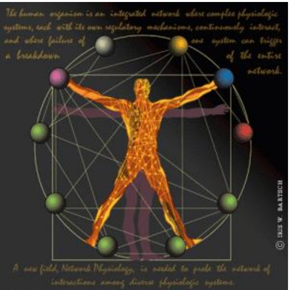
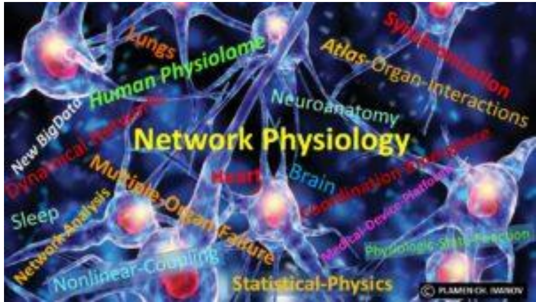
First International Summer Institute on Network Physiology (ISINP)

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

The Networks of the Self
2. Critical Illness and Critical Care

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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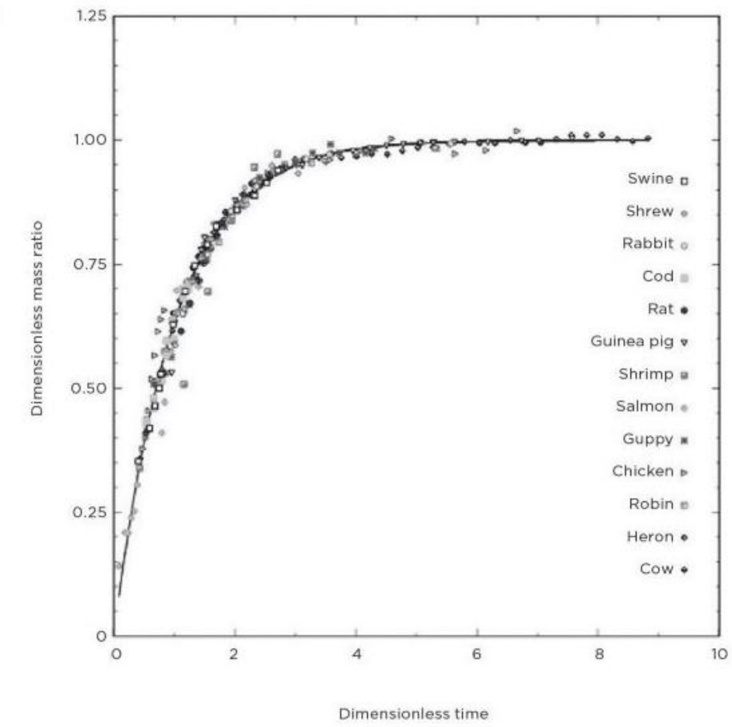
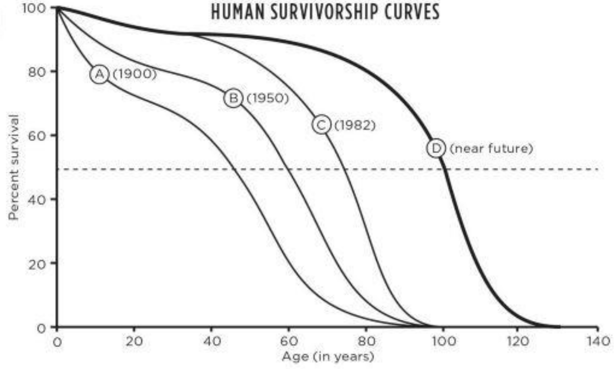
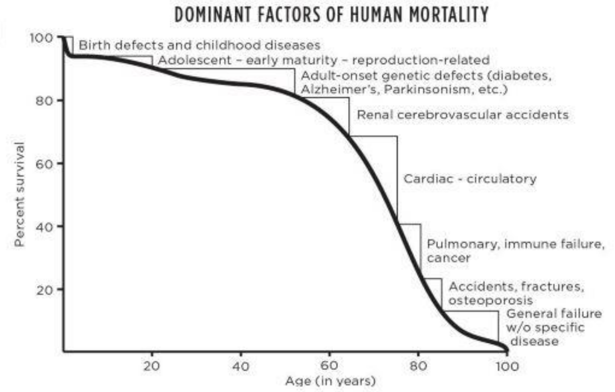
Let’s Look at Ordinary Life for a Moment

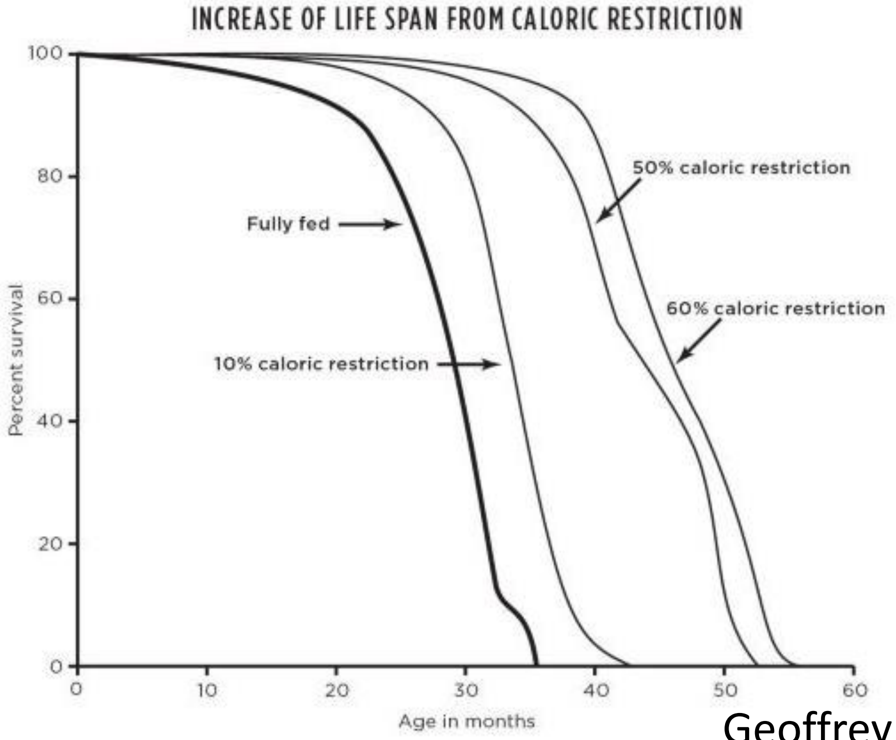


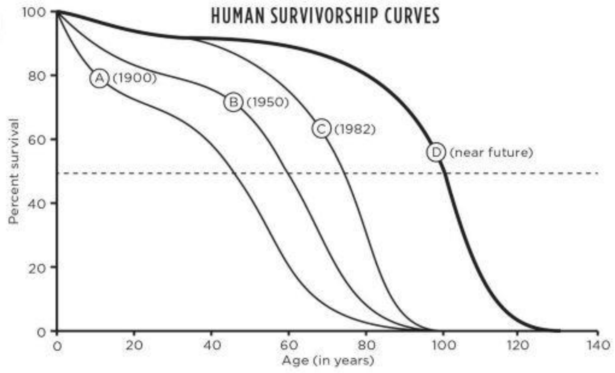


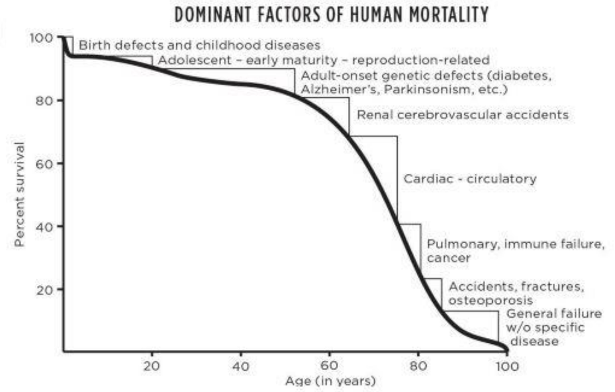


Geoffrey West, **Scale**

Let's Look at Ordinary Life for a Moment







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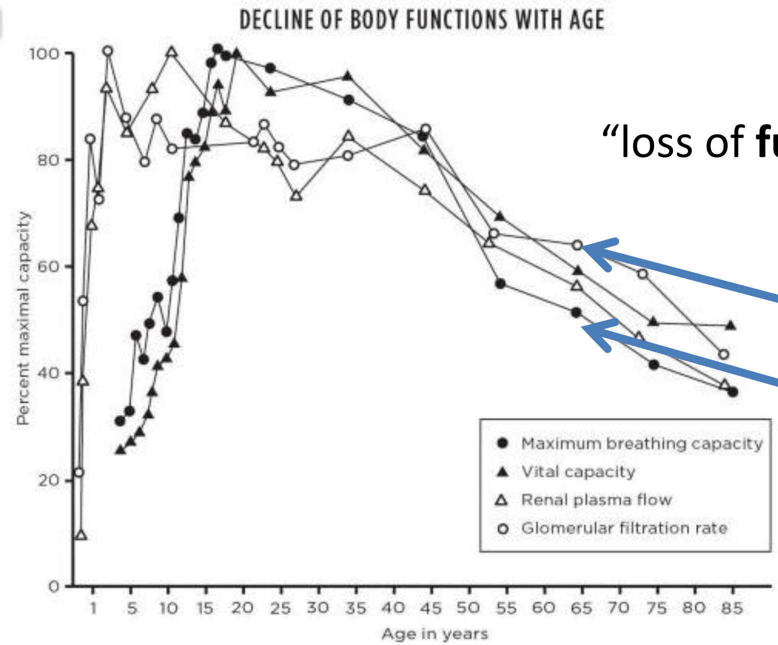
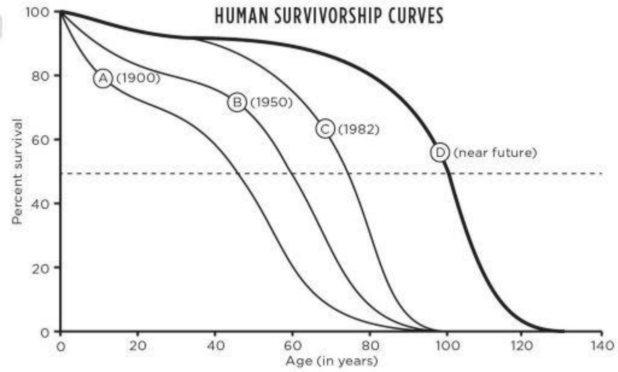
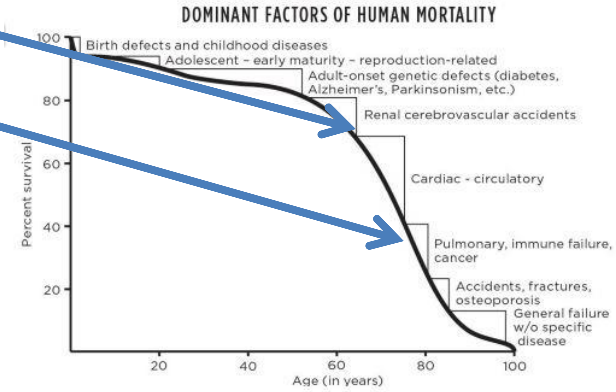
Let's Look at Ordinary Life for a Moment



"loss of **functional** reserve"





At some point, a "vital function" declines to the point that it is inadequate
To support life. This may be a slow decline, or it may be a sudden change.
Either way, the person becomes my patient because s/he is "critically ill"

Geoffrey West, **Scale**

In a "Network Conception" of physiology, what can go wrong that affects function?-Nodes and Ends

The excess of nodes

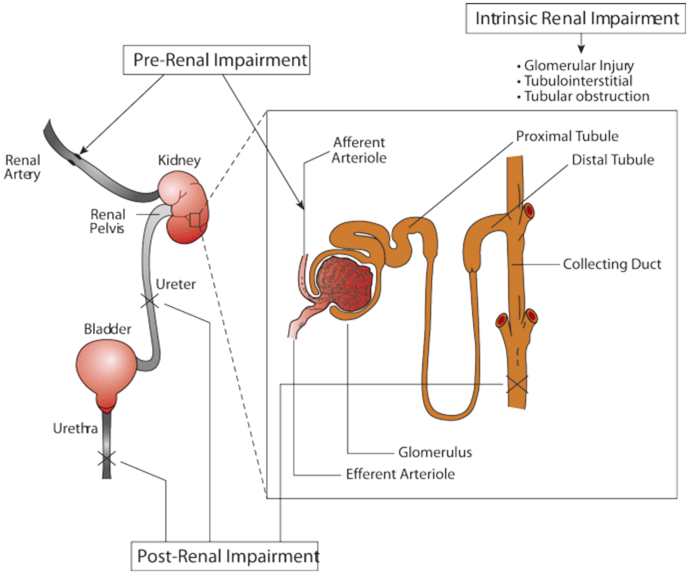
- Cancers
- Accumulation of dysfunctional immune memory cells

The disappearance of end-organs

- Diabetes Mellitus
  - Nerves: feet, GI, eyes
  - Capillaries
  - Beta cells (pancreas)
- **Kidney Failure**
  - **Glomeruli**

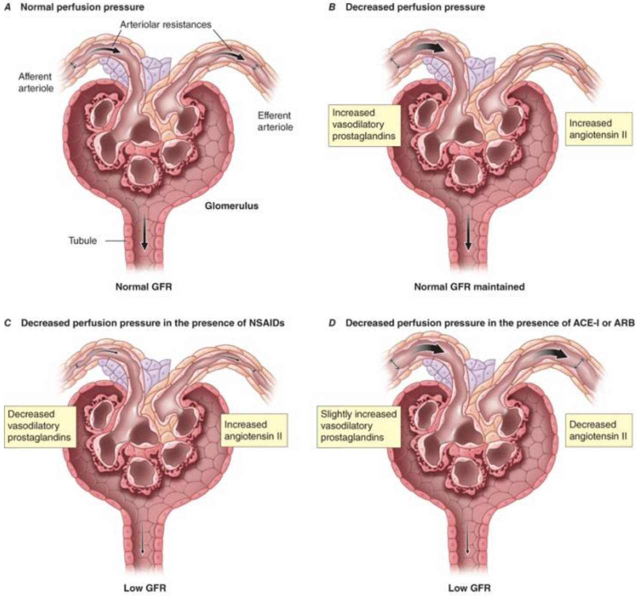
The kidney

High Level



Source: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM: *Pharmacotherapy: A Pathophysiologic Approach, 8th Edition*: www.accesspharmacy.com

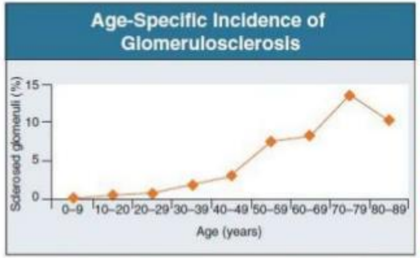
Glomeruli

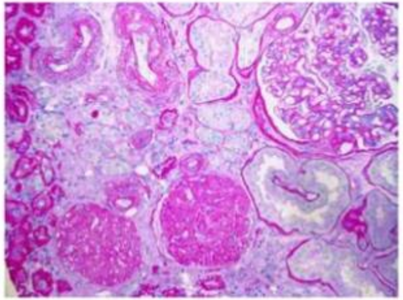


Source: D. L. Kasper, A. S. Fauci, S. L. Hauser, D. L. Longo, J. L. Jameson, J. Loscalzo: Harrison's Principles of Internal Medicine, 19th Edition.
www.accessmedicine.com

The kidney--failure

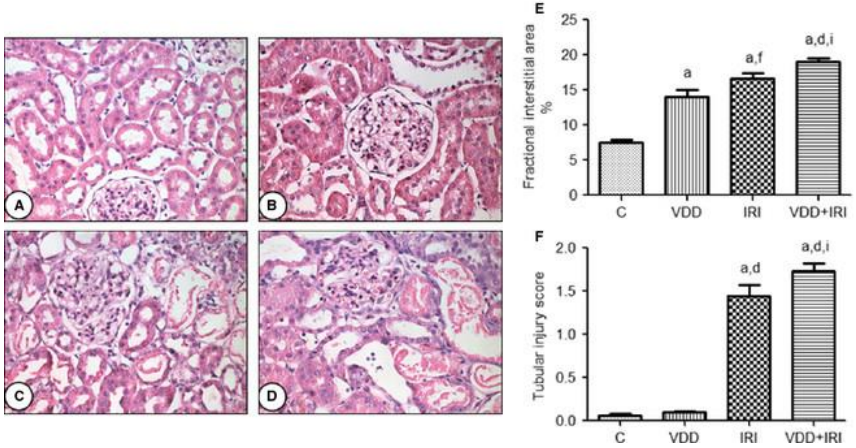
With age





The proportion of functioning glomeruli decreases with aging
The percentage of hyaline and sclerotic glomeruli increases

