

# **Complex Systems, Variability Analysis & Critical Care**

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# **Overview**

- Clinical problem
- Research paradigm
- Complex Systems
- Variability analysis
- Clinical Application

# Critical Care - history

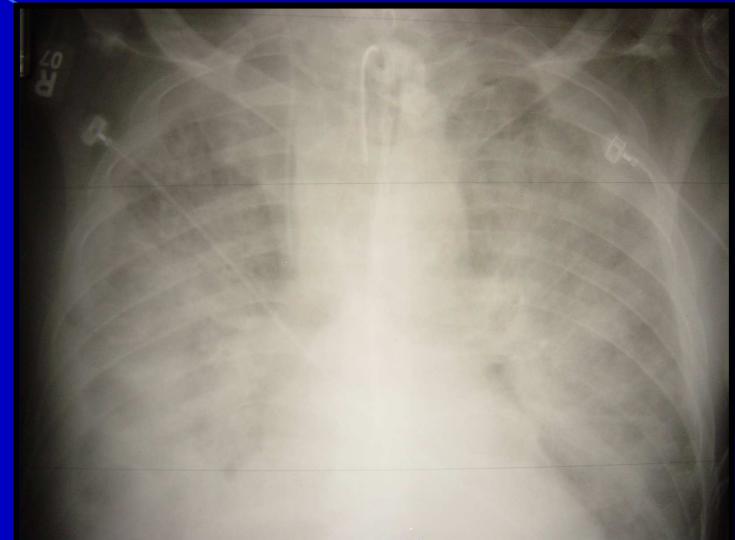
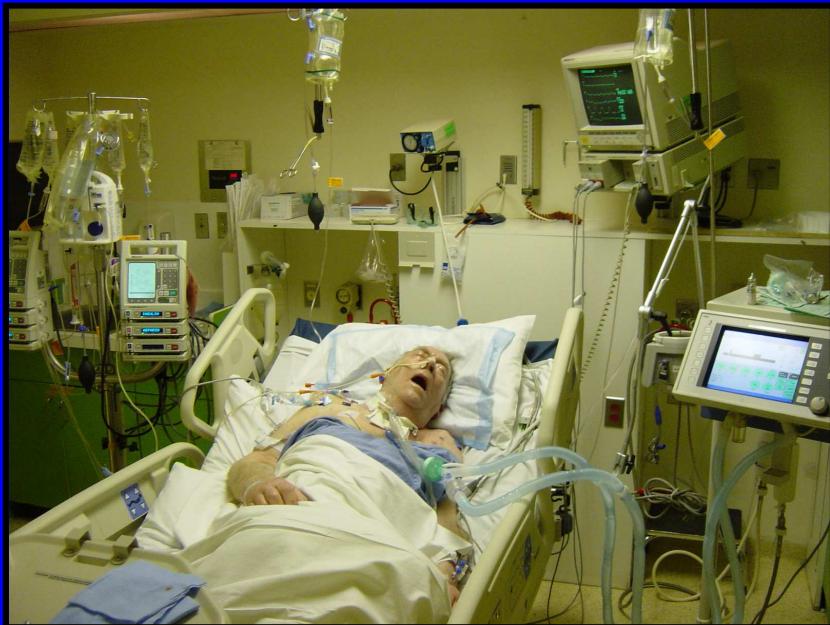
## Advances in care of the acutely injured patient

- WW I
  - Mortality due to irreversible “wound shock” 2° blood loss.
- Spanish Civil War & WW II
  - Liberal use of **blood transfusion** prevents “wound shock”.
  - Mortality due to **renal failure** 2° inadequate resuscitation.
- Korean War
  - **Crystallloid resuscitation** prevents renal failure & mortality.
- Vietnam War
  - Mortality 2° **Adult Respiratory Distress Syndrome (ARDS)**.
- 1970's
  - **Multiple Organ Dysfunction Syndrome (MODS)** surpasses hypoxia as principal cause of ICU mortality.

# Multiple Organ Dysfunction Syndrome (MODS)

- Leading cause of ICU mortality
  - Deitch EA, *Annals of Surgery* 1992; 216:117.
- Incidence: 15% ICU admissions.
  - Tran DD et al, *Critical Care Medicine* 1990; 18:474.
- Costs: >\$100,000/patient (~5x /survivor)
  - DeCamp MM et al, *JAMA* 1988; 260:530.
  - Beal AL et al, *JAMA* 1994; 271:226.

