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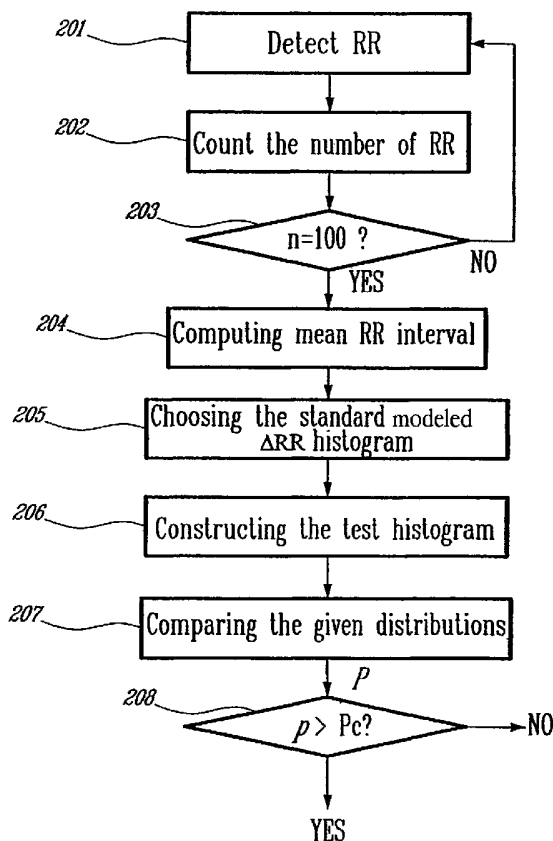
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(54) Title: DETECTION OF CARDIAC ARRHYTHMIA USING MATHEMATICAL REPRESENTATION OF STANDARD Δ RR PROBABILITY DENSITY HISTOGRAMS



(57) Abstract: There are many different serious cardiac arrhythmias. To detect cardiac arrhythmia of a patient, the present invention proposes to detect RR intervals of the patient wherein each RR interval is an interval between two heart beats, and to simulate standard probability density histograms of Δ RRs by means of a suitable probability distribution calculated through at least one mathematical formulae, wherein Δ RR is a difference between two successive RR intervals. Test probability density histograms of Δ RRs of the patient are constructed from the detected RR intervals. Finally, the standard and test histograms are compared to detect whether the patient suffers from cardiac arrhythmia. As non limiting examples, the standard probability density histograms of Δ RRs are modeled by a mathematical equation selected from the group consisting of : the Lorentzian distribution, the Gaussian distribution, the Student's *t*-distribution, and a probability distribution including a linear combination of the Lorentzian and Gaussian distribution.

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DETECTION OF CARDIAC ARRHYTHMIA USING MATHEMATICAL
REPRESENTATION OF STANDARD Δ RR PROBABILITY DENSITY
HISTOGRAMS

BACKGROUND OF THE INVENTION

5 1. FIELD OF THE INVENTION

The present invention relates to a method and a system for detecting cardiac arrhythmias from internally and/or externally detected activity of the heart by means of Δ RR intervals wherein the standard Δ RR probability density
10 histograms are fitted by a mathematical distribution.

2. BRIEF DESCRIPTION OF THE CURRENT TECHNOLOGY

Atrial fibrillation is a common and serious cardiac arrhythmia that is characterized by rapid, irregular atrial activation and is known to be associated with life
15 threatening sequelae such as stroke. The atrial activations are irregularly transmitted through the atrioventricular node leading to a correspondingly irregular sequence of ventricular activations as monitored by the ventricular interbeat (RR) intervals on the surface electrocardiogram
20 (ECG). An RR interval is an interval between two successive heart beats. Clinically, in the surface ECG, atrial fibrillation is diagnosed by absence of P waves (normally associated with the near synchronous activation of the atria) and a rapid irregular ventricular rate. P waves are
25 difficult to determine automatically and irregular baseline activity of the ECG is common in atrial fibrillation.

Although a number of different methods have been proposed to test for atrial fibrillation based on assessment of the RR intervals and/or the surface ECG, the detection of

atrial fibrillation based on this data nevertheless poses substantial problems [Murgatroyd, et al. "Identification of Atrial Fibrillation Episodes in Ambulatory Electrocardiographic Recordings: Validation of a Method for
5 Obtaining Labeled R-R Interval Files," *Pacing and Clinical Electrophysiology*, (1995), pp.1315-1320]. In the following description, the main strategies that have been proposed to assess atrial fibrillation based on knowledge of the RR intervals and/or ECG will be briefly reviewed.

10 Since RR intervals during atrial fibrillation have a larger standard deviation and a more rapid decay of the autocorrelation function, there are proposals that the standard deviation and the autocorrelation function can be used to distinguish atrial fibrillation from sinus rhythm
15 [Bootsma, et al. "Analysis of RR Intervals in Patients with Atrial Fibrillation at Rest and During Exercise," *Circulation*, (1970), pp.783-794]. Since other abnormal rhythms also have a large standard deviation of RR intervals and a rapid decay of the autocorrelation function, these
20 methods are difficult to apply in concrete situations.

Moody and Mark [G. Moody, et al. "A New Method for Detecting Atrial Fibrillation Using R-R Intervals," *Computers in Cardiology*, (1983), pp.227-230] classify RR
25 intervals as short, long or regular. They then construct a Markov model for the probabilities for transitions between RR intervals in each of the three different length classes. Atrial fibrillation data has typical transition probabilities not shared by normal rhythms or other
30 arrhythmia. Although the Markov model has high sensitivity for detecting atrial fibrillation, it tends to have a relatively low predictive value of a positive test.

Pincirolì and Castelli have investigated the morphology of histograms of RR intervals collected during atrial fibrillation and other arrhythmia [F. Pincirolì, et al. "Pre-clinical Experimentation of a Quantitative
5 *Synthesis of the Local Variability in the Original R-R Interval Sequence in the Presence of Arrhythmia*," *Automedica*, (1986), vol.6, pp.295-317. Pincirolì and Castelli, 1986]. They demonstrated that the histograms of the ratio between successive RR intervals show
10 characteristic differences between normal rhythm and atrial fibrillation. The histogram of the ratio between successive RR intervals is symmetrical to the mean value. No quantitative methods were proposed to quantify the symmetry or to use it to develop a quantitative test.

15 Since the baseline of the ECG is irregular during atrial fibrillation, Slocum [J. Slocum, et al. "Computer Detection of Atrial Fibrillation on the Surface
Electrocardiogram," *Computers in Cardiology*, (1987), pp.253-254] has proposed that the regularity of the baseline, as
20 determined by the power spectrum of the residual ECG after subtraction of the baseline of the QRS complexes can be used to detect atrial fibrillation. This method is necessarily sensitive to small amounts of noise that might corrupt the baseline of the ECG.

25 Implantable ventricular and atrial defibrillators are devices that distinguish atrial and ventricular fibrillation from other rhythms. Typically, electrodes in these devices record intracardiac activity directly from the atria and ventricles. The methods that are used to detect
30 atrial fibrillation in these devices cannot be easily applied to recordings that give information about the timing of the QRS complexes (U.S. Pat. No. 6,144,878, issued to

Schroepfel on November 7, 2000; U.S. Pat. No. 6,035,233 issued to Schroepfel on March 7, 2000; U.S. Pat. No. 5,749,900 issued to Schroepfel on May 24, 1998; U.S. Pat. No. 6,064,906 issued to Langberg et al. on May 16, 2000; 5 U.S. Pat. No. 5,772,604 issued to Langberg et al. on June 30, 1998; U.S. Pat. No. 6,061,592 issued to Nigam on May 9, 2000; U.S. Pat. No. 5,951,592 issued to Murphy on September 14, 1999; U.S. Pat. No. 5,941,831 issued to Turcott on August 24, 1999; U.S. Pat. No. 5,591,215 issued 10 to Greenhut et al. on January 7, 1997).

Analysis of a histogram of the interbeat intervals can be used to discriminate between ventricular fibrillation and ventricular tachycardia. By counting the number of beats in predetermined interval classes, an algorithm identifies a 15 given sequence as ventricular fibrillation or ventricular tachycardia (U.S. Pat. No. 5,330,508 issued to Gunderson on July 19, 1994). While the foregoing patent suggests that the invention is of value in detecting and treating atrial fibrillation (column 2, lines 29-31), it does not provide a 20 specific embodiment for detecting and treating atrial fibrillation.

Based on the foregoing review, it is apparent that there is a need for a method and a system for determining whether or not a given recording constitutes atrial 25 fibrillation based on the timing of the QRS complexes as measured from an internal and/or external monitor. Assessment of whether a patient is in atrial fibrillation based on the timing of the QRS complexes would be extremely useful, for example, for assessing the efficacy of specific 30 drugs of a patient fitted with a monitoring device that measures the timing of the QRS complexes.

It was shown previously that atrial fibrillation could be reliably detected and quantitated from the surface electrocardiogram based on the density histograms of the ΔRR collected during atrial fibrillation, where ΔRR is defined
5 as the difference between two successive RR intervals. Using the Kolmogorov-Smirnov test based on ΔRR resulted in high sensitivity and specificity in the MIT-BIH atrial fibrillation database. However, there remains a need to increase the accuracy of detection of atrial fibrillation
10 using the Kolmogorov-Smirnov test based on ΔRR . There is also a need to obtain rapid results that can be achieved by reducing the data storage load and computation time.

SUMMARY OF THE INVENTION

To increase the accuracy of detection and reduce
15 the storage requirements for the standard density histograms and therefore the computational load related to detection of atrial fibrillation or other cardiac arrhythmias, there is provided, in accordance with the present invention a method for detecting cardiac arrhythmia of a patient, comprising:

20 detecting RR intervals of the patient wherein each RR interval is an interval between two heart beats;

constructing standard probability density
histograms of ΔRR s collected during cardiac arrhythmia of a
plurality of subjects, wherein ΔRR is a difference between
25 two successive RR intervals;

modeling the standard probability density
histograms of ΔRR s by means of a suitable probability
distribution calculated through at least one mathematical
formulae;

constructing test probability density histograms of Δ RRs of the patient from the detected RR intervals of this patient; and

comparing the standard modeled histograms and the
5 test histograms to detect whether the patient suffers from cardiac arrhythmia.

