL_{12}: Distribution rate constant

Pharmacokinetics (PK) : Two-Compartment M

- IV model

$$\frac{dA_1}{dt} = -CL \times \frac{A_1}{V_1} + CL_{12} \times (\frac{A_2}{V_2} - \frac{A_1}{V_1})$$

$$\frac{dA_2}{dt} = CL_{12} \times (-\frac{A_2}{V_2} + \frac{A_1}{V_1})$$

$$[A_1(t), A_2(t)]\,|_{t=0} = (Dose, 0)$$

Central Compartment

Peripheral Compartment

CL_{12}: Distribution rate constant

IV

$Dose_{IV}$

Central Compartment A1/V1

Distribution Rate CL12

Peripheral Compartment A2/V2

Elimination Rate CL

Pharmacokinetics (PK)
: Two-Compartment M

- IV model

$$\frac{dA_1}{dt} = -CL \times \frac{A_1}{V_1} + CL_{12} \times (\frac{A_2}{V_2} - \frac{A_1}{V_1})$$

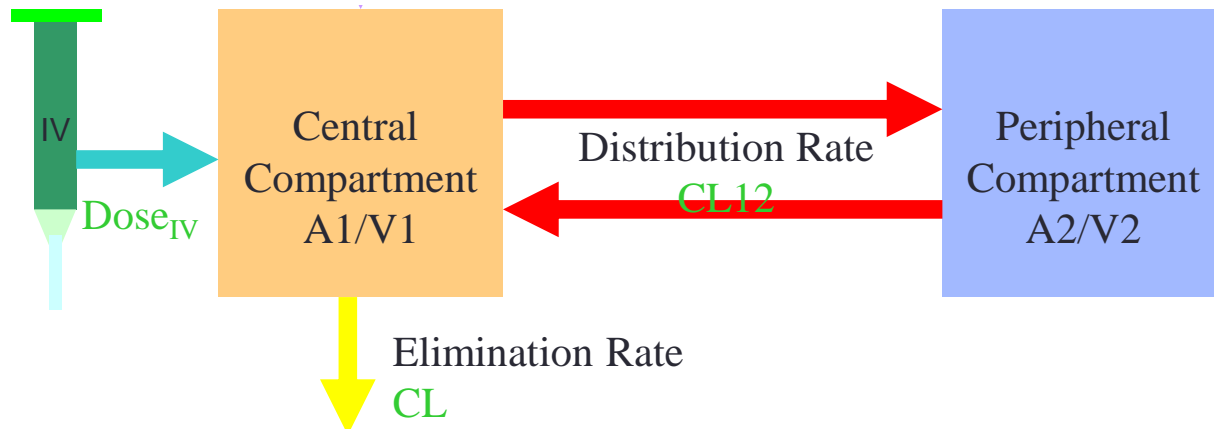$$\frac{dA_2}{dt} = CL_{12} \times (-\frac{A_2}{V_2} + \frac{A_1}{V_1})$$

$$[A_1(t), A_2(t)]\,|_{t=0} = (Dose, 0)$$

Central Compartment

Peripheral Compartment

Concentration

Time

Concentration

Time

CL_{12}: Distribution rate constant

IV

$Dose_{IV}$

Central Compartment A1/V1

Distribution Rate CL12

Peripheral Compartment A2/V2

Elimination Rate CL

Midazolam (MDZ) data: IV infusion
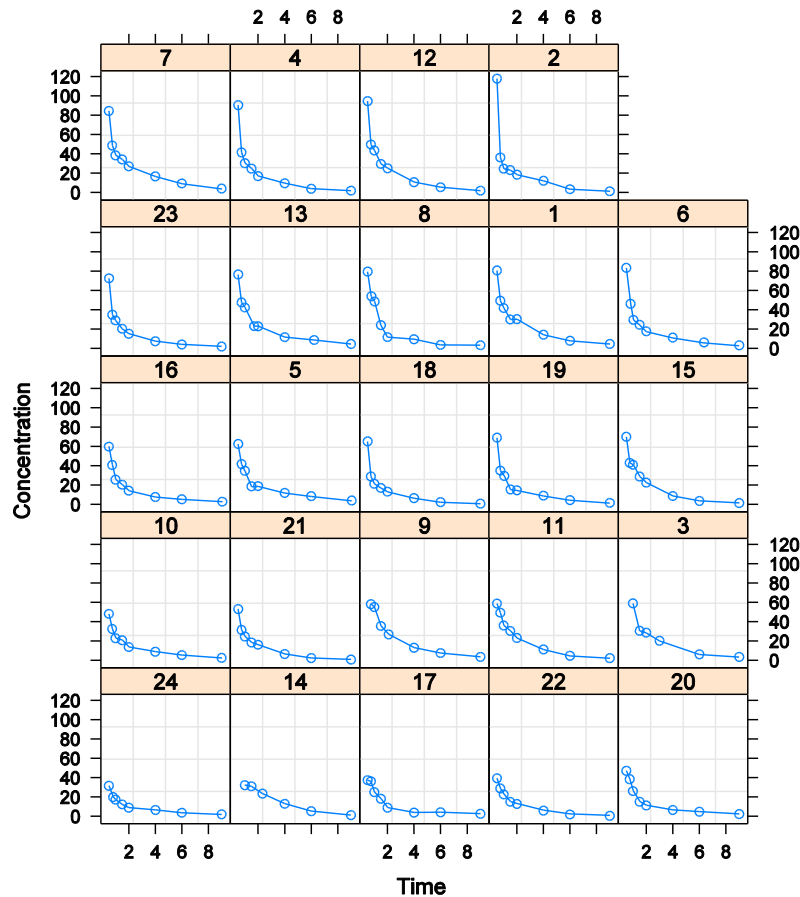
CYP3A is responsible for 60% of drugs' metabolism

CYP3A Substrates → standard CYP3A probe drug

24 volunteers, 18 to 55 years of age, received single dose of 2.74~4.80 mg MDZ intravenously (IV) and Blood samples were collected at 0.5, 0.75, 1, 1.5, 2, 4, 6, and 9 hours after IV MDZ dosing.

Mixed-Effects Model

- Provide a powerful and flexible tool for the analysis of balanced and unbalanced grouped data.

- A mixture of fixed and random factors

  - Fixed-effect (Population-level): the effects of the levels to one another
  - Random-effect (Subject-level): a random sample from a population of effects

Parameter estimation

- Estimation: EM-like Algorithms and Monte Carlo-based Algorithms

- EM Algorithm ➔
  - It can guarantee only up to local optima
  - Approximation needed if either E-step or M-step is intractable (no closed form available)
    - PK/PD models have the nonlinear differential equations
  - It gives us point estimates

- Monte Carlo Algorithm
  - It can guarantee global optima theoretically
  - It can deal with nonlinear functions
  - It can estimate the distribution of parameters (Bayesian approach)

Monte Carlo

- Given: a domain X and a distribution $p(x)$

Monte Carlo

- Given: a domain X and a distribution $p(x)$
- Draw a set of N samples independently
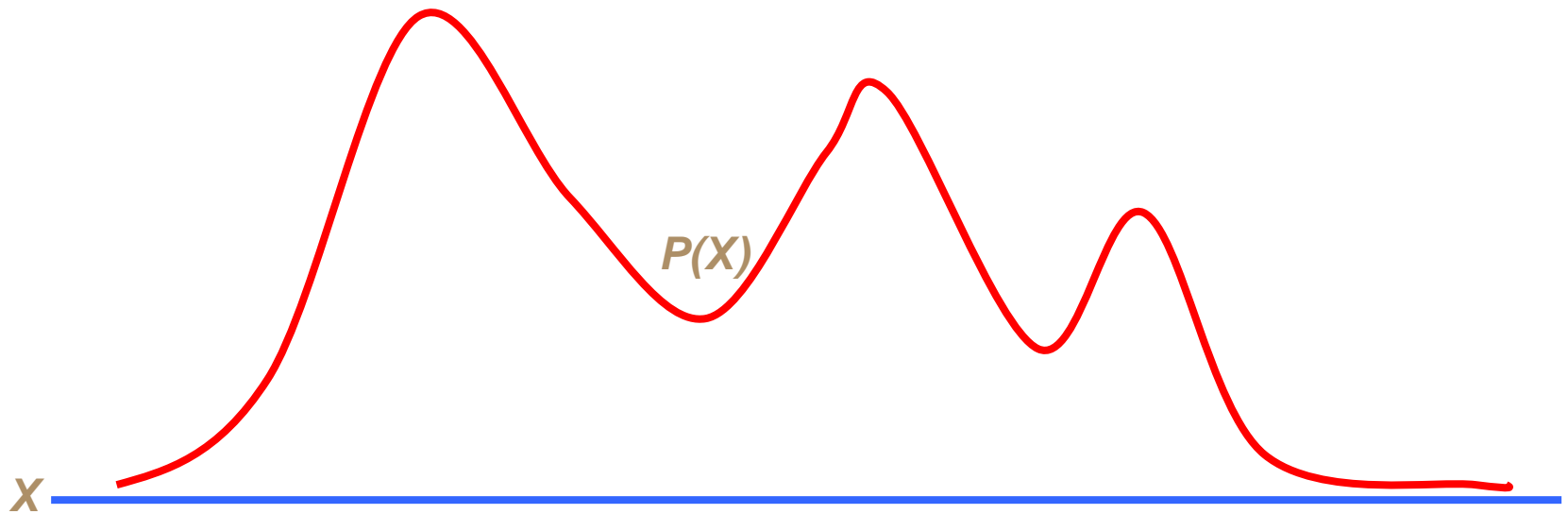
P(X)

X

Monte Carlo

- Given: a domain X and a distribution $p(x)$
- Draw a set of N samples independently
- Approximate the distribution by these samples

$P(X)$

X

Monte Carlo

- Given: a domain X and a distribution $p(x)$
- Draw a set of N samples independently
- Approximate the distribution by these samples

$$p_N(x) = \frac{1}{N} \sum_{i=1}^{N} 1(x^{(i)} \in X) \rightarrow p(x) \text{ as } N \rightarrow \infty$$

P(X)

X
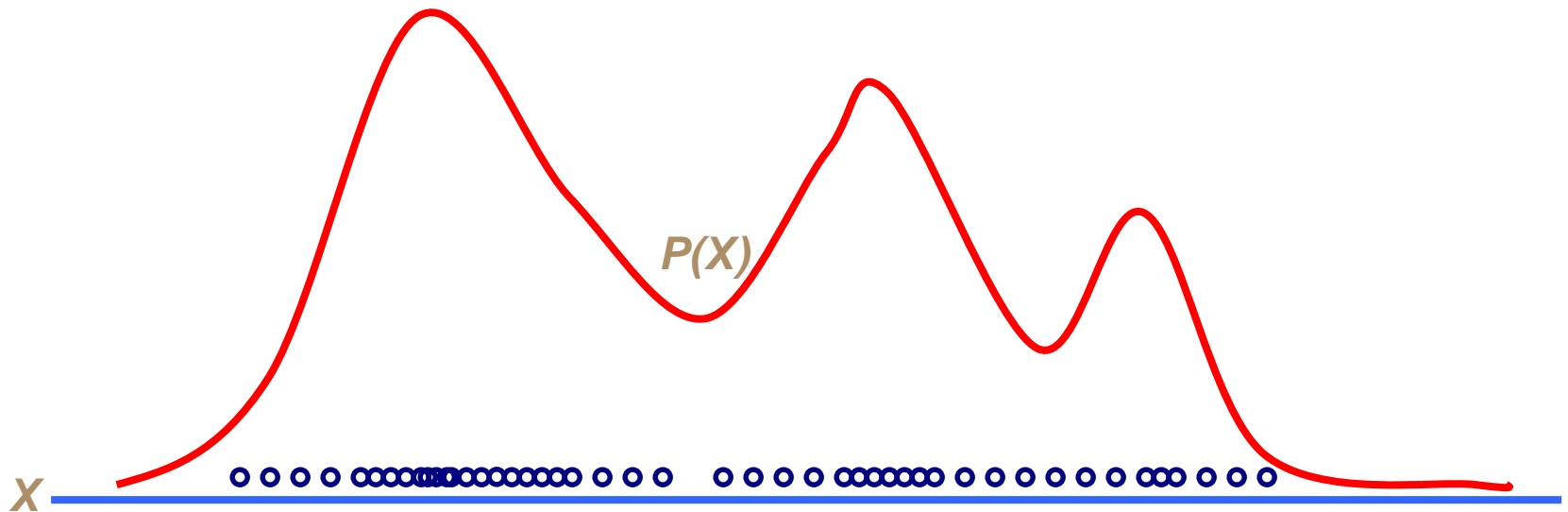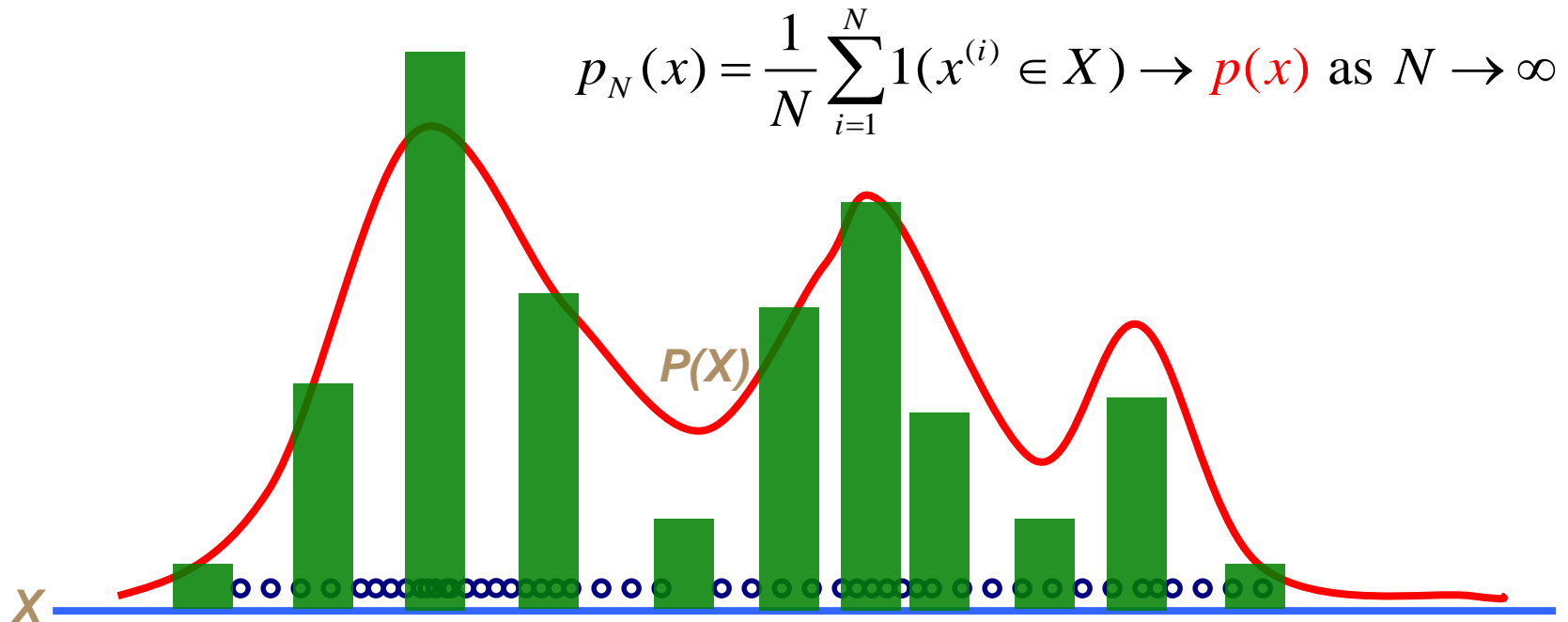
Monte Carlo

- Given: a domain *X* and a distribution *p(x)*
- Draw a set of N samples independently
- Approximate the distribution by these samples

These samples can be used

$\Rightarrow$ to compute expectations:

$$E_N(f) = \frac{1}{N}\sum_{i=1}^{N} f(x^{(i)}) \xrightarrow{N\to\infty} E(f) = \sum_{x} f(x)p(x)$$

$\Rightarrow$ to find a maximum:

$$\hat{x} = \arg_{x^{(i)}} \max[p(x^{(i)})]$$
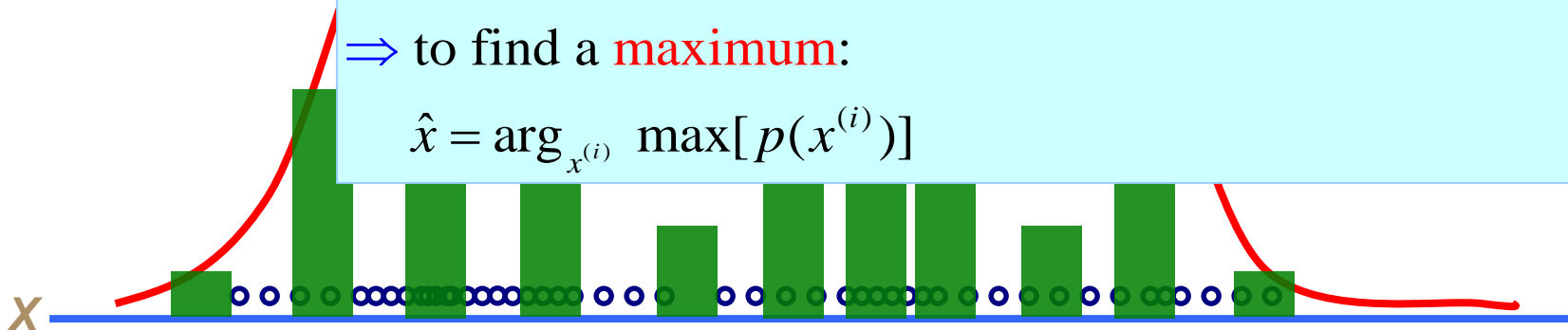
x

Monte Carlo-based Algorithms

- Non-Markovian Methods

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- Non-Markovian Methods

- Markovian Methods

Monte Carlo-based Algorithms

- Non-Markovian Methods

  - Rejection Sampling (Smith and Gelfand, 1992)
  - Ratio-of-uniforms method (Wakefield et al., 1994)
  - …

Monte Carlo-based Algorithms

- Non-Markovian Methods

    - Rejection Sampling (Smith and Gelfand, 1992)
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    - …

- Markovian Methods

    - Gibbs Sampling (Geman and Geman 1984)
    - Markov Chain Monte Carlo (MCMC) (Metropolis et al., 1953; Hastings, 1970)
        - Random-walk Metropolis (Roberts, 1995)
        - Independence Metropolis-Hasting (Roberts, 1995)
        - Reversible jump MCMC (Green, 1995)
        - …

Non-Markovian Method

[Rejection Sampling]

$\pi(x)$: intractable target density

$\pi(x) \propto f(x)$

Find a tractable envelope $h(x)$ s.t. $f(x) \leq c \cdot h(x)$

Repeat{

    (*) *Repeat*{

$$y \sim h(\cdot)$$

$$u \sim U(0,1)$$

$$\alpha = \frac{f(y)}{c \cdot h(y)}$$

$$x^{(t+1)} = \begin{cases} y \ \ if \ \ u \leq \alpha \\ \text{go to (*)} \ if \ u > \alpha \end{cases}$$

    }

    $t \leftarrow t+1$ }

Non-Markovian Method

[Rejection Sampling]

$\pi(x)$: intractable target density

$\pi(x) \propto f(x)$

Find a tractable envelope $h(x)$ s.t. $f(x) \le c \cdot h(x)$

It is not easy to find a tractable envelope function.

