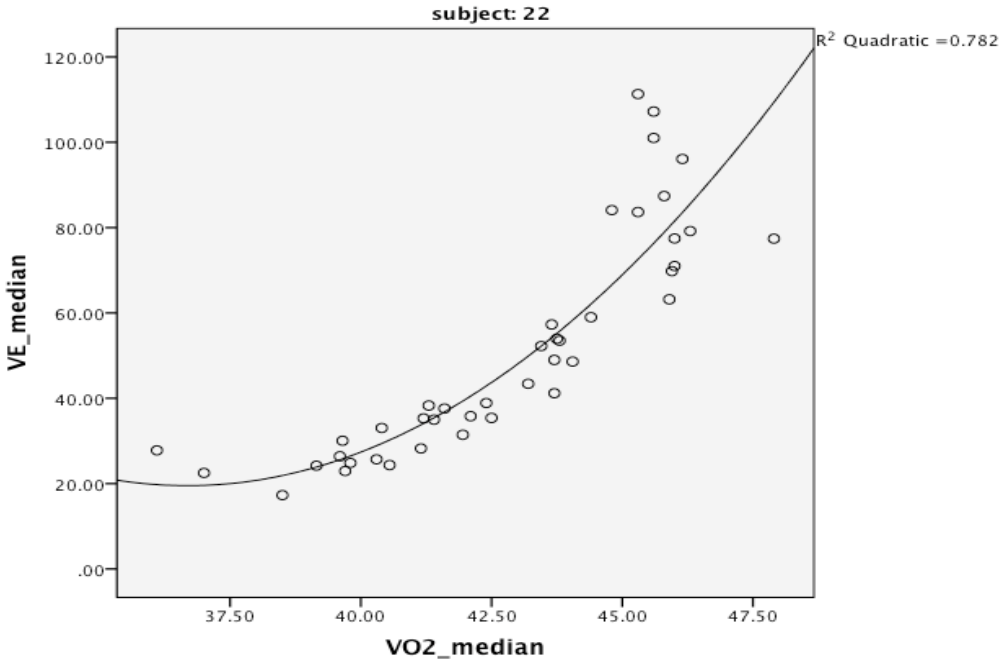
Integrative Physiology: A Source of Clinical Information

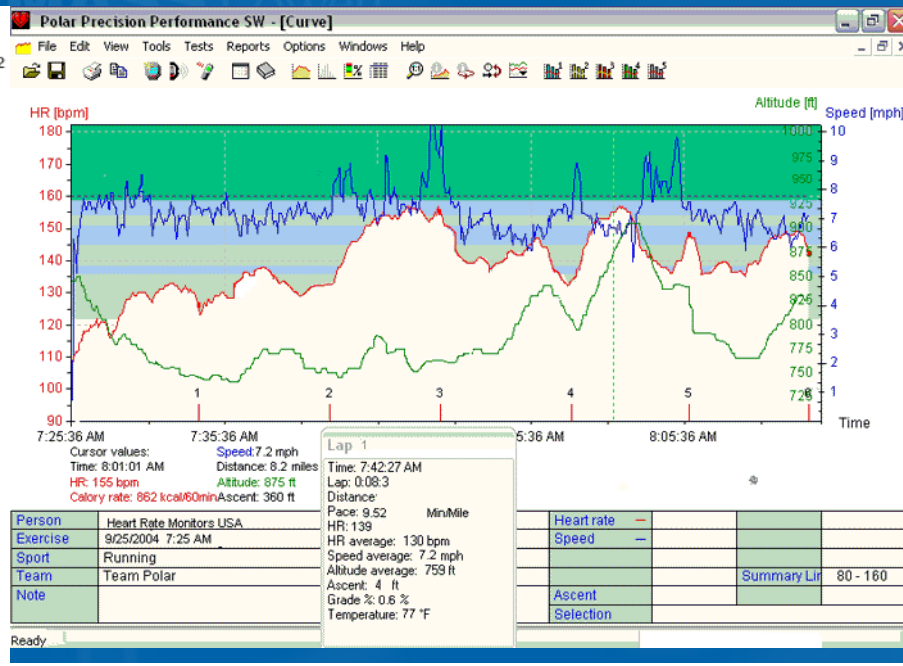
Sean Collins

University of Massachusetts Lowell

Integrative Physiology & Dynamics

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





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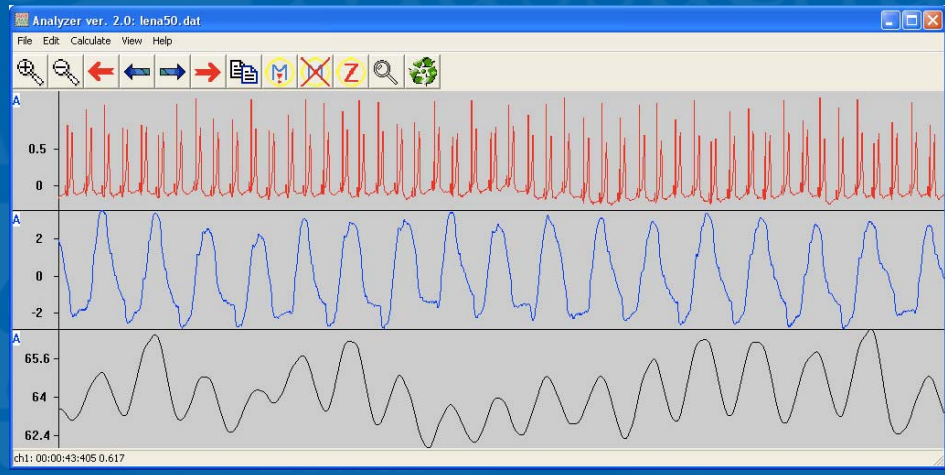
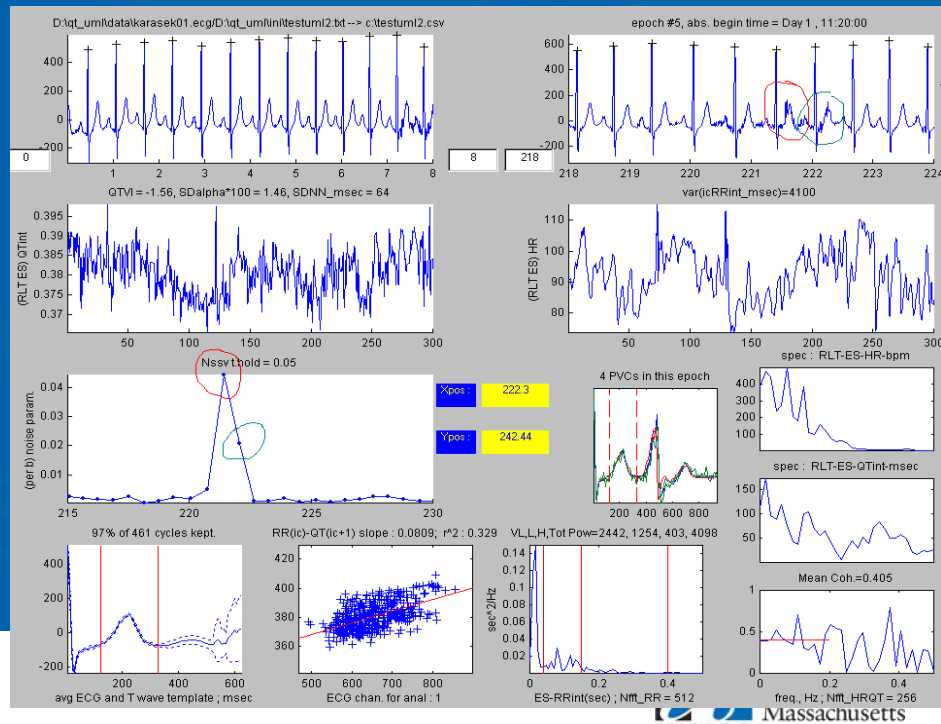
Clinical Information

- 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)





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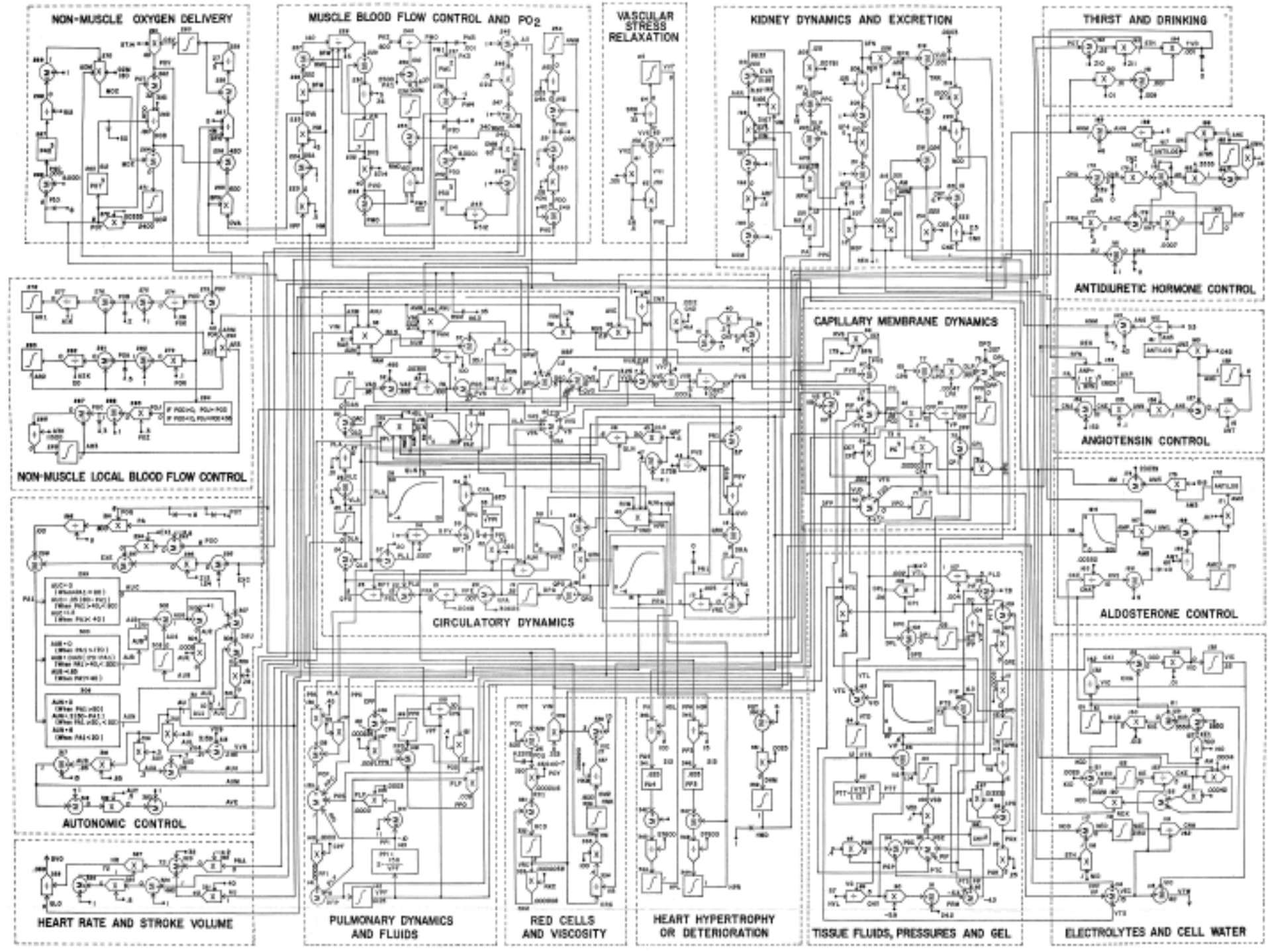
Clinical Evaluation

- 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)?


