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IN SILICO TRIALS OF AN OPEN-SOURCE ANDROID-BASED ARTIFICIAL PANCREAS: A NEW PARADIGM TO TEST SAFETY AND EFFICACY OF DO-IT-YOURSELF SYSTEMS

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Diabetes Technology and Therapeutics
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Abstract

Objective

Safety data on Do-It-Yourself Artificial Pancreas Systems (DIYAPS) are missing. The most widespread in Europe is the AndroidAPS implementation of the OpenAPS algorithm. We used the UVA/Padova Type 1 Diabetes Simulator to *in silico* test safety and efficacyof this algorithmin different scenarios.

Methods

We tested 5 configurations of the AndroidAPS algorithm differing in aggressiveness and patient´s interaction with the system. All configurations were tested with insulin sensitivity variation of ±30%. The most promising configurations were tested in real-life scenarios: over- and under-estimated bolus by 50%, bolus delivered 15 minutes before meal and late bolus delivered 15 minutes after meal. CGM time in ranges metrics were used to assess the glycemic control.

Results

In silico testing showed that open source closed-loop system AndroidAPS works effectively and safely. The best results were reached if AndroidAPS algorithm worked with microboluses and when half of calculated bolus was issued (mean glycemia 131 mg/dL, SD 27 mg/dL, Time in Range 91%, Time between 54-70 mg/dL<1% and Low Blood Glucose Index even <1). The meal bolus over and underestimation as well as late bolus did not have affect the Time in Range and, importantly, the Time between 54-70 mg/dL.

Conclusion

In silico testing proved that AndroidAPS implementation of the OpenAPS algorithm is safe and effective and it showed a great potential to be tested in prospective home setting study.

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Introduction

Artificial Pancreas (AP) clinical studies in the last 10 years have convincingly shown the benefits of this technology in adults and adolescents with Type 1 Diabetes (T1D) in terms of both dramatically reducing hypo-glycemic events as well as improving the Time In Range (TIR), i.e. the time spent in the 70-180 mg/dL range [1-2]. However available regulatory-approved AP systems for patients with T1D are lacking worldwide. This has stimulated the development of Do-It-Yourself AP Systems (DIYAPS) [3].

There are currently three main DIYAPS available: OpenAPS, AndroidAPS and Loop. "OpenAPS" [openaps.org] uses a small microcomputer to bridge communications with the insulin pump and the CGM sensors [3]. "AndroidAPS" [androidaps.readthedocs.io] uses a version of the OpenAPS algorithm, but the algorithm is hosted on smartphones and directly communicates with the CGM and insulin pumps using Bluetooth [4]. The OpenAPS algorithm predicts what BGs are/have been doing every 5 minutes. It measures the deviation of the estimated blood glucose from the target glucose value and calculates the required adaptions of insulin dosing in order to reach the glycemic target. The decision-making is based on the underlying basal rate, the current sensor-glucose value, the insulin pump dosing history, and the insulin sensitivity, etc [openaps.readthedocs.io]. There are two main versions of this algorithm: AMA (Advanced Meal Assist, oref0) working with changing of temporary basal only and SMB (SuperMicroBoluses, oref1) which works on the same principle like super bolus – borrowing insulin from the future [androidaps.readthedocs.io, openaps.readthedocs.io]. In contrast to previous two DIYAPS, "Loop" holds its own loop algorithm and it requires a small radio device to bridge communication between the insulin pump, CGM sensors and an iOS-operated device [loopkit.github.io].

None of DIYAPS has received CE (Certification Europe) marking nor U.S. Food and Drug Administration (FDA) approval to date and instructions and algorithms how to build these systems are available on websites and individuals with diabetes use them under their own responsibility. Despite these facts there are growing number of users of DIYAPS with closed-loop systems around the globe including adults, adolescent and children [3].

Diabetes Technology and Therapeutics
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The retrospective studies using patient´s self-reported data showed promising results and comparable with official systems [5,6], but the prospective data about the safety and efficacy are missing.

In silico clinical trials, which are defined as the use of individualized computer simulation in the development or regulatory evaluation of a medicinal product, medical device, or medical intervention, have been proposed as a possible strategy to reduce the regulatory costs of innovation and the time to market for biomedical products [7,8]. *In silico* clinical trials offer a new paradigm to test safety and efficacy of DIYAPS by using the UVA/Padova T1D simulator which in January 2008 has been accepted by FDA as a substitute to animal trials for the pre-clinical testing of certain insulin treatments, including AP [8]. This was a landmark change in the field of T1D AP research: for the first time a computer model has been accepted by a regulatory agency as a substitute of animal trials in the testing of insulin treatments. Since its introduction, this simulator enabled an important acceleration of AP studies, with a number of regulatory approvals obtained using *in silico* testing. A total of 140 candidate control algorithms have been formally evaluated by FDA resulting in 16 IDEs.

The aim of this report is to use *in silico* clinical trials to show safety and efficacy of algorithm running in DIYAPS using AndroidAPS due to the prevalence of compatible, Bluetooth-enabled insulin pumps. The main objective was to test AndroidAPS implementation of the OpenAPS algorithm (oref0, oref1) in 5 different configurations. The second objective was to test the algorithm in situation common in real-life such as advanced, late, under- and over-estimated bolus.

Research Design and Methods

The UVA/Padova Simulator

The recent version of the FDA-accepted UVA/Padova T1D simulator has been used which allows to move from single meal to multiple-day scenarios [9,10]. This version includes intra- and inter-day variability of insulin sensitivity, new distributions of Carbohydrate-to-insulin Ratio (CR) at breakfast, lunch, and dinner, and a model of dawn

Diabetes Technology and Therapeutics
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phenomenon, thus making this technology suitable for running multiple-meal scenarios and enabling a more robust design of artificial pancreas control algorithms.

The Control Algorithm

AndroidAPS is an implementation of the OpenAPS algorithm into user friendly smartphone app. The OpenAPS algorithm is a heuristic algorithm which makes multiple predictions of what might happen in the future based on the current glucose levels, insulin doses, carbohydrate consumption and personal profile. The profile includes following parameters: basal rates, insulin sensitivity factor (ISF), carbohydrate-to-insulin ratio (CR), duration of insulin action (DIA) and target glycemia [openaps.readthedocs.io]. This tailored setting enables individual insulin dosage by the algorithm. OpenAPS algorithms using a unique dynamic carbs absorption model where absorbed carbs are calculated from glycemia changes. This allowes accurate calculation of carbs on board (COB) [openaps.readthedocs.io, androidaps.readthedocs.io]. For detail see calculation section.

