# Glucose Response to Fast- and Long-Acting Insulin in People with Type 2 Diabetes

**Sarah Ellinor Engell** [*,**] **Tinna Björk Aradóttir** [**]
**Henrik Bengtsson** [**] **Magnus Ekelund** [**]
**John Bagterp Jørgensen** [*]

[*] *Technical University of Denmark, Department of Applied Mathematics and Computer Science, DK-2800 Kgs Lyngby, Denmark*
[**] *Novo Nordisk A/S, DK-2880 Bagsværd, Denmark*

**Abstract:** In type 2 diabetes (T2D), injections with long-acting insulin can become necessary to regulate blood glucose and avoid long-term complications. However, finding a safe and effective insulin dose, a process known as titration, is both challenging and time demanding. In this paper, we propose a new method for safe and rapid identification of a personalized insulin dose with long-acting insulin through short-term use of fast-acting insulin in an artificial pancreas (AP). To illustrate this novel concept, we simulate our method by modelling the glucose response to fast- and long-acting insulin in people with T2D. We apply a simple control-algorithm for the AP to adjust the insulin infusion rate during fasting periods. In this case-study, we simulate an insulin naïve T2D patient on AP treatment for one week, gradually adjusting the insulin infusion rate. After one week, we convert the insulin infusion rate, unit-to-unit, to a daily injection of long-acting insulin. We compare our method to titration with the standard of care 2-0-2 algorithm. Our simulations indicate that we can reduce the titration period from five weeks to a single week, whilst easing the burden on the patient.

*Keywords:* Mathematical Modeling, Physiological Model, Simulation, Type 2 Diabetes, Insulin

## 1. INTRODUCTION

Diabetes is a chronic disease where the body is unable to lower blood glucose levels sufficiently with the secretion of insulin. In type 2 diabetes (T2D), this regulatory deficiency is caused by an imbalance between insulin secretion and insulin sensitivity in the body. Left untreated, elevated glucose levels can lead to blindness, kidney failure and amputations, resulting in a high cost for both the individual and society. In late-stage T2D, insulin injections may become necessary to successfully regulate glucose levels. When initiating insulin treatment in T2D, daily injections of long-acting insulin can be used to lower glucose levels. If needed, fast-acting insulin can be added at meal times. The insulin dose must be selected carefully as too much insulin can result in life-threatening low blood glucose concentrations. To avoid overdoses, a lengthy iterative process called *titration* is used to gradually increase the amount of injected long-acting insulin such that the fasting glucose concentration reaches the normal range. Based on fasting self-measured blood glucose (SMBG) values, the patient adjusts the daily insulin dose until the desired glucose concentration is reached. This can take several months. Unfortunately, many patients never reach treatment goals as the burdensome titration task and a lack of confidence in the treatment can lead to adherence problems (Arnolds et al., 2013; Khunti et al., 2020).

The burden on the patient may be eased through automated insulin delivery. In recent years, several studies have shown promising results with automated insulin delivery, also known as an artificial pancreas (AP), for people with T2D (Bally et al., 2018; Taleb et al., 2019). An AP consists of three components; (i) a continuous glucose monitor (CGM), (ii) a control algorithm, and (iii) an insulin pump with fast-acting insulin. The components automatically measure glucose, adjust the insulin dose accordingly and deliver the dose to the user at a frequent interval, typically every five minutes. Multiple AP systems are available on the market for people with type 1 diabetes, however commercial AP systems for T2D have not yet been launched. Even though APs may become available as a treatment solution for T2D in the near future, AP-usage will require high levels of self-engagement and a specific skill-set from the user, such as learning to change the infusion set and learning to carb-count (Tanenbaum et al., 2017). Widespread usage of APs in the T2D population, may be hampered by high cost, the burden of device wear, and the individual's wish to conceal their condition to avoid being labelled as *sick*. In the light of this, the greater patient population's treatment needs may be met with simpler, less visible and cheaper treatment forms, such as injection-based insulin treatment. For successful injection-based treatment, a swift, safe and simple identification of the individual's insulin-need is critical.

Methods for quickly achieving target glucose levels have been used for decades in critical care (Rohrbach et al., 2017). Here, a gradual increase in intravenous insulin in-

[⋆] This project is funded by Innovation Fund Denmark through the Industrial PhD project 0153-00049B and by Novo Nordisk A/S.

