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Simultaneous optimization of a sparse sampling schedule for estimation of piperacillin population PK and individual T>MIC in severe sepsis patients

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Aim

Propose sparse design for simultaneous estimation of

- Population PK
- Individual T>MIC (Time above the minimum inhibitory concentration)

of piperacillin

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Background
Piperacillin/tazobactam

Empirical antibiotic treatment in septic patients

–Piperacillin/tazobactam (4g/0.5g) q8h

PK/PD targets

- 100% T>MIC
- 50% T>4xMIC

Extensive inter-individual PK variations i these patients

–Antibiotic dosing is a challenge

–Interest in deciding charachteristics in special populations

Design for two studies explored

–Children (Henrik Schrøder[1])

–**Severe sepsis patients** (Kristina Öbrink-Hansen[1])

1. Department of Infectious Diseases, Aarhus University Hospital - Skejby

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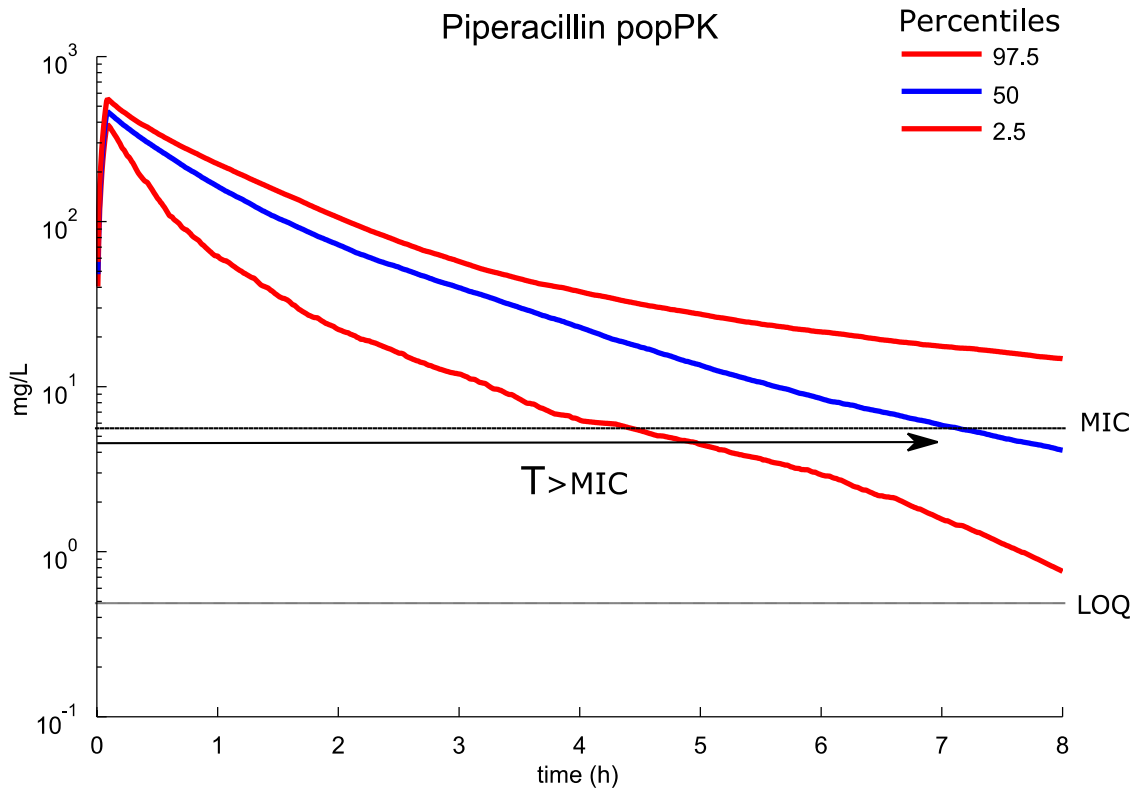
Background

