

Welcome!

2006 Heart Rate Variability



HRV 2006

Techniques,
Applications
and Future Directions

At
The Fairmont Copley Plaza Hotel
138 St. James Avenue, Boston, MA 02116

Under the direction of
Ary L. Goldberger, MD
George B. Moody
Chung-Kang Peng, PhD

Presented by

 **HARVARD MEDICAL SCHOOL**
Department of Continuing Education

 **BETH ISRAEL DEACONESS MEDICAL CENTER**
Department of Medicine

April 20 - 22 , 2006

Heart Rate Variability

HRV 2006: April, 2006

Overture: Why is Physiologic Variability Important?

Ary L. Goldberger, MD

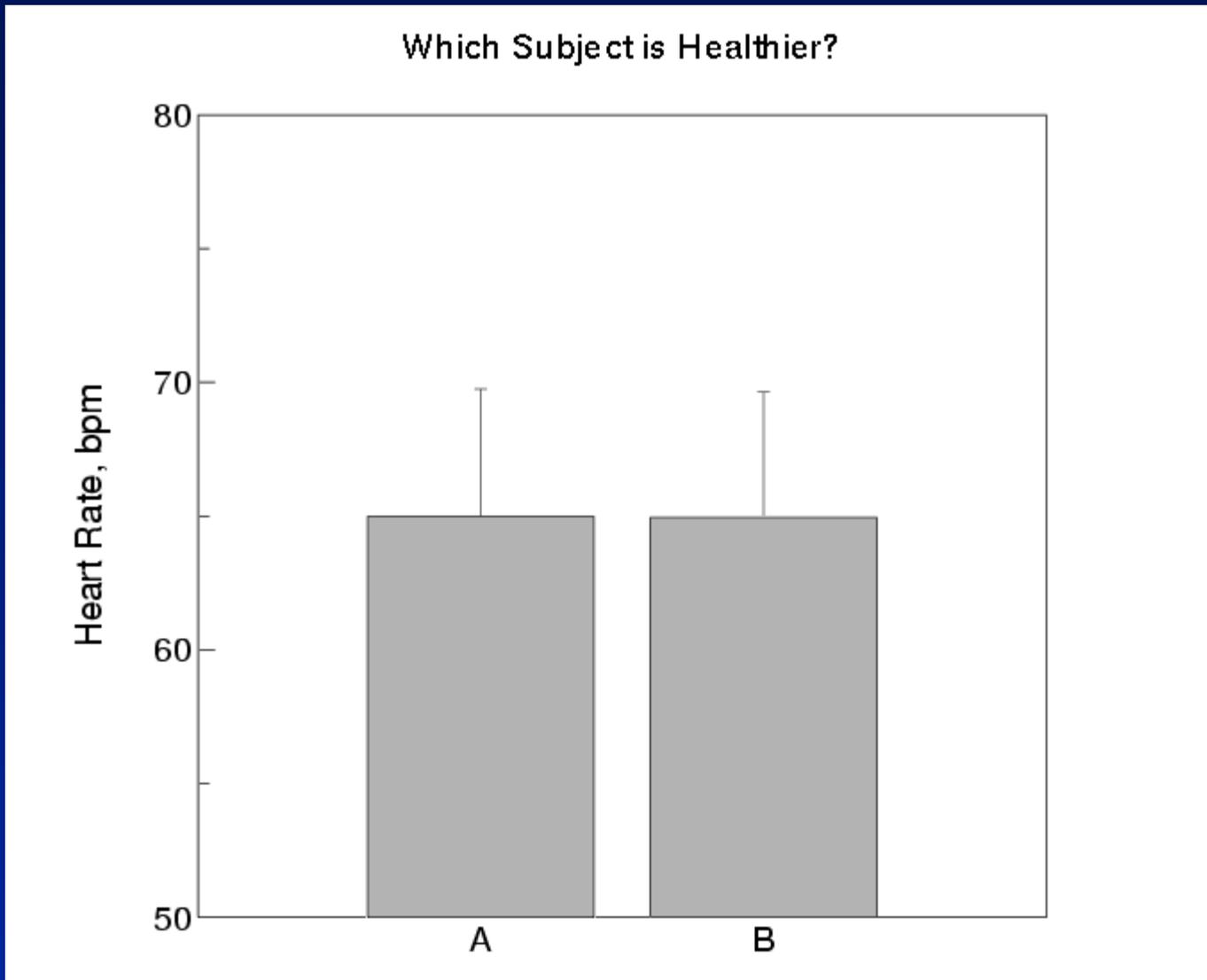
Director, Margret and H.A. Rey Institute for

Nonlinear Dynamics in Medicine

Beth Israel Deaconess Medical Center

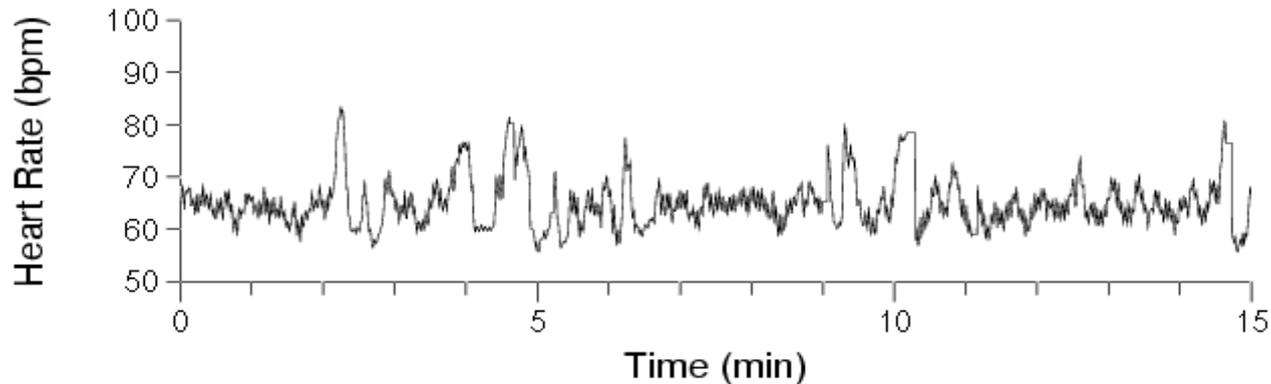
Harvard Medical School

Another Quiz: Which is the Healthier Subject?



