Available online at www.sciencedirect.com

ScienceDirect

IFAC PapersOnline CONFERENCE PAPER ARCHIVE

IFAC PapersOnLine 51-27 (2018) 86–91

Model-based Modified OGTT Insulin Sensitivity Test Design

Lui Holder-Pearson * **Sophie Bekisz** ** **Jennifer Knopp** *
Paul Docherty * **J. Geoffrey Chase** * **Thomas Desaive** **

* *Centre for Bio-Engineering, University of Canterbury, Christchurch, New Zealand (e-mail: lui.holderpearson@pg.canterbury.ac.nz).*
** *University of Liège, Liège, Belgium*

Abstract: Type 2 diabetes mellitus requires early, accurate, and efficient monitoring for best treatment. Current common diagnosis tools either test late-appearing symptoms, are low resolution, or are expensive in cost and time. A system of physiological models for the oral ingestion of glucose, subcutaneous injection of insulin, and glycaemic control, are used to generate a quantitative test for insulin sensitivity. The proposed test uses $35g$ of oral glucose, 2.0 units of rapid-acting insulin, and both intra-venous and finger-prick blood samples for insulin, C-peptides, and blood glucose levels frequently over a 2-hour period. The test is developed *in silico* to enable early and repetitive monitoring of the pathogenesis of type 2 diabetes. In conjunction with emerging technologies in insulin sensing and needle-free delivery and monitoring devices, there is a pathway with this test to provide more effective, efficient early diagnosis of diabetes risk.

Keywords: chronic diabetes care, physiological model, insulin, insulin sensitivity, OGTT

1. INTRODUCTION

Identification and monitoring of disease pathogenesis is essential to guide physicians' treatment options. The disease process of type 2 diabetes mellitus (T2D) is a chronic condition requiring regular monitoring for most appropriate treatment. As well as the chronic nature of T2D, the scale of the disease is also a factor increasing the necessity of efficient, accurate monitoring. A meta study of 751 studies that considered 4.4 million people showed that from 1980 to 2014 there was a global increase from 4.3% to 9.0% in the incidence of T2D. The global trend was not seen to be slowing (NCD Risk Factor Collaboration et al., 2016).

The pathogenesis of the disease, as can be seen in Figure 1, deviates from normal glucose tolerance (NGT) with a decrease in insulin sensitivity. This change is masked in the glycaemic control by an increase in the amount of insulin secreted by the pancreas. This stage is known as pre-diabetes, or impaired glucose tolerance (IGT). Because of the compensation of the pancreas, this aspect is not detected in measuring gross ability to control blood glucose levels (BGLs). As the disease progresses, the ability of the pancreas to create and secrete insulin saturates, and then decreases (Clark et al., 2001) causing the inability to regulate glucose, at which point T2D can be diagnosed.

The most common tests currently used for T2D are based on the ability to control blood glucose: either fasting BGL, or HbA1c, which is in essence a low-pass filter of BGL. The nature of these tests are unable to obtain quantifiable results for insulin secretion nor sensitivity, which are the key early-changing metrices. A more comprehensive test which specifically examines the post-prandial glucose is the oral glucose tolerance test (OGTT). The OGTT typically

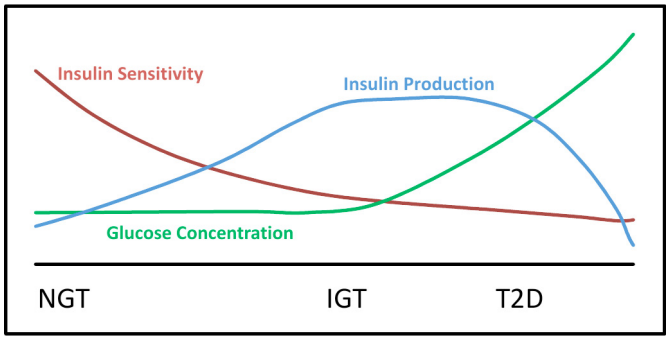

Fig. 1. Pathogenesis leading to type 2 diabetes mellitus (Docherty, 2011).

involves consuming 75g of liquid glucose, and taking blood glucose measurements at 0, 60, and 120 minutes. However, for early recognition of IGT as can be seen in Figure 1, either the insulin sensitivity or the amount of insulin secreted must be determined. Current common methods include giving the patient significant amounts of parenteral glucose or insulin, and then determining the rate of infusion of insulin or glucose, respectively, which results in a consistent BGL.