Piperacillin popPK model septic shock

Population parameter	Value (RSE%)	
	Typical	IIV
Cl (L/h)	3.6 (15.7%)	71.2%
V1 (L)	7.3 (11.8%)	57.8%
Q (L/h)	6.58 (16.4%)	
V2 (L)	3.9 (9.7%)	
β_{Pcrea} (L/ h) / (µmol/L)	-0.011 (11.9%)	
Proportional error (%)	14.7% (14.4%)	
Cmax (mg/L)	546 (363; 668)[a]	
Cmin (mg/L)	51.7 (10.7; 159.4)[a]	
$AUC_{0\text{-}8h}$ (mg/L*h)	1148 (739; 2492)[a]	
$t_{½}$ (h)	3.49 (1.62; 4.47)[a]	

Hansen 2015

15 patients
septic shock



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Background

ICU study severe sepsis

–Does piperacillin/tazobactam (4g/0.5g) q8h result in therapeutic plasma concentrations?

20 patients, 3 blood samples per patient

–Population PK: 4 (5) population fixed effects + 2 IIV and 1 error

–Fraction achieving >4xMIC at 50% of dose interval

–Fraction achieving >1xMIC at 100% of dose interval

How to set up a sampling schedule allowing this?

(Assume generally similar PK to septic schock)

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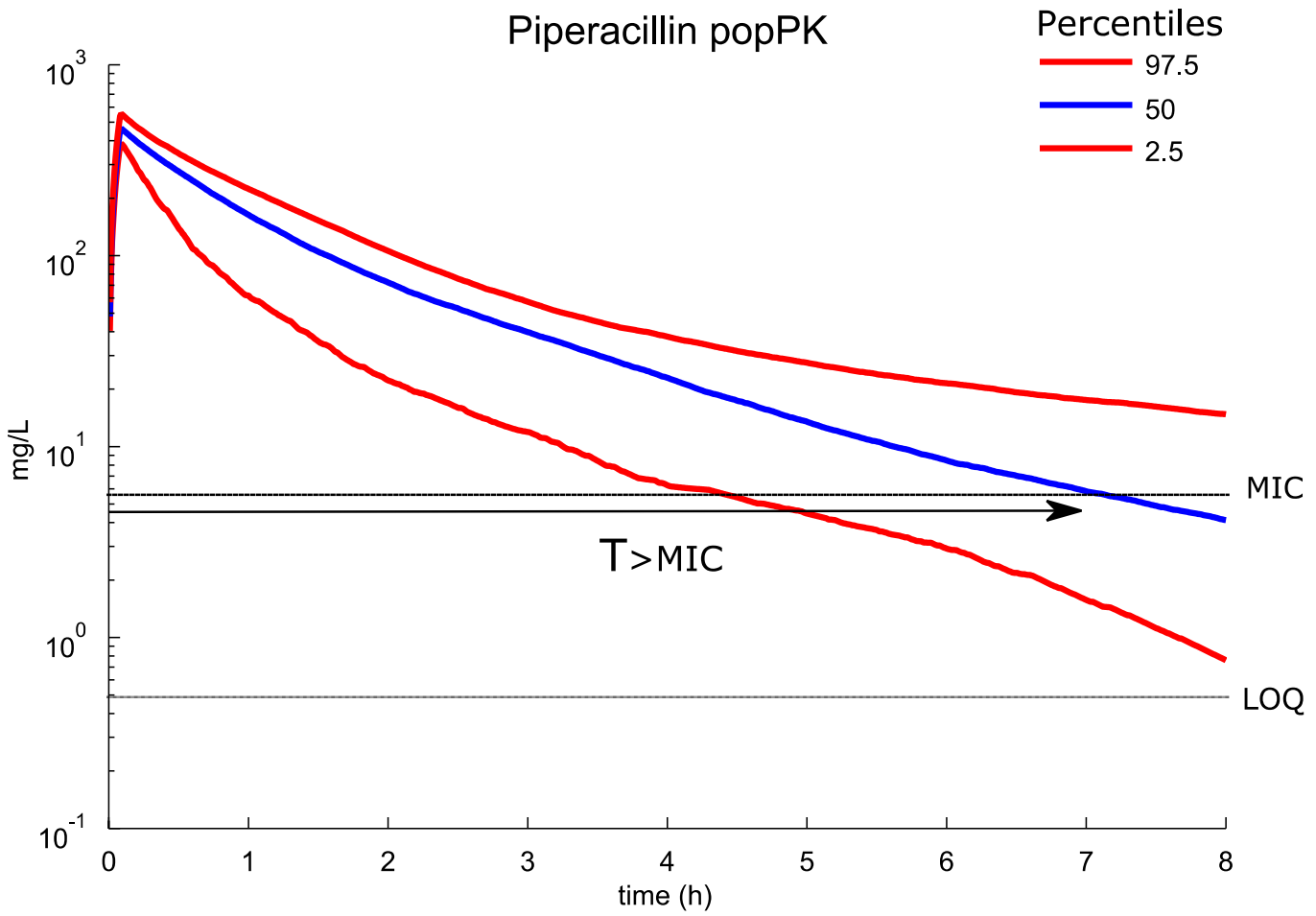
Background

