

Objective

- Visual predictive checks (VPCs) are standard model diagnostic tools, but they do not account for multimodal parameter distributions in mixture models.
- Present VPCs of mixture subpopulations are done by stratification based on the most likely subpopulation for an individual (MIXEST) as if it was a covariate. As MIXEST is not a covariate, but estimated with uncertainty from the data, this is suboptimal and biased.
- The aim of this project was to design VPCs for mixture models and thereby allow (i) the diagnosis of the mixture component aspects of the model, and (ii) more powerful assessment of other model components by reducing between-subpopulation variability from graphs.

Methods

- Mixture model specific VPCs were developed as a new option for the classical PsN/NONMEM vpc function: `vpc run1.mod -mix`
- As the mixture model analysis provides two types of allocation metrics, so does the VPCs implemented:

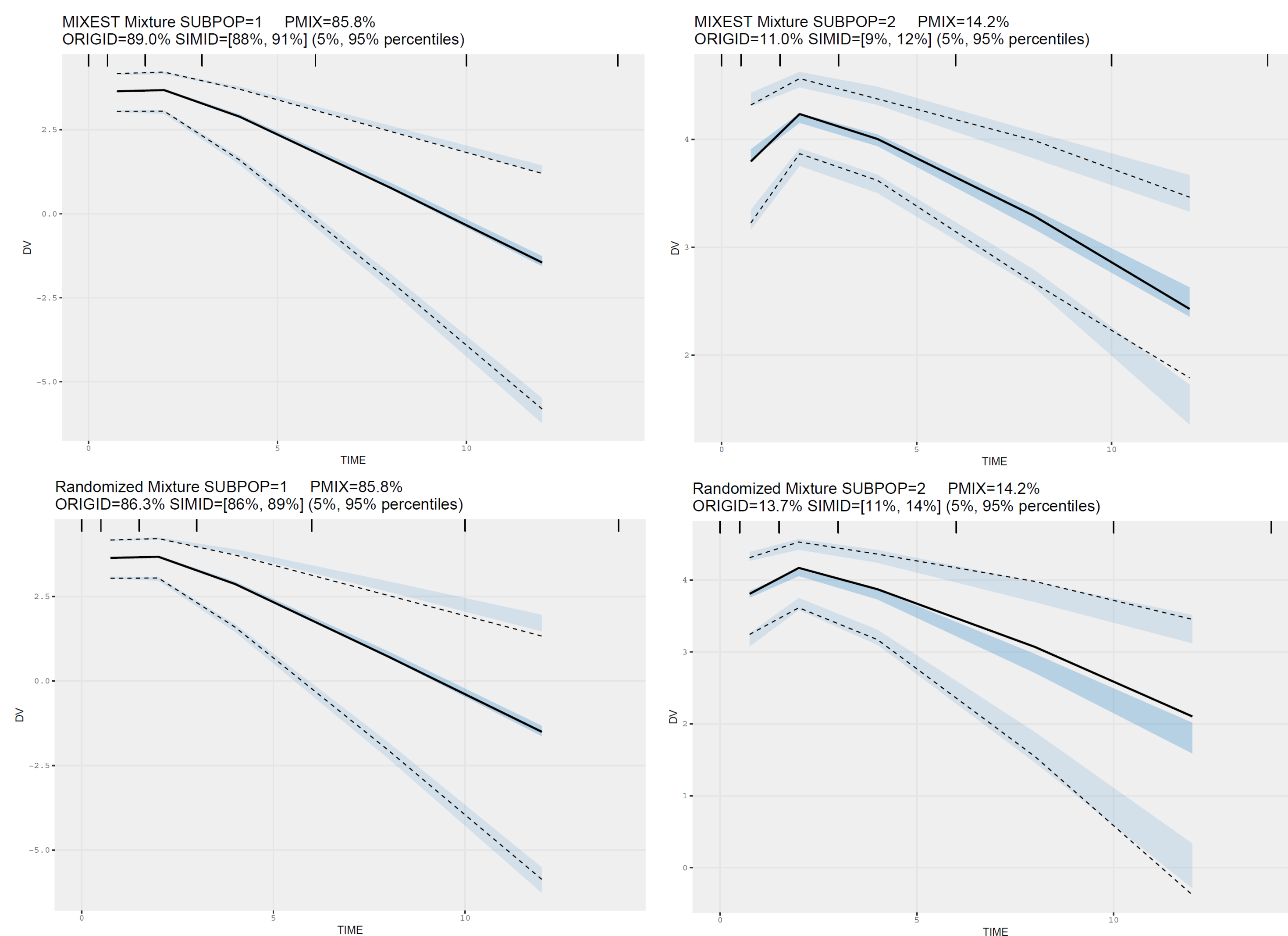
	MIXEST	PMIX
Description	Most likely subpopulation	Probability to belong to a subpopulation
Allocation strategy for the VPC	Deterministic according to the MIXEST value	Randomly according to the PMIX probability