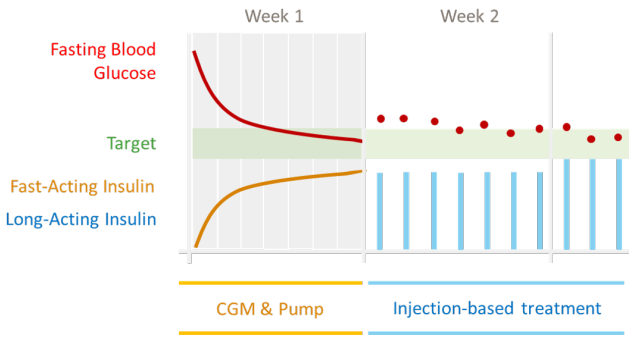


Fig. 1. The Dose Finder Concept. Short-term use of an artificial pancreas regulates the fasting blood glucose into the target range. The identified infusion rate is converted to a pen-based injection with long-acting insulin. Final dose-adjustments are made based on SMBG measurements and a standard of care algorithm.

fusion over two to three days is used to steer very high glucose concentrations into the target range. Upon reaching the target range, the infusion rate may be converted to an injection-based insulin dose (Kelly, 2014). The method is efficient, however, it is invasive and would not be considered applicable outside of critical care, where patients do not already have a intravenous catheter inserted. Similar to insulin delivered intravenously, literature suggests that a correlation exists between fast-acting insulin delivered in a pump and long-acting insulin injected from a pen (Aronson et al., 2016; Meneghini and Sparrow-Bodenmiller, 2010). We hypothesize, that the methods used in critical care can be mimicked through short-term usage of an AP. In this way, the AP system may enable a less burdensome initiation of injection-based insulin treatment.

In this paper, Section 2 presents The Dose Finder, a new method for rapid insulin titration using an artificial pancreas. To demonstrate The Dose Finder, we in Section 3 introduce a physiological model for simulating the glucose response to fast- and long-acting insulin in people with T2D. Section 4 describes a simple control algorithm for the AP. Section 5 presents the method we use to switch from AP to pen-based treatment. Our simulation setup is documented in Section 6. We present and discuss our results in Section 7 and 8, respectively, before concluding the paper in Section 9.

## 2. THE DOSE FINDER CONCEPT

We propose a new method, The Dose Finder, where we use an AP as a tool to find the insulin-need with fast-acting insulin. Figure 1 shows the Dose Finder concept.

The AP is used for a short time period, e.g. a week, and lowers fasting glucose levels into the target range by adjusting the insulin infusion rate. A short wear-time will allow the doctor to set up the AP for the patient, and the patient may *connect and forget* until the next doctor appointment. We only adjust insulin infusion rates during fasting periods, as the goal of the insulin treatment is to regulate fasting glucose rather than post-prandial glucose. After the AP period, we translate the identified insulin infusion rate from the pump into an injection-based

Table 1. The 2-0-2 Titration Algorithm for Long-Acting Insulin. Dose adjustments are based on the lowest SMBG value below target, or an average of the SMBG values from the past three days. (American Diabetes Association, 2021)

| SMBG [mmol/L] | Dose Adjustment [U] |
|---|---|
| $> 7.2$ | $+2$ |
| $4.4 - 7.2$ | No change |
| $< 4.4$ | $-2$ |
| Initial dose is 10 U | |

treatment with long-acting insulin. In the case where the optimal dose of long-acting insulin has not been identified after the AP period, we follow the dose translation with dose adjustments based on SMBG values and a standard of care (SoC) algorithm, such as the 2-0-2 titration algorithm shown in Table 1.

## 3. MATHEMATICAL MODELS

To simulate subjects with T2D treated with both fast- and long-acting insulin, we augment the integrated glucose-insulin (IGI) model (Jauslin et al., 2011; Røge et al., 2014) with an extended version of the exogenous insulin model from Hovorka et al. (2004). We include a subcutaneous glucose concentration compartment from Biagi et al. (2017) for simulating sensor measurements as input to the artificial pancreas. The resulting model consists of a submodel for carbohydrate (CHO) absorption, a pharmacodynamic (PD) model describing the interaction between glucose and insulin concentration, and two pharmacokinetic (PK) models to simulate the absorption dynamics of fast- and long-acting insulin. Figure 2 shows the model structure. We present the model equations in the following subsections and Table 2 lists selected parameter values.

