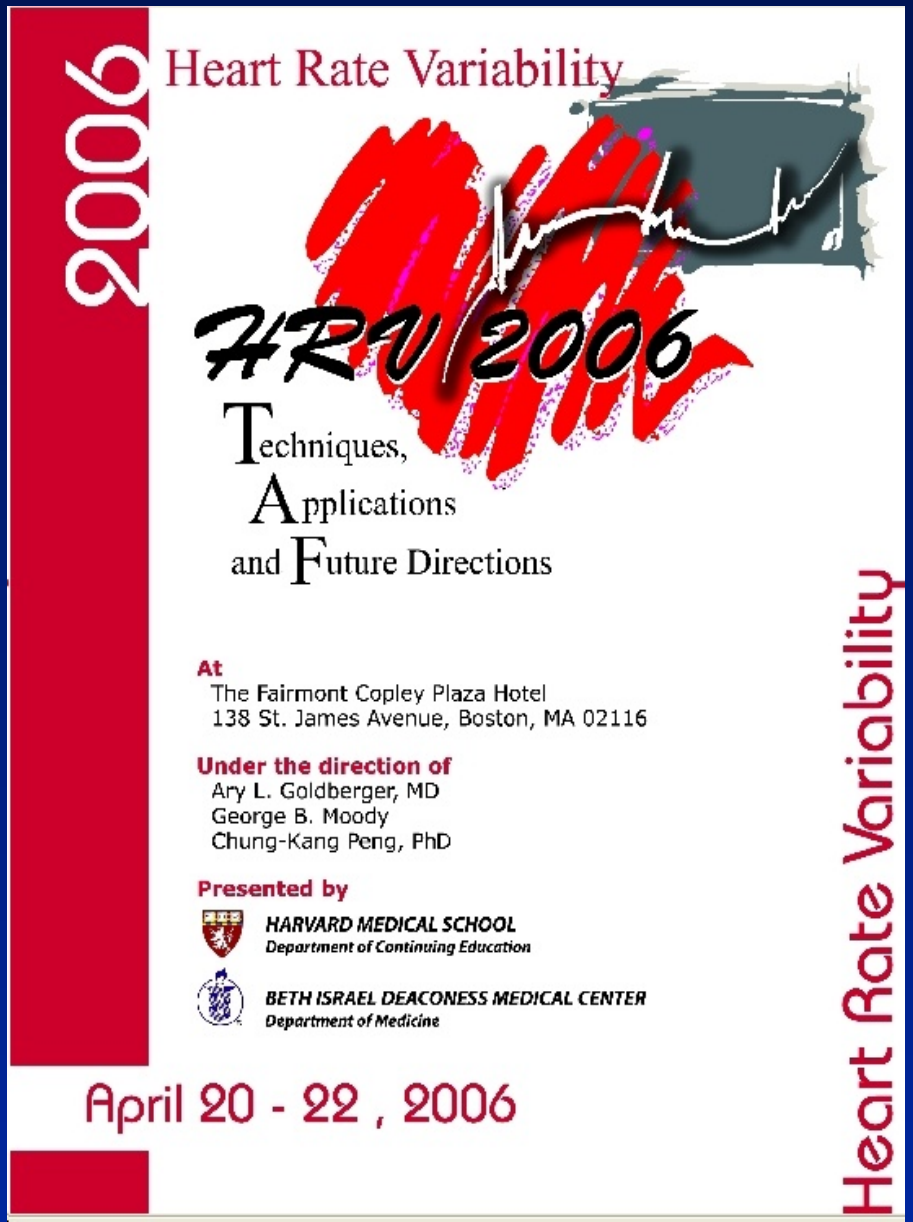
Welcome!


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?

