



(22) Date de dépôt/Filing Date: 2005/04/21

(41) Mise à la disp. pub./Open to Public Insp.: 2005/10/24

(45) Date de délivrance/Issue Date: 2009/08/18

(30) Priorité/Priority: 2004/04/24 (DE10 2004 020 160.9)

(51) Cl.Int./Int.Cl. *A61B 5/00* (2006.01),
A61B 5/145 (2006.01), *G06F 19/00* (2006.01)

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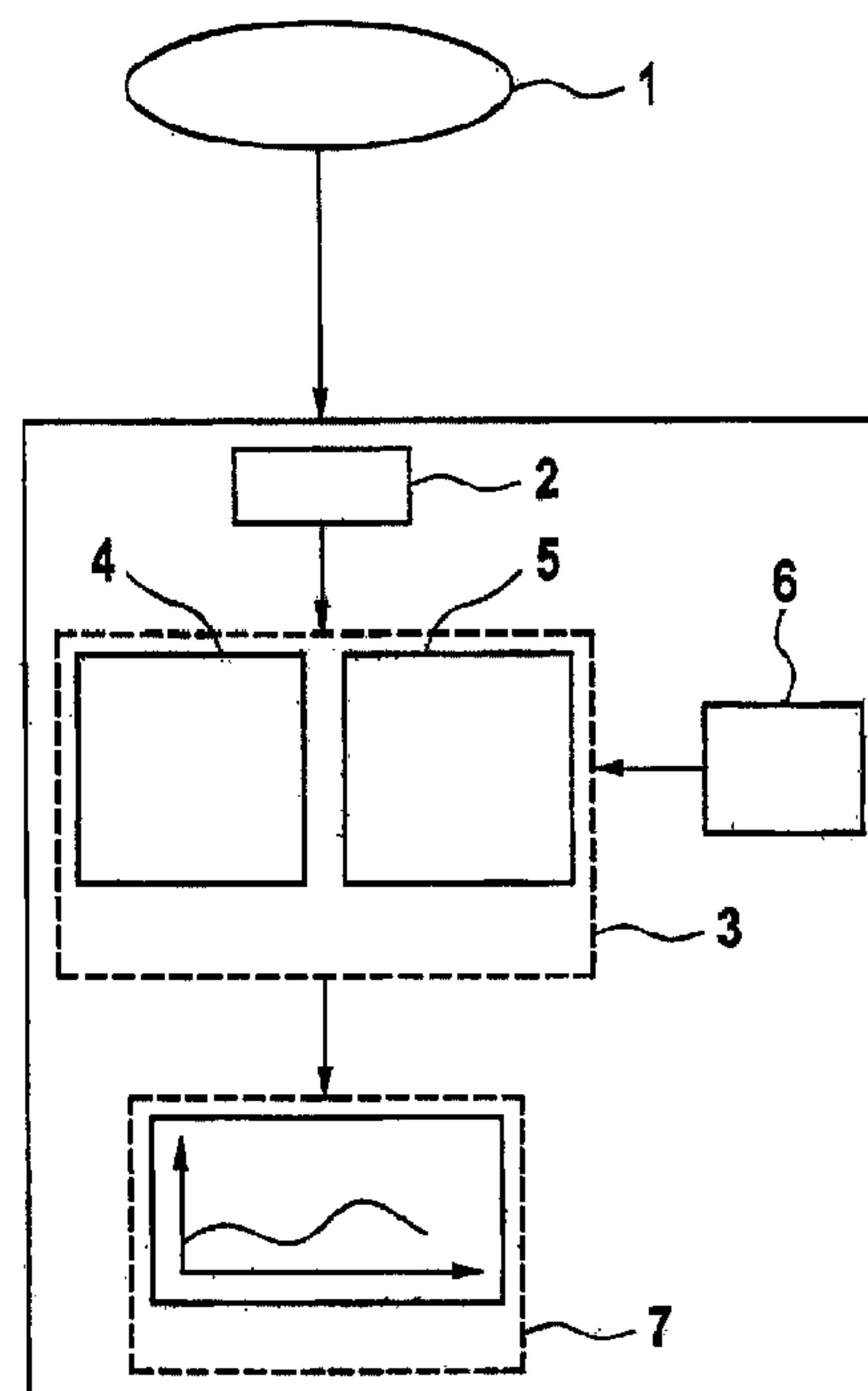
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(54) Titre : METHODE ET DISPOSITIF DE SURVEILLANCE DE LA CONCENTRATION D'UN ANALYTE DANS LE CORPS D'UN HUMAIN OU D'UN ANIMAL VIVANT

(54) Title: METHOD AND DEVICE FOR MONITORING AN ANALYTE CONCENTRATION IN THE LIVING BODY OF A HUMAN OR ANIMAL

$$\sigma^2 \geq \sum_{t_k \in U} [y(t_k) - F(t_k - \Delta t, t_{k-\Delta n} - \Delta t, t_{k-2\Delta n} - \Delta t, \dots, t_{k-(m-2)\Delta n} - \Delta t, t_{k-(m-1)\Delta n} - \Delta t)]^2 \quad (I)$$

$$y(t_{n0} + \Delta t) = F(t_{n0}, t_{n0} - \Delta n, \dots, t_{n0} - (m-2)\Delta n, t_{n0} - (m-1)\Delta n) \quad (II)$$



(57) Abrégé/Abstract:

The invention relates to a method for continuous monitoring of an analyte concentration by determining its progression in the living body of a human or animal, in which analyte values $y(t_n)$ correlating with the concentration to be determined are determined for consecutive points in time t_n . For predicting a prediction value for an analyte value $y(t_{n0} + \Delta t)$ over a prediction period Δt a function $F(t_k, t_{k-\Delta n}, t_{k-2\Delta n}, \dots, t_{k-(m-2)\Delta n}, t_{k-(m-1)\Delta n})$, which depends on analyte values $y(t_k)$, $y(t_{k-\Delta n})$, $y(t_{k-2\Delta n})$, \dots , $y(t_{k-(m-2)\Delta n})$, $y(t_{k-(m-1)\Delta n})$ is determined, which can be used to approximate the progression of the analyte values $y(t_n)$ at time t_{n0} in the vicinity U of an analyte value $y(t_{n0})$ with a pre-determined accuracy σ , such that (see formula I) whereby Δn is an integer, and-subsequently the function F is used to calculate the prediction value (see formula II)



RDG 112/00/DE

Abstract

5

The invention relates to a method for continuous monitoring of an analyte concentration by determining its progression in the living body of a human or animal, in which analyte values $y(t_n)$ correlating with the concentration to be determined are determined for consecutive points in time t_n . For predicting a prediction value for an analyte value $y(t_{n0} + \Delta t)$ over a prediction period Δt a function $F(t_k, t_{k-\Delta n}, t_{k-2\Delta n}, \dots, t_{k-(m-2)\Delta n}, t_{k-(m-1)\Delta n})$, which depends on analyte values $y(t_k), y(t_{k-\Delta n}), y(t_{k-2\Delta n}), \dots, y(t_{k-(m-2)\Delta n}), y(t_{k-(m-1)\Delta n})$ is determined, which can be used to approximate the progression of the analyte values $y(t_n)$ at time t_{n0} in the vicinity U of an analyte value $y(t_{n0})$ with a pre-determined accuracy σ , such that

20

$$\sigma^2 \geq \sum_{t_k \in U} [y(t_k) - F(t_{k-\Delta t}, t_{k-\Delta n} - \Delta t, t_{k-2\Delta n} - \Delta t, \dots, t_{k-(m-2)\Delta n} - \Delta t, t_{k-(m-1)\Delta n} - \Delta t)]^2$$

25 whereby Δn is an integer, and subsequently the function F is used to calculate the prediction value

$$y(t_{n0} + \Delta t) = F(t_{n0}, t_{n0} - \Delta n, \dots, t_{n0 - (m-2)\Delta n}, t_{n0 - (m-1)\Delta n})$$

RDG 112/00/DE

5 Applicant: Roche Diagnostics GmbH, Mannheim, Germany

Method and Device for Monitoring an Analyte Concentration
10 in the Living Body of a Human or Animal

The invention concerns a method and a device for
monitoring an analyte concentration in the living body of
15 a human or animal, in which analyte values $y(t_n)$
correlating with the concentration to be determined are
determined for consecutive points in time t_n .