The present invention also relates to a system for detecting cardiac arrhythmia such as atrial fibrillation in a patient, comprising:

10 a detector of RR intervals of the patient, wherein each RR interval is an interval between two heart beats;

a standard probability density histogram storage unit in which are stored standard probability density histograms of Δ RRs collected during cardiac arrhythmia of a
15 plurality of subjects, these standard probability density histograms of Δ RRs being modeled by means of a suitable probability distribution calculated through at least one mathematical formulae, and Δ RR being the difference between two successive RR intervals;

20 a test Δ RR histogram calculator supplied with the detected RR intervals from the detector and constructing test histograms of the Δ RRs of the patient; and

a standard and test Δ RR histograms comparator supplied with the standard modeled probability density
25 histograms and test histograms, this comparator comprising a detector of cardiac arrhythmia of the patient responsive to the comparison of the standard and test histograms.

As non limiting examples, the standard probability density histograms of Δ RRs are modeled by a mathematical equation selected from the group consisting of: the Lorentzian distribution, the Gaussian distribution, the Student's *t*-distribution, and a probability distribution comprising a linear combination of the Lorentzian and Gaussian distribution.

It is within the scope of the present invention to apply the above concept to detection of not only atrial fibrillation but also to other cardiac arrhythmias including in particular but not exclusively atrial flutter, multifocal atrial tachycardia, ventricular tachycardia, premature ventricular contractions, etc., as well as to detection of other body phenomenon involving electrical activity.

The foregoing and other objects, advantages and features of the present invention will become more apparent upon reading of the following non restrictive description of illustrative embodiments thereof, given by way of example only with reference to the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

In the appended drawings:

Figure 1 is a time series showing the RR intervals from subject 202 from the MIT-BIH arrhythmia database. The solid line directly under the time series of RR intervals shows the assessment of atrial fibrillation (indicated by AF) or non-atrial fibrillation (indicated by N) as reported in the database. The solid line at the bottom of Figure 1 indicates the assessment of atrial fibrillation, indicated by 1, and non-atrial fibrillation, indicated by 0, based on an algorithm presented herein.

Figure 2 is a flow chart illustrating an illustrative embodiment of the method according to the present invention, for detecting atrial fibrillation based on RR intervals.

5 Figure 3 is a block diagram of an illustrative embodiment of the system according to the present invention for implementing the method of Figure 2, for detecting atrial fibrillation based on RR intervals.

Figure 4 are curves comparing three sets of
10 standard Δ RR probability density (solid line) histograms (mean RR intervals 400-449 ms; 750-799 ms; and 1000-1049 ms) to the Lorentzian distribution (dotted line).

Figure 5 are curves comparing three sets of
15 standard Δ RR probability density (solid line) histograms (mean RR intervals 400-449 ms; 750-799 ms; and 1000-1049 ms) to the Gaussian distribution (dotted line).

Figure 6 are curves comparing three sets of
20 standard Δ RR probability density (solid line) histograms (mean RR intervals 400-449 ms; 750-799 ms; and 1000-1049 ms) to the Student's t -distribution (dotted line).

Figure 7 are curves comparing three sets of
25 standard Δ RR probability density (solid line) histograms (mean RR intervals 400-449 ms; 750-799 ms; and 1000-1049 ms) to a linear combination of the Lorentzian distribution and the Gaussian distribution (dotted line).

Figure 8 illustrates the fidelity (squared error ϵ^2) of curve fitting for the four mathematical representations of probability distributions "vs" empirical

distributions of standard density histograms as a function of mean RR intervals (ms).

Figure 9 is a block diagram of an illustrative embodiment of a test and standard Δ RR histogram comparator
5 forming part of the system of Figure 3.

Figure 10 is a curve illustrating the Kolmogorov-Smirnov (KS) test. A cumulative probability distribution based on patient test data is compared with a standard cumulative probability distribution. D is the greatest
10 distance between two cumulative probability distributions.

Figure 11 shows curves illustrating the Receiver Operating Characteristic curve (ROC) of the Kolmogorov-Smirnov test when applied to the MIT-BIH atrial fibrillation/flutter database using the: (a) Lorentzian
15 distribution; (b) Gaussian distribution; (c) Student's t -distribution; and (d) Combined probability distribution. The respective ROCs are compared to the ROCs derived from the standard density histograms.

Figure 12 shows curves illustrating the receiver
20 operating characteristic curve (ROC) of the Kolmogorov-Smirnov test when applied to the 200 series MIT-BIH arrhythmia database using the: (a) Lorentzian distribution (b) Gaussian distribution (c) Student's t -distribution and (d) Combined probability distribution. The respective ROCs
25 are compared to the ROCs derived from the standard density histograms.

Figure 13 is a curve illustrating the ROC related to the Kolmogorov-Smirnov test using the combined Lorentzian and Gaussian probability distributions and the 200 series of

the MIT-BIH arrhythmia database from which premature ventricular contractions is eliminated.

DETAILED DESCRIPTION OF THE ILLUSTRATIVE EMBODIMENTS,

Although the illustrative embodiments of the present invention will be described in relation to atrial fibrillation, it may be appreciated that the same concepts can be applied to detection of other cardiac arrhythmias including in particular but not exclusively atrial flutter, multifocal atrial tachycardia, ventricular tachycardia, premature ventricular contractions, etc. This concept can also be applied to detection of other body phenomenon involving electrical activity.

Data was obtained from the MIT-BIH atrial fibrillation/flutter database and the MIT-BIH arrhythmia database. The atrial fibrillation database contains 300 atrial fibrillation episodes, sampled at 250 Hz for 10 hours from Holter tapes of 25 subjects. Arrhythmia detection was carried out by trained observers and was confirmed by an independent evaluation. The timing of each QRS complex was determined by an automatic detector. The MIT-BIH arrhythmia database includes two categories (the 100 series and the 200 series) and contains 48 subjects. The 100 series includes normal sinus rhythm, paced rhythm, bigeminy, trigeminy and supraventricular tachycardia, but it does not contain atrial fibrillation. The 200 series includes eight atrial fibrillation subjects as well as atrial bigeminy, atrial flutter, supraventricular tachyarrhythmia, ventricular flutter and ventricular tachycardia.

Figure 1 is a typical time series of RR intervals from a patient with atrial fibrillation. Immediately under the recording is a solid marker line 101. When atrial

fibrillation occurs this marker line 101 is set to AF; otherwise it is set to N, which indicates a rhythm that is not atrial fibrillation. The graph of Figure 1 also shows a lower solid line 102 indicating the assessment of atrial
5 fibrillation, indicated by 1, and non-atrial fibrillation, indicated by 0, based on an algorithm according to the present invention. At the onset of atrial fibrillation, the rhythm dramatically changes to irregular with large fluctuation. In paroxysmal atrial fibrillation there is
10 sudden starting and stopping of atrial fibrillation.

The standard Δ RR probability density histograms are prepared as described hereinafter before the detection of atrial fibrillation.

RR intervals of the patient are first detected
15 (201 of Figure 2) through an internal and/or external RR interval detector 301 (Figure 3) detecting electrical activity of the heart beat of the patient.

Δ RR is defined as the difference between two successive RR intervals. In the illustrative embodiment,
20 blocks of 100 successive beats or RR intervals are processed during atrial fibrillation. For that purpose, the detected RR intervals from the detector 801 are counted (202 of Figure 2) by a RR interval counter 302 (Figure 3) until the number of detected RR intervals reaches 100 intervals (203
25 of Figure 2).

The mean value of each block of 100 RR intervals is computed (204 of Figure 2) by means of a calculator 303 from the RR intervals from the detector 301. Of course, the calculator 303 is supplied with the count from the counter
30 302. This mean value identifies the block of 100 RR intervals as falling into one of sixteen (16) different

classes, respectively corresponding to mean values of RR between 350-399 ms, 400-449 ms, 450-499 ms, 500-549 ms, 550-599 ms, 600-649 ms, 650-699 ms, 700-749 ms, 750-799 ms, 800-849 ms, 850-899 ms, 900-949 ms, 950-999 ms, 1000-1049 ms, 1050-1099 ms, and 1100-1049 ms. For each of the sixteen (16) classes, a standard Δ RR probability density histogram is compiled by lumping data together from all the subjects, for example the subjects of the above mentioned MIT-BIH atrial fibrillation/flutter database.

10 The resulting standard Δ RR probability density histograms are modeled, for example, by the Lorentzian distribution, Gaussian distribution, Student's t -test, or a linear combination of the Lorentzian and Gaussian distribution. In all cases there is excellent superposition
15 of the empirical standard Δ RR probability density histograms and those obtained by any one of the mathematical distributions described above as illustrated in Figures 4 to 8. In Figures 4-7, the solid line represents the standard Δ RR density histograms and the dotted line is the
20 corresponding standard Δ RR density histograms obtained by the respective mathematical distributions.

The Lorentzian distribution is defined by the equation:

$$L(x) = \frac{1}{\pi \cdot S} \left(\frac{1}{1 + \left(\frac{x}{S}\right)^2} \right)$$

25 where S is a scaling factor, and x is the standard Δ RR probability density histogram. The Lorentzian distribution is fitted to a set of data points of the standard Δ RR probability density histograms using the nonlinear least-

squares Marquardt-Levenberg algorithm implemented in gnuplot.

The cumulative probability distribution $\Phi_l(x)$ of the Lorentzian distribution is given by the integral:

$$\begin{aligned}\Phi_l(x) &= \int_{-\infty}^x L(t) dt \\ &= \int_{-\infty}^x \frac{1}{\pi \cdot S} \left(\frac{1}{1 + (t/S)^2} \right) dt \\ &= \frac{1}{\pi} \arctan\left(\frac{x}{S}\right) + \frac{1}{2}\end{aligned}$$

The scaling factor S_l can be expressed by a linear function of the mean RR interval x of the block.

$$S_l = a_0 + a_1 * x$$

where a_0 and a_1 are estimated from the scaling factors determined from the standard Δ RR probability density histograms.

