US 20060052679A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2006/0052679 A1**
     Kotulla et al.   (43) **Pub. Date: Mar. 9, 2006**

(54) **METHOD AND DEVICE FOR CONTINUOUS MONITORING OF THE CONCENTRATION OF AN ANALYTE**

(76) Inventors: **Reinhard Kotulla**, Lambsheim (DE); **Arnulf Staib**, Rossdorf (DE); **Ralph Gillen**, Papenburg (DE)

Correspondence Address:
Roche Diagnostics Corporation
9115 Hague Road
PO Box 50457
Indianapolis, IN 46250-0457 (US)

(57)   **ABSTRACT**

The present invention generally relates to a method for continuous monitoring of the concentration of an analyte by determining its change over time in the living body of a human or animal. A measurement variable value correlating with the desired concentration of the analyte are measured as the measurement signal (z_t) and the change over time of the concentration is determined from the measurement signal as the useful signal (y_t) using a calibration. A filter algorithm is used to reduce errors of the useful signal, which result from noise contained in the measurement signal. The filter algorithm includes an operation in which the influence of an actual measurement value on the useful signal is weighted using a weighting factor (V).
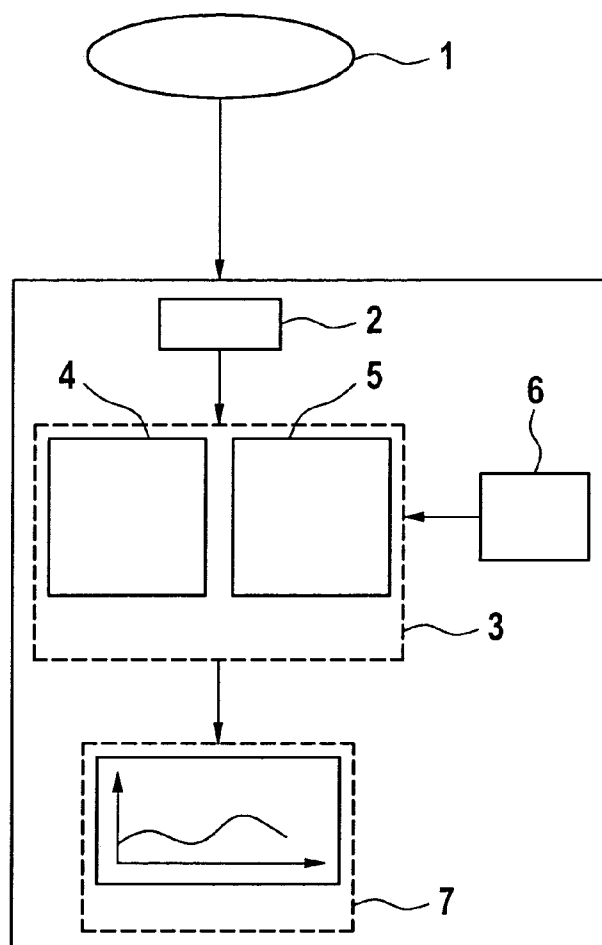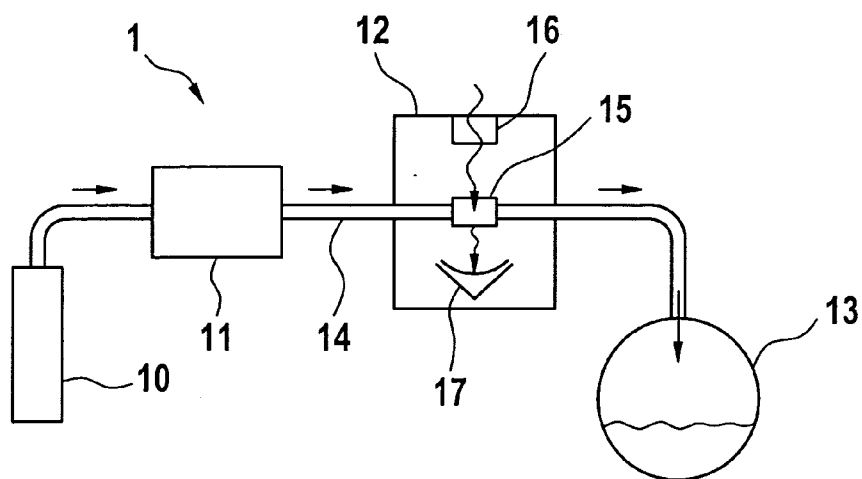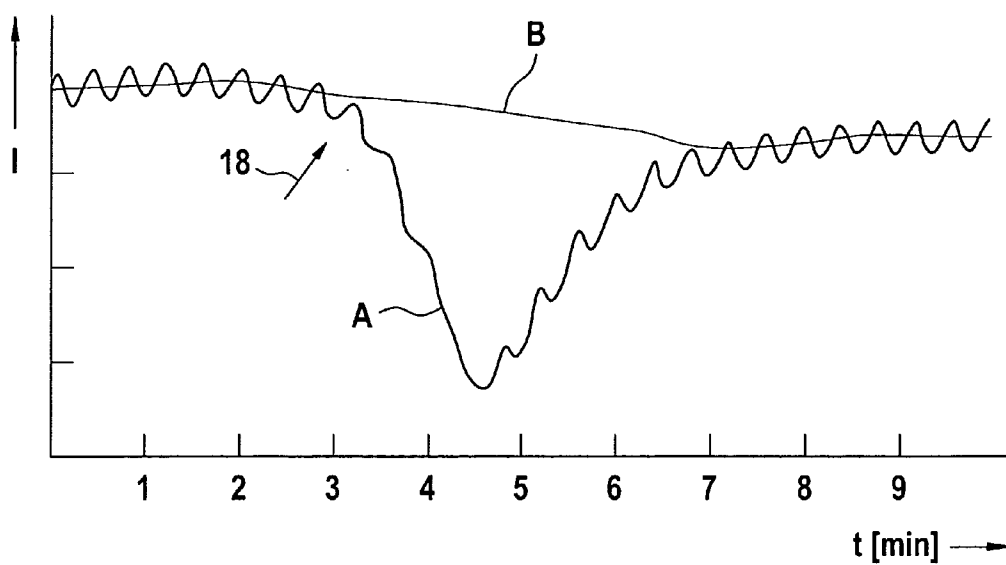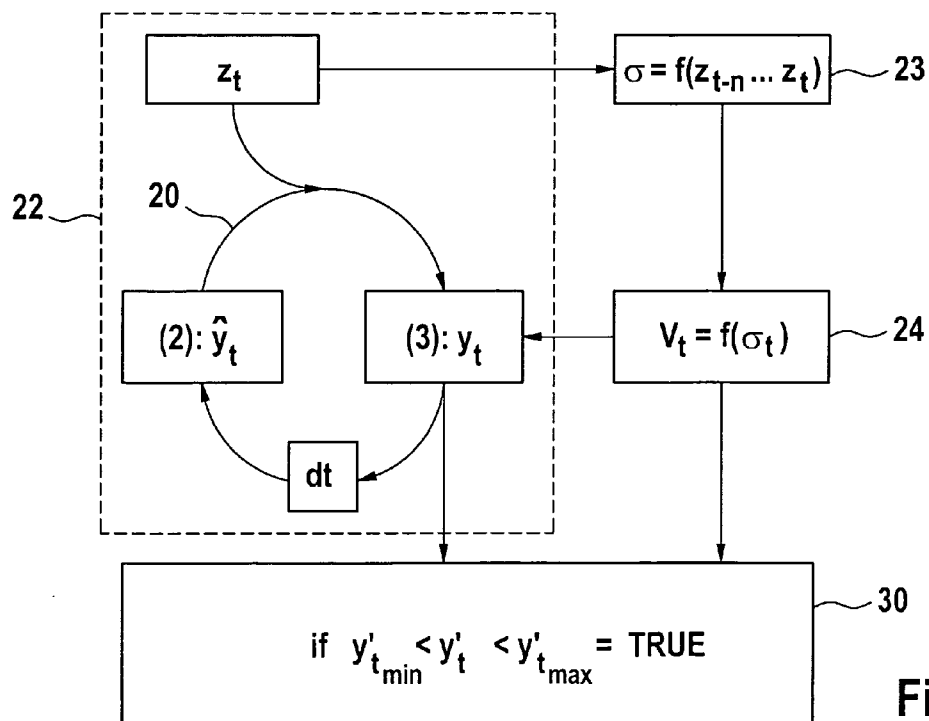
Fig. 1

