

A short introduction to machine learning and example of combination with population pharmacokinetics modeling

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Introduction to machine learning

- Machine learning (ML) is widely used in different aspects of our lives
 - Applications in image recognition (1), big data analysis, Quantitative structure-activity relationship; QSAR (2), discovery of a new antibiotic (3)
 - Increase of data availability
 - Computational power + dedicated packages (R & Python)

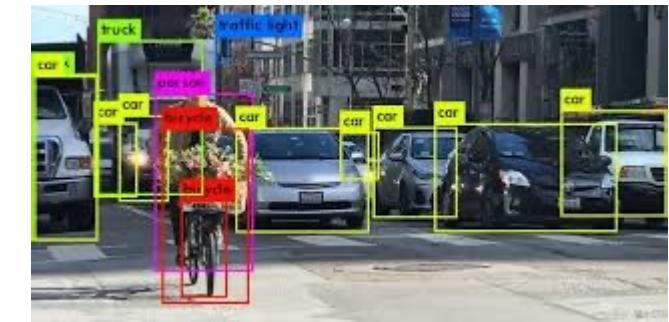
← Tweet

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](#)

10:03 PM · 20 nov. 2020 · Twitter for Android



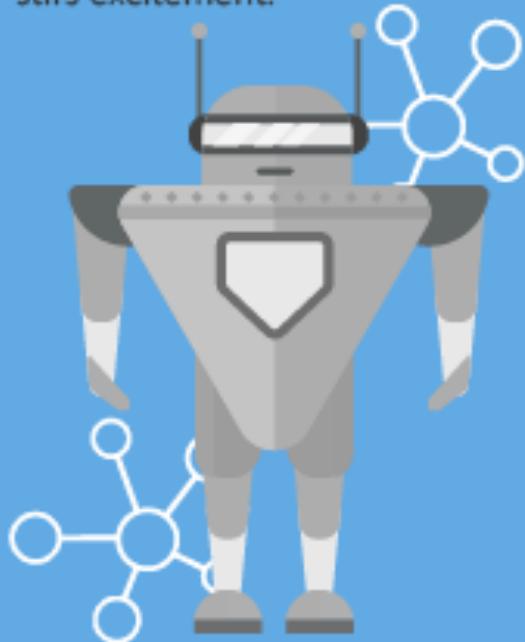
Shen, D., Wu, G. & Suk, H.-I. Deep Learning in Medical Image Analysis. *Annu. Rev. Biomed. Eng.* **19**, 221–248 (2017).

(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)

ARTIFICIAL INTELLIGENCE

Early artificial intelligence stirs excitement.



1950's

1960's

1970's

1980's

1990's

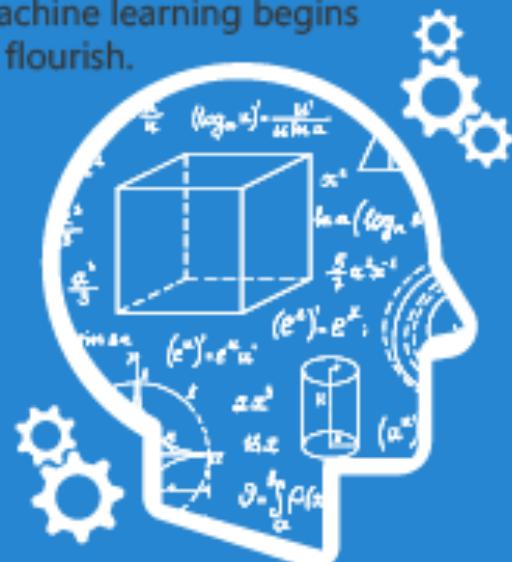
2000's

2010's

Dozen of different ML methods

MACHINE LEARNING

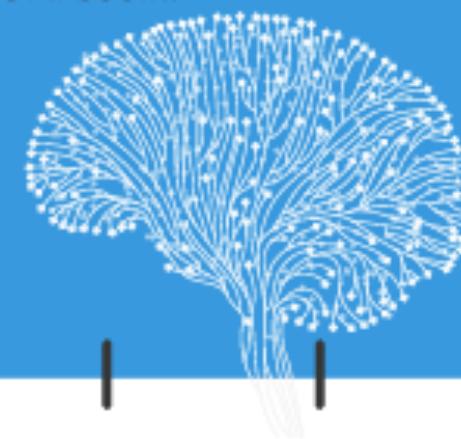
Machine learning begins to flourish.



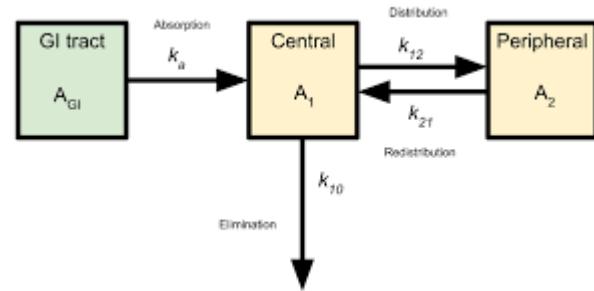
Neural networks

DEEP LEARNING

Deep learning breakthroughs drive AI boom.



Basic concepts



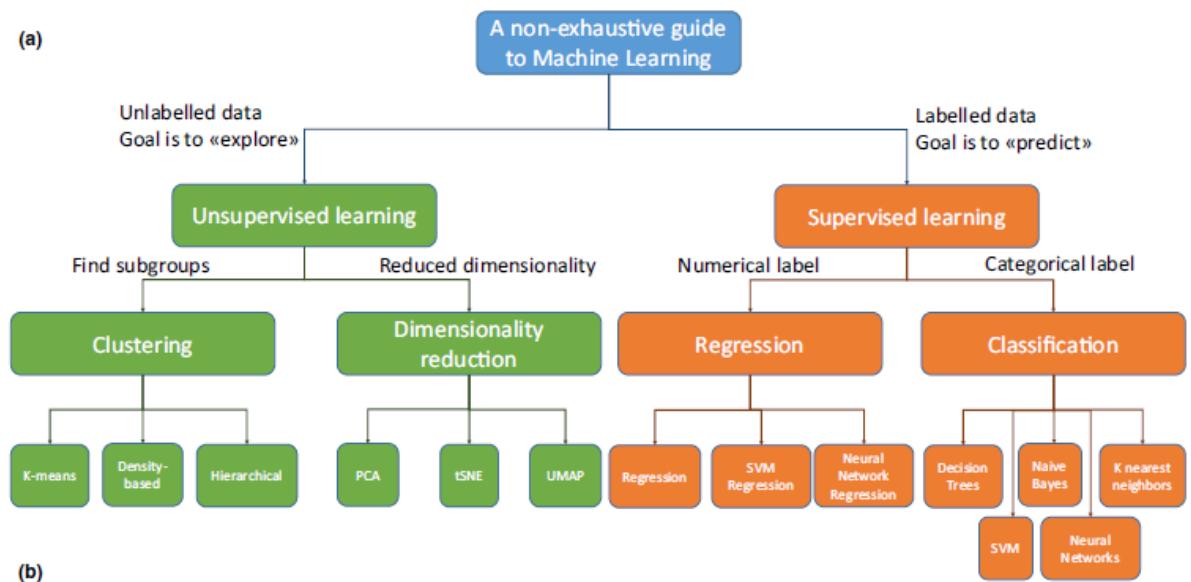
- Standard statistical approach:
 - a hypothesis → choice of a physiological or mechanistic model to describe the data
- ML:
 - No explicitly defined model
 - Complex algorithmic approach
 - Large numbers of free parameters and complex interactions
 - Goal → minimize errors between predicted and observed values (loss function).

Comparing 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.**
- Standard statistical approaches/ population pharmacokinetics → quantification of associations at a population scale and/or for the description of variabilities.
- ML methods → individual prediction
- ML methods particularly suited when there is a high degree of complexity/correlation between predictors (= “features”).

Methodology and Intention

- ML methods are heterogeneous, based on various mathematical approaches
- Supervised vs. unsupervised approaches
- Supervised:
 - Regression → minimisation of RMSE, MAE etc...
 - Classification → maximisation of accuracy, ROC-AUC, NPV, Sen, Spe, kappa...
 - 2 classes
 - Multiclasses



Badillo et al CPT 2020 « An Introduction to Machine Learning »

Model Evaluation in Machine Learning

Performance Metrics for Classification Problems

Accuracy

The number of correct predictions of the model on all predictions made.

$$\frac{(TP + TN)}{(TP + TN + FP + FN)}$$

Precision

The success rate of positive class predictions.

$$\frac{TP}{(TP + FP)}$$

Recall

The rate at which the positive class was guessed correctly.

$$\frac{TP}{(TP + FN)}$$

F1 Score

The harmonic mean of precision and recall values.

$$2 * \frac{Precision * Recall}{Precision + Recall}$$

AUC

The area under the ROC curve.

Confusion Matrix

		Predicted Class	
		+	-
Actual Class	+	True Positive (TP)	False Negative (FN)
	-	False Positive (FP)	True Negative (TN)

Performance Metrics for Regression Problems

Mean Squared Error (MSE)

The average squared difference between the estimated values and the actual value.

$$\frac{1}{n} \sum_{i=1}^n (y_i - \hat{y}_i)^2$$

Root Mean Squared Error (RMSE)

The square root of MSE. Generally, the lower the RMSE, the better.

$$\sqrt{\frac{1}{n} \sum_{i=1}^n (y_i - \hat{y}_i)^2}$$

MAE (Mean Absolute Error)

The mean of the absolute value of the errors.

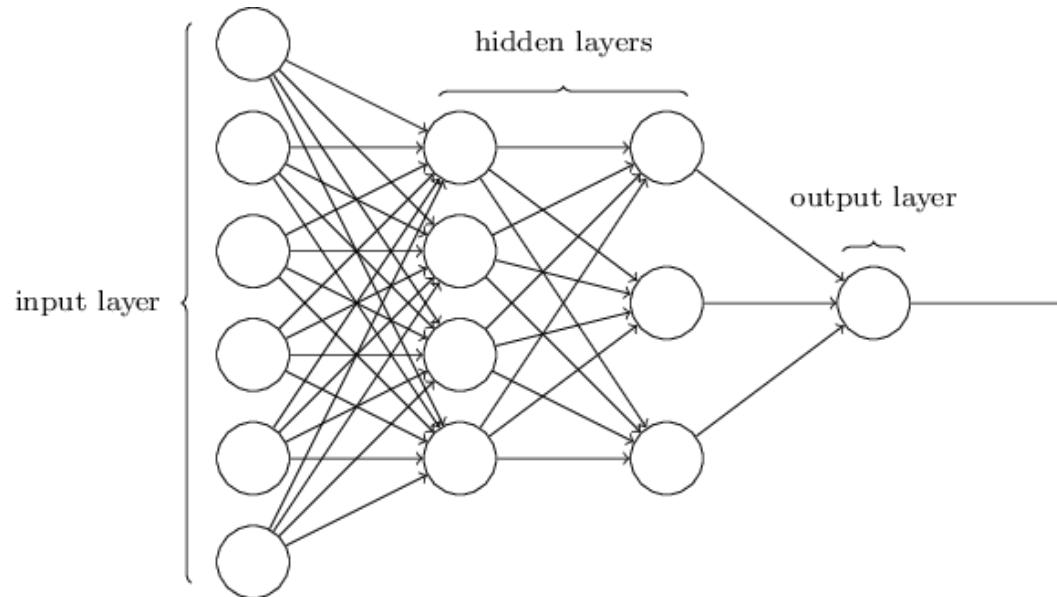
$$\frac{1}{n} \sum_{i=1}^n |y_i - \hat{y}_i|$$

R2 Score

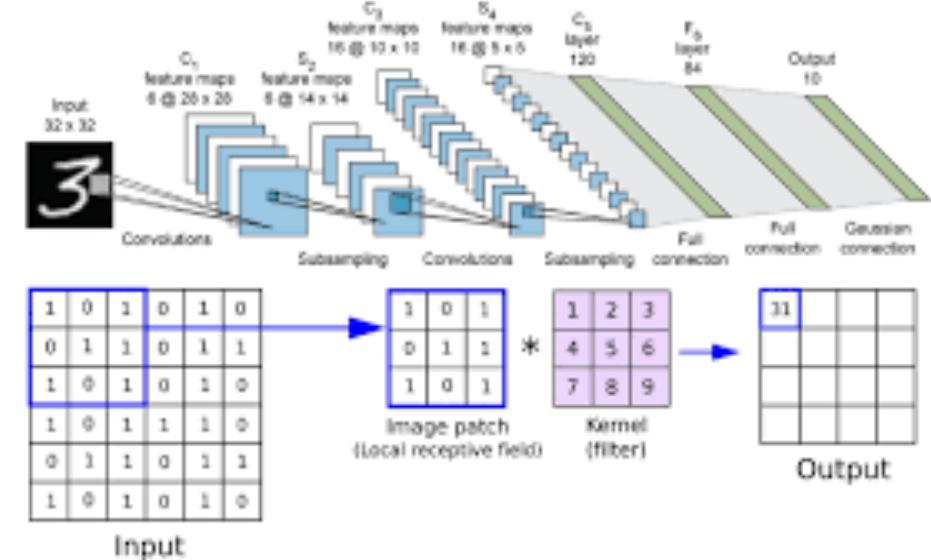
The percentage of the dependent variable explanation of the independent variables in the dataset.

Deep learning

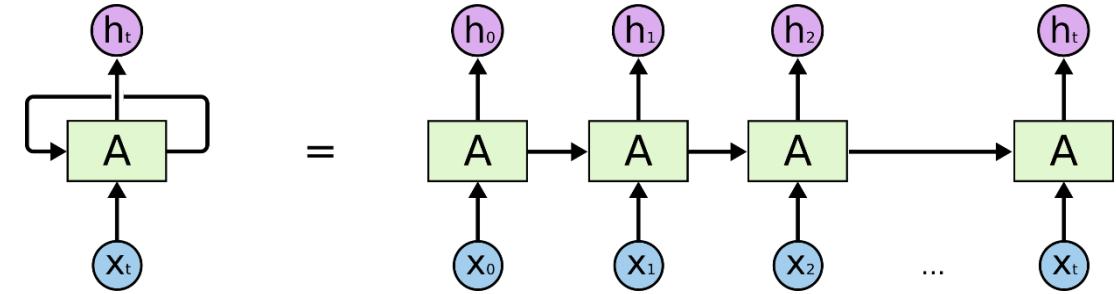
Dense fully connected NN/multilayer perceptron



Convolutional NN



Recurrent NN/ LSTM



The choice: ML or Deep Learning?

- Depends on the data and question you have
- $\sim \text{DL} > \text{ML}$ when $n > 10k$
- DL particularly useful when
 - feature engineering is tricky and takes a lot of effort.
 - hierarchical structure in the data (e.g. image)
- DL need a lot of computing resources

Letter | Published: 31 July 2019

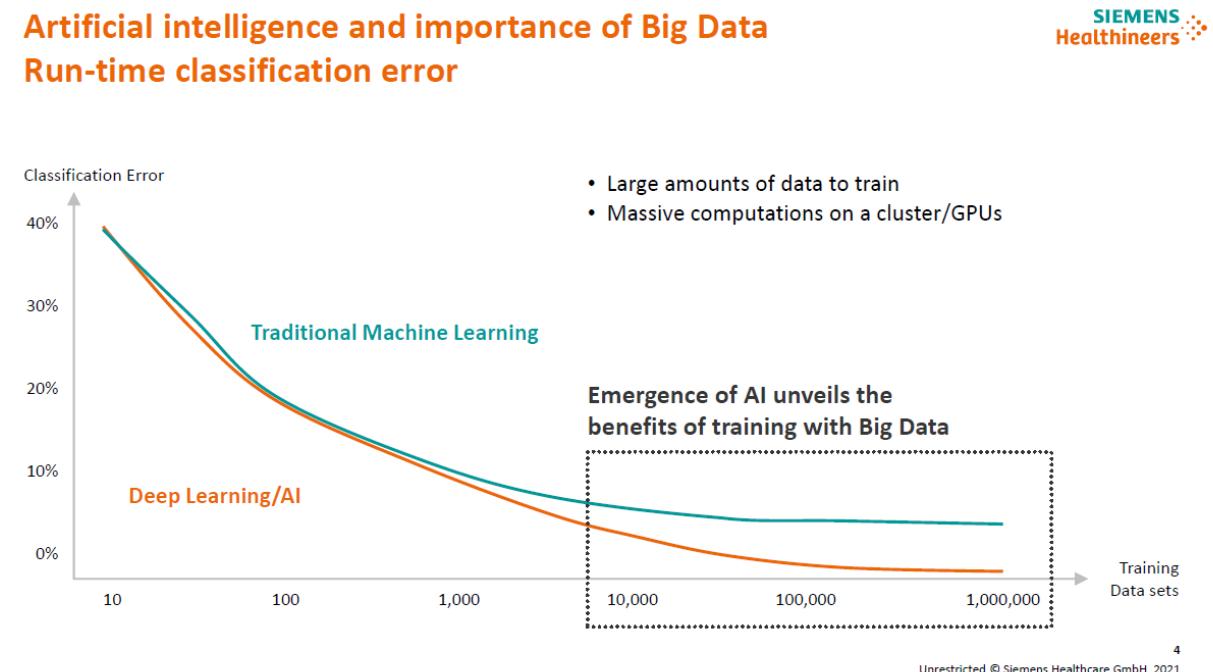
A clinically applicable approach to continuous prediction of future acute kidney injury

Nenad Tomašev , Xavier Glorot, [...] Shakir Mohamed

Nature 572, 116–119(2019) | Cite this article

32k Accesses | 166 Citations | 1589 Altmetric | Metrics

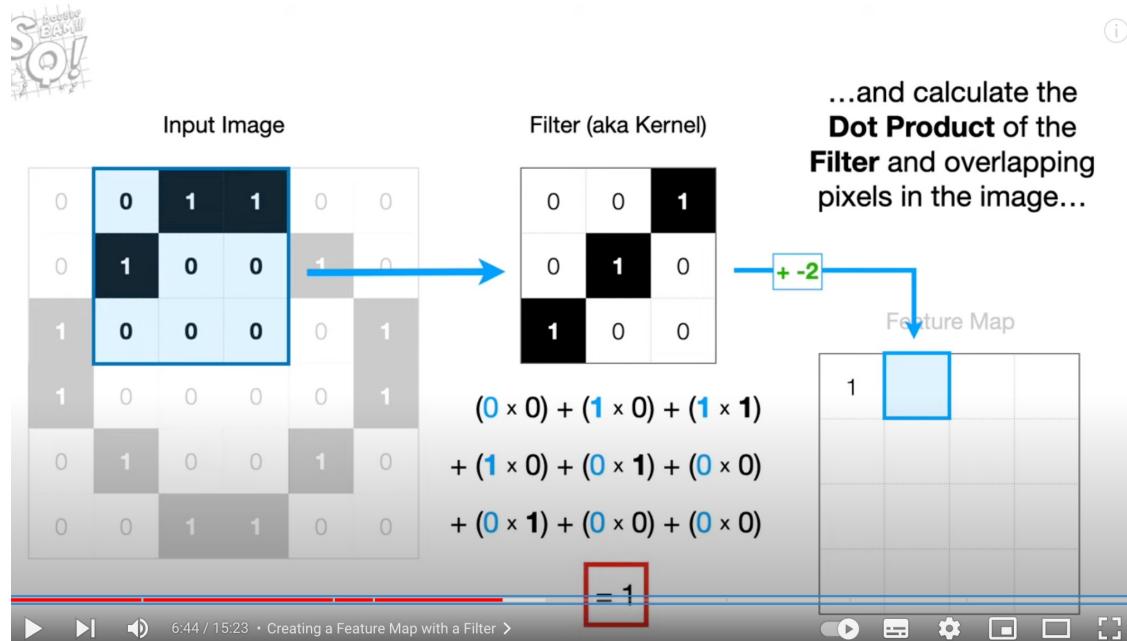
exemplar, our model was developed on a large, longitudinal dataset of electronic health records that cover diverse clinical environments, comprising 703,782 adult patients across 172 inpatient and 1,062 outpatient sites. Our model predicts 55.8% of all inpatient episodes of acute kidney injury and 90.2% of all acute kidney injuries that required subsequent



Dr Dorin Comaniciu, Artificial Intelligence for HealthCare,
From Hype to Value, AI4Health Winter School 2020

Type of data

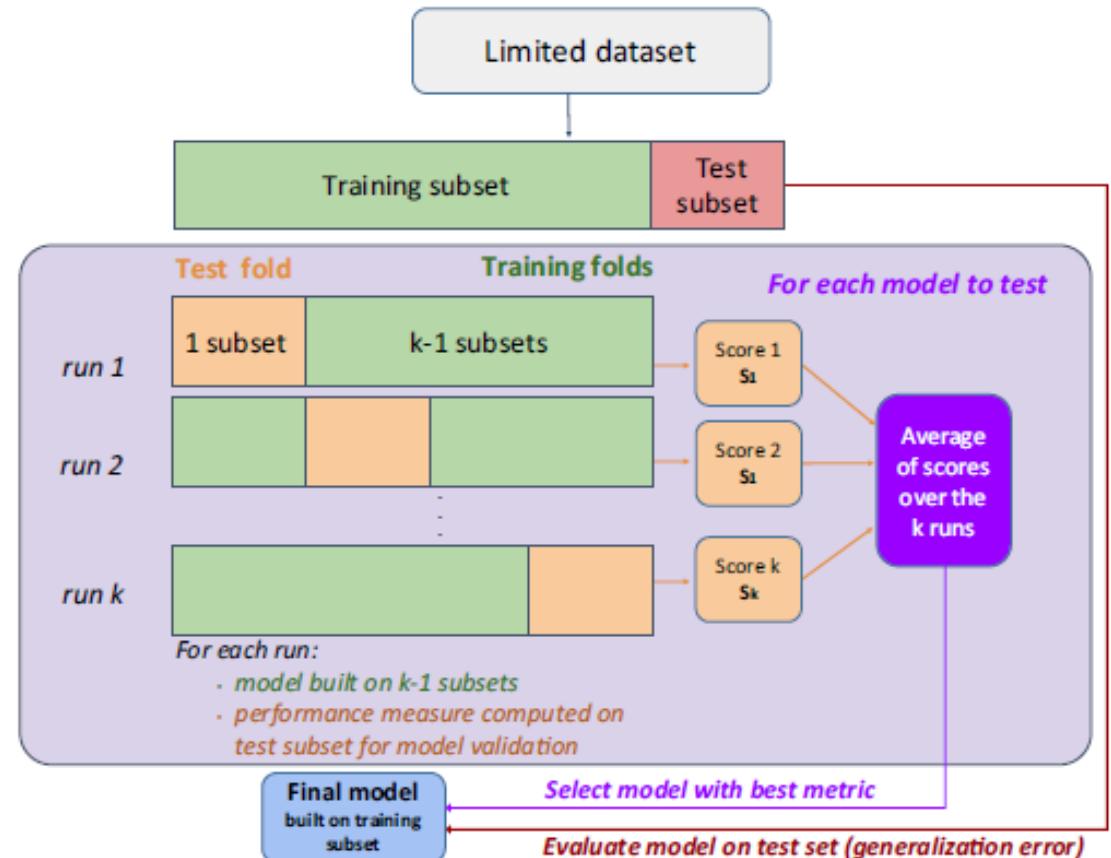
Année	Catégorie	Produit	Ventes	Evaluation p.
2017	Composants	Chaînes	200€	75 %
2015	Vêtements	Chaussettes	37€	22 %
2017	Vêtements	Cuissards	40€	22 %
2015	Vêtements	Shorts	133€	56 %
2017	Vêtements	Collants	360€	100 %
2015	Composants	Guidons	23€	35 %
2016	Vêtements	Chaussettes	23€	28 %
2016	Pièces détachées	Freins	34€	36 %
2016	Vélos	Vélos tout terrain	63€	40 %
2017	Composants	Freins	54€	38 %
2016	Accessories	Casques	170€	90 %
2016	Accessories	Feux	216€	90 %
2016	Accessories	Antivols	298€	90 %
2016	Composants	Axes de pédailler	10€	23 %
2015	Vêtements	Maillots	67€	5 %
2017	Pièces détachées	Axes de pédailler	6€	27 %
2015	Vélos	Vélos de route	35€	50 %
2017	Vêtements	Maillots	75€	40 %
2017	Accessories	Pneus et chambres	637€	90 %



