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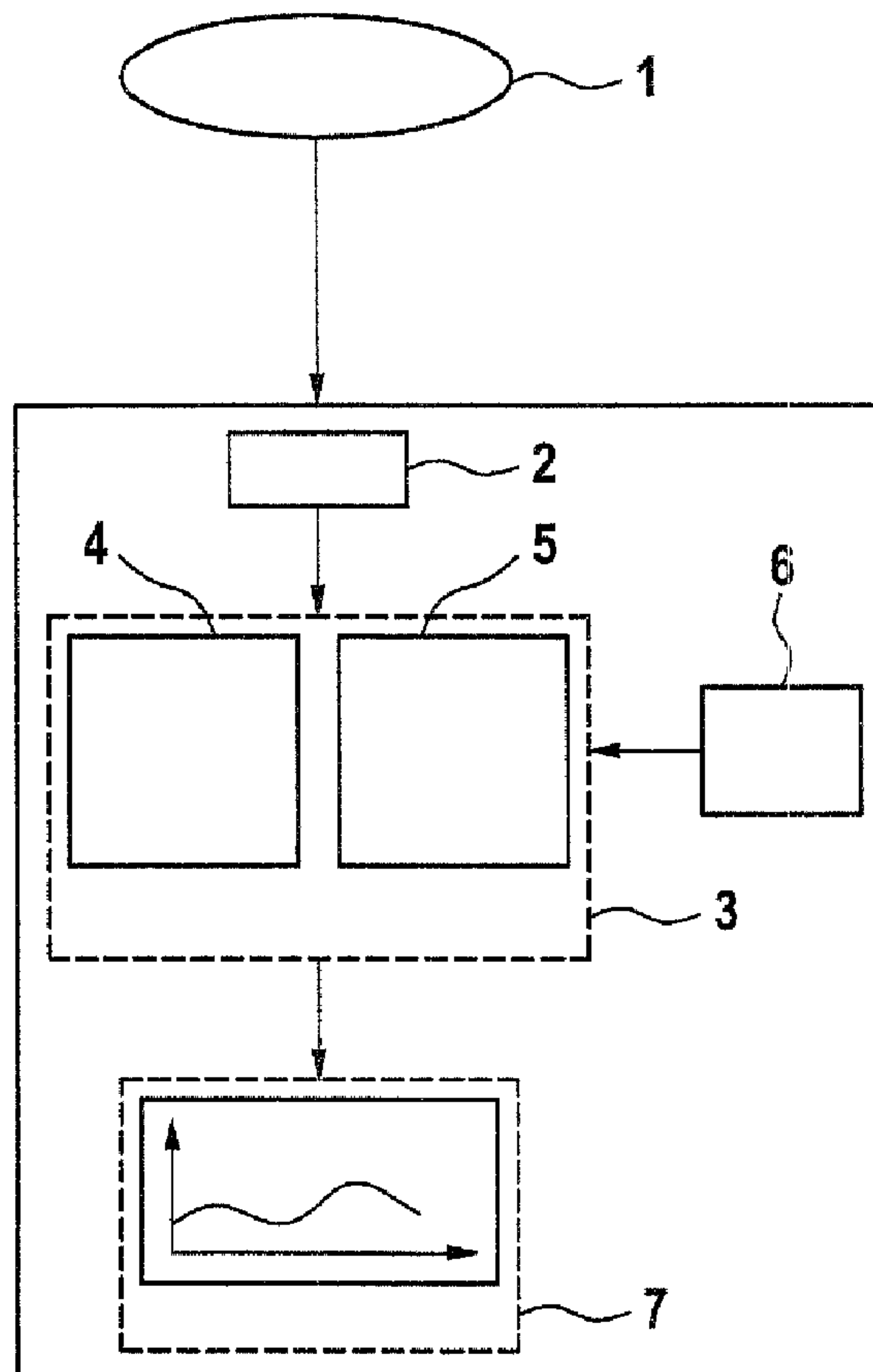
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(72) Inventeurs/Inventors:
KOTULLA, REINHARD, DE;
STAIB, ARNULF, DE;
GILLEN, RALPH, DE

(73) Propriétaire/Owner:
F. HOFFMANN-LA ROCHE AG, CH

(74) Agent: OGILVY RENAULT LLP/S.E.N.C.R.L.,S.R.L.

(54) Titre : METHODE ET DISPOSITIF DE SURVEILLANCE CONTINUE DE LA CONCENTRATION D'UN ANALYTE
(54) Title: METHOD AND DEVICE FOR CONTINUOUS MONITORING OF THE CONCENTRATION OF AN ANALYTE



(57) Abrégé/Abstract:

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, in which at sequential points in time, measurement values of a measurement variable correlating with the desired



(57) Abrégé(suite)/Abstract(continued):

concentration 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, the determination of the useful signal (y_t) from the measurement signal (z_t) including a filter algorithm in the time domain, by which errors of the useful signal, which result from noise contained in the measurement signal, are reduced, and the filter algorithm including an operation in which the influence of an actual measurement value on the useful signal is weighted using a weighting factor (V). During the continuous monitoring, 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. The weighting factor is dynamically adapted as a function of the signal variation parameter determined for the point in time of the actual measurement.

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Abstract

5

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, in which at sequential
10 points in time, measurement values of a measurement variable correlating with the desired concentration 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
15 calibration, the determination of the useful signal (y_t) from the measurement signal (z_t) including a filter algorithm in the time domain, by which errors of the useful signal, which result from noise contained in the measurement signal, are reduced, and the filter algorithm
20 including an operation in which the influence of an actual measurement value on the useful signal is weighted using a weighting factor (V). During the continuous monitoring, a signal variation parameter (σ_t) is determined on the basis of signal variations detected in
25 close chronological relationship with the measurement of the actual measurement value. The weighting factor is dynamically adapted as a function of the signal variation parameter determined for the point in time of the actual measurement.

