Towards more Realistic Clinical Trial Simulation: Establishing Inter-Correlations between Several Cytochrome P450 Enzyme Abundances in Human Liver

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Introduction

Success of clinical trial simulations greatly depends on identifying and incorporating true anatomical and physiological covariates when generating virtual populations. Recently, the inter-correlations between CYP450 (and UGT) metabolising enzymes in human liver microsomes have been reported[1, 2]. These data enable population-based PBPK models to more realistically assign CYP/UGT abundances when generating virtual subjects using Correlated Monte Carlo sampling.

Objectives

This work aims to determine the covariance matrix of a multivariate lognormal probability distribution of the CYP450 abundance values derived using reported data[1, 2] and compare the distribution of each CYP against those currently generated in the Simcyp Simulator (Version 14).

Methods

- The marginal distributions of each CYP450 are assumed to be log-normal and are checked by obtaining normal plots for the log transformed abundance values.
- The correlation and covariance matrices for the log transformed CYP abundance values have been calculated using R Package (V 3.1.2) (Figure 1).
- Eigenvalues of the covariance matrix have been tested for positivity and if negative eigenvalues occurred, then the nearest positive definite covariance matrix has been calculated[3, 4, 5] using 'nearPD' package in R.
- A new correlated sample has been obtained by calculating the Cholesky decomposition[3,4,5] of the nearest positive definite covariance matrix. A virtual population matching the real population demographics, assuming no inter-correlations between CYP enzymes (except that between CYP3A4 and CYP3A5) has been generated using the Simcyp Simulator V14 and the results were compared with the correlated Monte Carlo sampling data.

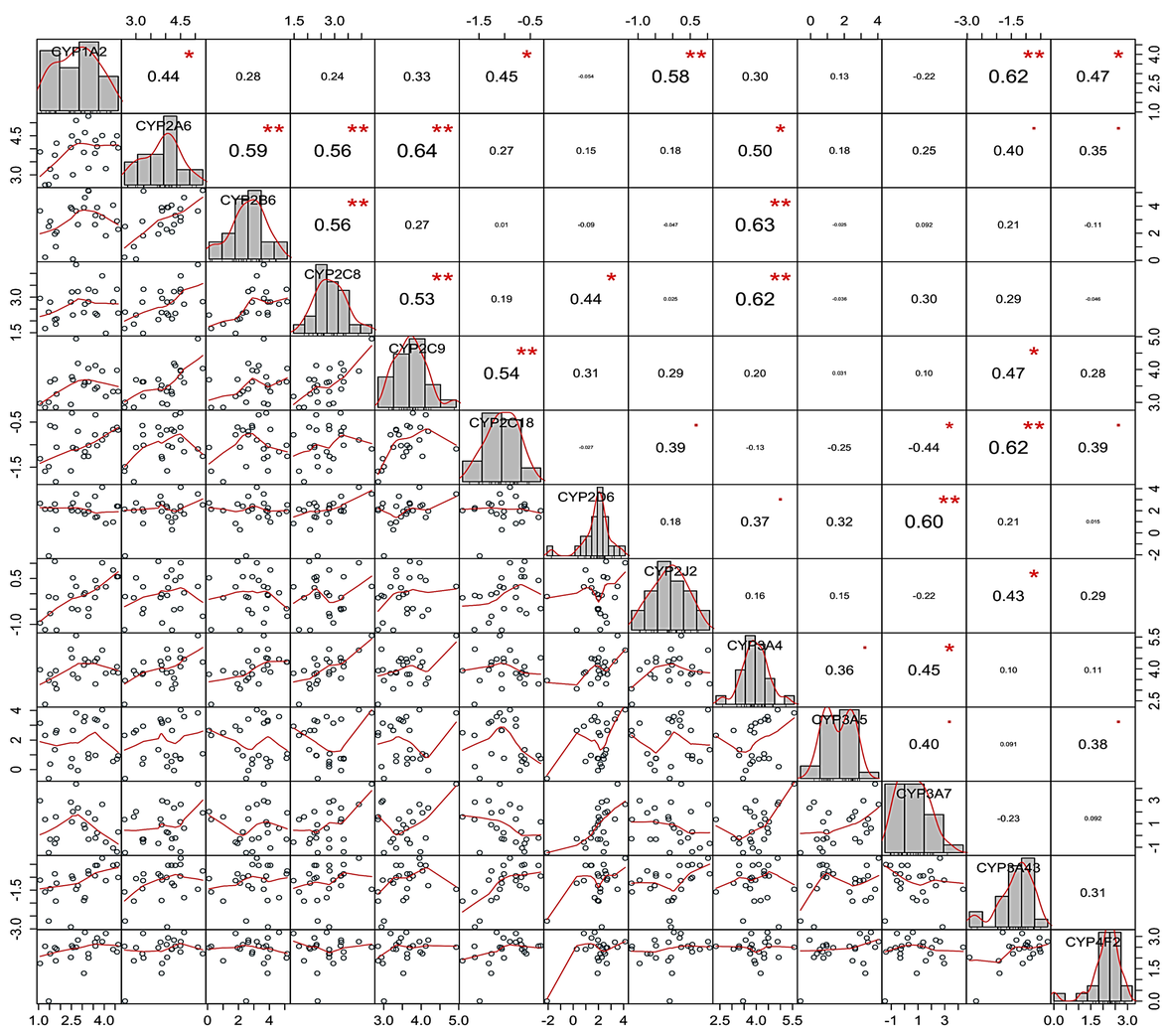

Figure 1. Upper triangle: Spearman correlations of log-transformed CYP abundance values from [1]. Diagonal: histogram of univariate values and Bottom triangle: bivariate scatterplots, with a fitted curve. Asterisks correspond to significance levels (p-values) according to (0.001,0.01,0.5,0.1,1) ⇔ ("***", "**", "*", ".", "").

