

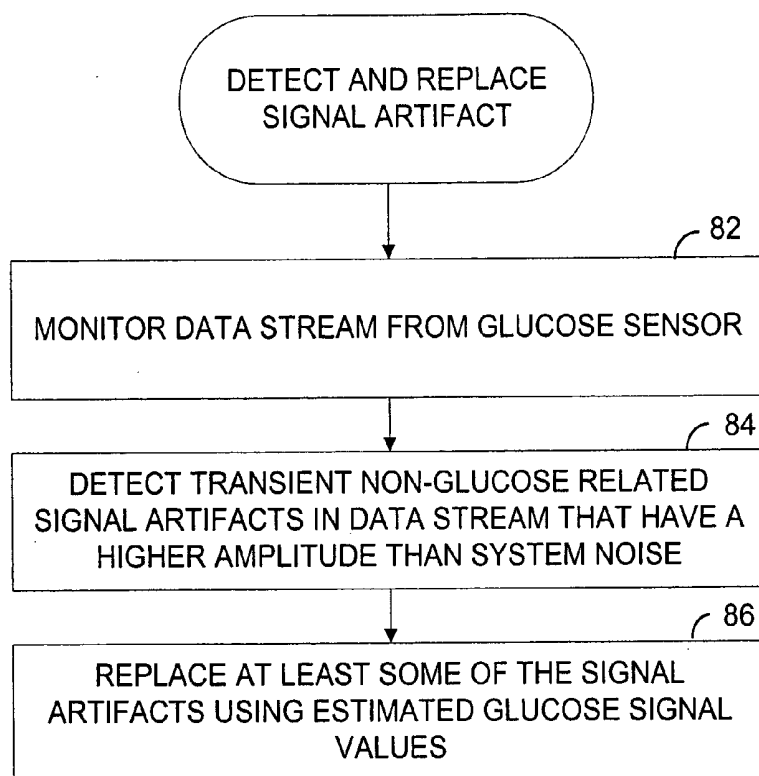


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(19) **United States**(12) **Patent Application Publication** (10) **Pub. No.: US 2005/0043598 A1****Goode, JR. et al.**(43) **Pub. Date: Feb. 24, 2005**(54) **SYSTEMS AND METHODS FOR REPLACING  
SIGNAL ARTIFACTS IN A GLUCOSE  
SENSOR DATA STREAM****Publication Classification**(51) **Int. Cl.<sup>7</sup>** ..... **A61B 5/00; A61B 5/05**(52) **U.S. Cl.** ..... **600/316; 600/347; 600/365**(75) **Inventors:** **Paul V. Goode JR.**, Murrieta, CA (US);  
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**Victoria Carr-Brendel**, San Diego, CA  
(US)(57) **ABSTRACT**

Systems and methods for minimizing or eliminating transient non-glucose related signal noise due to non-glucose rate limiting phenomenon such as ischemia, pH changes, temperatures changes, and the like. The system monitors a data stream from a glucose sensor and detects signal artifacts that have higher amplitude than electronic or diffusion-related system noise. The system replaces some or the entire data stream continually or intermittently including signal estimation methods that particularly address transient signal artifacts. The system is also capable of detecting the severity of the signal artifacts and selectively applying one or more signal estimation algorithm factors responsive to the severity of the signal artifacts, which includes selectively applying distinct sets of parameters to a signal estimation algorithm or selectively applying distinct signal estimation algorithms.

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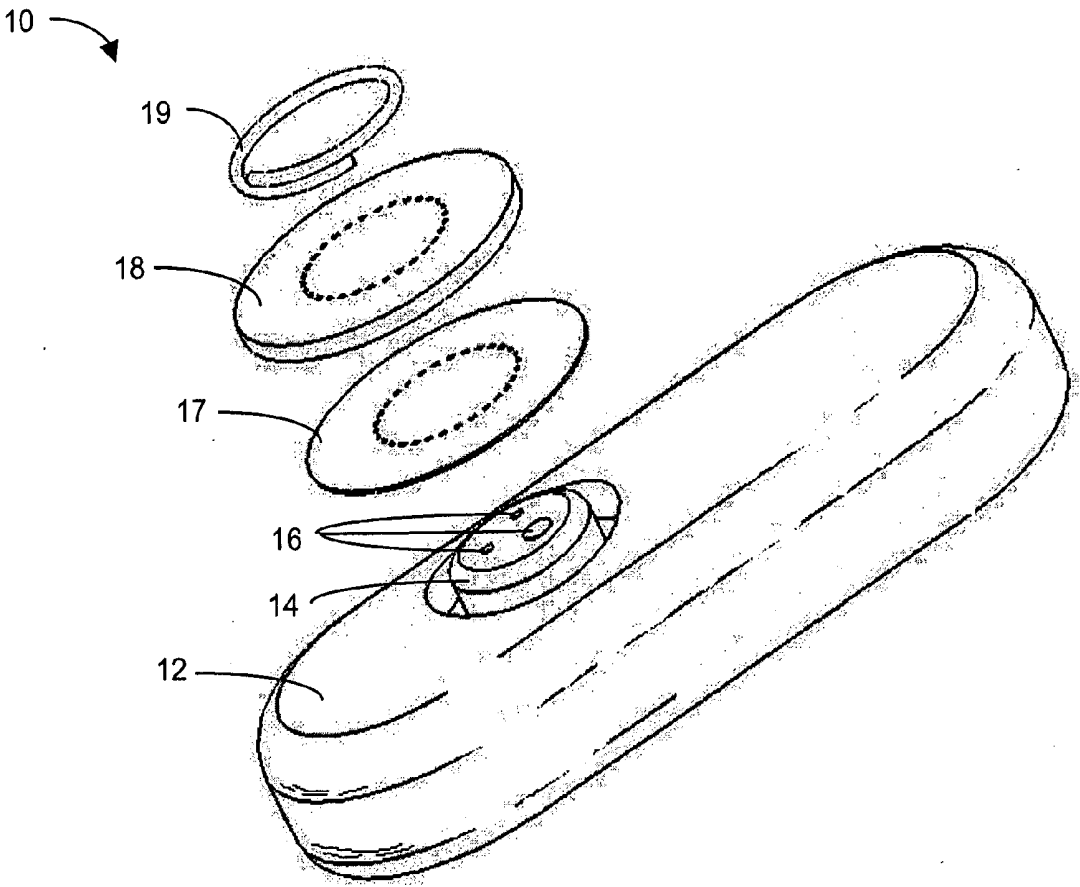