Fig. 2

Fig. 3

$$\text{if} \quad y'_{t_{min}} < y'_t < y'_{t_{max}} = \text{TRUE}$$
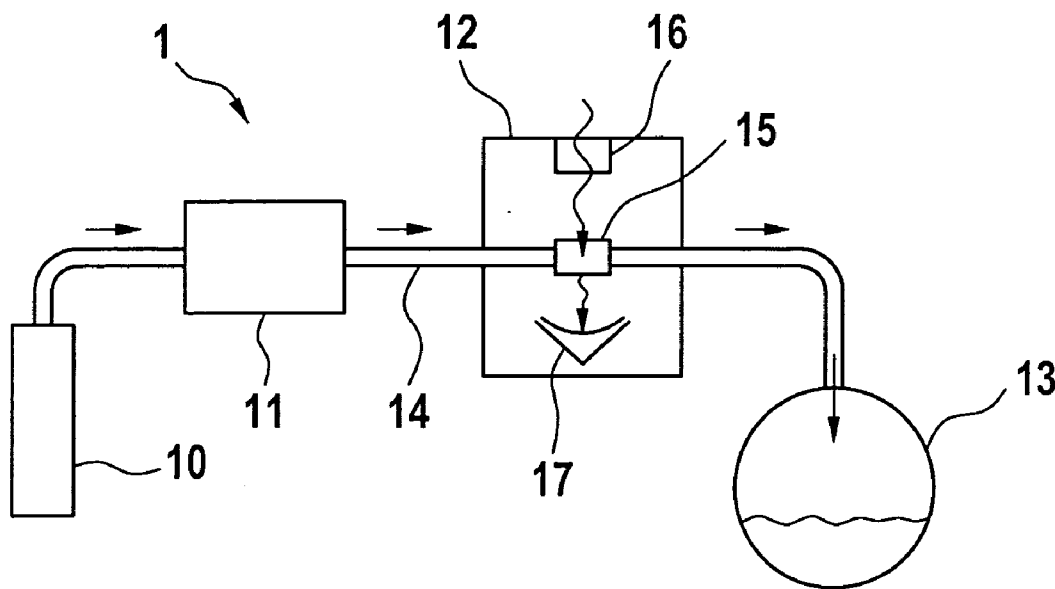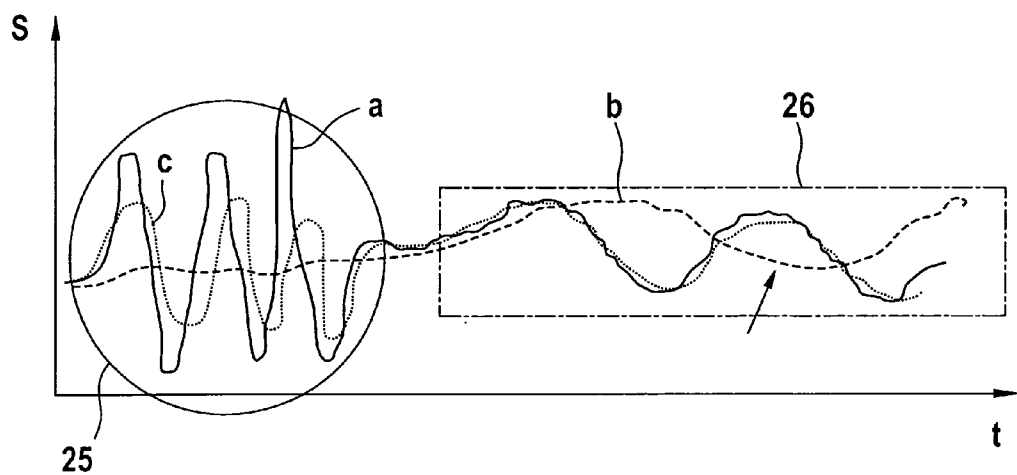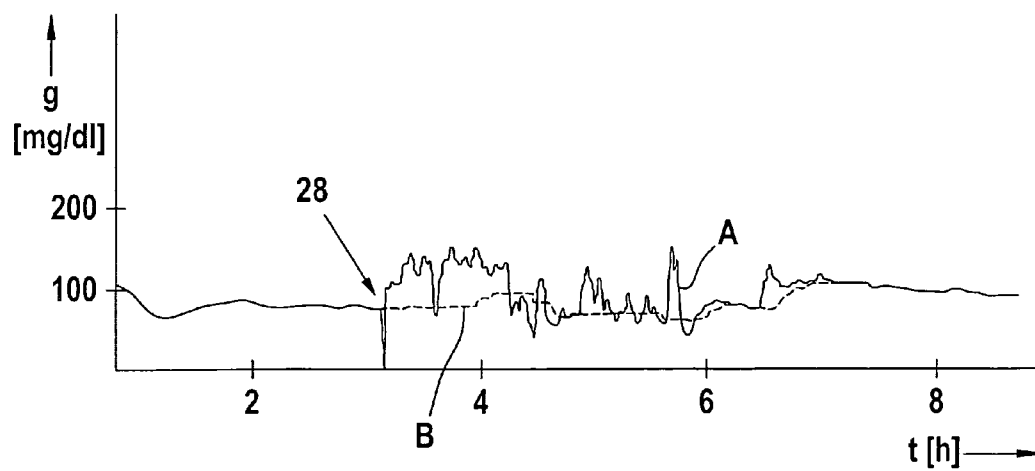
Fig. 4

Fig. 5

Fig. 6

METHOD AND DEVICE FOR CONTINUOUS MONITORING OF THE CONCENTRATION OF AN ANALYTE

REFERENCE TO RELATED APPLICATIONS

[0001] The present application is a Continuation of U.S. patent application Ser. No. 10/945,798, filed Sep. 21, 2004 which claims priority to German Patent Application No. 10343863.7, filed Sep. 23, 2003, which are hereby incorporated by reference in their entirety.

