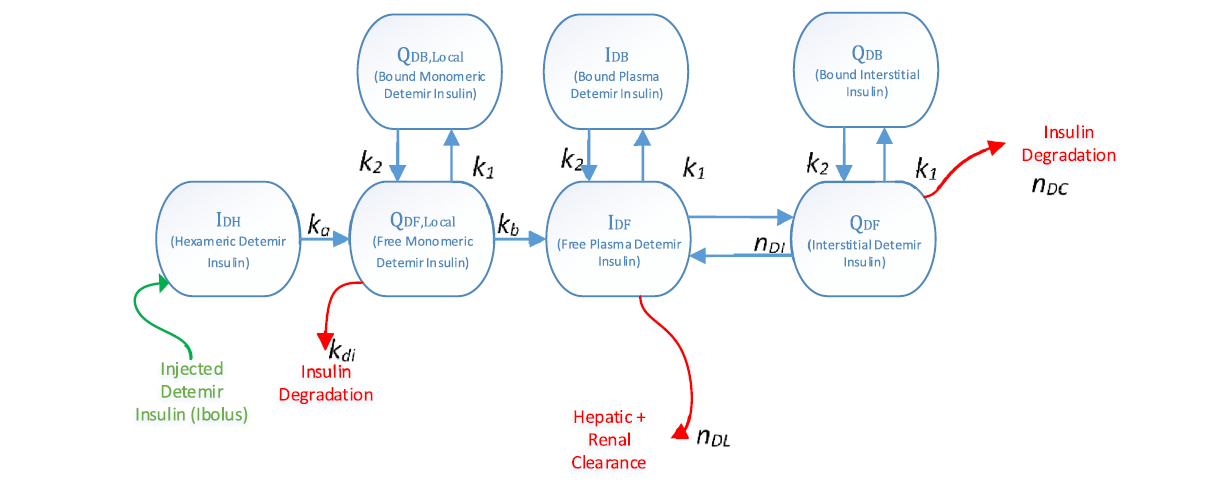
Hepatic Clearances

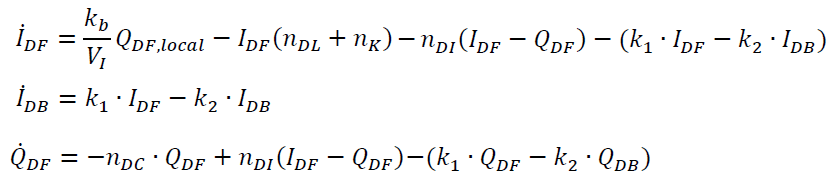
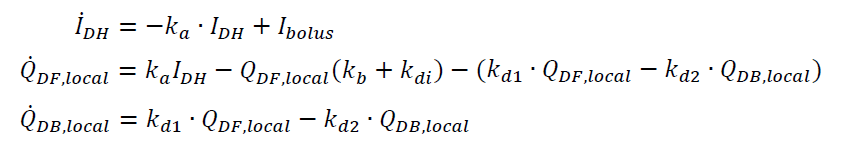
# Background

* Modelling insulin detemir

The insulin Determir model used is defined by seven compartments, each representing injected insulin Detemir in different locations, and in either bound or unbound states.



The interactions are defined by the following equations:



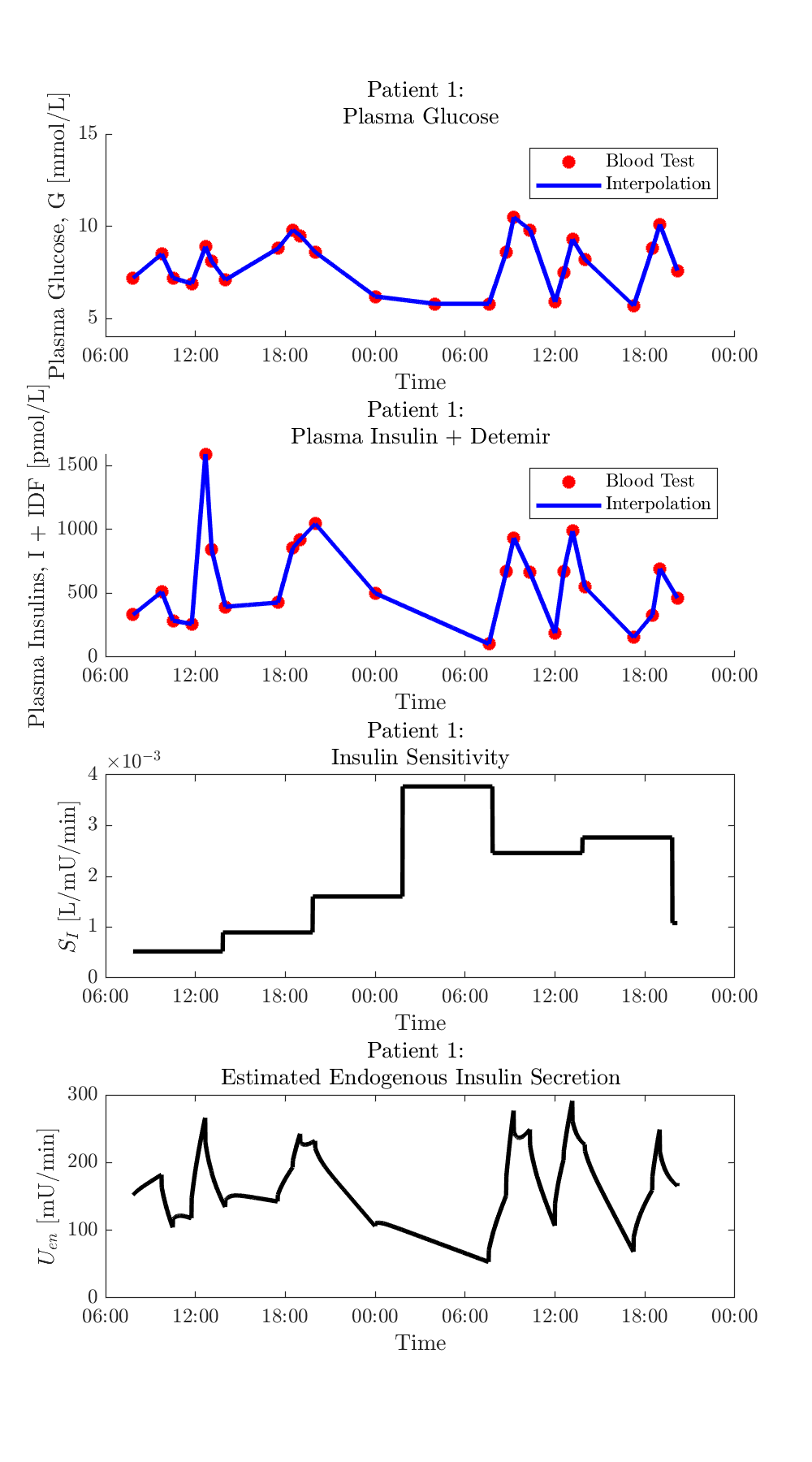
The glucose-insulin model used is:

