Evaluation of Optimal Sampling Designs using POPT and NONMEM

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ABSTRACT:

OBJECTIVE: Evaluate accuracy and precision of population parameter estimates, and accuracy of individual parameter estimates, obtained by NONMEM from POPT based sampling designs.

METHODS: Used POPT to obtain pragmatically constrained optimal sampling times for an oral linear 2-compartment model. Used NONMEM to obtain population and individual parameter estimates for data simulated from scenarios with and without IOV in population parameters, randomly perturbed sampling times, and sampling time recording errors.

RESULTS: In general, precision of NONMEM population parameter estimates were similar to standard error (SE) obtained from POPT, and bias was small. Individual estimates were good for clearance.

CONCLUSION: POPT provides a good means of screening and selecting a sampling design. However, simulations are recommended to confirm the adequacy of the selected design with respect to accuracy of individual parameter estimates, and robustness with respect to IOV and sampling time recording errors.

INTRODUCTION

- POPT is a set of MATLAB programs that provide optimal sampling times with respect to reducing uncertainty in population model parameter estimates
- POPT facilitates sparse sampling design by
  - Identifying sampling times that maximize information (minimize uncertainty) on population parameters
  - Providing estimates of uncertainty in population parameter estimates for a specified design
- POPT estimates of optimal sampling times and parameter uncertainty are based on D-optimality criteria applied to the Population Fisher Information Matrix (PFIM)
- However, POPT does not
  - Provide estimates of bias
  - Provide estimates of uncertainty in maximum a-posteriori (MAP) Bayesian individual parameter estimates, which are important for exposure-response analysis
  - Account for inter-occasion variability (IOV) in model parameters
  - Account for errors in recording sampling times

OBJECTIVES

- Evaluate accuracy of POPT estimates of precision in population parameters (measured by SE)
- Evaluate accuracy in population parameter estimates (measured by bias)
- Evaluate impact of IOV in model parameters and errors in recording sampling time on SE and bias
- Evaluate accuracy of individual parameter estimates (measured by MAE)

METHODS

Prior Information: Study Design and Sampling Constraints

- Study treatment: Oral doses of 100 mg QD, for 8 weeks
- Sampling design constraints:
  - Less sparse: 12 samples for drug concentration (4 samples within 8 hours after previous dose on 2 occasions, and 4 troughs)
  - More sparse: 5 samples for drug concentration (1 sample within 2 hours after previous dose on 1 occasion, and 4 troughs)
- Model: linear, 2-compartment model with 1st order absorption

METHODS (cont'd)

Table 1: Population PK Parameter Values

Parameter [Units] Fixed Effects	Value	Parameter [Units] Random-Effects[a]	Value [%]	Parameter [Units] Residual Error	Value [%]
CL_{TV} [L/h]	10	P_{var} [b]	0.25 (50)	σ^2 Proportional	20
VC_{TV} [L]	30	KA_{var}	0.49 (70)	σ^2 Additive [ng/mL]	10
Q_{TV} [L/h]	8	$(P1:P2)_{covar}$ [c]	0.125 (0.5)		
VP_{TV} [L]	80				
KA_{TV} [1/h]	1.5				

[a] Random Effects parameters estimates are shown as variance (CV%) for diagonal elements and covariance (correlation) for off-diagonal elements
[b] Variance of P, P: CL, VC, Q, and VP
[c] Covariance of P1 and P2, P1 and P2: CL, VC, Q, and VP, but P1 and P2 are different

- Selected optimal sampling design with POPT (subject to pragmatic design constraints) and obtained POPT estimates of SE
- Simulated drug concentrations for each of following 5 scenarios (500 simulated trials each) :

Table 2: Description of Simulation Scenarios

Scenarios	# of Subj	Sampling Times	Remarks
Balanced	200	12 samples (incl. 4 troughs)	Less sparse schedule
Unbalanced	50	5 samples (incl. 4 troughs)	Less sparse schedule
	150	8 samples + 4 troughs	More sparse schedule
Unbalanced + IOV	50	1 sample + troughs	20% IOV on relative bioavailability (F_R)
	150	8 samples + 4 troughs	
Unbalanced + Random Sampling Times	50	1 sample + troughs	Non-troughs: up to ±0.25 hr window Trough: ±1 hr window
	150	8 samples + 4 troughs	
Unbalanced + Random Sampling Times + Recording Error	50	1 sample + troughs	Non-troughs: up to ±0.25 hr window Trough: ±1 hr window Recording times: nominal sampling times
	150	8 samples + 4 troughs	

- Obtained NONMEM estimates of population and individual parameters using first-order conditional method with interaction (FOCEI) for each simulated trial
- Calculated bias and precision for population parameters, and mean absolute error (MAE) of individual parameters for each scenario

$$Bias\% = 100\frac{\frac{1}{N}\sum_{j=1}^{N} Estimated_j\text{-}Actual}{Actual}$$

$$Precision\% = 100\frac{\sqrt{\frac{1}{N-1}\sum_{j=1}^{N}\left(Estimated_j\text{-}Actual\right)^2}}{Actual}$$

$$MAE_j\% = \frac{100}{M}\sum_{i=1}^{M}\frac{\left|Estimated_{i,j}\text{-}Actual_{i,j}\right|}{Actual_{i,j}}$$

