npj | digital medicine

Article

Published in partnership with Seoul National University Bundang Hospital

https://doi.org/10.1038/s41746-025-01679-y

Human-machine co-adaptation to automated insulin delivery: a randomised clinical trial using digital twin technology

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Most automated insulin delivery (AID) algorithms do not adapt to the changing physiology of their users, and none provide interactive means for user adaptation to the actions of AID. This randomised clinical trial tested human-machine co-adaptation to AID using new 'digital twin' replay simulation technology. Seventy-two individuals with T1D completed the 6-month study. The two study arms differed by the order of administration of information feedback (widely used metrics and graphs) and in silico co-adaptation routine, which: (i) transmitted AID data to a cloud application; (ii) mapped each person to their digital twin; (iii) optimized AID control parameters bi-weekly, and (iv) enabled users to experiment with what-if scenarios replayed via their own digital twins. In silico co-adaptation improved the primary outcome, time-in-range (3.9–10 mmol/L), from 72 to 77 percent ($p < 0.01$) and reduced glycated haemoglobin from 6.8 to 6.6 percent. Information feedback did not have additional effect to AID alone. (Clinical Trials Registration: NCT05610111 (November 10, 2022)).

Rigorous clinical trials established Automated Insulin Delivery (AID) systems as viable and superior to standard care treatment for type 1 diabetes (T1D)[1–8]. AID systems have firmly transitioned to the clinical practice of T1D and made first strides into insulin-using type 2 diabetes as well[9,10]. Several commercial systems are available, and multiple publications reported outcomes of their real-world use by thousands of people for extended periods of time[11–15]. Meta analyses affirmed that AID systems work as intended, improving glycaemic control and the clinical outcomes for those with T1D[16–19]. However, while the most advanced AID systems have consistently shown improvements in overnight glycaemic control, virtually all studies to date point to the fact that achieving optimal control during the day is still a problem[1,16,20]. This results from typically fewer disturbances occurring at night, e.g. no meals or exercise that are the major contributors to daytime glucose fluctuations. Consequently, the vast majority of contemporary AID systems are 'hybrid', in that the user is expected to announce meals to the system and prompt prandial insulin boluses[1,3,4,7,17]. While clinical trials with fully-automated AID systems are ongoing, the current engineering opinion is that full automation would require continual adaptation of the AID algorithm to the changing physiology and behaviours of its user[21].

It has been also observed that after an initial improvement in glycaemic control, virtually all contemporary AID systems rapidly reach a performance 'plateau', typically achieving a steady time in the target range (TIR, 3.9–10 mmol/L) of 70–75 percent[1,11–13]. The reason for this saturation effect is generally unclear, but an informed speculation is that patients using AID systems do not adapt well to the system's actions. This stems from the fact that the information feedback provided by AID software is typically limited to summary statistics, e.g. TIR and times above/below the target range, an ambulatory glucose profile (AGP)[22] based on continuous glucose monitoring (CGM) data and, occasionally, advice based on artificial intelligence methods[23–26]. This information is generally passive and does not provide the user with specific instructions on how to optimise their AID system parameters, or with interactive means to assess what would happen if they changed parameters of their AID treatment regimen.

A computer simulation model of human genotype, phenotype, physiology, or behaviour is capable of representing a person's metabolic system including their glycaemic profile and is often termed a 'digital twin'. Because treatment approaches can be tested fast and cost-effectively on digital twins prior to implementing in the clinical practice, they are considered key to personalised medicine[27]. In diabetes, the concept of digital twins began in 2008 when a computer simulator of the human metabolic system, jointly developed at the Universities of Padova and Virginia, was accepted by the Food and Drug Administration (FDA) as a substitute to animal trials in the

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testing of insulin treatment strategies[28]. Today, this simulation environment is widely used for research and regulatory purposes[29]. The current version is equipped with over 6000 digital twins of people with type 1 and type 2 diabetes, allowing for various in silico trials.

