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Impact of sampling procedure on individual pharmacokinetic parameter estimation methods

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INTRODUCTION AND OBJECTIVES

Therapeutic drug monitoring represents one of the main applications of Pharmacometrics; due to its relevance variations in sampling procedures and their effect on parameter estimations are a key factor for enabling the adequate analysis of the forthcoming data. The main aims of this project are (i) to assess the impact of sampling procedure variation on parameter estimation and (ii) to evaluate the estimation robustness of different estimation algorithms in all scenarios tested.

In this work, the objective was to apply Two-Stage Delta Global Sensibility Analysis (GSA) to select the target parameters to be estimated using the Iterative Two Stage Method (I2S) to achieve the aims of the project.

METHODOLOGY AND RESULTS

Workflow strategy

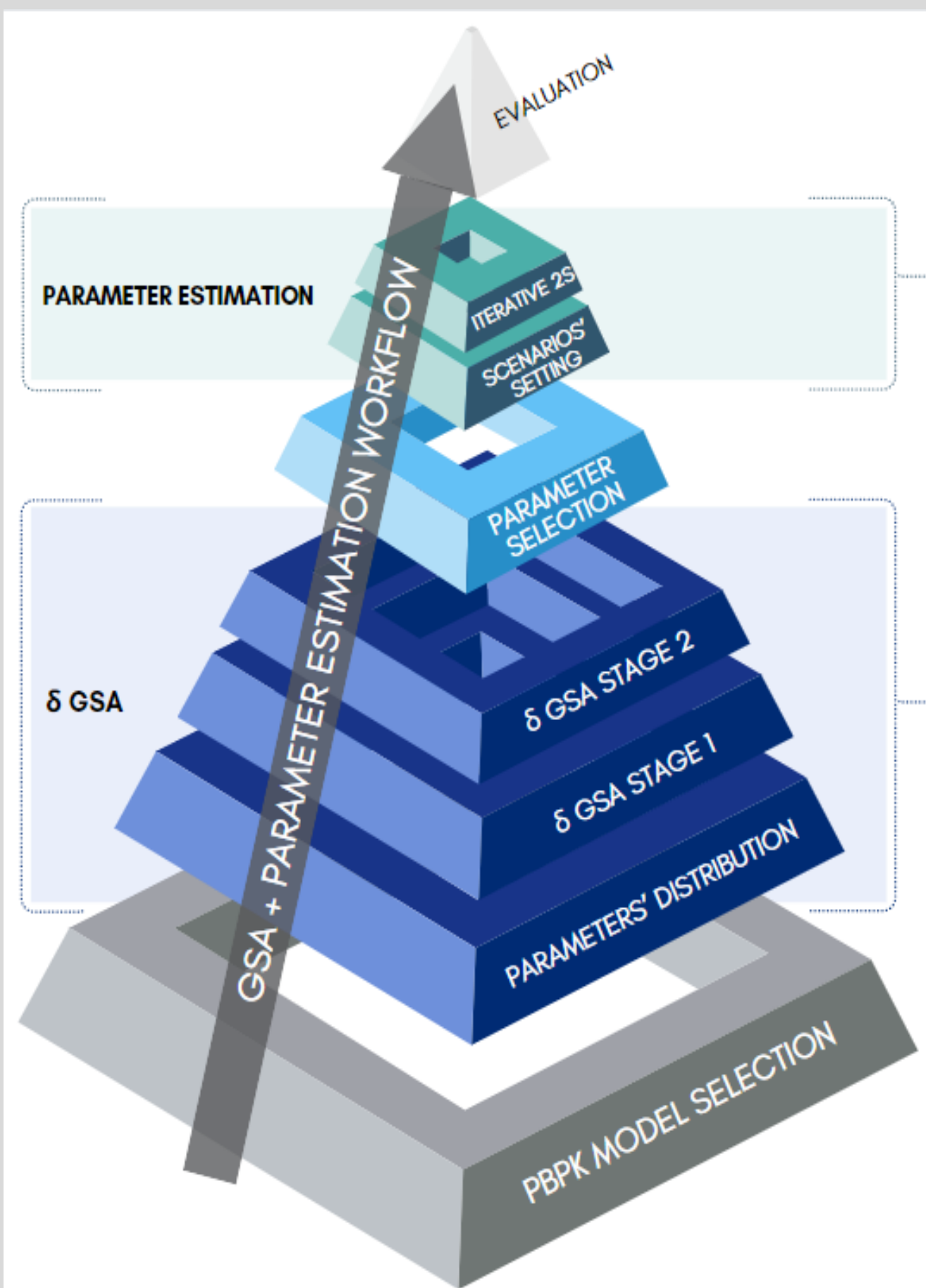


Figure 1. Strategy followed for the development of the Two-stage delta Global Sensibility Analysis [2] and the parameter estimation. For the moment, only the results until Step 4 have been obtained.

