Complex analysis of circulation

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Agenda: Complex analysis of circulation

- Basic Research
- Diagnostics of Heart Disease
- Application of Methods in Therapy
- Conclusion

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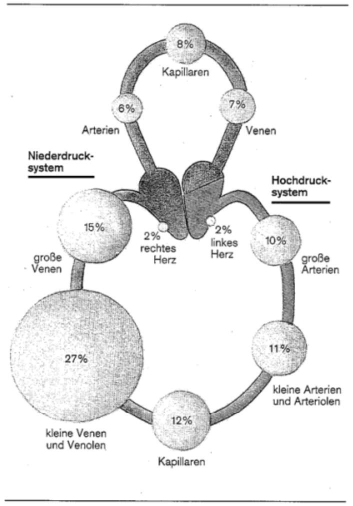
The Cardiovascular System: Complex Interaction

Patient and Implant: An Open Cybernetic System

- **Comorbidities**
- **Patient „Compliance“**
- **Mental Activity**
- **Etiology**
- **External Interaction**
- **Clinical Baseline Factors**
- **„Reverse Remodelling“**
- **Therapy Options**
- **Sensor Drift**
- **Spontaneous Fluctuations**



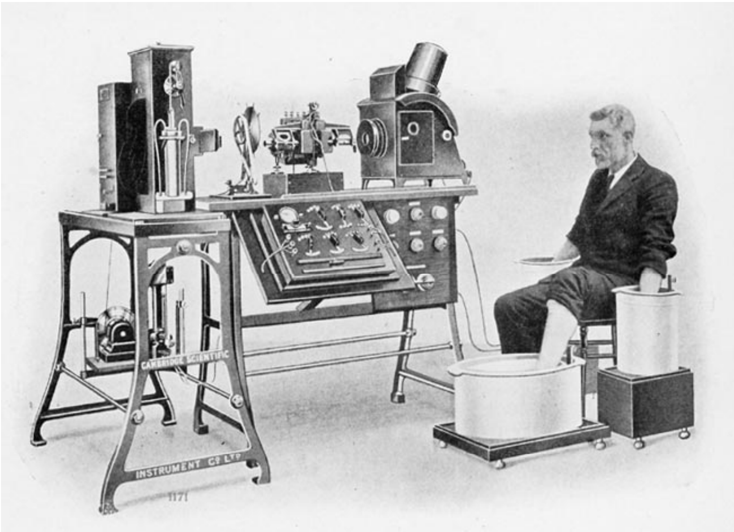
→ Complex Systems Theory, Pattern Recognition, **Time Series Analysis**

Overview of Methods and Disciplines

- Analysis of signal morphology (ECG, Impedance,…)
- Theory of excitable media (cellular interactions)
- (Spectral-)analysis of spontaneous fluctuations (HRV)
- Nonlinear dynamics and chaos theory
- Theory of stochastic systems
- Complex pattern recognition
- Several other approaches

Sensors and Diagnostics

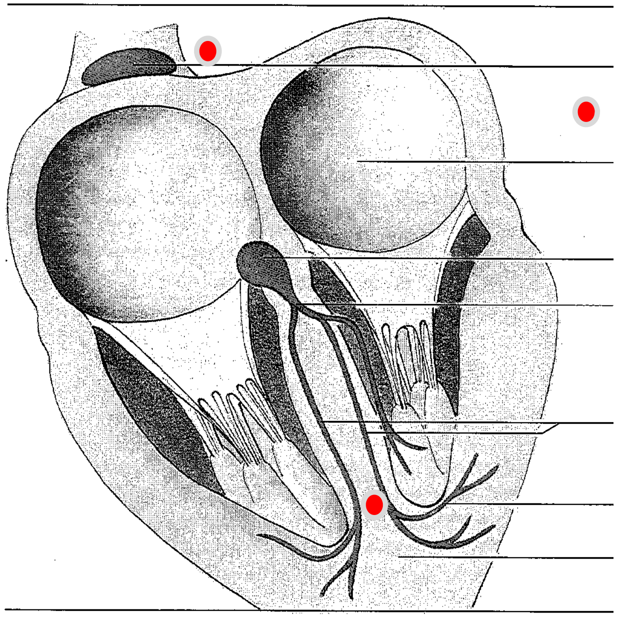
Surface-ECG



Photograph of a Complete Electrocardiograph, Showing the Manner in which the Electrodes are Attached to the Patient, In this Case the Hands and One Foot Being Immersed in Jars of Salt Solution

Wikipedia

Intracardiac electrogram (iEGM)



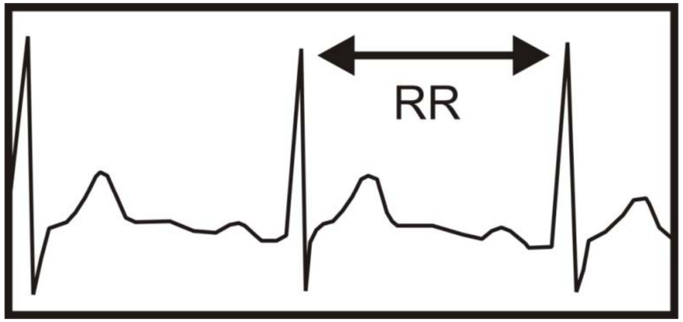
Klinke/Silbernagel (1994)

