

A Review on Recent Patents in Digital Processing for Cardiac Electric Signals (II): Advanced Systems and Applications

Óscar Barquero-Pérez, Rebeca Goya-Esteban, Felipe Alonso-Atienza, Jesús Requena-Carrión, Estrella Everss, Arcadi García-Alberola and José L. Rojo-Álvarez*

*Department of Signal Theory and Communications, University Rey Juan Carlos, Madrid, Spain,
Arrhythmia Unit, University Hospital Virgen de la Arrixaca, Murcia, Spain*

Received: December 24, 2008; Accepted: January 19, 2009; Revised: January 20, 2009

Abstract: Digital signal processing algorithms for cardiac recordings have been paid much attention in recently disclosed patents. In this second part of our review of the state-of-art patents, systems for sudden cardiac death prediction, as well as for apnea analysis, are summarized. Advanced digital signal processing algorithms for cardiac electric signals are specifically reviewed, including independent component decompositions, and nonlinear methods (chaos, fractals, and entropies). Finally, systems aiming to solve the inverse problem in electrocardiography are presented. Concluding remarks on these systems and on the whole review are discussed.

Keywords: Electrocardiogram, electrogram, digital signal processing, cardiac signal, heart rate variability, T wave alternans, signal-averaged ECG, ischemia.

1. INTRODUCTION

In the companion paper [1], a compilation of recent patents on digital processing algorithms for cardiac signals analysis has been presented. This review included systems for basic feature extraction of the electric signals recorded from electrodes in the skin (called electrocardiogram, ECG), or from electrode systems in catheters placed inside the heart (called electrograms, EGM). Systems for analyzing cardiac arrhythmias in different applications have also been assembled therein.

In this paper, we include relevant higher-level systems that use digital processing algorithms in advanced applications related with electrocardiology and with cardiac electrophysiology environments. Specifically, the problem of accurate sudden cardiac death (SCD) prediction [2,3] has been targeted by a large number of disclosed systems. Also, apnea analysis [4] has been addressed in the recently disclosed patents. Special attention is paid here to advanced signal processing algorithms, such as blind source separation techniques or nonlinear analysis procedures including chaos, fractals and entropy principled algorithms, which have been disclosed as a part of advanced application systems. Finally, the inverse problem in electrocardiography [5], consisting of creating an anatomically detailed image of the electrical underlying cardiac activity from a diversity of electric signals, continues to be a field in which disclosed advanced systems aim to give to the clinician the best view of the cardiac electric activity.

The structure of this second part of the review is as follows. Section 2 deals with patents devoted to SCD risk stratification and prediction. Section 3 briefly deals with

sleep and apnea related patents. Section 4 summarizes the most relevant advanced algorithms and signal processing techniques. Section 5 is specifically devoted to the inverse problem electrocardiography, which nowadays is still one of the major problems to be solved. Finally, Section 6 contains some concluding remarks on the system in this paper, together with global considerations that can be extracted from the complete review.

2. SCD PREDICTION

Risk stratification is an important tool to identify patients at high risk of suffering an episode of SCD in order to implement preventive therapies. These techniques include the analysis of QT dispersion and dynamicity, ischemia detection via ST segment analysis, heart rate variability (HRV) and heart rate turbulence (HRT) analysis, high frequency late potentials (LP) measurements, or T wave alternan (TWA) analysis [2]. Data required for these techniques are usually obtained via skin electrodes, such as Holter or event recorders.

2.1. QT Measurements

Increased duration of the QT interval is associated with an increased risk of cardiac arrhythmias and SCD in several clinical scenarios. Hence, the dispersion and the prolongation of the QT interval have been proposed as markers for SCD prediction [6]. Two orientations can be pointed out for recent patents in this setting, which are the proposal of new markers based on signal processing and the proposal of modifications in the definition of the prediction system.

Advanced Markers

In [3], a quantitative method for measuring QT intervals from ambulatory ECG recordings is presented, in which beat-to-beat data representative of cardiac interval are collected over an extended period of time. A series of bins,

*Address correspondence to this author at the B004, Universidad Rey Juan Carlos, Camino del Molino s/n, 28943-Fuenlabrada (Madrid), Spain; Tel: (+34) 91 488 8464; Fax: (+34) 91 488 75 00; E-mail: joseluis.rojo@urjc.es

each of which has a defined value range, is defined. The collected data are organized into the bins in accordance with the value of the data and the value range of the bin. The percentage of data in each bin is calculated to detect the percentage of beats that exceed a user-defined threshold. In [7], an ECG analyzer is disclosed which is capable of estimating the contour positions of the atrium and the ventricle from multichannel ECG waveforms. Moreover, useful information can be obtained for prediction of the SCD, such as the position of the maximum excitation propagation point, the distribution of LP as a marker of depolarization, or the distribution of RT segment dispersion as a marker of repolarization, which are displayed together with the estimated contour positions.

Improved Systems

Conventional analysis of non-invasive cardiac parameters for SCD risk stratification usually focuses on single aspects of the patient's electrophysiology, such as repolarization (QT variability) and depolarization (QRS duration) processes or autonomous system state (HRV, HRT). In [8], a system is disclosed for estimating the vulnerability to SCD from depolarization and repolarization measurements, by analyzing the variation between representative values of an ECG signal. Examples of relationship between depolarization and repolarization can be given by the QRS-T angle (angular difference between a QRS vector and a T vector) or the QRS duration versus T duration. In [9], risk stratification from ECG and one (marker of ischemia) or two (necrotic marker) *in vitro* diagnostic assays are proposed.

Systems for monitoring in implantable cardiac devices (ICD) have also been disclosed. In [2], an ICD is capable of recording a physiological signal in response to at least one of a number of risk stratification measured triggers, hence allowing the long-term risk monitoring from the ICD. In [10], inter-patient comparison for risk stratification of future heart failure decompensation is discussed. The system receives the data from an ICD, determines a reference group related to the patient, determines a reference group dataset from the reference group with patient data that is of a similar type received from the patient device generates a model of the reference group dataset, and automatically compares the received data to a model in order to derive a risk index for the patient.

2.2. Ischemia

In general, the susceptibility of a patient to suffer a heart attack can be assessed by examining the heart for evidence of ischemia, this is insufficient blood flow to the heart tissue itself resulting in an insufficient oxygen supply, during periods of elevated heart activity. In general, the cardiovascular system responds to changes in physiological stress by adjusting the heart rate. This adjustment normally occurs along with corresponding changes in the duration of the QT intervals and an average action potential duration measured as the QT interval at each ECG lead may be considered as an

indicator of cardiac systolic activity varying in time. The QT intervals variability, separately or in combination with heart rate analysis, has been suggested as an effective tool for the assessment of patient susceptibility to SCD [11]. A number of markers have been proposed for ischemia detection from the skin ECG and some of them are next summarized.

Methods Based on Electrophysiological Mechanisms

In [11], a method is disclosed which collects RR intervals from the patient during gradually increasing and decreasing heart rate (exercise load). Comparison of both data intervals using their difference yields a measurement of cardiac ischemia during exercise, with a greater difference indicating greater ischemia. This process reflects almost exclusively the conduction in the heart muscle, minimizing the effect of rapid transients of autonomic nervous system and hormonal control. In [12], inventors state that prolongation of the QT interval, rather than shortening, is one of the first detectable symptoms of transmural ischemia, and hence a system for its measuring is disclosed which makes a comparison with baseline from the patient level. In [13], a method for discriminating between ischemic and cardiac memory effects is disclosed which calculates the direction of the T wave vector, diagnosing ischemia if its angle is in $(75^\circ, 200^\circ)$ or cardiac memory if it is in $(-90^\circ, 0^\circ)$.

Methods Based on Measurements from Patient Data Bases

In [14], a new methodology for the detection, localization and quantification of acute myocardial ischemia is proposed. Monopolar ECG array of leads are converted into multichannel spectrum and autocorrelation domains, and several decision variables are identified from the autospectra, such as the spectral peak (lower than 15 Hz during ischemia) and the width 50% below the peak (lower than 20 Hz during ischemia). Threshold levels from a Neyman-Pearson test are used for comparison with these variables to determine the probability of ischemic conditions. A method and an apparatus in [15] acquire multiple lead ECG and analyzes their global features, in particular, the projection coefficients obtained from projecting a concatenated vector of representative heartbeat data onto sets of basis vectors that define an acute cardiac ischemic ECG subspace and a non-ischemic ECG subspace. Local features, such as morphological features or clinical information, can be included to enhance the detection of ischemic condition. Subspaces are obtained from sets of representative examples of patient data. In [16], coronary disfunction is identified by comparing some feature in the PQRST interval with the same feature in a database from ECG investigation of numerous subjects with documented condition. A score is obtained which, combined with ejection fraction, provides with an indication of risk. Also, the presence of rhomboids following a QRS complex in the frequency domain plots is indicative of risk. In [17], the Hermite coefficients of the ECG signal are obtained, and an artificial neural network (ANN) is used for evaluating ischemia by comparison to a previously documented dataset of ECG examples from patients.

2.3. HRV Algorithms

Under normal conditions, the heart rate is not constant, instead there exists a natural variation of the time intervals between consecutive heart beats. The normal heart rhythm is controlled by the cardiac sinoatrial (SA) node, which is responsible for the generation of quasi-periodic heart beats. The SA node is further modulated by innervations from both the sympathetic and the vagal branches of the autonomic nervous system (ANS). Both branches have antagonist roles, for instance, sympathetic activation increases the heart rate whereas vagal activation slows it down. In rest conditions there is a balance state between these systems that is responsible for the variability in the intervals between consecutive heart beats.

