Master thesis : INSULIN SENSITIVITY TESTING MODEL - BASED SUBCUTANEOUS - ORAL INSULIN SENSITIVITY TESTING

Auteur : Bekisz, Sophie
Promoteur(s) : Desaive, Thomas
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Insulin Sensitivity Testing

Model-Based Subcutaneous-Oral Insulin Sensitivity Testing

SOPHIE BEKISZ

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Under the supervision of Prof. Mr Thomas Desaive and Prof. Mr J. Geoffrey Chase

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The prevalence of diabetes, particularly Type 2 Diabetes (T2D), is dramatically rising and reaching epidemic proportions. Diabetes and its complications are thus become a major public health problem, with an economic cost of approximately 1 % of Growth Domestic Product (GDP), and equal social burden. Pathogenesis of type 2 diabetes includes insulin resistance, or low insulin sensitivity, describing the impaired capacity of the body to regulate glucose. Insulin resistance develops long before the final state of the disease. The diagnosis of pre-diabetes and eventual T2D is thus possible years before type 2 diabetes eventuates. Irreparable damage can be prevented by early detection, offering the opportunity to delay or eliminate development of diabetes, reducing cost and social burden.

Current diabetes tests do not use insulin sensitivity directly but detect the disease on the basis of late-appearing symptoms, particularly rising glucose levels, when it is already in a critical, near diabetes situation, or later. Among these diagnosis tools, the Oral Glucose Tolerance Test (OGTT) is the most recommended and able to detect pre-diabetes. In contrast, insulin sensitivity tests are either low resolution, and/or costly, invasive, time-consuming, and not adapted for a large population screening, However, the Dynamic Insulin Sensitivity and Secretion Test (DISST) is a power model-based diagnostic tool without these issues, but could potentially be made much simpler.

This master thesis is part of a larger research project at the University of Canterbury (Christchurch, New Zealand), aiming at translating the DISST model-based test to a less invasive version. The proposed protocol uses 35 g of

oral glucose and 2 units of rapid-acting insulin. The insulin injection is performed subcutaneously with a needle free and painless injection device. The number of blood samples is reduced and some are extracted with less invasive finger-prick methods with an eye toward eventual needle free sensing technology under development. Blood samples are collected over a 2-hour period and assessed for blood glucose, C-peptide and insulin. This model-based subcutaneous-oral insulin sensitivity testing would allow direct identification of the insulin sensitivity and thus provide crucial information about diabetes status and progression. It would also enable the same low-cost hierarchy of tests like the DISST.

The DISST model is originally a glycaemic control model. It is modified in this research to consider oral glucose absorption and subcutaneous insulin injection kinetics as employed in this new test. A gastrointestinal glucose sub-model, a subcutaneous insulin delivery sub-model, and a glycaemic control sub-model are thus combined. Even though these different sub-models have been validated separately, the overall system model needs validation, which is the main goal of this research.

A sensitivity analysis is performed to demonstrate the robustness of the model, as well as the potential accuracy of this new kind of Dynamic Insulin Sensitivity and Secretion Test (DISST). It identifies critical, sensitive model parameters in the context of the combined overall system model. This *in silico* investigation also provides a means to highlight any model and protocol weakness.

A single parameter sensitivity analysis is conducted first, where the effects of model parameters on model outcomes are analysed individually. Parameters with the biggest influence on blood glucose evolutions are identified. Changes of parameters always lead to a coherent modification of blood glucose evolution and no non-physiological behaviour is observed, providing initial model validation. Clinically significant modifications are not detected for most parameters.

The results of this single parameter sensitivity analysis are used to perform a multiple parameter Monte Carlo investigation. This study defines the potential range and resolution of the overall system model, as well as the inter-subject and intra-subject variability. This analysis consolidates the model validation. The multiple parameter sensitivity analysis is then applied to the now validated model to assess protocol safety.

