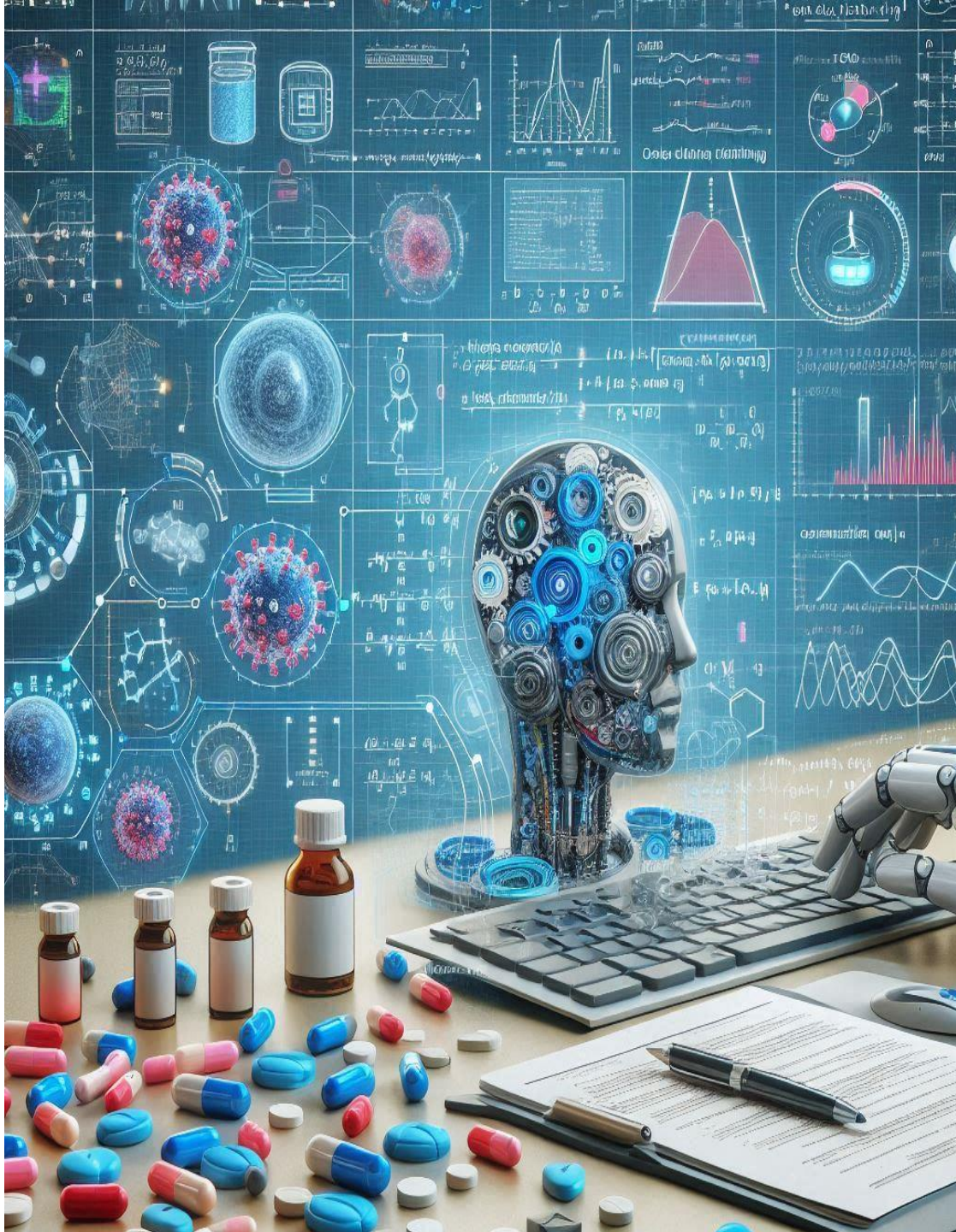
Machine learning for pharmacometrics: examples of applications



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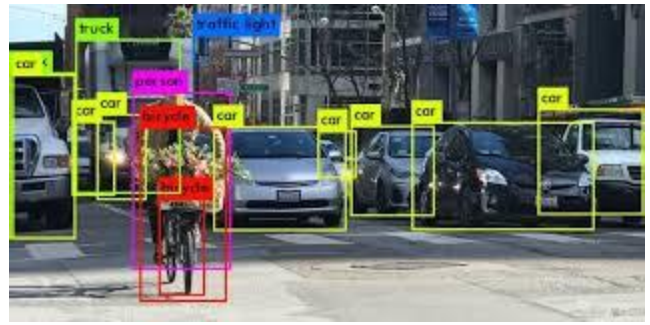
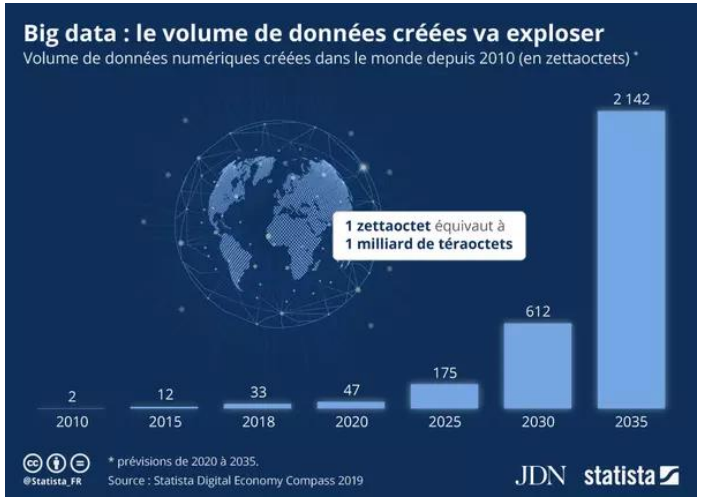
Maasai Team – Inria/3IA – Université Côte d'Azur

Introduction to machine learning

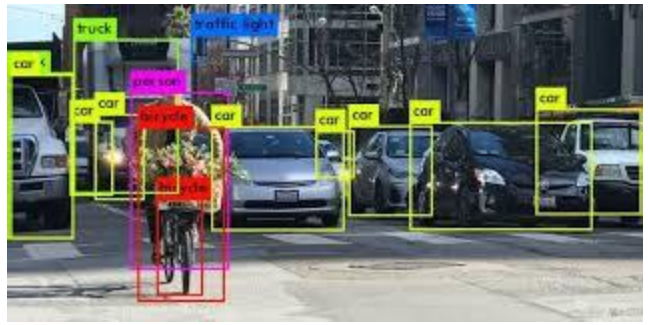
- Machine learning (ML) is widely used in different aspects of our lives
  - Image recognition[1]
  - Text generation (ChatGPT or Gemini)
  - Big data analysis
  - Quantitative structure-activity relationship (QSAR)[2]
  - Discovery of a new antibiotic[3]
  - Alpha fold DeepMind[4]
  - Increase of data availability
  - Computational power + dedicated packages (R & Python)





[1] Shen, D., Wu, G. & Suk, H.-I. Deep Learning in Medical Image Analysis. *Annu. Rev. Biomed. Eng.* **19**, 221–248 (2017).
[2] Chan, H. C. S., Shan, H., Dahoun, T., Vogel, H. & Yuan, S. Advancing Drug Discovery via Artificial Intelligence. *Trends Pharmacol. Sci.* **40**, 592–604 (2019)
[3] Stokes, J. M. *et al.* A Deep Learning Approach to Antibiotic Discovery. *Cell* **180**, 688-702.e13 (2020)
[4] Jumper et al Highly accurate protein structure prediction with AlphaFold *Nature* 583–589 (2021)

Introduction to machine learning



← Tweet

François Chollet
@fchollet

With tools like Colab, Keras, and TensorFlow, virtually anyone can solve in a day, with no initial investment, problems that would have required an engineering team working for a quarter and $20k in hardware in 2014

Traduire le Tweet

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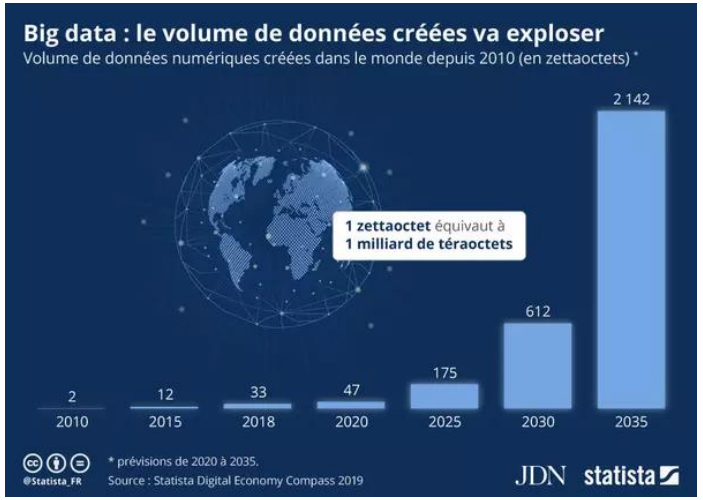