A method of this type and a suitable device are described
20 in US 5,507,288, for example. This concerns in particular
the continuous monitoring of the glucose concentration in
the body of a patient, which is of crucial medical
significance. Study results have demonstrated that
extremely serious long-term corollaries of diabetes
25 mellitus (for example blinding of the patient due to
retinopathy) can be prevented by continuous in vivo
monitoring of the time profile of the glucose
concentration. This allows the dosage of the medication
required (insulin) to be adjusted exactly at any point in
30 time and thus the blood sugar levels to be kept within
narrow limits at all times like in a healthy person.

In order for the medication process to be as efficient as
possible it is desired to be able to determine not only a
35 current value of the concentration of an analyte, but

also predict future concentration values. The prediction of future values of the concentration of an analyte is of particular significance in the case of diabetes, not only in order to be able to counteract an increase of the blood glucose concentration beyond a critical value by administering insulin, but also to alert the patient to an imminent decrease of the blood glucose concentration below a critical value and the associated danger of fainting such that this can be prevented by timely uptake of carbohydrates.

The prediction of a future concentration of an analyte value in the living body of a human or animal is made significantly more complicated by the fact that concentration values depend not only on historic values, but also on other parameters, such as food and medication intake or physical exercise.

A method for monitoring the blood glucose concentration is known from US 6,272,480 B1, in which an artificial neuronal network is used to derive a prediction of future blood glucose values from a time series of glucose concentrations that were measured. However, a significant disadvantage of artificial neuronal networks is that they need to be trained prior to their use and yield unreliable results when confronted with time series data outside of their training range.

From EP 1102194 A2, a method is known in which blood glucose concentration values measured at consecutive points in time are extrapolated taking into consideration patient-specific data, such as, in particular, any carbohydrate intake and insulin administration. For practical applications, the need to account for such patient-specific data is a major disadvantage, since

accounting for such data is difficult and often error-prone.

The invention seeks to provide means for continuous
 5 monitoring of the concentration of an analyte in the living
 body of a human or animal and predicting future
 concentration values. In particular, this method shall,
 aside from data of historic concentration values, not
 require any patient-specific data, such as food or insulin
 10 intake, for the prediction of future concentration values.

In one aspect, the invention provides a method for
 continuous monitoring of an analyte concentration by
 determining its progression in the living body of a human
 15 or animal, in which analyte values $y(t_n)$ correlating with
 the concentration to be determined are determined for
 consecutive points in time t_n , wherein for predicting an
 analyte value $y(t_{n0} + \Delta t)$ over a prediction period Δt , a
 function $F(t_k, t_{k-\Delta n}, t_{k-2\Delta n}, \dots, t_{k-(m-2)\Delta n}, t_{k-(m-1)\Delta n})$ is
 20 determined, which depends on analyte values $y(t_k)$, $y(t_{k-\Delta n})$,
 $y(t_{k-2\Delta n})$, \dots , $y(t_{k-(m-2)\Delta n})$, $y(t_{k-(m-1)\Delta n})$ and which can be used to
 approximate the progression of the analyte values $y(t_n)$ at
 time t_{n0} in a vicinity U of an analyte value $y(t_{n0})$ with a
 predetermined accuracy σ , such that

25

$$\sigma^2 \geq \sum_{t_k \in U} [y(t_k) - F(t_k - \Delta t, t_{k-\Delta n} - \Delta t, t_{k-2\Delta n} - \Delta t, \dots, t_{k-(m-2)\Delta n} - \Delta t, t_{k-(m-1)\Delta n} - \Delta t)]^2$$

30

(eq. 1),

whereby Δn , n_0 and m are integers,

and calculation of the prediction value using the following equation:

$$y(t_{n0} + \Delta t) = F(t_{n0}, t_{n0} - \Delta n, \dots \\ \dots, t(n_0 - (m-2)\Delta n), t(n_0 - (m-1)\Delta n))$$

5 (eq. 2).

In another aspect, the invention provides a device for continuous monitoring of a concentration of an analyte by determining its progression in the living body of a human
10 or animal, comprising a measuring unit, by means of which measured values of a measuring parameter that is correlated with the concentration to be determined are measured as measuring signals at consecutive points in time t_n , and an analytical unit, by means of which analyte values $y(t_n)$ that
15 are correlated with the concentration are determined from the measured values, the analytical unit being adapted for predicting an analyte value $y(t_{n0} + \Delta t)$ over a prediction period Δt by determining a function $F(t_k, t_{k-\Delta n}, t_{k-2\Delta n}, \dots, t_{k-(m-2)\Delta n}, t_{k-(m-1)\Delta n})$, which depends on analyte values $y(t_k), y(t_{k-\Delta n}), y(t_{k-2\Delta n}), \dots, y(t_{k-(m-2)\Delta n}), y(t_{k-(m-1)\Delta n})$, and can be used
20 to approximate the progression of the analyte values $y(t_n)$ at time t_{n0} in a vicinity U of an analyte value $y(t_{n0})$ with a predetermined accuracy σ , such that

$$25 \quad \sigma^2 \geq \sum_{t_k \in U} [y(t_k) - F(t_k - \Delta t, t_{k-\Delta n} - \Delta t, t_{k-2\Delta n} - \Delta t, \dots, t_{k-(m-2)\Delta n} - \Delta t, t_{k-(m-1)\Delta n} - \Delta t)]^2$$

whereby Δn , n_0 and m are integers, and subsequently the function F is used by the analytical unit to calculate a prediction value

$$y(t_{n_0} + \Delta t) = F(t_{n_0}, t_{n_0 - \Delta n}, \dots, t_{(n_0 - (m - 2)\Delta n)}, t_{(n_0 - (m - 1)\Delta n)}).$$

According to the method of the invention, the living body of a human or animal and the concentration of an analyte that is present therein are mathematically treated as a deterministic dynamic system with some possible interference by noise. The development of this system over time is then described as a phase trajectory in a phase space whose dimensionality depends on the number of independent variables influencing the concentration of the analyte to be determined. In the case of diabetes, for example, the number of ingested bread units and the quantity of insulin administered are variables of this type, on which future values of the blood glucose concentration depend.

For practical purposes, the number of variables, on which the analyte concentration to be determined depends, is usually unknown and consequently the dimensionality of the phase space, in which the development of the system over time can be described by means of the phase trajectory, is also unknown.

The invention utilizes the fact that there is no need to know the entire phase trajectory of the system in a possibly high-dimensional phase space in order to be able to predict an analyte value. For extrapolating a point on

the phase trajectory it is only necessary to know the phase trajectory in a vicinity of that point. In particular, there is no need to consider the entire phase space of the system for extrapolation, but rather it is
5 sufficient to study the dynamics in an artificial, reconstructed phase space of significantly lower dimensionality.

It is sufficient if the dimensionality is high enough to
10 account for all dominant degrees of freedom driving the dynamics of the system. Degrees of freedom with a negligible effect on the dynamics of the system can be left unaccounted for such that the dimensionality of the reconstructed phase space can be selected accordingly
15 lower.