Supervised Machine learning

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- Classical approach:
 - (tidying the data!)
 - Graphical exploration relationship outcome/predictors
 - Data splitting
 - Feature engineering (creation of informative predictors)
 - Tuning of algorithms hyperparameters by crossvalidation
 - Evaluation of the performances by crossvalidation once the best algorithm has been selected (to prevent overfitting)
 - Validation in test set and in external dataset(s)

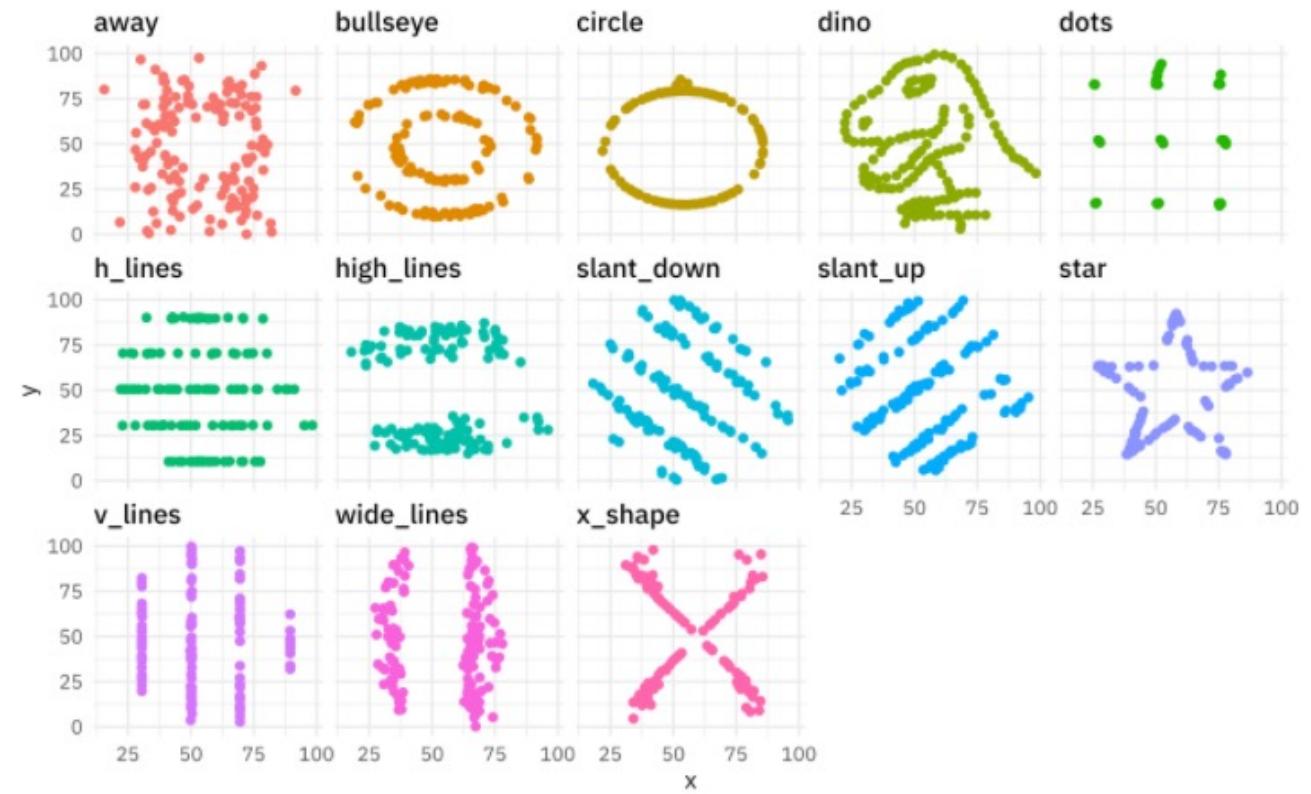


Importance of graphical exploration

```
datasaurus_dozen %>%
  group_by(dataset) %>%
  summarise(across(c(x, y), list(mean = mean, sd = sd)),
            x_y_cor = cor(x, y)
  )

## # A tibble: 13 x 6
##   dataset    x_mean   x_sd   y_mean   y_sd x_y_cor
##   <chr>      <dbl>   <dbl>   <dbl>   <dbl>   <dbl>
## 1 away       54.3    16.8    47.8    26.9   -0.0641
## 2 bullseye   54.3    16.8    47.8    26.9   -0.0686
## 3 circle     54.3    16.8    47.8    26.9   -0.0683
## 4 dino       54.3    16.8    47.8    26.9   -0.0645
## 5 dots        54.3    16.8    47.8    26.9   -0.0603
## 6 h_lines    54.3    16.8    47.8    26.9   -0.0617
## 7 high_lines 54.3    16.8    47.8    26.9   -0.0685
## 8 slant_down 54.3    16.8    47.8    26.9   -0.0690
## 9 slant_up   54.3    16.8    47.8    26.9   -0.0686
## 10 star       54.3    16.8    47.8    26.9   -0.0630
## 11 v_lines    54.3    16.8    47.8    26.9   -0.0694
## 12 wide_lines 54.3    16.8    47.8    26.9   -0.0666
## 13 x_shape   54.3    16.8    47.8    26.9   -0.0656
```

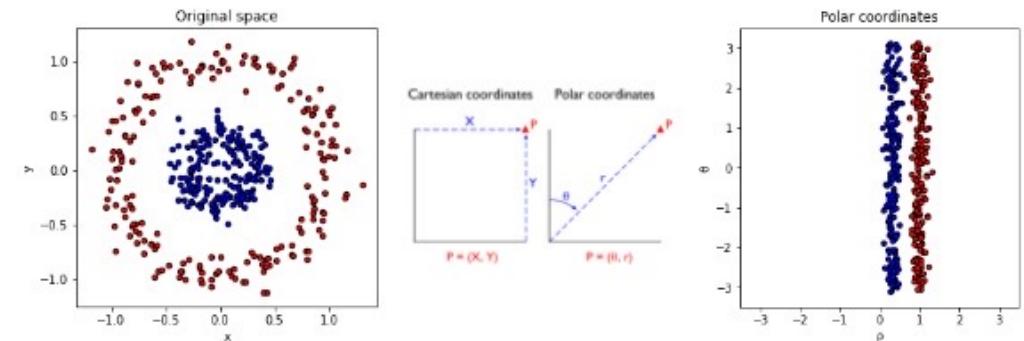
```
datasaurus_dozen %>%
  ggplot(aes(x, y, color = dataset)) +
  geom_point(show.legend = FALSE) +
  facet_wrap(~dataset, ncol = 5)
```



Feature engineering

- Transformation of feature to improve the performances of the ML algorithms:
 - Transforme (log, sqrt, logistic, box-cox...)
 - Normalize data (center and scale) → required for some ML approaches based on distance (e.g. SVM, MARS...)
 - Impute missing data (e.g. mean or median, linear, knn...) (1)
 - One hot encoding (neural network)
 - Remove highly correlated or zero variance features
 - Gather rare occurrences of a factor
 - Remove some uninformative variables (e.g ID)
→ be carefull to **data leakage** (2)
 - Creation of new informative predictors → require accurate knowledge of the field

Ex of transformation: modification of coordinates



Ex of transformation: one-hot encoding

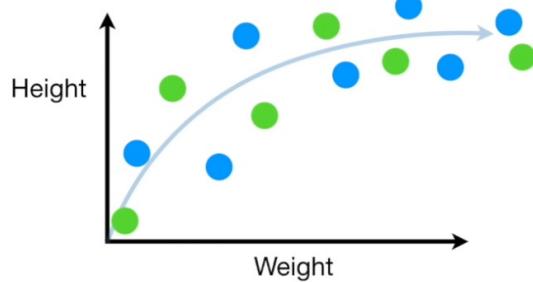
Color	Red	Yellow	Green
Red	1	0	0
Red	1	0	0
Yellow	0	1	0
Green	0	0	1
Yellow	0	0	1

(1) Julie Josse, Nicolas Prost, Erwan Scornet, Gaël Varoquaux. On the consistency of supervised learning with missing values. 2020. fffhal-02024202v3f

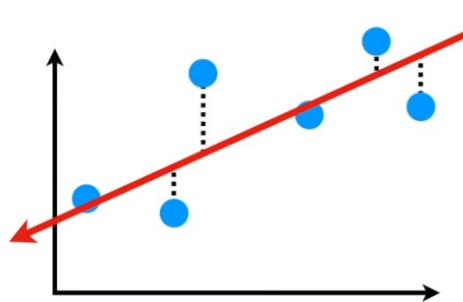
(2) Kapoor & Narayanan Leakage and reproducibility crisis in ML-based science Arxiv 2022

Problem of overfitting

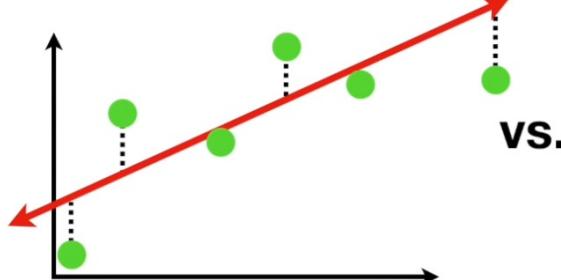
Data splitting



Few parameters: High bias

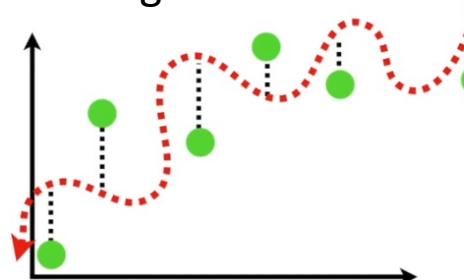


Low variance



vs.

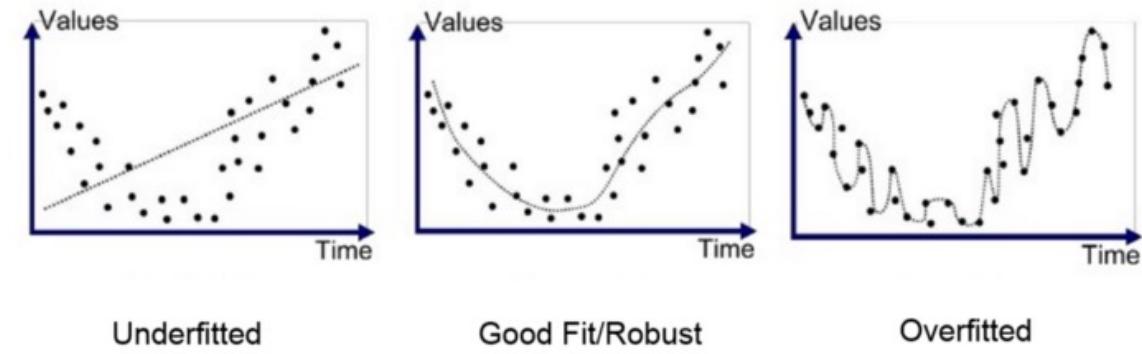
High variance



From StatQuest with Josh Starmer,
« Machine Learning Fundamentals:
Bias and Variance »

Several parameters: low bias

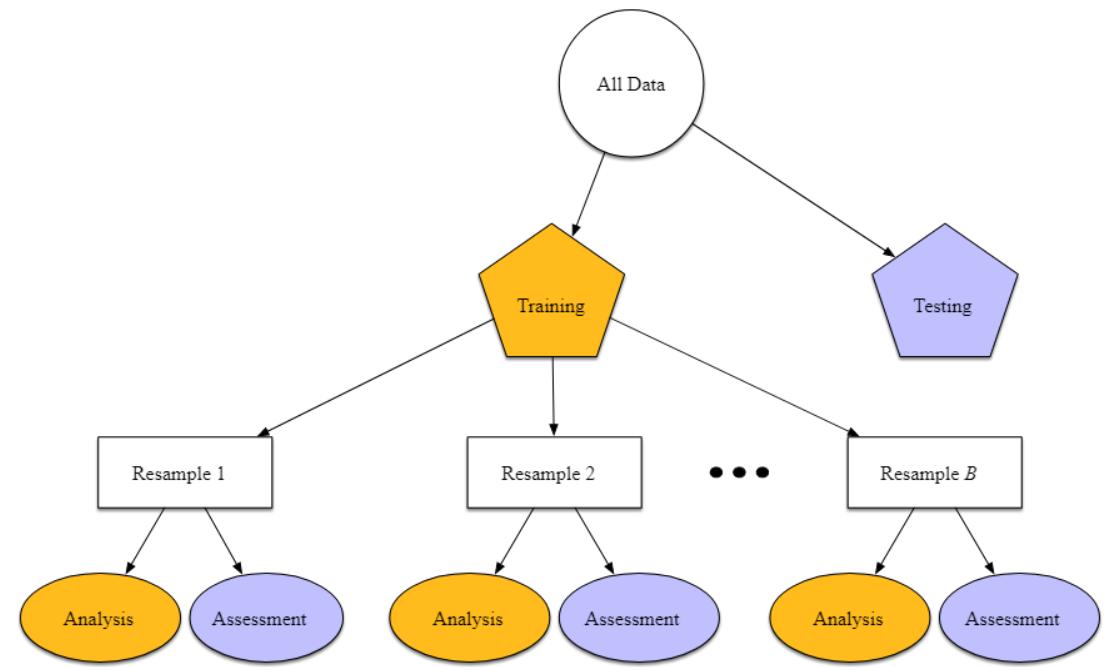
- Development and validation of a model in the same dataset → excellent performances:
- Increasing the number of parameters improve the performances but not reliable in another dataset → **bias-variance tradeoff**



Solution to prevent overfitting

- Crossvalidation
 - K-fold CV: randomly split the training dataset into 10 parts, investigate in 90% of the training dataset (= analysis set) and evaluate performances in the 10% remaining (= assessment set).
 - Bootstrap: resampling with replacements
- To estimate model performances and to tune the hyperparameters (find optimal parameters values for each ML algorithms)

Feature Engineering and Selection: A Practical Approach for Predictive Models. Routledge CRC Press at <<https://www.routledge.com/Feature-Engineering-and-Selection-A-Practical-Approach-for-Predictive-Models/Kuhn-Johnson/p/book/9781138079229>>

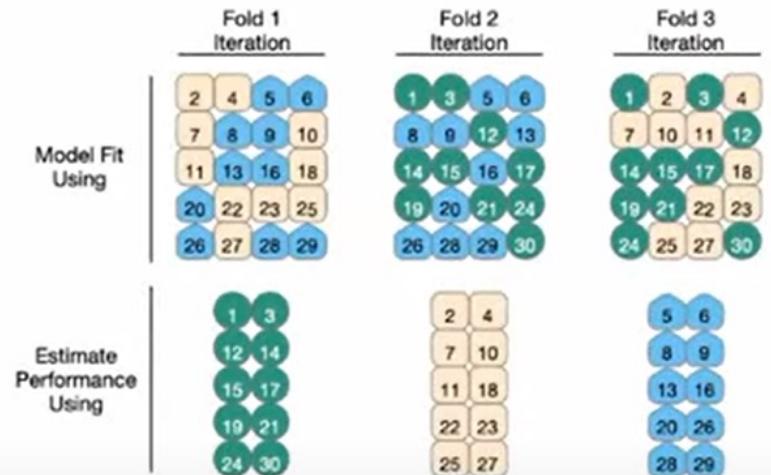


Crossvalidation & Bootstrapping

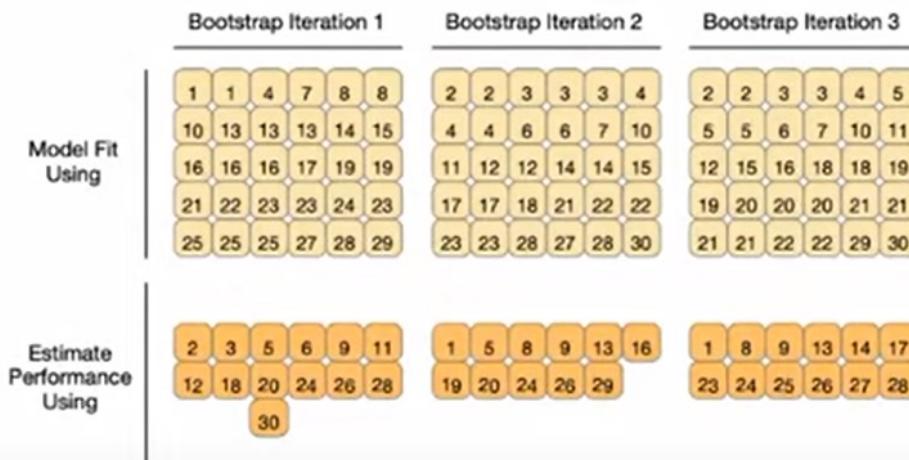
Cross-validation

Cross-validation

1	2	3	4	5	6
7	8	9	10	11	12
13	14	15	16	17	18
19	20	21	22	23	24
25	26	27	28	29	30

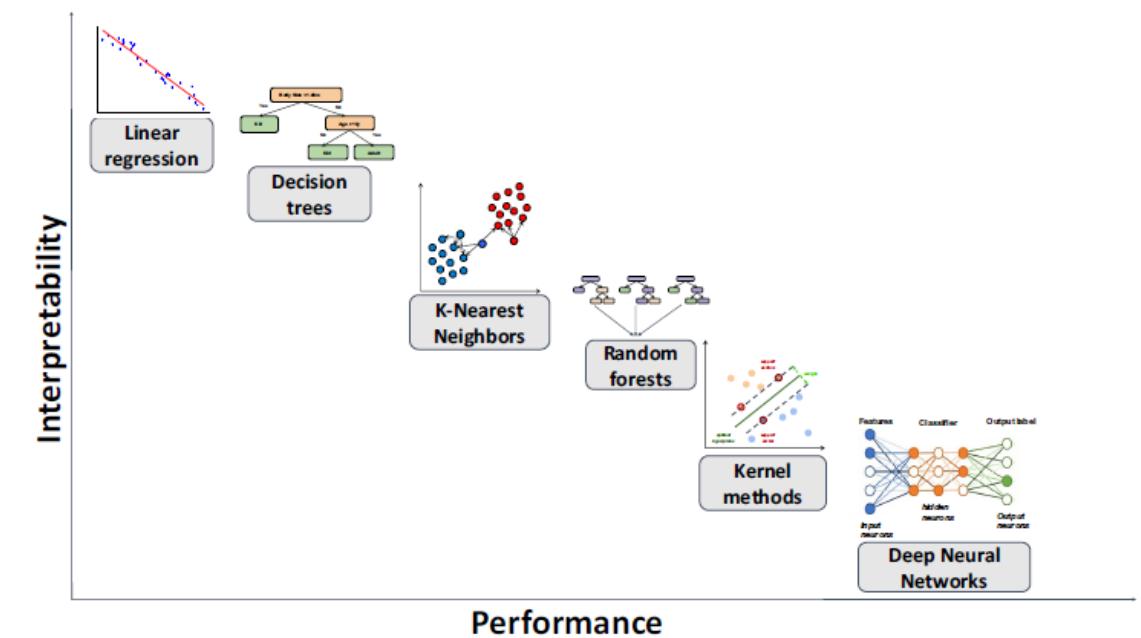


Bootstrapping



Simplicity and complexity in a black box

- Improvement of performance with decrease in interpretability → black box
- A lot of research is yet performed to interpret the complex models (ex SHAP ; SHapley Additive exPlanations) (1)
- Deep learning: complex neural network with lot of parameters to estimate (2)
- ML analysis requires a large volume of data, although it is difficult to give a precise value



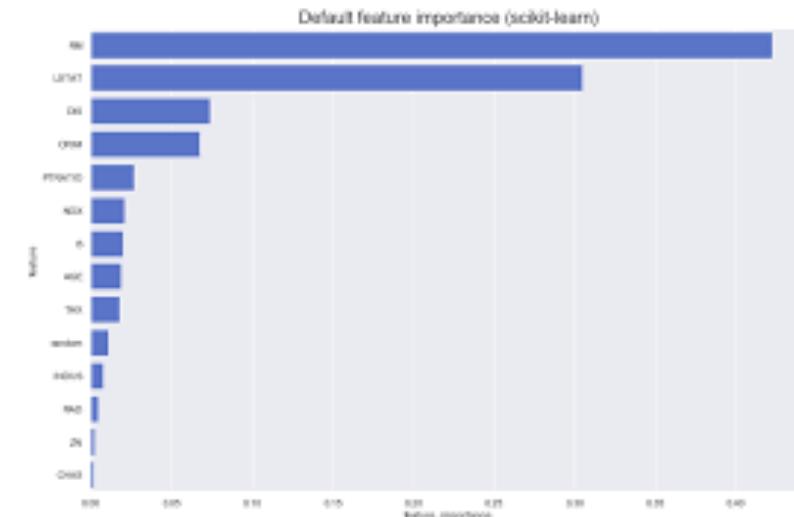
Badillo et al CPT 2020 « An Introduction to Machine Learning »

(1) Lundberg, Scott M., and Su-In Lee. "A unified approach to interpreting model predictions." Advances in Neural Information Processing Systems. 2017

(2) Yann LeCun, Yoshua Bengio, Geoffrey Hinton. "Deep Learning", Nature . 2015 May 28;521(7553):436-44.

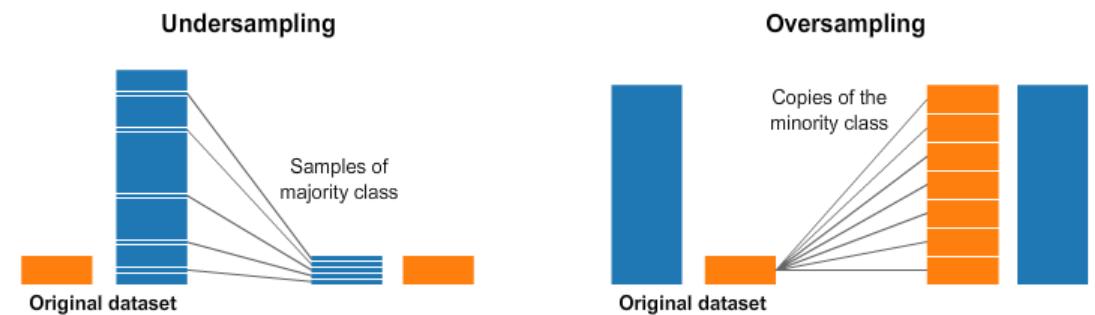
Explanation of the black box

- Ex VIP plot using random permutation:
 - Shuffle feature values.
 - if shuffling increases the model error → important
 - If not → unimportant
- Individuel SHAP force plot (1): comparison of output value to the base (mean) value and effect of each feature (+ / -) on the output value
- The Shapley value is the average marginal contribution of a feature value across all possible combination of features.

