Systems & Control Transactions

Research Article - Peer Reviewed Conference Proceeding
ESCAPE 35 - European Symposium on Computer Aided Process Engineering
Ghent, Belgium. 6-9 July 2025
Jan F.M. Van Impe, Grégoire Léonard, Satyajeet S. Bhonsale,
Monika E. Polańska, Filip Logist (Eds.)

PSE PRESS

Machine learning-enhanced Sensitivity Analysis for Complex Pharmaceutical Systems

Daniele Pessina[a,b], Roberto Andrea Abbiati[c], Davide Manca[d] and Maria M. Papathanasiou[a,b,*]

[a] Sargent Centre for Process Systems Engineering, Imperial College London, SW7 2AZ, United Kingdom
[b] Department of Chemical Engineering, Imperial College London, SW7 2AZ, United Kingdom
[c] Roche Pharma Research and Early Development, Predictive Modeling, F. Hoffmann-La Roche Ltd. Grenzacherstrasse 124, 4070 Basel, Switzerland
[d] PSE-Lab, Dipartimento di Chimica, Materiali e Ingegneria Chimica "Giulio Natta" Politecnico di Milano, Piazza Leonardo da Vinci 32, 20133 Milano, Italy
* Corresponding Author: maria.papathanasiou11@imperial.ac.uk

ABSTRACT

Pharmacokinetic and pharmacodynamic (PK/PD) models are used to predict drug transport in the body and to assess treatment efficacy and optimal dosage. The kinetic parameters embedded in the models, which define transport across body compartments or drug efficacy, can be linked to patient-specific characteristics; understanding the parameter space-model output relationship is critical towards linking patient population heterogeneity to the therapeutic outcome variability. Global Sensitivity Analysis (GSA) is a well-established tool used to examine parameter-to-parameter interactions, shedding light on underlying interactions towards enhanced system understanding. Despite its potential and usefulness, GSA performance is dependent to the model complexity; large-scale and nonlinear PK/PD models, which often have large sets of parameters, can render GSA challenging to perform, requiring excessive computational effort. Proposed approaches to reduce GSA complexity, such as segmentation in parameter subsets or the introduction of surrogate metamodels, become less effective as the number of kinetic parameters grows. In this work, we investigate the potential of Machine Learning (ML) to reduce the complexity of PK/PD models by exploring how the level of hybridisation can impact the GSA performance and, critically, whether the use of surrogates affects the resulting model sensitivity to parametric uncertainty. We show that ML-based surrogates can reliably identify parameter interactions and sensitivities while requiring only a limited number of simulations of the reference mechanistic model. Further, surrogates models effectively reduce the computational expenditure of GSA of multi-dimensional nonlinear PK/PD models. The accelerated execution of GSA enables performing patient cohort-specific analysis, with potential applications for optimal study design and for precision medicine.

Keywords: Pharmacokinetic modelling, Global Sensitivity Analysis, Surrogate modelling

INTRODUCTION

The efficacy of a pharmacological treatment depends on achieving adequate drug concentration at the designated target site within the body. Once administered, drug molecules undergo absorption, distribution, metabolism, and excretion (ADME) processes that collectively determine the drug's fate within the organism. Pharmacokinetics (PK) is the scientific discipline that studies these processes. Experimental PK traditionally involves administering a drug to a biological system, collecting samples (typically blood) at multiple time points, and measuring the drug concentration. This produces a concentration-time profile. If a relationship between concentration and pharmacological effect can be established, PK can be adopted as a surrogate indicator of the expected efficacy or toxicity. This information is essential for guiding dosing regimens, ensuring patient safety, and informing early-stage clinical drug development.

The field of PK has been substantially advanced by the introduction of mathematical modelling and

simulation approaches, collectively known as pharmacometrics. Classic pharmacometric analyses rely on ordinary differential equations to simulate drug concentration profiles in blood [1,2]. Over time, several PK modelling approaches have emerged: Population PK adopts nonlinear mixed-effects modelling to characterize the variability in PK parameters across patients; Physiologically-Based Pharmacokinetic (PBPK) models focus on an anatomically-based and physiology-driven representation of ADME processes to support inter-species extrapolation; PK/PD (pharmacodynamics) models link drug concentrations to biological effects to predict therapeutic and adverse outcomes.

