Integrating Python optimization algorithms inside PhysPK® (PK/PD/PBPK) software for improving PK estimation methods

Sergio Sánchez-Herrero[1,2], Marina Cuquerella-Gilabert[1,4], Serna, Jenifer[1], Rueda-Ferreiro, Almudena[1], Diego García-Álvarez[2].

[1]Simulation Department, Empresarios Agrupados Internacional S.A., Madrid, Spain; [2]Computer Science, Multimedia and Telecommunication Department, Universitat Oberta de Catalunya. Barcelona (Spain); [3]Department of Pharmacy and Pharmaceutical Technology and Parasitology, School of Pharmacy, University of Valencia, Valencia, Spain; [4]Department of Computer Science, University of Valladolid, Valladolid, Spain.

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INTRODUCTION

One of the most promising technological developments in pharmacokinetics is the use of **Artificial Intelligence (AI) methods**. **Machine Learning (ML) methods** offer the opportunity to implement innovative algorithms for quantifying individual or population pharmacokinetic parameters, including mean kinetics, interindividual kinetic variability, residual variability, intraindividual variability, and measurement error. PK/PD models need new computational methods and algorithms to enhance better predictions and optimization capabilities. **PhysPK®** models and calculations can be encapsulated and encrypted in a standalone **Python** application (Deck). This cutting-edge feature allows us to explore Python's optimization methods for quantifying pharmacokinetics, comparing them with quantifying pharmacokinetic parameters estimation methods like Two-Stage (TS), First Order methods (FOCE), and SAEM method.

OBJETIVES

We have explored Python's minimize optimization methods in a proof-of-concept for a two-compartment PopPK model. Our goal is to analyze the **SciPy optimize** functions for minimizing and compare their performance with classical **sequential quadratic programming (SQP) method and a Differential Evolution (DE),** which are commonly used in **PhysPK®** PK/PD analysis for the Two-Stage (TS) method.

METHODS

PhysPK® v.2.4.1 platform is a software based on first-principles modelling of complex systems with continuous and discrete time equations. **PhysPK®** has a set of methods and functions defined to estimate parameters and validate the final model a SQPS method and a genetic algorithm linked to FOCE-i methods [2-3]. The process is based on three phases (Figure 1). Any PK/PD can be encapsulated and encrypted in a standalone Python application (Deck) to manage and run models (Figure 2).

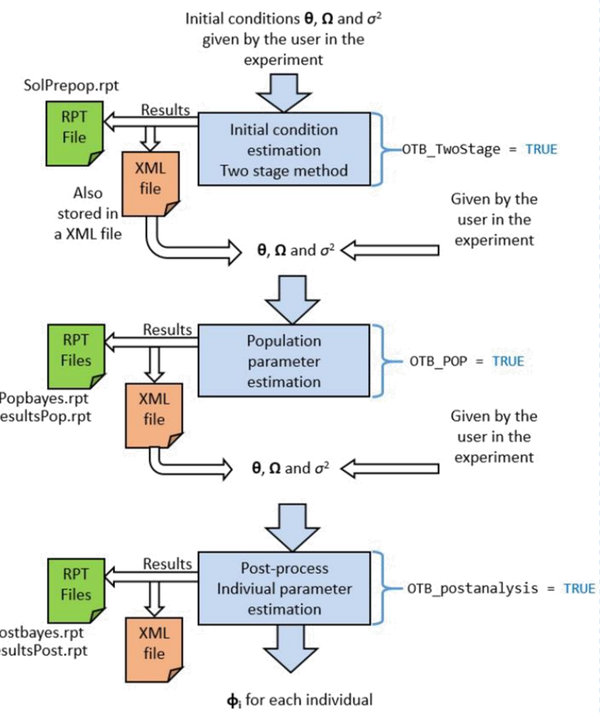


Figure 1. PhysPK® phases of a population study.

