

In Silico Evaluation Platform for Artificial Pancreatic β -Cell Development—A Dynamic Simulator for Closed-Loop Control with Hardware-in-the-Loop

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Abstract

Background: A critical step in algorithm development for an artificial β -cell is extensive in silico testing. Computer simulations usually involve only the controller software, leaving untested the hardware elements, including the critical communication interface between the controller and the glucose sensor and insulin pump.

Methods: An in silico simulation platform has been developed that uses all of the components of the clinical system. At the core is a comprehensive in silico population model that covers the variability of principal metabolic parameters observed in vivo, to replace the human subject, with the ability to use historical clinical data. A continuous glucose monitor, in this case either the Abbott Diabetes Care (Alameda, CA) FreeStyle Navigator[®] or the DexCom (San Diego, CA) STS7[®], is supplied with a glucose signal provided by the simulator. The Insulet (Bedford, MA) OmniPod[®] insulin pump is also interfaced with the simulator to provide insulin delivery data. These hardware elements are an integral part of the system under testing, which also includes the algorithm components.

Results: The system is unique in that it uses the same hardware components for simulations as are required in clinical trials, allowing for full-system level verification and validation. With a detailed mathematical model, a suite of patients can be simulated to reflect various conditions. Because all hardware is used, their related limitations are automatically included.

Conclusions: A complete artificial β -cell evaluation platform was realized with the flexibility to interface various algorithms and patient models, allowing for the systematic analysis of monitoring and control algorithms. The system facilitates a variety of tests and challenges to the software and the component devices, streamlining preclinical validation trials.

Introduction

WHETHER IN AVIATION, chemical process, automobile, and other industries, the development of a control algorithm for a real implementation needs to advance from requirements to computer-based simulations, prototyping, and finally to a full product implementation. This path often requires an additional milestone in the form of a complete system simulation that comprises a software part, usually the control algorithm, a hardware part (the devices, actuators and sensors), and a mathematical representation of the real system under control, which is referred to as hardware-in-the-loop (HIL). This simulation step is necessary for

verification and validation of both the system and its individual components, since the link between the software block and the hardware one can be problematic and usually involves time-consuming real-time testing.

The concept of HIL simulation is not a new one and has been used in the development of control algorithms in the energy,¹ automobile,²⁻⁴ manufacturing,⁵ and aviation^{6,7} industries. The development of an artificial β -cell is a complex task requiring HIL simulation studies in order to ensure system reliability and safety, which is integrated as part of the validation and verification of the system for regulatory purposes⁸ and which offers a way to assess the robustness of the control algorithm in a real-time implementation. Such a

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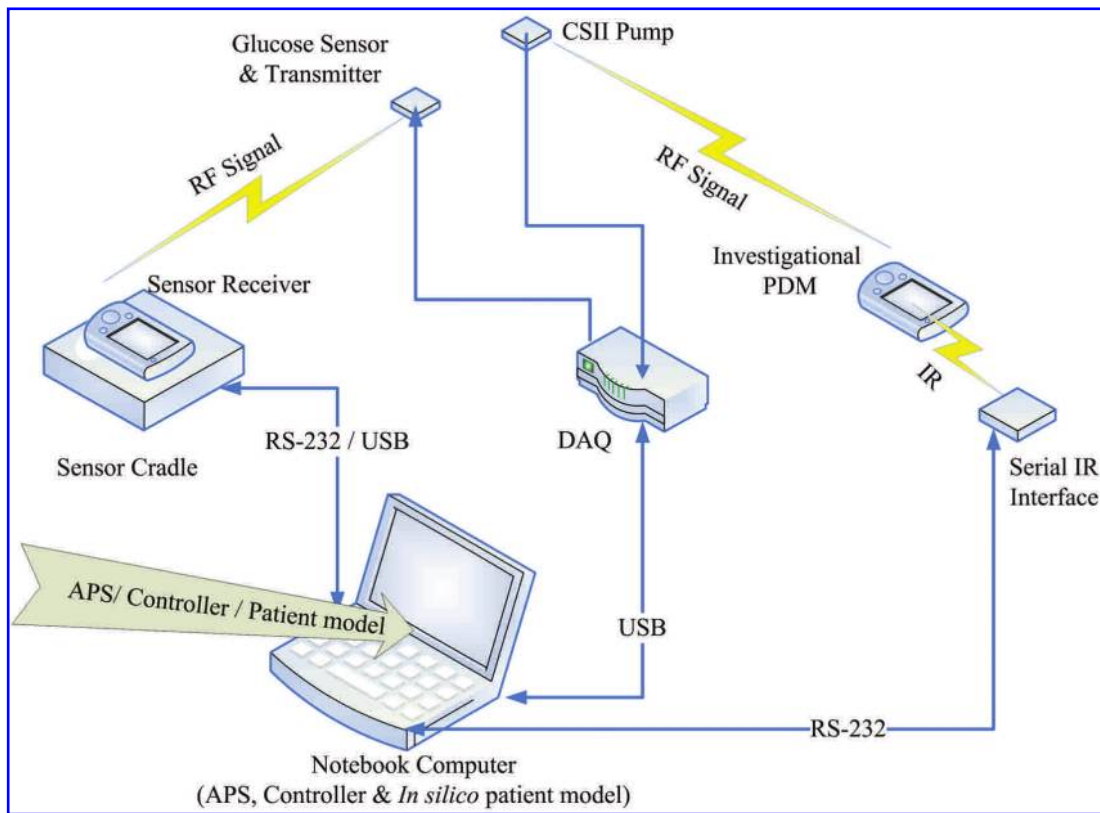


