# Challenges for Applied Network Physiology

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# Challenges: applying network physiology to clinical medicine

Doctors will look to discoveries in the new field of network physiology to help them take care of patients.

Many share the idea that we can detect some subacute potentially catastrophic deteriorations have *signatures of illness*.

If we can detect illness early, we can diagnose and treat early, and we should improve outcomes.

These are phenomena that applications of network physiology might seek to discover and quantify.

# Challenges: applying network physiology to clinical medicine

Here are examples if signatures of illness:

- rising heart rate and falling blood pressure early in hemorrhage
- bradycardia and oxygen desaturation in neonatal sepsis
- disrupted sinus arrhythmia in just about any illness or injury

Note that the abnormality may not lie in the measured value of one parameter, but in the way that two or more systems interact, or fail to, over time.

As we progress in the field and look to apply the principles of network physiology to the real world, we can stop to think about new challenges that, if met, would bend the arc toward the bedside.

# Ivanov on this topic:

- Studies on structural and dynamical aspects of physiological systems that transcend space and time scales.
- Functional forms of physiologic coupling, time variation and effects of pair-wise interactions on the dynamics and control of individual systems.
- Networks comprised of diverse physiological systems and associations between physiologic network structure and physiologic function.
- Evolution of pair-wise coupling and network topology with transitions across physiologic states; basic principles of hierarchical network reorganization.
- The role of time-dependent network interactions for emergent transitions in network topology and function.
- Manipulation, control and global dynamics of networks in response to clinical treatment.
- Information flow on network topology in relation to cellular and neuronal assemblies and autonomic control of organ systems.
- Networks of physiological networks transcending interactions of sub-systems to interactions among organs.
- Cascades of failure across systems as encountered in ICU critical care.

# Challenges: applying network physiology to clinical medicine

**1**: *New experimental paradigms*

I review the autonomic nervous system and suggest basic science and clinical scenarios to think about

**2**: *New measures for physiologic time series*

I show some new results, mostly published

**3**: *Isolate the physiological network of the hospitalized patient from the external networks*

I show some new results

# **Challenge 1**: *New experimental paradigms*

The *autonomic nervous system* couples the heart and the lungs via the brainstem.

*Inter- and intracellular signal transduction* are the ultimate mechanisms.

The *cholinergic anti-inflammatory pathway* is an exciting network to think about.

*Clinical situations may lead to changing network physiology.*

Carrara *et al. Ann. Intensive Care* (2021) 11:80
https://doi.org/10.1186/s13613-021-00869-7

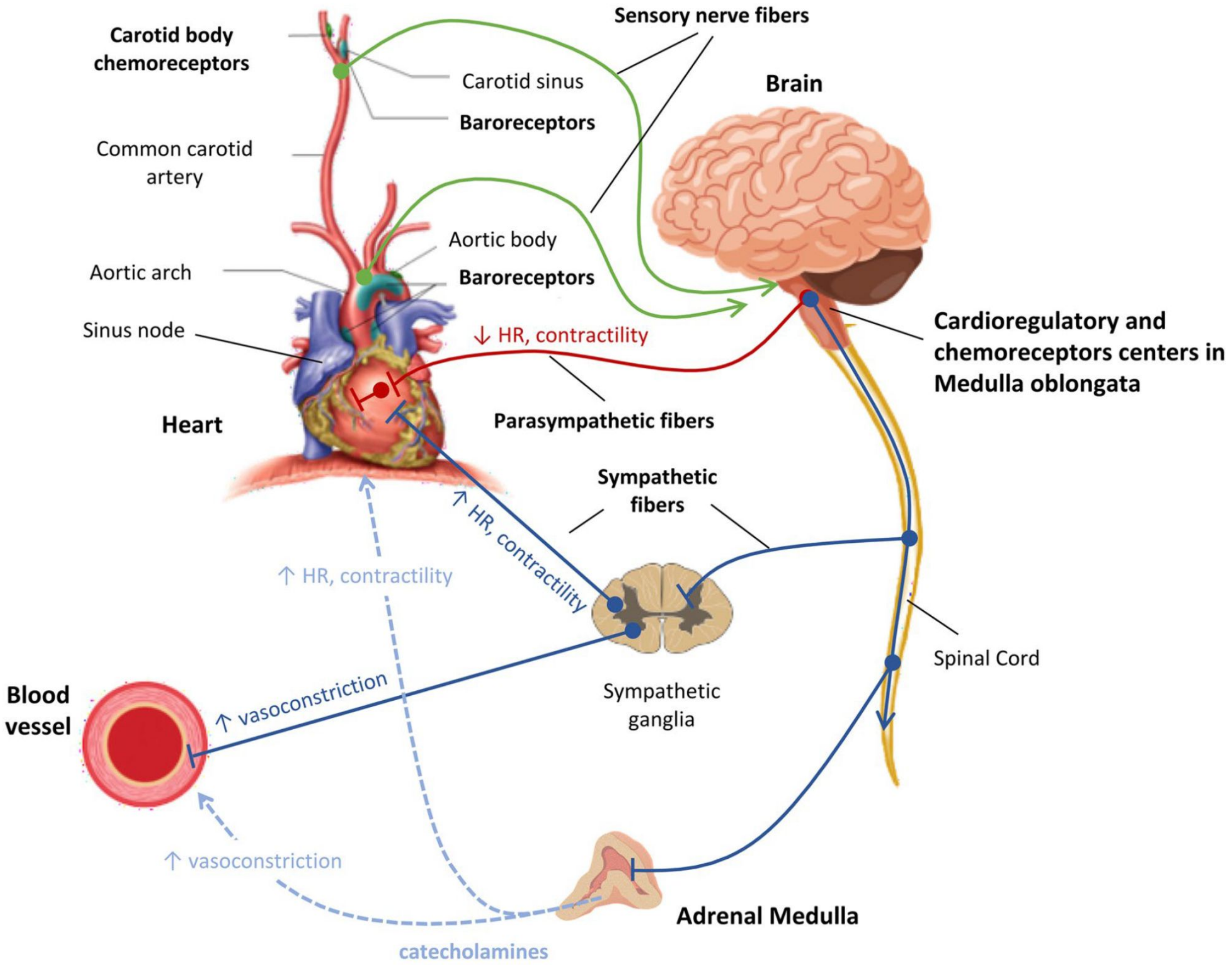
Annals of Intensive Care

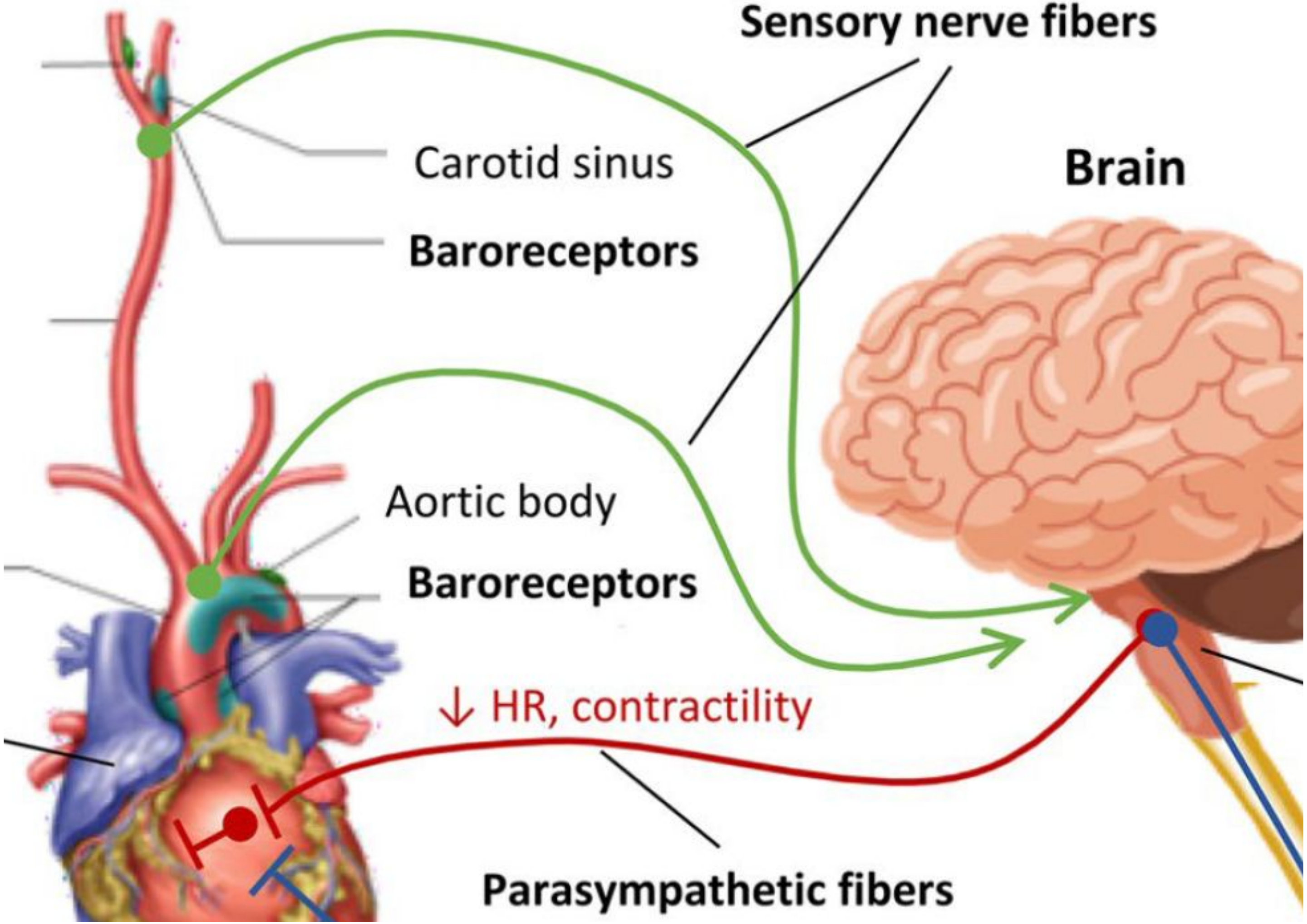
**REVIEW** **Open Access**



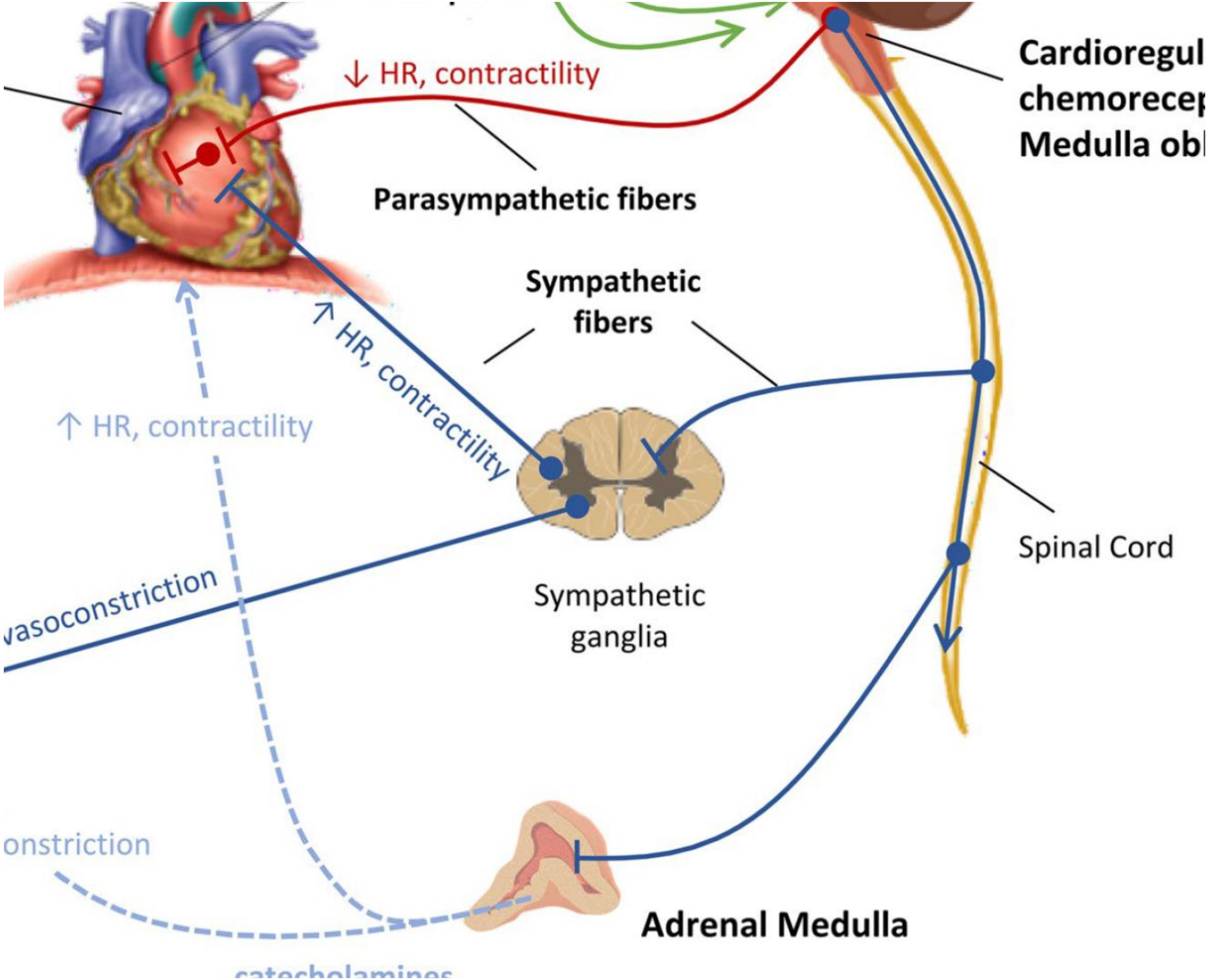
## The autonomic nervous system in septic shock and its role as a future therapeutic target: a narrative review

Marta Carrara[1†], Manuela Ferrario[1*†], Bernardo Bollen Pinto[2,3] and Antoine Herpain[4,5]

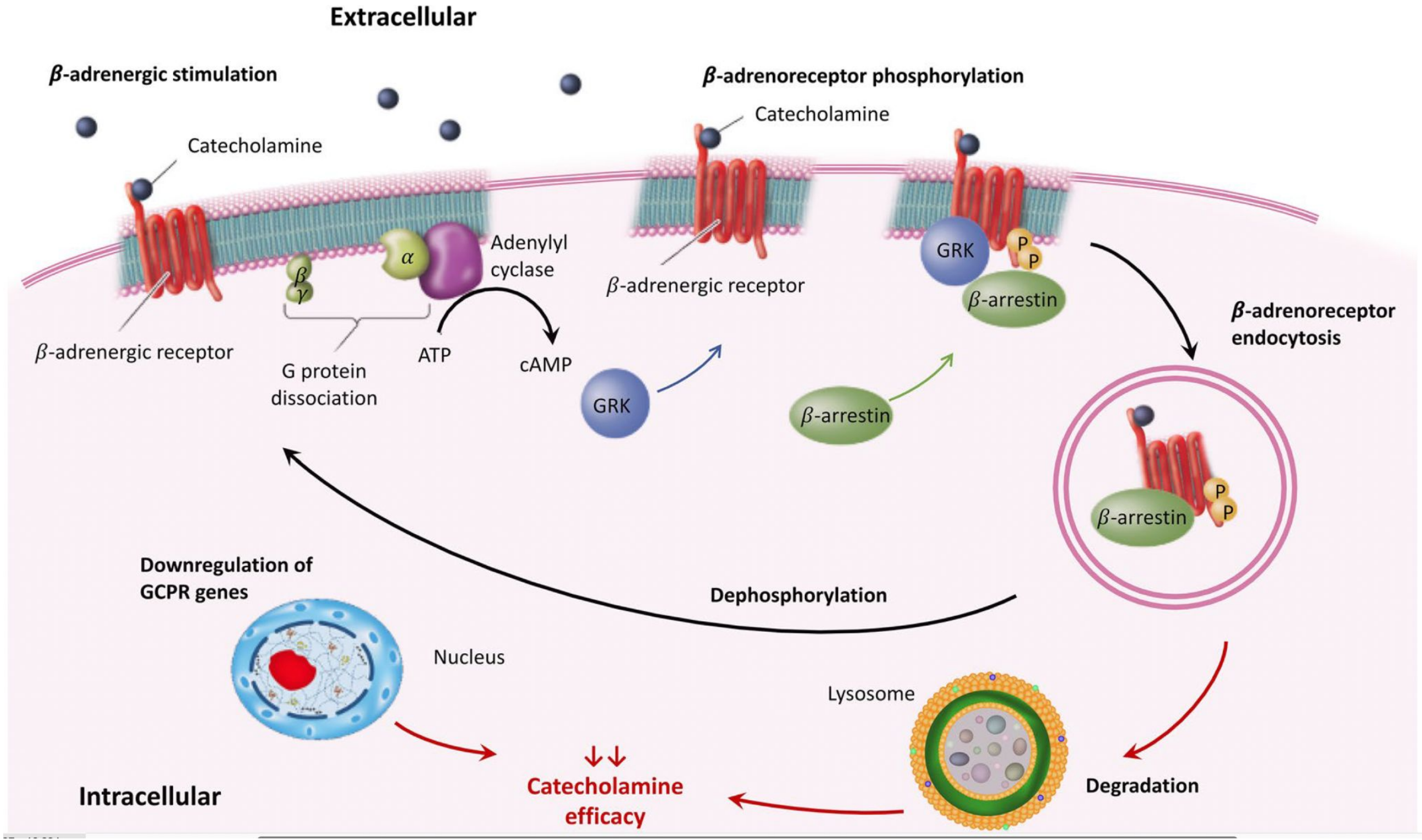

Carotid body chemoreceptors
Sensory nerve fibers
Carotid sinus
Baroreceptors
Brain
Common carotid artery
Aortic body
Aortic arch
Baroreceptors
Sinus node
↓ HR, contractility
Cardioregulatory and chemoreceptors centers in Medulla oblongata
Heart
Parasympathetic fibers
Sympathetic fibers
↑ HR, contractility
↑ HR, contractility
Spinal Cord
Blood vessel
↑ vasoconstriction
Sympathetic ganglia
↑ vasoconstriction
Adrenal Medulla
catecholamines

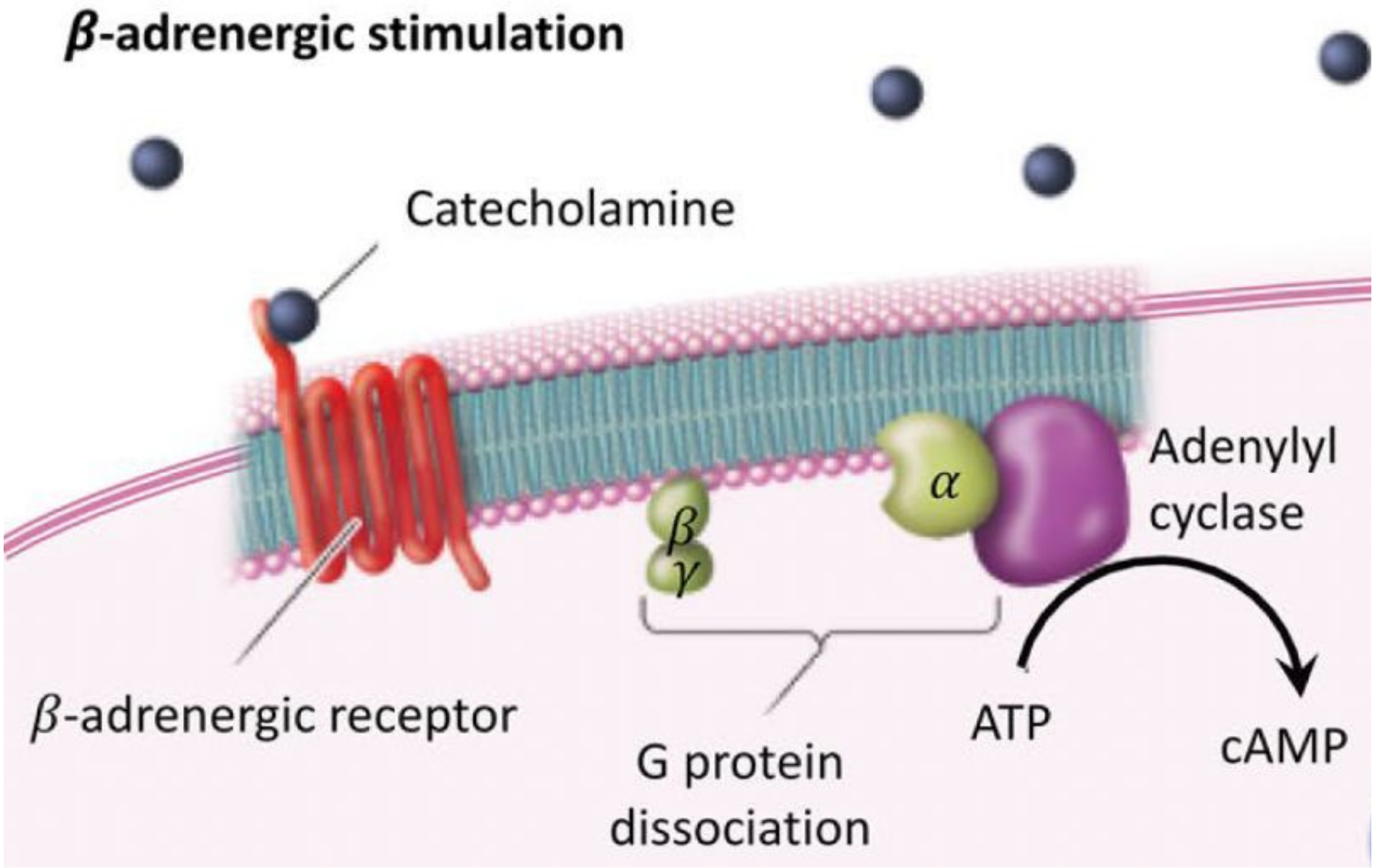


Sensory nerve fibers
Carotid sinus
Baroreceptors
Brain
Aortic body
Baroreceptors
↓ HR, contractility
Parasympathetic fibers