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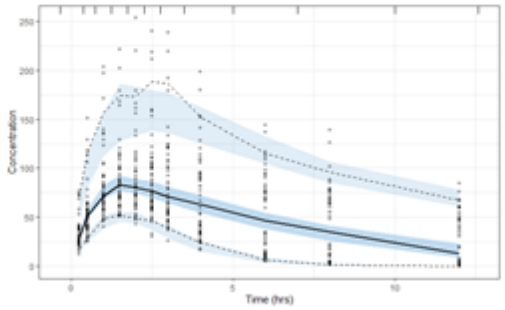
[4] Jumper et al Highly accurate protein structure prediction with AlphaFold *Nature* 583–589 (2021)

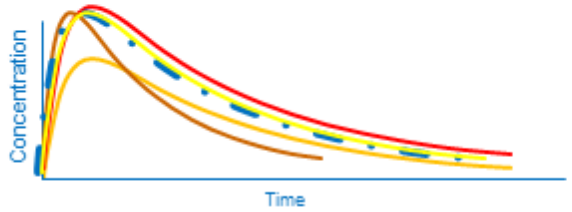
Applications of population pharmacokinetic modeling

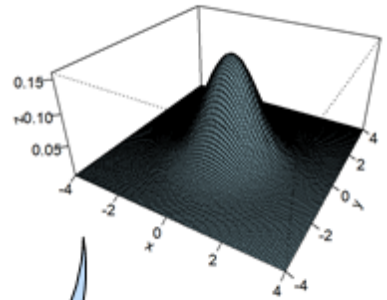
Internal model evaluation: Visual Predictive Check



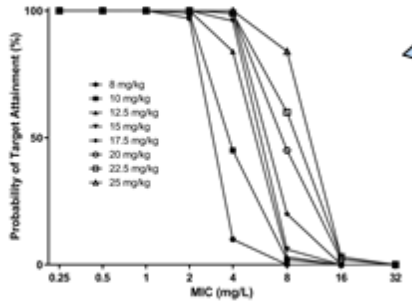
No exposure information available (i.e age, weight but no drug mesurement)
Monte Carlo Simulations (weighted sampling in the joint distribution)

Population pharmacokinetics model

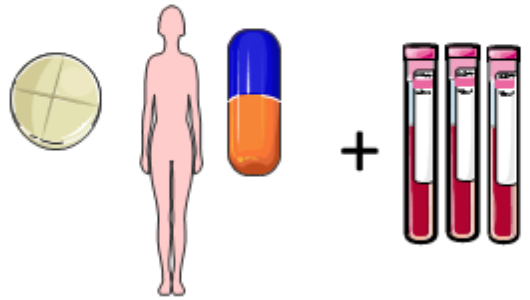




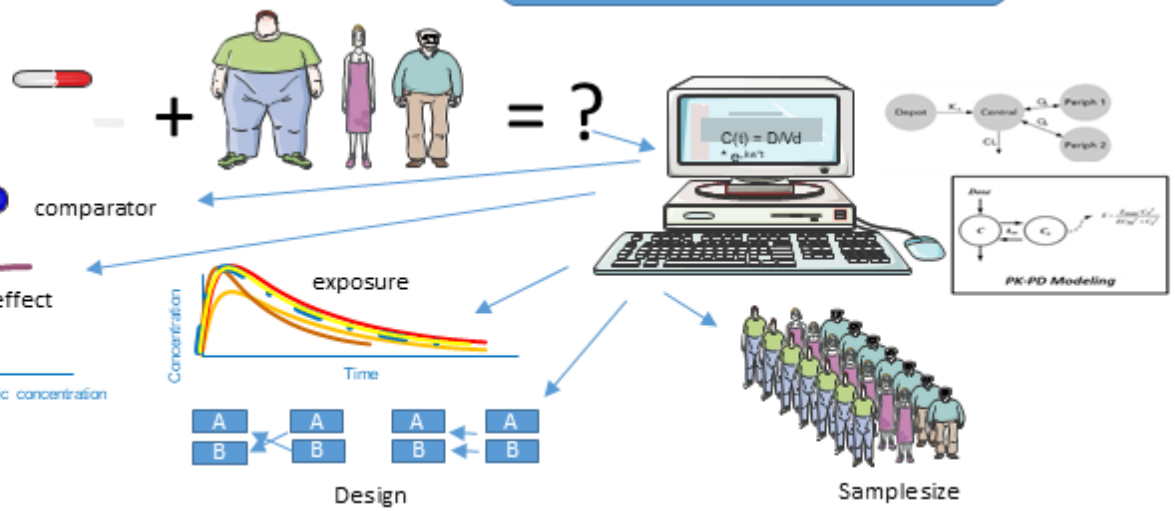
Probability of Target Attainment



Exposure information available (ie drug measurement) + covariable (ie age, weight))
MAP-BE



Clinical Trial Simulations

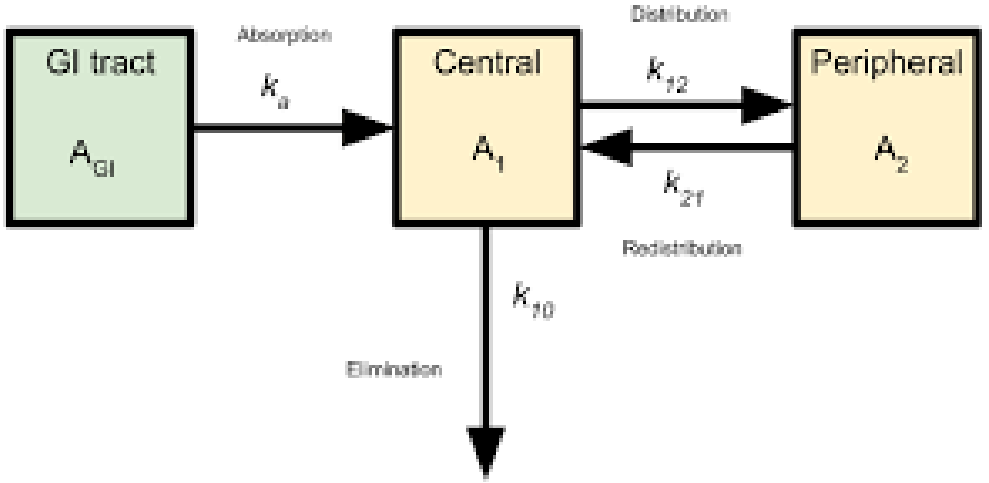


$$P(\theta|c) = P(c|\theta) * P(\theta) / P(c)$$

Dosing recommandation (MIPD)

Comparison of standard statistics vs ML

- **Standard statistical approach (POPPK):**
  - Based on understanding of biological processes, interpretable
  - but may be limited by current knowledge



- **Machine Learning:**
  - No explicitly defined physiological model (black box)
  - Complex algorithmic approach (e.g. Xgboost, neural network, SVM…)
  - Large numbers of free parameters and complex interactions

→ minimize errors between predicted and observed values (loss function)

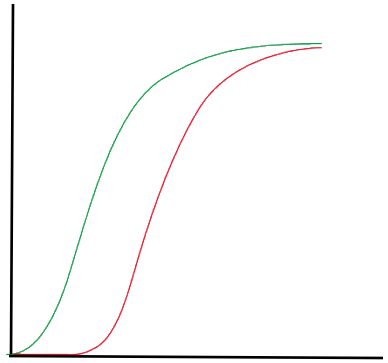
Comparison of standard statistics vs ML

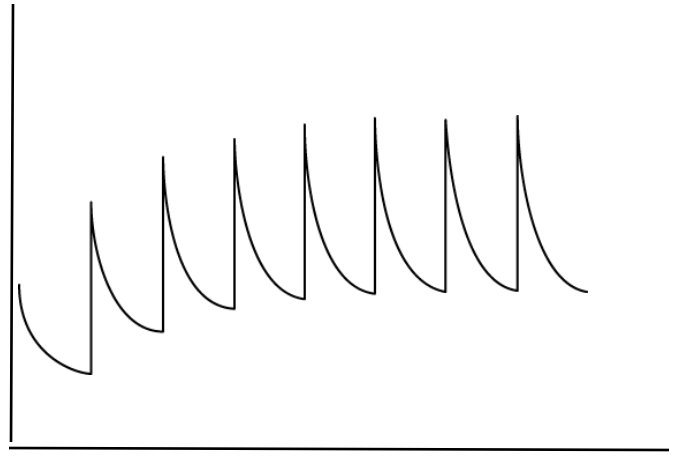
- In simple words
  - Standard statistics: data are entered into a model to predict results
  - ML approaches, the data are fed with the results to an algorithm that constructs the model **without *a priori* knowledge on the underlying associations (*data driven*).**
- ML methods → **individual prediction**
- ML methods particularly suited when there is a high degree of complexity/correlation between predictors (= “features”).

Standard statistics

Machine Learning

Use of Machine Learning in Pharmacometrics





> Clin Pharmacokinet. 2021 Feb;60(2):223-233. doi: 10.1007/s40262-020-00927-6.