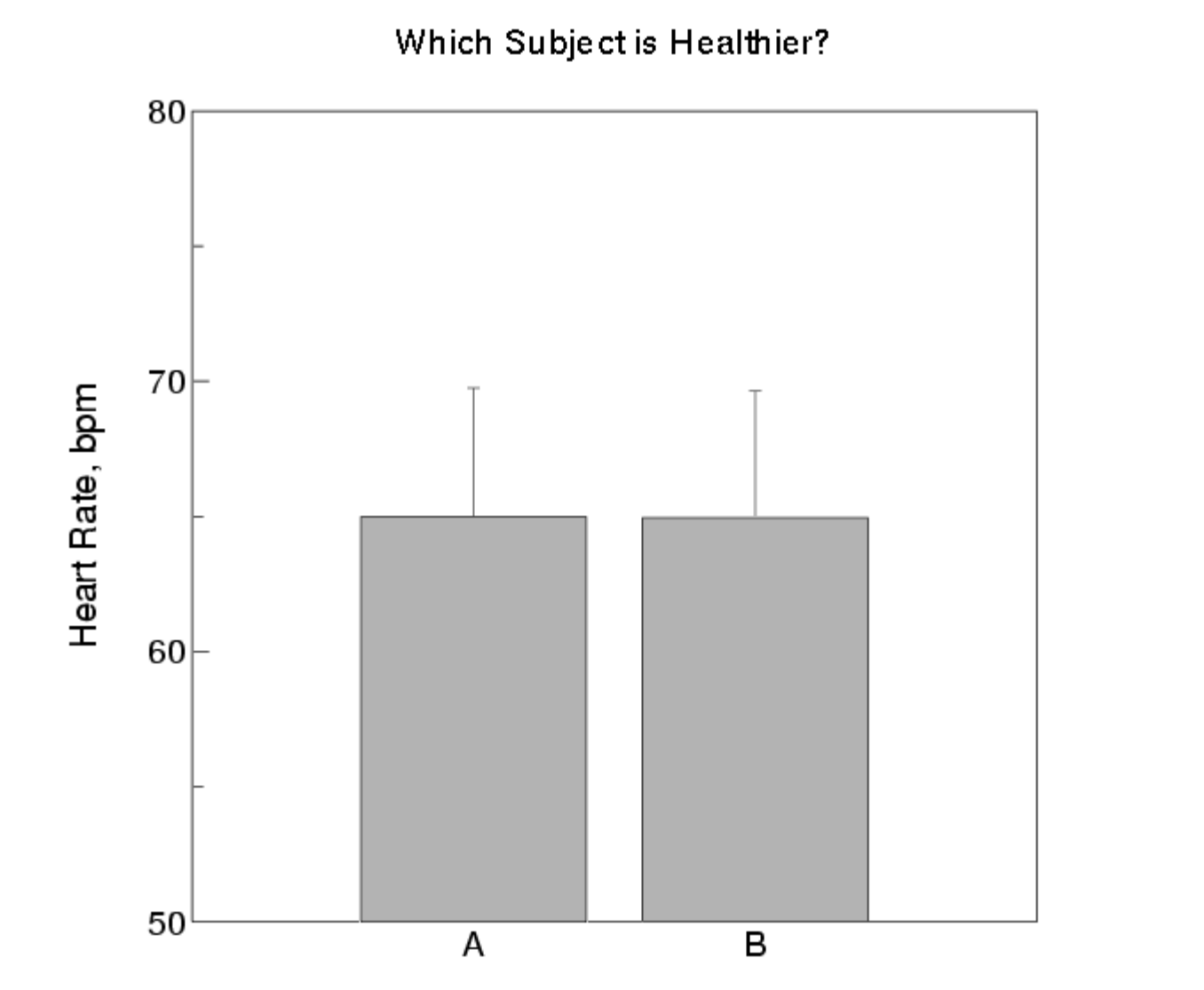
Ary L. Goldberger, MD

Director, Margret and H.A. Rey Institute for Nonlinear Dynamics in Medicine

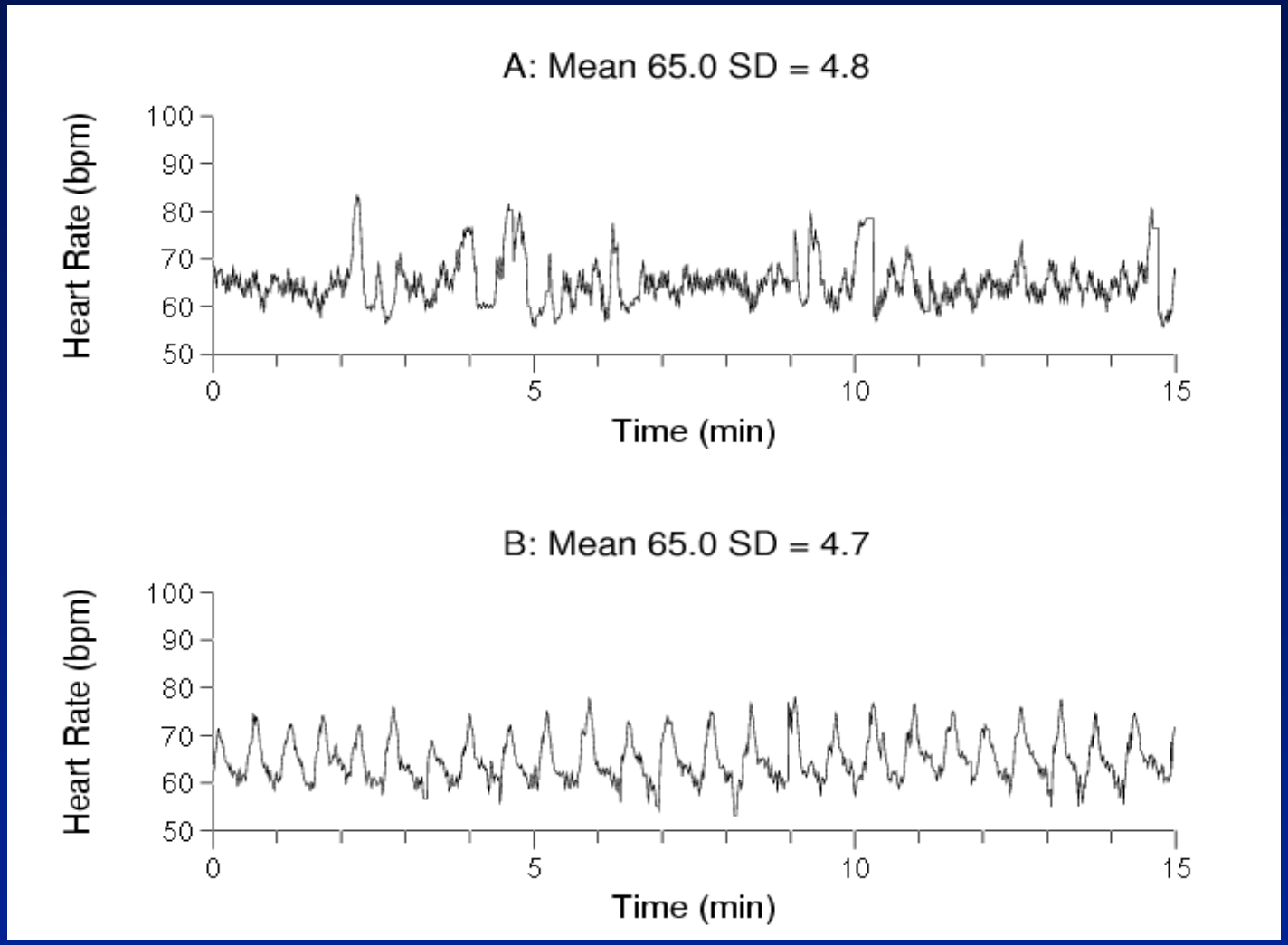
Beth Israel Deaconess Medical Center

Harvard Medical School

Another Quiz: Which is the Healthy Subject?



Variability vs. Complexity: Beyond ANOVA

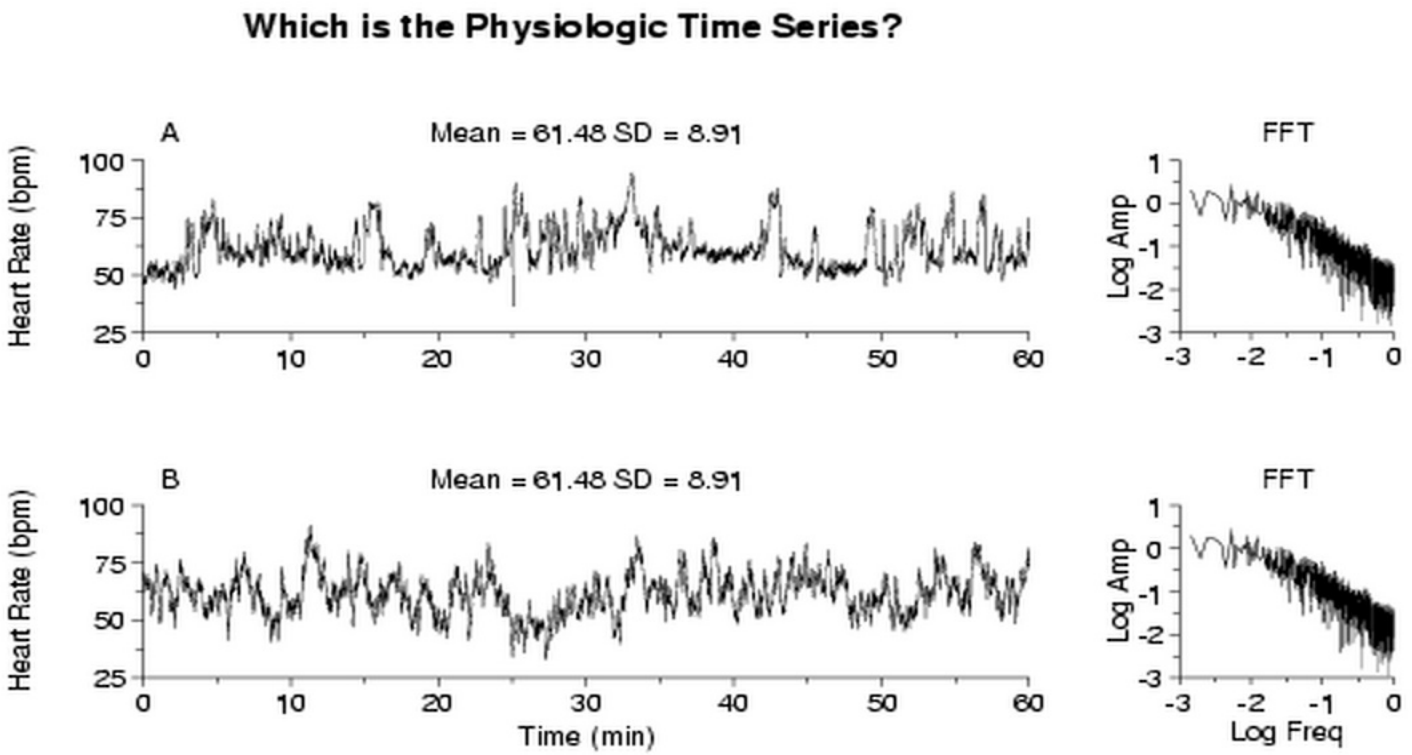


Healthy

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?