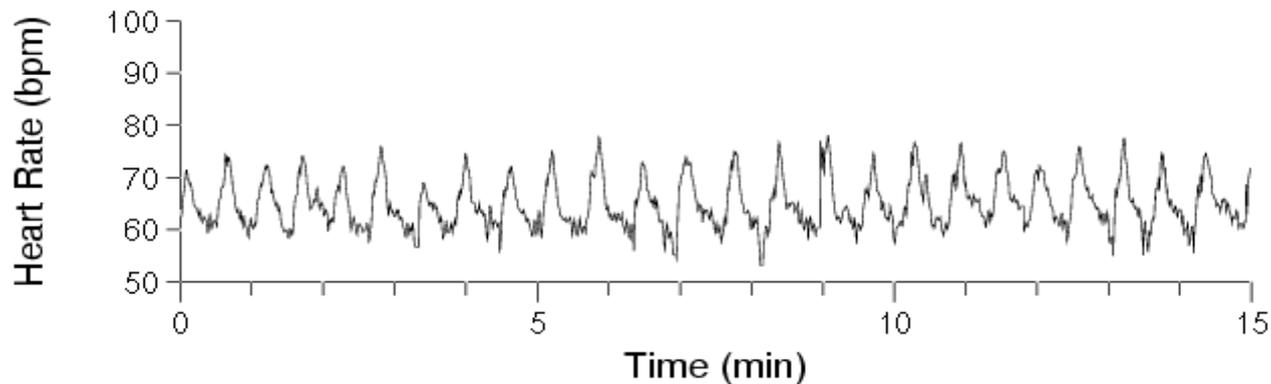
Variability vs. Complexity: Beyond ANOVA

A: Mean 65.0 SD = 4.8



Healthy

B: Mean 65.0 SD = 4.7

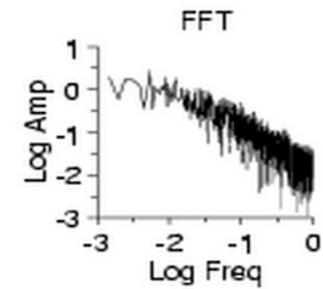
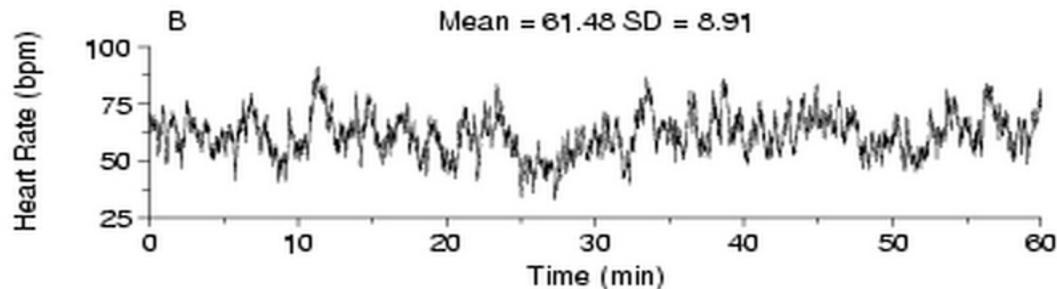
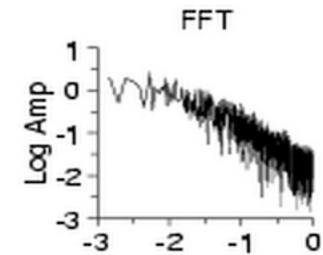
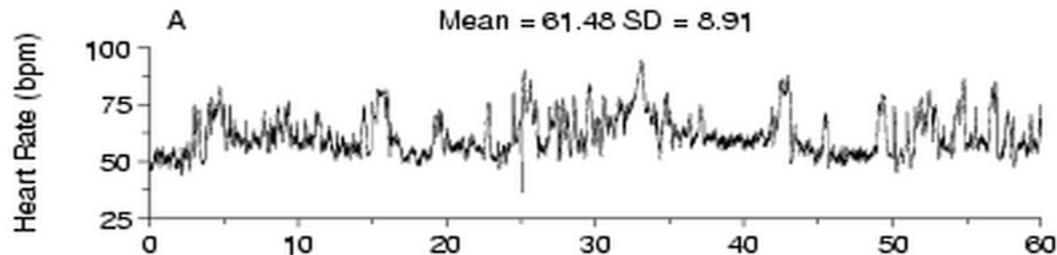


Sleep Apnea

- 1) Which is the healthy signal? &
- 2) What is the clinical diagnosis in the other case?

Extra Credit!

Which is the Physiologic Time Series?



Which is the physiologic time series?

Answer: Top One

1. Physiologic signals are the most complex in nature
3. Important basic/clinical information is “hidden” (encoded) in these fluctuations
5. Complexity degrades with pathology/aging

The often “noisy” variability actually is the signal and represents the nonlinear signaling mechanisms

Is the Body a Machine?

PHYSIOLOGICAL REVIEWS

Vol. IX

JULY, 1929

No. 3

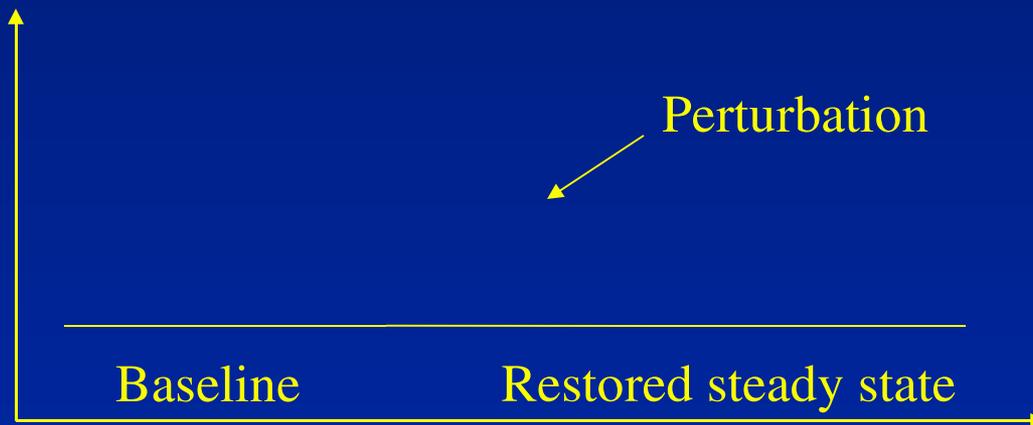
ORGANIZATION FOR PHYSIOLOGICAL HOMEOSTASIS

WALTER B. CANNON



Body as servo-mechanism type machine

- Importance of corrective mechanisms to keep variables “in bounds.”
- Underlying notion of “constant,” “single steady-state,” equilibrium-like” conditions.



