CLOSED-LOOP CONTROL OF INSULIN INFUSION

Abstract: Disclosed herein are devices, methods and systems for monitoring and detection of adverse events in a subject. In an embodiment, an insulin delivery device includes an insulin injection device in communication with a controller for controlling the insulin injection device. The controller is configured to receive a heart signal from one or more heart sensors, and a blood glucose signal from one or more blood glucose sensors. The controller is further configured to analyze changes in the heart rhythm of the subject based on the heart signal and determine, based on the changes in the heart rhythm and the blood glucose signal, whether the subject is and/or will be experiencing an adverse event. Upon determination that the subject is or will be experiencing an adverse event, the controller determines one or more parameters of delivery of insulin to be delivered to the subject. Finally, the controller is configured to control the injection device to deliver insulin to the subject in accordance with the determined one or more parameters of delivery.
CLOSED-LOOP CONTROL OF INSULIN INFUSION

CROSS REFERENCE TO RELATED APPLICATION

[0001] The present application claims priority to U.S. Non-Provisional Application No. 62/095,195, filed December 22, 2014, entitled "Closed-Loop Control of Insulin Infusion", the entire content of which is incorporated herein by reference.

TECHNICAL FIELD

[0002] This disclosure relates generally to monitoring and prevention of health related conditions of a subject, and in particular, to monitoring and prevention of adverse events.

BACKGROUND

[0003] Patients with diabetes are at a constant risk of hypoglycemia. Hypoglycemia often results in an increase in physical as well as psychosocial morbidity, and is a risk factor for an increased mortality. Hypoglycemia is common in patients with type 1 diabetes (T1D). Patients trying to improve or maintain a tight glycemic control suffer from a large number of episodes of asymptomatic hypoglycemia. Plasma glucose levels may be less than 60 mg/dl (3.3 mmol/l) 10% of the time, and on average, patients with T1D suffer from two weekly incidents of symptomatic hypoglycemia. Accordingly, patients with diabetes may experience thousands of hypoglycemic events over a lifetime. In addition, these patients have a 4.7-fold excess mortality risk compared to healthy subjects. One of the approaches to mitigating these risks is the use of continuous glucose monitoring (CGM) devices to detect and warn diabetic patients about an imminent hypoglycemic event. However, problems such as false positive alarms continue to exist.

SUMMARY

[0004] In an embodiment, a system for delivering a medicament to a subject is described. The system may include one or more biomarker sensors configured to measure a level of the biomarker of a subject, one or more heart sensors configured to measure changes in a heart rhythm of the subject, an injection device configured to deliver a medicament to the subject; and a controller for controlling the injection device. The
controller may be in communication with the one or more heart sensors, the one or more biomarker sensors, and the injection device. The controller may include a memory and one or more physical processors programmed with instructions. The sensor and controller may be wearable, directly attached to the skin or placed nearby the measuring/infusion area. The instructions when executed, cause the one or more physical processors to receive a biomarker signal from the one or more biomarker sensors, and a heart signal from the one or more heart sensors, analyze changes in the heart rhythm of the subject based on the heart signal, determine, based on the changes in the heart rhythm and the biomarker signal, whether there is and/or will be a change in a physiological condition of the subject, determine one or more parameters of delivery of the medicament to be delivered to the subject, and cause the injection device to deliver the medicament to the subject in accordance with the determined one or more parameters of delivery.

[0005] In an embodiment, a method for determining if a subject is and/or will be experiencing a hypoglycemic event is described. The method may include analyzing changes in a heart rhythm of a subject, analyzing a blood glucose signal from a blood glucose sensor, the blood glucose signal being an indicator of blood glucose levels of the subject, and determining, based on the changes in the heart rhythm and the blood glucose signal, whether the subject is and/or will be experiencing a hypoglycemic event.

[0006] In an embodiment, a device for insulin delivery is described. The device may include an insulin injection device in communication with a controller for controlling the insulin injection device. The controller may be configured to receive a heart signal from one or more heart sensors, and a blood glucose signal from one or more blood glucose sensors, analyze changes in the heart rhythm of the subject based on the heart signal, determine, based on the changes in the heart rhythm and the blood glucose signal, whether the subject is and/or will be experiencing a hypoglycemic event, determine, based on the determination that the subject is and/or will be experiencing a hypoglycemic event, one or more parameters of delivery of insulin to be delivered to the subject, and cause the injection device to deliver insulin to the subject in accordance with the determined one or more parameters of delivery.
In an embodiment, a medicament delivery device is described. The device may include a medicament infusion module configured to deliver the medicament to a subject, and a controller for controlling the medicament infusion module. The controller may include a memory and one or more physical processors programmed with instructions. The instructions when executed, cause the one or more physical processors to receive a biomarker signal from one or more biomarker sensors, and a heart signal from one or more heart sensors, analyze changes in a heart rhythm of the subject based on the heart signal, determine, based on the changes in the heart rhythm and the biomarker signal, whether there is and/or will be a change in a physiological condition of the subject, determine one or more parameters of delivery of the medicament to be delivered to the subject, and cause the medicament infusion device to deliver the medicament to the subject in accordance with the determined one or more parameters of delivery.

BRIEF DESCRIPTION OF DRAWINGS

In the present disclosure, reference is made to the accompanying drawings, which form a part hereof. In the drawings, similar symbols typically identify similar components, unless context dictates otherwise. Various embodiments described in the detailed description, drawings, and claims are illustrative and not meant to be limiting. Other embodiments may be used, and other changes may be made, without departing from the spirit or scope of the subject matter presented herein. It will be understood that the aspects of the present disclosure, as generally described herein, and illustrated in the Figures, can be arranged, substituted, combined, separated, and designed in a wide variety of different configurations, all of which are contemplated herein.

Figure 1 depicts an illustrative schematic of a control mechanism for a close-loop artificial pancreas based on a glucose monitor signal, in accordance with the principles and aspects of the present disclosure.

Figure 2 depicts an illustrative schematic of a control mechanism for a closed-loop artificial pancreas based on a glucose monitor signal and a heart rate signal, in accordance with the principles and aspects of the present disclosure.
Figure 3 depicts an illustrative process for a method of monitoring and predicting a change in a physiological condition using Heart Rate Variability (HRV) in combination with one or more biomarkers, in accordance with the principles and aspects of the present disclosure.

Figure 4 depicts an illustrative pattern recognition model, in accordance with the principles and aspects of the present disclosure.

Figure 5 depicts a block diagram of a device used for analysis of HRV data, in accordance with various aspects and principles of the present disclosure.

Figure 6 shows an example of detection of hypoglycemia based on HRV data and data from a Continuous Glucose Monitor (CGM) for a subject, in accordance with the principles and aspects of the present disclosure.

Figure 7 depicts an illustrative schematic of a feedback mechanism for an insulin pump, in accordance with the principles and aspects of the present disclosure.

Figure 8 depicts an illustrative schematic of a placement of glucose monitor, ECG monitor and insulin pump on a subject's body, in accordance with the principles and aspects of the present disclosure.

Figure 9 depicts an illustrative schematic of a placement of glucose monitor and insulin pump patches with built-in ECG electrodes and electronics on a subject's body, in accordance with the principles and aspects of the present disclosure.

Figure 10 depicts an illustrative schematic of a placement of glucose monitor and insulin pump with external ECG electrodes on a subject's body, in accordance with the principles and aspects of the present disclosure.

Figure 11 depicts an illustrative schematic of a placement of a single device functioning as glucose monitor, ECG monitor and insulin pump, on a subject's body, in accordance with the principles and aspects of the present disclosure.

