From In- to Out-patient Artificial Pancreas Studies: Results And New Developments
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Abstract: The Artificial Pancreas (AP) is a device for closed-loop modulation of insulin infusion, aiming to maintain patient glycemia in a nearly normal range. In the last decade AP prototypes using subcutaneous glucose sensing and subcutaneous insulin delivery have been extensively studied in clinical trials involving hospitalized patients. To ensure the highest level of patient safety, these studies usually employed very structured protocols and subcutaneous glucose measurements were accompanied by frequent and accurate blood glucose measurements via intravenous sampling. Therefore, in-patient studies were usually short and patients were often unable to move freely. The next step in the AP development is testing safety and efficacy of AP in a real-life scenario, outside the hospital environment and free of strict protocol prescriptions. This paper offers a review of some technological and algorithmic challenges posed by the in-to out-patient transition and reports the authors' experience in making this transition possible. Issues related to devices, telem medicine and control algorithms are discussed and out-patient clinical results are presented in support.

Keywords: Artificial Pancreas; Clinical Trials; Control of physiological and clinical variables

1. INTRODUCTION

Type 1 Diabetes Mellitus (TIDM) is a metabolic disease characterized by high blood glucose concentration, caused by autoimmune destruction of pancreatic beta-cells, responsible for insulin production. As a result, insulin has to be administered exogenously with the aim to maintain glucose concentration in a nearly normal range, in order to delay/minimize diabetes complications. At present, TIDM therapy usually relies on three-five measurements of blood glucose level per day, on the basis of which at least three insulin administrations (through injections or pumps) are performed. Effectiveness of the traditional therapy (with a slight imprecision called “open-loop” in the AP literature) depends on patients decision and experience. Automation of glycemic control promises to revolutionize diabetes management, by reducing patient burden and allowing more effective control. One of the major obstacles to the diffusion of automated glucose control devices proposed 40 years ago was the impossibility to frequently measure glucose concentrations in a noninvasive and accurate way. In the last two decades we assisted to the development of the Continuous Glucose Monitoring (CGM) technology, i.e. minimally invasive devices measuring glucose concentration in the interstitium (subcutaneous measurement) every 5 minutes or less. Stimulated by the availability of this new technology, researchers, industries and founding agencies invested increasing efforts on the development of minimally-invasive closed-loop glucose control using subcutaneous measurements and subcutaneous insulin delivery, the so called Artificial Pancreas (AP). Artificial Pancreas prototypes have employed a large variety of control techniques such as PID, [Dauber et al., 2013], fuzzy logic, [Nimri et al., 2013] and MPC [Breton et al., 2012, Elleri et al., 2013, Luijf et al., 2013]. Moreover, dual hormones systems infusing also glucagon have been proposed [Russell et al., 2012, Castle et al., 2010]. AP prototypes have been extensively studied in a hospital setting and more than 30 in-patient clinical trials conducted in the last 5 years have proved efficacy of automated closed-loop insulin infusion with respect to traditional pump-augmented therapy. A complete review of this large research effort is beyond the scope of these paper and we defer the interested reader to dedicated review papers such as Cobelli et al. [2011] or the recent Doyle III et al. [in press]. The next step in the AP development is testing safety and efficacy of AP prototypes in a real-life scenario, i.e. outside the hospital environment and free of strict protocol prescriptions. At the time this manuscript is written, a first two-day out-patient closed-loop study has been completed, testing feasibility of a wearable ambulatory AP system, first on two Cobelli et al. [Sept. 2012] and then on twenty adults
Kovatchev et al. [2013]. Moreover, out-patient overnight control was studied in a pediatric camp Phillip et al. [2013]. A number of other out-patient trials are presently being conducted or shortly scheduled.

This contribution does not attempt to do a comprehensive review of this rapidly evolving scenario but simply to illustrate some of the regulatory, technical and algorithmic challenges posed by the in- to out-patient transition and to describe the solution that the authors proposed. This is done by illustrating authors’ experience in this transition.

