AI/ML-enabled Pharmacometrics Workflows

Machine Learning-empowered Model Selection and Fast Screening of Covariates in Population Modeling

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IQ Workshop on AI/ML for D3
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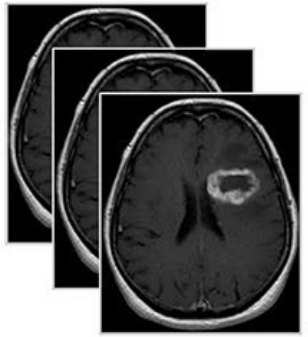
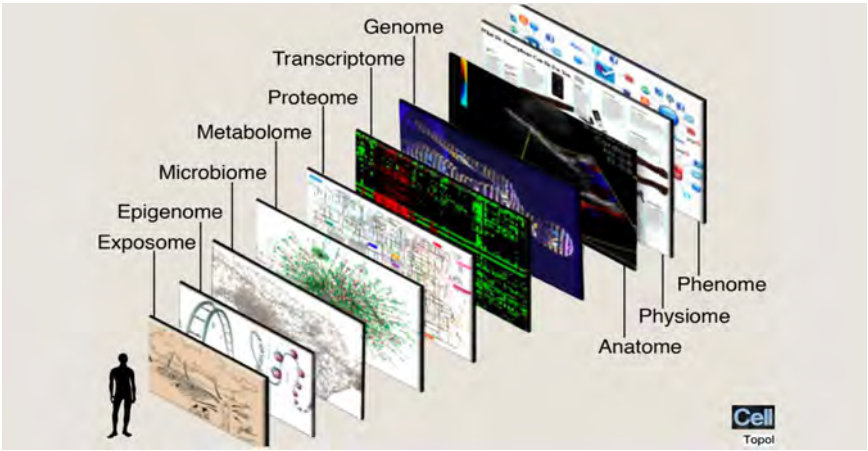
MERCK

Why do we need to bring model-informed drug development to the next level?

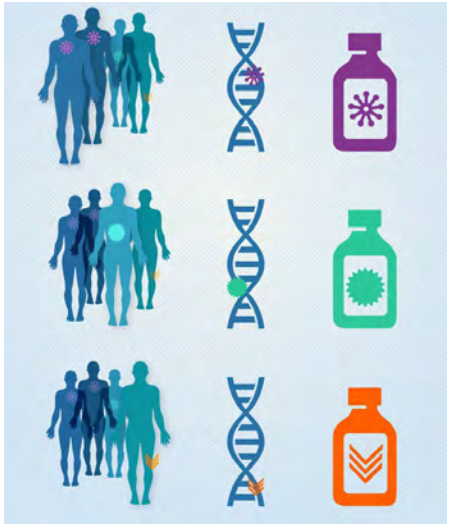
Towards MIDD 2.0

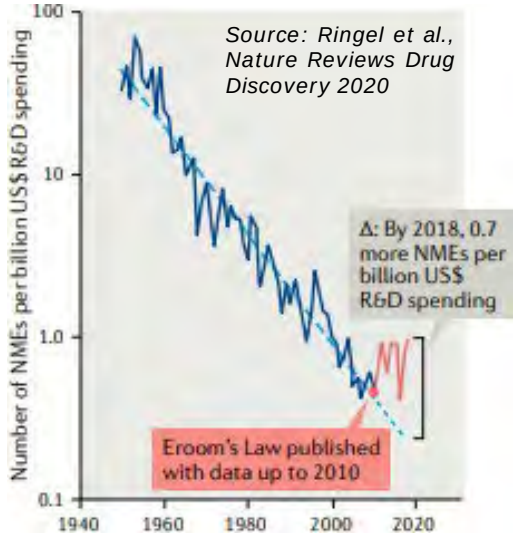
- **Growth** in multimodal, multisource, heterogeneous data
  - Clinical, RWD
  - Omics, images, …
  - Wearable devices
  - …





- **Demands**
  - Personalized Healthcare
  - Deliver more medicines at less cost





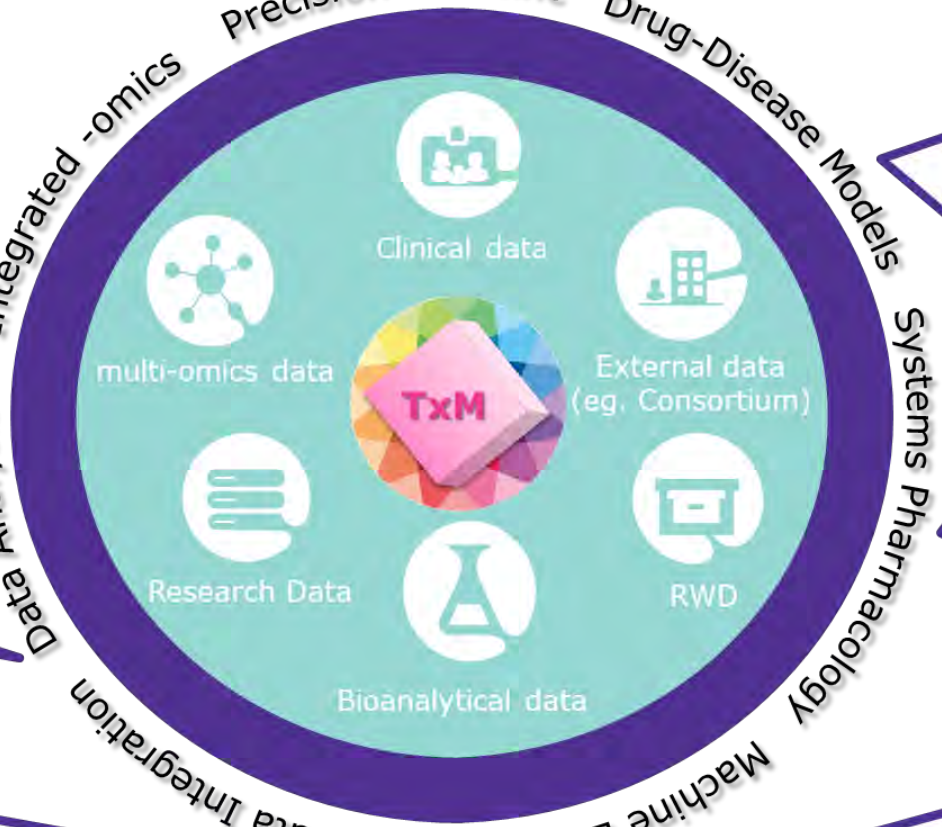
TxM pillars innovatively support forward- and back-translation

Advanced Analytics – Strategic Enablers

Advanced cloud-based platforms enabling precision medicine hypothesis generation and evaluation with high quality/high volume biomarker analysis and self-service tools for scientists

Reverse-translation of clinical trial -omics data into discovery, improving approaches to patient stratification, trial design, and target selection

Applications of AI/ML for biomarker optimization, digital pathology, and single-cell data analysis



Quantification of the dose-exposure-response relationship, together with factors affecting its variability, to bring best possible therapeutic *individualized* solutions with the optimal dose, regimen, and prescribing guidance