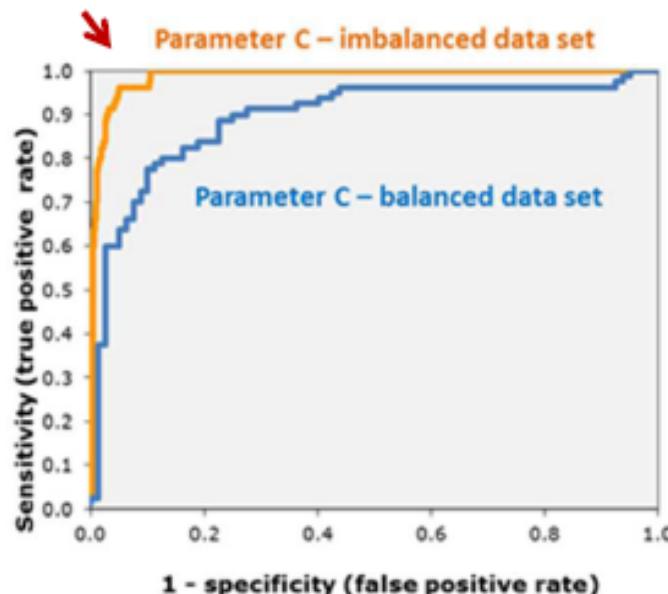
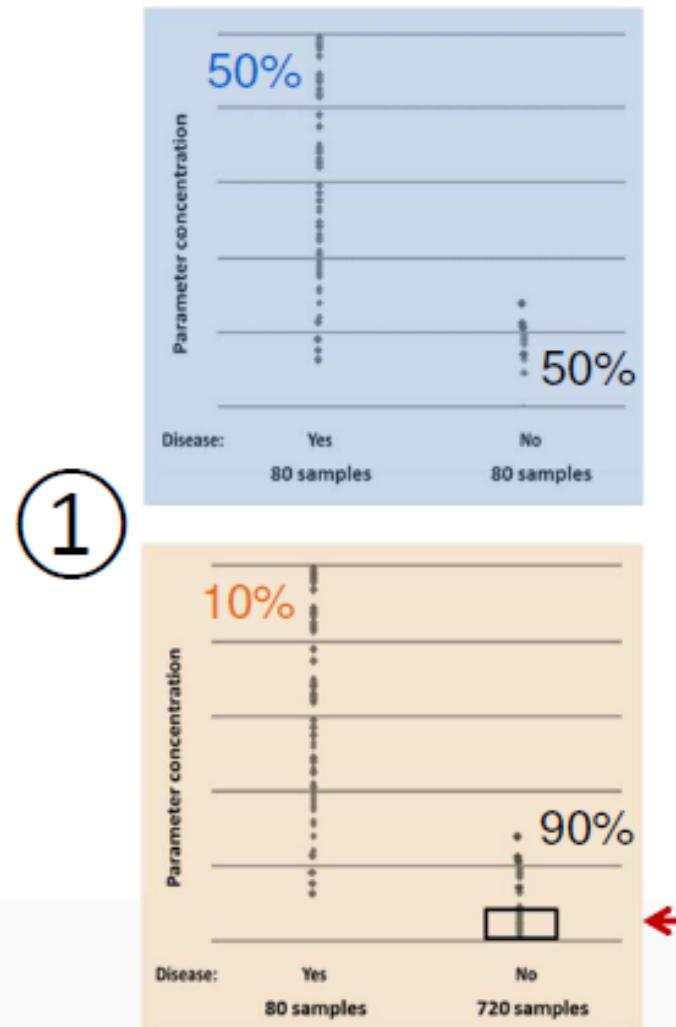


Classification problem of imbalanced data (1)

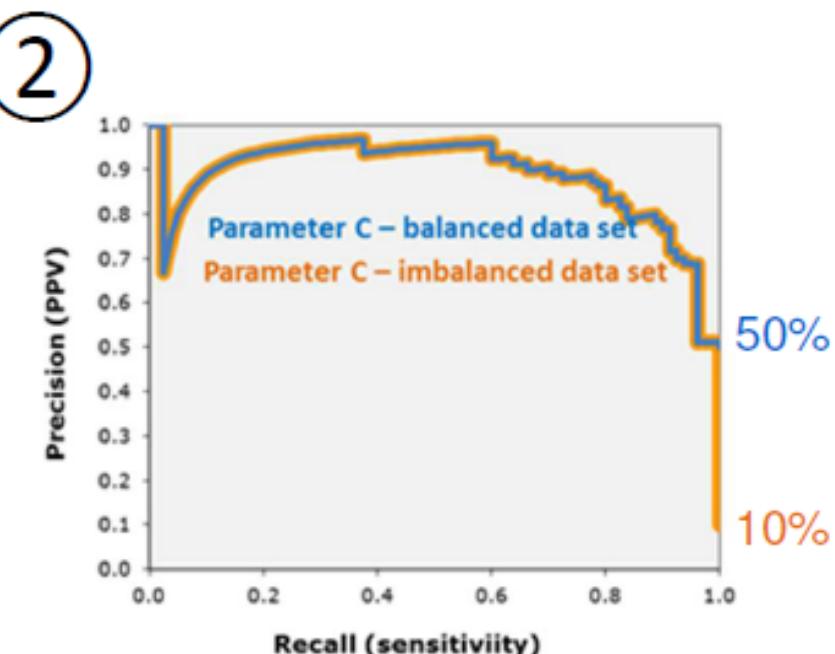
- Trap of accuracy:
 - Accuracy is $RP+RN/RP+FP+RN+FN$
 - Disease with 1% prevalence, classifying all the patients in non disease → accuracy=99%
- A widely adopted technique for dealing with highly unbalanced datasets consists of
 - removing samples from the majority class (under-sampling)
 - and / or adding more examples from the minority class (over-sampling)



Secondary endpoint: Precision Recall (= PR) curve of the scores



inflated ROC curve

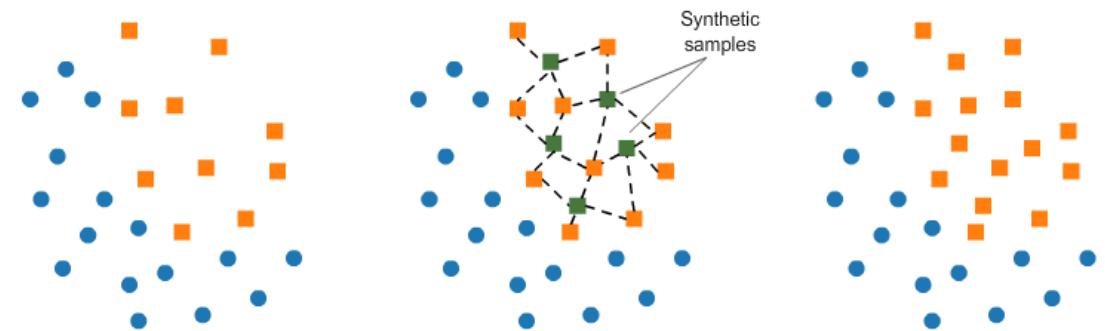


fair PR curve

PR curves are recommended for **imbalanced datasets**, as **true negatives** are not required for their calculations.

Classification problem of imbalanced data (2)

- More elaborated approaches
SMOTE (Synthetic Minority Oversampling Technique):
 - a random example from the minority class is first chosen.
 - Then k of the nearest neighbors for that example are found (typically $k=5$).
 - A randomly selected neighbor is chosen and a synthetic example is created at a randomly selected point between the two examples in feature space



Class imbalance metric

F_β score [edit]

A more general F score, F_β , that uses a positive real factor β , where β is chosen such that recall is considered β times as important as precision, is:

$$F_\beta = (1 + \beta^2) \cdot \frac{\text{precision} \cdot \text{recall}}{(\beta^2 \cdot \text{precision}) + \text{recall}}.$$

In terms of [Type I and type II errors](#) this becomes:

$$F_\beta = \frac{(1 + \beta^2) \cdot \text{true positive}}{(1 + \beta^2) \cdot \text{true positive} + \beta^2 \cdot \text{false negative} + \text{false positive}}.$$

Two commonly used values for β are 2, which weighs recall higher than precision, and 0.5, which weighs recall lower than precision.

Final step: prediction in the test set and external dataset

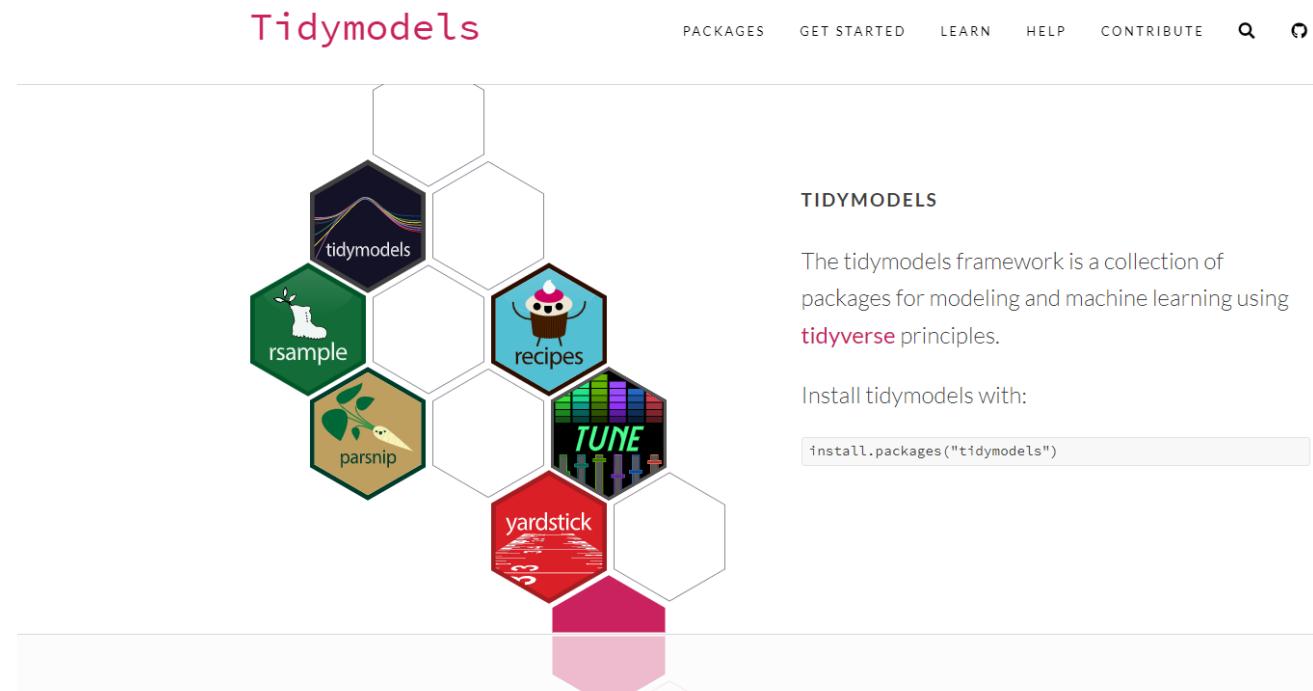
- Evaluation of the final model only one time in the test set
- Prediction of the outcome and comparison with the observed value
- Regression
 - Scatter plot with identity line or Bland-Altman analysis for regressions
- Classification:
 - confusion matrix with calculation of several metrics (e.g. accuracy, ROC AUC, precision, recall...).

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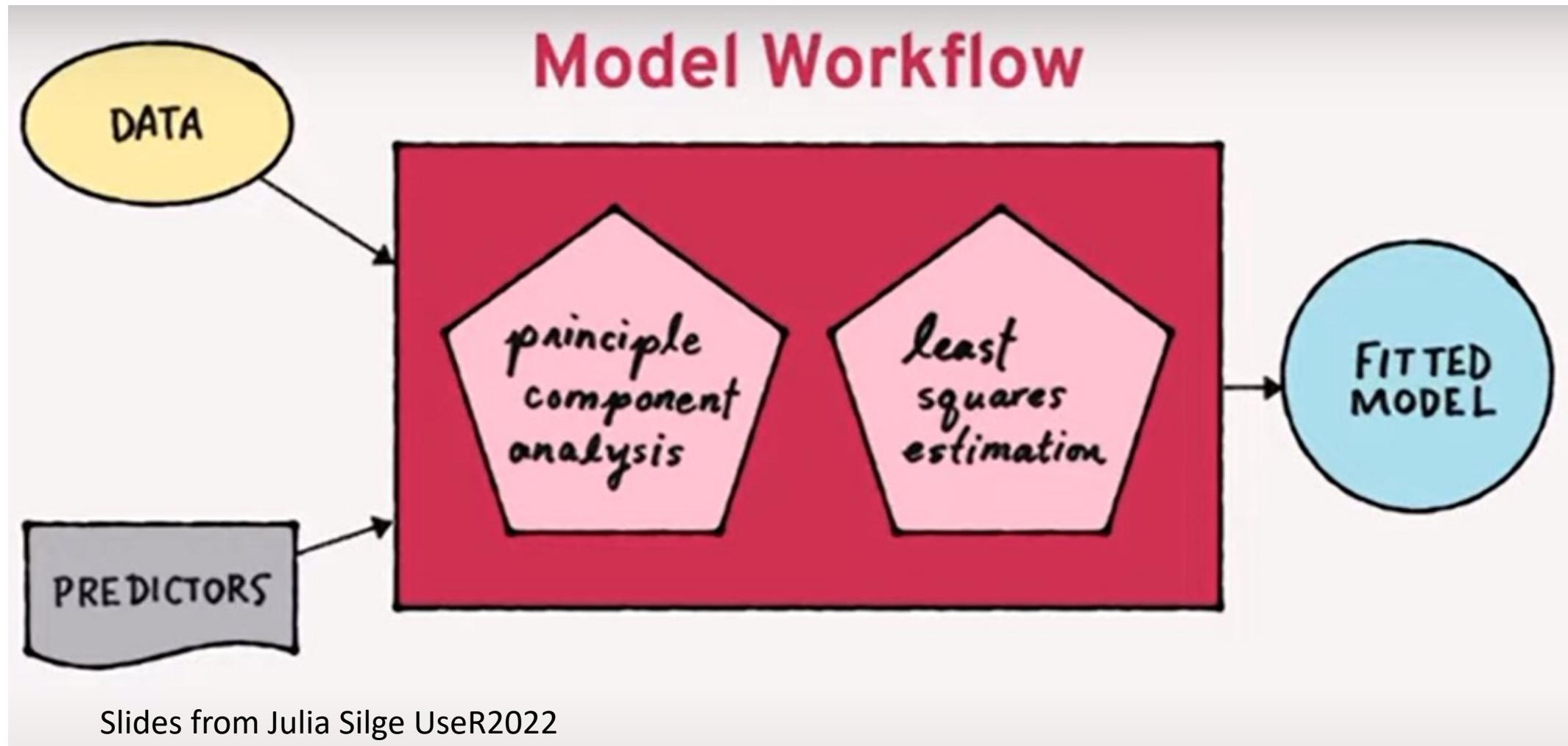
		Predicted labels		
		1	0	
Actual labels (observations)	1	True Positive (TP)	False Negative (FN)	Recall=TPR (True Positive Rate) $TPR = \frac{TP}{TP+FN}$
	0	False Positive (FP)	True Negative (TN)	Specificity = $\frac{TN}{TN+FP}$ False Positive Rate: $FPR = \frac{FP}{FP+TN}$
		Precision $\frac{TP}{TP + FP}$	False Negative Rate $\frac{FN}{TN + FN}$	Accuracy $\frac{TP + TN}{TP + TN + FP + FN}$

Tidymodels framework

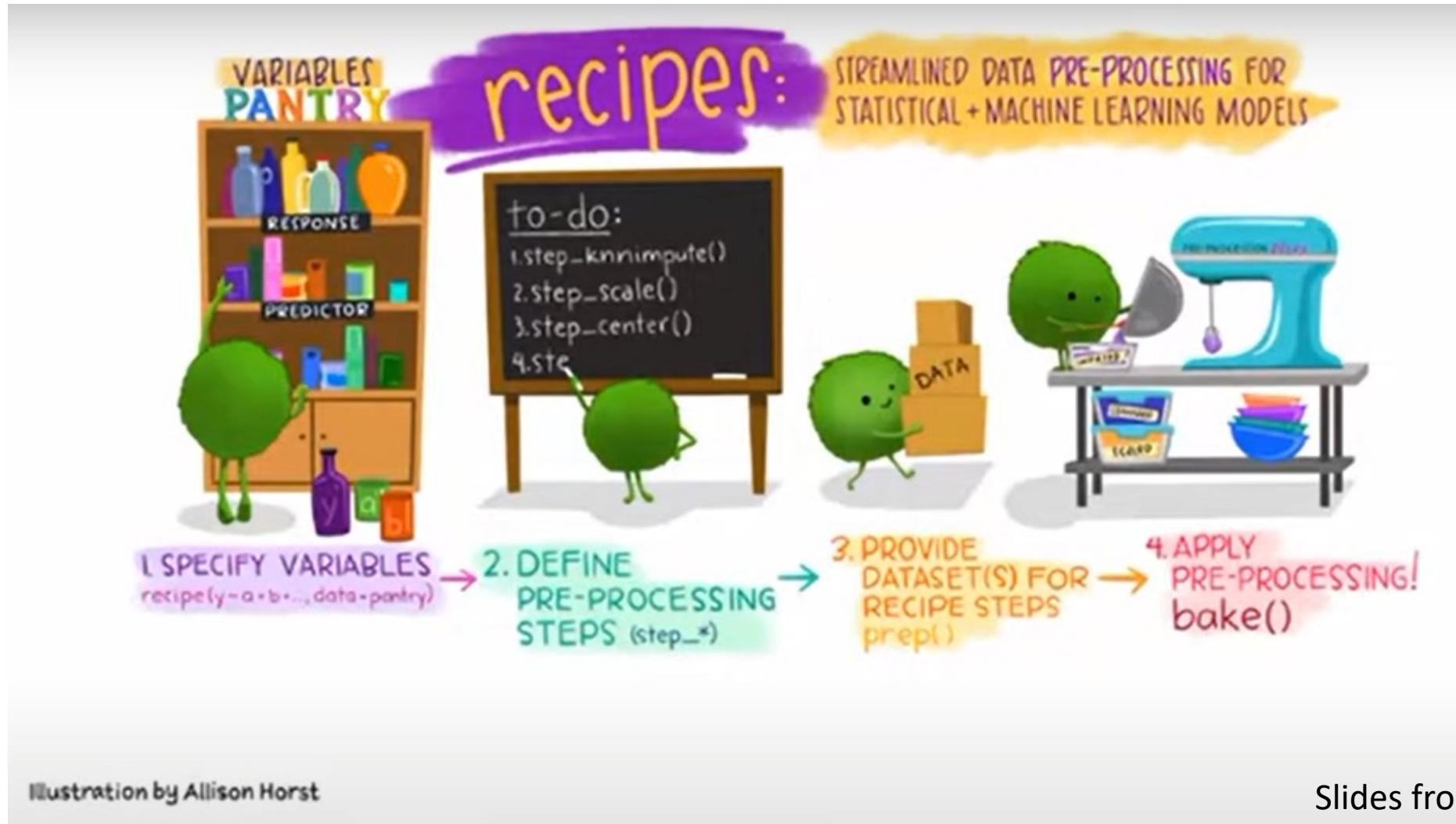
- Meta package of packages used in ML (equivalent to Scikit learn in Python)
- Packages used through the different steps of ML development
- Free book:
<https://www.tmwr.org/>



Where does the model starts?



Pre processing with Recipes

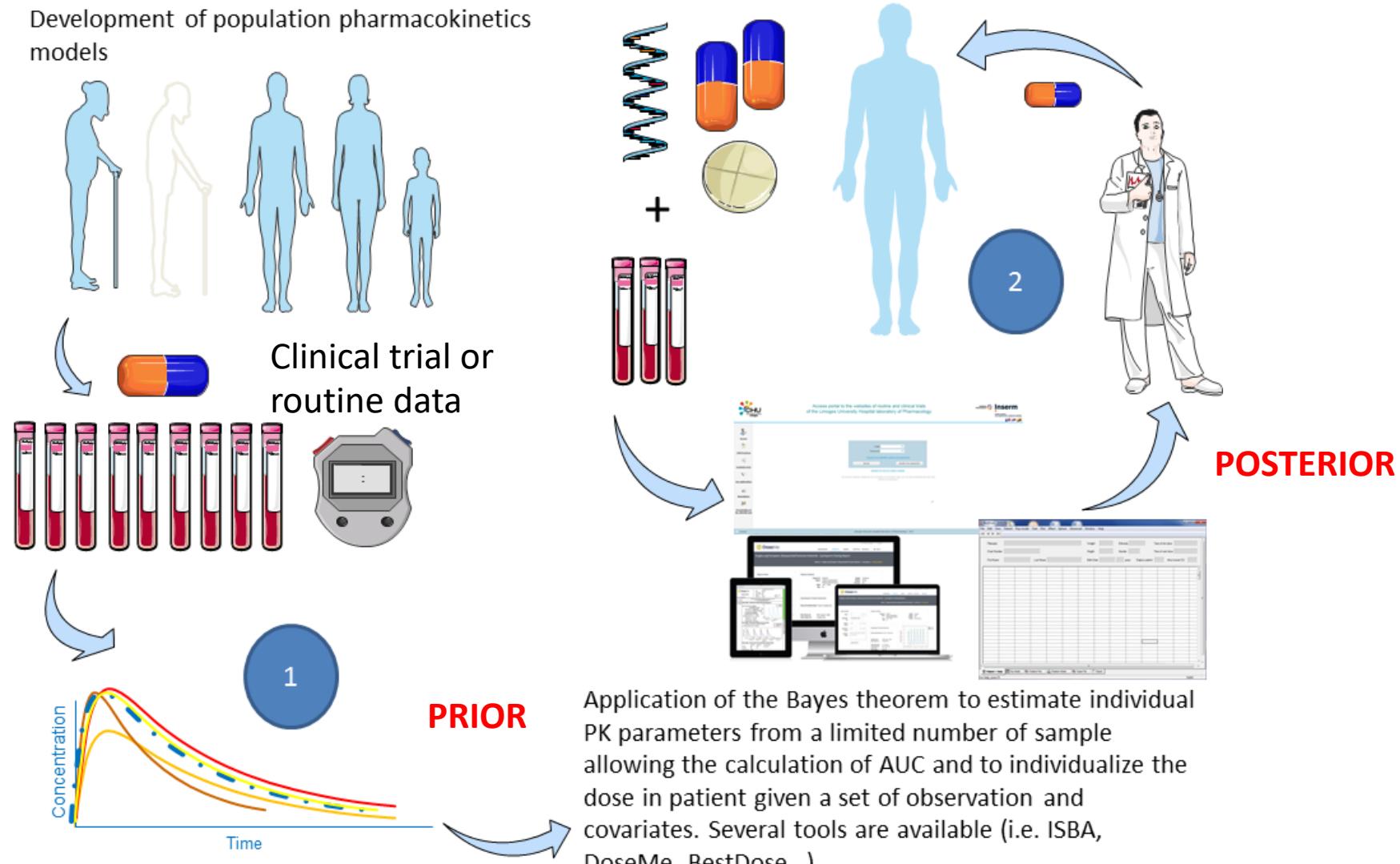


Example of application:
combination with population
pharmacokinetic modeling

Example of application:
estimation of
immunosuppressant exposure

Example of application to MIPD:
dose individualisation

Applying POPPK to routine care



Woillard JB, Saint-Marcoux F, Debord J, Åsberg A., Pharmacokinetic models to assist the prescriber in choosing the best tacrolimus dose. *Pharmacol Res.* 2018 Apr;130:316-321

Example of request

Dose adjustment for immunosuppressants providing:

- individual **inter-dose AUC** using Bayesian estimators /**3 blood samples** collected in the **first 3 hours following drug intake**
- one or a range of recommended dose(s) to reach the therapeutic target.
- the modelled concentration-time curve

Information sur la demande

Informations concernant l'indication

Indication	Transplantation rénale
Date	10/02/2015

Informations sur les traitements

Médicament	Tacrolimus
Spécialité	Prograf
Nombre de prises par jour	Dose 1 : 1.5 mg Dose 2 : 1.5 mg comprimé/gélule
Voie d'administration/forme	MMF

Contexte général de la demande

Motif de la demande	Contrôle d'une adaptation de posologie
Informations complémentaires	

Information sur les prélèvements

Heure de prise du médicament	09:00	
Date de prélèvement	04/03/2022	
Méthode de dosage	HPLC	
Temps depuis la dose (temps optimal)	Heure de prélèvement réelle	Concentration
0 min (0 min)	08:20	8.8 µg/l
60 min (60 min)	10:00	16.4 µg/l
180 min (180 min)	12:00	14.2 µg/l

Résultats

- Les AUCs cibles et les doses correspondantes sont données à titre indicatif.

