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Model predictive control with integral action for artificial pancreas

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ABSTRACT

A Model Predictive Control (MPC) approach with integral action, called Integral MPC (IMPC), for Artificial Pancreas systems is proposed. IMPC ensures beneficial effects in terms of regulation to target in presence of disturbances and model uncertainties. The proposed approach exploits individualized models identified by Constrained Optimization (CO) described in Messori et al. (2016). In order to assess the proposed IMPC in comparison with a previously published MPC, in silico experiments are carried out on realistic scenarios performed on the 100 virtual patients of the UVA/PADOVA simulator.

1. Introduction

Type 1 diabetes (T1D) is an important health problem in the world, that affects not only adults and adolescents, but also very young children. T1D is an autoimmune disease that leads to the irreversible destruction of the pancreatic beta cells, which are in charge of producing and releasing insulin. Insulin is the hormone which regulates the Blood Glucose (BG) level (glycemia). Since the pancreas is no longer able to produce insulin, the subject can experience chronic hyperglycemia (BG > 180 mg/dl), with an increasing risk of life-threatening events and severe long-term complications. Self-monitoring of BG is extremely important for individuals with T1D, they have to maintain this concentration inside the euglycemic range, spanning from 70 to 180 mg/dl. If on one hand exogenous insulin is needed to avoid hyperglycemia phenomena, on the other hand hypoglycemia (BG < 70 mg/dl) can be caused by possible erroneous insulin overestimation. T1D patients usually determine insulin on the basis of a therapy defined by the physician. This therapy is composed of basal insulin, a piecewise constant amount used to maintain a stable glycemia during fasting periods, and insulin boluses, impulse-like injections used to compensate the glucose rise caused by meals intake.

Insulin administration is performed through subcutaneous insulin pumps that can be programmed with the patient-specific therapy. The subcutaneous glucose concentration is measured through Continuous Glucose Monitor (CGM) devices. The combination of subcutaneous pump and CGM defines the Sensor Augmented Pump (SAP) therapy, which assists the patient in maintaining the glucose concentration within the safe range ([70–180] mg/dl). SAP therapy, however, needs manual interventions on the pump to properly adjust the insulin administration in presence of unexpected variations of the BG, due to disturbances such as physical exercise, stress, etc.

The automatic definition of insulin delivery based on glycemia readings has been investigated since the seventies, when the first concept of Artificial Pancreas (AP) appeared in the literature (Cobelli, Renard, & Kovatchev, 2011). The first versions of the AP did not include a real closed-loop due to the technological limitations. In the last 10 years, the availability of pump for continuous subcutaneous insulin infusion (CSII) and the increased accuracy of CGM sensors, brought to reality the long dreamed AP.

The AP system is composed of a CGM, an insulin pump and a control algorithm (see Fig. 1), which automatically defines the insulin deliver on the basis of the CGM readings (Cobelli, Dalla Man, Sparacino, Magni, De Nicolao, & Kovatchev, 2009; Doyle, Huyett, Lee, Zisser, & Dassau, 2014). This system aims to a complete automatic closed-loop control of the patient BG concentration. Thanks to the latest technological and methodological developments, nowadays the AP has become wearable and minimally invasive (Thabit & Hovorka, 2016).

One of the most recent AP architectures is composed of a control algorithm implemented on a device that communicates with a CGM and with a subcutaneous pump through wireless connections (Keith-Hynes, Mize, Robert, & Place, 2014; Messori, Cobelli, & Magni, 2015). This architecture has been validated in several clinical studies supported by the Juvenile Diabetes Research Foundation, the European Commission,

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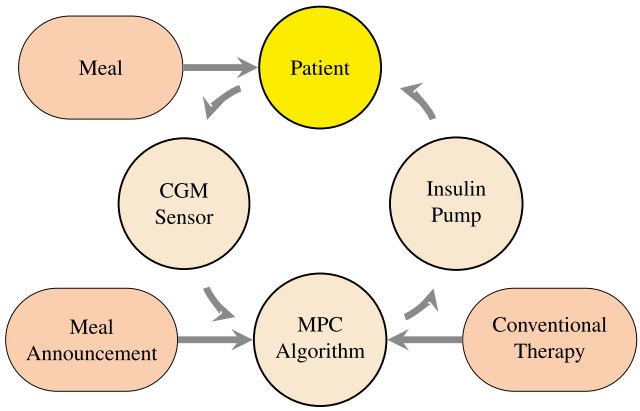

Fig. 1. Artificial pancreas architecture.

and the National Institutes of Health (Del Favero, Place, Kropff, Messori, Keith-Hynes, Visentin, et al., 2015; Kropff, Del Favero, Place, Toffanin, Visentin, Monaro, et al., 2015; Messori, Kropff, Del Favero, Place, Visentin, Calore, et al., 2017; Renard, Farret, Kropff, Bruttomesso, Messori, Place, et al., 2016; Russell, El-Khatib, Sinha, Magyar, McKeon, Goergen, et al., 2014; Thabit, Lubina-Solomon, Stadler, Leelarathna, Walkinshaw, Pernet, et al., 2014). These studies have been performed without animals trials thanks to the availability of the UVA/PADOVA simulator (Dalla Man, Micheletto, Lv, Breton, Kovatchev, & Cobelli, 2014; Kovatchev, Breton, Dalla Man, & Cobelli, 2009), a large scale in silico simulator able to reproduce the metabolic responses of diabetic subjects to meals and insulin administrations. This simulator was accepted by the Food and Drugs Administration (FDA) as a substitute to animal trials in the preclinical testing of AP control strategies since it offers a rich compartmental model equipped with 100 vectors of model parameters, the so-called "virtual patients", that well represents the entire population of diabetic patients. The mean parameters vector of these patients describes the so-called "average patient" that represents a patient with the average dynamics of the population.