$Repeat\{$

$(*) \; Repeat\{$

It causes to have much expensive computation times

$\quad y \sim h(\cdot)$

$\quad u \sim U(0,1)$

α does not depend on the previous sample

$\quad \alpha \leftarrow \dfrac{f(y)}{c \cdot h(y)}$

$x^{(t+1)} = \begin{cases} y & if \; u \le \alpha \\ \text{go to } (*) & if \; u > \alpha \end{cases}$

$\}$

$t \leftarrow t+1 \; \}$

Markovian Method

[MCMC]

$\pi(x)$: intractable target density

$\pi(x) \propto f(x)$

Find a tractable proposal $q(\cdot \mid x^{(t)})$

Initialize $x^{(0)}$

Repeat{

$y \sim q(\cdot \mid x^{(t)})$

$u \sim U(0,1)$

$$\alpha = \min\left(1, \frac{f(y)q(x^{(t)} \mid y)}{f(x^{(t)})q(y \mid x^{(t)})}\right)$$

$$x^{(t+1)} = \begin{cases} y & \text{if } u \leq \alpha \\ x^{(t)} & \text{if } u > \alpha \end{cases}$$

$t \leftarrow t+1$ }

Markovian Method

[MCMC]

$\pi(x):$ intractable target density

$\pi(x) \propto f(x)$

Find a tractable proposal $q(\cdot \mid x^{(t)})$

It is not difficult to find a tractable proposal function, e.g., multivariate normal distribution

Initialize $x^{(0)}$

Repeat{

$\quad y \sim q(\cdot \mid x^{(t)})$

$\quad u \sim U(0,1)$

α depends on the previous sample

$$\alpha = \min\left(1, \frac{f(y)q(x^{(t)} \mid y)}{f(x^{(t)})q(y \mid x^{(t)})}\right)$$

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$\quad t \leftarrow t+1 \ \}$

Nonlinear Mixed-Effects Model

- The first - stage model:

$$[\log y_{ij} \mid \theta_i, \tau^{-1}, t_{ij}] \sim \mathbf{N}(\log f(\theta_i, t_{ij}), \tau^{-1}), \ i = 1, ..., M; j = 1, ..., n_i$$

where $f(\theta_i, t_{ij})$ is a nonlinear function

- The second - stage model :

$$[\theta_i \mid \theta, \Sigma_p] \sim \mathbf{MVN}(\theta, \Sigma_p)$$

Random-Effects

Fixed-Effects

Nonlinear Mixed-Effects Model

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Historic data
Distribution of each parameter

Random-Effects
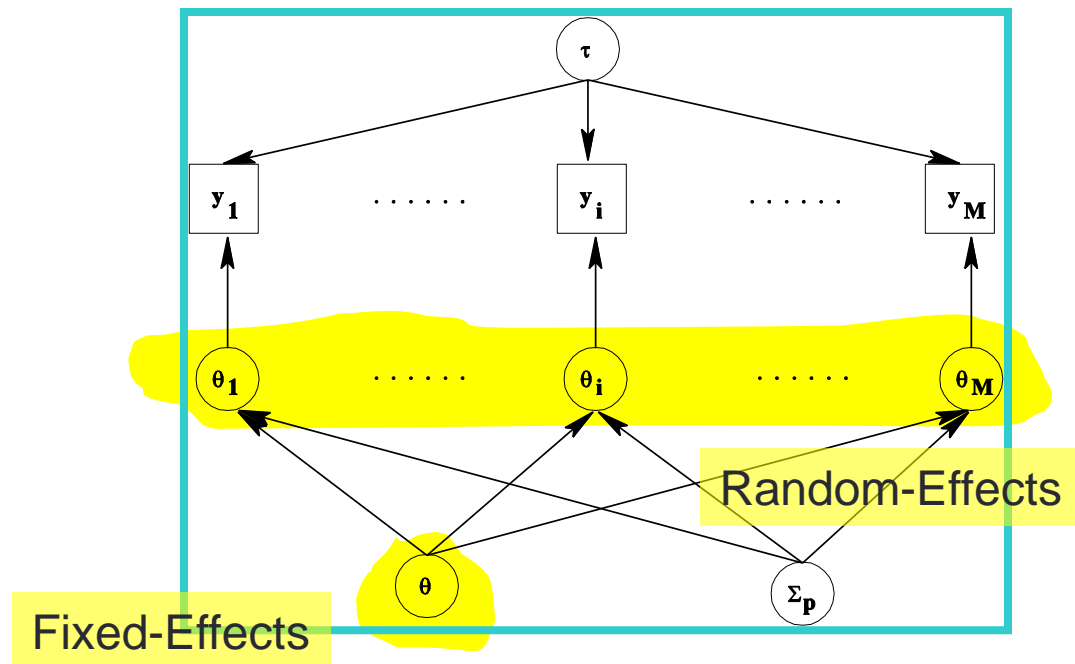
Fixed-Effects

(Bayesian MCMC) Nonlinear Mixed-Effects Model
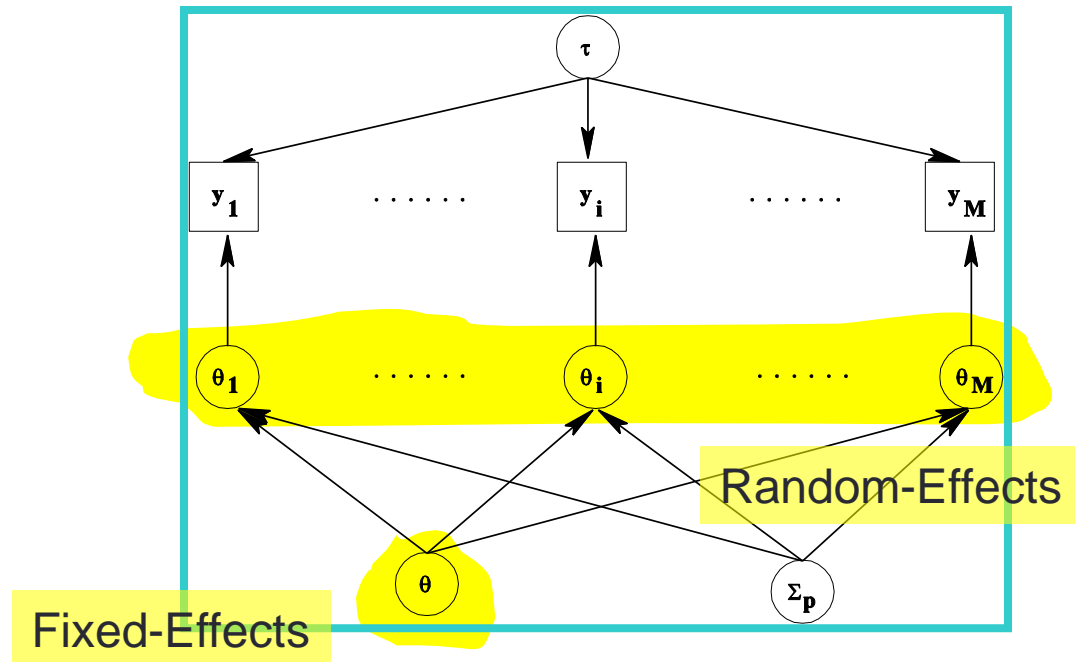
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- **The second - stage model :**

$$[\theta_i \mid \theta, \Sigma_p] \sim \mathbf{MVN}(\theta, \Sigma_p)$$

- **The third - stage model :**

$$[\tau] \sim Ga(\frac{v_0}{2}, \frac{\tau_0 v_0}{2})$$

$$[\theta] \sim \mathbf{MVN}(\mathbf{c}, \mathbf{C}_p)$$

$$[\Sigma_p^{-1}] \sim W(\rho, [\rho \mathbf{R}_p]^{-1})$$

Random-Effects

Fixed-Effects

Physiologically based PK drug interaction model
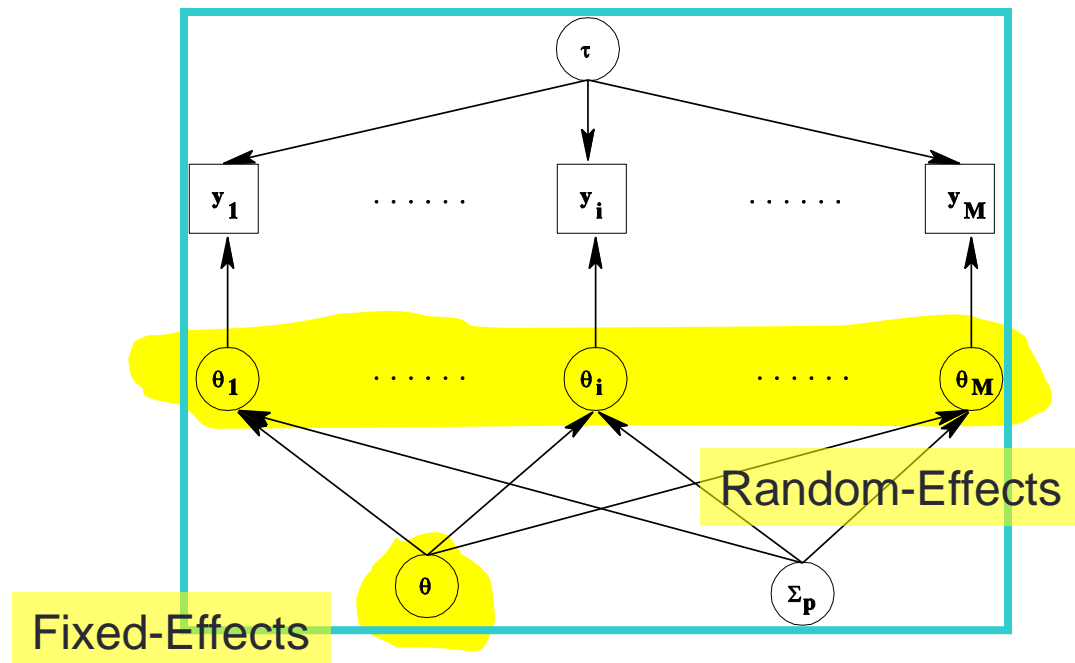
Physiologically based PK drug interaction model

Ketoconazole — Inhibitor (KTZ)   Substrate (MDZ) — Midazolam
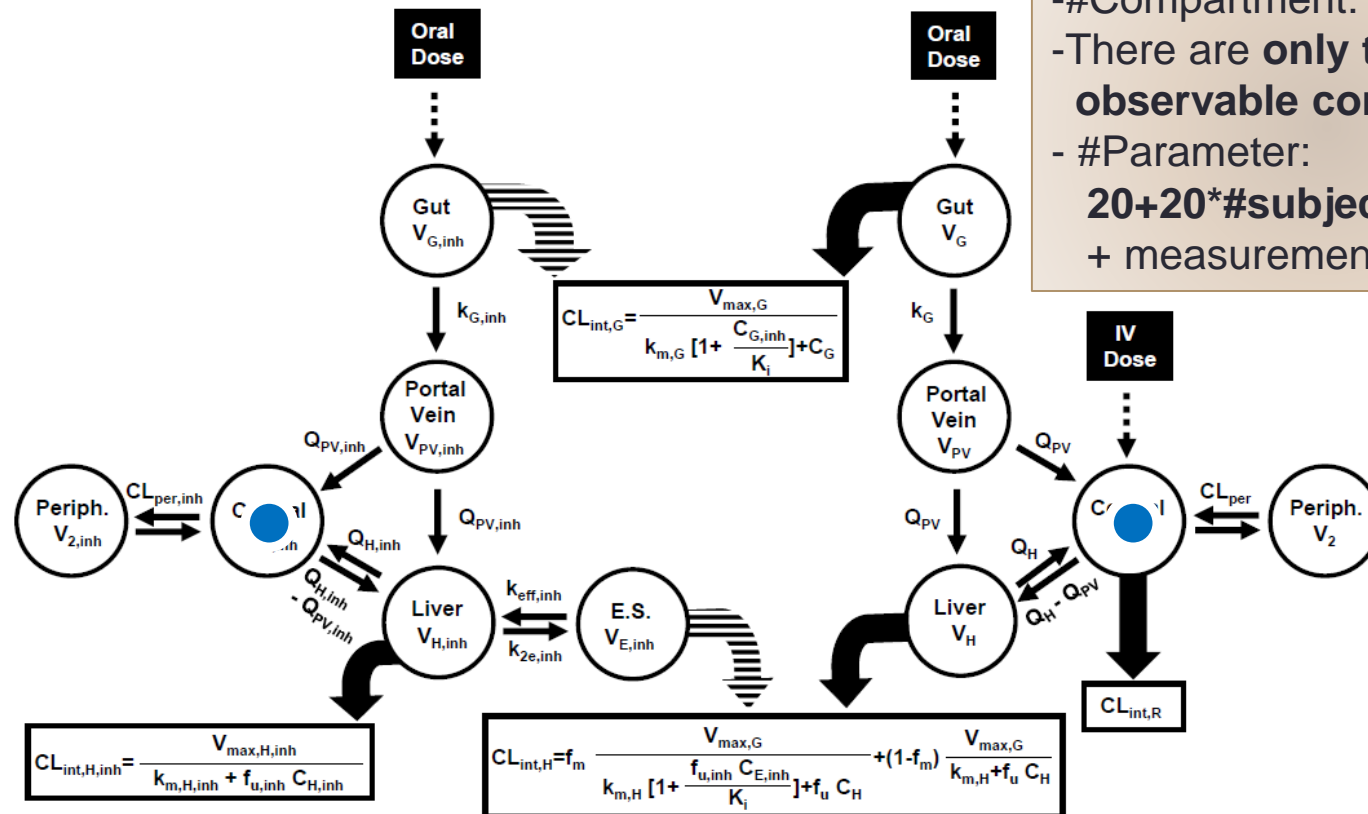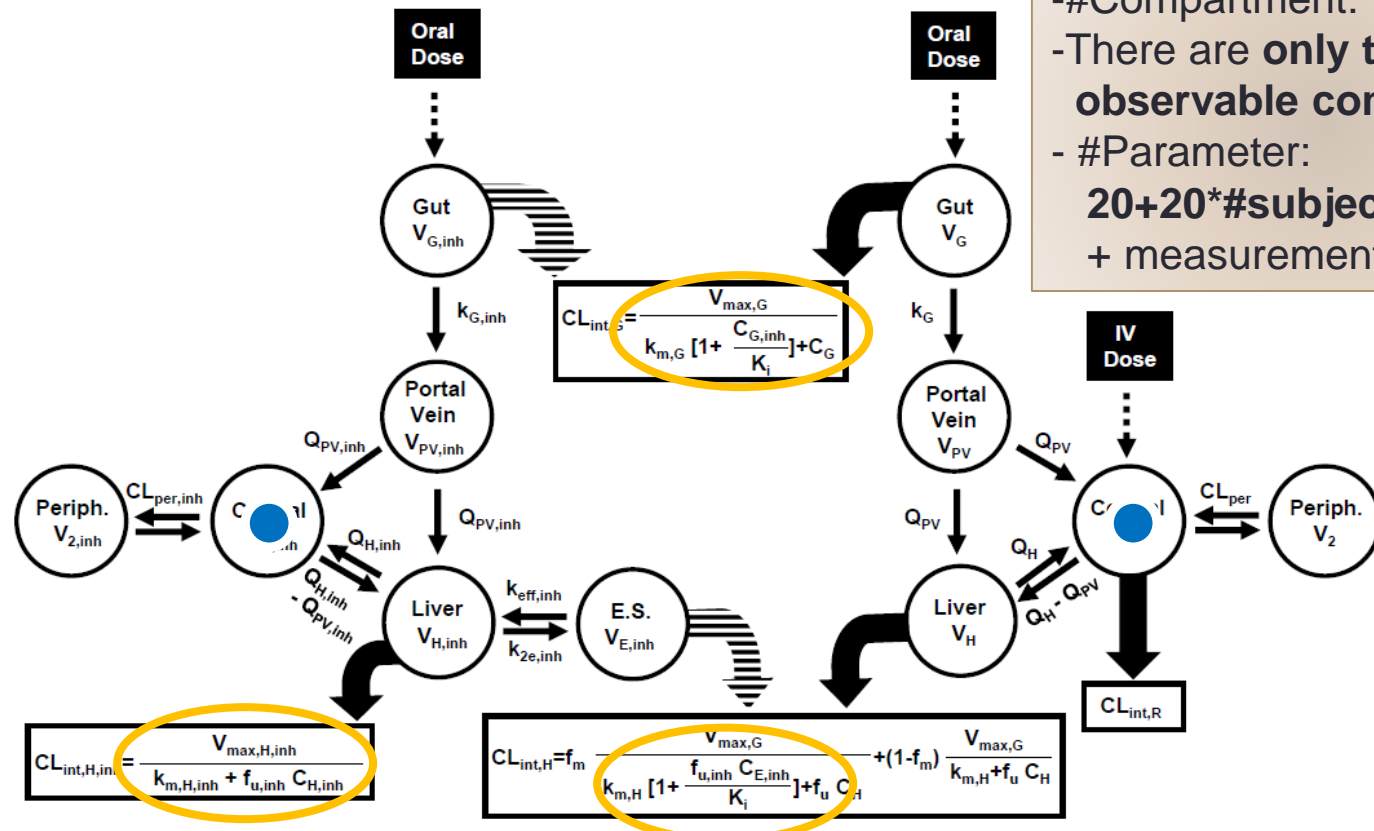
-#Compartment: 11
-There are **only two observable compartments**
- #Parameter:
  20+20*#subject
  + measurement error

Physiologically based PK drug interaction model

Practical Issues for Bayesian MCMC

- Global optima or local optima?
  - High-dimensionality makes it difficult to reach global optima

- The speed of convergence is slow
  - Proposal function (variance-covariance matrix)
  - Starting points (initial values)

- High correlation due to unidentifiable parameters (identifiability)
  - Michaelis-Menten kinetics equation

Three challenges of PK analysis

- Global Optimization: global maximum of the likelihood
  - What is an efficient approach to finding global optima?

- Convergence Rate: the speed of convergence
  - How to improve the speed of convergence?

- (Statistical) Identifiability of PK models
  - What can we do with the statistically unidentifiable parameters?

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An Efficient Global Search Algorithm

- NONMEM (Beal and Sheiner, 1980)
  - The most popular approaches to a population pharmacokinetics/pharmacodynamics (PK/PD) analysis for nonlinear mixed-effects models
  - Local optimization using a Broyden-Fletcher-Goldfarb-Shanno (BFGS) quasi-Newton algorithm

- A global search algorithm for nonlinear mixed-effects models to meet the challenges of the local optimization in NONMEM

Nonlinear mixed-effects models

- First-stage

$$log y_{ij} = log f(\phi_i, t_{ij}) + \epsilon_{ij}; i = 1, \ldots N; j = 1, \ldots, n_i \qquad (1)$$

  - N: the number of subjects
  - n_i: the number of observations from the ith subject
  - y_{ij}: the drug concentration at time t_{ij}
  - f: a nonlinear function of a subject-specific parameter vector ϕ_i

- Second-stage

$$\phi_i = A_i\beta + B_i b_i$$

  - A_i and B_i: known design matrices for fixed-effects β and random-effects b_i

Nonlinear mixed-effects models

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Laplacian estimation method
First-order estimation method
First-order conditional estimation methods

Particle Swarm Optimization (PSO)

$$\widehat{\beta} = argmx[l(\beta; Y, X)]$$

global best
local best

Kennedy and Eberhart, 1995; Eberhart and Kennedy, 1995
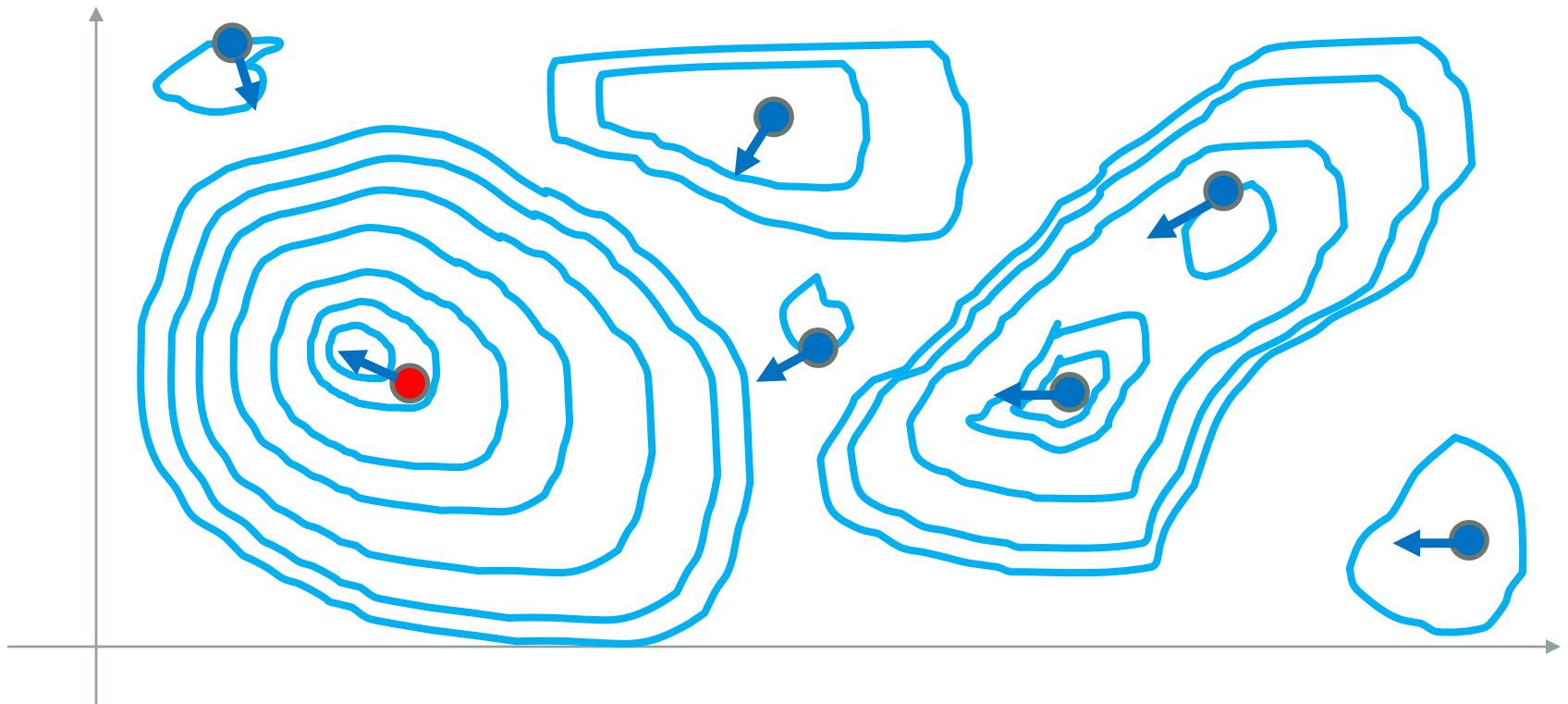
Particle Swarm Optimization (PSO)

- *k*-th iteration

$$v_{k+1}^p = w_k v_k^p + c_1 r_1 \left(x_{lbest}^p - x_k^p \right) + c_2 r_2 \left(x_{gbest} - x_k^p \right) \qquad (4)$$

$$x_{k+1}^p = x_k^p + v_{k+1}^p \qquad (5)$$

- *p = 1,…,P; P*: the population size
- $x_{(lbest)}^p$ and x_{gbest}: local best and global best, respectively
- v_{k+1}^p: the velocity
- w_k: inertia weight

$$w_k = w_{max} - \frac{k}{K} (w_{max} - w_{min})$$

- *c₁, c₂*: cognitive and social coefficient, respectively
- *r₁, r₂*: two random sequences in [0,1]
- *K*: total number iteration number

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  - $\varepsilon_{ij} \sim N(0, \sigma^2)$

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It requires expensive computation time

PSO-based mixed-effects modeling

- High-dimensional parameter space
  - Parameters to estimate
    - β: fixed-effects
    - σ^2: measurement error (variance-covariance matrix)
    - Ψ: inter-individual variance-covariance matrix
    - b_i: random-effects
  - E.g.: 5 fixed-effects, 5 random-effects, 10 subjects => $5 + 5 \times 10 = 50$ without variance estimation
- Expensive computation
- Slow speed of convergence

PSO-based mixed-effects modeling

- Hybrid approach
  - NONMEM + PSO
    - NONMEM: exploitation by a local optimization
    - PSO: exploration by a global optimization

PSO-based mixed-effects modeling

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    Reduce the population size

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    - NONMEM: exploitation by a local optimization
    - PSO: exploration by a global optimization
- Sacrifice random-effects
  - Random-effects by NONMEM
  - Fixed-effects and others by NONMEM+PSO

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Reduce the population size

Reduce the PSO parameter space

PSO-based mixed-effects modeling

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    - PSO: exploration by a global optimization

Reduce the population size

- Sacrifice random-effects
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Reduce the PSO parameter space

  - Fixed-effects and others by NONMEM+PSO

- Multivariate population
  - Grid population using univariate uniform distribution
  - Random-grid population using multivariate uniform distribution

PSO-based mixed-effects modeling

- Hybrid approach
  - NONMEM + PSO
    - NONMEM: exploitation by a local optimization
    - PSO: exploration by a global optimization

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Reduce the PSO parameter space

- Multivariate population
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Increase the population diversity

Nonlinear mixed-effects models

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$$\phi_i = A_i\beta + B_ib_i$$

Global + Local Optimization

  - A_i and B_i: known design matrices for fixed-effects β and random-effects b_i
  - $b_i \sim N(0, \Psi)$

Local Optimization

Convergence of PSO+NONMEM

- First-order stability analysis (expected value)
  - Trelea (2003)
  - The expected value of the position of each particle converges to its equilibrium

$$\frac{c_1 x_{lbest} + c_2 x_{gbest}}{c_1 + c_2}$$

$$iff$$

$$w < 1, c = \frac{c_1 + c_2}{2} > 0, 2w - c + 2 > 0$$

- PSO+NONMEM: $w \in [0.4, 0.9], c_1 = c_2 = 2$ ➜ $2 \cdot 0.4 - 2 + 2 > 0$

Convergence of PSO+NONMEM

- Second-order stability analysis (variance)
  - Jiang et al. (2007); Poli (2009); Poli et al. (2007)
  - The variance of the position of each particle converges to zero

$$iff$$

$$\frac{c_1 + c_2}{2} < \frac{12(w^2 - 1)}{5w - 7}$$

- PSO+NONMEM: $w \downarrow 0.4, c_1 = c_2 = 2$ ➔ $2 < 2.016$

Subject-specific parameter estimation: local or global?