Figure 12 depicts a graph of continuous glucose measurements and periodic single glucose measurements obtained from one subject.
[0021] Figure 13 depicts a time window used for predicting a single glucose measurement using continuous glucose measurements and heart variability data.

[0022] Figures 14A-14C depict comparison of various parameters for models using glucose only and glucose in conjunction with heart rate data for prediction of hypoglycemic events.


DETAILED DESCRIPTION

[0024] Before the present methods and systems are described, it is to be understood that this disclosure is not limited to the particular processes, methods and devices described herein, as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing the particular versions or embodiments only, and is not intended to limit the scope of the present disclosure which will be limited only by the appended claims. Unless otherwise defined, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art.

[0025] It must also be noted that as used herein and in the appended claims, the singular forms "a", "an", and "the" include plural reference unless the context clearly dictates otherwise. Thus, for example, reference to a "sensor" is a reference to one or more sensors and equivalents thereof known to those skilled in the art, and so forth. Nothing in this disclosure is to be construed as an admission that the embodiments described in this disclosure are not entitled to antedate such disclosure by virtue of prior invention. As used in this document, the term "comprising" means "including, but not limited to."

[0026] As used herein, the term "user" refers to a subject, human or animal, that uses the device or system disclosed herein. A user may be a person at risk for hypoglycemia such as, for example, a person having type I or type II diabetes.

[0027] Disclosed herein are systems of devices in close proximity to a person's body that cooperate for the benefit of the user. The communication of these devices is known as body area network (BAN), or wireless body area network (WBAN).
Disclosed herein are devices, methods and systems for monitoring and detection of information embedded in the autonomic nervous system in the heart rhythm of an individual. The methods disclosed herein may be further used during normal living (e.g., fasting, eating, activity, daily stress, etc.) because they are independent of ectopic beats, arrhythmia and artifacts which may normally limit the robustness of similar devices.

Disclosed herein are devices, methods and systems for monitoring and detection of adverse events such as hypoglycemia, hyperglycemia, or device safety issues during automated delivery of medication. The devices, method and systems disclosed herein may be further used for prevention of these events by controlled infusion of insulin in anticipation of an event, and transmitting this information to the user or a person associated with the user (e.g., a relative, or a caregiver).

An "open-loop system" e.g. a subcutaneous insulin pump with real-time continuous glucose monitoring (CGM) is currently being used for the management of type 1 diabetes in selected individuals. The limits of the open loop system are particularly seen in pediatric populations and in individuals with less motivation or with cognitive impairment. Furthermore, open-loop systems suffer from user errors, poor detection of alarms during sleep, and complacency with frequent alarming for hypoglycemia are problems with the current systems. These issues support the need for the development of control algorithms that automatically and accurately alter insulin infusion rates to achieve normal glucose levels during fasting, eating, activity, and daily stress. These and other drawbacks exist.

Figure 1 depicts a schematic of an automated mechanical glucose-responsive sensor-guided insulin infusion system also called an artificial pancreas or a "closed loop system." A closed-loop system may include, (as depicted in Figure 1): a continuous glucose monitoring (via a subcutaneous sensor or noninvasive e.g. Smart lens) device; a computerized closed loop controller to determine the proper insulin infusion rate and automatically adjusting insulin levels in a subject; and a subcutaneous insulin pump.

Figure 2 depicts a schematic of a closed-loop artificial pancreas that is controlled based on a continuous glucose monitor signal and a heart rate signal. A computerized closed-loop controller determines advent of hypoglycemic events and adjusts
insulin infusion rates so as to automatically adjust blood glucose levels in a patient. The insulin may be provided to the patient via, for example, a subcutaneous insulin pump.

[0033] In an embodiment, hypoglycemic events may be detected using changes in heart rate and heart rate variability (HRV) in conjunction with continuous glucose monitor signals. Advantageously, using heart rate and heart rate variability in conjunctions with continuous glucose monitoring as described herein improves detection of hypoglycemic events during normal living (e.g., during fasting, eating, activity, daily stress, etc.).

[0034] As used herein, "heart rate variability" (HRV) refers to variation in the time interval between heartbeats. HRV has been found to be a measure of the balance in the autonomic nervous system and is dependent on both internal and external changes in the body. Decreased parasympathetic nervous system activity or increased sympathetic nervous system activity results in reduced HRV. HRV may be measured using, for example, electrocardiogram, blood pressure, ballistocardiograms, pulse wave signals derived from photoplethysmograph, and so forth. In various embodiments, HRV may be measured at different sampling rates such as, for example, 0.01 Hz, 0.05 Hz, 0.1 Hz, 0.5 Hz, 1 Hz, 5 Hz, 10 Hz, 50 Hz, 100 Hz, 500 Hz, 1 kHz, and so forth or at any sampling rate between any two of these sampling rates.

[0035] By combining the complex dynamic/pattern of HRV with a surrogate measure of a biomarker it may be possible to improve the detection and prediction of a given change in a physiological condition which is measured by the biomarker surrogate. The HRV dynamic/pattern adds important information regarding the modulation of the autonomic nervous system and thereby can be used to clarify whether a change or event measured by the biomarker is of physiological significance, which could include a change or event of clinical interest that might require clinical intervention. This clarification is more significant when using a surrogate measure of a biomarker. For example, when the biomarker surrogate is CGM, there is a lag-time between CGM measurements and actual blood glucose levels (glucose levels in interstitial fluid lag behind blood glucose values) causing poor accuracy in event detection. Therefore, in terms of detection of hypoglycemia or hyperglycemia, CGM devices, have poor specificity and thus result in numerous false positive alerts. By combining pattern recognition of HRV with a CGM device the detection
and prediction of hypoglycemia or hyperglycemia may be significantly improved. Besides
detection and prediction of hypoglycemia or hyperglycemia the methods disclosed herein
may be used in any biomarker surrogates that are influenced by the autonomic nervous
system.

[0036] Figure 3 depicts an illustrative process for a method of monitoring and
predicting a change in a physiological condition using Heart Rate Variability (HRV) in
combination with one or more biomarkers according to an embodiment. At block 110, HRV
of a subject is measured by a sensor. The HRV data fed to a processor Pwhich, at block 150,
analyzes the HRV data based on a pre-determined algorithm. At block 130, processed HRV
data is combined (using, e.g., another processor not shown in Figure 1) with measurements
relating to one or more biomarkers BIOM from one or more sensors gathered at block 120
and analyzed for change in a physiological condition. This analysis may be fed back to
processor Pfor analysis at block 150. If the change in the physiological condition is deemed,
based on a pre-determined set of criteria, a reaction Ris provided at block 175.

[0037] In various embodiments, the patterns in the HRV data may be used to evaluate
the clinical relevance of each data point obtained from the biomarker measurements. For
example, in an embodiment, glucose measurement is used for detection of hypoglycemia. In
such embodiment, glucose levels are measured periodically (e.g., every 5 minutes) and
patterns in HRV data are used to determine whether a particular glucose measurement
indicates an onset of hypoglycemia. In other embodiments, other biomarkers may be used
and measurements obtained at a different frequency. In some embodiments, the biomarker
data may undergo processing similar to the HRV data.