Other sensors: e. g. activity, impedance,…

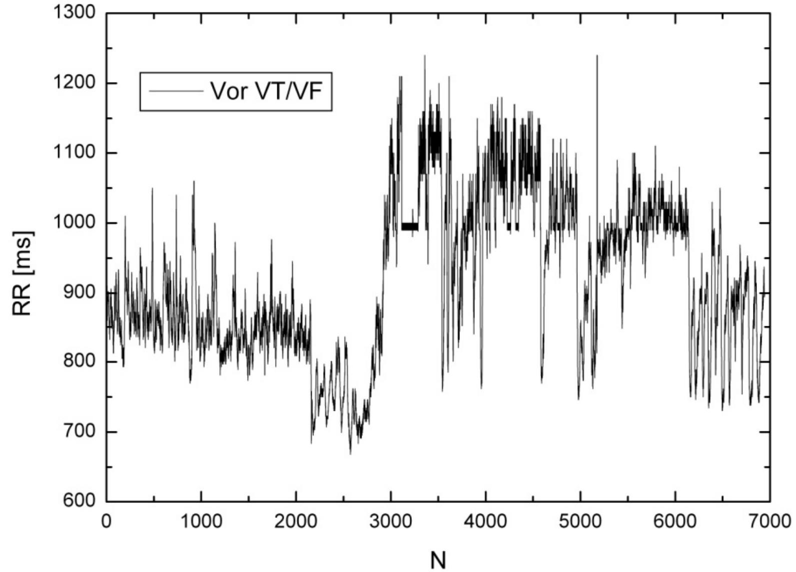
Fundamental Step: Construction of Interbeat Intervals

Extraction of Regulation Mechanisms by "RRI":

iEGM/ECG:



Time Series of RR Intervals



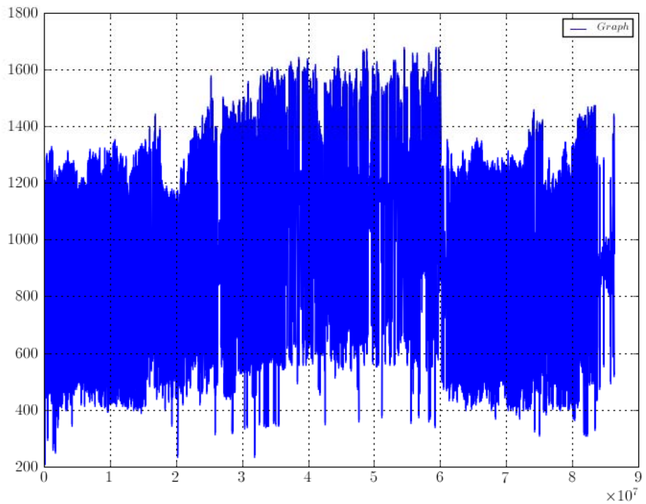
Spontaneous Fluctuations of Interbeat Intervals:

Provides Physiological Information

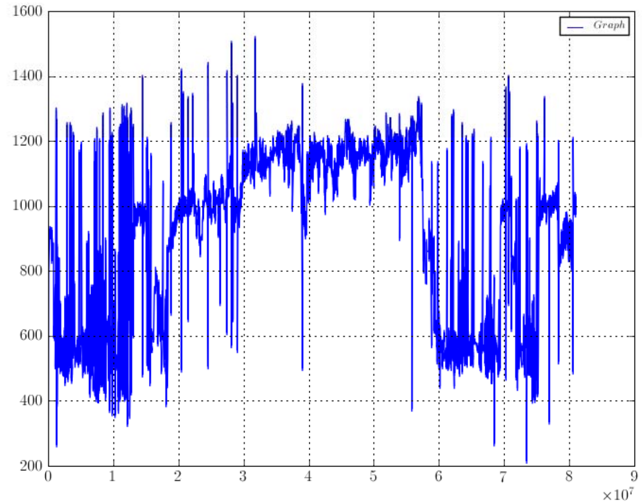
Importance of „Artifacts“ (Extrasystoles etc.)

Careful Extraction of Interbeat Interval :

Without Filtering



Postprocessed

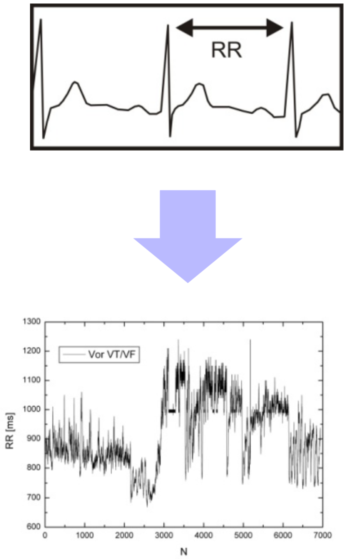


Rockstroh (2009)

- **Remarks:**
  - Contamination by active Implantat and complex arrhythmia
  - Postprocessing of automatic annotations unavoidable
  - Surface ECG is lacking atrial information

Spectral Analysis: Basics

Time Series of Interbeat Intervals (RR)



Spectral analysis of interbeat intervals

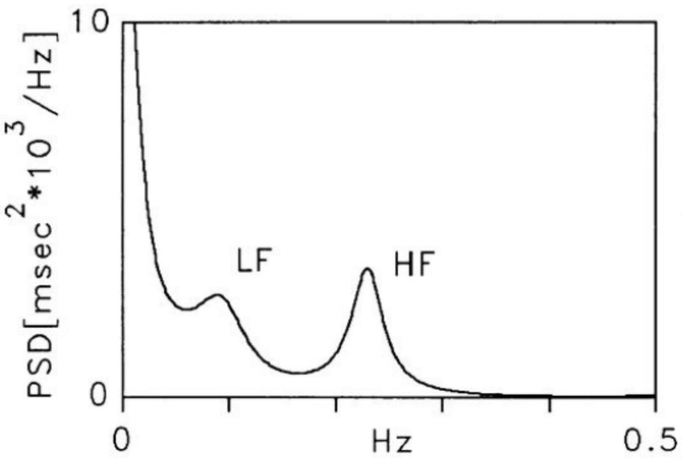


Abbildung:Leistungsspektrumsdichte

Akselrod (1985)

- **Characteristics:**
  - Applications: risk stratification, disease characterization
  - HF: breathing, LF: blood pressure, other processes (thermoregulation,…)
  - HF: fast vagal contribution, LF: sympathical contribution

