Using Machine Learning Surrogate Modeling for Faster QSP VP Cohort Generation

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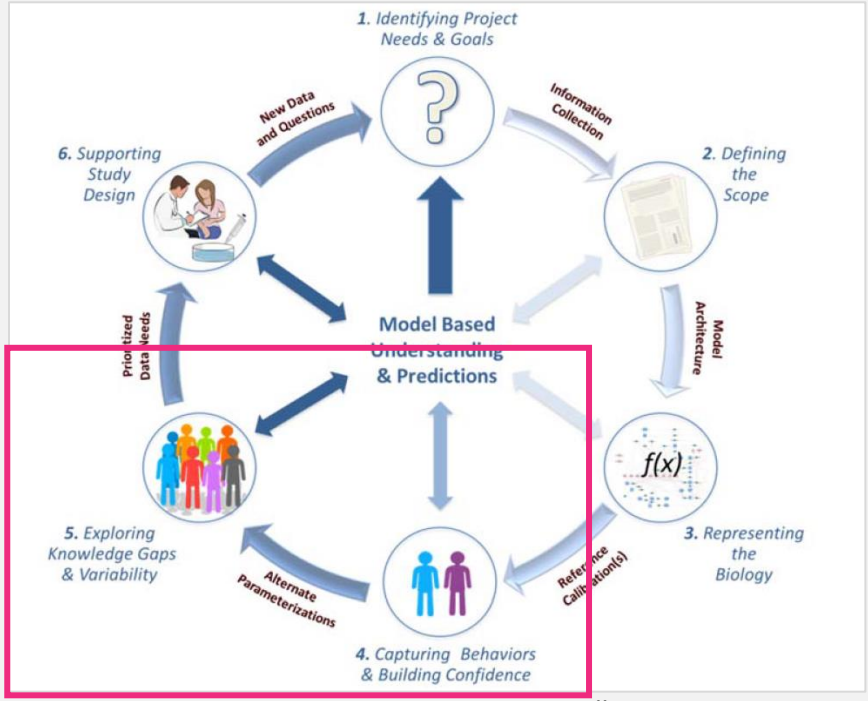
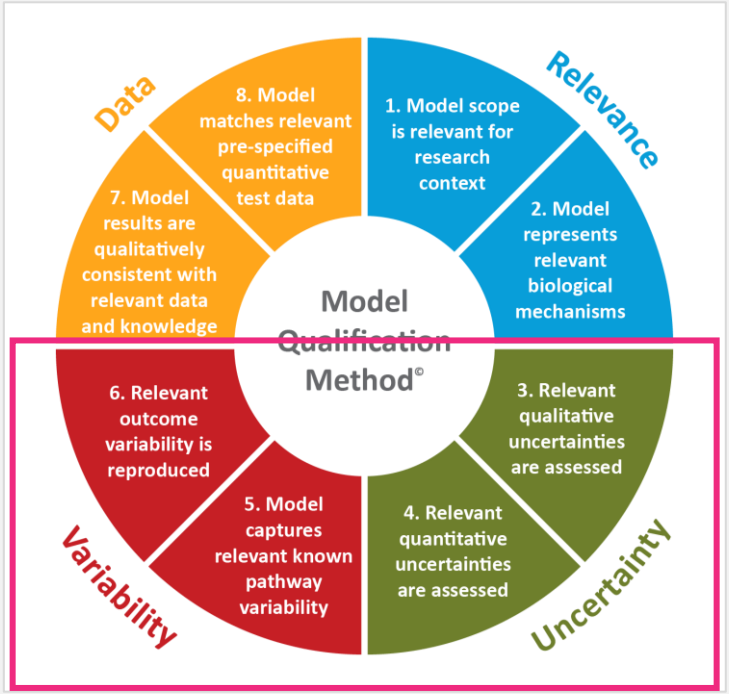
Virtual patients (VPs) are used in QSP modeling to explore the impact of variability and uncertainty.