Theorem 1. *Let us consider a linear mixed-effect model, i.e.*

$$f(\phi_i, t_{ij}) = A_i \beta + B_i b_i$$

in (1). If the parameters β, σ^2, and Ψ converge to their global optima, $\hat{\beta}, \widehat{\sigma^2},$ and $\widehat{\Psi}$, and $\hat{b}_i$ is a local optimum of the individual random-effect b_i, then $\hat{b}_i$ is its global optimum, given the ith observation y_i, $\hat{\beta}, \widehat{\sigma^2},$ and $\widehat{\Psi}$.

Subject-specific parameter estimation: local or global?

Theorem 2. Let us consider a nonlinear mixed-effect model, i.e., $f(\cdot)$ is nonlinear in (1). Suppose the parameters β, σ^2, and Ψ converge to their global optima, $\hat{\beta}, \widehat{\sigma^2}$, and $\widehat{\Psi}$, and $\hat{b}_i$ is a local optimum of the individual random-effect b_i. If $f(\cdot)$ is either concave and nonincreasing in b_i or convex and nondecreasing in b_i, then $\widehat{b}_i$ is its global optimum, given the ith observation y_i, $\hat{\beta}, \widehat{\sigma^2}$, and $\widehat{\Psi}$.

The flowchart of the proposed P-NONMEM

Kim and Li **2011**. *J. of PK. and PD.*
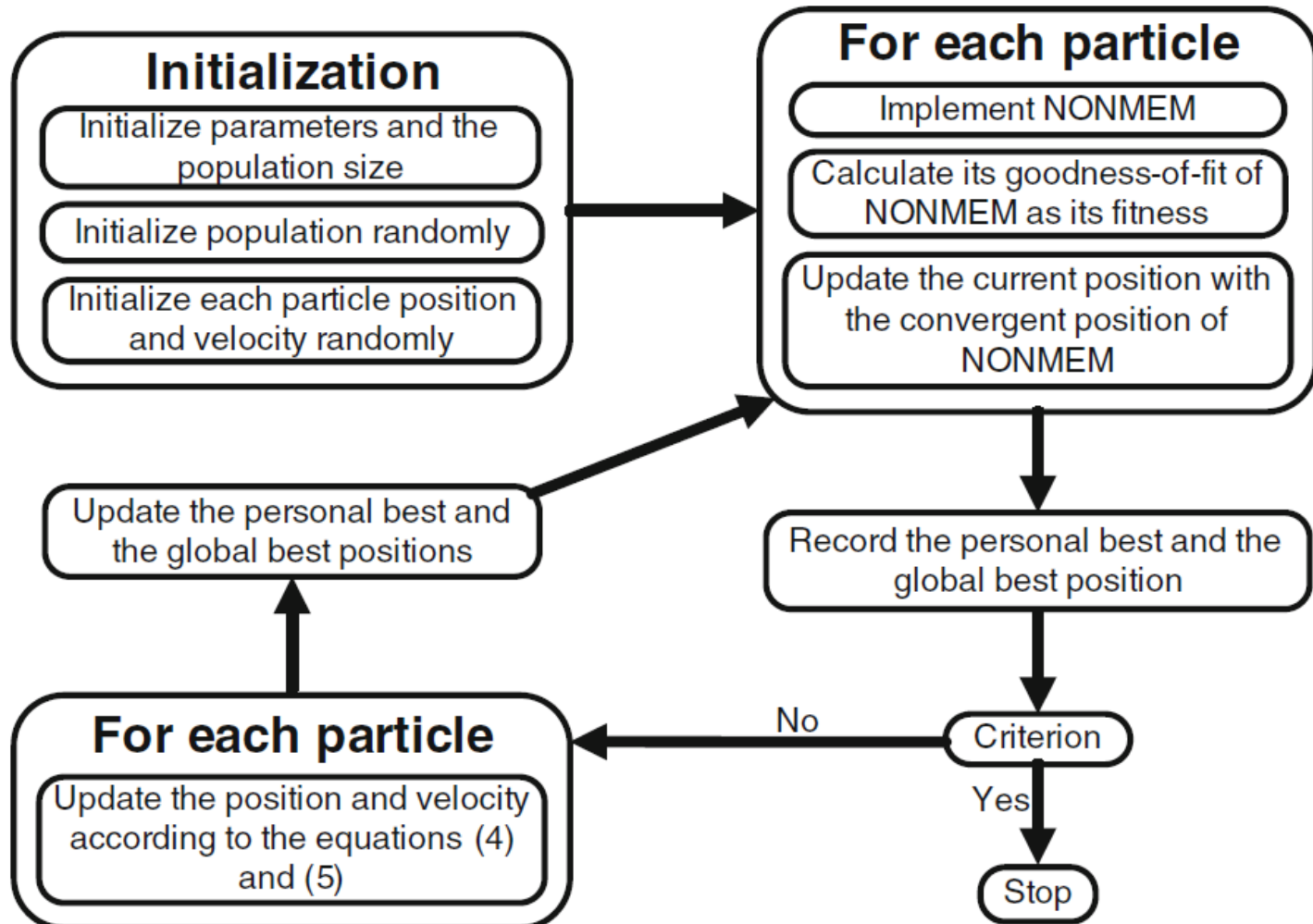
Simulation studies

PK example

$$\begin{cases} \frac{dA1(t)}{dt} = -\frac{Qh \cdot fu \cdot \frac{Vmax}{Km + \frac{A1(t)}{V1}}}{Qh + fu \cdot \frac{Vmax}{Km + \frac{A1(t)}{V1}}} \cdot \frac{A1(t)}{V1} + CL12 \cdot \left(-\frac{A1(t)}{V1} + \frac{A2(t)}{V2}\right) \\ \frac{dA2(t)}{dt} = CL12 \cdot \left(-\frac{A1(t)}{V1} + \frac{A2(t)}{V2}\right) \end{cases}$$

$$f(\Phi_i, t_{ij}) = \frac{A1(t)}{V1}$$

$$\Phi_i = A_i\beta + B_i b_i = A_i\beta + b_i$$

$$\beta = (logV1, logV2, logVmax, logKm)'$$

$$b_i = (V1_i)$$

$$A_i = \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix}$$
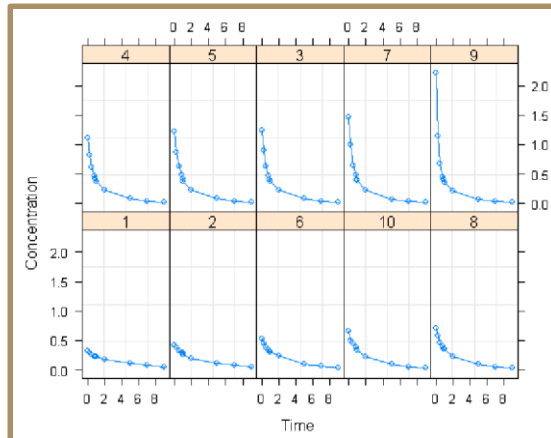
PD example

$$f(\Phi_i, x_{ij}) = \frac{Emax \cdot x_{ij}}{C50 + x_{ij}}$$

$$\Phi_i = A_i\beta + B_i b_i = A_i\beta + b_i$$

$$\beta = (logEmax, logC50)'$$

$$b_i = (Emax_i, C50_i)$$

$$A_i = \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix}$$
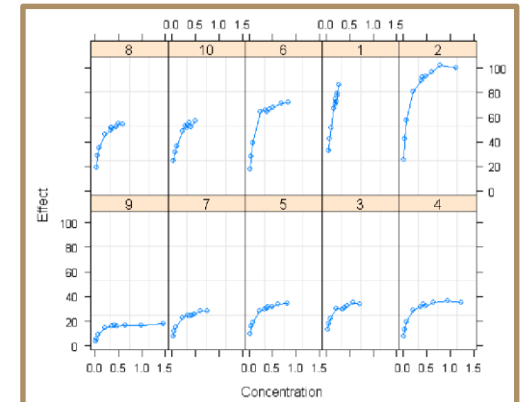
After 1-th Iteration
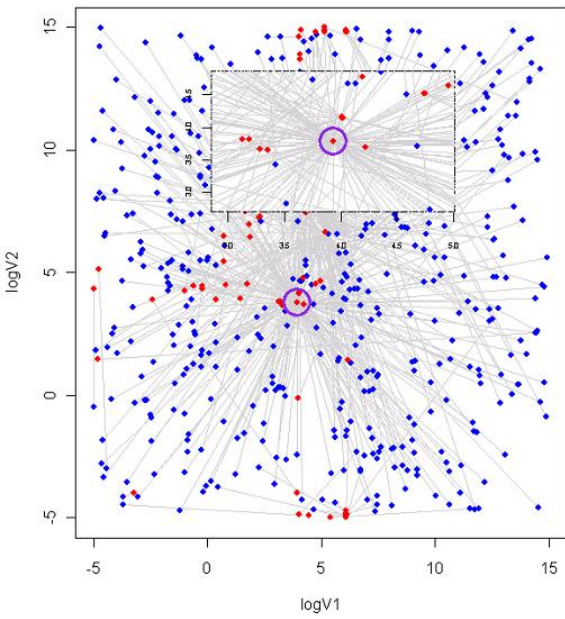
PK example
P=729 (=3^6)
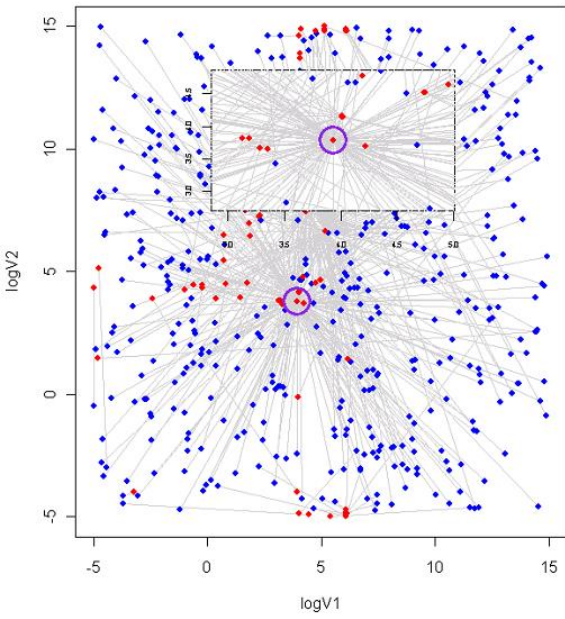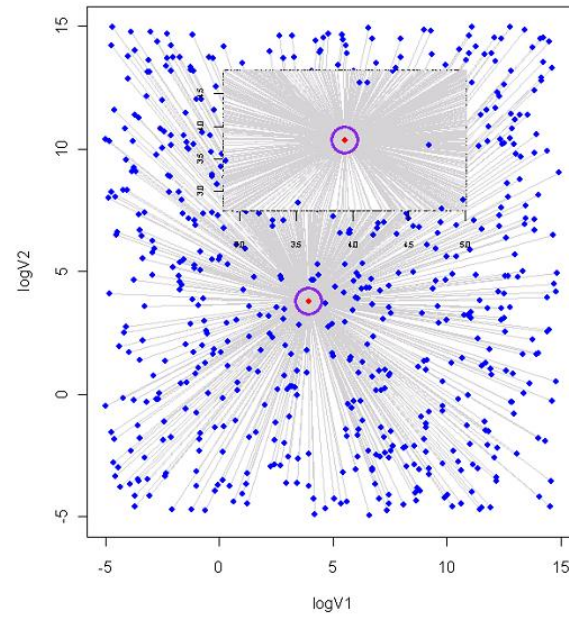
PK example
P=729 (=3⁶)

After 1-th Iteration
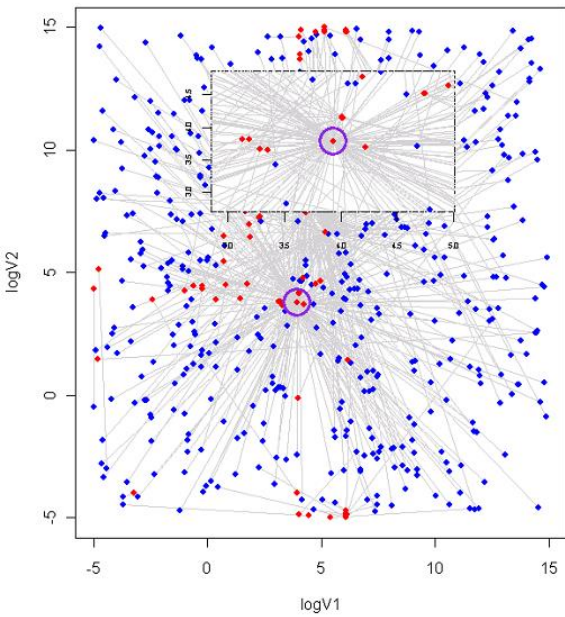
After 50-th Iteration
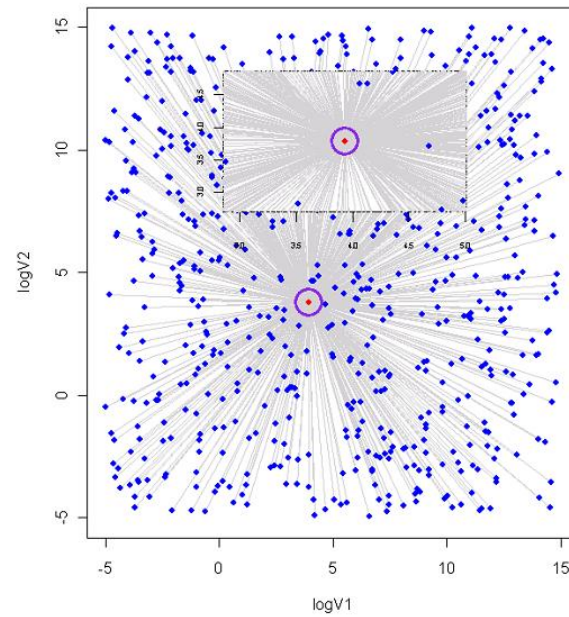
PK example
P=729 (=3^6)

PD example
P=243 (=3^5)

After 1-th Iteration

After 1-th Iteration

After 50-th Iteration

PK example
P=729 (=3^6)

After 1-th Iteration

After 20-th Iteration
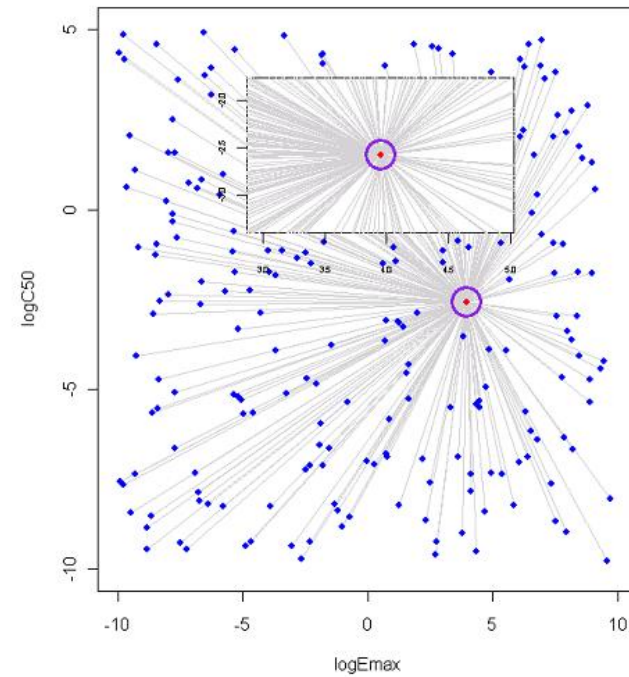
PD example
P=243 (=3^5)

After 1-th Iteration
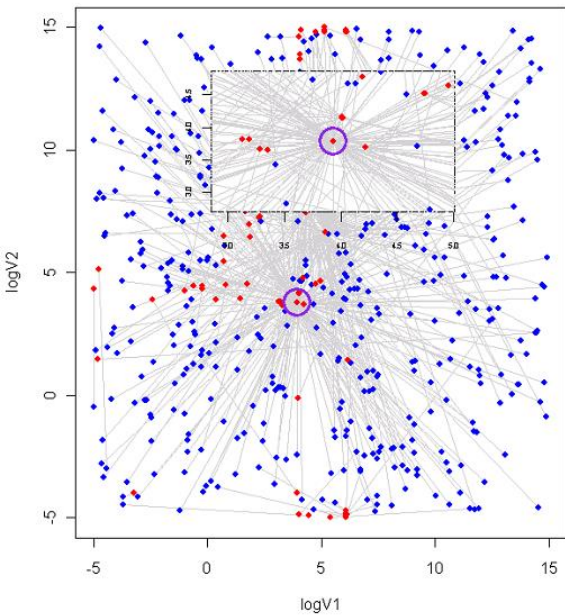
After 50-th Iteration
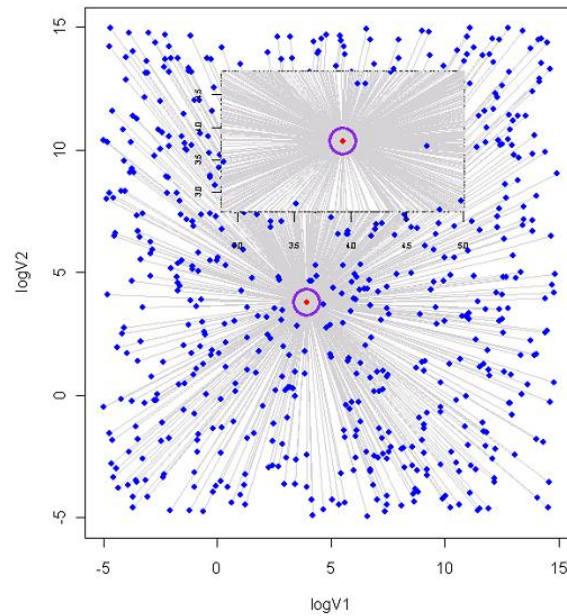
PK example
$P=729\ (=3^6)$

$$10^6 >> 3^6$$

$$10^5 >> 3^5$$

PD example
$P=243\ (=3^5)$
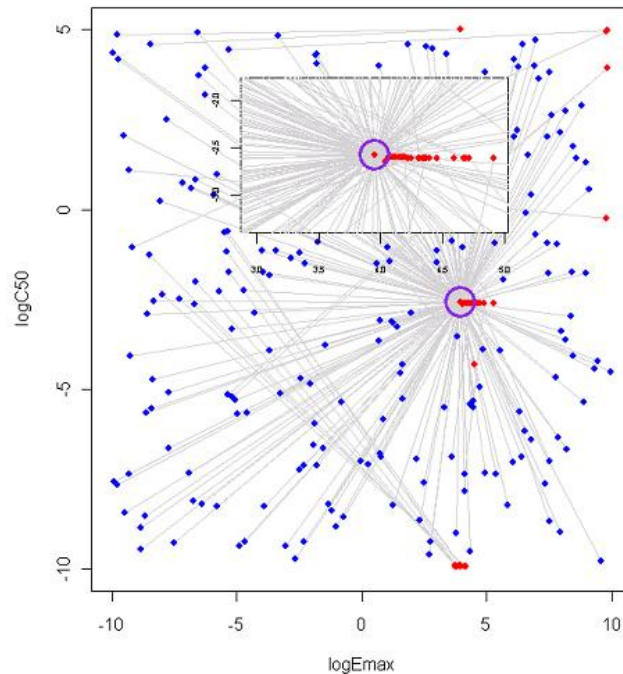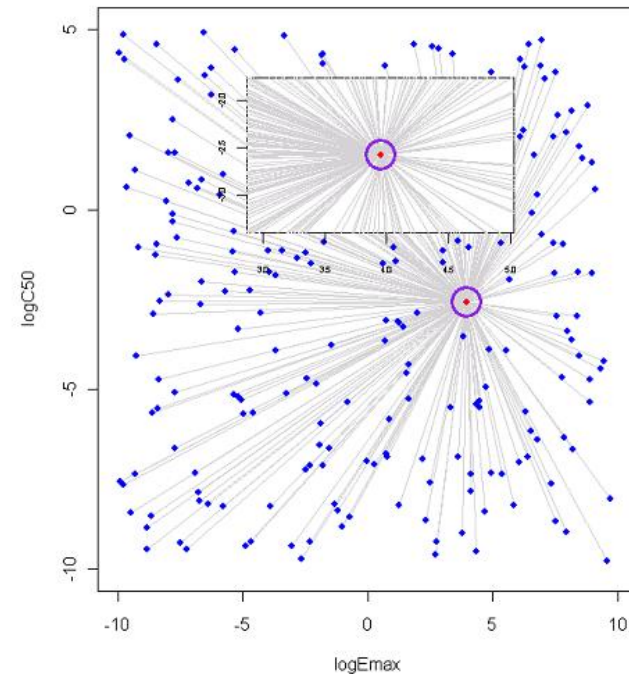
After 1-th Iteration

After 20-th Iteration

Subject-level parameter Absolute relative bias

Mean Squared Error of Prediction

PK example
P=729 (=3^6)

PK example *P*=729 (=3⁶)

PD example *P*=243 (=3⁵)

