VCU/NHLBI Workshop; March 13, 2009

The Pulse of Life: Fractals, Nonlinear Dynamics and Complexity in Health, Aging and Disease

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Professor of Medicine

Harvard Medical School

Outline of My Talk

- What is complex signals informatics (CSI)?
- Dynamical assays: new approach to personalized medicine?
- What is the NIH-funded (NIBIB/NIGMS) PhysioNet Resource for Complex Physiologic Signals and can it help you?

What is Complexity Science?

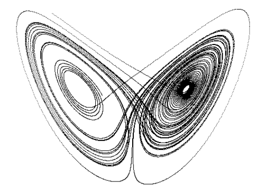
Complexity =
Nonlinear Dynamics
= Chaos Theory

But, <u>nonlinear chaos</u> is special type of dynamics and has absolutely nothing to do with chaos ("things are a mess") in usual sense (another talk)

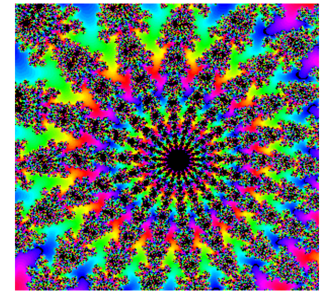
Nonlinear Dynamics in Everyday Language

- *"Straw that broke the camel's back" (small change causes big, discontinuous effect)*

- *"Life is a game of inches": sensitivity to initial conditions*



- *Whole is greater than sum of parts ("emergence")*



Part I

What is Complex Physiologic Signals Informatics (CSI)

And, frankly…

Why Should You Care?

What is Biomedical Informatics?

Biomedical Informatics:
Methods, Techniques and Theories

Bioinformatics

Imaging Informatics

Clinical Informatics

Public Health Informatics

Molecular & Cellular Processes

Tissues & Organs

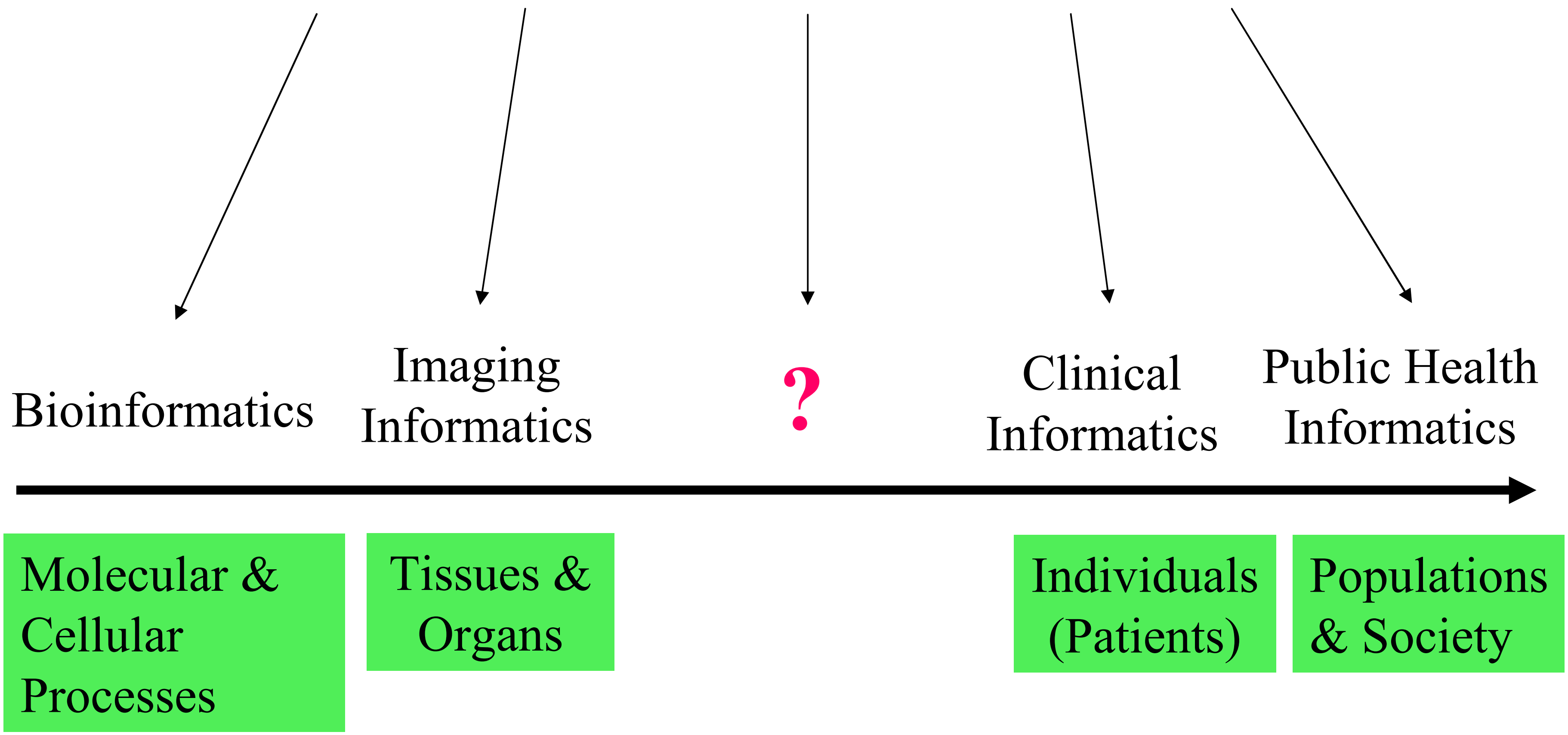
Individuals (Patients)

Populations & Society

Source: Journal of Biomedical Informatics

But, Between Genomics & Diagnostics Something is Missing…

Biomedical Informatics: Methods, Techniques and Theories



More Complete Picture

Biomedical Informatics:
Methods, Techniques and Theories

Bioinformatics

Imaging Informatics

Complex Signals Informatics

Clinical Informatics

Public Health Informatics

Molecular and Cellular Processes

Tissues and Organs

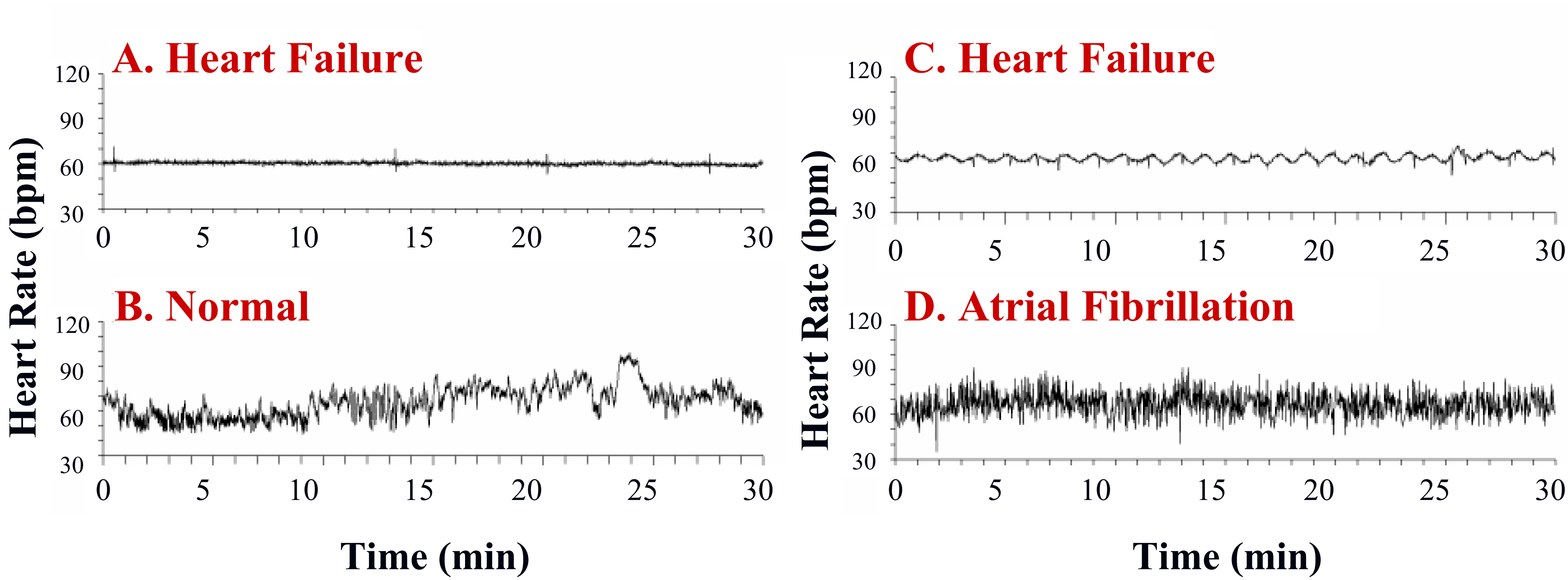
Diagnostic & Functional Dynamics

Individuals (Patients)

Populations And Society

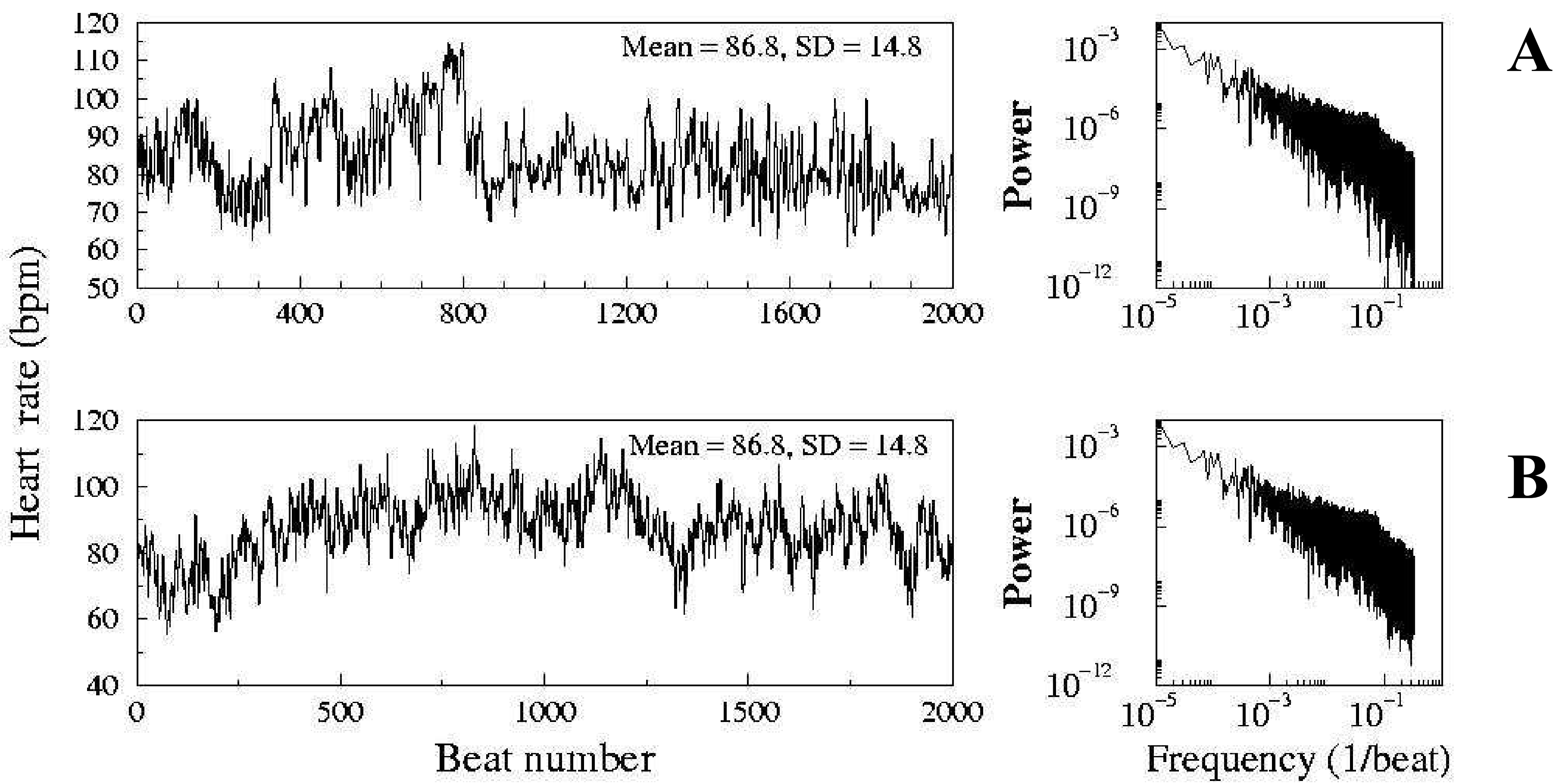
A Friendly (Ungraded!) Test

So, how good a physiologist/dynamicist are you?
Can you tell which heart rate pattern is healthy?*



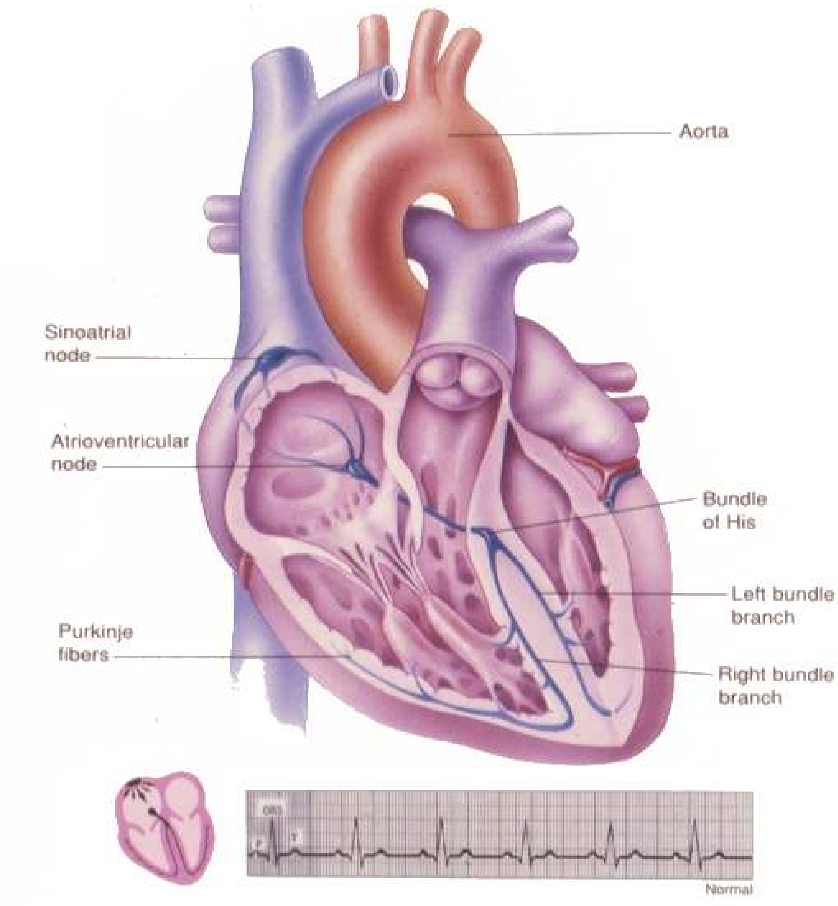
*Assume comparable activity. Note: only one is normal; other 3 from subjects at high risk of sudden cardiac arrest or stroke

Beyond FFT: Which is Physiologic ?

