

Optimal design for multiple response nonlinear models

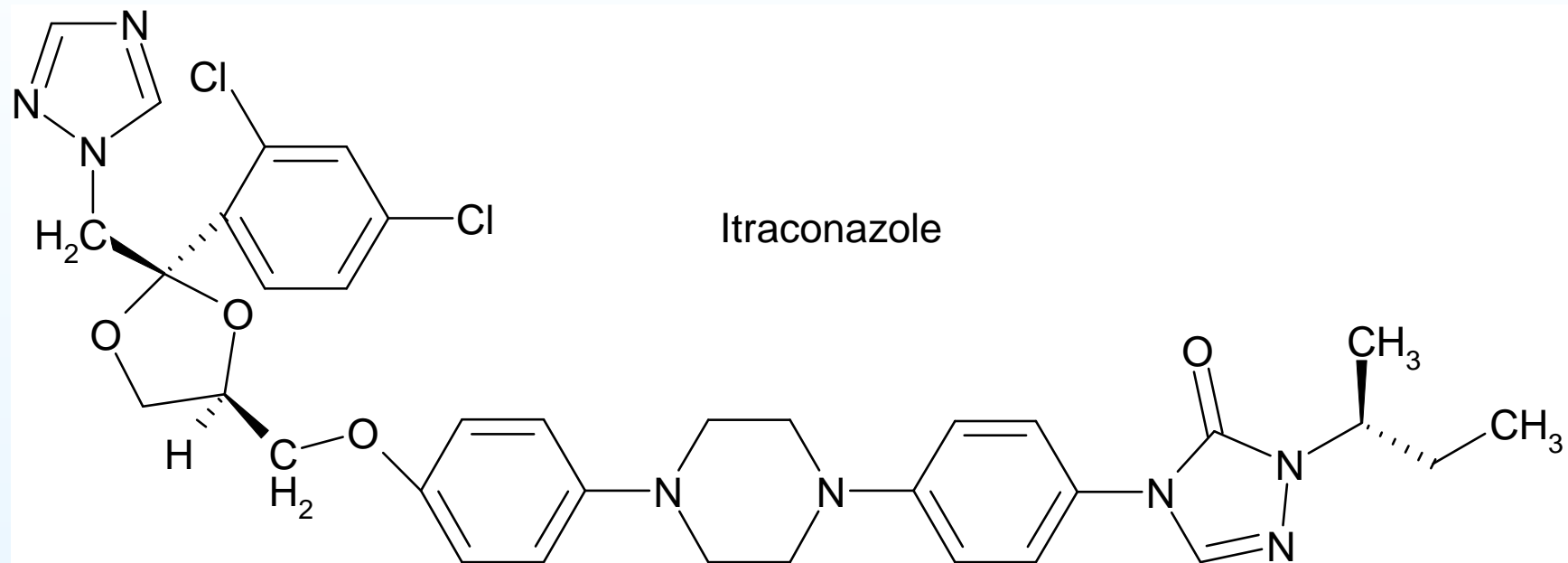
John Eccleston and Tim Waterhouse

School of Physical Sciences, University of Queensland

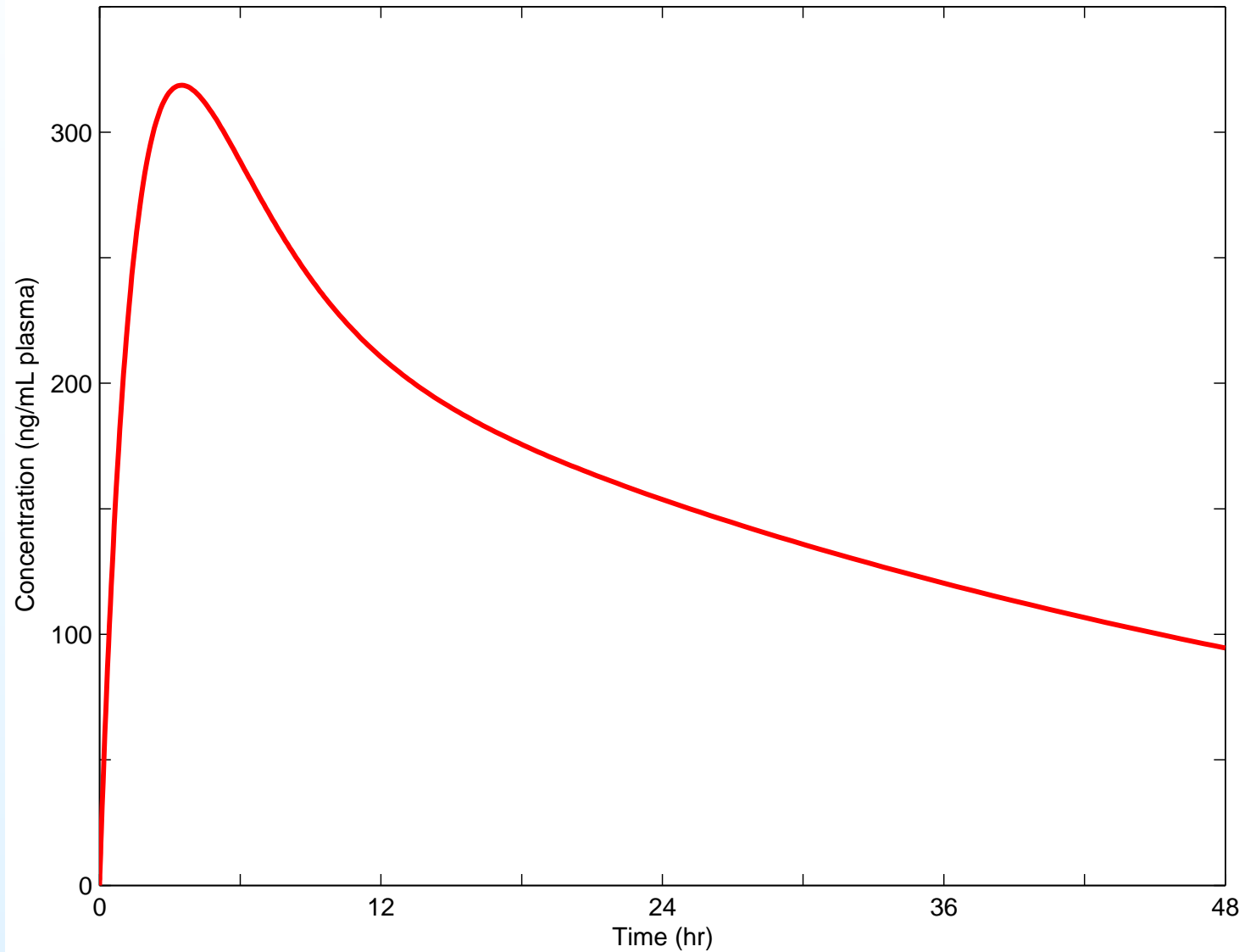
with

Steve Duffull and Stefanie Redmann

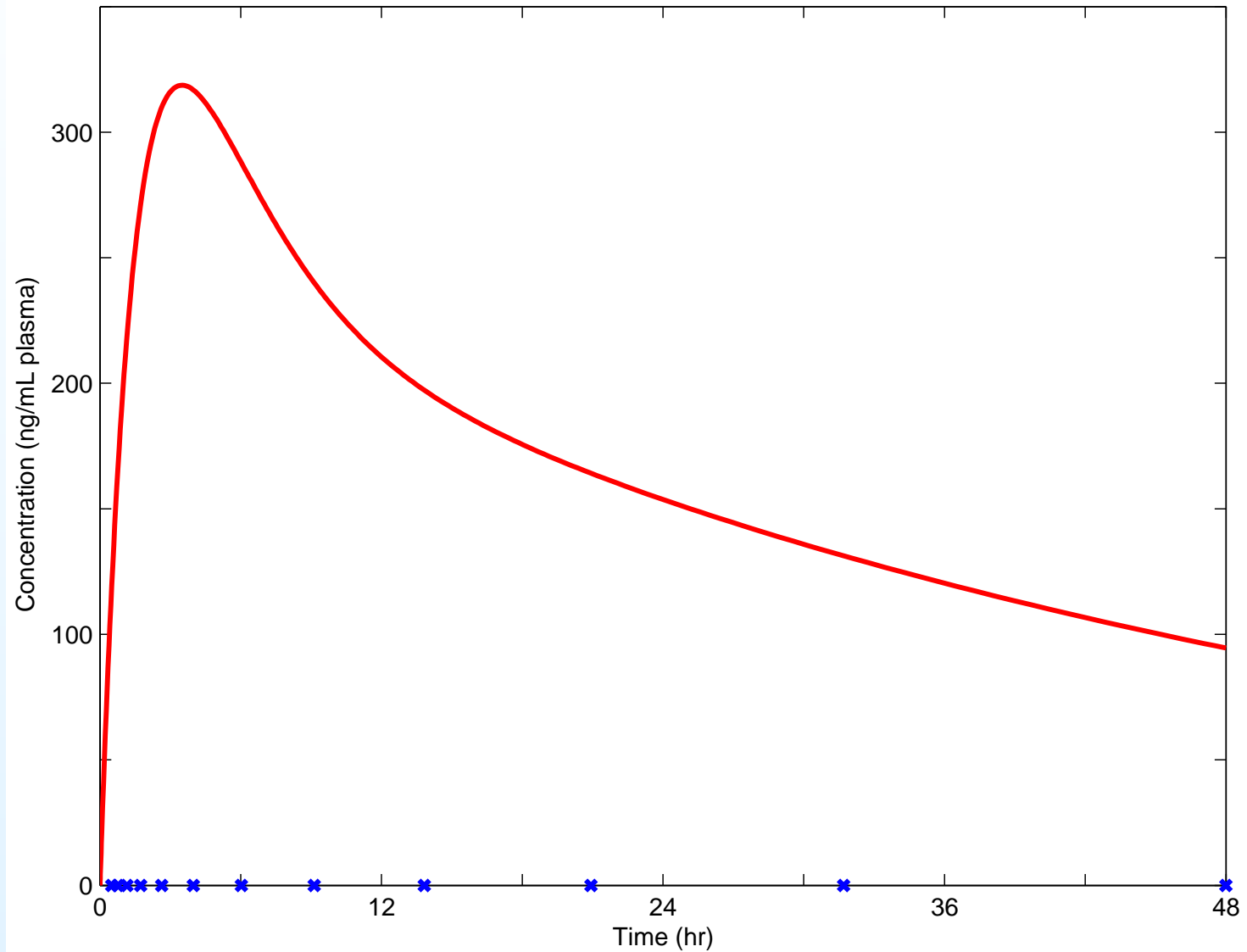
School of Pharmacy, UQ



Pharmacokinetic (PK) profile



Pharmacokinetic (PK) profile



Design of pharmacokinetic (PK) experiments

- 'Empirical' sampling schemes, sampling times taken on a roughly logarithmic scale over time of study

Design of pharmacokinetic (PK) experiments

- 'Empirical' sampling schemes, sampling times taken on a roughly logarithmic scale over time of study
- Sampling schemes increasingly being assessed by simulation

Design of pharmacokinetic (PK) experiments

- ‘Empirical’ sampling schemes, sampling times taken on a roughly logarithmic scale over time of study
- Sampling schemes increasingly being assessed by simulation
- Optimal design currently gaining ground
 - First published case of prospective optimal design used in real-life PK study: Green & Duffull (2003)

Talk outline

- Aims of study

Talk outline

- Aims of study
- Design constraints

Talk outline

- Aims of study
- Design constraints
- Description of compartmental models

Talk outline

- Aims of study
- Design constraints
- Description of compartmental models
- Design issues
 - Parameter estimation, multiple responses, model selection

Talk outline

- Aims of study
- Design constraints
- Description of compartmental models
- Design issues
 - Parameter estimation, multiple responses, model selection
- Optimal design

Talk outline

- Aims of study
- Design constraints
- Description of compartmental models
- Design issues
 - Parameter estimation, multiple responses, model selection
- Optimal design
- Design evaluation
 - Model discrimination
 - Standard errors
 - Parameter estimation under each model
 - Sampling windows

Aims of study

- Itraconazole: antifungal drug used to treat complications of cystic fibrosis (CF)

Aims of study

- Itraconazole: antifungal drug used to treat complications of cystic fibrosis (CF)
- Relatively little known about the pharmacokinetics (PK, concentration-time profile) of itraconazole in CF patients

Aims of study

- Itraconazole: antifungal drug used to treat complications of cystic fibrosis (CF)
- Relatively little known about the pharmacokinetics (PK, concentration-time profile) of itraconazole in CF patients
- Study required to assess PK behaviour of the drug in CF patients
 - Select most appropriate of two competing model structures
 - Efficiently estimate model parameters