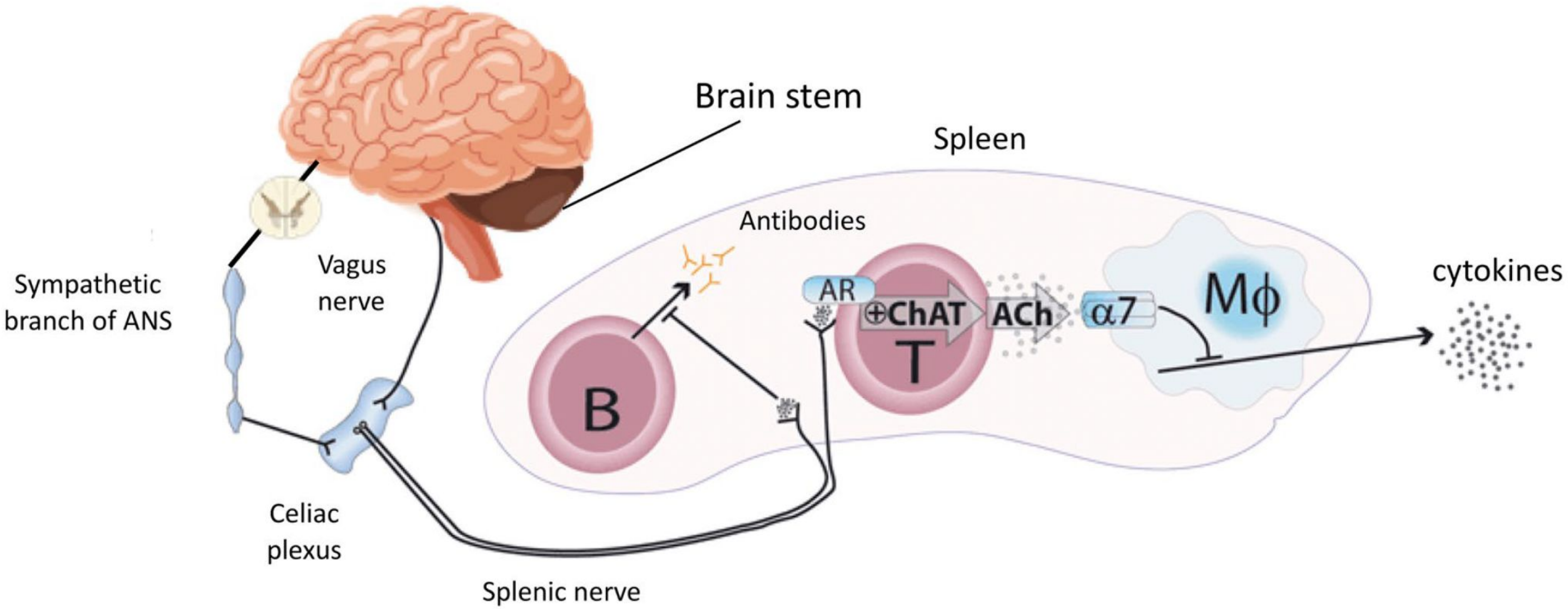


↓ HR, contractility
Cardioregul
chemorecep
Medulla obl
Parasympathetic fibers
Sympathetic
fibers
↑ HR, contractility
↑ HR, contractility
vasoconstriction
Sympathetic
ganglia
Spinal Cord
onstriction
Adrenal Medulla


Extracellular
β-adrenergic stimulation
Catecholamine
β-adrenergic receptor
G protein dissociation
α
β
γ
Adenylyl cyclase
ATP
cAMP
β-adrenoreceptor phosphorylation
Catecholamine
β-adrenergic receptor
GRK
β-arrestin
P
P
GRK
β-arrestin
β-adrenoreceptor endocytosis
β-arrestin
P
P
Dephosphorylation
Downregulation of GCPR genes
Nucleus
Lysosome
Degradation
↓↓
Catecholamine efficacy
Intracellular

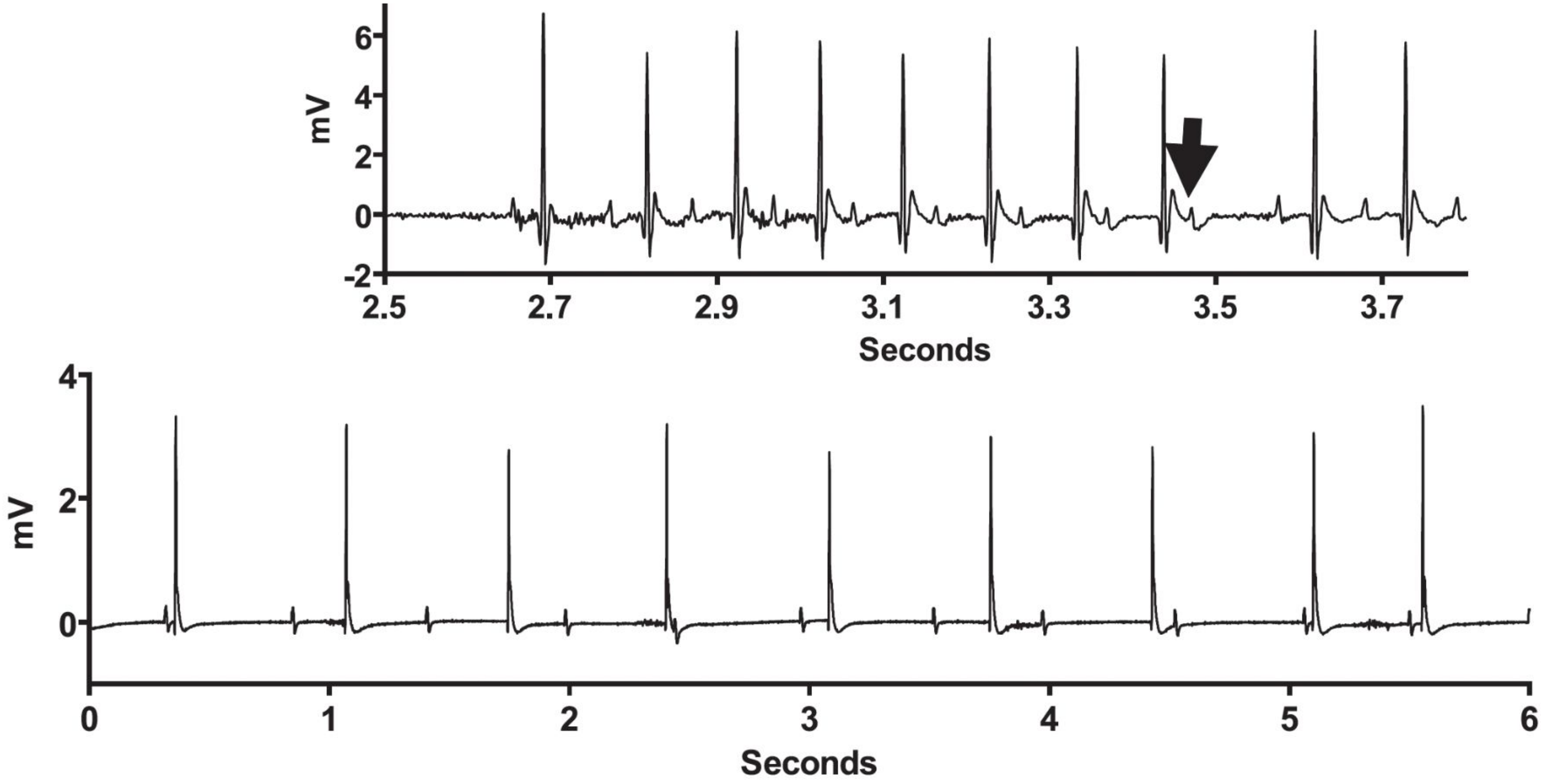

β-adrenergic stimulation
Catecholamine
β-adrenergic receptor
β
γ
α
G protein
dissociation
Adenylyl
cyclase
ATP
cAMP

# A new NP paradigm: Cholinergic anti-inflammatory pathway



# Direct evidence of the cholinergic anti-inflammatory pathway

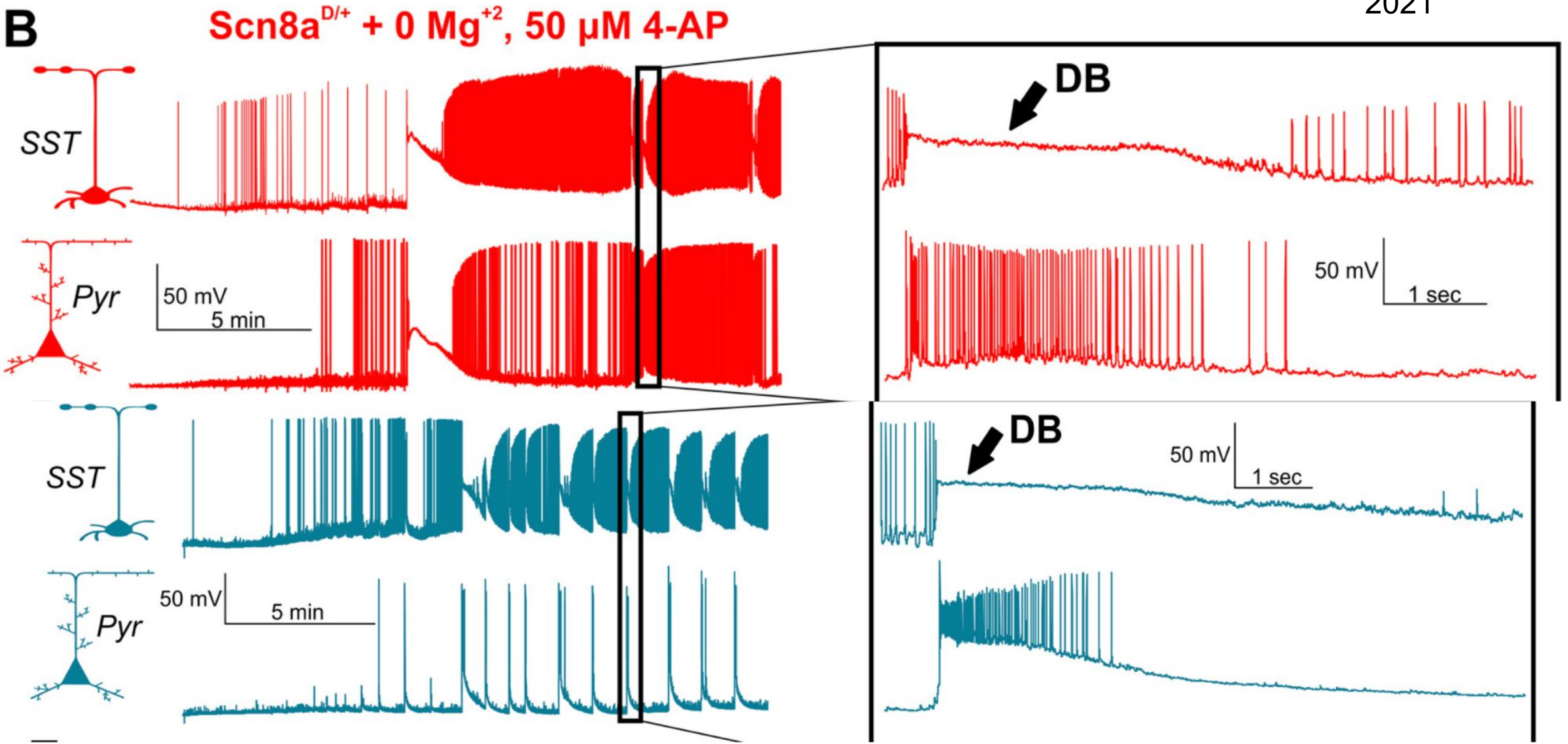
## Atrioventricular block in mice peritoneally-injected with micro-organisms




Fairchild KD
Am J Physiol
2009

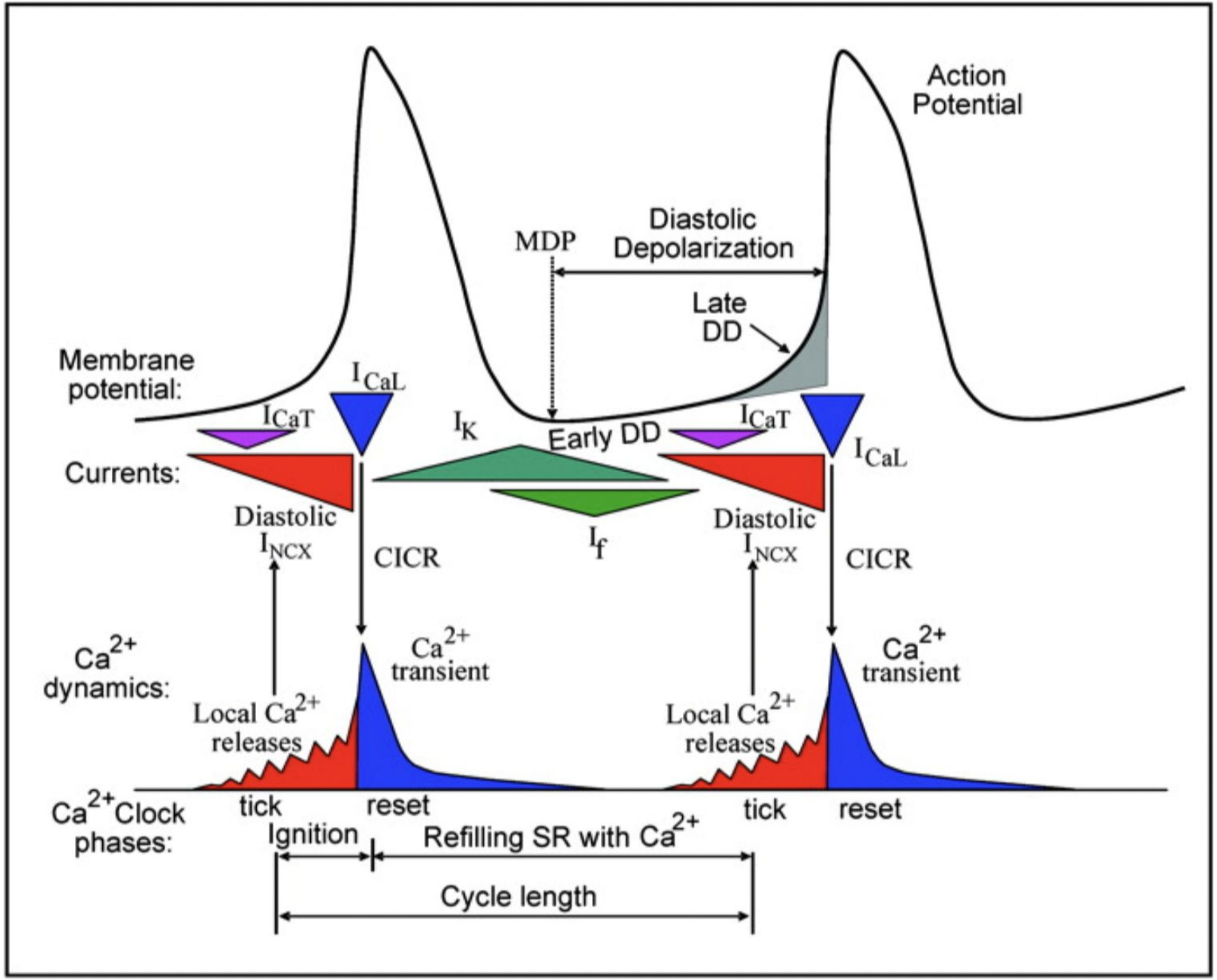
# A new NP paradigm: **inter**cellular physiological networks

Patel MK 2021



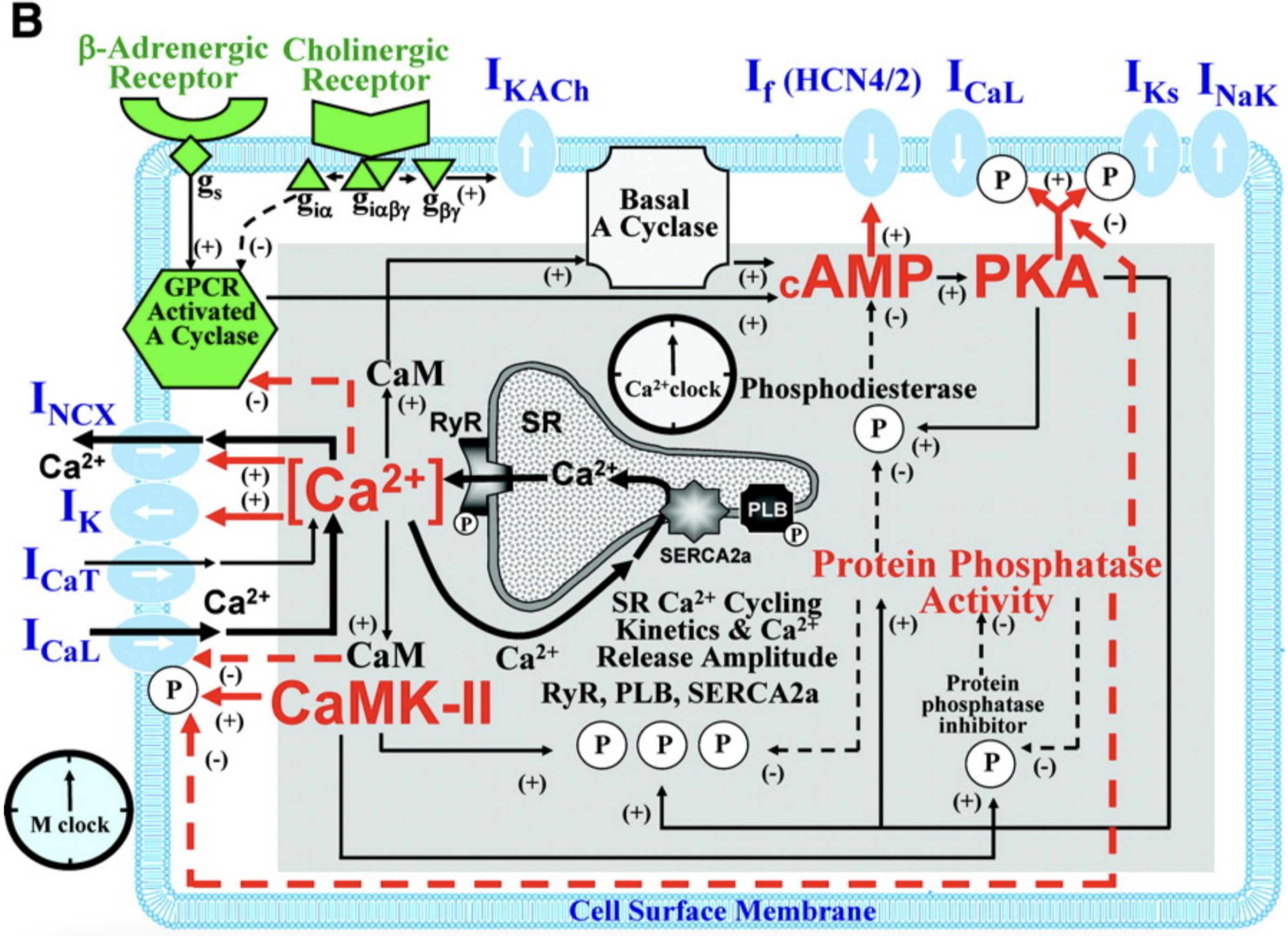
# A new NP paradigm: **intra**cellular physiological networks

Lakatta EG
2010



# A new NP paradigm: **intra**cellular physiological networks

Lakatta EG 2010



# Applied network physiology of the heart and lungs

There are at least three forms of interaction:

1. Respiratory sinus arrhythmia (Hales, 1756)
2. Cardiorespiratory synchronization (Schafer, Rosenblum, Kurths, Abel, 1998)
3. Time delay stability (Ivanov, 2012 or so)

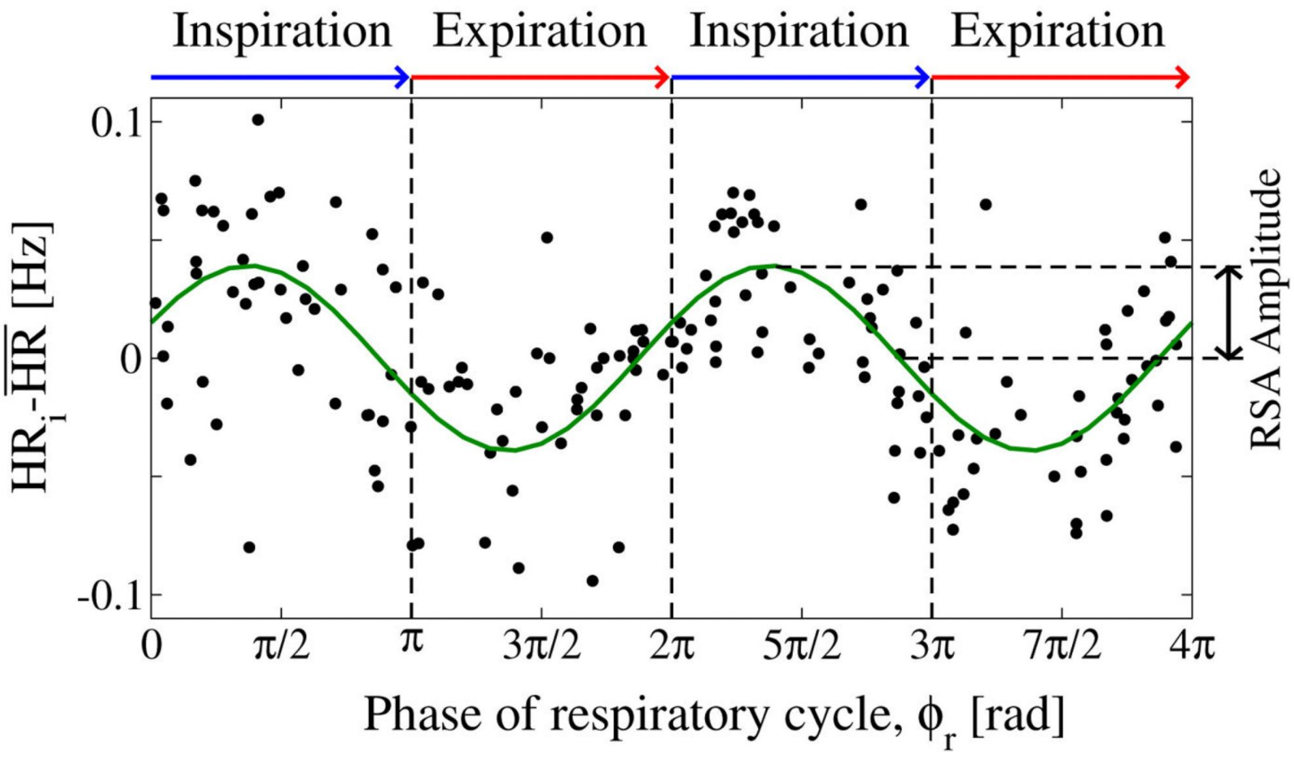
Schafer and Ivanov showed that RSA and CRS are different

Ivanov and coworkers show that time delay stability is different from the others

Thus, we have three different measures available to us from the standard time series of vital signs or other bedside continuous cardiorespiratory monitoring.