Optimization idea

Fixed sampling at 4 and 8h, optimize 1 sample freely across 2 groups

+ Simple
- 4h sample not necessarily good for popPK
- 4h sample has to be taken on time for 50% T>4xMIC
  → not convenient



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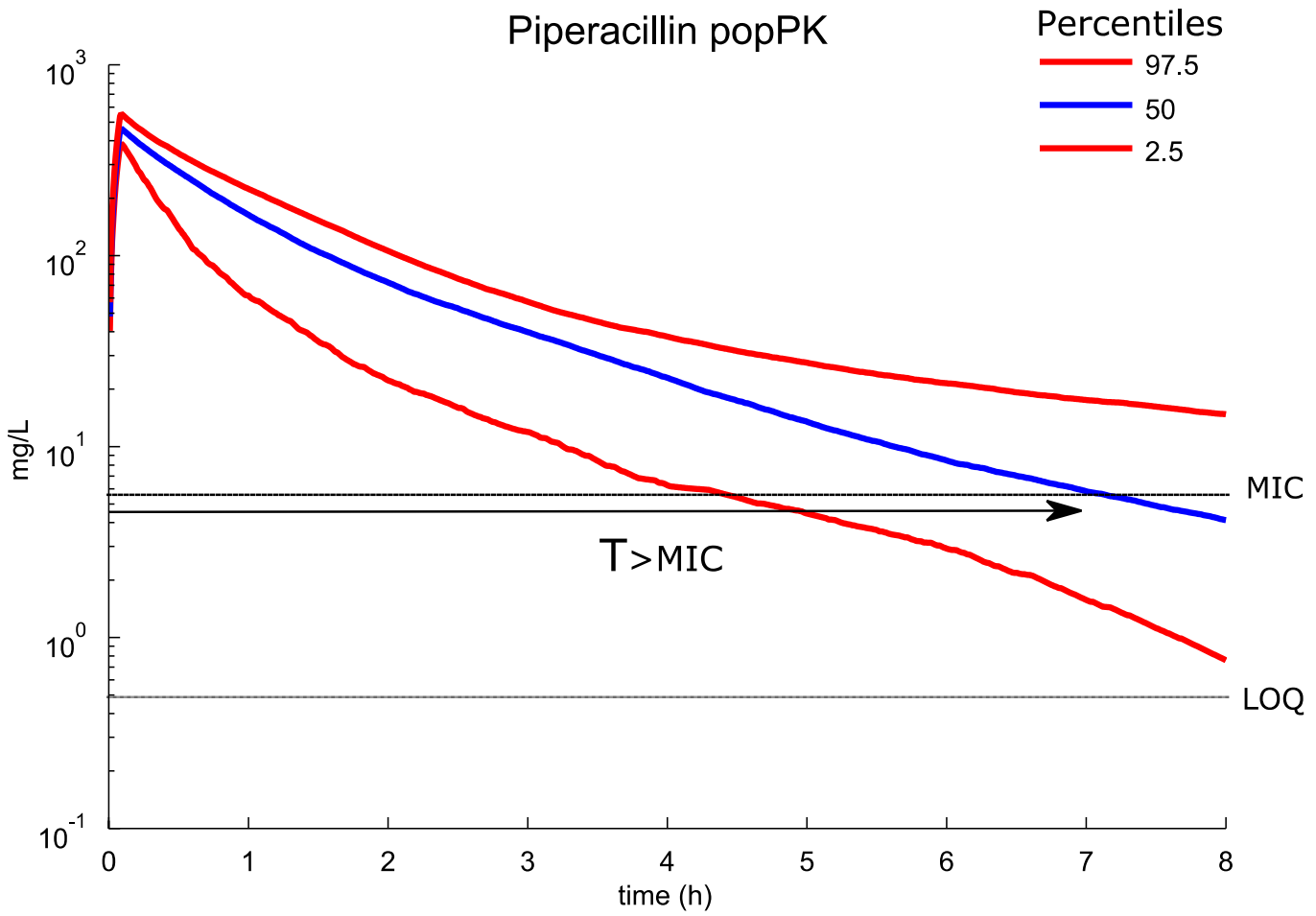
Background

