Designing an artificial pancreas architecture: the AP@home experience

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Received: 31 March 2014 / Accepted: 16 November 2014 / Published online: 28 November 2014
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Abstract The latest achievements in sensor technologies for blood glucose level monitoring, pump miniaturization for insulin delivery, and the availability of portable computing devices are paving the way toward the artificial pancreas as a treatment for diabetes patients. This device encompasses a controller unit that oversees the administration of insulin micro-boluses and continuously drives the pump based on blood glucose readings acquired in real time. In order to foster the research on the artificial pancreas and prepare for its adoption as a therapy, the European Union in 2010 funded the AP@home project, following a series of efforts already ongoing in the USA. This paper, authored by members of the AP@home consortium, reports on the technical issues concerning the design and implementation of an architecture supporting the exploitation of an artificial pancreas platform. First a PC-based platform was developed by the authors to prove the effectiveness and reliability of the algorithms responsible for insulin administration. A mobile-based one was then adopted to improve the comfort for the patients. Both platforms were tested on real patients, and a description of the goals, the achievements, and the major shortcomings that emerged during those trials is also reported in the paper.

Keywords Artificial pancreas · Glucose control algorithms · Remote monitoring · Diabetes mellitus type 1 · e-Health and m-health for diabetes management

1 Key terms

- **Artificial pancreas**: a closed-loop control system currently being researched for diabetes patients, which tries to emulate the behavior of a healthy pancreas. This encompasses the continuous delivery of insulin in order to control the blood glucose level based on its real-time monitoring.
- **Artificial pancreas platform**: refers to the technology concerning a specific artificial pancreas implementation. This is given by the combination of the hardware components (i.e., the computing device, the blood glucose sensor, and the insulin pump) together with the software algorithm able to compute in real time the amount of insulin required and actually administer it to the patient.
- **Artificial pancreas architecture**: throughout the paper, this term is used to refer to the broadest set of components supporting the use of the artificial pancreas. Those include the blood glucose sensor and the insulin pump, the regulation algorithm and the computing device for running it, and the remote data acquisition service and the application enabling patient monitoring through the web. The architecture specifies the roles of the components and the way in which they exchange information among each other.
2 Introduction

Diabetes Mellitus (T1DM) is a chronic disease characterized by the failure of pancreas beta cells to produce insulin which results in elevated blood glucose levels (BGL). The so-called hyperglycemia (i.e., BGL > 180 mg/dl) decreases both the quality of life and its expectancy, so it should be avoided. In order to control the BGL, diabetes patients have to be treated via exogenous insulin administration. If too much insulin is injected, BGL drops too low causing hypoglycemia (i.e., BGL < 70 mg/dl), which causes coma, brain damage, or even death. The two major treatments for T1DM consist either in administering a small number of multiple daily insulin injections (MDII) according to the corresponding BGL readings or in using a pump delivering insulin micro-boluses during the whole day as needed, the so-called continuous subcutaneous insulin infusion (CSII).

Nowadays, CSII is being used as the preferred insulin treatment by T1DM patients, since it reduces BGL fluctuations during the day [30, 36]. T1DM patients are trained to acquire glucose readings several times per day, on which basis they adapt their CSII regimens. The latest advances in biotechnologies are already producing sensors able to accomplish continuous glucose monitoring (CGM) [13, 23, 27, 38], while new methodologies and techniques are being investigated to achieve this goal also through noninvasive means [40]. As a consequence, they are paving the way toward a closed-loop control scheme known as the artificial pancreas (AP) [3, 9, 32]. That system is mainly composed of three different parts: a sensor that continuously monitors blood or tissue glucose levels, an algorithm that defines the amount of insulin to be delivered [14], possibly guaranteeing an adequate level of flexibility with respect to meal times, carbohydrates quantities, and physical activities [1], and an infusion pump which actually delivers the insulin.

AP prototypes have been extensively researched at hospital settings during the past decade, and several inpatient clinical trials proved the efficacy of automated closed-loop insulin infusion with respect to traditional pump therapy; see [8] for a review. To ensure patient safety, those studies employed very structured protocols with CGM sensors complemented by frequent and accurate BGL measurements in venous blood. Their closed-loop sessions were short, with a high level of discomfort due to the use of wired connections. Introducing the AP as a regular treatment required a new research action that started at the turn of the last decade and involves testing the safety and the efficacy of AP prototypes on a longer timescale (up to several months) in real-life scenarios without strict protocol prescriptions and including telemedicine services for care personalization [19].

The AP@home project, funded in 2010 by the European Union (EU), is among the first ones undertaking this challenging task that involves several actors with different professional skills. This paper illustrates the design of the AP architecture conceived by the authors and the implementation of two AP platforms supporting the AP@home studies. It also discusses the remote monitoring facilities setup to collect patient data during the trials and enforce patient safety at a distance. The methodological and technical design phases occurred since the project inception are described along with the preliminary trials that have been accomplished on the enrolled patients preceding the main project study. For each study, the achievements and the main problems experienced will be discussed. All the trials planned within the AP@home project are conducted in accordance with the ethics principles set forth in the Declaration of Helsinki and are subject to the approval by the medical ethics committees of all the participating centers.

