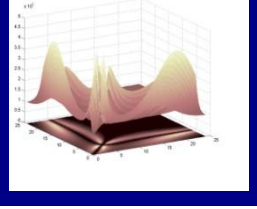

Minimal cost designs for an early phase clinical study

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Introduction

- Designs for PKPD studies mainly focus on improving the precision of parameter estimation
  - By optimising dose, dosing regimen and/or sampling schedule
- Upper boundary of the design space → most precise estimates
- A cost penalty has been incorporated in optimal design methods but as a design constraint [1-4]
  - Studies are penalised for number of patients and blood samples but not for study failure
- An empirical value of power is usually chosen *a priori*, often 80%

[1] Mentré M et al. *Biometrika*. 1997;84:429–442.
[2] Retout S et al. *Communication in Statistics*. 2009;8:3351–3368.
[3] Gagnon R et al. *Journal of Biopharmaceutical Statistics*. 2005;15:143–163.
[4] Bazzoli C et al. www.page-meeting.org/?abstract=1710.

Phase II clinical studies

- The drug is tested in target patients for the (usually) first time
- Explore dose effect relationship and assess for safety
- Population PK explored in phase I study of healthy volunteers, and then applied to design a phase IIa study
- PK of healthy volunteers (prior) = PK of patients (target)?
- How to best design the study when we have uncertainty about the underlying structure of dose-response?

The balance between cost and power

- If we don't consider cost then the upper boundary of ethical constraints provides the best design
- Penalising cost reduces precision and increases the risk of failure
- Setting power *a priori* is arbitrary, what is the best power?
- What does power mean from a cost perspective?
- It is often assumed: cost $\propto$ power & power $\propto$ cost

Aims

- To determine if a design exists that
  - Naturally balances the cost of a clinical study with the probability of study success
    - Without arbitrary constraints on the design space
    - Without the need to define power *a priori*
- To determine the influence of different cost structures on the design

Design variables

$$\xi = \left\{ Np, Ns, DDD, Ts \middle| Ns \right\}$$

Np = number of patients

Ns = number of samples per patient

DDD = defined daily dose

Ts|*Ns* = blood sampling times conditioned on number of samples per patient

Expenditure

- For each patient:

  Expenditure for samples = sampling days $\times Ns \times Cs$

  Expenditure for drug = study duration (days) $\times DDD \times Cd$

- Resource expenditure of a study:

$$X(\xi) = \$\left[Np \times \left(Cp + \text{Expenditure for samples} + \text{Expenditure for drug}\right)\right]$$

Cost of a study

$$\text{Cost} = \begin{cases} X(\xi) \quad ; & \text{study successfu} \\ X(\xi) + X(\xi_0) + X(TP) \quad ; & \text{study failed} \end{cases}$$

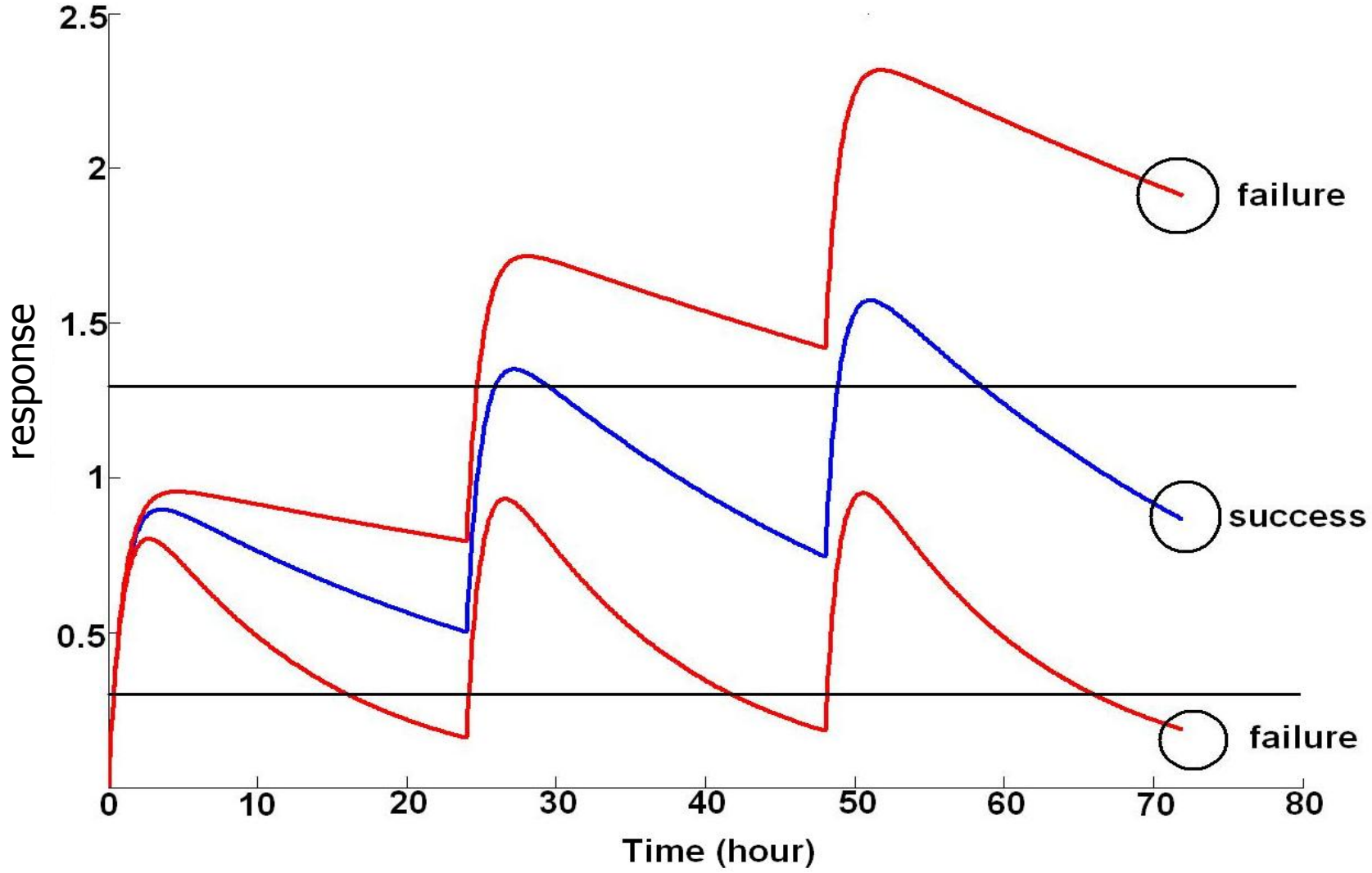
$X(\xi_0)$: cost to redo the study using a previous empirical (and more intensive) design