### *3.1 Glucose Sub-Model*

In the IGI model, glucose is split between the central $G_c(t)$ [mmol] and the peripheral compartment $G_p(t)$ [mmol],

$$\dot{G}_c(t) = EGP + R_A(t) + \frac{Q}{V_p}G_p(t) - \frac{1}{V_G}(CL_G + CL_{GI}I_E(t) + Q)G_c(t) \quad (1a)$$

$$\dot{G}_p(t) = \frac{Q}{V_G}G_c(t) - \frac{Q}{V_p}G_p(t) \quad (1b)$$

where the plasma concentration is the glucose in the central compartment divided by the distribution volume, $V_G$ [L]. Glucose enters the central compartment through the endogenous glucose production, $EGP$ [mmol/min], the absorbed meals, $R_A(t)$ [mmol/min], and from the peripheral glucose compartment via the inter-compartmental clearance, $Q$ [L/min]. $V_p$ [L] is the distribution volume in the peripheral compartment. Both glucose-dependent clearance, $CL_G$ [L/min], and insulin-dependent clearance, $CL_{GI}$ [L/min/(pmol/L)], remove glucose from the central compartment. $I_E$ [pmol/L] is the insulin effect compartment.

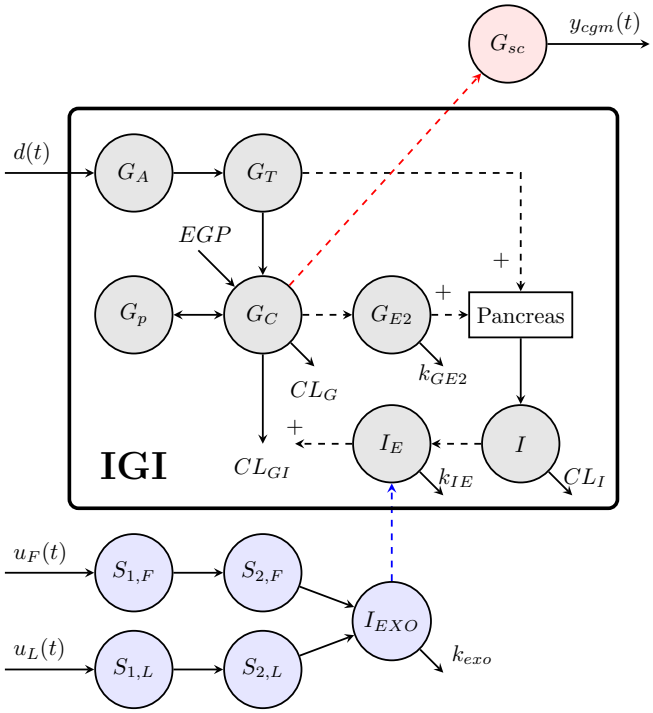


Fig. 2. Model structure for the augmented IGI model. The original model compartments have been augmented with absorption models for fast- and long-acting insulin (blue) and a compartment for subcutaneous glucose concentration (red).

### *3.2 Carbohydrate Absorption Model*

The IGI model describes oral meal ingestion with a two-compartment model,

$$\dot{G}_A(t) = d(t)A_G - k_a G_A(t) \tag{2a}$$
$$\dot{G}_T(t) = k_a G_A(t) - k_a G_T(t) \tag{2b}$$
$$R_A = \frac{k_a}{M_{wG}} G_T(t) \tag{2c}$$

where $d(t)$ [mg/min] is the amount of ingested carbohydrates (CHO). $G_A$ [mg] and $G_T$ [mg] represent the amounts of CHO in the absorption and the transit phase, respectively. $A_G$ [unitless] describes the bio-availability of the CHO. $k_a$ [1/min] is a rate constant for the absorption of CHO. The absorbed meals, $R_A$ [mmol/min] enter the central glucose compartment. To match units of $R_A$ and $G_c$, we convert $G_T$ to [mmol/min] by dividing with the molecular weight of glucose $M_{wG} = 180.1559$ mg/mmol.