Délai post greffe/1ere administration d'IS

Taux résiduel estimé par méthode Bayésienne

C max estimée par méthode Bayésienne

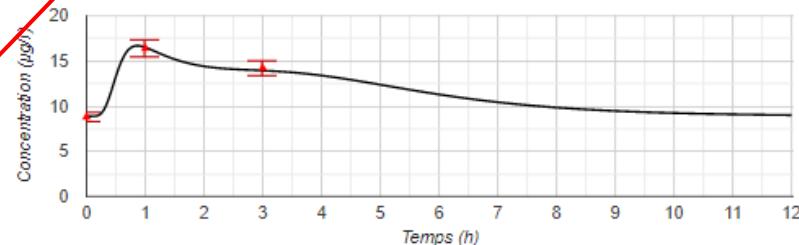
AUC (0-12h) estimée par méthode Bayésienne

2579 Jour(s)

8.9 µg/l

16.7 µg/l

139 h.µg/l

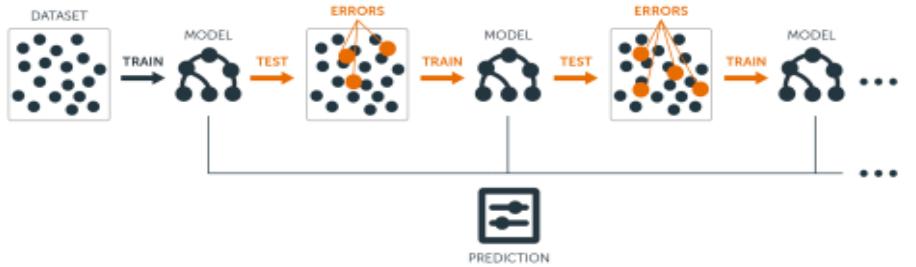


Nombre de prises par jour

2

Posologie actuelle (par prise)

1,5 mg

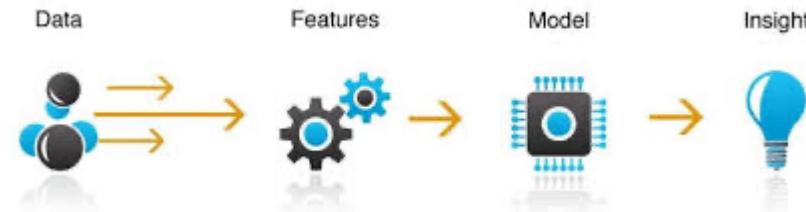


Tacrolimus study (1)

- TDM C₀ vs AUC best marker in the last consensus conference (2) or AUC/C₀ ratio (3) but complicated to measure.
- Population pharmacokinetic modeling and MAP BE based on 3 samples / goal standard to estimate AUC
- Several priors in our ISBA website → require the validation by a trained pharmacologist under 48h
- Goal:
 - to develop Xgboost algorithms to estimate TAC interdose AUC, based 2 or 3 blood concentrations and a few predictors
 - to compare their performances to that of MAP-BE in external validation datasets.

- (1) Woillard, J.-B., Labriffe, M., Debord, J. & Marquet, P. Tacrolimus exposure prediction using machine learning. *Clin. Pharmacol. Ther.* (2020).doi:10.1002/cpt.2123
- (2) Brunet, M. et al. Therapeutic drug monitoring of tacrolimus personalized therapy: second consensus report. *Ther. Drug Monit.* 41, 261–307 (2019).
- (3) Woillard JB, Monchaud C, Saint-Marcoux F, Labriffe M, Marquet P. Can the Area Under the Curve/Trough Level Ratio Be Used to Optimize Tacrolimus Individual Dose Adjustment? *Transplantation* 2023 Jan 1;107(1):e27-e35

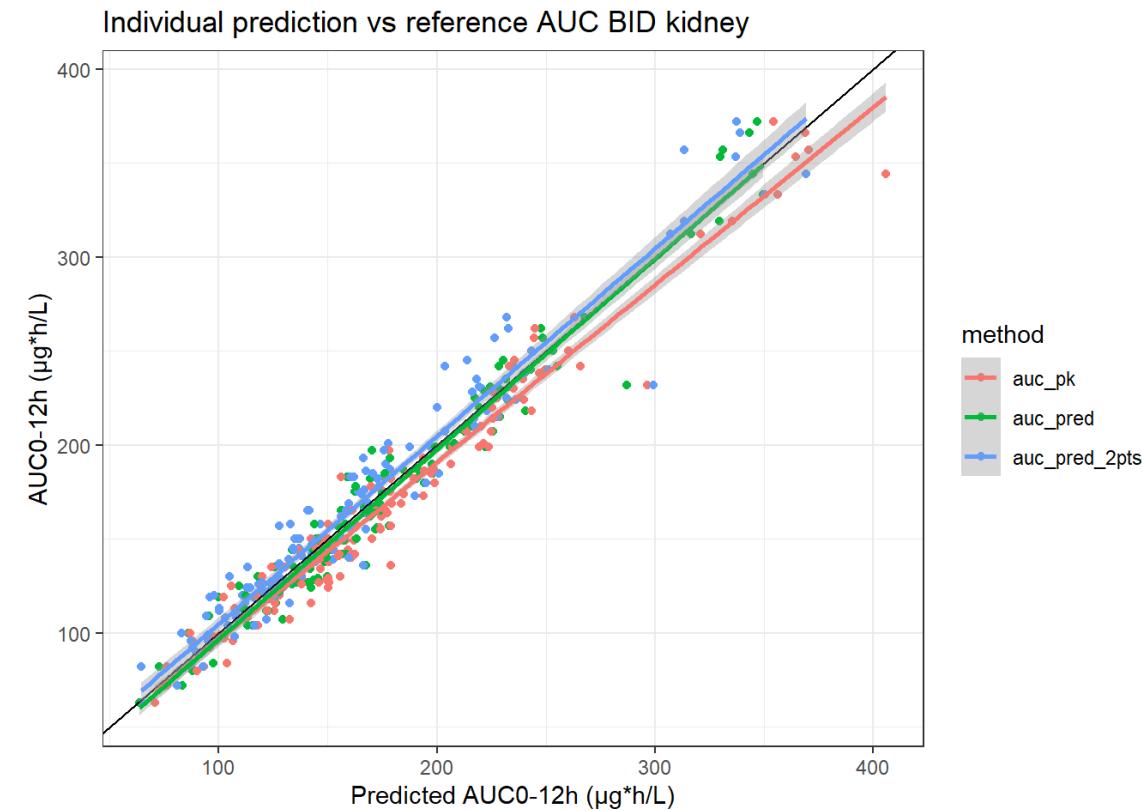
Feature engineering:



- TAC concentration binned into 3 theoretical time classes
 - C0 sampled at $t = 0$ minutes
 - 1 hour (C1 sampled between 30 and 100 minutes)
 - 3 hours (C3 sampled between 140 and 220 minutes) → 3 columns per patient.
- Creation of new variables
 - relative deviation with respect to the theoretical times:
 - Ex sampling time = 1.06 hours → relative time difference = $(1.06 - 1)/1 = 0.06$.
 - differences between the concentrations C1–C0, C1–C3, and C3–C0 → information about delayed absorption peaks.
- Type of transplant split into 5 categories: kidney, lung, heart, and liver, “other” category for all the other indications.

ML / a posteriori TAC exposure

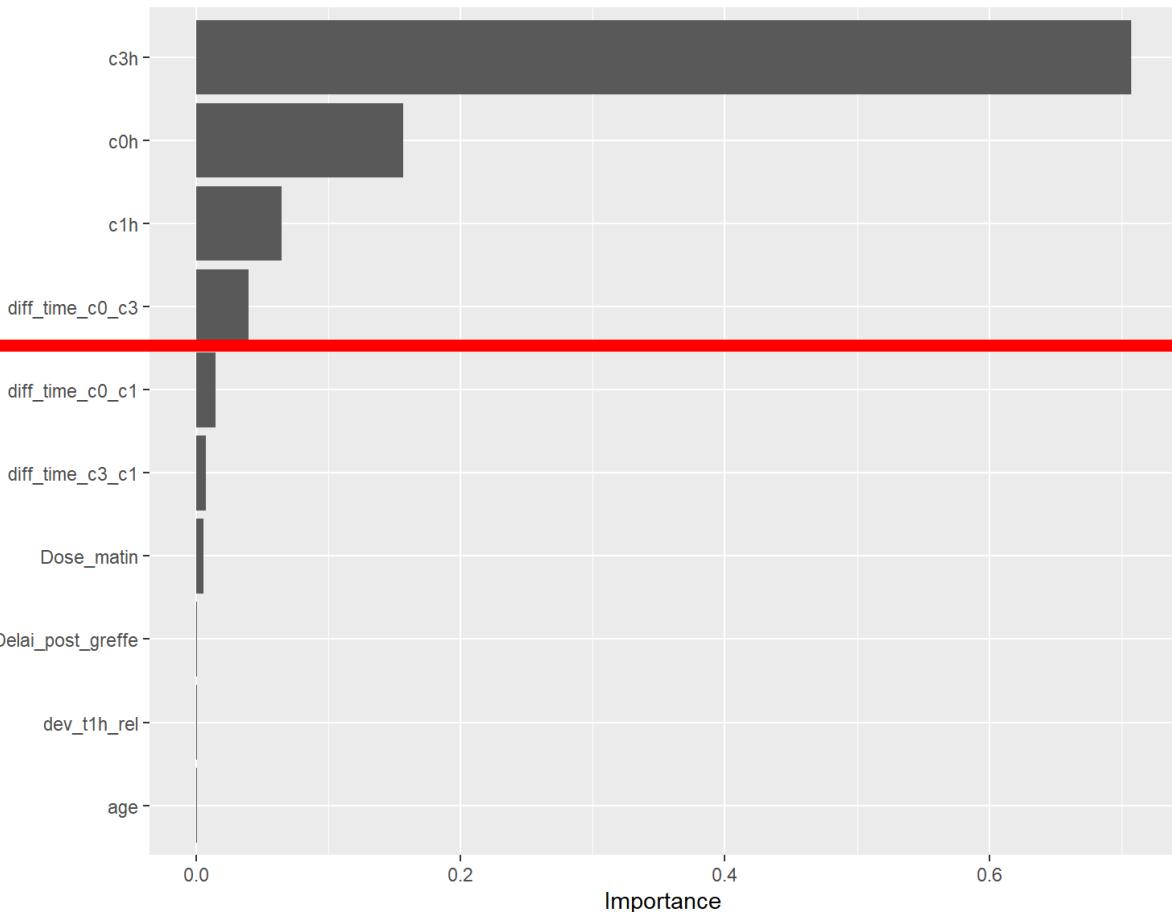
- Development of a ML model to predict the TAC AUC (TDM) based on ISBA data (<https://abis.chu-limoges.fr/login>):
3 individual concentrations / a few covariates
→ ~5000 AUC/~2000 patients
- Excellent performances in external full PK profiles vs ref AUC (trapezoidal) based **on 2 or 3 samples**
- Bias/RMSE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



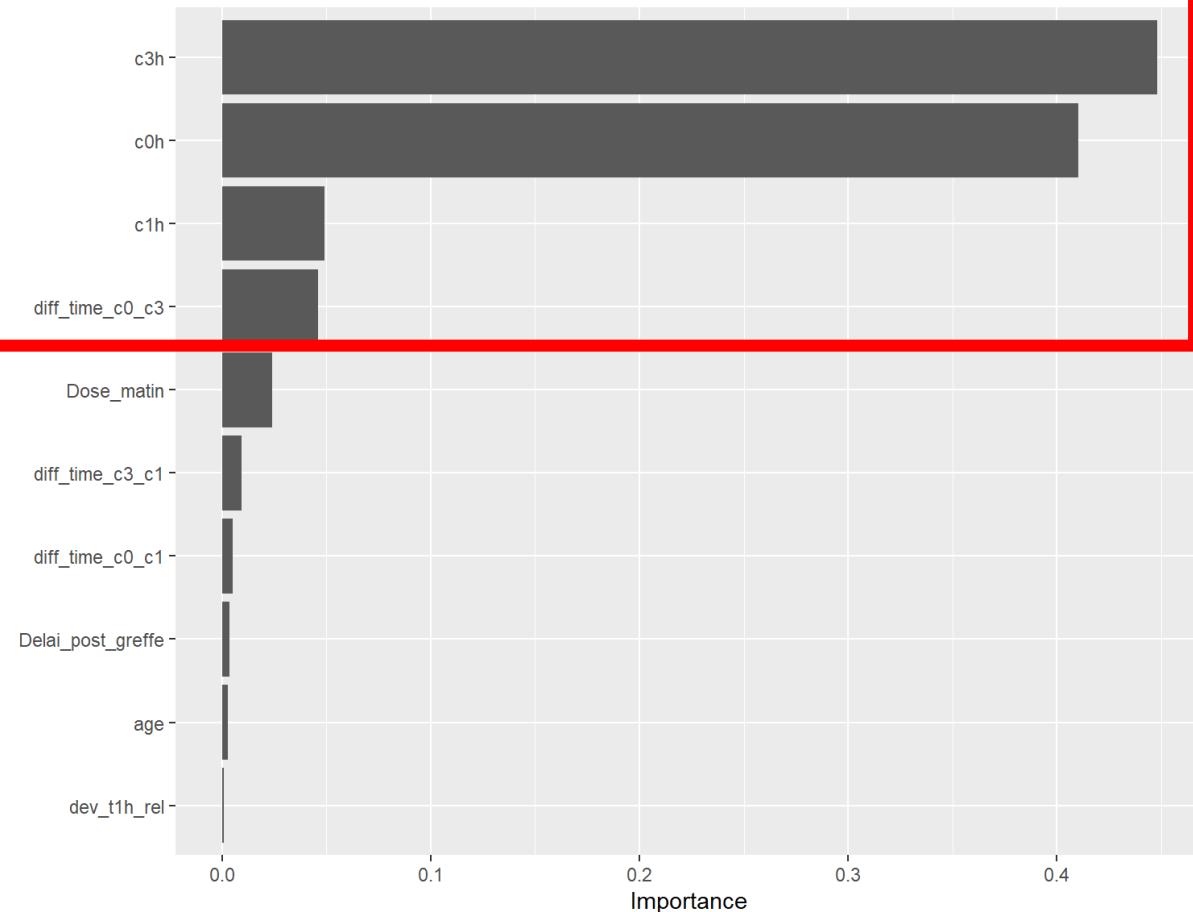
Study	Method	Relative MPE (%)	Relative RMSE (%)
TAC BID kidney 1 ¹¹ (n = 137)	Xgboost 2 concentrations	-0.6	9.0
	MAP-BE 3 concentrations	5.1	9.6
TAC BID kidney 2 ⁷ (n = 34)	Xgboost 2 concentrations	-1.0	9.1
	MAP-BE 3 concentrations	2.8	9.1
TAC QD kidney ⁷ (n = 41)	Xgboost 2 concentrations	-0.6	10.8
	MAP-BE 3 concentrations	2.1	13.2
TAC BID liver ¹⁴ (n = 68)	Xgboost 2 concentrations	3.3	12.9
	MAP-BE 3 concentrations	-3.4	11.2
TAC QD liver ¹⁴ (n = 91)	Xgboost 2 concentrations	-0.4	12.3
	MAP-BE 3 concentrations	-3.5	15.7
TAC BID heart ^{15,16} (n = 47)	Xgboost 2 concentrations	-0.4	9.7
	MAP-BE 3 concentrations	-0.7	9.1

Interpretability: which variable are the most important

TD TAC



OD TAC



Interface developed for demonstration

- Tacrolimus
- https://jbwoillard.shinyapps.io/App-6_tacro_ml/

Tacrolimus AUC calculator using a machine learning approach

TAC BID & 3 concentrations TAC BID & 2 concentrations TAC QD & 3 concentrations TAC QD & 2 concentrations

For research purposes only, not dedicated to clinical use

Type of transplantation: Renal

Tacrolimus trough concentration (µg/L): 7

Values between 0.1 and 34 are accepted, model has not been tested for values out of this range

Tacrolimus concentration at 1h (µg/L): 15

Values between 2 and 83 are accepted, model has not been tested for values out of this range

Precise time of sampling C1h (min): 60

Values between 30 and 100 are accepted, model has not been tested for values out of this range

Tacrolimus concentration at 3h (µg/L): 13

Values between 2 and 46 are accepted, model has not been tested for values out of this range

Precise time of sampling C3h (min): 180

Values between 140 and 220 are accepted, model has not been tested for values out of this range

Morning dose (mg): 2.5

Values between 0.2 and 18 are accepted, model has not been tested for values out of this range

Estimated AUC_{0-12h} value = 125 µg*h/L



- Mycophenolic acid
- https://jbwoillard.shinyapps.io/App-7_mmf_ml/

Mycophenolate Mofetil AUC calculator using a machine learning approach

MMF 3 concentrations MMF 2 concentrations

For research purposes only, not dedicated to clinical use

Type of transplantation: Renal

Associated IS drug: Tacrolimus

Exact value of time 20min (min): 20

Values between 10 and 30 are accepted, model has not been tested for values out of this range

MPA concentration at 20min (mg/L): 20

Values between 0.05 and 90 are accepted, model has not been tested for values out of this range

Exact value of time 1h (min): 60

Values between 45 and 75 are accepted, model has not been tested for values out of this range

MPA concentration at 1h (mg/L): 15

Values between 0.05 and 59 are accepted, model has not been tested for values out of this range

Exact value of time 3h (min): 180

Values between 160 and 200 are accepted, model has not been tested for values out of this range

MPA concentration at 3h (mg/L):



+ New request

List of Requests

Optimal times

Patients

NOM1688 Prenom1688 

10/05/1999

Center
Center 12473Prescriber: Dr House
Requester: M. Expert Angéla

Number : 10260

Pending

Data used for the calculation

Description

EnARMH 

Comparison of results

- Warning: There is no targeted AUC defined for this drug. The decision on drug adaptation will be your liability.
For information, the targeted AUC for Advagraf in adult kidney transplantation and the corresponding doses to reach the targeted AUC are :

Selected model

Time elapsed between transplantation and request

EnARMH

Trough level (Bayesian estimate)

1825 Day(s)

Cmax (Bayesian estimate)

7,2 µg/l

12,6 µg/l

AUC (0-24h) Bayesian estimate

240,6 h.µg/l

1- C0 target µg/l	2- Corresponding targeted AUCs	3- Recommended doses to reach these targets
3 - 7	130 - 235	2,5 to 4,8 mg
5 - 10	180 - 310	3,8 to 6,5 mg
8 - 12	260 - 365	5,3 to 7,3 mg
10 - 15	310 - 440	6,5 to 9,0 mg

Number of intakes per day

1

Current dose (per intake)

5 mg

As an indication, the AUC (0-24h) estimated by Machine Learning method
(L Porthier et al Eur J Clin Pharmacol. 2023 Feb;79(2):311-319)

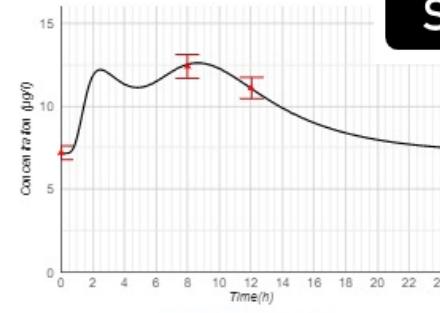
236 h.µg/l

Information request

Launch a calculation

Validate this result

History of requests for this patient



NOM1688 Prenom1688

10/05/1999

Center
Center 12473

Prescriber: Dr House
Requester: M. Expert Angéla

Number : 10259
Pending

+ New request

>List of Requests

Optimal times

Patients

- Targeted AUC and corresponding doses are provided for information purpose only.

Selected model

Time elapsed between transplantation and request

Trough level (Bayesian estimate)

Cmax (Bayesian estimate)

PARMH

1825 Day(s)

6,3 µg/l

15,7 µg/l

AUC (0-12h) Bayesian estimate

114,2 h.µg/l

1- CO target µg/l	2- Corresponding targeted AUCs	3- Recommended doses to reach these targets
3 - 7	75 - 130	2,5 to 4,0 mg
5 - 10	100 - 170	3,0 to 5,0 mg
8 - 12	140 - 200	4,5 to 6,0 mg

Number of intakes per day

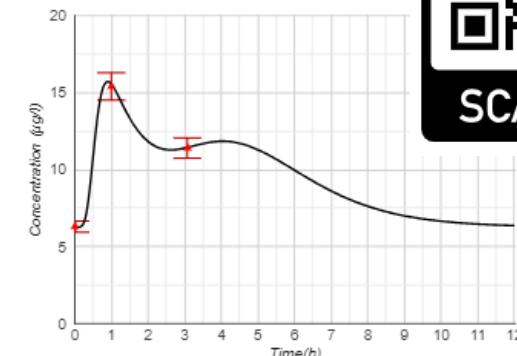
2

Current dose (per intake)

3,5 mg

As an indication, the AUC (0-12h) estimated by Machine Learning method
(Woillard et al. Clin Pharmacol Ther 2020)

114 h.µg/l



+ AUC/c0 correlation



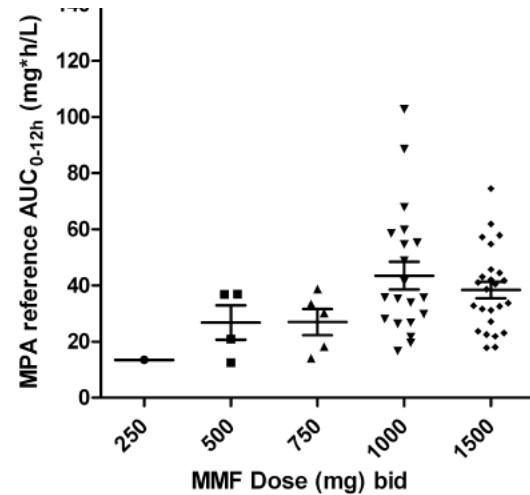
Information request

Launch a calculation

Validate this result

Mycophenolic acid study

- MMF / immunosuppressant largely used in transplantation:
 - narrow therapeutic index
 - large interindividual variability for a same dose
 - → TDM consensually recommended (Bergan et al TDM 2021)
- Poor correlation between C₀ and AUC
- POPPK MAP BE based on 3 samples = goal standard to estimate interdose AUC
- Several priors in our ISBA website → require the validation by a trained pharmacologist under 48h
- Goal: to develop Xgboost algorithms to estimate MMF interdose AUC, based 2 or 3 blood concentrations and a few predictors, and to compare their performance to that of MAP-BE in external validation datasets.



Woillard JB et al Pharmacol Res. 2015

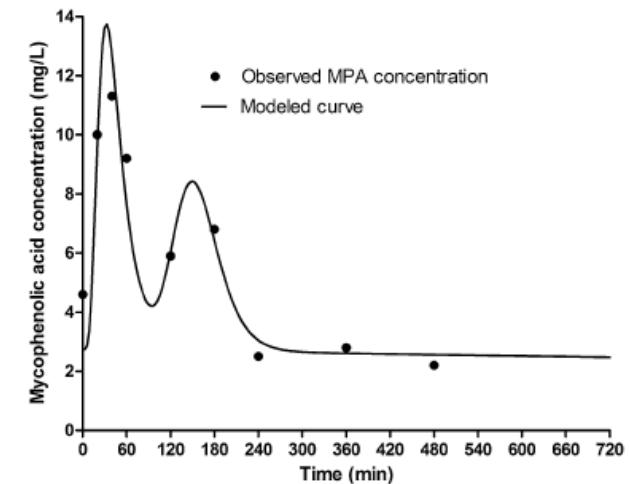
Application to prediction of MMF exposure

- Same methodology as for TAC but larger dataset: 12877 AUC/3 concentrations and validation in heart and kidney transplant patients
- Results:
 - Bias <5% & imprecision ~15-20% in external validation from 3 sample ML model → better than MAP-BE but still high
 - Imprecision using 2 sample ML model ~ 20-25% → too high
 - Performances quite disappointing in comparison to TAC

Study	Method	All patients			
		Relative MPE (%)	Relative RMSE (%)	Bias out of ±20% n (%)	Bias out of ±10% n (%)
PCCP study (n=128 / n 1 st month = 49)	Xgboost 2 concentrations	-1.2	24.2	46 (35.9)	80 (62.5)
	Xgboost 3 concentrations	-4.0	19.0	39 (30.5)	76 (59.4)
	MAP-BE 3 concentrations	1.0	19.9	37 (28.9)	81 (63.3)
Stablocine (n=20)	Xgboost 2 concentrations	1.5	17.8	4 (20)	10 (50)
	Xgboost 3 concentrations	2.8	14.7	2 (10)	8 (40)
	MAP-BE 3 concentrations	9.3	20.5	7 (35)	9 (45)
CONCEPT (n=67)	Xgboost 2 concentrations	-0.8	26.3	27 (40)	42(63)
	Xgboost 3 concentrations	-1.1	22.5	14 (21)	43(64)
	MAP-BE 3 concentrations	2.1	25.1	18 (27)	40 (60)
PIGREC (n=75/ n 1 st month = 20)	Xgboost 2 concentrations	2.5	23.1	31 (41)	44 (59)
	Xgboost 3 concentrations	-1.2	15.6	17 (23)	41 (55)
	MAP-BE 3 concentrations	3.5	17.3	17 (23)	47 (63)

Explanations

- MPA: very complex pharmacokinetics/ diverse individual profiles → highly difficult to model (imprecision ~20% in the literature for MMF).
- Weak correlation between dose/AUC and AUC/single time point.
- Very challenging to develop accurate ML algorithms for MPA = worse case scenario → possible for all the other drugs for which TDM is performed.
- ML = algorithm predict very accurately a reference value: if the reference contain noise, the ML model will learn the true value + noise
- Solution: train ML models in very large, full-profile dataset (decrease in the measurement error uncertainty) → however large database are very difficult to collect in practice.



