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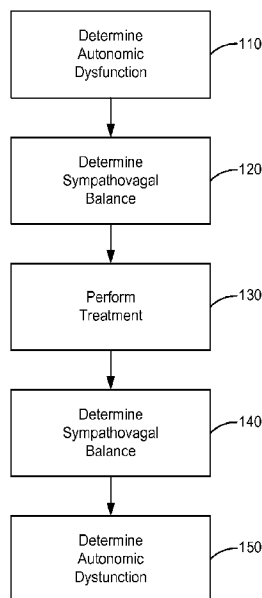


Figure 1

(57) Abstract: Methods and systems for analyzing the state of an autonomic dysfunction of an autonomic nervous system for caring for a patient are disclosed. In some embodiments, the method includes measuring an autonomic nervous system condition, and calculating a root of a sum of values. One or more of the values is equal to a sum of difference values raised to an exponent, and the difference values are each equal to a difference of a first index value and a second index value. The first and second index values are each calculated based on the autonomic nervous system condition. The method also includes displaying, via a display unit, a representation of the calculated root.

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STIMULATIVE ELECTROTHERAPY USING AUTONOMIC NERVOUS SYSTEM CONTROL

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application is related to U.S. Patent No. 7,092,849, titled 'EXTRACTING CAUSAL INFORMATION FROM A CHAOTIC TIME SERIES,' granted August 15, 2006, the content of which is incorporated herein by reference in its entirety. This application is also related to the following applications filed herewith: U.S. Patent Application Attorney Docket No. 89562-000400US-874044, titled "METHOD AND APPARATUS FOR AUTONOMIC NERVOUS SYSTEM SENSITIVITY-POINT TESTING", U.S. Patent Application Attorney Docket No. 89562-000500US-874022, titled "COMPUTER IMPLEMENTED TRAINING OF A PROCEDURE," and Attorney Docket No. 89562-001000US-876815, titled "METHOD AND APPARATUS FOR STIMULATIVE ELECTROTHERAPY," the contents of all of which are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

[0002] The present invention generally pertains to a method and apparatus for extracting information from a chaotic time series of data generated based on the autonomic nervous system of a patient, and using the information to enhance therapy administered to the patient. More precisely, the present invention pertains to a method and apparatus for analyzing the state of a patient before and after treatment.

BACKGROUND OF THE INVENTION

[0003] The autonomic nervous system (ANS), with its sympathetic and parasympathetic subsystems, governs involuntary actions of the cardiac muscle and every visceral organ in the body. The ANS is not directly accessible to voluntary control. Instead, it operates

in an autonomic fashion on the basis of autonomic reflexes and central control. One of its major functions is the maintenance of homeostasis within the body. The ANS further plays an adaptive role in the interaction of the organism with its surroundings.

[0004] Heart rate variability has been shown to be a powerful means of assessing the influence of the ANS on the cardiac system. Heart rate variability is therefore a powerful indicator of the state of the ANS, and can be used as an effective means of assessing the state of physiological conditions related to the ANS, such as chronic pain.

[0005] In many diseases, the sympathetic and/or parasympathetic subsystems of the ANS are affected, leading to autonomic dysfunction. It is then important to have reliable and representative measures of the activity and the state of the ANS.

[0006] Three main classes of methods are used to recover information about the ANS from the heart rate variability: spectral analysis (also called time domain analysis), statistics and calculation of a correlation dimension (or any related dimension). These methods do not give easy interpretable outcomes. Moreover, they lack reliability and are often not mathematically appropriate in their considered application.

[0007] Without reliable and representative measures of the ANS, effects of treatment for certain conditions can be measured only subjectively. For example, to measure pain, a patient may be asked to rate their pain level on a scale of 1-10.

BRIEF SUMMARY OF THE INVENTION

[0008] One inventive aspect is a method of analyzing the state of an autonomic dysfunction of an autonomic nervous system. The method includes measuring an autonomic nervous system condition, and calculating a root of a sum of values. One or more of the values is equal to a sum of difference values raised to an exponent, and the difference values are each equal to a difference of a first index value and a second index value. The first and second index values are each calculated based on the autonomic nervous system condition. The method also includes displaying, via a display unit, a representation of the calculated root.

[0009] Another inventive aspect is a system for analyzing the state of an autonomic dysfunction of an autonomic nervous system. The system includes means for measuring

an autonomic nervous system condition, and means for calculating a root of a sum of values, where one or more of the values is equal to a sum of difference values raised to an exponent. The difference values are each equal to a difference of a first index value and a second index value, and the first and second index values are each calculated based on the autonomic nervous system condition. The system also includes means for displaying, via a display unit, a representation of the calculated root.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] Fig. 1 is a flowchart illustrating a method of caring for a patient.

[0011] Fig. 2 is a flowchart illustrating a method of calculating autonomic dysfunction, which can be used in the method of figure 1.

[0012] Fig. 3 is a flowchart illustrating a method of treating a patient, which can be used in the method of figure 1.

[0013] Fig. 4 is a chart which can be used to determine a parameter value for use in the method of figure 3 based on a measured characteristic of the ANS of the patient.

DETAILED DESCRIPTION OF THE INVENTION

[0014] Particular embodiments of the invention are illustrated herein in conjunction with the drawings.

[0015] Various details are set forth herein as they relate to certain embodiments.

However, the invention can also be implemented in ways which are different from those described herein. Modifications can be made to the discussed embodiments by those skilled in the art without departing from the invention. Therefore, the invention is not limited to particular embodiments disclosed herein.

[0016] Particular biological events produced by a patient are governed by the ANS of the patient. Thus, a condition of the ANS of the patient may be determined through appropriate analysis of data representing the particular events. Furthermore, because the condition of the ANS of the patient may be related to one or more conditions for which the patient may seek treatment, the analysis of the data representing the biological events may be used as a quantitative measurement of the one or more conditions.

5 [0017] For example, the biological events may be related to the cardiac system of the patient. Thus, data representing heart rate or heart rate variability of the patient may be used to determine a measurement of pain experienced by the patient. Additionally or alternatively the biological events may be related to the respiratory system or to brain activity of the patient.

[0018] In some embodiments, conditions correlated with the biological events include one or more of chronic pain, anxiety, depression, and sleep problems.

10 [0019] Fig. 1 is a flowchart illustrating a method 100 of caring for a patient. The patient may be seeking treatment for one or more conditions which may be measured through analysis of data related to biological events governed by the ANS of the patient. For example, the patient may be experiencing chronic pain.

15 [0020] According to the method 100, before treatment, autonomic dysfunction and Sympathovagal balance are determined. In addition, following treatment, autonomic dysfunction and Sympathovagal balance are again determined. A difference between before and after values of the autonomic dysfunction and Sympathovagal balance of the patient may be used as an indication of the efficacy of the treatment.

[0021] In step 110, autonomic dysfunction is determined.

20 [0022] In some embodiments, one or more methods and/or systems described in appendix 1 is used to determine autonomic dysfunction. For example, data representing biological events produced by the patient, which are governed by the ANS of the patient may be recorded using an apparatus described in appendix 1. In addition, one or more data analysis methods and systems described in appendix 1 may be used to calculate an autonomic dysfunction of the patient based on the recorded biological event data.

25 [0023] In some embodiments, methods and/or systems not described in the appendix 1 may be used to the autonomic dysfunction of the patient. For example, a method of determining an autonomic dysfunction of the patient described below with reference to figure 2 may be used.

[0024] In step 120, Sympathovagal balance is determined.

[0025] In some embodiments, one or more methods and/or systems described in appendix 1 is used to determine Sympathovagal balance. For example, data representing biological events produced by the patient, which are governed by the ANS of the patient may be recorded using an apparatus and/or method described in appendix 1. In addition, one or more data analysis methods and systems described in appendix 1 may be used to calculate a Sympathovagal balance of the patient based on the recorded biological event data. In some embodiments, the recorded biological event data used to calculate the autonomic dysfunction of the patient is also used to calculate the Sympathovagal balance of the patient.

[0026] In some embodiments, a balance curve is calculated using one or more methods and systems described in appendix 1, and Sympathovagal balance is determined based on one or more parameters extracted from balance curve. For example, one or more of the minimum, the maximum, the midpoint, the mean, and the median for either the horizontal or vertical axis values may be used as the Sympathovagal balance. Additionally or alternatively, the presence of loops or upholding of long flat transitions may be used as the Sympathovagal balance.

[0027] In some embodiments, methods and/or systems not described in the appendix 1 may be used to the Sympathovagal balance of the patient.

[0028] In step 130, a treatment is performed on the patient. In some embodiments, the treatment comprises providing electrical stimulus to selected sites on the body of the patient. Alternatively, one or more other treatments may be performed on the patient. For example, physical therapy, other forms of stimulation, manipulation, and pain medication, such as opioids.

[0029] In some embodiments, a method of treating the patient described below with reference to figure 3 may be used.

[0030] In step 140, following the treatment, Sympathovagal balance of the patient is again determined. The Sympathovagal balance determined after the treatment may be compared with the Sympathovagal balance determined prior to the treatment. The comparison may be used to judge efficacy of the treatment.

[0031] In some embodiments, in step 140, the Sympathovagal balance of the patient is determined using systems and methods substantially identical to the systems and methods used in step 120 to determine the Sympathovagal balance of the patient prior to the treatment. In some embodiments, the methods and systems used in step 140 to determine the Sympathovagal balance of the patient after the treatment may be different from the methods and systems used in step 120 to determine the Sympathovagal balance of the patient prior to the treatment.

[0032] In step 150, following the treatment, an autonomic dysfunction of the patient is again determined. The autonomic dysfunction determined after the treatment may be compared with the autonomic dysfunction determined prior to the treatment. The comparison may be used to judge efficacy of the treatment.

[0033] In some embodiments, in step 150, the autonomic dysfunction of the patient is determined using systems and methods substantially identical to the systems and methods used in step 110 to determine the autonomic dysfunction of the patient prior to the treatment. In some embodiments, the methods and systems used in step 150 to determine the autonomic dysfunction of the patient after the treatment may be different from the methods and systems used in step 110 to determine the autonomic dysfunction of the patient prior to the treatment.

[0034] In some embodiments, the method of figure 1 is repeated. For example, the method of figure 1 may be used in a first treatment session. As part of the first treatment session, an efficacy of the first treatment may be judged based on the comparisons of the autonomic dysfunction and Sympathovagal balance values before and after the first treatment. Likewise, the method of figure 1 may be used in a second treatment session. Similar to the first treatment session, as part of the second treatment session, an efficacy of the second treatment may be judged based on comparisons of the autonomic dysfunction and Sympathovagal balance values before and after the second treatment. In some embodiments, the second treatment session includes about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 minutes, hours, days, weeks, months, or years after the first treatment session.

[0035] In addition, autonomic dysfunction and Sympathovagal balance values determined as part of the second treatment session may be compared with autonomic dysfunction and Sympathovagal balance values determined as part of the second treatment session. Such a comparison may indicate efficacy of the treatment over multiple treatment sessions.

[0036] Fig. 2 is a flowchart illustrating a method 200 of calculating an autonomic dysfunction of a patient. The method 200 can be used, for example, in the method 100 illustrated in figure 1. In some embodiments, the method 200 illustrated in figure 2 is performed separately and distinct from the method 100 illustrated in figure 1. In addition, the method 100 illustrated in figure 1 may use a method of calculating autonomic dysfunction which is different from the method 200 illustrated in figure 2.

[0037] According to the method 200, an autonomic dysfunction is calculated based on recorded data representing biological events which are governed by the ANS of the patient.

[0038] In step 210, a first index ANSindex1 and a second index ANSindex2, are calculated according to methods and systems described in appendix 1. In alternative embodiments, ANSindex1 and ANSindex2 may be calculated using different methods and systems. In some embodiments, ANSindex1 and ANSindex2 may be calculated in response to each of a plurality of successive biological events. For example, in response to each of a number of heartbeats as measured, for example, with an EKG, ANSindex1 and ANSindex2 values may be calculated. In some embodiments, ANSindex1 and ANSindex2 values may be calculated in response to each of a series of 400 heartbeats. In some embodiments, ANSindex1 and ANSindex2 values may be calculated in response to each of a series of 512 heartbeats. In some embodiments, the data from a certain number of heartbeats, for example 60, are used for calibration, or other purposes. In some embodiments, the heartbeats are successive.

[0039] In step 220, a set of difference values (DV) is calculated. Each difference value of the set is calculated based on the ANSindex1 and ANSindex2 values calculated in response to one of the successive biological events, as described with reference to step 210. For example, in step 210, for each of the successive biological events, an

ANSindex1 value and an ANSindex2 value are calculated, and in step 220 a difference value between the ANSindex1 value and the ANSindex2 value for each successive biological event is calculated. The difference values calculated for all of the biological events forms the set of difference values.

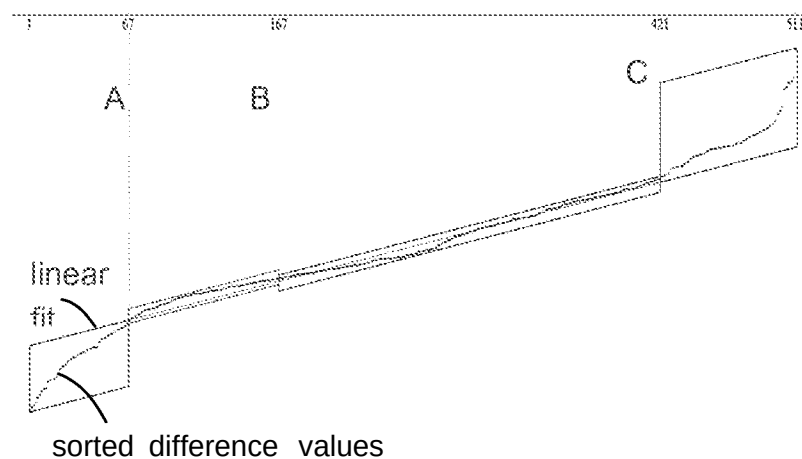
5 [0040] For example, in some embodiments,

$$D V_i = \text{ANSindex2}_i - \text{ANSindex1}_i,$$

where i is an index indicating data points.

[0041] In step 230, the set of difference values is sorted. For example, the set of difference values may be sorted from lowest difference value to highest difference value.
10 In other embodiments the second difference values may be sorted from highest difference value to lowest difference value.

[0042] Plot 1 illustrates an example of a set of sorted difference values. The difference values are plotted in the sorted order, with the lower difference values being plotted to the left of the higher difference values, and where the distance from the horizontal axis corresponds with the value of each of the sorted difference values. Plot 1 also shows a linear fit reference line.
15 linear fit reference line.



Plot 1

[0043] In step 240, the sorted difference values are separated into different regions. For example, four regions may be defined. Indicators A, B, and C identify boundaries between adjacent regions of the example set of difference values shown in Plot 1. In this example, the indicators A, B, and C align with difference values 67, 167, and 421, respectively. In some embodiments, the regions are determined based on the linearity or second derivative of the sorted difference values. For example, each region may include the difference values which correspond to points where the second derivative differs by less than a threshold. In some embodiments, regions may be determined by alternate crossing of a middle portion linear or cubic fit, and/or a distance within various thresholds to a linear or cubic fit.

[0044] Each of the regions may correspond with a certain characteristic of the ANS of the patient. For example, the first and last, lower and upper regions may correspond respectively to a profound altered state and a superficial transient change of autonomic function whereas the quasi-linear middle regions may indicate a melded durable state of autonomic homeostasis.