A Machine Learning Approach to Estimate the Glomerular Filtration Rate in Intensive Care Unit Patients Based on Plasma Iohexol Concentrations and Covariates

Jean-Baptiste Woillard [1 2 3], Charlotte Salmon Gandonnière [4], Alexandre Destere [5 6 7], Stephan Ehrmann [4 8], Hamid Merdji [9 10], Armelle Mathonnet [11], Pierre Marquet [5 6 7], Chantal Barin-Le Guellec [6 12 13]

Affiliations + expand

PMID: 32794122 DOI: 10.1007/s40262-020-00927-6

> Pharm Res. 2022 Oct;39(10):2497-2506. doi: 10.1007/s11095-022-03351-6. Epub 2022 Aug 3.

Optimization of Vancomycin Initial Dose in Term and Preterm Neonates by Machine Learning

Laure Ponthier [1 2], Pauline Ensuque [2], Alexandre Destere [1 3], Pierre Marquet [1 4], Marc Labriffe [1 4], Evelyne Jacqz-Aigrain [5], Jean-Baptiste Woillard [6 7]

Affiliations + expand

PMID: 35918452 DOI: 10.1007/s11095-022-03351-6

Epub 2024 Mar 19.

A machine learning approach to predict daptomycin exposure from two concentrations based on Monte Carlo simulations

Cyrielle Codde [1], Florence Rivals [2], Alexandre Destere [3], Yeleen Fromage [2], Marc Labriffe [2 4], Pierre Marquet [2 4], Clément Benoist [4], Laure Ponthier [4], Jean-François Faucher [1], Jean-Baptiste Woillard [2 4]

> Kidney Int Rep. 2023 Nov 3;9(1):134-144. doi: 10.1016/j.ekir.2023.10.023. eCollection 2024 Jan.

Optimization of Rituximab Therapy in Adult Patients With PLA2R1-Associated Membranous Nephropathy With Artificial Intelligence

Alexandre Destere [1 2], Maxime Teisseyre [3 4 5], Diane Merino [1], Marion Cremoni [4 6], Alexandre O Gérard [1 5], Thomas Crepin [7], Noémie Jourde-Chiche [8], Daisy Graça [3 4 6], Kévin Zorzi [3 4], Céline Fernandez [3 4], Vesna Brglez [3 4 6], Sylvia Benzaken [6], Vincent L M Esnault [3 5], Sylvain Benito [9], Milou-Daniel Drici [1], Barbara Seitz-Polski [3 4 5 6]

Epub 2024 Mar 16.

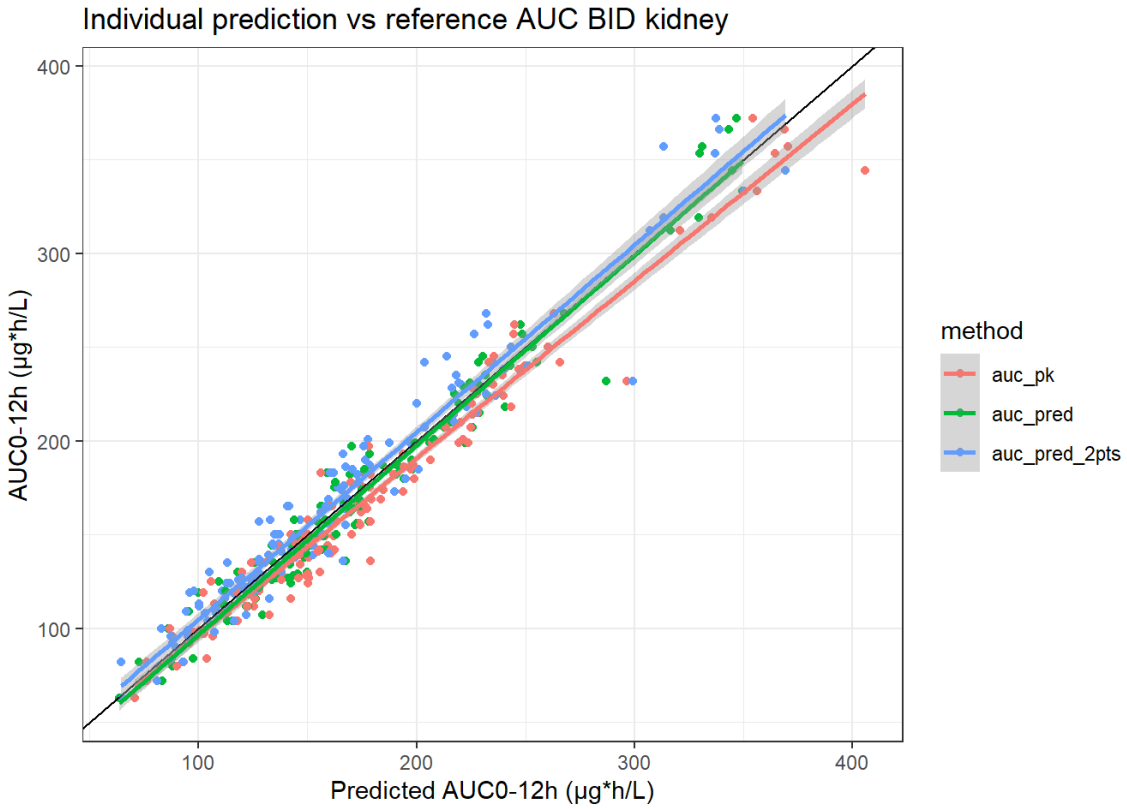
Optimization of Ganciclovir and Valganciclovir Starting Dose in Children by Machine Learning

Laure Ponthier [1 2], Julie Autmizguine [3 4 5], Benedicte Franck [6 7], Anders Åsberg [8 9], Philippe Ovetchkine [4], Alexandre Destere [10], Pierre Marquet [1 11], Marc Labriffe [1 11], Jean-Baptiste Woillard [12 13]

Affiliations + expand

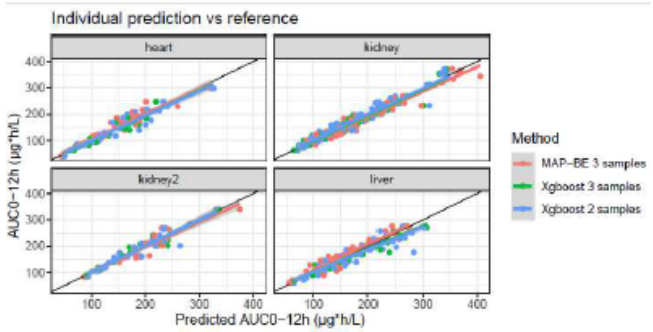
Example: A posteriori TAC exposure

- Development of a ML model to predict the TAC AUC (TDM) based on ISBA data **(https://abis.chu-limoges.fr/login):** 3 individual concentrations / a few covariates → ~5000 AUC/~2000 patients
- Excellent performances in external full PK profiles vs ref AUC (trapezoidal) based **on 2** or 3 samples
- Bias/RMSE external data (e.g. in kidney transplant recipients) =
  - **ML** 3 samples: 2.1%/7.7%
  - **ML** 2 samples: -2.4%/8.8%
  - **POPPK** 3 samples: 5%/9.6%

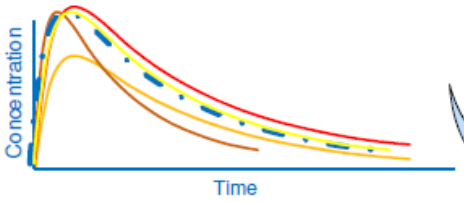


Woillard *et al.* CPT 2021

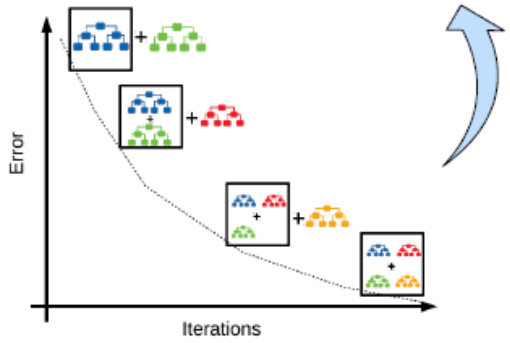
In the case of a limited number of data → simulations to train ML algorithm?