FIG. 1

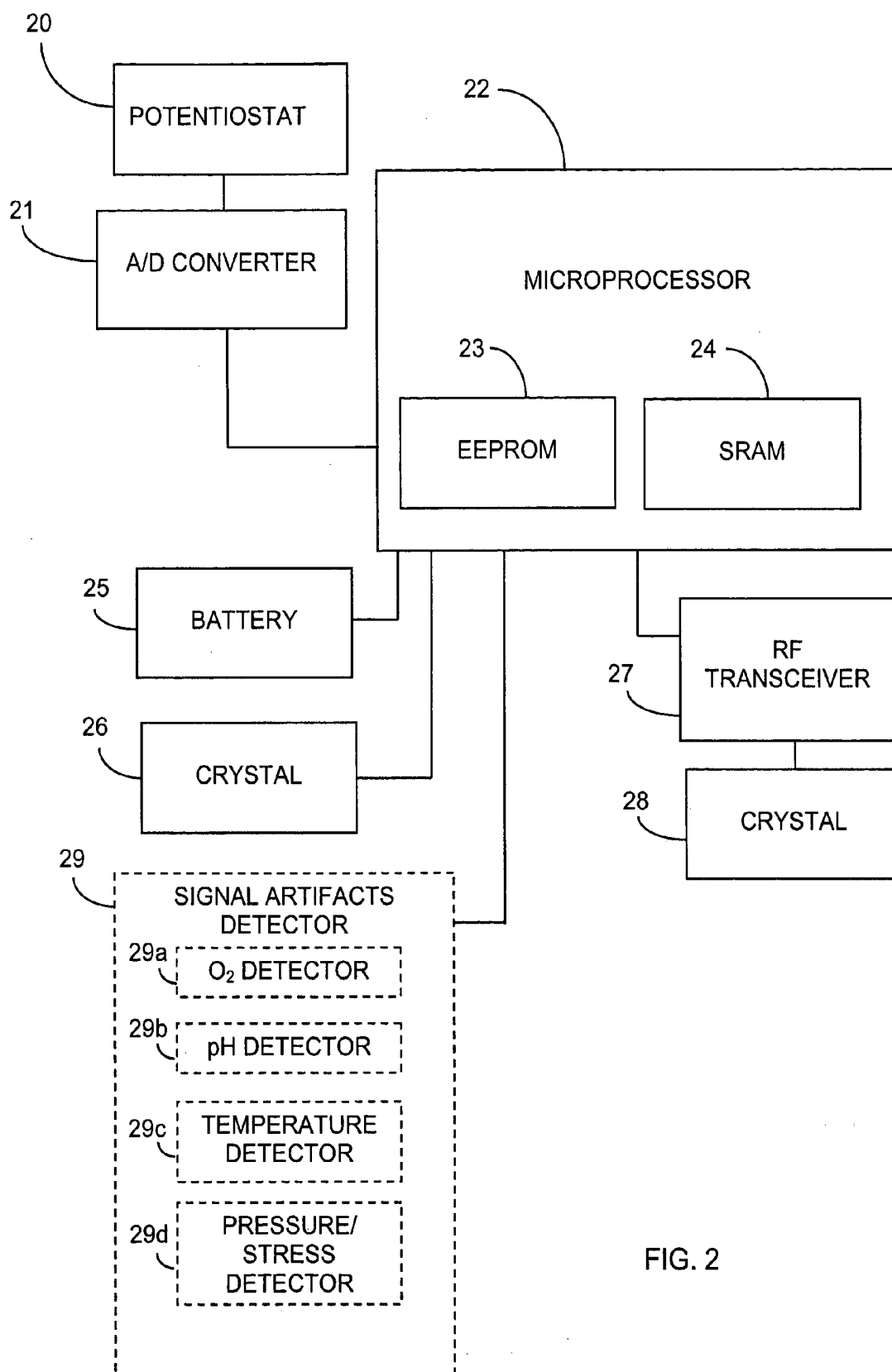


FIG. 2

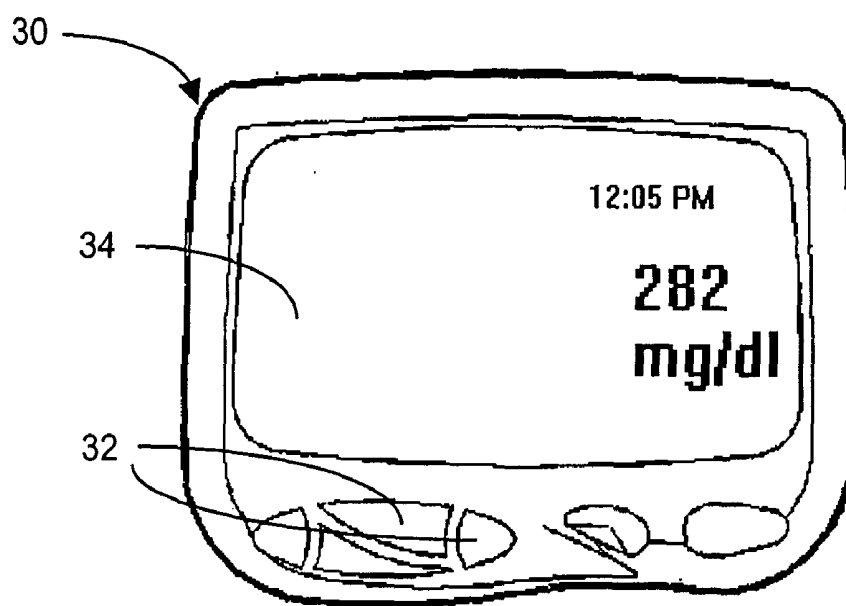


FIG. 3A

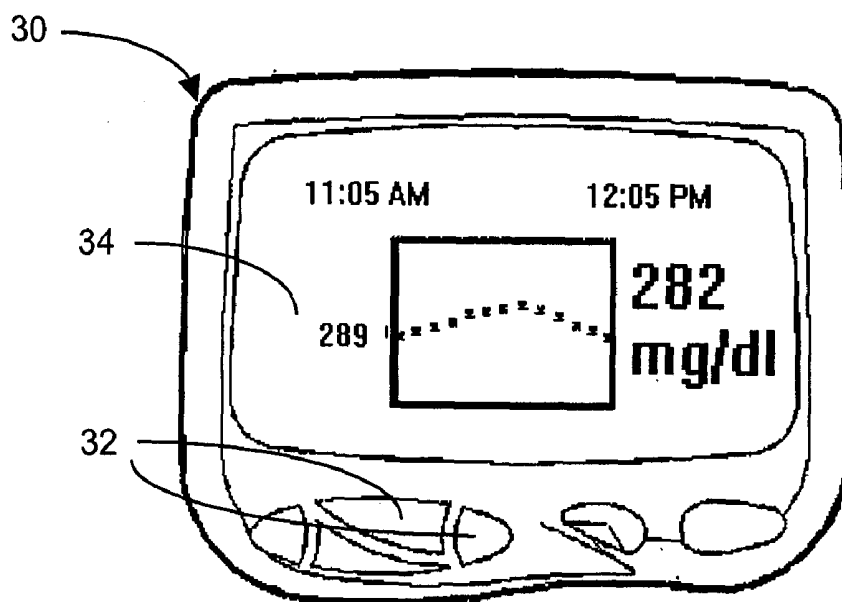


FIG. 3B

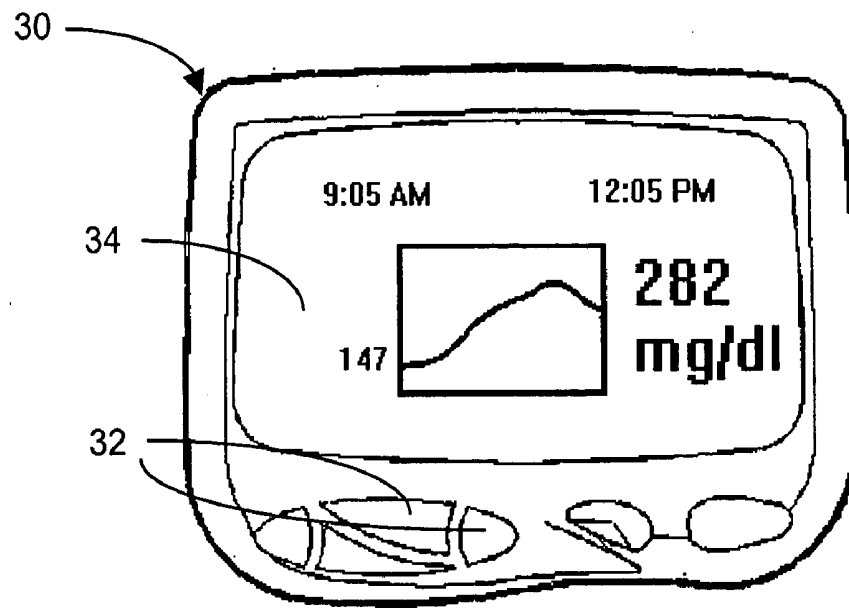


FIG. 3C

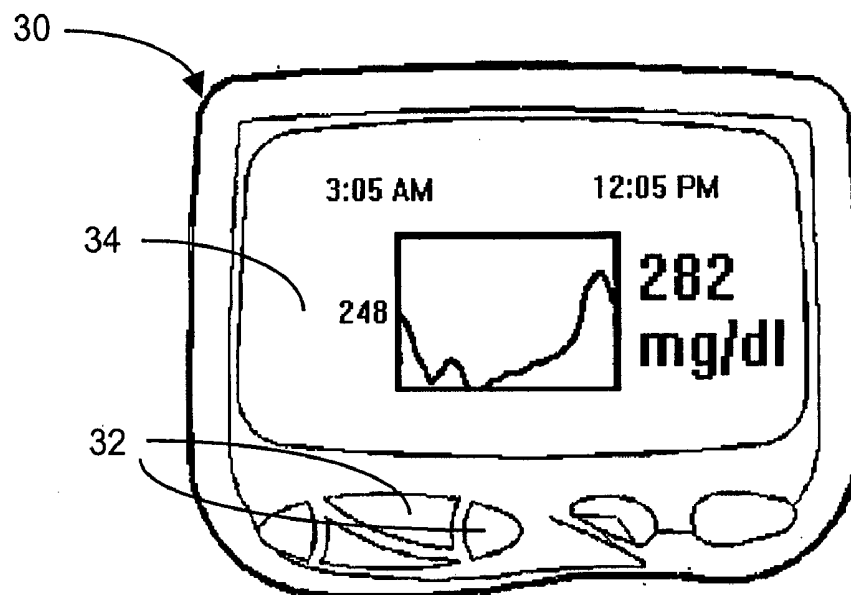


FIG. 3D

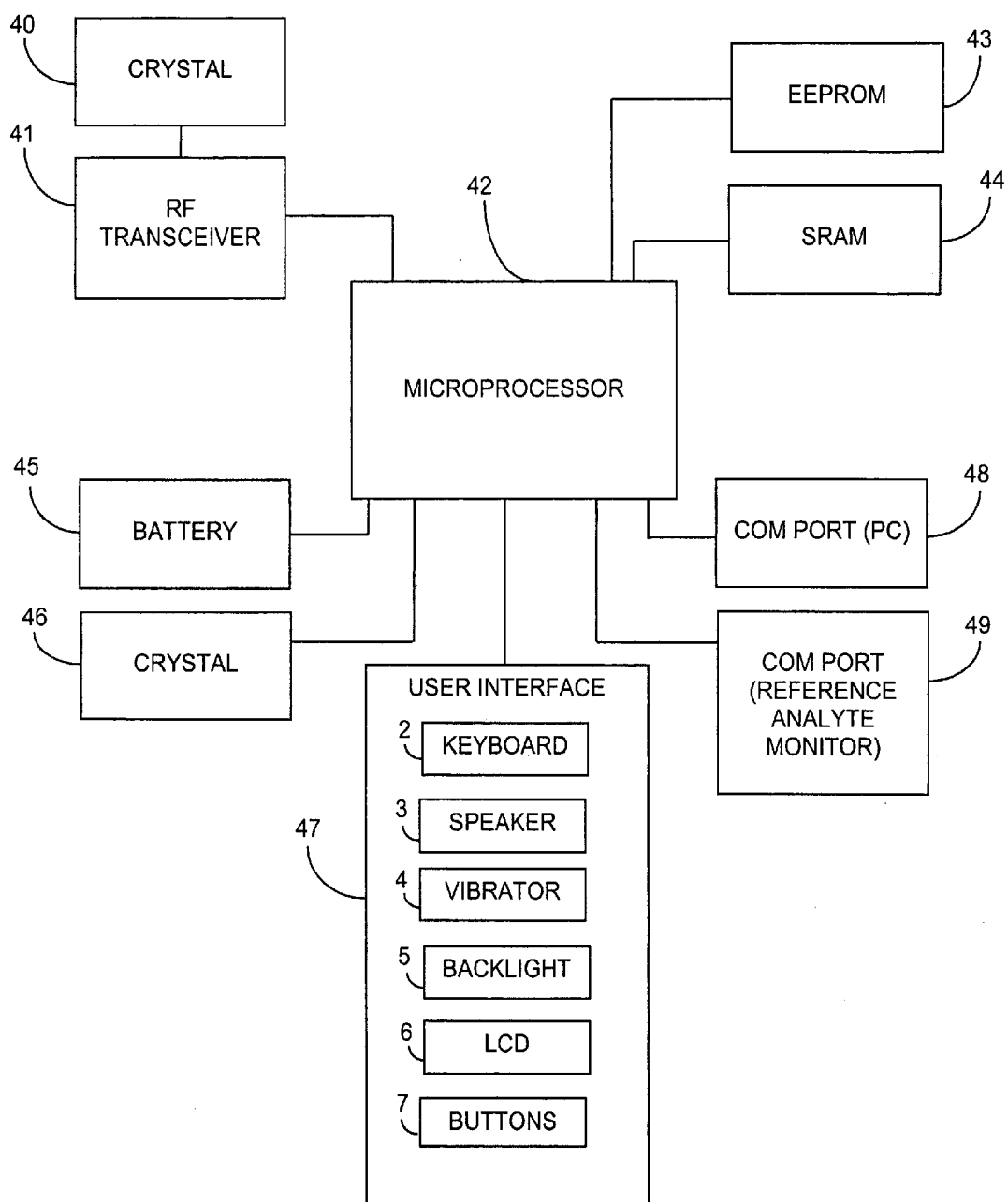


FIG. 4

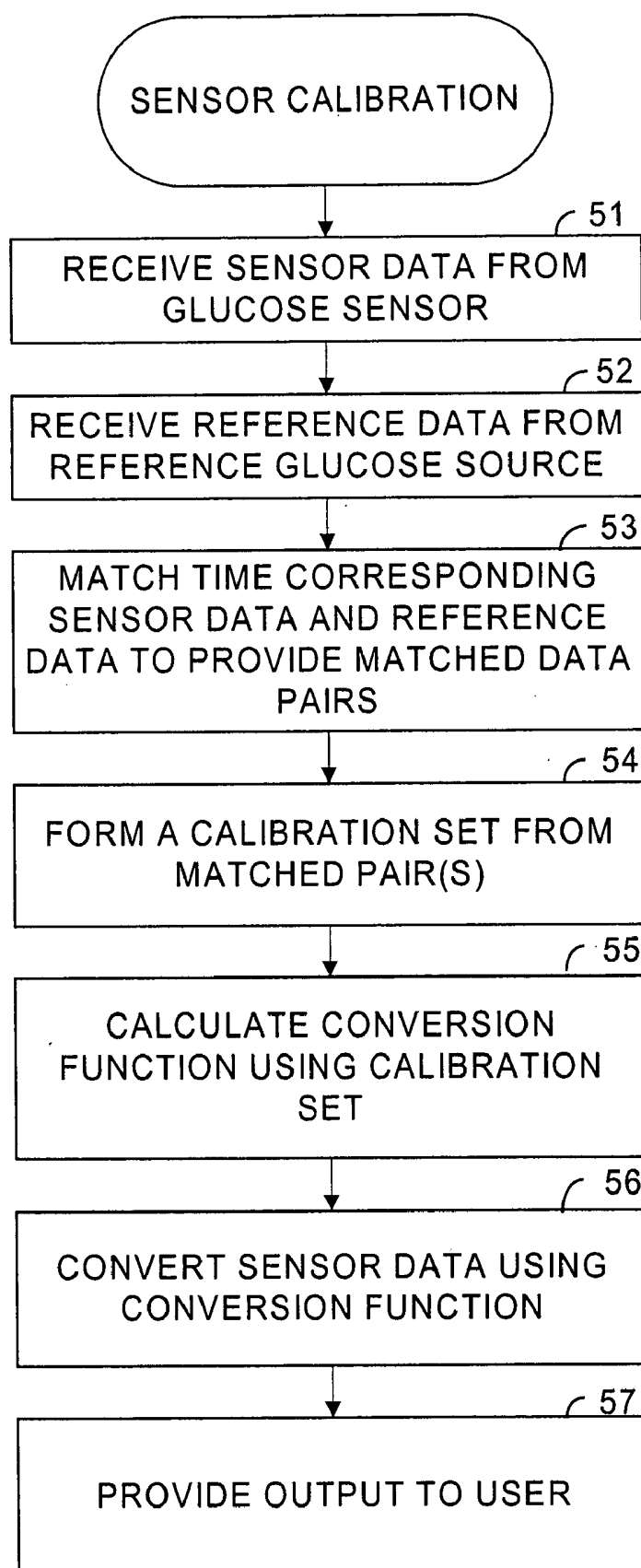


FIG. 5

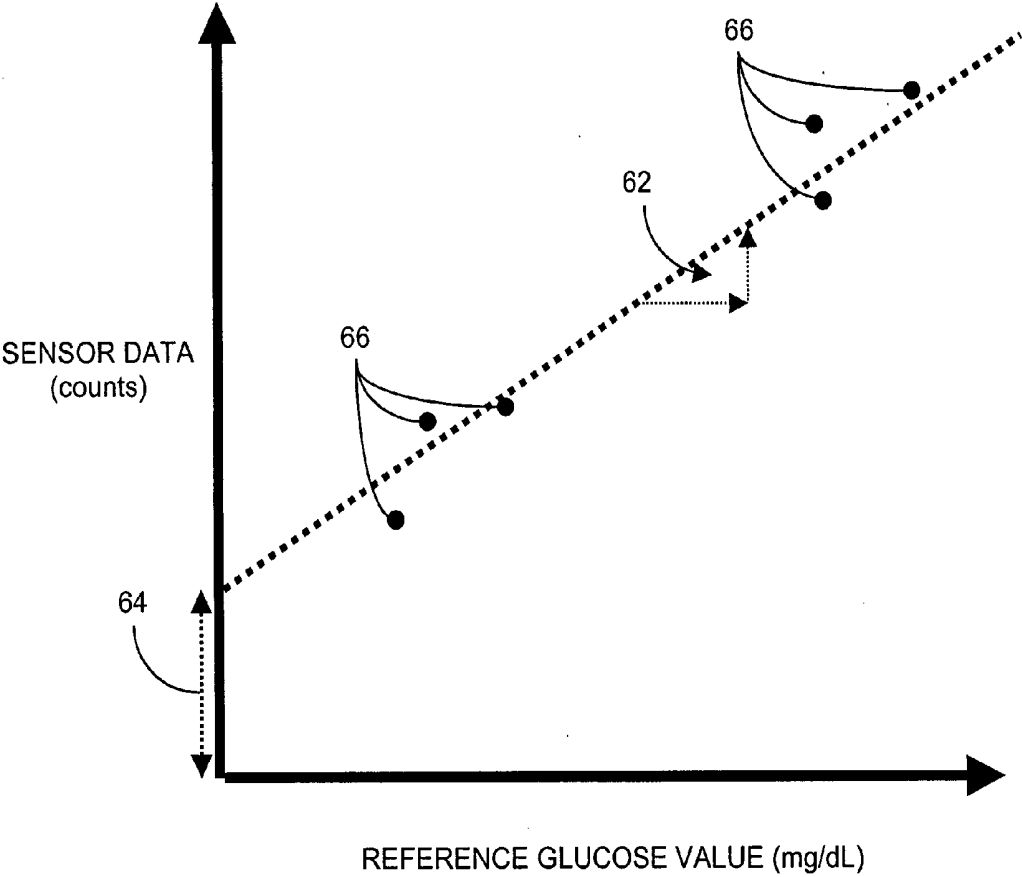


FIG. 6



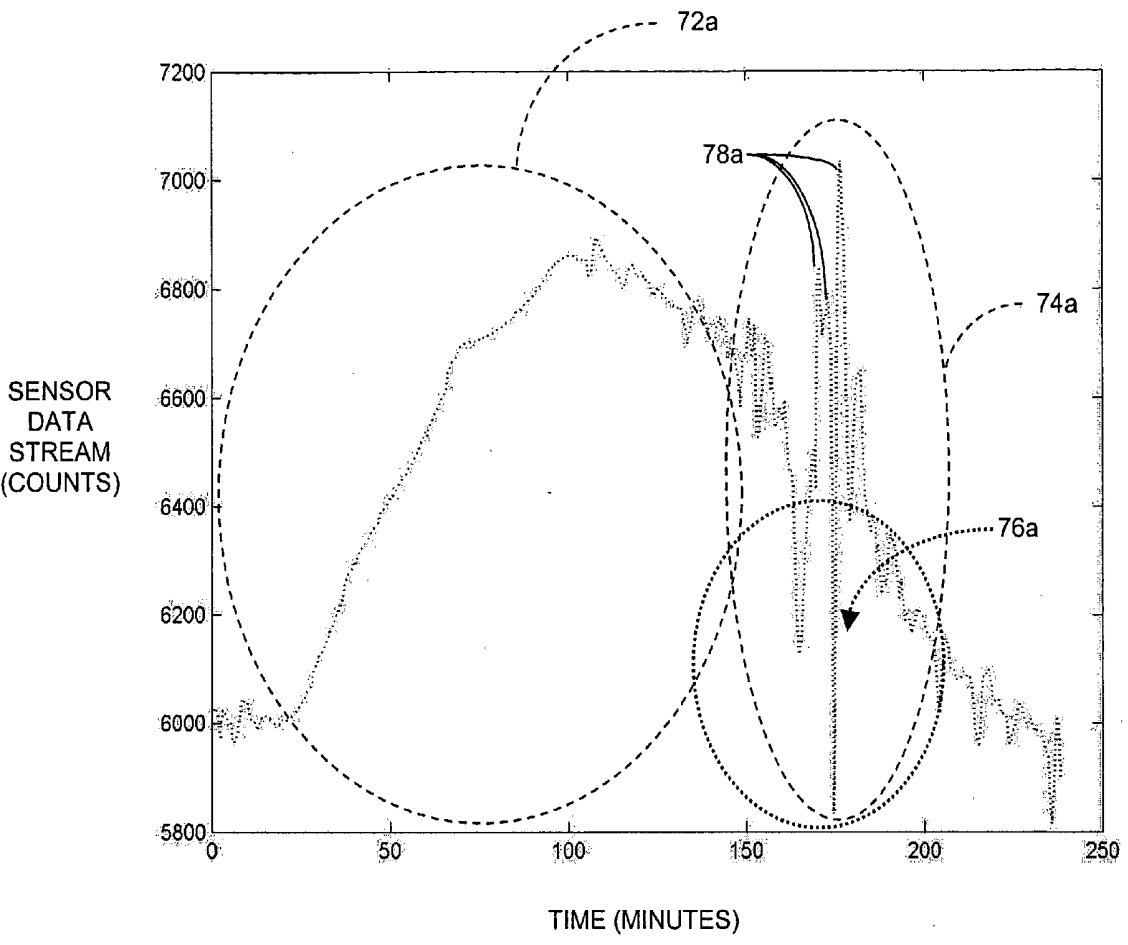


FIG. 7A

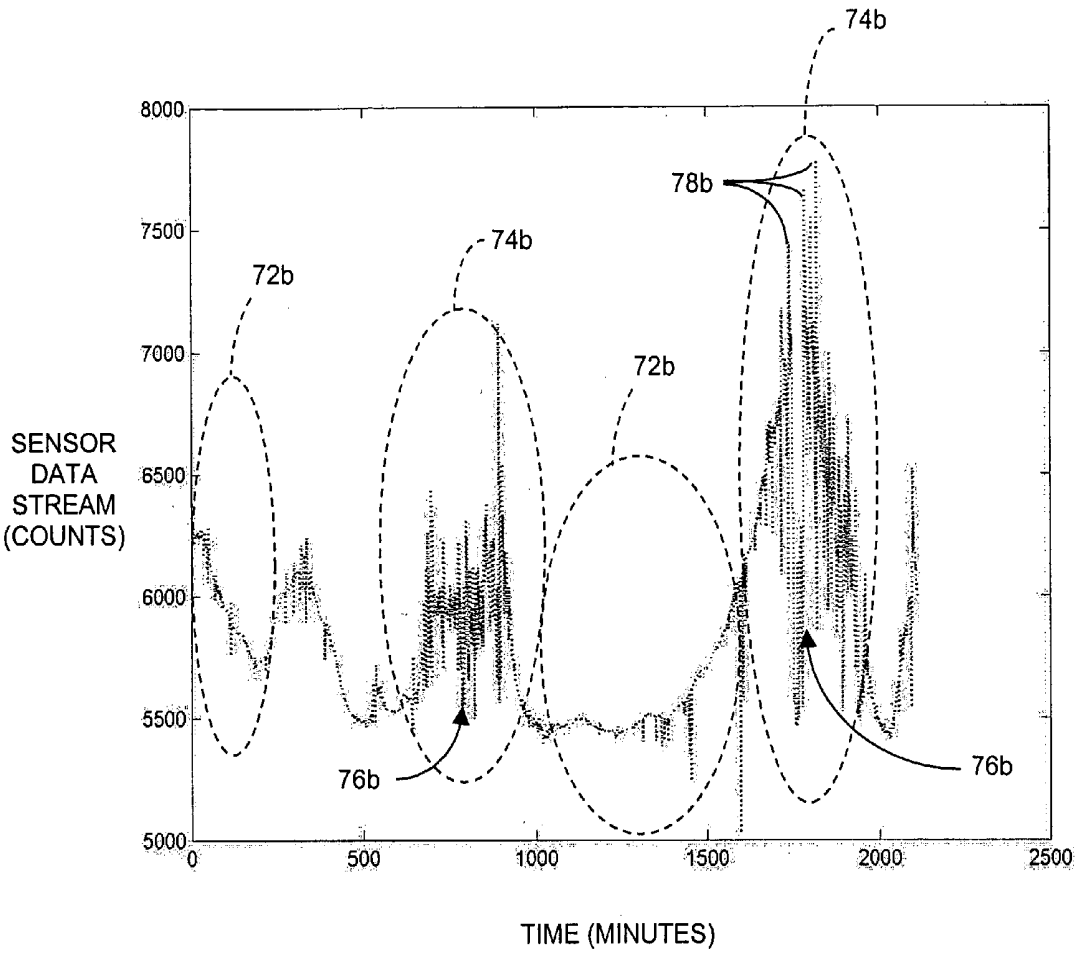


FIG. 7B

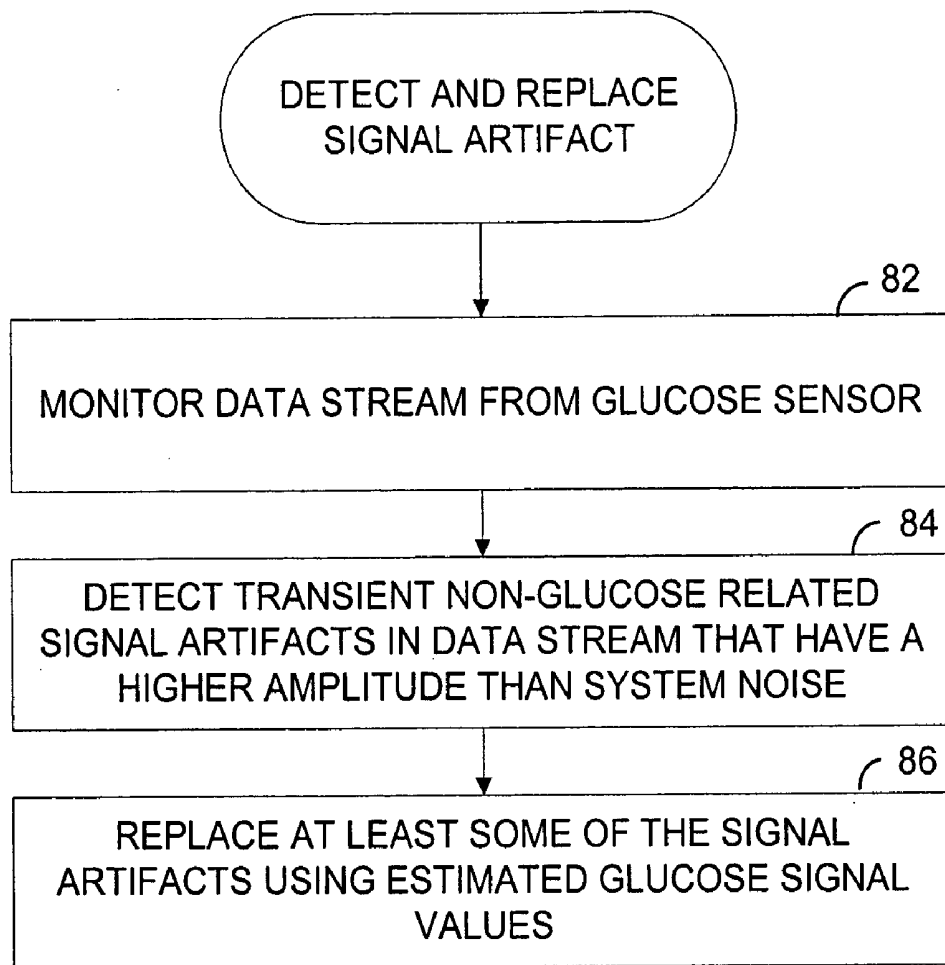


FIG. 8

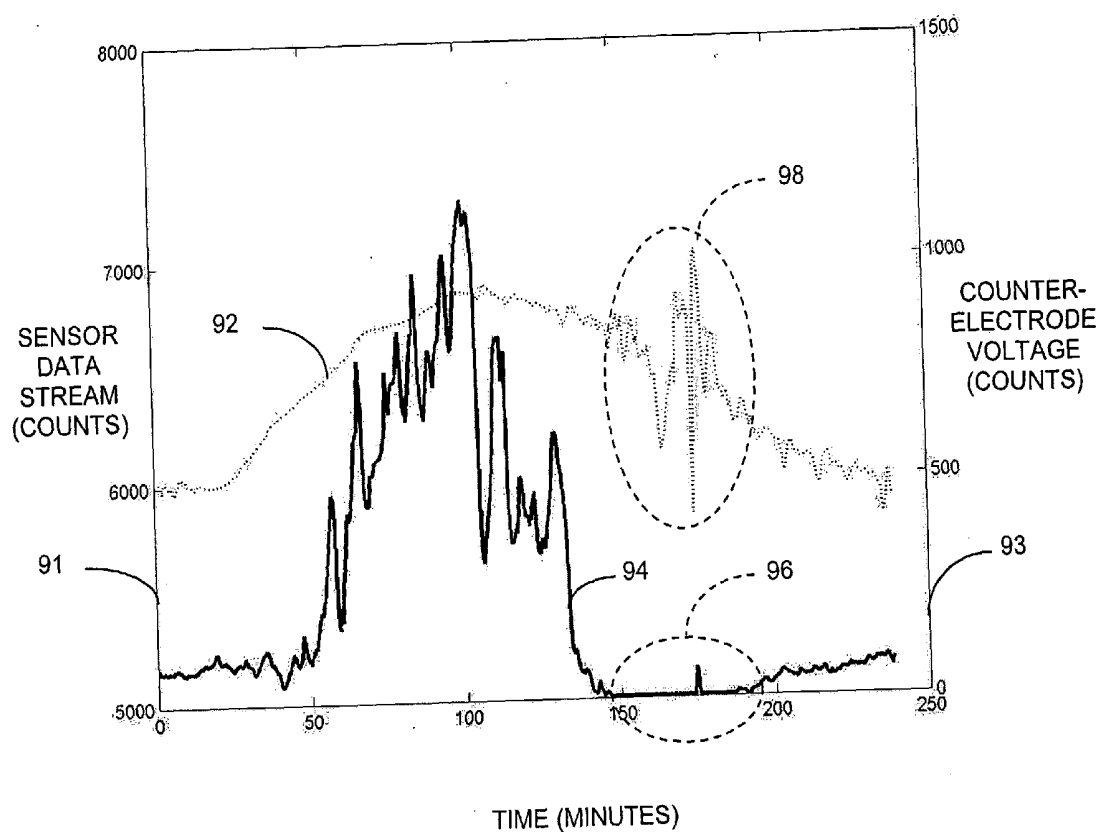


FIG. 9

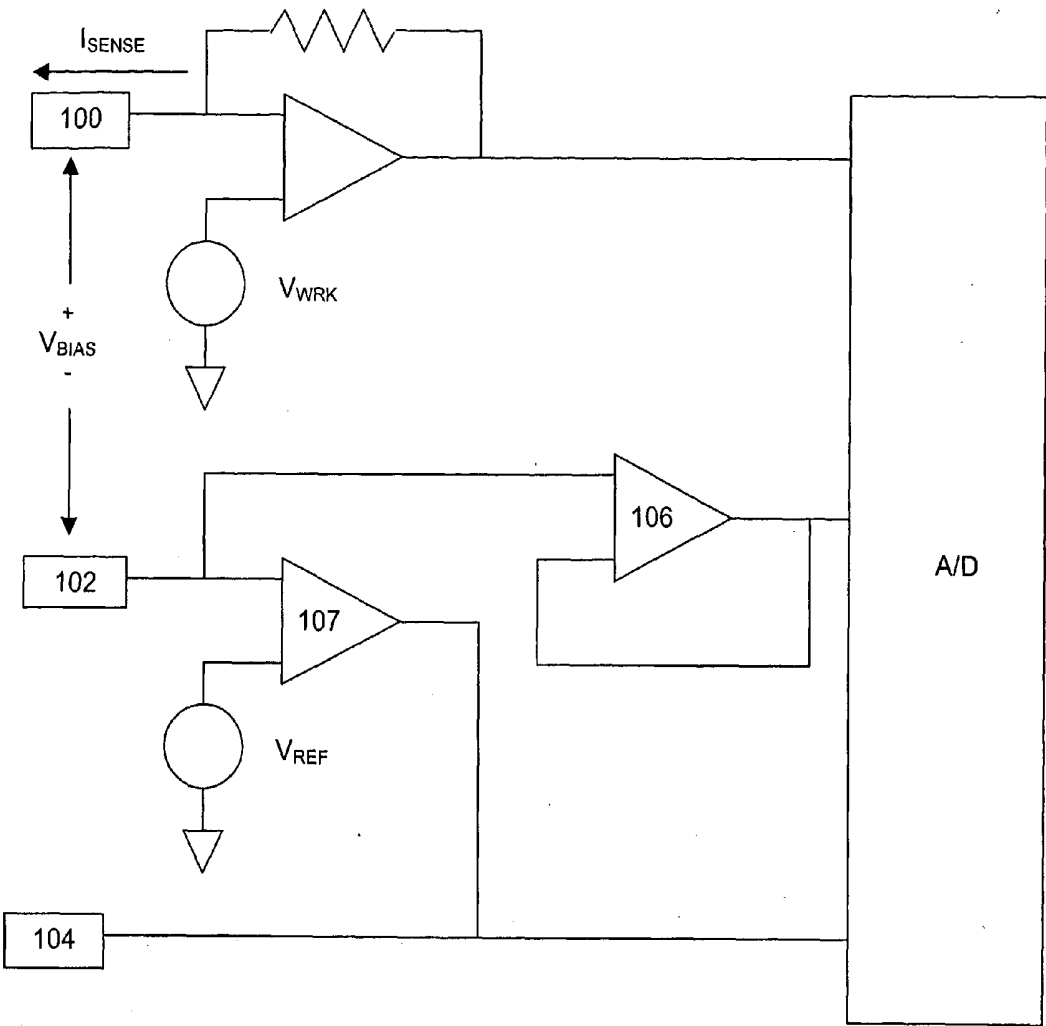


FIG. 10A

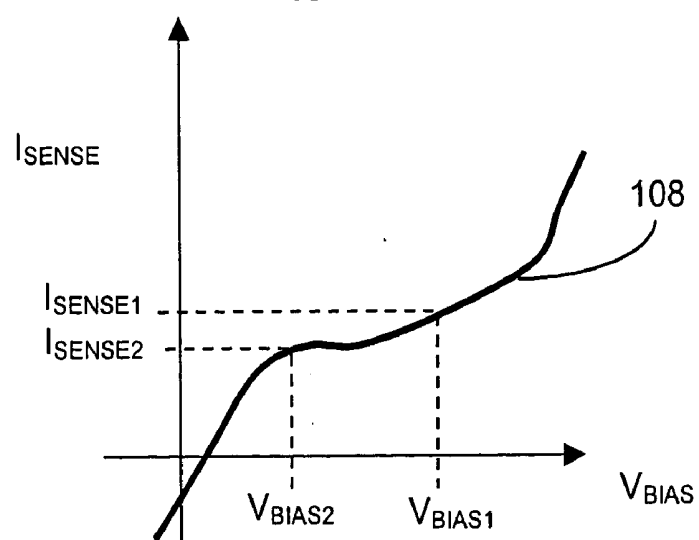


FIG. 10B

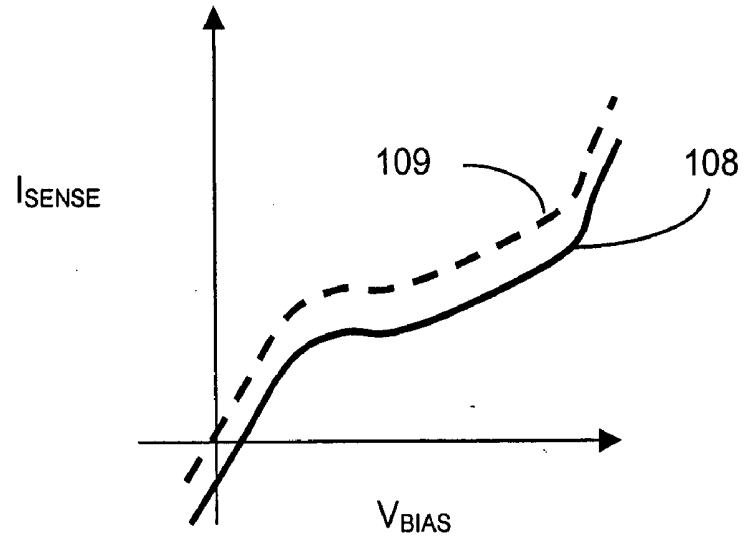


FIG. 10C

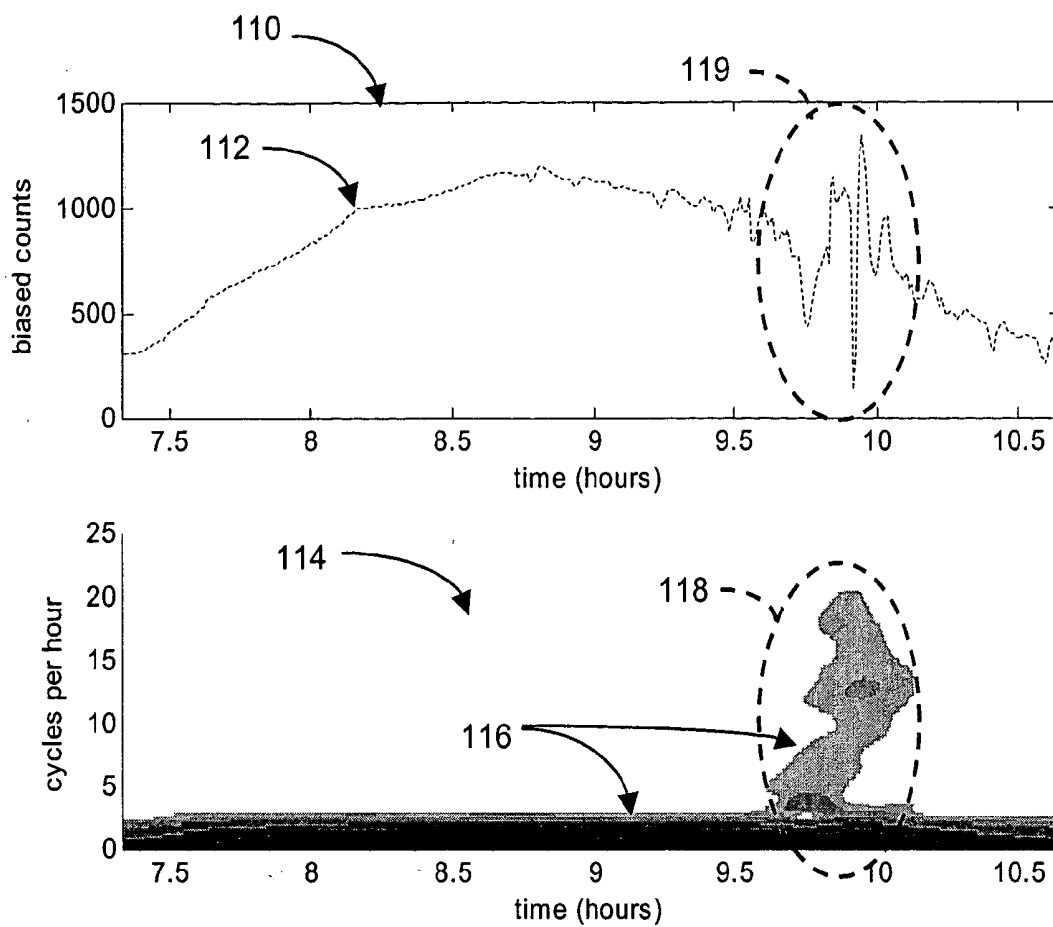


FIG. 11

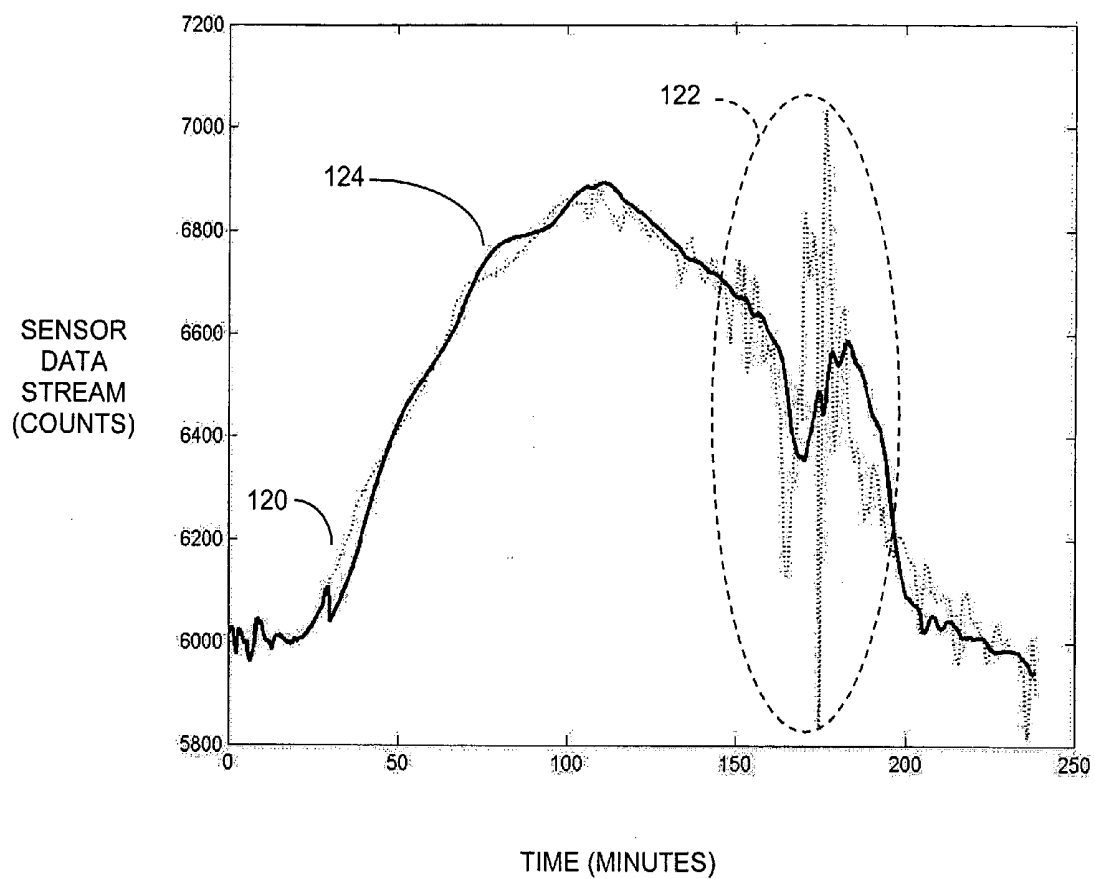


FIG. 12



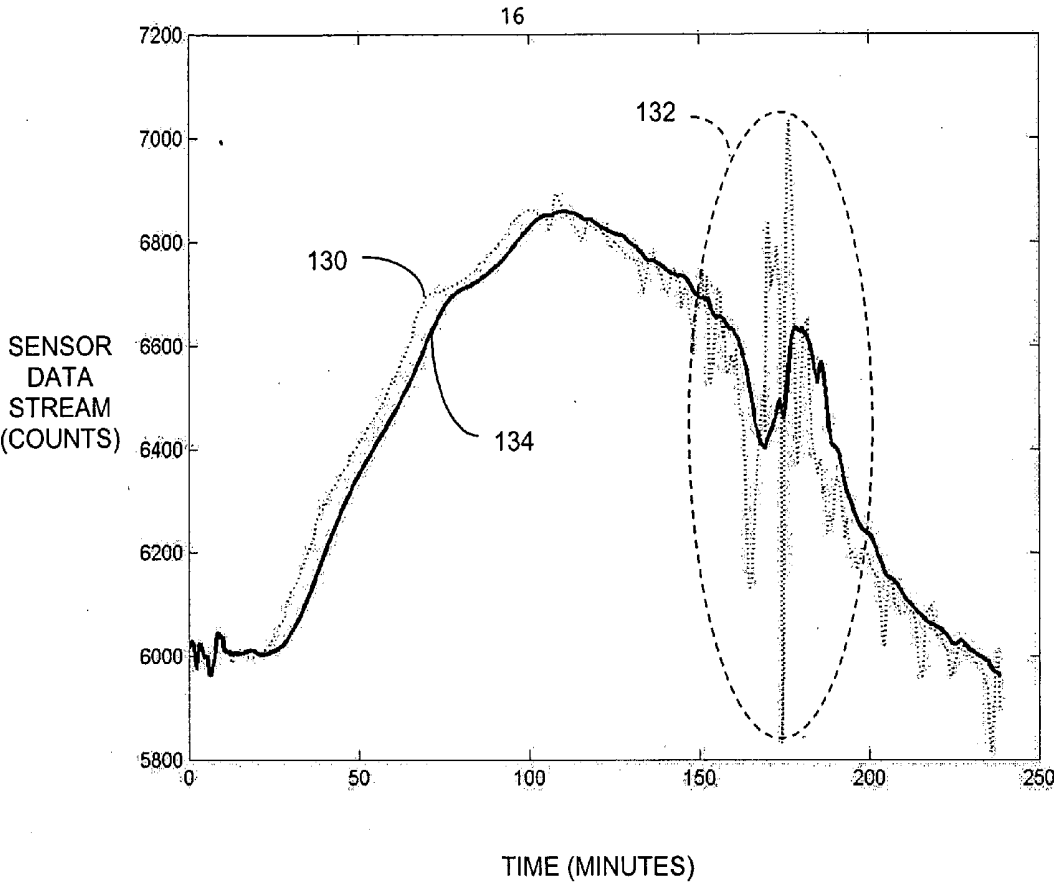


FIG. 13

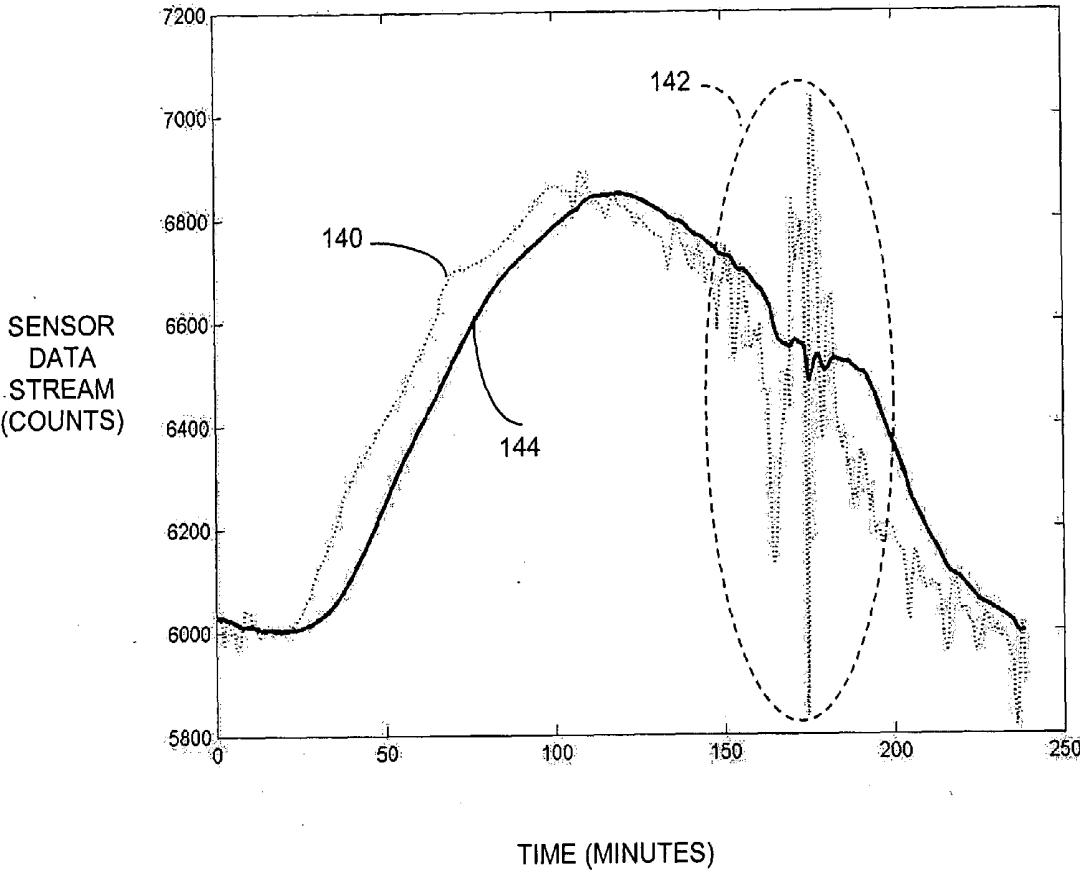


FIG. 14

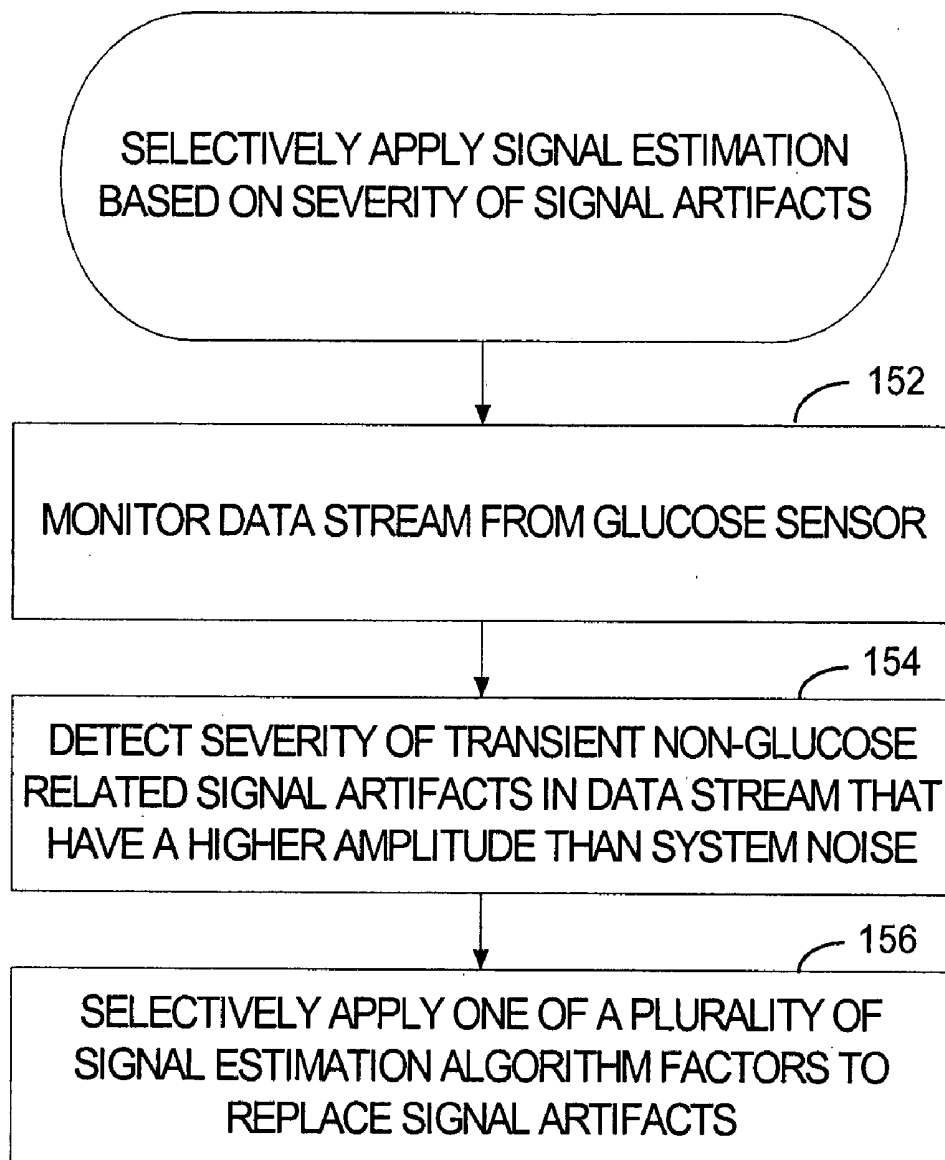


FIG. 15

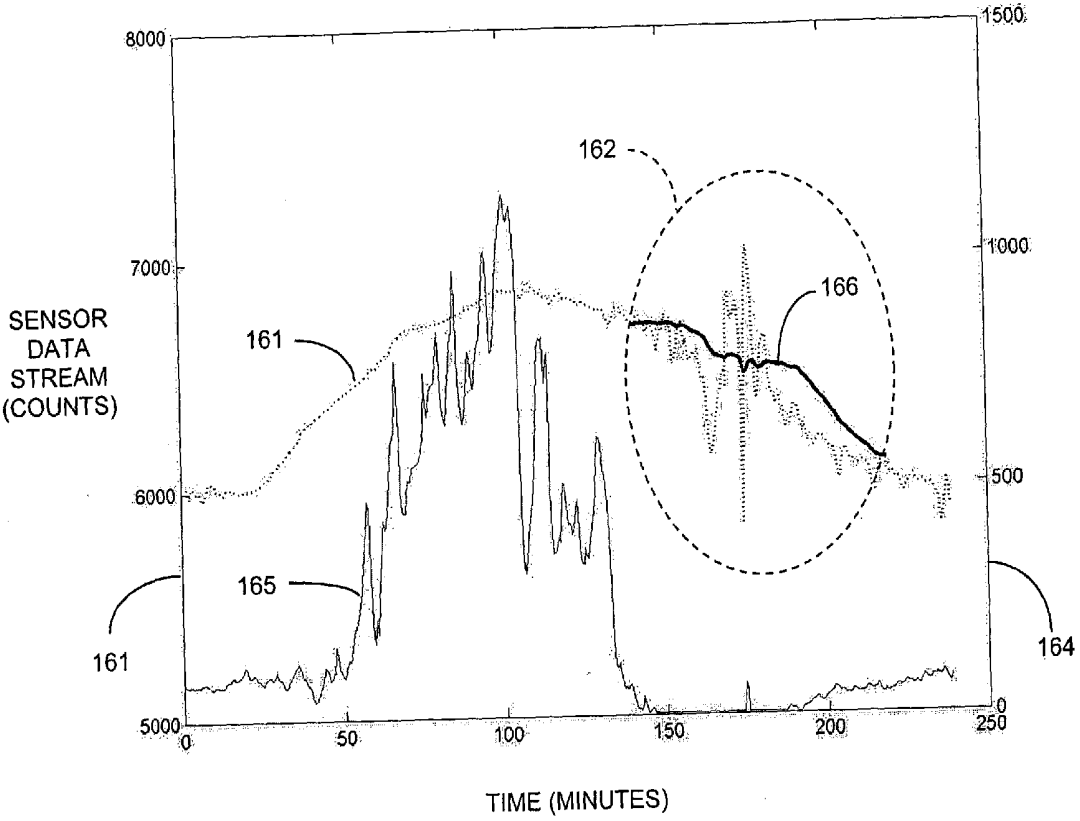


FIG. 16

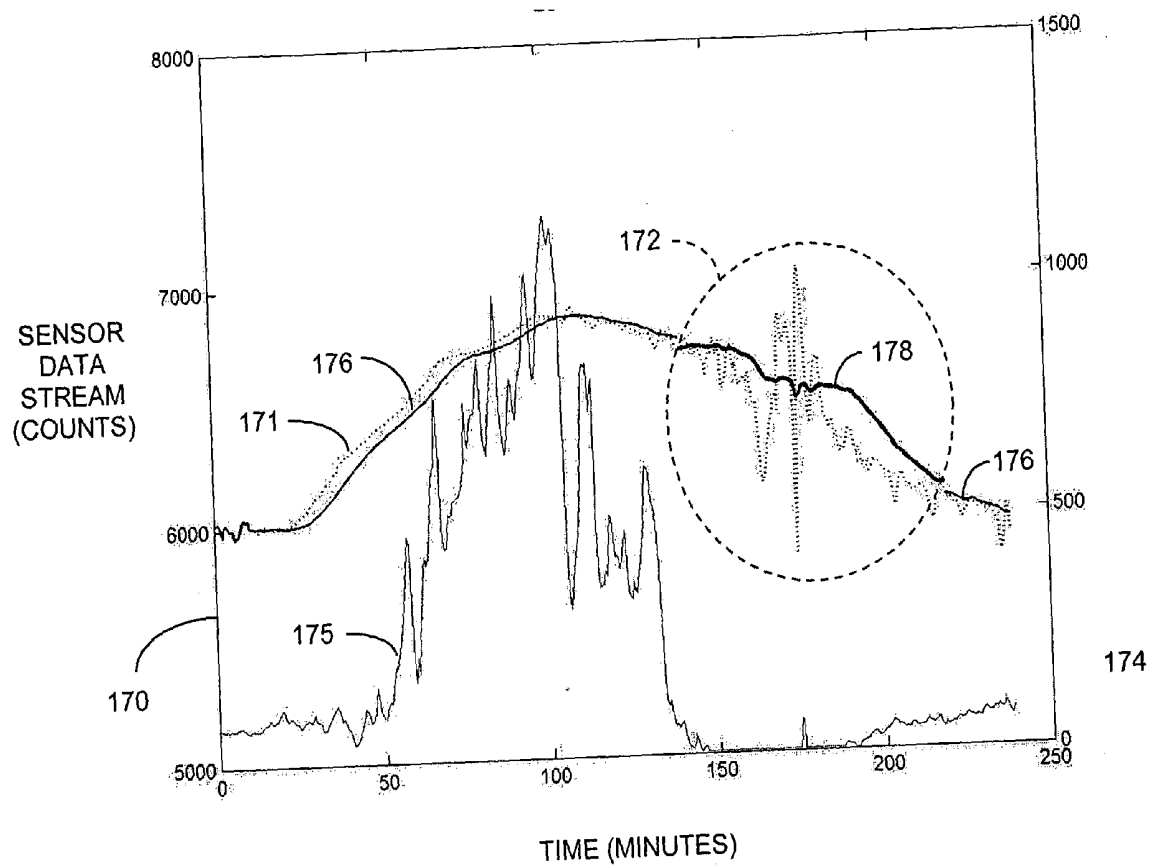


FIG. 17

## SYSTEMS AND METHODS FOR REPLACING SIGNAL ARTIFACTS IN A GLUCOSE SENSOR DATA STREAM

### FIELD OF THE INVENTION

[0001] The present invention relates generally to systems and methods for processing data received from a glucose sensor. Particularly, the present invention relates to systems and methods for detecting and replacing transient non-glucose related signal artifacts, including detecting, estimating, predicting and otherwise minimizing the effects of signal artifacts in a glucose sensor data stream.

### BACKGROUND OF THE INVENTION

[0002] Diabetes mellitus is a disorder in which the pancreas cannot create sufficient insulin (Type I or insulin dependent) and/or in which insulin is not effective (Type 2 or non-insulin dependent). In the diabetic state, the victim suffers from high blood sugar, which causes an array of physiological derangements (kidney failure, skin ulcers, or bleeding into the vitreous of the eye) associated with the deterioration of small blood vessels. A hypoglycemic reaction (low blood sugar) is induced by an inadvertent overdose of insulin, or after a normal dose of insulin or glucose-lowering agent accompanied by extraordinary exercise or insufficient food intake.

[0003] Conventionally, a diabetic person carries a self-monitoring blood glucose (SMBG) monitor, which typically comprises uncomfortable finger pricking methods. Due to the lack of comfort and convenience, a diabetic will normally only measure his or her glucose level two to four times per day. Unfortunately, these time intervals are so far spread apart that the diabetic will likely find out too late, sometimes incurring dangerous side effects, of a hyperglycemic or hypoglycemic condition. In fact, it is not only unlikely that a diabetic will take a timely SMBG value, but additionally the diabetic will not know if their blood glucose value is going up (higher) or down (lower) based on conventional methods.

[0004] Consequently, a variety of transdermal and implantable electrochemical sensors are being developed for continuous detecting and/or quantifying blood glucose values. Many implantable glucose sensors suffer from complications within the body and provide only short-term and less-than-accurate sensing of blood glucose. Similarly, transdermal sensors have run into problems in accurately sensing and reporting back glucose values continuously over extended periods of time. Some efforts have been made to obtain blood glucose data from implantable devices and retrospectively determine blood glucose trends for analysis, however these efforts do not aid the diabetic in determining real-time blood glucose information. Some efforts have also been made to obtain blood glucose data from transdermal devices for prospective data analysis, however similar problems have occurred.

[0005] Data streams from glucose sensors are known to have some amount of noise, caused by unwanted electronic and/or diffusion-related system noise that degrades the quality of the data stream. Some attempts have been made in conventional glucose sensors to smooth the raw output data stream representative of the concentration of blood glucose in the sample, for example by smoothing or filtering of

Gaussian, white, random, and/or other relatively low amplitude noise in order to improve the signal to noise ratio, and thus data output.

### SUMMARY OF THE INVENTION

[0006] Systems and methods are provided that accurately detect and replace signal noise that is caused by substantially non-glucose reaction rate-limiting phenomena, such as ischemia, pH changes, temperature changes, pressure, and stress, for example, which are referred to herein as signal artifacts. Detecting and replacing signal artifacts in a raw glucose data can provide accurate estimated glucose measurements to a diabetic patient so that they can proactively care for their condition to safely avoid hyperglycemic and hypoglycemic conditions.

[0007] In a first embodiment a method is provided for analyzing data from a glucose sensor, including: monitoring a data stream from the sensor; detecting transient non-glucose related signal artifacts in the data stream that have a higher amplitude than a system noise; and replacing at least some of the signal artifacts using estimated glucose signal values.

[0008] In an aspect of the first embodiment, the data signal obtaining step includes receiving data from one of non-invasive, minimally invasive, and invasive glucose sensor.

[0009] In an aspect of the first embodiment, the data signal obtaining step includes receiving data from one of an enzymatic, chemical, physical, electrochemical, spectrophotometric, polarimetric, calorimetric, iontophoretic, and radiometric glucose sensor.

[0010] In an aspect of the first embodiment, the data signal obtaining step includes receiving data from a wholly implantable glucose sensor.

[0011] In an aspect of the first embodiment, the signal artifacts detection step includes testing for ischemia within or proximal to the glucose sensor.

[0012] In an aspect of the first embodiment, the ischemia testing step includes obtaining oxygen concentration using an oxygen sensor proximal to or within the glucose sensor.

[0013] In an aspect of the first embodiment, the ischemia testing step includes comparing a measurement from an oxygen sensor proximal to or within the glucose sensor with a measurement from an oxygen sensor distal from the glucose sensor.

[0014] In an aspect of the first embodiment, the glucose sensor includes an electrochemical cell including a working electrode and a reference electrode, and wherein the ischemia-testing step includes pulsed amperometric detection.

[0015] In an aspect of the first embodiment, the glucose sensor includes an electrochemical cell including working, counter and reference electrodes, and wherein the ischemia-testing step includes monitoring the counter electrode.

[0016] In an aspect of the first embodiment, the glucose sensor includes an electrochemical cell including working, counter and reference electrodes, and wherein the ischemia-testing step includes monitoring the reference electrode.

[0017] In an aspect of the first embodiment, the glucose sensor includes an electrochemical cell including an anode and a cathode, and wherein the ischemia-testing step includes monitoring the cathode.

[0018] In an aspect of the first embodiment, the signal artifacts detection step includes monitoring a level of pH proximal to the sensor.

[0019] In an aspect of the first embodiment, the signal artifacts detection step includes monitoring a temperature proximal to the sensor.

[0020] In an aspect of the first embodiment, the signal artifacts detection step includes comparing a level of pH proximal to and distal to the sensor.

[0021] In an aspect of the first embodiment, the signal artifacts detection step includes comparing a temperature proximal to and distal to the sensor.

[0022] In an aspect of the first embodiment, the signal artifacts detection step includes monitoring a pressure or stress within the glucose sensor.

[0023] In an aspect of the first embodiment, the signal artifacts detection step includes evaluating historical data for high amplitude noise above a predetermined threshold.

[0024] In an aspect of the first embodiment, the signal artifacts detection step includes a Cone of Possibility Detection Method.

[0025] In an aspect of the first embodiment, the signal artifacts detection step includes evaluating the data stream for a non-physiological rate-of-change.