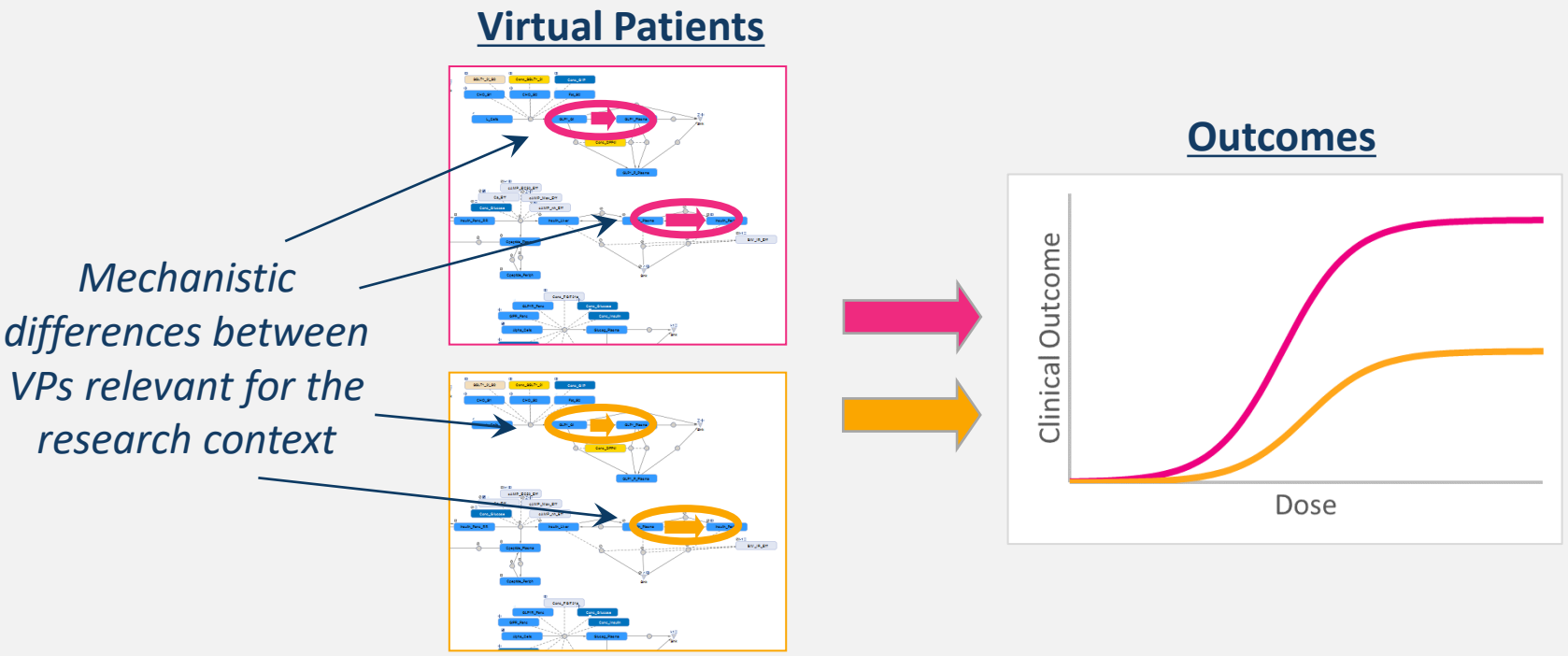
Gadkar 2016 PMID: 27299936



Friedrich 2016 PMID: 26933515

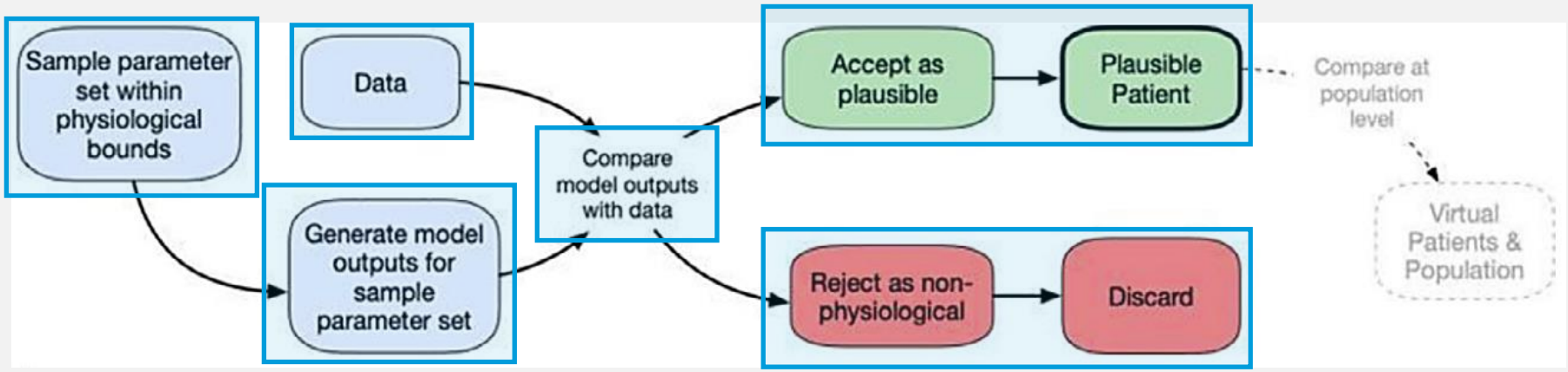
- A standard part of the QSP workflow is to use VPs to investigate:
  - Are conclusions and recommendations robust to mechanistic differences?
  - Would inferences change under different assumptions?
  - What mechanistic differences between patients could explain clinical variability?