Negligible degrees of freedom are found especially for dynamic systems, in which a sub-system is weakly coupled to the remaining system. Considering diabetes as an
20 example, a sub-system, that depends on the administered quantity of insulin, ingested bread units and physical exercise, is weakly coupled to hormonal regulation mechanisms, which also exert an influence on the blood sugar levels.

25 A time series of analyte values $y(t_n)$ determined for consecutive points in time t_n contains in principle all of the information regarding the dynamic behavior of the system. Therefore, from a finite number of analyte values
30 $y(t_n)$ determined for consecutive points in time t_n - often as few as approx. 10 analyte values in the vicinity of the point to be extrapolated are sufficient - a local approximation of the phase trajectory in the vicinity of an analyte value $y(t_{n0})$ at point in time t_{n0} can be
35 determined and extrapolated into the future by a

prediction period Δt such that a prediction value of an analyte value $y(t_{n0} + \Delta t)$ can be calculated.

It is important that the analyte values used to determine the function F and thus a local approximation of the phase trajectory were not determined for points in time t_n that are too close to each other. Otherwise there is a risk that an observed progression is based mainly on measuring errors and noise effects and does not reflect the dynamics over time of a concentration change of the analyte.

In order to be able to reduce the influence of inevitable measuring errors to the extent possible by statistical methods it is desired to determine analyte values $y(t_n)$ for consecutive points in time t_n that are as close to each other as possible. Therefore, it may be necessary not to use all analyte values $y(t_n)$ determined for directly consecutive points in time t_n for determining a local approximation of the phase trajectory, but rather only every second, third or n -th such analyte value that has been determined.

For this reason, equation 1 includes a parameter Δn to ensure that the analyte values $y(t_n)$ that are used to determine the function F were measured for consecutive points in time t_n that are separated by sufficiently large time intervals.

Whether or not a function F as determined can be used to approximate the time profile of the analyte values $y(t_n)$ with a pre-determined accuracy, can be tested by means of equation 1. In principle, it is necessary to sum up over all points in time t_k from the vicinity U of the analyte value $y(t_{n0})$ at time t_{n0} . However, this does not exclude

that individual analyte values $y(t_n)$ recognized as erroneous, for example by means of applying suitable filters, are ignored. The function F can be a non-linear function and depend not only on the analyte values, but
 5 in addition on their first and second time derivative. However, it is preferable for the function F to be a linear function. It has proven to be particularly favorable to represent the function F using coefficients a_0 to a_m as follows:

10

$$F = a_0 + \sum_{j=1}^m y(t_{(k-(m-j)\Delta n)}) a_j$$

In practice, the coefficients, a_0 to a_m , can be determined by minimizing the following sum:

$$15 \quad \sum_{t_k \in U} \left[y(t_k) - a_0 - \sum_{i=1}^m y(t_{(k-(m-i)\Delta n)} - \Delta t) a_i \right]^2$$

In doing so, the vicinity U must be selected such that it contains a sufficient number of points in time t_n for the determination of the coefficients, a_0 to a_m .

20

The method according to the invention can be applied in several steps in order to determine from a prediction value $y(t_{n_0} + \Delta t)$ another prediction value $y(t_0 + 2\Delta t)$ even further in the future. A prediction value $y(t_0 + n\Delta t)$ can
 25 thus be determined by multiple application of the method. In the process, it is important that the coefficients, a_0 to a_m , used to approximate the progression of the analyte values in the vicinity U are re-determined in each step for a vicinity U that is shifted by the prediction period
 30 Δt .

Instead of predicting an analyte value $y(t_n)$ for a point in time t_n in the future by means of multiple application of the method in multiple steps, it is also feasible to
5 use a suitably larger prediction period Δt and coefficients, a_0 to a_m , determined accordingly to predict in a single step an analyte value $y(t_n + \Delta t)$ in the distant future. However, it has been found that stepwise application of the method provides for a more accurate
10 prediction over extended periods of time.

The finding that the dynamic behavior of a deterministic system can be described by a finite number of analyte values $y(t_n)$ that are determined for consecutive points
15 in time t_n is based on the "Takens time delay embedding" method described in the publication by T. Schreiber in Phys. Rep. 85, 1-64 (1999). According to the terminology used in the publication of T. Schreiber, the interval between consecutive points in time, for which analyte
20 values $y(t_n)$ are determined, is called delay time. Reference is made to the publication of T. Schreiber in a supplementing fashion.

The invention and preferred embodiments are illustrated
25 in more detail in the following with reference to the figures. The features illustrated and described in the following can be used individually or in combination in order to create preferred further refinements of the invention. In the figures:

30

Fig. 1 shows a block diagram of a device according to the invention;

Fig. 2 shows a schematic sketch of a sensor suited for the invention;

5 Fig. 3 shows a measuring signal of a sensor according to Fig. 2;

Fig. 4 shows measured blood glucose concentration values and blood glucose concentration values predicted for a period of 30 minutes; and

10

Fig. 5 shows a schematic example of a phase space with data points.

The essential components of a device according to the invention are shown in Fig. 1. A sensor 1 measures values at consecutive points in time t_n . The resulting measurement signal is then transmitted - wireless in the case shown - to a receiver 2 which in turn transmits the measurement signal to an analytical unit 3 containing a microprocessor 4 and a data storage unit 5.

20 Alternatively, both data and commands can be transmitted to the analytical unit 3 by an input unit 6. The results are output by an output unit 7 which may include a display and other common output means. It is self-evident that data processing in the analytical unit 3 is performed in a digital fashion, and corresponding transformers for transforming analogous signals into digital signals are provided. More detailed explanations are not required in this context, since the basic design of devices of this type is known (from US 5,507,288, for example) and the invention is suitable for a broad range of measuring techniques, in which - as described above - different measuring signals that are correlated with the desired working signal are measured.

Fig. 2 shows in the form of a schematic sketch a sensor 1, in which an implantable catheter 10 is used to aspirate interstitial fluid from the subcutaneous fatty tissue by means of a pump 11 and to aspirate the fluid through a photometric measuring unit 12 into a disposal container 13. Inside the photometric measuring unit 12, the tubing 14, through which the fluid is being transported, contains a transparent measuring cell 15, into which primary light emitted by a light sensor 16 is guided. The secondary light resulting from passage of the measuring cell 15 is then measured by means of a photo-detector 17 and the resulting signal processed by means of measuring electronics (not shown) to generate a raw signal, which - as is shown in Fig. 1 in an exemplary fashion - is transmitted to an analytical unit 3. The analytical unit 3 is used to determine from the raw signal analyte values $y(t_n)$ that are correlated with the concentration to be determined for consecutive points in time t_n . In the scope of the exemplary embodiment, these analyte values $y(t_n)$ represent the blood glucose level of a subject at a time t_n .

It is self-evident that the analyte values $y(t_n)$ can also be determined by other methods, for example methods based on an enzymatic conversion of glucose and subsequent electrochemical detection of the hydrogen peroxide formed in the process.

Fig. 3 shows a curve representing the progression of the blood glucose level of a subject. The two crosses drawn in Fig. 3 denote, in an exemplary fashion, one prediction value each that was determined for a prediction period of 30 minutes by the method to be described in the following. As shown by the good agreement of the left cross and the curve represented as a continuous line, the

accuracy of the predicted values is good. It is self-evident that this applies only if the blood glucose level is not affected by an administration of insulin or uptake of carbohydrates during the prediction interval. The
5 right cross in Fig. 3 shows a prediction value that is below a critical threshold value. In the case of a prediction value being this low, a warning signal is generated in order to alert a patient to a dangerous decrease in the blood glucose level such that the
10 decrease can be counteracted by ingestion of carbohydrates.

