Determining the relative efficacy of a number of PID and PD models that relate insulin secretion to bolus induced glucose excursions

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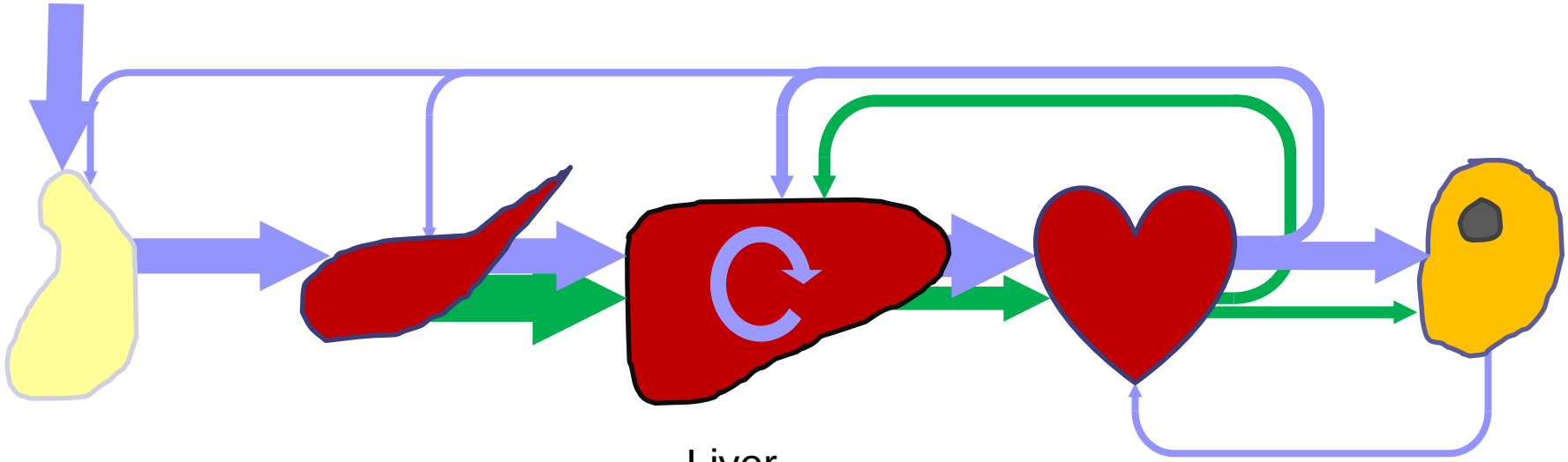
Motivation

In a healthy individual, insulin is secreted at a rate that achieves minor postprandial glucose excursions, and healthy homeostasis. The amount of insulin to be secreted is determined by a number of factors, but the most prominant are the glucose level, and the change in glucose level (gradient).