2. A MODULAR CONTROL APPROACH

A layered architecture for artificial pancreas has been recently proposed in Kovatchev et al. [2009] and was then refined in Patek et al. [2012]. The architecture, reported in Figure 1(a) decouples functionalities among modules, allowing independent development and solving integration hurdles. The bottom module, called Safety Supervision Module (SSM) is in charge to guarantee patient safety and it is authorized to override upper-layers commands to reduce proposed insulin infusion if patient safety is predicted at risk. Results presented in this paper have been obtained using a Kalman-filter based SSM that computes a real-time estimate of the patient’s metabolic state based on CGM and insulin infusion data. This estimate is used to predict hypo- and hyperglycemia risks 30-45min ahead. If a risk for hypoglycemia is predicted, the SSM attenuates automatically any insulin requests proportionally to the predicted risk level. Proportionality factor is determined by the upper module (Initialization Module), with readily available patient characteristics, e.g. body weight, insulin to carbohydrate ratio and basal insulin delivery. The intermediate module, called Range Control Module (RCM), is in charge to modulate insulin injection to maximize time in nearly-normal range. In this paper we will consider two possible implementations of this module: a heuristic controller (Hyperglycemia Mitigation Module) and a Model Predictive Control (MPC) algorithm.

2.1 Hypoglycemia and Hyperglycemia Mitigation System

The Hyperglycemia Mitigation Module (HMM) is a heuristic controller whose primary target is to guarantee patient safety, rather than aiming to tight glycemic control. By design, it ensures conservative insulin injection to avoid hypoglycemic episodes induced by overtreatment. HMM proposes the standard therapy and it intervenes, at most once every hour, only if hyperglycemia risk is predicted. Intervention consists of a correction bolus targeting 150 mg/dl, whose amount is computed on the basis of predicted glucose value and patient’s standard therapy parameters. As a further safety measure against possible errors in the prediction, only 50% of the computed bolus is actually delivered. The modular controller employing SSM and HMM is called Hypo and Hyperglycemia Mitigation System (H2MS).

2.2 Modular MPC

A less conservative implementation of the Range Control Module is bases on a MPC regulator (Magni et al. [2007], Soru et al. [2012], Toffanin et al. [2013]). In this case control action aims to enforce tight glycemic control. The controller is informed of the individual’s conventional therapy but every 15 minutes the controller is allowed to deviate from standard therapy if so does the optimal infusion computed with MPC techniques. The adopted formulation employs pre-meal boluses triggered by the patient announcement and employs an estimate of carbohydrates content of the meal provided by the patient. Aggressiveness of the MPC regulator is individualized for each subject by the upper module (Initialization Module) based on readily available patient characteristics, e.g. body weight, insulin to carbohydrate ratio and basal insulin delivery (Soru et al. [2012], Toffanin et al. [2013]). The modular controller employing SSM and the MPC implementation is called Modular MPC, or simply MPC.

3. IN-PATIENT STUDIES

[Breton et al., 2012] reports two in-patient studies testing with both H2MS and Modular MPC. H2MS was tested on 11 adolescents enrolled at University of Virginia (UVA, Charlottesville, Virginia) and on 15 adults enrolled at UVA and University Montpellier, (MTP, France). In the following we will focus on adults only. Modular MPC was tested on 12 subjects enrolled at MTP and University of Padova.

3.1 Study Design

The two studies shared 22h protocol prescribing an open-loop and a closed-loop admission in randomized order. In both admissions glycemic control was challenged by moderate exercise at 16:00 and dinner at 19:00. Before bed time, at 22:30 a snack was served and patients encouraged to sleep. Breakfast was served at 8:00 and just after the patient was discharged. During the closed-loop admission, closed-loop started at 14:00. The pump, Insulet Omnipod (Insulet Corporation, Bedford, MA) was inserted at the beginning of the admission and filled with Humalog Insulin (Eli Lilly and Company, Indianapolis, IN). Two CGM sensors were inserted two days before the admission. Dexcom Seven Plus (DexCom, Inc., San Diego, CA) was used at UVA and Padova, while Navigator (Abbot Diabetes Care Inc, Alameda, CA) was used in Montpellier. In both admissions CGM and insulin data were automatically transferred by a dedicated software, the APS (University of California, Santa Barbara, CA, USA), running on MatLab 2009b (MathWorks Inc, Natick, MA, USA). During both admissions, frequent blood samples were collected, at least one every 30 minutes and more frequently during exercise (every 5 min) and meals (every 10 min). Blood glucose was measured on that samples using YSI2300 STAT Plus analyzer (Yellow Spring Instrument, Lynchford House, Franborough, United Kingdom). To guarantee the highest level of safety and the correct functioning of the devices a two persons team, composed by a physician and an engineer, were constantly attending the admission.