...OR

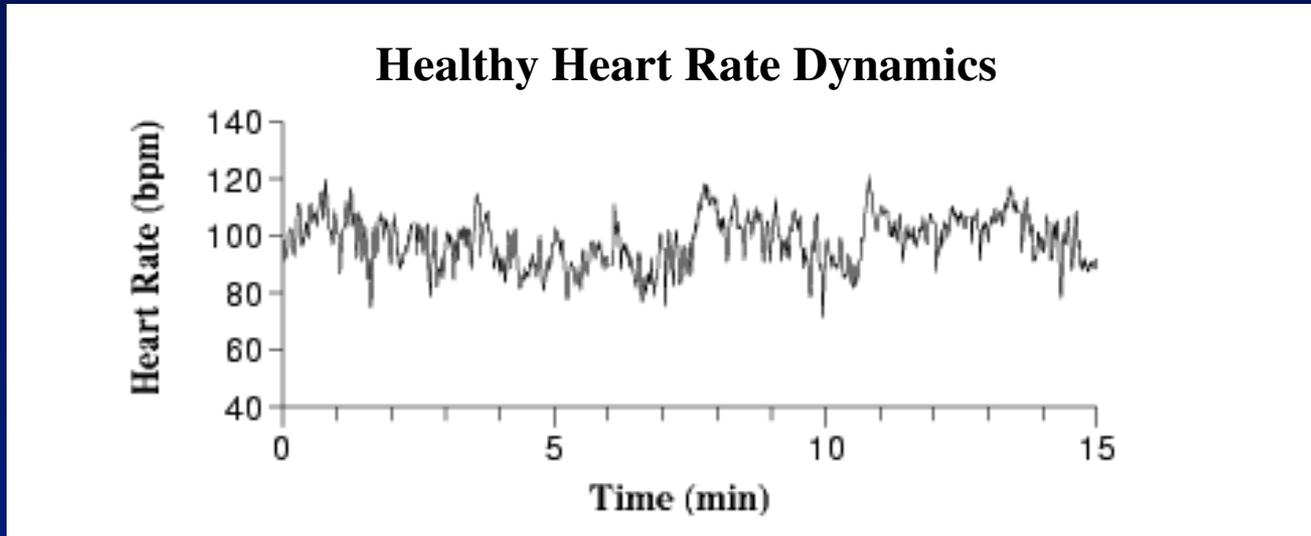
Homeostasis Revisited

...OR

Is complex spatio-temporal variability a *mechanism* of healthy stability?

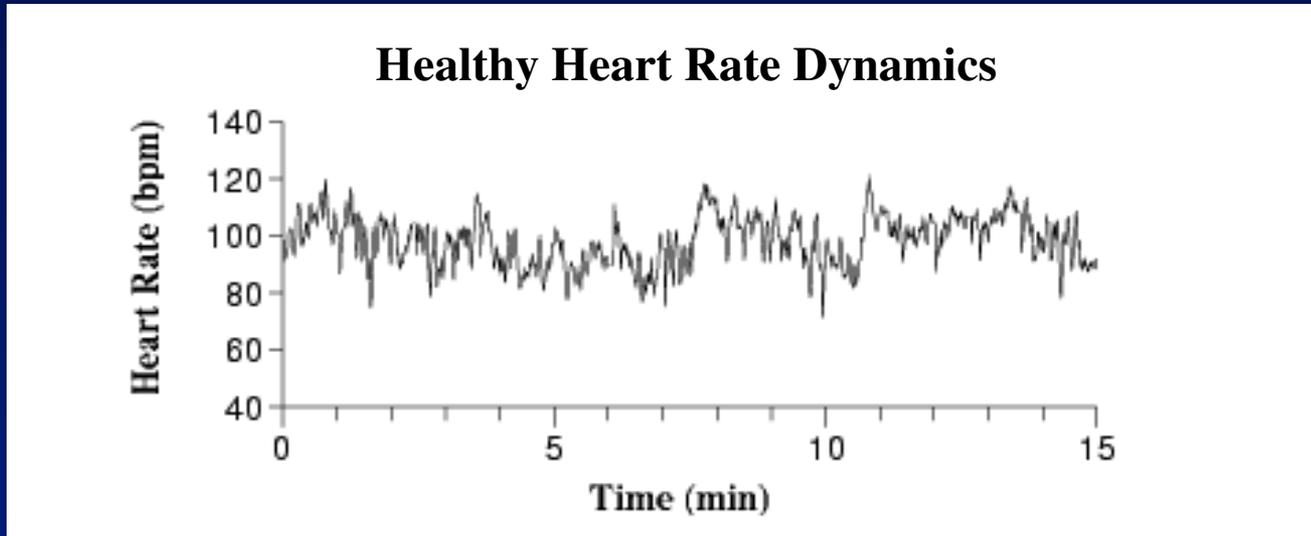
And, therefore, do we need fundamentally to rethink all notions of mechanisms and causality in physiology

Some Hallmarks of Healthy Complexity



- Nonstationarity
 - *Statistics change with time*
- Nonlinearity
 - *Components interact in unexpected ways (“cross-talk”)*
- Multiscale Organization
 - *Fluctuations/structures may have fractal organization*
- Time Irreversibility
 - *Fluctuations related to nonequilibrium dynamics*

Three “Nons” of Complexity



- **Nonstationarity**
 - *Statistics change with time*
- **Nonlinearity**
 - *Components interact in unexpected ways (“cross-talk”)*
- **Multiscale Organization**
 - *Fluctuations/structures may have fractal organization*
- **Time Irreversibility**
 - *Nonequilibrium dynamics underlie fluctuations*

Is Your World Linear or Nonlinear?

- **Linear Process:**

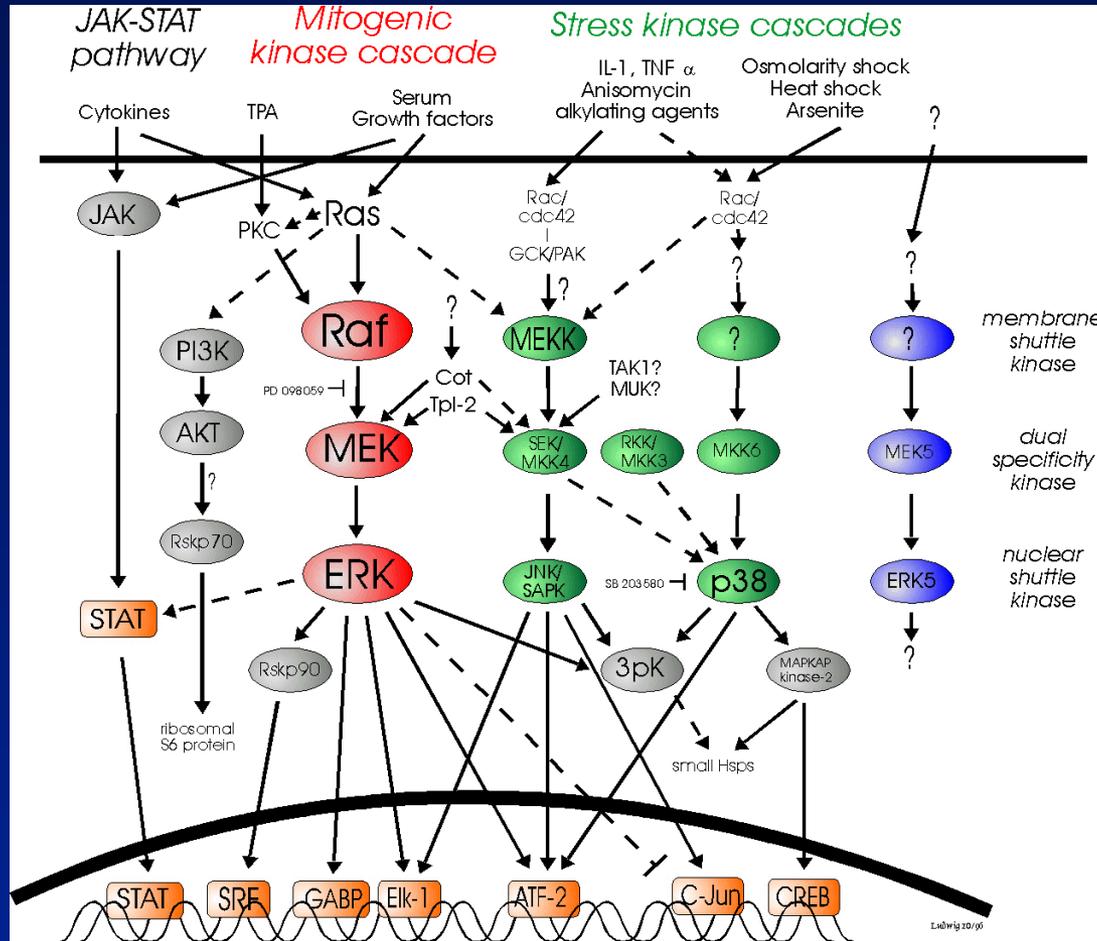
- Simple rules \rightarrow simple behaviors
- Things add up
- Proportionality of input/output
- High predictability, no surprises