Aims of study

- Itraconazole: antifungal drug used to treat complications of cystic fibrosis (CF)
- Relatively little known about the pharmacokinetics (PK, concentration-time profile) of itraconazole in CF patients
- Study required to assess PK behaviour of the drug in CF patients
 - Select most appropriate of two competing model structures
 - Efficiently estimate model parameters
- The drug's main metabolite, hydroxyitraconazole, also exhibits antifungal behaviour, so we also wish to model its response

Design constraints

- 30 patients

Design constraints

- 30 patients
- 3 elementary designs, 10 patients in each group

Design constraints

- 30 patients
- 3 elementary designs, 10 patients in each group
- Patients studied on two occasions

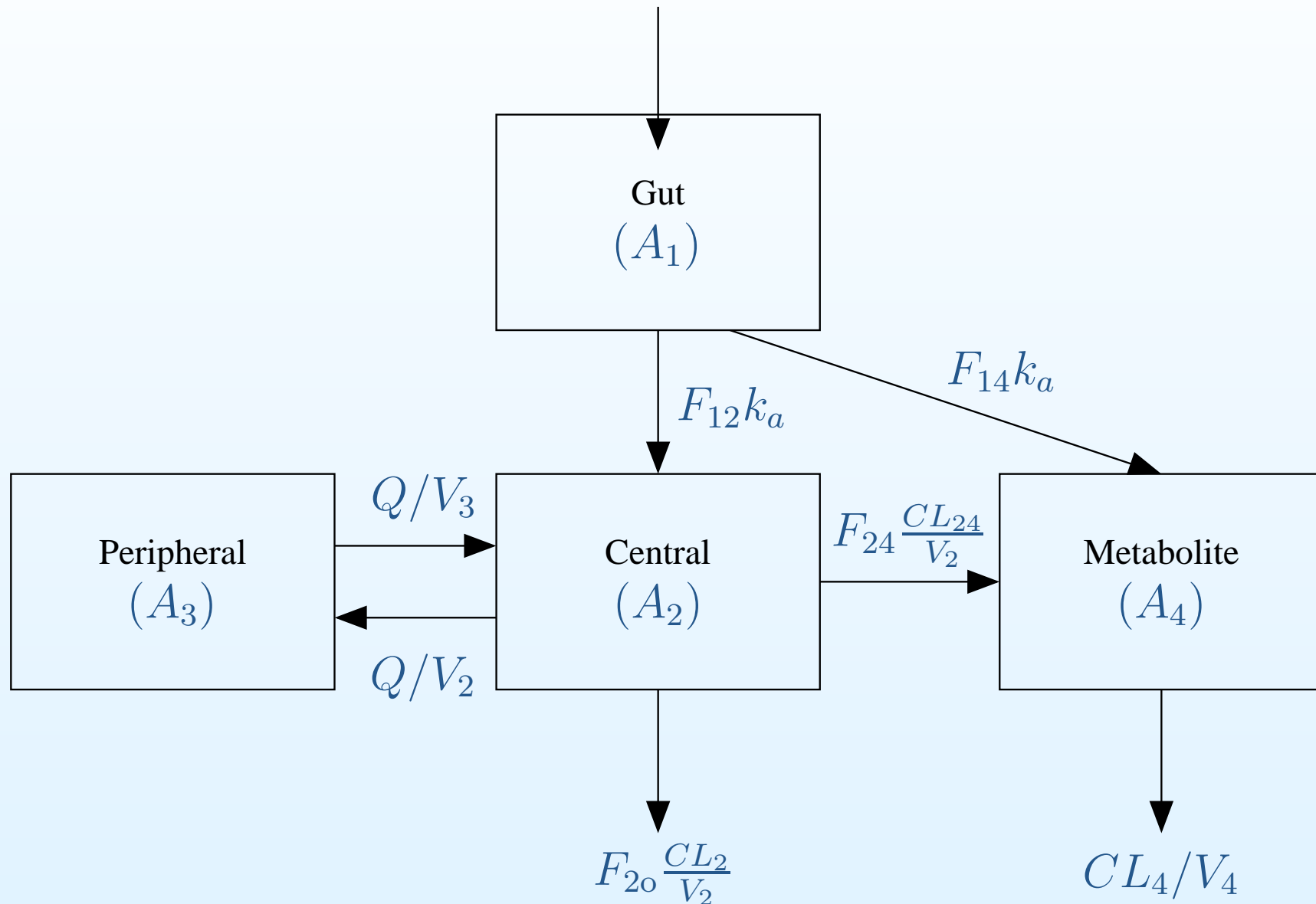
Design constraints

- 30 patients
- 3 elementary designs, 10 patients in each group
- Patients studied on two occasions
 - Capsule dose on first occasion, followed by solution dose on second occasion