NON-MUSCLE OXYGEN DELIVERY
MUSCLE BLOOD FLOW CONTROL AND PO_2
VASCULAR STRESS RELAXATION
KIDNEY DYNAMICS AND EXCRETION
THIRST AND DRINKING
ANTIDIURETIC HORMONE CONTROL
ANGIOTENSIN CONTROL
ALDOSTERONE CONTROL
CAPILLARY MEMBRANE DYNAMICS
NON-MUSCLE LOCAL BLOOD FLOW CONTROL
CIRCULATORY DYNAMICS
AUTONOMIC CONTROL
HEART RATE AND STROKE VOLUME
PULMONARY DYNAMICS AND FLUIDS
RED CELLS AND VISCOSITY
HEART HYPERTROPHY OR DETERIORATION
TISSUE FLUIDS, PRESSURES AND GEL
ELECTROLYTES AND CELL WATER

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

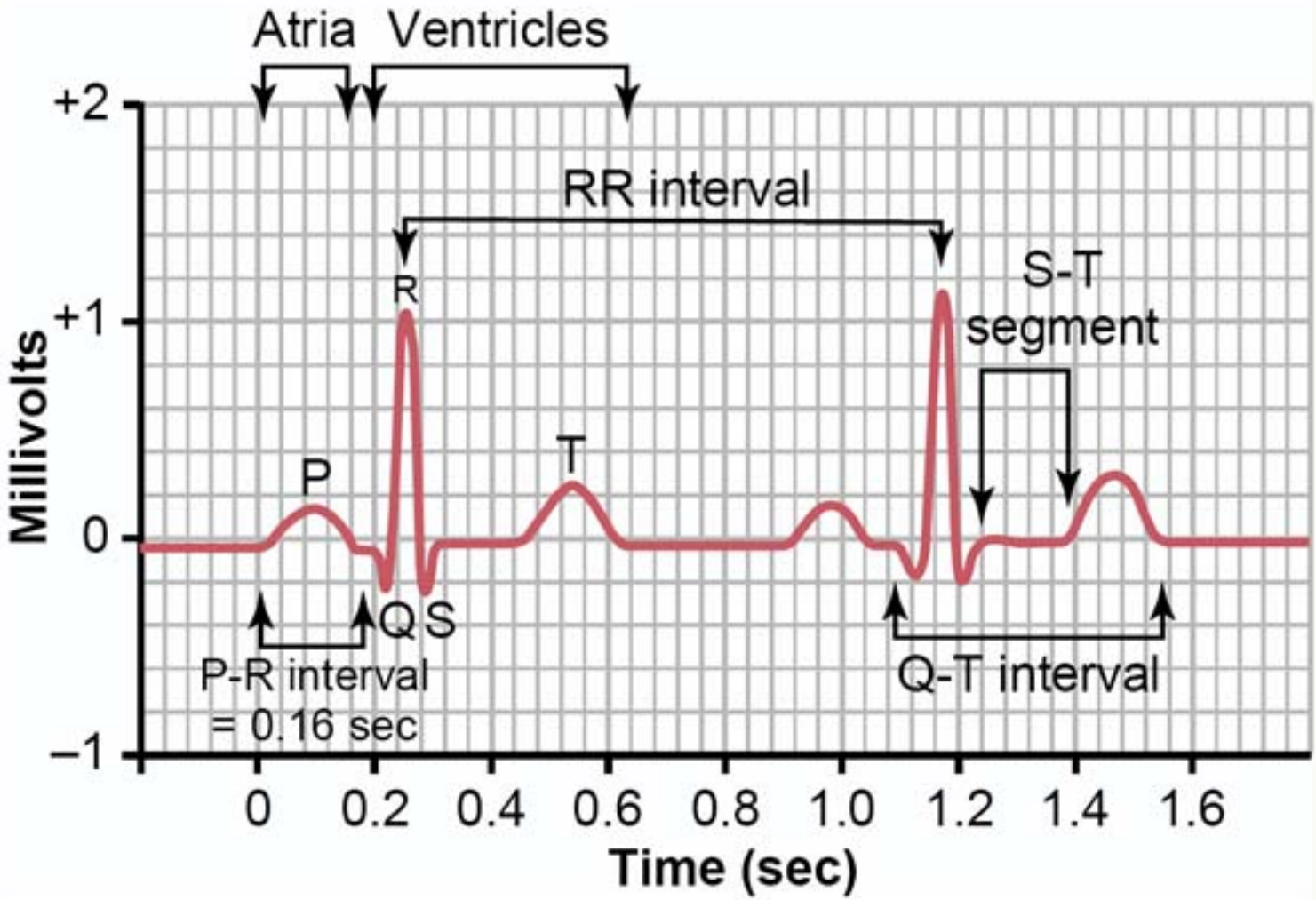
- Assumption 1: there are far more dynamic patterns available than are currently utilized
- Assumption 2: understanding these patterns will improve physiological & clinical understanding
- General Approach: discerning clinically meaningful dynamic patterns requires an integrative physiological approach 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)

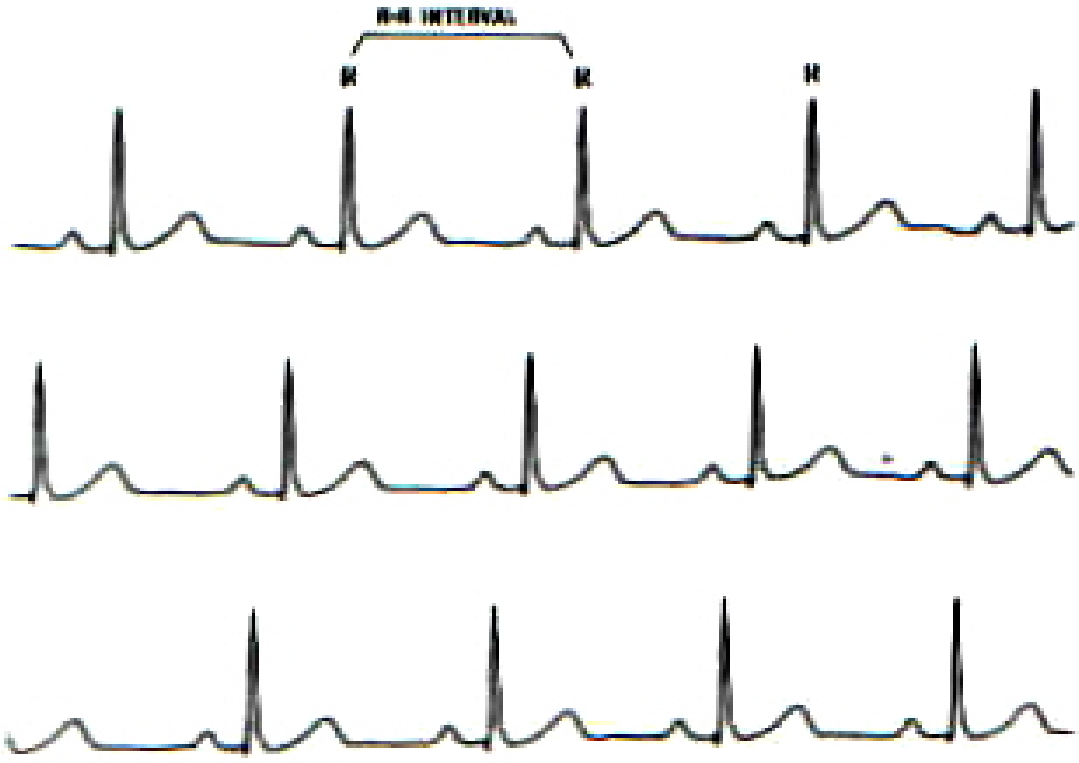
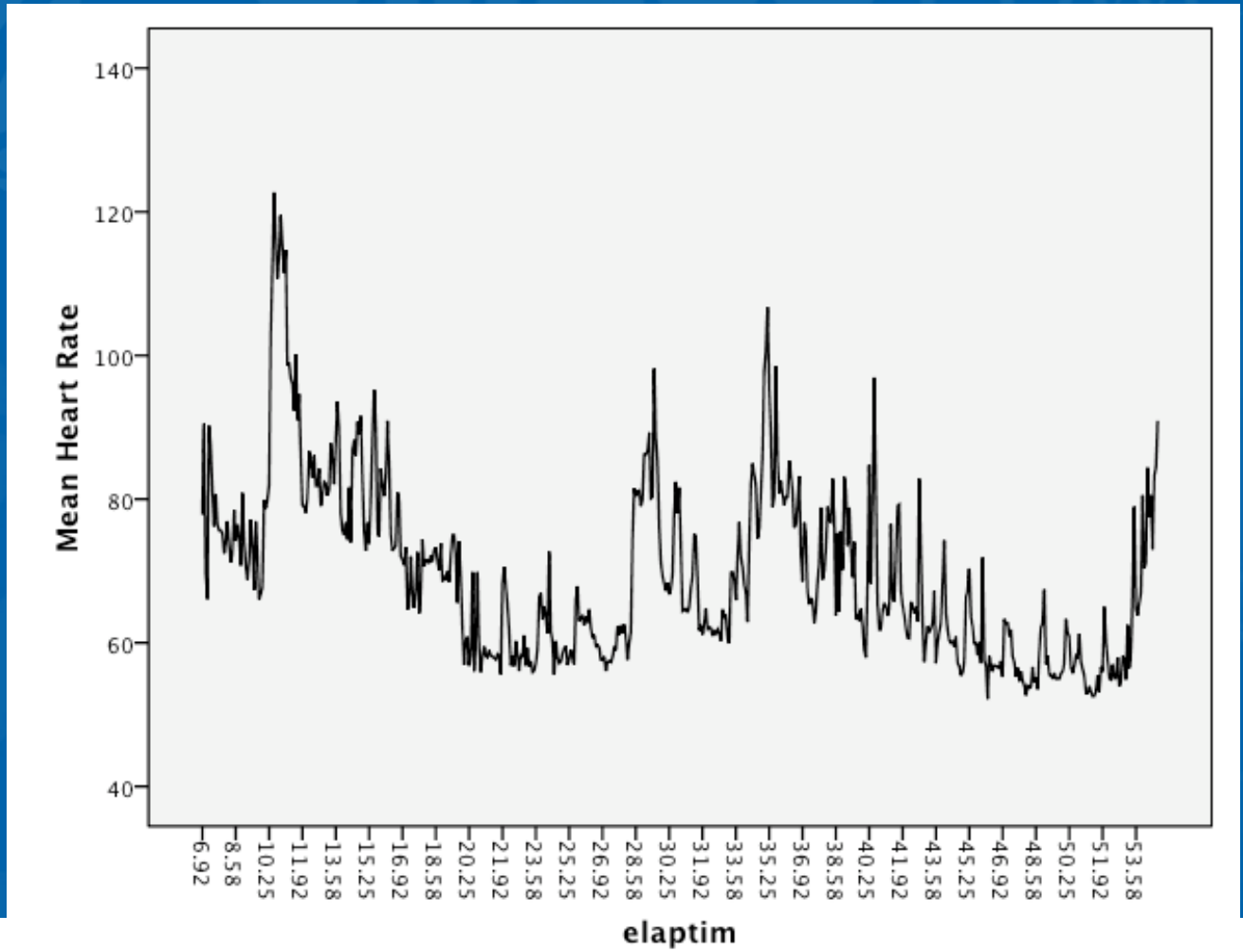


Figure 1. Normal R-R intervals from an electorcardiogram.