# MODS



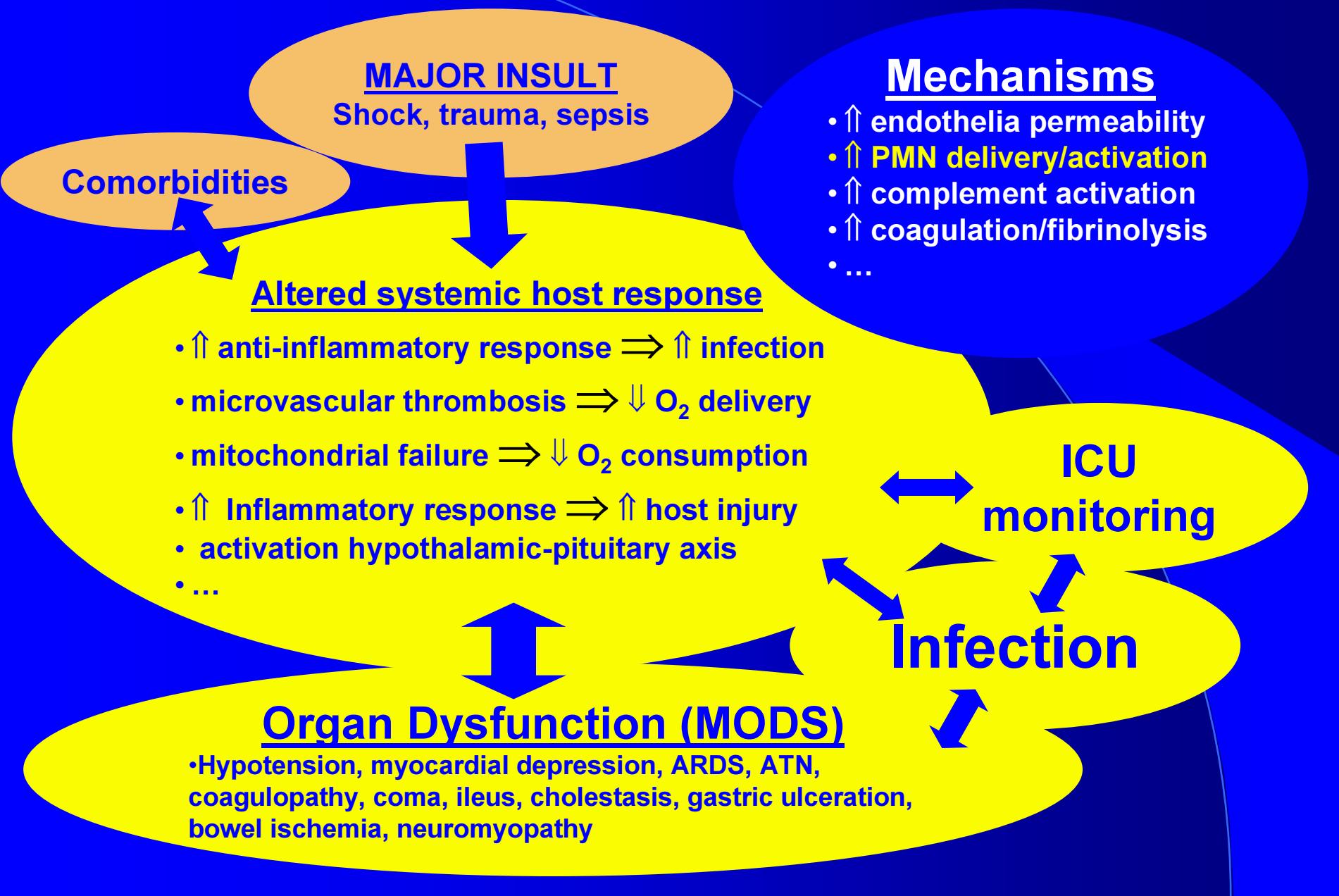
Why do research?

How do research?