[0045] In step 250, information represented in the set of sorted difference values is used to calculate an autonomic dysfunction of the patient. Various mathematical methods may be used.

[0046] For example, a value V_r may be determined for each of the four regions. In some embodiments, the value for each region is determined by summing the difference values of the region. Alternatively, the value for each region may be determined by summing the difference values of the region raised to an exponent. For example, the exponent may be 2, 3, 4, 5, or another value. In some embodiments, the exponent may not be a whole number, may be irrational, and/or may be negative. As a nonlimiting example, the value for each of the regions may be determined by summing the difference values of the region raised to the fourth power.

[0047] For example, in some embodiments,

$$V_r = \sum_1^n (Dv_i)^4,$$

where i is a summing index indicating data points in the region, n is the number of points in the region, and r identifies the region.

[0048] In some embodiments, the values for the regions are each multiplied by a coefficient (c) specific to the region associated therewith. For example, the value associated with the first region may be multiplied by a coefficient equal to -8.2045, the value associated with the second region may be multiplied by a coefficient equal to 1.769, the value associated with the third region may be multiplied by a coefficient equal to 0.90025, and the value associated with the fourth region may be multiplied by a coefficient equal to 1.903. Alternatively, the coefficient for the first region may be equal to -9.215, the coefficient for the second region may be equal to -530, the coefficient for the third region may be equal to 0.7, and the coefficient for the fourth region may be equal to 1.23. Other coefficient values may be used.

[0049] In some embodiments, the values multiplied by their respective coefficients are summed. Further, a constant C may be added to the summed values multiplied by their respective coefficients. For example, -2600 may be added to the summed values multiplied by their respective coefficients. Alternatively, the constant C may be equal to -1650.

[0050] In some embodiments, the coefficient values { $a \rightarrow -8.2045$, $b \rightarrow 1.769$, $c \rightarrow 0.90025$, $d \rightarrow 1.903$, offset $\rightarrow -2600$ } are used with a lower sampling rate for the input EKG signal (for example, 300Hz), and the coefficient values { $a \rightarrow -9.215$, $b \rightarrow -530$, $c \rightarrow 0.7$, $d \rightarrow 1.23$, offset $\rightarrow -1650$ } are used with a higher sampling rate for the input EKG signal (for example, 600Hz or 1.2kHz).

[0051] To calculate the autonomic dysfunction AD, the result of the summing may be raised to an exponent equal to the inverse of the exponent used for determining the values associated with each region.

[0052] For example, in some embodiments,

$$AD = \left(C + \sum_1^n c_i V_i \right)^{1/4},$$

[0053] where i is a summing index indicating regions, and n is the number of regions.

[0054] In some embodiments, a value representing the calculated autonomic dysfunction is graphically shown on a display associated with an apparatus used for calculating the autonomic dysfunction.

5 [0055] Fig. 3 is a flowchart illustrating a method 300 of treating a patient. The method 300 can be used in the method 100 illustrated in figure 1. In some embodiments, the method 300 illustrated in figure 3 may be performed separately and distinct from the method 100 illustrated in figure 1. In addition, the method 100 illustrated in figure 1 may use a method of treating a patient which is different from the method 300 illustrated in figure 3. For example, physical therapy, other forms of stimulation, manipulation, and
10 pain medication, such as opioids.

[0056] In the method 300, the patient is treated by electrically stimulating points on the patient's skin to which the autonomic nervous system is sensitive.

15 [0057] In step 310, locations on the patient's skin having autonomic nervous system sensitivity are identified. For example, a graphical representation of a least a portion of the patient's body having sensitivity points identified may be referenced. In some embodiments, the locations correspond with locations identified as acupuncture points.

20 [0058] In step 320, an electrical stimulus source generator is adjusted so as to provide an appropriate stimulus signal. For example, one or more parameters, such as at least one of a frequency, an amplitude, a DC offset, a power, and a treatment duration may be programmed into the electrical stimulus source generator. In some embodiments, the electrical stimulus source generator is programmed with a value determined based on a value calculated based on biological event data. For example, one or more values associated with autonomic dysfunction or Sympathovagal balance may be used to determine one or more values for the one or more parameters to be program into the
25 electrical stimulus source generator.

[0059] For example, figure 4 illustrates a chart which can be used to determine a parameter value for use in the method of figure 3 based on a measured characteristic of the ANS of the patient. Specifically, figure 4 illustrates a chart which can be used to determine a power setting for the electrical stimulus source generator. In this example,

the power setting is determined based on a value related to Sympathovagal balance. In this example, a higher power setting is used for a higher calculated Sympathovagal balance value. Similar charts may be additionally or alternatively used to determine other parameters for programming the electrical stimulus source generator based on a measured characteristic of the ANS of the patient.

[0060] In step 330, an electrical stimulus is provided to the locations identified in step 310. For example, a needle may be inserted at each of the identified locations, where the needle is attached to the electrical stimulus source generator. In addition, a circuit completion path, such as a ground path, is provided by attaching a circuit completion electrode from the electrical stimulus source generator to the patient. The electrical stimulus is provided to the patient through the needles inserted at the locations identified in step 310 by the electrical stimulus source generator, which has been programmed with the parameter values of step 320.

[0061] Though the present invention is disclosed by way of specific embodiments as described above, those embodiments are not intended to limit the present invention. Based on the methods and the technical aspects disclosed above, variations and changes may be made to the presented embodiments by those skilled in the art without departing from the spirit and the scope of the present invention.

APPENDIX 1**EXTRACTING CAUSAL INFORMATION FROM A CHAOTIC TIME
SERIES**

5

CROSS-REFERENCES TO RELATED APPLICATIONS**[0001]** NOT APPLICABLE**BACKGROUND OF THE INVENTION**10 **[0002]**

The present invention generally pertains to a method and apparatus for extracting causal information from a chaotic time series. More precisely, the present invention pertains to a method and apparatus for analyzing the state of a first system from a time-varying signal representing a chaotic series of time intervals between quasi-periodical events produced by a second system governed by the first system. In a typical, but non-exclusive, application of the invention, the first system is the autonomous nervous system (ANS) and the second system is the cardiac system.

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Measures of heart rate variability (HRV) have been shown to be a powerful means of assessing the influence of the ANS on the cardiac system. Indeed, the ANS, with its sympathetic and parasympathetic subsystems, governs involuntary actions of the cardiac muscle and every visceral organs in the body.

25

The ANS is not directly accessible to voluntary control. Instead, it operates in an autonomic fashion on the basis of autonomic reflexes and central control. One of its major functions is the maintenance of homeostasis within the body. The ANS further plays an adaptive role in the interaction of the organism with its surroundings.

In many diseases, the sympathetic and/or parasympathetic parts of the ANS are affected leading to autonomic dysfunction. It is then important to have reliable and representative measures of the activity and the state of the ANS.

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Three main classes of methods are used to recover information about the ANS from the heart rate variability: spectral analysis (also called time domain analysis), statistics and

APPENDIX 1

calculation of a correlation dimension (or any related dimension). These methods do not give easy interpretable outcomes. Moreover, they lack reliability and are not mathematically appropriate in their considered application.

5 BRIEF SUMMARY OF THE INVENTION

[0003]

The present invention aims at remedying the above-mentioned shortcomings of the prior art and proposes, to this effect, a method for analyzing the state of a first system from a time-varying signal representing a chaotic series of time intervals between quasi-periodical events
10 produced by a second system governed by the first system, the method comprising the steps of extracting envelope information from the time-varying signal, constructing a phase space for the time-varying signal, extracting information on the relative positions of points corresponding to the time-varying signal in the phase space, combining the envelope and the position information and, based on this combination, providing information on the state of the
15 first system.

Thus, the present invention exploits the fractal geometry of the time-varying signal and combines an envelope calculation scheme with an evaluation of the dispersion of points in a reconstructed phase space. The present inventors have found that such a combination enables emphasizing the variations of significance in the chaotic series of time intervals while
20 dismissing the variations of no significance, thus providing precise information on the state of the first, underlying system.

A more dynamic and reactive response to a change in the state of the first system may be obtained in the invention by calculating two envelopes for the series of time intervals, namely a first upper envelope calculated in the direction of the chronological order and a
25 second upper envelope calculated in the direction opposite to the chronological order.

The present invention makes also possible to discriminate the sympathetic and parasympathetic components of the ANS and, by means of two different calculations defined in appended claim 16, to describe the instantaneous state of each of these components.

30 Other advantageous features of the method according to the invention are defined in appended claims 2, 4-15 and 17.

APPENDIX 1

The present invention further concerns a computer program and an apparatus for executing the above-mentioned method, the former being defined in appended claim 18 and the latter being defined in appended claims 19-37.

5 BRIEF DESCRIPTION OF THE DRAWINGS

[0004]

A detailed description of preferred embodiments of the invention is given below with reference to the appended drawings in which:

- figure 1 is a flow chart of the method according to the invention;
- 10 - figures 2 and 3 respectively show, as a general illustration, how two different envelopes, one determined in the direction of the chronological order and the other determined in the direction opposite to the chronological order, may be obtained from a given time-varying signal;
- figure 4 diagrammatically shows an example of a phase space obtained in the
15 method according to the invention;
- figure 5 shows a time-varying signal representing RR intervals derived from an electrocardiogram;
- figure 6 shows a superposition of curves obtained by the method according to the invention and each representing an instantaneous state of what is believed to be the
20 parasympathetic component of the ANS;
- figure 7 shows the time variations of two indices obtained by the method according to the invention;
- figure 8 shows the time variation of another index obtained by the method according to the invention;
- 25 - figure 9 is a block-diagram of a system in which the method according to the invention is implemented.

DETAILED DESCRIPTION OF THE INVENTION

[0005]

APPENDIX 1

With reference to figure 1, a method for analyzing the state of the ANS comprises steps S1 to S13.

In step S1, a first time-varying signal or data representing quasi-periodical events produced by a biological system governed by the ANS of a patient is acquired. The said
5 biological system is, for example, the cardiac, respiratory or brain system of the patient. The first time-varying signal is a raw signal, i.e. a non-smoothed and non-filtered signal. Thus, all variations of this signal are kept, including micro-variations.

In step S2, the quasi-periodical events in the first time-varying signal are detected and the time intervals between these quasi-periodical events are calculated so as to form a second
10 time-varying signal or data, called "time-interval signal", taking discrete values consisting of the series of calculated time intervals. Such a series of time intervals is known to be chaotic. In a preferred embodiment of the invention, the time-varying signal acquired in step S1 is the electrocardiogram (ECG) of the patient and the time intervals calculated in step S2 are the
15 RR intervals, i.e. the intervals between the R waves of the ECG. Figure 5 shows, by way of illustration, an example of a time-interval signal obtained in step S2 in the case of such RR intervals. Each point in the signal of figure 5 corresponds to a calculated time interval. Such a signal is known in the art as being fractal.

In practice, step S2 is performed in real time, i.e. each time an event occurs in the first time-varying signal, this event is detected and the time interval between this event and the
20 preceding one is calculated. In the same manner, the algorithm formed by the following steps S3 to S13 is performed each time a time interval is calculated by step S2.

In step S3 a time window W is defined. The upper limit L_i of time window W is the instant corresponding to the last time interval calculated in step S2. The lower limit L_o is set such that the width $L_x - L_o$ of time window W corresponds to a predetermined number N of
25 calculated time intervals. In other words, the window W encompasses the last (current) calculated time interval and the N-1 preceding calculated time intervals. The predetermined number N corresponds to the time scale in which the state of the ANS is to be determined and visualized. This number may be selected by the user. Its default value is, for example, 40.

In step S4, two convex or upper envelopes of the time-interval signal obtained in step S2 are
30 calculated in window W. One of these envelopes is calculated in the direction of the chronological (temporal) order, from the lower limit L_o of time window W up to the upper limit L_i . The other one is calculated in the direction opposite to the chronological order, from

APPENDIX 1

the upper limit L_i down to the lower limit L_o , and then reset in the chronological order. By way of general illustration, figures 2 and 3 respectively show for a given arbitrary signal SIG in window W the corresponding upper envelope E_c as calculated in the direction of the chronological order and the corresponding upper envelope E_{nc} as calculated in the direction opposite to the chronological order. As is apparent from these figures, the two envelopes are different and thus contain different, complementary information on the variations of the signal SIG. It is recalled that the upper envelope of a given signal $f(t)$ is given by the following formula:

$$f(s) = \max_{1 \leq t \leq s} f(t).$$

- 10 The upper envelopes as obtained in step S4 of the present invention are each in the form of a table or vector having N values, each of which corresponds to one of the discrete values taken by the time-interval signal. The table corresponding to the upper envelope calculated in the direction of the chronological order will be referred to in the following as ForwHull and the table corresponding to the upper envelope calculated in the direction opposite to the
- 15 chronological order as BackwHull.

- The sequence of step S5 to S10 is performed in parallel with step S4. Step S5 consists in constructing a several-dimensional phase space for the portion of the time-interval signal in window W. The notion of phase space is known per se in the field of mathematical physics. A scheme for construction of the phase space and reasons for this construction are described,
- 20 for example, in the paper entitled "Geometry from a Time Series" by Packard et al, Physical Review Letters, Volume 45, Number 9, 1 September 1980 and in the paper entitled "Predicting Chaotic Time Series" by Farmer et al, Physical Review Letters, Volume 59, Number 8, 24 August 1987. The present invention follows the precited scheme and, as such, the phase space is constructed in the following manner: from the series of values taken by the
- 25 time-interval signal in window W, designated by $X_1, X_2, X_3, \dots, X_N$ from the lower limit L_o to the upper limit L_i , vectors, e.g. three-dimensional, are constructed using a time lag or shift, e.g. of four. Thus, typically, the first vector will have as its first component the first value X_1 of the time-interval signal in window W, as its second component the fifth value X_5 of the time-interval signal in window W, and as its third component the ninth value X_9 of the time-
- 30 interval signal in window W. The second vector will have as its first component the second value X_2 of the time-interval signal in window W and as its second and third components the sixth and tenth values X_6, X_{10} of the time-interval signal in window W, and so on.

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Preferably, in order to obtain a number N of such vectors, the series of vectors is completed by repeating the last complete vector as many times as necessary at the end of the series. The vectors obtained are listed below:

$$\begin{pmatrix} X_1 \\ X_5 \\ X_9 \end{pmatrix}, \begin{pmatrix} X_2 \\ X_6 \\ X_{10} \end{pmatrix}, \begin{pmatrix} X_3 \\ X_7 \\ X_{11} \end{pmatrix}, \dots, \begin{pmatrix} X_{N-8} \\ X_{N-4} \\ X_N \end{pmatrix}, \begin{pmatrix} X_{N-8} \\ X_{N-4} \\ X_N \end{pmatrix}, \dots, \begin{pmatrix} X_{N-8} \\ X_{N-4} \\ X_N \end{pmatrix}.$$

- 5 Although in the preferred embodiment of the invention the dimension of the vectors, i.e. the dimension of the phase space, and the time lag are respectively equal to three and four, these dimension and time lag may be different. When such dimension and time lag are different, it is however preferable to keep their product equal to 12.

- The vectors obtained as described above each represent a point in the phase space. The
 10 present inventors have observed that, rather than being distributed randomly, the points of the phase space form clusters of points, each of which represents a common equilibrium state of the ANS. As an illustration, figure 4 shows the phase space obtained during a tilt test applied to a patient, i.e. a test in which the patient is levered from a horizontal position to a quasi-vertical one (angle of 80°). As can be seen, this phase space includes two separate clusters of
 15 points CL1, CL2. Each of these clusters of points CL1, CL2 corresponds to one of the above-mentioned horizontal and quasi-vertical positions.