Heart Rate – 48 Ambulatory Hours



Collins et al, AJIM, 2005

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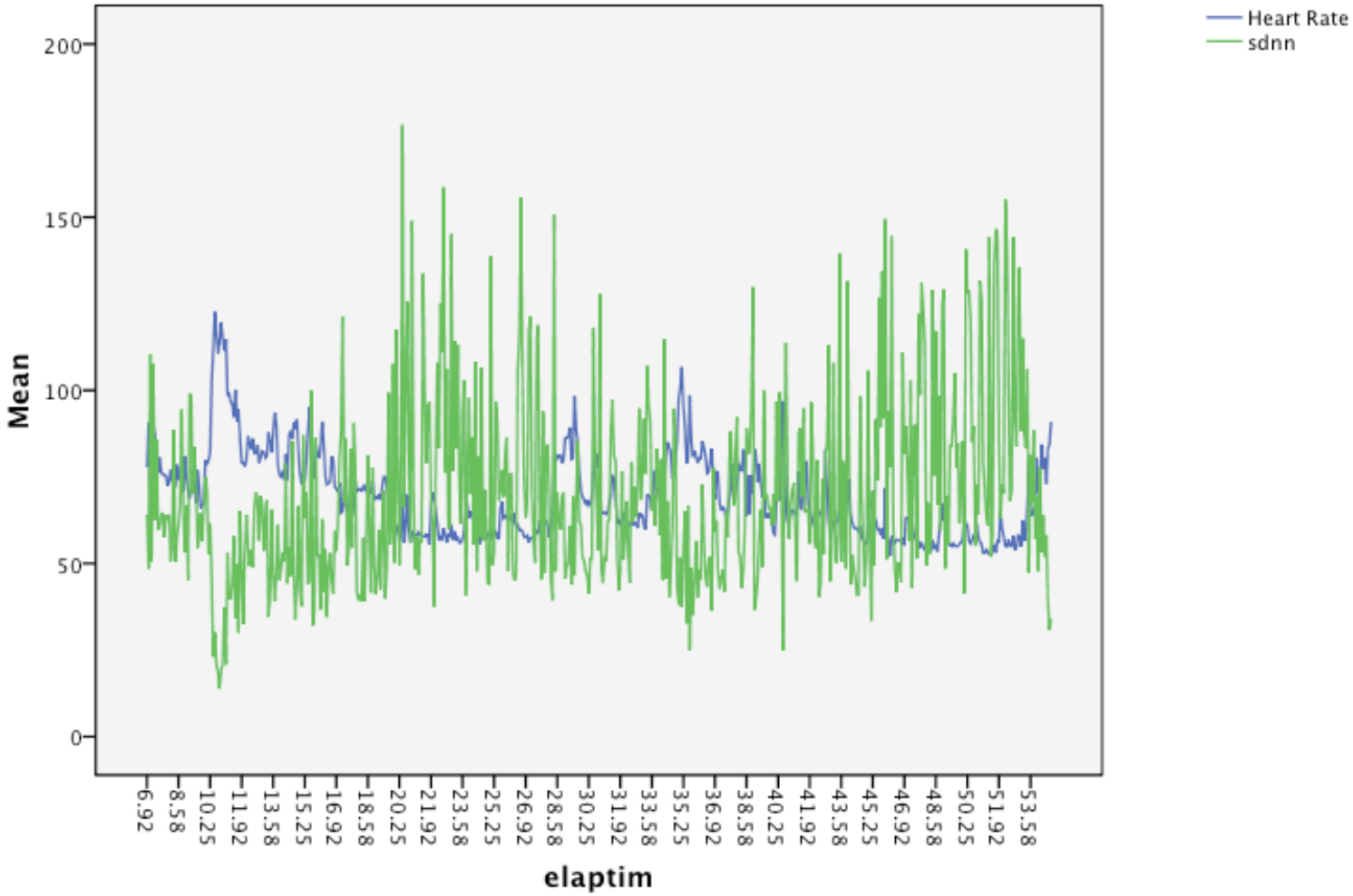
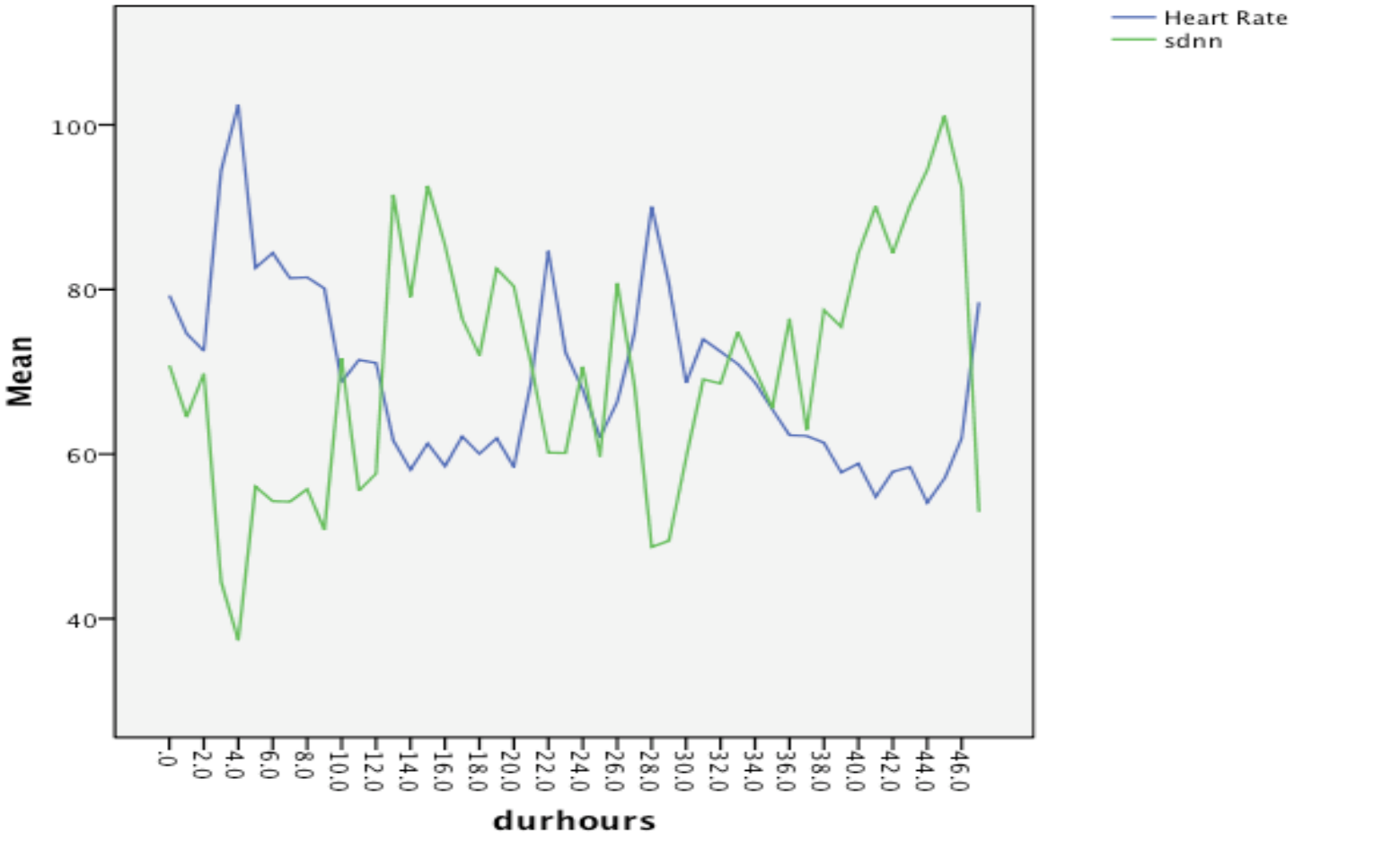
HR & HRV – 48 Ambulatory Hours



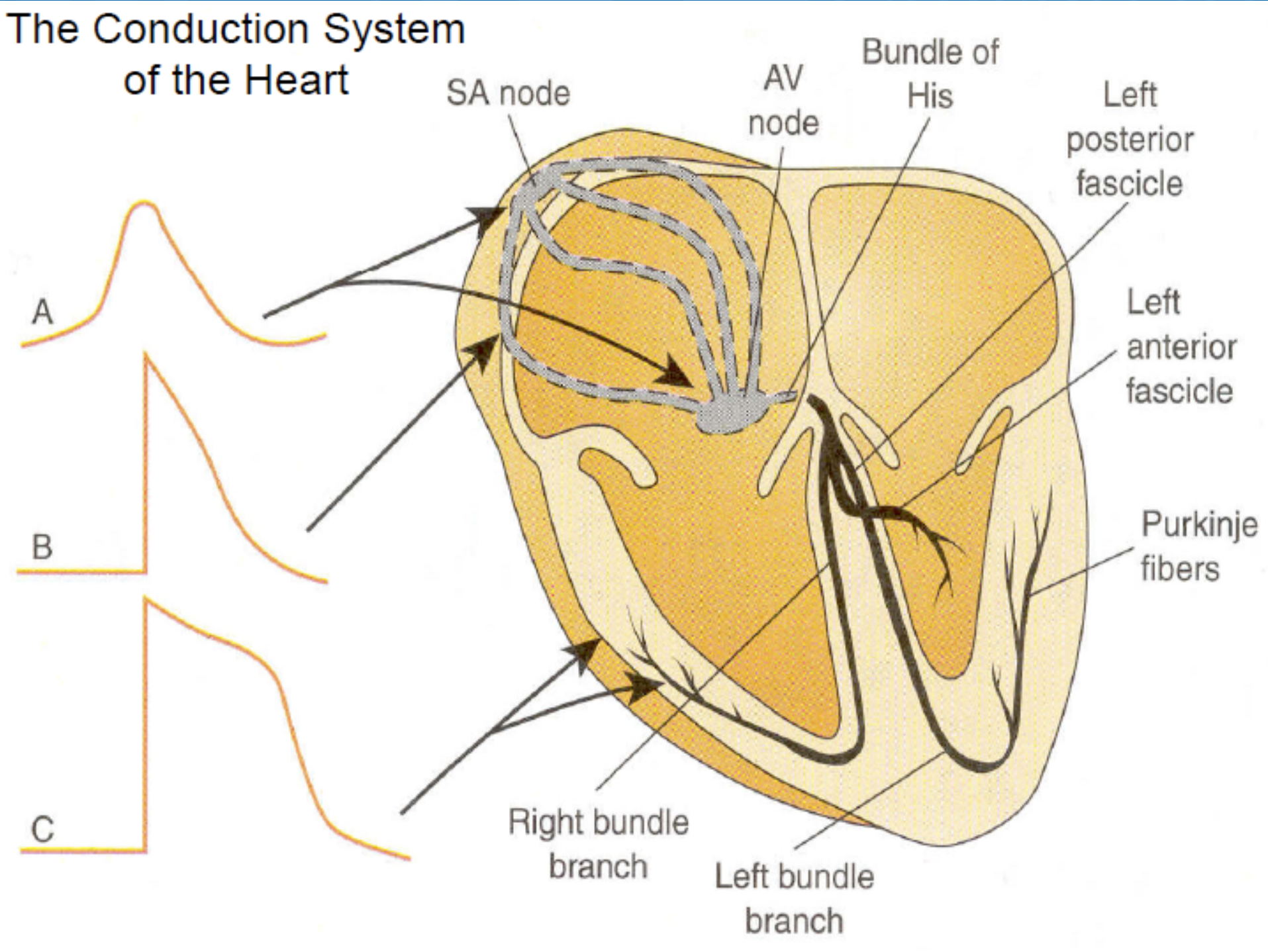
Collins et al, AJIM, 2005

HR & HRV – 48 Hours (q 1 hour)