30

(Fig. 4)

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10 Method and device for continuous monitoring of the
 concentration of an analyte

 The present invention relates to a method and a device
15 for continuous monitoring of the concentration of an
 analyte by determining its change over time in the living
 body of a human or animal. The term "continuous
 monitoring (CM)" is used hereafter for this purpose.

20 A CM method and device is described, for example, in

 (1) US Patent 5,507,288.

 A main task is the continuous monitoring of the
25 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
30 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.

35

The present invention relates in particular to CM of glucose. Further information can be taken from document (1) and the literature cited therein.

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.

An invasive measurement method is described, for example, in

2) US Patent 6,584,335.

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.

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.

Different non-invasive methods are discussed in Document
5 (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
10 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
15 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
20 irradiation point.

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
25 sequential points in time (measurement signal) using a microprocessor system and a suitable algorithm. This analysis algorithm includes the following partial algorithms:

- a) a filter algorithm, by which errors of the useful
30 signal resulting from signal noise contained in the measurement signal are reduced and
- b) a conversion algorithm, in which a functional relationship determined by calibration, which relationship describes the correlation between
35 measurement signal and useful signal, is used.

The Commissioner of Patents

The Examiner maybe inclined to consider the “measurement noise matrix” $R(i)$ as a signal variation parameter. Upon review of figure 3D of *Knobbe et al.* giving a recursion equation for calculating the *Kalman* gain. This equation corresponds to equation (6) of the instant patent application, wherein $R(i)$ of *Knobbe et al.* corresponds to the measurement error covariance matrix V of the application. However, $R(i)$ of *Kalman et al.* is not a quantity the determination of which depends on the actual point of time. It is also not a quantity which depends on the measurement signal, even less is it a quantity for signal variations which are determined from measurement values including values detected during the preceding 30 minutes.

In the description of *Knobbe et al.* the measurement noise matrix is assumed to have a constant value R (see figure 3B of *Knobbe et al.*, last line on the left side). The same is also true with respect to the values of an exemplary embodiment shown in the same drawing giving constant values 15^2 and 5^2 respectively which are assumed for the time periods “before 20 hours” and “after 20 hours”. The same constant values may be found in the program codes shown in table 4 on page 19 of *Knobbe et al.* as well as on page 10 (lines 1 and 4).

Nowhere in *Knobbe et al.* is there any description of an equation or other information allowing calculation of a time-dependent changing value of R , let alone the possibility to adapt this value dynamically depending on changes of the measurement signal over time.

There is also no reason to use a quantity of R which changes over time because, in *Knobbe et al.*, the measurement covariance matrix serves - as usual - to remove standard white noise which can be (and generally is) assumed to be constant.

The latter difference discussed above already indicates that the methodic aspect of *Knobbe et al.* does not relate to the specific application or problem to reduce the influence of NNNC-noise.

(6) US Patent 5,921,937

(7) EP 0 910 023 A2

5 (8) WO 01/38948 A2

(9) US Patent 6,317,662

(10) US Patent 6,575,905 B2

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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:

- 15 - measurement noise: such noise signal components follow a normal distribution having a constant standard deviation around the correct (physiological) measurement signal
 - 25 - 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.
- 30
- 35

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

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.

In one aspect of the invention there is provided a method for continuous monitoring of an analyte concentration by determining a change over time of the analyte in a 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, 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 time dependent signal variation parameter (σ_t) related to an actual point of time on the basis of signal variations detected in close chronological relation to the measurement of the actual measurement value;

said time dependent signal variation parameter being a measure for signal variations for a period of time preceding an actual measurement value and

6a

being determined on the basis of measurement values including values which were measured less than 30 minutes before the measurement of the actual 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, the weighting factor being changed in such a direction that the influence of the actual measurement value is reduced with increasing standard deviation of the measurement signal.

In another aspect of the invention there is provided a device for continuous monitoring of a concentration of an analyte by determining a change over time of the analyte in a 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 a 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;

the filter algorithm including operation, in which influence of an actual measurement value on the useful signal is weighted using a weighting factor (V), such that a time dependent 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,

the time dependent signal variation parameter being a measure for signal variations for a period of time preceding an actual measurement value and being determined on the basis of measurement values including values which were measured less than 30 minutes before the measurement of the actual value; and

6b

the weighting factor being dynamically adapted as a function of the signal variation parameter determined for the point in time of the actual measurement, the weighting factor being changed in such a direction that the influence of the actual measurement value is reduced with increasing σ standard deviation of the measurement signal.

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.

- Fig. 1 shows a block diagram of a device according to the present invention;
- Fig. 2 shows a schematic diagram of a sensor suitable for the present invention;
- Fig. 3 shows a measurement signal of a sensor as shown in Figure 2;

Fig. 4 shows a symbolic flowchart to explain the algorithm used in the scope of the present invention;

5 Fig. 5 shows a graphic illustration of typical signal curves to explain the problem solved by the present invention;

Fig. 6 shows a graphic illustration of experimentally obtained measurement results.

10 The essential components of a device according to the present invention are shown in Figure 1. 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
15 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
20 display and other typical output means. Of course, the data processing is performed digitally in the analysis unit 3 and corresponding converters for converting analog signals into digital signals are provided. More detailed explanations are not necessary in this regard, because
25 the basic construction of devices of this type is known (from Document 1, for example) and 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
30 signal are obtained.

