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A New Virtual Environment for Testing and Hardware Implementation of Closed-loop Control Algorithms in the Artificial Pancreas

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Abstract— **This article presents a new simulation tool for designing and testing blood glucose control algorithms in patients with type 1 diabetes. The control algorithms can be designed and implemented either with textual or graphical programming languages or by importing them from several frameworks. Realistic scenarios and protocols can be customized and built through graphical user interfaces, where several outcomes are available to evaluate control performance. Sophisticated models of the glucose–insulin system, as well as representative models of the instrumentation, have been included. Unlike existing systems, this simulation tool allows integrating the control algorithms into an electronic control unit, thus reusing the entire code in a straightforward way.**

I. Introduction

DIABETES mellitus is a metabolic disease characterized by high blood glucose levels resulting from the inability of the pancreas to produce insulin due to destruction of the beta cells of the Islets of Langerhans (type 1 diabetes) or the chronic degradation in its efficiency to promote glucose transport into the cells (type 2 diabetes). These deficiencies eventually result in several complications, such as cardiovascular disease, chronic renal failure, retinal damage, nerve damage, and microvascular damage [1], [2].

Studies by the Diabetes Control and Complications Trial (DCCT) [3] demonstrated that improved glucose control significantly reduces the rate at which diabetes-related complications occur in patients with type 1 diabetes (T1D). According to this result, a safe range of euglycemia has been established as the control objective for T1D patients. Such a glucose control objective is achieved by "emulating" normal pancreas insulin secretion with intensive insulin therapies.

An intensive insulin therapy, either with multiple daily injections or with a continuous subcutaneous insulin infusion (CSII) through a pump, is based on the administration of basal insulin to provide an insulin rate at night and between meals, and bolus insulin delivered as correction for high glucose levels and food intake. This treatment is known as open-loop control as no feedback data about real-time glucose are used to adjust the insulin requirements, which the physician and the patients set from discrete fingerstick glucose measurements.

Current technological advances allow acquisition of real-time data from continuous glucose monitoring (CGM) systems promoting research related with the development of closed-loop insulin delivery systems, also called an artificial pancreas (AP) [4]. The AP involves three components: a CGM device to measure glucose concentration in the subcutaneous tissue; a control algorithm to compute the appropriate amount of insulin according to the desired glucose level; and an insulin pump to deliver the computed insulin doses subcutaneously [5].

The AP development requires testing closed-loop control algorithms in animals or humans with the approval of regulatory agencies. This procedure involves several constraints related to resource demanding and ethical issues. To accelerate such a development process, simulation environments are used to optimize clinical designs, and to evaluate the safety or improve the performance of control algorithms.

Designing closed-loop control strategies in the simulation environment requires the simulated behavior of real T1D patients through models of the glucose–insulin system [6]. More advanced models do not reflect real behavior completely, because they do not account for important physiological variables, such as stress, physical activity, and so on, but they are useful to rule out or to improve inappropriate control designs.

For this, Hovorka et al.'s model [7] has been used for both simulation and experimental control purposes [8],[9]. Similarly, DallaMan et al.'s model developed by Cobelli's group in Padova, Italy [10] was implemented in the UVa (University of Virginia) simulator [11], and accepted by the United States (US) Food and Drug Administration agency as a substitute for animal trials in the preclinical testing of closed-loop control in T1D.

Regarding integration of the insulin pump and the CGM systems in simulation environments, simple models are usually used or are omitted. Nevertheless, in the case of the CGM, Breton and Kovatchev [12] developed a model to describe the measurement error used to replace the typical Gaussian noise added in this case [13]. Despite showing a sophisticated level of abstraction, Facchinetti et al. [14]

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dismissed this model, partly owing to the difficulty of having perfect calibration when working with data collected *in vivo*. However, as happens with the models of the glucose–insulin system, the Breton and Kovatchev model is still useful for excluding deficient control designs.

Currently, only a few simulation tools related to T1D have been created to support the closed-loop control algorithm design [11], [15], and most of them are considered for educational purposes only [16]–[19]. Hardware implementation must always be addressed for its inclusion in a commercial device once the control algorithm has been validated clinically. However, so far no algorithm has shown the flexibility of integrating the control algorithm developed straightforwardly into an electronic control unit (ECU), reusing the entire code, as the platform presented here does. This kind of code integration would facilitate the development of more sophisticated AP prototypes.

The aim of this work was to build a complete software framework to design closed-loop blood glucose controllers through T1D virtual patients associated with models of the glucose–insulin system, and powerful graphic tools for realistic scenario building, where the control algorithm performance can be tested within an ECU without changes to the original code.

II. Methods

A graphical system design (GSD) approach [20] was suggested in the simulator development as this allows reusing the complete control algorithm code in an ECU device without changes.

The simulator design was divided in sections to cover and adapt each component involved in AP experiments.

A. Virtual patient

To perform a model-based simulation of the glucose–insulin system, models of the subcutaneous insulin absorption, carbohydrates digestion and absorption, and the insulin–glucose dynamics are required. Figure 1 shows the relationship among these processes.

