Journal of Diabetes Science and Technology
Volume 3, Issue 5, September 2009

SYMPOSIUM

Automatic Data Processing to Achieve a Safe Telemedical Artificial Pancreas

M. Elena Hernando, Ph.D.,[1,2] Gema García-Sáez, M.S.,[1,2] Iñaki Martínez-Sarriegui, M.S.,[1,2] Agustín Rodríguez-Herrero, M.S.,[1,2] Carmen Pérez-Gandía, M.S.,[1,2] Mercedes Rigla, M.D., Ph.D.,[2,3] Alberto de Leiva, M.D., Ph.D.,[2,3] Ismael Capel, M.D.,[3] Belén Pons, M.S.,[3] and Enrique J. Gómez, Ph.D.[1,2]

Abstract

Background:

The use of telemedicine for diabetes care has evolved over time, proving that it contributes to patient self-monitoring, improves glycemic control, and provides analysis tools for decision support. The timely development of a safe and robust ambulatory artificial pancreas should rely on a telemedicine architecture complemented with automatic data analysis tools able to manage all the possible high-risk situations and to guarantee the patient's safety.

Methods:

The Intelligent Control Assistant system (INCA) telemedical artificial pancreas architecture is based on a mobile personal assistant integrated into a telemedicine system. The INCA supports four control strategies and implements an automatic data processing system for risk management (ADP-RM) providing short-term and medium-term risk analyses. The system validation comprises data from 10 type 1 pump-treated diabetic patients who participated in two randomized crossover studies, and it also includes *in silico* simulation and retrospective data analysis.

Results:

The ADP-RM short-term risk analysis prevents hypoglycemic events by interrupting insulin infusion. The pump interruption has been implemented *in silico* and tested for a closed-loop simulation over 30 hours. For medium-term risk management, analysis of capillary blood glucose notified the physician with a total of 62 alarms during a clinical experiment (56% for hyperglycemic events). The ADP-RM system is able to filter anomalous continuous glucose records and to detect abnormal administration of insulin doses with the pump.

Conclusions:

Automatic data analysis procedures have been tested as an essential tool to achieve a safe ambulatory telemedical artificial pancreas, showing their ability to manage short-term and medium-term risk situations.

J Diabetes Sci Technol 2009;3(5):1039-1046

Author Affiliations: [1]Bioengineering and Telemedicine Group, Polytechnic University of Madrid, Madrid, Spain; [2]CIBER-BBN, Network of Research for Bioengineering, Biomaterials and Nanomedicine, Barcelona, Spain; and [3]Endocrinology Department, Hospital de Sant Pau, Barcelona, Spain

Abbreviations: (ADP-RM) automatic data processing for risk management, (BG) blood glucose, (CGM) continuous glucose monitoring, (INCA) Intelligent Control Assistant system, (MPC) model predictive control, (PDA) personal digital assistant, (RI) risk index

Keywords: decision support, diabetes, glucose prediction, telemedical artificial pancreas

Corresponding Author: M. Elena Hernando, Grupo de Bioingeniería y Telemedicina, ETSI Telecomunicación, Ciudad Universitaria s/n, 28040 Madrid, Spain; email address elena@gbt.tfo.upm.es

Introduction

The aim of an artificial pancreas is to calculate the optimum insulin delivery to maintain the patient in a normoglycemic state, taking the blood glucose (BG) concentration as the main input of the algorithm. An ambulatory artificial pancreas requires using the subcutaneous route, both for glucose measurement and for insulin delivery, due to the invasiveness of the intravenous route. However, the major difficulties facing closed-loop systems based on the subcutaneous route are the insulin absorption time and delays associated with subcutaneous glucose with respect to the glucose concentration in the blood.

In recent decades, two main types of closed-loop control algorithms have been employed in clinical studies: the classical feedback control method known as proportional-integral-derivative controller[1,2] and model predictive control (MPC).[3,4] Other techniques include adaptive control,[5] adaptive inverse control,[6] fuzzy control,[7] neural predictive control,[8] and robust control.[9,10] Glucose control after meals is usually poor mainly because of the delays associated with glucose measurement and insulin action, but the control is improved when used at night under fasting conditions.[3]

Up until now, all the clinical studies with closed-loop algorithms have been conducted in a hospital setting under tight supervision. During clinical experiments, risk management becomes crucial in order to minimize health hazards for patients. Several mechanisms have to be considered to avoid data loss, device malfunction, or wrong decision making that might affect the patient's health. These circumstances lead to the development of appropriate automatic procedures to manage all the possible high-risk situations to guarantee patients' safety.