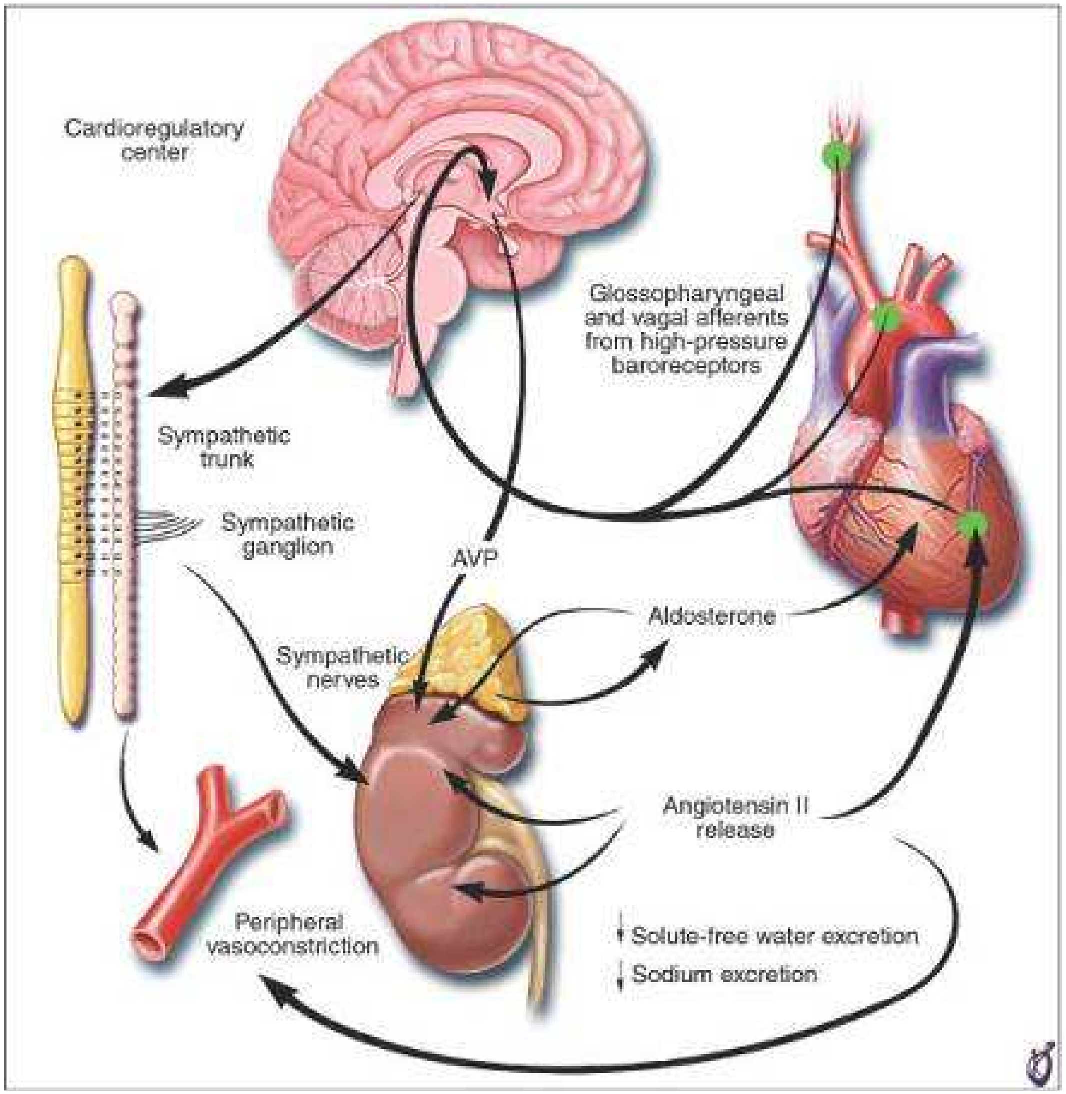


Answer: Stay tuned for Madalena's talk

The Heart: Cardiologist's (Reductionist) View of Things



The Heart—More Systemic (Networked) Model



- Cascades of coupled, nonlinear feedback networks interacting over a wide range of temporal/spatial scales

Nature 1999:399:461
PNAS: 2002:99 (Suppl 1):2466

Three Key Concepts

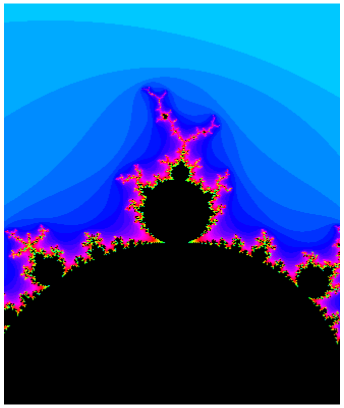
1. Physiologic signals and anatomic structures are the most complex in nature

2. Important clinical information is “hidden” (encoded) in nonlinear fluctuations and patterns

3. Complexity degrades with pathology, aging & biotoxicity

The way physiology changes from one instant to the next tells an important story about health/disease

Why are Physiologic Signals So Complex?

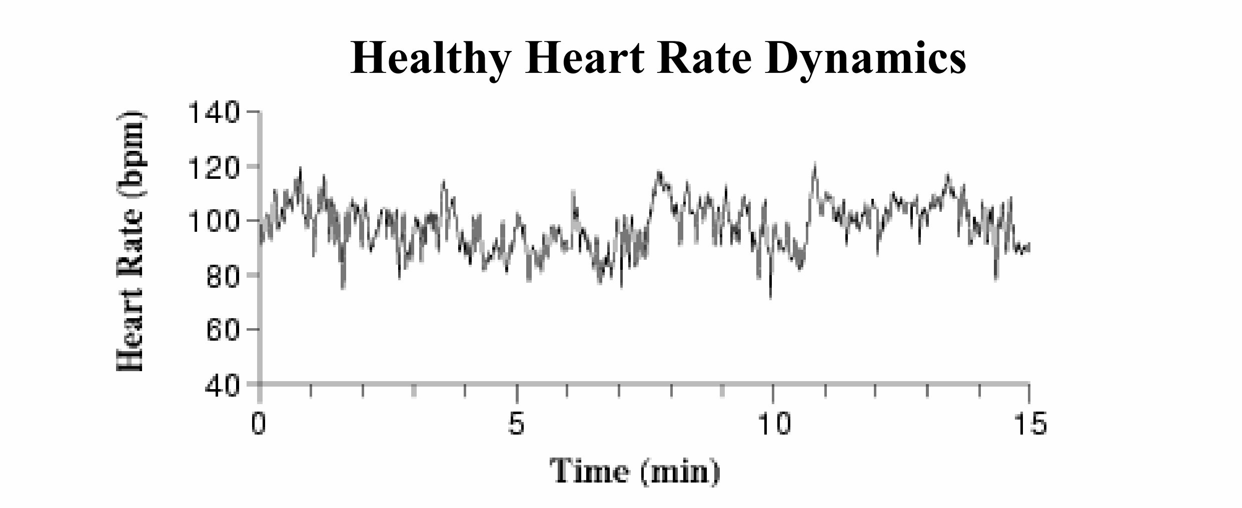


1. Healthy physiologic systems are regulated by many interacting control mechanisms that operate over multiple time scales

2. Therefore, the output signals exhibit *temporal correlations*: current value ($t=t_i$) is partially determined by previous values (t_{i-1}, t_{i-2},…)

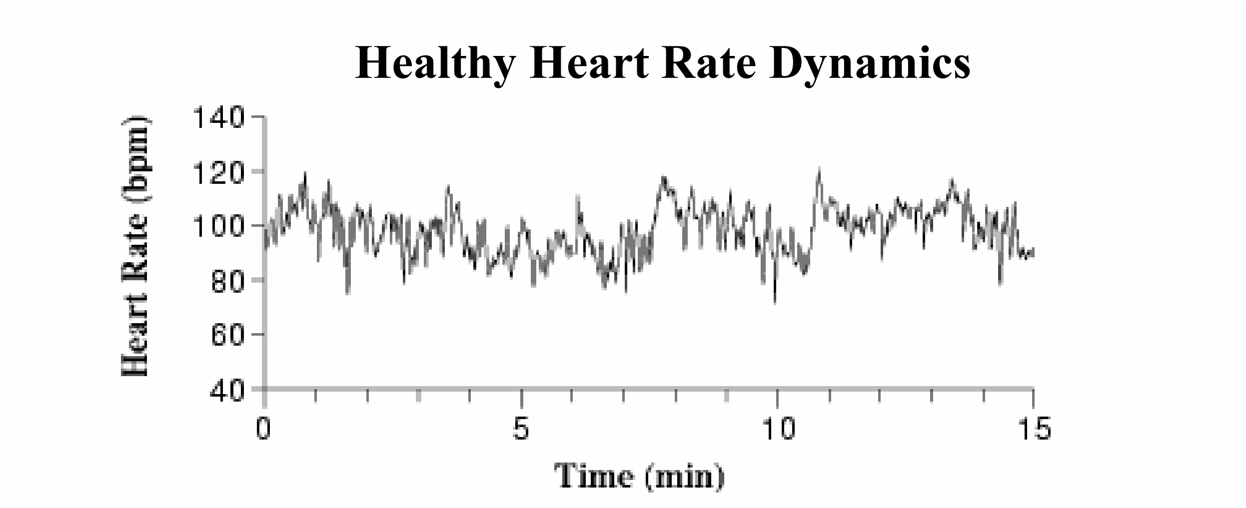
3. Physiologic systems have to adapt to an ever-changing, unpredictable environment

Some Hallmarks of Healthy, Adaptive Complexity



- Nonstationarity
  - *Statistics change with time*
- Nonlinearity
  - *Components interact in unexpected ways ("cross-talk")*
- Multiscale (fractal) Organization
  - *Fluctuations/structures have no characteristic scale*
- Time Irreversibility
  - *Nonequilibrium dynamics underlie fluctuations*

Some Hallmarks of Healthy, Adaptive Complexity



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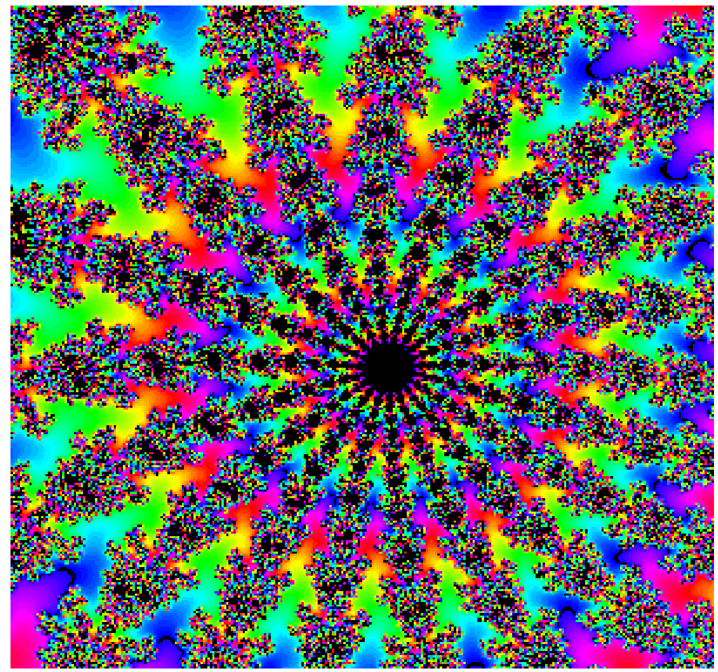
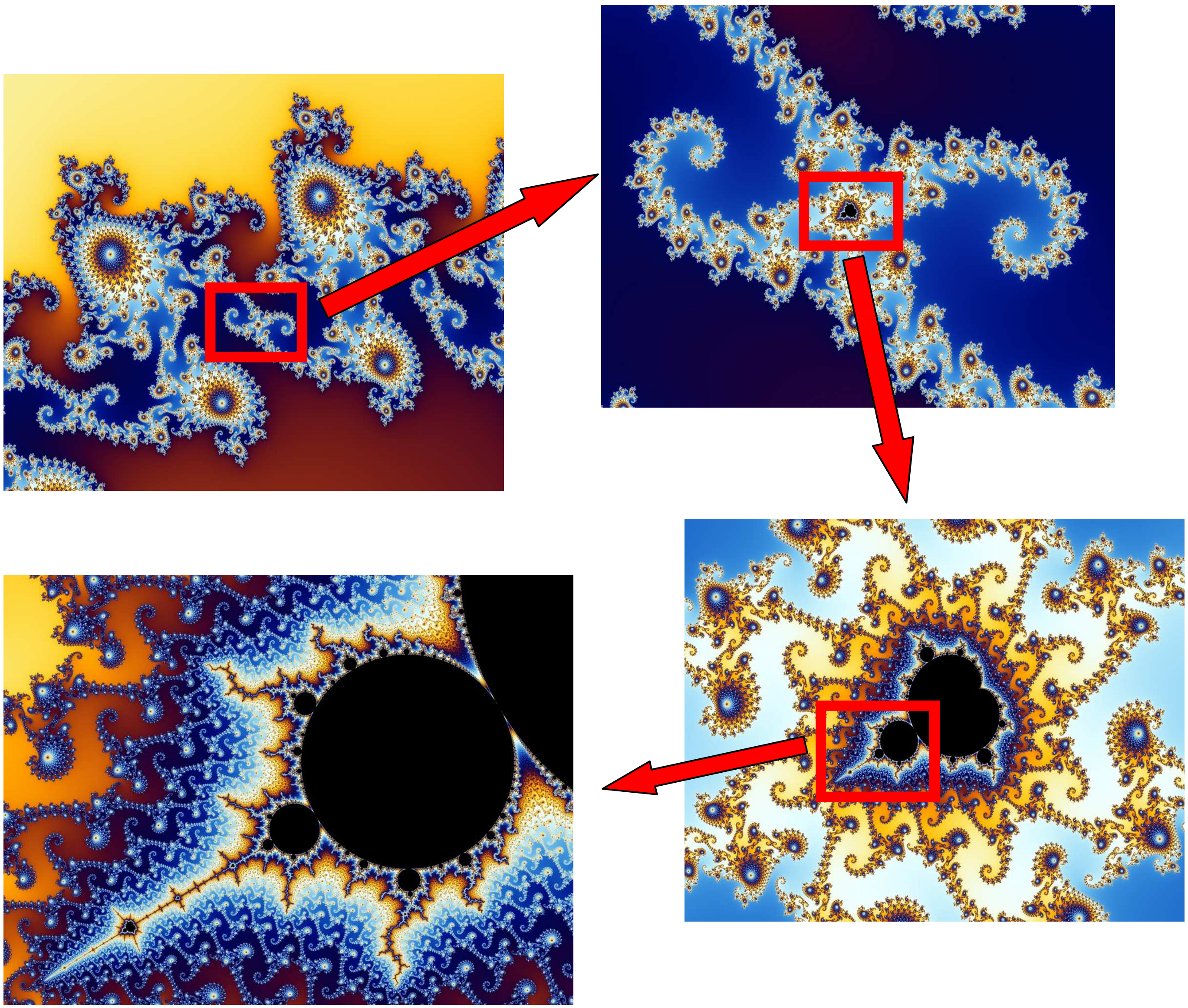
Complicated vs. Complex