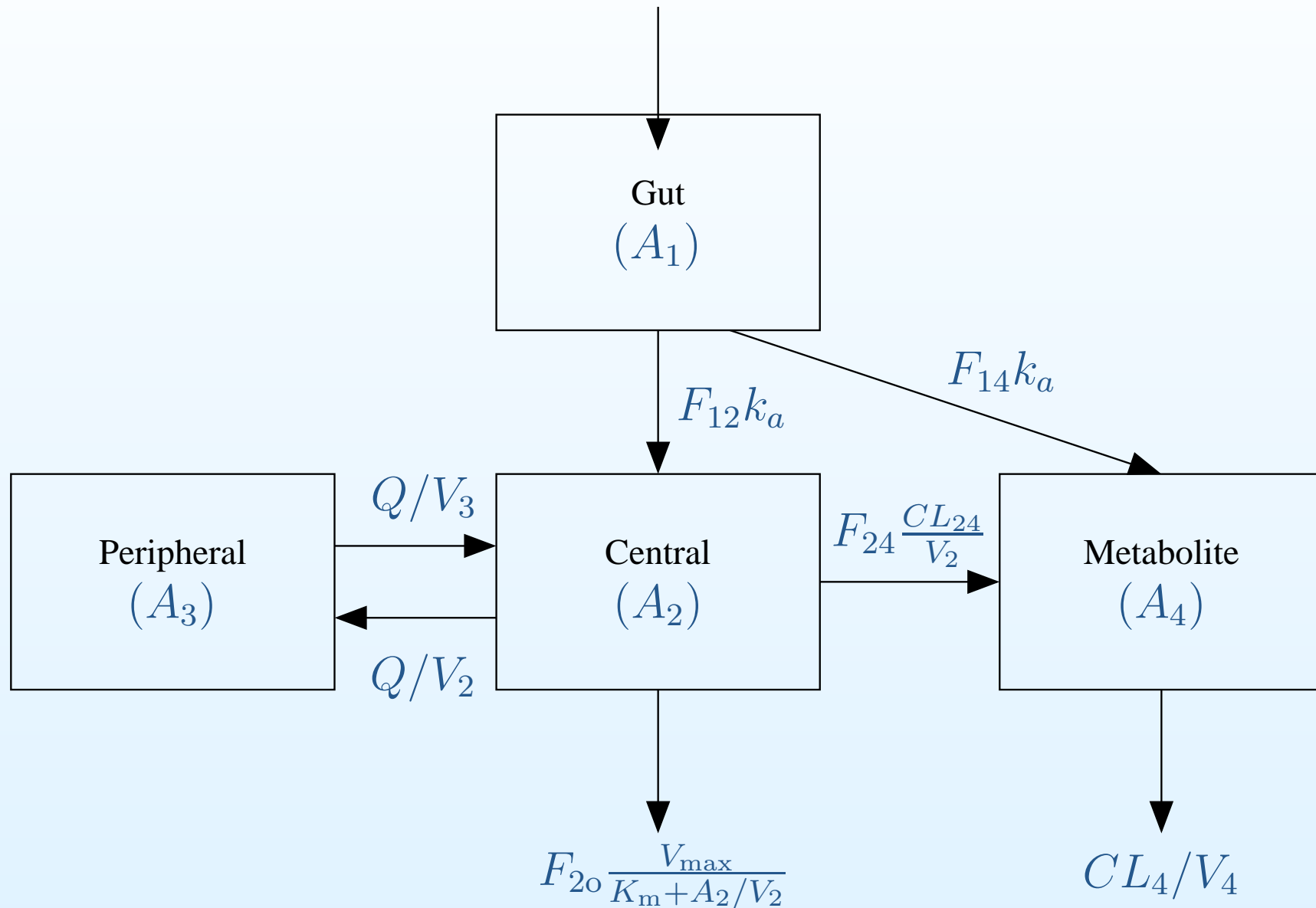
Design constraints

- 30 patients
- 3 elementary designs, 10 patients in each group
- Patients studied on two occasions
 - Capsule dose on first occasion, followed by solution dose on second occasion
 - May take 4 samples from each patient, at any time up to 72 hours after each dose

Itraconazole: compartmental model



Itraconazole: compartmental model



Itraconazole: compartmental model

$$\frac{dA_1}{dt} = -F_{12}k_a A_1 - F_{14}k_a A_1$$

$$\begin{aligned} \frac{dA_2}{dt} = & F_{12}k_a A_1 + \frac{Q}{V_3} A_3 - \frac{Q}{V_2} A_2 - F_{24} \frac{CL_{24}}{V_2} A_2 \\ & - F_{20} \frac{CL_2}{V_2} A_2 \end{aligned}$$

$$\frac{dA_3}{dt} = \frac{Q}{V_2} A_2 - \frac{Q}{V_3} A_3$$

$$\frac{dA_4}{dt} = F_{14}k_a A_1 + F_{24} \frac{CL_{24}}{V_2} A_2 - \frac{CL_4}{V_4} A_4$$

Itraconazole: compartmental model

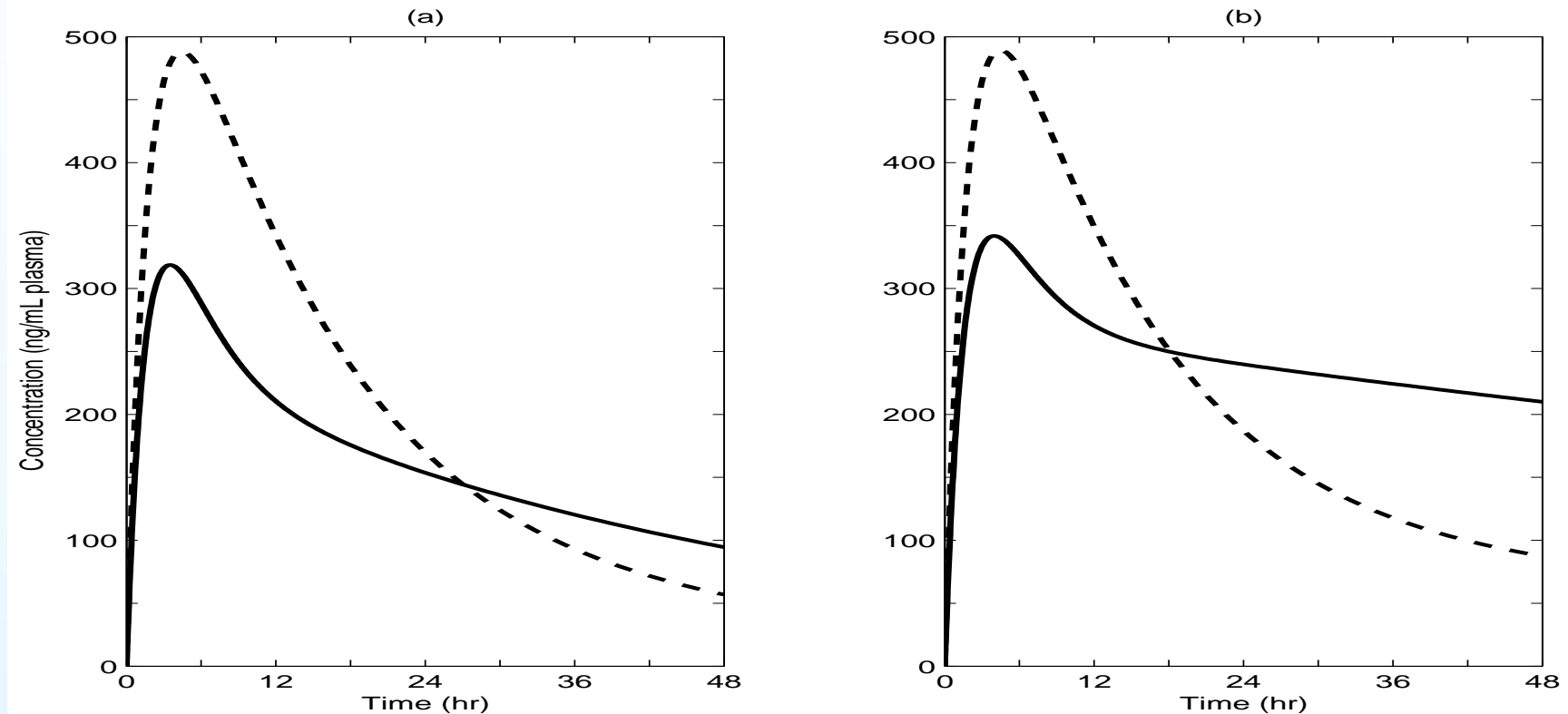
$$\frac{dA_1}{dt} = -F_{12}k_a A_1 - F_{14}k_a A_1$$