- Step S6 consists in lowering the dimension of the phase space in order to get information on the positions of the points relative to one another. Step S6 more specifically consists in orthogonally projecting the points of the phase space, i.e. the points corresponding to the
 20 above-mentioned vectors, onto a space of lower dimension on which an order relation can be established. Typically, step S6 projects the points of the phase space onto a straight line that minimizes the average distance between these points and the straight line. Such a straight line passes through the clusters of points, as shown in figure 4 at reference sign SL. It may be obtained through a conventional linear fit method. The straight line is given an
 25 orientation, which may be selected arbitrarily but preferably according to the axis of the phase space the straight line is most parallel to.

- Once all the points of the phase space have been projected onto the above-mentioned straight line, step S7 calculates the relative distances between the projected points while respecting the chronological order of these points. Precisely, step S7 first calculates the distance
 30 between the first point in the chronological order, i.e. the projected point corresponding to the

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first vector or point ($\mathbf{X}_i, \mathbf{X}_5, \mathbf{X}_9$), and the second point in the chronological order, i.e. the projected point corresponding to the second vector or point ($\mathbf{X}_2, \mathbf{X}_6, \mathbf{X}_{10}$), then between the first point and the third point in the chronological order, then between the first point and the fourth point in the chronological order, and so on. Then step S7 calculates the distance

5 between the second point in the chronological order and the third point in the chronological order, then between the second point and the fourth point in the chronological order, then between the second point and the fifth point in the chronological order, and so on. Then step S7 calculates the distance between the third point and the fourth point in the chronological order, then between the third point and the fifth point in the chronological order, and so on.

10 Step S7 thus calculates $N(N+1)/2$ distances. Due to the orientation given to the projection straight line on which the points are located, these distances are either positive or negative (the value zero being considered, for example, as a positive value). All these distances are set in a table and arranged therein in the order in which they have been calculated. Such a table is representative of an average distance between the clusters of points in the several-

15 dimension phase space.

In step S8, the positive and negative distances calculated in step S7 are discriminated. More specifically, first and second tables Tinc, Tdec are created including respectively the positive distances and the absolute value of the negative distances, the values in each of these tables Tinc, Tdec keeping the same order as in their original table, that is the temporal order.

20 The tables Tinc, Tdec created in step S8 may have different lengths. In step S9, starting from the latest (most recent) temporal position in each of the tables Tinc, Tdec, the first encountered group of N successive values with highest mean average is chosen and kept in the table, the other values being dismissed, thus reducing the dimension of each of these tables to N. Furthermore, if one of these kept N values in the table Tinc or Tdec is lower than

25 a predetermined value R, it is replaced in the corresponding table Tinc or Tdec by the preceding value in the group of N values. The predetermined value R may be selected by the user. This value R represents the minimum variation of time interval between events in the first time-varying signal considered as being of significance for the user. The two tables obtained at the end of step S9 will be referred to in the following as Cine (table including the

30 positive distances) and Cdec (table including the absolute value of the negative distances).

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In step S10, the tables Cine and Cdec are combined with the upper envelopes ForwHull and BackwHull to provide information on the instantaneous state of the ANS. To this effect, step 10 carries out two different calculations, called CT1 and CT2, which are exposed below:

CT1:

$$5 \quad \underline{Coeffinc}_1 = B + (4 - AA - 5B + AAB) \cdot \underline{Cine} - B \cdot \underline{Cdec}$$

$$\underline{Coeffdec}_1 = B - B \cdot \underline{Cine} + (AA - AAB - B) \cdot \underline{Cdec}$$

$$\underline{ANSigram}^{\wedge} = 1 - \frac{2 \cdot \text{normcoeff}}{3} \cdot (\underline{Coeffinc}_1 \cdot \underline{ForwHull} + \underline{Coeffdec}_1 \cdot \underline{BackwHull})$$

where A and B are predetermined constants which, in the preferred embodiment of the invention, are each equal to 0.5, normcoeff is a normalization coefficient,

- 10 $\underline{Coeffinc}_1 \cdot \underline{ForwHull}$ is the term-by-term product of the tables Coeffinci and ForwHull and $\underline{Coeffdec}_1 \cdot \underline{BackwHull}$ is the term-by-term product of the tables Coeffdeci and BackwHull;

CT2:

$$\underline{Coeffinc}_2 = \frac{B}{3} + 4(1-B) \cdot (1-A) \cdot \underline{Cinc}$$

$$\underline{Cgeffdec}_2 = \frac{B}{3} + 4(1-B) \cdot A \cdot \underline{Cdec}$$

$$15 \quad \underline{ANSigram}_2 = 1 - \frac{2 \cdot \text{normcoeff}}{3} \cdot (\underline{Coeffinc}_2 \cdot \underline{ForwHull} + \underline{Coeffdec}_2 \cdot \underline{BackwHull})$$

where A and B are the same predetermined constants as in CT1, normcoeff is the same normalization coefficient as in CT1, $\underline{Coeffinc}_2 \cdot \underline{ForwHull}$ is the term-by-term product of the tables Coeffinc₂ and ForwHull and $\underline{Coeffdec}_2 \cdot \underline{BackwHull}$ is the term-by-term product of the tables Coeffdec2 and BackwHull.

- 20 According to the present inventors, the table ANSigrani₁ as obtained above by the calculation CT1 is representative of the state of the parasympathetic component of the ANS and the table ANSigrani₂ as obtained above by the calculation CT2 is representative of the state of the sympathetic component of the ANS. Thus, the present invention not only provides information on the state of the ANS but can also discriminate the sympathetic and
- 25 parasympathetic components of the ANS. In practice, as will be apparent in the following,

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each of the tables ANSigrami and ANSigram₂ will be presented to the user in the form of a curve linking the points of the table. The shape of this curve will be directly interpretable by the user. For example, flat ANSigrami and ANSigram₂ curves will indicate a low reactivity of the ANS whereas observing e.g. a persistent increasing slope in these curves will indicate a change of pace in the time intervals, i.e., in the case of the first time-varying signal being an ECG, a change of the cardiac activity. The user will also have the possibility to compare the morphology of these curves with previously seen curve morphologies to precisely identify a trouble affecting the patient. Furthermore, the point-by-point subtraction of one of the curves ANSigrami and ANSigram₂ from the other will give the user a view of the balance between the sympathetic and the parasympathetic subsystems, balance which was discovered by the present inventors to be non-linear.

In step SI 1, a first index ANSindex₁ is calculated for representing a complexity exponent of the table or curve ANSigrami and a second index ANSindex₂ is calculated for representing a complexity exponent of the table or curve ANSigram₂. The index ANSindex₁, respectively ANSindex₂, is a number which is high when the corresponding curve ANSigrami, respectively ANSigram₂, exhibits large fluctuations and which is low when the curve ANSigrami, respectively ANSigram₂, exhibits small fluctuations, i.e. is almost rectilinear. These indices are typically calculated as a Bouligand dimension normalized as exterior, for example in the following manner:

$$ANSindex_1 = \text{Floor} \left[\left(6 + \frac{9375}{12} \cdot \left(\frac{\log(ANSlength_1)}{\log \sqrt{range_1^2 + N^2}} - 1 \right) \right) \cdot (\sqrt{5} + 1) \right]$$

$$ANSindex_2 = \text{Floor} \left[\left(6 + \frac{1875}{12} \cdot \left(\frac{\log(ANSlength_2)}{\log \sqrt{range_2^2 + N^2}} - 1.045 \right) \right) \cdot (\sqrt{5} + 1) \right]$$

where Floor designates the integer part, which returns zero if the argument is negative, ANSlength₁ and ANSlength₂ respectively designate the length of the curve ANSigrami and the length of the curve ANSigram₂, range₁ designates the difference between the last value and the first value of the curve ANSigrami and range₂ designates the difference between the last value and the first value of the curve ANSigram₂.

In step S12 an index ANSirisk is calculated which represents a risk or probability that the shape of the curves ANSigrami and ANSigram₂ will change at the next event in the first

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time-varying signal (i.e., in the case of an ECG, at the next R wave detected), which would mean a probability of change of the state of the ANS. This index ANSirisk represents, in other words, the degree of activity of the ANS. The calculation of index ANSirisk is based on one of tables Tine and Tdec obtained in step S8, preferably on table Tdec in the case indicated above in relation with step S6 where the orientation of the projection straight line is chosen according to the axis this straight line is most parallel to. This index ANSirisk is typically determined in the following manner: first, one determines the number a_i of values in the table Tdec which are greater than a predetermined number $rstart$, the number a_2 of values in the table Tdec which are greater than $rstart+1$, the number a_3 of values in the table Tdec which are greater than $rstart+2$, ..., and the number $a_{rstop-rstart}$ of values in the table Tdec which are greater than $rstop$, where $rstop$ is also a predetermined number. Then, a weighted average of the numbers a_i is calculated:

$$ANSrisk = \frac{\sum_{i=1}^{rstop-rstart} a_i \cdot (rstart + i)}{\sum_{i=1}^{rstop-rstart} (rstart + i)}$$

Preferred relations for determining the numbers $rstart$ and $rstop$ are given below:

$$rstart = \left\lfloor 3 \cdot \overline{Reenter - R} + 2 \cdot \overline{Reenter - N} + RstCenter - 26 \right\rfloor$$

$$rstop = \left\lfloor -rstart + 0.5 \cdot \overline{RstCenter - 3.95 - 1.43rstart} + RstCenter + 16 \right\rfloor$$

where, preferably, $RstCenter=21$, $Rcenter=10$ and $Vcenter=30$.

In step S13, the curves ANSigram₁ and ANSigram₂ and the indices ANSindex₁, ANSindex₂ and ANSirisk are displayed. Preferably, the first time-varying signal is also displayed.

Then the algorithm returns to step S2 for the next event in the time-varying signal acquired from the patient.

An example of a result obtained with the method according to the present invention will now be exposed in relation with figures 5 to 8.

In figure 5 is illustrated a signal representing the RR intervals of a healthy patient during a period of five minutes. Between instants t_0 and t_i in this period, a tilt test is applied to the patient. As can be seen, a change of pace occurs in the RR intervals between the instants t_0 and t_i . However, in practice, such a change of pace can be detected on the RR interval signal

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only a certain time after the instant t_0 , once the general decrease of the signal is distinguishable. In the example of figure 5, the instant from which one can observe, with the sole use of conventional means, that a change of pace has occurred is about an instant designated by t_2 which is relatively close to the instant t_i . It is also to be mentioned that, for certain patients, a tilt test does not always cause a clear change of pace in the RR intervals, hence the difficulty of detecting the change.

Figure 6 shows a superposition of the curves $ANSigram_i$ obtained during the tilt test between the instants t_0 and t_i . Each one of these curves is a "photography" of the instantaneous state of what is believed to be the parasympathetic component of the ANS after a beating of the patient's heart or, more precisely, after an RR interval has been determined. In figure 6, the darker a curve is, the more recent it is. It can be seen that the shape of the curve $ANSigram_i$ evolves rapidly between the instants t_0 and t_i , which means that the method according to the invention is very reactive. As only the morphology of this curve is significant, no scale is needed, an aspect ratio being however predetermined for displaying the curve.

Figure 7 shows on a same diagram a series of indices $ANSindex_i$ and a series of indices $ANSindex_2$ obtained during the above-mentioned five-minute period. The indices $ANSindex_i$ are represented by crosses and the indices $ANSindex_2$ by rectangles. It is interesting to note that the index $ANSindex_i$ increases at the beginning of the tilt and reaches a peak well before the instant t_i at which the patient is at the 80° position and even well before the aforementioned instant t_2 observed with the traditional means, whereas the index $ANSindex_2$ increases slowly at the beginning of the tilt, until a first peak situated well after the instant t_i . Thus, the index $ANSindex_i$ reacts rapidly whereas the index $ANSindex_2$ has a slower reaction. Once the patient has reached the position at 80° , the index $ANSindex_i$ decreases while the index $ANSindex_2$ takes over and exhibits different waves. All this is perfectly coherent with what is currently known on the behaviors of the sympathetic and parasympathetic subsystems. In particular, the presence of the aforementioned waves in the index $ANSindex_2$ can be explained by the release of catecholamine hormones by the sympathetic subsystem.

Figure 8 shows the evolution of the index $ANSirisk$ during the above-mentioned five-minute period. One can see that this index exhibits a peak substantially in the middle of the tilt period between instants t_0 and t_i . In practice, rather than being displayed as a curve as shown

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in figure 8, the index ANSirisk may be presented to the user in the form of a gauge moving upward and downward as a function of time.

The method as described above is typically performed by a suitably programmed processor. As shown in figure 9, the processor, designated by reference 1, is connected via a suitable interface (not shown) to the output of an acquisition unit 2. The acquisition unit 2 is associated with electrodes 2a connected to the patient and performs analog-to-digital conversion to produce the first time-varying signal representing the quasi-periodical events. The acquisition unit 2 is, for example, an ECG unit. A display unit 3 is connected to the processor 1 to display the results provided by the method according to the invention, such as the curves ANSigrami and ANSigrani2, the difference between these curves ANSigrami and ANSigram₂, the indices ANSindexi and ANSindex₂, a historical record of these indices ANSindexi and ANSindex₂ (see figure 7), and/or the index ANSirisk, as well as the first time-varying signal.

In practice, several embodiments are possible for arranging the units 1, 2, 3 relative to one another. According to a first embodiment, the processor 1 and the display unit 3 are part of a laptop computer connected, for example via a USB port, to the acquisition unit 2. According to a second embodiment, the processor 1 is part of a plug-in electronic board. According to a third embodiment, the processor 1, the acquisition unit 2 and the display unit 3 are part of a stand-alone apparatus further comprising a main board, a printer, a media recorder (CD-ROM, . . .), a battery, etc. According to a fourth embodiment, the processor 1 and the display unit 3 are part of a handheld device such as, for example, a cellphone, a Palm OS (registered trademark) device, a PocketPC (registered trademark) device, any personal digital assistant, etc.

Furthermore, in some embodiments, the connection between the electrodes 2a and the acquisition unit 2, that between the acquisition unit 2 and the processor 1, and/or that between the processor 1 and the display unit 3 may be wireless connections, such as Bluetooth (registered trademark) connections.

The present invention as described above may be used in various applications, in particular in all situations where an evaluation of the ANS is expected for diagnostic or prognostic procedures concerning, for example:

- (1) Cardiology:

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- risk stratification (for arrhythmia, coronary diseases, arterial hypertension,. ..)
- dosing beta-blockers
- indication of pace maker of syncopic patient
- prognostic factor of myocardial infarction

5 2) Endocrinology:

- diabetology and risk assessment
- evaluation of dysautonomia

3) Anaesthesiology:

- better dosing of analgesics and hypnotics

10 - monitoring of cardioprotection

- evaluation of syncope risk during rachianaesthesia and epidural anaesthesia

4) Gynaecology and obstetrics:

- foetal monitoring, detection of foetal distress

5) Pain control and therapy:

- 15 - adapting dosage of analgesics
- coupling with PCA (Patient Controlled Analgesia)
- evaluation of pain in babies and children

6) Sleep disease:

- detection of SAS (sleep apnoea)

20 7) Heart transplant:

- detection of rejection
- evaluation of ANS reinnervation of the heart

Although the invention has been described above in the context of the ANS, it will be clearly apparent to the skilled person that the principle of the invention may be applied to different

25 systems than the ANS, in particular different biological systems, provided that the events in

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the original time-varying signal are quasi-periodical and that the corresponding series of time intervals is chaotic, i.e. strongly dependent on initial conditions.

