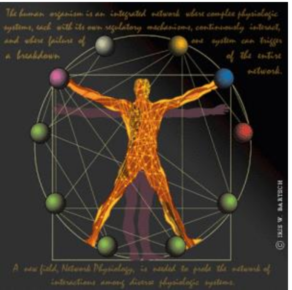
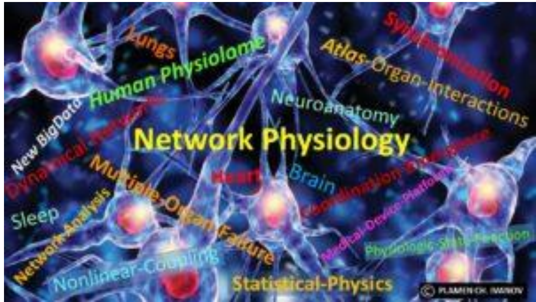
[**First International Summer Institute on Network Physiology (ISINP)**]()

“Physics-envy is the curse of biology.”
Joel Cohen, *Science* **1971**, *172*, 675

The Networks of the Self
1. Health, Healthy States and Physiologic Resilience.

Timothy G. Buchman, PhD, MD, FACS, FCCP, MCCM
Director, Emory Critical Care Center
External Faculty, Santa Fe Institute





Speaker Disclosure and Disclaimer

- Editor-in-Chief, ***Critical Care Medicine*** (stipend)
- Advisor, ***James S. McDonnell Foundation*** (travel, lodging, honorarium)
- External Faculty, ***Santa Fe Institute*** (travel, lodging, honorarium)
- Presenter, ***Various Universities*** (travel, lodging, honorarium)

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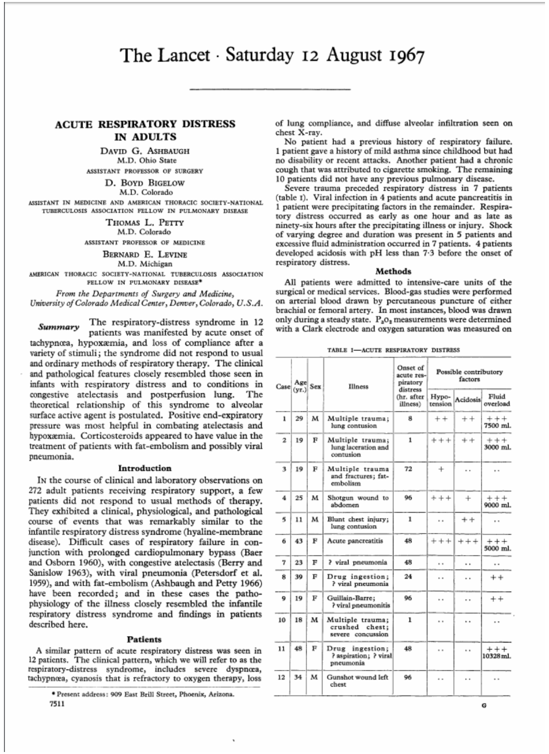
We begin with thanks to our organizer

Let us go back 50 years…

Italian Fashion - 1967



The Lancet · Saturday 12 August 1967

ACUTE RESPIRATORY DISTRESS IN ADULTS

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D. BOYD BIGELOW
M.D. Colorado
ASSISTANT IN MEDICINE AND AMERICAN THORACIC SOCIETY-NATIONAL TUBERCULOSIS ASSOCIATION FELLOW IN PULMONARY DISEASE

THOMAS L. PETTY
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BERNARD E. LEVINE
M.D. Michigan
AMERICAN THORACIC SOCIETY-NATIONAL TUBERCULOSIS ASSOCIATION FELLOW IN PULMONARY DISEASE*

From the Departments of Surgery and Medicine, University of Colorado Medical Center, Denver, Colorado, U.S.A.

Summary The respiratory-distress syndrome in 12 patients was manifested by acute onset of tachypnœa, hypoxæmia, and loss of compliance after a variety of stimuli; the syndrome did not respond to usual and ordinary methods of respiratory therapy. The clinical and pathological features closely resembled those seen in infants with respiratory distress and to conditions in congestive atelectasis and postperfusion lung. The theoretical relationship of this syndrome to alveolar surface active agent is postulated. Positive end-expiratory pressure was most helpful in combating atelectasis and hypoxæmia. Corticosteroids appeared to have value in the treatment of patients with fat-embolism and possibly viral pneumonia.

Introduction

IN the course of clinical and laboratory observations on 272 adult patients receiving respiratory support, a few patients did not respond to usual methods of therapy. They exhibited a clinical, physiological, and pathological course of events that was remarkably similar to the infantile respiratory distress syndrome (hyaline-membrane disease). Difficult cases of respiratory failure in conjunction with prolonged cardiopulmonary bypass (Baer and Osborn 1960), with congestive atelectasis (Berry and Sanislow 1963), with viral pneumonia (Petersdorf et al. 1959), and with fat-embolism (Ashbaugh and Petty 1966) have been recorded; and in these cases the pathophysiology of the illness closely resembled the infantile respiratory distress syndrome and findings in patients described here.

Patients

A similar pattern of acute respiratory distress was seen in 12 patients. The clinical pattern, which we will refer to as the respiratory-distress syndrome, includes severe dyspnœa, tachypnœa, cyanosis that is refractory to oxygen therapy, loss of lung compliance, and diffuse alveolar infiltration seen on chest X-ray.

No patient had a previous history of respiratory failure. 1 patient gave a history of mild asthma since childhood but had no disability or recent attacks. Another patient had a chronic cough that was attributed to cigarette smoking. The remaining 10 patients did not have any previous pulmonary disease.

Severe trauma preceded respiratory distress in 7 patients (table I). Viral infection in 4 patients and acute pancreatitis in 1 patient were precipitating factors in the remainder. Respiratory distress occurred as early as one hour and as late as ninety-six hours after the precipitating illness or injury. Shock of varying degree and duration was present in 5 patients and excessive fluid administration occurred in 7 patients. 4 patients developed acidosis with pH less than 7·3 before the onset of respiratory distress.

Methods

All patients were admitted to intensive-care units of the surgical or medical services. Blood-gas studies were performed on arterial blood drawn by percutaneous puncture of either brachial or femoral artery. In most instances, blood was drawn only during a steady state. P_aO_2 measurements were determined with a Clark electrode and oxygen saturation was measured on

TABLE I—ACUTE RESPIRATORY DISTRESS

Case	Age (yr.)	Sex	Illness	Onset of acute respiratory distress (hr. after illness)	Possible contributory factors		
					Hypotension	Acidosis	Fluid overload
1	29	M	Multiple trauma; lung contusion	8	++	++	+++ 7500 ml.
2	19	F	Multiple trauma; lung laceration and contusion	1	+++	++	+++ 3000 ml.
3	19	F	Multiple trauma and fractures; fat-embolism	72	+	..	..
4	25	M	Shotgun wound to abdomen	96	+++	+	+++ 9000 ml.
5	11	M	Blunt chest injury; lung contusion	1	..	++	..
6	43	F	Acute pancreatitis	48	+++	+++	+++ 5000 ml.
7	23	F	? viral pneumonia	48	..	..	..
8	39	F	Drug ingestion; ? viral pneumonia	24	..	..	++
9	19	F	Guillain-Barre; ? viral pneumonitis	96	..	..	++
10	18	M	Multiple trauma; crushed chest; severe concussion	1	..	..	..
11	48	F	Drug ingestion; ? aspiration; ? viral pneumonia	48	..	..	+++ 10328 ml.
12	34	M	Gunshot wound left chest	96	..	..	..

* Present address: 909 East Brill Street, Phoenix, Arizona.

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Medical News - 1967

A report of 12 patients

Summary The respiratory-distress syndrome in 12 patients was manifested by acute onset of tachypnœa, hypoxæmia, and loss of compliance after a variety of stimuli; the syndrome did not respond to usual and ordinary methods of respiratory therapy. The clinical and pathological features closely resembled those seen in infants with respiratory distress and to conditions in congestive atelectasis and postperfusion lung. The theoretical relationship of this syndrome to alveolar surface active agent is postulated. Positive end-expiratory pressure was most helpful in combating atelectasis and hypoxæmia. Corticosteroids appeared to have value in the treatment of patients with fat-embolism and possibly viral pneumonia.

Discussion

The ætiology of this respiratory-distress syndrome remains obscure. Despite a variety of physical and possibly biochemical insults the response of the lung was similar in all 12 patients. In this small series of patients, it is impossible to assign a relative value to shock, fluid overload, acidosis, prior hypoxæmia, trauma, aspiration, and viral infection. Most patients had combinations of these insults in varying degrees of severity.

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Medical News - 1967

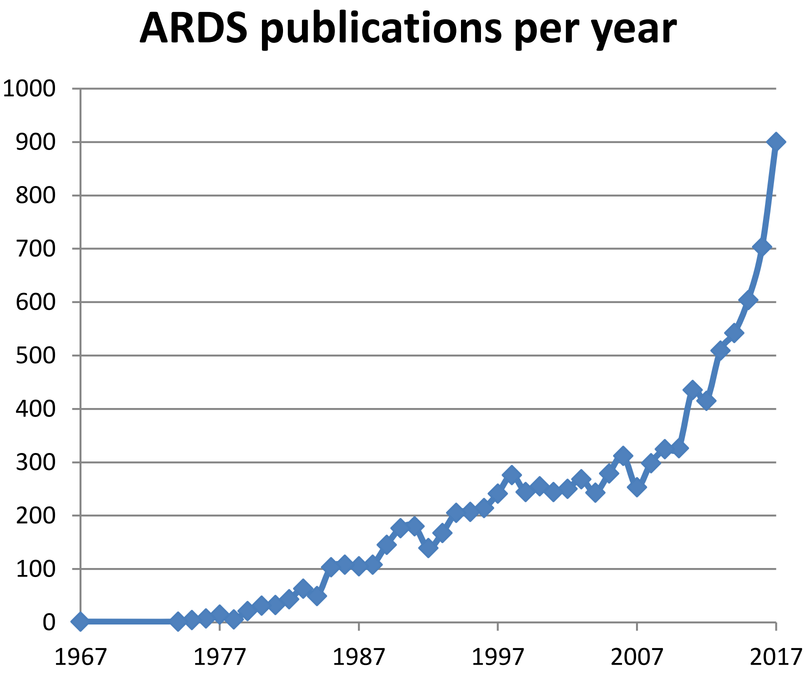
[Trends in the incidence of noncardiogenic acute respiratory failure: The role of race*]

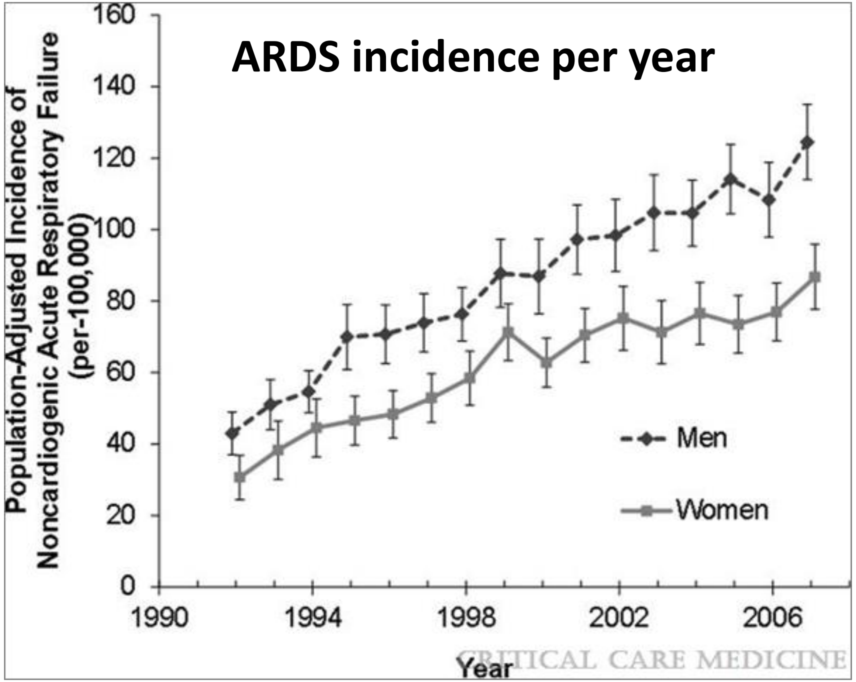
Cooke, Colin R.; Erickson, Sara E.; Eisner, Mark D.; Martin, Greg S.

Critical Care Medicine. 40(5):1532-1538, May 2012.