$$\begin{aligned} \frac{dA_2}{dt} = & F_{12}k_a A_1 + \frac{Q}{V_3} A_3 - \frac{Q}{V_2} A_2 - F_{24} \frac{CL_{24}}{V_2} A_2 \\ & - F_{20} \frac{V_{\max}}{K_m + A_2/V_2} A_2 \end{aligned}$$

$$\frac{dA_3}{dt} = \frac{Q}{V_2} A_2 - \frac{Q}{V_3} A_3$$

$$\frac{dA_4}{dt} = F_{14}k_a A_1 + F_{24} \frac{CL_{24}}{V_2} A_2 - \frac{CL_4}{V_4} A_4$$

Itraconazole: Typical response curves



Concentration-time profiles of itraconazole (solid line) and hydroxyitraconazole (dashed line) after a 200 mg solution dose of itraconazole, with (a) linear elimination of the drug; and (b) nonlinear elimination of the drug.

Experimental design

- An experimental design on 3 points:

$$\xi = \left\{ \xi_1 \quad \xi_2 \quad \xi_3 \right\}$$

- $\xi_j = (t_{j1}, \dots, t_{j8})$ is an *elementary design*, consisting of 8 sampling times: 4 samples following the capsule dose, 4 samples following the solution dose

Experimental design

- An experimental design on 3 points:

$$\xi = \left\{ \xi_1 \quad \xi_2 \quad \xi_3 \right\}$$

- $\xi_j = (t_{j1}, \dots, t_{j8})$ is an *elementary design*, consisting of 8 sampling times: 4 samples following the capsule dose, 4 samples following the solution dose
- 10 patients are allocated to each elementary design

Experimental design

- An experimental design on 3 points:

$$\xi = \left\{ \xi_1 \quad \xi_2 \quad \xi_3 \right\}$$

- $\xi_j = (t_{j1}, \dots, t_{j8})$ is an *elementary design*, consisting of 8 sampling times: 4 samples following the capsule dose, 4 samples following the solution dose
- 10 patients are allocated to each elementary design
- Eg. a patient may be allocated to the following elementary design, with sampling times in hours:

$$\xi_j = \left(\underbrace{0.5, 1, 4, 8}_{\text{time after capsule}}, \underbrace{0.5, 8, 12, 36}_{\text{time after solution}} \right)$$

Optimal design

- Given the form of the model, how do we best select design ξ to efficiently estimate parameter vector θ ?

Optimal design

- Given the form of the model, how do we best select design ξ to efficiently estimate parameter vector θ ?
- Cramer-Rao Lower Bound:
 $\text{Var}(\hat{\theta}) \geq (\text{Fisher information matrix})^{-1}$

Optimal design

- Given the form of the model, how do we best select design ξ to efficiently estimate parameter vector θ ?
- Cramer-Rao Lower Bound:
 $\text{Var}(\hat{\theta}) \geq (\text{Fisher information matrix})^{-1}$
- D -optimality: maximise determinant of Fisher information matrix

Information matrix

- Fisher information matrix:

$$M(\boldsymbol{\theta}, \xi) = -\mathbb{E} \left[\frac{\partial^2 \ell(\boldsymbol{\theta}; \mathbf{Y})}{\partial \boldsymbol{\theta} \partial \boldsymbol{\theta}^T} \right]$$

Information matrix

- Fisher information matrix:

$$M(\boldsymbol{\theta}, \xi) = -\mathbb{E} \left[\frac{\partial^2 \ell(\boldsymbol{\theta}; \mathbf{Y})}{\partial \boldsymbol{\theta} \partial \boldsymbol{\theta}^T} \right]$$

- Nonlinear mixed effects model, PK parameters vary randomly between subjects:

$$y_{ij} = \eta(\theta_j, t_{ij}) + \epsilon_{ij}$$

where $\theta_j = \beta + b_j$, and $b_j \sim N(0, \Sigma)$

Information matrix

- Fisher information matrix:

$$M(\boldsymbol{\theta}, \xi) = -\mathbb{E} \left[\frac{\partial^2 \ell(\boldsymbol{\theta}; \mathbf{Y})}{\partial \boldsymbol{\theta} \partial \boldsymbol{\theta}^T} \right]$$

- Nonlinear mixed effects model, PK parameters vary randomly between subjects:

$$y_{ij} = \eta(\theta_j, t_{ij}) + \epsilon_{ij}$$

where $\theta_j = \beta + b_j$, and $b_j \sim N(0, \Sigma)$

- Information matrix cannot be written down in closed form

Information matrix

- Fisher information matrix:

$$M(\boldsymbol{\theta}, \xi) = -\mathbb{E} \left[\frac{\partial^2 \ell(\boldsymbol{\theta}; \mathbf{Y})}{\partial \boldsymbol{\theta} \partial \boldsymbol{\theta}^T} \right]$$

- Nonlinear mixed effects model, PK parameters vary randomly between subjects:

$$y_{ij} = \eta(\theta_j, t_{ij}) + \epsilon_{ij}$$

where $\theta_j = \beta + b_j$, and $b_j \sim N(0, \Sigma)$

- Information matrix cannot be written down in closed form
- Retout and Mentré (2003) use first-order Taylor expansion of model to approximate $M(\boldsymbol{\theta}, \xi)$