Woillard JB et al Clinical Pharmacokinet, 2018

Development from full PK profiles: example of envarsus®

- Objective : develop ML algorithm/ full PK profile (reference AUC = trapezoidal rule)
→ predict envarsus® AUC_{0-24h} based on 2 concentrations and compare performances to PKPOP-EB
- Methods :
 - Full PK profiles (12 conc.) phase 2 in 113 patients liver + 97 kidney
 - Evaluation of performances in 2 independent datasets
 - 16 kidney transplant patients
 - 48 liver transplant patients

European Journal of Clinical Pharmacology
<https://doi.org/10.1007/s00228-022-03445-5>

RESEARCH

Application of machine learning to predict tacrolimus exposure in liver and kidney transplant patients given the MeltDose formulation

Laure Ponthier^{1,2} · Pierre Marquet^{1,3} · Dirk Jan A. R. Moes⁴ · Lionel Rostaing⁵ · Bart van Hoek⁶ · Caroline Monchaud^{1,3} · Marc Labriffe^{1,3} · Jean Baptiste Woillard^{1,3} 

Table 1 Patient characteristics in the analysis, assessment, train, test, and external sets

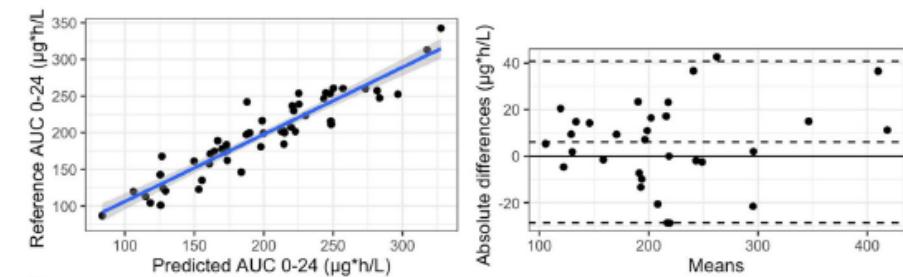
Variables	Analysis set N = 130	Assessment set N = 28	Training set (analysis + assessment set) N = 158	Test set N = 52	External set Renal N = 16	External set Liver N = 48
Age (years)	49 (11)	47 (11)	49 (11)	48 (12)	49 (16)	54 (12)
Daily dose (mg)	5.0 (3.0)	3.6 (1.7)	4.8 (2.9)	5.2 (3.0)	4.2 (2.4)	2.5 (1.5)
Sex: male (%)	82 (63.1%)	14 (50.0%)	96 (60.8%)	36 (69.2%)	9 (56.2%)	35 (68.6%)
Hematocrit (%)	40.7 (4.8)	40.2 (3.7)	40.7 (4.6)	39.8 (4.6)	40.4 (4.3)	40.6 (4.5)
AUC0-24 ($\mu\text{g}^*\text{h/L}$)	207 (74.)	209 (61)	207 (73)	205 (53)	202 (78)	152 (66)
Liver n (%)	68 (52.31%)	19 (67.86%)	87 (100.00%)	26 (50%)	0 (0%)	48 (100%)
Kidney n (%)	62 (47.69%)	9 (32.14%)	71 (100.00%)	26 (50%)	16 (100%)	0 (0%)
Concentration at 0 h	6.2 (2.3)	6.4 (2.1)	6.2 (2.3)	6.3 (2.1)	6.3 (2.2)	5.0 (2.1)

Continuous variables are presented as mean (SD) and categorical variables as n (%)

Results

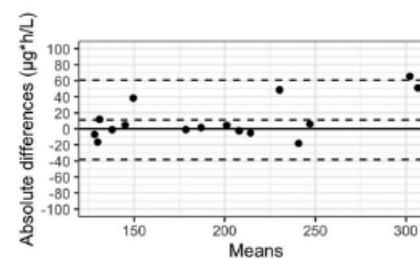
- MARS algorithm 2 samples t0-12h
 - Test set: bias = – 1.9%, imprecision = 10.06%
- External data 2 samples t0-12h
 - Kidney: bias = – 3.1%/imprecision = 11.1%
 - Liver: bias = – 3.4%/imprecision = 9.86%
- → performances similar or better compared to PKPOP-EB with **2 vs 3 samples**
- → similar performances compared to ML algorithms developed from ISBA

Base test

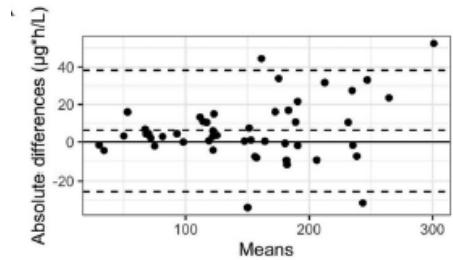


Validation externe

Rein



Foie



Iohexol CL prediction using ML in ICU patients from a small dataset

- Objective: predict iohexol CL using an Xgboost model based on 2 concentrations in ICU patients
- Method: 86 patients full PK profiles split into train (75%) and test (25%) sets
- Tuning of parameters and evaluation in the train set by crossvalidation
- Validation in the test set
- Results
 - ML bias = 0.3 ml/min, imprecision = 6.2 ml/min
 - MAP-BE bias = -0.9 ml/min, imprecision = 5.7 ml/min

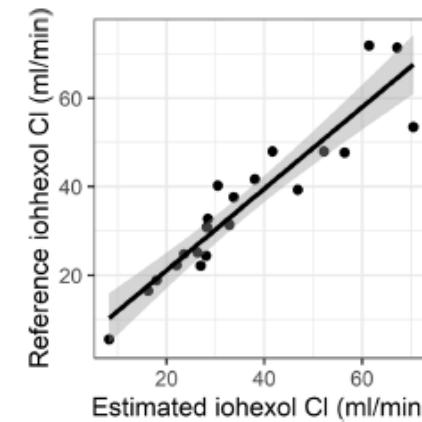
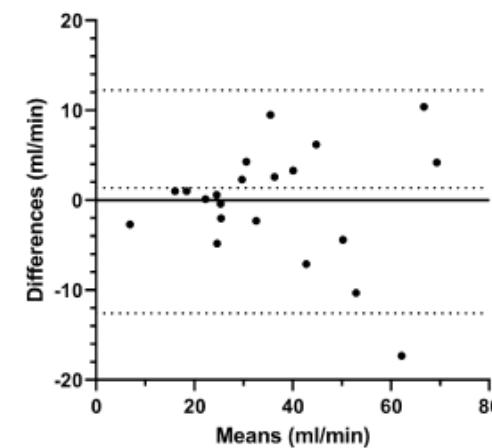
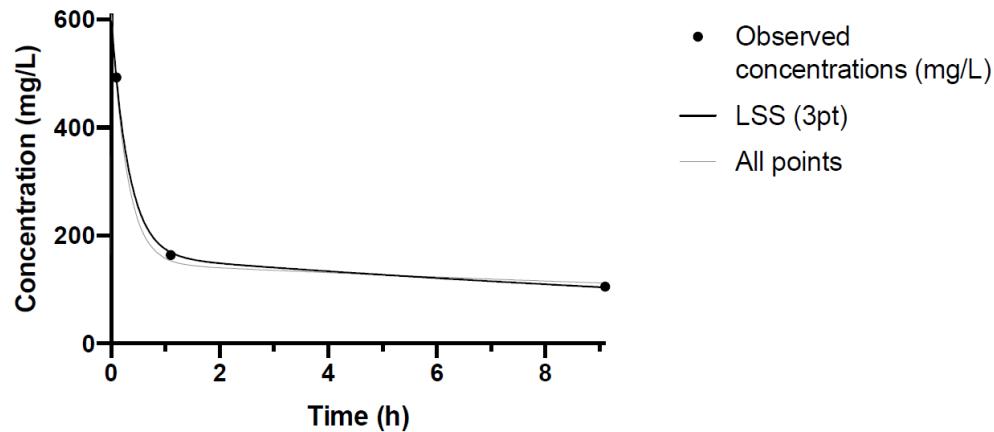


Fig. 1 Iohexol clearance (Cl) estimated using the Xgboost model vs reference Cl in the test set



Evaluation of this model in external populations

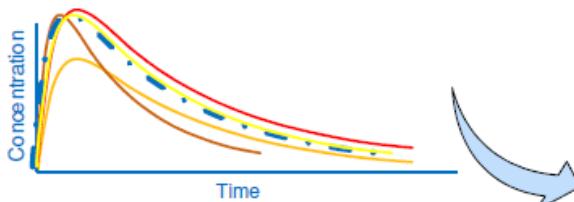
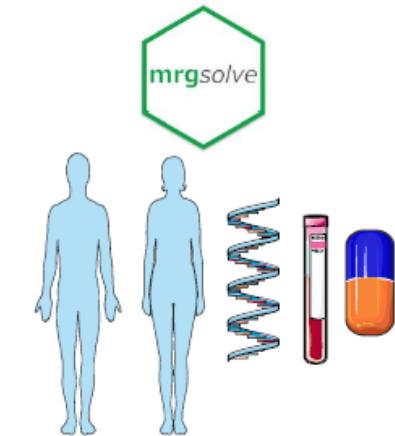
- Poor performances in external population compared to those of the MAP-BE (manuscript in preparation Destere et al)
- → limit of the development of such algorithms in small datasets: poor generalisability



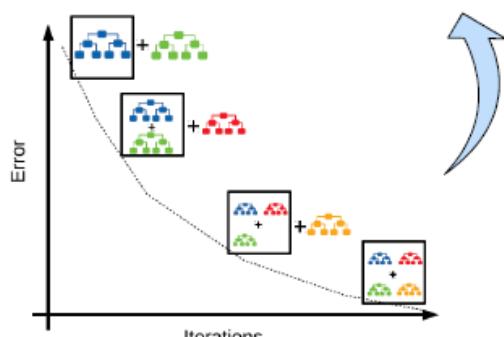
		Kidney transplant patients	Stable ICU patients	Cirrhotic patients
MAP-BE (ITSIM)	Relative MPE (%)	- 3.8	- 1.1	1.2
	RMSE (%)	12.1	6.0	3.7
	Bias out of the $\pm 20\%$ interval	1/21	0/9	0/64
Machine Learning	Relative MPE (%)	13.8	-16.3	1.2
	RMSE (%)	16.8	19.8	30.4
	Bias out of the $\pm 20\%$ interval	5/16	4/9	23/64

Unpublished data

Perspective: development from simulations

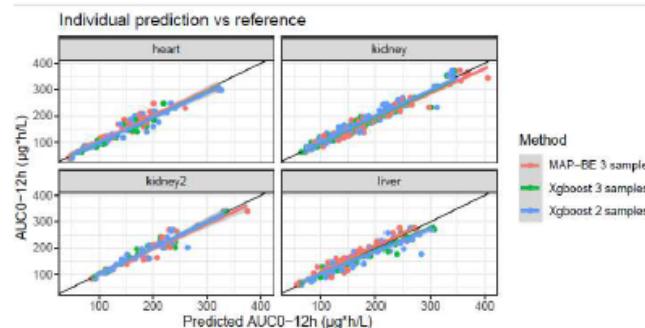


- 9000 tacrolimus Monte Carlo simulations performed from a population pharmacokinetic model in mrgsolve
- Application of filters to remove unrealistic simulated profiles



<http://tvash.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



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

Pharmacological Research 167 (2021) 105578



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



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

Jean-Baptiste Woillard ^{a,b,c,*}, Marc Labriffe ^{a,b,c}, Aurélie Prémaud ^{a,b}, Pierre Marquet ^{a,b,c}

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^b INSERM, IPRITT, U1248, F-87000 Limoges, France

^c Department of Pharmacology and Toxicology, CHU Limoges, F-87000 Limoges, France

		Trained using simulated PK profiles (Woillard et al Pharmacol Res 2021)			Trained using real actual exposure data (Woillard et al Clin Pharmacol Ther 2021)		
Study	Method	Relative MPE (%)	Relative RMSE (%)	Relative errors out of ±20% n (%)	Relative MPE (%)	Relative RMSE (%)	Relative errors out of ±20% n (%)
Kidney transplantation 1 ⁵ (n = 137)	Xgboost 2 concentrations	1.08	8.55	3 (2.2)	-0.6	9.0	3 (2.2)
	Xgboost 3 concentrations	3.28	7.98	1 (0.7)	2.9	8.1	2 (1.4)
Kidney transplantation 2 ⁶ (n = 34)	Xgboost 2 concentrations	0.69	9.0	2 (5.9)	-1.0	9.1	2 (5.9)
	Xgboost 3 concentrations	0.27	8.1	0 (0)	-0.1	7.3	0 (0)
Liver transplantation ⁷ (n = 68)	Xgboost 2 concentrations	5.9	12.9	6 (8.8)	3.3	12.9	7 (10.3)
	Xgboost 3 concentrations	3.7	8.8	2 (2.9)	4.1	9.9	3 (4.4)
Heart transplantation ^{8,9} (n = 47)	Xgboost 2 concentrations	3.2	11.4	4 (8.5)	-0.4	9.7	2 (4.2)
	Xgboost 3 concentrations	3.4	9.1	2 (4.2)	5.4	10.8	3 (6.4)

How many simulations?

Received: 11 February 2022 | Revised: 26 April 2022 | Accepted: 28 April 2022

DOI: 10.1002/psp.4.12810

ARTICLE



Machine learning algorithms to estimate everolimus exposure trained on simulated and patient pharmacokinetic profiles

Marc Labriffé^{1,2} | Jean-Baptiste Woillard^{1,2} | Jean Debord^{1,2} | Pierre Marquet^{1,2}

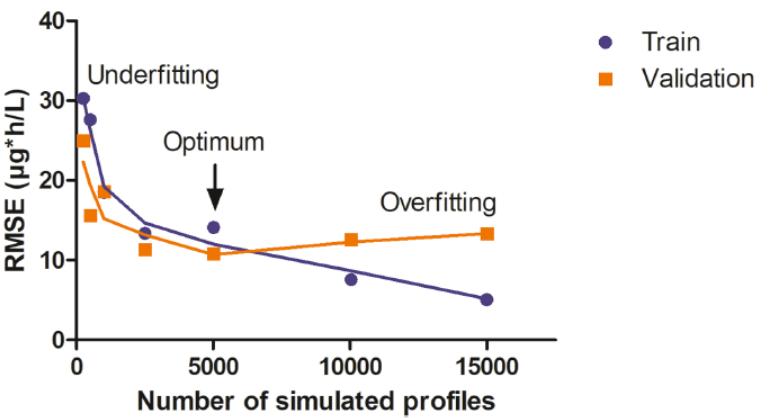


FIGURE 1 Plot of everolimus AUC_{0-12h} prediction RMSE in the training (blue) and the external validation (orange) datasets, according to the number of simulations used to train the XGBoost algorithm. Points represent the performance of each XGBoost model, lines are a smoothed representation of trends. AUC_{0-12h}, 0–12-h area under the concentration-time curve; RMSE, root mean square error; XGBoost, extreme gradient boosting, an optimized gradient boosting machine learning method

TABLE 2 Performance of the XGBoost algorithms at estimating everolimus AUC_{0-12h} in the different sorts of training, testing, and external validation datasets

	Train set (n = 75%)	Test set (n = 25%)	External validation set (n = 114 full PK profile)	
	XGBoost	XGBoost	XGBoost (n = 114)	MAP-I (n = 9)
508 patient PK profiles	RMSE, µg·h/L	15.2	15.4	18.0
	Normalized RMSE (%)	13.5	13.8	17.2
	R ²	0.921	0.922	0.873
	Relative MPE (%)	1.9	4.5	4.5
	Number of MPE out of the ±20% interval n	41 (10.8%)	20 (15.7%)	17 (14.9%)
500 simulated + 508 patient PK profiles	RMSE, µg·h/L	32.1	23.3	12.5
	Normalized RMSE (%)	24.9	17.2	11.9
	R ²	0.880	0.942	0.939
	Relative MPE (%)	-0.4	0.8	0.0
	Number of MPE out of the ±20% interval n	50 (6.6%)	26 (10.3%)	5 (4.4%)
1003 simulated PK profiles	RMSE, µg·h/L	18.5	19.0	18.6
	Normalized RMSE (%)	12.6	12.8	17.8
	R ²	0.970	0.970	0.919
	Relative MPE (%)	1.7	1.6	9.4
	Number of MPE out of the ±20% interval n	39 (5.2%)	13 (5.2%)	22 (19.3%)
1003 simulated + 508 patient PK profiles	RMSE, µg·h/L	19.2	10.7	14.1
	Normalized RMSE (%)	13.6	7.8	13.4
	R ²	0.967	0.986	0.924
	Relative MPE (%)	0.5	0.0	1.2
	Number of MPE out of the ±20% interval n	50 (4.4%)	17 (4.5%)	8 (7.0%)
2508 simulated PK profiles	RMSE, µg·h/L	13.4	15.1	11.4
	Normalized RMSE (%)	8.6	10.2	10.9
	R ²	0.987	0.982	0.951
	Relative MPE (%)	0.1	0.1	1.4
	Number of MPE out of the ±20% interval n	8 (0.4%)	4 (0.6%)	8 (7.0%)
2508 simulated + 508 patient PK profiles	RMSE, µg·h/L	12.5	14.7	12.2
	Normalized RMSE (%)	8.5	10.2	11.7
	R ²	0.987	0.981	0.942
	Relative MPE (%)	0.3	0.2	3.0
	Number of MPE out of the ±20% interval n	39 (1.7%)	17 (2.3%)	7 (6.1%)
5016 simulated PK profiles	RMSE, µg·h/L	14.1	11.2	10.8
	Normalized RMSE (%)	9.3	7.3	10.3
	R ²	0.985	0.990	0.956
	Relative MPE (%)	0.1	0.1	1.6
	Number of MPE out of the ±20% interval n	9 (0.2%)	2 (0.2%)	7 (6.1%)

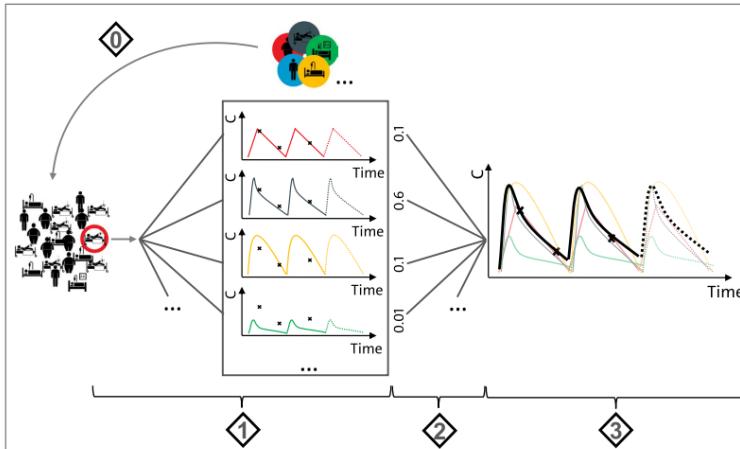
Vancomycin AUC prediction



Pharmaceutical Research
<https://doi.org/10.1007/s11095-022-03252-8>

RESEARCH PAPER

- Development of ML model to predict vancomycin AUC from 6000 simulated patients from 6 POPPK models (Uster et al CPT 2021)
- Comparison of performances to the MAA previously developed



Uster et al CPT 2021

A Machine Learning Approach to Predict Interdose Vancomycin Exposure

Mehdi Bououda¹ · David W. Uster² · Egor Sidorov³ · Marc Labriffe^{1,3} · Pierre Marquet^{1,3} · Sebastian G. Wicha² · Jean-Baptiste Woillard^{1,3}

Bououda et al Pharmaceutical Res 2022

Table II Performances of the General Algorithm Developed in the Overall Population in the Training set (10 fold cross-validation) and in the Test Set

		A priori	1 Occasion	2 Occasion	General Model Fit
Training	RMSE \pm SD (mg*h/L) *	76.0 ± 1.040	40.0 ± 0.438	37.6 ± 0.394	30.0 ± 0.368
	$R^2 \pm SD$ *	0.223 ± 0.0176	0.785 ± 0.0064	0.809 ± 0.005	0.879 ± 0.002
Testing	Relative MPE (%)	11.0	3.2	2.7	1.7
	Relative RMSE (%)	39.6	19.1	17.6	13.8
Model averaging [2]	RMSE (mg*h/L)	76.5	41.2	38.8	30.8
	R^2	0.226	0.776	0.800	0.874
Model averaging [2]	Relative MPE (%)	9.18	3.3	2.8	1.3
	Relative RMSE (%)	37.1	18.9	17.4	13.7
Model averaging [2]	Relative MPE (%)	10.87	2.8	2.7	1.6
	Relative RMSE (%)	36.30	18.8	16.7	12.8

*RMSE & standard deviation obtained after 10-fold cross-validation. MPE is Mean Prediction error and RMSE is root mean square error (i.e. imprecision)

Vancomycin AUC prediction

- External validation in real patient → excellent performances
MPE/RMSE<1.5/12% for the 2 samples model in comparison to different POPPK approaches
 - Model Averaging; MAA and Model Selection; MSA from Uster et al 2021
 - Pkjust website of Limoges University Hospital (<https://pharmaco.chu-limoges.fr/>)

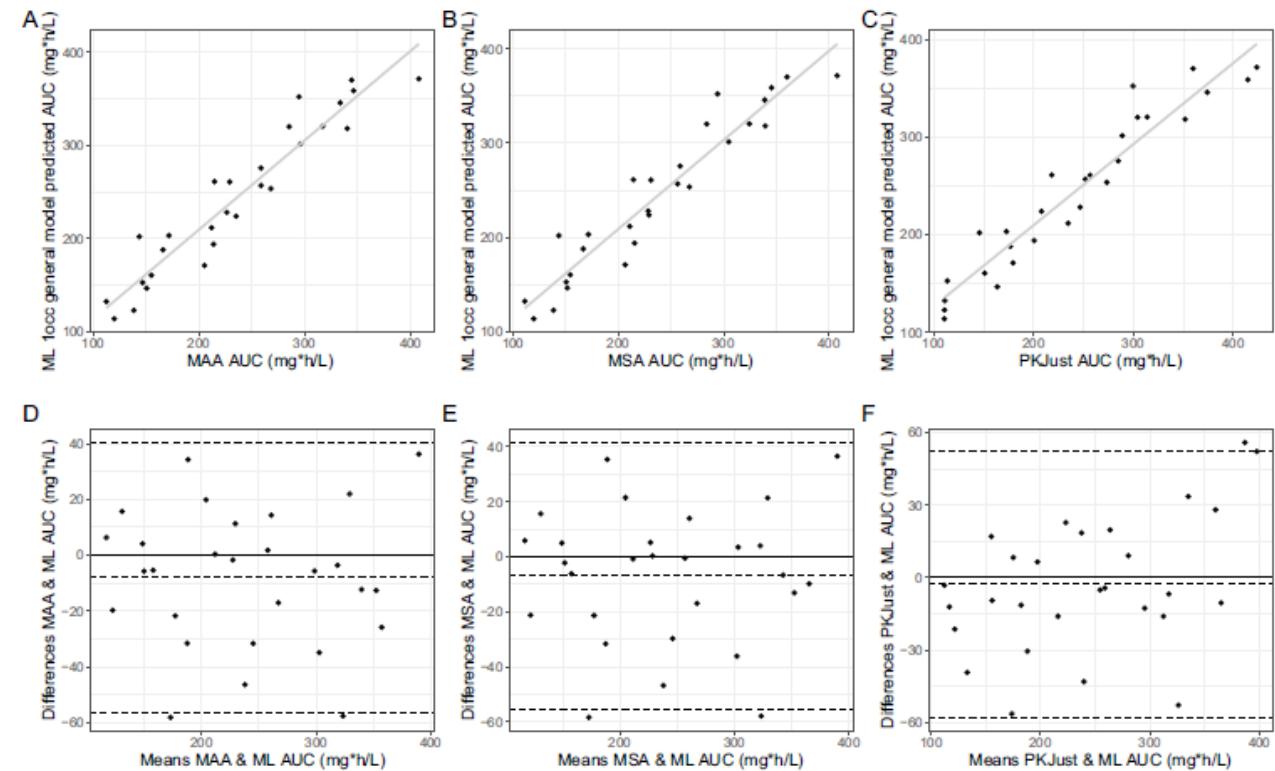


Fig. 4 Scatter plot of ML vs the model averaging algorithm (MAA) (A), model selection algorithm (MSA) (B) and PKJust (C) AUC estimations and Bland Altman curve presenting the difference as function of the mean between ML and the MAA (D), MSA (E) or PKJust (F) AUC estimations.