Optimization idea

Define individual c-optimality criterion for 100% T>MIC and 50% T>4xMIC

\+ Optimization directly on measure of interest

- Complex
- Needs to account for MIC distribution in the design



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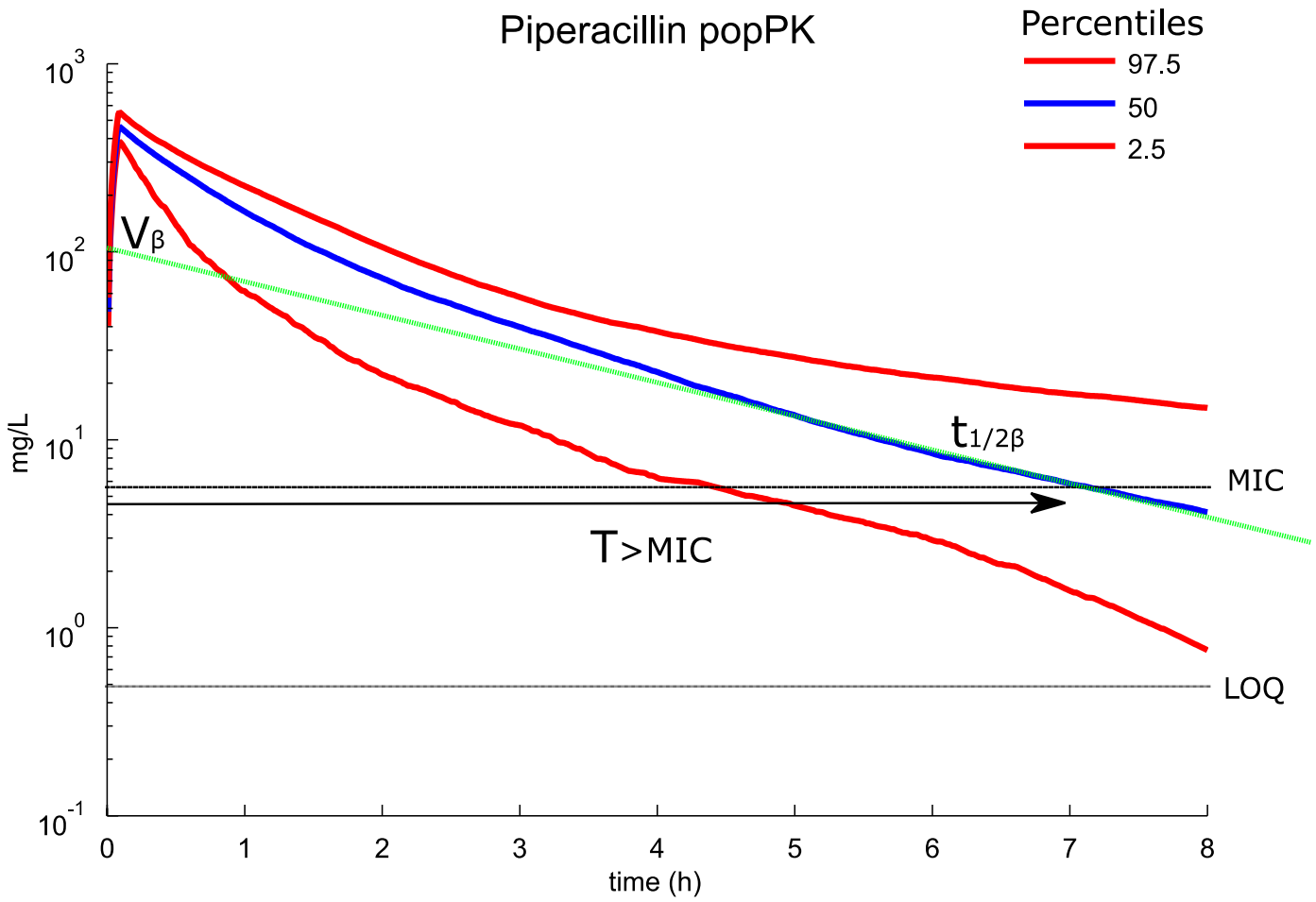
Background

