Bayesian Whole Body Population Physiologically Based Pharmacokinetic Approach for Characterization of Interindividual Variability of Diazepam

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Overview

- Whole Body Physiologically-based pharmacokinetic (WBPBPK) models predict tissue concentration and preform extrapolation to different population groups but do not capture the variability of clinical PK data
- Bayesian inference for PBPK models offers the advantage of extracting information not only at the individual, but also at the population level as well.
- Insertion of covariates can introduce greater prediction capability at the individual level.
- The purpose of this work is to insert gender and weight covariates into the physiological parameters of the Diazepam PBPK model and update selected physiological parameters through a Bayesian framework, as a first step to identify the sources of the observed variability.

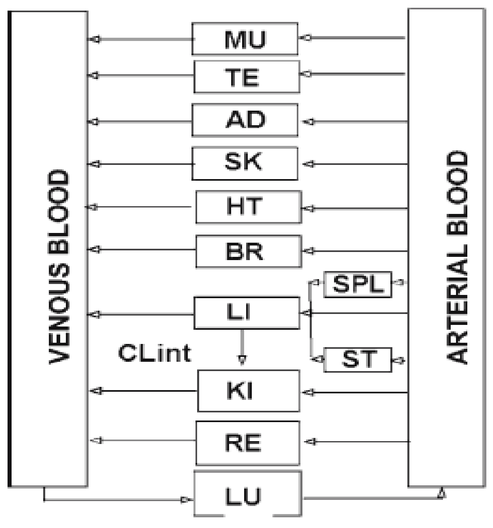

Figure 1:Schematic presentation of a WBPBPK for Diazepam (Figure taken from [1].)

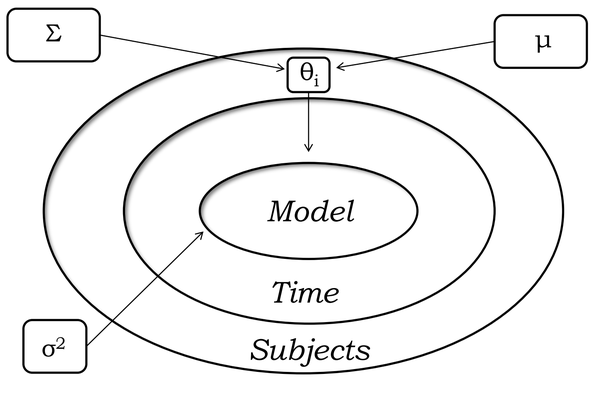

Figure 2:Schematic presentation of the information flow of the Bayesian hierarchical WBPBPK.

Methods

- The structure of the WBPBPK was previously modeled in [1]. Data refer to Diazepam plasma concentration samples of 23 individuals after a bolus IV infusion [2]. Study concentrations were between 5-10 mg but since no information on individual dosing was available, a uniform dose of 7mg was assumed.
- The hierarchical model developed consists of three stages:

  1st stage: $p(\log(y_{ij}\,|\theta_i,\sigma^2)\sim Normal(\log(f(t_{ij},\theta_i)),\sigma^2)$

  2nd stage: $p(\theta_i|\mu,\Omega)\sim Multivariate\_Lognormal(\mu,\Omega)$

  3rd stage: $p(\mu)\sim Multivariate_{Lognormal(\bar{\mu},\Sigma)}, p(\sigma^2)\sim \text{Cauchy}(x_0,\gamma), \Omega=\Delta Q\Delta$

  $p(\delta^2)\sim \text{Cauchy}(\grave{x_0},\grave{\gamma}), p(\text{Q})\sim ikj\_corr(\eta)$

  where Δ is a diagonal matrix with $\Delta_{ii}=\delta_i{}^2$ (variance of the parameters) and Q is the correlation matrix.
- Body weight (BW) was introduced as a covariate to all tissue flows (Q), which were expressed as a percentage of cardiac output (CO): $Q_i = \alpha_i \cdot, CO_i, CO_i = 187 \cdot BW_i{}^{0.81}$ (in mL/min)[3]. The flow percentages were retrieved from [4].
- BW and gender were introduced as a covariate in tissue volumes. For every gender a specified polynomial defined the organ volume: $V_i = A_i + \text{B}_i \cdot \frac{BW}{1000} + \Gamma_i \cdot \left(\frac{BW}{1000}\right)^2 + \Delta_i \cdot (\frac{BW}{1000})^3 + \text{E}_i \cdot (\frac{BW}{1000})^4 + \text{Z}_i \cdot (\frac{BW}{1000})^5$ [5].
- Tissue to plasma partition coefficient were considered to be constant and were calculated based on simulations using data from the posterior analysis in [1].
- Only hepatic clearance and certain physiological parameters were estimated, the latter being chosen by local sensitivity analysis .

Results

- Local sensitivity analysis showed that mainly pertubation of tissue volumes had impact on the output (Figure 3).
- The first hierarchical model considered only clearance as a population parameter in order to compare the model with and without covariates. The model which included covariates presented better fitting as seen in Figure 4
- The Bayesian model was built in RSTAN v.2.15.1 [6].
- The MCMC process involved 4 chains, each consisting of 1000 iteration from which the first 500 were warmup iterations and were discarded.