Improve patient care

Research Paradigm

# Pathophysiology of MODS



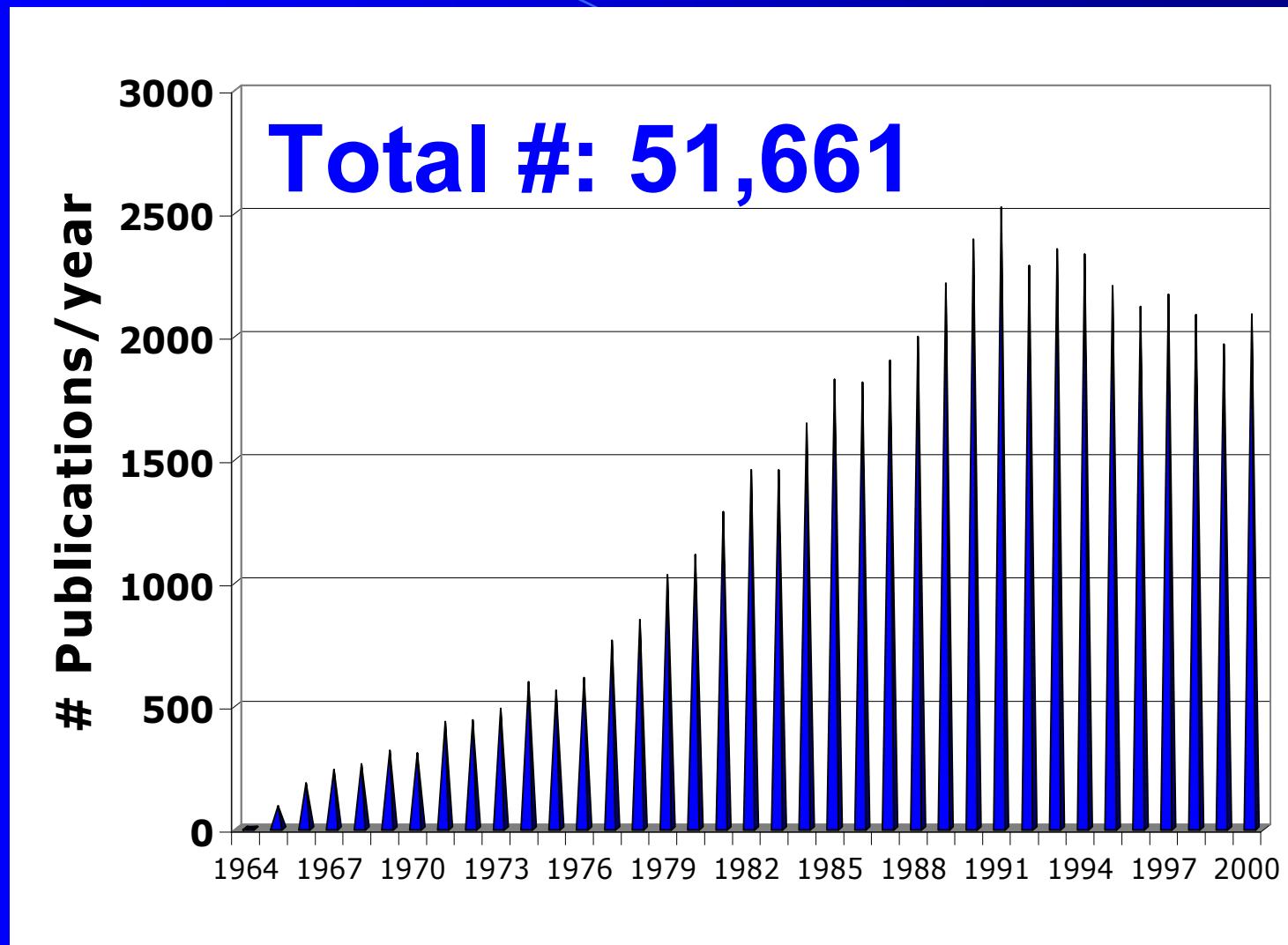
# Research Example

## The Neutrophil (PMN)



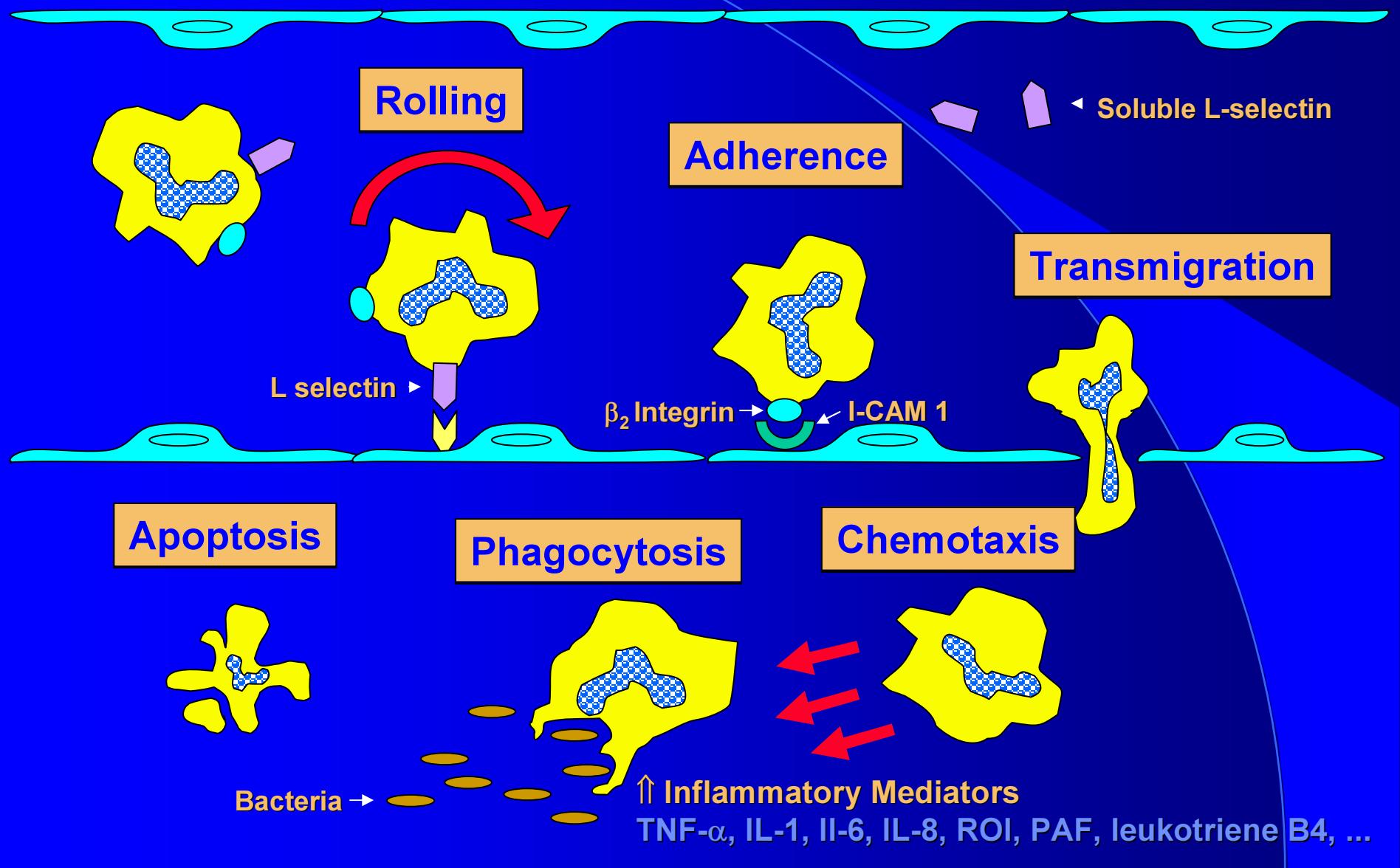
- “Foot soldier” of systemic inflammatory response
- ⇒ Comprises >90% circulating phagocytes
- ⇒ First & most abundant inflammatory cell / 24 hrs
  