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

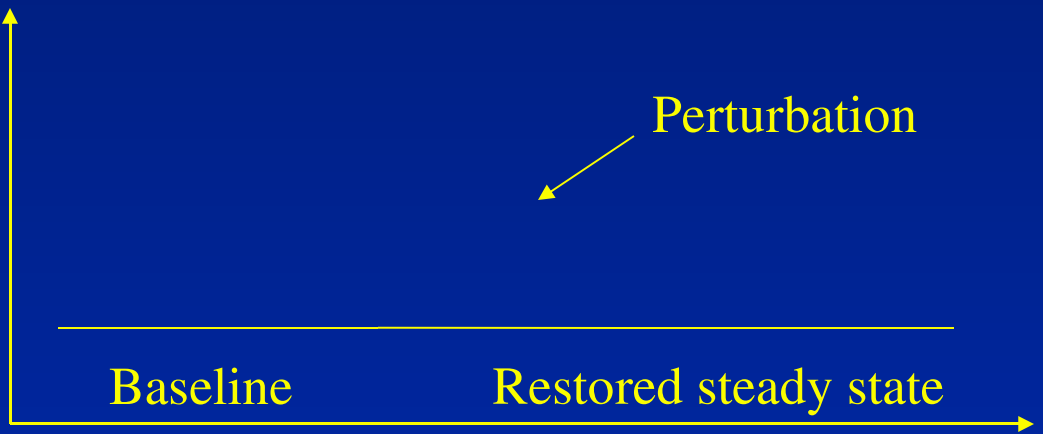
Vol. IX JULY, 1929 No. 3

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

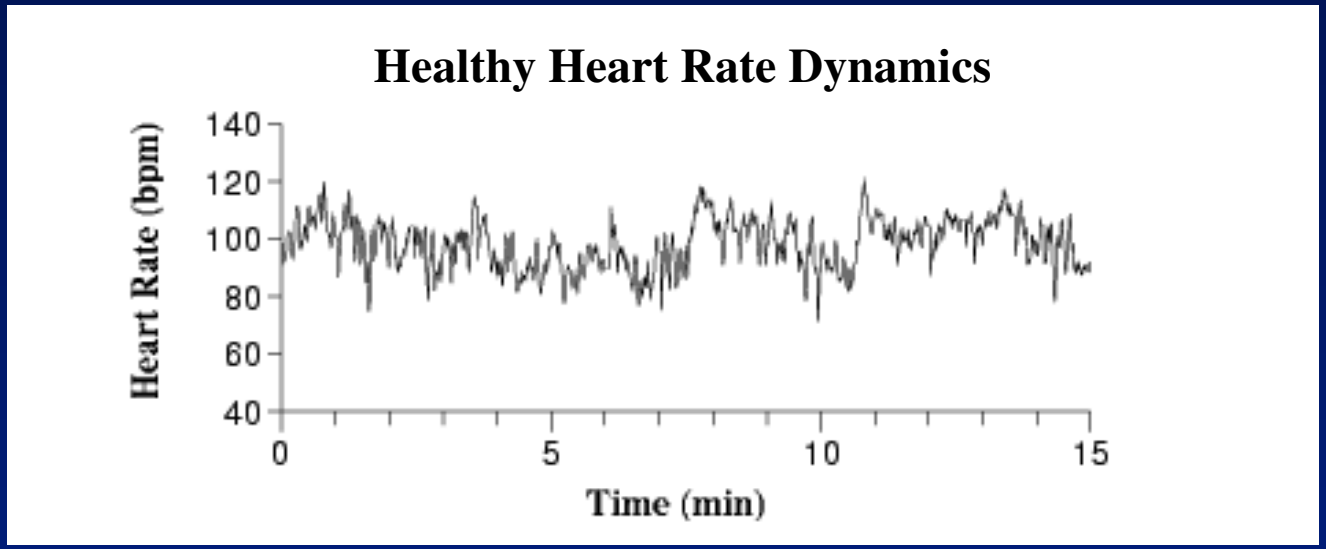
Homeostasis Revisited

…OR

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

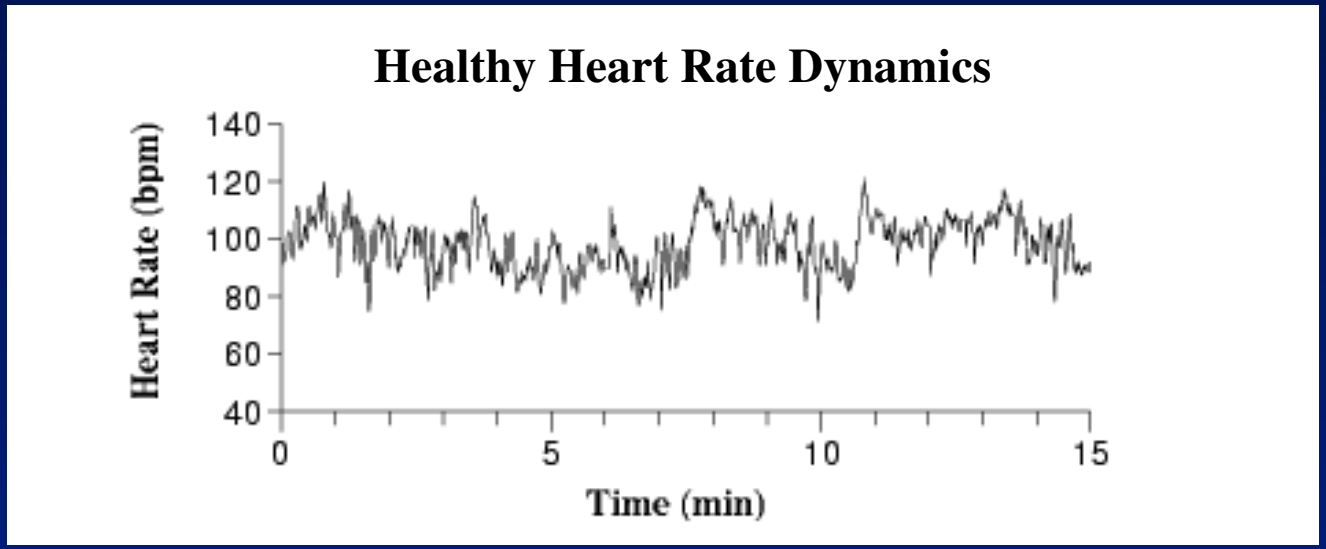
And, therefore, do we need fundamentally to rethink all notions of mechanisms and causality in physiology

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*
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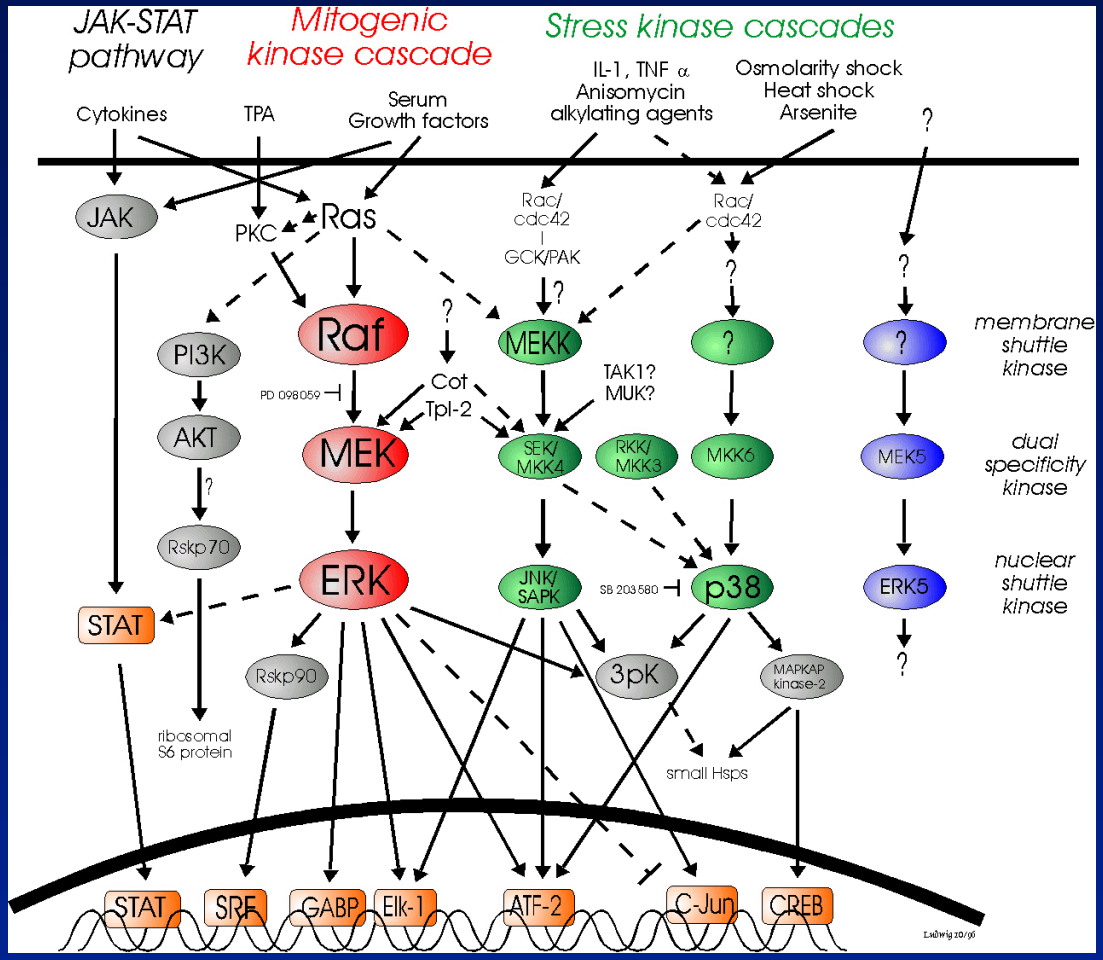
  - *Fluctuations/structures may have fractal organization*
- Time Irreversibility
  - *Nonequilibrium dynamics underlie fluctuations*

Is Your World Linear or Nonlinear?