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WHAT IS CLAIMED IS:

1 1. A method for analyzing the state of a first system from a time-varying
2 signal representing a chaotic series of time intervals between quasi-periodical events
3 produced by a second system governed by the first system, the method comprising the steps
4 of:

5 a) extracting envelope information from the time-varying signal,
6 b) constructing a phase space for the time-varying signal,
7 c) extracting information on the relative positions of points corresponding
8 to the time-varying signal in the phase space,
9 d) combining the envelope and the position information,
10 e) based on this combination, providing information on the state of the
11 first system.

1 2. The method according to claim 1, wherein the steps a) to e) are
2 repeated each time a new time interval appears in the time-varying signal.

1 3. The method according to claim 1 or 2, wherein the step a) comprises
2 calculating a first upper envelope of the time-varying signal in the direction of the
3 chronological order and calculating a second upper envelope of the time-varying signal in the
4 direction opposite to the chronological order.

1 4. The method according to any one of claims 1 to 3, wherein the step b)
2 comprises constructing vectors on the basis of values taken by the time-varying signal using a
3 determined dimension for the phase space and a determined time lag.

1 5. The method according to any one of claims 1 to 4, wherein the step c)
2 comprises projecting said points corresponding to the time-varying signal in the phase space
3 onto a lower-dimension space on which an order relation can be established, and calculating
4 distances between the projected points.

1 6. The method according to any one of claims 1 to 4, wherein the step c)
2 comprises projecting said points corresponding to the time-varying signal in the phase space
3 onto a straight line that minimizes the average distance between said points and the straight
4 line, and calculating distances between the projected points.

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1 7. The method according to claim 5 or 6, wherein the step c) further
2 comprises discriminating positive and negative distances in said calculated distances.

1 8. The method according to claim 7, wherein an index representing a
2 probability that a change of the state of the first system occurs at the next event is calculated
3 based on said positive distances or said negative distances.

1 9. The method according to any one of claims 1 to 8, wherein the step e)
2 comprises providing said information on the state of the first system to a display unit.

1 10. The method according to any one of claims 1 to 9, wherein the time-
2 varying signal is a raw signal.

1 11. The method according to any one of claims 1 to 10, wherein the first
2 system is the autonomous nervous system.

1 12. The method according to claim 11, wherein the second system is the
2 cardiac system, the quasi-periodical events are R waves of an electrocardiogram and the
3 chaotic series of time intervals are RR intervals derived from said electrocardiogram.

1 13. The method according to claim 11 or 12, wherein the step d) comprises
2 performing a first combination calculation providing first data representative of the
3 parasympathetic component of the autonomous nervous system and performing a second
4 combination calculation providing second data representative of the sympathetic component
5 of the autonomous nervous system.

1 14. The method according to claim 11 or 12, wherein the step d) comprises
2 performing a first combination calculation providing first data and performing a second
3 combination calculation providing second data, the point-by-point subtraction of either of
4 these first and second data from the other representing a balance between the parasympathetic
5 and the sympathetic component of the ANS.

1 15. The method according to claim 13 or 14, further comprising
2 calculating a first index representative of a complexity exponent of a first curve defined by
3 said first data and/or calculating a second index representative of a complexity exponent of a
4 second curve defined by said second data.

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16. The method according to claim 1 or 2, wherein the first system is the autonomous nervous system, the step a) comprises calculating a first upper envelope ForwHull of the time-varying signal in the direction of the chronological order and calculating a second upper envelope BackwHull of the time-varying signal in the direction opposite to the chronological order, the step c) comprises projecting said points corresponding to the time-varying signal in the phase space onto a lower-dimension space on which an order relation can be established, calculating distances between the projected points and discriminating positive and negative distances in said calculated distances, and the step d) comprises performing the following two combination calculations:

$$\underline{Coeffinc}_1 = B + (A - AA - 5B + AAB) \cdot \underline{Cine} - B \cdot \underline{Cdec}$$

$$\underline{Coeffdec}_1 = B - B \cdot \underline{Cine} + (AA - AAB - B) \cdot \underline{Cdec}$$

$$\underline{ANSigram}_1 = 1 - \frac{2 \cdot \text{normcoeff}}{3} \cdot (\underline{Coeffinc}_1 \cdot \underline{ForwHull} + \underline{Coeffdec}_1 \cdot \underline{BackwHull})$$

and

$$\underline{Coeffinc}_2 = \frac{B}{3} + 4(1 - B) \cdot (1 - A) \cdot \underline{Cine}$$

$$\underline{Coeffdec}_2 = \frac{B}{3} + A(1 - B) \cdot A \cdot \underline{Cdec}$$

$$\underline{ANSigram}_2 = 1 - \frac{2 \cdot \text{normcoeff}}{3} \cdot (\underline{Coeffinc}_2 \cdot \underline{ForwHull} + \underline{Coeffdec}_2 \cdot \underline{BackwHull})$$

where A and B are predetermined constants, normcoeff is a normalization coefficient, and Cine and Cdec are vectors representing respectively said positive and negative distances, and wherein said information provided in the step e) comprises the vectors ANSigram₁ and ANSigram₂.

17. The method according to claim 16, wherein the step d) further comprises calculating the following two indices:

$$\underline{ANSindex}_1 = \text{Floor} \left[\left(6 + \frac{9375}{12} \cdot \left(\frac{\log(\underline{ANSlength}_1)}{\log \sqrt{\text{range}_1^2 + N^2}} - 1 \right) \right) \cdot (\sqrt{5} + 1) \right]$$

$$\underline{ANSindex}_2 = \text{Floor} \left[\left(6 + \frac{1875}{12} \cdot \left(\frac{\log(\underline{ANSlength}_2)}{\log \sqrt{\text{ranged} + N^2}} - 1.045 \right) \right) \cdot (\sqrt{5} + 1) \right]$$

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5 where Floor designates the integer part, which returns zero if the argument is
6 negative, ANSlength₁ and ANSlength₂ respectively designate the length of a first curve
7 defined by the vector ANSigram₁ and the length of a second curve defined by the vector
8 ANSigram₂, range₁ designates the difference between the last value and the first value of the
9 first curve, range₂ designates the difference between the last value and the first value of the
10 second curve, and N designates a predetermined number equal to the dimension of the
11 vectors ANSigram₁ and ANSigram₂.

1 18. A computer program for, when implanted in a processor, analyzing the
2 state of a first system from a time-varying signal representing a chaotic series of time
3 intervals between quasi-periodical events produced by a second system governed by the first
4 system, comprising instruction codes for performing the method according to any one of
5 claims 1 to 17.

1 19. An apparatus for analyzing the state of a first system from a time-
2 varying signal representing a chaotic series of time intervals between quasi-periodical events
3 produced by a second system governed by the first system, comprising processing means
4 programmed to perform the method according to any one of claims 1 to 17.

1 20. An apparatus for analyzing the state of a first system from a time-
2 varying signal representing a chaotic series of time intervals between quasi-periodical events
3 produced by a second system governed by the first system, the apparatus comprising:
4 means for extracting envelope information from the time-varying signal,
5 means for constructing a phase space for the time-varying signal,
6 means for extracting information on the relative positions of points
7 corresponding to the time-varying signal in the phase space,
8 means for combining the envelope and the position information, and
9 means for providing information on the state of the first system based on this
10 combination.

1 21. The apparatus according to claim 20, further comprising means for
2 repeating the envelope information extracting, phase space constructing, position information
3 extracting, information combining and information providing steps each time a new time
4 interval appears in the time-varying signal.

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1 22. The apparatus according to claim 20 or 21, wherein said means for
2 extracting envelope information comprises means for calculating a first upper envelope of the
3 time-varying signal in the direction of the chronological order and means for calculating a
4 second upper envelope of the time-varying signal in the direction opposite to the
5 chronological order.

1 23. The apparatus according to any one of claims 20 to 22, wherein said
2 means for constructing the phase space comprises means for constructing vectors on the basis
3 of values taken by the time-varying signal using a determined dimension for the phase space
4 and a determined time lag.

1 24. The apparatus according to any one of claims 20 to 23, wherein said
2 means for extracting position information comprises means for projecting said points
3 corresponding to the time-varying signal in the phase space onto a lower-dimension space on
4 which an order relation can be established, and means for calculating distances between the
5 projected points.

1 25. The apparatus according to any one of claims 20 to 23, wherein said
2 means for extracting position information comprises means for projecting said points
3 corresponding to the time-varying signal in the phase space onto a straight line that
4 minimizes the average distance between said points and the straight line, and means for
5 calculating distances between the projected points.

1 26. The apparatus according to claim 24 or 25, wherein said means for
2 extracting position information further comprises means for discriminating positive and
3 negative distances in said calculated distances.

1 27. The apparatus according to claim 26, further comprising means for
2 calculating an index representing a probability that a change of the state of the first system
3 occurs at the next event based on said positive distances or said negative distances.

1 28. The apparatus according to any one of claims 20 to 27, wherein said
2 means for providing information comprises a display unit for displaying said information on
3 the state of the first system.

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1 29. The apparatus according to any one of claims 20 to 28, wherein the
2 time-varying signal is a raw signal.

1 30. The apparatus according to any one of claims 20 to 29, wherein the
2 first system is the autonomous nervous system.

1 31. The apparatus according to claim 30, wherein the second system is the
2 cardiac system, the quasi-periodical events are R waves of an electrocardiogram and the
3 chaotic series of time intervals are RR intervals derived from said electrocardiogram.

1 32. The apparatus according to claim 30 or 31, wherein said combining
2 means comprises means for performing a first combination calculation providing first data
3 representative of the parasympathetic component of the autonomous nervous system and
4 means for performing a second combination calculation providing second data representative
5 of the sympathetic component of the autonomous nervous system.

1 33. The apparatus according to claim 30 or 31, wherein said combining
2 means comprises means for performing a first combination calculation providing first data
3 and means for performing a second combination calculation providing second data, the point-
4 by-point subtraction of either of these first and second data from the other representing a
5 balance between the parasympathetic and the sympathetic component of the ANS.

1 34. The apparatus according to claim 32 or 33, further comprising means
2 for calculating a first index representative of a complexity exponent of a first curve defined
3 by said first data and/or means for calculating a second index representative of a complexity
4 exponent of a second curve defined by said second data.

1 35. The apparatus according to claim 20 or 21, wherein the first system is
2 the autonomous nervous system, the envelope information extracting means comprises means
3 for calculating a first upper envelope ForwHull of the time-varying signal in the direction of
4 the chronological order and means for calculating a second upper envelope BackwHull of the
5 time-varying signal in the direction opposite to the chronological order, the position
6 information extracting means comprises means for projecting said points corresponding to
7 the time-varying signal in the phase space onto a lower-dimension space on which an order
8 relation can be established, means for calculating distances between the projected points and

APPENDIX 1

means for discriminating positive and negative distances in said calculated distances, and the combining means comprises means for performing the following two combination calculations:

$$\underline{Coeffinc}_1 = \beta + (4 - 4A - 5B + AAB) \cdot \underline{Cinc} - B \cdot \underline{Cdec}$$

$$\underline{Coeffdec}_1 = B - B \cdot \underline{Cinc} + (4A - AAB - B) \cdot \underline{Cdec}$$

$$\underline{ANSigram}^1 = 1 - \frac{2 \cdot \underline{normcoeff} \cdot (\underline{Coeffinc}_1 \cdot \underline{pnrwHull} + \underline{Coeffdec}_1 \cdot \underline{BackwHull})}{3}$$

and

$$\underline{Coeffinc}_2 = \frac{B}{3} + 4(1 - B) \cdot (1 - A) \cdot \underline{Cinc}$$

$$\underline{Coeffdec}_2 = \frac{B}{3} + 4(1 - B) \cdot A \cdot \underline{Cdec}$$

$$\underline{ANSigram}_2 = 1 - \frac{2 \cdot \underline{normcoeff} \cdot (\underline{Coeffinc}_2 \cdot \underline{pnrwHull} + \underline{Coeffdec}_2 \cdot \underline{BackwHull})}{3}$$

where A and B are predetermined constants, normcoeff is a normalization coefficient, and Cinc and Cdec are vectors representing respectively said positive and negative distances, and wherein said information provided in the step e) comprises the vectors ANSigram₁ and ANSigram₂.

36. The apparatus according to claim 35, wherein the combining means further comprises means for calculating the following two indices:

$$\underline{ANSindex}_1 = \text{Floor} \left[\left(6 + \frac{9375}{12} \cdot \left(\frac{\log(\underline{ANSlength}_1)}{\log \sqrt{\text{range}_1^2 + N^2}} - 1 \right) \right) \cdot (\sqrt{5} + 1) \right]$$

$$\underline{ANSindex}_2 = \text{Floor} \left[\left(6 + \frac{1875}{12} \cdot \left(\frac{\log(\underline{ANSlength}_2)}{\log \sqrt{\text{range}_2^2 + N^2}} - 1.045 \right) \right) \cdot (\sqrt{5} + 1) \right]$$

where Floor designates the integer part, which returns zero if the argument is negative, ANSlength₁ and ANSlength₂ respectively designate the length of a first curve defined by the vector ANSigram₁ and the length of a second curve defined by the vector ANSigram₂, range₁ designates the difference between the last value and the first value of the first curve, range₂ designates the difference between the last value and the first value of the second curve, and N designates a predetermined number equal to the dimension of the vectors ANSigram₁ and ANSigram₂.

APPENDIX 1

- 1 37. The apparatus according to any one of claims 19 to 36, further
2 comprising means for acquiring said quasi-periodical events on a patient.

EXTRACTING CAUSAL INFORMATION FROM A CHAOTIC TIME SERIES

ABSTRACT OF THE DISCLOSURE

A method for analyzing the state of a first system, such as the autonomous nervous system, from a time-varying signal representing a chaotic series of time intervals between quasi-periodical events produced by a second system, such as the cardiac system, governed by the first system, comprises the steps of extracting envelope information from the time-varying signal (S4), constructing a phase space for the time-varying signal (S5), extracting information on the relative positions of points corresponding to the time-varying signal in the phase space (S6, S7), combining the envelope and the position information (S10) and, based on this combination, providing information on the state of the first system (S13).