3.2 Data Analysis and Results

Frequent YSI measurement allow reconstructing an accurate continuous blood glucose profile simply by linear interpolation. Interpolated profile was then used to compute percent time in target [70-180] mg/dl, percent time
in tight target [80-140] mg/dl, percent time in hypo (below 70 mg/dl), percent time in hyper (above 180 mg/dl) and mean BG. Results reported in Breton et al. [2012] are summarized in Figure 1(b), that compares glucose profiles obtained by open- and closed-loop control. Population mean profile is depicted for both admission, together with an inter-quartile population envelope, accounting for inter-patient variability. As suggested by Figure 1(b), upper panel, H2MS allows to improve time spent in near normoglycemia significantly with respect to traditional therapy. As expected by the design of H2MS, time spent in tight glycemic range did not differ between the two admissions overnight. Improved glycemic control was achieved with simultaneous significant reduction of hypo. For what concerns the MPC controller Breton et al. [2012] shows that overall percent time in near normoglycemia increased significantly and that percent time in tight control increased significantly overnight while improvements in tight control on the overall data were not statistically significant, due to the effect of meal perturbation. Improved glucose control was achieved without significant increase in the risk of hypoglycemia and with a significant decrease in the overall average plasma glucose.

3.3 H2MS and MPC

A comparison between the two controllers was performed in Breton et al. [2012], restricting the analysis to the adult population only, and using univariate ANOVA with open-loop performance included as a covariate to compensate for the difference in the baseline standard therapy in the two populations, apparent also in Figure 1(b). Breton et al. [2012] reports that MPC and H2MS both increased time spent in near normoglycemia similarly while MPC increased overnight time spent in tight glycemic control further, compared with H2MS. The comparison of the occurrence of hypoglycemia in H2MS and MPC was not conclusive.

4. OUT-PATIENT STUDIES

Table 1 reports a summary of the study conducted from 2011 by the author groups. Except for minor modifications all but one study shared the same non-randomized design summarized in the following section. The main differences were related to the DiAs technology used to communicate with pump and sensor and to the control algorithm employed.

4.1 DiAs: A Wearable Platform for Out-patient AP

Even if enabling automated data transfer, the APS used in in-patient in Breton et al. [2012], Luijf et al. [2013] is not suited for out-patient real-life studies, since it limits patient mobility due to many wired connections among the components. Recently, an important step forward for the implementation of an ambulatory artificial pancreas has been proposed at University of Virginia, Keith-Hynes et al. [2013]. The system, called Diabetes Assistant (DiAs), is capable to connect with pump and sensor and to command either open-loop insulin delivery or closed-loop control running a suitably programmed control algorithm. Both modes of operation included fully-automated transfer of data from the sensor to DiAs and commands from DiAs to the insulin pump. The central component of the DiAs system is an off-the-shelf smart phone running the Android operating system (OS). To ensure the operation of the smart phone as a medical device, its OS was modified to disable processes not related to clinical operation and
to include self-checks of system integrity. The communications between DiAs and the peripherals (pump and sensor) were wireless, giving the patient the freedom to be fully detached from the DiAs controller. The DiAs system can be used with many different pumps and a number of sensors, but in our published out-patient studies Cobelli et al. [Sept. 2012], Kovatchev et al. [2013], Del Favero et al. [in press] it was used with the Omnipod Insulin Pump (Insulet Corp, Bedford, MA) and with DexCom Seven Plus (DexCom, Inc., San Diego, CA) sensor. Since direct Bluetooth communication is not available in these pump and sensor, the system components worn by the patient included a Bluetooth-USB hub connected to an iDex - an experimental device from Insulet Corp combining a DexCom Seven Plus receiver and Omnipod PDM.

