SUPPLEMENTARY DATA

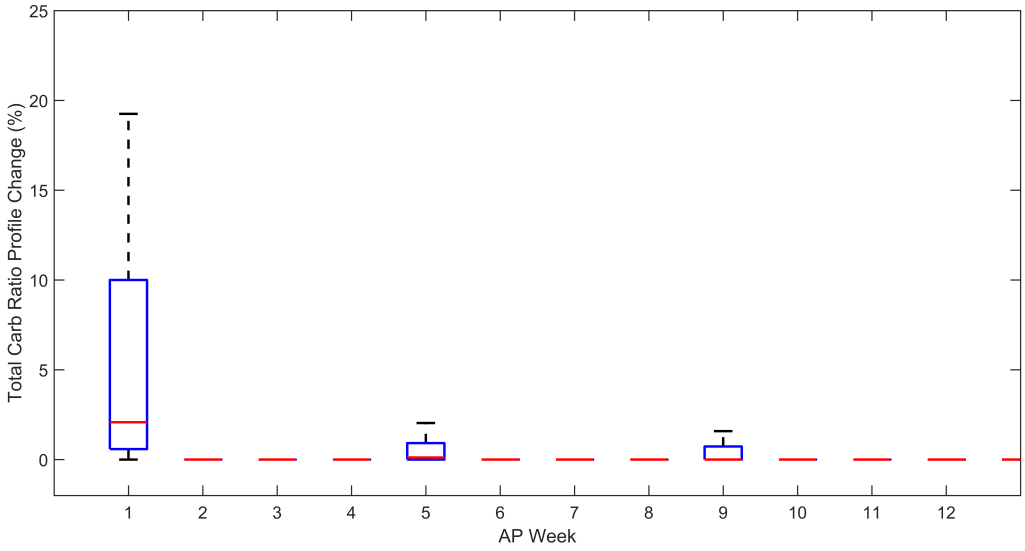
Basal Profile Adaptation Algorithm

Carbohydrate Ratio Optimization and Adaptation Algorithm

Supplementary Figure 1. Schematic showing components of the closed-loop system. The insulin pump and Dexcom G4 Share AP CGM receiver with 505 algorithm were connected wirelessly via bluetooth to the Diabetes Assistant (DiAs) smartphone device. The Zone Model Predictive Control Artificial Pancreas algorithm ran on the DiAs. If connectivity was lost between the devices, the pump would revert to giving the pre-programmed basal rate and function as a normal insulin pump. Remote web based monitoring was available to clinical staff, who received SMS-text message alerts for specific safety conditions.