TECHNICAL FIELD

[0002] The present invention generally relates to a method and a device for continuous monitoring of the concentration of an analyte. In particular, the invention relates to determining the analyte's change over time in the living body of a human or animal. The term "continuous monitoring (CM)" is used hereafter for this purpose.

BACKGROUND

[0003] A CM method and device is described, for example, in U.S. Pat. No. 5,507,288.

[0004] A main task is the continuous monitoring of the concentration of glucose in the body of the patient, which is of great medicinal significance. Studies have led to the result that extremely grave long-term effects of diabetes mellitus (for example, blinding because of retinopathy) can be avoided if the change over time of the concentration of the glucose is continuously monitored in vivo. Continuous monitoring allows to dose the required medication (insulin) precisely at each point in time and to keep the blood sugar level always within narrow limits, similarly to a healthy person.

[0005] The present invention relates in particular to CM of glucose. Further information can be taken from document (1) and the literature cited therein. The content of this document is incorporated herein by reference.

[0006] The present invention is, however, also suitable for other applications in which the change over time of an analyte in the living body (useful signal) is derived from a measurement signal, which comprises measurement values, measured at sequential points in time, of a measurement variable correlating with the concentration desired. The measurement signal may be measured invasively or non-invasively.

[0007] An invasive measurement method is described, for example, in

[0008] U.S. Pat. No. 6,584,335.

[0009] Here a hollow needle carrying a thin optical fiber is stuck into the skin, light is irradiated under the skin surface through the optical fiber, and a modification of the light through interaction with interstitial liquid which surrounds the optical fiber is measured. In this case, the measurement signal comprises measurement values obtained from light which is returned through the optical fiber into a measurement device after the interaction. For example, the measurement signal may comprise spectra of the light which are measured at sequential points in time.

[0010] Another example of invasive measurement methods is the monitoring of concentrations by means of an electrochemical sensor which may be stuck into the skin. An electrical measurement variable, typically a current, is thus determined as the measurement variable which is correlated with the concentration of the analyte.

[0011] Different non-invasive methods are discussed in Document (1). These include spectroscopic methods in which light is irradiated directly (i.e., without injuring the skin) through the skin surface into the body and diffusely reflected light is analyzed. Methods of this type have achieved some importance for checking the change over time of oxygen saturation in the blood. For the analysis of glucose alternative methods are preferred, in which light is irradiated into the skin in a strongly localized manner (typically punctually) and the useful signal (course of the glucose concentration) is obtained from the spatial distribution of the secondary light coming out of the skin in the surroundings of the irradiation point. In this case the measurement signal is formed by the intensity profile, measured at sequential points in time, of the secondary light in the surroundings of the irradiation point.

[0012] A common feature of all methods of this type is that the change of the concentration over time (useful signal) is determined from the measurement values measured at sequential points in time (measurement signal) using a microprocessor system and a suitable algorithm. This analysis algorithm includes the following partial algorithms: a filter algorithm, by which errors of the useful signal resulting from signal noise contained in the measurement signal are reduced and a conversion algorithm, in which a functional relationship determined by calibration, which relationship describes the correlation between measurement signal and useful signal, is used.

[0013] Typically, these parts of the analysis algorithm are performed in the described sequence, i.e., first a filtered measurement signal is obtained from a raw measurement signal by filtering and the filtered signal is then converted into the useful signal. However, this sequence is not mandatory. The raw measurement signal can also be first converted into a raw useful signal and then filtered to obtain the final useful signal. The analysis algorithm may also include further steps in which intermediate variables are determined. It is only necessary in the scope of the present invention that the two partial algorithms a) and b) are performed as part of the analysis algorithm. The partial algorithms a) and b) may be inserted anywhere into the analysis algorithm and performed at any time.

[0014] The present invention relates to cases in which time domain filter algorithms are used. Kalman filter algorithms are particularly common for this purpose. More detailed information on filter algorithms of this type is disclosed by the following literature citations, some of which also describe chemical and medical applications:

[0015] S. D. Brown: The Kalman filter in analytical chemistry, Analytica Chimica Acta 181 (1986), 1-26.

[0016] K. Gordon: The multi-state Kalman filter in medical monitoring, Computer Methods and Programs in Biomedicine 23 (1986), 147-154.

