(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
29 August 2013 (29.08.2013)

WIPO | PCT

(10) International Publication Number
WO 2013/123549 A1

(51) International Patent Classification:
A61B 5/046 (2006.01) *A61B 5/0468* (2006.01)
A61B 5/0472 (2006.01) *A61N 1/37* (2006.01)
A61B 5/0402 (2006.01) *A61N 1/39* (2006.01)

(21) International Application Number:
PCT/AU2013/000146

(22) International Filing Date:
20 February 2013 (20.02.2013)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2012900625 20 February 2012 (20.02.2012) AU

(71) Applicant: **ADELAIDE RESEARCH & INNOVATION PTY LTD** [AU/AU]; Level 14, 115 Grenfell Street, Adelaide, South Australia 5000 (AU).

(72) Inventors: **GANESAN, Anand Narayan**; 18 Rosetta Street, Collinswood, South Australia 5081 (AU). **KUKLIK, Pawel**; Zwirki i Wigury 2, PL-16-030 Suprasi (PL). **SANDERS, Prashanthan**; 30 Brandreth Street, Tusmore, South Australia 5065 (AU).

(74) Agent: **DIBBENS, Justin**; Dibbens Intellectual Property, Level 3, 97 Pirie Street, Adelaide, South Australia 5000 (AU).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

(54) **Title**: METHOD FOR IDENTIFYING A CARDIAC REGION FOR ABLATION

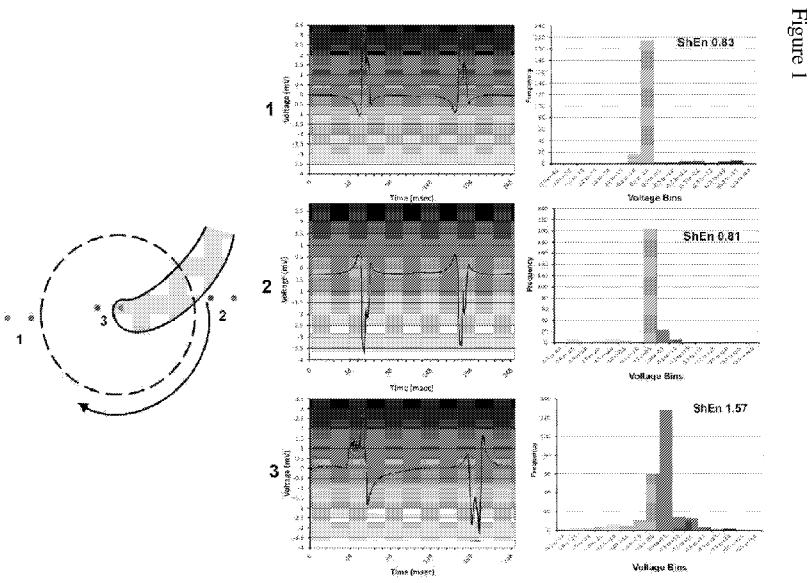


Figure 1

(57) **Abstract**: The present disclosure relates to methods for identifying a cardiac region for ablation, methods of treating a subject susceptible to or suffering from a cardiac arrhythmia, systems for identifying a cardiac region for ablation and computer-readable media. Certain embodiments provide a method of identifying a cardiac region for ablation to prevent and/or treat a cardiac arrhythmia, the method comprising determining one or more electrical waveform characteristics at a plurality of cardiac sites, identifying a cardiac region of maximal variance of the one or more electrical waveform characteristics, and identifying the cardiac region of maximal variance of the one or more electrical waveform characteristics as the cardiac region for ablation to prevent and/or treat the cardiac arrhythmia.

WO 2013/123549 A1

METHOD FOR IDENTIFYING A CARDIAC REGION FOR ABLATION

PRIORITY CLAIM

[001] This application claims priority to Australian provisional patent application 2012900625 filed on 20 February 2012, the content of which is hereby incorporated by reference.

FIELD

[002] The present disclosure relates to a method for identifying a cardiac region for ablation to prevent and/or treat a cardiac arrhythmia. The present disclosure also relates to methods of treating a subject susceptible to or suffering from a cardiac arrhythmia, systems for identifying a cardiac region for ablation and computer-readable media.

BACKGROUND

[003] Cardiac arrhythmias are rhythms of the heart that are abnormal. There are several kinds of arrhythmias, depending on the nature of the abnormal heart rhythm. Cardiac arrhythmias, such as atrial fibrillation, are extremely prevalent. For example, atrial fibrillation is the most prevalent arrhythmia, the incidence of which increases with age and tends to occur more in males than females. Approximately 4% of people over the age of 60 have experienced an episode of atrial fibrillation and this disorder accounts for one-third of hospital admissions for cardiac rhythm disturbances. Over 2.2 million people are believed to have AF in the United States alone.

[004] Although atrial fibrillation is often asymptomatic, it may cause palpitations or chest pain. Prolonged atrial fibrillation often results in the development of congestive heart failure and/or stroke. Heart failure develops as the heart attempts to compensate for the reduced cardiac efficiency, while stroke may occur when thrombi form in the atria, pass into the blood stream and lodge in the brain. Pulmonary emboli may also develop in this manner.

[005] Clinically atrial fibrillation is diagnosed by irregular rhythm and an absence of P waves on an ECG. In addition, the ECG of a patient with atrial fibrillation will usually show a narrow QRS complex, although it may be wide if abnormal conduction or partial or full interruption of electrical conduction in the bundle blocks is present.

[006] Current methods for treating atrial fibrillation include electric and/or chemical cardioversion and laser ablation. Anticoagulants, such as warfarin, dabigatran, and heparin, are also typically prescribed in order to avoid stroke.

[007] Chemotherapeutic treatment of atrial fibrillation includes heart rate control drugs, cardiac glycosides, beta-blockers, and calcium channel blockers which seek to reduce the heart rate to one that is closer to normal to reduce symptoms, and rhythm control drugs which seek to restore and maintain the regular heart rhythm. However, many of the common agents used to treat atrial fibrillation are relatively toxic and/or have a range of undesirable side effects.

[008] Ablation is another procedure that may be utilised in some patients to control atrial fibrillation. This procedure requires an assessment of the cardiac region contributing to the fibrillation and subsequently cauterizing a region of cardiac muscle to disrupt the arrhythmia. However, despite advances in ablation technologies the procedure is still lengthy and difficult, particularly in relation to identification of the region to be ablated. In addition, the success of the procedure and the risk of complications improve when the ablation is conducted by an electrophysiologist with extensive experience in ablating atrial fibrillation, who must interpret various parameters during the procedure to arrive at a suitable region for ablation.

[009] Accordingly, there is a need to provide improved methods to prevent and/or treat cardiac arrhythmias, and in particular, to address one or more problems relating to use of ablation for preventing and/or treating cardiac arrhythmias and/or to provide one or more advantages.

SUMMARY

[0010] The present disclosure relates to the identification of a cardiac region for ablation to prevent and/or treat a cardiac arrhythmia.

[0011] Certain embodiments of the present disclosure provide a method of identifying a cardiac region for ablation to prevent and/or treat a cardiac arrhythmia, the method comprising:

determining one or more electrical waveform characteristics at a plurality of cardiac sites;

identifying a cardiac region of maximal variance of the one or more electrical waveform characteristics; and

identifying the cardiac region of maximal variance of the one or more electrical waveform characteristics as the cardiac region for ablation to prevent and/or treat the cardiac arrhythmia.

[0012] Certain embodiments of the present disclosure provide a method of treating a subject susceptible to or suffering from a cardiac arrhythmia, the method comprising:

determining one or more electrical waveform characteristics at a plurality of cardiac sites in the subject;

identifying a cardiac region of maximal variance of the one or more electrical waveform characteristics; and

ablating the cardiac region of maximal variance in the subject, thereby treating the subject.

[0013] Certain embodiments of the present disclosure provide a method of preventing and/or treating a cardiac arrhythmia in a subject, the method comprising:

determining one or more electrical waveform characteristics at a plurality of cardiac sites in the subject;

identifying a cardiac region of maximal variance of the one or more electrical waveform characteristics; and

ablating the cardiac region of maximal variance in the subject, thereby treating the subject.

[0014] Certain embodiments of the present disclosure provide a method of identifying a cardiac region for ablation to prevent and/or treat a cardiac arrhythmia, the method comprising:

determining voltage amplitude at a plurality of cardiac sites;

identifying a cardiac region of maximal distribution of voltage amplitude; and

identifying the cardiac region of maximal distribution of voltage amplitude as the cardiac region for ablation to prevent and/or treat the cardiac arrhythmia.

[0015] Certain embodiments of the present disclosure provide a method of identifying a cardiac region for ablation to prevent and/or treat a cardiac arrhythmia, the method comprising:

determining Shannon entropy of voltage amplitude distribution at a plurality of cardiac sites;

identifying a cardiac region of maximal Shannon entropy; and

identifying the cardiac region of maximal Shannon entropy as the cardiac region for ablation to prevent and/or treat the cardiac arrhythmia.

[0016] Certain embodiments of the present disclosure provide a method of identifying a cardiac region for ablation to prevent and/or treat a cardiac arrhythmia, the method comprising:

determining one or more electrical waveform characteristics at a plurality of cardiac sites;

identifying a cardiac region of maximal complexity of distribution of the one or more electrical waveform characteristics; and

identifying the cardiac region of maximal complexity of distribution of the one or more electrical waveform characteristics as the cardiac region for ablation to prevent and/or treat cardiac arrhythmia.

[0017] Certain embodiments of the present disclosure provide a method of identifying a cardiac region for ablation to prevent and/or treat a cardiac arrhythmia, the method comprising:

using a computer processor means to receive data associated with one or more electrical waveform characteristics obtained from a plurality of cardiac sites and process the data to generate a map of the variance of the one or more electrical waveform characteristics; and

using the map to identify a region for ablation.

[0018] Certain embodiments of the present disclosure provide a method of identifying a cardiac region for ablation to prevent and/or treat a cardiac arrhythmia, the method comprising:

using a computer processor means to receive data associated with voltage amplitude obtained from a plurality of cardiac sites and process the data to generate a map of the variance of the voltage amplitude; and

using the map to identify a region for ablation.

[0019] Certain embodiments of the present disclosure provide a method of identifying a cardiac region for ablation to prevent and/or treat a cardiac arrhythmia, the method comprising:

using a computer processor means to receive data associated with one or more electrical waveform characteristics obtained from a plurality of cardiac sites and process the data to generate a map of the variance of Shannon entropy of the one or more electrical waveform characteristics; and

using the map to identify a region for ablation.

[0020] Certain embodiments of the present disclosure provide a method of identifying a cardiac region for ablation to prevent and/or treat cardiac arrhythmia, the method comprising:

using a computer processor means to receive data associated with one or more electrical waveform characteristics obtained from a plurality of cardiac sites and process the data to identify a cardiac region of maximal variance of the one or more electrical waveform characteristics; and

identifying the cardiac region of maximal variance as the region for ablation.

[0021] Certain embodiments of the present disclosure provide a method of identifying a cardiac rotor region, the method comprising:

determining one or more electrical waveform characteristics at a plurality of cardiac sites;

identifying a cardiac region of maximal variance of the one or more electrical waveform characteristics; and

identifying the cardiac region of maximal variance of the one or more electrical waveform characteristics as the cardiac rotor region.

[0022] Certain embodiments of the present disclosure provide a method of identifying a selected cardiac region, the method comprising:

determining one or more electrical waveform characteristics at a plurality of cardiac sites;

identifying a cardiac region of maximal variance of the one or more electrical waveform characteristics; and

identifying the cardiac region of maximal variance of the one or more electrical waveform characteristics as the selected cardiac region, wherein the selected cardiac region comprises one or more of a cardiac rotor region, a region of endocardial/epicardial breakthrough, a region of transmural reentry, and a region of discontinuous propagation.

[0023] Certain embodiments of the present disclosure provide a system for cardiac mapping, the system comprising a computer processor means configured to receive data associated with one or more electrical waveform characteristics obtained from a plurality of cardiac sites and process the data to generate a map of variance in the electrical waveform characteristics.

[0024] Certain embodiments of the present disclosure provide a system for cardiac mapping, the system comprising a computer processor means configured to receive data associated with voltage amplitude obtained from a plurality of cardiac sites and process the data to generate a map of the variance in the voltage amplitude.

[0025] Certain embodiments of the present disclosure provide a system for cardiac mapping, the system comprising a computer processor means configured to receive data associated with one or more electrical waveform characteristics obtained from a plurality of cardiac sites and process the data to generate a map of the variance of Shannon entropy of the one or more electrical waveform characteristics.

[0026] Certain embodiments of the present disclosure provide a system for cardiac mapping, the system comprising a computer processor means configured to receive data associated with one or more electrical waveform characteristics obtained from a plurality of cardiac sites and process the data to identify a cardiac region of maximal variance of the one or more electrical waveform characteristics.

[0027] Certain embodiments of the present disclosure provide a computer-readable medium encoded with programming instructions executable by a computer processor means to allow the computer processor means to receive data associated with one or more electrical waveform characteristics obtained from a plurality of cardiac sites and process the data to generate a map of variance in the electrical waveform characteristics.

[0028] Certain embodiments of the present disclosure provide a computer-readable medium encoded with programming instructions executable by a computer processor means to allow the computer processor means to receive data associated with voltage amplitude obtained from a plurality of cardiac sites and process the data to generate a map of variance of the voltage amplitude.

[0029] Certain embodiments of the present disclosure provide a computer-readable medium encoded with programming instructions executable by a computer processor means to allow the computer processor means to receive data associated with one or more electrical waveform characteristics obtained from a plurality of cardiac sites and process the data to generate a map of variance of Shannon entropy of the one or more electrical waveform characteristics.

[0030] Certain embodiments of the present disclosure provide a computer-readable medium encoded with programming instructions executable by a computer processor means to allow the computer processor means to receive data associated with one or

more electrical waveform characteristics obtained from a plurality of cardiac sites and process the data to identify a cardiac region of maximal variance of the one or more electrical waveform characteristics.

[0031] Other embodiments are disclosed herein.

BRIEF DESCRIPTION OF THE FIGURES

[0032] Certain embodiments are illustrated by the following figures. It is to be understood that the following description is for the purpose of describing particular embodiments only and is not intended to be limiting with respect to the description.

[0033] Figure 1 shows a schematic-A simple example of a rotating wave is shown. The histogram is formed by binning each sample of the bipolar signal into voltage bins. 0.5mV bins are used for the purpose of illustration in this schematic. Bipoles at positions 1 & 2 experience consistent activation direction, with narrow voltage amplitude histograms, and low Shannon entropy. Importantly, the largest bin in the histogram is near the zero, reflecting the high proportion of signal values from near the isoelectric line. The bipole at position 3, nearest to the pivot sees a sharp local deflection (green), but secondary activity as the wavefront turns, including intermediate activity (yellow) and inverted potential (red). Signal values are binned in a broader range of voltage bins, and it consequently has a higher Shannon entropy.

[0034] Figure 2 shows (A) Representative membrane potential map during simulated spiral wave. Position 1 is near the spiral wave tip, position 3 is at the periphery, and position 2 is intermediate. (B) A snapshot showing spiral wave tracking with the normalized voltage algorithm. (C) Example electrograms. Panels 1 & 2 show EGMs with sharp local deflections, and narrow voltage histograms(right panels), and low ShEn. The EGM from the pivot zone (panel 3) shows predominantly positive deflections in activations 1, 2, as the spiral wavefront encounters the bipole from below. As the spiral tip encounters the bipole at EGM 3, an inverted double split potential, with intermediate electrical activity is seen. The voltage histogram is broader at the pivot (Position 3, C-right panels). It has a higher ShEn. (D) Standardized ShEn shows an inverse correlation with increasing pivot distance. (E) Shannon entropy maps with

bipoles calculated in the orthogonal orientations. The region of highest Shannon entropy common to both maps.

[0035] Figure 3 shows distribution of ShEn in isolated rat atria. (A) Normalized voltage map at 3 consecutive timepoints, clockwise rotation is seen. (B) Example electrograms from locations 1-3. At site 3, sharp local deflections, secondary electrical activity is seen between sharp local deflections (dotted area) (C) ShEn map shows highest entropy in the upper left near the pivoting zone. (D) The LAT map for the first rotation is shown (red represents early, purple represents late activation). (E) Distribution of ShEn shows a spatial gradient away from the pivot (F) Aggregated Shannon entropy for 12 episodes of rotational activation. Pearson's correlation coefficient is -0.54, $p<0.001$.

[0036] Figure 4 shows distribution of ShEn in re-entry during sheep atrial fibrillation, simple example. (A) Normalized voltage map showing anticlockwise rotation. In this case, rotation lasts for only two cycles (red arrows). (B) Example electrograms from locations 1-3 (clipped at ±2mV).Passage of sharp deflections is shown (red arrow). Secondary activity (inverted potentials, intermediate activity) is seen at the pivot EGM 3. Its voltage histogram is broader. (C) ShEn map shows the highest entropy at lower left corner near the pivot zone. (D) The LAT map for the first rotation is shown (red is early activation, purple is late activation). (E) Distribution of ShEn shows a spatial gradient away from the pivot zone.

[0037] Figure 5 shows distribution of ShEn in re-entry during sheep atrial fibrillation, complex example. (A) Normalized voltage map during re-entry in sheep AF, showing anticlockwise rotation. The rotational activation can be seen to gradually drift towards the upper left corner of the plaque (also see Movie Snapshots-appendix). (B) Example electrograms from locations 1-3 (clipped at ±2mV). In the right panel, voltage histogram values show a progressively broader distribution towards the pivot. (C) ShEn map shows the highest entropy in the upper left corner near the pivoting zone. (D) The LAT map for the first rotation is shown (red is early activation, purple is late activation). (E) Distribution of ShEn showing a spatial away from the pivot zone. High ShEn is smeared towards the upper left region of the plaque, consistent with drift of the rotation towards the corner. (F) Distribution of ShEn for all n=13 sheep rotational

episodes, showing inverse correlation with pivot distance. Pearson's correlation coefficient was -0.49, $p<0.001$.

[0038] Figure 6(A) shows example of signal adjacent to termination site. ShEn Z-score was 3.11; CFE-mean was 60ms. (B) Scatterplot of ShEn Z-score vs. CFE-mean. There was a weak but significant correlation with CFE. (C) For the highest 10% of CFE-mean, the correlation between ShEn Z-score and CFE-mean was not statistically significant.