The analyte values $y(t_n)$ shown in Fig. 3 in the form of a curve were determined from measured values that were
15 recorded at intervals of 1 second each. To use a measuring rate this high is advantageous in that sufficient data is available for statistical processing of the measured values, but it is not obligatory. For many applications, it is sufficient to determine measured
20 values at intervals of a few minutes, e.g. every 2 to 5 minutes.

In the embodiment shown, the measured values were processed by means of a filter algorithm that includes an
25 operation, in which the influence of a current measured value on the working signal is weighted by means of a weighting factor ("controllable filter algorithm"), whereby a signal variation parameter (related in each case to the current point in time, i.e. changing over
30 time) is determined on the basis of signal variations detected in a close temporal relationship to the measurement of the current measured value, and the weighting factor is adapted dynamically as a function of the signal variation parameter determined for the current
35 measured value for the point in time. Filter algorithms

of this type are known as Kalmann filter algorithms and have been described, for example, in DE 10343863.7.

For the purposes of the method described in the following, extensive statistical processing of the measured values is not obligatory. Alternatively, it is also feasible, for example, to average over several measured values to obtain an analyte value $y(t_n)$ or to obtain exactly one analyte value $y(t_n)$ from each measured value.

The analyte values $y(t_n)$ determined are then used to determine first the function, $F(t_k, t_{k-\Delta n}, t_{k-2\Delta n}, \dots, t_{k-(m-2)\Delta n}, t_{k-(m-1)\Delta n})$, which depends on analyte values $y(t_k), y(t_{k-\Delta n}), y(t_{k-2\Delta n}), \dots, y(t_{k-(m-2)\Delta n}), y(t_{k-(m-1)\Delta n})$ and approximates the progression of the analyte values in a vicinity U of a point in time t_{n0} at a pre-determined accuracy σ^2 . Although the progression of the analyte values $y(t_n)$ is usually not linear, it has been found that a linear function of the type

$$F = a_0 + \sum_{j=1}^m y\left(t_{(k-(m-j)\Delta n)}\right) a_j$$

with coefficients a_0 to a_m suffices. The value of the parameter, m , of function $F(t_k, t_{k-\Delta n}, t_{k-2\Delta n}, \dots, t_{k-(m-2)\Delta n}, t_{k-(m-1)\Delta n})$ (e.g. in a_m and $t_{k-(m-1)\Delta n}$) describes the dimensionality of the phase space, in which the dynamical behavior of the system is approximated.

The coefficients, a_0 to a_m , can be determined by minimizing the equation

$$\sigma^2 \geq \sum_{t_k \in U} \left[y(t_k) - a_0 - \sum_{i=1}^m y(t_{(k-(m-i)\Delta n) - \Delta t}) a_i \right]^2$$

for various analyte values $y(t_k)$ from the vicinity U . If measured values are detected at a high measuring rate and
 5 analyte values $y(t_n)$ are determined for accordingly tightly spaced points in time t_n , it is advantageous not to include each and every analyte value that was determined in the equation above for the determination of the coefficients a_0 bis a_m , but instead, for example,
 10 only every second or third analyte value such that Δn is not necessarily equal to 1, but rather can be a different integer. Although, in principle, the sum for all points in time t_k in the vicinity U of the time t_{n0} should be obtained in the equation stated above, this does not
 15 exclude that analyte values $y(t_k)$ recognized to be outliers, for example by means of suitable filters, are not included in the analysis.

Ideally, the times t_n , for which the analyte values $y(t_n)$
 20 are determined, should be at equidistant time intervals from each other. However, analyte values in a living body of a human or animal possess such high auto-correlation when viewed over extended periods of time, that minor deviations from a constant measuring rate affect the
 25 accuracy of the prediction values only to a small degree. For example, the concentrations of lactate - under aerobic conditions - or creatinine display high auto-correlation over a period of several hours. Even
 30 relatively rapidly varying analytes, such as glucose, show an auto-correlation coefficient in excess of 0.8 over a period of 30 minutes.

The value of the parameter m in the function $F(t_k, t_{k-\Delta n}, t_{k-2\Delta n}, \dots, t_{k-(m-2)\Delta n}, t_{k-(m-1)\Delta n})$, i.e. the dimensionality of

the relevant phase space, cannot be stated generally for all possible cases, in which the concentration of an analyte in the living body of a human or animal must be monitored. This is due mainly to the fact that the
5 concentration of the various analytes of medical interest depend on different numbers of independent variables. In the case of the blood glucose concentration of a diabetes patient, two such variables are known, i.e. the quantity of bread units ingested and the quantity of insulin
10 administered. In general, it can be said that the parameter does not need to be larger than twice the number of independent variables plus 1. Therefore, $m = 5$ in the present exemplary embodiment illustrated by means of Fig. 3.

15

As has been mentioned above, the value of the parameter m corresponds to the dimensionality of a phase space reconstructed according to the "Takens time delay embedding" method, in which the dynamic behavior of the
20 system can be described. For practical purposes, m usually has at most a value between 3 and 10, preferably between 5 and 8, and can be determined empirically. One option for determining the dimensionality of the phase space and thus the value of this parameter is provided by
25 the method of so-called "false nearest neighbour" analysis as described in a publication by M.B. Kennel et al., Phys. Rev. A 45 3403 (1995). Reference is made to this publication in a supplementing fashion.

30 Once the coefficients, a_0 to a_m , have been determined they can be used to calculate a prediction value

$$y(t_{n0} + \Delta t) = a_0 + \sum_{j=1}^m y(t_{(n0-(m-j)\Delta n)}) a_j$$

Subsequently, a prediction value determined accordingly is compared to a predetermined lower and/or upper
 5 threshold value and a warning signal is generated if that value is below or above the threshold value, respectively.

When a patient responds to a warning signal of this type
 10 by ingesting carbohydrates or administering a dose of insulin, it takes a while before the blood glucose concentration is affected by such ingestion of carbohydrates or administration of insulin. For this reason, it is usually necessary to predict analyte value
 15 10 to 90 minutes, preferably 20 to 40 min, into the future such that there is sufficient time to counteract a dangerous increase or decrease of the analyte concentration. It has been found that analyte values are better predicted over extended periods of time if, rather
 20 than selecting an accordingly large prediction period (e.g. $\Delta t = 30$ min) in a single step, the procedure is applied in multiple smaller steps of 5 minutes, for example. In each additional step coefficients a_0 to a_m are determined for an already calculated prediction value
 25 $y(t_{n0} + \Delta t)$, which coefficients are used to approximate the progression of analyte values $y(t_n)$ in a vicinity U of the analyte value at point in time $t_{n0} + \Delta t$. The results are used to calculate another prediction value
 $y(t_{n0} + 2\Delta t)$. In a stepwise procedure of this type, the
 30 prediction period Δt of the individual steps should be selected to be equal to the interval between times t_n , for which the analyte values $y(t_n)$ used for calculating

the prediction values were determined. If the time interval between consecutive points in time t_n equals dt , this means that the prediction period is given by $\Delta t = dt \cdot \Delta n$.

5

The method described above cannot only be used to predict future analyte values, but also to test analyte values $y(t_n)$ that were determined for the past and identify false analyte values $y(t_n)$ which are due to outliers or measuring errors. The generally very good agreement between the measured analyte values $y(t_n)$ and the prediction values is shown in Figure 4 in an exemplary fashion. The smooth continuous curve represents the time profile of the prediction values, whereas the curve showing strong short-term variations represents the time profile of the measured values. The prediction period was 2 min, and a total of 15 steps were performed consecutively such that analyte values were predicted for a period of 30 minutes. Therefore, the y axis does not represent the blood glucose concentration in Figure 4, but rather the intensity of the measuring signal on which the blood glucose determination is based as detected electrochemically (in units of nanoampere).