In this manuscript, we integrate the previously unrelated AID and digital twin technologies into a system that automatically maps each AID user to their corresponding digital twin in a cloud-based ecosystem. Through simulation, this system optimises typical therapy parameters, such as carbohydrate ratio (CR), correction factor (CF) and basal rate, proposing an optimised solution that adapts biweekly to the patient's changing physiology and behaviour[30]. Additionally, it allows patients to experiment with their own data using interactive computer simulation, providing insights into the potential outcomes of changing AID parameters. This latter feature was first tested in pilot clinical studies[31,32], refined and deployed in the larger 6-month randomised clinical trial reported below.

Table 1 | Demographics and baseline characteristics

	Entire population (*N* = 72)	Group A (escalation) (*N* = 38)	Group B (de-escalation) (*N* = 34)
Age (years)	42.8 (15.1)	41.6 (15.5)	44.1 (14.7)
	[19.0 - 69.0]	[19.0–69.0]	[19.0–68.0]
Weight (kg)	82.7 (18.9)	83.2 (21.3)	82.1 (16.2)
	[53.1–137.3]	[53.1–137.3]	[54.4–131.5]
Height (cm)	168.0 (9.4)	168.7 (10.2)	167.2 (8.4)
	[149.9–190.5]	[149.9–190.5]	[149.9–182.9]
Screening glycated haemoglobin (%)	6.8 (0.8)	6.7 (0.7)	6.8 (0.8)
	[5.3–9.2]	[5.4–8.5]	[5.3–9.2]
Gender			
-Male	29.2%	23.7%	35.3%
-Female	68.1%	71.1%	64.7%
-Other	1.4%	2.6%	0.0%
-Prefer not to answer	1.4%	2.6%	0.0%
Race			
-White	93.1%	94.7%	91.2%
-Black/African American	4.2%	2.6%	5.9%
-Other	2.8%	2.6%	2.9%
Ethnicity			
-Non-Hispanic	91.7%	94.7%	88.2%

Results are reported as mean (SD) [range] for continuous variables and as a percentage over the total for categorical variables

Results

Participant characteristics

Seventy-seven individuals were recruited and 72 completed the 6-month study (Supplementary Fig. 7 includes the flow of the participants). Five participants withdrew: 1 screen failure, 3 prior to and 1 after randomisation due to initiation of GLP-1 RA treatment. Two participants were new to AID use at the start of the study. For the duration of the trial, participants continued to use their Control-IQ systems. The demographic and baseline glycaemic characteristics of those who completed the study are presented in Table 1.

Primary outcome

In Group A, the primary outcome—TIR (3.9 to 10 mmol/L)—remained unchanged during AID and the subsequent Information Feedback (IF) period but increased when participants switched to Adaptive Bio-behavioural Control (ABC) use. In Group B, TIR increased immediately after activating the ABC system and remained elevated after ABC was turned off during the subsequent IF and AID alone periods.

Figure 1 presents the trajectories of the two groups throughout the study: the increase in TIR after switching to ABC was ~4 percentage points for both groups (mean difference: −3.67%, confidence interval: [−5.13, −2.22], $p < 0.001$). In Group B, retaining the benefits of ABC during the 6-week period following ABC discontinuation suggests sustained effect of co-adaptation for a certain period of time. As presented in Table 2, a linear mixed-effects model for TIR found a significant intervention effect ($p < 0.01$) and significant interaction between group and intervention ($p = 0.04$), meaning that the difference in TIR across interventions was statistically different between Group A and Group B. This result suggests that the TIR improvement in Group A is due to the ABC intervention and should not be attributed to study participation effect. Age was a statistically significant factor for the primary outcome TIR (3.9–10.0) mmol/L,