- External evaluation in 286 full PK profiles in kidney, heart and liver transplant recipients and comparison of predicted $AUC_{0\text{-}12h}$ to that of the MAP Bayesian estimation based on the 0, 1 and 3h limited sampling strategy



- 9000 tacrolimus Monte Carlo simulations performed from a population pharmacokinetic model in mrgsolve
- Application of filters to remove unrealistic simulated profiles



http://tvas.me/articles/2019/08/26/Block-Distributed-Gradient-Boosted-Trees.html

Development of Xgboost machine learning algorithms :

- Splitting into a training (75%) and a test (25%) set subsets.
- Ten-fold cross-validation applied to the training set to tune the hyperparameters and evaluate the model performance

Pharmacological Research 167 (2021) 105578

Contents lists available at ScienceDirect

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journal homepage: www.elsevier.com/locate/yphrs

Estimation of drug exposure by machine learning based on simulations from published pharmacokinetic models: The example of tacrolimus

Jean-Baptiste Woillard [a,b,c,*,1], Marc Labriffe [a,b,c], Aurélie Prémaud [a,b], Pierre Marquet [a,b,c]

[a] Univ. Limoges, IPPRITT, F-87000 Limoges, France
[b] INSERM, IPPRITT, U1248, F-87000 Limoges, France
[c] Department of Pharmacology and Toxicology, CHU Limoges, F-87000 Limoges, France

		Trained from simulations		Trained from ISBA*	
Organ transplanted	Method	Relative MPE (%)	relative RMSE (%)	Relative MPE (%)	relative RMSE (%)
kidney 1 (n = 137)	Xgboost 2 concentrations	1.08	8.5	-0.6	9.0
kidney 2 (n = 34)	Xgboost 2 concentrations	0.7	9.0	-1.0	9.1
liver (n = 68)	Xgboost 2 concentrations	5.9	12.9	3.3	12.9
heart (n = 47)	Xgboost 2 concentrations	3.2	11.4	-0.4	9.7

Paves the way / development of ML algorithms for TDM in different therapeutic areas / importance to validate on “real” data.

***https://abis.chu-limoges.fr/login / Woillard CPT 2021**

Ganciclovir in pediatrics: first dose prediction (PhD works L Ponthier)

- Monte Carlo simulations → 10800 patients from literature POPPK models (2 GCV IV, 3 GCV oral)
- Train of a classification ML model to predict AUC0-24h at SS in the target (40-60 mg*h/L)
- Iterative search of the first dose that maximise the target attainment
- Comparison of theoretical target attainment after administration of the dose ML with POPPK literature formulae

Ponthier *et al.* ClinPK 2024

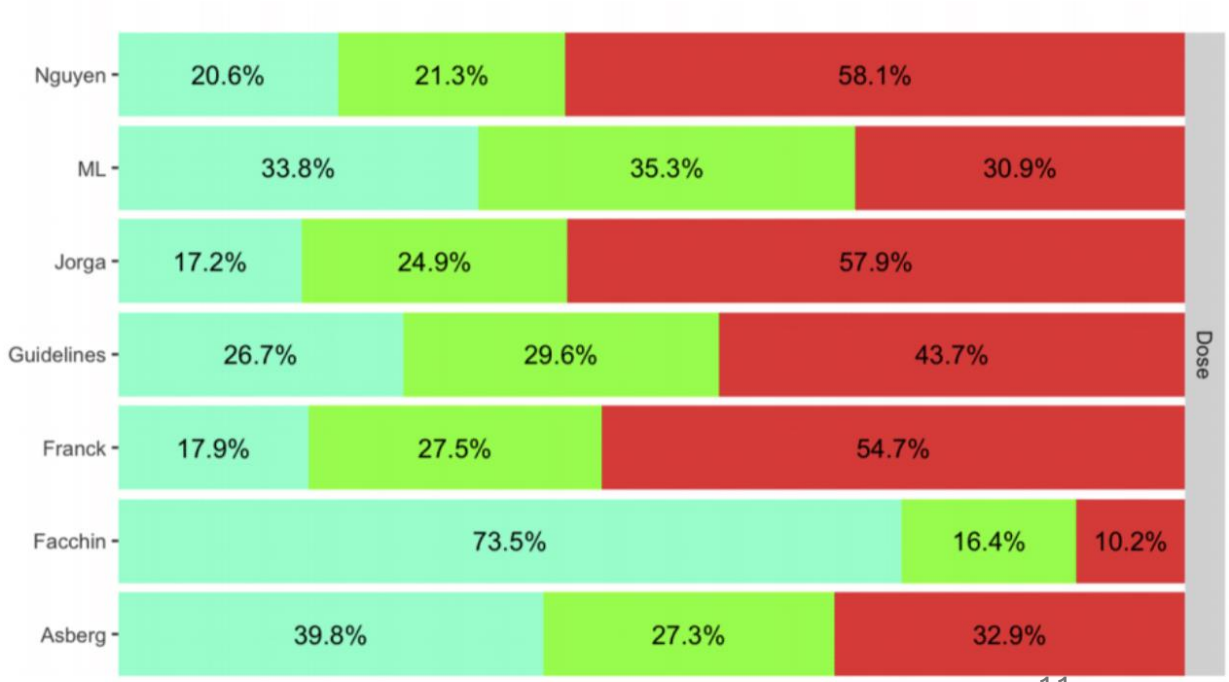
Clinical Pharmacokinetics
https://doi.org/10.1007/s40262-024-01362-7

ORIGINAL RESEARCH ARTICLE

Check for updates

Optimization of Ganciclovir and Valganciclovir Starting Dose in Children by Machine Learning

Laure Ponthier[1,2] · Julie Autmizguine[3,4,5] · Benedicte Franck[6,7] · Anders Åsberg[8,9] · Philippe Ovetchkine[4] · Alexandre Destere[10] · Pierre Marquet[1,11] · Marc Labriffe[1,11] · Jean-Baptiste Woillard[1,11]



Simulated test set for VGCV

Rituximab in anti-PLA2R1 GEM

- Train of a classification ML model to predict underexposure at month-3
- Rationalization of features based on biological criteria

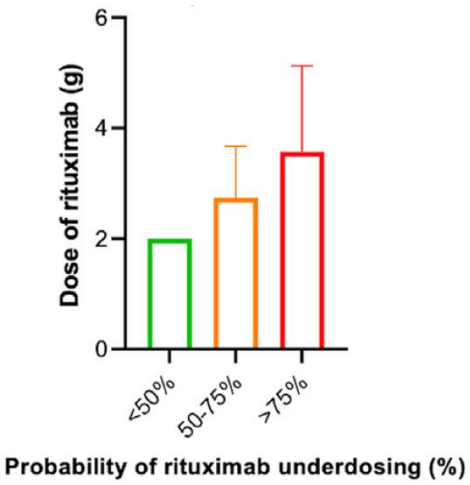
Association of Variables	Accuracy
Age + Gender + BSA	0.4559
Age + Gender + BSA + GFR on D0	0.5294
Age + Gender + BSA + GFR on D0 + CD19 on D0	0.5
Age + Gender + BSA + GFR on D0 + anti-PLA2R1 antibody titer on D0	0.5441
Age + Gender + BSA + GFR on D0 + anti-PLA2R1 antibody titer on D0 + weight	0.5417
Age + Gender + BSA + GFR on D0 + anti-PLA2R1 antibody titer on D0 + height	0.5441
Age + Gender + BSA + GFR on D0 + anti-PLA2R1 antibody titer on D0 + BMI	0.4559
Age + Gender + BSA + GFR on D0 + anti-PLA2R1 antibody titer on D0 + serum albumin on M0	0.6324
Age + Gender + BSA + anti-PLA2R1 antibody titer on D0 + serum albumin on D0	0.6471
Age + Gender + BSA + anti-PLA2R1 antibody titer on D0 + serum albumin on D0 + serum creatinine on D0	0.6618
Age + Gender + BSA + anti-PLA2R1 antibody titer on D0 + serum albumin on D0 + serum creatinine on D0 + use of angiotensin-converting enzyme inhibitors	0.6471
Age + Gender + BSA + anti-PLA2R1 antibody titer on D0 + serum albumin on D0 + serum creatinine on D0 + use of angiotensin II receptor blockers	0.6471
Age + Gender + BSA + anti-PLA2R1 antibody titer on D0 + serum albumin on D0 + serum creatinine on D0 + use of furosemide	0.6471
Age + Gender + BSA + anti-PLA2R1 antibody titer on D0 + serum albumin on D0 + serum creatinine on D0 + use of hydrochlorothiazide	0.6471
Age + Gender + BSA + anti-PLA2R1 antibody titer on D0 + serum albumin on D0 + serum creatinine on D0 + serum albumin on D15	0.72
Age + Gender + BSA + serum albumin on D0 + serum creatinine on D0 + serum albumin on D15 + serum creatinine on D15	0.72
Age + Gender + BSA + anti-PLA2R1 antibody titer on D0 + serum albumin on M0 + serum creatinine on D0 + serum albumin on D15 + serum creatinine on D15	0.794
Age + Gender + BSA + anti-PLA2R1 antibody titer on D0 + serum albumin on D0 + serum creatinine on D0 + serum albumin on D15 + serum creatinine on D15 + number of visits	0.748
Age + Gender + BSA + anti-PLA2R1 antibody titer on D0 + serum albumin on D0 + serum creatinine on D0 + serum albumin on D15 + serum creatinine on D15 + proteinuria on D0	0.7647
Age + Gender + BSA + anti-PLA2R1 antibody titer on D0 + serum albumin on D0 + serum creatinine on D0 + serum albumin on D15 + serum creatinine on D15 + proteinuria on D15	0.75
All predictors ($N = 21$)	0.7353