25 The analyte values $y(t_k), y(t_{k-\Delta n}), y(t_{k-2\Delta n}), \dots, y(t_{k-(m-2)\Delta n}), y(t_{k-(m-1)\Delta n})$, on which the function F depends, are considered in the "Takens time delay embedding" method to represent the coordinates of a reconstructed phase space, in which the dynamic behavior of the system is approximated and extrapolated. These coordinates are also called delay coordinates. For the calculation, it can be advantageous to transform the coordinates $y(t_k), y(t_{k-\Delta n}), y(t_{k-2\Delta n}), \dots, y(t_{k-(m-2)\Delta n}), y(t_{k-(m-1)\Delta n})$ and determine F as a function of a set of transformed coordinates $Ty(t_k), Ty(t_{k-\Delta n}), \dots, Ty(t_{k-(m-1)\Delta n})$.

35

It is preferable to perform a linear transformation on the set of coordinates. Hereby, it is useful for the transformed coordinates to be so-called latent

5 coordinates aligned along the main axes of a so-called ellipsoid of variance, as is illustrated in Figure 5. An ellipsoid of variance of this type is drawn in a two-dimensional phase space in Figure 5, which phase space is represented by its delay coordinates, $y(t)$ and $y(t-k)$.

10 The ellipsoid of variance surrounds data points that are indicated by black circles, which, when connected according to their sequence in time, form a phase trajectory.

15 The ellipsoid of variance can be calculated from the scattering of the data points in the phase space, whereby the main axes of the ellipsoid indicate the variance of the data points in the corresponding direction of the phase space. Figure 5 also shows the new phase space

20 obtained by transformation along with its coordinates, $T(1)$ and $T(2)$. The first latent coordinate $T(1)$ extends along the largest axis of inertia of the ellipsoid of variance, the second latent coordinate $T(2)$ along the second-to-largest axis of inertia. Numerically, a

25 transformation to latent coordinates can be performed for example by so-called principal component analysis (M. Otto, Chemometrics, Wiley, Weinheim (Germany), 1999, pages 124 to 133) or singular value decomposition (W.H. Press et al., Numerical Recipes, Cambridge University

30 Press, Cambridge (UK), 1989, pages 52 to 61).

By performing a transformation to latent coordinates of this type, it is possible to achieve that one or several of the transformed coordinates have a negligible effect

35 on the function F at the predetermined accuracy σ such

that only a correspondingly smaller number of transformed coordinates needs to be included in the analysis in the calculation of function F.

5 These and other features and advantages of the present invention should be more fully understood from the above detailed description of the invention taken together with the accompanying claims. It is noted that the scope of the claims is defined by the recitations therein and not
10 by the specific discussion of the features and advantages set forth in the present description.

It is noted that terms like "preferably", "commonly" and "typically" are not utilized therein to limit the scope
15 of the claimed invention or to imply that certain features are critical, essential or even important to applications 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
20 particular embodiment of the present invention.

CLAIMS:

1. Method for continuous monitoring of an analyte concentration by determining its progression in the living body of a human or animal, in which analyte values $y(t_n)$ correlating with the concentration to be determined are determined for consecutive points in time t_n ,

wherein for predicting an analyte value $y(t_{n0}+\Delta t)$ over a prediction period Δt a function $F(t_k, t_{k-\Delta n}, t_{k-2\Delta n}, \dots, t_{k-(m-2)\Delta n}, t_{k-(m-1)\Delta n})$ is determined, which depends on analyte values $y(t_k), y(t_{k-\Delta n}), y(t_{k-2\Delta n}), \dots, y(t_{k-(m-2)\Delta n}), y(t_{k-(m-1)\Delta n})$ and which can be used to approximate the progression of the analyte values $y(t_n)$ at time t_{n0} in a vicinity U of an analyte value $y(t_{n0})$ with a pre-determined accuracy σ , such that

$$\sigma^2 \geq \sum_{t_k \in U} [y(t_k) - F(t_k - \Delta t, t_{k-\Delta n} - \Delta t, t_{k-2\Delta n} - \Delta t, \dots, t_{k-(m-2)\Delta n} - \Delta t, t_{k-(m-1)\Delta n} - \Delta t)]^2$$

whereby Δn , n_0 and m are integers, and

calculating a prediction for the analyte value $y(t_{n0}+\Delta t)$ by using the following equation

$$y(t_{n0} + \Delta t) = F(t_{n0}, t_{n0} - \Delta n, \dots, t_{n0} - (m-2)\Delta n, t_{n0} - (m-1)\Delta n).$$

2. Method according to claim 1, wherein the function F depends on analyte values $y(t_k), y(t_{k-\Delta n}), y(t_{k-2\Delta n}), \dots, y(t_{k-(m-2)\Delta n}), y(t_{k-(m-1)\Delta n})$.

$2\Delta n), \dots, y(t_{k-(m-2)\Delta n}), y(t_{k-(m-1)\Delta n})$ and on their first time derivatives.

3. Method according to claim 1 or 2, wherein the function F depends on analyte values $y(t_k), y(t_{k-\Delta n}), y(t_{k-2\Delta n}), \dots, y(t_{k-(m-2)\Delta n}), y(t_{k-(m-1)\Delta n})$ and on their first and second time derivatives.
4. Method according to any one of claims 1 to 3, wherein the function F contains linear or square terms.
5. Method according to any one of claims 1 to 4, wherein the function F is a linear function.
6. Method according to any one of claims 1 to 5, wherein the function F can be represented by coefficients a_0 to a_m as follows

$$F = a_0 + \sum_{j=1}^m y\left(t_{(k-(m-j)\Delta n)}\right) a_j.$$

7. Method according to claim 6, wherein the coefficients, a_0 to a_m , are determined by minimizing the sum

$$\sum_{t_k \in U} \left[y(t_k) - a_0 - \sum_{i=1}^m y\left(t_{(k-(m-i)\Delta n)} - \Delta t\right) a_i \right].$$

8. Method according to claim 6 or 7, wherein the coefficients, a_0 to a_m , are determined by solving a system of linear equations which contains one equation each of the type

$$y(t_k) = a_0 + \sum_{j=1}^m y(t_{(k-(m-j)\Delta n) - \Delta t}) a_j$$

for at least $m+1$ different analyte values $y(t_k)$ from the vicinity U of the point in time t_{n0} .

9. Method according to claim 8, wherein the system of equations contains more than $m+1$ equations and is solved numerically by approximation to determine the coefficients, a_0 to a_m .
10. Method according to any one of claims 1 to 9, wherein the analyte values $y(t_n)$ used to determine the function F are obtained by numerical processing, in particular by filtering, of measured values.
11. Method according to any one of claims 1 to 10, wherein in an additional step the function $F(t_k, t_{k-\Delta n}, t_{k-2\Delta n}, \dots, t_{k-(m-2)\Delta n}, t_{k-(m-1)\Delta n})$ is adapted in a vicinity U of an analyte value $y(t_{n0} + \Delta t)$ at a point in time $t_n = t_{n0} + \Delta t$ for a calculated prediction value $y(t_{n0} + \Delta t)$, such that the adapted function F approximates the progression of analyte values $y(t_n)$ in the vicinity U with a predetermined accuracy and an additional prediction value $y(t_{n0} + 2\Delta t)$ is calculated therefrom.
12. Method according to any one of claims 1 to 11, wherein the analyte values $y(t_n)$ used to calculate the prediction value are determined for consecutive points in time t_n which are separated by intervals of 30 seconds to 5 minutes, preferably by 1 to 3 minutes.