Scipy.optimize.minimize optimize method provides functions for minimizing objective functions. It includes solvers for nonlinear problems (with support for both local and global optimization algorithms), linear programing, constrained and nonlinear least-squares, root finding, and curve fitting [4] :

- Constrained Optimization BY Linear Approximation (**COBYLA**)
- Sequential Least Squares Programming (**SLSQP**)
- Broyden–Fletcher–Goldfarb–Shanno (**BFGS**)
- Truncated Newton (**TNC**)
- Davidon–Fletcher–**Powell**,
- Conjugate gradient method (**CG**)
- Limited-memory BFGS (**L-BFGS-B**)
- **Nelder-Mead**
- **Differential Evolution**
- **Least Squares**

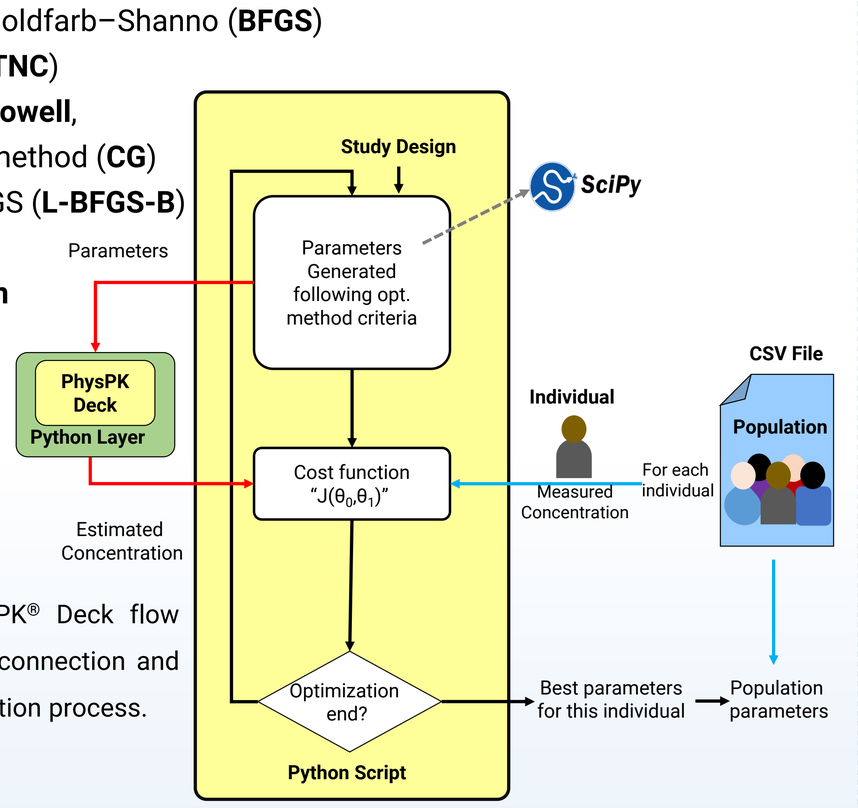


Figure 2. PhysPK® Deck flow diagram of the connection and intercommunication process.

These optimization methods were used to optimize a two-comparmental PK model based on real data real data patient from plasma concentrations in µg/mL of Monoclonal Antibody for extra-vascular administration to estimate CL, CLd, Vc and Vp [5].

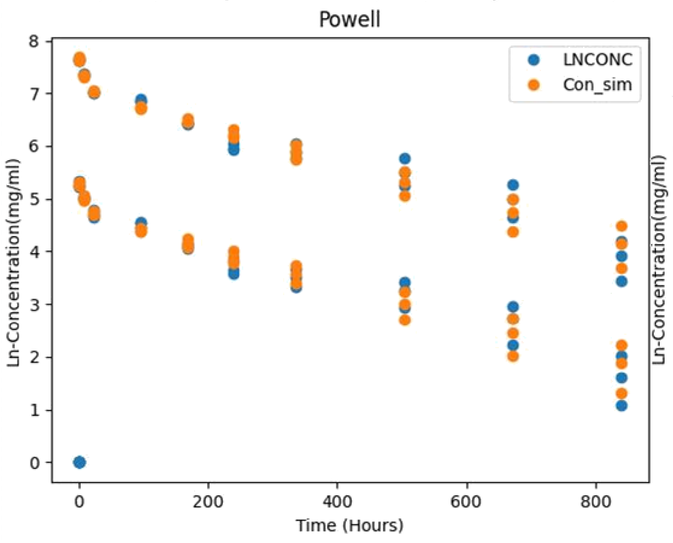
RESULTS

- **Two-comparmental PopPK model for Monoclonal Antibody extra-vascular administration [5].**