STEP 1 PBPK model and parameter selection

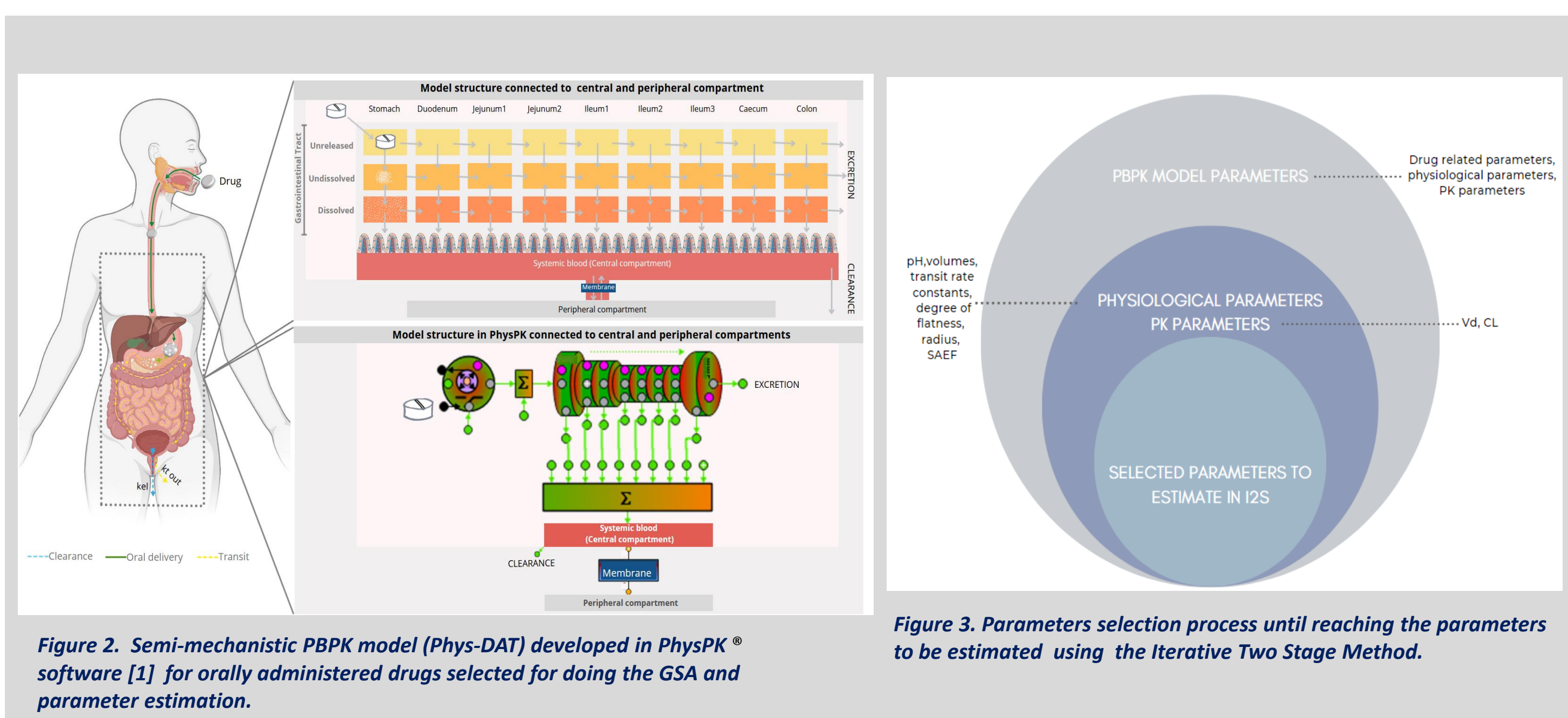


Figure 3. Parameters selection process until reaching the parameters to be estimated using the Iterative Two Stage Method.