With vitamin deficiency and insult



In a “Network Conception” of physiology, what can go wrong that affects function?-Connections and Regulations

Loss of Connections

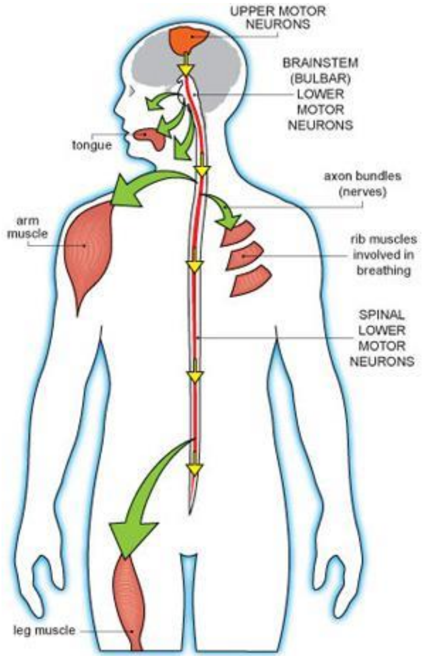
- Pruning of trees (isolation of end organs)
  - Ordinary arterial vascular disease
  - **Amyotrophic Lateral Sclerosis**
- Loss of network/network interconnections
  - Within nests
  - Across types

Failure of (Negative) Feedback

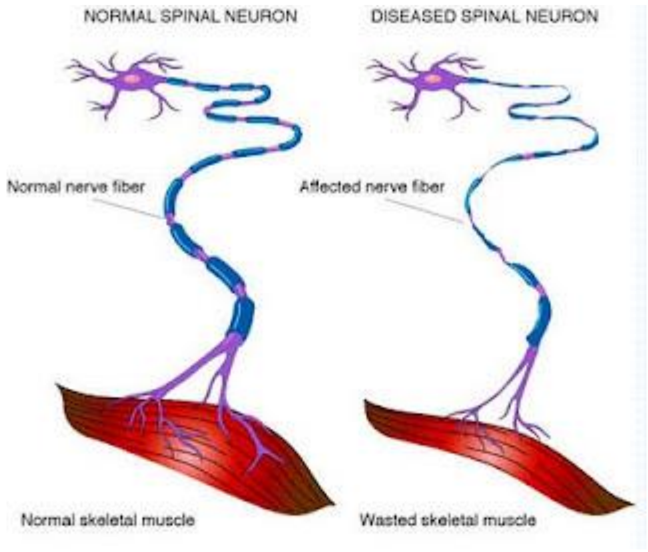
- Autoimmune diseases
- Reentrant tachycardias
- Cancers of many types (cellular level)
- Autonomously functioning tissues (pituitary adenomas)

In a "Network Conception" of physiology, what can go wrong that affects function?-Connections and Regulations

Loss of Connections



Loss of Connections



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Failure of (Negative) Feedback

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- Reentrant tachycardias
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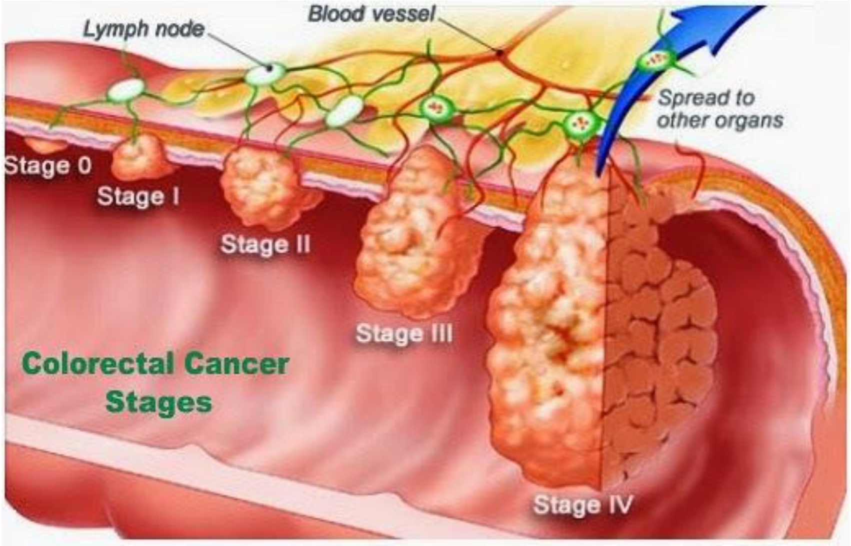
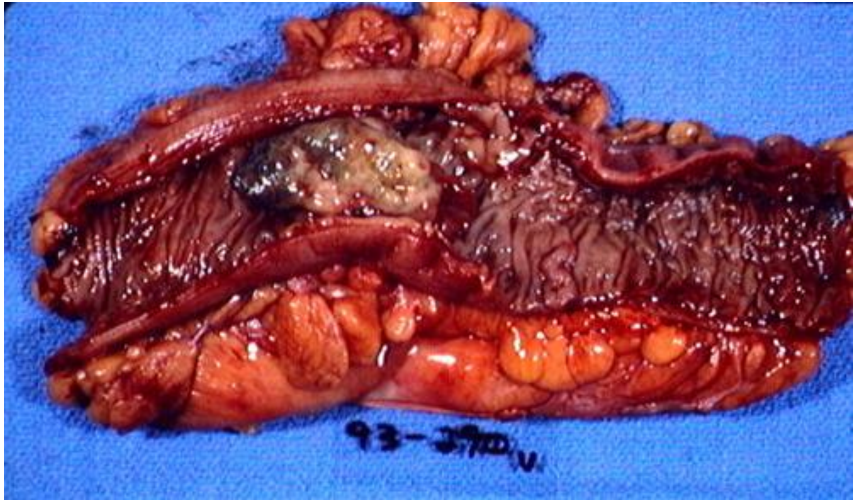
- Autonomously functioning tissues (pituitary adenomas)

Let’s talk colon cancer….

What it looks like

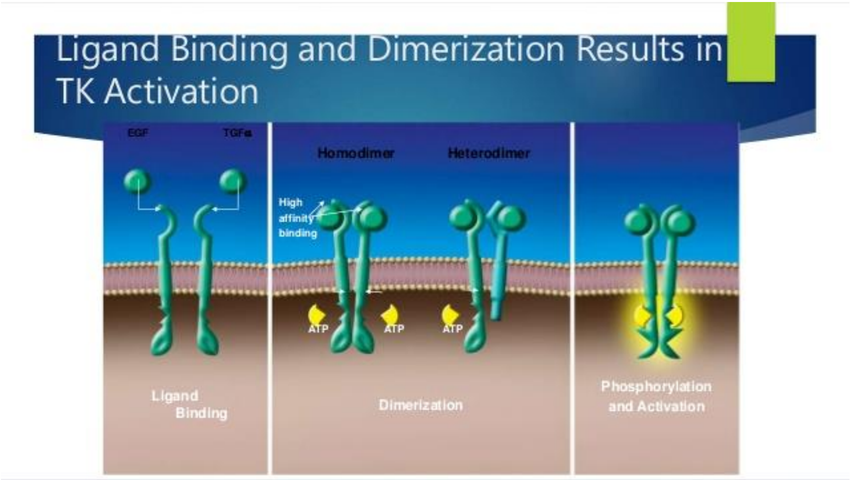


What it looks like

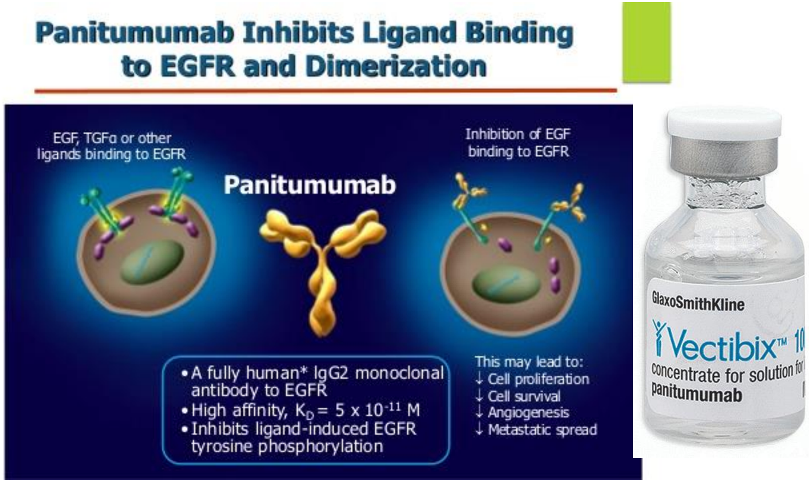


Let’s Stop those Cells!!!
Epidermal Growth Factor

Schematic—at the Cell Surface

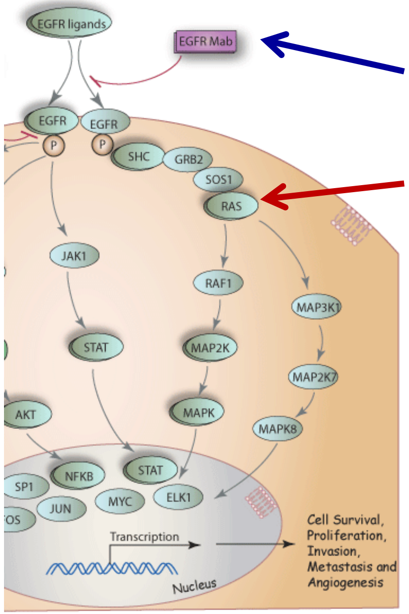


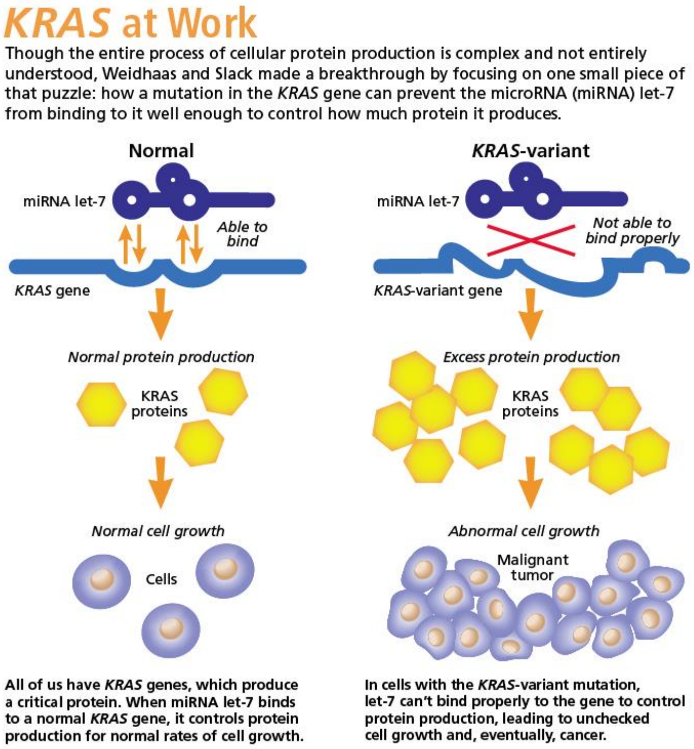
Stop it!



What does this have to do with networks?

So there's a network

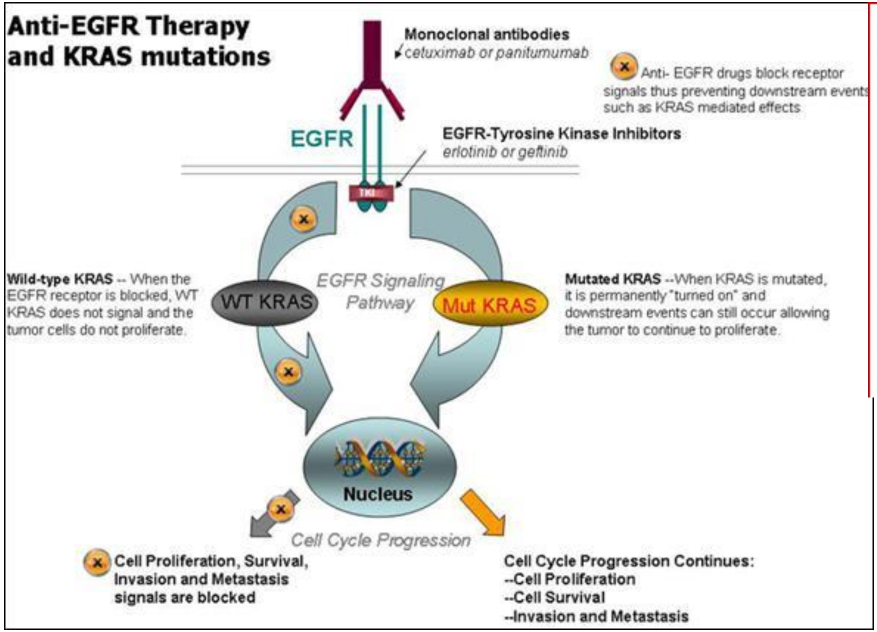


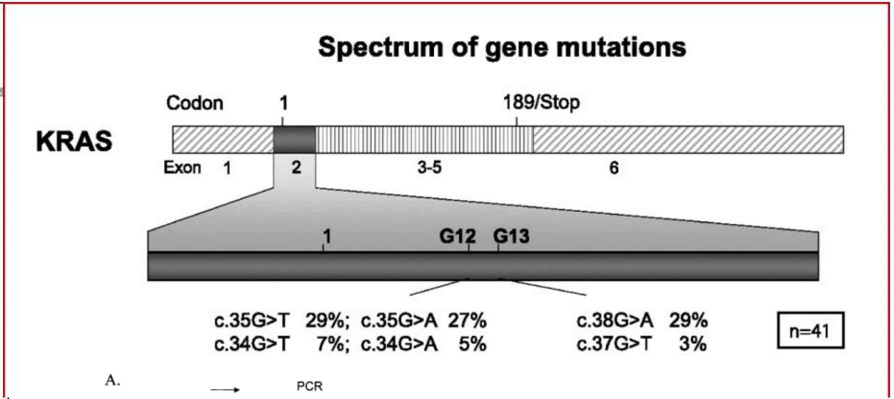


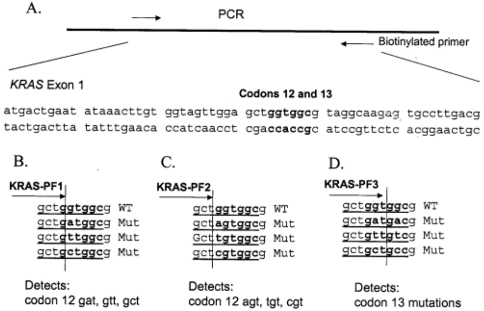
What does this have to do with networks?

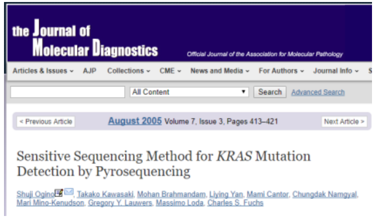
Those EGFR antibodies work only if KRAS is normal

Screen for network mutations first!