Because the trial received ethics approval during the writing of this master thesis (April 30, 2018), I have been able to assist the first experimental assay practically using the model. The first clinical pilot test, carried on subject 1, is described. With the results obtained, a rapid parametric identification is performed to assess insulin sensitivity and further validate the model developed. However, as those experiments are still in their early days, the aim of this part of the project is more related to a proof of concept of the model, as well as a personal achievement, to see how could the model be useful for real clinical experiments.
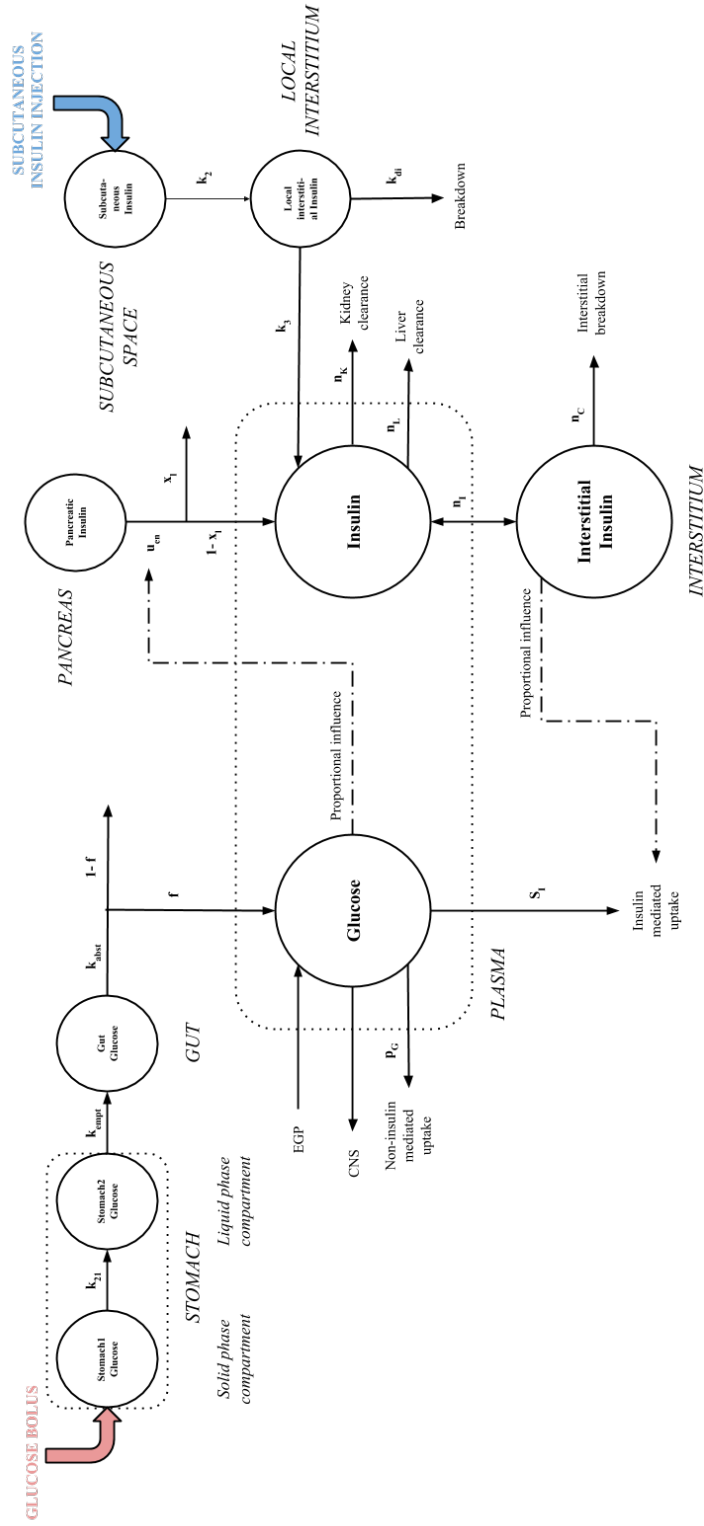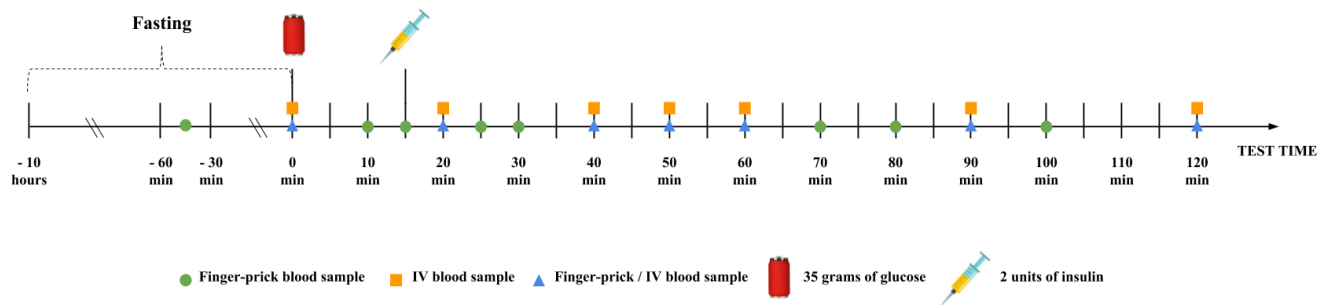
Figure 1 :

