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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, telemedicine 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 (T1DM) 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, T1DM 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

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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