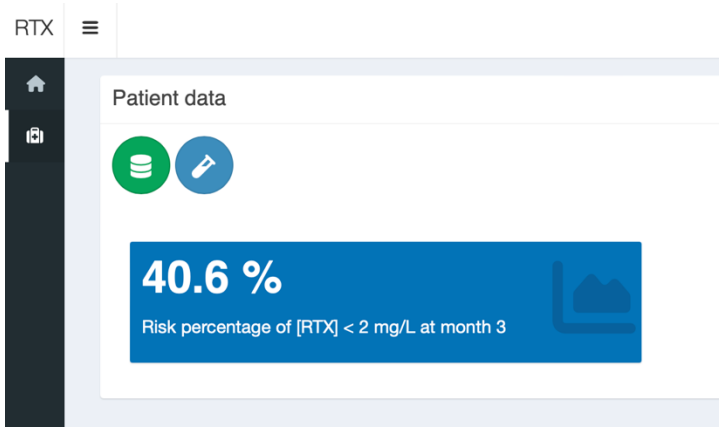
Performance Assessment Criteria	Training Data Set	Testing Data Set
Accuracy (%)	79.4	79.2
No information rate (%)	69.1	54.2
Sensitivity (%)	78.7	84.6
Specificity (%)	81.0	72.7
Positive predictive value (%)	90.2	78.6
Negative predictive value (%)	63.0	80.0
F-score (%)	84.1	81.5

Optimization of Rituximab Therapy in Adult Patients With PLA2R1-Associated Membranous Nephropathy With Artificial Intelligence

Alexandre Destere[1,9,10], Maxime Teisseyre[2,3,4,10], Diane Merino[1], Marion Cremoni[3,5], Alexandre O Gérard[1,4], Thomas Crepin[6], Noémie Jourde-Chiche[7], Daisy Graça[2,3,5], Kévin Zorzi[2,3], Céline Fernandez[2,3], Vesna Brglez[2,3,5], Sylvia Benzaken[5], Vincent L.M. Esnault[2,4], Sylvain Benito[8], Milou-Daniel Drici[1,10] and Barbara Seitz-Polski[2,3,4,5,10]

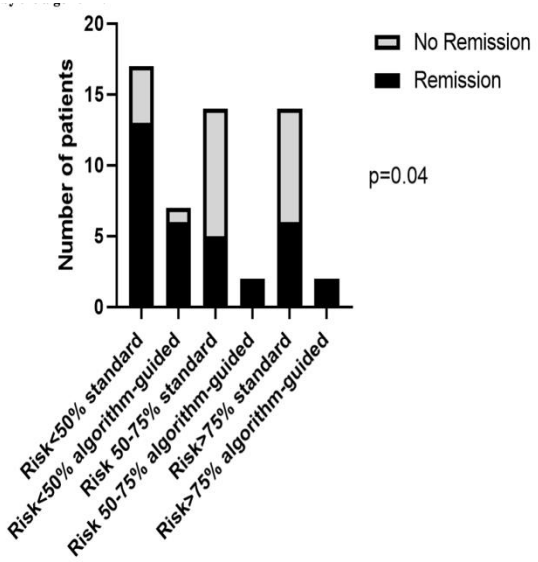
Destere *et al.* KIR 2023





Rituximab in anti-PLA2R1 GEM (preliminary study of hospital clinical research program PHRC)

- Calculation of underexposure prediction and derivation of individualized dose
  - < 50 % : 1g x 2 (D0 and D15)
  - 50-75% : 1g x 3 (D0, D15 and M1)
  - > 75 % : 1g x 4 (D0, D15, M1 and M1.5)
- Reference : previous patient treated by RTX
- N = 11 patients
  - < 50 % : 7
  - 50-75% : 2
  - > 75 % : 2

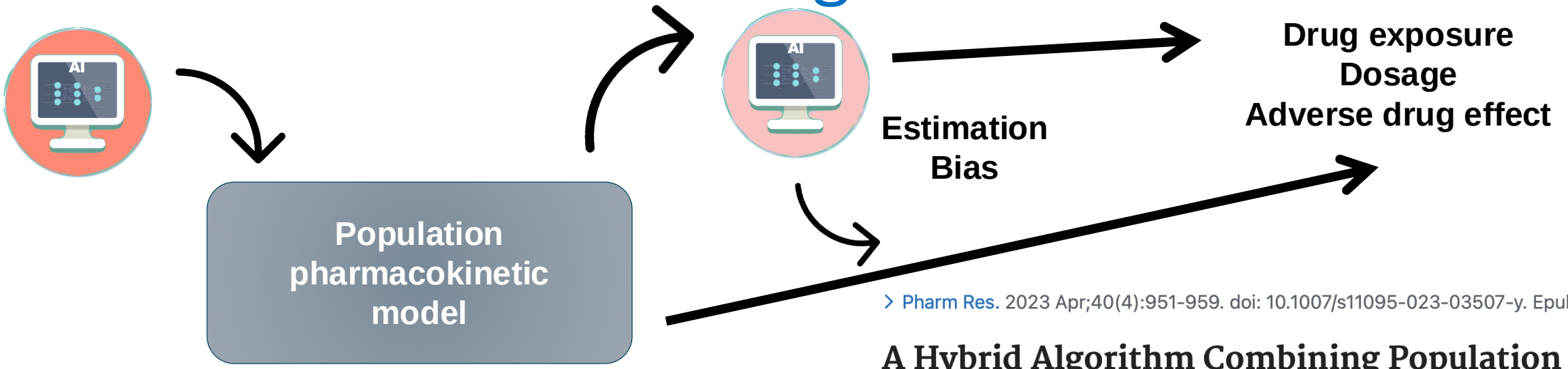


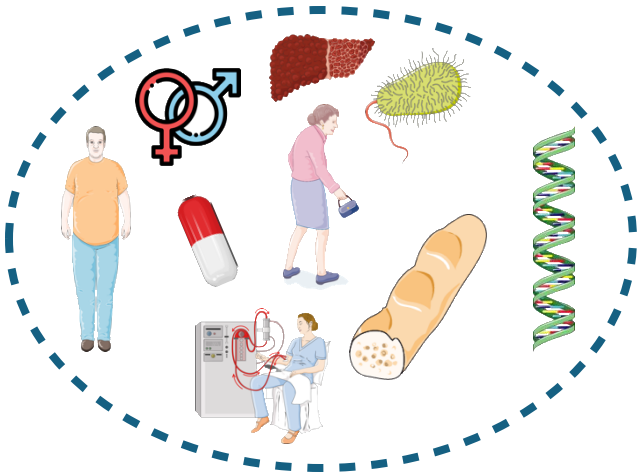
Artificial intelligence to guide rituximab therapy in patients with PLA2R1-associated membranous nephropathy

Maxime Teisseyre*[1,2,3,4], Alexandre Destere*[5,6], Marion Cremoni[1,2,3,4], Sonia Boyer-Suavet[7], Alexandre Karamé[8], Léa Corlu[9], Gabrielle Duneau[10], Kévin Zorzi[1,3], Céline Fernandez[1,3], Vesna Brglez[1,3,4], Sylvia Benzaken[4], Guillaume Favre[2], Vincent L. M. Esnault[1,2], Sylvain Benito[11], and Barbara Seitz-Polski [1,2,3,4]

Trials	n	Immunological remission*	Clinical remission
Algorithm-guided rituximab treatment	11	91 %	91%
GEMRITUX rituximab (23)	37	50%	35%
GEMRITUX NIAT (23)	38	12%	21%
RI-CYCLO rituximab (24)	37	63%	51%
RI-CYCLO cyclophosphamide-corticosteroid (24)	37	50%	65%
MENTOR rituximab (22)	65	52%	35%
MENTOR cyclosporin (22)	65	28%	49%
STARMEN tacrolimus-rituximab (32)	43	70%	44%
STARMEN cyclophosphamide-corticosteroid (32)	43	92%	74%
High-dose rituximab (15)	28	78%	64%

Use of Machine Learning in Pharmacometrics





› Pharm Res. 2023 Apr;40(4):951-959. doi: 10.1007/s11095-023-03507-y. Epub 2023 Mar 29.