- **Nonlinear Process:**

- Simple rules \rightarrow complex behaviors
- Small changes may have huge effects
- Low predictability & anomalous behaviors
- Whole \neq sum of parts (“emergent” properties)

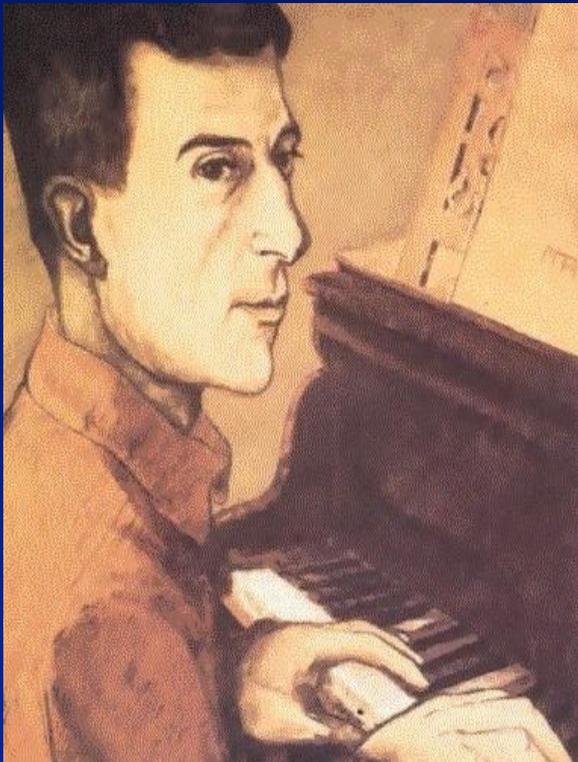
So Then, What's Wrong with this General Type of Signal Transduction Picture?



Answer: No feedback; No nonlinearity
 Complicated! but ...*Complex* dynamics missing!

Complex vs Complicated

“ ... Complex,” said Maurice Ravel, about his own artistic aims, “never complicated.”



51

A page of musical notation for piano, showing measures 318 through 330. The score is written in G major and 3/4 time. It features complex rhythmic patterns, including sixteenth and thirty-second notes, and dynamic markings such as *pp*, *dim.*, and *mf*. The notation includes various ornaments and phrasing slurs, illustrating the 'complex' nature of Ravel's style.

*** Danger ***

Linear Fallacy: Widely-held assumption that biological systems can be largely understood by dissecting out *micro-components* or *modules* and analyzing them in isolation.

“Rube Goldberg physiology”

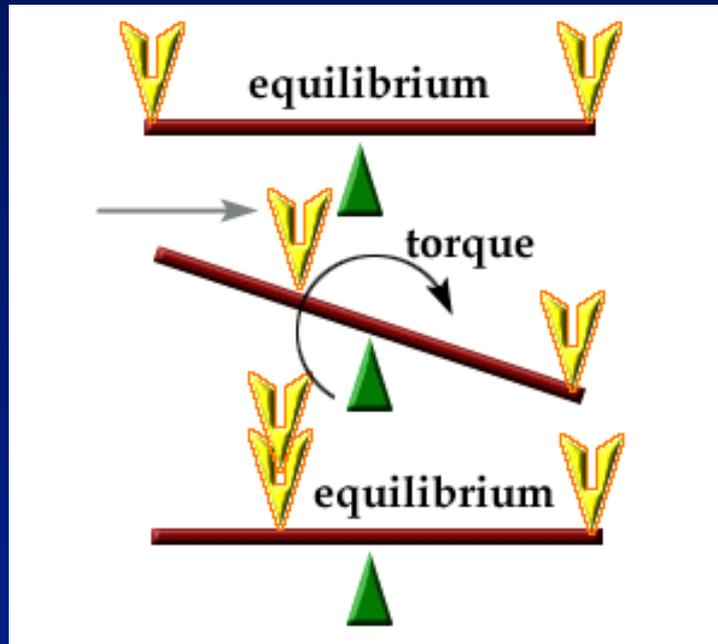


Healthy Dynamics: An Equilibrium State?

Health

Disease

Recovery



Another fallacy. But there is an equilibrium state...
...death

Nonlinear Mechanisms in Physiology

- Bad news: physiology is complex!
- Good news: there are certain general mechanisms that do not depend on details of system (*universalities*)

Wonderful World of “Hidden”

Complexity/Nonlinear Mechanisms in Physiology

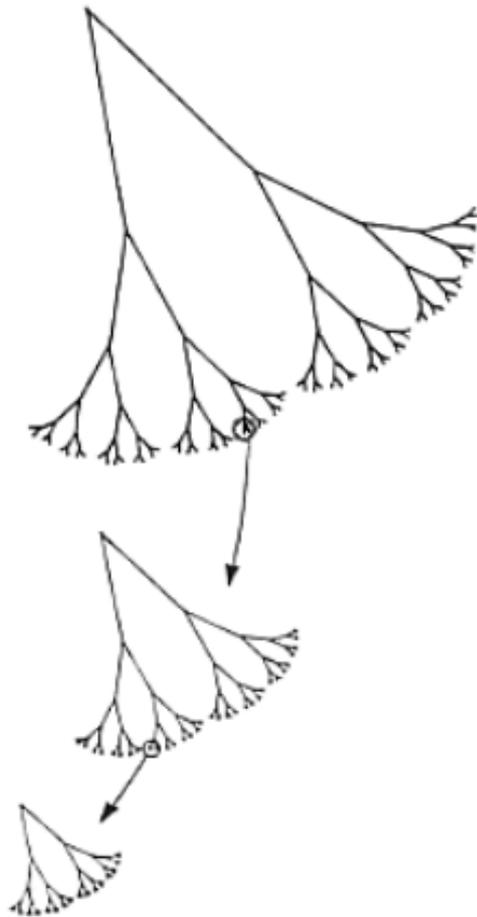
- Bifurcations
- Nonlinear oscillations
- Deterministic chaos
- Time asymmetry
- Fractals
- Nonlinear waves: spirals/scrolls/solitons
- Stochastic resonance
- Complex networks
- Hysteresis
- Emergence