Insulin sensitivity is defined as the relative change of concentration of glucose due to uptake by skeletal muscle over a given time, for a given concentration of insulin.

Detection of pre-diabetes during the early IGT stage allows early treatment, which is achievable given a quantitative test for insulin sensitivity. For some time there has been evidence to suggest early treatment of pre-diabetics with insulin results in better outcomes, both in terms of cessation of the disease process and also reducing the inci-

10.1016/j.ifacol.2018.11.662

dence of complications associated with diabetes (ORIGIN Trial Investigators and others, 2012).

To treat pre-diabetes, effective identification is required. The test protocol designed here attempts to create such a test to allow widespread testing at a minimal cost. Furthermore it would allow definitive information into the progression of the disease, leaving behind the contemporary 'yes-no-maybe' testing style most commonly used. The test proposed here is an oral glucose test with subcutaneous (SC) insulin. The addition of insulin provides a greater signal strength to distinguish between IGT with a low S_I, and IGT with a low endogenous insulin production, thus accurately diagnosing within pre-diabetes.

2. MODELLING

To model the entire system for the test, a gastrointestinal (GI) glucose model, a SC insulin delivery model, and glycaemic control model are combined. A graphical overview of this system can be seen in Figure A.1 — at the end of the paper for convenience.

2.1 GI modelling

The GI model system uses a three-compartment non-linear model with compartments q_{sto1}, q_{sto2}, and q_{gut}, the value of which represents the amount of glucose in each respective compartment (Dalla Man et al., 2006). Specifically, q_{sto1} and q_{sto2} represent the solid and the liquid stages of the stomach respectively, and q_{gut} the glucose which has passed into the intestines. The model is defined:

$$\begin{aligned} \dot{q}_{sto1}(t) &= -k_{21} \cdot q_{sto1}(t) + D\delta(t) \\ \dot{q}_{sto2}(t) &= -k_{empt}(q_{sto}) \cdot q_{sto2}(t) + k_{21} \cdot q_{sto1}(t) \\ \dot{q}_{gut}(t) &= -k_{abs} \cdot q_{gut}(t) + k_{empt} \cdot q_{sto2}(t) \\ Ra(t) &= f \cdot k_{abs} \cdot q_{gut}(t) \end{aligned} \tag{1}$$

In Equation Set 1, k_{21} is the rate constant of grinding, D the amount of glucose ingested, δ the dirac delta, k_{abs} the rate at which glucose is absorbed from the gut into the blood stream, Ra is the rate at which glucose appears in the blood stream, and f a scaling factor which accounts for incomplete absorption and first-pass hepatic clearance. The rate at which the stomach empties into the gut — k_{empt} — is a function of the total amount of remaining glucose in the two stomach compartments relative to D, defined:

$$\begin{aligned} k_{empt}(q_{sto}) &= k_{min} + \frac{k_{max} - k_{min}}{2} \cdot \{tanh\big[\alpha(q_{sto} - b \cdot D)\big] \\ &\quad - tanh\big[\beta(q_{sto} - c \cdot D)\big] + 2\} \\ q_{sto}(t) &= q_{sto1}(t) + q_{sto2}(t) \\ \alpha &= \frac{5}{2 \cdot D \cdot (1-b)} \\ \beta &= \frac{5}{2 \cdot D \cdot c} \end{aligned} \tag{2}$$

The constants b and c are defined as the points at which k_{empt} intersects k_{mean}; the mean of k_{max} and k_{min}. The non-linear behaviour of Equation Set 2 can be seen graphically in Figure 2. Because the test developed here uses only glucose dissolved in liquid, the grinding constant $k_{21} = 1$ bypasses the solid phase.