Further additional feature is the automatic detection of insulin sensitivity changes (Autosens). It analyzes historical data on-the-go and makes adjustments if it recognized that sensitivity to insulin has changed. Autosens provides percentual change of primary insulin sensitivity (ISF) defined in patient´s profile. The algorithm takes the Autosens into account in calculation to keep blood glucose within the target range [openaps.readthedocs.io]. We used the Oref1 Autosens detection in *in silico* testing which calculates the sensitivity from 8h data in the past or from last site change, if it is less than 8h ago [androidaps.readthedocs.io].

Basic calculation of the control algorithm

The algorithm includes following steps:

Bolus calculation

$$B = \frac{C}{CR} + \frac{(G_c - G_e)}{ISF} + \frac{COB}{CR} - IOB_{bolus} - IOB_{basal}$$

where B[U] is calculated bolus, C [g] is the estimated carbohydrate intake, CR [g/U] is carbohydrate-to-insulin Ratio (CR), G_c [mg/dL] is current glycemia, G_e [md/dl] is estimated

target glycemia, ISF [mg/dL/U] is the insulin sensitivity factor, COB [g] is estimated residual amount of carbohydrates from previous meals, IOB_{bolus} [U] is active insulin from previous boluses, IOB_{basal} [U] is active insulin from previous temporary basal changes and $IOB_{activity}$ [U/min] insulin activity.

IOB and Insulin activity calculation

Let

t [min] … time after bolus

t_p [min] … insulin peak time

t_d [min] … Duration of Insulin Action (DIA)

and

$$\tau = t_p \cdot \frac{1 - \frac{t_p}{t_d}}{1 - 2 * \frac{t_p}{t_d}} \qquad a = 2 * \frac{\tau}{t_d} \qquad S = \frac{1}{1 - a + (1 + a) * e^{\frac{-t_d}{\tau}}}$$

then

$$IOB_{contribution}(B, t) = B * (1 - S * (1 - a) * \left(\left(\frac{t^2}{\tau * t_d * (1 - a)} - \frac{t}{\tau} - 1\right) * e^{\frac{-t}{\tau}} + 1\right))$$

$$IOB_{activity}(B, t) = B * \frac{S}{\tau^2} * t * \left(1 - \frac{t}{t_d}\right) * e^{\frac{-t}{\tau}}$$

and

$$IOB_{bolus}(t) = \sum_B IOB_{contribution}(B, t)$$

$$IOB_{activity}(t) = \sum_B IOB_{activity}(B, t)$$

Diabetes Technology and Therapeutics
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Basal IOB calculation:

Basal IOB calculation is calculated by dividing temporary basal into 5 minutes chunks and processed like small bolus

$$\mathrm{B_i} = \frac{(\mathrm{TBR_i} - \mathrm{BR_i}) * 5}{\mathrm{D}}$$

where B_i [U] is insulin contribution of one chunk, TBR_i [U/h] temporary basal running, BR_i [U/h] common basal rate and D [min] is TBR duration.

Then

$$\mathrm{IOB_{basal}(t)} = \sum_{\mathrm{TBR}} \sum_{\mathrm{i}} \mathrm{IOB_{contribution}(B_i, t)}$$

and total IOB

$$\mathrm{IOB(t)} = \mathrm{IOB_{basal}(t)} + \mathrm{IOB_{bolus}(t)}$$

COB (Carbs-On-Board) calculation

Let

$$\Delta(\mathrm{t}) = \mathrm{G_t} - \mathrm{G_{t-5min}}$$

$$\mathrm{D(t)} = \Delta(\mathrm{t}) - \mathrm{IOB_{activity}(t)} * \mathrm{ISF} * 5$$

$$\mathrm{C_{absorbed}(t)} = D(t) * CR \,/\, ISF$$

where

D [mg/dL]... the difference between real glycemia change and expected insulin impact

Δ(t) [mg/dL] … 5 minutes glycemia change

$C_{absorbed}$[g] … carbs absorbed by body within last 5 minutes

then

$$\mathrm{COB(t)} = \sum C - \sum \mathrm{C_{absorbed}(t)}$$

Diabetes Technology and Therapeutics
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where

C [g] … consumed carbs

COB(t) [g] … remaining (unabsorbed) carbs

Safety values

Because new CGM measurements are received every 5 minutes, OpenAPS algorithm continually recalculates the insulin dosing adjustments required to keep BG in the target range. If the CGM provides erroneous data, such as due to dying sensor or a compression event (when patient is lying directly on the sensor and restricts the blood flow), OpenAPS algorithm reacts conservatively by withholding or slightly increasing insulin dosing. If 5, 10, or 15 minutes later the new data from the CGM indicates that the currently running temporary basal rate is no longer appropriate, OpenAPS algorithm simply cancels the temporary basal and return to the normally scheduled basal rate or make other dosing adjustments if necessary. By ensuring that all available information, including BG level, trend information and insulin dosing history, are used in determining all insulin dosing decisions, OpenAPS algorithm safely corrects high BG levels while minimizing hypoglycemia risk [openaps.readthedocs.io, androidaps.readthedocs.io].

In addition, OpenAPS algorithm is designed to simply and safely fall back to the patient's pre-programmed basal therapy whenever it receives conflicting information about what the appropriate course of action is (or when any required information is missing). For example, if BG is predicted to eventually go low but is actually rising at that moment, OpenAPS algorithm cancels any temporary basal and wait to see whether BG continues rising or begins to fall, and only then begin issuing the appropriate temporary basal commands [openaps.readthedocs.io, androidaps.readthedocs.io].

Additionally, OpenAPS algorithm further ensures safety by falling back to traditional "low glucose suspend" mode when current BG is below a configured threshold and falling or not rising fast enough. This ensures that insulin infusion is completely withheld while BG

Diabetes Technology and Therapeutics
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remains low for any reason, until it starts to recover, which maximizes the ability to recover from hypoglycemia [openaps.readthedocs.io, androidaps.readthedocs.io].

For the *in silico* simulation we used following safety parameters: maximum basal rate 10 U/h, maximum IOB 10U, which are higher than the commonly used values and are not limiting the algorithm more than other safety restrictions in place.

Five algorithm configurations of AndroidAPS have been tested:

1) AMA; AMA - Advanced meal assist

   Android APS works with changing temporary basal rate only while the premeal bolus is calculated by the bolus calculator and the full bolus is issued. AMA allows the system to high-temp basal rate more quickly after a meal bolus when carbohydrate information is entered. The basal is subject to a maximum limitation to 4 times the max basal value from profile and 3 times the current basal.