The complexity of a fully automated artificial pancreas makes the in-hospital evaluation scenario the only possible option over the coming years. However, research must be carried out to apply some of the artificial pancreas benefits to ambulatory scenarios, while managing all the possible high-risk situations and guaranteeing the patient's safety. The first step is to postpone the idea of having a 24-hour fully automated ambulatory artificial pancreas and to start looking for hybrid solutions that combine closed-loop algorithms with the prediction of hypo- and hyperglycemia, decision support tools, and hand-held terminals to provide patients with mobility, decision support, reminders, and feedback from health care providers.

The use of telemedicine systems for diabetes care enables assessment of the patient's condition and presents relevant clinical data for physicians to detect the need for therapy changes. The contribution of telemedicine systems to diabetes care has evolved over time. Earlier experiences with telemedicine were aimed at facilitating remote monitoring of a patient's BG levels from home through their transmission to the hospital.[11–13] Most interactive telemedicine services have been developed using a distributed approach to integrate patient applications, implemented on a personal computer or a hand-held device, and medical workstations used by physicians and nurses at the hospital.[14–16]

Telemedicine provides an integrated approach to information technology tools, which enhances cooperation between users and information and knowledge sharing, and is able to support the infrastructure required to build a safe ambulatory artificial pancreas. The architectural design has to guarantee the interoperability between patient and professional environments and between different devices of the platform. It is recommended that open source platforms and plug-and-play hardware and software connectivity systems be included to make middleware development easier.[17]

The latest generation of telemedicine platforms implements distributed architectures that spread the users' interaction mechanisms and integrates advanced systems based on more powerful, portable, and easy-to-use terminals and applications for patients, such as electronic diaries implemented in Web applications,[18–20] mobile phones,[21] or smart personal assistants[22] to register BG, insulin, diet, physical exercise, and so on.

Some electronic data management experiences that could be useful for risk management can be found in the literature: (1) the use of predictors of hypo- and hyperglycemic events that help the user anticipate his/her actions by predicting near-future BG values,[23–25] (2) the automatic generation of alarms after the detection of anomalous situations,[26] (3) decision support tools to help professionals in therapy planning,[27] (4) decision support tools for patients, such as computer-assisted insulin delivery systems,[28–33] and (5) clinical reminder systems that have been studied extensively[34] showing positive effects in diabetes. Our approach combines several of these strategies through a telemedicine system. The aim is to hasten the implementation of a telemedical artificial pancreas.

This article describes the risk management and supervision procedures implemented in the Intelligent Control Assistant system (INCA) telemedical infrastructure to support a robust and safe artificial pancreas for ambulatory use. The preliminary results of short-term and medium-term data analyses are reported.

Methods

The Intelligent Control Assistant System

The INCA is a telemedical architecture that integrates a personal digital assistant (PDA)-based personal assistant for patients, which manages a continuous glucose monitoring (CGM) sensor and an insulin pump. The telemedicine system supports several loops of control and offers Web-based access to CGM and continuous insulin infusion data to diabetic patients and physicians.[35]

The INCA concept defines four control strategies, each of which is supported by a special setup of the personal assistant:

1. *Patient control:* the patient can monitor data coming from different medical devices (insulin pump, sensors in glucose monitors, glucose meter) and decide to change his/her insulin pump programming. The process is supervised a posteriori by physicians through the telemedical information system.

2. *Doctor control:* health care professionals suggest changes in the therapy after checking monitoring data with a remote access. Patients then operate the devices to follow the physician's advice.

3. *Personal loop control algorithms:* closed-loop algorithms implemented in a portable device provide a real-time control of the insulin pump based on continuous glucose data.

4. *Remote loop control algorithms:* medical devices can be programmed remotely through a portable device according to physicians' prescriptions or by automatic control procedures implemented in the telemedical information system.

Implementation of these personal and remote control strategies led to development of a robust system provided with real-time bidirectional communication for remote interaction with the patient's medical devices from either the patient's personal network or long distance from the hospital.

The personal assistant runs in a PDA using a mobile network to access the remote loop and supports tele-monitoring, telecare, and remote information services.[22] The personal assistant is able to work as a stand-alone system, supported by its own local application and data repository, and communicates with different medical devices through a personal wireless network that provides the patient with mobility and independence in his/her daily life.

The personal assistant is able to act upon patients' local requests for information retrieval and medical device operation and upon remote requests originated by physicians. It interacts with remote components of the telemedical system at the telemedicine central server without intervention of the patient.

Communications are activated on user demand in two scenarios: (1) to force bidirectional data exchange between the telemedical information system and the personal assistant and (2) to carry out remote control of medical devices through the telemedicine server when demanded by patients or physicians through Web access. The mobile personal assistant is the central user device for the control of patients' conditions, for adjustment of medical parameters, and for communication with physicians.

