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Introduction

- In PBPK simulations, the expression profiles of **drug metabolizing enzymes and transporters (DMETs)** are essential parameters in predicting the drugs' pharmacokinetics.
- Reliable PBPK model predictions of drug behaviors depend on the **accurate characterization of DMETs**.
- Due to shared regulatory mechanisms, DMET genes often demonstrate **correlated expression patterns**.
- It remains unclear which joint distribution modelling approach best captures these relationships.

Aim

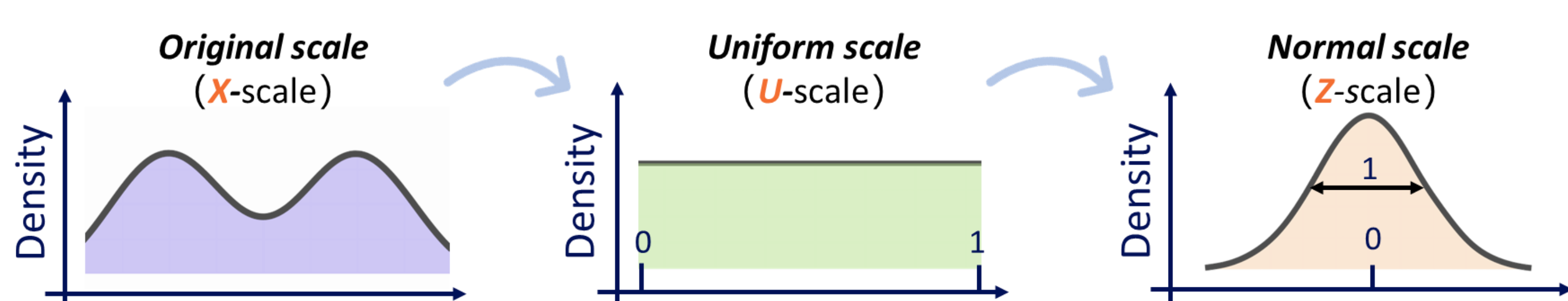
- Develop and compare joint distribution models for DMETs
- Provide recommendations on the joint distribution modelling choices
- Demonstrate the incorporation of DMETs data in a typical PBPK workflow, using *selegiline* as a case study

Methods

Data

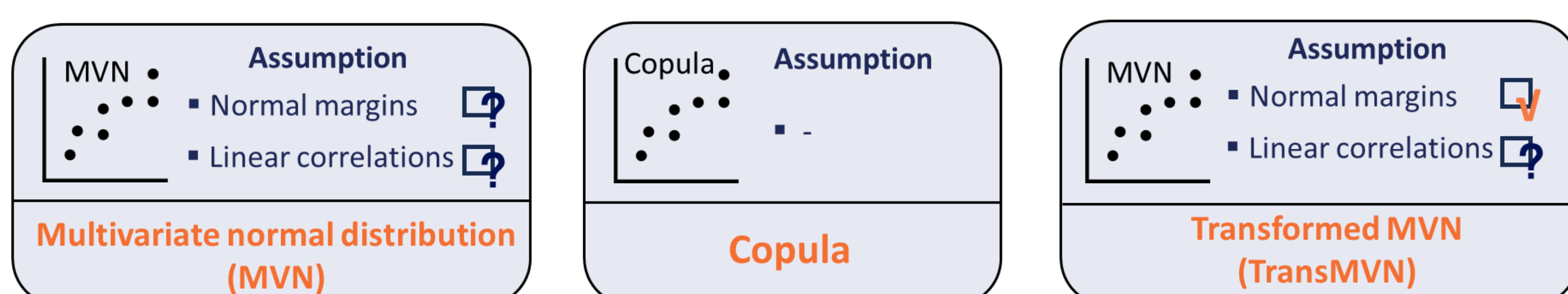
- GTEx database¹
- 226 liver samples
- Four DMET RNA-seq datasets
- Data transformation

Each DMET dataset on the original scale (**X-scale**) can be transformed into the uniform scale (**U-scale**) and the standard normal scale (**Z-scale**).



Joint distribution models

- Joint distribution models, including multivariate normal distribution (**MVN**), copula² and transformed MVN (**transMVN**), were developed using data on **X**-, **U**- and **Z**-scales, respectively.



