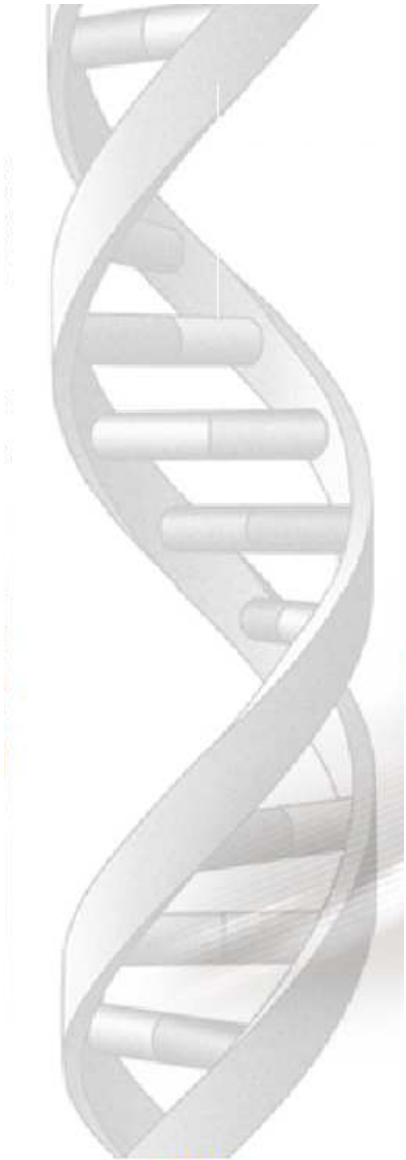
VCU, Richmond, VA
March 13th, 2009

NIH – NHLBI Workshop Series



Complexity *vs* Variability: Taking and Interpreting Measurements from Real-World Data

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Outline of My Talk:

1. Description of the multiscale entropy (MSE) method, which quantifies the information content of a signal over multiple time scales
2. Applications of MSE to dynamical analysis of: 1) heartbeat in health and disease; 2) balance control; 3) red blood cell membrane motions; and 4) EEG signals
3. Description of the multiscale time irreversibility (MTI) method, which quantifies the degree of temporal irreversibility of a signal over multiple time scales
4. Applications of MTI to dynamical analysis of heartbeat in health and disease

Two complementary approaches to gain some insight into physiologic control

- Write down the system's equations of motion in terms of its components
- Quantify the macroscopic behavior of the system

Why do we need quantitative descriptions at the integrative system level?

Reductionist approaches never fully work in biological systems

Our goals

- To characterize and quantify the dynamics of biological systems at the integrative (macroscopic) level
- Understanding how the system responds to perturbations (micro to macro)

Underlying Notions/Hypotheses

- Biological systems countinuously exchange information/matter/energy with their environment in order to adapt
- The complexity of a biological system is an indicator of the system's *capacity* to adapt and function in an ever changing environment
- The system that can better adapt to the most external challenges (stresses) will have the advantage for survival
- Complexity degrades with pathology, aging & drug toxicity

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

How to Measure “Complexity”?

- Meaningful complexity measures should account for multiple time scales inherent in healthy dynamics

- We (Costa, Goldberger and Peng) introduced a new **multiscale entropy** (MSE) method motivated by previous work of Zhang and Pincus/Moorman *et al* and our own work on fractal scaling

* Phys Rev Lett 2002;89:068102 & Phys Rev E 2005; 71:021906

Multiscale Entropy

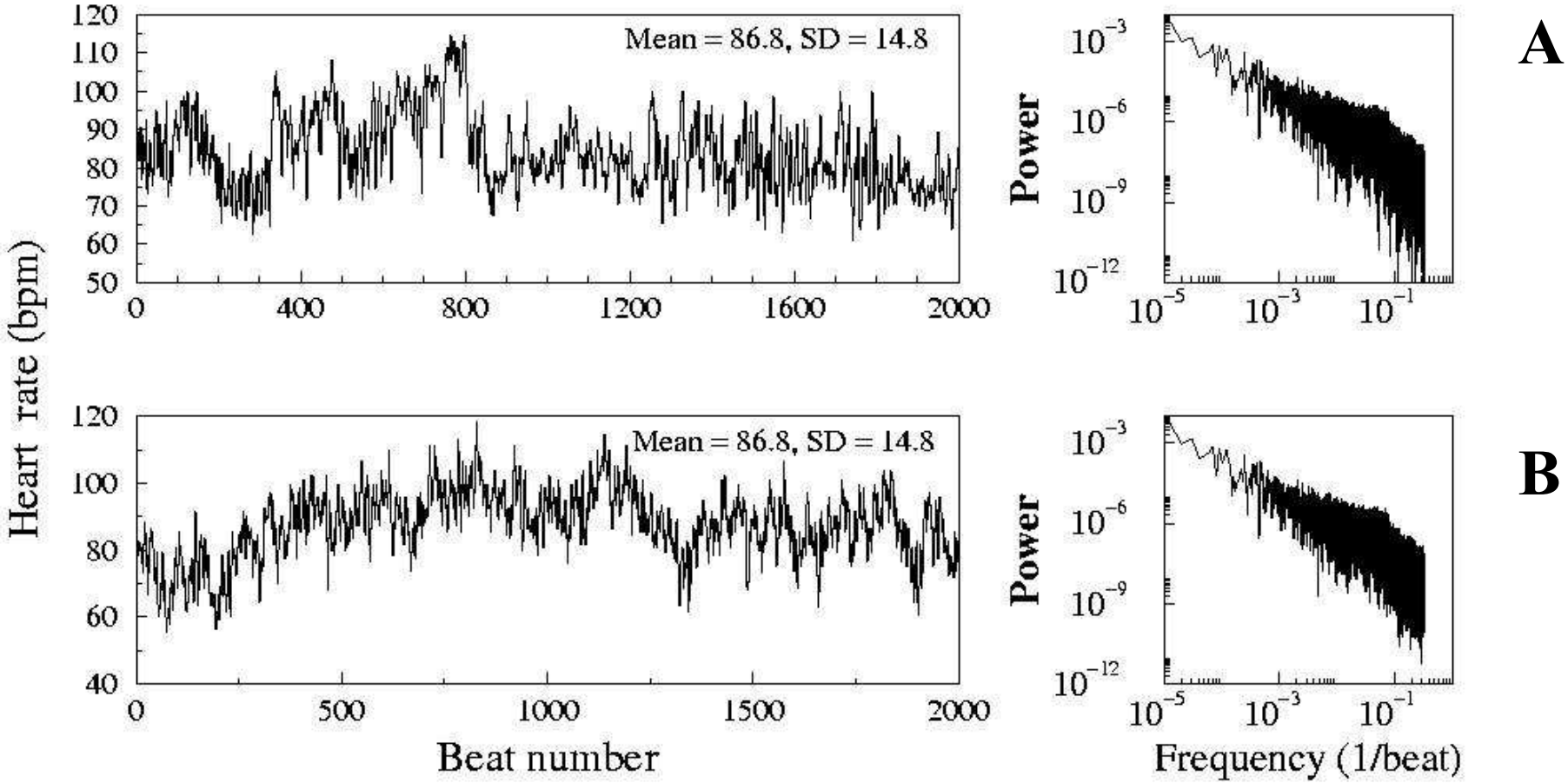
MSE is a method to quantify system's complexity by examining the information richness of an output signal

Costa, Goldberger, Peng: *Phys Rev Lett* 2002;89:068102

Cardiovascular Engineering 2008

Advances in Adaptive Engineering 2009

Beyond FFT: Which is Physiologic ?



Surrogate data generator: Schreiber T, Schmitz A. Improved surrogate data for nonlinearity tests. Phys Rev Lett 1996;77:635–8.

Shannon's Entropy

- Single variable:

$$H(X) = -\sum_{x_i \in \Theta} p(x_i) \log p(x_i)$$

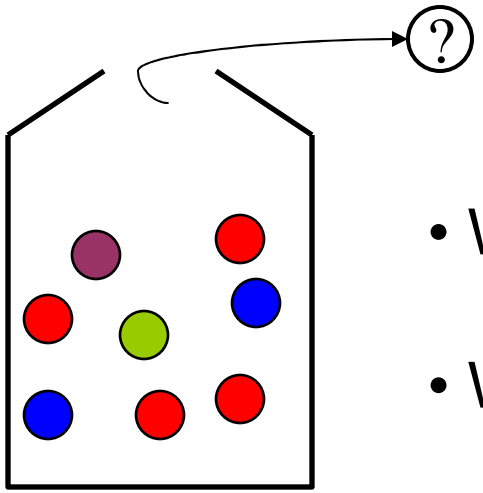
(The entropy H(X) of a random variable is a measure of this average uncertainty.)

- Time series:

$$H_n = H(X_1, X_2, \ldots, X_n)$$

$$= -\sum_{x_1 \in \Theta_1} \cdots \sum_{x_n \in \Theta_n} p(x_1, \ldots, x_n) \log p(x_1, \ldots, x_n),$$

Choosing balloons randomly



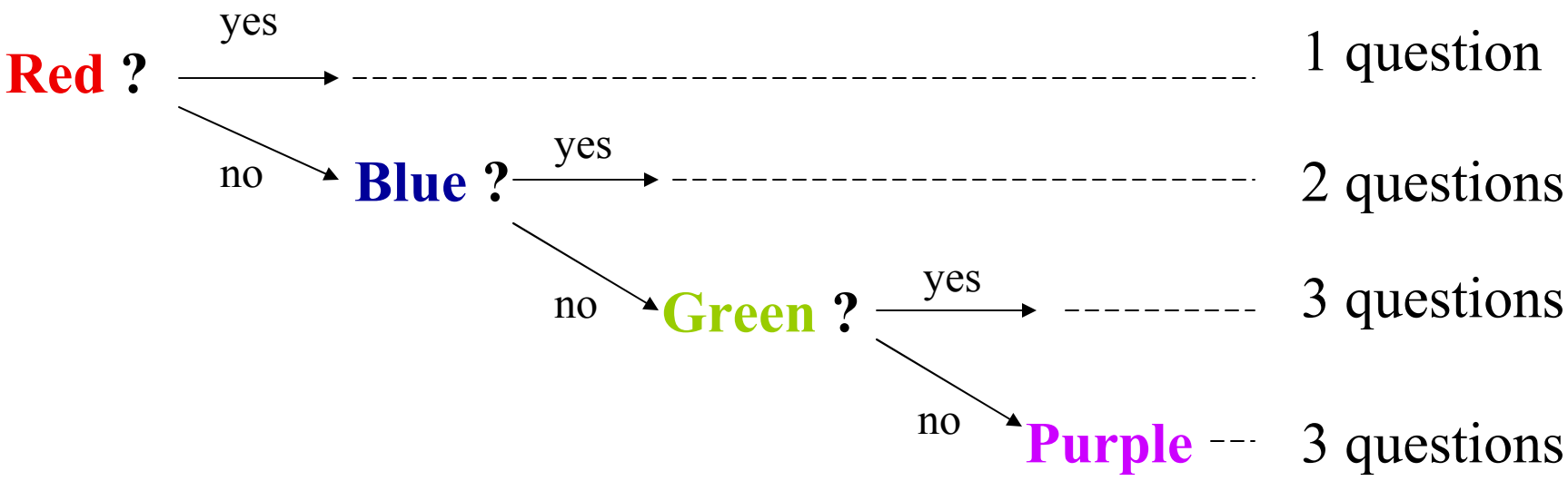
- What is the best sequence of questions ?
- What is the average number of questions ?