Quantitative Systems Pharmacology (QSP) is a related modelling discipline that builds upon the pharmacometric approach by incorporating systems biology concepts [3]. QSP models can be used to link molecular, cellular, tissue, and organ-level data into multi-scale, mechanistic frameworks. QSP has a broad application space, models typically capture the dynamics of a biological system undergoing disease progression with or without the modulatory intervention of a therapy and considering the inter-individual differences. This integrative approach enables the bridging of empirical data and mechanistic understanding, thereby informing rational drug design, hypothesis testing, and personalized therapeutic strategies.

For mechanistic approaches like PBPK or QSP, model parameterization is critical. During model design, the parameterization strategy has implications on model identifiability and model fit. During model application, alternative parameterization of the same underlying model structure is used to characterize the diversity across patient population or disease status and therefore project the consequential disease progression/treatment variability. Here, sensitivity analysis is adopted to study the role of the various model parameters on the model endpoint. Collectively, identifiability and sensitivity analyses are fundamental tools employed to determine whether unique parameter values can be inferred from available data, to ascertain whether model structures require simplification, and to quantify how parameter values influence model outputs of interest.

Classical sensitivity analysis involves perturbing individual parameters from a reference set and evaluating changes in model outputs. In contrast, global sensitivity analysis (GSA) considers the entire parameter space, recognizing that biological parameters often exist as distributions rather than fixed values. GSA identifies which parameters most strongly influence model outputs across a wide range of plausible parameter values, thereby providing a more comprehensive understanding of parameter importance under uncertainty. Some concrete examples of applications of GSA in QSP include: (i) identification of disease pathways which significantly influence outcome and should therefore be primary focus of research, (ii) support of patient stratification, by selecting those whose characteristics are more strongly associated to an endpoint of interest, (iii) model complexity reduction, by identifying the most relevant model components related to the endpoint of interest and therefore reducing the structure to include only them, or (iv) provide rationale for the creation of reduced-order surrogate models.

Each individual patient has unique characteristics, such as age, and sex, or the presence of adverse conditions. When performing GSA, these individual characteristics are aggregated into a broader parameter space representing an entire cohort, meaning the sensitivity analysis results reflect the response of the whole ensemble rather than specific individuals. This generalization, while necessary for computational tractability, can lead to suboptimal decisions in experimental design for preclinical trials, particularly when certain subpopulations (such as pediatric patients within a mixed-age population, or critically-ill patients in a mixed-health population) have distinct characteristics that significantly influence the PK/PD response and the resultant sensitivity [4], [5]. The developed therapeutic strategy might under- or over-dosage specific cohorts within the population and result in sub-optimal therapeutic outcomes. The ability to perform cohort-specific GSA would enable more targeted sensitivity analyses, allowing for better understanding of parameter importance within specific subpopulations and potentially leading to more effective experimental designs for these groups and improved parametric identifiability.

GSA of a mechanistic PK model for a single set of parametric bounds requires a high number of simulations and computational time; this approach quickly becomes intractable if cohort-specific GSA with multiple sets of parameters is to be explored. One approach to reduce GSA complexity involves parameter grouping, which does not however universally consider the whole parametric domain [6]. Metamodelling-based GSA methods struggle with high-dimensional problems as they become computationally intractable to train and predict [7].

Machine-learning surrogates have been widely used by the Process Systems community to reduce the computational expenditure of complex mechanistic models [8]. After training on a set of input and output samples generated by the mechanistic model, the surrogate can predict model outputs quicker, albeit at a reduced fidelity if the surrogate structure and training points are not chosen carefully; surrogate accuracy is affected by the number of training samples used, surrogate type and surrogate structure, which is generally problem-specific and therefore must be tailored to the mechanistic model available.

