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EDITORIAL

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The status of nonlinear dynamics in the analysis of heart rate variability

About the time when heart rate variability (HRV) was being increasingly discussed as a tool for risk stratification after myocardial infarction (6a, 13, 19), chaos theory was being propagated in popular science publications. Striking about most of the latter works was that, although heart rate regulation was the focus of nonlinear dynamics (NLD) and was seen as a particularly lucid example of chaos in physiology (see for example Gleick (8)), there were very few scientific papers on which such claims could be based. Notable exceptions were, for example, the work of Kobayashi and Musha (14), Babloyantz and Destexhe (1), and Goldberger and West (9). In the following years increasing efforts were made to determine the chaotic nature of cardiac activity by applying analysis methods from nonlinear systems theory. For instance, on the presumption of an underlying chaotic attractor, scaling properties of the generating dynamics were estimated on the basis of dimensional analysis (4, 12, 20, 28). It was however soon realized that there are fundamental difficulties involved which include the noisy nature of biological signals, the restricted length of the data available and the problems with non-stationarity. This has led to a shift of the notation from chaos to complexity, irregularity, or randomness and has resulted in the development of measures and analysis techniques which are deemed more appropriate and more practical in application with respect to HRV. Examples of the former include the approximate entropy (22), the renormalized entropy (15), binary entropies (5) and the recently introduced 'information domain' strategies of Porta (25). These all do not assume chaotic dynamics but are based on information theoretical approaches to the high-dimensional dynamics in living organisms. Others focus on fractal-like scaling properties, 1/f spectral characteristics, self-similarity, or heart rate turbulence, which also extend the field of classical NLD analysis.

Pioneering and also very important to mention are the approaches developed to detect synchronization or coordination in multivariate physiological data, particularly between heart rate, beat-to-beat blood pressure, and respiratory signals (e.g. see articles in IEEE Eng Med Biol Mag (1998) volume 17 and refs. 2, 18, 23, 24). The renascence of cardiorespiratory coordination analysis (7), for example, seems to provide a clue to physiologically important synergetic phenomena which play a main part in guaranteeing both stability and flexibility in physiological control processes (11). As the development of these techniques is still in progress and they have rarely been used in clinical practice (e.g. 21), synchronization analysis is not addressed in this issue, but clinicians should remember to keep an eye on further developments in this important field.

Furthermore, in the context of looking for deterministic chaos in heart rate dynamics, the generation of surrogate data is recommended and has already been successfully applied in many studies. Hypothesis testing on the basis of surrogate data helps to identify nonlinear components in the system under examination (27, 29), and to judge whether group differences, indicated by NLD measures, are truly due to nonlinear processes or not.

In spite of this historical development and a general interest in, if not fascination for, these new ideas and techniques (see for example, (6)), their application in cardiology, by the mid-1990s, was reported only intermittently. This is reflected in the fact that standard publications on HRV included very limited treat-

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ment of nonlinear analytic methods and their possible role (3, 18). Indeed, in a review on HRV in this journal from 1994 (Herzschr Elektrophys (1994) vol. 5, suppl. 2), only cursory mention of dynamical models and their application is made. Since then, however, further theoretical work has been done and there has been an increase in studies demonstrating that nonlinear measures may reveal clinically relevant aspects of heart period or heart rate dynamics which are not apparent in the analysis of the time and frequency domain (e.g. 16, 17, 26). The purpose of this special issue is to show that the analytic methods based on NLD have developed to the point where they can make valuable contributions not only to the understanding of cardiac rhythms but also that they may aid in the identification of patients with various pathologies and who may be at risk for arrhythmia.

The contribution of Mäkikallio and co-workers serves to give an overview of the various nonlinear measures which are available for the estimation of the risk for cardiac arrhythmias. These include those that attempt to estimate the degree of complexity such as correlation dimension and Lyapunov exponents, the information content such as Kolmogorov entropy, or the fractal properties reflecting temporal scaling invariance on the basis of detrended fluctuation analysis and power slope laws. The rationale for such measures was well as advantages and limitations are discussed. The experience to date has shown that measures involving fractal properties perform well in predicting mortality in patients groups such as those with recent myocardial infarction, heart transplant, chronic heart failure and the elderly. Futhermore patients with ventricular tachyarrhythmias could be identified on the basis of dimensions, fractal scaling exponents and scatter plot diagrams. These measures often showed changes prior to the onset of ventricular fibrillation. Similarly, the authors report on work which demonstrates that both approximate entropy and fractal scaling exponents can serve as predictors for atrial fibrillation. They conclude that, although nonlinear methods demonstrate potential in risk stratification which complements linear analysis, broad clinical trials are necessary which link such measures with the outcome of intervention.