A Hybrid Algorithm Combining Population Pharmacokinetic and Machine Learning for Isavuconazole Exposure Prediction

Alexandre Destere [1 2], Pierre Marquet [1 3], Marc Labriffe [1 3], Milou-Daniel Drici [2], Jean-Baptiste Woillard [4 5]

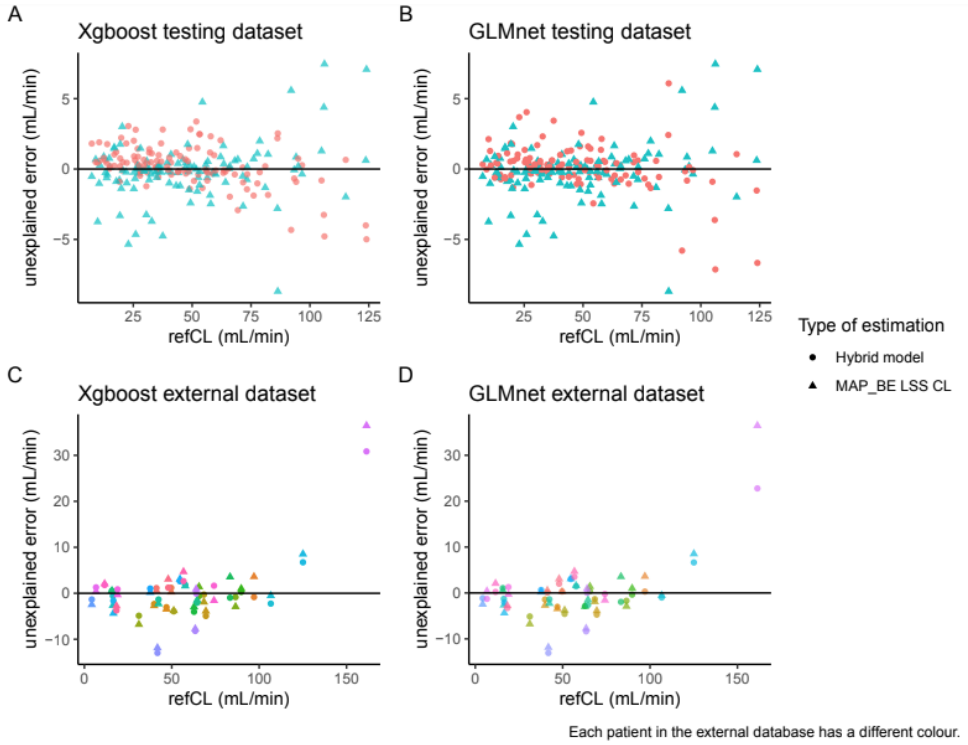
› Clin Pharmacokinet. 2022 Aug;61(8):1157-1165. doi: 10.1007/s40262-022-01138-x. Epub 2022 May 31.

A Hybrid Model Associating Population Pharmacokinetics with Machine Learning: A Case Study with Iohexol Clearance Estimation

Alexandre Destere [1 2 3], Pierre Marquet [1 2], Charlotte Salmon Gandonnière [4], Anders Åsberg [5 6], Véronique Loustaud-Ratti [1 7], Paul Carrier [7], Stephan Ehrmann [4 8], Chantal Barin-Le Guellec [1], Aurélie Premaud [1], Jean-Baptiste Woillard [9 10]

Hybrid model: combination of ML and POPPK to keep interpretability: iohexol (PhD works A Destere) (1)

- Simulation of 500 patients / iohexol for estimation of iohexol CL (GFR) from a literature POPPK model (2)
- MAP-BE on simulations
  - All samples (REF)
  - 3 samples (LSS)
  - Calculation of residual error (REF – LSS)
- Train ML algorithm to learn residual error (**from data obtained by MAP-BE**: observed concentrations, PK parameters + featured engineering eg diff between observed concentrations)
- Evaluation in the train (10-fold CV), test and external real data



1-Destere A et al. A Hybrid Model Associating Population Pharmacokinetics with Machine Learning: A Case Study with Iohexol Clearance Estimation. *Clin Pharmacokinet*. 2022

2-Destere A et al. A single Bayesian estimator for iohexol clearance estimation in ICU, liver failure and renal transplant patients. *Br J Clin Pharmacol*. 2022;88:2793–801.

Hybrid model: combination of ML and POPPK to keep interpretability: iohexol (PhD works A Destere) (1)

	Training		Testing		External	
	MAP-BE LSS	Hybrid model Xgboost	MAP-BE LSS	Hybrid model Xgboost	MAP-BE LSS	Hybrid model Xgboost
MPE%	-2.0	-0.3	-1.0	0.7	-3.7	-2.2
RMSE%	10.1	7.5	6.2	5.7	14.3	10.9
MPE out of ± 20% (%)	4.0	2.8	1.7	0.9	13.9	8.3

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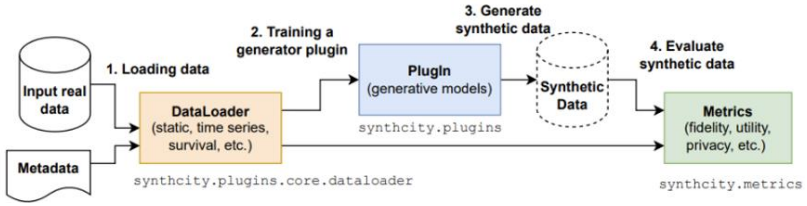
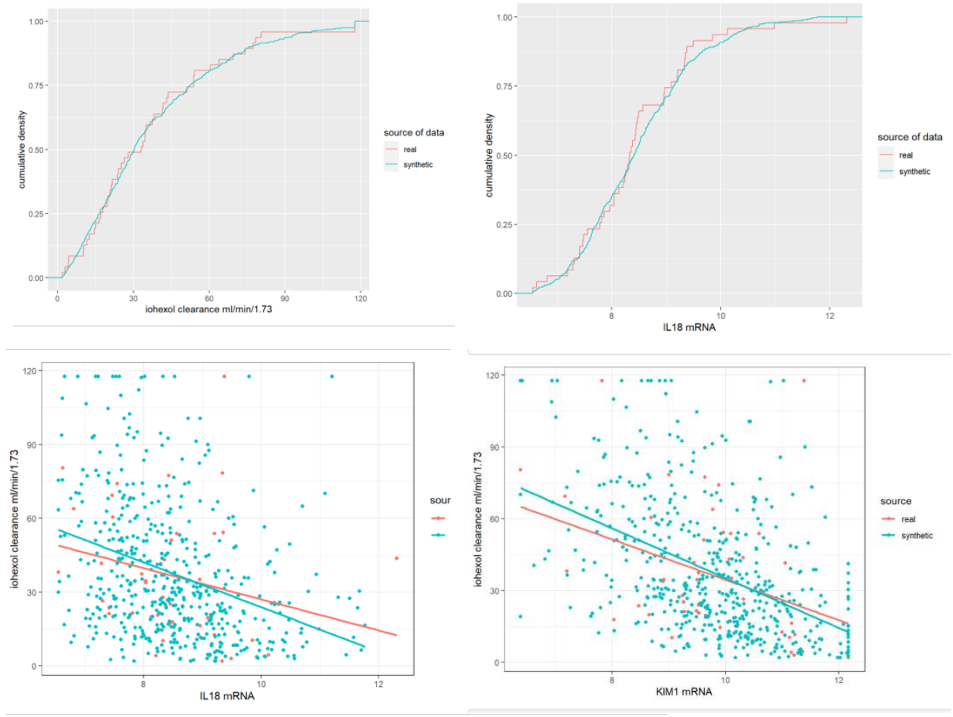
Creation of synthetic patients by ML/DL

synthcity

- Creation of virtual patients: continuous or categorical variables regardless of their distribution (e.g., GAN)
- Balance between **utility and privacy**
- Improvement of predictive model performances (limited data = often the case in Pharmacometrics)
- Alternative to federated learning: creation of virtual data twin of local data → **sharing between centers** (useful for multicentric projects)



Qian *et al.* 2023 https://arxiv.org/abs/2301.07573



Recent synthetic data approach privacy validated by CNIL (French National commission for informatics & privacy)