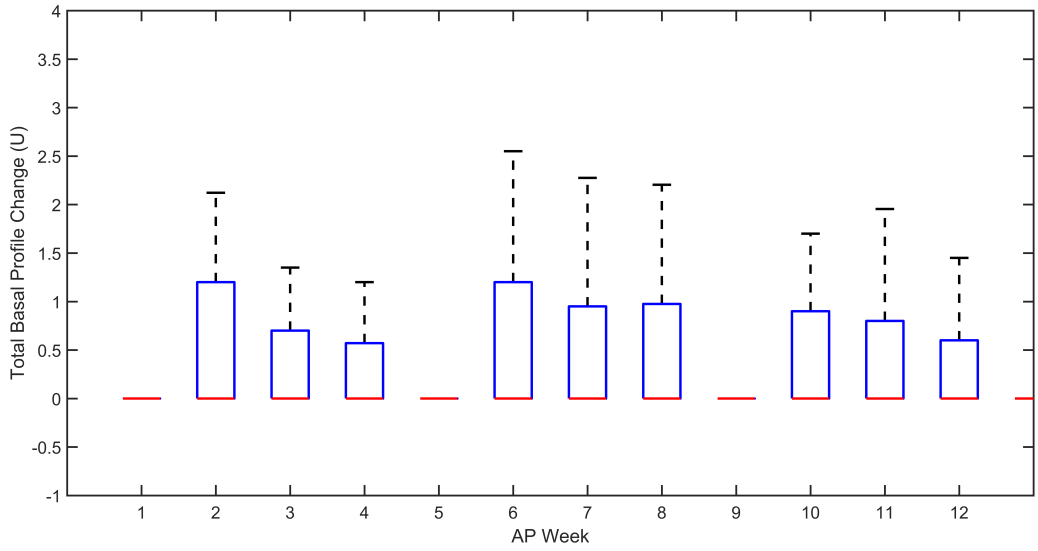
SUPPLEMENTARY DATA

Supplementary Figure 2. Month to month change in total carbohydrate ratio (% change). Total carbohydrate ratio profile changes showed a significant change with the first adaptation. After the first month of AP, there was convergence with minimal changes to carbohydrate ratios.



SUPPLEMENTARY DATA

Supplementary Figure 3. Week to week change in basal insulin rate profile (absolute unit change). Nominal basal rates were adjusted throughout the trial to reflect changing insulin needs of subjects.



SUPPLEMENTARY DATA

Supplementary Table 1. Baseline demographics for the 30 enrolled patients who completed the 1 week baseline CGM augmented data collection period.

Characteristic	
Age, years, mean ± SD	43.5 ± 13
Gender, n, %	
Female	17 (57%)
Male	13 (43%)
Weight, kg, mean ± SD	79.9 ± 19.2
Body mass index, kg/m^2, mean ± SD	27.3 ± 6.1
HbA1c at AP Start	
%, mean ± SD	7.0 ± 0.8
mmol/mol, mean ± SD	53 ± 8.7
Duration of diabetes, years, mean ± SD	26.9 ± 13.1
TDI,	
U/day, mean ± SD	43.3 ± 15.6
U/kg/day, mean ± SD	0.5 ± 0.2

SUPPLEMENTARY DATA

Supplementary Table 2. Total daily insulin (TDI) (units/day) and TDI Bolus (units/day) for each subject during the study outcome weeks compared to the SAP Run-In period. In addition, total percent time in use of AP is listed.

	SAP Run-In		Week 4 AP vs. SAP Run-In		Week 8 AP vs. SAP Run-In		Week 12 AP vs. SAP Run-In		% Overall AP Use
Subject	**TDI**	**TDI Bolus**	**TDI**	**TDI Bolus**	**TDI**	**TDI Bolus**	**TDI**	**TDI Bolus**	
202002	23.5	11.9	22.2	8.5	24.9	8.7	22.3	6.1	93.2
203002	36.8	16.1	42.1	14.5	42.7	14.0	42.8	14.0	88.9
205001	40.3	16.1	57.0	19.3	46.4	15.6	49.6	15.6	89.8
206001	42.9	24.4	72.6	33.6	75.9	34.6	68.9	32.1	84.7
207001	79.7	26.4	93.3	35.3	99.6	30.8	96.8	23.8	69.1
208001	46.4	24.3	47.2	15.1	66.1	14.7	55.3	14.5	90.8
209001	23.7	18.2	23.5	16.3	23.5	17.6	24.9	17.9	90.3
211001	24.6	12.6	23.5	6.4	25.6	6.4	25.3	7.5	88.8
212001	39.7	18.8	43.5	9.7	35.0	6.8	41.9	9.4	76.3
213001	32.8	15.0	32.9	11.5	29.1	10.6	29.3	10.7	91.4
301001	24.5	12.8	27.1	13.2	26.5	14.4	26.4	14.2	79.4
301003	76.5	37.1	80.4	35.7	86.5	36.1	101.1	47.6	93.3
301004	29.0	9.3	29.5	9.4	24.3	5.6	26.9	4.9	94.5
301005	30.9	7.9	37.0	7.1	42.3	5.2	50.1	11.2	70.8
301007	35.5	27.2	47.5	27.8	38.0	20.1	36.0	21.4	94.1
301008	30.0	9.3	43.2	10.8	43.1	6.6	39.9	7.3	73.8
301009	22.4	5.0	27.9	2.5	33.6	8.0	32.0	8.7	89.7
301010	24.0	15.4	29.8	18.3	25.2	16.5	23.8	16.5	87.9
301011	60.6	35.3	70.0	26.7	76.4	26.1	73.8	28.7	57.1
301012	23.3	10.9	28.5	8.4	40.6	12.6	28.6	7.9	90.0
401001	49.7	22.2	50.4	16.5	47.1	17.3	n/a	n/a	89.7
402001	18.1	11.1	22.6	10.5	23.9	10.2	25.4	10.5	95.5
403001	22.3	10.0	42.8	18.6	42.0	17.4	37.4	15.4	90.2
404001	41.6	22.5	32.3	13.7	28.8	8.3	31.6	9.3	89.5
406001	27.4	7.4	28.2	7.3	25.4	4.3	25.6	5.4	95.7
407001	33.4	16.0	29.8	8.9	28.1	12.7	28.7	10.3	95.4
408001	40.5	14.8	65.1	26.1	56.4	18.5	73.5	28.0	84.9
409001	27.0	14.2	28.3	10.3	29.9	11.3	31.6	12.2	79.4
410001	17.3	8.5	48.8	20.4	44.4	15.5	50.4	17.8	92.4
411001	26.8	14.4	37.0	15.0	38.4	18.9	32.8	13.4	83.9
Mean±SD	35.0±15.4	16.5±7.9	42.1±18.5	15.9±8.9	42.3±20.0	14.8±8.2	42.5±21.4	15.3±9.4	86.3±9.0
Estimate			7.09	-0.59	7.28	-1.66	7.77	-1.16	
95% CI			(3.97,10.22)	(-2.34,1.20)	(4.16,10.41)	(-3.45,0.14)	(4.61,10.93)	(-2.97,0.66)	
p-value			<0.001	0.515	<0.001	0.07	<0.001	0.208	