65493330V.1

Fig.1

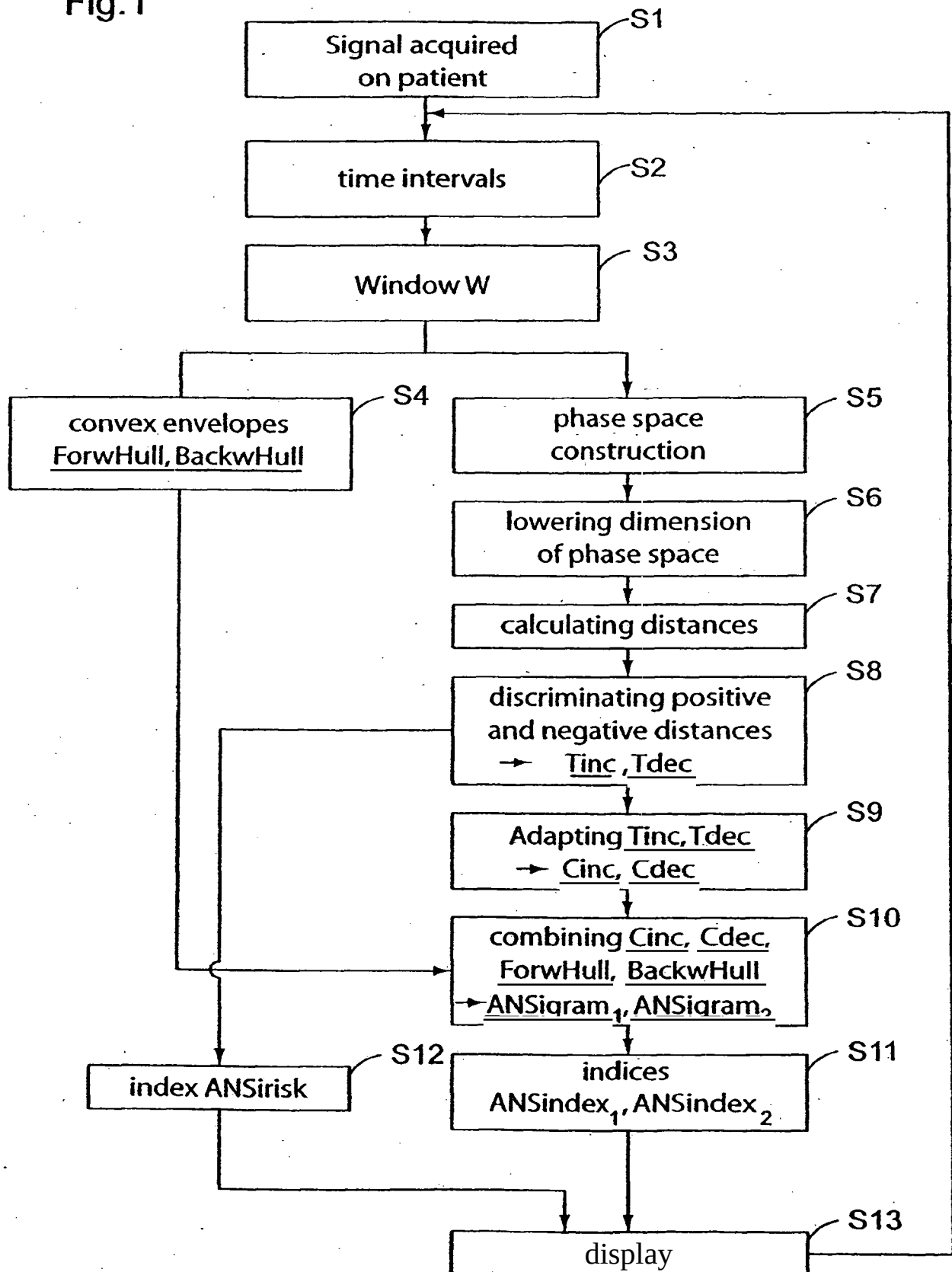


Fig.2

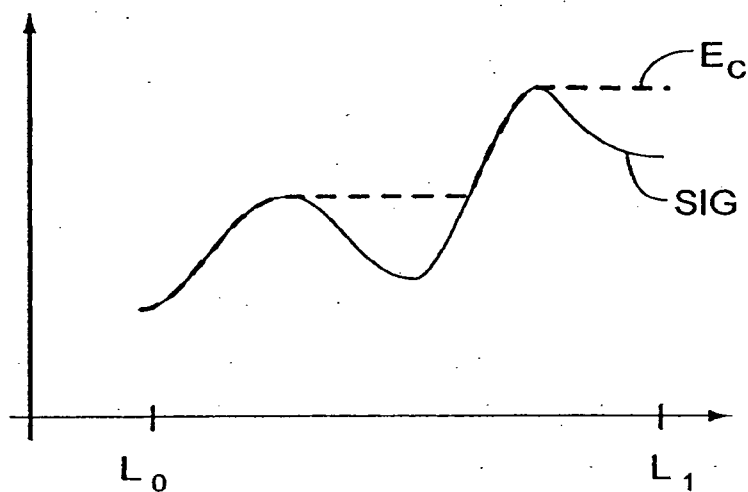


Fig.3

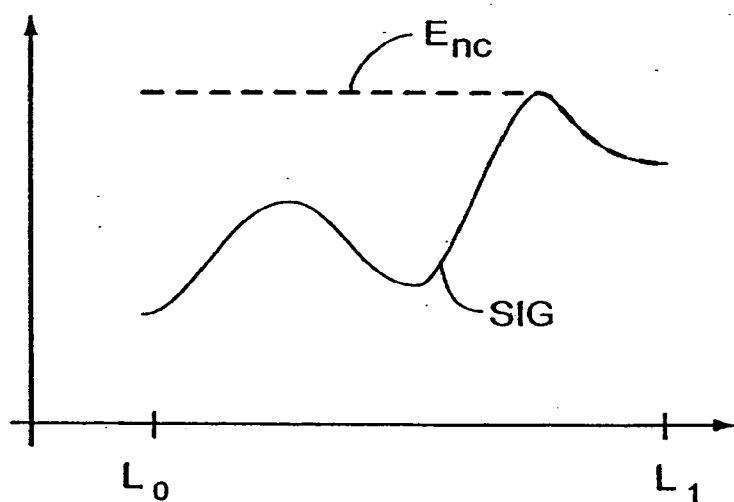


Fig.4

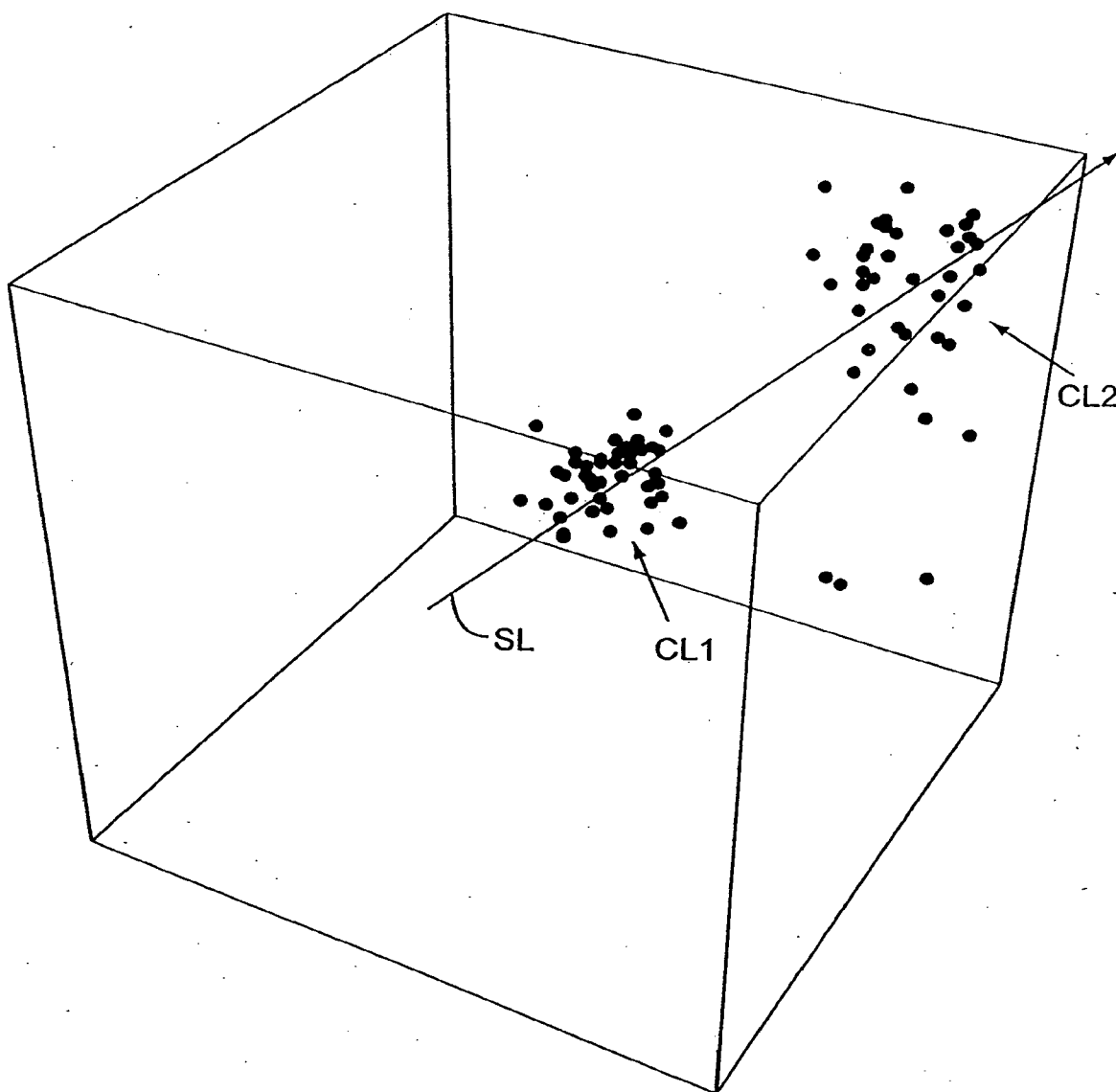


Fig. 5

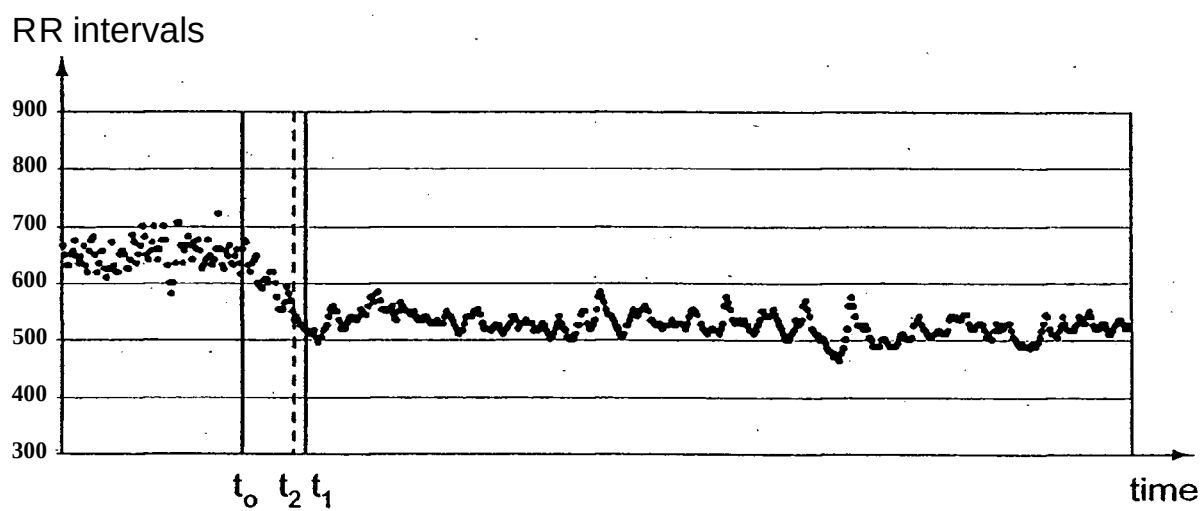


Fig. 6

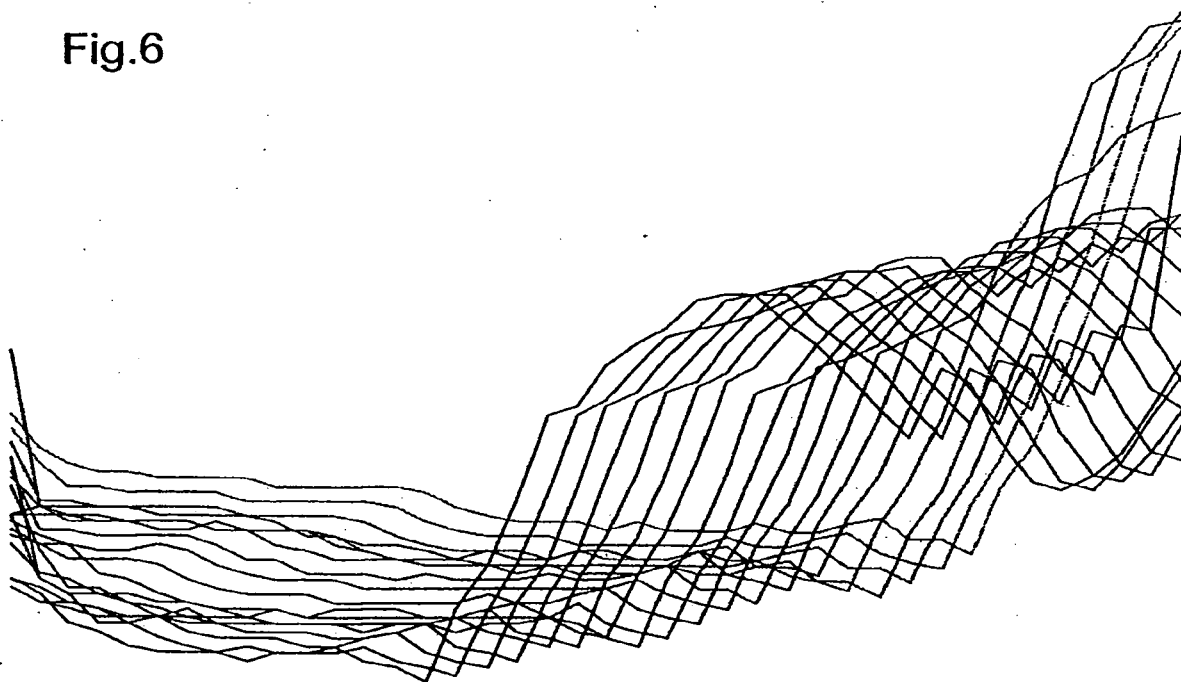


Fig.7

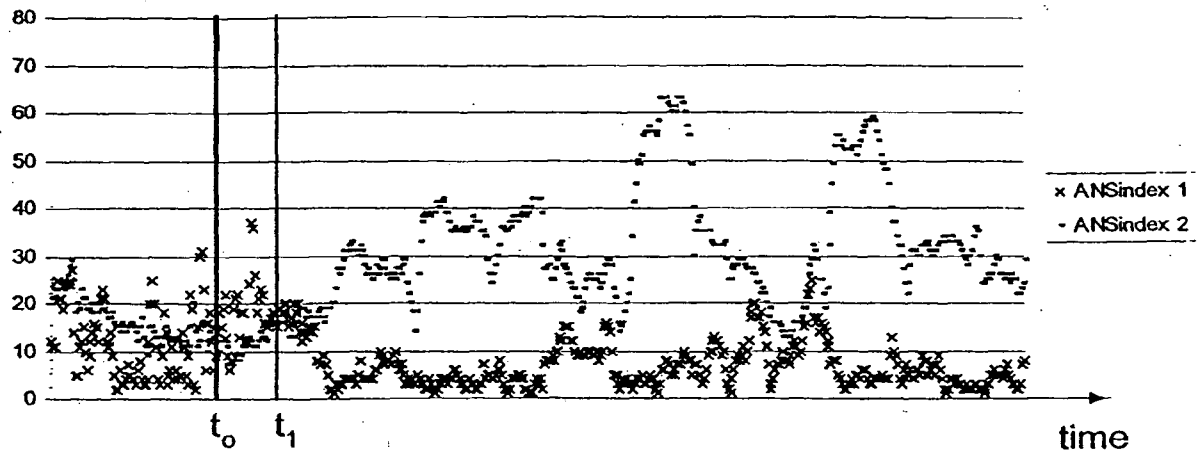