Figure 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
35 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
5 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
10 electronics (not shown) into a raw signal, which - as shown for exemplary purposes in Figure 1 - is transmitted to an analysis unit 3.

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

Variations of the flow of the interstitial liquid from the body into the photometric measurement unit 12 lead to regular, relatively small signal variations, which are
25 referred to as "fluidic modulation". After approximately three minutes, at the point in time identified with the arrow 18, an inhibition of the liquid flow occurred, which may be caused, for example, by movement of the patient or by the entrance of a cell particle into the
30 catheter 10. This inhibition of the flow leads to a large drop of the raw measurement signal A. This is an example of the fact that not all noise signals are distributed normally, with essentially constant standard deviation, around the signal corresponding to the actual
35 physiological measurement value. Rather also interfering

contributions of the type shown here exist, for which these conditions do not apply (NNNC noise). The object of the present invention is to perform the required filtering even in such cases in such a manner that a
5 useful signal results which corresponds as closely as possible to the actual physiological concentration of the analyte. An example for such a useful signal is shown in Figure 3 as thin line B.

10 The basis of a filter algorithm operating in the time domain, which the present invention relates to, is a system model that describes the change over time of the variables of interest and their relationship to one another. The functional relationship which describes the
15 development of the system from time t to time $t+1$ is as follows:

$$(1) \quad \mathbf{y}_{t+1} = f_t(\mathbf{y}_t, \mathbf{y}_{t-1}, \dots, \mathbf{u}_t, \mathbf{u}_{t-1}, \dots).$$

20 Therein, $\mathbf{y}_t$ and $\mathbf{u}_t$ are vectors, which are referred to as state vectors and vectors of input variables, respectively. The state vector $\mathbf{y}_t$ contains the variables of physiological interest and optionally check variables, which allow to check the measurement, as will be
25 described in greater detail below. In the CM method, these include the desired analyte concentration, for example, the glucose concentration g_t in the blood. The speed of change of the analyte concentration $g_t' = dg_t/dt$ is suitable as a check variable. The state variable $\mathbf{y}_t$
30 may also contain model variables related to the measurement method. For example, in the case of a measurement result of the type shown in Figure 3, it is advantageous to incorporate fluidic modulations into the system model. These modulations may be described using
35 their time-dependent frequency ω_t and the amplitude A_t ,

which is also time-dependent. Therefore, four system variables result for the experiment described on the basis of Figures 2 and 3: g_t, A_t, ω_t, g_t' .

5 Input variables which, in the field of automatic control, correspond to control variables and are therefore not measured themselves are entered into the vector u_t . In the case of glucose monitoring, for example, the administered insulin quantity given and the bread
10 exchange units supplied are suitable input variables, because they both influence the glucose concentration in the blood. If these input variables are used, the vector u_t has two elements: insulin dose and bread exchange units. A characteristic feature of input variables is
15 that no prediction of their future values is necessary in the scope of the filter algorithm.

The mentioned variables of the state vector y_t and the input vector u_t are, of course, only to be understood as
20 examples. The present invention relates to greatly varying systems which require different system models. It is not necessary to use the models in a discrete form. The continuous form with the corresponding differential equations may also be used.

25 A characteristic feature of filter algorithms in the time domain, to which the present invention refers, is that they include an alternating sequence of predictions and corrections. A prediction of the system state ("predictor
30 step") is followed by a subsequent correction of this prediction on the basis of a further measurement value ("corrector step").

In a predictor step, the actual value of the state variable y_t at the point in time t is predicted using the system equation (1):

$$5 \quad (2) \quad \hat{y}_t = f_{t-1}(y_{t-1}, y_{t-2}, \dots; u_{t-1}, u_{t-2}, \dots) + W_{t-1}$$

In this equation, $\hat{y}_t$ identifies the value of the state vector at the point in time t which is estimated (predicted) using the data of the previous point in time
10 $(t-1)$; W_t identifies a system error vector.

In the case of a recursive filter algorithm, the calculation of each predictor step is not performed by taking all preceding points in time $(t-1, t-2, t-3, \dots)$
15 into consideration, but rather by using a weighted sum of smoothed signal values. In the example of a linear Kalman algorithm, the corresponding equation may be written as follows:

$$20 \quad (2a) \quad \hat{y}_t = A_{t-1}y_{t-1} + Bu_{t-1} + w_{t-1}$$

In this equation, A_t is the system matrix and B is the input matrix. In the general (non-linear) case, f_t is to be preset or is to be calculated from data determined up
25 to this point.

In the corrector step, the prediction is corrected on the basis of an actual measurement value according to

$$30 \quad (3) \quad y_t = \alpha_t \hat{y}_t + \beta_t \Delta_t$$

In this equation, Δ_t is a variable which represents a measure of the deviation of an actual measurement value z_t from the predicted value and is referred to as the
35 "innovation".

$$(4) \quad \Delta_t = \mathbf{z}_t - \mathbf{h}(\hat{\mathbf{y}}_t)$$

Further it is taken into consideration that typically the
 5 system variables cannot be observed directly. The linkage
 between the measurement values and the state variables is
 provided by means of a measurement model (measurement
 function $\mathbf{h}_t$) according to:

$$10 \quad (5) \quad \mathbf{z}_t = \mathbf{h}_t(\mathbf{y}_t) + \mathbf{v}_t$$

The noise of the measurement values is taken into
 consideration by $\mathbf{v}_t$.