Spectral Analysis: Methods

Overview

- **Spectral analysis**:
    - Fourier transformation
    - Lomb-Scargle Periodogram
    - Bayesian-Spectrum-Estimate
    - Wavelet-Transformation

- **Time-Frequency Analysis**:
    - Short-Fourier-Transformation
    - Wigner-Ville Transformation
    - Time-dependent autoregression
    - Continuous wavelet transformation

Example: FFT

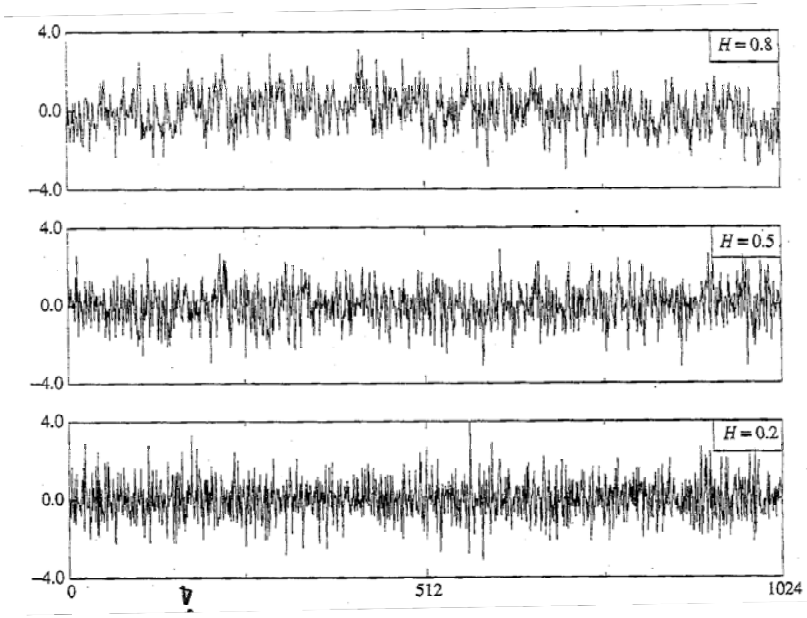
$$F(k) = \sum_{t=1}^{N}\left(\frac{x_t}{N}\cos\left(2\pi t\frac{k}{N}\right)\right) - i\sum_{t=1}^{N}\left(\frac{x_t}{N}\sin\left(2\pi t\frac{k}{N}\right)\right)$$

$$\begin{aligned}F(k) &= \sum_{j=0}^{N-1} \mathrm{e}^{2\pi ijk/N} f_j = \\ &= \sum_{j=0}^{N/2-1} \mathrm{e}^{2\pi ik(2j)/N} f_{2j} + \sum_{j=0}^{N/2-1} \mathrm{e}^{2\pi ik(2j+1)/N} f_{2j+1} = \\ &= \sum_{j=0}^{N/2-1} \mathrm{e}^{2\pi ikj/(N/2} f_{2j} + \sum_{j=0}^{N/2-1} \mathrm{e}^{2\pi ikj/(N/2)} f_{2j+1} = \\ &= F_k^g + W^k F_k^u \quad \text{mit} \quad W = \mathrm{e}^{2\pi i/N}\end{aligned}$$

- **Special Problems**:
    - Nonstationarity and artifacts
    - Additional information due to multiscalar time resolution
    - Preprocessing and free parameters (Hurst, multifractal spectrum)

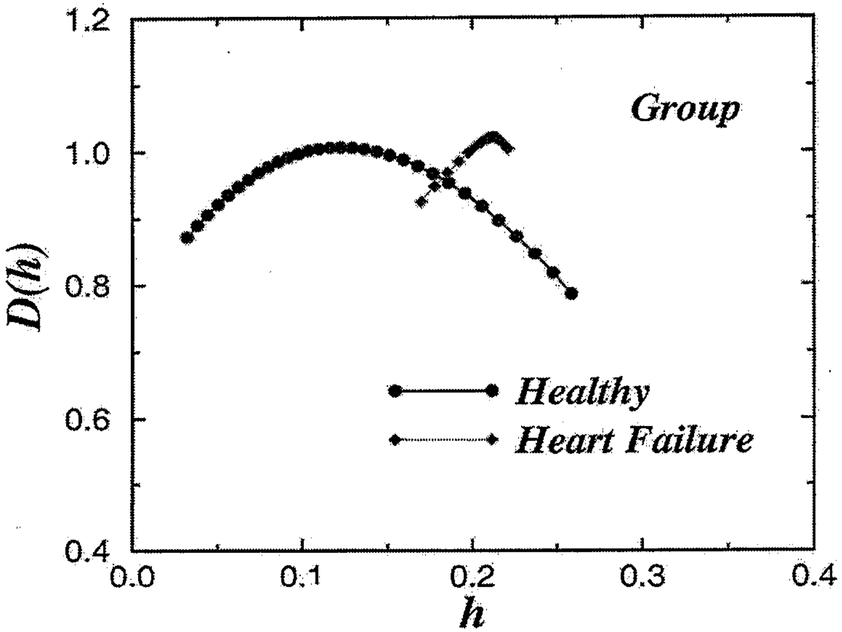
Fractal and Multifractal Analysis

Hurst's Scale Exponent



Bassingthwaighte (1995)