8 balls: 4 reds 2 blues1 green, 1 purple

Draw one randomly

Choosing balls randomly (con't)

- Best set of questions (Huffman Code):



Choosing balloons randomly (con't)

- Average number of questions :

P(●) x 1 + P(●) x 2 + P(●) x 3 + P(●) x 3

$\frac{1}{2}$ x 1 + $\frac{1}{4}$ x 2 + $\frac{1}{8}$ x 3 + $\frac{1}{8}$ x 3 = 1.75

- Entropy = $-\sum_i p_i \log_2(p_i)$

= $\frac{1}{2}\times\log_2\left(\frac{1}{2}\right)+\frac{1}{4}\times\log_2\left(\frac{1}{4}\right)+\left(\frac{1}{8}\right)\times\log_2\left(\frac{1}{8}\right)+\left(\frac{1}{8}\right)\times\log_2\left(\frac{1}{8}\right)$ = 1.75 bits

The entropy H(X) of a random variable is a measure of this average uncertainty

Kolmogorov-Sinai (KS) Entropy

Let us consider a $\mathcal{D}$-dimensional dynamical system. Suppose that the phase space of the system is partitioned into hypercubes of content $\varepsilon^{\mathcal{D}}$ and that the state of the system is measured at intervals of time δ. Let $p(k_1, k_2, \ldots, k_n)$ denote the joint probability that the state of the system is in the hypercube k_1 at $t=\delta$, in the k_2 at $t=2\delta$, and in the hypercube k_n at $t=n\delta$. The Kolmogorov-Sinai (KS) entropy is defined as

$$H_{KS} = -\lim_{\delta\to 0}\lim_{\varepsilon\to 0}\lim_{n\to\infty}\frac{1}{n\delta}\sum_{k_1,\ldots,k_n} p(k_1,\ldots,k_n)\log p(k_1,\ldots,k_n)$$

$$H_{KS} = \lim_{\delta\to 0}\lim_{\varepsilon\to 0}\lim_{n\to\infty}(H_{n+1} - H_n).$$

The KS entropy measures the mean rate of creation of information, i.e., the decrease of uncertainty obtained by knowing the current state of the system given its past history

K_2 Entropy

- $u_m(i)=\{x_i,\ldots,x_{i+m-1}\}$
- $n_i^m(r)$ is the number of vectors that satisfies: $d[u_m(i)-u_m(j)] \le r$ (d is the Euclidean distance)
- $C_i^m(r) = n_i^m(r)/(N-m+1)$
- $C^m(r) = \Sigma_i C_i^m(r)$ is the probability that any 2 vectors are close to each other
- Grassberger and Procaccia defined K_2, a lower bound of the KS entropy

$$K_2 = \lim_{N\to\infty} \lim_{m\to\infty} \lim_{r\to 0} -\ln[C^{m+1}(r) - C^m(r)].$$

Sample Entropy

- Sample entropy is defined as:

$$S_E(m,r,N) = -\ln\frac{U^{m+1}(r)}{U^m(r)}.$$

d is maximum difference between components of a vector

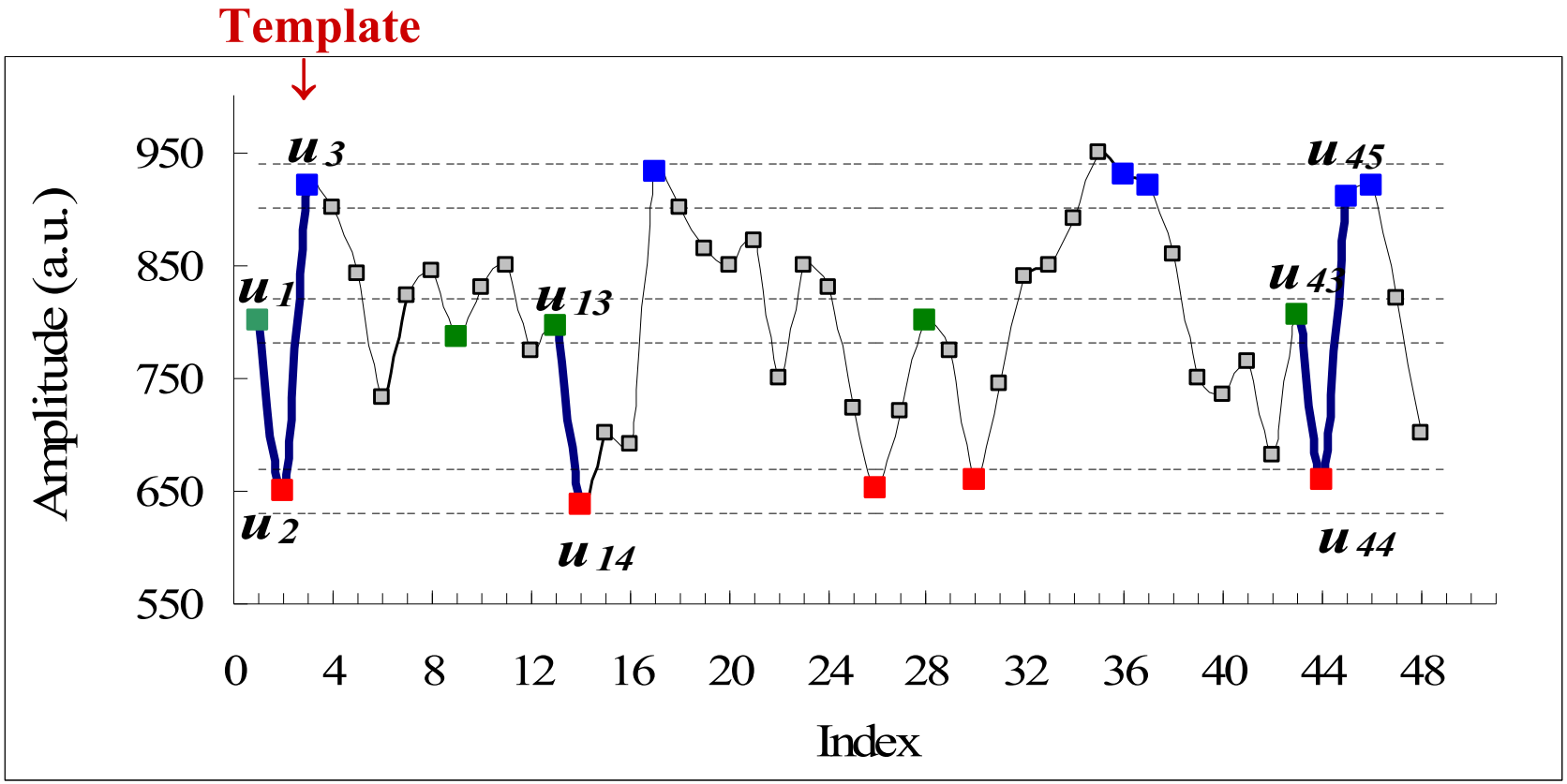
Self-matches are not counted

$$S_E(m,r,N) = \ln\frac{\sum_{i=1}^{N-m} n_i'^m}{\sum_{i=1}^{N-m} n_i'^{m+1}},$$

SE is the negative of the natural logarithm of the conditional probability that sequences close to each other for *m* consecutive data points will also be close to each other when one more data point is added.

Sample Entropy (SampEn)

Ex: (m = 2) SampEn = ln (patterns of length 2) – ln (patterns of length 3)



There are 2 vectors that match the template $\{u_1, u_2\}$ and 1 vector that matches the template $\{u_1, u_2, u_3\}$. Therefore, the number of matching patterns of length $m = 2$ is 2 and the number of matching patterns of length $m = 3$ is 1. Repeat procedure for the next templates.

Multiscale Entropy (MSE) Algorithm

Step 1. Coarse-grain the time series for looking at different scales

Step 2. Calculate entropy for each coarse-grained series

Step 3. Plot entropy as a function of scale factor

Step 4. Analyze the MSE curve profiles

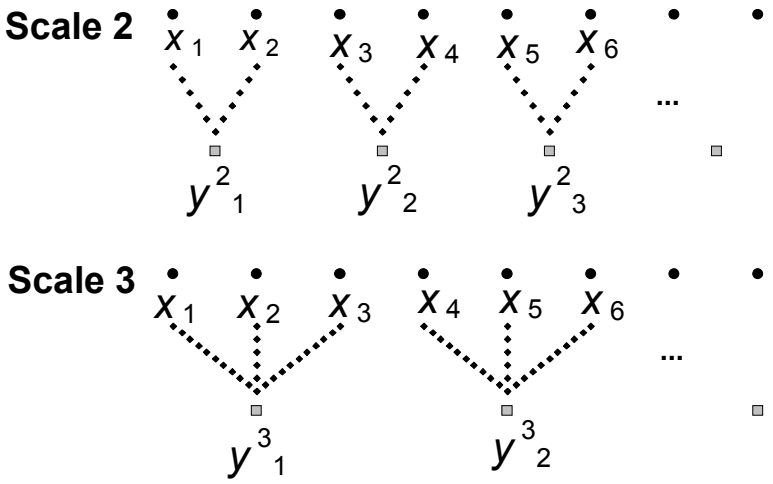
References:

M. Costa, A.L. Goldberger, C.-K. Peng. *Physical Review Letters* 2002;89:068102

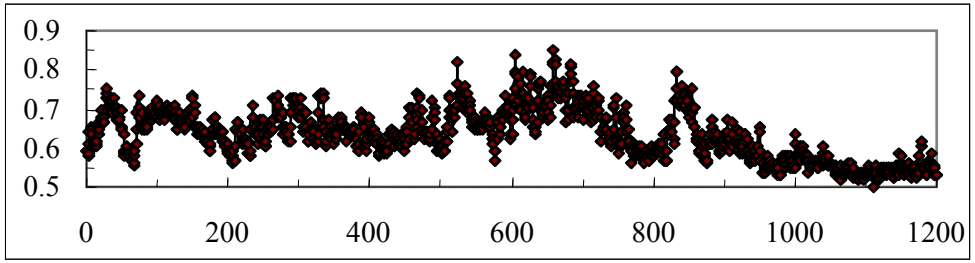
M. Costa, A.L. Goldberger, C.-K. Peng. *Physical Review E* 2005;95:198102

Coarse-graining Procedure for Multiscale Entropy (MSE) Analysis

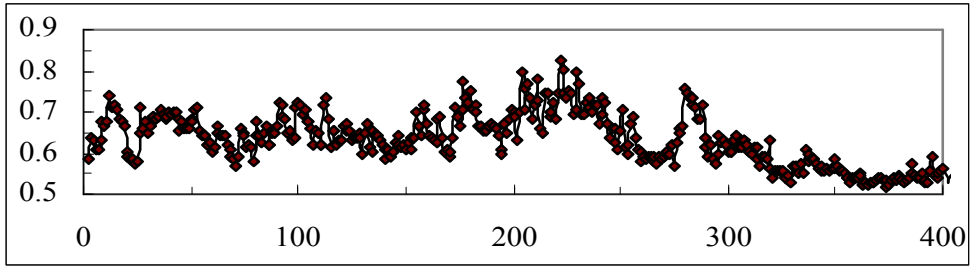
Coarse-graining schematic



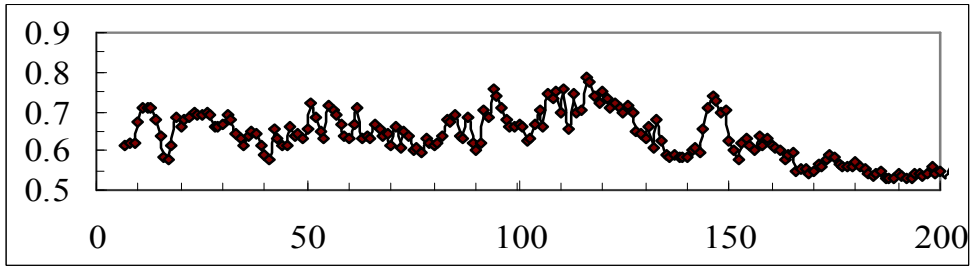
Scale 1: Original heartbeat time series



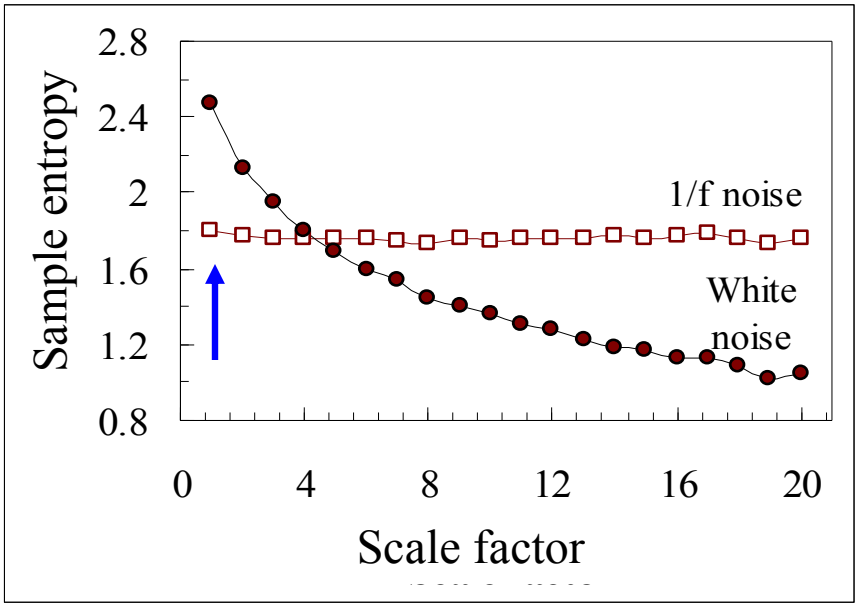
Coarse-grained: Scale 3



Coarse-grained: Scale 6



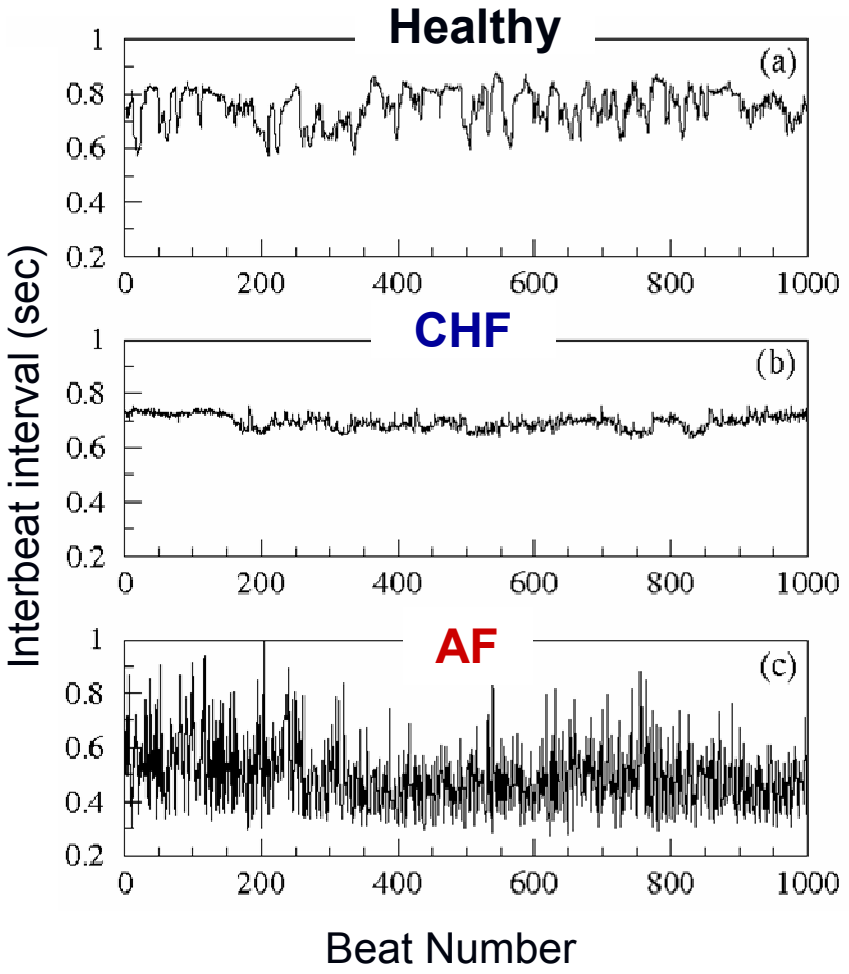
Which is More Complex: 1/f or White Noise?