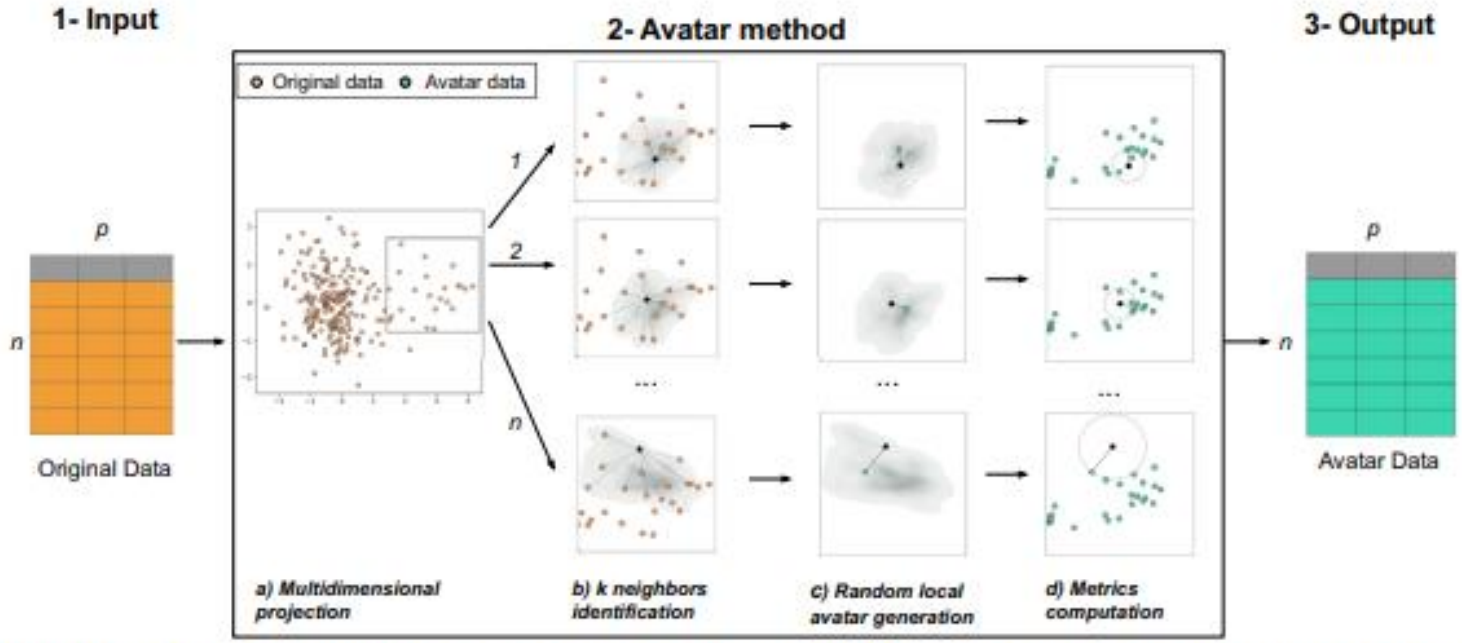
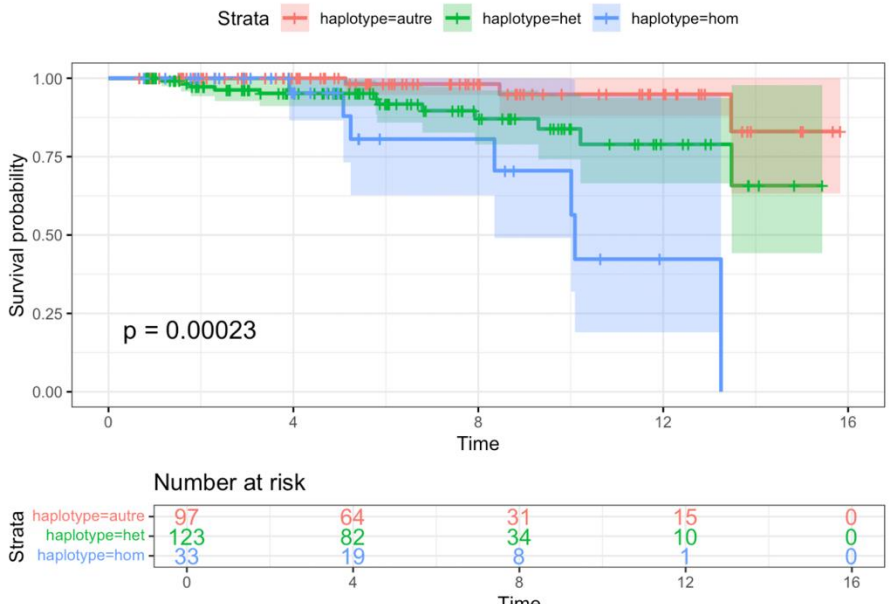


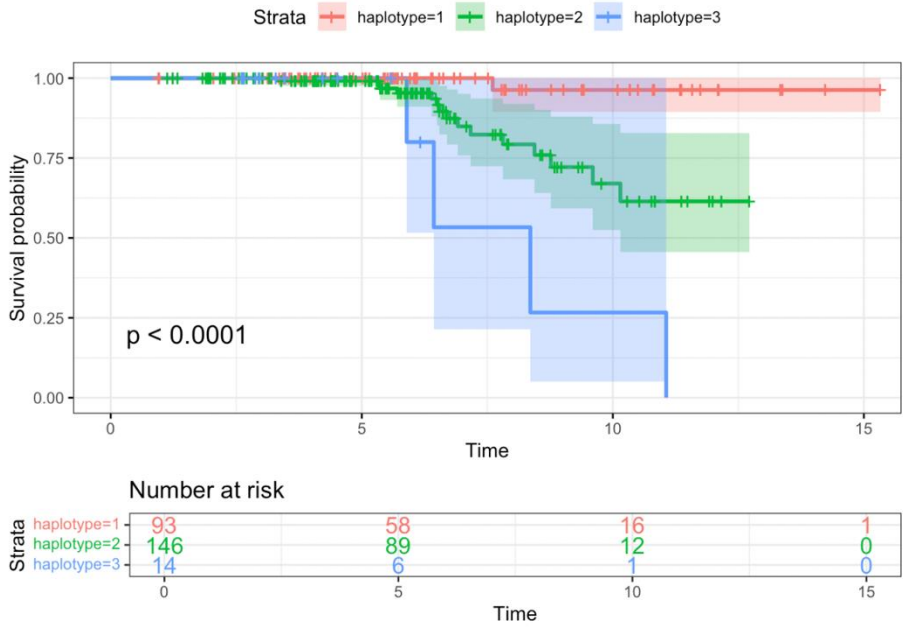
Fig. 5 The Avatar method uses local modeling to stochastically generate a synthetic individual, termed an avatar simulation. (1) Original pseudonymized sensitive data. **(2)** The core of the Avatar method consists of four steps: (a) individuals are projected in a multidimensional space; (b) pairwise distances are computed to find the k nearest neighbors (here $k = 12$) in a reduced space; (c) a synthetic individual is pseudo-randomly generated in the subspace defined by the neighbors; (d) privacy metrics are evaluated. **(3)** Output of the dataset of synthetic data. More details are provided online (https://docs.octopize.io/).

Guillaudeux et al Nature Digital Med 2023 *Patient-centric synthetic data generation, no reason to risk reidentification in biomedical data analysis*

Original data



Avatar k=10



Benchmarking of different approaches

Algorithm	KL inverse	KS test	DCR* [5th-50th-95th]	NNDR* [5th-50th-95th]	AUC ROC#
Original data	NA	NA	NA	NA	NA
Avatar k=5	0.87	0.72	[0.28-0.57-1.00]	[0.14-0.33-0.75]	0.581
Avatar k=5 augmented	0.93	0.92	[0.09-0.42-1.51]	[0.05-0.27-0.94]	0.534
Avatar K k=10	0.79	0.90	[0.50-1.00-2.14]	[0.34-0.72-0.97]	0.550
Avatar k=10 augmented	0.89	0.91	[0.19-0.68-1.51]	[0.10-0.47-0.94]	0.518
Avatar k=20	0.77	0.89	[0.47-1.04-1.90]	[0.34-0.74-0.98]	0.503
Avatar k=20 augmented	0.76	0.88	[0.47,1.01,1.87]	[0.32-0.74-0.94]	0.474
CT-GAN	0.78	0.88	[0.83-1.78-3.39]	[0.52-0.87-0.99]	0.234
CT-GAN augmented	0.89	0.91	[0.81-1.87-3.62]	[0.52-0.87-0.99]	0.345
survVAE	0.84	0.89	[0.89-1.01-2.99]	[0.55-0.88-0.99]	0.298
survVAE augmented	0.86	0.90	[0.86-1.94-3.08]	[0.54-0.90-0.99]	0.367

Woillard et al. CPT PS, 2024

Synthetic data in POPPK

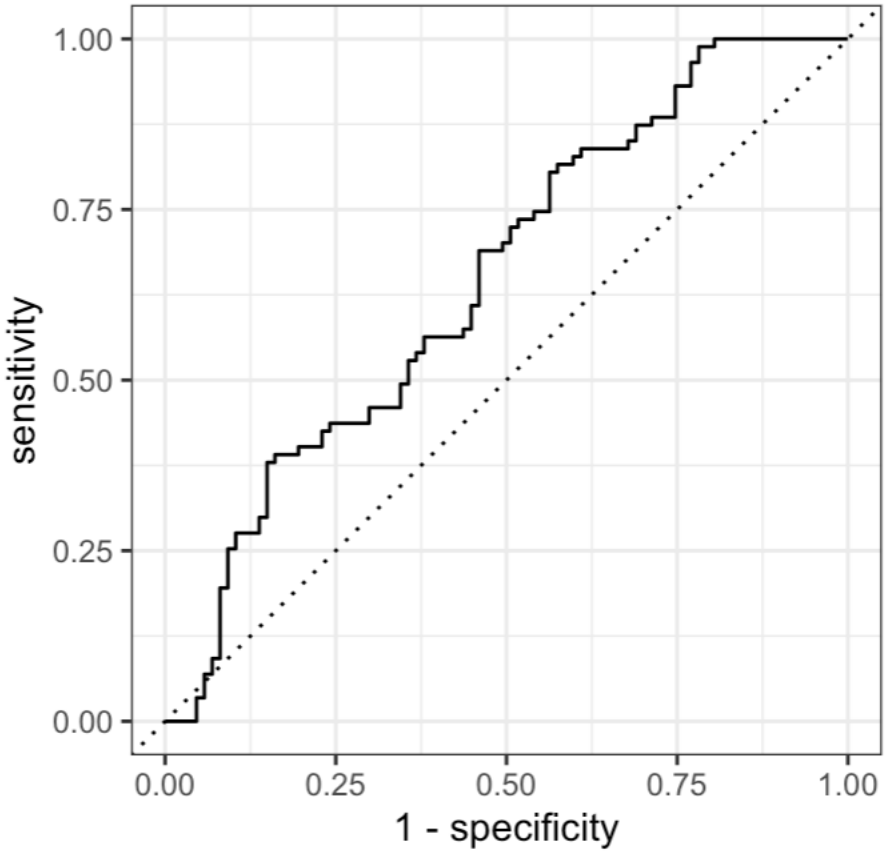
Can synthetic data be the key to overcoming data sharing in pharmacometrics? A case study of tacrolimus in heart transplant patients