Subject-level parameter Absolute relative bias

Mean Squared Error of Prediction
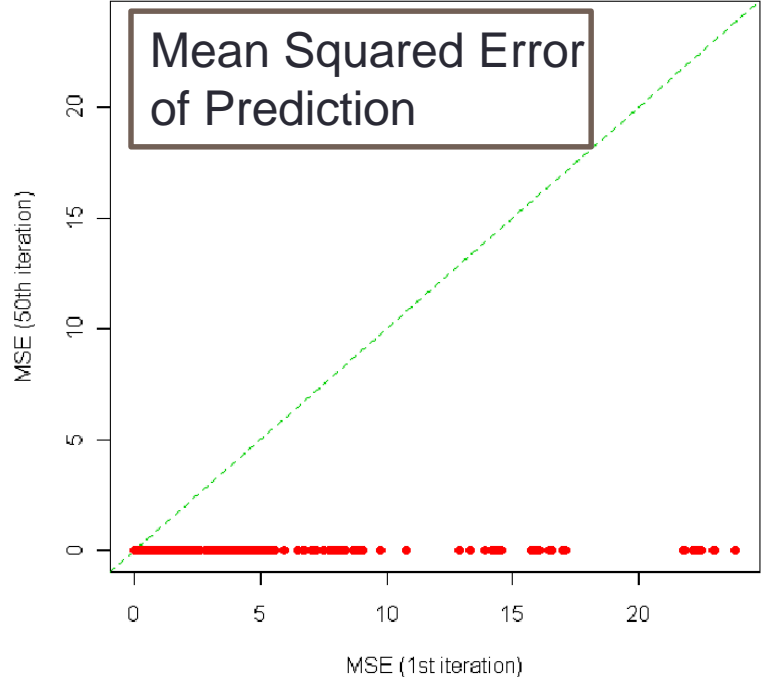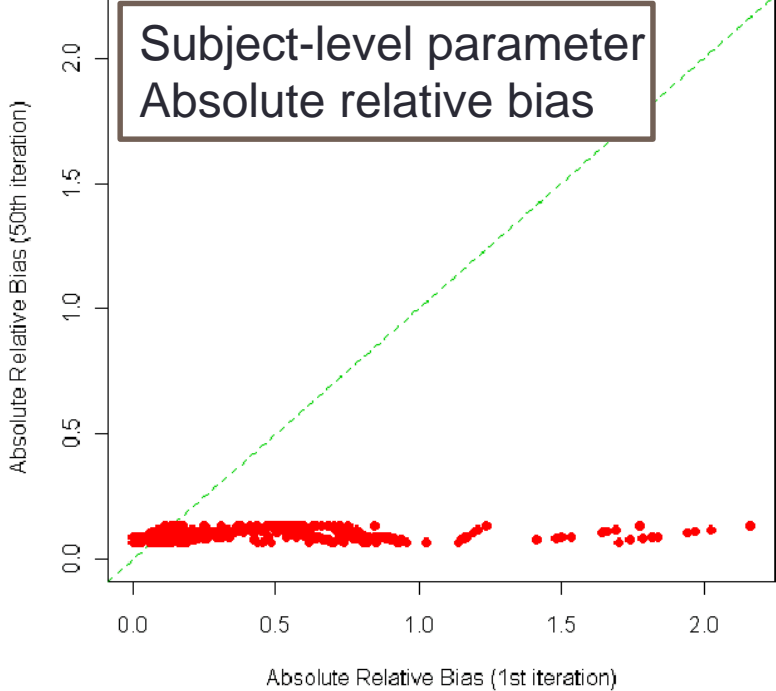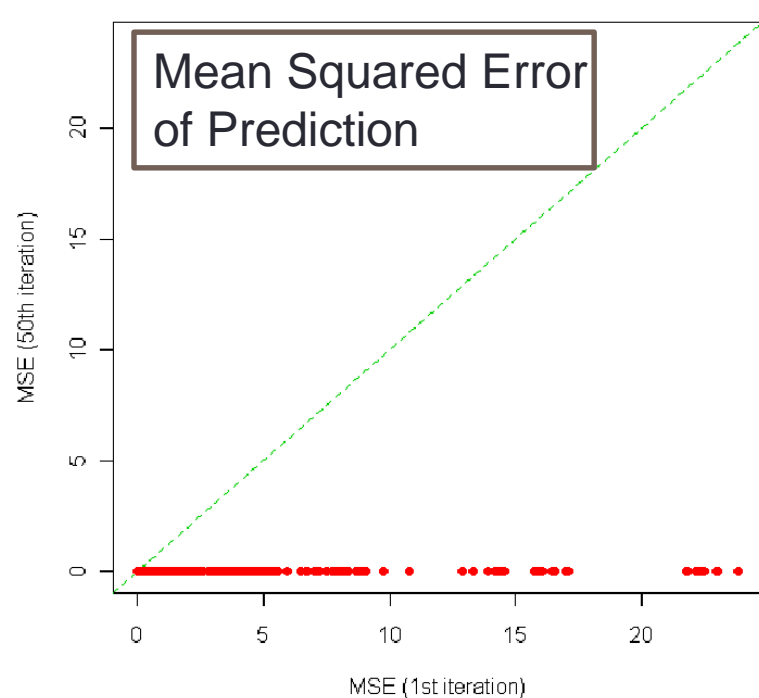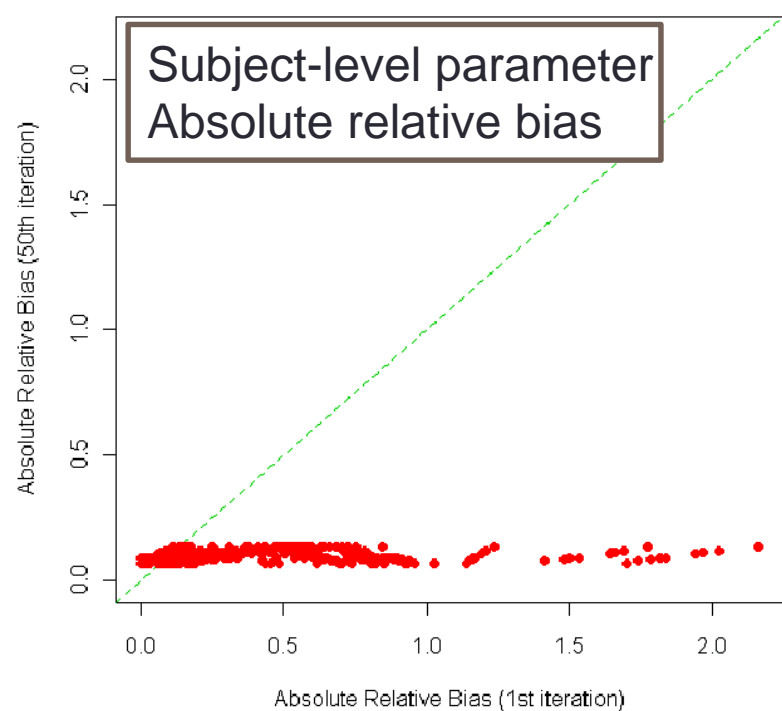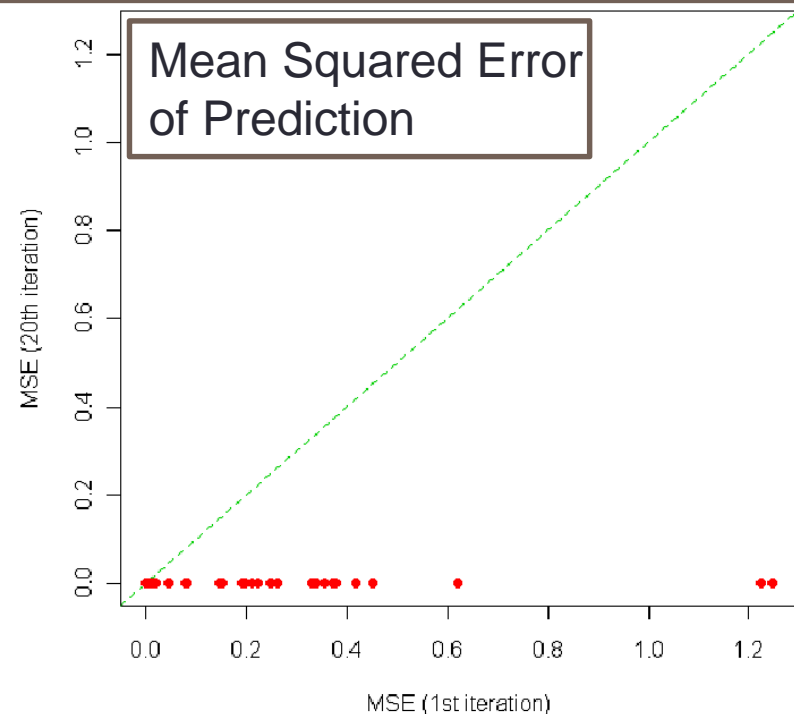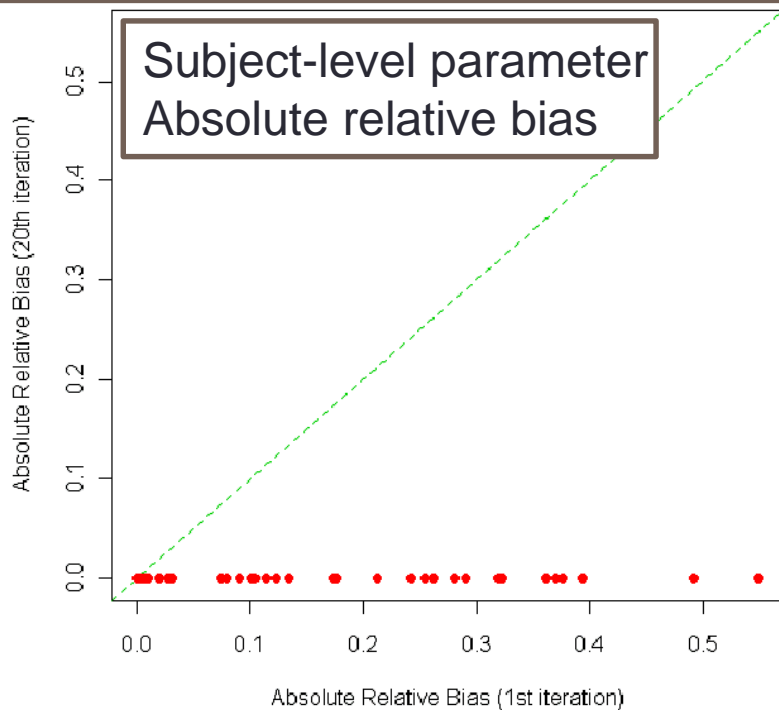
Summary

- The proposed P-NONMEM is not sensitive to initial value selection.

- Even when the initial values are far away from their global optimal, P-NONMEM almost guarantees the global optimization.

- P-NONMEM guarantees the global optimization for fixed effect and variance parameters.

- Under certain regularity conditions, it also leads to global optimization for random effects

Outline

- Pharmacokinetics (PK) analysis
  - Global optimization
  - Identifiability
- Two-stage single-arm phase 2 clinical trial designs
  - Simon's two-stage and Lin and Shih's adaptive designs
  - Adaptive designs with three target response rates

Mathematical Identifiability

- For PK models the corresponding equations are

$$\dot{x}(t) = f(x(t), B(\theta)u(t), \theta, t), \quad x(0) = x_0$$

$$y(t) = G(x(t), B(\theta)u(t), \theta, t)$$

(1)

$x(t)$: the state variables

$x(0)$: the initial conditions

$u(t)$: the input to the system

$B(\theta)$: the matrices depending on θ

$y(t)$: observations

- A single parameter θ of Equation (1) is ***globally identifiable*** if there exists a <u>unique</u> solution for θ

- A parameter with <u>countable or uncountable</u> number of solutions is ***locally identifiable or unidentifiable***

Mathematical Identifiability

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- A single parameter θ of Equation (1) is ***globally identifiable*** if there exists a unique solution for θ

> **Given a model formation and <u>noise-free (perfect)</u> data**
> **Which parameters of the model are identifiable?**
> **(Bellman and Astrom, 1970)**

- A para_____ ____ __ of solutions is ***locally identifiable or unidentifiable***

Statistical Identifiability

$$\dot{\mathbf{x}}(t) = \mathbf{f}(\mathbf{x}(t), \mathbf{B}(\theta)\mathbf{u}(t), \theta, t), \quad \mathbf{x}(0) = \mathbf{x}_0$$

$$\mathbf{y}(t) = \mathbf{G}(\mathbf{x}(t), \mathbf{B}(\theta)\mathbf{u}(t), \theta, t) + \varepsilon(t)$$

$\mathbf{x}(t)$: the state variables

$\mathbf{x}(0)$: the initial conditions

$\mathbf{u}(t)$: the input to the system

$\mathbf{A}(\theta)$, $\mathbf{B}(\theta)$: the matrices depending on θ

$\mathbf{y}(t)$: observations

Statistical Identifiability

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Given (a perfect model structure and) experimental (noise) data
Is it possible to uniquely and accurately estimate the parameters?

Statistical Identifiability

$$\dot{\mathbf{x}}(t) = \mathbf{f}(\mathbf{x}(t), \mathbf{B}(\theta)\mathbf{u}(t), \theta, t), \quad \mathbf{x}(0) = \mathbf{x_0}$$

$$\mathbf{y}(t) = \mathbf{G}(\mathbf{x}(t), \mathbf{B}(\theta)\mathbf{u}(t), \theta, t) + \varepsilon(t)$$

$\mathbf{x}(t)$: the state variables

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$\mathbf{u}(t)$: the input to the system

$\mathbf{A}(\theta), \ \mathbf{B}(\theta)$: the matrices depending on θ

$\mathbf{y}(t)$: observations

**Given (a perfect model structure and) experimental (noise) data
Is it possible to uniquely and accurately estimate the parameters?**

- Estimates of the statistical identifiability are highly depending on **the quality of the data**

Michaelis-Menten (MM) Kinetics

- MM Kinetics Equation: $V(t) = \dfrac{dC(t)}{dt} = \dfrac{Vmax \cdot C(t)}{Km + C(t)}$

  - **$V(t)$**: the overall velocity of the reaction
  - **$Vmax$**: the maximum velocity
  - **Km**: MM constant
  - **$C(t)$**: the concentration
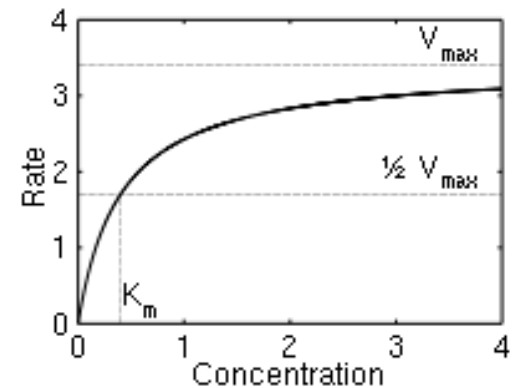
from wikipedia

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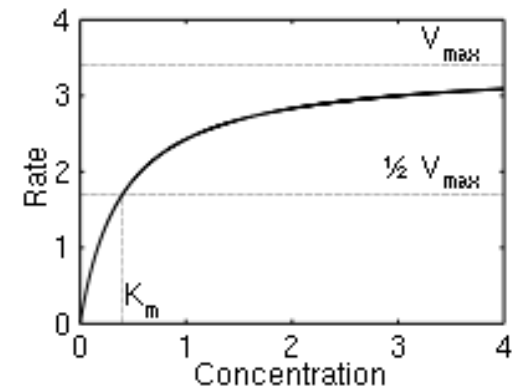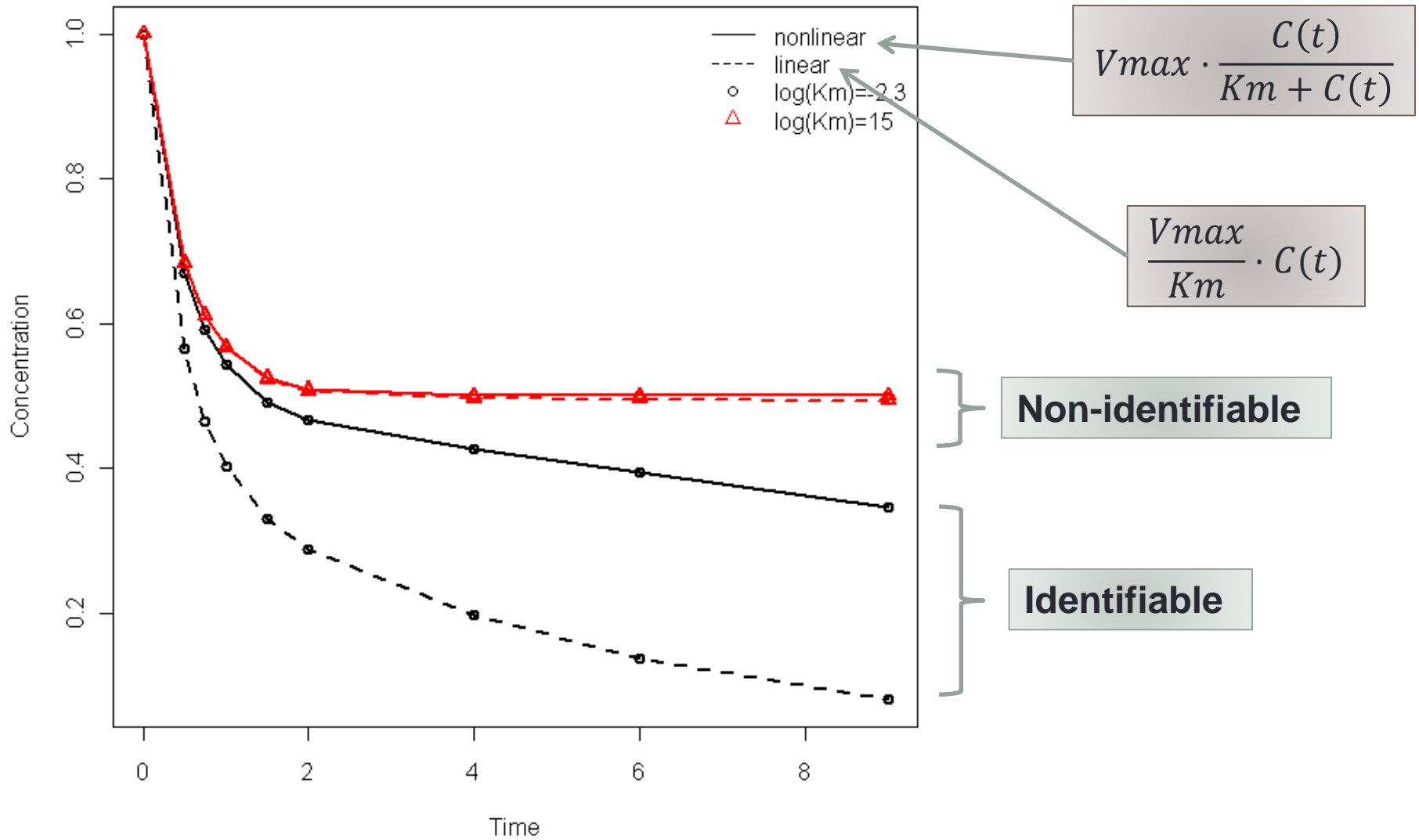
from wikipedia

$$V(t) = \frac{Vmax \cdot C(t)}{Km + C(t)} \approx \frac{Vmax \cdot C(t)}{Km} \text{ if } C(t) \ll Km.$$

$$V(t) = \frac{Vmax \cdot C(t)}{Km + C(t)} \approx Vmax \text{ if } C(t) \gg Km.$$

$$Vmax \cdot \frac{C(t)}{Km + C(t)}$$

$$\frac{Vmax}{Km} \cdot C(t)$$

Non-identifiable

Identifiable

What's the matter?

- Derivative-based optimization
  - Singularity
  - NONMEM uses derivative-based optimizations
- Bayesian approach
  - No theoretical concern for both mathematical and statistical identifiability
    - No singularity issue due to priors (Lindley, 1971)
  - Poor convergence of MCMC (Poirier, 1998; Gelfand and Sahu, 1999; Eberly and Carlin, 2000)

What's new?

- NONMEM is replaced with a derivative-free local optimization

- Convergence criteria
  - The local best-quartile method
  - The global best-variance method
  - The local best-quartile-variance method

Kim and Li **2014**. *CMPB.*

The local best-quartile method

- Suppose θ^k is the $S \times p$ matrix of the population (local best) of size S and the p parameters at kth iteration, i.e.,

$$\theta^k = \begin{bmatrix} \theta_{11}^k & \cdots & \theta_{1p}^k \\ \vdots & \ddots & \vdots \\ \theta_{S1}^k & \cdots & \theta_{Sp}^k \end{bmatrix},$$

  where θ_{ij}^k is the local best of ith particle of jth parameter at kth iteration, $1 \leq i \leq S$, $1 \leq j \leq p$.

- The difference between the first and third quartiles for each parameter is calculated based on $\hat{\theta}^k$, i.e.,

$$d_j^k = \left| Q_1^{kj} - Q_3^{kj} \right|, \textit{ where } j = 1, \ldots, p,$$

  obtaining the maximum difference of all the parameters as the following

$$d^k = \max_{j=1,2,\ldots,p} d_j^k.$$

- The $p \times p$ correlation matrix of θ^k, i.e.,

$$\Omega^k = \begin{bmatrix} 1 & \cdots & \omega_{1p} \\ \vdots & \ddots & \vdots \\ \omega_{p1} & \cdots & 1 \end{bmatrix}$$

- Its maximum and minimum eigenvalues, λ_{max}^k and λ_{min}^k, are estimated to calculate the ratio of two eigenvalues, $\rho^k = \left| \frac{\lambda_{min}^k}{\lambda_{max}^k} \right|$.

- If at least one parameter has $d_j^k = 0$, then the eigenvalues cannot be obtained, so we will assign zero to ρ^k in this case.

The global best-variance method

- Suppose ψ^k is the $k \times p$ matrix consisting of the global best for each parameter up to kth iteration,

$$\psi^k = \begin{bmatrix} \psi_1^1 & \cdots & \psi_p^1 \\ \vdots & \ddots & \vdots \\ \psi_1^k & \cdots & \psi_p^k \end{bmatrix},$$

where ψ_j^i is the global best of jth parameter at $i$the iteration and l^k is the vector of the loglikehood of each global best of size k such as $l^k = (l^1, l^2, \ldots, l^k)$. Then the reduced matrix is obtained based on the user-defined window size, w.

$$\psi_w^k = \begin{bmatrix} \psi_1^{k-w+1} & \cdots & \psi_p^{k-w+1} \\ \vdots & \ddots & \vdots \\ \psi_1^k & \cdots & \psi_p^k \end{bmatrix},$$

where $k \geq w > 0$, and the reduced loglikehood vector is $l_w^k = (l^{k-w+1}, l^{k-w+2}, \ldots, l^k)$.