Information matrix: Approximation

$$\mathbf{M}(\boldsymbol{\theta}, \xi) \approx \frac{1}{2} \begin{bmatrix} \mathbf{A}(\mathbf{E}, \mathbf{V}) & \mathbf{C}(\mathbf{E}, \mathbf{V}) \\ \mathbf{C}^T(\mathbf{E}, \mathbf{V}) & \mathbf{B}(\mathbf{E}, \mathbf{V}) \end{bmatrix},$$

where $\mathbf{E} \approx \mathbf{E}(\mathbf{Y})$, $\mathbf{V} \approx \text{Var}(\mathbf{Y})$, and

$$(\mathbf{A}(\mathbf{E}, \mathbf{V}))_{mn} = 2 \frac{\partial \mathbf{E}^T}{\partial \beta_m} \mathbf{V}^{-1} \frac{\partial \mathbf{E}}{\partial \beta_n}, \quad m, n = 1, \dots, p$$

$$(\mathbf{B}(\mathbf{E}, \mathbf{V}))_{mn} = \text{tr} \left(\frac{\partial \mathbf{V}}{\partial \lambda_m} \mathbf{V}^{-1} \frac{\partial \mathbf{V}}{\partial \lambda_n} \mathbf{V}^{-1} \right) \\ m, n = 1, \dots, p + 2$$

$$(\mathbf{C}(\mathbf{E}, \mathbf{V}))_{mn} = \text{tr} \left(\frac{\partial \mathbf{V}}{\partial \lambda_m} \mathbf{V}^{-1} \frac{\partial \mathbf{V}}{\partial \beta_n} \mathbf{V}^{-1} \right) \\ m = 1, \dots, p + 2, n = 1, \dots, p$$

Multiple responses: Draper & Hunter (1966)

- Fixed effects model with r responses:

$$y_i^{(a)} = \eta^{(a)}(\boldsymbol{\theta}, \mathbf{x}_i) + \epsilon_i^{(a)} \quad (a = 1, \dots, r; i = 1, \dots, n)$$

$$E(\epsilon_i^{(a)}) = 0; \quad E(\epsilon_i^{(a)} \epsilon_j^{(b)}) = 0 \text{ for } i \neq j;$$

$$E((\epsilon_i^{(a)})^2) = \sigma_a^2 = \sigma_{aa}; \quad E(\epsilon_i^{(a)} \epsilon_i^{(b)}) = \rho_{ab} \sigma_a \sigma_b = \sigma_{ab} \text{ for } a \neq b$$

- Covariance matrix for i th set of responses:

$$\Sigma = \{\sigma_{ab}\}_{a,b=1,\dots,r} = \begin{bmatrix} \sigma_{11} & \sigma_{12} & \cdots & \sigma_{1r} \\ \sigma_{21} & \sigma_{22} & \cdots & \sigma_{2r} \\ \vdots & \vdots & \ddots & \vdots \\ \sigma_{r1} & \sigma_{r2} & \cdots & \sigma_{rr} \end{bmatrix}$$

Multiple responses: Draper & Hunter (1966)

Information matrix:

$$\mathbf{M}(\boldsymbol{\theta}, \boldsymbol{\xi}) = \sum_{a=1}^r \sum_{b=1}^r \sigma^{ab} \mathbf{F}_a^T \mathbf{F}_b,$$

where

$$\mathbf{F}_a = \left[\frac{\partial \eta^{(a)}(\boldsymbol{\theta}, \mathbf{x}_1)}{\partial \boldsymbol{\theta}}, \dots, \frac{\partial \eta^{(a)}(\boldsymbol{\theta}, \mathbf{x}_n)}{\partial \boldsymbol{\theta}} \right], \quad a = 1, \dots, r$$
$$\boldsymbol{\Sigma}^{-1} = \{\sigma^{ab}\}_{a,b=1,\dots,r}$$

Model discrimination

- Two candidate models (linear & nonlinear elimination of drug)

Model discrimination

- Two candidate models (linear & nonlinear elimination of drug)
- T -optimality criterion (Atkinson & Fedorov, 1975) quite computationally expensive

Model discrimination

- Two candidate models (linear & nonlinear elimination of drug)
- T -optimality criterion (Atkinson & Fedorov, 1975) quite computationally expensive
- Time is of the essence!

Model discrimination

- Two candidate models (linear & nonlinear elimination of drug)
- T -optimality criterion (Atkinson & Fedorov, 1975) quite computationally expensive
- Time is of the essence!
- Recent work (Waterhouse et al, 2004) show that designs maximising the product of D -optimality criteria can be quite efficient in terms of both parameter estimation and model discrimination

Model discrimination

- Two candidate models (linear & nonlinear elimination of drug)
- T -optimality criterion (Atkinson & Fedorov, 1975) quite computationally expensive
- Time is of the essence!
- Recent work (Waterhouse et al, 2004) show that designs maximising the product of D -optimality criteria can be quite efficient in terms of both parameter estimation and model discrimination
- Maximize

$$|\mathbf{M}_1(\boldsymbol{\theta}^1, \boldsymbol{\xi})|^{1/p_1} |\mathbf{M}_2(\boldsymbol{\theta}^2, \boldsymbol{\xi})|^{1/p_2}$$

Optimised design

Group (q)	N_q	Elementary design ξ_q (hrs:mins)	
		Capsule	Solution
1	10	1:14	0:17
		8:56	3:55
		25:49	3:56
		51:45	3:56
2	10	6:13	0:18
		9:50	4:06
		29:29	4:06
		29:29	72:00
3	10	8:08	0:17
		28:00	4:22
		72:00	27:08
		72:00	72:00

Optimised design: practical considerations

- Sample times are very precise

Optimised design: practical considerations

- Sample times are very precise
 - Not likely to have an actual sample time of 25hr, 49min after dose

Optimised design: practical considerations

- Sample times are very precise
 - Not likely to have an actual sample time of 25hr, 49min after dose
 - Better to assign a 'window' of time in which to take a sample, eg. anywhere between 24hr and 27hr after dose

Optimised design: practical considerations

- Sample times are very precise
 - Not likely to have an actual sample time of 25hr, 49min after dose
 - Better to assign a 'window' of time in which to take a sample, eg. anywhere between 24hr and 27hr after dose
- A few cases of replicated sampling times

Optimised design: practical considerations

- Sample times are very precise
 - Not likely to have an actual sample time of 25hr, 49min after dose
 - Better to assign a 'window' of time in which to take a sample, eg. anywhere between 24hr and 27hr after dose
- A few cases of replicated sampling times
 - Eg. 2 samples to be taken at 29hr, 29min

Optimised design: practical considerations

- Sample times are very precise
 - Not likely to have an actual sample time of 25hr, 49min after dose
 - Better to assign a 'window' of time in which to take a sample, eg. anywhere between 24hr and 27hr after dose
- A few cases of replicated sampling times
 - Eg. 2 samples to be taken at 29hr, 29min
 - Assign 2 sampling windows either side of this point: 28 → 29.5hr, 29.5 → 31hr