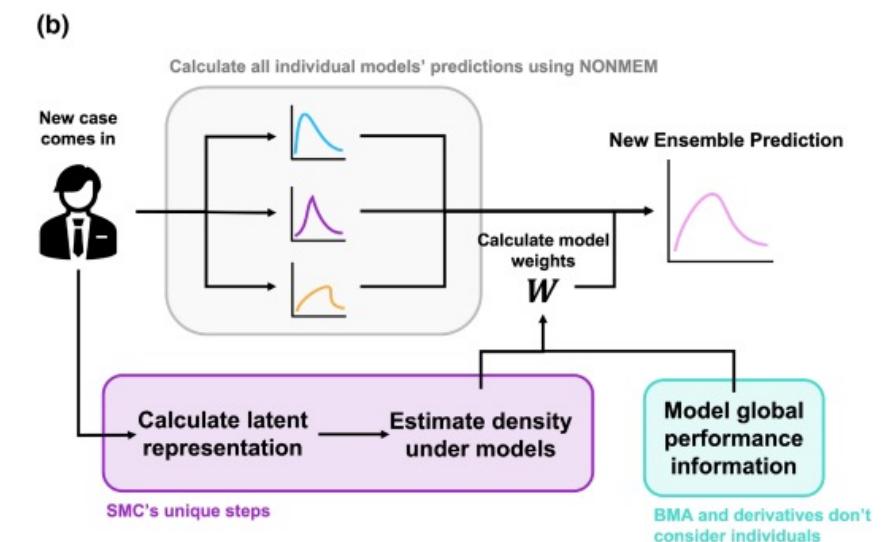
Vancomycin AUC prediction

- Model averaging approach (MAA) proposed in Ulster et al → weighted prediction (1)
- Bououda et al Xgboost model (2) to predict exposure based on individual features (a priori) +/- observations (a posteriori)
- SMC (3) → project patients characteristics (a priori) +/- observations (a posteriori) in a decreased dimension latent space + gaussian density under models → to calculate the weights to applied to each model

(1) Uster et al CPT 2021

(2) Bououda et al Pharmaceutical res 2022

(3) Chan et al CPT-PS 2022



Van der Schaar lab Cambridge UK

Vancomycin AUC prediction

	MAA	ML Xgboost	SMC
A priori MPE%	10.87	9.18	5.0
A priori RMSE%	36.30	37.1	36.0
A posteriori MPE% 1 occ	2.8	3.3	1.9
A posteriori RMSE% 1 occ	18.8	18.9	19.0

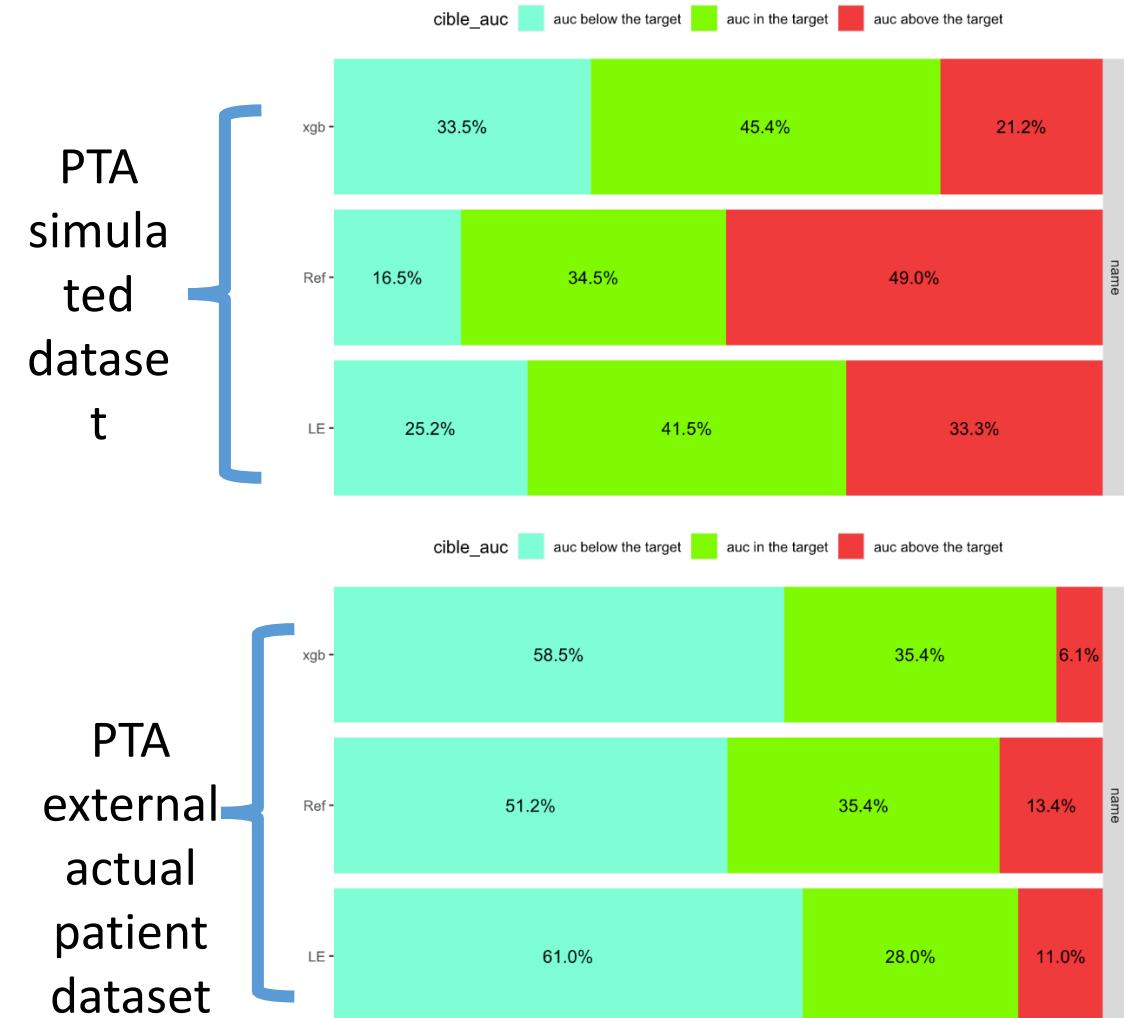
(1) Uster et al CPT 2021

(2) Bououda et al Pharmaceutical res 2022

(3) Chan et al CPT-PS 2022

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

- **Objective:** Develop and validate a ML model using POPPK simulations to optimize the initial dose of vancomycin in neonates and compare it to a literature-based equation (LE).
- **Methods: Simulations:** 1900 PK profiles created using Monte Carlo simulations.
- **Evaluation:** Compared ML and LE dosing in simulated data and 82 real patients.
- **Key Results:** XGBoost outperformed LE with a higher target attainment rate (45.4% vs. 41.5% in simulations; 35.4% vs. 28% in real patients).



vancomycin first dose

For research purposes only, not dedicated to clinical use

ref = ponthier et al PhD thesis

current weight (grams):

1200

Values between 500 and 5000 are accepted, model has not been tested for values out of this range

creatinine values (micromoles/L):

45

Values between 40 and 145 are accepted, model has not been tested for values out of this range

post natal age (sem):

32

Values between 24 and 45 are accepted, model has not been tested for values out of this range

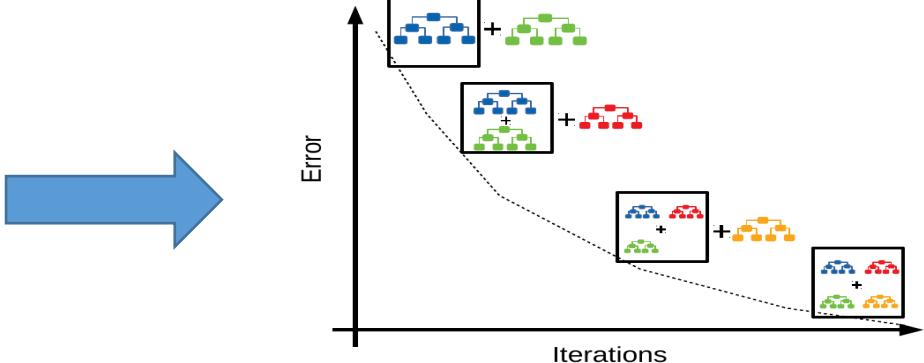
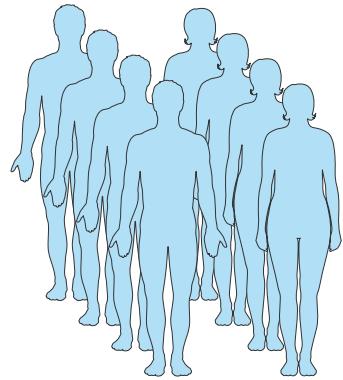
vancomycin continuous dose to infuse 37 mg/24h



**Randomised controled
prospective study to be
started soon to evaluate
these results in real life
conditions**

A priori and a posteriori Daptomycin/Ganciclovir

Master 1 M. Bououda, Master 2 C. Codde, H. Sayadi / PhD works L. Ponthier



First dose prediction based on individual characteristics:
Iterative search of dose maximizing a target

Prediction of a drug exposure based on LSS



Pharmacology | Full-Length Text

Application of machine-learning models to predict the ganciclovir and valganciclovir exposure in children using a limited sampling strategy

Laure Ponthier,^{1,2} Bénédicte Franck,³ Julie Autmizguine,^{4,5,6} Marc Labriffe,^{1,7} Philippe Ovetchkine,⁴ Pierre Marquet,^{1,7} Anders Åberg,^{8,9} Jean-Baptiste Woillard^{1,7}

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

ORIGINAL RESEARCH ARTICLE

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

Laure Ponthier^{1,2}, Julie Autmizguine^{3,4,5}, Bénédicte Franck^{5,7}, Anders Åberg^{8,9}, Philippe Ovetchkine⁴, Alexandre Destere¹⁰, Pierre Marquet^{1,11}, Marc Labriffe^{1,11}, Jean-Baptiste Woillard^{1,11}



Clinical Pharmacokinetics
<https://doi.org/10.1007/s40262-024-01405-z>

ORIGINAL RESEARCH ARTICLE

A Machine Learning Algorithm to Predict the Starting Dose of Daptomycin

Florence Rivals¹, Sylvain Goutelle^{2,3,4}, Cyrielle Codde^{5,6}, Romain Garreau^{2,3,4}, Laure Ponthier⁶, Pierre Marquet^{1,6}, Tristan Ferry^{4,7,8}, Marc Labriffe^{1,6}, Alexandre Destere⁹, Jean-Baptiste Woillard^{1,6}



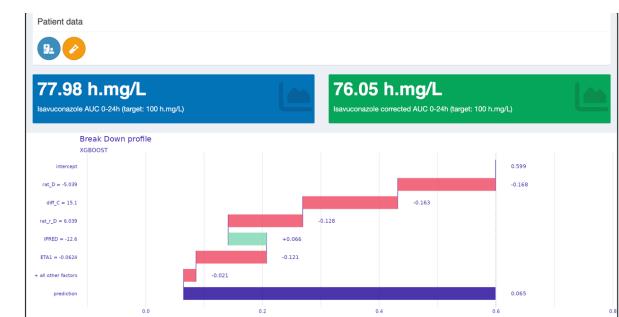
AMERICAN SOCIETY FOR MICROBIOLOGY
Antimicrobial Agents and Chemotherapy

Antimicrobial Chemotherapy | Full-Length Text



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}

Development of interface for demo



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

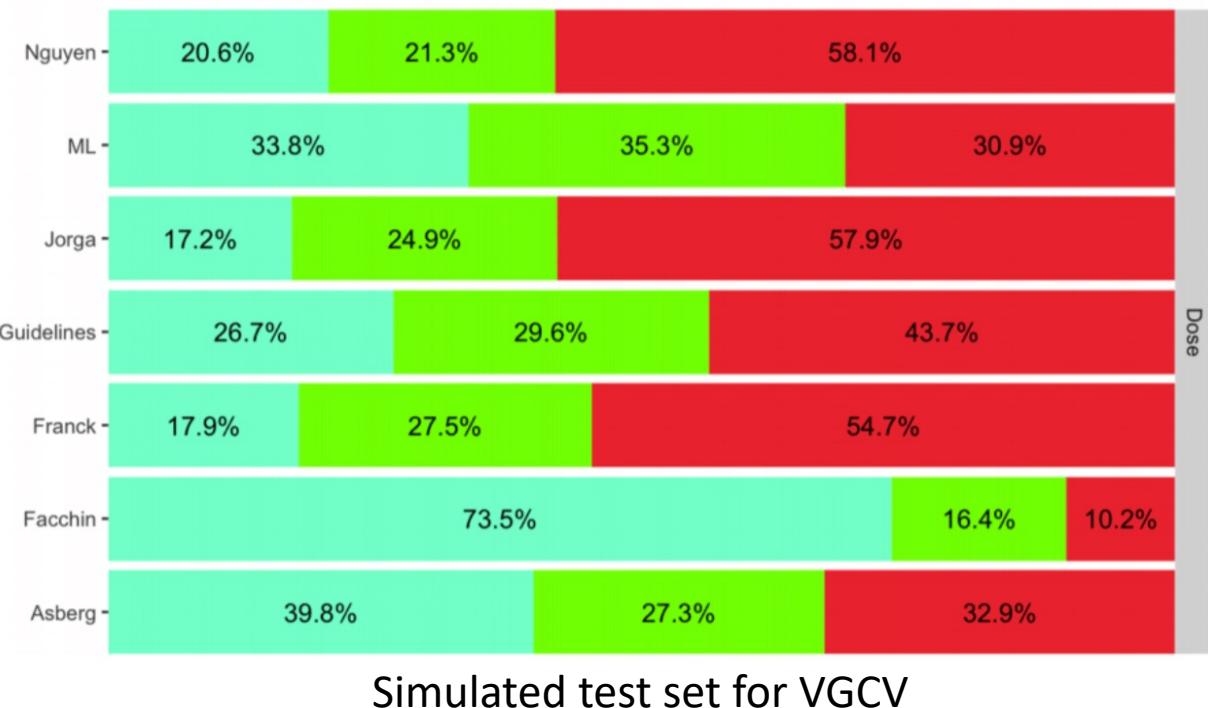


Clinical Pharmacokinetics
<https://doi.org/10.1007/s40262-024-01362-7>

ORIGINAL RESEARCH ARTICLE

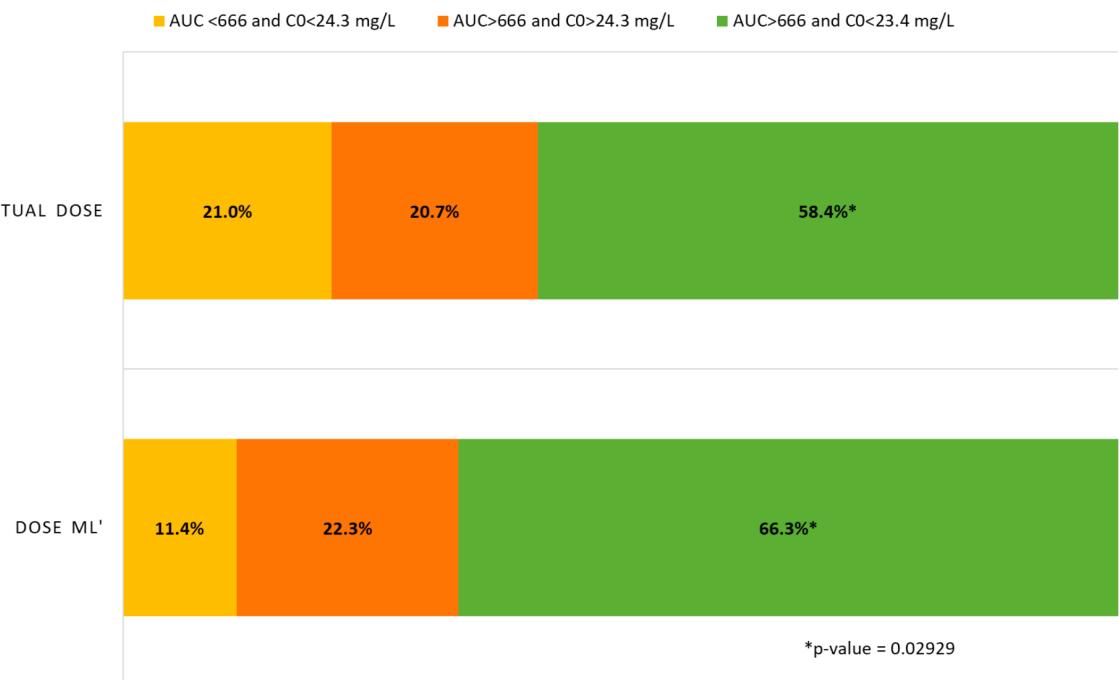
Optimization of Ganciclovir and Valganciclovir Starting Dose in Children by Machine Learning

Laure Ponthier^{1,2} · Julie Autmizguine^{3,4,5} · Benedicte Franck^{6,7} · Anders Åsberg^{8,9} · Philippe Ovetchkine⁴ · Alexandre Destere¹⁰ · Pierre Marquet^{1,11} · Marc Labriffe^{1,11} · Jean-Baptiste Woillard^{1,11}



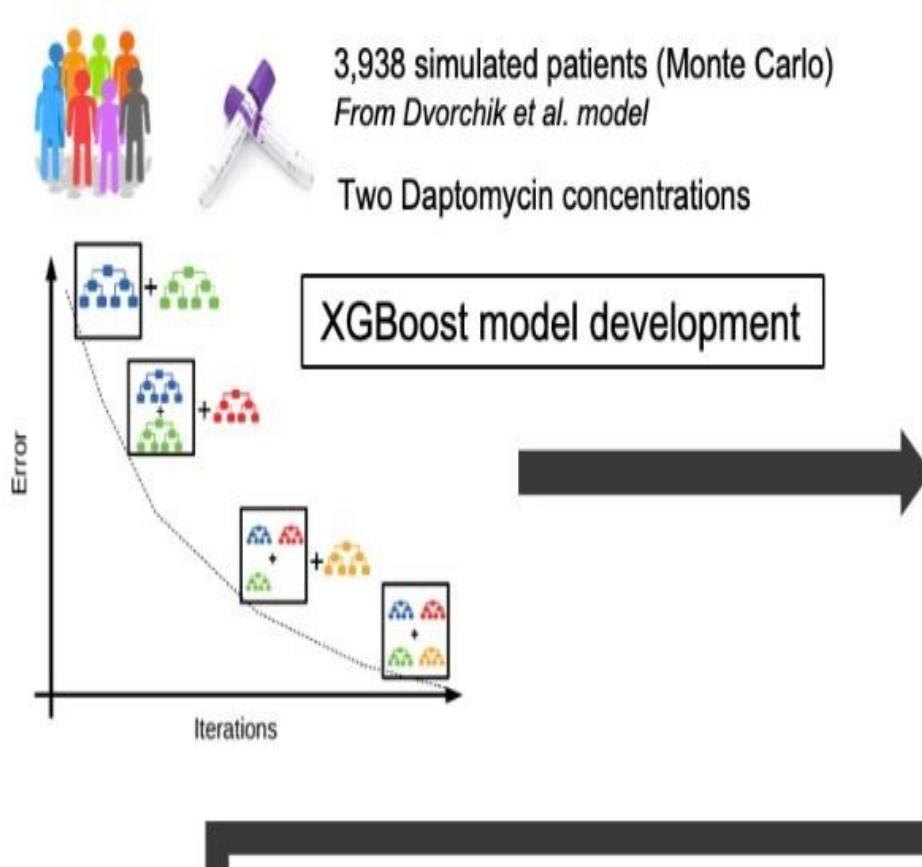
Daptomycin: first dose prediction (F Rivals M2 works)

- Implementation of literature POPPK model of daptomycin (Dvorchik et al AAC 2004) in the mrgsolve R package
- Simulation of 4950 pharmacokinetic profiles with doses ranging from 4 to 12mg/kg.
- Iterative search for the optimal dose of daptomycin maximizing the event ($AUC/CMI>666$ & $C_{min}<24.3$ mg/L).
- Evaluation in simulations and in an external database of real patients in comparison to population pharmacokinetics → no difference with POPPK



Daptomycin a posteriori estimation of exposure

Codde et al AAC 2024

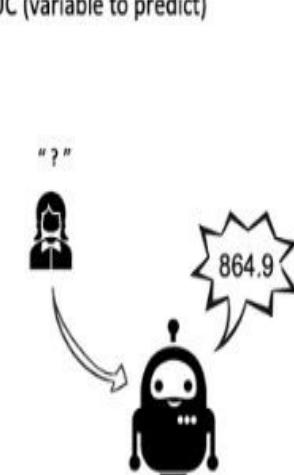


x	→	y
Male A and his 7 covariates		853.4
Female B and her 7 covariates		1048
Male C and his 7 covariates		765.9
Male D and his 7 covariates		697.2



Daptomycin AUC prediction

x: predictors = conc_C0, conc_C1, Diff_C1C0, dose,
CREATCL, SEX, WT
y: AUC (variable to predict)

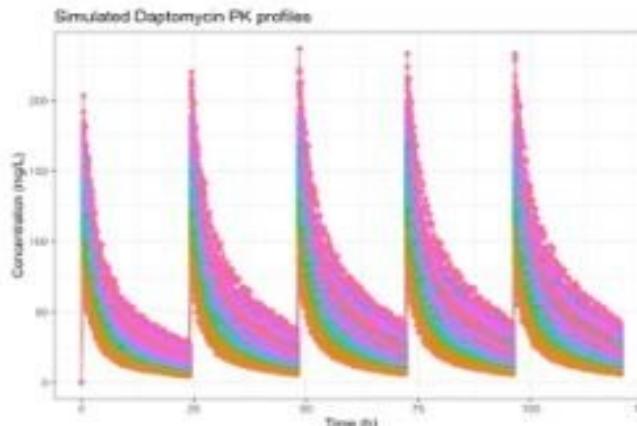
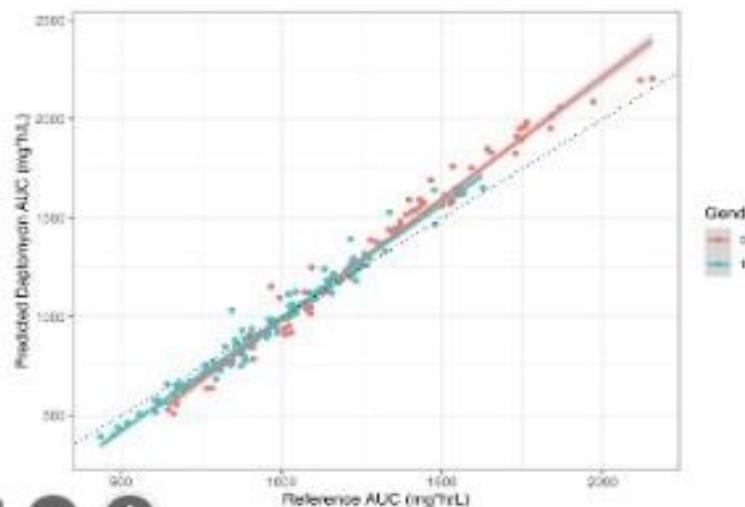
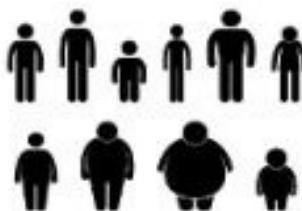


Imprecision of AUC predictions:
RMSE training set: 30.80 mg*h/L
RMSE testing set: 24.90 mg*h/L



External validation

250 simulated patients (Monte Carlo)
From Garreau et al. model



Imprecision of AUC predictions:
RMSE validation set: 85.64 mg*h/L



Daptomycin AUC prediction using machine learning

Sex:**Temperature (°celsius):**

Values between 36.1 and 40.1°C are accepted, model has not been tested for values out of this range