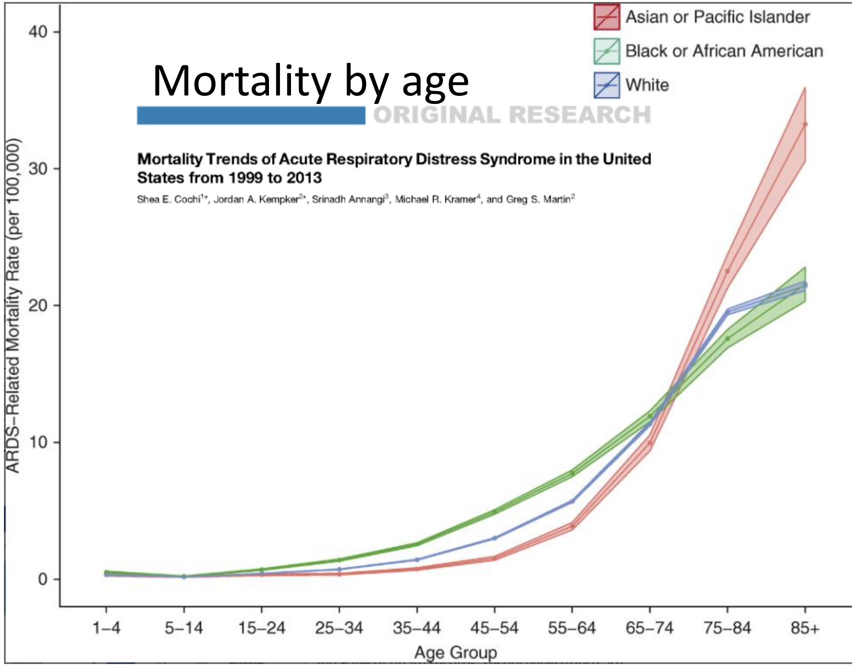
doi: 10.1097/CCM.0b013e31824518f2

Since 1967





ARDS

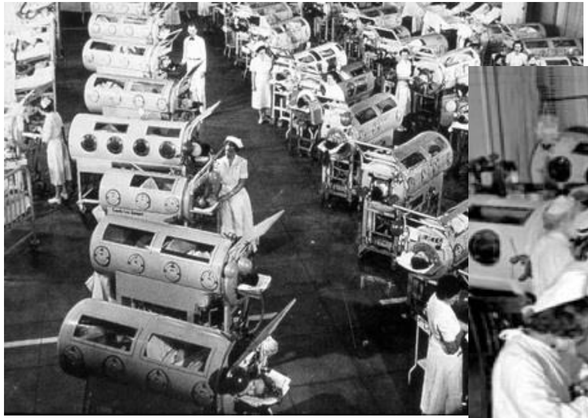


Lowest estimate of USA deaths attributable to ARDS:

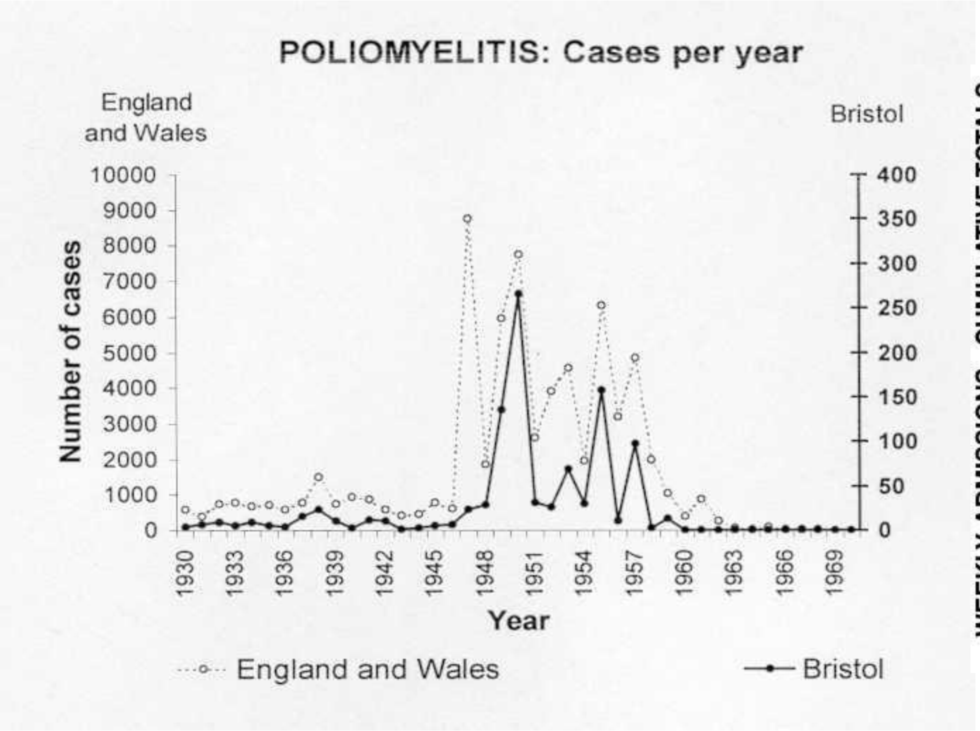
150,000 per year

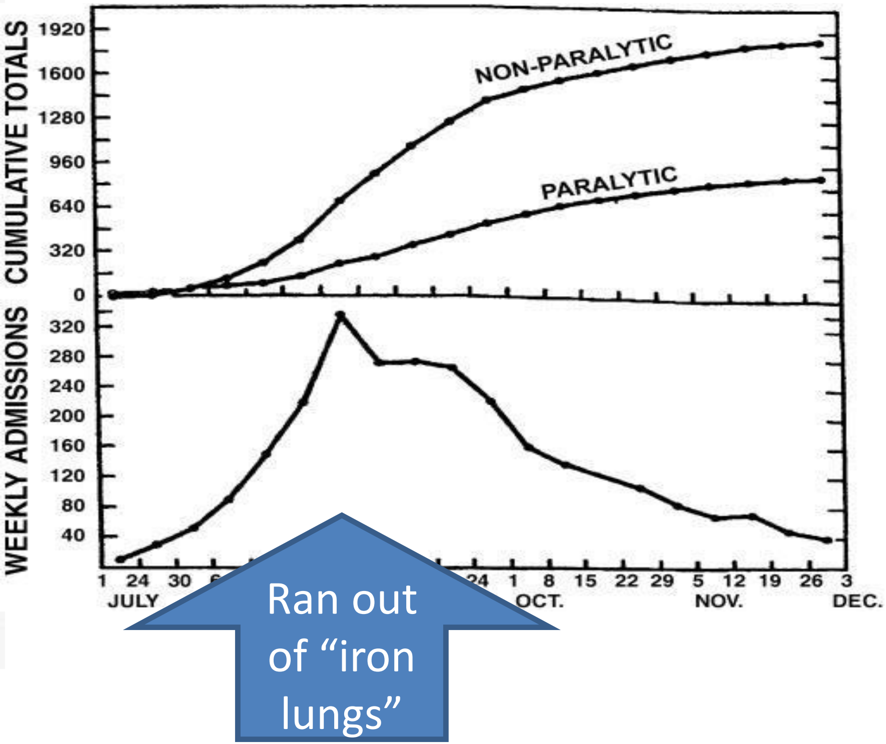
Why was ARDS unknown before 1967?
What happened to make treatment possible?

Poliomyelitis and the Iron Lung



Summer, 1952


POLIOMYELITIS: Cases per year
England and Wales
Bristol
Number of cases
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
400
350
300
250
200
150
100
50
0
1930
1933
1936
1939
1942
1945
1948
1951
1954
1957
1960
1963
1966
1969
Year
England and Wales
Bristol


CUMULATIVE TOTALS
1920
1600
1280
960
640
320
0
NON-PARALYTIC
PARALYTIC
WEEKLY ADMISSIONS
320
280
240
200
160
120
80
40
JULY
OCT.
NOV.
DEC.
Ran out of “iron lungs”

Innovation in Scandinavia, 1952

August 1952:

Tracheostomy plus positive pressure ventilation.

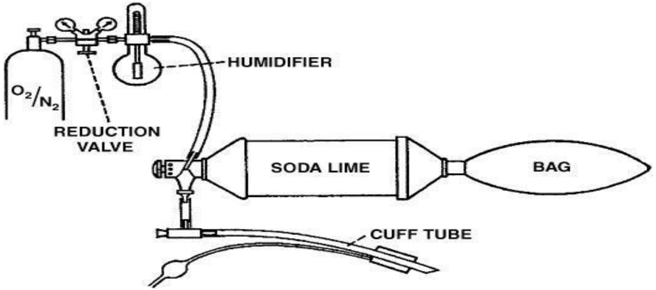
Prior respiratory mortality:

90%

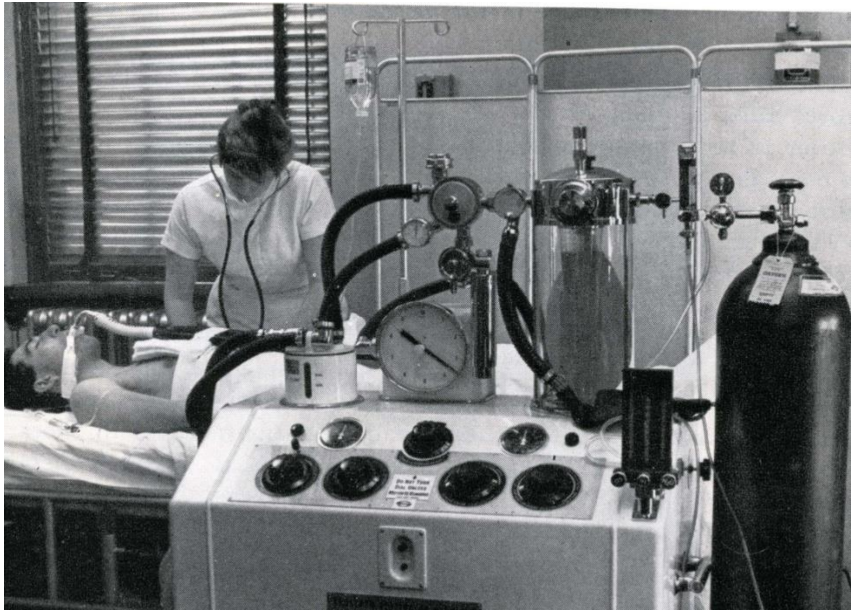
Four months later

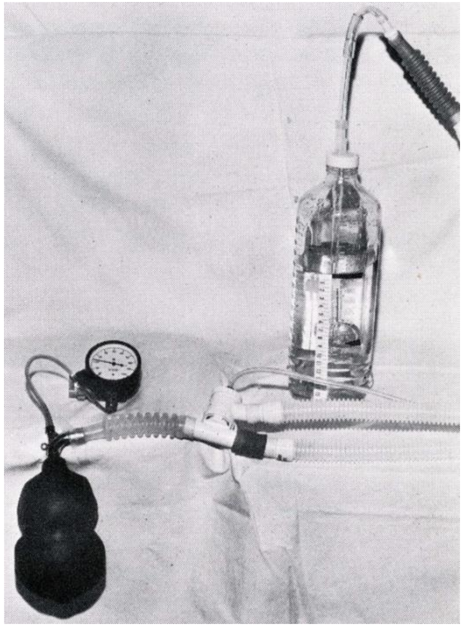
With innovation: 25%

Dr. Bjørn Ibsen



15 years later, the tools to treat ARDS were at hand

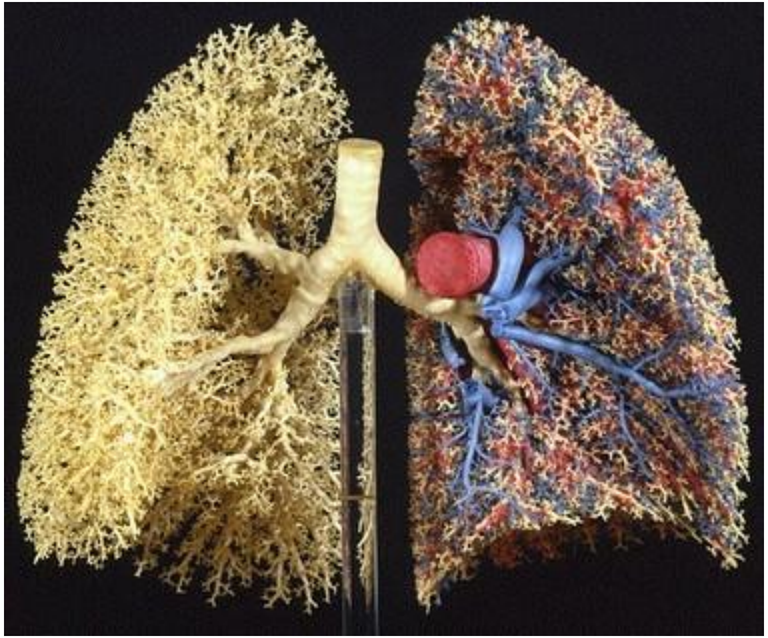




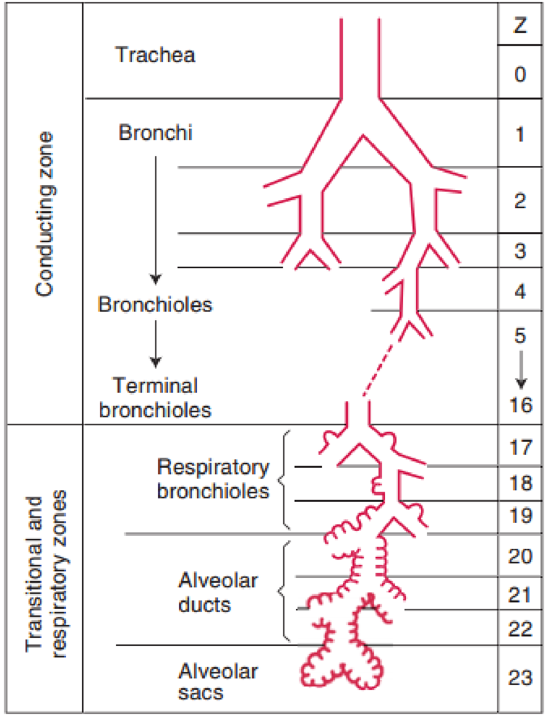
Normal

ARDS

The (dual fractal) Anatomy of the Lung



Airways Blood Vessels

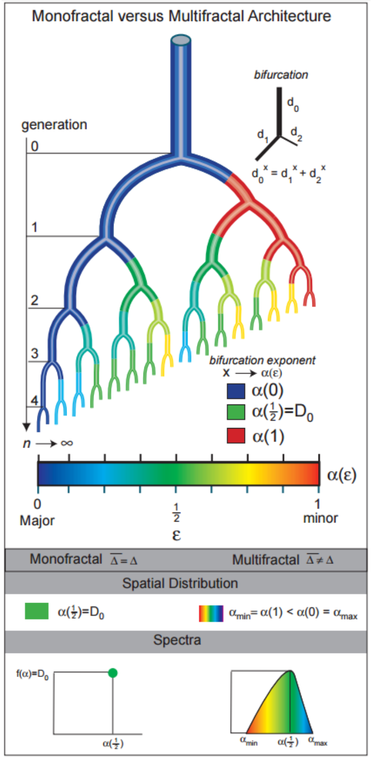


Cyclic flow

quasi-continuous flow

Airway (schematic)

Monofractal v multifractal conceptualtizations



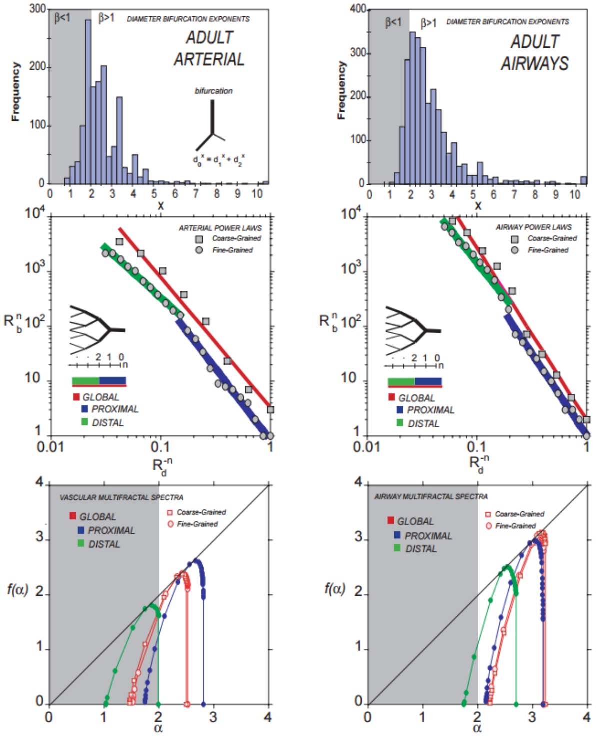
Origin of Fractal Branching Complexity in the Lung

STEPHEN H. BENNETT[1], MARLOWE W. ELDRIDGE[2], CARLOS E. PUENTE[3], RUDOLF H. RIEDI[4], THOMAS R. NELSON[5], BOYD W. GOETZMAN[1], JAY M. MILSTEIN[1], SHIAM S. SINGHAL[6], KEITH HORSFIELD[7], MICHAEL J. WOLDENBERG[8]

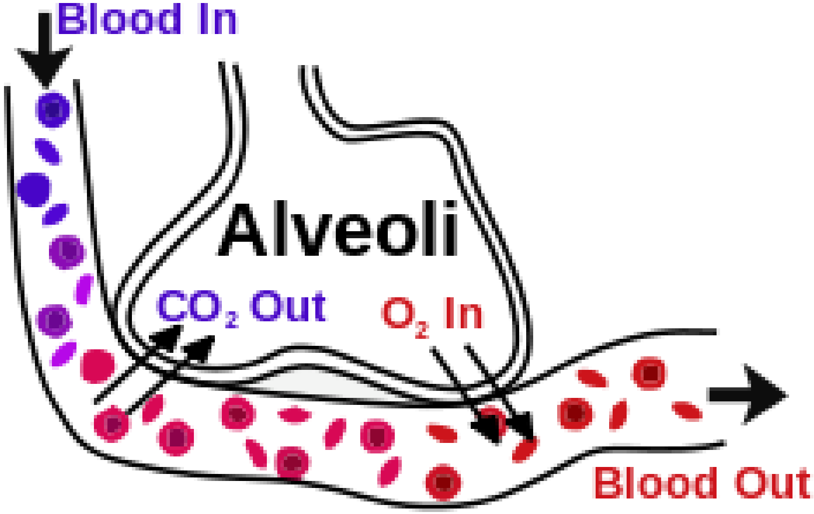
The design of larger transport vessels in the lung were found to exhibit fractal branching complexity with an origin consistent with systems in nature conforming to a self-organized critical state.