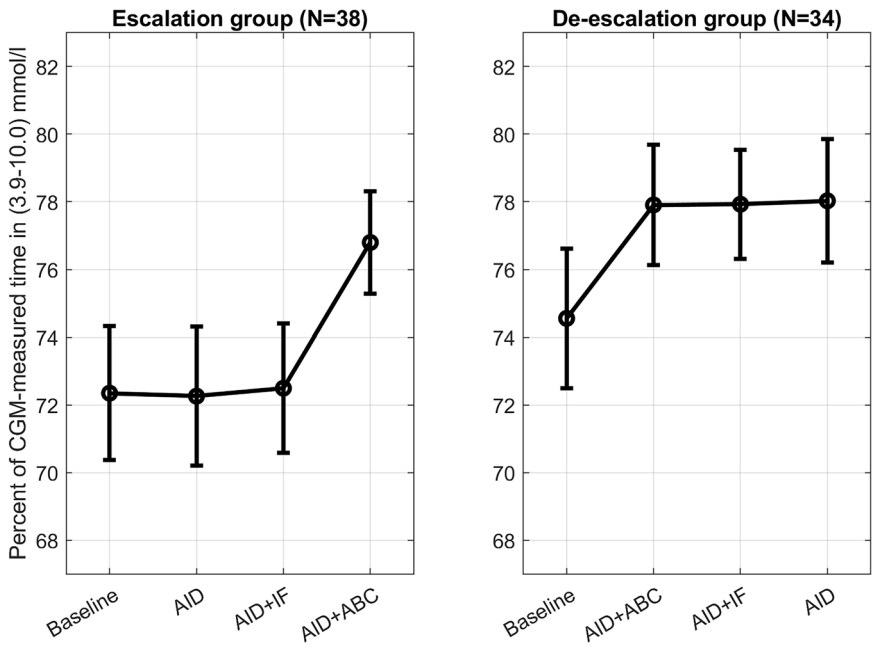

Fig. 1 | Percentage of CGM-measured time in range (3.9–10 mmol/L) between escalation (left panel) and de-escalation (right panel) groups, across different interventions. Circles indicate mean values, whereas error bars indicate mean ± standard error intervals.

Table 2 | Primary and secondary glycaemic outcomes, stratified by groups

	Group A (Escalation) ($N = 38$)			Group B (De-escalation) ($N = 34$)				
	AID	AID + IF	AID + ABC	AID + ABC	AID + IF	AID	Intervention	Group × Intervention
CGM-measured time in range 3.9–10 mmol/l (percent)	72.26 (12.65)	72.49 (11.77)	76.80 (9.20)	77.91 (10.41)	77.93 (9.40)	78.03 (10.52)	<0.01	0.04
CGM-measured time below 3.9 mmol/l (6am–12pm) (percent)	1.68 (1.74)	1.68 (1.50)	1.98 (1.62)	1.90 (1.27)	2.09 (1.57)	1.97 (1.74)	0.72	0.33
CGM-measured time above 10 mmol/l (6am–12pm) (percent)	26.84 (13.63)	27.57 (12.81)	22.34 (9.52)	20.81 (9.70)	21.01 (9.40)	21.00 (10.55)	<0.01[a]	0.01[a]
CGM-measured coefficient of variation (6am–12pm) (percent)	33.04 (4.77)	33.42 (3.87)	33.71 (5.29)	32.30 (5.58)	33.33 (5.56)	31.68 (6.01)	0.07[a]	0.01[a]
CGM-measured average glucose level (mmol/L)	8.58 (1.16)	8.54 (1.09)	8.16 (0.73)	8.05 (0.80)	8.04 (0.76)	8.02 (0.84)	<0.01[a]	0.04[a]

The p values are obtained via linear mixed-effects, introducing group, intervention and age as fixed factors, a group × intervention contrast and a random intercept for each participant.
[a]These analyses are considered exploratory, and the p values are presented only for illustration. No conclusions about statistical significance can be derived for the secondary outcomes.
Results are reported as mean (SD)

$p < 0.001$, but was not significantly related to hypoglycaemia - the time below 3.9 mmol/L. Gender and Race were not related to any of these outcomes and had no significant impact on the glycaemic benefits achieved with the ABC system.