- Linear Process:
  - Simple rules → simple behaviors
  - Things add up
  - Proportionality of input/output
  - High predictability, no surprises

- Nonlinear Process:
  - Simple rules → complex behaviors
  - Small changes may have huge effects
  - Low predictability & anomalous behaviors
  - Whole ≠ sum of parts ("emergent" properties)

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

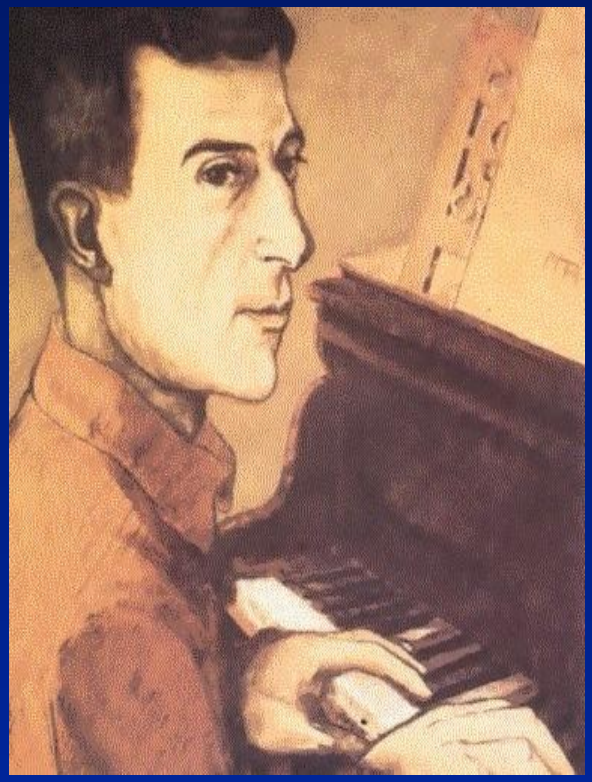


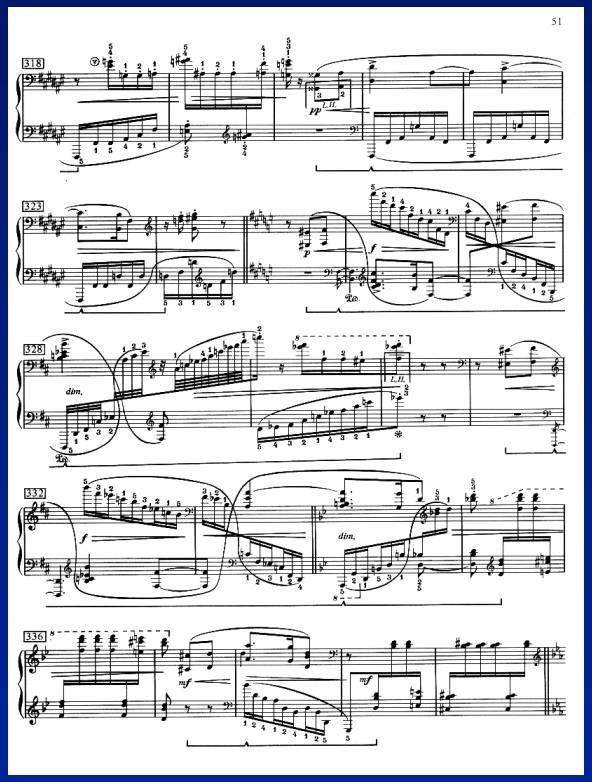
Answer: No feedback; No nonlinearity

Complicated! but …*Complex* dynamics missing!

Complex vs Complicated

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

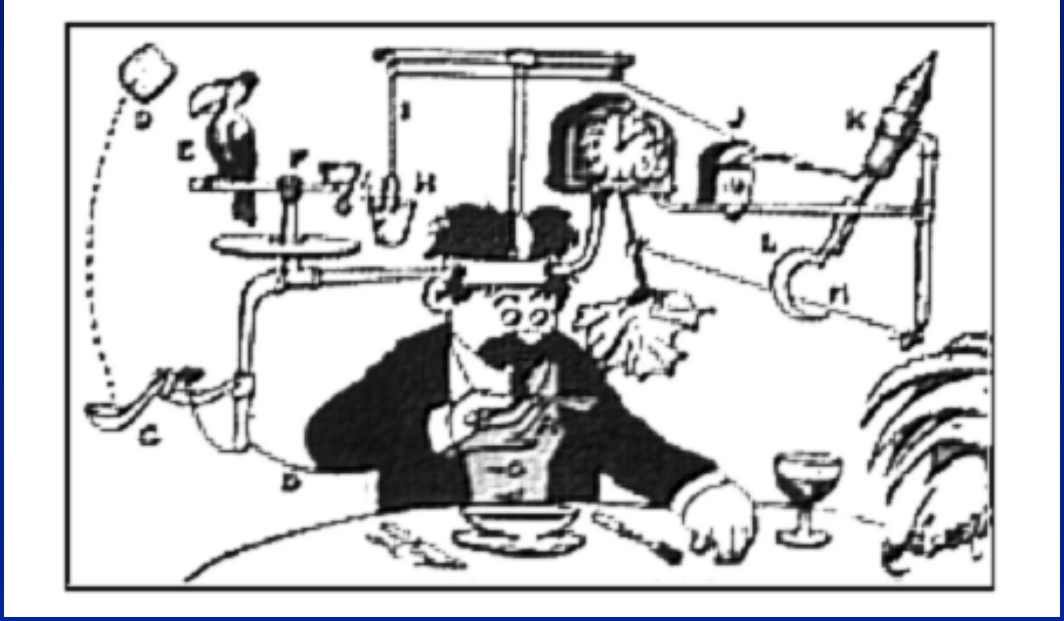




*** Danger ***

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"

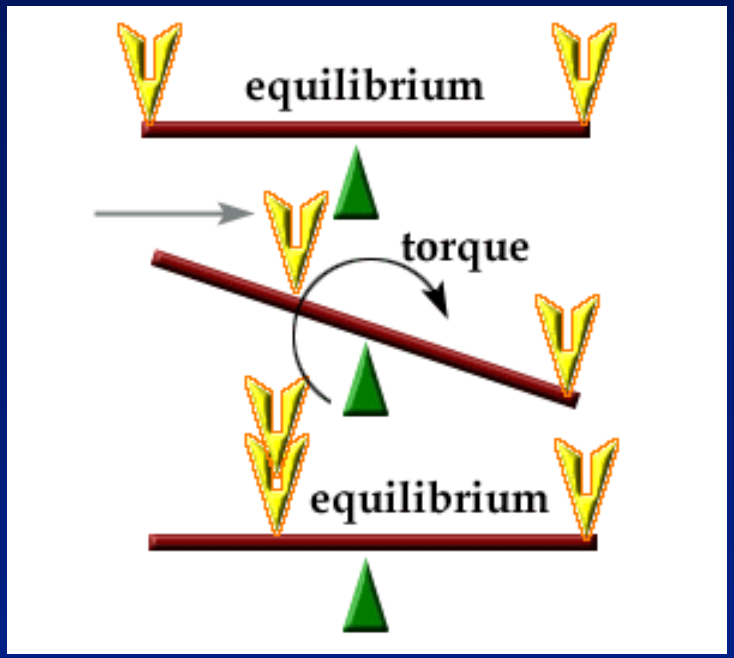


Healthy Dynamics: An Equilibrium State?