VPs facilitate exploration of how mechanistic differences affect outcomes.

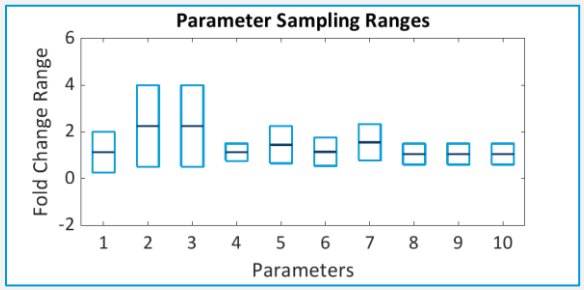


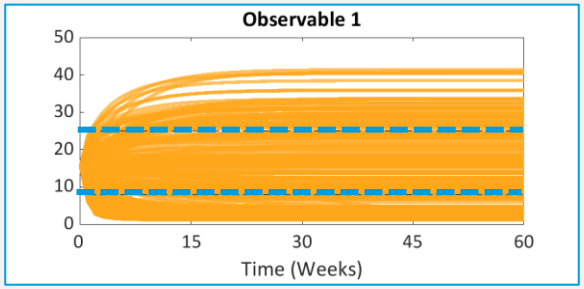
- Mechanistic differences are typically implemented as different parameter values
- We can typically set constraints:
  - Input: Physiological bounds on parameter values
  - Output: Clinical ranges observed on endpoints and biomarkers

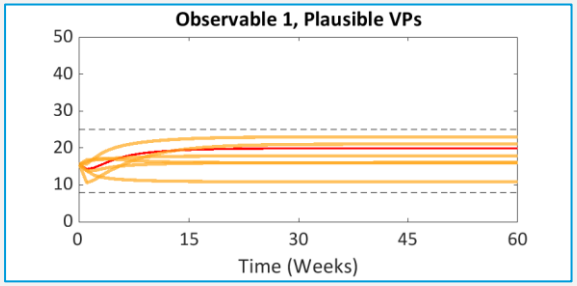
Systematic VP creation process checks if the randomly sampled parameters produce reasonable outcomes.

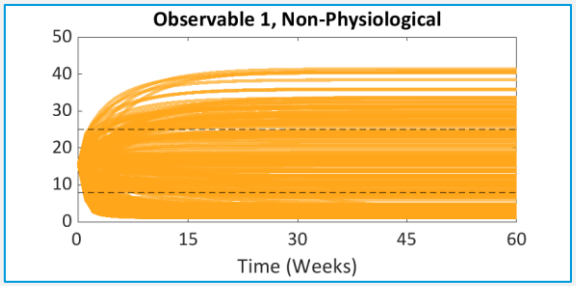


Rieger et al. 2021 PMID: 33938162



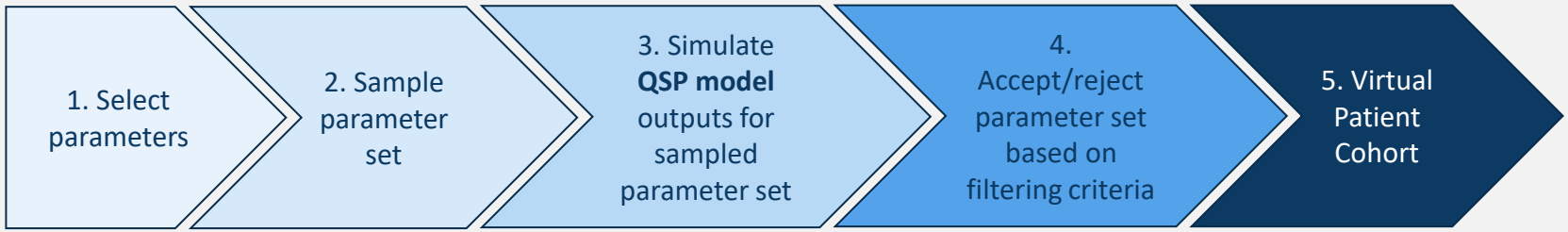






In one traditional method, possible VPs are simulated with the full QSP model and filtered.