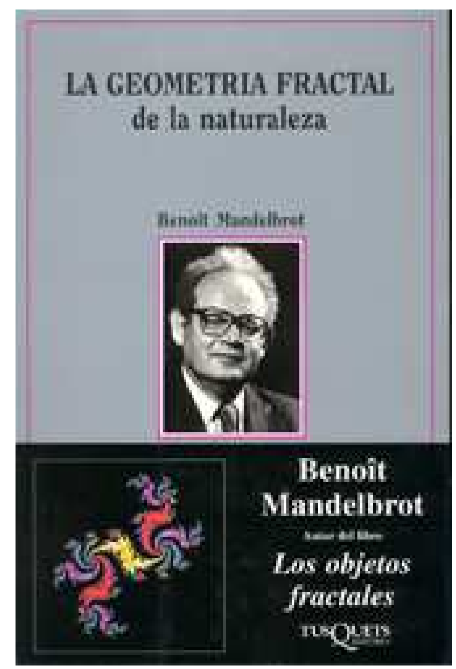
kaleidoscope *vs.* fractal

Mandelbrot Set:
Self-Similar Complexity

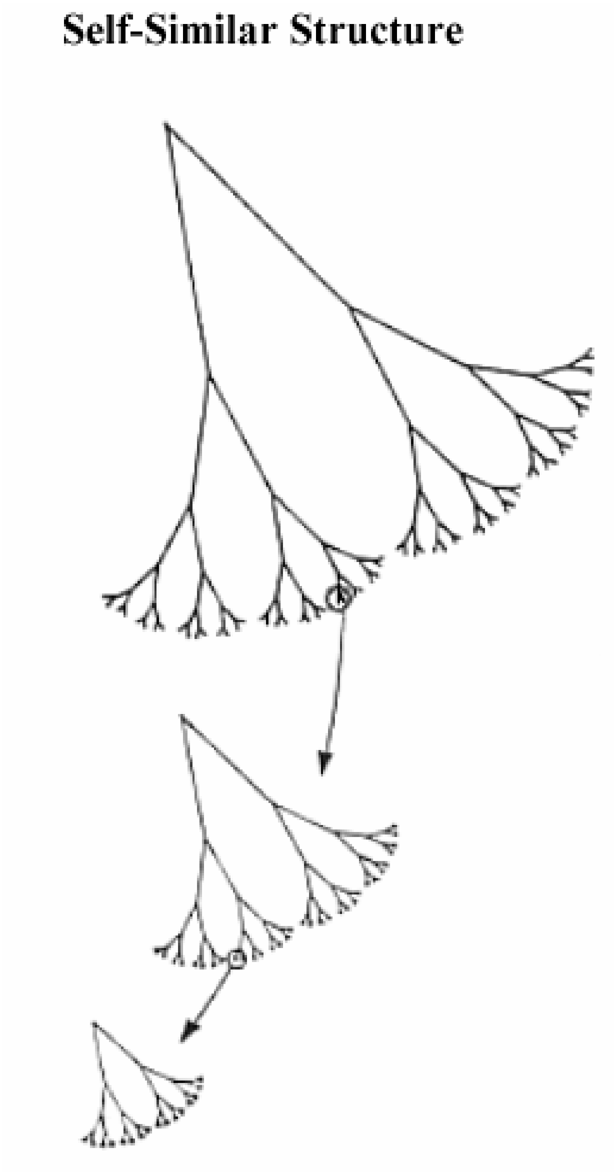


Simple recipe!

$$z_{n+1} = z_n^{\ 2} + c$$



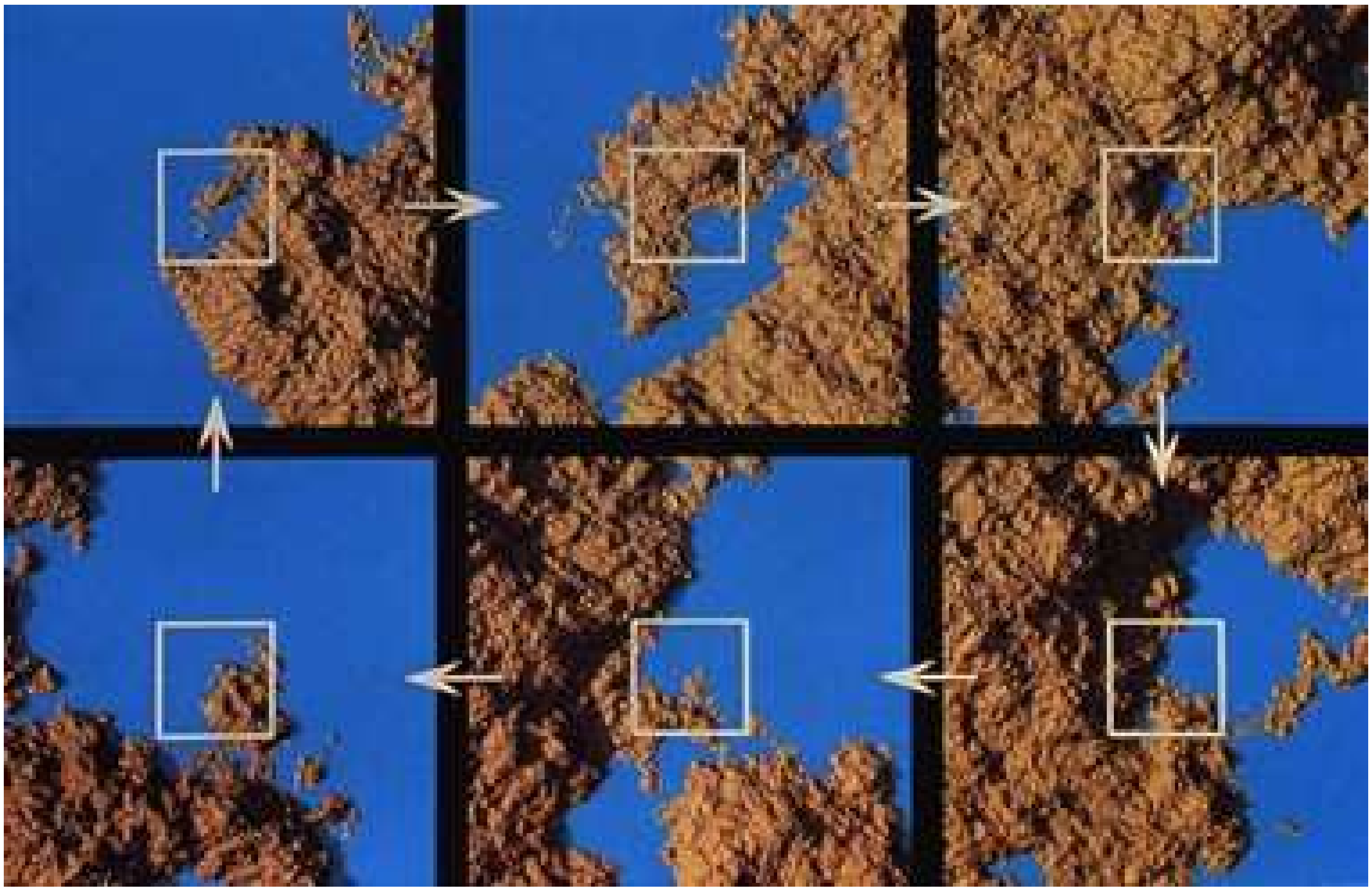
In Simplest Terms: What is a Fractal?



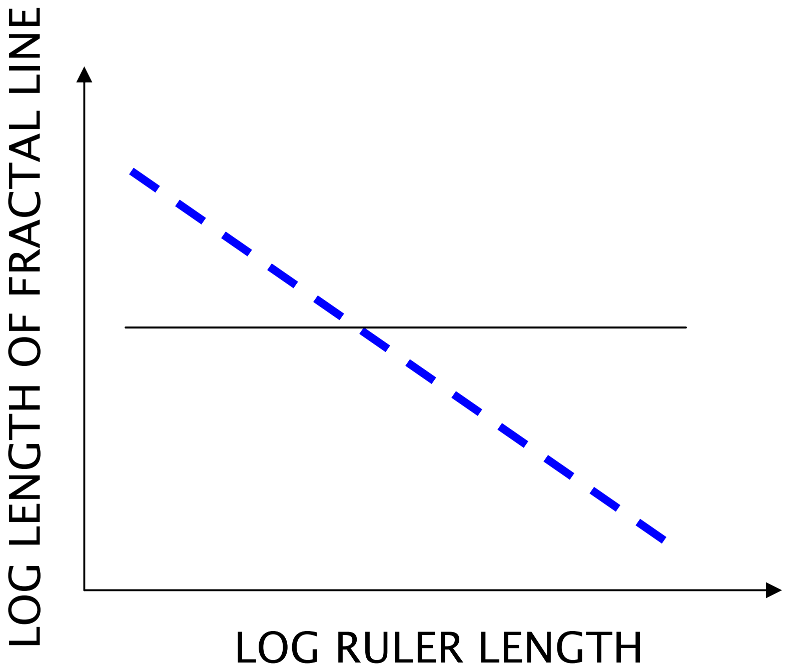
Fractal: A tree-like object or process, composed of sub-units (and sub-sub-units, etc) that resemble the larger scale structure

- This internal look-alike property is known as *self-similarity* or *scale-invariance*
- Fractals have no characteristic (single) scale

Fractal Coastline: Self-Similarity

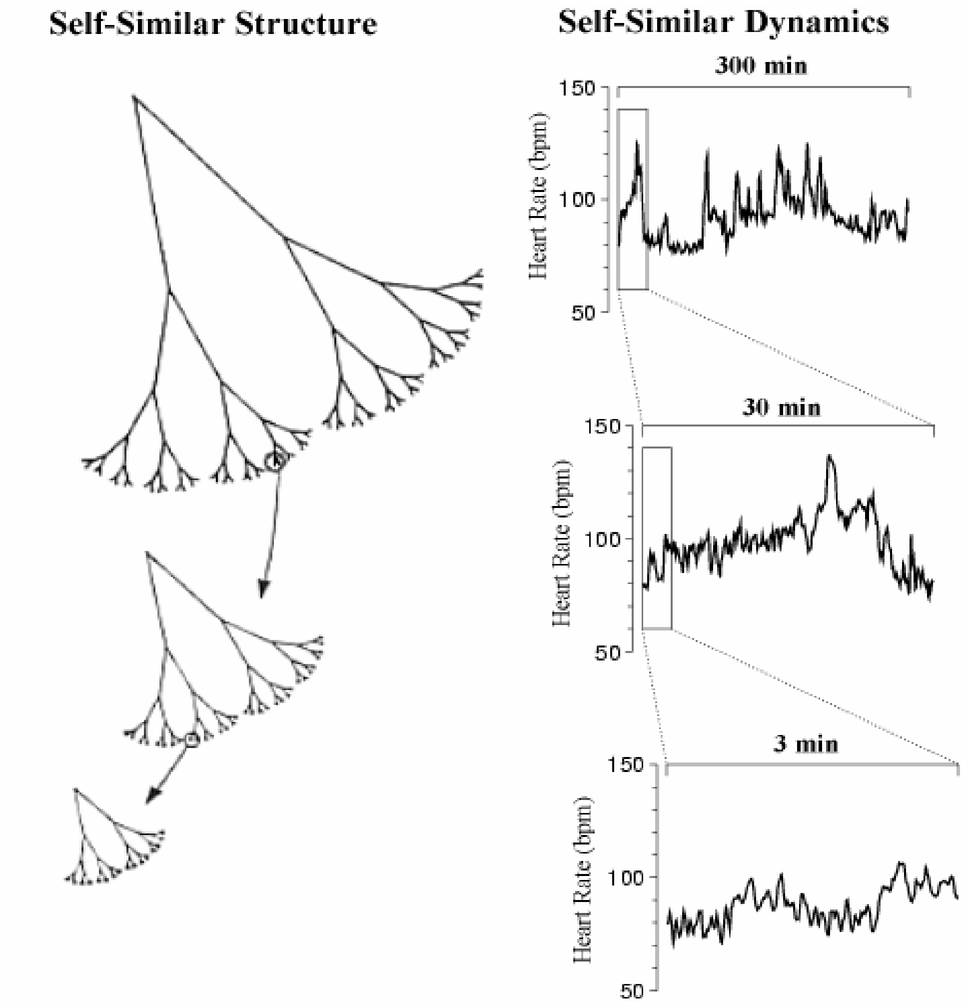


Fractals and Power Laws



Fractals produce power laws: *smaller* the measuring stick, *longer* the coastline

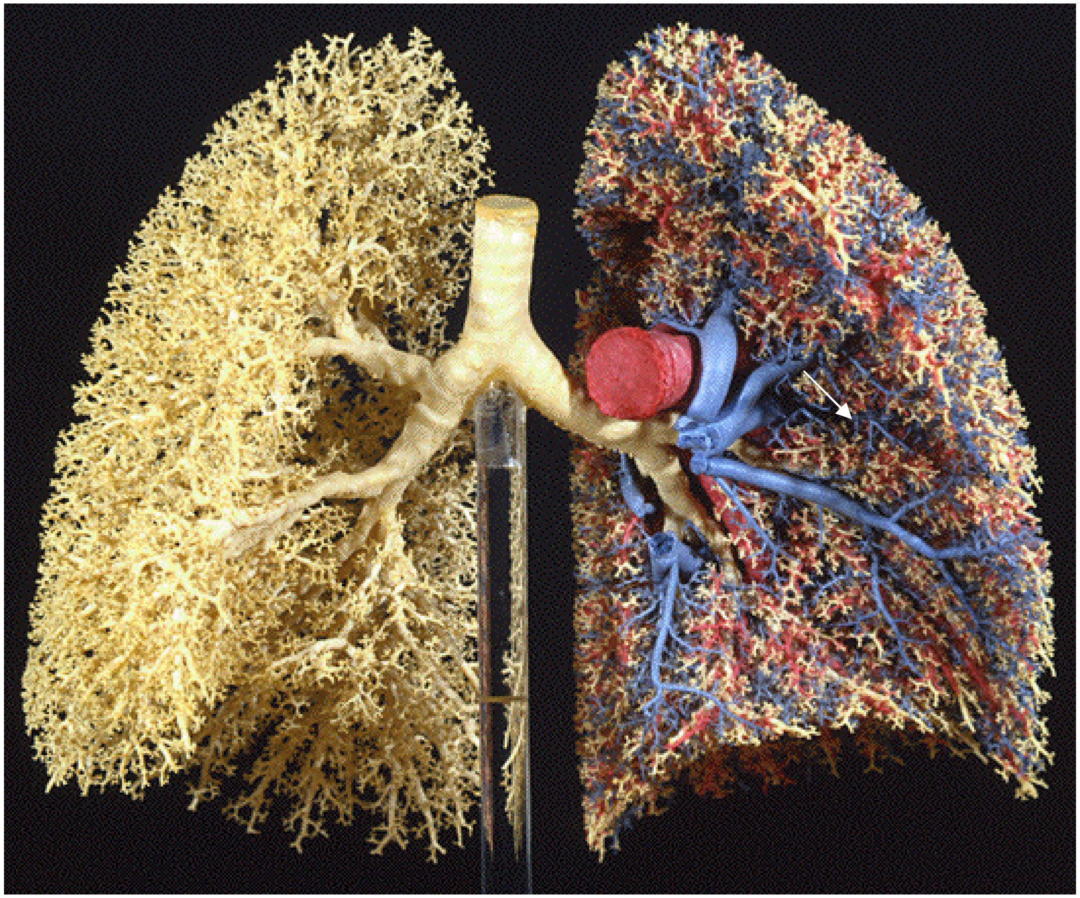
Fractals Also Universal Design Principle in Nature

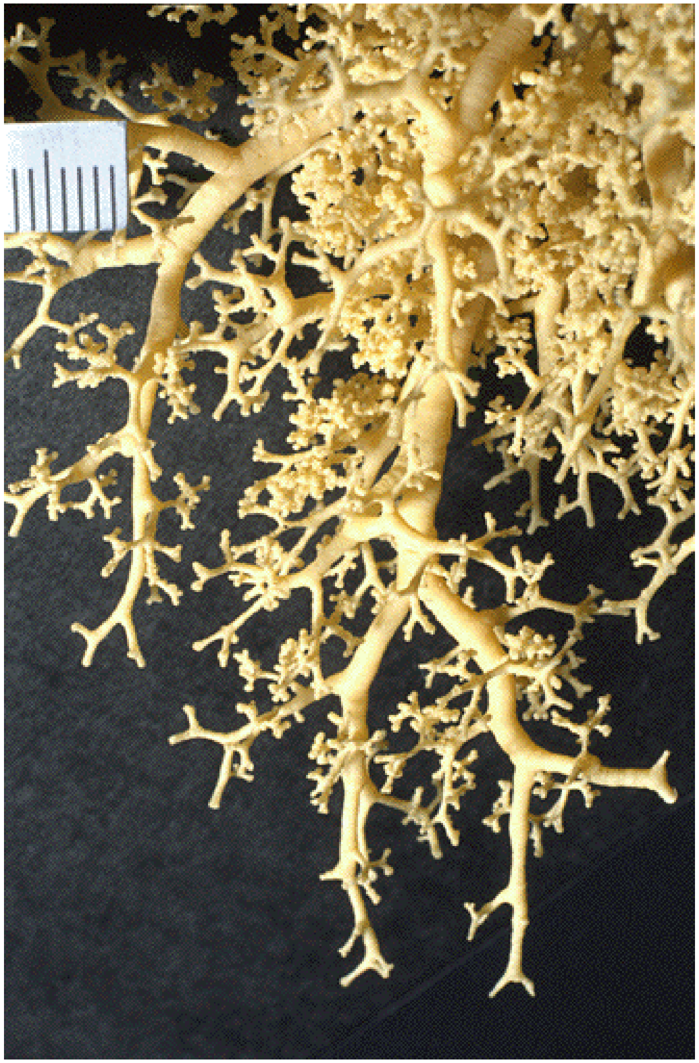


Fractal **:** Complex tree-like object or hierarchical process, composed of sub-units (and sub-sub-units, etc) that resemble the larger scale design