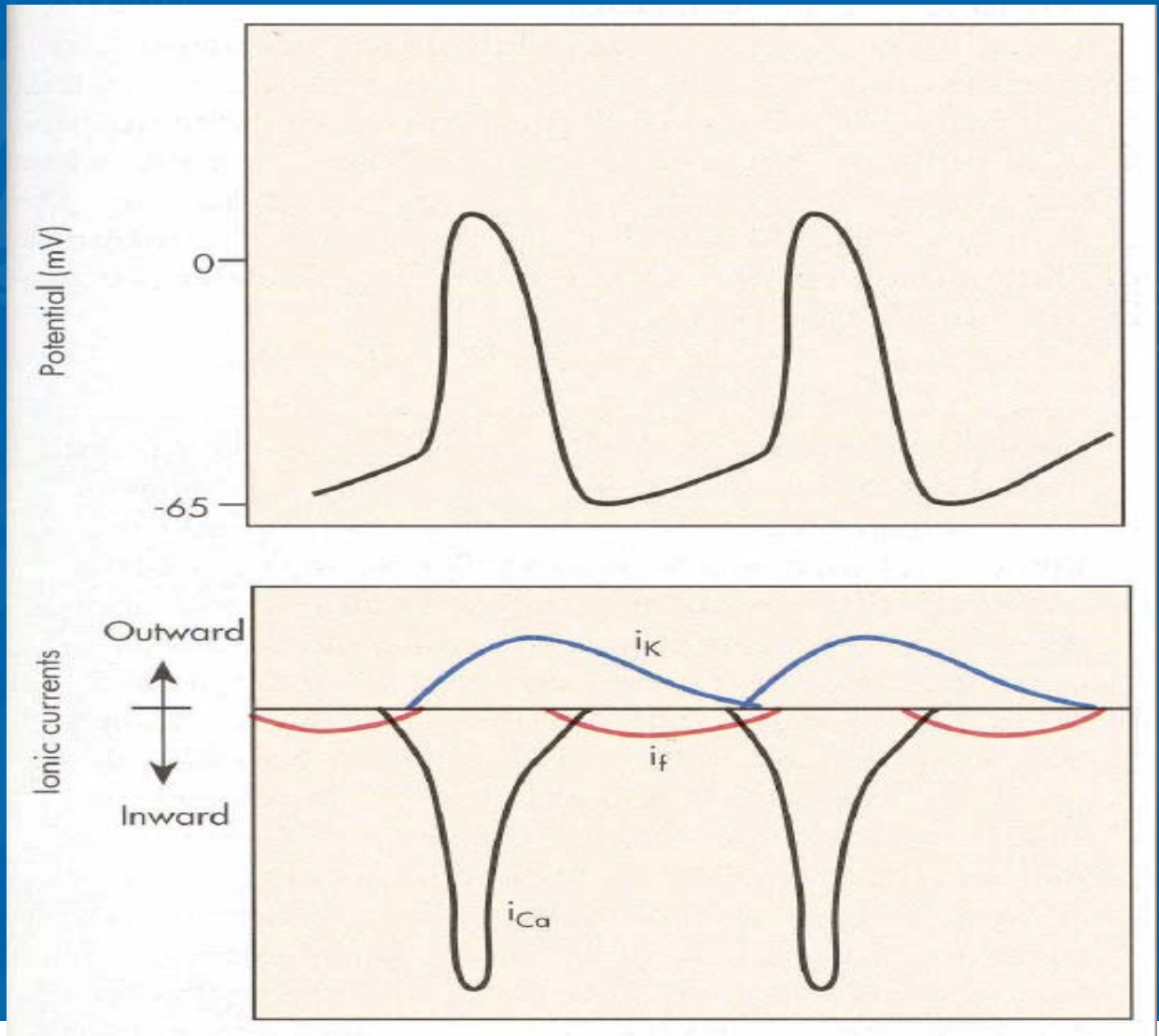


Collins et al, AJIM, 2005

The Conduction System of the Heart

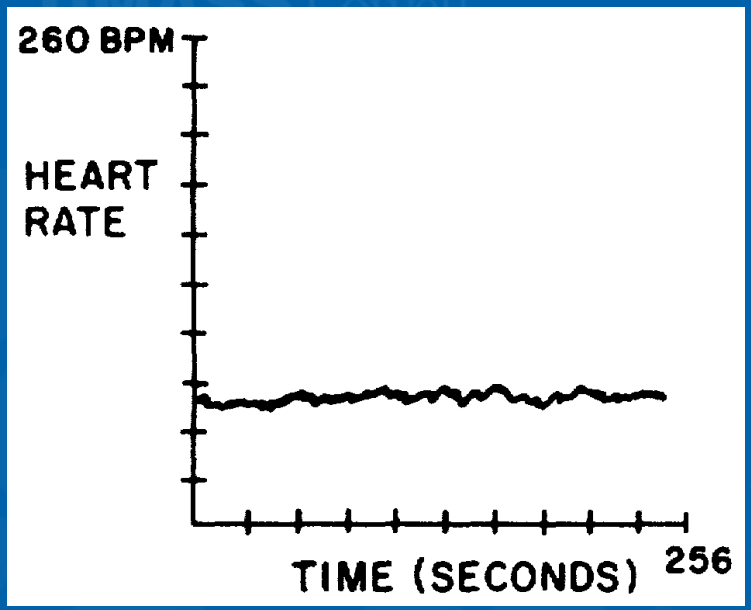


Action potential of sino-atrial node

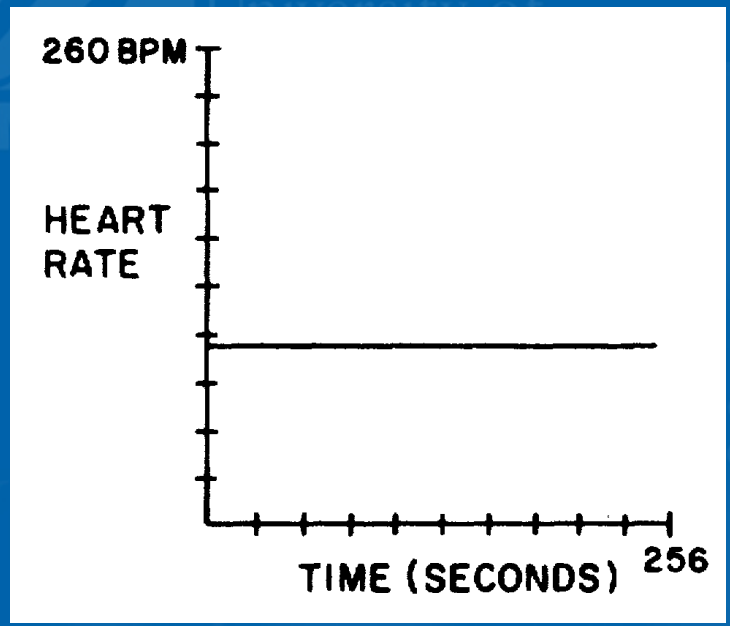


Heart rate consistency….

Control Subject



Cardiac Transplant Subject



Sands KEF, et al, Circulation 79:76-82, 1989

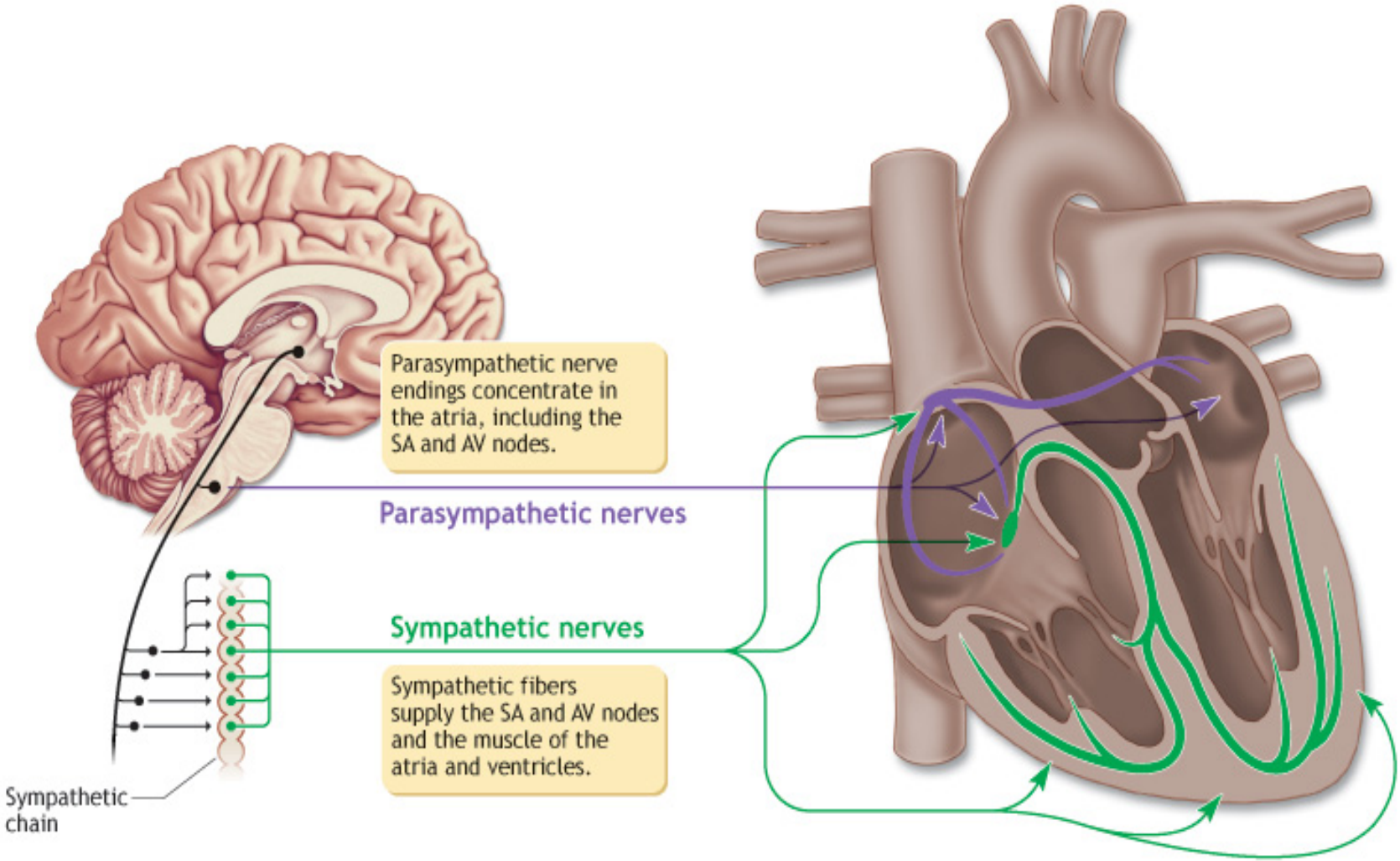


Figure 16.4. Distribution of sympathetic and parasympathetic nerve fibers to the myocardium. Sympathetic nerve fiber endings secrete the neurohormone epinephrine. Sympathetic fibers supply the SA and AV nodes and the muscle of the atria and ventricles. Parasympathetic nerve endings secrete acetylcholine.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