DETAILED DESCRIPTION

[0039] The present disclosure relates to identifying a region for cardiac ablation for preventing and/or treating a cardiac arrhythmia.

[0040] Certain embodiments of the present disclosure are directed to methods of identifying a cardiac region for ablation, methods of treating a subject susceptible to or suffering from a cardiac arrhythmia, methods of preventing and/or treating a cardiac arrhythmia in a subject, methods of identifying a cardiac rotor region, systems for identifying a cardiac region for ablation, and computer-readable media encoded with programming instructions executable by a computer processor means.

[0041] Certain disclosed embodiments of the present disclosure provide methods, systems and computer readable media that have one or more combinations of advantages.

[0042] The present disclosure is based, at least in part, on the recognition that (i) the pivot is critical to the rotors postulated to maintain atrial fibrillation (AF); (ii) wavefronts circling the pivot should broaden the distribution of bipolar signal amplitude, due to direction information encoded in bipolar EGMs; and (iii) statistical measures of signal amplitude distribution, such as Shannon Entropy, can be used to differentiate the pivot from surrounding regions of the rotor, and therefore be a useful tool for clinical rotor mapping.

[0043] Certain embodiments of the present disclosure provide a method of identifying a cardiac region for ablation to prevent and/or treat a cardiac arrhythmia.

[0044] Certain embodiments of the present disclosure provide a method of identifying a cardiac region for ablation to prevent and/or treat a cardiac arrhythmia, the method comprising:

determining one or more electrical waveform characteristics at a plurality of cardiac sites;

identifying a cardiac region of maximal variance of the one or more electrical waveform characteristics; and

identifying the cardiac region of maximal variance of the one or more electrical waveform characteristics as the cardiac region for ablation to prevent and/or treat a cardiac arrhythmia.

[0045] In certain embodiments, the cardiac region for ablation comprises all and/or part of a region of wave pivot, a region of endocardial/epicardial breakthrough, a region of transmural reentry, and/or a region of discontinuous propagation. In certain embodiments, the cardiac region for ablation comprises a region overlapping, near and/or adjacent to any one or more of the aforementioned regions.

[0046] In certain embodiments, the methods of the present disclosure may be used to identify one or more of a cardiac rotor region, a region of endocardial/epicardial breakthrough, a region of transmural reentry, and a region of discontinuous propagation.

[0047] Methods for cardiac ablation are known, and include non-surgical and surgical methods of ablation. For example, the use of catheters that emit radio frequency waves and generate heat to produce a small scar on a specific part of the heart tissue can be used for ablation. Other methods of cardiac ablation are contemplated.

[0048] In certain embodiments, the cardiac region for ablation comprises a rotor (which may also be referred to herein as a "wave pivot") and/or a part thereof. In certain embodiments, the cardiac region for ablation comprises a region near a rotor. In certain embodiments, the cardiac region for ablation comprises a region adjacent to a rotor. In certain embodiments, the cardiac region for ablation comprises a region overlapping a

rotor.

[0049] In certain embodiments, the cardiac arrhythmia comprises an atrial arrhythmia, a ventricular arrhythmia and/or a junctional arrhythmia. In certain embodiments, the cardiac arrhythmia is a cardiac tachyarrhythmia, or atrial fibrillation.

[0050] In certain embodiments, the atrial fibrillation is acute atrial fibrillation, spontaneous atrial fibrillation or chronic atrial fibrillation.

[0051] In certain embodiments, the atrial fibrillation comprises one or more of acute atrial fibrillation, spontaneous atrial fibrial, chronic atrial fibrillation, paroxysmal atrial fibrillation, recurrent atrial fibrillation, persistent atrial fibrillation, or permanent atrial fibrillation.

[0052] In certain embodiments, the methods of the present disclosure are suitable for identifying a cardiac region for ablation in a subject.

[0053] In certain embodiments, the subject is human subject. In certain embodiments, the subject is a mammalian subject, a livestock animal (such as a horse, a cow, a sheep, a goat, a pig), a domestic animal (such as a dog or a cat) and other types of animals such as monkeys, rabbits, mice and laboratory animals. Veterinary applications of the present disclosure are contemplated.

[0054] In certain embodiments, the subject is suffering from a cardiac arrhythmia.

[0055] In certain embodiments, the subject is suffering from atrial fibrillation. In certain embodiments, the subject is suffering from acute atrial fibrillation, chronic atrial fibrillation, spontaneous atrial fibrillation, paroxysmal atrial fibrillation, recurrent atrial fibrillation, persistent atrial fibrillation, or permanent atrial fibrillation.

[0056] In certain embodiments, the subject is susceptible to a cardiac arrhythmia.

[0057] In certain embodiments, the subject is susceptible to atrial fibrillation. In certain embodiments, the subject is susceptible to acute atrial fibrillation, chronic atrial

fibrillation, spontaneous atrial fibrillation, paroxysmal atrial fibrillation, recurrent atrial fibrillation, persistent atrial fibrillation, or permanent atrial fibrillation.

[0058] In certain embodiments, the methods of the present disclosure may be used to prevent and/or treat a cardiac arrhythmia. For example, the methods may be used to identify a cardiac region for ablation to prevent and/or treat atrial fibrillation.

[0059] The term "preventing", and related terms such as "prevention" and "prevent", refer to obtaining a desired effect in terms of arresting or suppressing the appearance of one or more symptoms in the subject. The term "treatment", and related terms such as "treating" and "treat", refer to obtaining a desired effect in terms of improving the condition of the subject, ameliorating, arresting, suppressing, relieving and/or slowing the progression of one or more symptoms in the subject, a partial or complete stabilization of the subject, a regression of the one or more symptoms, or a cure of a disease, condition or state in the subject.

[0060] In certain embodiments, the methods, systems and computer readable media of the present disclosure comprise determining one or more electrical waveform characteristics at a plurality of cardiac sites.

[0061] Methods for determining cardiac electrical waveform characteristics are known. Cardiac electrical activity may be measured by a known method and the signals obtained used to determine the cardiac electrical waveform characteristics. The signals may be obtained by variety of methods, including unipolar signals, bipolar signals, a combination of unipolar and bipolar signals and virtual signals (for example reconstructed using non-contact methods such as body surface potential mapping or intracardiac array, which are known). Other methods for determining cardiac electrical waveform characteristics are contemplated.

[0062] In certain embodiments, the one or more electrical waveform characteristics comprise voltage amplitude and/or waveform direction. Other types of waveform characteristics are contemplated.

[0063] In certain embodiments, the one or more electrical waveform characteristics comprises voltage amplitude distribution.

[0064] In certain embodiments, the one or more electrical waveform characteristics comprise waveform direction.

[0065] In certain embodiments, the one or more electrical waveform characteristics comprises the extent of chaotic wavefronts/waveforms. In certain embodiments, the one or more electrical waveform characteristics comprise chaotic behaviour of wavefronts/waveforms.

[0066] In certain embodiments, the one or more electrical waveform characteristics comprises voltage amplitude distribution and waveform direction.

[0067] In certain embodiments, the determining of the one or more electrical waveform characteristics comprises measuring the one or more waveform characteristics at a plurality of sites. In certain embodiments, the plurality of cardiac site comprises two or greater sites, 10 or greater sites, 100 or greater sites, or 500 or greater sites.

[0068] In certain embodiments, the methods, systems and computer readable media of the present disclosure comprise identifying variance of the one or more electrical waveform characteristics.

[0069] The term "variance" refers to a measure of the complexity of data, based on the properties of the data and/or characteristics of its distribution. Measures of variance include, for example, signal entropy (for example Shannon Entropy, Approximate entropy, Sample entropy, Kolmogorov entropy, Maximal Lyapunov exponents), standard deviation or other measures of statistical variance, Kurtosis and L-moments.

[0070] Methods for determining variance are known.

[0071] In certain embodiments, the determination of variance comprises determination of disorder and/or unpredictability.

[0072] In certain embodiments, the determination of variance of the one or more electrical wavelength characteristics, or the determination of the complexity of the distribution, comprises use of the following equation, as described herein:

$$H = -\sum_{i=0}^{i=n} p_i \ln p_i,$$

[0073] In certain embodiments, a computer algorithm employing the above equation is used to process and/or transform signal data. Other methods for processing and/or transforming signal data are described herein.

[0074] In certain embodiments, the determination of electrical waveform characteristics comprises determination of the complexity of the distribution of the one or more electrical waveform characteristics. Methods for determining complexity of signal or data distribution are known.

[0075] In certain embodiments, the determination of variance comprises determination of entropy. The measurement of entropy may be implemented in a variety of mathematical forms, such as Shannon entropy. In certain embodiments, the determination of variance comprises determination of Shannon entropy.

[0076] Other examples include, for example, determination of one or more of Rényi entropy, Tsallis entropy, approximate entropy (ApEn), sample entropy (SampleEn), Kolmogorov entropy, Maximal Lypaunov exponent and Fisher information.

[0077] In certain embodiments, the determination of variance comprises determination of the complexity of the distribution of the one or more electrical waveform characteristics. In certain embodiments, the determination of the complexity of the distribution comprises determination of entropy. The measurement of entropy may be implemented in a variety of mathematical forms, such as Shannon entropy. In certain embodiments, the determination of the complexity of the distribution comprises determination of Shannon entropy. Other examples include, for example, determination of one or more of Rényi entropy, Tsallis entropy, approximate entropy (ApEn), sample

entropy (SampleEn), Kolmogorov entropy, Maximal Lypaunov exponent and Fisher information.

[0078] Certain embodiments of the present disclosure provide a method of identifying a cardiac region for ablation to prevent and/or treat a cardiac arrhythmia, the method comprising:

determining one or more electrical waveform characteristics at a plurality of cardiac sites;

identifying a cardiac region of maximal complexity of distribution of the one or more electrical waveform characteristics; and

identifying the cardiac region of maximal complexity of distribution of the one or more electrical waveform characteristics as the cardiac region for ablation to prevent and/or treat cardiac arrhythmia.

[0079] In certain embodiments, the maximal complexity of distribution of the one or more electrical waveform characteristics comprises maximal complexity of the distribution of the voltage amplitudes.

[0080] The term "maximal" as used herein means the greatest value determined, and includes an acceptable error range for that particular value, depending (in part) on how the value is measured or determined. In certain embodiments, the maximal value includes an acceptable error range of 1 standard deviation. When used in reference to a region, the term "maximal' refers to an area or region where the parameter of interest generally reaches it greatest value, within an acceptable error range. It will also be appreciated that ablation of a region of maximal variance or maximal complexity may include all or part of that area or region so identified, and may also include an area or region of lower variance or complexity.

[0081] In certain embodiments, identifying a cardiac region of maximal variance of the one or more electrical waveform characteristics comprises identifying a cardiac region of maximal variance by mapping using the plurality of cardiac sites.

[0082] In certain embodiments, the variance at the plurality of sites is determined so as to produce a map or pattern of variance, and the region of maximal variance identified from the map or distribution pattern.

[0083] In certain embodiments, identifying a cardiac region of maximal variance of the one or more electrical waveform characteristics comprises identifying a region of maximal variance associated with the waveform characteristics determined at one or more of the plurality of cardiac sites.

[0084] In certain embodiments, a site with the greatest variance is identified as the cardiac region of maximal complexity of distribution.

[0085] In certain embodiments, the cardiac region of maximal variance of the one or more electrical waveform characteristics comprises a cardiac region of maximal entropy, for example Shannon entropy.

[0086] In certain embodiments, the cardiac region of maximal variance of the one or more electrical waveform characteristic comprises a cardiac region of maximal variance of waveform direction.

[0087] In certain embodiments, identifying a cardiac region of maximal complexity of distribution of the one or more electrical waveform characteristics comprises identifying a cardiac region of maximal complexity of distribution by mapping using the plurality of cardiac sites.

[0088] In certain embodiments, the complexity of distribution at the plurality of sites is determined to identify a map or pattern of complexity of distribution, and the region of maximal complexity of distribution identified from the map or pattern.

[0089] In certain embodiments, identifying a cardiac region of maximal complexity of distribution of the one or more electrical waveform characteristics comprises identifying a region of maximal complexity of distribution associated with the waveform characteristics determined at one or more of the plurality of cardiac sites.

[0090] In certain embodiments, the site with the greatest complexity of distribution is identified as the cardiac region of maximal complexity of distribution.

[0091] In certain embodiments, the cardiac region of maximal complexity of distribution of the one or more electrical waveform characteristics comprises a cardiac region of maximal entropy for example Shannon entropy.

[0092] In certain embodiments, the cardiac region of maximal complexity of distribution of the one or more electrical waveform characteristic comprises a cardiac region of maximal complexity of distribution of waveform direction.

[0093] In certain embodiments, the identifying of a region for ablation comprises identifying a region of maximal variance of the one or more electrical waveform characteristics, as described herein.

[0094] In certain embodiments, the identifying of a region for ablation comprises identifying a region of maximal complexity and/or variance of the distribution of the one or more electrical waveform characteristics, as described herein.

[0095] In certain embodiments, the determining one or more electrical waveform characteristics comprises sequential measurement.

[0096] In certain embodiments, the determining one or more electrical waveform characteristics comprises sequential measurement of the one or more of the waveform characteristics from at least two of the plurality of cardiac sites. In certain embodiments, the determining one or more electrical waveform characteristics comprises sequential measurement of the one or more of the waveform characteristics at substantially all of the plurality of cardiac sites. Methods for sequentially measuring of electrical waveform characteristics are known.

[0097] In certain embodiments, the determining one or more electrical waveform characteristics comprises simultaneous measurement.

[0098] In certain embodiments, the determining one or more electrical waveform characteristics comprises simultaneous measurement, or substantially simultaneous measurement, of the one or more of the waveform characteristics at the plurality of cardiac sites. Methods for simultaneously measuring electrical waveform characteristics are known.

[0099] In certain embodiments, the determining of one or more electrical waveform characteristics comprises electrocardiography. Methods for using electrocardiography are known. In certain embodiments, the method comprises measuring one or more electrical waveform characteristics by electrocardiography. Other methods of measuring electrical waveform characteristics are contemplated.

[00100] In certain embodiments, the determining of one or more electrical waveform characteristics comprises bipolar electrocardiography. In certain embodiments, the method comprises measuring one or more electrical waveform characteristics by bipolar electrocardiography. Other types of electrocardiography are contemplated.

[00101] In certain embodiments, the determining of the one or more electrical waveform characteristics comprises spatial and/or temporal visualization or representation of the one or more electrical waveform characteristics. For example, a map may be generated to spatially and/or temporally visualise the one or more electrical waveform characteristics.

[00102] In certain embodiments, the identifying of the cardiac region of maximal variance of the one or more electrical waveform characteristics comprises generating a map of the one or more electrical waveform characteristics. In certain embodiments, the map shows the one or more electrical waveform characteristics with time. In certain embodiments, the map shows changes in the one or more electrical waveform characteristics with time.

[00103] In certain embodiments, the identifying of the cardiac region of maximal complexity of distribution of the one or more electrical waveform characteristics comprises generating a map of the one or more electrical waveform characteristics. In certain embodiments, the map shows the one or more electrical waveform

characteristics with time. In certain embodiments, the map shows changes in the one or more electrical waveform characteristics with time.

[00104] In certain embodiments, the map is a two dimensional map. In certain embodiments, the map is a three dimensional map. In certain embodiments, a cardiac representation is correlated with the map. For example, the cardiac representation may comprise a cardiac image, such as generated by MRI.

[00105] In certain embodiments, a computer processor means is configured to receive data associated with the electrical waveform characteristics at the plurality of cardiac sites. Computer processor means are known and devices including computer processor means are known. Examples of devices incorporating a computer processor means include a computer, a portable device, a device for implantation, or a device for wireless transmission, all of which are known.

[00106] In certain embodiments, the computer processor means comprises a computer-readable medium encoded with programming instructions executable by the computer processor means to allow the computer processor means to receive data associated with one or more electrical waveform characteristics obtained from a plurality of cardiac sites and process the data to generate a map of variance in the one or more electrical waveform characteristics, or to generate a map of complexity of distribution of the one or more electrical waveform characteristics.

[00107] Certain embodiments of the present disclosure provide a method of identifying a cardiac region for ablation to prevent and/or treat a cardiac arrhythmia by determining the voltage amplitude at a plurality of cardiac sites.

[00108] Certain embodiments of the present disclosure comprise a method of identifying a cardiac region for ablation to prevent and/or treat a cardiac arrhythmia, the method comprising:

determining voltage amplitude at a plurality of cardiac sites;

identifying a cardiac region of maximal distribution of voltage amplitude; and

identifying the cardiac region of maximal distribution of voltage amplitude as the cardiac region for ablation to prevent and/or treat the cardiac arrhythmia.

[00109] Certain embodiments of the present disclosure provide a method of identifying a cardiac region for ablation to prevent and/or treat a cardiac arrhythmia by determining Shannon entropy of voltage amplitude distribution at a plurality of cardiac sites.

[00110] Certain embodiments of the present disclosure provide a method of identifying a cardiac region for ablation to prevent and/or treat a cardiac arrhythmia, the method comprising:

determining Shannon entropy of voltage amplitude distribution at a plurality of cardiac sites;

identifying a cardiac region of maximal Shannon entropy; and

identifying the cardiac region of maximal Shannon entropy as the cardiac region for ablation to prevent and/or treat the cardiac arrhythmia.

[00111] Certain embodiments of the present disclosure provide a method of treating a subject susceptible to or suffering from a cardiac arrhythmia, the method comprising identifying a cardiac region for ablation by a method as described herein and ablating the cardiac region in the subject, thereby treating the subject. Methods for ablation are described herein.

[00112] Certain embodiments of the present disclosure provide a method of treating a subject susceptible to or suffering from a cardiac arrhythmia, the method comprising:

determining one or more electrical waveform characteristics at a plurality of cardiac sites in the subject;

identifying a cardiac region of maximal variance of the one or more electrical waveform characteristics; and

ablating the cardiac region of maximal variance in the subject, thereby treating the subject.

[00113] Certain embodiments of the present disclosure provide a method of preventing and/or treating a cardiac arrhythmia in a subject, the method comprising identifying a cardiac region for ablation by a method as described herein and ablating the cardiac region in the subject, thereby preventing and/or treating the cardiac arrhythmia in the

subject.

