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(54) **UNIFIED PLATFORM FOR MONITORING AND CONTROL OF BLOOD GLUCOSE LEVELS IN DIABETIC PATIENTS**

VEREINHEITLICHTE PLATTFORM ZUR ÜBERWACHUNG UND STEUERUNG DES BLUTZUCKERSPIEGELS BEI DIABETESPATIENTEN

PLATEFORME UNIFIÉE POUR LA SURVEILLANCE ET LA RÉGULATION DES NIVEAUX DE GLUCOSE DANS LE SANG CHEZ DES PATIENTS DIABÉTIQUES

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Description

BACKGROUND OF THE INVENTION

[0001] Diabetes mellitus (DM), often simply referred to as diabetes, is a group of metabolic diseases characterized by high glucose levels in the blood (i.e. hyperglycemia), either because the body does not produce enough insulin (Type 1 DM or T1DM), or because cells do not respond to the insulin that is produced (Type 2 DM or T2DM). Intensive treatment with insulin and with oral medications to maintain nearly normal levels of glycemia (i.e. euglycemia) markedly reduces chronic complications in both T1DM and T2DM [1,2,3], but may risk symptomatic hypoglycemia and potentially life-threatening severe hypoglycemia. Therefore, hypoglycemia has been identified as the primary barrier to optimal diabetes management [4,5]. People with T1DM and T2DM face a lifelong optimization problem: to maintain strict glycemic control without increasing their risk for hypoglycemia. However, the struggle for close glycemic control could result in large blood glucose (BG) fluctuations over time. This process is influenced by many external factors, including the timing and amount of insulin injected, food eaten, physical activity, etc. In other words, BG fluctuations in diabetes are the measurable result of the interactions of a complex and dynamic biological system, influenced by many internal and external factors.

[0002] The optimization of this system depends largely on self-treatment behavior, which has to be informed by glucose monitoring and has to utilize data and technology available in the field. The currently accessible data sources include self-monitoring of blood glucose (SMBG), continuous glucose monitoring (CGM), as well as assessment of symptoms and self-treatment practices. The available treatments include medication (exclusively for T2DM), multiple daily insulin injections (MDI), and insulin pumps (CSII - continuous subcutaneous insulin injection). Currently, these treatments are at various stages of development and clinical acceptance, with SMBG now a routine practice, CGM rapidly developing, and emerging integrated systems that combine CGM with CSII and pave the way for the artificial pancreas of the near future.

Self-Monitoring of Blood Glucose

[0003] Contemporary home BG meters offer convenient means for frequent and accurate BG determinations through SMBG [6,7]. Most meters are capable of storing BG readings (typically over 150 readings) and have interfaces to download these readings into a computing device such a PC. The meters are usually accompanied by software that has capabilities for basic data analysis (e.g. calculation of mean BG, estimates of the average BG over the previous two weeks, percentages in target, hypoglycemic and hyperglycemic zones, etc.), logging of the data, and graphical representations of the BG data (e.g. histograms, pie charts, etc.). In a series of studies we have shown that specific risk analysis of SMBG data could also capture long-term trends towards increased risk for hypoglycemia [8, 9,10], and could identify 24-hour periods of increased risk for hypoglycemia [11,12]. The basics of the risk analysis are presented below. The methods outlined here have been applied to both SMBG and CGM data.

[0004] Evaluating Risk for Hypoglycemia and Hyperglycemia: These methods are based on the concept of Risk Analysis of BG data [13], and on the recognition of a specific asymmetry of the BG measurement scale that can be corrected by a mathematical data transformation [14]. The risk analysis steps are as follows:

1. Symmetrization of the BG scale: A nonlinear transformation is applied to the BG measurements scale to map the entire BG range (20 to 600 mg/dl, or 1.1 to 33.3 mmol/l) to a symmetric interval. The BG value of 112.5 mg/dl (6.25 mmol/l) is mapped to zero, corresponding to zero risk for hypo- or hyperglycemia. The analytical form of this transformation is $f(BG,\alpha,\beta) = [(\ln(BG))^{\alpha}-\beta]$, $\alpha, \beta > 0$, where the parameters are estimated as $\alpha=1.084$, $\beta=5.381$, $\gamma=1.509$, if BG is measured in mg/dl and $\alpha=1.026$, $\beta=1.861$, $\gamma=1.794$ if BG is measured in mmol/l [14].
2. Assignment of a risk value to each SMBG reading: We define the quadratic risk function $r(BG)=10f(BG)^2$. The function $r(BG)$ ranges from 0 to 100. Its minimum value is achieved at BG=112.5 mg/dl (a safe euglycemic BG reading), while its maximum is reached at the extreme ends of the BG scale. Thus, $r(BG)$ can be interpreted as a measure of the risk associated with a certain BG level. The left branch of this parabola identifies the risk of hypoglycemia, while the right branch identifies the risk of hyperglycemia.
3. Computing measures of risk for hypoglycemia and glucose variability: Let $x_1, x_2, \ldots x_n$ be a series of n BG readings, and let $rl(BG)=r(BG)$ if $f(BG)<0$ and 0 otherwise; $rh(BG)=r(BG)$ if $f(BG)>0$ and 0 otherwise. Then the Low Blood Glucose Index (LBGI) is computed as:

$$LBGI = \frac{1}{n}\sum_{i=1}^{n} rl(x_i)$$

[0005] In other words, the LBGI is a non-negative quantity that increases when the number and/or extent of low BG readings increases. In studies, the LBGI typically accounted for 40-55% of the variance of future significant hypoglycemia in the subsequent 3-6 months [8,9,10], which made it a potent predictor of hypoglycemia based on SMBG. Similarly, we compute the High Blood Glucose Index (HBGI) as follows:

$$HBGI = \frac{1}{n}\sum_{i=1}^{n} rh(x_i)$$

[0006] The HBGI is a non-negative quantity that increases when the number and/or extent of high BG readings increases.

Continuous Glucose Monitoring

[0007] Since the advent of continuous glucose monitoring technology 10 years ago [15,16,17], which initially had limited performance particularly in the hypoglycemic range [18,19], significant progress has been made towards versatile and reliable CGM devices that not only monitor the entire course of BG day and night, but also provide feedback to the patient, such as alarms when BG reaches preset low or high levels. A number of studies have documented the benefits of continuous glucose monitoring [20,21,22,23] and charted guidelines for clinical use and its future as a precursor to closed-loop control [24,25,26,27]. However, while CGM has the potential to revolutionize the control of diabetes, it also generates data streams that are both voluminous and complex. The utilization of such data requires an understanding of the physical, biochemical, and mathematical principles and properties involved in this new technology. It is important to know that CGM devices measure glucose concentration in a different compartment - the interstitium. Interstitial glucose (IG) fluctuations are related to BG presumably via the diffusion process [28,29,30]. To account for the gradient between BG and IG, CGM devices are calibrated with capillary glucose, which brings the typically lower IG concentration to corresponding BG levels. Successful calibration would adjust the amplitude of IG fluctuations with respect to BG, but would not eliminate the possible time lag due to BG-to-IG glucose transport and the sensor processing time (instrument delay). Because such a time lag could greatly influence the accuracy of CGM, a number of studies were dedicated to its investigation, yielding various results [31,32,33,34]. For example, it was hypothesized that if glucose fall is due to peripheral glucose consumption the physiologic time lag would be negative, i.e. fall in IG would precede fall in BG [28,35]. In most studies IG lagged behind BG (most of the time) by 4-10 minutes, regardless of the direction of BG change [30,31]. The formulation of the push-pull phenomenon offered reconciliation of these results and provided arguments for a more complex BG-IG relationship than a simple constant or directional time lag [34,36]. In addition, errors from calibration, loss of sensitivity, and random noise confound CGM data [37]. Nevertheless, the accuracy of CGM is increasing and may be reaching a physiological limit for subcutaneous glucose monitoring [38,39,40].

The Artificial Pancreas

[0008] The next step in the progression of diabetes management is automated glucose control, or the artificial pancreas, which links a continuous glucose monitor with an insulin pump. A key element of this combination is a closed-loop control algorithm or method, which monitors blood glucose fluctuations and the actions of the insulin pump, and recommends insulin delivery at appropriate times.