Fig.8

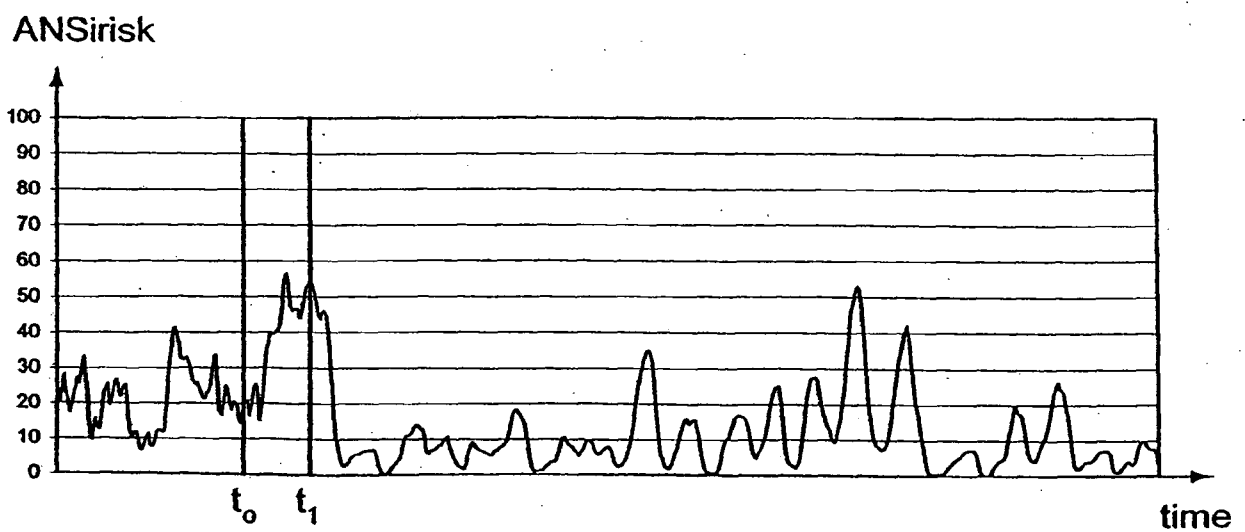
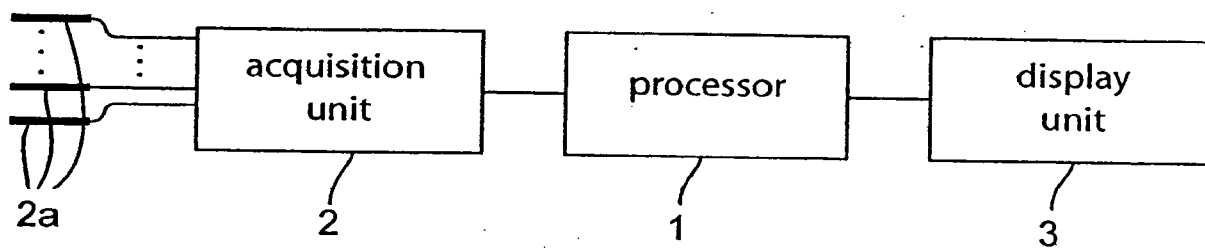


Fig.9



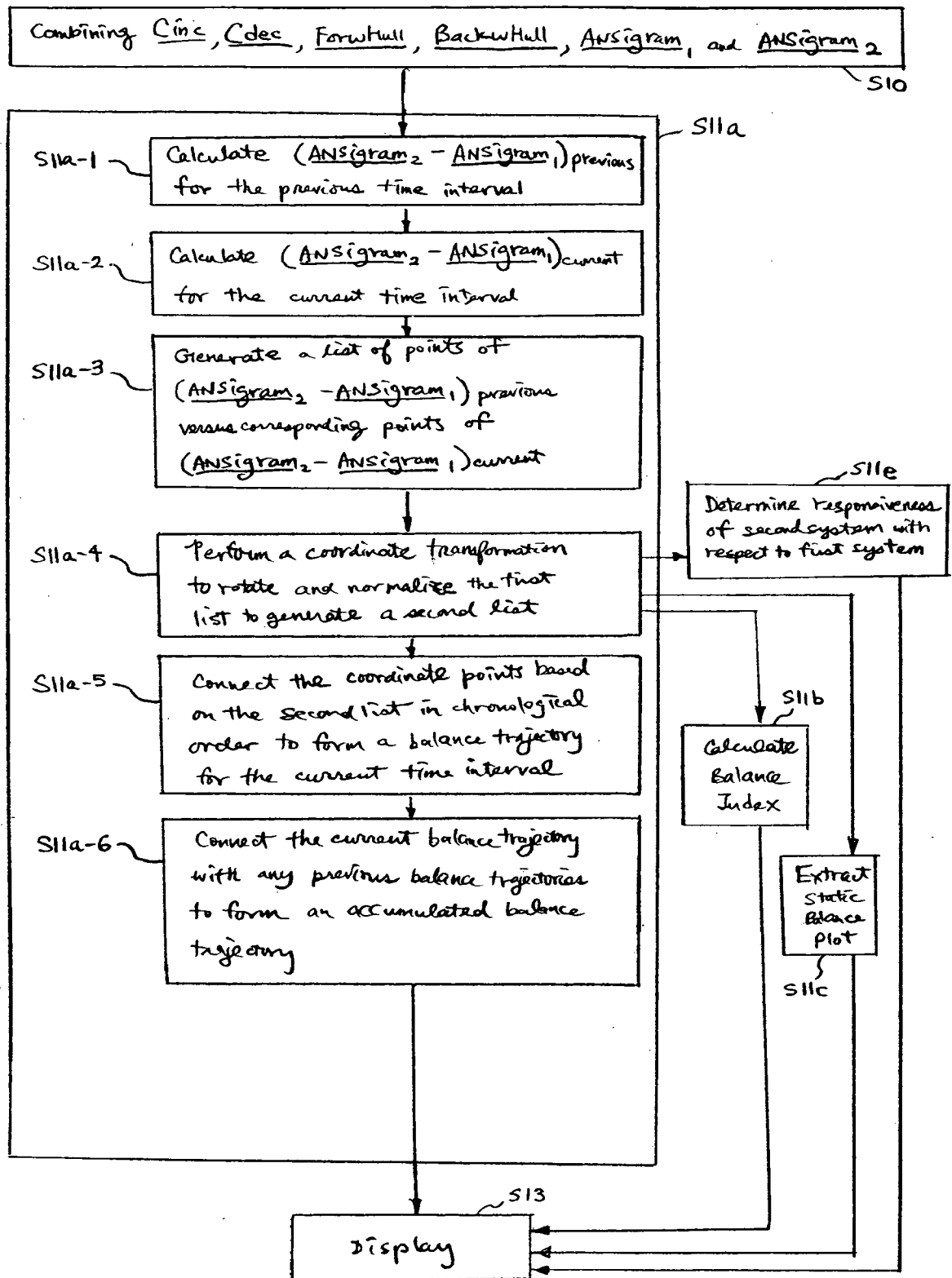


FIG. 10

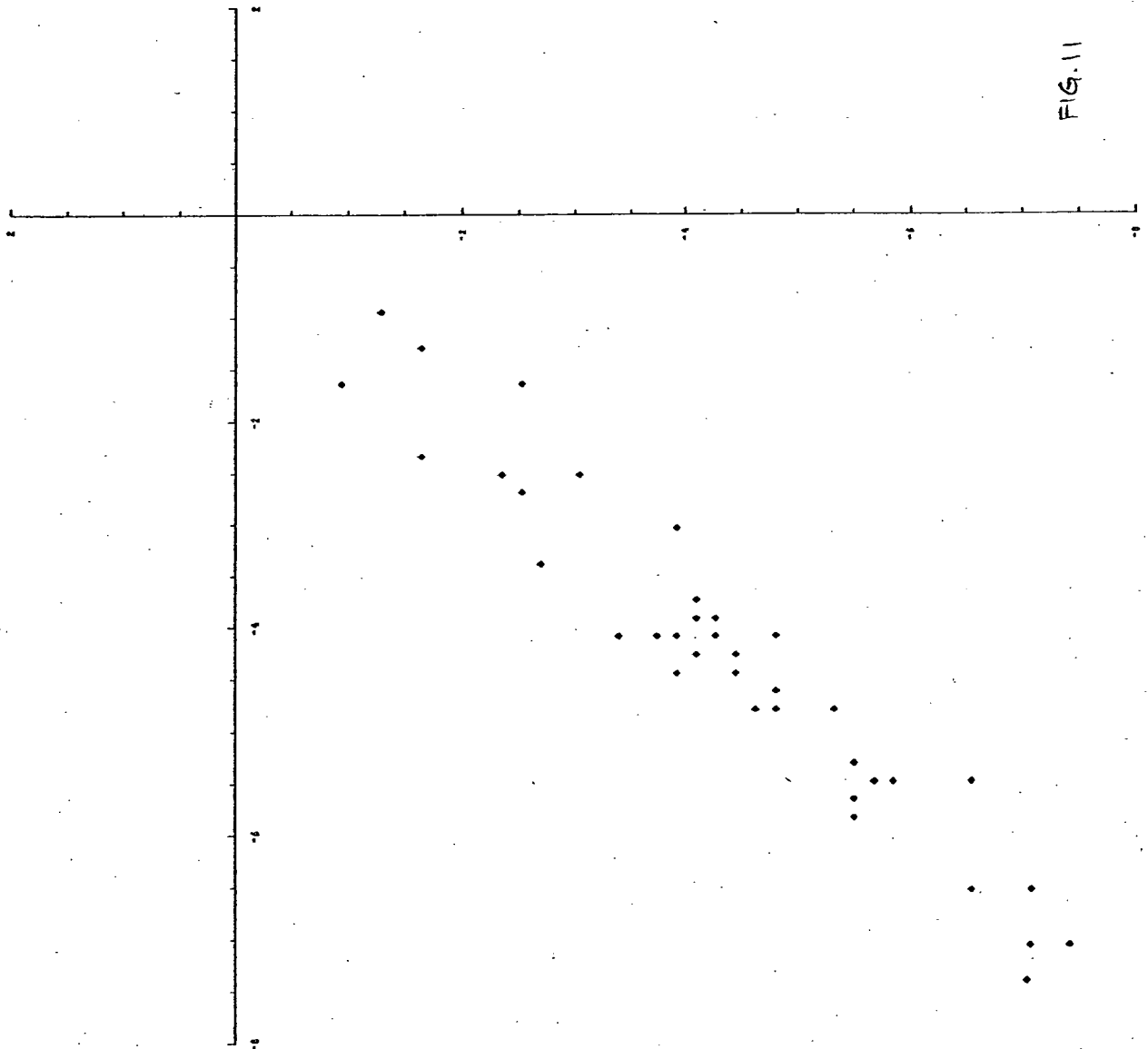




Fig. 12

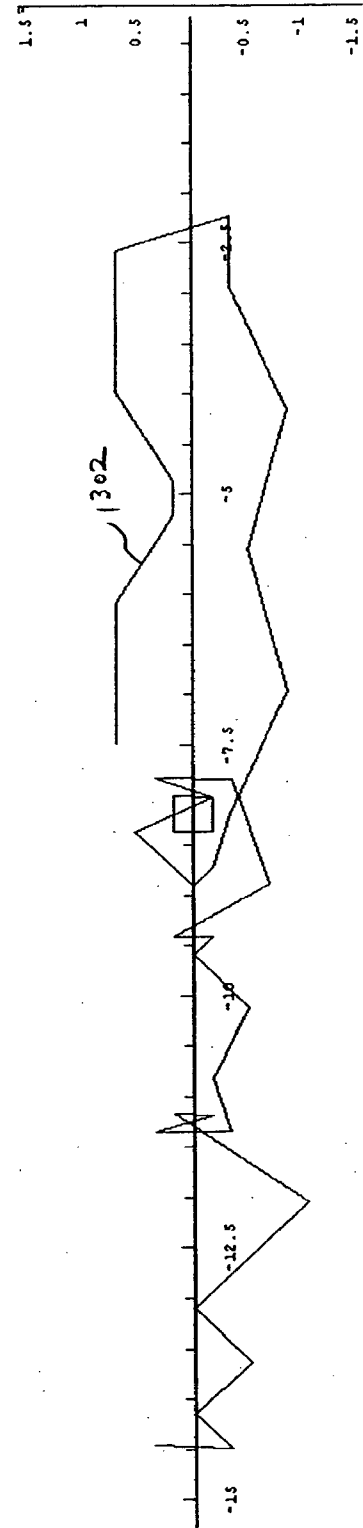
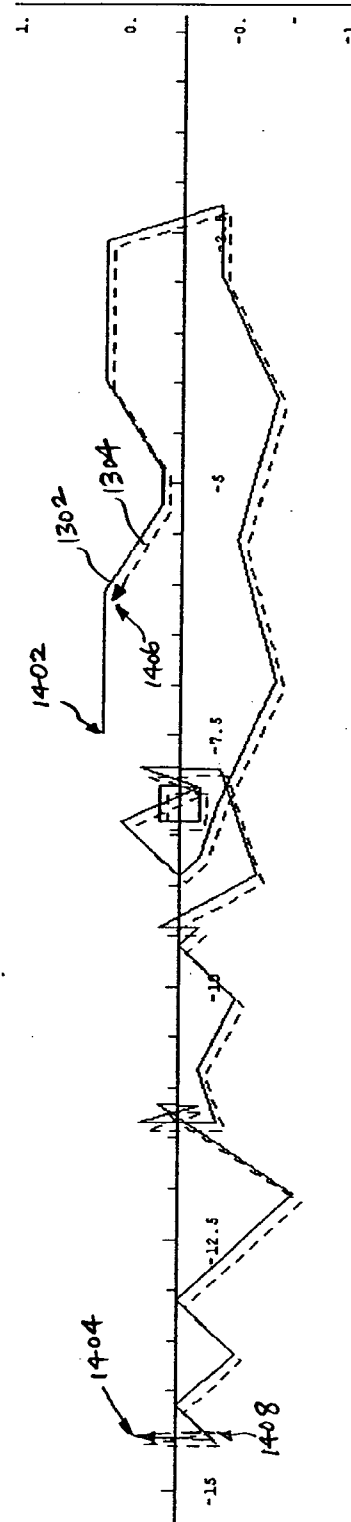
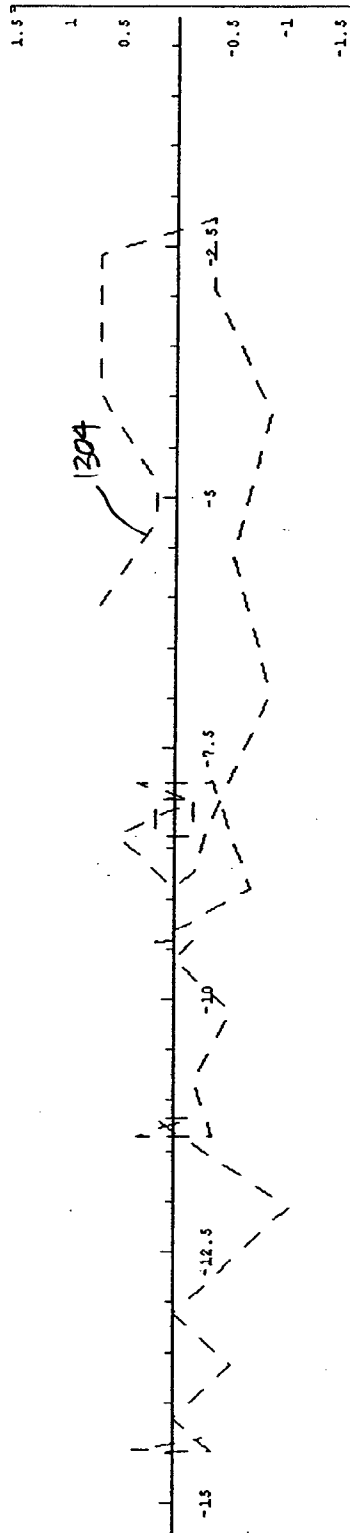