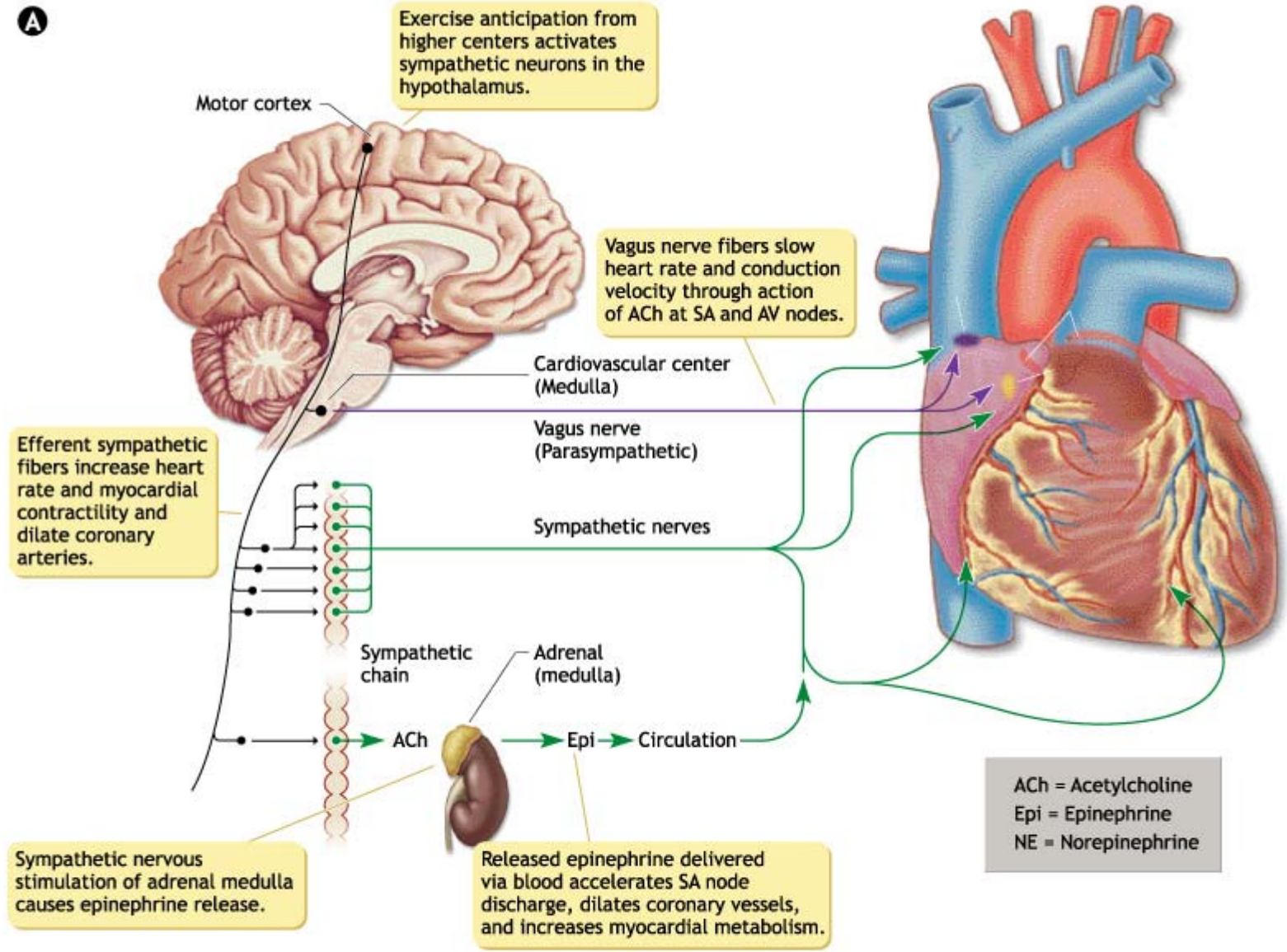
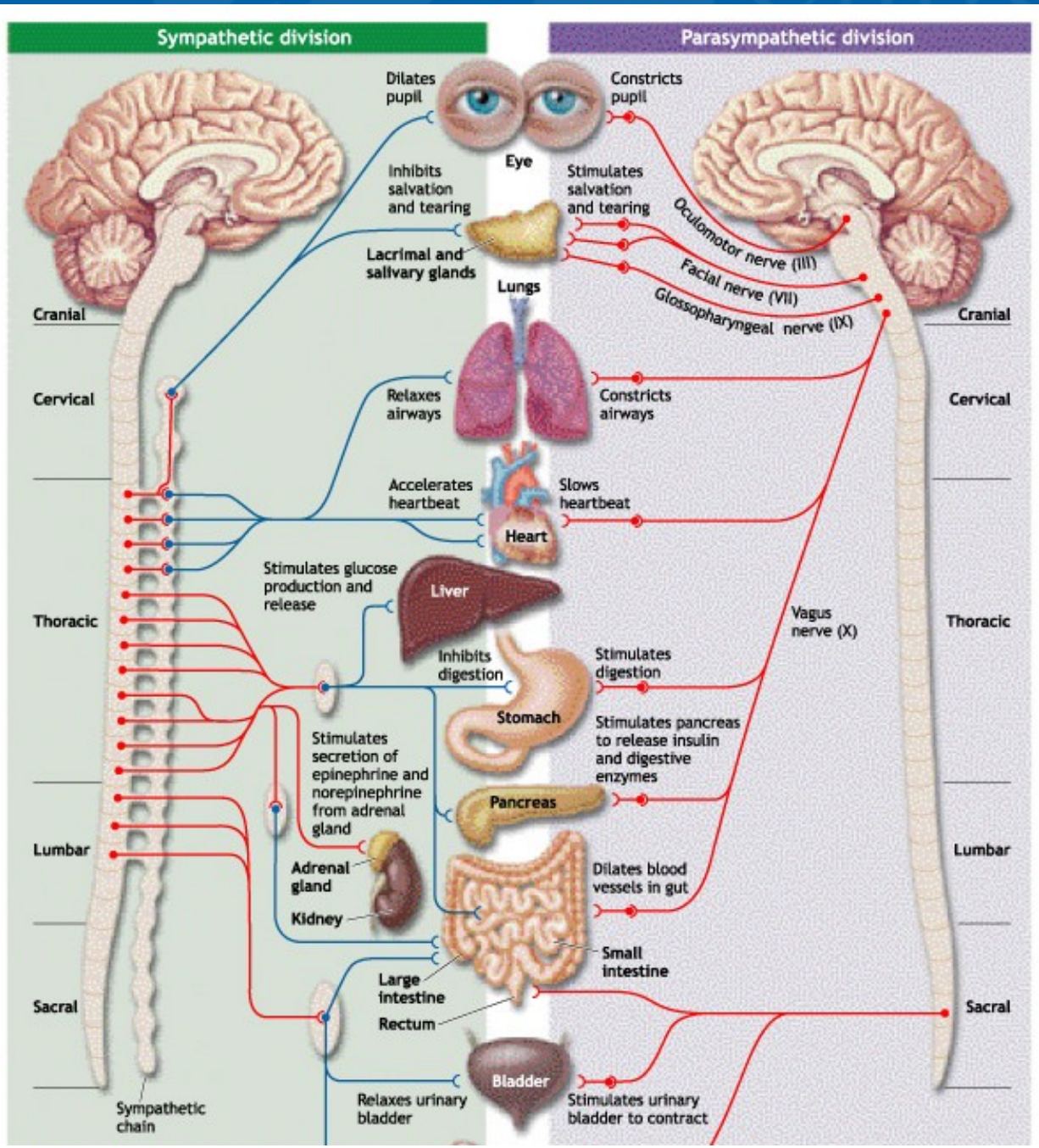


Figure 16.10. A. Regulation of heart rate under normal conditions. Heart transplantation results in cardiac denervation. This removes vagal and sympathetic efferent stimulation to the myocardium. Consequently, circulating epinephrine from the adrenal medulla provides the primary mechanism to regulate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



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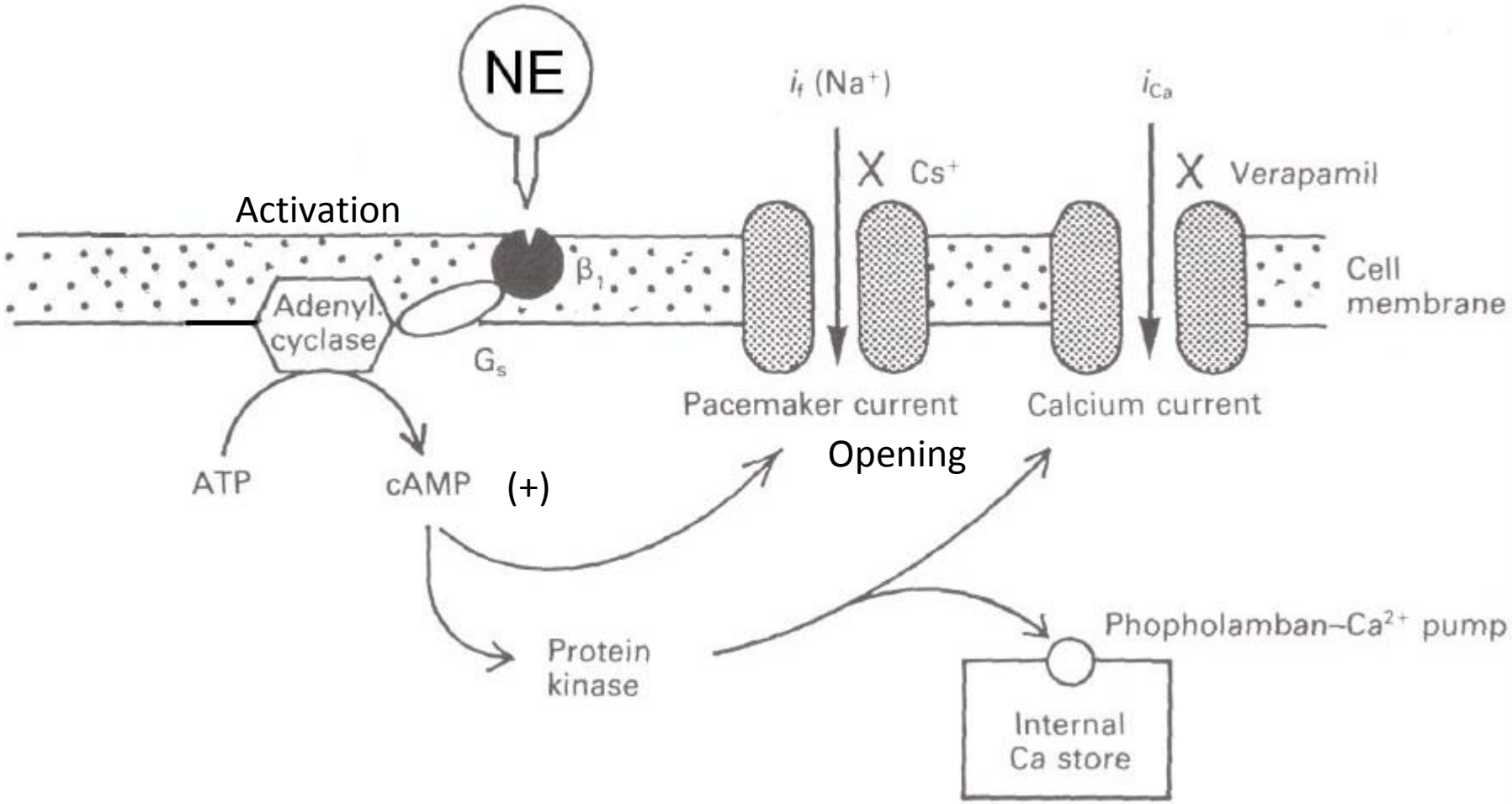
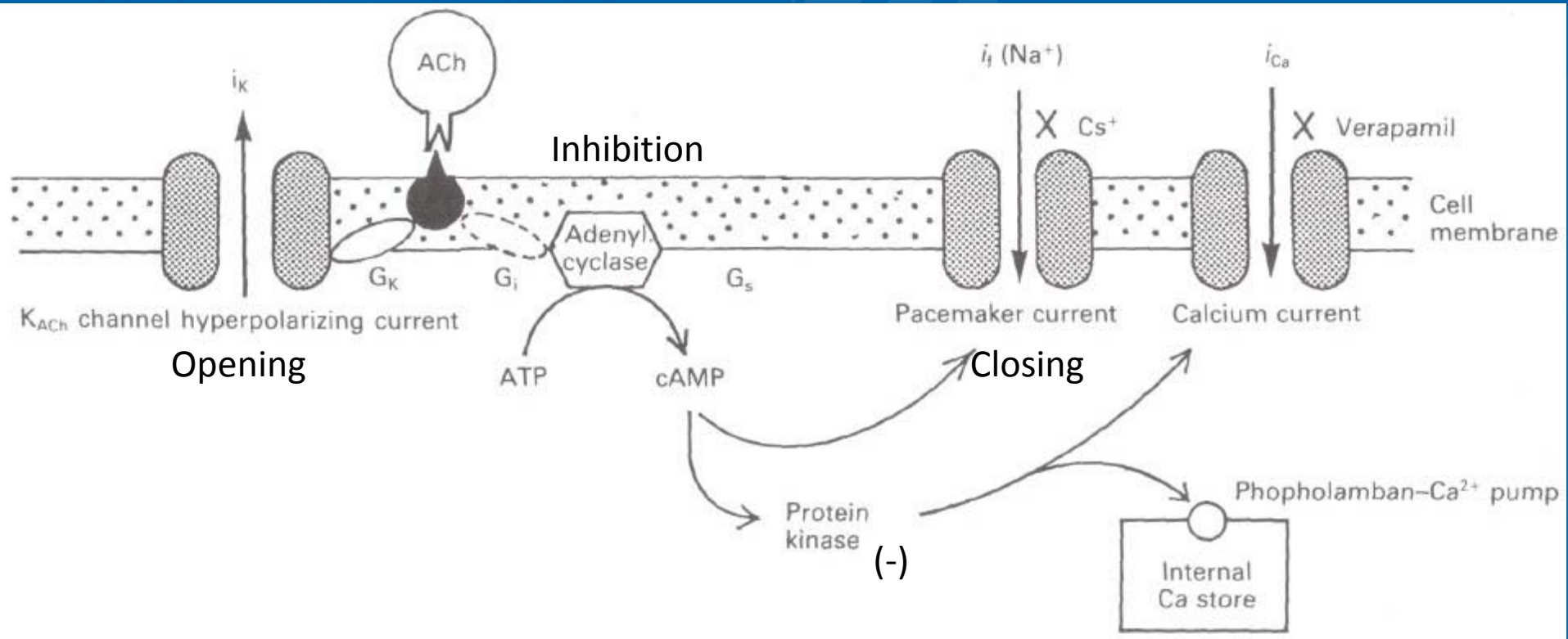
Sympathetic (adrenergic) receptor stimulation increases heart rate