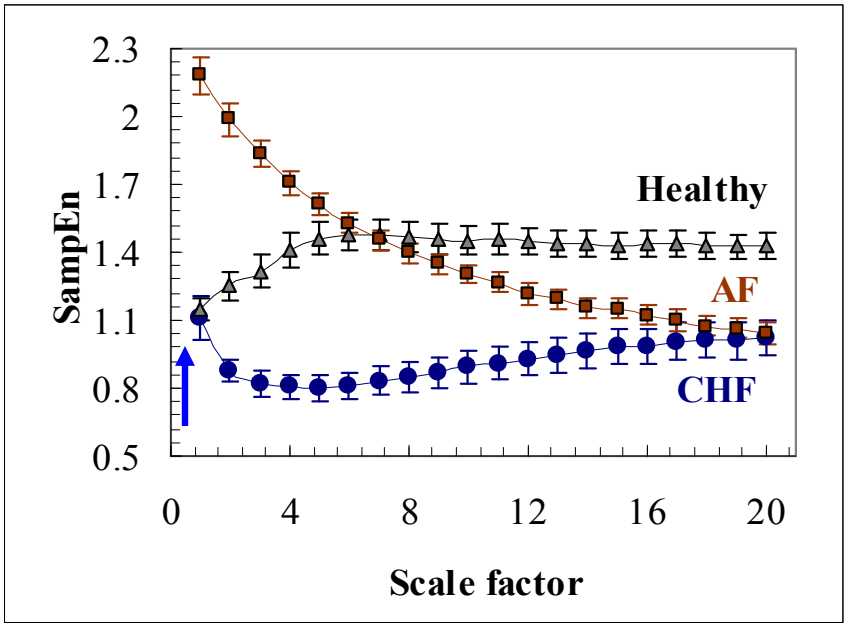


- Entropy for coarse-grained white noise time series monotonically decreases with scale
- Entropy for coarse-grained 1/f time series remains constant for all scales consistent with the fact that 1/f noise has complex structures across multiple scales

1/f noise more complex than white noise

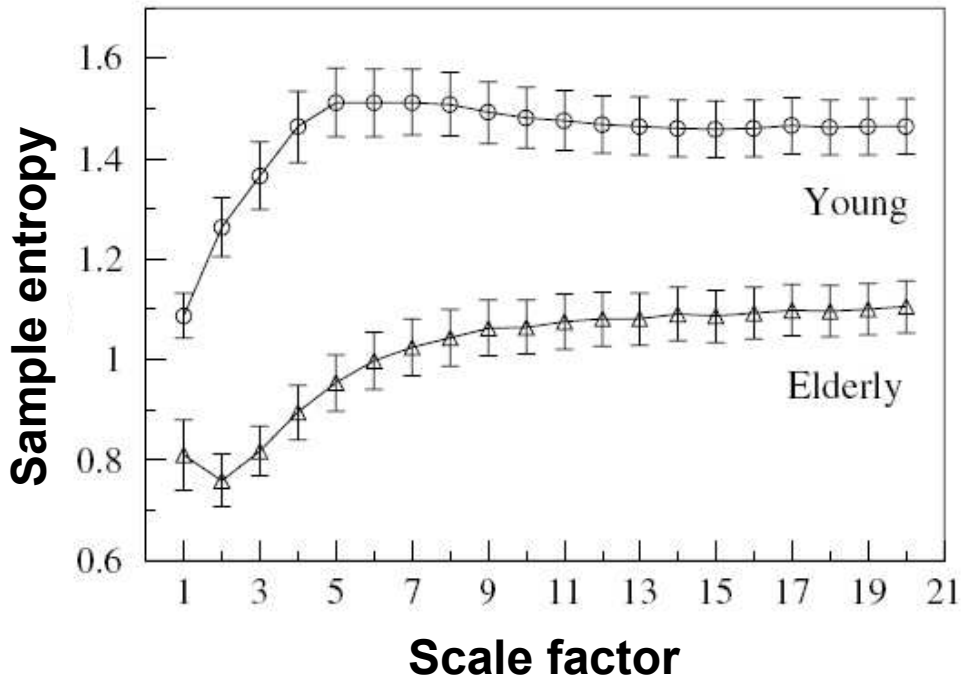
Example I: Multiscale Entropy (MSE) of Heart Rate Dynamics





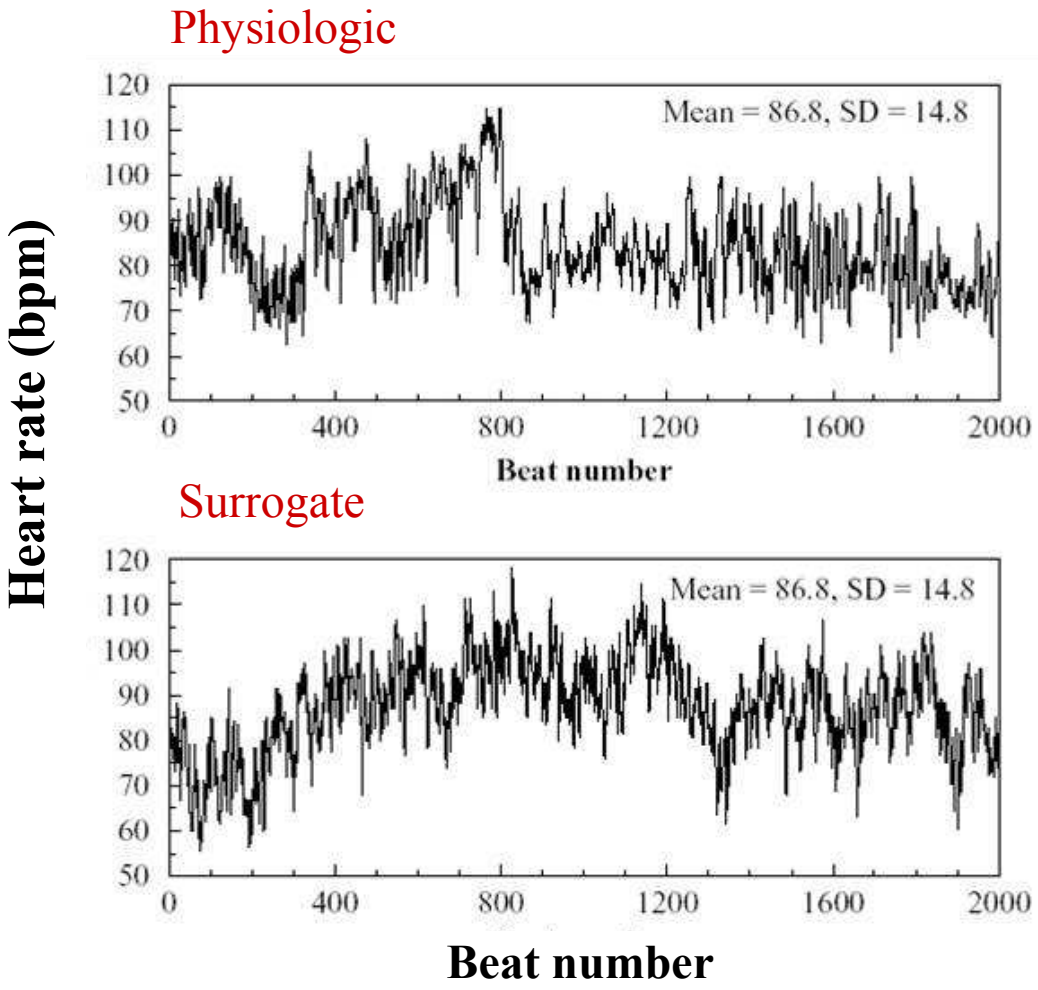
- Healthy (n=18)
- Congestive Heart Failure (CHF; n=15)
- Atrial Fibrillation (AF; n=9)

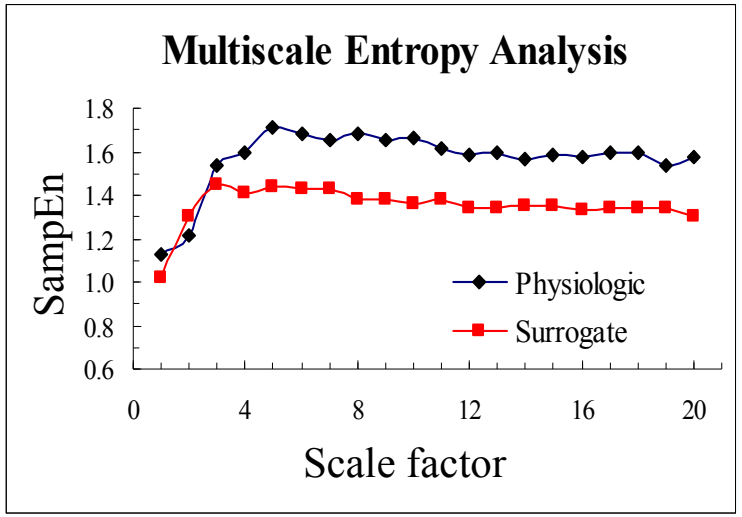
Multiscale Complexity of Heartbeat Time Series Decreases with Aging



Costa M, Goldberger AL, Peng CK.
Multiscale entropy analysis of complex physiologic time series.
Phys Rev Lett 2002;89:068102.

MSE: Physiologic *vs* Surrogate Data





Thus, the physiologic time series is more complex than the phase randomized surrogate time series

Complexity Tutorials & Software Freely Available at PhysioNet (www.physionet.org)

Multiscale Entropy Analysis (MSE)

Madalena Costa, Ary L. Goldberger and C.-K. Peng

Beth Israel Deaconess Medical Center, Boston, USA

A detailed description of the multiscale entropy algorithm and its application can be found in:

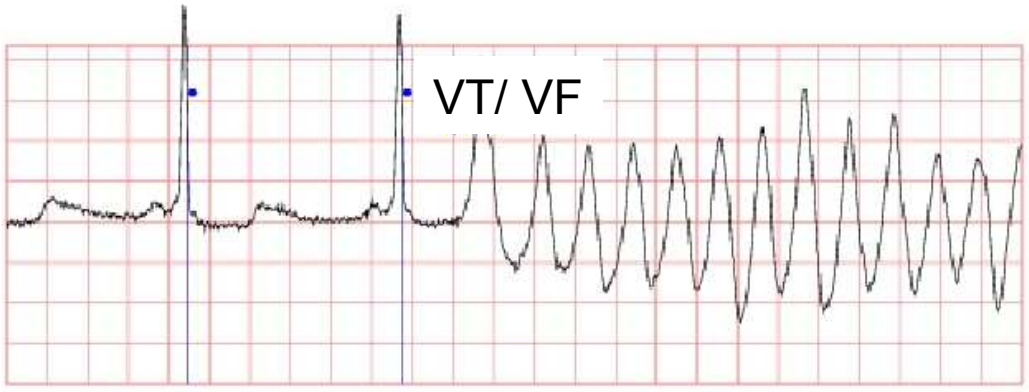
- Costa M., Goldberger A.L., Peng C.-K. Multiscale entropy analysis of biological signals. *Phys Rev E* 2005;71:021906.
- Costa M., Goldberger A.L., Peng C.-K. Multiscale entropy analysis of physiologic time series. *Phys Rev Lett* 2002; 89:062102.

Complex Signals and Drug Toxicity: The Cardiac Arrhythmia Suppression Trial (CAST)

- CAST: famous study designed to test the hypothesis that the suppression of isolated premature ventricular complexes (PVCs) in survivors of myocardial infarction (heart attack) would decrease death from sustained ventricular arrhythmias
- Patients were randomly assigned to receive one of 3 “anti-arrhythmic” drugs or placebo
- The mortality rate was 3 times higher for the groups taking “anti-arrhythmic” drugs than placebo
- The study was discontinued!

Question

Could the harmful effects of these anti-arrhythmic drugs have been anticipated?