[0017] K. Gordon, A. F. M. Smith: Modeling and monitoring biomedical time series, Journal of the American Statistical Association 85 (1990), 328-337.

[0018] U.S. Pat. No. 5,921,937

[0019] EP 0 910 023 A2

[0020] WO 01/38948 A2

[0021] U.S. Pat. No. 6,317,662

[0022] U.S. Pat. No. 6,575,905 B2

[0023] As noted, the filter algorithm is used for the purpose of removing noise signals which are contained in the raw measurement signal and would corrupt the useful signal. The goal of every filter algorithm is to eliminate this noise as completely as possible, but simultaneously avoid to disturb the measurement signal. This goal is especially difficult to achieve for in vivo monitoring of analytes, because the measurement signals are typically very weak and have strong noise components. Special problems arise because the measurement signal typically contains two types of noise, which differ significantly in regard to the requirements for the filter algorithm: measurement noise: such noise signal components follow a normal distribution having a constant standard deviation around the correct (physiological) measurement signal non-physiological signal changes, which are caused, for example, by movements of the patient and changes of the coupling of a measurement sensor to the skin to which it is connected. They are typically neither distributed normally around the physiological measurement signal, nor is the standard deviation from the physiological measurement signal constant. For such noise components of the raw signal the term NNNC (non-normal, non-constant)-noise is used hereafter.

SUMMARY

[0024] The present invention is based on the technical problem to achieve a better precision of CM methods by improving the filtering of noise signals.

[0025] According to the present invention this is achieved by means of a filter algorithm which includes an operation in which the influence of an actual measurement value on the useful signal is weighted using a weighting factor ("controllable filter algorithm"), a signal variation parameter (related in each case to the actual point in time, i.e. time-dependent) is determined on the basis of signal variations detected during the continuous monitoring in close chronological connection with the measurement and the weighting factor is adapted dynamically as a function of the signal variation parameter determined for the point in time of the actual measurement.

[0026] The present invention, including preferred embodiments, will be described in greater detail hereafter on the basis of the figures. The details shown therein and described in the following may be used individually or in combination to provide preferred embodiments of the present invention.

BRIEF DESCRIPTION OF THE DRAWINGS

[0027] The following detailed description of the embodiments of the present invention can be best understood when read in conjunction with the following drawings, where like structure is indicated with like reference numerals and in which:

[0028] FIG. 1 shows a block diagram of a device according to the present invention;

[0029] FIG. 2 shows a schematic diagram of a sensor suitable for the present invention;

[0030] FIG. 3 shows a measurement signal of a sensor as shown in FIG. 2;

[0031] FIG. 4 shows a symbolic flowchart to explain the algorithm used in the scope of the present invention;

[0032] FIG. 5 shows a graphic illustration of typical signal curves to explain the problem solved by the present invention;

[0033] FIG. 6 shows a graphic illustration of experimentally obtained measurement results.

[0034] Skilled artisans appreciate that elements in the figures are illustrated for simplicity and clarity and have not necessarily been drawn to scale. For example, the dimensions of some of the elements in the figures may be exaggerated relative to other elements to help improve understanding of the embodiment(s) of the present invention.

DETAILED DESCRIPTION

[0035] The following description of the preferred embodiment is merely exemplary in nature and is in no way intended to limit the invention or its application or uses.

[0036] The components of a CM device according to the present invention are shown in FIG. 1. As shown, a sensor 1 measures measurement values at sequential points in time. This measurement signal is transmitted—wirelessly, in the case shown—to a receiver 2, from which the measurement signal is further transmitted to an analysis unit 3, which contains a microprocessor 4 and a data memory 5. Data and commands may also be transmitted to the analysis unit 3 via an input unit 6. Results are output using an output unit 7, which may include a display and other typical output means. The data processing is performed digitally in the analysis unit 3 and corresponding converters for converting analog signals into digital signals are provided. The present invention is suitable for a wide range of measurement techniques in which—as explained at the beginning—different measurement signals correlating to the desired useful signal are obtained.

[0037] FIG. 2 shows a sensor 1 in the form of a schematic diagram, in which an implantable catheter 10 is used in order to suction interstitial liquid from the subcutaneous fatty tissue by means of a pump 11. The tissue is then suctioned through a photometric measurement unit 12 into a waste container 13. The line 14 by which the interstitial liquid is transported contains a transparent measurement cell 15 which is arranged in the photometric measurement unit 12, into which primary light originating from a light emitter 16 is irradiated. The secondary light resulting after passing the measurement cell 15 is measured using a photodetector 17 and processed by means of a measurement electronics (not shown) into a raw signal, which—as shown for exemplary purposes in FIG. 1—is transmitted to an analysis unit 3.