The changes in complexity in the pulmonary circulation are dynamic suggesting that the lung is a complex adaptive system lacking a universal fractal design, and is not a strictly self-similar branching network.

Figure 3.Human Pulmonary Arterial and Airway Systems

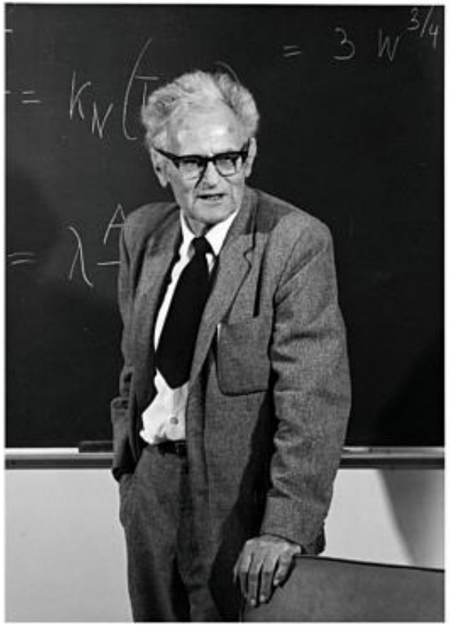


At the ends of a fractal tree…
simple, repeating, near-identical modules

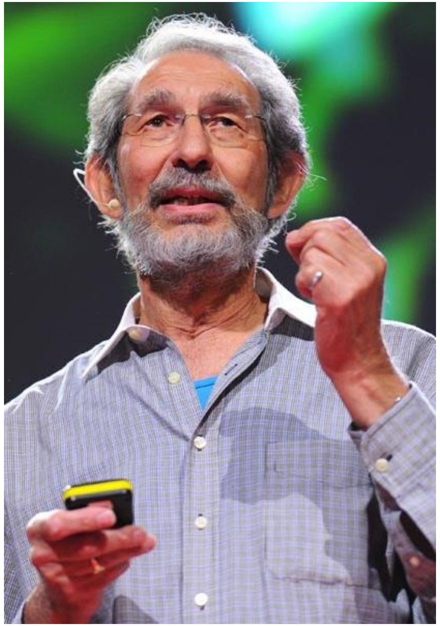


Why does the “fractalcality” arise?

Max Kleiber



Geoffrey West



Why does the "fractalcality" arise?

Max Kleiber – empiric

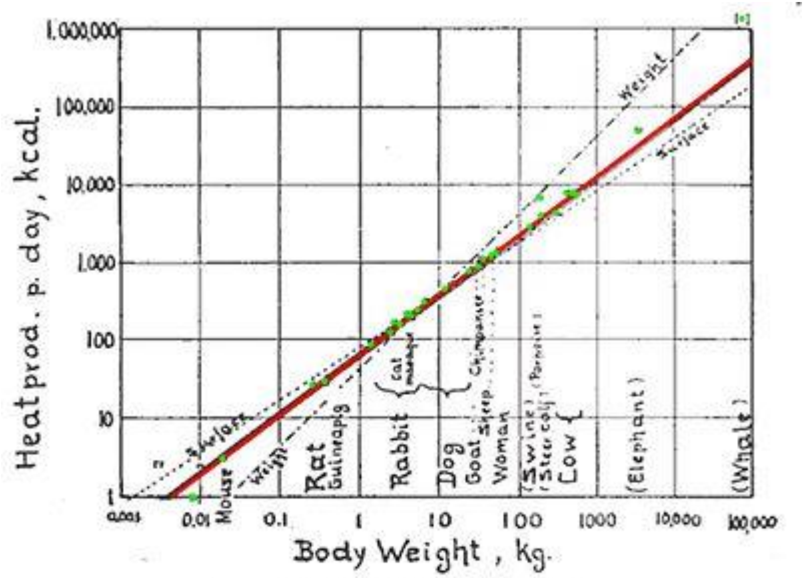
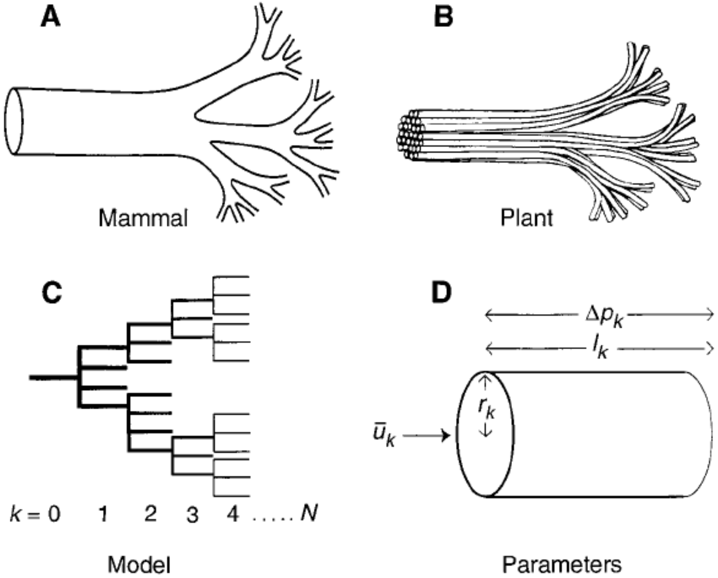


Fig. 1. Log. metabol. rate/log body weight

Slope=3/4

Geoffrey West – first principles



A General Model for the Origin of Allometric Scaling Laws in Biology

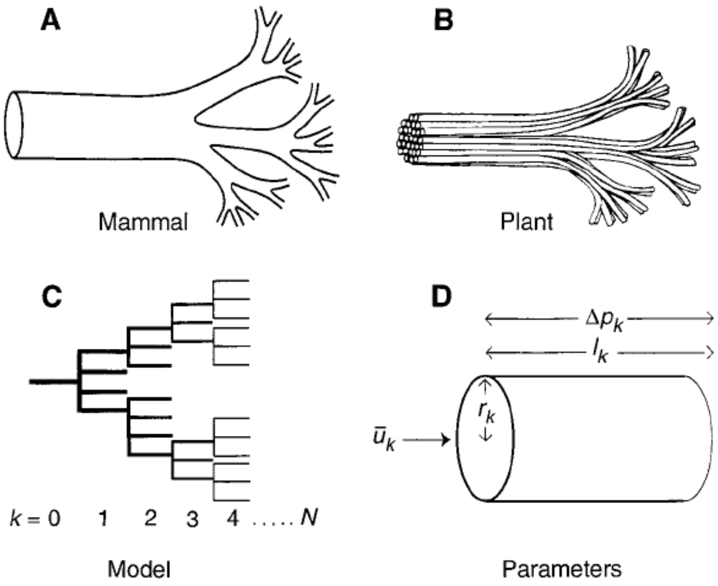
Geoffrey B. West, James H. Brown,* Brian J. Enquist

Why does the “fractalcality” arise?

Basic Rules

- Growth is programmatic, not blueprinted
  - Fills space/size limited
    - Hierarchical branching
  - (Microscopic) uniform end-organ modules
  - **Minimize energy needed to move fluid through the system**
- Sum of the cross-sectional areas of the daughter tubes leaving the branch point is the same as the cross-sectional area of the parent tube coming into it.

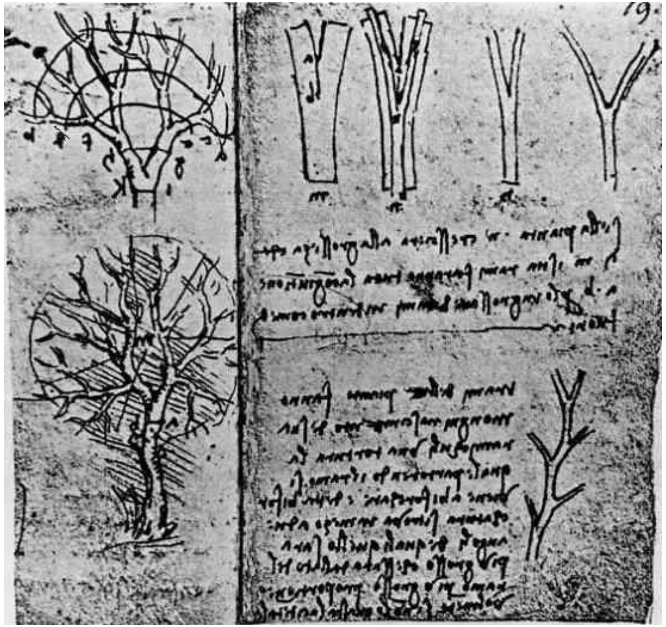
Consequences



Why does the “fractalcality” arise?

Leonardo da Vinci 1452-1519

From his notebook

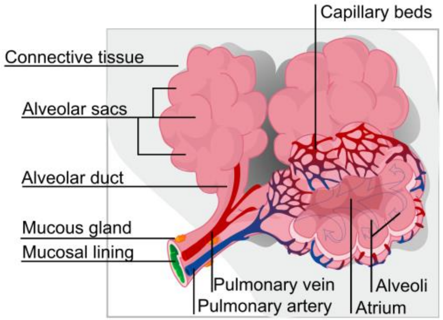


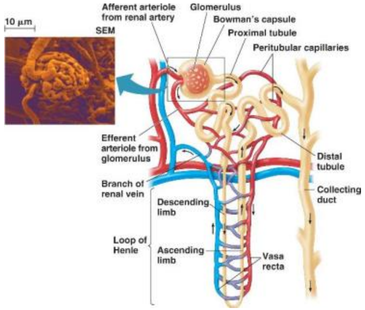
Fractal Aspects of the Respiratory System

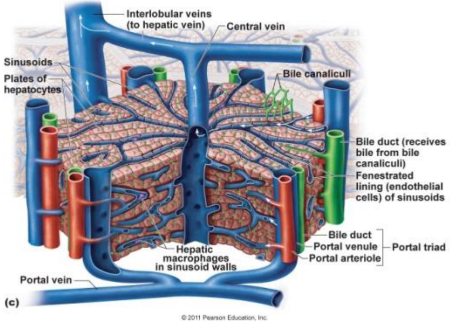
QUANTITY	PREDICTED	OBSERVED
Tracheal radius	3/8 = 0.375	0.39
Interpleural pressure	0 = 0.00	0.004
Air velocity in trachea	0 = 0.00	0.02
Lung volume	1 = 1.00	1.05
Volume flow to lung	3/4 = 0.75	0.80
Volume of alveolus	1/4 = 0.25	No data
Tidal volume	1 = 1.00	1.041
Respiratory frequency	-1/4 = -0.25	-0.26
Power dissipated	3/4 = 0.75	0.78
Number of alveoli	3/4 = 0.75	No data
Radius of alveolus	1/12 = 0.083	0.13
Area of alveolus	1/6 = 0.167	No data
Area of lung	11/12 = 0.92	0.95
O_2 diffusing capacity	1 = 1.00	0.99
Total resistance	-3/4 = -0.75	-0.70
O_2 consumption rate	3/4 = 0.75	0.76

