Non–linear Time Series Analysis: Methods and Applications to Atrial Fibrillation

B.P.T. Hoekstra[1], C.G.H. Diks[2], M.A. Allessie[3] and J. DeGoede[4]

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[1]Division of Image Processing, Department of Radiology, Leiden University Medical Center, The Netherlands
[2]Center for Nonlinear Dynamics in Economics and Finance, Department of Economics and Econometrics, University of Amsterdam, The Netherlands
[3]Cardiovascular Research Institute, Department of Physiology, Maastricht University, The Netherlands
[4]Department of Physiology, University of Leiden, The Netherlands

Address: B.P.T. Hoekstra, Leiden University Medical Center, Division of Image Processing, Department of Radiology, P.O. Box 9600, 2300 RC Leiden, The Netherlands. Tel: +31–71–526 2137; Fax: +31–71–526 6801; Email: B.P.T.Hoekstra@LUMC.NL

Summary

We apply methods from nonlinear statistical time series analysis to characterize electrograms of atrial fibrillation. These are based on concepts originating from the theory of nonlinear dynamical systems and use the empirical reconstruction density in reconstructed phase space. Application of these methods is not restricted to deterministic chaos but is valid in a general time series context. We illustrate this by applying three recently proposed nonlinear time series methods to fibrillation electrograms: 1) a test for time reversibility in atrial electrograms during paroxysmal atrial fibrillation in patients; 2) a test to detect differences in the dynamical behaviour during the pharmacological conversion of sustained atrial fibrillation in instrumented conscious goats; 3) a test for general Granger causality to identify couplings and information transport in the atria during fibrillation. We conclude that a characterization of the dynamics via the reconstruction density offers a useful framework for the nonlinear analysis of electrograms of atrial fibrillation.

Keywords: atrial fibrillation, Granger causality, nonlinear time series analysis, reconstruction density, time reversibility

Introduction

Physiological time series typically are short, nonlinear and noisy. Such time series usually cannot be studied satisfactorily by linear time series analysis. Although linear techniques such as Fourier analysis are useful to study characteristic oscillations in detail, these methods fail to detect any nonlinear correlations present and cannot provide a complete characterization of the underlying dynamics.

Over the lasts two decades many nonlinear time series methods have been developed in the theory of nonlinear dynamics, commonly known as chaos theory. These methods are suited to characterize the dynamics in noise free, low–dimensional deterministic systems and have proven highly successful in characterizing irregular (chaotic) time series from mathematical models and well–controlled physical experiments.

Biological systems are subjected to changes in their environment triggered both by stochastic sources and feedback control mechanisms. Hence, time series recorded from the natural world consist of a mixture of random and deterministic features in which chaos in a strong sense can hardly be expected. Although much initial work was inspired by the idea that chaos might be omnipresent in nature and focused on whether observed irregularity was chaos or noise, it has become increasingly clear that such a sharp distinction between deterministic chaos and randomness cannot be made [1].

Here we adopt a different point of view on nonlinear time series analysis and demonstrate that concepts originating from the theory of nonlinear dynamics can be used to characterize the underlying dynamics of physiological time series. In particular, we apply recently developed statistical nonlinear time series methods which are based on the reconstruction density.

We present a test for time reversibility [2] which is applied to discriminate and classify atrial electrograms of acute atrial fibrillation (AF) in patients undergoing open–chest surgery. The test has been previously applied to characterize the dynamics of EEG epochs recorded before and during an epileptical seizure [3].

We also present a test to detect differences between reconstruction densities [4] which is applied to electrograms of sustained AF in instrumented conscious goats to characterize changes in the dynamics during the pharmacological conversion of sustained AF by the class IC anti–arrhythmic agent cibenzoline. The test is also used to investigate if the fibrillation electrograms are stationary by comparing different segments of the recorded time series.

We previously studied linear and nonlinear association lengths to characterize spatial organization during AF [5, 6]. However, the association lengths do not provide the direction of couplings and the flow of information between different atrial sites. In 1969, Granger [7] introduced an operational definition of causality between two variables. This so–called Granger causality is well suited to identify the relevant space–time couplings in the activation pattern of AF. The testing for Granger causality has mostly been performed in a linear framework. Here we propose to test for general Granger causality, i.e. linear as well as nonlinear causality, as a first step in the characterization of the space–time pattern of electrical heart activity.

The nonlinear time series methods presented here have in common that they are based on the reconstruction density in reconstructed phase space. A characterization of the dynamics via the reconstruction density offers a useful framework for the analysis of electrograms of atrial fibrillation in particular and time series in general.

Methods

Reconstructed Phase Space and Reconstruction Density

The reconstruction theorem proved by Takens [8] is the starting point for many nonlinear time series methods. Given a scalar–valued time series $\{x_i\}_{i=1}^{\infty}$, the state of a deterministic dynamical system can be represented in a reconstructed phase space by defining m–dimensional delay vectors

$$\vec{x}_i = (x_i,\, x_{i-\tau},\, \ldots,\, x_{i-(m-1)\tau}), \tag{1}$$

where τ is the reconstruction delay and m is the embedding dimension.