Weight (kg):

Values between 48 and 153 kg are accepted, model has not been tested for values out of this range

Creatinine clearance (Cockcroft and Gault ml/min/1.73m²):

Values between 14 and 150 mL/min are accepted, model has not been tested for values out of this range

Daptomycin dose (mg):

Values between 190 and 1800 mg are accepted, model has not been tested for values out of this range

C0 (Trough concentration):

Values between 0.16 and 100 mg/L are accepted, model has not been tested for values out of this range

C1 (Concentration 1h after beginning of infusion):

Values between 26 and 262 mg/L are accepted, model has not been tested for values out of this range

Target AUC/MIC > 666 mg.h.L in case of *S.aureus* infection

No toxicity AUC< 939 mg.h.L

Falcone M, Russo A, Cassetta MI, Lappa A, Tritapepe L, d'Eltorre G, et al. Variability of pharmacokinetic parameters in patients receiving different dosages of daptomycin: is therapeutic drug monitoring necessary? J Infect Chemother Off J Jpn Soc Chemother. août 2013;19(4):732-9
Safdar N, Andes D, Craig WA. In vivo pharmacodynamic activity of daptomycin. Antimicrob Agents Chemother. janv 2004;48(1):63-8
Garreau R, Pham TT, Bourguignon L, Millet A, Parant F, Bussy D, et al. Daptomycin Exposure as a Risk Factor for Daptomycin-Induced Eosinophilic Pneumonia and Muscular Toxicity. Clin Infect Dis. juill 2023;ciad386



ccodde.shinyapps.io/Daptomycin_AUC/

Bookmarks PK ABIS INSERM R_tidyverse_ML_b... Machine Learning (L... Portail Fac ML Tous les favoris

Daptomycin AUC 0-24h predicted: 653.1 mg.h/L

Target AUC/MIC > 666 mg.h.L in case of *S.aureus* infection
No toxicity AUC< 939 mg.h.L

Falcone M, Russo A, Cassetta MI, Lappa A, Tritapepe L, d'Errico G, et al. Variability of pharmacokinetic parameters in patients receiving different dosages of daptomycin: is therapeutic drug monitoring necessary? *J Infect Chemother Off J Jpn Soc Chemother.* août 2013;19(4):732-9
Safdar N, Andes D, Craig WA. In vivo pharmacodynamic activity of daptomycin. *Antimicrob Agents Chemother.* janv 2004;48(1):63-8
Garreau R, Pham TT, Bourguignon L, Millet A, Parant F, Bussy D, et al. Daptomycin Exposure as a Risk Factor for Daptomycin-Induced Eosinophilic Pneumonia and Muscular Toxicity. *Clin Infect Dis.* juill 2023;ciad386

Break Down profile

xgb

Factor	Contribution
Intercept	5.4
conc_C0 = 5.4	5.4
conc_C1 = 78.6	78.6
dose = 650	-3.281
WT = 65	+10.376
Diff_C1C0 = 73.2	+3.77
CREATCL = 72	+4.617
SEX = 0	+4.204
+ all other factors	+3.097
prediction	653.09

1033.047
-312.909
653.09

Sex:
Female

Temperature (°celsius):
37.2

Values between 36.1 and 40.1°C are accepted, model has not been tested for values out of this range

Weight (kg):
65

Values between 48 and 153 kg are accepted, model has not been tested for values out of this range

Creatinine clearance (Cockcroft and Gault ml/min/1.73m²):
72

Values between 14 and 150 mL/min are accepted, model has not been tested for values out of this range

Daptomycin dose (mg):
650

Values between 190 and 1800 mg are accepted, model has not been tested for values out of this range

C0 (Trough concentration):
5.4

Values between 0.16 and 100 mg/L are accepted, model has not been tested for values out of this range

C1 (Concentration 1h after beginning of infusion):
78.6

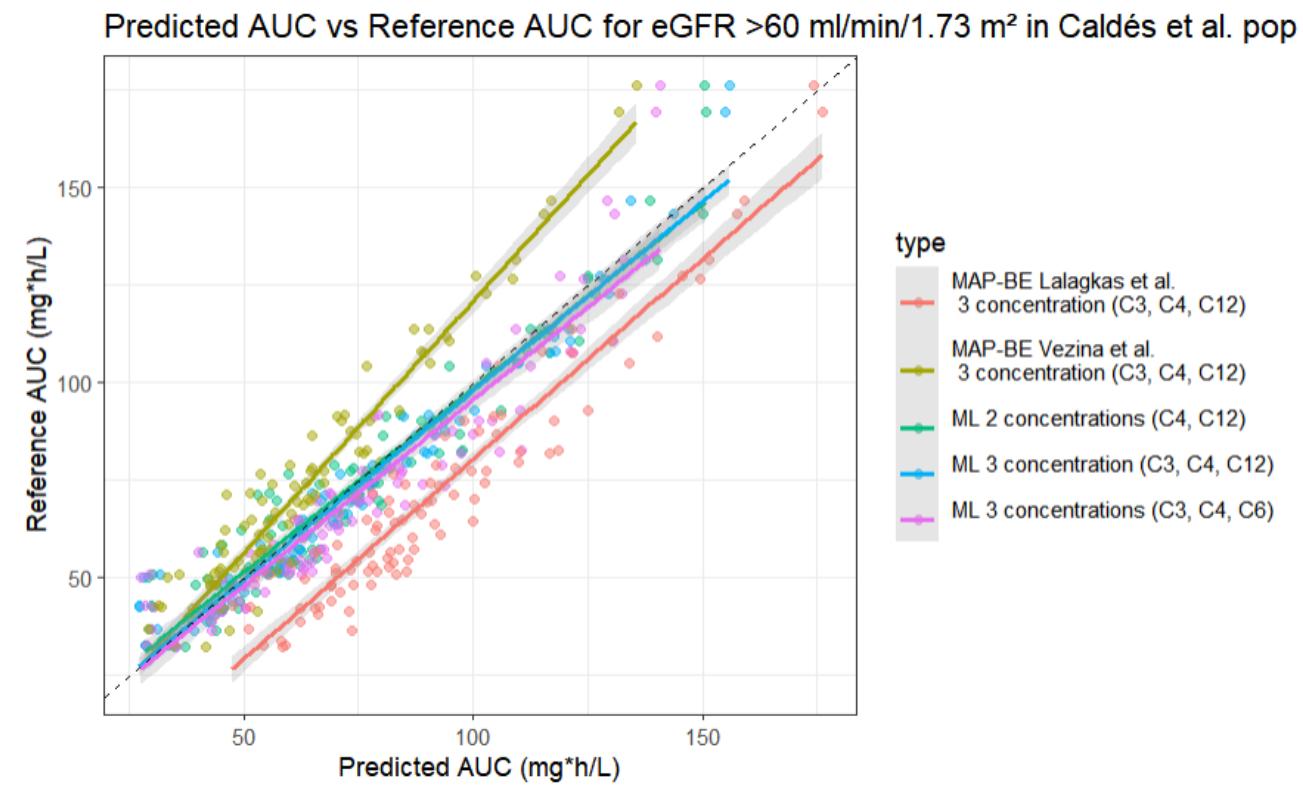
Values between 26 and 262 mg/L are accepted, model has not been tested for values out of this range

Calculate AUC

SCAN ME

Ganciclovir adult exposure prediction (H Sayadi M2 works)

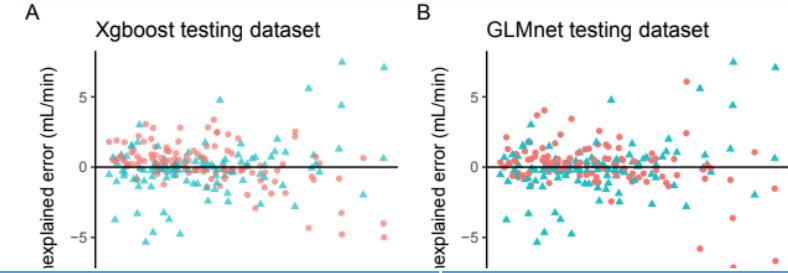
- Implementation of 2 literature POPPK model of prophylactic VGCV in solid organ transplantation (1,2)
- Simulation of 5000 pharmacokinetic profiles for 3 renal function groups
 - >60 ml/min
 - 40-59 ml/min
 - 25-39 ml/min
- Training of a ML model to predict AUC based on 2 or 3 concentrations + eGFR
- Simulation of a validation dataset from 2 other literature POPPK model (3,4)
- Evaluation in comparison to MAP-BE POPPK (1,2) in the validation set (3 and 4)
- → ML more generalizable than MAP-BE



Sayadi et al article under writing

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



	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

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.

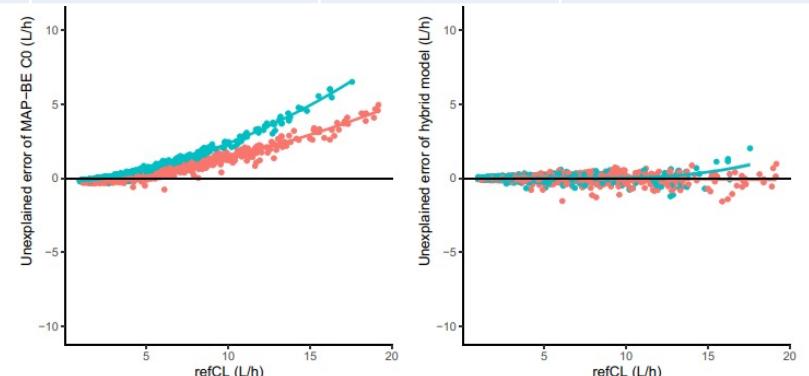
Hybrid model: combination of ML and POPPK to keep interpretability: isavuconazole (PhD works A Destere) (1)

	Training		Testing		External	
	MAP-BE LSS	Hybrid model Xgboost	MAP-BE LSS	Hybrid model Xgboost	MAP-BE LSS	Hybrid model Xgboost
MPE%	3.4	-0.15	3.6	-0.5	7.8	-0.3
RMSE%	11.2	3.4	11.4	3.5	16.3	5.2
MPE out of $\pm 20\%$ (%)	7.6	0.2	5.6	0.0	22.4	0.0

(1) Destere et al Pharm Res 2023

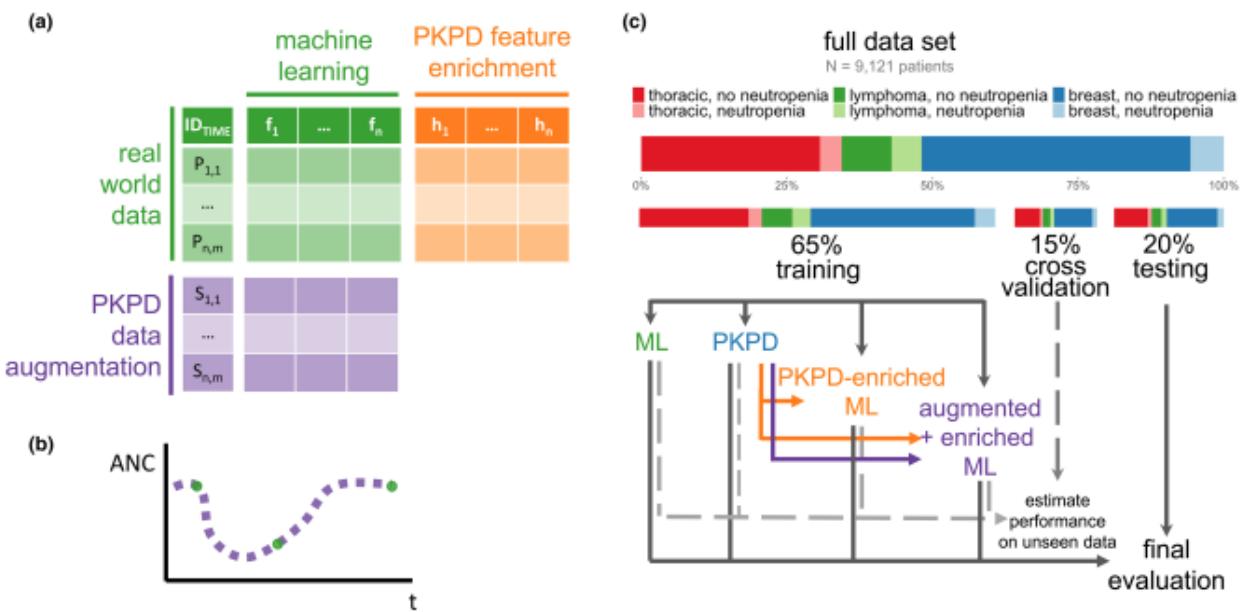
(2) Wu et al AAC 2020

(3) Desai et al AAC 2016

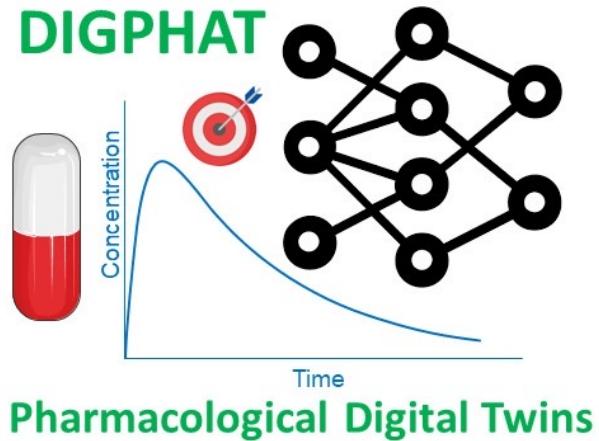


Hybrid models PK/PD ML

- Hybrid PK/PD ML model to predict chemotherapy induced neutropenia
- Enriched with the estimated PK/PD parameters / Augmented developed based on both simulations and observed data
- PKPD-enrichment of ML models improves prediction of grade 3–4 neutropenia (increase in precision (61%) & and recall (39%) vs PKPD model predictions (47%, 33%) or vs base ML model (51%, 31%).



Hughes et al CPT-PS 2023



Multi-scale and longitudinal data modelling in pharmacology: toward digital pharmacological twins

Consortium DIGPHAT

48 months

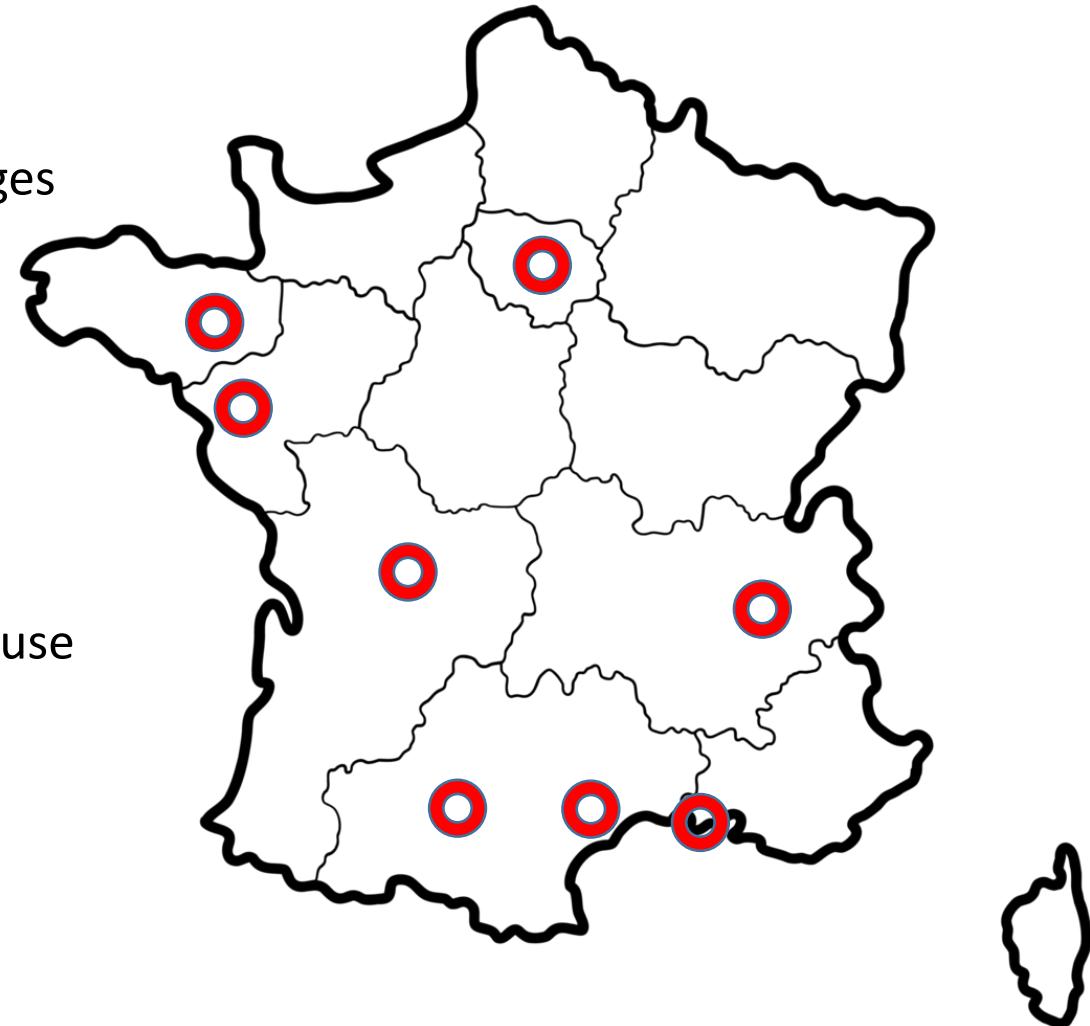
This project is a part of the global Santé Numérique PEPR with a specific focus on the different scales of pharmacology. It contributes to the axe 1 PEPR by the development of innovative models in pharmacology.

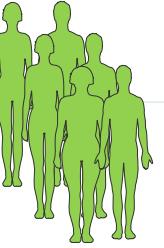
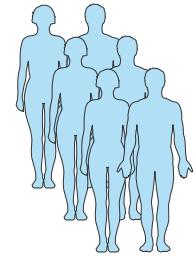
This work is part of the DIGPHAT project which was supported by a grant from the French government, managed by the National Research Agency (ANR), under the France 2030 program, with reference ANR-22-PESN-0017.



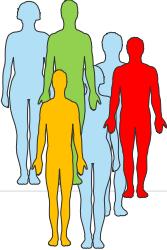
Consortium DIGPHAT

- Coordinators
 - Jean-Baptiste Woillard MCU-PH INSERM, Univ & CHU Limoges
 - Christophe Battail CR CEA, INSERM, Univ. Grenoble Alpes
- Partners
 - Julie Josse INRIA-INSERM, Centre INRIA, Univ. Montpellier
 - Moreno Ursino INSERM, Centre INRIA, Univ. Paris Cité
 - Emmanuelle Comets/Florian Lemaitre/MC Verdier INSERM, IRSET, Univ. Rennes
 - Etienne Chatelut/ Melanie White Koning Univ. & CHU Toulouse
 - Sebastien Benzekry Centre INRIA, Univ. Aix-Marseille
 - Matthieu Grégoire Univ. & CHU Nantes
 - Françoise Stanke Univ. & CHU Grenoble Alpes
- Multidisciplinary consortium with expertise in pharmacology, integrative genomics, and mechanistic or AI-based modelling.





Implementation of mechanistic Ordinary Differential Equation models from literature: Monte Carlo simulations to generate synthetic patients

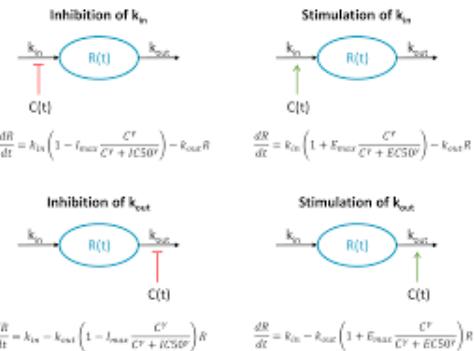


A library for generating and evaluating synthetic tabular data..

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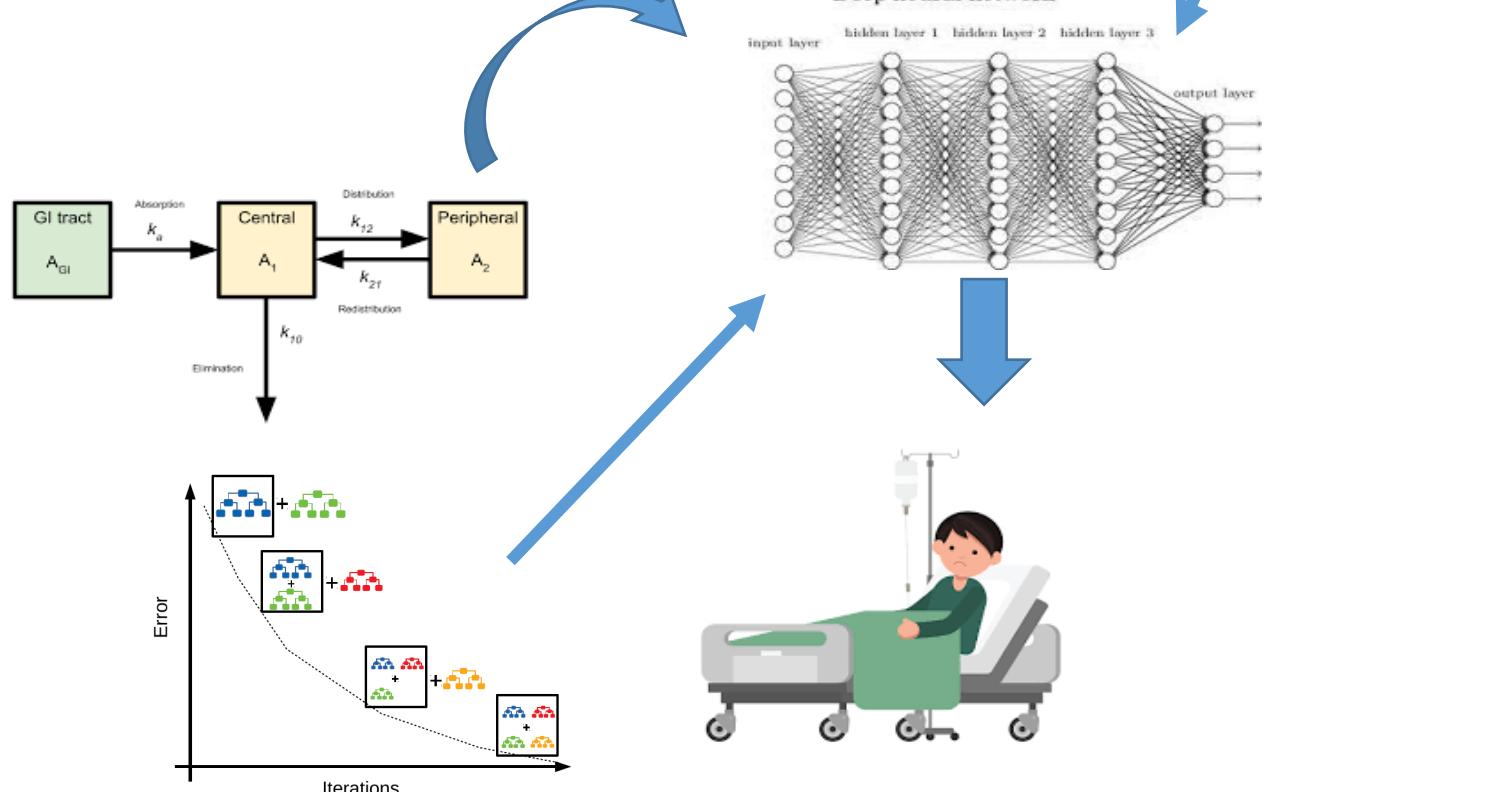
Transformation into synthetic data) = anonymisation

