

Introduction: Cardiovascular physics

Niels Wessel and Jürgen Kurths

Department of Physics, University of Potsdam, Am Neuen Palais 10, Potsdam, 14415, Germany

William Ditto

J. Crayton Pruitt Family Department of Biomedical Engineering, University of Florida, Gainesville, Florida 32611-6131

Robert Bauernschmitt

Department of Cardiovascular Surgery, German Heart Center Munich, Lazarettstr. 36, Munich, 80636, Germany

(Received 26 February 2007; accepted 1 March 2007; published online 30 March 2007)

The number of patients suffering from cardiovascular diseases increases unproportionally high with the increase of the human population and aging, leading to very high expenses in the public health system. Therefore, the challenge of cardiovascular physics is to develop high-sophisticated methods which are able to, on the one hand, supplement and replace expensive medical devices and, on the other hand, improve the medical diagnostics with decreasing the patient's risk. Cardiovascular physics—which interconnects medicine, physics, biology, engineering, and mathematics—is based on interdisciplinary collaboration of specialists from the above scientific fields and attempts to gain deeper insights into pathophysiology and treatment options. This paper summarizes advances in cardiovascular physics with emphasis on a workshop held in Bad Honnef, Germany, in May 2005. The meeting attracted an interdisciplinary audience and led to a number of papers covering the main research fields of cardiovascular physics, including data analysis, modeling, and medical application. The variety of problems addressed by this issue underlines the complexity of the cardiovascular system. It could be demonstrated in this Focus Issue, that data analyses and modeling methods from cardiovascular physics have the ability to lead to significant improvements in different medical fields. Consequently, this Focus Issue of *Chaos* is a status report that may invite all interested readers to join the community and find competent discussion and cooperation partners. © 2007 American Institute of Physics. [DOI: [10.1063/1.2718395](https://doi.org/10.1063/1.2718395)]

Allegorically, the human heart may be compared with the engine of a car, enabling movement and functionality, both due to an inherent oscillator. However, in contrast to the completely regular action of a perfectly working car engine, the healthy heart's performance is irregular. The intervals between heartbeats widely fluctuate and the diagnostic value of cardiovascular dynamics and its complex variability via data analysis and modeling techniques are an important challenge for physicians, as well as for mathematicians, biologists, and physicists. Therefore, we consider that the time has come to define and establish a new field of interdisciplinary cardiovascular research: *cardiovascular physics*. It is based on the works of specialists mentioned above and attempts to gain deeper insight into pathophysiology and treatment options through a collaborative approach.

Spontaneous fluctuations of cardiovascular signals such as heart rate and blood pressure had already been described more than 100 years ago.^{1,2} However, the physiological interpretation of these variabilities is still an interesting and exciting research area. The fluctuations of heart rate and blood pressure represent not only oscillations around a fixed value; they are the expression of several influences such as respiration and different self-regulating rhythms. The analysis of heart rate variability (HRV) has become a powerful tool for the assessment of autonomic control. HRV measure-

ments have proven to be independent predictors of sudden cardiac death after acute myocardial infarction, chronic heart failure, or dilated cardiomyopathy.³⁻⁵ Moreover, it has been shown that short-term HRV analysis already yields a prognostic value in risk stratification independent of that of clinical and functional variables.⁶ However, the underlying regulatory mechanisms are still poorly understood.

Standard methods of HRV analysis include time and frequency domain parameters,⁴ often being referred to as linear methods. Time domain parameters are based on classic statistical methods derived from the beat-to-beat intervals as well as the differences between them. Mean heart rate is the simplest parameter, but the standard deviation over the whole time series (sdNN) is the most prominent HRV measure for estimating overall HRV. Frequency domain HRV parameters enable a distinct division into spectrum components of the heart rate dynamics.⁷ There are mainly two different techniques for spectral analysis: methods based on fast Fourier transform (FFT) and parametric autoregressive model estimations of wavelet approaches. The results using different spectral methods, however, should be comparable (apart from differences in time and frequency resolution).