We will only be concerned with stationary time series. We will follow the methodology of Takens [9] in order to give a definition of stationarity which can be applied to a single time series rather than to an ensemble of time series. In this methodology a time series by definition is called stationary if its reconstruction measure exists, defined by

$$\rho(\vec{x}) = \lim_{L\to\infty} \frac{1}{L} \sum_{i=1}^{L} \delta(\vec{x} - \vec{x}_i), \tag{2}$$

where $\delta(\cdot)$ is the Dirac delta function. In practice where we have time series of finite length we approximate the reconstruction density by the empirical reconstruction density, given by

$$\rho(\vec{x}) = \frac{1}{L} \sum_{i=1}^{L} \delta(\vec{x} - \vec{x}_i), \tag{3}$$

where $L = N - (m-1)\tau$, and N is the length of the time series.

We can study the reconstruction density without proposing a model for the time series. For example, it can be examined if the reconstruction density has a certain symmetry. In the

following section a test is presented which explores the symmetry with respect to time reversal. Next, we elaborate on a test which was designed to examine if two given time series have the same reconstruction density. This test can also be used to investigate (strict) stationarity by comparing different segments of an observed time series. Finally, we consider a test for general Granger causility to study the direction of couplings and the information transport between different spatial positions on the atria.

Test for Time Reversibility

A time series is (time) reversible if its statistical properties are invariant under reversal of time direction. This means that the time series "looks the same" read forward or backward in time. Otherwise the time series is said to be (time) irreversible.

If a time series is generated by a linear Gaussian random process, the result is a reversible time series. Furthermore, all static transformations of the time series preserve reversibility. Therefore, if reversibility can be ruled out, the null hypothesis that the time series is a realization of a static transformation of a linear Gaussian random process can be rejected.

We will briefly describe a test for reversibility proposed by Diks et al. [2]. We want to test the null hypothesis that the reconstruction density ρ of the delay vectors is invariant under time reversal for all embedding dimensions m and reconstruction delays τ, i.e.

$$H_0 : \qquad \rho(\vec{x}) = \rho(P\vec{x}),$$

where P denotes the time reversal operator which is defined by

$$P(x_i,\, x_{i-\tau},\, \cdots,\, x_{i-(m-1)\tau}) = (x_{i-(m-1)\tau},\, \cdots,\, x_{i-\tau},\, x_i). \tag{4}$$

A squared distance Q_r between the time forward and time reversed reconstruction densities is defined as

$$Q_r \;=\; \frac{1}{2}\,(d\sqrt{\pi})^m \int \mathrm{d}\vec{x}\;\; (\;\rho'(\vec{x}) - \rho'(P\vec{x})\;)^2\,, \tag{5}$$

in which $\rho'(\vec{x})$ is defined as the convolution

$$\rho'(\vec{x}) = \int \mathrm{d}\vec{r}\;\rho(\vec{r})\;\kappa(\vec{x}-\vec{r}), \tag{6}$$

where $\kappa(\cdot)$ is a Gaussian distribution defined by

$$\kappa(\vec{x}) = \left(\frac{2}{\pi d^2}\right)^{m/2}\;\exp(-2|\,\vec{x}\,|^2/d^2), \tag{7}$$

with $|\cdot|$ denoting the Euclidean norm in $\mathbf{R}^m$. The parameter $d > 0$ is a bandwidth, which is the length scale at which the reconstruction densities $\rho(\vec{x})$ and $\rho(P\vec{x})$ are compared.

Q_r can be estimated unbiasedly from the set of delay vectors $\{\vec{x}_i\}_{i=1}^N$ sampled independently from $\rho(\vec{x})$. The result is [2]

$$\widehat{Q_r} \;=\; \frac{2}{N\,(N-1)}\;\sum_{i<j} w_{ij}, \tag{8}$$

where

$$w_{ij} = \exp(-|\,\vec{x}_i - \vec{x}_j\,|^2/d^2) - \exp(-|\,\vec{x}_i - P\vec{x}_j\,|^2/d^2). \tag{9}$$

Under the H_0 the expected value of $\widehat{Q}_r$ is equal to zero and its standard deviation σ_r is given by

$$\sigma_r \;=\; \frac{2}{N\,(N-1)}\;\left(\sum_{i<j} w_{ij}^2\right)^{1/2}. \tag{10}$$

The test statistic S_r is now defined as

$$S_r = \frac{\widehat{Q}_r}{\sigma_r}. \tag{11}$$

Under the H_0, S_r has expected value zero and unit standard deviation. We remark that the asymptotic distribution of S_r may not be normal. However, assuming unimodality, reversibility can be rejected at a rejection probability of at most 0.05 when the test statistic gets larger than three [10].

In the derivation of the test statistic S_r we have assumed that the delay vectors are sampled independently from the reconstruction density $\rho(\vec{x})$. However, this is an oversimplification, since the reconstruction procedure by itself introduces dependence among the delay vectors. Furthermore, dynamical structure in the time series will introduce additional dependences. In order to reduce their effects, we excluded all pairs $(\vec{x_i}, \vec{x_j})$ which are closer in time than some lag W as proposed by Theiler [11]. Furthermore, higher order dependences between delay vectors were suppressed by comparing non–overlapping blocks consisting of ℓ consecutive delay vectors, instead of single pairs of delay vectors [4]. The parameter ℓ is preferably chosen large with respect to the characteristic time scale of the time series.

Insight into the presence of irreversibility in the time series may already be obtained from a visual inspection of a two–dimensional phase plot. By interchanging the two components of the delay vectors, which is equivalent to mirroring the phase plot in the main diagonal, it can be visually inspected if the plot is symmetric with respect to this operation. If not, it can be concluded that the time series is irreversible.