- Multicentric Data
 - Preclinical
 - Omics
 - Clinical trials
 - Cellular



Development of

- Mechanistic ODE PK and PK/PD models
- Data driven models

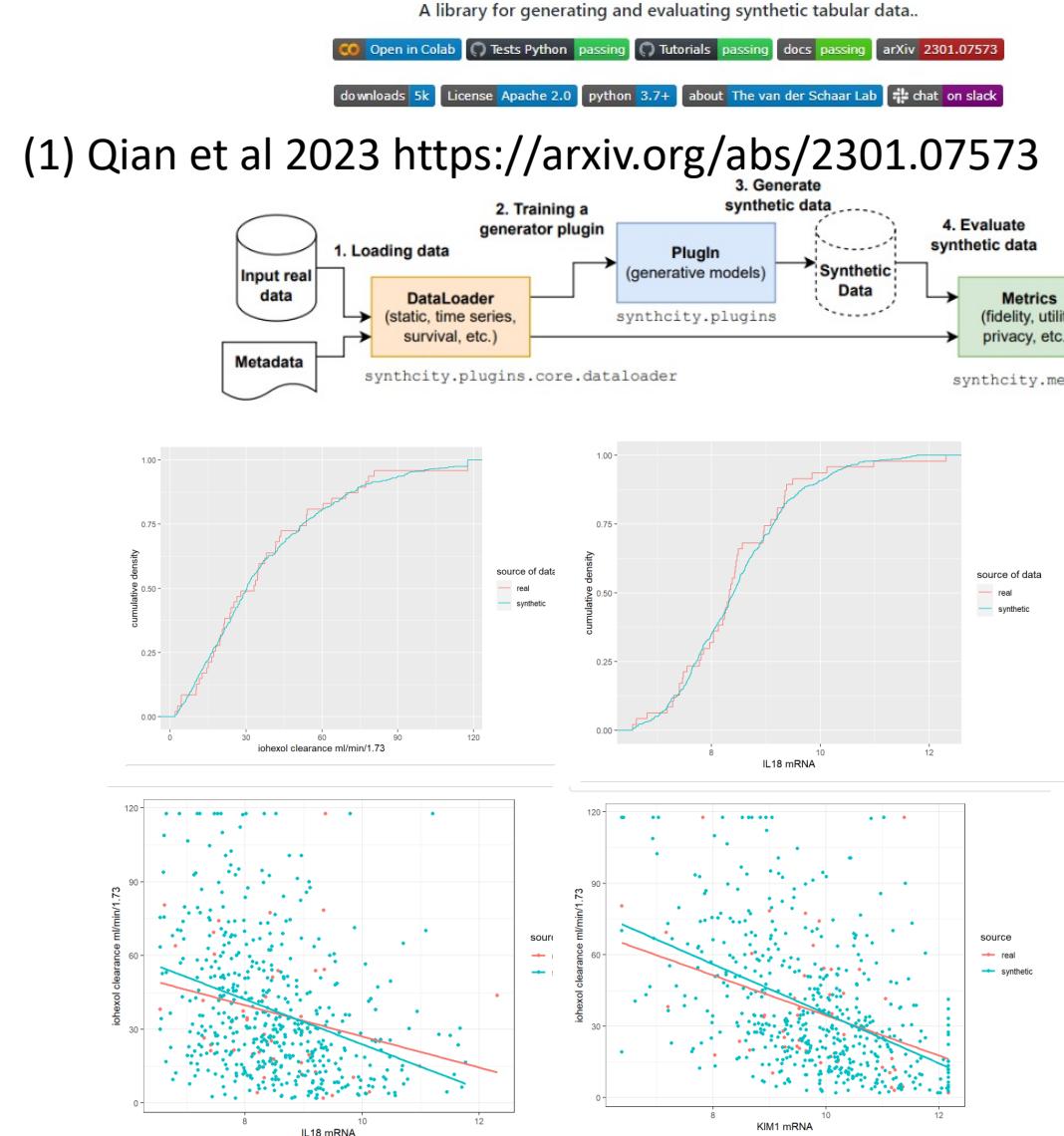


Synthesis of virtual patients using ML/DL

VdS lab (1)



- Synthesis 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)



A recent synthetic data approach to ensure data privacy, validated by CNIL (French National Committee for Informatics & Liberty)

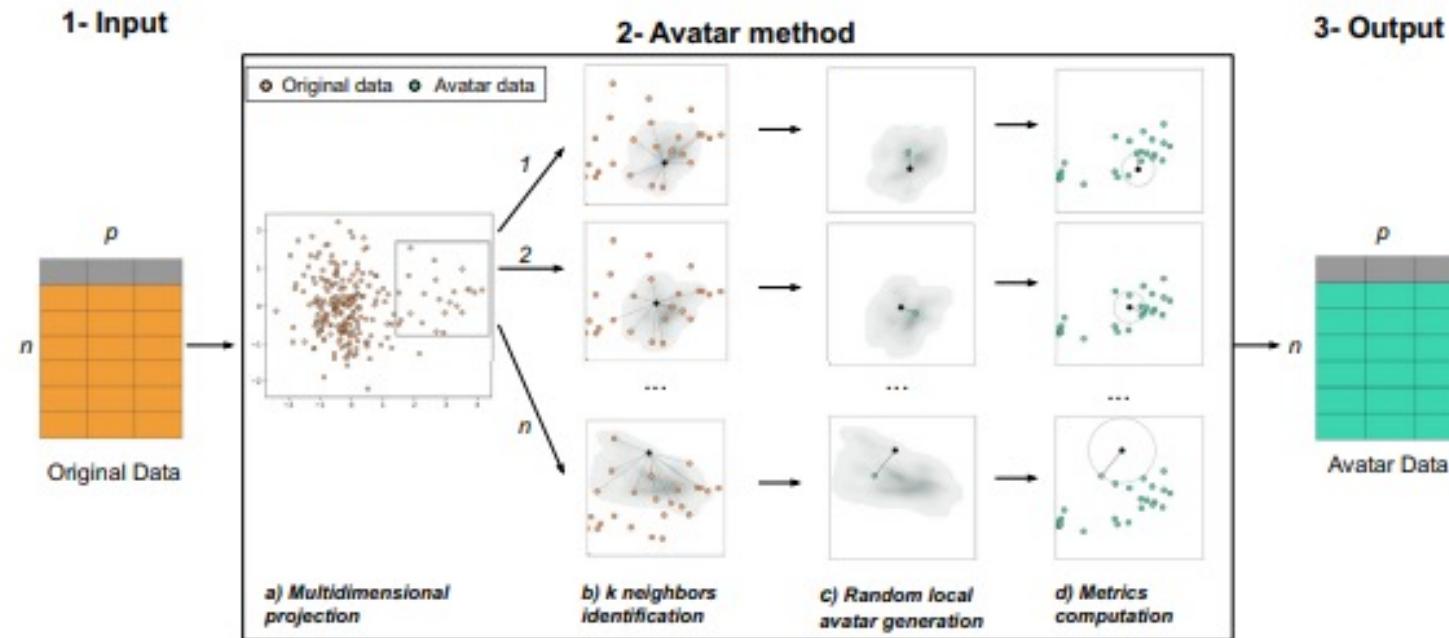
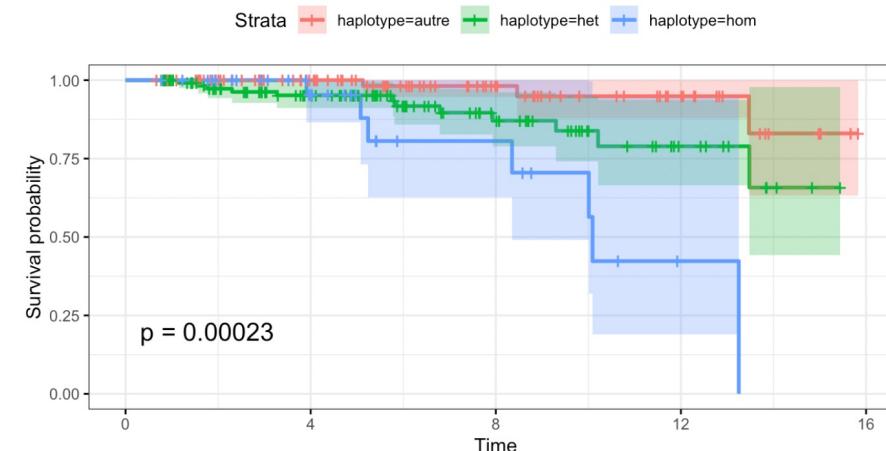


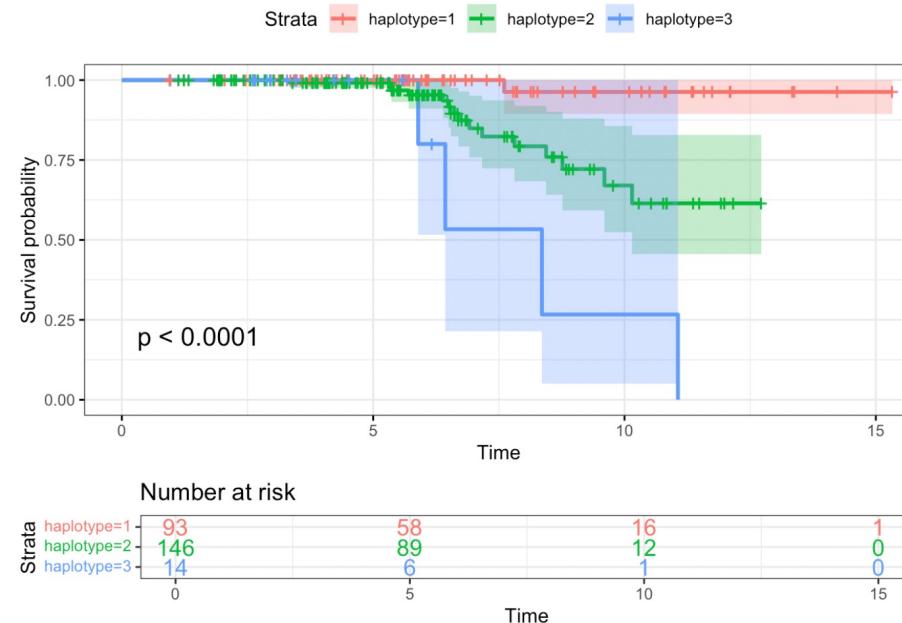
Fig. 5 The Avatar method uses local modeling to stochastically generate a synthetic individual, termed an avatar simulation. (1) Original pseudonymized sensitive data. (2) The core of the Avatar method consists of four steps: (a) individuals are projected in a multidimensional space; (b) pairwise distances 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 2025: To be or not to be, when synthetic data meets clinical pharmacology: A Focused Study on Pharmacogenetics
; *Distance to closest record, nearest neighbor distance ratio

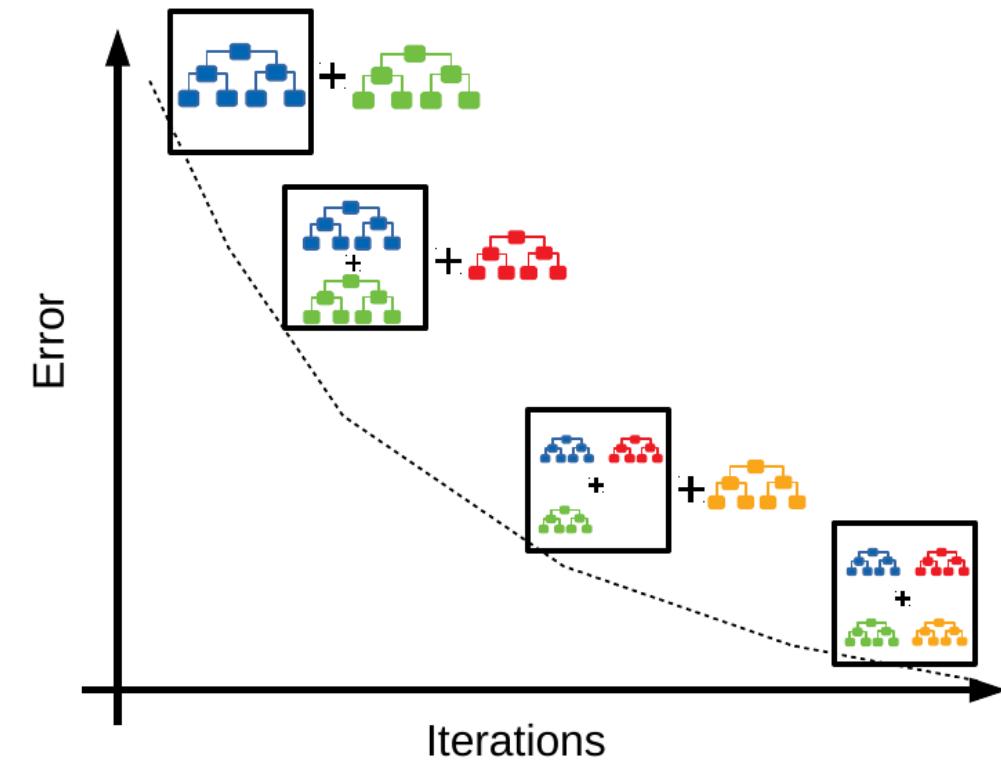
Example of code for simulations for
isavuconazole



Presentation of algorithms
used

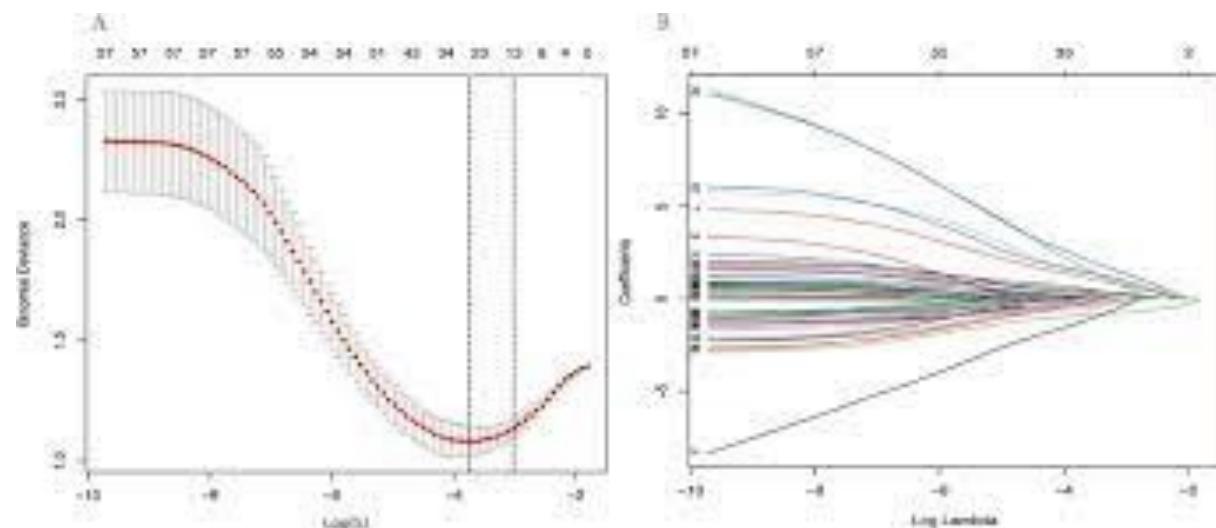
Xgboost

- When using gradient boosting
 - for regression, the weak learners are regression trees,
 - each regression tree maps an input data point to one of its leafs that contains a continuous score.
 - XGBoost minimizes a regularized (L1 and L2) objective function that combines a convex loss function (based on the difference between the predicted and target outputs) and a penalty term for model complexity (in other words, the regression tree functions).
 - The training proceeds iteratively, adding new trees that predict the residuals or errors of prior trees that are then combined with previous trees to make the final prediction.
 - It's called gradient boosting because it uses a gradient descent algorithm to minimize the loss when adding new models.



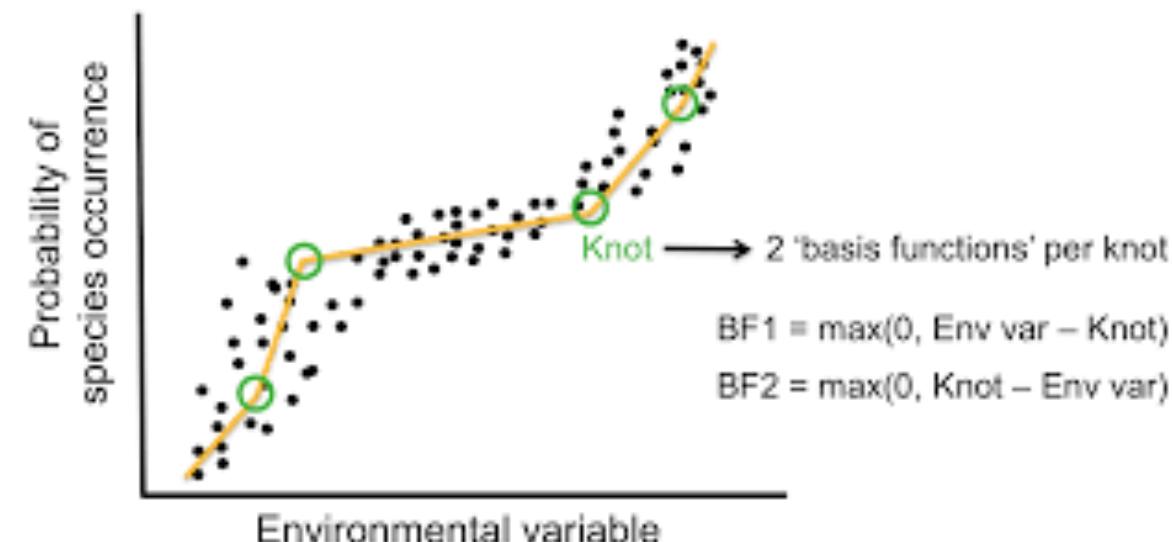
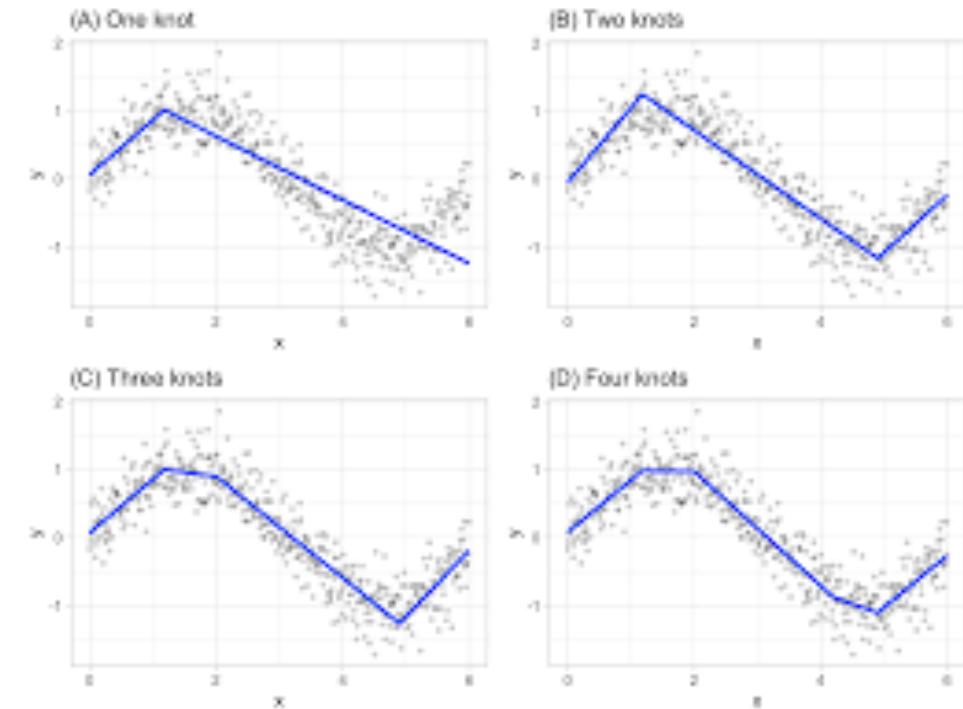
Penalised regression

- The standard linear model (or the ordinary least squares method) performs poorly in a situation, where you have a large multivariate data set containing a number of variables superior to the number of samples.
- A better alternative is the **penalized regression** allowing to create a linear regression model that is penalized, for having too many variables in the model, by adding a constraint in the equation (James et al. 2014, P. Bruce and Bruce (2017)). This is also known as **shrinkage** or **regularization** methods.
- The consequence of imposing this penalty, is to reduce (i.e. shrink) the coefficient values towards zero. This allows the less contributive variables to have a coefficient close to zero (ridge = L2) or equal zero (LASSO = L1).
- Note that, the shrinkage requires the selection of a tuning parameter (lambda) that determines the amount of shrinkage.



MARS

- Multivariate Adaptive Regression Splines, or MARS, → algorithm for complex non-linear regression problems.
- The MARS algorithm involves discovering a set of simple piecewise linear functions that characterize the data and using them in aggregate to make a prediction → in a sense, the model is an ensemble of linear functions.
- Each function is piecewise linear, with a knot at the value t corresponding to linear splines.
- How was the cut point determined? Each data point for each predictor is evaluated as a candidate cut point by creating a linear regression model with the candidate features, and the corresponding model error is calculated.
- Once the full set of features has been created, the algorithm sequentially removes individual features that do not contribute significantly to the model equation. This “pruning” procedure assesses each predictor variable and estimates how much the error rate was decreased by including it in the model.



Support vector machine

- **Margins and Support Vectors:**

The main concept of SVM (Support Vector Machine) is to find a hyperplane (a line in 2D, a plane in 3D, etc.) that best separates the data classes. The SVM aims to **maximize the margin**, which is the distance between the hyperplane and the closest data points from each class, called **support vectors**.

- **Classification:**

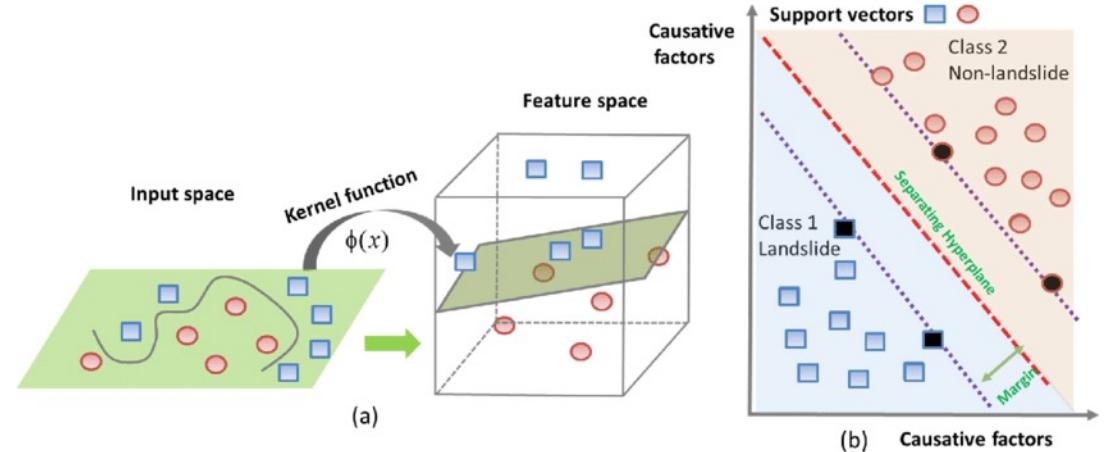
In classification tasks, the SVM uses the hyperplane to distinguish between two classes. Data points on each side of the hyperplane are assigned to different classes.

- **Kernels:**

One of the key advantages of SVM is its ability to handle **non-linear data** through kernel functions. These functions transform the data into a higher-dimensional space where they can be **linearly separated**. Common kernels include **linear, polynomial, and RBF (Radial Basis Function)**.

- **Regression and Anomaly Detection:**

Although primarily used for classification, SVM can be adapted for regression (**SVR - Support Vector Regression**), where the goal is to find the hyperplane that best fits the data.



MLP

- **Layered Architecture:**

The MLP (Multi-Layer Perceptron) consists of multiple layers of neurons: an **input layer**, one or more **hidden layers**, and an **output layer**. Each neuron in a layer is connected to all neurons in the next layer, forming a **densely connected network**.

- **Forward Propagation:**

Input data flows through the network from the input layer to the output layer. At each layer, the data is transformed by a **linear combination**, followed by a **non-linear activation function** (such as ReLU, sigmoid, or tanh).

- **Learning via Backpropagation:**

After forward propagation, the **output error** (the difference between the prediction and the actual value) is computed. This error is then **backpropagated** through the network, allowing the **connection weights** to be adjusted in order to minimize the error.

- **Optimization and Loss:**

Optimization is often performed using **stochastic gradient descent (SGD)** or more advanced variants (such as **Adam**). A **loss function** (such as **mean squared error for regression** or **cross-entropy for classification**) is used to measure the model's error.