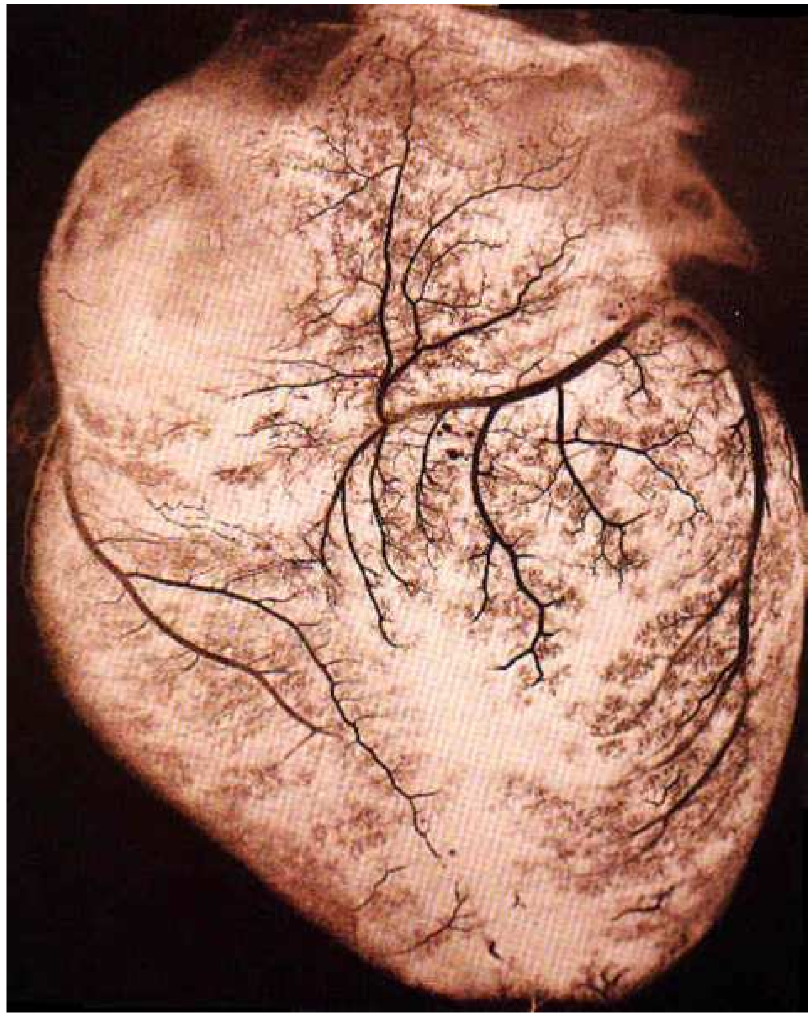
As noted, this internal look-alike property is known as ***self-similarity*** or ***scale-invariance***

Fractal Distribution Network: The Bronchial Tree





Fractal Arteriogenesis: Coronary Artery Tree



Fractals in the Body (Con't): Renal Vascular System

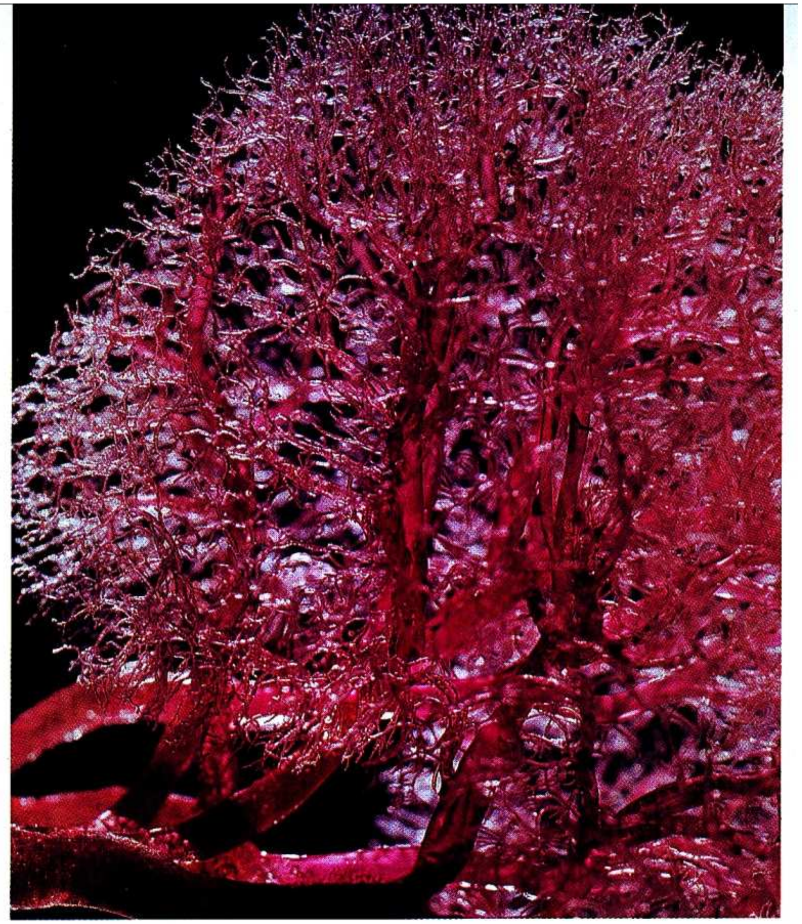
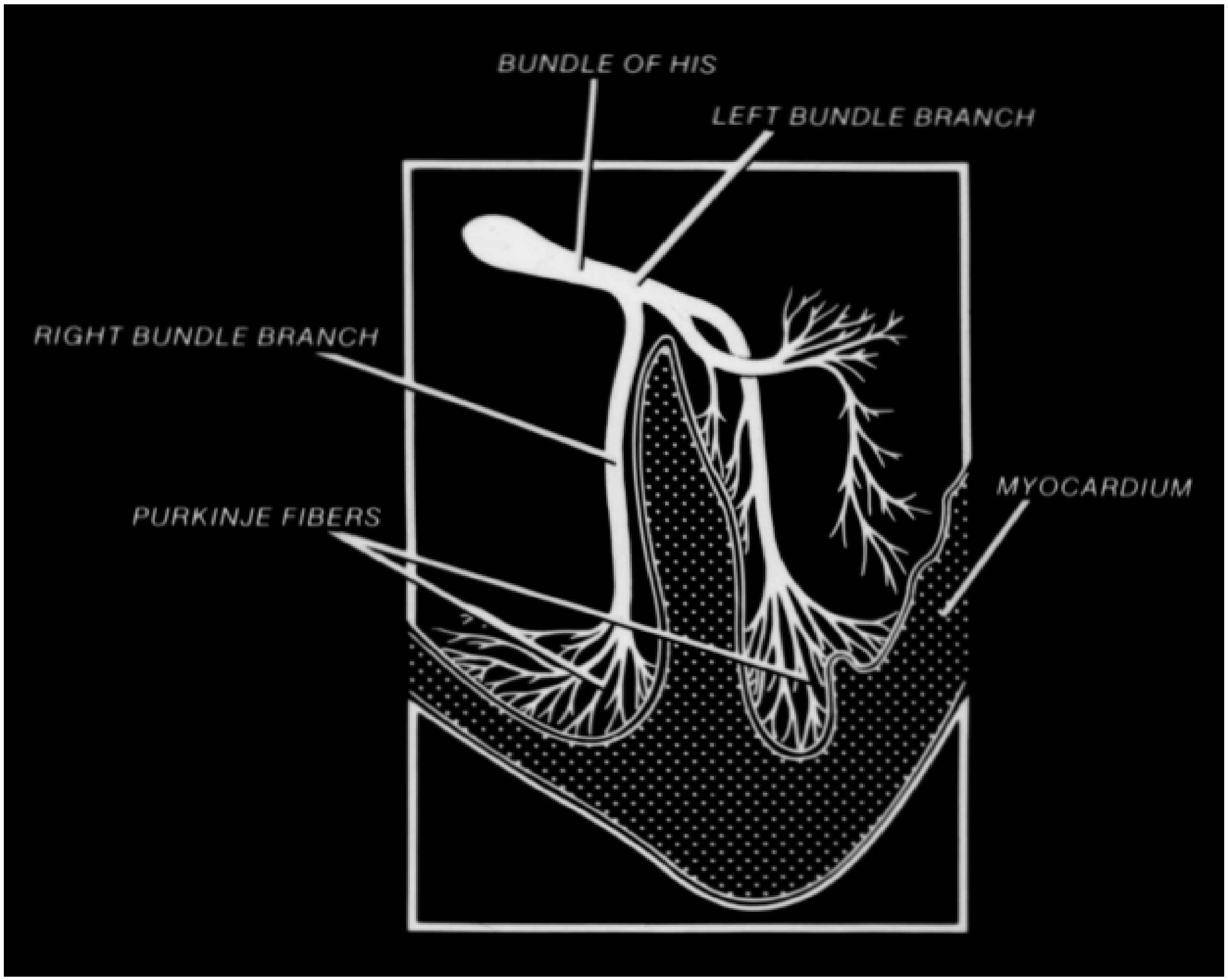


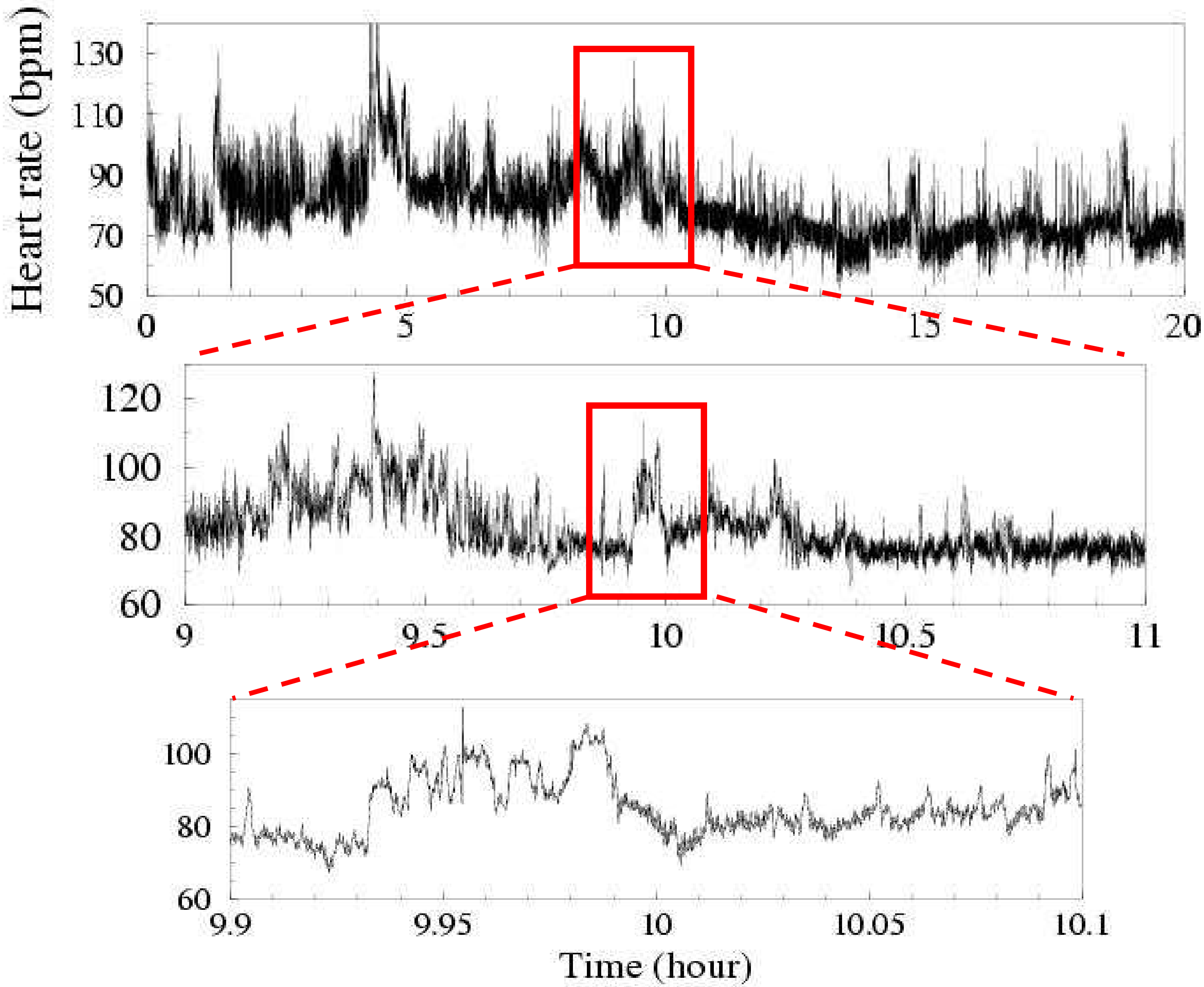
Plate 2: Cast of a child's kidney, venous and arterial system, © Manfred Kage, Institut für wissenschaftliche Fotografie.

Peitgen, Jurgens and Saupe,
"Chaos and Fractals", p. 176
Springer-Verlag 1992.

Fractal Heart:
His-Purkinje Conduction Network

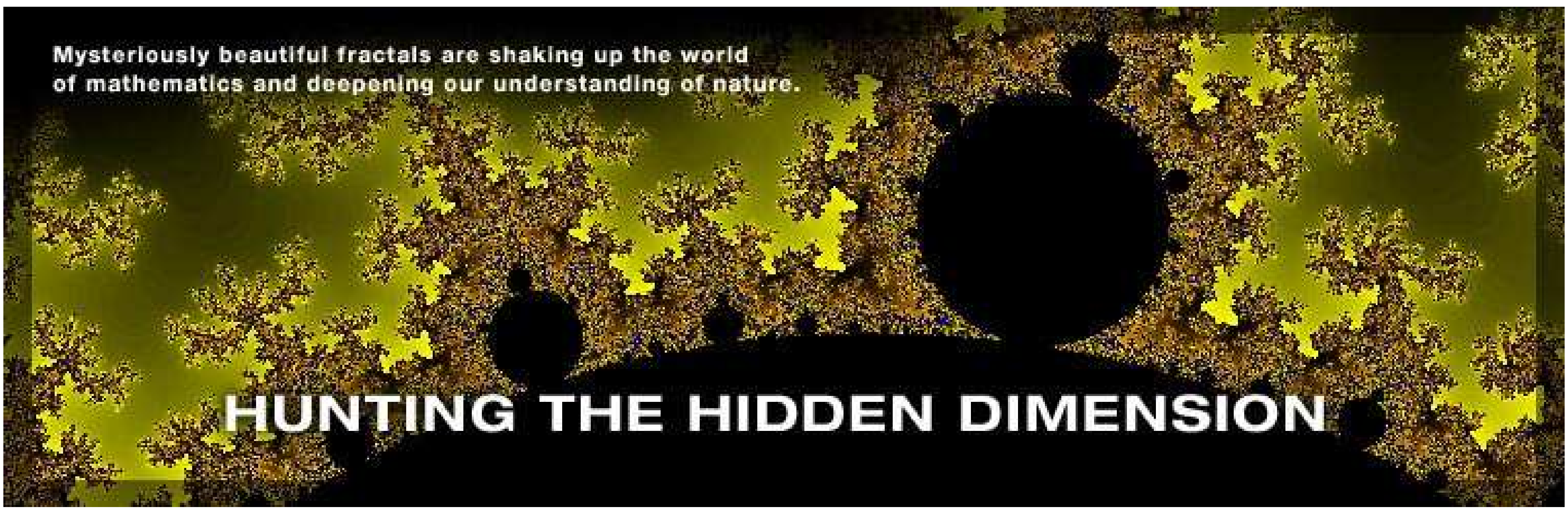


Healthy Heartbeat is Fractal



PBS-NOVA Show on Complexity/Fractals

“Hunting the Hidden Dimension”: October 28, 2008



Why is it Physiologic to be Fractal?