2) SMB_FB; SMB – SuperMicroBolus with the full bolus issued

   The second configuration consists of AndroidAPS working with SuperMicroBoluses while the premeal bolus is calculated by the bolus calculator and the full bolus is issued. SuperMicroBolus works on the same principle as super bolus, borrowing insulin from the future. The system issues small micro boluses and turns off basal for next 30 min if needed to safely balance out the peak insulin timing. This allows the system to adjust the blood glucose faster than otherwise would be achieved with temporary basal rates in AMA. The SuperMicroBolus is limited to 30 minutes of the current regular basal rate and to ½ of the insulin required amount (how much insulin is needed to bring patient to target range), as well as must not exceed the remaining portion of your maxIOB setting in preferences [openaps.readthedocs.io].

Diabetes Technology and Therapeutics
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3) SMB_HB; SMB SuperMicroBolus with the half of full bolus issued

   The third configuration consists of AndroidAPS working with SuperMicroBoluses while the premeal bolus is calculated by bolus calculator however only the half of calculated bolus is issued. This initial bolus, which only partly covers the carbohydrates (e.g. 1/2 of the estimated amount), is delivered and SuperMicroBoluses deliver the rest of any needed insulin.

4) SMB_CA; SMB SuperMicroBolus with no bolus, carbs announcement only

   The fourth configuration consists of AndroidAPS working with SuperMicroBoluses without meal bolus delivery. The algorithm receives the carb announcement (small or large meal) and performs all prandial insulin dosing using subsequent SuperMicroBoluses.

5) SMB; SMB SuperMicroBolus with no carbs announcements at all – full closed loop

   The last configuration is the AndroidAPS working with SuperMicroBoluses without bolus or carb announcement, relying on AndroidAPS' UnAnnouncedMeal (UAM) feature to deliver SuperMicroBoluses once the prandial BG rise is detected by CGM. In this case AndroidAPS works as a fully closed-loop [openaps.readthedocs.io].

In Silico Scenario

The 5 configurations of the algorithm are tested on the 100 *in silico* T1D virtual subjects on a 2-day Scenario, Scenario 1 (var sensitivity), characterized by a fixed random ±30% variation of the nominal insulin sensitivity from the beginning and throughout the trial. Three main meals per day are considered at 8:00 A.M., 1:00 P.M., and 8:00 P.M. containing 60, 60, and 80 g of CHO, respectively, and a snack of 30 g at 5:00 P.M. during the first day; at 8:00 A.M., 1:00 P.M., and 7:00 P.M. containing 50, 35, and 80 g of CHO, respectively, and two snacks at 10:00 A.M. and 10:00 P.M. containing 15 and 20 g during the second day. If the BG falls below 65 mg/dL, the protocol prescribes a rescue carbohydrate dose of 16 g, defined as hypotreatment (ht). Two ht are separated by at least 30 min. The CGM sensor is affected by the error noise described in [9,10].

Diabetes Technology and Therapeutics
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Configuration 2 and 3 of the algorithm are also tested onthe 100 *in silico* subjects on 4 robustness scenarios, all lasting 2 days with the same subjects' diet of Scenario 1 in order to make them comparable. The first two, Scenario 2 (over bolus) and Scenario 3 (under bolus), are characterized by a random 50% underestimation and overestimation of the carbohydrate contents, respectively. In particular, under and over-estimated boluses are tested: a 50g of carbohydrate meal was either underestimated by maximum 50% (bolus of 25g-49g of carbohydrate) or overestimated by maximum 50% (bolus of 51-75g of carbohydrate). The last two scenarios, Scenario 4 (anticipated bolus) and Scenario 5 (late bolus), are characterized by a fixed anticipation or delay of the meal announcement respect to the mealtime, respectively, in addition to the fixed random ±30% variation of the nominal insulin sensitivity tested in Scenario 1 (var sensitivity). In particular, advance and late boluses are tested: we simulated similar scenario for advance bolus delivered 15 minutes before meal (due to delayed mealtime) and late bolus delivered 15 minutes after meal.

Glucose Control Metrics

Performance metrics follow the consensus metrics for AP and CGM trials [11,12] and include mean (M) BG, standard deviation (SD), coefficient of variation (CV), percentage of time spent in euglycemic range [70-180] mg/dL (TIR), percentage of time spent in tight range [70-140] mg/dL (Ttt), percentage of time spent above 250 mg/dL (Ta), percentage of time spent between 54 and 70 mg/dL (T54-70) and Low Blood Glucose Index (LBGI). The average ht occurrences per patient (#ht) are also considered in the analysis. These metrics are computed overall during day & night (O), during night (N, 0:00 pm - 8:00 am), and as an average of all the post-prandial (PP) periods (4h).

Median [25^{th},75^{th}percentiles] for non-Gaussian and mean (± standard deviation) for Gaussian distributed data otherwise are reported for the various indices. To evaluate the significant differences, the more appropriated statistical test is selected based on the characteristics of the data distributions.

Diabetes Technology and Therapeutics
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Results

Scenario 1: Variation Insulin Sensitivity

The glucose profiles are shown in Figure 1 as median [25th,75thpercentiles] over the 100 *in silico* patients of the UVA/Padova simulator while the glucose control metrics are reported in Table 1.

As shown in Figure 1 and Table 1, all the configurations are able to avoid hyperglycemia above 250 mg/dL overall keeping the glucose in the range 70-180 mg/dL for about 90% of the time, with over 60% of the time in the tight target 70-140 mg/dL. Time in range 54-70 mg/dL is lower than 1.5% for all the configurations. The mean remains below 137 mg/dL for all the configurations. Low Blood Glucose Index (LBGI in Table 1) is lower than 1 without #ht. In Figure 1 a good glucose control is shown for all the proposed configurations. The most problematic meal is the snack at 10:00 during the second day, where AMA and SMB_FB result in some hypoglycemia; however, the others (SMB_HB, SMB_CA and SMB) are able to manage this meal without hypoglycemia episodes.

Scenario 2 & 3: Over & Under Bolusing calculating

The meal bolus overestimation by random +50% did not have an effect on % time spent in TIR (97.01 [93.0,100]%), as well as underestimation (85.47 [74.6, 91.2]%), in both tested configurations, as showed in Table 2. The SMB_HB configuration was more effective in hypoglycemia (T54-70%) prevention than SMB_FB (1.09[0, 2.03]%) vs (2.12[0.85, 3.75]%).

Scenario 4 & 5: Anticipated & Late Bolus

The best results were reached with boluses in advance, however, the late bolus resulted in no additional time in hyperglycemia and importantly % time between 54-70 mg/dL did not differ as well (0.69 [0, 1.68]%) vs (0.99 [0, 1.86]%) as showed in Table 3. The glycemic variability did not change in all 4 tested scenarios.