13. Method according to any one of claim 1 to 12, wherein the analyte values $y(t_n)$ used to calculate the prediction value or one of the prediction values are determined for times t_n which are separated by an interval corresponding to the prediction period Δt .
14. Method according to any one of claims 1 to 13, wherein the number of the coefficients, a_0 to a_m , is 4 to 11, preferably 6 to 9.
15. Method according to any one of claims 1 to 14, wherein the function F is determined as a function of values $Ty(t_k), Ty(t_{k-\Delta n}), Ty(t_{k-2\Delta n}), \dots, Ty(t_{k-(m-2)\Delta n}), Ty(t_{k-(m-1)\Delta n})$, which were determined by means of a transformation, preferably a linear transformation, from analyte values $y(t_k), y(t_{k-\Delta n}), y(t_{k-2\Delta n}), \dots, y(t_{k-(m-2)\Delta n}), y(t_{k-(m-1)\Delta n})$, whereby the transformation is selected such that at least one of the values $Ty(t_k), Ty(t_{k-\Delta n}), Ty(t_{k-2\Delta n}), \dots, Ty(t_{k-(m-2)\Delta n}), Ty(t_{k-(m-1)\Delta n})$ has a negligible influence on the function F at the predetermined accuracy σ .
16. Device for continuous monitoring of an analyte concentration by determining its progression in the living body of a human or animal, comprising a measuring unit (12), by means of which values of a measuring parameter that is correlated with the concentration to be determined are measured as measuring signals at consecutive points in time t_n , and an analytical unit (3), by means of which analyte values $y(t_n)$ that are correlated with the concentration are determined from the measured values,

the analytical unit (3) being adapted for predicting an analyte value $y(t_{n0}+\Delta t)$ over a prediction period Δt by determining a function $F(t_k, t_{k-\Delta n}, t_{k-2\Delta n}, \dots, t_{k-(m-2)\Delta n}, t_{k-(m-1)\Delta n})$, which depends on analyte values $y(t_k)$, $y(t_{k-\Delta n})$, $y(t_{k-2\Delta n})$, ..., $y(t_{k-(m-2)\Delta n})$, $y(t_{k-(m-1)\Delta n})$ and can be used to approximate the progression of the analyte values $y(t_n)$ at time t_{n0} in a vicinity U of an analyte value $y(t_{n0})$ with a pre-determined accuracy σ , such that

$$\sigma^2 \geq \sum_{t_k \in U} [y(t_k) - F(t_k - \Delta t, t_{k-\Delta n} - \Delta t, t_{k-2\Delta n} - \Delta t, \dots, t_{k-(m-2)\Delta n} - \Delta t, t_{k-(m-1)\Delta n} - \Delta t)]^2$$

whereby Δn , n_0 and m are integers, and subsequently the function F is used by the analytical unit (3) to calculate a prediction for the analyte value $y(t_{n0}+\Delta t)$ by using the following equation

$$y(t_{n0} + \Delta t) = F(t_{n0}, t_{n0} - \Delta n, \dots, t_{n0 - (m-2)\Delta n}, t_{n0 - (m-1)\Delta n}).$$

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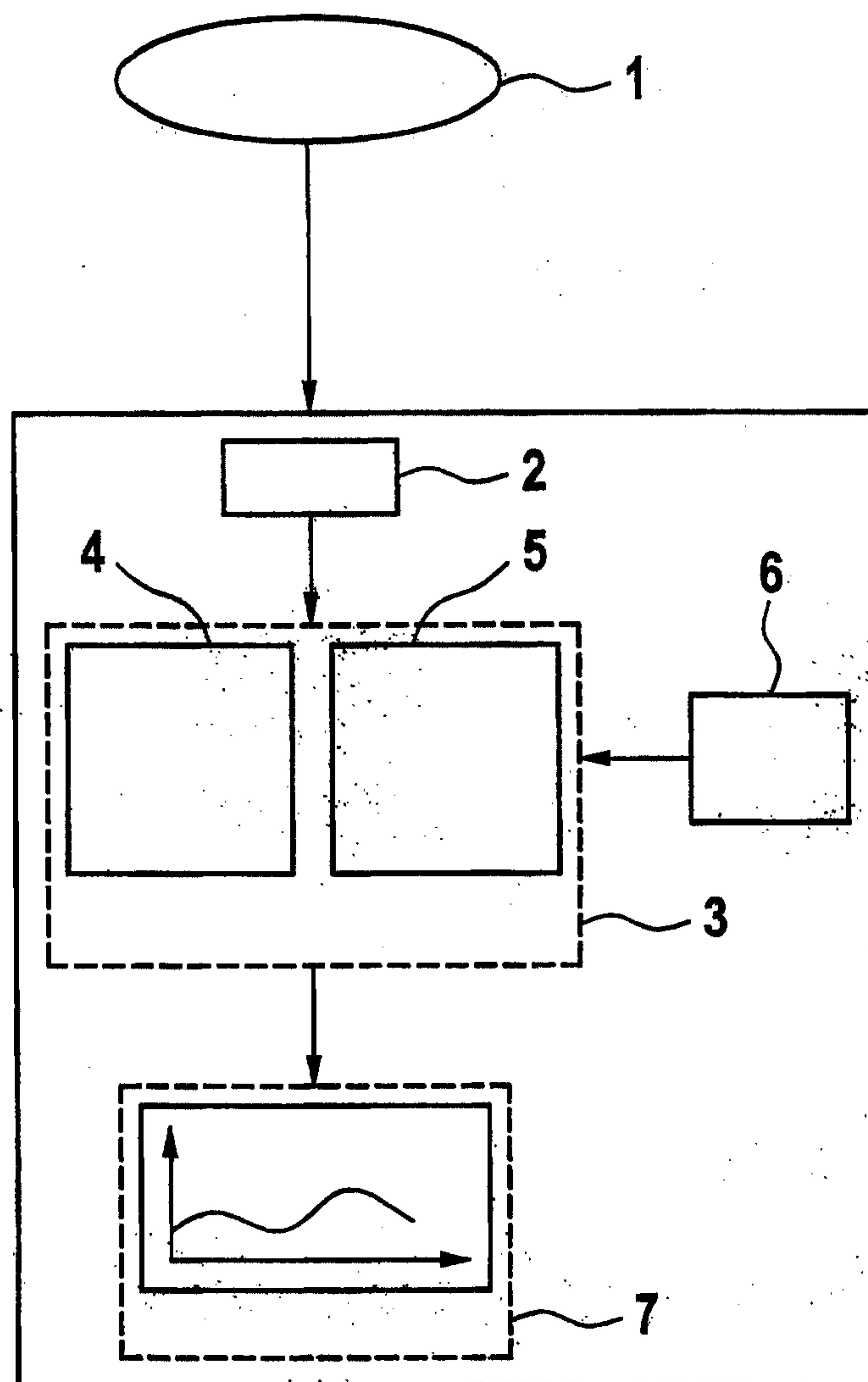