- Healthy function requires capability to cope with unpredictable environments

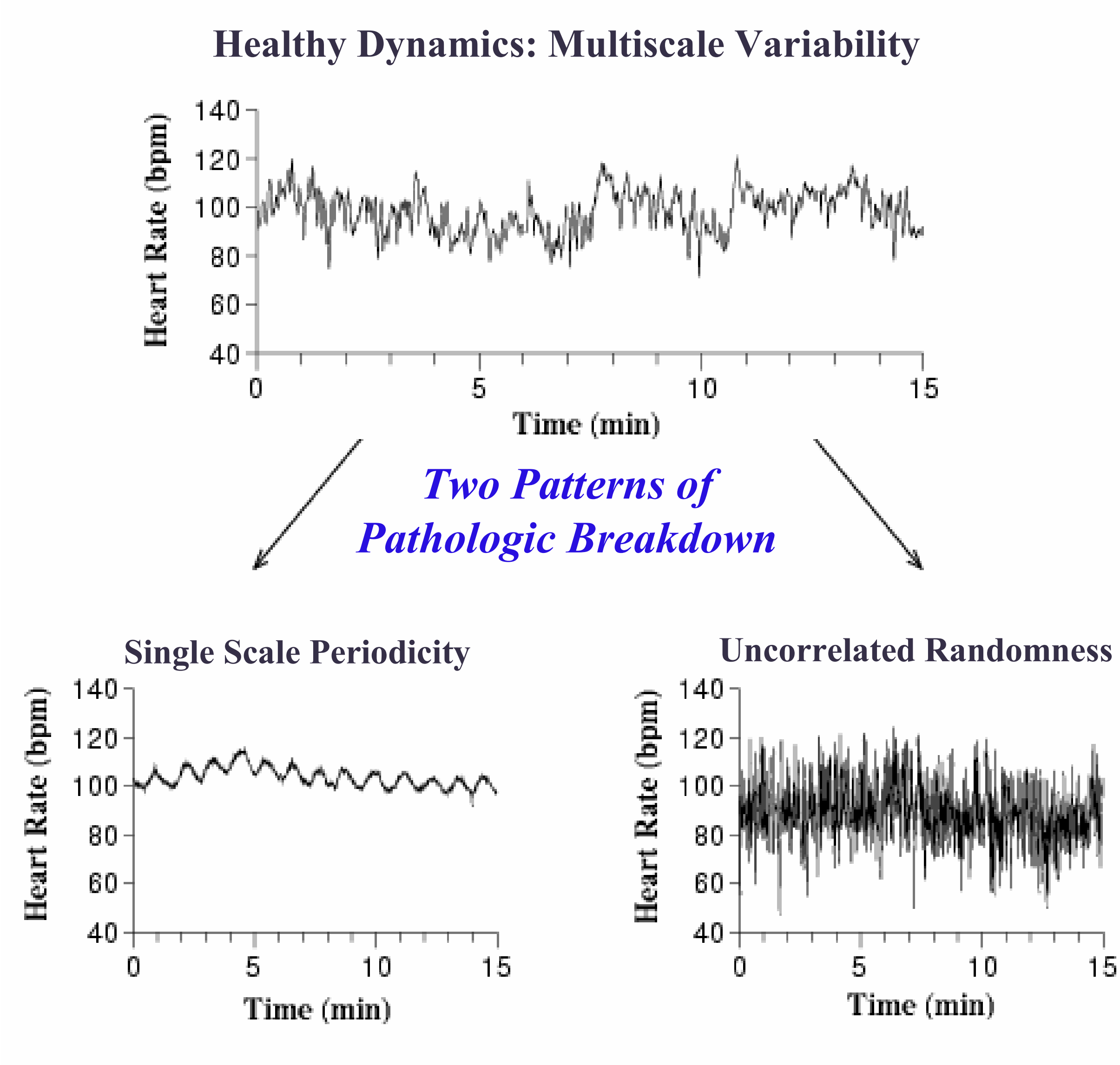
- Scale-free (fractal) systems generate broad range of long-range *correlated* responses $\rightarrow$ adaptability

- Absence of characteristic time scale helps prevent getting locked into a rigid (single) pattern of response (*mode-locking*) - Goose-Step or Tacoma Narrows Bridge Syndromes

Disastrous Pathologic Oscillations in Engineering

The Tacoma Narrows Bridge Collapse (1940)

Collapse of Complexity with Disease



Healthy dynamics poised between too much order and total randomness.

Nature 1999; 399:461
Phys Rev Lett 2002; 89 : 068102

Loss of Complexity with Disease

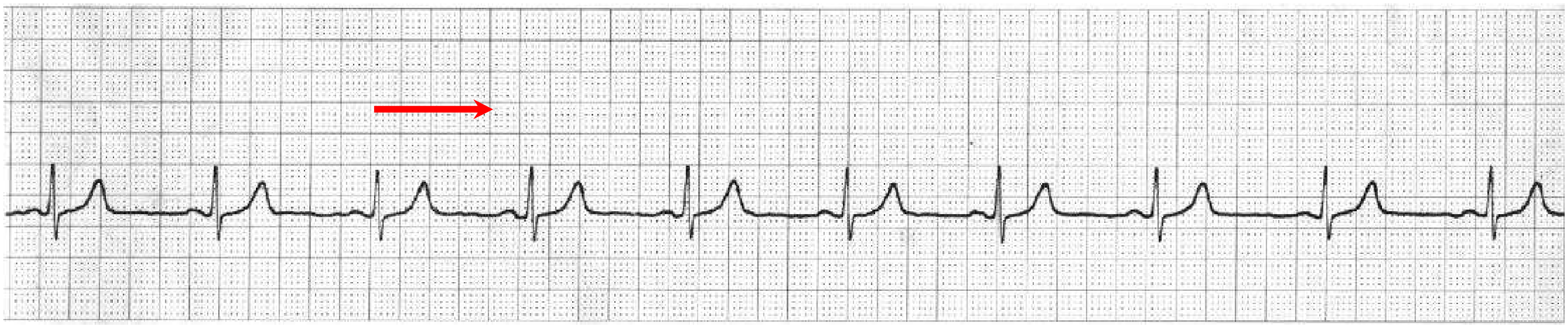
- The output of physiologic systems often becomes more regular and predictable with disease

- The practice of medicine **<u>not</u>** possible without such predictable behaviors – doctors look for characteristic patterns: *principle of stereotypy*

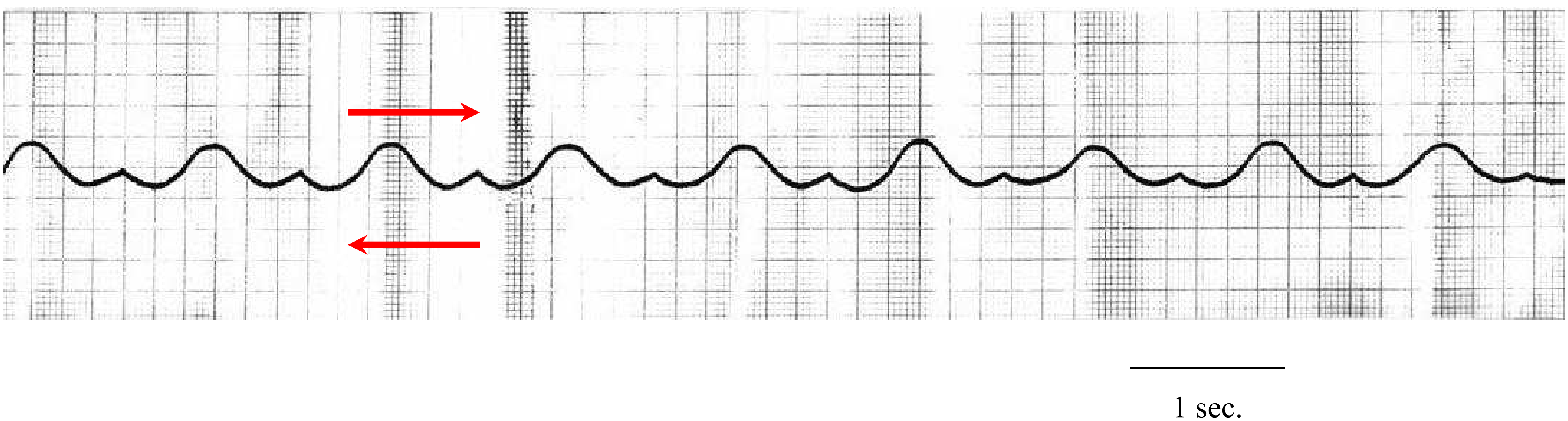
- Healthy function: multi-scale, information-rich dynamics much harder to characterize!

The Arrow of Time: Loss of Temporal Asymmetry in Dying Heart

Normal Heart: Time Asymmetric



Dying Heart: Time Symmetric



Loss of Nonlinear Complexity Resolves Medical Paradox

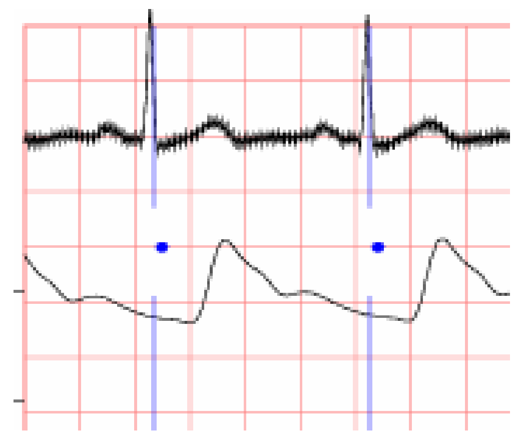
Patients with wide range of disorders/syndromes often display strikingly predictable (ordered) dynamics: Reorder vs. Disorder

Examples:

- **Cheyne-Stokes breathing**
- **Obstructive sleep apnea**
- **Parkinsonism / Tremors**
- **Obsessive-compulsive behavior**
- **Nystagmus**
- **Monomorphic ventricular tachycardia**
- **Torsade(s) de pointes**
- **Hyperkalemia → "Sine-wave" ECG**
- **Cyclic neutropenia**
- **Cyclic flow reductions in arterial stenosis**

Part II

- Personalized Medicine and Complex Signals Informatics



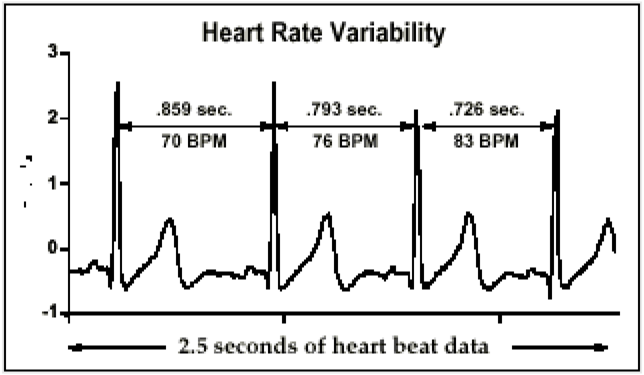
Measuring Complexity and Complexity-Loss

Complementary metrics & approaches needed: no single tool suffices!

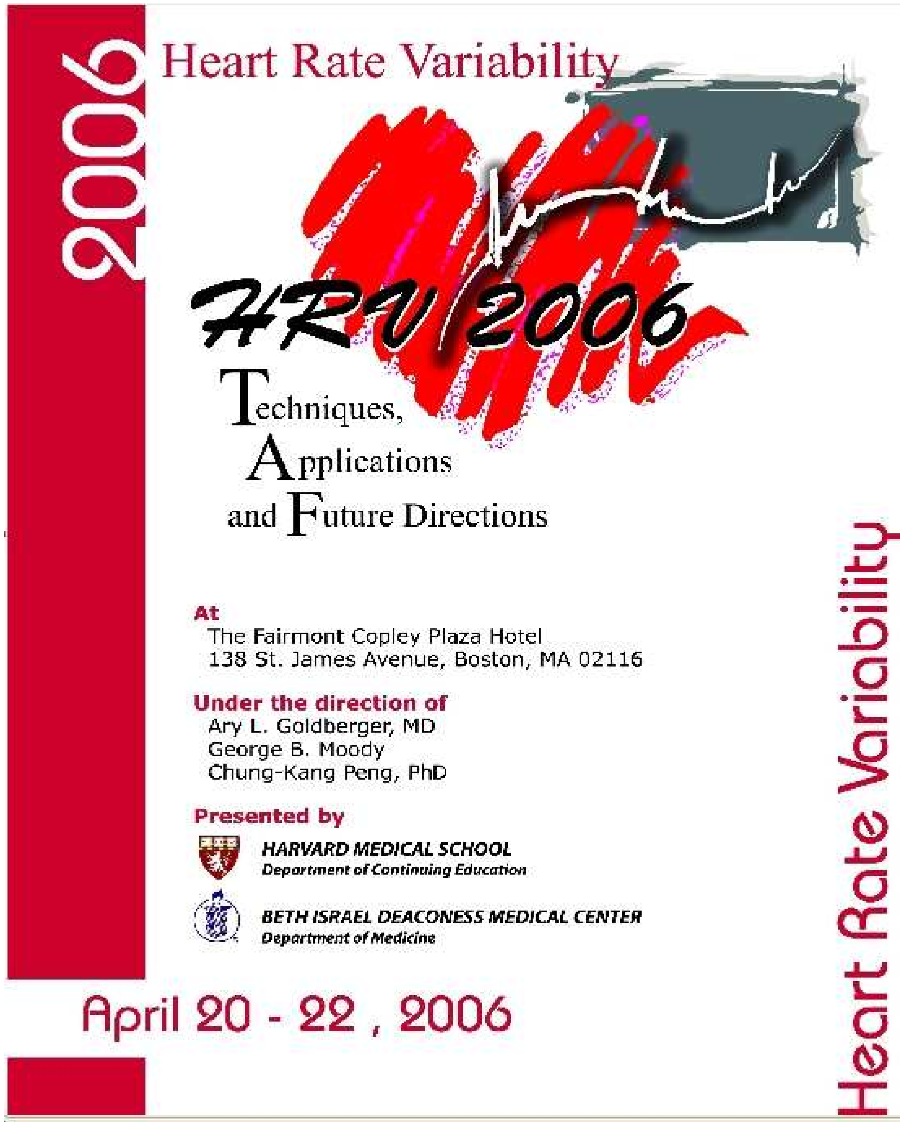
- Time and frequency domain
- Fractal/multifractal scaling exponents
- Entropy-related (Information theoretic)
- Time irreversibility
- Coupling/synchronization

What is HRV? Who Cares?