Diabetes Technology and Therapeutics
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Discussion

T1D related technology is currently mainly focused on the development of the artificial pancreas, however, there are currently only a few commercial AP systems with limited availability [13, 14, 15].

The published studies investigating DIYAPS have consistently demonstrated significant improvement in a variety of clinical and patient reported outcomes, with no accompanying severe adverse events [3, 4, 5, 6, 16, 17] but the opinion of educated public on DIYAPS remains very sceptical. However, we must keep in mind that the DIYAPS are the only ones readily accessible, regardless of the socio-economic status or the country of origin.

The *in silico* testing of the closed-loop control algorithm is regarded as a prerequisite for clinical trials of artificial pancreas. To our knowledge, this is the first study testing DIYAPS algorithm *in silico* and demonstrating the safety and efficacy of the AndroidAPS implementation of oref0 and oref1 of the OpenAPS algorithm. Our results are consistent with data of the DIYAPS in the real-life. Braune et al. show data from various DIYAPS reaching the TIR of 80.7% [15], a study by Melmer et al analyzing donated data from CGM records of adults using a variety of version of the algorithm OpenAPS and AndroidAPS with the TIR of 80% [5]. The retrospective analyses of data of children with T1D using AndroidAPS (oref0) by Jiranova [16] reported TIR over 80% as well. Direct comparison with controlled closed-loop studies is not possible, however all 5 five tested configurations show results superior or comparable to official or academic tested AP technology [14,15,18,19,20,21,22,23,24,25] with TIR above 90% and TIT above 60% in each of the tested configurations. On the other hand, the real-life data from DIYAPS reported a slightly higher time below 70 mg/dL of 5% [3, 17] when compared to *in silico* testing, but the time below 54 mg/dL of less than 1% was comparable.

Our *in silico* study showed that the oref1 version (using SuperMicroBolus) is more effective than the oref0 (changing temporary basal only) in hyperglycemia correction, especially in the postprandial period. The necessity of precise carbohydrate counting is a limitation of current commercial hybrid closed loop systems. It does not relieve the

Diabetes Technology and Therapeutics
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patients of their daily tasks and the postprandial glucose control remains suboptimal, mostly due to post meal hyperglycemia [25]. This is even more pronounced in younger children [26] where high variability of daily insulin requirements [27] and morning resistance [28] play a crucial role. The *in silico* testing has proved that all of the tested configurations were effective in reducing post-meal hyperglycemia. However, the configurations 1 (AMA) and 2 (SMB_FB) were effective usually at the cost of post-meal hypoglycemia. Interestingly, post-meal hypoglycemia was avoided in the configuration 3 (SMB_HB), which combines half a dose of the premeal bolus and several smaller SuperMicroBoluses for correction of post-prandial hyperglycemia. The SMB_HB was additionally able to maintain post-prandial glycemia after morning snack below 170 mg/dL if the bolus was administered 15 minutes before the meal and below 180 mg/dL if the bolus was administered 15 minutes after or with the meal. Importantly, the configuration 3 (SMB_HB) did not lead to increase of post meal hypoglycemia in all tested scenarios as opposed to study by Lee presenting Enhanced hybrid closed loop G670 [17].

Several studies suggested including glucagon to the closed-loop delivery in order to avoid hypoglycaemia [30,31]. On the other hand, Castle el al showed that the time in hypoglycemia on the single hormone closed loop did not differ markedly from dual hormone closed loop -1.3% vs. 2.8%, respectively [32]. We have demonstrated that an appropriate response to over- or underestimated meal bolus prevented prolonged hypo-/hyperglycemia, which are both common scenarios expected to occur in the real world use of the device. The *in silico* results were even more promising than in the study by Chase and Chernavysky et al, which studied the effect of over, under and missed bolus with a single hormone AP system [33, 34], but these findings need to be confirmed by the real-life results.

However, a noted limitation of this paper is that the results have been obtained *in silico* on a 2-day protocol. Our results are consistent with the results reported by studies describing real-life data DIY systems users. However, DIY technologies are typically used by a highly, motivated and technology-skilled population of individuals with T1D, which may cause a selection bias. The simulation results provides the preliminary evidence of safety and efficacy and needs to be confirmed by standard randomized clinical trials. Importantly,

our promising *in silico* data cannot guarantee safety if the AndroidAPS would be use in an inappropriate way by ignoring the safety tools in the profile setting.

To conclude, the results show that the DIYAPS algorithm was safe in each of the five configurations tested. It was able to minimize glycemic excursions, including both prolonged hypo- and hyperglycemia. Our results are very promising as currently only 17% of all children and adolescents with T1D achieve the HbA1c<58 mmol/mol [35]. Simplifying diabetes management might improve the quality of life of T1D patients, especially by reducing the need for precise carbohydrate counting. At the same time, it is crucial not to increase the risk of hypoglycemia. The configuration 3 of AndroidAPS (SMB_HB) has shown efficacy in hypoglycemia prevention (<1%) while increasing TIR (91%), and is recommended as the version of AndroidAPS and/or OpenAPS algorithm to be used for further efficacy assessment in prospective control trials for T1D patients of all ages.

Diabetes Technology and Therapeutics
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References

1. Weisman, A., Bai, J. W., Cardinez, M., et al. Effect of artificial pancreas systems on glycaemic control in patients with type 1 diabetes: a systematic review and meta-analysis of outpatient randomised controlled trials. The Lancet Diabetes &Endocrinology, 2017, 5(7): 501-512.

2. Kovatchev, Boris P. Metrics for glycaemic control-from HbA_{1c} to continuous glucose monitoring. Nature Reviews Endocrinology, 2017, 13(7): 425.

3. Lewis, D., Leibrand, S., & #OpenAPS Community. Real-world use of open source artificial pancreas systems. Journal of diabetes science and technology, 2016, 10(6): 1411-1411.

4. Petruzelkova, L., Soupal, J., Plasova, V. et al. ExcellentGlycemicControlMaintained by Open-Source Hybrid Closed-LoopAndroidAPSDuring and AfterSustainedPhysicalActivity. Diabetes TechnolTher., 2018, 20(11):744-750.

5. Melmer, A., Züger, T., Lewis, DM., Leibrand, S., et al.Glycaemiccontrol in individualswith type 1 diabetes usingan open source artificialpancreassystem (OpenAPS). Diabetes ObesMetab., 2019, 21(10):2333-2337.

6. Litchman ML, Lewis D, Kelly LA, Twitter Analysisof #OpenAPS DIY ArtificialPancreas Technology Use SuggestsImproved A1C and QualityofLife, J Diabetes SciTechnol., 2019, 13(2):164-170.