Multifractal Spectrum

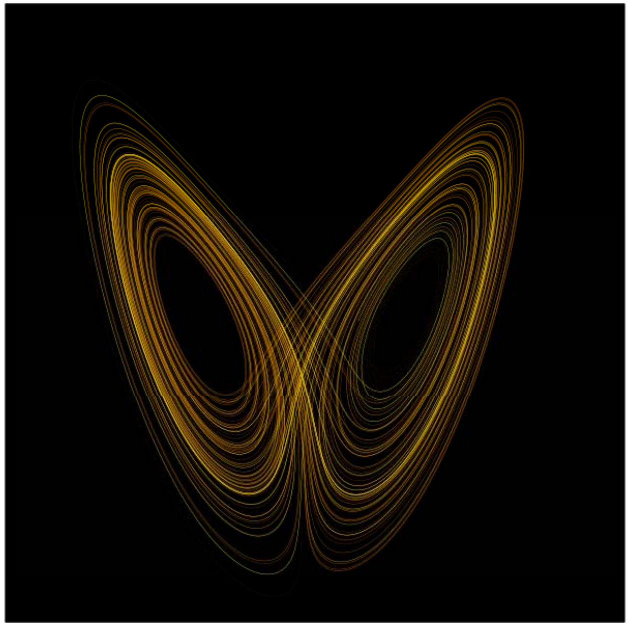


Stanley (1998)

- **Remarks:**
  - Variety of methods for determination
  - Artifacts, long measurement, specificity?

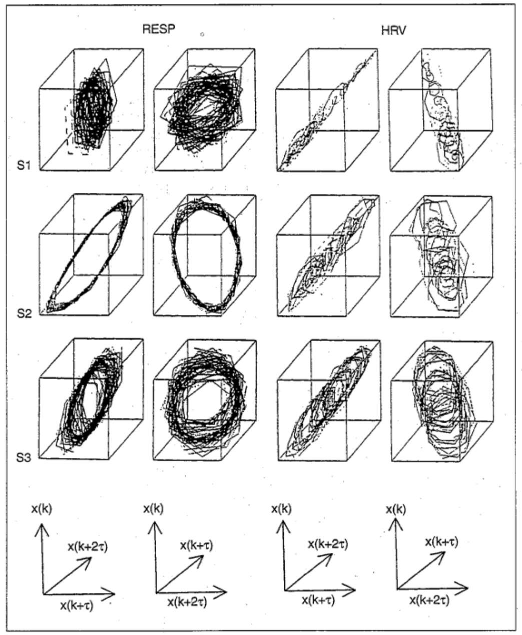
Chaos Theory: Nonlinear Analysis

Lorenz Attractor



Wikipedia

Phase Space Plots

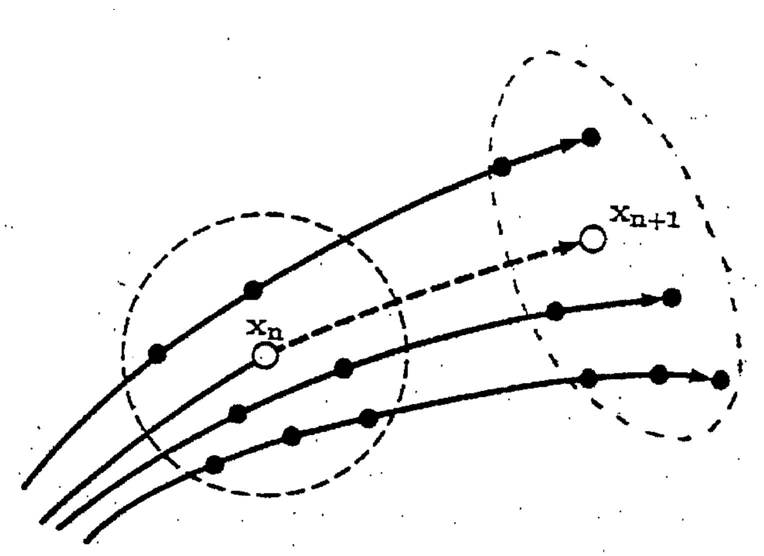


Hoyer 1997

- Approach: Nonlinear coupling of many degrees of freedom
- Consequence: System restricted to low dimensional subspace
- Problem: stochastic properties and nonstationarity

Nonlinear Dynamics: Exponential Divergence

Lyapunov Exponent



Kurths (1995)

Some Formulae

$$\lambda(x_0) = \lim_{N\to\infty} \frac{1}{N} \ln \left| \frac{df^N(x_0)}{dx} \right|$$

Kolmogorov-Entropie:

$$H_K = -\lim_{\tau\to 0}\lim_{\epsilon\to 0}\lim_{d\to\infty} \frac{1}{d\tau} \sum_{i_1,\ldots,i_d} p(i_1,\ldots,i_d) \ln p(i_1,\ldots,i_d)$$

Kolmogorov-Entropie (alternativ):

$$H_K = \lim_{\tau\to 0}\lim_{\epsilon\to 0}\lim_{d\to\infty} \left(H_{S,d+1} - H_{S,d}\right) \quad \text{mit}$$

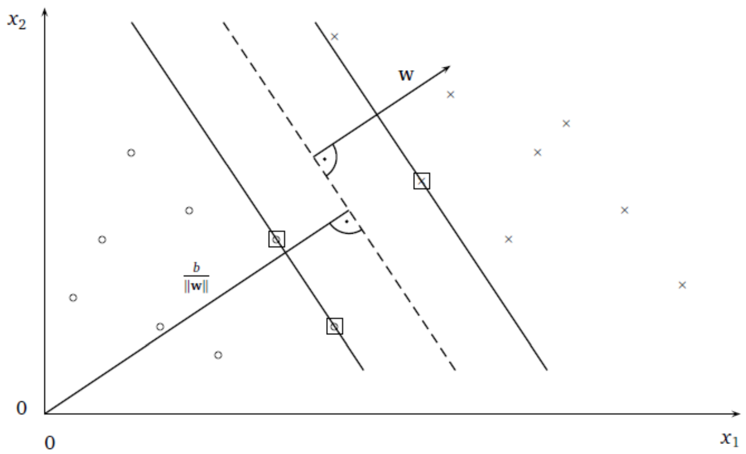
$$H_{S,d} = -\sum_{x_i \cdots x_d} p(x_1,\ldots,x_d) \log p(x_1,\ldots,x_d)$$

Problems:

- Parameters, nonstationarity, high-dimensionality, long-term measurement
- Application: short term prediction of tachyarrhythmia

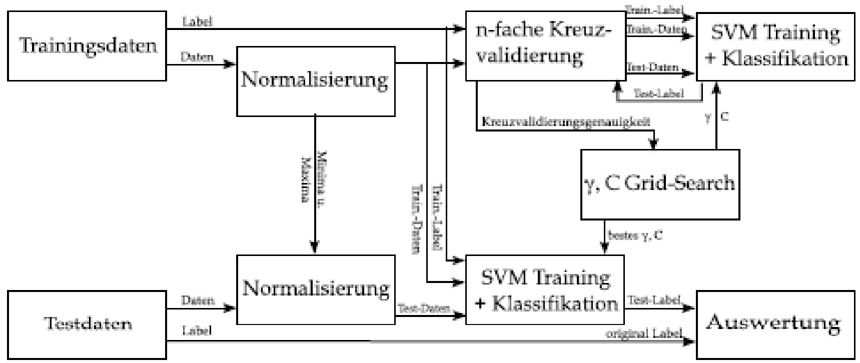
Pattern Recognition in Multiparameter Settings

Support Vector Machines
Classification



Ebert (2010)

Typical Training Process
in Machine Learning

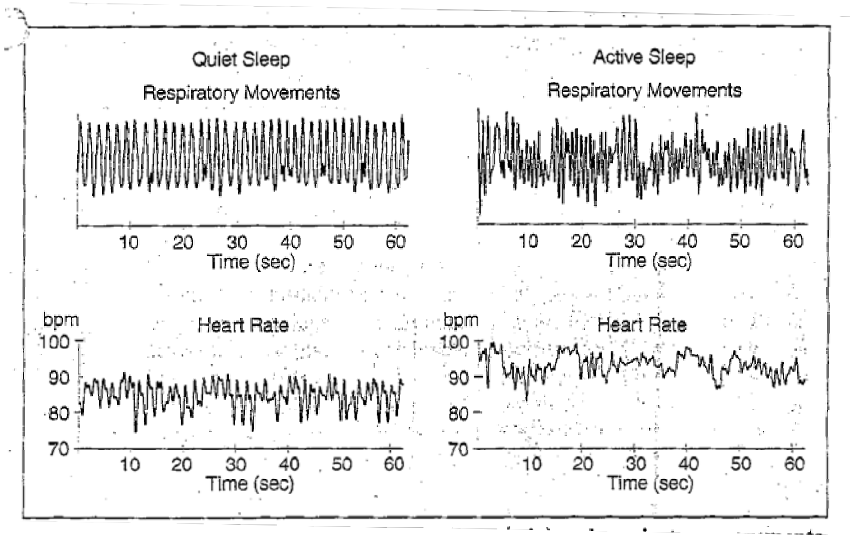


Bast (2009)

- **Approach:**
  - Combinations of many sensor signals and derived values
  - Solution: Complex pattern recognition and data mining
  - Classification of arrhythmia and disease progression

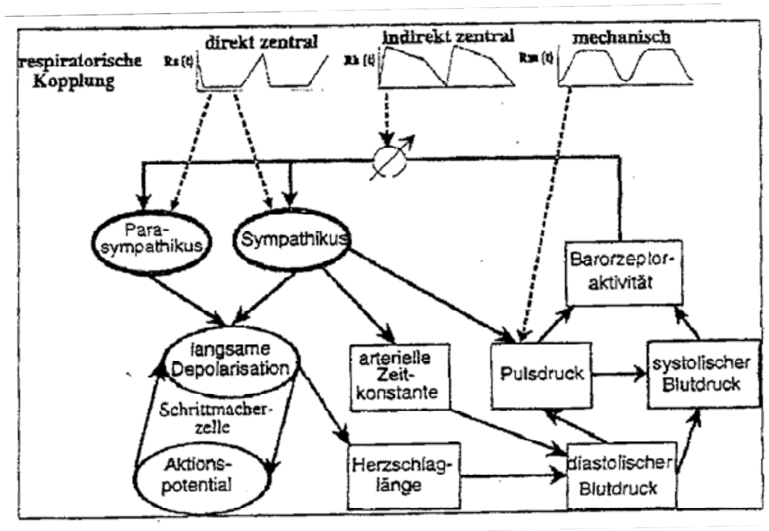
Coupling of Heart Beat and Breathing

Sleep Analysis



Hoyer (1998)

Modelling



Schiek (1995)

- **Remarks:**
  - Close physiological correlation of heart beat and breathing
  - Methods: correlation analysis, transinformation and others
  - Applications: sleep apnea detection (relevance e. g. heart failure)

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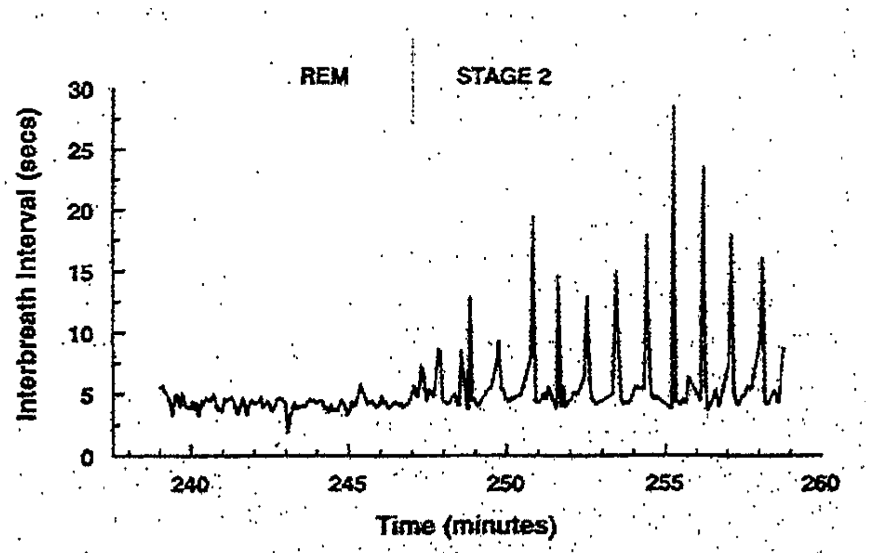
Sleep Apnea: A Common Syndrome