SUPPLEMENTARY DATA

Supplementary Table 3. Physician overrides of the automated learning system (at end of each week). During the study, physicians reviewed with patients the weekly algorithmic adaptation recommendations for basal rate (BR) changes and monthly algorithmic adaptation recommendations for carbohydrate ratio (CR) changes. Study physicians declined the automated recommendation for carbohydrate ratio 21 times, and 14 times for basal rate (90% acceptance rate of the algorithmic adaptations). Details of how often recommendations were overridden and when in the study these overrides occurred is listed by week in the table. If a physician chose to make manual adjustments to insulin delivery settings at any time in between the scheduled algorithmic adjustments, this was also counted as an override of the algorithmic recommendations.

Study Week	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Number of BR Overrides			3	1	1	2	3	1			3	
Number of CR Overrides	6			6	1			8				

SUPPLEMENTARY DATA

Supplementary Table 4. Summary of adverse events.[a]

Event	1 Week Run-in Period [b]	12 Weeks Closed-Loop Use
Protocol Related		
Severe hyperglycemia/DKA	0	0
Hypoglycemia requiring assistance	0	1
Inflammation at site of sensor insertion	2	4
Ketonemia related to illness	0	0
Ketonemia related to infusion set occlusion	1	4
Protocol Unrelated		
Miscellaneous Infection [c]	1	4
Toe Laceration	0	1
Ligament Strain	0	2
Rotator Cuff Tear	0	1
Anxiety Attack	0	1
Hospitalization due to:		
Acute Coronary Syndrome	0	1
Costochondritis	0	1

[a] A data safety monitoring board (DSMB) and each sites local IRB were used to adjudicate all serious adverse events.
[b] The sensor-augmented pump (SAP) run-in phase consisted of device training and 1 week of SAP data collection using the study devices.
[c] Infections: UTI, tinea pedis, gastroenteritis, gynecological yeast infection, paronychia.

SUPPLEMENTARY DATA

Basal Profile Adaptation Algorithm

Previously algorithms for adapting the basal profile in a "run-to-run" framework have been proposed for open-loop insulin pump therapy ([1]-[4]). In this case, the adaptation of the basal profile is implemented via a heuristic method specifically designed to be utilized within the context of "closed-loop" control.