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

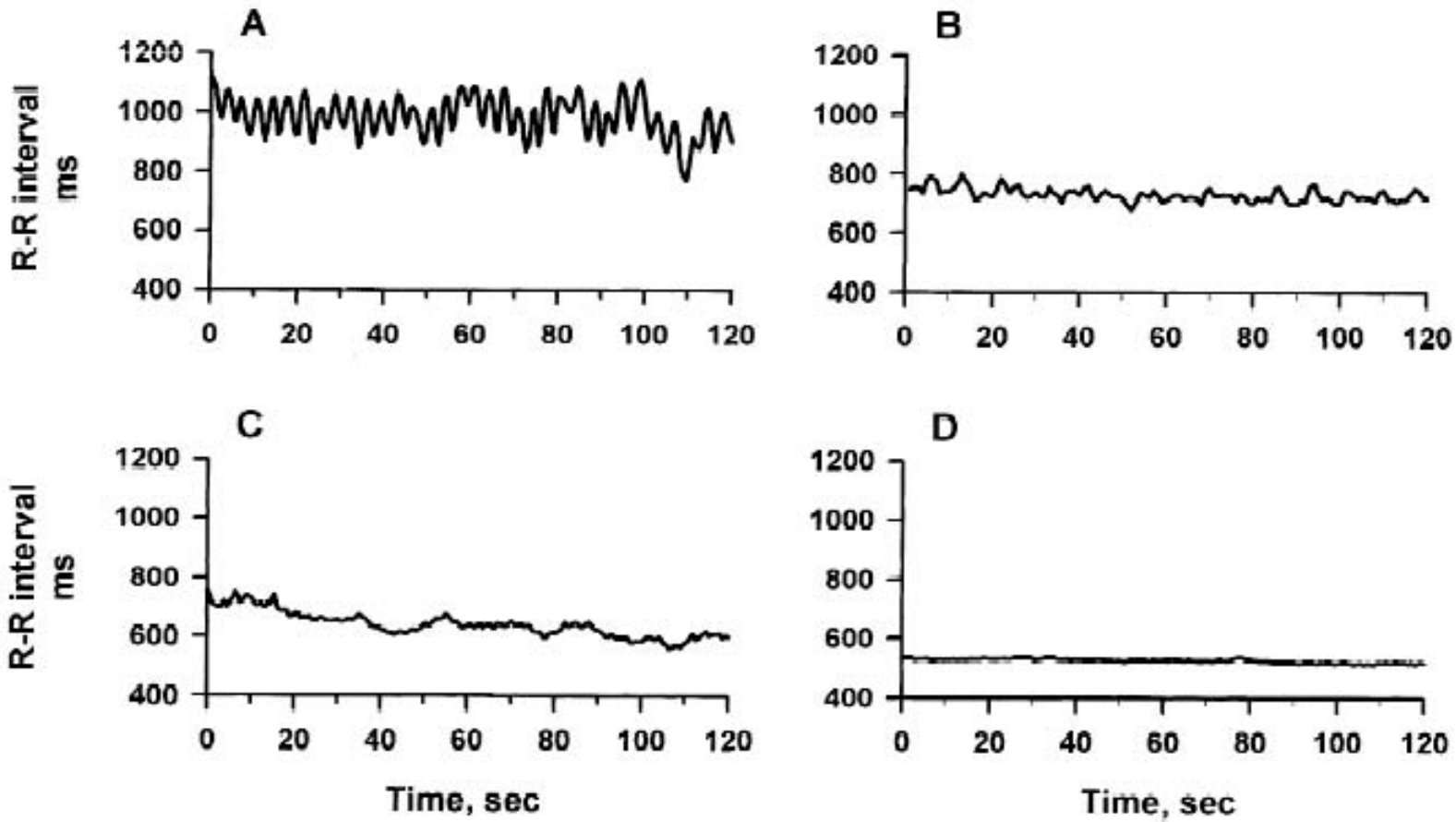
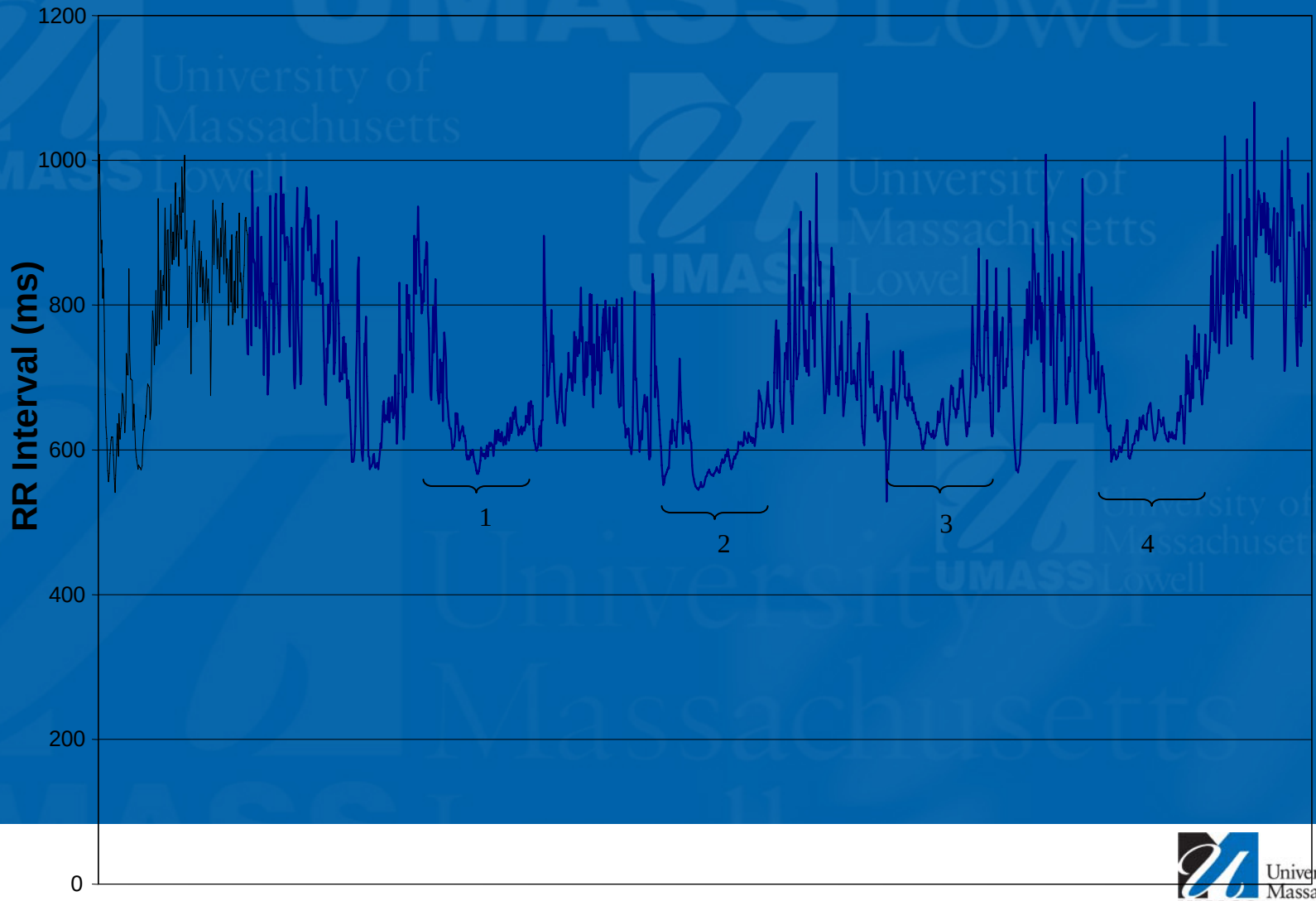
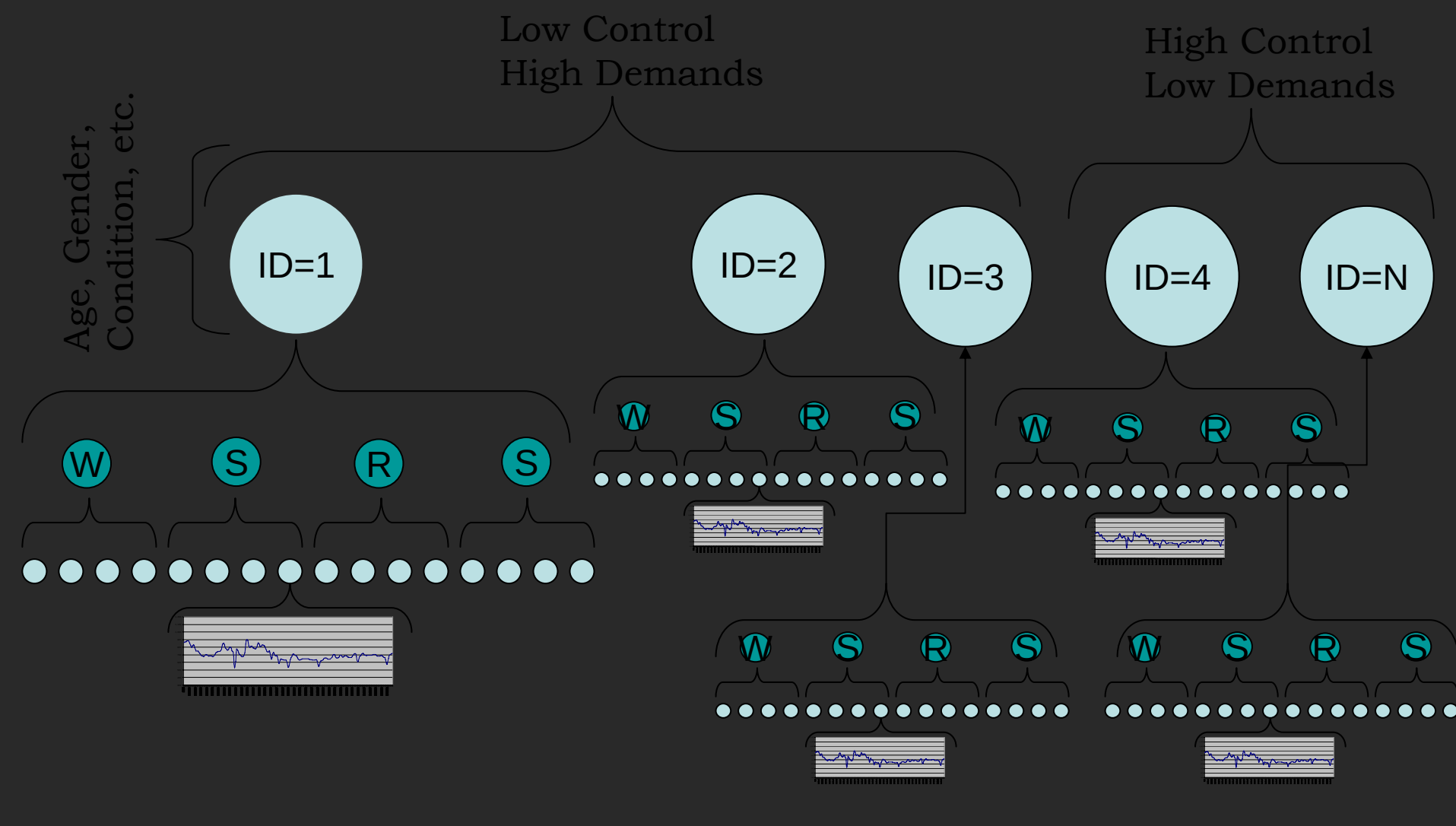