This work explores how machine-learning

Table 1: Kinetic parameter descriptions with lower and upper bounds for training and GSA

Name	Description	Training LB	Training UB	GSA LB	GSA UB
$j_{\text{PT-P}}$	Mass transfer coefficient from poorly-perfused tissues to plasma compartments	0.191	0.767	0.240	0.720
$j_{\text{P-PT}}$	Mass transfer coefficient from plasma to poorly-perfused tissues compartments	0.191	0.767	0.240	0.720
$j_{\text{P-HO}}$	Mass transfer coefficient from plasma to highly-perfused organs compartments	0.265	1.06	0.331	0.99
$j_{\text{HO-P}}$	Mass transfer coefficient from highly-perfused organs to plasma compartments	0.0179	0.0715	0.0224	0.0671
k_{E}^{P}	Plasma elimination kinetic rate constant	0.69	2.77	0.866	2.60
k_{E}^{T}	Tissues elimination kinetic rate constant	0.0253	0.101	0.0317	0.0950
$\text{Eff}^{\text{Liver}}$	Hepatic efficiency of elimination	0.0576	0.231	0.0720	0.216
$\text{Eff}^{\text{Plasma}}$	Kidney efficiency of elimination	0.158	0.631	0.197	0.590

surrogates can be used to reduce the computational expenditure involved with generating predictions for GSA and enable cohort-specific GSA of PK models. Importantly, the goal of GSA is to probe the PK model and corresponding parameter space for improved understanding and assessment of parameter identifiability, and not to identify influential parameters to formulate a reduced-order model and train a smaller surrogate. GSA is first carried out with a mechanistic PK model to confirm the high computational expenditure involved with the method, and use the identified sensitivity indices as reference for the surrogate-enabled GSA. Feed-forward Neural Networks and Random Forests surrogates are then trained on a much-smaller number of samples and used to generate GSA samples in a fraction of the time required with a fully-mechanistic methodology. The effort to reach GSA convergence and sensitivity index misidentification are assessed.

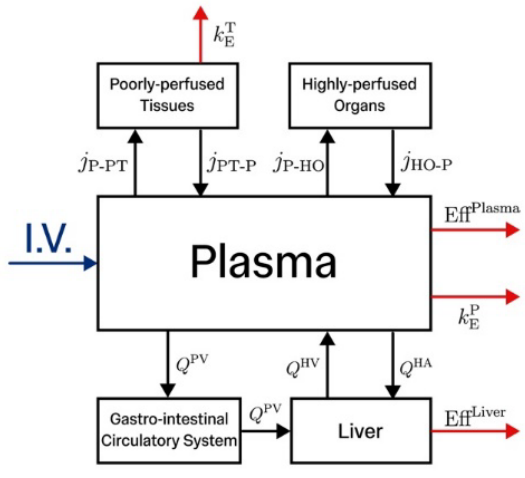

Figure 1: Compartmental structure of the mechanistic PK model from Abbiati (2016) [1]

METHODOLOGY

Mechanistic PK models

In this work we employ a validated minimal-PBPK model from Abbiati *et al.* (2016) [1], that describes the transport of a small-molecule drug, Remifentanil, through the human body (Figure 1). The model is experimentally validated against measurements from 6 patients and 4 drug dosages, and is therefore suitable to be used as a platform for cohort-specific PK modelling, as well as cohort-specific GSA.

The model assumes the drug is administered intravenously (IV) to the plasma compartment and is distributed via the circulatory system to the liver and the other body organs, here lumped into the Poorly-perfused Tissues (PT) (fat, bones, heart, skin, muscles) and Highly-perfused organs (HP) (brain, kidneys, spleen) compartments. The model considers mass transfer between the plasma and the two compartments (PT and HP), as well as elimination of the drug from the PT, plasma and liver compartments. The model predicts the drug concentration profiles for each of the 5 compartments, using 8 input parameters (Table 1). To reduce the computational expenditure, the scalar Area Under the Curve (AUC) output is considered. The AUC, often used with PK models, is the concentration profile integral over time for each compartment and measures drug exposure in the body [9]. The reader is referred to Abbiati *et al.* (2016) [1] for the complete set of model equations and further model formulation details.

