III-04

Inter Occasion Variability (IOV) in Individual Optimal Design (OD)

UPPSALA UNIVERSITET

Anders N. Kristoffersson, Lena E. Friberg, Joakim Nyberg

Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden

Introduction

Background

IOV may adversely affect the precision of maximum a posteriori (MAP) estimated individual parameters and have long been recognized to impact the potential of feedback individualization of dosing regimens [1]. However, the inclusion of IOV in OD for MAP estimation of individual parameters has not been previously investigated. Here methods for individual OD in the presence of IOV will be tested on a complex Colistin PK model [2] as well as a simple 1-compartment IV bolus model (1-CIV)

Objective

Explore additions to the previously described FIM_{MAP} [3] to handle the presence of IOV in two test models in terms of:

- Individual parameter precision
- Calculation run-times

Methods

Test models

The Colistin PK-model (Figure 1 left) with IIV and IOV and a combined error model was implemented with one occasion per dosing interval (12 h) with 9 MIU (270 mg CBA) CMS as loading dose (30-min infusion), followed by a maintenance dose of 4.5 MIU (135 mg CBA) q12 h. Both CMS and Colistin were measured. 1-CIVwas implemented with an additive error and a 6 h dosing interval (Figure 1 right). In the Colistin PK model the IIV and IOV deviations (η, κ) were uniquely identifiable (disregarding residual error, σ). For 1-CIV the η and κ deviations were not uniquely identifiable.

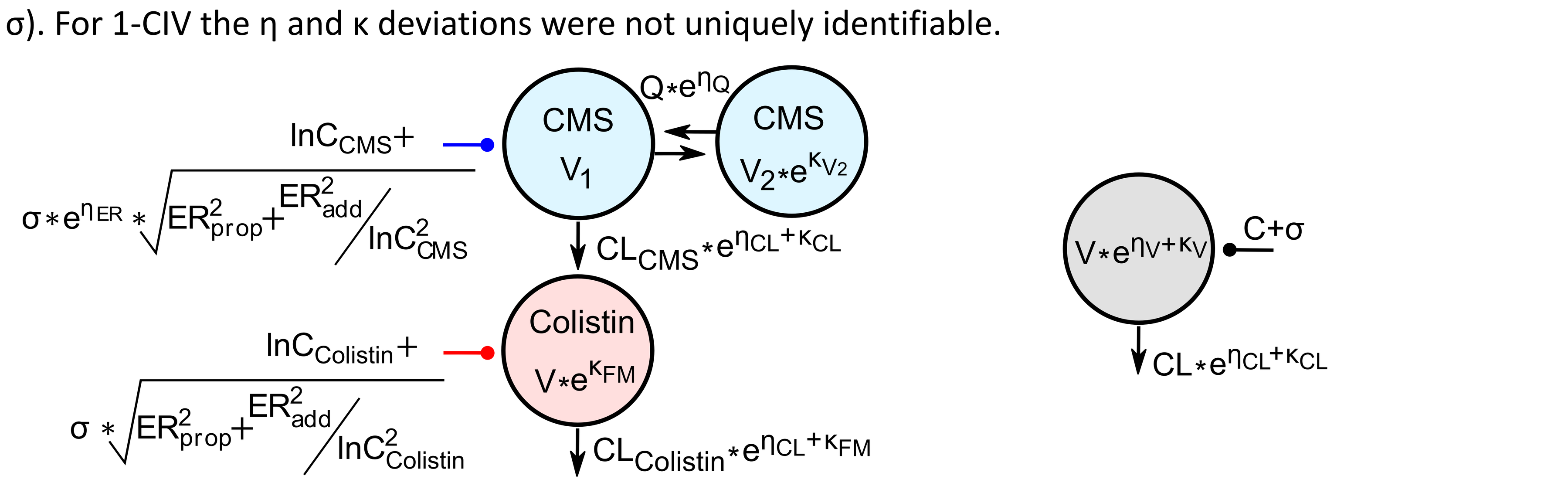

Figure 1. Left: The Colistin PK model with two compartments for the prodrug CMS and one compartment for formed Colistin. Right: The simple constructed one compartment model, 1-CIV.

Individual maximum a posteriori design criterion - FIM_{MAP}

The inverse FIM_{MAP} is the lower bound for the posterior individual covariance matrix. To calculate the FIM_{MAP} (also known as the Bayesian Information Matrix [4]) the population model is transformed to an individual model and integrated over all possible individual values, i.e. the prior population variance, Ω. The expected variance of the individual parameters may then be minimized by maximizing the FIM_{MAP}.

$$\mathbf{FIM}_{MAP} = \mathrm{E}_{\Omega}[\mathbf{FIM}(\mathbf{X},\mathbf{\Theta})] + \mathbf{\Omega}^{-1} \approx \frac{1}{n}\sum_{i=1}^{n}\mathbf{FIM}(\mathbf{X},\mathbf{\Theta}_i) + \mathbf{\Omega}^{-1}$$

Where n is the number of individual parameter sets sampled, X is the design, Θ_i is the parameter vector for individual i, and Ω the population prior IIV covariance matrix.

