Summary of Hepatic Clearance Identifiability

The central result of the work completed so far is that the addition of an insulin bolus to plasma increases the identifiability of (hepatic insulin clearance) and (first-pass hepatic clearance).

Two sets of patients are assessed:

* N=10 from DISST study (“Christchurch”)
* N=10 from CREBRF study (“Auckland”)

The practical identifiability of and in a system is assessed by performing a grid search over a range of () values. Each pair of parameter values is used to simulate the plasma insulin concentration over time; each simulation is then compared to the insulin assay data, producing an error surface over a range of parameter values. The mean squared error metric is used to compare a simulation to the data.

A system with high practical identifiability will produce an error surface with a distinct local minimum within a physiological range (, ). A system with low practical identifiability will have a large range of parameter values which give an error value close to a minimum. To assess the identifiability of the parameters in these datasets, a measure for the size of this parameter range is required.

A set of () pairs can be said to give a ‘similar’ simulation result if the difference between their simulation errors is comparable to that expected by standard assay error. A *minimum error region* for an error surface is therefore defined as being all points that are ‘similar’ to its local minimum, as found by the grid search.

To investigate the relationship between assay error and simulation error for a given patient, a Monte Carlo experiment with 1000 trials is performed. For each Monte Carlo trial, each insulin assay sample is perturbed by a normally-distributed random variable whose standard deviation is 5% of the respective assay value. The resulting data vector is then used to forward simulate the model.

(Note: is the data vector used in the -th Monte Carlo simulation. is the -th insulin assay sample. represents element-wise multiplication.)

The resulting distribution of mean squared errors represents the expected distribution of simulation errors with assay error of up to 15% on each data point. As such, one standard deviation of this distribution, , explains 68% of . Therefore, the *minimum error region* is defined as the set of all points whose simulation error is within of the local minimum.

As the same model is used in both the Christchurch and Auckland studies, any inter-study variation in the general shapes of the minimum error regions must be explained by differences in properties of the data.

The size of the minimum error region can be explained by the [graphical ID] As discussed in [graphical ID] paper, identifiability can be explained by a high level of distinction between the coefficients.

The identifiability of parameters can be assessed by comparing the profiles of their coefficients in the governing model equation:

The equation is integrated over time and rearranged:

The integrated equation is evaluated between and each time in a specified interval up until , the final time in the simulation. The distinction between coefficients, , is defined by the 2-norm of the difference between the mean-normalised coefficients at each time .

As a development to Docherty’s definition, this metric is divided by the number of time intervals over which the integral is evaluated () to normalise it and enable comparison between datasets.