The INCA platform has been designed following a modular approach that makes the integration of different medical devices and/or control algorithms possible. The system has integrated communications with three different medical devices (glucose meter OneTouch Ultra®, LifeScan) that communicates via a serial cable or Bluetooth™, Disetronic D-TRON™ plus insulin pump (Disetronic, Burgdorf, Switzerland) that communicates with the personal assistant using the infrared port, and a continuous glucose sensor prototype based on micro-dialysis that communicates via Bluetooth. The personal assistant integrates a closed-loop control module that implements an algorithm based on a nonlinear MPC with Bayesian learning that has been tested previously.[36]

The four control strategies have been evaluated technically in the laboratory with prototype devices. Additionally, we completed two clinical experiments[37,38] that tested control strategies #1 and #2. Their results provided useful information about difficulties in the use of personal assistant technology and the impact of CGM on patients' metabolic control. The clinical evaluation of

strategies #3 and #4 remains to be completed due to the current reliability and availability of CGM sensors and insulin pumps with real-time reading and remote control in ambulatory conditions.

Automatic Data Processing for Risk Management (ADP-RM) and Decision Support

The architecture of the telemedical system implements an automatic data processing system for risk management and decision support that exploits available monitoring data. The ADP-RM system is very flexible, allowing the use of different communication channels with the users. In case of abnormal situations, alarms are notified through short message service messages, email messages, and/or Web-based messages. The mode of alarm reception is configured by the user according to his/her preferences or depending on the degree of importance.

In our case, data analysis is performed on two different timescales: (1) short-term risk analysis and (2) medium-term analysis of the patient's metabolic state.

1. Short-term risk analysis: The goal is to prevent risky events, detect them, and react when required. As a result, notifications are sent to patients and operation of the medical device is modified (i.e., interruption of insulin infusion). The ADP-RM is performed in real time by the personal assistant whenever a new measurement is recorded and uses the following input as CGM and insulin infusion data.

- **Detection of hypoglycemic events and pump interruption**: Insulin infusion is interrupted when the glucose level has a negative trend and goes below a threshold (G ≤100 mg/dl). The insulin pump infusion is restarted when the glucose trend is positive and rises to the pump reactivation threshold (G ≥80 mg/dl). If the pump is interrupted for more than 1 hour, a minimum microbolus is administered to prevent the crystallization of insulin in the catheter. Other alternatives for pump suspension could consider hypoglycemia prediction algorithms[39] or, instead of using a glucose threshold, start the pump interruption when output of the closed-loop algorithm is a negative insulin infusion, reflecting an insulinemia excess.[40]

- **Detection of glucose sensor failure**: Our design of clinical closed-loop experiments requires patients to wear two redundant CGM sensors. In this scenario, the system performs an automatic comparison between the paired sensor samples. A sensor failure event is activated when discrepancies are greater than 25%. An alarm is triggered to get a capillary BG reading that helps decide whether, despite the differences between the two sensors, sensor #1 is still working acceptably or if it is possible to switch to the backup sensor while the active sensor is being recalibrated. If both sensors need to be recalibrated, it is necessary to stop the automatic closed-loop control.

- **Prediction**: A glucose forecast model based on artificial neural networks is applied to CGM data.[41] The input information is the current time and the glucose recorded during the preceding 20 minutes, and the output of the network is the glucose prediction at the prediction horizon time. The predictor model is trained individually for each patient. A Levenberg–Marquardt back propagation optimization training algorithm is used. This training algorithm takes between 1.5 and 2.5 hours, depending on parameter adjustments, on a standard person computer, for a training data set of six CGM daily profiles per patient (288 glucose readings per day). We considered the accuracy between original and predicted continuous glucose profiles, calculated as the root mean square error, and the mean delay to assess the performance of the predictor.

2. Medium-term analysis of the patient's metabolic state: The goal is to get a complete overview of the patient's daily patterns and changes over time. The results are therapy adjustments or modifications in the closed-loop running parameters. The ADP-RM is carried out within the telemedicine central server and is activated or triggered periodically by the reception of new data.

- **Assessment of the patient's control.** Remote ADP-RM procedures are based on data recorded in the server. Continuous glucose measurements, BG measurements, and insulin data concerning doses administered by patients have been considered to be the most important parameters in detecting anomalous patterns.

  a. **Capillary BG measurements.** The ADP-RM system reminds patients to send BG data after 4 days without data being sent and detects anomalous situations regarding hypoglycemic and hyperglycemic events. The ADP-RM generates alarms in the following situations: (i) two consecutive BG measurements higher than 300 mg/dl, (ii) BG measurements above 400 mg/dl, or (iii) BG below 70 mg/dl.