The mechanistic model used in this work comprises 8 ordinary differential equations which were solved in Python with an implicit time-stepping algorithm ($t_{end} = 120$ min, abstol $= 10^{-4}$, relative tol. $= 10^{-2}$). The AUC is calculated with trapezoidal integration of the calculated concentration profiles.

Surrogate modelling

Here, surrogate models are developed and assessed for their suitability as computationally-efficient substitutes of the mechanistic model. Table 1 summarises the upper and lower bounds used for the training of the models, as well as the GSA later on. To ensure that the surrogate models are not performing extrapolation during GSA, the bounds of the SA are chosen to be tighter than the ones used for the training of the surrogates. Latin Hypercube sampling (LHS) is used to generate 4096 training data points. Input samples are standardized in the $[-1, 1]$ interval before training the surrogate models. The surrogates are trained to predict each output's AUC for a given combination of kinetic parameters.

Table 2: Collected hyper-parameters for the neural net and random-forests surrogates

Surr.	Hyper-parameter			
RF	*# of estimators*		*Max depth*	
	100		25	
NN	*# of hidden layers*	*# of neurons*	*Learning rate*	*Training epochs*
	5	32	0.015	450

Random Forests (RF) and feed-forward neural nets (NN) single-output surrogates from the `scikit-learn` library are tested in this work. RF hyper-parameters (# of estimators and maximum depth of the ensemble) are optimised by grid-searching possible surrogate structures with 5-fold cross-validation to minimise the test root-mean-squared error (RMSE). NN hyper-parameters (# of hidden layers, # of neurons in each layer, learning rate, training epochs) are similarly optimised using the `Optuna` library and a 'Tree-structured Parzen' algorithm to efficiently search the possible combinations. Although the optimal NN structures differ between each output, they are fixed to a single, common combination before the surrogates are used for GSA. The final hyper-parameters are collected in Table 2.

Global sensitivity analysis

The GSA method is model-agnostic and proceeds identically regardless of the model type used. Variance-based GSA (Sobol method) is performed using the SALIB library to calculate first-, second- and total-order sensitivity indices [10]. To perform GSA for a given parameter domain, an input matrix with $N(2D + 2)$ parameter combinations is generated by SALIB which follows a quasi-random Sobol sequence (N is a power of 2 and D is the number of input dimensions). Each combination is then simulated to collect predicted AUC values for each output, after which sensitivity indices can be calculated. GSA convergence for each output is assessed by summing all parameter's first- and second- order indices; convergence is indicated by sums which approach 1 and the identified sensitivities remain stable across different sample sizes, as suggested by Sarrazin *et al.* (2016) [11]. First-order Sobol' sensitivity indices quantify the independent effect that a varying parameter θ_i has on the model output of interest, neglecting cross-parameter interactions. In its' computation, the effect of other parameters is averaged out, such that they can be excluded. Total-order Sobol' sensitivity indices instead group both the independent effect and the cross-parameter interactions of θ_i, calculated by subtracting the effect of all other parameters. The reader is referred to Saltelli (2008) [10] for further details.