7. Viceconti, M., Cobelli, C., Haddad, T., et al. In silico assessment of biomedical products: the conundrum of rare but not so rare events in two case studies. Proceedings of the Institution of Mechanical Engineers, Part H: Journal of Engineering in Medicine, 2017, 231(5): 455-466.

8. Kovatchev, B. P., Breton, M., Dalla Man, C., et al. In silico preclinical trials: a proof of concept in closed-loop control of type 1 diabetes. Journal of diabetes science and technology, 2009, 3(1): 44-55.

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9. Visentin, R., Campos-Náñez, E., Schiavon, M., et al. The UVA/Padova type 1 diabetes simulator goes from single meal to single day. Journal of Diabetes Science and Technology, 2018, 12(2): 273-281.

10. Toffanin, C., Visentin, R., Messori, M., et al. Toward a run-to-run adaptive artificial pancreas: In silico results. IEEE Transactions on Biomedical Engineering, 2018, 65(3): 479-488.

11. Maahs, D. M., Buckingham, B. A., Castle, J. R., et al. Outcome measures for artificial pancreas clinical trials: a consensus report. Diabetes Care, 2016, 39(7): 1175-1179.

12. Batellino, T., Danne T., Bergenstal, RM., et al, Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range, Diabetes Care, 2019, 42(8): 1593-1603.

13. Garg, S., Weinzimer, S., Tamborlane, W., et al. Glucose Outcomes with the In-Home Use of a Hybrid Closed-Loop Insulin Delivery System in Adolescents and Adults with Type 1 Diabetes. Diabetes TechnolTher. 2017, 19(3):155-163.

14. Brown SA, Kovatchev BP, Raghinaru D et al. Six-Month Randomized, Multicenter Trial of Closed-Loop Control in Type 1 Diabetes. N Engl J Med. 2019 Oct 31;381(18):1707-1717.

15. Sherr JL, Buckingham BA, Forlenza GP et al. Safety and Performance oftheOmnipod Hybrid Closed-LoopSystem in Adults, Adolescents, and Childrenwith Type 1 Diabetes Over 5 DaysUnder Free-LivingConditions.Diabetes TechnolTher. 2019 Oct 29.

16. Braune, K., O'Donnell, S., Cleal, B., et al. Real-World Use of Do-It-YourselfArtificialPancreas Systems in Children and AdolescentsWith Type 1 Diabetes: Online Survey and AnalysisofSelf-ReportedClinicalOutcomes. JMIR MhealthUhealth., 2019, 7(7):e14087.

17. Jiranova, P., Sumnik, Z., Kozak, M., et al. Children with optimally controlled type 1 diabetes profit from the switch from sensor-augmented pump to AndroidAPS Hybrid Closed Loop. DTT under review.

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18. Bally, L., Thabit, H., Kojzar, H., Mader, JK., et al. Day-and-night glycaemiccontrolwithclosed-loop insulin delivery versus conventional insulin pump therapy in free-livingadultswithwellcontrolled type 1 diabetes: an open-label, randomised, crossover study.Lancet Diabetes Endocrinol., 2017, 5(4):261-270.

19. Lee MH, Vogrin S, Paldus B, et al. Glucose Control in Adults with Type 1 Diabetes Using a Medtronic Prototype Enhanced-Hybrid Closed-Loop System: A Feasibility Study,DiabetesTechnolTher., 2019, 21(9):499-506.

20. Forlenza GP, Ekhlaspour L, Breton Met al.Successful At-Home Use of the Tandem Control-IQ Artificial Pancreas System in Young Children During a Randomized Controlled Trial. Diabetes TechnolTher. 2019, 21(4):159-169.

21. Stone MP, Agrawal P, Chen X at al.Retrospective Analysis of 3-Month Real-World Glucose Data
After the MiniMed 670G System Commercial Launch,DiabetesTechnolTher., 2018, 20(10):689-692.

22. Del Favero S, Boscari F, Messori M, et al.Randomized summer camp crossover trial in 5- to 9-year-old children: outpatient wearable artificial pancreas is feasible and safe, Diabetes Care,2016, 39(7):1180-1185.

23. Messori M, Kropff J, DelFavero S, et al. IndividuallyAdaptiveArtificialPancreas in SubjectswithType 1 Diabetes: A One-MonthProof-of-Concept Trial in Free-LivingConditions, Diabetes Technology andTherapeutics, 2017, 19(10): 560-571.

24. Renard E, Farret A, Kropff J, et al. Day and Night Closed-LoopGlucoseControl in PatientsWith Type 1 Diabetes Under Free-LivingConditions: Resultsof a Single-Arm1-MonthExperienceComparedWith a PreviouslyReportedFeasibility Study ofEvening and Night atHome, Diabetes Care, 2016, 39(7): 1151-1160.

25. Tauschmann M, Allen JM, Wilinska ME, et al.Day-and-Night Hybrid Closed-Loop Insulin Delivery in AdolescentsWith Type 1 Diabetes: A Free-Living, RandomizedClinicalTrial,Diabetes Care, 2016, 39(7):1168-1174. doi: 10.2337/dc15-2078. Epub 2016 Jan

26. Dovc K, Boughton C, Tauschmann M, Thabit H et al. YoungChildrenHaveHigher Variability of Insulin Requirements: ObservationsDuring Hybrid Closed-Loop Insulin Delivery, Diabetes Care, 2019, 42(7):1344-1347.

27. Tansey M, Beck R, Ruedy K et al.Persistently high glucose levels in youngchildren with type 1 diabetes,Pediatr Diabetes., 2016, 17(2):93-100. doi: 10.1111/pedi.12248. Epub 2014 Dec 11.

28. Nicolajsen T, Samuelsson A, Hanas R.et al. Insulin dosesbefore and oneyearafter pump start: childrenhave a reverseddawnphenomenon,J Diabetes SciTechnol., 2012, 6(3):589-594.

29. AlemzadehR, Hoffmann RG, DasguptaM. Development of optimal kids insulin dosing system formulas for young children with type 1 diabetes mellitus,Diabetes TechnolTher., 2012, 14(5):418-422. doi: 10.1089/dia.2011.0184. Epub 2012 Jan 12.

30. Peters TM, Haidar A.Dual-hormone artificialpancreas: benefits and limitationscomparedwith single-hormone systems,Diabet Med., 2018, 35(4):450-459.

31. Gingras V, Smaoui MR, CameliCet al.Impact of erroneous meal insulin bolus with dual-hormone artificial pancreas using a simplified bolus strategy - A randomized controlled trial, Sci Rep., 20188(1):2621.

32. Castle JR, El Youssef J, Wilson LM, Reddy R et al. Randomized Outpatient Trial of Single- and Dual-Hormone Closed-Loop Systems That Adapt to Exercise Using Wearable Sensors, Diabetes Care, 2018, 41(7):1471-1477.