15 In the case of a linear Kalman algorithm (cf. equation
 2a), the measurement equation is

$$(5a) \quad \mathbf{z}_t = \mathbf{H}_t \cdot \mathbf{y}_t + \mathbf{V}_t,$$

20 $\mathbf{H}_t$ referring to the measurement matrix.

For example, in the continuous monitoring of glucose
 using an electrochemical sensor, a current i is measured
 which is correlated with the glucose concentration g_t . In
 25 that example $\mathbf{h}_t$ describes the correlation of the state
 variable g_t with the measurement variable i (current),
 which is an element of the vector $\mathbf{z}_t$.

In the given example of photometric glucose detection
 30 using filter-assisted compensation of the fluidic
 modulation, a non-linear measurement model is used which
 links the photometric measurement signal z_t to the system
 variables of glucose concentration g_t , amplitude A_t , and
 frequency ω_t of the fluidic modulation:

$$35 \quad z_t = g_t + A_t \cdot \sin(\omega_t \cdot t).$$

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.

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:

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

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:

$$(6) \quad K_t = P_t \cdot H_t \cdot (P_t \cdot H_t + V)^{-1}$$

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

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.

Figure 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.

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 Figure 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 $z_{t-n} \dots z_t$). 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).

The present invention does not have the goal of weighting
5 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
10 the method is less complex.

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,
15 the following general rules apply:

- 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
20 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
25 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.
- Independently of the equations used in a particular
30 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.

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

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

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

and the slope φ of a linear smoothing function is calculated as

$$(8) \quad \varphi = \frac{3(\delta z_1 - \delta z_4) + \delta z_2 - \delta z_3}{10}$$

The standard deviation of the four values of the difference $\delta 1, \delta 2, \delta 3, \delta 4$ in relation to the linear smoothing function is

$$(9) \quad \sigma_t = \left[\frac{1}{3} (\delta z_1 - (\varepsilon + 1,5\varphi))^2 + \frac{1}{3} (\delta z_2 - (\varepsilon + 0,5\varphi))^2 + \frac{1}{3} (\delta z_3 - (\varepsilon - 0,5\varphi))^2 + \frac{1}{3} (\delta z_4 - (\varepsilon - 1,5\varphi))^2 \right]^{1/2}$$

On the basis of this standard deviation σ_t , 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

5

$$(10) \quad V_t = (\sigma_o + \sigma_t)^\gamma$$

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

In the example of a controllable recursive filter, the weighting factors α_t, β_t from equation (3) are a function
15 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.

As already explained, equations (7) through (10) only
20 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
25 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
30 requirements.

Three typical graphs of a signal S are plotted against time t in Figure 5, specifically:

- a) as a solid line, a raw signal with strong non-
35 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.

5 b) 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.

10 c) 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.

Evidently, in the case of curve b the strong variations are filtered well within the circle 25, but in the
15 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 variations in the region 25 is
20 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
25 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.

30 Figure 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.

10

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".

15

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 Figure 2, can be used.

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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 Figure 4 compares the value of y_t' to a minimum value and a maximum value. The value y_t is

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only accepted as correct if y_t' lies within these limits. Such a comparison would not be possible using the useful signal A in Figure 6, because the insufficiently filtered non-physiological variations would lead to false alarms.

Claims:

1. A method for continuous monitoring of an analyte concentration by determining a change over time of the analyte in a 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, 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 time dependent signal variation parameter (σ_t) related to an actual point of time on the basis of signal variations detected in close chronological relation to the measurement of the actual measurement value;

said time dependent signal variation parameter being a measure for signal variations for a period of time preceding an actual measurement value and being determined on the basis of measurement values including values which were measured less than 30 minutes before the measurement of the actual 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, the weighting factor being changed in such a direction that the influence of the actual measurement value is reduced with increasing standard deviation of the measurement signal.

2. 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.
3. 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.
4. The method according to any one of claims 1 to 3, wherein the filter algorithm is a recursive filter algorithm.
5. The method according to claim 4, wherein the filter algorithm is a Kalman filter algorithm.
6. The method according to claim 5, characterized in that the filter algorithm is a linear Kalman filter algorithm.
7. The method according to any one of claims 1 to 6, wherein variables of a system model upon which the filter algorithm is based comprise a check variable.
8. The method according to claim 7, wherein the check variable is a time derivative, wherein the time derivative is the first time derivative of the analyte concentration.
9. A device for continuous monitoring of a concentration of an analyte by determining a change over time of the analyte in a 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 a 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;

the filter algorithm including operation, in which influence of an actual measurement value on the useful signal is weighted using a weighting factor (V), such that a time dependent 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,

the time dependent signal variation parameter being a measure for signal variations for a period of time preceding an actual measurement value and being determined on the basis of measurement values including values which were measured less than 30 minutes before the measurement of the actual value; and

the weighting factor being dynamically adapted as a function of the signal variation parameter determined for the point in time of the actual measurement, the weighting factor being changed in such a direction that the influence of the actual measurement value is reduced with increasing standard deviation of the measurement signal.