# Respiratory sinus arrhythmia (RSA)

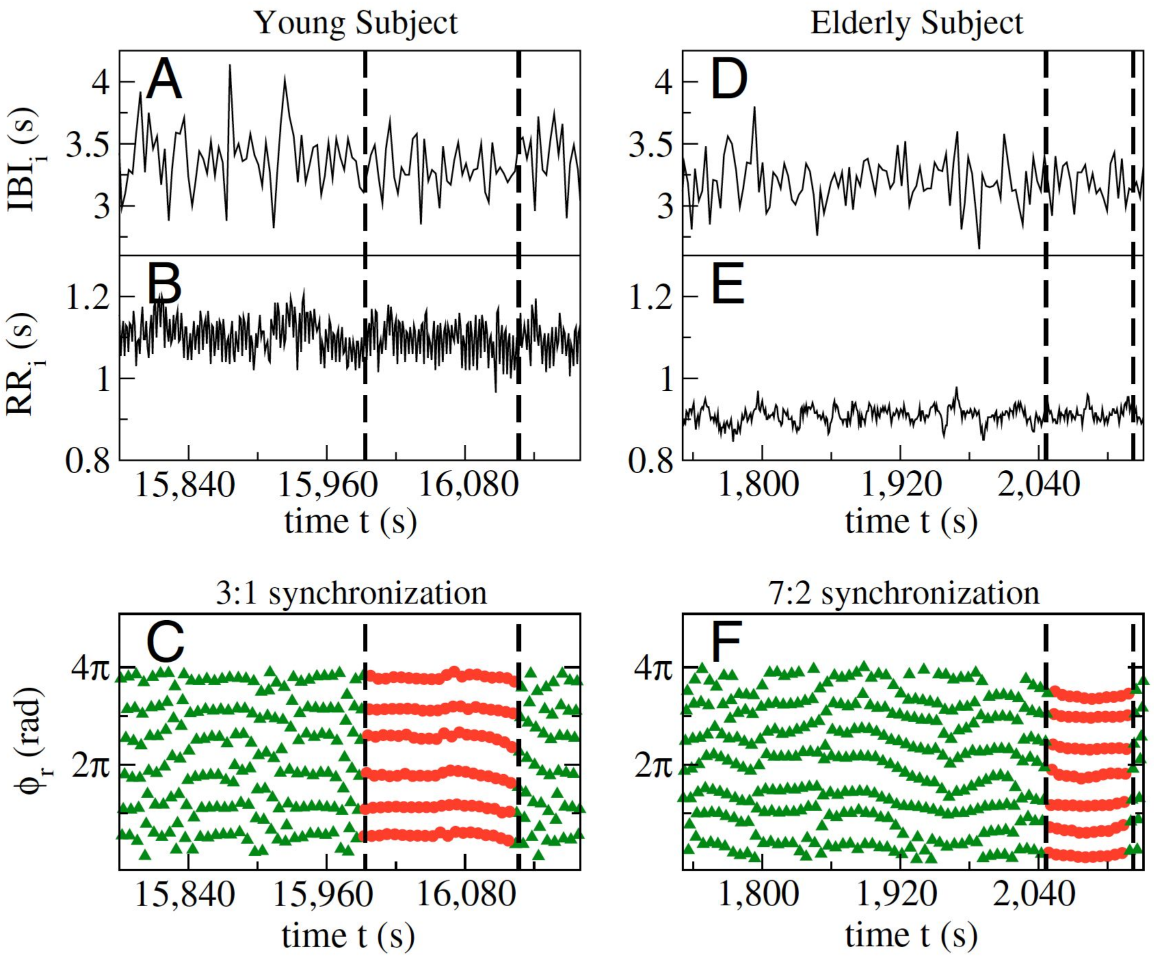
Heartbeats speed up in inhalation and slow down in exhalation.

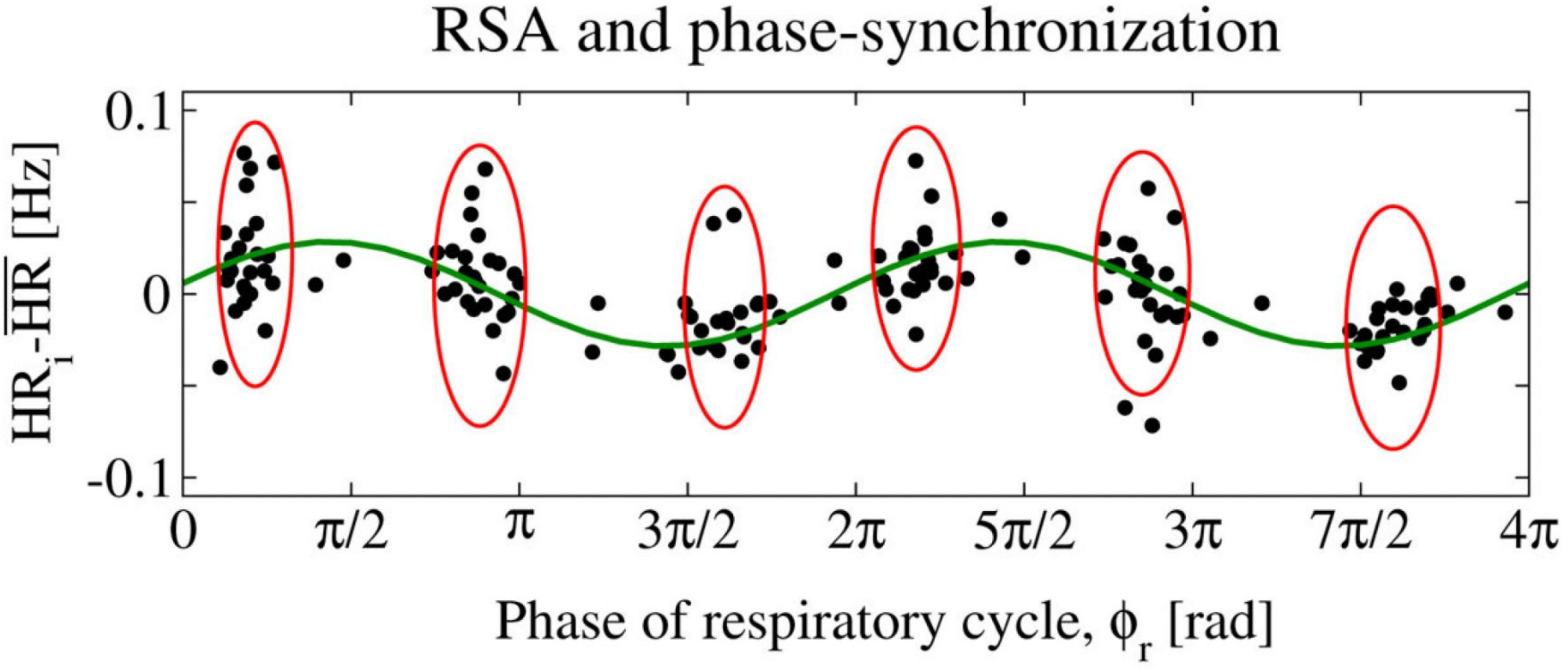


# Cardiorespiratory synchronization

Heartbeats are locked into place with respect to the phase of the breathing.

Average length ~ 30 sec



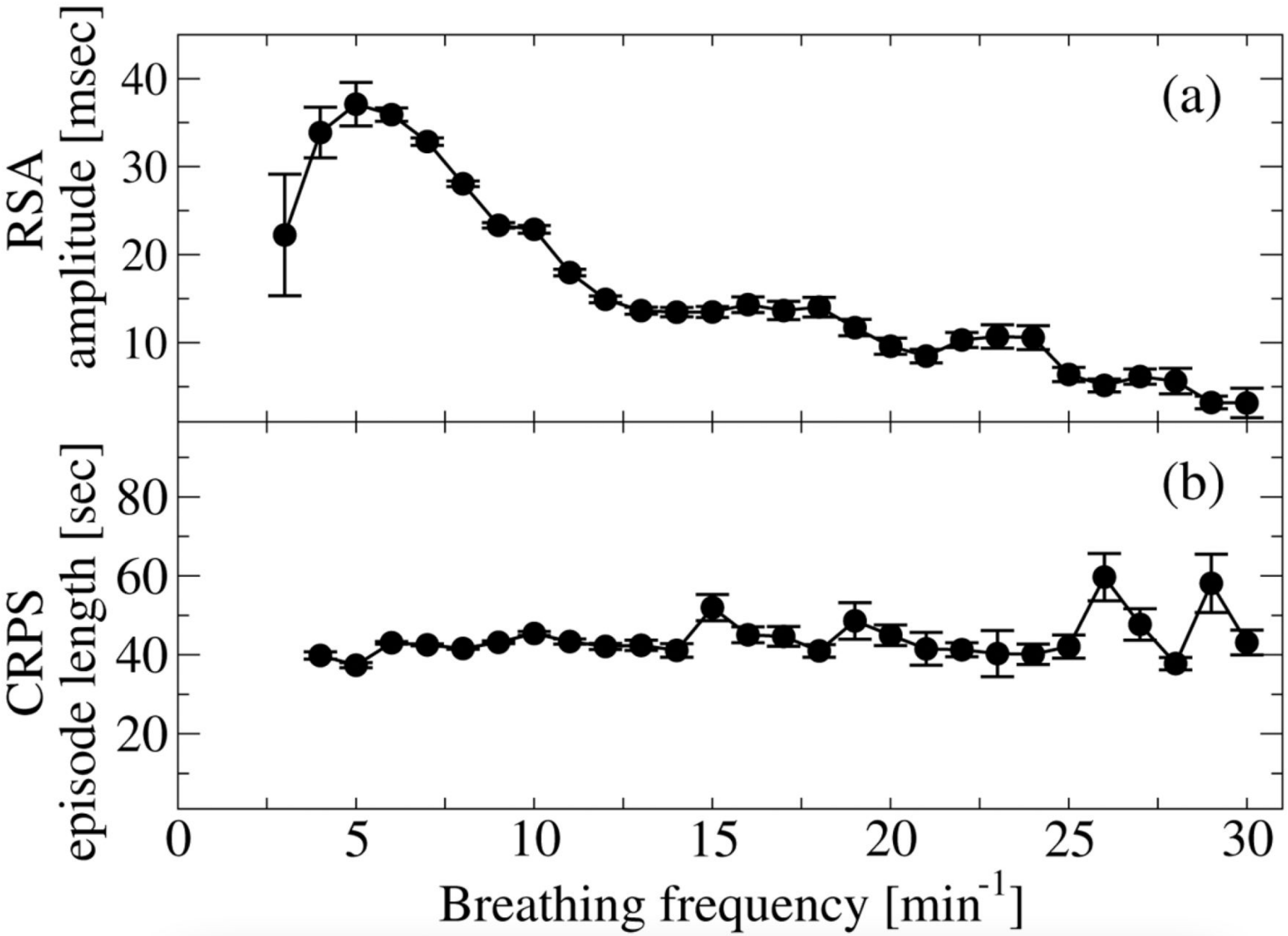


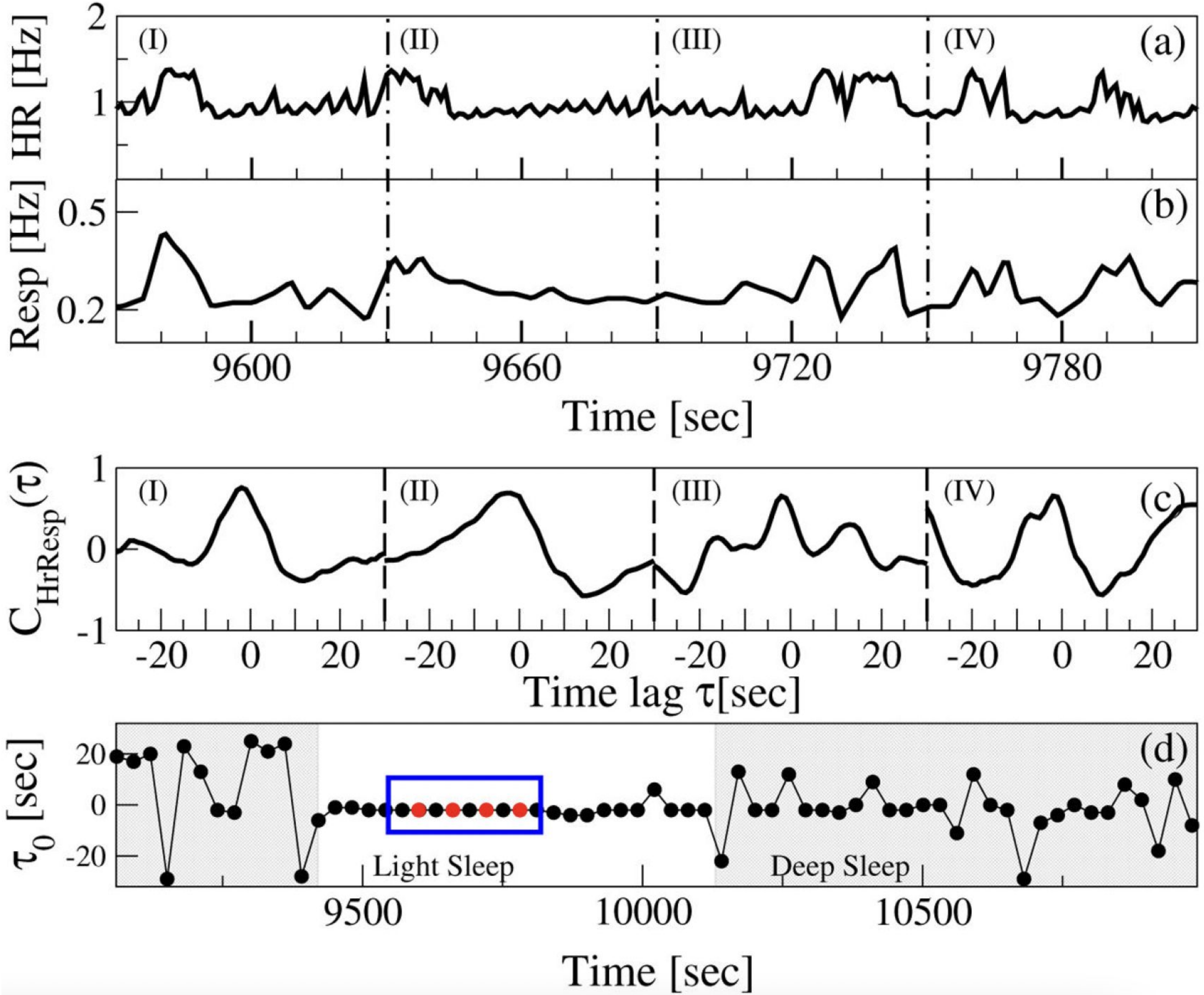
RSA and phase-synchronization
0.1
0
-0.1
$HR_i-\overline{HR}$ [Hz]
0
π/2
π
3π/2
2π
5π/2
3π
7π/2
4π
Phase of respiratory cycle, $\phi_r$ [rad]

Respiratory sinus arrhythmia increases with slow breathing

Cardiorespiratory synchronization does not

*An important observation.*






# TIme delay stability.

The lag of the maximum correlation coefficient stays constant.

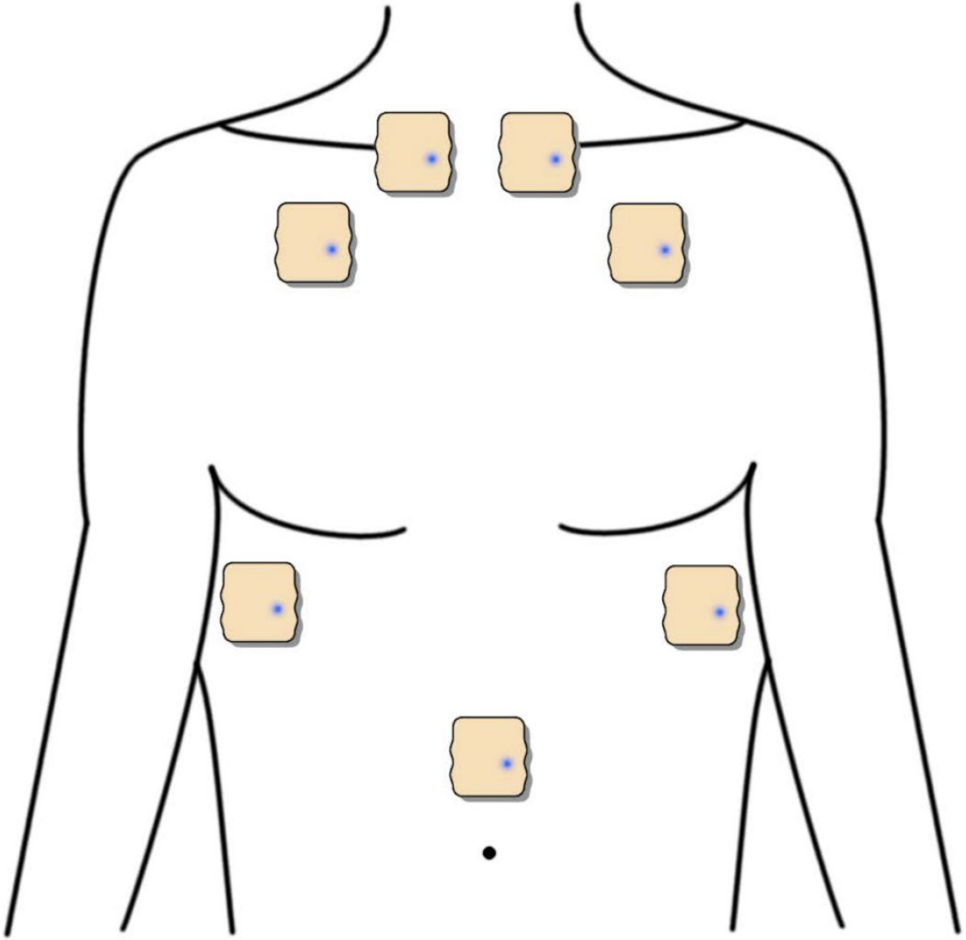
Average duration is ~ 3 minutes, different from CRS or RSA (though note that durations would change if thresholds were changed)

# What if breathing dynamics change?

All the measures are robust to ordinary variation in breathing rate because they normalize each breath to $2\pi$ radians.

And this has been OK because clinicians are not much aware of breathing beyond its rate.  (This has included me.)

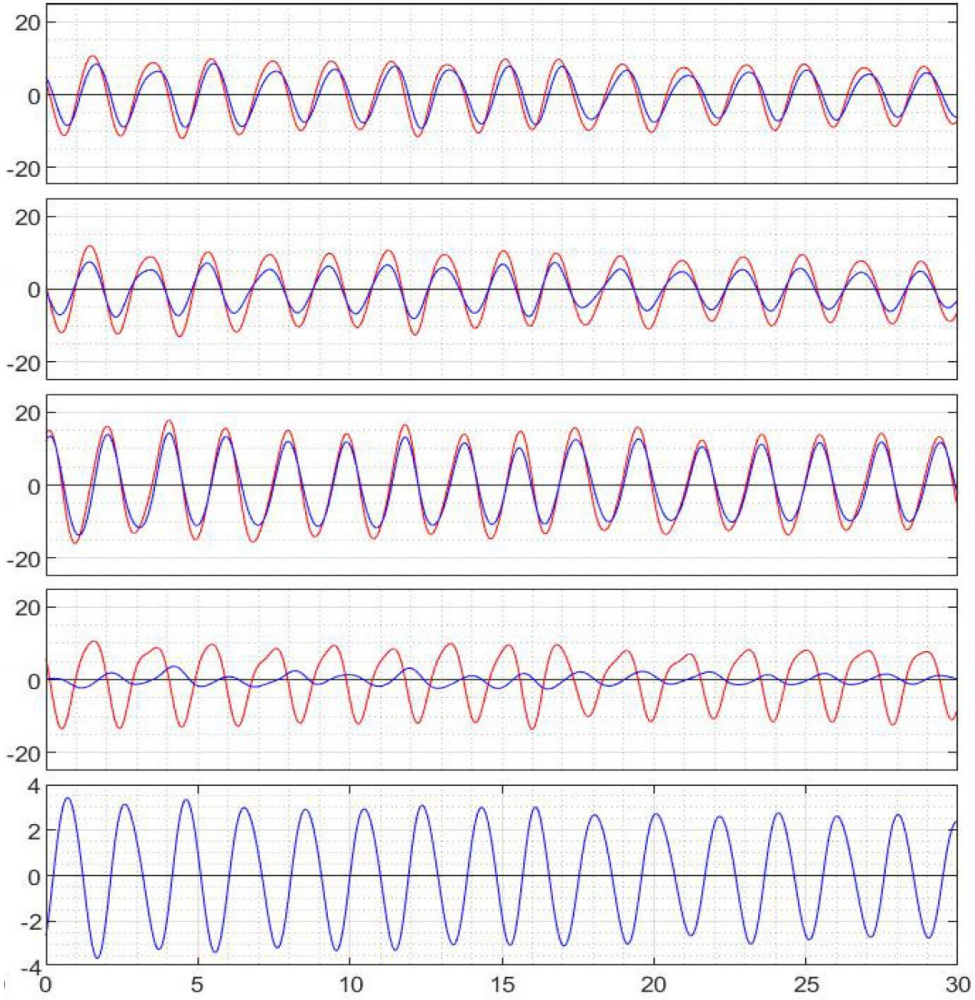
But here is new work that has changed my mind and opens the door for new work in the applied network physiology of the heart and lungs, hitherto largely confined to sleep studies.



My colleague SM Gadrey, MD, a hospital internal medicine physician, wanted to quantify clinical ideas about breathing like “fast,” “labored,” heaving,” and so on.

He placed sensors on the chest of 20 volunteers in an exercise lab to work out the technique.

He then approached >100 emergency department patients and made multiple 2-minute recordings.