The fundamental insight that governs the basal profile adaptation algorithm is that, in the context of closed-loop control, the basal profile serves as an operational set point for the control algorithm, which, in turn, determines the actual amount of insulin to deliver at each time period. This presents a different problem than in the open-loop context where the basal profile directly indicates the pump's basal insulin infusion rate. *In silico* observations have indicated that an improperly set basal profile can lead to undesirable oscillatory behavior in the system dynamics under closed loop control algorithms. Thus, when adapting the basal profile, the adaptation algorithm utilizes both the aggregate of risk in terms of hypo and hyperglycemic events that the subject experiences over the course of a given run (in this study one week) as well as any consistent deviations away from the basal profile in the amount of non-meal related insulin which the controller delivers. This process will end up being biased towards overall adjustments in of the current total profile upwards or downwards as opposed to a "fracturing" of the profile following the specific behavior of the controller. This is desirable since the purpose of the basal profile in the closed-loop context is to give a functional operating point for the controller, and simulation have indicated that swings in the amount of insulin the controller may deliver (or in BG) at specific time periods can be due to an overall too high or too low setting for basal profile throughout the day, not merely a maladjustment of the profile at the problem time periods.

After initializing parameters the algorithm proceeds by the following steps:

1) The CGM data for the given run is evaluated to ascertain regions of actionable BG risk. The asymmetric risk function is calculated for each time period t by the formula:

$$BG_{risk}(t) = \frac{1}{\log\left(\sqrt{\frac{BG_{lo}}{BG_{hi}}}\right)^2} \cdot \log\left(\frac{BG(t)}{\sqrt{BG_{hi}BG_{lo}}}\right)^2$$

where BG_{lo}, and BG_{hi} are threshold parameters. This risk is partitioned into components for high and low blood glucose risks:

$$BG_{riskHi}(t) = \begin{cases} BG_{risk}(t) & BG_{risk}(t) \geq \sqrt{BG_{hi} \cdot BG_{lo}} \\ 0 & otherwise, \end{cases}$$

$$BG_{riskLow}(t) = \begin{cases} BG_{risk}(t) & BG_{risk}(t) < \sqrt{BG_{hi} \cdot BG_{lo}} \\ 0 & otherwise. \end{cases}$$

A moving average of these values is taken for each day, and that quantity averaged over the course of the run to give an indication of opportunities for risk mitigation for both hyper- and hypoglycemia. Since in this process it is possible for both risk for high and low BG to be present during the same time period of the day we look for such instances—considered to be un-addressable— in order to pre-empt labelling such time periods specifically as high or low BG "risk zones" due to the presence of the other type of risk. The remaining periods where the computed high or low BG risk exceeds the chosen threshold parameters are labelled respectively as high or low BG "risk zones".

2) The algorithm tracks, over a fixed number of days, delivered insulin that is not related to meals I(t), the algorithms computes percentile values for the amount of non-meal related insulin delivered for each time-of-day: $I_{percentilehi}(t)$ and $I_{percentilelo}(t)$. (In the study, these values are computed from insulin delivery over seven days at the 66th and 33rd, respectively.) Next, deviations from basal rate are calculated for each time of day by

$$Delivered_{above}(t) = \begin{cases} I_{Percentile_{hi}}(t) - B(t) & I(t) > B(t) \\ 0 & otherwise, \end{cases}$$

$$Delivered_{below}(t) = \begin{cases} B(t) - I_{Percentile_{low}}(t) & I(t) < B(t) \\ 0 & otherwise. \end{cases}$$

where B(t) is the daily basal insulin profile. These quantities are then summed over the entire daily time period to give average total deviations in insulin delivered above or below the basal rate in excess of the set thresholds as

$$Total_{above} = \int_{t_{start}}^{t_{end}} Delivered_{above}(t)dt.$$

With $Total_{below}$ defined symmetrically.

3) The algorithm overall is biased towards mitigating hypo over hyperglycemic events. On a first pass the algorithm looks for zones of hypoglycemic risk as determined in step 1 overlapping with chronic under delivery of non-meal insulin as determined in step 2 that are of a large enough size to be actionable. If such zones are discovered they are denoted as the set $Zone^*_{HypoRisks}$.