The Gaussian distribution is defined by the equation

$$G(x) = \frac{1}{\sqrt{2\pi}\sigma} \exp\left(-\frac{(x-\mu)^2}{2\sigma^2}\right),$$

where μ represents the mean value, and σ represents the standard deviation. Here, σ corresponds to the standard deviation of the standard Δ RR probability density histograms σ_{std} . The cumulative probability distribution ($\Phi_g(x)$) of the Gaussian distribution is expressed by the error function ($\text{erf}(x)$).

$$\begin{aligned}
\Phi_g(x) &= \int_{-\infty}^x G(t) dt \\
&= \int_{-\infty}^x \frac{1}{\sqrt{2 \cdot \pi} \sigma} \exp\left(-\frac{t^2}{2\sigma^2}\right) dt \\
&= \left\{ \operatorname{erf}\left(\frac{x}{\sqrt{2}\sigma_{std}}\right) + 1 \right\} / 2
\end{aligned}$$

The error function is a special case of the incomplete gamma function, which has an approximate expression. The error function is estimated using the approximation of the incomplete gamma function. As the coefficient of variation is approximately constant during atrial fibrillation, the standard deviation of the Gaussian distribution is also expressed by a linear function of the mean RR interval x of the block:

$$S_t = a_0 + a_1 * x$$

The Student's t -distribution is defined by the equation:

$$T_m(x) = \frac{\Gamma\left(\frac{m+1}{2}\right)}{\Gamma\left(\frac{m}{2}\right)\sqrt{m \cdot \pi} S} \left\{ 1 + \frac{1}{m} \left(\frac{x}{S} \right)^2 \right\}^{-\frac{m+1}{2}}$$

where m is the degree of freedom. Here, we assume $m=6$. The mean value of the Student's t -distribution is 0. The variance of the student's t -distribution σ_t^2 is $\frac{m}{m-2}$ ($m>3$). For $m \rightarrow \infty$ it approaches the Gaussian distribution. The student's distribution can be modified by a scaling factor S to fit the standard ΔRR probability density histogram. S is determined by the ratio between the standard deviation of the standard ΔRR probability density histogram (σ_{std}) and that of the Student's t -distribution.

15

$$S = \frac{\sigma_{std}}{\sigma_t},$$

where $\sigma_t = \sqrt{\frac{3}{2}}$. By integrating the Student's t-distribution, we obtain a cumulative probability distribution:

$$\begin{aligned}\Phi_t(x) &= \int_{-\infty}^x T_6(t) dt \\ &= \int_{-\infty}^x \frac{\Gamma(\frac{7}{2})}{\Gamma(3)\sqrt{6\pi}S} \left\{ 1 + \frac{1}{6} \left(\frac{t}{S} \right)^2 \right\}^{-\frac{7}{2}} dt \\ &= \frac{3}{16} \cos^4 \left(\arctan \left(\frac{x}{\sqrt{6}S} \right) \right) + \frac{3}{4} \sin \left(\arctan \left(\frac{x}{\sqrt{6}S} \right) \right) + \frac{1}{2}\end{aligned}$$

5

where x presents the standard ARR probability density histogram. The scaling factor S is expressed by the linear function of the mean RR interval x of the block:

$$S_t = a_0 + a_1 * x$$

10

The combined probability distribution is defined by a linear combination of the Lorentzian distribution and the Gaussian distribution as defined by:

$$\begin{aligned}\phi(x) &= aL(x) + bG(x) \\ &= \frac{a}{\pi \cdot S} \frac{1}{1 + \left(\frac{x}{S} \right)^2} + \frac{b}{\sqrt{2\pi}\sigma} \exp \left(-\frac{x^2}{2\sigma^2} \right)\end{aligned}$$

As a corollary the integration of $\phi(x)$ ranging from $-\infty$ to ∞ is equal to 1.

15

$$\int_{-\infty}^{\infty} \phi(x) dx = 1$$

From the above equation we derive that $a+b=1$.
The cumulative probability distribution is defined by the
integration of $\phi(x)$ ranging between $-\infty$ and x .

$$\Phi_c(x) = \int_{-\infty}^x \phi(t) dt$$

$$= \frac{a}{\pi} \arctan\left(\frac{x}{S}\right) + \frac{b}{2} \operatorname{erf}\left(\frac{x}{\sqrt{2}\sigma_c}\right) + \frac{1}{2}.$$

5 The parameters, a (or b), S , and σ_c are determined
by the curve fitting using the nonlinear least-squares
Marquardt-Levenberg algorithm implemented in gnuplot. The
intermediate value of a , S , and σ_c are interpolated from the
known values determined from the standard ΔRR probability
10 density histograms.

The resulting modeled histograms are taken to be
the standard modeled ΔRR probability density histograms for
atrial fibrillation, sorted by the mean RR interval as
indicated hereinabove and stored in storage unit 304 (Figure
15 3). In other words, a standard ΔRR histogram selector 305
chooses the standard modeled ΔRR probability density
histogram corresponding to the class in which the computed
mean value of RR intervals (from 204 in Figure 2) of the
block of 100 RR intervals under consideration falls (205 of
20 Figure 2).

Obviously, it is within the scope of the present
invention to construct the standard modeled ΔRR probability
density histograms using a different number of consecutive
RR intervals, for example 25, 50 or any other number of
25 consecutive RR intervals. It is also within the scope of
the present invention to construct the standard modeled ΔRR
probability density histograms using mean RR intervals that

lie in other ranges, for example 300-399 ms, 400-499 ms, 500-599 ms, etc.

Test Δ RR probability density histograms are constructed (206 of Figure 2) by a calculator 306 from the data obtained from the patient (test record) through the detector 301. As indicated in the foregoing description, the blocks of 100 successive RR intervals are determined by the counter 302. In the test Δ RR histogram calculator 306 a sequence of 100 RR intervals is centered on each beat in turn, and the relevant test Δ RR probability density histograms are calculated.

In order to test for atrial fibrillation in a test record, a standard cumulative probability distribution is calculated as indicated above depending on the used mathematical distribution, and a test cumulative probability distribution is computed by integrating the area under the curves of the test Δ RR probability density histograms. These standard and test cumulative probability distributions are compared (207 and 208 of Figure 2) through a comparator 307.

The similarities between the test histograms for a given patient and the standard histograms are evaluated in the comparator 307 using the above mentioned Kolmogorov-Smirnov (KS) test (207 and 208 of Figure 2). Advantageously, premature ventricular contractions are eliminated prior to performing the Kolmogorov-Smirnov test.

Referring to Figure 9, a calculator 901 computes the cumulative probability distribution of the standard modeled Δ RR probability density histograms as described hereinabove depending on the used mathematical distribution. A calculator 902 computes the cumulative probability

distribution of the test ARR probability density histograms. According to the KS test, one assesses if two given distributions are different from each other. In other words, the greatest vertical distance D (Figure 10) between the two cumulative probability distributions is measured by a calculator 903 which returns a p value in the following manner:

$$p \equiv Q(\lambda) = 2 \sum_{j=1}^{\infty} (-1)^{j-1} e^{-2j^2 \lambda^2}$$

where $\lambda = (\sqrt{N} + 0.12 + 0.11/\sqrt{N}) * D$. N is the number of data

points in the test cumulative probability distribution. A detector 904 determines whether the p value is greater than a certain, appropriately selected threshold P_c , and detection of $p > P_c$ indicates that the cumulative probability distributions are not significantly different from one another. Since the standard ARR probability density histograms are representative of atrial fibrillation, a value of $p > P_c$ constitutes a positive identification of atrial fibrillation (or more accurately failure to reject the hypothesis that the test cumulative probability distribution is not atrial fibrillation) (208 in Figure 2).

The results were assessed by four categories as followed: true positive (TP) -- atrial fibrillation is classified as atrial fibrillation; true negative (TN) -- non-atrial fibrillation is classified as non-atrial fibrillation; false negative (FN) -- atrial fibrillation is classified as non-atrial fibrillation; false positive (FP) -- non-atrial fibrillation is classified as atrial fibrillation. Sensitivity and specificity are defined by $TP/(TP+FN)$ and $TN/(TN+FP)$, respectively. The predictive value of a positive test (PV+) and the predictive value of a

negative test (PV-) are defined by $TP/(TP+FP)$ and $TN/(TN+FN)$, respectively.

The Kolmogorov-Smirnov test is first applied to the MIT-BIH atrial fibrillation database and a_0 and a_1 are
 5 determined by the linear regression. For the Lorentzian distribution, $a_0=-58.6216$ and $a_1=0.28269$. For the Gaussian distribution, $a_0=-23.002632$ and $a_1=0.343006$. For the Student's t -distribution, $a_0=-18.78158$ and $a_1=0.280063$.
 10 Figures 11 shows the ROC (Receiver Operating Characteristic Curve) of the Kolmogorov-Smirnov test for the MIT-BIH atrial fibrillation database. The accuracy of the Kolmogorov-Smirnov test for the MIT-BIH atrial fibrillation database is summarized in Table 1.

Table 1

15 Accuracy of the Kolmogorov-Smirnov test for the MIT-BIH atrial fibrillation database

Distribution	P_c	Sensitivity	Specificity	PV+	PV-
Lorentzian distribution	0.0021	96.2	96.2	94.7	97.2
Gaussian distribution	0.0004	95.7	95.7	94.1	96.9
Student's t -distribution	0.0014	96.1	96.1	94.7	97.2
Combined distribution	0.003	96.6	96.6	95.3	97.5
Empirical distribution	0.0039	96.5	96.5	95.2	97.5

It can be appreciated from the data of Table 1 that the linear combination of the Loretzian distribution
 20 and the Gaussian distribution improves the ROC of the Kolmogorov-Smirnov test compared to the ROC of the Kolmogorov-Smirnov test of other single distributions.

Figure 12 shows the ROC of the Kolmogorov-Smirnov test applied to the 200 series of the MIT-BIH arrhythmia
 25 database, which is the test data set. The data is also summarized in Table 2. The linear combination of the Lorentzian distribution and Gaussian distribution (with

$P_c=0.003$) improves the sensitivity compared to the empirical standard histograms, while the other parameters (Specificity, PV+, PV-) are not significantly changed.