[0009] The artificial pancreas idea can be traced back to developments that took place over thirty years ago when the possibility for external BG regulation in people with diabetes had been established by studies using intravenous (i.v.) glucose measurement and i.v. infusion of glucose and insulin. Systems such as the Biostator™ have been introduced and used in hospital settings to maintain normoglycemia (or euglycemia) by exerting both positive (via glucose or glucagon) and negative (via insulin) control [51,52,53,54,55]. Detailed descriptions of the major early designs can be found in [56,57,58,59,60,61]. More work followed, spanning a broader range of BG control techniques, powered by physiologic mathematical modeling and computer simulation control [62,63,64,65]. A review of methods for i.v. glucose control can be found in [66]. However, i.v. closed-loop control remains cumbersome and unsuited for outpatient use. An alternative to extracorporeal i.v. control has been presented by implantable intra-peritoneal (i.p.) systems employing intravenous BG sampling and i.p. insulin delivery [67,68]. The implementation of these systems, however, requires considerable surgery. Thus, with the advent of minimally-invasive subcutaneous (s.c.) CGM, increasing academic and industrial effort has been focused on the development of s.c.- s.c. systems, using CGM coupled with an insulin infusion pump and a control algorithm or method [69,70,71,72]. In September 2006, the Juvenile Diabetes Research Foundation (JDRF) initiated the Artificial Pancreas Project and funded a consortium of centers to carry closed-loop control research [73]. So far, encouraging pilot results have been reported by several centers [74,75,76,77,78].

[0010] Thus, in the past 30 years the monitoring and control of BG levels in diabetes has progressed from assessment of average glycemia once in several months, through daily SMBG, to minutely CGM. The increasing temporal resolution of the monitoring technology has enabled increasingly intensive diabetes treatment, from daily insulin injections or oral medication, through insulin pump therapy, to the artificial pancreas of the near future.

[0011] US 2009/006129 describes a diagnosis, therapy and prognosis system (DTPS) to help a healthcare provider or patient in diagnosing, treating and interpreting data. The apparatus provides data collection based on protocols, and a mechanism for testing data integrity and accuracy. The data is then analysed to characterise the patient's metabolic state to provide a diagnosis.

[0012] US 2010/185175 describes a system for at least partial closed-loop control of a medical condition. The system comprises a medical fluid pump and a continuous analyte monitor and controller. The controller includes a processor that controls delivery of the medical fluid based on data received from the continuous analyte monitor.

BRIEF SUMMARY OF THE INVENTION

[0013] As evident from the discussion above, a multitude of methods exist for BG monitoring and control in diabetes, ranging from traditional SMBG, medication, and MDI treatment, to CGM and artificial pancreas. These methods are currently dissimilar and there is no system that can handle more than one monitoring or control method at a time. An aspect of an embodiment of the present invention introduces the first flexible system capable of utilizing data from different monitoring techniques and capable of providing assistance to patients with diabetes at several scalable levels, ranging from advice about long-term trends and prognosis to real-time automated closed-loop control (artificial pancreas). These scalable monitoring and treatment strategies are delivered by a unified system - named by the present inventors as the Diabetes Assistant **(DiAs)** platform - that provides a foundation for implementation of various monitoring, advisory, and automated diabetes treatment algorithms or methods. The DiAs recommendations are tailored to the specifics of an individual patient, and to the patient risk assessment at any given moment. Some nonlimiting and exemplary unique characteristics of DiAs are:

- Informed by a Body Sensor Network;
- Modular - layered architecture distributes data processing tasks across various application modules; individual modules are easily replaceable;
- Scalable - naturally support new and expanded functionality, multiple data sources, and multiple data utilization strategies;
- Portable - DiAs can run easily on portable computing devices, such as a cell phone, tablet computer, portal digital assistant (PDA), etc; thus it is deployable on a wide variety of rugged, inexpensive, and readily available devices;
- Local and Global modes of operation - certain processes and patient interactions are available through the portable device; other services and remote monitoring of subject and system states are available via wireless communications (e.g. 3G, WiFi, etc.).

[0014] According to the invention there are provided an apparatus and a method according to claims 1 and 10. Preferable features of the invention are defined in the dependent claims.

BRIEF SUMMARY OF THE DRAWINGS

[0015]

Figure 1 is a schematic illustration of the DiAs platform inputs and outputs according to an aspect of the invention;
Figure 2 is a schematic illustration of DiAs processes and services according to an aspect of the invention;
Figure 3 is a block diagram of the DiAs system including applications and communication functions according to an embodiment of the invention;
Figure 4 shows an example implementation of the DiAs system on a cell phone platform according to an embodiment of the invention;
Figure 5 is a schematic illustration of an implementation of the DiAs system as a hub for a body sensor network; and
Figure 6 is a schematic block diagram of an example data processing system for implementation of the present invention in whole or in part.

DETAILED DESCRIPTION OF THE INVENTION

Overview

[0016] As shown in Fig. 5, a principal application of the DiAs system is the dynamic aggregation of body sensor network (BSN) data toward the goal of supporting long-term and efficient treatment of diabetes. DiAs is based on a wearable or handheld Diabetes Assistant platform that collects and pre-processes data from each individual's BSN, and uploads summary statistics to a remote location. The interface/algorithmic/methodology framework of DiAs: (i) ensures plug and play functionality with different metabolic sensors, (ii) allows for a general framework for prioritization of sensor data, making it clear how scarce computational, memory, and communication resources will be allocated to various sensing modalities, (iii) manages access to multiple uplink channels of varying reliability to a remote site, and (iv) resolves tradeoffs relating to where heavy computations should be performed (e.g., locally within the DiAs platform or remotely).

DiAs Inputs and Outputs

[0017] Fig. 1 presents the data sources available to the DiAs platform and the output services that DiAs provides. The data sources include SMBG, CGM, insulin delivery data (MDI and CSII), and other BSN data inputs such as heart rate, body accelerometer data, blood pressure, respiration, EKG data, etc. Depending on data availability (intermittent or continuous, blood glucose alone, or a multivariate data stream), DiAs provides different types of services that can be generally classified as:

- Local Services: Applications that run on a portable

device (e.g. a cell phone or tablet computer) communicating with an array of self-SMBG monitoring and CGM devices, an array of insulin delivery devices, and with other sensors in a BSN. The local service of DiAs is equipped with intelligent processing to provide an array of patient services, including safety supervision, local alerts, patient advisory functions, and closed-loop control (described further below);

- Global Services: A centralized server communicating with multiple local services to provide different levels of data processing, advice, and training to patients; enable remote monitoring of glucose control profiles (e.g. parents monitoring remotely their children with diabetes); enable global alerts (e.g. a 911 call with GPS service to pinpoint a patient in need of emergency assistance), and to provide a physician-oriented information service presenting key data for multiple patients at a glance.

DiAs Processes

[0018] The general flow of DiAs processes is presented in Fig. 2 and includes the following steps:

1. Incoming data are directed to a Data Availability Classifier (DAC), which assesses the frequency, dimensionality, and quality of the incoming data. Based on the assessment, the DAC recommends different classes of data processing algorithms for the incoming data. Many of these algorithms already exist and are generally known, and can be classified as follows:

◦ SMBG: This is currently the most established algorithmic class, including methods for the retrieval of SMBG data, evaluation of glycemic control, estimation of the risk for hypoglycemia, and information displays. SMBG acquisition and processing methods are described in several U.S. patents and published patent applications (see references [79-85]). A 5-year clinical trial testing a SMBG-based system in 120 people with T1DM was recently completed, resulting in improved glycemic control, reduction of the risk for severe hypoglycemia, and high patient approval rating (results published in [86]);
◦ CGM: Key elements applicable to these methods have been defined (references [87-92]). These methods are currently under development and testing in a large NIH-funded research project (Grant RO1 DK 085623, Principal Investigator Dr. Boris Kovatchev);
◦ CGM + insulin pump: Most of the methods applicable to CGM alone have extensions capable of dealing with input/output to/from an insulin pump. We have recently completed an extensive series of clinical trials of closed-loop control to date.
◦ Other: Heart rate changes can be used to indicate periods of physical activity, and more specifically periods of increased insulin sensitivity associated with exercise. These data inform diabetes control at several levels, including risk assessment for hypoglycemia and closed-loop control [93,94].

2. The first step of data processing is Patient State Estimation, given available data and using one of the methods described above. The state estimation results in assessment of the patient's risk status, which can be based on the risk analysis metrics presented in the background discussion above, and on biosystem observers or sensors, which process physiologic (and possibly behavioral) data to produce quantitative biosystem state estimators. These algorithms or methods are based on underlying mathematical models of the human metabolism and a Kalman filter, which produces system state estimation. Each system state estimator is a physiological or behavioral parameter of importance to the functioning of a person. The ensemble (vector) of biosystem estimators for a particular person represents the status of this person in terms of the blood glucose trend, availability of insulin, and risk for hypoglycemia. In essence, biosystem observers personalize the metabolic observation to a specific subject and extract composite information from the vast array of raw data that allows the precise evaluation of the subject's condition. It is anticipated that the biosystem observers will reside within a wearable DiAs system, while their summarized output will be sent to both the local predictive and control algorithms or methods and to remote observers as follows:

◦ The primary output from the Patient State Estimation will be assessment of the patient's risk status for hypo- or hyperglycemia, based on the risk analysis and the LBGI/HBGI presented above. If the data quality and density is adequate for the risk status of the patient (e.g. the patient is in a steady state performing regular SMBG resulting in LBGI and HBGI lower than certain preset thresholds), then DiAs refers the data to algorithms that maintain the current patient status or fine-tune the patient's glycemic control. These algorithms can work in either an advisory or automated (closed-loop control) mode as follows:

◦ In advisory mode, DiAs activates the following services modules:

□ Advisory Module 1: Prediction of elevated risk for hypoglycemia (24 hours ahead);

☐ Advisory Module 2: Bolus calculator suggesting pre-meal insulin doses;
☐ Advisory Module 3: Suggestion of basal rate profiles for the next 24 hours.