[00114] Certain embodiments of the present disclosure provide a method of preventing and/or treating a cardiac arrhythmia in a subject, the method comprising:

determining one or more electrical waveform characteristics at a plurality of cardiac sites in the subject;

identifying a cardiac region of maximal variance of the one or more electrical waveform characteristics; and

ablating the cardiac region of maximal variance in the subject, thereby treating the subject.

[00115] Methods for ablation are as described herein.

[00116] In certain embodiments, ablation of a region of maximal variance or maximal complexity includes all or part of the region. In certain embodiments, ablation of a region of maximal variance or maximal complexity includes an adjacent area or region. In certain embodiments, ablation of a region of maximal variance or maximal complexity also includes an area or region of lower variance or complexity.

[00117] In certain embodiments, one or more of electrograph electrodes may be used to ablate tissue in the vicinity of the electrodes. In certain embodiments, a multi-electrode device may be used to measure cardiac signals and ablate selected cardiac regions.

[00118] Certain embodiments of the present disclosure provide a method of treating a subject susceptible to or suffering from atrial fibrillation, the method comprising identifying a cardiac region for ablation by a method as described herein and ablating the cardiac region in the subject, thereby treating the subject.

[00119] Certain embodiments of the present disclosure provide a method of preventing and/or treating a atrial fibrillation in a subject, the method comprising identifying a cardiac region for ablation by a method as described herein and ablating the cardiac region in the subject, thereby preventing and/or treating atrial fibrillation in the subject.

[00120] Certain embodiments of the present disclosure provide a method of identifying one or more of a cardiac rotor region, a region of endocardial/epicardial breakthrough, a region of transmural reentry, and a region of discontinuous propagation.

[00121] Certain embodiments of the present disclosure prove a method of identifying a cardiac rotor region, the method comprising:

determining one or more electrical waveform characteristics at a plurality of cardiac sites;

identifying a cardiac region of maximal variance of the one or more electrical waveform characteristics; and

identifying the cardiac region of maximal variance of the one or more electrical waveform characteristics as the cardiac rotor region.

[00122] Certain embodiments of the present disclosure prove a method of identifying a selected cardiac region, the method comprising:

determining one or more electrical waveform characteristics at a plurality of cardiac sites;

identifying a cardiac region of maximal variance of the one or more electrical waveform characteristics; and

identifying the cardiac region of maximal variance of the one or more electrical waveform characteristics as the selected cardiac rotor region, wherein the selected cardiac region comprises one or more of a cardiac rotor region, a region of endocardial/epicardial breakthrough, a region of transmural reentry, or a region of discontinuous propagation.

[00123] Certain embodiments of the present disclosure prove a method of identifying a cardiac rotor region, the method comprising:

determining one or more electrical waveform characteristics at a plurality of cardiac sites;

identifying a cardiac region of maximal complexity of distribution of the one or more electrical waveform characteristics; and

identifying the cardiac region of maximal complexity of distribution of the one or more electrical waveform characteristics as the cardiac rotor region.

[00124] Certain embodiments of the present disclosure prove a method of identifying a selected cardiac region, the method comprising:

determining one or more electrical waveform characteristics at a plurality of cardiac sites;

identifying a cardiac region of maximal complexity of distribution of the one or more electrical waveform characteristics; and

identifying the cardiac region of maximal complexity of distribution of the one or more electrical waveform characteristics as the selected cardiac rotor region, wherein the selected cardiac region comprises one or more of a cardiac rotor region, a region of endocardial/epicardial breakthrough, a region of transmural reentry, or a region of discontinuous propagation.

[00125] Certain embodiments of the present disclosure provide a method of preventing and/or treating a cardiac arrhythmia in a subject by identifying one or more of a cardiac rotor region, a region of endocardial/epicardial breakthrough, a region of transmural reentry, and a region of discontinuous propagation as described herein, and ablating one or more of the aforementioned regions in the subject, thereby preventing and/or treating the cardiac arrhythmia in the subject.

[00126] Certain embodiments of the present disclosure provide a method of preventing and/or treating a cardiac arrhythmia in a subject, the method comprising identifying a cardiac rotor region as described herein and ablating the cardiac rotor region in the subject, thereby preventing and/or treating cardiac arrhythmia in the subject.

[00127] Certain embodiments of the present disclosure provide a method of identifying a cardiac region for ablation to prevent and/or treat a cardiac arrhythmia using a computer processor means.

[00128] Certain embodiments of the present disclosure provide a method of identifying a cardiac region for ablation to prevent and/or treat a cardiac arrhythmia, the method comprising:

using a computer processor means to receive data associated with one or more

electrical waveform characteristics obtained from a plurality of cardiac sites and process the data to generate a map of the variance of the one or more electrical waveform characteristics; and

using the map to identify a region for ablation.

[00129] Certain embodiments of the present disclosure provide a method of identifying a cardiac region for ablation to prevent and/or treat a cardiac arrhythmia, the method comprising:

using a computer processor means to receive data associated with one or more electrical waveform characteristics obtained from a plurality of cardiac sites and process the data to generate a spatial and/or temporal visualization of the variance of the one or more electrical waveform characteristics; and

using the visualisation to identify a region for ablation.

[00130] Certain embodiments of the present disclosure provide a method of identifying a cardiac region for ablation to prevent and/or treat a cardiac arrhythmia, the method comprising:

using a computer processor means to receive data associated with one or more electrical waveform characteristics obtained from a plurality of cardiac sites and process the data to generate a map of complexity of distribution of the one or more electrical waveform characteristics; and

using the map to identify a region for ablation.

[00131] In certain embodiments, the identifying of a region for ablation comprises identifying a region of maximal variance of the one or more electrical waveform characteristics, as described herein.

[00132] In certain embodiments, the identifying of a region for ablation comprises identifying a region of maximal complexity and/or variance of the distribution of the one or more electrical waveform characteristics, as described herein.

[00133] In certain embodiments, the computer processor processes or transforms the data by using an algorithm to provide a value of variance or measure of complexity of

distribution. Examples of algorithms are as described herein.

[00134] In certain embodiments, the algorithm processes or transforms the data using an algorithm that provides a value of entropy, such as Shannon entropy. Other measures for determining variance or complexity of distribution are as described herein.

[00135] In certain embodiments, the determination of variance comprises determination of the complexity of the distribution of the one or more electrical waveform characteristics. In certain embodiments, the determination of the complexity of the distribution comprises determination of entropy, as described herein. The measurement of entropy may be implemented in a variety of mathematical forms, such as Shannon entropy. In certain embodiments, the determination of the complexity of the distribution comprises determination of Shannon entropy. Other examples include, for example, determination of one or more of Rényi entropy, Tsallis entropy, approximate entropy (ApEn), sample entropy (SampleEn), Kolmogorov entropy, Maximal Lypaunov exponent and Fisher information.

[00136] In certain embodiments, the processing of the data comprises determination of variance by calculation comprising calculation of Shannon entropy, as described herein.

[00137] In certain embodiments, the data associated with one or more electrical waveform characteristics comprises voltage amplitude and/or waveform direction, as described herein

[00138] In certain embodiments, the one or more electrical waveform characteristics comprises voltage amplitude distribution, as described herein.

[00139] In certain embodiments, the data associated with one or more electrical waveform characteristics is obtained from sequential measurement of the one or more of the waveform characteristics at least two of the plurality of cardiac sites, as described herein.

[00140] In certain embodiments, the data associated with one or more electrical waveform characteristics is obtained from simultaneous measurement of the one or

more of the waveform characteristics at the plurality of cardiac sites, as described herein

[00141] In certain embodiments, the method comprises determining of one or more electrical waveform characteristics by electrocardiography, as described herein. In certain embodiments, the determining of one or more electrical waveform characteristics comprises bipolar electrocardiography, as described herein.

[00142] In certain embodiments, the determining of one or more electrical waveform characteristics comprises spatial and/or temporal representation or visualization of the one or more electrical waveform characteristics, as described herein. For example, a map may be used to spatially and/or temporally visualise the one or more electrical waveform characteristics. In certain embodiments, the map shows the one or more electrical waveform characteristics with time.

[00143] In certain embodiments, the map is a two dimensional map, as described herein. In certain embodiments, the map is a three dimensional map, as described herein. In certain embodiments, a cardiac representation is correlated with the map, as described herein. For example, the cardiac representation may comprise a cardiac image, such as generated by MRI.

[00144] In certain embodiments, the method comprises means for spatial and/or temporal representation or visualization. In certain embodiments, the method comprises means to display a map. Means for spatial and/or temporal visualisation, including displaying a map, are known. For example a computer with a display monitor may be used.

[00145] In certain embodiments, the cardiac region for ablation comprises one or more of a cardiac rotor region, a region of endocardial/epicardial breakthrough, a region of transmural reentry, and a region of discontinuous propagation, as described herein.

[00146] In certain embodiments, the cardiac arrhythmia is atrial fibrillation. In certain embodiments, the atrial fibrillation comprises acute atrial fibrillation, spontaneous atrial fibrial, chronic atrial fibrillation, paroxysmal atrial fibrillation, recurrent atrial fibrillation, persistent atrial fibrillation, or permanent atrial fibrillation.

[00147] Certain embodiments of the present disclosure provide a method of treating a subject susceptible to or suffering from cardiac arrhythmia, the method comprising identifying a cardiac region for ablation by the method as described herein, and ablating the cardiac region in the subject, thereby treating the subject.

[00148] Certain embodiments of the present disclosure provide a method of treating a subject susceptible to or suffering from cardiac arrhythmia, the method comprising identifying a cardiac region for ablation by using a computer processor means as described herein and ablating the cardiac region in the subject, thereby treating the subject.

[00149] Certain embodiments of the present disclosure provide a method of treating a subject susceptible to or suffering from cardiac arrhythmia, the method comprising generating a spatial and/or temporal visualisation of variance and complexity of distribution as described herein and ablating the cardiac region in the subject, thereby treating the subject.

[00150] Certain embodiments of the present disclosure provide a method of identifying a cardiac region for ablation to prevent and/or treat a cardiac arrhythmia, the method comprising:

using a computer processor means to receive data associated with voltage amplitude obtained from a plurality of cardiac sites and process the data to generate a map of the variance of the voltage amplitude; and

using the map to identify a region for ablation.

[00151] Certain embodiments of the present disclosure provide a method of identifying a cardiac region for ablation to prevent and/or treat a cardiac arrhythmia, the method comprising:

using a computer processor means to receive data associated with voltage amplitude obtained from a plurality of cardiac sites and process the data to generate a map of the complexity of distribution of the voltage amplitude; and

using the map to identify a region for ablation

[00152] Certain embodiments of the present disclosure provide a method of identifying a cardiac region for ablation to prevent and/or treat a cardiac arrhythmia, the method comprising:

using a computer processor means to receive data associated with one or more electrical waveform characteristics obtained from a plurality of cardiac sites and process the data to generate a map of the variance of Shannon entropy of the one or more electrical waveform characteristics; and

using the map to identify a region for ablation.

[00153] Certain embodiments of the present disclosure provide a method of identifying a cardiac region for ablation to prevent and/or treat cardiac arrhythmia, the method comprising:

using a computer processor means to receive data associated with one or more electrical waveform characteristics obtained from a plurality of cardiac sites and process the data to identify a cardiac region of maximal variance of the one or more electrical waveform characteristics; and

identifying the cardiac region of maximal variance as the region for ablation.

[00154] Certain embodiments of the present disclosure provide a method of identifying a cardiac region for ablation to prevent and/or treat cardiac arrhythmia, the method comprising:

using a computer processor means to receive data associated with one or more electrical waveform characteristics obtained from a plurality of cardiac sites and process the data to identify a cardiac region of maximal complexity of distribution of the one or more electrical waveform characteristics; and

identifying the cardiac region of maximal complexity of distribution as the region for ablation.

[00155] Certain embodiments of the present disclosure provide a system for identifying a cardiac region for ablation to prevent and/or treat a cardiac arrhythmia.

[00156] Certain embodiments of the present disclosure provide a system for identifying a cardiac region for ablation to prevent and/or treat a cardiac arrhythmia, the system

comprising a computer processor means configured to receive data associated with one or more electrical waveform characteristics and process the data, as described herein.

[00157] Certain embodiments of the present disclosure provide a system for cardiac mapping, the system comprising a computer processor means configured to receive data associated with one or more electrical waveform characteristics obtained from a plurality of cardiac sites and process the data to generate a map of variance in the electrical waveform characteristics.

[00158] Certain embodiments of the present disclosure provide a system for cardiac mapping, the system comprising a computer processor means configured to receive data associated with one or more electrical waveform characteristics obtained from a plurality of cardiac sites and process the data to generate a map of complexity of distribution of the one or more electrical waveform characteristics.

[00159] In certain embodiments, the map comprises a region of maximal variance of the one or more electrical waveform characteristics.

[00160] In certain embodiments, the map comprises a region of maximal complexity of distribution variance of the one or more electrical waveform characteristics.

[00161] In certain embodiments, the processing of the data comprises determination of variance by calculation comprising calculation of entropy, for example Shannon entropy.

[00162] In certain embodiments, the data associated with one or more electrical waveform characteristics comprises voltage amplitude and/or waveform direction.

[00163] In certain embodiments, the one or more electrical waveform characteristics comprises voltage amplitude distribution.

[00164] In certain embodiments, the data associated with one or more electrical waveform characteristics is obtained from sequential measurement of the one or more of the waveform characteristics from at least two of the plurality of cardiac sites.

[00165] In certain embodiments, the data associated with one or more electrical waveform characteristics is obtained from simultaneous measurement of the one or more of the waveform characteristics at the plurality of cardiac sites.

[00166] In certain embodiments, the system comprises an electrocardiograph device. In certain embodiments, the electrocardiograph device provides bipolar electrocardiographic data.

[00167] In certain embodiments, the map is a two dimensional map, as described herein. In certain embodiments, the map is a three dimensional map, as described herein.

[00168] In certain embodiments, the computer processor is configured to receive data associated with a cardiac representation and process the data so as to correlate a cardiac representation with the map. Receiving and processing the data are as described herein.

[00169] In certain embodiments, the system comprises means to display the map.

[00170] In certain embodiments, the system comprises a computer-readable medium encoded with programming instructions which when implemented in the system cause the system to receive the data associated with one or more electrical waveform characteristics obtained from a plurality of cardiac sites and process the data to generate a map of the distribution of variance in the electrical waveform characteristics.

[00171] In certain embodiments, the system comprises a computer-readable medium encoded with programming instructions which when implemented in the system cause the system to receive the data associated with one or more electrical waveform characteristics obtained from a plurality of cardiac sites and process the data to generate a map of the complexity of distribution of the one or more electrical waveform characteristics.

[00172] In certain embodiments, the system further comprises one or more of the following: i) one or more electrodes; one or more leads, such as one or more unipolar leads or bipolar leads; and a display means such as a display monitor.

[00173] Certain embodiments of the present disclosure provide a system for cardiac mapping, the system comprising a computer processor means configured to receive data associated with voltage amplitude obtained from a plurality of cardiac sites and process the data to generate a map of the variance in the voltage amplitude.

[00174] Certain embodiments of the present disclosure provide a system for cardiac mapping, the system comprising a computer processor means configured to receive data associated with voltage amplitude obtained from a plurality of cardiac sites and process the data to generate a map of the complexity of distribution variance in the voltage amplitude.

[00175] Certain embodiments of the present disclosure provide a system for cardiac mapping, the system comprising a computer processor means configured to receive data associated with one or more electrical waveform characteristics obtained from a plurality of cardiac sites and process the data to generate a map of the variance of Shannon entropy of the one or more electrical waveform characteristics.

[00176] Certain embodiments of the present disclosure provide a system for cardiac mapping, the system comprising a computer processor means configured to receive data associated with one or more electrical waveform characteristics obtained from a plurality of cardiac sites and process the data to identify a cardiac region of maximal variance of the one or more electrical waveform characteristics.

[00177] Certain embodiments of the present disclosure provide a system for cardiac mapping, the system comprising a computer processor means configured to receive data associated with one or more electrical waveform characteristics obtained from a plurality of cardiac sites and process the data to identify a cardiac region of maximal complexity of distribution of the one or more electrical waveform characteristics.

[00178] Certain embodiments of the present disclosure provide a computer program for instructing a computer processing means to perform a method as described herein.

[00179] Certain embodiments of the present disclosure provide a computer-readable medium encoded with programming instructions executable by a computer processor

means.

[00180] Certain embodiments of the present disclosure provide a computer-readable medium encoded with programming instructions executable by a computer processor means to perform a method as described herein.

[00181] Certain embodiments of the present disclosure provide a computer-readable medium encoded with programming instructions executable by a computer processor means to allow the computer processor means to receive data associated with one or more electrical waveform characteristics obtained from a plurality of cardiac sites and process the data to generate a map of variance in the electrical waveform characteristics.

[00182] Certain embodiments of the present disclosure provide a computer-readable medium encoded with programming instructions executable by a computer processor means to allow the computer processor means to receive data associated with one or more electrical waveform characteristics obtained from a plurality of cardiac sites and process the data to generate a map of complexity of distribution of the one or more electrical waveform characteristics.

[00183] Computer readable medium are known, and include for example a hard drive, a disk such as a floppy disk, or a CD-ROM, and include non-insertable and insertable media.

[00184] In certain embodiments, the map comprises a region of maximal variance of the one or more electrical waveform characteristics, as described herein. In certain embodiments, the map comprises a region of maximal complexity of distribution of the one or more electrical waveform characteristics, as described herein.

[00185] Use of a computer processor means to receive data associated with one or more electrical waveform characteristics and process the data are as described herein. In certain embodiments, the processing of the data comprises determination of variance by calculation comprising calculation of Shannon entropy, as described herein.

[00186] In certain embodiments, the processing of the data comprises determination of complexity of distribution by calculation comprising calculation of Shannon entropy, as described herein.

[00187] In certain embodiments, the data associated with one or more electrical waveform characteristics comprises voltage amplitude and/or waveform direction, as described herein. In certain embodiments, the one or more electrical waveform characteristics comprises voltage amplitude distribution, as described herein.