HRV is the variation in the intervals between consecutive heart beats or equivalently, the variation between consecutive instantaneous heart rates. This signal allows noninvasive investigation of the ANS state and related diseases by the study of such variations. Classical methods for quantifying HRV include temporal methods and spectral methods. Both have been used for decades in order to characterize HRV [18-21].

Time Domain Methods

Time domain methods are simpler than spectral methods on computational terms. Chronologically, they were the first to be used in HRV analysis, and they still continue to be very used nowadays [21, 22-25].

Spectral Methods

Power spectral density (PSD) analysis provides the information of how power (variance) is distributed as a function of frequency. HRV found in healthy subjects during rest is influenced by respiratory activity as well as by feed-

back mechanism of the systems for regulation of temperature and blood pressure. The different systems oscillate spontaneously at rest with characteristic frequencies in different intervals. By quantifying the power of the spectral components of the HRV signal information about pathologies related to cardiac autonomic function may be pointed out. The spectral domain is divided into different frequency intervals, then the spectral power is measured in each interval and associated with the physiologic response of the heart to sympathetic or vagal stimulation [20,21,26-28].

Some of the revised patents use only temporal methods or spectral methods. However most of these patents use both kind of methods, one as a complement to the other.

HRV Risk Stratification

HRV has been proposed for risk stratification of lethal arrhythmias after acute myocardial infarction, as well as for the prognosis of SCD episodes [22,29,30]. After a myocardial infarction, the innervation level of the heart decreases, and part of the nervous control of this organ can be lost see Fig. (1). The HRV reflects this control loss and it makes possible the classification of cardiac SCD groups [24]. In [31], a statistic based HRV analysis method is disclosed. The method captures the ECG signal, performs analog-digital conversion of the ECG signal and the peaks of the ECG signal are selected. Then, the standard deviation of the heights, durations and inter-peak intervals of the peaks are calculated. The peaks whose heights, durations or inter-peak durations fall beyond a standard deviation are removed. The remaining peaks are sampled and interpolated to form a consecutive peak signal. Finally, a spectrum analysis of the peak signal is calculated, as follows: First, a linear drift is eliminated from the signal and a Hamming computation is employed to prevent the mutual leakage between individual

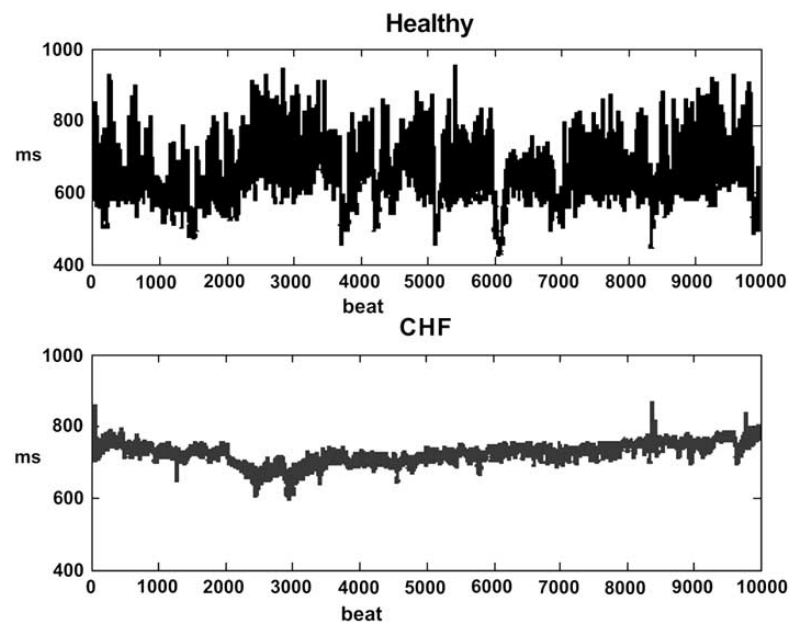


Fig. (1). Example of a HRV signal from a healthy subject (above) and a HRV signal from a subject suffering from Congestive Heart Failure (down).

frequency components. After that, Fast Fourier Transform (FFT) is performed to obtain the PSD and the effects of sampling and Hamming computation are compensated. The powers of the low frequency (LF), high frequency (HF) bands of the PSD and LF/HF ratio are quantified. In [32], a method is shown for calculating the HRV to be used in an ECG monitor. The method scans the ECG signal from the ECG monitor and determines a number of discrete representative values of the HRV signal. The measured values are evaluated on the basis of the Fourier Transform (FT). The invention suggests the replacement of the known FFT by an approximation method which, based on the FT, replaces numerical vector values for calculating the frequency spectrum of the measured values by a limited number of roughly approximated vector values that reflect the course of the Fourier vectors. This method allows a considerable reduction of the computation and memory needs, and thus its application in ICD.

HRV Applications

HRV is used to quantify the efficacy of baroreflex activation therapy (BAT) for the treatment of hypertension or other physiological conditions or diseases. In [33], the HRV analysis is further used to determine the need for adjusting the BAT. In [34], the use of the estimated HRV is suggested to determine a HRV index using also adjustment factors such as heart rate, age, gender or blood pressure. The estimation of the HRV is done by statistical and spectral methods.

Although much progress has been made using the tools of HRV to characterize Holter recordings, little work has been done with exercise testing where the effects of the ANS are pronounced. It is estimated that the risk of SCD is 17-20 times greater during exercise than during the resting phases that dominate Holter recordings. In [35], new methods are provided for characterizing the temporal and spectral characteristics of the HRV during the exercise test and integrating disparate metrics for risk stratification. In [36], a method is shown for determining the state of entrainment between biological systems such as heart rhythms, respiration or blood pressure, based on a determination of HRV and an evaluation of the PSD thereof. Entrainment reflects a harmonious balance between the two branches of the ANS within the body. The method first determines the PSD and then calculates an entrainment parameter, which is a measure of the power distribution in the HRV spectrum. High parameter values occur when this power is concentrated within a relatively narrow range of frequencies, and lower values when the power is distributed over a broader range of frequencies.

2.4. LP Algorithms

It has been recognized [37] that a diseased state in the ventricular myocardium may slow the conduction velocity of the electrical impulse in small areas of this anatomical region. Regions of slow conduction may sustain reentrant activation, which in turn is the main mechanism for clinically

relevant ventricular arrhythmias. The late activation of the slow conducting areas yields a low-amplitude potential that shows up at the end of the QRS signal, called a LP. Special data acquisition techniques are required to detect and measure such tiny potentials. In general, two techniques for high resolution electrocardiography had been available, namely, signal averaging, which relies on the noise being random and on the addition of a large number of signals resulting in noise cancellation and high gain ECG, which relies on very high gain amplifiers.

Two main groups of patents can be found in this application. The first ones aim to improve the spectral description of the LP domain, either by improving the bandpass filtering stage, or by showing the time-frequency representation of the LP domain. The second ones use advanced methods for noise cancellation to the microvolt level.

Bidirectional and Bispectral Filters

Several alternative methods have usually focused on the filtering settings. In [38], a system was disclosed for detecting minute LP, which filters the QRS signal bidirectionally (normal and time reversed), and then separately processed both signals with a window function before their summation. The summed signal is passed through a smoothing function for yielding an output signal of ideal phase that delineates any LP within the QRS complex, including high-frequency potentials in the Fourier spectrum. In [39], another system for bispectral filtering is proposed, which obtains the QRS onset from a number of beats and then uses two filters (passband of 70-200 Hz and 40-200 Hz) to establish the QRS offset and for accurate determination of RMS (voltage values for the terminal 40 ms of the waveform) and of low amplitude signals (from downside slope of the R peak to the QRS offset). The system also uses a spectral filtering for the ECG input signals with 150-250 Hz bandpass, allowing the determination of additional high frequency activity in the midportions of the QRS complex.

QRS Spectrograms

Previous LP analysis methods rely on bandpass filters for measuring the presence and magnitude of LP in predefined spectral bands. In [40], a system is disclosed which performs the spectrogram, i.e. Fourier analysis of short overlapping time segments, of the QRS complex in high resolution ECG, which are used to plot time-spectral maps showing changes in the frequency spectral content of the ECG along the QRS period. A risk indicator for ventricular tachyarrhythmia, the spectral turbulence, is further calculated by using correlations and statistical evaluations of the spectral contour in the QRS time segment pairs. In [41], another time-frequency domain characterization is disclosed. Several small signal segments are selected in an ECG waveform, for instance, 20 to 70 ms overlapping windows with steps of 2 ms. Two autoregressive models are used, maximum entropy method and least-squares adaptive filter, for estimating the time series coefficients and yielding the spectrum. This approach has the usual advantages of nonparametric vs parametric methods for spectral estimation.

Advanced Noise Cancellation Systems

In [42], an improvement of LP conventional analysis first removes low frequency noise and common mode signals (60 Hz noise and its harmonics). The remaining electrical interference caused by underlying muscle tissue, nerve tissue and environmental noise, is removed with an adaptive filter, using at least two ECG leads. In [43], a real time system is disclosed, aiming to obtain high resolution measurements from ambulatory Holter, which performs digital signal averaging of initially selected signals (10 to 15 minutes, approximately 1000 beats), and signal averaged template is correlated with each beat in order to accept only a previously defined correlation coefficient level (0.98), yielding summated results that have eliminated nonrepetitive noise to less than a microvolt. In [44], the signal-to-noise ratio of ECG is enhanced by time-synchronizing a number of cardiac cycles to form a signal ensemble and then determining the correlation between the signals in the ensemble in time intervals. The correlation is used to determine an optimum filter characteristic for the ECG signal to enhance the signal-to-noise ratio of the ECG signals.

