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Artificial Pancreas: from in-silico to in-vivo ⋆

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Abstract: Type 1 diabetes is a disease caused by an autoimmune reaction. The Artificial Pancreas (AP) is an automatic closed-loop system composed of a subcutaneous glucose sensor, a subcutaneous insulin pump and a device on which a control algorithm and a human interface are implemented. The last years have seen an accelerated improvement of these three components that became more reliable and compact, making the system safer, wearable, and usable in real life. An overview on AP and its components is presented together with an introduction on the in-silico tools used to develop and tune the control algorithm and to make pre-clinical tests. Particular attention is devoted to the design of a Model Predictive Control, to the choice of the model and of the constraints, and to the definition of the most relevant performance indices. Most of the choices have been driven by the experience gained by both in-silico and in-vivo trials. In-silico experiments involved thousand of hours of simulations on the Food and Drug Administration accepted simulator equipped with 100 adult virtual patients. In-vivo experiments, of which a complete list is presented, involved about forty thousand hours of trials, first, conducted in a clinical environment and, then, at home.

Keywords: Artificial Pancreas, Predictive control, Linear systems, Biomedical control, Biomedical systems.

1. INTRODUCTION

Type 1 Diabetes Mellitus (T1DM) is a disease in which the body is incapable to autonomously regulating Blood Glucose (BG) concentration, also called glycemia. The causes of this disease are still unclear, but genetic heredity is thought to play an important role in determining who is likely to develop T1DM, that typically occurs in children and young adults (though it can appear at any age). T1DM is characterized by a lack of insulin due to the destruction of insulin-producing beta cells in the pancreas and, as a consequence, the patient can encounter *hyperglycemia* (i.e. high BG concentration). In order to avoid hyperglycemia, the patient needs exogenous insulin infusions that have to be properly tuned. On the other hand, insulin overestimation could bring the patient into a *hypoglycemia* state (i.e. low BG concentration), that can seriously compromise the patient health. The severity of the disease motivated the interest of the scientific community and of several organizations to find a doable and reliable solution.
The Artificial Pancreas (AP) was born as a system thought to automate the exogenous insulin supply and its first appearance as a commercial device dates from 1974 (Pfeiffer et al. (1974)). This version needed venous access, was highly invasive and non-portable, and the patient had to be hospitalized. Recently, several research projects on AP were supported by the Juvenile Diabetes Research Foundation (JDRF), the European Commission, and the National Institutes of Health (see Bequette (2012), Cobelli

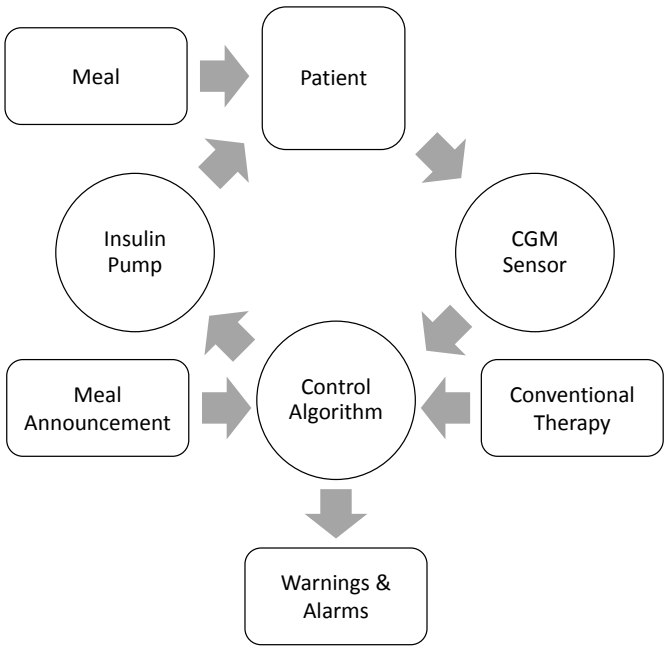

Fig. 1. Conceptual AP representation. Circled elements represent the main AP components.