QSP Model-Based VP Creation Workflow*



Challenges:

- The **vast majority** of sampled parameter combinations do **NOT** lead to plausible VPs
- Running the **full QSP model** for each parameter combination is computationally expensive

*Is there a less computationally expensive way to know which **parameter sets** produce **acceptable outcomes**?*

*NOTE: Optimization approaches can make this process more efficient (e.g., see Allen et al. 2016 PMID 27069777). The essential workflow presented here is convenient for benchmarking.

Surrogate modeling is used to improve efficiency in other engineering disciplines.

"Surrogate models are simplified approximations of more complex, higher-order models. They are used to **map input data to outputs** when the actual relationship between the two is unknown or computationally expensive to evaluate."

Williams 2021, https://doi.org/10.1016/B978-0-323-88506-5.50071-1

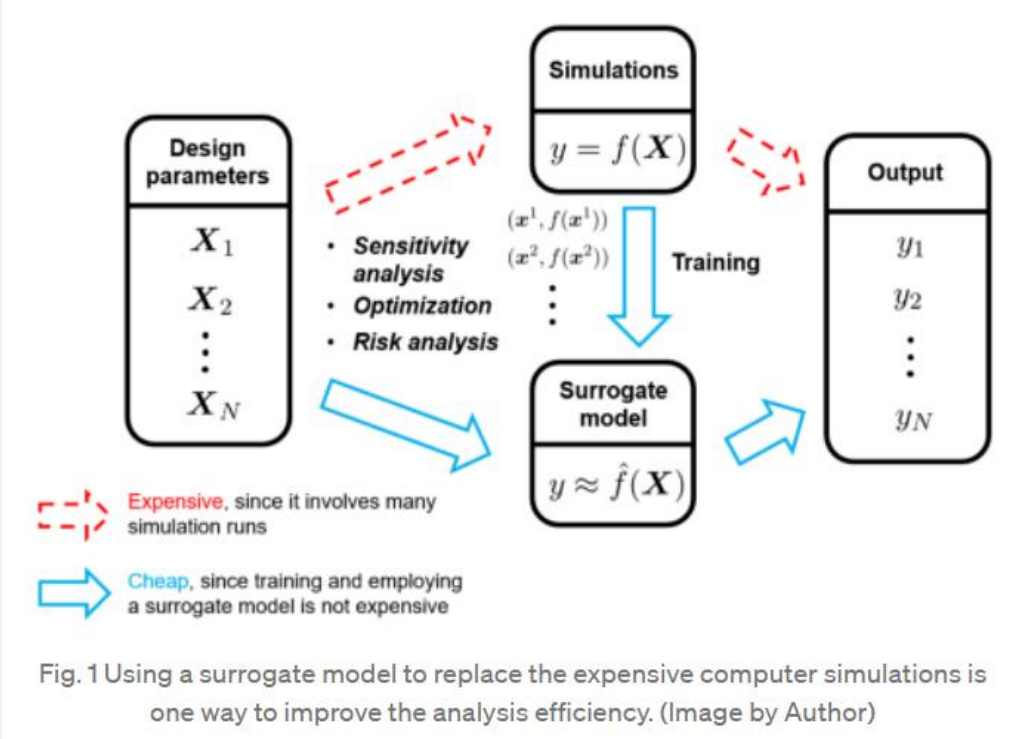
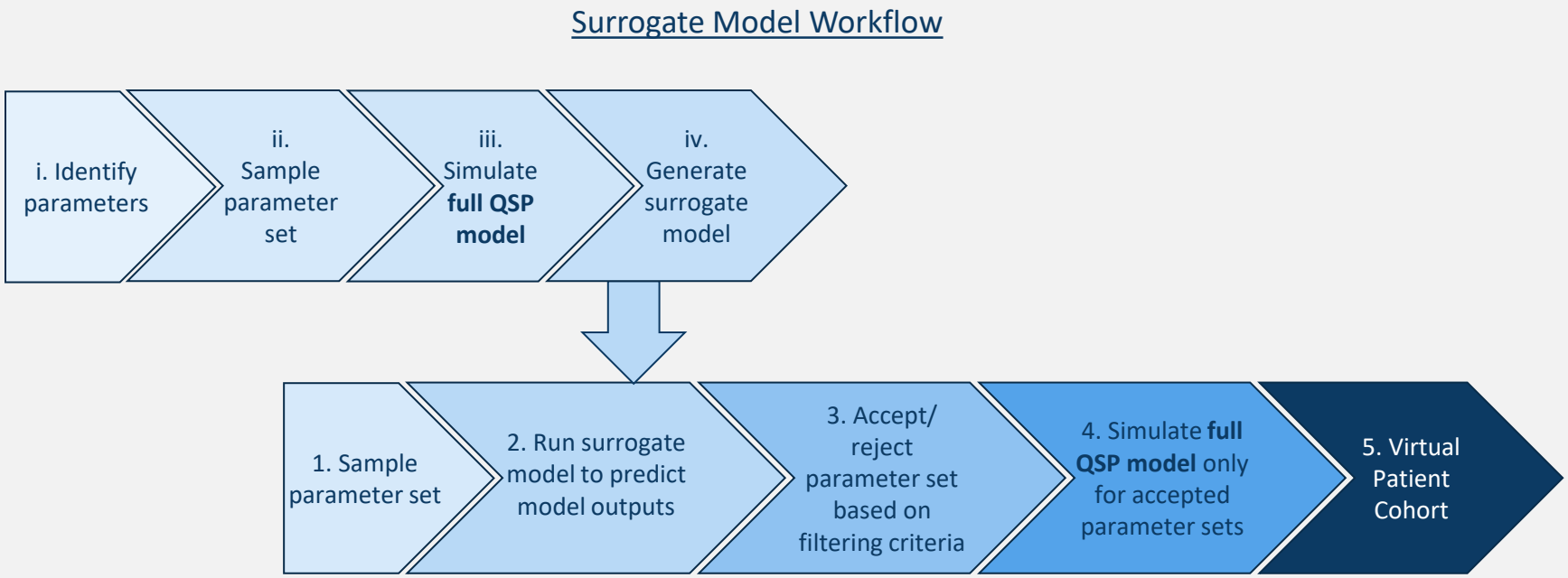