Fig. 13a



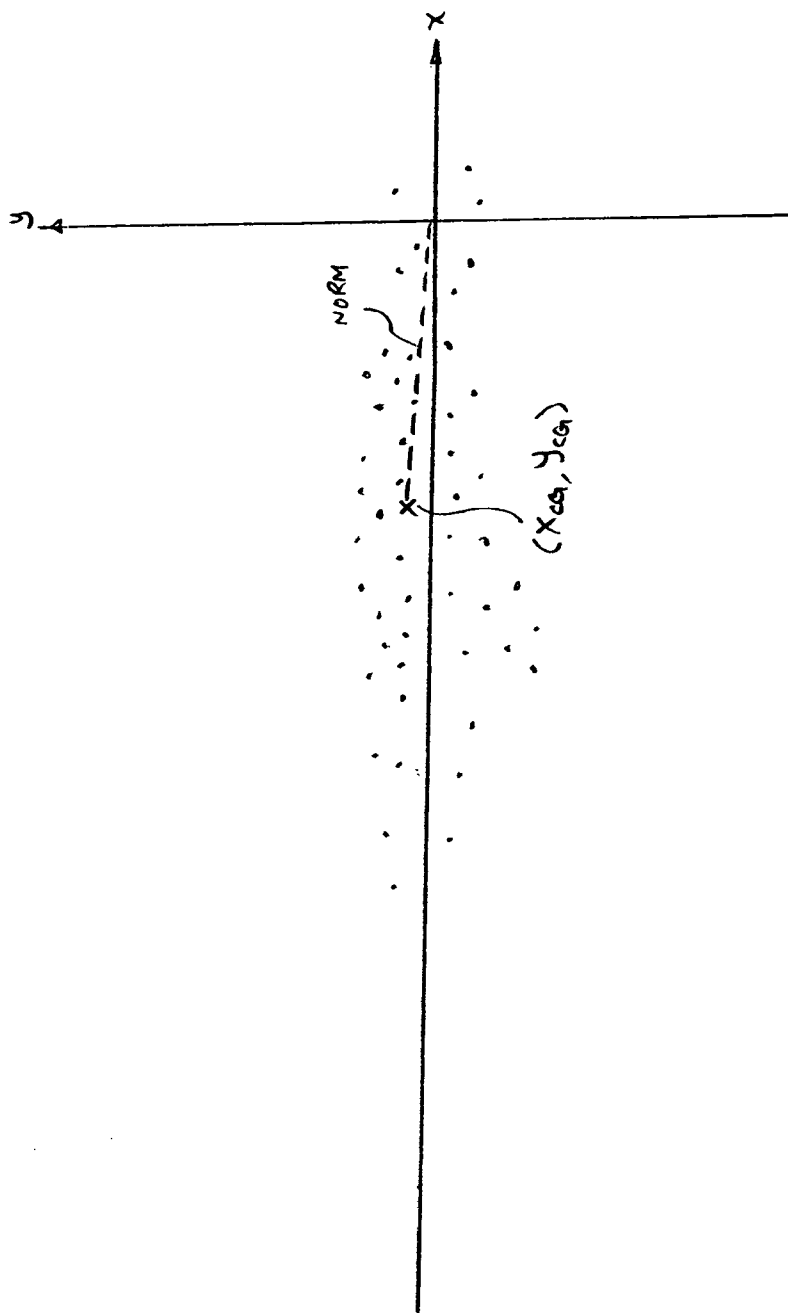


FIG. 15



FIG. 16

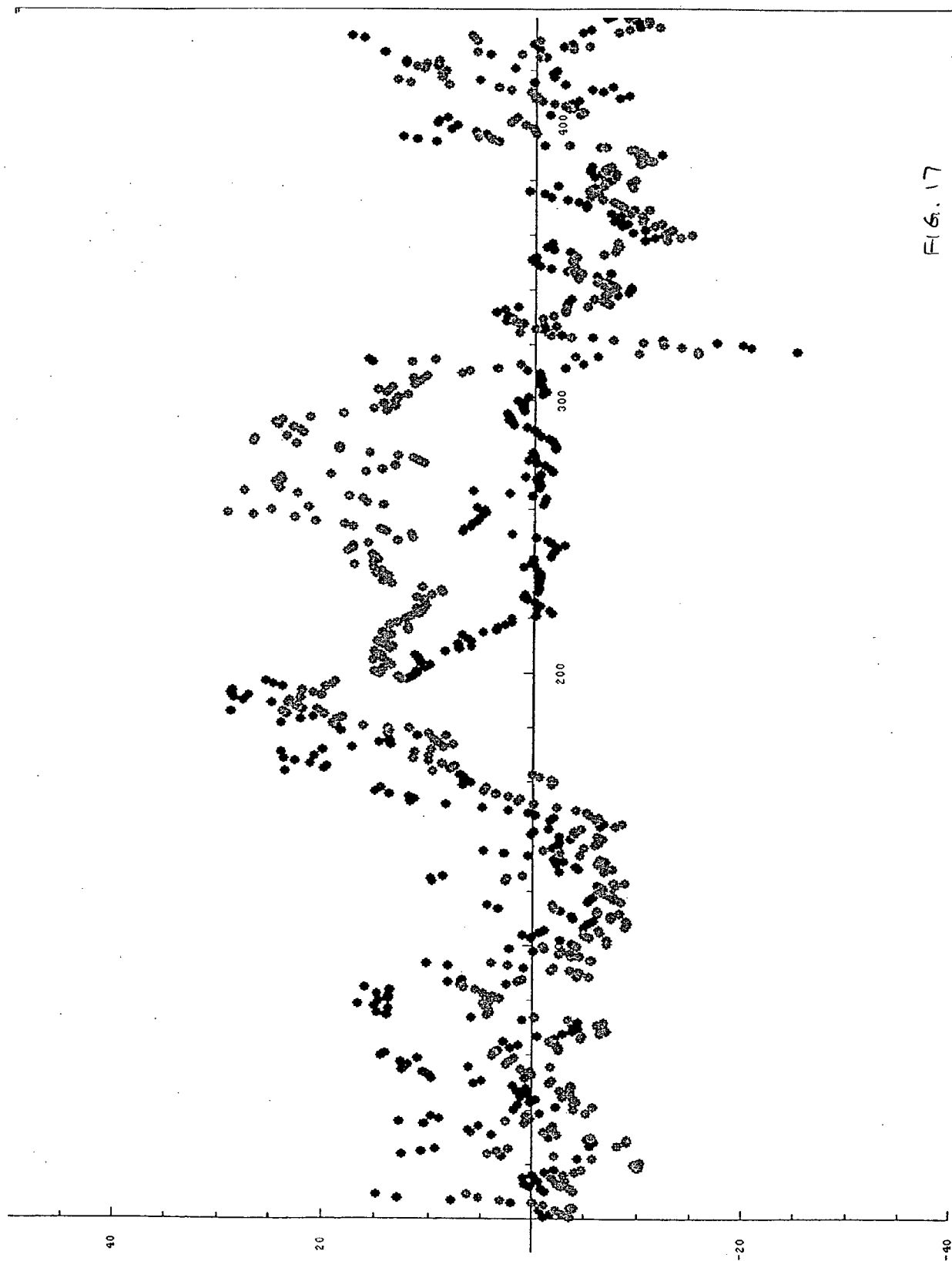
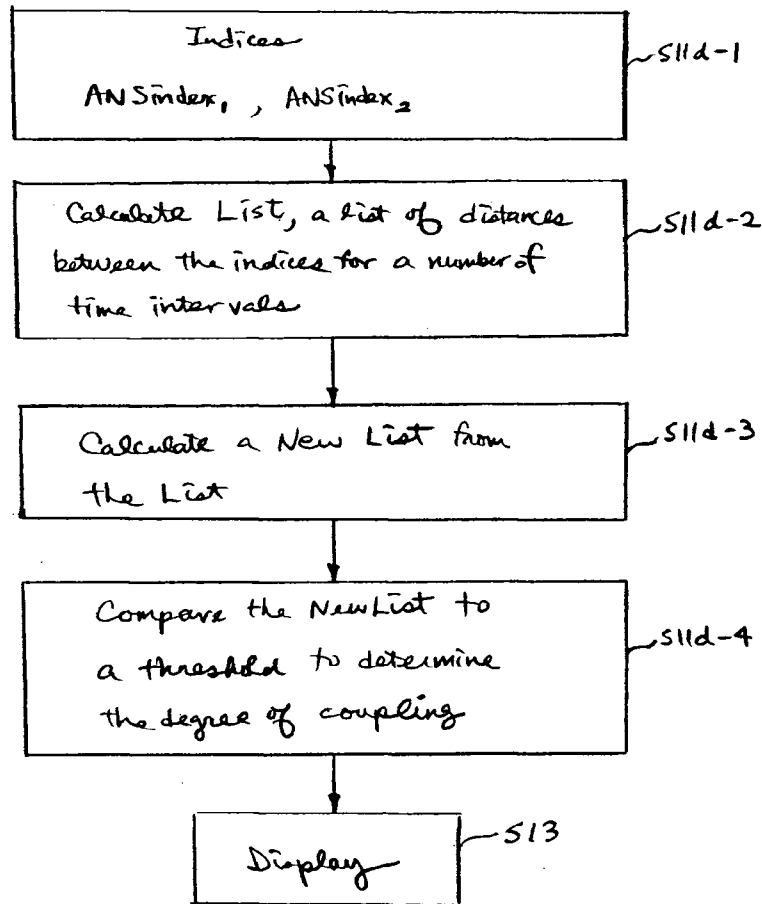


FIG. 17



F(6r, 1&

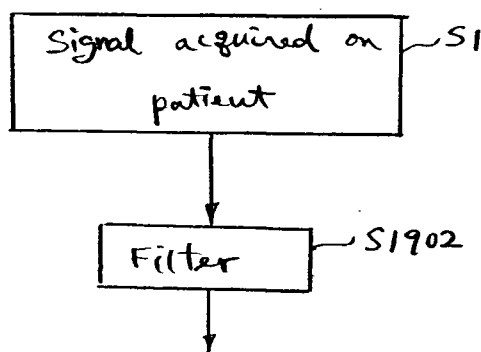


FIG. 19

WHAT IS CLAIMED IS:

- 1 1. A method of analyzing a degree of an autonomic dysfunction of an
2 autonomic nervous system, the method comprising:
3 measuring an autonomic nervous system condition;
4 calculating a root of a sum of values, wherein one or more of the values is equal
5 to a sum of difference values raised to an exponent, wherein the difference values are each equal
6 to a difference of a first index value and a second index value, and wherein the first and second
7 index values are each calculated based on the autonomic nervous system condition; and
8 displaying, via a display unit, a representation of the calculated root.
- 1 2. The method of claim 1, wherein the difference values belong to a subset of
2 a set of difference values, and wherein the subset comprises a plurality of difference values of
3 the set which are sequential when the set of difference values is sorted by value.
- 1 3. The method of claim 2, wherein the set comprises four subsets.
- 1 4. The method of claim 2 or 3, wherein the boundaries between subsets are
2 defined based on a second derivative of the set.
- 1 5. The method of any of claims 1-4, wherein the exponent is the inverse of
2 the root.
- 1 6. The method of any of claims 1-5, wherein the root is a fourth root.
- 1 7. The method of any of claims 1-6, wherein measuring the autonomic
2 nervous system condition comprises measuring a heart rate over time.
- 3 8. The method of any of claims 1-7, wherein the first and second index
4 values are:

$$ANSindex^{\wedge} = Floor \left[\left(6 + \frac{9375}{1^2} \cdot \left(\frac{\log(ANSlength,)}{\{\log \sqrt{range_1^2 + N^2}\}} - 1 \right) \right) \cdot (\sqrt{5} + 1) \right], \text{ and}$$

$$ANSindex_2 = Floor \left[\left(6 + \frac{1875}{12} \cdot \left(\frac{\log\{ANSlength_2\}}{\log \sqrt{ranged + N^2}} - 1.045 \right) \right) \cdot (\sqrt{5} + 1) \right]$$

wherein Floor designates the integer part, which returns zero if the argument is negative, ANSlength₁ and ANSlength₂ respectively designate the length of a first curve defined by the vector ANSigram₁ and the length of a second curve defined by the vector ANSigram₂, range₁ designates the difference between the last value and the first value of the first curve, range₂ designates the difference between the last value and the first value of the second curve, and N designates a predetermined number equal to the dimension of the vectors ANSigram₁ and ANSigram₂,

wherein:

$$\underline{ANSigram_1} = 1 - \frac{2 \cdot \text{normcoeff}}{3} \cdot (\underline{Coeffinc_1} \cdot \underline{ForwHull} + \underline{Coeffdec_1} \cdot \underline{BackwHull})$$

$$\underline{ANSigram_2} = 1 - \frac{2 \cdot \text{normcoeff}}{3} \cdot (\underline{Coeffinc_2} \cdot \underline{ForwHull} + \underline{Coeffdec_2} \cdot \underline{BackwHull}),$$

wherein:

ForwHull is a first upper envelope of the time-varying signal in the direction of the chronological order,

BackwHull is a second upper envelope of the time-varying signal in the direction opposite to the chronological order,

$$\underline{Coeffinc_1} = B + (4 - AA - 5B + 4AB) \cdot \underline{Cine} - B \cdot \underline{Cdec},$$

$$\underline{Coeffdec_1} = B - B \cdot \underline{Cinc} + (4A - 4AB - B) \cdot \underline{Cdec},$$

$$\underline{Coeffinc_2} = \frac{B}{3} + 4(1 - \beta) \cdot (1 - A) \cdot \underline{Cine}, \text{ and}$$

$$\underline{Coeffdec_2} = \frac{B}{3} + 4(1 - B) \cdot A \cdot \underline{Cdec}, \text{ and}$$

wherein A and B are predetermined constants, normcoeff is a normalization coefficient, and Cine and Cdec are vectors respectively representing the positive and negative distances.

9. A system for analyzing a degree of an autonomic dysfunction of an autonomic nervous system, the system comprising:

means for measuring an autonomic nervous system condition;

means for calculating a root of a sum of values, wherein one or more of the values is equal to a sum of difference values raised to an exponent, wherein the difference values are each equal to a difference of a first index value and a second index value, and wherein the first and second index values are each calculated based on the autonomic nervous system condition; and

means for displaying, via a display unit, a representation of the calculated root.

10. The system of claim 9, wherein the difference values belong to a subset of a set of difference values, and wherein the subset comprises a plurality of difference values of the set which are sequential when the set of difference values is sorted by value.

11. The system of claim 10, wherein the set comprises four subsets.

12. The system of claim 10 or 11, wherein the boundaries between subsets are defined based on a second derivative of the set.

