Ground-breaking Software for Modelling, Simulation, Optimization, Estimation and Validation Applications in Drug Development Timeline Processes.

Sánchez-Herrero, Sergio[1]; Serna, Jenifer[1]; Diego García-Álvarez[2]; Rueda-Ferreiro, Almudena[1].

[1]Simulation Department, Empresarios Agrupados Internacional S.A., Madrid, Spain.

[2]Computer Department, University of Valladolid, Valladolid, Spain.

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INTRODUCTION

- The drug development process achieve greater safety, efficiency, cost effectiveness and timeliness drug testing for humans [1].
- A growing number of regulatory submissions include mathematical pharmacokinetics models that simulates the concentration of a drug over time in tissue(s) and blood [2].
- **There is not any software to manage** Non-Compartmental analysis, Compartmental PK/PD models and physiologically based pharmacokinetic (PBPK) estimation and simulation models in a unique object-orientated software.

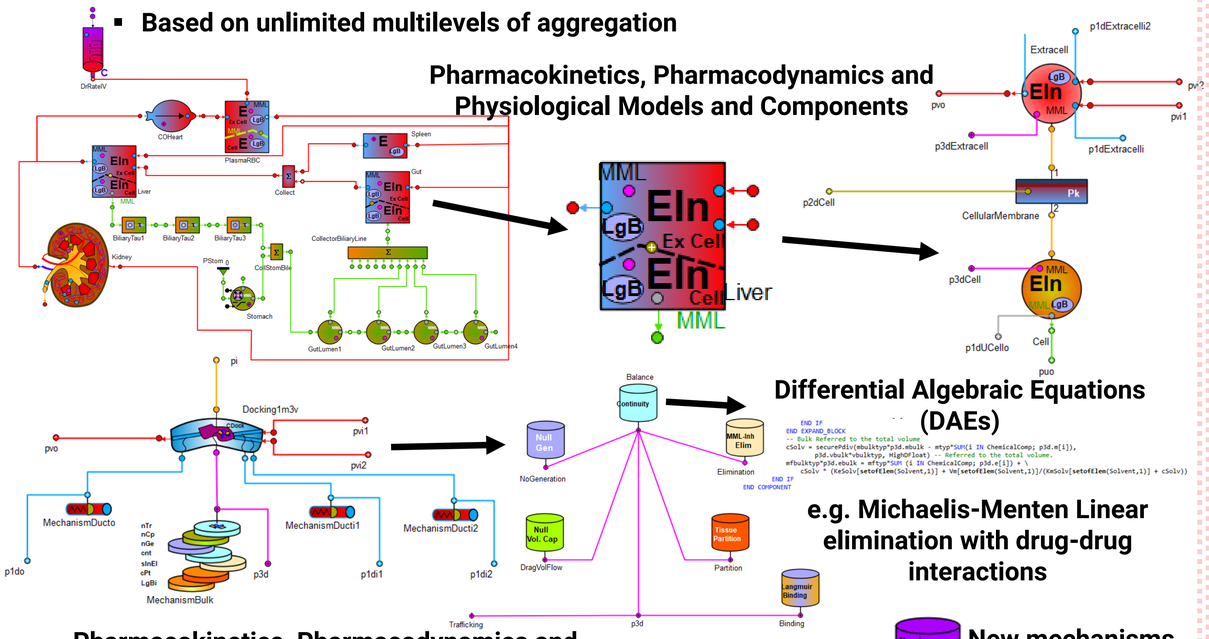
OBJECTIVES

1. To explore PhysPK architecture based on top-down programming capacity for continuous-discrete systems to L-ADME and physiological mechanisms.
2. To show NCA, QSP, PK/PD/PBPK validated models with PhysPK.
3. To export and connect with external tools like excel or python.