◦ In closed-loop control mode, DiAs activates the following service modules:

☐ Control Module 1: Real-time detection and prevention of hypoglycemia;
☐ Control Module 2: Stochastic control of pre-meal insulin boluses, and
☐ Control Module 3: Deterministic control of basal rate and overnight steady state.

◦ If the data quality and density is inadequate for the risk status of the patient (e.g. the patient is at high risk for hypoglycemia, hyperglycemia, or both as indicated by the LBGI and HBGI exceeding certain preset thresholds), then:

◦ In advisory mode, DiAs recommends enhanced monitoring (e.g. more frequent SMBG or switching to CGM for a certain period of time);
◦ In automated control mode, DiAs switches the monitoring device to higher frequency SMBG measurement or to CGM mode (Note: such flexible monitoring devices are not currently manufactured, but are anticipated to be available in the future).

[0019] Fig. 3 presents a detailed schematic of the DiAs architecture:

◦ Central to this architecture is the Biometric State Estimator, which is the hub for exchange of data between the DiAs monitoring devices and algorithmic services or related methods. The Biometric State Estimator may also exchange data with remote physicians and/or patient care centers over the Internet through a network interface;
◦ The inputs used for state estimation are provided by various peripheral devices that monitor blood glucose fluctuations (SMBG Service, CGM Service), execute insulin delivery (Pump Service), or monitor other physiological parameters (Heart Rate Service, Esc. Service) as shown in Fig. 3;
◦ In turn, the Biometric State Estimator provides feedback to these devices as determined by a Safety Service, which assesses the integrity of the received data and judges whether the peripheral input/output devices are functioning properly. Methods employed by the Safety Service include previously introduced detection of CGM sensor errors [91] or judging the safety of insulin delivery [92];
◦ DiAs Applications may include various advisory and/or control algorithms, system and patient state alarms and indicators. These applications may be external to the DiAs system, and may be developed by third parties. Such applications may use DiAs services provided that they comply with the data exchange standards of the system. For example, a Hyperglycemia Mitigation Service (HMS) is a closed-loop control algorithm or method included in one of the embodiments of DiAs;

[0020] The user interface with the DiAs system can be custom designed to meet the needs of specific DiAs implementations. One such implementation of a user interface is shown in Fig. 4:

☐Two "traffic lights" signify the patient's present risk status for hypoglycemia and hyperglycemia, respectively, indicating low risk (green light), moderate risk/system action to mitigate the risk (yellow light) and high risk/necessity for immediate human intervention (red light);
☐ Several system/patient status inquiry icons open additional interfaces allowing the patient to access graphical and numerical representation of his/her glucose control, or inform the system of events (such as carbohydrate intake or exercise), which are treated as additional inputs by the DiAs analytical system;
◦ Network service (described in the next section) ensures remote monitoring and transmission of alerts and critical information in high-risk states.

Implementation of DiAs

[0021] Fig. 5 shows two major components of a DiAs implementation as a Body Sensor Network:

◦ Local Services (within the wearable/portable DiAs device) use predictive and control algorithms or methods based on simplified models of the human metabolic system that are trackable in real time. These are simple, typically linearized macro-level models that focus only on the principal system components. One example of such a model is the classic Minimal Model of Glucose Kinetics developed 30 years ago [95]. Available algorithms or methods include assessment, prediction, and control of glucose fluctuations in diabetes:

☐ Risk analysis of metabolic state with respect to normative limits;
☐ Detection of abrupt system changes, i.e. transitions of the system (person) from a stable to a critical state;
☐ Prediction of trends and gradual system changes, and outcome evaluation;
☐ Estimation of the probability for abrupt critical transitions;
☐ Warnings, alarms, and advisory messages

when critical thresholds are approached;
☐ Automated intervention to prevent critical events;
☐ Communication to remote location and global algorithms or methods.

As shown in Fig. 5, a portable DiAs device (such as shown in Fig. 4) is communicatively connected (e.g. wirelessly through a wireless communication protocol such as Bluetooth, IEEE 802.11, etc.) to a plurality of BSN sensors, such as an ICP sensor, ECG sensor, blood pressure sensor, pulse oximetry sensor, inertial sensor, EMG sensor, artificial pancreas sensor, etc. Additionally, the DiAs device may have an interface to accept SMBG data.

◦ Global services rely on predictive and control algorithms or methods deployed at a central location and receiving information from an array of individual system observers. These algorithms or methods will be based on large-scale probability models, risk analysis, clustering, and discriminant algorithms or methods. The output of these algorithms or methods will allow:

☐ The monitoring of vital signs and metabolic processes by health care providers;
☐ The detection of critical cases that require immediate intervention;
☐ Collection of population-level anonymous public health statistics of interest to health care organizations.

◦ Software/Hardware Implementation: Central to DiAs is a scalable software stack with a modular design that can be efficiently adapted to a variety of hardware platforms. The software architecture, the availability of suitable hardware platforms and opportunities to transfer software modules to commercial partners will factor into the choice of DiAs operating systems. For clinical trials and ambulatory implementation, hardware is needed that is portable, rugged, reliable, inexpensive and easily available. In this regard, a cell phone or a tablet computer could be selected. Consequently, the DiAs system may run within a customized version of the Android operating system. Android has a robust development environment, is available with source code, is backed by Google and runs on an ever-increasing array of cell phones and tablets from a variety of manufacturers. Android is being adopted by many commercial developers for new embedded software projects. Although many current products with embedded control software either have no operating system at all or use a simple control loop the trend is towards basing new embedded software projects on Android and embedded Linux. Since Android is built on top of Linux, an Android-based operating system for DiAs would allow transfer of software code to industry partners for commercial use. Android also provides a rich software development kit that supports multi-touch graphical user interface design, data communications, geo-location and telephony. Specifically:

☐ At the highest level the AAPP Software Stack is composed of three major functional blocks: Device I/O Services, Core Services, and Control. As described above, Fig. 3 presents a diagram of the software stack depicting these blocks.
☐ Device I/O Services handles all communication with sensors, pumps and other devices and provides a data interface to other elements of the system. The Device I/O modules store SMBG, CGM, and delivered insulin data and provide it to other components upon request.
☐ Device I/O modules also implement a sensor and pump command service that validates and delivers commands received from the Safety Service.
☐ Core Services is responsible for providing a runtime environment for applications such as the Closed-Loop Control App or the User Advice App and for supervising their operation. It generates state estimates based upon available data and provides this data to applications upon request.
☐ Safety Service screens insulin bolus commands for safety before delivering them to the pump module and monitors the functioning of I/O devices detecting errors and potentially unsafe deviations.

[0022] While a preferred operating system has been discussed above, it will be recognized by those skilled in the art that the DiAs system may be implemented using any operating system that has features necessary to implement the DiAs system as contemplated above.

[0023] Turning now to Fig. 6, a functional block diagram is shown for a computer system **600** for exemplary implementation of an embodiment or portion of an embodiment of the present invention. For example, a method or system of an embodiment of the present invention may be implemented using hardware, software or a combination thereof and may be implemented in one or more computer systems or other processing systems, such as personal digit assistants (PDAs) equipped with adequate memory and processing capabilities. In an example embodiment, the invention was implemented in software running on a general purpose computer **600** as illustrated in **Figure 6.** The computer system **600** may includes one or more processors, such as processor **604.** The Processor **604** is connected to a communication infrastructure **606** (e.g., a communications bus, cross-over bar, or network). The computer system **600** may include a display interface **602** that forwards graphics, text, and/or other

data from the communication infrastructure **606** (or from a frame buffer not shown) for display on the display unit **630.** Display unit **630** may be digital and/or analog.

[0024] The computer system **600** may also include a main memory **608,** preferably random access memory (RAM), and may also include a secondary memory **610.** The secondary memory **610** may include, for example, a hard disk drive **612** and/or a removable storage drive **614,** representing a floppy disk drive, a magnetic tape drive, an optical disk drive, a flash memory, etc. The removable storage drive **614** reads from and/or writes to a removable storage unit **618** in a well known manner. Removable storage unit **618,** represents a floppy disk, magnetic tape, optical disk, etc. which is read by and written to by removable storage drive **614.** As will be appreciated, the removable storage unit **618** includes a computer usable storage medium having stored therein computer software and/or data.