Fig. 1. Trendgrams showing fluctuation of beat-to-beat R–R interval in various conditions. R–R intervals were measured from 2-min ECG in a healthy young subjects during supine rest (A), mental arithmetic stress testing (B), and ergometer exercise testing (C) and in a patients with severe congestive heart failure at rest (D).

RR Intervals During Fitts Test



Job Strain & HRV Study: General Statistical Modeling of Contrasts: Multilevel/Hierarchical Data Structure



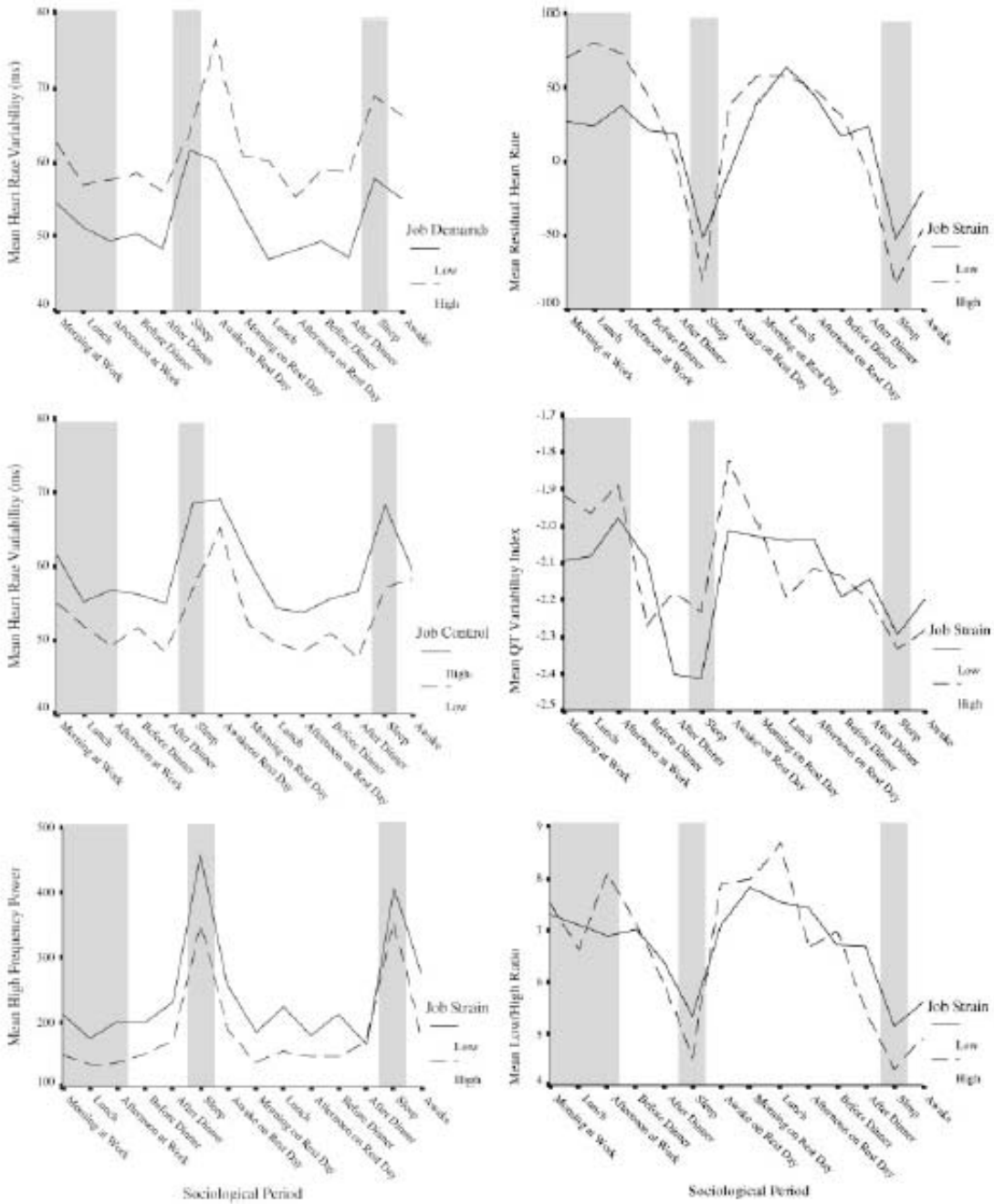


FIGURE 1. Heart rate variability and high frequency power during sociological periods.

FIGURE 2. Sympathetic variables during sociological periods between strain groups.

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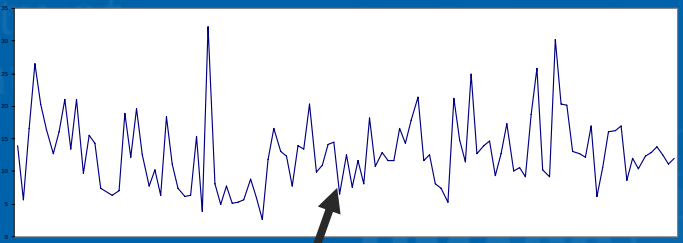
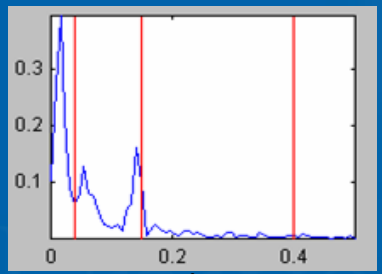
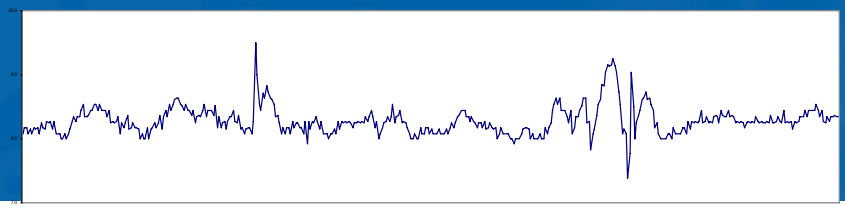


2 Hour vagal activity series

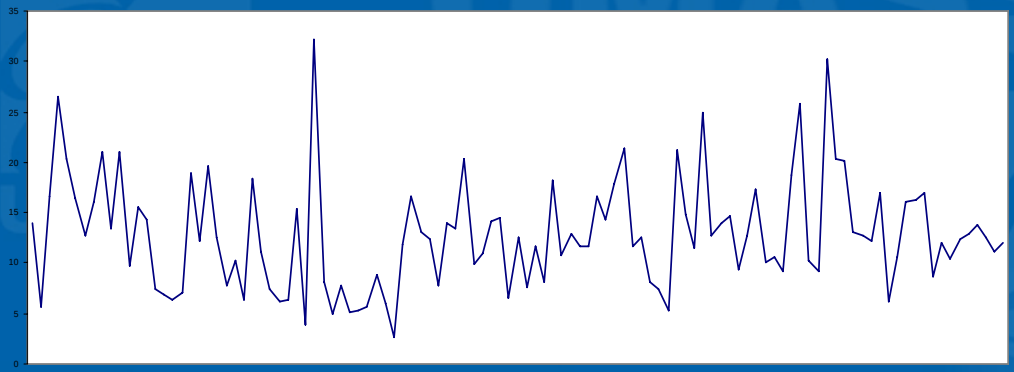


Power Spectrum
Extract variance for vagal activity



5 Minute
RR Series

Regulatory System Variance

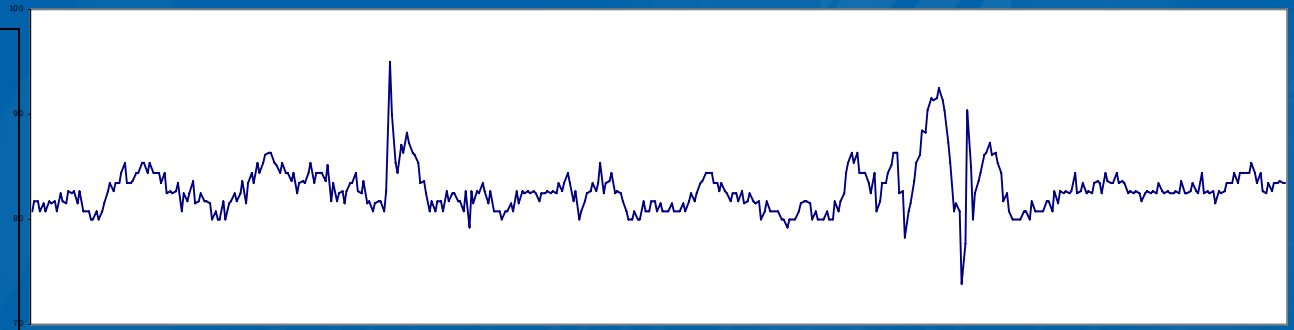


System Regulation

HFP Time Series
(Vagal Control)