RESULTS AND DISCUSSION

The calculated first-, second- and total-order sensitivity indices for each of the 5 outputs of the mechanistic model are reported in Figure 2 and Table 3. The chosen sensitivity threshold ($S_{\theta,\,\mathrm{Tot.}}$ = 0.05) to segregate parameters into critical and non-critical sets indicates non-critical parameters cause less than 5% variance of the output variable of interest. The same critical set of parameters ($j_{\mathrm{PT\text{-}P}}$, $j_{\mathrm{P\text{-}PT}}$, $k_{\mathrm{E}}^{\mathrm{P}}$) is identified for the first 4 outputs (C_{Plasma}, C_{PT}, C_{GICS}, C_{Liver}) of the model, while a larger set ($j_{\mathrm{PT\text{-}P}}$, $j_{\mathrm{P\text{-}PT}}$,$j_{\mathrm{P\text{-}HO}}$,$j_{\mathrm{HO\text{-}P}}$, $k_{\mathrm{E}}^{\mathrm{P}}$) is identified for C_{HO}. Non-negligible second-order interactions between the critical parameters are also identified, indicating the presence of correlations between parameters which can impede effective parameter estimation and identification of PK models. In the context of PK/PD models parametrised against measurements from human patients, the plasma is the only compartment considered to be easily-measurable as sampling other compartments involves invasive procedures. The sensitivity indices reveal that only 3 out of 8 parameters are identifiable within the parameter domain used for GSA. Three of the non-critical parameters, $j_{\mathrm{P\text{-}HO}}$, $j_{\mathrm{HO\text{-}P}}$ and $\mathrm{Eff}^{\mathrm{Plasma}}$, directly affect the plasma compartment to a lesser extent than the critical parameters and inestimable. The remaining two parameters, $k_{\mathrm{E}}^{\mathrm{T}}$ and $\mathrm{Eff}^{\mathrm{Liver}}$, already classed as non-critical with respect to the C_{PT} and C_{Liver} outputs respectively, do not cause significant-enough interactions in the plasma to be estimable by drug concentration measurements in the plasma alone.

Feed-forward neural networks (NNs) and Random Forests (RF) full-order surrogates are trained on 4096 Latin Hypercube samples from the mechanistic model. The surrogates are then used to generate the necessary Sobol-indexed samples for GSA. While other surrogate models (such as Gaussian Process regressors and Radial Basis Function interpolators) were tested, they could not reliably approximate the PK model and were therefore omitted from the presented work.