13. The system of any of claims 9-12, wherein the exponent is the inverse of the root.

14. The system of any of claims 9-13, wherein the root is a fourth root.

15. The system of any of claims 9-14, wherein measuring the autonomic nervous system condition comprises measuring a heart rate over time.

16. The system of any of claims 9-15, wherein the first and second index values are:

$$ANSindex_1 = \text{Floor} \left[\left(6 + \frac{9375}{12} \cdot \left(\frac{\log(ANSlength_1)}{\log \sqrt{range_1^2 + N^2}} - 1 \right) \right) \cdot (\sqrt{5} + 1) \right], \text{ and}$$

$$ANSindex_2 = \text{Floor} \left[\left(6 + \frac{1875}{12} \cdot \left(\frac{\log(ANSlength_2)}{\log \sqrt{range_2^2 + N^2}} - 1.045 \right) \right) \cdot (\sqrt{5} + 1) \right]$$

wherein Floor designates the integer part, which returns zero if the argument is negative, ANSlength₁ and ANSlength₂ respectively designate the length of a first curve defined by the vector ANSigram₁ and the length of a second curve defined by the vector ANSigram₂, range₁ designates the difference between the last value and the first value of the first curve, range₂ designates the difference between the last value and the first value of the second curve, and N designates a predetermined number equal to the dimension of the vectors ANSigram₁ and ANSigram₂,

wherein:

$$\underline{ANSigram}_1 = 1 - \frac{2 \cdot \underline{normcoe} \cdot \underline{ff}}{3} \cdot (\underline{Coeffinc}_1 \cdot \underline{ForwHull} + \underline{Coeffdec}_1 \cdot \underline{BackwHull})$$

$$\underline{ANSigram}_2 = 1 - \frac{2 \cdot \underline{normcoe} \cdot \underline{ff}}{3} \cdot (\underline{Coeffinc}_2 \cdot \underline{ForwHull} + \underline{Coeffdec}_2 \cdot \underline{BackwHull}),$$

wherein:

ForwHull is a first upper envelope of the time-varying signal in the direction of the chronological order,

BackwHull is a second upper envelope of the time-varying signal in the direction opposite to the chronological order,

$$\underline{Coeffinc}_1 = B + (4 - AA - 5B + AAB) \cdot \underline{Cine} - B \cdot \underline{Cdec},$$

$$\underline{Coeffdec}_1 = B - B \cdot \underline{Cine} + (4A - AAB - B) \cdot \underline{Cdec},$$

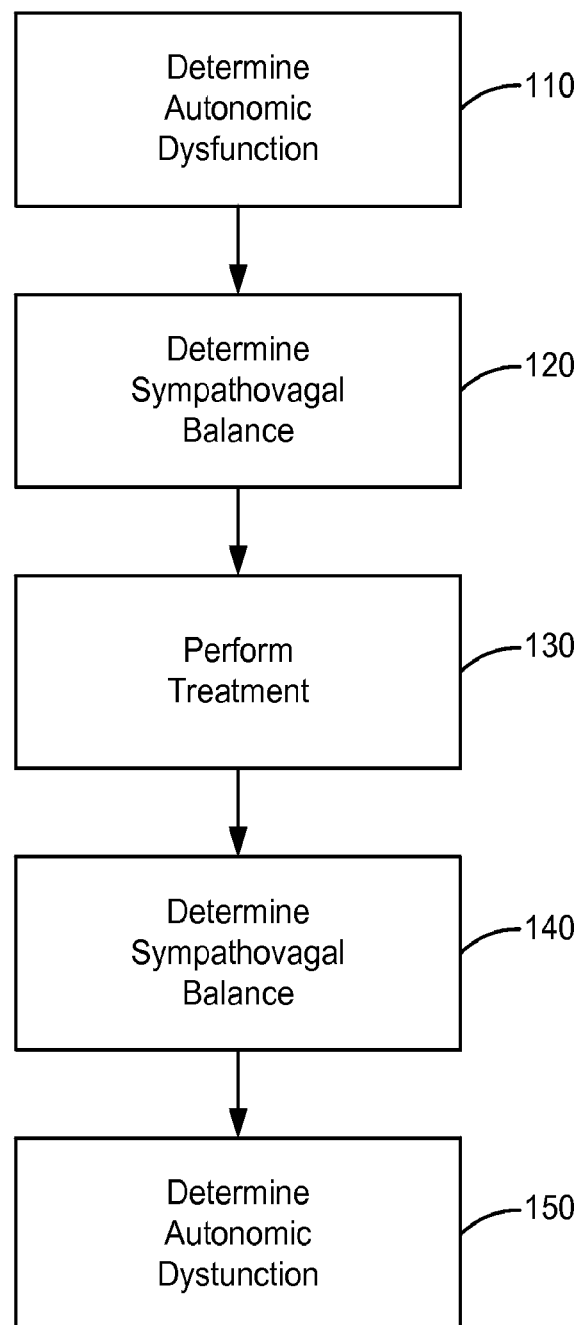
$$\underline{Coeffinc}_2 = \frac{B}{3} + 4(1 - B) \cdot (1 - A) \cdot \underline{Cine}, \text{ and}$$

$$\underline{Coeffdec}_2 = \frac{B}{3} + 4(1 - B) \cdot A \cdot \underline{Cdec}, \text{ and}$$

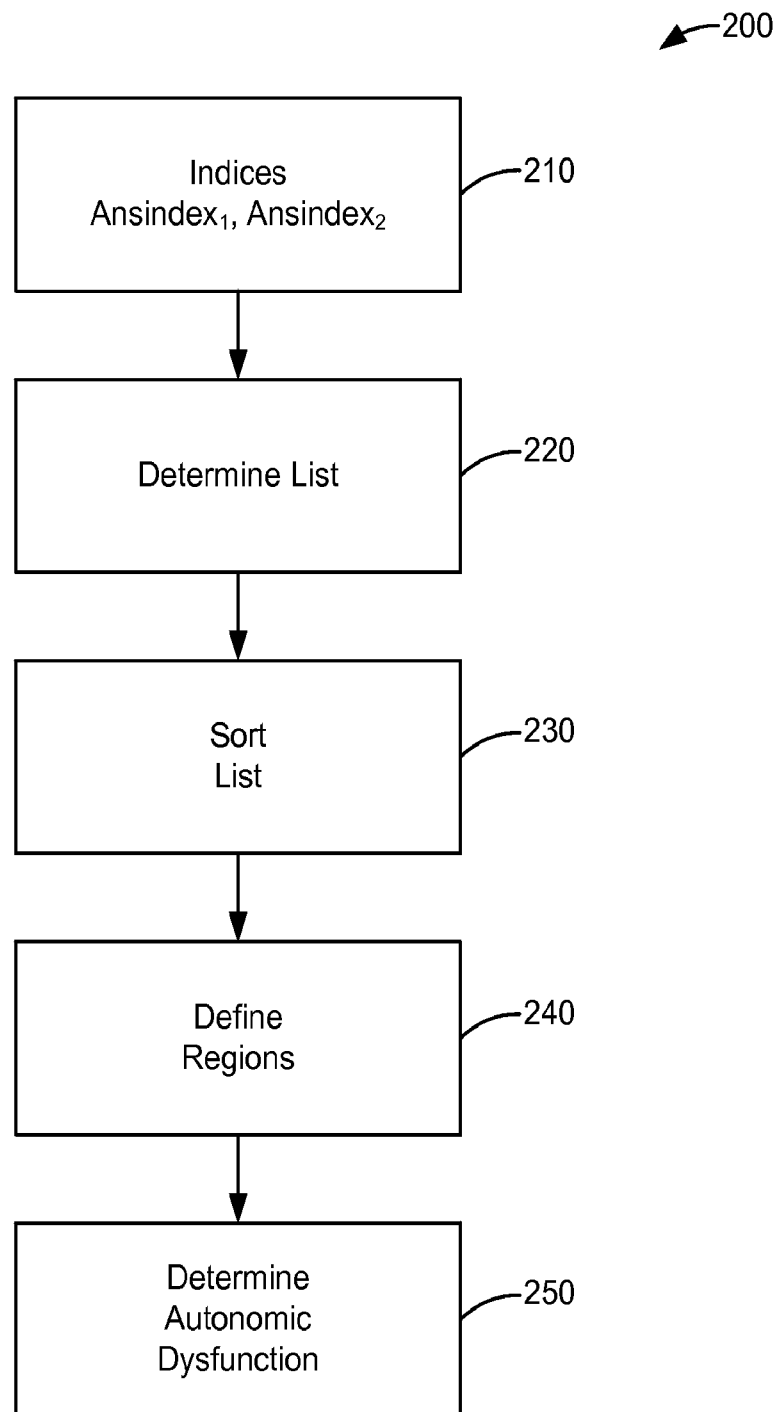
wherein A and B are predetermined constants, normcoeff is a normalization coefficient, and Cine and Cdec are vectors respectively representing the positive and negative distances.

1/4

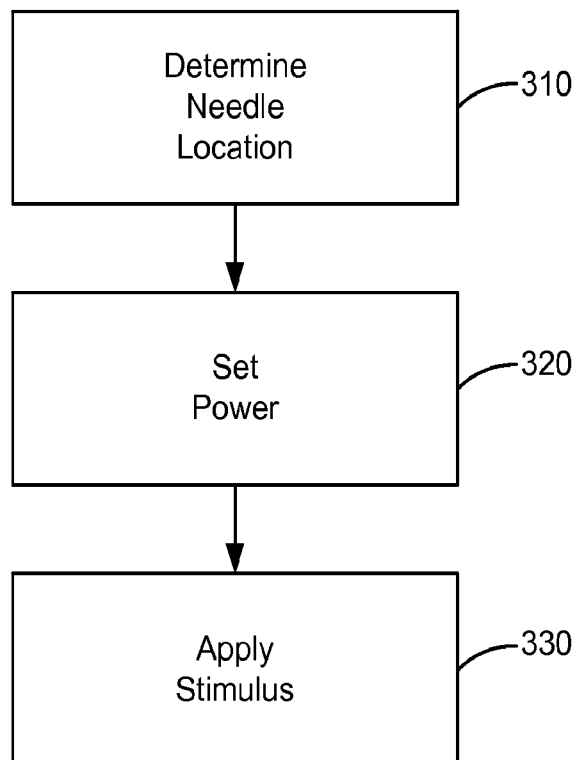
100

**Figure 1**

2/4

**Figure 2**

300

**Figure 3**

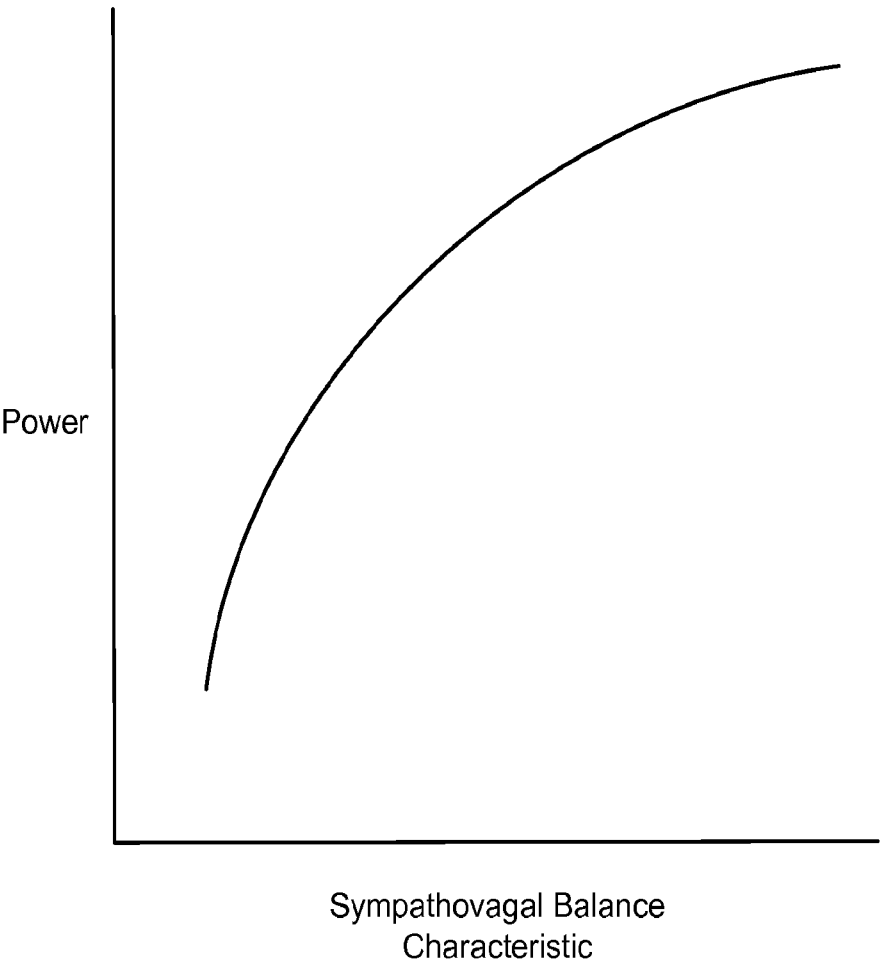


Figure 4

INTERNATIONAL SEARCH REPORT

international application No.

PCT/US 13/45712

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61 B 5/00 (2014.01)

USPC - 600/300

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC(8) - A61B 5/00 (2014.01)

USPC - 600/300

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

600/481, 529, 544-547, 552-559

{Search term limited; see below}

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

PubWest (PGPB, USPT, EPAB, JPAB); Google; PatBase (All);

Search Terms:

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 2007/0219455 A1 (WONG et al.) 20 September 2007 (20.09.2007) Entire document, especially Abstract, para[0014] and para[0072]- para[0079].	1-3, 9-11 ----- 4, 12
Y	US 2009/0292180 A1 (MiROW) 26 November 2009 (26.11.2009) Abstract, para[0051], para[0169]- para[0171], para[0178]- para[0179] and Claims 1-3.	4, 12

☐ Further documents are listed in the continuation of Box C.

* Special categories of cited documents:

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

18 March 2014 (18.03.2014)

Date of mailing of the international search report

09 APR 2014

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-3201

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300

PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

international application No.

PCT/US 13/45712

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 5-8, 13-16
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

专利名称(译)	使用自主神经系统控制的刺激性电疗		
公开(公告)号	EP3007611A4	公开(公告)日	2017-07-05
申请号	EP2013887010	申请日	2013-06-13
[标]申请(专利权)人(译)	迪彦希斯有限公司		
申请(专利权)人(译)	dyansys , Inc.		
当前申请(专利权)人(译)	dyansys , Inc.		
[标]发明人	NAGESHWAR SRINI		
发明人	NAGESHWAR, SRINI		
IPC分类号	A61B5/00		
CPC分类号	A61B5/02405 A61B5/0456 A61B5/4035 A61B5/4821 A61B5/4836 A61B5/4893 A61B5/7264 A61N1/36017 A61N1/36053		
其他公开文献	EP3007611A1		
外部链接	Espacenet		

摘要(译)

公开了用于分析自主神经系统的自主神经功能障碍的状态以用于护理患者的方法和系统。在一些实施例中，该方法包括测量自主神经系统状况，以及计算值之和的根。一个或多个值等于提高到指数的差值之和，并且差值各自等于第一索引值和第二索引值的差。基于自主神经系统条件计算第一和第二指标值。该方法还包括经由显示单元显示所计算的根的代表。