- ⇒ Necessary for host defense
- ⇒ Implicated in host injury

# Neutrophil Publications

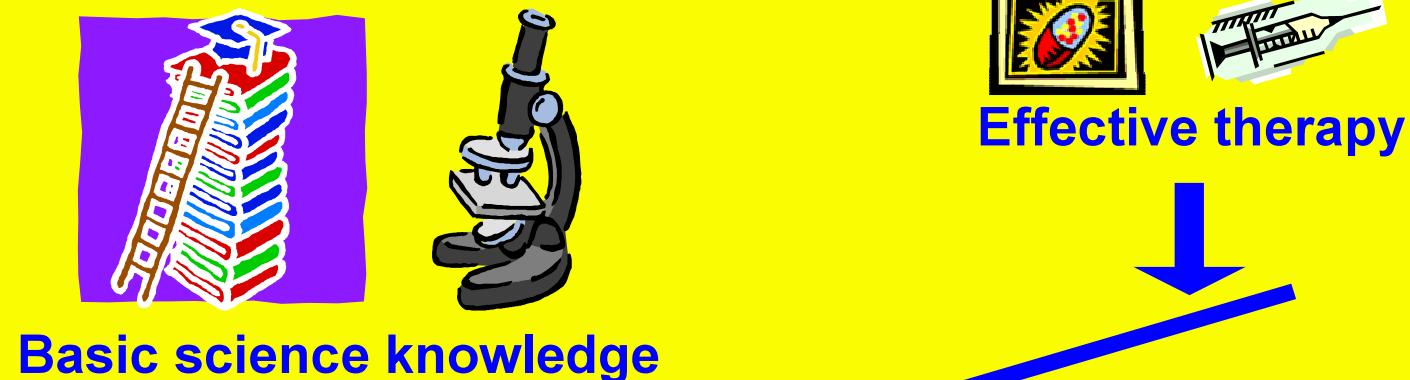


PubMED search: “neutrophil” as keyword

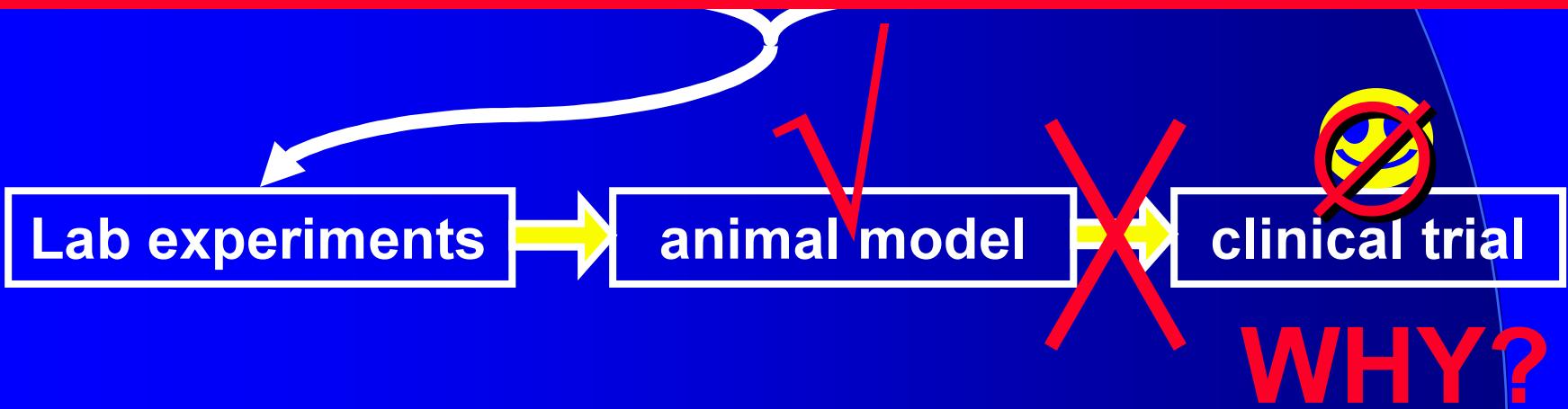
# Neutrophil Delivery & Clearance



# Bench / bedside imbalance



Effective therapy



# Research Paradigm

## Basic Science

- Analytic, reductionist
- Define parts, mechanisms, relationships, association with illness, ...
- Process:
  - *In vitro* lab  $\Rightarrow$  *in vivo* lab  $\Rightarrow$  animal exp'ts  $\Rightarrow$  clinic
- **Bench  $\Rightarrow$  Bedside**

## Epidemiology

- Population science
- Risk factors, statistics, treatment efficacy, ...
- Process:
  - Reviews, case control, cohort, meta-analysis, RCT's
- **Evidence based Medicine**

Missing?

Individual System

Time

# Complex System

## Definition

It is a system made of parts; whose properties are not fully explained by understanding the properties of the component parts.

- Gallagher R, Appenzeller T, *Science*, 284:79, 1999.

# Complex System

## Parts

- Number - large & variable
- Deterministic
- Non-linear relationships
- Reproducible response
- Spatial connectivity
- Variability over time

## System

- Properties disappear when parts separated
- Far from equilibrium
- Unpredictable response
- Display **negative entropy**
- Stability over time

# **Principles of a Complex System**

## **1. System creates order**

- Violates 2'nd Law Thermodynamics
- Emergent order = systemic properties
- Systemic properties  $\Leftrightarrow$  health vs. disease

## **2. Response to insult unpredictable**

- Cascade, avalanche behaviour
- Sensitivity to initial conditions
- Response determines outcome

# MODS: Observation

- The host response to sepsis, shock or trauma is a complex system.
- Response to intervention is unpredictable; controlled experiments may not apply to ICU.
- The emergent properties of the host response define health vs. disease, resulting in MODS.
- Emergent properties may be differentiated by altered **variability** & connectivity of the individual parts of the system.
  - Seely AJE, Christou NV. *Crit Care Med*, 28:2193 2000.

