The OFVPPC: A simulation objective function based diagnostic

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Introduction and Objectives

Clinical relevant conclusions are drawn from model based analysis that aims to quantify mechanisms of the system under study. Ability to assess the model adequacy through appropriate diagnostics is crucial in pharmacometrics.

Using the principles of a posterior predictive check [1] we suggest a simulation-based model diagnostic, the OFVPPC, which relies on the information content present in the objective function value (OFV) to detect model misspecifications, outliers and estimation method limits.

Methods

From final model estimates 1000 stochastic simulations and estimations (SSE) implemented in PsN [2] are performed in NONMEM [3], with a full estimation or an evaluation (MAXEVAL=0, a.k.a. MAX=0) of the model. The population (obsPOFV) and individual OFVs (obsIOFV) based on observed data are compared to the corresponding distributions of OFVs based on simulated data (simPOFV and simIOFV). Potential obsIOFV outliers are identified in relation to the corresponding simIOFV distribution and the distances for each obsIOFV from its corresponding simIOFV distribution. In particular distances are defined as the absolute value of the obsIOFV deviation from the simIOFV mean divided by the simIOFV standard deviation. To support the final model decision also IOFV NPDE [4] are calculated.

DATA

The technique was tested on simulated and real data (*Table I-II*) exploring model misspecification due to the approximation of the model given the estimation method and/or a misspecification of the structural and stochastic model components:

Table I. Main features of the simulated data used

Simulated data	*N° subjects*	*N° samples*	*Hypothesis tested*
1 parameter model	100	500	*Estimation methods*
1 cpt model	1000	11000	*Stochastic misspecification*
1 cpt model with alag	1000	11000	*Structural misspecification*
Moxonidine sim	74	1022	*Individual outlying data*

Table II. Main features of the real data used

Real data	*N° subjects*	*N° samples*	*Description*
Moxonidine [5]	74	1022	*1 cpt with 1st order absorption pk model*
Prazosin [6]	64	1061	*1 cpt with 1st order absorption pk model*

Results

SIMULATED DATA

The *1 parameter model* is used to show the *underperformance of the FO method* particularly with the increase of the nonlinearity achieved by shifting Ω from 0.1 to 0.5 and 2 (*Figure 1*).

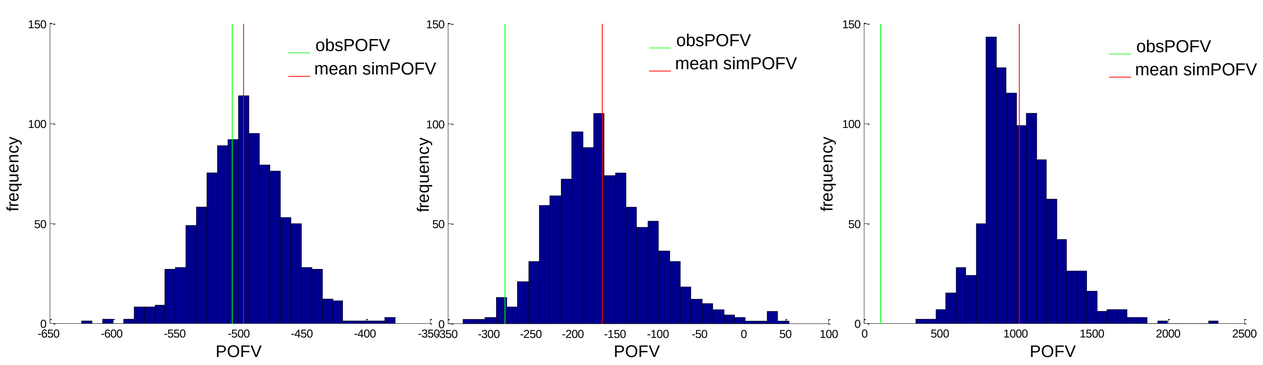

Figure 1. **1 parameter model with increasing nonlinearity and consequently misspecification of FO in the POFV**

The same model was used to show that on average the drop of simPOFV (Delta) with MAX=9999 and simPOFV with MAX=0 is close to the degrees of freedom (dof) introduced by the population parameters (*Figure 2*). This relation can be blurred by local minima so we suggest to use the option MCETA together with MAX=0 (*Figure 3*).