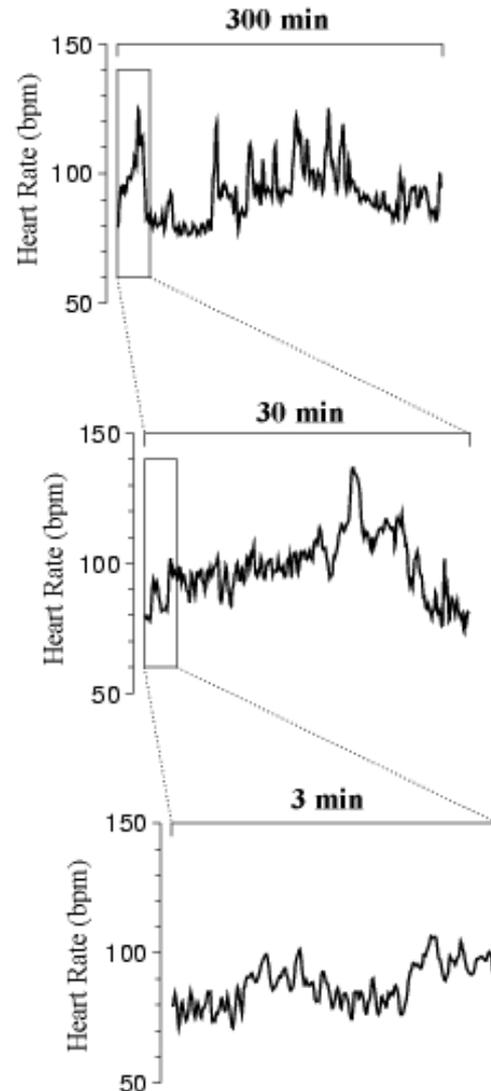
Goldberger et al. PNAS 2002 99 Suppl. 1: 2466-2472.

Are there Fractal Processes in Biology?

Self-Similar Structure



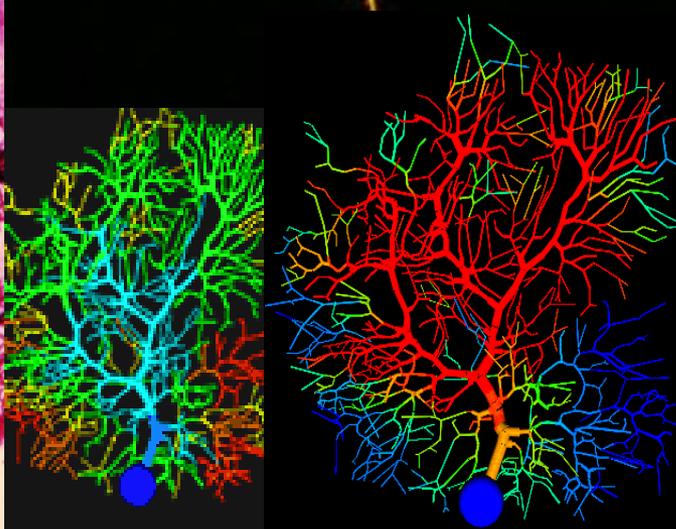
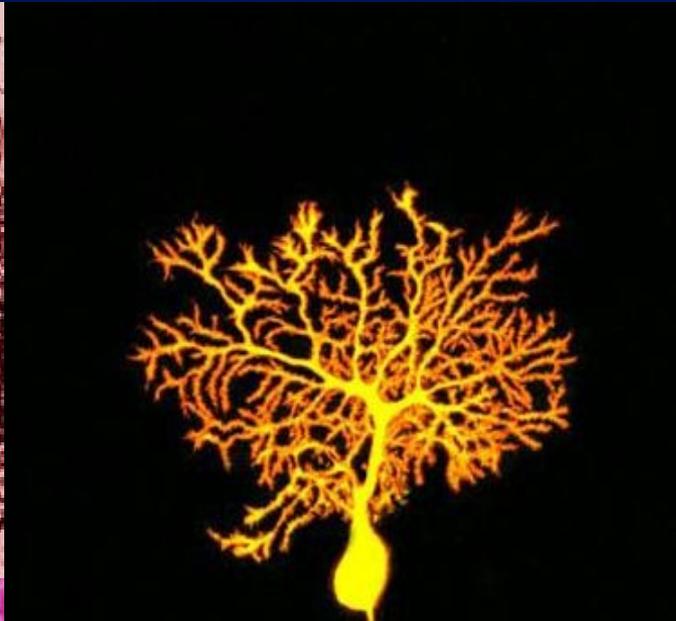
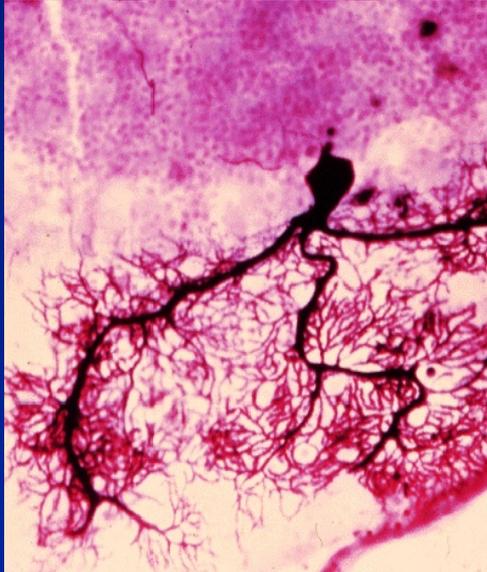
Self-Similar Dynamics