# Variability Analysis ( $\Delta/t$ )

## Existing applications

- HR
- BP
- Interbreath Intervals
- Tidal volume
- Airway impedance
- P0.1 pressure
- ...
- EEG
- Glucose
- Neutrophil counts
- Renal blood flow
- GH variability
- LH variability
- ...

# **Technology of Variability Analysis**

- 1. Time Domain analysis**
- 2. Frequency Domain analysis**
- 3. Entropy measurement**
- 4. Power Law analysis**
- 5. Detrended Fluctuation analysis**
- 6. ...**

# 1) Time Domain Analysis

- Data evaluated as a series in time
- Measure variation with time-based stats:
  - Standard Deviation
  - Variance
  - Long term variation:
    - Eg: Standard Deviation of data averaged over fixed periods (e.g. SDANN)
  - Short term variation
    - Eg: Root mean square Standard Deviation (RMSSD) = Square root of mean squared differences of consecutive data points

# Time domain analysis

E.g. Heart Rate Variability (HRV)

- variation of interbeat interval
  - R-R interval - measure on EKG
  - Measurement and analysis of HRV
    - Glass L, Kaplan D. *Med Prog Through Tech* 1993; 19:115.
    - Task Force, *Circulation* 1996; 93:1043.

Healthy  $\Rightarrow$  high degree of HRV  
Sick  $\Rightarrow$  decreased HRV

# Variability - time domain

- Applications - examples:
  - ↓ HRV predicts mortality with dilated cardiomyopathy
    - Tuininga YS et al, Br Heart J 1994; 72:509.
  - ↓ HRV predicts mortality post MI
    - Bigger JT et al, Am J Cardiol 1988; 61:208
  - ↓ HRV associated with cardiac sudden death
    - Singer D. J *Electrocardiol* 1988; 21:S46.
  - ...
- Advantages/caveats
  - Simple to compute
  - Bias due to non-stationarity
  - Does not reliably distinguish distinct signals

## 2) Frequency Domain Analysis

- Measure variation by frequency:
  - Fast-Fourier Transform: time  $\Rightarrow$  frequency
- Power Spectrum
  - Plot of amplitude (power) vs Frequency
  - Total area under curve = Power = Variance
  - First performed on heart rate variability
    - Akselrod S et al, *Science* 1981; 213:220.
- Assumptions
  - Linearity & stationarity

# Frequency Domain Analysis

## Examples of ICU applications

- **Sepsis:** ↓ total HRV, ↓ LF HRV, ↓ LF/HF
  - Garrard CS et al, Clin Aut Res 1993; 3:5.
  - Annane D et al. Am J Resp Crit Care Med 1999; 160:458.
  - Korach M et al, Crit Care Med 2001; 29: 1380.
- **Evaluation of mechanism of  $\Delta$  HRV power spectrum - sleep, posture, activity**
  - Furlan R et al. Circulation 1990; 81:537.

# Frequency Domain Analysis

## E.g. HRV in sepsis

Cardiac variability in critically ill adults: Influence of sepsis

Marion Korach; Tarek Sharshar, MD; Irène Jarrin; Jean-Pierre Fouillot, MD; Jean-Claude Raphaël, MD; Philippe Gajdos, MD; Djillali Annane, MD, PhD

*Critical Care Medicine* 2001; 29:1380-85

- 26 medical ICU pts, day 1, 30 min HR analysis, & removal of ectopic beats  $\rightarrow$  interpolation
- Power Spectrum calculated with FFT
  - Integration of VLF (0.02-0.04 Hz), LF (0.04-0.16), HF (0.16-0.30)
- Low LF/HF associated  $\rightarrow$  sepsis & mortality
  - LF/HF <1  $\Leftrightarrow$  likelihood ratio of 6.5 for sepsis
  - May identify patients with sepsis earlier  $\Rightarrow$  earlier therapy

### 3) Entropy Analysis

- Signal entropy = measure of irregularity, related to the information within signal
  - Regular repeating signal - low entropy
  - Irregular non-repeating signal - high entropy
- Approximate entropy (ApEn)
  - Measurement of proportion and degree to which vectors within data set that repeat themselves within the set.
  - SM Pincus, *Proc Natl Acad Sci USA* 1991.

# Approximate Entropy

- Natural information parameter for an approximating Markov Chain; closely related to Kolmogorov entropy
- Can be applied to short, noisy series
  - $100 < N < 5000$  data points
- Conditional probability that two sequences of  $m$  points are similar within a tolerance  $r$ 
  - Pincus SM, Goldberger AL, Am J Physiol 1994; 266:H1643
- Other entropy measures:
  - Cross-ApEn - compare two related time series
  - Sample entropy - does not count self matches
    - Richman JS, Moorman JR, Am J Physiol Heart Circ Phys 2000; 278:H2039.

# Variability - Entropy Analysis: examples

## ICU Applications of Approximate Entropy

- ↓ HRV ApEn after IV endotoxin (rabbits & humans)
  - Goldstein B et al, *Crit Care Med* 1995; 23:1694.
  - Godin PJ et al, *Crit Care Med* 1996; 24:1117.
- ↓ HRV ApEn in patients with MODS (correlated with severity)
  - Garrard CS et al, *Clin Auton Res* 1993; 3:5.
  - Goldstein B et al, *Critical Care Medicine* 1998; 26:352.