- $SD(\psi_w^k) = \max_{j=1,\ldots,p} SD_w(\psi_j^k);$
- $SD(l_w^k) = \sqrt{Var(l^{k-w+1}, l^{k-w+2}, \ldots, l^k)},$

$$\text{where } SD_w(\psi_j^k) = \sqrt{Var\left(\psi_j^{k-w+1}, \psi_j^{k-w+2}, \ldots, \psi_j^k\right)}.$$

The local-quartile-variance method

- $SD\left(d_w^k\right) = \sqrt{Var(d^{k-w+1}, d^{k-w+2}, \ldots, d^k)};$
- $SD\left(\rho_w^k\right) = \sqrt{Var(\rho^{k-w+1}, \rho^{k-w+2}, \ldots, \rho^k)}.$

Convergence diagnostics

If $SD\left(\rho_w^k\right)$ is less than equal to the user-defined cutoff value (α) with the window size of w, LPSO will be considered as converged to a global optimum. Furthermore, if d^k is greater than the user-defined cutoff value (β), the model is considered as non-identifiable, where k is the number of iterations to converge which is identified by $SD\left(\rho_w^k\right)$. The general guideline for α and β is 0.001 and one, respectively.

Simulation

- ## The constants of PSO
    - $(c_1, c_2, w_{max}, w_{min}, K) = (2,2,0.9,0.3,5000)$
    - #particles of each parameter: 10 for PSO and 5 for LPSO.
    - The parameter boundaries = $(-20, 20)$.
    - The true values are $\theta^{true} = (0, -2.3)$ for the identifiable case and $(0,15)$ for non-identifiable case.

- For both PSO and LPSO, the same seed number was used to generate the initial population.

$$Vmax \cdot \frac{C(t)}{Km + C(t)}$$

$$\frac{Vmax}{Km} \cdot C(t)$$

Non-identifiable

Identifiable

(a) After 1st iteration

Fig. 4 – The scatter-box plots between log V_{max} and log K_m for PSO and LPSO. The plots in the left and right columns are for PSO and LPSO, respectively, and the first and second rows are for identifiable and non-identifiable cases. The solid lines in the plot indicate the true values for each parameter.

Fig. 4 – The scatter-box plots between log V_{max} and log K_m for PSO and LPSO. The plots in the left and right columns are for PSO and LPSO, respectively, and the first and second rows are for identifiable and non-identifiable cases. The solid lines in the plot indicate the true values for each parameter.

(b) After 500th iteration

Fig. 4 – The scatter-box plots between log V_{max} and log K_m for PSO and LPSO. The plots in the left and right columns are for PSO and LPSO, respectively, and the first and second rows are for identifiable and non-identifiable cases. The solid lines in the plot indicate the true values for each parameter.

(c) After 5000th iteration

Identifiable
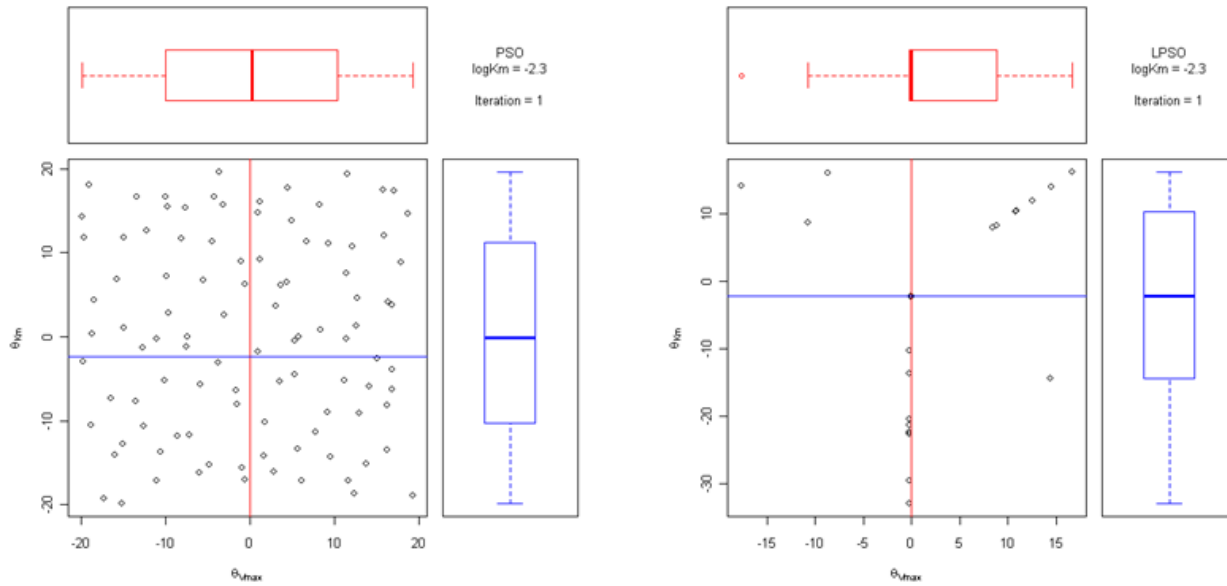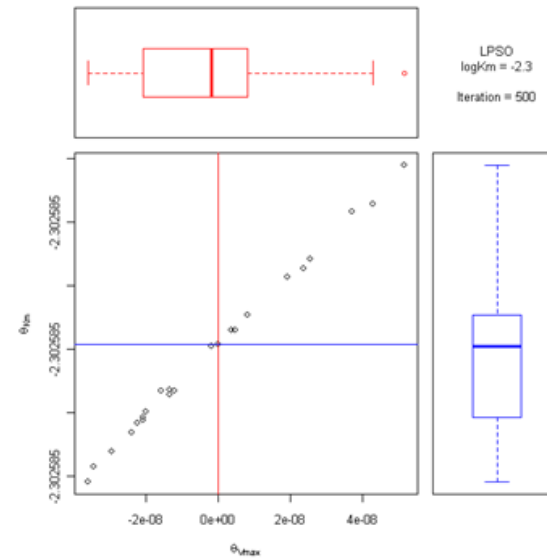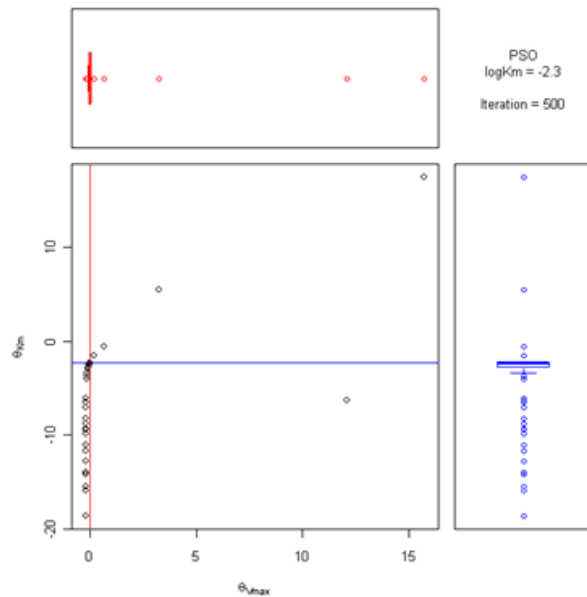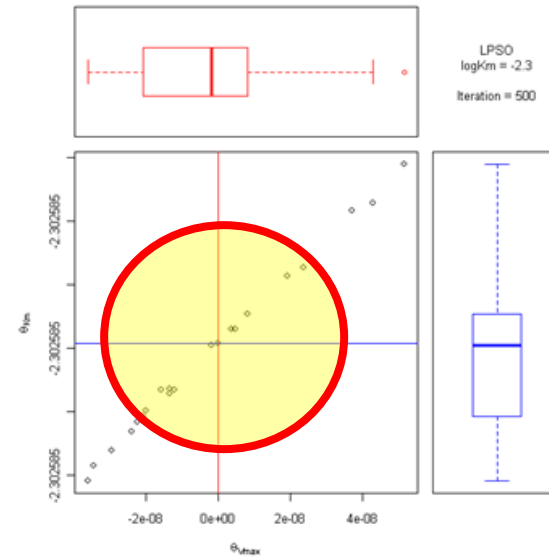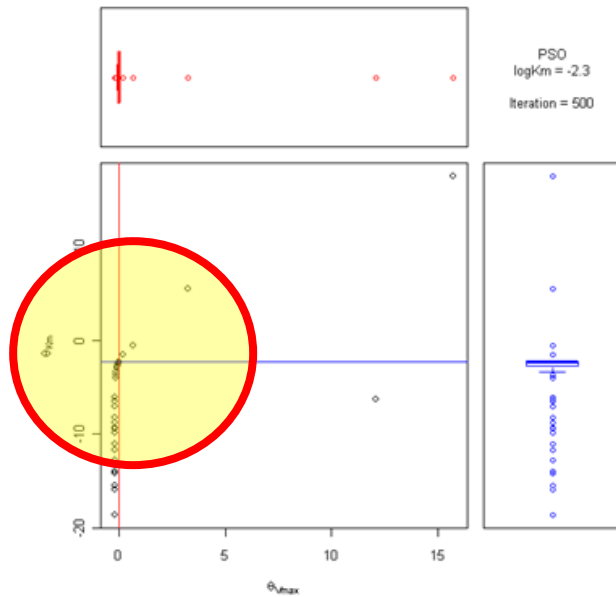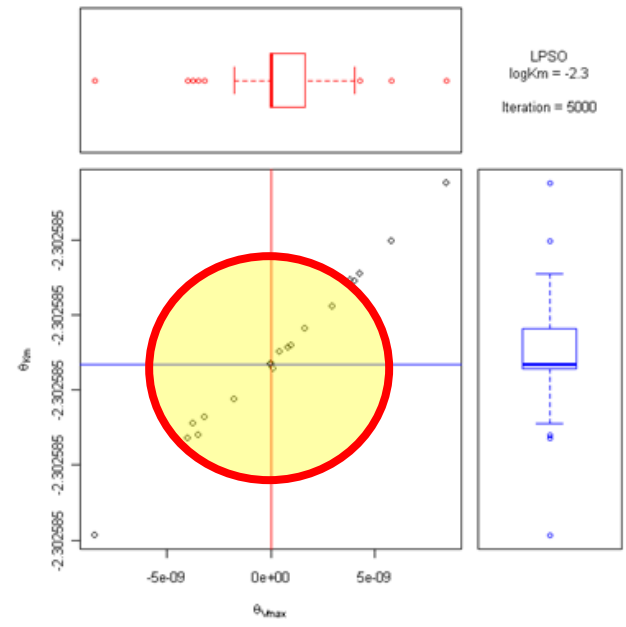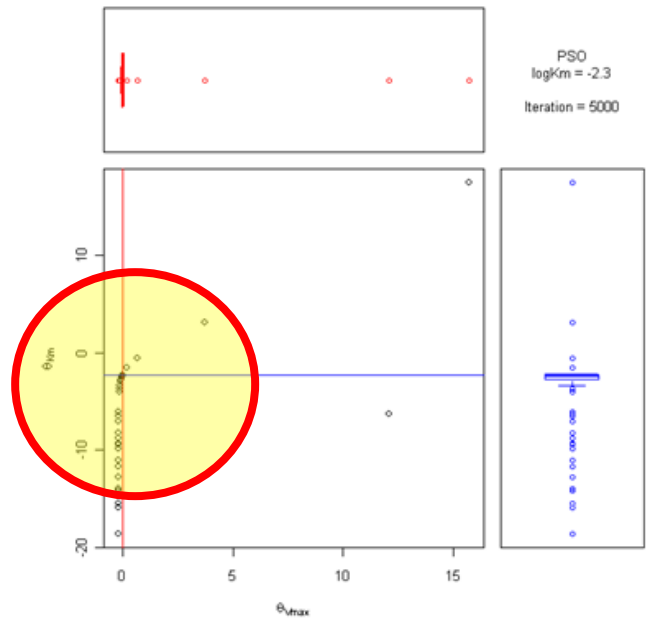
Non-identifiable
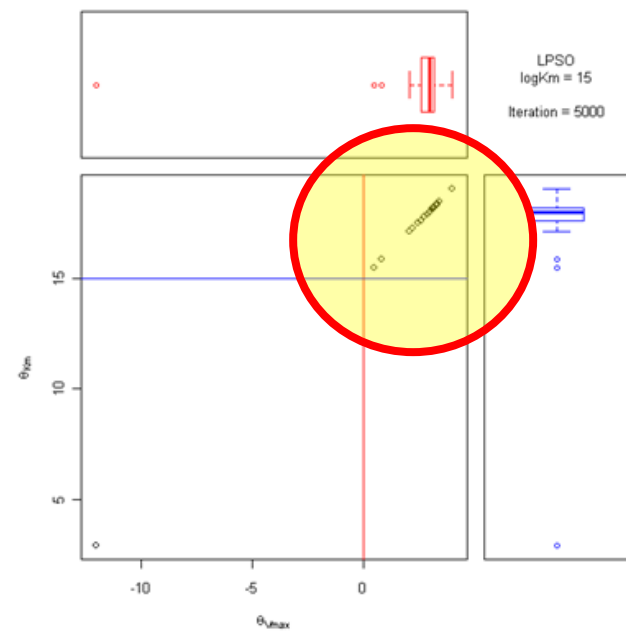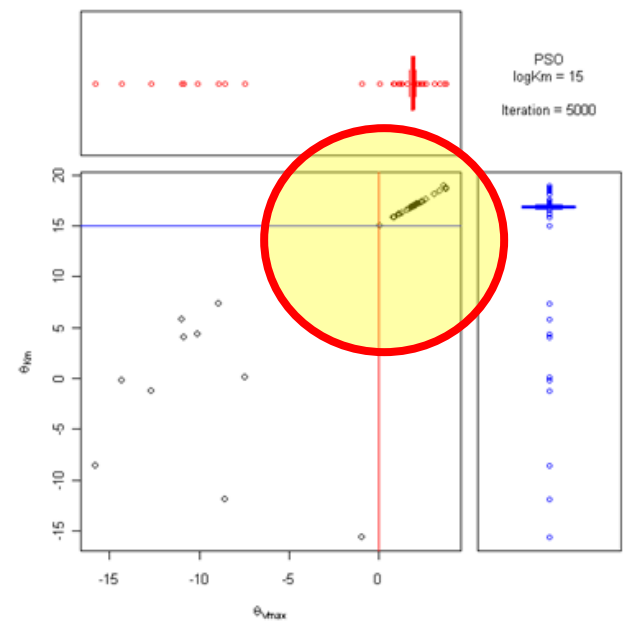
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Summary

- A novel version of PSO is proposed with enhancing the convergence of the local best using a derivative-free local optimization algorithm, which is called LPSO.

- LPSO converges to a global optimum much faster than PSO does.

- Since PSO is a derivative-free algorithm and a derivative-free local optimization is combined, the proposed LPSO becomes a derivative-free global optimization algorithm so that LPSO can be applied to the parameter estimation regardless of the identifiability.

- Several convergence diagnostic measures are proposed and evaluated through both the simulation studies and clinical PK data analysis.

Outline

- Pharmacokinetics (PK) analysis
  - Global optimization
  - Identifiability

- Two-stage single-arm phase 2 clinical trial designs
  - Simon's two-stage and Lin and Shih's adaptive designs
  - Adaptive designs with three target response rates

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Clinical Trial Phases

Drug is accepted for marketing

| Phase I Safety | Phase II Activity | Phase III Evaluation | Phase IV Long-term monitor |

Phase	No. of Patients	Length of Phase	Goal	Success rate
1	Small (20-100)	Short (several months)	-Dose finding trials -Safety, dosages (Maximum tolerated dose (MTD)), efficacy	70%
2	Small (30-500)	Short (several months to 2 years)	-Screening trials -Effectiveness and short-term safety	33%
3	Large (500-3000)	Longer (1-4 years)	-Safety and effectiveness	25-30%
4	Huge (>3000)	Long-long (>20 years)	-post-marketing monitor -long-term safety and rare adverse effects	70-90%

Phase II Trials

- Provide initial assessment of efficacy or 'clinical activity'
  - Screen out ineffective drugs
  - Identify promising new drugs for further evaluation
- Further define safety and toxicity
- Minimize cost of the trial
  - Minimize number of patients exposed to an ineffective treatment
  - Enroll as few patients as "necessary" to show benefit or failure

Phase II study

- Single-arm phase II study (Phase IIA)
  - Response rate is often used as its primary end point
  - Small number of patients enrolled
  - Reliance on historical controls for an estimation of expected response rate
  - Gehan's design (1961); Simon's two-stage designs (1989); predictive probability design (2008), etc.
- Randomized phase II trial (Phase IIB)
  - Simon et al's ranking and selection randomized design (1985); randomized discontinuation design (2002); Bayesian adaptive designs, etc.

Simon's Two-Stage Designs

• X: the number of responders
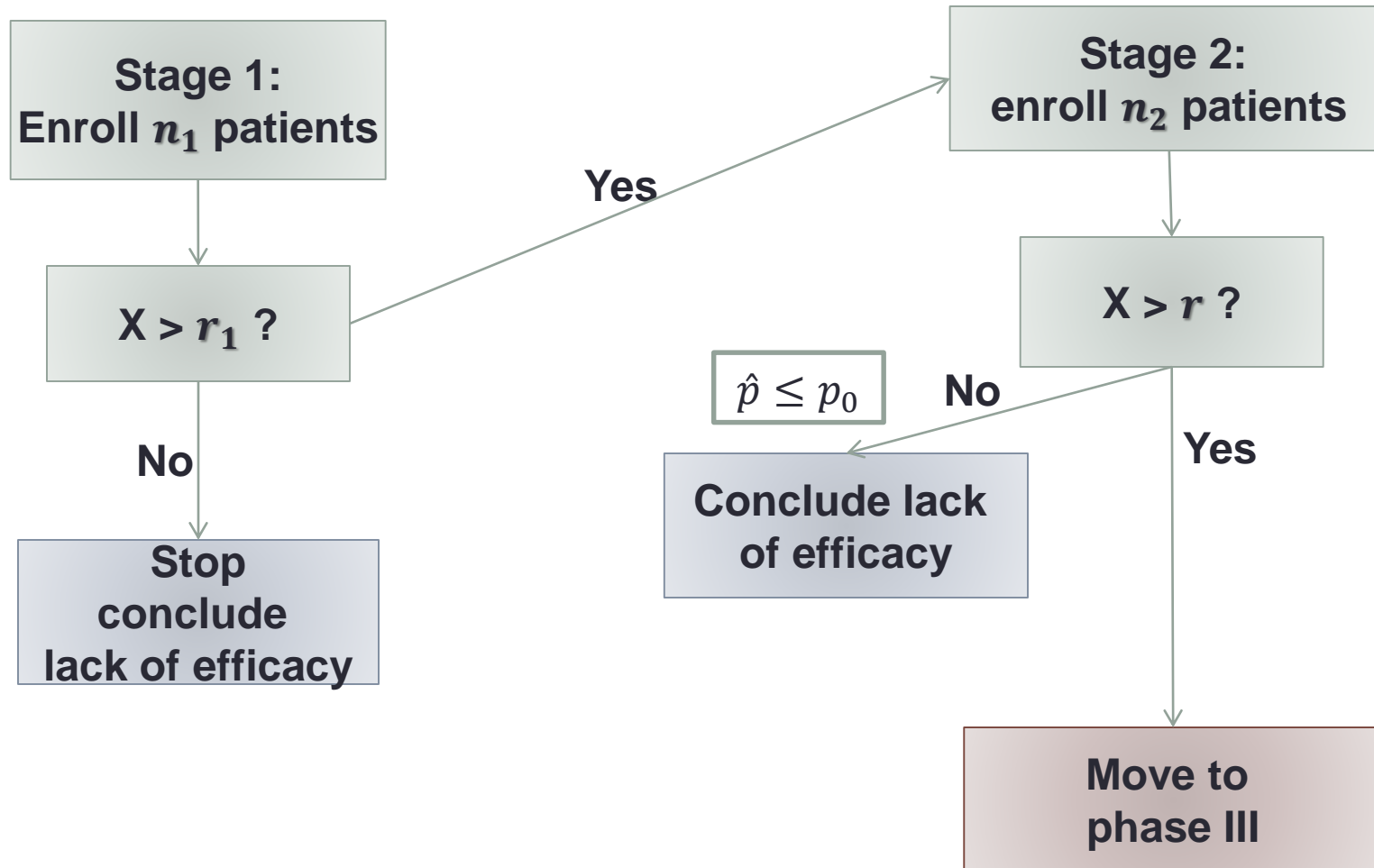
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- X: the number of responders
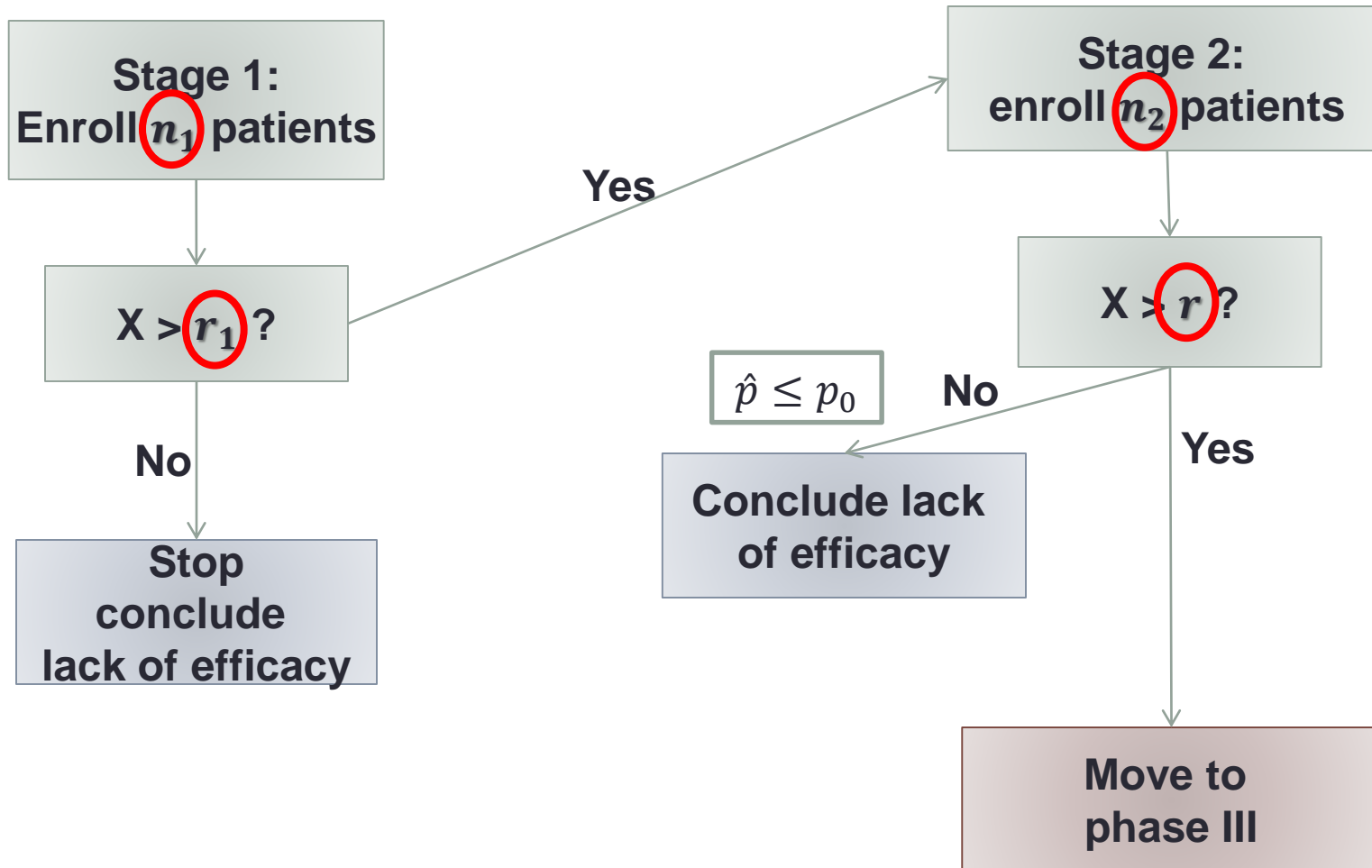
Simon's Two-Stage Designs