[0026] In an aspect of the first embodiment, the signal artifacts detection step includes monitoring the frequency content of the signal.

[0027] In an aspect of the first embodiment, the frequency-content monitoring step includes performing an orthogonal basis function-based transform.

[0028] In an aspect of the first embodiment, the transform is a Fourier Transform or a wavelet transform.

[0029] In an aspect of the first embodiment, the artifacts replacement step includes performing linear or non-linear regression.

[0030] In an aspect of the first embodiment, the artifacts replacement step includes performing a trimmed mean.

[0031] In an aspect of the first embodiment, the artifacts replacement step includes filtering using a non-recursive filter.

[0032] In an aspect of the first embodiment, the non-recursive filtering step uses a finite impulse response filter.

[0033] In an aspect of the first embodiment, the artifacts replacement step includes filtering using a recursive filter.

[0034] In an aspect of the first embodiment, the recursive filtering step uses an infinite impulse response filter.

[0035] In an aspect of the first embodiment, the artifacts replacement step includes a performing a maximum average algorithm.

[0036] In an aspect of the first embodiment, the artifacts replacement step includes performing a Cone of Possibility Replacement Method.

[0037] In an aspect of the first embodiment, the method further includes estimating future glucose signal values based on historical glucose values.

[0038] In an aspect of the first embodiment, the glucose future estimation step includes algorithmically estimating the future signal value based using at least one of linear regression, non-linear regression, and an auto-regressive algorithm.

[0039] In an aspect of the first embodiment, the glucose future estimation step further includes measuring at least one of rate-of-change, acceleration, and physiologically feasibility of one or more signal values and subsequently selectively applying the algorithm conditional on a range of one of the measurements.

[0040] In an aspect of the first embodiment, the glucose sensor includes an electrochemical cell including working, counter, and reference electrodes, and wherein the artifacts replacement step includes normalizing the data signal based on baseline drift at the reference electrode.

[0041] In an aspect of the first embodiment, the signal artifacts replacement step is substantially continual.

[0042] In an aspect of the first embodiment, the signal artifacts replacement step is initiated in response to positive detection of signal artifacts.

[0043] In an aspect of the first embodiment, the signal artifacts replacement step is terminated in response to detection of negligible signal artifacts.

[0044] In an aspect of the first embodiment, the signal artifacts detection step includes evaluating the severity of the signal artifacts.

[0045] In an aspect of the first embodiment, the severity evaluation is based on an amplitude of the transient non-glucose related signal artifacts.

[0046] In an aspect of the first embodiment, the severity evaluation is based on a duration of the transient non-glucose related signal artifacts.

[0047] In an aspect of the first embodiment, the severity evaluation is based on a rate-of-change of the transient non-glucose related signal artifacts.

[0048] In an aspect of the first embodiment, the severity evaluation is based on a frequency content of the transient non-glucose related signal artifacts.

[0049] In an aspect of the first embodiment, the artifacts replacement step includes selectively applying one of a plurality of signal estimation algorithm factors in response to the severity of the signal artifacts.

[0050] In an aspect of the first embodiment, the plurality of signal estimation algorithm factors includes a single algorithm with a plurality of parameters that are selectively applied to the algorithm.

[0051] In an aspect of the first embodiment, the plurality of signal estimation algorithm factors includes a plurality of distinct algorithms.

[0052] In an aspect of the first embodiment, the step of selectively applying one of a plurality of signal estimation algorithm factors includes selectively applying a predetermined algorithm that includes a set of parameters whose values depend on the severity of the signal artifacts.

[0053] In an aspect of the first embodiment, the method further includes discarding at least some of the signal artifacts.

[0054] In an aspect of the first embodiment, the method further includes projecting glucose signal values for a time during which no data is available.

[0055] In a second embodiment, a method is provided for processing data signals obtained from a glucose sensor including: obtaining a data stream from a glucose sensor; detecting transient non-glucose related signal artifacts in the data stream that have a higher amplitude than a system noise; and selectively applying one of a plurality of signal estimation algorithm factors to replace non-glucose related signal artifacts.

[0056] In an aspect of the second embodiment, the data signal obtaining step includes receiving data from one of non-invasive, minimally invasive, and invasive glucose sensor.

[0057] In an aspect of the second embodiment, the data signal obtaining step includes receiving data from one of an enzymatic, chemical, physical, electrochemical, spectrophotometric, polarimetric, calorimetric, iontophoretic, and radiometric glucose sensor.

[0058] In an aspect of the second embodiment, the data signal obtaining step includes receiving data from a wholly implantable glucose sensor.

[0059] In an aspect of the second embodiment, the signal artifacts detection step includes testing for ischemia within or proximal to the glucose sensor.

[0060] In an aspect of the second embodiment, the ischemia testing step includes obtaining oxygen concentration using an oxygen sensor proximal to or within the glucose sensor.

[0061] In an aspect of the second embodiment, the ischemia testing step includes comparing a measurement from an oxygen sensor proximal to or within the glucose sensor with a measurement from an oxygen sensor distal from the glucose sensor.

[0062] In an aspect of the second embodiment, the glucose sensor includes an electrochemical cell including a working electrode and a reference electrode, and wherein the ischemia-testing step includes pulsed amperometric detection.

[0063] In an aspect of the second embodiment, the glucose sensor includes an electrochemical cell including working, counter and reference electrodes, and wherein the ischemia-testing step includes monitoring the counter electrode.

[0064] In an aspect of the second embodiment, the glucose sensor includes an electrochemical cell including working, counter and reference electrodes, and wherein the ischemia testing step includes monitoring the reference electrode.

[0065] In an aspect of the second embodiment, the glucose sensor includes an electrochemical cell including an anode

and a cathode, and wherein the ischemia-testing step includes monitoring the cathode.

[0066] In an aspect of the second embodiment, the signal artifacts detection step includes monitoring a level of pH proximal to the sensor.

[0067] In an aspect of the second embodiment, the signal artifacts detection step includes monitoring a temperature proximal to the sensor.

[0068] In an aspect of the second embodiment, the signal artifacts detection step includes comparing a level of pH proximal to and distal to the sensor.

[0069] In an aspect of the second embodiment, the signal artifacts detection step includes comparing a temperature proximal to and distal to the sensor.

[0070] In an aspect of the second embodiment, the signal artifacts detection step includes monitoring the pressure or stress within the glucose sensor.

[0071] In an aspect of the second embodiment, the signal artifacts detection step includes evaluating historical data for high amplitude noise above a predetermined threshold.

[0072] In an aspect of the second embodiment, the signal artifacts detection step includes a Cone of Possibility Detection Method.

[0073] In an aspect of the second embodiment, the signal artifacts detection step includes evaluating the signal for a non-physiological rate-of-change.

[0074] In an aspect of the second embodiment, the signal artifacts detection step includes monitoring the frequency content of the signal.

[0075] In an aspect of the second embodiment, the frequency-content monitoring step includes performing an orthogonal basis function-based transform.

[0076] In an aspect of the second embodiment, the transform is a Fourier Transform or a wavelet transform.