Stomach and intestines

Pancreas

Liver

Circulatory system

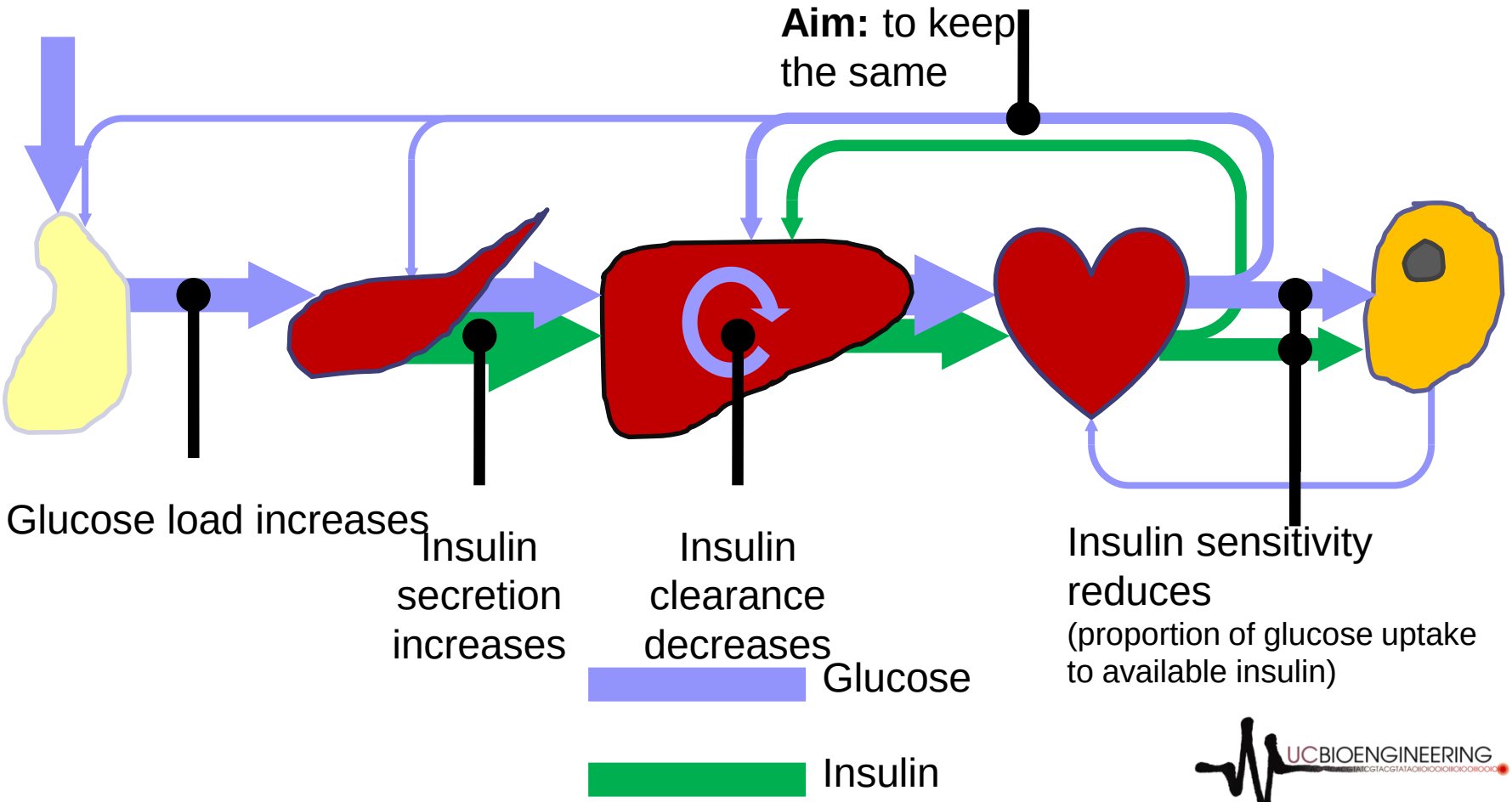
Peripheral cells

Glucose

Insulin

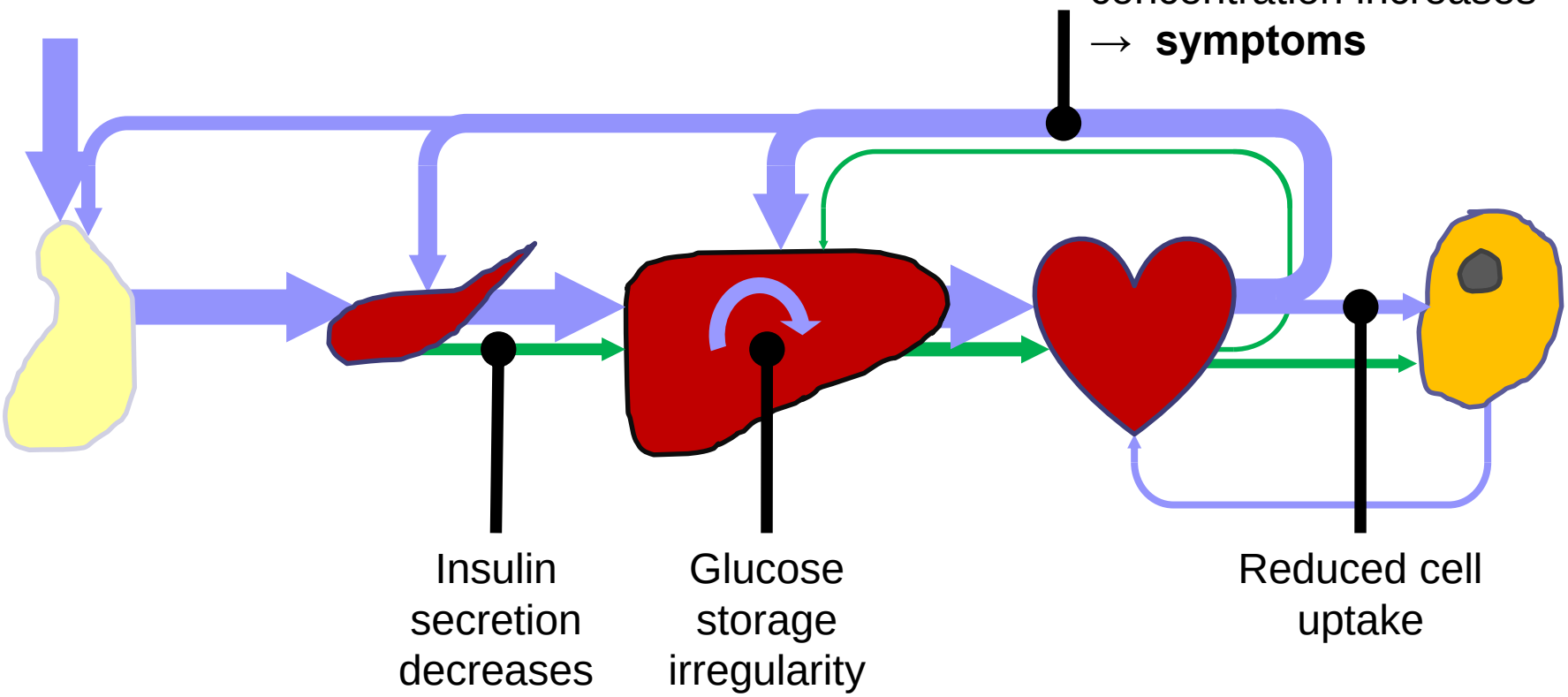
Motivation

However, as an individual progresses towards diabetes the amount of insulin required to deal with the glucose loads increases. This is ultimately driven by low insulin sensitivity



Motivation

The diabetes state has lower insulin secretion capability, and thus, glucose levels increase.



The goal of this research is to find how to effectively model these phenomena using our modelling framework.

The DISST model

The dynamic insulin sensitivity and secretion test (DISST) was developed to occupy a niche in isnulin sensitivity tests for moderate cost, but high information yield. Most models of the insulin glucose dynamic were not well-suited to the length of test that we desired, and thus, we modified exisitng models and strategies.

C-peptide: Adaptation of Van Cauters pharmaco kinetic model

Insulin: Directly description of pharmacokinetics using literature values and patient-specific variables