[00188] In certain embodiments, the data associated with one or more electrical waveform characteristics is obtained from sequential measurement of the one or more of the waveform characteristics from at least two of the plurality of cardiac sites, as described herein. In certain embodiments, the data associated with one or more electrical waveform characteristics is obtained from simultaneous measurement of the one or more of the waveform characteristics at the plurality of cardiac sites, as described herein.

[00189] In certain embodiments, the data associated with one or more electrical waveform characteristics system comprises electrocardiograph data, as described herein. In certain embodiments, the electrocardiographic data comprises bipolar electrocardiographic data.

[00190] In certain embodiments, the map is a two dimensional map, as described herein. In certain embodiments, the map is a three dimensional map, as described herein.

[00191] In certain embodiments, instructions allow the computer processor to receive data associated with a cardiac representation and process the data so as to correlate a cardiac representation with the map.

[00192] In certain embodiments, the instructions allow a display means to display the map.

[00193] Certain embodiments of the present disclosure provide a computer-readable medium encoded with programming instructions executable by a computer processor means to allow the computer processor means to receive data associated with voltage amplitude obtained from a plurality of cardiac sites and process the data to generate a map of variance of the voltage amplitude.

[00194] Certain embodiments of the present disclosure provide a computer-readable medium encoded with programming instructions executable by a computer processor means to allow the computer processor means to receive data associated with voltage amplitude obtained from a plurality of cardiac sites and process the data to generate a map of complexity of distribution of the voltage amplitude.

[00195] Certain embodiments of the present disclosure provide a computer-readable medium encoded with programming instructions executable by a computer processor means to allow the computer processor means to receive data associated with one or more electrical waveform characteristics obtained from a plurality of cardiac sites and process the data to generate a map of variance of Shannon entropy of the one or more electrical waveform characteristics.

[00196] Certain embodiments of the present disclosure provide a computer-readable medium encoded with programming instructions executable by a computer processor means to allow the computer processor means to receive data associated with one or more electrical waveform characteristics obtained from a plurality of cardiac sites and process the data to identify a cardiac region of maximal variance of the one or more electrical waveform characteristics.

[00197] Certain embodiments of the present disclosure provide a computer-readable medium encoded with programming instructions executable by a computer processor means to allow the computer processor means to receive data associated with one or more electrical waveform characteristics obtained from a plurality of cardiac sites and process the data to identify a cardiac region of maximal complexity of distribution of the one or more electrical waveform characteristics.

[00198] Certain embodiments of the present disclosure provide a computer processor means comprising a computer-readable medium, as described herein.

EXAMPLE 1 – Bipolar electrograms during rotational atrial activation.

[00199] (i) Introduction

[00200] Focal self-maintaining sources called rotors have been suggested as a potential mechanism for atrial fibrillation (AF)[1-4]. Despite the first demonstrations of rotors driving experimental AF more than a decade ago[2], clinically mapping rotors has proved difficult. We have sought to identify bipolar electrogram (EGM) mapping characteristics at rotor sites.

[00201] An important signal property of the bipolar EGM is the direct relationship between wavefront direction and EGM amplitude[5,6]. We recognised that changing wavefront direction near the rotor pivot should lead to: a) an early local deflection as the wavefront initially passes, and b) secondary deflections-consisting of inverted double split potentials[7, 8] and intermediate electrical activity between the initial and inverted potentials. In contrast, bipoles located at the periphery of rotating waves should have relatively stable EGM morphology, due to consistency of wavefront direction.

[00202] We recognised that these differences in EGM morphology between pivot zone and periphery should lead to differences in the distribution of signal values, that could be quantified with a statistical measure of the distribution of amplitude values within the signal histogram, such as Shannon entropy (ShEn)[9] (Figure 1). Specifically, changing wavefront direction near the pivot should cause a broader distribution in the bipolar voltage histogram (Figure 1, point 3), and should therefore have a higher ShEn than signals drawn from the periphery (Figure 1, points 1 & 2).

[00203] We therefore studied 3 systems of rotational wavefront propagation, recorded in the bipolar configuration: (i) Simulated bipolar recordings in a 2-dimensional model spiral wave (ii) Rotational activation in isolated rat atria recorded with a multi-electrode bipolar array and (iii) Epicardial plaque recordings of induced atrial fibrillation in

hypertensive sheep. To further demonstrate utility, we studied ShEn distribution and its relationship to arrhythmia termination in human AF ablation cases.

[00204] (ii) Methods

[00205] Computer Simulation of a Spiral Wave

[00206] To investigate bipolar electrogram formation during rotating electrical activity, we studied electrogram characteristics in a 2-dimensional 5cmx 5cm atrial myocyte sheet based on Courtemanche-Ramirez-Nattel human atrial action potential kinetics10. Model details are presented below. Spiral waves were induced in the model by cross-field stimulation with orthogonal planar waves.

[00207] Animal Experiments

[00208] Procedures were conducted in accordance with local guidelines, with approval provided by the Animal Ethics Committees of the University of Adelaide and SA Pathology, Australia.

[00209] Rat Model

[00210] Rat electrophysiology studies (EPS) were carried out as previously described[11], with experimental details set out below. In brief, circus activation was induced in isolated rat atria by programmed stimulation in n = 12 Wistar-Kyoto rats[12]. EPS was performed with a multi-electrode array (0.1mm diameter, 0.5mm inter-electrode distance, Nucleus Medical, Adelaide, Australia), which recorded 80 bipolar electrograms. Electrograms were sampled at 4000Hz and bandpass filtered from 10-500Hz (Lab System Pro, Bard Electrophysiology). We studied sustained arrythmias lasting more than 2 seconds.

[00211] Sheep model

[00212] In sheep, we studied episodes of induced AF from the previously described 1-kidney 1-clip model of ovine hypertension[13]. Open-chest EPS was undertaken under

general anesthesia, with a 128-electrode biatrial plaque (5-mm interelectrode distance)[13, 14]. EGMs were sampled at 1000 Hz, and bandpass filtered from 30-500Hz (Lab System Pro, Bard Electrophysiology). AF episodes lasting more than 20 seconds induced with rapid atrial pacing were selected for study.

[00213] Human AF recordings

[00214] Human AF recordings were obtained from patients undergoing catheter ablation for symptomatic drug-refractory AF prior to ablation. A detailed procedural protocol is provided below. The study protocol was approved by the Institutional Clinical Research and Ethics Committee and all patients provided written informed consent. Patients underwent high-density biatrial mapping with a 5-spine, 20 pole catheter (1mm electrodes, 4-4-4mm inter-electrode spacing; PentaRay; Biosense-Webster). A minimum 500 points were acquired by sequential mapping during spontaneous or induced AF prior to ablation. At each map site, the catheter was held stationary for 8-seconds, after fluoroscopic endocardial contact verification. Recordings were acquired at 1,200Hz, band-pass filtered from 30-500Hz with their locations annotated on electroanatomic maps (NavX, St Jude Medical). CFAE analysis was performed in NavX. After mapping, patients underwent circumferential pulmonary vein ablation. Details of ShEn were not available to guide the procedure.

[00215] Signal Processing

[00216] Electrogram analysis and signal processing were performed in a custom C++ software package (EPAS, Nucleus Medical, Adelaide)[14].

[00217] Mapping of rotational episodes

[00218] To rapidly screen arrhythmia episodes for rotational activation, we constructed normalized voltaged voltage movies. The local normalized voltage was calculated as the absolute value of the local integral of bipolar slope in a 20ms window, divided by the maximum voltage amplitude in a local 200ms window, to account for signal amplitude variability over the recording duration. Details are presented below. Rotational activation was defined as circular activation within the recording region. Rotation

episodes were verified with semi-automated local activation time maps (LAT) maps, with default annotation set to bipolar peak voltage. The pivot was defined as the center of rotation on the first LAT map showing circular activation.

[00219] Shannon Entropy Map Construction

[00220] The Shannon entropy measures the distribution of signal values within the signal histogram, and provides a guide to information content. ShEn was calculated in three steps: 1) Each sample was binned according to its amplitude (0.01mv fixed amplitude bins) into a voltage histogram; 2) The relative probability density p was calculated for each bin, defined as the number of counts in an amplitude bin divided by the sum of bin counts in all bins; 3) The Shannon entropy H was defined as:

$$H = -\sum_{i=0}^{i=n} p_i \ln p_i,$$

[00221] where n is the number of amplitude bins, and p is the probability of any sample falling within a particular amplitude bin. EGMs in which the signal has few states (ie stable morphology) have a narrow distribution in the voltage histogram, and low ShEn (Figure 1, top panels). EGMs containing a number of different types of deflections have a broader distribution of signal values in the voltage histogram, and a higher ShEn (Figure 1, lowest panel). We estimated the ShEn for each bipolar electrode for the whole duration of rotational activation in each of the model systems. We constructed maps of ShEn for each rotational episode. In the human AF data, we calculated ShEn for each 8-second recording.

[00222] CFAE Analysis

[00223] Complex fractionated atrial electrogram (CFAE) analysis was performed on human data using automated software to calculate the CFE-mean[15]. CFE-mean measures fractionation as the average time duration between consecutive deflections. For detection, the deflection must: (1) exceed an adaptive “peak-to-peak sensitivity” threshold; (2) possess a “downstroke” morphology in which the leading local maximum

and the trailing local-minimum amplitude occurs within a time "duration" set to avoid far-field event detection; and (3) exceed a "refractory" period from the previous detection [15]. When all criteria are met, a yellow "tick-mark" is placed at the instant of maximum-negative slope. Our settings were refractory period of 30 ms, peak-to-peak sensitivity of 0.1 mV, and duration of 10 ms, although are values may be selected. Points with over annotation of noise or under-annotation of index signal were removed.

[00224] Statistical Analysis

[00225] Statistical analysis was performed in SPSS. Data are presented as mean±SD. Standardized scores (Shannon z-score) were calculated within subjects for ShEn measurements. Linear associations between standardized Shannon entropy scores and variables of interest (distance from pivot, and CFE-mean) were assessed with Pearson's correlation coefficient. Statistical significance was established at $p<0.05$. Statistical analyses were performed in SPSS version 19 (IBM, Armonk, NY).

[00226] Computer Simulation of Spiral Wave

[00227] To investigate bipolar electrogram formation during rotating electrical activity, we studied electrogram characteristics in a 2-dimensional 5cmx 5cm atrial myocyte sheet based on Courtemanche-Ramirez-Nattel human atrial action potential kinetics[10]. Model details are presented below. Spiral waves were induced in the model by cross-field stimulation with orthogonal planar waves.

[00228] We investigated bipolar EGM formation in a two-dimensional sheet based on Courtemanche-Ramirez-Nattel human atrial action potential kinetics[10]. The model mesh contained 100x100 elements with 0.5 mm spatial distance (resulting in 5cm x 5cm sample size). Mesh elements were diffusively coupled (no-flux boundary conditions) with diffusion coefficient equal to 0.3 resulting in conduction velocity approximately 1m/s. Conductivity for IK_r, IK_s was set to 0.2 ns/pF. Unipolar signals were calculated at each mesh node as:

$$u_{i,j}(t) = c \sum_{k,l=0}^{k,l=N} \frac{\nabla v_{k,l}(t)}{r_{k,l}^2}$$

[00229] where $u_{i,j}(t)$ is unipolar voltage at node i,j, c is a scaling coefficient, $v_{k,l}$ is transmembrane voltage at node k,l and $r_{k,l}$ is a distance between (k,l) and (i,j) node. Bipolar voltage was calculated as a difference of unipolar voltages at fixed spatial distance (set to 5mm in our study)

$$w_{i,j}(t) = u_{i,j}(t) - u_{i+S,j}(t)$$

[00230] Where $w_{i,j}$ is a bipolar voltage at node (i,j) and S is a parameter controlling the interelectrode spacing (set to 10 in our study to result in 5mm interelectrode spacing). Spiral waves were induced by cross-field stimulation with orthogonal planar waves.

[00231] Rat Electrophysiology Studies

[00232] Rat electrophysiology studies were carried out as previously described[11]. In detail, Wistar-Kyoto rats (n=12) were anesthetized with intraperitoneal injection of ketamine (60 mg/kg) and medetomidine (0.5 mg/kg), and the atria harvested for electrophysiologic study (EPS) using a custom-built multi-electrode array (MEA) (Nucleus Medical, Australia). The MEA contained 90 monofilament Ag/AgCl wire electrodes (0.1mm diameter, 0.5mm inter-electrode distance), yielding 80 bipolar electrograms. Electrograms were sampled at 4000Hz and filtered from 10-500Hz (LabSystem Pro, Bard Electrophysiology). Excised atria were superfused with modified HEPES buffer (in mM: NaCl 134, KCl 4, NaH_2PO4 1.2, MgSO4 1.2, Glucose 11, HEPES 10, pH 7.4) with 100% O_2 at 37°C.

[00233] Re-entrant activity was induced with programmed atrial extrastimulation. Eight

basic (S1) stimuli were introduced at 400ms to 100ms, with 100-ms decrements, followed by atrial extrastimuli (S2) in 10-ms decrements. The endpoint was atrial effective refractory period, or the induction of sustained tachycarrhythmia.

[00234] Sheep AF episodes

[00235] In sheep, we studied episodes of induced AF from the previously described 1-kidney 1-clip model of ovine hypertension[13]. EPS was undertaken under general anesthesia, with intravenous sodium thiopentone (15¡V20 mg/kg) and maintained with isoflurane (2%¡V4%) in 100% oxygen[13]. In this model, hypertension was induced by unilateral nephrectomy and contralateral renal artery clamping. Open-chest electrophysiology study was performed after bilateral thoracotomy with a 128-electrode biatrial plaque (5-mm interelectrode distance) as previously described.[13, 14]

[00236] Electrograms were sampled at 1000 Hz, and filtered from 30-500Hz (LabSystem Pro, Bard Electrophysiology).

[00237] AF episodes were induced with rapid atrial pacing from the right atrial appendage. Rapidly decremented pacing was commenced at a 200-ms cycle length until AF initiation or loss of 1:1 atrial capture. AF was defined as a rapid irregular atrial rhythm on the surface ECG. AF episodes lasting longer than 20 seconds were studied.

[00238] Bipolar Electrogram Annotation of Rotational Activation

[00239] Wavefront propagation in cardiac mapping is traditionally assessed by isochronal maps constructed by sequential local activation time (LAT) annotation. In the unipolar mode, local activation is by consensus annotated as the maximum negative first-derivative of the local unipolar voltage (dV/dt).[5, 6] For bipolar electrograms, a variety of activation detection points including onset, peak, maximum absolute amplitude, major deflection of the rectified bipolar electrogram, and maximum absolute dV/dT have been used.[5, 6]

[00240] In our study, we were interested in identifying episodes of rotational activation

in mapped bipolar EGM fields. We were more interested in the propagation sequence than the precise timing of individual electrograms. In terms of computational implementation, each of the common methods of activation detection used for bipolar electrograms may require adjustment to individual electrogram annotation.

[00241] Normalized Voltage Algorithm

[00242] To overcome the difficulties associated with activation detection, we implemented a normalized voltage algorithm to screen the wavefront propagation sequence.

[00243] The normalized voltage was calculated in two steps:

[00244] 1. Calculation of a measure of the local variability of the signal using sliding window:

$$u(t_k) = \sum_{m=k-\frac{T}{2\Delta t}}^{m=k+\frac{T}{2\Delta t}} \left| \frac{v(t_m) - v(t_{m-1})}{\Delta t} \right|$$

[00245] where T is the size of the sliding window (20 ms in this study), and v(t) is original voltage signal at time t. Function u(t) increases in value when sliding window starts to overlap with deflection in signal and has a low value in periods of electrical silence.

[00246] 2. Normalization of u(t) according to peak value within predefined segments. Whole signal was divided into segments of 200 ms length. Within each segment, u(t) was divided by a maximum value of u(t) within this segment. The resulting signal (which is referred to as the normalized voltage) ranges between 0 and 1.

[00247] The normalized voltage algorithm was used to construct sequential propagation movies, enabling rapid classification of wavefront propagation in each system. Episodes

of rotational activation were identified as circular movement of electrical activity within the mapped bipolar field (Figs 1-4). The normalized voltage algorithm is associated with loss of information regarding activation timing, but relative position in the activation sequence is preserved. Circus wavefront propagation identified in normalized movies was verified with conventional LAT maps constructed with semi-automated software. The bipolar peak voltage was used as the default annotation location.

[00248] Human AF recordings

[00249] Human AF recordings were obtained from patients undergoing catheter ablation for symptomatic drug-refractory AF. All anti-arrhythmic drugs, with the exception of amiodarone, were ceased $\geq$5 half-lives before the study. All patients received pre-procedural anticoagulation with warfarin (INR 2-4) for $\geq$6 weeks and underwent trans-esophageal echocardiography to exclude left atrial thrombus. The study protocol was approved by the Institutional Clinical Research and Ethics Committee and all patients provided written informed consent for the procedure.

[00250] In brief, the left atrium was accessed using a single transeptal puncture. Following transeptal access, bolus unfractionated heparin was utilized to maintain the activated clotting time between 250-350 seconds. Patients underwent high-density biatrial mapping with a 5-spine, 20 pole catheter (1mm electrodes separated by 4-4-4mm inter-electrode spacing; PentaRay; Biosense-Webster). The PentaRay catheter was stabilized using a long vascular sheath (Preface, Biosense-Webster or SL0 Braided, St Jude Medical). A minimum 500 points were acquired by sequential mapping during spontaneous or induced AF prior to ablation. At each map site, the catheter was held stationary for 8-seconds, after endocardial contact was fluoroscopically verified. Recordings were acquired at 1,200Hz, band-pass filtered from 30-500Hz with their locations annotated on electroanatomic maps (NavX, St Jude Medical). CFAE analysis was performed in NavX.

[00251] After mapping, patients underwent circumferential pulmonary vein ablation with an end-point of isolation confirmed by circumferential mapping (Lasso, Biosense-Webster) with either elimination or dissociation of pulmonary venous potentials. Ablation of the pulmonary veins was performed using a delivered power of 30 W with

irrigation rates of 30 ml/min. Additional substrate modification by linear ablation (roof-line or mitral isthmus ablation) or targeting regions of CFAE was performed in patients with AF episodes persisting for > 48 hours, structural heart disease or with marked left atrial dilatation (longest diameter >57 mm). Cavo-tricuspid isthmus ablation with an endpoint of bidirectional isthmus block was performed only in patients with a history of typical flutter or if mapping confirmed typical flutter during the procedure. The endpoint of substrate modification was either electrophysiologically confirmed linear conduction block established via pacing maneuvers or the elimination of local fractionation. Substrate modification was performed using a delivered power of 30-35 W with irrigation rates of 30-60 ml/min. Details of ShEn were not available to guide the procedure.