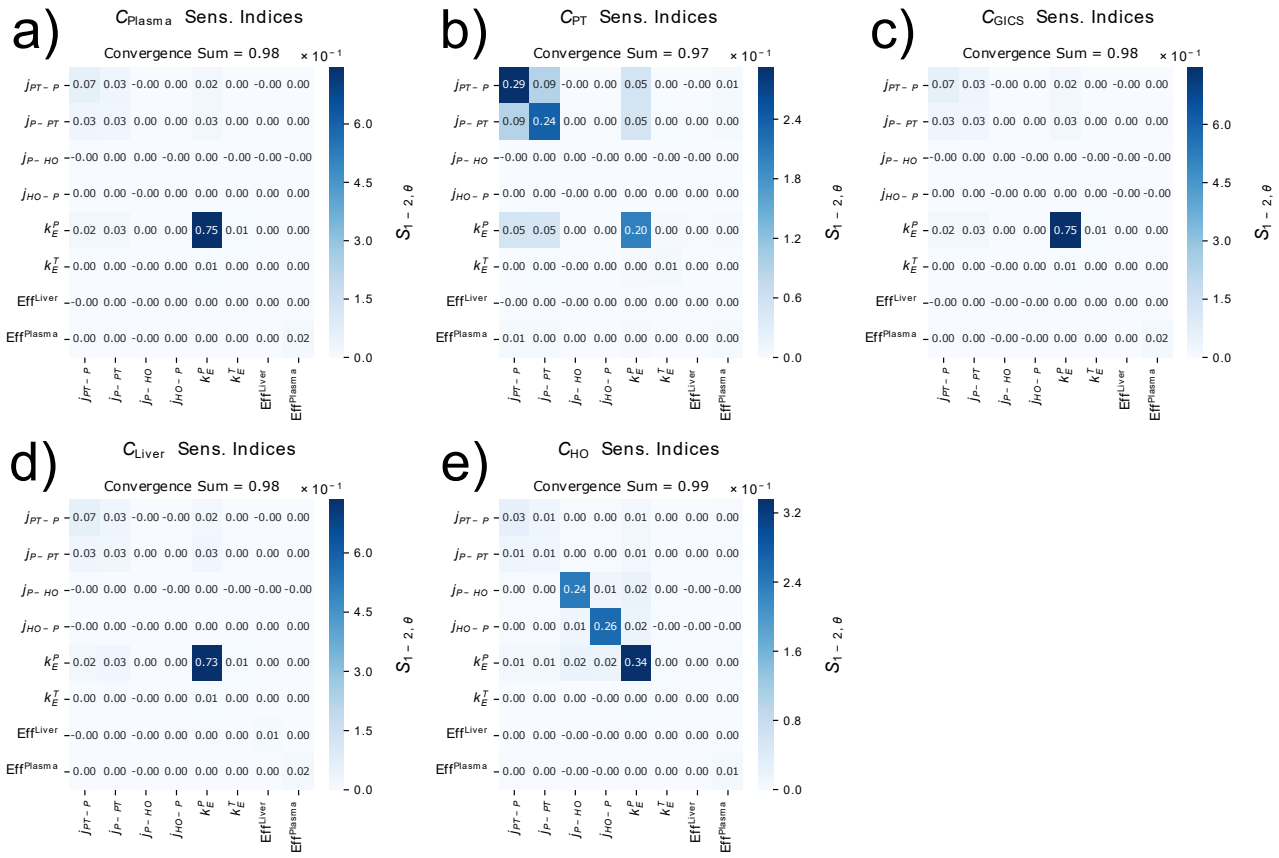

Figure 2: 1st, 2nd Order Sensitivity Indices of the mechanistic model for a) C_{Plasma}, b) C_{PT}, c) C_{GICS}, d) C_{Liver}, e) C_{HO}, calculated with 1179648 simulations

Table 3: Total-order sensitivity indices of the mechanistic model calculated with 1179648 simulations

Parameter	Mechanistic Model Total-Order Sensitivity Indices $S^T_{\theta,\text{Mech.}}$				
	C_{Plasma}	C_{PT}	C_{GICS}	C_{Liver}	C_{HO}
$j_{PT\text{-}P}$	0.16	0.5	0.16	0.16	0.07
$j_{P\text{-}PT}$	0.13	0.44	0.13	0.13	0.05
$j_{P\text{-}HO}$	0.02	0.01	0.02	0.02	0.29
$j_{HO\text{-}P}$	0	0	0	0	0.30
k_E^P	0.85	0.36	0.85	0.83	0.42
k_E^T	0.01	0.02	0.01	0.01	0
Eff^{Liver}	0	0	0	0.02	0
Eff^{Plasma}	0.04	0.02	0.04	0.03	0.02

Importantly, LHS is chosen over a Sobol' sequence for the generation of training data as it led to more accurate surrogates, as Sobol sequences do not capture points at the parametric bounds as effectively. The generation of GSA samples with surrogates introduces minimal computational expenditure compared to the training data generation and GSA decomposition and analysis, making the LHS more effective than a Sobol' sequence for surrogate training. Fewer training samples (1024) were also assessed. The trained surrogates however had low AUC prediction accuracy, which led to different GSA indices compared to the mechanistic model. Each surrogate's AUC prediction error was generally lowest in the middle of the parametric bounds, increasing as the lower or upper bounds were approached.

Table 4: GSA convergence sums for an increasing number of samples of the mechanistic model

Output	294,912 Simulations	1,179,648 Simulations
C_{Plasma}	0.93	0.98
C_{PT}	0.9	0.97
C_{GICS}	0.93	0.98
C_{Liver}	0.93	0.98
C_{HO}	0.96	0.99

Convergence sums for increasing numbers of samples are reported in Table 4. The computational difficulty involved in performing GSA of PK models is evident by the results with 295,000 samples; the low sums indicate

that for all outputs except C_{HO} GSA remains un-converged. Over 1 million simulations are needed to observe stable sensitivity indices and achieve GSA convergence of the mechanistic PK model, which in turn leads to high computational expenditure requirements to perform GSA and examine model and parametric sensitivity.