Left and right sternocleidomastoids

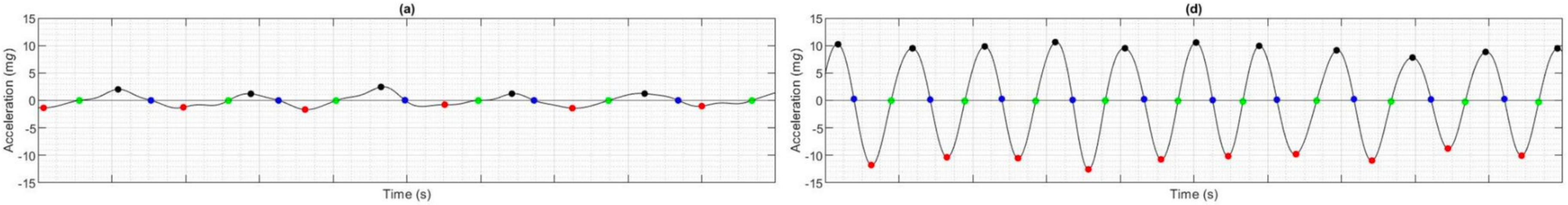
Left and right 2nd intercostal spaces

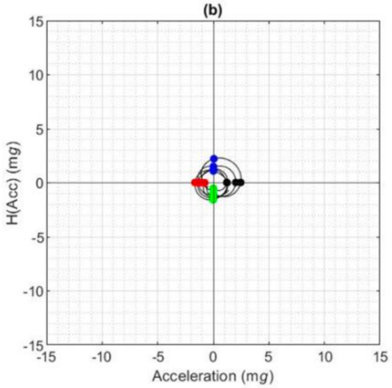
Left and right 8th intercostal spaces

Abdomen and back

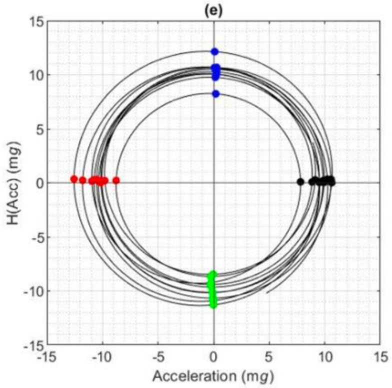
Au standard - flow meter in the nose

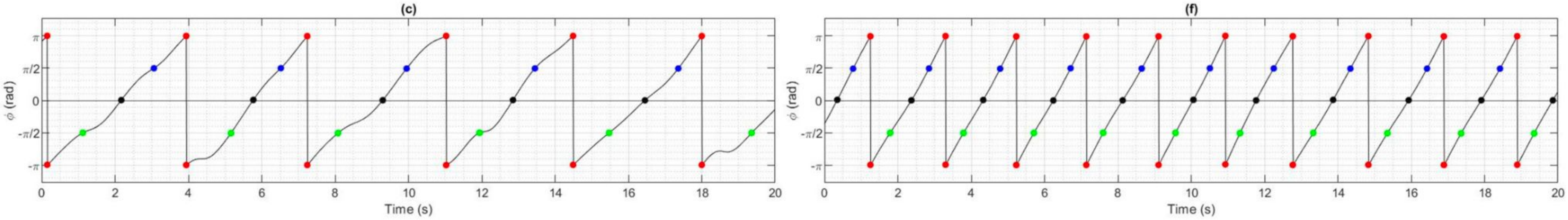
***Any clinical observations?***



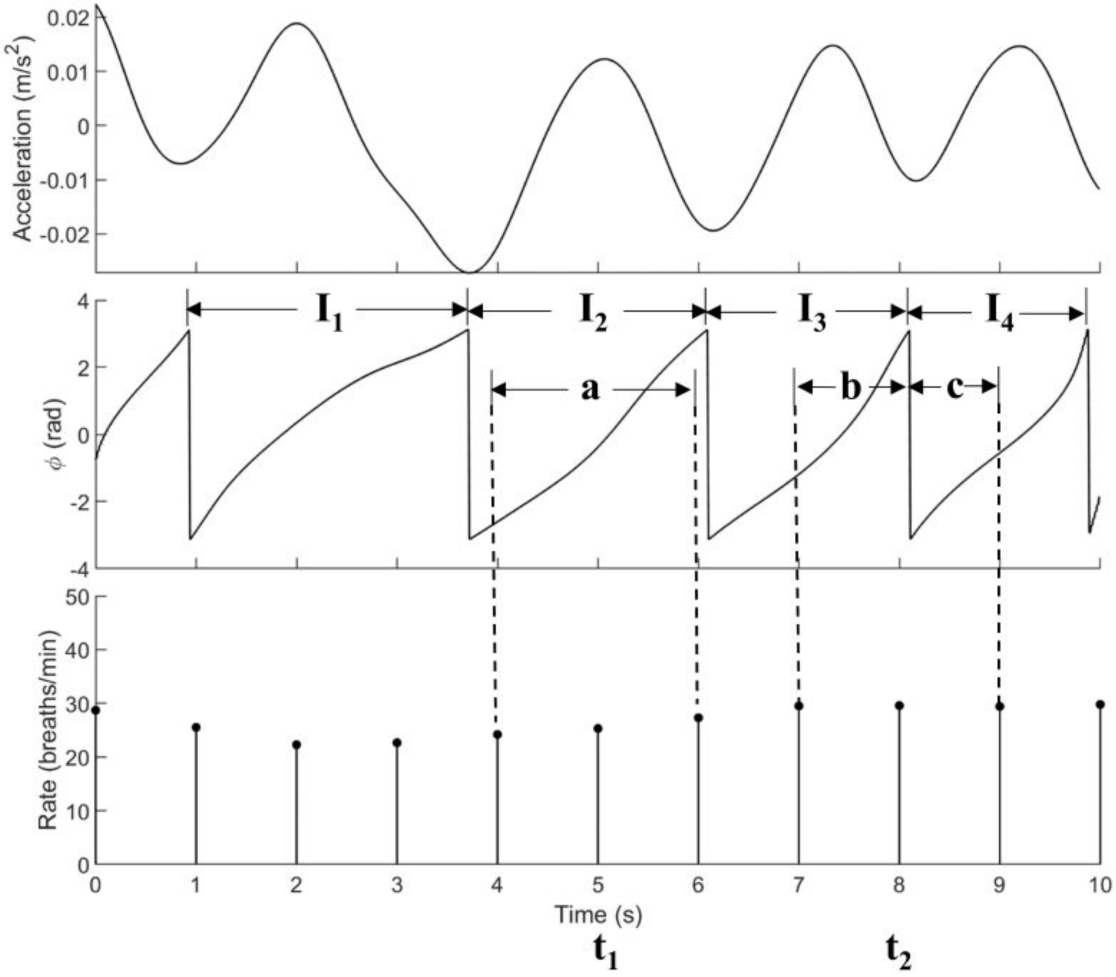

I introduced him to the works of Schafer, Ivanov, and others.



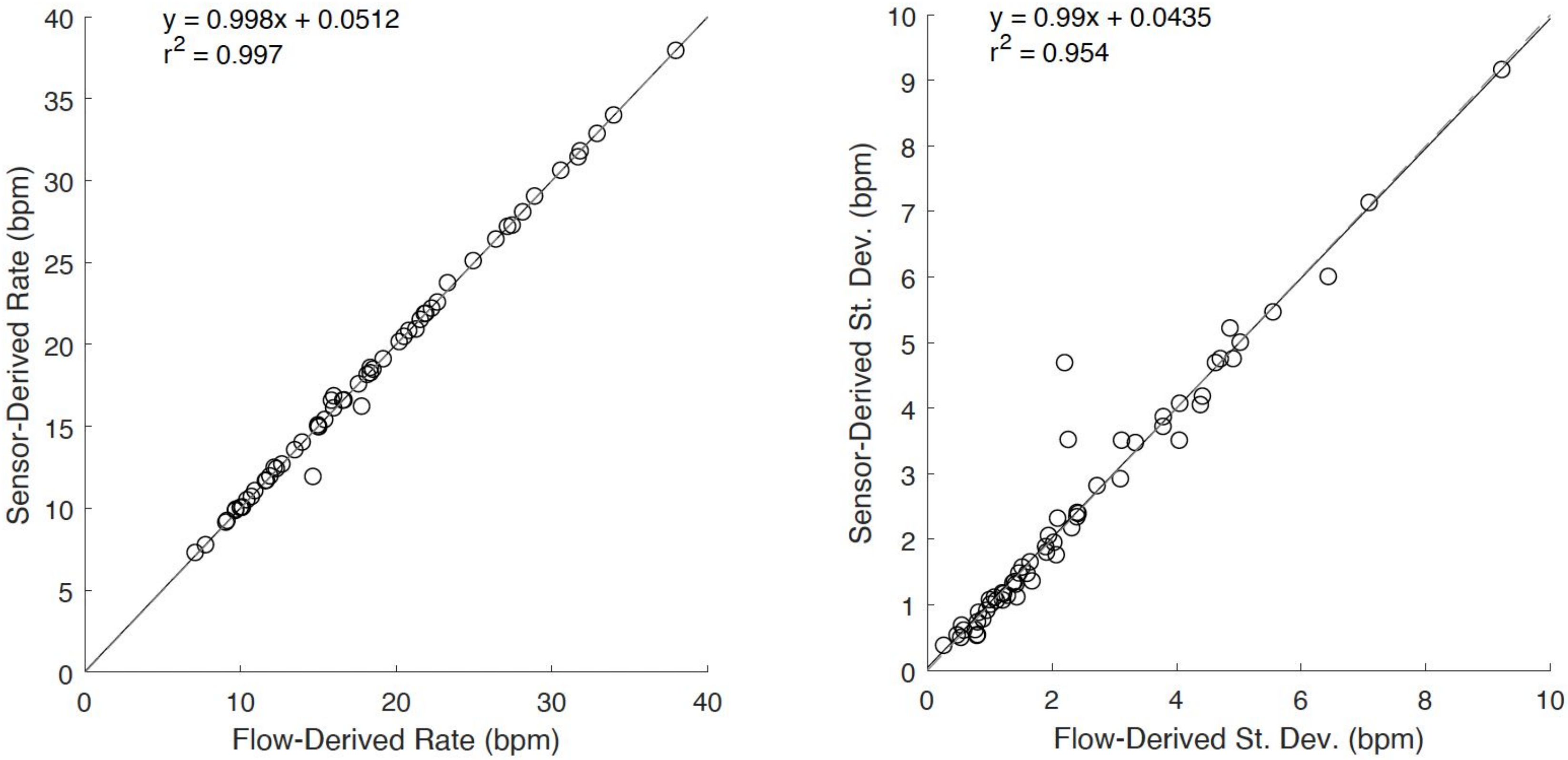



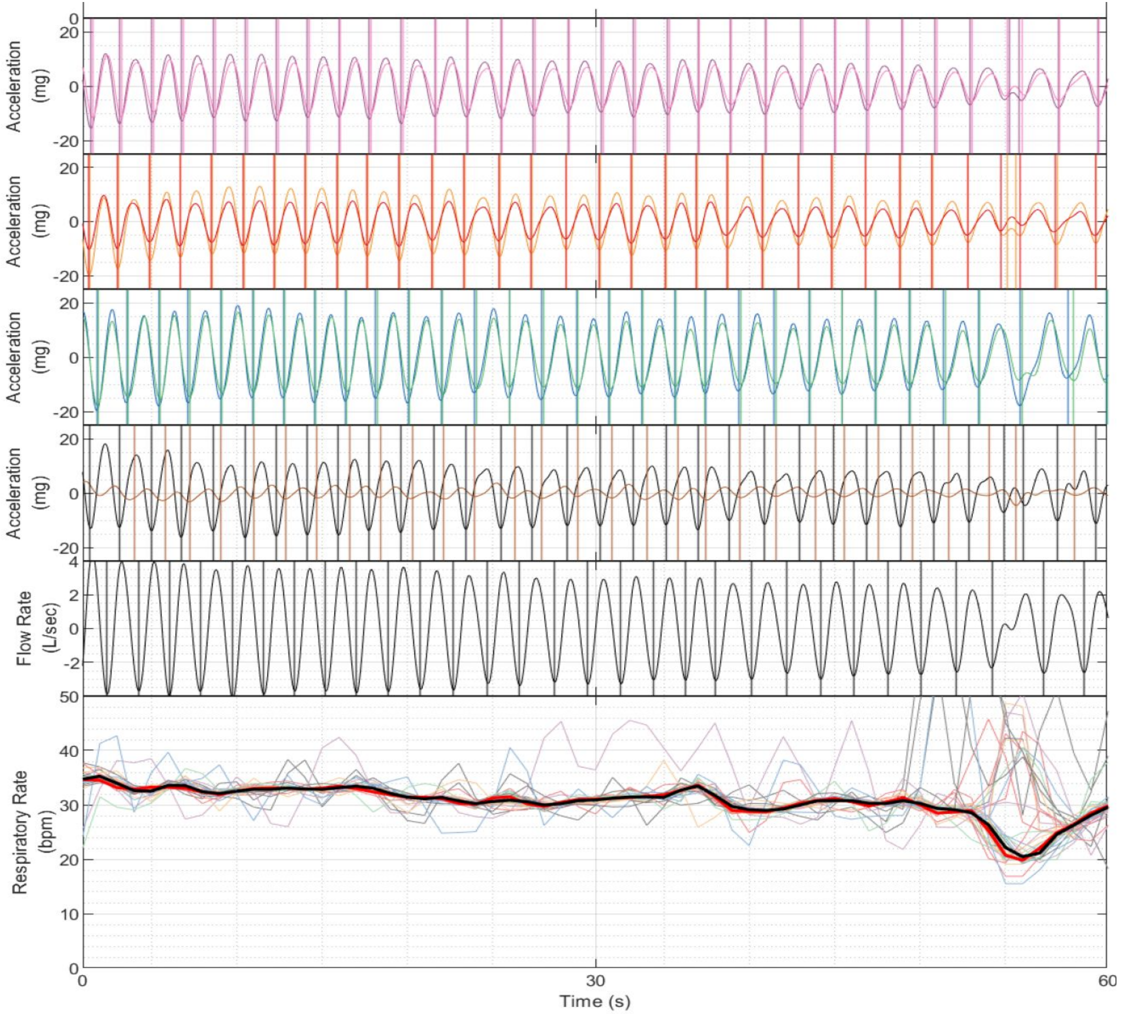
He used a 1Hz interpolation scheme to help the determination of breathing rates.

This is derived from the work of R Berger in the 1980s toward HRV analyses in the frequency domain.



# The new method counted rates well c/w flow meter

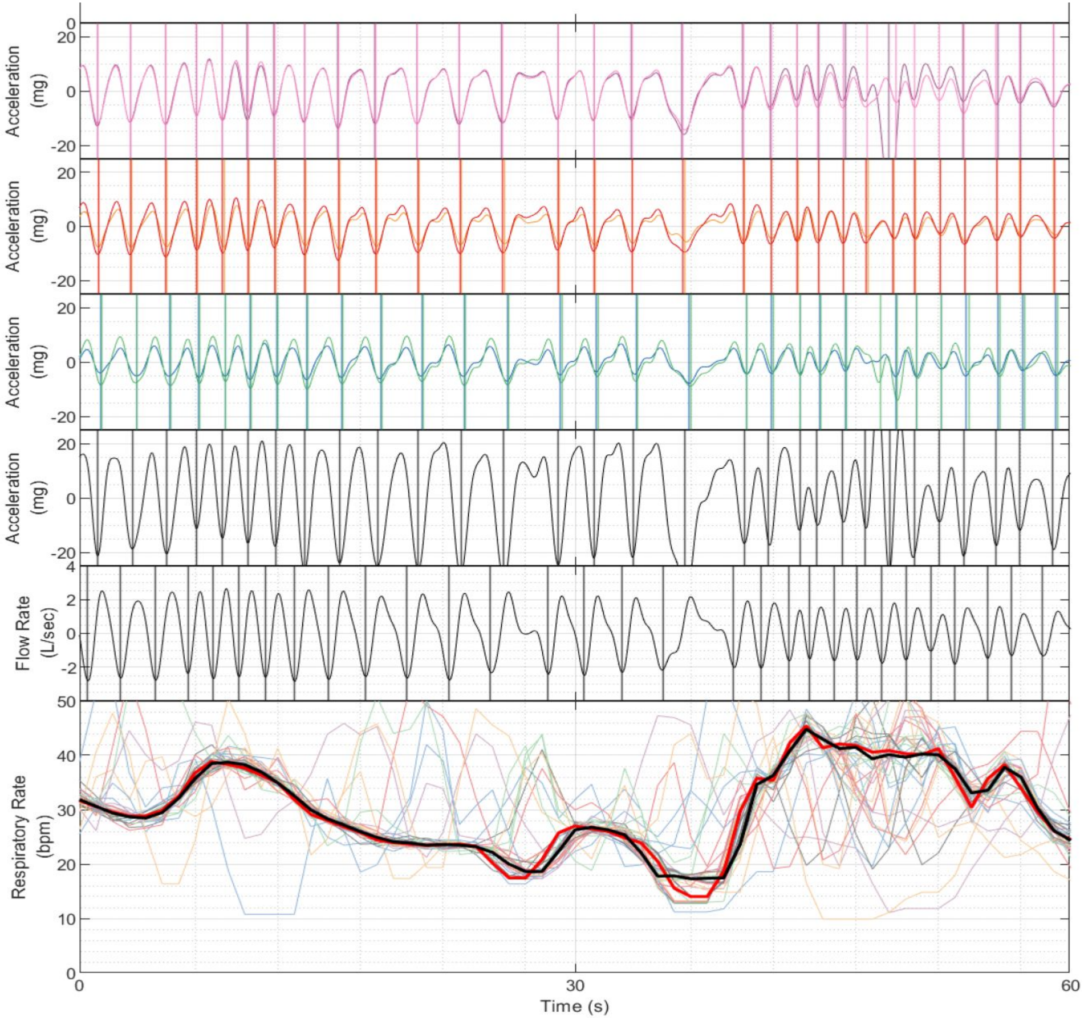





Emergency room patient:

Fast breathing - >30 breaths/minute

Went home uneventfully

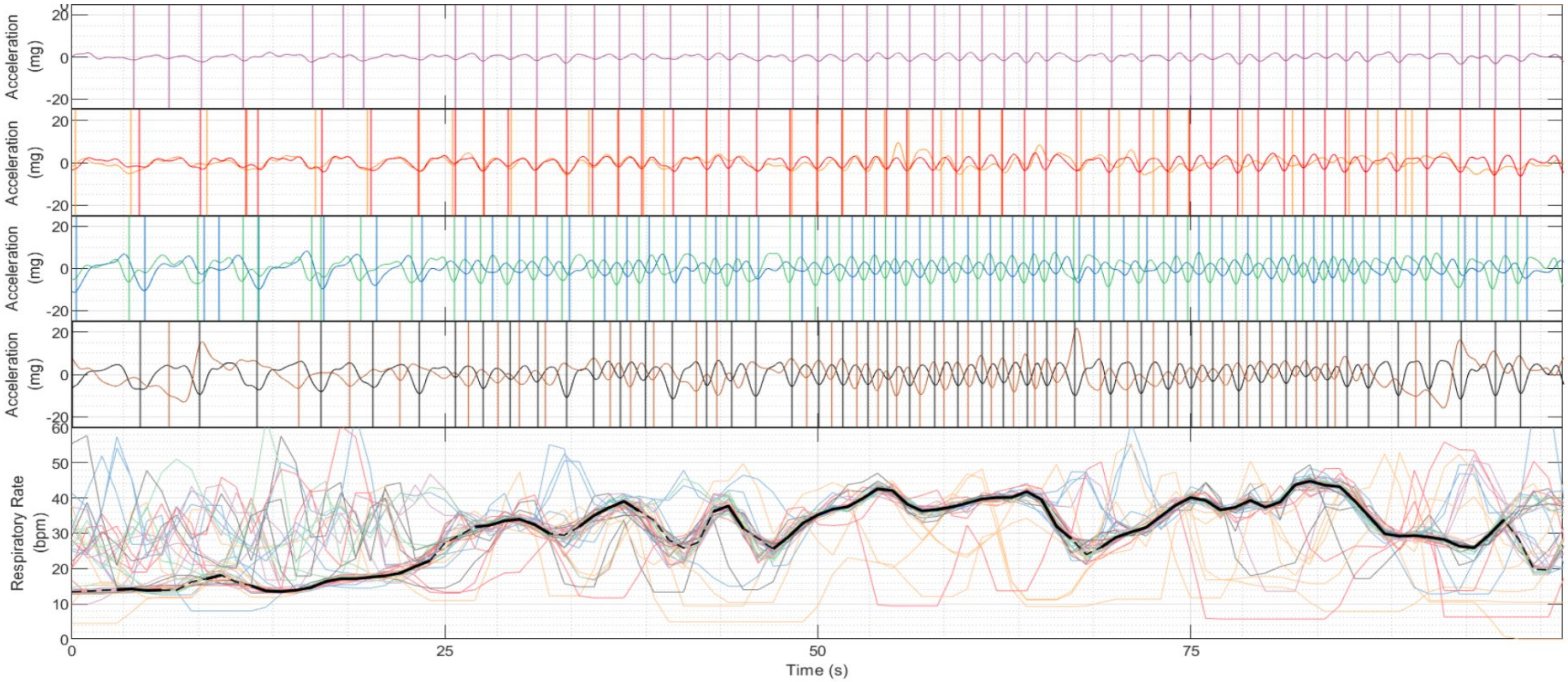



Emergency room patient:

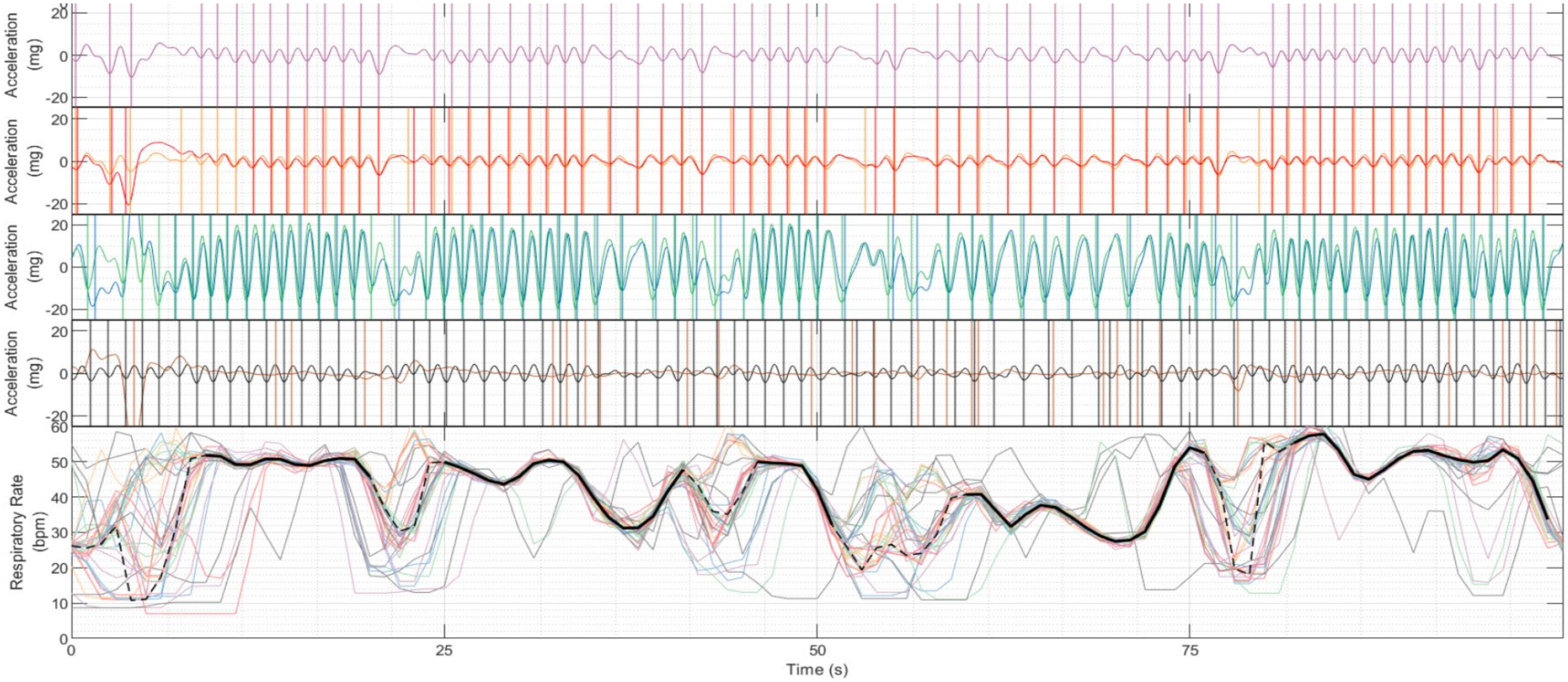
Fast breathing -
>30 breaths/minute some, but not all, of the time