For example, Fig. 1 shows a right atrial electrogram (RA) of AF and a surrogate electrogram constructed from the measured electrogram by the procedure of phase randomization in the frequency domain [12]. From the lack of symmetry in the phase plot of the measured electrogram (there are more points above the main diagonal than below), it may be concluded that the electrogram is irreversible. In contrast, the distribution of points in the phase plot of the surrogate electrogram is symmetric and therefore suggests that the surrogate time series is reversible. This is indeed the case, since the surrogate electrogram is by construction a realization of a linear Gaussian random process.

Finally, we remark that a test for time reversibility is not a test for linearity, since there exist stationary nonlinear processes that are time reversible. On the other hand, time irreversibility indicates nonlinearity or non–Gaussianity.

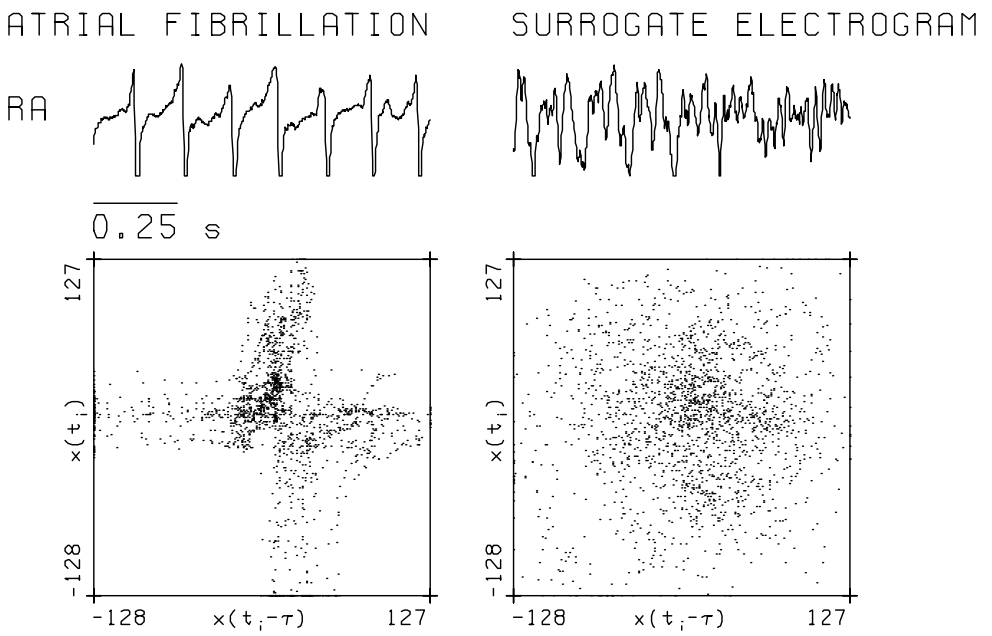

Figure 1: Upper panels: A right atrial epicardial unipolar electrogram (RA) of atrial fibrillation in a patient and a surrogate electrogram constructed from the measured time series. Lower panels: Phase plots constructed from the electrograms. In the phase plot of the measured electrogram (lower left panel) there are more points above the main diagonal than below. From this lack of symmetry in the phase plot it may be concluded that the electrogram is irreversible. In contrast, the distribution of points in the phase plot of the surrogate electrogram (lower right panel) is symmetric. This suggests that the surrogate time series is reversible. The delay τ was chosen equal to the first minimum of the mutual information function, and was 48 ms for the measured electrogram and 12 ms for the surrogate electrogram.

Test to Detect Differences between Reconstruction Densities

A test for detecting differences between reconstruction densities has been proposed by Diks et al. [4]. Here we will briefly describe the test which is based on a general distance notion between m–dimensional reconstruction densities $\rho_1(\vec{r})$ and $\rho_2(\vec{r})$ in $\mathbf{R}^m$. We want to test the null hypothesis that the two reconstruction densities are identical, viz.

$$H_0 : \qquad \rho_1(\vec{r}) = \rho_2(\vec{r}).$$

A squared distance Q_c is defined as

$$Q_c = (d\sqrt{\pi})^m \int \mathrm{d}\vec{r} \ \left(\ \rho_1'(\vec{r}) - \rho_2'(\vec{r}) \ \right)^2 , \tag{12}$$

in which $\rho_k'(\vec{r})$ is defined as the convolution

$$\rho_k'(\vec{r}) = \int \mathrm{d}\vec{s} \ \rho_k(\vec{s}) \ \kappa(\vec{r} - \vec{s}) \qquad (k = 1, 2), \tag{13}$$

where $\kappa(\cdot)$ is a Gaussian distribution defined by

$$\kappa(\vec{r}) = \left(\frac{2}{\pi d^2} \right)^{m/2} \ \exp(-2|\,\vec{r}\,|^2/d^2), \tag{14}$$

with $|\cdot|$ denoting the Euclidean norm in $\mathbf{R}^m$. The parameter $d > 0$ is the bandwidth, which is the length scale at which the reconstruction densities $\rho_1(\vec{r})$ and $\rho_2(\vec{r})$ are compared.