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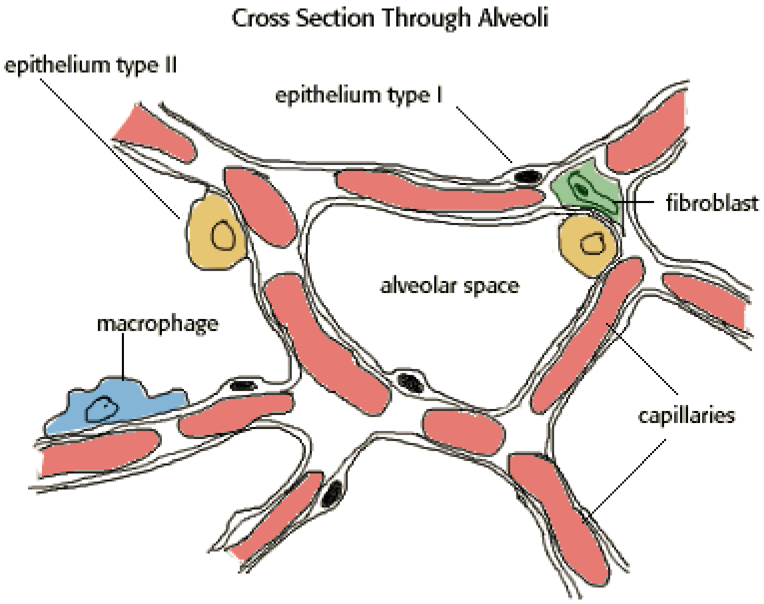
Sensitive Sequencing Method for *KRAS* Mutation Detection by Pyrosequencing

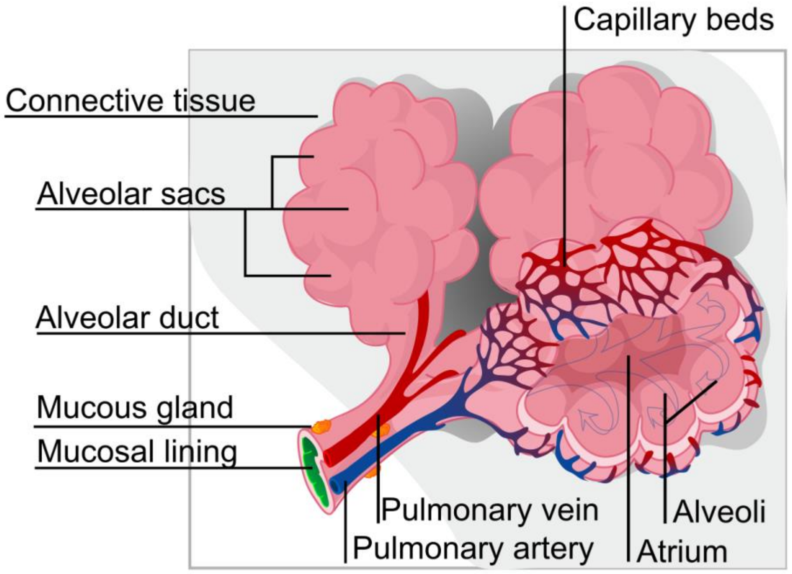
Shuji Ogino, Takako Kawasaki, Mohan Brahmandam, Liying Yan, Mami Cantor, Chungdak Namgyal, Mari Mino-Kenudson, Gregory Y. Lauwers, Massimo Loda, Charles S. Fuchs

Let's go back to the "simple" case of the lung and focus on the end units

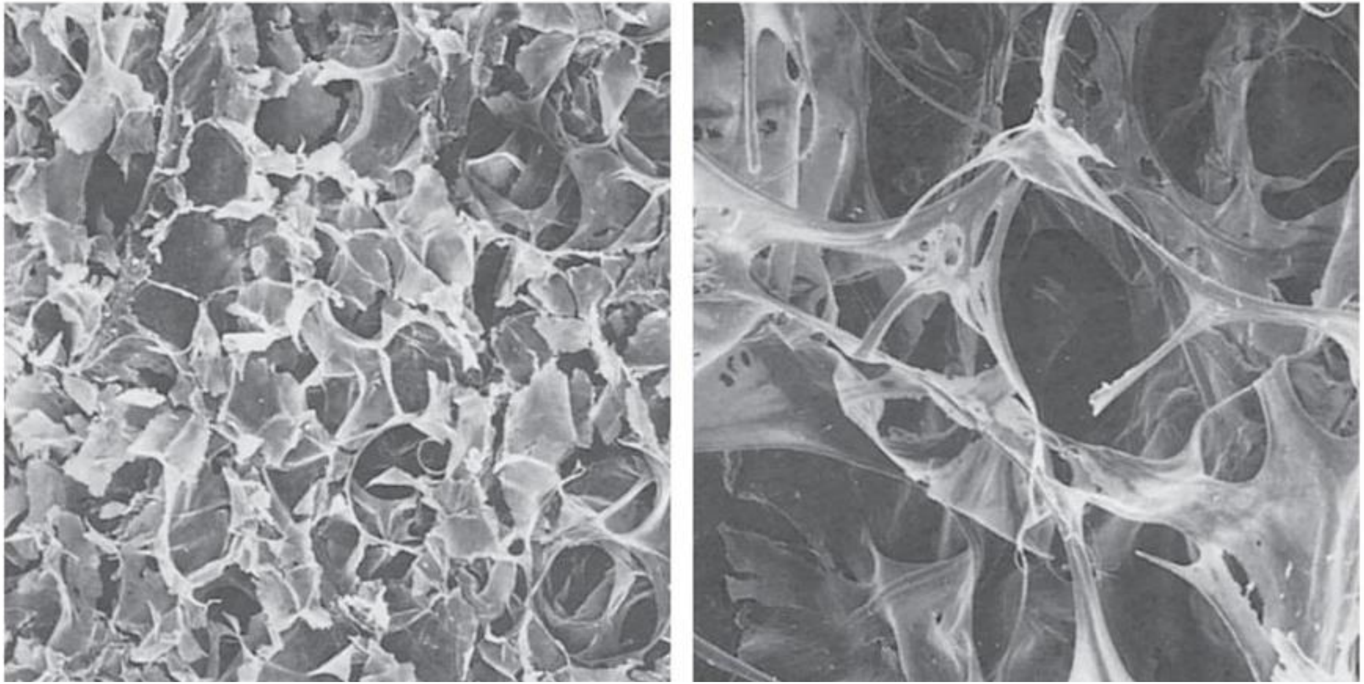
Cross section



3-D Version



So we can just lose end units



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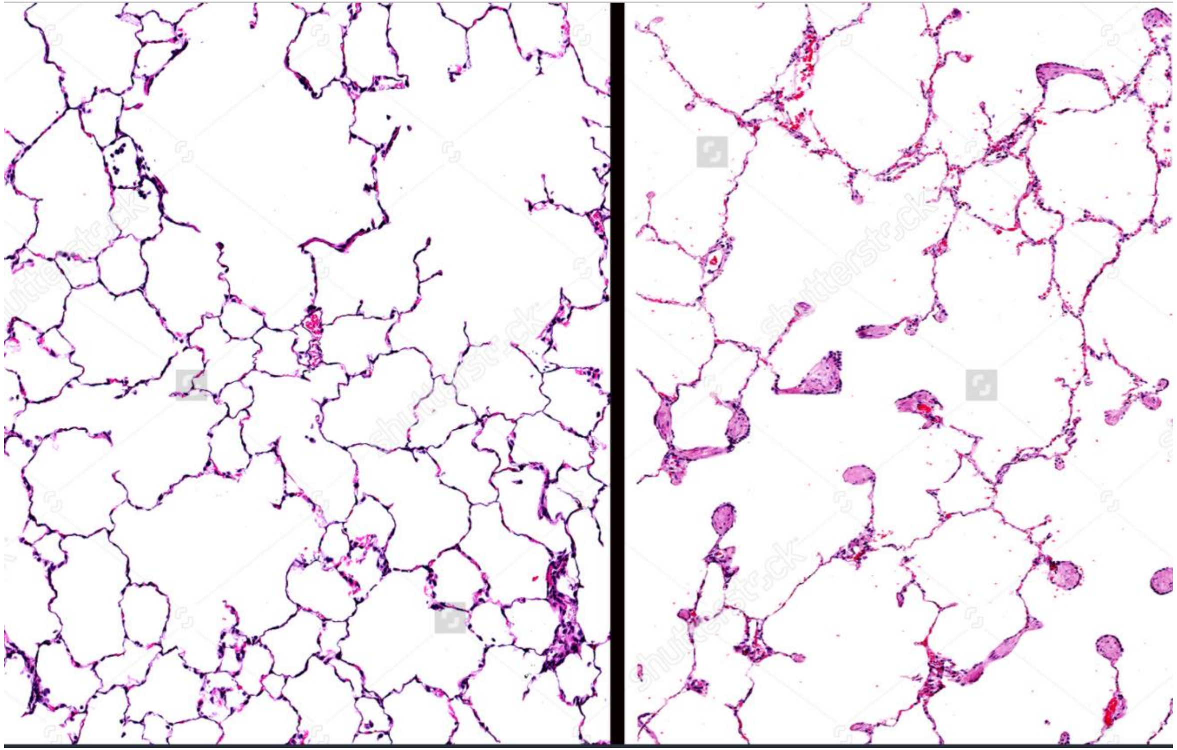
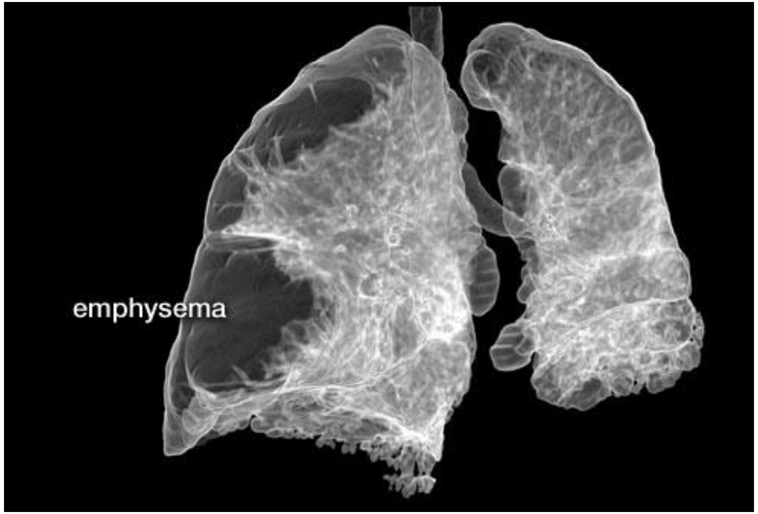
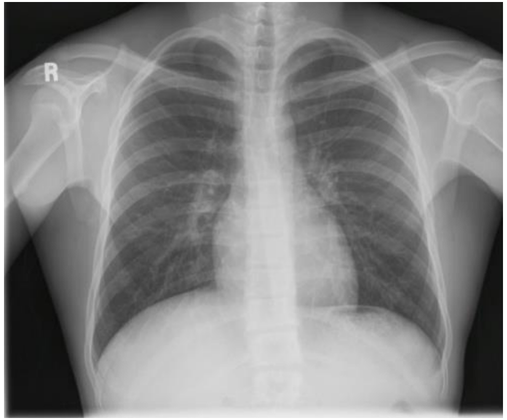


So we can just lose end units



So this is emphysema;
Most common cause
is smoking, of course



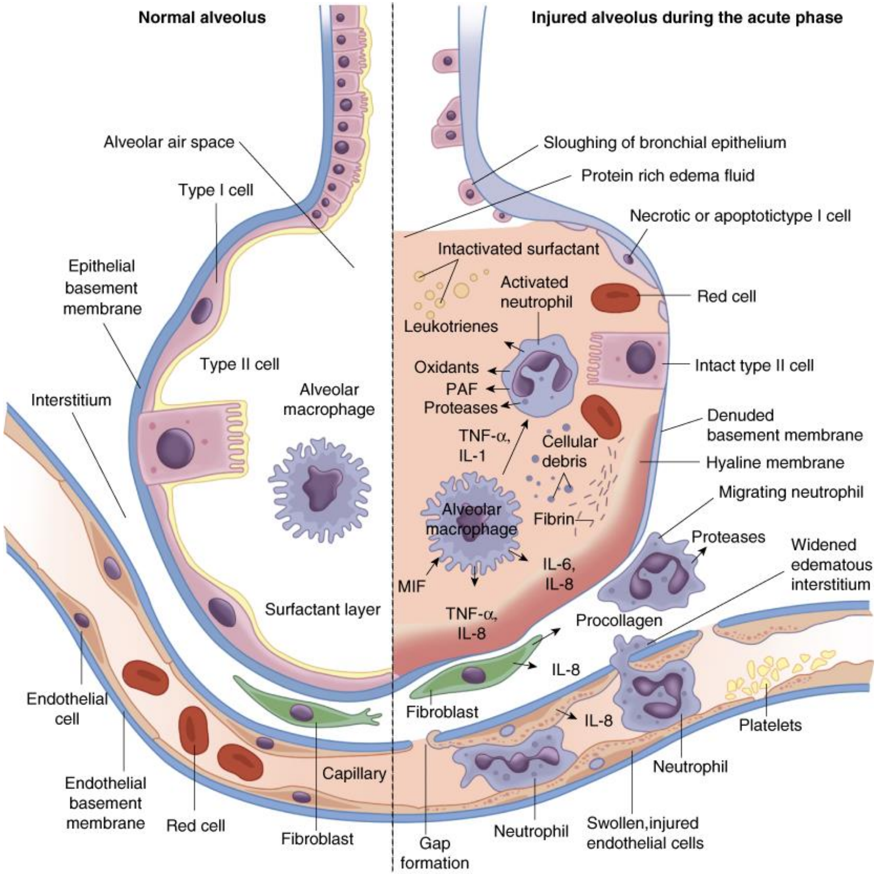
normal

Normal

ARDS

Air is
“black”

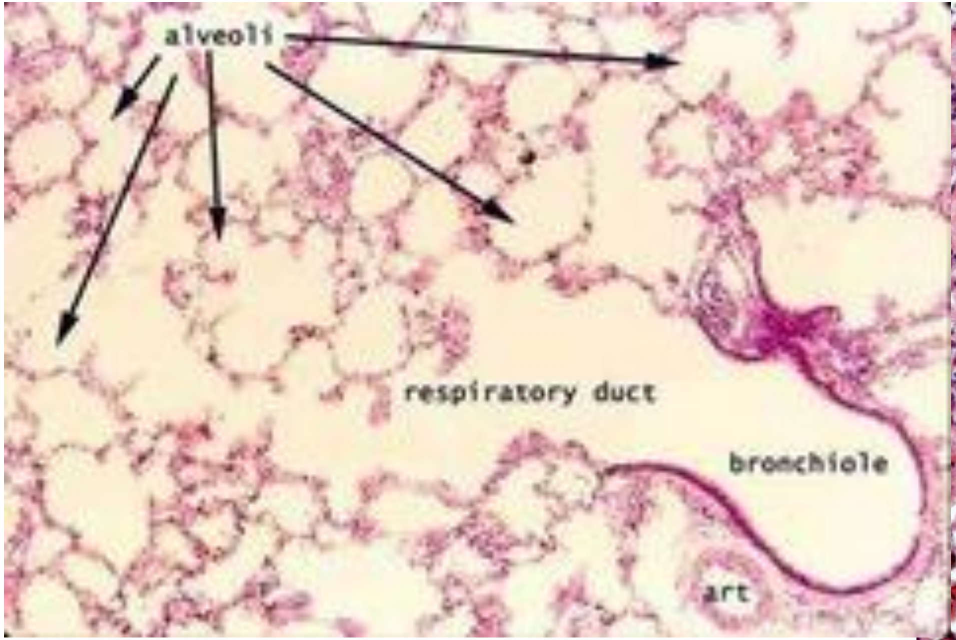
Water
(and bone)
are “white”



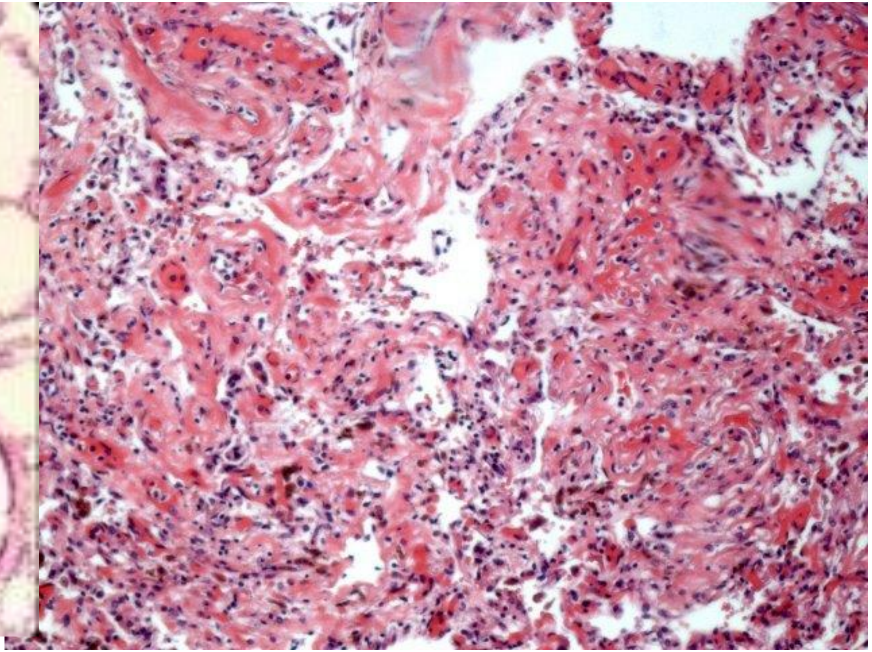
Source: McKean S, Ross JJ, Dressler DD, Brotman DJ, Ginsberg JS: *Principles and Practice of Hospital Medicine*: www.accessmedicine.com

Under the microscope:

Normal ARDS

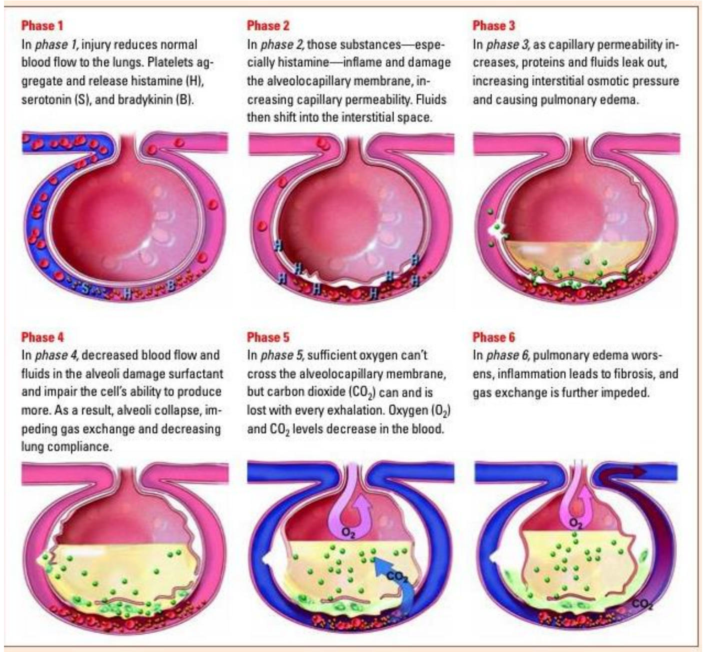


Mostly empty alveoli



Alveoli full of protein rich (pink) fluid and inflammatory cells

What has happened?
What to do?