3 The AP@home project: description and clinical trials

The AP@home project [18] was funded in 2010 by the EU within the 7th Framework Programme in order to reduce the time for the ultimate adoption of the AP as a routine treatment for T1DM patients. The main goals included an extensive tuning and validation of the control algorithms and the development of an AP platform prototype to demonstrate its effectiveness as a treatment and support the accomplishment of the trials planned. To this aim, a multinational task force was assembled involving six clinical partners of the AP@home consortium spread all over Europe: Profil Institute for Metabolic Research GmbH in Neuss, Germany; Academic Medical Centre in Amsterdam, the Netherlands (AMS); Institute of Metabolic Science of the University of Cambridge, United Kingdom; Medical University of Graz, Austria; Department of Clinical and Experimental Medicine of the University of Padova, Italy (PAD); and Endocrinology Department of the Centre Hospitalier Universitaire in Montpellier, France (MPL).

The ultimate goal of the project was the accomplishment of a major trial lasting several months, demonstrating the possibility of continuously administering an insulin therapy through an AP without any intervening clinical, technical, or organizational issue. To prepare for it, some preliminary studies were planned over an increasing amount of time. In Table 1, we provide an outline of the already accomplished studies, while a more detailed description follows.

Study 1 (test with a PC-based AP) The very first study of the project was planned in 2011 to confirm the possibility of regulating blood glucose entirely through a control algorithm based on real-time CGM readings. Two algorithms developed by members of the AP@home consortium have been tested and compared with the traditional open-loop therapy. For safety reasons, the study was scheduled
to occur at a clinic and was also the shortest one planned, encompassing experiments lasting for only 1 day. The control algorithm was implemented on a Personal Computer (PC), in order to support the rapid prototyping of the platform. That study also provided a safe environment to test the overall architecture developed including the remote monitoring service.

- **Protocol Summary:** The trial was set to start at 19:00 after the patient checked in at the clinic. The AP platform was set to run in closed-loop mode, if an algorithm was being tested, or in open-loop mode, in the case of a control experiment. An evening meal of 80 g carbohydrates was served followed by sleep from 23:00 to 7:00 on the day after. Then, a breakfast of 50 g carbohydrates was given, followed by a lunch of 60 g at noon. In the afternoon, two exercise sessions were planned each lasting 15 min and finally the patient discharge occurred at 18:00.

**Study 2A/2B (adoption of a mobile-based AP)** A subsequent study involving outpatients was conceived, and to preserve the patients’ mobility and comfort, it was decided to adopt a platform to be used as a wearable device. The aim was to further test the algorithms and make sure that the AP platform could be autonomously operated by patients without any external intervention. An additional goal was to prove that the operation of the wearable AP platform could be remotely supervised by the clinical staff and be safe for the home trial. The study was planned at a hotel in order to emulate as much as possible the home environment. Patients were lodged in separate rooms for their privacy and comfort, while an emergency team was standing by, ready to take control of any possible adverse situation. The study was first started in 2012 (Study 2A), but due to some problems experienced with the hardware, it was discontinued. It was then successfully restarted one year later in 2013 adopting exactly the same protocol (Study 2B).

- **Protocol Summary:** This trial was spread over 3 days, with an overall duration of 42 h, including two consecutive nights. It started at 18:00 of day 1 with open-loop control across the whole night until 7:00 of day 2 (i.e., 13 h). It then switched to closed loop at 7:00 of day 2 with some training of the patient on the AP platform until 18:00 (i.e., 11 h) and involved remote monitoring from 18:00 of day 2 to 12:00 of day 3 (i.e., 18 h).

Besides the above-mentioned studies that were the subject of clinical investigations, additional experiments were also occasionally accomplished to test the AP platforms as we progressed toward the improvement of their methodological or technological aspects.

**Table 1** Synopsis of the preliminary studies accomplished during the AP@home project

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Setting</th>
<th>Span</th>
<th>AP platform</th>
<th>Remote monitoring</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (2011)</td>
<td>Inpatient (Clinic)</td>
<td>23 h</td>
<td>Personal Computer APS + Custom sw component Insulet Omnipod Dexcom Seven Plus</td>
<td>No (test only)</td>
<td>Comparing two validated closed-loop algorithms versus patient self-control with CSII in terms of glycemic control Three admissions (23 h) for each patient</td>
</tr>
<tr>
<td>2A (2012)</td>
<td>Outpatient (Hotel)</td>
<td>42 h</td>
<td>Smartphone DiAs (Sony Xperia) Insulet Omnipod Dexcom Seven Plus iDex + Bluetooth Adapter</td>
<td>Yes</td>
<td>Patient training and empowerment First night: open loop Second night: closed loop</td>
</tr>
<tr>
<td>2B (2013)</td>
<td>Outpatient (Hotel)</td>
<td>42 h</td>
<td>Smartphone DiAs (Galaxy Nexus) Roche AccuCheck Spirit Combo Dexcom G4 + Bluetooth Adapter</td>
<td>Yes</td>
<td>Patient training and empowerment First night: open loop Second night: closed loop</td>
</tr>
</tbody>
</table>

**4 Methods**

A comprehensive architecture was needed encompassing both an AP platform and a remote monitoring service to be used during outpatient trials to guarantee the patients’ safety. Since the studies had different requirements, two different AP platforms have been designed by the authors along with the architecture required for their operation which evolved over time.

