Introduction to Diabetes Technology
Insulin Treatment for People with Type 2 Diabetes

1 What is the challenge in Type 2 Diabetes?

Type 2 diabetes (T2D) is a progressive disease, leading to the need for repeated treatment intensification. In late stage T2D, life-style changes and oral treatments become insufficient to lower blood glucose (BG) levels. Typically, the next step is to initiate insulin treatment through a lengthy titration process using daily injections of long-acting insulin. To determine the optimal daily insulin dose, patients "titrate" by increasing the daily dose over a period of a few months until the desired BG level is reached. The health care professionals (HCPs) provide patients with tables and a flow chart instructing them whether to increase or decrease the dose depending on BG measurements. Patients take home a considerable amount of paperwork to follow and fill out. This procedure requires significant work by the patient and can cause stress and confusion, which eventually leads to non-adherence. Failed insulin titration is reflected in persistent high BG levels and eventually diabetes related complications. In severe cases, these include kidney failure, blindness and amputations.

For some patients, long-acting insulin is insufficient to keep the blood glucose in check after meals. In this case, rapid-acting insulin (bolus insulin) is added to the treatment regimen by the HCP. Bolus dose calculations are based on the patient's diet and his/her physiological state. It is crucial to estimate an accurate dose, as too much insulin induces dangerously low blood glucose.

In this project, we investigate how to ease the burden on people with T2D. We simulate a virtual patient with the integrated glucose-insulin model. We examine how an insulin pump may be used to automatically find the right daily dose of long-acting insulin. Additionally, we investigate how to optimize the bolus dose based on what the patient is eating.

2 The Integrated Glucose-Insulin Model

In diabetes technology, we use models to improve the current standard of care. This can be by running virtual clinical trials to evaluate new dosing strategies and drug combinations on a cohort of simulated patients. Models may also be used to personalize treatment. This is done by fitting models to an individual's clinical data and using the identified model for dose-guidance.

Several simulation models exist for type 2 diabetes. In this project, we will focus on the Integrated Glucose-Insulin Model, often referred to as the IGI model.

2.1 Model Structure

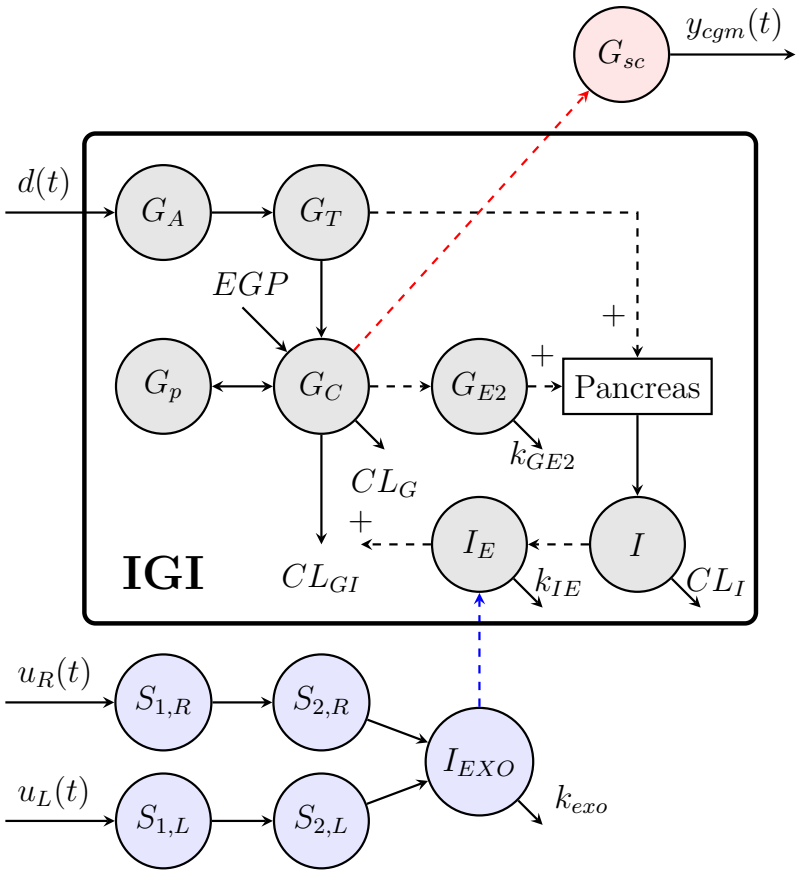

Figure 1: Model Structure for the Augmented IGI Model. The original model compartments have been augmented with absorption models for rapid- and long-acting insulin (blue) and a compartment for subcutaneous glucose concentration (red). $d(t)$ is meal intake and $u_R(t)$ and $u_L(t)$ are infusions/injections of rapid- and long-acting insulin, respectively.