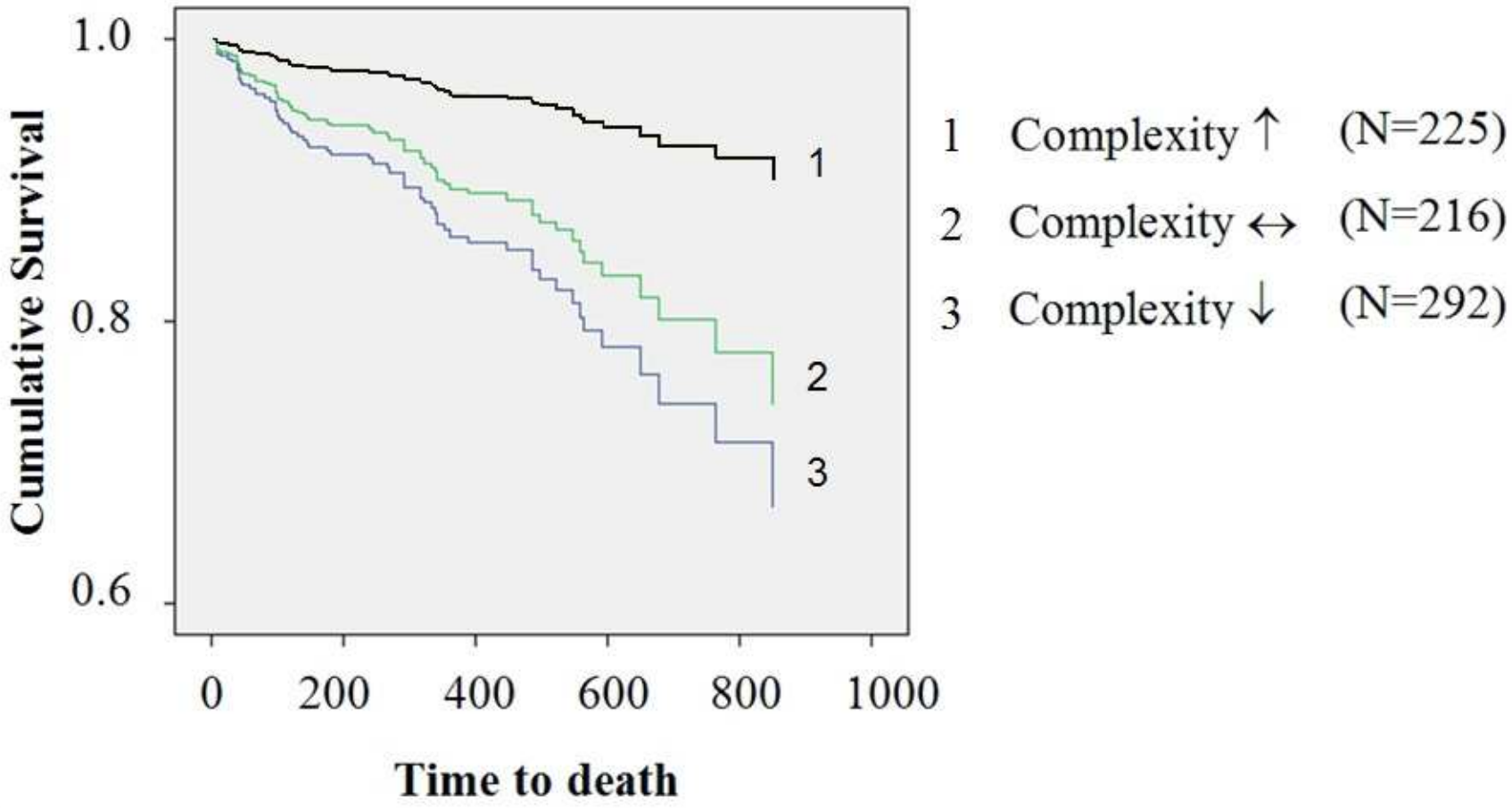


Underlying Hypothesis

- Drugs or other biologically active agents that decrease dynamical complexity are potentially toxic

- The greater the reduction in system complexity the higher the risk for the individual

Complexity and Biotoxicity: Cardiac Drug Trial



Loss of complexity predicts mortality

Preliminary Results Summary

- Certain cardiac drugs decreased normal sinus rhythm complexity (especially flecainide and encainide) in the CAST study
- Multiscale entropy (MSE) was independent of left ventricular ejection fraction in predicting mortality
- No traditional heart rate variability measure predicted mortality
- Greater decrease in MSE, greater the risk

Example II: Complexity and Human Postural Control

A Letters Journal Exploring the Frontiers of Physics

March 2007

EPL, **77** (2007) 68008
doi: 10.1209/0295-5075/77/68008

www.epljournal.org

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]

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[2] *Hebrew SeniorLife, Institute for Aging Research, Division of Gerontology, Beth Israel Deaconess Medical Center - 1200 Center Street, Boston, MA 02215, USA*
[3] *Center for BioDynamics and Department of Biomedical Engineering, Boston University - 111 Cummington Street, Boston, MA 02215, USA*
[4] *Center for Ocean-Land-Atmosphere Studies - 4041 Powder Mill Road, Suite 302, Calverton, MD 20705, USA*
[5] *Research Center for Adaptive Data Analysis, National Central University - Chungli, Taiwan, ROC*

Europhysics Letters, March 2007

Experimental Design

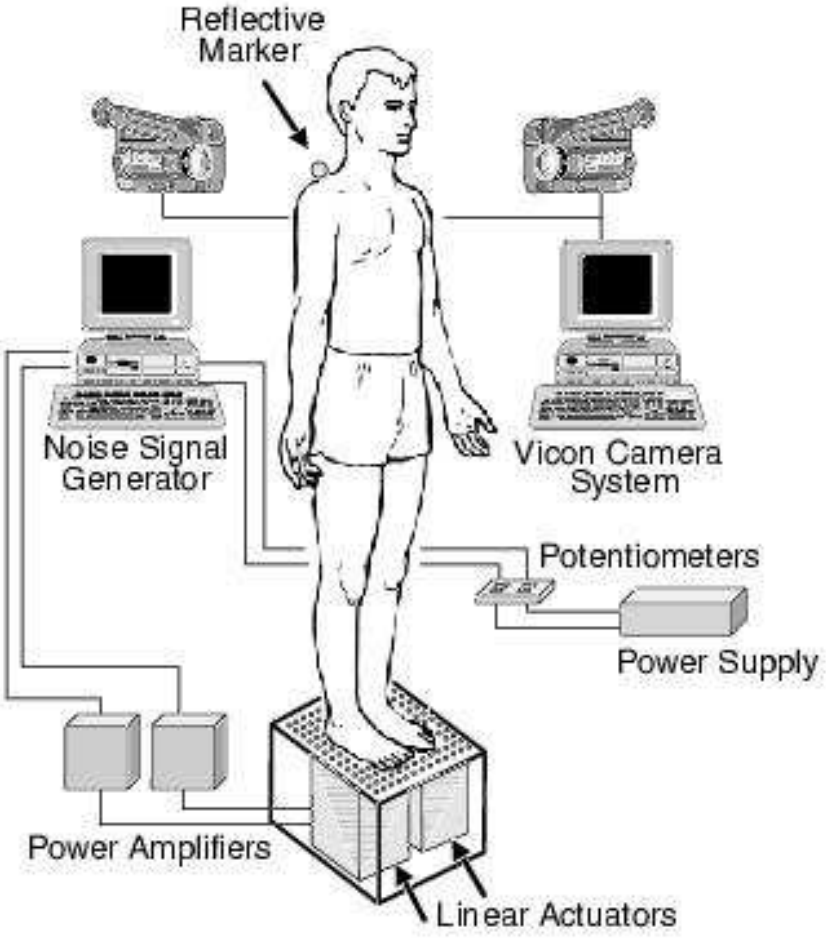


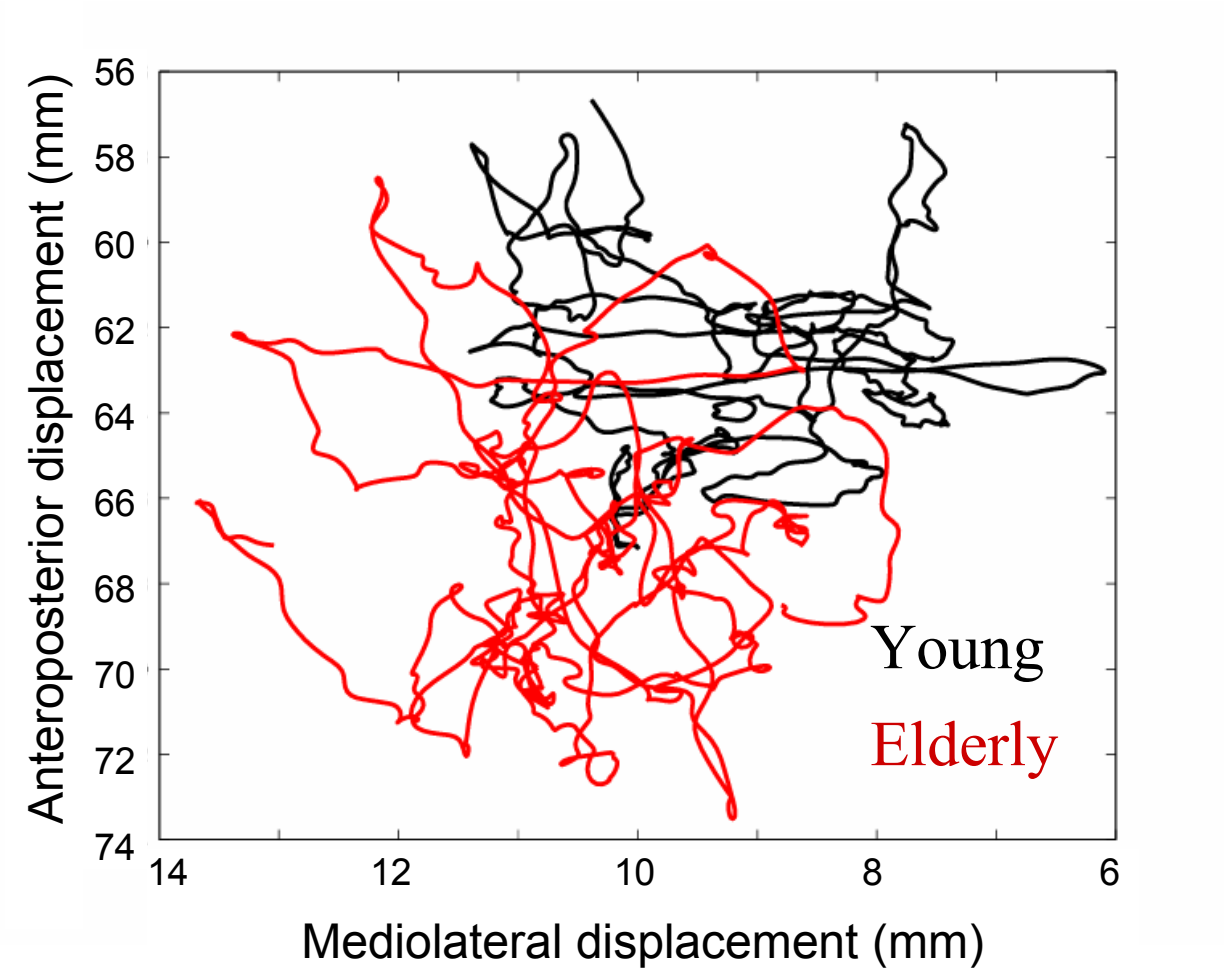
FIG. 1. A schematic diagram of the experimental setup.

- **Experiment I – Analysis of COP (sway) dynamics**
  - 15 healthy young
  - 22 healthy elderly
  - 22 fallers
- **Experiment II – Noise-Enhanced Human Balance Control *#**
  - 15 healthy young
  - 12 healthy elderly

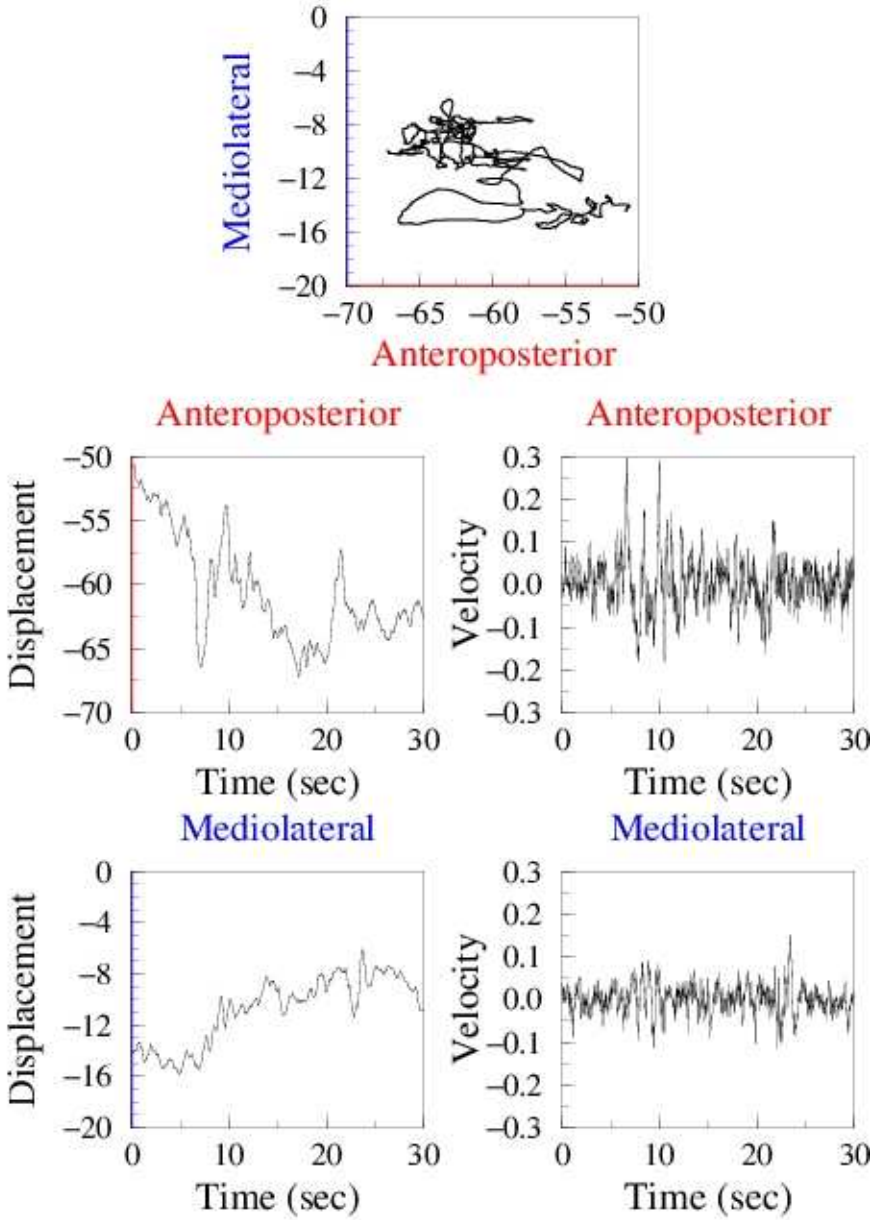
*A Priplata, J Niemi, J Harry, LA Lipsitz, and JJ Collins. Lancet 2003;**362**:1123.