FIG. 1. Schematic showing the components of the HIL and identifying the communication links for each specific device.⁹ IR, infrared.

system can also be used as a training environment for the medical personnel who will use the system in a clinical setting.

An illustration of a closed-loop artificial β -cell platform with HIL is presented in Figure 1, where the only difference from a clinical implementation of the system is the replacement of the subject with a mathematical model, in this case of insulin–glucose dynamics for type 1 diabetes mellitus (T1DM). The other components of the platform are (a) a computer that runs both the control algorithm, as part of the artificial pancreas software (APS) system, and the *in silico* mathematical model of the patient (if desired, these could also be run on independent computers), (b) a continuous glucose monitor (CGM), e.g., Freestyle Navigator[®] (Abbott Diabetes Care, Inc., Alameda, CA) or STS7[®] (DexCom, Inc., San Diego CA), and (c) a continuous subcutaneous insulin infusion (CSII) pump (OmniPod[®], Insulet Corp., Bedford, MA). The devices (sensor and pump) have two connection/communication pathways. On one end, they are connected to the APS system as they would normally be used in a clinical test, with the pump receiving commands for insulin infusion and the sensor providing glucose measurements. At the other end these devices are interfaced through a data acquisition (DAQ) card to the *in silico* mathematical model. The infusion pump hardware is monitored for the delivery of insulin (which is then provided as an input to the mathematical model), and the interstitial glucose concentration output of the model is provided to the glucose sensor unit.

Materials and Methods describes the HIL environment and the communication links between the software and the

hardware. Results and Conclusions then provide a validation and verification of the system for a closed-loop simulation of an artificial pancreatic β -cell implementation.

Materials and Methods

The *in silico* test platform, which is developed in MATLAB[®] (The MathWorks, Inc., Natick, MA), can be divided into two main parts, hardware and software, where the latter can be further divided into two distinct software entities (denoted by the dashed rectangles in Fig. 2). The first one is the APS,¹⁰ which is the actual system used in clinical trials. This system is responsible for receiving glucose measurements in real time from the CGM, calculating a new infusion rate, and setting the new rate on the CSII pump. The second part is the *in silico* patient simulator, which is based on a mathematical model (or historical clinical data) of the glucose–insulin dynamics of a patient with type 1 diabetes, and the interface of the simulator with the pump and sensor hardware.