33. Chase HP, Doyle FJ 3rd, Zisser H. Multicenter closed-loop/hybrid meal bolus insulin delivery with type 1 diabetes,DiabetesTechnolTher., 2014, 16(10):623-32.

34. Cherñavvsky DR, DeBoer MD, Keith-Hynes Pet al. Use of an artificial pancreas among adolescents for a missed snack bolus and an underestimated meal bolus, Pediatr Diabetes, 2016, 17(1):28-35.

35. Foster NC, Beck RW, Miller KM et al.Stateof Type 1 Diabetes Management and Outcomesfromthe T1D Exchange in 2016-2018, Diabetes TechnolTher., 2019, 21(2):66-72.

Table 1: Glucose metrics for all the 5 configurations of the algorithm on Scenario 1 (var sensitivity).

		Scenario 1 (var sensitivity)		
		O	N	PP
M (mg/dl)	AMA	128.28 (±22.90)	119.21 [110.77, 138.61]	130.19 (±26.26)
	SMB_FB	125.20 (±22.02)	116.41 [105.06, 133.23]	128.58 (±25.37)
	SMB_HB	131.41 (±20.62)	116.96 [106.81, 135.15]	137.91 (±23.53)
	SMB_CA	136.39 (±21.14)	117.90 [107.36, 135.94]	145.33 (±24.22)
	SMB	136.37 (±21.11)	117.78 [108.23, 135.93]	145.30 (±24.19)
SD (mg/dl)	AMA	26.96 [20.33, 32.49]	14.49 [10.46, 18.63]	29.20 [21.69, 35.62]
	SMB_FB	26.40 [19.95, 32.07]	14.28 [10.61, 19.07]	28.13 [21.06, 35.12]
	SMB_HB	27.37 [21.58, 33.77]	14.09 [10.91, 18.83]	28.00 [20.86, 34.57]
	SMB_CA	30.19 [24.06, 36.50]	14.20 [10.90, 18.75]	31.11 [23.44, 37.78]
	SMB	30.33 [23.82, 36.18]	14.17 [10.94, 18.50]	31.39 [23.06, 37.56]

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CV (mg/dl)	AMA	0.22 (±0.18)	0.11 [0.08, 0.15]	0.22 [0.16, 0.28]
	SMB_FB	0.22 (±0.18)	0.12 [0.09, 0.16]	0.23 [0.16, 0.29]
	SMB_HB	0.22 (±0.06)	0.11 [0.09, 0.16]	0.21 [0.16, 0.27]
	SMB_CA	0.23 (±0.05)	0.12 [0.09, 0.16]	0.22 [0.17, 0.27]
	SMB	0.23 (±0.05)	0.12 [0.09, 0.16]	0.22 [0.17, 0.27]
TIR (%)	AMA	90.70 [85.23, 96.79]	100.00 [94.02, 100.00]	87.77 [78.68, 95.67]
	SMB_FB	90.42 [85.21, 97.03]	100.00 [92.35, 100.00]	87.86 [79.56, 96.22]
	SMB_HB	91.15 [82.96, 96.32]	100.00 [92.49, 100.00]	89.81 [74.23, 95.48]
	SMB_CA	89.31 [77.49, 95.04]	100.00 [92.98, 100.00]	86.24 [67.33, 93.86]
	SMB	89.10 [77.82, 95.28]	100.00 [93.32, 100.00]	86.22 [66.94, 93.88]
Ttt (%)	AMA	65.03 [45.56, 82.56]	86.16 [60.71, 100.00]	58.16 [36.98, 78.06]
	SMB_FB	68.60 [49.55, 84.12]	89.01 [69.47, 100.00]	59.00 [39.31, 79.03]
	SMB_HB	63.80 [42.92, 82.49]	90.13 [68.36, 100.00]	50.40 [29.65, 74.75]
	SMB_CA	59.08 [39.00, 76.71]	89.78 [67.25, 100.00]	41.48 [27.06, 67.16]
	SMB	59.04 [39.10,	90.82 [67.25, 100.00]	41.74 [27.20, 66.97]

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		77.40]		
Ta (%)	AMA	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]
	SMB_FB	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]
	SMB_HB	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]
	SMB_CA	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]
	SMB	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]
T54-70 (%)	AMA	1.41 [0.00, 3.42]	0.00 [0.00, 0.00]	2.00 [0.00, 3.71]
	SMB_FB	1.48 [0.00, 3.85]	0.00 [0.00, 0.00]	1.78 [0.00, 4.05]
	SMB_HB	1.37 [0.00, 2.93]	0.00 [0.00, 0.00]	1.12 [0.00, 3.19]
	SMB_CA	1.06 [0.00, 2.26]	0.00 [0.00, 0.00]	0.45 [0.00, 2.52]
	SMB	1.08 [0.00, 1.98]	0.00 [0.00, 0.00]	0.38 [0.00, 2.45]
#ht	AMA	0.00 [0.00, 5.00]	0.00 [0.00, 0.00]	0.00 [0.00, 5.00]
	SMB_FB	2.00 [0.00, 6.00]	0.00 [0.00, 0.00]	0.50 [0.00, 5.00]
	SMB_HB	0.00 [0.00, 3.50]	0.00 [0.00, 0.00]	0.00 [0.00, 3.00]
	SMB_CA	0.00 [0.00, 3.00]	0.00 [0.00, 0.00]	0.00 [0.00, 2.00]
	SMB	0.00 [0.00, 3.00]	0.00 [0.00, 0.00]	0.00 [0.00, 2.00]
LBGI	AMA	0.86 [0.16, 2.56]	0.06 [0.00, 0.49]	0.93 [0.11, 3.46]
	SMB_FB	0.98 [0.18, 2.68]	0.17 [0.00, 0.94]	1.02 [0.12, 3.23]
	SMB_HB	0.66 [0.14, 1.64]	0.17 [0.00, 0.71]	0.44 [0.06, 1.77]
	SMB_CA	0.50 [0.14, 1.27]	0.16 [0.00, 0.66]	0.31 [0.06, 1.25]
	SMB	0.50 [0.13, 1.23]	0.16 [0.00, 0.68]	0.30 [0.06, 1.21]

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Table 2: Glucose metrics of the 100 in silico patients for configuration 2 and 3 of the algorithm on Scenario 2 (over bolus) and Scenario 3 (under bolus) reported as media (±SD) for normally distributed data and as median [25th – 75th percentiles] otherwise. Meal bolus randomly over- and under-estimated (+/-50%). The significant results are highlighted in bold. P-value (p) significance levels are:
a := p < 0.001, b := p < 0.01, c := p < 0.05.