2.5. TWA Algorithms

TWA is defined as a beat-to-beat consistent fluctuation in the repolarization morphology, which can be observed in the ECG and EGM signals under adequate conditions [45]. TWA has been shown to be related to cardiac instability and increased arrhythmogenicity. Moreover, clinical studies suggest that large amplitude microscopic (microvolt level) TWA is associated to a high risk of SCD [46]. Thus, TWA is considered as a strong marker of cardiac electrical instability and may be useful for SCD risk stratification [47].

In this subsection, patents for TWA detection in ECG and EGM are presented. Some of the revised patents focus only on the detection stage, while others also include post-detection therapy.

TWA Detection on ECG

Non-invasive techniques for assessing myocardial electrical stability often involve analysis of the beat-to-beat alternation in the morphology of the ECG. In [48], a method is disclosed which optimizes the detection of the small alternans signal, by taking into account both the anticipated physiological nature of the signals origin and introducing several signal measurements. The ECG from the patient is divided into individual cardiac cycles and the amplitude of four segments of the repolarization portion and the depolarization portion of each cardiac cycle are measured. Based upon these measurements, digital signal processing is used to generate eigenvariables. A spectral density is calculated for each of the eigenvariables and these spectral densities can be used to determine both the presence of alternans and the respiratory frequency.

In [46], a system for quantifying TWA and ST segment of an ECG is presented. The system receives a digitized ECG, which is used to calculate an odd median complex for the odd beats in the ECG and an even median complex for

the even beats in the ECG. The odd median complex and the even median complex are then compared to obtain an estimate of the amplitude of beat-to-beat alternation in the T wave morphology.

TWA Detection in EGM

Using intracardiac EGM, alternans are considerably larger than the microvolt TWA detected using surface electrodes and hence, direct measurement of repolarization-phase amplitude differences between even-numbered and odd-numbered heart beats can be done without aggregate statistical techniques. In [49], an invention is presented which permits control stimuli to be delivered in response to real-time alternans data using a suitable nonlinear-dynamical control algorithm see Fig. (2). Timing and amplitude of the stimuli is designed to terminate the alternans rhythm. Because the control technique is adaptive, it is able to estimate underlying nonlinear dynamics and has flexibility to withstand rhythm nonstationarities. With such control, potential routes to a ventricular arrhythmia are eliminated. In [50], a method is provided for assessing TWA using cardiac EGM signals received from implanted electrodes. A T wave signal parameter is measured from signals received by an automatic gain control sense amplifier. A TWA measurement is computed from a beat-by-beat comparison of T wave parameter measurement or using frequency spectrum techniques. TWA assessment further includes discriminating concordant and discordant TWA in a multi-vector TWA assessment and determining the association of a TWA measurement with QRS alternans, mechanical alternans and other physiological events. A prediction of a pathological cardiac event is made in response to a TWA assessment.

3. SLEEP APNEA

Sleep apnea is a breathing disorder characterized by brief interruptions of breathing during sleep. Central sleep apnea occurs when the brain fails to send the appropriate signals to the breathing muscles to initiate respiration, whereas obstructive sleep apnea occurs when air cannot flow through the patient's nose or mouth although efforts to breathe continue. Unknown to the patient, this results in heavy snoring, periods of no breathing and frequent arousals, which are abrupt changes from deep to light sleep. This also results in low levels of oxygen and increased levels of carbon dioxide in the blood, causing an arousal. In normal sleep, the non-rapid eye movement phase has a reduction in central respiratory drive, resulting in a regular pattern of breathing, and the patient's heart rate, blood pressure, stroke volume, cardiac output, and systemic vascular resistance all decrease. This state of hemodynamic and autonomic relaxation reduces the myocardial workload, but with sleep apnea the non-regular pattern of breathing results in abnormal hemodynamic and cardiovascular responses [4] that can be related to the occurrence of arrhythmias or even SCD.

Therefore, respiratory signals have been often analyzed together with ECG signals. The system in [4] acquires respiration (via impedance, acoustic, or other data) and ECG data from the patient and analyzes them in order to

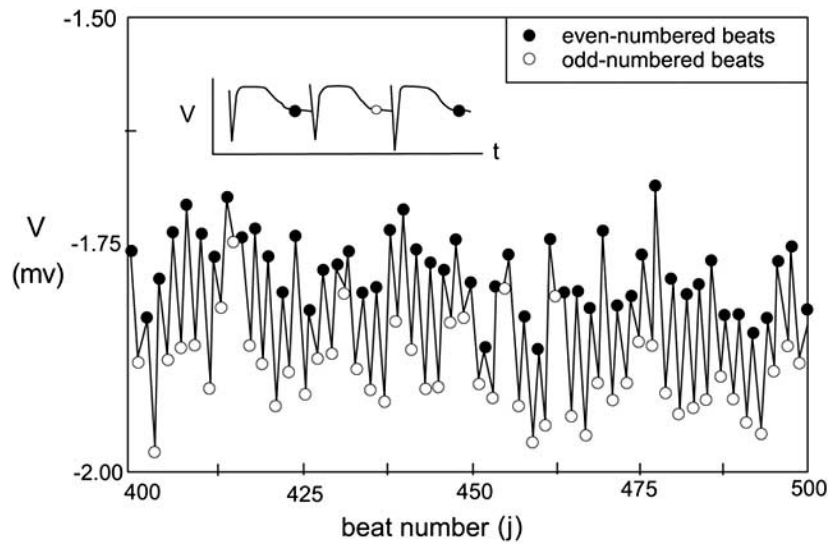


Fig. (2). The Figure shows the amplitude values of 100 successive beats after a fiducial point. A distinct alternation between the even-numbered and odd-numbered beats is apparent (adapted from [49]).

determine a correlation between sleep apnea and sudden cardiac death. In [51], a method and an apparatus for ECG-derived sleep disordered breathing monitoring, cardiac events detection and HRV monitoring, is disclosed for real-time application. In [52], a system is disclosed which carries out heart rate measurements of a patient at least during two sleep stages before the operation to obtain preoperative heart rate data, and calculating a dynamic HRV measurement by using non-linear analysis. In [53], a device is disclosed for simultaneous monitoring of cardiac activity, respiratory rate, and evaluation of sleep states of a user, which evaluates cardiac activity, HRV and ECG derived respiratory rate (from the R waves series) for evaluation of sleep disorders. In [54], respiration patterns are obtained via integration of intracardiac EGM, which are used to detect apnea, hyperpnea, and other disorders, and to deliver appropriate therapy.

4. ADVANCED ALGORITHMS

In this section, patents on the application of advanced signal processing techniques to the analysis of cardiac signals are presented. Having a solid theoretical foundation, these methods are claimed when reporting specific improvements for the cardiac signal processing setting, and they are used as the basis principle for applications such as the extraction of morphological features, the classification and quantification of the cardiac signals or the ECG and EGM signal compression. These advanced algorithms can be broadly split into four different groups, namely, time-frequency analysis using wavelet transform (WT), statistical methods using principal component analysis (PCA), independent component analysis (ICA) and nonlinear methods. After a brief theoretical introduction to the processing techniques and some examples of cardiac signal applications in the literature, different patents on each processing technique are briefly described.

4.1. WT Analysis

The WT can be seen as a time-frequency signal analysis. While the FT compares the similarity of a signal with a set of sine waves of different frequencies, the WT compares the signal with finite waves and their scaled versions, the so-called wavelets. A wavelet is an oscillating function whose energy is concentrated in time to better represent transient, nonstationary signals. This type of function involves two parameters, one for time translation and another for time scaling, which allow to analyze the joint presence of global waveforms related to large scales as well as fine waveforms corresponding with small scales [26]. The continuous WT of a continuous-time signal $x(t)$ is defined by the correlation between $x(t)$ and a scaled, translated version of a function $\varphi(t)$ called mother wavelet,

$$W_x(s, \tau) = \int_{-\infty}^{+\infty} x(t) \frac{1}{\sqrt{s}} \varphi\left(\frac{t-\tau}{s}\right) dt \quad (1)$$

where $s > 0$ is the scale parameter, and τ is the translation parameter.

Wavelet analysis is useful in the processing of biological signals for which the time localization is essential. Specifically, relevant tasks in ECG analysis are the detection of QRS complexes, T wave and P wave or the determination of beat-to-beat time and frequency parameters. In these applications, the ability of wavelet functions to time-widths adapting to each frequency provides with more accurate results than other classical approaches. WT has also been used for detection of myocardial ischemia and for cardiac signal denoising, e.g. in ECG recordings for removal of the 50 Hz noise (soft thresholding on the ECG wavelet coefficients) and baseline wander elimination [55,56].

Cardiac Signal Denoising

In [57], a WT based denoising technique for EGM is presented. In the preferred embodiment, one EGM is decomposed in the time-scale domain by using a set of finite wavelets. Some of the wavelets include the majority of information indicative of the EGM, while the others basically include noise. Then, a thresholding procedure can be performed on the wavelets to eliminate noise while preserving the information of the EGM. It is possible to apply different thresholds for the wavelets in different scales in order to improve the denoising. Following the thresholding, the wavelets are converted back into a denoised EGM via inverse WT.

Cardiac Events Classification

In patent [58], wavelet analysis capabilities to scrutinize fine structures and transients in nonstationary signals are applied to the study of different phenomena in EGM signals. The EGM is represented by a finite set of wavelets, yielding a decomposition in the time-scale domain. Then, a wavelet process unit is used to distinguish between occurrences of the following specific phenomena in EGM: (a) Large amplitude steep deflections, which correspond to primarily cardiac depolarizations at the given location; (b) Small amplitude steep deflections, which correspond to secondary cardiac depolarizations at the given location, e.g. commonly present during atrial fibrillation (AF); (c) Large amplitude shallow deflections, which correspond to a primary cardiac depolarization at a location that does not correspond to the sensing electrode, such as a ventricular depolarization sensed by an atrial electrode.