[0038] In various embodiments, physiological conditions may be induced under
controlled clinical conditions while gathering HRV data. In many embodiments, HRV data
may be gathered for up to 10 hours prior to induction of the physiological event and up to
10 hours after the induction of the physiological event. As such, incidence of various
features and patterns extracted from the HRV data may be correlated with the particular
physiological event being induced based on the analysis being performed.
HRV of a subject may be measured using any device or method. For example, in an embodiment, HRV of a subject is measured using electrocardiogram (ECG). Figure 4 depicts an illustrative pattern recognition model according to an embodiment. In various embodiments, analysis of HRV at block 150 may include, for example, preprocessing at block 210, feature extraction at block 220, feature reduction at block 230, and classification at block 240.

In embodiments where HRV is measured using ECG, a signal from the ECG is preprocessed, at block 210, for detection of peaks and calculation of RR-intervals. RR-interval, as used herein, is the interval between an Rwave and the next Rwave as measured by the ECG. The R-wave detection may be performed with various methods such as, for example, Pan and Tompkins with (a) bandpass filter, (b) differentiating, (c) squaring and (d) moving-window integration or signal energy analysis and moving-window.

In various embodiments, the verification of RR recording may be performed using one or more of the analysis tools such as, for example, Poincare Plots, Nonlinear analysis, or time-frequency analysis, and may be performed in time domain or frequency domain. Power spectra density may then be estimated using parametric or non-parametric models such as, for example, Welch’s method, auto regression, periodogram, Bartlett’s method, autoregressive moving average, maximum entropy, least-squares spectral analysis, and so forth.

In various embodiments, RR-intervals may be divided in epochs of several minutes. It will be understood by one skilled in the art that any time length of an epoch may be chosen and will depend on factors such as, for example, data sampling rate, processing power, memory available to the processor, efficiency of algorithms used for analysis, and so forth. In an embodiment, for example, duration of an epoch may be 5 minutes.

RR-interval outliers from each epoch may then be replaced with a mean from that particular epoch. Outliers, in some embodiments, may be defined as RR-intervals deviating 50% from previous data RR-interval or outside 3 standard deviations. Epochs may be analyzed using proprietary or commercially available tools. The analysis may be performed using one or more of analysis tools such as, for example, of Poincare Plots,
Nonlinear analysis, time-frequency analysis and performed in time domain or frequency domain. Power spectra density may then be estimated using parametric or non-parametric models such as, for example, Welch’s method, auto-regression, periodogram, Bartlett’s method, autoregressive moving average, maximum entropy, least-squares spectral analysis, and so forth.

[0044] Preprocessing of the ECG signal may be followed by feature extraction, at block 220. Preprocessed RR-interval data is sent to block 220 to find, preferably, a small number of features that are particularly distinguishing and/or informative for classification of the features based on physiological conditions being induced. In various embodiments, features extracted, at block 220, from the RR-interval data up to several epochs prior to the physiological event may be used for calculating various features. In some embodiments, analysis may be performed on data, for example, 10 epochs, 15 epochs, 20 epochs, 30 epochs, 40 epochs, 50 epochs, 100 epochs or any number of epochs therebetween, prior to the physiological event.

[0045] Analysis performed on the RR-interval data at block 220 may, in various embodiments, include, for example, differentiation, averaging, calculation of slope, ratios of instantaneous values, standard deviation, skewness, regression coefficients, slopes of regression ratios, and standardized moment, and so forth. Features extracted from the HRV data may include, for example, median heart rate average from particular epoch range prior to an event, or the skewness of standard deviation of normal-to-normal intervals from particular epoch range prior to an event, and so forth. In some embodiments, analysis of HRV may be performed in real-time during daily living, or in combination with control exercise or paced breathing.

[0046] RR-interval data extracted at block 220 may include a large number of different features may be evaluated for their ability to discriminate for a physiological event. Such features may then, be passed down to block 230 to be grouped to form patterns that may be indicative of a particular physiological event. At block 230, a ranking algorithm based on e.g. a t-test may be used, in some embodiments, for eliminating features that do not signify an event.
In some embodiments, the ranking algorithm may calculate an average separability criterion for each feature. Such a criterion may reflect the ability of the classification method to separate the means of any two classes of features in relation to the variance of each class. Subsequently, various features may be correlated with physiological events. Features with lowest separability may be eliminated if correlation with higher ranking features exceeds a threshold. In an embodiment, a correlation threshold of, for example, 0.7 may be used. In various embodiments, the correlation threshold may be chosen depending on the desired specificity and sensitivity of prediction of the physiological event. In many embodiments, cross-validation may be performed to reduce generalization errors.

Once the features are extracted and reduced, particular features may be chosen for their ability to predict a physiological event based on correlation factors. This is followed by classification, at block 240, of the features to correlate them with particular physiological events. Various classification models may then be used for classifying physiological events as normal or abnormal based on such features. For example, in an embodiment, non-probabilistic binary linear classifier support vector machine may be used. A skilled artisan will appreciate that other classification methods may be also used, alone or in combination. For example, linear classifier models such as Fisher's linear discriminant, logistic regression, naive Bayes classifier, Perceptron, may be used for classification. Other examples of classification models include, but are not limited to, quadratic classifiers, k-nearest neighbor kernel estimation, random forests decision trees, neural networks, Bayesian networks, Hidden Markov models, Gaussian mixture models, and so forth. In some embodiments, multi-class classification may also be used, if needed.

In an embodiment, at block 240, forward selection may be used to select a subset of features for optimal classification. This selection may be performed by including a cross-validation with, for example, 10 groups and allocating a particular number of events for training the model. Forward selection may start with no features followed by assessing each feature to find the best feature that correlates with the particular physiological event. Such feature may, then, be included in an optimal feature subset for appropriate classification. Selection of new features may be repeated until addition of new features does not result in improved predictive performance of the model.
[0050] Figure 5 depicts a block diagram of a device used for analysis of HRV data in accordance with various aspects and principles of the present disclosure. Device 300 used for analysis of HRV data may include processor 310 configured to run algorithm 320 that enables prediction or detection of a physiological event. Heart rhythm 350 along with at least one biomarker 375 and their time of measurement are received and analyzed by algorithm 320. In some embodiments, measurements of heart rhythm 350 and biomarker 375 may be entered manually. In other embodiments, the measurements may be transmitted automatically to processor 310 using a wired or a wireless connection to device 300. Algorithm 320 may include, calculating one or more statistical measures, at block 322, of heart rhythm 350 and biomarker 375 data. At block 324, the physiological state or change in the physiological state is estimated and analyzed for a possibility that the physiological state or change in the physiological state may be non-healthy. At block 326, an output is generated based on the analysis of block 324. For example, if it is determined, at block 324, that a change in physiological state is non-healthy, an alarm signal is generated at block 326. Device 300 may produce a reaction 340 based on the output generated at block 326. In various embodiments, reaction 340 may be a visual, audio, or audiovisual signal such as, for example, an alarm, a text message, a flashing light, and so forth.

[0051] In many embodiments, processor 310 may be part of a computer, a tablet, a smartphone, or a standalone device. In some embodiments, the device may have in-built sensors for measuring HRV data 350. For example, a smartphone having a light emitting diode (LED) capable of producing infra-red light and an optical sensor (e.g., a camera) may be able to obtain HRV data using IR thermography. In many embodiments, the device used for analyzing the HRV data may include, for example, a controlling unit (e.g., a digital signal processor or DSP), a memory (e.g., random access memory, and/or non-volatile memory), one or more sensors (e.g., IR sensors, electrodes, etc.), one or more feedback mechanisms (e.g., display, a printer, speakers, LEDs or other light sources, etc.), and/or one or more input ports. The device for analyzing HRV data may also include sensors for measuring and analyzing any other biomarker(s).