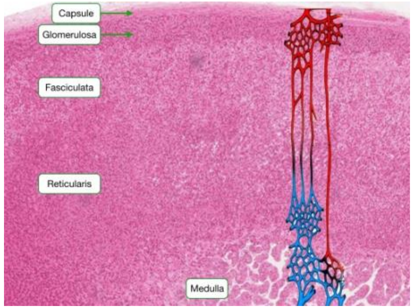
Lung volume scales linearly with mass

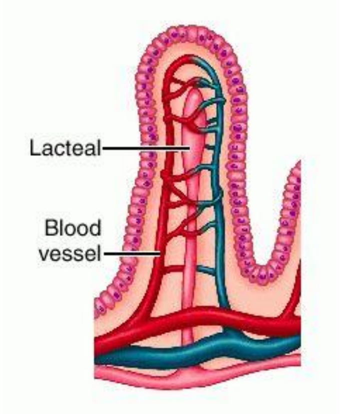
A sidebar on networks to terminal units

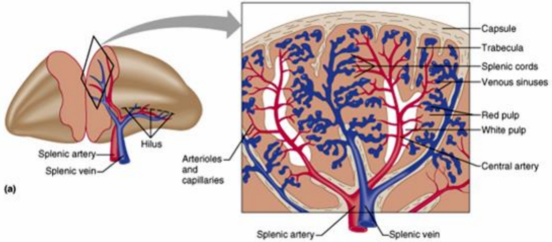




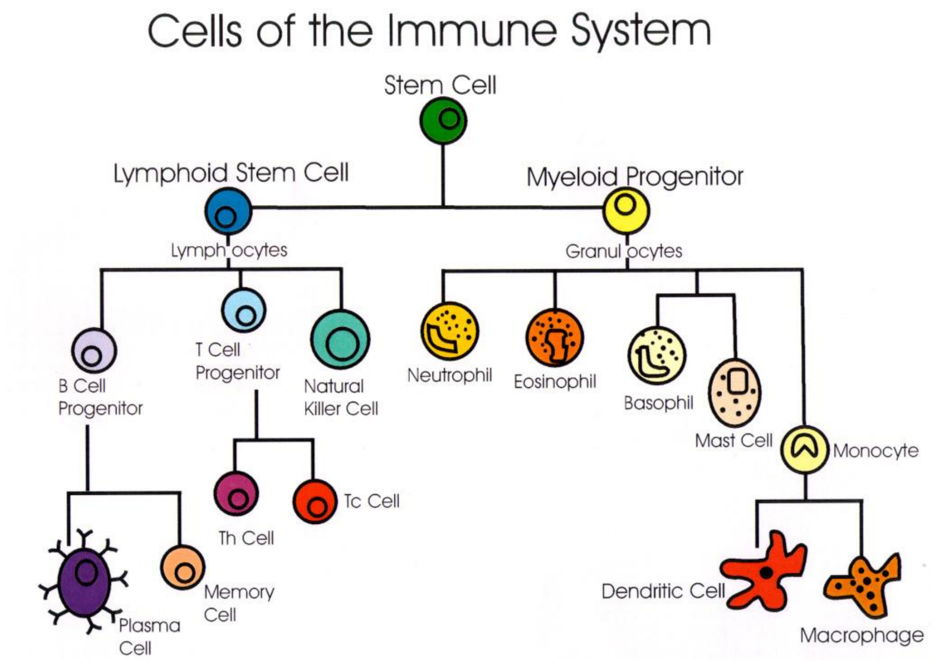


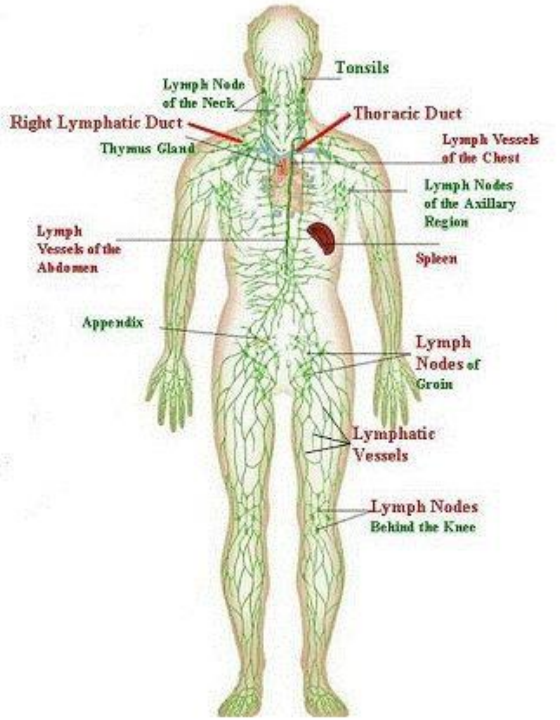




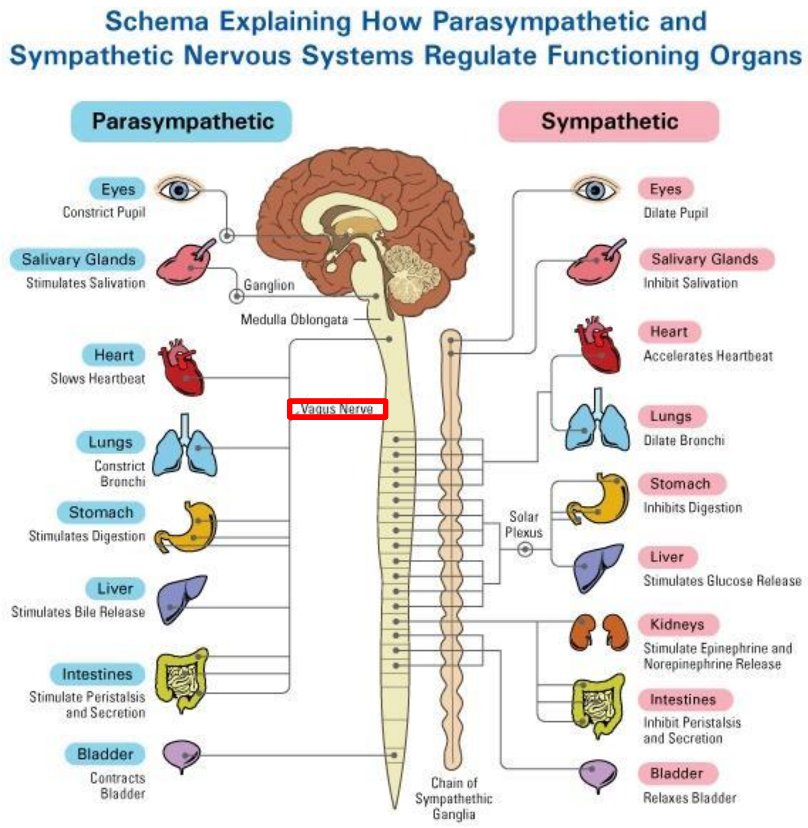


The Immune/Lymphatic System

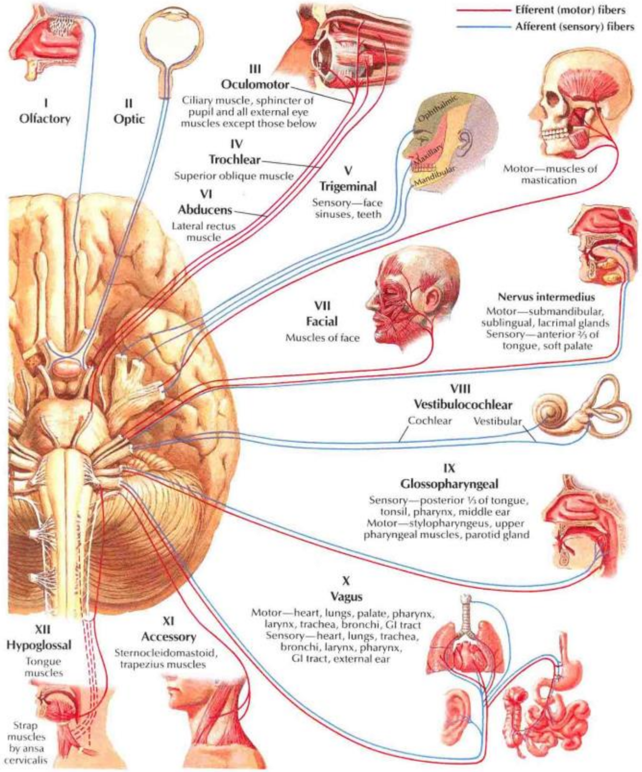


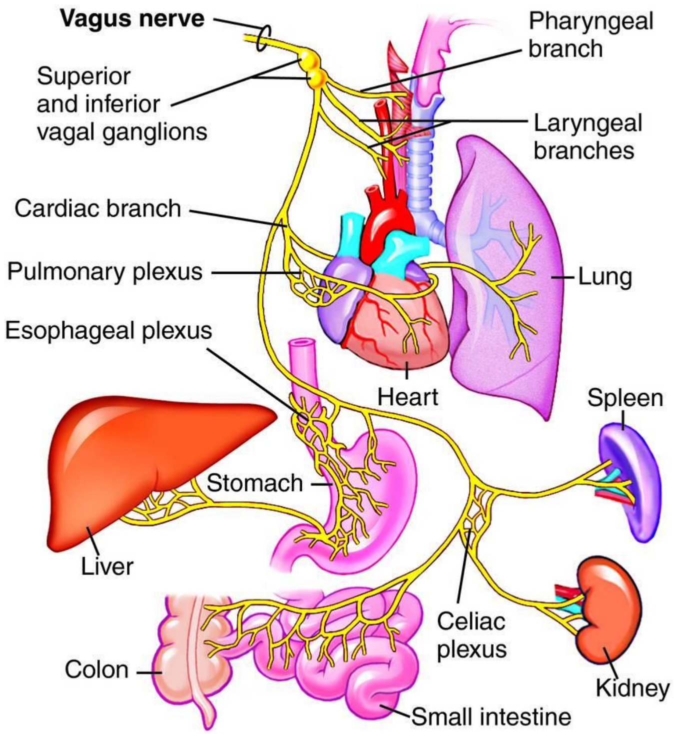


The Autonomic Nervous System



The Vagus Nerve (parasympathetic)





ONE CRANIAL NERVE ⟷ MASSIVE REGULATORY RESPONSIBILITY

Summary so far

- Visceral anatomy follows allometric scaling laws (ASL)
- Networks architected under those ASL have organ-independent features
  - Tissue cells that do “something”
    - End-units nearly identical in a given tissue
  - Blood flows supplying metabolic needs and clearance of metabolites, toxins
  - Embedded immune (regulatory) cells
  - Distributed nervous system controls (vagus, autonomics)
- Multiple networks sharing common (filled) spaces
- What could possibly go wrong????

Network Physiology

- Time to do some experiments
- YOU are the experimental subject
- You are welcome to opt out, otherwise

Experiment 1
"metronomic breathing"

Breathe IN

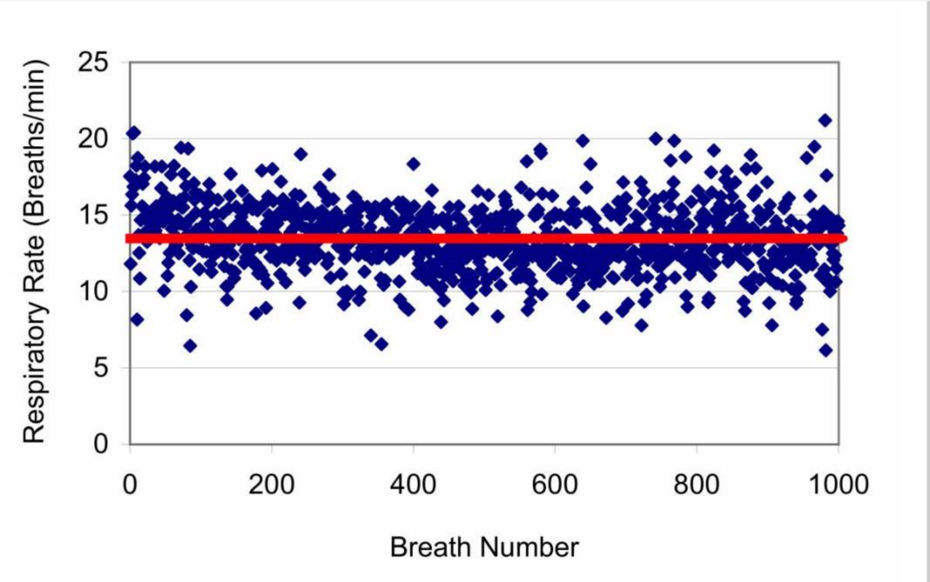
Breathe OUT

About 8 breaths/minute

"Regular" breathing doesn't quite feel right, does it?

Normal (spontaneous) Breathing is Fractal in Time

(and in Volume, Flow,…)



Respir Res. 2005; 6(1): 41. (Alan Mutch)

Many others before and after have made this observation

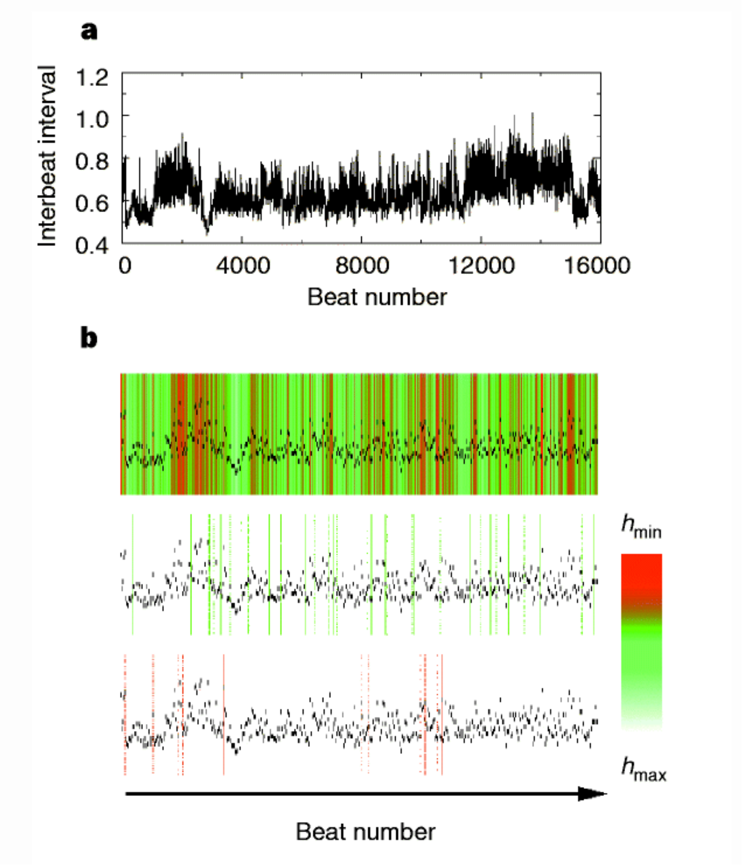
Normal Heart Rates are also (multi)Fractal in Time

Letters to Nature

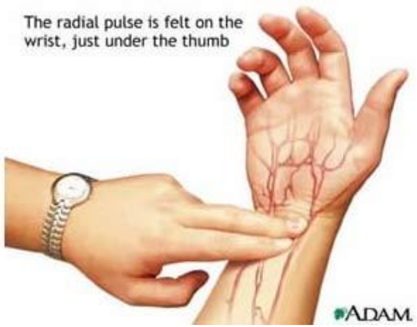
Nature **399**, 461-465 (3 June 1999) | doi:10.1038/20924; Received 2 March 1999; Accepted 7 April 1999

Multifractality in human heartbeat dynamics

Plamen Ch. Ivanov[1,2], Luís A. Nunes Amaral[1,2], Ary L. Goldberger[2], Shlomo Havlin[3], Michael G. Rosenblum[4], Zbigniew R. Struzik[5] & H. Eugene Stanley[1]



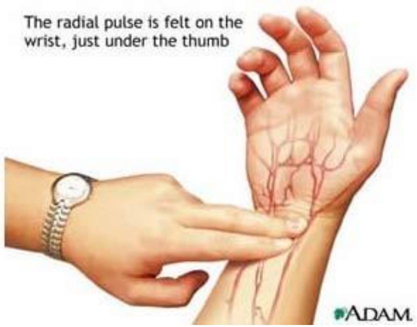
Experiment 2
“Respiratory Sinus Arrhythmia”

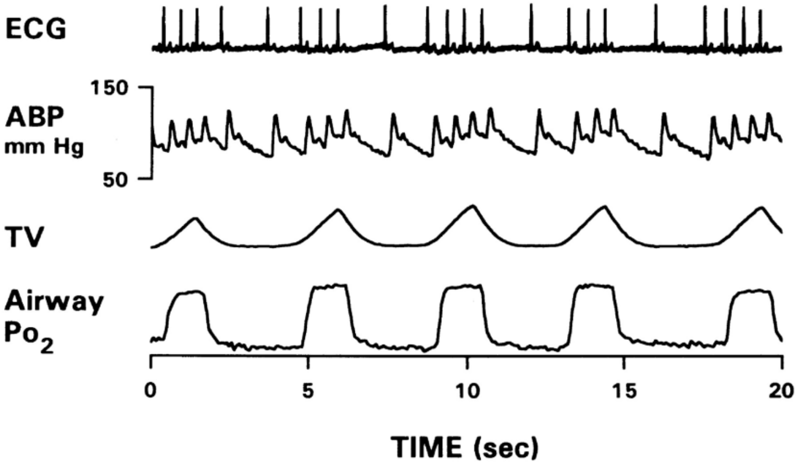


Take a DEEP breath in…HOLD IT… Let it ALL the way out…HOLD IT. Repeat.