The invention in [59] discloses a depolarization waveform classifier based on wavelet analysis which tries to overcome the problems in rate-based event classifiers. Rate-based methods of event categorization in ICD decrease their sensitivity and specificity when atrial and ventricular rates are similar because they are not capable of differentiating rhythms using morphological features. The WT approach approximates the human expert analysis because it correlates distinct morphological features at multiple scales. The choice of wavelet analysis is justified by the fact that depolarization events are limited in energy and duration.

4.2. PCA in ECG Analysis

PCA is a statistical technique whose aim is to reduce the dimensionality of a data set consisting of a large number of correlated variables into a few variables (so called principal components), while maintaining as much as possible of the information present in the original data set [60]. Depending on the field of application, it is also named the Karhunen-Loève transform (KLT), the Hotelling transform, or proper orthogonal decomposition. The principal components are uncorrelated and ordered so that the first few keep the most for the variation present in all of the original variables. In signal processing applications, PCA is performed on a set of time series rather than on a data set of variables.

PCA in ECG signal processing is usually applied to samples extracted from the same segment location of different periods of the signal [61]. The location within the beat differs depending on the application and may comprise the entire heartbeat or a particular activity, e.g. T wave in order to study the repolarization characteristics.

Then, the principal components can be obtained from the data by applying an orthonormal linear transformation under the constraint that principal components are mutually uncorrelated and form a subspace that has the largest variance.

PCA has been widely used in different ECG signal processing applications, namely: (a) Data compression, both for efficient storage retrieval and for transmission across communication systems [62, 63]; (b) Noise reduction [61]; (c) Feature extraction, in which a subset of the principal components plays the role of features used to identify and analyze the cardiac signal waveforms [61].

ECG Feature Extraction

In [64], a multidimensional ECG processing and display systems for near real-time analysis is disclosed. In the preferred embodiment, the ECG recording signals are arranged into a two-dimensional matrix, which is analyzed using Singular Value Decomposition (SVD), a factorization technique closely related to PCA (SVD is indeed a more general method of understanding the change of basis carried out by PCA). The singular vectors obtained are further analyzed in order to identify ECG signal components of interest (such as TWA or LP), e.g. selected singular vectors can be analyzed in the frequency domain by using FFT techniques or may be adaptively filtered to enhance the components of interest.

In [65], a method for evaluating an ECG is disclosed. The method measures the electrical activity of a patient and processes the measured electrical activity to form a multi-lead signal and extracts a segment of such signal. Then, the extracted segment is transformed into a synthesized signal that is most representative of the patient's electrical activity. The transformation is performed by using a PCA. Finally, the synthesized signal is evaluated.

In [66], high resolution spectral analysis in multichannel ECG is made by using SVD techniques, in which a plurality of sensor signals are combined to form a data vector, and a plurality of data vectors are combined to form a matrix. A SVD of this matrix yields the (thresholded) eigenvalues, in which the imaginary parts of the natural logarithms of the eigenvalues are the soft, spectral frequencies and the real parts of the natural logarithms of the eigenvalues are attenuation constants for these frequencies. A frequency histogram can then be generated, from which LP can be identified. In [67] a method for assessing repolarization abnormalities is disclosed, which uses at least two repolarization signals extracted from ECG signals, and at least two repolarization signal from two different locations. Then, PCA is performed on (at least) two repolarization signals in order to extract (at least) two eigenvectors, \mathbf{ev}_1

and \mathbf{ev}_2 . Then, the ECG signal is transformed in a plane defined by the two eigenvectors and a maximum vector \mathbf{MV} is determined. Finally, the system has a processor that determines the repolarization duration based on the \mathbf{MV} obtained.

In [68], a method for providing an accurate measurement of the QT interval and to find new T wave morphological features is described. These new features can be extracted from a composite beat formed from the eigenvectors obtained by PCA. Moreover, in an embodiment, a database of ECG signals is compiled for use as a reference library. This database is used to generate a model ECG PCA that is compared against the PCA computed on the collected ECG signals, this allows for automated morphological feature detection by determining confidence intervals of specific morphological features.

ECG Compression

In [69], an algorithm for compression of ECG recordings is presented. The algorithm can optionally reduce computation time and storage space required by exploiting the differing spectral densities in the PQ, QRS and ST blocks of a heartbeat to apply a multirate downsampling operation that retains the appropriate spectral information in each block. The downsampled beats are then padded to make them of uniform size and a Karhunen-Loève Transform (KLT) is applied to the sample set. The most significant coefficients from the KLT are retained for reconstruction according to two different criteria: (a) Variance criterion, which retains the same number of coefficients so that the average variance of the reconstructed sample set is controlled; (b) Quality criterion, which retains a different number of coefficients for each beat according to a quality index.

4.3. ICA in ECG Analysis

ICA is a method for finding underlying components from multivariate data, under the requirement of these components to be both statistically independent and nongaussian [70]. ICA is included in the group of blind source separation (BSS) techniques. In practical terms, it allows us to recover the original (independent) source signals from their corresponding observed and mixed signals, with little a priori available information. Usually, it is necessary as many mixed signals as source signals. A classical example is the cocktail-party problem, where the aim is to recover the voices of different speakers from the mixed ones in a cocktail-party [71]. The basic ICA approach uses the following linear model:

$$\mathbf{y} = \mathbf{A}\mathbf{s} \quad (5)$$

where vector \mathbf{S} represents m independent sources, matrix \mathbf{A} is the linear mixing of the sources, and vector \mathbf{y} is the set of observations. Therefore, ICA consists of estimating both matrix \mathbf{A} and sources \mathbf{s} , when only \mathbf{y} is observed.

Recently, the application of ICA techniques to ECG processing has received increased attention and development. These applications rely on the ECG satisfying some of the conditions for ICA, namely: (a) Current from different sources is mixed linearly at the ECG electrodes; (b) Time delays in signal transmission are negligible; (c) There appear to be fewer sources than mixtures; (d) Sources have nongaussian voltage distributions [72].

In the literature, two approaches using ICA techniques to ECG processing are mostly found. First, artefacts and noise removal from ECG have been addressed [73]. The main assumption in this application is that both, artefacts and noise, are reasonably independent of signals originating from the heart. Second, noninvasive foetal ECG extraction has been addressed [72,74]. In this application, ICA is used to decompose maternal and foetal ECG recorded simultaneously from skin electrodes on the mother's abdomen and chest.

Maternal-Foetal ECG Separation

In [75], a system for maternal-foetal monitoring is presented, which provides to the user with real-time, maternal ECG signals, maternal uterine activity signals, maternal heart rate, foetal ECG signals, and foetal heart rate. In this invention, all the transmitted electrical activity is recorded by electrodes placed on the skin surface, including maternal ECG, maternal skeletal muscle, uterine muscle, foetal skeletal muscle and foetal ECG. ICA algorithm is used to separate maternal and foetal ECG signals in a non-invasively way. Additionally, some post-processing signal is applied on the separated components to present clinical observations regarding maternal and foetal health. The proposed ICA algorithm is the so-called Mermaid ICA. This algorithm performs the source separation by minimizing the output mutual information (MI), which is a measure of the dependencies (linear or non-linear) between signals and it is null (minimum) when the signals are independent. The way to estimate the MI is by using Rényi's entropy. The optimization algorithm selected is the gradient descent. In order to simplify the computation of the gradient, the patent proposes project the sources onto an orthonormal space (using principal components analysis, PCA) and then rotates these projections into a space of minimal MI.

In patent [76], a heart signal device to obtain heart signal information from a pregnant mother is proposed. In particular, the device has the ability to make a determination of the foetal heart component signal based on the heart signal information. This patent tries to overcome one common problem in foetal ECG separation which is the fact that the noise in each ECG recording channel is different from that in the other channels. This is a relevant problem when the noise has a power similar to the foetal ECG signal power, which is usual in early stages of pregnancy. Therefore, in order to overcome these difficulties, in this patent, an ICA based separation sub-system is combined with a noise-reduction sub-system based on nonlinear blind adaptive filtering methods to reduce the effects of measurement noises.

ECG Signal Decomposition

Patent [77] proposes a system to receive ECG recording signals and then separating these signals in its original component signals. The hypothesis is that ECG recording signals are typically combinations of original signals from different sources such as the atria and ventricles that produce different spatial and temporal patterns of electrical activity. Apart from P wave, QRS complex and T wave, there could be also weak irregular oscillatory signals that suggest a heart arrhythmia. The QRS complex often masks the other components, difficulting their interpretation. Therefore, in this patent, an ICA approach to separate the recorded ECG signals is presented. The separated signals are additionally displayed to help physicians to analyze heart conditions and to identify probably locations of abnormal heart conditions. In the preferred embodiment, the separated signals by ICA are plotted on a chaos phase space portrait to allow an enhanced interpretation. Another patent related with the previous one [78] uses the same procedure to decompose cardiac signals, i.e. ICA methods to decompose ECG signals. However, in this patent a method to group the different components according to predefined criteria is provided.