- Fluid from the plasma is leaking into the airspaces
- Have to somehow stop the leak!

COMPARATIVE QUANTITATIVE MORPHOLOGY OF THE MAMMALIAN LUNG: DIFFUSING AREA

By PROF. S. M. TENNEY and J. E. REMMERS

D v Hampshire

O_2 consumption (liter h^{-1})	=	0.676	$\times M_b^{0.75}$
O_2 consumption per kilogram (liter h^{-1} kg^{-1})	=	0.676	$\times M_b^{-0.25}$
Lung ventilation rate (liter h^{-1})	=	20.0	$\times M_b^{0.75}$
Lung volume (liter)	=	0.063	$\times M_b^{1.02}$
Tidal volume (liter)	=	0.0062	$\times M_b^{1.01}$
Blood volume (liter)	=	0.055	$\times M_b^{0.99}$
Heart weight (kg)	=	0.0058	$\times M_b^{0.99}$
Respiration frequency (min^{-1})	=	53.5	$\times M_b^{-0.26}$
Heart rate (min^{-1})	=	241	$\times M_b^{-0.25}$

* If equations listed in this text are compared with similar equations given elsewhere, it is necessary to pay close attention to the units used. In this chapter the units are consistently liters O_2, hours, and kilograms. Recalculations between liters and milliliters and between hours, minutes, and seconds are a matter of simple arithmetic. However, if the body mass is expressed in grams instead of kilograms, the conversion is more complex. As an example, consider the equation for metabolic rate $V_{O_2} = 3.8\ M_b^{0.75}$ with the units milliliters, hours, and grams. If we convert the equation for use with kilograms, what will the coefficient 3.8 become? To insert kilograms, we must *divide* the gram mass (M_b) by 1000, but because the number 1000 is afterward raised to the 0.75 power, we must multiply the coefficient 3.8 by the same number ($1000^{0.75}$ or 177.83). This gives the equation $V_{O_2} = 3.8 \times 177.83 \times M_b^{0.75} = 676\ M_b^{0.75}$ (ml, h, kg), or $0.676\ M_b^{0.75}$ (liter, h, kg). These last units are those used in all equations in this chapter.

Table 5.9 Relationship for mammals between physiological variables and body mass (M_b in kilograms). * [Data selected from Adolph 1949; Drorbaugh 1960; Stahl 1967]

Lung Volume = 6.3% BW

Tidal Volume = 6.3 ml kg^{-1}

Acta Anaesthesiol Scand 2004; 48: 267–271
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ACTA ANAESTHESIOLOGICA SCANDINAVICA

Review Article

From ventilator-induced lung injury to physician-induced lung injury: Why the reluctance to use small tidal volumes?

J. VILLAR[1], R. M. KACMAREK[2] and G. HEDENSTIERNA[3]
[1]Hospital Universitario N.S. de Candelaria, Tenerife, Canary Islands, Spain; Adjunct Scientist, Research Center, St. Michael's Hospital, Toronto, Ontario, Canada, [2]Harvard Medical School, and Director, Respiratory Care, Massachusetts General Hospital, Boston, MA, and [3]Department of Medical Sciences, Clinical Physiology, Uppsala University, Stockholm, Sweden

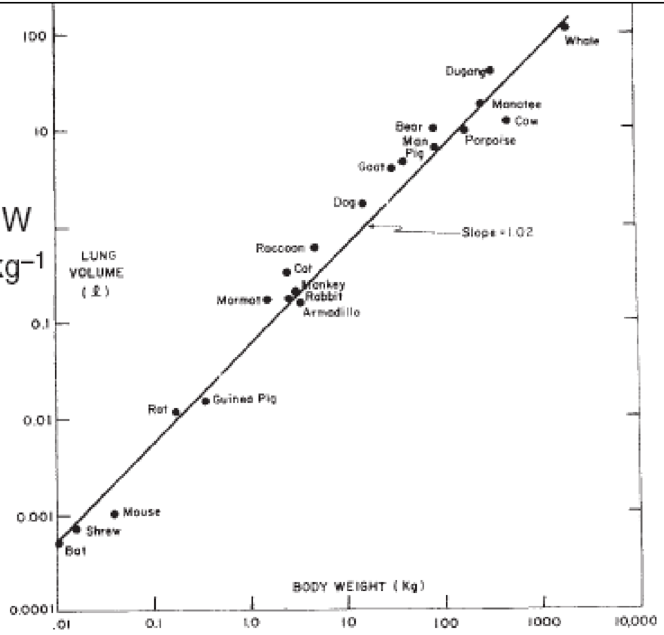
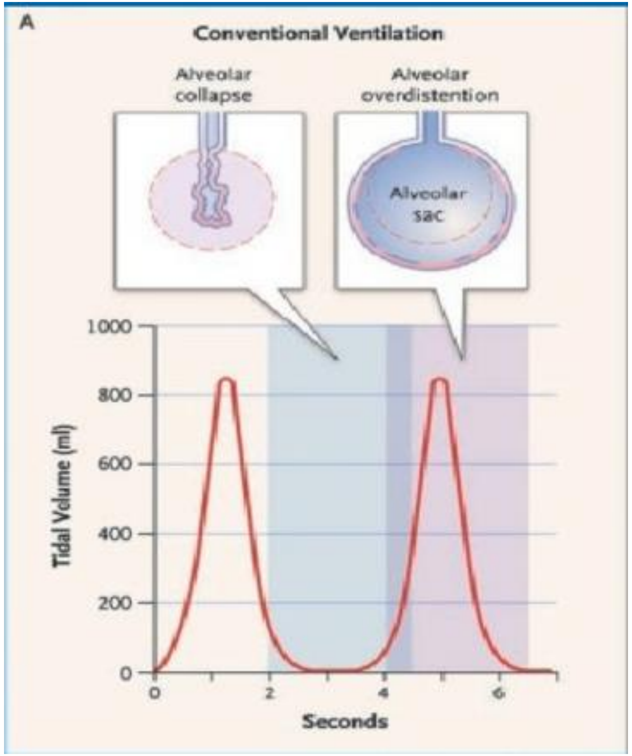
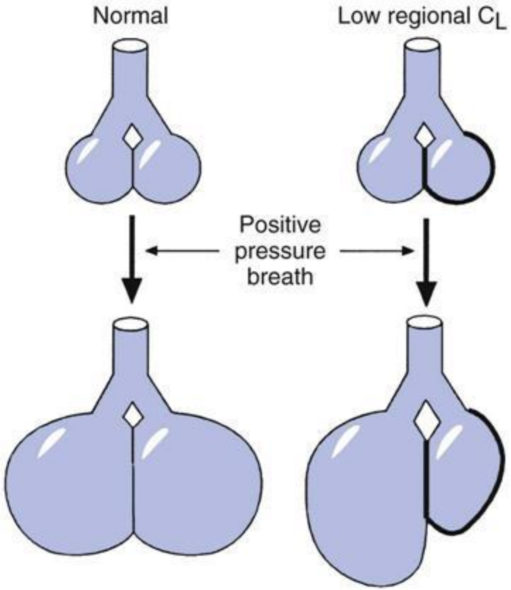


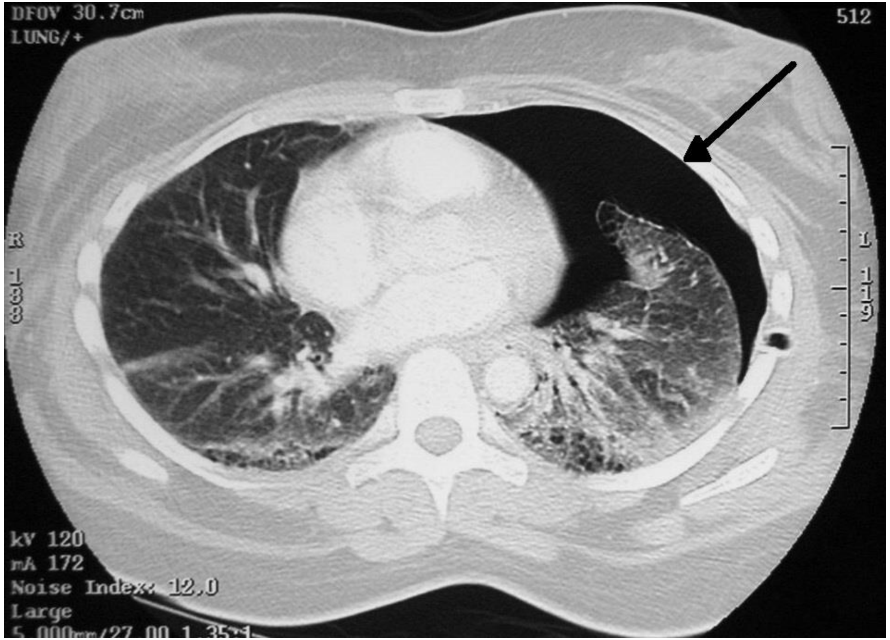
Fig. 1. Logarithmic plot of lung volume as a function of body-weight

1. “Just increase the airway pressure”





This turns out to be a bad idea



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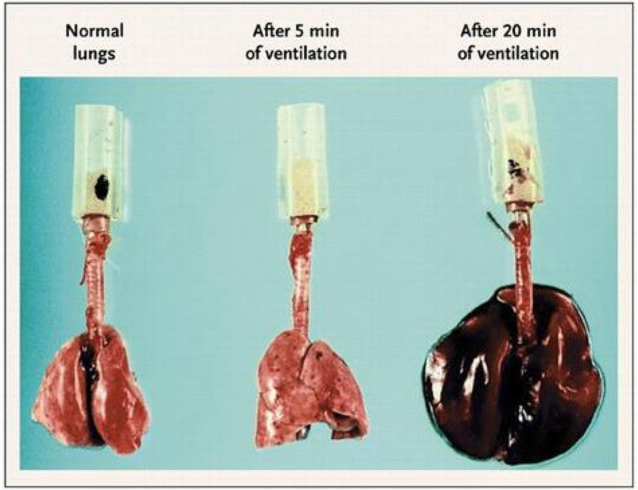


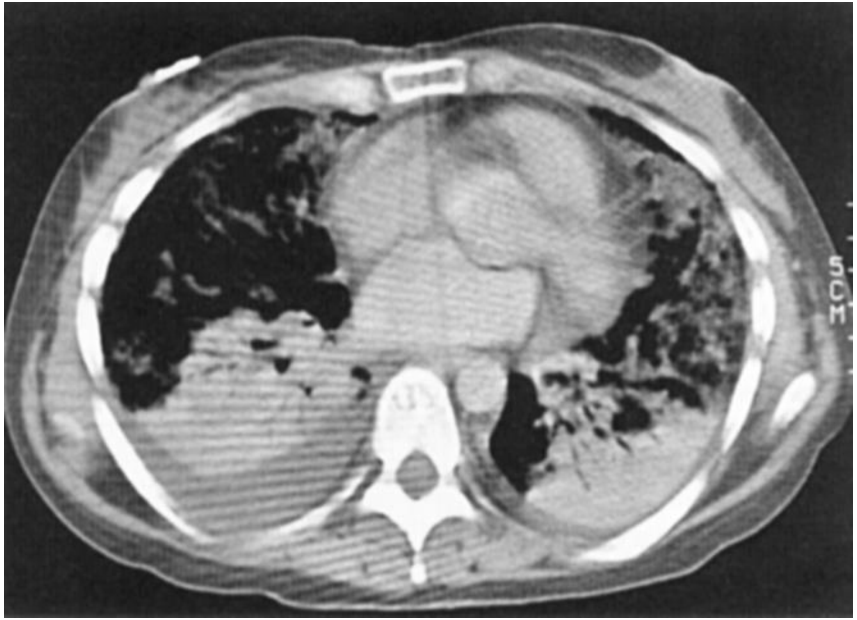
Normal

ARDS

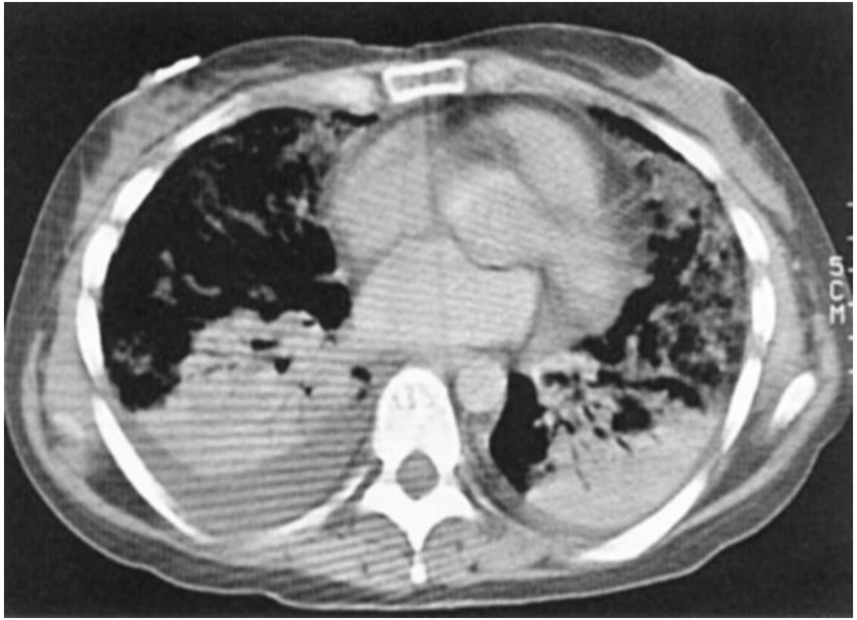
Air is
“black”