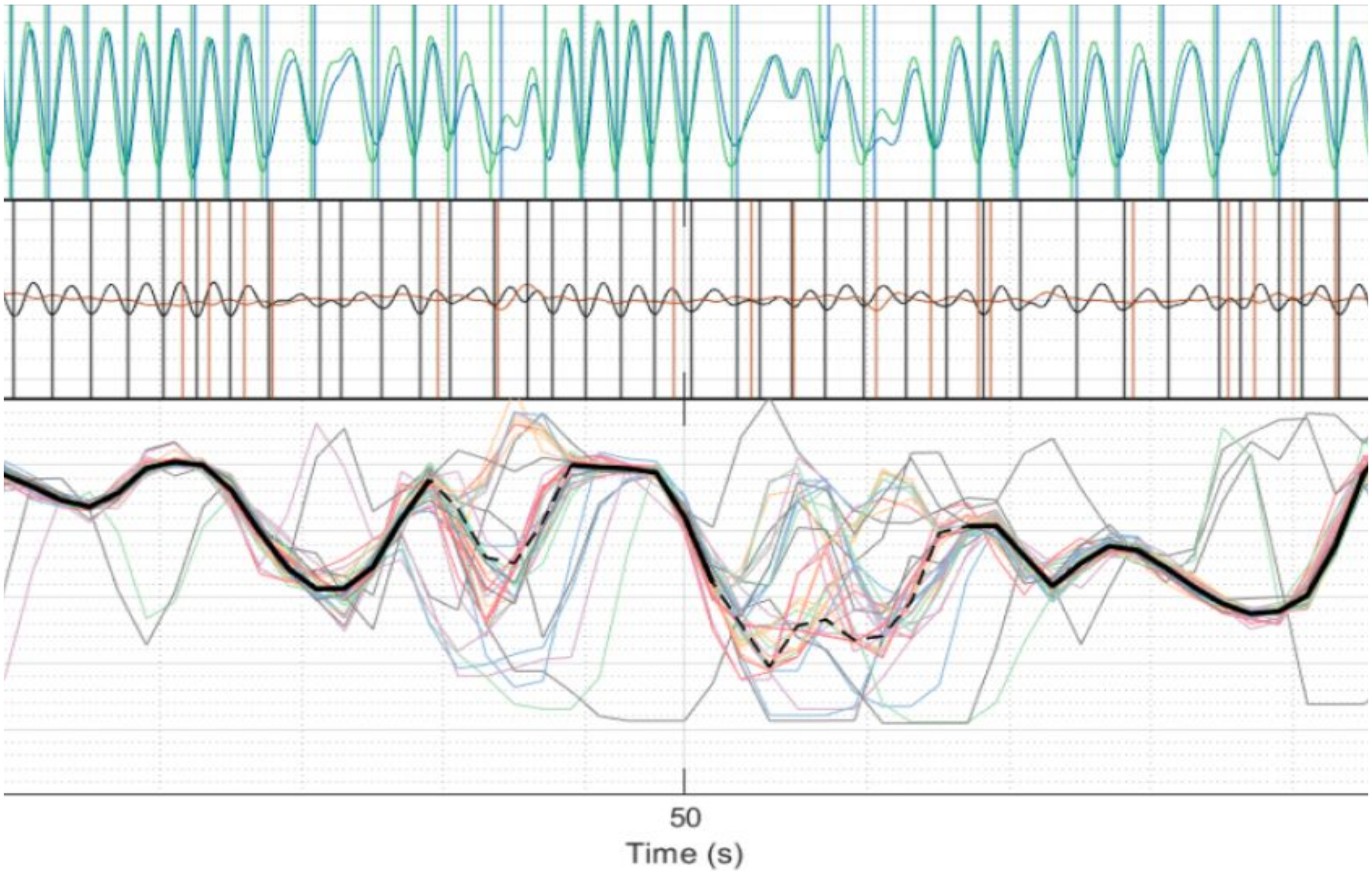
Admitted to ward

# Emergency room patient admitted to ICU

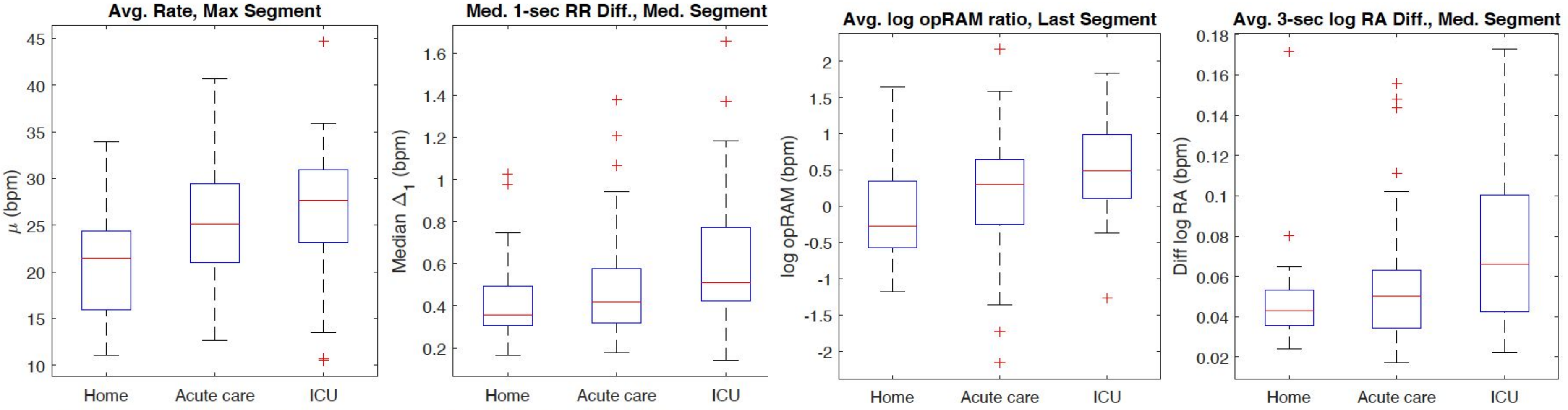


# Emergency room patient admitted to ICU




50
Time (s)

# Labored breathing predicts clinical outcome



What will the canonical analytic frameworks:

- respiratory sinus arrhythmia
- cardiorespiratory synchronization
- time delay stability

make of the very non-stationary, very informative breathing dynamics?

# Summary

Network physiology is an appealing clinical construct.

New experimental paradigms can extend the ideas to the bench and the bedside:

- Cholinergic anti-inflammatory pathway
- Nearby excitable cells
- Intracellular processes
- Clinical recordings from sick patients

# Challenges for Applied Network Physiology

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**1**: *New experimental paradigms*

I review the autonomic nervous system and suggest basic science and clinical scenarios to think about

**2**: *New measures for physiologic time series*

I show some new results, mostly published

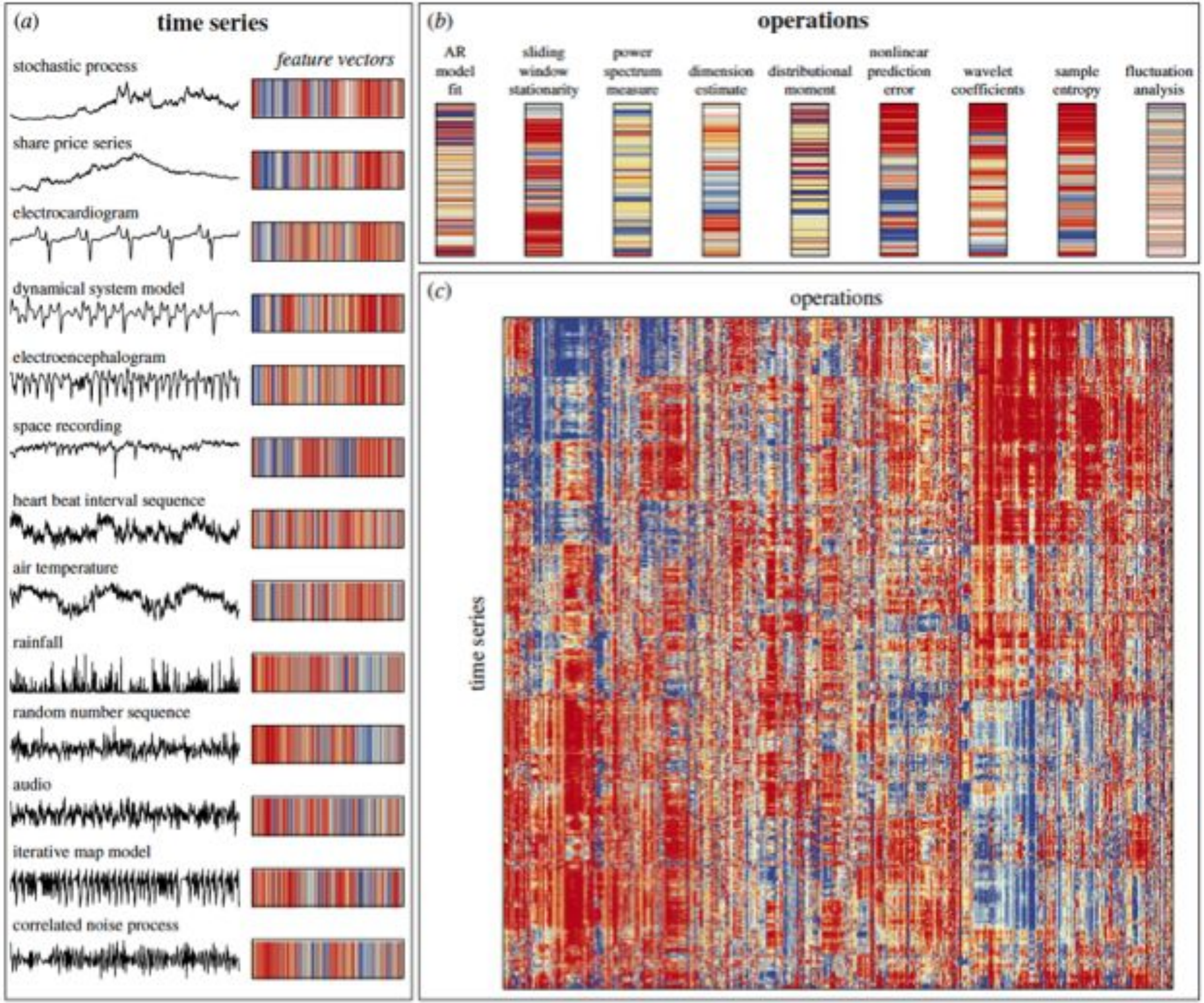
**3**: *Isolate the physiological network of the hospitalized patient from the external networks*

I show some new results

# **Challenge 2**: *New measures for physiologic time series*

Highly comparative time-series analysis

Fulcher, Little, Jones 2013 http://dx.doi.org/10.1098/rsif.2013.0048
Fulcher, Jones 2017 https://doi.org/10.1016/j.cels.2017.10.001
Fulcher … Jones 2020 https://doi.org/10.1038/s41597-020-0553-0



(a)
time series
feature vectors
stochastic process
share price series
electrocardiogram
dynamical system model
electroencephalogram
space recording
heart beat interval sequence
air temperature
rainfall
random number sequence
audio
iterative map model
correlated noise process
(b)
operations
AR model fit
sliding window stationarity
power spectrum measure
dimension estimate
distributional moment
nonlinear prediction error
wavelet coefficients
sample entropy
fluctuation analysis
(c)
operations
time series

**Table 4.** Families of algorithms implemented in highly comparative time series analysis.

| Family | Description | Example(s) |
|---|---|---|
| Distribution | Moments and other descriptive statistics | Mean, median, standard deviation |
| Correlation | Similarity of data points as a function of the time between them | Linear and nonlinear autocorrelation |
| Stationarity | Statistical properties do not change over time | Standard deviation of moments measured on different window lengths |
| Symbolic transforms | Convert ranges to letters and analyze their sequence | Frequency of successive increases |
| Entropy | Order and regularity | Sample entropy |
| Trend analysis | Fitting lines through data | Slope and intercept |
| Heart Rate Variability | Canonical analyses | Power spectral density ratios |
| Time Series Modelling | Fits time series model to data | Surprise |
| Wavelet | Properties of the time series wavelet spectrum | Wavelet decomposition of time series |
| Nonlinear Analysis | Nonlinear analysis methods | False nearest neighbors, Information dimension |
| Other | Extreme values | Moving threshold model |

# Application of highly comparative time-series analysis to neonatal ICU death

We implemented 2500 numerical algorithms on 300-point records of q2sec vital signs - 5 minutes of heart rate and oxygen saturation

About ⅓ led to NaN

We clustered the results of the rest using mutual information

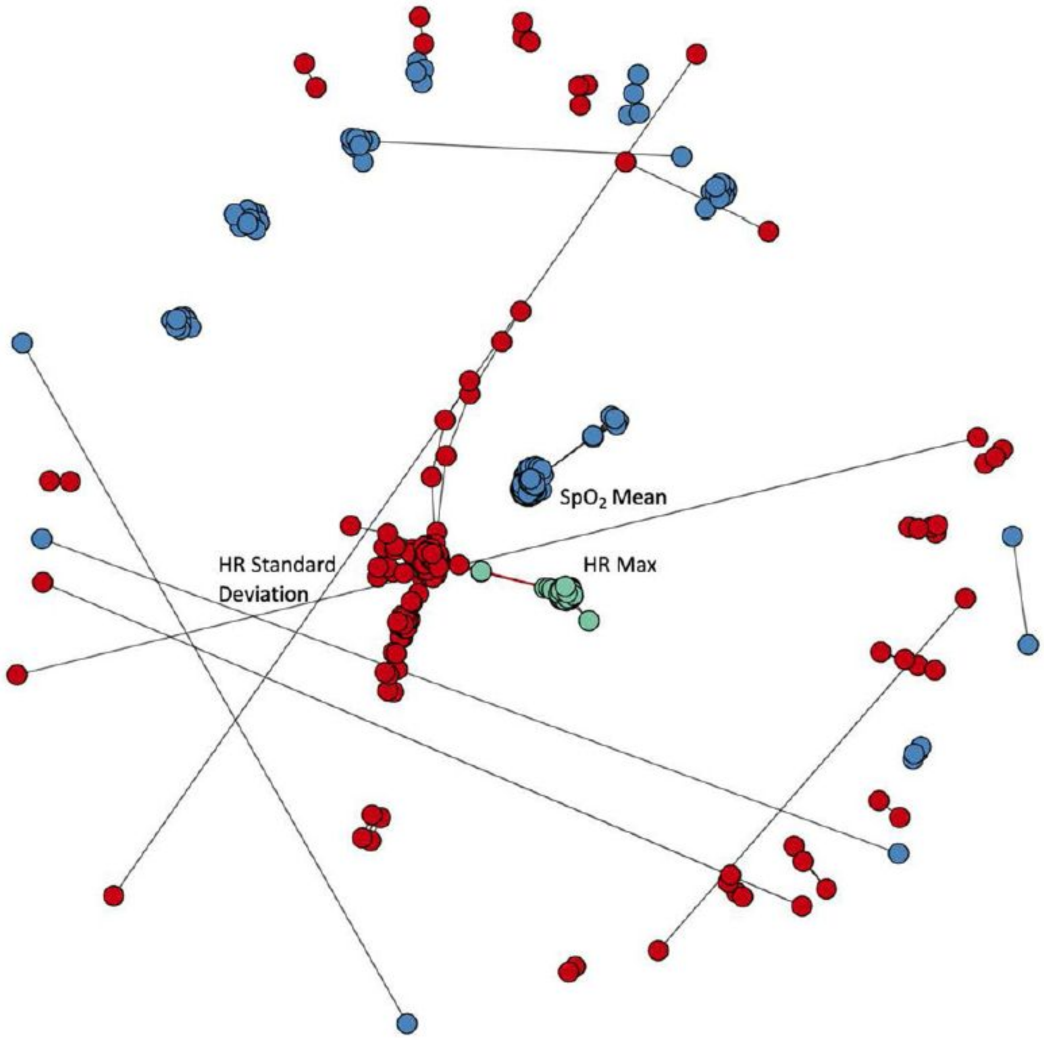
We characterized each cluster by a metric near the medoid that was interpretable

We chose the top 20 clusters

The result is a comprehensive toolbox of metrics from an unsupervised analysis

It can be used for any neonatal problem using, say, logistic regression

It can also give insight into new metrics of use in the neonatal ICU

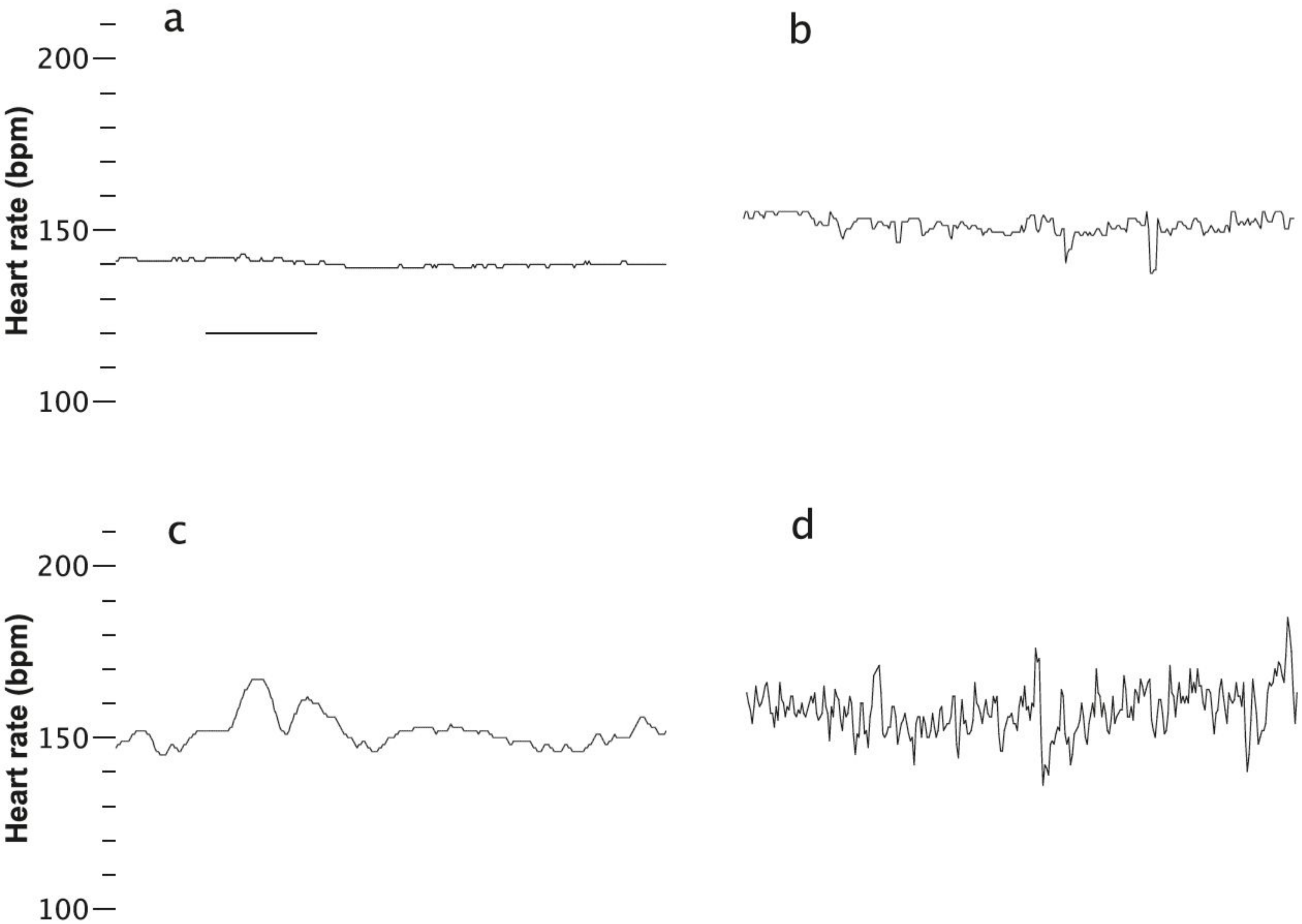


SpO$_2$ Mean
HR Max
HR Standard Deviation

# Application of highly comparative time-series analysis to neonatal ICU death

**Table 3.** Model performances as a function of days until death.

| Model name | Candidate features | Model size | ≤7 days |
|---|---|---|---|
| HR-$SpO_2$ - demographics | 21 | 6 | 0.853 |
| HR-$SpO_2$ | 20 | 5 | 0.828 |
| HR-$SpO_2$ | 20 | 3 | 0.821 |
| HR-$SpO_2$: cluster centers | 20 | 5 | 0.819 |
| HR | 10 | 5 | 0.809 |
| HR: successive increases | 1 | 1 | 0.799 |
| HR-$SpO_2$: means and SDs | 4 | 4 | 0.774 |
| $SpO_2$ | 10 | 5 | 0.765 |
| Demographics | 4 | 4 | 0.714 |


a
b
c
d
Heart rate (bpm)
200
150
100
Heart rate (bpm)
200
150
100

# New insights from highly comparative time-series analysis

**Surprisal**; conditional *p* of the next point given the recent distribution: low HRV

**Moving threshold**: extreme events in dynamical systems; large excursions

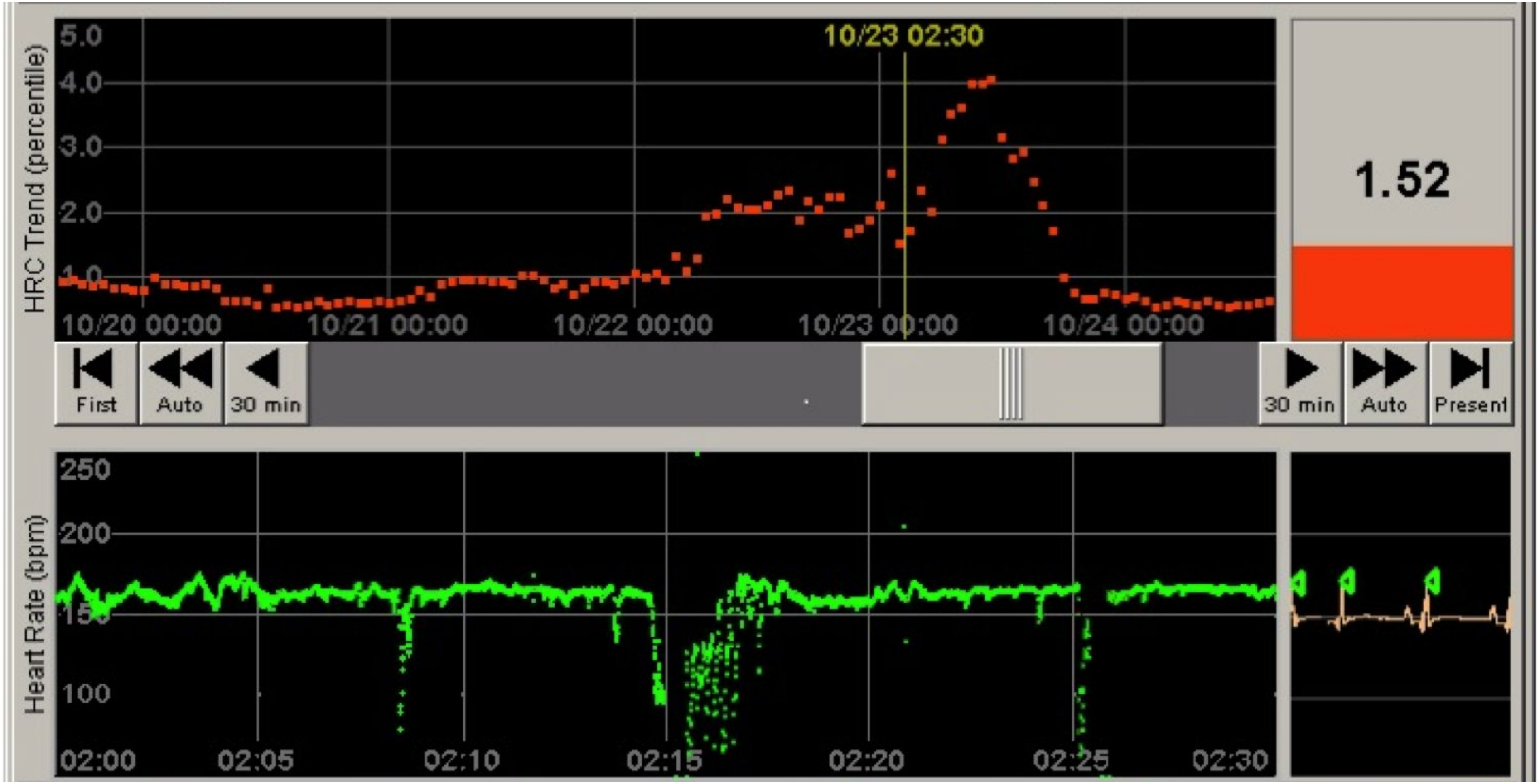
**Sucessive increases**: symbolic dynamics; lack of HR accelerations