The adjustment, α, in the basal profile is in this case determined by looking at the difference in the total insulin chronically delivered below and above the basal rate, scaled by the total amount of basal insulin which the profile indicates would be delivered in the $Zone^*_{HypoRisks}$, i.e.

$$\alpha = \frac{Total_{below} - Total_{above}}{\int_{Zone^{*}_{HypoRisks}} B(t)dt}$$

The new updated basal profile is then given by,

$$B^{*}_{new}(t) = B(t)\left(1 - \alpha \cdot \delta_{Zone^{*}_{HypoRisks}}(t)\right)$$

where

$$\delta_S(t) = \begin{cases} 1 & t \in S \\ ZAP & otherwise, \end{cases}$$

and where ZAP is a chosen "zone attribution parameter", indicating how much the overall change should be weighted towards the specific BG risk zones as opposed to an overall downward adjustment in the profile. After being passed through a leveling procedure to make sure that the change in profile is not excessive (or excessively fractured) the final updated profile is then obtained.

A symmetrical process used for upward adjustment in basal profile is triggered if no hypo risk zones are present.

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4. C.C. Palerm, H. Zisser, L. Jovanovič, F.J. Doyle III A run-to-run control strategy to adjust basal insulin infusion rates in type 1 diabetes J. Process Control, 18 (3) (2008), pp. 258–265.

SUPPLEMENTARY DATA

Carbohydrate Ratio Optimization and Adaptation Algorithm

The method proposed for carbohydrate ratio (CR) optimization [1] is based on the knowledge that CR is strictly related to subject insulin sensitivity (S_I) and in fact varies during the day as S_I does [2]. On the other hand, S_I can be estimated in each meal of the day from sensor-augmented insulin pump data (S_I^{SP}) with a simple formula, as reported in [3], and this allows to calculate the optimal CR for each meal exploiting sensor and pump data.
In particular, the algorithm described in [1] can be describe in three steps:

1) S_I^{SP} calculation. As reported in [3], for each meal, S_I^{SP} is estimated, for that meal, by using a simple algebraic formula:

$$S_I^{SP} = \frac{\frac{D \cdot f(t_{end})}{BW} - GEZI \cdot AUC(\Delta CGM) - V_G \cdot \left[CGM(t_{end}) - CGM(t_{meal})\right]}{\left[\frac{1}{CL}\int_{t_{meal}}^{t_{end}} Basal(t)dt + \sum_{t_i=t_{meal}}^{t_{end}} \left[\frac{Bolus(t_i)}{CL}\right]\right] \cdot \left[\frac{AUC(|\Delta CGM|)}{(t_{end} - t_{meal})}\right]} \quad \text{(A1)}$$

where D is the amount of ingested carbohydrates, *AUC* is the area under the curve calculated from the start (t_{meal}) to the end (t_{end}) of the meal, $f(t_{end})$ is the fraction of the ingested dose which has reached plasma at the end of the meal, ΔCGM and $|\Delta CGM|$ are the above basal and the absolute value of above basal glucose excursion, *Basal* is the basal insulin infusion rate during the meal, $Bolus(t_i)$ is the bolus injected at time t_i, *BW* is body weight, *CL* is plasma insulin clearance, calculable from subject's age and height and BW as in [4]. The glucose effectiveness at zero insulin (*GEZI*) [5][1]and the volume of glucose distribution V_G [6] are fixed to population values.