Secondary outcomes

Table 2 presents the changes in the secondary outcomes. Because the CGM-measured percent time below 3.9 mmol/L during the day did not change significantly, all subsequent analyses were considered exploratory and their p values are presented only for illustration. No conclusions about statistical significance can be derived for the secondary outcomes. Nevertheless, it is evident that, with the expected low incidence of hypoglycaemia in this population[1,13], ABC effectively and safely reduced exposure to hyperglycaemia.

By study design, all participants were AID users at randomisation, resulting in good baseline control—the baseline average glycated haemoglobin was 6.8 ± 0.8 percent (range 5.3–9.2 percent). Nevertheless, by the end of the study, glycated haemoglobin was further reduced to 6.6 ± 0.5 percent (range 5.6–7.8 percent), consistent with the improvement in TIR and most prominent for those who were at suboptimal glycaemic control at baseline. Supplementary Table 2 reports glycated haemoglobin at screening and end of study.

Stratification by baseline glycaemic control

Table 3 stratifies the participants by baseline glycated haemoglobin levels (below 6.5 percent, 6.5–7.0 percent, 7.0–7.5 percent and above 7.5 percent) showing that the improvement attributed to the use of the ABC system was most prominent in the group that had suboptimal baseline glycaemic control—for those with baseline glycated haemoglobin above 7.0 percent, TIR increased by ~5 percentage points, which is considered clinically significant effect, $p = 0.01$. Nevertheless, TIR improvement, albeit non-significant, was registered also by those with optimal baseline glycated haemoglobin below 6.5 percent—their TIR increased by ~1.2 percentage points from the beginning to the end of the ABC intervention.

In total, 30 out of 72 participants (41%) achieved a 5 percentage points clinically meaningful improvement of TIR at the end of the ABC phase. Of these participants, 20/28 had baseline TIR below 70 and 10/44 had baseline TIR above 70%, confirming that the ABC intervention was most efficient for those at suboptimal control. Supplementary Fig. 8 details further the progression of treatment effect in 2-week increments during the ABC phase. The data is stratified by baseline HbA1c as in Table 3 (below 6.5 percent, 6.5–7.0 percent, 7.0–7.5 percent and above 7.5 percent), showing that the effect of ABC was most prominent for those at suboptimal control at the baseline, e.g. the subgroups with baseline HbA1c ≥ 7.0% improved their baseline TIR by ~5 percentage points. Generally, those already at optimal control (baseline HbA1c < 7%) did not improve their TIR over time.

Adverse events

There were no adverse events in the trial including no cases of severe hypoglycaemia or diabetic ketoacidosis (DKA).

ABC system use

On average, the participants logged into the ABC system 0.9 (±0.4) times per day. The improvement in TIR did not correlate with the number of system interactions. Although participants were free to accept or decline the recommendations provided by the ABC app, deviations from recommendations were minimal—only 23 out of a total of 504 recommendations, corresponding to 4.6 percent of the total.

Discussion

AID is currently the best-practice treatment for T1D and is also increasingly used in insulin-treated type 2 diabetes. Several commercial systems are now available in the U.S, and several others are cleared in Europe. A number of publications reported outcomes of real-world AID use by thousands of people for extended periods of time[11–15,33,34]. All contemporary AID systems

Table 3 | Comparison between the percentage of time in range 3.9–10.0 mmol/l at the beginning (weeks 1–2) and end (weeks 15–16) of the AID + ABC intervention, stratified by baseline glycated haemoglobin