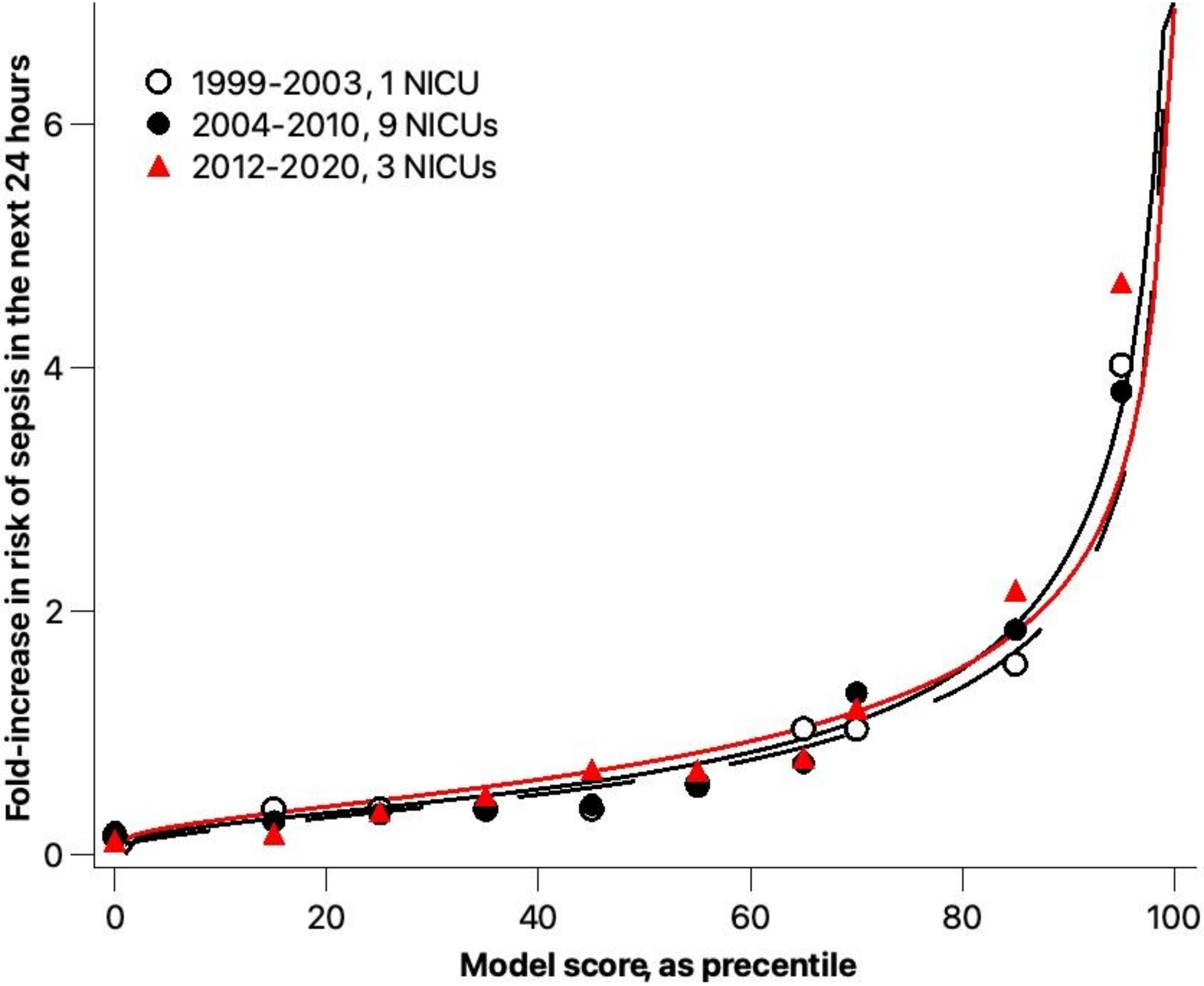
**Random walk**: many statistics on the fit of a model; slow decline in O2 saturation

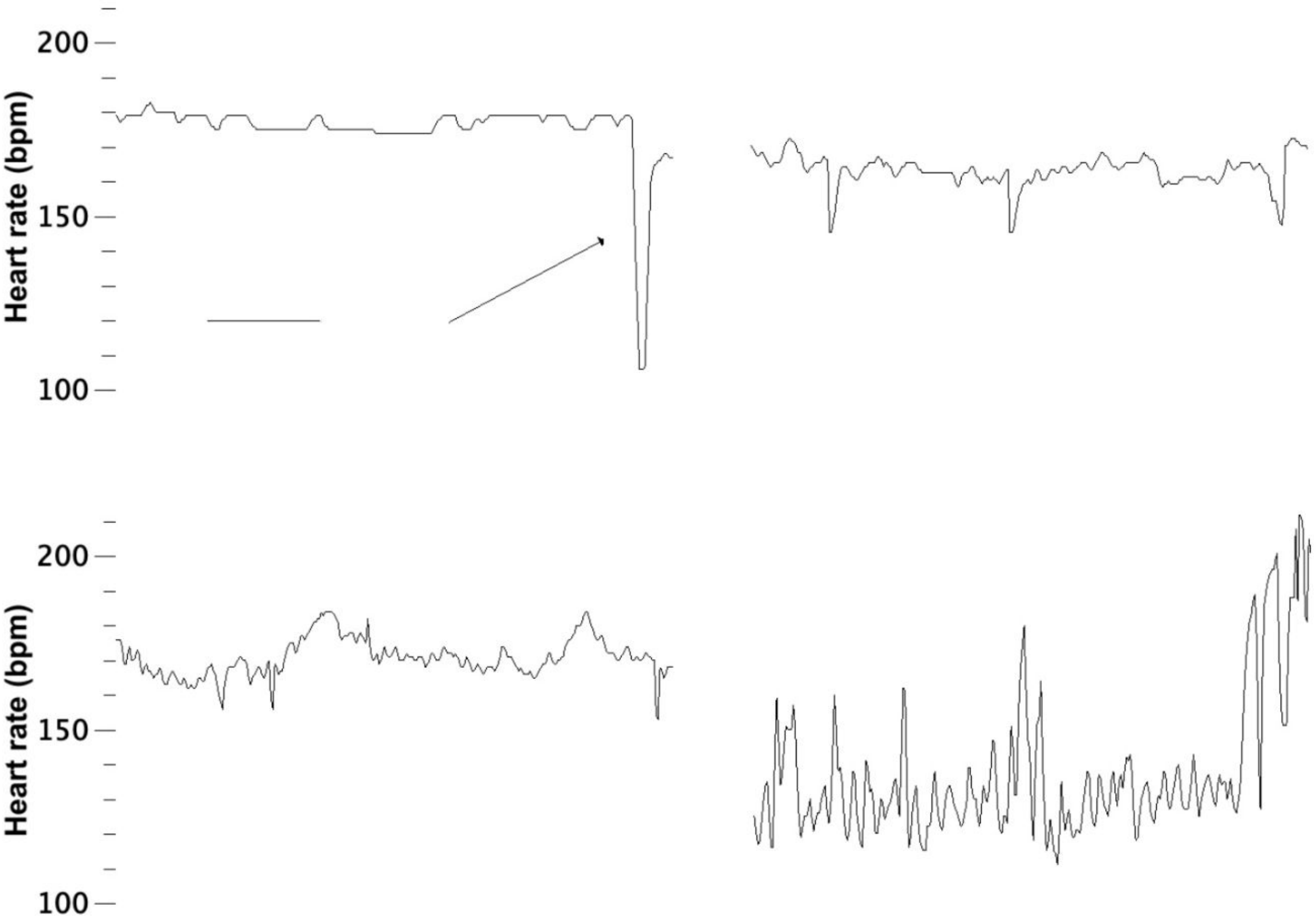
# Highly comparative time-series analysis vs neonatal sepsis

# Abnormal heart rate characteristics precede neonatal sepsis

Moorman, others 2001




1999-2003, 1 NICU
2004-2010, 9 NICUs
2012-2020, 3 NICUs
Fold-increase in risk of sepsis in the next 24 hours
0
2
4
6
0
20
40
60
80
100
Model score, as precentile


200
150
100
Heart rate (bpm)
200
150
100
Heart rate (bpm)

## **Challenge 3**: *Isolate the physiological network of the hospitalized patient from the external networks*

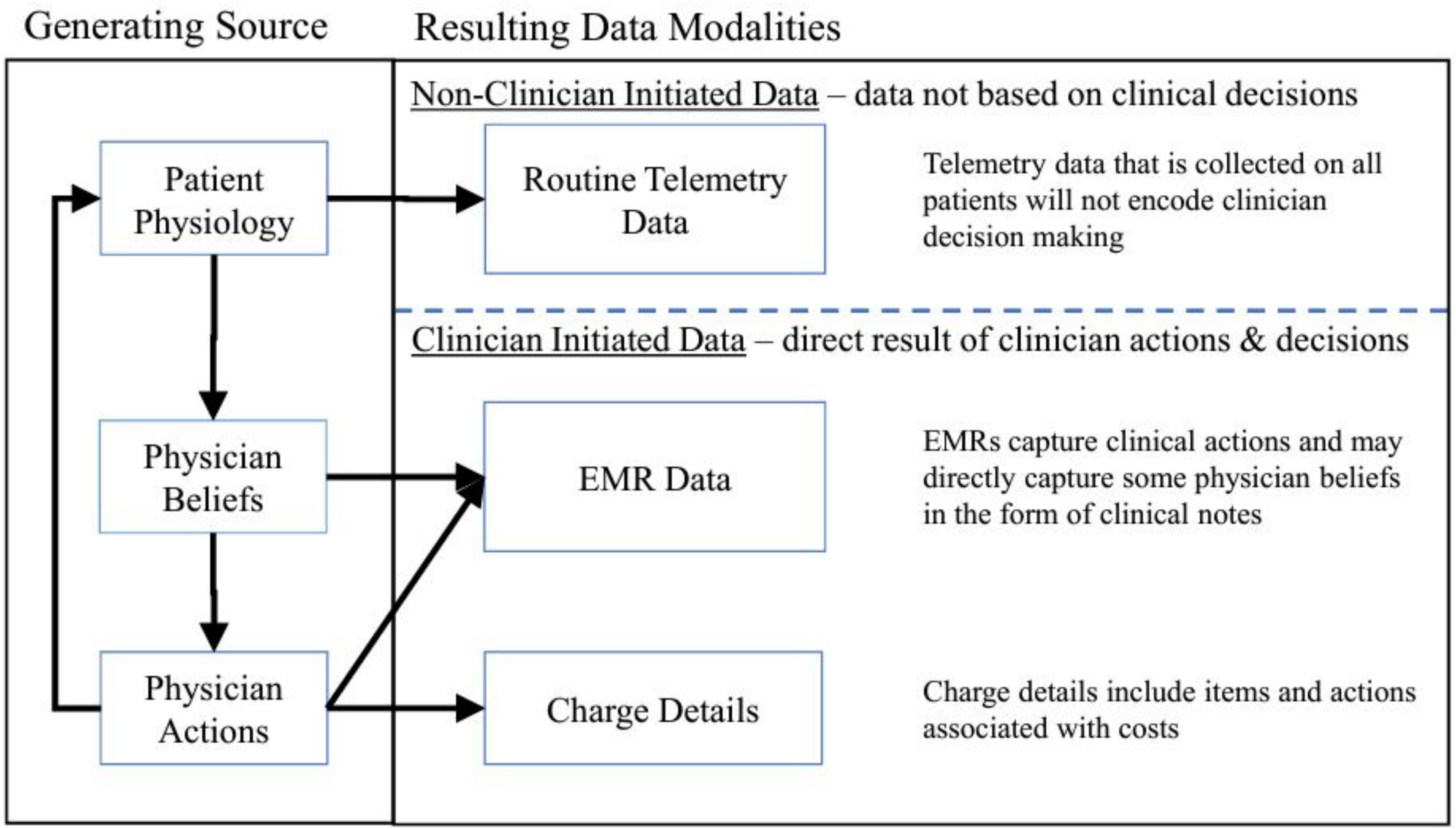
The hospital patient is part of a complex network of care providers, tests, and medications along with the dynamics of the illness.

It is an important challenge to separate the dynamics of the patient's illness from the decisions - and distractions - of the clinicians.

Physiology should change first, but we base much of our hope for early detection of illness on information in the Electronic Health Record, a narrative of what is on the clinicians' minds.

# Here is what the clinician ordered: what is the diagnosis?

| Description | Department | Quantity |
|---|---|---|
| EKG Routine tracing only | EKG | 1 |
| ECHO 2D W/OR W/O M-Mode complete W/color flow | Cardiology | 1 |
| ER Level V | Emergency room | 1 |
| XR Chest 2 views | Diagnostic imaging | 1 |
| Culture blood | Laboratory | 2 |
| Partial thromboplastin time (PTT) | Laboratory | 1 |
| Prothrombin time (PT) | Laboratory | 1 |
| Complete CBC AUTO W/O DIFF | Laboratory | 1 |
| TROPONIN QN | Laboratory | 2 |
| B-Type natriuretic peptide | Laboratory | 1 |
| Lactate/lactic acid | Laboratory | 1 |
| Creatine kinase (CPK) MB only | Laboratory | 1 |
| Creatine kinase (CPK) | Laboratory | 2 |
| Comprehensive metabolic panel | Laboratory | 1 |
| Therapeutic/DIAG INJ IV push single INITI SUB/drug | IV Therapy | 1 |
| DOCUSATE NA, COLACE CAP 100 mg | Pharmacy | 1 |
| Aspirin Tab 325 mg (EA) | Pharmacy | 1 |
| Moxifloxacin, Avelox IVPB 400 mg | Pharmacy | 1 |
| Moxifloxacin, Avelox tab 400 mg | Pharmacy | 1 |
| Metoprolol, lopressor tab 25 mg | Pharmacy | 1 |
| Ipratropium, atrovent INH SOL 0.02% 2.5 ml | Pharmacy | 1 |
| Heparin NA VL 5000 U/ml 1 ml | Pharmacy | 1 |
| Furosemide, Lasix tab 20 mg | Pharmacy | 2 |
| Albuterol, proventil INH SOL 0.083% 3 ml (2.5 mg) | Pharmacy | 3 |
| R&B Telemetry private | Room and board | 1 |


Generating Source
Resulting Data Modalities
Non-Clinician Initiated Data – data not based on clinical decisions
Patient Physiology
Routine Telemetry Data
Telemetry data that is collected on all patients will not encode clinician decision making
Clinician Initiated Data – direct result of clinician actions & decisions
Physician Beliefs
EMR Data
EMRs capture clinical actions and may directly capture some physician beliefs in the form of clinical notes
Physician Actions
Charge Details
Charge details include items and actions associated with costs

## **Challenge 3**: *Isolate the physiological network of the hospitalized patient from the external networks*

In addition to the decisions of clinicians, there are their distractions.

The actions of one agent are coupled to those of other agents - for example, the sudden illness of a patient might lead to a flurry of actions by one more clinicians, coupled in that one might order a test but another sees the result and acts upon it.

Or the extreme illness of one patient might distract clinicians from the other patients, whose standard tests and actions are delayed and disorganized .

## **Challenge 3**: *Isolate the physiological network of the hospitalized patient from the external networks*

We are approaching the problem by quantifying the surprisal of blood tests in our hospital over the years before and during the pandemic.

Entropy is a quantitative measure of surprise
Entropy is a characteristic and invariant measure of a dynamical system, like length or volume
We can apply these foundational ideas to hospitals, wards and clinicians

# A feeling for $-\sum p(x_i) \log p(x_i)$ in information

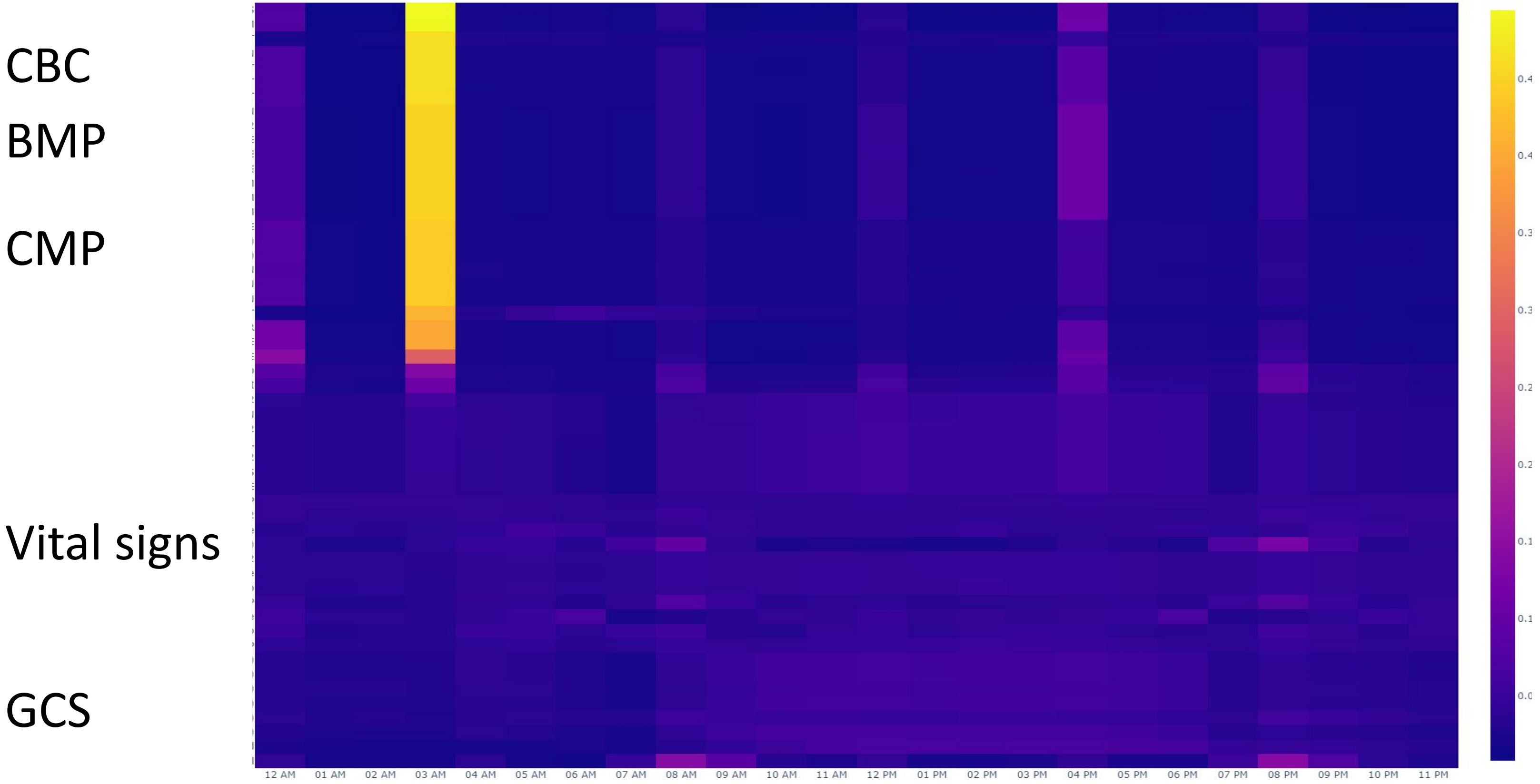
- We wish to have a measure of the surprise that we feel when we see the next point in a time series, $x_i$
- One way is the inverse of the probability $p(x_i)$ or $1/ p(x_i)$. Low probability points generate big surprise.
- Think about the surprise of the next points – multiplying the 2 probabilities seems extreme. Rather, it seems we should be adding.
- Thus let's use the log $p(x_i)$, or, in this case, - log $p(x_i)$ for the inverse
- We can then estimate the surprise of the entire time series as the sum of all the – log $p(x_i)$.
- And to estimate the average, we can take the expectation, or

$$H(X) = -\mathbb{E}[\log p(x_i)] = -\sum_{i}^{n} p(x_i) \log p(x_i)$$

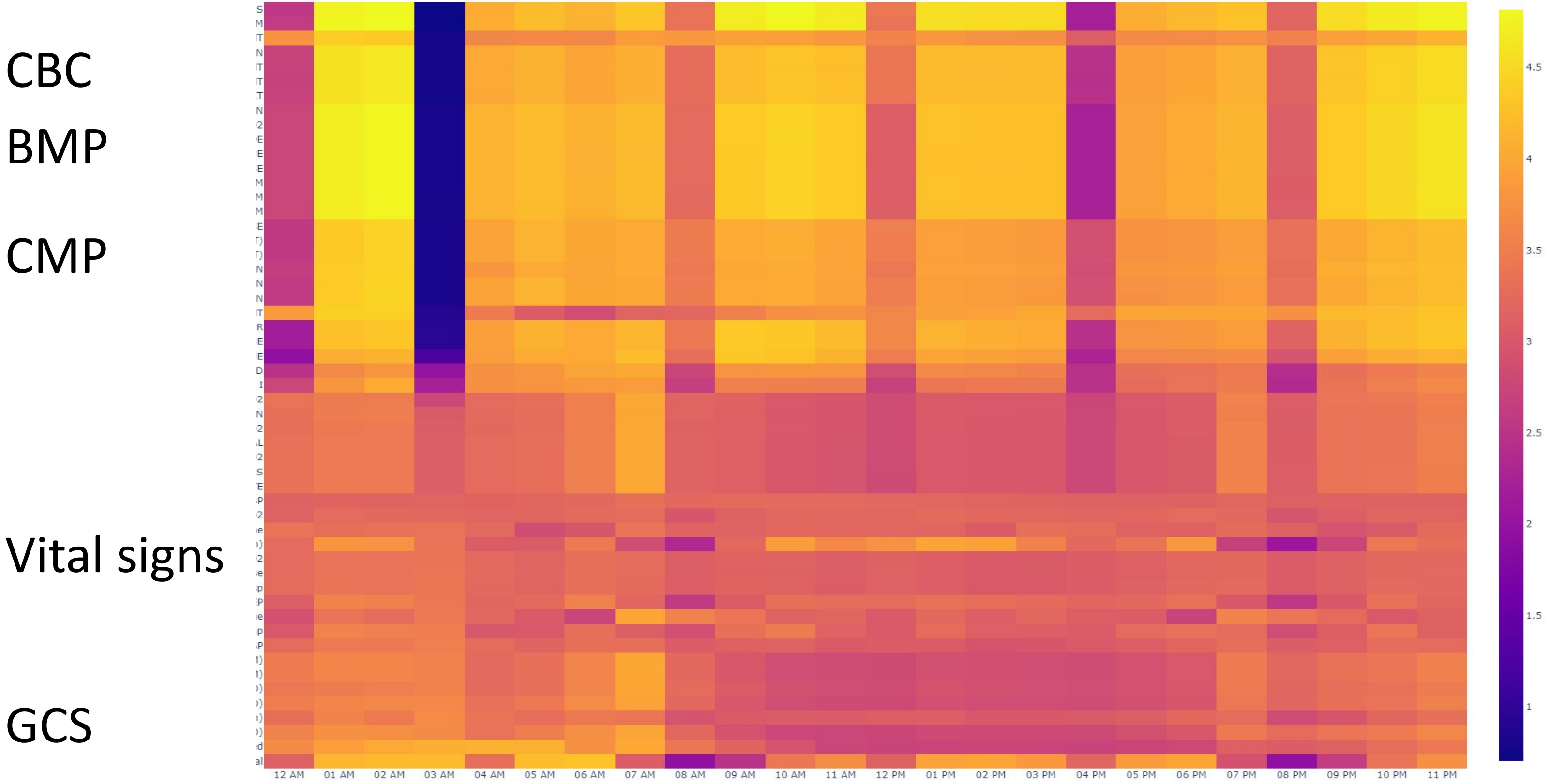
# Can we apply these ideas to hospital care? The patients and clinicians