[0077] In an aspect of the second embodiment, the artifacts replacement step includes performing linear or non-linear regression.

[0078] In an aspect of the second embodiment, the artifacts replacement step includes performing a trimmed mean.

[0079] In an aspect of the second embodiment, the artifacts replacement step includes filtering using a non-recursive filter.

[0080] In an aspect of the second embodiment, the non-recursive filtering step uses a finite impulse response filter.

[0081] In an aspect of the second embodiment, the artifacts replacement step includes filtering using a recursive filter.

[0082] In an aspect of the second embodiment, the recursive filtering step uses an infinite impulse response filter.

[0083] In an aspect of the second embodiment, the artifacts replacement step includes performing a maximum average algorithm.

[0084] In an aspect of the second embodiment, the artifacts replacement step includes performing a Cone of Possibility algorithm.



[0085] In an aspect of the second embodiment, the method further includes estimating future glucose signal values based on historical glucose values.

[0086] In an aspect of the second embodiment, the glucose future estimation step includes algorithmically estimating the future signal value based using at least one of linear regression, non-linear regression, and an auto-regressive algorithm.

[0087] In an aspect of the second embodiment, the glucose future estimation step further includes measuring at least one of rate-of-change, acceleration, and physiologically feasibility of one or more signal values and subsequently selectively applying the algorithm conditional on a range of one of the measurements.

[0088] In an aspect of the second embodiment, the glucose sensor includes an electrochemical cell including working, counter, and reference electrodes, and wherein the artifacts replacement step includes normalizing the data signal based on baseline drift at the reference electrode.

[0089] In an aspect of the second embodiment, the selective application step is substantially continual.

[0090] In an aspect of the second embodiment, the selective application step is initiated in response to positive detection of signal artifacts.

[0091] In an aspect of the second embodiment, the selective application step is terminated in response to detection of negligible signal artifacts.

[0092] In an aspect of the second embodiment, the signal artifacts detection step includes evaluating the severity of the signal artifacts.

[0093] In an aspect of the second embodiment, the severity evaluation is based on an amplitude of the transient non-glucose related signal artifacts.

[0094] In an aspect of the second embodiment, the severity evaluation is based on a duration of the transient non-glucose related signal artifacts.

[0095] In an aspect of the second embodiment, the severity evaluation is based on a rate-of-change of the transient non-glucose related signal artifacts.

[0096] In an aspect of the second embodiment, the severity evaluation is based on a frequency content of the transient non-glucose related signal artifacts.

[0097] In an aspect of the second embodiment, the selective application step applies the one of a plurality of signal estimation algorithm factors in response to the severity of the signal artifacts.

[0098] In an aspect of the second embodiment, the plurality of signal estimation algorithm factors includes a single algorithm with a plurality of parameters that are selectively applied to the algorithm.

[0099] In an aspect of the second embodiment, the plurality of signal estimation algorithm factors includes a plurality of distinct algorithms.

[0100] In an aspect of the second embodiment, the selective application step includes selectively applying a predetermined algorithm that includes a set of parameters whose values depend on the severity of the signal artifacts.

[0101] In an aspect of the second embodiment, the method further includes discarding at least some of the signal artifacts.

[0102] In an aspect of the second embodiment, the selective application step further includes projecting glucose signal values for a time during which no data is available.

[0103] In a third embodiment, a system is provided for processing data signals obtained from a glucose sensor, including: a signal processing module including programming to monitor a data stream from the sensor over a period of time; a detection module including programming to detect transient non-glucose related signal artifacts in the data stream that have a higher amplitude than a system noise; and a signal estimation module including programming to replace at least some of the signal artifacts with estimated glucose signal values.

[0104] In an aspect of the third embodiment, the signal processing module is adapted to receive data from one of non-invasive, minimally invasive, and invasive glucose sensor.

[0105] In an aspect of the third embodiment, the signal processing module is adapted to receive data from one of an enzymatic, chemical, physical, electrochemical, spectrophotometric, polarimetric, calorimetric, iontophoretic, and radiometric glucose sensor.

[0106] In an aspect of the third embodiment, the signal processing module is adapted to receive data from a wholly implantable glucose sensor.

[0107] In an aspect of the third embodiment, the detection module includes programming to for ischemia detection.

[0108] In an aspect of the third embodiment, the detection module includes programming to detect ischemia from a first oxygen sensor located proximal to or within the glucose sensor.

[0109] In an aspect of the third embodiment, the detection module further includes programming to compare a measurement from a first oxygen sensor located proximal to or within the glucose sensor with a measurement from a second oxygen sensor located distal to the glucose sensor for ischemia detection.

[0110] In an aspect of the third embodiment, the detection module further includes programming to detect ischemia using pulsed amperometric detection of an electrochemical cell including a working electrode and a reference electrode.

[0111] In an aspect of the third embodiment, the detection module further includes programming to detect ischemia by monitoring a counter electrode of an electrochemical cell that includes working, counter and reference electrodes.

[0112] In an aspect of the third embodiment, the detection module further includes programming to detect ischemia by monitoring a reference electrode of an electrochemical cell that includes working, counter and reference electrodes.

[0113] In an aspect of the third embodiment, the detection module further includes programming to detect ischemia by monitoring a cathode of an electrochemical cell.

[0114] In an aspect of the third embodiment, the detection module monitors a level of pH proximal to the glucose sensor.

[0115] In an aspect of the third embodiment, the detection module monitors a temperature proximal to the glucose sensor.

[0116] In an aspect of the third embodiment, the detection module compares a level of pH proximal to and distal to the sensor.

[0117] In an aspect of the third embodiment, the detection module compares a temperature proximal to and distal to the glucose sensor.

[0118] In an aspect of the third embodiment, the detection module monitors a pressure or stress within the glucose sensor.

[0119] In an aspect of the third embodiment, the detection module evaluates historical data for high amplitude noise above a predetermined threshold.

[0120] In an aspect of the third embodiment, the detection module includes programming to perform a Cone of Possibility to detect signal artifacts.

[0121] In an aspect of the third embodiment, the detection module evaluates the data stream for a non-physiological rate-of-change.

[0122] In an aspect of the third embodiment, the detection module monitors the frequency content of the signal.

[0123] In an aspect of the third embodiment, the detection module monitors the frequency content including performing an orthogonal basis function-based transform.

[0124] In an aspect of the third embodiment, the orthogonal basis function-based transform includes a Fourier Transform or a wavelet transform.

[0125] In an aspect of the third embodiment, the signal estimation module estimates glucose signal values using linear or non-linear regression.

[0126] In an aspect of the third embodiment, the signal estimation module estimates glucose signal values using a trimmed mean.

[0127] In an aspect of the third embodiment, the signal estimation module estimates glucose signal values using a non-recursive filter.

[0128] In an aspect of the third embodiment, the non-recursive filter is a finite impulse response filter.

[0129] In an aspect of the third embodiment, the signal estimation module estimates glucose signal values using a recursive filter.

[0130] In an aspect of the third embodiment, the recursive filter is an infinite impulse response filter.

[0131] In an aspect of the third embodiment, the signal estimation module estimates glucose signal values using a maximum average algorithm.

[0132] In an aspect of the third embodiment, the signal estimation module estimates glucose signal values using a Cone of Possibility Replacement Method.

[0133] In an aspect of the third embodiment, the signal estimation module further includes programming to estimate future glucose signal values based on historical glucose values.

[0134] In an aspect of the third embodiment, the future glucose signal value programming includes algorithmically estimating the future signal value based using at least one of linear regression, non-linear regression, and an auto-regressive algorithm.

[0135] In an aspect of the third embodiment, the signal estimation module further includes programming to measure at least one of rate-of-change, acceleration, and physiologically feasibility of one or more signal values, and wherein the signal estimation module further includes programming to selectively apply an algorithm responsive to value of one of the measurements from the detection module.

[0136] In an aspect of the third embodiment, signal estimation module includes programming to normalize the data stream based on baseline drift at a reference electrode of a glucose sensor that includes an electrochemical cell including working, counter, and reference electrodes.

[0137] In an aspect of the third embodiment, the signal estimation module continually replaces the data stream with estimated signal values.

[0138] In an aspect of the third embodiment, the signal estimation module initiates signal replacement of the data stream in response to positive detection of signal artifacts.

[0139] In an aspect of the third embodiment, the signal estimation module terminates signal replacement in response to detection of negligible signal artifacts.

[0140] In an aspect of the third embodiment, the detection module evaluates the severity of the signal artifacts.

[0141] In an aspect of the third embodiment, the detection module evaluates the severity of the signal artifacts based on an amplitude of the transient non-glucose related signal artifacts.

[0142] In an aspect of the third embodiment, the detection module evaluates the severity of the signal artifacts based on a duration of the transient non-glucose related signal artifacts.

[0143] In an aspect of the third embodiment, the detection module evaluates the severity of the signal artifacts based on a rate-of-change of the transient non-glucose related signal artifacts.

[0144] In an aspect of the third embodiment, the detection module evaluates the severity of the signal artifacts based on a frequency content of the transient non-glucose related signal artifacts.

[0145] In an aspect of the third embodiment, the signal estimation module includes programming to selectively apply one of a plurality of signal estimation algorithm factors in response to the severity of the signal artifacts.

[0146] In an aspect of the third embodiment, the plurality of signal estimation algorithm factors includes a single algorithm with a plurality of parameters that are selectively applied to the algorithm.

[0147] In an aspect of the third embodiment, the plurality of signal estimation algorithm factors includes a plurality of distinct algorithms.

[0148] In an aspect of the third embodiment, the signal estimation module selectively applies a set of parameters

whose values depend on the severity of the signal artifacts to one of a predetermined algorithm.

[0149] In an aspect of the third embodiment, the detection module includes programming to discard at least some of the signal artifacts.

[0150] In an aspect of the third embodiment, the signal estimation module includes programming to project glucose signal values for a time during which no data is available.

[0151] In a fourth embodiment, a system is provided for processing data signals obtained from a glucose sensor, the system including: a signal processing module including programming to monitor a data stream from the sensor over a period of time; a detection module including programming to detect transient non-glucose related signal artifacts in the wherein the plurality of signal estimation algorithm factors include a plurality of distinct algorithms data streams that have a higher amplitude than a system noise; and a signal estimation module including programming to selectively apply one of a plurality of signal estimation algorithm factors to replace non-glucose related signal artifacts.

[0152] In an aspect of the fourth embodiment, the signal processing module is adapted to receive data from one of non-invasive, minimally invasive, and invasive glucose sensor.

[0153] In an aspect of the fourth embodiment, the signal processing module is adapted to receive data from one of an enzymatic, chemical, physical, electrochemical, spectrophotometric, polarimetric, calorimetric, iontophoretic, and radiometric glucose sensor.

[0154] In an aspect of the fourth embodiment, the signal processing module is adapted to receive data from a wholly implantable glucose sensor.

[0155] In an aspect of the fourth embodiment, the detection module includes programming to detect ischemia within or proximal to the glucose sensor.

[0156] In an aspect of the fourth embodiment, the detection module includes programming to obtain oxygen concentration using an oxygen sensor proximal to or within the glucose sensor.

[0157] In an aspect of the fourth embodiment, the detection module includes programming to compare a measurement from an oxygen sensor proximal to or within the glucose sensor with a measurement from an oxygen sensor distal from the glucose sensor.

[0158] In an aspect of the fourth embodiment, the detection module includes programming to detect ischemia using pulsed amperometric detection of an electrochemical cell that includes a working electrode and a reference electrode.

[0159] In an aspect of the fourth embodiment, the detection module includes programming to monitor a counter electrode of a glucose sensor that includes an electrochemical cell including working, counter and reference electrodes.

[0160] In an aspect of the fourth embodiment, the detection module includes programming to monitor a reference electrode of a glucose sensor that includes an electrochemical cell including working, counter and reference electrodes.

[0161] In an aspect of the fourth embodiment, the detection module includes programming to monitor a cathode of

a glucose sensor that includes an electrochemical cell including an anode and a cathode.

[0162] In an aspect of the fourth embodiment, the detection module includes programming to monitor a level of pH proximal to the glucose sensor.

[0163] In an aspect of the fourth embodiment, the detection module includes programming to monitor a temperature proximal to the glucose sensor.

[0164] In an aspect of the fourth embodiment, the detection module includes programming to compare a level of pH proximal to and distal to the glucose sensor.

[0165] In an aspect of the fourth embodiment, the detection module includes programming to compare a temperature proximal to and distal to the sensor.

[0166] In an aspect of the fourth embodiment, the detection module includes programming to monitor a pressure or stress within the glucose sensor.

[0167] In an aspect of the fourth embodiment, the detection module includes programming to evaluate historical data for high amplitude noise above a predetermined threshold.

[0168] In an aspect of the fourth embodiment, the detection module includes programming to perform Cone of Possibility Detection.

[0169] In an aspect of the fourth embodiment, the detection module includes programming to evaluate the signal for a non-physiological rate-of-change.

[0170] In an aspect of the fourth embodiment, the detection module includes programming to monitor the frequency content of the signal.

[0171] In an aspect of the fourth embodiment, the detection module performs an orthogonal basis function-based transform to monitor frequency content.

[0172] In an aspect of the fourth embodiment, the transform is a Fourier Transform or a wavelet transform.

[0173] In an aspect of the fourth embodiment, the signal estimation module estimates glucose signal values using linear or non-linear regression.

[0174] In an aspect of the fourth embodiment, the signal estimation module estimates glucose signal values using a trimmed mean.

[0175] In an aspect of the fourth embodiment, the signal estimation module estimates glucose signal values using a non-recursive filter.

[0176] In an aspect of the fourth embodiment, the non-recursive filter is a finite impulse response filter.

[0177] In an aspect of the fourth embodiment, the signal estimation module estimates glucose signal values using a recursive filter.

[0178] In an aspect of the fourth embodiment, the recursive filter is an infinite impulse response filter.

[0179] In an aspect of the fourth embodiment, the signal estimation module estimates glucose signal values using a maximum average algorithm.

[0180] In an aspect of the fourth embodiment, the signal estimation module estimates glucose signal values using Cone of Possibility Replacement Method algorithm.

[0181] In an aspect of the fourth embodiment, the signal estimation module further includes programming to estimate future glucose signal values based on historical glucose values.

[0182] In an aspect of the fourth embodiment, future glucose signal value programming includes algorithmically estimating the future signal value based using at least one of linear regression, non-linear regression, and an auto-regressive algorithm.

[0183] In an aspect of the fourth embodiment, the signal estimation module further includes programming to measure at least one of rate-of-change, acceleration, and physiologically feasibility of one or more signal values, and wherein the signal estimation module further includes programming to selectively apply an algorithm responsive to value of one of the measurements from the detection module.

[0184] In an aspect of the fourth embodiment, the signal estimation module includes programming to normalize the data stream based on baseline drift at a reference electrode of a glucose sensor that includes an electrochemical cell including working, counter, and reference electrodes.

[0185] In an aspect of the fourth embodiment, the signal estimation module continually replaces the data stream with estimated signal values.

[0186] In an aspect of the fourth embodiment, the signal estimation module initiates signal replacement of the data stream in response to positive detection of signal artifacts.

[0187] In an aspect of the fourth embodiment, the signal estimation module terminates signal replacement in response to detection of negligible signal artifacts.

[0188] In an aspect of the fourth embodiment, the detection module evaluates the severity of the signal artifacts.

[0189] In an aspect of the fourth embodiment, the detection module evaluates the severity of the signal artifacts based on an amplitude of the transient non-glucose related signal artifacts.

[0190] In an aspect of the fourth embodiment, the detection module evaluates the severity of the signal artifacts based on a duration of the transient non-glucose related signal artifacts.

[0191] In an aspect of the fourth embodiment, the detection module evaluates the severity of the signal artifacts based on a rate-of-change of the transient non-glucose related signal artifacts.

[0192] In an aspect of the fourth embodiment, the detection module evaluates the severity of the signal artifacts based on a frequency content of the transient non-glucose related signal artifacts.

[0193] In an aspect of the fourth embodiment, the signal estimation module includes programming to selectively apply one of a plurality of signal estimation algorithm factors in response to the severity of the signal artifacts.

[0194] In an aspect of the fourth embodiment, the plurality of signal estimation algorithm factors includes a single algorithm with a plurality of parameters that are selectively applied to the algorithm.

[0195] In an aspect of the fourth embodiment, the plurality of signal estimation algorithm factors includes a plurality of distinct algorithms.

[0196] In an aspect of the fourth embodiment, the signal estimation module selectively applies a set of parameters whose values depend on the severity of the signal artifacts to one of a predetermined algorithm.

[0197] In an aspect of the fourth embodiment, the detection module includes programming to discard at least some of the signal artifacts.

[0198] In an aspect of the fourth embodiment, the signal estimation module includes programming to project glucose signal values for a time during which no data is available.

[0199] In a fifth embodiment, an implantable glucose monitoring device is provided including: a glucose sensor; and a processor operatively linked to the sensor designed to receive a data stream from the sensor; wherein the processor is programmed to analyze the data stream and to detect transient non-glucose related signal artifacts in the data stream that have a higher amplitude than system noise, and to replace at least some of the signal artifacts with estimated values.

#### BRIEF DESCRIPTION OF THE DRAWINGS

[0200] FIG. 1 is an exploded perspective view of a glucose sensor in one embodiment.

[0201] FIG. 2 is a block diagram that illustrates sensor electronics in one embodiment.

[0202] FIGS. 3A to 3D are schematic views of a receiver in first, second, third, and fourth embodiments, respectively.

[0203] FIG. 4 is a block diagram of receiver electronics in one embodiment.

[0204] FIG. 5 is a flow chart that illustrates the process of calibrating the sensor data in one embodiment.

[0205] FIG. 6 is a graph that illustrates a linear regression used to calibrate the sensor data in one embodiment.

[0206] FIG. 7A is a graph that shows a raw data stream obtained from a glucose sensor over a 4 hour time span in one example.

[0207] FIG. 7B is a graph that shows a raw data stream obtained from a glucose sensor over a 36 hour time span in another example.

[0208] FIG. 8 is a flow chart that illustrates the process of detecting and replacing transient non-glucose related signal artifacts in a data stream in one embodiment.

[0209] FIG. 9 is a graph that illustrates the correlation between the counter electrode voltage and signal artifacts in a data stream from a glucose sensor in one embodiment.

[0210] FIG. 10A is a circuit diagram of a potentiostat that controls a typical three-electrode system in one embodiment.

[0211] FIG. 10B is a diagram known as Cyclic-Voltammetry (CV) curve, which illustrates the relationship between applied potential ( $V_{BIAS}$ ) and signal strength of the working electrode ( $I_{SENSE}$ ) and can be used to detect signal artifacts.

[0212] FIG. 10C is a diagram showing a CV curve that illustrates an alternative embodiment of signal artifacts detection, wherein pH and/or temperature can be monitoring using the CV curve.

[0213] FIG. 11 is a graph and spectrogram that illustrate the correlation between high frequency and signal artifacts observed by monitoring the frequency content of a data stream in one embodiment.

[0214] FIG. 12 is a graph that illustrates a data stream obtained from a glucose sensor and a signal smoothed by trimmed linear regression that can be used to replace some of or the entire raw data stream in one embodiment.

[0215] FIG. 13 is a graph that illustrates a data stream obtained from a glucose sensor and a FIR-smoothed data signal that can be used to replace some of or the entire raw data stream in one embodiment.

[0216] FIG. 14 is a graph that illustrates a data stream obtained from a glucose sensor and an IIR-smoothed data signal that can be used to replace some of or the entire raw data stream in one embodiment.

[0217] FIG. 15 is a flowchart that illustrates the process of selectively applying signal estimation based on the severity of signal artifacts on a data stream.

[0218] FIG. 16 is a graph that illustrates selectively applying a signal estimation algorithm responsive to positive detection of signal artifacts on the raw data stream.

[0219] FIG. 17 is a graph that illustrates selectively applying a plurality of signal estimation algorithm factors responsive to a severity of signal artifacts on the raw data stream.

#### DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0220] The following description and examples illustrate some exemplary embodiments of the disclosed invention in detail. Those of skill in the art will recognize that there are numerous variations and modifications of this invention that are encompassed by its scope. Accordingly, the description of a certain exemplary embodiment should not be deemed to limit the scope of the present invention.

#### Definitions

[0221] In order to facilitate an understanding of the preferred embodiments, a number of terms are defined below.

[0222] The term “EEPROM,” as used herein, is a broad term and is used in its ordinary sense, including, without limitation, electrically erasable programmable read-only memory, which is user-modifiable read-only memory (ROM) that can be erased and reprogrammed (e.g., written to) repeatedly through the application of higher than normal electrical voltage.

[0223] The term “SRAM,” as used herein, is a broad term and is used in its ordinary sense, including, without limitation, static random access memory (RAM) that retains data bits in its memory as long as power is being supplied.

[0224] The term “A/D Converter,” as used herein, is a broad term and is used in its ordinary sense, including, without limitation, hardware and/or software that converts analog electrical signals into corresponding digital signals.

[0225] The term “microprocessor,” as used herein, is a broad term and is used in its ordinary sense, including, without limitation a computer system or processor designed to perform arithmetic and logic operations using logic circuitry that responds to and processes the basic instructions that drive a computer.

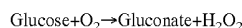
[0226] The term “RF transceiver,” as used herein, is a broad term and is used in its ordinary sense, including, without limitation, a radio frequency transmitter and/or receiver for transmitting and/or receiving signals.

[0227] The term “jitter,” as used herein, is a broad term and is used in its ordinary sense, including, without limitation, noise above and below the mean caused by ubiquitous noise caused by a circuit and/or environmental effects; jitter can be seen in amplitude, phase timing, or the width of the signal pulse.

[0228] The terms “raw data stream” and “data stream,” as used herein, are broad terms and are used in their ordinary sense, including, without limitation, an analog or digital signal directly related to the measured glucose from the glucose sensor. In one example, the raw data stream is digital data in “counts” converted by an A/D converter from an analog signal (e.g., voltage or amps) representative of a glucose concentration. The terms broadly encompass a plurality of time spaced data points from a substantially continuous glucose sensor, which comprises individual measurements taken at time intervals ranging from fractions of a second up to, e.g., 1, 2, or 5 minutes or longer.

[0229] The term “counts,” as used herein, is a broad term and is used in its ordinary sense, including, without limitation, a unit of measurement of a digital signal. In one example, a raw data stream measured in counts is directly related to a voltage (e.g., converted by an A/D converter), which is directly related to current from the working electrode. In another example, counter electrode voltage measured in counts is directly related to a voltage.

[0230] The terms “glucose sensor” and “member for determining the amount of glucose in a biological sample,” as used herein, are broad terms and are used in an ordinary sense, including, without limitation, any mechanism (e.g., enzymatic or non-enzymatic) by which glucose can be quantified. For example, some embodiments utilize a membrane that contains glucose oxidase that catalyzes the conversion of oxygen and glucose to hydrogen peroxide and gluconate, as illustrated by the following chemical reaction:



[0231] Because for each glucose molecule metabolized, there is a proportional change in the co-reactant O<sub>2</sub> and the product H<sub>2</sub>O<sub>2</sub>, one can use an electrode to monitor the current change in either the co-reactant or the product to determine glucose concentration.

[0232] The terms “operably connected” and “operably linked,” as used herein, are broad terms and are used in their ordinary sense, including, without limitation, one or more components being linked to another component(s) in a manner that allows transmission of signals between the components. For example, one or more electrodes can be used to detect the amount of glucose in a sample and convert that information into a signal, e.g., an electrical or electromagnetic signal; the signal can then be transmitted to an

electronic circuit. In this case, the electrode is “operably linked” to the electronic circuitry. These terms are broad enough to include wireless connectivity.

[0233] The term “electronic circuitry,” as used herein, is a broad term and is used in its ordinary sense, including, without limitation, the components of a device configured to process biological information obtained from a host. In the case of a glucose-measuring device, the biological information is obtained by a sensor regarding a particular glucose in a biological fluid, thereby providing data regarding the amount of that glucose in the fluid. U.S. Pat. Nos. 4,757,022, 5,497,772 and 4,787,398, which are hereby incorporated by reference, describe suitable electronic circuits that can be utilized with devices including the biointerface membrane of a preferred embodiment.

[0234] The term “substantially” as used herein, is a broad term and is used in its ordinary sense, including, without limitation, being largely but not necessarily wholly that which is specified.

[0235] The term “proximal” as used herein, is a broad term and is used in its ordinary sense, including, without limitation, near to a point of reference such as an origin, a point of attachment, or the midline of the body. For example, in some embodiments of a glucose sensor, wherein the glucose sensor is the point of reference, an oxygen sensor located proximal to the glucose sensor will be in contact with or nearby the glucose sensor such that their respective local environments are shared (e.g., levels of glucose, oxygen, pH, temperature, etc. are similar).

[0236] The term “distal” as used herein, is a broad term and is used in its ordinary sense, including, without limitation, spaced relatively far from a point of reference, such as an origin or a point of attachment, or midline of the body. For example, in some embodiments of a glucose sensor, wherein the glucose sensor is the point of reference, an oxygen sensor located distal to the glucose sensor will be sufficiently far from the glucose sensor such that their respective local environments are not shared (e.g., levels of glucose, oxygen, pH, temperature, etc. may not be similar).

[0237] The term “electrochemical cell,” as used herein, is a broad term and is used in its ordinary sense, including, without limitation, a device in which chemical energy is converted to electrical energy. Such a cell typically consists of two or more electrodes held apart from each other and in contact with an electrolyte solution. Connection of the electrodes to a source of direct electric current renders one of them negatively charged and the other positively charged. Positive ions in the electrolyte migrate to the negative electrode (cathode) and there combine with one or more electrons, losing part or all of their charge and becoming new ions having lower charge or neutral atoms or molecules; at the same time, negative ions migrate to the positive electrode (anode) and transfer one or more electrons to it, also becoming new ions or neutral particles. The overall effect of the two processes is the transfer of electrons from the negative ions to the positive ions, a chemical reaction.

[0238] The term “potentiostat,” as used herein, is a broad term and is used in its ordinary sense, including, without limitation, an electrical system that controls the potential between the working and reference electrodes of a three-electrode cell at a preset value. It forces whatever current is

necessary to flow between the working and counter electrodes to keep the desired potential, as long as the needed cell voltage and current do not exceed the compliance limits of the potentiostat.

[0239] The term “electrical potential,” as used herein, is a broad term and is used in its ordinary sense, including, without limitation, the electrical potential difference between two points in a circuit which is the cause of the flow of a current.

[0240] The term “host,” as used herein, is a broad term and is used in its ordinary sense, including, without limitation, mammals, particularly humans.