A Priplata, J Niemi, M Salen, J Harry, LA Lipsitz, and JJ Collins. PRL 2002;**89**:238101

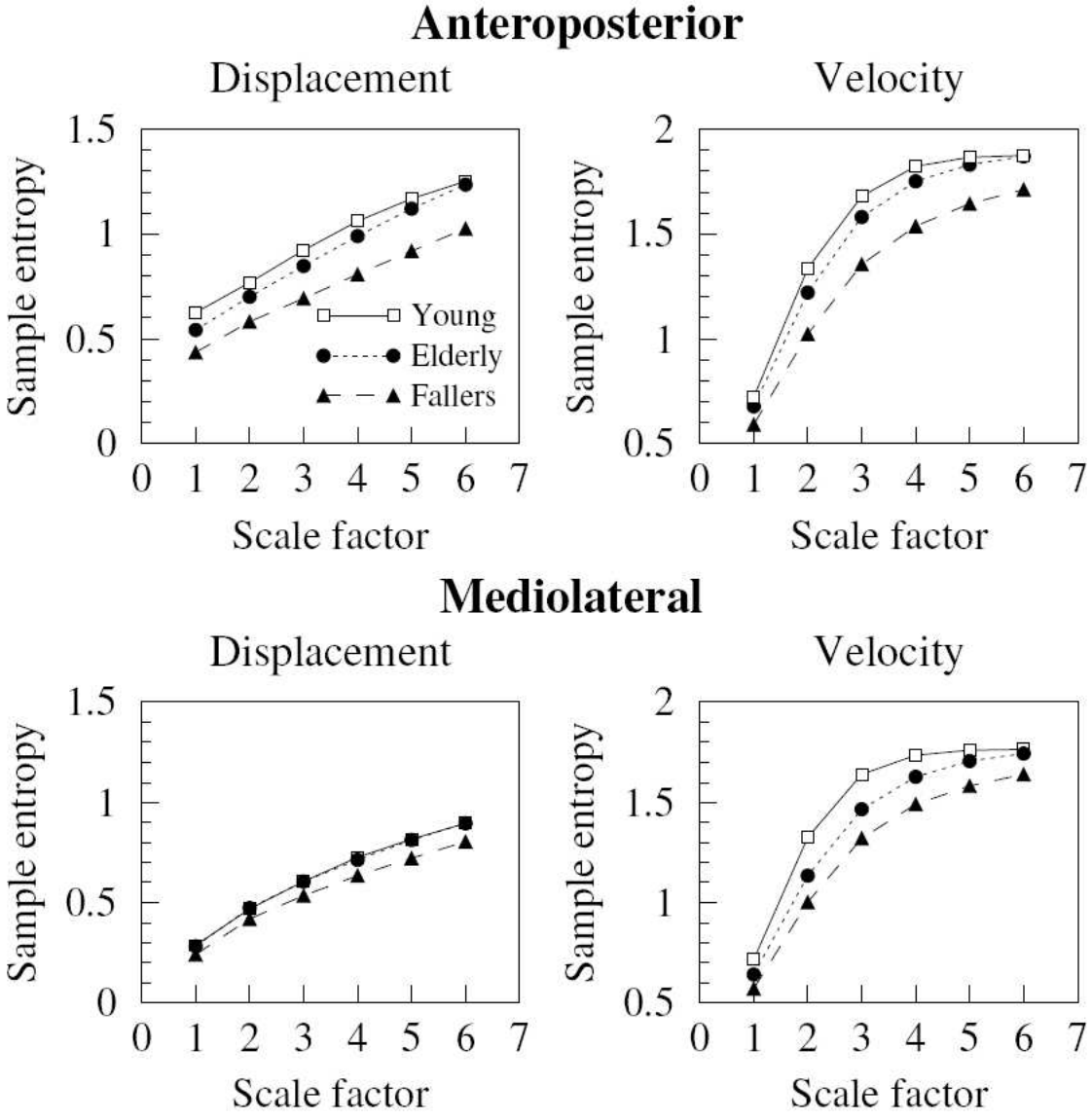
Center of Pressure Data



Time Series of Postural Sway



Multiscale Entropy (MSE) Analysis of Center of Pressure Time Series



Stochastic Resonance-based Intervention

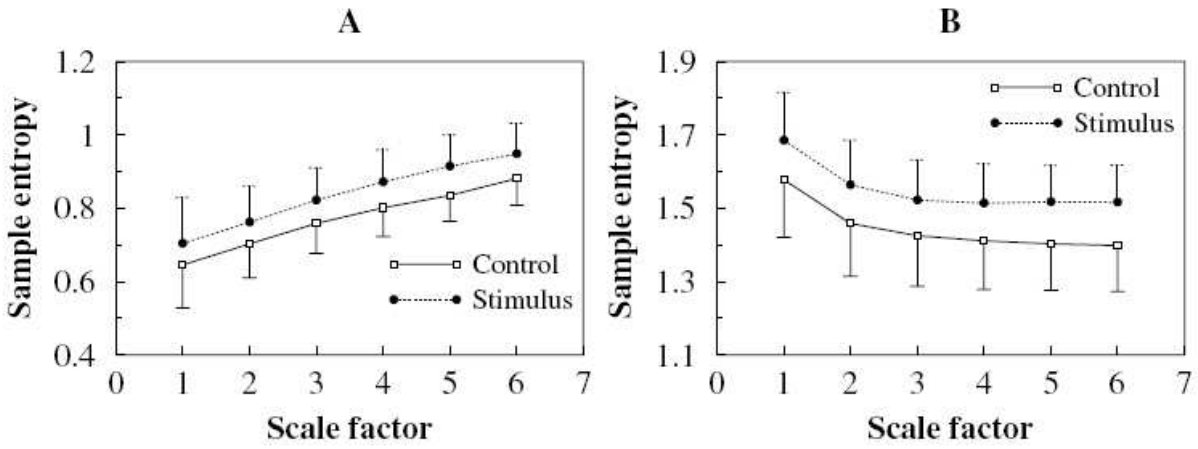
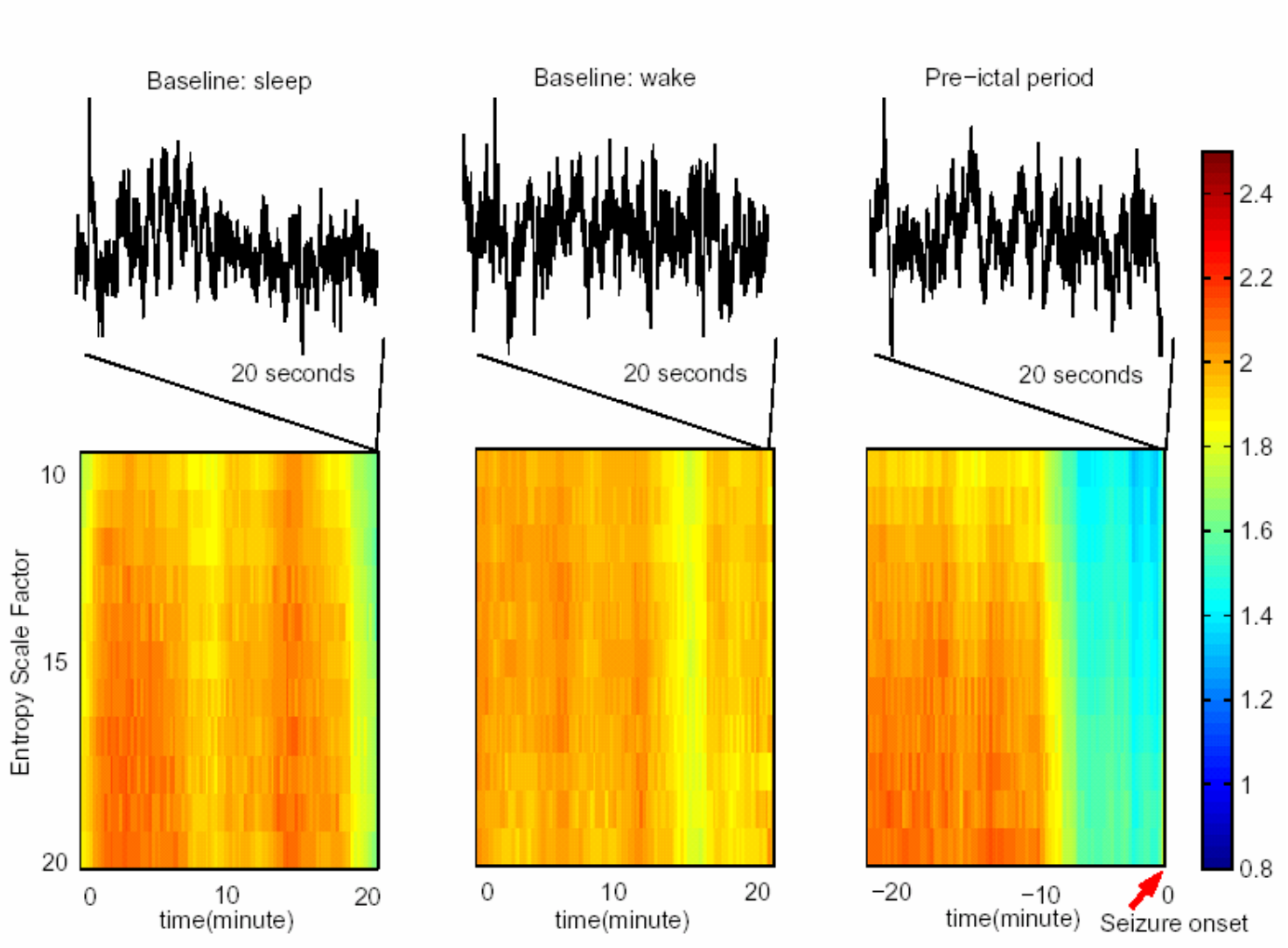


Fig. 2: MSE analysis of: A) anteroposterior and B) mediolateral postural displacement sway time series recorded under free-running (control) conditions and with subsensory noise stimulation (stimulus) from a healthy elderly subjects. Time series were detrended using the empirical mode decomposition method. The symbols represent mean values of sample entropy (SampEn) for all subjects and all trials and error bars represent standard errors. Parameters for the calculation of SampEn were: $m = 2$ and $r = 0.15$.