- Heart Rate Variability (HRV): not same as complexity
- Thousands of papers—no clinical applications of traditional HRV in practice: HRV “gap”
- Important physiologic implications and some emerging clinical ones



Complex Dynamics: Theme of Recent Course

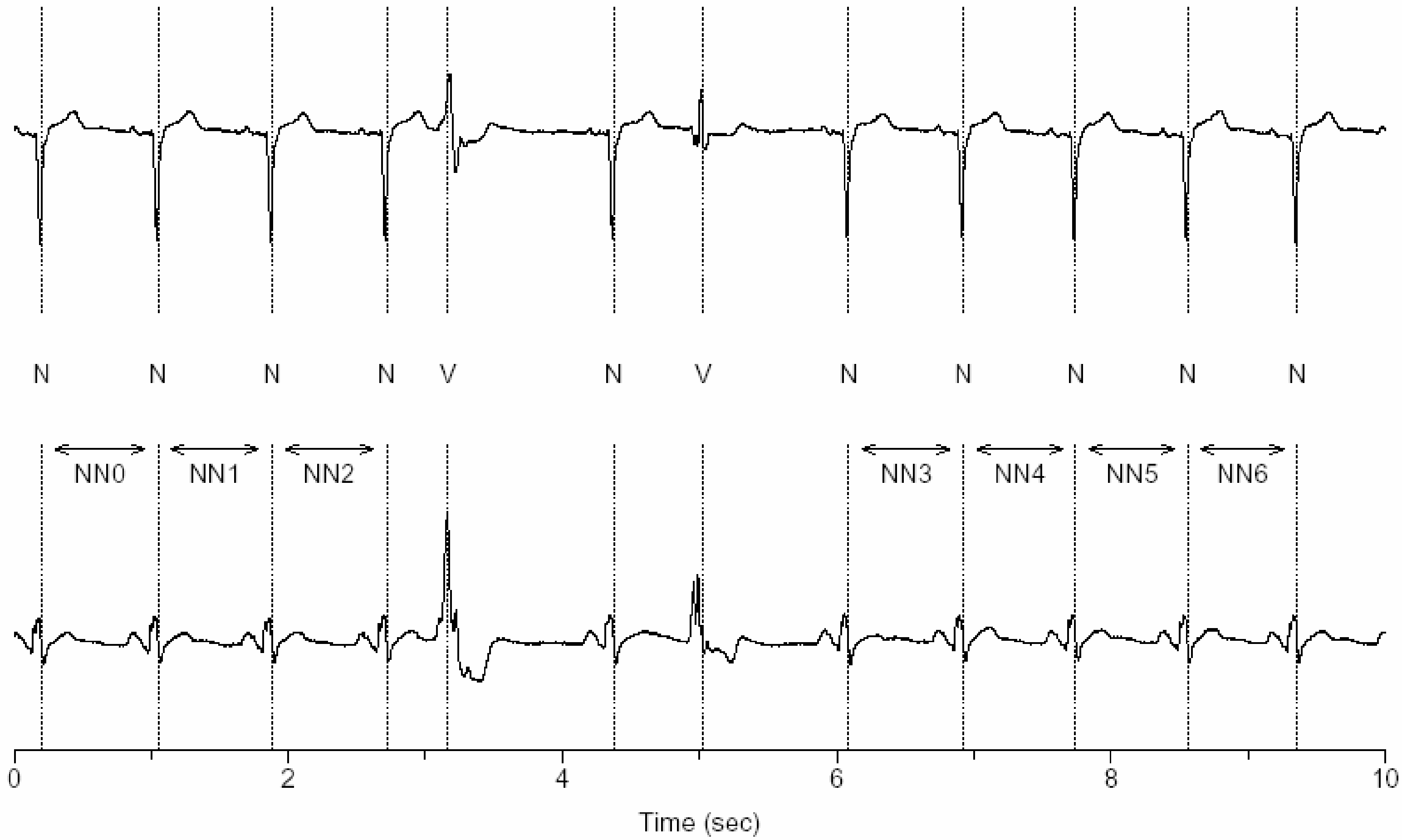


Syllabus freely available at NIH/PhysioNet website

www.physionet.org

From RR to NN

Sinus rhythm time series is derived from the RR sequence by extracting only normal sinus to normal sinus (NN) intervals



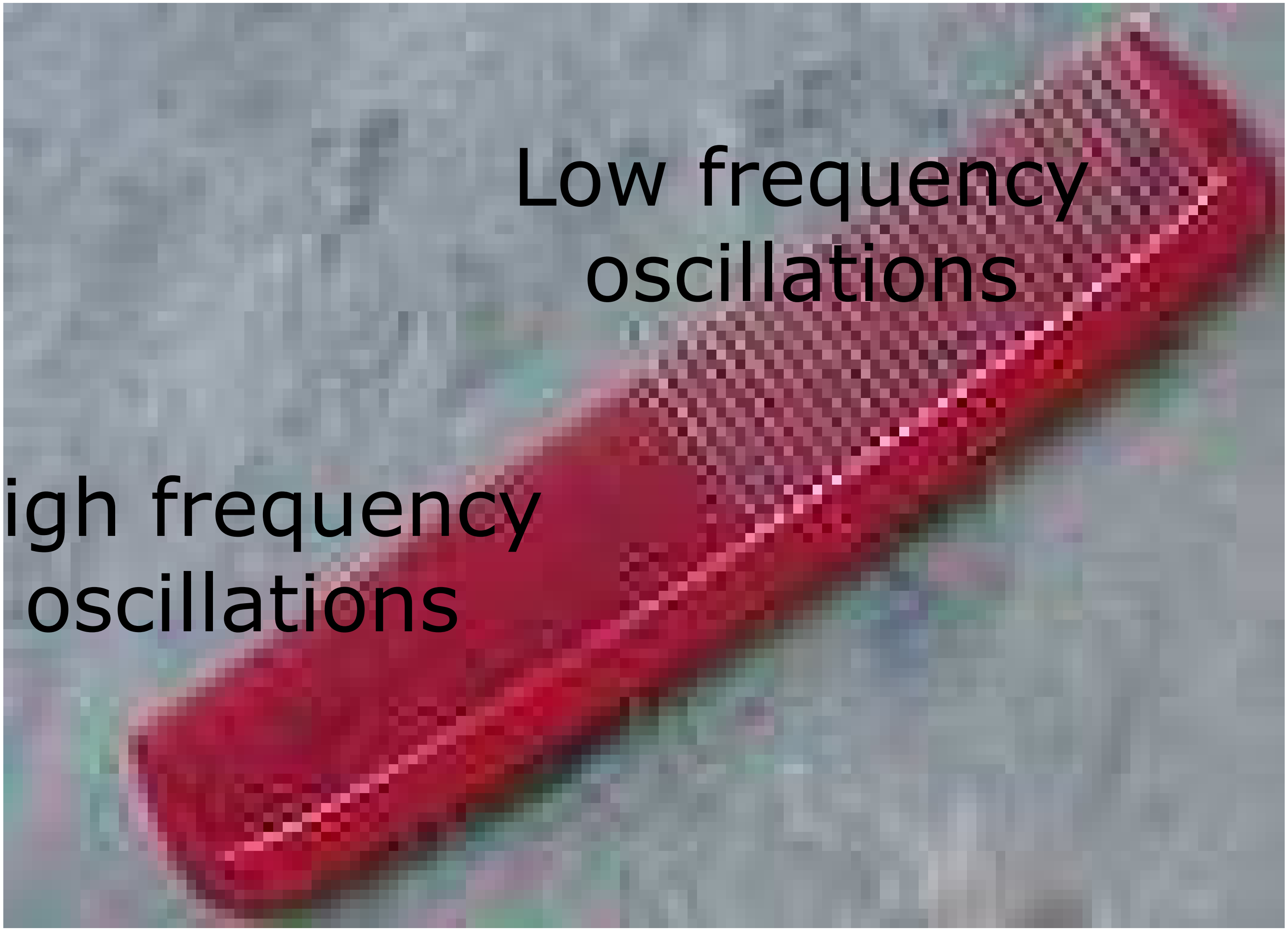
Common Time Domain Measures

- AVNN : Average of all NN intervals
- SDNN : Standard deviation of all NN intervals
- SDANN : Standard deviation of the average of NN intervals in all 5-minute segments of a **24-h recording**
- SDNNIDX (ASDNN) : Mean of the standard deviation in all 5-minute segments of a **24-h recording**
- rMSSD : Square root of the mean of the squares of the differences between adjacent NN intervals
- pNN50 : Percentage of differences between adjacent NN intervals that are >50 msec; one member of the larger pNNx family

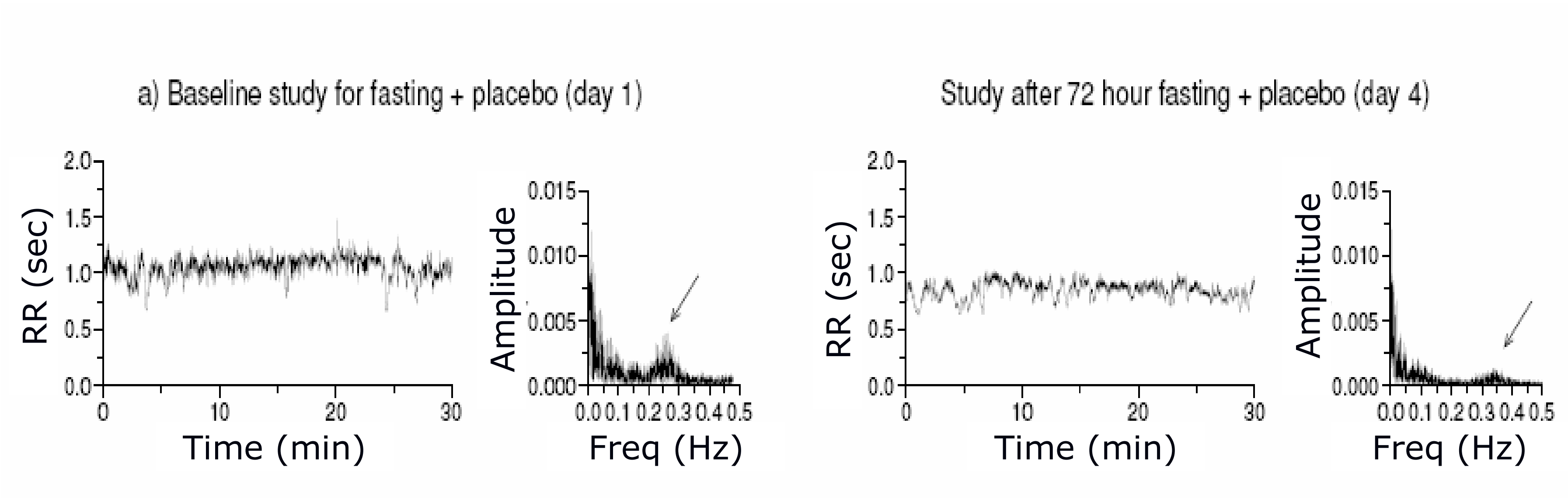
Common Frequency Domain Measures

- Total power : Total NN interval spectral power up to 0.4 Hz (same as variance)
- ULF (Ultra-low frequency) power : Total NN interval spectral power up to 0.003 Hz. of a **24-h recording**
- VLF (Very Low Frequency) power : Total NN interval spectral power between 0.003 and 0.04 Hz.
- LF (Low Frequency) power : Total NN interval spectral power between 0.04 and 0.15 Hz
- HF (High Frequency) power : Total NN interval spectral power between 0.15 and 0.4 Hz.
- LF/HF ratio : Ratio of low to high frequency power

“Comb” test



Fasting and HRV



Chan JL, Mietus JE, Raciti PM, Goldberger AL, Mantzoros CS. Clin Endocrinol 2007; 66:49-57

Cautions: HRV Dependent On…

- Data length
- Age
- Physical conditioning
- Activity
- Sleep/wake cycle and sleep phase
- Disease
- Drug effects
- Gender
- Posture, etc, etc

Measuring Cardiac Vagal Modulation: pNNx Family of HRV Statistics

- 1984: Ewing et al. introduced the NN50
  - Mean number of times per hour in which the change in successive NN intervals exceeds 50 msec
- 1988: Bigger et al. introduced pNN50
  - NN50 count / total NN count
- 2002: Mietus et al. introduced the pNNx family of statistics
  - NNx count / total NN count for values of $x \geq 0$
  - pNNx for $x < 50$ msec provided more robust discrimination between groups of interest

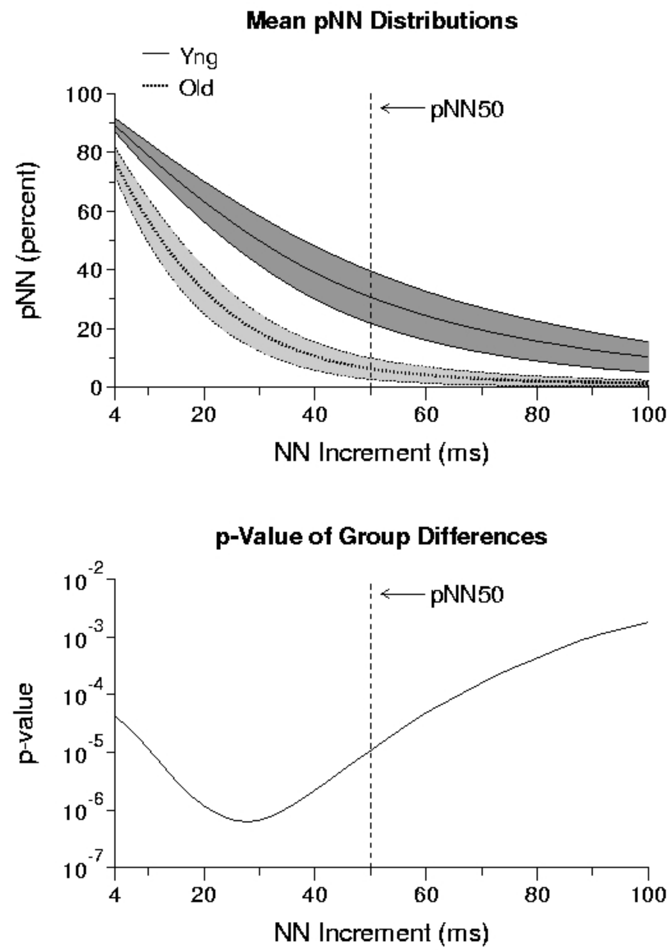
PNNx

pNN distributions for young subjects (n=20, ages 21-34) and old subjects (n=20, ages 68-85)