Strategies to include IOV in the FIM_{MAP}

i) **Inflate** - The prior was inflated with the IOV through model re-estimation.

$$\mathbf{FIM}_{MAP,i} = \mathbf{FIM}(\mathbf{X},\{\mathbf{\Theta}_\theta,\mathbf{\Theta}_{\eta i}\}) + \mathbf{\Omega}^{*-1}$$

Where Θ_θ is the vector of population parameters, $\Theta_{\eta i}$ is the vector of deviations from the typical population parameters for individual i, and Ω is the population prior covariance matrix inflated to include IOV.*

ii) **POPocc** - The IOV variability was included in the individual FIM as a population occasion random effect parameter.

$$\mathbf{FIM}_{MAP,i} = \mathbf{FIM}(\mathbf{X},\{\mathbf{\Theta}_\theta,\mathbf{\Theta}_{\eta i},\mathbf{\Pi}\}) + diag(\mathbf{\Omega}^{-1},\mathbf{0}_{p,p})$$

*Where Π is the covariance matrix for the IOV, $0_{p,p}$ is a zero matrix of dimension p*p and p is the number of occasion effects in the population model.*

iii) **MAPocc** - The occasion variability was added to the individual FIM as fixed effect occasion parameter sampled per occasion from the prior IOV distribution.

$$\mathbf{FIM}_{MAP,i} = \mathbf{FIM}(\mathbf{X},\{\mathbf{\Theta}_\theta,\mathbf{\Theta}_{\eta i},\ \mathbf{\Theta}_{\kappa 1,i},\mathbf{\Theta}_{\kappa 2,i}\ldots,\mathbf{\Theta}_{\kappa K,i}\}) + diag(\mathbf{\Omega},\mathbf{\Pi}_1,\mathbf{\Pi}_2\ldots,\mathbf{\Pi}_K)^{-1}$$

Where $\Theta_{\kappa j,i}$ *is the vector of occasion deviations for the j^{th} occasion of the i^{th} individual, K is the number of occasions and Π_j == Π.*

For comparison the IOV was excluded (Π=0), termed Ignore.

Optimization

- Optimization performed in the PopED optimal design software [5] using the ED_s criteria in combination with a prior FIM.
- Individual deviation parameters (η_{CL}, η_Q, η_{RE} for Colistin PK and η_V, η_{CL} for 1-CIV) set as interesting (optimization on these parameters), typical population value parameters fixed and residual variance parameters fixed.
- Colistin PK: 3 or 6 samples over 3 occasions 1-CIV: 5 samples over 4 occasions.

Design evaluation

- 10 000 simulations and MAP – re-estimations of the full model in NONMEM7.
- Calculate expected standard deviation (SD) and the observed root mean squared error (RMSE) of the Empirical Bayes Estimates (EBE:s).
- Compare with expected SD calculated from the expectation of the PopED inverse FIM_{MAP}.

Results

Design

The optimal sampling schedules are shown in Figure 2.

- Inflate does not change the design compared to Ignore.
- For Colistin PK MAP_{occ} and POP_{occ} concentrate the samples to the first occasion (the MAP_{occ} 6-sample design place one sample at 24h and the POP_{occ} 6-sample design one at 36h). Ignore spreads the samples across the occasions
- For 1-CIV MAP_{occ} and POP_{occ} spread the samples across the four occasions while Ignore only sample the first and last occasion.