- $H_0: p \leq p_0 \ vs. \ H_1: p \geq p_1, where \ p_0 < p_1$
  - $b(x, m, p) \, and \, B(x, m, p)$: the pmf and cdf for $x \sim Bin(m, p)$
  - $G(r_1, n_1, r, n, p)$: the prob of failing to reject H_0

$$= B(r_1, n_1, p) + \sum_{x=r_1+1}^{\min(r, n_1)} b(x, n_1, p) B(r - x, n_2, p)$$

  , where $n = n_1 + n_2$
  - $E(N|p) = n_1 + \left(1 - B(r_1, n_1, p)\right) n_2$: the expected sample size
- Greedy search (look for all cases) given α, β
  - $G(\boldsymbol{r_1, n_1, r, n}, p_0) \geq 1 - \alpha; G(\boldsymbol{r_1, n_1, r, n}, p_1) \leq \beta$
  - Optimum design (min EN_0)
  - Minimax design (min {max$N$})

Adaptive Two-Stage Designs

- Allow the sample size at the second stage to depend on the results at the first stage
  - Lin and Shih (2004)
  - Banerjee and Tsiatis (2006)

Lin and Shih (2004)

- p_0: the maximum uninteresting response rate
- p_1, p_2: two choices of the target response rates, where $p_0 < p_1 < p_2$

- n_1 patients will be enrolled to the first stage
- #(patients) for the second stage will depend on the number of observed responses in the first stage

Lin and Shih (2004)

- X: the number of observed responders
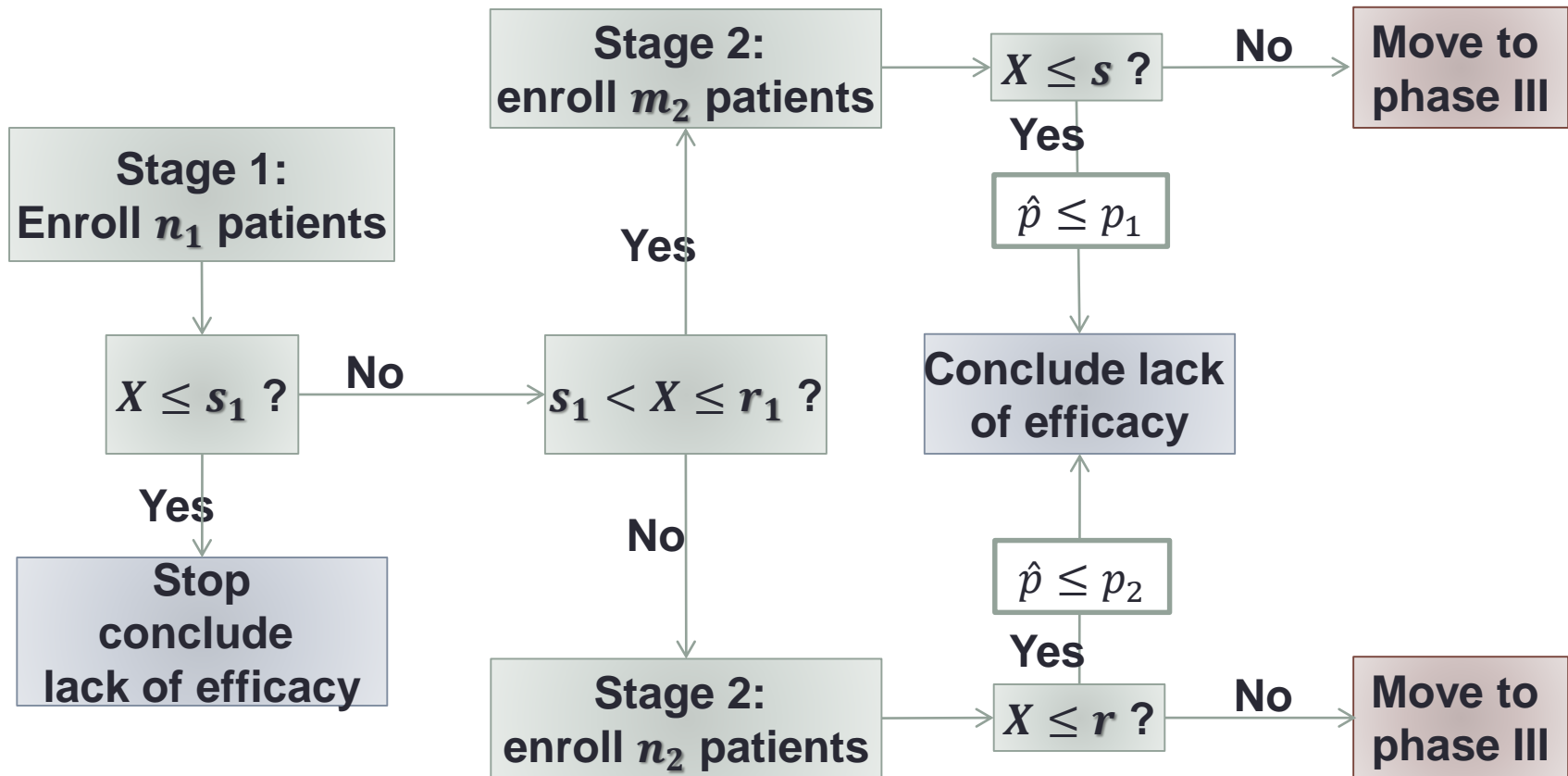
Lin and Shih (2004)

- X: the number of observed responders
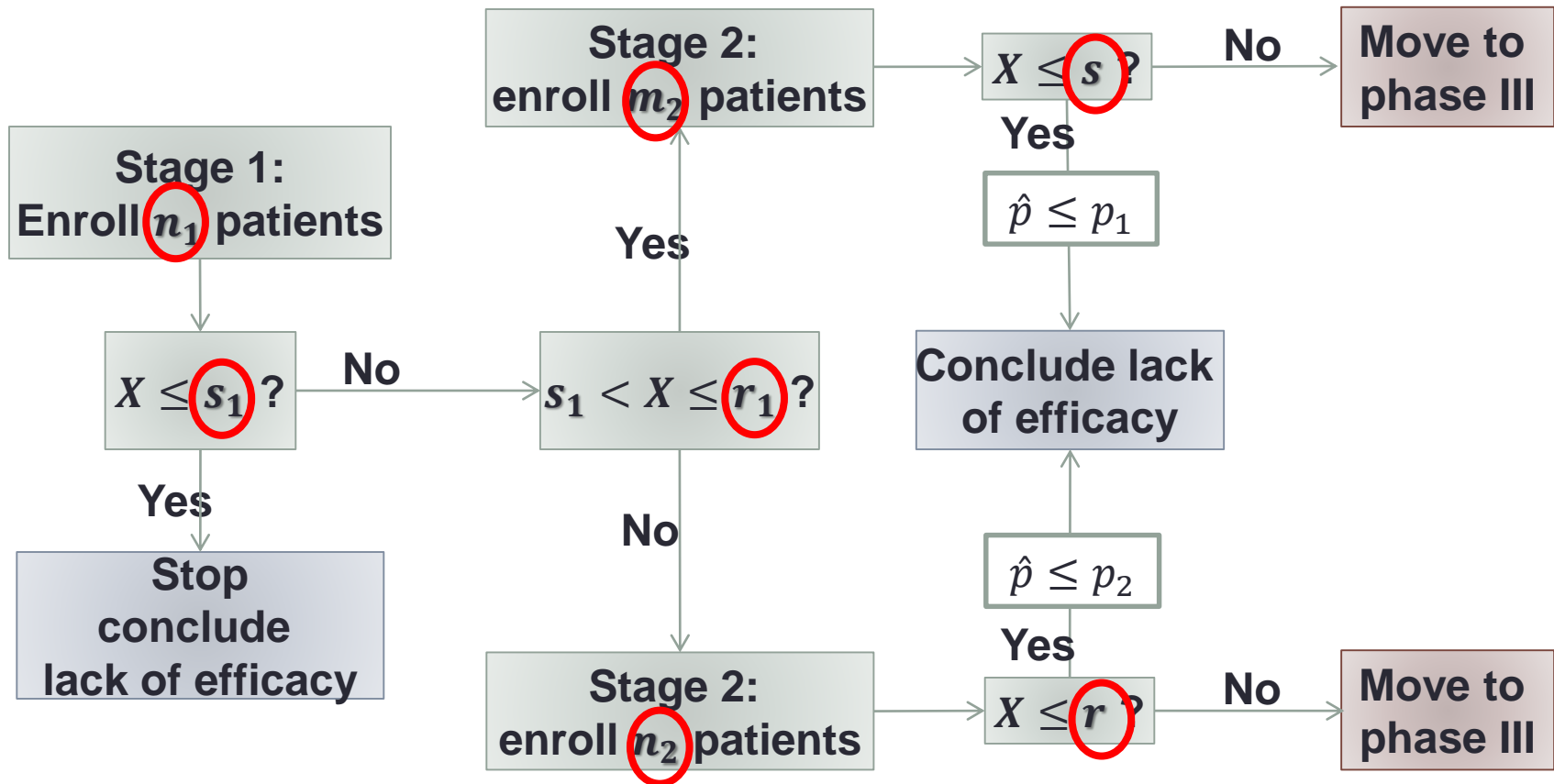
Lin and Shih (2004)

- $H_0: p \leq p_0 \ vs. \ H_1: p \geq p_1 \ or \ H_1: p \geq p_2 \ where \ p_0 < p_1 < p_2$
  - $b(x, m, p) \ and \ B(x, m, p)$: the pmf and cdf for $x \sim Bin(m, p)$
  - $G(s_1, r_1, n_1, s, m, r, n, p)$: the prob of failing to reject H_0

$$= B(s_1, n_1, p) + \sum_{x=s_1+1}^{\min(r_1, s)} b(x, n_1, p) B(s - x, m_2, p)$$

$$+ \sum_{x=r_1+1}^{\min(r, n_1)} b(x, n_1, p) B(r - x, n_2, p)$$

, where $m = m_1 + m_2$; $n = n_1 + n_2$
  - $E(N|p) = n_1 + \{(B(r_1, n_1, p) - B(s_1, n_1, p))m_2 + (1 - B(r_1, n_1, p))n_2\}$: the expected sample size

- Greedy search (look for all cases) given α, β_1, β_2
  - $G(s_1, r_1, n_1, s, m, r, n, p_0) \geq 1 - \alpha$
  - $G(s_1, r_1, n_1, s, m, r, n, p_1) \leq \beta_1$
  - $G(s_1, r_1, n_1, s, m, r, n, p_2) \leq \beta_2$

Optimality criteria

- $O1: \min\{EN_0\}$

- $O2: \min\left\{\max_i EN_i\right\}$

- $O3: \min\{\max(n, m)\}\ and\ \min\{EN_0\}$

- $O4: \min\{\max(n, m)\}\ and\ \min\left\{\max_i EN_i\right\}$

Motivation

- A single arm two-stage phase II trial to see the effect of head and neck cancer (HNC) on the incidence of obstructive sleep apnea (OSA).

- The maximum incidence rate of snoring and sleep apnea on healthy patients is **16.5% (i.e., $p_0 = 0.165$)**.

- Neither historical nor preliminary data available, except that the incidence rate of OSA will be higher in HNC patients.

- An empirical range of the target response rates, from **24.38% to 39.00%.**

- Simon's two-stage design (80% power and 5% level) ➔ the required sample sizes range from **30 to 197**

- Due to wide range of the target response rates, **Lin and Shih's approach will not be able to cover the great uncertainty**.

Extension to three choices?

- "We do not extend the selection to more than two prefixed possible response rates mainly **due to the complexity in the numerical solutions**, and also because it is **usually adequate** for practitioners to contemplate between two (high./low) choices of p_*."-Lin and Shih (2004)

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- "We do not extend the selection to more than two prefixed possible response rates mainly **due to the complexity in the numerical solutions**, and also because it is **usually adequate** for practitioners to contemplate between two (high./low) choices of p_*."-Lin and Shih (2004)

Lin and Shih (2004)
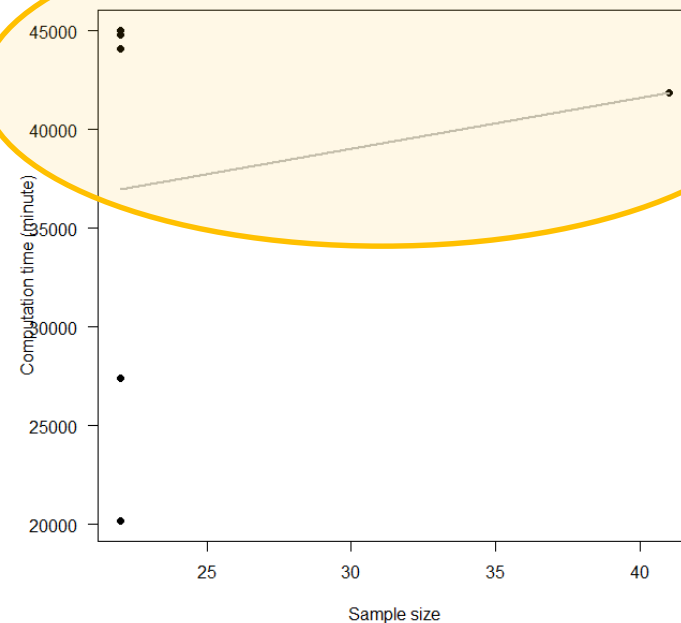
Sample size vs. Computation time

Simon's two-stage
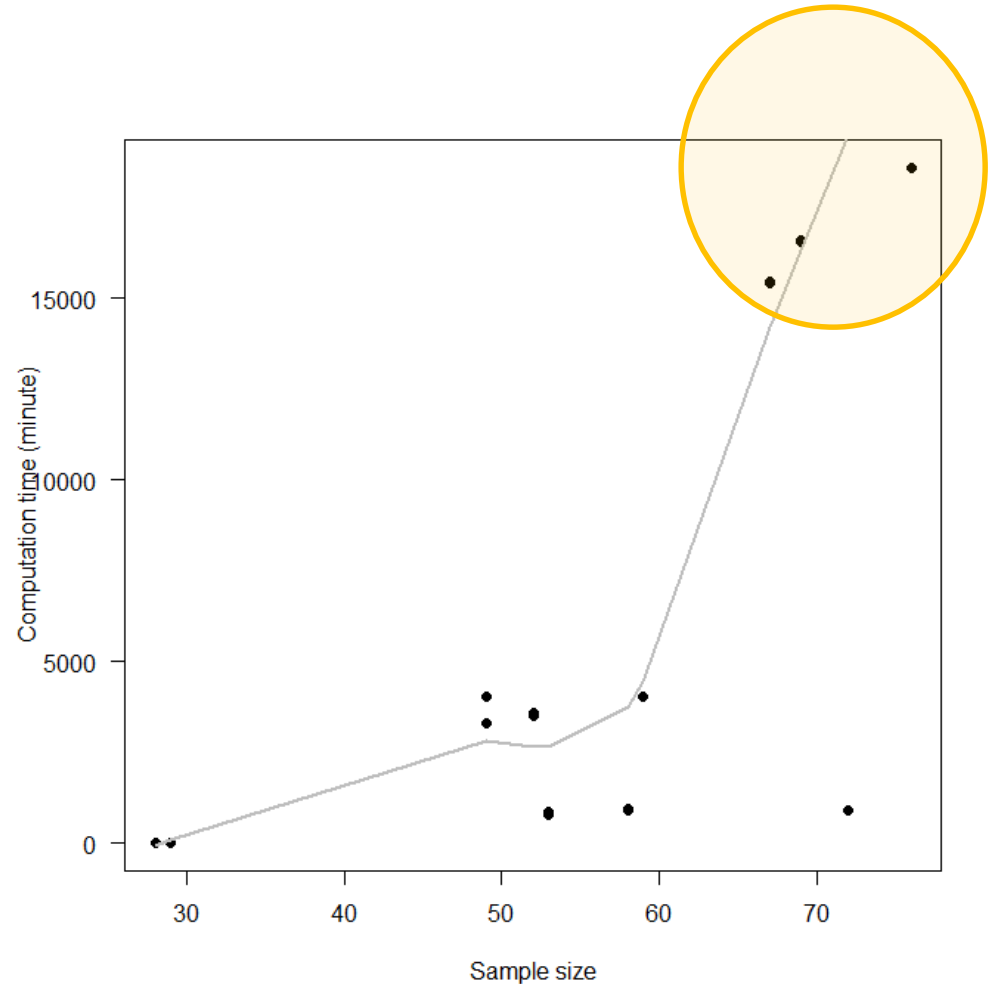
How to reduce the computational burden?

- Nonlinear
- No closed form solution
- Not differentiable

Particle Swarm Optimization (PSO)

$$v^p_{k+1} = w_k v^p_k + c_1 r_1 \left(x^p_{lbest} - x^p_k \right) + c_2 r_2 \left(x_{gbest} - x^p_k \right)$$

$$x^p_{k+1} = x^p_k + v^p_{k+1}$$

Discrete Particle Swarm Optimization (DPSO)

- *k*-th iteration

$$v_{k+1}^p = w_k v_k^p + c_1 r_1 \left(x_{lbest}^p - x_k^p \right) + c_2 r_2 \left(x_{gbest} - x_k^p \right)$$

$$x_{k+1}^p = x_k^p + v_{k+1}^p$$

- *p = 1,…,P; P*: the population size
- x_{lbest}^p and x_{gbest}: local best and global best, respectively
- v_{k+1}^p: the velocity
- w_k: inertia weight

$$w_k = round \left(w_{max} - \frac{k}{K} (w_{max} - w_{min}) \right)$$

- $r_1 c_1, r_2 c_2$: two random sequences in {0,1,2,…,n}; $n = c_1 \, or \, c_2$
- *K*: total number of iterations

Outline

- Pharmacokinetics (PK) analysis
  - Global optimization
  - Identifiability

- Two-stage single-arm phase 2 clinical trial designs
  - Simon's two-stage and Lin and Shih's adaptive designs
  - Adaptive designs with three target response rates

Extension of Lin and Shih (2004)
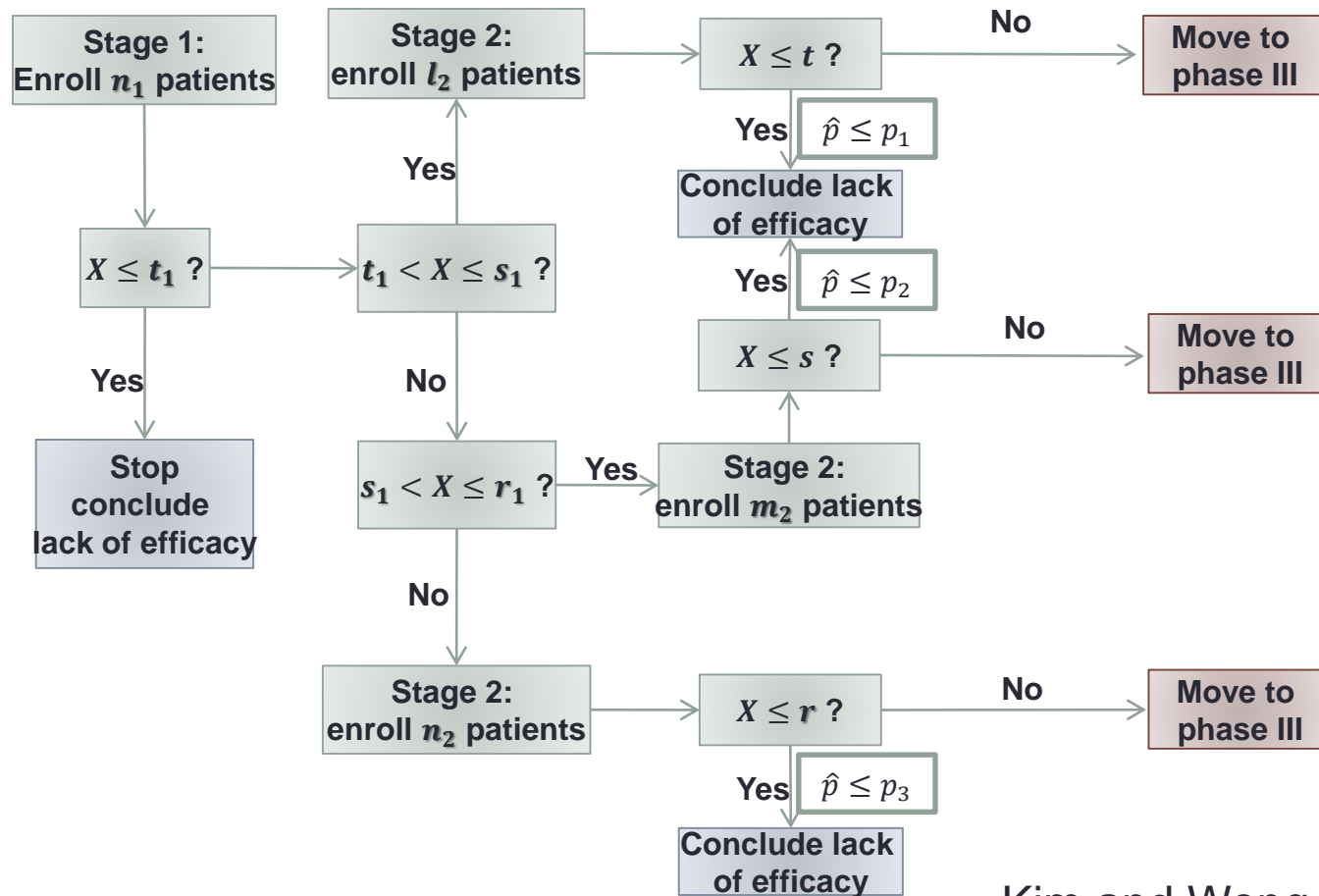
- X: the number of observed responders