  b. **Continuous glucose measurements.** Analysis is started once sensor data are downloaded to the

telemedicine system. The patient's metabolic state is considered anomalous when a 72-hour CGM recording reveals any of the following events: (i) variability measured with Kovatchev's risk index (RI), for RI >15,[42] (ii) rapid positive or negative slopes, defined as a change of more than 40 mg/dl in 20 minutes for sensor files with more than six increasing and/or decreasing slope changes, (iii) time in hyperglycemia >8 hours, or (iv) time in hypoglycemia >2 hours.

c. **Insulin administered.** Insulin data are obtained automatically from the patient's insulin pump. The ADP-RM activates analysis in a period of 2 weeks and generates an insulin alarm in any of the following situations: (i) daily insulin dose/weight >1.2 U/kg, (ii) percentage of bolus insulin versus basal insulin >75%, (iii) number of daily boluses >5, or (iv) number of daily basal profiles >5.

- **Adjustment of the insulin-to-carbohydrate ratio.** The personal assistant integrates a tool to optimally adjust the insulin-to-carbohydrate ratio for each patient. The tool is based on the clinically validated run-to-run algorithm.[43] The insulin-to-carbohydrate ratio allows calculation of the insulin bolus administered before each main meal (breakfast, lunch, and dinner) and can be used both to support everyday decisions on the part of ambulatory patients and to setup the closed-loop algorithms. Evaluation of the tool was carried out for technical performance, software usability, and agreement with clinical recommendations through an outpatient clinical trial.[44] The clinical impact of the system is being analyzed further in an ongoing cross-randomized clinical trial.

Automatic Data Processing Validation Methodology

Validation of the ADP-RM procedures was begun during the INCA clinical evaluation. Subsequently, validation was carried out retrospectively with experimental data collected from the previous clinical experiments. The two randomized crossover INCA studies (length: 4 weeks + 4 weeks for each experiment) included 10 type 1 pump-treated diabetic patients from Hospital de Sant Pau (Barcelona, Spain).

The first clinical experiment was devoted to comparing the use of the telemedicine system in supporting control strategies #1 and #2 versus traditional practice. Patients' decisions were based on BG self-monitoring and continuous insulin monitoring.[37] The second clinical experiment evaluated the clinical utility of control strategies #1 and #2 combining real-time CGM and continuous insulin monitoring. The design of the control phase was similar to that of the intervention phase in the first clinical trial. In the intervention phase, the 10 patients used the personal assistant and the telemedicine platform. Additionally, the patients had to wear a CGM sensor (Guardian™, Medtronic, Northridge, CA) in ambulatory conditions for 3 days a week for a total period of 1 month. This second experiment demonstrated the clinical benefits of real-time CGM together with the INCA system.[38]

The second stage for ADP-RM validation comprised a retrospective generation of alarms using experimental data recorded during the clinical experiments. Validation was performed with 40 CGM files downloaded from 10 type 1 diabetic patients using the Guardian 3 days a week for a period of 4 weeks. Data regarding the insulin administered were downloaded automatically from D-TRON Plus insulin pumps (Disetronic, Burgdorf, Switzerland) using the personal assistant. Pump data reception was simulated with a time window of 2 weeks.

Results

This section presents some validation results and examples for three automatic data processing methods: (a) assessment of patient's control, (b) detection of hypoglycemic events and pump interruption, and (c) detection of glucose sensor failure.

Assessment of Patient's Control

During the first INCA clinical experiment,[37] the ADP-RM analyzed capillary BG measurements and generated 62 alarms for the physician, most of them because of hyperglycemia (above 300 mg/dl) in two consecutive readings (56%), with no differences between the two study periods. Those alarms contributed to 44 remote therapy changes prescribed through the telemedical platform. Reminders to send BG data allowed frequent data transfer from patients to the physician in charge (3.27 ± 1.1 weekly transmissions of glucose meter data per patient). After the experimental phase of the clinical experiment, fructosamine decreased significantly (393 ± 32 vs 366 ± 25 μmol/liter; $p < 0.05$) and HbA1c tended to decrease (8.0 ± 0.6 vs 7.78 ± 0.6; $p = 0.073$), while no changes were observed during the control phase.[37]

The following presents results for the retrospective analysis:

- The ADP-RM analysis for CGM data-activated alarms in 20 out of the 40 sensor files, showing that a further

analysis on the part of the physician was required. **Figure 1** shows the alarm distribution: 2 sensor files with high variability (RI >15); 16 files presented rapid positive slope changes (40%); 15 files had rapid negative slope changes (37.5%); and 8 files presented more than 8 hours in hyperglycemia (20%); there were 6 files with more than 2 hours in hypoglycemia (15%). ADP-RM processing and alarm generation notification time was less than 5 seconds for all the files analyzed by the system.