### *3.3 Endogenous Insulin Sub-Model*

Endogenous insulin is described through the compartment, $I$ [pmol], with the secretion and elimination of insulin produced in the pancreas,

$$\dot{I}(t) = I_{sec}(t) - \frac{CL_I}{V_I} I(t) \tag{3a}$$
$$I_{sec}(t) = I_{sec,0} \cdot G_{CM2} \cdot INC(t) \tag{3b}$$
$$I_{sec,0} = CL_I \cdot I_{ss} \tag{3c}$$

where the insulin secretion, $I_{sec}$ [pmol/min], is regulated by the ability of glucose to stimulate secretion, $G_{CM2}$ [unitless], and the incretin effect, $INC$ [unitless]. The basal insulin secretion, $I_{sec,0}$ [pmol/min], is given by the product of the endogenous insulin clearance, $CL_I$ [L/min], and the insulin concentration at steady state, $I_{ss}$ [pmol/L].

### *3.4 Glucose Effect on Insulin Secretion*

The effect compartment, $G_{E2}$ [mmol/L], links the plasma glucose concentration to insulin secretion,

$$\dot{G}_{E2}(t) = k_{GE2}\frac{G_c(t)}{V_G} - k_{GE2}G_{E2}(t) \tag{4a}$$
$$G_{CM2}(t) = \left(\frac{G_{E2}(t)}{G_{ss}}\right)^{IPRG} \tag{4b}$$

where $k_{GE2}$ [1/min] is a rate constant. The glucose effect on insulin secretion, $G_{CM2}$, is determined through the baseline glucose concentration, $G_{ss}$ [mmol/L], and the control parameter $IPRG$ [unitless].

### *3.5 Incretin Effect*

Ingested meals can boost the insulin secretion through the incretin effect. In the IGI model, the effect is described as a saturable function,

$$INC(t) = 1 + \frac{E_{max} \cdot G_T(t)}{ED_{50} + G_T(t)} \tag{5}$$

where $E_{max}$ [unitless] is the maximal effect with which glucose in the transit compartment can affect insulin secretion, and $ED_{50}$ [mg] is the amount of glucose needed to obtain half of the $E_{max}$-effect.

### *3.6 PK model*

We augment the IGI model with the exogenous insulin model from Hovorka et al. (2004) to describe the absorption dynamics of fast- and long-acting insulin analogues. The absorption of exogenous insulin is described as a third-order system,

$$\dot{S}_{1,ia}(t) = u_{ia}(t) - \frac{1}{\tau_{ia}} S_{1,ia}(t) \tag{6a}$$
$$\dot{S}_{2,ia}(t) = \frac{1}{\tau_{ia}} S_{1,ia}(t) - \frac{1}{\tau_i a} S_{2,ia}(t) \tag{6b}$$
$$U_{I,ia}(t) = \frac{1}{\tau_{ia}} S_{2,ia}(t) \tag{6c}$$

where $u_{ia}(t)$ [U/min] is the amount of subcutaneously injected insulin analogue. The time constant, $\tau_{ia}$ [min], is the time to maximum insulin absorption for the specific analogue. $S_{1,ia}$ [U] and $S_{2,ia}$ [U] are absorption compartments and $U_{I,ia}$ [U/min] is the absorption rate. The absorption rates of fast- and long-acting insulin, $U_{I,F}$ and $U_{I,L}$, enter the exogenous insulin concentration compartment $I_{exo}$ [U/L],

$$\dot{I}_{exo}(t) = \frac{U_{I,F}(t) + U_{I,L}(t)}{V_{I,exo}} - k_{exo} I_{exo}(t) \tag{7}$$

$V_{I,exo}$ is the distribution volume for exogenous insulin and $k_{exo}$ [1/min] is the clearance rate.

### *3.7 Insulin Effect*

The insulin effect compartment describes the delay in glucose utilization caused by both endogenous and exogenous insulin,

$$\dot{I}_E(t) = \frac{k_{IE}}{V_I} \left( I(t) + c_f \cdot I_{exo}(t) \right) - k_{IE} I_E(t) \tag{8}$$

where $k_{IE}$ [1/min] is the rate constant describing the effect delay, and $V_I$ [L] is the insulin distribution volume. To align units, we multiply $I_{exo}$ [U/L] by the conversion factor $c_f$ [pmol/U] from Knopp et al. (2019).

### *3.8 Continuous Glucose Monitor Model*

CGMs measure glucose levels in the interstitial tissue. We use a model relating plasma glucose and interstitial glucose from Biagi et al. (2017),

$$\dot{G}_{sc}(t) = \frac{\frac{G_c(t)}{V_G} - G_{sc}(t)}{\tau_{sc}} \tag{9}$$

where the time constant $\tau_{sc}$ [min] describes the lag between glucose concentrations in plasma, $G_c(t)/V_G$, and the glucose concentration in the interstitial tissue, $G_{sc}$ [mmol/L].