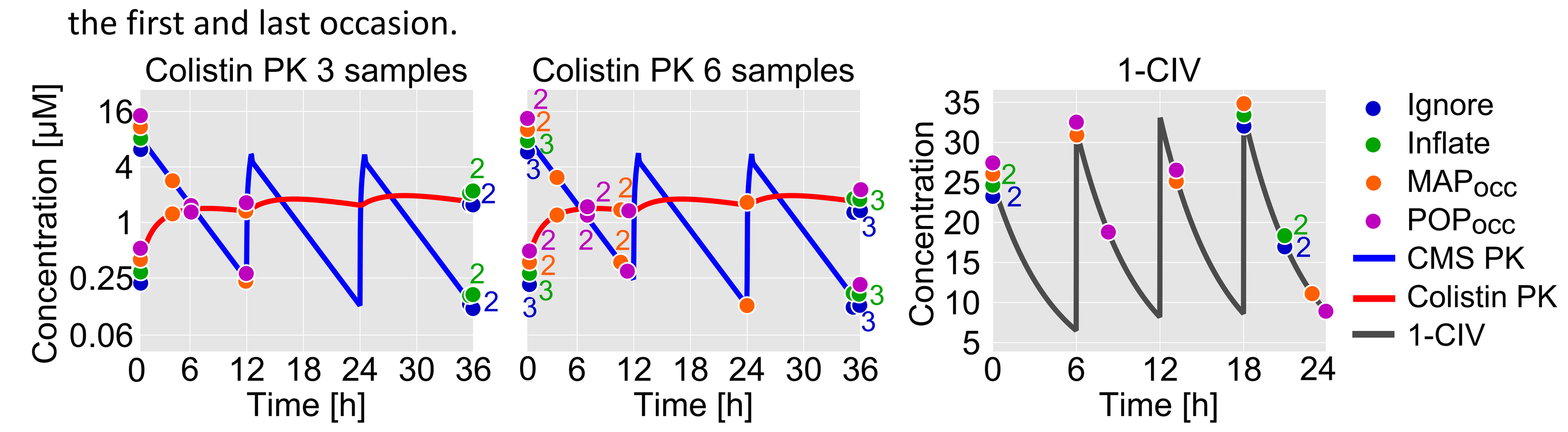

Figure 2. The optimal sampling times for the different methods. The number of replicate samples per design point are noted.

Parameter Precision

The results from the design evaluation are summarized in Figure 3.

- The PopED and NONMEM predicted SD corresponds well for methods MAP_{occ} and POP_{occ} and in general results in lower parameter RMSE compared to Ignore.