Q_c can be estimated unbiasedly from two sets of delay vectors, $\{\vec{x}_i\}_{i=1}^{N_1}$ and $\{y_i\}_{i=1}^{N_2}$, sampled independently from $\rho_1(\vec{r})$ and $\rho_2(\vec{r})$, respectively. The result is [4]

$$\begin{aligned}\widehat{Q_c} &= \frac{2}{N_1\,(N_1-1)}\sum_{1\le i<j\le N_1}\sum h(\vec{x}_i,\vec{x}_j) \;+\; \frac{2}{N_2\,(N_2-1)}\sum_{1\le i<j\le N_2}\sum h(\vec{y}_i,\vec{y}_j) \\ &\quad - \frac{2}{N_1\,N_2}\sum_{i=1}^{N_1}\sum_{j=1}^{N_2} h(\vec{x}_i,\vec{y}_j), \end{aligned} \tag{15}$$

in which

$$h(\vec{x}_i,\vec{x}_j) = \exp(-|\,\vec{x}_i - \vec{x}_j\,|^2/d^2). \tag{16}$$

The test statistic

$$S_c = \frac{\widehat{Q}_c}{\sigma_c} \tag{17}$$

is, under the null hypothesis that the two reconstruction densities are the same, distributed with zero mean and standard deviation equal to one. For a derivation of the standard deviation σ_c of $\widehat{Q}_c$ under the null hypothesis and conditionally on the set of $N_1 + N_2$ observed delay vectors we refer to [4]. The test statistic is derived under the assumption of independent delay vectors. The effect of dependencies is reduced in a similar way as for the reversibility test.

In general, S_c is not standard normally distributed, but assuming that it is unimodal, the null hypothesis can be rejected at a rejection probability of at most 0.05 when S_c gets larger than three [10]. Since $Q_c = 0$ if and only if $\rho_1(\vec{r}) = \rho_2(\vec{r})$, and larger than zero otherwise, the test is one–sided.

Test for general Granger Causality

Tests for Granger causality originate from econometrics where the challenge consists of detecting and characterizing dependences between variables within a noisy background. Consider two scalar–valued time series, $\{x_i\}_{i=1}^N$ and $\{y_i\}_{i=1}^N$. Intuitively, $\{y_i\}_{i=1}^N$ is a Granger cause of $\{x_i\}_{i=1}^N$ if past and present values of the variable y contain information about the distribution of future values of the variable x, not contained in past and present observations of x. This causality concept is based on predictability and is useful in empirical research on causal relationships among observed time series. The traditional approach to testing for Granger causality consists in comparing prediction errors of an autoregressive model of x with the prediction errors obtained by an augmented model which regresses x on past and current values of both x and y. This approach is appealing, since the test reduces to determining the significance of the coefficients in the augmented model of the terms that depend on past and current values of y. A disadvantage of such parametric testing is that modelling assumptions are required such as linearity of the regression structure. To eliminate possible problems resulting from model misspecification we will focus on a nonparametric test for nonlinear Granger causality.

Given two time series $\{x_i\}_{i=1}^N$ and $\{y_i\}_{i=1}^N$, we wish to test the null hypothesis

$$H_0: \qquad \{y_i\} \text{ is not Granger causing } \{x_i\}.$$

Consider the delay vectors

$$\vec{x}_i = (x_i,\, x_{i-\tau}, \ldots,\, x_{i-(k-1)\tau}), \qquad \vec{y}_i = (y_i,\, y_{i-\tau}, \ldots,\, y_{i-(l-1)\tau}) \tag{18}$$

of dimension k and l respectively, constructed from the time series $\{x_i\}_{i=1}^N$ and $\{y_i\}_{i=1}^N$. The idea of the test is to quantify the average amount of extra information on x_{i+1} contained in the delay vector $\vec{y}_i$, given that we already know $\vec{x}_i$.

The average amount of information a random variable $\vec{x}$ contains about a random variable $\vec{y}$ can be expressed as the generalized mutual information [13] of $\vec{x}$ and $\vec{y}$, which, in terms of generalized correlation integrals [13], reads

$$I_q(\vec{x}, \vec{y}, \epsilon) = \ln C_q(\vec{x}, \vec{y}, \epsilon) - \ln C_q(\vec{x}, \epsilon) - \ln C_q(\vec{y}, \epsilon). \tag{19}$$

For $q = 2$, $C_2(\vec{x}, \epsilon)$ is the fraction of distances between two independently chosen points according to the density $\rho(\vec{x})$, that is smaller than or equal to ϵ. The second order ($q = 2$) correlation integral is equal to the probability that a distance between two independent realisations of $\vec{x}$ is smaller than or equal to ϵ. For the sake of simplicity, the index q as well as the scale parameter ϵ are omitted in the notation of the correlation integrals in the sequel.

The average information about x_{i+1} contained in $\vec{x}_i$ and $\vec{y}_i$ jointly, is given by

$$I(\vec{x}_i, \vec{y}_i; x_{i+1}) = \ln C(\vec{x}_i, \vec{y}_i, x_{i+1}) - \ln C(\vec{x}_i, \vec{y}_i) - \ln C(x_{i+1}), \tag{20}$$

while the average information about x_{i+1} in $\vec{x}_i$ only is given by

$$I(\vec{x}_i; x_{i+1}) = \ln C(\vec{x}_i, x_{i+1}) - \ln C(\vec{x}_i) - \ln C(x_{i+1}). \tag{21}$$

By substracting these two information measures, we can quantify the average amount of extra information that $\vec{y}_i$ contains about x_{i+1} in addition to the information already contained in $\vec{x}_i$.