What happened to your pulse????

Experiment 2
"Respiratory Sinus Arrhythmia"





Heart rate increases during inspiration and decreases during expiration.

Nucleus ambiguus increases parasympathetic nervous system input to the heart via the vagus nerve. The vagus nerve decreases heart rate by decreasing the rate of SA node firing.

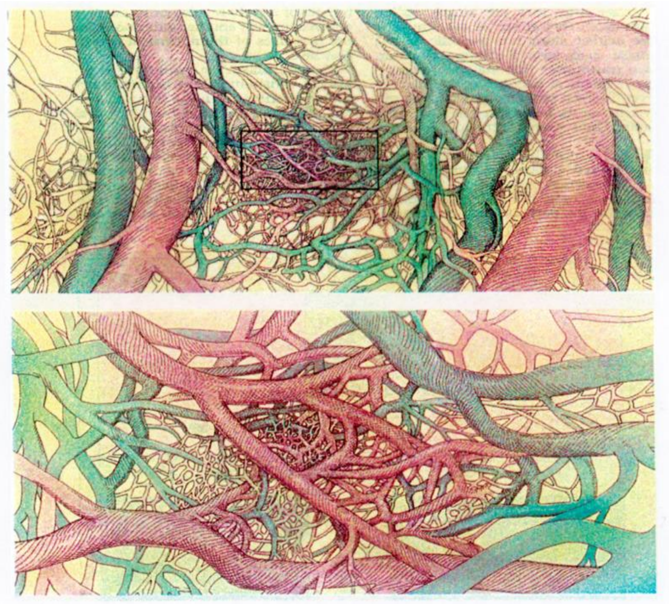
Upon expiration the cells in the nucleus ambiguus are activated and heart rate is slowed down. In contrast, inspiration triggers inhibitory signals to the nucleus ambiguus and consequently the vagus nerve remains unstimulated.

Experimental Conclusions

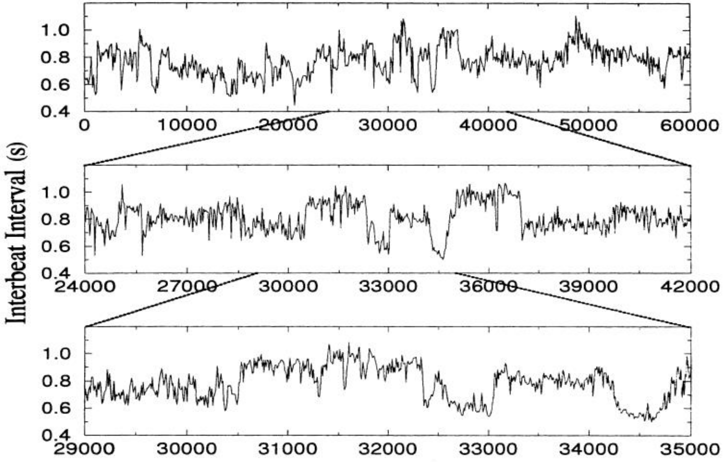
- Normal breathing (“ventilation”) is variable
  - Analysis shows that it is fractal in time and space
- The heart is coupled to ventilation
  - Provides an analytic framework (“weakly coupled oscillators”)

Given that "healthy" physiology resembles "healthy" anatomy…

Self-similar in space: blood vessels



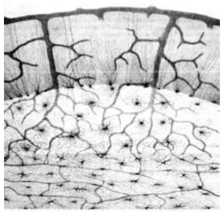
Self-similar in time: interbeat inervals



…we can ask if there is a clinically meaningful synthesis

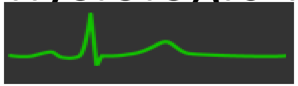
ANALYSIS

Biological Structures



Golgi (1843-1926)

Physiologic Time Series



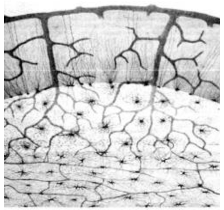
Einthoven (1860-1927)

SYNTHESIS

…we can ask if there is a clinically meaningful synthesis

ANALYSIS

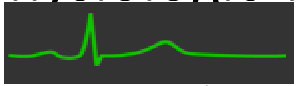
Biological Structures



Golgi (1843-1926)

Network Abstractions

Physiologic Time Series



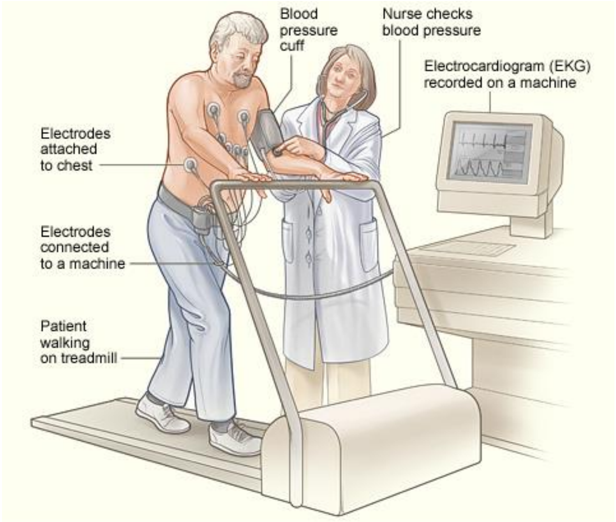
Einthoven (1860-1927)

SYNTHESIS

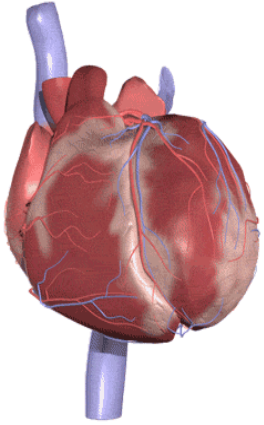
Modules and Modularity

Networks and Adaptation in Physiologic Time

Stress Test

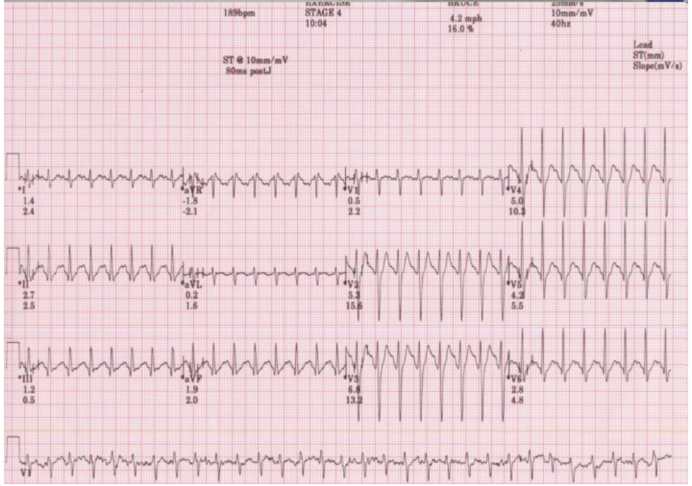


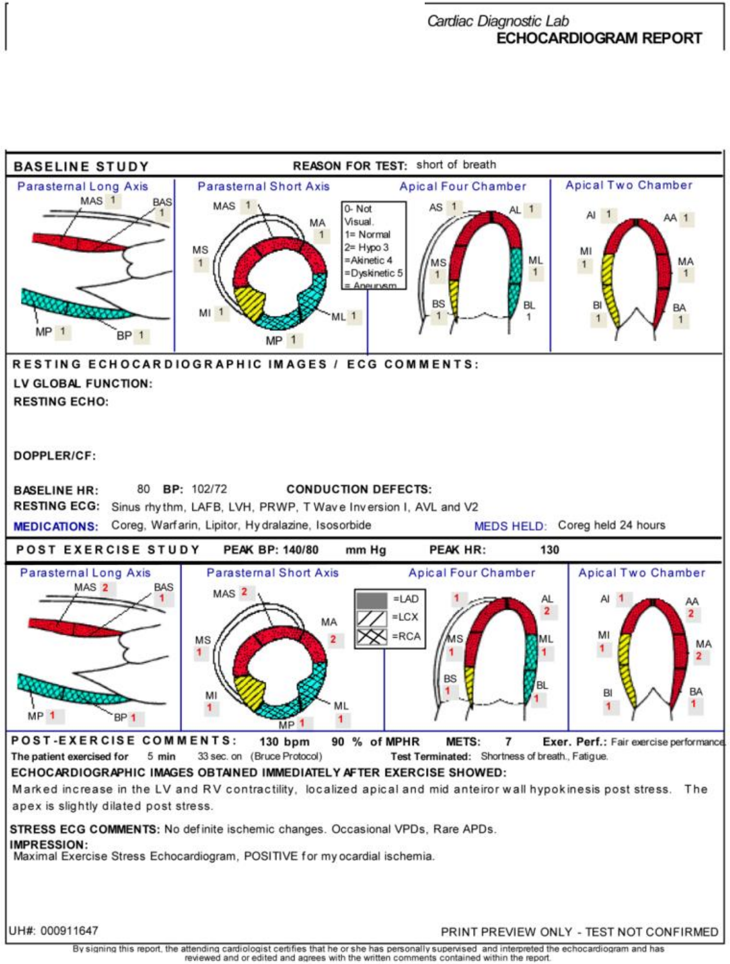
- Indirect reflection of arterial blood flow to heart during exercise
- 1st test 1929, now standardized
- Authentic exercise (or drug, dobutamine)



EVERY HOSPITAL DOES THESE

THIS IS WHAT THE CARDIOLOGIST SEES





Cardiac Diagnostic Lab
ECHOCARDIOGRAM REPORT

BASELINE STUDY REASON FOR TEST: short of breath

Parasternal Long Axis — Parasternal Short Axis — Apical Four Chamber — Apical Two Chamber

0- Not Visual. 1= Normal 2= Hypo 3 =Akinetic 4 =Dyskinetic 5 = Aneurysm

RESTING ECHOCARDIOGRAPHIC IMAGES / ECG COMMENTS:
LV GLOBAL FUNCTION:
RESTING ECHO:

DOPPLER/CF:

BASELINE HR: 80 BP: 102/72 CONDUCTION DEFECTS:
RESTING ECG: Sinus rhythm, LAFB, LVH, PRWP, T Wave Inversion I, AVL and V2
MEDICATIONS: Coreg, Warfarin, Lipitor, Hydralazine, Isosorbide MEDS HELD: Coreg held 24 hours

POST EXERCISE STUDY PEAK BP: 140/80 mm Hg PEAK HR: 130

Parasternal Long Axis — Parasternal Short Axis — Apical Four Chamber — Apical Two Chamber

=LAD =LCX =RCA

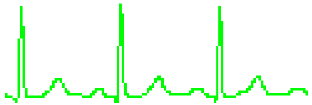
POST-EXERCISE COMMENTS: 130 bpm 90 % of MPHR METS: 7 Exer. Perf.: Fair exercise performance
The patient exercised for 5 min 33 sec. on (Bruce Protocol) Test Terminated: Shortness of breath., Fatigue.
ECHOCARDIOGRAPHIC IMAGES OBTAINED IMMEDIATELY AFTER EXERCISE SHOWED:
Marked increase in the LV and RV contractility, localized apical and mid anteiror wall hypokinesis post stress. The apex is slightly dilated post stress.

STRESS ECG COMMENTS: No definite ischemic changes. Occasional VPDs, Rare APDs.
IMPRESSION:
Maximal Exercise Stress Echocardiogram, POSITIVE for myocardial ischemia.

UH#: 000911647 PRINT PREVIEW ONLY - TEST NOT CONFIRMED

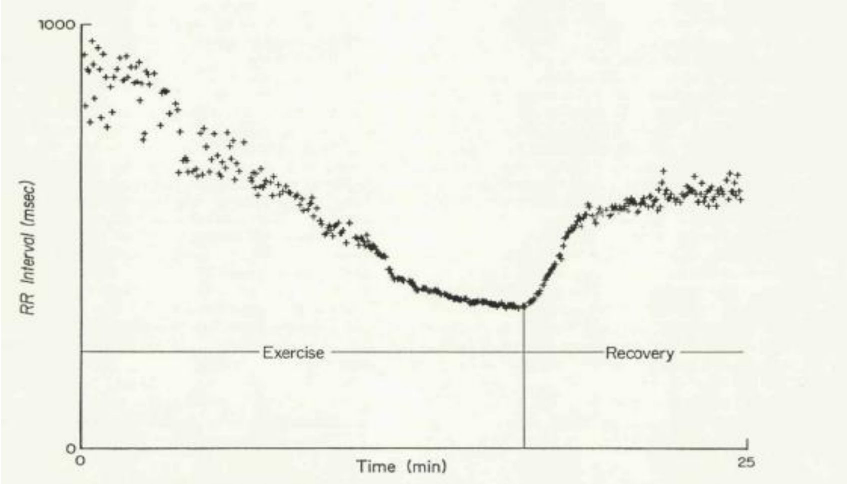
By signing this report, the attending cardiologist certifies that he or she has personally supervised and interpreted the echocardiogram and has reviewed and or edited and agrees with the written comments contained within the report.