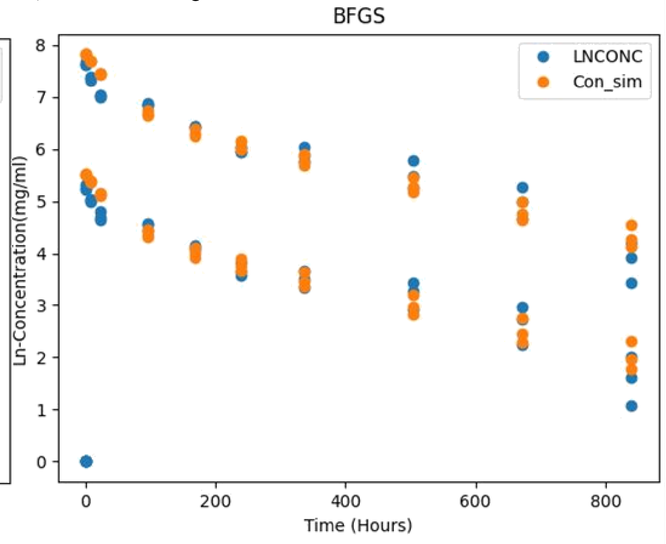
Population PK parameter estimates for Monoclonal Antibody extra-vascular administration 10 mg 3 patients and 100 mg 3 patients dose.

	Cl	Vc	Cld	Vp	AFE	AAFE	MPE	Run Time (Seconds)
REFERENCE [5]	6.89+/-0.53	49.15+/-2.57	45.5+/-8.15	34.61+/-4.56	-	-	-	
PHYSPK	7.02+/-0.33	48.79+/-1.04	49.02+/-3.07	33.17+/-1.5	1.004	1.004	0.2	35
Python								
Nelder-Mead	7.06+/-0.33	49.12+/-1.03	49.08+/-2.74	33.24+/-1.51	**0.999**	**1.005**	**-0.09**	**1403**
Powell	7.06+/-0.33	49.12+/-1.03	49.07+/-2.74	33.24+/-1.51	**0.999**	**1.005**	**-0.09**	**2667**
CG	5.97+/-0.48	40.03+/-0.03	40.0+/-0.0	10.0+/-0.0	0.641	1.717	-105.35	515
BFGS	7.02+/-0.33	48.79+/-1.04	49.02+/-3.07	33.17+/-1.5	**0.625**	**1.757**	**-116.00**	**674**
L-BFGS-B	6.87+/-0.44	40.0+/-0.0	10.01+/-0.01	40.0+/-0.0	0.665	1.659	-100.79	995
TNC	6.55+/-0.51	40.0+/-0.0	10.0+/-0.0	40.0+/-0.0	0.656	1.678	-102.46	1265
COBYLA	7.1+/-0.35	50.72+/-0.68	21.21+/-0.61	32.84+/-0.95	0.817	1.261	-32.50	3456
SLSQP	6.92+/-0.43	40.06+/-0.06	9.92+/-0.09	40.0+/-0.0	0.665	1.656	-102.06	399
Differential Evolution	7.07+/-0.33	49.20+/-1.06	48.83+/-2.43	33.44+/-1.4	**1.001**	**1.017**	**-0.16**	**7058**
Least Squares	7.07+/-0.36	45.12+/-2.65	16.05+/-2.23	41.73+/-3.11	0.774	1.477	-57.94	655

Cl, clearance for the central compartment; Vc, central volume; Cld, clearance for the periferical compartment; Vp, periferical volume; MPE, mean prediction error, AFE, average-fold error; AAFE, absolute average-fold error.



Population Simulation Ln-Concentration-Time for Cefepime. Plot for best Python results method. Blue, observed data. Orange, simulated data.



Population Simulation Ln-Concentration-Time for Cefepime. Plot for worst Python results method. Blue, observed data. Orange, simulated data.

CONCLUSIONS

PhysPK® open up a large promising research umbrella to integrate success optimization methods and algorithms widely used by Python in other areas inside pharmacokinetic environment. **PhysPK®** biosimulation software is already useful for estimating pharmacokinetic parameters, nevertheless, integrating innovate Python algorithms and methods could improve notoriously the tool. However, further research is needed to fully analyse the python integration methods. For example, restrictions based on pharmacokinetics approaches and future FOCE, Bayesian and SAEM analysis should be taken into account in compare with Python.

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