METHODS

- **Based on unlimited multilevels of aggregation**

Pharmacokinetics, Pharmacodynamics and Physiological Models and Components



Differential Algebraic Equations (DAEs)

e.g. Michaelis-Menten Linear elimination with drug-drug interactions

Pharmacokinetics, Pharmacodynamics and Physiological Mechanism

New mechanisms

Nuclear decay

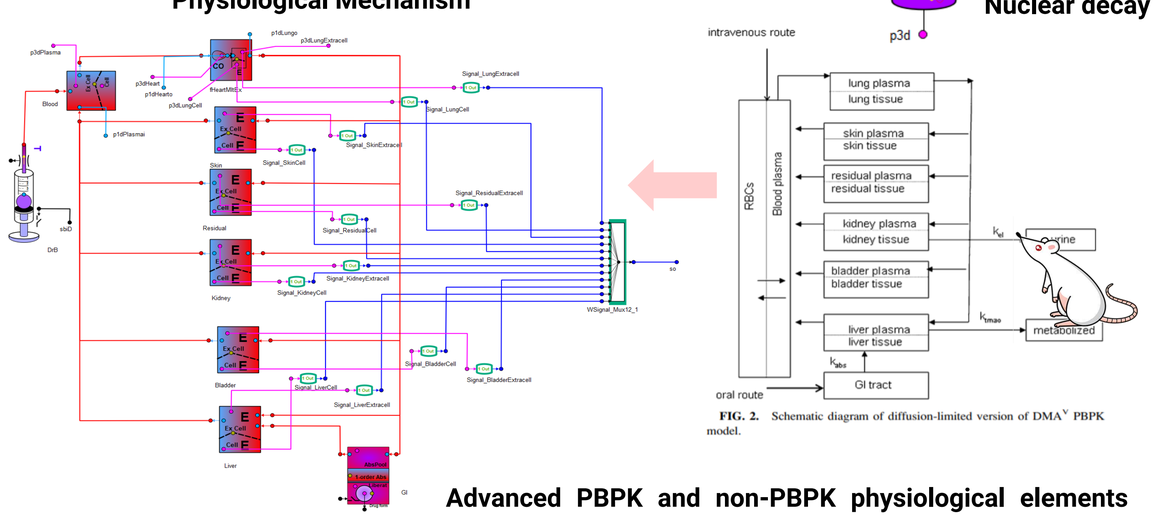
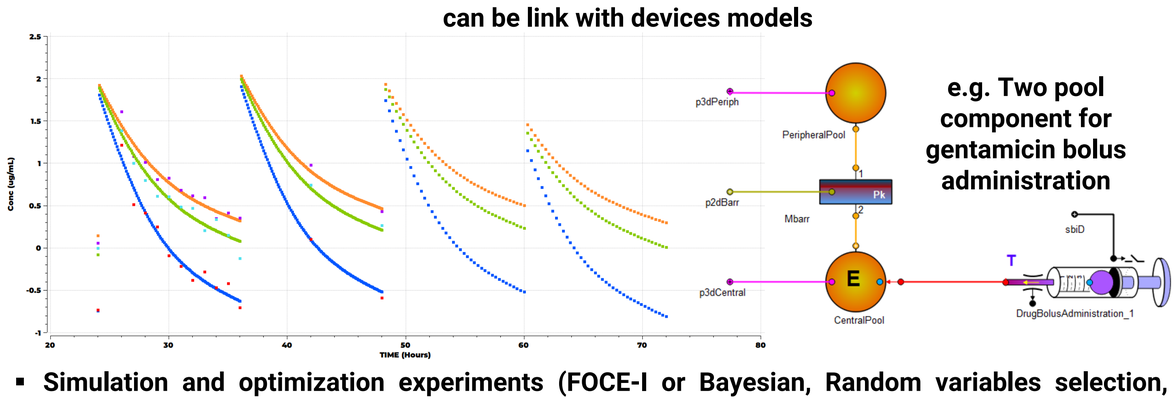


FIG. 2. Schematic diagram of diffusion-limited version of DMA^{V} PBPK model.

