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A hybrid model associating population pharmacokinetics and machine learning: a case study with iohexol clearance estimation

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Availability of Data and Material

The data that support the findings of this study can be obtained from Alexandre Destere on reasonable request (alexandre.destere@gmail.com).

Code Availability: The code is available as supplemental data 1

Authors' Contributions: AD, JBW, PM, AP contributed to the study conception and design. Material preparation, data collections were performed by CSG, AA, VLR, PC, SE, CBLG and analysis by AD & JBW The first draft of the manuscript was written by AD, JBW, PM and all authors read and commented on the previous versions of the manuscript

Keywords: iohexol; population pharmacokinetics; Bayesian estimator; glomerular filtration rate; Machine Learning

Abstract

Maximum a posteriori Bayesian estimation (MAP-BE) based on limited sampling strategy (LSS) and a population pharmacokinetic model (POPPK) is frequently used to estimate pharmacokinetic parameters in individuals, however with some uncertainty (bias). Recent works have shown that the performance in individual estimation or PK parameters can be improved by combining POPPK and Machine Learning (ML) algorithms. The objective of this work was to investigate the use of a hybrid ML/POPPK approach to improve individual iohexol clearance estimation.

The reference iohexol clearance values were derived from 500 simulated profiles (samples collected between 0.1 and 24.7h) using a POPPK model we recently developed in Monolix and obtained using all the concentration-time points available. Xgboost and glmnet algorithms able to predict the error of MAP-BE clearance (CL) estimates based on a LSS (0.1h, 1h and 9h) vs. reference values were developed in a training subset (75%) and were evaluated in a testing subset (25%) and in 36 real patients. The MAP-BE LSS estimated CL was corrected by the ML predicted error leading to a decrease in RMSE by 29%/ 24% and in the percentage of profiles with MPE% out of the $\pm 20\%$ bias by 60%/40% in the external validation dataset for the glmnet and Xgboost ML algorithms respectively. These results were attributable to a decrease in the eta-shrinkage (shrinkage for MAP-BE LSS=32.4%, glmnet=18.2% and Xgboost=19.4% in external dataset). In conclusion, this hybrid algorithm represents a significant improvement in comparison to MAP-BE estimation alone.

Study Highlights

- What question did this study address?

This study investigated the ability of a hybrid model associating MAP-BE POPPK and ML to improve individual iohexol CL estimation.

- What does this study add to our knowledge?

The hybrid models developed decreased by about 30% the MPE% and RMSE% in comparison to the MAP-BE alone.

- How might this change drug discovery, development, and/or therapeutics?

This hybrid approach could be generalized for drugs with complex pharmacokinetics and characterized by a large error when using MAP-BE for individual predictions.

1. Introduction

In addition to standard therapeutic drug monitoring, population pharmacokinetics (POPPK) modelling helps to individualise the dose of drugs characterized by a large inter-individual variability and a narrow therapeutic index [1,2]. Indeed, Maximum a Posteriori Bayesian Estimation (MAP-BE) based on prior and observed information, often based on a limited sampling strategy and some covariates, can estimate individual PK parameters (e.g., distribution volume, clearance) and/or exposure indices (e.g., the area under the concentration time curve, AUC) and help to derive a dose adjustment proposal. Machine-learning (ML) approaches have also recently been proposed to estimate drug exposure [3,4]. Each approach has drawbacks: ML seems to be more accurate than POPPK but less flexible (for instance with respect to sampling times), and it cannot be used to draw simulations. Recent studies proposed a combined use of POPPK and ML in order to choose the best POPPK structural model [5], select pertinent covariates [6], improve antibiotics clearance estimation on top of POPPK estimation with covariates [7], or to select patients in whom it would be better to use flat priors than conventional MAP-BE for vancomycin [8]. Indeed, MAP-BE can suffer from a systematic deviation called shrinkage and requires the use of flat priors to correct this problem [9]. In this latter example, the ML algorithm mainly learned from the error between observations and predictions to solve a binary problem with or without the use of flattened priors. Similarly, we hypothesize that based on features, ML can learn how to decrease the error (in a regression problem) resulting from POPPK and MAP-BE based on a limited sampling strategy (LSS). The estimation of the glomerular filtration rate using iohexol clearance (CL) could be a good case study: several population pharmacokinetic (POPPK) models [10–14] and one ML algorithm [15] have been developed to estimate iohexol plasma clearance based on limited sampling strategies. We recently published a POPPK model for iohexol CL estimation (in an intensive care unit (ICU), liver failure or renal transplant patients) [16] the results of which are very accurate in kidney transplant patients, but partially biased in stable ICU patients and slightly imprecise in unstable ICU patients. We made the hypothesis that such bias and imprecision could be decreased by the combination of ML and POPPK approaches.