A different view

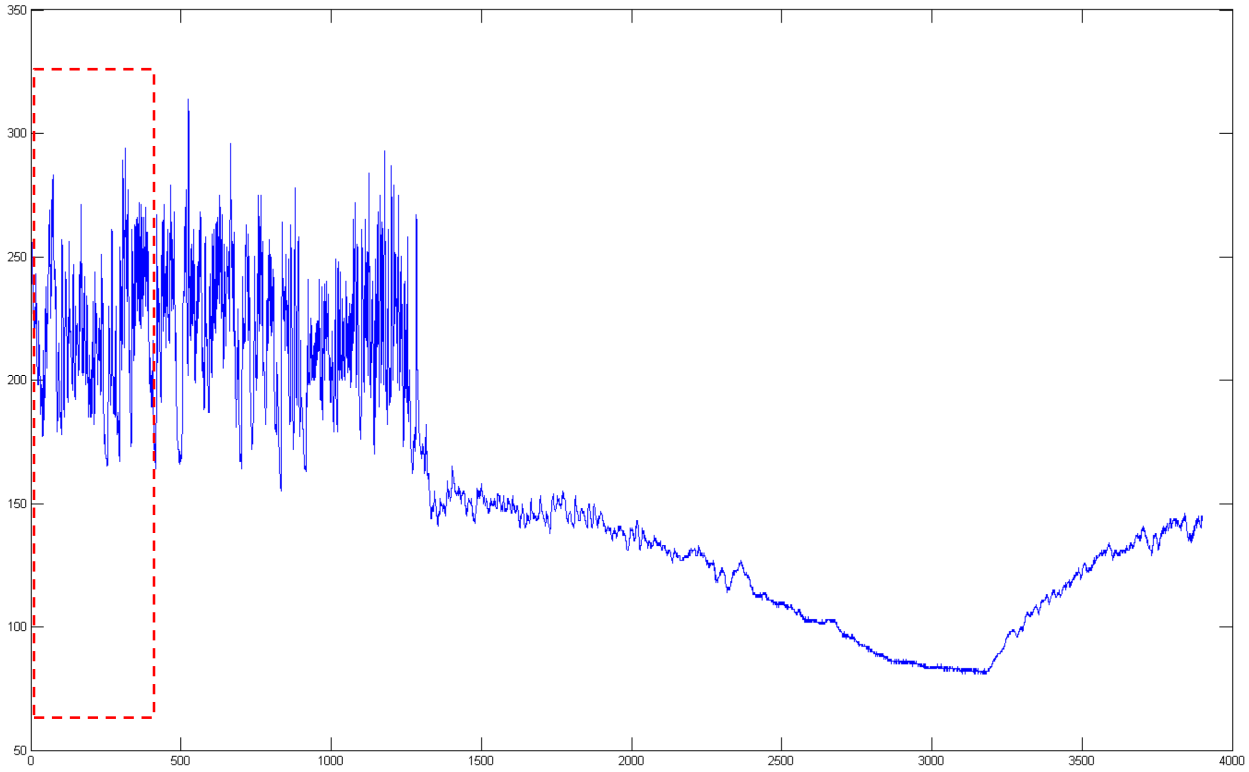


- Typically ~2500-4000 heartbeats
- Non-stationary by definition

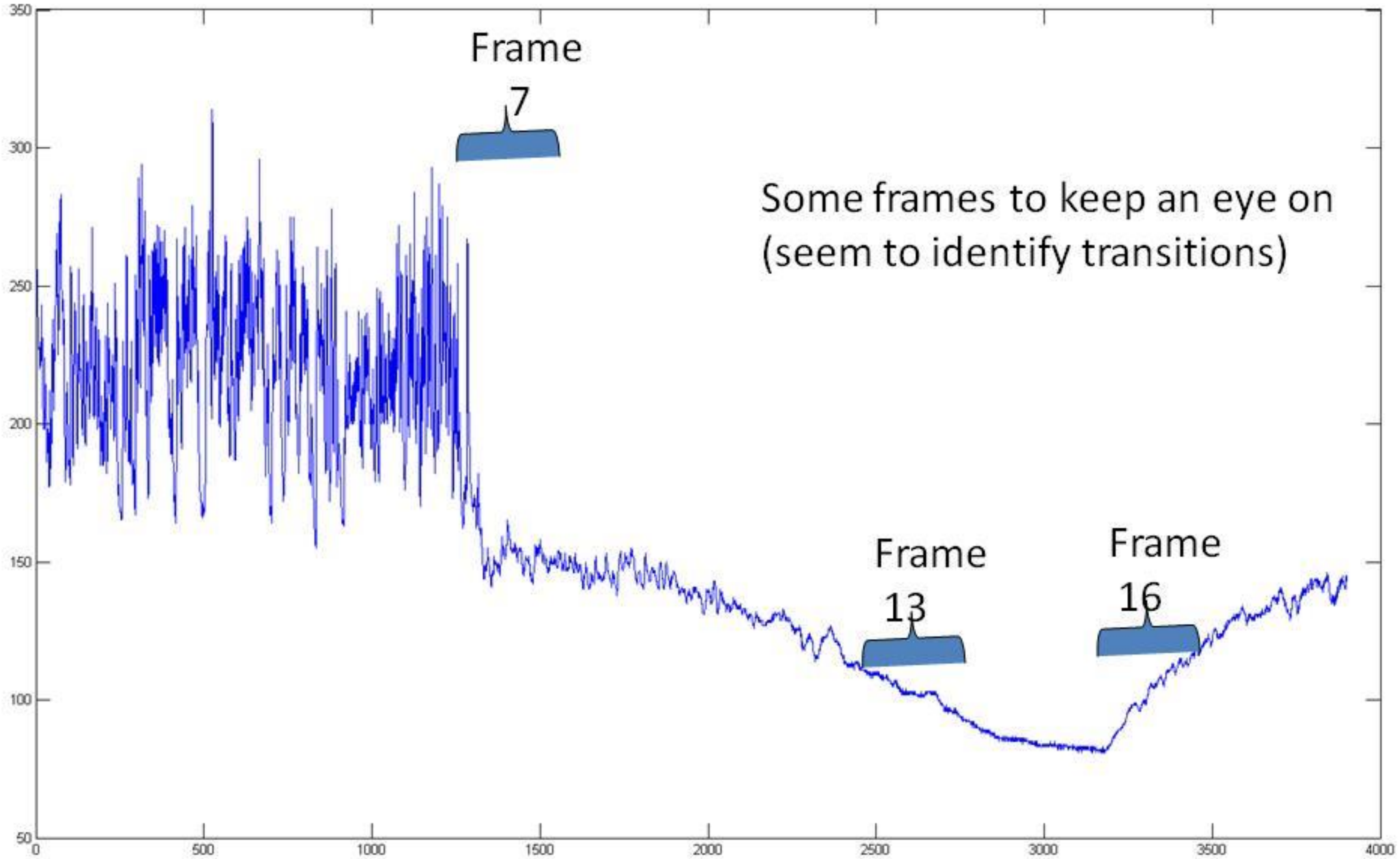
R-R intervals (rate)



A treadmill run

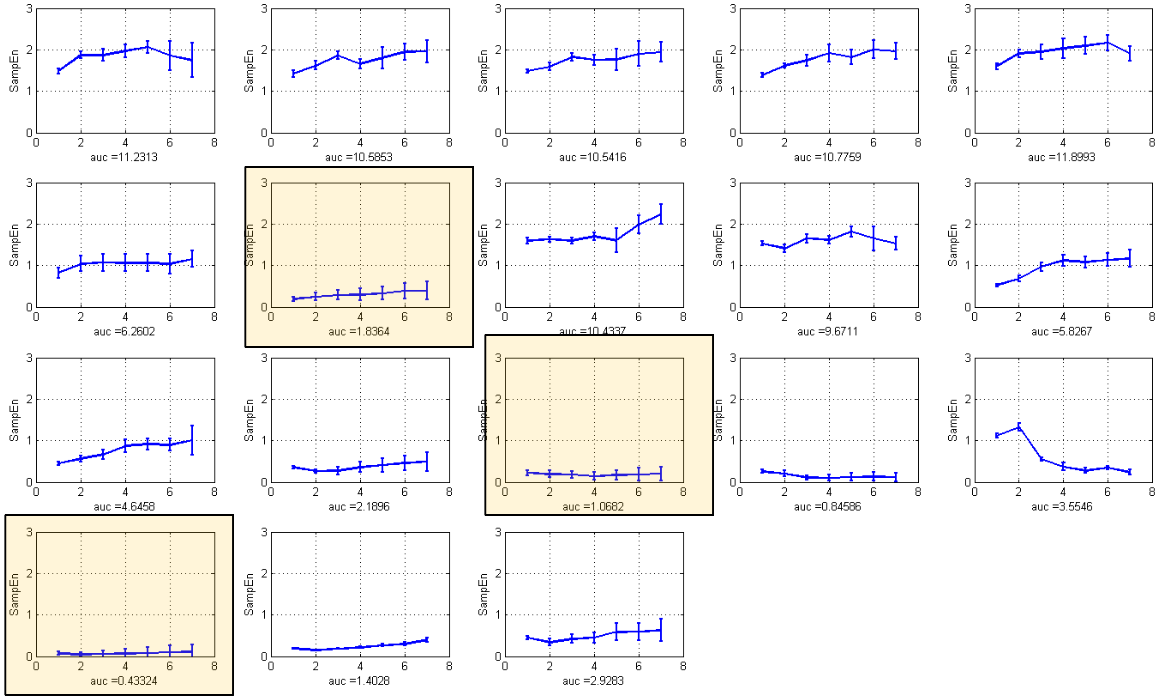


400
beats

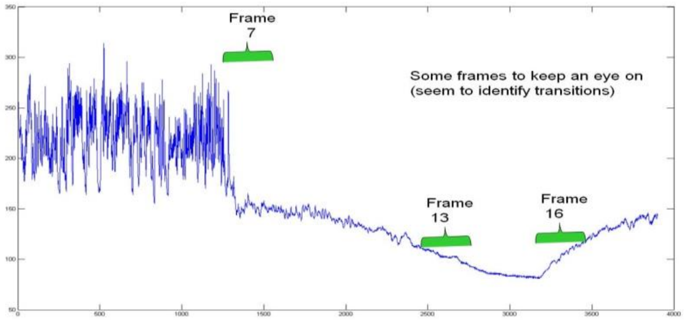


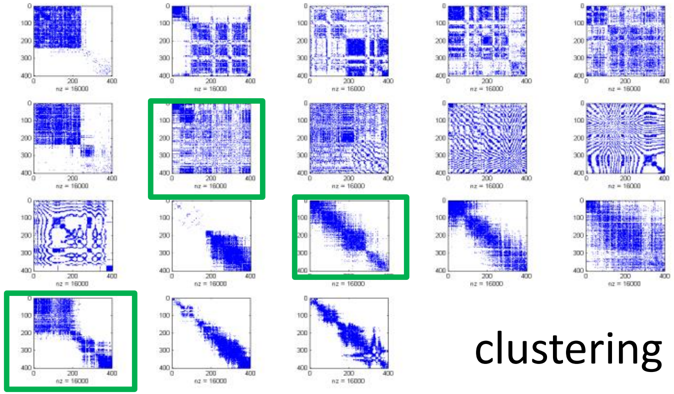
Frame 7
Frame 13
Frame 16
Some frames to keep an eye on
(seem to identify transitions)

Multiscale Entropy—
Randall Moorman will have much more to say

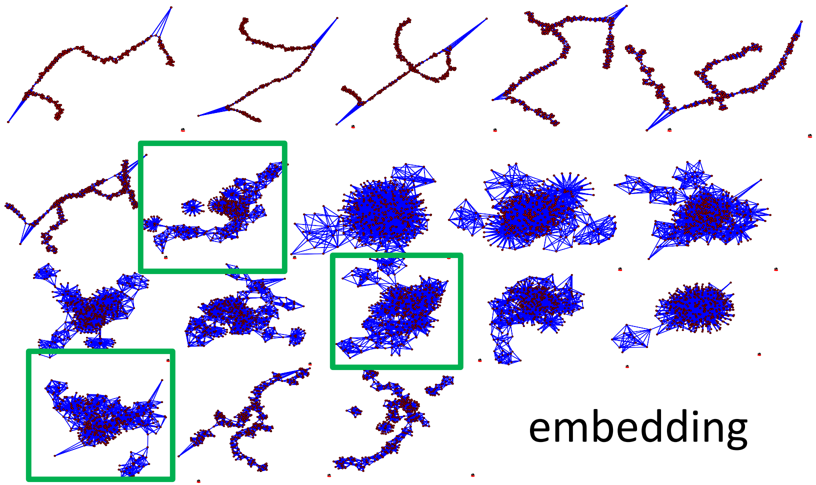


Network analyses—you will have much more to say

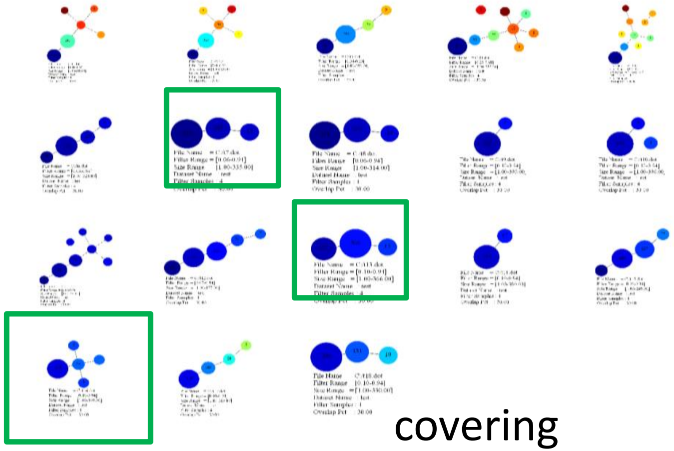




clustering

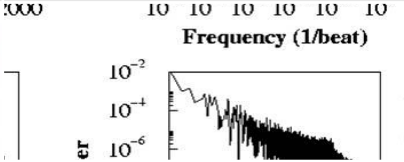
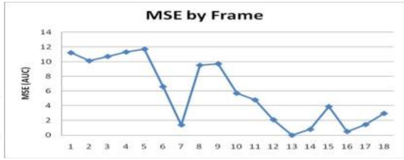
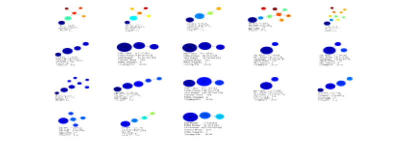


embedding



covering

Physiological Time Series

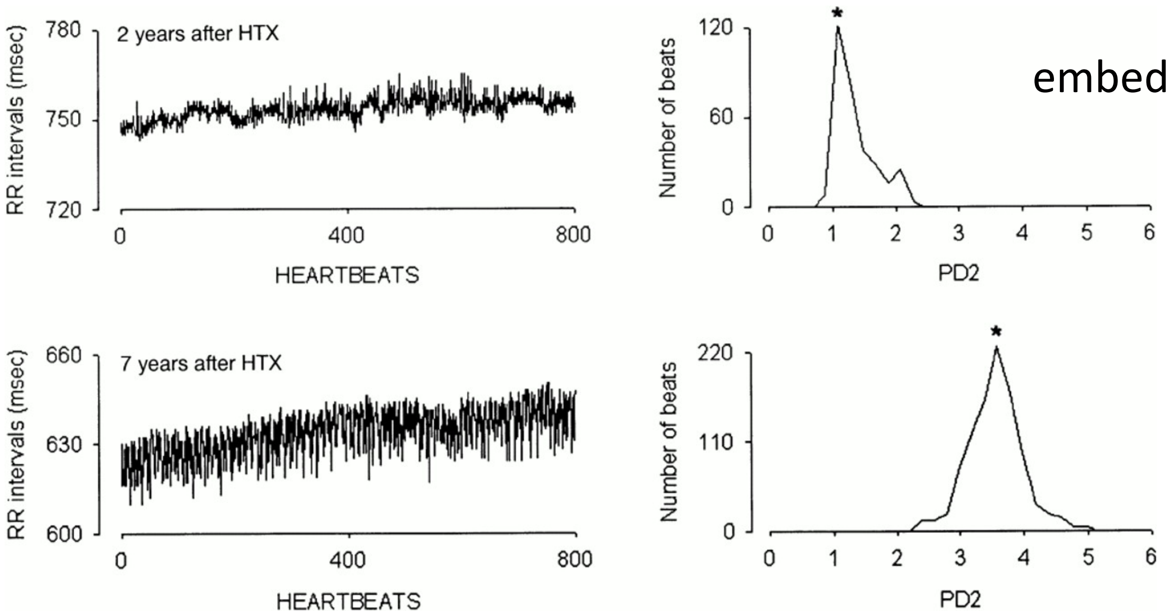
Domains for Time-Series Analysis			
Time (Conventional)	Frequency	Complexity (Variability)	Modularity
			