Model comparison

- Model performance**
Joint distribution models were evaluated by comparing the virtual population generated from each model with the observed population (marginal distribution and dependency structure).
- Multivariate normal test**
Statistical tests (Mardia and Royston MVN)^{3,4} were applied to the observed data on X-scale and Z-scale to assess multivariate normality and guide model selection.
- PBPK prediction of selegiline**
Selegiline, mainly metabolized by hepatic CYP2B6 and CYP2C19 enzymes, was used as a case study to demonstrate the integration of joint distribution models into PBPK simulations and to compare their predictions of intrinsic clearance (CL_{hep}) and AUC.

Results

Characterization of DMET expression data

- TransMVN and copula could well characterize the marginal distributions (**Fig 1A**) and dependency structure (**Fig 1B**) of observed CYP gene expression data.
- Similar results were also found for UGT, ABC and SLC datasets

Copula $\approx$ TransMVN $>$ MVN

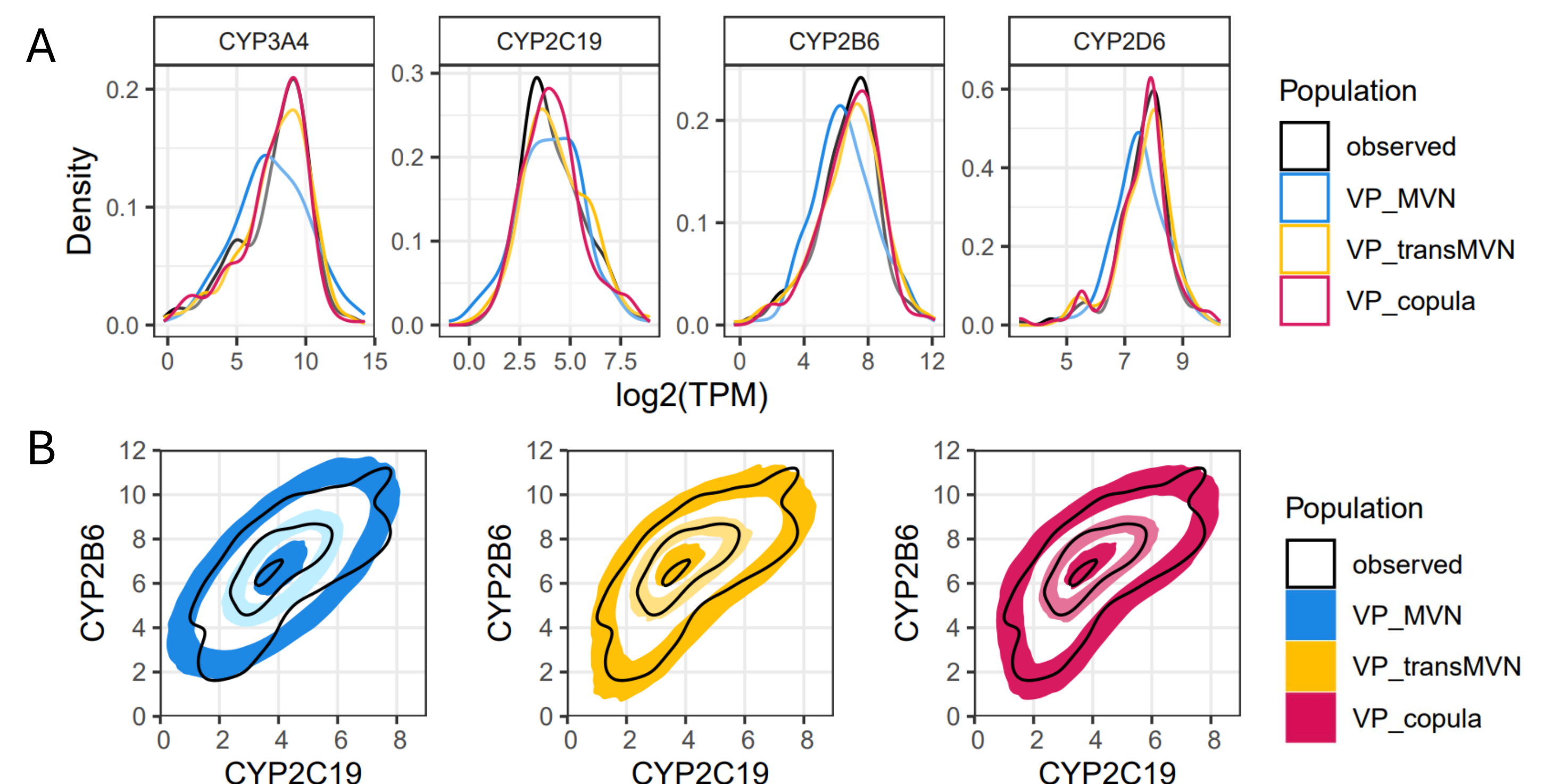


Fig 1 (A) Density curves and (B) DonutVPCs of CYP enzyme expression data from the observed population and virtual populations generated using MVN (VP_MVN), transMVN (VP_transMVN), and copula (VP_copula) models. Each VP consists of 22,600 individuals.

Decision tree for model recommendations

- Based on statistical MVN test outcomes, TransMVN and copula models were recommended across all DMET datasets (**Table 1**).

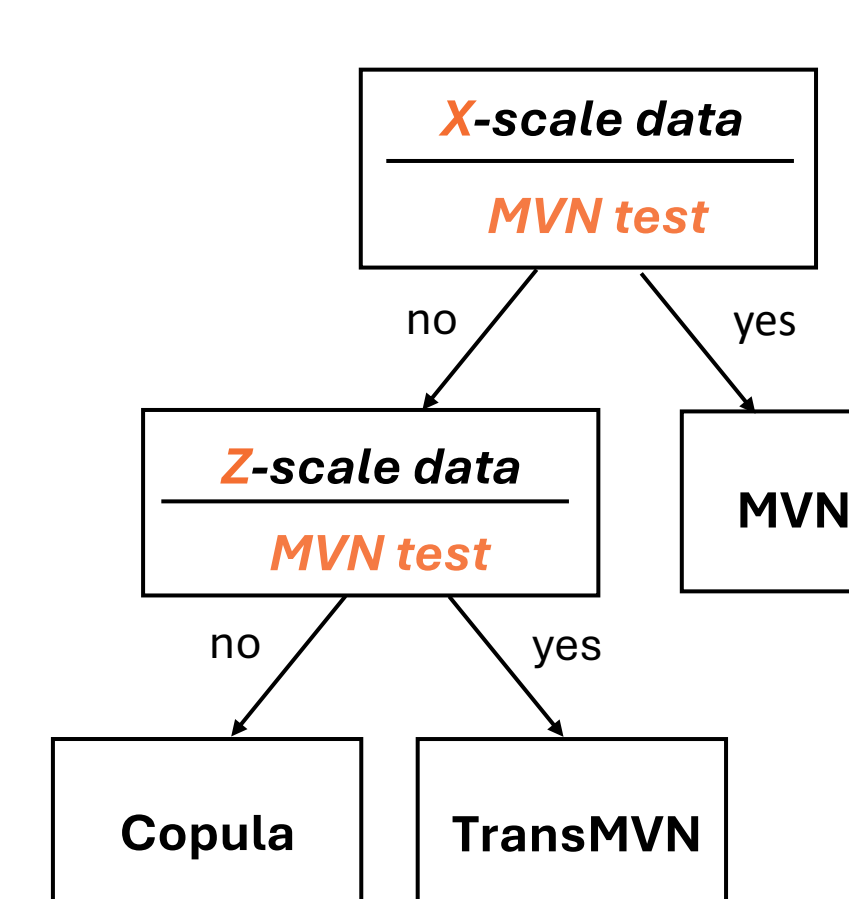


Table 1 Decision process for selecting joint distribution models for CYP, UGT, ABC, and SLC datasets.

DMET	Mardia MVN test			Royston MVN test		
	X-scale	Z-scale	Advice	X-scale	Z-scale	Advice
CYP	X	X	copula	X	✓	TransMVN
UGT	X	X	copula	X	✓	TransMVN
ABC	X	X	copula	X	✓	TransMVN
SLC	X	X	copula	X	X	copula

X: reject the MVN assumption; ✓: accept the MVN assumption

Translation into PBPK modelling framework

- PBPK predictions were obtained using simulated CYP expression data based on MVN, transMVN and copula models.