[00252] (ii) Results

[00253] To investigate the spatial distribution of ShEn during rotational activation, we studied recordings of rotational activity in simulated spiral waves, isolated rat atria, and induced ovine AF.

[00254] Simulation of electrogram morphology

[00255] We first studied ShEn distribution during simulated spiral waves. Figure 2A shows the membrane voltage representation of a spiral wave. Bipolar electrograms from 3 consecutive rotations are shown. EGM morphology away from the centre of rotation was stable, with a narrow distribution in the voltage histogram, and low ShEn (Figure 2A). In these EGMs, the largest histogram bin is near the zero voltage bin reflects the high number of signal values near the isoelectric line.

[00256] The EGM from the pivot zone shows a predominantly positive deflection in activations 1, 2, as the spiral wavefront encounters the bipole from below. As the tip encounters the bipole, electrograms 3 shows secondary slow intermediate activity and an inverted potential. The voltage histogram near the pivot zone has a broader distribution than the periphery. The highest ShEn occurs in the pivoting zone, with a spatial gradient observed towards the periphery (Pearson's R:-0.61, $p<0.001$) (Fig 1E). The distance from maximum ShEn to the pivot was 2mm. When the bipole field was

calculated in the orthogonal direction, a comparable distribution of signal entropy is seen. Similar locations of maximum ShEn are identified in both representations.

[00257] Rat Atria Experiments

[00258] The isolated rat atrial model used was similar to previous described models of circus activation[12]. Circus rotational waves were induced by programmed atrial stimulation.

[00259] Periods of sustained circus arrhythmia lasting greater than 2 seconds were selected for analysis. Sustained arrhythmia occurred in 8 out of 12 rats, with 12 sustained circus arrhythmias identified. Arrhythmia duration was 12.2±17 seconds.

[00260] In the example, clockwise rotational wavefront propagation is seen (Figure 3A). EGMs adjacent to the pivoting zone near the pivot show local deflections, and secondary electrical activity (Figure 3B, red dotted line). Maximum ShEn is located in the region adjacent to the pivoting zone (Figure 3B). The mean distance from maximum ShEn to the pivot was 0.8±0.7 mm. A spatial gradient of ShEn map is seen away from the pivot (Figure 3D). The aggregated results of 12 sustained arrhythmias were inversely correlated with pivot zone distance. (Pearson's correlation coefficient: -0.54, $p<0.001$; Figure 3F).

[00261] Ovine AF

[00262] To further evaluate bipolar EGM at rotation sites, we studied AF episodes from hypertensive sheep. In 11 sheep, we identified 22 episodes of AF sustained $\geq$ 20 seconds. We constructed normalized voltage activation movies to study AF episodes. 13 rotational epochs were identified. The duration of rotational epochs was 649 ± 260ms (4.2 ± 1.5 cycles), with cycle length 155 ± 24 ms.

[00263] Figure 4 shows a simple case of rotational activity lasting two cycles. The left panel shows clockwise rotation around the plaque (Figure 4A). The clockwise propagation of the sharp local deflection is shown with red arrow (Figure 4B). There is increased secondary activity near the pivot (EGM at position 3), including inverted

potentials and intermediate secondary activity (dotted arrow). After the rotation stops, secondary activity is reduced, and only sharp local deflections are present.

[00264] The voltage histogram for the pivot zone electrode is broader. The ShEn entropy map shows a spatial gradient of signal entropy away from the pivot (Figure 4D), and an inverse correlation with distance. (Figure 4E).

[00265] Figure 5 shows another sheep example demonstrating the effect of drifting rotation. Anticlockwise rotational wavefront propagation is seen to gradually drift across the plaque towards the upper left corner, before terminating after several rotations (Figure 5A, Movie Snapshots Appendix). The red arrow marks the passage of the sharp local deflections (Figure 5B). In the EGMs nearest the pivot, secondary activity is seen (dotted arrows). These EGMs have a broader voltage distribution (right panel). The mean distance from max ShEn to the pivot was 7±6mm. A spatial gradient of ShEn is seen in the example (Figure 5C). The aggregated distribution of standardized ShEn was inversely correlated with pivot distance (Pearson's R: -0.49, $p<0.001$).

[00266] Human AF recordings

[00267] To further investigate ShEN, we studied the relationship between ShEn and CFE-mean, in n=10 patients undergoing catheter ablation of AF. Overall, standardized ShEn was inversely correlated with CFE-mean (Pearson's R -0.279, $p<0.001$), although the correlation was weak. The relationship between the top 10% of ShEn points and corresponding CFE-mean points was weaker (Pearson's R: -0.61, p=0.44), suggesting that ShEn and CFE-mean may identify different sets of points. We specifically examined the distribution of ShEn, in the two cases of long-standing persistent AF who achieved termination during ablation in this cohort. In these cases, we compared ShEn at the cluster of 5 near the annotated site of termination, and the closest 15 points outside this cluster. The mean ShEn was higher at AF termination sites compared to neighbour areas (Z score difference 1.00, p=0.002) and the rest of atrium (Z score difference 0.83, p=0.02). An example high ShEn electrogram from one of these cases is shown (Figure 6A).

[00268] (iii) Discussion

[00269] This study used a novel approach to provide new information regarding the nature of bipolar electrograms during rotational electrical activation of the atria. The principal study findings are: i) differences in bipolar electrogram morphology are present during rotational electrical activation between the peripheral regions and pivot regions; ii) increased Shannon entropy is associated with bipolar EGMs associated with the pivot zone; iii) spatial gradient of bipolar electrogram ShEn exists between the pivoting zone and the peripheral regions; iv) in human AF data, ShEn was weakly correlated with CFE-mean overall, but not at the sites of highest ShEn. A limited association between higher ShEn and AF termination was observed in a small number of clinical cases.

[00270] Shannon entropy and rotational wavefront activation

[00271] To date, few data exist regarding EGM morphology during rotational wavefront activation with direct recording of bipolar electrograms. In our study, we found the EGM morphology near the pivot to consist of i) an early sharp local deflection, secondary activity due to ii) inverted double split potentials, and (iii) intermediate electrical activity. The inverted double split potential was seen in each of the model systems studied. Intermediate electrical activity was also seen in each of the systems. The morphology of secondary activity varied between the systems studied. Intermediate activity was continuous in the rat, and was the dominant type of secondary activity observed in the closely spaced MEA recordings. In sheep, where the bipoles were more widely spaced, a combination of inverted split potentials and intermediate activity was more commonly observed. Secondary activity may reflect slow conduction near the spiral wave tip, attributable to the maximal convex curvature of the wavefront in this region of the rotor[1, 16].

[00272] These morphological changes in the bipolar EGM near the pivot are reflected in the voltage histogram. The turning wavefront causes a broader distribution of signal values within the histogram in each of the model systems studied. This alteration in distribution causes an increase in the Shannon entropy. The highest ShEn was co-

localised with the pivot zone in the 3 model systems of wavefront rotation that were studied.

[00273] Relationship of the ShEn concept to signal fractionation/CFAE

[00274] A question of significant clinical importance is the relationship of ShEn to existing concepts of signal fractionation and CFAE. The concept of signal fractionation, defined as high-frequency low amplitude signals, first arose in studies of ventricular scar[17]. In AF, CFAE emerged as a significant concept from empirical clinical studies[18]. Despite nearly a decade of research, an ongoing debate exists about the mechanisms of CFAE[5], and no objective consensus CFAE definition exists[19], which may be a factor in the conflicting clinical outcomes of CFAE ablation[19, 20].

[00275] Shannon entropy represents a fundamentally different concept. The concept of signal entropy is commonly explained in terms of uncertainty[9]. Organised, regular signals are considered to have low uncertainty, and low ShEn. On the other hand, less organised, and more irregular signals have higher uncertainty, and higher Shannon entropy.

[00276] The bipolar EGM is a unique signal, in that wavefront direction information is embedded within the signal amplitude. The pivot zone of the spiral wave can be considered a special location, where the beat-to-beat direction of wavefront propagation is maximally uncertain. This idea underlies the concept of measuring signal uncertainty with ShEn across mapped bipolar EGM fields, and is reflected in the simulation and experimental evidence presented in the current study showing the relationship between the point of maximum ShEn and the pivot zone.

[00277] Morphologically, it is apparent that there are some similarities in between signals with higher ShEn and fractionated signals. In our study, a consistent but weak inverse correlation was observed between ShEn and CFE-mean. However, ShEn and CFE-mean measure quite different properties, and this may be reflected in the weaker correlation observed between the highest ShEn points and CFE-mean, and the interesting association of higher ShEn regions in AF termination with ablation.

[00278] An intriguing possibility for investigation is the possibility of using ShEn to facilitate selective CFAE targeting. Recent clinical data has suggested that a subset of CFAE with continuous electrical activity (CEA), may be responsible for a large proportion of any clinical benefit associated with CFAE ablation[24, 25]. These irregular EGMs are likely to be associated with very high Shannon entropy, suggesting that the benefit associated with CEA ablation may in some cases be attributable to inadvertent targeting of high entropy sites. The data presented in the current study suggest a possible mechanistic explanation for the benefit associated with CEA ablation.

[00279] Relationship to targeted rotor ablation in human AF

[00280] Recently, descriptions have been presented of targeted rotor ablation, leading to AF termination, recapitulating animal studies showing AF termination with ablation at the rotor phase singularity[26]. Basket catheters were used in conjunction with novel signal processing algorithms to perform phase reconstructions, allowing identification of the phase singularity as the target of ablation [27, 28]. One possibility that may emerge is the use of ShEn-based mapping as a complementary strategy after wide-area basket mapping has been performed. ShEn mapping could facilitate accurate localisation of the rotor pivot within a small area.

[00281] Conclusions

[00282] The data presented in the current study represent a conceptual shift in the use of bipolar EGMs. Shannon entropy represents a novel method to demonstrate differences in bipolar EGMs between the pivot and periphery at sites of rotational activation. These data suggest ShEn as an objective, mechanistically-based potential tool to map locally stable rotors.

[00283] (iv) References

[00284] 1. Jalife J. Deja vu in the theories of atrial fibrillation dynamics. Cardiovasc Res. 2011;89:766-775

[00285] 2. Mandapati R, Skanes A, Chen J, et al. Stable microreentrant sources as a

mechanism of atrial fibrillation in the isolated sheep heart. Circulation. 2000;101:194-199

[00286] 3. Haissaguerre M, Hocini M, Sanders P, et al. Localized sources maintaining atrial fibrillation organized by prior ablation. Circulation. 2006;113:616-625

[00287] 4. Atienza F, Almendral J, Moreno J, et al. Activation of inward rectifier potassium channels accelerates atrial fibrillation in humans: Evidence for a reentrant mechanism. Circulation. 2006;114:2434-2442

[00288] 5. de Bakker JM, Wittkampf FH. The pathophysiologic basis of fractionated and complex electrograms and the impact of recording techniques on their detection and interpretation. Circ Arrhythm Electrophysiol. 2010;3:204-213

[00289] 6. Stevenson WG, Soejima K. Recording techniques for clinical electrophysiology. J Cardiovasc Electrophysiol. 2005;16:1017-1022

[00290] 9. Shannon C. A mathematical theory of communication. Bell System Technical Journal. 1948;27:379–423, 623–656

[00291] 10. Courtemanche M, Ramirez RJ, Nattel S. Ionic mechanisms underlying human atrial action potential properties: Insights from a mathematical model. Am J Physiol. 1998;275:H301-321

[00292] 11. Lau DH, Mackenzie L, Shipp NJ, et al. Feasibility of high-density electrophysiological study using multiple-electrode array in isolated small animal atria. Clin Exp Pharmacol Physiol. 2010;37:1023-1027

[00293] 12. Allessie MA, Bonke FI, Schopman FJ. Circus movement in rabbit atrial muscle as a mechanism of trachycardia. Circ Res. 1973;33:54-62

[00294] 13. Lau DH, Mackenzie L, Kelly DJ, et al. Short-term hypertension is associated with the development of atrial fibrillation substrate: A study in an ovine hypertensive model. Heart Rhythm. 2010;7:396-404

[00295] 14. Lau DH, Mackenzie L, Kelly DJ, et al. Hypertension and atrial fibrillation: Evidence of progressive atrial remodeling with electrostructural correlate in a conscious chronically instrumented ovine model. Heart Rhythm. 2010;7:1282-1290

[00296] 15. Stiles MK, Brooks AG, Kuklik P, et al. High-density mapping of atrial fibrillation in humans: Relationship between high-frequency activation and electrogram fractionation. J Cardiovasc Electrophysiol. 2008;19:1245-1253

[00297] 16. Comtois P, Kneller J, Nattel S. Of circles and spirals: Bridging the gap between the leading circle and spiral wave concepts of cardiac reentry. Europace. 2005;7 Suppl 2:10-20

[00298] 17. Josephson ME, Wit AL. Fractionated electrical activity and continuous electrical activity: Fact or artifact? Circulation. 1984;70:529-532

[00299] 18. Nademanee K, McKenzie J, Kosar E, et al. A new approach for catheter ablation of atrial fibrillation: Mapping of the electrophysiologic substrate. J Am Coll Cardiol. 2004;43:2044-2053

[00300] 19. Calkins H, Brugada J, Packer DL, et al. Hrs/ehra/ecas expert consensus statement on catheter and surgical ablation of atrial fibrillation. Heart Rhythm. 2007;4:816-861

[00301] 20. Hayward RM, Upadhyay GA, Mela T, et al. Pulmonary vein isolation with complex fractionated atrial electrogram ablation for paroxysmal and nonparoxysmal atrial fibrillation: A meta-analysis. Heart Rhythm. 2011;8:994-1000

[00302] 24. Takahashi Y, O'Neill MD, Hocini M, et al. Characterization of electrograms associated with termination of chronic atrial fibrillation by catheter ablation. J Am Coll Cardiol. 2008;51:1003-1010

[00303] 25. Hunter RJ, Diab I, Thomas G, et al. Validation of a classification system to grade fractionation in atrial fibrillation and correlation with automated detection systems. Europace. 2009;11:1587-1596

[00304] 26. Chou CC, Chang PC, Wen MS, et al. Epicardial ablation of rotors suppresses inducibility of acetylcholine-induced atrial fibrillation in left pulmonary vein-left atrium preparations in a beagle heart failure model. J Am Coll Cardiol. 2011;58:158-166

[00305] 27. Narayan SM, Sehra R, Briggs C, et al. Rapid acute termination of human atrial fibrillation by focal impulse and rotor modulation: Early human experience. Heart Rhythm. 2011;8:S4

[00306] 28. Narayan SM, Sehra R, Briggs C, et al. Electrical rotors and repetitive focal beats are localized sources for human atrial fibrillation. Heart Rhythm. 2011;8:S125.

EXAMPLE 2 - Prospective Evaluation of ShEn Mapping as Novel Adjunctive AF ablation strategy to facilitate the targeting of AF rotors.

[00307] As described herein, we have demonstrated that the bipolar electrogram Shannon entropy (ShEn) distinguishes the pivot from periphery of AF rotors. We hypothesized targeted ablation of high Shannon entropy might therefore lead to AF termination and or AF cycle length slowing.

[00308] Methods

[00309] We conducted a prospective single centre open label pilot study, undertaking targeted ablation of regions of high Shannon entropy in 8 patients with persistent AFLA size 45±6mm, LVEF 52±5%). Patients were in spontaneous or induced AF lasting>10 minutes before mapping which was undertaken using a 20-pole PentaRay catheter and the NavX system (616±285 points/pt). After map acquisition, points were exported to a PC in the control where ShEn map was constructed. The top 10% of regions of ShEn were identified, and annotated on the NavX map to guide ablation. Ablation of pre-identified ShEn regions was performed after wide antral circumferential ablation (WACA) with an endpoint of pulmonary vein isolation. No additional CFAE or linear ablation performed. Pre-specified endpoints were: (i) AF cycle length change (≥5ms); and (ii) AF termination.

[00310] Results

[00311] AF termination occurred in 6/8 cases, with 2/8 cases requiring cardioversion to sinus rhythm. 3/8 cases terminated during WACA, with 2/3 of these cases coinciding with pre-specified high ShEn. 3/8 cases terminated during ablation in pre-specified high ShEn regions. Mean AF cycle length change post PV isolation was 12.3±15ms (p=0.07), and AF cycle slowing post-ShEn ablation was 32.7±26ms (p=0.02). Sites of ShEn region termination included the anterior base of LA appendage, anterior to the right PVs, roof, posterior wall, and left superior PV ridge. 7/8 cases remained in sinus rhythm at median follow-up 186 days (IQR 212 days).

[00312] Conclusion

[00313] Directed ablation of high ShEn regions, as a marker of the pivot zone of AF rotors, is associated with termination of AF and/or AF cycle length slowing in selected AF patients.

EXAMPLE 3 - Shannon Entropy Localization of the Pivot Zone of Atrial Fibrillation Rotors-Effect of Recording Conditions

[00314] We have shown that high Shannon entropy (ShEn), a statistical measure of information uncertainty, localizes to the pivot of rotors recorded with bipolar electrograms, in computer simulation and animal experimental models, and that targeted ablation of high ShEn EGMs is associated with slowing and or termination in human AF. The aim of this study was to evaluate the ability of ShEn to colocalize the pivot zone of under simulated AF rotors conditions.

[00315] Methods

[00316] Bipolar EGM recordings were studied in the Courtemanche human atrial myocyte models. Rotors were simulated in 2-dimensional sheets. Each model mesh contained 100x100 elements with 0.5 mm spatial distance (resulting in 5cm x 5cm sample size). Mesh elements were diffusively coupled (no-flux boundary conditions). Unipolar EGMs were calculated, at each mesh element, which were used to construct

bipolar EGMs. The pivoting trajectory of the spiral wave tip was phase integration. ShEn was calculated as an index of amplitude distribution for each bipole for each rotor. We simulated the effects of: (i) bipolar EGM inter-electrode distance, (ii) EGM filtering, with simulated high-pass Butterworth filters with cutoffs at 0.5,10,and 30Hz, and (iii) ShEn box size.