If past observations of y contain no extra information about future values of x, one has $I(\vec{x}_i, \vec{y}_i; x_{i+1}) = I(\vec{x}_i; x_{i+1})$. If, on the other hand, past observations of y do contain information on current and future values of x, we expect $I(\vec{x}_i, \vec{y}_i; x_{i+1}) > I(\vec{x}_i; x_{i+1})$. This suggests using the quantity

$$\begin{aligned} Q &= I(\vec{x}_i, \vec{y}_i; x_{i+1}) - I(\vec{x}_i; x_{i+1}) \\ &= \ln C(\vec{x}_i, \vec{y}_i, x_{i+1}) - \ln C(\vec{x}_i, \vec{y}_i) - \ln C(\vec{x}_i, x_{i+1}) + \ln C(\vec{x}_i) \end{aligned} \tag{22}$$

as a test statistic.

A bootstrap test for nonlinear Granger causality was recently proposed in a climatological study by Diks and Mudelsee [14], who used Q as a test statistic. For computational efficiency we confine ourselves here to a method of Hiemstra and Jones [15], who use the second order ($q = 2$) correlation integral and asymptotic distribution theory rather than the bootstrap method of Diks and Mudelsee [14]. Hiemstra and Jones test the relationship

$$\frac{C(\vec{x}_i, \vec{y}_i, x_{i+1})}{C(\vec{x}_i, \vec{y}_i)} = \frac{C(\vec{x}_i, x_{i+1})}{C(\vec{x}_i)}, \tag{23}$$

by calculating

$$T = \frac{C(\vec{x}_i, \vec{y}_i, x_{i+1})}{C(\vec{x}_i, \vec{y}_i)} - \frac{C(\vec{x}_i, x_{i+1})}{C(\vec{x}_i)}. \tag{24}$$

The statistics Q and T are closely related: apart from a logarithmic transformation, Hiemstra and Jones test the same null hypothesis as with the statistic Q in Eq. (22).

T depends on the length N of the time series and it was shown that, asymptotically, $\sqrt{N}\ T(N)/\sqrt{\sigma^2(N)}$ is standard normally distributed under the null hypothesis. Together with the consistent estimator for $\sigma^2(N)$, given in the appendix of Hiemstra and Jones [15], the asymptotic distribution can be calculated.

Hiemstra and Jones suggest rejecting the null hypothesis whenever T is too large, since higher values of T are expected when past values of y contain information on future values of x. However, we often found significantly negative values of T in our analysis. Anomalies like these can be traced back to the use of the second order ($q = 2$) correlation integral. Negative values of T can be avoided by implementing tests based on the first order ($q = 1$) correlation integral, or by analyzing ranks rather than the raw data [16]. For computational efficiency we opted for the second order correlation integral so that a two–sided test is necessary.

Materials and Results

In this section we present the results of the nonlinear time series analysis. The test for reversibility is applied to electrograms of paroxysmal AF in a group of patients. The test for comparing reconstruction distributions and the test for Granger causality are illustrated by a typical example of sustained atrial fibrillation in a goat which was converted to sinus rhythm by infusion of the class IC drug cibenzoline.

Testing for Time Reversibility during Paroxysmal Atrial Fibrillation in Patients

Episodes of electrically induced AF were recorded from patients during surgery for an accessory atrio–ventricular conduction pathway (Wolff–Parkinson–White syndrome). There were no indications that the atria in these patients behaved physiologically abnormal, and normal spread of activation was observed during sinus rhythm and rapid atrial pacing. The induced episodes of AF were short–lasting and terminated spontaneously.

In a previous high–density mapping study [17] the local activation pattern of AF was recorded from the right atrial free wall and visualized by constructing isochronal activation maps. Atrial fibrillation was classified into three types (I–III) of increasing spatio–temporal complexity, based on the number of fibrillation wavelets and the amount of conduction block observed in the activation maps. Briefly, type I activation was characterized as single, broad uniformly propagating wavefronts with only small areas of slow conduction or block. During type II, the activation pattern was characterized by at most two fibrillation waves, in combination with conduction block. Type III was defined by the presence of three or more wavelets associated with zones of slow conduction and multiple regions of conduction block.

We analyzed sets of five right atrial epicardial unipolar electrograms of AF (duration 4 seconds) from the 244–lead mapping electrode in nine patients, selecting three patients of each type of AF from the high–density mapping study. The same datasets were used in a previous nonlin-