[0025] In alternative embodiments, secondary memory **610** may include other means for allowing computer programs or other instructions to be loaded into computer system **600.** Such means may include, for example, a removable storage unit **622** and an interface **620.** Examples of such removable storage units/interfaces include a program cartridge and cartridge interface (such as that found in video game devices), a removable memory chip (such as a ROM, PROM, EPROM or EEPROM) and associated socket, and other removable storage units **622** and interfaces **620** which allow software and data to be transferred from the removable storage unit **622** to computer system **600.**

[0026] The computer system **600** may also include a communications interface **624.** Communications interface **124** allows software and data to be transferred between computer system **600** and external devices. Examples of communications interface **624** may include a modem, a network interface (such as an Ethernet card), a communications port (e.g., serial or parallel, etc.), a PCMCIA slot and card, a modem, etc. Software and data transferred via communications interface **624** are in the form of signals **628** which may be electronic, electromagnetic, optical or other signals capable of being received by communications interface **624.** Signals **628** are provided to communications interface **624** via a communications path (i.e., channel) **626.** Channel **626** (or any other communication means or channel disclosed herein) carries signals **628** and may be implemented using wire or cable, fiber optics, blue tooth, a phone line, a cellular phone link, an RF link, an infrared link, wireless link or connection and other communications channels.

[0027] In this document, the terms "computer program medium" and "computer usable medium" are used to generally refer to media or medium such as various software, firmware, disks, drives, removable storage drive **614,** a hard disk installed in hard disk drive **612,** and signals **628.** These computer program products ("computer program medium" and "computer usable medium") are means for providing software to computer system **600.** The computer program product may comprise a computer useable medium having computer program logic thereon. The invention includes such computer program products. The "computer program product" and "computer useable medium" may be any computer readable medium having computer logic thereon.

[0028] Computer programs (also called computer control logic or computer program logic) are may be stored in main memory **608** and/or secondary memory **610.** Computer programs may also be received via communications interface **624.** Such computer programs, when executed, enable computer system **600** to perform the features of the present invention as discussed herein. In particular, the computer programs, when executed, enable processor **604** to perform the functions of the present invention. Accordingly, such computer programs represent controllers of computer system **600.**

[0029] In an embodiment where the invention is implemented using software, the software may be stored in a computer program product and loaded into computer system **600** using removable storage drive **614,** hard drive **612** or communications interface **624.** The control logic (software or computer program logic), when executed by the processor **604,** causes the processor **604** to perform the functions of the invention as described herein.

[0030] In another embodiment, the invention is implemented primarily in hardware using, for example, hardware components such as application specific integrated circuits (ASICs). Implementation of the hardware state machine to perform the functions described herein will be apparent to persons skilled in the relevant art(s).

[0031] In yet another embodiment, the invention is implemented using a combination of both hardware and software.

[0032] In an example software embodiment of the invention, the methods described above may be implemented in SPSS control language or C + + programming language, but could be implemented in other various programs, computer simulation and computer-aided design, computer simulation environment, MATLAB, or any other software platform or program, windows interface or operating system (or other operating system) or other programs known or available to those skilled in the art.

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[0034] The devices, systems, computer program products, and methods of various embodiments of the invention disclosed herein may utilize aspects disclosed in the following references, applications, publications and patents:

A. International Patent Application Serial No. PCT/US2011/029793, Kovatchev et al., entitled Method, System, and Computer Program Product for Improving the Accuracy of Glucose Sensors Using Insulin Delivery Observation in Diabetes," filed March 24, 2011
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LL. International Patent Application Publication No. WO 2004/052204 A1, Kim, Kwan-Ho, Blood Glucose Monitoring System, June 24, 2004; International Patent Application Serial No. PCT/KR2003/000398, filed February 28, 2003.

Claims

1. A system for managing glycemic control of a patient, comprising:

   an input module configured to accept input data from one or more of a plurality of diverse blood glucose measurement devices and one or more of a plurality of diverse insulin delivery devices;
   a data classifier module configured to assess the frequency, dimensionality and quality of data accepted by said input module to classify said input data and to determine appropriate processing of said input data according to its classification;
   a patient state estimation module configured to process input data in accordance with at least one data processing algorithm corresponding to the classification of the input data as determined by the data classifier module;
   a patient risk status module configured to determine a level of risk of said patient with respect to abnormal glycemic states using processed data from said patient state estimation module; and
   an output module configured to output advisory messages, patient alerts, and control signals for said blood glucose measurement devices and said insulin delivery devices based on the level of risk determined by said patient risk status module.

2. A system as set forth in claim 1, wherein said input data is classified as one of SMBG data, SMBG plus insulin pump data, CGM data, or CGM plus insulin pump data.

3. A system as set forth in claim 1, wherein said input module is further configured to receive data from at least one of a heart rate sensor, a blood pressure sensor, an accelerometer sensor, and a ECG/EKG sensor.

4. A system as set forth in claim 1, wherein said input module is further configured to receive data from a plurality of different physiological sensors for said patient, said plurality of sensors forming a body sensor network.

5. A system as set forth in claim 1, further comprising a telecommunications module configured to communicate patient status data to at least one of a remote

health care provider, an emergency responder, and a public health care organization.

6. A system as set forth in claim 1 wherein said diverse insulin delivery devices comprise a multiple daily insulin injection pump and a continuous subcutaneous insulin injection pump, the system further comprising a safety service module configured to analyze data from at least one of said insulin injection pumps and to determine an operational state of said pump from said data analysis.

7. A system as set forth in claim 6, wherein said safety service module is further configured to screen insulin bolus commands for safety prior to said commands being delivered to an insulin injection pump.

8. A system as set forth in claim 1, wherein said control signals are configured to cause monitoring of said patient to be modified from a current level of monitoring to a higher level of monitoring in dependence on a determined risk status of said patient and a determination of data quality and/or density.

9. A system as set forth in claim 1, wherein said control signals are configured to carry out closed-loop control of insulin delivery to said patient in dependence on a determined risk status of said patient.

10. A method for managing glycemic control of a patient, comprising:

accepting at an input module input data from one or more of a plurality of diverse blood glucose measurement devices and one or more of a plurality of diverse insulin delivery devices;
assessing the frequency, dimensionality and quality of data accepted by said input module to classify said input data and to determine appropriate processing of said input data according to its classification;
processing input data in accordance with at least one data processing algorithm corresponding to the classification of the input data as determined by the data classifier module;
determining a level of risk of said patient with respect to abnormal glycemic states using processed data from said patient state estimation module; and
outputting from an output module advisory messages and patient alerts based on the level of risk determined by said patient risk status module.

11. A method as set forth in claim 10, further comprising receiving data from at least one of a heart rate sensor, a blood pressure sensor, an accelerometer sensor, and an ECG/EKG sensor.

12. A method as set forth in claim 10, further comprising receiving data from a plurality of different physiological sensors for said patient, said plurality of sensors forming a body sensor network.

13. A method as set forth in claim 10, further comprising communicating patient status data to at least one of a remote health care provider, an emergency responder, and a public health care organization over a telecommunications network.

14. A method as set forth in claim 10 wherein said diverse insulin delivery devices comprise a multiple daily insulin injection pump and a continuous subcutaneous insulin injection pump, further comprising analyzing data from at least one of said insulin injection pumps and determining an operational state of said pump from said data analysis.

15. A method as set forth in claim 10, wherein the method further comprises outputting control signals causing monitoring of said patient to be modified from a current level of monitoring to a higher level of monitoring in dependence on a determined risk status of said patient and a determination of data quality and/or density.

Patentansprüche

1. System zur Steuerung der Blutzuckerkontrolle eines Patienten, umfassend:

Eingabemodul, das konfiguriert ist, Eingabedaten von einer oder mehreren einer Vielzahl von verschiedenen Blutzuckermessvorrichtungen und einer oder mehreren einer Vielzahl von verschiedenen Insulinabgabevorrichtungen zu akzeptieren;
Datenklassifizierermodul, das konfiguriert ist, die Häufigkeit, Dimensionalität und Qualität von Daten zu bewerten, die von dem Eingabemodul akzeptiert werden, um die Eingabedaten zu klassifizieren und um eine geeignete Verarbeitung der Eingabedaten gemäß ihrer Klassifizierung zu bestimmen;
Patientenzustandsschätzmodul, das konfiguriert ist, Eingabedaten in Übereinstimmung mit mindestens einem Datenverarbeitungsalgorithmus entsprechend der Klassifizierung der Eingabedaten, wie durch das Datenklassifiziermodul bestimmt, zu verarbeiten;
Patientenrisikozustandsmodul, das zum Bestimmen eines Risikozustands des Patienten in Bezug auf anormale Blutzuckerzustände unter Verwendung verarbeiteter Daten von dem Patientenzustandsschätzungsmodul konfiguriert ist; und

Ausgabemodul, das konfiguriert ist, ratschlaggebende Mitteilungen, Patientenalarme und Steuersignale für die Blutzuckermessvorrichtungen und die Insulinzuführungsvorrichtungen basierend auf dem Risikoniveau, das von dem Patientenrisikozustandsmodul bestimmt wird, auszugeben.