- The ADP-RM analysis for insulin pump data activated the following alarms: 7 alarms for daily insulin dose/weight >1.2 U/kg; 1 alarm for percentage of basal insulin versus bolus insulin >75%; 42 alarms for number of daily boluses >5; and 1 alarm for number of basal profiles >5. The process to simulate alarms consisted of emulating the ADP-RM analysis performed every 2 weeks. We found that ADP-RM processing and alarm generation notification time was less than 3 seconds in all the cases considered.

Detection of Hypoglycemic Events and Pump Interruption

Figure 2 shows an example of pump interruption in a 30-hour simulation of closed-loop control.[6] Insulin infusion is interrupted when the glucose level falls below a threshold (G ≤100 mg/dl) and is resumed when the glucose trend is positive and rises to the pump reactivation threshold (G ≥80 mg/dl). Infusion of an isolated microbolus can be observed when the pump is interrupted for more than 60 minutes in order to avoid obstruction of the catheter. Pump interruption prevents hypoglycemic events, although future work needs to address the aim of achieving normoglycemia after pump suspension.

Detection of Glucose Sensor Failure

Figure 3 shows, as an example, a simulation of how the detection of glucose sensor failure could be managed when the patient is wearing two glucose sensors. In two different situations, the glucose values of the CGM sensors differ by more than 25% and the patient is notified to get a capillary BG measurement. In the first event, the BG reading would confirm that sensor #1 is still working within the acceptable limits so no action would need to be taken. In the second event, it would be necessary to change to the measurements of sensor #2 while the patient is notified to recalibrate sensor #1. It would not be necessary to disrupt the closed-loop algorithm because of sensor failure.

Conclusions

This article focused on the role of automatic data processing methods that contribute to achieving a safe ambulatory telemedical artificial pancreas. Use of the INCA platform with always-on mobile networks enables the periodic update of data from the patient scenario to the telemedical server and the performance of short-term and medium-term risk analyses.

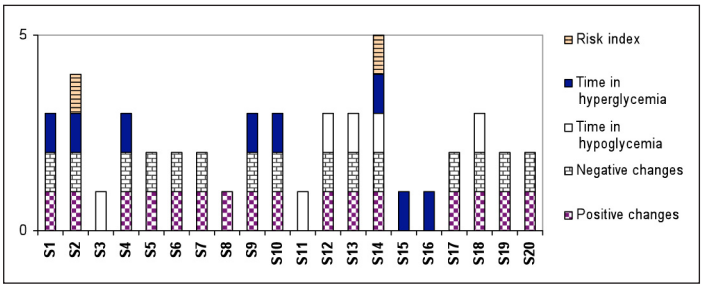

Figure 1. Events that generated alarm notifications for each sensor file.

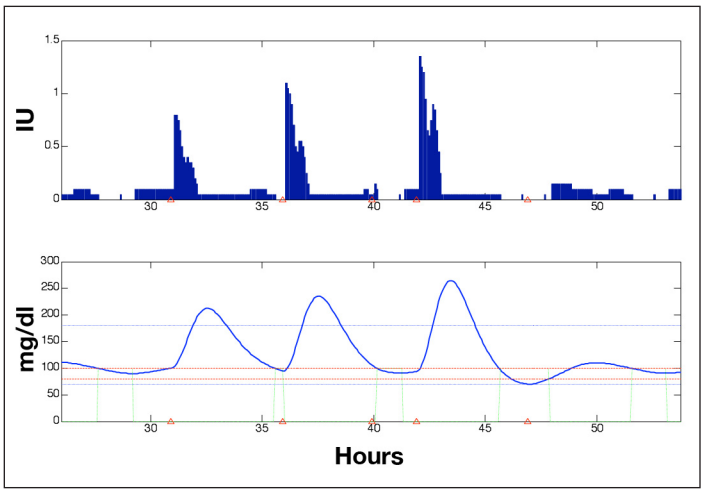

Figure 2. Pump interruption during a closed-loop control simulation. **(Top)** Insulin infusion; **(bottom)** subcutaneous glucose concentration. Triangles represent meal intakes. IU, international unit.

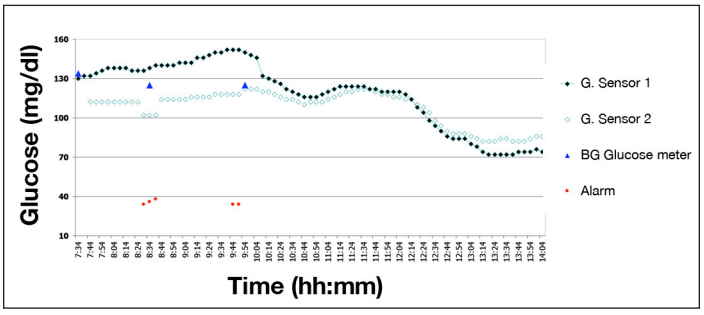

Figure 3. Example of alarms generated after the detection of glucose sensor failures.