Baseline glycated haemoglobin	Percent time in range 3.9–10.0 mmol/l weeks 1–2 of study	Percent time in range 3.9–10.0 mmol/l weeks 15–16 of study	Mean difference [confidence interval]	*p* value
≥7.5 percent (*N* = 12)	59.40 (9.96)	65.07 (5.21)	5.68 [−0.07, 11.42]	0.05
≥7 percent, <7.5 percent (*N* = 15)	69.92 (9.25)	74.50 (8.96)	4.58 [0.81, 7.65]	0.02
≥6.5 percent, <7 percent (*N* = 24)	77.25 (9.12)	77.92 (7.62)	0.67 [−2.86, 4.12]	0.70
<6.5 percent (*N* = 21)	83.06 (10.45)	84.26 (9.49)	1.21 [−2.58, 4.99]	0.51

Time in range is reported as mean (standard deviation)
The improvement in TIR is higher for those at higher baseline glycated haemoglobin values.

perform significantly better than both multiple daily injections or sensor-augmented insulin pump therapy. However, a common effect is observed across AID systems and studies: following a rapid initial improvement after switching from another therapy, AID systems reach a 'ceiling' of ~70–75 average percent time in the target range (3.9–10 mmol/L). This ceiling effect points at the limitations of the current hybrid closed-loop devices: few of their control algorithms adapt to the changing physiology of their users and, besides event alarms, none provide specific actionable information via interaction with their users.

The objective of this randomised controlled trial was to test the effectiveness of a new ABC system, which aimed simultaneous co-adaptation of the control parameters of an AID algorithm to the changing physiology and behaviour of its user, and users' behavioural modification via interactive understanding of AID actions. While adaptive AID algorithms exist, the unique element of the ABC system is its Web Simulation Tool (WST)—to the best of our knowledge, the WST is the only system capable of mapping its users to their corresponding 'digital twins' and thereby allowing two modes of interaction: (i) biweekly advice to the user regarding optimal AID parameter settings and, most importantly, (ii) in silico replay of 'what if' treatment scenarios. The latter appears to be a powerful tool allowing people with diabetes to see what would happen if they adjusted some parameters of their otherwise complex and virtually incomprehensible AID algorithm.

The results from this 6-month clinical trial involving 72 people with T1D confirm that such an interactive approach can improve glycaemic control beyond the capabilities of the AID system alone. Both TIR and glycated haemoglobin improved significantly, despite their initially very good values, without insulin treatment intensification that would result in increased risk for hypoglycaemia. Moreover, there are indications that the improvement was selective, affecting most those who were at poorest control at baseline (Table 3), i.e. AID users who likely need most support adapting to their systems. Additional messages from this trial include: (i) Information feedback typically employed by contemporary AID software has negligible added effect on glycaemic control; (ii) An initial 4-week period of ABC use appears sufficient to achieve full system effect (Supplementary Fig. 7), and (iii) the effects of the interactive ABC lasted for at least 6 weeks after the system was turned off, indicating that future ABC use may be intermittent, depend on the willingness of the user to engage.

There were no adverse events reported by the study participants during the duration of the clinical trial. The study participants who were enroled in the clinical trial viewed the application daily and some participants reported viewing the app multiple times a day. The participants were consistently engaged and communicated effectively with the study team with only one drop-out post-randomisation after starting a GLP-1 receptor agonist suggesting adherence.

Currently, ABC is specific to one AID system—Control-IQ by Tandem Diabetes Care. While the base simulation model—well known in the field as the UVA/Padova simulator[29]—has been shared widely during the past 15 years and the process of generating digital twins is independent from the AID system used—the data needed are standard, e.g. CGM, insulin, meals[35], the rest of the ABC system is specific to the control algorithm used by the AID system. Adapting the ABC concept to other AID algorithms is possible in principle, but would require some effort and resources. To do so, the ABC-control algorithm interface would need to be adapted as follows: (i) to replay what-if scenarios, the ABC would need to accurately represent the action of the AID control algorithm, and (ii) because each AID system has different tunning 'knobs', to recommend appropriate adjustments, the ABC would need to know which are the modifiable control algorithm parameters.