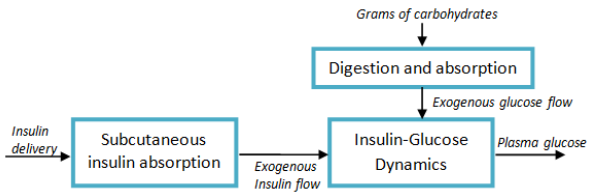

Fig. 1. Glucose-insulin system.

Besides the glucose-insulin system model, the essential part of a simulator with a control design purpose is the parameter sets of such a model, also called virtual patients. Hence, a virtual patient cohort is needed to evaluate the glucose control algorithms.

It should also be noted that some physiological variables in real T1D patients, such as insulin sensitivity, vary during the day, and this must be considered to have realistic simulations.

B. Glucose sensor

The degree of influence that the glucose sensor can produce in the control algorithm performance is related mainly to the measurement errors, but technical constraints must also be considered. For this reason, a model to simulate the measurement errors is required that considers technical issues.

Moreover, no device is exempt from failure, and for this reason, the simulator must incorporate those device failures that may affect AP experiments.

C. Insulin pump

Incorrect insulin delivery influences the glucose control algorithm performance. In this way, the deviations present in the expected value of the insulin basal delivery or the insulin bolus must be considered.

In addition, the simulator must incorporate the technical constraints and failures of insulin pumps that may affect AP experiments in the same way as the sensor glucose does.

D. Protocol and outcomes measures

An appropriate protocol design must include basic information about the experiment. The duration of the experiment, the regulation period, start of commutation, carbohydrate size, time and duration of meals, time and size of prandial insulin boluses, and the profile of insulin basal delivery must all be considered.

Several outcomes to cover the statistical measures of control algorithm performance are needed. The average glucose concentration is usually informed through the mean: mean premeal; mean postmeal; percent time spent within, above, and below the target zone; low blood glucose index (LBGI); and high blood glucose index (HBGI). Graphical outcomes are the risk trace, the histogram and the aggregate glucose concentration, the Poincare plot, the control variability grid, and the grading system.

III. Results

A. Implementation

To follow the GSD approach and take advantage of reusing the code in different operating systems and ECU targets, the NI LabVIEW platform was used. It is noteworthy that the graphical code can be compiled to the C language with LabVIEW toolkits to keep its portability with systems like insulin pumps, where it is not supported.

B. User interfaces

Individual menus were implemented to customize the behavior of virtual patients, the CGM system, insulin pumps, protocol settings, and outcomes measures.

Figure 2 shows the main user interface, and the user uses this to access each scenario component. In this menu, a summary box is used to inform the reader of any changes in the scenario. In addition, options to load and save settings were implemented on each menu, providing flexibility for adjusting scenarios.

1) Virtual patients

As an illustration of the glucose–insulin system, the model presented in [7] was implemented, and the six parameter sets reported in [21] were used. However, any model or combination of submodels can be used as long as they can generate a virtual patient population.

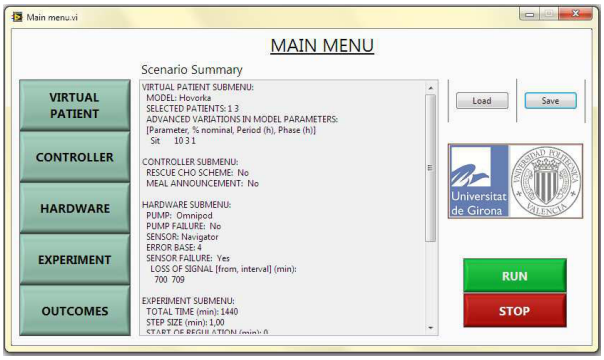

Fig. 2. Simulator main menu.

Intrapatient variability was introduced through the sinusoidal oscillations of parameters whose amplitude, period, and phase are adjusted according to scenario requirements. Figure 3 shows the virtual patient menu.

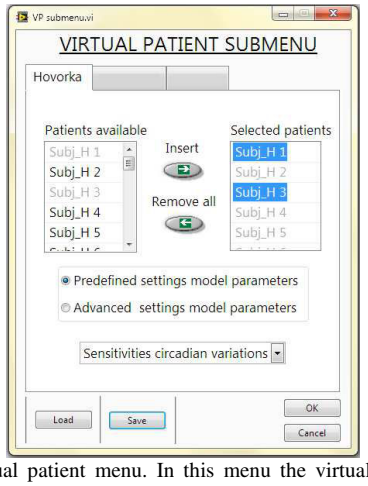

Fig. 3. Virtual patient menu. In this menu the virtual patients are selected and the intra-patient variability adjusted in two ways: Selecting a predefined variability or setting individually the parameter variability according to particular needs.

2) Insulin pump and glucose sensor

The measurement errors present in the FreeStyle Navigator CGM system were simulated using the Breton and Kovatchev model [12]. The frequency of display readings was implemented as a technical constraint, and as a failure in the glucose sensor, a loss of signal customizable by the user was included.