[0038] FIG. 3 shows the typical graph of a raw measurement signal as curve A obtained using a sensor as shown in FIG. 2. The intensity I of the secondary light is measured at a specific wavelength and plotted against the time t in minutes. FIG. 3 is based on a CM experiment in which the measurement values for curve A were measured at intervals of one second each.

ables of glucose concentration g_t, amplitude A_t, and frequency ω_t of the fluidic modulation:

$$z_t = g_t + A_t \cdot \sin(\omega_t \cdot t).$$

[0057] According to equation (3), the influence of the actual measurement value (contained in the innovation Δ_t) on the filtered useful signal value y_t is weighted by the factors α_t and β_t. The described algorithm is therefore a controllable filter algorithm.

[0058] In the case of a Kalman filter, $\alpha_t=1$ for every point in time and $\beta_t=K_t$. K_t refers to the Kalman gain. Accordingly, the corrector equation is as follows:

$$y_t = \hat{y}_t + K_t \Delta_t \qquad (3a)$$

[0059] Further details regarding the Kalman gain K_t and more detailed information on the algorithm may be taken from the relevant literature, as cited above. Expressed descriptively, the Kalman gain is a measure of the weight given to additional measurement values. The Kalman gain is calculated anew in every iteration step of the filter algorithm according to an equation which may be written in simplified form (for the linear case) as follows:

$$K_t = P_t \cdot H_t \cdot (P_t \cdot H_t + V)^{-1}$$

[0060] Here, P_t designates the Kalman error covariance matrix. V designates the measurement error covariance matrix in the conventional Kalman algorithm.

[0061] Equation (6) shows that the elements of K_t may assume only values between 0 and 1. If the assumed measurement error V is relatively large in relation to the Kalman error covariance P_t, K_t is small, i.e., the particular actual measurement value is given relatively little weight. In contrast, if V is small in relation to P_t (multiplied by H_t), a strong correction occurs due to the actual measurement value.

[0062] **FIG. 4** shows in graphic form the iteration loop **20** which is the basis of the filter procedure. Alternately a corrector step which takes an actual measurement value z_t into consideration, and, after a time step dt, a predictor step for a new point in time are performed. For example, the corrector step may be calculated according to equation (3) or (3a) and the predictor step according to equation (2) or (2a). This part of the algorithm is referred to as the filter core **22**. As explained, it may be implemented in different ways, as long as it is an algorithm operating in the time domain and it includes an operation in which the influence of an actual measurement value z_t on the filter useful signal y_t is weighted using a weighting factor α_t, β_t, or K_t, respectively.

[0063] An important improvement of the filtering is achieved in the scope of the present invention in that, on the basis of signal variations detected in close chronological relationship with the measurement of the actual measurement value z_t, a signal variation parameter, designated here as σ_t, is determined and the weighting of the influence of the actual measurement value z_t is dynamically adapted in the context of the corrector step as a function of σ_t. This is shown in graphic form in **FIG. 4**: box **23** symbolizes the calculation of the variation parameter σ_t as a function of the measurement signal in a preceding period of time (measurement values $z_{t-n} \ldots z_t$). Box **24** symbolizes the calculation of the weighting factor taken into consideration in the corrector step (here, for example, the measurement error covariance V, which influences the Kalman gain), as a

function of the signal variation parameter σ_t. The weighting factor is a time-dependent (dynamically adapted) variable (in this case V_t).

[0064] The present invention does not have the goal of weighting different filter types—like a filter bank—by applying weighting factors. For this purpose, a series of system models analogous to equation (2) would have to be defined, one model for each filter of the filter bank. This is not necessary in the present invention, whereby the method is less complex.

[0065] No precise mathematical rules may be specified for the functional relationships used in steps **23** and **24**, because they must be tailored to each individual case. However, the following general rules apply:

> [0066] The signal variation parameter is determined as a function of measurement values which have a close chronological relationship to the particular actual measurement value. In this way, the speed of adaption of the filter is sufficient. The determination of the signal variation parameter is preferably based on measurement values which were measured less than 30 minutes, preferably less than 15 minutes, and especially preferably less than 5 minutes before the measurement of the actual measurement value. At the least, measurement values from the periods of time should be included in the algorithm for determining the signal variation parameter.

> [0067] Independently of the equations used in a particular case, the principle applies that with decreasing signal quality (i.e., for example, increase of the standard deviation of the measurement signal), the signal variation parameter and therefore the weighting factor (or possibly the weighting factors) are changed in such a direction that the influence of the currently actual measurement value is reduced.

[0068] The standard deviation, which may be calculated as follows, is suitable as the signal variation parameter, for example.