The core of an AP system is the control algorithm, which is in charge of estimating the proper quantity of insulin to deliver in order to keep the BG in the euglycemic range during fasting, meal, and postprandial periods. This approach is commonly called Control-to-Range (CtR) (Kovatchev, Patek, Dassau, Doyle III, Magni, De Nicolao, et al., 2009) since it aims to define the insulin treatment in order to keep the glucose within a certain target glucose range, thus avoiding extreme glucose fluctuations, specifically via prevention of hypoglycemia and reduction of postprandial hyperglycemia. This task is particularly challenging because of the system architecture, which uses a subcutaneous route both for insulin infusion and glucose sensing. Indeed, the insulin delivery via subcutaneous pumps is affected by inherent delays due to the insulin absorption dynamics as well as the indirect measurements of the blood glucose via the subcutaneous tissue. The subcutaneous glucose measurements are also affected by CGM sensor noise.

Among the possible control strategies, which include classical Proportional–Integral–Derivative (PID) control (Huyett, Dassau, Zisser, & Doyle III, 2015; Marchetti, Barolo, Jovanovic, Zisser, & Seborg, 2008; Steil, 2013; Steil, Palerm, Kurtz, Voskanyan, Roy, Paz, et al., 2011; Weinzimer, Steil, Kurtz, Swan, & Tamborlane, 2006) or Fuzzy Logic (FL) (Atlas, Nimri, Miller, Grunberg, & Phillip, 2010; Miller, Nimri, Atlas, Grunberg, & Phillip, 2011; Nimri, Atlas, Ajzensztejn, Miller, Oron, & Phillip, 2012), Model Predictive Control (MPC) resulted to be a very effective and promising solution (Bequette, 2012; Breton, Farret, Bruttomesso, Anderson, Magni, Patek, et al., 2012; Doyle et al., 2014; Grosman, Dassau, Zisser, Jovanovič, & Doyle III, 2010; Hovorka, Canonico, Chassin, Haueter, Massi-Benedetti, Orsini Federici, et al., 2004; Luijf, DeVries, Zwinderman, Leelarathna, Nodale, Caldwell, et al., 2013; Magni, Raimondo, Bossi, Dalla Man, De Nicolao, Kovatchev et al., 2007; Wilinska, Budiman, Taub, Elleri, Allen, Acerini, et al., 2009).

The basic version of the MPC considered in this study was presented in Toffanin, Messori, Di Palma, De Nicolao, Cobelli, and Magni (2013), and has been successfully used in several outpatient clinical study since 2013 (Del Favero, Boscari, Messori, Rabbone, Bonfanti, Sabbion, et al., 2016; Del Favero et al., 2015; Favero, Bruttomesso, Palma, Lanzola, Visentin, Filippi, et al., 2014; Kropff et al., 2015; Messori et al., 2017; Renard et al., 2016). The algorithm showed good control performance also in free-living conditions although the MPC was synthesized by considering a non-individualized linear model. In fact, this algorithm exploits a model obtained via linearization of the "average" nonlinear model of the UVA/PADOVA simulator (Dalla Man et al., 2014; Kovatchev, Breton, Dalla Man, & Cobelli, 2009). Since diabetic patients are affected by significant inter-subject variability, further improvements could be achieved by considering patient-individualized models. To this aim, new identification techniques have been investigated (Bhattacharjee & Sutradhar, 2016; Bock, François, & Gillet, 2015; Kirchsteiger, Pölzer, Johansson, Renard, & del Re, 2011; Laguna, Rossetti, Ampudia-Blasco, Vehí, & Bondia, 2014; Messori, Toffanin, Del Favero, De Nicolao, Cobelli, & Magni, 2016; Percival, Wang, Grosman, Dassau, Zisser, Jovanovič, et al., 2011; Turksoy, Quinn, Littlejohn, & Cinar, 2014).

In this work an individualized Integral MPC (IMPC) is proposed. The individualized models are identified by the Constrained Optimization (CO) procedure described in Messori et al. (2016). This procedure can produce individualized models affected by steady-state errors, thus, an integral action is added to increase the glucose control robustness with respect to model uncertainties, moving from a CtR to a Control-to-Target (CtT) approach. The goal of the new approach is keeping the glucose within the safe range but also leading it to the specific target. Moreover, the presence of the integral action eases the identification process, since the control designer can focus on the identification of the dynamic part of the individualized model rather than on the static gain.

A preliminary version of the work has been presented in Incremona, Messori, Toffanin, Cobelli, and Magni (2017) where a basic version of the proposed algorithm is discussed and tested in simulation on a short-duration scenario. Here the approach is extended to improve the meal compensation. The algorithm is evaluated on a relative long period (14-day scenario) characterized by meal variations, in terms of administration time and carbohydrate content, and insulin sensitivity variations with respect to their nominal values. The IMPC is compared to the MPC synthesized using the same individual models, in order to evaluate the beneficial effect given by the integral action. The new IMPC guarantees good in silico performance, robustness to uncertainties on insulin sensitivity and meals amount and time; it is able to reduce hyperglycaemia without negatively affecting hypoglycaemia and to reduce the average glucose.

This paper is organized as follows. In Section 2 the considered glucose–insulin model is introduced and the control problem to solve is formulated. In Section 3 the proposed IMPC strategy is discussed. In Section 4 the simulation environment, the realistic scenario for in silico experiments, and the outcome metrics for the statistical analysis are reported. In Section 4.5 the results are presented in comparison with the MPC without integral action. Some conclusions are gathered in Section 5.

2. Problem formulation

In this section the control problem is formulated and the glucose–insulin model, taken into account to design the control law, is hereafter presented.