2. System nach Anspruch 1, wobei die Eingabedaten von einem von SMBG-Daten, SMBG plus-Insulinpumpendaten, CGM-Daten oder CGM plus-Insulinpumpendaten klassifiziert werden.

3. System nach Anspruch 1, wobei das Eingabemodul ferner konfiguriert ist, Daten von mindestens einem von einem Herzfrequenzsensor, einem Blutdrucksensor, einem Beschleunigungsmess-Sensor und einem ECG/EKG-Sensor zu empfangen.

4. System nach Anspruch 1, wobei das Eingabemodul ferner konfiguriert ist, Daten von einer Vielzahl von verschiedenen physiologischen Sensoren des Patienten zu empfangen, wobei die Vielzahl von Sensoren ein Körpersensornetzwerk bildet.

5. System nach Anspruch 1, ferner umfassend ein Telekommunikationsmodul, das konfiguriert ist, Patientenzustandsdaten an mindestens einen von einem entfernten Gesundheitsdienstleister, einem Notfallhelfer und einer öffentlichen Gesundheitsdienstleistungsorganisation zu übermitteln.

6. System nach Anspruch 1, wobei die verschiedenen Insulinabgabevorrichtungen eine Insulineinspritzpumpe für mehrfache tägliche Abgaben und eine subkutane Insulineinspritzpumpe für kontinuierliche Abgaben umfassen, wobei das System ferner ein Sicherheitsservicemodul umfasst, das zum Analysieren von Daten von mindestens einer der Insulineinspritzpumpen konfiguriert ist und um aus der Datenanalyse einen Betriebszustand der Pumpe zu bestimmen.

7. System nach Anspruch 6, wobei das Sicherheitsservicemodul ferner konfiguriert ist, Insulinbolusbefehle aus Sicherheitsgründen zu überprüfen, bevor die Befehle an eine Insulineinspritzpumpe abgegeben werden.

8. System nach Anspruch 1, wobei die Steuersignale konfiguriert sind, zu bewirken, dass die Überwachung des Patienten von einem aktuellen Überwachungsniveau auf ein höheres Überwachungsniveau, in Abhängigkeit von einem bestimmten Risikozustand des Patienten und einer Bestimmung der Datenqualität und/oder Dichte, geändert wird.

9. System nach Anspruch 1, wobei die Steuersignale konfiguriert sind, eine Regelung der Insulinabgabe an den Patienten mit Rückkopplung, in Abhängigkeit von einem bestimmten Risikozustand des Patienten, durchzuführen.

10. Verfahren zur Steuerung der Blutzuckerkontrolle eines Patienten, umfassend:

Akzeptieren von Eingabedaten von einer oder mehreren einer Vielzahl von verschiedenen Blutzuckermessvorrichtungen und einer oder mehreren einer Vielzahl von verschiedenen Insulinabgabevorrichtungen an einem Eingabemodul;
Bewerten der Häufigkeit, Dimensionalität und Qualität von Daten, die von dem Eingabemodul akzeptiert werden, um die Eingabedaten zu klassifizieren und um eine geeignete Verarbeitung der Eingabedaten entsprechend ihrer Klassifizierung zu bestimmen;
Verarbeiten von Eingabedaten in Übereinstimmung mit mindestens einem Datenverarbeitungsalgorithmus entsprechend der Klassifizierung der Eingabedaten, wie diese durch das Datenklassifizierermodul bestimmt werden;
Bestimmen eines Risikoniveaus des Patienten in Bezug auf anomale Blutzuckerzustände unter Verwendung verarbeiteter Daten von dem Patientenzustandsschätzungsmodul; und
Ausgeben von ratschlaggebenden Mitteilungen und Patientenalarmen von einem Ausgabemodul basierend auf dem Risikoniveau, das durch das Patientenrisikozustandsmodul bestimmt wird.

11. Verfahren nach Anspruch 10, ferner umfassend das Empfangen von Daten von mindestens einem von einem Herzfrequenzsensor, einem Blutdrucksensor, einem Beschleunigungsmess-Sensor und einem ECG/EKG-Sensor.

12. Verfahren nach Anspruch 10, ferner umfassend das Empfangen von Daten von einer Vielzahl von verschiedenen physiologischen Sensoren für Patienten, wobei die Vielzahl von Sensoren ein Körpersensornetzwerk bildet.

13. Verfahren nach Anspruch 10, ferner umfassend das Übermitteln von Patientenzustandsdaten an mindestens einen von einem entfernten Gesundheitsdienstleister, einem Notfallhelfer und einer öffentlichen Gesundheitsdienstleistungsorganisation über ein Telekommunikationsnetzwerk.

14. Verfahren nach Anspruch 10, wobei die verschiedenen Insulinabgabevorrichtungen eine Insulineinspritzpumpe für mehrfache tägliche Abgaben und eine subkutane Insulineinspritzpumpe für kontinuier-

liche Abgaben umfassen, ferner umfassend das Analysieren von Daten von mindestens einer der Insulineinspritzpumpen und das Bestimmen eines Betriebszustands der Pumpe aus besagter Datenanalyse.

15. Verfahren nach Anspruch 10, wobei das Verfahren ferner das Ausgeben von Kontrollsignalen zum Veranlassen der Änderung der Überwachung des Patienten von einem aktuellen Überwachungsniveau auf ein höheres Überwachungsniveau, in Abhängigkeit von einem bestimmten Risikozustand des Patienten und einer Bestimmung der Datenqualität und/oder Dichte, umfasst.

Revendications

1. Système pour la gestion du contrôle glycémique d'un patient, comprenant :

un module d'entrée configuré pour accepter des données d'entrée depuis un ou plusieurs parmi une pluralité de différents dispositifs pour la mesure de glycémie et un ou plusieurs parmi une pluralité de différents dispositifs d'administration d'insuline ;
un module classificateur de données configuré pour l'évaluation de la fréquence, de la dimensionnalité et de la qualité de données acceptées par ledit module d'entrée pour classifier lesdites données d'entrée et pour déterminer un traitement adéquat desdites données d'entrée selon leur classification ;
un module d'estimation d'état du patient configuré pour traiter des données d'entrée selon au moins un algorithme de traitement de données correspondant à la classification des données d'entrée telle que déterminée par le module classificateur de données ;
un module du statut de risque pour le patient configuré pour déterminer un niveau de risque dudit patient par rapport aux états anormaux de glycémie à l'aide de données traitées dudit module d'estimation d'état du patient ; et
un module de sortie configuré pour émettre des messages consultatifs, des alertes pour les patients et des signaux de commande pour lesdits dispositifs de mesure de glycémie et pour lesdits dispositifs d'administration d'insuline sur base du niveau de risque déterminé par ledit module du statut de risque pour le patient.

2. Système selon la revendication 1, dans lequel lesdites données d'entrée sont classifiées selon un groupe de données parmi les données SMBG, les données SMBG et de la pompe à insuline, les données de CGM, ou les données de CGM et de la pompe à insuline.

3. Système selon la revendication 1, dans lequel ledit module d'entrée est en outre configuré pour recevoir des données d'au moins un parmi un capteur du rythme cardiaque, un capteur de pression sanguine, un capteur accélérométrique et un capteur ECG/EKG.

4. Système selon la revendication 1, dans lequel ledit module d'entrée est en outre configuré pour recevoir des données depuis une pluralité de différents capteurs physiologiques pour ledit patient, ladite pluralité de capteurs formant un réseau de capteurs corporels.

5. Système selon la revendication 1, comprenant en outre un module de télécommunications configuré pour communiquer les données d'état du patient à au moins un parmi un fournisseur à distance de soins de santé, un répondeur d'urgence et une organisation publique de soins de santé.

6. Système selon la revendication 1, dans lequel lesdits différents dispositifs d'administration d'insuline comprennent une pompe à injection d'insuline multiple quotidienne et une pompe à injection d'insuline sous-cutanée continue, le système comprenant en outre un module de service de sécurité configuré pour analyser des données d'au moins un parmi lesdites pompes à injection d'insuline et pour déterminer un état fonctionnel de ladite pompe à partir de ladite analyse de données.

7. Système selon la revendication 6, dans lequel ledit module de service de sécurité est en outre configuré pour contrôler des commandes du bolus d'insuline pour des raisons de sécurité avant que lesdites commandes soient transmises à une pompe à injection d'insuline.

8. Système selon la revendication 1, dans lequel lesdits signaux de commande sont configurés pour provoquer la modification de la surveillance dudit patient d'un niveau actuel de surveillance à un niveau supérieur de surveillance en fonction d'un état déterminé de risque dudit patient et une détermination des densité et/ou qualité des données.