Fig. 1 Using a surrogate model to replace the expensive computer simulations is one way to improve the analysis efficiency. (Image by Author)

Guo 2020, https://towardsdatascience.com/an-introduction-to-surrogate-modeling-part-i-fundamentals-84697ce4d241

Surrogate models may offer a more efficient alternative workflow for VP cohort generation.

ROSA



A Psoriasis PhysioPD™ case study will illustrate how to use surrogate models for VP cohort generation.

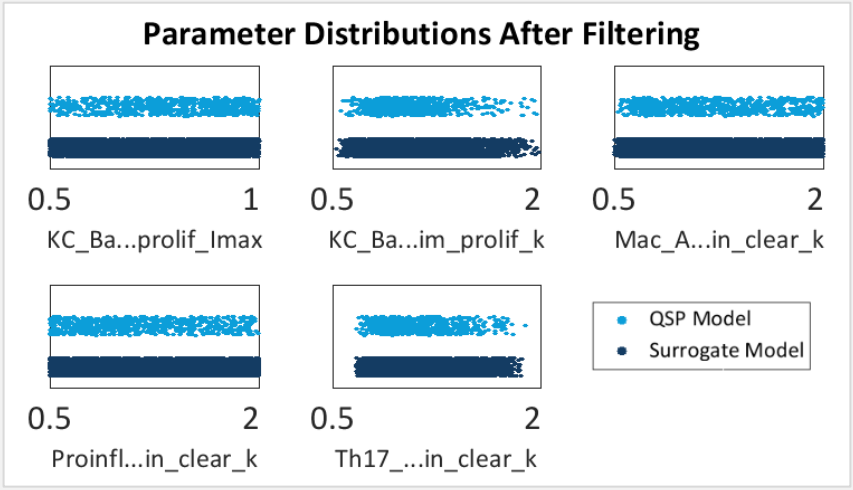
- A psoriasis QSP model with 28 dynamic species was used as the example platform for this case study
- Parameter ranges were set in terms of fold change around a reference virtual patient
- Physiological ranges for observables were obtained from literature data