[0052] In an embodiment, HRV measurements 350 may be combined, at block 322, with measurements of blood glucose levels 375 for monitoring and prediction of hypoglycemia. In such embodiments, HRV data 350 may be combined with, e.g., blood
glucose measurements 375 taken over a period of time prior to a hypoglycemic event. Patterns from the combination of HRV and blood glucose data may be used to discriminate between normoglycemia and hypoglycemia. A model may be trained by analyzing HRV features over, e.g., 10-20 epochs combined with blood glucose measurements prior to an induced hypoglycemic event. Once trained to discriminate between normoglycemic events and hypoglycemic events, the model may then be used to predict, at block 324, the occurrence of a hypoglycemic event based on HRV and blood glucose measurements.

[0053] Blood glucose data 375 may be obtained intermittently or continuously. In some embodiments, it may be possible to obtain blood glucose data using non-invasive technologies that include, for example, infra-red detection, ultrasound or dielectric spectroscopy and so forth. In many embodiments, such technologies may be integrated with equipment used for obtaining HRV data. In other embodiments, an implanted chip may be used for obtaining continuous blood glucose data.

[0054] Table 1 provides a list of biomarkers that may be used in concert with HRV for predicting and monitoring various physiological conditions.

<table>
<thead>
<tr>
<th>Physiological condition</th>
<th>Examples of Biomarker or surrogate measure of a biomarker</th>
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<tr>
<td>Epileptic attack</td>
<td>EEG, EMG, motion detection</td>
</tr>
<tr>
<td>Asthma attack</td>
<td>EEG, breathing (sounds and rate)</td>
</tr>
<tr>
<td>Panic attack</td>
<td>EEG, ECG, breathing (sounds and rate), sudomotor function</td>
</tr>
<tr>
<td>Heart attack or event</td>
<td>ECG, pulse wave velocity</td>
</tr>
<tr>
<td>Sudden hypotension</td>
<td>Blood pressure</td>
</tr>
<tr>
<td>Sleep apnea</td>
<td>EEG, breathing (sounds and rate)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>ECG, EMG, motion detection</td>
</tr>
<tr>
<td>Stress, including post-traumatic stress</td>
<td>EEG, bioimpedance, breathing (sounds and rate)</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>Bioimpedance, nerve conduction, EEG, EMG, dlorimeter, vibration testing, motion detection</td>
</tr>
<tr>
<td>Dehydration</td>
<td>Blood pressure, bioimpedance, breathing</td>
</tr>
<tr>
<td>Liveness detection</td>
<td>Bioimpedance</td>
</tr>
<tr>
<td>Lie detection</td>
<td>Polygraph</td>
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Table 1: List of biomarkers or biomarker surrogates used for detection/prediction for physiological events/conditions (EEG - Electroencephalogram; EMG - Electromyography; ECG - Electrocardiography).
Another embodiment is implemented as a program product for implementing systems and methods described herein. Some embodiments can take the form of an entirely hardware embodiment, an entirely software embodiment, or an embodiment containing both hardware and software elements. One embodiment is implemented in software, which includes but is not limited to firmware, resident software, microcode, etc.

Furthermore, embodiments can take the form of a computer program product (or machine-accessible product) accessible from a computer-readable or computer-readable medium providing program code for use by or in connection with a computer or any instruction execution system. For the purposes of this description, a computer-readable or computer readable medium can be any apparatus that can contain, store, communicate, propagate, or transport the program for use by or in connection with the instruction execution system, apparatus, or device.

The medium can be an electronic, magnetic, optical, electromagnetic, infrared, or semiconductor system (or apparatus or device). Examples of a computer-readable medium include a semiconductor or solid-state memory, magnetic tape, a removable computer diskette, a random access memory (RAM), a read-only memory (ROM), a rigid magnetic disk, and an optical disk. Current examples of optical disks include compact disk - read only memory (CD-ROM), compact disk - read/write (CD-R/W), and DVD.

A data processing system suitable for storing and/or executing program code will include at least one processor coupled directly or indirectly to memory elements through a system bus. The memory elements can include local memory employed during actual execution of the program code, bulk storage, and cache memories which provide temporary storage of at least some program code in order to reduce the number of times code must be retrieved from bulk storage during execution.

The logic as described above may be part of the design for an integrated circuit chip. The chip design is created in a graphical computer programming language, and stored in a computer storage medium (such as a disk, tape, physical hard drive, or virtual hard drive such as in a storage access network). If the designer does not fabricate chips or the photolithographic masks used to fabricate chips, the designer transmits the resulting design
by physical means (e.g., by providing a copy of the storage medium storing the design) or electronically (e.g., through the Internet) to such entities, directly or indirectly. The stored design is then converted into the appropriate format (e.g., GDSII) for the fabrication.

[0060] The resulting integrated circuit chips can be distributed by the fabricator in raw wafer form (that is, as a single wafer that has multiple unpackaged chips), as a bare die, or in a packaged form. In the latter case, the chip is mounted in a single chip package (such as a plastic carrier, with leads that are affixed to a motherboard or other higher level carrier) or in a multichip package (such as a ceramic carrier that has either or both surface interconnections or buried interconnections). In any case, the chip is then integrated with other chips, discrete circuit elements, and/or other signal processing devices as part of either (a) an intermediate product, such as a motherboard, or (b) an end product.

[0061] Figure 7 depicts a feedback mechanism for controlling an insulin pump. In an embodiment, a closed-loop artificial pancreas may be implemented with a computerized controller that uses the pattern of HRV and CGM signals for controlling an infusion rate of insulin via an insulin pump. In such an embodiment, the computerized controller implements an algorithm described herein to predict onset of adverse events such as hypoglycemia, hyperglycemia, or device safety issues during automated delivery of insulin. For example, the computerized controller may shut off insulin infusion if the algorithm predicts that a hypoglycemic event is impending and send notification to the patient, an emergency responder, or a caregiver associated with the patient. In various embodiments, the controller may additionally contain a GPS tracking sensor. In such embodiments, the notification may include the location of the patient so that a caregiver or an emergency responder can locate the patient with relative ease.

[0062] In an embodiment, a closed-loop artificial pancreas system may include a glucose monitor, an ECG monitor and an insulin pump placed on a subject’s body. Figure 8 depicts a relative placement of the glucose monitor, the ECG monitor and the insulin pump on the subject’s body. In such an embodiment, the glucose monitor may be a continuous glucose measurement monitor, which includes sensors for collecting glucose data and electronics for analyzing the collected glucose data. The ECG monitor may include electrodes and electronics for collecting and analyzing heart rate and heart rate variability.
signals as described elsewhere herein. The insulin pump may include microfluidic channels for appropriately delivering insulin (e.g., through subcutaneous infusion) to the subject, and electronics for controlling the rate of flow of insulin via the microfluidic channels. The glucose monitor and the ECG monitor may be connected to the insulin pump via wired or wireless connections.

[0063] In an embodiment, a closed-loop artificial pancreas system (which, in some embodiments, may be a wearable device) may include a glucose monitor and an insulin pump having built-in ECG electrodes. Figure 9 depicts a relative placement of the glucose monitor and the insulin pump in such an embodiment. The insulin pump of such an embodiment may include patches with built-in electrodes for ECG measurements, thereby minimizing the area of the body where the wearable device is attached, leading to better compliance and patient comfort. The glucose monitor and the insulin pump may be connected via a wired (as depicted) or a wireless connection. The electronics for analyzing the ECG and CGM data, and controllers for controlling the delivery of insulin maybe integrated within the insulin pump.

