Investigating Impacts of Model Parameters Correlations in Global Sensitivity Analysis: Determining the Most Influential Parameters of a Minimal PBPK Model of Midazolam

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Background

Sensitivity analysis has been widely used to identify the most influential model parameters affecting pre-specified model outputs. In local sensitivity analysis (LSA) usually parameters are scanned in one or two dimensions while keeping all the rest of model parameters fixed. However, global sensitivity analysis (GSA) allows simultaneously evaluating the relative contributions of each individual parameter to the model output variance by varying all parameters over the entire intended parameter space. Hence the sensitivity or influence of a parameter to model output in GSA is measured without fixing values of all the rest input parameters. This allows ranking the importance of parameters considering their uncertainty and influence on the variation of outputs. GSA is gaining attention in the PBPK modelling and systems biology and pharmacology [1-4]. GAS can provide information about the model structure or driving mechanisms for physiology or biological responses. We present an application of three GSA methods, namely Morris, Sobol, and extended Sobol method to a minimal-PBPK (mPBPK) model of Midazolam. The primary aim is to identify the most influential model parameters affecting the pharmacokinetic (PK) properties of interest. We also investigated the effect of ignoring correlations of model parameters on their rankings. Despite known correlations between biological and drug parameters, they are rarely considered in conduct of GSA.

Table 1, parameter values and distributions for Midazolam

Parameters	Unit	Values/Distribution
f_a	n/a	Weibull (8.86, 0.94)
k_a	1/h	Lognorm(1.05, 0.09)
Fg	n/a	Norm(0.47, 0.01)
BP	n/a	Norm(0.64, 1.05e-3)
f_u	n/a	Lognorm(-3.46, 1e-3)
K_{pliver}	n/a	Lognorm(-0.21, 9.6e-3)
A_{CYP3A4}	pmol P450	Lognorm(15.84, 0.26)
A_{CYP3A5}	pmol P450	Lognorm(15.72, 0.18)
A_{UGT1A4}	pmol UGT	Lognorm(14.92, 0.18)
$V_{m,CYP3A4}$	pmol/min/pmol of isoform	5.23
$V_{m,CYP3A5}$	pmol/min/pmol of isoform	19.7
$V_{m,CYP3A4}$	pmol/min/pmol of isoform	5.2
$V_{m,CYP3A5}$	pmol/min/pmol of isoform	4.03
$V_{m,UGT1A4}$	pmol/min/mg microsomal protein	445
$K_{m,CYP3A4}$	µM	2.16
$K_{m,CYP3A5}$	µM	4.16
$K_{m,CYP3A4}$	µM	31.8
$K_{m,CYP3A5}$	µM	34.8
$K_{m,UGT1A4}$	µM	40.3
Q_{HA}	L/h	Lognorm(3.05, 1.44e-2)
Q_{PV}	L/h	Lognorm(4.19, 1.05e-2)
BW	kg	Lognorm(4.30, 3.8e-2)
*V_{pv}	L	Norm(0.008, 6.4e-7)
V_{liver}	L	Lognorm(0.39, 2.97e-2)
V_{ss}	L/kg	Norm(0.91, 4.09e-2)
*CL_R	L/h	Norm(0.085, 4.6e-3)
K_{in}	1/h	0.2
K_{out}	1/h	0.25
V_{sac}	L/kg	0.23

*parameter was assumed to be normally distributed with 10% CV.

Methods

- Midazolam, a BCS class II drug that has been widely used in anaesthesia due to its favourable safety profile, and rapid anxiolytic effect or as preanesthetic medication for children [5, 6].
- Morris, Sobol, and extended Sobol methods were used to determine the most influential model parameters for the intended PK properties, i.e. Cmax, Tmax, and AUC, of an mPBPK model of Midazolam given orally (Figure 1).
- Morris and Sobol are GSA methods designed for models where the model parameters are not correlated [7]. Nevertheless, exSobol method is designed to handle a model with correlated model parameters [8].
- System parameters, such as body weight (BW), blood flow rate, tissue volume, tissue to plasma partition coefficient, enzyme abundance, etc., and their correlations were considered in this study (Table 1 and Figure 2).
- The influential parameters were determined using these three GSA methods independently. Subsequently, influential parameters picked up by Morris and Sobol methods were compared to those by exSobol to explore how considering correlations could affect appropriately identifying and ranking influential model parameters (Table 2).