The aim of this work was to investigate the use of ML to predict the error in individual estimations resulting from MAP-BE based on LSS (MAP-BE LSS) and on a POPPK model, to improve the individual estimation of iohexol clearance and glomerular filtration rate (GFR) by means of this hybrid approach.

2. Material & Methods

2.1. Population Pharmacokinetics

2.1.1. Data simulation

The population parameters and relevant covariates of our recent published population pharmacokinetics (POPPK) model [16] were used to simulate 500 patients with 250 concentration samples between 0.1 and 24.7h with Simulx [17]. Briefly, it consisted in a 2cp model with combined (proportional and additive) residual error and included the following: bodyweight, type of patient (stable or unstable ICU, renal transplant, and liver failure patients) as covariates on the central volume (V1); and serum creatinine and type of patient on CL. A dose of 3235 mg, generally administered in this indication was used for the simulations. Some filters were applied to extreme values of the simulated PK parameters (V1, CL and K12) so as to restrict the range to that of the original publication (exclusion of 1% extreme percentiles). It is noteworthy that all simulated K21 values were already in this range. The CL parameter obtained for each simulated patient by application of MAP-BE to the 250 simulated samples was considered to be the reference (refCL).

2.1.2. Estimation of the differences between reference CL (refCL) and MAP-BE LSS CL (MAP-BE LSS CL)

The concentrations at 0.1, 1 and 9h (LSS selected in the original article) were extracted from the simulated concentrations and the MAP-BE LSS CL was calculated. The raw error between the refCL and MAP-BE LSS CL was calculated using the following formula:

$$\text{Error} = \text{refCL} - \text{MAP BE LSS CL}$$

Then ML algorithms were trained to predict this error and to correct the MAP-BE LSS CL. The improvement of the iohexol CL prediction (MPE and RMSE) was evaluated.

2.2. Machine Learning approaches

2.2.1. Preparation of the data and feature engineering

Simulations were split into a training (75%) and a testing (25%) datasets and concentrations at 0.1, 1 and 9h, covariates and estimated PK parameters based on MAP-BE LSS were extracted. Features engineering was applied by calculating: (i) the differences among the observed concentrations (OC) (OC0.1-OC1, OC0.1-OC9 and OC1-OC9), (ii) the ratios among the observed concentrations (OC1/OC0.1, OC9/OC0.1 and C9/C1), (iii) the relative ratios among the observed concentrations ((OC0.1-OC1)/OC1, (OC0.1-OC9)/OC9 and (OC1-OC9)/OC9), (iv) the differences between observed and MAP-BE LSS estimated concentrations (EC) at each time (OC0.1-EC0.1, OC1-EC1, OC9-EC9) and (v) the ratios between observed and MAP-BE LSS estimated concentrations (OC0.1/EC0.1, OC1/EC1, OC9/EC9). Finally, a total of 29 features (PK parameters estimated by MAP-BE LSS, simulated covariates...) were available for the development of the ML algorithm.