SC-OG-ICING-2 model overview.

Figure 2 :

Protocol of this new Dynamic Insulin Sensitivity and Secretion Test (DISST).
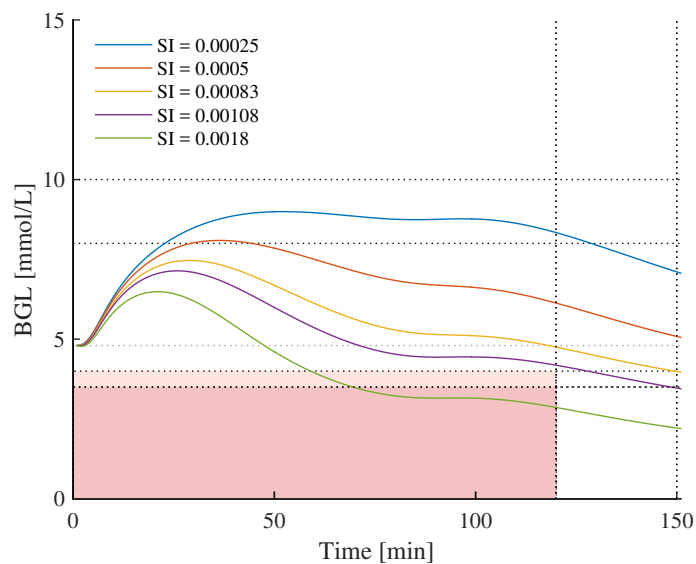

Figure 3 :

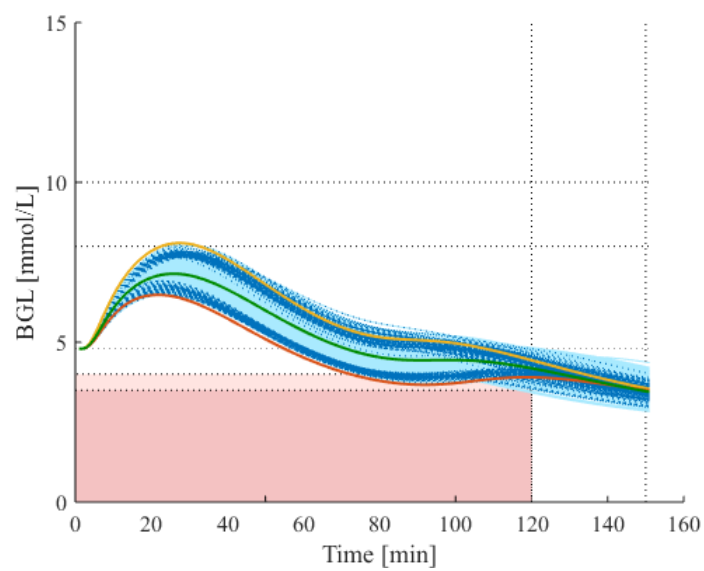*Influence of insulin sensitivity on blood glucose evolution.*

Figure 4 :

Example of multiple parameter Monte Carlo sensitivity analysis ($S_I = 0.00108$ L.(mU.minà$^{-1}$).