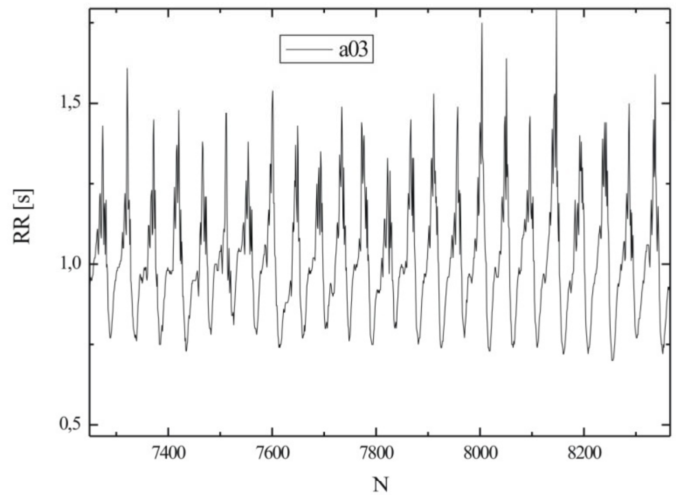
>800000 Patients in Germany (estimate)

Oscillations of Breathing



Kryger (1991)

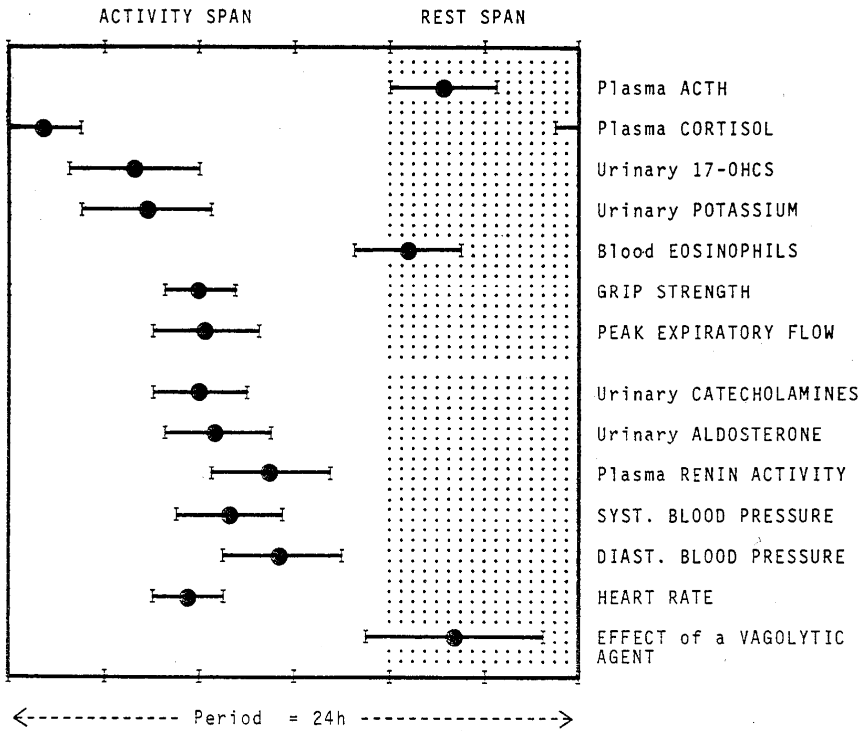
Interbeat Intervals



Meyer (2005)

- **Characteristics:**
  - May result in cardiovascular disease
  - Marker of disease such as heart failure
  - High morbidity and mortality

Circadian Variation: Cosinor Analysis



Reinberg, A., Smolensky, M. (1983)

$$f(t) = M + A\cos(\omega t + \phi)$$

$$\beta = A\cos\phi; \quad \gamma = -A\sin\phi$$

$$\begin{cases} n\hat{M} + \left(\sum_{j=1}^{n} x_j\right)\hat{\beta} + \left(\sum_{j=1}^{n} z_j\right)\hat{\gamma} = \sum_{j=1}^{n} y_j \\ \left(\sum_{j=1}^{n} x_j\right)\hat{M} + \left(\sum_{j=1}^{n} x_j^2\right)\hat{\beta} + \left(\sum_{j=1}^{n} x_j z_j\right)\hat{\gamma} = \sum_{j=1}^{n} x_j y_j \\ \left(\sum_{j=1}^{n} z_j\right)\hat{M} + \left(\sum_{j=1}^{n} x_j z_j\right)\hat{\beta} + \left(\sum_{j=1}^{n} z_j^2\right)\hat{\gamma} = \sum_{j=1}^{n} z_j y_j \end{cases}$$

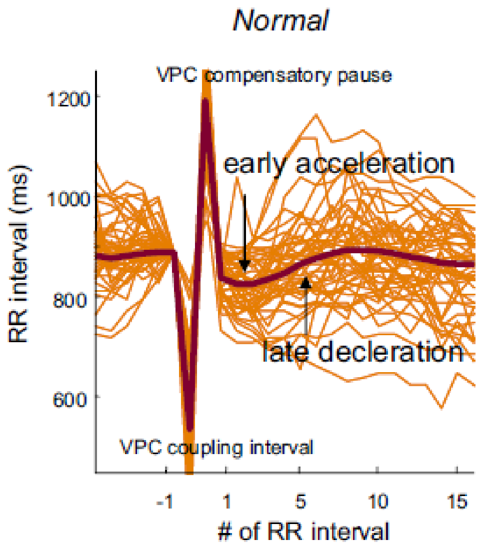
Nelson (1991)