- We wish to know what the clinician thinks
- We can get insight by what the clinician does, and when
- *E.g.*, we can ask if the actions are surprising, like labs at 1AM
- We can use:
  - $-\ln p$ as the **surprise factor for a single event**
  - $-\sum \ln p$ as the **total surprise of a group of events**, and
  - $-\sum p \ln p$ as the **average surprise over a period of time**
- We know $p$ for vital signs, lab tests, medications, …

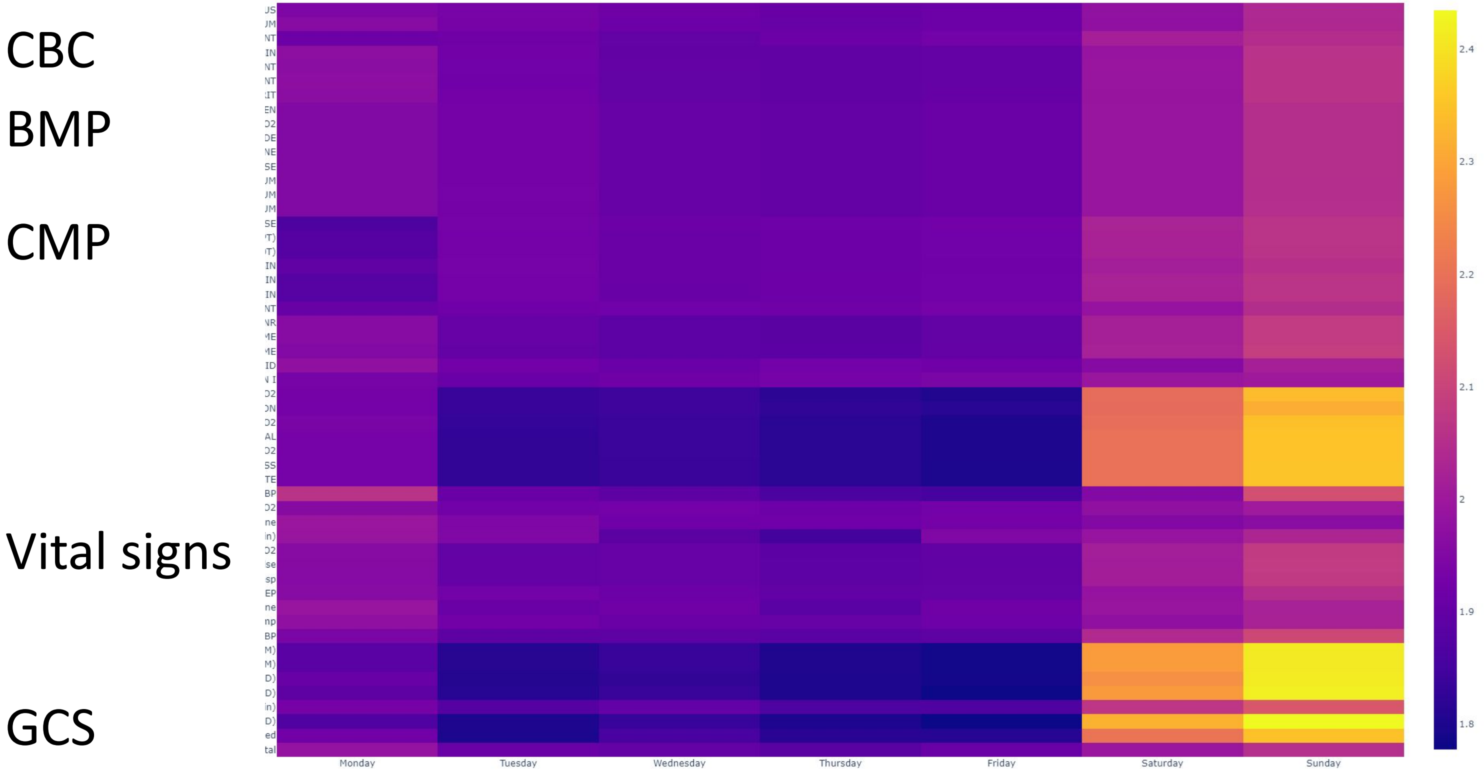
# *p*(labs, vital signs) by hour of day



# Surprisal = - ln $p$(labs, vital signs) by hour of day



# Surprisal = - ln *p*(labs, vital signs) by day of week



# Can we apply these ideas to hospital care? The ward

We will take another view, that of the ward as a dynamical system

# Kolmogorov and Sinai 1958 and 1959

- Employed Shannon's entropy as an invariant measure of a *well-behaved dynamical system* – a new concept was that new values of a dynamical process could be estimated with a certainty (or uncertainty) that was characteristic of the system itself
- Thus the entropy of K and S is:

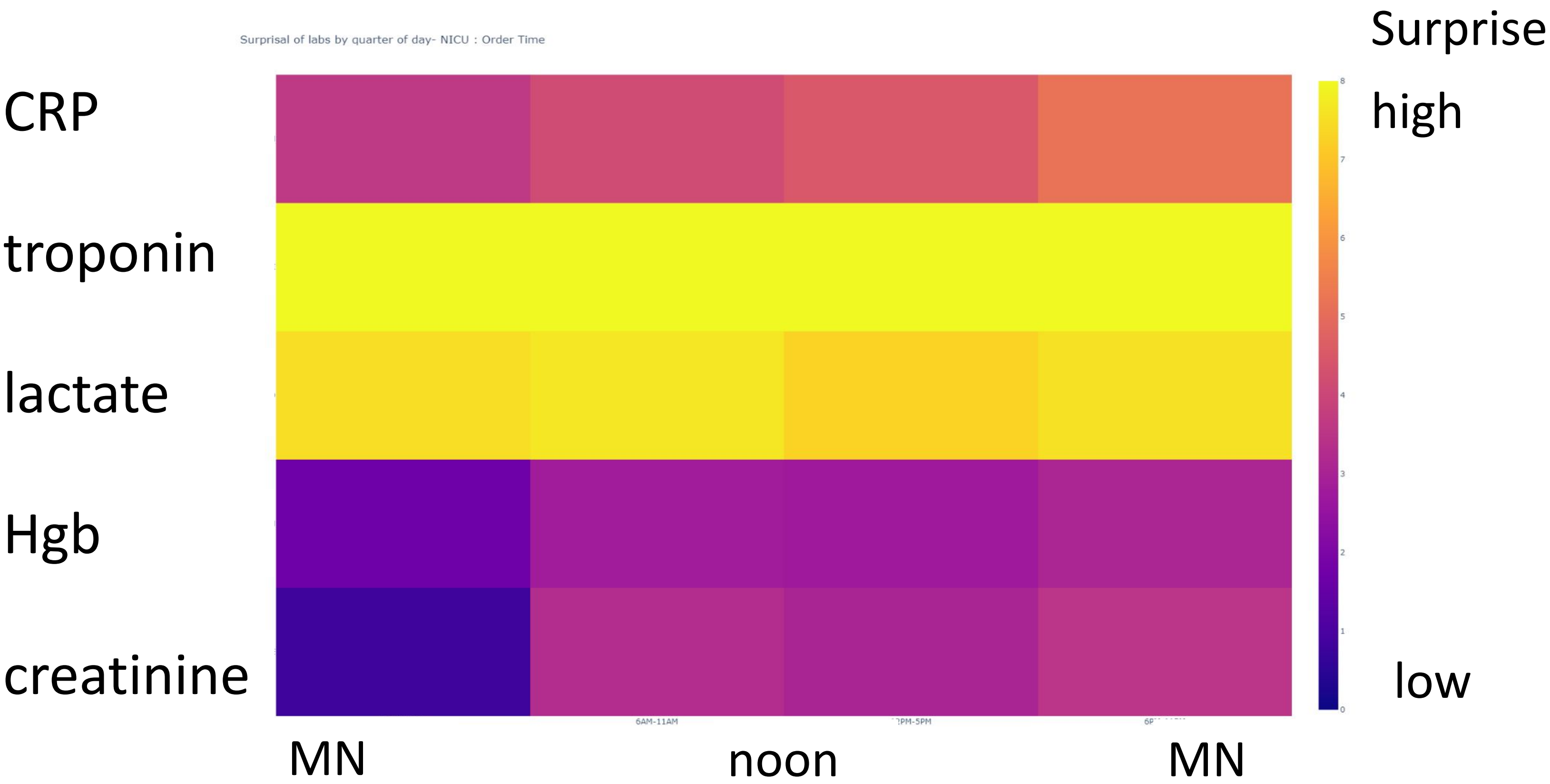
$$H_{KS} = -\lim_{\delta\to 0}\lim_{\varepsilon\to 0}\lim_{n\to\infty}\frac{1}{n\delta}\sum_{k_1,\ldots,k_n} p(k_1,\ldots,k_n)\log p(k_1,\ldots,k_n)$$

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

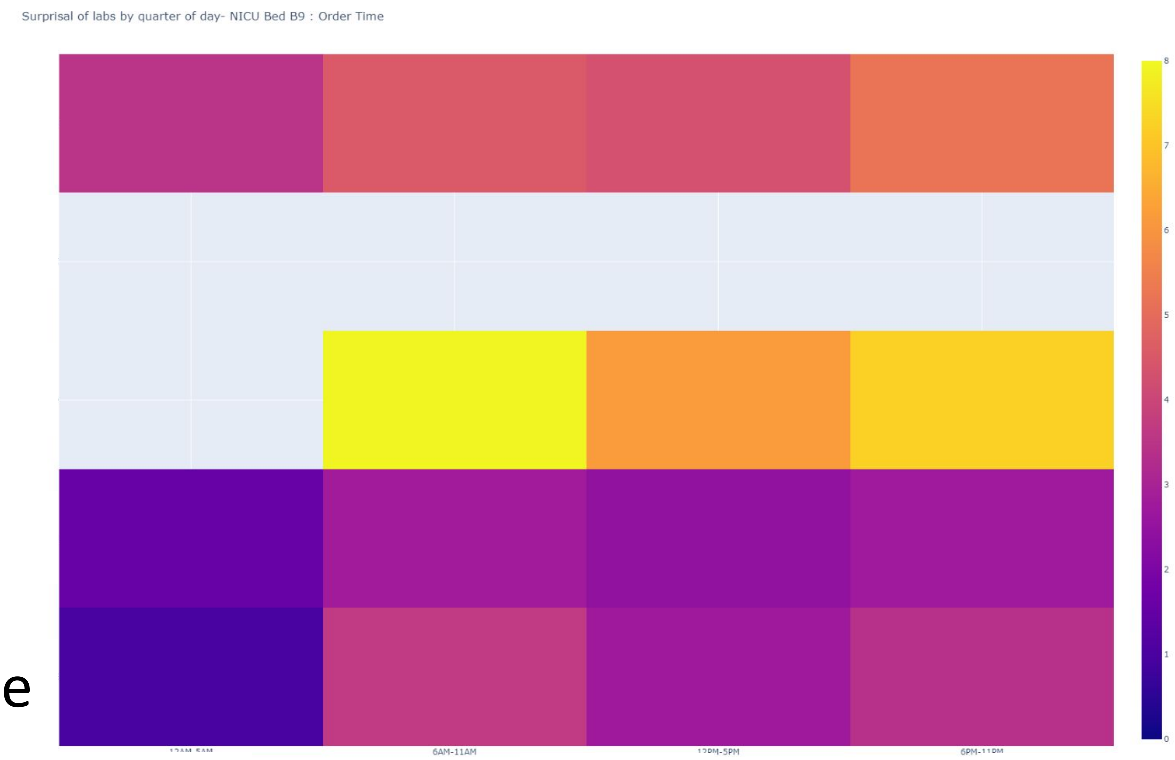
# Kolmogorov and Sinai 1958 and 1959

- The intuitive interpretation is that each new state in the evolving dynamical system can be expected with greater or lesser uncertainty if one knows the preceding states
- This degree of uncertainty is a invariant measure or characteristic of a *well-behaved* dynamical system
- Is this thinking applicable to the hospital?
- Yes, if the hospital is a well-behaved dynamical system, an *ergodic* one
- A single bee in its lifetime will go everywhere that the hive does in a day
- The *p*(labs and vital signs) in a single bed in the NICU or on 4E will have the same map as the whole ward.

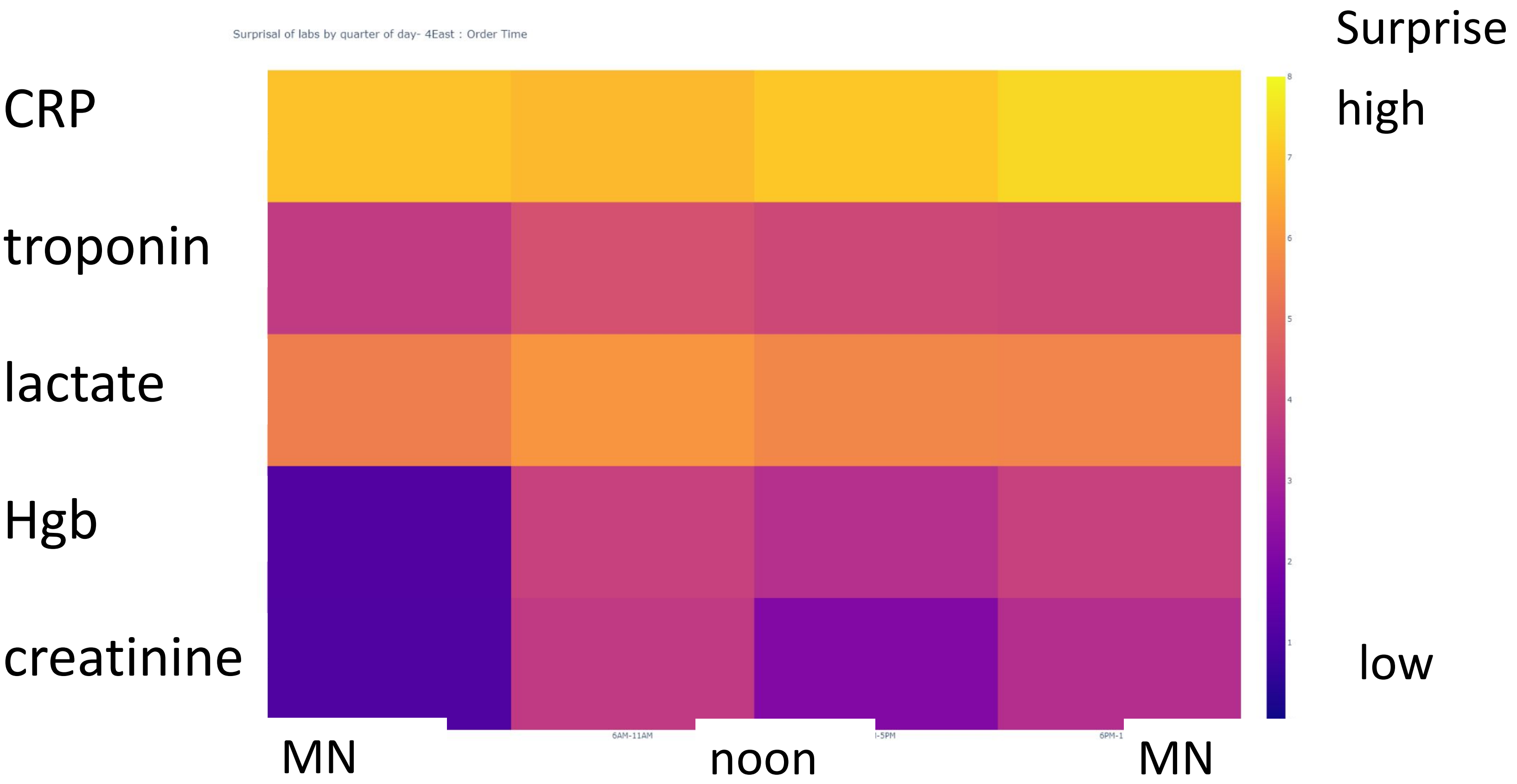
# Surprisal of Labs - NICU



# Surprisal of labs – NICU Bed B09



# Surprisal of labs – 4East



# Surprisal of labs – 4East Bed 3A

Surprise

high

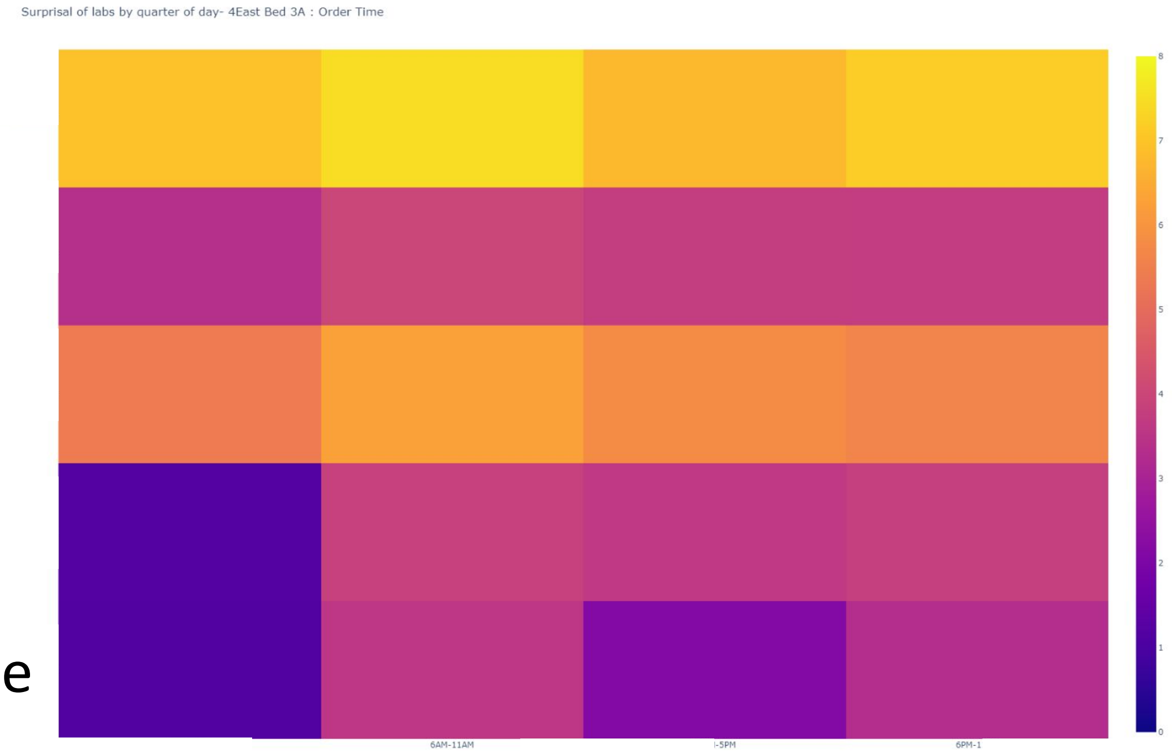
CRP

troponin

lactate

Hgb

creatinine




low

MN

noon

MN

# Are those maps the same?

- We need a measure of the difference between two entropies
- This is called the mutual entropy or Kullback-Leibler divergence.
- It amounts to the difference in - ln *p*, but is written:
- $D_{KL} = -\sum p \ln p/q$
- If there is no difference, then $D_{KL} = 0$.
- $D_{KL}$ p=NICU B9 and q=NICU: 0.0258
- $D_{KL}$ p=4East 3A and q=4East: 0.0061
- $D_{KL}$ p=NICU and q=4East: 0.3307
- $D_{KL}$ p=4East and q=NICU: 0.6175

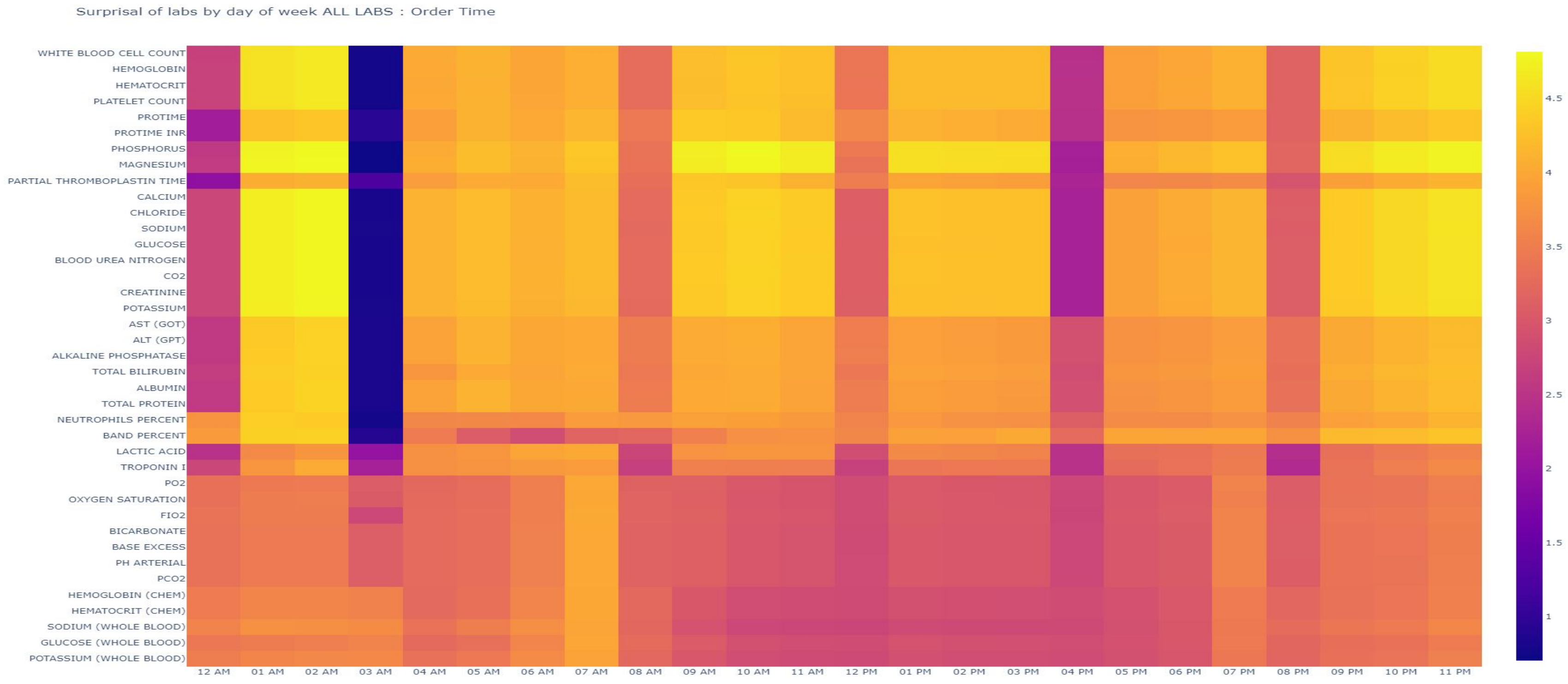
# Can we apply these ideas to hospital care?
# The hospital

Can we consider the hospital a well-behaved dynamical system?