Integrated 'system-level' mechanistic modeling to characterize MoA and pharmacological drug–target interactions in biological systems

Applications of AI/ML into population and translational Systems Pharmacology modeling to accelerate analyses and enable the integration of variety of data amenable to AI/ML

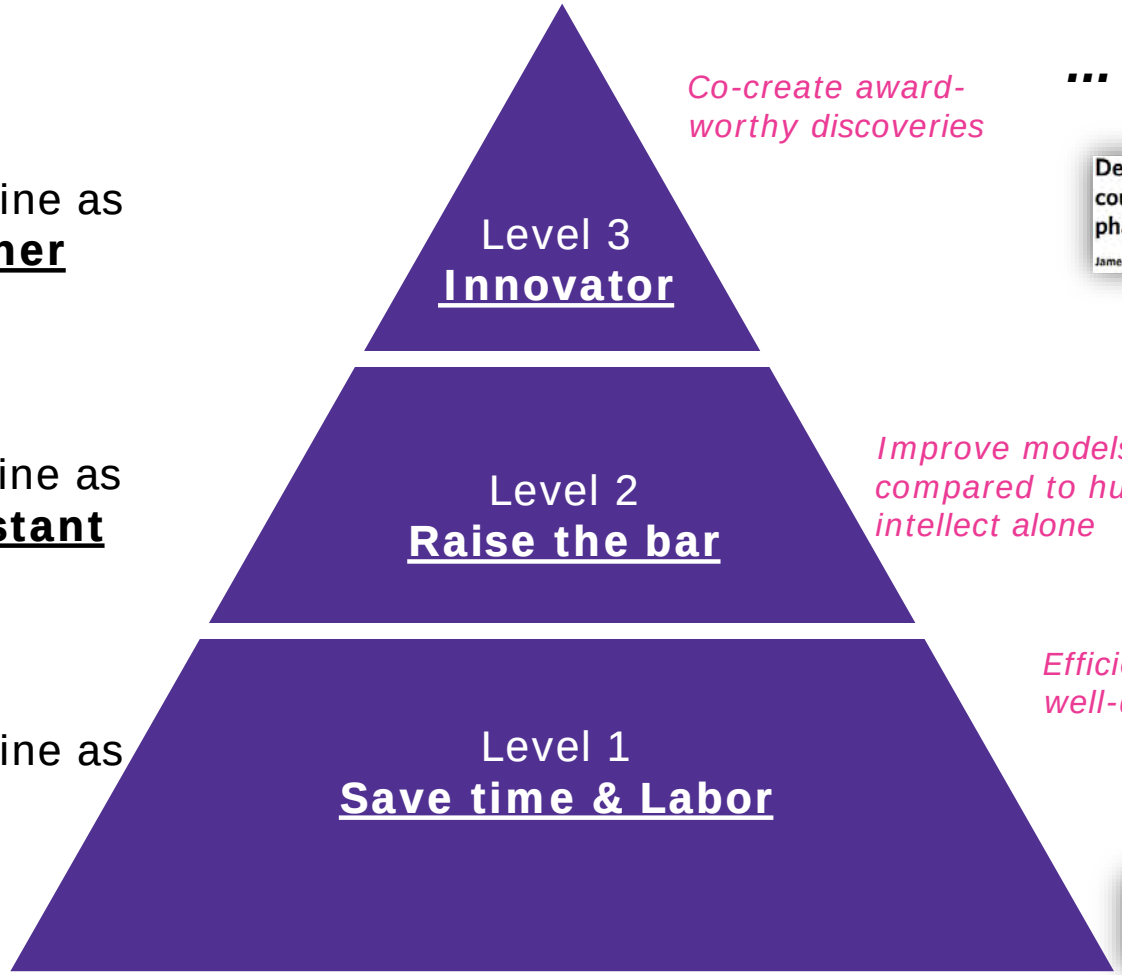
Source: Terranova, N., Venkatakrishnan, K., & Benincosa, L. J. *The AAPS Journal*, *2021*

Machine Intelligence to advance MIDD at various levels

Machine as **Partner**

Machine as **Assistant**

Machine as **Tool**



Co-create award-worthy discoveries

Improve models compared to human intellect alone

Efficiently carry out well-defined tasks

… More to come

Predicting disease activity in patients with multiple sclerosis: An explainable machine-learning approach in the Mavenclad trials

Sreetama Basu[1] | Alain Munafo[1] | Ali-Frederic Ben-Amor[2] | Sanjeev Roy[2] | Pascal Girard[1] | Nadia Terranova[1]

Deep learning prediction of patient response time course from early data via neural-pharmacokinetic/ pharmacodynamic modelling

James Lu[1], Brendan Bender[2], Jin Y. Jin[1] and Yuanfang Guan[2]

Machine Learning Analysis of Individual Tumor Lesions in Four Metastatic Colorectal Cancer Clinical Studies: Linking Tumor Heterogeneity to Overall Survival

Diego Vera-Yunca,[1] Pascal Girard,[2] Zinnia P. Parra-Guillen,[1,3] Alain Munafo,[2] Iñaki F. Trocóniz,[1,3] and Nadia Terranova[2,4]

A Machine-Learning Approach to Identify a Prognostic Cytokine Signature That Is Associated With Nivolumab Clearance in Patients With Advanced Melanoma

Rui Wang[1,2], Xiao Shao[1], Junying Zheng[1,3], Abdel Saci[1], Xiaozhong Qian[1], Irene Pak[2], Amit Roy[2], Akintunde Bello[2], Jasmine I. Rizzo[4], Fareeda Hosein[4], Rebecca A. Moss[4], Megan Wind-Rotolo[1] and Yan Feng[3,*]

Pharmacometric modeling and machine learning analyses of prognostic and predictive factors in the JAVELIN Gastric 100 phase III trial of avelumab

Nadia Terranova[1] | Jonathan French[2] | Haiqing Dai[3] | Matthew Wiens[2] | Akash Khandelwal[4] | Ana Ruiz-Garcia[5] | Juliane Manitz[3] | Anja von Heydebreck[4] | Mary Ruisi[3] | Kevin Chin[3] | Pascal Girard[1] | Karthik Venkatakrishnan[3]

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Long short-term memory recurrent neural network for pharmacokinetic-pharmacodynamic modeling

Xiangyu Liu[1,2], Chao Liu[2], Ruihao Huang[3], Hao Zhu[2], Qi Liu[2], Sunanda Mitra[1], and Yaning Wang[2]

A hybrid machine learning/pharmacokinetic approach outperforms maximum a posteriori Bayesian estimation by selectively flattening model priors

Jasmine H. Hughes ✉ Ron J. Keizer

Development of a System for Postmarketing Population Pharmacokinetic and Pharmacodynamic Studies Using Real-World Data From Electronic Health Records

Fast screening of covariates in population models empowered by machine learning

Emeric Sibieude[1,2] · Akash Khandelwal[3] · Jan S. Hesthaven[4] · Pascal Girard[2] · Nadia Terranova[2]

Stably Accelerating Stiff Quantitative Systems Pharmacology Models: Continuous-Time Echo State Networks as Implicit Machine Learning