4.4. Nonlinear Analysis

Nonlinear signal processing techniques require the construction, estimation, and evaluation of nonlinear models of the signals under study (e.g. cardiac signals) under the hypothesis that they are generated by the output of chaotic dynamical systems. Chaotic dynamics provide with a possible explanation for the different complex and erratic patterns that appear in many cardiac signals, such as the heart rate. The term chaos is used to describe certain dynamical systems that may exhibit behaviours which are highly sensitive to small perturbations in the initial conditions and exhibit such unpredictable behaviours that structured signals seem to be random [79]. The different nonlinear methods that are usually applied to cardiac signals can be split into three different groups: Chaos Theory methods, Fractal Theory methods, and Information Theory methods.

Chaos Theory methods are based on analysis of the nonlinear dynamic attractors in phase spaces. A key issue in practical application of these methods is the Takens' Theorem, which states that by using only a measured signal generated as an output of the chaotic system, it is possible to build a reconstructed phase space (and therefore a reconstructed geometrical attractor), that preserves the properties of the dynamical system. The characterization of reconstructed attractors is usually done by estimating the Lyapunov Exponents and the Fractal Dimension (FD) of the attractor. The former describes the unpredictability of the underlying system as a result of the sensitivity on initial conditions, whereas the latter, usually estimated by the correlation dimension, quantifies the number of actual degrees of freedom of the system, that is, it measures its complexity. The main applications of these methods on cardiac signals have been the following: Nonlinear noise

reduction in ECG by using phase space projections [80]; Foetal ECG extraction [81]; Analysis of ECG during sinus rhythm and arrhythmia, using correlation dimension to distinguish between ventricular fibrillation (VF) and other arrhythmias [82]; And HRV assessment by using correlation dimension and Lyapunov exponents [83].

Fractal Theory methods are based on the analysis of self-similarity and correlation properties of time series. Several different methods have been used to quantify these properties in cardiac signals, especially to HRV time series. The aim of such methods is to estimate a scaling exponent, usually related to the so-called Hurst exponent, in order to quantify the correlation properties. Two of the most widely used methods are the Rescaled Range Method and the Detrended Fluctuation Analysis (DFA) [84]. This kind of methods has been used on RR series for risk stratification of SCD [85].

Information Theory methods use different entropy estimators in order to quantify the complexity, i.e. irregularity, of the analyzed signals. Entropy estimators can be split into two different categories, namely, spectral entropies and embedding entropies. Spectral entropy estimators use the amplitude components of the power spectrum of the signal as the probabilities in entropy calculations, whereas embedding entropy estimators use the time series to estimate the entropy. The entropy methods, namely Approximate Entropy (ApEn) and Sample Entropy (SampEn), have been widely applied assessing heart rate irregularity [86], and they also have been used on ECG signals in order to predict AF [87].

Patents with Chaos Theory

In [88], an indication is provided of a significant parameter for clinical evaluation of ventricular LP from a parameter measuring the LP complexity. The computed index is the FD of the LP attractor, the last one being reconstructed in a three dimensional voltage phase space from the ECG signals, and it is computed as:

$$FD = \frac{\log(L)}{\log(DD)} \quad (6)$$

where L is the total length of the attractor and DD is the spherical extent diameter. The parameter is compared with a certain threshold to indicate the SCD risk.

In patent [89], inventors propose a method to predict the onset of cardiac pathologies using a fractal index, i.e. an estimation of the fractal dimension. To compute this index, at least three ECG leads are required, then, a spatial curve is defined from the lead value, as a reconstructed attractor, from which the fractal index is obtained. The invention allows for the fractal index being calculated as a function of time, thus the rate of change of the index can be monitored. A negative rate of change indicates normal cardiac activity, whereas a positive one indicates pathological cardiac activity.

In [90], a method for assessing the risk of SCD is disclosed, which determines correlation parameters of NN intervals with rate dependent fluctuations of ECG para-

meters, by measuring the persistence of rate dependent patterns of ventricular ectopy in the ECG or in other similar recordings. Proposed suitable parameters are coupling interval of premature ventricular complexes to sinus beat, time intervals between consecutive ventricular beats, number of intervening sinus beats between two ventricular beats, and onset of bigeminy after short-long RR sequences.

Patents with Fractal Theory

In patent [91], a method to estimate the Hurst exponent from a time series data is presented. The invention gives an application example to assess the HRV by using the method proposed in different contexts, e.g. distinguish alcoholic subjects from normal ones. The algorithm computes a scaling exponent D from a phase space reconstruction, and the Hurst exponent, H , is obtained as:

$$H = 2 - D \quad (7)$$

Patents with Information Theory

In patents [92,93], the details for ApEn calculation are disclosed. Fig. (3) represents a flow chart of the algorithm to compute ApEn from a time series. According to these inventions, ApEn is a regularity statistic that quantifies the unpredictability of fluctuations in a time series, therefore, ApEn reflects the likelihood that similar patterns of observations will not be followed by additional similar observations. Quantitative values can be assigned to measure the degree of regularity of different time series. Authors present some particular applications, among them, the use of ApEn for computing the regularity of the beat-to-beat HRV data derived from an ECG. In [94], a straightforward application of ApEn is proposed for the algorithm as a part of an implanted defibrillator. The device continuously monitors a patient's heart rate to detect the presence of fibrillation and repeatedly computes the ApEn of a series representing the fibrillation heart at a moment in time. When

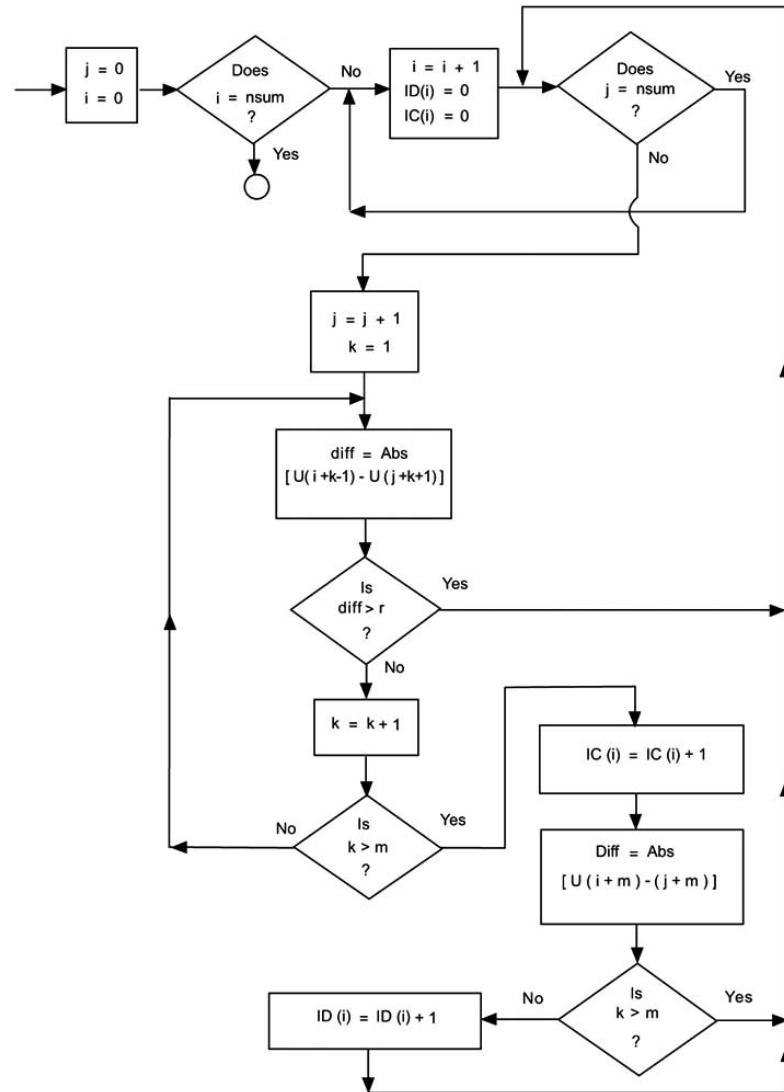


Fig. (3). Data processing system for computing the ApEn (from [92]).

the ApEn value meets a predetermined relation with respect to a threshold value, the system activates an energy delivery unit to defibrillate the heart with a low level shock. The process continues until defibrillation is achieved.

In [95], and ICD is disclosed which includes a unit for detecting and classifying arrhythmia episodes based on an irregularity parameter and on a complexity parameter. In this case, the irregularity and complexity parameter selected is the SampEn, which is a modification of ApEn statistic, developed by Richman and Moorman in order to overcome the two major limitations of the ApEn, namely, the dependence on the time series length and the relative consistence [96]. The irregularity parameter is computed over a cycle length data series, whereas the complexity parameter is computed over feature vectors extracted from the heart beats, so that this complexity parameter measures the morphological complexity. The arrhythmia detection and classification is achieved by comparing the SampEn values, irregularity and complexity parameters, with defined thresholds.

Combination of Nonlinear Methods

There are also some patents that propose the use of one or more indices using different nonlinear methods (chaos, fractal and information methods). In [97], several indices (entropy indices, chaos dimensionality indices as scaling exponent or correlation coefficient) are obtained from the heart rate in order to determine the degree of randomness, and they are combined to establish a dynamic control of the heart rate. The indices are continuously monitored and, if the degree of randomness falls below a threshold value, this indicates that the heart rate may be too coherent, so that a warning signal is generated indicating a significant risk of onset of a tachyarrhythmia. The system, in order to prevent the tachyarrhythmia, delivers overdrive pacing, or if already initiated, a more aggressive therapy is applied.