Kim and Wong **2017**. *SMMR.*

Extension of Lin and Shih (2004)

- X: the number of observed responders

Kim and Wong **2017**. *SMMR.*
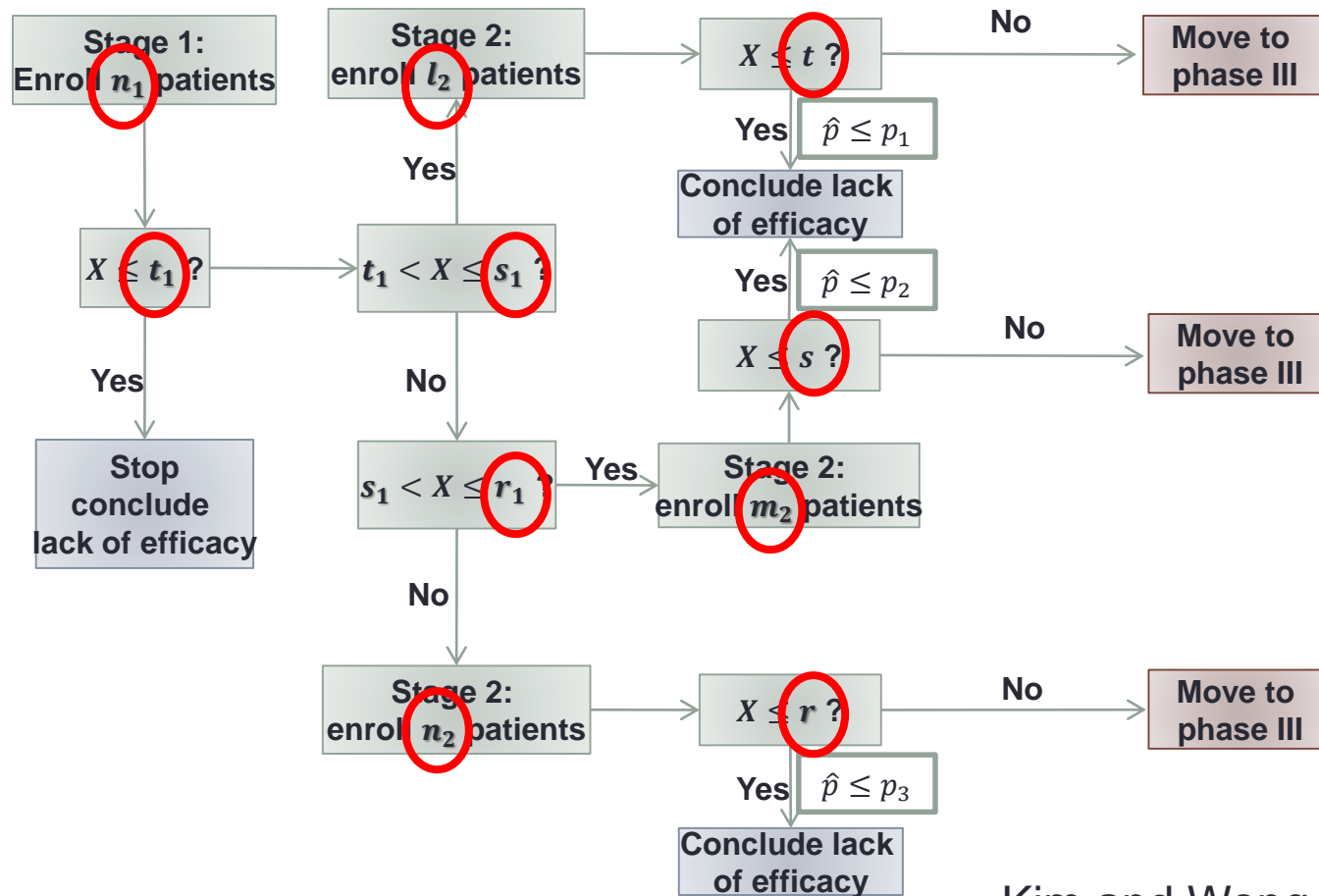
Extension of Lin and Shih (2004)

- $H_0: p \leq p_0 \ vs. \ H_1: p \geq p_1 \ or \ H_1: p \geq p_2 \ or \ H_1: p \geq p_3, where \ p_0 < p_1 < p_2 < p_3$
  - $b(x, m, p) and \ B(x, m, p)$: the pmf and cdf for $x \sim Bin(m, p)$
  - $G(s_1, r_1, n_1, s, m, r, n, p)$: the prob of failing to reject H_0

$$= B(t_1, n_1, p) + \sum_{x=t_1+1}^{\min(s_1, t)} b(x, n_1, p) B(t - x, l_2, p)$$

$$+ \sum_{x=s_1+1}^{\min(r_1, s)} b(x, n_1, p) B(s - x, m_2, p) + \sum_{x=r_1+1}^{\min(r, n_1)} b(x, n_1, p) B(r - x, n_2, p)$$

, where $l = l_1 + l_2; \ m = m_1 + m_2; \ n = n_1 + n_2$

- $E(N|p) = n_1 + \{(B(s_1, n_1, p) - B(t_1, n_1, p))l_2 + (B(r_1, n_1, p) - B(s_1, n_1, p))m_2 + (1 - B(r_1, n_1, p))n_2\}$: the expected sample size

- Greedy search (look for all cases) given $\alpha, \beta_1, \beta_2, \beta_3$
  - $G(s_1, r_1, n_1, s, m, r, n, p_0) \geq 1 - \alpha$
  - $G(s_1, r_1, n_1, s, m, r, n, p_1) \leq \beta_1$
  - $G(s_1, r_1, n_1, s, m, r, n, p_2) \leq \beta_2$
  - $G(s_1, r_1, n_1, s, m, r, n, p_3) \leq \beta_3$

Optimality criteria

- $O1: \min\{EN_0\}$

- $O2: \min\left\{\max_i EN_i\right\}$

- $O3: \min\{\max(l, n, m)\} \text{ and } \min\{EN_0\}$

- $O4: \min\{\max(l, n, m)\} \text{ and } \min\left\{\max_i EN_i\right\}$

Finding initial values

- G-DPSO
  - Within this smaller domain, we searched for an appropriate set of initial values using the same strategy as the greedy search did for the rest of the parameters.

- D-DPSO
  - Use when the number of target responses is two or more.
  - Find the initial set of values using an optimal set of values decided by the case with the one less number of target response.

Table 1. Various adaptive two-stage optimal designs with one target response when $\alpha = 0.05$ and $\beta = 0.20$.

p_0	p_1	Optimal criteria	Method	s_1/n_1	s/n	$1-\alpha$	β	$E(N\|p_0)$	$E(N\|p_1)$
0.05	0.20	C1	GS	0/10	3/29	0.953	0.199	17.624	26.960
			G-DPSO	0/10	3/29	0.953	0.199	17.624	26.960
		C2	GS	0/11	3/28	0.956	0.199	18.330	26.540
			G-DPSO	0/11	3/28	0.956	0.199	18.330	26.540
		C3	GS	0/11	3/28	0.956	0.199	18.330	26.540
			G-DPSO	0/11	3/28	0.956	0.199	18.330	26.540
		C4	GS	0/11	3/28	0.956	0.199	18.330	26.540
			G-DPSO	0/11	3/28	0.956	0.199	18.330	26.540
0.20	0.35	C1	GS	5/22	19/72	0.951	0.200	35.368	63.855
			G-DPSO	5/22	19/72	0.951	0.200	35.368	63.855
		C2	GS	3/21	15/53	0.950	0.200	41.148	51.941
			G-DPSO	3/21	15/53	0.950	0.200	41.148	51.941
		C3	GS	6/31	15/53	0.950	0.198	40.436	51.983
			G-DPSO	6/31	15/53	0.950	0.198	40.436	51.983
		C4	GS	3/21	15/53	0.950	0.200	41.148	51.941
			G-DPSO	3/21	15/53	0.950	0.200	41.148	51.941
0.55	0.70	C1	GS	15/26	48/76	0.952	0.195	42.021	69.735
			G-DPSO	15/26	48/76	0.952	0.195	42.021	69.735
		C2	GS	20/35	43/67	0.953	0.200	45.802	64.662
			G-DPSO[a]	20/35	43/67	0.953	0.200	45.802	64.662
		C3	GS	20/35	43/67	0.953	0.200	45.802	64.662
			G-DPSO	20/35	43/67	0.953	0.200	45.802	64.662
		C4	GS	20/35	43/67	0.953	0.200	45.802	64.662
			G-DPSO[b]	20/35	43/67	0.953	0.200	45.802	64.662

a,b: The number of particles was increased from 10 to 20 and the population size was increased from 10,000 to 70,000.

Two-stage single-arm phase 2 clinical trial designs

Table 1. Various adaptive two-stage optimal designs with one target response when $\alpha = 0.05$ and $\beta = 0.20$.

p_0	p_1	Optimal criteria	Method	s_1/n_1	s/n	$1-\alpha$	β	$E(N\mid p_0)$	$E(N\mid p_1)$
0.05	0.20	C1	GS	0/10	3/29	0.953	0.199	17.624	26.960
			G-DPSO	0/10	3/29	0.953	0.199	17.624	26.960
		C2	GS	0/11	3/28	0.956	0.199	18.330	26.540
			G-DPSO	0/11	3/28	0.956	0.199	18.330	26.540
		C3	GS	0/11	3/28	0.956	0.199	18.330	26.540
			G-DPSO	0/11	3/28	0.956	0.199	18.330	26.540
		C4	GS	0/11	3/28	0.956	0.199	18.330	26.540
			G-DPSO	0/11	3/28	0.956	0.199	18.330	26.540
0.20	0.35	C1	GS	5/22	19/72	0.951	0.200	35.368	63.855
			G-DPSO	5/22	19/72	0.951	0.200	35.368	63.855
		C2	GS	3/21	15/53	0.950	0.200	41.148	51.941
			G-DPSO	3/21	15/53	0.950	0.200	41.148	51.941
		C3	GS	6/31	15/53	0.950	0.198	40.436	51.983
			G-DPSO	6/31	15/53	0.950	0.198	40.436	51.983
		C4	GS	3/21	15/53	0.950	0.200	41.148	51.941
			G-DPSO	3/21	15/53	0.950	0.200	41.148	51.941
0.55	0.70	C1	GS	15/26	48/76	0.952	0.195	42.021	69.735
			G-DPSO	15/26	48/76	0.952	0.195	42.021	69.735
		C2	GS	20/35	43/67	0.953	0.200	45.802	64.662
			G-DPSO[a]	20/35	43/67	0.953	0.200	45.802	64.662
		C3	GS	20/35	43/67	0.953	0.200	45.802	64.662
			G-DPSO	20/35	43/67	0.953	0.200	45.802	64.662
		C4	GS	20/35	43/67	0.953	0.200	45.802	64.662
			G-DPSO[b]	20/35	43/67	0.953	0.200	45.802	64.662

a,b: The number of particles was increased from 10 to 20 and the population size was increased from 10,000 to 70,000.

Table S1. Computation time corresponding to **Table 1**; Various adaptive 2-stage optimal designs with one target response when $\alpha = 0.05$ and $\beta = 0.20$.

p_0	p_1	Optimal criteria	Method	Computation time (minute)
0.05	0.20	C1	GS	0.09
			G-DPSO	2.51
		C2	GS	0.1
			G-DPSO	2.32
		C3	GS	0.09
			G-DPSO	2.35
		C4	GS	0.09
			G-DPSO	2.39
0.20	0.35	C1	GS	15.15
			G-DPSO	2.87
		C2	GS	14.25
			G-DPSO	2.66
		C3	GS	13.04
			G-DPSO	2.59
		C4	GS	13.43
			G-DPSO	2.72
0.55	0.70	C1	GS	310.23
			G-DPSO	3.44
		C2	GS	258.06
			G-DPSO	9.28
		C3	GS	256.76
			G-DPSO	2.93
		C4	GS	257.66
			G-DPSO	9.40

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p_0	p_1	Optimal criteria	Method	Computation time (minute)
0.05	0.20	C1	GS	0.09
			G-DPSO	2.51
		C2	GS	0.1
			G-DPSO	2.32
		C3	GS	0.09
			G-DPSO	2.35
		C4	GS	0.09
			G-DPSO	2.39
0.20	0.35	C1	GS	15.15
			G-DPSO	2.87
		C2	GS	14.25
			G-DPSO	2.66
		C3	GS	13.04
			G-DPSO	2.59
		C4	GS	13.43
			G-DPSO	2.72
0.55	0.70	C1	GS	310.23
			G-DPSO	3.44
		C2	GS	258.06
			G-DPSO	9.28
		C3	GS	256.76
			G-DPSO	2.93
		C4	GS	257.66
			G-DPSO	9.40

Table 2. Various adaptive two-stage optimal designs with two target responses when $\alpha = 0.05$, $\beta_1 = 0.20$ and $\beta_2 = 0.10$.

p_0	p_1	p_2	Optimal criteria	Method	$s_1/r_1/n_1$	s/m	r/n	$1-\alpha$	β_1	β_2	$E(N|p_0)$	$E(N|p_1)$	$E(N|p_2)$
0.05	0.20	0.25	C1	GS	0/1/9	3/30	4/41	0.957	0.199	0.094	17.548	33.383	36.119
				G-DPSO	0/1/10	3/28	3/31	0.953	0.199	0.088	17.481	27.940	29.254
				D-DPSO	0/1/8	4/41	3/36	0.952	0.200	0.107	18.821	32.980	34.532
			C2	GS	0/2/16	3/29	3/22	0.955	0.199	0.082	22.978	24.097	23.249
				G-DPSO	0/2/14	3/29	3/21	0.954	0.200	0.084	21.444	23.925	22.982
				D-DPSO	0/2/14	3/29	3/21	0.954	0.200	0.084	21.444	23.925	22.982
			C3	GS	0/4/9	4/41	5/22	0.960	0.174	0.084	20.831	36.333	37.668
				G-DPSO	0/5/11	3/28	6/25	0.956	0.199	0.083	18.330	26.505	27.179
				D-DPSO	0/5/11	3/28	6/25	0.956	0.199	0.083	18.330	26.505	27.179
			C4	GS	0/2/16	3/29	3/22	0.955	0.199	0.082	22.978	24.097	23.249
				G-DPSO	0/2/15	3/28	3/23	0.957	0.197	0.078	21.796	24.533	24.007
				D-DPSO	0/2/15	3/28	3/23	0.957	0.197	0.078	21.796	24.533	24.007
0.20	0.35	0.40	C1	G-DPSO	4/9/20	17/62	10/36	0.952	0.199	0.069	35.487	53.869	53.499
				D-DPSO	5/10/22	19/72	11/36	0.951	0.199	0.078	35.311	60.004	60.179
			C2	G-DPSO	8/12/37	16/57	13/41	0.950	0.196	0.059	42.913	46.949	44.252
				D-DPSO	5/10/29	16/56	11/36	0.951	0.196	0.055	43.094	46.415	42.638
			C3	G-DPSO	6/11/27	16/58	13/43	0.950	0.200	0.063	35.833	51.406	50.886
				D-DPSO	3/10/21	15/53	11/36	0.950	0.200	0.058	41.131	50.629	49.683
			C4	G-DPSO	8/12/38	16/56	13/43	0.952	0.200	0.057	43.830	47.337	45.224
				D-DPSO	3/10/21	15/53	11/36	0.950	0.200	0.058	41.131	50.629	49.683
0.55	0.70	0.75	C1	G-DPSO	15/20/26	48/76	27/39	0.951	0.200	0.053	41.807	63.720	61.521
				D-DPSO	15/20/26	48/76	27/39	0.951	0.200	0.053	41.807	63.720	61.521
			C2	G-DPSO	24/28/41	47/73	30/45	0.951	0.194	0.039	48.872	55.463	50.268
				D-DPSO	11/17/24	45/70	30/45	0.951	0.199	0.043	57.956	59.756	54.718
			C3	G-DPSO	13/20/25	43/67	25/42	0.951	0.194	0.038	47.730	62.880	61.206
				D-DPSO	14/20/26	43/67	23/39	0.950	0.199	0.041	45.163	59.975	56.926
			C4	G-DPSO	25/30/44	44/68	32/49	0.950	0.197	0.037	51.862	56.540	52.457
				D-DPSO	10/16/21	43/67	28/41	0.950	0.200	0.044	51.907	60.628	57.152

Table S2. Computation time corresponding to **Table 2**; Various adaptive 2-stage optimal designs with two target responses when $\alpha = 0.05$, $\beta_1 = 0.20$ and $\beta_2 = 0.10$.

p_0	p_1	p_2	Optimal criteria	Method	Computation time (minute)
0.05	0.20	0.25	C1	GS	697.41
				G-DPSO	3.49
				D-DPSO	5.07
			C2	GS	335.84
				G-DPSO	3.49
				D-DPSO	4.89
			C3	GS	456.9
				G-DPSO	3.48
				D-DPSO	4.95
			C4	GS	734.74
				G-DPSO	3.4
				D-DPSO	4.92
0.20	0.35	0.40	C1	G-DPSO	10.6
				D-DPSO	5.86
			C2	G-DPSO	10.24
				D-DPSO	5.54
			C3	G-DPSO	11.44
				D-DPSO	5.6
			C4	G-DPSO	11.07
				D-DPSO	5.58
0.55	0.70	0.75	C1	G-DPSO	147.31
				D-DPSO	5.89
			C2	G-DPSO	131.2
				D-DPSO	5.64
			C3	G-DPSO	197.07
				D-DPSO	5.86
			C4	G-DPSO	193.18
				D-DPSO	5.68

Table S2. Computation time corresponding to **Table 2**; Various adaptive 2-stage optimal designs with two target responses when $\alpha = 0.05$, $\beta_1 = 0.20$ and $\beta_2 = 0.10$.

p_0	p_1	p_2	Optimal criteria	Method	Computation time (minute)
0.05	0.20	0.25	C1	GS	697.41
				G-DPSO	3.49
				D-DPSO	5.07
			C2	GS	335.84
				G-DPSO	3.49
				D-DPSO	4.89
			C3	GS	456.9
				G-DPSO	3.48
				D-DPSO	4.95
			C4	GS	734.74
				G-DPSO	3.4
				D-DPSO	4.92
0.20	0.35	0.40	C1	G-DPSO	10.6
				D-DPSO	5.86
			C2	G-DPSO	10.24
				D-DPSO	5.54
			C3	G-DPSO	11.44
				D-DPSO	5.6
			C4	G-DPSO	11.07
				D-DPSO	5.58
0.55	0.70	0.75	C1	G-DPSO	147.31
				D-DPSO	5.89
			C2	G-DPSO	131.2
				D-DPSO	5.64
			C3	G-DPSO	197.07
				D-DPSO	5.86
			C4	G-DPSO	193.18
				D-DPSO	5.68

Table 3. Various adaptive two-stage optimal designs with three target responses when $\alpha = 0.05$, $\beta_1 = 0.20$, $\beta_2 = 0.10$, and $\beta_3 = 0.05$.

p_0	p_1	p_2	p_3	Optimal criteria	Method	$s_1/r_1/q_1/n_1$	s/l	r/m	q/n	$1-\alpha$	β_1	β_2	β_3	$E(N|p_0)$	$E(N|p_1)$	$E(N|p_2)$	$E(N|p_3)$
0.05	0.20	0.25	0.30	C1	G-DPSO	0/1/4/10	3/28	3/31	5/28	0.953	0.200	0.088	0.037	17.481	27.841	29.020	29.593
					D-DPSO	0/1/2/9	4/36	3/34	3/31	0.959	0.199	0.093	0.044	18.816	30.463	31.375	31.691
				C2	G-DPSO	0/1/2/13	3/31	3/28	3/20	0.951	0.200	0.088	0.036	21.158	23.725	22.613	21.636
					D-DPSO	0/1/2/14	4/36	3/33	3/19	0.952	0.198	0.094	0.043	24.391	24.899	22.847	21.245
				C3	G-DPSO	0/2/5/11	3/28	3/28	6/21	0.956	0.200	0.084	0.033	18.330	26.458	27.042	27.116
					D-DPSO	0/3/4/11	3/29	5/29	5/22	0.953	0.198	0.085	0.034	18.761	27.101	27.437	27.172
				C4	G-DPSO	0/1/2/15	3/28	3/27	3/24	0.958	0.198	0.077	0.026	21.698	24.904	24.615	24.354
					D-DPSO	0/1/2/14	4/32	3/30	3/22	0.960	0.198	0.079	0.028	22.675	25.189	24.130	23.260
0.20	0.35	0.40	0.45	C1	G-DPSO	5/9/10/24	17/61	10/36	11/32	0.952	0.200	0.064	0.017	36.401	48.570	45.349	40.823
					D-DPSO	5/11/13/22	19/72	12/36	14/32	0.951	0.200	0.078	0.028	35.355	62.126	63.957	61.554
				C2	G-DPSO	5/9/10/29	17/60	13/44	11/34	0.951	0.197	0.061	0.015	44.649	45.199	40.615	37.117
					D-DPSO	3/6/8/19	19/67	11/38	9/31	0.950	0.194	0.060	0.016	43.149	47.817	43.504	39.094
				C3	G-DPSO	4/9/13/22	16/57	10/39	16/36	0.951	0.196	0.059	0.014	37.889	50.724	49.244	46.353
					D-DPSO	3/8/9/17	17/62	12/36	11/28	0.951	0.197	0.070	0.024	37.230	54.484	54.003	50.929
				C4	G-DPSO	5/9/10/26	16/57	13/44	11/34	0.950	0.197	0.059	0.013	38.717	46.656	43.284	39.542
					D-DPSO	4/8/11/24	18/64	11/36	12/28	0.952	0.193	0.068	0.026	44.584	48.279	42.940	37.622
0.55	0.70	0.75	0.80	C1	G-DPSO	15/20/21/26	48/76	29/43	23/31	0.951	0.199	0.052	0.010	41.812	63.491	60.658	51.947
					D-DPSO	10/15/16/19	46/72	23/39	18/29	0.951	0.198	0.047	0.008	44.911	62.696	60.681	54.260
				C2	G-DPSO	17/22/23/32	47/73	32/48	24/35	0.950	0.195	0.041	0.005	51.994	54.810	46.623	39.493
					D-DPSO	8/13/14/17	46/72	27/39	21/31	0.951	0.195	0.048	0.009	52.800	62.503	58.360	51.268
				C3	G-DPSO	15/20/21/27	46/72	27/41	24/35	0.951	0.192	0.041	0.005	44.743	59.648	54.638	46.497
					D-DPSO	12/17/18/22	47/74	26/39	24/32	0.950	0.197	0.054	0.014	44.314	63.001	60.007	52.356
				C4	G-DPSO	17/22/23/32	47/73	32/48	24/35	0.950	0.195	0.041	0.005	51.994	54.810	46.623	39.493
					D-DPSO	7/12/14/16	45/70	26/39	19/31	0.951	0.200	0.044	0.006	55.302	60.783	56.534	50.252

