Application of Global Sensitivity Analysis Methods to Determine the most Influential Parameters of a Minimal PBPK Model of Quinidine

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The PAGE 2017 meeting, Budapest, Hungary I-03

Background

Sensitivity analysis is used to evaluate the effect of model parameters on its outputs in various areas including systems biology and systems pharmacology [1-2]. We present an application of Global Sensitivity Analysis (GSA) methods to a minimal-Physiologically-Based PK (mPBPK) model of Quinidine (Fig. 1), a model drug, to identify the most influential model parameters affecting the PK properties of interest.

- Elementary effect GSA method (Morris screening) and variance-based GSA methods (extended Fourier Amplitude Sensitivity Test - eFAST, Sobol method, and extended Sobol method - exSobol) [2-4] were used to study the influence of model parameters (Table 1) on the simulated PK properties, i.e. C_{max}, T_{max}, and AUC, of a mPBPK model [5] of Quinidine given orally.
- Morris screening, eFAST, and Sobol are GSA methods proposed for a model with non-correlated variables; exSobol method [4] is designed to handle a model with correlated variables. In exSobol analysis, moderate correlations are assumed between BW and V_{ss} (ρ=0.5), and Q_{HA} and Q_{pv} (ρ=0.6).
- The sensitivity indices from Morris screening were mean (μ or μ*), standard variance (σ), and global index ($\sqrt[2]{\mu^{*2}+\sigma^2}$) of estimated elementary effects [6]. For variance-based GSA methods, two sensitivity indices were calculated, i.e. first-order sensitivity index (S_i) evaluating the effect of each parameter without considering its interaction with others, and total sensitivity index (S_{Ti}) assessing the impact of parameters considering their potential interactions.
- The performance of GSA methods was also evaluated on non-linear and non-monotonic Ishigami-Homma function by comparing the estimated sensitivity indices/importance with analytical solutions.

- In the mPBPK model of Quinidine, GSA sensitivity indices (Table 2) suggest that 1) Dose, BW, V_{ss}, BP, fu, Fg, and fa, are the parameters to influence C_{max}; 2) k_a and f_u are the key influential parameters for T_{max}; 3) fu, Dose, CL_{uint}, Fg, f_a, and BP, have a high impact on AUC_{24h} (Fig. 2).
- Qualitative Morris screening can be as sufficient as quantitative Sobol and eFAST methods to identify the importance of model parameters when comparing with analytical solutions for Ishigami-Homma function.

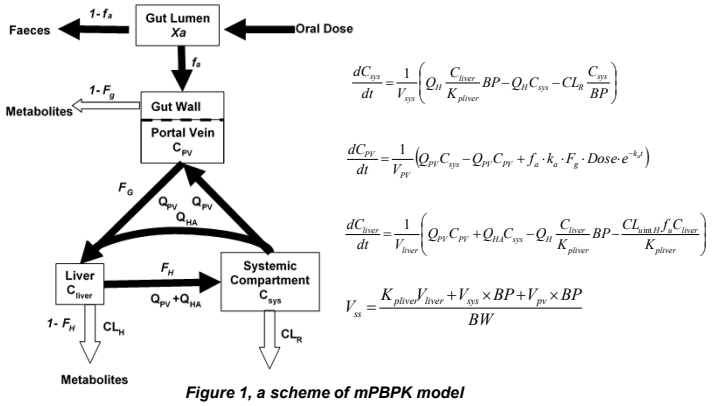

Figure 1, a scheme of mPBPK model

Table 1, parameter ranges for Quinidine

Parameters	Abbreviation	Unit	Min^	Max^
Dose	Dose	mg	50	500
Fraction of absorption	f_a	n/a	0.41	1
Absorption rate	k_a	1/h	1.23	4.76
Gut availability	F_g	n/a	0.39	1
Blood to plasma concentration ratio	BP	n/a	0.55	1.22
Fraction of unbound drug in plasma	f_u	n/a	0.08	1
Liver tissue to plasma partition coefficient	K_{pliver}	n/a	1.77	6.84
Hepatic intrinsic clearance	CL_{uintH}	L/h	40.27	155.22
Hepatic arterial blood flow	Q_{HA}	L/h	10.34	39.87
Portal vein blood flow	Q_{PV}	L/h	30.24	116.54
Body weight	BW	kg	33.3	128.16
Volume of portal vein	V_{pv}	L	0.03	0.13
Volume of liver	V_{liver}	L	0.66	2.55
Distribution volume in plasma	V_{ss}	L/kg	0.82	3.17
Renal clearance rate with respect to plasma	CL_R	L/h	0.80	3.10

^parameter ranges apart from Dose were estimated using 95% CI of default parameters in Simcyp simulator V16 with 30% CV. 20% CV was presumed for BP. Max or min values for f_a, F_g, and f_u were adjust to [0,1], if exceed.

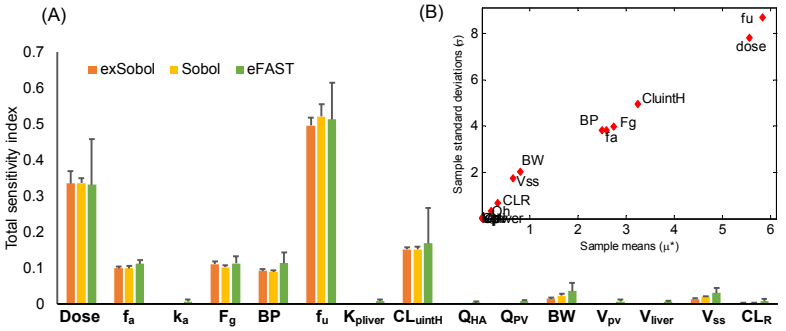

Figure 2, Sensitivity measures for AUC_{24h} by (A) exSobol, Sobol, eFAST, and (B) Morris method

Table 2, Ranked influential parameters for Quinidine*

		Dose	f_a	k_a	F_g	BP	f_u	K_{pliver}	CL_{uintH}	Q_{HA}	Q_{PV}	BW	V_{pv}	V_{liver}	V_{ss}	CL_R
C_{max}	Morris	1	5	9	7	4	6	8		10		3			2	
	eFAST	1	6	10	7	4	5	8		9		3			2	
	Sobol	1	7	9	5	4	6	8		10		2			3	
	exSobol	1	7	9	5	4	6	8		10		2			3	
T_{max}	Morris			1			2	5		6		3			4	
	eFAST			1			2	5		6		4			3	
	Sobol			1			2	5		6		4			3	
	exSobol			1			2	5		6		4			3	
AUC_{24h}	Morris	2	5		4	6	1	3			7				8	
	eFAST	2	6		4	5	1	3			8				7	
	Sobol	2	5		4	6	1	3			7				8	
	exSobol	2	5		4	6	1	3			7				8	

**Morris global index was used to rank the input factors, while total sensitivity index were adopted for other methods.*

- Knowing the physicochemical and plasma/blood binding properties of Quinidine the determined ranking is as expected.
- In this case, the qualitative Morris screening method was as informative of the quantitative methods, e.g. eFAST, Sobol and exSobol.

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