Health

Disease

Recovery



Another fallacy. But there is an equilibrium state…

…death

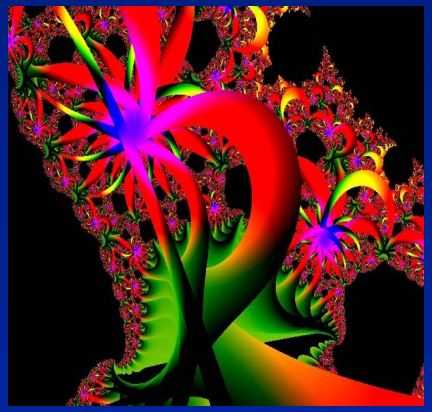
Nonlinear Mechanisms in Physiology

- 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

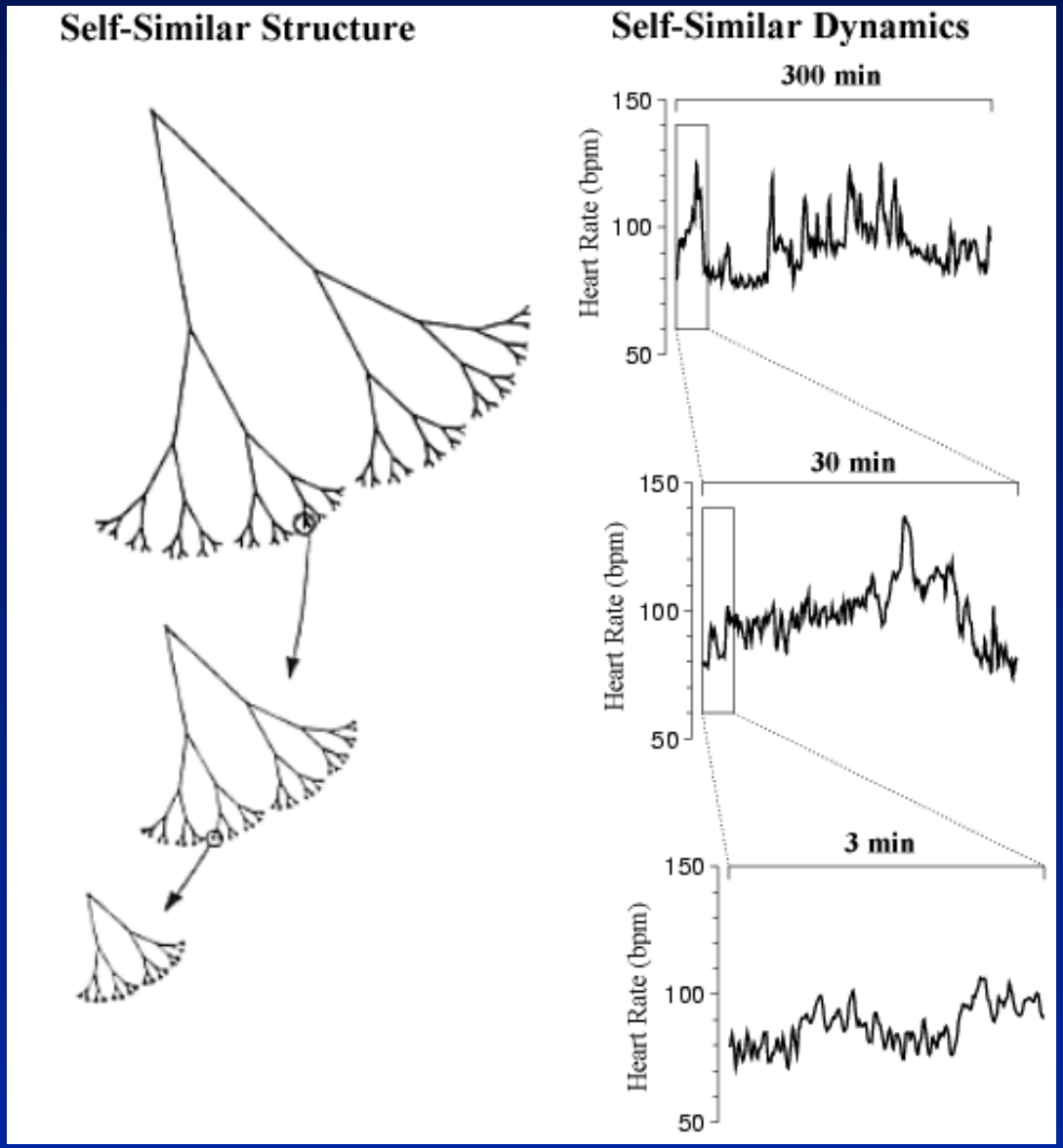
- Bifurcations
- Nonlinear oscillations
- Deterministic chaos
- Time asymmetry
- Fractals

- Nonlinear waves: spirals/scrolls/solitons
- Stochastic resonance
- Complex networks
- Hysteresis
- Emergence



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

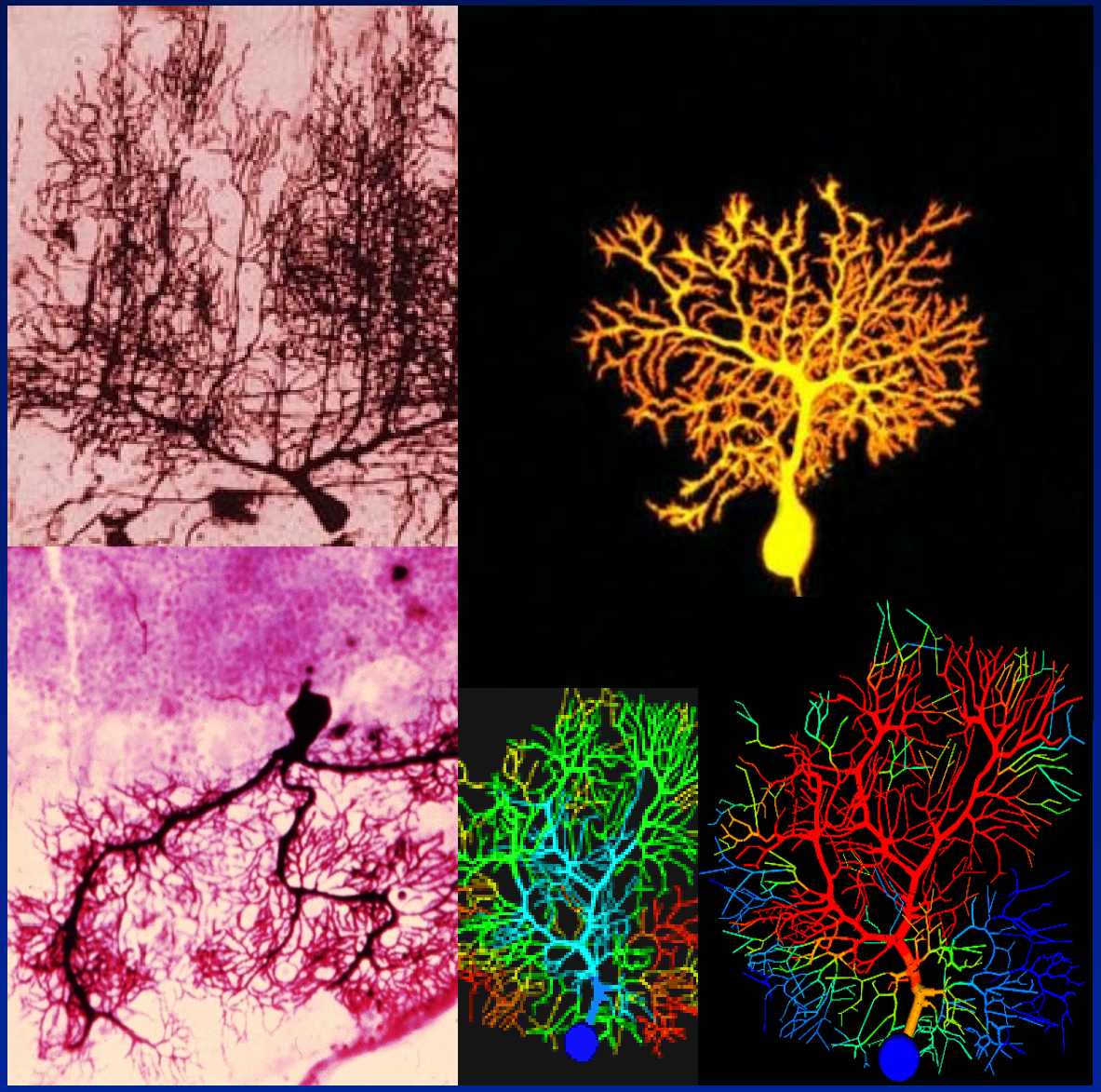
Are there Fractal Processes in Biology?