NOTE: *M* = # of subjects/simulated trial; *N* = # of simulated trials/scenario

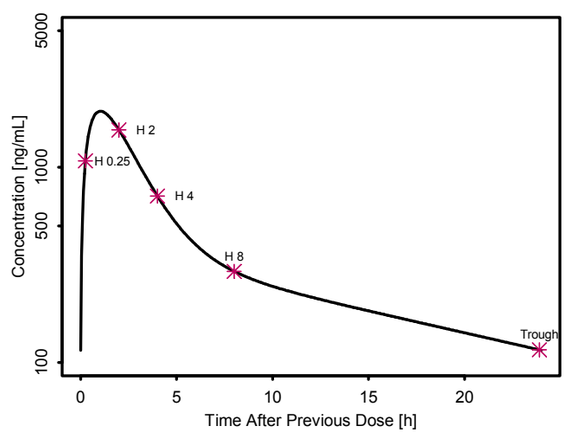
RESULTS

Table 3: Optimal Sampling Times [h post-dose]

POPT	0.14	1.92	4	7.55	23.9
Constrained (Pragmatic)	0.25[a]	2	4	8	23.9[b]

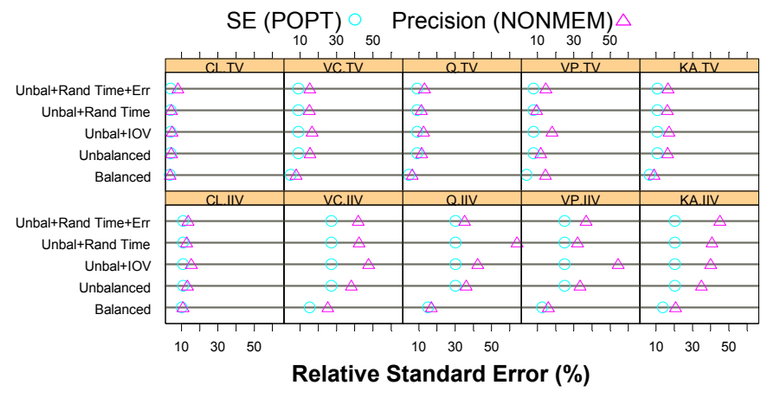
[a] sample was also taken for the more sparse patients
[b] fixed sampling time

Figure 1: Constrained (Pragmatic) Optimal Sampling Times within Dosing Interval



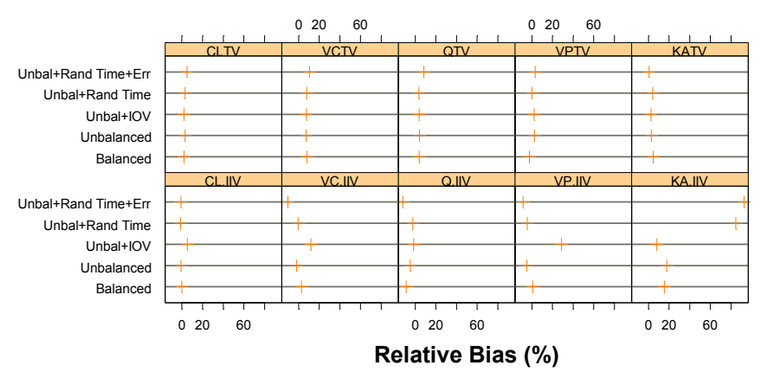
RESULTS (cont'd)

Figure 2: Evaluation of Uncertainty in Population Parameters Determined by POPT and NONMEM



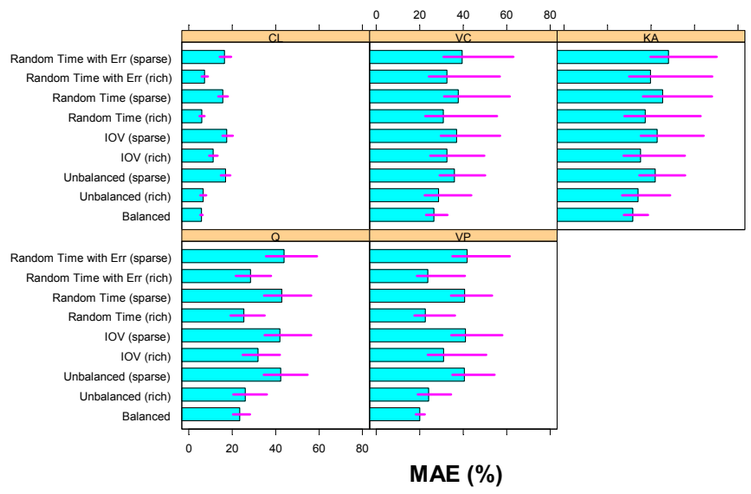
POPT estimates of SE for all population typical value (TV) parameters and IIV of CL are similar to the precision of NONMEM estimates. POPT estimates of SE for IIV of VC, Q, VP and KA are smaller than the precision of NONMEM estimates.

Figure 3: Evaluation of Accuracy in Population Parameters Estimated by NONMEM



Small to negligible (<20%) bias for all population parameters except IIV of VP (IOV scenario) and KA (Random Sampling Time and Random Sampling Time with Recording Error scenarios).

Figure 4. Evaluation of Accuracy in Individual Parameter Estimates



- MAE of CL (individual estimates) was less than 20% for all scenarios and smaller than the other parameters.
- MAEs of all parameters from unbalanced scenarios were smaller for the richly sampled subjects relative to that of the sparsely sampled subjects.

CONCLUSION

- POPT determined optimal designs and resulted in population parameter estimates that had small bias (in general)
- POPT SE estimates were in good agreement with precision obtained with NOMEM for the fixed effect parameters, POPT SE estimates for random effect parameters were overly optimistic for some scenarios and parameters
- Clinical trial simulation is useful for
  - Investigating the effect of factors not accounted for by POPT (such as IOV, error in recording sampling time)
  - Evaluating accuracy of individual parameter estimates for further exposure-response modeling

ACKNOWLEDGEMENT
Stephen Duffull for providing POPT and User's Manual
Website:
http://www.winpopt.com/files/POPT_Installation_and_User_Guide.pdf