p-values for the separation of groups <u>(t-test)</u>

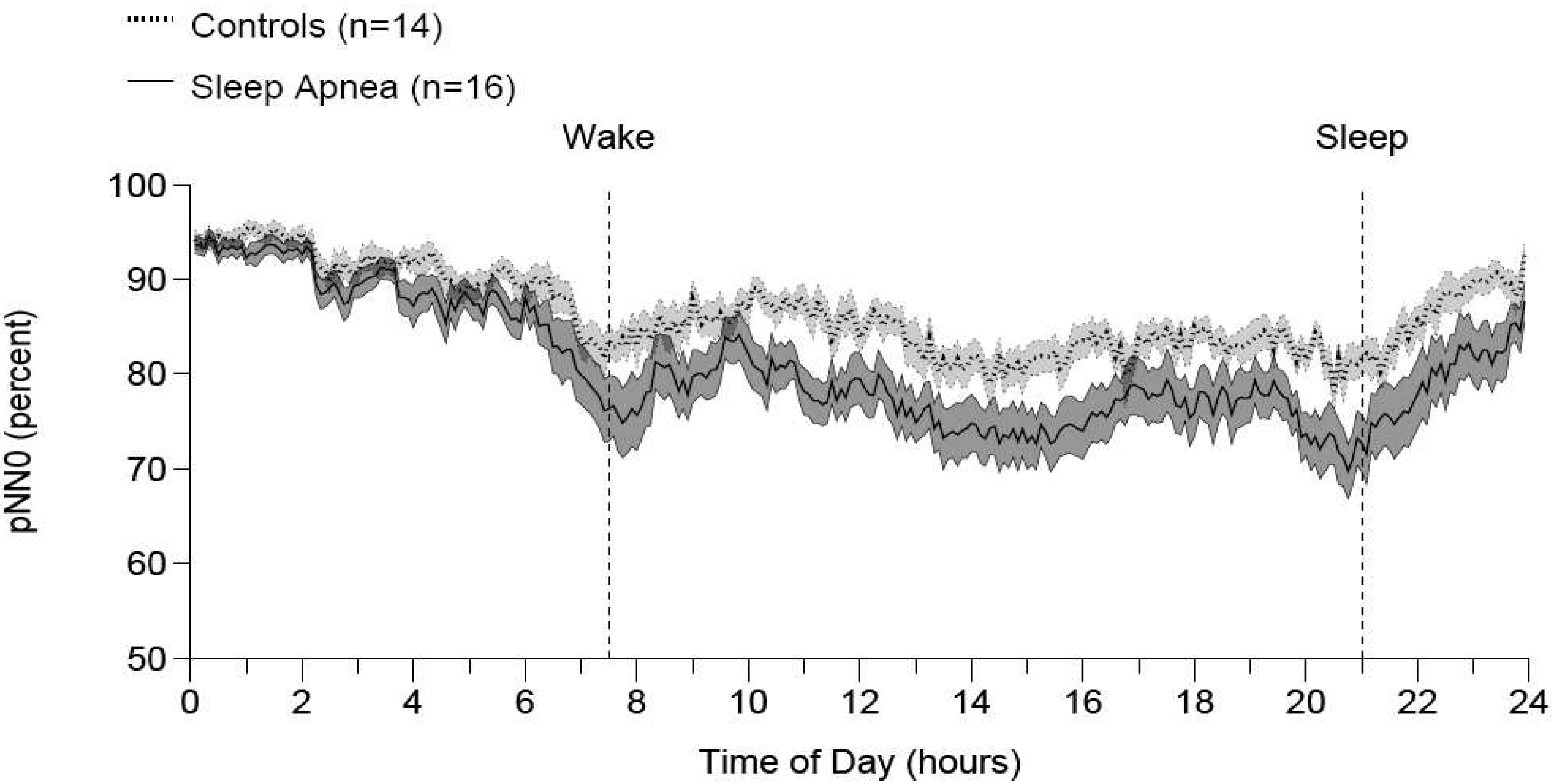
pNN50 : $p<10^{-4}$

pNN28 : $p<10^{-6}$



Data from www.physionet.org

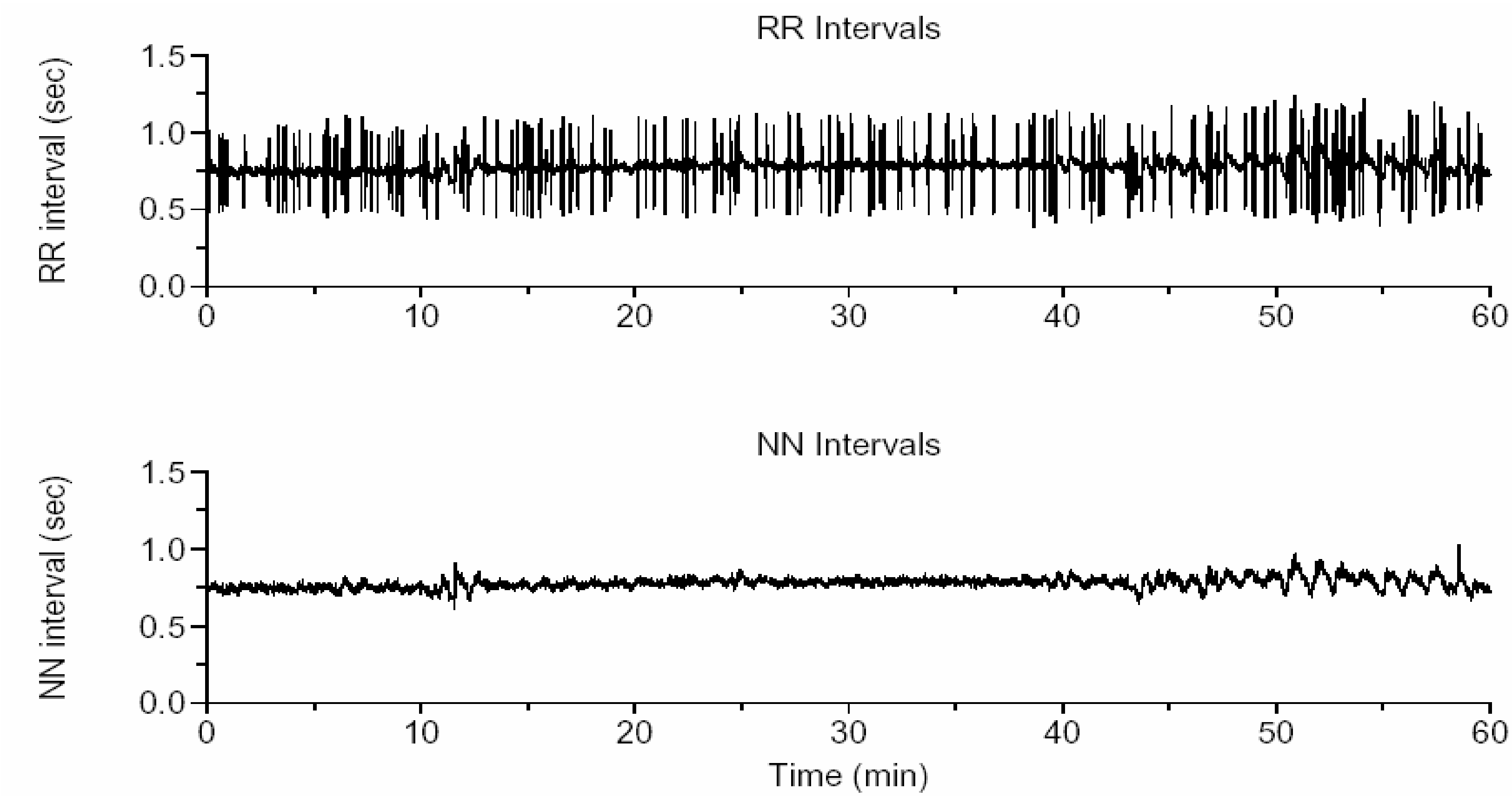
Loss of daytime cardiac vagal modulation in sleep apnea hypopnea syndrome



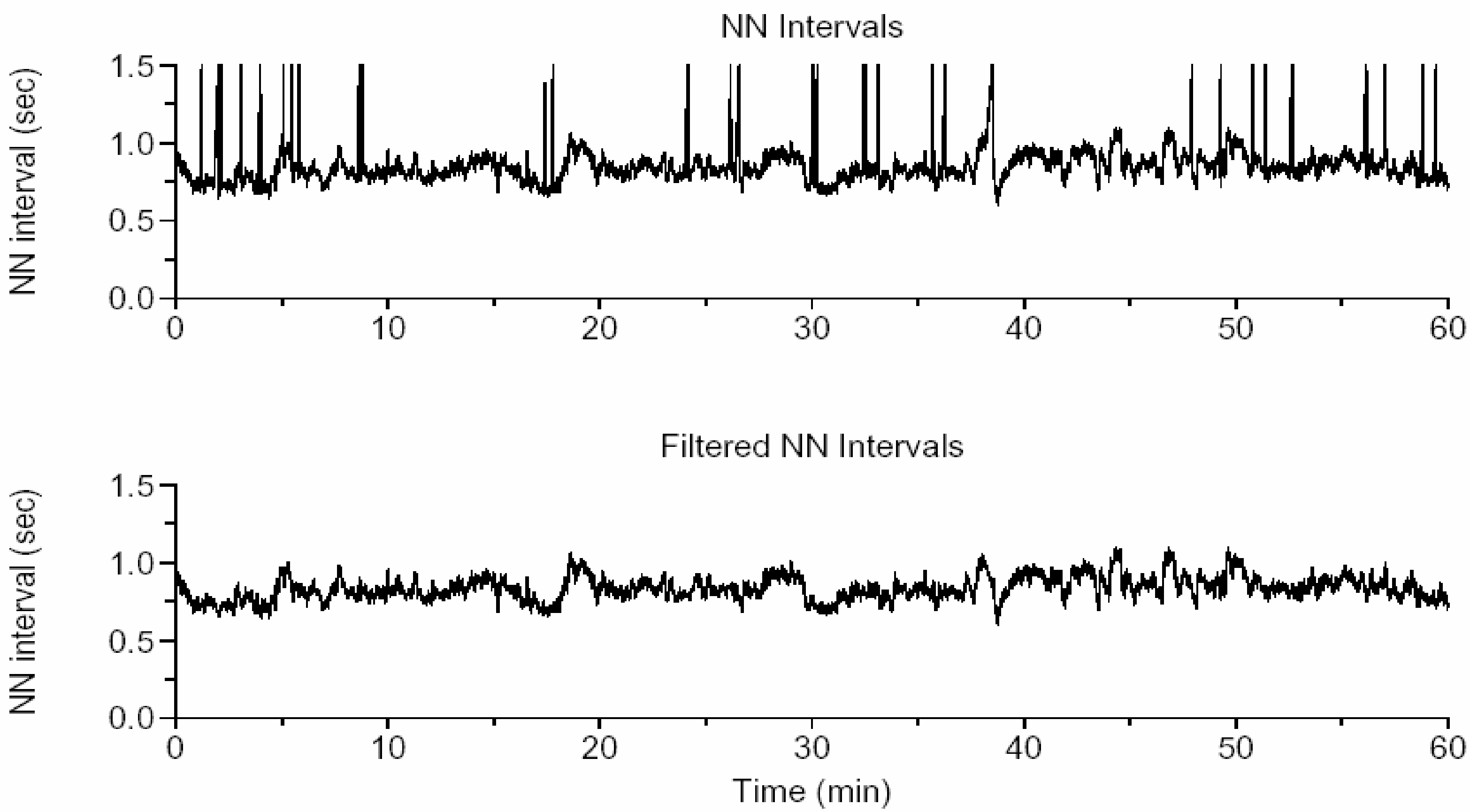
Unpublished data courtesy of Steven Shea and Michael Hilton, Brigham and Women's Hospital

Real world data are messy!

Sinus rhythm time series in the presence of frequent PVCs



Outliers due to missed normal beat detections



Part III

PhysioNet: The NIH Research Resource for Complex Physiologic Signals

NIH Research Resource for Complex Physiologic Signals: *"PhysioNet"*

www.physionet.org

>800,000 visitors to date!

Free Data, Software &Tutorials on Complexity and Fractals

Faces of PhysioNet

1- George Moody
2- Roger Mark
3- Ary Goldberger
4- Mohammed Saeed
5- Mauricio Villarroel
6- C-K Peng
7- Madalena Costa
8- Joe Mietus
9- Gari Clifford

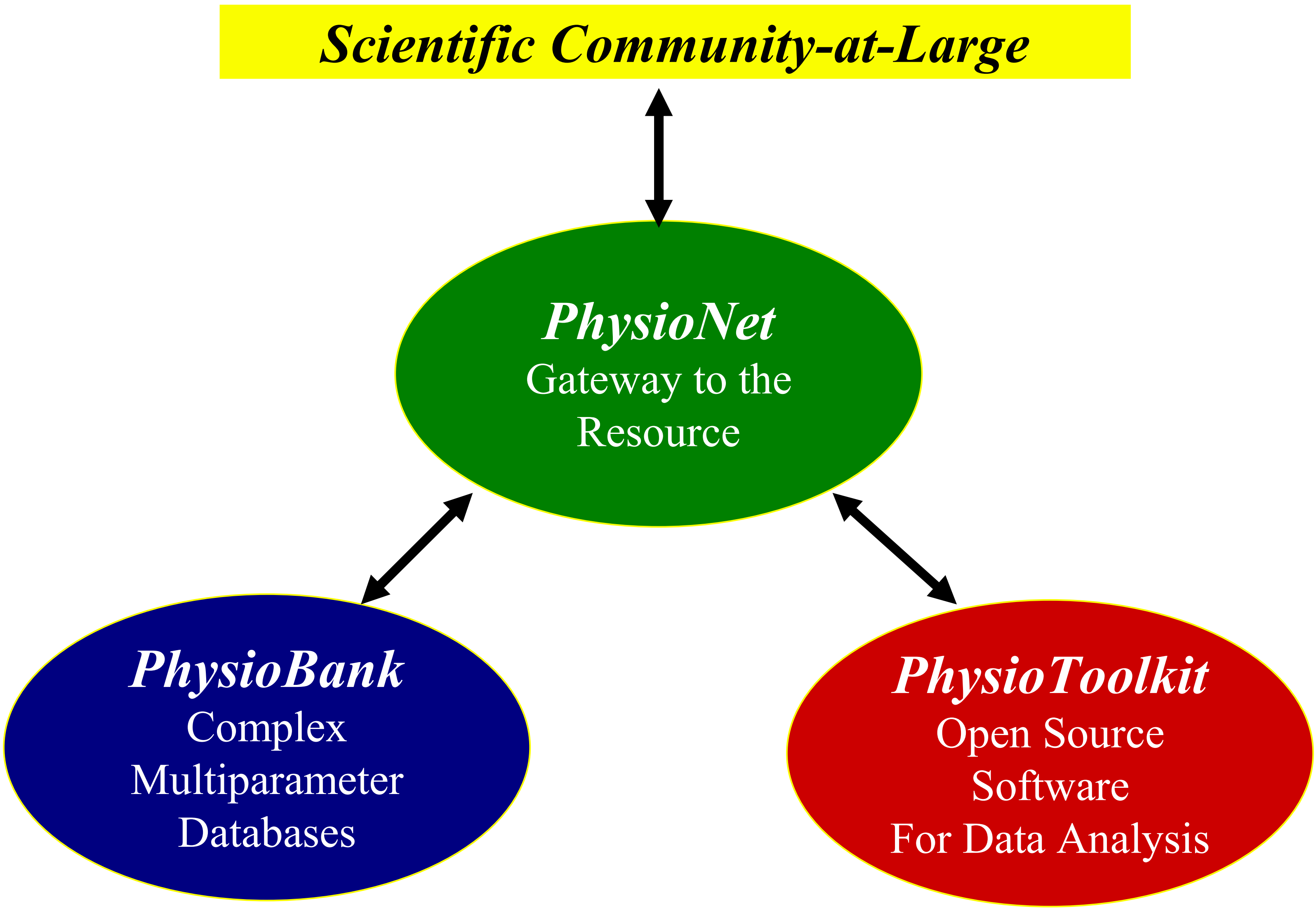
What is PhysioNet?

A unique NIH-funded (NIBIB/NIGMS) web-based resource intended to support current research & stimulate new investigations in the study of complex biomedical and physiologic signals

Three closely interdependent components:

- ❑ Data repository (PhysioBank)
- ❑ Free-access website (physionet.org)
- ❑ Library of related software (PhysioToolkit)

Design of the PhysioNet Website



What is in PhysioBank?

PhysioBank currently includes:

>40 collections of cardiopulmonary, neural, and other biomedical signals from healthy subjects and patients with a variety of conditions with major public health implications, including sudden cardiac death, congestive heart failure, epilepsy, gait disorders, sleep apnea, and aging.