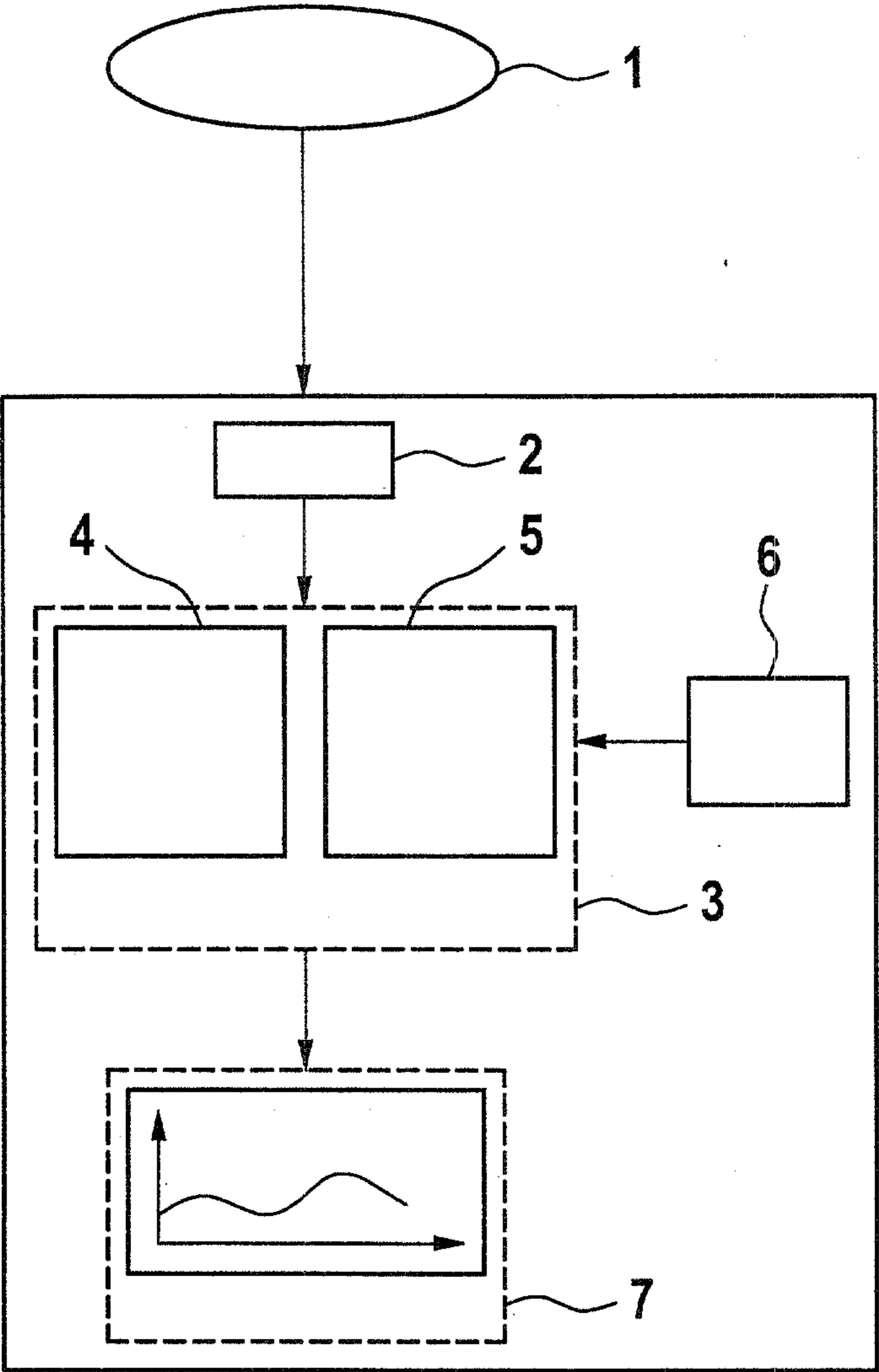


Fig. 1

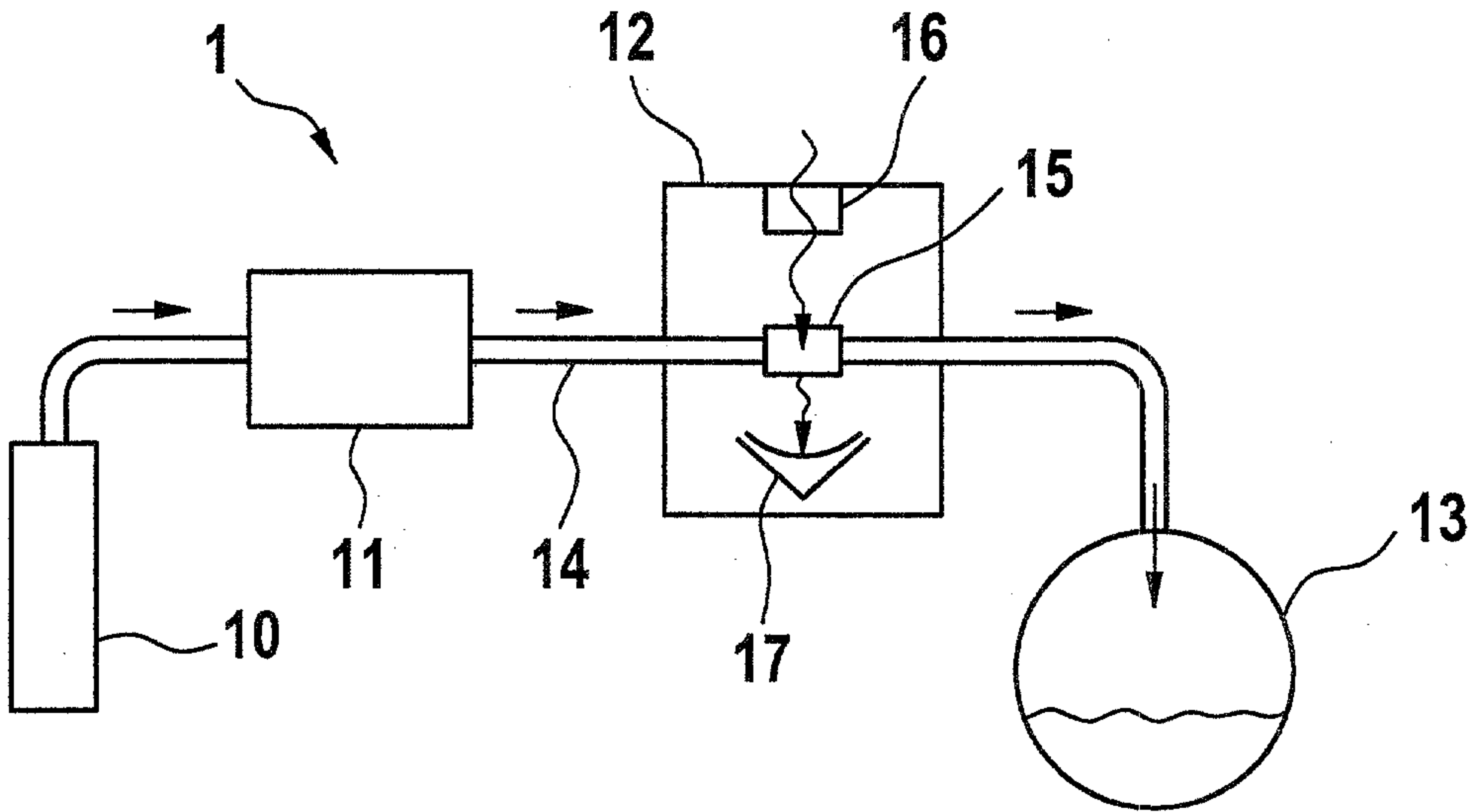