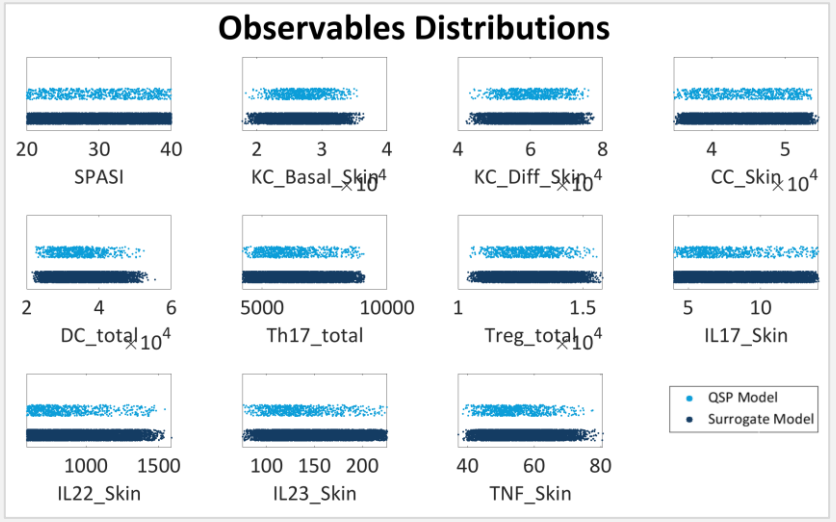
Parameter	Fold Change
KC_Basal_Skin_density_prolif_kmax	0.5 – 1
KC_Basal_Skin_stim_prolif_k	0.5 – 2
Mac_Act_Skin_clear_k	0.5 – 2
Proinflam_Cyt_Skin_clear_k	0.5 – 2
Th17_Act_Skin_clear_k	0.5 – 2

Observable	Constraint Bounds	Units
SPASI	20 – 40	--
Basal KC	≤44,000	cells/mm^2
Differentiated KC	≤99,000	cells/mm^2
CC	≤77,000	cells/mm^2
Dendritic Cells	≤174,800	cells/mm^2
Th17	≤10,640	cells/mm^2
Treg	≤21,280	cells/mm^2
IL17	≤14	pg/mL
IL23	≤226	pg/mL
TNF	≤90	pg/mL

The use of surrogate models to generate VPs does not diminish sampling or outcome variability.

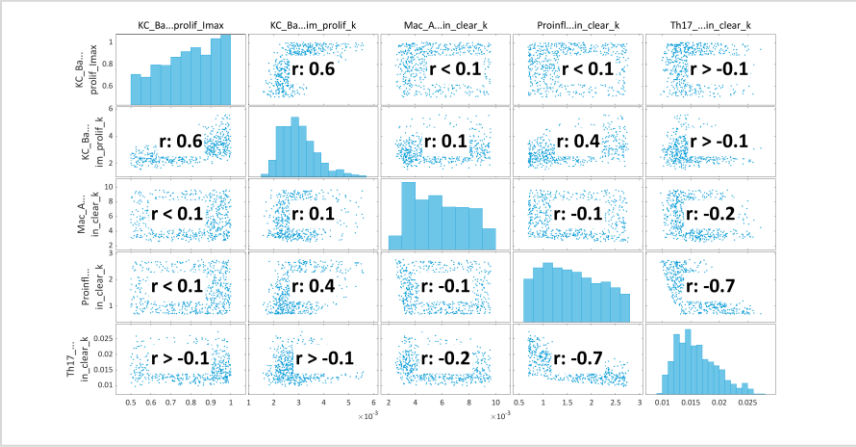
- The distributions of sampled parameters generated by both the traditional and surrogate modeling approaches were found to cover the proposed sampling ranges
  - Since the original QSP method generated fewer VPs, the coverage is not as dense
- Similarly, the range of observable outputs were found to be consistent between both methods



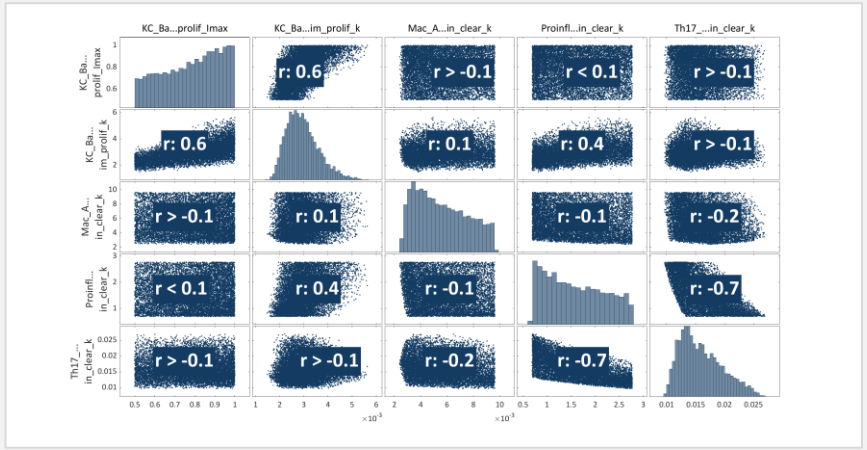


Relationships between parameters were found to be consistent with the full QSP model.