**4.1 Study 1: Design of the initial AP architecture and the PC-based AP platform**

Even though by the time the project was conceived both wireless CGM sensors and insulin pumps were already on
the market, the specifications for their operation were not publicly available nor were the manufacturers inclined to provide those in terms of a non-disclosure agreement to the AP@home consortium members for research purposes. Since the main goal of the first study was to prove the effectiveness of the regulation algorithms, instead of building an AP platform from scratch it was decided to build it on top of the artificial pancreas system (APS), which is a prototyping environment developed at the University of California Santa Barbara (UCSB) in collaboration with the Sansum Diabetes Research Institute [10]. The APS runs on a PC taking the burden of hardware integration upon itself, through the exposure of a software interface for communicating with CGM sensors and insulin pumps. It also includes an application programmer interface (API) supporting the inclusion of closed-loop algorithms coded using a wide set of languages (e.g., C, C++, and MATLAB®) and a graphical user interface (GUI) for operating it. However, the APS offers a fixed input–output structure for exchanging information with the control algorithm without any possibility of extending the GUI. Thus, complex experiments that require the acquisition of additional parameters cannot be performed. For example, the APS displays BGL only as mg/dl, and it is unable to display additional data in its GUI such as the alarms related to the risk of hypo- and hyperglycemia. Moreover, it is not possible to enter additional information during an experiment, such as sensor calibration or physical exercise, nor to select a specific algorithm to be applied depending on the experiment. However, we needed a platform able to support two different algorithms, besides the open-loop control mode in order to accomplish the first study dubbed “Comparison of two Artificial pancreas systems for closed-loop blood glucose control versus open-loop control in patients with Type I diabetes” (CAT). The two algorithms included the “international Artificial Pancreas” (iAP) developed within a collaboration among European and American research centers [31, 37] and the algorithm developed by Hovorka and his team in Cambridge (CAM) [20].

Due to the limitations of the APS, a new platform was designed and implemented by the authors on top of it to support the open-loop control strategy and the two control algorithms, which are characterized by substantially different contextual and operational requirements. The algorithms are written in different languages, require different information and have different sampling rates. Thus, the platform had to reconcile all those issues providing a uniform environment for acquiring and representing data, invoking the algorithms, driving the pump and consistently displaying any information to the user. The overall architecture adopted for the AP platform used in Study 1 is shown in Fig. 1.

The Main Controller Unit (MCU) represents its core and interacts with the APS to communicate with the hardware devices, stores their data into a Local Repository, and invokes the algorithms through the Data Abstraction Layer (DAL). Additionally, it also exploits the GUI for receiving commands or acquiring data by the user and displaying results. At every cycle time, the MCU acquires the BGL readings. Then, it calls the DAL which encodes a parameter file and invokes the algorithm required by the experiment that is stored as a separate program installed on the same PC. When the algorithm has completed the calculation, DAL reads the results file and passes the computed value of

![Diagram of AP platform](image_url)

**Fig. 1** The architecture of the AP platform supporting multiple algorithms built on top of the APS that was used in Study 1

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the insulin to the MCU, which then forwards it to the APS for the actual delivery.

Albeit the PC-based AP platform was only meant to accomplish the very first in-hospital trial, a telemedicine system was also developed by the authors in sight of supporting the subsequent outpatient trials. Systems for the remote monitoring of vital signals are already available [2], and there is a strong belief that telemedicine will play a key role in the next generation of medical care systems, operating the remote acquisition of physiological parameters, processing them in real time, and possibly issuing alarms [41]. The telemedicine component was introduced by improving an agent-based infrastructure previously developed by us for providing generic monitoring services to chronic patients [4]. We took advantage of this study to test it, and we enabled the researchers involved in the controller design to remotely monitor the experiments in real time. The telemedicine component was made available as a remote agent (TMD Remote Agent) installed as a separate application on the PC, and provided a transparent bidirectional synchronization link with the clinic repository [5].

4.2 Study 2A/2B: Adaptation of the AP architecture to the mobile context

Providing support for home studies definitely called for the availability of an embedded or mobile device to be used as an AP platform in order to preserve the patient’s mobility and comfort. Thus, we updated the architecture already adopted for the PC-based study preparing for the adoption of the AP in the patients’ everyday life routine. In so doing, we put a special emphasis on the remote monitoring issues [24] also in sight of a possible integration of the AP within a suitable middleware supporting a bidirectional interaction with the clinic [25, 29]. This may be helpful in regularly and transparently accomplishing any test required to tune up the controller and provide an individualization of the treatment [17].