Advanced PBPK and non-PBPK physiological elements can be link with devices models



e.g. Two pool component for gentamicin bolus administration

- **Simulation and optimization experiments (FOCE-I or Bayesian, Random variables selection, Covariate exploration, Sensitivity Analysis, Montecarlo, goodness of fit (GOF), Virtual prediction check, Virtual population or Bootstrap.**

CONCLUSIONS

- **PhysPK provides re-usable and flexible NCA analysis and PK/PD/PBPK/QSP** modelling, simulation, optimization, estimation and validation methods and experiments.
- This unique approach could achieve **greater efficiency, cost effectiveness and timeliness in drug development process**.
- In addition, **export models and connect with python** will allow us to engage with new cutting-edge technologies like Artificial Intelligence.

REFERENCES

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[3] The IQnca R package. https://iqnca.intiquan.com/
[4] Hosseini, Iraj, et al. "gPKPDSim: a SimBiology®-based GUI application for PKPD modeling in drug development." Journal of pharmacokinetics and pharmacodynamics 45.2 (2018): 259-275.
[5] Evans, Marina V., et al. "A physiologically based pharmacokinetic model for intravenous and ingested dimethylarsinic acid in mice." Toxicological sciences 104.2 (2008): 250-260.
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RESULTS

NCA

- **Single oral dose:**

WinNonlin oral dose data versus PhysPK

NCA Metrics	PhysPK	WinNonlin
ID	9026	9026
Adjuested R^2	0.922	0.922
R^2	0.961	0.961
N_points_Lambda_Z	3	3
Lambda_Z	0.155	0.155
HL_Lambda_Z	4.488	4.488
Max_rate	1497.6	1497.6
Tmax_rate	5	5
Rate_last	62.4	62.4
Mid_Pt_last	21	21
AURC_Last	8970.544	8970.544
AURC_Infinity	9374.553	9374.553
AURC_Infinity_pred	9420.527	9420.527
Vol_UR	1171	1171
Amount_Recovered	8642.7	8642.7
Percent_Recovered	86.427	86.427
Calculation_method	Linear	Linear