		Scenario 2 (over bolus)		
		O	N	PP
M (mg/dl)	SMB_FB	**118.82 (± 11.26)**	119.80 [111.64, 130.38]	**115.98 [108.69, 126.60]**
	SMB_HB	**124.23^{a} (± 11.31)**	119.06 [112.16, 129.58]	**124.25^{a} [117.71, 133.09]**
SD (mg/dl)	SMB_FB	**24.01 [18.87, 29.54]**	12.76 [9.53, 16.63]	**25.39 [19.31, 31.24]**
	SMB_HB	**22.16^{c} [16.70, 28.39]**	12.78 [9.34, 15.89]	**23.34^{b} [16.95, 30.15]**
CV (mg/dl)	SMB_FB	**0.21 [0.16, 0.26]**	0.10 [0.08, 0.13]	**0.22 [0.17, 0.27]**
	SMB_HB	**0.18^{a} [0.14, 0.22]**	0.10 [0.07, 0.13]	**0.18^{a} [0.14, 0.24]**
TIR (%)	SMB_FB	**94.13 [89.86, 98.18]**	100.00 [100.00, 100.00]	**92.41 [86.34, 97.17]**
	SMB_HB	**97.01^{a} [93.01, 100.00]**	100.00 [100.00, 100.00]	**96.14^{a} [91.27, 100.00]**
Ttt (%)	SMB_FB	**80.82 [64.01, 89.29]**	91.72 [76.29, 100.00]	**76.58 [62.09, 87.20]**

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	SMB_HB	**78.48[b] [60.27, 89.85]**	92.63 [76.70, 100.00]	**73.56[a] [56.45, 87.10]**
Ta (%)	SMB_FB	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]
	SMB_HB	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]
T54-70 (%)	SMB_FB	2.12 [0.85, 3.75]	0.00 [0.00, 0.00]	2.83 [0.48, 5.47]
	SMB_HB	**1.09[a] [0.00, 2.03]**	0.00 [0.00, 0.00]	**0.79[a] [0.00, 2.93]**
#ht	SMB_FB	**5.00 [1.00, 8.00]**	0.00 [0.00, 0.00]	**4.00 [0.00, 8.00]**
	SMB_HB	**2.00[a] [0.00, 5.00]**	0.00 [0.00, 0.00]	**0.00[a] [0.00, 4.00]**
LBGI	SMB_FB	**1.43 [0.56, 2.54]**	0.08 [0.01, 0.34]	**1.94 [0.48, 3.06]**
	SMB_HB	**0.60[a] [0.23, 1.45]**	0.08 [0.01, 0.30]	**0.64[a] [0.15, 1.74]**
		Scenario 3 (under bolus)		
		O	N	PP
M (mg/dl)	SMB_FB	**137.22 (± 13.91)**	**121.96 [112.89, 131.78]**	**141.99 [134.39, 155.86]**
	SMB_HB	**142.61[a] (± 15.22)**	**122.92[a] [113.15, 133.04]**	**149.90[a] [141.46, 163.80]**
SD (mg/dl)	SMB_FB	**33.51 [26.38, 41.96]**	**13.60 [10.24, 17.54]**	**37.75 (± 12.53)**
	SMB_HB	**35.48[a] [28.44, 44.37]**	**13.86[b] [10.44, 17.74]**	**39.83[a] (± 13.50)**
CV (mg/dl)	SMB_FB	**0.25 (± 0.06)**	**0.11 [0.08, 0.14]**	0.26 (±0.07)
	SMB_HB	**0.26[a] (± 0.06)**	**0.11[c] [0.08, 0.14]**	0.26 (±0.07)

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TIR (%)	SMB_FB	**87.09 [77.94, 93.94]**	**100.00 [100.00, 100.00]**	**81.15 [67.09, 91.10]**
	SMB_HB	**85.47[a] [74.61, 91.17]**	**100.00[b] [99.65, 100.00]**	**77.82[a] [61.21, 87.32]**
Ttt (%)	SMB_FB	**57.50 [44.67, 71.40]**	**88.87 [72.81, 100.00]**	**44.42 (± 18.08)**
	SMB_HB	**53.82[a] [40.63, 67.16]**	**86.65[a] [69.05, 99.30]**	**38.83[a] (± 16.79)**
Ta(%)	SMB_FB	**0.00 [0.00, 1.28]**	0.00 [0.00, 0.00]	**0.00 [0.00, 1.95]**
	SMB_HB	**0.00[a] [0.00, 2.79]**	0.00 [0.00, 0.00]	**0.00[a] [0.00, 4.09]**
T54-70 (%)	SMB_FB	**1.18 [0.00, 2.12]**	0.00 [0.00, 0.00]	**1.24 [0.00, 2.76]**
	SMB_HB	**0.90[b] [0.00, 1.82]**	0.00 [0.00, 0.00]	**0.45[c] [0.00, 2.43]**
#ht	SMB_FB	**2.00 [0.00, 6.00]**	0.00 [0.00, 0.00]	**2.00 [0.00, 5.00]**
	SMB_HB	**1.50[a] [0.00, 5.00]**	0.00 [0.00, 0.00]	**0.00[a] [0.00, 3.50]**
LBGI	SMB_FB	**0.64 [0.21, 1.80]**	**0.07 [0.00, 0.43]**	**0.58 [0.11, 1.97]**
	SMB_HB	**0.42[a] [0.14, 1.25]**	**0.05[a] [0.00, 0.34]**	**0.30[a] [0.05, 1.27]**

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Table 3: Glucose metrics of the 100 in silico patients for configuration 2 and 3 of the algorithm on Scenario 4 (anticipated bolus) and Scenario 5 (late bolus) reported as media (±SD) for normally distributed data and as median [25th – 75th percentiles] otherwise. Meal bolus administered 15 minutes after meal. The significant results are highlighted in bold. P-value (p) significance levels are:

a := p < 0.001, b := p < 0.01, c := p < 0.05.