[0241] The phrase “continuous glucose sensing,” as used herein, is a broad term and is used in its ordinary sense, including, without limitation, the period in which monitoring of plasma glucose concentration is continuously or continually performed, for example, at time intervals ranging from fractions of a second up to, e.g., 1, 2, or 5 minutes, or longer.

[0242] The term “sensor head,” as used herein, is a broad term and is used in its ordinary sense, including, without limitation, the region of a monitoring device responsible for the detection of a particular glucose. The sensor head generally comprises a non-conductive body, a working electrode (anode), a reference electrode and a counter electrode (cathode) passing through and secured within the body forming an electrochemically reactive surface at one location on the body and an electronic connection at another location on the body, and a multi-region membrane affixed to the body and covering the electrochemically reactive surface. The counter electrode typically has a greater electrochemically reactive surface area than the working electrode. During general operation of the sensor a biological sample (e.g., blood or interstitial fluid) or a portion thereof contacts (directly or after passage through one or more membranes or domains) an enzyme (e.g., glucose oxidase); the reaction of the biological sample (or portion thereof) results in the formation of reaction products that allow a determination of the glucose level in the biological sample. In some embodiments, the multi-region membrane includes an enzyme domain (e.g., glucose oxidase), and an electrolyte phase (e.g., a free-flowing liquid phase comprising an electrolyte-containing fluid, as described further below).

[0243] The term “electrochemically reactive surface,” as used herein, is a broad term and is used in its ordinary sense, including, without limitation, the surface of an electrode where an electrochemical reaction takes place. In the case of the working electrode, the hydrogen peroxide produced by the enzyme catalyzed reaction of the glucose being detected reacts creating a measurable electronic current (e.g., detection of glucose utilizing glucose oxidase produces  $H_2O_2$  as a by product,  $H_2O_2$  reacts with the surface of the working electrode producing two protons ( $2H^+$ ), two electrons ( $2e^-$ ) and one molecule of oxygen ( $O_2$ ) which produces the electronic current being detected). In the case of the counter electrode, a reducible species, e.g.,  $O_2$  is reduced at the electrode surface in order to balance the current being generated by the working electrode.

[0244] The term “electronic connection,” as used herein, is a broad term and is used in its ordinary sense, including, without limitation, any electronic connection known to those

in the art that can be utilized to interface the sensor head electrodes with the electronic circuitry of a device such as mechanical (e.g., pin and socket) or soldered.

[0245] The terms “operably connected” and “operably linked,” as used herein, are broad terms and are used in their ordinary sense, including, without limitation, one or more components being linked to another component(s) in a manner that allows transmission of signals between the components, e.g., wired or wirelessly. For example, one or more electrodes can be used to detect the amount of analyte in a sample and convert that information into a signal; the signal can then be transmitted to an electronic circuit means. In this case, the electrode is “operably linked” to the electronic circuitry.

[0246] The term “sensing membrane,” as used herein, is a broad term and is used in its ordinary sense, including, without limitation, a permeable or semi-permeable membrane that can be comprised of two or more domains and is typically constructed of materials of a few microns thickness or more, which are permeable to oxygen and may or may not be permeable to glucose. In one example, the sensing membrane comprises an immobilized glucose oxidase enzyme, which enables an electrochemical reaction to occur to measure a concentration of glucose.

[0247] The term “biointerface membrane,” as used herein, is a broad term and is used in its ordinary sense, including, without limitation, a permeable membrane that can be comprised of two or more domains and is typically constructed of materials of a few microns thickness or more, which can be placed over the sensor body to keep host cells (e.g., macrophages) from gaining proximity to, and thereby damaging, the sensing membrane or forming a barrier cell layer and interfering with the transport of glucose across the tissue-device interface.

[0248] The term “Clarke Error Grid,” as used herein, is a broad term and is used in its ordinary sense, including, without limitation, an error grid analysis, which evaluates the clinical significance of the difference between a reference glucose value and a sensor generated glucose value, taking into account 1) the value of the reference glucose measurement, 2) the value of the sensor glucose measurement, 3) the relative difference between the two values, and 4) the clinical significance of this difference. See Clarke et al., “Evaluating Clinical Accuracy of Systems for Self-Monitoring of Blood Glucose,” *Diabetes Care*, Volume 10, Number 5, September-October 1987, which is incorporated by reference herein in its entirety.

[0249] The term “physiologically feasible,” as used herein, is a broad term and is used in its ordinary sense, including, without limitation, the physiological parameters obtained from continuous studies of glucose data in humans and/or animals. For example, a maximal sustained rate of change of glucose in humans of about 4 to 5 mg/dL/min and a maximum acceleration of the rate of change of about 0.1 to 0.2 mg/dL/min are deemed physiologically feasible limits. Values outside of these limits would be considered non-physiological and likely a result of signal error, for example. As another example, the rate of change of glucose is lowest at the maxima and minima of the daily glucose range, which are the areas of greatest risk in patient treatment, thus a physiologically feasible rate of change can be set at the maxima and minima based on continuous studies

of glucose data. As a further example, it has been observed that the best solution for the shape of the curve at any point along glucose signal data stream over a certain time period (e.g., about 20 to 30 minutes) is a straight line, which can be used to set physiological limits.

[0250] The term “ischemia,” as used herein, is a broad term and is used in its ordinary sense, including, without limitation, local and temporary deficiency of blood supply due to obstruction of circulation to a part (e.g., sensor). Ischemia can be caused by mechanical obstruction (e.g., arterial narrowing or disruption) of the blood supply, for example.

[0251] The term “system noise,” as used herein, is a broad term and is used in its ordinary sense, including, without limitation, unwanted electronic or diffusion-related noise which can include Gaussian, motion-related, flicker, kinetic, or other white noise, for example.

[0252] The terms “signal artifacts” and “transient non-glucose related signal artifacts that have a higher amplitude than system noise,” as used herein, are broad terms and are used in their ordinary sense, including, without limitation, signal noise that is caused by substantially non-glucose reaction rate-limiting phenomena, such as ischemia, pH changes, temperature changes, pressure, and stress, for example. Signal artifacts, as described herein, are typically transient and characterized by a higher amplitude than system noise.

[0253] The terms “low noise,” as used herein, is a broad term and is used in its ordinary sense, including, without limitation, noise that substantially decreases signal amplitude.

[0254] The terms “high noise” and “high spikes,” as used herein, are broad terms and are used in their ordinary sense, including, without limitation, noise that substantially increases signal amplitude.

[0255] The term “frequency content,” as used herein, is a broad term and is used in its ordinary sense, including, without limitation, the spectral density, including the frequencies contained within a signal and their power.

[0256] The term “spectral density,” as used herein, is a broad term and is used in its ordinary sense, including, without limitation, power spectral density of a given bandwidth of electromagnetic radiation is the total power in this bandwidth divided by the specified bandwidth. Spectral density is usually expressed in Watts per Hertz (W/Hz).

[0257] The term “orthogonal transform,” as used herein, is a broad term and is used in its ordinary sense, including, without limitation, a general integral transform that is defined by

$$g(\alpha) = \int_a^b f(t)K(\alpha, t)dt,$$

[0258] where  $K(\alpha, t)$  represents a set of orthogonal basis functions.

[0259] The term “Fourier Transform,” as used herein, is a broad term and is used in its ordinary sense, including,

without limitation, a technique for expressing a waveform as a weighted sum of sines and cosines.

[0260] The term “Discrete Fourier Transform,” as used herein, is a broad term and is used in its ordinary sense, including, without limitation, a specialized Fourier transform where the variables are discrete.

[0261] The term “wavelet transform,” as used herein, is a broad term and is used in its ordinary sense, including, without limitation, a transform which converts a signal into a series of wavelets, which in theory allows signals processed by the wavelet transform to be stored more efficiently than ones processed by Fourier transform. Wavelets can also be constructed with rough edges, to better approximate real-world signals.

[0262] The term “chronoamperometry,” as used herein, is a broad term and is used in its ordinary sense, including, without limitation, an electrochemical measuring technique used for electrochemical analysis or for the determination of the kinetics and mechanism of electrode reactions. A fast-rising potential pulse is enforced on the working (or reference) electrode of an electrochemical cell and the current flowing through this electrode is measured as a function of time.

[0263] The term “pulsed amperometric detection,” as used herein, is a broad term and is used in its ordinary sense, including, without limitation, an electrochemical flow cell and a controller, which applies the potentials and monitors current generated by the electrochemical reactions. The cell can include one or multiple working electrodes at different applied potentials. Multiple electrodes can be arranged so that they face the chromatographic flow independently (parallel configuration), or sequentially (series configuration).

[0264] The term “linear regression,” as used herein, is a broad term and is used in its ordinary sense, including, without limitation, finding a line in which a set of data has a minimal measurement from that line. Byproducts of this algorithm include a slope, a y-intercept, and an R-Squared value that determine how well the measurement data fits the line.

[0265] The term “non-linear regression,” as used herein, is a broad term and is used in its ordinary sense, including, without limitation, fitting a set of data to describe the relationship between a response variable and one or more explanatory variables in a non-linear fashion.

[0266] The term “mean,” as used herein, is a broad term and is used in its ordinary sense, including, without limitation, the sum of the observations divided by the number of observations.

[0267] The term “trimmed mean,” as used herein, is a broad term and is used in its ordinary sense, including, without limitation, a mean taken after extreme values in the tails of a variable (e.g., highs and lows) are eliminated or reduced (e.g., “trimmed”). The trimmed mean compensates for sensitivities to extreme values by dropping a certain percentage of values on the tails. For example, the 50% trimmed mean is the mean of the values between the upper and lower quartiles. The 90% trimmed mean is the mean of the values after truncating the lowest and highest 5% of the values. In one example, two highest and two lowest mea-

surements are removed from a data set and then the remaining measurements are averaged.

[0268] The term “non-recursive filter,” as used herein, is a broad term and is used in its ordinary sense, including, without limitation, an equation that uses moving averages as inputs and outputs.

[0269] The terms “recursive filter” and “auto-regressive algorithm,” as used herein, are broad terms and are used in their ordinary sense, including, without limitation, an equation in which includes previous averages are part of the next filtered output. More particularly, the generation of a series of observations whereby the value of each observation is partly dependent on the values of those that have immediately preceded it. One example is a regression structure in which lagged response values assume the role of the independent variables.

[0270] The term “signal estimation algorithm factors,” as used herein, is a broad term and is used in its ordinary sense, including, without limitation, one or more algorithms that use historical and/or present signal data stream values to estimate unknown signal data stream values. For example, signal estimation algorithm factors can include one or more algorithms, such as linear or non-linear regression. As another example, signal estimation algorithm factors can include one or more sets of coefficients that can be applied to one algorithm.

[0271] As employed herein, the following abbreviations apply: Eq and Eqs (equivalents); mEq (milliequivalents); M (molar); mM (millimolar);  $\mu$ M (micromolar); N (Normal); mol (moles); mmol (millimoles);  $\mu$ mol (micromoles); nmol (nanomoles); g (grams); mg (milligrams);  $\mu$ g (micrograms); Kg (kilograms); L (liters); mL (milliliters); dL (deciliters);  $\mu$ L (microliters); cm (centimeters); mm (millimeters);  $\mu$ m (micrometers); nm (nanometers); h and hr (hours); min. (minutes); s and sec. (seconds); ° C. (degrees Centigrade).

[0272] Overview

[0273] The preferred embodiments relate to the use of a glucose sensor that measures a concentration of glucose or a substance indicative of the concentration or presence of the glucose. In some embodiments, the glucose sensor is a continuous device, for example a subcutaneous, transdermal, or intravascular device. In some embodiments, the device can analyze a plurality of intermittent blood samples. The glucose sensor can use any method of glucose-measurement, including enzymatic, chemical, physical, electrochemical, spectrophotometric, polarimetric, calorimetric, iontophoretic, radiometric, or the like.

[0274] The glucose sensor can use any known method, including invasive, minimally invasive, and non-invasive sensing techniques, to provide a data stream indicative of the concentration of glucose in a host. The data stream is typically a raw data signal that is used to provide a useful value of glucose to a user, such as a patient or doctor, who may be using the sensor. It is well known that raw data streams typically include system noise such as defined herein; however the preferred embodiments address the detection and replacement of “signal artifacts” as defined herein. Accordingly, appropriate signal estimation (e.g., filtering, data smoothing, augmenting, projecting, and/or other methods) replace such erroneous signals (e.g., signal artifacts) in the raw data stream.



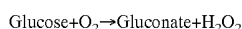
**[0275]** Glucose Sensor

**[0276]** The glucose sensor can be any device capable of measuring the concentration of glucose. One exemplary embodiment is described below, which utilizes an implantable glucose sensor. However, it should be understood that the devices and methods described herein can be applied to any device capable of detecting a concentration of glucose and providing an output signal that represents the concentration of glucose.

**[0277]** FIG. 1 is an exploded perspective view of one exemplary embodiment comprising an implantable glucose sensor **10** that utilizes amperometric electrochemical sensor technology to measure glucose concentration. In this exemplary embodiment, a body **12** and head **14** house the electrodes **16** and sensor electronics, which are described in more detail below with reference to FIG. 2. Three electrodes **16** are operably connected to the sensor electronics (FIG. 1) and are covered by a sensing membrane **17** and a biointerface membrane **18**, which are attached by a clip **19**.

**[0278]** In one embodiment, the three electrodes **16**, which protrude through the head **14**, include a platinum working electrode, a platinum counter electrode, and a silver/silver chloride reference electrode. The top ends of the electrodes are in contact with an electrolyte phase (not shown), which is a free-flowing fluid phase disposed between the sensing membrane **17** and the electrodes **16**. The sensing membrane **17** includes an enzyme, e.g., glucose oxidase, which covers the electrolyte phase. The biointerface membrane **18** covers the sensing membrane **17** and serves, at least in part, to protect the sensor **10** from external forces that can result in environmental stress cracking of the sensing membrane **17**.

**[0279]** In the illustrated embodiment, the counter electrode is provided to balance the current generated by the species being measured at the working electrode. In the case of a glucose oxidase based glucose sensor, the species being measured at the working electrode is  $H_2O_2$ . Glucose oxidase catalyzes the conversion of oxygen and glucose to hydrogen peroxide and gluconate according to the following reaction:



**[0280]** The change in  $H_2O_2$  can be monitored to determine glucose concentration because for each glucose molecule metabolized, there is a proportional change in the product  $H_2O_2$ . Oxidation of  $H_2O_2$  by the working electrode is balanced by reduction of ambient oxygen, enzyme generated  $H_2O_2$ , or other reducible species at the counter electrode. The  $H_2O_2$  produced from the glucose oxidase reaction further reacts at the surface of working electrode and produces two protons ( $2H^+$ ), two electrons ( $2e^-$ ), and one oxygen molecule ( $O_2$ ).

**[0281]** In one embodiment, a potentiostat is employed to monitor the electrochemical reaction at the electrochemical cell. The potentiostat applies a constant potential to the working and reference electrodes to determine a current value. The current that is produced at the working electrode (and flows through the circuitry to the counter electrode) is proportional to the amount of  $H_2O_2$  that diffuses to the working electrode. Accordingly, a raw signal can be produced that is representative of the concentration of glucose in the user's body, and therefore can be utilized to estimate a meaningful glucose value, such as described herein.

**[0282]** One problem with raw data stream output of enzymatic glucose sensors such as described above is caused by transient non-glucose reaction rate-limiting phenomenon. For example, if oxygen is deficient, relative to the amount of glucose, then the enzymatic reaction will be limited by oxygen rather than glucose. Consequently, the output signal will be indicative of the oxygen concentration rather than the glucose concentration, producing erroneous signals. Other non-glucose reaction rate-limiting phenomenon could include temperature and/or pH changes, for example. Accordingly, reduction of signal noise, and particularly replacement of transient non-glucose related signal artifacts in the data stream that have a higher amplitude than system noise, can be performed in the sensor and/or in the receiver, such as described in more detail below in the sections entitled "Signal Artifacts Detection" and "Signal Artifacts Replacement."

**[0283]** FIG. 2 is a block diagram that illustrates one possible configuration of the sensor electronics in one embodiment. In this embodiment, a potentiostat **20** is shown, which is operatively connected to electrodes **16** (FIG. 1) to obtain a current value, and includes a resistor (not shown) that translates the current into voltage. An A/D converter **21** digitizes the analog signal into "counts" for processing. Accordingly, the resulting raw data stream in counts is directly related to the current measured by the potentiostat **20**.

**[0284]** A microprocessor **22** is the central control unit that houses EEPROM **23** and SRAM **24**, and controls the processing of the sensor electronics. It is noted that certain alternative embodiments can utilize a computer system other than a microprocessor to process data as described herein. In other alternative embodiments, an application-specific integrated circuit (ASIC) can be used for some or all the sensor's central processing. The EEPROM **23** provides semi-permanent storage of data, for example, storing data such as sensor identifier (ID) and programming to process data streams (e.g., programming for signal artifacts detection and/or replacement such as described elsewhere herein). The SRAM **24** can be used for the system's cache memory, for example for temporarily storing recent sensor data.

**[0285]** A battery **25** is operatively connected to the microprocessor **22** and provides the necessary power for the sensor **10**. In one embodiment, the battery is a Lithium Manganese Dioxide battery, however any appropriately sized and powered battery can be used (e.g., AAA, Nickel-cadmium, Zinc-carbon, Alkaline, Lithium, Nickel-metal hydride, Lithium-ion, Zinc-air, Zinc-mercury oxide, Silver-zinc, or hermetically-sealed). In some embodiments the battery is rechargeable. In some embodiments, a plurality of batteries can be used to power the system. A Quartz Crystal **26** is operatively connected to the microprocessor **22** and maintains system time for the computer system as a whole.

**[0286]** An RF Transceiver **27** is operably connected to the microprocessor **22** and transmits the sensor data from the sensor **10** to a receiver (see FIGS. 3 and 4). Although an RF transceiver is shown here, some other embodiments can include a wired rather than wireless connection to the receiver. In yet other embodiments, the receiver can be transcutaneously powered via an inductive coupling, for example. A second quartz crystal **28** provides the system time for synchronizing the data transmissions from the RF

transceiver. It is noted that the transceiver **27** can be substituted with a transmitter in other embodiments.

[0287] In some embodiments, a Signal Artifacts Detector **29** includes one or more of the following: an oxygen detector **29a**, a pH detector **29b**, a temperature detector **29c**, and a pressure/stress detector **29d**, which is described in more detail with reference to signal artifacts detection. It is noted that in some embodiments the signal artifacts detector **29** is a separate entity (e.g., temperature detector) operatively connected to the microprocessor, while in other embodiments, the signal artifacts detector is a part of the microprocessor and utilizes readings from the electrodes, for example, to detect ischemia and other signal artifacts.

[0288] Receiver

[0289] FIGS. **3A** to **3D** are schematic views of a receiver **30** including representations of estimated glucose values on its user interface in first, second, third, and fourth embodiments, respectively. The receiver **30** comprises systems to receive, process, and display sensor data from the glucose sensor **10**, such as described herein. Particularly, the receiver **30** can be a pager-sized device, for example, and comprise a user interface that has a plurality of buttons **32** and a liquid crystal display (LCD) screen **34**, and which can optionally include a backlight. In some embodiments, the user interface can also include a keyboard, a speaker, and a vibrator, as described below with reference to FIG. **4**.

[0290] FIG. **3A** illustrates a first embodiment wherein the receiver **30** shows a numeric representation of the estimated glucose value on its user interface, which is described in more detail elsewhere herein.

[0291] FIG. **3B** illustrates a second embodiment wherein the receiver **30** shows an estimated glucose value and approximately one hour of historical trend data on its user interface, which is described in more detail elsewhere herein.

[0292] FIG. **3C** illustrates a third embodiment wherein the receiver **30** shows an estimated glucose value and approximately three hours of historical trend data on its user interface, which is described in more detail elsewhere herein.

[0293] FIG. **3D** illustrates a fourth embodiment wherein the receiver **30** shows an estimated glucose value and approximately nine hours of historical trend data on its user interface, which is described in more detail elsewhere herein.

[0294] In some embodiments, a user can toggle through some or all of the screens shown in FIGS. **3A** to **3D** using a toggle button on the receiver. In some embodiments, the user will be able to interactively select the type of output displayed on their user interface. In other embodiments, the sensor output can have alternative configurations.

[0295] FIG. **4** is a block diagram that illustrates one possible configuration of the receiver's **30** electronics. It is noted that the receiver **30** can comprise a configuration such as described with reference to FIGS. **3A** to **3D**, above. Alternatively, the receiver **30** can comprise other configurations, including a desktop computer, laptop computer, a personal digital assistant (PDA), a server (local or remote to the receiver), or the like. In some embodiments, the receiver **30** can be adapted to connect (via wired or wireless con-

nection) to a desktop computer, laptop computer, PDA, server (local or remote to the receiver), or the like, in order to download data from the receiver **30**. In some alternative embodiments, the receiver **30** can be housed within or directly connected to the sensor **10** in a manner that allows sensor and receiver electronics to work directly together and/or share data processing resources. Accordingly, the receiver's electronics can be generally referred to as a "computer system."

[0296] A quartz crystal **40** is operatively connected to an RF transceiver **41** that together function to receive and synchronize data streams (e.g., raw data streams transmitted from the RF transceiver). Once received, a microprocessor **42** processes the signals, such as described below.

[0297] The microprocessor **42** is the central control unit that provides the processing, such as calibration algorithms stored within EEPROM **43**. The EEPROM **43** is operatively connected to the microprocessor **42** and provides semi-permanent storage of data, storing data such as receiver ID and programming to process data streams (e.g., programming for performing calibration and other algorithms described elsewhere herein). SRAM **44** is used for the system's cache memory and is helpful in data processing.

[0298] A battery **45** is operatively connected to the microprocessor **42** and provides power for the receiver. In one embodiment, the battery is a standard AAA alkaline battery, however any appropriately sized and powered battery can be used. In some embodiments, a plurality of batteries can be used to power the system. A quartz crystal **46** is operatively connected to the microprocessor **42** and maintains system time for the computer system as a whole.

[0299] A user interface **47** comprises a keyboard **2**, speaker **3**, vibrator **4**, backlight **5**, liquid crystal display (LCD) **6**, and one or more buttons **7**. The components that comprise the user interface **47** provide controls to interact with the user. The keyboard **2** can allow, for example, input of user information about himself/herself, such as mealtime, exercise, insulin administration, and reference glucose values. The speaker **3** can provide, for example, audible signals or alerts for conditions such as present and/or predicted hyper- and hypoglycemic conditions. The vibrator **4** can provide, for example, tactile signals or alerts for reasons such as described with reference to the speaker, above. The backlight **5** can be provided, for example, to aid the user in reading the LCD in low light conditions. The LCD **6** can be provided, for example, to provide the user with visual data output such as is illustrated in FIGS. **3A** to **3D**. The buttons **7** can provide for toggle, menu selection, option selection, mode selection, and reset, for example.

[0300] Communication ports, including a PC communication (com) port **48** and a reference glucose monitor com port **49** can be provided to enable communication with systems that are separate from, or integral with, the receiver **30**. The PC com port **48**, for example, a serial communications port, allows for communicating with another computer system (e.g., PC, PDA, server, or the like). In one exemplary embodiment, the receiver **30** is able to download historical data to a physician's PC for retrospective analysis by the physician. The reference glucose monitor com port **49** allows for communicating with a reference glucose monitor (not shown) so that reference glucose values can be downloaded into the receiver **30**, for example, automatically. In

one embodiment, the reference glucose monitor is integral with the receiver **30**, and the reference glucose component **49** allows internal communication between the two integral systems. In another embodiment, the reference glucose monitor component **49** allows a wireless or wired connection to reference glucose monitor such as a self-monitoring blood glucose monitor (e.g., for measuring finger stick blood samples).

**[0301]** Calibration

**[0302]** Reference is now made to **FIG. 5**, which is a flow chart that illustrates the process of initial calibration and data output of the glucose sensor **10** in one embodiment.

**[0303]** Calibration of the glucose sensor **10** comprises data processing that converts a sensor data stream into an estimated glucose measurement that is meaningful to a user. Accordingly, a reference glucose value can be used to calibrate the data stream from the glucose sensor **10**.

**[0304]** At block **51**, a sensor data receiving module, also referred to as the sensor data module, receives sensor data (e.g., a data stream), including one or more time-spaced sensor data points, from a sensor via the receiver, which can be in wired or wireless communication with the sensor. Some or all of the sensor data point(s) can be replaced by estimated signal values to address signal noise such as described in more detail elsewhere herein. It is noted that during the initialization of the sensor, prior to initial calibration, the receiver **30** (e.g., computer system) receives and stores the sensor data, however it may not display any data to the user until initial calibration and eventually stabilization of the sensor **10** has been determined.

**[0305]** At block **52**, a reference data receiving module, also referred to as the reference input module, receives reference data from a reference glucose monitor, including one or more reference data points. In one embodiment, the reference glucose points can comprise results from a self-monitored blood glucose test (e.g., from a finger stick test). In one such embodiment, the user can administer a self-monitored blood glucose test to obtain glucose value (e.g., point) using any known glucose sensor, and enter the numeric glucose value into the computer system. In another such embodiment, a self-monitored blood glucose test comprises a wired or wireless connection to the receiver **30** (e.g. computer system) so that the user simply initiates a connection between the two devices, and the reference glucose data is passed or downloaded between the self-monitored blood glucose test and the receiver **30**. In yet another such embodiment, the self-monitored glucose test is integral with the receiver **30** so that the user simply provides a blood sample to the receiver **30**, and the receiver **30** runs the glucose test to determine a reference glucose value.

**[0306]** Certain acceptability parameters can be set for reference values received from the user. For example, in one embodiment, the receiver may only accept reference glucose values between about 40 and about 400 mg/dL.

**[0307]** At block **53**, a data matching module, also referred to as the processor module, matches reference data (e.g., one or more reference glucose data points) with substantially time corresponding sensor data (e.g., one or more sensor data points) to provide one or more matched data pairs. In one embodiment, one reference data point is matched to one time corresponding sensor data point to form a matched data

pair. In another embodiment, a plurality of reference data points are averaged (e.g., equally or non-equally weighted average, mean-value, median, or the like) and matched to one time corresponding sensor data point to form a matched data pair. In another embodiment, one reference data point is matched to a plurality of time corresponding sensor data points averaged to form a matched data pair. In yet another embodiment, a plurality of reference data points are averaged and matched to a plurality of time corresponding sensor data points averaged to form a matched data pair.