[0064] In an embodiment, the insulin pump may include electronics for collecting and analyzing the ECG data, electronics for analyzing the combination of the ECG data and the CGM data, and controllers for controlling the delivery of insulin. In such an embodiment, the ECG electrodes may be external to the insulin pump (as depicted in Figure 10). The glucose monitor may be connected to the insulin pump via a wired or a wireless connection.

[0065] In an embodiment, the glucose monitor, the ECG monitor, and the insulin pump may be integrated within a single device, as depicted in Figure 11.

[0066] In one embodiment the glucose monitor, the ECG monitor, and the insulin pump may be combined with one or more of the wearable’s sensors, shown in table 2, such as motions, breathing, EMG or EEG sensors.

[0067] The foregoing detailed description has set forth various embodiments of the devices and/or processes by the use of diagrams, flowcharts, and/or examples. Insofar as such diagrams, flowcharts, and/or examples contain one or more functions and/or operations, it will be understood by those within the art that each function and/or
operation within such diagrams, flowcharts, or examples can be implemented, individually and/or collectively, by a wide range of hardware, software, firmware, or virtually any combination thereof.

[0068] Those skilled in the art will recognize that it is common within the art to describe devices and/or processes in the fashion set forth herein, and thereafter use engineering practices to integrate such described devices and/or processes into data processing systems. That is, at least a portion of the devices and/or processes described herein can be integrated into a data processing system via a reasonable amount of experimentation.

[0069] The herein described subject matter sometimes illustrates different components contained within, or connected with, different other components. It is to be understood that such depicted architectures are merely exemplary, and that in fact many other architectures can be implemented which achieve the same functionality. In a conceptual sense, any arrangement of components to achieve the same functionality is effectively "associated" such that the desired functionality is achieved. Hence, any two components herein combined to achieve a particular functionality can be seen as "associated with" each other such that the desired functionality is achieved, irrespective of architectures or intermediate components.

[0070] With respect to the use of substantially any plural and/or singular terms herein, those having skill in the art can translate from the plural to the singular and/or from the singular to the plural as is appropriate to the context and/or application. The various singular/plural permutations may be expressly set forth herein for sake of clarity.

[0071] All references, including but not limited to patents, patent applications, and non-patent literature are hereby incorporated by reference herein in their entirety.

[0072] Embodiments illustrating the devices, methods and systems described herein may be further understood by reference to the following non-limiting examples:

**EXAMPLES**

Detection of Hypoglycemia based on Heart Rate Variability and CGM data
Embodiments described in the examples may utilize the devices, methods and processes described herein with respect to Figures 3-5.

Data collection:

Data from 10 patients was obtained. 10 adults with type 1 diabetes were recruited for studies into hypoglycemia under clinical settings. None of the patients with diabetes had a history of cardiovascular disease. None of the patients were taking drugs affecting the cardiovascular system, and all had normal electrocardiograms.

On the study day, hypoglycemia was induced by a single subcutaneous bolus of insulin aspart. Subjects were placed in a hospital bed with the back rest elevated to a comfortable position. Equipment for measuring the ECG (lead II) and a CGM device (Guardian RT, Minimed, Inc., Northridge, CA) producing a reading every 5 minutes were mounted and an intravenous cannula was placed in an antecubital vein in both forearms. Blood samples for measurements of insulin were taken at the beginning and end of a baseline period. Throughout the experiment, blood glucose measurements were obtained frequently from earlobe capillary blood.

Blood glucose readings were spline resampled with a rate of 5 minutes equivalent to each reading of the CGM device. The blood glucose readings were used as reference for periods/events with hypoglycemia and categorize events as (i) hypoglycemia - defined as the point of time of a blood sample closest to the value of 3 mmol/l glucose, and normoglycemia - defined as the point of time of a blood sample approximately 1 hour prior to the hypoglycemic event.

Once the HRV and blood glucose data is collected, all data processing was performed using custom analysis software developed in MATLAB R2011b (Mathworks, Natick, MA).

Preprocessing:

The ECG V5 signal was used for detection of peaks and calculation of RR-intervals. RR-intervals were divided in epochs of 5 minutes during the trial. RR-interval outliers from each epoch were replaced with the mean from that particular epoch. Outliers
were defined as RR-intervals deviating 50% from previous data RR-interval or outside 3 standard deviations.

[0079] Epochs were analyzed using HRV analysis software (HRVAS) module and 103 measures ranging from time domain, Poincare, Nonlinear, time-frequency to frequency domain were derived from the epoch. Two different models were used to estimate power spectra density: welch and auto regression.

Feature extraction and reduction:

[0080] In short, feature extraction and reduction is performed to find preferably small number of features that are particularly distinguishing or informative for the classification. Measures derived from RR-interval epochs 10-40 prior to an event were used for calculating multiple features. Table 2 shows calculations used to combine different epoch measures.

<table>
<thead>
<tr>
<th>Description</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Differentiation</td>
<td>( M_y \text{epc}<em>{x1} - M_y \text{epc}</em>{x2} )</td>
</tr>
<tr>
<td>Averaging</td>
<td>( \mu (M_y \text{epc}<em>{x1}, M_y \text{epc}</em>{x2}) )</td>
</tr>
<tr>
<td>Slope</td>
<td>( \alpha (M_y \text{epc}<em>{x1}, M_y \text{epc}</em>{x2}) )</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>( \sigma (M_y \text{epc}<em>{x1}, M_y \text{epc}</em>{x2}) )</td>
</tr>
<tr>
<td>Skewness</td>
<td>( Y_l (M_y \text{epc}<em>{x1}, M_y \text{epc}</em>{x2}) )</td>
</tr>
<tr>
<td>Ratio</td>
<td>( M_y \text{epc}<em>{x1} / M_y \text{epc}</em>{x2} )</td>
</tr>
</tbody>
</table>

Table 2: List of equations used to combine HRV measures into features. \( M_y \) represent a HRV measure \( y \), \( \text{epc}_{x} \) represent an 5 minutes RR-interval epoch, \( \mu \) is the arithmetic mean, \( \alpha \) is the slope regression coefficients, \( \sigma \) is the standard deviation, \( Y_l \) is the third standardized moment.

[0081] Example of features could be (a) the median heart rate averaged from epochs 10-20 prior to an event or (b) the skewness of standard deviation of Normal-to-Normal intervals (SDNN) from epochs 10-40 prior to an event.

[0082] To classify the patterns, 3296 different features were evaluated for their discrimination abilities. A ranking algorithm based upon a t-test was used to eliminate features. The ranking algorithm calculates an average separability criterion for each feature, which is the ability to separate the means of the two classes in relation to the variance of each class. The features are then correlated, and the feature with the lowest separability criteria is eliminated if correlation with higher ranking features exceeds the threshold. In this study a correlation threshold of 0.7 was used. To ensure that the features obtained
would not be over fitted, i.e. to reach a low generalization error, a cross-validation method was used. A total of the best 20 features were used to inclusion in the classification model.

Classification model:

[0083] Non-probabilistic binary linear classifier Support vector machines (SVM) was used to classify the events of normoglycemia and the events of hypoglycemia. First a forward selection method was used to select a subset of features for the optimal classification model. This selection was done including a cross-validation with ten groups, leaving 2 events out for classification and 18 events for training. Forward selection starts with no features and assesses every single feature and finds the best feature. This feature is then included as part of the optimal feature subset. All other features are added again to form a two-feature subset etc. this is repeated until new features doesn't increase the performance.