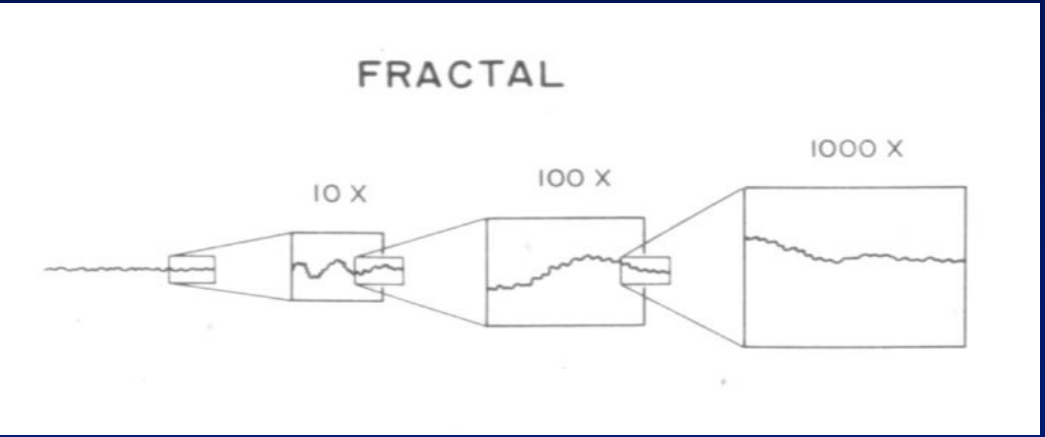
Fractal: A tree-like object or **process**, composed of sub-units (and sub-sub-units, etc) that resemble the larger scale structure

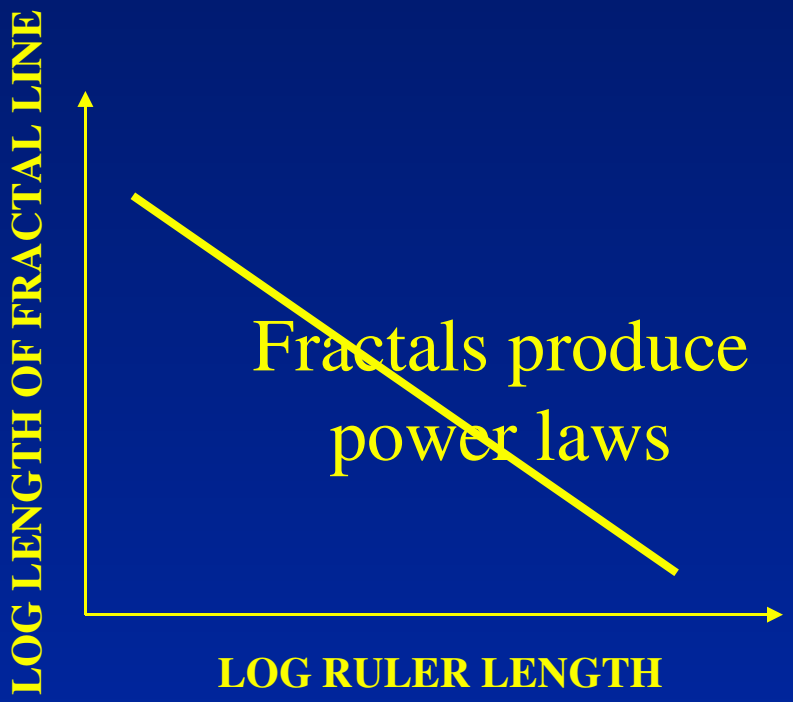
Self-similarity (scale invariance), therefore, may be a property of dynamics as well as structure

Fractals and Information Transmission: Purkinje Cells in Cerebellum



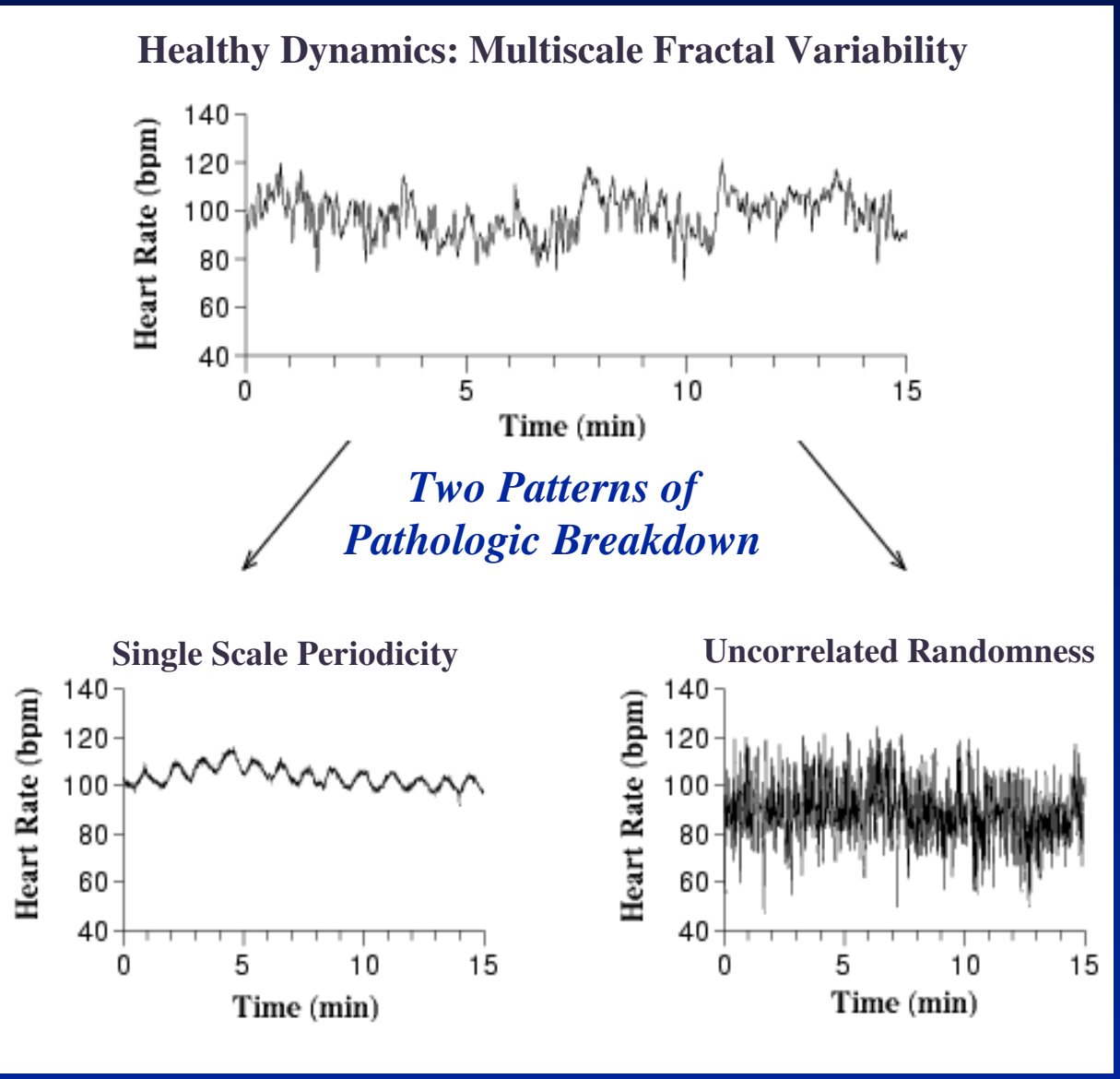
Fractals and Power Laws





Fractals produce power laws

Fractal Complexity Degrades with Disease



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

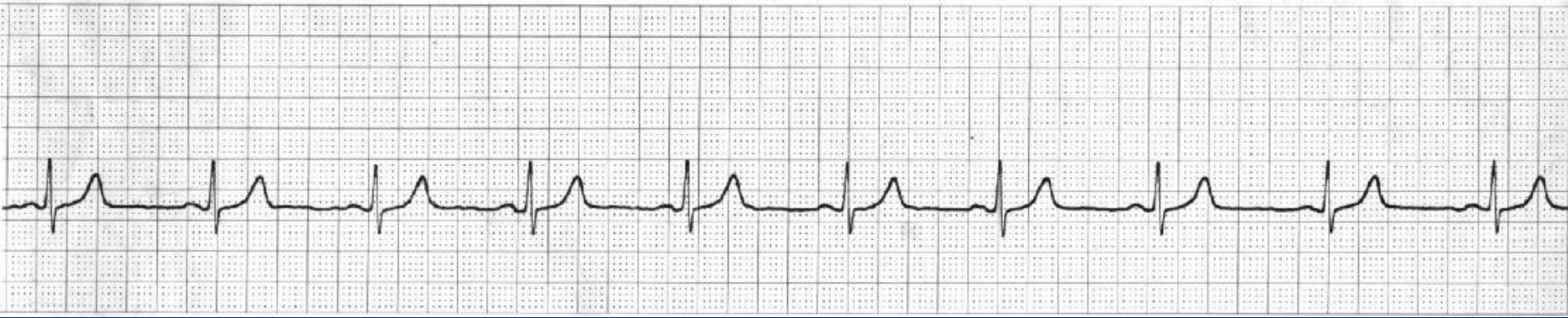
Patients with wide range of disorders/syndromes often display strikingly predictable (ordered) dynamics: Reorder vs. Disorder

Examples:

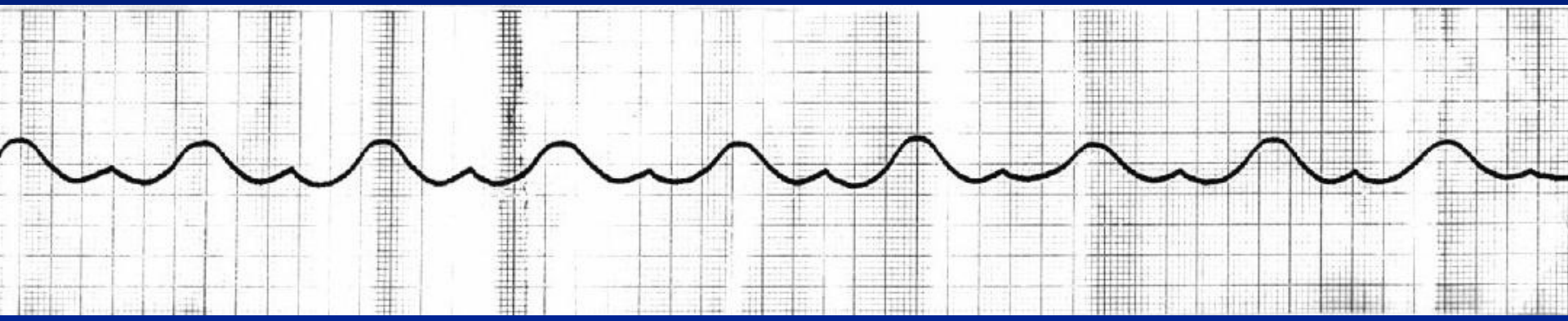
- Cheyne-Stokes breathing
- Obstructive sleep apnea
- Parkinsonism / Tremors
- Obsessive-compulsive behavior
- Nystagmus
- Monomorphic ventricular tachycardia
- Torsades de pointes
- Hyperkalemia → "Sine-wave" ECG
- Cyclic neutropenia
- Cyclic flow reductions in arterial stenosis

Loss of Complexity in Dying Heart

Normal Heart



Dying Heart



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:

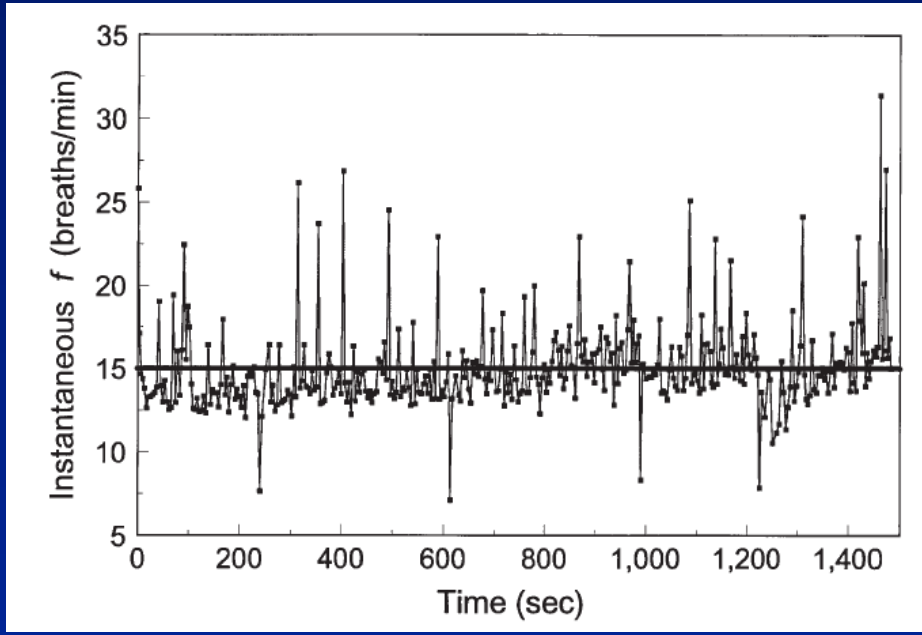
- Multiscale nonlinear interactions
- Emergent phenomena
- Nonequilibrium dynamics

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

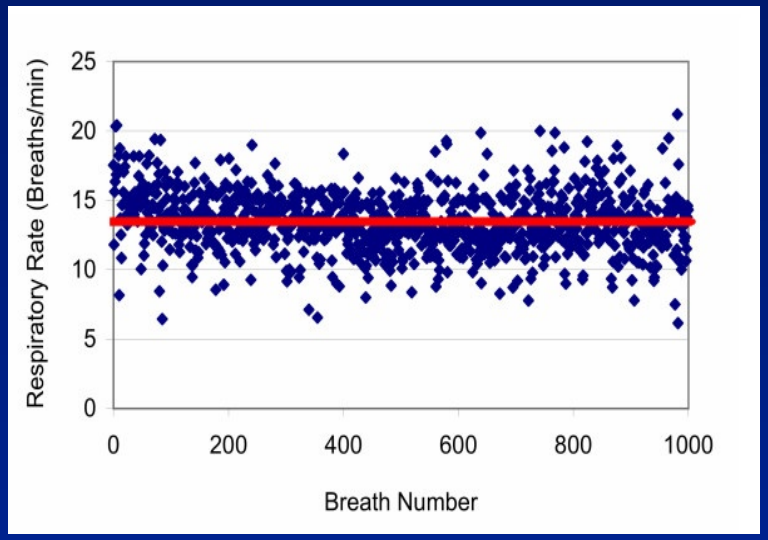
Department of Anaesthesia and Neuroanaesthesia Research Laboratory, Faculty of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada

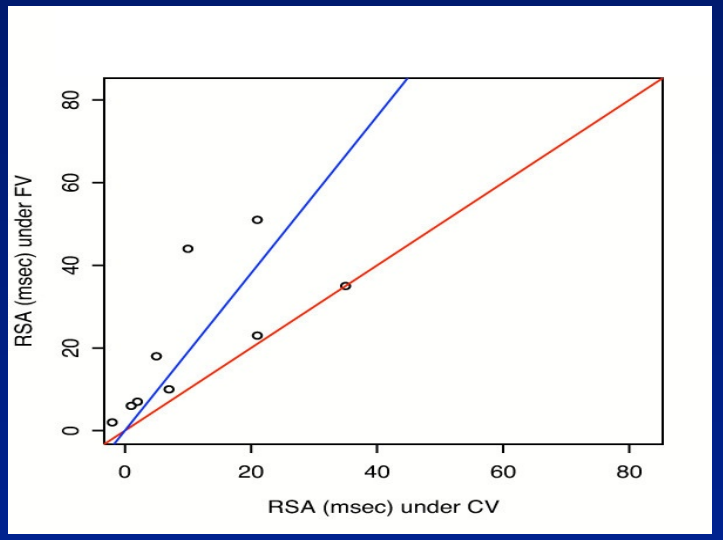


Am J Respir Crit Care Med 2000; 162: 319

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)

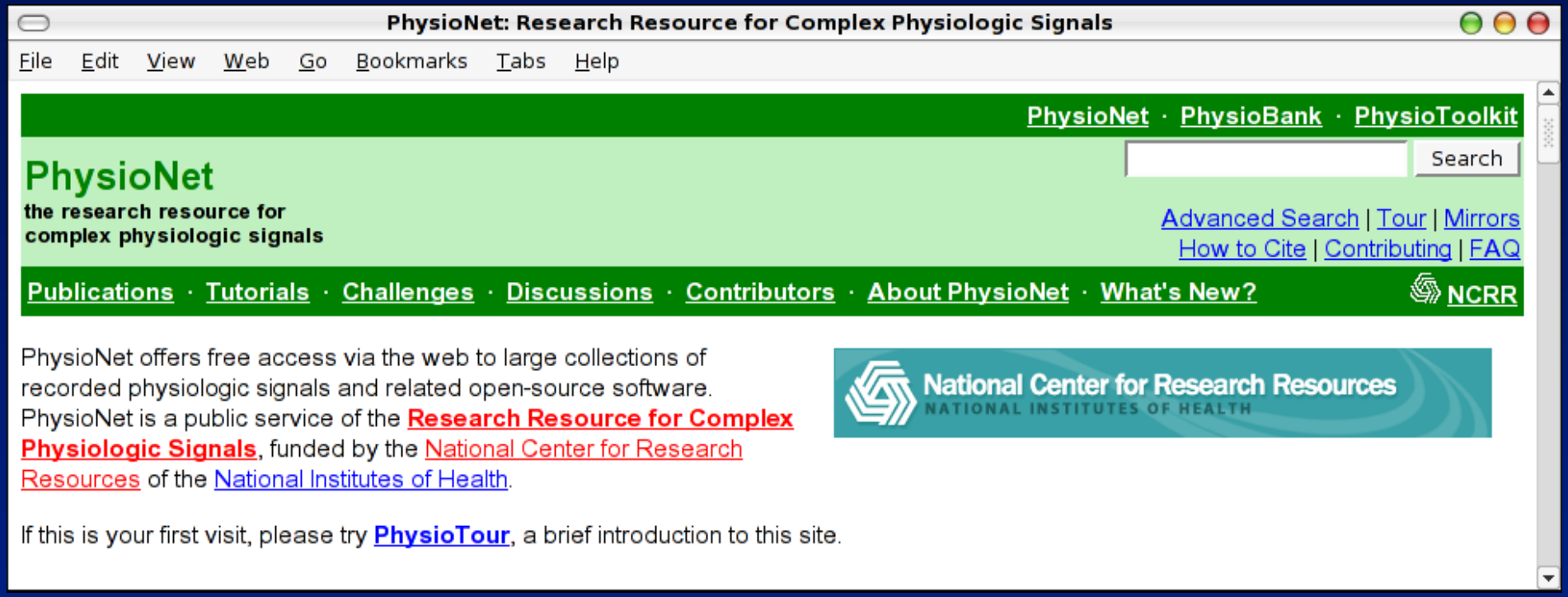
- How to overcome limitations of Fourier methods for time series that are intrinsically nonstationary
- Importance of looking at original and rawest forms of data (ECG to HRV time series)
- Importance and uses of open-access databases and open-source software. Need for providing such data and software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

