

Sensitivity

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Definitions

Validation. The process of determining the degree to which a model is an accurate representation of the real world from the perspective of the intended uses of the model (taken from AIAA, 1998).

Qualification. The process of establishing confidence in a PBPK platform to simulate a certain scenario, in a specific context, on the basis of scientific principles, and ability to predict a large dataset of independent data thereby showing the platforms ability to predict a certain purpose. In the context of PBPK models, qualification is purpose and platform version specific (EMA 2016)

Sensitivity. The study of how uncertainty in the output of a model (numerical or otherwise) can be apportioned to different sources of uncertainty in the model input (Saltelli et al., 2004)

Variability refers to variations due to inherent factors or natural causes of the system and ***uncertainty*** refers to variations caused by errors in assumptions and observations of the system (Nesterov 2001)

Identifiability

- **Structural Identifiability:** even with perfect data you cannot estimate the parameters
eg $y = a + (b/c).x$
- **Deterministic identifiability:** if the model is structurally identifiable, if the data is poor then you still may not be able to estimate the parameters
eg $y = V_{max}.C/(K_m + C)$

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1824

**STRUCTURAL IDENTIFIABILITY ANALYSIS OF SOME SEMI-
PHYSIOLOGICALLY BASED AND WHOLE BODY PHYSIOLOGICAL
BASED (WBPBPK) PHARMACOKINETIC MODELS**

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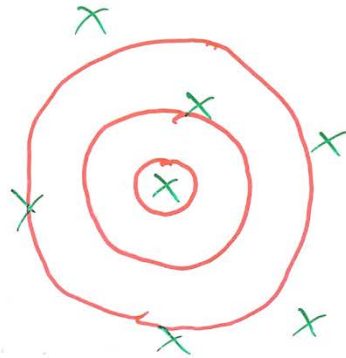
PAGE meeting 2005