The ADP-RM system supports everyday decisions made by ambulatory patients and it also secures decisions during closed-loop experiments. The system can filter huge amounts of monitoring data and assesses the patient's metabolic control, improving physicians' decision making. The ADP-RM aids in the early diagnosis of anomalous situations by generating automatic alarms when a departure of the patient's parameters from predefined ranges is detected. Alarms for BG measurements have been tested successfully in clinical experiments, as well as retrospectively, on the basis of CGM records and continuous insulin infusion data.

The INCA platform can also serve as a complement for in-hospital closed-loop control experiments to manage critical situations, such as severe hypoglycemias or device malfunction that might pose a risk to the patient. It represents an alternative to make clinical experiments more flexible and safer, requiring less supervision and helping pave a safe path for development of the ambulatory artificial pancreas.

Further clinical evaluation of the ADP-RM methods presented is needed to demonstrate their impact on patient control. Our current efforts are focused on (1) validation of the run-to-run bolus calculator together with telemedicine to improve patients' daily decisions, (2) implementation and evaluation of prediction tools in order to determine their ability to avoid situations of hypoglycemia and hyperglycemia by using CGM measurements, and (3) implementation of multiparametric analysis to extract better conclusions about the patient's metabolic control by combining the information provided by different medical devices.

Funding:

This work was partially supported by the Spanish FIS grant from the Ministry of Health and Consumer Affairs "ADVISING"- FIS PI060437 and CIBER-BBN (PREDIRCAM).

References:

1. Steil GM, Rebrin K, Darwin C, Hariri F, Saad MF. Feasibility of automating insulin delivery for the treatment of type 1 diabetes. Diabetes. 2006;55(12):3344-50.
2. Marchetti G, Barolo M, Jovanovic L, Zisser H, Seborg DE. A feedforward-feedback glucose control strategy for type 1 diabetes mellitus. J Process Control. 2008;18(2):149-62.
3. Schaller HC, Schaupp L, Bodenlenz M, Wilinska ME, Chassin LJ, Wach P, Vering T, Hovorka R, Pieber TR. On-line adaptive algorithm with glucose prediction capacity for subcutaneous closed loop control of glucose: evaluation under fasting conditions in patients with Type 1 diabetes. Diabet Med. 2006;23(1):90-3.
4. Parker RS, Doyle FJ 3rd, Peppas NA. A model-based algorithm for blood glucose control in Type I diabetic patients. IEEE Trans Biomed Eng. 1999;46(2):148-57.
5. Roman H. Management of diabetes using adaptive control. Int J Adaptive Control Signal Processing. 2005;19(5):309-25.
6. Rodríguez-Herrero A, Hernando ME, Pérez-Gandía C, García-Saez G, Rigla M, de Leiva A, Gómez EJ. Adaptive inverse algorithm for closed-loop control in diabetes. Proceedings of the 1st International Conference on Advanced Technologies & Treatments for Diabetes; 2008 Feb 27; Prague, Czech Republic. p. 46.
7. Campos-Delgado DU, Femat R, Ruiz-Velazquez E, Gordillo-Moscoso A. Knowledge-based controllers for blood glucose regulation in type I diabetic patients by subcutaneous route. Intelligent Control IEEE Int Symp. 2003;592-7.
8. Trajanoski Z, Wach P. Evaluation of subcutaneous route for closed-loop control of insulin delivery: numerical and experimental studies. Eng Med Biol Soc. IEEE 17th Annual Conference 1995;2:1357-8.
9. Kienitz KH, Yoneyama T. A robust controller for insulin pumps based on H-infinity theory. IEEE Trans Biomed Eng. 1993;40(11):1133-7.
10. Parker RS, Doyle FJ 3rd, Ward JH, Peppas NA. Robust H-infinity glucose control in diabetes using a physiological model. AIChE J. 2000;46(12):2537-49.
11. Billiard A, Rohmer V, Roques M, Joseph M, Suraniti S, Giraud P, Limal J, Fressinaud P, Marre M. Telematic transmission of computerized blood glucose profiles for IDDM patients. Diabetes Care. 1991;14(2):130-4.
12. Ahring KK, Ahring JP, Joyce C, Farid NR. Telephone modem access improves diabetes control in those with insulin-requiring diabetes. Diabetes Care. 1992;15(8):971-5.
13. Marrero DG, Kronz KK, Golden MP, Wright JC, Orr DP, Fineberg NS. Clinical evaluation of computer-assisted self-monitoring of blood glucose system. Diabetes Care. 1989;12(5):345-50.
14. Gómez EJ, del Pozo F, Hernando ME. Telemedicine for diabetes care: the DIABTel approach towards diabetes telecare. Med Inform (London). 1996;21(4):283-95.
15. Bellazzi R, Larizza C, Montani S, Riva A, Stefanelli M, d'Annunzio G, Lorini R, Gomez EJ, Hernando E, Brugues E, Cermeno J, Corcoy R, de Leiva A, Cobelli C, Nucci G, Del Prato S, Maran A, Kilkki E, Tuominen J. A telemedicine support for diabetes management: the T-IDDM project. Comput Methods Programs Biomed. 2002;69(2):147-61.
16. Shea S, Weinstock RS, Starren J, Teresi J, Palmas W, Field L, Morin P, Goland R, Izquierdo RE, Wolff LT, Ashraf M, Hilliman C, Silver S, Meyer S, Holmes D, Petkova E, Capps L, Lantigua RA. A randomized trial comparing telemedicine case management with usual care in older, ethnically diverse, medically underserved patients with diabetes mellitus. J Am Med Inform Assoc. 2006;13(1):40-51.
17. Hernando ME, Pascual M, Salvador C H, García-Sáez G, Rodríguez-Herrero A, Martínez-Sarriegui I, Gómez EJ. Definition of information technology architectures for continuous data management and medical device integration in diabetes. J Diabetes Sci Technol. 2008;2(5):899-905.
18. Bellazzi R, Arcelloni M, Bensa G, Blankenfeld H, Brugues E, Carson E, Cobelli C, Cramp D, Annunzio G, De Cata P, De Leiva A, Deutsch T, Fratino P, Gazzaruso C, Garcìa A, Gergely T, Gómez E, Harvey F, Ferrari P, Hernando E, Boulos MK, Larizza C, Ludekke H, Maran A, Nucci G, Pennati C, Ramat S, Roudsari A, Rigla M, Stefanelli M. Design, methods, and evaluation directions of a multi-access service for the management of diabetes mellitus patients. Diabetes Technol Ther. 2003;5(4):621-9.
19. Cho JH, Chang SA, Kwon HS, Choi YH, Ko SH, Moon SD, Yoo SJ, Song KH, Son HS, Kim HS, Lee WC, Cha BY, Son HY, Yoon KH. Long-term effect of the internet-based glucose monitoring system on HbA1c reduction and glucose stability: a 30-month follow-up study for diabetes management with a ubiquitous medical care system. Diabetes Care. 2006;29(12):2625-31.