APS

The APS is divided into three component human machine interfaces (HMIs) that run under MATLAB: a main interface, an interface for the sensor, and another for the pump. The main interface presents all the information to the physician and oversees the closed-loop controller. The sensor HMI controls the sensor, logs all communication with the device, and transfers 1-min glucose readings to the main interface. Similarly, the pump HMI controls the pump, logs all communi-

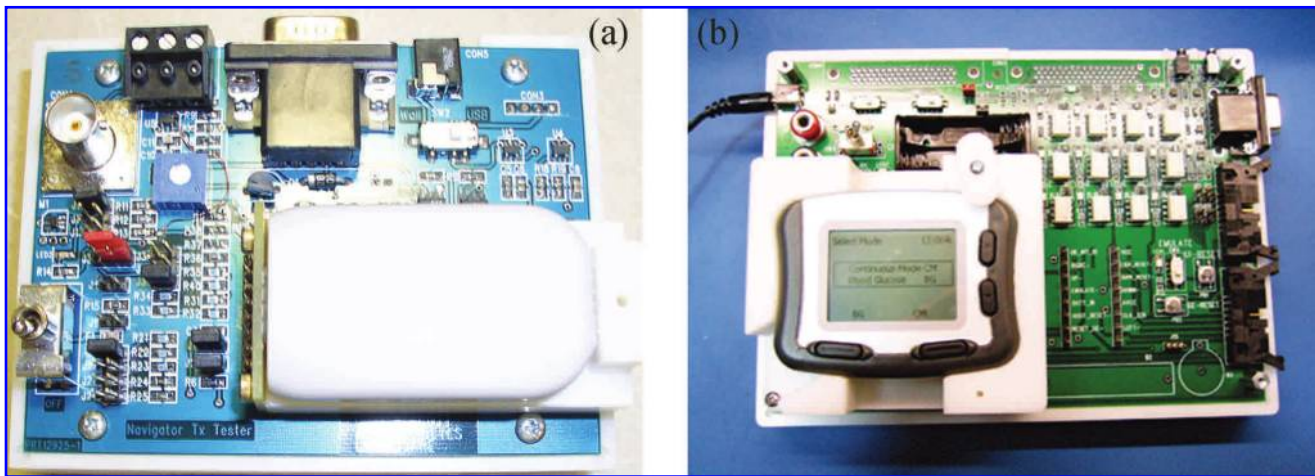


FIG. 3. (a) Dynamic SimVivo (signal from the PC). (b) FreeStyle Navigator Cradle (signal to the PC).

metabolism, such as the model of Hovorka et al.¹² or Dalla Man et al.^{13,14} The simulator block has two inputs—the first one is the insulin microbolus, and the second one is meal information—and the output of the model is interstitial glucose concentration. It should be noted that appropriate selection of an *in silico* model requires that one address such important issues as time lags related to subcutaneous insulin delivery and glucose sensing, as well as sensitivity and calibration errors inherent with CGM. A multifunction input-output card (USB-6008, National Instruments Corp., Austin, TX) is used to convert the mathematical model's output to an electrical current, which is relayed to the CGM sensor transmitter unit. On the CSII pump side, a digital input port detects when a microbolus is delivered by the pump by sensing the rising edge of the plunger actuation signal. These delivery data are then provided to the patient model.

Hardware interfacing

The hardware interfacing requires customized units from the device manufacturers, as described below, for use with the Abbott FreeStyle Navigator, the DexCom STS7, and the Insulet OmniPod.

Communication with the FreeStyle Navigator transmitter requires the Dynamic SimVivo (Abbott Diabetes Care) (Fig. 3a), which is a research tool designed to connect directly to a FreeStyle Navigator transmitter to simulate the output of a FreeStyle Navigator sensor inserted into the interstitial space of a human body. It connects to a FreeStyle Navigator transmitter using test point connections located within the battery compartment of the transmitter and using the transmitter sensor contact pads. It interfaces with the computer through the DAQ card that allows the control of the simulated sensor signal. The tool also provides a means of controlling the local temperature in the vicinity of the transmitter to minimize variation in the measured signal due to the FreeStyle Navigator's temperature-dependent calibration scheme. Historical sensor data (current from the glucose sensor and temperature readings from the subject) can also be provided to the SimVivo unit instead of a pure mathematical model.