Optimised design: practical considerations

- Sample times are very precise
 - Not likely to have an actual sample time of 25hr, 49min after dose
 - Better to assign a 'window' of time in which to take a sample, eg. anywhere between 24hr and 27hr after dose
- A few cases of replicated sampling times
 - Eg. 2 samples to be taken at 29hr, 29min
 - Assign 2 sampling windows either side of this point: 28 → 29.5hr, 29.5 → 31hr
- Loss of efficiency due to sub-optimal sampling times is assessed

Optimised design with sampling windows

Group (q)	N_q	Capsule		Solution	
		Elementary design	Sampling window	Elementary design	Sampling window
		ξ_q^c (hrs:mins)	(hrs)	ξ_q^s (hrs:mins)	(hrs)
1	10	1:14	0.1 → 3.0	0:17	0.1 → 1.0
		8:56	7.0 → 10.0	3:55	3.0 → 3.5
		25:49	24.0 → 27.0	3:56	3.5 → 4.0
		51:45	50.0 → 53.0	3:56	4.0 → 4.5
2	10	6:13	5.0 → 8.0	0:18	0.1 → 1.0
		9:50	8.0 → 11.0	4:06	3.0 → 4.0
		29:29	28.0 → 29.5	4:06	4.0 → 5.0
		29:29	29.5 → 31.0	72:00	69.0 → 72.0
3	10	8:08	7.0 → 10.0	0:17	0.1 → 1.0
		28:00	26.5 → 29.5	4:22	3.0 → 6.0
		72:00	69.0 → 70.5	27:08	26.0 → 29.0
		72:00	70.5 → 72.0	72:00	69.0 → 72.0

Design evaluation

- The optimal design was evaluated in terms of several aspects

Design evaluation

- The optimal design was evaluated in terms of several aspects
 - Loss of efficiency due to sub-optimal sampling times taken from the sampling windows

Design evaluation

- The optimal design was evaluated in terms of several aspects
 - Loss of efficiency due to sub-optimal sampling times taken from the sampling windows
 - D -efficiency under each of the two competing models

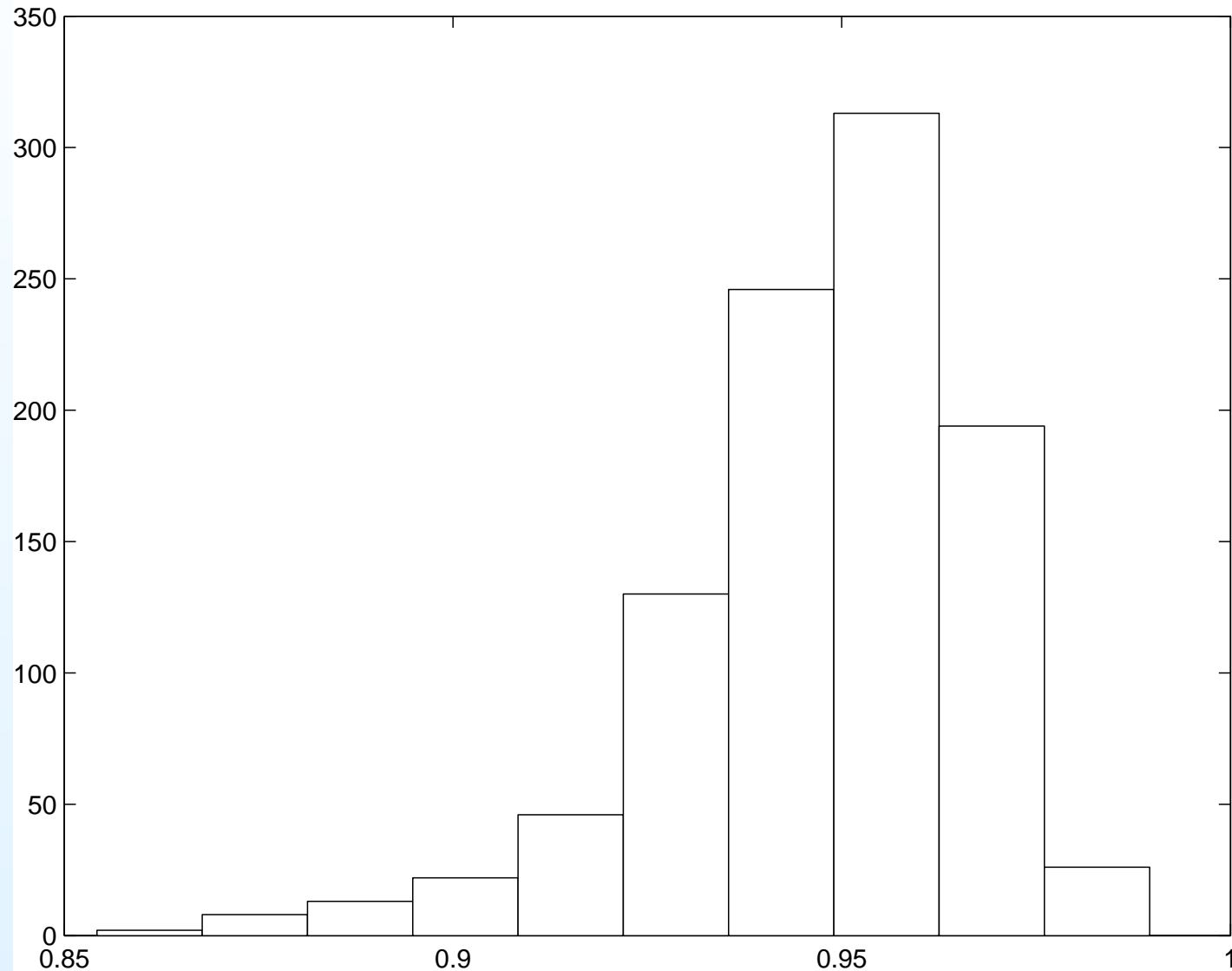
Design evaluation

- The optimal design was evaluated in terms of several aspects
 - Loss of efficiency due to sub-optimal sampling times taken from the sampling windows
 - D -efficiency under each of the two competing models
 - Standard errors of parameter estimates

Design evaluation

- The optimal design was evaluated in terms of several aspects
 - Loss of efficiency due to sub-optimal sampling times taken from the sampling windows
 - D -efficiency under each of the two competing models
 - Standard errors of parameter estimates
 - Ability to discriminate between two competing models