20. Kim C, Kim H, Nam J, Cho M, Park J, Kang E, Ahn C, Cha B, Lee E, Lim S, Kim K, Lee H. Internet diabetic patient management using a short messaging service automatically produced by a knowledge matrix system. Diabetes Care. 2007;30(11):2857-8.

21. Farmer AJ, Gibson OJ, Dudley C, Bryden K, Hayton PM, Tarassenko L, Neil A. A randomized controlled trial of the effect of real-time telemedicine support on glycemic control in young adults with type 1 diabetes (ISRCTN 46889446). Diabetes Care. 2005;28(11):2697-702.

22. Garcia-Saez G, Hernando ME, Martinez-Sarriegui I, Rigla M, Torralba V, Brugues E, de Leiva A, Gomez EJ. Architecture of a wireless Personal Assistant for telemedical diabetes care. Int J Med Inform. 2009;78(6):391-403.

23. Bremer T, Gough DA. Is blood glucose predictable from previous values? A solicitation for data. Diabetes. 1999;48(3):445-51.

24. Gillis RS, Palerm CC, Zisser H, Jovanovic L, Seborg DE, Doyle FJ 3rd. Glucose estimation and prediction through meal responses using ambulatory subject data for advisory mode model predictive control. J Diabetes Sci Technol. 2007;1(6):825-33.

25. Sparacino G, Zanderigo F, Corazza S, Maran A, Facchinetti A, Cobelli C. Glucose concentration can be predicted ahead in time from continuous glucose monitoring sensor time-series. IEEE Trans Biomed Eng. 2007;54(5):931-7.

26. Hernando ME, Garcia-Sáez G, Gomez EJ, del Pozo F. Intelligent alarms integrated in a multi-agent architecture for diabetes management. Transact Institute Measurement Control. 2004;26(3):185-200.

27. Montani S, Bellazzi R, Portinale L, d'Annunzio G, Fiocchi S, Stefanelli M. Diabetic patients management exploiting case-based reasoning techniques. Comput Methods Programs Biomed. 2000;62(3):205-18.

28. Beyer J, Schrezenmeir J, Schulz G, Strack T, Kustner E, Schulz G. The influence of different generations of computer algorithms on diabetes control. Comput Methods Programs Biomed. 1990;32(3-4):225-32.