Heart rate and blood pressure variability reflect the complex interactions of many different control loops of the cardiovascular system. In relation to the complexity of the sinus

node activity modulation system, a predominantly nonlinear behavior has to be assumed. Thus, the detailed description and classification of dynamical changes using time and frequency measures is often not sufficient, especially in dynamical diseases as characterized by Mackey and Glass.^{8,9} Thus, the matching of the mathematical fields of nonlinear dynamics and medicine has to be achieved.¹⁰

Nonlinear dynamical systems often show complicated temporal, spatial, and spatiotemporal behavior. Theory of nonlinear dynamics provides fundamental mathematical concepts, such as phase space, attractors, stability, and bifurcation analysis to characterize these complex systems. Specifically, these methods enable us to categorize and understand complex behavior of the cardiovascular system. In this Focus Issue on “*Cardiovascular Physics*” the current state-of-the-art recent developments and trends in this field are introduced. The contributions are separated into data analysis, cardiac modeling, and applications, whereas this distinction in the majority of papers is overlapping. Most data analysis techniques should not stand alone without clinical applications, whereas the modeling approaches should be used for physiological understanding. Moreover, these methods of cardiovascular physics will be recognized by physicians only after verification in large patient groups by providing a significant improvement in diagnosis and/or therapy. And even in case that one method provides evidence for significant diagnostic improvement, its introduction into clinical practice remains questionable if no physiological interpretation of the phenomenon can be given or if it was not compared to established tools of risk stratification. In fact, the increased computational power available for data analysis and cardiac modeling allows more sophisticated analyzing techniques and higher-resolution models. However, this additional information will only be clinically helpful if there is adequate progress in the understanding of physiological processes.

Obviously, the demand for methodological tools of cardiovascular physics that are clinically approved and robust seems to be unfulfilled. One reason could be that there is still missing a connection between cardiovascular variability and myocardial modeling. With this Focus Issue we want to, on the one hand, initiate new links of data analysis with modeling techniques to reach the aim of clinical applications. On the other hand, these methods could lead to the substitution of sometimes painful, invasive techniques by noninvasive methods that provide equivalent information. An already known application is computer-assisted, minimally invasive surgery, where computer models supplement additional information for the physicians. In the quest of performing less invasive surgical procedures, the lack of visual information has to be compensated by computer- and sensor-based models providing all the information necessary to ensure the same level of safety as compared to open procedures. Likewise, noninvasive diagnostic tools augmented by sophisticated methods of data analysis are able to substitute hazardous and cumbersome invasive procedures. The success of cardiovascular physics research finally is assessed by clinical applicability, respectively, by strong clinical implications. Thus, this Focus Issue is intended to assemble physicists, engineers, and physicians. Without a strong interdisciplinary

cooperation, no successful research in this field can be performed.

A workshop held in Bad Honnef, Germany, in May 2005, provided an overview of recent advances of cardiovascular physics to study dynamical diseases. The meeting attracted an interdisciplinary audience of physicians, mathematicians, biologists, engineers, and physicists. This joint effort will be reflected by the following papers covering the main research fields of cardiovascular physics, including data analysis, modeling, and medical application. Although we emphasize material covered at the workshop, we also include other work in order to provide a more balanced overview of the field.

DATA ANALYSIS

During the past decades it was shown that tools from linear system theory can provide valuable information. More recently, tools from nonlinear dynamics improved the diagnostic value beyond that achieved by using solely linear parameters.^{11–15}

An interesting interdisciplinary data analysis approach is introduced in this Focus Issue by Kantelhardt *et al.*¹⁶ with the phase rectified signal averaging technique. They provide a methodology for reliable characterization of beat-to-beat intervals without the need for preprocessing and applied it to a huge medical database. The introduced acceleration and deceleration capacity could also be useful for other medical studies. The physiological mechanisms underlying and the clinical applicability yet has to be defined. Cantini *et al.*¹⁷ present a contribution on the cardiac resynchronization therapy in patients receiving a pacemaker for biventricular stimulation. They performed a study on a small group of pacemaker patients: electrocardiographic signal was recorded during the activity of the pacemaker programmed at different atria-ventricular delays and under spontaneous cardiac activity. The obtained signals suggested the hypothesis that besides the synchronization of ventricular contraction the pacemaker stimulus could also induce an unperceived (undetected) effect on the sinoatrial node, ascribable to a mechanism of phase resetting. Porta *et al.*¹⁸ provide an integrated approach for information-domain analysis based on entropy rate, local nonlinear prediction, and pattern classification based on symbolic analysis under the unifying framework provided by uniform quantization. Their approach provides a list of normalized and non-normalized indexes useful to quantify and typify complexity over very short data series. Applying this approach to 24 h Holter recordings, the authors could demonstrate that this approach is useful and reliable even under nonstandardized conditions. Voss *et al.*¹⁹ analyzed the suitability of the nonlinear method’s short-term symbolic dynamics, detrended fluctuation, and Poincaré plot analysis in comparison to heart rate and blood pressure variability analysis for a noninvasive risk stratification in dilated cardiomyopathy patients. They could show that the application of these nonlinear methods improves considerably the risk stratification in their patient group. Hoyer *et al.*²⁰ assessed the interplay between mechanisms acting on different time scales by autonomic information flow functions. The methods and results presented in this paper may improve the