No surrogate models



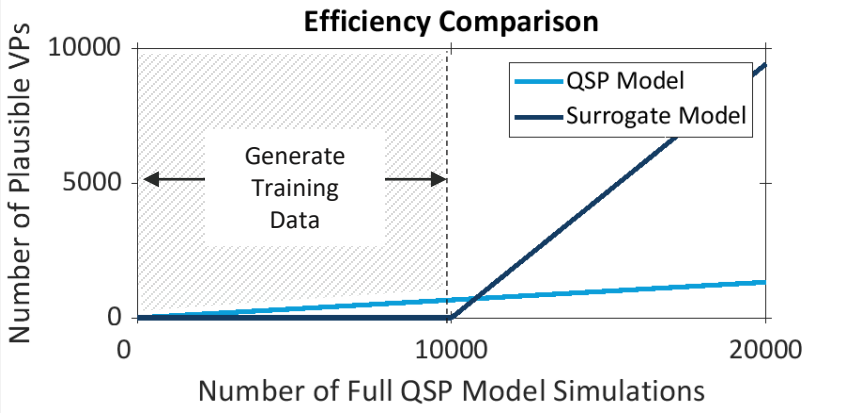
Surrogate models



- Correlation coefficients were calculated to explore the pairwise relationships between parameters
- Parameter correlations for the parameters sampled by the surrogate modeling technique were found to match those generated by the traditional approach

Surrogate models showed increased efficiency compared to the traditional QSP-model method.

- Surrogate model workflow requires an initial investment (10,000 simulations) to create the surrogate models
- After generation of the surrogate models, 10,000 simulations were found to generate ~9,400 plausible VPs using the surrogate modeling approach

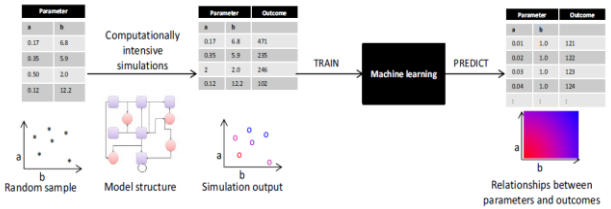


Surrogate models generate more plausible VPs with fewer QSP model simulations and no loss of diversity.

- Virtual patients are an essential component of QSP modeling
- Generation of VP cohorts with sufficient variability can be time-consuming
- Surrogate models increase computational efficiency by pre-screening parameter sets likely to yield valid VPs prior to full simulation with the QSP model
- This method generates virtual patient cohorts with similar sampling and outcome diversity compared to traditional methods

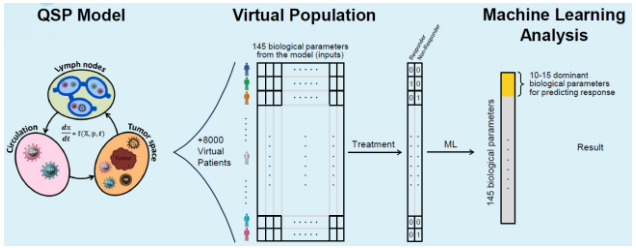
Trends in applications of AI in pharmacology

Surrogate modelling



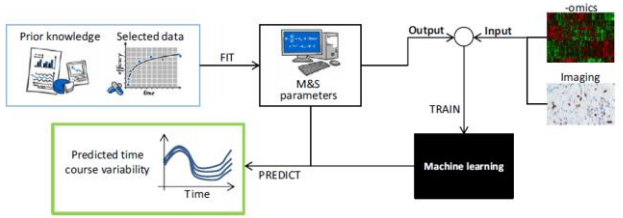
Hutchinson L, Steiert B, Soubret A, Wagg J, Phipps A, Peck R, Charoin JE, Ribba B. Models and Machines: How Deep Learning Will Take Clinical Pharmacology to the Next Level. *CPT Pharmacometrics Syst Pharmacol*. 2019 Mar;8(3):131-134.