2.2.2. Machine Learning analysis

Algorithms to predict errors between refCL and the MAP-BE LSS CL were developed using the Tidymodels framework in R [18] and two types of algorithms in parallel: xgboost [19] and penalised generalised linear regression (glmnet) [20]. Ten-fold cross-validation was applied to the training set to tune the hyperparameters and evaluate the model performances (based on the r^2). The algorithm predicted error was then added to the MAP-BE LSS to obtain the corrected CL (corCLr), as follows:

$$\text{corCL} = \text{MAP BELSS CL} + \text{algorithm predicted error}$$

Finally, the performances of iohexol clearance prediction with this hybrid model in the training dataset (using 10-fold cross-validation) and the testing dataset were evaluated by calculating the relative mean prediction error (MPE%), the relative root mean squared error (RMSE%) and the percentage of profiles with MPE% out of the $\pm 20\%$ interval between the corCL and refCL. Variable importance plots were drawn to evaluate the most important features in each algorithm.

2.2.3. External validation

The performance of the 2 machine learning algorithms to correct the MAP-BE LSS CL were evaluated in 36 real patients of the independent validation dataset [16]. They were the same patients as those in the original article but not used in the development of the POPPK model. Plots of the unexplained error of estimated iohexol CL

obtained using MAP-BE LSS and the hybrid model in the testing and external datasets were drawn to show the improvements made by the latter.

2.2.4. Evaluation of the shrinkage

The η shrinkage implication in the hybrid model correction was evaluated and compared to the recently published approach in Baklouti et al.[9] based on the Locally Estimated Scatterplot Smoothing (LOESS)

The shrinkage of MAP-BE LSS, hybrid models and LOESS were estimated in training, testing and external dataset using the formula used in Monolix [21]:

$$Shrinkage = 1 - \frac{var(\eta CL_x)}{\omega_{CL}^2}$$

With x= method used; ηCL_x = random effect of the parameter; $\omega^2 CL$ = variance of the parameter estimate

The random effects correction improvement (η) for each correction method was measured using the formula proposed in Baklouti et al. [9].:

$$Overall Improvement = 1 - \frac{\sum[\eta CL - \eta CL_x]^2}{\sum[\eta CL - \eta CL_{MAP BE LSS}]^2}$$

with x=hybrid model or LOESS.

3. Results

3.1. Simulated data

After excluding the 1% extreme percentiles of CL, V1 and k12, 468 simulated profiles from 250 samples remained. The summary of the features used as predictors in the Machine learning algorithms are presented in Table 1. They consisted in MAP-BE estimated individual PK parameters, Observed Concentrations (OC), Estimated Concentrations (EC), simulated covariates and the 15 newly created features. No statistical difference was observed between the features used in the training and testing datasets. The distribution of MAP-BE LSS CL, and of the error between refCL and MAP-BE LSS CL are presented in Figure 1. Glmnet and Xgboost predicted the error with $r^2 \pm SD = 0.66 \pm 0.03$ and 0.64 ± 0.03 in the training set, and $r^2 = 0.94 \pm 0.07$ and 0.70 ± 0.05 in the testing set, respectively. The performances of each hybrid algorithm (corCL) to correct the MAP-BE LSS CL are presented in Table 2. The variables importance plots of the 2 ML algorithms are also presented in Figure 2. They showed that the ratio between OC and EC at 9h' that corresponds to the ratio between the concentration observed at 9h and the one predicted by the MAP-BE LSS was found by both ML algorithms as

very important while other variables were selected only for one or another method. The unexplained errors between the MAP-BE LSS and the hybrid model with either Xgboost or glmnet in the testing set are presented in Figure 3 (3A and 3B).

3.2. Performance to correct the MAP-BE LSS CL in actual data

The performances of MAP-BE LSS and the hybrid algorithms with either glmnet or xgboost to predict the refCL in the external datasets are presented in Table 2, and the plot of the corresponding unexplained errors in Figure 3 (3C and 3D). Whatever the hybrid model chosen, the performance to predict refCL was better than MAP-BE LSS.