**Structural Identifiability of Physiologically Based
Pharmacokinetic Models**

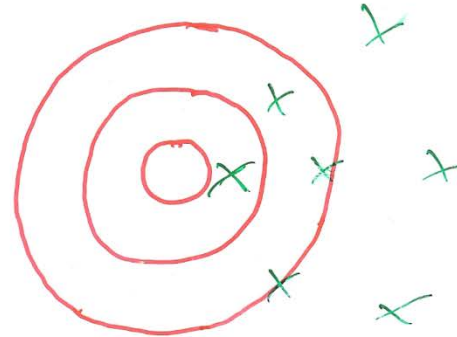
James W. T. Yates

*Journal of Pharmacokinetics and Pharmacodynamics, Vol. 33,
No. 4, August 2006*

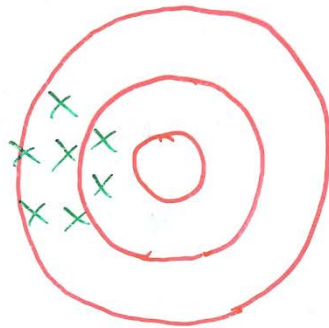
Bias and Precision



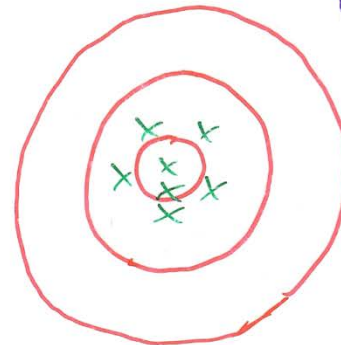
accurate but not precise



not accurate and not precise



precise but not accurate



precise and accurate

Local sensitivity

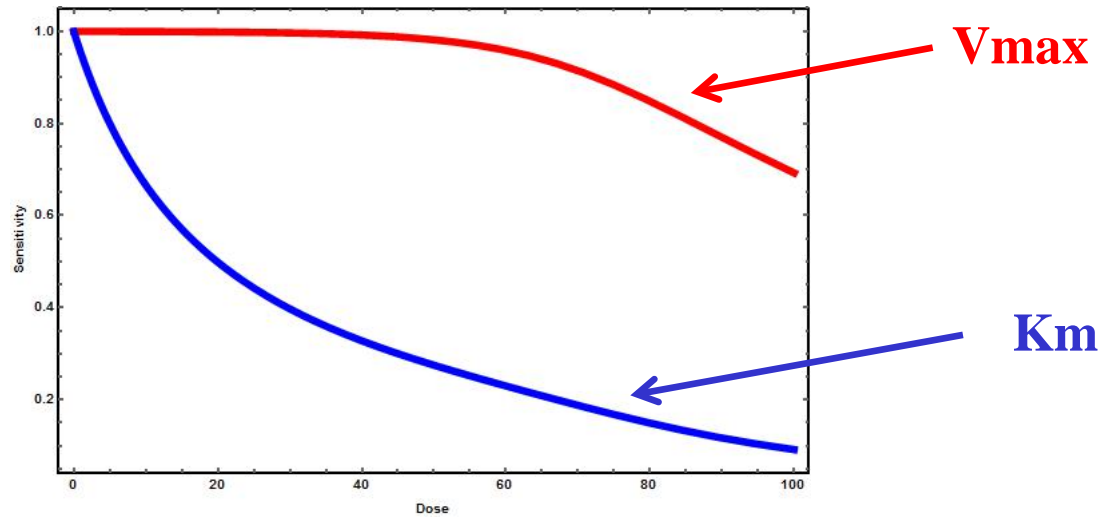
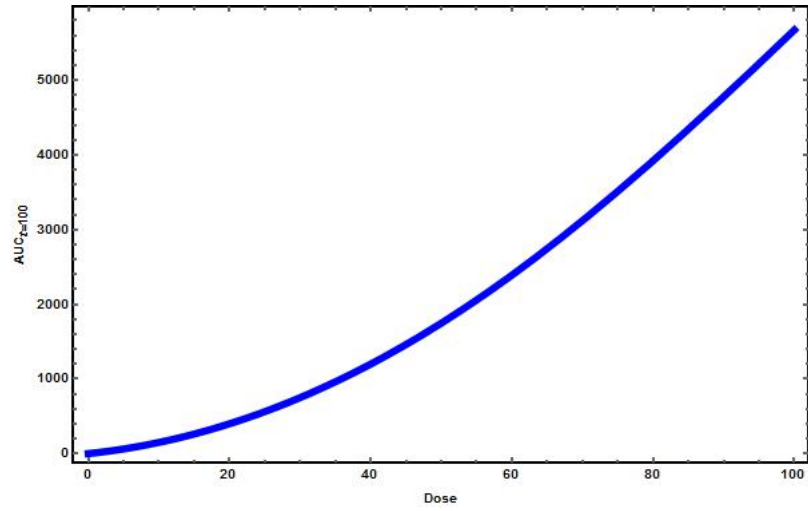
Michaelis-Menten

$$\frac{dC}{dt} = \frac{-V_{\max} \cdot C}{K_m + C}$$

$$C(0) = D$$

$$\frac{dAUC}{dt} = C$$

$$S_{ij}(t_m) = \frac{p_j}{AUC_i} \cdot \left. \frac{\partial AUC_i}{\partial p_j} \right|_{t=t_m}$$