Out-patient testing showed that the wired connection among the iDex and the relay device is prone to failure and proved to be the weak point of the system. Also wireless communication among iDex and pump/sensor lacks of the robustness requested for continuous use at home. Given that Insulet had to stop supporting development and maintenance program of the iDex device, the authors’ team decided to resort to other pumps, allowing direct connection wireless connection with the phone. In particular, Tandem pump has been integrated in the system, through the Low Power Bluetooth access that the pump provides and used in Kovatchev et al. [in press]. Unfortunately, Low Power Bluetooth is not available in most of the Android smartphones currently on the market and an external hardware, implementing this communication standard, had to be included in the system. Furthermore, Roche AccuCheck Pump has also been integrated and thanks to the standard Bluetooth access it provides, no extra hardware was needed. Our last out-patient study was conducted with this configuration. Both Bluetooth and Low Power Bluetooth connection proved to be highly robust connections, well suited for sustained domestic use. Standard Bluetooth implemented on Roche pump was particularly satisfactory in terms of connection range and automatic reconnection. A major technological step for-ward has been the appearance on the market and the integration in the system of the new Dexcom sensor, G4 platinum Christiansen et al. [2013], Garcia et al. [2013]. This sensor outperforms significantly its predecessor providing much more accurate measurements and guaranteeing more stable wireless connection among transmitter placed on patient abdomen and Dexcom receiver. Nevertheless, such a receiver has not accessible wireless link. Therefore, the current version of the system still requires either a direct wired connection between DiAs and Dexcom receiver or the use of a relay device bridging the information. This limitation will be finally overcome in the near future with the approval by regulatory bodies to the use of Dexcom G5 sensor, that will allow direct connection of the DiAs smartphone with the sensor transmitter placed on patient abdomen, without intermediate devices.

For what concerns user-DiAs interaction, it takes place using a Graphical User Interface allowing sensor calibrations, insertion of meal carbohydrate content, pre-meal capillary glucose level, and other information the subject wished to provide (e.g. exercise or hypoglycemia treatment). Moreover, the interface can display CGM traces and insulin delivery graphs. Finally, the user interface can be used to initialize the system with the insulin dose, basal rate, carbohydrate ratio and correction factor. User interaction is required also when the system signals imminent risk for hypo- or hyperglycemia. In fact, the system is equipped with two traffic-light signals presenting the degree of risks for hypo- or hyperglycemia as follows:
Study Design

The two studies shared a 42h non-randomized protocol, with the first study with the same protocol testing Modular MPC on 6 adults, held at the University of Padova, Italy. The experiments conducted in the last two years give us the possibility to discuss out-patient control achieved by the two algorithms previously tested in-patient. In particular, Kovatchev et al. [2013] reports data of pilot out-patient study with the same protocol testing Modular MPC on 6 adults, held at the University of Padova, Italy. Del Favero et al. [in press] reports data of pilot out-patient study setting the DiAs streams patient and system data in real-time to a telemonitoring website (Lanzola et al. [in press], Place et al. [2013]), exploiting the smartphone 3G connectivity. Accessing to the website via an ordinary PC, the study team was able to monitor from a remote location the status of the multiple patients and to check the correct functioning of the systems throughout the trial, without interfering/interacting with the experiment unless requested by protocol safety measures or for system troubleshooting. In the studies reported here, lasting less than 48 hours, the study team was constantly monitoring patients’ data and systems status. Moreover the team was requested to remain in the vicinity of the patients, to guarantee prompt intervention. In view of the upcoming month-lasting studies, where 24/7 monitoring will not be possible, a web-based remote alarm system, possibly sending e-mail messages to the study team if need, have been introduced and its effectiveness validated.

4.3 Assessment of Clinical Outcomes

During hospital trials, accurate BG measurements are collected by means of dedicated instruments, e.g. YSI or the Haemocue (Angelhom, Sweeden), whose accuracy and precision are comparable to gold standard laboratory measurements. However, all these techniques are invasive as they require either a blood drop from a finger-prick or venous blood sampling, so that frequent measurements are possible only in in-patient setting and for a short time. Straightforward employment of CGM traces for a clinical trial assessment may be a suboptimal choice, as recently shown in Hovorka et al. [2013], since CGM sensor accuracy and precision limit the possibility to realistically assess glycemic control achieved. The issue holds both for closed-loop and open-loop. Three contributions have explicitly dealt with the problem of using CGM for a clinical trial assessment. The first one, proposed by Kovatchev and Breton, 2012 and discussed in Beck et al. [2013], is an unpublished document prepared for the Food and Drug Administration. In the other contribution, [Hovorka et al., 2013], the authors proposed two algorithms for CGM-based trial assessment: the first based on an offline retrospective CGM adjustment; the second, rather than attempting to reduce CGM error, aims to reduce the bias in the CGM-based estimation of time-in-target, time-below-target and time-above-target, by probabilistically accounting for the possibility that the true BG could lay in a different range with respect to that of CGM. The third contribution is Del Favero et al. [2014], where the problem of BG-profile reconstruction from CGM traces is faced with a constrained semi-blind deconvolution algorithm that exploits the high accuracy of (possibly sparse) BG references collected. The algorithm has two steps: first, it estimates the unknown parameters of the model accounting for plasma-interstitium diffusion and sensor inaccurate calibration; then, it estimates BG performing a regularized deconvolution of CGM data, subject to the additional constraint that the reconstructed BG profile has to lay within the confidence interval of the available BG references. The authors of the three methods have validated them on clinical data showing their effectiveness in reducing the error committed when assessing a clinical trial with respect to the use of CGM data only. At the present time a comparison of the three methods on the same dataset is not available.