Fig. 2

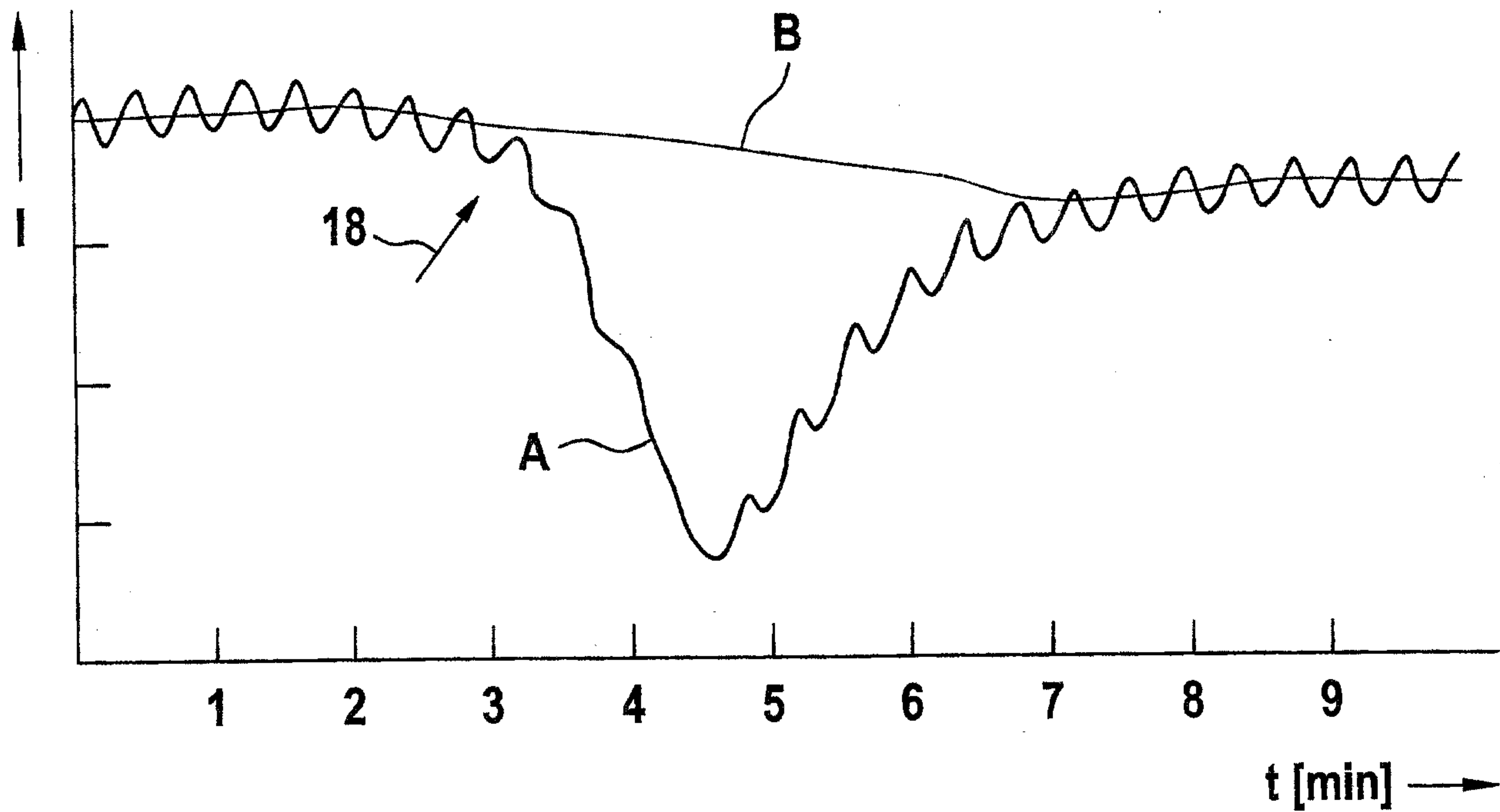


Fig. 3