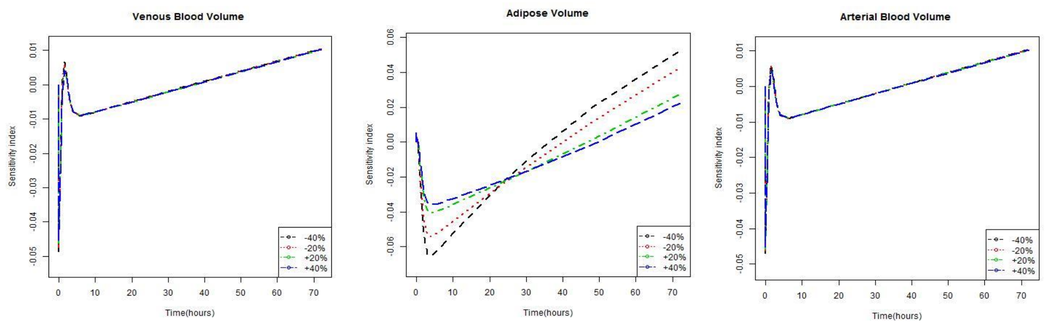

Figure 3:The three most important physiological parameters according to local sensitivity analysis.

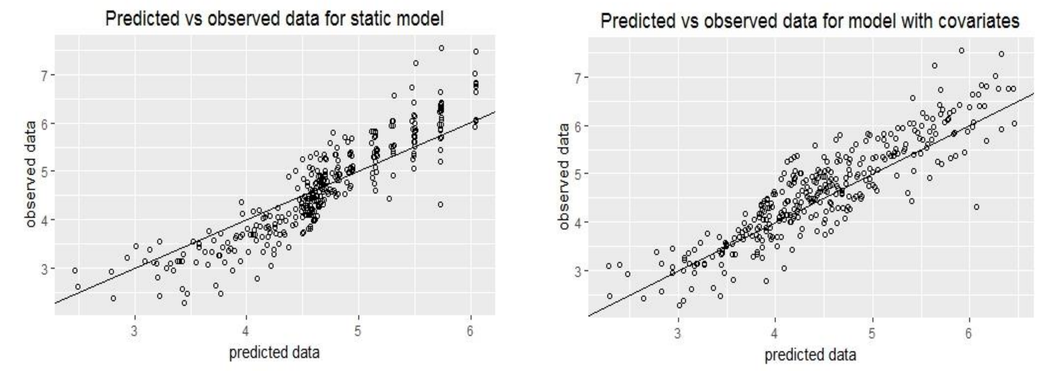

Figure 4: Observed (y-axis) vs. predicted (x-axis) values on the log scale for the regular model (left) and the model with covariates (right). A better fit, closer to the identity line is observed in the second model.

- The second model included venous and arterial blood BW percentages as population parameters as well.
- Closure of the volume balance was achieved in each iteration, past sampling, through recalculation of the volume of the Rest of The Body (ROB) compartment.
- Convergence was achieved for all parameters (Rhat_i =1).
- Prior uncertainty was reduced for clearance and venous blood volume percent but not for arterial blood volume percent (Figure 4).
- Visual predictive check showed the model did not accurately follow the data trends in the initial time stage, as seen in Figure 6.

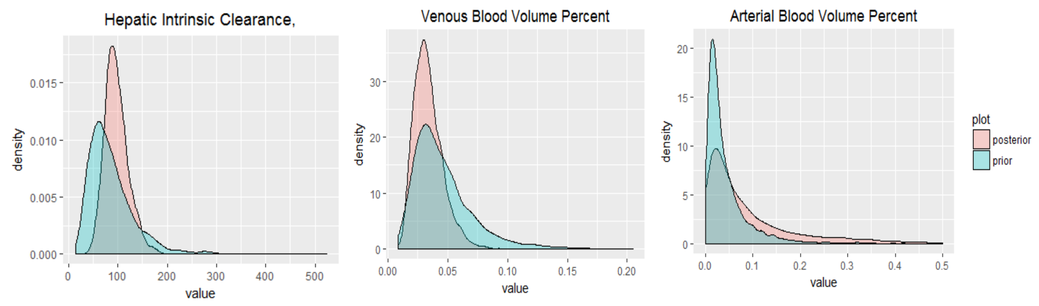

Figure 5:Prior (emerald) vs. posterior (pink) distributions of the three parameters of the model.

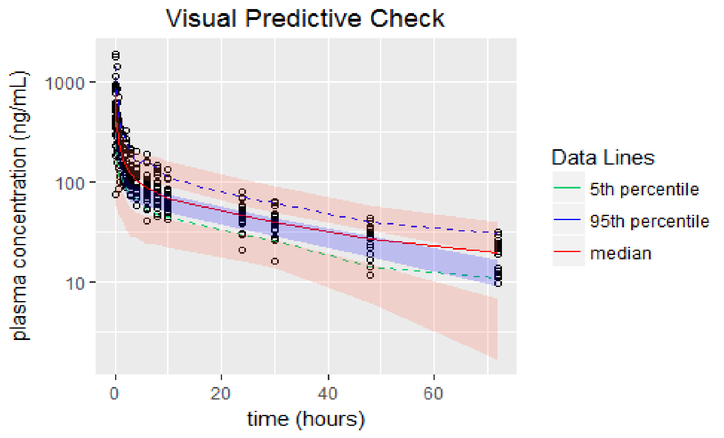

Figure 6: Visual Predictive Check for the fully developed WBPBPK model. Patient's data are depicted with hollow dots, while the shaded areas represent 95% confidence interval of the corresponding prediction percentiles .

Conclusions

We employed a full Bayesian framework to update an existing WBPBPK model through the use of clinical PK data. The introduction of covariates to the physiological parameters proved to provide better fitting. Following that, two important physiological parameters were considered to be random variables and included in the model along with the hepatic clearance. The visual predictive check showed satisfactory fitting for all but the initial time stage.

Our future plans include performing a global sensitivity analysis in order to more accurately recognize the most influential physiological parameters and then insert more of them in the Bayesian model to achieve better fitting. Moreover, a more precise predictor of organ volumes and flows should be considered, ideally including body height. For that purpose, we intend to apply this methodology to more informative data sets.

References:

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