In Fig. 2, we illustrate the component architecture of that infrastructure, which sees the AP platform on the left. This encompasses an Insulin Pump, a CGM Sensor, and an Embedded Device hosting the control algorithm. The pump and the sensor communicate with the embedded device through links implemented either as wired serial connections or as wireless ones exploiting some proprietary radio technology. The embedded device is then linked to the Network Device through a Bluetooth™ connection, which is a low-power wireless link. According to the figure, the network device may be implemented through either a smartphone or a PC and acts as a relay enabling the further transmission of patient data to the Clinic Server using Wi-Fi, UMTS, or GPRS connections depending on the specific conditions of the setting.

The transmission of data to the clinic server takes place through the usual network protocols providing authentication and enforcing security such as https at the transport level, while SyncML, which is an advanced synchronization protocol for exchanging data, was used at the session level [35]. On top of those, we developed a high-level layer, modeled after a multi-agent paradigm, able to provide interoperability among a wide range of platforms including mobile devices, smartphones, tablets, and PCs [6]. That layer, besides providing valuable features such as bandwidth and traffic optimization, also allows a bidirectional data exchange. Thus, the AP is not limited to sending data upstream to the clinic but may also receive some information from it. The exploitation of an AP platform able to update its control law was considered at the beginning of the project but it has not been actually implemented due to regulatory and practical reasons.

On the clinic side, data are merged into the personal health record so that they may be accessed through a regular web application. The services we envisioned from the beginning of the project include those shown in the right part of Fig. 2. Online monitoring allows either tracking patient data in real time or possibly reviewing those for inspection at a later time. During the home experiments, safety will mostly depend on alert messages generated on the server upon the occurrence of dangerous situations and sent to the interested parties. Finally, the possibility of downloading whole segments of a patient experiment for the accomplishment of extended analyses and reports is
meant to be used by the researchers to assess the effectiveness of BGL control on patients and accomplish extended checks on the AP platform functionality.

An attempt to develop an AP platform from scratch based on an embedded device has been pursued within the AP@home project consortium. However, the same problems concerning the interfacing of that platform with the external environment showed up again, forcing the consortium team to look for a different solution. It was decided to rely on a device developed outside the project consortium to operate the pump and the sensor also for the outpatient trials. In this case, the Diabetes Assistant (DiAs) was selected, which is a dedicated AP platform built on top the Android™ mobile operating system by the researchers at the University of Virginia (UVA) [22]. DiAs may be considered as a platform for the AP development and testing rather than a complete AP system in itself. This happens because the open source of the Android™ specification along with its highly modular design allows for the decomposition of the whole DiAs into a large set of task-specific modules. The core, for example, is represented by the Biometrics Database module acting as a central hub where all the patient and system data are stored. Around that core, the AP Controller module is located which is responsible for driving the Pump Service and the CGM Service modules acting as drivers toward the external devices. A Network Service module is responsible for exchanging data between the central database and the clinic server, while a special emphasis has been devoted by the developers to the DiAs UI module. This module allows operating the device, setting the control mode in open loop or closed loop, calibrating the CGM sensor or announcing meals in order to deliver the extra insulin boluses required to compensate the carbohydrates intake. DiAs UI always has control of the touchscreen leaving no possibility to the user of closing the application.

Thanks to the modular design; many of the DiAs modules may be separately and independently replaced with different ones without affecting the functionality of the rest of the system. Thus, we borrowed its core functionality, including its capability of interacting with the CGM sensor and insulin pump which is achieved using special versions of those devices made available for that purpose to the DiAs developers directly by the manufacturers. We focused instead on the implementation of the AP Controller module encoding the algorithm responsible for insulin delivery and the Network Service exchanging data with the clinic that were developed as separate Android™ applications.

The controller, following the modular architecture presented in [31], was designed to implement a control-to-range strategy encompassing two algorithmic components: a Safety Supervision module [21] and an automated Range Correction module [37, 39]. Moreover, with the adoption of the DiAs, the smartphone encompassed the functionality of both the embedded device and the network device shown in Fig. 2 without any more need to use a PC. Thus, the TMD Remote Agent formerly depicted in Fig. 1 has been ported to Android™ as the Network Service module exploiting the connectivity of the smartphone to send data to the remote clinic. To better enforce the separation with the DiAs, a module called Telemedicine Bridge has been developed with the specific purpose of encapsulating the required functionality of fetching data from the DiAs Biometrics Database.

5 Results

In this section, we illustrate the main technical outcomes of the preliminary studies accomplished within the AP@home project that were aimed at assessing the effectiveness of the architecture, pointing out their main achievements, their problems, and the lessons learned after each one.

5.1 Study 1: The first in-hospital trial

The devices selected for this trial were the Dexcom Seven Plus™ (Dexcom Inc, San Diego, CA) as the CGM sensor and the Insulet Omnipod™ (Insulet Corp, Bedford, MA) as the pump for insulin delivery. That pump is composed of an insulin reservoir applied to the patient and a remote controller unit (called PDM) communicating wirelessly with the former. The AP platform was developed by the University of Pavia on top of the APS that run on a PC and controlled the pump through a custom-made version of the PDM. It included a main GUI, shown in Fig. 3, that is portioned into three different logical blocks. The left part includes pushbuttons to notify events originated externally such as glucose readings, sensor calibration, exercises, while the central one shows the main charts plotting the real-time glucose level and the insulin delivery rate. On the top of the right part are grouped the controls allowing the selection of the algorithm to be started, a summary of patient information, and an indication of the next action to be accomplished, while on the bottom right, there is a customizable area where optional panels are shown depending on the selected algorithm. For the iAP, which is the algorithm currently selected in the figure, the traffic lights indicating the risks of hypo- and hyperglycemia are available. The last interface control included in the right part is the telemedicine activation panel for enabling the data transfer to the server.