Table 2

5 Accuracy of the Kolmogorov-Smirnov test
for the MIT-BIH arrhythmia database

Distribution	P_c	Sensitivity	Specificity	PV+	PV-
Lorentzian distribution	0.0021	97.5	82.0	55.9	99.3
Gaussian distribution	0.0004	97.8	80.4	53.9	99.4
Student's <i>t</i> -distribution	0.0014	96.0	83.1	57.0	98.9
Combined distribution	0.003	96.0	84.7	59.5	98.9
Empirical distribution	0.0039	93.5	84.9	59.2	98.2

Using the probability distribution from the linear combination of the Lorentzian and Gaussian distribution, the
10 Kolmogorov-Smirnov test was also applied to the 100 series
of the MIT-BIH arrhythmia database. The results (illustrated
in Table 3) are classified, as indicated hereinabove, into
four categories: true positive (TP) -- atrial fibrillation
is classified as atrial fibrillation; true negative (TN) --
15 non-atrial fibrillation is classified as non-atrial
fibrillation; false negative (FN) -- atrial fibrillation is
classified as non-atrial fibrillation; false positive (FP)
-- non-atrial fibrillation is classified as atrial
fibrillation.

20 As also indicated in the foregoing description,
sensitivity and specificity are defined by $TP/(TP+FN)$ and
 $TN/(TN+FP)$, respectively. The predictive value of a
positive test (PV+) and the predictive value of a negative
test (PV-) are defined by $TP/(TP+FP)$ and $TN/(TN+FN)$,
25 respectively.

Table 3

Accuracy of the Kolmogorov-Smirnov test for
100 series of the MIT-BIH arrhythmia database ($P_c=0.003$)

record	TP	TN	FN	FP
100	0	2173	0	0
101	0	1765	0	0
102	0	2087	0	0
103	0	1984	0	0
104	0	2129	0	0
105	0	2472	0	0
106	0	1798	0	129
107	0	2037	0	0
108	0	1663	0	0
109	0	2432	0	0
111	0	2024	0	0
112	0	2439	0	0
113	0	1695	0	0
114	0	1779	0	0
115	0	1853	0	0
116	0	2312	0	0
117	0	1435	0	0
118	0	2178	0	0
119	0	1858	0	29
121	0	1763	0	0
122	0	2376	0	0
123	0	1418	0	0
124	0	1519	0	0
total	0	45189	0	158

5 Using the method described herein, table 3 shows
that subject 106, characterized as having premature
ventricular contractions, emerges as false positive. It is
known that frequent premature ventricular contractions often
disturb the detection of atrial fibrillation. Figure 13
10 shows that both specificity and sensitivity are improved
when premature ventricular contractions (PVC) are removed
from the 200 series of the MIT-BIH arrhythmia database and
the Kolmogorov-Smirnov test is applied to the combined
Lorentzian and Gaussian probability distribution.

It will appear to those of ordinary skill in the art that the method of Figure 2 and the system of Figure 3 can be implemented through a properly programmed computer.

It is also within the scope of the present
5 invention to use signals other than the RR intervals,
histograms other than Δ RR probability density histograms,
tests other than the KS test, and series of Δ RRs other than
100, and that other methods besides the Komogorov-Smirnov
test can be used to compare test histograms with the
10 standard histograms.

It should further be mentioned that the present invention is appropriate for analysis using RR intervals collected from an implanted device or a device that does not invade the body.

15 Although the present invention has been described hereinabove by way of illustrative embodiment thereof, this embodiment can be modified at will, within the scope of the appended claims, without departing from the spirit and nature of the subject invention.

CLAIMS:

1. A method for detecting cardiac arrhythmia of a patient, comprising:

detecting RR intervals of the patient wherein each
5 RR interval is an interval between two heart beats;

constructing standard probability density
histograms of Δ RRs collected during cardiac arrhythmia of a
plurality of subjects, wherein Δ RR is a difference between
two successive RR intervals;

10 modeling the standard probability density
histograms of Δ RRs by means of a suitable probability
distribution calculated through at least one mathematical
formulae;

constructing test probability density histograms
15 of Δ RRs of the patient from the detected RR intervals of
said patient; and

comparing the standard modeled histograms and the
test histograms to detect whether the patient suffers from
cardiac arrhythmia.

20 2. A method for detecting cardiac arrhythmia as
defined in claim 1, wherein simulating standard probability
density histograms of Δ RRs comprises modeling the standard
probability density histograms of Δ RRs by a mathematical
equation selected from the group consisting of: the
25 Lorentzian distribution, the Gaussian distribution, the
Student's *t*-distribution, and a probability distribution
including a linear combination of the Lorentzian and
Gaussian distribution.

3. A method of for detecting cardiac arrhythmia as defined in claim 1, wherein said cardiac arrhythmia is atrial fibrillation.

4. A method for detecting cardiac arrhythmia as
5 defined in claim 1, wherein comparison of the standard modeled histograms and the test histograms to detect whether the patient suffers from cardiac arrhythmia comprises performing a Kolmogorov-Smirnov test, said method further comprising eliminating premature ventricular contractions
10 prior to performing the Kolmogorov-Smirnov test.

5. A system for detecting cardiac arrhythmia of a patient, comprising:

a detector of RR intervals of the patient, wherein each RR interval is an interval between two heart beats;

15 a standard probability density histogram storage unit in which are stored standard probability density histograms of Δ RRs collected during cardiac arrhythmia of a plurality of subjects, said standard probability density histograms of Δ RRs being modeled by means of a suitable
20 probability distribution calculated through at least one mathematical formulae, and Δ RR being a difference between two successive RR intervals;

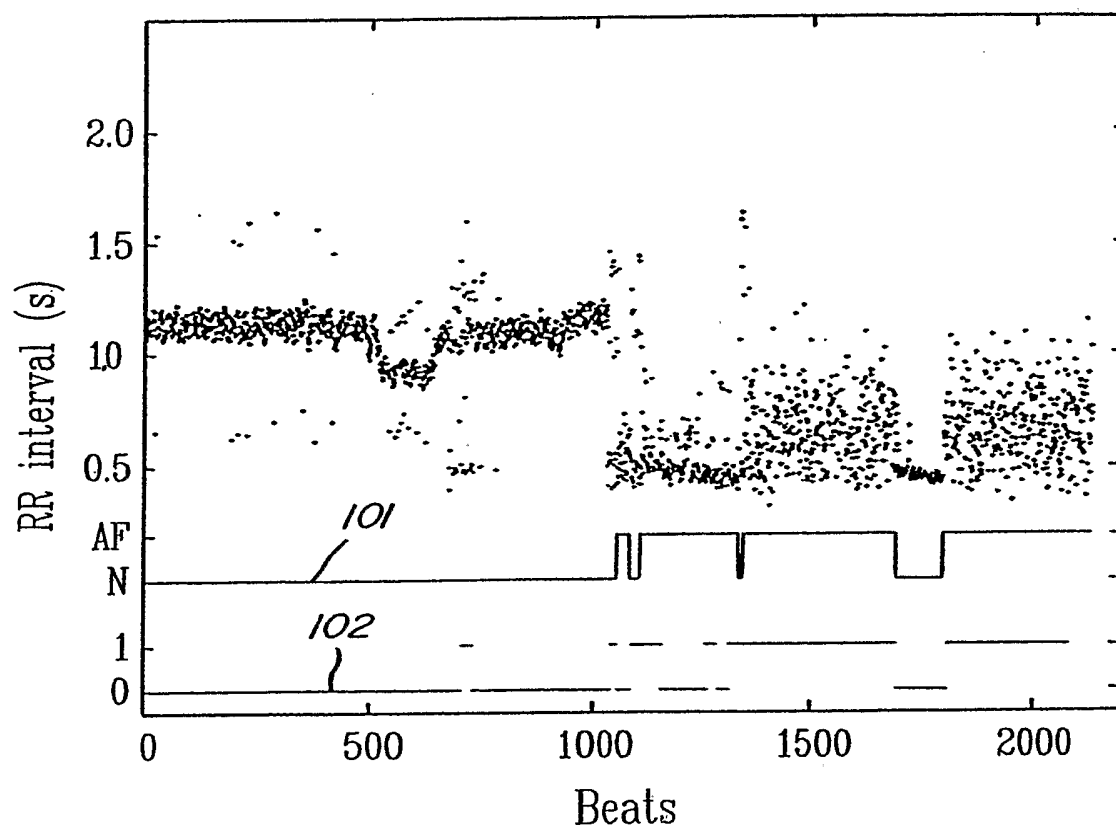
a test Δ RR histogram calculator supplied with the detected RR intervals from the detector and constructing
25 test histograms of the Δ RRs of the patient; and

a standard and test Δ RR histograms comparator supplied with the standard modeled histograms and test histograms, this comparator comprising a detector of cardiac

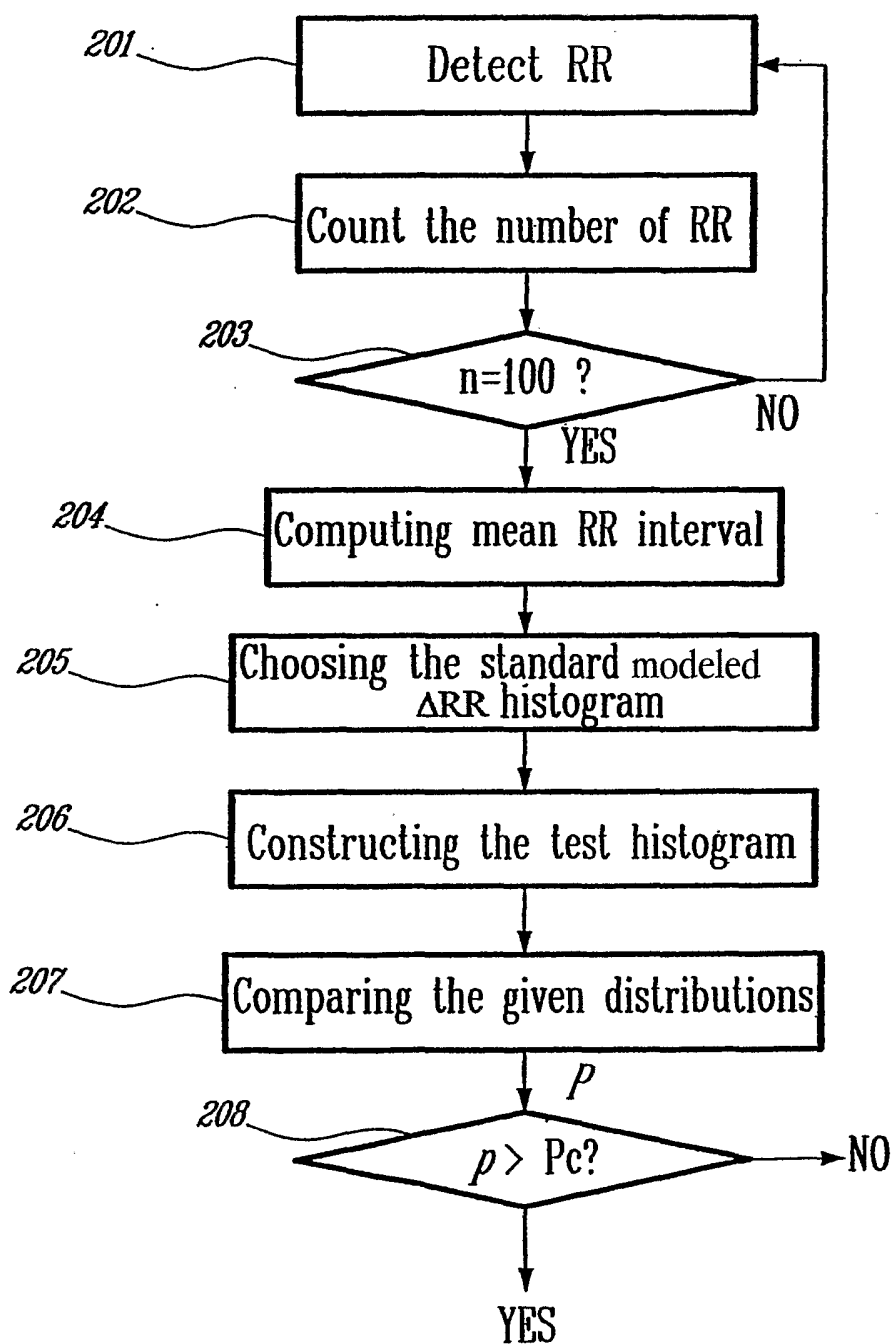
arrhythmia of the patient responsive to the comparison of the standard and test histograms.