Fig. 1

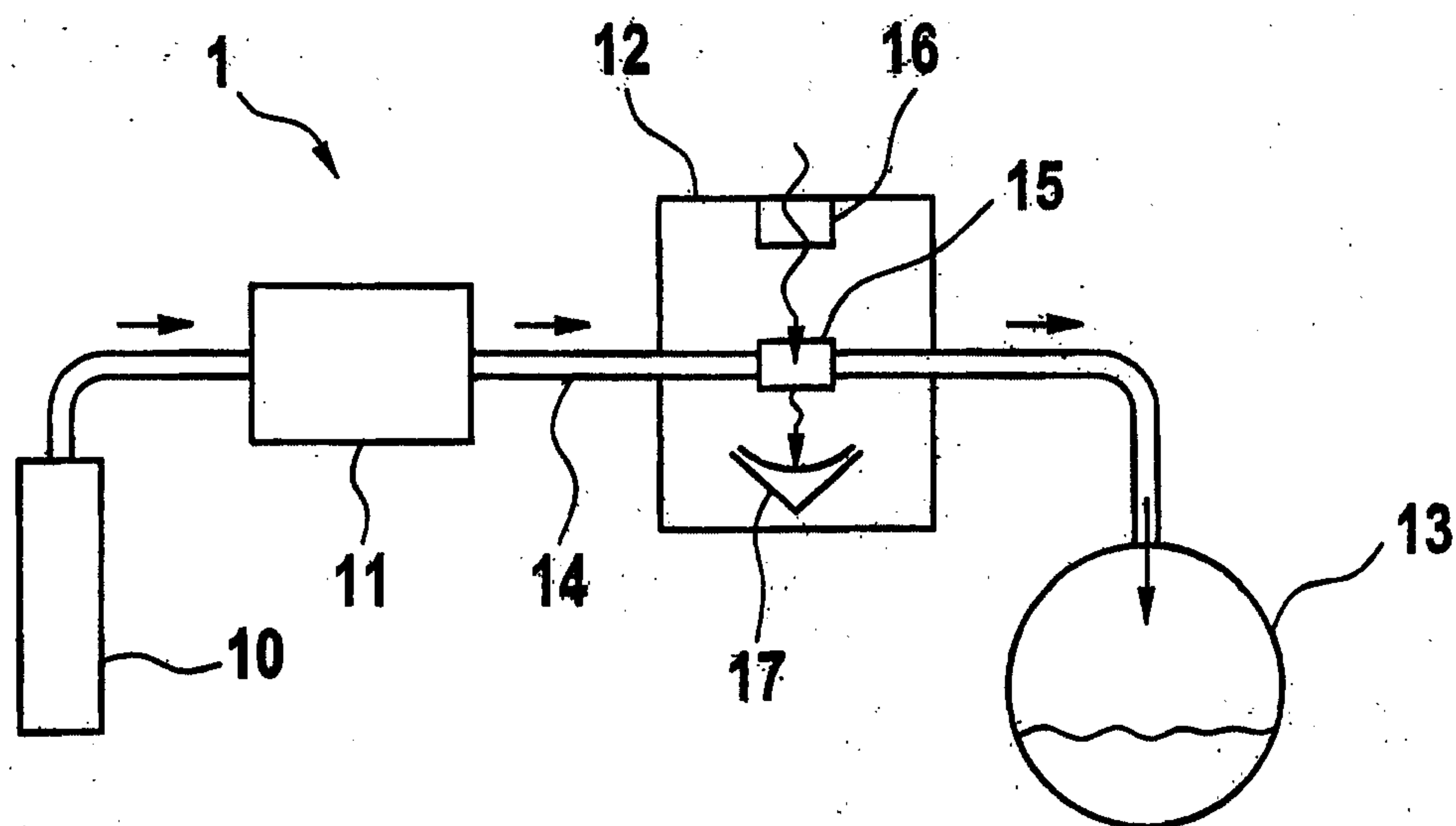


Fig. 2

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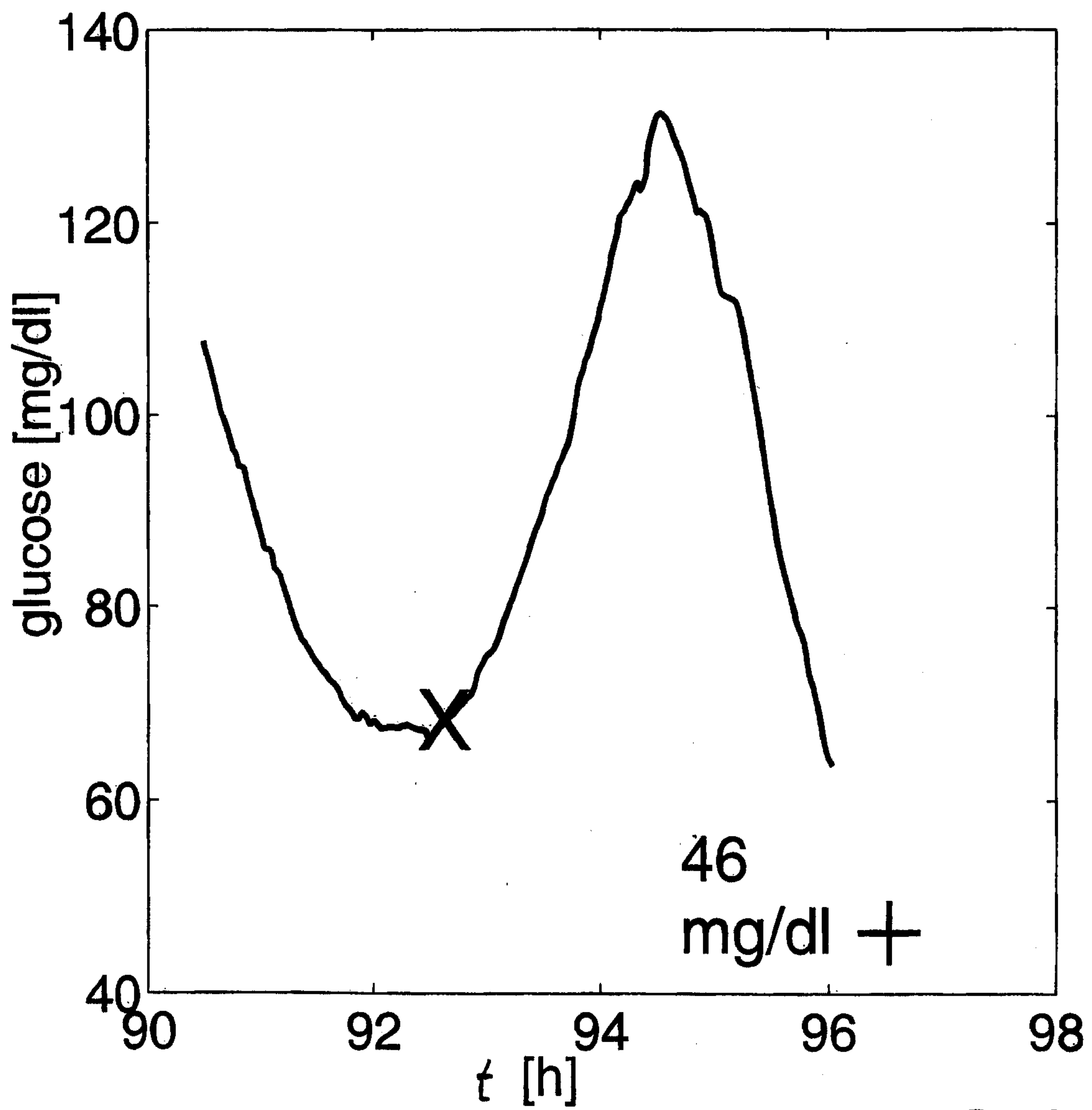