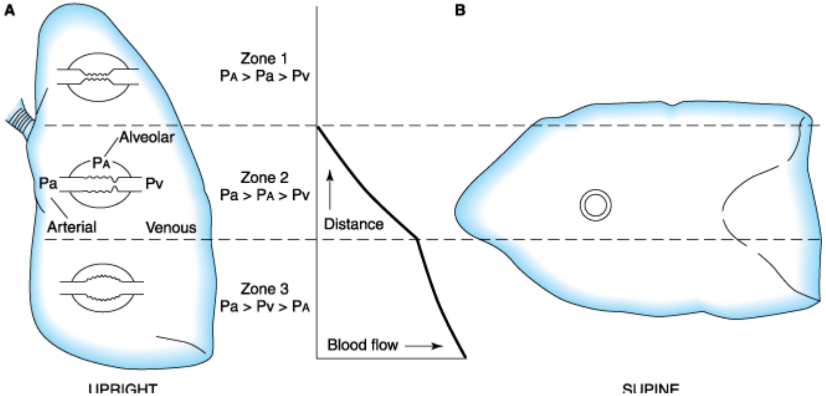
Water
(and bone)
are “white”

Some physics:
the network is in the gravitational field



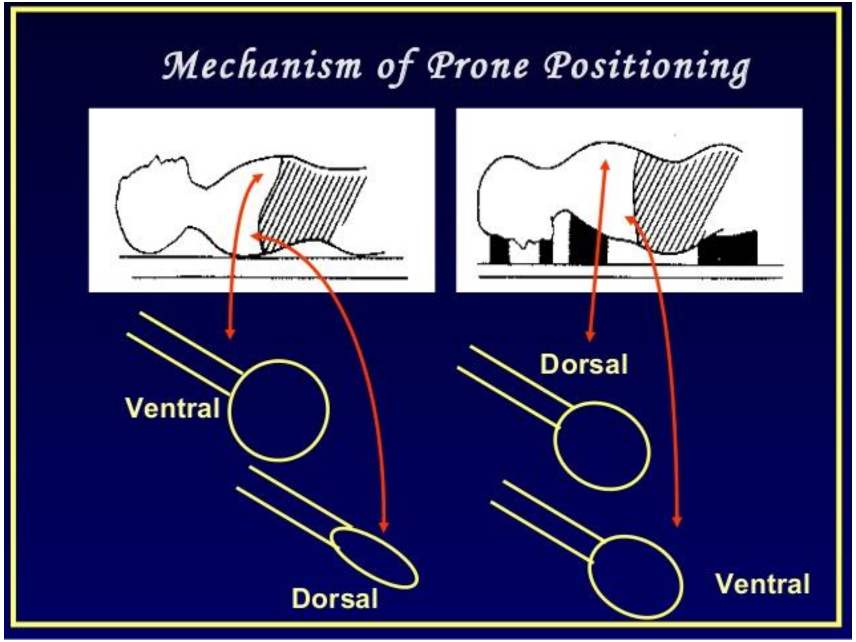
Gravity does a lot to the respiratory network

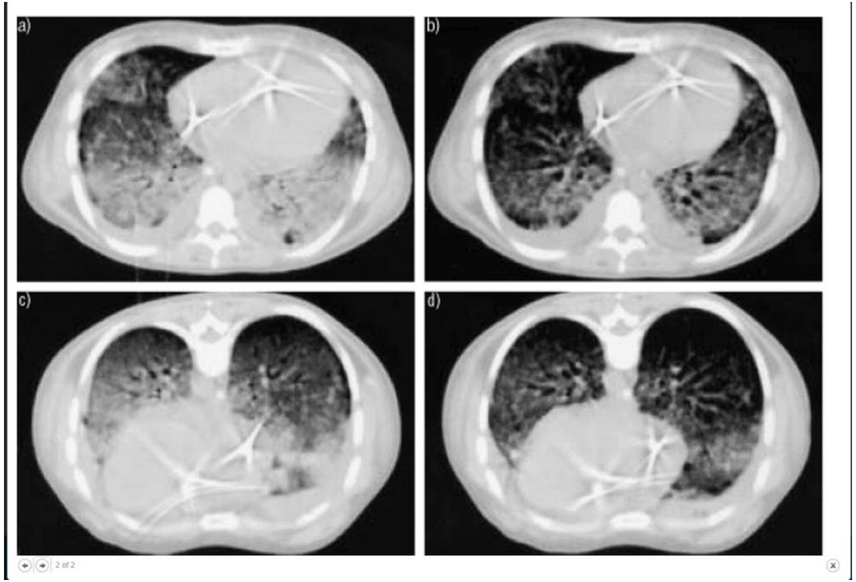




Source: Morgan GE, Mikhail MS, Murray MJ: *Clinical Anesthesiology*, 4th Edition: http://www.accessmedicine.com

So we can use gravity to advantage

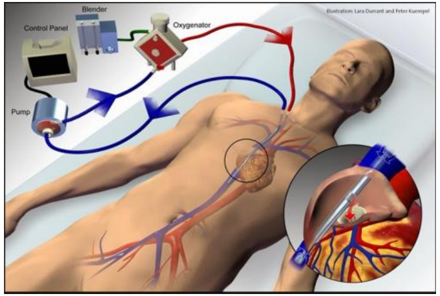




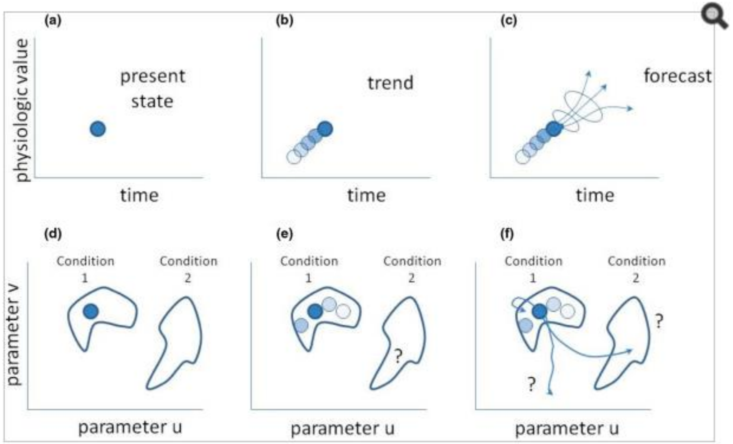
What we are really trying to do is buy time

- Biological networks have two additional characteristics
  - Self repairing (for the most part)
  - Tendency to couple
    - Weak oscillators

- One way to "buy time" is to take the network off line and allow for self-repair

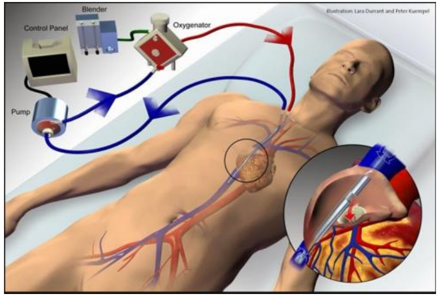


What we are really trying to do is buy time—and nudge the network into a different attractor



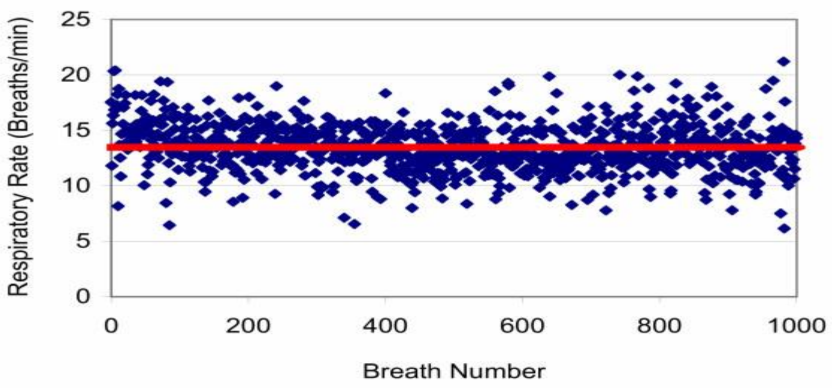
Temporal evolution of physiologic state. **(a-c)** Conventional display; **(d-f)** state space representation.

- One way to "buy time" is to take the network off line and allow for self-repair
- "artificial lung"



Fact: Biological oscillators often have irregular (“aperiodic”) dynamics

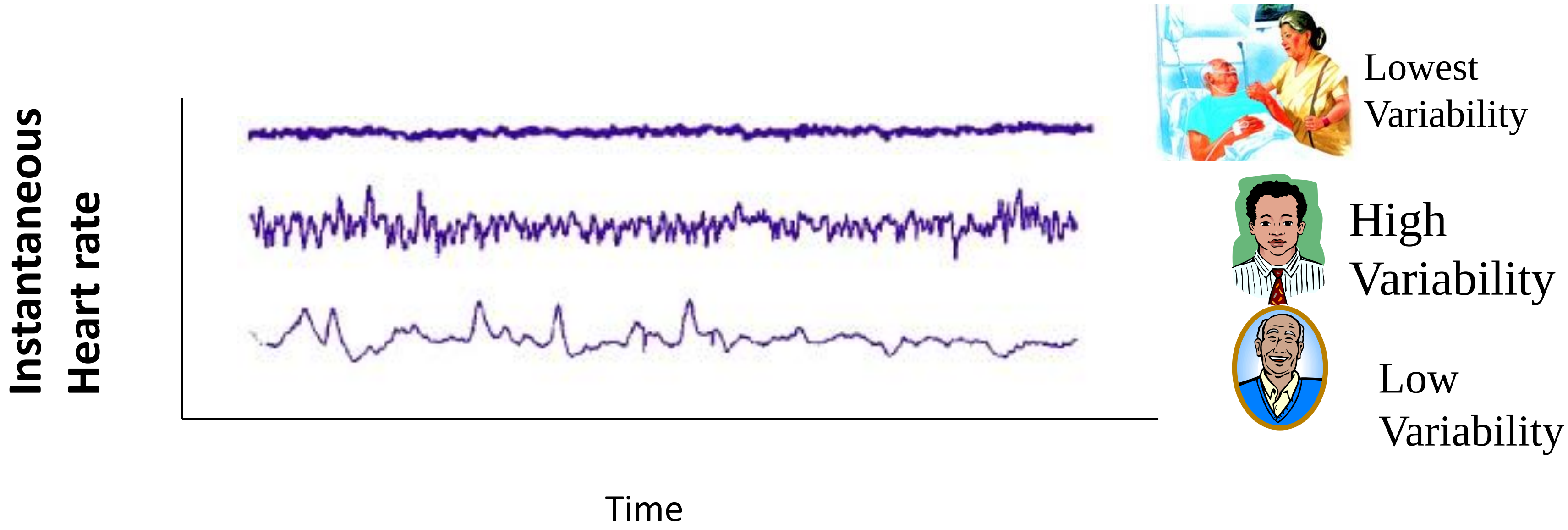
- Readily observed
  - Respiratory rate
  - Blood pressure
- Readily detectable
  - Insulin levels
  - Interbeat intervals of the heart
- Appreciable (only) in the lab
  - Cell cycle
  - Calcium transients



Normal, healthy human
Medical record:
“RR=14/min, regular”

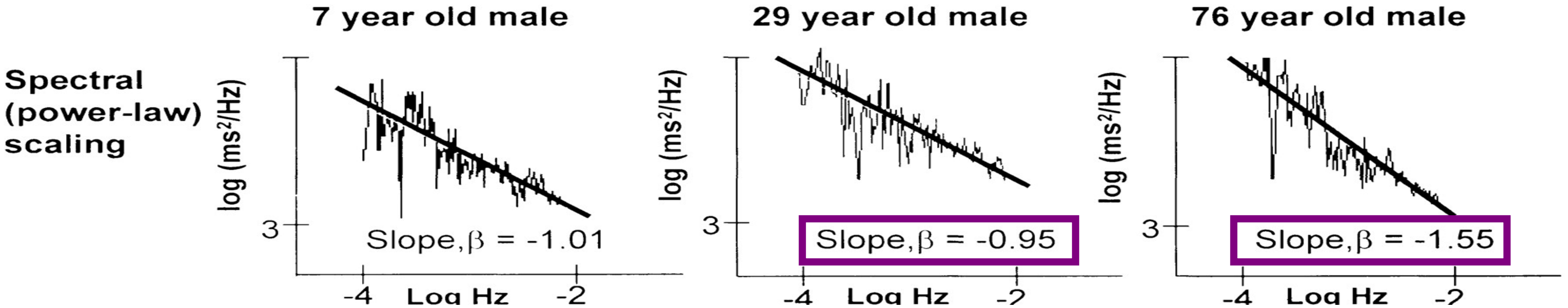
A BRIEF SIDEBAR ON AGING

Aging and illness:
associated with decomplexification of dynamics



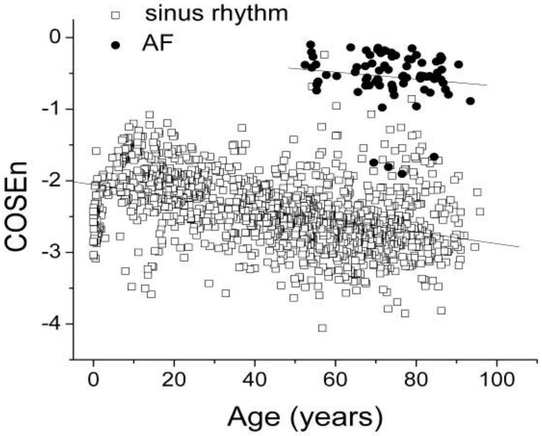
Variability in heart rate diminishes slowly past middle age

Pikkujamsa SM, et al Circulation. 1999 Jul 27;100(4):393-9.

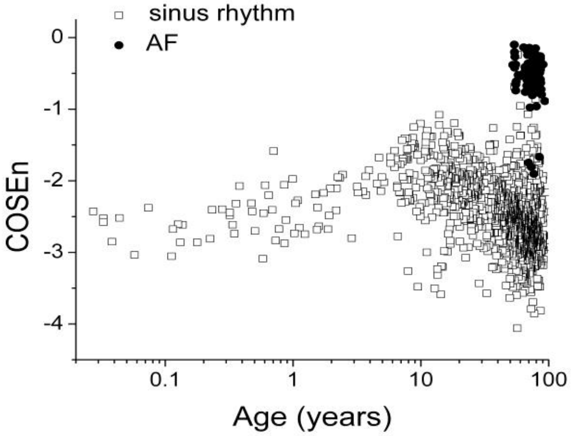


From Dr. Moorman's Group: Age, Entropy

A

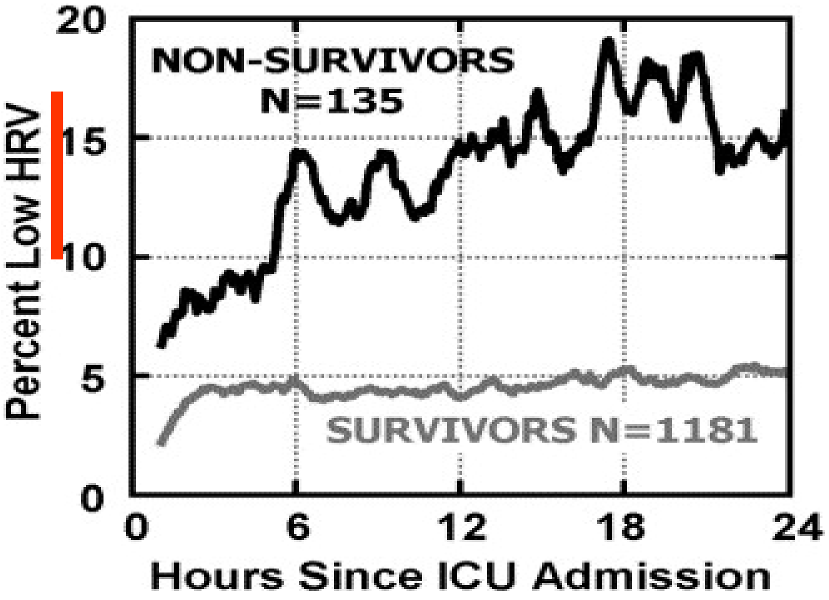


B



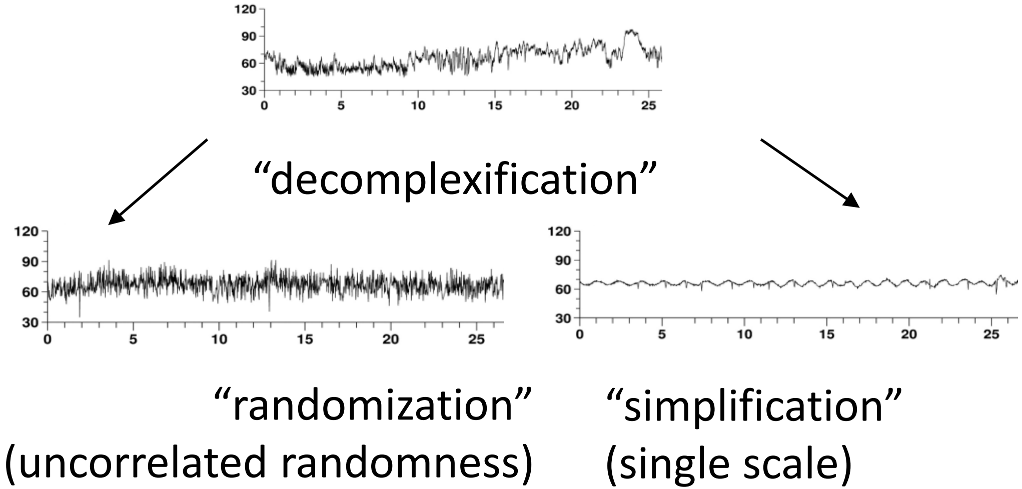
Loss of variability predicts failure to survive trauma