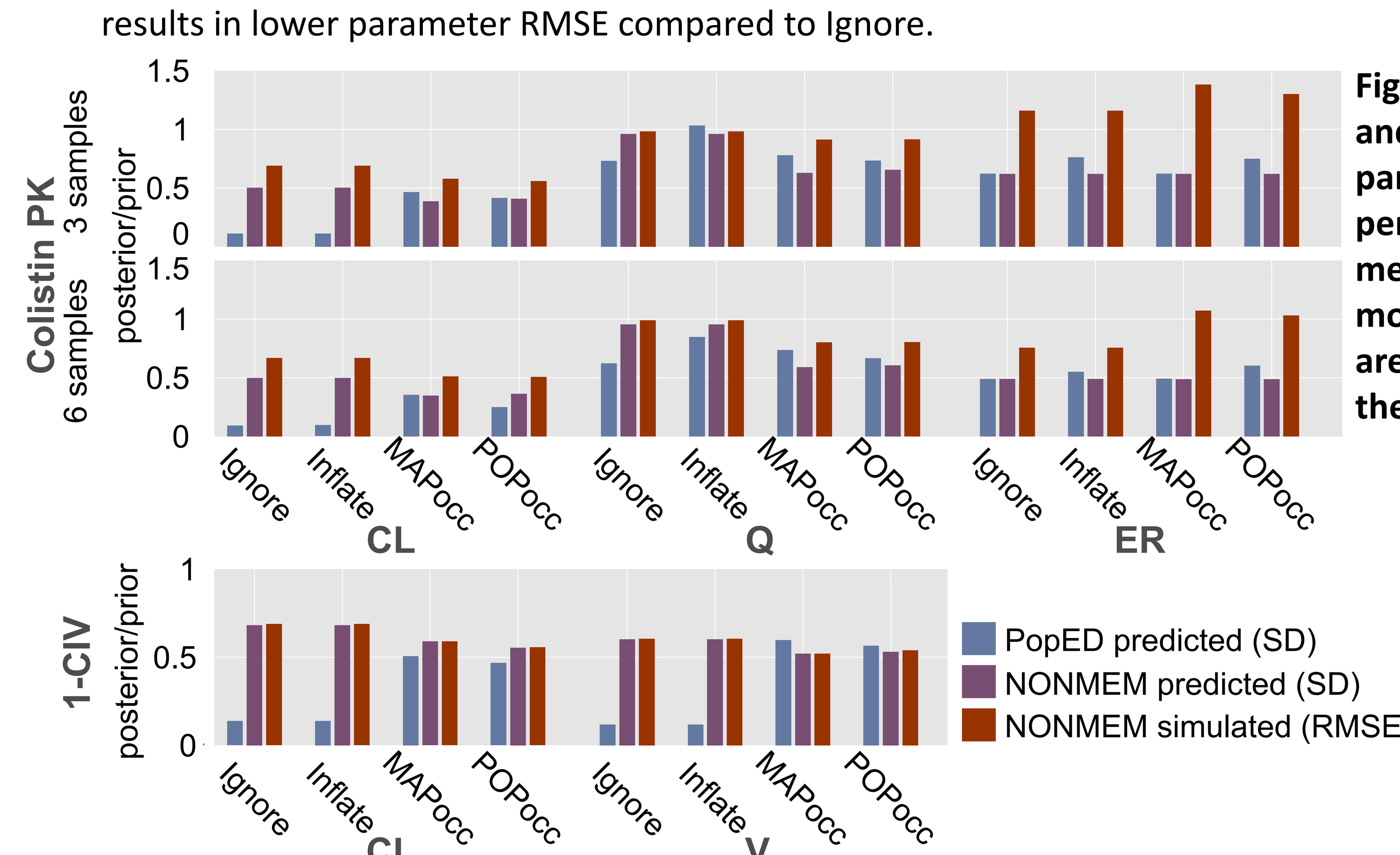

Figure 3. Predicted and simulated parameter precision per parameter and method for the test models. The values are normalized to the prior IIV SD.

Run times

Compared to Ignore one FIM evaluation takes 1, 2 and 40 times longer for methods Inflate, MAP_{occ} and POP_{occ} respectively for Colistin 3-samp. For 1-CIV the corresponding numbers are 1, 5 and 47 times longer respectively. (Figure 4)

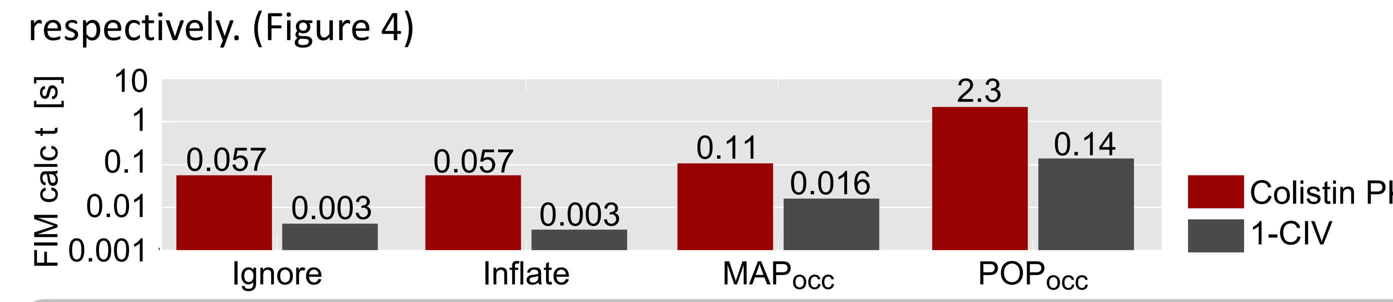

Figure 4. Runtime on a 2.7 GHz intel i7 machine for one FIM calculation.

Conclusions

- Three novel methods to include IOV in OD for MAP individual parameter estimation were evaluated.
- Omission of IOV from the FIM_{MAP} was detrimental to the design performance (EBE RMSE) and provided overly optimistic PopED SD predictions.
- MAP_{occ} and POP_{occ} minimized the IOV contribution to the IIV EBE estimate by concentrating samples to the first occasion for Colistin PK . For 1-CIV the ability to discriminate between IIV and IOV EBE:s was maximized by sampling all occasions.
- In the investigated cases POP_{occ} was much slower than MAP_{occ}, however this could change if the number of occasions and/or occasion effects were to increase.
- **Based on EBE RMSE as well as run times we would recommend method MAP_{occ} for individual OD with models including IOV.**

References

1. Karlsson, M.O. and L.B. Sheiner, *The importance of modeling interoccasion variability in population pharmacokinetic analyses.* Journal of Pharmacokinetics and Biopharmaceutics, 1993. **21**(6): p. 735-750
2. Mohamed, A.F., et al., *Application of a Loading Dose of Colistin Methanesulphonate (CMS) in Critically Ill Patients: Population Pharmacokinetics, Protein Binding and Prediction of Bacterial Kill.* Antimicrobial Agents and Chemotherapy, 2012.
3. Hennig, S., et al., *Application of the Optimal Design Approach to Improve a Pretransplant Drug Dose Finding Design for Ciclosporin.* The Journal of Clinical Pharmacology, 2012. **52**(3): p. 347-360.
4. Merlé, Y. and F. Mentré, *Bayesian design criteria: Computation, comparison, and application to a pharmacokinetic and a pharmacodynamic model.* Journal of Pharmacokinetics and Pharmacodynamics, 1995. **23**(1): p. 101-125.
5. Nyberg, J., et al., *PopED: An extended, parallelized, nonlinear mixed effects models optimal design tool.* Computer Methods and Programs in Biomedicine, 2012. **108**(2): p. 789-805

Acknowledgments

This work was sponsored by the Swedish Foundation for Strategic Research (SSF)