29. Peterson CM, Jovanovic L, Chanoch LH. Randomized trial of computer-assisted insulin delivery in patients with type I diabetes beginning pump therapy. Am J Med. 1986;81(1):69-72.

30. Chiarelli F, Tumini S, Morgese G, Albisser AM. Controlled study in diabetic children comparing insulin-dosage adjustment by manual and computer algorithms. Diabetes Care. 1990;13(10):1080-4.

31. Skyler JS, Skyler DL, Seigler DE, O'Sullivan MJ. Algorithms for adjustment of insulin dosage by patients who monitor blood glucose. Diabetes Care. 1981;4(2):311-8.

32. Zisser H, Robinson L, Bevier W, Dassau E, Ellingsen C, Doyle FJ, Jovanovic L. Bolus calculator: a review of four smart insulin pumps. Diabetes Technol Ther. 2008;10(6):441-4.

33. Schrezenmeir J, Dirting K, Papazov P. Controlled multicenter study on the effect of computer assistance in intensive insulin therapy of type 1 diabetics. Comput Methods Programs Biomed. 2002;69(2):97-114.

34. Shea S, DuMouchel W, Bahamonde L. A meta-analysis of 16 randomized controlled trials to evaluate computer- based clinical reminder systems for preventive care in the ambulatory setting. J Am Med Inform Assoc. 1996;3(6):399-409.

35. Gómez EJ, Hernando Pérez ME, Vering T, Rigla Cros M, Bott O, García-Sáez G, Pretschner P, Brugués E, Schnell O, Patte C, Bergmann J, Dudde R, de Leiva A. The INCA system: a further step towards a telemedical artificial pancreas. IEEE Trans Inf Technol Biomed. 2008;12(4):470-9.

36. Hovorka R, Chassin LJ, Wilinska ME, Canonico V, Akwi JA, Federici MO, Massi-Benedetti M, Hutzli I, Zaugg C, Kaufmann H, Both M, Vering T, Schaller HC, Schaupp L, Bodenlenz M, Pieber TR. Closing the loop: the adicol experience. Diabetes Technol Ther. 2004;6(3):307-18.

37. Rigla M, Hernando ME, Gómez EJ, Brugués E, García-Sáez G, Torralba V, Prados A, Erdozain L, Vilaverde J, de Leiva A. A telemedicine system that includes a personal assistant improves glycemic control in pump-treated patients with type 1 diabetes. J Diabetes Sci Technol. 2007;1(4):505-10.

38. Rigla M, Hernando ME, Gomez EJ, Brugues E, Garcia-Saez G, Capel I, Pons B, de Leiva A. Real-time continuous glucose monitoring together with telemedical assistance improves glycemic control and glucose stability in pump-treated patients. Diabetes Technol Ther. 2008;10(3):194-9.

39. Buckingham B, Cobry E, Clinton P, Gage V, Caswell K, Kunselman E, Cameron F, Chase HP. Preventing hypoglycemia using predictive alarm algorithms and insulin pump suspension. Diabetes Technol Ther. 2009 1;11(2):93-7.

40. Cengiz E, Swan KL, Tamborlane WV, Steil GM, Steffen AT, Weinzimer SA. Is an automatic pump suspension feature safe for children with type 1 diabetes? An exploratory analysis with a closed-loop system. Diabetes Technol Ther. 2009 1;11(4):207-10.

41. Pérez-Gandía C, Hernando ME, Facchinetti A, Sparacino G, Cobelli C, Gómez EJ. A methodology to compare prediction algorithms from continuous glucose monitoring data. Proceedings of the 2nd Conference on Advanced Technologies & Treatments for Diabetes; 2009 Feb 25; Athens, Greece. p. 202.

42. Kovatchev BP, Clarke WL, Breton M, Brayman K, McCall A. Quantifying temporal glucose variability in diabetes via continuous glucose monitoring: mathematical methods and clinical application. Diabetes Technol Ther. 2005;7(6):849-62.

43. Palerm CC, Zisser H, Bevier WC, Jovanovic L, Doyle FJ 3rd. Prandial insulin dosing using run-to-run control: application of clinical data and medical expertise to define a suitable performance metric. Diabetes Care. 2007;30(5):1131-6.

44. García-Sáez G, Dassau E, Zisser H, Jovanovic L, Hernando ME, Rigla M, Gómez EJ, de Leiva A, Doyle FJ 3rd. Telemedicine system for enhanced glycemic control--a bolus advisory utility based on run-to-run algorithm. Proceedings of the 1st International Conference on Advanced Technologies & Treatments for Diabetes; 2008 Feb 27; Prague, Czech Republic. p. 79.