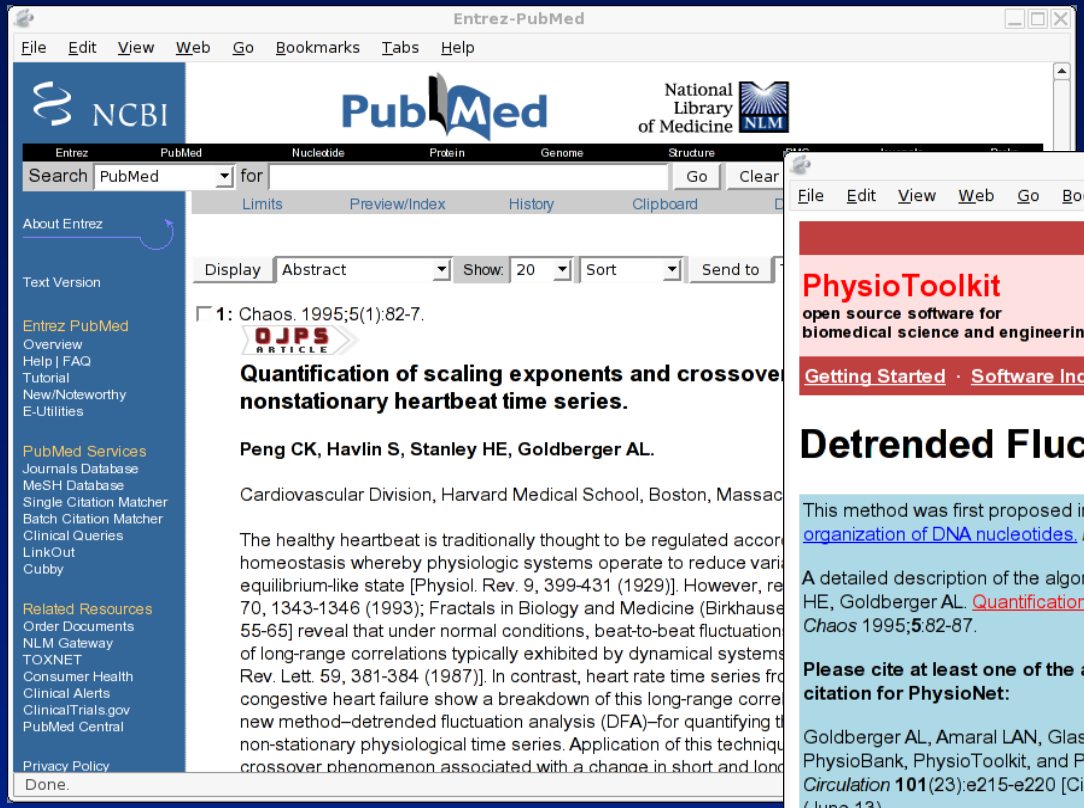


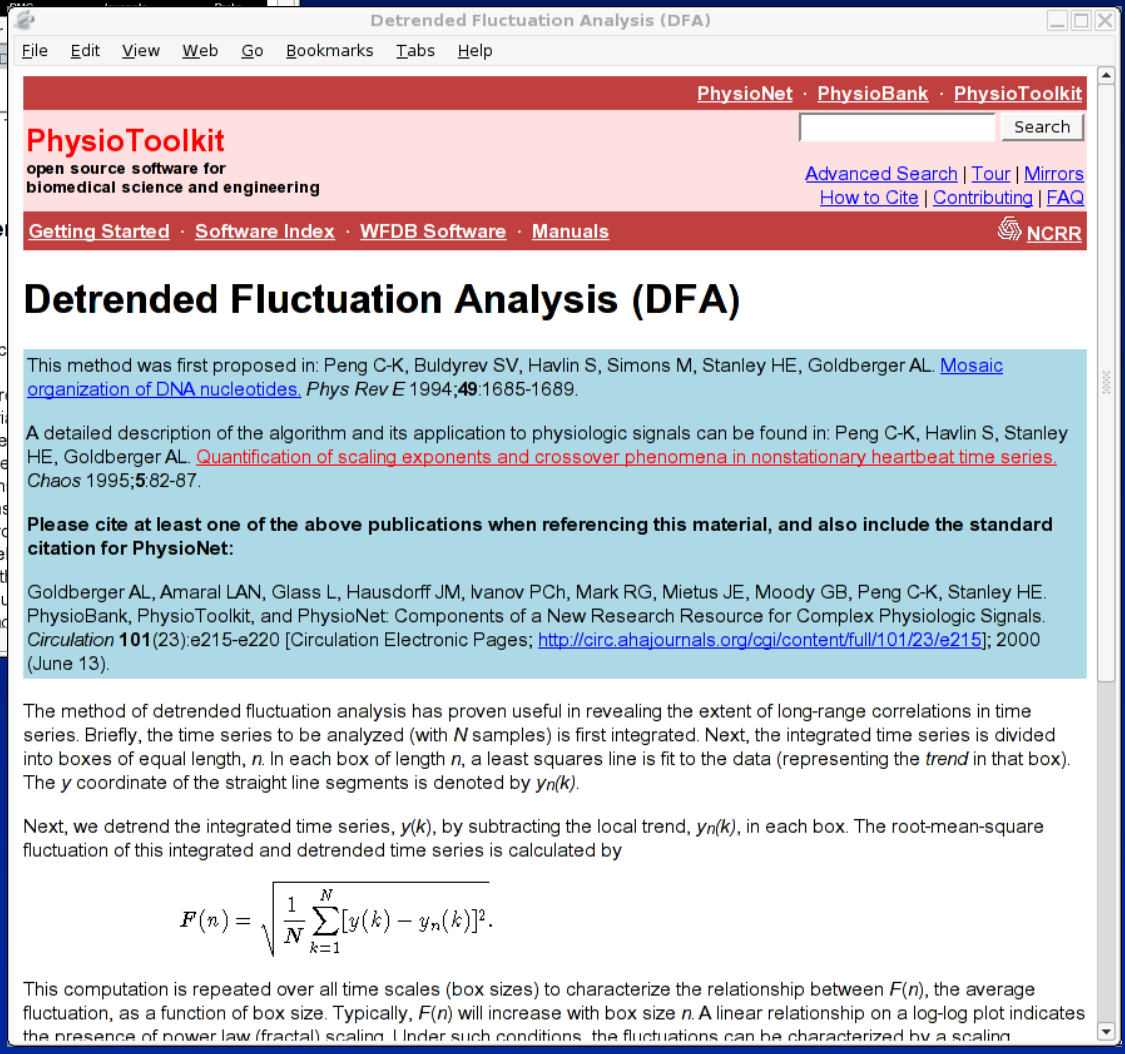
www.physionet.org

500,000+ visits to date

>4 terabytes of data downloaded!

Software/Tutorials for Data Analysis





>600 publications citing DFA

~400 since 1999

So Welcome to HRV 2006!