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et al. (2009), El-Khatib et al. (2010), Hovorka et al. (2010), Weinzimer et al. (2008), Russel et al. (2014), Del Favero et al. (2015), and Thabit et al. (2014)) and today, thanks to the latest technology developments, the system has become non-invasive, safe, and wearable. The AP main components are a subcutaneous (sc) insulin pump, a sc glucose sensors or Continuous Glucose Monitor (CGM), and a Control Algorithm (CA) that is executed on a portable device. The AP components interaction is represented by the circled elements in Fig. 1. The CGM provides a quasi-continuous measurement of sc glucose to CA, which has to evaluate the optimal quantity of insulin to infuse to the patient. The algorithm suggestion is then sent to the sc insulin pump, that infuses the desired quantity of insulin in the patient sc tissue. CA can manage additional external information like the meal announcement and the conventional therapy (as described in the following), and can produce warning messages and alarms, if necessary. This system is non-invasive for the patient, but has to deal with significant noise and delays in the glycemia readings and important delays on the insulin absorption (see Cobelli et al. (2011)). Moreover, the patients are characterized by an important intra- and inter- variability, making the CA design challenging.

2. SIMULATOR

In order to minimize the design cost and time of a reliable AP, some simulators have been developed by different research groups based on specific models of diabetic patients (see (Cobelli et al., 2009)). A simulator can be exploited to design and test different control algorithms entirely in-silico, i.e. by simulating a large amount of hours of experiments in different scenarios. Indeed, by considering a proper model of the CGM measurement noise and by considering the insulin pump hardware properties (e.g. infusion quantization), the simulations can reproduce the cycle of Fig. 1 without involving any diabetic patient (i.e. the real AP components are substituted with simulated components and the patient is substituted with a model). In order to cope with patient intervariability, simulators are usually equipped with a set of model parameters representing a population of diabetic patients having different characteristics. In this work we focus on the UVA/Padova simulator, that is the only one approved by the American Food and Drugs Administration (FDA) as a substitute of pre-clinical animal tests. It is equipped with a virtual population composed of 300 virtual patients, 100 adults, 100 adolescents, and 100 children (see (Dalla Man et al., 2014) for the most recent version). An example of the simulated patients intervariability is depicted in Fig. 2, where the BG simulations of 10 adult vitual patients of the UVA/Padova simulator are shown. Despite the same insulin and meals, each patient has a different BG trend. Fig. 2 also shows the euglycemic range, which is defined as the BG range spanning from 70 mg/dl to 180 mg/dl and is considered to be a safe interval where the patient glycemia should remain in order to avoid hypo- and hyperglycemia phenomena.

3. GLUCOSE CONTROL

The main task of AP is to automatically maintain the patient BG concentration within a safe range. This difficult task requires an architecture designed to maximize the efficacy of CA and to minimize the risks for the patient. An improved version of the modular architecture presented in (Kovatchev et al., 2009), (Cobelli et al., 2011), and (Patek et al., 2012)) is proposed. The improved architecture is divided in four main layers and includes various modules, as shown in Fig. 3. The off-line layer represents all the information that the AP system needs to be properly initialized and individualized for a specific patient. The real time layer includes the controller, which is driven by the CA, and the modules that interact with the controller during the system operation. This layer operates with a synchronous sampling time compatible with the dynamic of the system (i.e. 15 minutes), but must be also able to handle asynchronous events like a meal announcement. The continuous time layer typically operates with a lower sampling time (i.e. 5 minutes) and interacts with the insulin pump and CGM, that are included in the hardware layer.

3.1 Initialization & Individualization

The aim of the off-line layer is to deal with the patients inter-variability. In fact the CA must be properly initialized and individualized using the patient clinical information acquired by the physician, that is passed into the initialization & individualization module, as shown in Fig. 3. The most common used patient information is the so called Conventional Therapy (CT) that has been defined by the physician and is based on the patient characteristics. It contains the information about the patient basal insulin, that is the insulin needed to maintain the glycemia concentration equal to the basal glucose value during the fasting periods. CT also contains the so called Carbo Ratio (CR) and Correction Factor (CF) parameters, that are directly correlated to the insulin boluses needed to compensate glycemia during each postprandial (PP) period. A better individualization can also be achieved if data collected in previous in-vivo experiments performed on the same patient are available. In this case model identification techniques can be implemented. Model and/or parameter individualization can be also periodically updated in order to adapt the CA to possible slow changes in patient metabolism. This adaptation strategy has to be computed off-line since it requires a high computational burden and/or is memory demanding.

3.2 Adaptation Module

The controller individualization performed in the off-line layer can be modified on-line by taking into account some information provided by the patients or data collected in the previous period. The algorithms designed for this layer must have low computation and memory requirements. The algorithms based on a Run-To-Run (R2R) for example typically satisfy these requirements because they need very simple data computations and are based only on the last day.
Several R2R strategies based on sporadic BG measurements [1] were successfully tested in-silico and in-vivo. For instance, a day-by-day adaptation was studied for basal

[1] BG concentration can be autonomously measured on venous blood obtained by fingerstick or fingerprick.