4.4 Control Algorithms

The experiments conducted in the last two years give us the possibility to discuss out-patient control achieved by the two algorithms previously tested in-patient. In particular, Kovatchev et al. [2013] reports an out-patient studies testing H2MS on 20 adults studied in two European centers (University of Padova, Italy and University of Montpellier, France) and in two US centers (University of Virginia, Charlottesville, Virginia, and Sansum Diabetes Research Institute, Santa Barbara, California). Recently, Del Favero et al. [in press] reports data of pilot out-patient study with the same protocol testing Modular MPC on 6 adults, held at University of Padova, Italy.

Study Design

The two studies shared 42h non-randomized protocol...
prescribing first 14h of open-loop and the remaining 28h of closed-loop. Study admission started at about 18:00, therefore in both open- and closed-loop portion glycemic control was challenged dinner, served at about 19:30, and both portions include one night. Automated control was activated at about 07:45 and hence closed-loop was further challenged by two breakfasts at about 8:00 of study day 2 and 3 and by lunch at about 12:00 of study day 2. DexCom Seven Plus sensor (DexCom, Inc., San Diego, CA) was inserted 2/3 days prior to admission and patient usual insulin pump was replaced by a Omnipod Insulin Pump (Insulet Corp, Bedford, MA), filled with their usual insulin, at the beginning of the admission. Both open- and closed-loop were delivered through the DiAs. The large majority of the study was conducted in a hotel/guesthouse nearby the university hospital and the subjects were free to move in the facility and in its immediate vicinities. Dinner was consumed at the hotel restaurant where patients were invited to choose a dinner menu in line with their daily habits both in terms of meal amount and composition. After dinner patients spent the night in their hotel room. Throughout the night the study team was available in a nearby room. Two protocol differences among European and US centers, had to be included to fulfill local regulatory requirements. European patients were moved in the university hospital and spent there the first 10 hours of closed-loop, although free to move within the structure (no intravenous blood sampling was requested). In the US centers, during night-time, RCM module was to be stopped and only SSM module was allowed to remain active, possibly reducing basal if hypoglycemia was forecasted.

Data Analysis
Although the studies were not designed and powered to compare open- and closed-loop, nor to compare H2MS and modular MPC, a preliminary comparative analysis is of interest. In view of the US-EU design difference, possibly biasing the comparison, in the following analysis we discard US data where nocturnal full-control was not possible, and limit ourselves to European centers data: 10 patients with H2MS and 6 patients with Modular MPC. Furthermore, since the proposed analysis focus on control performance rather than on overall system performance, we removed data portions where glycemic control is affected by hardware malfunctioning. For a detailed analysis of system functioning we refer the reader to Kovatchev et al. [2013], Del Favero et al. [in press]. The retrofitting techniques mentioned in section 4.3 were applied to the recorded CGM traces and the enhanced profiles were used to computed the same metrics introduce in section 3.2. All data are reported as mean ± standard error, except for time-in-hypoglycemia, reported as median, inter-quartile range given the skewness of the distribution. Results are summarized in Figure 3, where population mean profile is depicted together with the ± standard deviation envelope. Closed-loop profile in not superimposed to open-loop one as in Figure 1(b) since the study is non randomized and prescribes open-loop first.