Fig. 3

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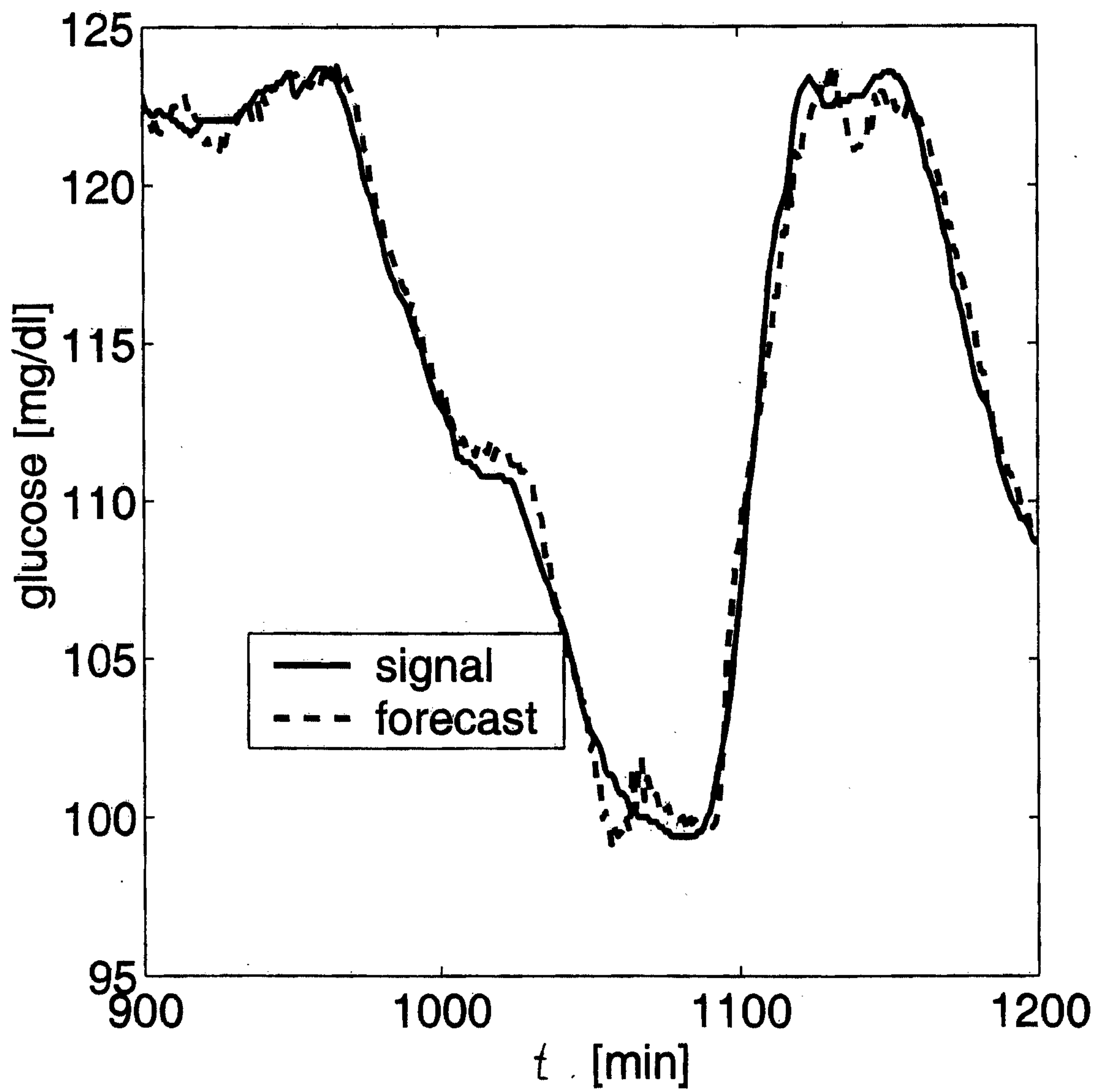


Fig. 4

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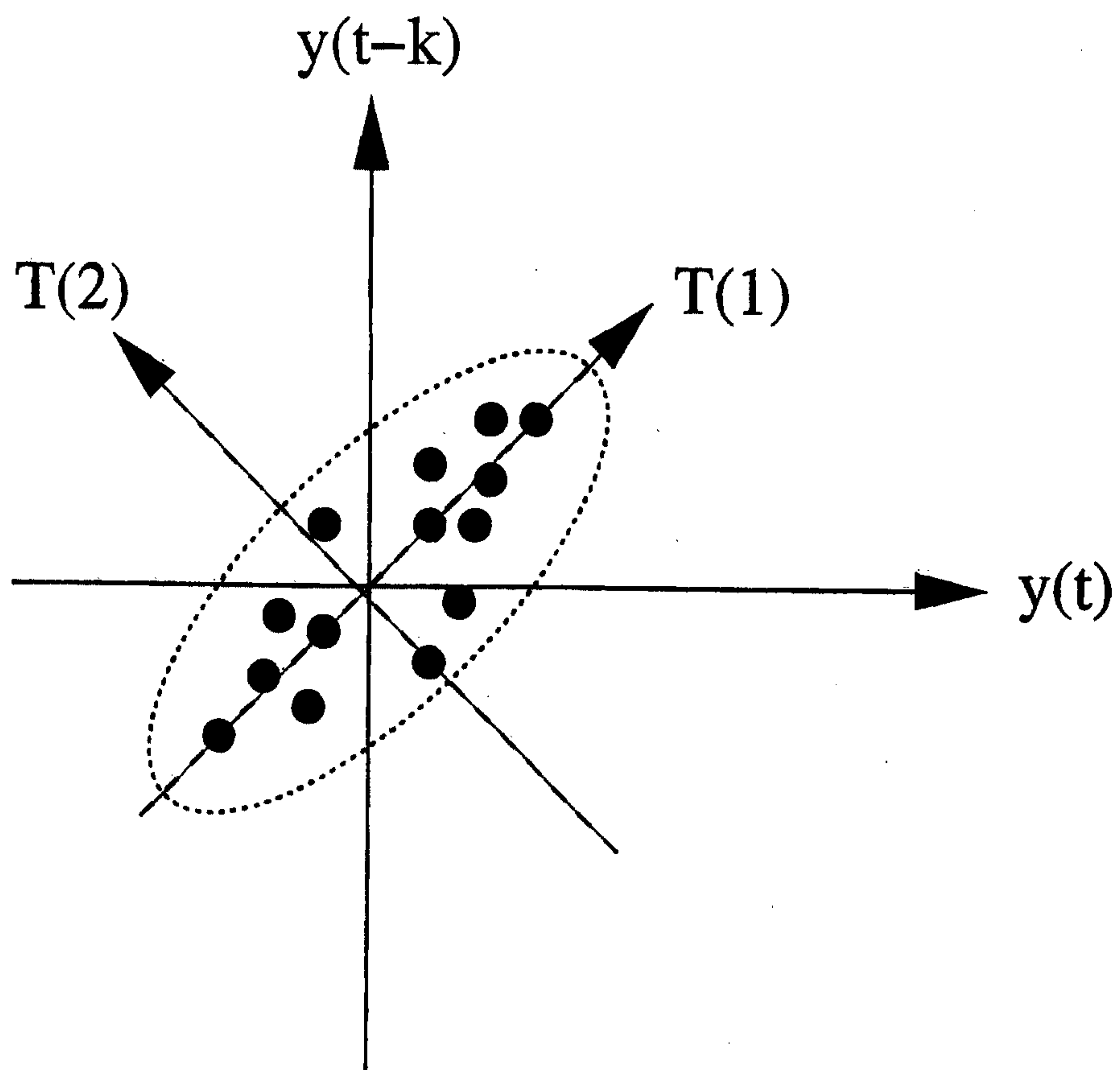


Fig. 5

$$\sigma^2 \geq \sum_{t_k \in U} [y(t_k) - F(t_k - \Delta t, t_k - \Delta n - \Delta t, t_k - 2\Delta n - \Delta t, \dots, t(k - (m-2)\Delta n) - \Delta t, t(k - (m-1)\Delta n) - \Delta t)]^2 \quad (I)$$

$$y(t_{n0} + \Delta t) = F(t_{n0}, t_{n0} - \Delta n, \dots, t(n0 - (m-2)\Delta n), t(n0 - (m-1)\Delta n)) \quad (II)$$