STEP 2 Distribution of model parameters (from STEP 1)

Table 1. Distribution of model parameters selected from the PBPK model considered for the GSA.

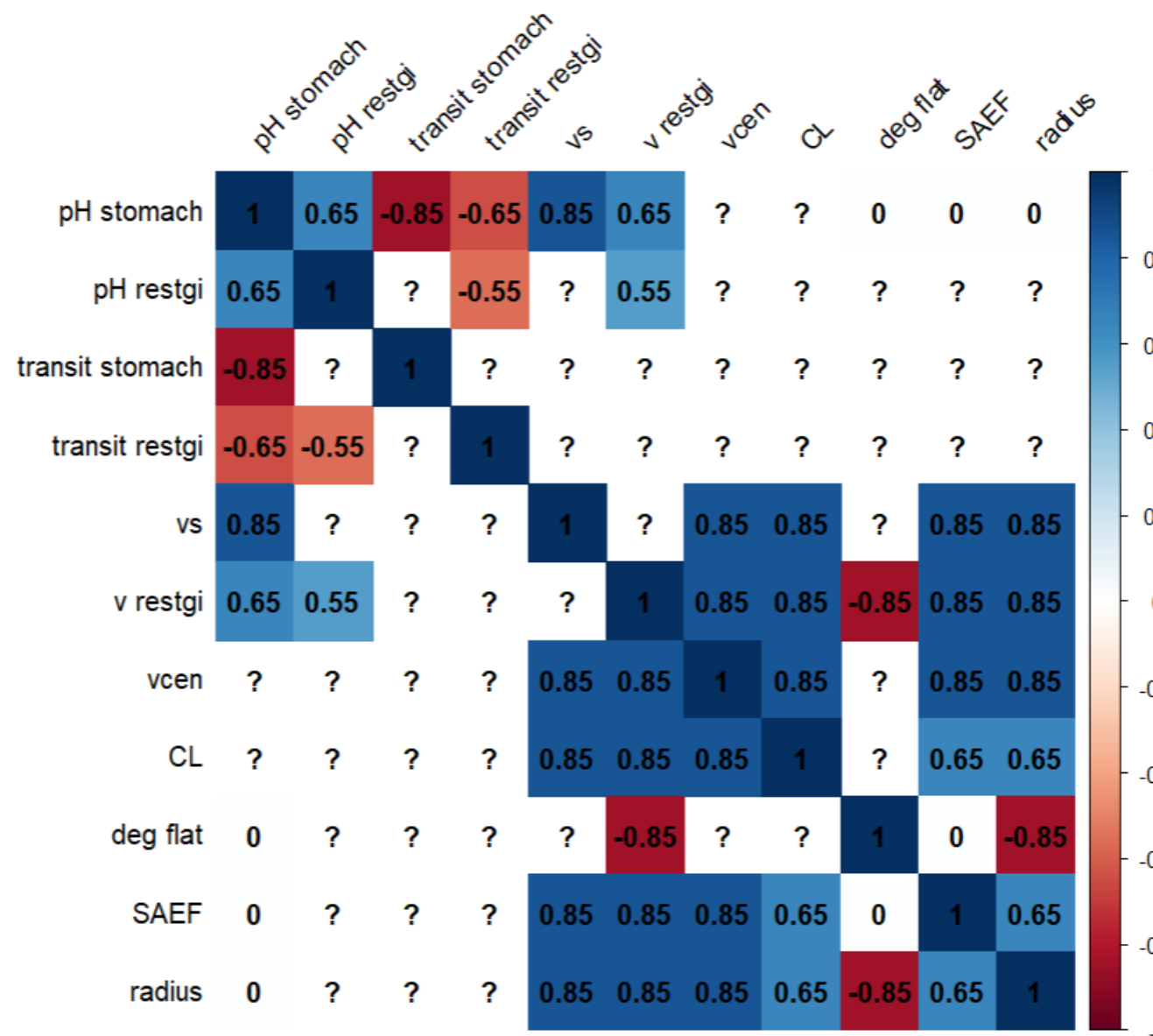
Parameters	System parameters										PK parameters	
	pH _{stomach}	v _{stomach}	transit _{stomach}	deg _{flat}	pH _{restgi}	v _{restgi}	transit _{restgi}	cs _{restgi}	radius	SAEF	CL	vcen
Units	-	mL	h	-	-	mL	h	mg/ml	cm	-	L/h	L
CV (%)	3	10	20	10	3	10	20	50	10	10	20	20
Description	Stomach pH	Stomach volume	Stomach transit	Degree of flatness	pH for the rest of GI tracts	Volume of the rest of the GI tract	Transit for the rest of the GI tract	Drug solubility for the rest of GI	Radius of the rest of GI tract	SAEF of the rest of the GI tract	Clearance	Central volume