After GSA convergence was confirmed, limited sensitivity indices mispredictions from the two surrogates are identified. The NN-derived simulation results lead to a converged GSA with the same number of samples as the mechanistic PK model. As observed from the negligible deviation in indices reported in Table 5, NN-derived GSA identified the same critical sets of parameters for each output, along with identical sensitivity and identifiability trends of the mechanistic model in a fraction of the time. Sensitivity index errors with respect to each output and parameter are limited to 1-3% at most and can be considered identical to the mechanistic-derived results. RF-derived GSA instead requires an increased number of samples for GSA to fully converge, and on average had greater sensitivity mispredictions than the NN surrogate. While identical critical parameter sets are identified for the first four outputs, only $j_{\text{P-HO}}$,$j_{\text{HO-P}}$ and k_{E}^{P} are identified as critical with respect to C_{HO}; $S_{j_{\text{PT-P}},\text{T}}$ and $S_{j_{\text{P-PT}},\text{T}}$ are underpredicted to be below the critical threshold. For this reason, RF-enabled GSA leads to different parameter criticality conclusions compared to the mechanistic and NN-enabled GSA.

Assessing the computational expenditure, the mechanistic GSA took 14291 s (14190 s for sample generation) and the NN GSA took 243 s (137 s for net training on CPU) to simulate 1.1 million samples, while the RF GSA took 911 s (13 s for RF training) to simulate 4.7 million samples. Surrogate-enabled GSA leads to a noticeable reduction in runtime. Regardless of the surrogates' training requirement, the mechanistic GSA was slower by at least 1 order of magnitude, highlighting the surrogate's ability to lighten the computational burden involved with GSA while producing GSA results.

Table 5: NN-derived total-order sensitivity index deviations from the mechanistic model

Parameter	Neural Net - $S^T_{\theta,\text{Mech.}} - S^T_{\theta,\text{NN.}}$				
	C_{Plasma}	C_{PT}	C_{GICS}	C_{Liver}	C_{HO}
$j_{\text{PT-P}}$	0.01	0.02	-0.01	0.01	0
$j_{\text{P-PT}}$	0.01	0.02	0.01	0.02	0
$j_{\text{P-HO}}$	0	0	0	0	0
$j_{\text{HO-P}}$	0	0	0	0	0
k_{E}^{P}	0.01	0.01	0.01	0	0
k_{E}^{T}	0	0	0	0	0
$\text{Eff}^{\text{Liver}}$	0	0	0	0	0
$\text{Eff}^{\text{Plasma}}$	0	0	0	0	0
Conv. Sum	0.96	0.95	0.95	0.97	0.98

Table 6: RF-derived total-order sensitivity index deviations from the mechanistic model

Parameter	Random Forests - $S^T_{\theta,\text{Mech.}} - S^T_{\theta,RF.}$				
	C_{Plasma}	C_{PT}	C_{GICS}	C_{Liver}	C_{HO}
$j_{\text{PT-P}}$	0	0	0	0	0.03
$j_{\text{P-PT}}$	0.02	0.02	0.02	0.02	0.03
$j_{\text{P-HO}}$	0.02	0.01	0.02	0.01	-0.01
$j_{\text{HO-P}}$	0	0	0	0	-0.01
k_{E}^{P}	0	0	0	-0.02	-0.02
k_{E}^{T}	0.01	0.02	0.01	0.01	0
$\text{Eff}^{\text{Liver}}$	0	0	0	0.01	0
$\text{Eff}^{\text{Plasma}}$	0.02	0.01	0.02	0.02	0.01
Conv. Sum	0.97	0.96	0.97	0.97	0.98

CONCLUSIONS

Global Sensitivity Analysis is a necessary tool for the development and application of PK and QSP models since it informs model structure design and enables parametric analysis. These are crucial to characterize biological variability across the patient population in relation to disease features and response to therapy. However, the large computational requirements of GSA when applied to large-scale and non-linear models limits its adoption and application in the pharma R&D space. In this work, we have shown how GSA computational requirements can be lowered by integrating machine-learning surrogates of the original mechanistic ODE model, trained on a significantly reduced number of mechanistic simulations, into the GSA framework. We tested two surrogate models based on Random Forests and on Feed-forward neural nets. The GSA with Random Forests surrogates identified a slightly-reduced critical set of parameters compared to the GSA conducted with the reference ODE-based model. Feed-forward neural nets were instead able to accurately predict mechanistic model outputs and consequently identify identical sensitivity indices and parameter criticality with minimal error (maximum deviation <3%). We show that surrogates can reliably capture parameter interactions from a limited set of training data derived from the ODE-based PK model and with a fraction of the computational expenditure compared to a fully ODE-based workflow. The ML-enhanced GSA is suitable for PBPK models given their mathematical features (ODE-based, non-linear and multi-parametric). The methodology is expected to be applicable to other modelling approaches, like PK/PD and QSP, that have similar mathematical characteristics. Surrogate-based GSA approach is especially valuable for the pharma R&D modeling community when implementing large differential equation-based model like PBPK or QSP, which typically require thorough identifiability and sensitivity analyses, as well