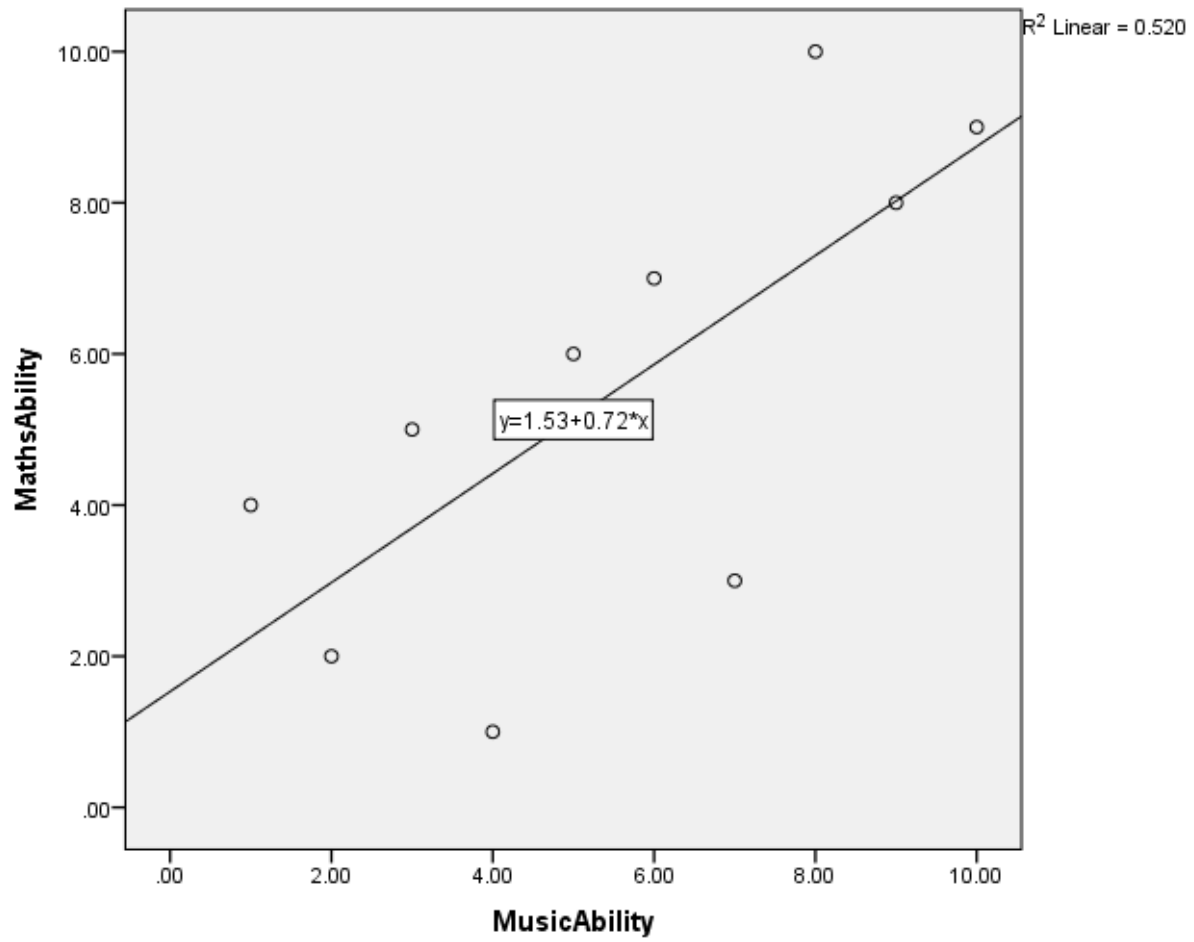


Global sensitivity

Kendall (Biometrika 1942)

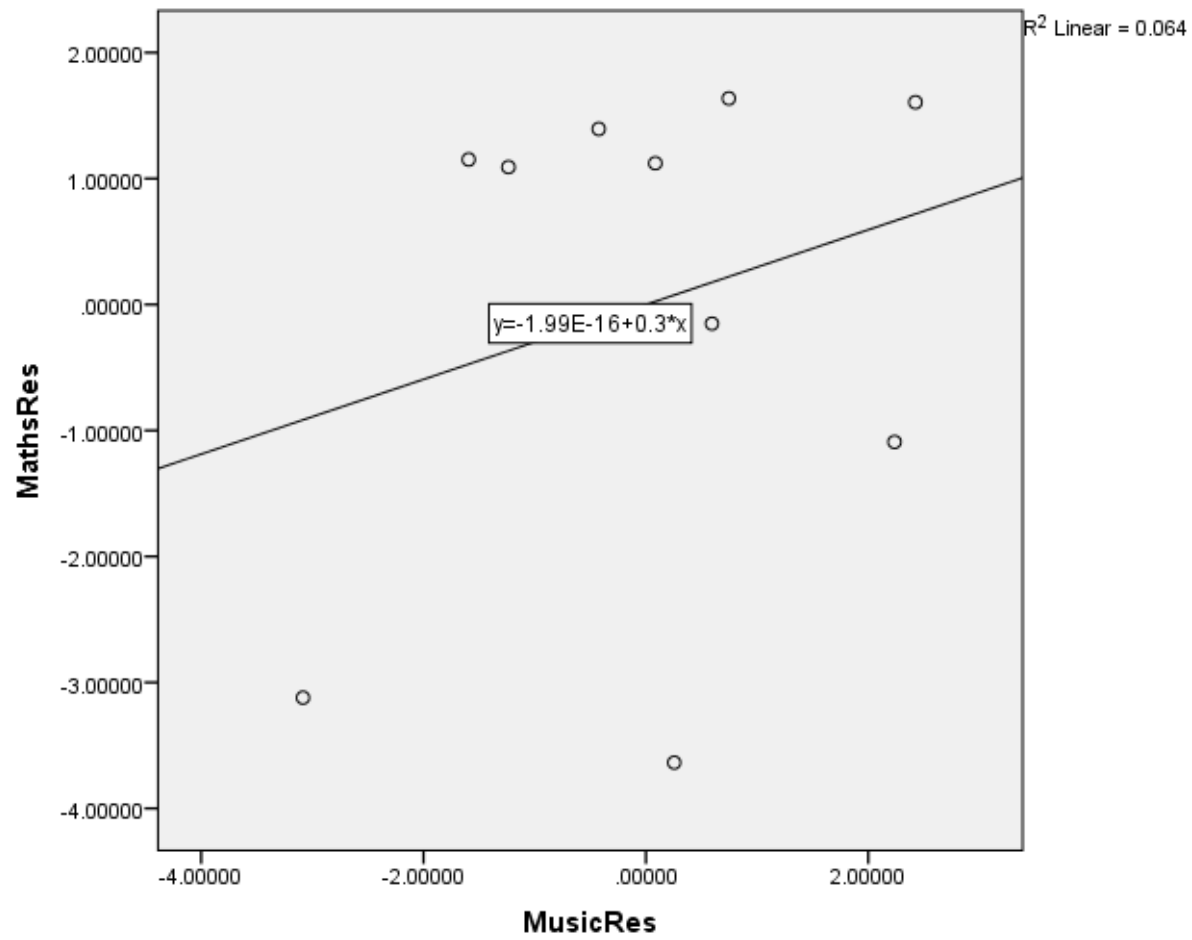
Intelligence	1	2	3	4	5	6	7	8	9	10
Maths ability	1	4	5	6	2	7	3	9	8	10
Musical ability	4	1	3	5	2	6	7	10	9	8