[0069] If one assumes that the determination of the standard deviation is based on the actual measurement values z and four preceding measurement values z_1 to z_4, and if the difference between z and the preceding values is referred to as δz ($\delta z_n = z - z_n$), the average value ϵ is calculated as

$$\varepsilon = \frac{1}{4}(\delta z_1 + \delta z_2 + \delta z_3 + \delta z_4) \qquad (7)$$

> [0070] and the slope ϕ of a linear smoothing function is calculated as

$$\varphi = \frac{3(\delta z_1 - \delta z_4) + \delta z_2 - \delta z_3}{10}$$

5

[0071] The standard deviation of the four values of the difference $\delta1$, $\delta2$, $\delta3$, $\delta4$ in relation to the linear smoothing function is

$$\sigma_t = \left[\frac{1}{3}(\delta z_1 - (\varepsilon + 1.5\varphi))^2 + \frac{1}{3}(\delta z_2 - (\varepsilon + 0.5\varphi))^2 + \right. \qquad (9)$$

$$\left. \frac{1}{3}(\delta z_3 - (\varepsilon - 0.5\varphi))^2 + \frac{1}{3}(\delta z_4 - (\varepsilon - 1.5\varphi))^2 \right]^{\frac{1}{2}}$$

[0072] On the basis of this standard deviation at, a dynamic (time-dependent) measurement error covariance V_t, which is included in a filter core with the Kalman algorithm, may be calculated, for example, according to

$$V_t = (\sigma_o + \sigma_t)^\gamma$$

[0073] In this case, σ_o and γ are constant parameters which characterize the filter, and which may be set to tailor the chronological behavior of the filter, in particular its adaptivity, to a particular application.

[0074] In the example of a controllable recursive filter, the weighting factors α_t, β_t from equation (3) are a function of the signal variation parameter in such a manner that with increasing σ_t, factor α_t becomes larger and factor β_t becomes smaller.

[0075] As already explained, equations (7) through (10) only represent one of numerous possibilities for calculating a signal variation parameter and, based thereon, a weighting factor for a controllable filter algorithm in the time domain. The standard deviation, which may, of course, be calculated using a varying number of measurement values, can be replaced by variables which represent a measure for the signal variations in a period of time preceding an actual measurement value. The term "signal variation parameter" is used generally to identify a mathematical variable which fulfills these requirements.

[0076] Three typical graphs of a signal S are plotted against time t in **FIG. 5**, specifically:

[0077] as a solid line, a raw signal with strong non-physiological variations in the time period enclosed by circle **25** and oscillates significantly less in the time period enclosed by rectangle **26**, these variations being essentially physiological.

[0078] as a dashed line, a useful signal, which was obtained from the raw signal a) using a Kalman filter, whose measurement error covariance was set corresponding to the variation of the raw signal in the circle **25**.

[0079] as a dotted line, a useful signal which was obtained from the raw signal a) using a Kalman filter, whose measurement error covariance was set corresponding to the graph of the raw signal in the rectangle **26**.

[0080] Evidently, in the case of curve b the strong variations are filtered well within the circle **25**, but in the rectangle **26**, the signal b reflects the physiological variations of the raw signal insufficiently. The useful signal c, in contrast, follows the physiological variations in the region **26** well, while the filtering of the non-physiological varia-

tions in the region **25** is insufficient. The conventional Kalman filter algorithm therefore allows no setting which leads to optimal filtering for the different conditions shown. In contrast, the present invention does not even require knowledge of the maximum variations of measurement values. The filter algorithm adapts itself automatically to the changes in the signal course and provides a filtered signal which corresponds to the curve b in the circle **25** and to the curve c in the rectangle **26**.

[0081] **FIG. 6** shows corresponding experimental results from a CM experiment for glucose monitoring. A useful signal resulting from conventional filtering is shown as the solid curve A (glucose concentration in mg/dl) over the time in hours. The dashed curve B is the useful signal filtered according to the present invention. At the point in time marked with the arrow **28**, the patient begins to move which interferes with the signal curve. Although there is very little variation of the free analyte concentration, the noise caused by the movement (NNNC noise) cannot be filtered out by the conventional filter. In contrast, using the filtering according to the present invention, a useful signal is obtained which approximates the physiological glucose curve very closely.

[0082] Significant additional reliability may be achieved if the filtering extends not only to the desired analyte concentration, but rather additionally to at least one further variable, which is designated "check variable". This may be a variable derived from the analyte concentration, in particular its first, second, or higher derivative versus time. Alternatively, an additional measurement variable, such as the flow of the interstitial liquid at the sensor shown in **FIG. 2**, can be used.