physiological understanding of the complex cardiovascular system. Cerutti *et al.*²¹ considered six of the most widespread methods for the evaluation of the scaling parameter in long-memory processes and tested their performances on simulated time series as well as on physiological data. Almost all considered methods were successful in distinguishing among the real patient groups with almost equivalent performances. Peng *et al.*²² propose a generic approach to address the challenge of categorizing dynamical signals based on some fundamental assumptions of statistical physics and information theory. The key idea of the analysis is the connection between dynamical patterns of the output signal and the underlying dynamical microstates without *a priori* knowledge. Using their measure of dissimilarity, they can categorize different types of symbolic sequences by using standard clustering algorithms.

MODELING

Quantification of the spatiotemporal dynamics of propagating waves of a cardiac excitation is of fundamental importance to understanding electrophysiological phenomena. Such quantification is accomplished via a range of continually evolving techniques of cardiac-excitation modeling.^{23–29}

Trayanova *et al.*³⁰ offer an alternative approach to the study of arrhythmia generation and termination in the heart: realistic three-dimensional multiscale modeling of electrical activity in the heart. They could demonstrate that such modeling is a powerful tool in uncovering new electrophysiological insights with strong clinical implications that could be used to further the development of new antiarrhythmic therapies. Alonso *et al.*³¹ show that negative filament tension occurs in one of the most widely used ionic models of cardiac tissue, the Luo-Rudy phase 1 model, and determine the region of parameters for this instability. In clinical practice this approach could be useful for cardiac arrhythmias in conditions of low excitability. Zebrowski *et al.*³² investigate a nonlinear oscillator model which is able to reproduce certain phenomena that occur in clinically measured human heart rate: irregular heart rate, asystole, sinus arrest, vagal paradox, certain kinds of heart block, and others. The extension of the model into more than one dimension will be an interesting research area with strong clinical implications. Benson *et al.*³³ analyze models of ectopic ventricular beats, which are triggered by abnormal excitation initiated within the ventricular muscle and sometimes can lead to life threatening arrhythmias. The authors use reaction-diffusion excitable medium models, where the reaction terms describe cardiac cell electrophysiology, and the diffusion terms the electronic spread of potential in the myocardial tissue. Kanakov *et al.*³⁴ are modeling the dynamics of spatiotemporal patterns of excitation in inhomogeneous cultures depending on coupling strength. The authors interpret their results of modeling in terms of synchronization theory. This is an outstanding approach since several available experimental results, such as formation of target and spiral waves in cultures, are reproduced by this modeling. De la Casa *et al.*³⁵ show that it is possible to attenuate spiral waves by planar wave fronts with periods longer than the rotational period of the spiral, and address the problem of how to control spiral

attenuation in excitable media, which has strong clinical implications. Marsh *et al.*³⁶ have constructed a model of 22 interacting nephrons, including surface as well as deep nephrons. The model shows that, for physiologically reasonable parameter values, the deep nephrons do not synchronize with the superficial nephrons even though they are coupled via the same blood supply. This lack of synchronization introduces an asymmetry into the system that may be responsible for the development of chaotic dynamics in animal models of hypertension. Bauer *et al.*³⁷ report on simulations leading to alternans and secondary effects such as 1:2 conduction block in three-dimensional simulations for an anatomically realistic model of the rabbit ventricles. The authors prove the predictive power of bifurcation and stability analysis in the corresponding one-dimensional model equations as well as their ability to test simplified mathematical theories such as the restitution hypothesis. Cao *et al.*³⁸ review turbulence control in excitable systems, by using a local periodic pacing method, and give implications to realistic cardiac defibrillation.