## 4) Power Law Analysis

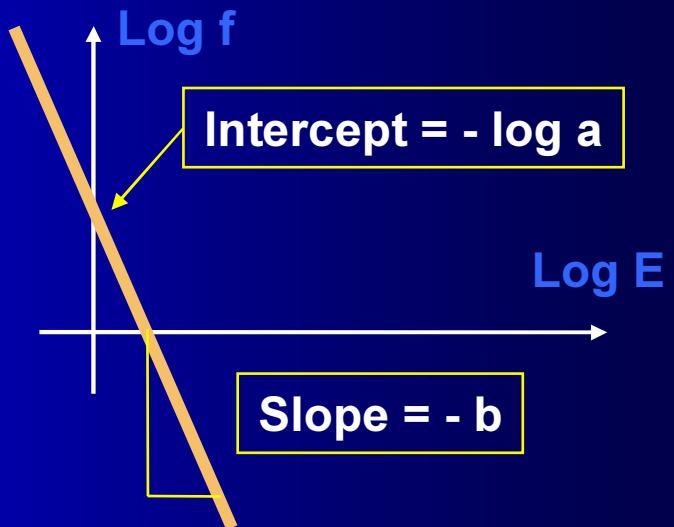
- Data evaluated in frequency domain
- Measures long range order (over time scales)
- Data obeys Power Law: Magnitude of variation is inversely proportional to frequency of occurrence.

$$aE^b = 1/f$$

**E** = amplitude of variation

**f** = frequency of its occurrence

**a,b** = constants



# **Power Law Analysis**

## **E.g. HRV in critically ill pts with MODS**

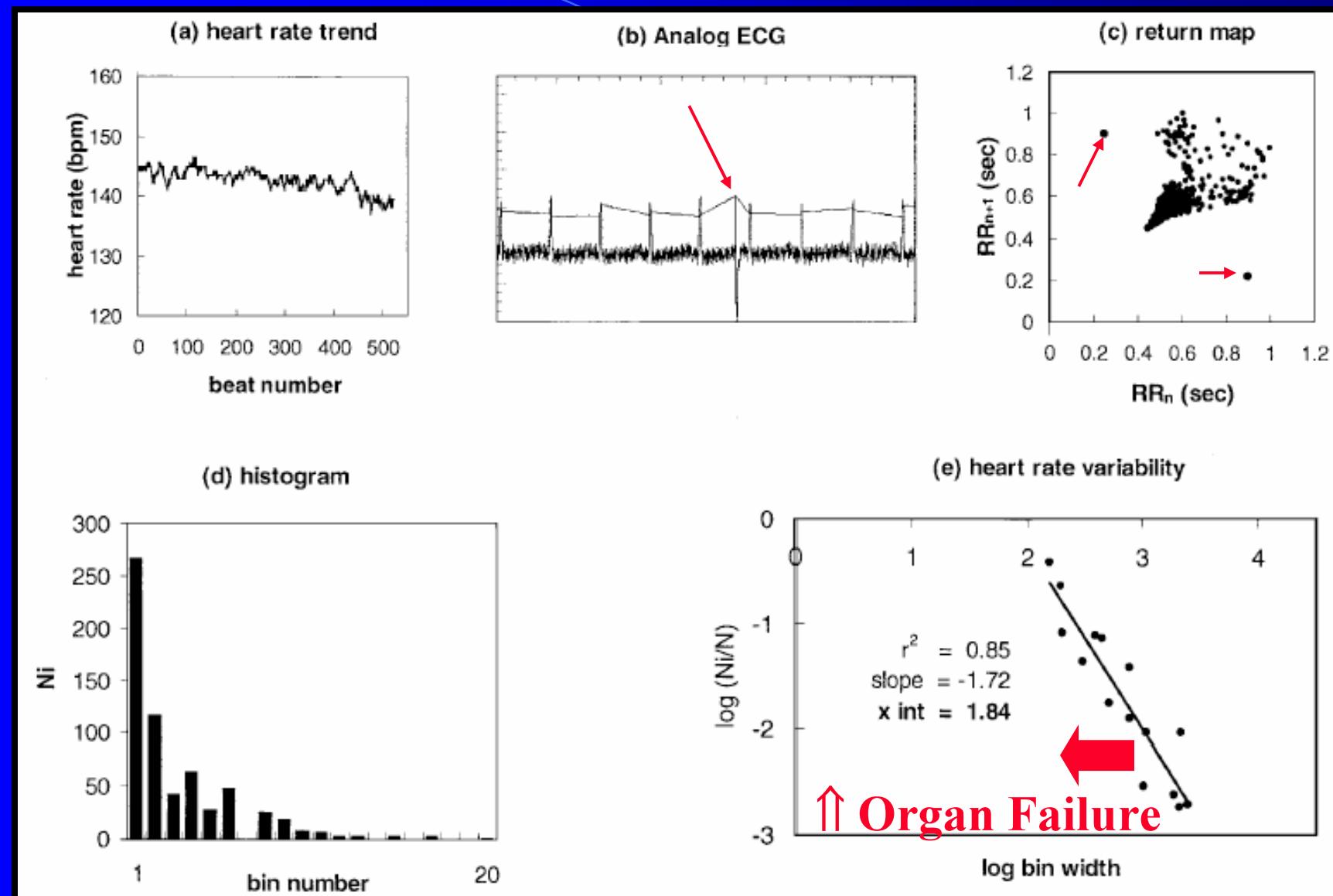
Novel method to quantify loss of heart rate variability in pediatric multiple organ failure\*

Shane M. Tibby, MRCP; Helena Frndova, PhD; Andrew Durward, FCP; Peter N. Cox, MD, MBChB

*Critical Care Medicine* 2003; 31:2059.