References

- [1] Cuquerella-Gilabert M et. al; Comput Methods Programs Biomed. 2024 Jan;243:107929. doi: 10.1016/j.cmpb.2023.107929. Epub 2023 Nov 18
- [2] De Carlo A. et al; J Pharmacokinet Pharmacodyn 50, 395–409 (2023). <https://doi.org/10.1007/s10928-023-09872-w>
- [3] Carlo A. et al; Comput Methods Programs Biomed. 2023 Jun;235:107517. doi: 10.1016/j.cmpb.2023.107517. Epub 2023 Mar 31
- [4] Pasotti et al; Modelling for Synthetic Biology.2014 (45-564) ISBN 9780124115576, <https://doi.org/10.1016/B978-0-12-411557-6.00023-9>.

METHODOLOGY AND RESULTS

STEP 3 GSA stage 1



STEP 4 GSA stage 2

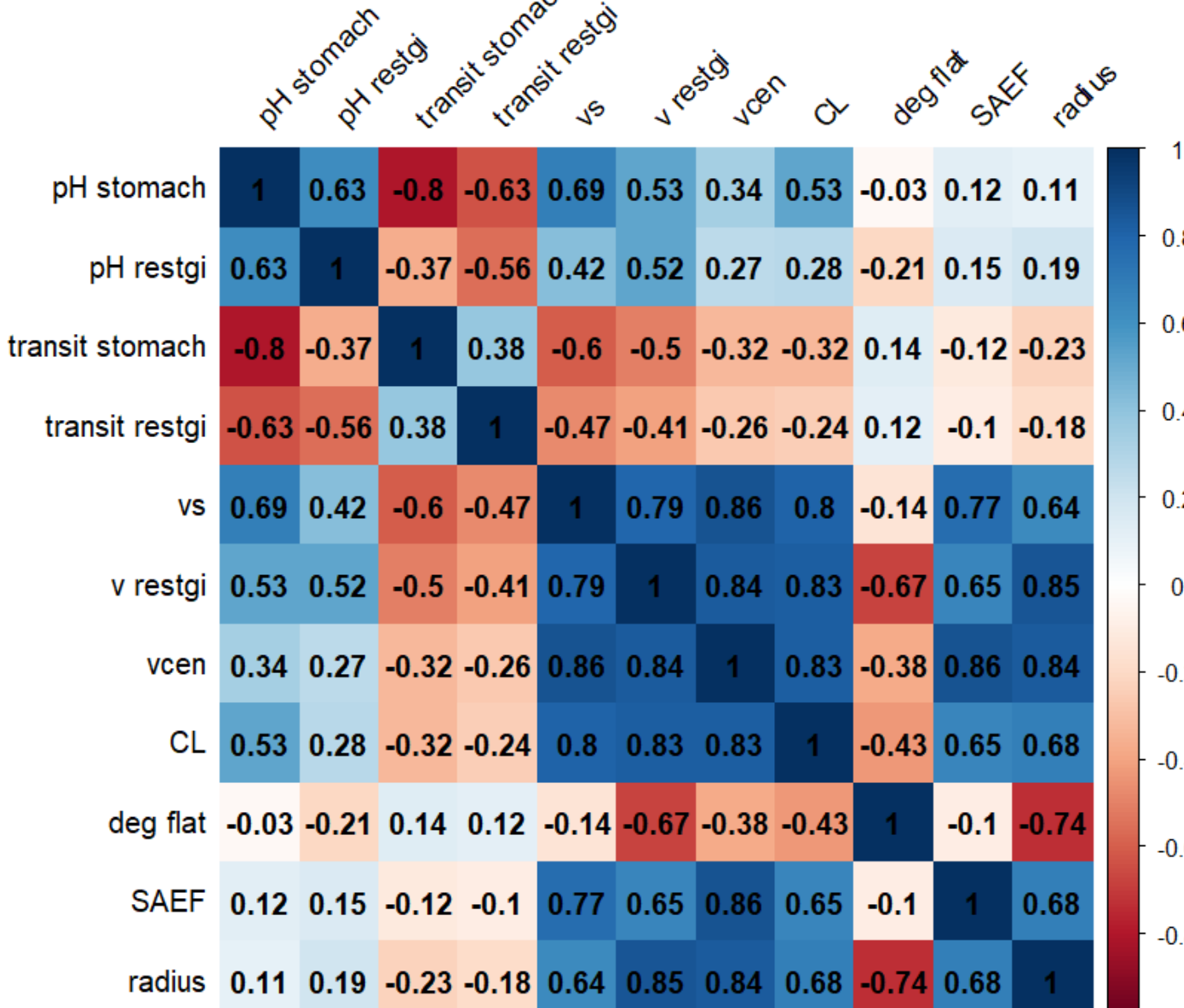


Figure 4. Correlation matrix before the estimation of unknown correlations.

Figure 5. Correlation matrix obtained after the estimation of unknown correlations with the R package mvLognCorrEst [3]

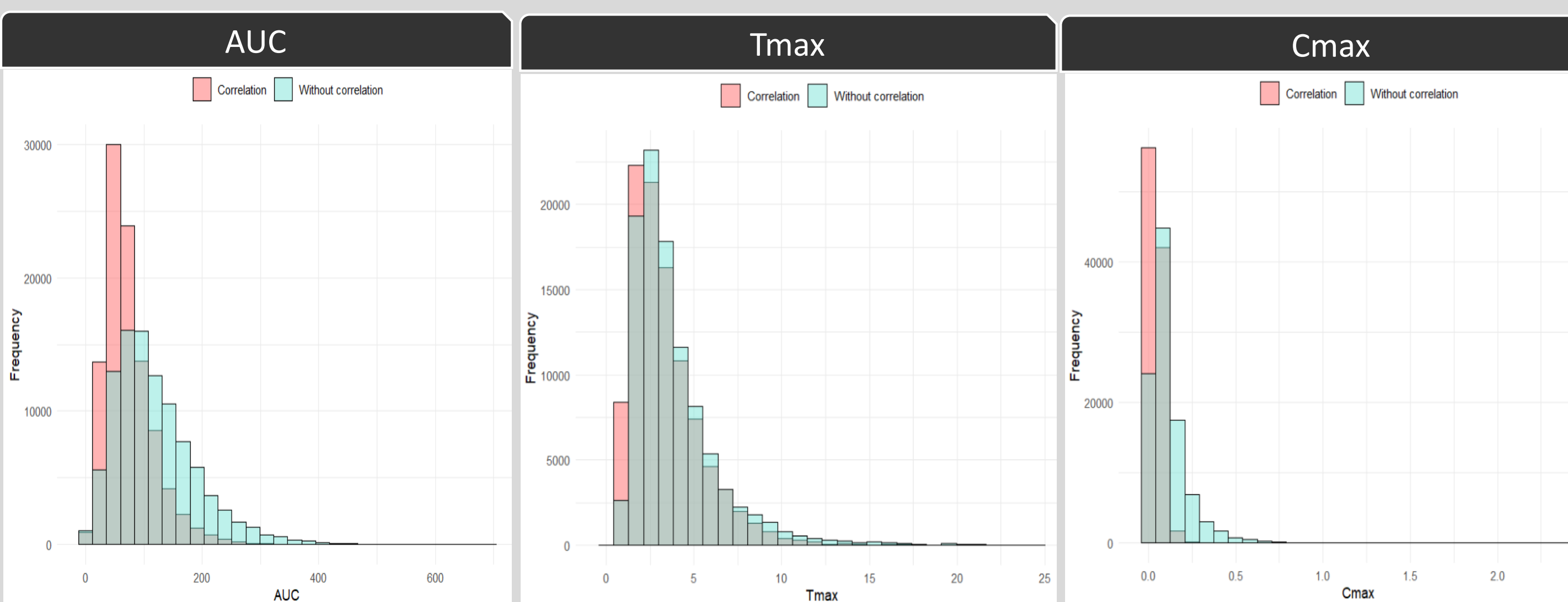


Figure 6. Histograms of AUC, Cmax and Tmax considering and ignoring correlations.