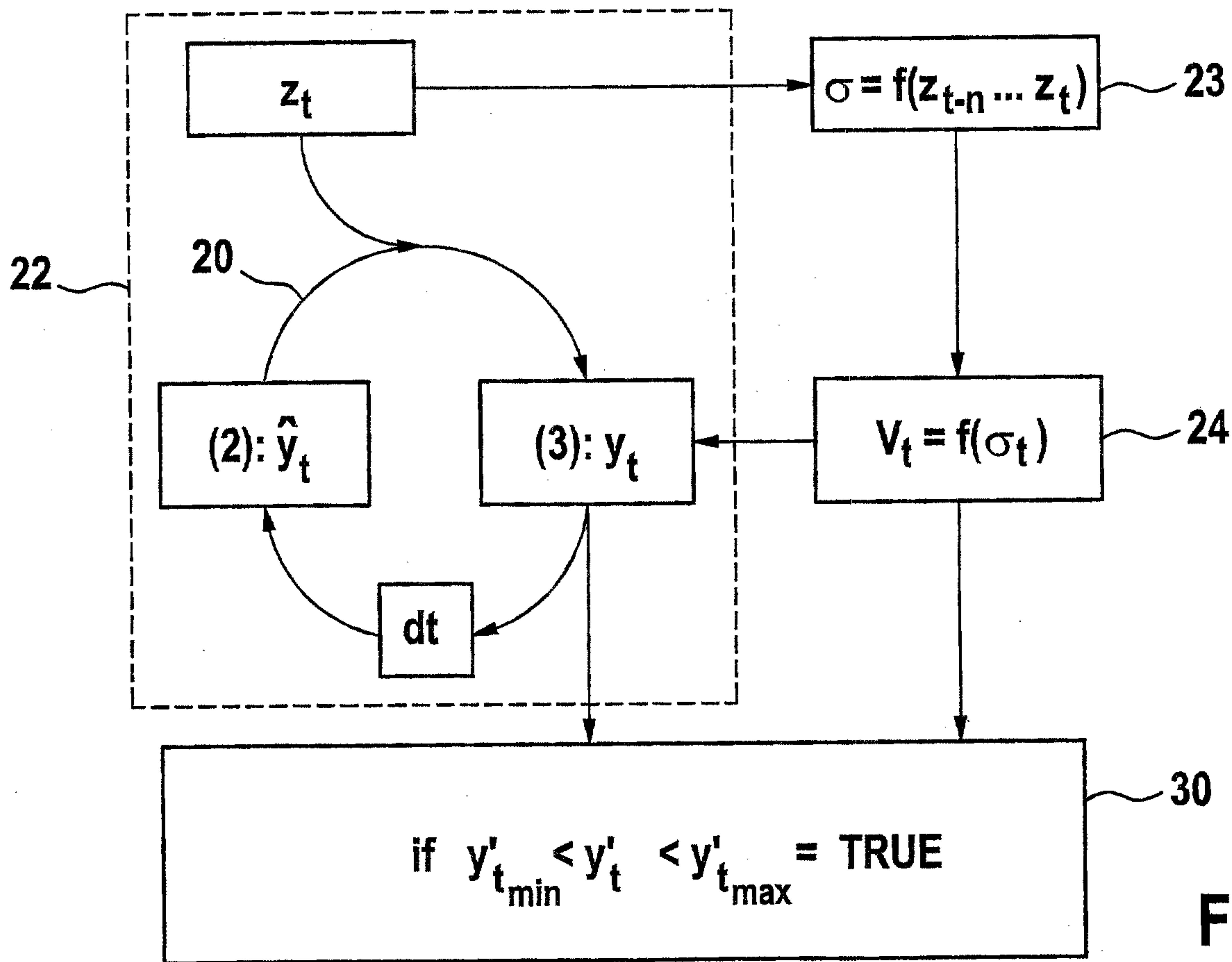


Fig. 4

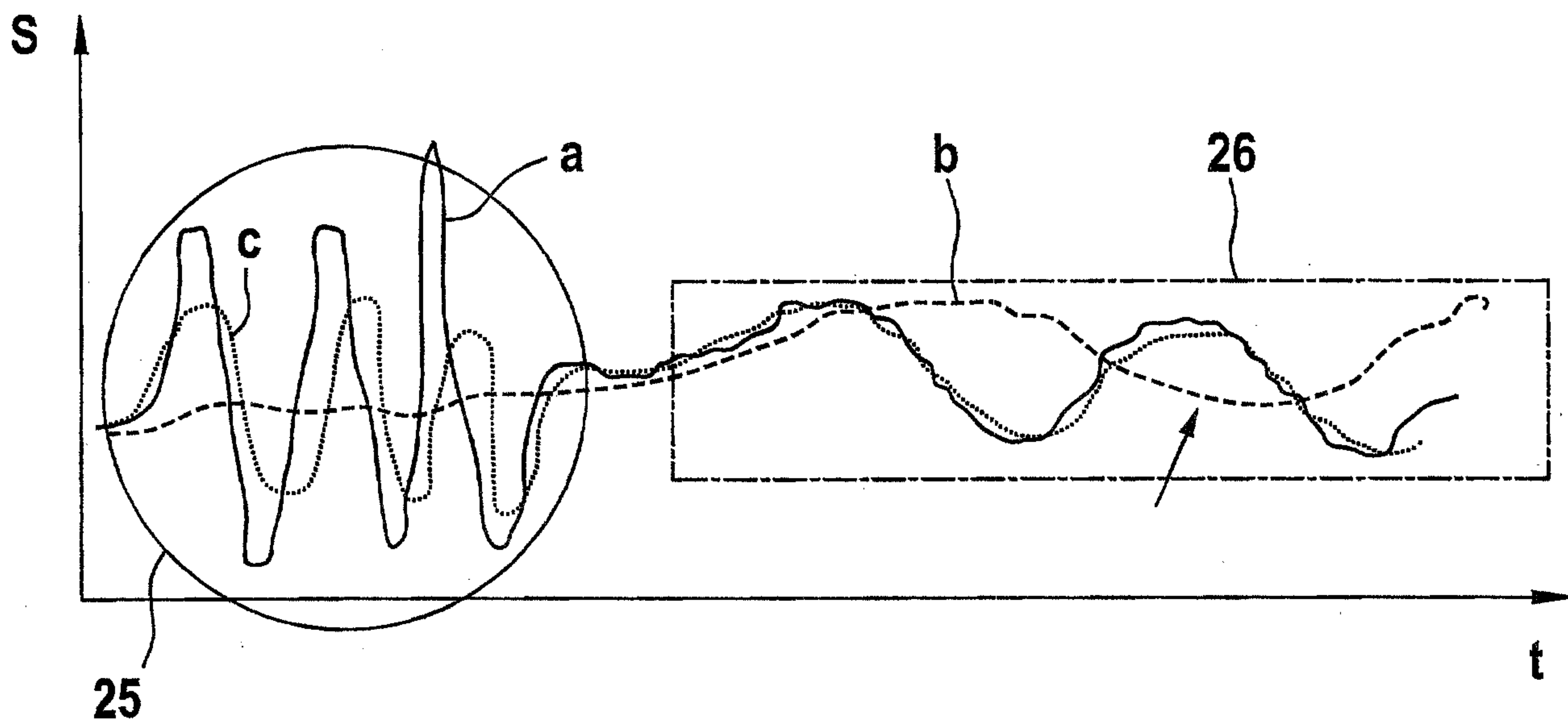