3.3. Evaluation of the shrinkage and the improvement of prediction of individual random effects (η) in training, testing and external dataset

The shrinkage of the MAP-BE, Hybrid models (Xgboost and glmnet) and LOESS method are presented in Table 3. The shrinkage obtained with the Xgboost hybrid model was similar to the one obtained with the LOESS method while the one obtained with the glmnet hybrid model was decreased. Regarding the improvement of prediction of random effects (η) in the training and testing datasets, glmnet obtained the best results (33.6% & 82.5%) in comparison to Xgboost (33.8% & 4.2%) and LOESS method (17.3% & -12.9). Similar result were observed in the external dataset as the glmnet had the highest improvement (45.5%) compared to the Xgboost hybrid model (33.4%) and the LOESS method (20.1%). The performances in terms of RMSE and MPE or profiles outside the $\pm 20\%$ interval were still better for both ML approaches in comparison to the LOESS in the training, testing and external datasets.

4. Discussion

In this study, we developed a hybrid model that associates MAP-BE LSS backed on a POPPK model on the one hand, and a ML algorithm on the other, to improve the performance of individual estimation of iohexol plasma clearance mainly by correcting the shrinkage. We observed a decrease in MPE%, RMSE% and the percentage of profiles out of the $\pm 20\%$ MPE interval with the hybrid models vs MAP-BE LSS alone. The advantage of this approach is that the use of a hybrid model allows conserving interpretability of the predictions contrary to ML algorithms alone, while benefiting from the powerful data-driven reduction of error brought by ML.

The glmnet algorithm yielded the best results in terms of percentage of estimations out of the $\pm 20\%$ bias interval while the imprecision was almost similar to the Xgboost and this latter had a lower mean bias. That led us to select the penalised glmnet due to the lower percentage of profiles out of the $\pm 20\%$ bias interval.

The performance of refCL estimation was highly improved when using the hybrid models with about 30% decrease in MPE% and RMSE% in the external dataset in comparison to the standard MAP-BE approach. The shrinkage observed after correction in the external dataset, whatever the methods used (LOESS recently developed by Baklouti et al [9](23%), the glmnet hybrid model (18.2%) or Xgboost hybrid model (19.4%)), was improved in comparison to the MAP-BE approach (Table 3). However, although the decrease in shrinkage is similar between the methods, the overall improvement and the performances in terms of individual predictions (MPE, RMSE and percentage of bias out of the $\pm 20\%$ interval) were higher with the hybrid models in comparison to LOESS. The shrinkage and improvement evaluate different things: the first one evaluates the spread of the estimated parameter while the second one evaluates the precision of the random effect of the parameter estimation in comparison to the one of the MAP-BE. Finally, the MPE and RMSE evaluated the performance of the prediction in the PK parameter itself.

Performance improvement with hybrid ML and POPPK algorithms has previously been reported by other studies. Hughes & Keizer developed a hybrid model to choose whether flat priors must be applied or not for MAP-BE and they observed a decrease in RMSE of 12-22% (5-18% for the 2 features ML algorithm) vs MAP-BE alone. Tang et al recently developed an extra tree regressor to predict an individual clearance based on individual covariates and MAP-BE CL predicted by population pharmacokinetic models and individual concentrations for six antibiotics. They found a mean decrease in mean residual error up to 71.3% in comparison to POPPK alone. This work has similarities with the present study. However, the authors directly predicted the CL using the ML approach but not the error and they did not include the other posthoc PK parameters in the predictors (except clearance) and no feature engineering was performed [7]. We chose on the contrary to predict the error between refCL and MAP-BE LSS CL estimates since it gives direct access to the amount of correction brought by the ML algorithm. Additionally, feature engineering allowed an improvement in prediction as highlighted by the VIP plot that shows that the OC/EC ratio 9h has a strong importance in error prediction whatever the ML algorithm used. As the algorithms being different (glmnet is derived from regression and xgboost from boosting), this explains why the features selected are different. The ratio between OC and EC at 9h between the observed concentration and the one predicted by the POPPK model provides useful information about the difference between the true and estimated CL.