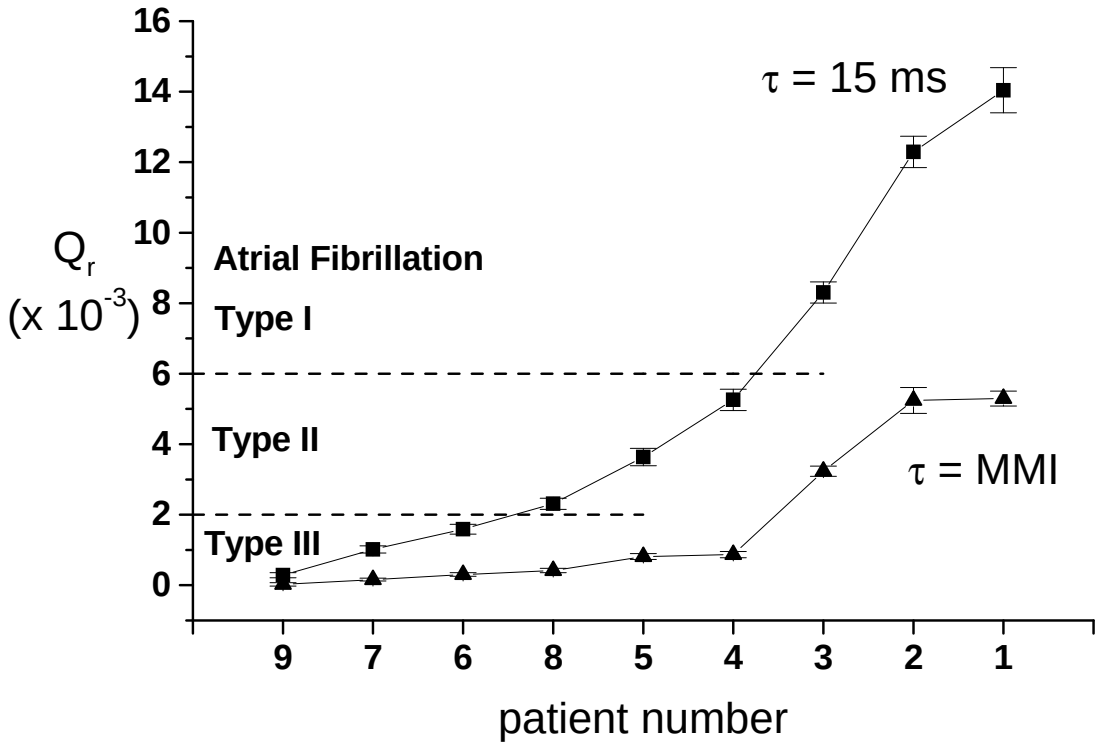

Figure 2: Ranking of the patients according to increasing values of the reversibility statistic Q_r. Results are presented as mean of five local electrograms, error bars denote one standard deviation. A higher degree of irreversibility (larger Q_r values) corresponds to a decreasing degree of complexity observed in activation maps of atrial fibrillation. Boundary values separating the different types of atrial fibrillation are indicated with dotted lines. The abscissa shows the patient numbers according to the classification (patient 1–3: Type I, patient 4–6: Type II, patient 7–9: Type III) based on the degree of complexity of activation patterns visualized from high–density mapping for the curve $\tau = 15$ ms. MMI denotes the average first minimum of the mutual information function.

ear analysis of AF electrograms [18], to which we refer for details on the patient characteristics and the data acquisition and selection.

The parameters for the reversibility test applied to the electrograms of paroxysmal AF in patients were chosen as follows. The delay τ was set equal to the lag corresponding to the first minimum of the mutual information function (MMI) which was typically 30 ms, corresponding to about one quarter of the mean fibrillation cycle length. Furthermore, embedding dimension $m = 5$ and bandwidth $d = 0.5\,\sigma$, where σ is the standard deviation of the time series normalized to $1/(2\sqrt{3})$ [2]. To reduce the effect of dependences we chose the Theiler correction $W = \tau$, and the block length $\ell = 5\tau$ corresponded roughly to the length of the mean fibrillation interval.

Fig. 2 shows the ranking of the patient population according to increasing average values of the reversibility measure Q_r. The difference between the two curves shown was the choice of the delay: apart from the value $\tau = $ MMI (triangles), also a smaller and fixed delay of $\tau = 15$ ms was used (squares). In the latter case we set $W = 2\tau$ and the block length $\ell = 10\tau$ to keep these parameter values comparable to the case $\tau = $ MMI.

The tuning of the delay τ resulted in an improved resolution of the reversibility statistic in going from type I to type III patients. Using the fixed delay of 15 ms, the transition was

characterized by a more gradual and smooth change of Q_r covering a wider range of values. The Spearman rank correlation of the patient numbering and the reversibility measure Q_r for $\tau =$ 15 ms was 0.95, demonstrating a close match between the classifications of AF based on the reversibility test and high–density mapping. The classification based on time reversibility is also consistent with a previously reported classification based on the (coarse–grained) correlation dimension and entropy [18].

For the chosen parameter values the average value of S_r was about 0 to 5 for type III, 5 to 10 for type II, and 10 to 13 for type I of AF. Thus, the highest degree of irreversibility was found in AF electrograms recorded from type I activation patterns, while time reversible electrograms were characteristic for type III of AF. These results point out that the null hypothesis of a static transformation of a linear Gaussian random process can be rejected for electrograms of type I of AF. This is consistent with the results of a test for linearity based on the method of surrogate data reported in [18], where the null hypothesis of a static (monotonous) tranformation of a linear Gaussian random process was rejected in AF electrograms of type I.

Testing for Differences between Reconstruction Densities during Pharmacological Conversion of Sustained Atrial Fibrillation in Goats

Data were collected from pharmacological experiments in instrumented conscious goats in which sustained AF (duration $>$ 24 hours) had been induced by continuous maintenance of AF via a programmable artificial pacemaker [19], which reinitiated AF whenever fibrillation had ceased and sinus rhythm was detected.