The primary function of the Navigator Receiver Data Extraction Cradle (Abbott Diabetes Care) (Fig. 3b) is to allow the minute-by-minute transfer of FreeStyle Navigator data to the computer. It is used with the FreeStyle Navigator receiver to enable the extraction of data stored in the receiver's user interface and/or glucose engine. It connects to a FreeStyle Navigator receiver using test point connections located within the battery compartment of the receiver. The cradle itself has no software or adjustable components and is designed to work with an appropriate PC-based software application as a laboratory tool or in a clinical research setting by qualified and trained personnel.

A similar unit, the Glucose Simulator (DexCom), is used to mount the STS7 transmitter as if it were inserted by the patient. This simulator unit interfaces with the computer using the DAQ card that supplies the simulated sensor signal in the same way as done with the Navigator SimVivo unit. However, for the STS7 receiver, no additional hardware is needed to transfer sensor data in real-time from the receiver to the computer, which is done using a universal serial bus (USB) port.

The communication with the CSII pump also has two parts. (1) The OmniPod Personal Diabetes Manager (PDM) (Fig. 4a), which was modified by Insulet for this purpose (closed-loop investigational PDM), communicates with the computer using a proprietary serial protocol by means of an infrared link. The PDM receives commands, including microbolus commands, from the OmniPod HMI. (2) The PDM then transfers the commands to the pod by way of radio-frequency (RF) transmission.

Given that the actual insulin pump is sealed, there is no easy way to access the electrical signals needed to provide this information back to the *in silico* simulator. Instead, an engineering board that replicates the pod's functionality (Fig. 4b, bottom) is used. This board behaves in exactly the same way as an actual pod, with the exception that the insulin delivery is only simulated. A test point on the board is used to acquire the signal (using an input port on the DAQ unit) that triggers the actuation of the pump mechanism that propels the plunger in the actual pod. This information is then passed on to the simulator.