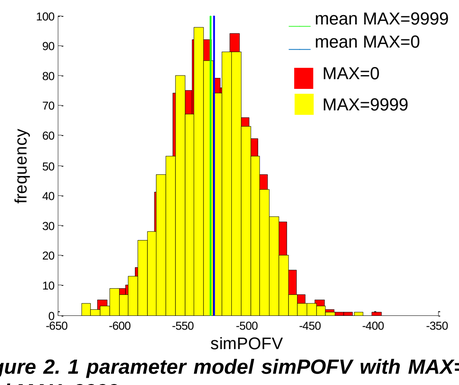

Figure 2. 1 parameter model simPOFV with MAX=0 and MAX=9999

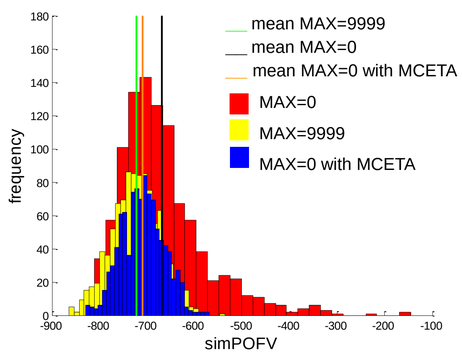

Figure 3. Moxonidine model simPOFV with MAX=0, MAX=9999 and MAX=0 with MCETA

	Mean(simPOFV)
MAX=9999	-529.30
MAX=0	-526.28
Delta	3.02
Expected dof	3.00

	Mean(simPOFV)		*Mean(simPOFV)*
MAX=9999	-724.85	MAX=9999	-724.85
MAX=0	-669.31	MAX=0 with MCETA	-713.84
Delta	55.54	Delta	11.00
Expected dof	12.00	Expected dof	12.00

The *1 compartment model* was used to test a misspecification on a *stochastic model component*: the correlation term in the Ω matrix is deleted (*Figure 4*).

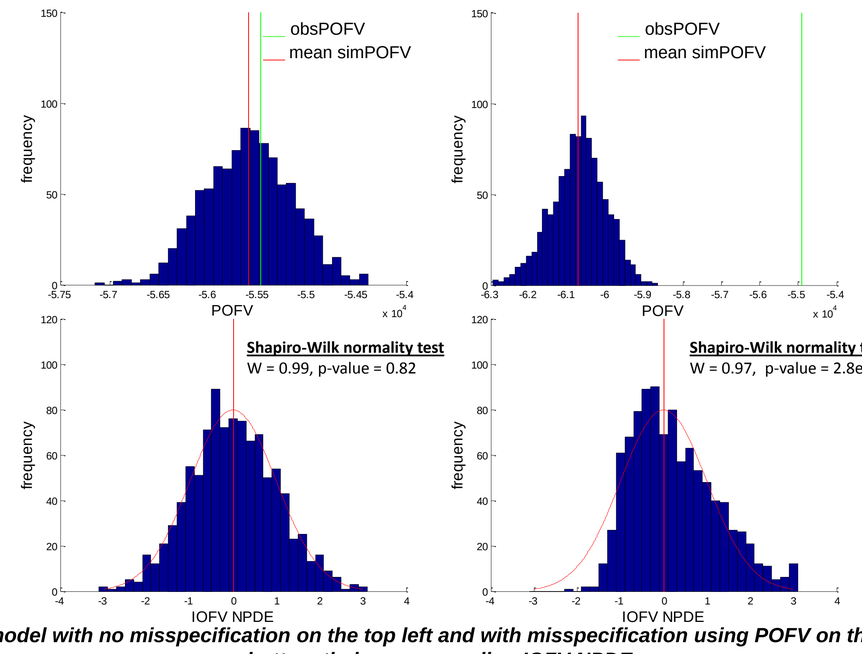

Figure 4. 1 cpt model with no misspecification on the top left and with misspecification using POFV on the top right. On the bottom their corresponding IOFV NPDE.

The *1 cpt model with alag* was used to test a misspecification on *the structural level of the model* by using instead a 1 cpt model without alag (*Figure 5*).

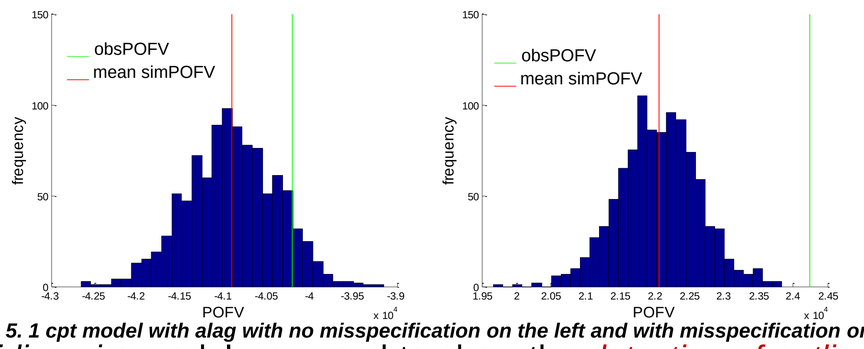

Figure 5. 1 cpt model with alag with no misspecification on the left and with misspecification on the right

The *moxonidine sim* model was used to show the *detection of outliers*. All the five outliers introduced were detected using the simIOFV distribution (*Figure 6*) and the distances (*Table III*).