Further, the ABC system can only interact with those who are responsible for their diabetes management, e.g. adults or adolescents. The management of T1D in children is a co-regulation process typically involving parents or caregivers. While most AID systems are approved to work in paediatric population, e.g. for ages 2 and older, the ABC requires decision making that usually involves adult supervision. Nevertheless, in future studies, ABC could be used by parents or caregivers who upload their

children data and from there interact with the system in a similar way—the base simulation model includes child metabolic profiles[29]. In conclusion, to the best of our knowledge, this study offers the first example of breaking the 'ceiling effect' of AID via interactive human-machine co-adaptation. This involves adapting the user to the system's work and the system to the user's changing physiology and behaviour. Emerging 'digital twin' technologies, which program certain characteristics, such as a person's glucose-insulin metabolism, into a computer application, not only enable rapid therapy parameter optimisation but also offer educational support to make diabetes management more accessible. Directions for further studies include: exploring broader applicability of the concept of human-machine interaction for the management of diabetes, usability of ABC in different AID platforms and different age groups, as well as long-term sustainability of the observed benefits.

Methods

Procedure

This randomised controlled clinical trial tested the effectiveness of a new ABC system. The ABC technology and the study protocol were approved by the FDA Investigational Device Exemption #G220224 on September 23, 2022, and subsequently by the Institutional Review Board at the University of Virginia (HSR 220300). The trial was registered with ClinicalTrials.gov, NCT05610111, recruitment began on January 18, 2023, and the study was completed on September 28, 2024.

Study participants

All participants signed informed consent forms. The inclusion criteria were adults diagnosed with T1D, ages 18–70 years, who had been using an insulin pump for at least 6 months. At randomisation, participants were required to be using the t:slim X2 insulin pump with Control-IQ technology (Tandem Diabetes Care, San Diego, California) and Dexcom G6 CGM sensors (Dexcom, Inc., San Diego, California). Participants had to have a total daily insulin dose of at least 10 units, with no other restrictions related to their diabetes control, such as limits on glycated haemoglobin at enrolment. Concurrent use of any non-insulin glucose-lowering agents, except for metformin or GLP-1 receptor agonists, was excluded following screening (including pramlintide, DPP-4 inhibitors, SGLT-2 inhibitors and sulfonylureas). Complete inclusion and exclusion criteria are detailed in Supplementary Table 1.

Study design

Supplementary Fig. 1 presents the design of this single-centre outpatient study in the United States: participants were randomised 1:1 into two groups, which differed by the order of introduction of the ABC system. Group A (Escalation group) began with a 2-week baseline period on AID alone, followed by 4 weeks of AID + information feedback (AID + IF), followed by 16 weeks of the complete ABC system that included information feedback plus co-adaptation using the ABC system (AID + ABC). Group B (De-escalation group) experienced these conditions in reverse order. The complete ABC system was activated after randomisation for 16 weeks, then downgraded to AID + IF for 4 weeks and finally to AID alone for the last 2 weeks. The study design (Supplementary Fig. 1) included periods of AID, IF and ABC of unequal length. This was done considering that: (i) All participants were on AID at recruitment and therefore a 2-week AID period was sufficient to confirm the degree of their glycaemic control—this corresponds to a standard 2-week AGP[22]; (ii) The participants were generally familiar with information summaries provided by their commercial AID systems. Here, the IF module provides additional summaries and risk analysis, but is not offering actionable advice; thus, a 4-week exposure to this module was considered sufficient to gauge its effect; (iii) The ABC is an entirely new concept that offers both actionable advice (e.g. algorithm parameter change) and interactive simulation. Thus, we expected that study participants would have a learning curve until the effect of ABC becomes apparent. Following this logic and to make the lengths of the IF and ABC time periods selected for analysis comparable, we used the last 4 weeks of ABC to gauge outcomes.