Glucose: An adaptation of the Minimal Model with differing patient-specific parameters.

The DISST model

Measured: G, I, C , U_X, P_X

a-priori: $k_{1\text{-}3}$, n_K, n_C, n_I, V_P, V_Q, a_I, p_G

Simulated: Q, Y

Identified: U_N, n_L, x_L, V_G, SI

Plasma C-peptide

$$\dot{C} = k_2 Y - (k_1 + k_3)C + \frac{U_N}{V_P}$$

Interstitial C-peptide

$$\dot{Y} = k_1 C - k_2 Y$$

Plasma insulin

$$\dot{Q} = \frac{n_I}{V_Q}(I - Q) - n_C Q$$

Interstitial insulin

$$\dot{I} = -n_K I - n_L \frac{I}{1 + \alpha_I I} + \frac{n_I}{V_P}(Q - I) + \frac{U_X}{V_P} + (1 - x_L)\frac{U_N}{V_P}$$

Glucose

$$\dot{G} = -p_G(G - G_B) - SI(GQ - G_B Q_B) + \frac{P_X}{V_G}$$

The DISST model adaptation

The current research considers new models of insulin secretion where the degree of PID_{UB} PID_{UB}secretion is defined by the glucose states.

PID_{UB}

$$U_N = U_B + \phi_P (G - G_B) + \phi_I \int_0^t G - G_B dt + \phi_D \left\langle \frac{dG}{dt} \right\rangle$$

PD_{UB}

$$U_N = U_B + \phi_P (G - G_B) + \phi_D \left\langle \frac{dG}{dt} \right\rangle$$