Ranjan Anantharaman[1,2], Anas Abdelrehim[1], Anand Jain[1], Avik Pal[1,2], Danny Sharp[1,2], Utkarsh[1], Chris Rackauckas[1,2,3]

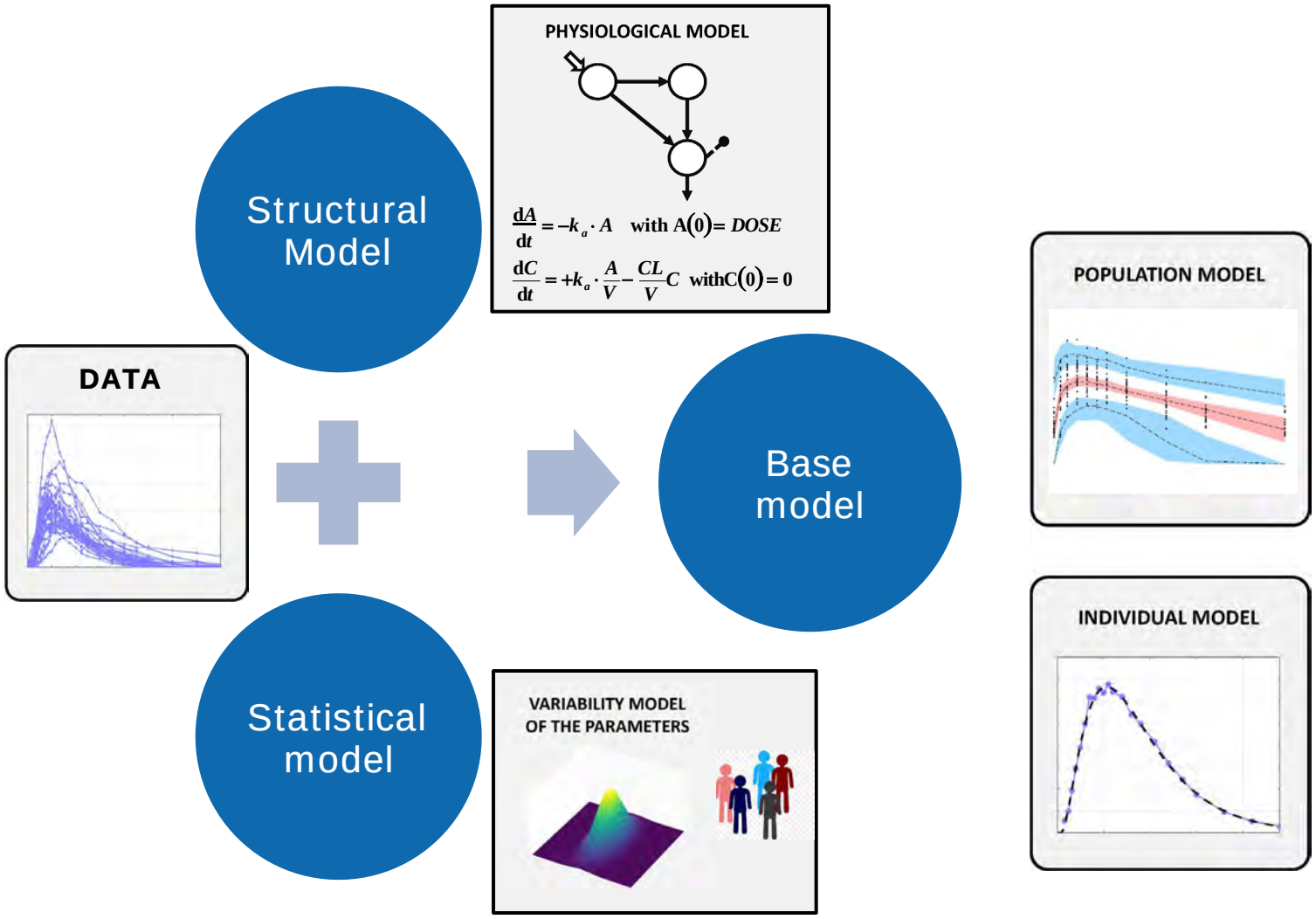
Population pharmacokinetic model selection assisted by machine learning

Emeric Sibieude[1,2] · Akash Khandelwal[3] · Pascal Girard[2] · Jan S. Hesthaven[4] · Nadia Terranova[2]

with the courtesy of James Lu, Genentech

Population model building is a step-by-step process towards a ‘‘fit-for-purpose’’ model

Standard PMX Workflow



Population model building is a step-by-step process towards a ‘‘fit-for-purpose’’ model

Standard PMX Workflow

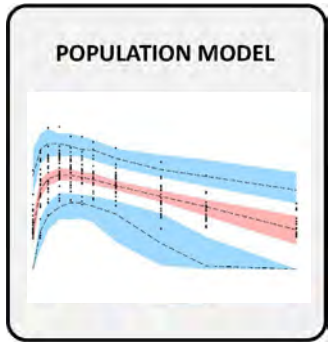
Structural Model

Statistical model

COVARIATES OF THE SUBJECTS

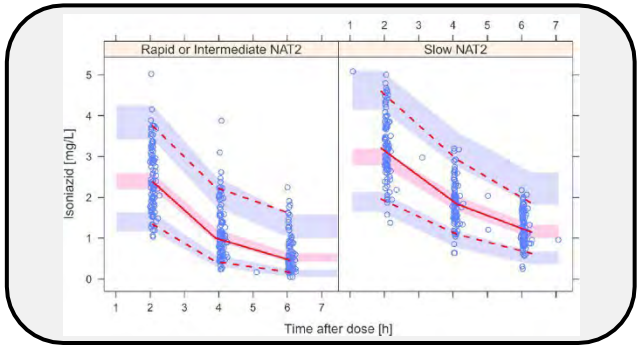
ID	AGE	H	BW	BMI	BSA
101	32	182	90	27	2.1
102	45	184	78	23	2.0
103	37	175	75	25	1.9
⋮	⋮	⋮	⋮	⋮	⋮