5. INVERSE PROBLEM IN ELECTROCARDIOGRAPHY

Methods for mapping the electrical activity of the heart have been receiving growing interest in order to accurately localize the origin of irregular beats, to identify their causes, and to deliver a proper treatment. Recent mapping systems aim to construct an instantaneous image of the epicardial or endocardial electrical activity of the heart from remote signals, measured on electrodes placed on the body surface or inside the cardiac chambers, respectively. Both the epicardial and endocardial mapping systems involve processing the ECG torso and the EGM signals to estimate the cardiac sources (potentials) from a number of probing electrodes which is referred as the Inverse Problem in Electrocardiography (IPE). The IPE is highly ill-posed due to the limited number of electrode sensors compared to the cardiac sources and the attenuation and spatial smoothing inside the torso (for epicardial mapping) or inside the heart (for endocardial mapping). Thus, inherent limitations of the IPE often results in oscillatory or non-physiological cardiac waveforms since small perturbations of the data, such as measurement errors or noise, result in large perturbation of

the solution. To stabilize and to constrain the solution of the IPE, regularization techniques are needed, which represent a trade-off between measured data fit and a priori imposed constraints. The most popular realizations of regularization techniques are the SVD and zero-order Tikhonov regularization performed by the regularized least squares (RLS) algorithm. Both regularization methods need, however, a priori knowledge of a free parameter whose value can significantly distort the results.

5.1. Forward Problem

To solve the IPE previously requires, in general, modelling the physical relationship between the measured potentials, the epicardial or endocardial potentials and the electrical volume conduction medium defined by the torso and heart. This model may be represented as

$$\mathbf{v}_p = \mathbf{A} \cdot \mathbf{v}_e \quad (8)$$

where \mathbf{v}_p is a $N_p \times 1$ vector representing the measured ECG or EGM signal on the probing electrodes, \mathbf{v}_e represents a $N_e \times 1$ vector of electric potential, i.e. the electrical activity at the epicardium or endocardium, and \mathbf{A} is the $N_p \times N_e$ transfer matrix accounting for the influence of the volume conductor medium (torso for epicardial mapping, blood for endocardial mapping). Therefore, matrix \mathbf{A} is given by the geometry and the conductivity of the defined volume conductor.

The relationship expressed in Equation (8) constitutes the so-called forward problem from which the IPE can be stated. It is worth noting that the forward problem does not take into account the time dependence, since quasi-static conditions apply, that is, the electrical activity of the heart instantaneously creates a potential field within the whole body. Thus, for each time instant, a direct solution of the IPE could be obtained by inverting the matrix \mathbf{A} . However, \mathbf{A} is generally undetermined ($N_p \ll N_e$) and ill-conditioned, and therefore this matrix cannot be directly inverted by conventional methods. In consequence, regularizations techniques are to be used.

Following the two different approaches to the IPE, namely epicardial and endocardial mapping, related patents can accordingly be divided into two scenarios, as presented in the next subsections.

5.2. Epicardial Mapping

The one-dimensional ECG recording constitutes a smooth projection of the three-dimensional electrical activity of the heart and in consequence the ECG signal might fail to localize certain bioelectric events of the heart. For this reason, a number of non-invasive methods to reconstruct epicardial potentials from ECG signals have been proposed giving rise to a number of work related patents see Fig. (4a). Patents associated to epicardial mapping have mainly focused on regularization methods to mitigate the ill effects of the IPE.

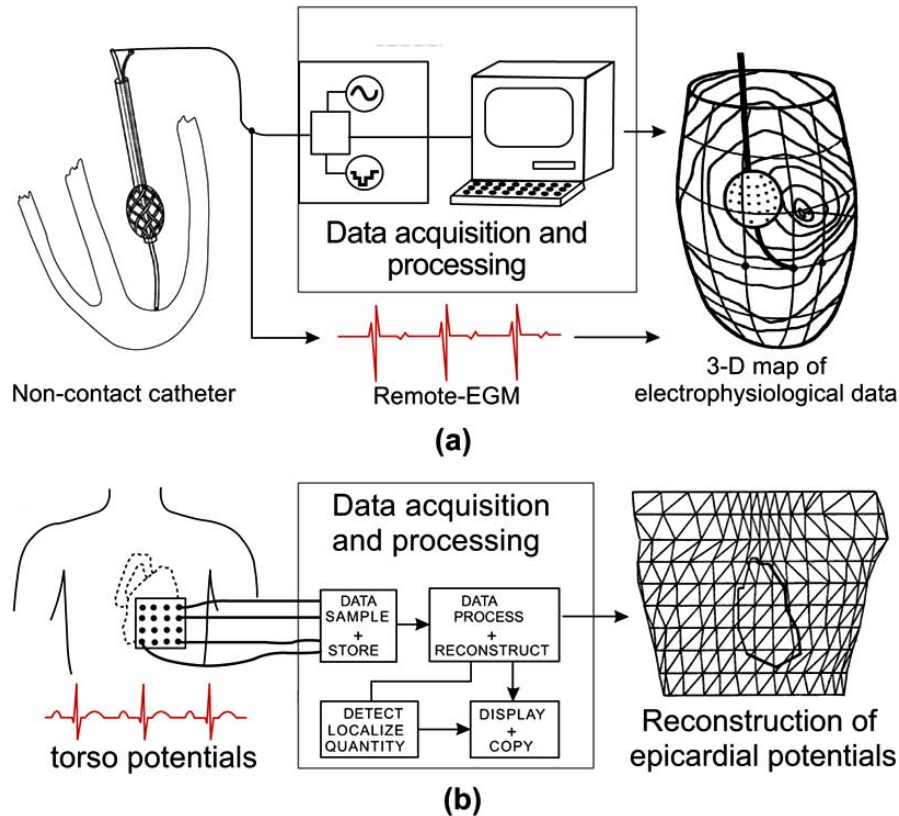


Fig. (4). Inverse problem in electrocardiography. (a) Acquisition system for epicardial mapping (adapted from [5]). (b) Acquisition system for endocardial inverse problem from multiple signals (adapted from [104]).

In [5], an epicardial mapping method is proposed by using a rectangular array of 6×8 electrodes disposed on the front part region of torso surface nearest to the heart. This method assumes a prior knowledge of a selected forward model (matrix \mathbf{A}) which is calculated by obtaining the geometry and conductivity of the volume conductor (torso and epicardium surfaces and interior organs) from computerized tomography (CT) scan images. Their particular implementation provides an inverse solution based on the minimum relative entropy (MRE) criteria. The MRE is a frequency domain method that iteratively estimates the power spectrum of the epicardial potentials according to the selected forward model to fit the measured torso signal spectrum.

More recently [98], a torso vest containing 240 electrodes was developed to construct a body surface potential map (BSPM) from which inferring the electrical activity of the epicardium. A forward matrix \mathbf{A} is also computed from the geometric model obtained by CT scan, magnetig resonance imaging (MRI) or X-ray. The inverse solution is performed by means of the generalized minimum residual (GMRes) which is an iterative method for inverting the matrix \mathbf{A} without imposing constraints to the solution.

Instead of reconstructing the magnitude of the epicardial potentials, in [99] a three-dimensional map is built for parameters of interest associated with cardiac cell potentials, such as the depolarization or the repolarization time. For this

purpose, the inventors used a cardiac source model accounting for the epicardial potentials (\mathbf{v}_e) from which a lumped-parameter model was defined. States of this model were estimated by using an extended Kalman filter according to the residual difference between the measured ECG and the corresponding simulated ECG. This pseudo-ECG was computer-generated from the forward matrix \mathbf{A} and the epicardial source model.

Other interesting approaches [100,101] extract information about the cardiac electrical activity from the ECG signals, while not performing an inverse solution. In these patents, signals from the torso electrodes are processed to compute the two-dimensional Laplacian of the surface potential, which constitutes an alternative representation of the electrical activity of the heart.

5.3. Non-contact Endocardial Mapping

Common electrophysiological studies measure the electric potentials present on the interior surface of the heart to localize regions of abnormal electrical behaviour, hence allowing for a proper diagnosis and treatment. These endocardial mapping procedures are traditionally performed by sequentially advancing an electrode catheter into contact with the endocardium in many locations along many heartbeats, and subsequently inferring endocardial activation maps from the set of measured EGM. However, traditional endocardial mapping systems present certain difficulties

such as the limited number of electrodes being used and the long time consumption of the procedure. Therefore, alternative mapping systems are recently being introduced which take simultaneous measurements from an intracardiac non-contact electrode array to construct an instantaneous image of the endocardial electrical activity see Fig. (4b). To address the non-contact endocardial mapping problem in terms of the IPE different approaches have been proposed. In [102,103] a non-expandable non-contact multielectrode catheter to reconstruct the endocardial potentials and isochrones is disclosed. Different shapes of the terminal portion of the probe catheter were evaluated, including “J”, “U”, “O”, helix and pigtail curve shapes. Forward matrix A was generated based on the estimated geometry of the endocardium with X-ray and the a priori known geometry of the probe. Inverse calculation was implemented by using a Tikhonov regularization algorithm whose free parameter was determined by the composite residual and smoothing operator (CRESO) method.

A non-contact expandable 24 electrodes catheter was developed [104] to produce a spherical geometric shape. Based on the characteristic shape of the probe, Laplace equation accounting for the relationship between the endocardial potentials and the probe potentials can be calculated analytically and thus the electrical activity of the selected heart chamber is reconstructed. As mentioned in different patents, the accuracy of the inverse reconstruction increased with increased number of electrodes in the probe catheter. Under this consideration, in [105] a non-contact endocardial mapping system is designed which includes a moving probe to increase the number of measured signals and hence improving the inverse calculation. This moving catheter, however, requires a complicated location and synchronization system in order to properly combine the information obtained from different locations. Also, a RLS algorithm is selected as the regularization method.

In [106], the work is focused on a regularization technique for the non-contact endocardial mapping, with potential application to other inverse problems. A Duncan and Horn formulation of the Kalman filter is proposed, which is a temporal iterative method based on constraining the solution not to vary from one time instant to the other.