PID_{only}

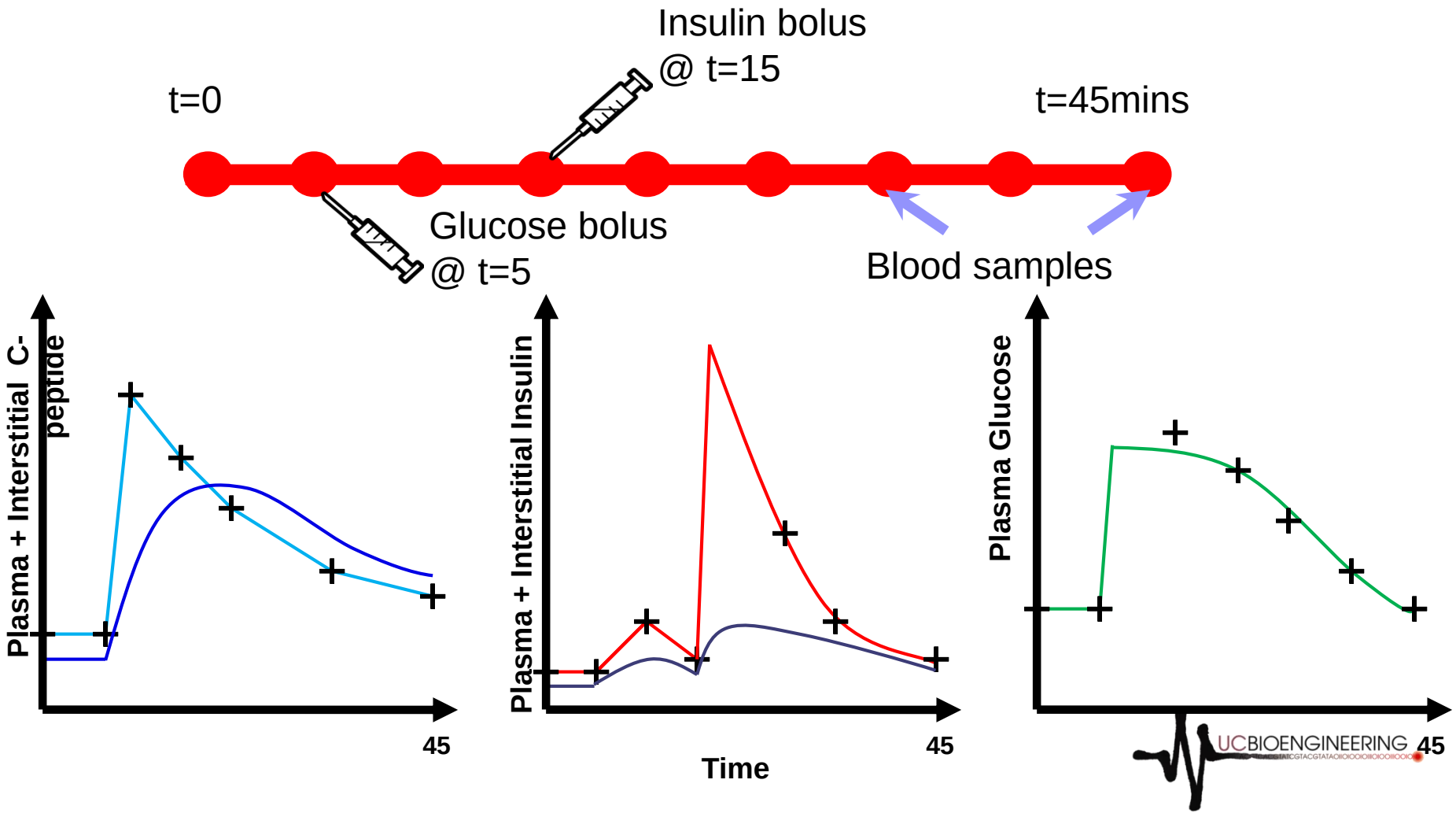
$$U_N = \phi_P G + \phi_I \int_0^t G - G_B dt + \phi_D \left\langle \frac{dG}{dt} \right\rangle$$

PD_{only}

$$U_N = \phi_P G + \phi_D \left\langle \frac{dG}{dt} \right\rangle$$

The DISST

The DISST is effectively a short duration IM-IVGTT that measures glucose, inuslin and C-peptide at 5-10 minute intervals.