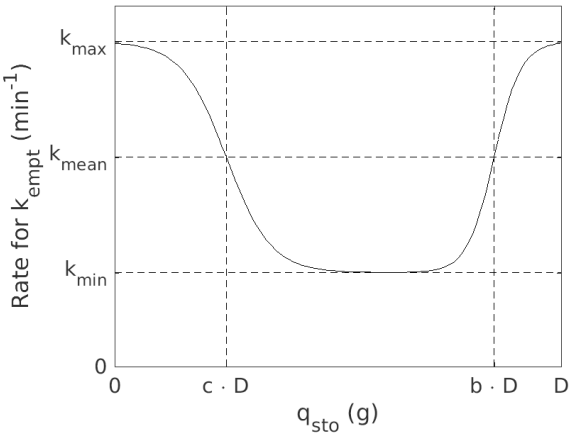

Fig. 2. Depiction of k_{empt} as a function of q_{sto}.

2.2 SC insulin model

Because the SC insulin used in the test is a monomeric preparation, the model is simplified from other insulin formulations (Wong et al., 2008) to only two compartments; the subcutaneous space into which the insulin is injected — I_{SC} — and the local interstitium Q_{local}. It is important to note the local interstitium is a separate compartment from the interstitium within the glycaemic control model. There is a small amount of breakdown within the local interstitium prior to being absorbed into the bloodstream, but it is assumed the local interstitium is sufficiently small to be negligible in glucose uptake. Mathematically, the governing equations are defined:

$$\begin{aligned} \dot{I}_{SC}(t) &= -k_2 \cdot I_{SC}(t) + \delta(t - T) \cdot I_{bolus} \\ \dot{Q}_{local}(t) &= -k_3 \cdot Q_{local}(t) + k_2 \cdot I_{SC}(t) - k_{di} \cdot Q_{local}(t) \end{aligned} \tag{3}$$

Where k_2 is the rate constant defining the diffusion from the SC space into the local interstitium, T the time the insulin is given relative to the start of the test, I_{bolus} the amount of insulin injected, k_3 the rate constant defining the insulin being absorbed into the plasma, and k_{di} the breakdown of insulin in the local interstitium.

2.3 Glycaemic control model

The inputs from both the oral glucose and SC insulin models are subsequently handled by the glycaemic control model (Lotz et al., 2008). The glycaemic control model as shown in Equations 4 – 6 takes into account glucose uptake both mediated by insulin and not, and insulin secretion and uptake. It incorporates compartments for plasma glucose, G, plasma insulin , I, and interstitial insulin, Q, and is defined:

$$\dot{G}(t) = -p_g \cdot (G(t) - G_{fast}) - \frac{S_I \cdot G(t) \cdot Q(t)}{1 + \alpha_G \cdot Q(t)} + \frac{Ra(t) + EGP - CNS}{V_G} \tag{4}$$

$$\dot{I}(t) = - n_K \cdot I(t) - n_L \cdot \frac{I(t)}{1 + \alpha_I \cdot I(t)} - n_I \cdot (I(t) - Q(t)) + \frac{k_3 \cdot \dot{Q}_{local}(t) + (1 - x_L) \cdot u_{en}(G)}{V_I} \tag{5}$$