The overall duration of each experiment in Study 1 was 23 h during which a continuous supervision was scheduled to ensure the safety of the patient, and a team of physicians and engineers was always awake to oversee the status of the
The study protocol was submitted for its approval to the Ethical Committees of each clinic research center in which the studies were to be performed. Three centers (i.e., PAD, AMS, and MPL) out of six were allowed to accomplish a fully closed-loop control provided that the enrolled patients signed an informed consent. The trial enrolled eight patients at each center where they underwent three separate admissions corresponding to the three algorithms used (i.e., iAP, CAM, and open loop). Across the whole trial information about sensor, pump, algorithm, APS or operating system failures and any other relevant event occurred was recorded in a worksheet (both in an electronic form and in a paper one). At the end, all the data collected by the AP platform were sent jointly with the worksheets via e-mail to all the involved researchers for performance and statistical data analysis.

Based on those data, in Table 2, we summarize the performance and functionality of the AP platform. One patient in the AMS center withdrew due to health problems not related to the AP (see column No. of patients), and the MPL center did not use the AP platform in open loop, so its patients only underwent two admissions. Since each admission corresponds to a single session with the AP platform, the overall expected session number was 61. However, a session could have been interrupted due to intervening problems, in which case more than one is counted for each admission. This is portrayed by the figures in the Actual sessions column, while the number of Broken sessions is also explicitly indicated. A broken session represents the need of restarting the AP platform due to the occurrence of some problem, but does not indicate by itself any loss of data. In fact, as indicated in the

![Image of the main GUI of the AP platform adopted in Study 1, captured during an ongoing experiment using the iAP algorithm.](image)

**Fig. 3** The main GUI of the AP platform adopted in Study 1, captured during an ongoing experiment using the iAP algorithm.

**Table 2** Summary of the major faults emerged during Study 1 involving the AP platform implemented on the PC

<table>
<thead>
<tr>
<th>Center</th>
<th>No. of patients</th>
<th>Expected sessions</th>
<th>Actual sessions</th>
<th>Broken sessions</th>
<th>Restored sessions</th>
<th>Pump problems</th>
<th>Sensor problems</th>
<th>Software problems</th>
<th>Generic problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMS</td>
<td>7</td>
<td>21</td>
<td>34</td>
<td>13</td>
<td>11</td>
<td>8</td>
<td>9</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>MPL</td>
<td>8</td>
<td>16</td>
<td>24</td>
<td>8</td>
<td>1</td>
<td>12</td>
<td>10</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>PAD</td>
<td>8</td>
<td>24</td>
<td>37</td>
<td>13</td>
<td>5</td>
<td>7</td>
<td>25</td>
<td>26</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>23</td>
<td>61</td>
<td>95</td>
<td>34</td>
<td>17</td>
<td>27</td>
<td>44</td>
<td>45</td>
<td>6</td>
</tr>
</tbody>
</table>
was restarted by resuming the previous state only resulting in a minor pause during the affected experiment.

Table 2 also gives a summary figure concerning the problems occurred during the trial causing those interruptions, organizing them into four categories. **Pump problems** include any misbehavior related to the insulin pump, such as an occlusion of the device, a meal bolus not delivered, the pump going out of work, problems related to the pump receiver, or any other failure. **Sensor problems** capture any problem related to the sensor device applied on the patient or to its proprietary data receiver. Those involve erroneous values or no data, or failures to establish a connection with the receiver for more than 20 min. **Software problems** specifically address the AP platform implementation, while **Generic problems** include any other cause, such as user errors or problems with other devices not directly connected with the system (e.g., the bike used for exercising). The center experiencing the highest number of problems was PAD, where a sensor notified a lot of failures and often required the restart of the entire system. The MPL center experienced an average number of pump and sensor problems similar to AMS, but the latter did not report any generic problem.

Most of the software problem occurrences addressing the AP platform were related to the interaction between the APS and software drivers of both hardware devices (e.g., when a CGM sensor failed, the manufacturers’ receiver tool integrated in the APS often required a restart with a consequent need to restart the entire AP platform). Sometimes this involved also a system restart or even caused an operating system crash. Some causes of the problems occurred in AMS and PAD were not identified: the system just stopped working and required a full restart. In summary, the AP platform in itself was the cause of 15 problems, out of the 45 reported, which were ascribed to internal causes. Following each experiment, all failures were carefully analyzed by the AP@home team. We then used that information to improve the AP platform by preparing an updated release for the next experiments planned.