In the case of the insulin pump, the error model was assumed uncorrelated, with a zero mean and a constant coefficient of variation (CV) [9]. According to the insulin pump, a specific CV can be set using data from the experimental test informed in [22]. The basal and bolus increments were implemented as technical constraints.

Regarding types of failures in insulin pumps in real-life scenarios, three effects were considered: non-delivery, constant delivery, and partial delivery of CSII.

3) Protocol and outcomes measure

These menus were implemented following the suggestions described in the methods section. Figure 4 shows the protocol menu.

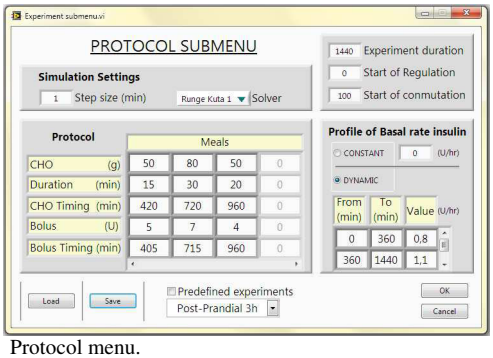

Fig. 4. Protocol menu.

C. Hardware testing

The ECU target is represented here by the NICompactRIO cRIO-9014, which is a reconfigurable test and control system with a real-time processor that can execute control algorithms deterministically, perform data logging, has several peripherals for data exchange, and hardware modules to interface with digital and analogical input/output signals.

Figure 5 shows a scheme to explain the hardware implementation created to demonstrate the performance of control algorithms when the entire code without changes is reused in the ECU. Figure 6 shows the real assembly in the laboratory.

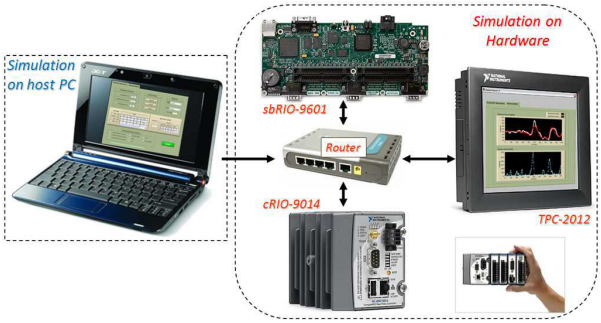

Fig. 5. Schematic of hardware network. First the simulator runs on a PC, then the control algorithm is embedded onto the cRIO through the router used to connect devices each other with TCP-IP protocol, the glucose sensor and insulin pump performance are developed by the NI SingleBoardRIO sbRIO-9601, and finally the glucose and insulin delivered traces are shown in the touch panel TPC-2012.

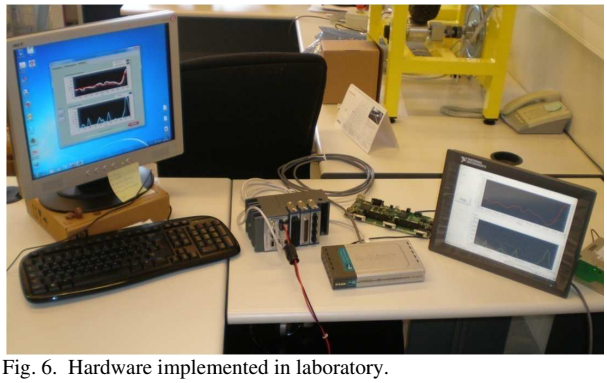

Fig. 6. Hardware implemented in laboratory.

IV. Discussion

A general methodology based on precedent simulator designs was presented. To improve or cover additional simulations, the models proposed here to represent each AP component can be updated, changed, or replaced.

By using different models associated with each subsystem of the glucose–insulin system, a heterogeneous cohort of virtual patients can be generated, where each virtual patient is defined by the parameter sets relating to the combination of submodels composed.

This simulator with both textual and graphical programming standard languages, through either LabVIEW or other programming platforms, drives the design of the control algorithms.

Including basal profiles from protocols of open-loop treatments can be used on closed-loop control; for example, the design of control algorithms focused on improving the postprandial excursions of meal intakes.

Unlike other simulators, the present work moved a step beyond by integrating and embedding the control algorithm in an ECU target without time-consuming or specific low-level knowledge, following a GSD approach. The result was successful and could be interpreted as a contribution to alternative ways toward developing new and faster AP hardware prototypes.

The ECU target used in this work, the CompactRIO device, is an important model of reference in several areas, such as automotive and medical devices, where high performance and robustness is required [23]. The results obtained so far demonstrate the device flexibility of connectivity with PC systems and other targets to exchange data and code reuse. However, we acknowledge that integration of the CompactRIO with real glucose sensors and insulin pumps is required to verify the communication and conditioning with this kind of device.

V. Conclusion

A simulator to design and test blood glucose control algorithms was created, where realistic scenarios can be specified to simulate AP experiments. Implementing a GSD approach, the deployment of control algorithms on ECU targets was accelerated.

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