### *3.9 Parameters*

We use parameter values from Røge et al. (2014) and Hovorka et al. (2004) for the IGI model and the exogenous insulin dynamics, respectively. To simulate long-acting insulin, we introduce $\tau_L = 12$ h as in Aradóttir et al. (2017). The endogenous glucose production ($EGP$) is taken from Røge et al. (2014) and is normalized to a body weight of 70 kg in order to match the distribution volumes ($V_G, V_p, V_I$) that are stated to be proportional body weight and are normalized to 70 kg. For the lag to the subcutaneous glucose compartment, we select a time constant from the distribution in Biagi et al. (2017). To convert from pmol to U, we use the conversion from Knopp et al. (2019).

Table 2. Model Parameters

| | Parameter | Value | Source |
|---|---|---|---|
| $\tau_{sc}$ | [min] | 10 | Biagi et al. (2017) |
| $\tau_F$ | [min] | 55 | Hovorka et al. (2004) |
| $\tau_L$ | [min] | 720 | Aradóttir et al. (2017) |
| $k_{exo}$ | [1/min] | 0.138 | Hovorka et al. (2004) |
| $EGP$ | [mmol/min] | 0.574 | Røge et al. (2014) |
| $c_f$ | [pmol/U] | 6000 | Knopp et al. (2019) |

## 4. AP CONTROL ALGORITHM

We implement a simple control algorithm to simulate closed-loop control with the AP. Inspired by the integral component in PID-controllers, we adjust the insulin infusion rate $u_F$ at every sample based on the integrated error,

$$v(k) = v(k-1) + K_i \cdot (y_{ref} - y_{cgm}(k)) \cdot T_s \tag{10a}$$
$$u_F(k) = \max(v(k), 0) \tag{10b}$$

where $k$ is the sample number, $K_i$ $\left[\frac{U \cdot L}{min^2 \cdot mmol}\right]$ is the integral gain, and $T_s$ [min] is the sample time. The error term is the difference between the reference value, $y_{ref} =$ 5.8 mmol/L, and the glucose concentration measured by the CGM sensor, $y_{cgm}(k)$. We set $v(0) = 0$. As negative insulin infusion rates are not physiologically possible, we constrain the infusion rate to $u_F(k) \leq 0$ U/min.

Sudden drops in blood glucose values can be uncomfortable for patients. We select $K_i = -3 \cdot 10^{-6} \frac{U \cdot L}{min^2 \cdot mmol}$ to ensure a balance between rapid convergence towards the reference value and a smooth transition for patient comfort. We wish to regulate the the insulin infusion rate such that the fasting glucose is lowered into the target range. To avoid adjusting $u_F$ during post-prandial peaks, meals are announced to the controller. Following a meal announcement, the controller is switched off for 5.5 hours and the insulin infusion rate is fixed to the latest $u_F$ value.

## 5. SWITCH FROM PUMP TO PEN

For this simplified case simulation, we assume that the bio-availability of fast-acting insulin delivered in a pump is identical to that of long-acting insulin injected in a pen. We calculate the long-acting insulin dose as the total amount of insulin delivered with the pump during 24 hours using the identified insulin infusion rate,

$$u_L[\text{U/day}] = \frac{24[\text{h/day}] \cdot 60[\text{min/h}] \cdot u_F[\text{U/sample}]}{T_s[\text{min/sample}]} \tag{11}$$

The calculated dose, $u_L$, is injected daily prior to breakfast. As fast-acting and long-acting insulin have different dynamics, a direct switch from pump to pen will result in a rise in blood glucose. This happens because the effect of the fast-acting insulin disappears before the long-acting insulin becomes effective. In critical care, the transition from intravenous to subcutaneous insulin treatment is often overlapped to avoid a rise in blood glucose (Kelly, 2014). Likewise, we compensate for the difference in dynamics by continued infusion of fast-acting insulin for 2 hours after the first injection with long-acting insulin. Starting one week after the transition from pump to pen, we apply a standard of care titration algorithm for final dose adjustments until dose convergence.