$$\dot{Q} = n_I\big(I(t) - Q(t)\big) - n_c \cdot Q(t) \tag{6}$$

Where in Equation 4, p_g is the non-insulin mediated uptake, G_{fast} is the fasting BGL, S_I is the insulin sensitivity, EGP is the endogenous glucose production, CNS the glucose consumption attributed to the central nervous system, and V_G the volume of distribution of glucose, and α_g the insulin binding saturation constant. EGP is iteratively solved such that at $G(t) = G_{fast}$, and with no exogenous glucose nor insulin, the system is in steady state. In Equation 5, n_K is the renal insulin clearance, n_L the hepatic insulin clearance rate, α_I the hepatic clearance saturation constant, n_I the trans-endothelial diffusion rate between the plasma and interstitial compartments, x_L the first pass constant as endogenous secretion, u_{en}, is secreted into the portal vein, and V_I the volume of distribution of insulin. In Equation 6 n_c is the insulin degradation rate.

Endogenous insulin secretion by the pancreas is modelled as a simple limited, proportional response depicted in Figure 3, and defined:

$$u_{en}(G) = \left\{ \begin{array}{ll} u_{min}, & \text{for } G(t) \leq G_{fast} \\ f(G), & \text{otherwise} \\ u_{max}, & \text{for } f(G) \geq u_{max} \end{array} \right\}, \tag{7}$$
$$f(G) = k_{sec} \cdot G(t) + k_{offset}$$

Fig. 3. Endogenous pancreatic release as a function of the blood glucose level.

As C-peptide and insulin are secreted in equimolar quantities, the the rate of secretion of C-peptide can be directly ascertained from Equation 7.

Units and example values parameters in Equations 1 - 7 can be seen in Table 1.

Table 1. Values used for the forward simulation of NGT, IGT, and T2D subjects. Sources: (1) - Dalla Man et al. (2006), (2) - Wong (2008), (3) - Lotz et al. (2008), (4) - Docherty (2011), (5) - Pretty (2012). Note A: Test design parameters. Note B: Measured. Note C: Solved for in steady state.

Parameter	Value	Units	Source
Gut			
k_{21}	1.0	min^{-1}	(1)
D	35	g	A
k_{abs}	0.205	min^{-1}	(1)
b	0.85	-	(1)
c	0.25	-	(1)
k_{max}	0.043	min^{-1}	(1)
k_{min}	0.013	min^{-1}	(1)
SC Insulin			
k_2	0.0104	min^{-1}	(2)
k_3	0.060	min^{-1}	(2)
T	15	min	A
I_{bolus}	2000	mU	A
k_{di}	0.006	min^{-1}	(2)
ICING			
p_g	0.04	min^{-1}	(3)
G_{fast}	4.8	$mmol \cdot L^{-1}$	B
S_I	10.8	$10^{-4} L \cdot (mU \cdot min)^{-1}$	(4)
	6.9	IGT	
	3.1	$T2D$	
EGP	0.96	$mmol \cdot min^{-1}$	C
CNS	0.30	$mmol \cdot min^{-1}$	(3)
V_G	12.2	L	(3)
α_G	0.0154	min^{-1}	(3)
n_K	0.060	min^{-1}	(3)
n_L	0.0324	min^{-1}	(3)
α_I	0.0017	$L \cdot mU^{-1}$	(3)
n_I	0.006	min^{-1}	(3)
x_L	0.67	-	(3)
n_c	0.032	min^{-1}	(3)
V_I	4.0	L	(3)
u_{min}	16.7	$mU \cdot min^{-1}$	(5)
u_{max}	267	$mU \cdot min^{-1}$	(5)
k_{sec}	14.9	$mU \cdot L \cdot (mmol \cdot min)^{-1}$	(5)
	25	IGT	
	4.1	T2D	
k_{offset}	-50	$mU \cdot min^{-1}$	(5)
	-75	IGT	
	-13	T2D	
Initial			
q_{sto1}	D	g	A
q_{sto2}	0	g	
q_{gut}	0	g	
I_{SC}	0	mU	
Q_{local}	0	mU	
G	G_{fast}	$mmol \cdot L^{-1}$	B
I	15	$mU \cdot L^{-1}$	B
Q	9	$mU \cdot L^{-1}$	C

3. RESULTS

Combining these models and using the parameters and typical parameter values defined in Table 1, a forward simulation can be carried out for the consumption of a sugary drink and the injection of small amount of SC insulin. The results of the simulation done using numerical integral methods can be seen in Figure 4. These are done with variance in the species with greatest clinical relevance for the pathogenesis of T2D.