6. A system for detecting cardiac arrhythmia as defined in claim 3, wherein the simulator comprises a
5 standard ΔRR probability density histograms modeling unit using a mathematical equation selected from the group consisting of: the Lorentzian distribution, the Gaussian distribution, the Student's t -distribution, and a probability distribution comprising a linear combination of
10 the Lorentzian and Gaussian distribution.

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**Fig. 1**

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**Fig. 2**

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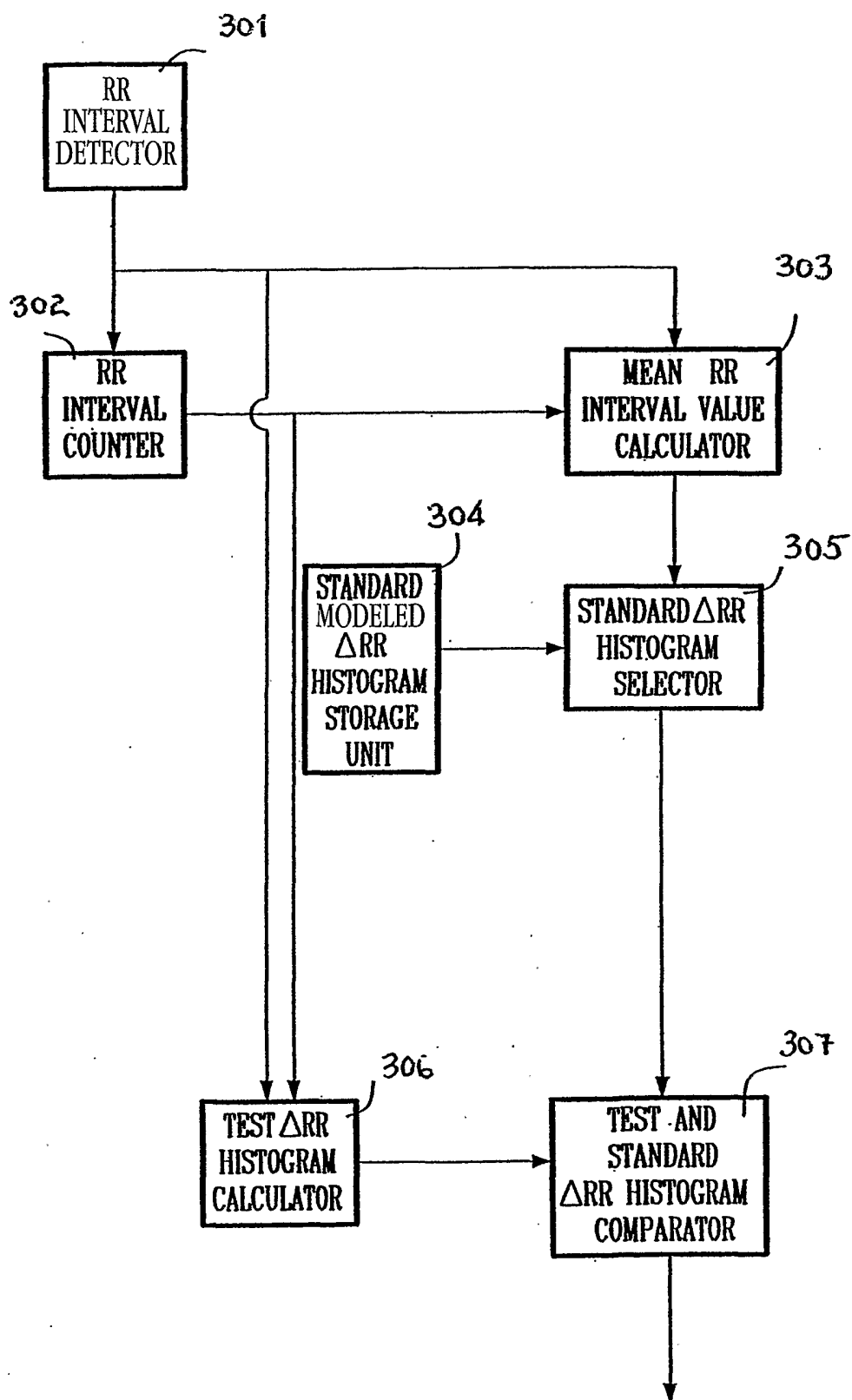
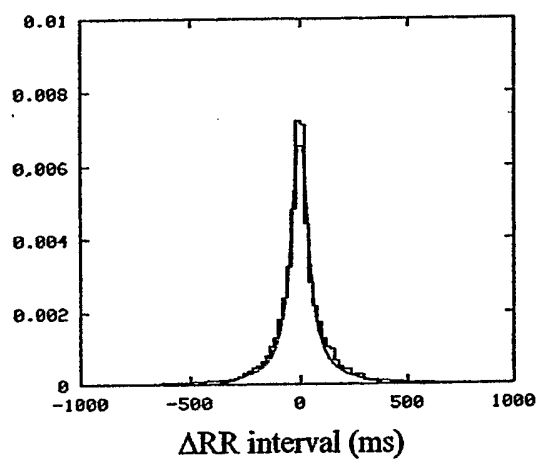


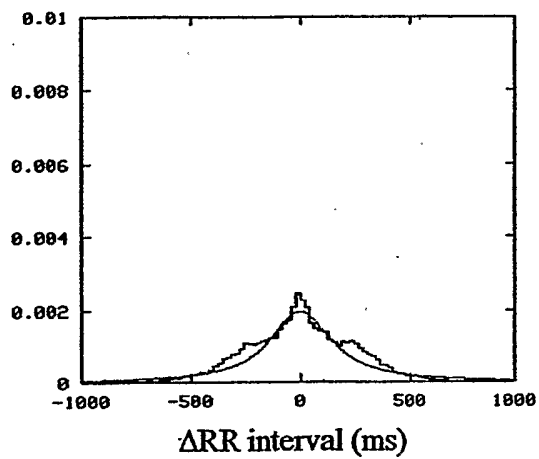
Fig. 3

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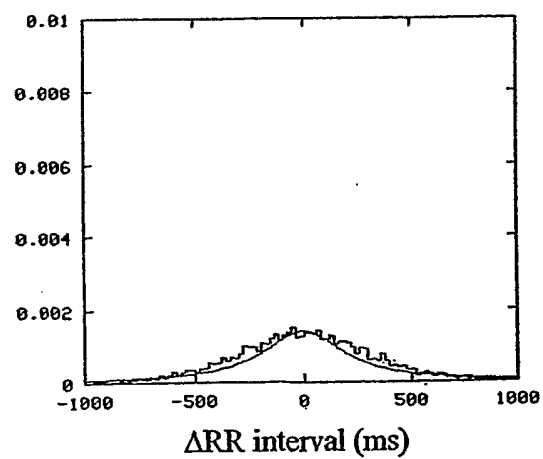
(a) 400 – 449 ms