Design evaluation: Sampling windows



Design evaluation: Marginal D -efficiency

- D -optimal designs were found for each of the two models, ξ_1^* (linear elimination of drug) and ξ_2^* (nonlinear elimination)

Design evaluation: Marginal D -efficiency

- D -optimal designs were found for each of the two models, ξ_1^* (linear elimination of drug) and ξ_2^* (nonlinear elimination)
- Calculated efficiency of the product optimal design, ξ^* , with respect to each model:

$$\text{Eff}_u(\xi, \xi_u^*) = \frac{|M^u(\boldsymbol{\theta}^u, \xi)|^{1/p_u}}{|M^u(\boldsymbol{\theta}^u, \xi_u^*)|^{1/p_u}}, \quad u = 1, 2$$

Design evaluation: Marginal D -efficiency

- D -optimal designs were found for each of the two models, ξ_1^* (linear elimination of drug) and ξ_2^* (nonlinear elimination)
- Calculated efficiency of the product optimal design, ξ^* , with respect to each model:

$$\text{Eff}_u(\xi, \xi_u^*) = \frac{|M^u(\theta^u, \xi)|^{1/p_u}}{|M^u(\theta^u, \xi_u^*)|^{1/p_u}}, \quad u = 1, 2$$

$$\text{Eff}_1(\xi^*, \xi_1^*) = 0.9640$$

$$\text{Eff}_2(\xi^*, \xi_2^*) = 0.9591$$

Design evaluation: Standard errors

- For each model, 100 data sets were generated by simulation, models were fitted with NONMEM software

Design evaluation: Standard errors

- For each model, 100 data sets were generated by simulation, models were fitted with NONMEM software
- Calculated standard deviation of parameter estimates

Design evaluation: Standard errors

- For each model, 100 data sets were generated by simulation, models were fitted with NONMEM software
- Calculated standard deviation of parameter estimates
- Simulated standard errors compared to predictions from the inverse of the information matrix

Design evaluation: Standard errors

- For each model, 100 data sets were generated by simulation, models were fitted with NONMEM software
- Calculated standard deviation of parameter estimates
- Simulated standard errors compared to predictions from the inverse of the information matrix
- Predicted standard errors were fairly close to those obtained in simulations

Design evaluation: Standard errors

- For each model, 100 data sets were generated by simulation, models were fitted with NONMEM software
- Calculated standard deviation of parameter estimates
- Simulated standard errors compared to predictions from the inverse of the information matrix
- Predicted standard errors were fairly close to those obtained in simulations
- Fixed effect coefficients of variation around 10-20%

Design evaluation: Standard errors

- For each model, 100 data sets were generated by simulation, models were fitted with NONMEM software
- Calculated standard deviation of parameter estimates
- Simulated standard errors compared to predictions from the inverse of the information matrix
- Predicted standard errors were fairly close to those obtained in simulations
- Fixed effect coefficients of variation around 10-20%
- Coefficients of variation of Between Subject Variability around 50-100%

Design evaluation: Standard errors

- For each model, 100 data sets were generated by simulation, models were fitted with NONMEM software
- Calculated standard deviation of parameter estimates
- Simulated standard errors compared to predictions from the inverse of the information matrix
- Predicted standard errors were fairly close to those obtained in simulations
- Fixed effect coefficients of variation around 10-20%
- Coefficients of variation of Between Subject Variability around 50-100%
- Typical of nonlinear mixed effects models in PK studies

Design evaluation: Model discrimination

- Power tests: using results of previous simulations, for data generated under each model, fitted models using NONMEM, select 'best' model based on $-2 \log L$

Design evaluation: Model discrimination

- Power tests: using results of previous simulations, for data generated under each model, fitted models using NONMEM, select 'best' model based on $-2 \log L$
- Data generated under linear model: correct model chosen 74% of the time

Design evaluation: Model discrimination

- Power tests: using results of previous simulations, for data generated under each model, fitted models using NONMEM, select 'best' model based on $-2 \log L$
- Data generated under linear model: correct model chosen 74% of the time
- Data generated under nonlinear model: correct model chosen 100% of the time

Discussion

- Design was optimised to accommodate for:

Discussion

- Design was optimised to accommodate for:
 - Multiple nonlinear models with no analytic solution

Discussion

- Design was optimised to accommodate for:
 - Multiple nonlinear models with no analytic solution
 - Discriminate between models

Discussion

- Design was optimised to accommodate for:
 - Multiple nonlinear models with no analytic solution
 - Discriminate between models
 - Estimate parameters well under each model

Discussion

- Design was optimised to accommodate for:
 - Multiple nonlinear models with no analytic solution
 - Discriminate between models
 - Estimate parameters well under each model
 - Multiple responses

Discussion

- Design was optimised to accommodate for:
 - Multiple nonlinear models with no analytic solution
 - Discriminate between models
 - Estimate parameters well under each model
 - Multiple responses
 - Sampling windows: design points flexible

Discussion

- Design was optimised to accommodate for:
 - Multiple nonlinear models with no analytic solution
 - Discriminate between models
 - Estimate parameters well under each model
 - Multiple responses
 - Sampling windows: design points flexible
- Study still underway: results pending!

References

1. Green B. and Duffull S.B. (2003) Prospective evaluation of a D -optimal designed population pharmacokinetic study. *Journal of Pharmacokinetics and Pharmacodynamics* **30**, 145–161.
2. Retout S. and Mentré F. (2003). Further developments of the Fisher information matrix in nonlinear mixed effects models with evaluation in population pharmacokinetics. *Journal of Biopharmaceutical Statistics* **13**, 209–227.
3. Draper N.R. and Hunter W.G. (1966). Design of experiments for parameter estimation in multiresponse situations. *Biometrika* **53**, 525–533.
4. Waterhouse T.H., Eccleston J.A., and Duffull S.B. (2004). On optimal design for discrimination and estimation. In J. Antoch, ed., *COMPSTAT 2004 - Proceedings In Computational Statistics: 16th Symposium Held In Prague, Czech Republic, 2004*, pp. 1963–1970, Physica-Verlag.
5. Waterhouse T.H., Redmann S., Duffull S.B., and Eccleston J.A. Optimal design for model discrimination and parameter estimation for itraconazole population pharmacokinetics in cystic fibrosis patients. *Journal of Pharmacokinetics and Pharmacodynamics*. To appear.