[0084] A subset of features selected is then used for the final classification model, which also included a ten-fold cross-validation. Sensitivity and specificity is used to evaluate the classification model.

Results:

[0085] A total of 903 samples equivalent to 4515 minutes among 10 patients with 16 hypoglycemic events were analyzed and classified using the model. The sample-based evaluation yielded a ROC AUC of 0.98. With a specificity of 99% the model had a sensitivity of 79%. This is a significant improvement over CGM alone. Event-based, the model classified all hypoglycemic events correctly, did not detect any false-positive events and had a lead-time of 22 ± (12) minutes. CGM alone was able to detect 12 out of 16 events with a lead-time 0 ± (11) minutes. Figure 6 shows the data for one patient where CGM alone detects hypoglycemia, indicated by 430, late after the real onset, indicated by 410, while the present method detects the hypoglycemic event, indicated by 420, one minute after the real onset.

Example 2: Prediction and improved detection of spontaneous hypoglycemic events

Methods
Participants: A total of 21 (13 men and 8 women) adults with long lasting T1D were recruited. The patients were 58 ± 10 years old, had a diabetes duration of 34 ±12 years and a HbA1c 7.9 ± 0.7 %, and 11 participants had peripheral neuropathy measured by biothesiometer. All participants were prone to hypoglycemia, i.e. they had experienced at least two episodes of severe hypoglycemia within the last year. None of the patients had a history of cardiovascular disease or were taking drugs affecting the cardiovascular system. All patients had a normal electrocardiogram. The study protocols were approved by the local ethics committee and the study conducted according to the principles of the "Helsinki Declaration II". All patients gave their written informed consent.

Study design: ECG was measured from lead II using a digital Holter monitor (SpiderView Plus; ELA Medical, Montrouge, France). At the same time, CGM was monitored using a Guardian Real-Time Continuous Glucose Monitoring System (Medtronic MiniMed, Northridge, CA, USA) with the prevailing glucose level blinded. At 11 PM a cannula was placed into an antecubital arm vein. Blood glucose samples were taken at hourly intervals until 7 AM the next morning. At 8 AM, participants were sent home with the monitoring equipment and they were instructed to calibrate the CGM at least four times a day. Monitoring ended on Sunday at 8 PM. A total of 72 hours of continuous CGM and ECG data were available for each participant.

Data processing: The ECG was analyzed using custom analysis software developed in MatLab (Version R2014a; MathWorks, Natick, MA, USA). ECG QRS detection was implemented based on the methods of Pan and Tompkins with (a) bandpass filter, (b) differentiating, (c) squaring and (d) moving-window integration (19). Initial R-peaks were identified with a threshold and a minimum time distance of 250 ms from the moving-window integration output. R detections were then found as the highest point in the original signal within the timeframe of the initial detected peak. Inter-beat intervals were derived from the R detections and interpolation was used to remove outliers based on 2-StdHRV. The filtered HRV signal was inspected manually and periods with substantial noisy signals were labeled for excluding glucose measurements with appertaining corrupted HRV. The HRV signal was analyzed with a five min, 90% overlapping sliding window calculating typical derived measures describing HRV; heart rate, SDNN (Standard deviation of all NN intervals), SDANN (Standard deviation of the averages of NN intervals in all 5 min segments of the
entire recording), pNNx (Proportion of pairs of adjacent NN intervals differing by more than 50 ms), RM SSD (The square root of the mean of the sum of the squares of differences between adjacent NN intervals), VLF (Power in very low frequency range, <0.04 Hz), LF (Power in low frequency range, 0.04-0.15 Hz), HF (Power in high frequency range, 0.15-0.4 Hz), TP (total power of all frequencies), LF/HF (ratio of LF and HF), entropy.

The CGM signal was spline resampled to remove short periods with dropouts. Dropouts defined as periods with no measurements shorter than 15 minutes. Single measurement of glucose (SMG), such as blood plasma glucose or self-monitoring of blood glucose levels below 3.9 mmol/L (70 mg/dL) were labeled as a hypoglycemic event and otherwise as eu glycemia. Glucose spot measurements with corresponding CGM readings showing a discrepancy of 8 mmol/L (144 mg/dl) or more were considered as erroneous data in either the CGM or spot measurement and they were therefore excluded from further analysis. Furthermore, spot measurements within two hours after a hypoglycemic event were excluded since such an event may affect the heart rate during the recovery phase. Figure 12 shows CGM readings with corresponding SMG readings from one participant. The dashed line illustrates the threshold for labeling SMG reading as either hypoglycemic or euglycemic.

Pattern classification: We developed a pattern classification method to predict single measurements of glucose (SMG) into one of the two classes: being within the range of hypoglycemia, or euglycemia. The method was based on extracting features from the CGM signal and the derived HRV signal prior to the SMG. A classification model was applied, using features that produced the best prediction model. The approach is illustrated in Figure 13, where data in a 60 min prediction window 10 min prior to the SMG has been used to extract features for prediction. In short, we used different time intervals within the prediction window to calculate several derived features from the CGM and the corresponding HRV signals. The nature of this approach results in a large number of features. To eliminate uninformative features, we used a ranking and correlative method where the receiver operating characteristic (ROC) for every feature was calculated. The result was weighted based on the correlation with higher-ranking features. The 40 most informative features were kept and the rest were discarded. To find a subset of the most informative features for
model inclusion, we used forward selection and concurrently a 10-fold cross validation. The model used for classifying the patterns was based on logistic regression classification.

[0091] Performance: For evaluation of the hypothesis that HRV could add information in the prediction of hypoglycemia, we assessed and compared three different models; (i) one model (CGM) containing only the raw information from the CGM; (ii) one model (CGM*) containing features derived from the CGM signal in the prediction window and (iii) one model (CGM+HRV) containing both features derived from CGM and HRV. The classification performance was evaluated by sample-based sensitivity and specificity along with ROC and absolute number of true positives, true negatives, false positives and false negatives for a chosen best model. Each SMG reading was predicted as either hypoglycemic or euglycemic, and the truth of each classification was calculated subsequently. Calculation of the different model (i-iii) performances was based on the prediction window starting 0-30 min prior to the SMG readings. Hence, a prediction window starting 30 min prior to the reading will yield a 30-min prediction interval.

Results

[0092] A total of 12 hypoglycemic events and 237 euglycemic SMG readings were included in the 21 datasets. For a 20 min prediction of the SMG reading the: (i) CGM model had a ROC AUC of 0.69 with a corresponding sensitivity of 100% and a specificity of 69%. The CGM* model (ii) yielded a ROC AUC of 0.92 with a corresponding sensitivity of 100% and specificity of 71%. (iii) The CGM+HRV model yielded a ROC AUC of 0.96 with a corresponding sensitivity of 100% and specificity of 91%. The relative and absolute numbers for the 20 min prediction are seen in Table 3 and the corresponding ROC for the three models are depicted in Figure 14, which shows the comparison of the (ii) CGM* model and the (iii) CGM+HRV model with varying prediction times. Figure 14 shows the performance (ROC AUC and Specificity) of the models ii and iii as a function of prediction time. Such that a prediction of 30 min will give, a 30 min forecast. The CGM+HRV model is obtaining a higher specificity when sliding prediction time from 0 to 30 min, whereas the CGM* model is steadily losing prediction power. The difference between the models in the time dependent analysis is significant (p<0.05).