Correlations				
		Intelligence	MathsAbility	MusicAbility
Intelligence	Pearson Correlation	1	.758*	.830**
	Sig. (2-tailed)		.011	.003
	N	10	10	10
MathsAbility	Pearson Correlation	.758*	1	.721*
	Sig. (2-tailed)	.011		.019
	N	10	10	10
MusicAbility	Pearson Correlation	.830**	.721*	1
	Sig. (2-tailed)	.003	.019	
	N	10	10	10



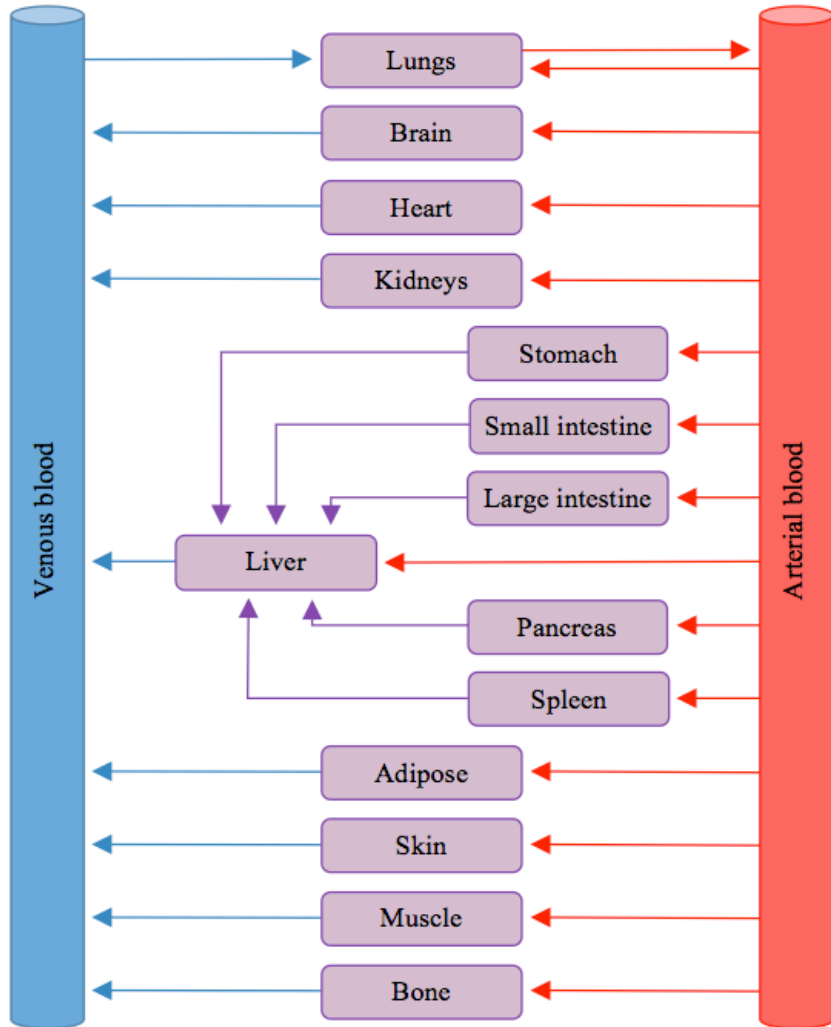
Correlations

Control Variables			MathsAbility	MusicAbility
Intelligence	MathsAbility	Correlation	1.000	.253
		Significance (2-tailed)	.	.511
		df	0	7
	MusicAbility	Correlation	.253	1.000
		Significance (2-tailed)	.511	.
		df	7	0