Base model



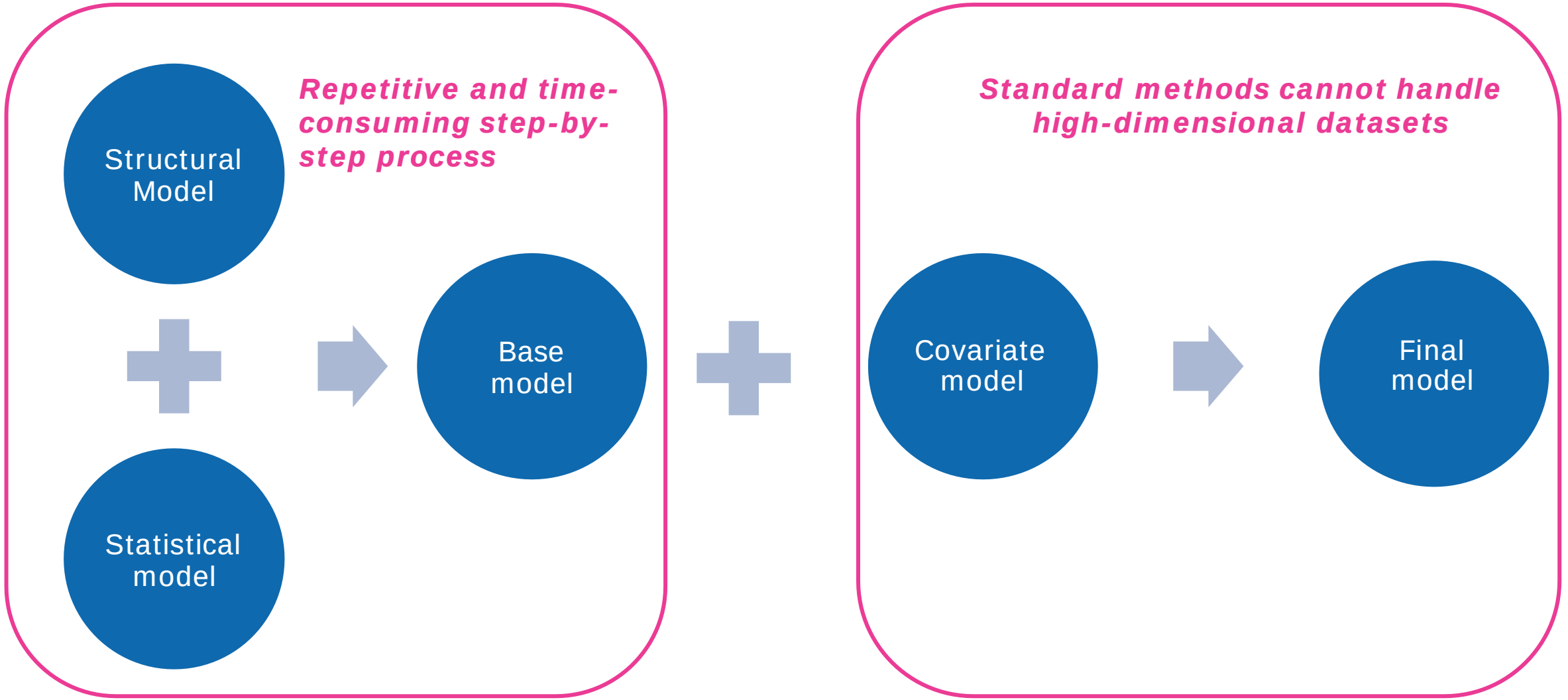
Covariate model

Final model



Population model building is a step-by-step process towards a ‘‘fit-for-purpose’’ model

Standard PMX Workflow



Increasing efficiency in Pharmacometrics model selection with ML/DL

AI/ML-enabled PMX Workflow

Structural Model

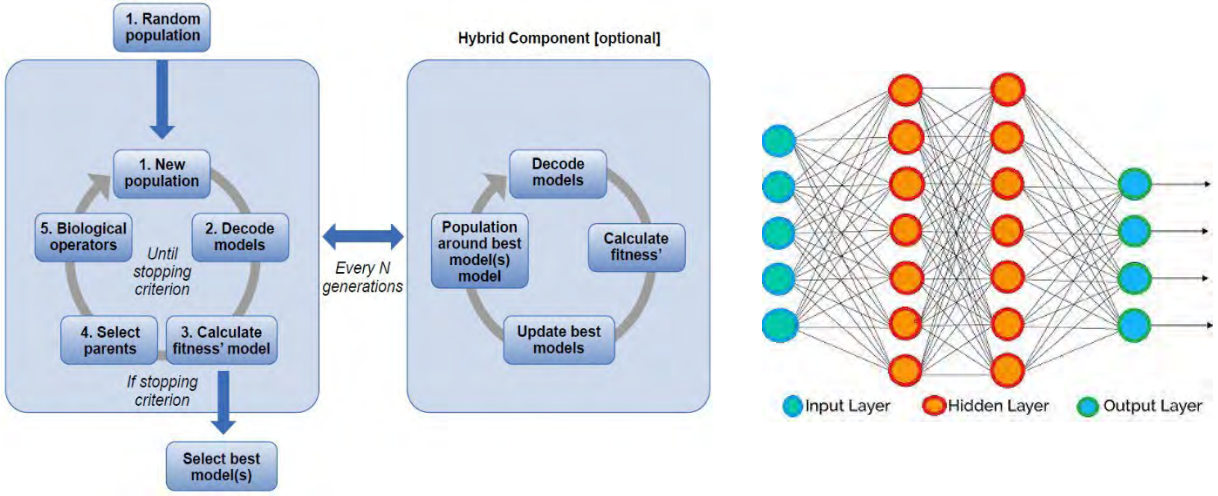
Statistical model

PMX methods could take several days to weeks, depending on previous knowledge

Base model

Genetic Algorithm *for automatic model selection in Monolix*

Neural Network *for prediction of model structure & parameters*

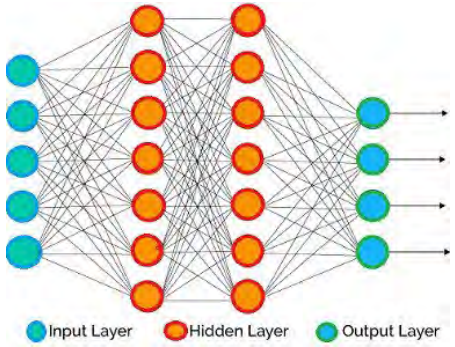


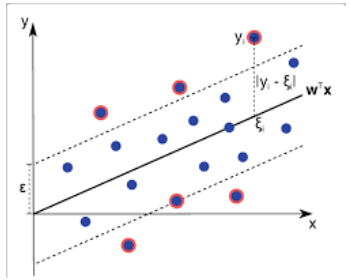
E. Sibieude, A. Khandelwal, J.S. Hesthaven, P. Girard, N. Terranova. *Population pharmacokinetic model selection assisted by machine learning*. J Pharmacokinet Pharmacodyn 2021

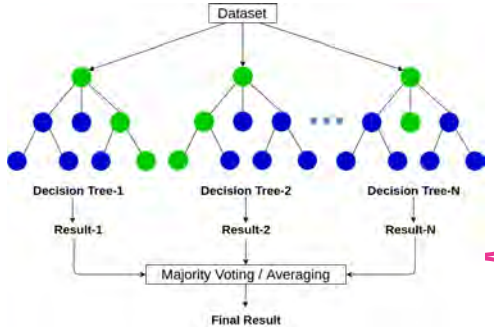
Increasing efficiency in Pharmacometrics covariate screening with ML/DL

AI/ML-enabled PMX Workflow

Random Forest (RF), Neural Network (NN), Support Vector Machine (SVM)
for fast screening of covariates