$X(TP)$: cost for time penalty

Hypothetical example

- Phase II like clinical study for a drug
- All patients received the same dose of drug given orally
- Dosing schedule = 3 doses at 24 hours dose interval
- Therapeutic range of the trough response for the 3rd dose is defined based on prior biomarker data
  [0.3 unit/L, 1.3 unit/L]
- The study is successful if > 60% of patients have trough response within the range
  - In this case response is concentration

Success criterion for a patient



The Model

$$C_{ij} = f\left(ka_i, CL_i, V_i, t_{ij}, DDD\right) \times e^{\varepsilon p_{ij}} + \varepsilon a_{ij}$$

$$f\left(ka_i, k_i, t_{ij}, DDD\right) = \frac{DDD \times ka_i}{V_i \times \left(ka_i \quad k_i\right)} \times \frac{e^{\left(k_i \times t_{ij}\right)}\left[1 \quad e^{\left(dn \times k_i \times di\right)}\right]}{1 \quad e^{\left(k_i \times di\right)}} \quad \frac{e^{\left(ka_i \times t_{ij}\right)}\left[1 \quad e^{\left(dn \times ka_i \times di\right)}\right]}{1 \quad e^{\left(ka_i \times di\right)}}$$

$$k_i = \frac{CL_i}{V_i} \qquad \boldsymbol{\theta}_i = \left(ka_i \quad CL_i \quad V_i\right)^{\mathrm{T}}$$

$$\log\left(\boldsymbol{\theta}_i\right) \sim N\left(\log \bar{\boldsymbol{\theta}}, \boldsymbol{\Omega}\right) \qquad \varepsilon_{p_{ij}} \overset{iid}{\sim} N\left(0, \sigma_p^2\right) \qquad \varepsilon_{a_{ij}} \overset{iid}{\sim} N\left(0, \sigma_a^2\right)$$

Describing Uncertainty

- Population PK parameters: $\boldsymbol{\Phi}_0 = \left(\bar{\boldsymbol{\theta}}, \boldsymbol{\Omega}, \sigma^2\right)$
- Hyperprior distribution

$$\bar{\boldsymbol{\theta}} \sim N\left(\boldsymbol{\mu}, \boldsymbol{\Sigma}\right) \qquad \boldsymbol{\Omega} \sim IW\left(\mathbf{R}, \nu\right) \qquad \sigma^2 \sim IG\left(a, b\right)$$

- Hyperprior parameter: $\mathbf{H} = \left\{\boldsymbol{\mu}, \boldsymbol{\Sigma}, \mathbf{R}, \nu, a, b\right\}$
- If the point estimates and the variance-covariance of the population PK parameters are available, the values of hyperparameters can be computed[1]

[1] Dokoumetzidis et al. *Journal of Biopharmaceutical Statistics*. 2008;18:662–676