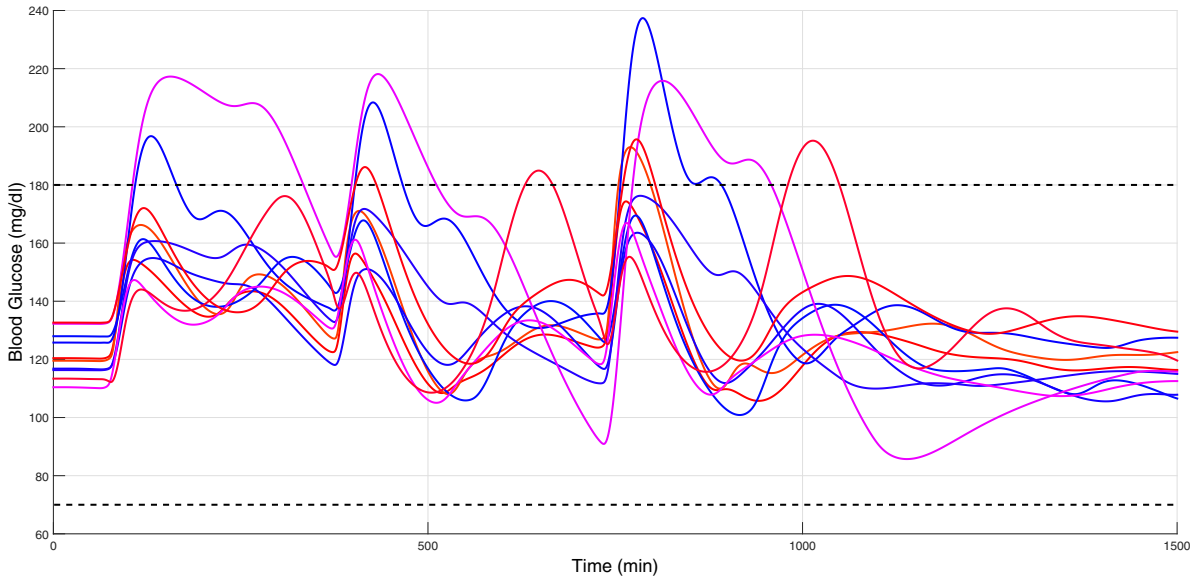

Fig. 2. BG simulations of 10 adult virtual patients of the UVA/Padova simulator. The black dashed lines represent the euglycemic range (i.e. $[70 - 180]$ mg/dl).

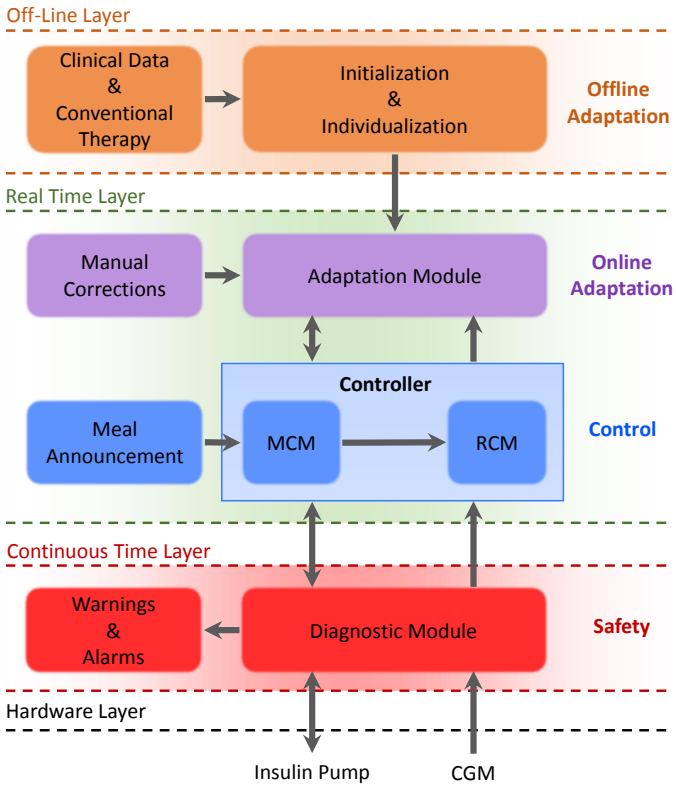

Fig. 3. Representation of the Artificial Pancreas modular architecture.

insulin (see (Palerm et al., 2008)), for insulin boluses (see (Doyle et al., 2001), (Zisser et al., 2005), (Owens et al., 2006), (Palerm et al., 2007a), and (Palerm et al., 2007b)), and for a model predictive controller cost function (Magni et al., 2009b). More recently, the study of (Toffanin et al., 2014) investigated the automatic day-by-day basal insulin adaptation based on CGM sc measurements. This approach was tested in-silico by gradually varying the insulin sensitivity of the UVA/Padova adult virtual patients. This R2R strategy significantly improved the BG control performance after one week. A more powerful strategy that adapts both insulin boluses and basal insulin is currently used in in-vivo clinical experiments.