- 50 pediatric ICU patients (104 measurements)
- HR measured for 5 min, removal of artifact
- Change in intercept correlated with organ failure, independent of age & HR
- Found Power Law superior to other techniques

# E.g. HRV in critically ill pts with MODS



# **Power Law Analysis**

**E.g. Respiratory Impedance  
Variability (Zvar) in asthma**

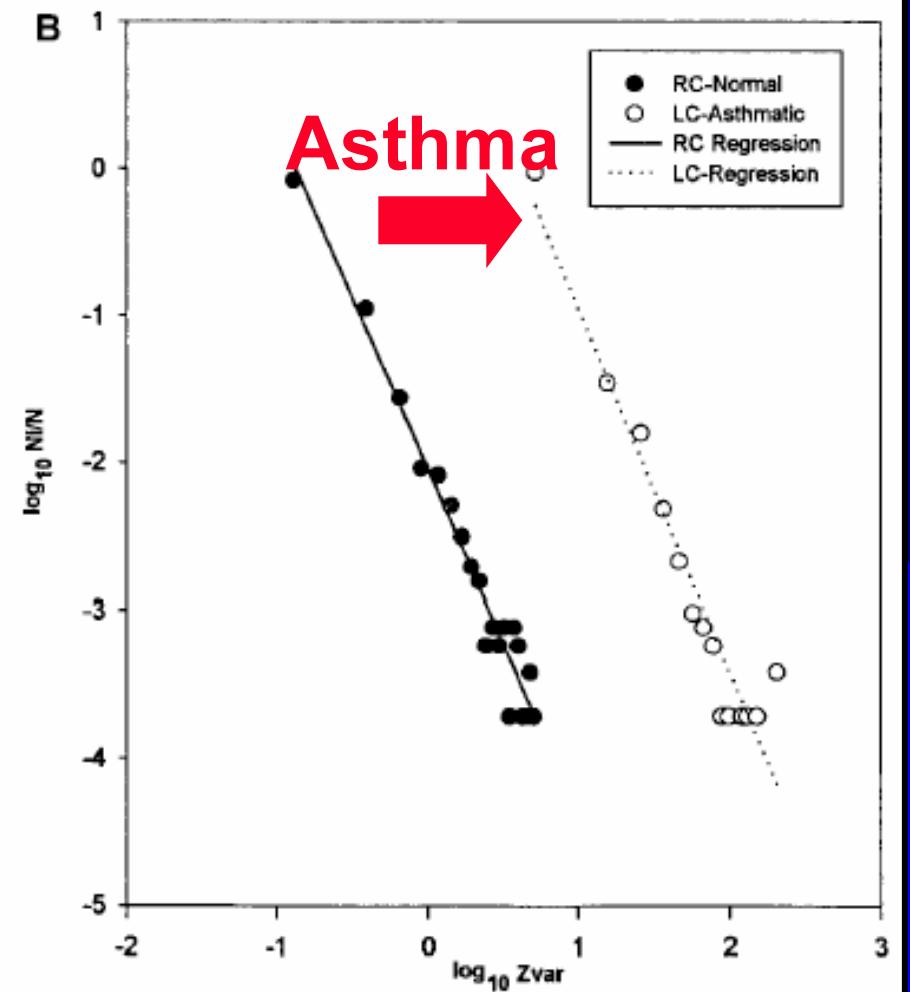
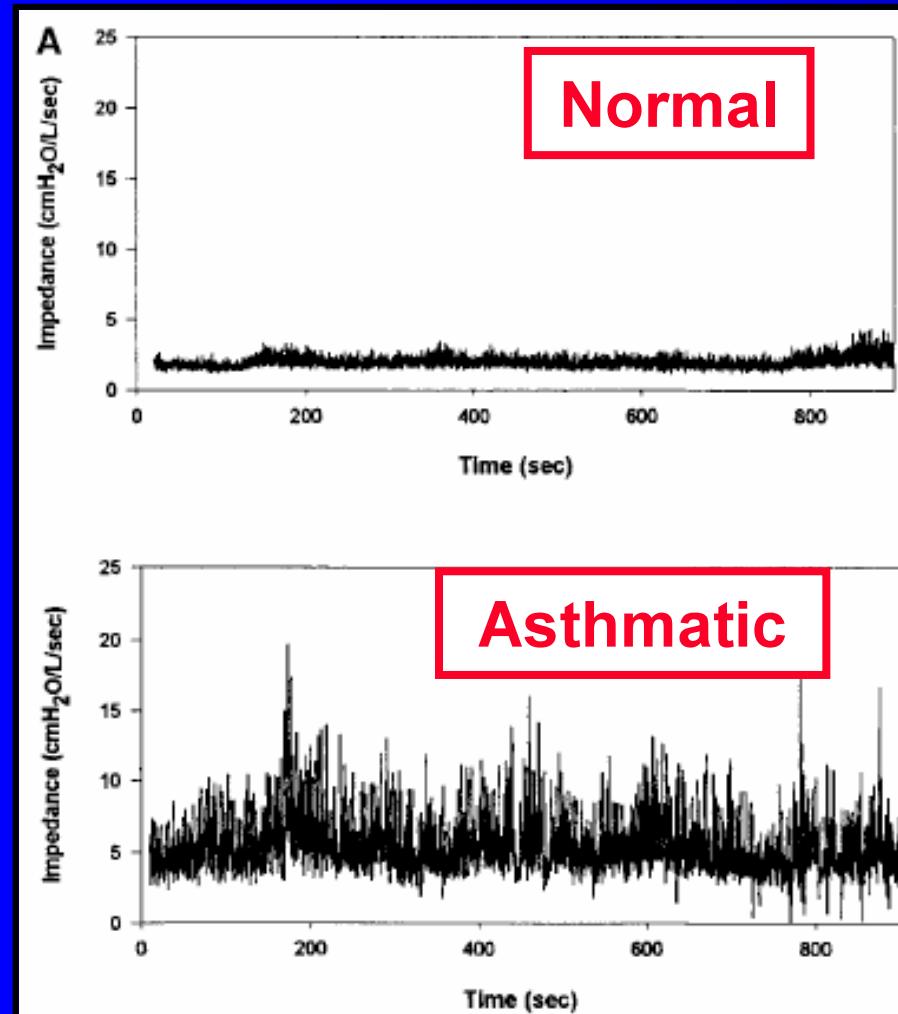
## **Deciphering the Homeokinetic Code of Airway Smooth Muscle**