## 6. SIMULATION SETUP

We simulate three different ways to initiate insulin for the same virtual patient with; (i) The 2-0-2 Titration Algorithm twice-weekly with titration on day 1 and 4, (ii) AP treatment until the translated insulin infusion rate

Table 3. Titration Results

| Titration Method | Dose at end of Week 1 | Week 2 | Week 4 | Final Dose | Titration Length |
|---|---|---|---|---|---|
| 2-0-2 | 12 U | 16 U | 24 U | 28 U | 5 weeks |
| AP | 35 U | 43 U | 45 U | 46 U | 5 weeks |
| DF | 35 U | 35 U | 35 U | 35 U | 1 week |

converges to a fixed pen-dose, and (iii) The Dose Finder: One week of AP followed by dose-conversion to long-acting insulin, and weekly dose-adjustments with the 2-0-2 algorithm, if needed. In all simulations, we assume full adherence. We start the study at midnight. We simulate three daily meals of 40 g, 55 g, and 60 g of carbohydrates with meal times at 7:00 AM, 1:00 PM and 7:00 PM, respectively. The duration of each meal is 15 minutes. SMBG values are recorded at 7:00 AM, and the three latest SMBG values are used as input to the 2-0-2 algorithm. We use a sample time of $T_s = 5$ min, and simulate insulin injections as a fixed rate over a five minute sample.

## 7. SIMULATION RESULTS

With our extension to the IGI model, we are able to simulate treatment with both fast- and long-acting insulin. Figure 3 illustrates the first 12 days of the Dose Finder scenario, where an AP is used for 7 days before switching to pen-based treatment. We see that the fasting glucose levels are reduced as the insulin infusion rate is gradually increased. The controller is mainly active overnight where the patient is fasting. After one week of AP treatment, the fasting blood glucose has been lowered from 12 mmol/L to 6 mmol/L and is within the target range. During AP treatment, all measured glucose concentrations are above or within the target range, and the treatment is considered safe. When transitioning from AP to injection-pen, a small rise is seen in the glucose values until they stabilize after 3-4 days of pen-treatment. After 3 days, all the fasting blood glucose values are within the target range, and no adjustments are needed with the 2-0-2 algorithm.

We compare the outcomes for the Dose Finder (DF) method to two other titration approaches in Table 3 and Figure 4. With the 2-0-2 algorithm, the dose converges after five weeks. We see that our method can reduce the titration period to a single week. If the AP period is extended, we can complete the titration period after five weeks and reach a lower fasting blood glucose value within the target range.

## 8. DISCUSSION

With one week of AP treatment, we can identify a dose of long-acting insulin that can bring the patient's blood glucose into the target range. We identify a dose of 35 U, however, our simulations show that several dose sizes will allow the patient to reach target. Some patients may desire a tighter target range, e.g. $4.0 - 6.0$ mmol/L. In this case, the patient will need additional dose-adjustments to reach target after the switch from AP to pen-based treatment. As another option, we can extend the AP period to reach a lower fasting blood-glucose before switching to pen-based treatment. When we run the AP, the dose converges to 46 U after five weeks. Due to integrator wind-up, the AP stabilizes the fasting blood glucose at 5 mmol/L. Although