The on-line adaptation can also be adjusted by manual corrections. The patient can modify some clinical parameters based on his particular state (e.g. sickness, stress, physical activity, etc.) and the adaptation module can use the history of the manual corrections to improve future automatic adaptations. By giving the patient the possibility to interact with the adaptation module, the system can store precious information about the patient habits (e.g. routine physical activity during the week), which could be considered for advanced strategies of individualization based on data mining techniques.

3.3 Meal control module

The controller module is composed of two sub-modules, as shown in Fig. 3. The meal control module (MCM) is implemented for meal compensation and uses meal announcement (MA) as an external information supplied by the patient (see (Soru et al., 2012) for details on MA). The range control module (RCM) is the core of the controller and it is described in Section 3.4. MA is used to inform the controller about the time and the estimated amount of carbohydrates of a meal. This information is used by the CA together with the CT to infuse the estimated insulin bolus needed to compensate a meal. The advantage of using MA is to inject an insulin bolus without waiting for the PP glycemia raising supplied by the CGM measurements, consequently improving the PP glucose control performance. MA represents additional knowledge that is available to the patient and that should be exploited to improve the BG control performance, especially within the PP periods. In case of a missing MA, in spite of an unavoidable worsening of the control performance, the AP system should remain able to operate safely.

3.4 Range control module

The core of the controller resides in the range control module (RCM), that is driven by a specific CA to maintain the BG concentration within a safe range. In the literature, several control algorithms based on Proportional Integrative Derivative schemes ((Steil et al., 2006) and (Marchetti et al., 2006)), on Fuzzy Logic (Atlas et al., 2010) and on Model Predictive Control (MPC) ((Hovorka et al., 2004), (Parker et al., 1999), (Magni et al., 2007), (Soru et al., 2012), (Hovorka, 2005), (Hovorka, 2006), (Grosman et al., 2010), (Dua et al., 2006), (Magni et al., 2009a), and (Patek et al., 2012)) have been proposed.
In the following a description of an MPC technique is proposed.

Model The model can be linear or nonlinear, but clinical evidence collected in various experiments indicates that a linear approximation may capture the essential dynamics for an efficient and safe BG control (Del Favero et al., 2014). One of the latest MPC for AP used in in-vivo clinical trials is presented in (Toffanin et al., 2013), whose process model is the linearization around a basal fictitious equilibrium of the average nonlinear model describing the adult virtual population of the UVA/Padova simulator (Dalla Man et al., 2014).
In order to improve the MPC performance and safety, the process model individualization is a key point that has to be properly investigated. Recent works have addressed the model individualization based on the CR clinical parameter (Messori et al., 2015), on nonparametric identification (Del Favero et al., 2014), on low-order linear models identification (Soru et al., 2012), and the use of these techniques in in-vivo experiments is currently under development. Another technique based on a multi-objective optimization problem has been proposed in (Maheshwari et al., 2012). It is worth to emphasize that the MPC model individualization based on clinical data is part of the off-line adaptation in the modular architecture of Fig. 3.

Cost function MPC is equipped with a cost function that drives the controller suggestions. In the AP context the cost function generally represents the risk associated to hypo- or hyperglycemia phenomena. The MPC proposed in (Toffanin et al., 2013) implements the following cost:

$$J(x(k), i(\cdot), k) = \sum_{j=0}^{\mathrm{PH}-1} \left(q(c(k+j) - y_0(k+j))^2 + (i(k+j) - i_0(k+j))^2\right) + \|x(k+N)\|_P^2 \quad (1)$$