Example of a PhysioBank Dataset

Many data collections in PhysioBank come from published studies

Maturation of gait dynamics: stride-to-stride variability and its temporal organization in children

J. M. HAUSDORFF,[1,2,3] L. ZEMANY,[1] C.-K. PENG,[1,3] AND A. L. GOLDBERGER[1,3]
[1]*Margret H. A. Rey Laboratory for Nonlinear Dynamics in Medicine,* [2]*Gerontology Division and Department of Medicine, Beth Israel Deaconess Medical Center, Boston 02215; and* [3]*Harvard Medical School, Boston, Massachusetts 02115*

Hausdorff, J. M., L. Zemany, C.-K. Peng, and A. L. Goldberger. Maturation of gait dynamics: stride-to-stride variability and its temporal organization in children. *J. Appl. Physiol.* 86(3): 1040–1047, 1999.—In very young children, immature control of posture and gait results in unsteady locomotion. In children of ~3 yr of age, gait appears relatively mature; however, it is unknown whether the dynamics of walking change beyond this age. Because stride dynamics depend on neural control, we hypothesized that motor control would continue to develop beyond age 3. To test this hypothesis, we measured the gait cycle duration on a stride-by-stride basis in 50 healthy 3- to 14-yr-old children (25 girls). Measurements of stride-to-stride variability were significantly larger both in the 3- and 4-yr-old children, compared with the 6- and 7-yr-old children, and in the 6- and 7-yr-old children, compared with the 11- to 14-yr-old children. Measurements of the temporal organization of gait also revealed significant age-dependent changes. The effects of age persisted even after adjusting for height. These findings indicate that mature stride dynamics may not be completely developed even in healthy 7-yr-old children and that different aspects of stride dynamics mature at different ages.

age; walking; spectral analysis; fractal analysis

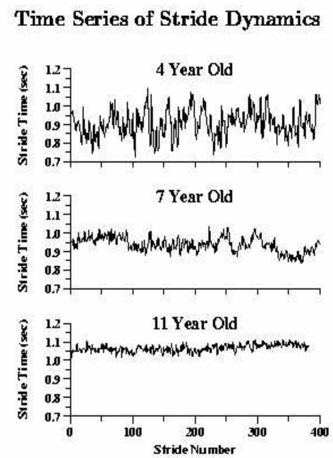
one stride to the next displays a subtle, "hidden" temporal structure that has been associated with long-range, fractal organization (11, 12). In contrast, in persons with neurological disease and in older persons, especially those with a history of falls, stride-to-stride variability increases, and the temporal organization of stride time dynamics is altered as well (3, 4, 7, 8, 10, 14).

These studies suggest that analysis of the stride time dynamics may also provide a window into the development of neuromuscular control in children. Given the apparent parallels between the immature gait of children and the unsteady gait of older persons and persons with neurological impairment (23), along with the subtle continued development of neural control beyond age 3, we hypothesized that stride time dynamics will not be fully matured at this age. In the present study, we tested this hypothesis by measuring stride-to-stride fluctuations in the gait cycle duration of healthy 3- to 14-yr-old children. More specifically, we sought *1*) to characterize the development of mature stride dynamics, *2*) to determine at what ages changes in gait dynamics occur, and *3*) to compare the gait dynamics of

Hausdorff et al., *J Appl Physiol* 86(3)1040-7 (1999)

Gait Maturation Database and Analysis

In very young children, immature control of posture and gait result in an unsteady gait. By about three years of age, gait appears relatively mature. However, it is unknown whether the dynamics of walking change beyond this age. Because stride dynamics depend on neural control, we hypothesized that gait dynamics would continue to develop beyond age three. To test this hypothesis, we measured the gait cycle duration on a stride-by-stride basis in healthy children (n=50) ages 3 to 14 years old, using a portable foot-switch device inserted inside of shoes. The figure on the right shows representative walking time series of 4, 7, and 11-year-old children.



- You are invited to download the complete database (available as a gzip-compressed UNIX tar archive (121K), or as individual files) and perform your own analyses. (WinZip users, please read this important note.)
- A Journal of Applied Physiology article describing an initial analysis of these data can be viewed in HTML format, PostScript format, and PDF format.
- For more information, please contact JM Hausdorff (jhausdorff@caregroup.harvard.edu).

What is PhysioToolkit?

Open-source software for physiologic signal processing and analysis:

- Detection of physiologically significant events using both classical techniques and novel methods
- Interactive display & characterization of signals; creation of new databases
- Physiologic signal modelling and for quantitative evaluation and comparison of analysis methods

Some PhysioNet Contributions Include Both Data and Software

Manuscript

Evaluation of an Automatic Threshold Based Detector of Waveform Limits in Holter ECG with the QT database

R. Jané[1], A. Blasi[1], J. García[2], P. Laguna[2]

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[2]Dep. Ingeniería Electrónica y Comunicaciones, Centro Politécnico Superior. Univ. de Zaragoza, Spain

Abstract

In this paper we evaluate a single-lead threshold based ECG wave boundaries detector with a QT database developed for validation purposes. We also identify its different sources of error distinguishing those that come from precision errors in boundary location from those that come from morphology misclassification. We obtain 71% of records with correct morphology identification ... in boundary location within manual referees variance. The re... ...pond to signals with poor SNR at the T wave, or morphology ... experts.

...n

...nformation can be determined by analyzing significant int... ...Q and others considered of interest. However, it is necess... ...each beat well defined. Automatic methods offer a useful ... diagnostic protocols in ECG signal processing equipment

...nals, as all biomedical signals, have several characteristic... ...r for automatic detectors: noise contaminating the signal ...vell defined waveform morphologies, absence of some wav... ...ppear), ambiguity when defining where the wave boundari... ...be a problem for expert cardiologists), etc. All those difficu... ...lter ECG recordings, due to the non-rest conditions of the

Data

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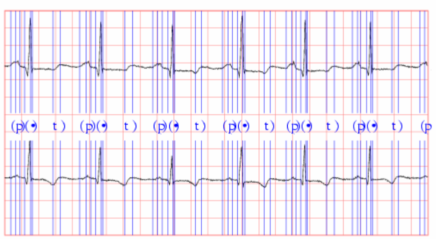
The QT Database



Each of the 105 records consists of a (text) header file, a (binary) signal file, and up to 9 (binary) annotation files, identified by suffix:

Suffix	*Meaning*
.hea	header file, describing signal file contents and format
.dat	signal file
.atr	reference beat annotations from original database (not available in all cases)
.man	reference beat annotations for selected beats only

Software

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Manuals

QRS detection and waveform boundary recognition using ecgpuwave

Name

ecgpuwave - QRS detector and waveform limit locator

Synopsis

ecgpuwave -r *record* **-a** *annotator* [*options* ...]

Description

ecgpuwave analyses an ECG signal from the specified *record*, detecting the QRS complexes and locating the beginning, peak, and end of the P, QRS, and ST-T waveforms. The output of **ecgpuwave** is written as a standard WFDB-format annotation file associated with the specified *annotator*. This file can be converted into text format using **rdann(1)** or viewed using **wave(1)** .

The QRS detector is based on the algorithm of Pan and Tompkins (reference 1) with some improvements that make use of slope information (reference 2). Optionally, QRS annotations

Other Contributions with Data & Software

epl A LETTERS JOURNAL EXPLORING THE FRONTIERS OF PHYSICS

March 2007

EPL, **77** (2007) 68008 www.epljournal.org
doi: 10.1209/0295-5075/77/68008

Noise and poise: Enhancement of postural complexity in the elderly with a stochastic-resonance–based therapy

M. COSTA[1], A. A. PRIPLATA[2,3], L. A. LIPSITZ[2], Z. WU[4], N. E. HUANG[5], A. L. GOLDBERGER[1] and C.-K. PENG[1]

Manuscript

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Noise Enhancement of Sensorimotor Function

Data

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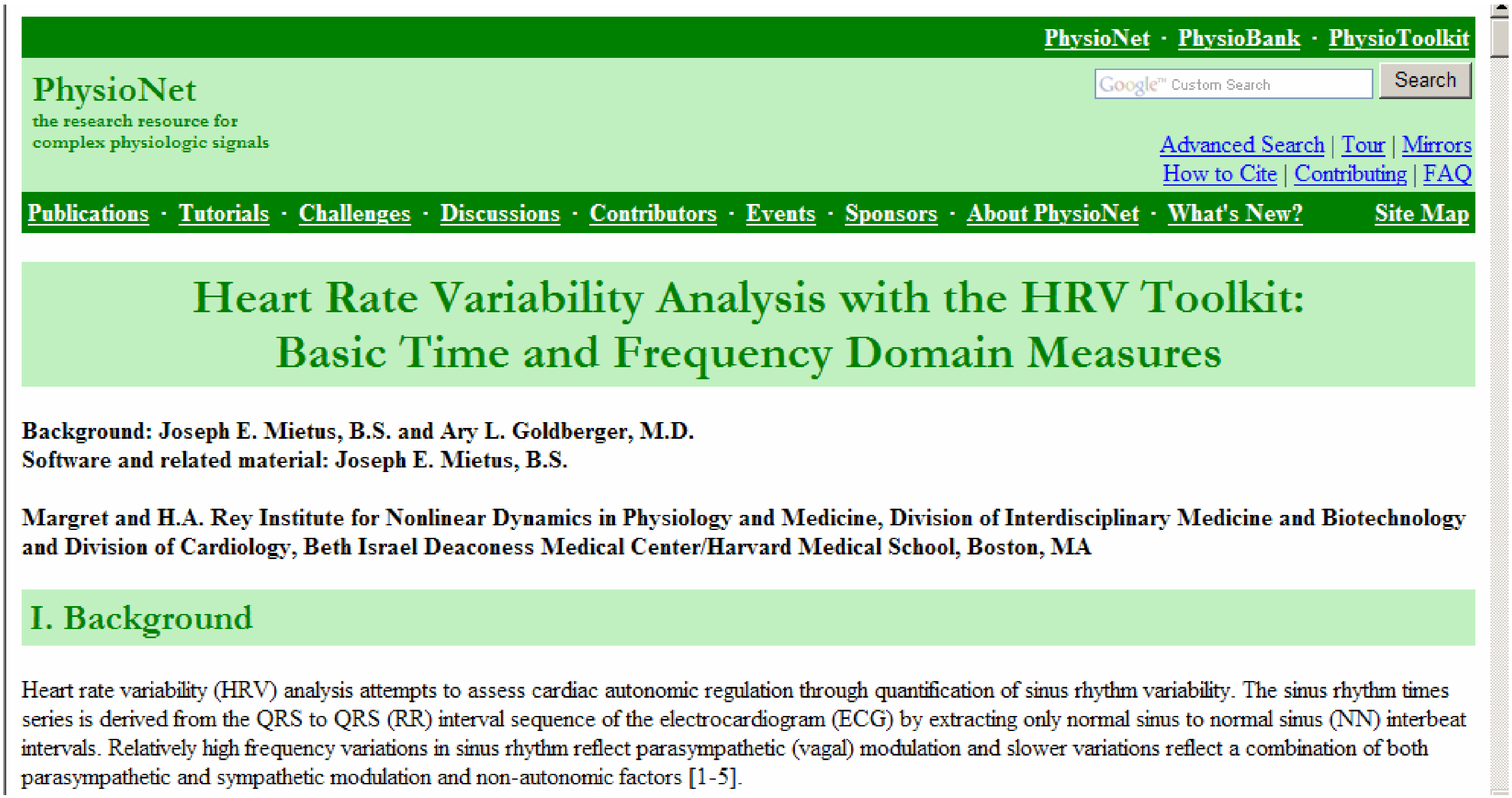
Multiscale Entropy Analysis

Software

Heart Rate Variability Toolkit and Tutorials*



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Heart Rate Variability Analysis with the HRV Toolkit: Basic Time and Frequency Domain Measures

Background: Joseph E. Mietus, B.S. and Ary L. Goldberger, M.D.
Software and related material: Joseph E. Mietus, B.S.

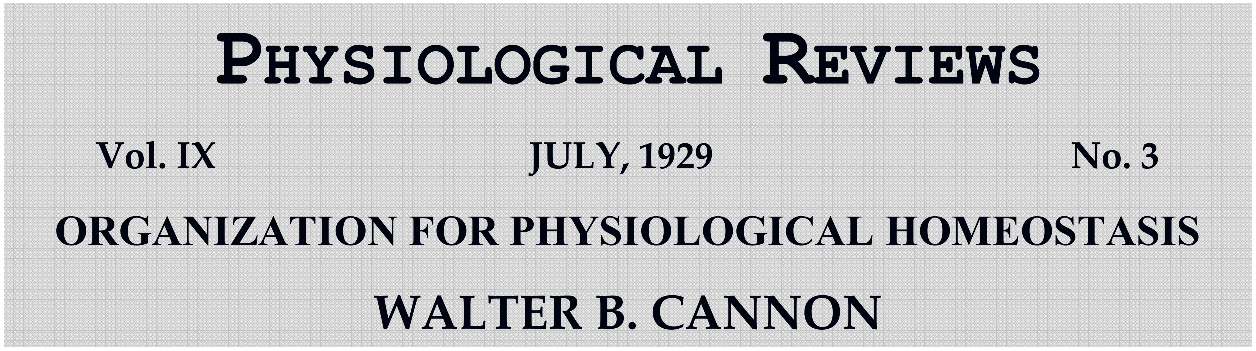
Margret and H.A. Rey Institute for Nonlinear Dynamics in Physiology and Medicine, Division of Interdisciplinary Medicine and Biotechnology and Division of Cardiology, Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, MA

I. Background

Heart rate variability (HRV) analysis attempts to assess cardiac autonomic regulation through quantification of sinus rhythm variability. The sinus rhythm times series is derived from the QRS to QRS (RR) interval sequence of the electrocardiogram (ECG) by extracting only normal sinus to normal sinus (NN) interbeat intervals. Relatively high frequency variations in sinus rhythm reflect parasympathetic (vagal) modulation and slower variations reflect a combination of both parasympathetic and sympathetic modulation and non-autonomic factors [1-5].

*Including discussion of special problems of HRV in elderly

So, Is the Body a Machine?


PHYSIOLOGICAL REVIEWS

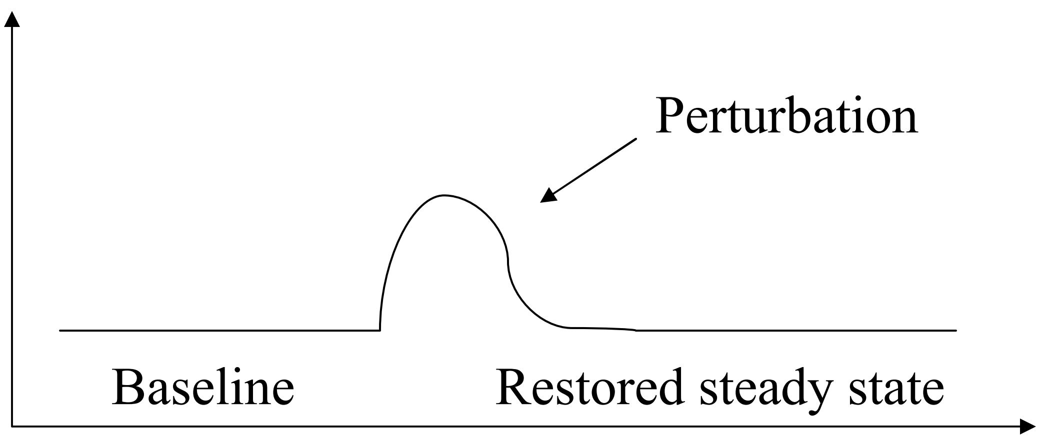
Vol. IX JULY, 1929 No. 3

ORGANIZATION FOR PHYSIOLOGICAL HOMEOSTASIS

WALTER B. CANNON

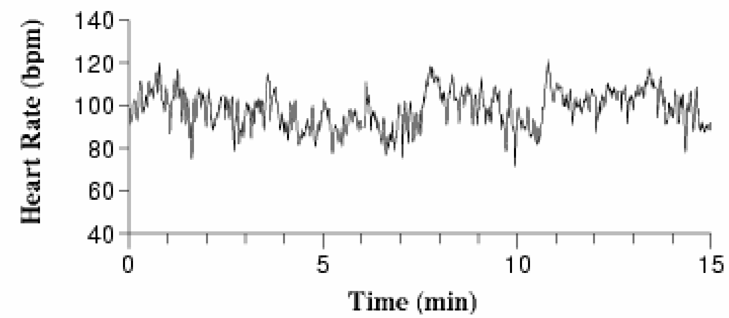
Body as servo-mechanism type machine

- Importance of corrective mechanisms to keep variables "in bounds"
- Notion of "constant," "single steady-state," or equilibrium-like" conditions



…OR

Homeostasis Revisited



...OR

- Is spatio-temporal complexity a *mechanism* of healthy stability?

- And, therefore, do we need fundamentally to rethink all notions of mechanisms and causality in physiology and open search for dynamical biomarkers of aging?

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