Optimization idea

T>MIC can be estimated from the individual V_β, λ_β. Optimize for precision in these.

+ Independent of MIC distribution
- compartmental popPK model

→ Define compound criteria for simultaneous optimization of individual NCA and popPK



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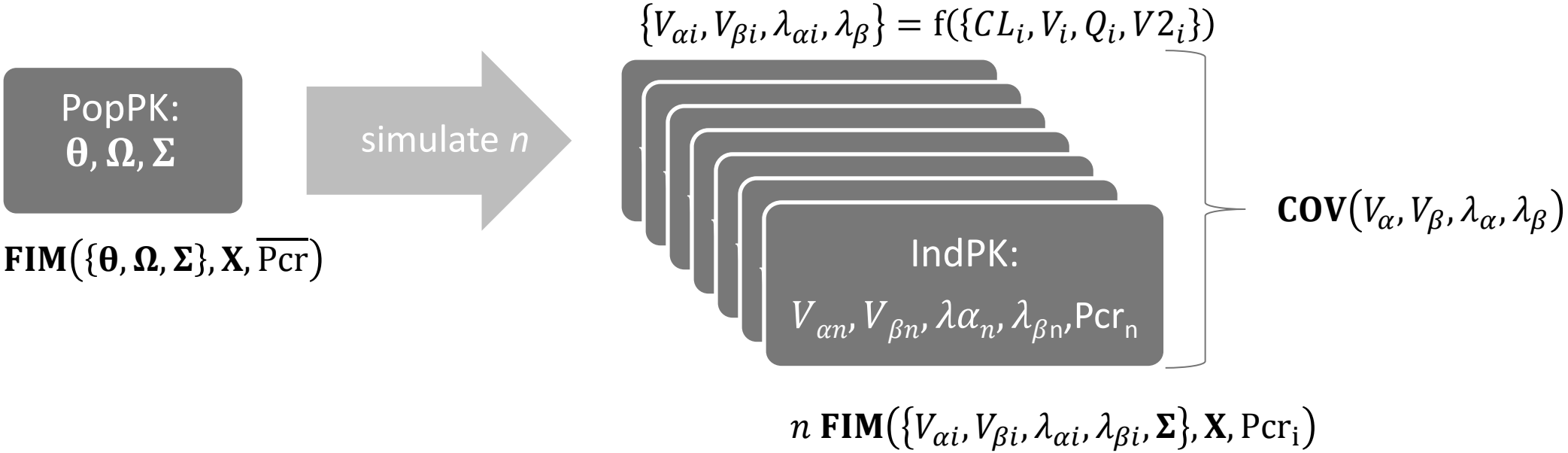
Methods

Optimisation critereon



$$\underset{\mathbf{x}}{argmax}\left[\ln\left(\frac{\left|\mathbf{FIM}(\{\boldsymbol{\theta}, \boldsymbol{\Omega}, \boldsymbol{\Sigma}\},\ \mathbf{X}, \overline{\mathrm{Pcr}})\right|}{\left|\mathbf{FIM}(\{\boldsymbol{\Sigma}\}, \mathbf{X}, \overline{\mathrm{Pcr}})\right|}\right) + \frac{1}{n}\sum_{i=1}^{n}\ln\left(\frac{\left(\left|\mathbf{FIM}(\{V_{\alpha i}, V_{\beta i}, \lambda_{\alpha i}, \lambda_{\beta i}, \boldsymbol{\Sigma}\}, \mathbf{X}, \mathrm{Pcr_i}) + \mathbf{COV}^{-1}(V_\alpha, V_\beta, \lambda_\alpha, \lambda_\beta)\right|\right)}{\left|\mathbf{FIM}(\{V_{\alpha i},\ \lambda_{\alpha i}, \boldsymbol{\Sigma}\}, \mathbf{X}, \mathrm{Pcr_i}) + \mathbf{COV}^{-1}(V_\alpha, \lambda_\alpha)\right|}\right)\right]$$