2) CR calculation. By rearranging the above equation, and since the pre-meal insulin bolus ($Bolus(t_{meal})$) which should be administered to compensate the carbohydrate intake is calculated by dividing the amount of carbohydrates ingested (*D*) by CR and assuming that the bolus is perfectly able to bring CGM back to the pre-meal value ($\Delta CGM(t_{end}) = 0$), one obtains

$$CR^{new} = \frac{S_I^{SP} \cdot BW \cdot \frac{AUC(|\Delta CGM|)}{t_{end} - t_{meal}}}{f(t_{end}) \cdot CL - GEZI \cdot BW \cdot CL \cdot \frac{AUC(\Delta CGM)}{D} - S_I^{SP} \cdot BW \cdot \frac{AUC(|\Delta CGM|)}{t_{end} - t_{meal}} \cdot \frac{AUC(Basal)}{D}} \quad \text{(A2)}$$

3) CR assessment. CGM data are noisy and error on cGM data can be propagate to optimal CR calculation. Thus, for safety reason, at this stage the estimated CR^{new} is compared against the one actually used for the same meal (CR^{old}) and the position of the subjects in the CVGA [7] for the same meal is considered. Briefly the CVGA is a tool that allows to graphically and numerically assess the quality of glycemic control, by representing a subject as a dot in the

Cartesian plane using minimum and maximum CGM values as coordinates. The plane is than divided in zones (A=target zone, B, C, D, E=bad control), according to the predefined values of CGM_{min} and CGM_{max}.
The optimal CR proposed by the algorithm (CR^{opt}) is thus determined according to the following rules:

$$\begin{aligned} CR^{opt} &= max\left(CR^{old}, CR^{new}\right) && \text{if} \quad CGM_{min} < 90\ mg/dL \\ CR^{opt} &= CR^{old} && \text{if} \quad CGM_{min} \geq 90\ mg/dL\ \&\ CGM_{max} \leq 180\ mg/dL \\ CR^{opt} &= min\left(CR^{old}, CR^{new}\right) && \text{if} \quad CGM_{min} \geq 90\ mg/dL\ \&\ CGM_{max} > 180\ mg/dL \end{aligned} \tag{A3}$$

In fact, if CGM during the meal was too low (CGM_{min} < 90 mg/dL; corresponding to B, lower B, lower C, lower and upper D and E zones) the proposed CR cannot be lower than CR^{old}. If glucose excursion during the meal was maintained within the target zone (90-180 mg/dL; corresponding to A zone), CR^{old} should not be changed. If CGM during the meal was too high (CGM_{max} > 180 mg/dL and $CGM_{min} \geq$ 90 mg/dL, corresponding to upper B and C zones), CR cannot be higher than CR^{old}.

Additional safety features for algorithm use in the field

The algorithm described above can be used to initialize and adapt the CR daily pattern, i.e. the three CR values used by a patient to calculate the optimal pre-meal boluses related to the three main meals (breakfast, lunch and dinner).

In principle, one day of CGM and CSII data would be sufficient to calculate the three CR values per day. However, in real-life conditions, noise on CGM data, calibration errors, sensor disconnections, pump malfunctions, missing information on carbohydrates content of the meals may badly impact the optimal CR estimation. To mitigate this problems we used, for the CR initialization, 7-days of CGM and CSII data. Seven days were considered to be a good compromise between the necessity of reject possible outliers in the single CR estimate and the willing of capture the latest optimal CR daily pattern. Basically, one first calculates the optimal CR for each available meal, as reported in the previous section, then labels each value as breakfast, lunch and dinner, according to the time of the day of each meal, then provides an average estimate of CR daily pattern and its variability (CV%) as previously described. According to physician recommendations, we set a maximum allowable deviation, with respect to the original CR pattern of 20%, to increase patient safety and make him more confident of algorithm suggestions.

Finally, since insulin sensitivity, and thus CR, daily pattern may vary with time, due to several factors, e.g. changes in patient habits, improvement/worsening of patient metabolic portrait, illness, etc, Optimal CR daily pattern was calculated before starting the closed-loop experiment and re-calculated every 4 weeks, using the 7 days of the last weeks in which basal insulin was

kept constant by experiment design, thus avoiding possible dangerous conflict between basal and CR adaptation.

In any case, the algorithm first checks if all the information needed for the calculation are available, including CGM, carbohydrate intake, bolus and basal insulin administration data. For instance, in the case of a skipped meal bolus, CR is not computed for that meal and a missing value is reported. This makes the algorithm robust to a missing meal bolus, since, as already stated, the final recommendation is done only if at least 3 CR values are available in the last week.

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