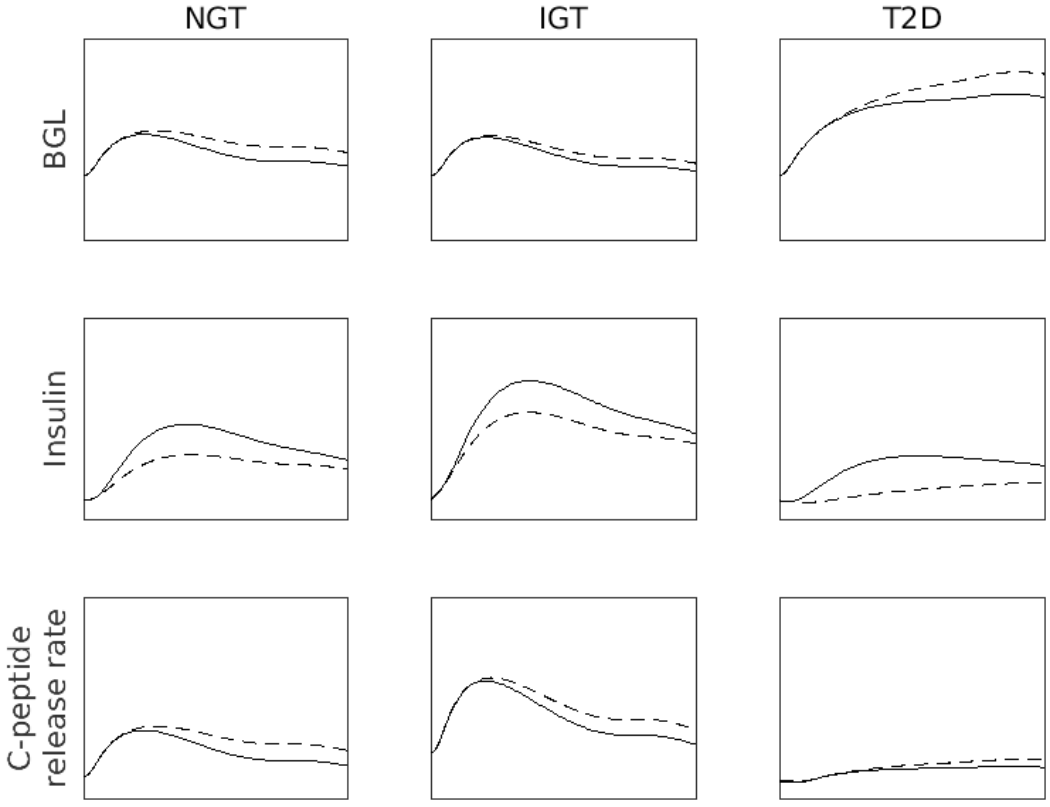

Fig. 4. Simulated comparison of the $35g$ OGTT (dashed line) with the modified test (solid line), in each of blood glucose levels, plasma insulin concentrations, and rate of C-peptide release as function of time, over a period of 120 minutes. The test is demonstrated for participants each with normal glucose tolerance, impaired glucose tolerance, and type 2 diabetes.

4. CLINICAL TRIAL

From analysis of literature for a range of parametric values a test for determining insulin sensitivity is proposed using the physiological model defined here. The test is similar to both the OGTT, and the more recently-developed DISTq (Docherty et al., 2013). The test differs from the OGTT in that instead of simply measuring BGL at time 0, 60, and 120 minutes, the BGL is done at a higher frequency throughout the 120 minutes, and insulin and C-peptides are also assayed. It differs from DISTq in that the glucose is delivered enterally and the insulin subcutaneously, and due to much slower appearance rates must therefore be conducted over a longer period of time.