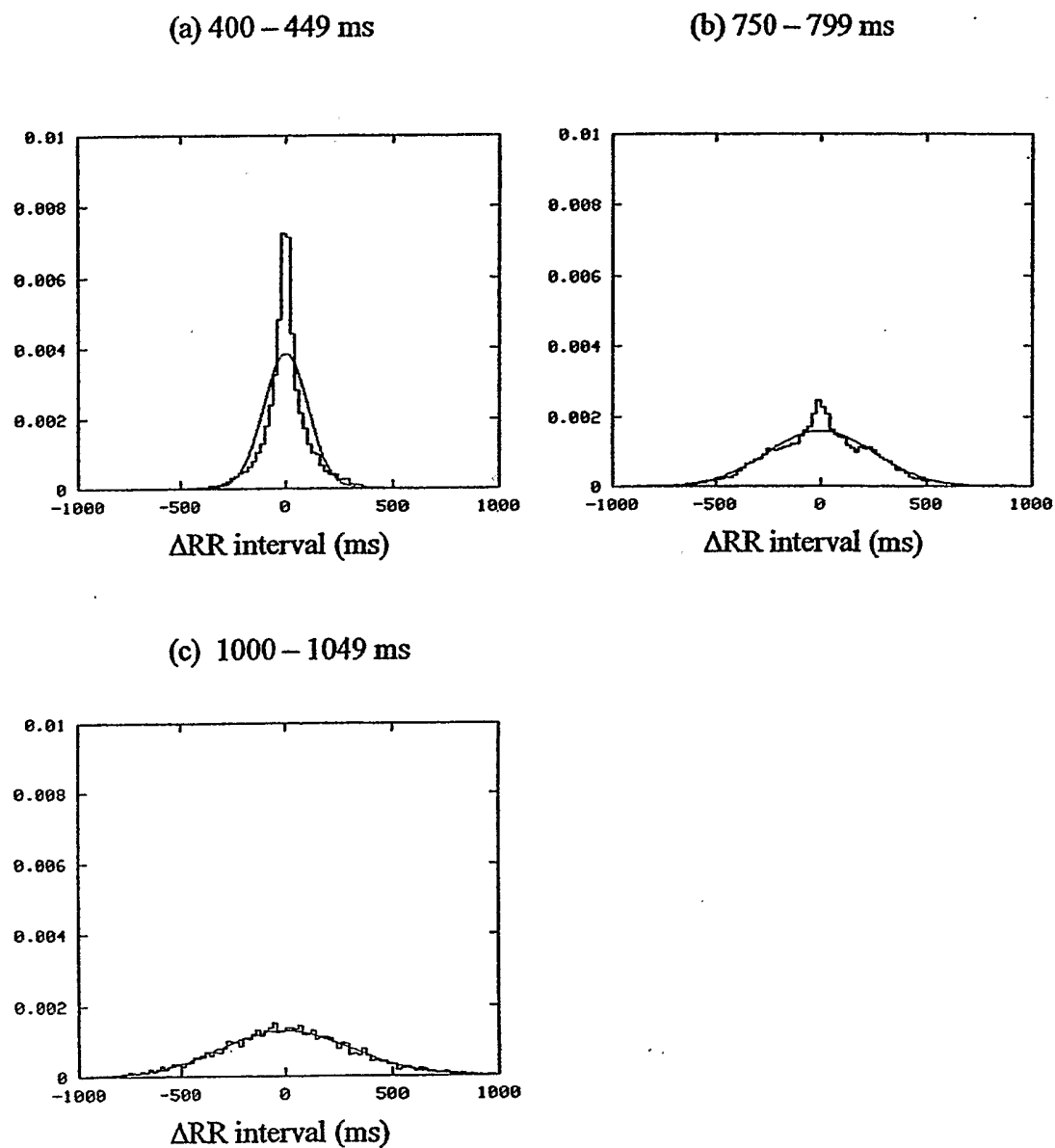
(b) 750 – 799 ms



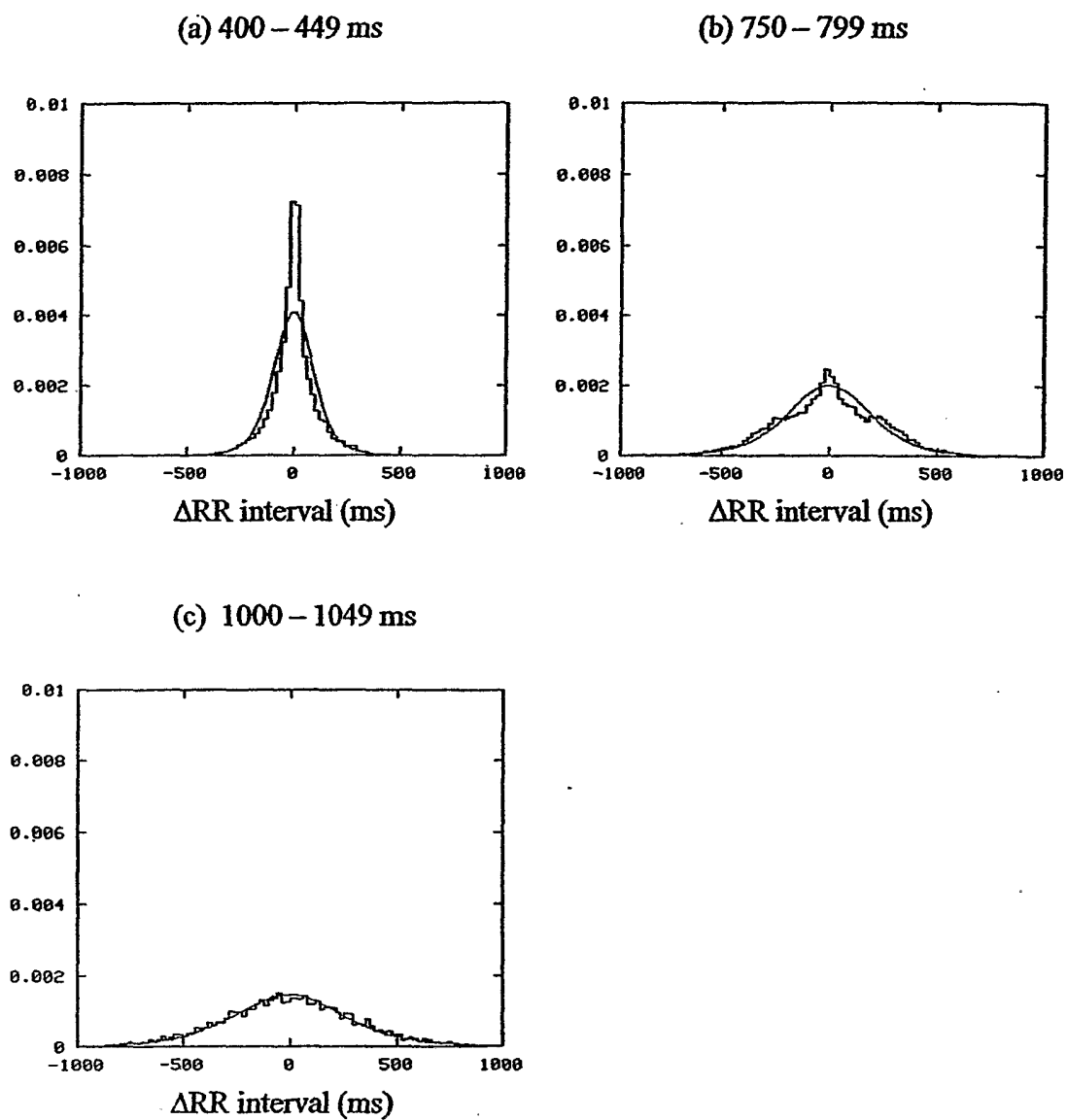
(c) 1000 – 1049 ms

**Fig. 4**

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**Fig. 5**

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**Fig. 6**