**CHENG-LI QUE, G. MAKSYM, and PETER T. MACKLEM**

**Am J Respir Crit Care Med Vol 161. pp S161-S163, 2000**

- Increased Zvar in asthma patients
- Predicts severity of asthma attacks
  - Macklem PT et al, *Annals RCPSC* 1998; 4:194.

# Respiratory Impedance Variability (Zvar)



Macklem PT et al, *Annals RCPSC* 1998; 4:194.

# **5) Detrended Fluctuation Analysis (DFA)**

- DFA is a measure of long range order = patterns of variation across time scales.
- Based upon a modified root mean square of a random walk
- Designed to distinguish between fluctuations 2° environment vs. those 2° intrinsic dynamics of the system.
- Does not assume stationarity.
- Integrated, detrended calculation.
  - Peng CK, et al. *Phys Rev E* 1994; 49:1685-9.

# Detrended Fluctuation Analysis

- **Step 1: Integrated series**
  - Average the N values of  $B_i$  in dataset ( $B_{ave}$ )
  - Create sum of differences between individual values & average

$$y(k) = \sum_{i=1}^k [B(i) - B_{ave}]$$

- $Y(k)$  represents an evaluation of trends
- **Step 2: Detrended time series**

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

- **Step 3: Calculate relationship between  $F(n)$  &  $n$**
- **Step 4: Calculate scaling exponents**
  - Log  $F(n)$  vs. log  $n$  - straight line with slope  $\alpha$
  - Two straight lines:  $\alpha_1$  ( $n < 11$ ) &  $\alpha_2$  ( $11 < n < 10,000$ )
    - Peng CK et al; Phys Rev E 1994; 49:1685

# **Detrended Fluctuation Analysis**

## **E.g. application to critical care**

Linear and nonlinear analysis of hemodynamic signals during sepsis and septic shock

Daniel Toweill, BSChE; Karen Sonnenthal, RN, MSNP; Brent Kimberly, BA; Susanna Lai, BS; Brahm Goldstein, MD, FAAP, FCCM

**(Crit Care Med 2000; 28:2051–2057)**

- 30 pediatric ICU pts with sepsis ± shock
- 5-10 min recordings, Day 1, 2, 3, 7, 14, 21, ...
- ↑ heart rate DFA scaling exponent with shock
  - Sepsis:  $\text{HR } \alpha 1.00 \pm 0.07$
  - Septic shock  $\text{HR } \alpha 1.22 \pm 0.06$  ( $p = 0.02$ )

# Variability Analysis Summary

- Specific patterns of variation  $\Leftrightarrow$  health
- Altered patterns of variation  $\Leftrightarrow$  illness
- Correlation with ICU severity of illness
- Consider artifact, duration, stationarity
- No single technique provides complete description
- Ongoing research regarding optimal signal characterization

# Critical Care - future

Physiologic data acquisition system and database for the study of disease dynamics in the intensive care unit\*

Brahm Goldstein, MD, FCCM; James McNamee, PhD; Bruce A. McDonald, PhD; Miles Ellenby, MD; Susanna Lai, BS; Zhiyoung Sun, MS; Donald Krieger, PhD; Robert J. Sclabassi, MD, PhD

*Critical Care Medicine* 2003; 31:433.

- Real-time continuous data acquisition
- Analysis of parametric & waveform signals
  - Includes HR, BP, CVP, PAP, LAP, RAP, ICP, T, O<sub>2</sub> sat
- Facilitates dynamical mathematical analysis
- Future: describe pathophysiologic ICU disease states in real time

# **Conclusions**

## **General**

- **Multiple organ dysfunction is the leading cause of death in critically ill patients.**
- **Complexity science is complementary to basic science and epidemiology.**
- **Controlled animal experiments may not apply in an uncontrolled ICU environment.**
- **Variability analysis offers a technique to evaluate systemic properties continuously.**

# **Conclusions**

## **Clinical benefit**

- **Multiple technique variability analysis offers novel technology to determine severity of illness in critically ill patients.**
  - **Continuous or real time ICU patient monitoring may improve outcome by identifying which patients respond to intervention, and when.**
- **Exciting application of math in medicine**

# Information & references

- Internet resources
  - *PhysioNet, PhysioBank, PhysioToolkit;*  
<http://www.physionet.org>
- Computers & monitoring in critical care
  - Adam Seiver, K Niemenen
- Heart rate variability in critical care
  - Brahm Goldstein, Tim Buchman
- Interpretation of variability
  - Ary Goldberger, DE Vaillancourt, KM Newell, Paul Godin
- Techniques of Variability Analysis
  - HK Stanley, CK Peng, SM Pincus, Peter Macklem

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