<table>
<thead>
<tr>
<th>MODEL</th>
<th>SEN</th>
<th>SPE</th>
<th>AUC</th>
<th>TP</th>
<th>TN</th>
<th>FP</th>
<th>FN</th>
</tr>
</thead>
</table>
Table 3: Performance represented as sensitivity (SEN), specificity (SPE), area under curve (AUC), true positive (TP), true negative (TN), false positive (FP) and false negative (FN) - with a prediction of 20 minutes. Performance compared between that of CGM (current reading), CGM* algorithm with features from the CGM and CGM+HRV algorithm with features from both CGM and HRV.

<table>
<thead>
<tr>
<th>(I) CGM</th>
<th>100%</th>
<th>68%</th>
<th>69%</th>
<th>12</th>
<th>161</th>
<th>76</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>(II) CGM*</td>
<td>100%</td>
<td>71%</td>
<td>92%</td>
<td>12</td>
<td>168</td>
<td>69</td>
<td>0</td>
</tr>
<tr>
<td>(III) CGM + HRV</td>
<td>100%</td>
<td>91%</td>
<td>96%</td>
<td>12</td>
<td>216</td>
<td>21</td>
<td>0</td>
</tr>
</tbody>
</table>

Example 3: Closed-loop system during daily living

In the closed-loop system the insulin pump/CGM device controls when to dose with insulin and glucagon to prevent hypoglycemia. Using a closed-loop system as describing in this application at all time would be ideally, but may not be possible during daily living. Device safety issues during automated delivery of medication may be issue during daily living, CGM, Heart rate measurement device and insulin pump must work independently and as plug-and-play and connect automatically and securely with wireless body area network (or similar technology) every time the devices are in range of each other. Minor devices failures e.g. low battery in heart rate monitor, must not affect the improved detection of low blood glucose in CGM device. According to the result in Example 2 Table 3. The CGM* model (ii) yielded a ROC AUC of 0.92 with a corresponding sensitivity of 100% and specificity of 71%. (iii) The CGM+HRV model yielded a ROC AUC of 0.96 with a corresponding sensitivity of 100% and specificity of 91%.

Therefore, we developed a pattern classification method to predict single measurements of glucose (SMG) into one of the two classes: being within the range of hypoglycemia, or euglycemia. The method was based on extracting features from the CGM the pattern prior to the SMG. A classification model was applied, using features that produced the best prediction model. The approach is illustrated in Figure 14, without HRV, where data in a 60 min prediction window 10 min prior to the SMG has been used to extract features for prediction. In short, we used different time intervals within the prediction window to calculate several derived features from the CGM signals. The nature of this approach results in a large number of features. To eliminate uninformative features, we used a ranking and correlative method where the receiver operating characteristic (ROC) for
every feature was calculated. The result was weighted based on the correlation with higher-ranking features. The 40 most informative features were kept and the rest were discarded. To find a subset of the most informative features for model inclusion, we used forward selection and concurrently a 10-fold cross validation. The model used for classifying the patterns was based on logistic regression classification.

[0096] In order to achieve the maximum protection and the possibility to predict low blood glucose both the CGM and HR must be recorded in real-time and the algorithm will automatically use both measurements. However, if the heart rate measurement device is removed the algorithm will continue to work and only use the CGM measurements.

**Case story**

[0097] Patient J is an active young person with type 1 diabetes. He uses a continuous glucose monitoring device (CGM) on a daily basis. As shown in Figure 15A, today his glucose levels have been alternating - and at this point in time (T) his blood glucose has declined but is still within the normal range. Should Patient J do something to prevent additional decline or is the declining blood glucose within normal daily variations?

[0098] As shown in Figure 15B, Patient J is lucky he uses a smart watch that enables continuous heart rate (HR) monitoring device. The CGM device, with the algorithm installed and HR data (HRV) are connecting automatically and securely with wireless body area networks (or similar technology) every time Patient J takes his watch on. In order to achieve the maximum protection and the possibility to predict low blood glucose both the CGM and HR are be recorded in real time. However, the CGM may also use the algorithm alone to just to detect low blood glucose. If there is an error in Patient J's watch e.g. low battery, then the algorithm will continue to operate and improve detection of low blood glucose in CGM device as shown in table 3 of the application.

[0099] As shown in Figure 15C, already obtained CGM and HR data comprise information about the type of decline Patient J is experiencing. Therefore, as shown in Figure 15D, Patient J has the tools to determine whether the blood glucose decline could lead to an episode of severe and potentially life threatening hypoglycemia.
As shown in Figure 15E, the preHypo algorithm uses this historically obtained data from Patient J's CGM and HRV device to predict the glucose waveform. It is all done automatically by his smart-watch (and/or CGM device). The data is filtered and processed to obtain a sequence of mathematically derived features.

The patterns from Patient J's data resemble pattern from other data, which have led to a hypoglycemic episode. Therefore, Patient J's smart phone flags Patient J, alarming him that he should be cautious. This is done by triggering a customized and personalized alarm from Patient J's smart watch. Thereby enable Patient J to intervene by timely drinking or eating sugary fluids (juice) or food. As shown in Figure 15F, after food intake the preHypo algorithm will detect the raising blood sugar and give a personalized feedback to Patient J.

If Patient J had used his closed-loop system all this had happened automatically without alarm or need for Patient J to intervene by timely drinking.

While various aspects and embodiments have been disclosed herein, other aspects and embodiments will be apparent to those skilled in the art. The various aspects and embodiments disclosed herein are for purposes of illustration and are not intended to be limiting, with the true scope and spirit being indicated by the following claims.
CLAIMS

What is claimed is:

1. A system comprising:
   one or more biomarker sensors configured to measure a level of the biomarker of a subject;
   one or more heart sensors configured to measure changes in a heart rhythm of the subject;
   an injection device configured to deliver a medicament to the subject; and
   a controller in communication with the one or more heart sensors, the one or more biomarker sensors, and the injection device, the controller comprising a memory and one or more physical processors programmed with instructions, wherein the instructions when executed, cause the one or more physical processors to:
      receive a biomarker signal from the one or more biomarker sensors, and a heart signal from the one or more heart sensors,
      analyze changes in the heart rhythm of the subject based on the heart signal,
      determine, based on the changes in the heart rhythm and the biomarker signal, whether there is and/or will be a change in a physiological condition of the subject,
      determine one or more parameters of delivery of the medicament to be delivered to the subject, and
      cause the injection device to deliver the medicament to the subject in accordance with the determined one or more parameters of delivery.

2. The system of claim 1, wherein the biomarker comprises blood glucose.

3. The system of claim 2, wherein the instructions further cause the one or more physical processors to determine, based on the changes in the heart rhythm and the blood glucose signal, whether the subject is and/or will be experiencing an adverse event.
4. The system of claim 1, wherein the medicament comprises insulin and the injection device comprises an insulin pump.

5. The system of claim 1, wherein the one or more parameters of delivery include volume of medicament, rate of infusion of the medicament, a periodicity of medicament delivery, or any combination thereof.

6. The system of claim 1, wherein the heart signal comprises an electrocardiogram.

7. The system of claim 1, wherein the biomarker signal is generated and/or measured continuously.

8. The system of claim 1, wherein analysis of changes in the heart rhythm is performed using a software algorithm configured for detecting patterns or changes in patterns of the heart rhythm.

9. A method comprising:
   analyzing changes in a heart rhythm of a subject;
   analyzing a blood glucose signal from a blood glucose sensor, the blood glucose signal being an indicator of blood glucose levels of the subject; and
   determining, based on the changes in the heart rhythm and the blood glucose signal, whether the subject is and/or will be experiencing an adverse event.