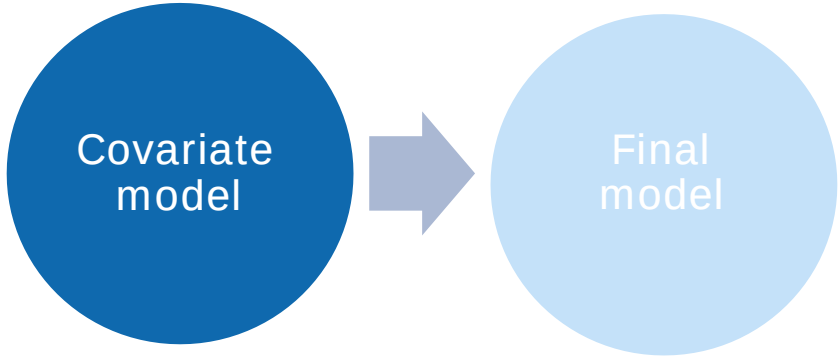


Regression

1. Prediction of parameters value from features
2. Features importance and model evaluation

vs. PMX Methods
SCM, LASSO, COSSAC (w/SAMBA)

Standard methods cannot handle high-dimensional datasets



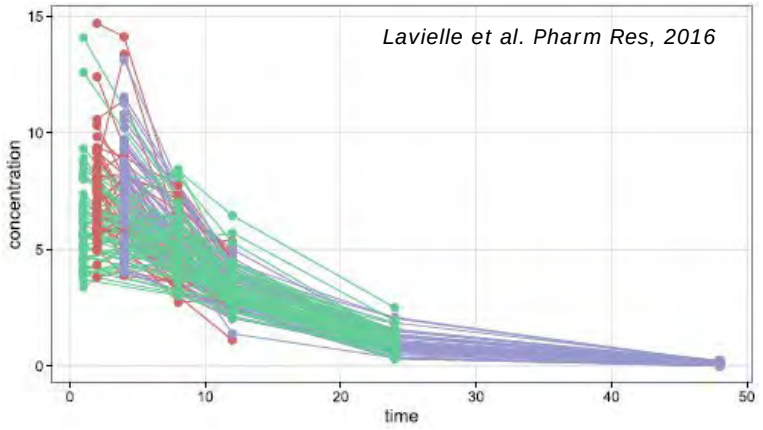
- SCM: Stepwise Covariate Building (Karlsson et al.,1998)
- COSSAC: COnditional Sampling use for Stepwise Approach based on Correlation tests (Chauvin et al. , 2018)

E. Sibieude, A. Khandelwal, J.S. Hesthaven, P. Girard, N. Terranova. *Fast screening of covariates in population models empowered by machine learning*. J Pharmacokinet Pharmacodyn 2021

PMX and ML methods were assessed in scenarios with different levels of complexity

Simulated use cases

Starting from **one-compartment population PK model** with oral absorption, **3800 virtual populations** were generated across 38 scenarios differing in the number of true and false covariates, covariates correlation, effect size and shrinkage



$$CL_i = CL_{pop} \cdot (1 + cov_i \cdot \beta_1) \cdot \left(\frac{wt_i}{median(wt)}\right)^{\beta_2} \cdot \eta_i$$

Scenario	#CAT	#COT	#CAF	#COF
Scenario 1	0	1	1	1
Scenario 2	1	1	1	1
Scenario 3	1	1	3	5
Scenario 4	1	2	3	5
Scenario 5	1	3	5	10
Scenario 6	2	2	5	10

Covariate Correlation \ Effect	Small Effect (<20%)	High Effect (>40%)
Small correlation (<0.3)	a	b
Medium correlation (>0.3,<0.6)	c	d
High correlation (>0.6)	e	f

Scenarios 7a and 7b with higher shrinkage (30%-65%) had reduced samples

CAT: categorical true, COT: continuous true, CAF: categorical false, COF: continuous false

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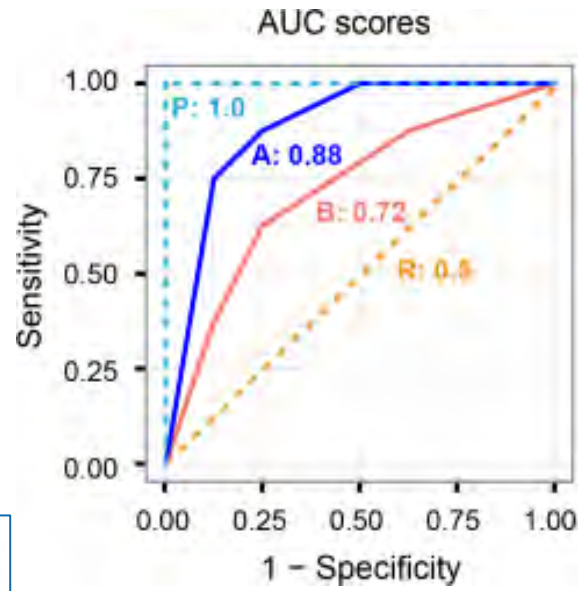
After selection of covariates, F1 scores and ROC can be computed
Evaluation metrics

- Importance scores were used to perform covariate selection for ML methods

		Predicted Class: Positive	Predicted Class: Negative	
Actual Class	Positive	True Positive (TP)	False Negative (FN) **Type II Error**	**Sensitivity** $\frac{TP}{(TP+FN)}$
Actual Class	Negative	False Positive (FP) **Type I Error**	True Negative (TN)	
		Precision $\frac{TP}{(TP+FP)}$		

$$F1 = 2 \cdot \frac{precision \cdot recall}{precision + recall}$$



- The performance of ML methods was assessed with **AUROC** (area under the ROC)
- **F1 scores** were computed to compare selection results across PMX and ML methods