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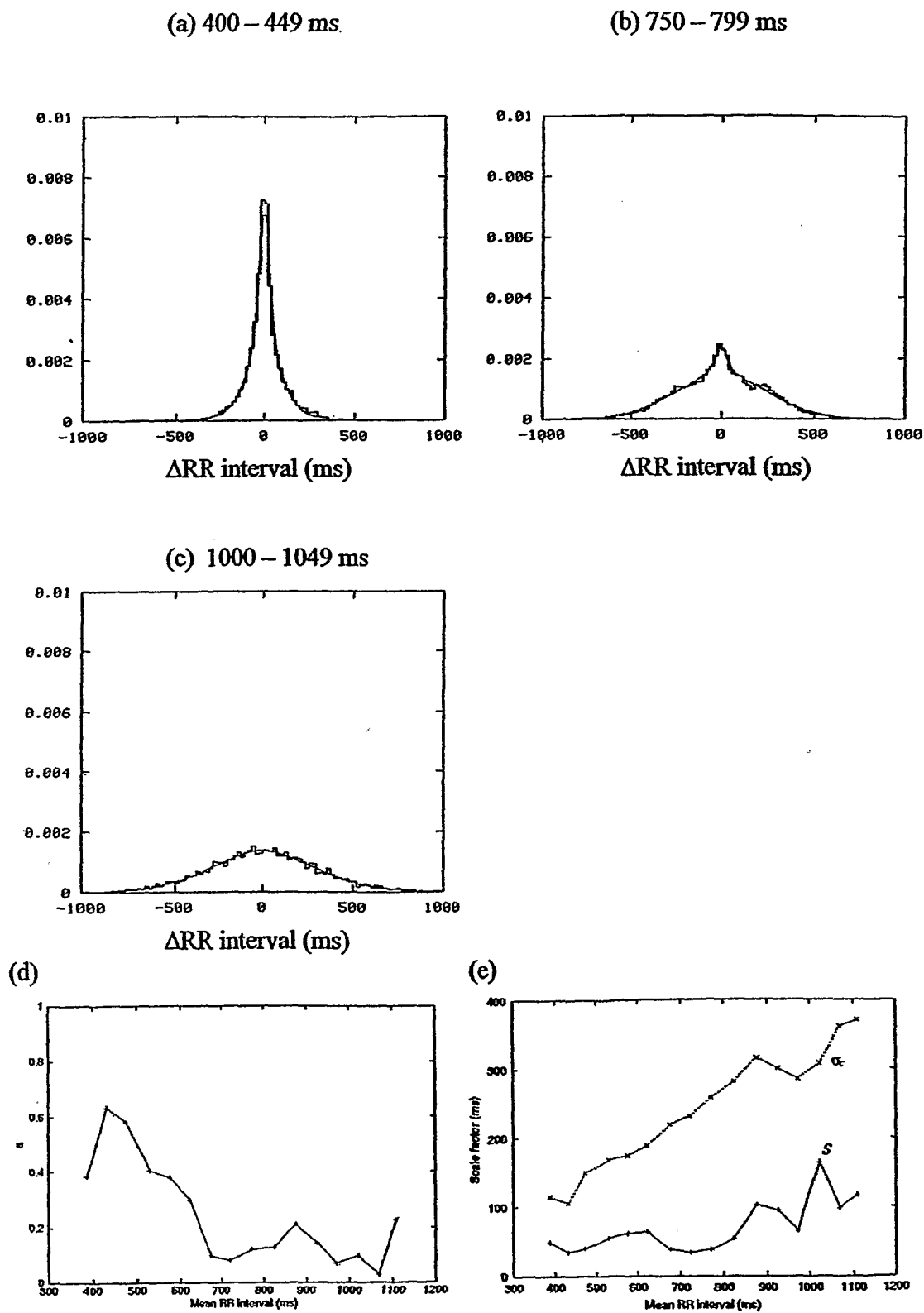
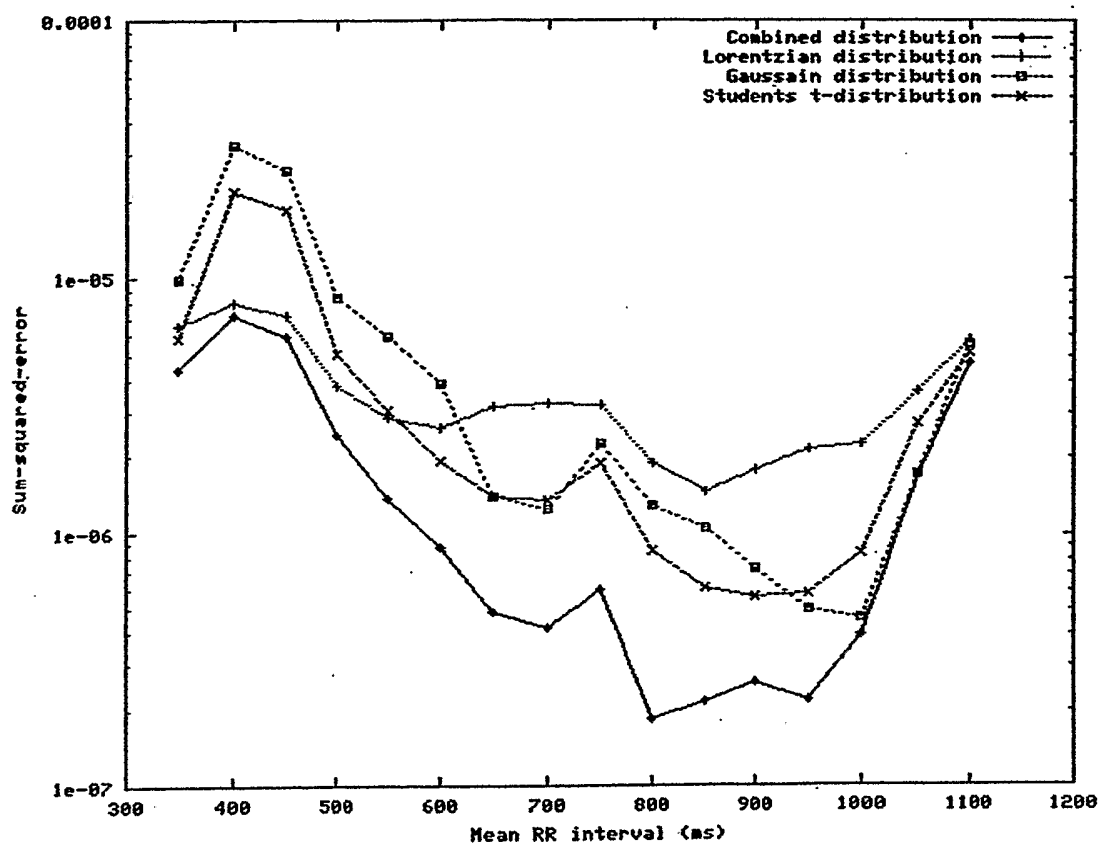
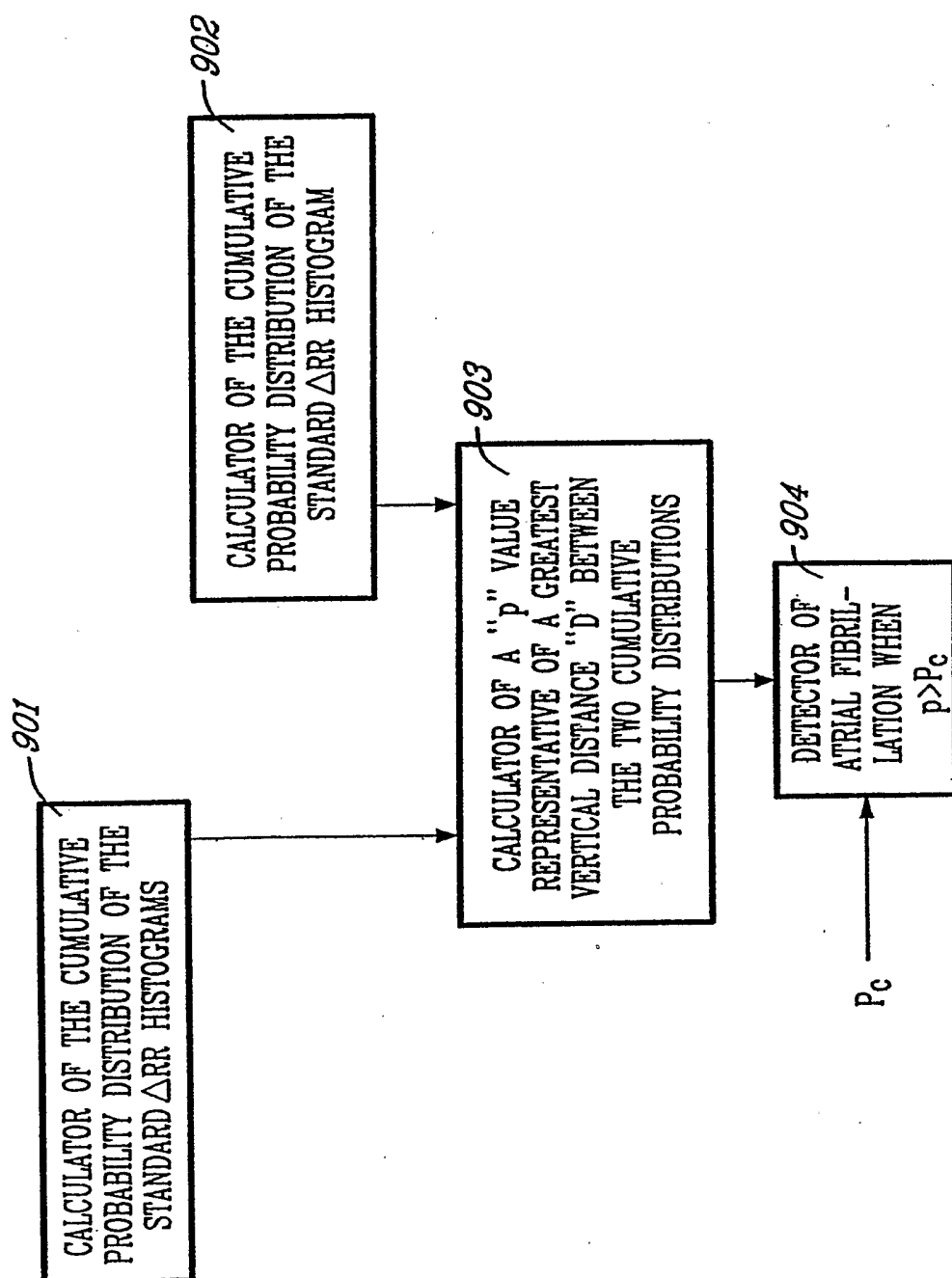


Fig. 7

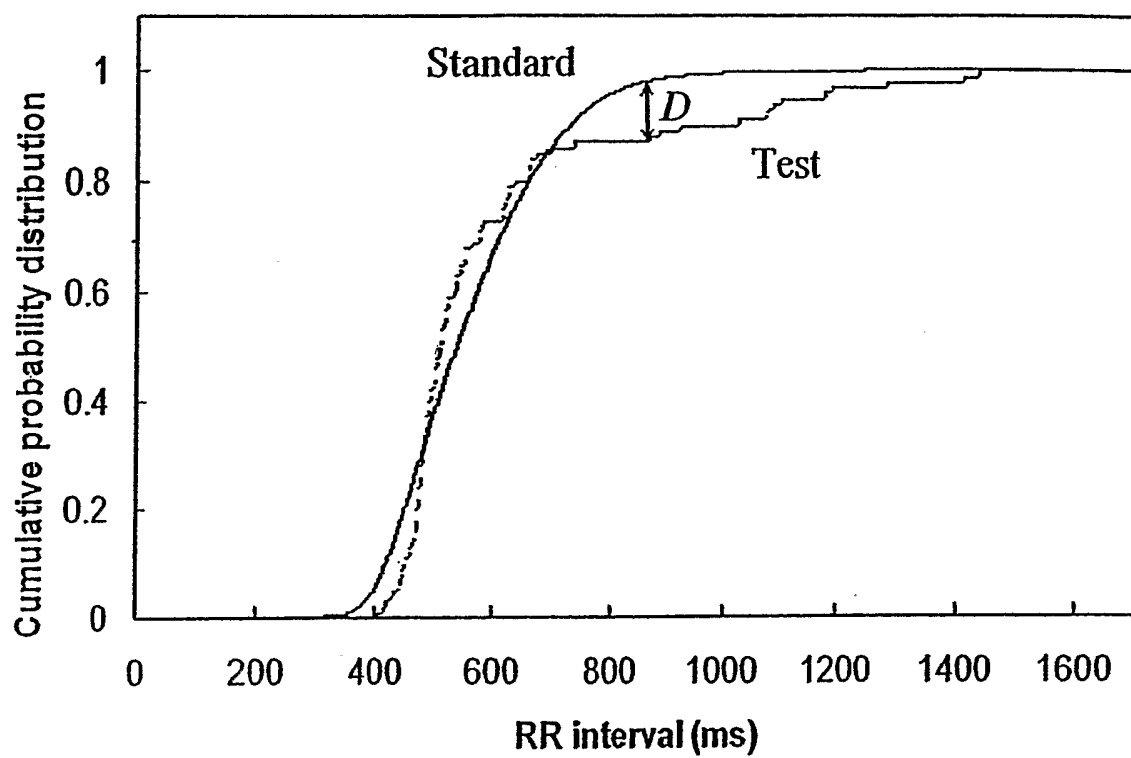
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**Fig. 8**