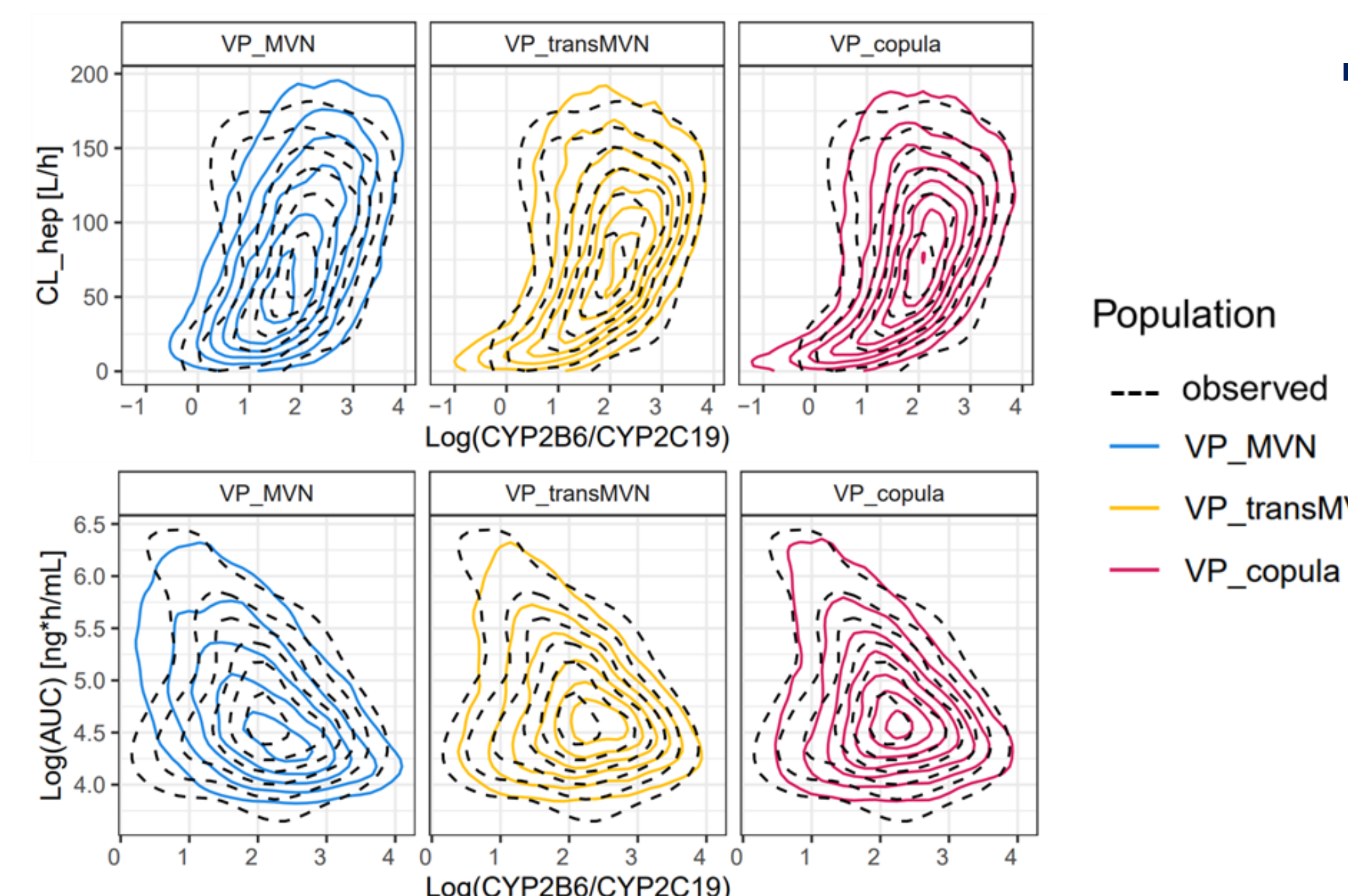


Fig 2 Density contours showing the relationships between PBPK predictions (CL_{hep}, upper; AUC, lower) and CYP enzyme expression.

- For selegiline, CYP2B6 and CYP2C19 profile simulated from MVN showed slight deviations in its relationship to PBPK predictions compared to transMVN and copula models (**Fig 2**).

Conclusions

- The transMVN method and copulas could well capture DMET expression dependencies.
- The decision tree could aid model selection but should be complemented by examining the data structure.
- Further work needs to be done based on the protein expression data to improve (virtual) DMET-based PBPK predictions.