Inventors in [107] state that the distribution of the surface charge or of dipole densities in the heart chamber is a much better indicator of cardiac arrhythmias than electric potentials. Based on this assumption, firstly the electric potential at the endocardium is determined by contact or non-contact mapping procedures. Then, endocardial potentials are transformed into surface charge densities or dipole densities according to the Electromagnetic Field Theory.

Lastly, pace mapping systems are to be considered. They do not state a forward and inverse formulation, but still they allow identifying intracardiac arrhythmogenic foci. [108, 109]. In a first state, an arrhythmogenic situation is induced and the effect is visualized in the surface ECG. Then the cardiac chamber is mapped in different locations and paced in selected potential foci. ECG signals obtained during

pace mapping are compared to arrhythmia induced ECG signals. The location from which pacing results in the same ECG is considered to be the origin of the arrhythmia.

6. CURRENT & FUTURE DEVELOPMENTS

Applications of digital signal processing include signal conditioning, noise reduction, cardiac event sensing, heart dynamics visualization, arrhythmia detection, monitoring of patient's physiological condition and sudden cardiac death risk stratification and prediction. A large number of patents on digital processing techniques with application in electric cardiac signal analysis continue to be disclosed every year. In this review, representative examples of the most relevant topics have been compiled and briefly described. Usually the algorithm is linked to an apparatus and patents for signal processing procedures do not come alone.

SCD Prediction

A number of works have been developed on HRV characterization claiming its utility as a clinical tool. This trend is expected to continue due to the promising results that have been obtained. Many of the patents on HRV, besides analyzing the HRV signal, present a complete system, first extracting the ECG signal and constructing the HRV signal. Most of them apply both temporal and spectral methods for the HRV measurement in order to improve its characterization.

Recent clinical works have presented the TWA as a strong marker of cardiac electrical instability and several patents have been presented for TWA detection, both in the surface ECG and in the intracardiac EGM. Some of the revised patents focus only on the detection stage, while others also include postdetection therapy. Despite their low intensity, TWA detection on the ECG has the significant advantage of being a non-invasive tool over detection on EGM. Further works are expected to be disclosed in both branches due to their useful clinical applications.

Advanced Algorithms

The diverse nature, aims, and scope of patents involving digital signal processing in cardiac electrophysiology, show that these techniques have a broad range of applications. Taking electric signals such as surface ECG and intracardiac EGM as the input, the techniques of digital signal processing that we have encountered range from basic methods, such as signal filtering, to more advanced ones, such as wavelet transform and non-linear analysis. Chronologically, we have observed that the use of processing methods follows the same trends as in other areas of research. Thus, the early 90's saw the emergence of non-linear analysis, including chaos, fractals, and entropy measurements.

Advanced signal processing techniques have been applied for two main purposes, namely: Signal denoising (which comprehends noise removal as well as signal compression and foetal ECG extraction), feature extraction, and cardiac event detection and classification. Algorithms addressing signal denoising usually employ WT analysis and statistical methods (PCA and ICA). In particular, noise

removal on EGM has been achieved using WT; ECG signal compressions has been performed using PCA, whereas foetal extraction from maternal-foetal ECG has been developed using, preferably, ICA techniques. Feature extraction for morphological analysis is also based on WT and statistical methods. Nonlinear methods are usually used in cardiac event detection and classification due to the fact that these methods commonly provide with a single value which can quantify the complexity (chaos theory methods), correlation properties (fractal theory methods) and irregularity (information theory methods) of the signal. This value can be used straightforwardly to distinguish between different cardiac states or events which have different degrees of complexity.

A problem shared by advanced methods is the high computational cost. These methods are usually both time and memory consuming. Such limitation implies that these algorithms are hard to implement in small devices as ICD or Pacemakers. Therefore, it is necessary to develop new algorithms, computationally less demanding, in order to overcome this restriction. An example in this direction is *ApEn*, which is a method to estimate the entropy of short data series, overcoming the need for long series as in classical entropy estimation methods. In fact, some patents presented in this paper implement the *ApEn* algorithm in ICDs in order to distinguish between different arrhythmias.

Inverse Problem in Electrocardiography

Since the first applications of digital signal processing to electric cardiac signals measured on electrode systems, many efforts have been made to visualize the complex bioelectric patterns that propagate on the internal or external surface of the heart. Patents devoted to the IPE highlight this situation where a number of inventions dating from the early 90's. Since then, a great advancement has been documented in the three-dimensional representation of heart and torso geometric models. Conversely, little improvements can be assessed in the solutions of the IPE, which always demonstrate a limited scope. Specifically, epicardial mapping inventions draw attention to the regularization techniques to tackle the IPE. Nevertheless, the proposed solutions do not provide accurate enough results then limiting their potential use in real medical settings. On the other hand, patents associated to the non-contact endocardial mapping focus on the signal acquisition and electrodes positioning systems rather than the signal processing regularization procedures which are normally based on traditional Tikhonov techniques.

Even so, commercial approaches for non-contact endocardial mapping procedures have been recently presented. These systems have reactivated the interest for clinicians, researchers and manufacturers in utilizing non-contact techniques in electrophysiological studies. However, the accuracy of the reconstructed electrical information is still inferior to present mapping systems and this situation has restricted its application in the EP laboratories. Therefore, challenges of future inventions regarding epicardial or endocardial mapping systems should consider providing

detailed anatomical reconstruction as well as accurate electrophysiological characteristics.

In general terms, given the large number of items that have been presented all around the world in these last years, any attempt to summarize all of them in some few pages will be too limited and hence, this work aimed to be just an overview on the most significant applications. We want to stress that we did not exclude from consideration those disclosed patents which have not yet been subsequently used, because they could still become relevant. Nevertheless, additionally to the review of scientific literature, the review of the patents in this environment can give us an excellent landscape on what has happened and what could be happening in the near future.

ACKNOWLEDGEMENT

This work has been partially supported by Projects TEC2007-68096-C02/TCM from Ministerio de Ciencia e Innovación and URJC-CM-2008-CET-3732 from Comunidad de Madrid.

CONFLICT OF INTEREST

None.

REFERENCES

- [1] Goya-Esteban R, Barquero-Pérez O, Alonso-Atienza F, *et al.* A review on recent patents in digital processing for cardiac electric signals (I): From basic systems to arrhythmia analysis. *Recent Patents on Biomedical Engineering* 2009; In this issue.
- [2] Krause, P.G.: US20070255345 (2007).
- [3] Callahan, T., Shell, W.: US20020095095 (2002).
- [4] Rowlandson, G.I., Albert, D., Dorsey, P.: US20050234313A1 (2005).
- [5] Nikias, L.C., Brooks, D.H., Siegel, J.H., Fabian, M.: US4961428 (1990).
- [6] Algra A, Tijssen JG. QTc prolongation measured by standard 12-lead electrocardiography is an independent risk factor for sudden death due to cardiac arrest. *Circulation* 1991; 83(6): 1888-1894.
- [7] Kawada, H., Inui, K., Nakai, K., Itoh, M.: US20070276274 (2007).
- [8] Xue, J.Q., Rowlandson, G.I., Albert, D.: US20050234353 (2005).
- [9] Crosby, P., Morris, D., Soane, M.: WO2004103150 (2004).
- [10] Cazares, S., Peterson, J., Sachanandani, H., *et al.*: US20080162182 (2008).
- [11] Starobin, J., Chernyak, Y.B.: US20020042578 (2002).
- [12] Kenigsberg, D., Khanal, S., Kowalski, M., Krishnan, S.: WO2005077267 (2005).
- [13] Shvilkin, A.V., Josephson, M.E.: US20070129640 (2007).
- [14] Siegel, J.H., Nikias, C.L.: US005365426 (1994).
- [15] Joo, T., Hampton, D.R., Schmitt, P., Medema, D., Niskanen, R.: WO9955226 (1999).
- [16] Seegobin, R.D.: US20016223073 (2001).
- [17] Mugler, D.H., Acharya, S., Gopalakrishnan, R.: US20060052717 (2006).
- [18] Akselrod S. Power spectrum analysis of heart rate fluctuation: A quantitative probe of beat-to-beat cardiovascular control. *Science* 1981; 213: 220-222.
- [19] Rompelman AJ, Coenen RM, Kitney RI. Measurement of heart rate variability. *MBEC* 1977; 15: 233-239.
- [20] Bigger JT, Fleiss JL, Steinman RC, Rolnitzky LM, Kleiger RE, Rottman JN. Frequency domain measures of heart period variability and mortality after myocardial infarction. *Circulation* 1992; 85(1): 164-171.
- [21] Piskorski J, Guzik P. Geometry of the Poincaré plot of RR intervals and its asymmetry in healthy adults. *Physiol Measurement* 2007; 28: 287-300.