Clinical data

- We are using data from an maco-nutrient (dietary fibre) intervention.
- 82 female particiapnts. All had a BMI greater than 25, or identified as at risk of diabetes via other means.
- Each undertook 3 tests over 10 weeks yielding 200 tests.
- Details in: Te Morenga *et al.* 2010 Effect of a relatively high protien high fibre diet on body composition and metaboic risk factors in overweight women. Eur J Clin Nutr 64(11) 1323-31

Parameter Identification Approach

1. Initially, a deconvolution (direct inversion) approach was undertaken to develop an estimate of U_N.

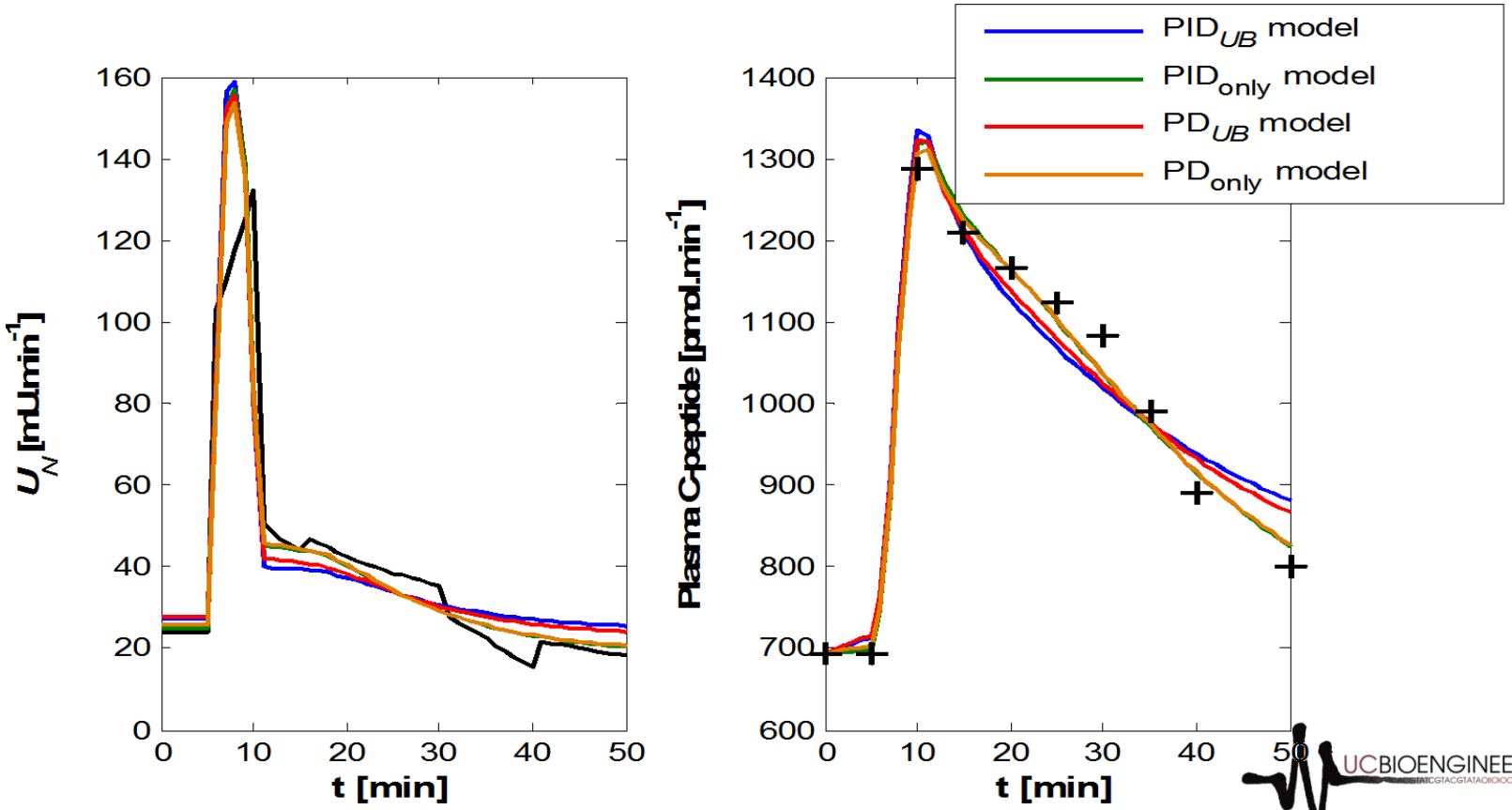
2. The iterative integral method was then used to identify insulin pharmacokinetic parameters. (Docherty 2012 MBEC 50(2))