[00317] Results

[00318] In each of the model systems, the highest region of ShEn colocalized with the pivoting region identified by the spiral wave tip trajectory. ShEn was inversely correlated with distance from the visual pivoting centre in each model system. ShEn was inversely correlated with distance from the pivot zone (Pearson's r=-0.61, $p<0.001$). The region of maximum ShEn remained colocalized with the pivot zone over simulated inter-electrode spacing from 0.5mm-8mm. Max ShEn colocalized with the pivot zone in ShEn box size from 0.01mV-1mV. Max ShEn remained colocalized with the pivot over a range of bipolar EGM cut-off frequencies.

[00319] Conclusion

[00320] These data confirm ShEn as a mechanistically-based tool to map locally stable rotors and indicate that ShEn mapping may be used as an adjunctive ablation strategy in clinical AF ablation.

EXAMPLE 4 - Bipolar Electrogram Shannon Entropy Enables Localization of the Pivot Zone of Rotors-Implications for AF ablation

[00321] The pivot is critical to the rotors postulated to maintain AF. We reasoned that wavefronts circling around the pivot should broaden the distribution of bipolar electrogram signal amplitude, due to direction information encoded in bipolar EGMs. We hypothesized that Shannon entropy (ShEn), a statistical measure of signal amplitude distribution, could be used to differentiate the pivot from surrounding regions of the rotor, and therefore may be a useful tool to assist clinical rotor mapping.

[00322] Methods

[00323] Bipolar EGM recordings were studied in 3 models systems. The models were: (i) Induced rotational activation in isolated rat atria (R) recorded with a multi-electrode array (80x1mm bipoles) (ii) In vivo epicardial plaque recordings of induced AF in hypertensive sheep (S) (1K1C, 128x5mm bipoles) (iii) Computer simulations (CS) of rotors in 2D atrial myocyte (RNC model, 64x5mm bipoles). In each model, rotor episodes were identified with voltage propagation movies, and verified with semi-automated local activation time (LAT) maps. The pivot was defined as the rotation center. ShEn was calculated as an index of amplitude distribution for each bipole for each rotation episode (0.01mV bins).

[00324] Results

[00325] We analyzed rotation episodes in animals (R: 12 rotors, duration 80±81 cycles, S: 22 AF episodes, 13 rotors, 4.2±1.5 cycles), and CS (4 cycles). The maximum ShEn bipole (max ShEn) was consistently co-located with the pivot zone (R: 10/12, S: 11/13, CS 1/1). Mean distance from max ShEn to pivot was: R 0.8±0.7 mm, S: 7±6mm, CS 2mm). ShEn was consistently inversely correlated with pivot zone distance (Pearson's r: R -0.54, $p<0.001$ S -0.49, $p<0.001$, CS -0.61, $p<0.001$).

[00326] Conclusions

[00327] These data suggest ShEn as a mechanistically-based potential tool to map locally stable rotors, implementable by sequential single or multi-electrode catheter mapping.

[00328] Reference to any prior art in this specification is not, and should not be taken as, an acknowledgment or any form of suggestion that this prior art forms part of the common general knowledge in any country.

[00329] Also, it must be noted that, as used herein, the singular forms "a", "an" and "the" include plural aspects unless the context already dictates otherwise.

[00330] Throughout this specification, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element or integer or group of elements or integers but not the exclusion of any other element or integer or group of elements or integers.

[00331] The description provided herein is in relation to several embodiments which may share common characteristics and features. It is to be understood that one or more features of one embodiment may be combinable with one or more features of the other embodiments. In addition, a single feature or combination of features of the embodiments may constitute additional embodiments.

[00332] The subject headings used herein are included only for the ease of reference of the reader and should not be used to limit the subject matter found throughout the disclosure or the claims. The subject headings should not be used in construing the scope of the claims or the claim limitations.

[00333] Future patent applications may be filed on the basis of the present application, for example by claiming priority from the present application, by claiming a divisional status and/or by claiming a continuation status. It is to be understood that the following claims are provided by way of example only, and are not intended to limit the scope of what may be claimed in any such future application. Nor should the claims be considered to limit the understanding of (or exclude other understandings of) the present disclosure. Features may be added to or omitted from the example claims at a later date.

[00334] Although the present disclosure has been described with reference to particular examples, it will be appreciated by those skilled in the art that the disclosure may be embodied in many other forms.

CLAIMS

1. A method of identifying a cardiac region for ablation to prevent and/or treat a cardiac arrhythmia, the method comprising:

determining one or more electrical waveform characteristics at a plurality of cardiac sites;

identifying a cardiac region of maximal variance of the one or more electrical waveform characteristics; and

identifying the cardiac region of maximal variance of the one or more electrical waveform characteristics as the cardiac region for ablation to prevent and/or treat the cardiac arrhythmia.

2. The method according to claim 1, wherein the cardiac arrhythmia comprises atrial fibrillation.

3. The method according to claims 1 or 2, wherein the atrial fibrillation comprises acute atrial fibrillation, spontaneous atrial fibrial, chronic atrial fibrillation, paroxysmal atrial fibrillation, recurrent atrial fibrillation, persistent atrial fibrillation, or permanent atrial fibrillation.

4. The method according to any one of claims 1 to 3, wherein the determination of electrical waveform characteristics comprises determination of variance of the one or more electrical wavelength characteristics.

5. The method according to claim 4, wherein the determination of variance comprises determination of entropy associated with the one or more electrical waveform characteristics.

6. The method according to claim 5, wherein the determination of variance comprises determination of Shannon entropy associated with the one or more electrical waveform characteristics.

7. The method according to any one of claims 4 to 6, wherein the determination of variance comprises determination of complexity of distribution of the one or more

electrical waveform characteristics.

8. The method according to any one of claims 1 to 7, wherein the one or more electrical waveform characteristics comprise voltage amplitude and/or waveform direction.

9. The method according to any one of claims 1 to 8, wherein the cardiac region of maximal variance of the one or more electrical waveform characteristic comprises a cardiac region of maximal voltage amplitude distribution.

10. The method according to any one of claims 1 to 9, wherein the cardiac region of maximal variation of the one or more electrical waveform characteristics comprises a cardiac region of maximal Shannon entropy.

11. The method according to any one of claims 1 to 10, wherein the cardiac region of maximal variance of the one or more electrical waveform characteristic comprises a cardiac region of maximal change of waveform direction.

12. The method according to any one of claims 1 to 11, wherein the determining of one or more electrical waveform characteristics comprises sequential measurement of the one or more of the waveform characteristics at least two of the plurality of cardiac sites.

13. The method according to any one of claims 1 to 11, wherein the determining one or more electrical waveform characteristics comprises simultaneous measurement of the one or more of the waveform characteristics at the plurality of cardiac sites.

14. The method according to any one of claims 1 to 13, wherein the determining of one or more electrical waveform characteristics comprises electrocardiography.

15. The method according to claim 14, wherein the determining of one or more electrical waveform characteristics comprises bipolar electrocardiography.

16. The method according to any one of claims 1 to 15, wherein the determining of

one or more electrical waveform characteristics comprises spatial and/or temporal visualization of the one or more electrical waveform characteristics.

17. The method according to any one of claims 1 to 16, wherein the identifying of the cardiac region of maximal distribution of the one or more electrical waveform characteristics comprises generating a map of the one or more electrical waveform characteristics.

18. The method according to claim 17, wherein the map is a two dimensional map.

19. The method according to claim 17, wherein the map is a three dimensional map.

20. The method according to any one of claims 17 to 20, wherein a cardiac representation is correlated with the map.

21. The method accordingly to any one of claims 1 to 20, wherein a computer processor means is configured to receive data associated with the electrical waveform characteristics at the plurality of cardiac sites.

22. The method according to any one of claims 1 to 21, wherein the cardiac region for ablation is one or more of a cardiac rotor region, a region of endocardial/epicardial breakthrough, a region of transmural reentry, and a region of discontinuous propagation.

23. A method of identifying a cardiac region for ablation to prevent and/or treat a cardiac arrhythmia, the method comprising:

determining voltage amplitude at a plurality of cardiac sites;

identifying a cardiac region of maximal distribution of voltage amplitude; and

identifying the cardiac region of maximal distribution of voltage amplitude as the cardiac region for ablation to prevent and/or treat the cardiac arrhythmia.

24. A method of identifying a cardiac region for ablation to prevent and/or treat a cardiac arrhythmia, the method comprising:

determining Shannon entropy of voltage amplitude distribution at a plurality of

cardiac sites;

identifying a cardiac region of maximal Shannon entropy; and

identifying the cardiac region of maximal Shannon entropy as the cardiac region for ablation to prevent and/or treat the cardiac arrhythmia.

25. A method of identifying a cardiac region for ablation to prevent and/or treat a cardiac arrhythmia, the method comprising:

determining one or more electrical waveform characteristics at a plurality of cardiac sites;

identifying a cardiac region of maximal complexity of distribution of the one or more electrical waveform characteristics; and

identifying the cardiac region of maximal complexity of distribution of the one or more electrical waveform characteristics as the cardiac region for ablation to prevent and/or treat cardiac arrhythmia.

26. A method of identifying a cardiac region for ablation to prevent and/or treat a cardiac arrhythmia, the method comprising:

using a computer processor means to receive data associated with one or more electrical waveform characteristics obtained from a plurality of cardiac sites and process the data to generate a map of the variance of the one or more electrical waveform characteristics; and

using the map to identify a region for ablation.

27. The method according to claim 26, wherein the cardiac arrhythmia comprises atrial fibrillation.

28. The method according to claims 26 or 27, wherein the atrial fibrillation comprises acute atrial fibrillation, spontaneous atrial fibrial, chronic atrial fibrillation, paroxysmal atrial fibrillation, recurrent atrial fibrillation, persistent atrial fibrillation, or permanent atrial fibrillation.

29. The method according to any one of claims 26 to 28, wherein the identifying of a region for ablation comprises identifying a region of maximal variance of the one or more electrical waveform characteristics.

30. The method according to any one of claims 26 to 29, wherein the processing of the data comprises determination of variance by calculation comprising calculation of entropy.

31. The method according to any one of claims 26 to 30, wherein the processing of the data comprises determination of variance by calculation comprising calculation of Shannon entropy.

32. The method according to any one of claims 26 to 31, wherein the data associated with one or more electrical waveform characteristics comprises voltage amplitude and/or waveform direction.

33. The method according to any one of claims 26 to 32, wherein the data associated with one or more electrical waveform characteristics is obtained from sequential measurement of the one or more of the waveform characteristics at least two of the plurality of cardiac sites.

34. The method according to any one of claims 26 to 32, wherein the data associated with one or more electrical waveform characteristics is obtained from simultaneous measurement of the one or more of the waveform characteristics at the plurality of cardiac sites.

35. The method according to any one of claims 26 to 34, wherein the method comprises determining of one or more electrical waveform characteristics by electrocardiography.

36. The method according to claim 35, wherein the determining of one or more electrical waveform characteristics comprises bipolar electrocardiography.

37. The method according to any one of claims 26 to 36, wherein the determining of one or more electrical waveform characteristics comprises spatial and/or temporal representation of the one or more electrical waveform characteristics.

38. The method according to any one of claims 26 to 37, wherein the identifying of the cardiac region of maximal distribution of the one or more electrical waveform characteristics comprises generating a map of the one or more electrical waveform characteristics.

39. The method according to claim 38, wherein the map is a two dimensional map.

40. The method according to claim 38, wherein the distribution map is a three dimensional map.

41. The method according to any one of claims 38 to 40, wherein a cardiac representation is correlated with the map.

42. The method according to any one of claims 39 to 41, wherein the method comprises means to display the map.

43. The method according to any one of claims 26 to 42, wherein the cardiac region for ablation is one or more of a cardiac rotor region, a region of endocardial/epicardial breakthrough, a region of transmural reentry, and a region of discontinuous propagation.

44. A method of identifying a cardiac region for ablation to prevent and/or treat a cardiac arrhythmia, the method comprising:

using a computer processor means to receive data associated with voltage amplitude obtained from a plurality of cardiac sites and process the data to generate a map of the variance of the voltage amplitude; and

using the map to identify a region for ablation.

45. A method of identifying a cardiac region for ablation to prevent and/or treat a cardiac arrhythmia, the method comprising:

using a computer processor means to receive data associated with one or more electrical waveform characteristics obtained from a plurality of cardiac sites and process the data to generate a map of the variance of Shannon entropy of the one or more electrical waveform characteristics; and

using the map to identify a region for ablation.

46. A method of identifying a cardiac region for ablation to prevent and/or treat cardiac arrhythmia, the method comprising:

using a computer processor means to receive data associated with one or more electrical waveform characteristics obtained from a plurality of cardiac sites and process the data to identify a cardiac region of maximal variance of the one or more electrical waveform characteristics; and

identifying the cardiac region of maximal variance as the region for ablation.

47. A method of treating a subject susceptible to or suffering from a cardiac arrhythmia, the method comprising:

identifying a cardiac region for ablation by the method according to any one of claims 1 to 46; and

ablating the cardiac region in the subject, thereby treating the subject.

48. A method of treating a subject susceptible to or suffering from a cardiac arrhythmia, the method comprising:

determining one or more electrical waveform characteristics at a plurality of cardiac sites in the subject ;

identifying a cardiac region of maximal variance of the one or more electrical waveform characteristics; and

ablating the cardiac region of maximal variance in the subject, thereby treating the subject.

49. A method of treating preventing and/or treating a cardiac arrhythmia in a subject, the method comprising:

identifying a cardiac region for ablation by the method according to any one of claims 1 to 46; and

ablating the cardiac region in the subject, thereby preventing and/or treating the cardiac arrhythmia in the subject.

50. A method of preventing and/or treating a cardiac arrhythmia in a subject, the method comprising:

determining one or more electrical waveform characteristics at a plurality of cardiac sites in the subject ;

identifying a cardiac region of maximal variance of the one or more electrical waveform characteristics; and

ablating the cardiac region of maximal variance in the subject, thereby preventing and/or treating the cardiac arrhythmia in the subject.

51. A method of identifying a cardiac rotor region, the method comprising:

determining one or more electrical waveform characteristics at a plurality of cardiac sites;

identifying a cardiac region of maximal variance of the one or more electrical waveform characteristics; and

identifying the cardiac region of maximal variance of the one or more electrical waveform characteristics as the cardiac rotor region.

52. A method of identifying a selected cardiac region, the method comprising:

determining one or more electrical waveform characteristics at a plurality of cardiac sites;

identifying a cardiac region of maximal variance of the one or more electrical waveform characteristics; and

identifying the cardiac region of maximal variance of the one or more electrical waveform characteristics as the selected cardiac region, wherein the selected cardiac region comprises one or more of a cardiac rotor region, a region of endocardial/epicardial breakthrough, a region of transmural reentry, and a region of discontinuous propagation.

53. A method of preventing and/or treating a cardiac arrhythmia in a subject, the method comprising:

identifying a region by the method according to claims 49 or 50; and

ablating the region in the subject, thereby preventing and/or treating the cardiac arrhythmia in the subject.

54. A system for identifying a cardiac region for ablation to prevent and/or treat a cardiac arrhythmia, the system comprising a computer processor means configured to

receive data associated with one or more electrical waveform characteristics and process the data using the method according to any one of claims 26 to 46.

55. A system for cardiac mapping, the system comprising a computer processor means configured to receive data associated with one or more electrical waveform characteristics obtained from a plurality of cardiac sites and process the data to generate a map of variance in the electrical waveform characteristics.

56. The system according to claim 55, wherein the map comprises a region of maximal variance of the one or more electrical waveform characteristics.

57. The system according to claims 55 or 56, wherein the processing of the data comprises determination of variance by calculation comprising calculation of Shannon entropy.

58. The system according to any one of claims 55 to 57, wherein the data associated with one or more electrical waveform characteristics comprises voltage amplitude and/or waveform direction.

59. The system according to claim 58, wherein the one or more electrical waveform characteristics comprises voltage amplitude distribution.

60. The system according to any one of claims 55 to 59, wherein the data associated with one or more electrical waveform characteristics is obtained from sequential measurement of the one or more of the waveform characteristics from at least two of the plurality of cardiac sites.

61. The system according to any one of claims 55 to 59, wherein the data associated with one or more electrical waveform characteristics is obtained from simultaneous measurement of the one or more of the waveform characteristics at the plurality of cardiac sites.

62. The system according to any one of claims 55 to 60, wherein the system comprises an electrocardiograph device.

63. The system according to claim 62, wherein the electrocardiograph device provides bipolar electrocardiographic data.

64. The system according to any one of claims 55 to 63, wherein the map is a two dimensional map.

65. The system according to any one of claims 55 to 64, wherein the map is a three dimensional map.

66. The system according to any one of claims 55 to 65, wherein the computer processor is configured to receive data associated with a cardiac representation and process the data so as to correlate a cardiac representation with the map.

67. The system according to any one of claims 55 to 66, wherein the system comprises means to display the map.

68. The system according to any one of claims 55 to 67, wherein the system comprises a computer-readable medium encoded with programming instructions which when implemented in the system cause the system to receive the data associated with one or more electrical waveform characteristics obtained from a plurality of cardiac sites and process the data to generate a map of the distribution of variance in the electrical waveform characteristics.

69. A system for cardiac mapping, the system comprising a computer processor means configured to receive data associated with voltage amplitude obtained from a plurality of cardiac sites and process the data to generate a map of the variance in the voltage amplitude.

70. A system for cardiac mapping, the system comprising a computer processor means configured to receive data associated with one or more electrical waveform characteristics obtained from a plurality of cardiac sites and process the data to generate a map of the variance of Shannon entropy of the one or more electrical waveform characteristics.

71. A system for cardiac mapping, the system comprising a computer processor means configured to receive data associated with one or more electrical waveform characteristics obtained from a plurality of cardiac sites and process the data to identify a cardiac region of maximal variance of the one or more electrical waveform characteristics.

72. A computer-readable medium encoded with programming instructions executable by a computer processor means to allow the computer processor means to receive data associated with one or more electrical waveform characteristics obtained from a plurality of cardiac sites and process the data to generate a map of variance in the electrical waveform characteristics.

73. The computer-readable medium according to claim 72, wherein the map comprises a region of maximal variance of the one or more electrical waveform characteristics.