Results

Multivariate Cramer-Test[6] (with kernel 'phiCramer' in R's cramer library) shows the dissimilarity between the empirical distributions of the correlated and uncorrelated samples with 95% CI critical T-statistic of 132.229 vs observed: 3151.635. Kernel density estimate visually showed the differences between the two distributions after removing {CYP2C19, CYP2E1}, {CYP3A43,CYP4F2} from 'Blue' and 'Red' populations respectively to have the same covariates in both) (Figure 2).

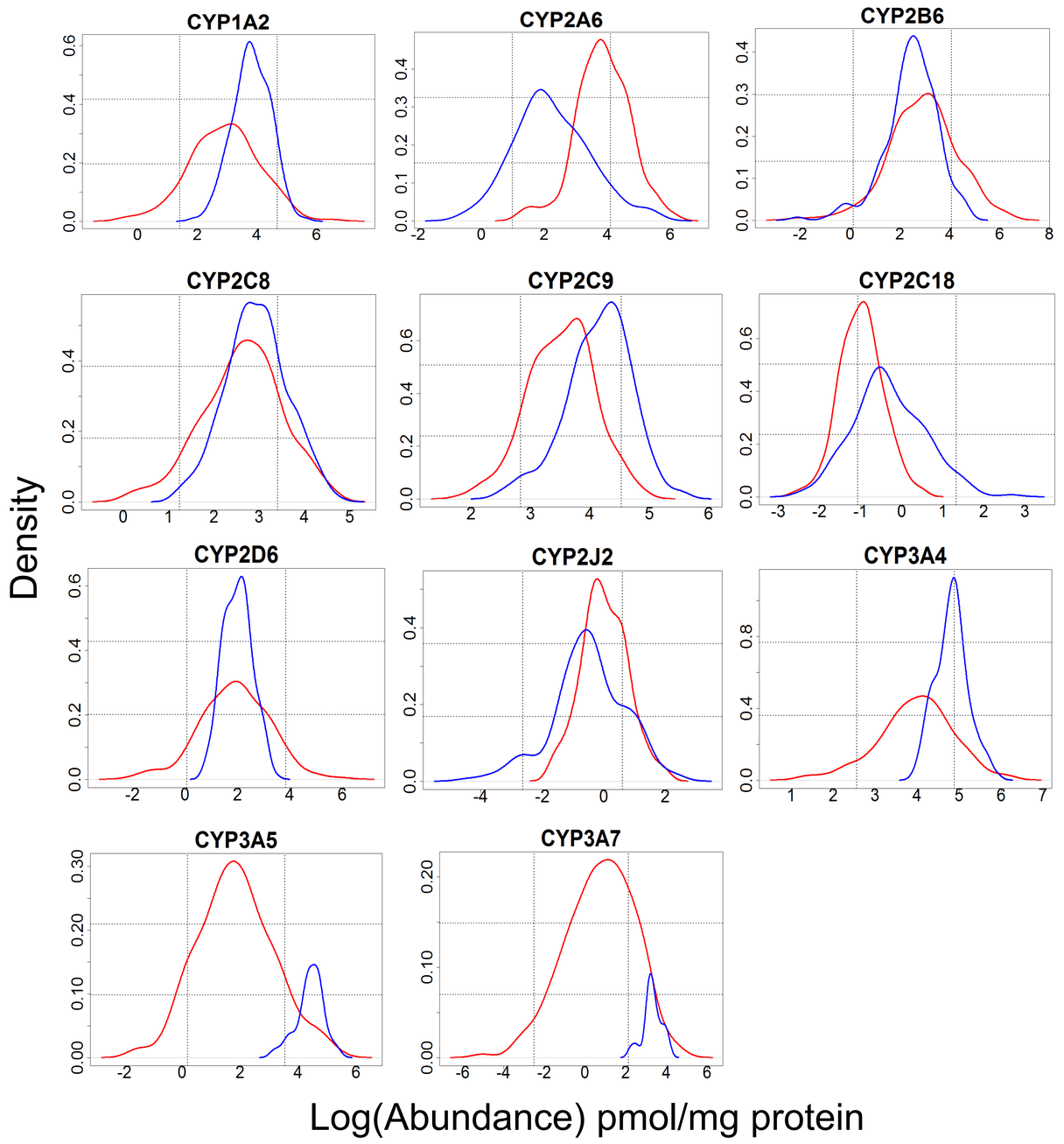

Figure 2. Kernel density estimates (via R 'density') with a Gaussian kernel showing the estimated densities of log transformed CYP abundance values for uncorrelated virtual population (Blue) and that of the correlated sample generated via covariance matrix (Red).

Conclusions

The correlation and covariance matrices for 13 CYP450 abundance values are generated and validated. It is shown that the simulated enzyme abundance values from uncorrelated and correlated distributions are dissimilar. We expect incorporation of correlations of enzyme abundances in population-based PBPK simulators results in more realistic virtual populations. This, in turn, will improve clinical study design. Further research is needed to establish inter-correlations of various transporter abundances which can have a significant impact on the drug concentration at the site of action and as a result on drug safety and efficacy.

References

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