where $i(k)$ is the insulin to be infused at each time k, $x(k)$ is the linearized model state, PH is the prediction horizon, $i_0(k)$ is the insulin suggested by the patient CT, $c(k)$ is the CGM measurement, $y_0(k)$ is the glucose set-point, P is the solution of the discrete time Riccati equation introduced to approximate an infinite horizon cost function and to improve stability property, and q is a parameter that quantifies the controller aggressiveness. Due to the patients variability, the latter needs to be properly calibrated to adapt the controller suggestions to a specific diabetic patient. Such calibration is part of the off-line adaptation of Fig. 3. It can be performed in-silico by considering the nonlinear models describing the virtual population and, then, by identifying a regression model based on clinical parameters that is used to adapt the cost function to any diabetic patient (Soru et al., 2012). In case the linear process model is identified from clinical data, the calibration procedure can be automatically performed on the identified model with a trial and error approach and the resulting optimal q value can be directly proposed for the diabetic patient (Soru et al., 2012).
Cost (1) is symmetric, since it associates the same risk to hypo- and hyperglycemia phenomena (i.e. the same risk is associated to glucose concentrations higher and lower than the set-point $y_0(k)$). A different approach consists on considering an asymmetric cost function, which associates a higher cost to hypo- with respect to hyperglycemia phenomena (Parker et al., 2000), (Magni et al., 2009a). The recent work of (Messori et al., 2015) proposed the following asymmetric cost function:

$$J_A(x(k), i(\cdot), \epsilon_1, \epsilon_2, \epsilon_3, \epsilon_4, c_H(\cdot), c_L(\cdot), k) = \sum_{i=0}^{PH-1} \left(||c_L(k+i)||_{q_L}^2 + ||c_H(k+i)||_q^2 + (i(k+i) - i_0(k+i))^2\right) + ||x(k+N)||_P^2 + \sum_{j=1}^{4} M_j \epsilon_j^2 \quad (2)$$

where $c_L(k)$ and $c_H(k)$ represent the sc glucose negative and positive variations with respect to $y_0(k)$, respectively, ϵ_j and M_j with $j = 1, 2, 3, 4$ are slack variables related to soft constraints with the associated weights, respectively, and the fixed weight $q_L >> q$ is related to hypoglycemia.

Constraints One of the major risks of a BG controller based on insulin only is to induce hypoglycemia. In this case, the AP system should produce an alarm to inform the patient about his state and the controller should stop the insulin infusion until a normal BG concentration is predicted to be recovered. It is also possible that the patient needs to assume some rapidly absorbing carbohydrates. In order to avoid these situations, MPC input constraints have to be properly designed to avoid insulin overestimation. On the other hand, insulin underestimation could increase the risk of hyperglycemia and of ketone bodies formation.
The following constrained finite horizon optimal control problem (FHOCP) has to be solved at each time k:

$$\begin{aligned} i^o(k) &= \arg\min_{i(\cdot)} J(x(k), i(\cdot), k) \\ i(k) &\in U(k) \quad \forall k \end{aligned} \quad (3)$$

where $i^o(k)$ is the optimal suggested insulin, and $U(k)$ is a time-varying compact set defining the admissible insulin at each time k. The input constraints improve the controller safety in presence of model uncertainties, but increase the computational burden needed to solve the FHOCP. In a real context, where regulatory limitations have to be fulfilled and where a portable device with limited energy and power is used to execute the CA, the implementation could result unfeasible. A possible alternative is to substitute (3) with its equivalent unconstrained closed-form formulation and to implement the constraints as explicit saturations, as explained in (Toffanin et al., 2013). As a result, a suboptimal solution of (3) is achieved at each time k without the need of an on-line optimizer and with the minimal computational burden. Moreover, as shown in (Messori et al., 2014), despite the sub-optimality nature of the resulting control law, it can be considered a good