Shrinkage is intrinsically linked to MAP-BE based on LSS. The level of shrinkage depends on the amount of individual information provided. We wanted to find out whether the hybrid approach corrects for low shrinkage and increases the estimation accuracy for different limited sampling strategy scenario. We evaluated this by simulating different LSS (1 and 6 samples) and evaluated their performances. We observed that LOESS, Xgboost or glmnet hybrid models still decreased the shrinkage and improved the individual predictions in comparison to the MAP-BE, even if only to a smaller extent (Supplemental data 2).

The benefit of applying such a ML approach to real data would allow learning from features that were not present during model building or that are more complex to implement in a POPPK context, or systemic bias in a clinical setting that simulations did not allow. However, this is very rarely possible due to the limited number of data available in PK studies.

Interestingly, we observed in the testing dataset, but not in real patient, that the corrections tend to be the highest for small values of iohexol CL that are also characterised by a large bias when using MAP-BE alone (Figure 3). These values are the most critical in routine care since they are used to characterise renal failure severity categories and, when needed to trigger the renal replacement procedure. The highest errors, even after corrections, were observed in the testing set and in real patients for the hyperclearance which on the contrary, are less critical in routine care. In this study, only the MAP-BE LSS CL was corrected by predicting the error between refCL and MAP-BE LSS. The correction was only applied to the iohexol clearance as it is the surrogate for GFR estimate. We agree that the correction of only one parameter is leading to changing the relationship with the other PK parameters as they are estimated simultaneously in a patient. However, the corrected parameter is not re-implemented in the POPPK model or used to perform simulations but only used in this case to estimate the GFR or more generally to calculate the AUC of a drug using the Dose/Clearance formula. The simultaneous correction of every PK parameters would require the use of deep learning approaches allowing to work on a vector of parameters but is not suited in the present case given the number of available data. This deserves further investigations.

We chose to use the POPPK model that we recently developed for the same dataset [16] instead of ones already published, for many reasons: first, we had the full structure including the PK parameters correlation matrix, allowing more precise simulations. Secondly, this model fits diverse target populations including ICU, renal transplant, and liver failure patients.

To improve the reliability of simulations, we choose to filter out the extreme values (1 percentiles) of the PK parameters, i.e. those that were distributed out of the original range [16]. We observed an improvement in

performances in comparison to the hybrid algorithm developed when keeping all the PK parameter values (data not shown). Probably the amount of data to be filtered out depends on the quality of the initial POPPK model and should be tuned. In our case, the simulated CL ranged between 3.9 and 183.4 ml/min, which is enough to cover most of the GFR values observed in routine care.

From a practical point of view, these hybrid models can be implemented in dedicated computer or mobile apps (including MAP-BE and ML residue correction) to be used in routine practice. The overall procedure and code of the method developed here is shown in supplemental data 1.

In the present study, we selected an accurate POPPK model to simulate PK profiles from which the ML algorithms could learn. A biased model would have led to the development of a biased hybrid model, hence poor generalisability and poor performance in independent datasets, which was obviously not the case here. Finally, this approach seems promising and needs to be investigated for other drugs with POPPK with a large residual error (e.g., mycophenolic acid, characterised by a complex pharmacokinetics) [22]. It is of note that the performances of forecasting concentrations into future occasions was not evaluated in this study as iohexol is administered only once. The ability of such an approach to forecast future occasions has to be investigated in further studies. In this case, the intra-individual variability will have to be learnt in addition to the inter-individual variability that is quite complicated based on simulations.