H2MS (Kovatchev et al., 2013)
As illustrated in Figure 3, also in the challenging outpatient settings we observe and improvement in overnight control using H2MS with respect to open-loop therapy, time-in-target from 73.47% ± 12.93% to 81.22% ± 8.74%. As expected by design and in agreement with in-patient results, time-in-tight-target is not improved and actually slightly worsen from 47.22% ± 12.27% to 46.26% ± 10.41% in the attempt to prevent hypoglycemia: time-in-hypo is reduced from 0% [0% 3.71%] to 0% [0% 0.55%]. The H2MS controller successful prevented hypo after dinner at difference with open-loop (time-in-hypo 0% [0% 1.85%]) at the expenses of a decreased time-in-target: from 80.61% ± 12.26% to 66.57% ± 15.02%. Although the closed-loop was challenged with more meals than open-loop, in terms of overall performance, percent time-in-target was on average above 75% with both treatments (75.37% ± 10.64% open-loop, 77.00% ± 8.05% closed-loop) reducing time-in-hypo (1.80% [0% 3.24%] vs 0.66% [0% 1.65%]).

Fig. 4. Meal Control achieved by the most recent version of the MPC algorithm in out-patient setting, [Del Favero et al., in press]

Modular MPC (Del Favero et al., in press)
Overnight control was slightly better on closed-loop with respect to open-loop: time-in-target, 89.40% ± 10.60% vs. 84.97% ± 7.05%; time-in-tight-target 59.07% ± 20.51% vs. 48.53% ±11.03%. Of note, in closed-loop no patient experienced nocturnal hypo, whereas in open-loop 1,77%, [0% 7.31%] time-in-hypo was observed. Dinner closed-loop control was better than open-loop control of the same meal on the previous day: time-in-target increased from 68.17% ± 13.55% to 94.84% ± 3.53 % and time-in-hypo was almost reduced to zero (5.06%, [0% 10.13%] vs. 0% [0% 0%]). Although the closed-loop was challenged with more meals than open-loop, in terms of overall performance, percent time-in-target was on average above 80% with both treatments (82.05% ± 5.64% open-loop vs. 84.66% ± 4.03% closed-loop) and an important reduction of time-in-hypo was observed with closed-loop (4.07% [2.26% 9.78%] open-loop vs. 0% [0% 1.16%] closed-loop). Of note, MPC ensured good control at all meals, as depicted in Figure 4. Lunch average control achieved by closed-loop was similar to the one achieved at dinner. No hypoglycemia was observed after lunch (12:00-16:00). Breakfast confirmed itself as the most difficult meal to control: both breakfasts had less time-in-target than dinner and lunch. In the first day breakfast, time-in-hypo was slightly higher than after dinner and lunch, while no hypoglycemia was observed after the second day breakfast. It is of interest to compare results achieved by the most recent version of the Modular MPC regulator, tested outpatient on 6 subjects in Del Favero et al. [in press], with the
previous version of the same algorithm, tested in-patient on 12 subjects, Breton et al. [2012], and with its simpler counterpart the H2MS, tested out-patient in Europe on 10 subjects, in Kovatchev et al. [2013]. Dinner (upper panel) and night (lower panel) are considered.

Fig. 5. Comparison of the most recent version of the Modular MPC regulator, tested out-patient on 6 subjects in Del Favero et al. [in press], with the previous version of the same algorithm, tested in-patient on 12 subjects, Breton et al. [2012], and with its simpler counterpart the H2MS, tested out-patient in Europe on 10 subjects, in Kovatchev et al. [2013]. Dinner (upper panel) and night (lower panel) are considered.

In this contribution we reviewed authors’ experience in the in-patient to out-patient transition, focusing on devices, telemicine and algorithm issues. In particular, for what concerns control algorithm, we illustrated how modularity in control architecture, allowed progressive deployment and testing of two control algorithms: the H2MS focusing on safety and the modular MPC aiming to enforce tight glycemic control. An out-patients comparison of the two controllers, analogous to what it was done in-patient in Breton et al. [2012], complements our illustration of this transition with new clinical results.

5. CONCLUSIONS

In this contribution we reviewed authors’ experience in the in-patient to out-patient transition, focusing on devices, telemicine and algorithm issues. In particular, for what concerns control algorithm, we illustrated how modularity in control architecture, allowed progressive deployment and testing of two control algorithms: the H2MS focusing on safety and the modular MPC aiming to enforce tight glycemic control. An out-patients comparison of the two controllers, analogous to what it was done in-patient in Breton et al. [2012], complements our illustration of this transition with new clinical results.

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