Simulation Study

- Population PK estimates from phase I study:

$$\hat{\bar{\boldsymbol{\theta}}} = (1, \quad 0.03, \quad 1)^{\mathrm{T}} \qquad \hat{\boldsymbol{\Omega}} = \begin{bmatrix} 0.1 & 0 & 0 \\ 0 & 0.1 & 0 \\ 0 & 0 & 0.1 \end{bmatrix} \qquad \hat{\sigma}_p^2 = 0.1 \qquad \hat{\sigma}_a^2 = 0.05 \,(\text{fixed})$$

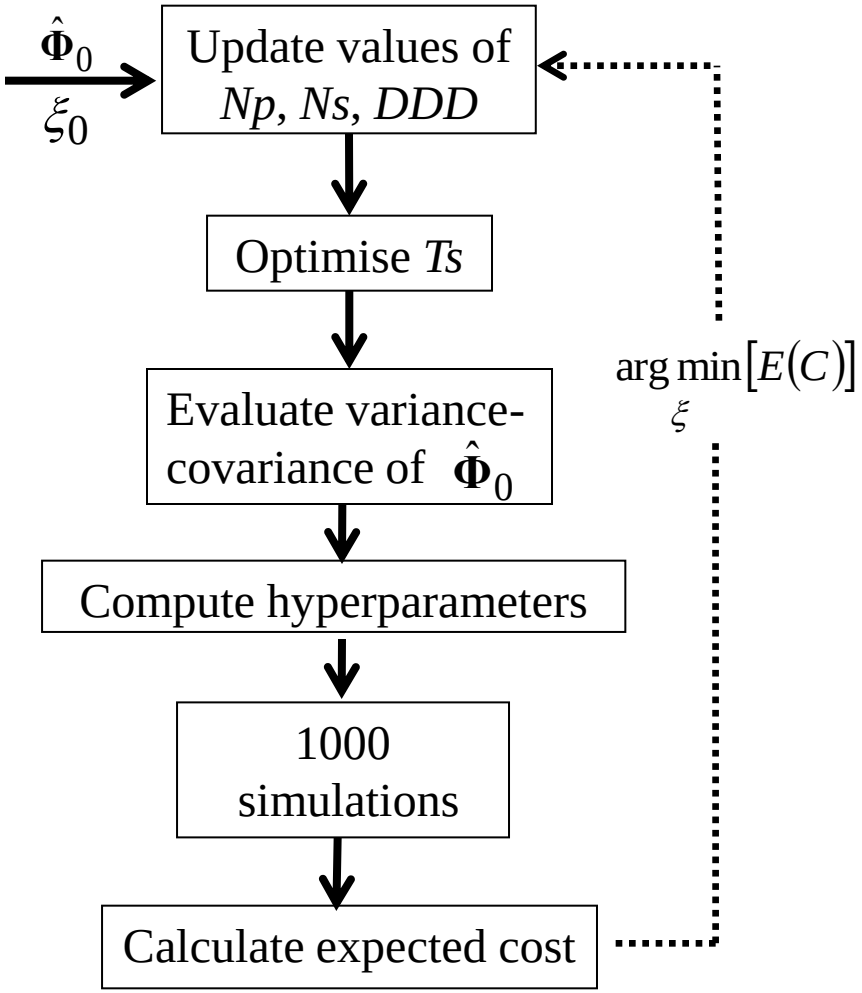
- Hyperprior distribution

$$\bar{\boldsymbol{\theta}} \sim N(\boldsymbol{\mu}, \boldsymbol{\Sigma}) \qquad \boldsymbol{\Omega} \sim IW(\mathbf{R}, \nu) \qquad \sigma^2_{prop} = IG(a, b)$$