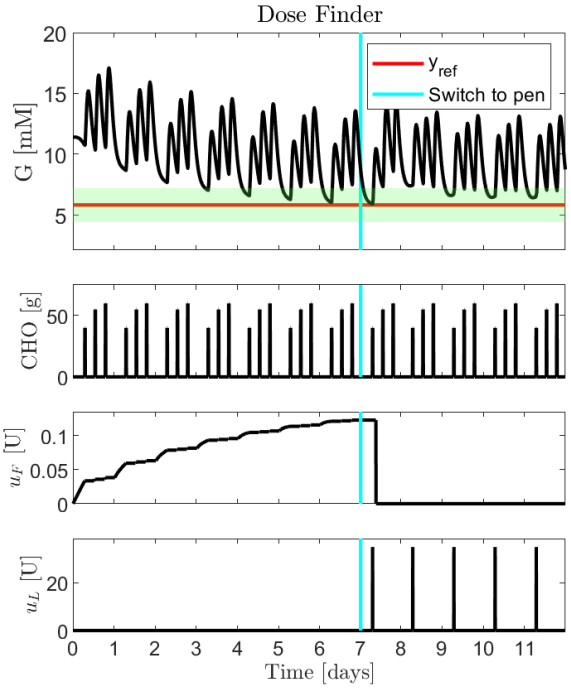


Fig. 3. Simulation of the Dose Finder. The panels from top to bottom show the glucose concentration, the consumed carbohydrates, the infused fast-acting insulin and the injected long-acting insulin, respectively. Over the first week, the AP adjusts the insulin infusion rate during fasting periods. At the start of week 2, the infusion rate is converted, unit-to-unit, to a daily, long-acting insulin dose administered pre-breakfast. Insulin infusion is continued for 2 hours after the first pen-injection to reduce the rise in glucose levels during transition. The green area shows the target range of $4.4 - 7.2$ mmol/L

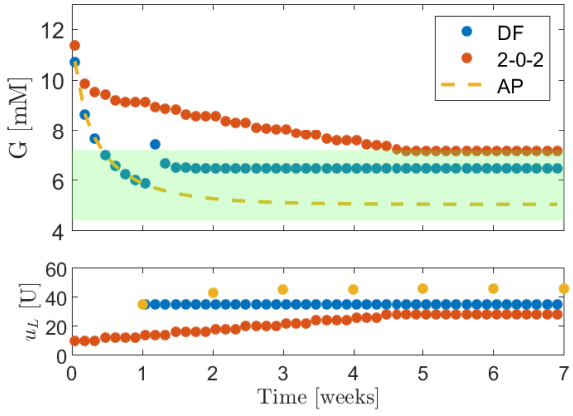


Fig. 4. Titration with The Dose Finder (DF), the 2-0-2 algorithm and the implemented artificial pancreas (AP). The upper panel shows the daily SMBG values for DF and 2-0-2, and the pre-breakfast CGM measurement for the AP. The lower panel shows the daily dose of long-acting insulin for DF and 2-0-2, and the unit-to-unit conversion of the fast-acting insulin delivered by the AP on the last day of each week.

the prolonged AP wear-time can quickly steer the blood glucose to a lower target, it comes at a cost. The patient would need frequent clinic visits to change the cartridge, infusion set, and sensor. Alternatively, the patient would have to learn to manage the AP themselves. Both scenarios complicate the procedure and may reduce the benefits compared to regular titration.

We simulate an ideal scenario where the patient is adherent and the measurements are without noise. In practice, titration periods may be extended greatly due to physiological variation, forgotten injections and misunderstood guidelines. Additionally, the safety of the control algorithm for the AP may be affected by unannounced meals and sensor noise. The control algorithm in this paper serves the purpose of visualizing the the Dose Finder concept and would need additional safety measures and extensive testing to be applicable in a clinical setup.

In our exogenous insulin compartment, the clearance of fast-acting insulin delivered in a pump and long-acting insulin delivered in a pen are identical. Aronson et al. (2016) showed that on average subjects with T2D who switch from pen-based treatment to insulin pumps will need 20% less insulin. If less insulin is needed in pumps, the unit-to-unit conversion we use to transition from AP to pen-based treatment can be considered safe as it systematically underestimates the insulin-need. As a result, the subject may need additional dose-adjustments in order to reach the final titration target after the switch to pen-based treatment. In future work, the difference between insulin delivery methods may be included in our model as an analogue-dependent clearance by implementing an $I_{exo}$-compartment for each analogue.

## 9. CONCLUSION

This work presents a model to simulate fast- and long-acting insulin in people with type 2 diabetes. With our model, we simulate how the insulin infusion rate from an artificial pancreas can be converted into a personalized dose of long-acting insulin delivered with an insulin pen. For a virtual patient initiating insulin treatment, we show that one initial week of AP treatment can reduce the titration period from five weeks to a single week compared to the standard of care 2-0-2 algorithm.

## REFERENCES


American Diabetes Association (2021). ADA's standards of medical care in diabetes. *Clinical Diabetes*, 39(1), 128. doi:10.2337/cd21-pe01.

Aradóttir, T.B., Boiroux, D., Bengtsson, H., Kildegaard, J., Orden, B.V., and Jørgensen, J.B. (2017). Model for Simulating Fasting Glucose in Type 2 Diabetes and the Effect of Adherence to Treatment. *IFAC-PapersOnLine*, 50(1), 15086–15091. doi:10.1016/j.ifacol.2017.08.2527.