- 1316 trauma patients
- Intermediate data density (HR q 5 min)
- Independently predicts hospital death by 12 h following injury



Two general failure modes of "healthy" distributions and dynamics

- Complete randomization
- Highly periodic

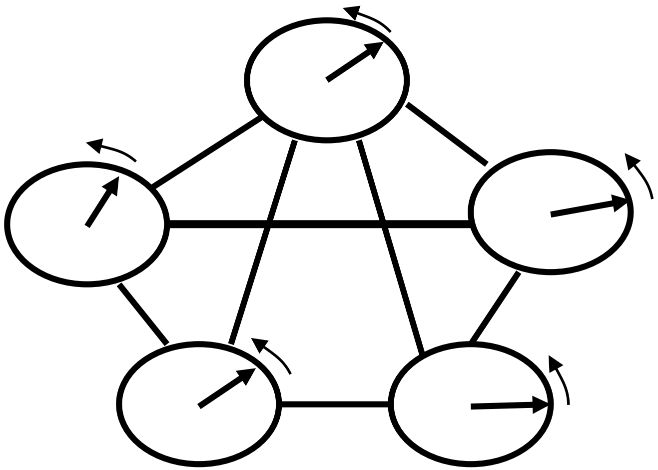


Uncoupling of biological oscillators: A complementary hypothesis concerning the pathogenesis of multiple organ dysfunction syndrome

Godin, Paul J. MD; Buchman, Timothy G. PhD MD, FCCM

Critical Care Medicine: July 1996 - Volume 24 - Issue 7 - pp 1107-1116

- Pathobiologic mechanism proposed two decades ago
- Supporting evidence in
  - Neonatal sepsis
  - Pediatric brain injury
  - Pediatric MOF
  - …



Uncoupling of biological oscillators: A complementary hypothesis concerning the pathogenesis of multiple organ dysfunction syndrome

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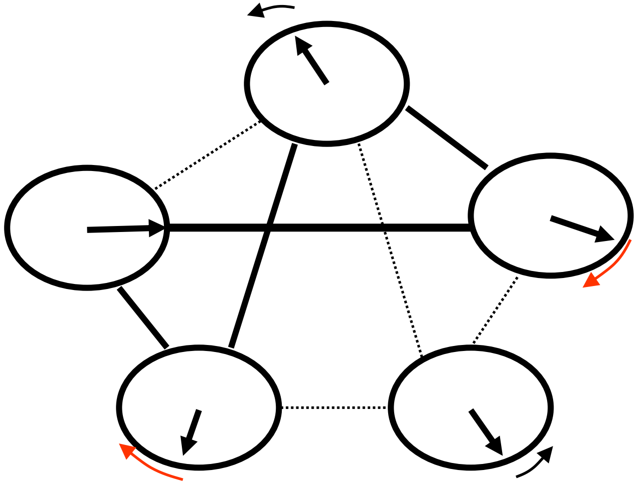
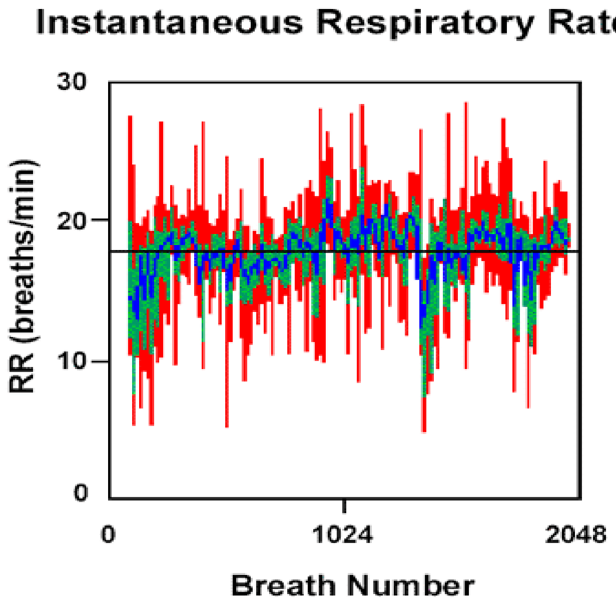
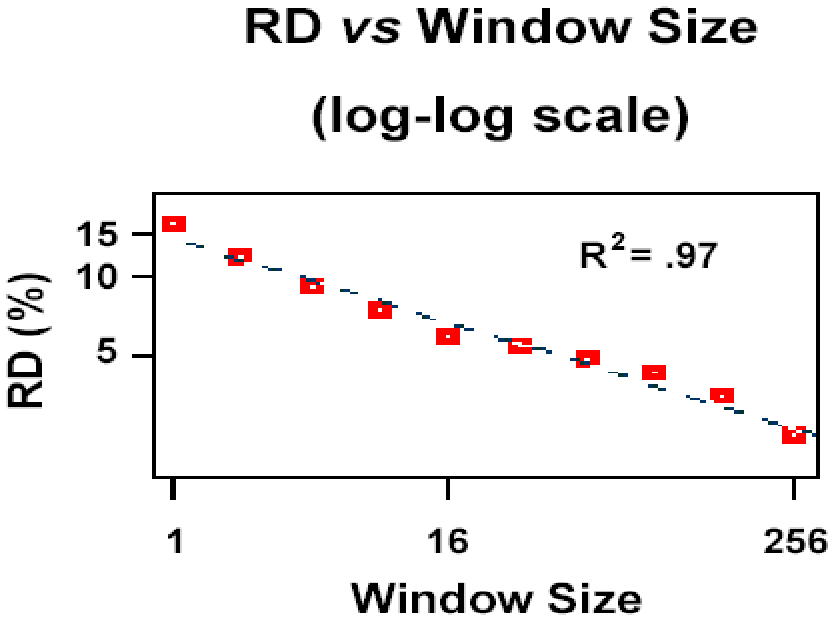
- Pathobiologic mechanism proposed a decade ago
- Supporting evidence in
  - Neonatal sepsis
  - Pediatric brain injury
  - Pediatric MOF
  - …
- Basic idea: as interconnections erode, delicate balance between synchronization and variation is lost, patients get “stuck” in stable but unfavorable states



BACK TO OUR STORY

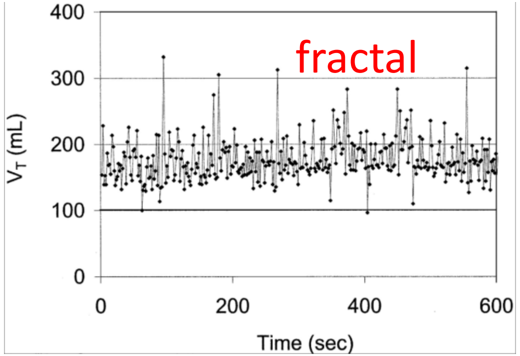
“Administer variability as therapy”: fractal ventilation

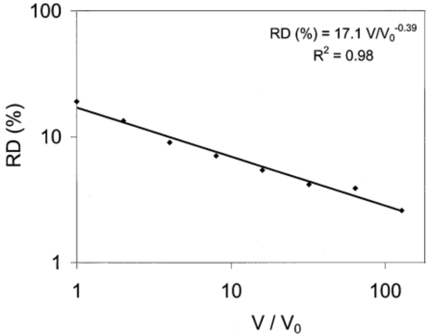


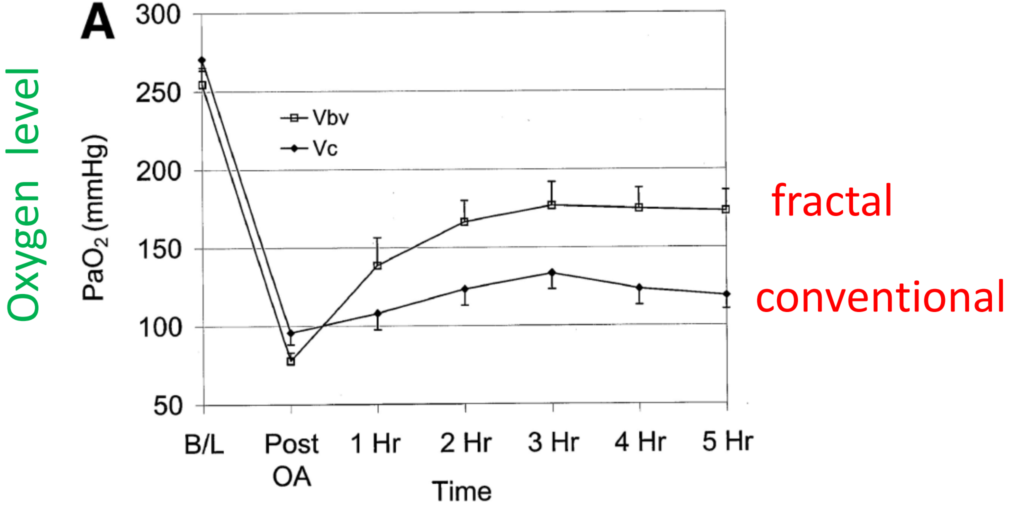


Multifractal structure in ordinary physiologic variation

“Administer variability as therapy”: fractal ventilation







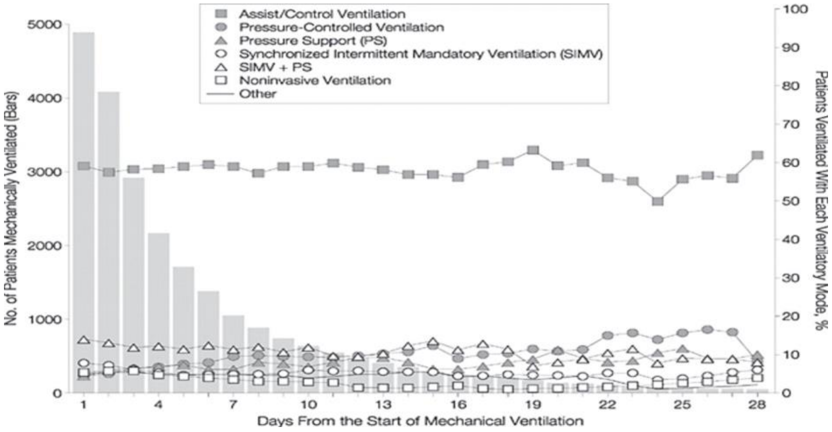
Improved Arterial Oxygenation with Biologically Variable or Fractal Ventilation Using Low Tidal Volumes in a Porcine Model of Acute Respiratory Distress Syndrome

ABDULAZIZ BOKER, M. RUTH GRAHAM, KEITH R. WALLEY, BRUCE M. McMANUS, LINDA G. GIRLING, ELIZABETH WALKER, GERALD R. LEFEVRE, and W. ALAN C. MUTCH

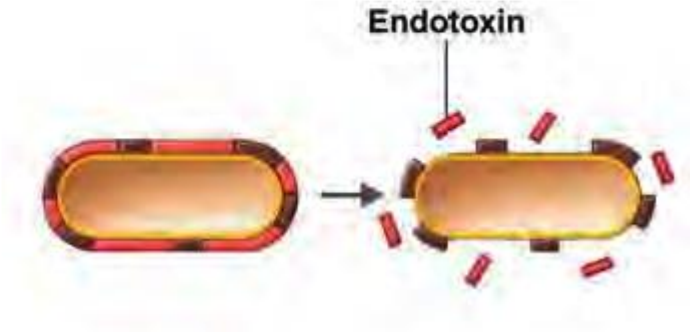
Department of Anesthesiology, University of Manitoba, Winnipeg; Department of Critical Care Medicine, and Department of Pathology and Laboratory Medicine, McDonald Research Laboratories/The iCapture Centre, University of British Columbia, Vancouver, Canada

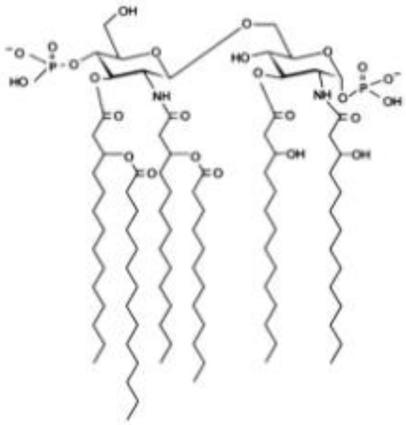
Yet physicians persist with “monotonous” (or invariant) support strategies

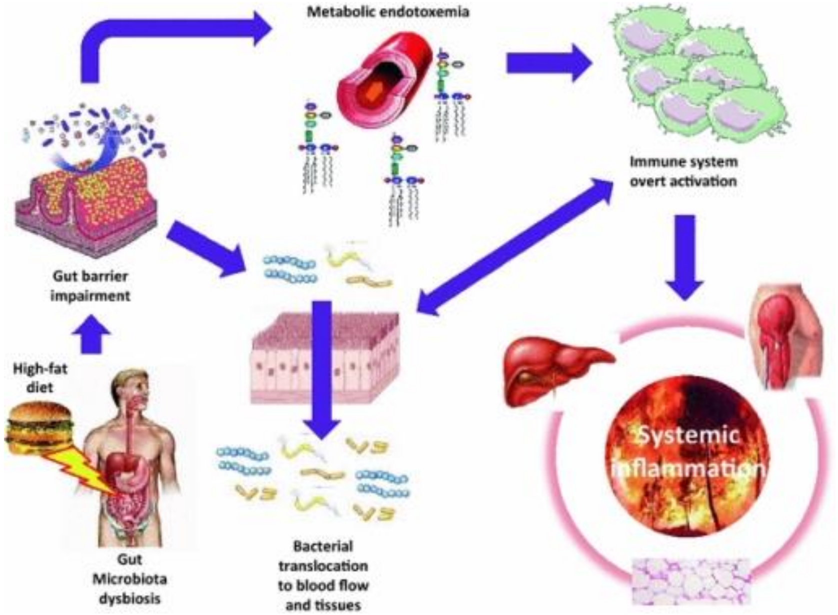
- On any given day in an ICU aggregate, more than 2/3 of the mechanically ventilated patients are receiving breaths **that do not differ from one to the next**



Endotoxemia

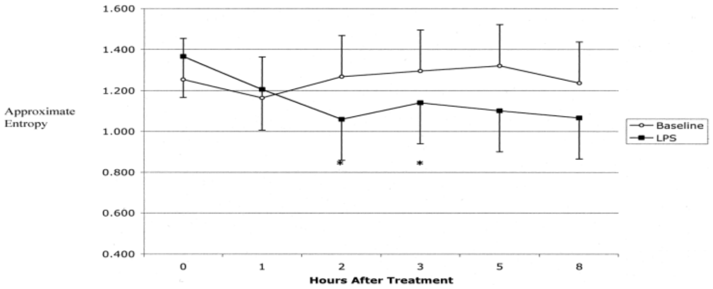




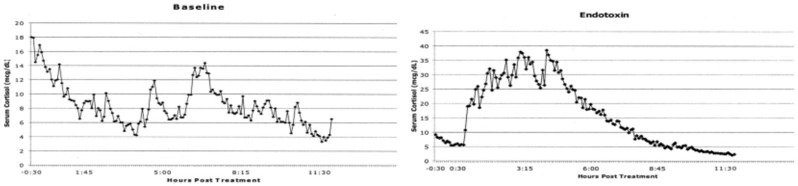


Decreased physiologic variability as a *generalized* response to human endotoxemia—experimental, 4 ng

- Organ level
  - heart rate
- Cell level
  - neutrophil phagocytosis
- Molecular level
  - Plasma cortisol