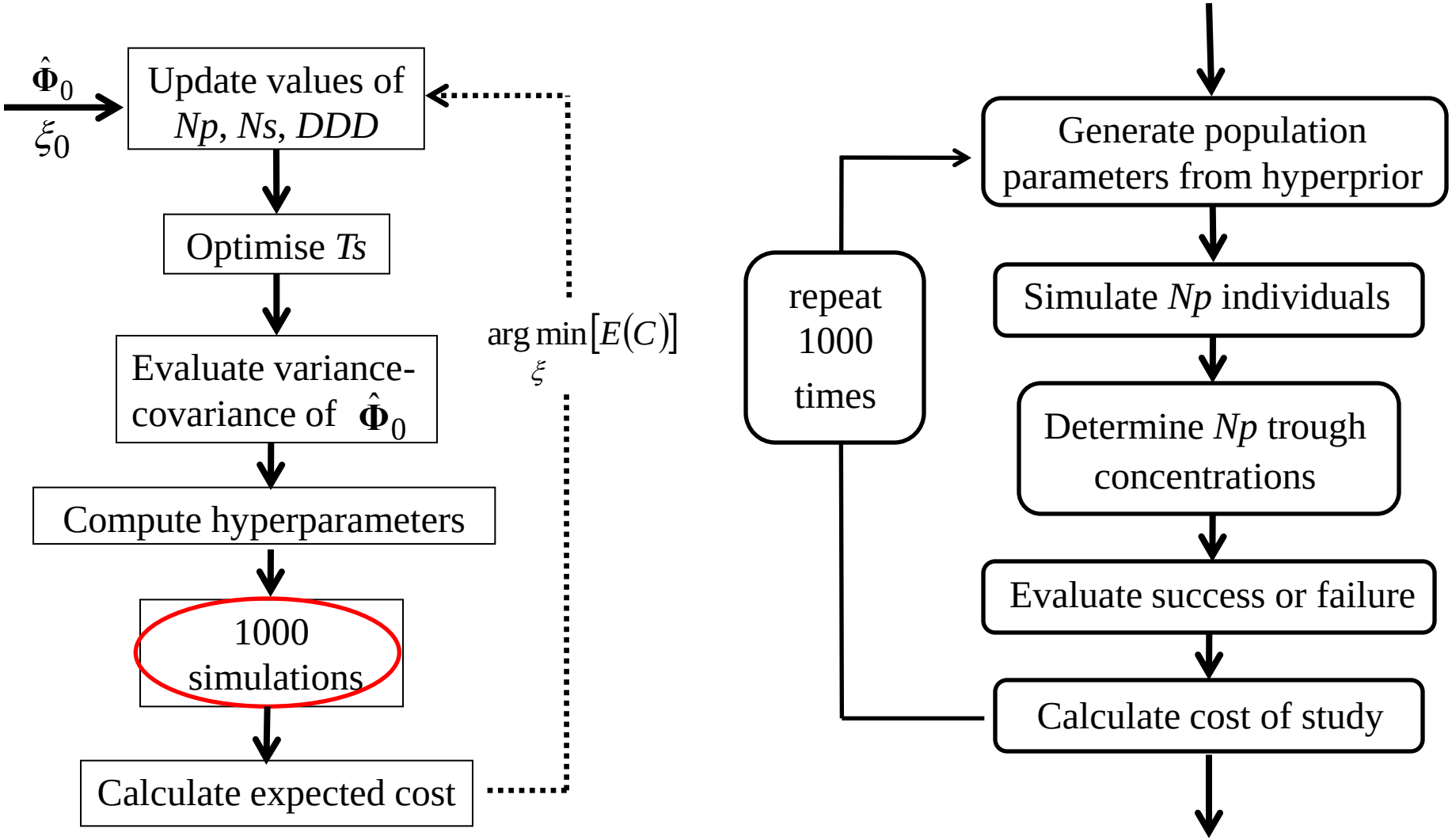
Assumptions

- We consider that ethical constraints and recruitment issues can be handled by penalising the cost per blood sample
- There was one elementary design for the study, which means one sampling schedule for all patients
- A failed study would be repeated with an empirical design
- Note we do not formally consider power in this analysis as we only consider the case where the drug works and alpha error therefore is not considered.

Procedure


$\hat{\Phi}_0$
ξ_0
Update values of *Np*, *Ns*, *DDD*
Optimise *Ts*
Evaluate variance-covariance of $\hat{\Phi}_0$
Compute hyperparameters
1000 simulations
Calculate expected cost
$\arg\min_{\xi}[E(C)]$

Procedure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Evaluate variance-covariance of $\hat{\Phi}_0$
Compute hyperparameters
1000 simulations
Calculate expected cost
$\arg\min_{\xi}[E(C)]$
Generate population parameters from hyperprior
Simulate *Np* individuals
Determine *Np* trough concentrations
Evaluate success or failure
Calculate cost of study
repeat 1000 times

Simulation Study

	Unit cost	Empirical design	Upper bound
Patient	$10000	70	100
Blood sample	$100 $500 $1000	8	35
DDD	$10	1	6

Result

	Cs	*Np*	*Ns*	*DDD*	$	Prob of success
No time penalty	100	33	18	3	582,520	0.918
	500	46	8	3	1,185,771	0.890
	1000	58	6	3	1,884,100	0.893
With time penalty	100	38	17	3	618,980	0.968
	500	53	8	3	1,279,500	0.953
	1000	63	6	3	2,012,600	0.932

Power

- Design for cost minimisation naturally results in study with appropriate power
- High prob success $\neq$ high cost & high cost $\neq$ high probability of success even when the design is optimised
- Setting power *a priori* did not ensure the best design
- Cost minimisation design is a more sensible way to design study

Conclusion

- There exists an optimal design that naturally balances the cost of a clinical study with the probability of study success
  - Without arbitrary constraints on the design space
  - Without the need to define the power *a priori*
- The design changed with different cost structure

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