Arnolds, S., Heise, T., Flacke, F., and Sieber, J. (2013). Common standards of basal insulin titration in T2DM. *Journal of Diabetes Science and Technology*, 7(3), 771–778. doi:10.1177/193229681300700323.

Aronson, R., Reznik, Y., Conget, I., Castañeda, J.A., Runzis, S., Lee, S.W., and Cohen, O. (2016). Sustained efficacy of insulin pump therapy compared with multiple daily injections in type 2 diabetes: 12-month data from the OpT2mise randomized trial. *Diabetes, Obesity and Metabolism*, 18(5), 500–507. doi:10.1111/dom.12642.

Bally, L., Thabit, H., Hartnell, S., Andereggen, E., Ruan, Y., Wilinska, M.E., Evans, M.L., Wertli, M.M., Coll, A.P., Stettler, C., and Hovorka, R. (2018). Closed-loop insulin delivery for glycemic control in noncritical care. *New England Journal of Medicine*, 379(6), 547–556. doi:10.1056/NEJMoa1805233.

Biagi, L., Ramkissoon, C.M., Facchinetti, A., Leal, Y., and Vehi, J. (2017). Modeling the error of the medtronic paradigm veo enlite glucose sensor. *Sensors (Switzerland)*, 17(6). doi:10.3390/s17061361.

Hovorka, R., Canonico, V., Chassin, L.J., Haueter, U., Massi-Benedetti, M., Federici, M.O., Pieber, T.R., Schaller, H.C., Schaupp, L., Vering, T., and Wilinska, M.E. (2004). Nonlinear model predictive control of glucose concentration in subjects with type 1 diabetes. *Physiological Measurement*, 25(4), 905–920. doi:10.1088/0967-3334/25/4/010.

Jauslin, P.M., Frey, N., and Karlsson, M.O. (2011). Modeling of 24-hour glucose and insulin profiles of patients with type 2 diabetes. *Journal of Clinical Pharmacology*, 51(2), 153–164. doi:10.1177/0091270010362536.

Kelly, J.L. (2014). Continuous insulin infusion: When, where, and how? *Diabetes Spectrum*, 27(3), 218–223. doi:10.2337/diaspect.27.3.218.

Khunti, K., Giorgino, F., Berard, L., Mauricio, D., and Harris, S.B. (2020). The importance of the initial period of basal insulin titration in people with diabetes. *Diabetes, Obesity and Metabolism*, 22(5), 722–733. doi:10.1111/dom.13946.

Knopp, J.L., Holder-Pearson, L., and Chase, J.G. (2019). Insulin Units and Conversion Factors: A Story of Truth, Boots, and Faster Half-Truths. *Journal of Diabetes Science and Technology*, 13(3), 597–600. doi:10.1177/1932296818805074.

Meneghini, L. and Sparrow-Bodenmiller, J. (2010). Practical aspects and considerations when switching between continuous subcutaneous insulin infusion and multiple daily injections. *Diabetes Technology and Therapeutics*, 12(SUPPL. 1). doi:10.1089/dia.2009.0184.

Røge, R.M., Klim, S., Kristensen, N.R., Ingwersen, S.H., and Kjellsson, M.C. (2014). Modeling of 24-hour glucose and insulin profiles in patients with type 2 diabetes mellitus treated with biphasic insulin aspart. *Journal of Clinical Pharmacology*, 54(7), 809–817. doi:10.1002/jcph.270.

Rohrbach, E.F., Webb, K., and Costello, T. (2017). Comparison of Two Intravenous Insulin Titration Methods in Hyperglycemic Crisis. *Journal of Pharmacy Technology*, 33(2), 72–77. doi:10.1177/8755122517690749.

Taleb, N., Carpentier, A.C., Messier, V., Ladouceur, M., Haidar, A., and Rabasa-Lhoret, R. (2019). Efficacy of artificial pancreas use in patients with type 2 diabetes using intensive insulin therapy: A randomized crossover pilot trial. *Diabetes Care*, 42(7), E107–E109. doi:10.2337/dc18-2406.

Tanenbaum, M.L., Adams, R.N., Hanes, S.J., Barley, R.C., Miller, K.M., Mulvaney, S.A., and Hood, K.K. (2017). Optimal Use of Diabetes Devices: Clinician Perspectives on Barriers and Adherence to Device Use. *Journal of Diabetes Science and Technology*, 11(3), 484–492. doi:10.1177/1932296816688010.