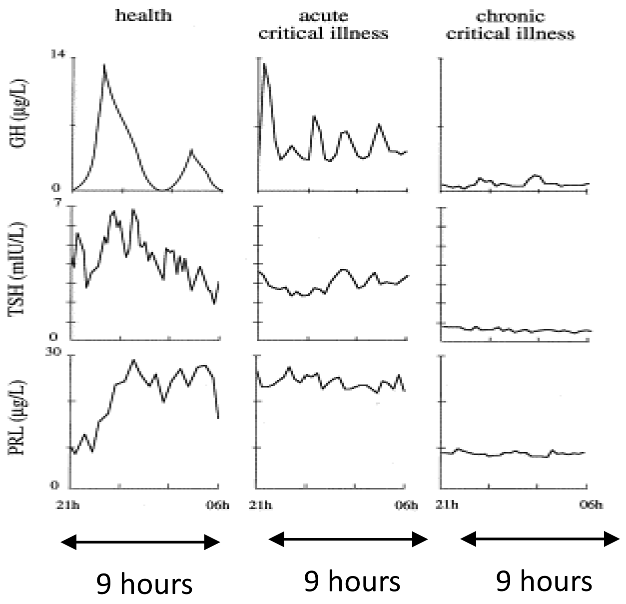
heart rate, approximate entropy



serum cortisol

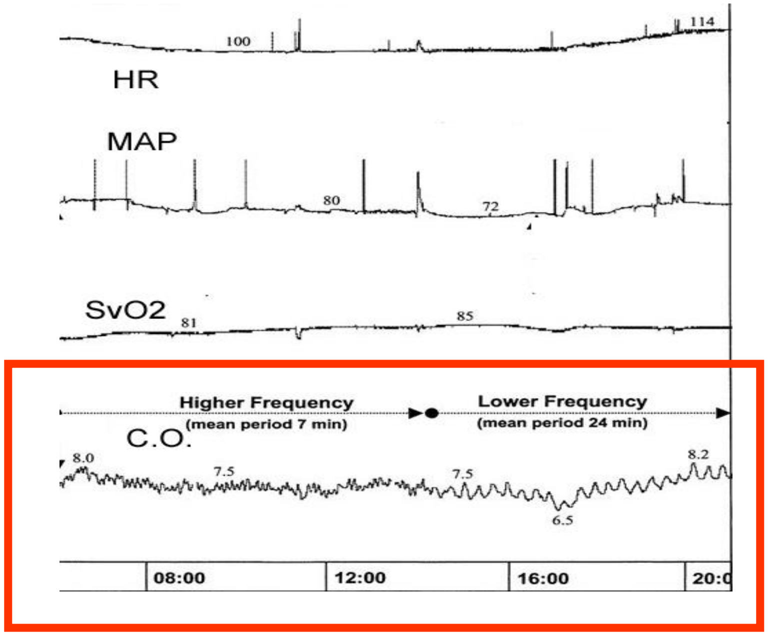
Decreased hormonal variability with long-term critical illness

- Initial response of pituitary to critical illness: increased levels and frequency of hormone secretion
- After 7-10 days of mechanical ventilation and other ICU support, secretion decomplexifies



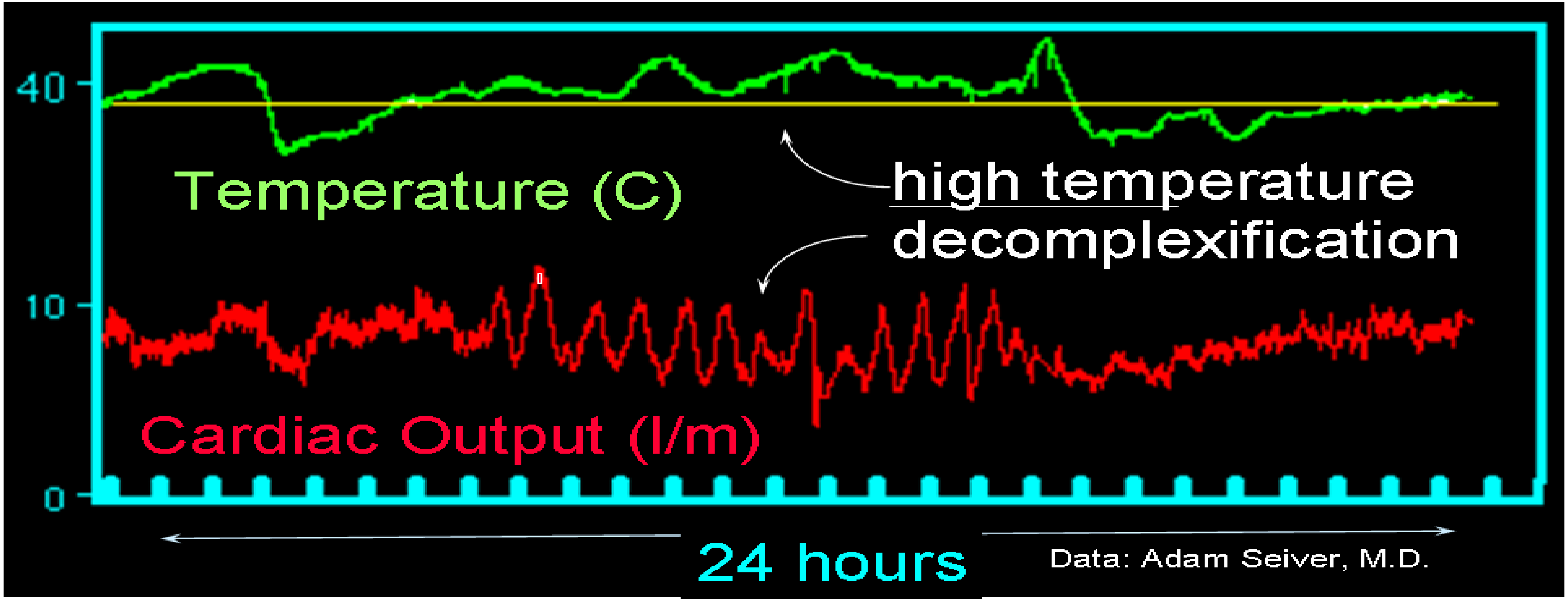
Uncoupling in real time: Clinical

- Ultra low-frequency oscillations in cardiac output
- Critically ill adults with sepsis, systemic inflammatory response syndrome, and multiple organ dysfunction syndrome



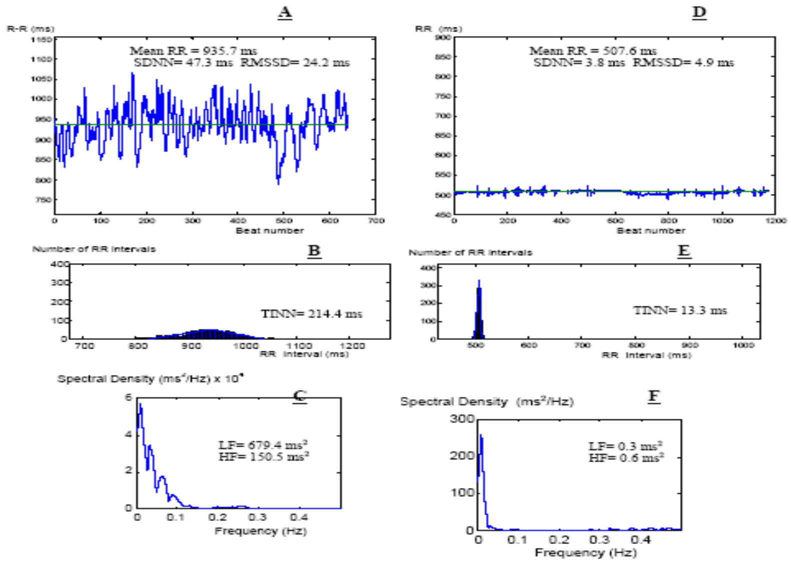
A young woman with fecal peritonitis:

Loss of complexity in C.O. assoc. with decompensation

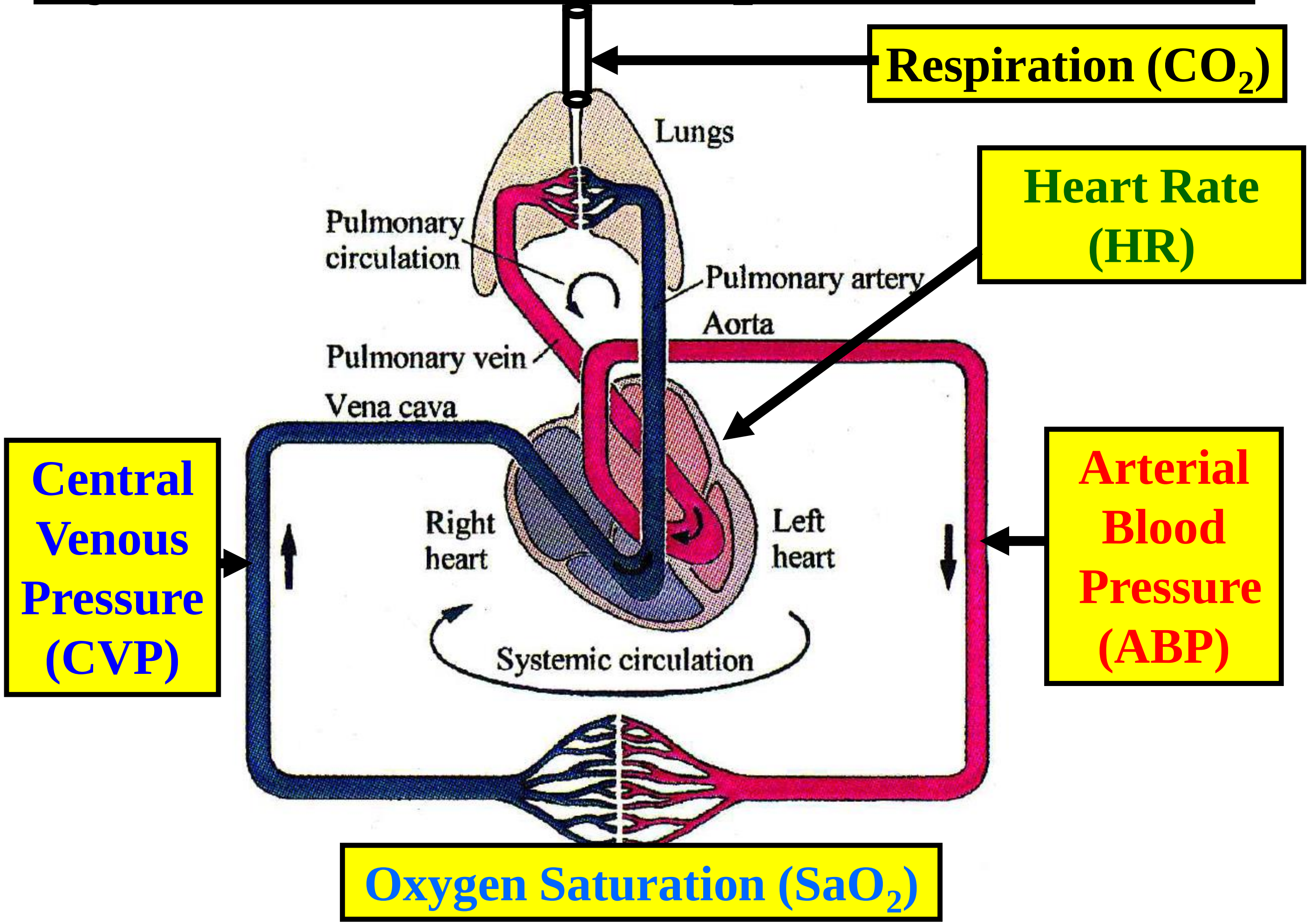


Loss of variability, uncoupling, predicts descent into multiple organ failure

- Two similarly septic (identical APACHE 2 scores) patients
- First 24 hr of data
- During the second 24 hr, the patient represented on the right (D,E,F) developed multiple organ failure and died on day 12.



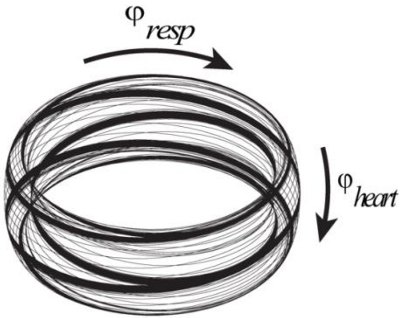
Dynamics in Two Coupled Dimensions

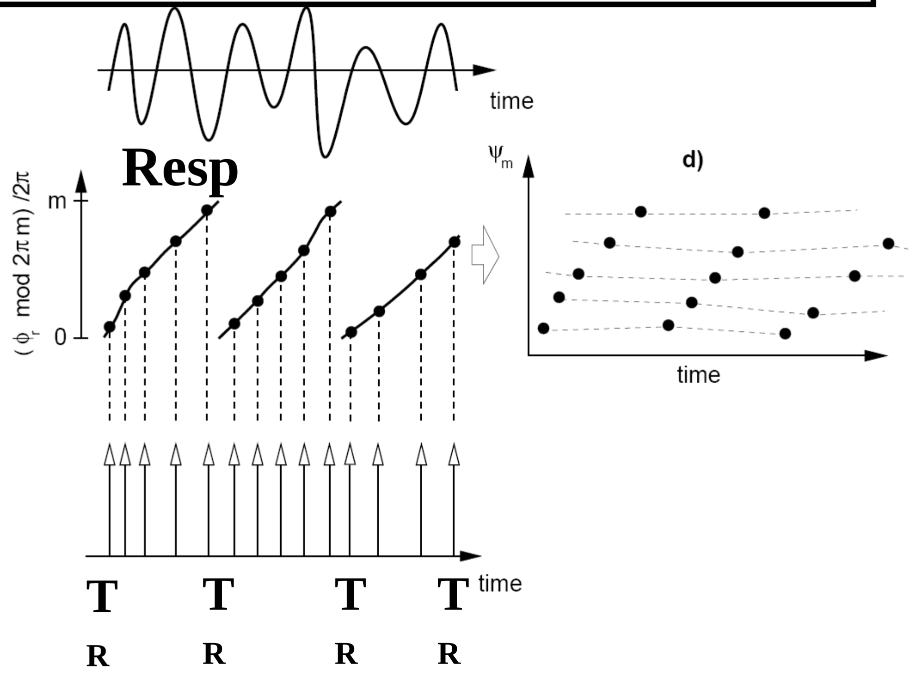


Synchrogram

phase of respiration at the time of R peak in ECG

$$\psi_m(t_n^{heart}) = \frac{1}{2\pi}\left[\varphi_{resp}(t_n^{heart}) \bmod 2\pi m\right]$$



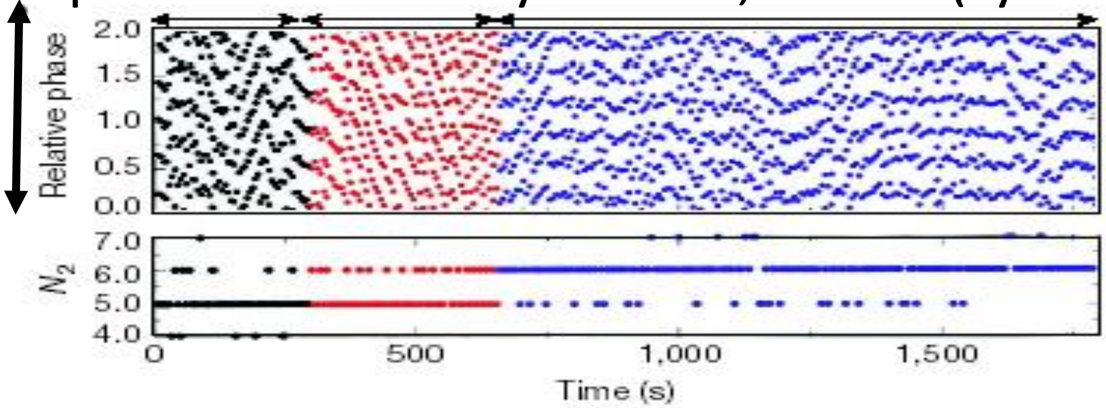


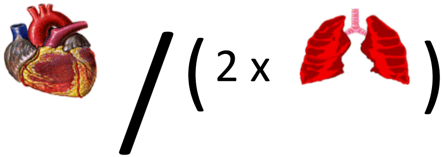
Familiar, dissimilar biological oscillators: heart and lung