Application: Progression of heart failure (rate at rest)

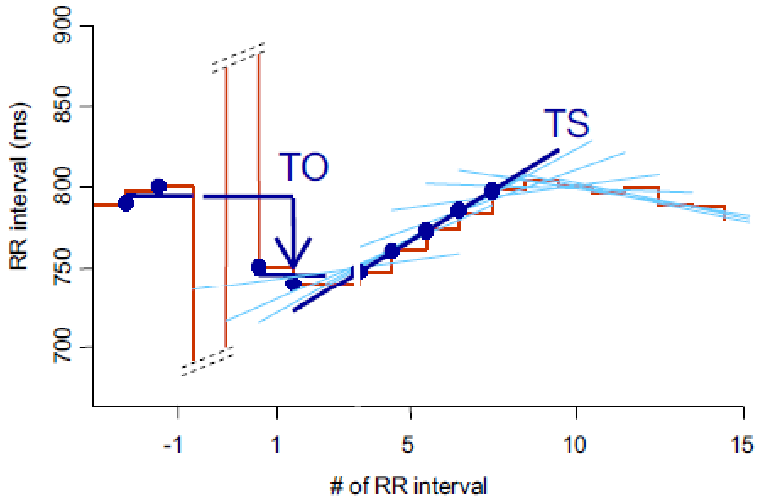
Heart Rate Turbulence (HRT): Change in Spontaneous Fluctuation

Premature Beats: Extrasystoles Provide additional Information

Premature Extrabeat



Regulatory Information

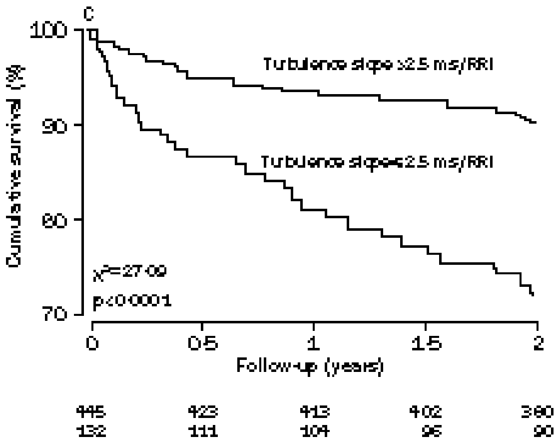


Bauer (2008)

- **Characteristics:**
  - Application: Risk stratification (SCD), Characterization (heart failure)
  - Extrasystoles: Both carrier of information and “artifacts”
  - Complex filtering problem

Risk Stratification of Sudden Cardiac Death

Heart Rate Turbulence Approach



Schmidt (1999)

Approach by Nonlinear Measures

$$D_q = \lim_{\epsilon \to 0} \frac{\log \sum_i \mu(B_i)^q}{(1-q)\log \epsilon}$$

μ: local attractor density function

Schmidt (1994), Söllner (1998), Skinner (1994), Liebert (1991)

- **Objective:**
  - Implantable defibrillators provide reliable protection
  - Patients who benefit are rarely known in advance
  - Identification of “responders” is necessary
  - No general solution yet

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Characterization of Heart Failure

Thermodynamical Approach

$$\Delta P_0 = P_0^{emp}(n) - P_0^{theo}(n)$$

$$\Delta P_1 = P_1^{emp}(n) - P_1^{theo}(n)$$

$$P_j = \exp\left(-\frac{E_j}{k_B T}\right) \Big/ Z$$

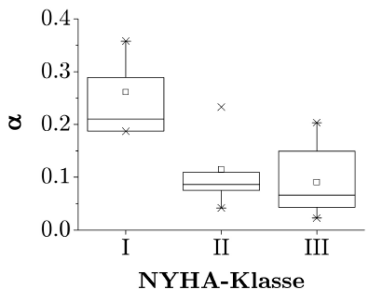
Meyer (2004)

Fokker-Planck Approach

$$\frac{d}{dt} X(t) = g[X(t), t] + \Gamma(t) \, .$$

$$\boxed{X(t) = X(0)\Xi(t) + \mathcal{X}(t) + \mathcal{G}(t) + [\Gamma * \Xi](t)}$$

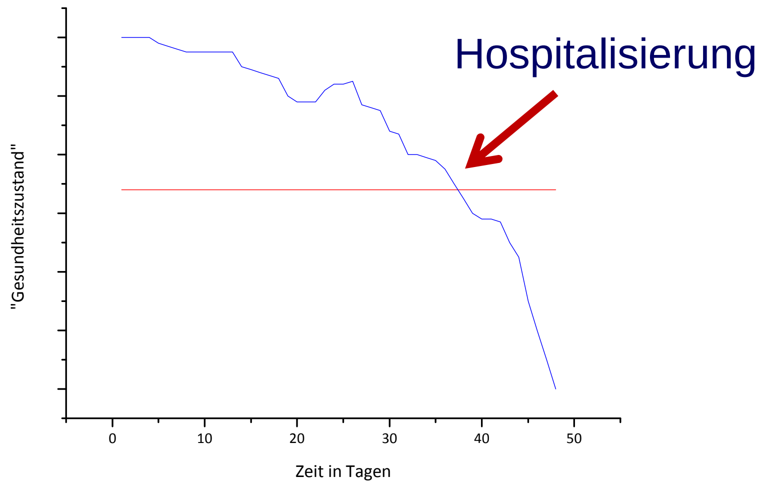
Kirchner (2008)