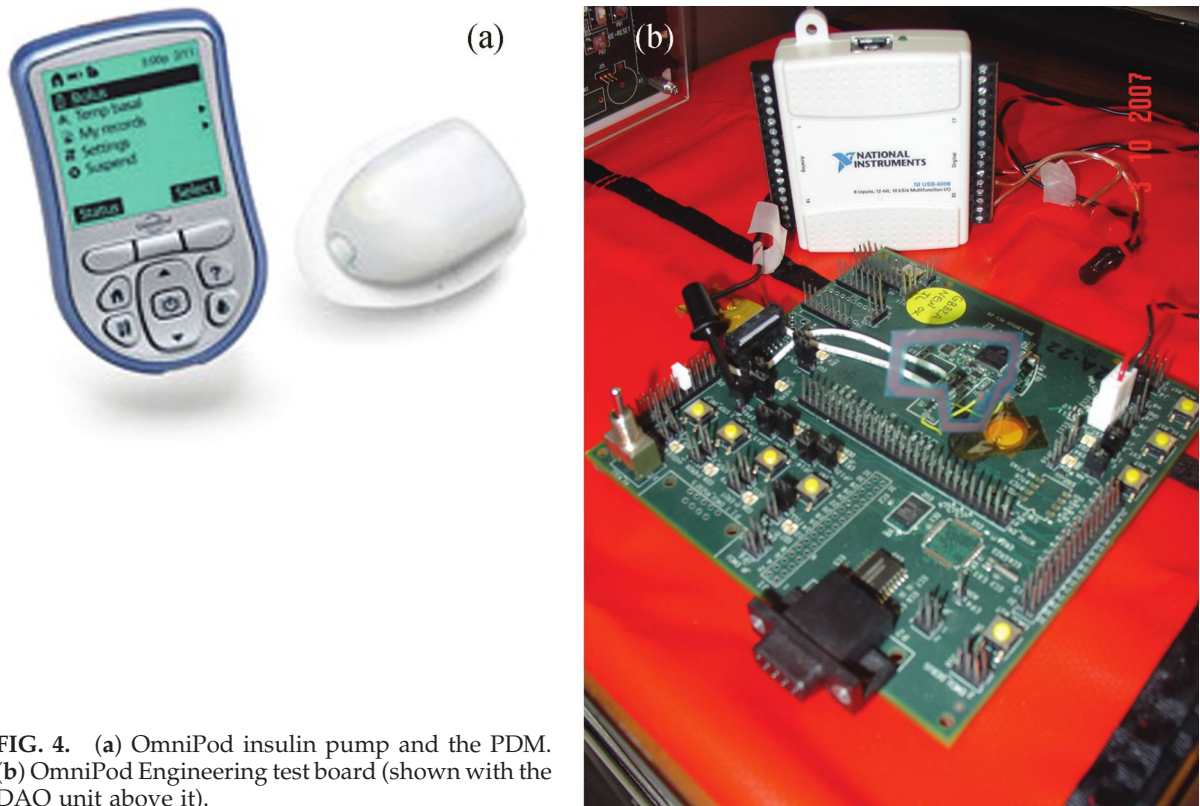


FIG. 4. (a) OmniPod insulin pump and the PDM. (b) OmniPod Engineering test board (shown with the DAQ unit above it).

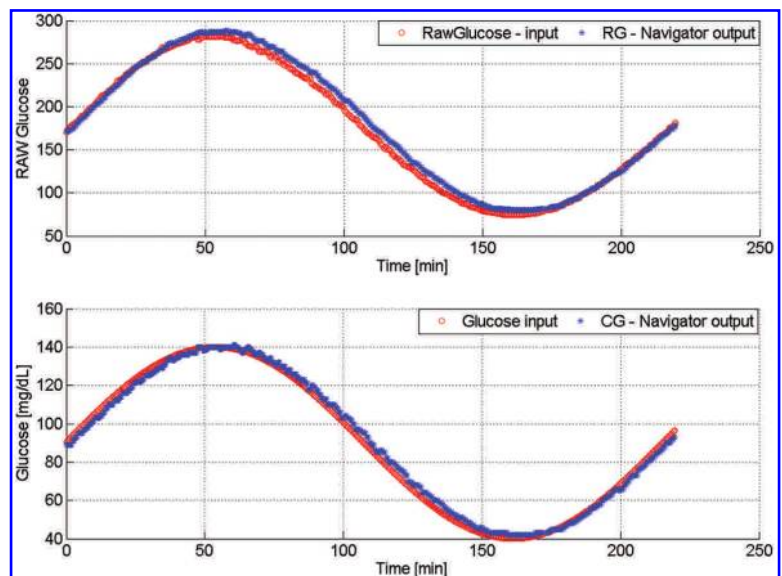
Results

A demonstration of the capabilities of the in silico test environment is presented for both verification and validation of a single component of the artificial β -cell and as a way to perform a fully closed-loop test with HIL as a step prior to a clinical trial. This demonstration has been carried out using the FreeStyle Navigator CGM and the OmniPod CSII pump.

Sensing loop verification and validation

As part of a component’s verification, there is a need to check the “sensing loop” that confirms that the glucose readings that are acquired by the main APS are accurate. This validation process is presented in Figure 5, where a glucose signal in the shape of a sinusoid is generated by the simulation environment and sent to the SimVivo unit and back to the receiver unit. As can be seen, the output of the

FIG. 5. Verification of the APS sensor HMI and its ability to present accurate glucose readings. (Upper panel) Input (in red) of raw glucose values to the SimVivo unit and the corresponding reading by the APS (in blue). (Lower panel) The corresponding calibrated glucose input and outputs.



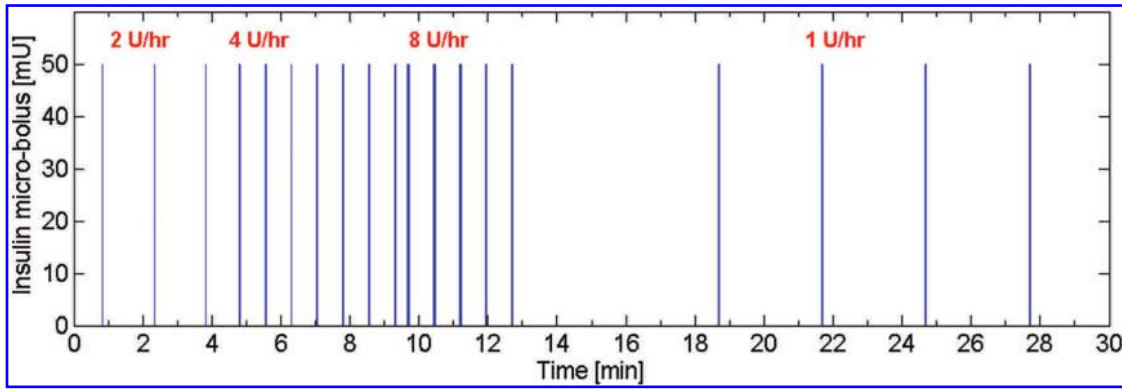


FIG. 6. Verification of the controller commands and the proper conversion to microboluses.

