An Approach to Incorporating Variability into a Quantitative Systems Pharmacology Model for Diabetes

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Objectives: To incorporate variability into a quantitative systems pharmacology (QSP) model for diabetes using observed patient-level data in order to generate virtual patients for trial design evaluation.

Methods: A QSP metabolism model of diabetes has been developed to simulate postprandial glucose (PPG) and HbA1c in type 1 and type 2 diabetes mellitus (DM) patients being treated with various therapies [1]. A model for variability was built by incorporating observed variability and correlations in DM patients from a large internal clinical trial database. Rather than estimate or assume variability of the underlying QSP model parameters, the output of the QSP model is instead treated only in terms of baselines and changes from baseline at discrete timepoints. This allows the observed data to be treated in a similar fashion: variabilities and correlations of the observed baselines and changes from baseline are calculated and used with the following model.

\[
\log(y_{jk}(t_k)) = (\mu_j(0) + \eta_{bkj}) + (\mu_j(t_k) - \mu_j(0)) + \eta_{ejk} + \epsilon_{ijk}
\]

An individual response at time \(t_k\) is modeled as a mean baseline plus a change from baseline, where the means \(\mu_j\) are either observed from patient-level data (for model fitting) or predicted by the QSP model (for simulation). Variabilities of between-subject (\(\eta\)) and within-subject (\(\epsilon\)) random effects are estimated from the data, along with the correlations between HbA1c and PPG random effects. The model was then used to simulate virtual patient data to be fed into trial design evaluation.

Results: The model with additive (on a log scale) change from baseline and additive between- and within-subject variability fit the observed data well, as exemplified by visual predictive checks (VPCs) (Figure 1).

Figure 1. VPCs of variability models for prediction-corrected, log-transformed (A) HbA1c and (B) PPG. Observed data is shown by solid (median) and dashed (2.5th and 97.5th percentiles) red lines. 95% confidence intervals of the simulated data’s percentiles are shown by red (median) and blue (2.5th and 97.5th percentiles) shaded areas.

Conclusions: A highly empirical approach to adding variability and correlation to the output of a QSP metabolism model resulted in a practical methodology that can generate predicted study population distributions suitable for statistical study design exercises.