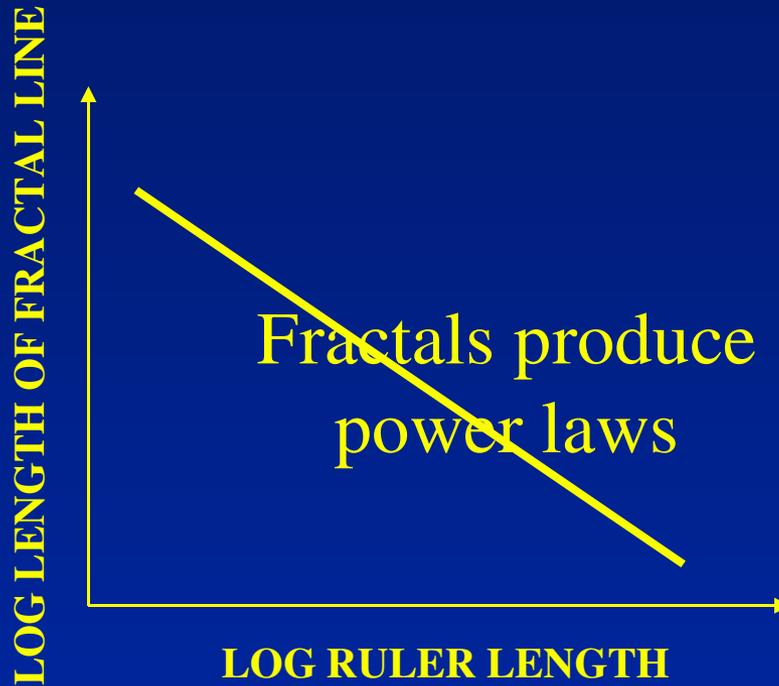
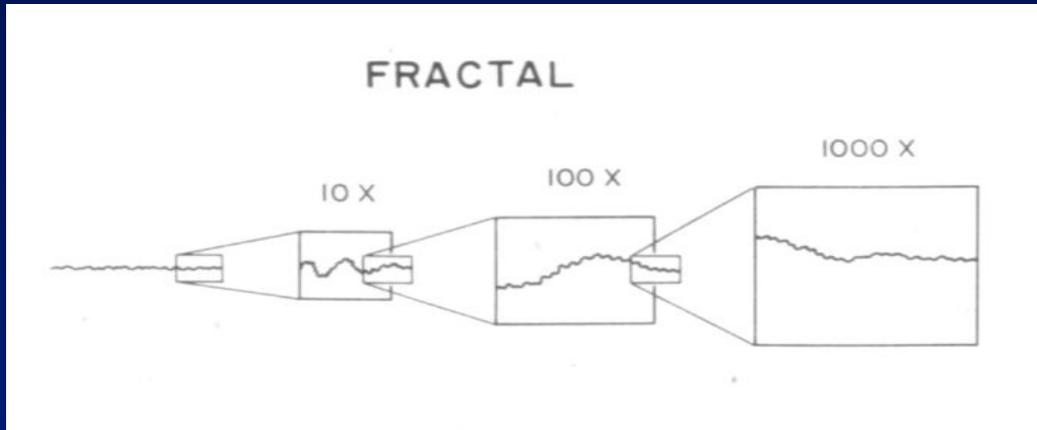
Fractal: A tree-like object or **process**, composed of sub-units (and sub-sub-units, etc) that resemble the larger scale structure

Self-similarity (scale invariance), therefore, may be a property of dynamics as well as structure

Fractals and Information Transmission: Purkinje Cells in Cerebellum

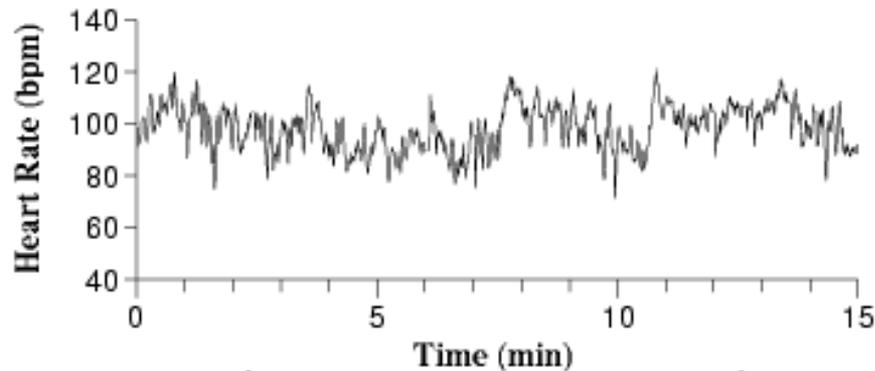


Fractals and Power Laws

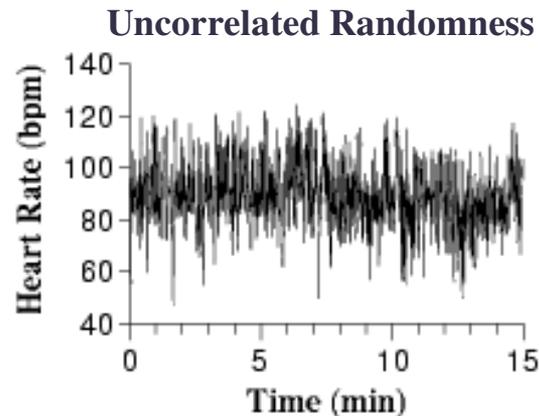
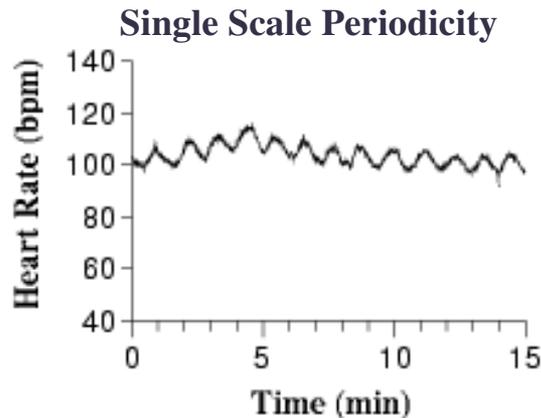


Fractal Complexity Degrades with Disease

Healthy Dynamics: Multiscale Fractal Variability



*Two Patterns of
Pathologic Breakdown*



*Healthy dynamics
poised between too
much order and total
randomness.*

*But randomness is
not chaos!*

Nature 1999; 399:461

Phys Rev Lett 2002; 89 : 068102

Loss of Complexity/Information with Disease

- The output of physiologic systems often becomes more regular and predictable with disease
- The practice of medicine not possible without such predictable behaviors – doctors look for characteristic patterns: *principle of stereotypy*
- Healthy function: multi-scale, information-rich dynamics much harder to characterize!

Loss of Fractal Complexity Resolves Medical Paradox

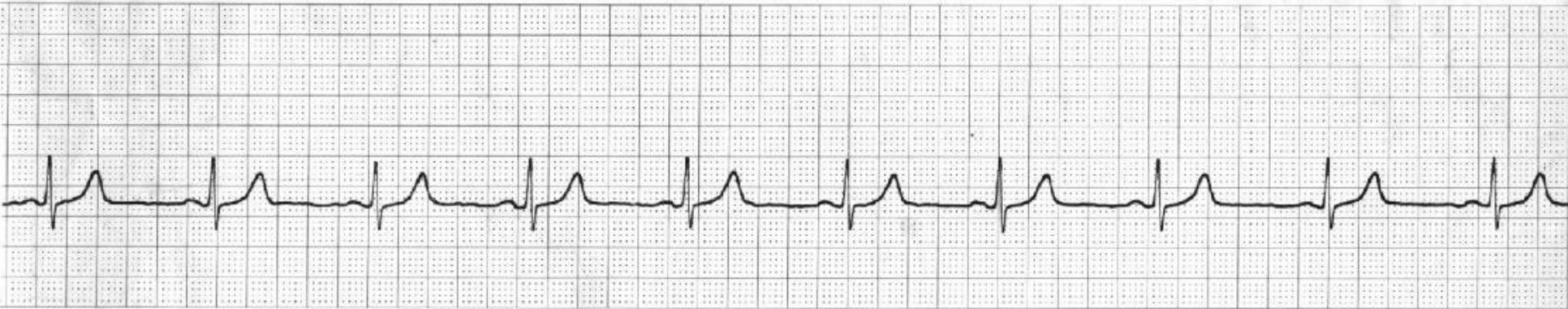
Patients with wide range of disorders/syndromes often display strikingly predictable (ordered) dynamics: Reorder vs. Disorder