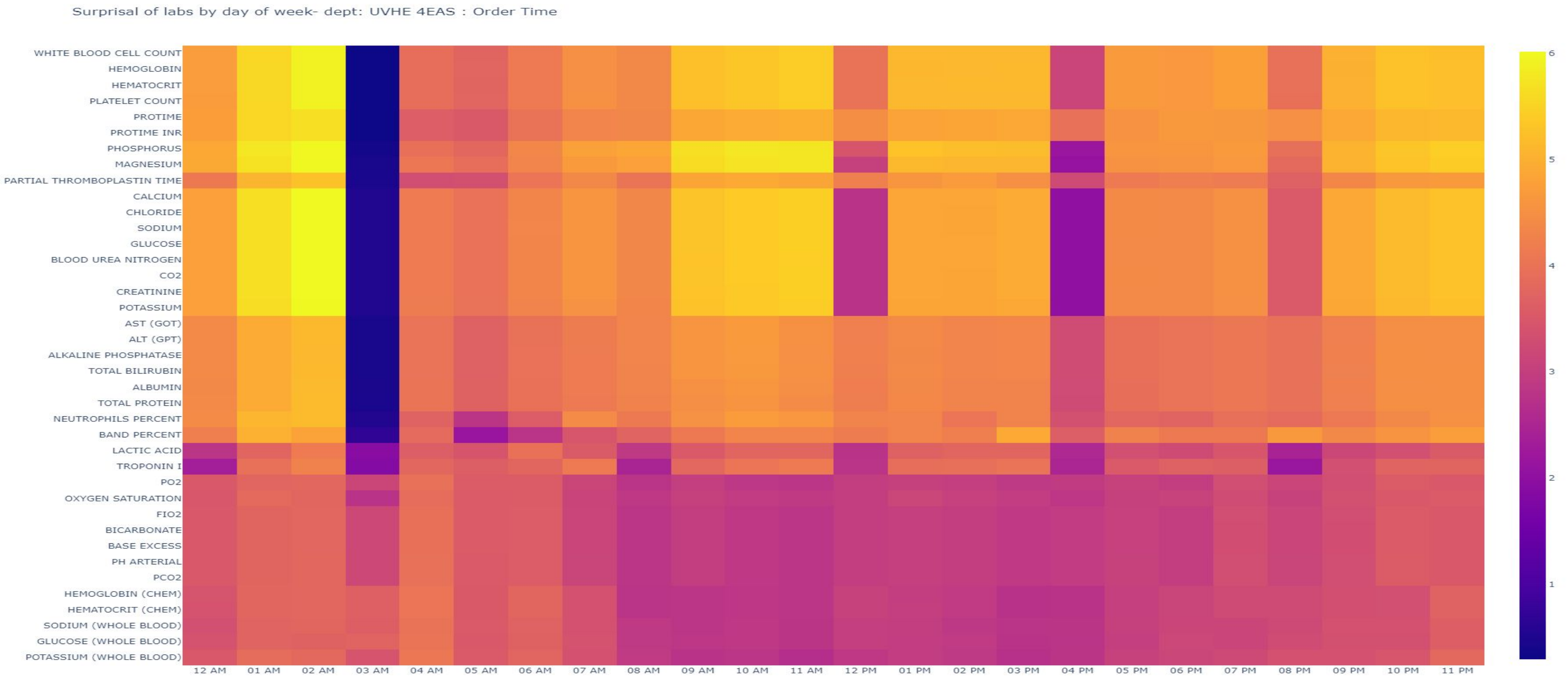
Intuitions:

The surprisal maps should look the same throughout the hospital

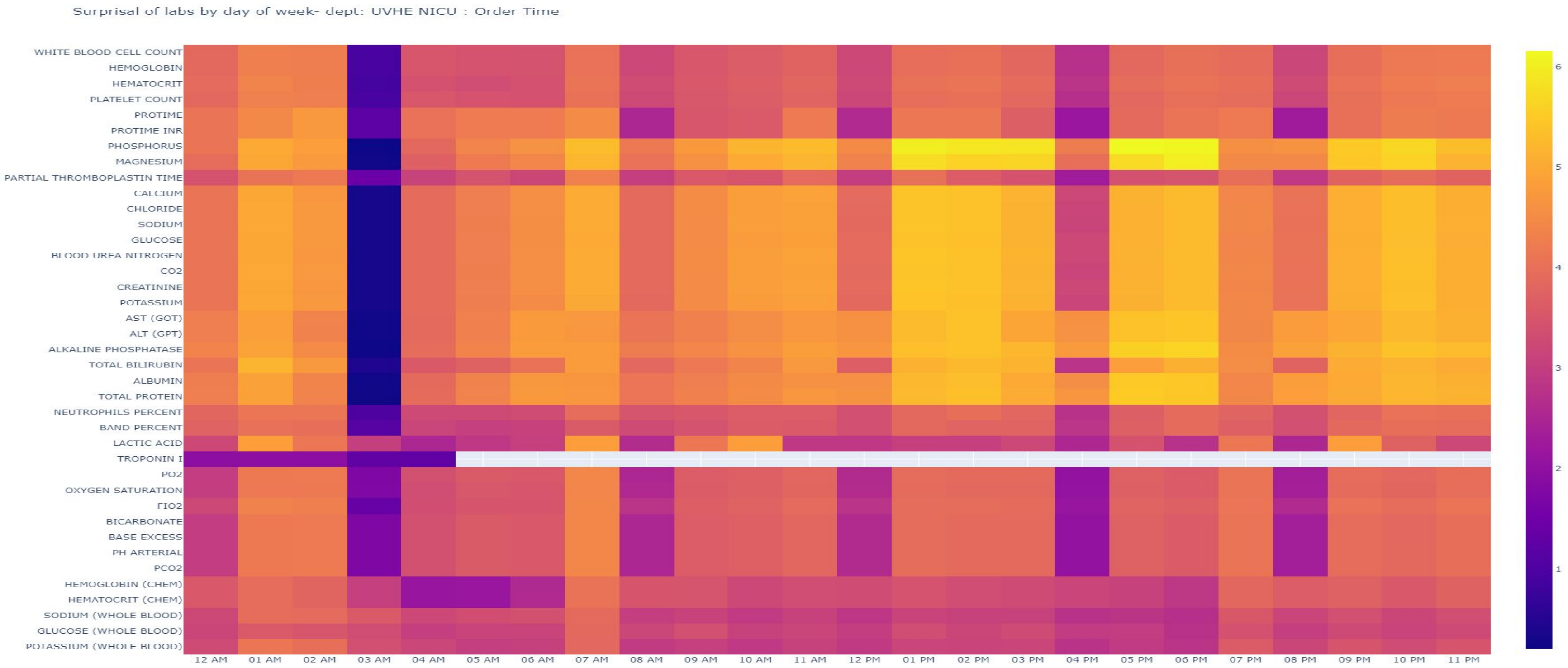
# Surprisal of labs by hour – UVa Hospital



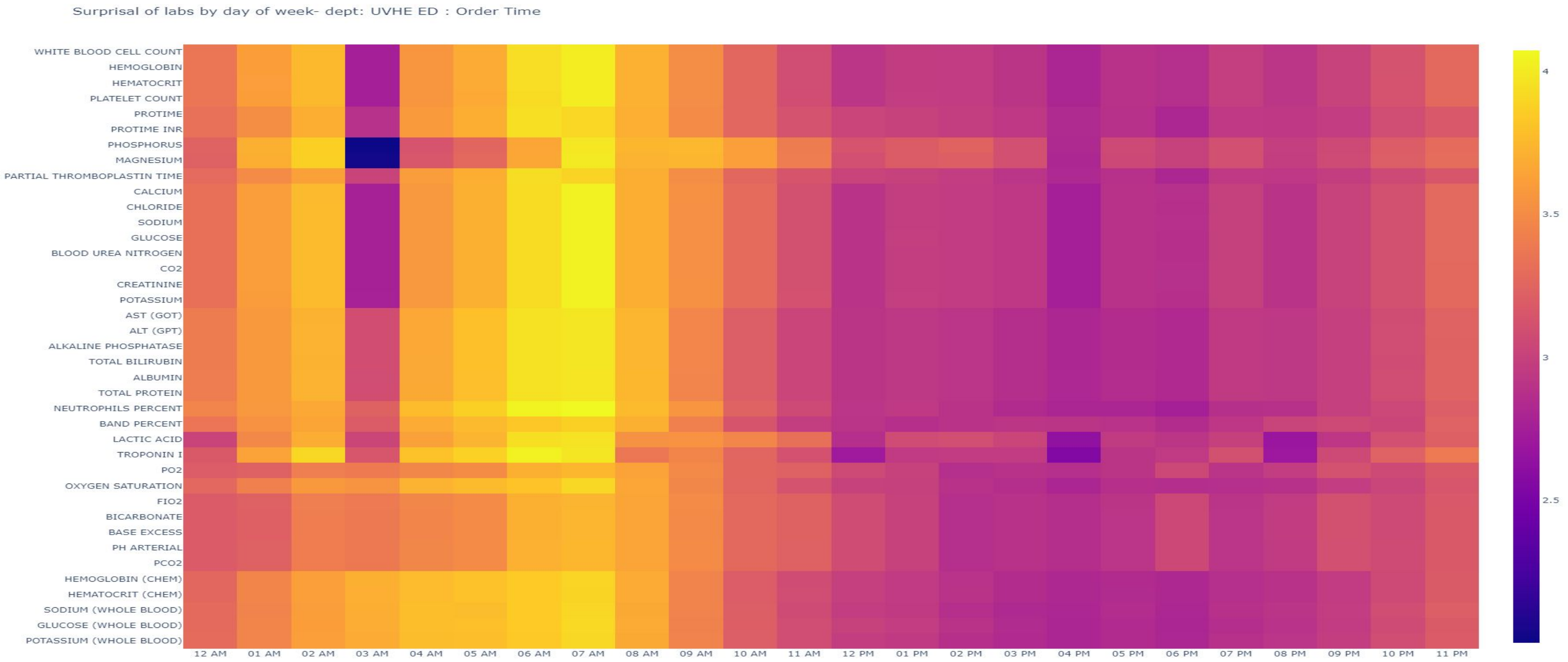
# Surprisal of lab by hour – 4East



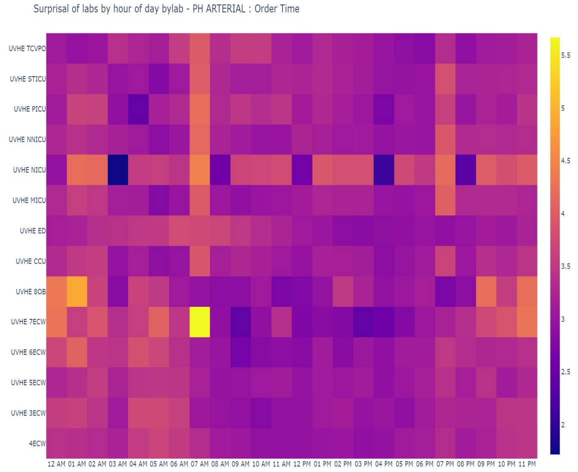
# Surprisal of labs by hour - NICU



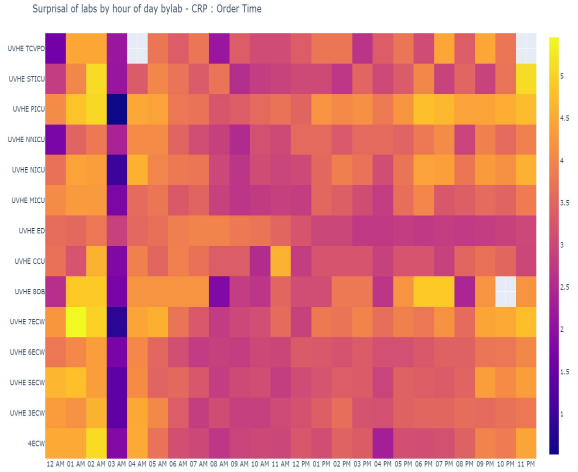
# Surprisal of labs by hour - ED



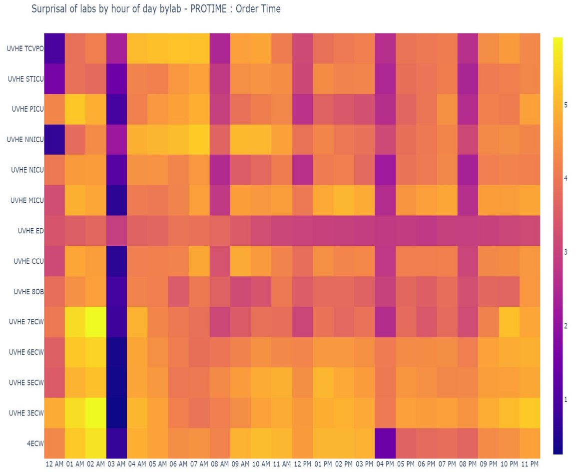
# Surprisal: By lab test




Arterial blood gas

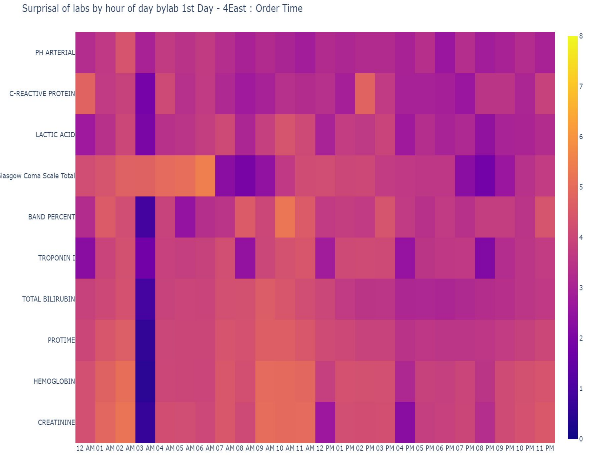



C-reactive protein

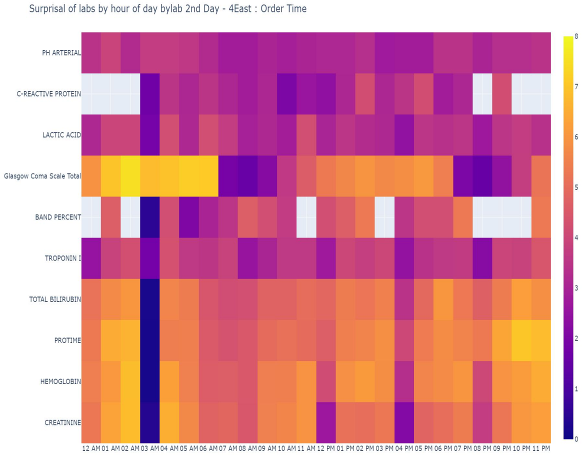



Prothrombin time

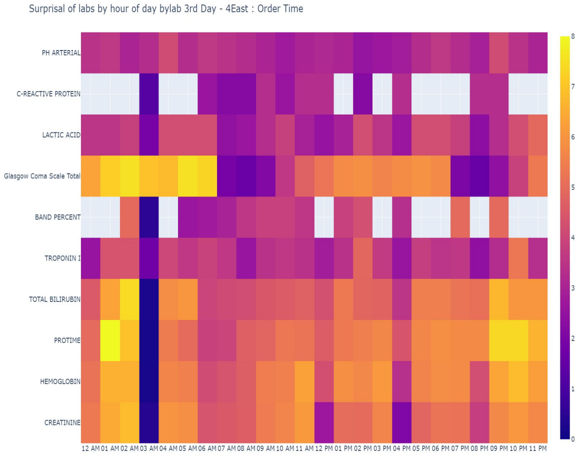
# Surprisal: By day of admission



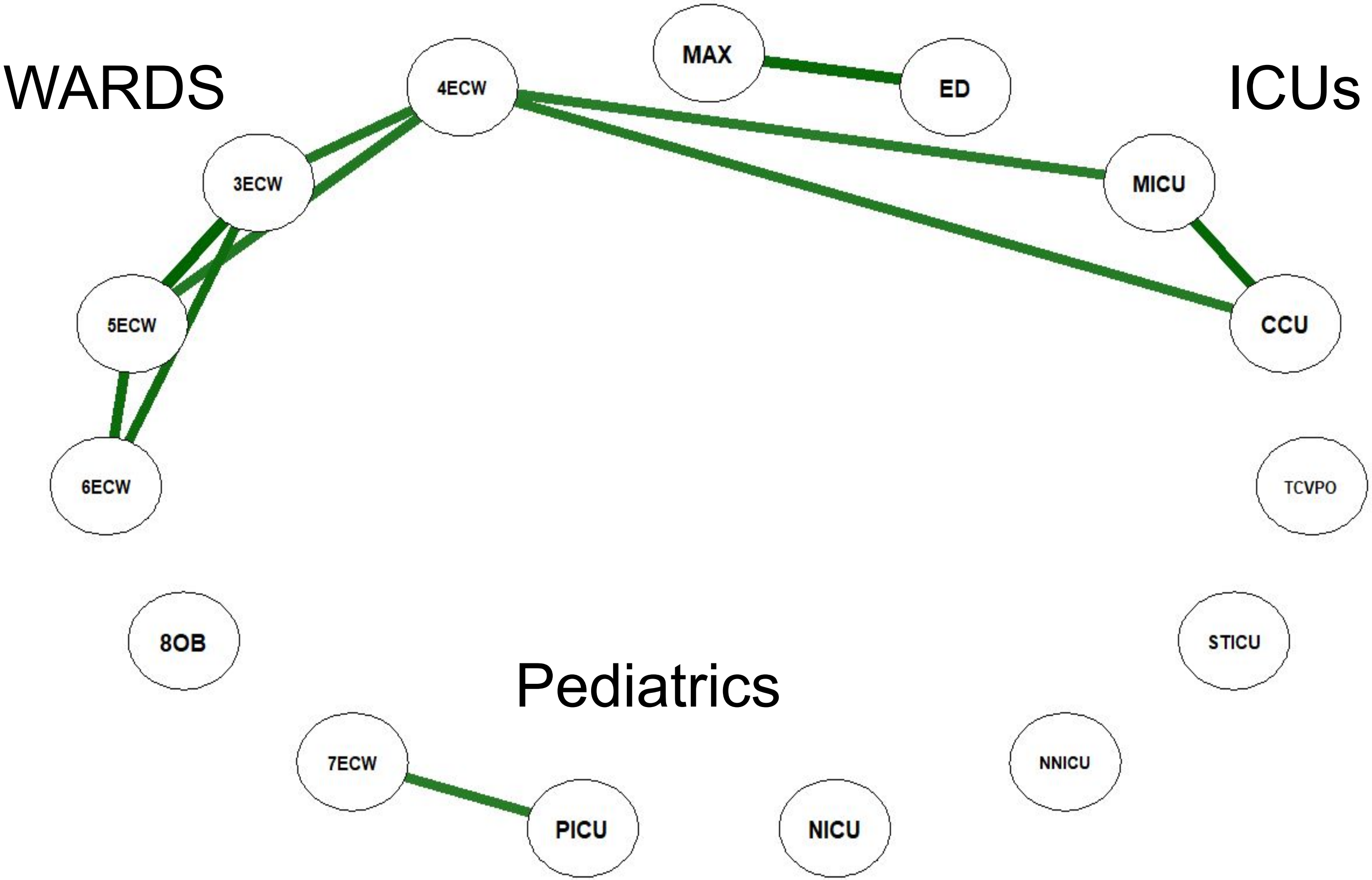

Admission



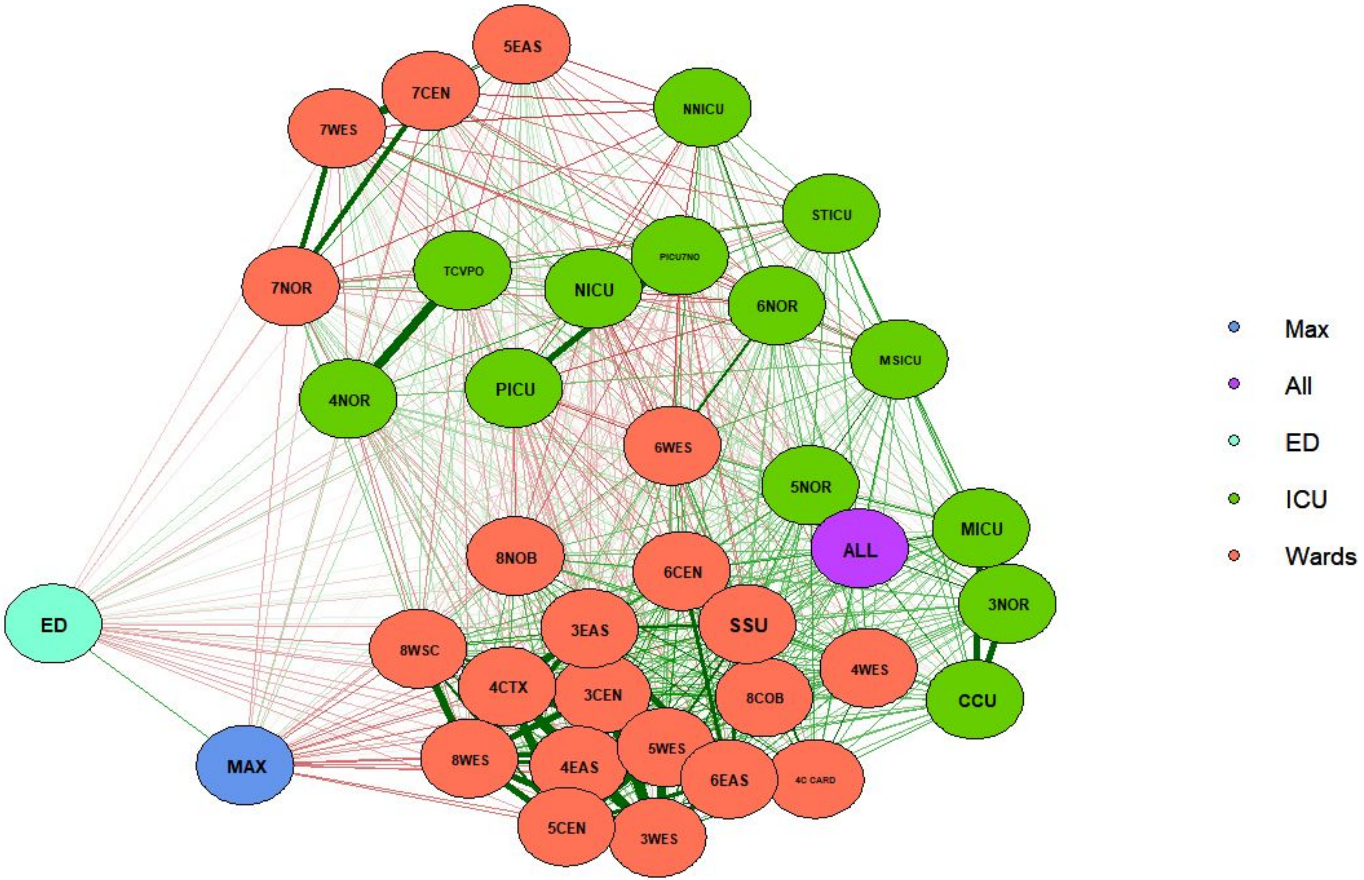

First hospital day




Second hospital day



WARDS
ICUs
Pediatrics
MAX
ED
4ECW
3ECW
5ECW
6ECW
8OB
7ECW
PICU
NICU
NNICU
STICU
TCVPO
CCU
MICU


5EAS
7CEN
7WES
NNICU
STICU
PICU7NO
TCVPO
NICU
7NOR
6NOR
MSICU
4NOR
PICU
6WES
5NOR
MICU
ALL
8NOB
6CEN
3NOR
ED
3EAS
SSU
8WSC
4WES
4CTX
3CEN
8COB
CCU
MAX
8WES
4EAS
5WES
6EAS
4C CARD
5CEN
3WES
Max
All
ED
ICU
Wards

# Summary

The ideas of network physiology can be extended by analysis of time series of new parameters identified by highly comparative time-series analysis

There are non-physiologic networks of importance in the care of the hospital patient