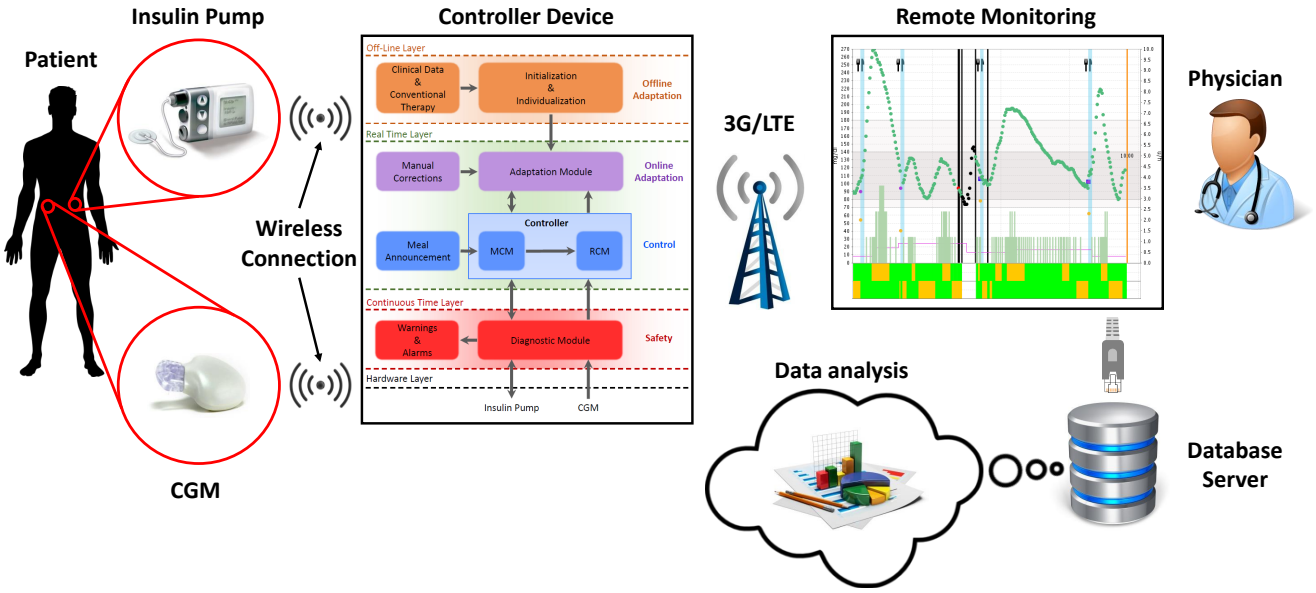

Fig. 4. Representation of the entire artificial pancreas system, which is integrated by a remote monitoring system and a database server used to store clinical data.

approximation of (3) and can be proposed for real-life implementation.

The design of soft-output constraints has recently been investigated in (Messori et al., 2015), where a *Rise Compensation / Drop Attenuation* mode has been proposed for BG control within the PP periods. The FHOCP was defined by considering the asymmetric cost function (2) and by including additional insulin integral constraints based on the patient CT. This control law needs to be computed on-line at each sampling time and, despite the promising achieved control performance, it is not yet used in in-vivo experiments.

3.5 Diagnostic module

The controller interaction with the hardware is mediated by a diagnostic module (DM), as shown in Fig. 3. DM has to continuously monitor the insulin pump and CGM connection status and to detect possible hardware failures, like pump occlusions or missing CGM measurements. In addition, DM implements an internal model used to predict the possibility of future hypo- or hyperglycemia based on the available CGM measurements and on the suggested insulin by RCM. In case of predicted hypoglycemia, DM can override the RCM insulin suggestions by reducing or stopping the insulin infusion. Moreover, DM has also to inform the patient about possible hazardous situations through warnings messages, which can include also acoustic alarms. In particular, since it is not possible to recover the patient from a severe hypoglycemia with only insulin reductions, external glucose administration is required. This safety system is useful during the night, when the patient is asleep and is not aware about his state. In case of predicted nocturnal hypoglycemia, DM can produce an alarm waking up the patient before encountering a possible coma, that in severe case can result in death. It is evident that by introducing this module there is a problem of possible false alarms that have to be minimized. However, DM has become a mandatory component of the AP, making the system safer and giving the patients the awareness to be continuously monitored (Patek et al., 2012).

4. SYSTEM IMPLEMENTATION

The implementation of a reliable and portable AP system is a demanding task that required several years of development. Today, the system has become portable, safe, and usable by the patient without a continuous medical and technical supervision. The final aim is to launch on the market a product suitable for type 1 diabetic patients and, for this reason, the system needs to be continually improved as the research makes progress.

A representation of the currently AP system is shown in Fig. 4. The patient is equipped with a sc insulin pump and with a sc CGM, that are wirelessly connected with the controller device described in Section 3. The controller device has the capability to communicate clinical data and alarms to a remote monitoring system, making a real-time supervision of the physician, if necessary, possible. The transmitted data are stored in a database server for analysis purpose, significantly improving the available knowledge about the patient habits and characteristics.

4.1 Inpatient to outpatient

The earliest AP versions were suited for inpatient clinical trials. The patient was hospitalized and equipped with a sc insulin pump and with a sc CGM, and the entire experiment was under the strictly supervision of physicians and engineers. Since there was no direct communication between the CA (which was executed on a separate laptop) and the insulin pump, the pump had to be manually commanded with the suggested insulin infusions, previously approved by a physician. This operation had to be repeated at each sampling time (i.e. every 15 minutes) making long-term clinical experiments (i.e. more than 24 hours) with a large number of patients practically impossible (see (Kovatchev et al., 2010)). Moreover, the aim of the earliest clinical experiments was to control the

Table 1. List of AP clinical trials driven by MPC.