- When the individual information is imperfect, there is a shrinkage-like bias for the MIXEST estimate towards the larger population. PMIX does not suffer such bias.
- In order to retrieve individual MIXEST and PMIX information from simulated data in the VPC, an evaluation step is necessary (MAXEVAL=0).
- Illustrative examples:
 - Simulated data with a bivariate covariate influencing CL. The covariate was replaced by a mixture model for the data analysis.
 - Real data with an irinotecan mixture model^{2,3} demonstrating 30% lower clearance of irinotecan metabolite (SN-38) in individuals with UGT1A1 homo/hetero vs wild-type genotype.

Results

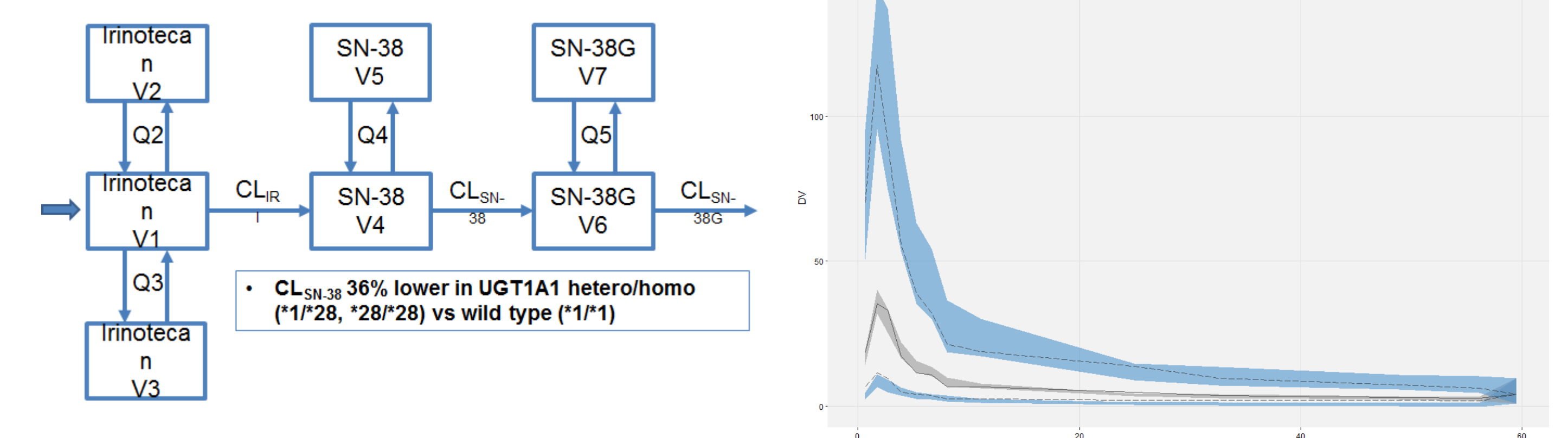
Mixture VPCs metrics: ORIGID and SIMID represent percentage of IDs allocated to each subpopulation for the original and simulated data respectively. For a good model an agreement is expected.