"Vital Signs"	HF/LF ratio	Entropies (ApEn,SampEn) DFA	Network Connectivitiy

We can reasonably conclude…

- Network abstractions provide an alternate and useful insight into variable human physiology, at least in response to daily stress

Recovery of adaptation following neural and immune isolation (here, after cardiac transplantation) may take **<u>years</u>** **<u>To adapt</u>**

Kresh Y, et al, Am J Physiol. (1998) 275: R720



embedding dimension

Evolution and adaptation

Evolution: Change in a population's **inherited** traits from **generation to generation**

Two components

Genetic Drift

Random mutation

DNA exchange

Natural Selection

Cooperation/Competition

Adaptation

They were contemporaries—
but not on the best of scientific terms

Charles Darwin, 1809-1882

Claude Bernard, 1813-1878

Physiology:
Late to embrace notion of adaptation

- Claude Bernard: Constancy in the internal environment (the milieu interieur)
- Walter B. Cannon: Stability in the internal environment (coordinated by processes that respond to changes)
- René Dubos: Homeostasis and adaptation are necessary for balance and survival

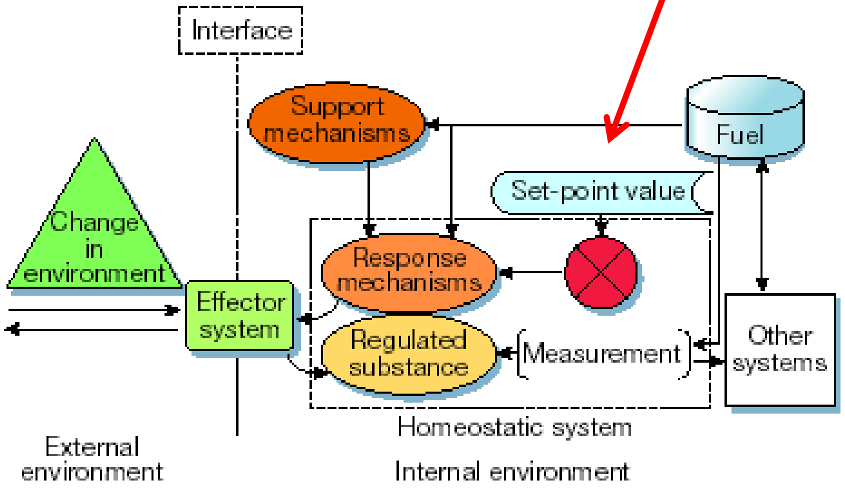
1850's

1910's

1950's

Physiology:
Homeostasis-Cannon's Conception

Is this a "fixed" value?



1910's

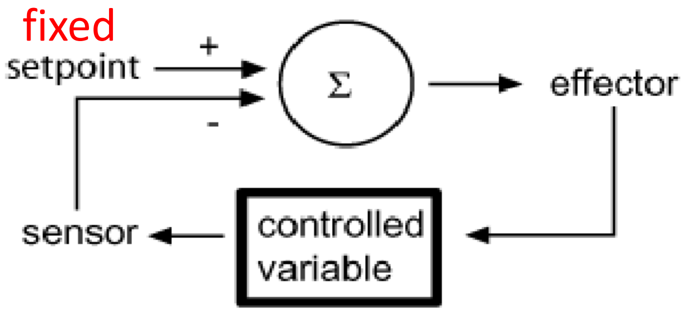
Adaptation and the "memory" of stress

Peter Sterling

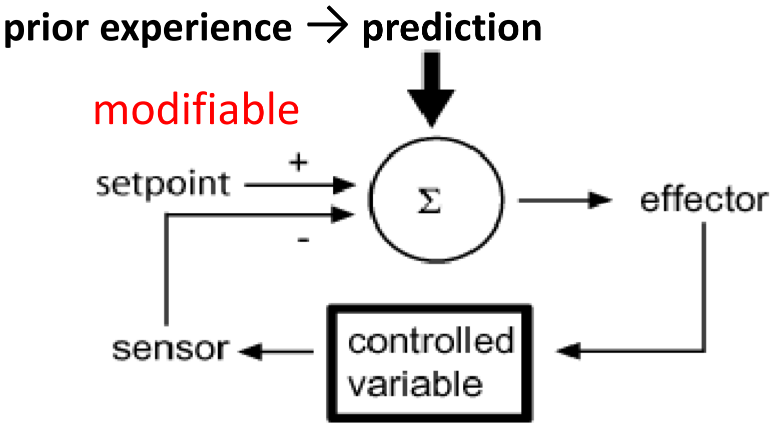
- Neuroscientist (Penn, active)
- First posited that biological systems <u>necessarily</u> adapted to the range of input stimuli as they <u>accumulated over time</u>
- Coined "allostasis"

Homeostasis vs. Allostasis

Homeostasis (Cannon)



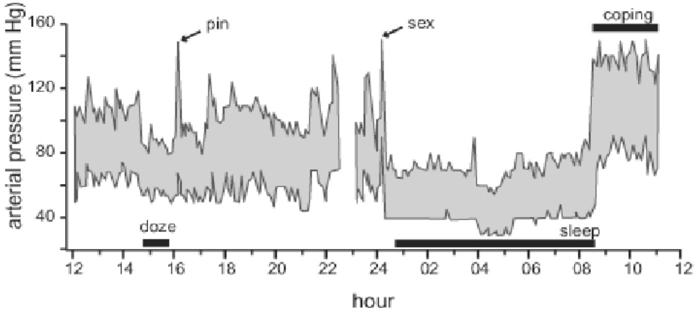
Allostasis (Sterling)



24 hour continuous blood pressure

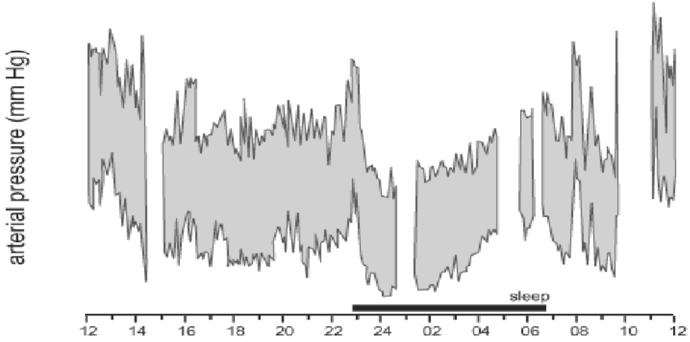
Bevan AT; Honour AJ; Stott FH **(1969).** Clin Sci 36:329.

Patient 1



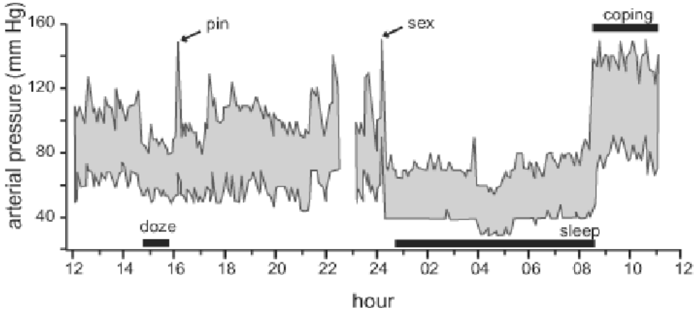
Patterns look more or less the same….

Patient 2



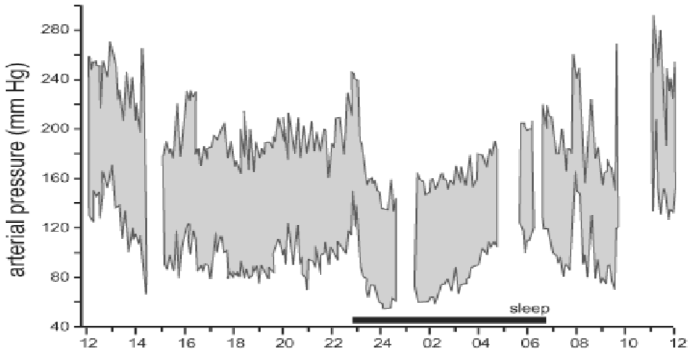
Responsiveness to fluctuating demand around a prediction (no inherent setpoint)

Normal: 110/70



But patients are entirely different…

HTN: 220/110



HYPOTHESIS

Adaptation

At all times, and at all granularities,
life is constantly adapting to its environment

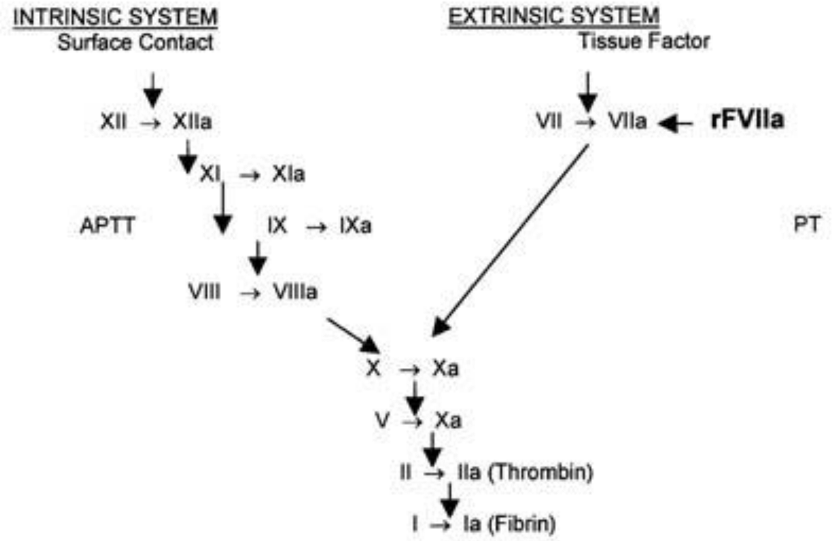
- Short time scales: homeostasis
- Intermediate time scales: allostasis
- Longest time scale: evolution

(Short and intermediate time scales:) Adaptive Network Physiology

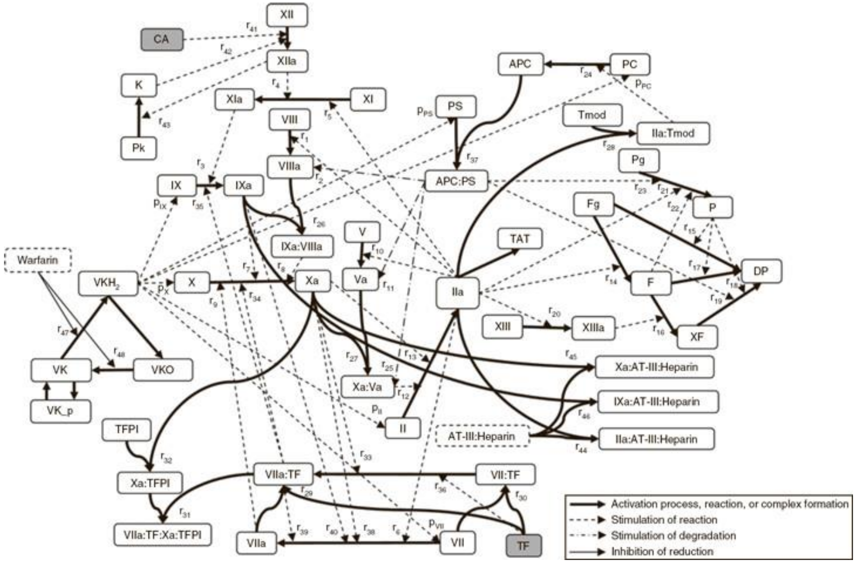
Implications for critically ill patients and their care:
Adaptive failure, support of adaptation

Alternate Views of Physiology: Coagulation

Conventional



Network



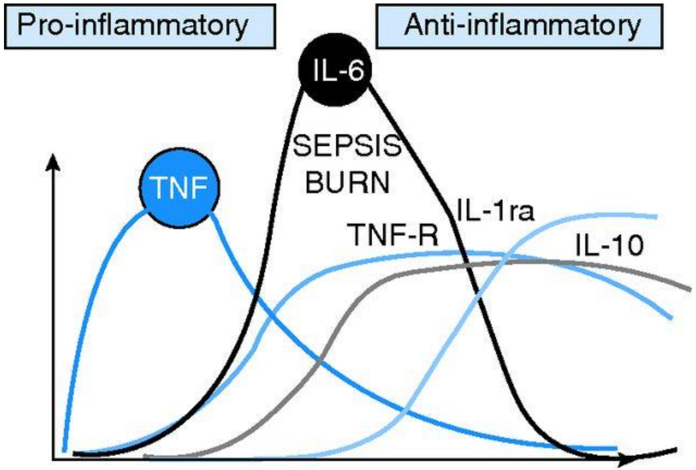
What could possibly go wrong from a network perspective?