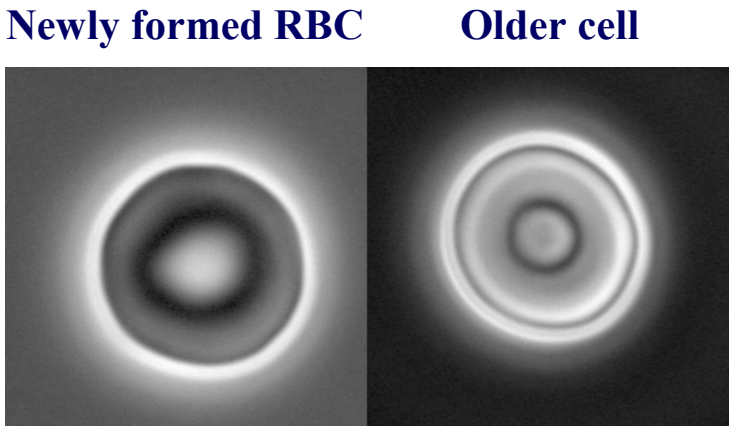
Example III: Forecasting Epilepsy



In collaboration with McCarthy's group

Example IV: Red Blood Cell (RBC) Membrane Motions*

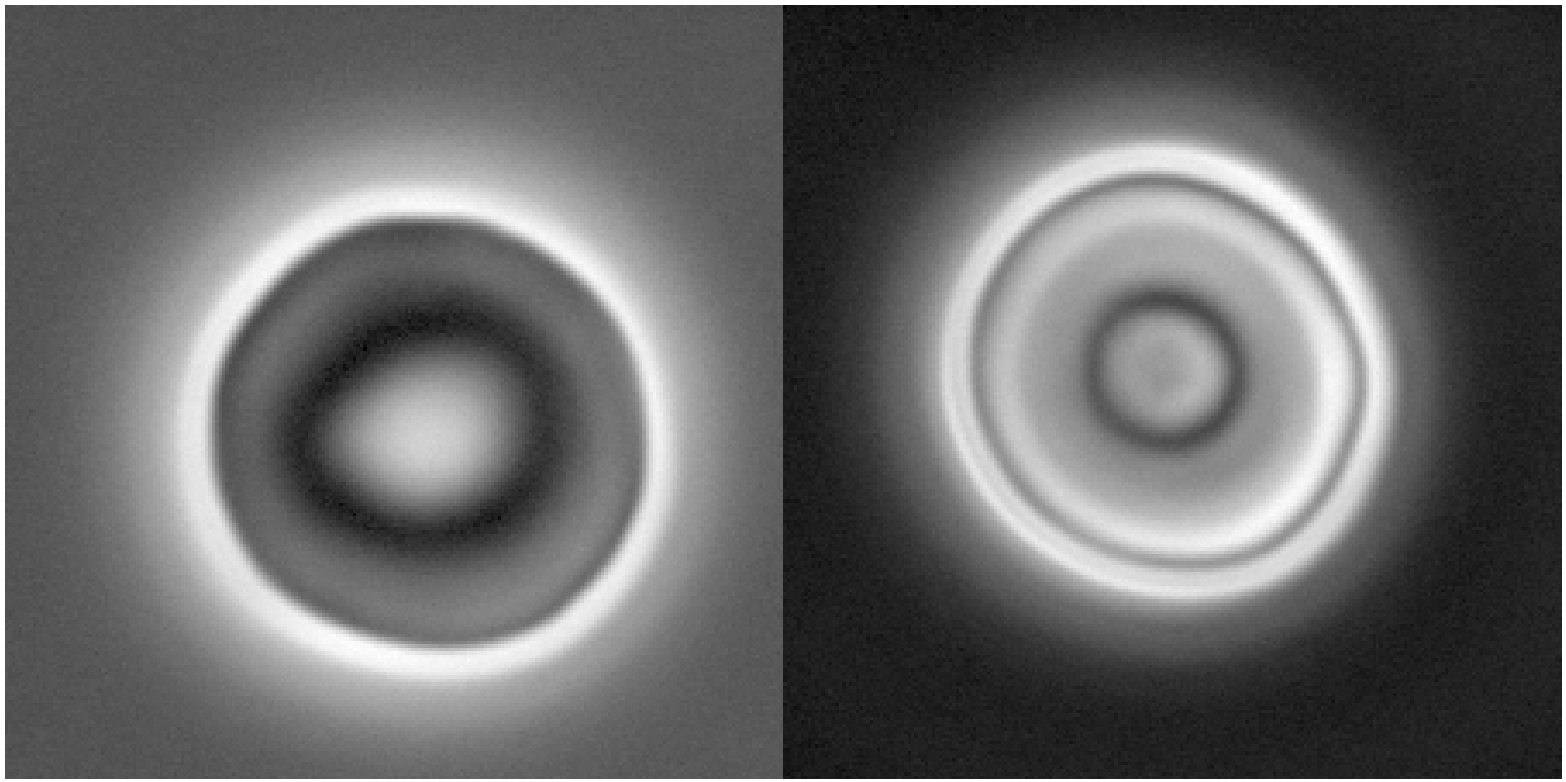
- RBC membranes have been know for decades to vibrate. These vibrations were thought to be random fluctuations
- We have just found that these subtle vibrations have a multiscale complex spatial-temporal structure
- Further, as RBCs age *in vivo,* the membrane dynamics loses complexity (information content measured by entropy over multiple scales)



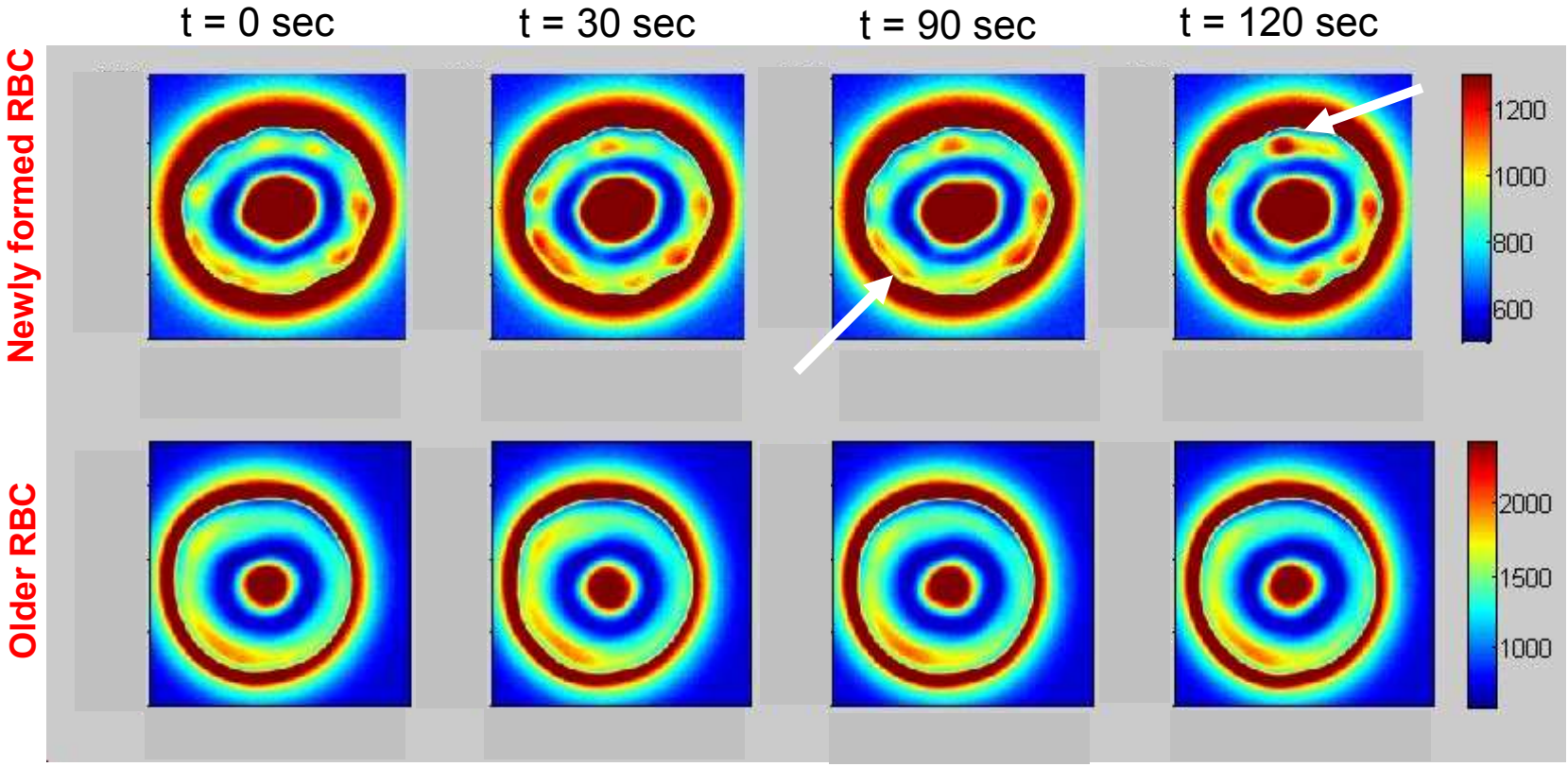
Phase contrast microscopy movie (25 frames/sec) from a newly formed (left) and an older (right) RBC from the same donor.

* Work done in collaboration with Anne Nicholson-Weller and Ionita Ghiran at the Division of Infectious Disease and Allergy-Inflammation, BIDMC

Newly formed RBC **Older cell**

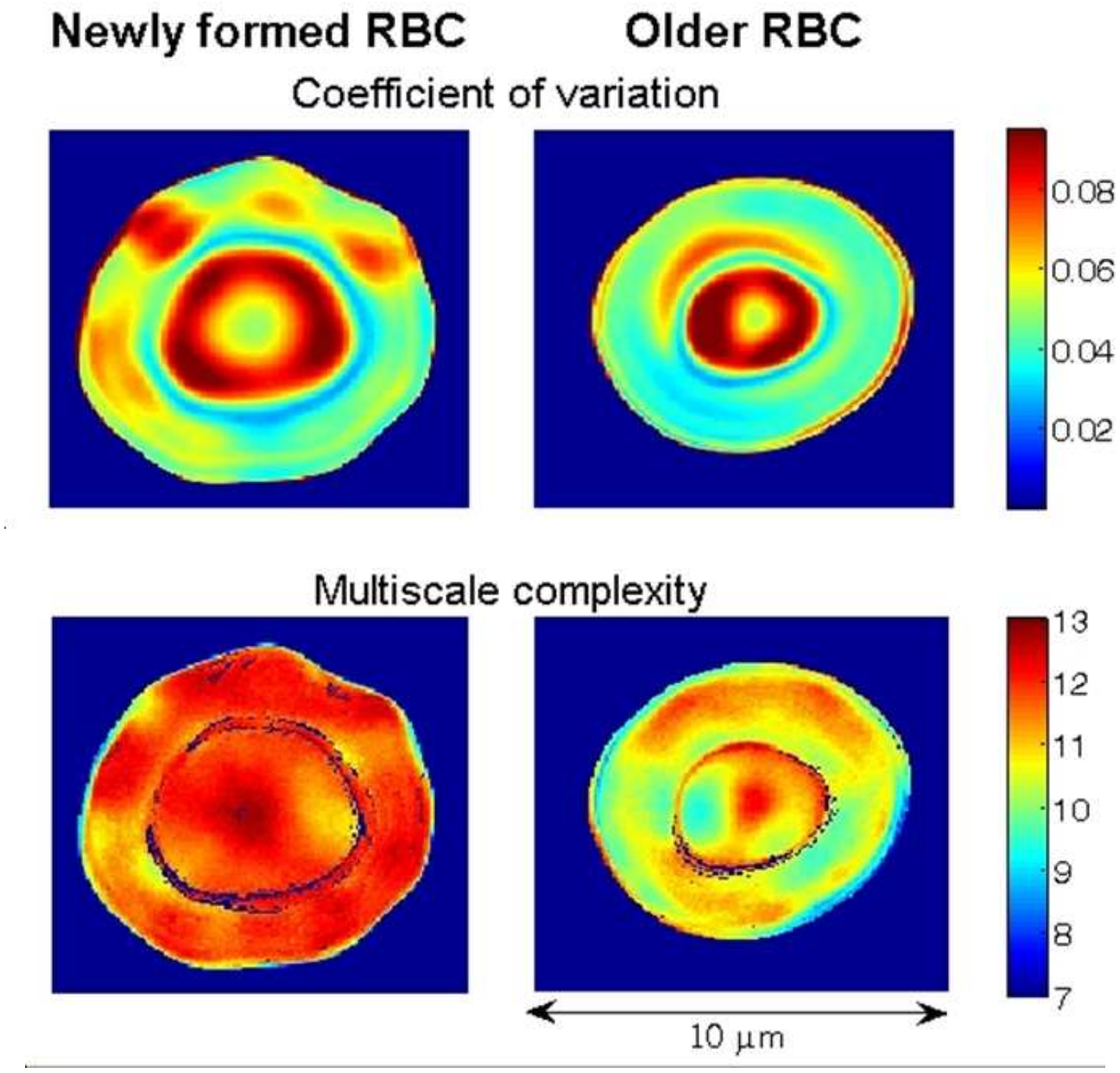


Loss of Human Red Blood Cell Membrane Complexity with *in vivo* Aging

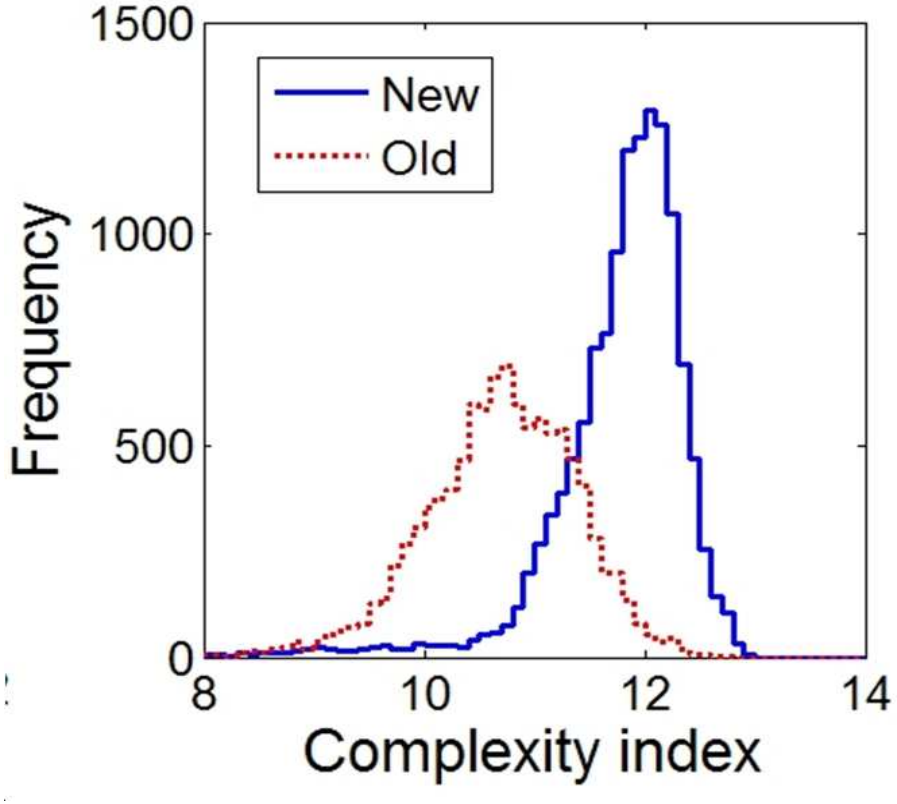


Colors map the magnitude of the membrane vibrations. The multi-focal transient domains (white arrows) in the newly formed cell correspond to areas of complex membrane vibrations. The older cell has less complex (more static) dynamics.