One measure that has found probalby the widest range of application in biological and medical settings is the approximate entropy (ApEn), introduced by Pincus and reviewed in his article in this issue. Its development was motivated, on the one hand, by the problems involved in applying methods quantifying the temporal complexity which were originally made for more physical and truly chaotic dynamics, and not for biological processes which do not meet the conditions of nonlinear time series analysis (see above). On the other hand, such biological processes demonstrate subtle, irregular patterns which call for quantification. In his contribution, Pincus describes the concepts on which ApEn is based and presents its definition as a model-independent statistic which quantifies irregularity in time series data. Several examples of the application of ApEn to RR inverval series are given, including studies in ventricular fibrillation, sleeping – waking states, hypertension, aging as well as prenatal and early life monitoring. Its use in a broad variety of settings is discussed and placed in the wider context to systems theory. Pincus also presents cross-ApEn, a measure which is well suited to quantify cross-correlation and synchrony between biological systems in general and between physiological signals in particular. Furthermore the relationship of ApEn to other measures is discussed. Some of its practical advantages include insensitivity to noise and outliers and the use in short time series.

In their contribution, Meesmann and colleagues focus on two nonlinear tools used in HRV analysis. First, 1/f fluctuations are presented which address the scaling properties of RR interval time series and likely reflect interactions of neuro-humoral control loops. This has been investigated in patients after myocardial infarction and heart transplants as well as in mortality of the elderly. Second, the application of scatter plots both in continuous ECG and in RR interval time series are discussed. These may allow automatic differentiation between supraventricular and ventricular rhythms as well as other forms of arrhythmia. Furthermore, apart from a critical discussion of the use of dimensional analysis, the application of perturbation analysis in patients with congestive heart failure or at risk for premature ventricular contractions is touched upon.

A variety of approaches which quantify the dynamics of short time series are presented by Wessel and co-workers. These include symbolic dynamics, renormalized entropy, finite time growth rates, the dual sequence method and, lastly, nonlinear regression and optimal transformations. After a formal introduction to the methods, studies demonstrating their application and assessing their merit are reported. In these studies, the following topics were investigated: risk stratification in patients after myocardial infarction, identification of patients with documented life threatening ventricular arrhythmias, early signs of sustained ventricular tachycardia or ventricular fibrillation, identification of patients with dilated cardiomyopathy and coupling between heart rate and blood pressure. With respect to prevention, the potential of finite time growth rates in the forecasting of ventricular tachycardia or ventricular fibrillation is of particular clinical interest.

Apart from these overviews, this issue also contains two papers presenting original work which demonstrate the application of novel approaches from the field of NLD. Porta and colleagues apply a newly developed nonlinear measure, corrected conditional entropy, to investigate the effect of sympathetic activation and regular periodical input (controlled breathing) on heart period complexity in healthy subjects. Comparing the results to standard frequency domain parameters leads to the conclusion that changes in complexity or information domain are not identical with changes in the frequency domain and that controlled breathing alone does not reduce complexity but is dependent on respiratory frequency, implying the involvement of different regulatory mechanisms. The importance of this work lies, among other things, in the comparison of standard measures of HRV and a nonlinear measure under well-defined conditions investigating known physiological mechanisms. This is a necessary prerequisite for assessment of nonlinear tools and needs to be done more comprehensively.

Finally, Cysarz et al. examine prenatal HRV, calculating the regularity of fetal RR interval time series on the basis of ApEn and estimating the nonlinear component using an improved surrogate data technique. In order to study the purely dynamical aspect of the series, binary sequences of the original series were constructed (2) and examined using a modified ApEn algorithm (5). It could be shown that the increase in fetal heart rate irregularity in the course of pregnancy is in part due to nonlinear temporal structures. Analysis of the binary sequences confirms the presence of a nonlinear component while demonstrating the loss of dependency on gestational age.

The articles in the present issue of *Herzschrittmacher & Elektrophysiologie* demonstrate impressively the power and the huge variety of HRV methods derived from NLD and related disciplines. Moreover, the reader will appreciate that there is no unique point of view which provides an overview of all existing methods to the normal user and accordingly, this special issue does not claim to be comprehensive. Nevertheless, differences between the methods are sometimes subtle, and the reader may rightly ask if they are crucial. Unfortunately, coherence in heart rate complexity research is poor, and guidelines for the use of complexity measures in diagnostics and prognostics of diseases related to regulatory dysfunction are still lacking. Thus it is not surprising that nonlinear methods are far from being applied in everyday clinical practice. What can be done in the future? In our opinion the community of researchers working in the field of nonlinear HRV analysis must come closer together. Data from clinical studies and/or data analysis computer programs should be exchanged such that data can be merged and analyzed in different laboratories with competing methods. This competition will not produce winners or losers but will hopefully result in clearing up the immense diversity of available nonlinear techniques. First important steps in this direction have been taken (10). This coordination of research, together with an increase in clinical data, will help to answer the most relevant question: Which method is appropriate when? To answer this question we need a task force to focus our efforts on effective application of the powerful tools offered by NLD for the analysis of HRV.

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