[0083] This check variable may, as explained above (for g_t', A_t, and ω_t), be included in the filter algorithm as a system variable. The filtering then also extends to the check variable, for which corresponding reliable smoothed useful signal values are available as the result of the filtering. These may then be compared to threshold values, in order to perform plausibility checks, for example. In the case of the glucose concentration, for example, it is known that the glucose concentration physiologically does not change by more than 3 mg/dl/min under normal conditions. A higher filtered value of the time derivative g_t' is a sign of a malfunction. Therefore the query **30** shown in **FIG. 4** compares the value of y_t' to a minimum value and a maximum value. The value y_t is only accepted as correct if y_t' lies within these limits. Such a comparison would not be possible using the useful signal A in **FIG. 6**, because the insufficiently filtered non-physiological variations would lead to false alarms.

[0084] In order that the invention may be more readily understood, reference is made to the following examples, which are intended to illustrate the invention, but not limit the scope thereof.

[0085] It is noted that terms like "preferably", "commonly", and "typically" are not utiliized herein to limit the cope of the claimed invention or to imply that certain features are critical, essential, or even important to the structure or function of the claimed invention. Rather, these terms are merely intended to highlight alternative or additional features that may or may not be utilized in a particular embodiment of the present invention.

[0086] For the purposes of describing and defining the present invention it is noted that the term "substantially" is

utilized herein to represent the inherent degree of incertainty that may be attributed to any quantitative comparison, value, measurement, or other representation. The term "substantially" is also utilized herein to represent the degree by which a quantitative representation may vary from a stated reference without resulting in a change in the basic function of the subject matter at issue.

[0087] Having described the invention in detail and by reference to specific embodiments thereof, it will be apparent that modifications and variations are possible without departing from the scope of the invention defined in the appended claims. More specifically, although some aspects of the present invention are identified herein as preferred or particularly advantageous, it is contemplated that the present invention is not necessarily limited to these preferred aspects of the invention.

[0088] As any person skilled in the art will recognize from the previous description and from the figures and claims, modifications and changes can be made to the preferred embodiment of the invention without departing from the scope of the invention as defined in the following claims.

What is claimed is:

1. A method for continuous monitoring concentration of an analyte by determining the analyte's change over time in the living body of a human or animal, the method comprising:

measuring at sequential points in time, measurement values of a measurement variable correlating with a desired concentration of the analyte;

measuring the measurement variable as a measurement signal (z_t);

determining the change over time of the concentration of the analyte from the measurement signal as a useful signal (y_t) by means of a calibration;

providing a filter algorithm in the time domain for determination of the useful signal (y_t) from the measurement signal (z_t), wherein the filter algorithm reduces errors of the useful signal resulting from noise contained in the measurement signal, wherein the filter algorithm includes an operation in which the influence of an actual measurement value on the useful signal is weighted by means of a weighting factor (V);

determining a signal variation parameter (σ_t) on the basis of signal variations detected in close chronological relation to the measurement of the actual measurement value; and

adapting dynamically the weighting factor as a function of the signal variation parameter determined for the point in time of the actual measurement.

2. The method according to claim 1, wherein measurement values, which are measured less than 30 minutes before the measurement of the actual measurement value, are used in the determination of the signal variations.

3. The method according to claim 1, wherein measurement values, which are measured less than 15 minutes before the measurement of the actual measurement value, are used in the determination of the signal variations.

4. The method according to claim 1, wherein measurement values, which are measured less than 5 minutes before the measurement of the actual measurement value, are used in the determination of the signal variations.

5. The method according to claim 1, wherein the filter algorithm is a recursive filter algorithm.

6. The method according to claim 5, wherein the filter algorithm is a Kalman filter algorithm.

7. The method according to claim 6, characterized in that the filter algorithm is a linear Kalman filter algorithm.

8. The method according to claim 1, wherein the variables of a system model upon which the filter algorithm is based comprise a check variable.

9. The method according to claim 8, wherein the check variable is a time derivative, preferably the first time derivative of the analyte concentration.

10. A device for continuous monitoring of a concentration of an analyte by determining the analyte's change over time in the living body of a human or animal, the device comprising:

a measurement unit, by which measurement values of a measurement variable correlating with the desired concentration are measured as the measurement signal (z_t) at sequential points in time;

an analysis unit, by which the change over time of the concentration is determined by means of a calibration as a useful signal (y_t) from the measurement signal, and

a filter algorithm in the time domain for determination of the useful signal (y_t) from the measurement signal (z_t) to reduce errors of the useful signal, which result from noise contained in the measurement signal;

wherein the filter algorithm includes operations, in which the influence of an actual measurement value on the useful signal is weighted using a weighting factor (V), such that a signal variation parameter (σ_t) is determined on the basis of signal variations detected in close chronological relationship with the measurement of the actual measurement value, wherein the weighting factor is dynamically adapted as a function of the signal variation parameter determined for the point in time of the actual measurement

* * * * *