Based on the results from forwards simulations such as those presented in Figure 4, an initial experimental test protocol was designed. This protocol involves ingesting $35g$ of dissolved glucose at time $t = 0$, followed 15 minutes later by a 2.0 units of rapid-acting monomeric insulin delivered via SC injection. Intra-venous blood species monitoring includes C-peptides taken intra-venously at $t = 0, 20, 40, 50, 60, 90, 120$, and point of care BGL tests at $t = -15, 0, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80, 90, 100, 120$. This protocol has been selected because it allows the examination of variability of glucose and insulin appearances, in addition to overall model validity. The data will also provide a proof-of-concept for the ability to quantify insulin sensitivity.

An application for a clinical trial to perform the test *in vivo* is currently before the University of Canterbury Human Ethics Committee. This will obtain data from up to 20 healthy subjects and 5 with an existing diagnosis of pre-diabetes or T2D. This will allow the results of the test to be demonstrated over a range of the pathogenesis of T2D. Information from this initial study will also future protocols with significant downsampling to be determined.

5. DISCUSSION

Figure 4 shows the *in silico* simulation responding appropriately to both the glucose and insulin. As true to Figure 1, the glucose-alone responses for both NGT and IGT are similar. However, the addition of the exogenous insulin has a greater impact with NGT, as there is still a higher insulin sensitivity compared to IGT. T2D sees a characteristically poor glucose response due to both low insulin sensitivity and secretion. As per Starling's curve (Clark et al., 2001), the insulin secretions in IGT are greater than NGT, and in T2D are very low. Overall, insulin secretion is lower for all stages of pathogenesis with the addition of exogenous

insulin. This outcome is not due to any explicit insulin suppression within the model, but instead because $u_{en}(G)$ is proportional to $G(t)$. Therefore the lowered BGL due to the action of the exogenous insulin implicitly suppresses the endogenous system. The expected C-peptide secretion rates echo this reduction of insulin secretion for each of NGT, IGT, and T2D.

By combining these models a system which estimates the principal physiological systems pertaining to glucose control, and which are affected by the pathogenesis of T2D, has been created. The individual models have all been validated independently and together through forward simulation provide results within the range of human variability, but have not been validated as one coherent system beyond *in silio* testing. Prior to the continuation of development and refinement of the test this will be done from the data obtained in the clinical trial.

There are some small, undeniable risks associated with delivering 2.0U of rapid-acting insulin. A Monte Carlo analysis has been completed over a range of reasonable physiological parameters which shows a low risk of hypoglycaemia associated with the trial. Furthermore, due to the high frequency of sampling, this will always be detected in the very early stages of hypoglycaemia.

Initially, the test will enable early diagnosis of IGT, at a resource cost somewhat greater than the OGTT. However, refinement resulting from initial trials is expected in the form of reduced sample points, confirmed safety, and a shorter test period. With advancements in insulin assay technology the cost will continue to decrease compared to the normal OGTT. The cost will only decrease with all of these refinements, and could conceivably become only slightly more expensive than the OGTT. These improvements will allow early and continuous monitoring of the disease process, and thus enable early treatment, improving patient outcomes at a lower cost to healthcare systems.

Beginning the development and refinement of this test now will allow for considerable advances with the development of other technologies. As point-of-care insulin sensing becomes more accessible (Malkoc et al., 2017), the test will be well poised to provide rapid quantifiable information about the pathogenesis of T2D. Another near-future technology which will empower the test is a needle-free insulin delivery mechanism (Ruddy et al., 2017). This would be especially powerful when combined with an automated, needle-free, point-of-care BGL sensor (Chang et al., 2015). Combining all of these technologies this test would potentially culminate into a fully-automated quantitative test for insulin sensitivity.