Practical Aspects of the Coagulation Network

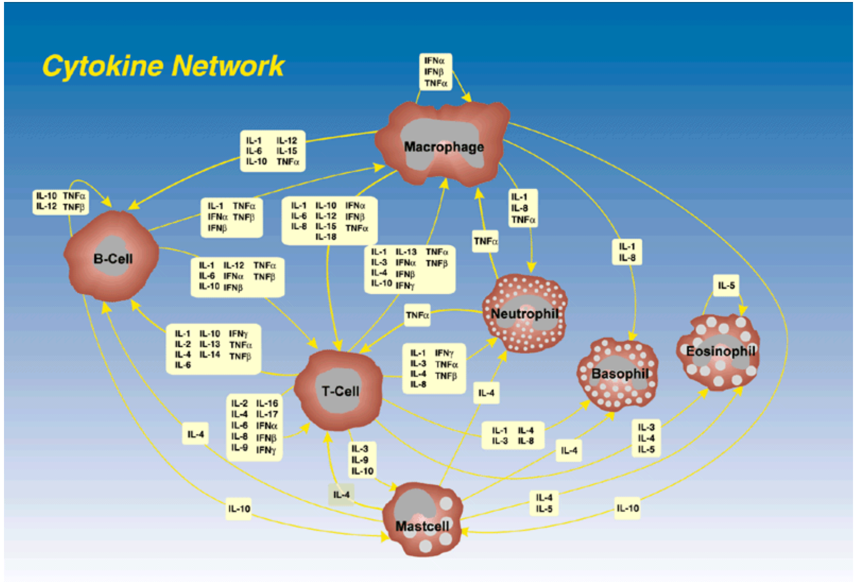
Kcentra®
Prothrombin Complex
Concentrate (Human)

Alternate Views of Physiology: Inflammation

Conventional



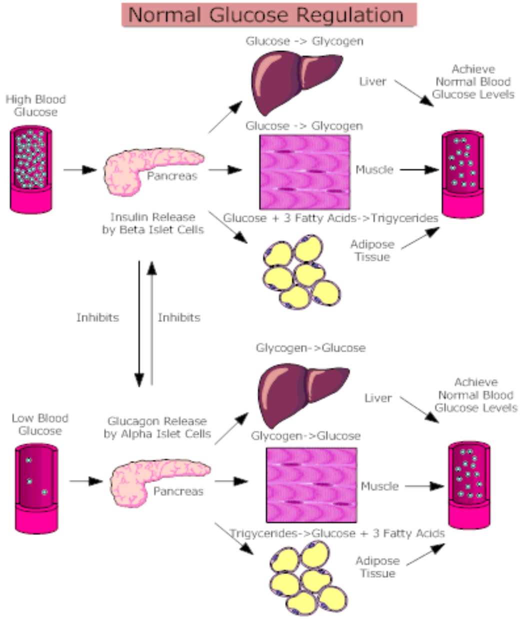
Network



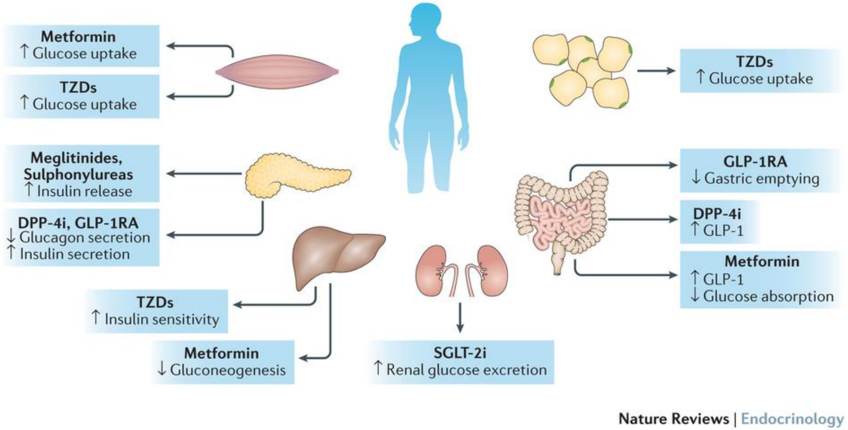
What could possibly go wrong from a network perspective?

Alternate View of Physiology: Glucose Regulation

Conventional



But then there are drugs that affect the network in unique and sometimes paradoxical ways



The mechanism for metformin action remains uncertain: metformin might target the liver to reduce gluconeogenesis and skeletal muscles to enhance peripheral glucose utilization[110], with a possible role in the gut to increase levels of glucagon-like peptide 1 (GLP-1) (Ref. 111). Sulfonylureas and meglitinides increase insulin secretion in the pancreas[112, 113]. Thiazolidinediones (TZDs) act as insulin sensitizers in skeletal muscle, adipose tissue and the liver[114]. GLP-1 receptor (GLP-1R) agonists (GLP-1RA) target the pancreas to increase insulin secretion and reduce glucagon production, as well as act in the gut to reduce gastric emptying[115]. Dipeptidyl peptidase 4 (DPP-4) inhibitors (DPP-4i) increase endogenous incretin levels by blocking the action of DPP-4 (Ref. 115). Sodium–glucose cotransporter 2 (SGLT-2) inhibitors (SGLT-2i) reduce renal glucose reabsorption[116].

Alternate Views of Physiology: Challenges

Conventional

- “repair broken point, restore functionality”
- Works in a few cases, mostly where there is a checkpoint

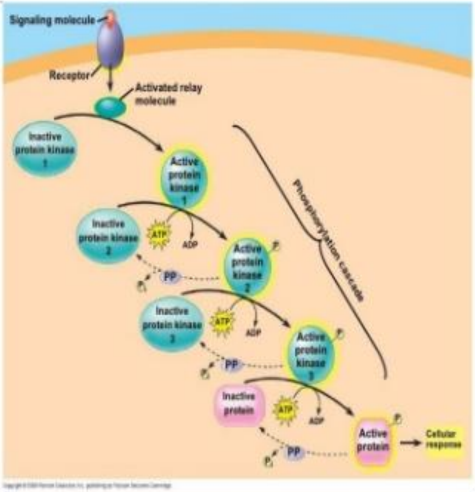
Network

- Parallelism leads to redundancy (a good thing)
- Curse of dimensionality
- Unanticipated consequences of perturbing complex systems (“butterfly wings”, etc.)

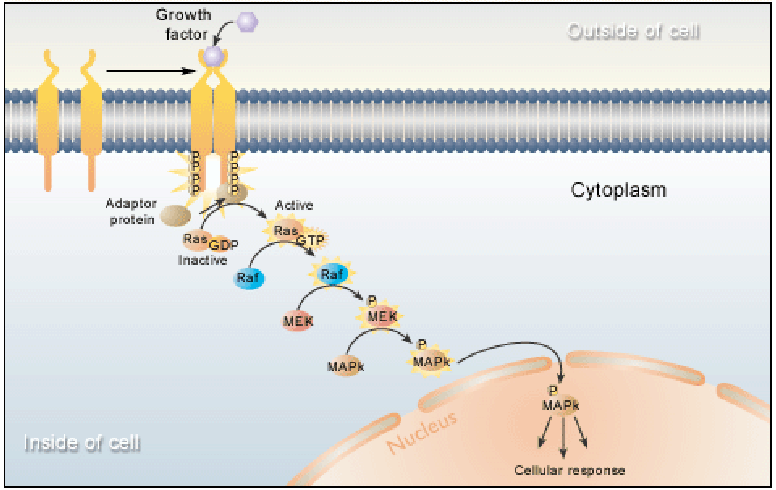
Kinase Cascades:
a study in modular duplications

Protein Kinase cascade

A series of protein kinase adding a phosphate group to the next protein in the sequence.

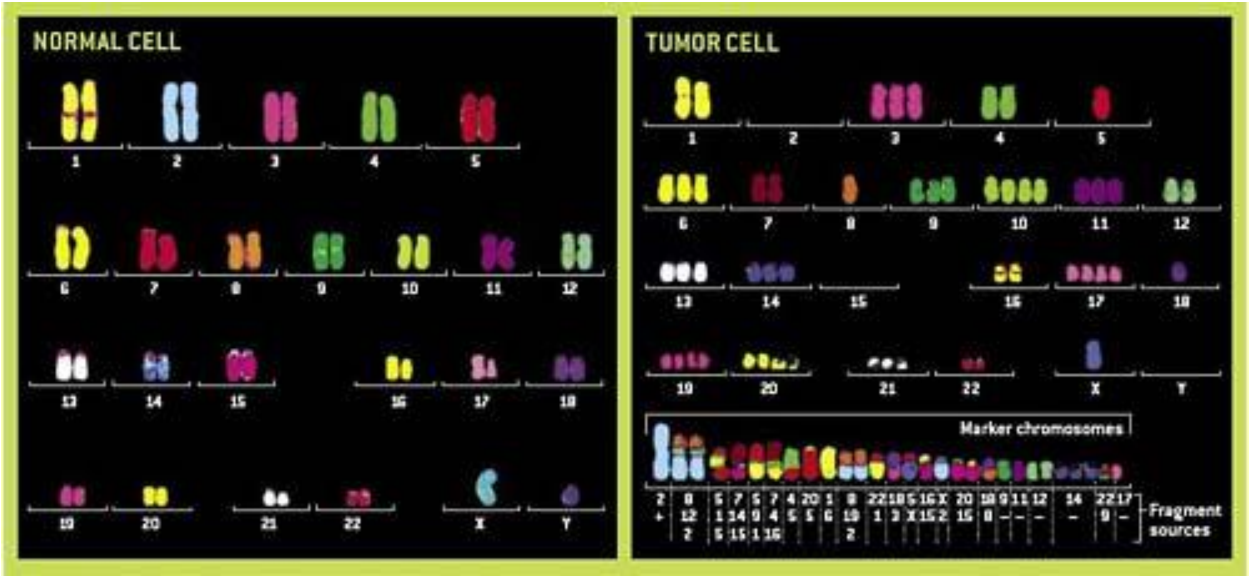


Protein Kinase Cascade



What could possibly go wrong from a network perspective?

All the way down to

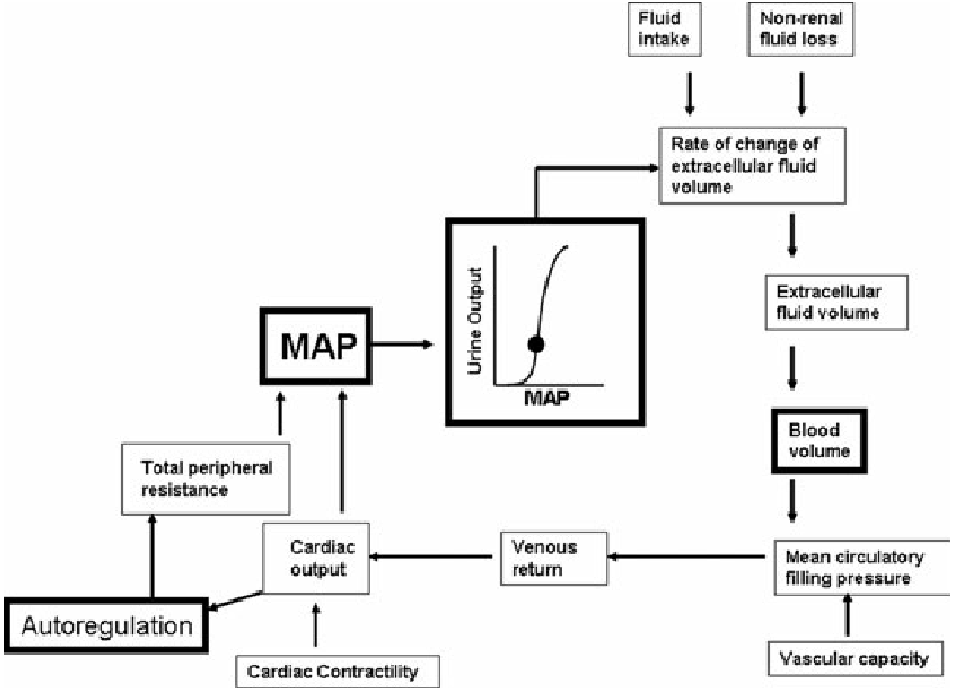


What could possibly go wrong from a network perspective?

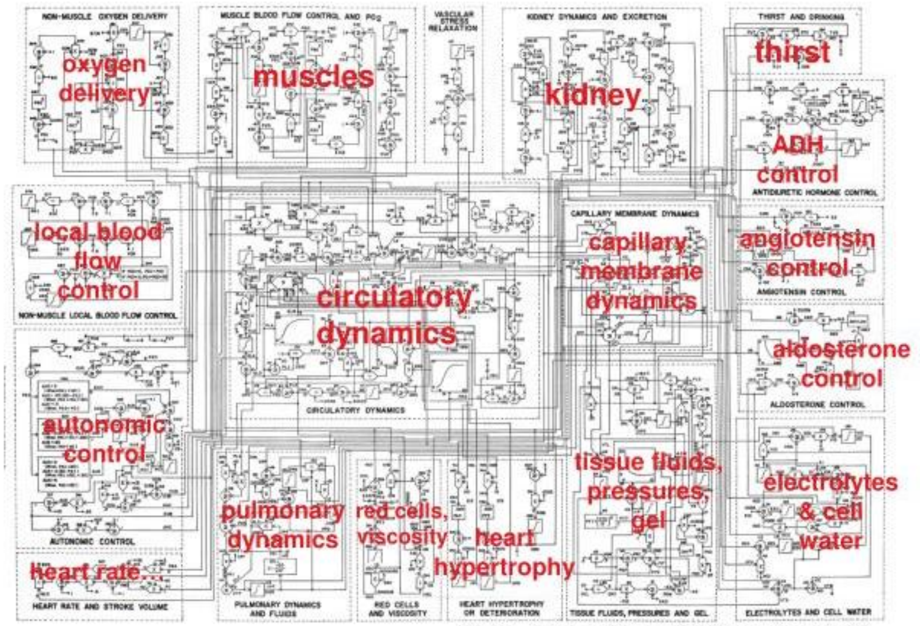
A closing thought (and experiment)

- I am sure that, by this time, you are thirsty (I know I am)..
- Which size will you drink?
- At what rate?
- What network(s) are affected?

This is part of what you are about to perturb



But it really looks more like this



Guyton, Coleman, Granger (1972) *Ann. Rev. Physiol.*

What could <u>possibly</u> go wrong from a network perspective?

Stay tuned…we will answer this question on Wednesday morning…!

Normal

ARDS

Summary for Lecture 1

- Network conceptualizations
  - Anatomy
  - Physiology
  - Pathophysiology
- A question or two to begin the discussion
  - What are the fundamental regulatory motifs?
  - What are the consequences of time delays in real networks?
  - What are the network consequences of “stress”, good stress (exercise) and bad stress (illness and overstress)?