The methods as described above already lead to a variety of applications in clinical medicine as demonstrated in the following papers. Van Leeuwen *et al.*³⁹ demonstrate that the implementation of symbolic dynamics and appropriate classification schemes on symbolic heartbeat sequences may lead to a better and more differentiated understanding of normal fetal physiological development, having strong implications in fetal arrhythmias. Malberg *et al.*⁴⁰ demonstrate that variability analysis in connection with Doppler examination of the uterine arteries is able to achieve a positive predictive value for preeclampsia of 70% already in the 18th–26th week of pregnancy. Their cardiovascular variability approach may offer a possibility of anticipating and treating hypertensive pregnancy disorders via early recognition. Schirdewan *et al.*⁴¹ investigated the capability of cardiac magnetic field mapping to detect patients suffering from hypertrophic cardiomyopathy. They introduced a combined diagnostic approach based on map topology quantification using Kullback-Leibler entropy and regional magnetic field strength parameters. The authors could show that this diagnostic algorithm allows not only detecting affected individuals, but also discriminates different forms of the disease. Penzel *et al.*⁴² provide a methodological review for the analysis of human autonomous nervous system during sleep based on heart rate and respiration. Cardiovascular consequences of disturbed sleep and sleep apnea are of particular high medical interest for sleep physicians because they present a risk factor for cardiovascular disorders such as hypertension, cardiac ischemia, sudden cardiac death, and stroke. The models, suggested by the authors, are useful to predict effects of aging in healthy subjects and effects of treatment in subjects with disordered breathing during sleep as well as in other sleep disorders.

The variety of problems addressed by this issue underlines the complexity of the cardiovascular system. It could be demonstrated in this Focus Issue, that data analyses and modeling methods from cardiovascular physics have the ability to lead to significant improvements in different medical fields. Consequently, this Focus Issue of *Chaos* is a status

report that may invite all interested readers to join the community and find competent discussion and cooperation partners. Patients as well as the whole society would benefit from a rapid use of cardiovascular physics potentials in clinical practice. The number of cardiovascular diseases increases unproportionally high with the increase of the human population and aging, leading to very high expenses in the public health system. Therefore, the challenge of cardiovascular physics is to develop high-sophisticated methods which are, on the one hand, able to supplement and replace expensive medical devices and, on the other hand, improve the medical diagnostics with a decreasing patient's risk.

ACKNOWLEDGMENTS

We thank the Wilhelm und Else Heraeus Foundation for their sponsorship of the Workshop "Cardiovascular Physics-Model Based Data Analysis of Heart Rhythm; 346. WE-Heraeus-Seminar" held in May 2005, in Bad Honnef, Germany, where this Focus Issue had its origin. J. K. and N. W. acknowledge financial support by the EU Network of Excellence, Grant No. NoE 005137 BioSim, as well as by the Deutsche Forschungsgemeinschaft Grants Nos. KU 837/23-1 and KU 837/20-1. R.B. acknowledges financial support by the Deutsche Forschungsgemeinschaft Grant No. BA 1581/4-1.