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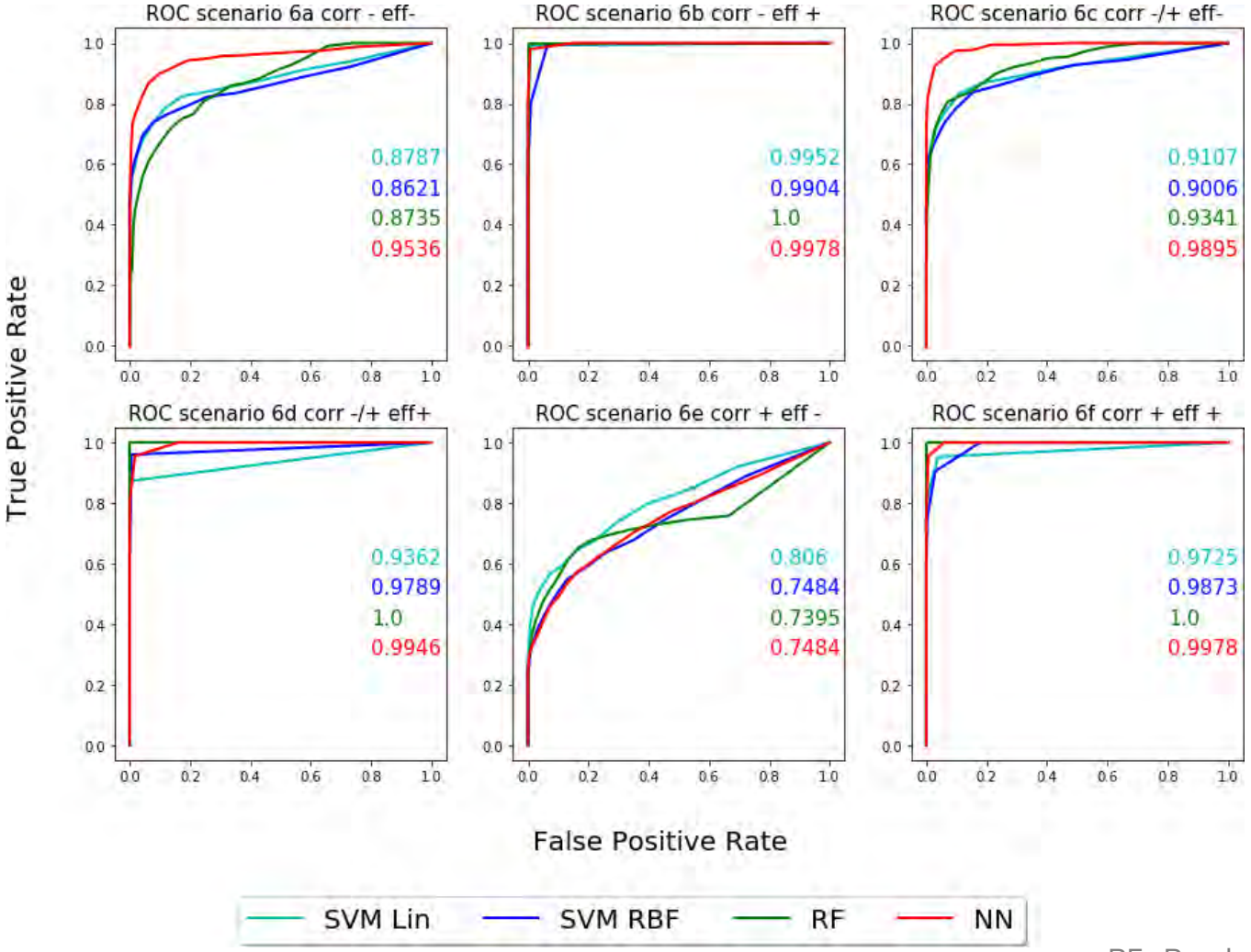
AUROC shows high ML performance across methods for most cases
Example of scenario 6 (2 CAT, 2 COT, 5 CAF, 10 COF)



- Covariate almost **perfectly separable** in two classes (True and False) in case of **high effect** (b, c, d).
- Difficulty to select covariates in case of small effect.
- Similar accuracy but **NN** did slightly **better**.
- AUROCs obtained by the ML methods are very good (> 0.90 on average)

RF: Random Forest; NN: Neural Network; SVM: Support Vector Machine

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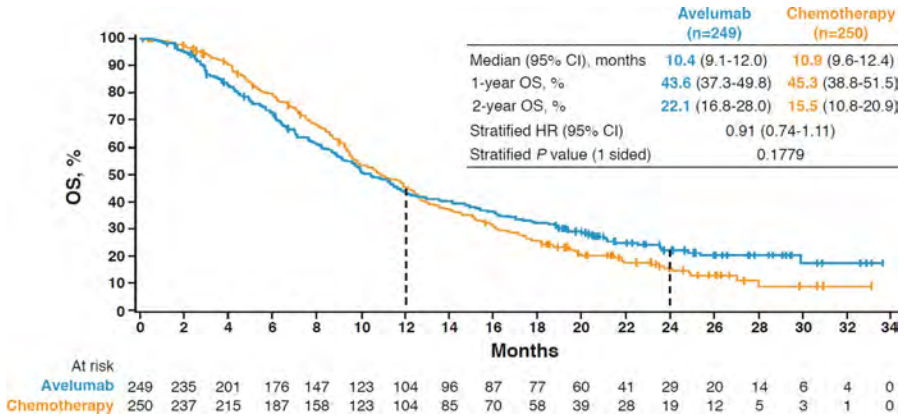
ML&PMX-based identification of prognostic and predictive factors of long-term overall survival and tumor growth dynamics

Avelumab JAVELIN Gastric trial

Superior survival prior to 12 months for chemotherapy continuation arms and better long-term survival for maintenance avelumab arm



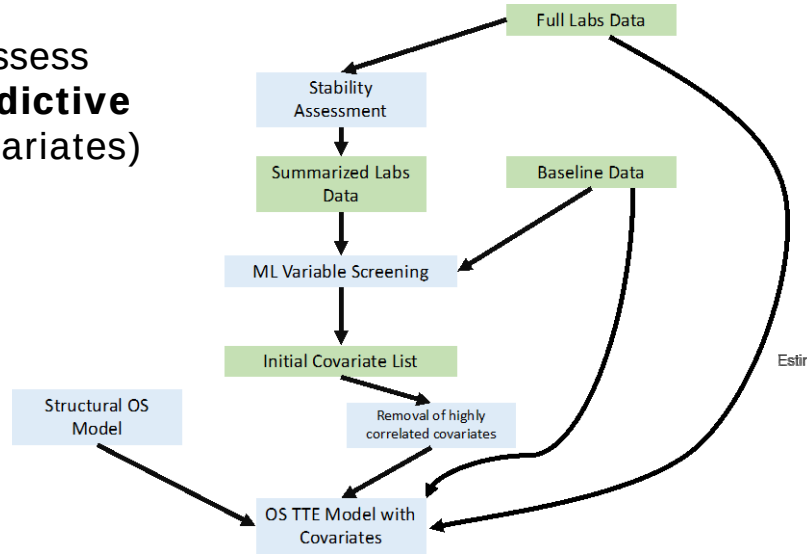
Is there a subpopulation that could benefit from avelumab?

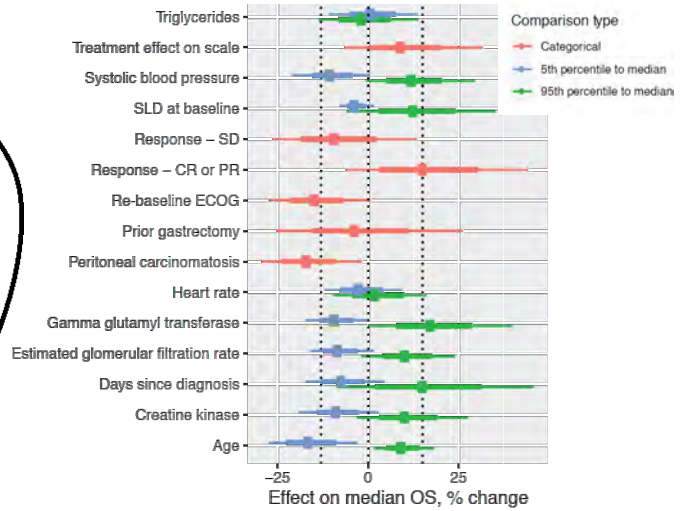
- Parametric **time-to-event** modeling for **OS**
- Modeling of **tumor growth dynamics**
- Identification of prognostic and predictive factors informed by ML

N. Terranova, J. French, H. Dai, M. Wiens,... & K. Venkatakrishnan. *Pharmacometric modeling and machine learning analyses of prognostic and predictive factors in the JAVELIN Gastric 100 phase III trial of avelumab*. CPT: PSP 2022