**[0308]** In one embodiment, a time corresponding sensor data comprises one or more sensor data points that occur, for example,  $15 \pm 5$  min after the reference glucose data timestamp (e.g., the time that the reference glucose data is obtained). In this embodiment, the 15 minute time delay has been chosen to account for an approximately 10 minute delay introduced by the filter used in data smoothing and an approximately 5 minute physiological time-lag (e.g., the time necessary for the glucose to diffusion through a membrane(s) of an glucose sensor). In alternative embodiments, the time corresponding sensor value can be more or less than in the above-described embodiment, for example  $\pm 60$  minutes. Variability in time correspondence of sensor and reference data can be attributed to, for example, a longer or shorter time delay introduced during signal estimation, or if the configuration of the glucose sensor **10** incurs a greater or lesser physiological time lag.

**[0309]** In some practical implementations of the sensor **10**, the reference glucose data can be obtained at a time that is different from the time that the data is input into the receiver **30**. Accordingly, it should be noted that the "time stamp" of the reference glucose (e.g., the time at which the reference glucose value was obtained) may not be the same as the time at which the receiver **30** obtained the reference glucose data. Therefore, some embodiments include a time stamp requirement that ensures that the receiver **30** stores the accurate time stamp for each reference glucose value, that is, the time at which the reference value was actually obtained from the user.

**[0310]** In some embodiments, tests are used to evaluate the best-matched pair using a reference data point against individual sensor values over a predetermined time period (e.g., about 30 minutes). In one such embodiment, the reference data point is matched with sensor data points at 5-minute intervals and each matched pair is evaluated. The matched pair with the best correlation can be selected as the matched pair for data processing. In some alternative embodiments, matching a reference data point with an average of a plurality of sensor data points over a predetermined time period can be used to form a matched pair.

**[0311]** At block **54**, a calibration set module, also referred to as the processor module, forms an initial calibration set from a set of one or more matched data pairs, which are used to determine the relationship between the reference glucose data and the sensor glucose data, such as described in more detail with reference to block **55**, below.

**[0312]** The matched data pairs, which make up the initial calibration set, can be selected according to predetermined criteria. In some embodiments, the number (n) of data pair(s) selected for the initial calibration set is one. In other embodiments, n data pairs are selected for the initial calibration set wherein n is a function of the frequency of the

received reference data points. In one exemplary embodiment, six data pairs make up the initial calibration set.

[0313] In some embodiments, the data pairs are selected only within a certain glucose value threshold, for example wherein the reference glucose value is between about 40 and about 400 mg/dL. In some embodiments, the data pairs that form the initial calibration set are selected according to their time stamp.

[0314] At block 55, the conversion function module uses the calibration set to create a conversion function. The conversion function substantially defines the relationship between the reference glucose data and the glucose sensor data. A variety of known methods can be used with the preferred embodiments to create the conversion function from the calibration set. In one embodiment, wherein a plurality of matched data points form the initial calibration set, a linear least squares regression is performed on the initial calibration set such as described in more detail with reference to FIG. 6.

[0315] At block 56, a sensor data transformation module uses the conversion function to transform sensor data into substantially real-time glucose value estimates, also referred to as calibrated data, as sensor data is continuously (or intermittently) received from the sensor. In other words, the offset value at any given point in time can be subtracted from the raw value (e.g., in counts) and divided by the slope to obtain the estimated glucose value:

$$\text{mg/dL} = \frac{(\text{rawvalue} - \text{offset})}{\text{slope}}$$

[0316] In some alternative embodiments, the sensor and/or reference glucose values are stored in a database for retrospective analysis.

[0317] At block 57, an output module provides output to the user via the user interface. The output is representative of the estimated glucose value, which is determined by converting the sensor data into a meaningful glucose value such as described in more detail with reference to block 56, above. User output can be in the form of a numeric estimated glucose value, an indication of directional trend of glucose concentration, and/or a graphical representation of the estimated glucose data over a period of time, for example. Other representations of the estimated glucose values are also possible, for example audio and tactile.

[0318] In one embodiment, such as shown in FIG. 3A, the estimated glucose value is represented by a numeric value. In other exemplary embodiments, such as shown in FIGS. 3B to 3D, the user interface graphically represents the estimated glucose data trend over predetermined a time period (e.g., one, three, and nine hours, respectively). In alternative embodiments, other time periods can be represented.

[0319] Accordingly, after initial calibration of the sensor, real-time continuous glucose information can be displayed on the user interface so that the user can regularly and proactively care for his/her diabetic condition within the bounds set by his/her physician.

[0320] In alternative embodiments, the conversion function is used to predict glucose values at future points in time.

These predicted values can be used to alert the user of upcoming hypoglycemic or hyperglycemic events. Additionally, predicted values can be used to compensate for the time lag (e.g., 15 minute time lag such as described elsewhere herein), so that an estimated glucose value displayed to the user represents the instant time, rather than a time delayed estimated value.

[0321] In some embodiments, the substantially real-time estimated glucose value, a predicted future estimated glucose value, a rate of change, and/or a directional trend of the glucose concentration is used to control the administration of a constituent to the user, including an appropriate amount and time, in order to control an aspect of the user's biological system. One such example is a closed loop glucose sensor and insulin pump, wherein the glucose data (e.g., estimated glucose value, rate of change, and/or directional trend) from the glucose sensor is used to determine the amount of insulin, and time of administration, that can be given to a diabetic user to evade hyper- and hypoglycemic conditions.

[0322] FIG. 6 is a graph that illustrates one embodiment of a regression performed on a calibration set to create a conversion function such as described with reference to FIG. 5, block 55, above. In this embodiment, a linear least squares regression is performed on the initial calibration set. The x-axis represents reference glucose data; the y-axis represents sensor data. The graph pictorially illustrates regression of matched pairs 66 in the calibration set. The regression calculates a slope 62 and an offset 64, for example, using the well-known slope-intercept equation ( $y=mx+b$ ), which defines the conversion function.

[0323] In alternative embodiments, other algorithms could be used to determine the conversion function, for example forms of linear and non-linear regression, for example fuzzy logic, neural networks, piece-wise linear regression, polynomial fit, genetic algorithms, and other pattern recognition and signal estimation techniques.

[0324] In yet other alternative embodiments, the conversion function can comprise two or more different optimal conversions because an optimal conversion at any time is dependent on one or more parameters, such as time of day, calories consumed, exercise, or glucose concentration above or below a set threshold, for example. In one such exemplary embodiment, the conversion function is adapted for the estimated glucose concentration (e.g., high vs. low). For example in an implantable glucose sensor it has been observed that the cells surrounding the implant will consume at least a small amount of glucose as it diffuses toward the glucose sensor. Assuming the cells consume substantially the same amount of glucose whether the glucose concentration is low or high, this phenomenon will have a greater effect on the concentration of glucose during low blood sugar episodes than the effect on the concentration of glucose during relatively higher blood sugar episodes. Accordingly, the conversion function can be adapted to compensate for the sensitivity differences in blood sugar level. In one implementation, the conversion function comprises two different regression lines, wherein a first regression line is applied when the estimated blood glucose concentration is at or below a certain threshold (e.g., 150 mg/dL) and a second regression line is applied when the estimated blood glucose concentration is at or above a

certain threshold (e.g., 150 mg/dL). In one alternative implementation, a predetermined pivot of the regression line that forms the conversion function can be applied when the estimated blood is above or below a set threshold (e.g., 150 mg/dL), wherein the pivot and threshold are determined from a retrospective analysis of the performance of a conversion function and its performance at a range of glucose concentrations. In another implementation, the regression line that forms the conversion function is pivoted about a point in order to comply with clinical acceptability standards (e.g., Clarke Error Grid, Consensus Grid, mean absolute relative difference, or other clinical cost function). Although only a few example implementations are described, other embodiments include numerous implementations wherein the conversion function is adaptively applied based on one or more parameters that can affect the sensitivity of the sensor data over time.

[0325] Additional methods for processing sensor glucose data are disclosed in copending U.S. patent application Ser. No. \_\_\_\_\_, filed Aug. 1, 2003 and entitled, "SYSTEM AND METHODS FOR PROCESSING ANALYTE SENSOR DATA," which is incorporated herein by reference in its entirety. In view of the above-described data processing, it should be obvious that improving the accuracy of the data stream will be advantageous for improving output of glucose sensor data. Accordingly, the following description is related to improving data output by decreasing signal artifacts on the raw data stream from the sensor. The data smoothing methods of preferred embodiments can be employed in conjunction with any sensor or monitor measuring levels of an analyte in vivo, wherein the level of the analyte fluctuates over time, including but not limited to such sensors as described in U.S. Pat. No. 6,001,067 to Shults et al.; U.S. Patent Application 2003/0023317 to Brauker et al.; U.S. Pat. No. 6,212,416 to Ward et al.; U.S. Pat. No. 6,119,028 to Schulman et al.; U.S. Pat. No. 6,400,974 to Lesho; U.S. Pat. No. 6,595,919 to Bemer et al.; U.S. Pat. No. 6,141,573 to Kumik et al.; U.S. Pat. No. 6,122,536 to Sun et al.; European Patent Application EP 1153571 to Varall et al.; U.S. Pat. No. 6,512,939 to Colvin et al.; U.S. Pat. No. 5,605,152 to Slate et al.; U.S. Pat. No. 4,431,004 to Bessman et al.; U.S. Pat. No. 4,703,756 to Gough et al.; U.S. Pat. No. 6,514,718 to Heller et al.; and U.S. Pat. No. 5,985,129 to Gough et al., each of which are incorporated in their entirety herein by reference.

#### [0326] Signal Artifacts

[0327] Typically, a glucose sensor produces a data stream that is indicative of the glucose concentration of a host, such as described in more detail above. However, it is well known that the above described glucose sensor is only one example of an abundance of glucose sensors that are able to provide raw data output indicative of the concentration of glucose. Thus, it should be understood that the systems and methods described herein, including signal artifacts detection, signal artifacts replacement, and other data processing, can be applied to a data stream obtained from any glucose sensor.

[0328] Raw data streams typically have some amount of "system noise," caused by unwanted electronic or diffusion-related noise that degrades the quality of the signal and thus the data. Accordingly, conventional glucose sensors are known to smooth raw data using methods that filter out this system noise, and the like, in order to improve the signal to

noise ratio, and thus data output. One example of a conventional data-smoothing algorithm includes a finite impulse response filter (FIR), which is particularly suited for reducing high-frequency noise (see Steil et al. U.S. Pat. No. 6,558,351).

[0329] FIGS. 7A and 7B are graphs of raw data streams from an implantable glucose sensor prior to data smoothing. FIG. 7A is a graph that shows a raw data stream obtained from a glucose sensor over an approximately 4 hour time span in one example. FIG. 7B is a graph that shows a raw data stream obtained from a glucose sensor over an approximately 36 hour time span in another example. The x-axis represents time in minutes. The y-axis represents sensor data in counts. In these examples, sensor output in counts is transmitted every 30-seconds.

[0330] The "system noise" such as shown in sections 72a, 72b of the data streams of FIGS. 7A and 7B, respectively, illustrate time periods during which system noise can be seen on the data stream. This system noise can be characterized as Gaussian, Brownian, and/or linear noise, and can be substantially normally distributed about the mean. The system noise is likely electronic and diffusion-related, or the like, and can be smoothed using techniques such as by using an FIR filter. The system noise such as shown in the data of sections 72a, 72b is a fairly accurate representation of glucose concentration and can be confidently used to report glucose concentration to the user when appropriately calibrated.

[0331] The "signal artifacts" such as shown in sections 74a, 74b of the data stream of FIGS. 7A and 7B, respectively, illustrate time periods during which "signal artifacts" can be seen, which are significantly different from the previously described system noise (sections 72a, 72b). This noise, such as shown in section 74a and 74b, is referred to herein as "signal artifacts" and more particularly described as "transient non-glucose dependent signal artifacts that have a higher amplitude than system noise." At times, signal artifacts comprise low noise, which generally refers to noise that substantially decreases signal amplitude 76a, 76b herein, which is best seen in the signal artifacts 74b of FIG. 7B. Occasional high spikes 78a, 78b, which generally correspond to noise that substantially increases signal amplitude, can also be seen in the signal artifacts, which generally occur after a period of low noise. These high spikes are generally observed after transient low noise and typically result after reaction rate-limiting phenomena occur. For example, in an embodiment where a glucose sensor requires an enzymatic reaction, local ischemia creates a reaction that is rate-limited by oxygen, which is responsible for low noise. In this situation, glucose would be expected to build up in the membrane because it would not be completely catabolized during the oxygen deficit. When oxygen is again in excess, there would also be excess glucose due to the transient oxygen deficit. The enzyme rate would speed up for a short period until the excess glucose is catabolized, resulting in high noise.

[0332] Analysis of signal artifacts such as shown sections 74a, 74b of FIGS. 7A and 7B, respectively, indicates that the observed low noise is caused by substantially non-glucose reaction dependent phenomena, such as ischemia that occurs within or around a glucose sensor in vivo, for example, which results in the reaction becoming oxygen

dependent. As a first example, at high glucose levels, oxygen can become limiting to the enzymatic reaction, resulting in a non-glucose dependent downward trend in the data (best seen in **FIG. 7B**). As a second example, certain movements or postures taken by the patient can cause transient downward noise as blood is squeezed out of the capillaries resulting in local ischemia, and causing non-glucose dependent low noise. Because excess oxygen (relative to glucose) is necessary for proper sensor function, transient ischemia can result in a loss of signal gain in the sensor data. In this second example oxygen can also become transiently limited due to contracture of tissues around the sensor interface. This is similar to the blanching of skin that can be observed when one puts pressure on it. Under such pressure, transient ischemia can occur in both the epidermis and subcutaneous tissue. Transient ischemia is common and well tolerated by subcutaneous tissue.

[0333] In another example of non-glucose reaction rate-limiting phenomena, skin temperature can vary dramatically, which can result in thermally related erosion of the signal (e.g., temperature changes between 32 and 39 degrees Celsius have been measured in humans). In yet another embodiment, wherein the glucose sensor is placed intravenously, increased impedance can result from the sensor resting against wall of the blood vessel, for example, producing this non-glucose reaction rate-limiting noise due to oxygen deficiency.

[0334] Because signal artifacts are not mere system noise, but rather are caused by specific rate-limiting mechanisms, methods used for conventional random noise filtration produce data lower (or in some cases higher) than the actual blood glucose levels due to the expansive nature of these signal artifacts. To overcome this, the preferred embodiments provide systems and methods for replacing at least some of the signal artifacts by estimating glucose signal values.

[0335] **FIG. 8** is a flow chart that illustrates the process of detecting and replacing signal artifacts in certain embodiments. It is noted that "signal artifacts" particularly refers to the transient non-glucose related artifacts that has a higher amplitude than that of system noise. Typically, signal artifacts are caused by non-glucose rate-limiting phenomenon such as described in more detail above.

[0336] At block **82**, a sensor data receiving module, also referred to as the sensor data module **82**, receives sensor data (e.g., a data stream), including one or more time-spaced sensor **10** data points. In some embodiments, the data stream is stored in the sensor for additional processing; in some alternative embodiments, the sensor **10** periodically transmits the data stream to the receiver **30**, which can be in wired or wireless communication with the sensor.

[0337] At block **84**, a signal artifacts detection module, also referred to as the signal artifacts detector **84**, is programmed to detect transient non-glucose related signal artifacts in the data stream that have a higher amplitude than system noise, such as described in more detail with reference to **FIGS. 7A and 7B**, above. The signal artifacts detector can comprise an oxygen detector, a pH detector, a temperature detector, and/or a pressure/stress detector, for example, the signal artifacts detector **29** in **FIG. 2**. In some embodiments, the signal artifacts detector at block **84** is located within the microprocessor **22** in **FIG. 2** and utilizes existing compo-

nents of the glucose sensor **10** to detect signal artifacts, for example by pulsed amperometric detection, counter electrode monitoring, reference electrode monitoring, and frequency content monitoring, which are described elsewhere herein. In yet other embodiments, the data stream can be sent from the sensor to the receiver which comprises programming in the microprocessor **42** in **FIG. 4** that performs algorithms to detect signal artifacts, for example such as described with reference to "Cone of Possibility Detection" method described in more detail below. Numerous embodiments for detecting signal artifacts are described in more detail in the section entitled, "Signal Artifacts Detection," all of which are encompassed by the signal artifacts detection at block **84**.

[0338] At block **86**, the signal artifacts replacement module, also referred to as the signal estimation module, replaces some or an entire data stream with estimated glucose signal values using signal estimation. Numerous embodiments for performing signal estimation are described in more detail in the section entitled "Signal Artifacts Replacement," all of which are encompassed by the signal artifacts replacement module, block **86**. It is noted that in some embodiments, signal estimation/replacement is initiated in response to positive detection of signal artifacts on the data stream, and subsequently stopped in response to detection of negligible signal artifacts on the data stream. In some embodiments, the system waits a predetermined time period (e.g., between 30 seconds and 30 minutes) before switching the signal estimation on or off to ensure that a consistent detection has been ascertained. In some embodiments, however, signal estimation/replacement can continuously or continually run.

[0339] Some embodiments of signal estimation can additionally include discarding data that is considered sufficiently unreliable and/or erroneous such that the data should not be used in a signal estimation algorithm. In these embodiments, the system can be programmed to discard outlier data points, for example data points that are so extreme that they can skew the data even with the most comprehensive filtering or signal estimation, and optionally replace those points with a projected value based on historical data or present data (e.g., linear regression, recursive filtering, or the like). One example of discarding sensor data includes discarding sensor data that falls outside of a "Cone of Possibility" such as described in more detail elsewhere herein. Another example includes discarding sensor data when signal artifacts detection detects values outside of a predetermined threshold (e.g., oxygen concentration below a set threshold, temperature above a certain threshold, signal amplitude above a certain threshold, etc). Any of the signal estimation/replacement algorithms described herein can then be used to project data values for those data that were discarded.

#### [0340] Signal Artifacts Detection

[0341] Analysis of signals from glucose sensors indicates at least two types of noise, which are characterized herein as 1) system noise and 2) signal artifacts, such as described in more detail above. It is noted that system noise is easily smoothed using the algorithms provided herein; however, the systems and methods described herein particularly address signal artifacts, by replacing transient erroneous signal noise caused by rate-limiting phenomenon with estimated signal values.

[0342] In certain embodiments of signal artifacts detection, oxygen monitoring is used to detect whether transient non-glucose dependent signal artifacts due to ischemia. Low oxygen concentrations in or near the glucose sensor can account for a large part of the transient non-glucose related signal artifacts as defined herein on a glucose sensor signal, particularly in subcutaneously implantable glucose sensors. Accordingly, detecting oxygen concentration, and determining if ischemia exists can discover ischemia-related signal artifacts. A variety of methods can be used to test for oxygen. For example, an oxygen-sensing electrode, or other oxygen sensor can be employed. The measurement of oxygen concentration can be sent to a microprocessor, which determines if the oxygen concentration indicates ischemia.

[0343] In some embodiments of ischemia detection, an oxygen sensor is placed proximal to or within the glucose sensor. For example, the oxygen sensor can be located on or near the glucose sensor such that their respective local environments are shared and oxygen concentration measurement from the oxygen sensor represents an accurate measurement of the oxygen concentration on or within the glucose sensor. In some alternative embodiments of ischemia detection, an oxygen sensor is also placed distal to the glucose sensor. For example, the oxygen sensor can be located sufficiently far from the glucose sensor such that their respective local environments are not shared and oxygen measurements from the proximal and distal oxygen sensors can be compared to determine the relative difference between the respective local environments. By comparing oxygen concentration proximal and distal oxygen sensor, change in local (proximal) oxygen concentration can be determined from a reference (distal) oxygen concentration.

[0344] Oxygen sensors are useful for a variety of purposes. For example, U.S. Pat. No. 6,512,939 to Colvin et al., which is incorporated herein by reference, discloses an oxygen sensor that measures background oxygen levels. However, Colvin et al. rely on the oxygen sensor for the data stream of glucose measurements by subtraction of oxygen remaining after exhaustion of glucose by an enzymatic reaction from total unreacted oxygen concentration.

[0345] In another embodiment of ischemia detection, wherein the glucose sensor is an electrochemical sensor that includes a potentiostat, pulsed amperometric detection can be employed to determine an oxygen measurement. Pulsed amperometric detection includes switching, cycling, or pulsing the voltage of the working electrode (or reference electrode) in an electrochemical system, for example between a positive voltage (e.g., +0.6 for detecting glucose) and a negative voltage (e.g., -0.6 for detecting oxygen). U.S. Pat. No. 4,680,268 to Clark, Jr., which is incorporated by reference herein, describes pulsed amperometric detection. In contrast to using signal replacement, Clark, Jr. addresses oxygen deficiency by supplying additional oxygen to the enzymatic reaction.

[0346] In another embodiment of ischemia detection, wherein the glucose sensor is an electrochemical sensor and contains a potentiostat, oxygen deficiency can be seen at the counter electrode when insufficient oxygen is available for reduction, which thereby affects the counter electrode in that it is unable to balance the current coming from the working electrode. When insufficient oxygen is available for the counter electrode, the counter electrode can be driven in its

electrochemical search for electrons all the way to its most negative value, which could be ground or 0.0V, which causes the reference to shift, reducing the bias voltage such as described in more detail below. In other words, a common result of ischemia will be seen as a drop off in sensor current as a function of glucose concentration (e.g., lower sensitivity). This happens because the working electrode no longer oxidizes all of the  $H_2O_2$  arriving at its surface because of the reduced bias. In some extreme circumstances, an increase in glucose can produce no increase in current or even a decrease in current.

[0347] FIG. 9 is a graph that shows a comparison of sensor current and counter-electrode voltage in a host over time. The x-axis represents time in minutes. The first y-axis 91 represents sensor counts from the working electrode and thus plots a raw sensor data stream 92 for the glucose sensor over a period of time. The second y-axis 93 represents counter-electrode voltage 94 in counts. The graph illustrates the correlation between sensor data 92 and counter-electrode voltage 94; particularly, that erroneous counter electrode function 96 where the counter voltages drops approximately to zero substantially coincides with transient non-glucose related signal artifacts 98. In other words, when counter-electrode voltage is at or near zero, sensor data includes signal artifacts.

[0348] In another embodiment of ischemia detection, wherein the glucose sensor is an electrochemical sensor and contains a two- or three-cell electrochemical cell, signal artifacts are detected by monitoring the reference electrode. This "reference drift detection" embodiment takes advantage of the fact that the reference electrode will vary or drift in order to maintain a stable bias potential with the working electrode, such as described in more detail herein. This "drifting" generally indicates non-glucose reaction rate-limiting noise, for example due to ischemia. It is noted that the following example describes an embodiment wherein the sensor includes a working, reference, and counter electrodes, such as described in more detail elsewhere herein; however the principles of this embodiment are applicable to a two-cell (e.g., anode and cathode) electrochemical cell as is understood in the art.

[0349] FIG. 10A is a circuit diagram of a potentiostat that controls a typical three-electrode system, which can be employed with a glucose sensor 10 such as described with reference to FIGS. 1 and 2. The potentiostat includes a working electrode 100, a reference electrode 102, and a counter electrode 104. The voltage applied to the working electrode is a constant value (e.g., +1.2V) and the voltage applied to the reference electrode is also set at a constant value (e.g., +0.6V) such that the potential ( $V_{BIAS}$ ) applied between the working and reference electrodes is maintained at a constant value (e.g., +0.6V). The counter electrode is configured to have a constant current (equal to the current being measured by the working electrode), which is accomplished by varying the voltage at the counter electrode in order to balance the current going through the working electrode 100 such that current does not pass through the reference electrode 102. A negative feedback loop 107 is constructed from an operational amplifier (OP AMP), the reference electrode 102, the counter electrode 104, and a reference potential, to maintain the reference electrode at a constant voltage.

[0350] In practice, a glucose sensor of one embodiment comprises a membrane that contains glucose oxidase that catalyzes the conversion of oxygen and glucose to hydrogen peroxide and gluconate, such as described with reference to **FIGS. 1 and 2**. Therefore for each glucose molecule metabolized there is a change equivalent in molecular concentration in the co-reactant  $O_2$  and the product  $H_2O_2$ . Consequently, one can use an electrode (e.g., working electrode **100**) to monitor the concentration-induced current change in either the co-reactant or the product to determine glucose concentration.

[0351] One limitation of the electrochemistry is seen when insufficient negative voltage is available to the counter electrode **104** to balance the working electrode **100**. This limitation can occur when insufficient oxygen is available to the counter electrode **104** for reduction, for example. When this limitation occurs, the counter electrode can no longer vary its voltage to maintain a balanced current with the working electrode and thus the negative feedback loop **107** used to maintain the reference electrode is compromised. Consequently, the reference electrode voltage will change or “drift,” altering the applied bias potential (i.e., the potential applied between the working and reference electrodes), thereby decreasing the applied bias potential. When this change in applied bias potential occurs, the working electrode can produce erroneous glucose measurements due to either increased or decreased signal strength ( $I_{SENSE}$ ).

[0352] **FIG. 10B** a diagram referred to as Cyclic-Voltammetry (CV) curve, wherein the x-axis represents the applied potential ( $V_{BIAS}$ ) and the y-axis represents the signal strength of the working electrode ( $I_{SENSE}$ ). A curve **108** illustrates an expected CV curve when the potentiostat is functioning normally. Typically, desired bias voltage can be set (e.g.,  $V_{BIAS1}$ ) and a resulting current will be sensed (e.g.,  $I_{SENSE1}$ ). As the voltage decreases (e.g.,  $V_{BIAS2}$ ) due to reference voltage drift, for example, a new resulting current is sensed (e.g.,  $I_{SENSE2}$ ). Therefore, the change in bias is an indicator of signal artifacts and can be used in signal estimation and to replace the erroneous resulting signals. In addition to ischemia, the local environment at the electrode surfaces can affect the CV curve, for example, changes in pH, temperature, and other local biochemical species can significantly alter the location of the CV curve.

[0353] **FIG. 10C** is a CV curve that illustrates an alternative embodiment of signal artifacts detection, wherein pH and/or temperature can be monitoring using the CV curve and diagnosed to detect transient non-glucose related signal artifacts. For example, signal artifacts can be attributed to thermal changes and/or pH changes in some embodiments because certain changes in pH and temperature affect data from a glucose sensor that relies on an enzymatic reaction to measure glucose. Signal artifacts caused by pH changes, temperature changes, changes in available electrode surface area, and other local biochemical species can be detected and signal estimation can be applied an/or optimized such as described in more detail elsewhere herein. In **FIG. 10C**, a first curve **108** illustrates an expected CV curve when the potentiostat is functioning normally. A second curve **109** illustrates a CV curve wherein the environment has changed as indicated by the upward shift of the CV curve.

[0354] In some embodiments, pH and/or temperature measurements are obtained proximal to the glucose sensor; in

some embodiments, pH and/or temperature measurements are also obtained distal to the glucose sensor and the respective measurements compared, such as described in more detail above with reference to oxygen sensors.