In this study we analyzed local unipolar epicardial electrograms of one minute duration recorded from the left and right atrial free wall. Since the electrograms were also used in a previous nonlinear analysis in which we investigated the anti–fibrillatory effects of the class IC agent cibenzoline on the dynamics of sustained AF in the same population of goats, we refer to [20] for details on the data acquisition and selection. Electrograms were measured during sustained AF (control) and when the AF interval had been prolonged to about 25%, 50% and 85% with respect to control. These episodes are referred to as CIB25, CIB50 and CIB85 hereafter. Ventricular far–field deflections were removed from the atrial unipolar electrograms by a coherent averaging procedure prior to the analysis. We also removed the mean value of the electrograms and normalized the two time series to a standard deviation of one.

Using the test to detect differences between reconstruction densities applied to the first and the second half of the measured electrograms, we checked that they were stationary.

In a previous nonlinear analysis of local fibrillation electrograms we suggested that cibenzoline does not significantly alter the dynamics of sustained AF other than a slowing down of the atrial activation due to a decreasing conduction velocity caused by the drug [20]. Here we further investigate this hypothesis by testing for differences between the reconstruction density during sustained AF and the reconstruction density during pharmacological conversion with cibenzoline.

Fig. 3 shows the results for the test statistic S_c estimated for the left and right atrial electrograms recorded from an instrumented goat during the pharmacological conversion of AF with

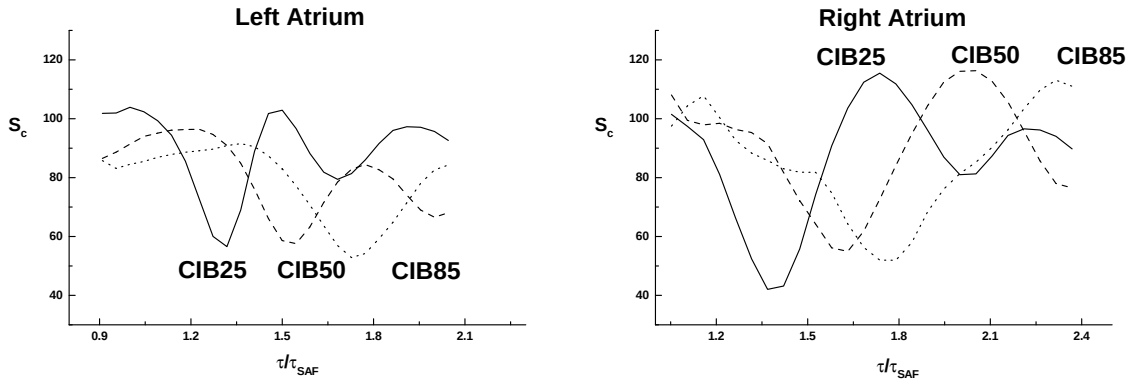

Figure 3: Test statistic S_c estimated for the left and right atrium of an instrumented goat during the pharmacological conversion of sustained atrial fibrillation (SAF). The delay vector distribution of fibrillation during increasing dose of cibenzoline was compared with the delay vector distribution of fibrillation during control. Electrograms during infusion of cibenzoline were measured when the fibrillation interval had been prolonged to about 25% (CIB25), 50% (CIB50) and 85% (CIB85) with respect to control. The delay τ was changed for the fibrillation electrograms recorded during infusion of cibenzoline, while the delay τ_{SAF} during control was fixed at 44 ms for the left atrial electrogram and at 38 ms for the right atrial electrogram. The results are shown as a function of the ratio τ/τ_{SAF}. Solid line, CIB25 vs. control; Dotted line, CIB50 vs. control; Double dotted line, CIB85 vs. control.

cibenzoline. The results are shown as a function of the ratio τ/τ_{SAF}, where the time delay τ_{SAF} of the electrograms of sustained atrial fibrillation (SAF) is fixed and the time delay τ of the electrograms during infusion of cibenzoline is changed within a chosen time interval. The parameters of the test were chosen as follows. The delay τ_{SAF} was set equal to the first minimum of the mutual information function, embedding dimension $m = 5$, bandwidth $d = 0.5\sigma$ where σ is the (overall) standard deviation of the two time series rescaled to $1/(2\sqrt{3})$ [4], and the segment length $\ell = 300$ ms. Prior to the analysis the time series were downsampled to $N = 15000$ (sample time interval 2 ms).

In Fig. 3 the statistic S_c shows oscillations, which reflect the presence of a characteristic frequency in the electrograms of atrial fibrillation. Also, the first minimum of S_c shifts to the right with increasing dose of cibenzoline, which illustrates the prolongation of the fibrillation interval with respect to control.

In case the changes in the dynamics induced by cibenzoline can be completely accounted for by the decrease in conduction velocity, the two reconstruction densities should be the same at $\tau_{\mathrm{min}}/\tau_{\mathrm{SAF}} = T/T_{\mathrm{SAF}}$, where T is the fibrillation interval during cibenzoline, T_{SAF} is the fibrillation interval during sustained AF and τ_{min} is the delay of the electrograms during cibenzoline corresponding to the minimum of the test statistic S_c. For the electrograms analyzed this equation holds true. However, the observed value S_c at τ_{min} remained much larger than three, indicating that the distributions are still highly different. Therefore, we can conclude that the dynamics changed in a more complex way than can be accounted for by a mere change in conduction velocity.