9. Système selon la revendication 1, dans lequel lesdits signaux de commande sont configurés pour exécuter une commande en circuit fermé d'administration d'insuline audit patient en fonction d'un état déterminé de risque dudit patient.

10. Procédé pour la gestion du contrôle glycémique d'un patient, comprenant :

l'acceptation au niveau d'un module d'entrée,

de données d'entrée depuis un ou plusieurs parmi une pluralité de différents dispositifs pour la mesure de glycémie et un ou plusieurs d'une pluralité de différents dispositifs d'administration d'insuline ;
l'évaluation de la fréquence, de la dimensionnalité et de la qualité de données acceptées par ledit module d'entrée pour classifier lesdites données d'entrée et pour déterminer le traitement adéquat desdites données d'entrée selon leur classification ;
le traitement de données d'entrée selon au moins un algorithme de traitement de données correspondant à la classification des données d'entrée telle que déterminée par le module classificateur de données ;
la détermination d'un niveau de risque dudit patient par rapport aux états anormaux de glycémie à l'aide de données traitées dudit module d'estimation d'état du patient ; et
l'émission à partir de messages consultatifs du module de sortie et d'alertes pour les patients sur base du niveau de risque déterminé par ledit module du statut de risque pour le patient.

11. Procédé selon la revendication 10, comprenant en outre la réception de données d'au moins un parmi un capteur du rythme cardiaque, un capteur de pression sanguine, un capteur accélérométrique et un capteur ECG/EKG.

12. Procédé selon la revendication 10, comprenant en outre la réception de données depuis une pluralité de différents capteurs physiologiques pour ledit patient, ladite pluralité de capteurs formant un réseau de capteurs corporels.

13. Procédé selon la revendication 10, comprenant en outre la communication de données d'état du patient à au moins un parmi un fournisseur à distance de soins de santé, un répondeur d'urgence et une organisation publique de soins de santé sur un réseau de télécommunications.

14. Procédé selon la revendication 10, dans lequel lesdits différents dispositifs d'administration d'insuline comprennent une pompe à injection d'insuline multiple quotidienne et une pompe à injection d'insuline sous-cutanée continue, comprenant en outre l'analyse de données d'au moins un parmi lesdites pompes à injection d'insuline et la détermination d'un état fonctionnel de ladite pompe à partir de ladite analyse de données.

15. Procédé selon la revendication 10, dans lequel le procédé comprend en outre l'émission de signaux de commande provoquant la modification de la surveillance dudit patient d'un niveau actuel de surveillance à un niveau supérieur de surveillance en fonction d'un état déterminé de risque dudit patient et une détermination des densité et/ou qualité des données.