[0355] In another implementation of signal artifacts detection, wherein temperature is detected, an electronic thermometer can be proximal to or within the glucose sensor, such that the temperature measurement is representative of the temperature of the glucose sensor's local environment. It is noted that accurate sensor function depends on diffusion of molecules from the blood to the interstitial fluid, and then through the membranes of the device to the enzyme membrane. Additionally, diffusion transport of hydrogen peroxide from the enzyme membrane to the electrode occurs. Therefore, temperatures can be a rate determining parameter of diffusion. As temperature decreases, diffusion transport decreases. Under certain human conditions, such as hypothermia or fever, the variations can be considerably greater. Additionally, under normal conditions, the temperature of subcutaneous tissue is known to vary considerably more than core tissues (e.g., core temperature). Temperature thresholds can be set to detect signal artifacts accordingly.

[0356] In another implementation, a pH detector is used to detect signal artifacts. In glucose sensors that rely on enzymatic reactions, a pH of the fluid to be sensed can be within the range of about 5.5 to 7.5. Outside of this range, effects may be seen in the enzymatic reaction and therefore data output of the glucose sensor. Accordingly, by detecting if the pH is outside of a predetermined range (e.g., 5.5 to 7.5), a pH detector may detect transient non-glucose related signal artifacts such as described herein. It is noted that the pH threshold can be set at ranges other than provided herein without departing from the preferred embodiments.

[0357] In an alternative embodiment of signal artifacts detection, pressure and/or stress can be monitored using known techniques for example by a strain gauge placed on the sensor that detects stress/strain on the circuit board, sensor housing, or other components. A variety of micro-electromechanical systems (MEMS) can be utilized to measure pressure and/or stress within the sensor.

[0358] In another alternative embodiment of signal artifacts detection, the microprocessor in the sensor (or receiver) periodically evaluates the data stream for high amplitude noise, which is defined by noisy data wherein the amplitude of the noise is above a predetermined threshold. For example, in the graph of **FIGS. 7A and 7B**, the system noise sections such as **72a** and **72b** have a substantially low amplitude noise threshold; in contrast to system noise, signal artifacts sections such as **74a** and **74b** have signal artifacts (noise) with an amplitude that is much higher than that of system noise. Therefore, a threshold can be set at or above the amplitude of system noise, such that when noisy data is detected above that amplitude, it can be considered “signal artifacts” as defined herein.

[0359] In another alternative embodiment of signal artifacts detection, a method hereinafter referred to as the “Cone of Possibility Detection Method,” utilizes physiological information along with glucose signal values in order define a “cone” of physiologically feasible glucose signal values within a human, such that signal artifacts are detected whenever the glucose signal falls outside of the cone of possibility. Particularly, physiological information depends



upon the physiological parameters obtained from continuous studies in the literature as well as our own observations. A first physiological parameter uses a maximal sustained rate of change of glucose in humans (e.g., about 4 to 5 mg/dL/min) and a maximum acceleration of that rate of change (e.g., about 0.1 to 0.2 mg/dL/min<sup>2</sup>). A second physiological parameter uses the knowledge that rate of change of glucose is lowest at the minima, which is the areas of greatest risk in patient treatment, and the maxima, which has the greatest long-term effect on secondary complications associated with diabetes. A third physiological parameter uses the fact that the best solution for the shape of the curve at any point along the curve over a certain time period (e.g., about 20-30 minutes) is a straight line. Additional physiological parameters can be incorporated and are within the scope of this embodiment.

[0360] In practice, the Cone of Possibility Detection Method combines any one or more of the above-described physiological parameters to form an algorithm that defines a cone of possible glucose levels for glucose data captured over a predetermined time period. In one exemplary implementation of the Cone of Possibility Detection Method, the system (microprocessor in the sensor or receiver) calculates a maximum physiological rate of change and determines if the data falls within these physiological limits; if not, signal artifacts are identified. It is noted that the maximum rate of change can be narrowed (e.g., decreased) in some instances. Therefore, additional physiological data could be used to modify the limits imposed upon the Cone of Possibilities Detection Method for sensor glucose values. For example, the maximum per minute rate change can be lower when the subject is sleeping or hasn't eaten in eight hours; on the other hand, the maximum per minute rate change can be higher when the subject is exercising or has consumed high levels of glucose, for example. In general, it has been observed that rates of change are slowest near the maxima and minima of the curve, and that rates of change are highest near the midpoint between the maxima and minima. It should further be noted that rate of change limits are derived from analysis of a range of data significantly higher unsustained rates of change can be observed.

[0361] In another alternative embodiment of signal artifacts detection, examination of the spectral content (e.g., frequency content) of the data stream can yield measures useful in detecting signal artifacts. For example, data that has high frequency, and in some cases can be characterized by a large negative slope, are indicative of signal artifacts and can cause sensor signal loss. Specific signal content can be monitored using an orthogonal transform, for example a Fourier transform, a Discrete Fourier Transform (DFT), or any other method known in the art.

[0362] FIG. 11 is a graph of 110 a raw data stream from a glucose sensor and a spectrogram 114 that shows the frequency content of the raw data stream in one embodiment. Particularly, the graph 110 illustrates the raw data stream 112 and includes an x-axis that represents time in hours and a y-axis that represents sensor data output in counts; the spectrogram 114 illustrates the frequency content 116 corresponding to the raw data stream 112 and includes an x-axis that represents time in hours corresponding to the x-axis of the graph 110 and a y-axis that represents frequency content in cycles per hour. The darkness of each point represents the amplitude of that frequency at that time.

Darker points relate to higher amplitudes. Frequency content on the spectrogram 114 was obtained using a windowed Discrete Fourier transform.

[0363] The raw data stream in the graph 110 has been adjusted by a linear mapping similar to the calibration algorithm. In this example, the bias (or intercept) has been adjusted but not the proportion (or slope). The slope of the raw data stream would typically be determined by some calibration, but since the calibration has not occurred in this example, the gray levels in the spectrogram 114 indicate relative values. The lower values of the graph 110 are white. They are colored as white below a specific value, highlighting only the most intense areas of the graph.

[0364] By monitoring the frequency content 116, high frequency cycles 118 can be observed. The high frequency cycles 118 correspond to signal artifacts 119 such as described herein. Thus, signal artifacts can be detected on a data stream by monitoring frequency content and setting a threshold (e.g., 30 cycles per hour). The set threshold can vary depending on the signal source.

[0365] In another alternative embodiment of signal artifacts detection, examination of the signal information content can yield measures useful in detecting signal artifacts. Time series analysis can be used to measure entropy, approximate entropy, variance, and/or percent change of the information content over consecutive windows (e.g., 30 and 60 minute windows of data) of the raw data stream. In one exemplary embodiment, the variance of the raw data signal is measured over 15 minute and 45 minute windows, and signal artifacts are detected when the variance of the data within the 15-minute window exceeds the variance of the data within the 45-minute window.

[0366] One or a plurality of the above signal artifacts detection models can be used alone or in combination to detect signal artifacts such as described herein. Accordingly, the data stream associated with the signal artifacts can be discarded, replaced, or otherwise processed in order to reduce or eliminate these signal artifacts and thereby improve the value of the glucose measurements that can be provided to a user.

[0367] Signal Artifacts Replacement

[0368] Signal Artifacts Replacement, such as described above, can use systems and methods that reduce or replace these signal artifacts that can be characterized by transience, high frequency, high amplitude, and/or substantially non-linear noise. Accordingly, a variety of filters, algorithms, and other data processing are provided that address the detected signal artifacts by replacing the data stream, or portion of the data stream, with estimated glucose signal values. It is noted that "signal estimation" as used herein, is a broad term, which includes filtering, data smoothing, augmenting, projecting, and/or other algorithmic methods that estimate glucose signal values based on present and historical data.

[0369] It is noted that a glucose sensor can contain a microprocessor or the like that processes periodically received raw sensor data (e.g., every 30 seconds). Although a data point can be available constantly, for example by use of an electrical integration system in a chemo-electric sensor, relatively frequent (e.g., every 30 seconds), or less frequent data point (e.g., every 5 minutes), can be more than sufficient for patient use. It is noted that accordingly Nyquist

Theory, a data point is required about every 10 minutes to accurately describe physiological change in glucose in humans. This represents the lowest useful frequency of sampling. However, it should be recognized that it is desirable to sample more frequently than the Nyquist minimum, to provide for sufficient data in the event that one or more data points are lost, for example. Additionally, more frequently sampled data (e.g., 30-second) can be used to smooth the less frequent data (e.g., 5-minute) that are transmitted. It is noted that in this example, during the course of a 5-minute period, 10 determinations are made at 30-second intervals.

**[0370]** In some embodiments of Signal Artifacts Replacement, signal estimation can be implemented in the sensor and transmitted to a receiver for additional processing. In some embodiments of Signal Artifacts Replacement, raw data can be sent from the sensor to a receiver for signal estimation and additional processing therein. In some embodiments of Signal Artifacts Replacement, signal estimation is performed initially in the sensor, with additional signal estimation in the receiver.

**[0371]** In some embodiments of Signal Artifacts Replacement, wherein the sensor is an implantable glucose sensor, signal estimation can be performed in the sensor to ensure a continuous stream of data. In alternative embodiments, data can be transmitted from the sensor to the receiver, and the estimation performed at the receiver; It is noted however that there can be a risk of transmit-loss in the radio transmission from the sensor to the receiver when the transmission is wireless. For example, in embodiments wherein a sensor is implemented in vivo, the raw sensor signal can be more consistent within the sensor (in vivo) than the raw signal transmitted to a source (e.g., receiver) outside the body (e.g., if a patient were to take the receiver off to shower, communication between the sensor and receiver can be lost and data smoothing in the receiver would halt accordingly). Consequently, It is noted that a multiple point data loss in the filter can take for example, about 25 to about 40 minutes for the data to recover to near where it would have been had there been no data loss.

**[0372]** In some embodiments of Signal Artifacts Replacement, signal estimation is initiated only after signal artifacts are positively detected, and stopped once signal artifacts are negligibly detected. In some alternative embodiments signal estimation is initiated after signal artifacts are positively detected and then stopped after a predetermined time period. In some alternative embodiments, signal estimation can be continuously or continually performed. In some alternative embodiments, one or more forms of signal estimation can be accomplished based on the severity of the signal artifacts, such as will be described with reference to the section entitled, "Selective Application of Signal Artifacts Replacement."

**[0373]** In some embodiments of Signal Artifacts Replacement, the microprocessor performs a linear regression. In one such implementation, the microprocessor performs a linear regression analysis of the  $n$  (e.g., 10) most recent sampled sensor values to smooth out the noise. A linear regression averages over a number of points in the time course and thus reduces the influence of wide excursions of any point from the regression line. Linear regression defines a slope and intercept, which is used to generate a "Projected Glucose Value," which can be used to replace sensor data.

This regression can be continually performed on the data stream or continually performed only during the transient signal artifacts. In some alternative embodiments, signal estimation can include non-linear regression.

**[0374]** In another embodiment of Signal Artifacts Replacement, the microprocessor performs a trimmed regression, which is a linear regression of a trimmed mean (e.g., after rejecting wide excursions of any point from the regression line). In this embodiment, after the sensor records glucose measurements at a predetermined sampling rate (e.g., every 30 seconds), the sensor calculates a trimmed mean (e.g., removes highest and lowest measurements from a data set and then regresses the remaining measurements to estimate the glucose value.

**[0375]** FIG. 12 is a graph that illustrates a raw data stream from a glucose sensor and a trimmed regression that can be used to replace some of or the entire data stream. The x-axis represents time in minutes; the y-axis represents sensor data output in counts. A raw data signal **120**, which is illustrated as a dotted line, shows a data stream wherein some system noise can be detected, however signal artifacts **122** can be particularly seen in a portion thereof (and can be detected by methods such as described above). The trimmed regression line **124**, which is illustrated as a solid line, is the data stream after signal estimation using a trimmed linear regression algorithm, such as described above, and appears at least somewhat "smoothed" on the graph. In this particular example, the trimmed regression uses the most recent 60 points (30 minutes) and trims out the highest and lowest values, then uses the leftover 58 points to project the next point. It is noted that the trimmed regression **124** provides a good estimate throughout the majority data stream, however is only somewhat effective in smoothing the data in during signal artifacts **122**. To provide an optimized estimate of the glucose data values, the trimmed regression can be optimized by changing the parameters of the algorithm, for example by trimming more or less raw glucose data from the top and/or bottom of the signal artifacts **122** prior to regression. Additionally It is noted that trimmed regression, because of its inherent properties, can be particularly suited for noise of a certain amplitude and/or characteristic. In one embodiment, for example trimmed regression can be selectively applied based on the severity of the signal artifacts, which is described in more detail below with reference to FIGS. 15 to 17.

**[0376]** In another embodiment of Signal Artifacts Replacement, the microprocessor runs a non-recursive filter, such as a finite impulse response (FIR) filter. A FIR filter is a digital signal filter, in which every sample of output is the weighted sum of past and current samples of input, using only some finite number of past samples.

**[0377]** FIG. 13 is a graph that illustrates a raw data stream from a glucose sensor and an FIR-estimated signal that can be used to replace some of or the entire data stream. The x-axis represents time in minutes; the y-axis represents sensor data output in counts. A raw data signal **130**, which is illustrated as a dotted line, shows a data stream wherein some system noise can be detected, however signal artifacts **132** can be particularly seen in a portion thereof (and can be detected by methods such as described above). The FIR-estimated signal **134**, which is illustrated as a solid line, is the data stream after signal estimation using a FIR filter,

such as described above, and appears at least somewhat “smoothed” on the graph. It is noted that the FIR-estimated signal provides a good estimate throughout the majority of the data stream, however like trimmed regression it is only somewhat effective in smoothing the data during signal artifacts **132**. To provide an optimized estimate of the glucose data values, the FIR filter can be optimized by changing the parameters of the algorithm, for example the tuning of the filter, particularly the frequencies of the pass band and the stop band. Additionally It is noted that the FIR filter, because of its inherent properties, can be particularly suited for noise of a certain amplitude and/or characteristic. In one embodiment, for example the FIR filter can be selectively applied based on the severity of the signal artifacts, which is described in more detail below with reference to FIGS. **15** to **17**. It is noted that the FIR-estimated signal induces a time lag on the data stream, which can be increased or decreased in order to optimize the filtering or to minimize the time lag, for example.

**[0378]** In another embodiment of Signal Artifacts Replacement, the microprocessor runs a recursive filter, such as an infinite impulse response (IIR) filter. An IIR filter is a type of digital signal filter, in which every sample of output is the weighted sum of past and current samples of input. In one exemplary implementation of an IIR filter, the output is computed using 6 additions/subtractions and 7 multiplications as shown in the following equation:

$$y(n) = \frac{a_0 * x(n) + a_1 * x(n-1) + a_2 * x(n-2) + a_3 * x(n-3) - b_1 * y(n-1) - b_2 * y(n-2) - b_3 * y(n-3)}{b_0}$$

**[0379]** This polynomial equation includes coefficients that are dependent on sample rate and frequency behavior of the filter. Frequency behavior passes low frequencies up to cycle lengths of 40 minutes, and is based on a 30 second sample rate. In alternative implementations, the sample rate and cycle lengths can be more or less. See Lynn “Recursive Digital Filters for Biological Signals” Med. & Biol. Engineering, Vol. 9, pp. 37-43, which is incorporated herein by reference in its entirety.

**[0380]** FIG. **14** is a graph that illustrates a raw data stream from a glucose sensor and an IIR-estimated signal that can be used to replace some of or the entire data stream. The x-axis represents time in minutes; the y-axis represents sensor data output in counts. A raw data signal **140**, which is illustrated as a dotted line, shows a data stream wherein some system noise can be detected, however signal artifacts **142** can be particularly seen in a portion thereof (and can be detected by methods such as described above). The IIR-estimated signal **144**, which is illustrated as a solid line, represents the data stream after signal estimation using an IIR filter, such as described above, and appears at least somewhat “smoothed” on the graph. It is noted that the IIR-estimated signal induces a time lag on the data stream, however it appears to be a particularly good estimate of glucose data values during signal artifacts **142**, as compared to the FIR filter (FIG. **13**), for example.

**[0381]** To optimize the estimation of the glucose data values, the parameters of the IIR filter can be optimized, for

example by increasing or decreasing the cycle lengths (e.g., 10 minutes, 20 minute, 40 minutes, 60 minutes) that are used in the algorithm. Although an increased cycle length can increase the time lag induced by the IIR filter, an increased cycle length can also better estimate glucose data values during severe signal artifacts. In other words, It is noted that the IIR filter, because of its inherent properties, can be particularly suited for noise of a certain amplitude and/or characteristic. In one exemplary embodiment, the IIR filter can be continually applied, however the parameters such as described above can be selectively altered based on the severity of the signal artifacts; in another exemplary embodiment, the IIR filter can be applied only after positive detection of signal artifacts. Selective application of the IIR filter based on the severity of the signal artifacts is described in more detail below with reference to FIGS. **15** to **17**.

**[0382]** It is noted that a comparison of linear regression, an FIR filter, and an IIR filter can be advantageous for optimizing their usage in the preferred embodiments. That is, an understanding the design considerations for each algorithm can lead to optimized selection and implementation of the algorithm, as described in the section entitled, “Selective Application of Signal Replacement Algorithms” herein. During system noise, as defined herein, all of the above algorithms can be successfully implemented during system noise with relative ease. During signal artifacts, however, computational efficiency is greater with an IIR-filter as compared with linear regression and FIR-filter. Additionally, although the time lag associated with an IIR filter can be substantially greater than that of the linear regression or FIR-filter, this can be advantageous during severe signal artifacts in order to assign greater weight toward the previous, less noisy data in signal estimation.

**[0383]** In another embodiment of Signal Artifacts Replacement, the microprocessor runs a maximum-average (max-average) filtering algorithm. The max-average algorithm smoothes data based on the discovery that the substantial majority of signal artifacts observed after implantation of glucose sensors in humans, for example, is not distributed evenly above and below the actual blood glucose levels. It has been observed that many data sets are actually characterized by extended periods in which the noise appears to trend downwardly from maximum values with occasional high spikes such as described in more detail above with reference to FIG. **7B**, section **74b**, which is likely in response to limitations in the system that do not allow the glucose to fully react at the enzyme layer and/or proper reduction of  $H_2O_2$  at the counter electrode, for example. To overcome these downward trending signal artifacts, the max-average calculation tracks with the highest sensor values, and discards the bulk of the lower values. Additionally, the max-average method is designed to reduce the contamination of the data with unphysiologically high data from the high spikes.

**[0384]** The max-average calculation smoothes data at a sampling interval (e.g., every 30 seconds) for transmission to the receiver at a less frequent transmission interval (e.g., every 5 minutes) to minimize the effects of low non-physiological data. First, the microprocessor finds and stores a maximum sensor counts value in a first set of sampled data points (e.g., 5 consecutive, accepted, thirty-second data points). A frame shift time window finds a maximum sensor counts value for each set of sampled data (e.g., each 5-point

cycle length) and stores each maximum value. The microprocessor then computes a rolling average (e.g., 5-point average) of these maxima for each sampling interval (e.g., every 30 seconds) and stores these data. Periodically (e.g., every 10<sup>th</sup> interval), the sensor outputs to the receiver the current maximum of the rolling average (e.g., over the last 10 thirty-second intervals as a smoothed value for that time period (e.g., 5 minutes)). In one example implementation, a 10-point window can be used, and at the 10<sup>th</sup> interval, the microprocessor computes the average of the most recent 5 or 10 average maxima as the smoothed value for a 5 minute time period.

[0385] In some embodiments of the max-average algorithm, an acceptance filter can also be applied to new sensor data to minimize effects of high non-physiological data. In the acceptance filter, each sampled data point (e.g., every 30-seconds) is tested for acceptance into the maximum average calculation. Each new point is compared against the most representative estimate of the sensor curve at the previous sampling interface (e.g., 30-second time point), or at a projection to a current estimated value. To reject high data, the current data point is compared to the most recent value of the average maximum values over a time period (e.g., 5 sampled data points over a 2.5 minute period). If the ratio of current value to the comparison value is greater than a certain threshold (e.g., about 1.02), then the current data point is replaced with a previously accepted value (e.g., 30-second value). If the ratio of current value to the comparison value is in at or within a certain range (e.g., about 1.02 to 0.90), then the current data point is accepted. If the ratio of current value to the comparison value is less than a certain threshold (e.g., about 0.90), then the current data point is replaced with a previously accepted value. The acceptance filter step and max-average calculation are continuously run throughout the data set (e.g., fixed 5-minute windows) on a rolling window basis (e.g., every 30 seconds).

[0386] In some implementations of the acceptance filter, the comparison value for acceptance could also be the most recent maximum of 5 accepted sensor points (more sensitive) or the most recent average over 10 averages of 5 maximum values (least sensitive), for example. In some exemplary implementations of the acceptance filter, the projected value for the current time point can be based on regression of the last 4 accepted 30-second values and/or the last 2 to 4 (5 to 15 min) of the 5-minute smoothed values, for example. In some exemplary implementations of the acceptance filter, the percentage comparisons of +2% and -10% of counts value would be replaced by percentage comparisons based on the most recent 24 hour range of counts values; this method would provide improved sensor specificity as compared to a method based on total counts.

[0387] In another embodiment of Signal Artifacts Replacement, the microprocessor runs a "Cone of Possibility Replacement Method." It is noted that this method can be performed in the sensor and/or in the receiver. The Cone of Possibility Detection Method utilizes physiological information along with glucose signal values in order to define a "cone" of physiologically feasible glucose signal values within a human. Particularly, physiological information depends upon the physiological parameters obtained from continuous studies in the literature as well as our own observations. A first physiological parameter uses a maximal

sustained rate of change of glucose in humans (e.g., about 4 to 5 mg/dl/min) and a maximum sustained acceleration of that rate of change (e.g., about 0.1 to 0.2 mg/min/min). A second physiological parameter uses the knowledge that rate of change of glucose is lowest at the maxima and minima, which are the areas of greatest risk in patient treatment, such as described with reference to Cone of Possibility Detection, above. A third physiological parameter uses the fact that the best solution for the shape of the curve at any point along the curve over a certain time period (e.g., about 20-25 minutes) is a straight line. It is noted that the maximum rate of change can be narrowed in some instances. Therefore, additional physiological data can be used to modify the limits imposed upon the Cone of Possibility Replacement Method for sensor glucose values. For example, the maximum per minute rate change can be lower when the subject is lying down or sleeping; on the other hand, the maximum per minute rate change can be higher when the subject is exercising, for example.

[0388] The Cone of Possibility Replacement Method utilizes physiological information along with blood glucose data in order to improve the estimation of blood glucose values within a human in an embodiment of Signal Artifacts Replacement. The Cone of Possibility Replacement Method can be performed on raw data in the sensor, on raw data in the receiver, or on smoothed data (e.g., data that has been replaced/estimated in the sensor or receiver by one of the methods described above) in the receiver.

[0389] In a first implementation of the Cone of Possibility Replacement Method, a centerline of the cone can be projected from a number of previous, optionally smoothed, incremental data points (e.g., previous four, 5-minute data points). Each predicted cone centerline point (e.g., 5 minute point) increases by the slope (S) (e.g., for the regression in counts/minute) multiplied by the data point increment (e.g., 5 minutes). Counts/mg/dL is estimated from glucose and sensor range calculation over the data set.

[0390] In this first implementation of the Cone of Possibility Replacement Method, positive and negative cone limits are simple linear functions. Periodically (e.g., every 5 minutes), each sensor data point (optionally smoothed) is compared to the cone limits projected from the last four points. If the sensor value observed is within the cone limits, the sensor value is retained and used to generate the cone for the next data point increment (e.g., 5-minute point). If the sensor value observed falls outside the high or low cone limit, the value is replaced by the cone limit value, and that value is used to project the next data point increment (e.g., 5 minute point, high point, or low point). For example, if the difference between two adjacent 5-minute points exceeds 20 mg/dL, then cone limits are capped at 20 mg/dL increments per 5 minutes, with the positive limit of the cone being generated by the addition of  $0.5 \cdot A \cdot t^2$  to mid cone value, where A is 0.1 mg/dL/min/min and t is 5 minute increments (A is converted to counts/min/min for the calculation), and the negative limit of the cone being generated by the addition of  $-0.5 \cdot A \cdot t^2$  to mid cone value. This implementation provides a high degree of accuracy and is minimally sensitive to non-physiological rapid changes.

[0391] The following table illustrates one example implementation of the Cone of Possibility Replacement Method, wherein the maximum sustained value observed for S is

about  $\pm 4$  mg/dL/min and the maximum value observed for A is about  $\pm 0.1$  mg/dL/min<sup>2</sup>:

| Time | Mid line<br>(mg/dL) | Positive Cone Limit    | Negative Cone Limit    |
|------|---------------------|------------------------|------------------------|
| 0    | 100                 | 100                    | 100                    |
| 5    | $100 + 5*S$         | $100 + 5*S + 12.5*A$   | $100 + 5*S - 12.5*A$   |
| 10   | $100 + 10*S$        | $100 + 10*S + 50*A$    | $100 + 10*S - 50*A$    |
| 15   | $100 + 15*S$        | $100 + 15*S + 112.5*A$ | $100 + 15*S - 112.5*A$ |
| 20   | $100 + 20*S$        | $100 + 20*S + 200*A$   | $100 + 20*S - 200*A$   |
| 25   | $100 + 25*S$        | $100 + 25*S + 312.5*A$ | $100 + 25*S - 312.5*A$ |

[0392] It is noted that the cone widens for each 5-minute increment for which a sensor value fails to fall inside the cone up to 30 minutes, such as can be seen in the table above. At 30 minutes, a cone has likely widened enough to capture an observed sensor value, which is used, and the cone collapses back to a 5-minute increment width. If no sensor values are captured within 30 minutes, the cone generation routine starts over using the next four observed points. In some implementations special rules can be applied, for example in a case where the change in counts in one 5-minute interval exceeds an estimated 30-mg/dL amount. In this case, the next acceptable point can be more than 20 to 30 minutes later. It is noted that an implementation of this algorithm includes utilizing the cone of possibility to predict glucose levels and alert patients to present or upcoming dangerous blood glucose levels.

[0393] In another alternative embodiment of cone widening, the cone can widen in set multiples (e.g., 20 mg/dL) of equivalent amounts for each additional time interval (e.g., 5 minute), which rapidly widens the cone to accept data.

[0394] It is noted that the numerical parameters represent only one example implementation of the Cone of Possibility Replacement Method. The concepts can be applied to any numerical parameters as desired for various glucose sensor applications.

