Integrative Physiology: A Source of Clinical Information

Sean Collins
Integrative Physiology & Dynamics

- Physiological dynamics: observable patterns in physiological variables over time (varying spatial & temporal scales)
Clinical Information

- Clinical information: Any variable that provides information about a human’s state – risk, disease status or classification, prognosis, etc – during a clinical evaluation.

Not surprising that dynamics (variance) provides an additional source of information as compared to only accounting for central tendency or amplitude.
Clinical Evaluation

- Process of abductive inference where we observe effects to draw inferences of cause
- Cause -> Effect (X -> Y)
- An individual has Y (which may be a set or pattern of information); and Y is an effect caused by X; therefore X
- Also called inference to the best explanation and the Inverse problem
Simple examples

• High cholesterol -> increase CVD risk
  – If also Lo HDL -> further increase
  – If also Hi LDL -> further increase
• Diabetes -> increased CVD risk
  – If also Lo HRV -> further increase
• Low physical function, despite relatively preserved organ function -> improved prognosis (Pulmonary example)
• Can we make better predictions by considering more data (temporal and/or spatial)?
Integrative Physiology related challenges in medicine

- Determining an individual’s state of health
- Monitoring health in a “healthy” person
- Diagnosing illness in an “unhealthy” person
- Inverse problem poses major barrier between clinical decision making and computational approaches to decision making
WHY ARE THE MEDICAL APPLICATIONS SO DIFFICULT?

• Models Work Well When They Are Used to Determine Effects From Causes [i.e., to PREDICT Results From Varied Internal Model Conditions]

• Complicated Models Are Not Easy to Use to Determine Causes From Effects [i.e., to PREDICT Internal Model Conditions From Defined Results – Generally Not Unique]
General Assumptions in my research agenda

• Assumption 1: there are far more dynamic patterns available than are currently utilized
• Assumption 2: understanding these patterns will improve physiological & clinical understanding
• General Approach: discerning clinically meaningful dynamic patterns requires an integrative physiological approach that combines empirical and theoretical of processes & disease states
General Questions

• What do patterns of dynamic processes tell us about pre-clinical and clinical status?

• Are there new pre-clinical states signifying physiological de-regulation that have alluded observation due to a lack of altered homeostasis and/or structural damage?

• How does understanding dynamic patterns improve clinical information (i.e. understanding, prediction, intervention) – are their patterns that have a stronger effect to cause mapping to solve the inverse problem?
Heart rate variability

- Are patterns of heart rate variability (HRV) associated with job strain, low social control, fatigue, exhaustion?
- Are patterns of vagal autonomic regulation associated with job strain or exhaustion?
- Are patterns of change in the ECG related to signs of fatigue?
Heart Rate (HR) – Heart Rate Variability (HRV)

Figure 1. Normal R-R intervals from an electrocardiogram.
Heart Rate – 48 Ambulatory Hours

Collins et al, AJIM, 2005
HR & HRV – 48 Ambulatory Hours

Collins et al, AJIM, 2005
HR & HRV – 48 Hours (q 1 hour)

Collins et al, AJIM, 2005
Action potential of sino-atrial node
Heart rate consistency....

Control Subject

Cardiac Transplant Subject

Figure 16.4. Distribution of sympathetic and parasympathetic nerve fibers to the myocardium. Sympathetic nerve fiber endings secrete the neurohormone epinephrine. Sympathetic fibers supply the SA and AV nodes and the muscle of the atria and ventricles. Parasympathetic nerve endings secrete acetylcholine. These fibers concentrate in the atria, including the SA and AV nodes.

Copyright © 2001 Lippincott Williams & Wilkins
Figure 16.10. A. Regulation of heart rate under normal conditions. Heart transplantation results in cardiac deavervation. This removes vagal and sympathetic efferent stimulation to the myocardium. Consequently, circulating epinephrine from the adrenal medulla provides the primary mechanism to regulate exercise heart rate.

Copyright © 2001 Lippincott Williams & Wilkins
Sympathetic division:
- Dilates pupil
- Inhibits salivation and tearing
- Lacrimal and salivary glands
- Eye
- Lungs
- Cranial
- Constricts pupil
- Odorimeter nerve (III)
- Facial nerve (VII)
- Glosopharyngeal nerve (IX)
- Cervical
- Constricts airways
- Accelerates heartbeat
- Heart
- Liver
- Inhibits digestion
- Stimulates glucose production and release
- Stimulates secretory function of epinephrine and norepinephrine from adrenal gland
- Thoracic
- Stomach
- Pancreas
- Stimulates digestion
- Stimulates pancreas to release insulin and digestive enzymes
- Lumbar
- Adrenal gland
- Kidney
- Large intestine
- Rectum
- Sympathetic chain
- Relaxes urinary bladder
- Bladder
- Stimulates urinary bladder to contract
- Sacral
- Small intestine
- Thoracic
- Veus nerve (X)
- Lumbar
- Cervical
- Sympathetic chain
- Cranial
- Constricts airways
- Accelerates heartbeat
- Heart
Sympathetic (adrenergic) receptor stimulation increases heart rate.
Parasympathetic (vagal, cholinergic) receptor (muscarinic) decreases heart rate
HRV : Autonomic Physiology

Both the rate and variation of heart beats are the result of a complex interaction of the PNS and SNS.