Trials	Clinical Centres	Hours of CL	MPC Reference	Clinical Reference
JDRF (2008)	PAD MPL UVA	290	(Magni et al., 2007)	(Kovatchev et al., 2010)
JDRF pilot (2010)	PAD MPL	216	(Patek et al., 2012)	(Breton et al., 2012)
JDRF (2011)	PAD MPL UVA STF SDRI CLD SCMCI	2900	(Patek et al., 2012)	(Zisser et al., 2014) (Chase et al., 2014)
AP@home (2011)	PAD MPL AMS CAM GRAZ NEUS	1081	(Soru et al., 2012)	(Luijf et al., 2013)
AP@home pilot outpatient (2012)	PAD	168	(Toffanin et al., 2013)	(Del Favero et al., 2014)
JDRF outpatient (2013)	PAD MPL SDRI UVA	420	(Toffanin et al., 2013)	(Kovatchev et al., 2014)
AP@home outpatient (2013)	PAD MPL AMS	364	(Toffanin et al., 2013)	(Del Favero et al., 2015)
AP@home outpatient (2014)	PAD MPL AMS	21504	(Toffanin et al., 2013)	Submitted
AP@home 24h & R2R outpatient (2015) Trial in progress	PAD MPL AMS	> 10000	–	–

BG concentration during the night, when the patient was sleeping and no meals had to be controlled. Afterwards, automatic meal compensation was gradually introduced and it is currently one of the most difficult task to be successfully accomplished. A further challenging task is represented by the management of physical activity, that is currently under investigation. From a technological point of view, a very important step ahead was the development of the APS (Dassau et al., 2008), that allowed a fully automatic closed-loop. This system was adopted in the first large clinical experiments ((Luijf et al., 2013), (Zisser et al., 2014), (Chase et al., 2014)). APS, however, was not suited for outpatient real-life studies, since it limited patient mobility due to many wired connections among the components and was characterized by a PC based implementation.

Clinical experiments outside the hospital environment forced the development of a portable platform, usable by the patient without medical and technical support. This goal was reached with the introduction of the Diabetes Assistant (DiAs) (see (Kovatchev et al., 2012) and (Keith-Hynes et al., 2014)), a system running on a commercially available smart phone, as shown in Fig. 5, that implements the modular architecture of Fig. 3. The patient is informed about the predicted risk of hypo- or hyperglycemia through a traffic light system, and can read the current and the past measured glycemia together with the history of the insulin infusions. The patient interacts with the system through touch screen buttons, and the graphical user interface contains also information about the whole system status (e.g. the system operating mode, the CGM and the insulin pump statuses, the device connection to the network, the battery level, etc.). DiAs can also show warning messages or throw alarms in case of system malfunctions or when possible hazardous situations are detected.

Table 1 shows a list of clinical trials completed with the AP developed by our group, that is characterized by an increasing complexity. The involved clinical centres were the Universities of Padova (PAD), Montpellier (MPL), Virginia (UVA), Cambridge (CAM), Graz (GRZ), Stanford (STF), the Profil Institute for Metabolic Research GmbH (NEUS), the Sansum Diabetes Research Institute (SDRI), the Barbara Davis Center for Childhood Diabetes in Colorado (CLD), and the Schneider Children's Medical Center in Israel (SCMCI). Inpatient clinical experiments started in 2008 and protracted till 2012. Outpatient experiments started in 2012, where the patient was accommodated in a hotel room and a technical and medical teams were hosted in the same hotel for interventions in case of unexpected system faults. Starting from 2014, patients were allowed to autonomously use the AP system at home during dinner, night and breakfast for long periods (two months). Today, thanks to the reliability achieved with the current implementation (Fig. 4), patients can autonomously use the AP system 24 hours per day for long periods (one month). All these experiments are promoted by the JDRF and by the EU FP7 project.

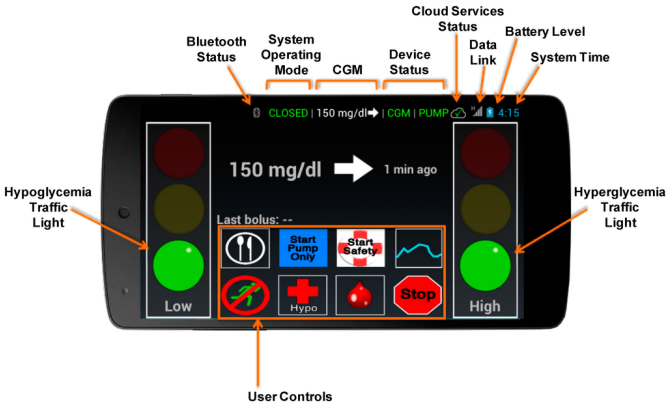

Fig. 5. Diabetes Assistant graphical user interface.