In conclusion, we developed a hybrid model associating MAP-BE that rely on a POPPK model and machine learning algorithms yielding improved estimation of individual iohexol plasma clearance mainly due to the decrease of η shrinkage of MAP-BE based on the LSS. The results obtained with this hybrid algorithm show a strong improvement in comparison to MAP-BE alone and a good improvement in comparison to a recently published approach that deshrink individual random effects [9].

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Table 1 Characteristics of the simulated profiles in the training and testing subsets.

| | Overall | Training | Testing | Student test p-value |
|--------------------------------------|--------------------|--------------------|--------------------|----------------------|
| n | 468 | 351 | 117 | |
| OC0.1 (mean (SD)) | 373.56 (147.12) | 375.03 (145.61) | 369.13 (152.09) | 0.707 |
| EC0.1 (mean (SD)) | 373.05 (144.96) | 374.43 (143.36) | 368.91 (150.20) | 0.722 |
| OC1 (mean (SD)) | 164.28 (64.33) | 163.59 (62.41) | 166.34 (70.03) | 0.69 |
| EC1 (mean (SD)) | 163.56 (62.73) | 162.92 (60.95) | 165.47 (68.04) | 0.704 |
| OC9 (mean (SD)) | 52.24 (37.52) | 52.66 (37.53) | 50.96 (37.61) | 0.671 |
| EC9 (mean (SD)) | 51.91 (36.88) | 52.34 (36.89) | 50.64 (36.97) | 0.666 |
| MAP-BE CL (mean (SD)) | 2.98 (1.84) | 2.97 (1.88) | 2.99 (1.72) | 0.927 |
| MAP-BE V1 (mean (SD)) | 8.54 (4.07) | 8.44 (3.94) | 8.85 (4.45) | 0.341 |
| MAP-BE k12 (mean (SD)) | 1.64 (0.89) | 1.65 (0.87) | 1.60 (0.93) | 0.595 |
| MAP-BE k21 (mean (SD)) | 1.25 (0.51) | 1.24 (0.45) | 1.27 (0.64) | 0.518 |
| Serum creatinine (mean (SD)) | 132.07 (76.43) | 131.22 (75.43) | 134.65 (79.63) | 0.675 |
| Weight (mean (SD)) | 77.43 (19.83) | 77.63 (19.95) | 76.85 (19.54) | 0.714 |
| Type of patients (%) | | | | 0.801 |
| Liver failure | 22 (4.7) | 17 (4.8) | 5 (4.3) | |
| Unstable ICU | 235 (50.2) | 180 (51.3) | 55 (47.0) | |
| Stable ICU | 56 (12.0) | 42 (12.0) | 14 (12.0) | |
| Kidney transplant | 155 (33.1) | 112 (31.9) | 43 (36.8) | |
| OC0.1-OC1 difference (mean (SD)) | 209.28 (107.64) | 211.44 (107.26) | 202.79 (108.99) | 0.452 |
| OC0.1-OC9 difference (mean (SD)) | 321.32 (140.39) | 322.37 (138.94) | 318.17 (145.22) | 0.78 |
| OC1-OC9 difference (mean (SD)) | 112.04 (55.13) | 110.93 (52.96) | 115.38 (61.31) | 0.45 |
| OC0.1/OC1 ratio (mean (SD)) | 2.35 (0.69) | 2.37 (0.69) | 2.29 (0.68) | 0.291 |
| OC0.1/OC9 ratio (mean (SD)) | 18.07 (41.65) | 17.13 (35.73) | 20.90 (55.85) | 0.397 |
| OC1/OC9 ratio (mean (SD)) | 6.65 (11.84) | 6.40 (10.72) | 7.38 (14.75) | 0.441 |
| OC0.1/OC1 relative ratio (mean (SD)) | 1.35 (0.69) | 1.37 (0.69) | 1.29 (0.68) | 0.291 |
| OC0.1/OC9 relative ratio | 17.07 (41.65) | 16.13 (35.73) | 19.90 | 0.397 |