Figure 1: DiAs Inputs and Outputs

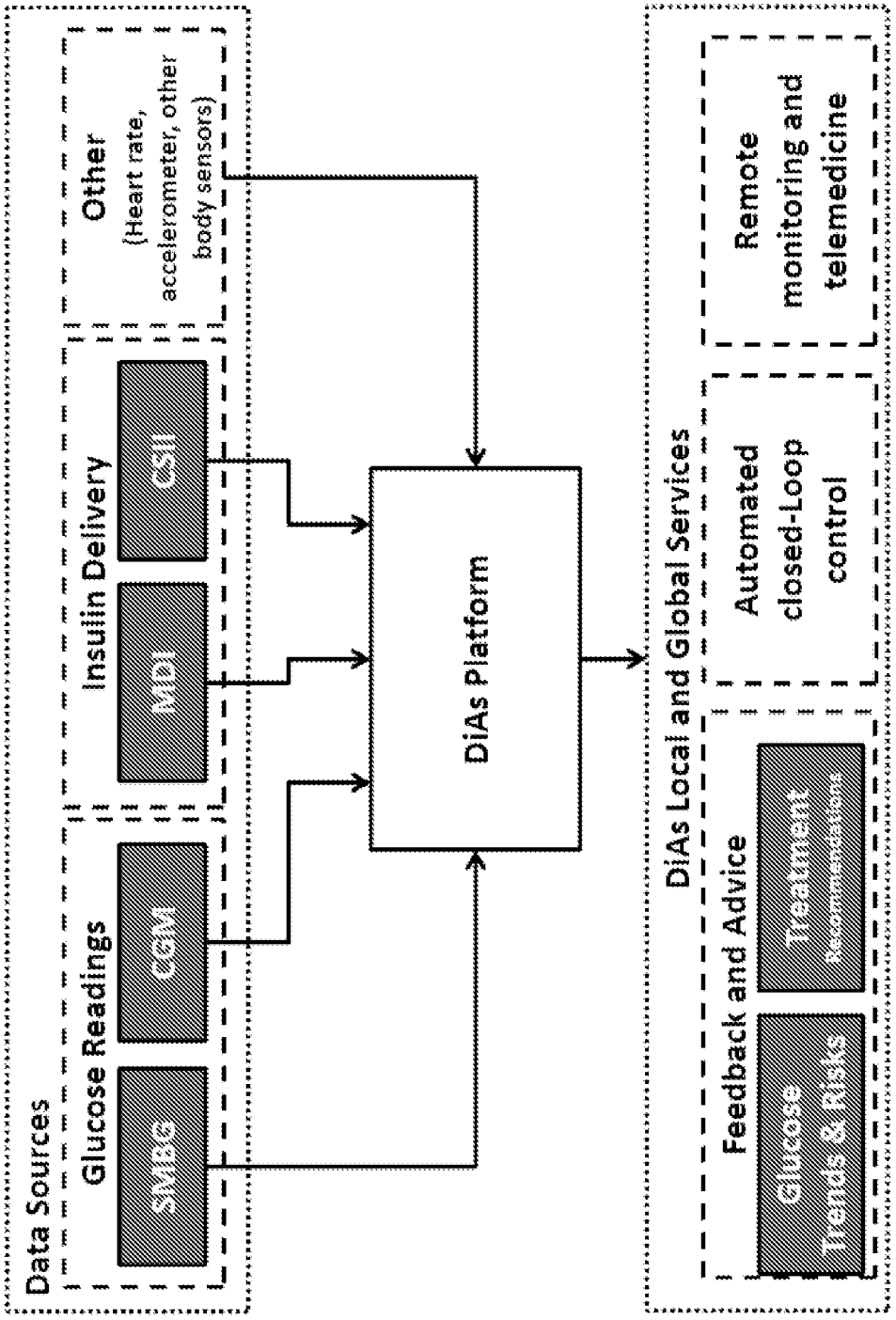


Figure 2: DiAs Processes and Services

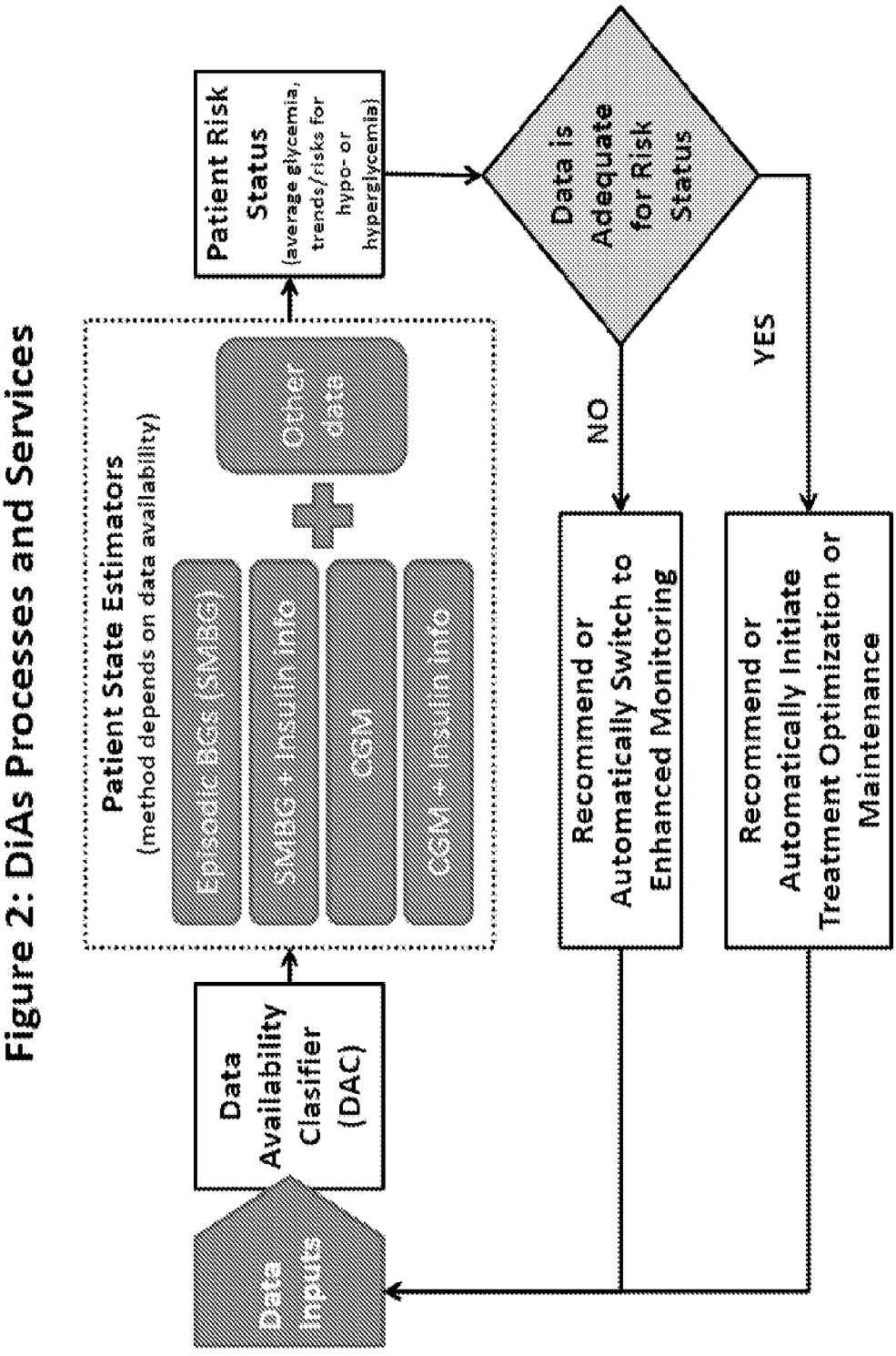
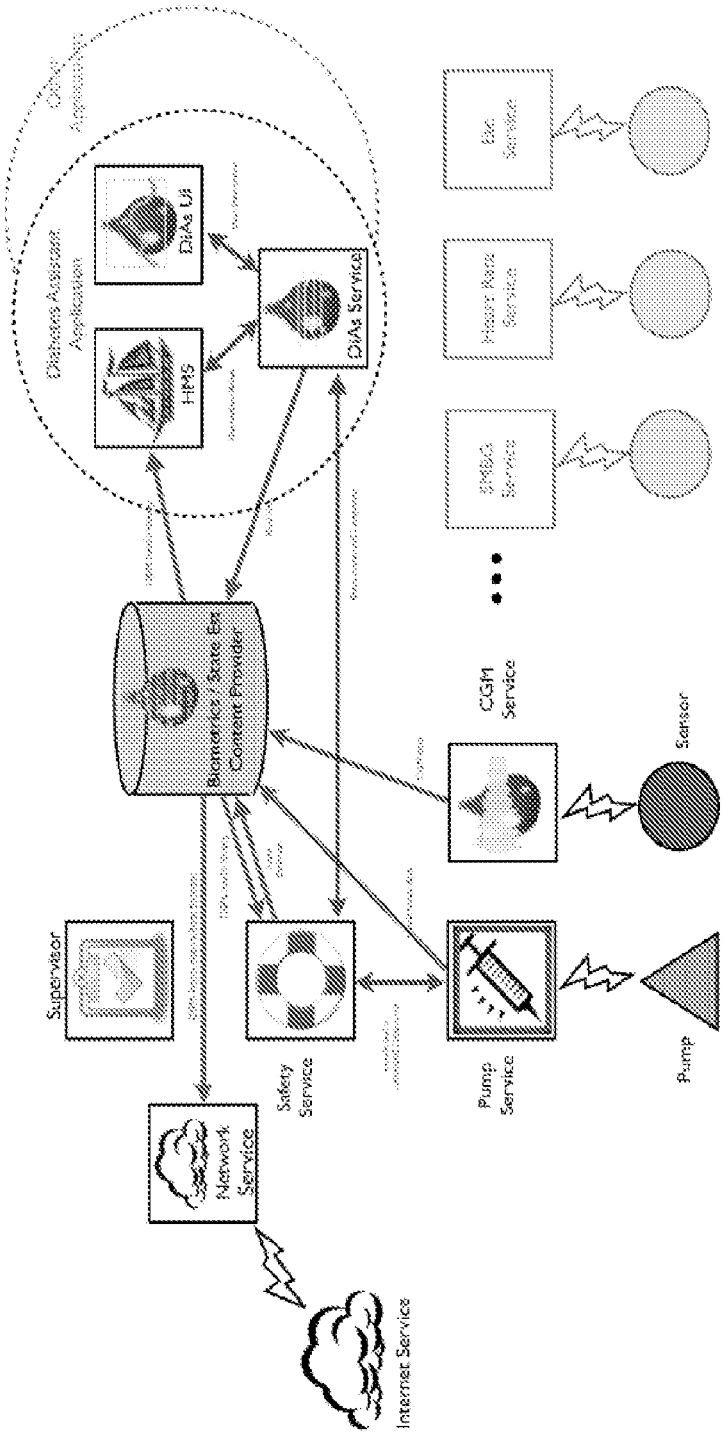


Figure 3: Detailed DiAs Block Diagram



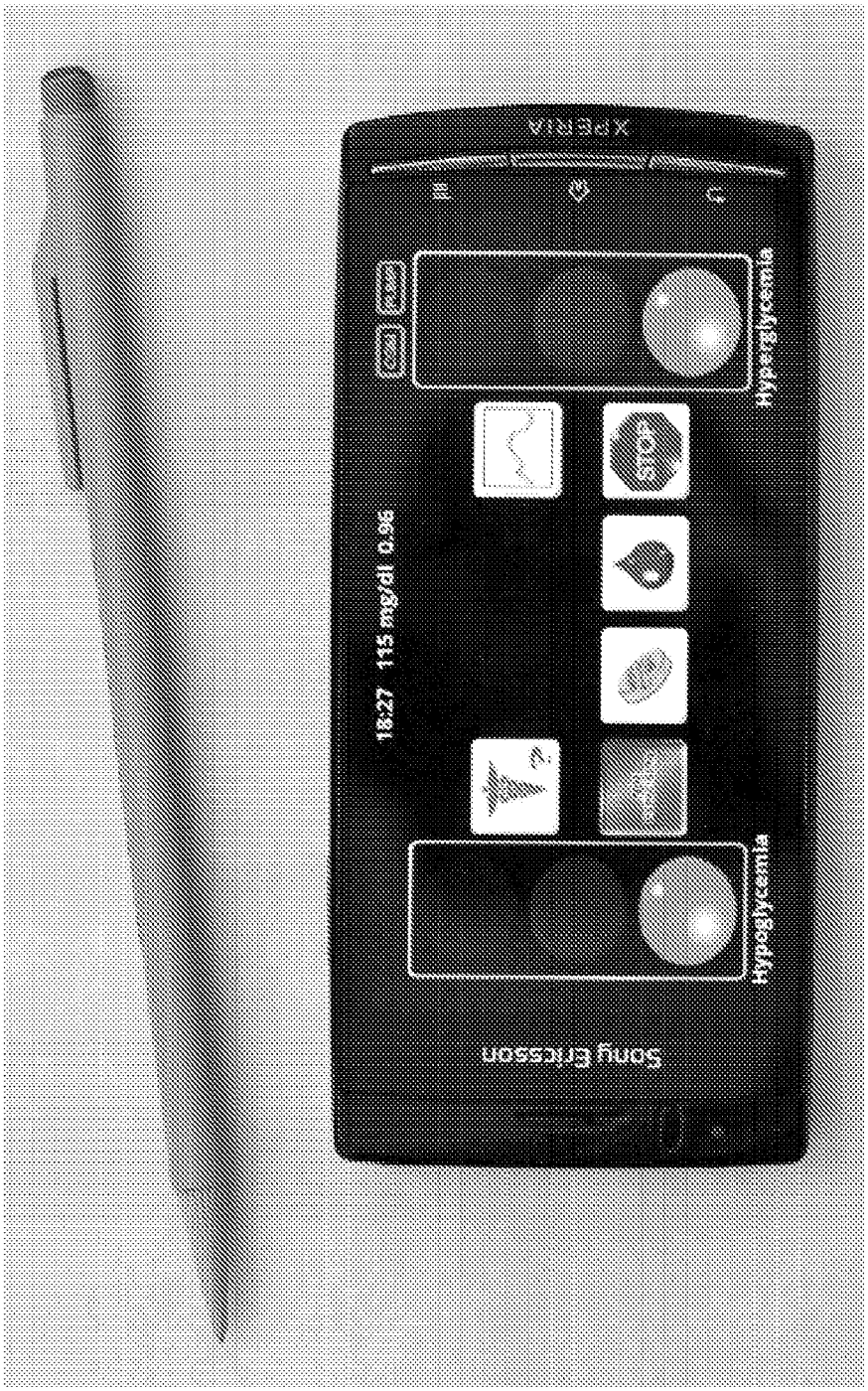
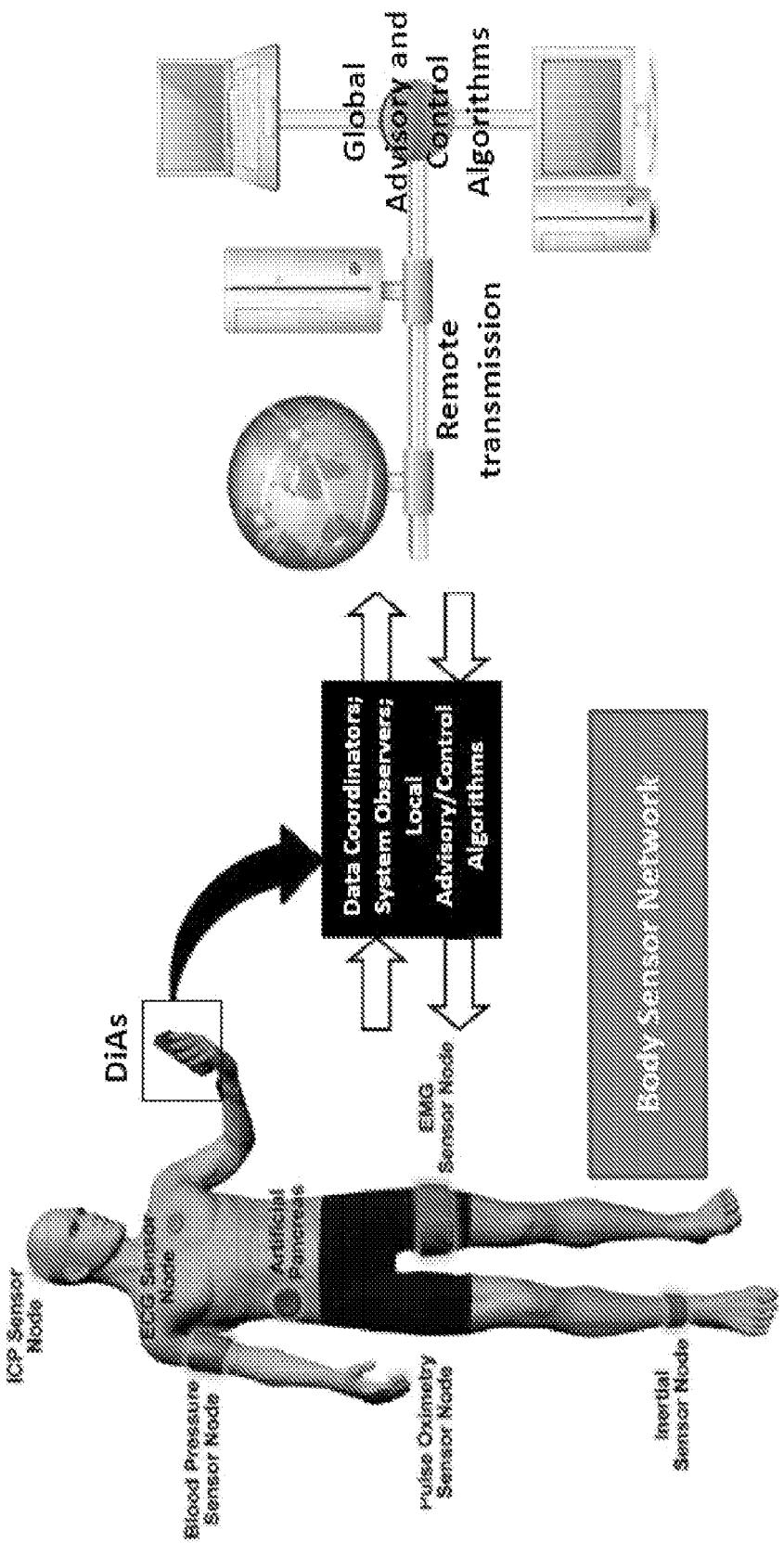