Analysis of RBC Membrane Dynamics



Analysis of RBC Membrane Dynamics: (Con't)



Complexity analysis may be used to determine "physiologic" age and functionality of RBCs.

Future Directions/Practical Applications

- To analyze the conditions under which donated blood for transfusion is stored.
- Newly published data indicate that the infusion of stored erythrocytes is associated with an increased risk of infarction in patients with unstable angina, worsening shock in the case of trauma and acute respiratory distress syndrome in ICU patients.
- It is possible that more physiologic methods of storing blood will prevent the erythrocytes from becoming pro-inflammatory and pro-thrombotic.
- Dynamical analysis may provide a robust means to perform high-throughput, systematic screening for the most physiologic blood storage techniques.

Fundamental Properties of Living Systems: Subcellular Domains to Integrated Organisms

- Complex variability is a marker of healthy (adaptive) dynamics
- Collapse of complexity: aging and disease (and biotoxins)
- Restoration of complexity is a marker of therapeutic benefit

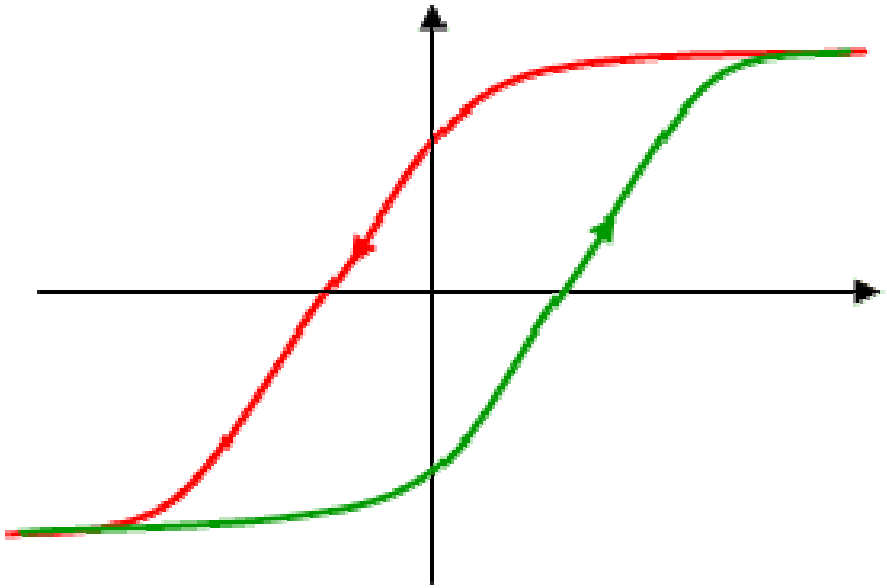
Part 2: Back to the Future: Multiscale Time Irreversibility (Time Asymmetry)

Multiscale Time Irreversibility (MTI): Background

- Fundamental property of non-equilibrium dynamics related to the unidirectionality of energy flow
- Definition: lack of invariance of the statistical properties of a signal under the operation of time reversal
- Current methods are single scale-based and lead to inconsistent results in physiologic signal analysis

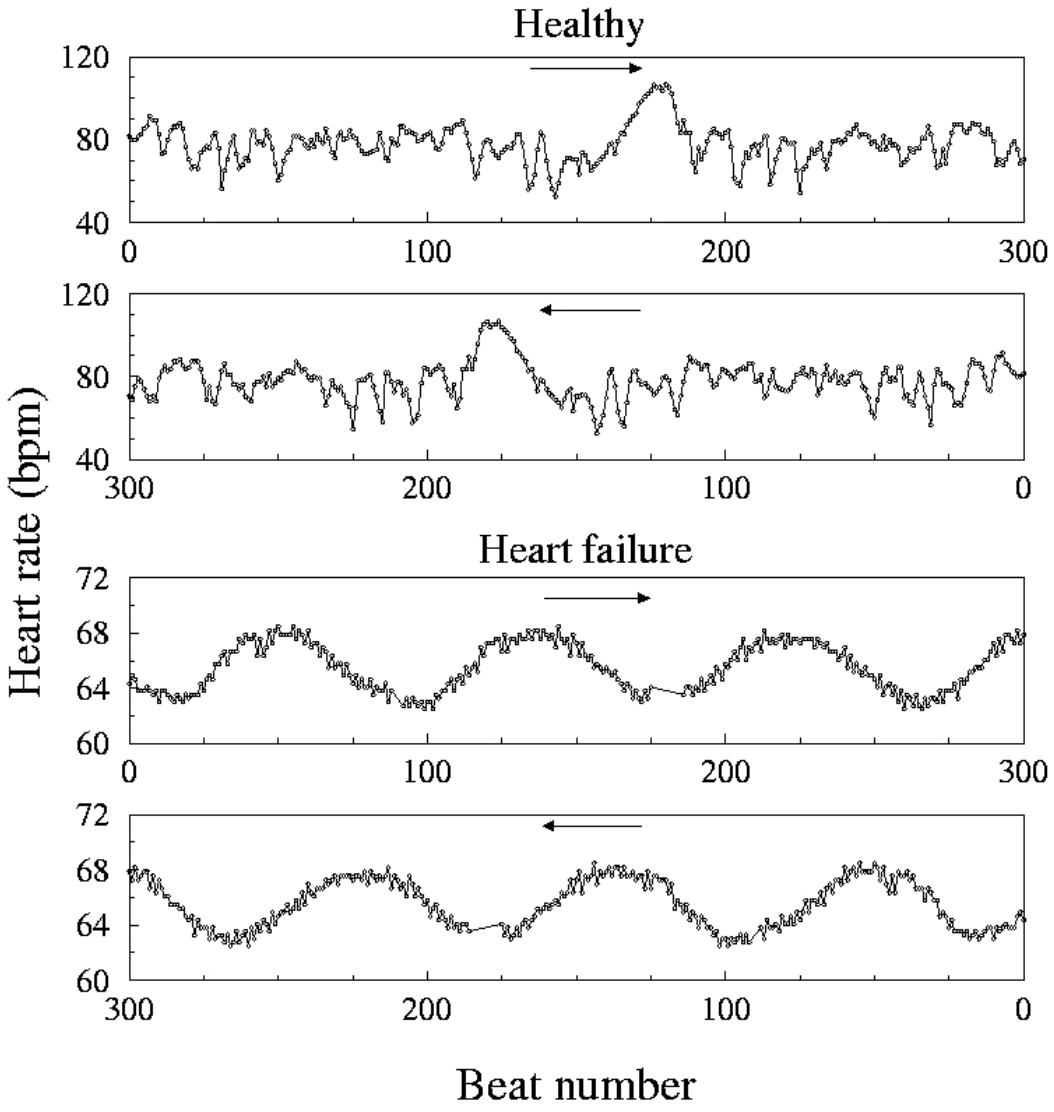
Costa, Goldberger, Peng. Phys Rev Lett 2005;95:198102

What is Hysteresis?



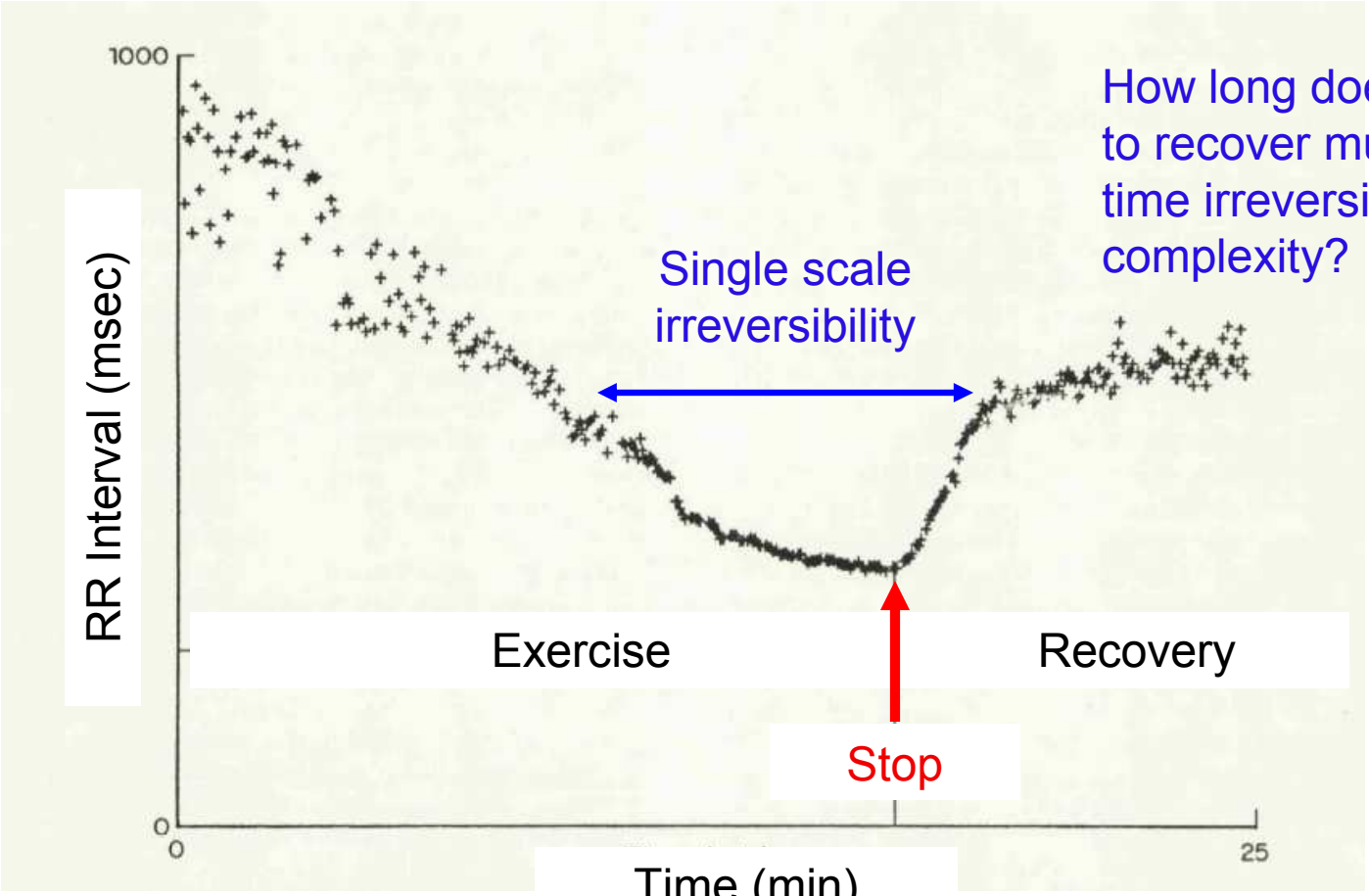
- A fundamental mechanism of time irreversibility is hysteresis
- The area inside the hysteresis loop equals the work done in the cycle

Multiscale Time Irreversibility (MTI): Hypotheses



- Time irreversibility is greatest for healthy physiologic dynamics, which have the highest adaptability
- Time irreversibility decreases with aging and disease

Questions for Future Research (Con't)



From: Jonnalagedda et al. PACE 1987;10:485

Multiscale Time Irreversibility (MTI): Algorithm

- Coarse-grain time series
- Quantify the degree of temporal irreversibility for each coarse-grained time series
- Integrate the values of temporal irreversibility for each coarse-grained time series over a range of time scales

Multiscale Time Asymmetry Measure

PHYSICAL REVIEW LETTERS

Broken Asymmetry of the Human Heartbeat: Loss of Time Irreversibility in Aging and Disease

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Time irreversibility, a fundamental property of nonequilibrium systems, should be of importance in assessing the status of physiological processes that operate over a wide range of scales. However, measurement of this property in living systems has been limited. We provide a computational method derived from basic physics assumptions to quantify time asymmetry over multiple scales and apply it to the human heartbeat time series in health and disease. We find that the multiscale time asymmetry index is highest for a time series from young subjects and decreases with aging or heart disease. Loss of time irreversibility may provide a new way of assessing the functionality of living systems that operate far from equilibrium.

Phys Rev Lett, 2005;95:198102.