1. Simulated data:

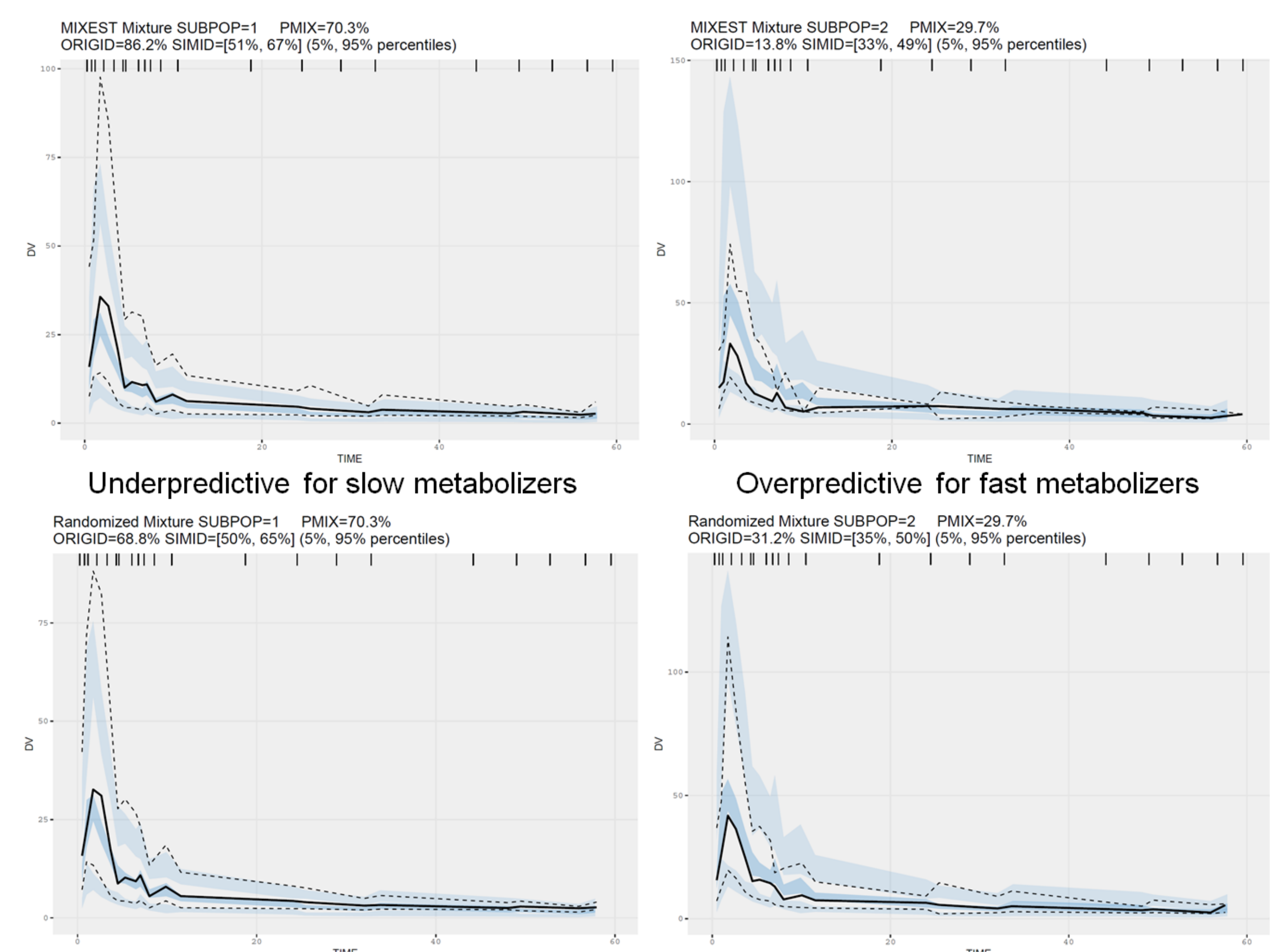


- The simulated example shows how the new implementation is allocating varying numbers of individuals to each subpopulation for each simulation.
- As opposed to treating MIXEST as a covariate, Thus, the simulation procedure mimics what is happening with real data:
 - For MIXEST, allocation is biased for both real and simulated data
 - For PMIX, allocation is unbiased for both real and simulated data

2. Real data:



Normal VPC for irinotecan mixture model^{2,3}: model misspecification not evident.



Mixture VPCs for irinotecan model: model misspecification evident.

- The irinotecan mixture model was found to be over-predictive for fast metabolizers while under-predictive in case of slow metabolizers. This misspecification was not evident from the standard normal VPCs.

Conclusions

- A graphical and statistical comparison of observations and predictions derived from the multimodal distributions in mixture models is presented.
- Partitioning of data between subpopulations can be done in two ways depending upon the underlying information (MIXEST or PMIX).
- These approaches can be a useful diagnostic tool for the development and evaluation of mixture models in the future.

1. Karlsson KC, Savic RM, Hooker AC, and Karlsson MO. Modeling Subpopulations with the \$MIXTURE Subroutine in NONMEM: Finding the Individual Probability of Belonging to a Subpopulation for the Use in Model Analysis and Improved Decision Making. AAPS J. 2009; 11(1): 148–154.

2. Jiménez BJ and Ruixo JJP. Influencia de los polimorfismos genéticos en UGT1A1, UGT1A7 y UGT1A9 sobre la farmacocinética de irinotecán, SN-38 y SN-38G. Farm Hosp. 2013; 37(2): 111-27.

3. Xie R, Mathijssen RH, Sparreboom A, Verweij J and Karlsson MO. Clinical pharmacokinetics of irinotecan and its metabolites in relation with diarrhea. Clin Pharmacol Ther. 2002; 72(3): 265-75.