Figure 4: Implementation of DiAs on a Cell Phone Platform

Figure 5: Implementation of DiAs - Hub for Body Sensor Network



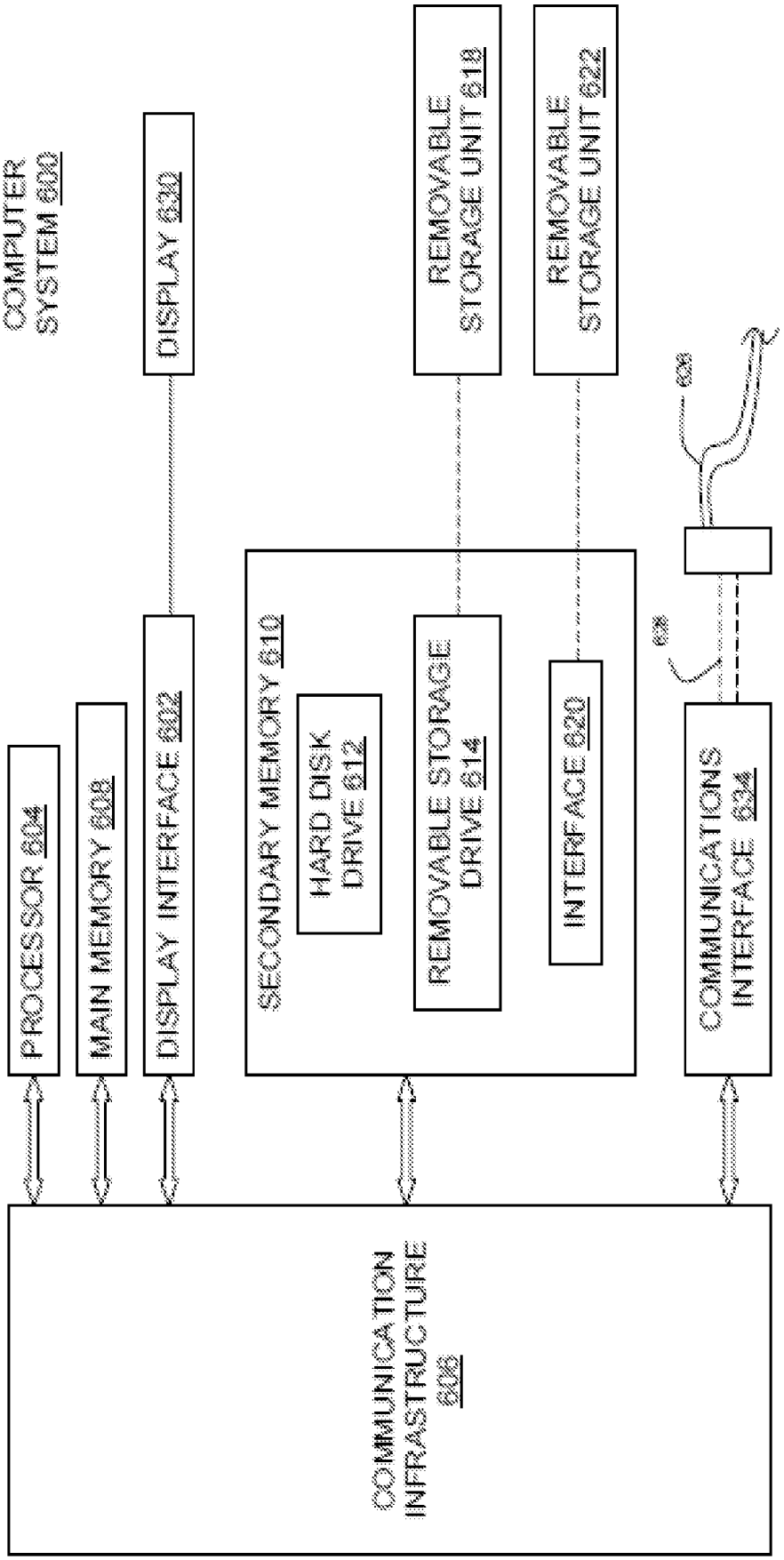

COMPUTER SYSTEM 600
PROCESSOR 604
MAIN MEMORY 608
DISPLAY INTERFACE 602
DISPLAY 630
SECONDARY MEMORY 610
HARD DISK DRIVE 612
REMOVABLE STORAGE DRIVE 614
INTERFACE 620
REMOVABLE STORAGE UNIT 618
REMOVABLE STORAGE UNIT 622
COMMUNICATIONS INTERFACE 624
COMMUNICATION INFRASTRUCTURE 606
626
628

FIG. 6

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专利名称(译)	监测和控制糖尿病患者血糖水平的统一平台		
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摘要(译)

灵活的系统，能够利用来自不同监测技术的数据，并能够在几个可扩展的水平上为糖尿病患者提供帮助，范围从长期趋势和预后的建议到实时自动闭环控制（人工胰腺）。这些可扩展的监测和治疗策略由称为糖尿病助手（DiAs）平台的统一系统提供。该系统为实施各种监测，咨询和自动化糖尿病治疗算法或方法提供了基础。 DiAs建议针对个体患者的具体情况以及任何给定时刻的患者风险评估而定制。