The parameters we wish to fit are nL (hepatic insulin clearance) and xL (first-pass hepatic clearance).  
nL defines the rate that the liver clears insulin from the blood. This clearance occurs at a rate of mU/min.  
xL similarly defines the rate that insulin excreted from the pancreas () enters blood plasma. This appearance occurs at a rate of mU/min.

Measured patient data includes:

* Plasma glucose,
* Total plasma insulin,
* C-peptides,

A sample of data, with which nL and xL are fitted, is provided below:





# The Approach

* Attempting to fit nL and xL using multiple linear regression

**Preliminary Processing**

1. Use van Cauter method to estimate from measured C-peptide data.
2. Forward simulate the ID model to get (unbound insulin Detemir in plasma)
3. Subtract from measured , and interpolate over simulation time to get (human insulin in plasma)
4. Use the analytical solution for the Q equation to find :

where and .

**Fitting nL/xL**

1. Integrate the I equation and assemble into the appropriate form for fitting nL/xL
2. Solve the integrals at each minute to form A and b matrices.
3. Solve with MLR (MATLAB’s A\b) to get nL/xL.

# The Problem

## Faliure of Multiple Linear Regression

First attempts at fitting nL and xL to the entire period of data using the above process result in nL being fitted to ~0, and xL being fitted to ~1.



Physiologically, these values describe no endogenous insulin entering blood plasma, and no plasma insulin being cleared by the liver. As a result, forward simulation of the glucose-insulin model shows plasma insulin clearing to 0 (or, clearly non-physiologically, lower), and plasma glucose rapidly increasing, with no insulin presence to clear it.



Plotting each individual term of the integrated I equation highlights what’s occurring when ~nL=0 and ~xL = 1.



Figure

It is evident from this plot that the right-hand-side of the equation is dominated by the term, which just so happens to match the integral multiplying xL. While the and terms are also similar, their smaller magnitudes means that they are ultimately ignored by the least-squares fitting. This can be made clear by approximating the remaining RHS terms away:

It is apparent from this arrangement that xL = ~1 and nL ~= 0 are “sensible” values for making the LHS equal to the RHS.

To demonstrate this issue in another way, Figure 2 shows the two columns of A, as well as b, over time. It is apparent that column 2 of A is much closer to b than column 1 of A, due to the prominence of the term. It is therefore understandable that nL (coefficient of column 1 of A) is fit to ~0, explaining almost none of b; and that xL (coefficient of column 2 of A) is fit to ~1, explaining almost all of b.



Figure

## Grid Search for Better Fit

Good fit values for nL and xL can alternatively be found by grid search. Physiological ranges of nL values from 0.05 to 0.20 (in increments of 0.01), and of xL values from 0.4 to 0.7 min-1 (in increments of 0.1 min-1) comprised the grid. For each pair of values, the model was forward simulated and the mean squared error of the resulting prediction for plasma insulin was found.

For the above patient data, the pair of values resulting in the most accurate simulation was nL = 0.18, and xL = 0.4 min-1. The resulting forward simulation is shown below.



## Error Analysis

Percentage error of simulation relative to measured data points, with results as follows.

|  |  |  |
| --- | --- | --- |
| Mean % Error | MLR Fit | Grid Search |
| G | 961.3%\* | 22.6% |
| I + IDF | 94.04% | 38.5% |

\*With nL = 0 and xL = 1, G increases indefinitely, making this not a meaningful measure of accuracy.

# Further Attempts

To improve the ability of MLR to fit nL, specific integration windows were selected around the areas of highest insulin activity. The motivation this is to increase the relative significance of the terms, such that the similar requires a non-zero nL coefficient to match it.