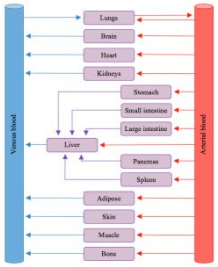
Ingalls_ACoP_2015

Evaluation of PBPK models: identifiability and sensitivity techniques from engineering



midazolam (Bjorkman '01, '04)

Structural Identifiability results



Parameter	Nominal Value	Overall Sensitivity
CL_{int}	19.3	1.022
P_{fat}	2	0.2978
P_{muscle}	0.45	0.1748
P_{other}	0.45	0.05385
P_{liver}	1.7	0.02629
P_{skin}	0.63	0.02583
P_{lung}	1.7	0.02341
P_{brain}	1.1	0.02189
P_{small}	1.5	0.009289
$P_{kidneys}$	1.4	0.008177
P_{heart}	1.6	0.007179
P_{bone}	0.1	0.005777
P_{large}	1.5	0.004194
$P_{stomach}$	2.4	0.003097
P_{spleen}	1	0.001704
$P_{pancreas}$	1	0.0008753

Local sensitivity coefficients:

$$S_{ij}(t_m) = \left. \frac{k_j}{y_i} \frac{\partial y_i}{\partial k_j} \right|_{t=t_m}$$

y: output
 k: parameter
 t: measurement time

Overall sensitivity measure:

$$S_j^{rms} = \sqrt{\frac{1}{n} \sum_i \sum_m [S_{ij}(t_m)]^2}$$

Physiologically Based Pharmacokinetic Modeling of a Homologous Series of Barbiturates in the Rat: A Sensitivity Analysis

Ivan A. Nestorov,^{1,2,3} Leon J. Aarons,² and Malcolm Rowland²

Received November 26, 1996—Final August 5, 1997

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Assessing drug distribution in tissues expressing P-glycoprotein using physiologically based pharmacokinetic modeling: identification of important model parameters through global sensitivity analysis

Frederique Fenneteau • Jun Li • Fahima Nekka

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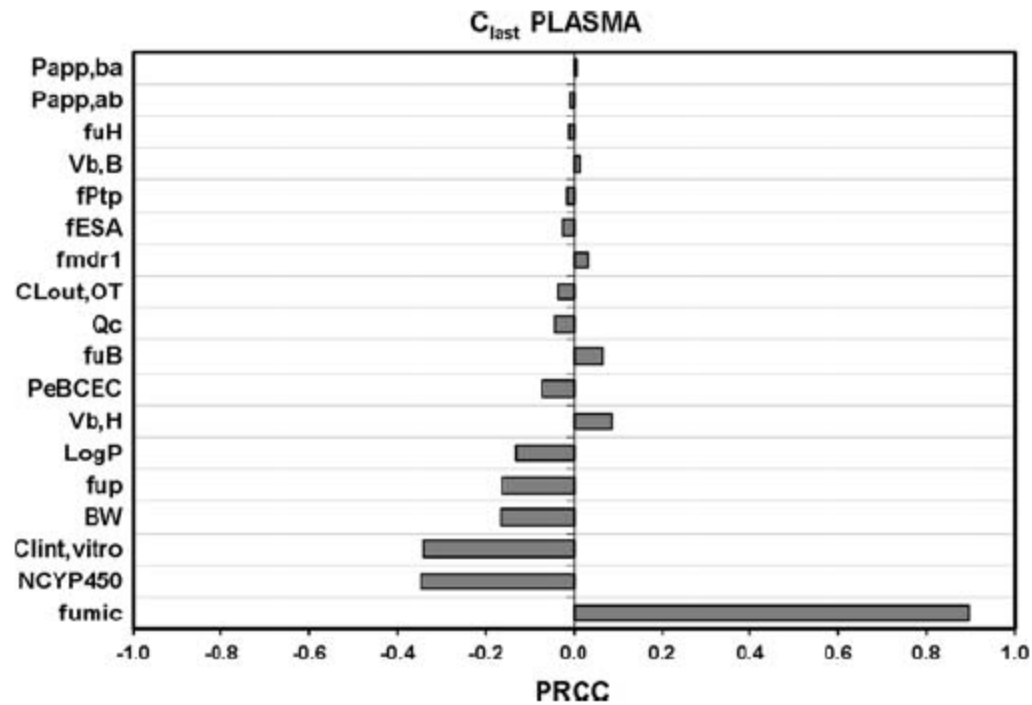


Fig. 5 PRCC between each of the eighteen parameters and C_{last} of domperidone predicted in mice plasma

Global methods

- **PCC and PRCC**
- **Sobol (Saltelli)**
- **eFAST**