74. The computer-readable medium according to claims 72 or 73, wherein the processing of the data comprises determination of variance by calculation comprising calculation of Shannon entropy.

75. The computer-readable medium according to any one of claims 72 to 74, wherein the data associated with one or more electrical waveform characteristics comprises voltage amplitude and/or waveform direction.

76. The computer-readable medium according to any one of claims 72 to 75, wherein the data associated with one or more electrical waveform characteristics is obtained from sequential measurement of the one or more of the waveform characteristics from at least two of the plurality of cardiac sites.

77. The computer-readable medium according to any one of claims 72 to 75, wherein the data associated with one or more electrical waveform characteristics is obtained from simultaneous measurement of the one or more of the waveform characteristics at the plurality of cardiac sites.

78. The computer-readable medium according to any one of claims 72 to 77, wherein the data associated with one or more electrical waveform characteristics system comprises electrocardiograph data.

79. The computer-readable medium according to claim 78, wherein the electrocardiographic data comprises bipolar electrocardiographic data.

80. The computer-readable medium according to any one of claims 72 to 79, wherein the map is a two dimensional map.

81. The computer-readable medium according to claim any one of claims 72 to 79, wherein the map is a three dimensional map.

82. The computer-readable medium according to any one of claims 72 to 81, wherein the instructions allow the computer processor to receive data associated with a cardiac representation and process the data so as to correlate a cardiac representation with the map.

83. The computer-readable medium according to any one of claims 72 to 82, wherein the instructions allow a display means to display the map.

84. A computer-readable medium encoded with programming instructions executable by a computer processor means to allow the computer processor means to receive data associated with voltage amplitude obtained from a plurality of cardiac sites and process the data to generate a map of variance of the voltage amplitude.

85. A computer-readable medium encoded with programming instructions executable by a computer processor means to allow the computer processor means to receive data associated with one or more electrical waveform characteristics obtained from a plurality of cardiac sites and process the data to generate a map of variance of Shannon entropy of the one or more electrical waveform characteristics.

86. A computer-readable medium encoded with programming instructions

executable by a computer processor means to allow the computer processor means to receive data associated with one or more electrical waveform characteristics obtained from a plurality of cardiac sites and process the data to identify a cardiac region of maximal variance of the one or more electrical waveform characteristics.

87. A computer processor means comprising a computer-readable medium according to any one of claims 72 to 86.

Figure 1

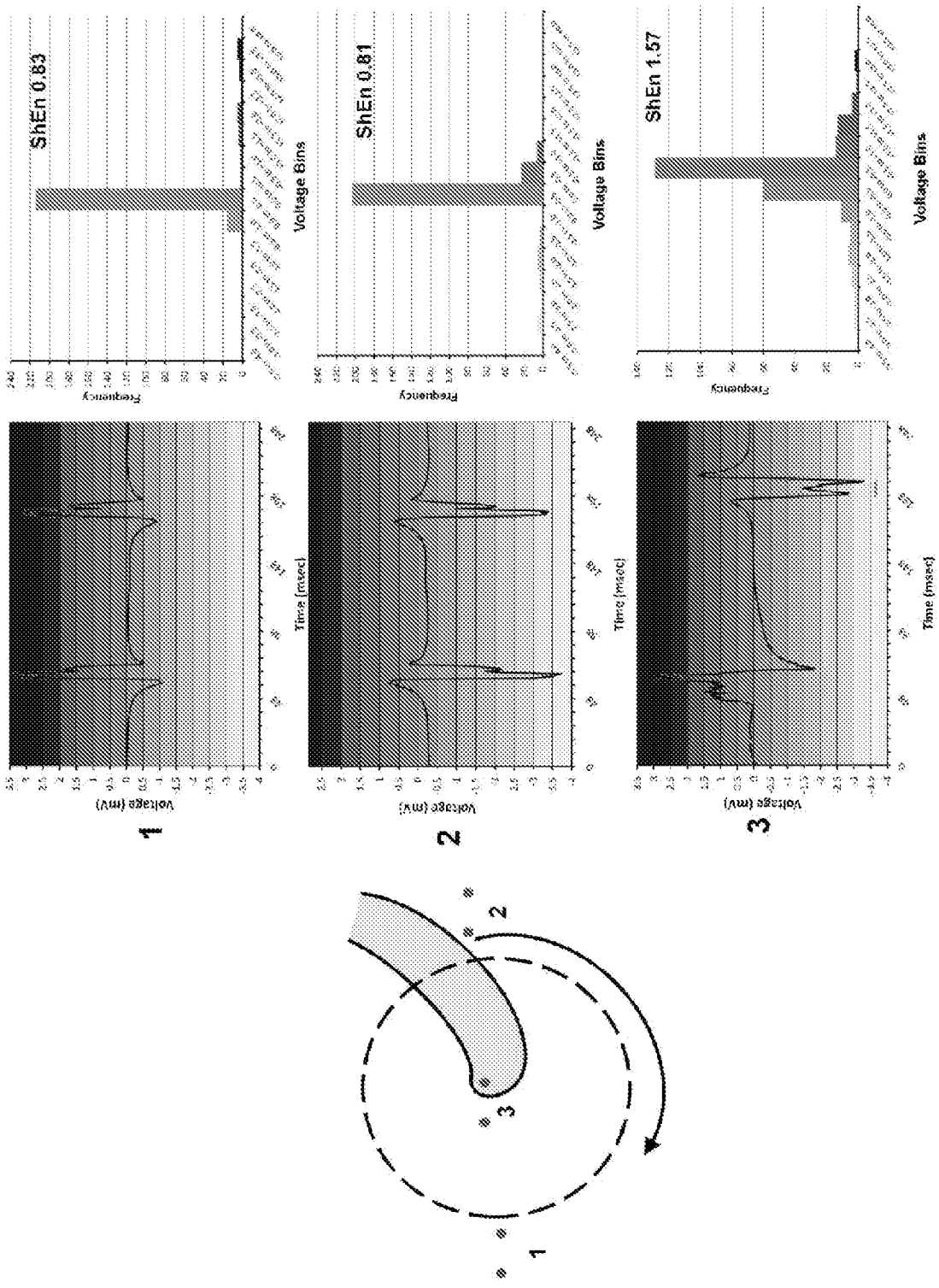

ShEn 0.83
ShEn 0.81
ShEn 1.57
Voltage Bins
Frequency
Voltage (mV)
Time (msec)
1
2
3

Figure 2

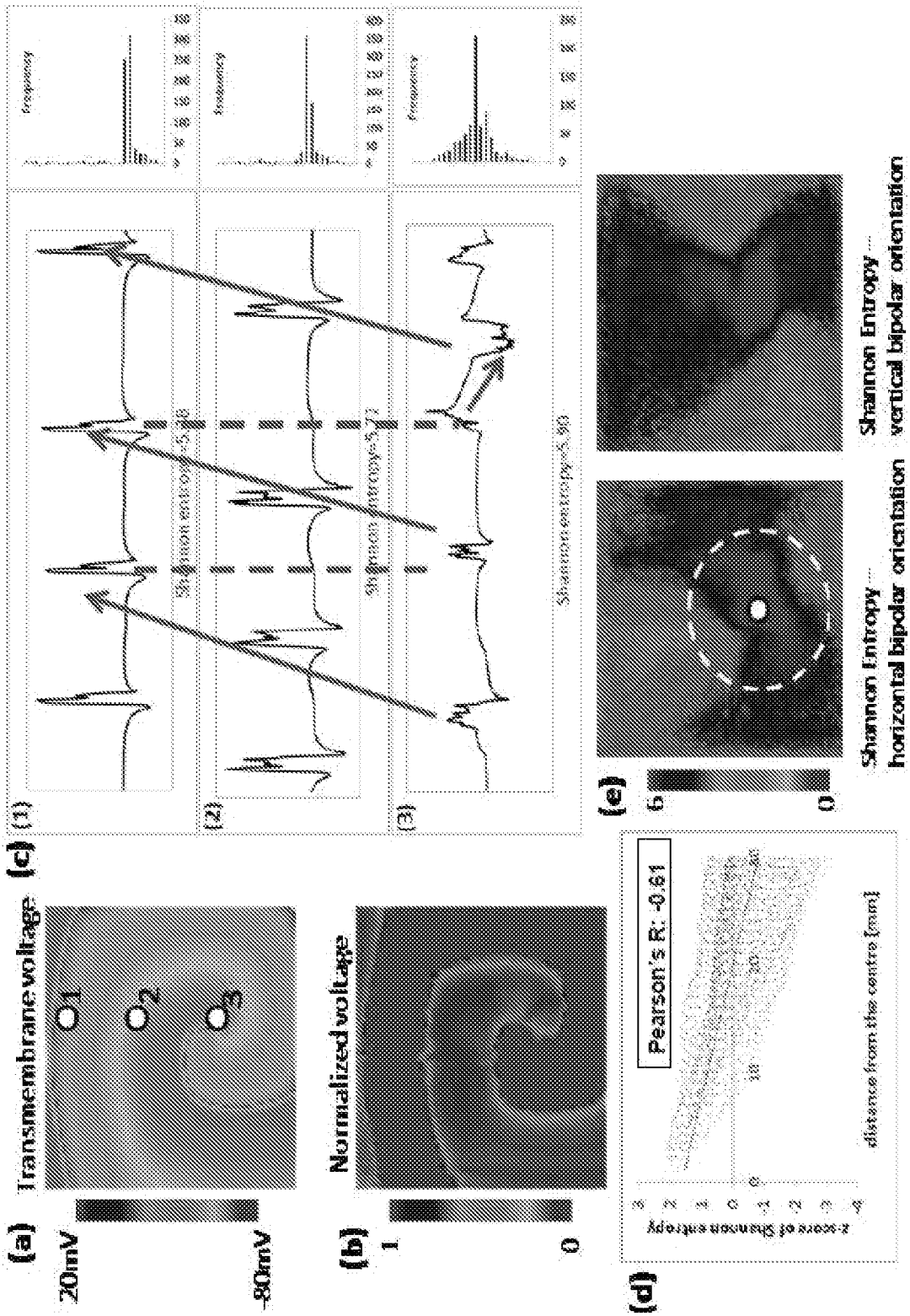

(a)
Transmembrane voltage
20mV
-80mV
O1
O2
O3
(b)
Normalized voltage
1
0
(c)
(1)
(2)
(3)
Frequency
(d)
Pearson's R: -0.61
z-score of Shannon entropy
distance from the centre [mm]
(e)
6
0
Shannon Entropy -- horizontal bipolar orientation
Shannon Entropy -- vertical bipolar orientation

Figure 3

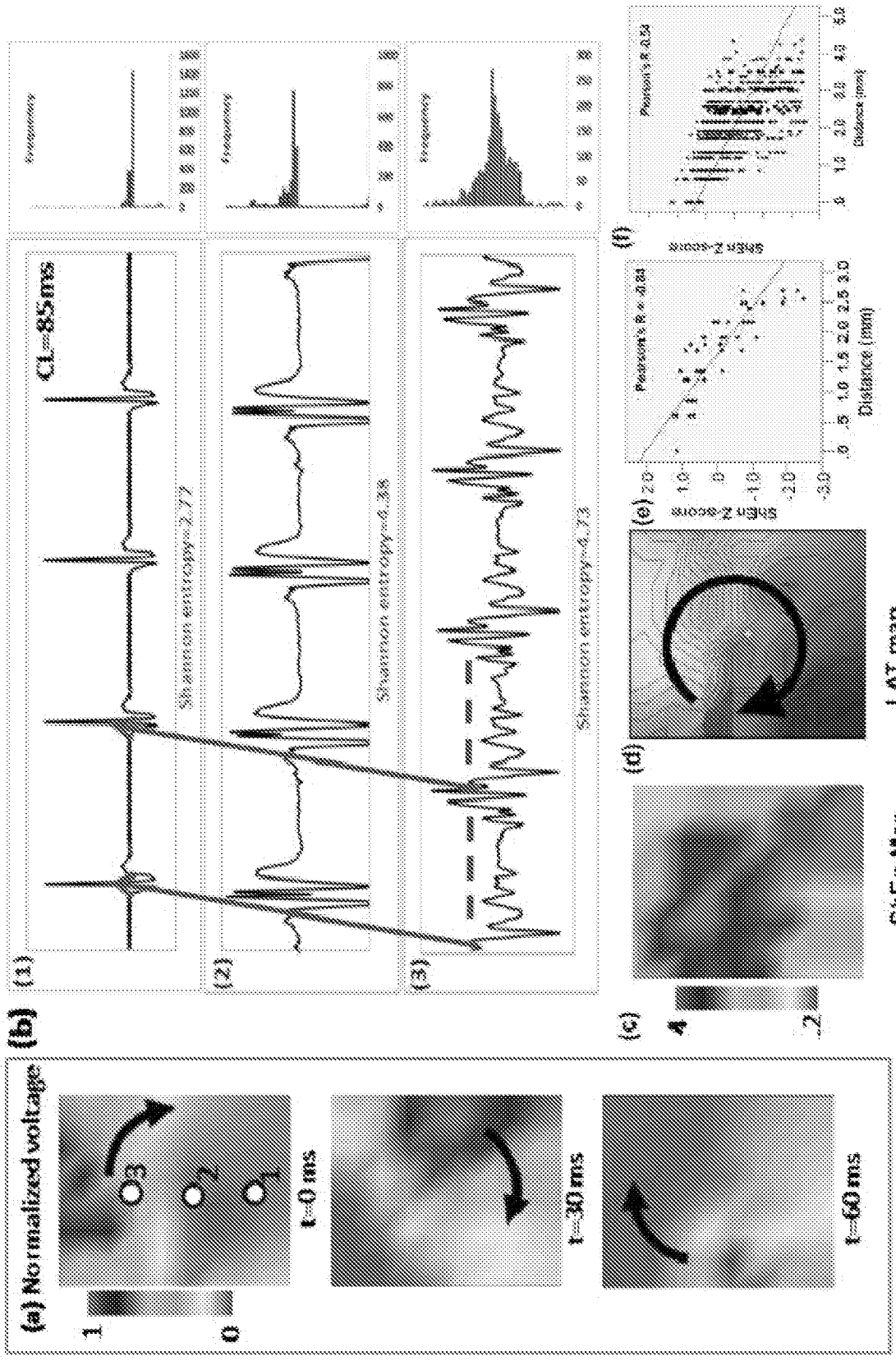

(a) Normalized voltage
1
0
O3
O2
O1
t=0 ms
t=30 ms
t=60 ms
(b)
CL=85ms
(1)
(2)
(3)
Shannon entropy=2.77
Shannon entropy=4.38
Shannon entropy=4.73
Frequency
(c)
4
2
ShEn Map
(d)
LAT map
(e)
ShEn Z-score
Distance (mm)
(f)
ShEn Z-score
Distance (mm)

Figure 4

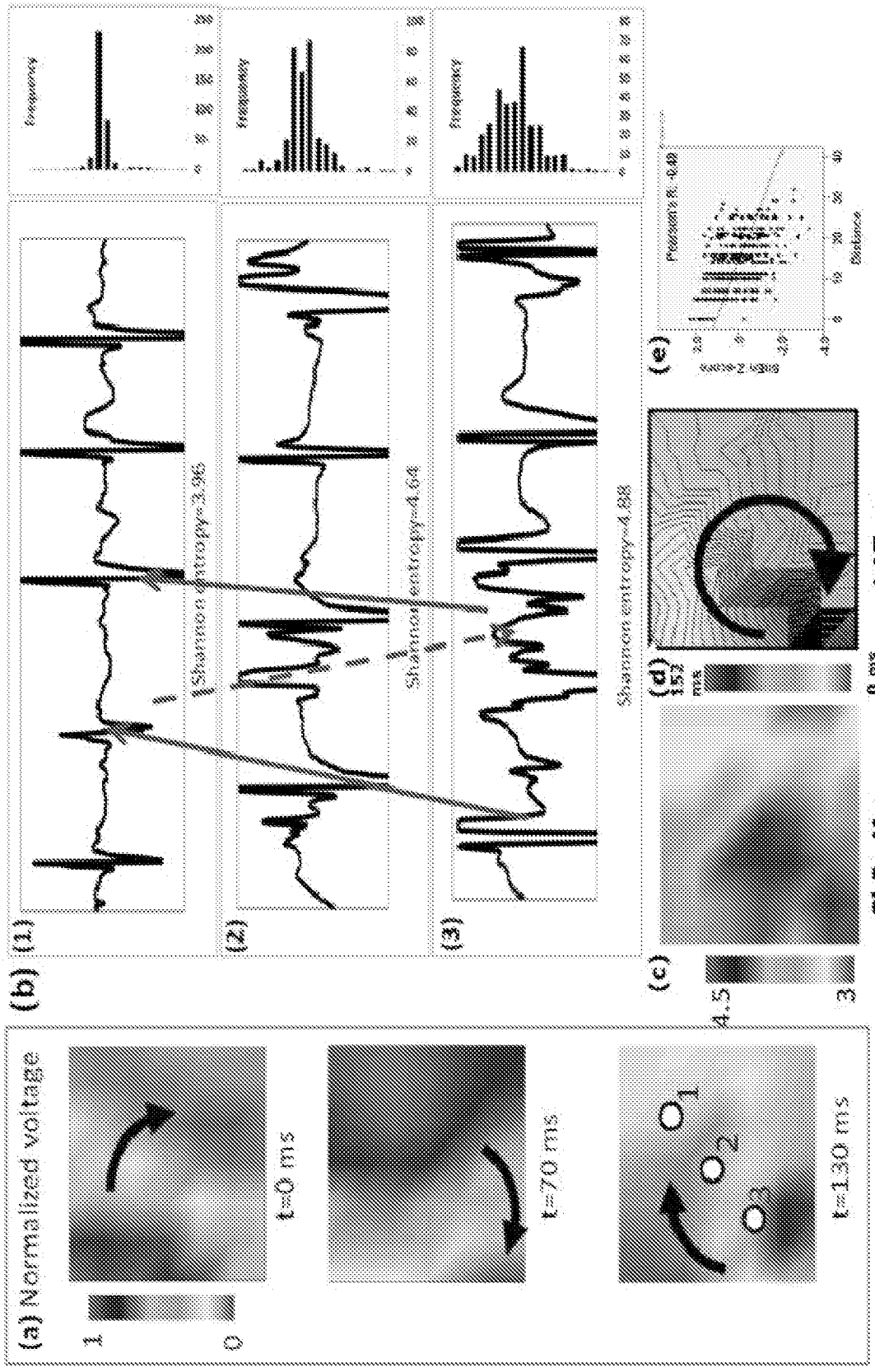

(a) Normalized voltage
1
0
t=0 ms
t=70 ms
t=130 ms
O1
O2
O3
(b)
(1)
(2)
(3)
Shannon entropy=3.96
Shannon entropy=4.64
Shannon entropy=4.88
frequency
(c)
4.5
3
ShEn Map
(d)
157 ms
0 ms
LAT map
(e)
Pearson's R: -0.49
Distance