GSA results obtained for AUC, Cmax and Tmax

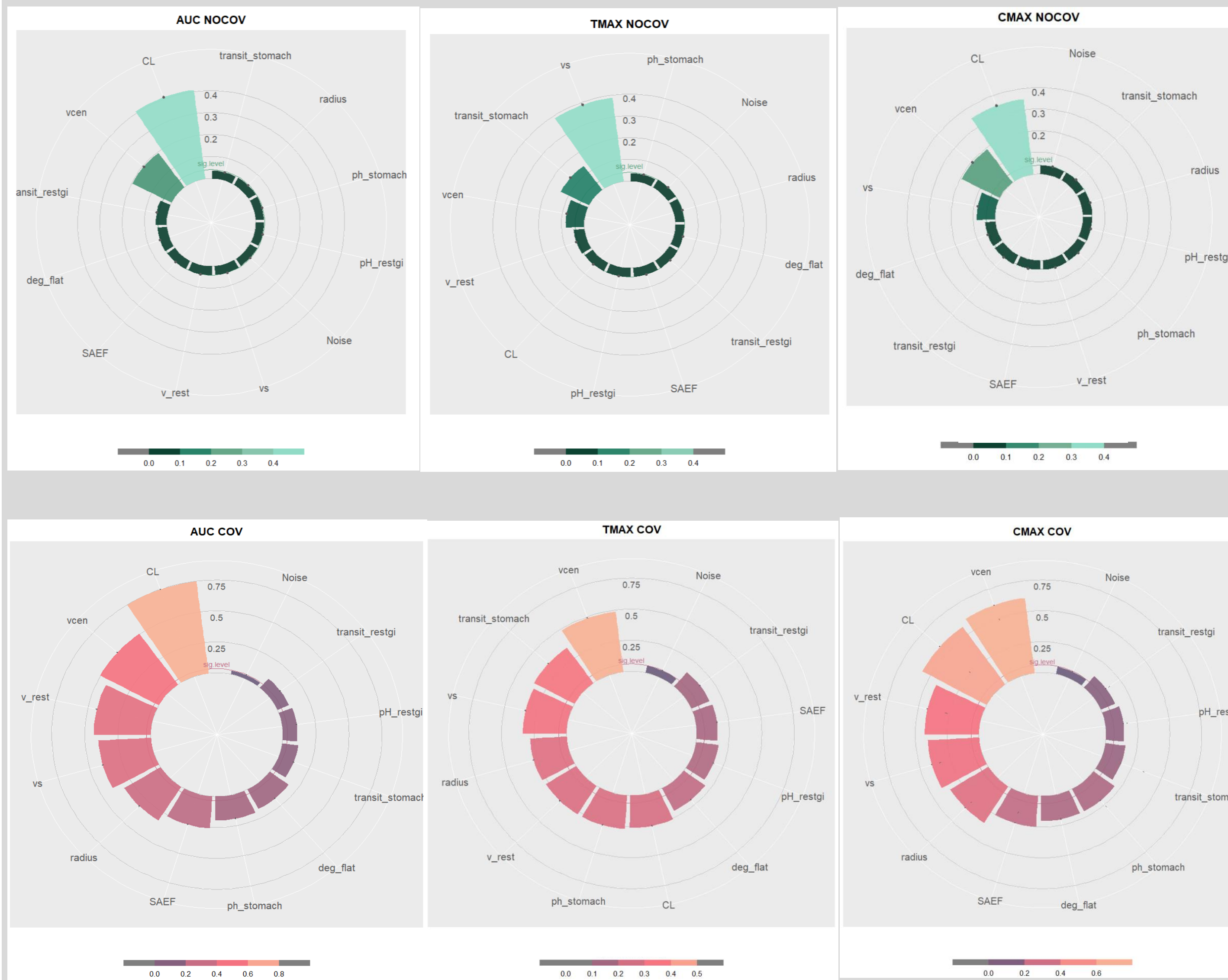


Figure 7. Results of the Two-Stages GSA on AUC, Cmax and Tmax, showing the results before and after applying the correlation matrix. "Sig. level" line refers to the significance limit.

CONCLUSIONS

- Two step delta GSA method can be a useful tool for understanding PBPK absorption models
- The most relevant parameters in the GSA were clearance, central volume and stomach volume.
- The parameters impacting the most on AUC and Cmax were clearance and central volume.
- The parameters impacting the most on Tmax were central volume, stomach transit and stomach volume.

Acknowledgements



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