- ¹H. P. Koepchen and K. Thureau, "Untersuchungen über Zusammenhänge zwischen Blutdruckwellen und Ateminnervation," *Pflügers Arch.* **267**, 10–26 (1958).
- ²C. Ludwig, "Beiträge zur Kenntnis des Einflusses der Respirationsbewegungen auf den Blutumlauf im Aortensystem," *Arch. Anat. Physiol.* **13**, 242–302 (1847).
- ³R. E. Kleiger, J. P. Miller, J. T. Bigger, and A. J. Moss, "Decreased heart rate variability and its association with increased mortality after acute myocardial infarction," *Am. J. Cardiol.* **59**, 256–262 (1987).
- ⁴A. J. Camm, M. Malik, J. T. Bigger *et al.*, "Heart rate variability—Standards of measurement, physiological interpretation, and clinical use," *Circulation* **93**, 1043–1065 (1996).
- ⁵H. Tsuji, M. G. Larson, F. J. Venditti, E. S. Manders, J. C. Evans, C. L. Feldman, and D. Levy, "Impact on reduced heart rate variability on risk for cardiac events," *Circulation* **94**, 2850–2855 (1996).
- ⁶M. T. La Rovere, G. D. Pinna, R. Maestri, A. Mortara, S. Capomolla, O. Febo, R. Ferrari, M. Franchini, M. Gnemm, C. Opasich, P. G. Riccardi, E. Traversi, and F. Corbelli, "Short-term heart rate variability predicts sudden cardiac death in chronic heart failure patients," *Circulation* **107**, 565–570 (2003).
- ⁷S. Akselrod, D. Gordon, F. A. Ubel, D. C. Shannon, A. C. Barger, and R. C. Cohen, "Power spectrum analysis of heart rate fluctuation: A quantitative probe of beat-to-beat cardiovascular control," *Science* **213**, 220–222 (1981).
- ⁸M. C. Mackey and L. Glass, "Oscillation and chaos in physiological control systems," *Science* **197**, 287–289 (1977).
- ⁹L. Glass and M. C. Mackey, "Pathological conditions resulting from instabilities in physiological control systems," *Ann. N.Y. Acad. Sci.* **316**, 214–35 (1979).
- ¹⁰J. Belair, L. Glass, U. An Der Heiden, and J. Milton, "Dynamical disease-identification, temporal aspects and treatment strategies of human illness," *Chaos* **5**, 1–7 (1995).
- ¹¹Y. Yamamoto, R. L. Hughson, and Y. Nakamura, "Autonomic nervous system responses to exercise in relation to ventilatory threshold," *Chest* **101**, 206S–210S (1992).
- ¹²M. G. Signorini, S. Cerutti, S. Guzzetti, and R. Parola, "Non-linear dynamics of cardiovascular variability signals," *Methods Inf. Med.* **33**, 81–84 (1994).
- ¹³C. K. Peng, S. Havlin, H. E. Stanley, and A. L. Goldberger, "Quantification of scaling exponents and crossover phenomena in nonstationary heartbeat time series," *Chaos* **5**, 82–87 (1995).
- ¹⁴J. Kurths, A. Voss, P. Saparin, A. Witt, H. J. Kleiner, and N. Wessel, "Quantitative analysis of heart rate variability," *Chaos* **5**, 88–94 (1995).
- ¹⁵C. Schafer, M. G. Rosenblum, J. Kurths, and H. H. Abel, "Heartbeat synchronized with ventilation," *Nature (London)* **392**, 239–240 (1998).
- ¹⁶J. W. Kantelhardt, A. Bauer, A. Schumann, P. Barthel, R. Schneider, M. Malik, and G. Schmidt, "Phase-rectified signal averaging for the detection of quasi-periodicities and the prediction of cardiovascular risk," *Chaos* **17**, 015112 (2007).
- ¹⁷F. Cantini, M. Varanini, A. Macerata, M. Piacenti, M. A. Morales, and R. Balocchi, "Cardiac resynchronization therapy and phase resetting of the sinoatrial node: A conjecture," *Chaos* **17**, 015106 (2007).
- ¹⁸A. Porta, L. Faes, M. Masé, G. D'Addio, G. D. Pinna, R. Maestri, N. Montano, R. Furlan, S. Guzzetti, G. Nollo, and A. Malliani, "An integrated approach based on uniform quantization for the evaluation of complexity of short-term heart period variability: Application to 24 h Holter recordings in healthy and heart failure humans," *Chaos* **17**, 015117 (2007).
- ¹⁹A. Voss, R. Schröder, S. Trübner, M. Görnig, H. R. Figulla, and A. Schirdewan, "Comparison of non-linear methods symbolic dynamics, detrended fluctuation and Poincaré plot analysis in risk stratification in patients with dilated cardiomyopathy," *Chaos* **17**, 015120 (2007).
- ²⁰D. Hoyer, B. Frank, C. Götz, P. K. Stein, J. J. Zebrowski, R. Baranowski, M. Palacios, M. Vallverdú, P. Caminal, A. B. de Luna, and H. Schmidt, "Interactions between short-term and long-term cardiovascular control mechanisms," *Chaos* **17**, 015110 (2007).
- ²¹S. Cerutti, F. Esposti, M. Ferrario, R. Sassi, and M. G. Signorini, "Long-term invariant parameters obtained from 24-h Holter recordings: A comparison between different analysis techniques," *Chaos* **17**, 015108 (2007).
- ²²C. K. Peng, A. C. C. Yang, and A. L. Goldberger, "Statistical physics approach to categorize biologic signals: From heart rate dynamics to D. N. A. sequences," *Chaos* **17**, 015115 (2007).
- ²³B. van der Pol and J. van der Mark, "The heartbeat considered as a relaxation oscillation and an electrical model of the heart," *Philos. Mag.* **6**, 763 (1928).
- ²⁴A. Babloyantz and A. Destexhe, "Is the normal heart a periodic oscillator?," *Biol. Cybern.* **58**, 203–211 (1988).
- ²⁵A. V. Panfilov and P. L. Kerkhof, "Quantifying ventricular fibrillation: In silico research and clinical implications," *IEEE Trans. Biomed. Eng.* **51**, 195–196 (2004).
- ²⁶O. V. Aslanidi, A. Bailey, V. N. Biktashev, R. H. Clayton, and A. V. Holden, "Enhanced self-termination of re-entrant arrhythmias as a pharmacological strategy for antiarrhythmic action," *Chaos* **12**, 843–851 (2002).
- ²⁷A. M. Pertsov, J. M. Davidenko, R. Salomonsz, W. T. Baxter, and J. Jalife, "Spiral waves of excitation underlie reentrant activity in isolated cardiac muscle," *Circ. Res.* **72**, 631–650 (1993).
- ²⁸D. J. Christini and L. Glass, "Introduction: Mapping and control of complex cardiac arrhythmias," *Chaos* **12**, 732–739 (2002).
- ²⁹A. Garfinkel, M. L. Spano, W. L. Ditto, and J. N. Weiss, "Controlling cardiac chaos," *Science* **257**, 1230–1235 (1992).
- ³⁰H. Arevalo, B. Rodriguez, and N. Trayanova, "Arrhythmogenesis in the heart: Multiscale modeling of the effects of defibrillation shocks and the role of electrophysiological heterogeneity," *Chaos* **17**, 015103 (2007).
- ³¹S. Alonso and A. V. Panfilov, "Negative filament tension in the Luo-Rudy model of cardiac tissue," *Chaos* **17**, 015102 (2007).
- ³²J. J. Zebrowski, K. Grudziński, T. Buchner, P. Kuklik, J. Gac, G. Gielera, P. Sanders, and R. Baranowski, "Pulse rate modulation and pulse cessation, vagal paradox, intermittency and amplitude death in the conduction system of the heart—a nonlinear oscillator model," *Chaos* **17**, 015121 (2007).
- ³³A. P. Benson, G. Halley, P. Li, W. C. Tong, and A. V. Holden, "Virtual cell and tissue dynamics of ectopic activation of the ventricles," *Chaos* **17**, 015105 (2007).
- ³⁴O. I. Kanakov, G. V. Osipov, C. K. Chan, and J. Kurths, "Cluster synchronization and spatio-temporal dynamics in networks of oscillatory and excitable Luo-Rudy cells," *Chaos* **17**, 015111 (2007).
- ³⁵M. A. de la Casa, F. J. de la Rubia, and P. C. Ivanov, "Patterns of spiral wave attenuation by low-frequency periodic planar fronts," *Chaos* **17**, 015109 (2007).
- ³⁶D. J. Marsh, O. V. Sosnovtseva, E. Mosekilde, and N. H. Holstein-Rathlou, "Collective phenomena in a vascular-coupled nephron tree," *Chaos* **17**, 015114 (2007).
- ³⁷S. Bauer, G. Röder, and M. Bär, "Alternans and the influence of ionic channel modifications, Cardiac 3D simulations and 1D numerical bifurcation analysis," *Chaos* **17**, 015104 (2007).