| | | | | | |
|---------------------------------------|--------------|--------------|-----------------|-------|--|
| (mean (SD)) | | | (55.85) | | |
| OC1/OC9 relative ratio (mean (SD)) | 5.65 (11.84) | 5.40 (10.72) | 6.38 (14.75) | 0.441 | |
| OC0.1-EP0.1 difference (mean (SD)) | 0.51 (3.64) | 0.60 (3.60) | 0.22 (3.74) | 0.33 | |
| OC0.1-EP0.1 difference (mean (SD)) | 0.72 (2.87) | 0.68 (2.69) | 0.87 (3.37) | 0.526 | |
| OC0.1-EP0.1 difference (mean (SD)) | 0.33 (1.29) | 0.33 (1.28) | 0.32 (1.34) | 0.976 | |
| OC0.1-EP0.1 ratio (mean (SD)) | 1.00 (0.0.1) | 1.00 (0.0.1) | 1.00 (0.0.1) | 0.297 | |
| OC1/EC1 ratio (mean (SD)) | 1.00 (0.02) | 1.00 (0.02) | 1.00 (0.02) | 0.921 | |
| OC9/EC9 ratio (mean (SD)) | 0.99 (0.07) | 0.99 (0.07) | 0.99 (0.07) | 0.833 | |

OCx: Observed concentrations at x hours; ECx: Estimated concentrations at x hours; CL: Clearance; V1: central volume; k12: transfer constant of central to peripheric volume; k21: transfer constant of peripheric to central volume

Table 2 Performance of the different models to predict refCL in the training, testing and external datasets.

| | MAP- BE LSS | Training | | | MAP- BE LSS | Testing | | | MAP- BE LSS | External | | |
|---|----------------|----------------------------|---------------------------|-------|----------------|----------------------------|---------------------------|-------|----------------|----------------------------|---------------------------|-------|
| | | Hybrid model Xgboost | Hybrid model GLMnet | LOESS | | Hybrid model Xgboost | Hybrid model GLMnet | LOESS | | Hybrid model Xgboost | Hybrid model GLMnet | LOESS |
| MPE% | -2.0 | -0.3 | -0.3 | -0.3 | -1.0 | 0.7 | 0.2 | 0.8 | -3.7 | -2.2 | -3.7 | -2.6 |
| RMSE% | 10.1 | 7.5 | 7.2 | 8.7 | 6.2 | 5.7 | 2.4 | 6.3 | 14.3 | 10.9 | 10.2 | 12.3 |
| Profiles with MPE% outside the $\pm 20\%$ interval (%) | 4.0 | 2.8 | 2.9 | 3.1 | 1.7 | 0.9 | 0 | 1.7 | 13.9 | 8.3 | 5.6 | 11.1 |

Table 3 Shrinkage evaluation for ML algorithms and the method described in Baklouti et al [9] in comparison to MAP-BE LSS

| | Training | Testing | External |
|----------------------|----------|---------|----------|
| MAP-BE LSS | 17.6 | 32.1 | 32.4 |
| Hybrid Model Xgboost | 7.1 | 25.4 | 19.4 |
| Hybrid Model glmnet | -2.4 | 26.7 | 18.2 |
| Loess method [9] | 6.7 | 22.9 | 23.0 |

MAP-BE LSS: Maximum a posteriori bayesian estimator based on LSS

Figure legends

Figure 1 Histogram of maximum a posteriori bayesian estimation of iohexol plasma CL based on the 0.1h, 1h and 9h limited sampling strategy and difference (error) between the reference CL and MAP-BE CL in the simulated dataset

Figure 2 Variable Importance Plots of the glmnet and Xgboost Machine Learning algorithms

Figure 3 Plots of the unexplained error of MAP-BE and hybrid models vs reference iohexol plasma CL in the testing and external datasets for Xgboost and glmnet algorithms