- [22] Malik M. Heart rate variability. Standards of measurement physiological interpretation and clinical use. *Eur Heart J* 1996; 17: 345-381.
- [23] Mietus JE, Peng CK, Henry I, Goldsmith RL, Goldberger AL. The pNNx files: re-examining a widely used heart rate variability measure. *Heart* 2002; 88: 378-380.
- [24] Malik M, Farrell T, Cripps T, Camm AJ. Heart rate variability in relation to prognosis after myocardial infarction: Selection of optimal processing techniques. *Eur Heart J* 1989; 10: 1060-1074.
- [25] Brennan M, Palaniswami M, Kamen P. Do existing measures of poincaré plot geometry reflect nonlinear features of heart rate variability? *IEEE Trans Biomed Eng* 2001; 48(11): 1342-1347.
- [26] Sörnmo L, Laguna P. *Bioelectrical Signal Processing in Cardiac and Neurological Applications*. Elsevier Academic Press, 2005.
- [27] Huikuri HV, Makikallio T, Airaksinen KE, Mitrani J, Castellanos, R, Myerburg AJ. Measurement of heart rate variability: A clinical tool or a research toy? *J Am College Cardiol* 1999; 34(7): 1878-1883.
- [28] Rojo-Álvarez JL, Martínez-Ramón M, Figueiras AR, García A, Artés, A robust support vector algorithm for nonparametric spectral analysis. *IEEE Signal Proc Letters* 2003; 10(11): 320-323.
- [29] Fallen E. Clinical utility of heart rate variability. *Cardiac Electrophysiol Rev* 1997; 1(3): 347-351.
- [30] Kleiger RE. Heart rate variability: Measurement and clinical utility. *Auton Nerv Syst* 2005; 10(1): 88-101.
- [31] Kuo, T.B., Yanf, C.C.: US20040230130 (2004).
- [32] Meier, J.H., Fournie, E.: US20010016694A1 (2001).
- [33] Rossing, M., Kieval, R.S., Erwin, E., Pedersen, B.D., Braginsky, V.: US20080009916 (2008).
- [34] Proctor, K.G., Duncan, C.R.: US20070276275 (2007).
- [35] Hadley, D.M.: US20070208266 (2007).
- [36] Childre, L., Atkinson, M.: WO0051677 (1999).
- [37] Berbari EJ. Recording from the body surface of arrhythmogenic ventricular activity during the s-t segment. *Am J Cardiol* 1978; 41: 697-701.
- [38] Albert, D.E., Berbari, E.J.: US005025794 (1991).
- [39] Albert, D.E., Lander, P.: US005117833 (1992).
- [40] Kelen, G., Henkin, R.: EP0462690A1 (1991).
- [41] Haberl, R., Schels, H.F.: US005211179 (1993).
- [42] Cano, G.G.: US005341811 (1994).
- [43] Delmar, B.E.: WO9404075 (1994).
- [44] Sörnmo, L., Ohlsson, T.: US5564428 (1996).
- [45] Martínez JP, Olmos S. Methodological principles of T wave alternans analysis: A unified framework. *IEEE Trans Biomed Eng* 2005; 52(4): 599-613.
- [46] Nearing BD, Verrier RL. Modified moving average analysis of T-wave alternans to predict ventricular fibrillation with high accuracy. *J Applied Physiol* 2002; 92: 541-549.
- [47] Watanabe M, Fenton FH, Evans S, Hastings HM, Karma A. Mechanisms for discordant alternans. *J Cardiovasc Electrophysiol* 2001; 12(2): 196-206.
- [48] Mortara, D.W.: US20040176696 (2004).
- [49] Cristini, D.J., Stein, K.M., Lerman, B.: WO0234123 (2002).
- [50] Zhou, X., Mullen, T., Gillberg, J.M., Stadler, R.W.: US20060116592 (2006).
- [51] Burton, D.: US20070032733 (2007).
- [52] Laitio, T., Scheinin, H., Huikuri, H., Viertio-Oja, H., Meriläinen, P.: US20080167565 (2008).
- [53] Mischynski, D.J., Bukhman, V.: US20050148895 (2005).
- [54] Koh, S.: US2008007404799 (2008).
- [55] Jayachandran ES, Joseph P. *Wavelets and its application in cardiology*. Advances in Cardiac Signal Processing. Springer 2007.
- [56] Akay, M. Time frequency and wavelets in biomedical signal processing. IEEE Press 1997.
- [57] Houben, R.: US20040193065 (2004).
- [58] Houben, R.: US20040210147 (2004).
- [59] de Voir, C.: US20060167364 (2008).
- [60] Jolliffe IT. *Principal component analysis*, Springer 2002.
- [61] Castells F, Laguna P, Sörnmo L, Bollmann A, Millet J. Principal component analysis in ECG signal processing. *EURASIP J Appl Signal Process* 2007; 1: 98.
- [62] Olmos S, Millán M, García J, Laguna P. ECG data compression with the Karhunen-Loève transform. *Proc Computers Cardiol* 1996; 1(1): 253-256.
- [63] Blanchett T, Kember G, Fenton A. KLT-based quality controlled compression of single-lead ECG. *IEEE Trans Biomed Eng* 1998; 45(7): 942-945.
- [64] Hutson, W.: WO9410905 (1994).
- [65] Xue, J.Q., Strujik, J.J., Andersen, M., Graff, C., Hardahl, T.: EP1935336 (2008).
- [66] Haardt, M., Strobach, P.: US005560367 (1996).
- [67] Couderc, J., Vaglio, M.: US20070208265 (2007).
- [68] Xue, J.: US20080132799 (2008).
- [69] Blanchett, T., Kember, G., Fenton, A.: US20006152883 (2000).
- [70] Hyvarinen A, Karhunen J, Oja E. *Independent component analysis*. Wiley-Interscience, 2001.
- [71] Hyvarinen A. Survey on independent component analysis. *Neural Comput Surv* 1999; 2: 94-128.
- [72] Jung T, Makeig S, Lee T, Mckeown MJ, Brown G, Bell AJ, Sejnowski TJ. Independent component analysis of biomedical signals. *Proc Int workshop on independent component analysis and signal separation* 2000; 633-644.
- [73] He T, Clifford G, Tarassenko L. Application of independent component analysis in removing artefacts from the electrocardiogram. *Neural Comput Appl* 2006; 15(2): 105-116.
- [74] Cardoso JF. Multidimensional independent component analysis. *Proc. Int. Workshop on Higher-Order Stat*; 1998; 111-120.
- [75] Marossero, D., Euliano, T.Y., Euliano, N.R., Principe, J.C.: US20050267377 (2005).
- [76] Graupe, M., Graupe, D., Suliga, P., Zhong, Y.: WO2005044101 (2005).
- [77] Jung, T., Duann, J.: WO03003905 (2003).
- [78] Duann, J., Jung, T.: WO2006044699 (2006).
- [79] Clifford G, Azuaje F, McSharry P. *Advanced methods and tools for ECG data analysis*, Artech House Inc, Norwood USA (2006).
- [80] Schreiber T, Kaplan D. Nonlinear noise reduction for electrocardiograms. *Chaos* 1996; 6: 87-92.
- [81] Richter M, Schreiber T, Kaplan DT. Fetal ECG extraction with nonlinear state-space projections. *IEEE Transactions on Biomedical Engineering* 1998; 45(1): 133-137.
- [82] Yu D, Small M, Harrison RG, Robertson C, Clegg G, Holzer M, Sterz F. Measuring temporal complexity of ventricular fibrillation. *Physical Letters A* 2000; 265(1-2): 68-75.
- [83] Malik M, Camm J. *Dynamic Electrocardiography*. Blackwell Future, 2004.
- [84] Bassingthwaite J, Liebowitch L, West B. *Fractal physiology*. Oxford University Press, 1994.
- [85] Huikuri TM, Soren H, Lars K, et al. Fractal analysis of heart rate dynamics as a predictor of mortality in patients with depressed left ventricular function after acute myocardial infarction. *Am J Cardiol* 1999; 83(6): 836-839.
- [86] Pincus S, Goldberger A. Physiological time-series analysis: what does regularity quantify? *Am J Physiol Heart Circ Physiol* 1994; 266(4): H1643-1656.
- [87] Alcaraz R, Rieta JJ. Wavelet bidomain sample entropy analysis to predict spontaneous termination of atrial fibrillation. *Physiological Measurement* 2008; 29(1): 65-80.
- [88] Escalona, J.O.: WO9428494 (1994).
- [89] Schreck, D.M.: US20040002661 (2004).
- [90] Glass, L., Lerma, C., Goldberger, A.: WO2008003181 (2008).
- [91] DePetrillo, P.B.: US20006144877 (2000).
- [92] Pincus, S.M., Neidorff, R.A.: US5191524 (1993).
- [93] Pincus, S.M., Neidorff, R.A.: US5769793 (1998).
- [94] Karagueuzian, H., Chen, P.: WO9850108 (1998).
- [95] Li, D.: US20060281999 (2006).
- [96] Richman JS, Moorman JR. Physiological time-series analysis using approximate entropy and sample entropy. *Am J Physiol Heart Circ Physiol* 2000; 278(6): H2039-2049.
- [97] Kroll, M.W.: US20046775571 (2004).
- [98] Rudy, Y., Ramanathan, C., Ghanen, R., Jia, P.: US20030120163 (2003).
- [99] Chen, Y., Thomenius, K., Yang, T., Teng, F., Zhang, Y., Zhou, J., Xue, J.: US20080177192 (2008).

- [100] Cohen, R.J.: US005146926 (**1992**).
- [101] Tarjan, P.P., Lu, C.C., Besio, W.G.: US20030236466 (**2003**).
- [102] Rudy, Y.: WO9906112 (**1999**).
- [103] Rudy, Y.: US2005006839588 (**2005**).
- [104] Beatty, G.E., Kagan, J., Budd J.R.: US20050043604 (**2005**).
- [105] Harlev, D., Amariglio, L.: WO2007146864 (**2007**).

- [106] Berrier, K.L.: US2008007433730 (**2008**).
- [107] Scharf, C., Kasche, A.: WO2008014629 (**2008**).
- [108] Pappone, C.: US20070060829 (**2007**).
- [109] Stolarski, S., Turgeman, A., Bartal, M., Abbo, R., Govari, A., Ephrath, Y., Altmann, A.C.: EP1943945A1 (**2008**).