6. CONCLUSIONS

By combining GI, SC insulin, and internal insulin and glucose systems, a succinct model for type 2 diabetes has been developed. This system is powerful in its ability to aid both diagnosis and treatment of diabetes. The insulin sensitivity test developed will allow accurate and efficient monitoring of the pathogenesis of diabetes, and combines well with emerging technologies to further advantage it.

REFERENCES

Chang, J.H., Hogan, N.C., and Hunter, I.W. (2015). A needle-free technique for interstitial fluid sample acquisition using a lorentz-force actuated jet injector. *Journal of Controlled Release*, 211, 37–43.

Clark, A., Jones, L.C., de Koning, E., Hansen, B.C., and Matthews, D.R. (2001). Decreased insulin secretion in type 2 diabetes: a problem of cellular mass or function? *Diabetes*, 50(suppl 1), S169.

Dalla Man, C., Camilleri, M., and Cobelli, C. (2006). A system model of oral glucose absorption: validation on gold standard data. *IEEE Transactions on Biomedical Engineering*, 53(12), 2472–2478.

Docherty, P. (2011). *Evalulation and development of the DISST for numerous clinical applications*. Ph.D. thesis, Mechanical Engineering, University of Canterbury.

Docherty, P.D., Berkeley, J.E., Lotz, T.F., Te Morenga, L., Fisk, L.M., Shaw, G.M., McAuley, K.A., Mann, J.I., and Chase, J.G. (2013). Clinical validation of the quick dynamic insulin sensitivity test. *IEEE Transactions on Biomedical Engineering*, 60(5), 1266–1272.

Lotz, T.F., Chase, J.G., McAuley, K.A., Shaw, G.M., Wong, X.W., Lin, J., LeCompte, A., Hann, C.E., and Mann, J.I. (2008). Monte carlo analysis of a new model-based method for insulin sensitivity testing. *Computer methods and programs in biomedicine*, 89(3), 215–225.

Malkoc, A., Probst, D., Lin, C., Khanwalker, M., Beck, C., Cook, C.B., and La Belle, J.T. (2017). Enhancing glycemic control via detection of insulin using electrochemical impedance spectroscopy. *Journal of diabetes science and technology*, 11(5), 930–935.

NCD Risk Factor Collaboration et al. (2016). Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4·4 million participants. *The Lancet*, 387(10027), 1513–1530.

ORIGIN Trial Investigators and others (2012). Basal insulin and cardiovascular and other outcomes in dysglycemia. *N Engl J Med*, 2012(367), 319–328.

Pretty, C. (2012). *Analysis , classification and management of insulin sensitivity variability in a glucose-insulin system model for critical illness*. Ph.D. thesis, Mechanical Engineering, University of Canterbury.

Ruddy, B.P., Dixon, A.W., Williams, R.M.J., and Taberner, A.J. (2017). Optimization of portable electronically controlled needle-free jet injection systems. *IEEE/ASME Transactions on Mechatronics*, 22(5), 2013–2021.

Wong, J., Chase, J.G., Hann, C.E., Shaw, G.M., Lotz, T.F., Lin, J., and Le Compte, A.J. (2008). A subcutaneous insulin pharmacokinetic model for computer simulation in a diabetes decision support role: validation and simulation. *Journal of diabetes science and technology*, 2(4), 672–680.

Wong, X.W. (2008). *Model-Based Therapeuticsa for Type 1 Diabetes Mellitus*. Ph.D. thesis, Mechanical Engineering, University of Canterbury.