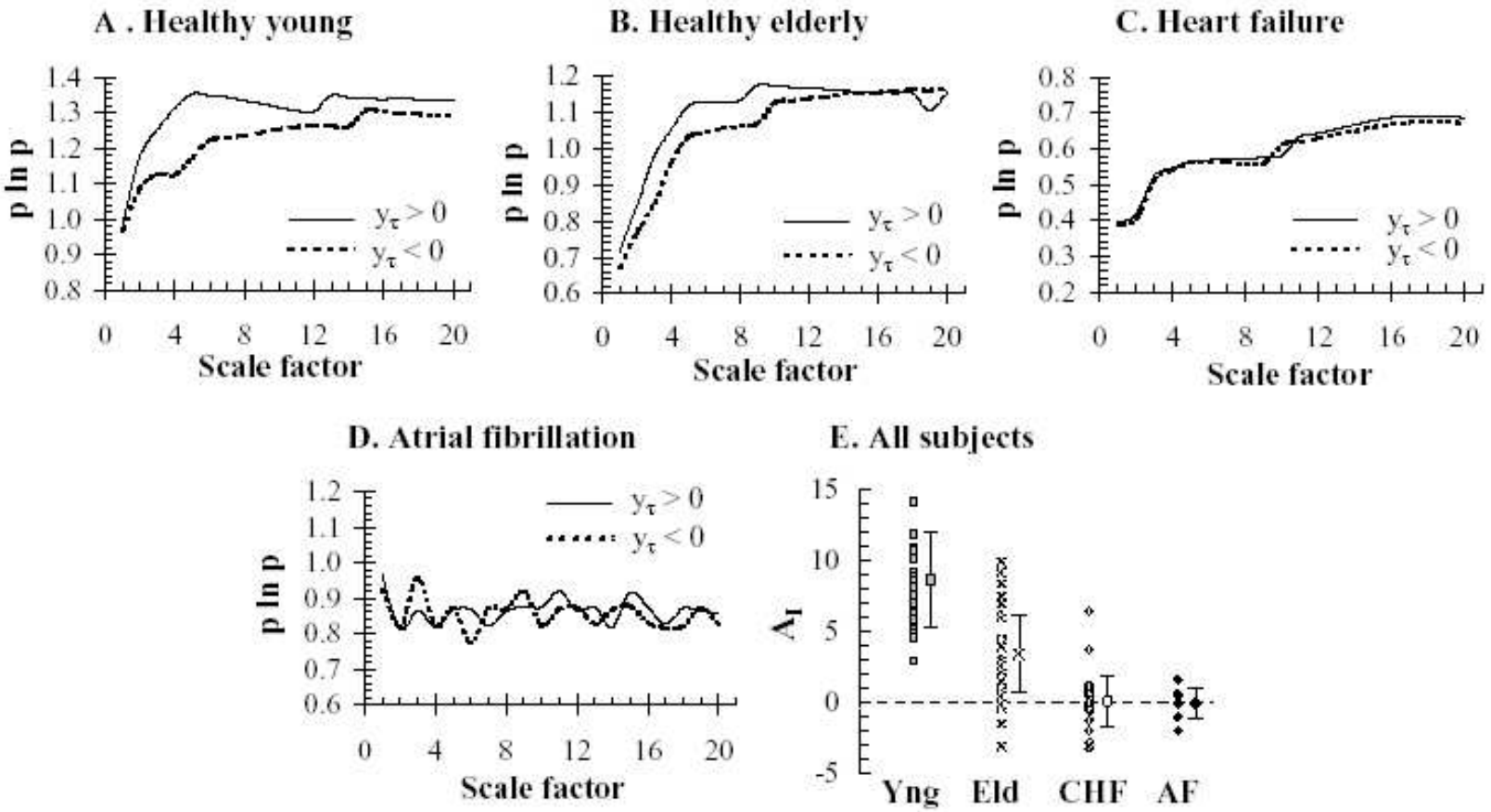
Time Irreversibility of Interbeat Interval Time Series

1. For each coarse-grained time series, we:
   i. Calculate the difference between consecutive data points
   ii. Calculate the percentage of positive $p(y_\tau > 0)$ and negative $p(y_\tau < 0)$ increments
   iii. The asymmetry index $A_i(\tau)$ is calculated by the equation:

$$A_i(\tau) = \frac{P(y_\tau>0)\ln P(y_\tau>0) - P(y_\tau<0)\ln P(y_\tau>0)}{P(y_\tau>0)\ln P(y_\tau>0) + P(y_\tau<0)\ln P(y_\tau>0)}$$

2. Over a range of time scales the asymmetry index is calculated by the equation: $\Sigma_{\tau=1} A_i(\tau)$.

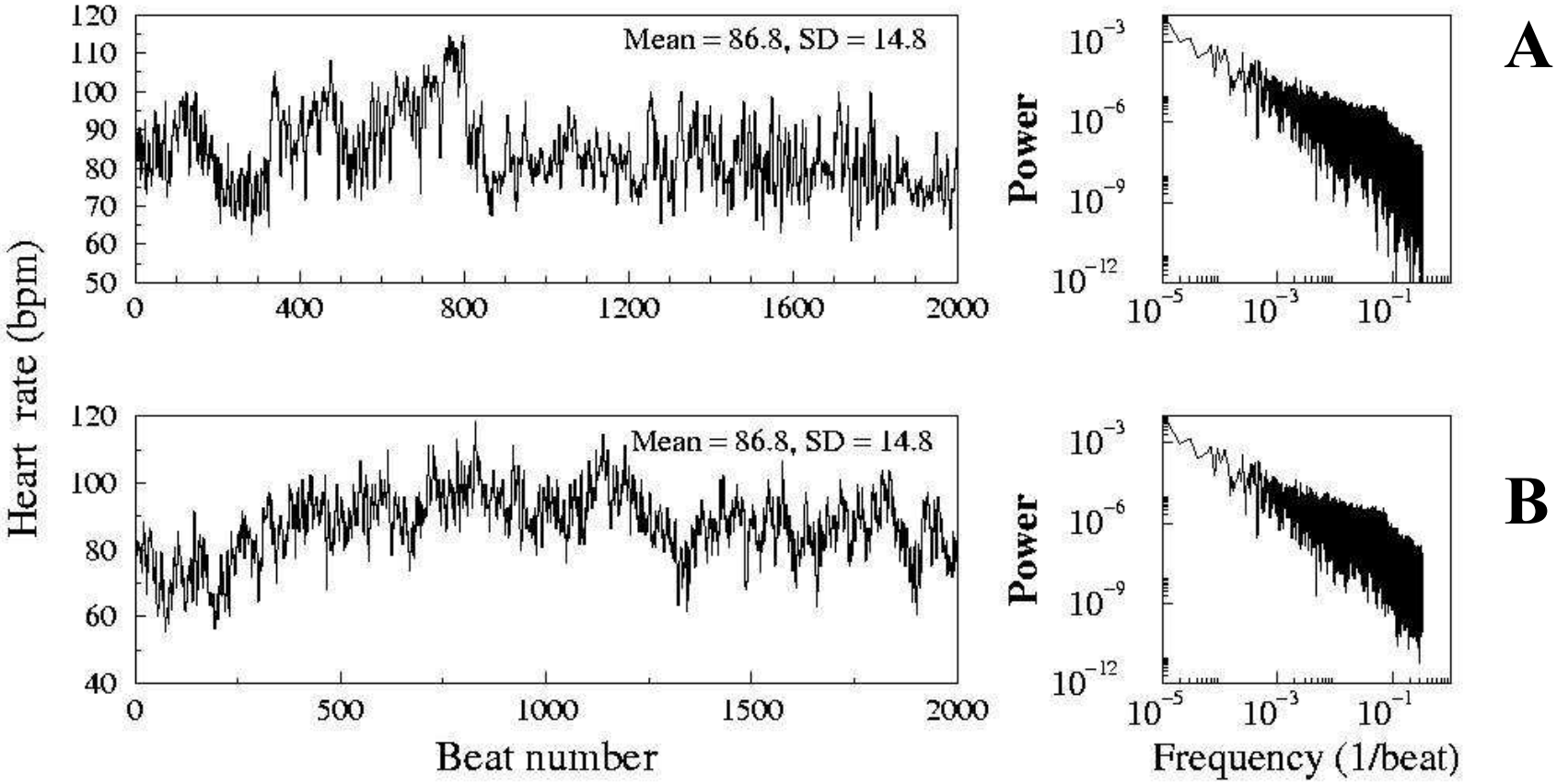
Time Irreversibility Analysis: Heart Rate Dynamics



Healthy (n = 26)
Congestive Heart Failure (n = 43)
Atrial Fibrillation (n = 9)

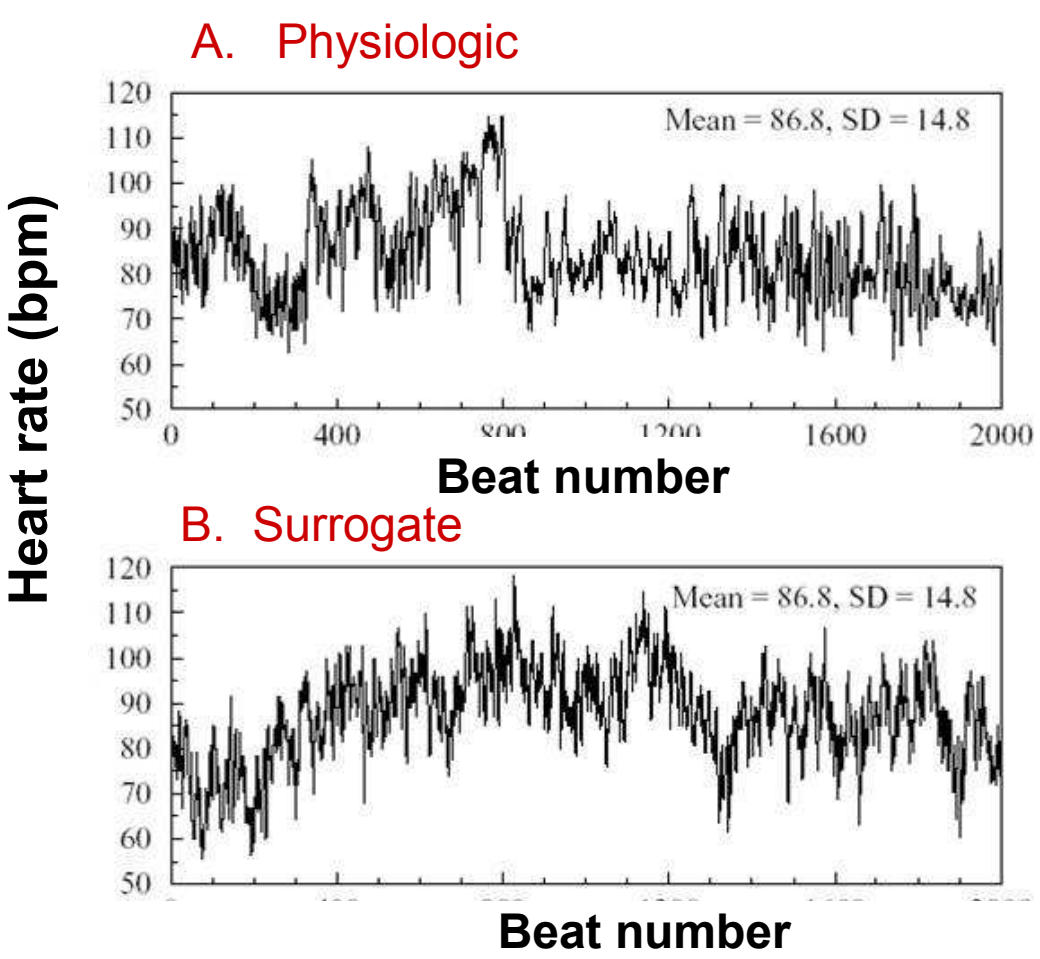
Data available at www.physionet.org

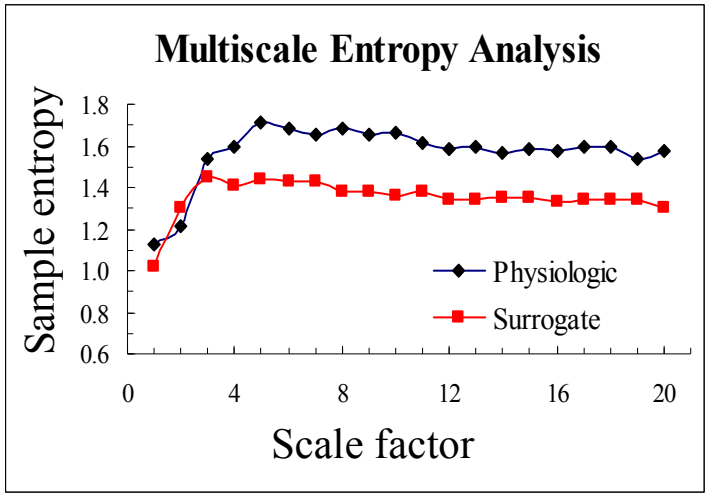
Beyond Traditional HRV: Which is Physiologic ?



A: Physiologic B: Surrogate (phase randomized)

Applying New Multiscale Measures





Multiscale Time Asymmetry

- **Physiologic:** Asymmetry index = 3.4
- **Surrogate:** Asymmetry index = 0.5

Thus, the physiologic time series is more complex and more time irreversible than the phase randomized surrogate time series

Final Conclusions

- Complex variability is a marker of healthy (adaptive) dynamics
- Complexity breaks down with aging and disease

Future Directions

- To develop mathematical models that account for the observed multiscale dynamical properties of physiologic systems
- Quantify other properties of complex systems: a) their degree of non-stationarity, b) coupling between signals