From a clinical point of view, this trial showed that both algorithms provided a safe glycemic control reducing the percentage of time spent in hypoglycemia (i.e., BGL < 70 mg/dl) during closed loop by three times with respect to open loop (6.4 % for open loop, 2.1 % for iAP, and 2.0 % for CAM). The time spent in the target range was similar in closed loop and open loop [28].

### 5.2 Study 2A: The first outpatient trial

The devices used were the same already adopted for Study 1: the Dexcom Seven Plus™ and the Insulet Omnipod™. The AP platform in this case was the DiAs running on a Sony Xperia™ mobile phone on top of which we installed the controller and the data synchronization modules. Since Bluetooth™ connectivity was not available on that pump and sensor, the AP platform also comprised an iDex™, that is an experimental device from Insulet Corp. combining the Dexcom Seven Plus™ receiver and the Insulet Omnipod™ PDM. The iDex™ had an USB interface that was plugged into an adapter which in turn forwarded the signals onto a wireless Bluetooth™ connection. During the study, the main interface for overseeing the patients was implemented through a web application developed to peruse patient data by the interested parties once they had been transferred to the clinic server. Figure 4 reports a screenshot of that application showing the chart that is dynamically updated during a trial, replicating the DiAs UI panel and reporting in real time the values acquired by the CGM sensor and the insulin micro-boluses delivered. The chart complements those data with many other useful information such as hypo- and hyperglycemia risk values, sensor calibrations, meals, hypo treatments or manually entered notes. Information about the patient is always shown in the top panel, while additional tabs provide different views over patient data. On its left side a summary panel reports the last CGM reading, the current hypo- and hyperglycemia risk values rendered in terms of a pair of traffic lights and the glycemia trend. Visual and acoustic alarms are available to provide notifications about situations requiring an acknowledgement. The application also provides a comprehensive monitoring view including the summary panels of all the active patients so that the staff is always aware of their statuses. That feature has been extremely useful during the hotel trials to detect situations requiring a prompt intervention.

After a test involving two patients in PAD, the trial was planned in fall 2012 enrolling four patients at each of the three centers allowed to accomplish fully automated closed-loop experiments (i.e., AMS, MPL, and PAD). The main technical summary is shown in Table 3. In the last column, the number of periods spent in different control modes is reported, where a period is defined as a time interval encompassing the same control mode. Since according to the protocol only a single mode switch was foreseen at 7:00 of day 2, the average of 12 periods per patient in PAD and 10 in AMS indicates a problem. The cause was found in the connection between the iDex™ and the relay device that was prone to failure and proved to be the weak link of the chain. In fact, as a safety measure, whenever no glucose data are sent for more than 15 min, the DiAs switches to open-loop control. That problem caused frequent restarts of the DiAs and turned out to be a serious problem for the patients and the staff overseeing the trial. With respect to this, the remote monitoring application has been instrumental in alerting the staff, even overnight. In PAD, the problem was managed in cooperation with the patients, and all experiments were eventually completed, but in AMS, it caused a downtime, as it appears from the total and average
Fig. 4 The chart panel of the web application for the remote monitoring of patient data in real time
times per patient (see first column) which is 43.25 h in PAD but only 22.71 h in AMS. Consequently, it was also decided to cancel the MPL trial. In an effort to better track the origin of those problems, soon after the PAD trial was over, and before starting the one in AMS, an enhanced system for reporting log messages was set up. This justifies the number of log records sent (see the Log column) which is 0 for PAD and 96 for AMS.

From the clinical point of view, this very limited trial showed a very promising dinner control in closed loop with respect to open loop. In particular, the time-in target (70–180 mg/dl) was 94.83 versus 68.2 % and time-in hypo (<70 mg/dl) was 1.25 versus 11.9 %. Overnight control was also satisfactory [12].

5.3 Study 2B: The second outpatient trial

Insulet Corp. discontinued the development and maintenance program of the iDex™ device. Therefore, the authors’ team decided to switch to the Roche AccuCheck Spirit Combo™ Pump that offers a native Bluetooth™ connectivity, thus enabling a direct link with the smartphone. Moreover, a major technological step forward was given by the new Dexcom G4 Platinum™ sensor [7] that significantly outperforms its predecessor, provides more accurate measurements, and guarantees a more stable wireless connection between the transmitter placed on patient abdomen and the Dexcom receiver. However, since the receiver itself could not be accessed wirelessly, an intermediate relay device was still required to forward the acquired signal over a Bluetooth™ link.

The switch required a complete rewriting of the driver. Nevertheless, this time period was also used by the DiAs developers to tune up the internals of their application that had dramatically evolved, resulting in a continuous update of the Biometrics Database acting as a hub with respect to all the satellite modules. Those fixes took almost a year work and were accomplished by the UVA developers since involved a restructuring of the DiAs internal functionality.

The trial was restarted in fall 2013 as Study 2B under exactly the same conditions of Study 2A enrolling 12 patients at 3 centers with each experiment lasting for 42 h [26]. Its main technical outcomes are reported in Table 4, where statistics are separately reported for each center as well as overall. The average experiment duration on all 12 patients is 43.07 h, witnessing that no downtime was experienced. Moreover, the last column shows that the average number of control modes on all patients is 3, which is close to the expected figure of 2 also proving the increased stability and reliability of the whole AP system over such an extended period.