3. The Gauss-Newton approach was then used to identify parameters of the Glucose model.

4. Finally, the glucose profile determined is used to model U_N against the measured C-peptide values using the IIM.

Outcomes

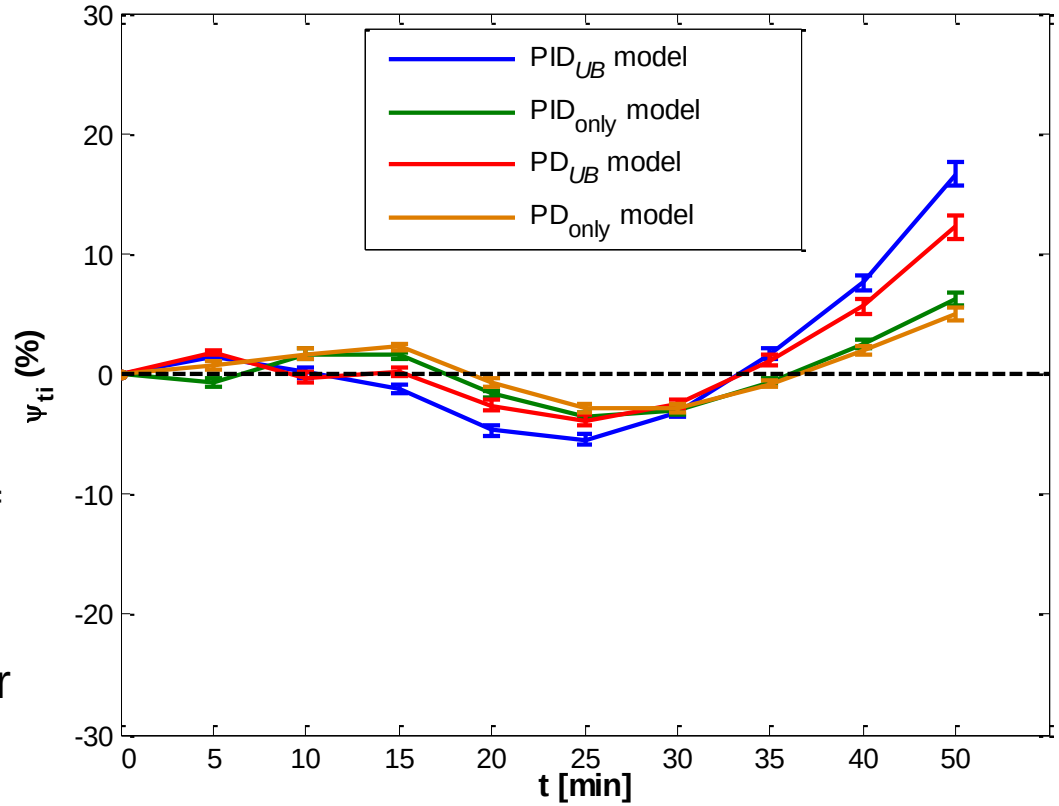
The model was succesfully identifed and yielded simulations that effectively met the data-points within about 2x the CV of the assay. The model roles effectively caught the sharp increase in the rate of production after the bolus, and were modulated effectively by the current levels of glucose in the blood.



Outcomes

The residuals indicate that the broadly adhered to the data but also yielded the following insights:

- There are clearly unmodelled phenomena.
- The integral term doesnt help much – just a little
- Determining a steady state U_B actually reduces the precision of the model. Hence a linear secretion responce to total glucose rather than glucose over basal is appropriate.



Interpretation

- PD models with potentiation factors have previously been mooted as a possibility by a number of groups.

- Using standard PID approaches to model the pancreatic responses to glucose excusions yields outcomes that fit data obtained by the DISST test relatively well.

- There are unmodelled factors that imply non-linearity in response at higher glucose levels – potentially, Michaelis-menton saturation.

- Very simple modelling of the fasting state yields the best residuals. Overall, we found that the best model was also the simplest!

$$U_N = \phi_P G + \phi_D \left\langle \frac{dG}{dt} \right\rangle$$

Future work

1. Develop the methods to work in tandem across IV and oral tests – investigate incretin.

2. Incorporate recently developed interpretation of the basal state of glucose for individuals with established diabetes.

3. Consider methods of reducing clinical intensity while retaining clinically relevent outcomes.

4. Characterise changes in ϕ_P, ϕ_D and ϕ_I during the pathogenesis of diabetes

5. Enhance parameter identification techniques to optmise all parameters concurrently.

Many thanks!

Many thanks for listening to my *hastily* prepared presentation!

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Questions?

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