- ³⁸Z. Cao, P. Li, H. Zhang, and G. Hu, "Turbulence control with local pacing and its implication in cardiac defibrillation," *Chaos* **17**, 015107 (2007).
- ³⁹P. van Leeuwen, D. Cysarz, S. Lange, D. Geue, and D. Groenemeyer, "Quantification of fetal heart rate regularity using symbolic dynamics," *Chaos* **17**, 015119 (2007).
- ⁴⁰H. Malberg, R. Bauernschmitt, A. Voss, T. Walther, R. Faber, H. Stepan, and N. Wessel, "Analysis of cardiovascular oscillations: New approach to the early prediction of pre-eclampsia," *Chaos* **17**, 015113 (2007).
- ⁴¹A. Schirdewan, A. Gapelyuk, R. Fischer, L. Koch, H. Schütt, U. Zacharzowsky, R. Dietz, L. Thierfelder, and N. Wessel, "Cardiac magnetic field map topology quantified by Kullback-Leibler entropy identifies patients with hypertrophic cardiomyopathy," *Chaos* **17**, 015118 (2007).
- ⁴²T. Penzel, N. Wessel, M. Riedl, J. W. Kantelhardt, S. Rostig, M. Glos, A. Suhrbier, H. Malberg, and I. Fietze, "Cardiovascular and respiratory dynamics during normal and pathological sleep," *Chaos* **17**, 015116 (2007).