Examples:

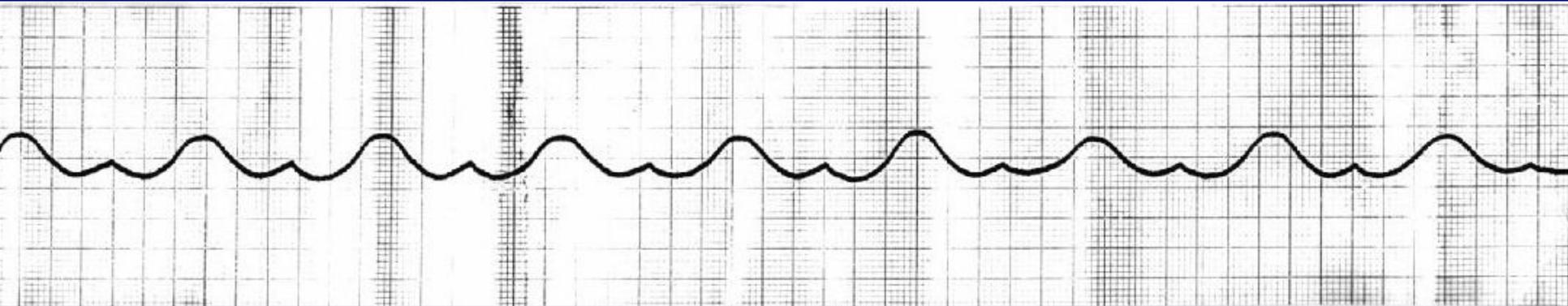
- Cheyne-Stokes breathing
- Obstructive sleep apnea
- Parkinsonism / Tremors
- Obsessive-compulsive behavior
- Nystagmus
- Monomorphic ventricular tachycardia
- Torsades de pointes
- Hyperkalemia → “Sine-wave” ECG
- Cyclic neutropenia
- Cyclic flow reductions in arterial stenosis

Loss of Complexity in Dying Heart

Normal Heart



Dying Heart



1 sec.

Measuring Complexity Loss

Many (!) algorithms and approaches

- Time and frequency domain
- Fractal/multifractal
- Entropy-related
- Time irreversibility
- Coupling/synchronization

What are Origins of this Complexity

Likely a challenge of the century!

Involving models/”mechanisms” with:

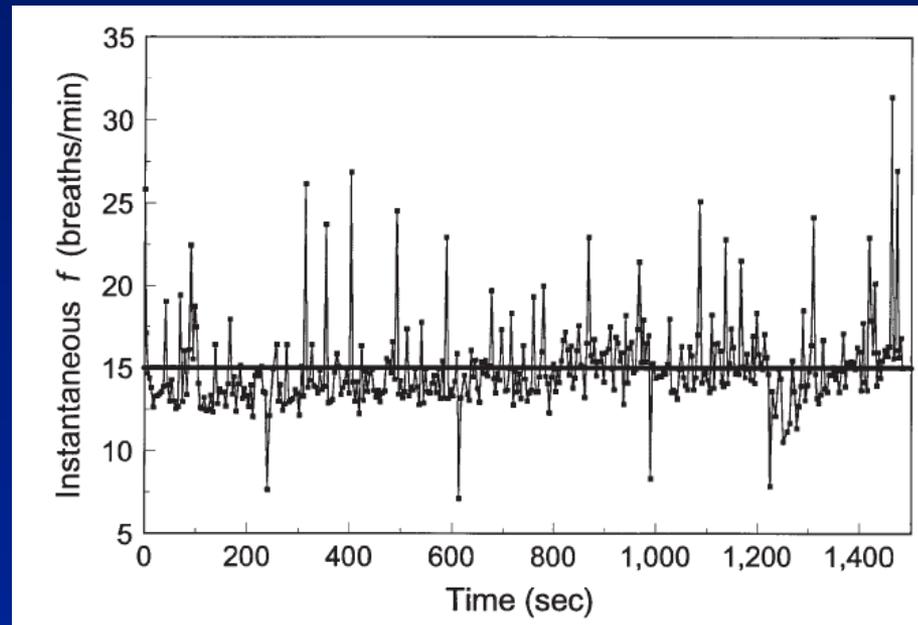
- Multiscale nonlinear interactions
- Emergent phenomena
- Nonequilibrium dynamics

Is Complex Variability Therapeutic?

Biologically Variable or Naturally Noisy Mechanical Ventilation Recruits Atelectatic Lung

W. ALAN C. MUTCH, STEFAN HARMS, M. RUTH GRAHAM, STEPHEN E. KOWALSKI, LINDA G. GIRLING,
and GERALD R. LEFEVRE

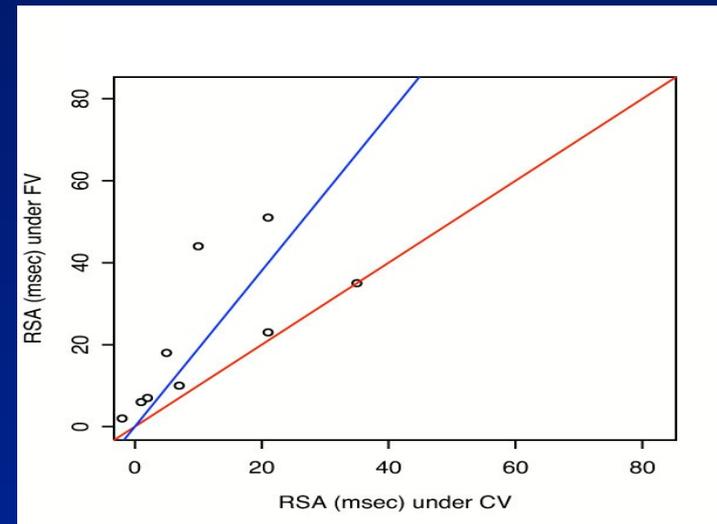
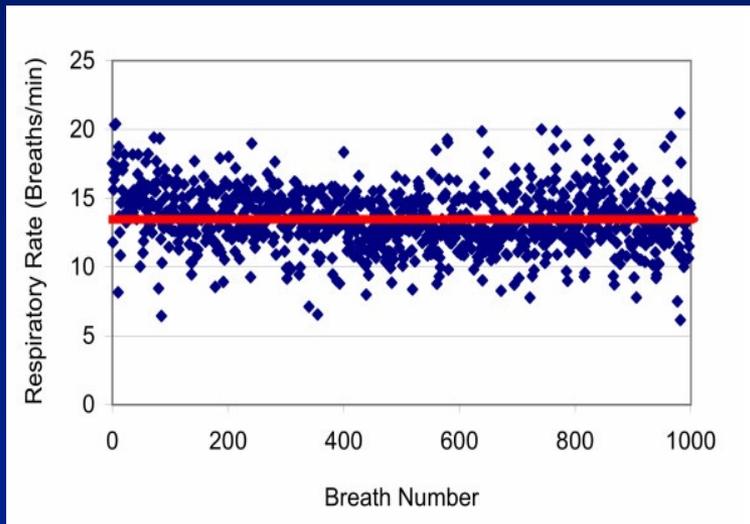
Department of Anaesthesia and Neuroanaesthesia Research Laboratory, Faculty of Medicine, University of Manitoba,
Winnipeg, Manitoba, Canada



Am J Respir Crit Care Med 2000; 162: 319

Therapeutic Fractal Variability?