[0395] In another implementation of the Cone of Possibility Replacement Method sensor calibration data is optimized using the Clarke Error Grid, the Consensus Grid, or an alternative error assessment that assigns risk levels based on the accuracy of matched data pairs. In an example using the Clarke Error Grid, because the 10 regions of the Clarke Error Grid are not all symmetric around the  $Y=X$  perfect regression, fits to the grid can be improved by using a multi-line regression to the data.

[0396] Accordingly the pivot point method for the counts vs. glucose regression fit can be used to optimize sensor calibration data to the Clarke Error Grid, Consensus Grid, or other clinical acceptability standard. First, the glucose range is divided according to meter values (e.g., at 200 mg/dL). Two linear fitting lines are used, which cross at the pivot point. The coordinates of the pivot point in counts and glucose value, plus the slope and intercept of the two lines are variable parameters. Some of pivot point coordinates (e.g., 4 out of 6) and slope or intercept of each line can be reset with each iteration, while the chosen coordinates define the remainder. The data are then re-plotted on the Clarke Error Grid, and changes in point placement and percentages in each region of the grid are evaluated. To optimize the fit

of a data set to a Clark Error Grid, the regression of counts vs. reference glucose can be adjusted such that the maximum number of points are in the A+B zones without reducing the A+B percentage, and the number of points are optimized such that the highest percentage are in the A zone and lowest percentage are in the D, E and C zones. In general, the points should be distributed as evenly as possible around the  $Y=X$  line. In some embodiments, three distinct lines optimized for clinical acceptability can represent the regression line. In some embodiments, an additional useful criterion can be used to compute the root mean squared percentage bias for the data set. Better fits are characterized by reduction in the total root mean squared percentage bias. In an alternative implementation of the pivot point methods, a predetermined pivot (e.g., 10 degree) of the regression line can be applied when the estimated blood is above or below a set threshold (e.g., 150 mg/dL), wherein the pivot and threshold are determined from a retrospective analysis of the performance of a conversion function and its performance at a range of glucose concentrations.

[0397] In another embodiment of Signal Artifacts Replacement, reference changes in electrode potential can be used to estimate glucose sensor data during positive detection of signal artifacts from an electrochemical glucose sensor, the method hereinafter referred to as reference drift replacement. In this embodiment, the electrochemical glucose sensor comprises working, counter, and reference electrodes, such as described with reference to FIGS. 1, 2 and 10 above. This method exploits the function of the reference electrode as it drifts to compensate for counter electrode limitations during oxygen deficits, pH changes, and/or temperature changes such as described in more detail above with reference to FIGS. 10A, 10B, and 10C.

[0398] Such as described with in more detail with reference to FIG. 10A a potentiostat is generally designed so that a regulated potential difference between the reference electrode 102 and working electrode 100 is maintained as a constant. The potentiostat allows the counter electrode voltage to float within a certain voltage range (e.g., from between close to the +1.2V observed for the working electrode to as low as battery ground or 0.0V). The counter electrode voltage measurement will reside within this voltage range dependent on the magnitude and sign of current being measured at the working electrode and the electroactive species type and concentration available in the electrolyte adjacent to the counter electrode 104. This species will be electrochemically recruited (e.g., reduced/accepting electrons) to equal the current of opposite sign (e.g., oxidized/donating electrons) occurring at the working electrode 100. It has been discovered that the reduction of dissolved oxygen or hydrogen peroxide from oxygen converted in the enzyme layer are the primary species reacting at the counter electrode to provide this electronic current balance in this embodiment. If there are inadequate reducible species (e.g., oxygen) available for the counter electrode, or if other non-glucose reaction rate limiting phenomena occur (e.g., temperature or pH), the counter electrode can be driven in its electrochemical search for electrons all the way to ground or 0.0V. However, regardless of the voltage in the counter electrode, the working and counter electrode currents must still maintain substantially equivalent currents. Therefore, the reference electrode 102 will drift upward creating new oxidizing and reducing potentials that maintain equal currents at the working and counter electrodes.

[0399] Because of the function of the reference electrode 102, including the drift that occurs during periods of signal artifacts (e.g., ischemia), the reference electrode can be monitored to determine the severity of the signal artifacts on the data stream. Particularly, a substantially direct relationship between the reference electrode drift and signal artifacts has been discovered. Using the information contained within the CV curve (FIGS. 10B and/or 10C), the measured glucose signal ( $I_{\text{SENSE}}$ ) can be automatically scaled accordingly to replace these undesired transient effects on the data stream. It is noted that the circuit described with reference to FIG. 10A can be used to determine the CV curve on a regularly scheduled basis or as needed. To this end, the desired reference voltage and applied potential are made variable, and the reference voltage can be changed at a defined rate while measuring the signal strength from the working electrode, which allows for generation of a CV curve while a sensor is in vivo.

[0400] In alternative implementations of the reference drift replacement method, a variety of algorithms can therefore be implemented that replaces the signal artifacts based on the changes measured in the reference electrode. Linear algorithms, and the like, are suitable for interpreting the direct relationship between reference electrode drift and the non-glucose rate limiting signal noise such that appropriate conversion to signal noise compensation can be derived.

[0401] In other embodiments of Signal Artifacts Replacement, prediction algorithms, also referred to as projection algorithms, can be used to replace glucose data signals for data which does not exist because 1) it has been discarded, 2) it is missing due to signal transmission errors or the like, or 3) it represents a time period (e.g., future) for which a data stream has not yet been obtained based on historic and/or present data. Prediction/projection algorithms include any of the above described Signal Artifacts Replacement algorithms, and differ only in the fact that they are implemented to replace time points/periods during which no data is available (e.g., for the above-described reasons), rather than including that existing data, within the algorithmic computation.

[0402] In some embodiments, signal replacement/estimation algorithms are used to predict where the glucose signal should be, and if the actual data stream varies beyond a certain threshold of that projected value, then signal artifacts are detected. In alternative embodiments, other data processing can be applied alone, or in combination with the above-described methods, to replace data signals during system noise and/or signal artifacts. Selective Application of Signal Replacement Algorithms

[0403] FIG. 15 is a flow chart that illustrates a process of selectively applying signal estimation in embodiments.

[0404] At block 152, a sensor data receiving module, also referred to as the sensor data module, receives sensor data (e.g., a data stream), including one or more time-spaced sensor data points, such as described in more detail with reference to block 82 in FIG. 8.

[0405] At block 154, a signal artifacts detection module, also referred to as the signal artifacts detector 154, is programmed to detect transient non-glucose related signal artifacts in the data stream that have a higher amplitude than system noise, such as described in more detail with reference

to block 84 in FIG. 8. However, the signal artifacts detector of this embodiment can additionally detect a severity of signal artifacts. In some embodiments, the signal artifacts detector has one or more predetermined thresholds for the severity of the signal artifacts (e.g., low, medium, and high). In some embodiments, the signal artifacts detector numerically represents the severity of signal artifacts based on a calculation for example, which representation can be used to apply to the signal estimation algorithm factors, such as described in more detail with reference to block 156.

[0406] In one exemplary embodiment, the signal artifacts detection module evaluates the amplitude and/or frequency of the transient non-glucose related signal artifacts, which amplitude and/or frequency can be used to define the severity in terms of a threshold (e.g., high or low) or a numeric representation (e.g., a value from 1 to 10). In another exemplary embodiment, the signal artifacts detection module evaluates a duration of the transient non-glucose related signal artifacts, such that as the duration increases, a severity can be defined in terms of a threshold (e.g., short or long) or a numeric representation (e.g., 10, 20, 30, 40, 50, or 60 minutes). In another exemplary embodiment, the signal artifacts detection module evaluates the frequency content from a Fourier Transform and defines severity in terms of a threshold (e.g., above or below 30 cycles per hour) or a numeric representation (e.g., 50 cycles per hour). All of the signal artifacts detection methods described herein can be implemented to include determining a severity of the signal artifacts, threshold, and/or numerical representations.

[0407] At block 156, the signal artifacts replacement module, also referred to as the signal estimation module, selectively applies one of a plurality of signal estimation algorithm factors in response to the severity of said signal artifacts.

[0408] In one embodiment, signal artifacts replacement is normally turned off, except during detected signal artifacts. In another embodiment, a first signal estimation algorithm (e.g., linear regression, FIR filter etc.) is turned on all the time, and a second signal estimation algorithm optimized for signal artifacts (e.g., IIR filter, Cone of Possibility Replacement Method, etc.) is turned on only during positive detection of signal artifacts.

[0409] In another embodiment, the signal replacement module comprises programming to selectively switch on and off a plurality of distinct signal estimation algorithms based on the severity of the detected signal artifacts. For example, the severity of the signal artifacts can be defined as high and low. In such an example, a first filter (e.g., trimmed regression, linear regression, FIR, Reference Electrode Method, etc.) can be applied during low signal artifacts and a second filter (e.g., IIR, Cone of Possibility Method, etc.) can be applied during high signal artifacts. It is noted that all of the above signal replacement algorithms can be selectively applied in this manner based on the severity of the detected signal artifacts.

[0410] FIG. 16 is a graph that illustrates a embodiment wherein the signal replacement module comprises programming to selectively switch on and off a signal artifacts replacement algorithm responsive to detection of signal artifacts. The x-axis represents time in minutes; the first y-axis 160 represents sensor data output in counts. A raw data signal 161, which is illustrated as a dotted line, shows

a data stream wherein some system noise can be detected; however signal artifacts **162** can be particularly seen in a portion thereof. The second y-axis **164** represents counter-electrode voltage in counts; counter electrode voltage data **165** is illustrated as a solid line. It is noted that a counter voltage drop to approximately zero in this example, which is one of numerous methods provided for detecting signal artifacts, detects signal artifacts **162**. Accordingly, when the system detects the signal artifacts **162**, an IIR-filter is selectively switched on in order to replace the signal artifact with an IIR-estimated glucose signal **166**, which is illustrated as a heavy solid line. The IIR filter is switched off upon detection of negligible signal artifacts (e.g., counter electrode voltage increasing from about zero in this embodiment).

[0411] FIG. 17 is a graph that illustrates an embodiment wherein the signal artifacts replacement module comprises programming to selectively apply different signal artifacts replacement algorithms responsive to detection of signal artifacts. The x-axis represents time in minutes; the first y-axis **170** represents sensor data output in counts. A raw data signal **171**, which is illustrated as a dotted line, shows a data stream wherein some system noise can be detected; however signal artifacts **172** can be particularly seen in a portion thereof. The second y-axis **174** represents counter-electrode voltage in counts; counter electrode voltage data **175** is illustrated as a solid line. It is noted that a counter voltage drop to approximately zero in this example, which is one of numerous methods provided for detecting signal artifacts, detects signal artifacts **172**.

[0412] In this embodiment, an FIR filter is applied to the data stream during detection of negligible or no signal artifacts (e.g., during no noise to system noise in the data stream). Accordingly, normal signal noise (e.g., system noise) can be filtered to replace the data stream with an FIR-filtered data signal **176**, which is illustrated by a slightly heavy solid line. However, upon positive detection of signal artifacts (e.g., detected by approximately zero counter electrode voltage in this embodiment), the FIR filter is switched off and an IIR-filter is switched on in order to replace the signal artifacts with an IIR-filtered glucose signal **178**, which is illustrated as a heavy solid line. The IIR filter is subsequently switched off and the FIR filter is switched back on upon detection of negligible signal artifacts (e.g., counter electrode voltage increasing from about zero in this embodiment).

[0413] In another embodiment, the signal replacement module comprises programming to selectively apply different parameters to a single signal artifacts replacement algorithm (e.g., IIR, Cone of Possibility Replacement Method, etc.). As an example, the parameters of an algorithm can be switched according to signal artifacts detection; in such an example, an IIR filter with a 30-minute cycle length can be used during times of no noise or system noise and a 60-minute cycle length can be used during signal artifacts. As another example, the severity of the signal artifacts can be defined as short and long; in such an example, an IIR filter with a 30-minute cycle length can be used during the short signal artifacts and a 60-minute cycle length can be used during long signal artifacts. As yet another example, the severity of the signal artifacts can be defined by a numerical representation; in such an example, the numerical representation can be used to calculate the parameters of the signal

replacement algorithm (e.g., IIR, Cone of Possibility Replacement Method, and Reference Drift Method).

[0414] The above description provides several methods and materials of the invention. This invention is susceptible to modifications in the methods and materials, as well as alterations in the fabrication methods and equipment. Such modifications will become apparent to those skilled in the art from a consideration of this application or practice of the invention provided herein. Consequently, it is not intended that this invention be limited to the specific embodiments provided herein, but that it cover all modifications and alternatives coming within the true scope and spirit of the invention as embodied in the attached claims. All patents, applications, and other references cited herein are hereby incorporated by reference in their entirety.

What is claimed is:

1. A method for analyzing data from a glucose sensor, comprising:

monitoring a data stream from the sensor;

detecting transient non-glucose related signal artifacts in the data stream that have a higher amplitude than a system noise; and

replacing at least some of the signal artifacts using estimated glucose signal values.

2. The method of claim 1, wherein the data signal obtaining step comprises receiving data from one of non-invasive, minimally invasive, and invasive glucose sensor.

3. The method of claim 1, wherein data signal obtaining step comprises receiving data from one of an enzymatic, chemical, physical, electrochemical, spectrophotometric, polarimetric, calorimetric, iontophoretic, and radiometric glucose sensor.

4. The method of claim 1, wherein the data signal obtaining step comprises receiving data from a wholly implantable glucose sensor.

5. The method of claim 1, wherein the signal artifacts detection step comprises testing for ischemia within or proximal to the glucose sensor.

6. The method of claim 5, wherein the ischemia testing step comprises obtaining oxygen concentration using an oxygen sensor proximal to or within the glucose sensor.

7. The method of claim 5, wherein the ischemia testing step comprises comparing a measurement from an oxygen sensor proximal to or within the glucose sensor with a measurement from an oxygen sensor distal from the glucose sensor.

8. The method of claim 5, wherein the glucose sensor comprises an electrochemical cell comprising a working electrode and a reference electrode, and wherein the ischemia-testing step comprises pulsed amperometric detection.

9. The method of claim 5, wherein the glucose sensor comprises an electrochemical cell comprising working, counter and reference electrodes, and wherein the ischemia-testing step comprises monitoring the counter electrode.

10. The method of claim 5, wherein the glucose sensor comprises an electrochemical cell comprising working, counter and reference electrodes, and wherein the ischemia-testing step comprises monitoring the reference electrode.

11. The method of claim 5, wherein the glucose sensor comprises an electrochemical cell comprising an anode and a cathode, and wherein the ischemia-testing step comprises monitoring the cathode.

12. The method of claim 1, wherein the signal artifacts detection step comprises monitoring a level of pH proximal to the sensor.

13. The method of claim 1, wherein the signal artifacts detection step comprises monitoring a temperature proximal to the sensor.

14. The method of claim 1, wherein the signal artifacts detection step comprises comparing a level of pH proximal to and distal to the sensor.

15. The method of claim 1, wherein the signal artifacts detection step comprises comparing a temperature proximal to and distal to the sensor.

16. The method of claim 1, wherein the signal artifacts detection step comprises monitoring a pressure or stress within the glucose sensor.

17. The method of claim 1, wherein the signal artifacts detection step comprises evaluating historical data for high amplitude noise above a predetermined threshold.

18. The method of claim 1, wherein the signal artifacts detection step comprises a Cone of Possibility Detection Method.

19. The method of claim 18, wherein the signal artifacts detection step comprises evaluating the data stream for a non-physiological rate-of-change.

20. The method of claim 1, wherein the signal artifacts detection step comprises monitoring the frequency content of the signal.

21. The method of claim 20, wherein the frequency-content monitoring step comprises performing an orthogonal basis function-based transform.

22. The method of claim 21, wherein the transform is a Fourier Transform or a wavelet transform.

23. The method of claim 1, wherein the artifacts replacement step comprises performing linear or non-linear regression.

24. The method of claim 23, wherein the artifacts replacement step comprises performing a trimmed mean.

25. The method of claim 1, wherein the artifacts replacement step comprises filtering using a non-recursive filter.

26. The method of claim 25, wherein non-recursive filtering step uses a finite impulse response filter.

27. The method of claim 1, wherein the artifacts replacement step comprises filtering using a recursive filter.

28. The method of claim 27, wherein the recursive filtering step uses an infinite impulse response filter.

29. The method of claim 1, wherein the artifacts replacement step comprises a performing a maximum average algorithm.

30. The method of claim 1, wherein the artifacts replacement step comprises performing a Cone of Possibility Replacement Method.

31. The method of claim 1, further comprising estimating future glucose signal values based on historical glucose values.

32. The method of claim 31, wherein glucose future estimation step comprises algorithmically estimating the future signal value based using at least one of linear regression, non-linear regression, and an auto-regressive algorithm.

33. The method of claim 32, further comprising measuring at least one of rate-of-change, acceleration, and physiologically feasibility of one or more signal values and subsequently selectively applying the algorithm conditional on a range of one of the measurements.

34. The method of claim 1, wherein the glucose sensor comprises an electrochemical cell comprising working, counter, and reference electrodes, and wherein the artifacts replacement step comprises normalizing the data signal based on baseline drift at the reference electrode.

35. The method of claim 1, wherein the signal artifacts replacement step is substantially continual.

36. The method of claim 1, wherein the signal artifacts replacement step is initiated in response to positive detection of signal artifacts.

37. The method of claim 1, wherein the signal artifacts replacement step is terminated in response to detection of negligible signal artifacts.

38. The method of claim 1, wherein the signal artifacts detection step comprises evaluating the severity of the signal artifacts.

39. The method of claim 38, wherein the severity evaluation is based on an amplitude of the transient non-glucose related signal artifacts.

40. The method of claim 38, wherein the severity evaluation is based on a duration of the transient non-glucose related signal artifacts.

41. The method of claim 38, wherein the severity evaluation is based on a rate-of-change of the transient non-glucose related signal artifacts.

42. The method of claim 38, wherein the severity evaluation is based on a frequency content of the transient non-glucose related signal artifacts.

43. The method of claim 38, wherein the artifacts replacement step comprises selectively applying one of a plurality of signal estimation algorithm factors in response to the severity of the signal artifacts.

44. The method of claim 43, wherein the plurality of signal estimation algorithm factors comprise a single algorithm with a plurality of parameters that are selectively applied to the algorithm.

45. The method of claim 43, wherein the plurality of signal estimation algorithm factors comprise a plurality of distinct algorithms.

46. The method of claim 43, wherein the step of selectively applying one of a plurality of signal estimation algorithm factors comprises selectively applying a predetermined algorithm that comprises a set of parameters whose values depend on the severity of the signal artifacts.

47. The method of claim 1, further comprising discarding at least some of the signal artifacts.

48. The method of claim 1, further comprising projecting glucose signal values for a time during which no data is available.

49. A method for processing data signals obtained from a glucose sensor, the method comprising:

obtaining a data stream from a glucose sensor;

detecting transient non-glucose related signal artifacts in the data stream that have a higher amplitude than a system noise; and

selectively applying one of a plurality of signal estimation algorithm factors to replace non-glucose related signal artifacts.



**50.** The method of claim 49, wherein the data signal obtaining step comprises receiving data from one of non-invasive, minimally invasive, and invasive glucose sensor.

**51.** The method of claim 49, wherein data signal obtaining step comprises receiving data from one of an enzymatic, chemical, physical, electrochemical, spectrophotometric, polarimetric, calorimetric, iontophoretic, and radiometric glucose sensor.

**52.** The method of claim 49, wherein the data signal obtaining step comprises receiving data from a wholly implantable glucose sensor.

**53.** The method of claim 49, wherein the signal artifacts detection step comprises testing for ischemia within or proximal to the glucose sensor.

**54.** The method of claim 53, wherein the ischemia testing step comprises obtaining oxygen concentration using an oxygen sensor proximal to or within the glucose sensor.

**55.** The method of claim 53, wherein the ischemia testing step comprises comparing a measurement from an oxygen sensor proximal to or within the glucose sensor with a measurement from an oxygen sensor distal from the glucose sensor.

**56.** The method of claim 53, wherein the glucose sensor comprises an electrochemical cell comprising a working electrode and a reference electrode, and wherein the ischemia-testing step comprises pulsed amperometric detection.

**57.** The method of claim 53, wherein the glucose sensor comprises an electrochemical cell comprising working, counter and reference electrodes, and wherein the ischemia-testing step comprises monitoring the counter electrode.

**58.** The method of claim 53, wherein the glucose sensor comprises an electrochemical cell comprising a working electrode, a counter electrode, and a reference electrode, and wherein the ischemia testing step comprises monitoring the reference electrode.

**59.** The method of claim 53, wherein the glucose sensor comprises an electrochemical cell comprising an anode and a cathode, and wherein the ischemia-testing step comprises monitoring the cathode.

**60.** The method of claim 49, wherein the signal artifacts detection step comprises monitoring a level of pH proximal to the sensor.

**61.** The method of claim 49, wherein the signal artifacts detection step comprises monitoring a temperature proximal to the sensor.

**62.** The method of claim 49, wherein the signal artifacts detection step comprises comparing a level of pH proximal to and distal to the sensor.

**63.** The method of claim 49, wherein the signal artifacts detection step comprises comparing a temperature proximal to and distal to the sensor.

**64.** The method of claim 49, wherein the signal artifacts detection step comprises monitoring the pressure or stress within the glucose sensor.

**65.** The method of claim 49, wherein the signal artifacts detection step comprises evaluating historical data for high amplitude noise above a predetermined threshold.

**66.** The method of claim 49, wherein the signal artifacts detection step comprises a Cone of Possibility Detection Method.

**67.** The method of claim 66, wherein the signal artifacts detection step comprises evaluating the signal for a non-physiological rate-of-change.

**68.** The method of claim 49, wherein the signal artifacts detection step comprises monitoring the frequency content of the signal.

**69.** The method of claim 68, wherein the frequency-content monitoring step comprises performing an orthogonal basis function-based transform.

**70.** The method of claim 69, wherein the transform is a Fourier Transform or a wavelet transform.

**71.** The method of claim 49, wherein the artifacts replacement step comprises performing linear or non-linear regression.

**72.** The method of claim 71, wherein the artifacts replacement step comprises performing a trimmed mean.

**73.** The method of claim 49, wherein the artifacts replacement step comprises filtering using a non-recursive filter.

**74.** The method of claim 73, wherein non-recursive filtering step uses a finite impulse response filter.

**75.** The method of claim 49, wherein the artifacts replacement step comprises filtering using a recursive filter.

**76.** The method of claim 75, wherein the recursive filtering step uses an infinite impulse response filter.

**77.** The method of claim 49, wherein the artifacts replacement step comprises a performing a maximum average algorithm.

**78.** The method of claim 49, wherein the artifacts replacement step comprises performing a Cone of Possibility algorithm.

**79.** The method of claim 49, further comprising estimating future glucose signal values based on historical glucose values.

**80.** The method of claim 79, wherein glucose future estimation step comprises algorithmically estimating the future signal value based using at least one of linear regression, non-linear regression, and an auto-regressive algorithm.

**81.** The method of claim 80, further comprising measuring at least one of rate-of-change, acceleration, and physiologically feasibility of one or more signal values and subsequently selectively applying the algorithm conditional on a range of one of the measurements.

**82.** The method of claim 49, wherein the glucose sensor comprises an electrochemical cell comprising working, counter, and reference electrodes, and wherein the artifacts replacement step comprises normalizing the data signal based on baseline drift at the reference electrode.

**83.** The method of claim 49, wherein the selective application step is substantially continual.

**84.** The method of claim 49, wherein the selective application step is initiated in response to positive detection of signal artifacts.

**85.** The method of claim 49, wherein the selective application step is terminated in response to detection of negligible signal artifacts.

**86.** The method of claim 49, wherein the signal artifacts detection step comprises evaluating the severity of the signal artifacts.

**87.** The method of claim 86, wherein the severity evaluation is based on an amplitude of the transient non-glucose related signal artifacts.

**88.** The method of claim 86, wherein the severity evaluation is based on a duration of the transient non-glucose related signal artifacts.

**89.** The method of claim 86, wherein the severity evaluation is based on a rate-of-change of the transient non-glucose related signal artifacts.

**90.** The method of claim 86, wherein the severity evaluation is based on a frequency content of the transient non-glucose related signal artifacts.

**91.** The method of claim 86, wherein the selective application step applies the one of a plurality of signal estimation algorithm factors in response to the severity of the signal artifacts.

**92.** The method of claim 91, wherein the plurality of signal estimation algorithm factors comprise a single algorithm with a plurality of parameters that are selectively applied to the algorithm.

**93.** The method of claim 91, wherein the plurality of signal estimation algorithm factors comprise a plurality of distinct algorithms.

**94.** The method of claim 91, wherein the selective application step comprises selectively applying a predetermined algorithm that comprises a set of parameters whose values depend on the severity of the signal artifacts.

**95.** The method of claim 49, further comprising the step of discarding at least some of the signal artifacts.

**96.** The method of claim 95, wherein the selective application step further comprises projecting glucose signal values for a time during which no data is available.

**97.** A system for processing data signals obtained from a glucose sensor, the system comprising:

a signal processing module comprising programming to monitor a data stream from the sensor over a period of time;

a detection module comprising programming to detect transient non-glucose related signal artifacts in the data stream that have a higher amplitude than a system noise; and

a signal estimation module comprising programming to replace at least some of the signal artifacts with estimated glucose signal values.

**98.** A system for processing data signals obtained from a glucose sensor, the system comprising:

a signal processing module comprising programming to monitor a data stream from the sensor over a period of time;

a detection module comprising programming to detect transient non-glucose related signal artifacts in the wherein the plurality of signal estimation algorithm factors comprise a plurality of distinct algorithms data stream that have a higher amplitude than a system noise; and

a signal estimation module comprising programming to selectively apply one of a plurality of signal estimation algorithm factors to replace non-glucose related signal artifacts.

**99.** An implantable glucose monitoring device, comprising:

a glucose sensor; and

a processor operatively linked to the sensor designed to receive a data stream from the sensor;

wherein the processor is programmed to analyze the data stream and to detect transient non-glucose related signal artifacts in the data stream that have a higher amplitude than system noise, and to replace at least some of the signal artifacts with estimated values.

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#### 摘要(译)

用于最小化或消除由于非葡萄糖速率限制现象（例如缺血，pH变化，温度变化等）引起的瞬时非葡萄糖相关信号噪声的系统和方法。该系统监测来自葡萄糖传感器的数据流，并检测具有比电子或扩散相关系统噪声更高幅度的信号伪影。该系统连续地或间歇地替换一些或整个数据流，包括特别针对瞬态信号伪像的信号估计方法。该系统还能够检测信号伪像的严重性并且响应于信号伪像的严重性选择性地应用一个或多个信号估计算法因子，其包括选择性地应用不同的参数组应用于信号估计算法或选择性地应用不同的信号。估计算法。