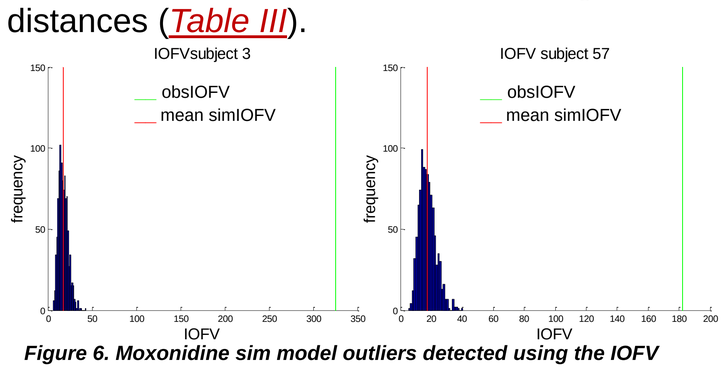

Figure 6. Moxonidine sim model outliers detected using the IOFV

Table III. Moxonidine sim biggest distances

Ranking	*Biggest distances*	*Subject id*
1	57.24	3
2	30.99	57
3	29.41	7
4	14.49	25
5	11.20	42
6	2.65	40
7	2.62	52
8	2.54	35

REAL DATA

The models have the obsPOFV inside the simPOFV distribution. For prazosin no individual outliers were detected whereas 5 outliers were detected for moxonidine (*Figures 7-8*).

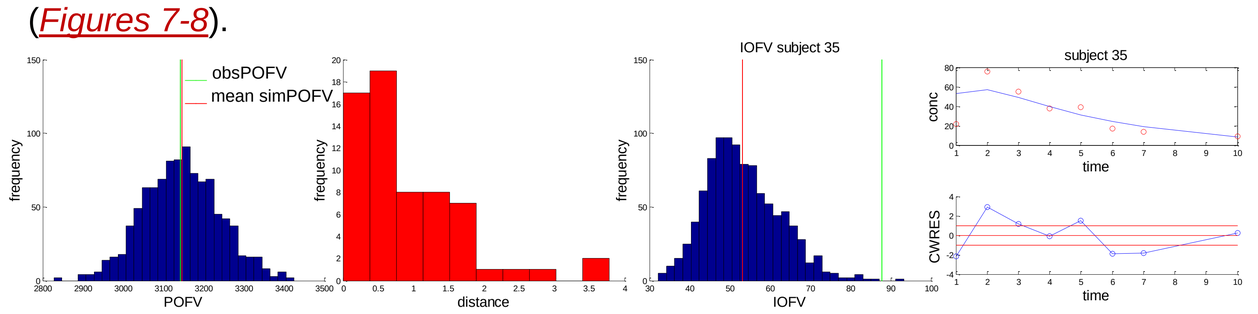

Figure 7. Prazosin model: from the left the POFV graph, the individual distances and the IOFV graph with its corresponding CWRES and fit of the subject with biggest distance.

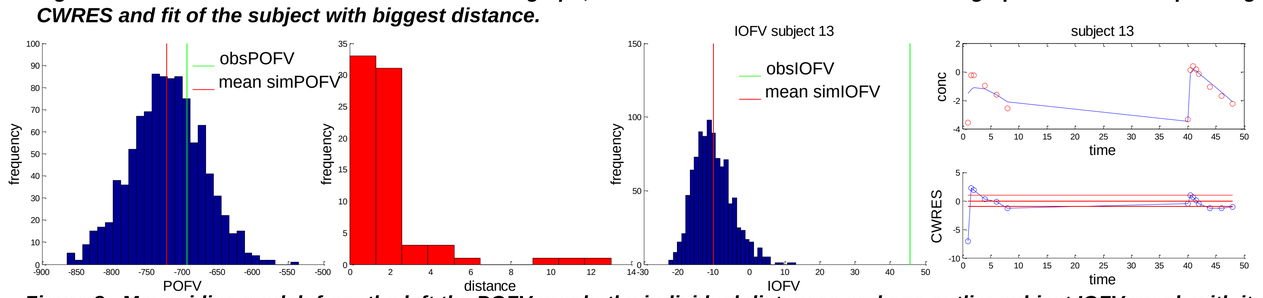

Figure 8. Moxonidine model: from the left the POFV graph, the individual distances and one outlier subject IOFV graph with its corresponding CWRES and fit.

Discussion and Conclusions

The OFV information, a sensitive measure that sums up the model fit, was exploited to build a simulation-based diagnostic tool to be used during model building and for detection of outliers. The OFVPPC is an overall method with potential to identify model misspecifications, but not always informative concerning model aspect needing improvement. Indication of structural and/or stochastic model misspecification is evident when obsPOFV is higher than simPOFV distribution and shortcoming of estimation method is evident as a lower obsPOFV compared to the simPOFV distribution. Individuals with data not well-described by the model are identified from obsIOFV being higher than corresponding simIOFV distribution.

References

[1] Y Yano et al. J Pharmacokinet Pharmacodyn, 28(2):171-92, Apr 2001.

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[6] M O Karlsson et al. J Pharmacokinet Biopharm, 21(6): 735-750, Dec 1993.