Table 3. Various adaptive two-stage optimal designs with three target responses when $\alpha = 0.05$, $\beta_1 = 0.20$, $\beta_2 = 0.10$, and $\beta_3 = 0.05$.

p_0	p_1	p_2	p_3	Optimal criteria	Method	$s_1/r_1/q_1/n_1$	s/l	r/m	q/n	$1-\alpha$	β_1	β_2	β_3	$E(N\|p_0)$	$E(N\|p_1)$	$E(N\|p_2)$	$E(N\|p_3)$
0.05	0.20	0.25	0.30	C1	G-DPSO	0/1/4/10	3/28	3/31	5/28	0.953	0.200	0.088	0.037	17.481	27.841	29.020	29.593
					D-DPSO	0/1/2/9	4/36	3/34	3/31	0.959	0.199	0.093	0.044	18.816	30.463	31.375	31.691
				C2	G-DPSO	0/1/2/13	3/31	3/28	3/20	0.951	0.200	0.088	0.036	21.158	23.725	22.613	21.636
					D-DPSO	0/1/2/14	4/36	3/33	3/19	0.952	0.198	0.094	0.043	24.391	24.899	22.847	21.245
				C3	G-DPSO	0/2/5/11	3/28	3/28	6/21	0.956	0.200	0.084	0.033	18.330	26.458	27.042	27.116
					D-DPSO	0/3/4/11	3/29	5/29	5/22	0.953	0.198	0.085	0.034	18.761	27.101	27.437	27.172
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				C3	G-DPSO	4/9/13/22	16/57	10/39	16/36	0.951	0.196	0.059	0.014	37.889	50.724	49.244	46.353
					D-DPSO	3/8/9/17	17/62	12/36	11/28	0.951	0.197	0.070	0.024	37.230	54.484	54.003	50.929
				C4	G-DPSO	5/9/10/26	16/57	13/44	11/34	0.950	0.197	0.059	0.013	38.717	46.656	43.284	39.542
					D-DPSO	4/8/11/24	18/64	11/36	12/28	0.952	0.193	0.068	0.026	44.584	48.279	42.940	37.622
0.55	0.70	0.75	0.80	C1	G-DPSO	15/20/21/26	48/76	29/43	23/31	0.951	0.199	0.052	0.010	41.812	63.491	60.658	51.947
					D-DPSO	10/15/16/19	46/72	23/39	18/29	0.951	0.198	0.047	0.008	44.911	62.696	60.681	54.260
				C2	G-DPSO	17/22/23/32	47/73	32/48	24/35	0.950	0.195	0.041	0.005	51.994	54.810	46.623	39.493
					D-DPSO	8/13/14/17	46/72	27/39	21/31	0.951	0.195	0.048	0.009	52.800	62.503	58.360	51.268
				C3	G-DPSO	15/20/21/27	46/72	27/41	24/35	0.951	0.192	0.041	0.005	44.743	59.648	54.638	46.497
					D-DPSO	12/17/18/22	47/74	26/39	24/32	0.950	0.197	0.054	0.014	44.314	63.001	60.007	52.356
				C4	G-DPSO	17/22/23/32	47/73	32/48	24/35	0.950	0.195	0.041	0.005	51.994	54.810	46.623	39.493
					D-DPSO	7/12/14/16	45/70	26/39	19/31	0.951	0.200	0.044	0.006	55.302	60.783	56.534	50.252

Table S3. Computation time corresponding **Table 3**; Various adaptive 2-stage optimal designs with three target responses when α = 0.05, β_1 = 0.20, β_2 = 0.10, and β_3 = 0.05.

p_0	p_1	p_2	p_3	Optimal criteria	Method	Computation time (minute)
0.05	0.20	0.25	0.30	C1	G-DPSO	5.49
					D-DPSO	5.75
				C2	G-DPSO	5.32
					D-DPSO	5.64
				C3	G-DPSO	5.42
					D-DPSO	5.69
				C4	G-DPSO	5.3
					D-DPSO	5.66
0.20	0.35	0.40	0.45	C1	G-DPSO	1592.3
					D-DPSO	6.42
				C2	G-DPSO	1581.77
					D-DPSO	6.32
				C3	G-DPSO	1602.55
					D-DPSO	6.33
				C4	G-DPSO	1584.49
					D-DPSO	6.34
0.55	0.70	0.75	0.80	C1	G-DPSO	41962.35
					D-DPSO	6.49
				C2	G-DPSO	41384.16
					D-DPSO	6.39
				C3	G-DPSO	41835.97
					D-DPSO	6.45
				C4	G-DPSO	41498.29
					D-DPSO	6.38

Table S3. Computation time corresponding **Table 3**; Various adaptive 2-stage optimal designs with three target responses when $\alpha = 0.05$, $\beta_1 = 0.20$, $\beta_2 = 0.10$, and $\beta_3 = 0.05$.

p_0	p_1	p_2	p_3	Optimal criteria	Method	Computation time (minute)
0.05	0.20	0.25	0.30	C1	G-DPSO	5.49
					D-DPSO	5.75
				C2	G-DPSO	5.32
					D-DPSO	5.64
				C3	G-DPSO	5.42
					D-DPSO	5.69
				C4	G-DPSO	5.3
					D-DPSO	5.66
0.20	0.35	0.40	0.45	C1	G-DPSO	1592.3
					D-DPSO	6.42
				C2	G-DPSO	1581.77
					D-DPSO	6.32
				C3	G-DPSO	1602.55
					D-DPSO	6.33
				C4	G-DPSO	1584.49
					D-DPSO	6.34
0.55	0.70	0.75	0.80	C1	G-DPSO	41962.35
					D-DPSO	6.49
				C2	G-DPSO	41384.16
					D-DPSO	6.39
				C3	G-DPSO	41835.97
					D-DPSO	6.45
				C4	G-DPSO	41498.29
					D-DPSO	6.38

Figure 2. Expected sample sizes under the null hypothesis for the 4 criteria C1–C4 with 1, 2 or 3 target alternatives estimated by D–DPSO for 3 scenarios (from left to right): (i) $p_0 = 0.05, p_1 = 0.20, p_2 = 0.25, p_3 = 0.30$, (ii) $p_0 = 0.20, p_1 = 0.35, p_2 = 0.40, p_3 = 0.45$, and (iii) $p_0 = 0.55, p_1 = 0.70, p_2 = 0.75, p_3 = 0.80$. Error rates were set at $\alpha = 0.05, \beta_1 = 0.20, \beta_2 = 0.10$ and $\beta_3 = 0.05$
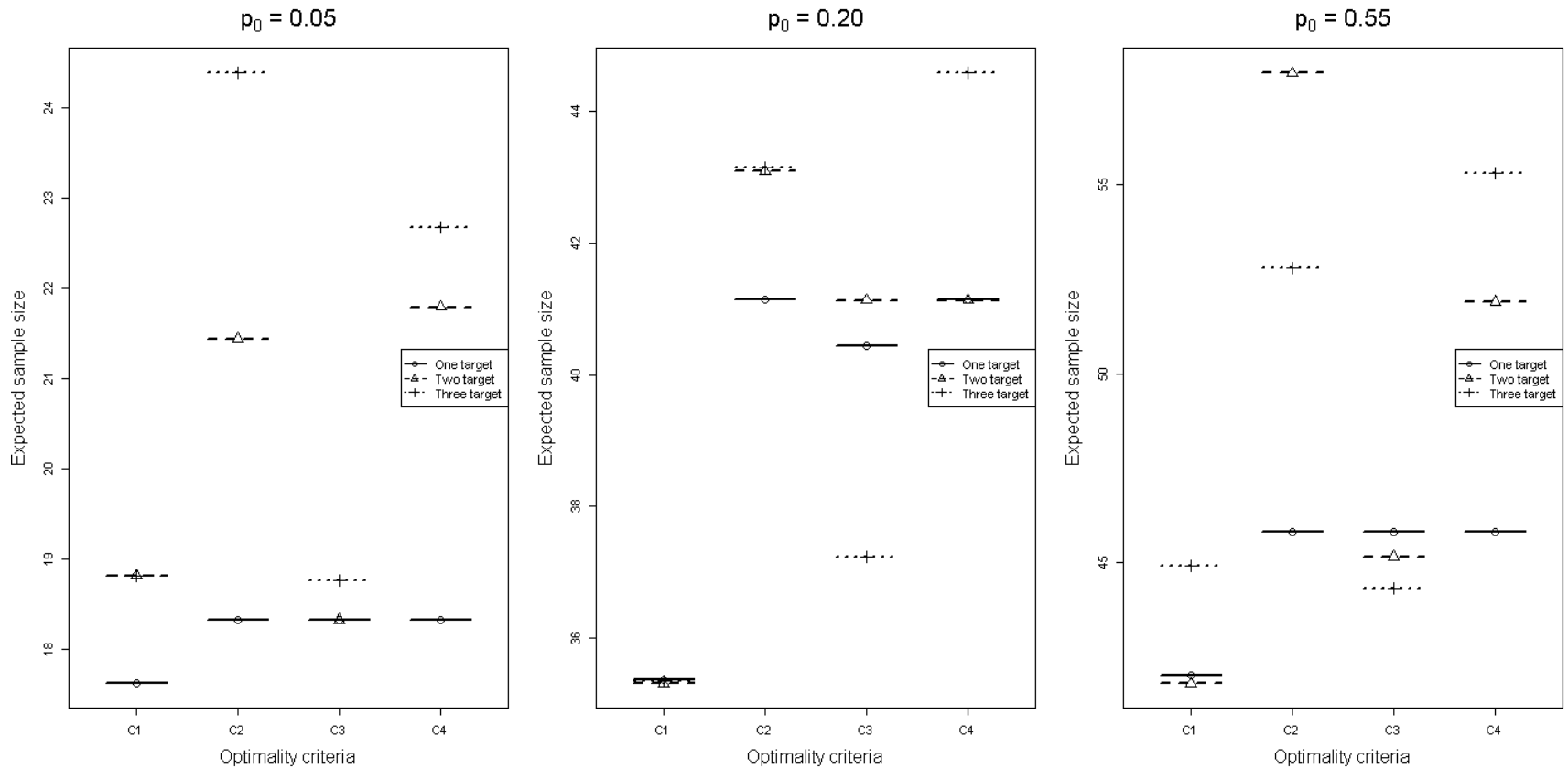
Figure 2. Expected sample sizes under the null hypothesis for the 4 criteria C1–C4 with 1, 2 or 3 target alternatives estimated by D–DPSO for 3 scenarios (from left to right): (i) $p_0 = 0.05, p_1 = 0.20, p_2 = 0.25, p_3 = 0.30$, (ii) $p_0 = 0.20, p_1 = 0.35, p_2 = 0.40, p_3 = 0.45$, and (iii) $p_0 = 0.55, p_1 = 0.70, p_2 = 0.75, p_3 = 0.80$. Error rates were set at $\alpha = 0.05, \beta_1 = 0.20, \beta_2 = 0.10$ and $\beta_3 = 0.05$
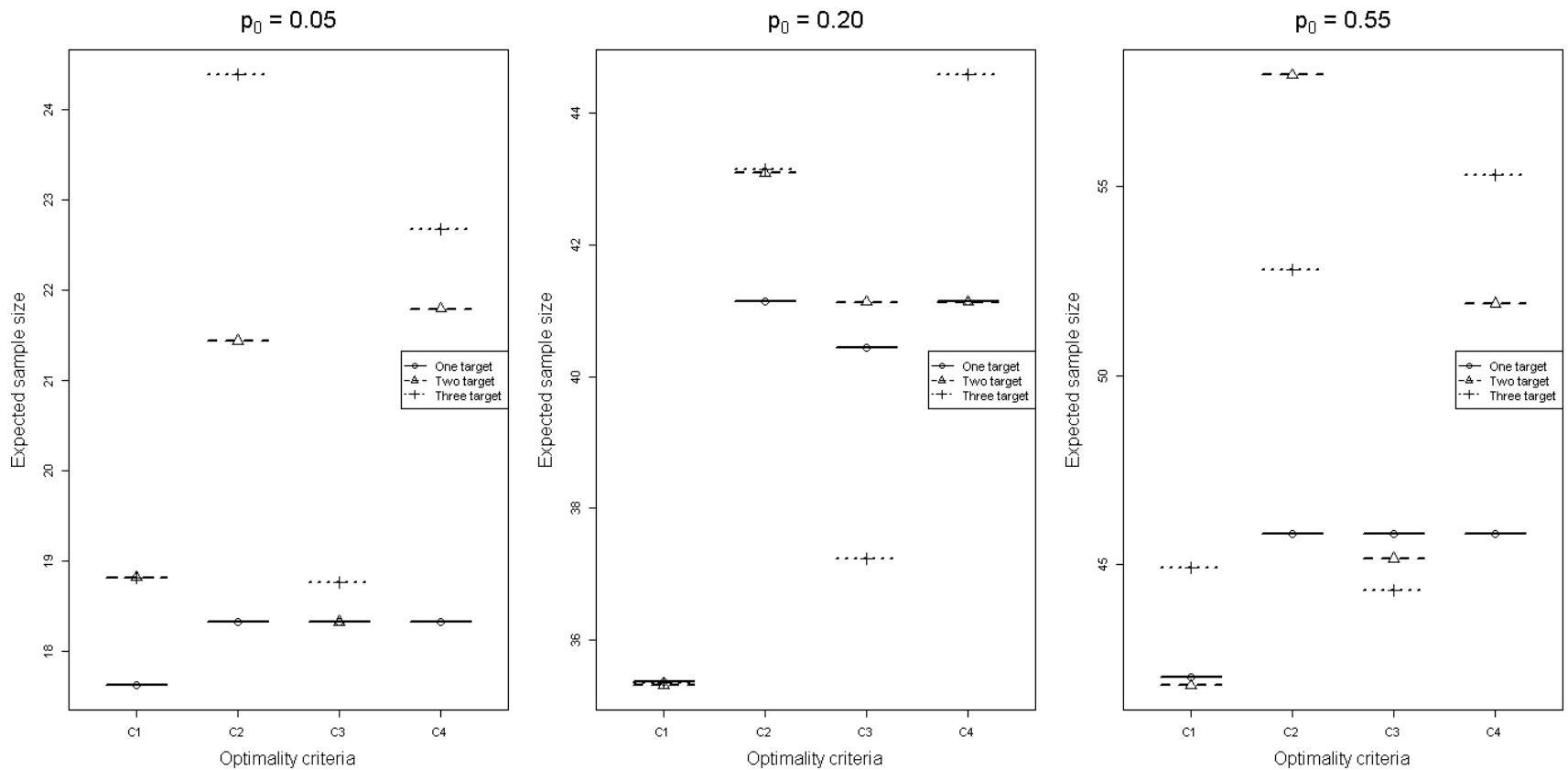
There is **no clear winner** that consistently requires the smallest expected sample sizes

Motivation

- A single arm two-stage phase II trial to see the effect of head and neck cancer (HNC) on the incidence of obstructive sleep apnea (OSA).

- The maximum incidence rate of snoring and sleep apnea on healthy patients is **16.5% (i.e., $p_0 = 0.165$)**.

- Neither historical nor preliminary data available, except that the incidence rate of OSA will be higher in HNC patients.

- An empirical range of the target response rates, from **24.38% to 39.00%.**

- Simon's two-stage design (80% power and 5% level) ➔ the required sample sizes range from **30 to 197**

- Due to wide range of the target response rates, Lin and Shih's approach will not be able to cover the great uncertainty.

Obstructive sleep apnea (OSA)

- To assess the effect of HNC on the incidence of OSA compared to healthy patients.
- p0 = 16.50%, p1 = **24.38%**, p2 = 31.69%, p3 = **39.00%**
- β1 = 0.20, β2 = 0.15, β3 = 0.10

Optimality criteria	$s_1/r_1/q_1/n_1$	s/l	r/m	q/n	$E(N|p_0)$	$E(N|p_1)$	$E(N|p_2)$	$E(N|p_3)$
OSA								
C1	2/8/9/21	39/188	13/55	10/39	136.92	167.28	157.91	124.73
C2 and C4	1/11/12/25	34/161	20/72	13/36	152.07	158.99	154.07	135.42
C3	1/8/9/17	37/177	12/58	10/35	144.40	166.73	167.70	153.87

Obstructive sleep apnea (OSA)

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- $p0 = 16.50\%$, $p1 = $ **24.38%**, $p2 = 31.69\%$, $p3 = $ **39.00%**
- $\beta1 = 0.20$, $\beta2 = 0.15$, $\beta3 = 0.10$

Optimality criteria	$s_1/r_1/q_1/n_1$	s/l	r/m	q/n	$E(N\mid p_0)$	$E(N\mid p_1)$	$E(N\mid p_2)$	$E(N\mid p_3)$
OSA								
C1	2/8/9/21	39/188	13/55	10/39	136.92	167.28	157.91	124.73
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C3	1/8/9/17	37/177	12/58	10/35	144.40	166.73	167.70	153.87

It can cover the wide variation of the total sample size (35~188)

Phase II study: BREAK-2

- A multicenter, international, single-arm, phase II study (BREAK-2) was carried out to assess the overall response rate of dabrafenib from patients with BRAFV 600E mutationpositive metastatic melanoma (Ascierto et al. (2013)).

- The null hypothesis was set at **p0 = 0.25** and the alternative hypothesis was set at **p1 = 0.40**. The trial wanted to recruit at least **85** patients and the plan was to declare the treatment a success if at least 29 patients responded.

- The efficacy results show that **76** patients with BRAFV 600E mutationpositive metastatic melanoma were enrolled and 45 patients (**59%**) had a confirmed response.

- Although its parent phase I study (Falchook *et al.* (2012)) showed the same type of patients had a response rate of **50%**, this phase II study chose the response rate of **40%** as an alternative hypothesis by lowering the response rate of phase I study.

- However, based on the phase I study, it would be of benefit if the higher response rate was explored in addition to 40% because the final response rate of the phase II study was 59%.

- $p0 = 0.25$, $p1 = 0.40$, $p2 = 0.50$, and $p3 = 0.55$
- $\beta 1 = 0.15$, $\beta 2 = 0.10$, and $\beta 3 = 0.05$

Optimality criteria	$s_1/r_1/q_1/n_1$	s/l	r/m	q/n	$E(N\mid p_0)$	$E(N\mid p_1)$	$E(N\mid p_2)$	$E(N\mid p_3)$
OSA								
C1	2/8/9/21	39/188	13/55	10/39	136.92	167.28	157.91	124.73
C2 and C4	1/11/12/25	34/161	20/72	13/36	152.07	158.99	154.07	135.42
C3	1/8/9/17	37/177	12/58	10/35	144.40	166.73	167.70	153.87
BREAK-2								
C1	4/10/11/19	26/80	14/44	12/34	51.522	72.216	65.961	58.879
C2 and C4	4/9/12/22	27/83	16/43	13/31	62.079	65.691	50.196	43.063
C3	2/7/9/13	25/77	15/44	14/39	55.526	70.032	66.463	62.186

- p0 = 0.25, p1 = 0.40, p2 = 0.50, and p3 = 0.55
- β1 = 0.15, β2 = 0.10, and β3 = 0.05

Optimality criteria	$s_1/r_1/q_1/n_1$	s/l	r/m	q/n	$E(N\mid p_0)$	$E(N\mid p_1)$	$E(N\mid p_2)$	$E(N\mid p_3)$
OSA								
C1	2/8/9/21	39/188	13/55	10/39	136.92	167.28	157.91	124.73
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BREAK-2								
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C2 and C4	4/9/12/22	27/83	16/43	13/31	62.079	65.691	50.196	43.063
C3	2/7/9/13	25/77	15/44	14/39	55.526	70.032	66.463	62.186

- **The total sample sizes at p1 = 0.4 is less than 85 (BREAK-2)**
- **The total sample size at p3 = 0.55 is 31~39, which is at least 46 patients less than 85 (BREAK-2)**

Summary

- A novel and effective nature-inspired stochastic population-based algorithm called discrete particle swarm optimization (DPSO) to find extended two-stage adaptive designs.

- Algorithms based on a greedy search invariably failed to find extended two-stage adaptive designs and an improved version of DPSO, called D-DPSO finds the optimum.

- When the problem is simplified to one or two target response rates, D-DPSO outperformed their peers by a wide margin.

Thank you for being patient!

EM Algorithms

- Expectation (E) step

  - Use current parameters to estimate the missing data

$$Q(\theta) = E_{\mathbf{z}}\left[\log p\left(\mathbf{y}, \mathbf{z} \mid \theta\right) \Big| \mathbf{y}\right] = \int_{-\infty}^{\infty} p\left(\mathbf{z} \mid \mathbf{y}, \theta_n\right) \log p\left(\mathbf{y}, \mathbf{z} \mid \theta\right) d\mathbf{z}$$

- Maximization (M) step

  - Use estimated missing data to perform ML/MAP parameter estimation

$$\theta_{n+1} = \arg\max_{\theta} Q(\theta)$$

- Repeat EM steps, until convergence

EM Algorithms

- Expectation (E) step

  - Use current parameters to estimate the missing data

  $$Q(\theta) = E_{\mathbf{z}}\left[\log p(\mathbf{y}, \mathbf{z} \mid \theta) \,\middle|\, \mathbf{y}\right] = \int_{-\infty}^{\infty} p(\mathbf{z} \mid \mathbf{y}, \theta_n) \log p(\mathbf{y}, \mathbf{z} \mid \theta) \, d\mathbf{z}$$

- Maximization (M) step

  - Use estimated missing data to perform ML/MAP parameter estimation

  $$\theta_{n+1} = \arg\max_{\theta} Q(\theta)$$

- Repeat EM steps, until convergence

EM Algorithms: some limitations

- Its limiting position can strongly depend on its starting position
- Its speed of convergence can be slow
- It can converge to local maxima or saddle points
- Either E-step or M-step is intractable (no closed form available)
  - Pharmacokinetics/pharmacodynamics (PK/PD) models have nonlinear differential equations

- …