- **IV infusion single dose [3]:**

WinNonlin subject 1 **IV infusion single dose data versus PhysPK**

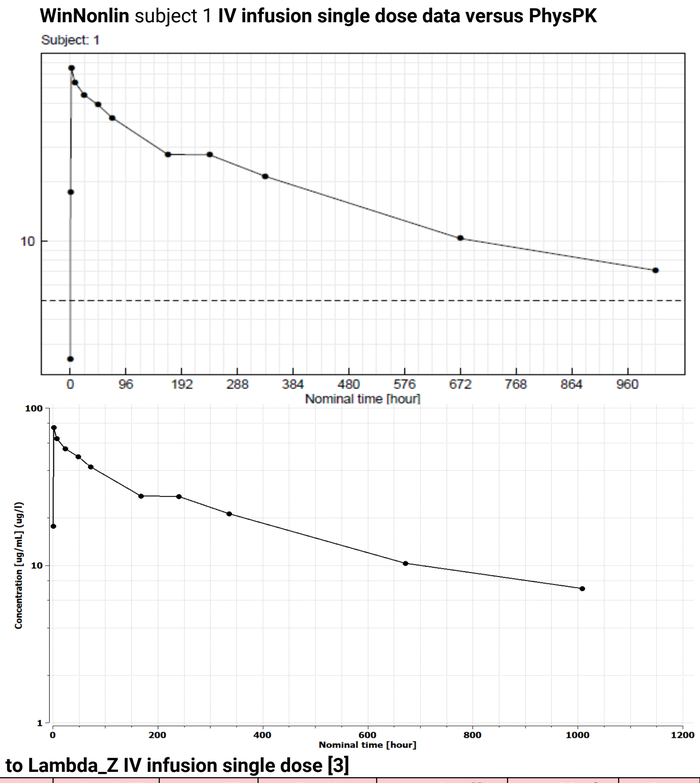
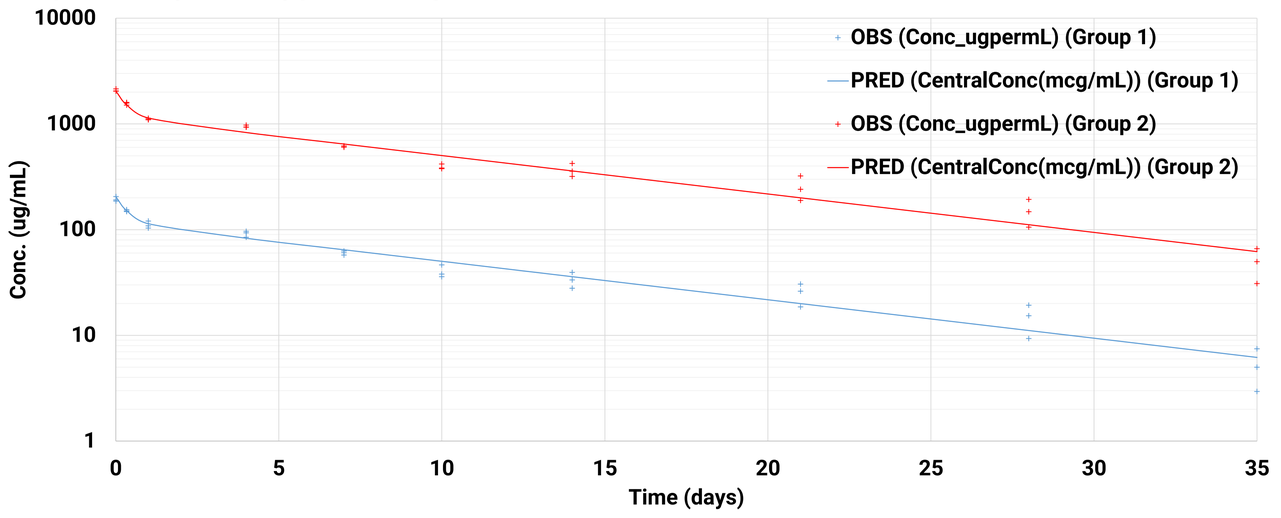


Table PK parameter related to Lambda_Z IV infusion single dose [3]

Subj. 1	R2	R2ADJ	NLAMZ	LAMZ	T1/2	AUC All	AUCInf.	CL
IQnca	0.982	0.970	5	0.011	398.976	19367.20	23453.9	0.023
PhysPK	0.982	0.970	5	0.011	398.976	19356.42	23443.2	0.023

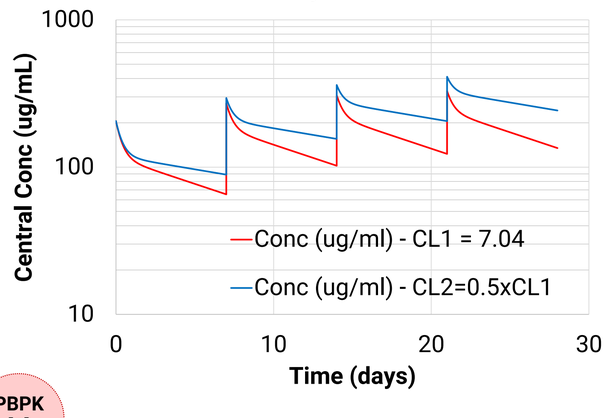
Pop PK/PD [4]

Population PhysPK study pooled fitting results

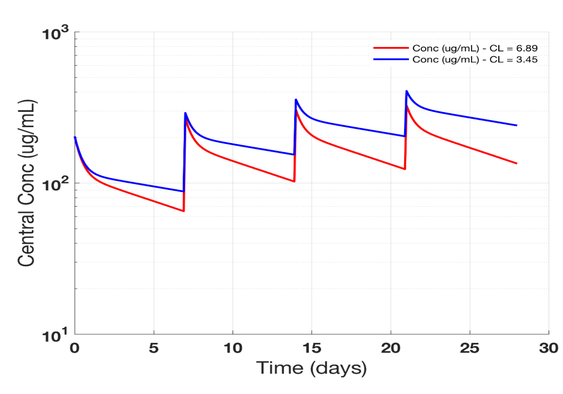


Simulation scenario: CL_2 =0.5xCL_1 (ml/kg/day) [4]