Figure 5

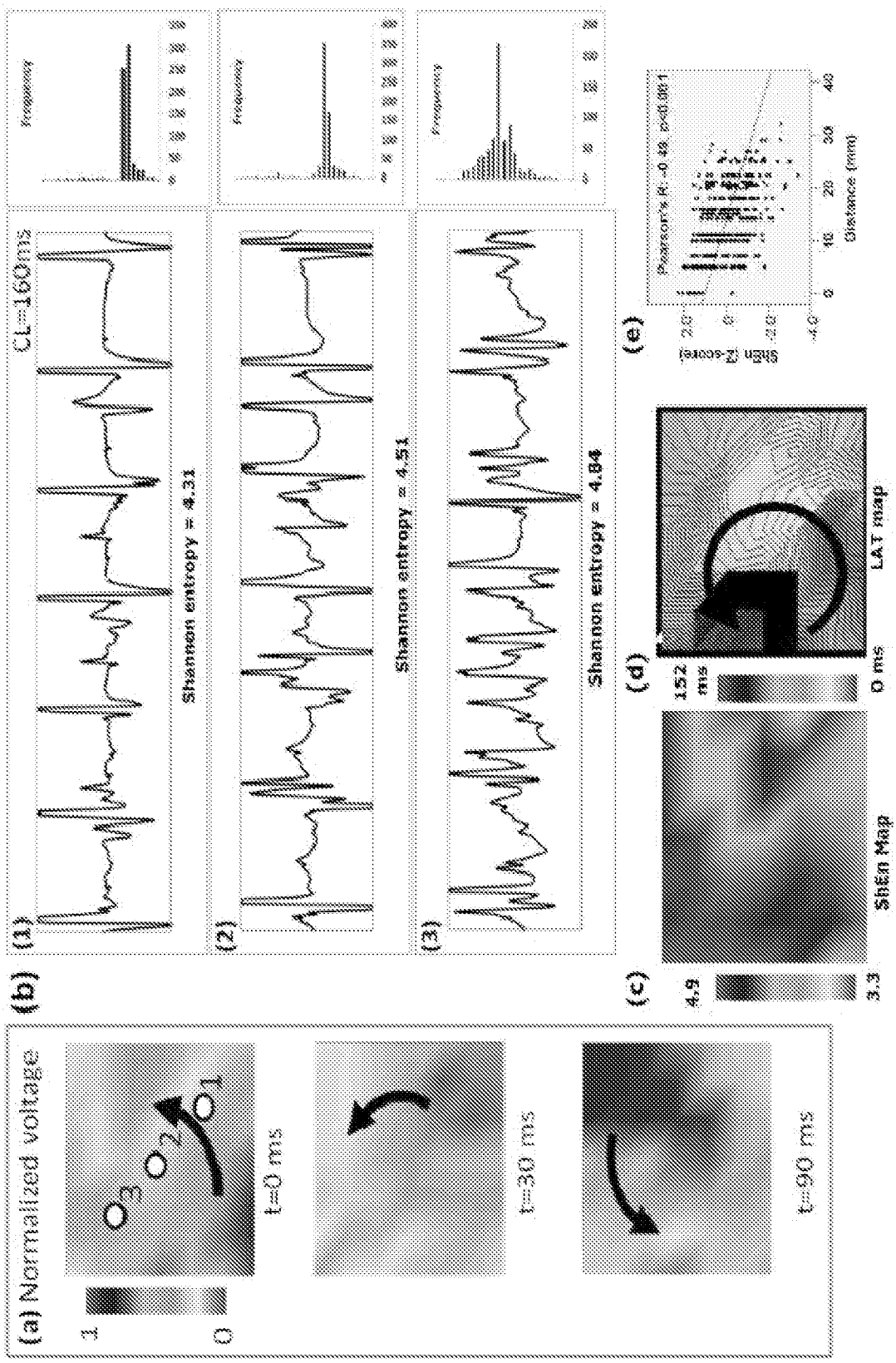
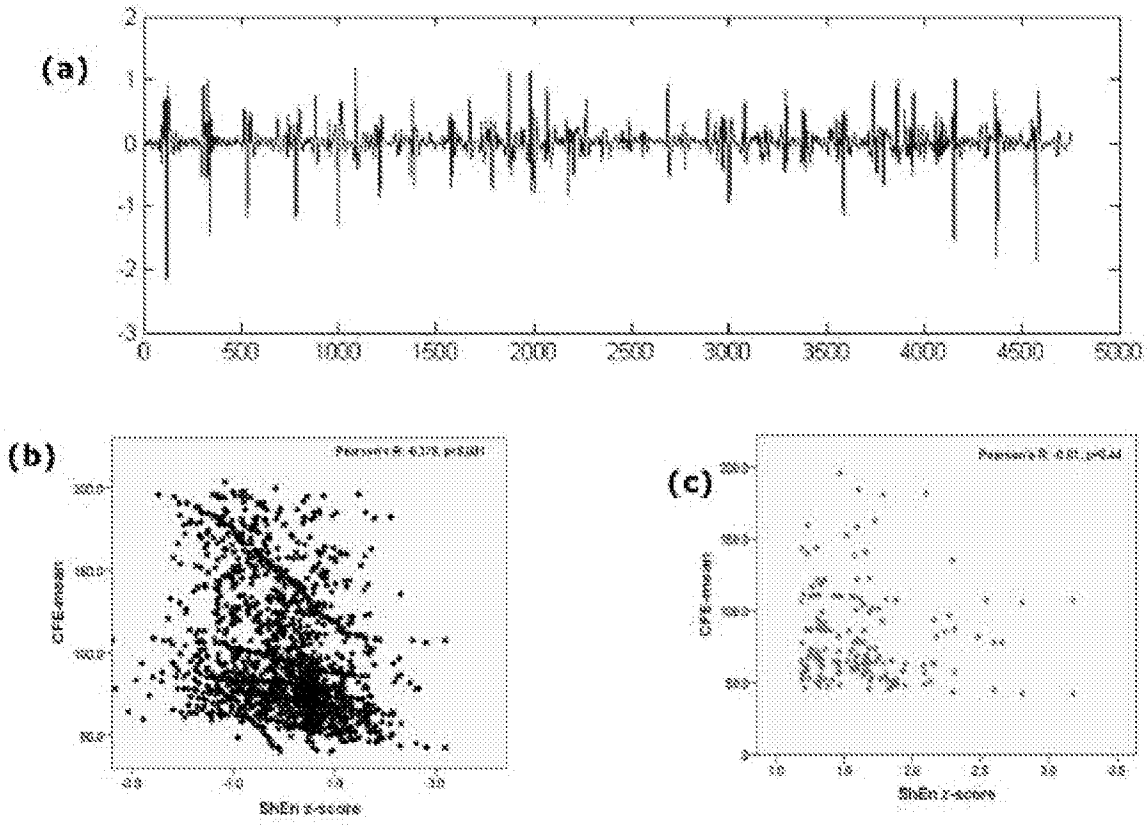

(a) Normalized voltage
1
0
O_3 O_2 O_1
t=0 ms
t=30 ms
t=90 ms
(b)
CL=160ms
(1)
Shannon entropy = 4.31
(2)
Shannon entropy = 4.51
(3)
Shannon entropy = 4.84
Frequency
(c)
4.9
3.3
ShEn Map
(d)
152 ms
0 ms
LAT map
(e)
ShEn (Z-score)
Distance (mm)

Figure 6


(a)
2
1
0
-1
-2
-3
0
500
1000
1500
2000
2500
3000
3500
4000
4500
5000
(b)
CFE/minute
ShEn z-score
(c)
CFE/minute
ShEn z-score

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2013/000146

A. CLASSIFICATION OF SUBJECT MATTER

A61B 5/046 (2006.01) A61B 5/0472 (2006.01) A61B 5/0402 (2006.01) A61B 5/0468 (2006.01) A61N 1/37 (2006.01) A61N 1/39 (2006.01)

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)

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 practicable, search terms used)

EPODOC, WPI, including classification marks A61B5-, A61N- and keywords such as cardiac, heart, fibrillation, arrhythmia, ablation, assessing, monitor, detect, region, zone, area, identify, variation, variability, statistical measures, Entropy, Shannon entropy, and the like.

Internet-based databases such as Google Scholar were searched with similar keywords and phrases formed by them: cardiac, region, mapping, identify, fibrillation, variability, variance, Entropy, Shannon entropy,maximum, maximal, ablation and the like.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 April 2013	19 April 2013

Name and mailing address of the ISA/AU

AUSTRALIAN PATENT OFFICE
PO BOX 200, WODEN ACT 2606, AUSTRALIA
Email address: pct@ipaustralia.gov.au
Facsimile No.: +61 2 6283 7999

Authorised officer

Viara Van Raad
AUSTRALIAN PATENT OFFICE
(ISO 9001 Quality Certified Service)
Telephone No. +61 262223643

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2013/000146

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

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

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

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

See Supplemental Box for Details

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

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		International application No. PCT/AU2013/000146
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	RODRIGO, M. et al. 'Causality Relation Map: A Novel Methodology for the Identification of Hierarchical Fibrillatory Processes' Computing in Cardiology 2011 IEEE, 2011, Vol.(38), pages 173-176 page 173, part '1.' page 175, part '4.1.' ln. 17-20; part '4.2'; page 176; part '5. Discussion'	1-87
X	KIM, Y. et al. 'Spatiotemporal Complexity of Ventricular Fibrillation Revealed by Tissue Mass Reduction in Isolated Swine Right Ventricle. Further Evidence for the Quasiperiodic Route to Chaos Hypothesis' Journal of Clinical Investigation, 1997,Vol. 100(10):pages 2486-2500 Figs. 2 and 3, pages 2488, 2489.	1-87
X	MASSÈ, S. et al. 'Ventricular Fibrillation in Myopathic Human Hearts: Mechanistic Insights From in Vivo Global Endocardial and Epicardial Mapping' American Journal of Physiology-Heart and Circulatory Physiology, 2007, Vol. 292(6),pages H2589-H2597 pages H2589 - H2593, Figs. 4, 6 and 7 and related text	1-87
	US 2009/0259266 A1 (ZHANG et al.) 15 October 2009	
X	Abstract, Figs. 2-5, para [0003]-[0005], para [0014], para [0021]-[0030]	55-87
Y	entire document, para[0003]-[0005], [0021]-[0030]	1-54
	US 6658285 B2 (POTSE et al.) 02 December 2003	
Y	Figs 7, 8, 9A, 9B; col. 4, ln. 47-55 and col. 8, ln. 41-63; col. 10, ln.49-col. 11, ln. 11.	1-54
	US 7715907 B2 (KOERTGE et al.) 11 May 2010	
Y	Abstract, Figs. 1 and 2, elements 'Exciting Time', 'Dominant Frequency' or "Energy level,' and 'FEM Mapping AF,' elements (220), (222), Fig. 1 and elements (104)-(108), col. 1, ln.19- col. 4, ln. 27.	1-54
X	MASÈ, M. et al.'Quantification of synchronization during atrial fibrillation by Shannon entropy: validation in patients and computer model of atrial arrhythmias,' Physiological Measurement, 2005, Vol. 26, pages 911-923. entire document, pages 914-923, esp. equations, Figs. 1-7, page 922, last paragraph, last line.	1-87

Supplemental Box

Continuation of: **Box III**

This International Application does not comply with the requirements of unity of invention because it does not relate to one invention or to a group of inventions so linked as to form a single general inventive concept.

This Authority has found that there are different inventions based on the following features that separate the claims into distinct groups:

- Claims 1-22, 46, 48, 50-52 and claims 47, 49, 53, 54 (in part) are directed to a method of indentifying a cardiac region for ablation to prevent or treat a cardiac arrhythmia, the method comprising determining one or more electrical waveform characteristics at a plurality of cardiac sites and identifying the cardiac region of maximal variance as the cardiac region for ablation. The feature of of identifying a cardiac region by electrical waveform having maximal variance is specific to this group of claims.

- Claim 23 and claims 47, 49, 53(in part) are directed to a method of indentifying a cardiac region for ablation the method comprising determining voltage amplitude at a plurality of cardiac sites and identifying a cardiac region of maximal distribution of voltage amplitude and identifying the cardiac region of maximal distribution of voltage amplitudes as the cardiac region for ablation to prevent and to treat the cardiac arrhythmia. The feature of of identifying a cardiac region by electrical waveform having maximal distribution of voltage amplitude is specific to this group of claims.

- Claims 24 and 47, 49, 53 (in part) are directed to a method of indentifying a cardiac region for ablation the method comprising determining Shannon Entropy of voltage amplitude at a plurality of cardiac sites and identifying a cardiac region of maximal Shannon Entropy and identifying the cardiac region of maximal distribution of voltage amplitudes as the cardiac region for ablation to prevent and to treat the cardiac arrhythmia . The feature of of identifying a cardiac region by comprising determining Shannon Entropy of voltage amplitude at a plurality of cardiac sites is specific to this group of claims.

- Claims 25 and 47, 49, 53 (in part) are directed to a method of indentifying a cardiac region for ablation the method comprising determining maximal complexity of distribution of one or more electrical waveform characteristics and identifying the cardiac region of the said maximal complexity of distribution as the cardiac region for ablation to prevent and to treat the cardiac arrhythmia. The feature of of creating a maximal complexity distribution of the electrical waveform characteristics to idnetify a region of ablation is specific to this group of claims.

- Claims 26-44 and 47, 49, 53, 54 (in part) are directed to a method of indentifying a cardiac region for ablation to prevent and to treat the cardiac arrhythmia, the method comprising using a computer processor means to receive data associated with one or more electrical waveform characteristics obtained from a plurality of cardiac sites and process the data to generate a map of variance of one or more electrical waveform and using the map to identify a region for ablation. The feature of of creating a map of the variance of the electrical waveform characteristics to idnetify a
- region of ablation is specific to this group of claims is specific to this group of claims.

- Claim 45 and 47, 49, 53 (in part) are directed to a method of indentifying a cardiac region for ablation to prevent and to treat the cardiac arrhythmia, the method comprising using a computer processor means to

receive data associated with one or more electrical waveform characteristics obtained from a plurality of cardiac sites and process the data to generate a map of the variance of Shannon Entropy and using the map to identify a region for ablation. The feature of of generating a map of the variance of Shannon Entropy and using the map to identify a region for ablation is specific to this group of claims.

- Claims 55-87 are directed to a system for cardiac mapping/computer readable medium comprising a computer processor means (or the computer readable medium itself) configured to receive data associated with one or more electrical waveform characteristics obtained from a plurality of cardiac sites and process the data via programming instructions to generate a map of variance and/or to identify cardiac region with maximal variance or the maximal variance of Shannon Entropy in the electrical waveform characteristics. The feature of of the computed processor/computer medium processing data configured to generate a map of variance and/or indentify maximal variance or the maximum variance of Shannon Entropy for cardiac mapping is specific to this group of claims.

PCT Rule 13.2, first sentence, states that unity of invention is only fulfilled when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding special technical features. PCT Rule 13.2, second sentence, defines a special technical feature as a feature which makes a contribution over the prior art.

When there is no special technical feature common to all the claimed inventions there is no unity of invention.

In the above groups of claims, the identified features may have the potential to make a contribution over the prior art but are not common to all the claimed inventions and therefore cannot provide the required technical relationship. The only feature common to all of the claimed inventions and which provides a technical relationship among them is maximal variance of electrical waveform data to identify the cardiac sites for ablation to treat arrhythmia.

However this feature does not make a contribution over the prior art because it is disclosed in:
D1: RODRIGO, M. et al. 'Causality Relation Map: A Novel Methodology for the Identification of Hierarchical Fibrillatory Processes' Computing in Cardiology 2011 IEEE, 2011, Vol.(38), pages 173-176.

Therefore in the light of this document this common feature cannot be a special technical feature. Therefore there is no special technical feature common to all the claimed inventions and the requirements for unity of invention are consequently not satisfied *a posteriori*.

See for example D1's disclosure about the identification of the cardiac site discussed on pages 175-176 and depicted by Fig. 1 noting the lowest organization index as indication of maximal variance of data and mapping the data in spatio-temporal maps (note Box VIII for clarification of interpretation).

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/AU2013/000146**

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**
US 2009/0259266 A1	15 Oct 2009	US 2009259266 A1	15 Oct 2009
US 6658285 B2	02 Dec 2003	AU 4576701 A	24 Sep 2001
		AU 4744001 A	24 Sep 2001
		AU 4920601 A	24 Sep 2001
		AU 5386101 A	24 Sep 2001
		AU 5705201 A	23 Oct 2001
		US 6556860 B1	29 Apr 2003
		US 6584343 B1	24 Jun 2003
		US 2001056245 A1	27 Dec 2001
		US 6615075 B2	02 Sep 2003
		US 2002038093 A1	28 Mar 2002
		US 6658285 B2	02 Dec 2003
		US 2001056289 A1	27 Dec 2001
		US 6760620 B2	06 Jul 2004
		US 2002026220 A1	28 Feb 2002
		US 6931273 B2	16 Aug 2005
		US 2004015194 A1	22 Jan 2004
		US 2005182336 A1	18 Aug 2005
		WO 0167950 A1	20 Sep 2001
		WO 0167952 A1	20 Sep 2001
		WO 0167953 A1	20 Sep 2001
		WO 0167954 A1	20 Sep 2001
		WO 0176461 A2	18 Oct 2001
US 7715907 B2	11 May 2010	CN 101254096 A	03 Sep 2008
		US 2008214945 A1	04 Sep 2008
		US 7715907 B2	11 May 2010

End of Annex

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/AU2013/000146**

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.