This trial was successful also from a clinical standpoint, resulting in a significant reduction in the percent time in hypoglycemia (i.e., BGL < 70 mg/dl) in closed loop with respect to open loop in both the overall period and overnight. Overnight, a statistically significant improvement in the percent time in the target range (i.e., 70–180 mg/dl) was also experienced with average glucose levels similar during both periods [11].

The success demonstrated the feasibility of deploying the AP outside the hospital when it is managed directly by

### Table 3  Technical summary of the outcomes of Study 2A, accomplished using a mobile-based AP platform in fall 2012

<table>
<thead>
<tr>
<th>Center (pat #)</th>
<th>Tot. time (pat. avg)</th>
<th>CGM (pat.avg.)</th>
<th>CSII (pat.avg.)</th>
<th>Calibr. (pat.avg.)</th>
<th>Log (pat.avg.)</th>
<th>Periods (pat.avg.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAD (4)</td>
<td>172.99 h (43.25 h)</td>
<td>1,877 (469)</td>
<td>1,849 (462)</td>
<td>23 (6)</td>
<td>0 (0)</td>
<td>48 (12)</td>
</tr>
<tr>
<td>AMS (4)</td>
<td>90.82 h (22.71 h)</td>
<td>738 (184)</td>
<td>738 (184)</td>
<td>17 (4)</td>
<td>96 (24)</td>
<td>39 (10)</td>
</tr>
</tbody>
</table>

### Table 4  Technical summary of the outcomes of Study 2B, the second outpatient trial using a mobile-based AP platform occurred in fall 2013

<table>
<thead>
<tr>
<th>Center (pat #)</th>
<th>Tot. time (pat. avg)</th>
<th>CGM (pat.avg.)</th>
<th>CSII (pat.avg.)</th>
<th>Calibr. (pat.avg.)</th>
<th>Log (pat.avg.)</th>
<th>Periods (pat.avg.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAD (4)</td>
<td>175.96 h (43.99 h)</td>
<td>2,039 (510)</td>
<td>2,054 (514)</td>
<td>32 (8)</td>
<td>203 (51)</td>
<td>12 (3)</td>
</tr>
<tr>
<td>AMS (4)</td>
<td>174.84 h (43.71 h)</td>
<td>2,007 (502)</td>
<td>1,938 (485)</td>
<td>33 (8)</td>
<td>277 (69)</td>
<td>14 (4)</td>
</tr>
<tr>
<td>MPL (4)</td>
<td>166.04 h (41.51 h)</td>
<td>1,962 (491)</td>
<td>1,955 (489)</td>
<td>17 (4)</td>
<td>58 (15)</td>
<td>11 (3)</td>
</tr>
<tr>
<td>Total (12)</td>
<td>516.84 h (43.07 h)</td>
<td>6,008 (501)</td>
<td>5,947 (496)</td>
<td>82 (7)</td>
<td>538 (45)</td>
<td>37 (3)</td>
</tr>
</tbody>
</table>
the patient, and telemedicine is the only mean of overseeing the experiments. As a last step toward the final major study of the AP@home project, an extra trial was accomplished in December 2013–January 2014 enrolling only 3 patients over 5 days at their homes. It was aimed at assessing the patients’ abilities in dealing with the AP for 5 days in a row in a completely unattended environment. From this point of view, the results have been very encouraging, while on the technical side, they replicated those of Study 2B, clearing the way for the major study which is presently under way.

6 Discussion

The experience gained during the AP@home project carries with it a number of lessons that will help in the future steps of the project, but also contains a number of paradigmatic issues that may be of general interest for many other “Information and Communication Technologies (ICT) for health” initiatives. We illustrate in the following paragraphs some of the most significant issues we faced.

• **Implementation and testing.** The overall validation strategy foreseen by the project was based on the assumption that the AP components could be tested by increasing the system complexity through a series of incremental steps. In particular, the in-hospital test was mainly designed to assess the control algorithms. Albeit this strategy, in principle, allows a better understanding of the pros and cons of every single component, it has the disadvantage of relying every time on a different technology to run the test. Unfortunately, as it happened in our case, problems may arise due to the specific ad hoc setups that are designed to test the components. As a lesson learned, in AP-like systems, it is crucial to assess as quickly as possible the complete ICT architecture. Usability aspects, that include checking the robustness of the code and the speed and reliability of communication links, are so important that their functionality should always be tested from the very beginning.

• **Technological and regulatory barriers.** When the AP@home project started, it was agreed that the embedded device be implemented as a wearable component developed by a consortium partner. The Bluetooth™ link on the back end would have enabled the interoperability of that device with a smartphone, a tablet, or a PC for remotely sending data. However, when we moved to the mobile platform, we had to face a major difficulty concerning its implementation. The front-end link on the embedded device connecting the insulin pump and the CGM sensor turned out to be problematic because of proprietary and regulatory issues. Although some commercial sensors support wireless connections, they only provide their own software for downloading data using a proprietary receiver connected to a USB port on a PC. Moreover, the wireless connection of insulin pumps is usually based on a proprietary protocol for sending data using the Bluetooth™ technology. Finally, pumps only allow downloading data through the wireless link, while controlling the delivery of insulin boluses is forbidden by design. Accomplishing this latter task requires a special pump device with a different microcode running on it, that manufacturers only provide to certified partners. Although some devices with more open protocols exist, they do not own the CE mark. This, of course, is a strict requirement in order to use a device on patients within the EU. Thus, for the sake of continuing to make progress on algorithm development, we had to resort to a third party solution that was not foreseen at the beginning of the project.