Table 2, Ranked influential parameters for Midazolam

	C_{max}			T_{max}			AUC_{48h}		
	Morris	Sobol	exSobol	Morris	Sobol	exSobol	Morris	Sobol	exSobol
f_a	6	6	9	14			4	4	6
k_a	7	7	14	1	1	1	12		11
F_g	2	2	2	15			2	2	3
BP	8	8	11	8		7	6	6	10
f_u	9	9	12	7			5	5	
K_{pliver}	14		13	12			15		
Q_{HA}	11		8	9			13		8
Q_{PV}	10		10	6			10		9
BW	5	5	5	3	3	8	9		7
V_{pv}	13			11			16		
V_{liver}	16		7	10		6	14		5
V_{ss}	1	1	1	2	2	2	8		
CL_R	15			16			11		
A_{CYP3A4}	4	4	4	5	5	3	3	3	2
A_{CYP3A5}	3	3	3	4	4	4	1	1	1
A_{UGT1A4}	12		6	13		5	7		4

*For exSobol and Sobol, numbers with underline indicate input parameters with sensitivity index >0.01 and <0.1, i.e. parameters have moderate impact on the outputs but not significant. +For Morris screening, all input parameters were ranked based on its GI metric.

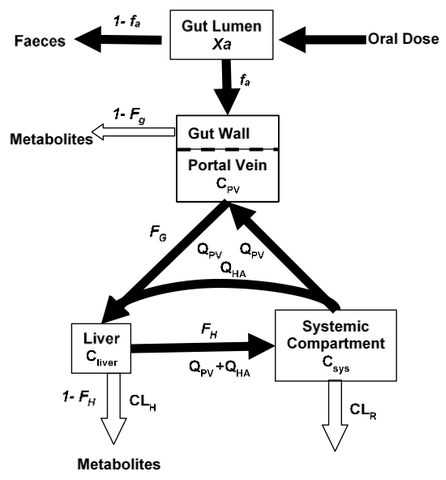

Figure 1, scheme of mPBPK model

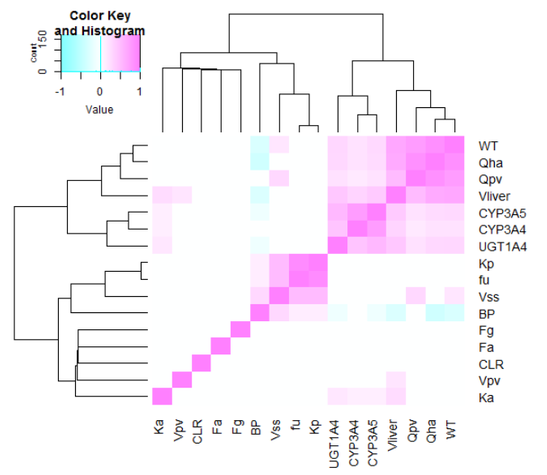

Figure 2, Correlation matrix for mPBPK model

Results

- The exSobol method suggests, Vss (volume of distribution at steady-state), Fg (fraction scape gut wall metabolism), enzyme abundance of CYP3A4 and CYP3A5, and BW, are the most important parameters determining Cmax; ka and Vss are identified as the most significant parameters determining Tmax; enzyme abundance of CYP3A5, CYP3A4, Fg, Vliver (the liver volume), and fa (fraction absorbed into enterocytes), have significant impact on AUC.
- Compared to exSobol, different sets or ranking of influential parameters were identified by Morris and Sobol due to lack of consideration of parameters correlation, which underestimated the effect of Vliver and the impact of UGT1A4 Abundance on the Midazolam AUC.
- Further, the qualitative Morris screening was as informative of the quantitative Sobol method, assuming there were not any correlations.

Conclusions

- Knowing Midazolam's physicochemical, metabolism and plasma/blood binding properties the determined ranking by exSobol are as expected. Without considering parameters correlation, GSA methods such as Morris and Sobol, can provide biased assessment of their influence on the model outputs of interest.
- A major weakness of GSA methods assuming independent input parameters is that unrealistic parameter combinations are more likely to be produced due to independent random sampling. Therefore, GSA results should be carefully used when using Morris and Sobol methods or when there are uncertainties around the model parameters correlations.
- It is important to bear in mind that GSA methods can only provide information about the explored 'model' rather than the reality it intends to represent. In other words, if a model mis-specifies the reality or inadequately represent it then the provided GSA outcomes can be either biased or incorrect.

References

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