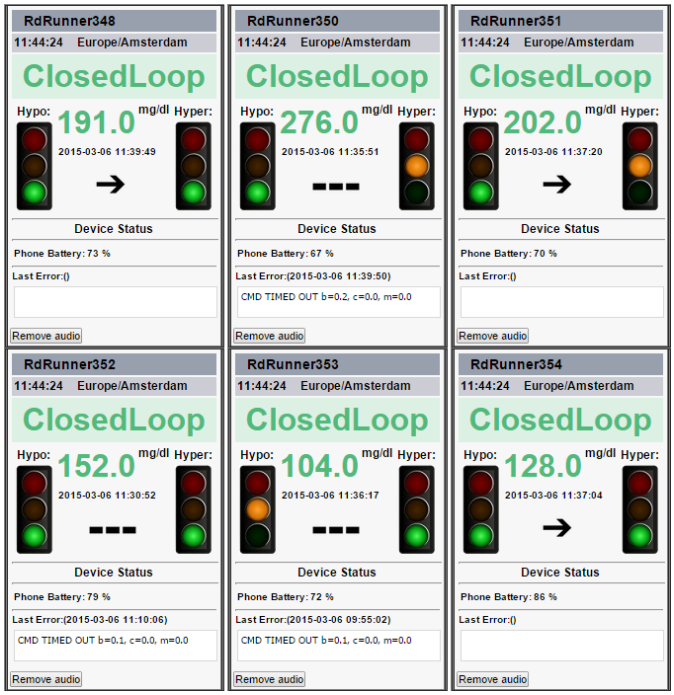

Fig. 6. Running sessions overview of the remote monitoring system. In this example six patients affiliated to the Amsterdam clinical center are remotely under control in real time.

4.2 Remote monitoring

The need to develop a safe portable platform motivated the integration of the controller device with a remote monitoring system. Thanks to the available wireless internet connection services (i.e. 3G and LTE high speed connections) and to the connectivity functionalities of the commercially available smart phones, the controller device can send real-time information of the patient state. Physicians can monitor their patients through a web-based GUI, as shown in Fig. 6, and can intervene in case of a critical situation. In addition to the patient state, the remote monitoring system also controls the system status, and sends the proper alarms in case of a system malfunction. An exhaustive description of the currently adopted monitoring system is presented in (Lanzola et al., 2011), (Capozzi and Lanzola, 2013), and (Lanzola et al., 2014).
The information transmitted by the controller device is stored in a database, that is subsequently used for data analysis. The purpose is to gain knowledge about the habits of the patients and about their characteristics, and to achieve more efficient off-line adaptations of the CA (see Fig. 3).

5. CONCLUSION

The last years have seen a significant acceleration of AP, a system designed to automatically regulate the exogenous insulin infusions needed to maintain the BG concentration within the euglycemic range in type 1 diabetic subjects. The system design has been accelerated by the introduction of several in-silico tools, that allowed to arrive at a safe and effective MPC based CA.

The experience achieved from thousands of hours of in-vivo clinical trials encouraged the design of a modular architecture exploited to minimize the patients risk, making outpatient clinical experiments possible and giving the patients the possibility to autonomously interact with the AP during their life. Furthermore, the development and the integration of a monitoring system increased the AP confidence of patients and physicians, and it made possible the real-time remote detection of possible risky situations. In the future, the AP system could be integrated with additional sensors to automatically detect the patient physical activity (e.g. heart rate sensors and pedometers); in addition, some manual tasks like the carbohydrate estimation for meal announcements could be automated (e.g. automatic carbohydrate estimation through an acquired image of the meal). The remote monitoring system could be directly integrated with the healthcare emergency services and, in case of detected hazardous situations, the system could have the possibility to automatically call the emergency and to alert the physician with a warning message (e.g. sms or email). Furthermore, in order to have the possibility to automatically track the patient position in serious emergency cases, a GPS system could be integrated in the controller device.
While the current AP is able to guarantee a safe and effective BG control, there are some aspects that have to be refined before declaring to be ready to launch a device in the market, especially for what concern meal control, model individualization, and the management of non-standard situations like physical activities, stressful situations and sickness. Nevertheless, the achieved results are very promising and, thanks to the research efforts, this project is reaching several milestones and is continually increasing our knowledge and experience.

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