Fractal ventilation enhances respiratory sinus arrhythmia



Mutch WAC et al. Respiratory Research 2005; 6: 41

Conclusions:

Physiologic Variability is Important!

- Insights into underlying physiologic (nonlinear) control mechanisms
- Dynamical biomarkers of pathology and aging
- Basis for novel stochastic resonance/complex variability-based therapies

HRV 2006: Invitation to Reinvigorate Field: Provocations, Queries and Working Themes

- The HRV “gap”: thousands of publications but still no direct bedside clinical application of traditional HRV in adult ICU/CCU or ward practice. Most clinicians have likely not heard of HRV.
- Is traditional HRV analysis too nonspecific and too (epi)-phenomenologic to be clinically useful?
- What does HRV teach about basic physiology and signaling?
- Are nonlinear dynamics/multiscale complexity analysis/fractals essential to understanding HRV or just a trendy affectation?

HRV 2006 Themes and Challenges (Con't)

- What are pitfalls and limitations of traditional & newer modes of analysis? Can you rely on “off the shelf” programs?
- Has HRV analysis ignored hidden information in ectopic beat dynamics: a post-CAST “syndrome”? Are PVCs “dark matter” of HRV universe?
- What are cutting-edge current and future areas of HRV and related analyses? E.g., Sleep & Chronobiology; Exercise; T-wave alternans and other risk stratification; Autonomic testing; Neonatal sepsis early ID

HRV 2006 Themes and Challenges (Con't)

- How to overcome limitations of Fourier methods for time series that are intrinsically nonstationary
- Importance of looking at original and rawest forms of data (ECG to HRV time series)
- Importance and uses of open-access databases and open-source software. Need for providing such data and software accompanying publications (Beyond PubMed)

Impediments to HRV Progress

- Original datasets have been largely unavailable or incompletely documented
- Original signal data are often discarded
- Investigators often use different, undocumented software tools on different databases



“ Babel-ography ”

NCRR Research Resource for Complex Physiologic Signals “PhysioNet”

The screenshot shows a web browser window titled "PhysioNet: Research Resource for Complex Physiologic Signals". The browser's menu bar includes "File", "Edit", "View", "Web", "Go", "Bookmarks", "Tabs", and "Help". The website header features a green navigation bar with links for "PhysioNet", "PhysioBank", and "PhysioToolkit". Below this, the "PhysioNet" logo is displayed in green, followed by the tagline "the research resource for complex physiologic signals". A search bar with a "Search" button is located on the right. Further right, there are links for "Advanced Search", "Tour", "Mirrors", "How to Cite", "Contributing", and "FAQ". A secondary green navigation bar contains links for "Publications", "Tutorials", "Challenges", "Discussions", "Contributors", "About PhysioNet", and "What's New?", along with the NCRR logo. The main content area contains a paragraph: "PhysioNet offers free access via the web to large collections of recorded physiologic signals and related open-source software. PhysioNet is a public service of the [Research Resource for Complex Physiologic Signals](#), funded by the [National Center for Research Resources](#) of the [National Institutes of Health](#)." To the right of this text is a banner for the "National Center for Research Resources" at the "National Institutes of Health". Below the main text, a note says: "If this is your first visit, please try [PhysioTour](#), a brief introduction to this site."

www.physionet.org

500,000+ visits to date

>4 terabytes of data downloaded!

Software/Tutorials for Data Analysis

The screenshot shows the Entrez-PubMed interface. The search bar contains the text "1: Chaos, 1995;5(1):82-7." The search results list a paper titled "Quantification of scaling exponents and crossover nonstationary heartbeat time series." by Peng CK, Havlin S, Stanley HE, and Goldberger AL. The abstract text is partially visible, discussing the regulation of the heartbeat and the application of detrended fluctuation analysis (DFA).

The screenshot shows the PhysioToolkit website. The page title is "Detrended Fluctuation Analysis (DFA)". The page includes a navigation bar with links for "PhysioNet", "PhysioBank", and "PhysioToolkit". The main content area contains the title "Detrended Fluctuation Analysis (DFA)" and a paragraph describing the method, citing Peng C-K, Buldyrev SV, Havlin S, Simons M, Stanley HE, and Goldberger AL. The page also includes a "Please cite at least one of the above publications when referencing this material, and also include the standard citation for PhysioNet:" section and a list of authors and their affiliations.

>600 publications citing DFA
~400 since 1999

The method of detrended fluctuation analysis has proven useful in revealing the extent of long-range correlations in time series. Briefly, the time series to be analyzed (with N samples) is first integrated. Next, the integrated time series is divided into boxes of equal length, n . In each box of length n , a least squares line is fit to the data (representing the *trend* in that box). The y coordinate of the straight line segments is denoted by $y_n(k)$.

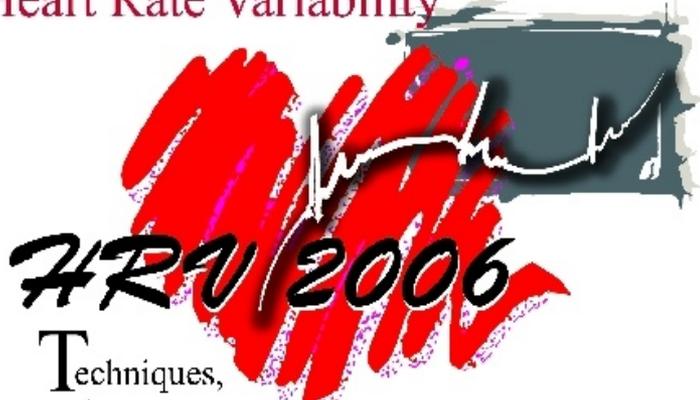
Next, we detrend the integrated time series, $y(k)$, by subtracting the local trend, $y_n(k)$, in each box. The root-mean-square fluctuation of this integrated and detrended time series is calculated by

$$F(n) = \sqrt{\frac{1}{N} \sum_{k=1}^N [y(k) - y_n(k)]^2}$$

This computation is repeated over all time scales (box sizes) to characterize the relationship between $F(n)$, the average fluctuation, as a function of box size. Typically, $F(n)$ will increase with box size n . A linear relationship on a log-log plot indicates the presence of power law (fractal) scaling. Under such conditions, the fluctuations can be characterized by a scaling

So Welcome to HRV 2006!

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