10. The method of claim 9, further comprising controlling delivery parameters of an insulin delivery system based on the determination that the subject is experiencing and/or will be experiencing an adverse event.

11. The method of claim 10, wherein delivery parameters include one or more of volume of insulin delivered to the subject, rate of infusion of insulin being delivered to the subject, a periodicity of insulin delivery, or any combination thereof.

12. The method of claim 9, wherein analyzing changes in the heart rhythm of the subject comprises detecting patterns or changes in patterns of the heart rhythm of the subject.
13. The method of claim 9, wherein analyzing changes in the heart rhythm of the subject comprises analyzing an electrocardiogram of the subject.

14. An insulin delivery device comprising:
   an insulin injection device in communication with a controller, the controller configured to:
   receive a heart signal from one or more heart sensors, and a blood glucose signal from one or more blood glucose sensors,
   analyze changes in the heart rhythm of the subject based on the heart signal,
   determine, based on the changes in the heart rhythm and the blood glucose signal, whether the subject is and/or will be experiencing an adverse event,
   determine, based on the determination that the subject is and/or will be experiencing an adverse event, one or more parameters of delivery of insulin to be delivered to the subject, and
   cause the injection device to deliver insulin to the subject in accordance with the determined one or more parameters of delivery.

15. The device of claim 14, wherein the one or more parameters of delivery include one or more of volume of insulin delivered to the subject, rate of infusion of insulin being delivered to the subject, a periodicity of insulin delivery, or any combination thereof.

16. The device of claim 14, wherein analyzing changes in the heart rhythm of the subject comprises detecting patterns or changes in patterns of the heart rhythm of the subject.

17. The device of claim 14, wherein analyzing changes in the heart rhythm of the subject comprises analyzing an electrocardiogram of the subject.

18. The device of claim 14, wherein the blood glucose signal is generated and/or measured continuously.

19. A device comprising:
   a medicament infusion module configured to deliver the medicament to a subject; and
a controller comprising a memory and one or more physical processors
programmed with instructions, wherein the instructions when executed, cause the
one or more physical processors to:

receive a biomarker signal from one or more biomarker sensors, and a heart
signal from one or more heart sensors,

analyze changes in a heart rhythm of the subject based on the heart signal,

determine, based on the changes in the heart rhythm and the biomarker
signal, whether there is and/or will be a change in a physiological condition of the
subject,


determine one or more parameters of delivery of the medicament to be
delivered to the subject, and

cause the medicament infusion device to deliver the medicament to the
subject in accordance with the determined one or more parameters of delivery.

20. The device of claim 19, wherein the medicament comprises insulin.

21. The device of claim 19, wherein the biomarker signal comprises a blood glucose
concentration of the subject.

22. The device of claim 19, wherein the one or more parameters of delivery include
volume of medicament, rate of infusion of the medicament, a periodicity of
medicament delivery, or any combination thereof.

23. A device comprising a controller comprising a processor configured to: (i) analyze
changes in a heart rhythm of a subject, (ii) analyze a blood glucose signal, the blood
glucose signal being an indicator of blood glucose levels of the subject; and (iii)
determine, based on the changes in the heart rhythm and the blood glucose signal,
whether the subject is and/or will be experiencing an adverse event.

24. The device of claim 23, further comprising a sensor for detecting the heart rhythm of
a subject and a sensor for detecting the blood glucose signal.

25. The device of claim 24, further comprising a medication infusion device.
Artificial Pancreas, Closed-Loop system today

Continuous glucose monitor (CGM) is used to control the insulin pump.

Figure 1
Close-loop with ECG

Glucose monitoring (CGM) → ECG (HRV) → Insulin pump

Figure 2
Figure 7
1) ECG monitor
2) CGM monitor
3) Insulin pump

Figure 8
(1) CGM
(2) insulin pump patches
(3) wire connecting CGM and insulin pump

Figure 9
(1) Single device for CGM, insulin infusion and ECG measurements
Figure 15D

Continuous heart rate monitoring device

Mean heart rate

time

Beat-to-beat signal
**INTERNATIONAL SEARCH REPORT**

**International application No**

PCT/IB2015/059899

<table>
<thead>
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<th>A. CLASSIFICATION OF SUBJECT MATTER</th>
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According to International Patent Classification (IPC) or to both national classification and IPC

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<th>B. FIELDS SEARCHED</th>
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<tr>
<td>Minimum documentation searched (classification system followed by classification symbols)</td>
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</table>

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
<thead>
<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<td>wo 2011/054042 AI (AIMEDICS PTY LTD [AU]; SKLADNEV VICTOR [AU]; TARNAVSKI STANISLAV [AU]) 12 May 2011 (2011-05-12) figures 1-2B -----</td>
<td>1-8, 14-25</td>
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[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"Z" document member of the same patent family

Date of the actual completion of the international search: 9 March 2016

Date of mailing of the international search report: 17/03/2016

Name and mailing address of the ISA/Authorized officer:

European Patent Office, P.B. 5818 Patentlaan 2
NL 2280 HV Rijswijk
Tel: (+31-70) 340 2040, Fax: (+31-70) 340 3016

Krassow, Hei ko
<table>
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<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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</table>
### Observations where certain claims were found unsearchable (Continuation of Item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. **X** Claims Nos.: 9-13
   - because they relate to subject matter not required to be searched by this Authority, namely:
     - see FURTHER INFORMATION sheet PCT/ISA/210

2. **☐** Claims Nos.: 
   - because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. **☐** Claims Nos.: 
   - because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Observations where unity of invention is lacking (Continuation of Item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

- see additional sheet

1. **☐** All required additional search fees were timely paid by the applicant, this international search report covers all searchable

2. **X** As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. **☐** As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. **☐** No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

- **☐** The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- **☐** The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- **☐** No protest accompanied the payment of additional search fees.
This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-8, 14-25

Claims 1-8 and 14-25:

1.1. claims: 1-8, 14-22

Claims 1-8 and 14-22 essentially define an injector device system comprising a sensor configured to measure a level of a biomarker of a subject; and a heart sensor configured to measure changes in a heart rhythm of the subject, and a processor determining a parameter of delivery of the medicament to be delivered to the subject, and cause the injection device to deliver the medicament to the subject.

1.2. claims: 23-25

Claims 23-25 essentially define a device comprising a controller comprising a processor configured to analyze changes in a heart rhythm of a subject, analyze a blood glucose signal, the blood glucose signal being an indicator of blood glucose levels of the subject; and determine, based on the changes in the heart rhythm and the blood glucose signal, whether the subject is and/or will be experiencing an adverse event.

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Conti nuation of Box II.1

Claims Nos.: 9-13

Claims 9-13 define subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT, and no search report has been drawn up on said claims. The subject-matter defined comprises methods for treatment of the human body by therapy, i.e. methods for infusing or injecting medical fluid, cf. claim 10: "... controlling delivery parameters of an insulin delivery system ...".
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<td></td>
<td>EP 1677668 Al</td>
<td>12-07-2006</td>
</tr>
<tr>
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<td></td>
<td>JP 2007508076 A</td>
<td>05-04-2007</td>
</tr>
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<td></td>
<td>WO 2005037092 Al</td>
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<td>AU 2010314810 A</td>
<td>21-06-2012</td>
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<td>12-09-2012</td>
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<td>WO 2009070675 A2</td>
<td>04-06-2009</td>
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