2.2 Model Equations

Carbohydrate Absorption:

$$\dot{G}_A(t) = d(t)A_G - k_a G_A(t) \tag{1}$$
$$\dot{G}_T(t) = k_a G_A(t) - k_a G_T(t) \tag{2}$$

Glucose-Insulin Dynamics:

$$\dot{G}_c(t) = EGP + \frac{k_a}{M_{wG}} G_T(t) + \frac{Q}{V_p} G_p(t) \tag{3}$$
$$- \frac{1}{V_G}(CL_G + CL_{GI} I_E(t) + Q) \cdot G_c(t) \tag{4}$$
$$\dot{G}_p(t) = \frac{Q}{V_G} G_c(t) - \frac{Q}{V_p} G_p(t) \tag{5}$$
$$\dot{G}_{E2}(t) = k_{GE2} \frac{G_c(t)}{V_G} - k_{GE2} G_{E2}(t) \tag{6}$$
$$\dot{I}(t) = CL_I \cdot I_{ss} \cdot \left(\frac{G_{E2}(t)}{G_{ss}}\right)^{IPRG} \cdot \left(1 + \frac{E_{max} \cdot G_T(t)}{ED_{50} + G_T(t)}\right) - \frac{CL_I}{V_I} I(t) \tag{7}$$
$$\dot{I}_E(t) = \frac{k_{IE}}{V_I} \left(I(t) + c_f \cdot I_{exo}(t)\right) - k_{IE} I_E(t) \tag{8}$$

Exogenous Insulin Absorption:

$$\dot{S}_{1,ia}(t) = u_{ia}(t) - \frac{1}{\tau_{ia}} S_{1,ia}(t) \tag{9}$$
$$\dot{S}_{2,ia}(t) = \frac{1}{\tau_{ia}} S_{1,ia}(t) - \frac{1}{\tau_i a} S_{2,ia}(t) \tag{10}$$
$$U_{I,ia}(t) = \frac{1}{\tau_{ia}} S_{2,ia}(t) \tag{11}$$
$$\dot{I}_{exo}(t) = U_{I,R}(t) + U_{I,L}(t) - k_{exo} I_{exo}(t) \tag{12}$$

Continuous Glucose Monitor:

$$\dot{G}_{sc}(t) = \frac{1}{\tau_{sc}} \left(\frac{G_c(t)}{V_G} - G_{sc}(t)\right) \tag{13}$$

This can be represented as

$$\dot{x}(t) = f(x(t), u_R(t), u_L(t), d(t), par) \tag{14}$$

where $x(t)$ contains the states in the model,

$$
\mathrm{x} = \begin{bmatrix} G_A \\ G_T \\ G_c \\ G_p \\ G_{E2} \\ I \\ I_E \\ S_{1,R} \\ S_{2,R} \\ U_{I,R} \\ S_{1,L} \\ S_{2,L} \\ U_{I,L} \\ I_{exo} \\ G_{sc} \end{bmatrix}
\begin{array}{ll} \text{mg} & \text{Meal intake - Glucose absorption} \\ \text{mg} & \text{Meal intake - Glucose transport} \\ \text{mmol} & \text{Glucose in plasma} \\ \text{mmol} & \text{Glucose in peripheral compartment} \\ \text{mmol/L} & \text{Glucose effect on insulin secretion} \\ \text{pmol} & \text{Insulin in plasma} \\ \text{pmol/L} & \text{Insulin effect} \\ \text{U} & \text{Rapid-acting insulin absorption} \\ \text{U} & \text{Rapid-acting insulin absorption} \\ \text{U/min} & \text{Absorption rate for rapid-acting insulin} \\ \text{U} & \text{Long-acting insulin absorption} \\ \text{U} & \text{Long-acting insulin absorption} \\ \text{U/min} & \text{Absorption rate for long-acting insulin} \\ \text{U} & \text{Exogenous insulin} \\ \text{mmol/L} & \text{Subcutaneous glucose concentration} \end{array}
$$

$u_R(t)$ [U/min] and $u_L(t)$ [U/min] are the infusion and injection of rapid- and long-acting insulin, respectively. $d(t)$ [mg/min] is the carbohydrate uptake through meals. Finally, *par* covers all the parameters in the model, listed in Table 1.

Table 1: Model Parameters for the Augmented IGI Model

M_{wG}	180.1559	[g/mol]	Molar weight of glucose
c_f	6000	[pmol/U]	Insulin unit conversion factor
A_G	0.8	unitless	CHO bioavailability
k_a	0.0214	[1/min]	CHO absorption constant
V_G	9.33	[L]	Distribution volume for central glucose compartment
V_p	8.56	[L]	Distribution volume for peripheral glucose
Q	0.442	[L/min]	Intercompartmental clearance of glucose
CL_G	0.0287	[L/min]	Insulin-independent glucose clearance
CL_{GI}	0.000355	[L/min/(pmol/L)]	Insulin-dependent glucose clearance
G_{ss}	5.93	[mmol/L]	Baseline glucose concentration
$IPRG$	1.42	unitless	Control parameter for glucose effect on insulin secretion
E_{max}	0.590	unitless	Maximal effect of G_T on the insulin secretion
ED_{50}	38.2	[mg]	Glucose amount in G_T resulting in half of E_{max}
I_{ss}	24.2	[pmol/L]	Insulin concentration at steady state
CL_I	1.22	[L/min]	Endogenous insulin clearance
V_I	6.09	[L]	Distribution volume for insulin
k_{GE2}	0.0289	[1/min]	Rate constant of glucose effect compartment
k_{IE}	0.0213	[1/min]	Rate constant of insulin effect compartment
EGP	$8.2 \cdot 10^{-3}$·BW	[mmol/min]	Endogenous glucose production
BW	70	[kg]	Body weight
τ_{sc}	10	[min]	Time delay to subcutaneous glucose
$k_{I,R}$	55	[min]	Rate constant for rapid-acting insulin absorption
$k_{I,L}$	720	[min]	Rate constant for long-acting insulin absorption
k_{exo}	0.138	[1/min]	Exogenous insulin clearance