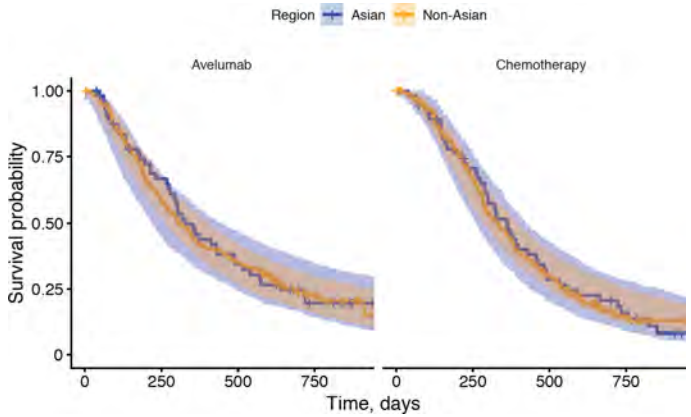
Disease models of OS and tumor growth dynamics were developed by integrating time-invariant and time-varying covariates efficiently informed by ML

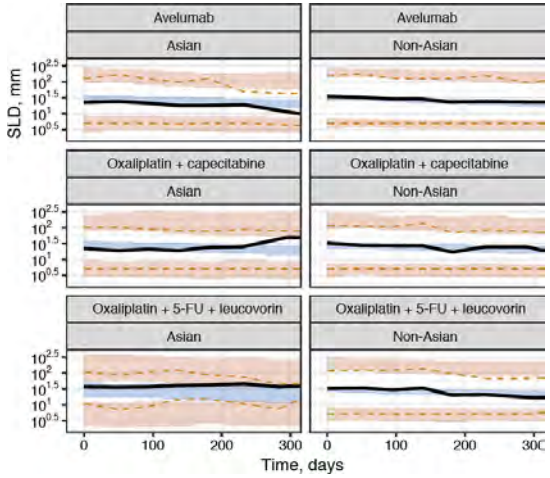
- Random Forest and SIDEScreen were used to assess baseline and time-varying **prognostic and predictive factors** for OS (89 covariates) and TGD (52 covariates)
- **Variable importance** was assessed based on Boruta, Permutation, random splits, Shapley





Lack of discernable differences in disease progression or outcomes between Asian and non-Asian populations





OS: Overall Survival; TGD: Tumor Growth Dynamics

Terranova et. al. CPT: PSP 2022

Take home message

ML enables
automatic model selection and fast covariate screening,
great efficiency with large datasets or complex models

Take home message

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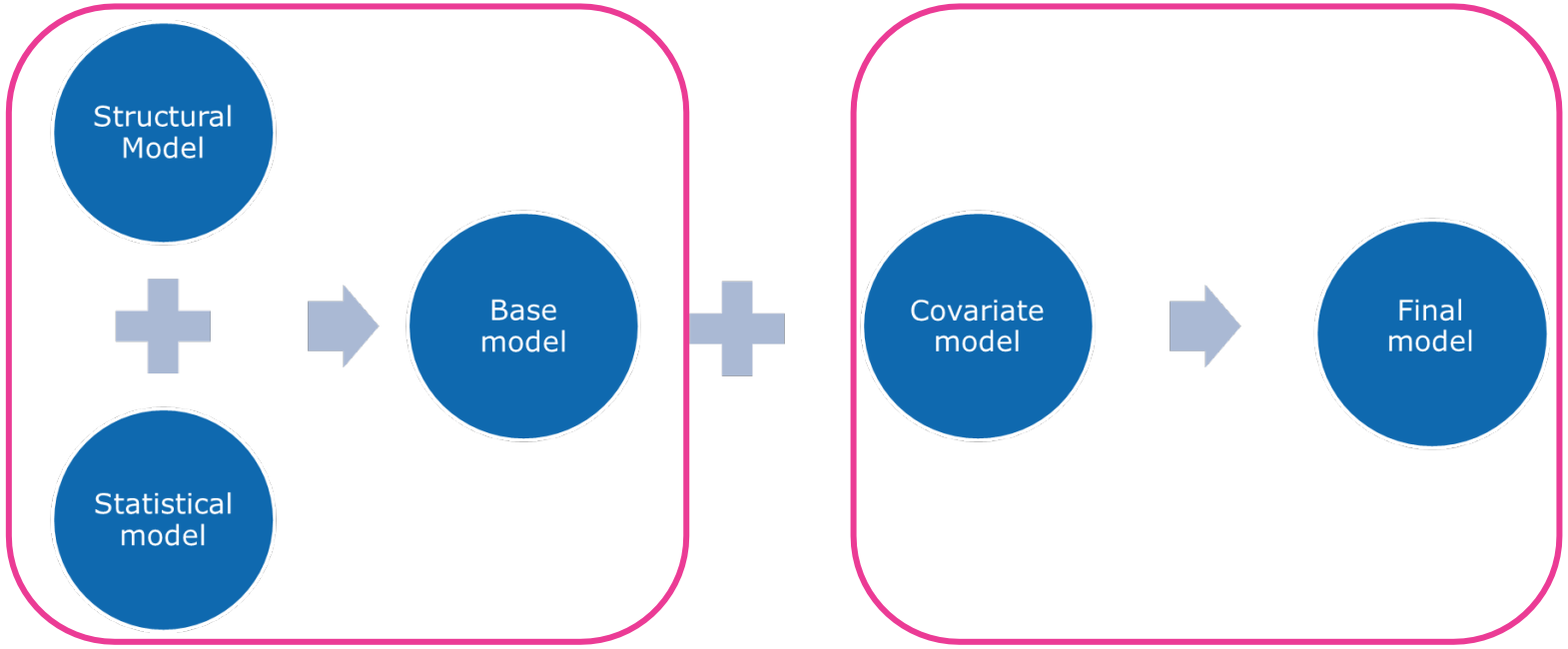

ML methods are significantly faster than traditional PMX

Computational costs

Average computational cost in hours

	SCM	COSSAC	SVM Lin	SVM RBF	RF	NN
Simple Scenario (≤5 covariates)	9.5 (4.8)	3.6 (1.7)	0.08 (0.06)	0.13 (0.09)	0.10 (0.02)	2.3 (0.29)
Complex Scenario (≥15 covariates)	87.6 (33.0)	13.0 (3.3)	0.55 (0.16)	0.68 (0.13)	0.16 (0.08)	7.75 (0.26)
Overall median	27.1 (40.3)	7.4 (5.2)	0.3 (0.2)	0.41 (0.2)	0.12 (0.06)	3.4 (2.4)

SCM, COSSAC and NN had parallelization of runs with multiple CPUs

LASSO (not shown) has runtimes comparable to SCM

- COSSAC runs 3.5 times faster than SCM
- ML runs from 8 (NN) to 225 (RF) times faster than SCM
- ML runs from 2 (NN) to 61 (RF) times faster than COSSAC

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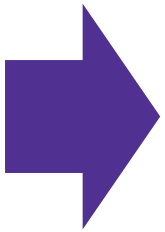
Similar results were obtained in a real data involving a complex PK model
Real use case

The developed framework was used on a clinical dataset of cetuximab PK.