PhysPK

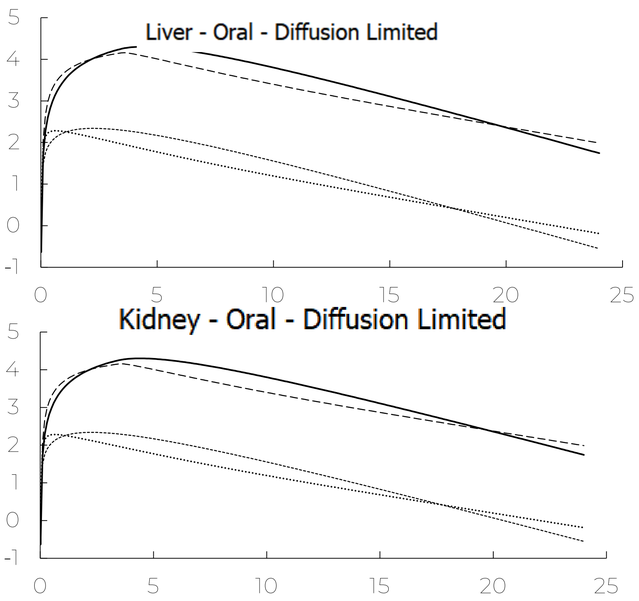


Hosseini, I. et al., 2018.

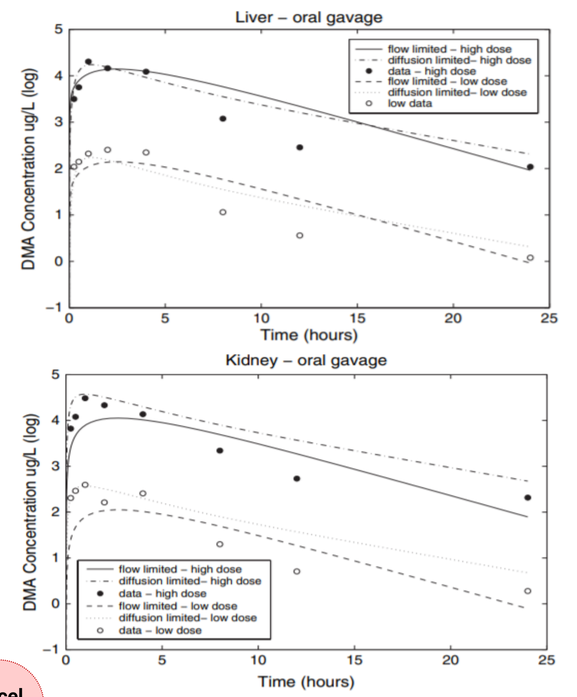


PBPK [5]

PhysPK

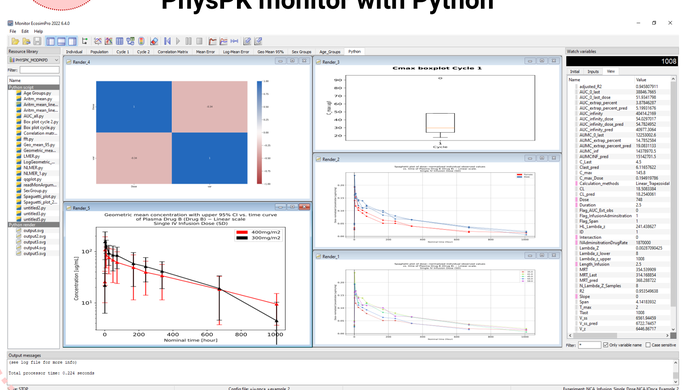


Evans *et al.*; 2008



Python

PhysPK monitor with Python



Excel [6]

Export models to Excel