Interesting part[1] of population FIM
Ds optimality

MAP (Bayesian FIM[2]) Ds optimality[3]
Sampling based COV(.) for NCA parameters

1. Atkinson 1992, Merlé & Mentré 1995, 3. Hennig 2012

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Methods
Optimization

20 ID, 3 sampling points per ID

2 groups, first and last sample the same time

Implemented in PopED 2.13

–RS-LS-SG optimization

–Reduced FIM, FO approximation

–100 constant individual samples, p-creatinin 50-200 µmol/L, latin-hypercube sampling

–BLOQ handled by setting sample information to zero

–Pcr covariate parameter fixed

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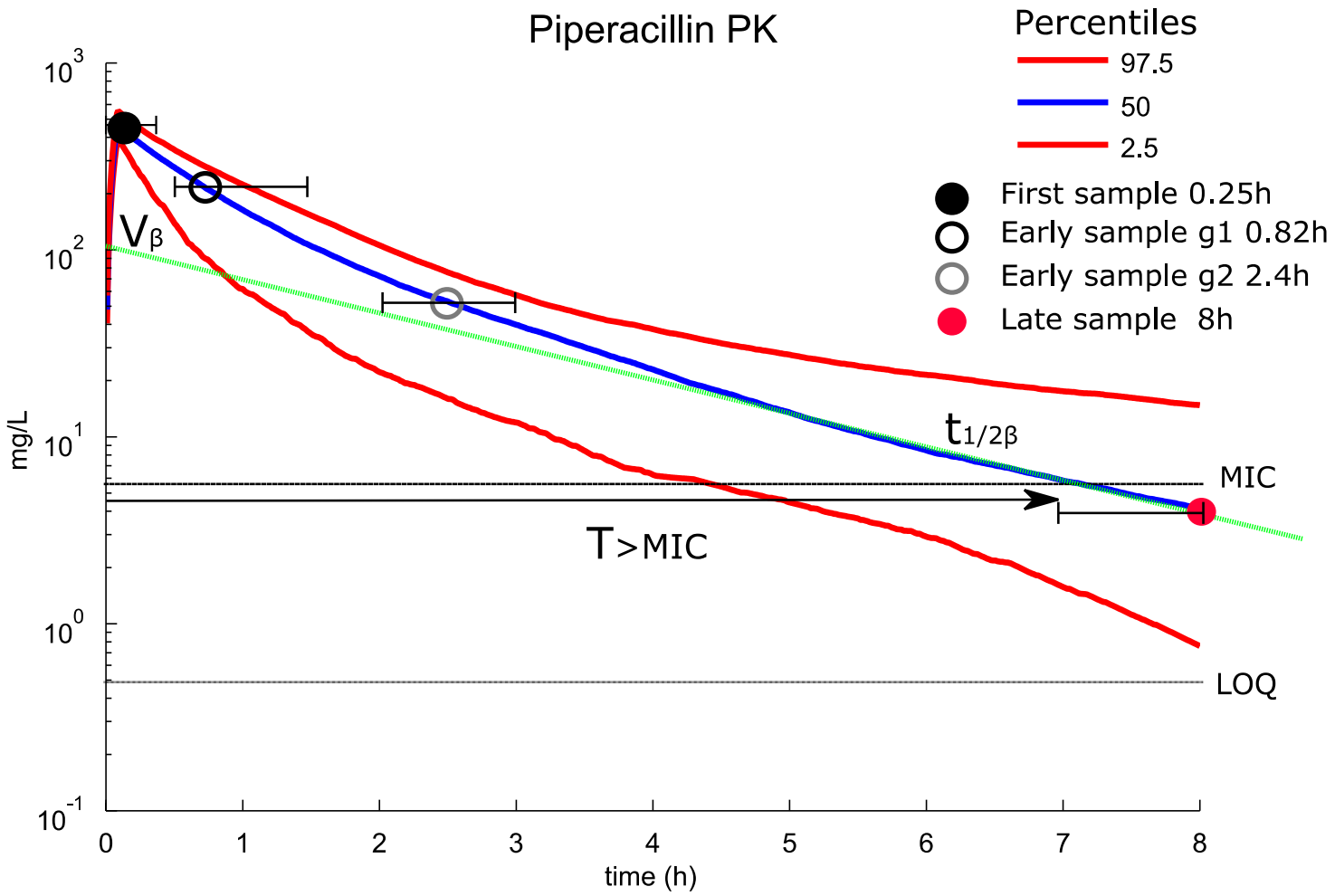
Results