- 30 covariates tested on clearance and central volume: patient-related factors (e.g., age, sex, creatinine clearance), therapy related-factors (e.g., co-medication), disease-related measurements (e.g., amphiregulin, interleukin-8).
- Base PK model: two-compartment model with Michaelis-Menten and linear elimination (Grisic et al. 2020)



Covariates selections were consistent across methods

ML-based selection was performed in less than 10 minutes

No comparison could be made with SCM as runtime exceeded 19 days

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Results were similar across methods with ML providing slightly higher accuracy

F1 results across methods

ML approaches				
	RF	**NN**	**SVM Linear**	**SVM RBF**
#scenario F1=1	18	16	15	16
Average F1 score	0.87 ± 0.06	0.89 ± 0.06	0.86 ± 0.05	0.86 ± 0.06

PMX approaches				
	SCM	**SCM_TR**	**COSSAC**	**COSSAC_TR**
#scenario F1=1	0	0	0	0
Average F1 score	0.84 ± 0.06	0.75 ± 0.07	0.79 ± 0.05	0.72 ± 0.06

Results showed

- ML, COSSAC and SCM very close in terms of accuracy (ML slightly better), but perfect selection (F1=1) is achieved by ML only
- COSSAC_TR, SCM_TR presented lower F1 as expected.
- The covariate effect size is the main driver of differences in accuracy across scenarios.
- Noise (#false covariates) has no impact on the results.
- Correlation between the covariates has no impact.
- Shrinkage has an impact.

In average ML outperforms PMX methods, and only ML algorithms made perfect selection across the 100 datasets.

RF: Random Forest; NN: Neural Network; SVM: Support Vector Machine

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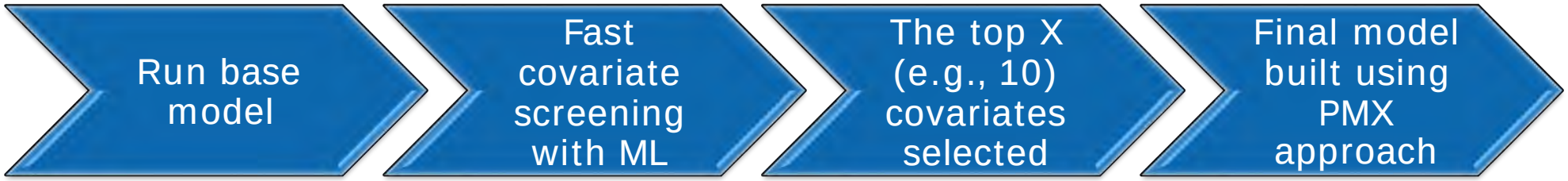
ML methods enable efficient and accurate model building
Results summary

- **ML** provides **a clear benefit for the fast screening of a larges set of covariates** with accuracy comparable/higher to **SCM** and **COSSAC**, and huge gain in runtimes (0.25-3 hours for ML vs. 15-73 hours for PMX)
  - As expected, scenarios with small effects size led to worst results for all the methods (1a, 1e, 5a).
  - Correlation between the covariates and number of false covariates have not a major impact on the selection.

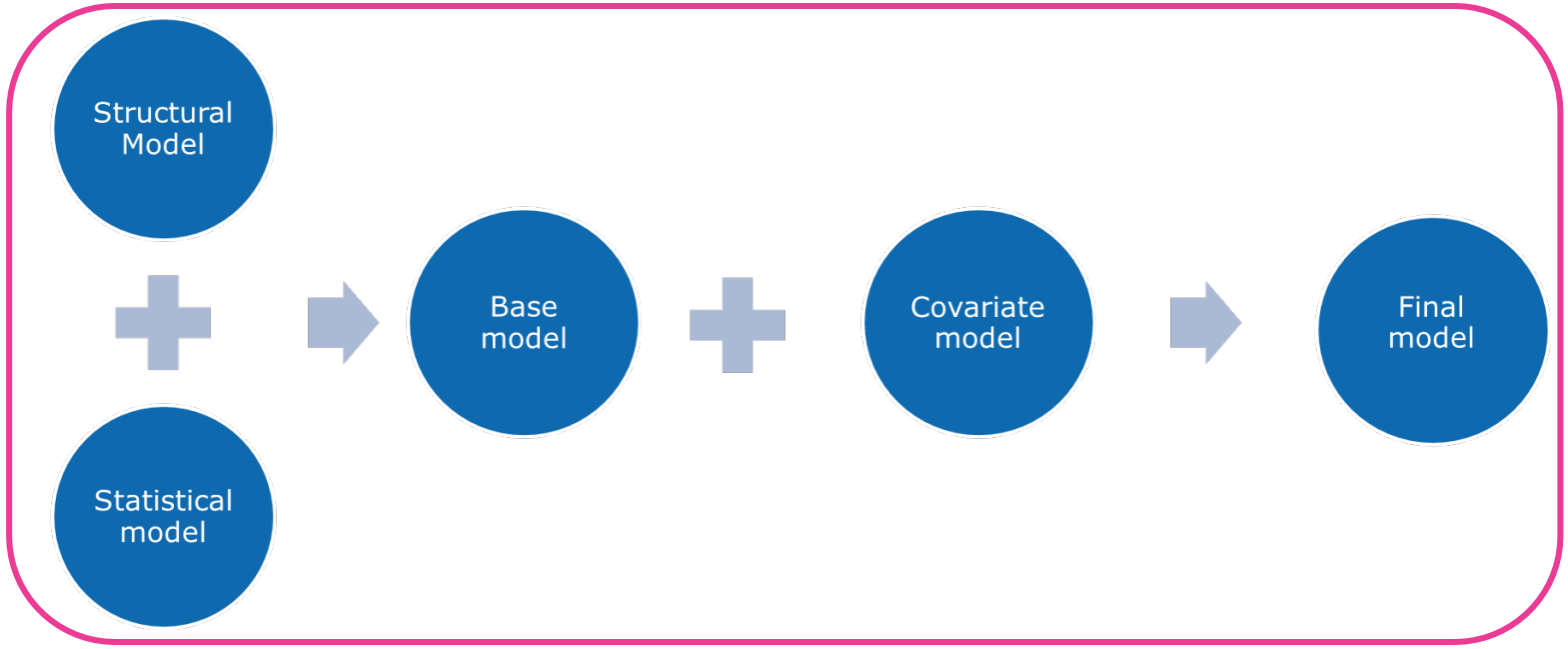
- The **developed ML framework** can be used to optimize population modeling in case of **large set of covariates** and then inform subsequent PMX model building steps towards a more clinical interpretation of the covariates.



Sibieude et. al. JPKPD 2021

Take home message

ML enables
automatic model selection and fast covariate screening,
great efficiency with large datasets or complex models



Acknowledgements

- Emeric Sibieude
- Pascal Girard, Akash Khandelwal
- Karthik Venkatakrishnan
- Lisa Benincosa
- Jonathan French, Matthew Wiens and Metrum team
- Avelumab Project Team

Take home message

ML enables
automatic model selection and fast covariate screening,
great efficiency with large datasets or complex models

ML-based model prediction of PK, PD, …