Identification of important predictors



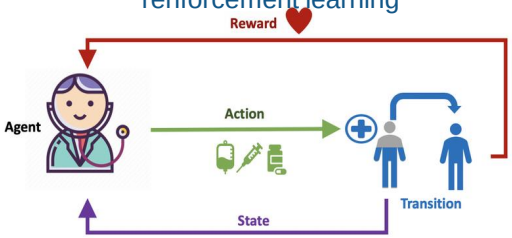
Lemaire V., Identifying Biological Signals Differentiating Responders and Non-Responders to MPDL3280A (Anti-PDL1) In NSCLC Using QSP Modeling of Immune Checkpoints. Talk at ASCPT in March 2019.

Integration of mechanistic modelling with -omics data



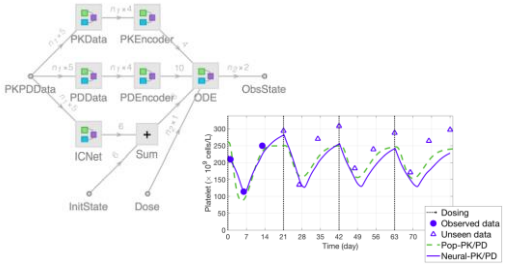
Hutchinson L, Steiert B, Soubret A, Wagg J, Phipps A, Peck R, Charoin JE, Ribba B. Models and Machines: How Deep Learning Will Take Clinical Pharmacology to the Next Level. *CPT Pharmacometrics Syst Pharmacol*. 2019 Mar;8(3):131-134.

Selection of clinical dosing regimen with renforcement learning



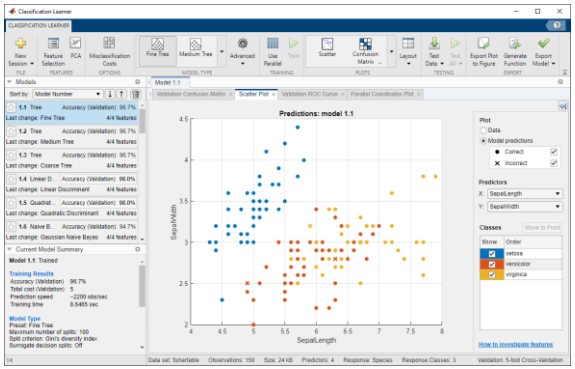
Liu S, See KC, Ngiam KY, Celi LA, Sun X, Feng M. Reinforcement Learning for Clinical Decision Support in Critical Care: Comprehensive Review. J Med Internet Res 2020;22(7):e18477. doi: 10.2196/18477

Neural ODE

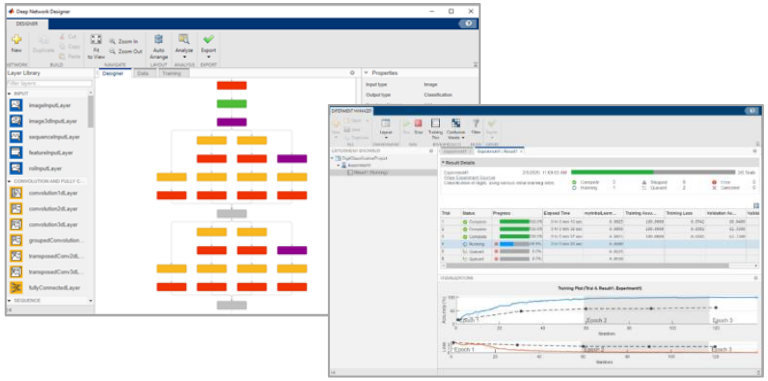


Lu, J., Bender, B., Jin, J.Y. et al. Deep learning prediction of patient response time course from early data via neural-pharmacokinetic/pharmacodynamic modelling. Nat Mach Intell 3, 696–704 (2021).

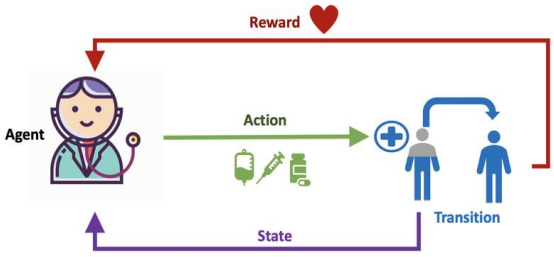
Getting started with AI



Classification Learner



Deep Learning



Reinforcement Learning

Source: Liu et al. Reinforcement Learning for Clinical Decision Support in Critical Care: Comprehensive Review. J Med Internet Res 2020;22(7):e18477. doi: 10.2196/18477

MATLAB Academy (mathworks.com)

Comments, Questions?

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