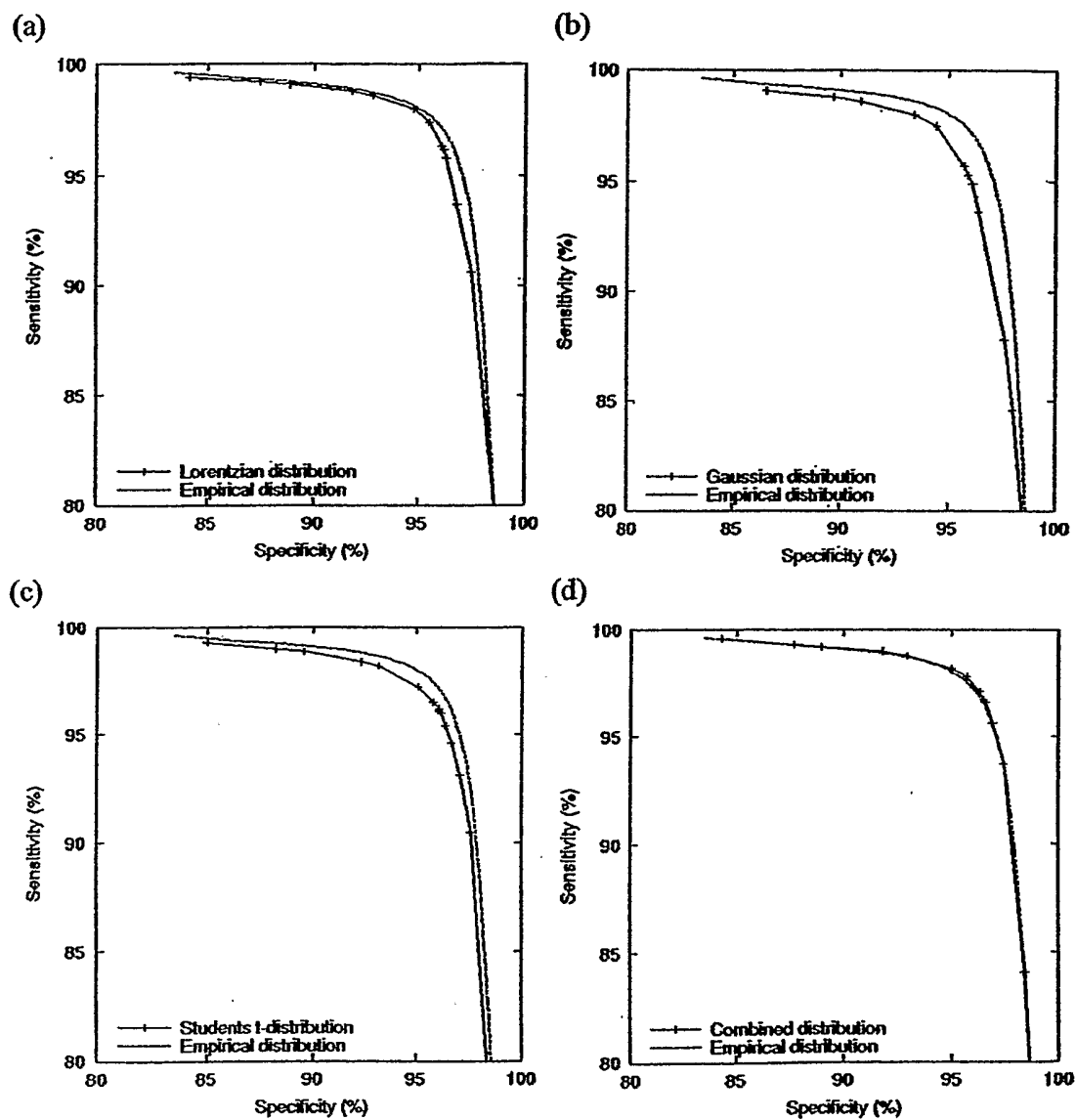
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**Fig. 9**

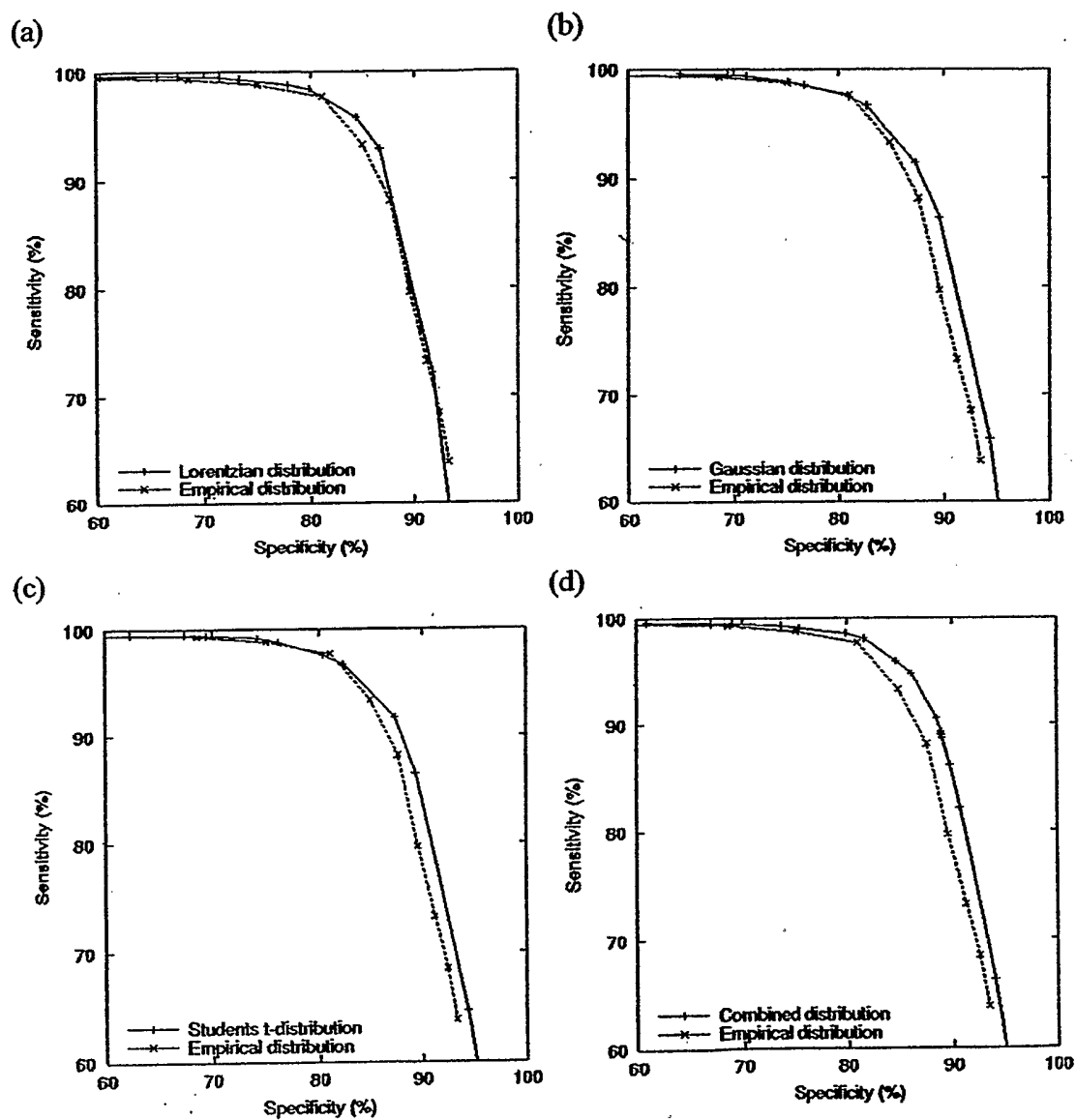
10/13

**Fig. 10**

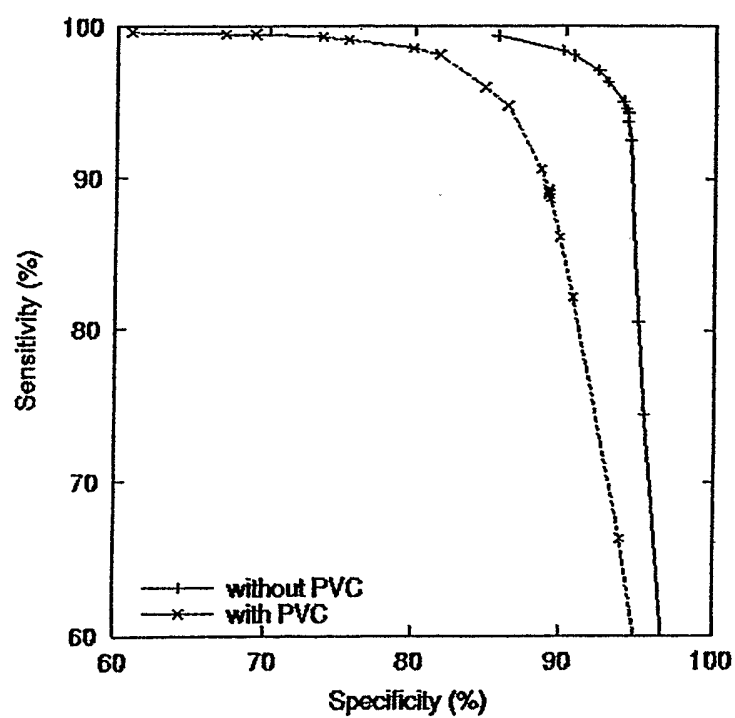
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**Fig. 11**

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**Fig. 12**

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**Fig. 13**

INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 03/00390

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61B5/046

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 7 A61B A61N

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

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

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 02 24068 A (UNIV MCGILL ; GLASS LEON (CA); TATENO KATSUMI (CA)) 28 March 2002 (2002-03-28) claims 8-13	5, 6
X	<p>--- TATENO K; GLASS L: "Automatic detection of atrial fibrillation using the coefficient of variation and density histograms of RR and deltaRR intervals" MEDICAL BIOLOGICAL ENGINEERING COMPUTING, vol. 39, no. 6, November 2001 (2001-11), pages 664-671, XP008017887 England * whole document *</p> <p>--- -/--</p>	5, 6

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

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Date of the actual completion of the international search

4 July 2003

Date of mailing of the international search report

11/07/2003

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Lommel, A

INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 03/00390

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 603 331 A (CARLSON GERRARD M ET AL) 18 February 1997 (1997-02-18) column 2, line 43 -column 3, line 8 column 3, line 40 -column 3, line 47 claims 1,15; figures 1A,1B -----	5,6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA 03/00390

Box I Observations where certain claims were found unsearchable (Continuation of item 1 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.: 1-4
because they relate to subject matter not required to be searched by this Authority, namely:
Rule 39.1(iv) PCT - Diagnostic method practised on the human or animal body
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.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 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 an additional fee, this Authority did not invite payment of any additional fee.
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.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/CA 03/00390

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0224068	A	28-03-2002	AU 9357201 A	02-04-2002
			WO 0224068 A1	28-03-2002
			EP 1322223 A1	02-07-2003
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US 5603331	A	18-02-1997	NONE	
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