Welcome!

Heart Rate Variability

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
Overture: Why is Physiologic Variability Important?

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Another Quiz: Which is the Healthy Subject?
Variability vs. Complexity: Beyond ANOVA

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

Healthy

Sleep Apnea
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?

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.
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.”
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?

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

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.

Are there Fractal Processes in Biology?
Fractals and Information Transmission: Purkinje Cells in Cerebellum
Fractals and Power Laws

Fractals produce power laws
Fractal Complexity Degrades with Disease

Healthy Dynamics: Multiscale Fractal Variability

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. MUTC, 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
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”
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.

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

Quantification of scaling exponents and crossovers in nonstationary heartbeat time series.

Peng CK, Havlin S, Stanley HE, Goldberger AL.

Cardiovascular Division, Harvard Medical School, Boston, Massachusetts, USA.

The healthy heartbeat is traditionally thought to be regulated according to homeostatic principles by physiological systems that operate to reduce variance from equilibrium-like state [Physiol Rev 89, 399-431 (1999)]. However, recent results reveal that heartbeat time series are fractal [Phys. Rev. Lett. 59, 381-384 (1987)]. In contrast, heart rate time series for congestive heart failure show a breakdown of this long-range correlation [Physiol. Rev. 70, 1343-1348 (1990)]. Fractal models of heartbeats have been shown to predict the behavior of the cardiovascular system in response to interventions [Nature 351, 683-684 (1991)].

The method of detrended fluctuation analysis (DFA) was introduced to quantify the non-stationary physiological time series. Application of this technique to crossovers in physiological time series associated with a change in short and long-term correlations leads to an understanding of the mechanisms underlying the observed phenomena.

Detrended Fluctuation Analysis (DFA)


Please cite at least one of the above publications when referencing this material, and also include the standard citation for PhysioNet:


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(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 exponent...
So Welcome to HRV 2006!

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