

## A User-friendly Tool for Analysis of Complex In Vitro Experimental Data

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### Complexity of *In Vitro* Assays

*In vitro* data analysis in whole cell systems is complex [1] and time consuming, yet accurate data analysis and informed data interpretation are crucial early in the drug development process, especially when *In Vitro-In Vivo* Extrapolation (IVIVE) approaches are being used.

A number of software tools exist for the analysis of *in vitro* data. However, these tools were developed for broad application and **do not**:

- support analysis of more complex *in vitro* experimental systems.
- possess appropriate statistical rigour.
- allow automated IVIVE.

### *In Vitro* Models (e.g. Transporters)

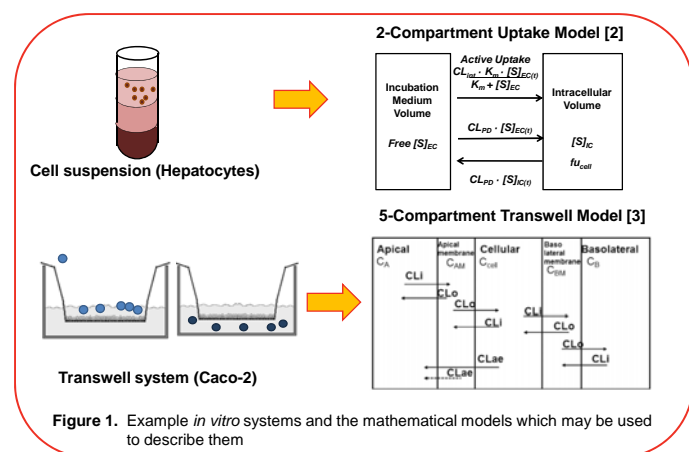


Figure 1. Example *in vitro* systems and the mathematical models which may be used to describe them

When using whole cell systems (Figure 1) there is a **need to account for**:

- Interplay between metabolic, passive diffusion and active transport processes
- Possible simultaneous time dependent inhibition and competitive inhibition
- Contribution of metabolites to enzyme inhibition
- Nonspecific binding
- Intracellular binding
- Intra & Inter-assay, between donor variability
- Potential outliers

### SIVA-Toolkit - Key Elements

- The SIVA-Toolkit is a user friendly tool for the analysis of complex *in vitro* experimental data. *In vitro* assays and associated models included in the SIVA-Toolkit are shown in Figure 2.

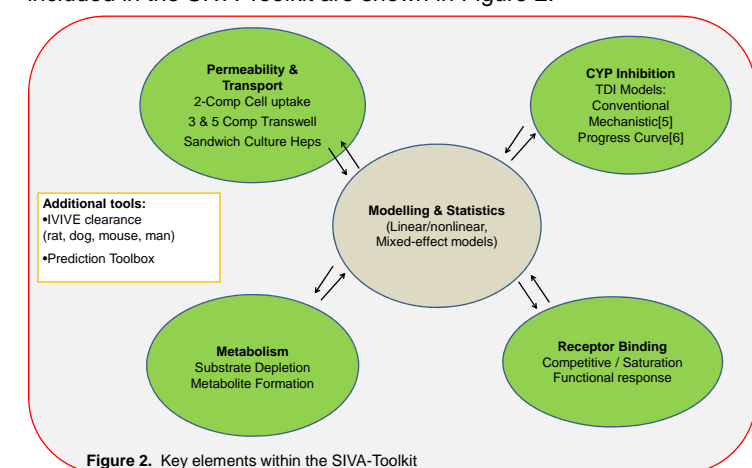


Figure 2. Key elements within the SIVA-Toolkit

### Importance of *In Vitro* Transporter Modelling

- Results from two studies [3],[4], showing the impact of modelling on the evaluation of P-glycoprotein (P-gp) kinetics are summarised in Figure 3 and Table 1.
- The likelihood of correctly simulating drug-drug interactions due to P-gp interactions with this compound will be very different if the correct kinetic parameters are not used.

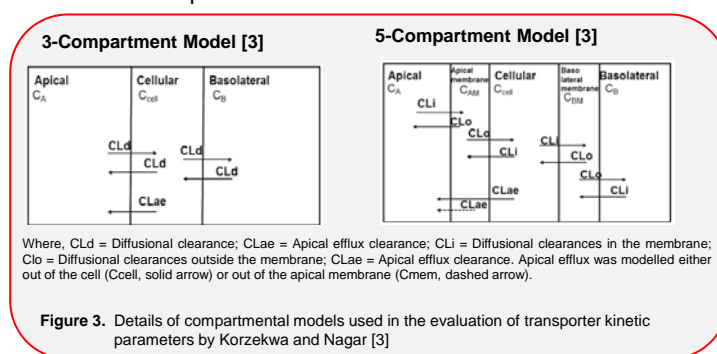


Table 1. Kinetic parameter estimates for P-gp mediated transport of Quinidine

Quinidine	$K_m$ ( $\mu M$ ) (MDRI-MDCKII)	$K_m$ ( $\mu M$ ) (P-gp induced Caco-2)	Fold Difference in estimated $K_m^*$
Conventional Michaelis-Menten Model [3]	19.9	4.5	--
3-Compartment [4]	0.339	0.234	19 - 59
3-Compartment [3]	0.255	0.228	20 - 78
5-Compartment [3]	0.203	0.175	26 - 100

\*Fold difference in estimated  $K_m$  (Michaelis-Menten constant), relative to conventional Michaelis-Menten approach.

### Advantages of SIVA-Toolkit

**Specialized** - Specifically designed for drug discovery and early drug development scientists.

**Easy to use**- Provides user-friendly graphical interfaces with pre-defined library models for currently available *in vitro* assays. Complex data analysis without the need to know a coding language.

**Links to other platforms** - Potential for linkage to other platforms (e.g. Phoenix)

**Statistical rigour** - Ready-made structural models are integrated in a user-friendly manner with powerful nonlinear fitting models in a statistical environment.

**Ease of documentation**- Provides formatted printable reports with a summary of input parameters, experimental details and results.

**Automated IVIVE**- Integration of *in vitro* metabolic clearance data with established IVIVE approaches and physiological scaling factors for extrapolation of hepatic clearance in multiple species (human, dog, rat, mouse).

### References

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