Simcyp In Vitro Analysis Toolkit (SIVA-Toolkit)

Technology Strategy Board
Driving Innovation

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

Simcyp (now Certara), Sheffield, UK

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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)

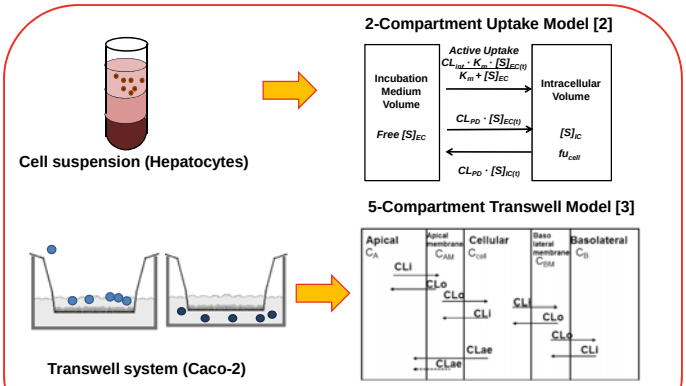


Figure 1. Example *in vitro* systems and the mathematical models which may be used to describe them

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.

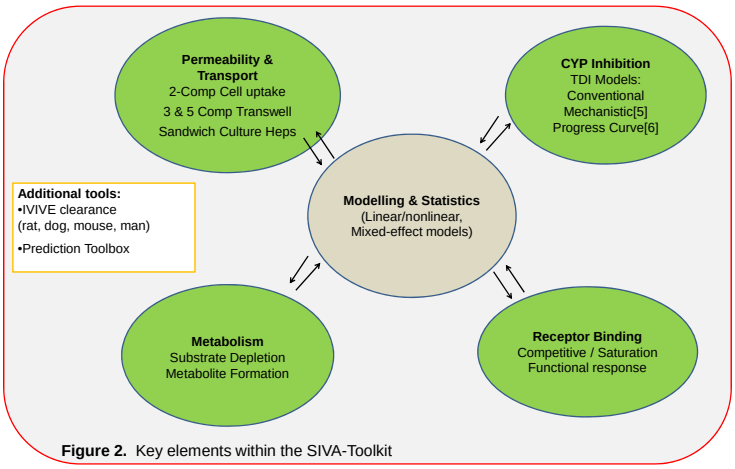
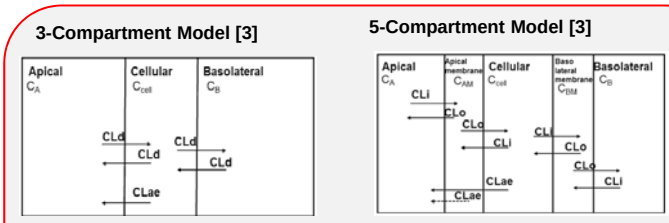


Figure 2. Key elements within the SIVA-Toolkit

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.



Where, CLd = Diffusional clearance; CLae = Apical efflux clearance; CLi = Diffusional clearances in the membrane; Clo = Diffusional clearances outside the membrane; CLae = Apical efflux clearance. Apical efflux was modelled either out of the cell (Ccell, solid arrow) or out of the apical membrane (Cmem, dashed arrow).

Figure 3. Details of compartmental models used in the evaluation of transporter kinetic parameters by Korzekwa and Nagar [3]

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

Quinidine	K_m (μM) (MDRI-MDCKII)	K_m (μM) (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

[1]. Zamek-Gliszczynski MJ *et al., Clin Pharmacol Ther.* 2013 Jul;94(1):64-79.

[2]. Poirier A *et al., Drug Metab Dispos.* 2008 Dec;36(12):2434-44.

[3]. Korzekwa K and Nagar S, *Pharm Res.* 2013 Aug 20. [Epub ahead of print].

[4].Tachibana T *et al., Pharm Res.* 2010 Mar;27(3):442-6.

[5]. Yang *et al., Eur J Pharm Sci.* 2007 Jul; 31(3-4):232-41

[6]. Burt *et al., Drug Metab Dispos.* 2012 Sep; 40(9): 165-67

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