as intensive computation for generating or simulating virtual patient populations. Future work should explore the rapid generation of individualised GSA profiles to assess optimal cohort-specific measurement strategies for effective parameter estimation of PK/PD and QSP models. Instead of lumping cohorts into a single population, cohort-specific GSA assessments can support clinical trial and PBPK model development. Drug dosage regimens can be more effectively tailored to population subsets, improving the therapeutic outcomes of all patients.

REFERENCES

1. R. A. Abbiati, G. Lamberti, M. Grassi, F. Trotta, and D. Manca, "Definition and validation of a patient-individualized physiologically-based pharmacokinetic model," *Computers & Chemical Engineering*, vol. 84, pp. 394–408, Jan. 2016, doi: 10.1016/j.compchemeng.2015.09.018.
2. FDA, "Division of Pharmacometrics," FDA. Accessed: Jan. 06, 2025. [Online]. Available: https://www.fda.gov/about-fda/cder-offices-and-divisions/division-pharmacometrics
3. R. A. Abbiati and C. Pichardo, "An introduction to Quantitative Systems Pharmacology for Chemical Engineers," *Phys. Sci. Rev.*, 2024, doi: 10.1515/psr-2024-0066.
4. R. F. W. De Cock, C. Piana, E. H. J. Krekels, M. Danhof, K. Allegaert, and C. A. J. Knibbe, "The role of population PK–PD modelling in paediatric clinical research," *Eur J Clin Pharmacol*, vol. 67, no. 1, pp. 5–16, May 2011, doi: 10.1007/s00228-009-0782-9.
5. E. Asín-Prieto, A. Rodríguez-Gascón, and A. Isla, "Applications of the pharmacokinetic/pharmacodynamic (PK/PD) analysis of antimicrobial agents," *Journal of Infection and Chemotherapy*, vol. 21, no. 5, pp. 319–329, May 2015, doi: 10.1016/j.jiac.2015.02.001.
6. R. Sheikholeslami, S. Razavi, H. V. Gupta, W. Becker, and A. Haghnegahdar, "Global sensitivity analysis for high-dimensional problems: How to objectively group factors and measure robustness and convergence while reducing computational cost," *Environmental Modelling & Software*, vol. 111, pp. 282–299, Jan. 2019, doi: 10.1016/j.envsoft.2018.09.002.
7. S. Shan and G. G. Wang, "Metamodeling for High Dimensional Simulation-Based Design Problems," *Journal of Mechanical Design*, vol. 132, no. 051009, May 2010, doi: 10.1115/1.4001597.
8. P. Daoutidis *et al.*, "Machine learning in process systems engineering: Challenges and opportunities," *Computers & Chemical Engineering*, vol. 181, p. 108523, Feb. 2024, doi: 10.1016/j.compchemeng.2023.108523.
9. J. D. Scheff, R. R. Almon, D. C. DuBois, W. J. Jusko, and I. P. Androulakis, "Assessment of Pharmacologic Area Under the Curve When Baselines are Variable," *Pharm Res*, vol. 28, no. 5, pp. 1081–1089, May 2011, doi: 10.1007/s11095-010-0363-8.
10. A. Saltelli, Ed., *Global sensitivity analysis: the primer*. Chichester, England ; Hoboken, NJ: John Wiley, 2008.
11. F. Sarrazin, F. Pianosi, and T. Wagener, "Global Sensitivity Analysis of environmental models: Convergence and validation," *Environmental Modelling & Software*, vol. 79, pp. 135–152, May 2016, doi: 0.1016/j.envsoft.2016.02.005.