FreeStyle Navigator tracks the input for both the raw and calibrated glucose readings. Furthermore, the ability of the APS to acquire accurate readings from the CGM using non-physiological signals satisfies one of the regulatory requirements for evaluating the tracking of changes in the glucose signal. Raw measurements presented to the sensor by the computer were transmitted to the receiver by an RF signal, transmitted to the computer through a serial port, and then read by the APS. Glucose values in the APS matched the original glucose signal supplied to the glucose sensor with a maximum measurement error of 6 mg/dL, where for 96%

of the data the error is less than 5 mg/dL, and for 63% of the data it is less than 3 mg/dL, with only one dropped measurement.

Infusion loop verification and validation

On the pump side, a verification and validation of the infusion rate commands that are being transmitted by the APS to the CSII pump hardware, and their conversion to microboluses, can also be done. Results of this process are presented in Figure 6, where the controller sends an infusion

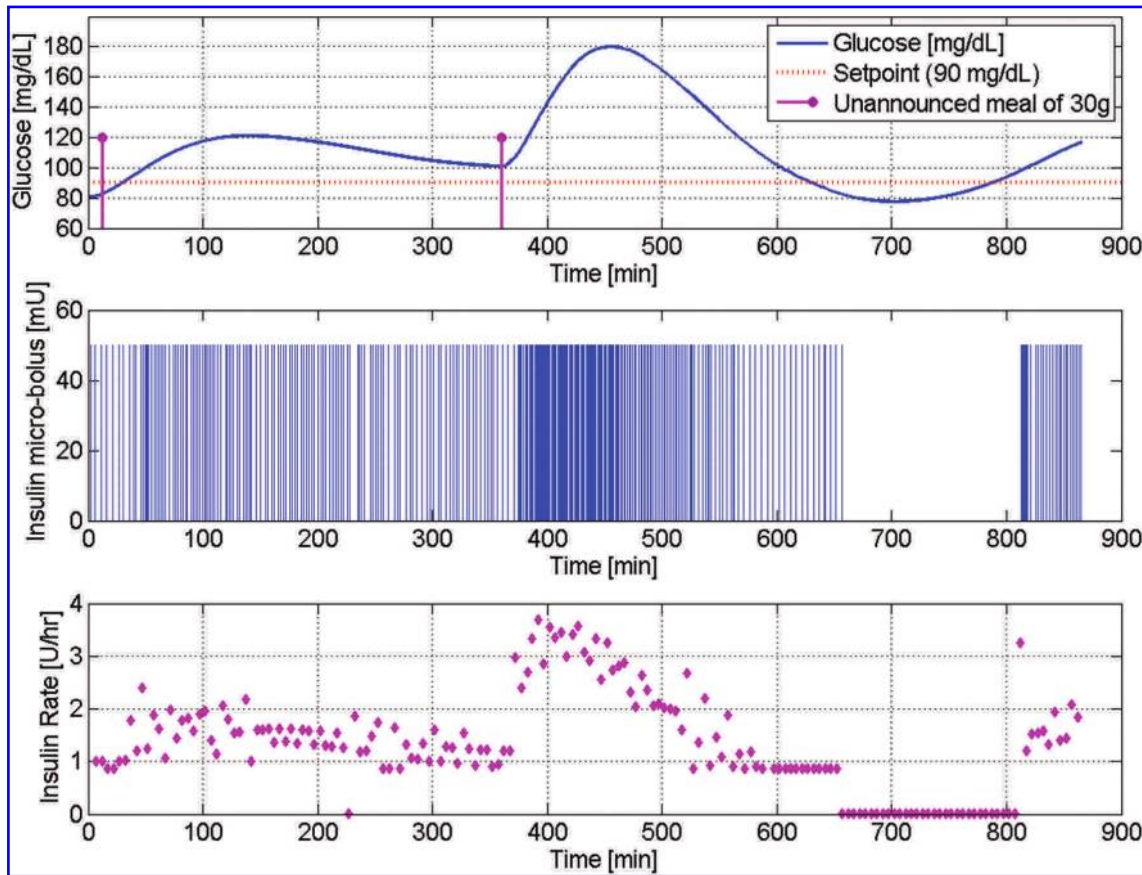


FIG. 7. Summary results of a full system test of a closed-loop in silico trial based on the compartmental model of Hovorka et al.¹² (Upper panel) Glucose tracing (as obtained from the FreeStyle Navigator CGM) in blue. Meal markers are shown as stems, and the controller setpoint of 90 mg/dL is given as a red dotted line. (Middle and lower panels) Delivered insulin as microboluses of 50 mU and as controller rate commands of U/h, respectively.