Outcomes and statistical analysis

The primary outcome was CGM-measured TIR (3.9–10 mmol/L) during the last 4 weeks of ABC system vs the 2 weeks on AID alone. The primary hypothesis was that ABC will be superior to AID at a significance level of $\alpha = 0.05$. To preserve the overall type 1 error for selected key secondary endpoints, a hierarchical testing procedure was used. If the primary analysis for TIR yielded a statistically significant result ($p < 0.05$), then testing proceeded to the next outcome in the following order: (i) CGM-measured percent time below 3.9 mmol/L during the day; (ii) CGM-measured percent time above 10 mmol/L during the day; (iii) CGM-measured coefficient of variation during the day, and (iv) CGM-measured mean glucose. This process continued moving to the next variable on the list until a non-significant result ($p \geq 0.05$) was observed, or all variables have been tested. If a non-significant result was encountered, then formal statistical hypothesis testing was terminated, and any remaining analyses were considered exploratory. Glycated haemoglobin was measured at the baseline and at the end of the study. Descriptive statistics and general linear models were used to tabulate and analyse the data, with the analysis performed in IBM SPSS 29. Glycaemic outcomes between the two groups were compared via linear mixed-effects, with group, intervention and age as fixed factors, a group × intervention contrast and a random intercept for each participant. Safety analyses were done to account for severe hypoglycaemia, DKA and adverse events with a possible relationship to the ABC system.

ABC technology

CGM and insulin delivery data from the participants' AID systems were uploaded automatically to a cloud-based platform for further processing. The data included time series of glucose values and insulin delivery with 5-min resolution. Participants could log into the ABC portal and interact with the system through an app on their phones, or via a web browser on a tablet or computer. Supplementary Figs. 2–5 provide screenshots of the main ABC screens, along with explanations of the corresponding modules described below:

The ABC system included an IF (information feedback) module, a Physiological Adaptation Module (PAM) and a WST. The IF module included traditional markers of glycaemic control progression, such as standard CGM metrics and AGP[22], as well as a calendar of daily risks for hypoglycaemia and hyperglycaemia allowing users to reflect upon days when high risks were encountered. Generally, the approaches behind the ABC modules are similar to those described in a recent review, which provides insights into the concepts, modelling methods and current capabilities of digital-twin mapping[35]. Thus, here we offer only a brief description: PAM uses CGM, insulin and meal data. The Identification-Replay-Optimisation approach described by Diaz et al.[30], is central to the digital twin mapping used in PAM. This approach involves identifying a subcutaneous minimal model of glucose-insulin dynamics using primarily users' glucose and insulin data. The workflow of PAM is presented in Supplementary Fig. 6: all PAM computations are executed in the background without user intervention. Daily, PAM processes CGM, insulin and meal data and runs a model identification to generate a digital twin. To reconstruct accurately observed scenarios and simulate what-if conditions, the data processing includes adjusting announced mealtimes and inferring unannounced meals from CGM and insulin data. Physical activity announcements to the AID system are considered in the replay simulation methodology as well. The ABC system also accounts for user behaviour related to hypoglycaemia treatments and insulin dosing (e.g. extended, aborted, or fixed boluses). Settings specific to the AID system employed by the trial are used to replay manual and automatic doses. Every 2 weeks, the system uses the digital twins to run multiple replay simulations, each time with slightly different therapy parameters (CR, CF and basal rate). The goal is to find optimal modulation factors for CR, CF and basal rate by applying up to 10% changes to each 4-h time segment.

The purpose of PAM was to track changes in the participant's physiological response to insulin delivery, adjust therapy parameters (CR, CF, basal rate) accordingly, and suggest modifications to the user for implementation in their AID systems. Therapy adjustments were limited to a maximum of ±10 percent of the original profile for safety reasons. Users could also experiment with their own data and try in silico what-if scenarios using the WST. For instance, they could explore the expected outcomes of lowering their CR by 10 percent or increasing their basal rate overnight. The expectation was that experimenting with their own data would provide users with insights into how the AID system works, thereby triggering behavioural adaptation.