Schäfer C, et al. Nature (1998) 392:239

Experiment: Healthy athlete, at rest (synchrogram)

4π,
2 cycles
of respiration



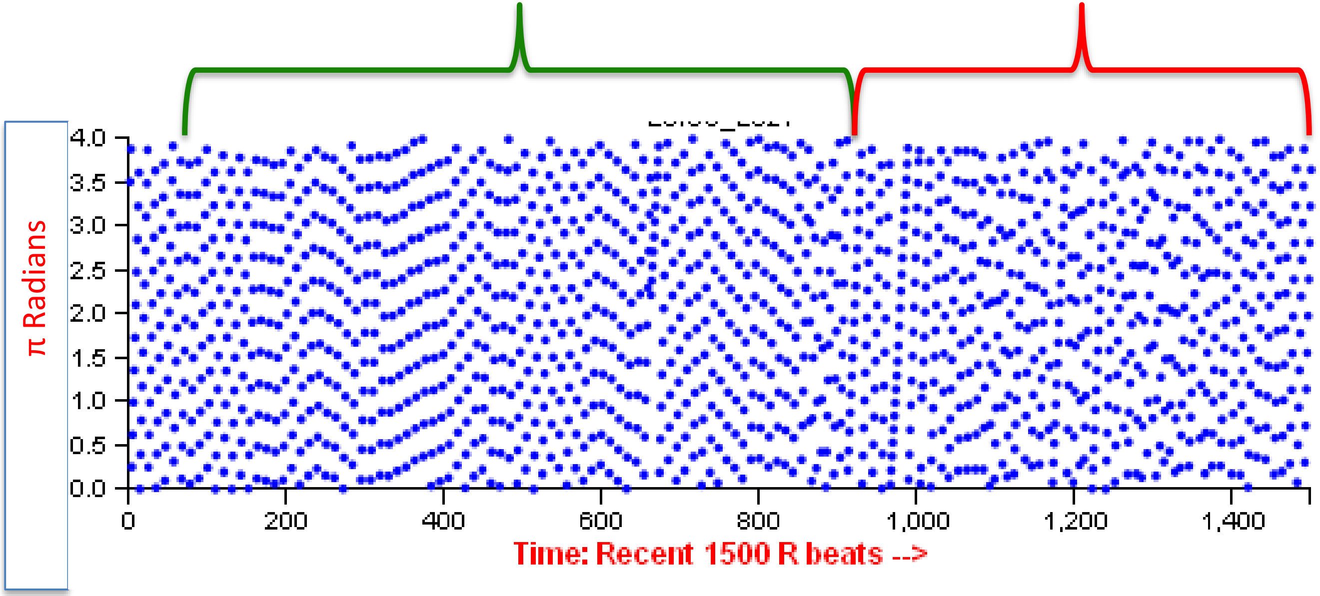


Coupled 5:2

Unsynchronized

Coupled 6:2

Synchrography in action: The ICU



Synchronization in the ICU

"Natural Clinical Experiment":

Spontaneous Breathing Trial (SBT)

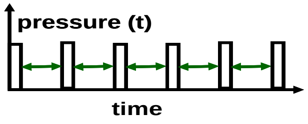
BEFORE

Controlled Ventilation:

assisted control (A/C)

$f=(12\text{-}18)\text{min}^{-1}=(0.2\text{-}0.3)\text{Hz}$

Tidal Volume=(6-10) mL/kg

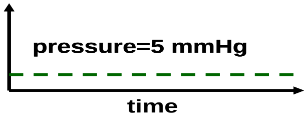


30 min

SBT

Spontaneous Breathing

continuous positive airway pressure (CPAP)



30 min

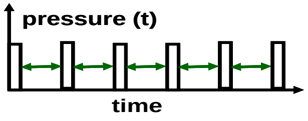
AFTER

Controlled Ventilation:

assisted control (A/C)

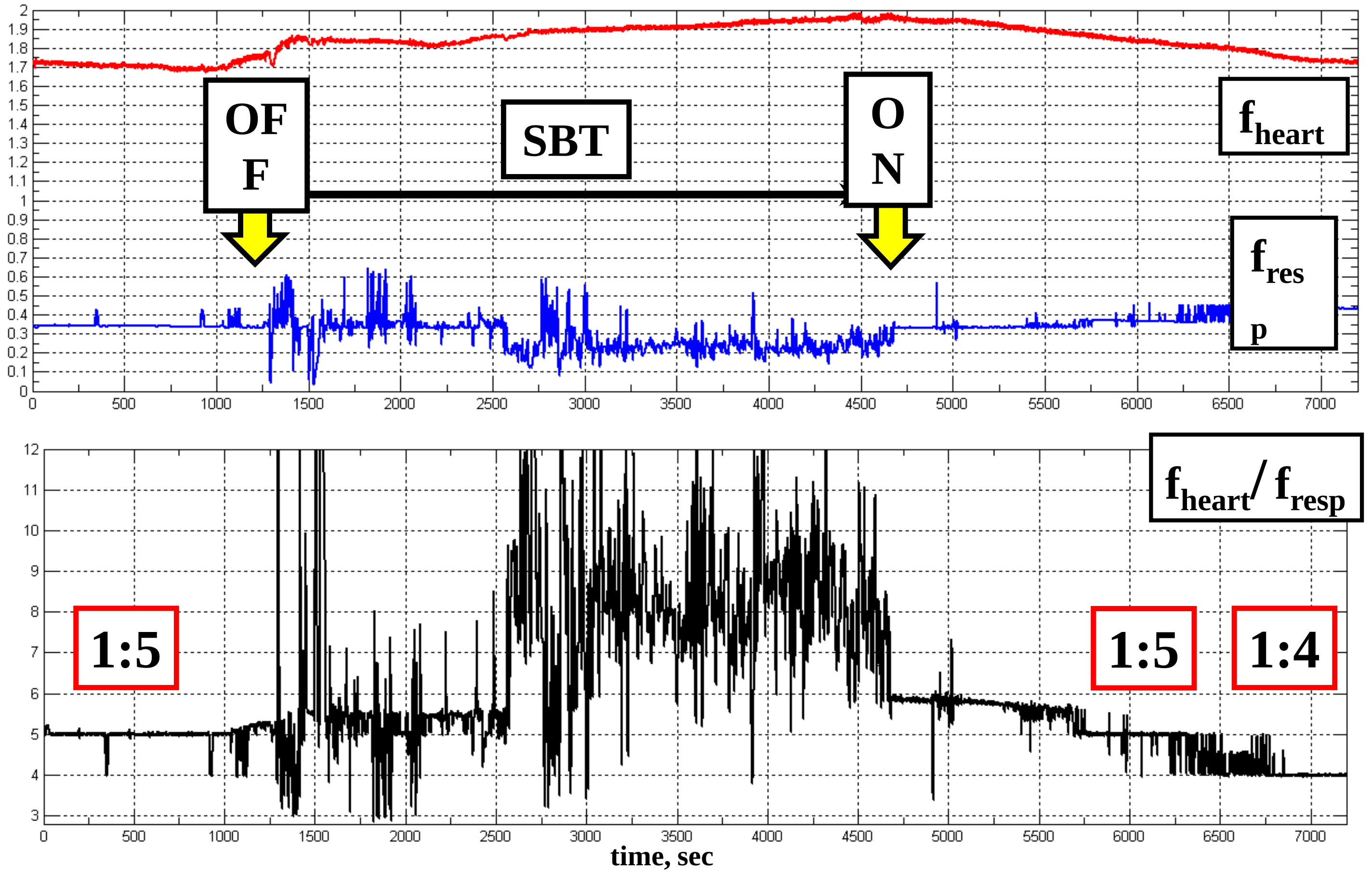
$f=(12\text{-}18)\text{min}^{-1}=(0.2\text{-}0.3)\text{Hz}$

Tidal Volume=(6-10) mL/kg



30 min

Instantaneous Frequency



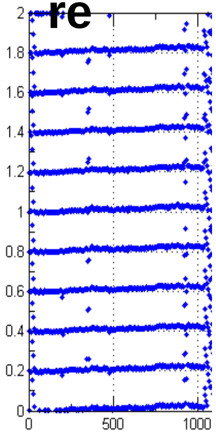
synchronization

no synchronization

synchronization

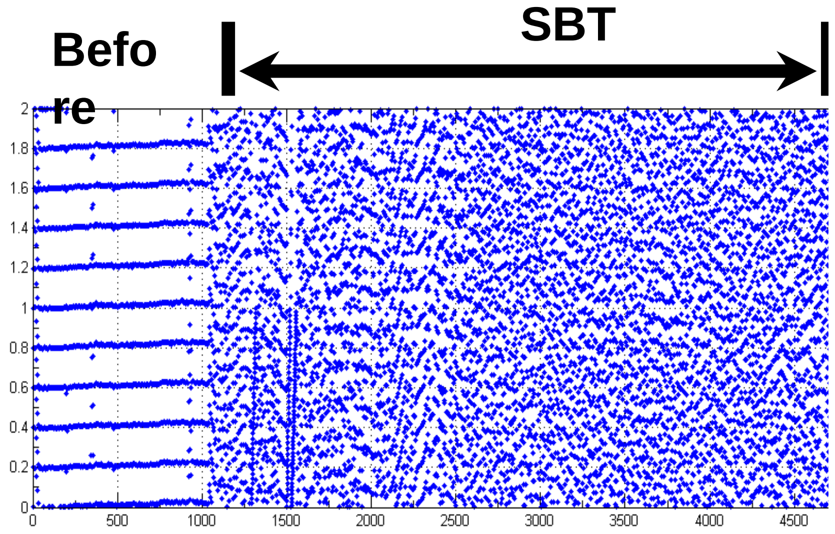
Synchronization in the ICU (phase)

Befo
re



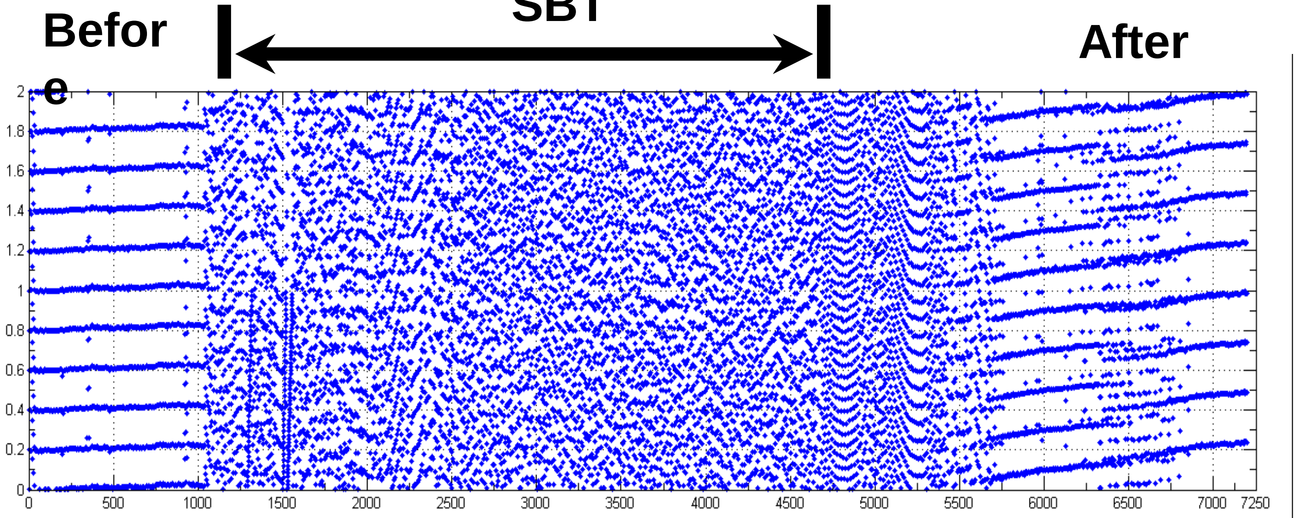
1:5

Synchronization in the ICU (phase)



1:5 Trying to adapt…and not doing well

Synchronization in the ICU (phase)

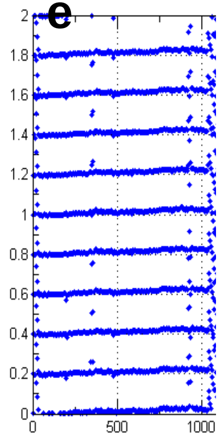


1:5 Trying to adapt…and not doing well 1:5 1:4

Seawell

Synchronization in the ICU (phase)

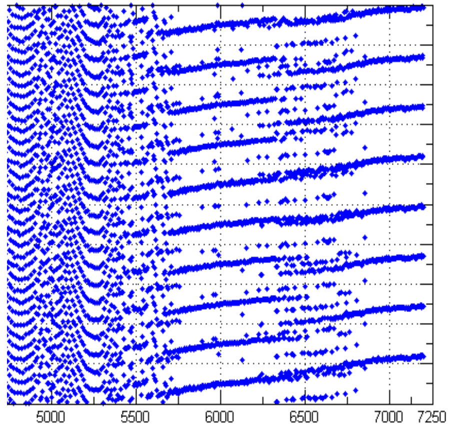
Befor
e



1:5

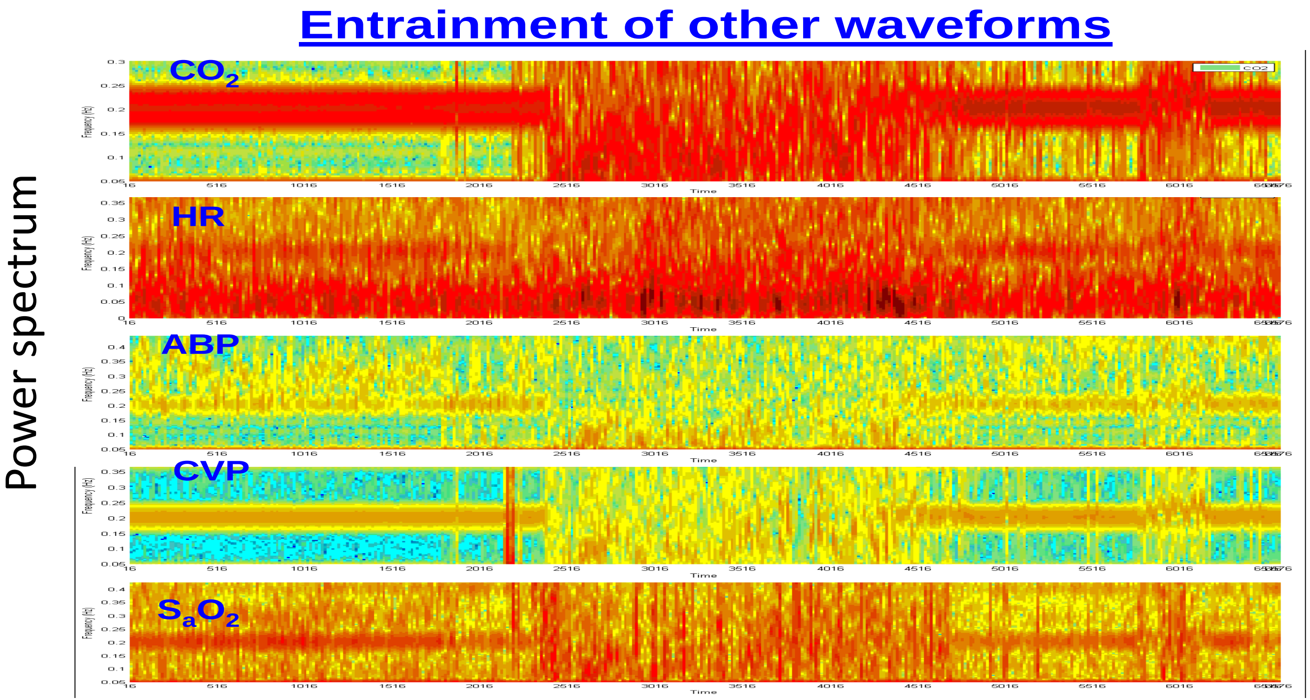
Adaptation from/to therapy

After



1:5 **1:4**

Projections into other systems



Summary

- Networks are the basis of physiology
- Pathophysiology is often the clinical manifestation of a "network gone bad"
  - "Fixing" the network can require ingenuity
  - "Fixing" the network can have unexpected effects
- Classifying the network anomalies is a first step
- Detecting network anomalies in clinical medicine is just beginning—you can help!