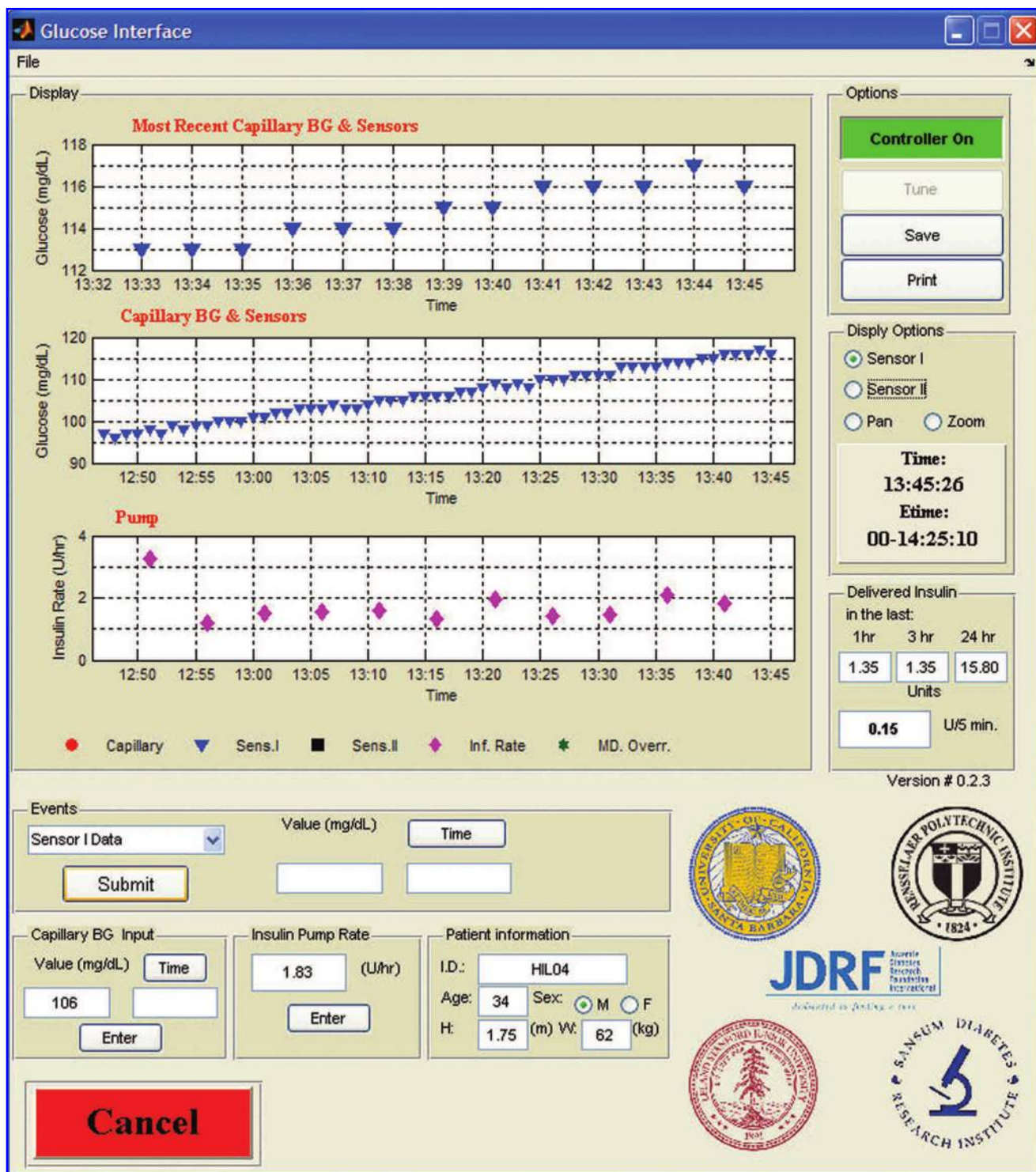


FIG. 8. A snapshot of the APS HMI at the end of the 14-h closed-loop in silico trial: (upper and middle panels) glucose tracing and (lower panel) insulin infusion rate. Data for the total delivered insulin in the last hour, 3 h, and 24 h, as well as subject demographic details, current infusion rate, and last calibration value are given.¹⁰ BG, blood glucose.

rate to the OmniPod HMI that converts it into a sequence of microboluses (each of 0.05 U). The microboluses are detected with the DAQ unit as described earlier. This process allows verification that a command was sent and received and that the correct number of microboluses in the right frequency is given (e.g., for a rate of 4 U/h, 80 microboluses should be given in an hour or over a 5-min period between six and

seven; as can be seen in Fig. 6, seven microboluses were given).

System verification and validation

An example of a full system validation is presented in Figures 7 and 8, where a 14-h, closed-loop, in silico test is per-

formed using the same clinical software (Fig. 8), the FreeStyle Navigator CGM, and the OmniPod CSII pump. For the in silico simulation we have selected the compartmental model of Hovorka et al.¹² of a T1DM patient, and for the controller we used a generic model predictive controller. The aims of this validation were as follows: (a) verify that the computational environment is stable and robust during a rather long trial, which is almost twice as long as initial closed-loop trials will be; (b) validate the artificial β -cell software for stability, functionality, data transfer, data logging, safety alarms, and display; (c) component validation of the sensor and the pump delivery rate, especially a zero rate; and (d) high-level verification of the controller performance in a real-time study by introducing external disturbances in the form of unannounced meals of 30 g of carbohydrate. As can be seen from Figures 7 and 8, and by analyzing the study results and logs, all aims were met.