The technology of the ABC system is a subject of the following patent applications:

(1) Applicant: University of Virginia Patent Foundation; Inventors: Boris P. Kovatchev, Patricio Colmegna, Jenny L. Diaz-Castañeda, and Maria Fernanda Villa Tamayo; Title: "System, Method, And Computer Readable Medium for Adaptive Bio-Behavioral Control (ABC) in Diabetes," described in: U. S. Provisional Patent Application Serial No. 63/448,082 filed on February 24, 2023; U. S. Provisional Patent Application Serial No. 63/459,060 filed on April 13, 2023; International Patent Application Serial No. PCT/US2024/016960 filed on February 22, 2024, and International Publication Number WO 2024/178261 A1, 29 August, 2024.

(2) Applicant: University of Virginia Patent Foundation; Inventors: Boris P. Kovatchev, Marc D. Breton, Ke Wang, and Patricio Colmegna; Title: "Method And System For Generating A User Tunable Representation of Glucose Homeostasis in Type 1 Diabetes Based on Automated Receipt of Therapy Profile Data", described in U. S. Provisional Patent Application Serial No. 63/065,948 filed on August 14, 2020 and International Patent Application Serial No. PCT/US2023/0352185 A1 filed on November 2, 2023.

Data availability

This study was supported by the U.S. National Instituted of Health and will therefore adhere to the NIH and Nature Portfolio Journals policies for data dissemination. Protocols and deidentified data will be made available upon request.

Code availability

The systems action and screenshots are described in the Supplementary materials and the system algorithms are described in a previous publication[30]. The software computing various metrics of glycemic control and generating the figures and tables of the ABC system is provided in this repository: https://github.com/jp993/abc_analysis. Thus, those skilled in the art should be able to reproduce the action of the ABC system in their own coding environment. Certain restrictions will be imposed on sharing the code of the replay simulation module (PAM)—this code is specific to the control algorithm used by the AID system; thus, the replay simulation code is not publicly available for proprietary reasons.

Received: 1 March 2025; Accepted: 25 April 2025;
Published online: 06 May 2025

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Acknowledgements

This study was supported by grant RO1 DK085623 from the National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The authors thank the engineering and clinical teams of the University of Virginia Center for Diabetes Technology for the development of the computer applications and the smooth execution of this study.

Author contributions

B.P.K. designed the study, was study sponsor for FDA purposes and wrote the first draft of this manuscript. P.C. designed and implemented the ABC system and its web-based monitoring portal, and was the lead engineer in the first year of the study. J.P. was the lead engineer in the second year of the study and was responsible for all data analyses. J.D.C. and M.V.T. supervised the technology and participated in the system design. C.L.K. designed the software architecture, developed and deployed the mobile ABC application. G.S. developed and maintained the web-based monitoring portal. C.A. was the project coordinator responsible for participant recruitment, device training, and retaining. M.S. and S.A.B. were the study physicians, with S.A.B. being responsible for all clinical aspects of the trial.

Competing interests

B.P.K. reports research grants handled by the University of Virginia from the National Institutes of Health, Novo Nordisk, Dexcom, and Tandem Diabetes Care. Additionally, B.P.K. has patents with royalties paid to Dexcom and Novo Nordisk, handled by the University of Virginia Licensing and Ventures Group. P.C. is at present an employee of Dexcom, Inc.; the work presented in this article was performed as part of his UVA appointment and is independent of his employment with Dexcom, Inc. J.P. has received research support through his previous institution from Dexcom. J.D.C. is at present an employee of Insulet Corp.; the work presented in this article was performed as part of her UVA appointment and is independent of her employment with Insulet. M.V.T., C.L.K., G.S., C.A. declare no conflicts. M.S. has received support to her institution from Dexcom, Insulet and Tandem Diabetes Care. S.A.B. has received research support through her institution from Dexcom, Insulet, Roche Diagnostics, Tandem Diabetes Care and Tolerion and has participated on a data monitoring board for MannKind.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41746-025-01679-y.

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