	Right Atrium			
Coupling	SAF	CIB25	CIB50	CIB85
I (%)	10	0	0	0
U (%)	40	30	30	30
B (%)	50	70	70	70

Table 1: Types of coupling between electrode pairs on the right atrium during sustained atrial fibrillation (SAF) and during infusion of cibenzoline when the fibrillation interval had been prolonged to about 25% (CIB25), 50% (CIB50) and 85% (CIB85) with respect to control (SAF). I, independent electrode pair (no coupling); U, unidirectionally coupled electrode pair; B, bidirectionally coupled electrode pair. Results are expressed as a percentage of the total number of electrode pairs.

	Left Atrium			
Coupling	SAF	CIB25	CIB50	CIB85
I (%)	0	0	0	0
U (%)	30	0	10	0
B (%)	70	100	90	100

Table 2: Types of coupling between electrode pairs on the left atrium during sustained atrial fibrillation (SAF) and during infusion of cibenzoline when the fibrillation interval had been prolonged to about 25% (CIB25), 50% (CIB50) and 85% (CIB85) with respect to control (SAF). I, independent electrode pair (no coupling); U, unidirectionally coupled electrode pair; B, bidirectionally coupled electrode pair. Results are expressed as a percentage of the total number of electrode pairs.

	Left and Right Atrium			
Coupling	SAF	CIB25	CIB50	CIB85
I (%)	52	32	48	0
U (R to L) (%)	32	24	20	24
U (L to R) (%)	12	12	8	0
B (%)	4	32	24	76

Table 3: Types of coupling between electrode pairs on the left (L) and right (R) atrium during sustained atrial fibrillation (SAF) and during infusion of cibenzoline when the fibrillation interval had been prolonged to about 25% (CIB25), 50% (CIB50) and 85% (CIB85) with respect to control (SAF). I, independent electrode pair (no coupling); U, unidirectionally coupled electrode pair; B, bidirectionally coupled electrode pair. Results are expressed as a percentage of the total number of electrode pairs.

Testing for general Granger Causality during Pharmacological Conversion of Sustained Atrial Fibrillation in Goats

We analyzed five unipolar epicardial electrograms selected from both the left and right atrial wall (interelectrode distance about 10–15 mm, sample time interval 20 ms, $N = 3000$). The parameters in the Hiemstra–Jones test were chosen as follows: $k = l = 2$, delay $\tau = 1$ (see Eq. 18) and the scale parameter $\epsilon = 1.0$, after rescaling each time series to a standard deviation of one. The results of the test are expressed in terms of p–values. We rejected the null hypothesis of no coupling (no Granger causality) between pairs of electrodes if the p–value was smaller than 0.05.

We distinguished three types of electrode pairs: I–pairs (independence) if we found no coupling between the two electrodes, U–pairs if the electrode pairs were coupled unidirectionally and B–pairs if the coupling was bidirectional. We calculated the percentage of all the I–pairs, U–pairs and B–pairs located on the right atrium, on the left atrium and on the left and right atrium, respectively. The results are summarized in Tables 1 to 3. A striking feature that emerges from our analysis is that bidirectional coupling between pairs of electrodes during atrial fibrillation increased on the right atrium, the left atrium as well as between both atria with increasing dose of cibenzoline.

We do not claim that our choice of the parameters of the Granger causality test is optimal in any sense. However, the choices made led to a procedure to characterize changes in the spatio–temporal atrial activation pattern during the pharmacological conversion of AF and the types of coupling defined here may be useful to study the dynamics of atrial fibrillation.

We emphasize that the concept of Granger causality is based on improved predictability when forecasting one time series with the use of a second one, and although it indicates a type of coupling, it is not straightforward to interpret the results of the test applied to electrograms of AF in physiological terms.

Concluding Remarks

The results of the test for reversibility show that it is possible to classify local electrograms of atrial fibrillation. This requires a procedure to choose the reconstruction parameters, as well as a choice of boundary values for the estimated nonlinear quantities to separate different types of atrial fibrillation. Application of the reversibility test to local electrograms of paroxysmal atrial fibrillation in patients illustrates the feasibility of this approach and demonstrates that, in principle, nonlinear time series methods based on the reconstruction density can be applied for routine classification of fibrillation electrograms.

The test for reversibility was optimized for discriminating different types of atrial fibrillation. Comparing the results obtained from the reversibility test applied to local electrograms with the characterization of atrial fibrillation based on the degree of complexity of activation maps as visualized from high–density mappping, it was found that the classification of atrial fibrillation by these two methods closely matched, although completely different criteria were used.

The test to detect differences between reconstruction densities turned out to be a sensitive

method to study the dynamics of atrial fibrillation during pharmacological intervention. It indicated clearly that the dynamics of atrial fibrillation changed in a more complex way than was apparent in our previous study on the effects of cibenzoline [20], in which it was concluded that the dynamics remained equivalent in spite of a decrease in conduction velocity induced by the drug.

To the best of our knowledge the concept of Granger causality has not been applied in the field of cardiology. The preliminary results presented here show that this concept is useful to characterize the space–time pattern of the electrical heart activity and merits further investigation.

It remains a challenge to interpret the results of a nonlinear time series analysis based on the reconstruction density in terms of physiological mechanisms. This may be accomplished by combining nonlinear complexity measures and electrophysiological parameters and may lead to a better understanding of the mechanisms of atrial fibrillation.

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