Conclusions

A complete testing platform for the artificial β -cell system was realized, allowing for the systematic analysis of monitoring and control algorithms. This unique system uses all of the hardware components for simulations as are used in clinical trials, allowing for both full component and system-level verification and validation. One of the highlights of this test environment is the ability to use various in silico T1DM patient models in combination with different control algorithms within the APS platform.

Such a test environment serves an essential function prior to clinical closed-loop trials, as it can be used as part of regulatory studies, algorithm testing, safety studies, and the training of medical personnel. This concept can, and should, be further developed to a full benchmark environment by integrating a comprehensive in silico mathematical model that can capture the inter- and intra-patient variation of T1DM subjects with an HMI that will allow simple execution of a predefined set of challenge scenarios and outcome measures for the testing of future closed-loop systems.

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Author Disclosure Statement

E.D., C.C.P., and F.J.D. III declare no competing financial interests exist. H.Z. has served in an advisory capacity for Insulet, MannKind Corporation, DexCom, Insulet, Lifescan, Inc., a Johnson & Johnson Company, and Medtronic MiniMed. B.A.B. has served in an advisory capacity for Medtronic MiniMed, Lifescan, Inc., a Johnson & Johnson Company, Unomedical, and Novo Nordisk. L.J. has served in an advisory capacity for Abbott Laboratories, Inc., Amylin Pharmaceuticals, Inc., DexCom, Eli Lilly and Company, Insulet, dLife Communications, Lifescan, Inc., a Johnson & Johnson Company, Novo Nordisk Inc., MannKind Corporation, Pfizer Inc., and Sanofi-Aventis.

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