• **Technology evolves too fast for clinical research.** Advances in ICT happen at a very fast pace that makes their testing very difficult within the current paradigm of clinical research. As witnessed by many telemicine trials, in particular in the T1DM area, the software solutions adopted become obsolete before the end of the clinical studies. For that reason, they require frequent changes and updates. This, of course, is barely compatible with the idea of testing a “device” that stays the same during a clinical study. The principle of separation of concerns [33] is a way to deal with the problem. While hardware (i.e., pumps, sensors, etc.) and safety critical software components (such as the control algorithm or the synchronization layers) can be tested as if they were drugs, the software interfaces as well as the “soft” communication components should be allowed more frequent changes. They should go through an adaptation process and be separately tested by means of faster studies, involving technological checks, questionnaires, and ethnographic research. This requires a fine-grained design of the clinical studies that is able to combine different methodologies and take into account different outcomes [15, 16].

• **Patient experience and expectations.** The involvement of patients deserves a special emphasis in the AP@home project. For pharmaceutical industries, it is quite customary to enroll patients into clinical trials, but in the majority of cases, they play a somewhat passive role. Their involvement is limited to assuming some drug and undergoing periodic tests during the trial or at its end. In other cases, they are asked to regularly and autonomously fill in a questionnaire to assess the effects of the drug. Despite the very short duration of the preliminary trials foreseen by AP@home, a high demand in terms of both discomfort as well as attentiveness and personal interest was asked to the patients. In order to participate, patients stayed for a whole day at the clinic during the very first trial, or changed their family hab-
its for two days during the hotel experiments. Moreover, they were aware that the AP, as a device automatically delivering insulin, could cause serious hazards if either it misbehaved or it was not properly managed by them. Nevertheless, despite those challenges, they volunteered proving a profound interest in the novelty of the treatment. We were very impressed by their proactive involvement in the trial. Their motivation in understanding the technology was well beyond the threshold required to grasp the basic operational skills required to operate the device. This is also the best guarantee of their involvement in sight of the current main trial.

The experience of AP@home, as well as of other concurrent projects, is likely to lead in the future to a more mature scenario characterized by two important aspects. On the one hand, manufacturers will provide fully integrated “smart” devices, embedding sensors and pumps with on-board closed-loop control algorithms. On the other hand, relying on the “Internet-of-things” technologies, such devices will provide network communication capabilities, thus enabling long-term monitoring and surveillance as well as the personalization of control algorithms [34]. The road toward this scenario may however be winding. There are several technical and methodological aspects that need improvements, including better tailoring of the algorithms to the single patients, potential use of biorhonal strategies, and improvement in subcutaneous sensors’ performance. Moreover, the safety aspects and the associated regulatory constraints may slower the diffusion and commercialization of closed-loop devices. Furthermore, the industrialization process may lead to the development of proprietary algorithms and software tools with limited capabilities of interfacing with other applications. Finally, the implementation of an AP-enabled treatment requires noteworthy economic and organizational efforts to fully exploit the capabilities of this promising technology. The role of the research community will thus be crucial, in order to drive and accelerate the transition from prototype to products in order to maximize the benefits for patients and for the whole society.

7 Conclusions

The paper summarizes the design and the development of ICT solutions for the AP@home project, funded by the European Union within the 7th framework program, and reports on the outcomes emerged through the clinical trials. Two different platforms have been implemented: a PC-based one, used to test the AP control algorithms, and a mobile solution for the patients at home. Although the methodological issues were challenging, the main problem emerged during the implementation of the platforms was a technical one indeed, dealing with the components interoperability. To overcome it, we have been forced to adopt in both cases third party solutions that limited the portability and the generality of our implementation and sometimes also affected its quality. Besides that, thanks to a three-step test, the technology has been improved and largely optimized in a joint effort with the third party developers. The control algorithm has been improved taking into account several real-life situations (e.g., the possibility to assume several consecutive meals) and the outcome data collected advocated the opportunity of accomplishing a longer-term trial at home. That trial, which represents the AP@home main study, is in progress at the time of this writing enrolling 12 patients at each of the tree centers involved (PAD, AMS, and MPL). Each control regimen will last for nearly two months with a washout period of one month in between. We believe that the report about our overall experience can be beneficial for the scientific community, and, for this reason, we detailed all issues that emerged along the project, highlighting problems and solutions and extracting some lessons learned.

Acknowledgments This research was funded through FP7 Grant Number 247138 from the European Commission to the AP@home consortium, http://www.apathome.eu.

Conflict of interest No competing financial interests exist involving any of the authors of the paper.

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