Sampling times



Convenience sampling windows

1. 10 - 20min
2. 0.5 - 1.5h
3. 2 - 3h
4. 7 - 8h

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Results

Precision and Shrinkage

	Pop PK* RSE**						
	V	Q	Vp	CL	IIV V	IIV CL	RES prop
no spread	0.19	0.53	0.20	0.13	0.00	0.21	0.02
spread	0.23	0.79	0.29	0.13	0.00	0.21	0.02

	Individual NCA SH***			
	V_α	V_β	λ_α	λ_β
no spread	0.15	0.14	0.59	0.01
spread	0.17	0.11	0.57	0.01

*Covariate parameter for Pcr not included (Fixed)
**PopED predicted

***Predicted from individual FIM (Kristoffersson 2015):

$$\mathbf{SH_{pred}} = 1 - \sqrt{\mathrm{diag}\left(\mathbf{I} - \left(\frac{1}{n}\sum_{i=1}^{n}(\mathbf{FIM_i} + \mathbf{Prior})^{-1}\right) \times \mathbf{Prior}\right)}$$

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Conclusion/Outlook

- Compound criterion defined
  - Combines population PK and individual NCA
  - (Could be extended by weighting etc.)
- Group-wise optimization of sparse sampling schedule
  - Predicted to achieve sufficient precision in popPK and low SH (high precision) in V_β, $\lambda\beta$ → allows T>MIC determination in patient
- Study recruitment is completed and analysis to be performed this summer

Aknowledgments

Phamacometrics group

Lena Friberg

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Department of Infectious Diseases

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Kristina Öbrink-Hansen

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Thank you for your attention

QUESTIONS/COMMENTS?

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BACKUP SLIDES

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Sepsis

Sepsis

–At least two SIRS criteria caused by known or suspected infection

Severe sepsis

–Sepsis with acute organ dysfunction (including hypoperfusion and hypotension) caused by sepsis

Septic shock

–Sepsis with persistent or refractory hypotension or tissue hypoperfusion despite adequate fluid resuscitation

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ICU study septic shock patients

- Does piperacillin/tazobactam (4g/0.5g) q8h result in therapeutic plasma concentrations in septic shock patients?
- 15 patients included
  - 8 blood-samples collected from the 3rd consecutive dosing interval
  - 2-compartment model
- Plasma-piperacillin concentrations varied considerably and were associated with p-creatinine
- Patients with impaired renal function were more likely to achieve predefined PK/PD targets than patients with preserved or augmented renal function.
- Prolonged infusion and frequent intermittent dosing increased PTA

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Compartmental to NCA

$$d = k_{12} + k_{21} + \frac{CL}{V}$$

$$\lambda_\alpha = \frac{1}{2} \times \left(d + \sqrt{d^2 - 4 \times k_{21} \times \frac{CL}{V}} \right)$$

$$\lambda_\beta = \frac{1}{2} \times \left(d - \sqrt{d^2 - 4 \times k_{21} \times \frac{CL}{V}} \right)$$

$$V_\alpha = V \times \frac{\lambda_\beta - \lambda_\alpha}{k_{21} - \lambda_\alpha}$$

$$V_\beta = V \times \frac{\lambda_\alpha - \lambda_\beta}{k_{21} - \lambda_\beta}$$