Fig. 5

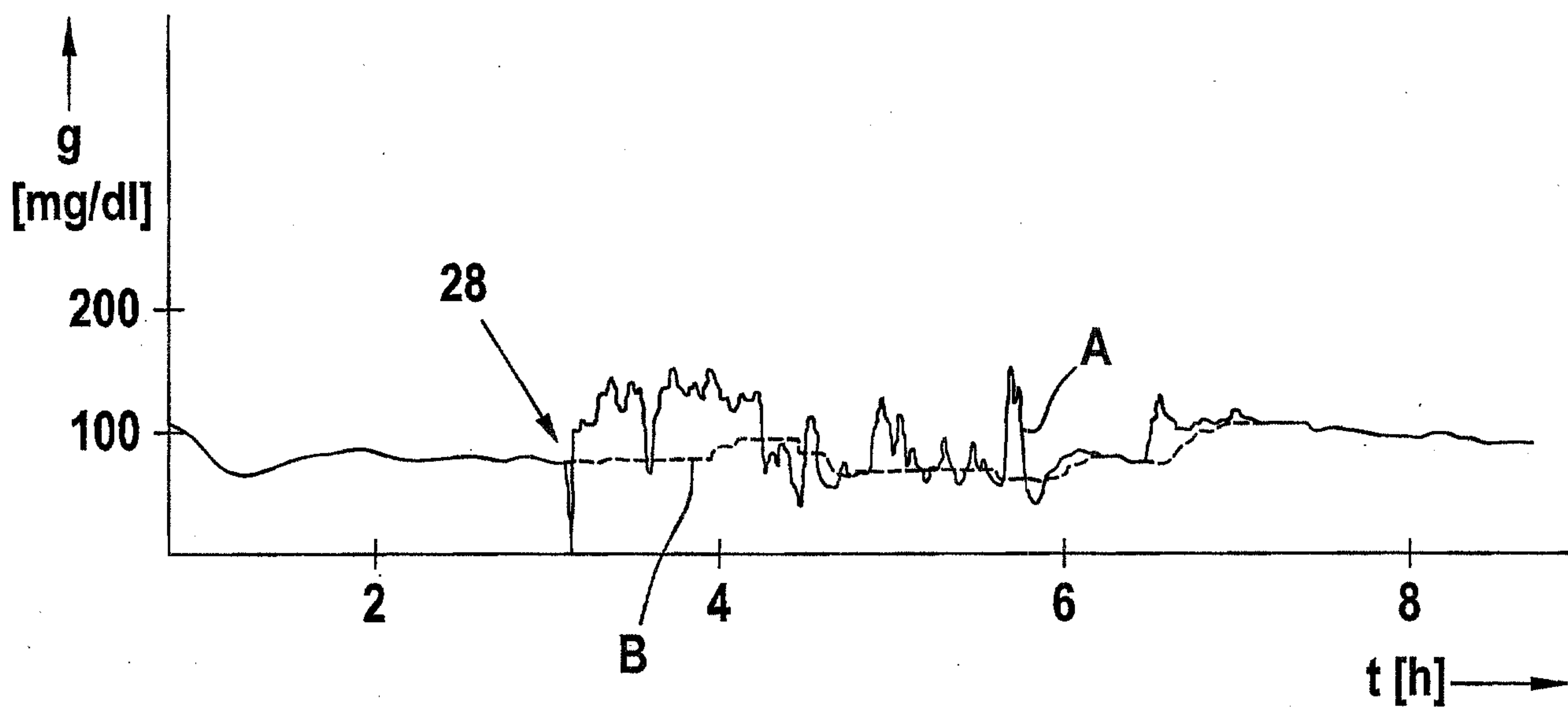


Fig. 6