Alexandre Destere[1,2], Adrien Paschier[3,4], Marc Labriffe[3,4], Clément Benoist[3,4], Pierre Marquet[3,4], Milou-Daniel Drici[1], Charles Bouveyron[2], Jean-Baptiste Woillard[3,4]

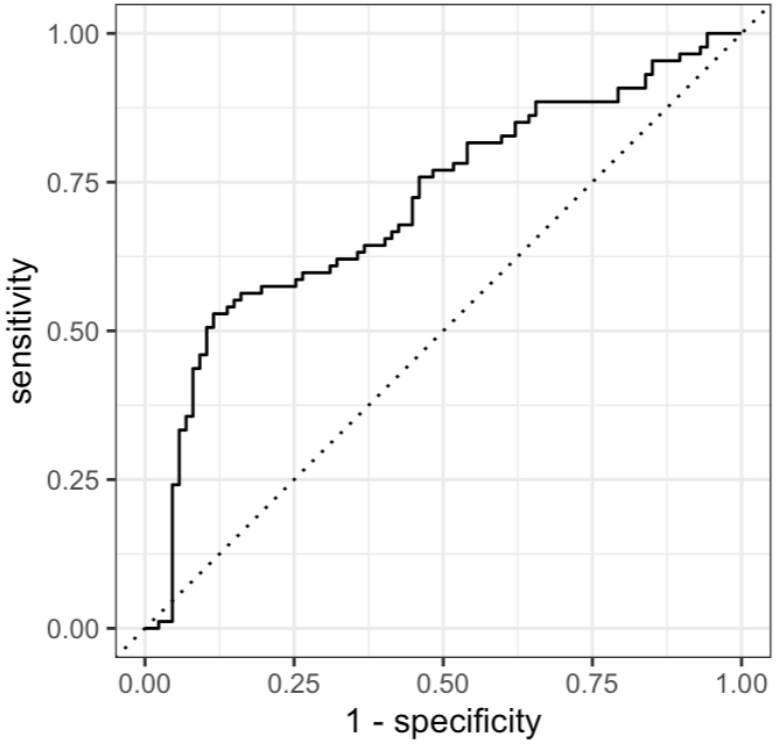
Under review CPT: PS

→ Evaluate the no-tracability of real data

→ Logistic regression to determine real or synthetic data



Avatar with K = 5



Avatar with K = 15

Synthetic data in POPPK

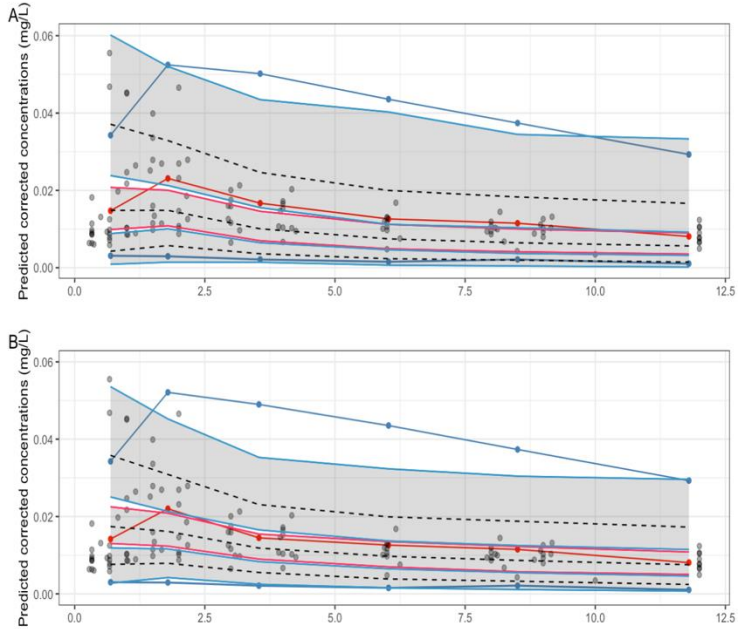
Can synthetic data be the key to overcoming data sharing in pharmacometrics? A case study of tacrolimus in heart transplant patients

Alexandre Destere[1,2], Adrien Paschier[3,4], Marc Labriffe[3,4], Clément Benoist[3,4], Pierre Marquet[3,4], Milou-Daniel Drici[1], Charles Bouveyron[2], Jean-Baptiste Woillard[3,4]

Under review CPT: PS

→ Evaluate the abilities of tabular generative algorithms to create synthetic PK to develop POPPK model

→ Focus on structural model



> Br J Clin Pharmacol. 2023 Dec;89(12):3584-3595. doi: 10.1111/bcp.15857. Epub 2023 Aug 10.

Tacrolimus population pharmacokinetics in adult heart transplant patients

	Paschier et al. Original development dataset	k=5	k=5 augmented	k=15	k=15 augmented	CTGAN	CTGAN augmented	TVAE	TVAE augmented
Best model	2cp ~ TrCp	2cp ~ TrCp	2cp ~ Tlag	2cp ~ TrCp	2cp ~ Tlag	2cp ~ Tlag	2cp ~ Tlag	2cp ~ TrCp	2cp ~ Tlag
Tlag (RSE%)	-		0.3 (3.3)	-	0.3 (0.7)	0.3 (14.4)	0.4 (6.9)	-	0.3 (6.0)
Ktr (RSE%)	4.74 (Fixed)	8.7 (19.1)	-	23.8 (NE)	-	-	-	7.1 (13.8)	-
Mtt (RSE%)	0.5 (11.4)	0.4 (8.17)	-	0.3 (54.2)	-	-	-	0.6 (6.8)	-
Ka (RSE%)	1.0 (8.4)	0.6 (7.7)	0.7 (3.2)	13.7 (67.7)	8.5 (6.3)	0.6 (6.5)	0.4 (6.6)	1.2 (22.6)	0.9 (7.0)
Cl (RSE%)	15.5 (10.9)	14.6 (8.7)	14.7 (4.6)	10.4 (NE)	0.2 (30.1)	14.7 (14.3)	14.7 (6.9)	11.5 (10.1)	10.2 (6.0)
V1 (RSE%)	21.2 (34.4)	10.5 (21.1)	23.8 (7.3)	146 (46.2)	175 (2.8)	29.4 (18.2)	19.2 (10.6)	0.0008 (NE)	27 (12.9)
Q (RSE%)	78.3 (11.2)	68.4 (8.4)	66.3 (4.8)	39.7 (97.3)	49.9 (5.2)	47.8 (21.1)	43.8 (8.8)	109 (16.7)	85.2 (6.7)
V2 (RSE%)	498.8 (16.7)	443 (15.5)	403 (6.4)	240 (NE)	2140 (3.5)	340 (54.7)	378 (13.2)	375 (17.8)	368 (9.9)
ωTlag (RSE%)	-	-	0.3 (12.6)	-	0.05 (13.5)	0.5 (19.1)	0.5 (9.0)	-	0.5 (10.1)
ωKtr (RSE%)	-	0.6 (26.6)	-	0.6 (105)	-	-	-	0.1 (109)	-
ωMtt (RSE%)	0.6 (16.0)	0.2 (31.7)	-	0.2 (135)	-	-	-	0.03 (143)	-
ωKa (RSE%)	0.2 (49.7)	0.2 (40.4)	0.2 (11.8)	0.8 (20.7)	0.5 (8.7)	0.1 (119.0)	0.2 (20.4)	0.3 (52.7)	0.2 3(23.5)
ωCl (RSE%)	0.7 (12.7)	0.4 (15.4)	0.5 (7.1)	0.6 (47.1)	0.7 (34.1)	0.6 (47.0)	0.6 (8.5)	0.4 (16.3)	0.5 (7.8)
ωV1 (RSE%)	2.5 (17.6)	0.3 (98.2)	0.6 (11.1)	0.2 (60.6)	0.3 (6.9)	0.2 (49.5)	0.3 (36.0)	3.2 (96.5)	0.4 (15.9)
ωQ (RSE%)	0.6 (16.4)	0.3 (17.8)	0.4 (8.2)	0.5 (78.4)	0.5 (7.0)	0.7 (18.4)	0.5 (12.0)	0.5 (17.7)	0.6 (9.8)
ωV2 (RSE%)	1.0 (16.2)	0.7 (17.5)	0.6 (8.3)	1.1 (69.9	0.4 (7.8)	0.5 (208)	0.8 (13.2)	0.8 (17.3)	0.9 (7.8)
a (mg/L)	-	-	-	-	-	-	-	-	-
b (%)	0.12 (4.3)	0.06 (5.8)	0.07 (2.7)	0.05 (9.3)	0.06 (2.6)	0.22 (6.5)	0.23 (2.6)	0.13 (5.4)	0.14 (2.6)

Inria Maasai

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Thanks !