PNS: hyperpolarizes SA node
   Due to high turnover of ACTH SA node responds faster = greater variation & higher frequency of periodic fluctuations.
   Partly responsible for RSA.

SNS: stimulates SA node = rapid firing
   Also less variance & lower frequency of periodic fluctuations
Fig. 1. Trendgrams showing fluctuation of beat-to-beat R–R interval in various conditions. R–R intervals were measured from 2-min ECG in a healthy young subjects during supine rest (A), mental arithmetic stress testing (B), and ergometer exercise testing (C) and in a patients with severe congestive heart failure at rest (D).
Job Strain & HRV Study:
General Statistical Modeling of Contrasts:
Multilevel/Hierarchical Data Structure

Age, Gender, Condition, etc.

ID=1

Low Control
High Demands

ID=2

ID=3

High Control
Low Demands

ID=4

ID=N

W
S
R
S

W
S
R
S

W
S
R
S

W
S
R
S

W
S
R
S
Power Spectrum
Extract variance for vagal activity

2 Hour vagal activity series

5 Minute RR Series
Beat-to-Beat Variability
RR Interval Series
5 – Minutes
Frequency Analysis – HFP (.15-.4 Hz)

System Regulation
HFP Time Series
(Vagal Control)
4 Hours (= 48 Epochs)

Regulatory System Variance

1 Epoch
Poincaré Plot for Entire Monitoring Period

Vagal Activity

Vagal Activity (+1 Epoch)

Line of Identity
Poincaré Plot for Low Strain Subject at Work

\[ R^2 = 0.552 \]
Poincaré Plot for High Strain Subject at Work

Vagal Activity

\[ R^2 = .641 \]
Poincaré Plot for Exhausted Subject at Work

\[ R^2 = .785 \]
Short Term Variation as Determined by Poincaré Plot Residuals
Berntson’s Doctrine of Autonomic Space

Sympathetic Activity

Parasympathetic Activity

Reciprocal:

Non-Reciprocal: Co – Activation & Co – Inhibition

UnCoupled – Sympathetic Activation
Autonomic Space & Overlying Functional Surface

Bernston et al, 1991
<table>
<thead>
<tr>
<th>Autonomic Dominance</th>
<th>Coordination Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sympathetic</td>
<td>Reciprocal</td>
</tr>
<tr>
<td></td>
<td>Unclassified</td>
</tr>
<tr>
<td></td>
<td>Other</td>
</tr>
<tr>
<td>Parasympathetic</td>
<td>Reciprocal</td>
</tr>
<tr>
<td></td>
<td>Unclassified</td>
</tr>
<tr>
<td></td>
<td>Other</td>
</tr>
</tbody>
</table>

- Subjects HR > Mean
- Subjects HR < Mean

If: HFPnu > .1 SD & Res HR < -.1 SD
OR
If: HFPnu < -.1 SD & Res HR > .1 SD

If: HFPnu and ResHR > .1 SD
If: HFPnu and ResHR < -.1 SD
If: HFPnu < .1 and > -.1 SD and ResHR > .25 or < -.25 SD
If: If: ResHR < .1 and > -.1 SD and HFPnu > .25 or < -.25 SD
Bernston’s Doctrine of Autonomic Space
Reciprocal Sympathetic Control

Bernston’s Doctrine of Autonomic Space
Reciprocal Sympathetic Control

Mean Reciprocal, Sympathetic

Strain & Exhaustion

- Low Strain
- High Strain
- Exhusted
Bernston’s Doctrine of Autonomic Space
Non Reciprocal Parasympathetic Control

Mean Non-Reciprocal, Parasympathetic

Strain & Exhaustion

- Exhausted
- High Strain
- Low Strain

Sociological Period
Current Work: HR Dynamics

• Are there non-linear heart rate dynamics that identify “system” exhaustion and denote a pre clinical physiological sign of “vital exhaustion” – or stress disequilibrium

• (Same collaborators)
Current Work: HR dynamics with exercise

- Do changes in HR dynamics during exercise provide additional information about pre-clinical status; or physiological response to demands?

Collaborator: John Ames, Qinetiq
Current Work: Pulse transit time (PTT)

- Does the HR – PTT; and/or HRV – PTTv pattern provide useful clinical information about cardiac autonomic – hemodynamic regulation?
- Relate to mechanisms by which low HRV is associated with CVD risk
Do you see the pattern?

• Pretty much any variable that we can collect data and create a time series has the potential to display informative dynamics – just need to look.

• Since there are so many possibilities – I limit myself to those with clinical information potential – those with a question toward practical utility.

• Much time is spent up front reasoning through what you expect to find and why……

• Empirical evidence is compared to models of our expectations.