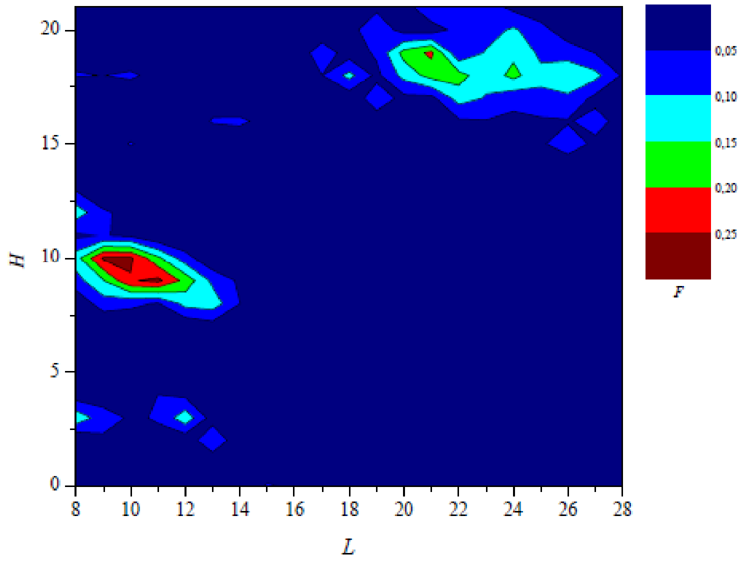
Classification of Grade of Heart Failure

Early Detection of „Decompensation“ of Heart Failure

Objective



Identification and Classification of Signals and free Parameters

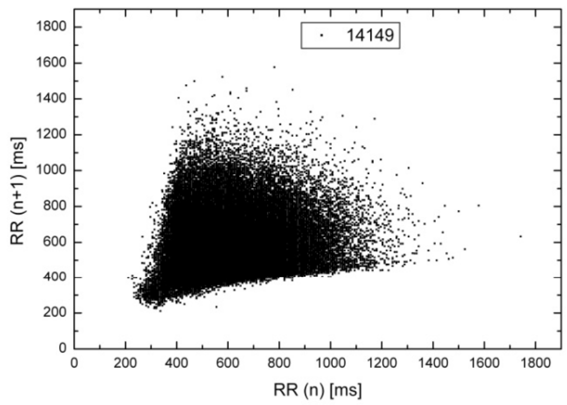


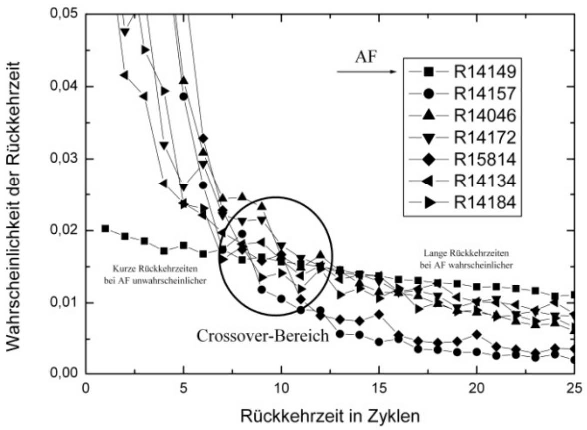
Ebert (2010)

Early detection may help to avoid hospitalization

Detection of Atrial Fibrillation

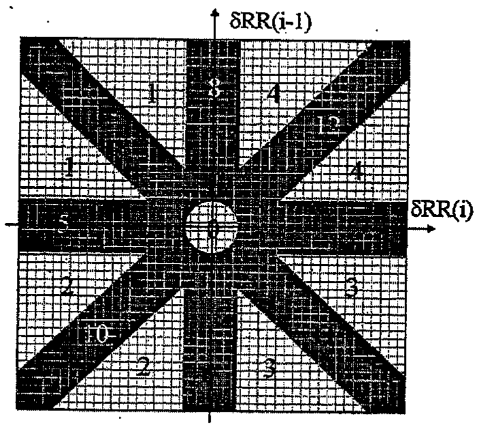
Analysis of Lorenz Plot





Meyer (2006)

Symbolic Dynamics



(a)

Segments	Sequence	δRR Values
0	SSS/LLL	$\lvert\delta RR\rvert < NSRmask$
1	S-L-S	$\lvert\delta RR(i-1)\rvert \neq \lvert\delta RR(i)\rvert$
2	L-M-S	$\lvert\delta RR(i-1)\rvert \neq \lvert\delta RR(i)\rvert$
3	L-S-L	$\lvert\delta RR(i-1)\rvert \neq \lvert\delta RR(i)\rvert$
4	S-M-L	$\lvert\delta RR(i-1)\rvert \neq \lvert\delta RR(i)\rvert$
5	L-L-S	One $\lvert\delta RR\rvert < NSRmask$
6	L-S-S	One $\lvert\delta RR\rvert < NSRmask$
7	S-S-L	One $\lvert\delta RR\rvert < NSRmask$
8	S-L-L	One $\lvert\delta RR\rvert < NSRmask$
9	S-L-S	$\delta RR(i-1) \cong -\delta RR(i)$
10	L-M-S	$\delta RR(i-1) \cong \delta RR(i)$
11	L-S-L	$\delta RR(i-1) \cong -\delta RR(i)$
12	S-M-L	$\delta RR(i-1) \cong \delta RR(i)$

(b)

Sarkar (2008)

Application: Improved monitoring and therapy of atrial fibrillation

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Conclusion: Complex Analysis of Circulation

Rationale: Complexity of Syndromes and Cardiovascular System

- **Specific Challenges and Approaches:**
  - Discrimination of atrial fibrillation and ventricular tachyarrhythmia
  - Determination of parameters like sleep apnea index
  - Short term prediction of tachyarrhithmia
  - Long term prediction of “adverse events”

→ Direct application, specific „patterns“

- **More Common Challenges and Approaches:**
  - Development of new means of diagnosis
  - Explanation of physiological/pathophysiological mechanisms
  - Modelling and understanding of therapies
  - Understanding of “Physics of the Heart”

→ Interdisciplinary and transferable methods

Bolshoe Spasibo!
Vielen Dank!