Appendix A. GRAPHICAL DEPICTION OF THE MODEL SYSTEM

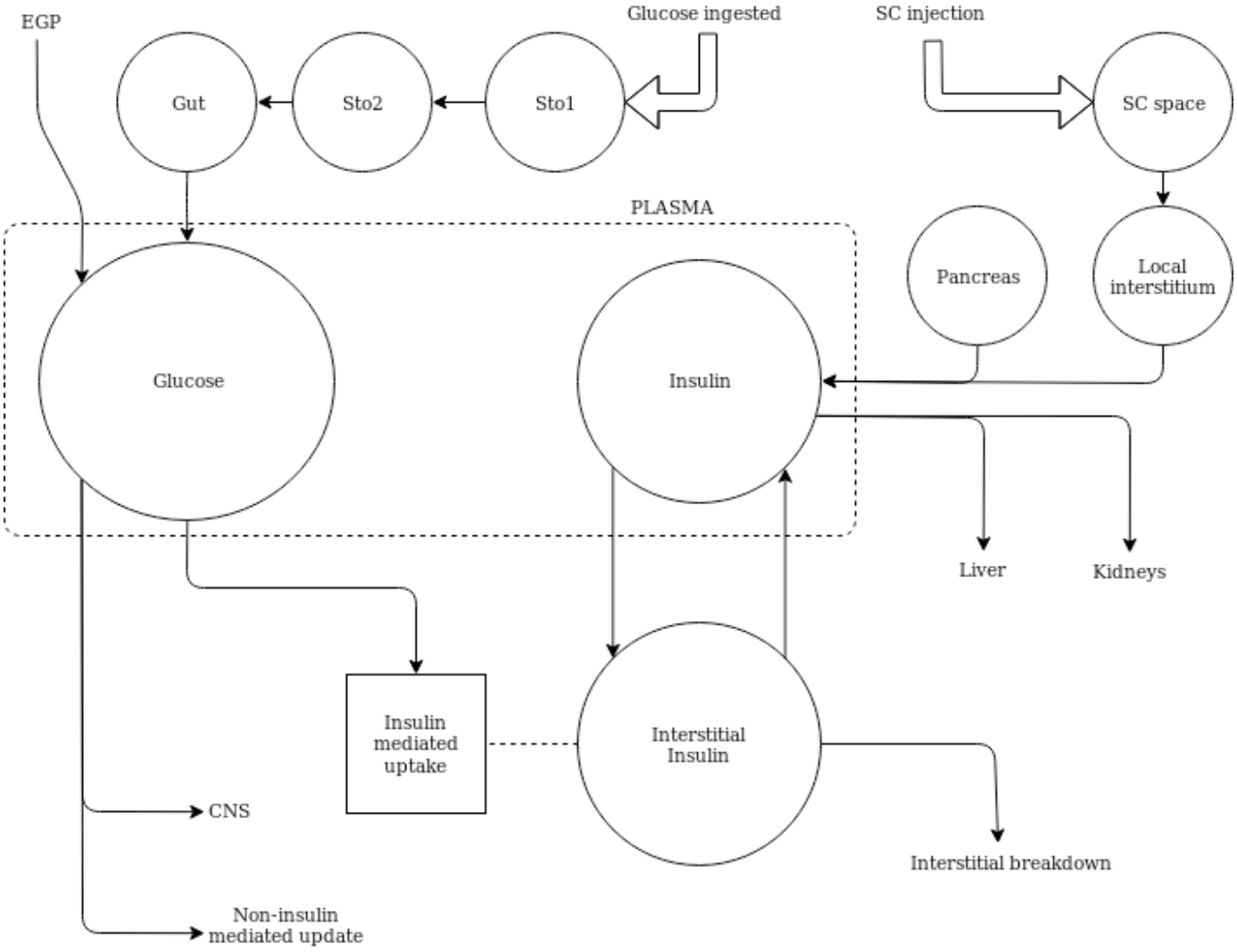

Fig. A.1. Overview of the computational models combined to form the system. Sto1, Sto2, and Gut compartments are controlled by the GI model, the SC space and local interstitium by the SC insulin model, and the glucose and both plasma and interstitial insulin compartments by the glycaemic control models.