		Scenario 4 (anticipated bolus)		
		O	N	PP
M (mg/dl)	SMB_FB	**128.49 (± 21.61)**	**120.31 [111.77, 137.23]**	**130.97 (± 25.13)**
	SMB_HB	**135.41^{a} (± 19.71)**	**121.34^{a} [112.73, 139.01]**	**141.33^{a} (± 22.66)**
SD (mg/dl)	SMB_FB	**24.81 [19.96, 30.56]**	**13.30 [10.26, 17.40]**	26.88 [21.61, 33.86]
	SMB_HB	**25.51^{c} [19.76, 31.89]**	**13.57^{b} [10.53, 17.20]**	26.91 [19.91, 33.74]
CV (mg/dl)	SMB_FB	0.21 [0.16, 0.24]	**0.11 [0.08, 0.14]**	**0.21 [0.17, 0.26]**
	SMB_HB	0.20 [0.16, 0.23]	**0.11^{c} [0.08, 0.13]**	**0.19^{a} [0.15, 0.25]**
Tt (%)	SMB_FB	92.33 [86.19, 96.81]	100.00 [94.02, 100.00]	89.67 [80.70, 95.48]
	SMB_HB	92.59 [82.56, 98.07]	100.00 [95.06, 100.00]	90.15 [72.77, 97.72]
Ttt70-140 (%)	SMB_FB	**61.78 [45.75, 84.45]**	86.72 [63.98, 100.00]	**53.33 [36.01, 78.94]**

Diabetes Technology and Therapeutics
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	SMB_HB	**57.25[a] [38.56, 80.51]**	86.09 [64.12, 100.00]	**45.10[a] [27.23, 75.13]**
Ta250 (%)	SMB_FB	**0.00 [0.00, 0.00]**	0.00 [0.00, 0.00]	**0.00 [0.00, 0.00]**
	SMB_HB	**0.00[b] [0.00, 0.00]**	0.00 [0.00, 0.00]	**0.00[b] [0.00, 0.00]**
Tr54-70 (%)	SMB_FB	**1.39 [0.00, 2.99]**	0.00 [0.00, 0.00]	**1.83 [0.00, 4.24]**
	SMB_HB	**0.69[a] [0.00, 1.68]**	0.00 [0.00, 0.00]	**0.00[a] [0.00, 2.21]**
#ht	SMB_FB	**3.00 [0.00, 6.00]**	0.00 [0.00, 0.00]	**3.00 [0.00, 6.00]**
	SMB_HB	**0.00[a] [0.00, 4.00]**	0.00 [0.00, 0.00]	**0.00[a] [0.00, 3.00]**
LBGI	SMB_FB	**0.79 [0.16, 1.91]**	0.06 [0.00, 0.33]	**1.03 [0.11, 2.29]**
	SMB_HB	**0.37[a] [0.07, 1.01]**	0.05 [0.00, 0.31]	**0.30[a] [0.04, 1.20]**
		Scenario 5 (late bolus)		
		O	N	PP
M (mg/dl)	SMB_FB	**131.51 (± 21.39)**	**119.15 [112.44, 136.24]**	**135.80 (± 25.09)**
	SMB_HB	**137.27[a] (± 19.72)**	**121.08[a] [113.28, 138.69]**	**144.25[a] (± 22.83)**
SD (mg/dl)	SMB_FB	**27.15 [20.50, 32.07]**	**13.02 [9.90, 17.96]**	**29.54 [21.11, 34.50]**
	SMB_HB	**27.97[a] [21.93, 33.67]**	**13.33[c] [9.89, 18.37]**	**30.07[a] [21.65,**

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				34.49]
CV (mg/dl)	SMB_FB	**0.21 [0.16, 0.25]**	**0.11 [0.08, 0.14]**	**0.22 [0.15, 0.28]**
	SMB_HB	**0.21[c] [0.17, 0.25]**	**0.11[c] [0.08, 0.14]**	**0.21[c] [0.16, 0.26]**
TIR(%)	SMB_FB	**91.13 [83.25, 97.28]**	**100.00 [95.83, 100.00]**	**87.32 [76.37, 95.93]**
	SMB_HB	**90.18[a] [79.85, 96.51]**	**100.00[c] [94.23, 100.00]**	**87.93[a] [69.56, 95.74]**
Ttt (%)	SMB_FB	**61.63 [44.03, 79.17]**	**87.55 [64.67, 100.00]**	**51.24 [31.70, 73.08]**
	SMB_HB	**56.77[a] [38.37, 77.39]**	**87.00[c] [64.39, 100.00]**	**40.60[a] [25.94, 68.97]**
Ta (%)	SMB_FB	**0.00 [0.00, 0.00]**	0.00 [0.00, 0.00]	**0.00 [0.00, 0.00]**
	SMB_HB	**0.00[b] [0.00, 0.00]**	0.00 [0.00, 0.00]	**0.00[b] [0.00, 0.00]**
T54-70 (%)	SMB_FB	1.11 [0.00, 1.96]	0.00 [0.00, 0.00]	**1.19 [0.00, 2.83]**
	SMB_HB	0.99 [0.00, 1.86]	0.00 [0.00, 0.00]	**0.79[c] [0.00, 2.64]**
#ht	SMB_FB	**2.00 [0.00, 6.00]**	0.00 [0.00, 0.00]	**0.50 [0.00, 5.50]**
	SMB_HB	**0.50[a] [0.00, 4.00]**	0.00 [0.00, 0.00]	**0.00[a] [0.00, 4.00]**
LBGI	SMB_FB	**0.53 [0.08, 1.77]**	0.06 [0.00, 0.30]	**0.47 [0.05, 2.38]**
	SMB_HB	**0.42[a] [0.07, 1.15]**	0.05 [0.00, 0.31]	**0.26[a] [0.03, 1.24]**

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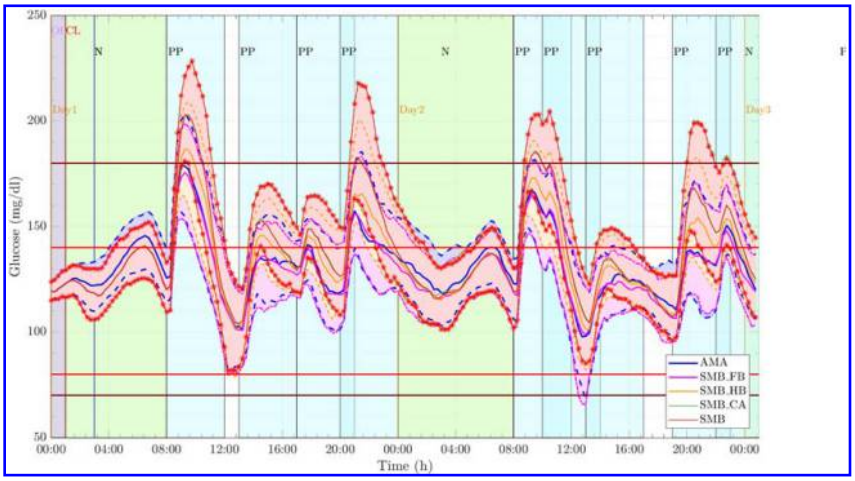

Figure 1: Glucose profiles of the 100 *in silico* patients reported as median [25th – 75th percentiles] for all the 5 proposed configurations of the algorithm on Scenario 1 (var sensitivity).