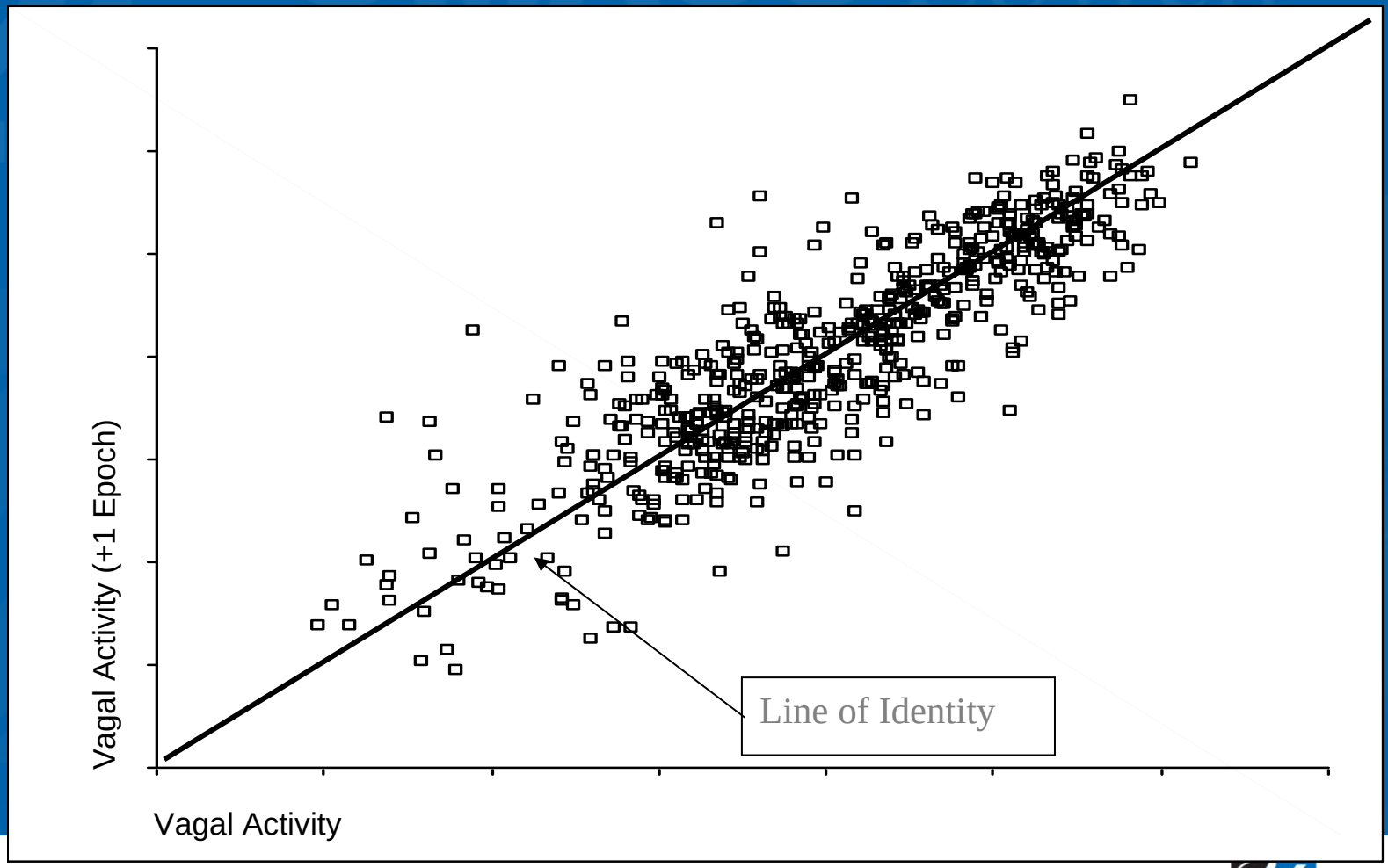
4 Hours (= 48 Epochs)

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

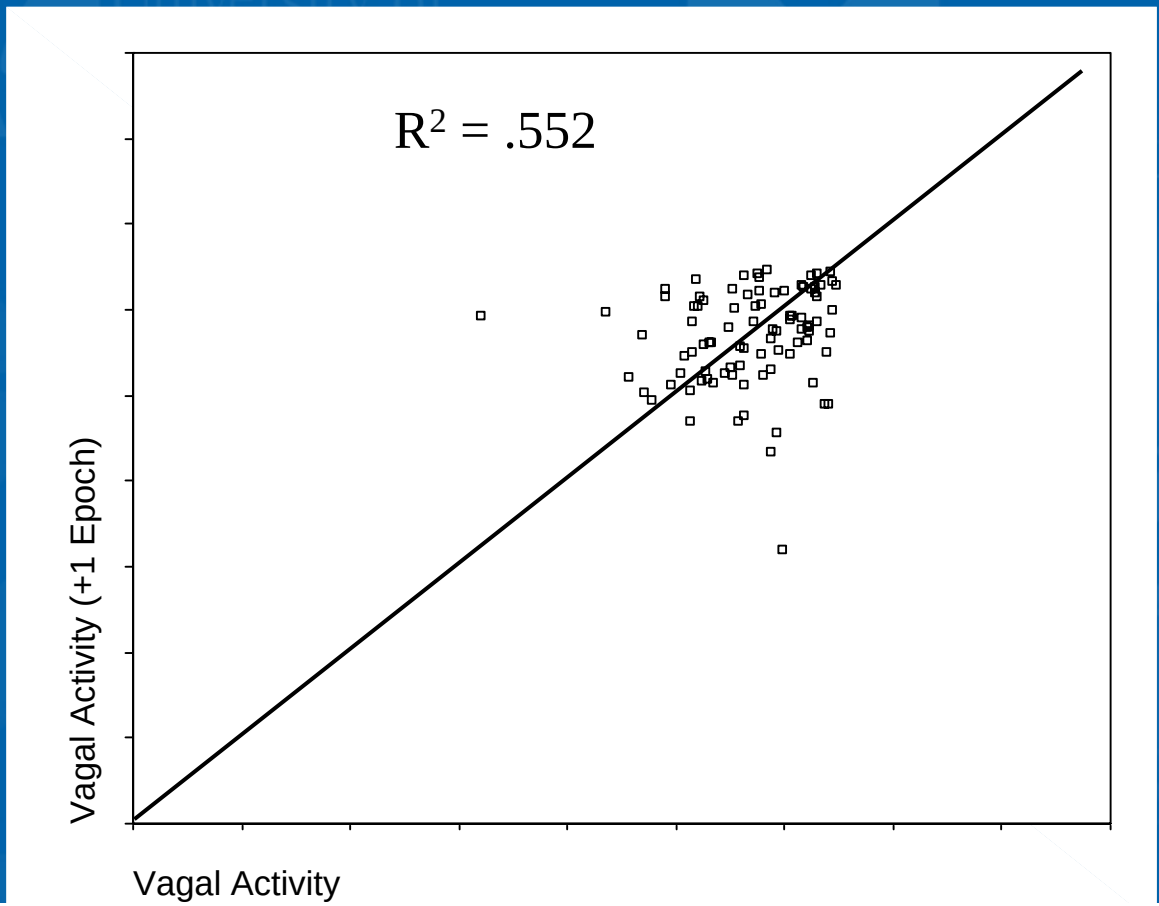


1 Epoch

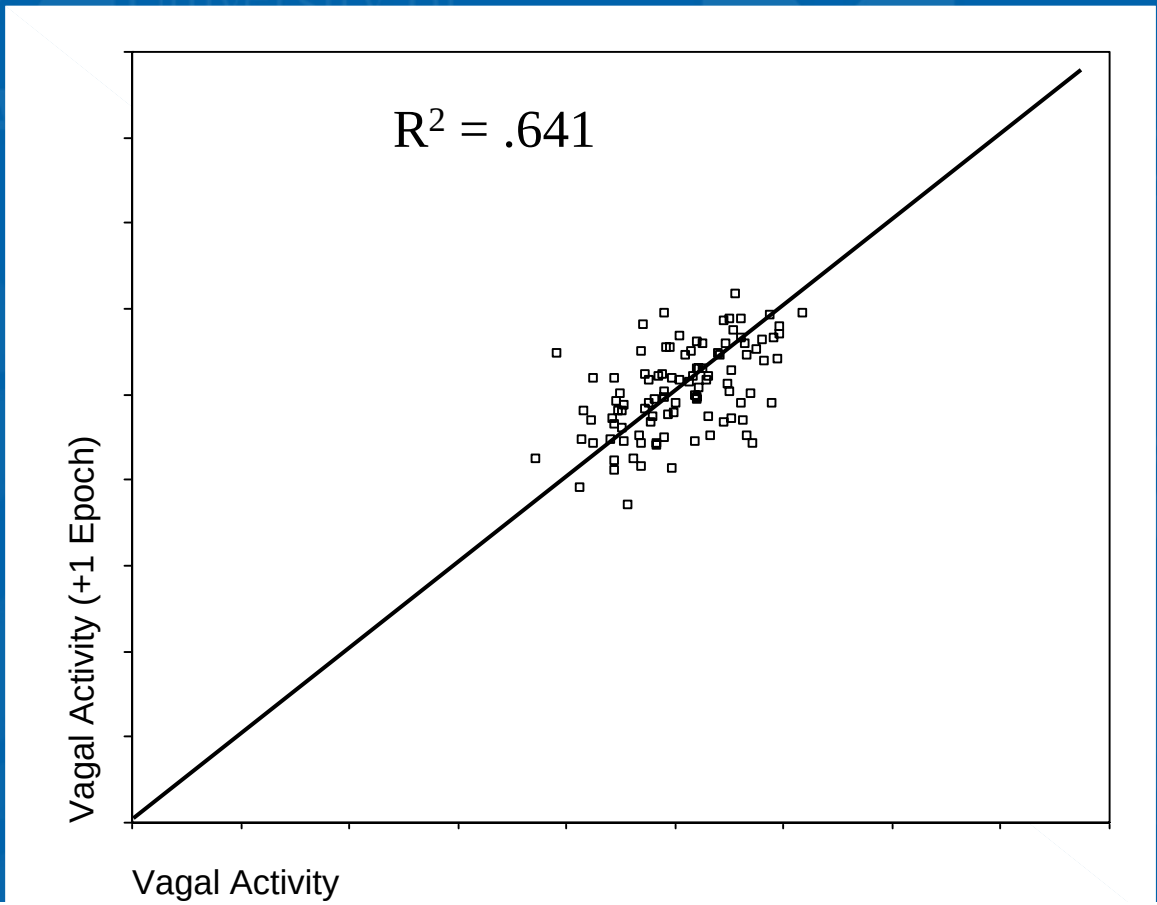
Poincaré Plot for Entire Monitoring Period



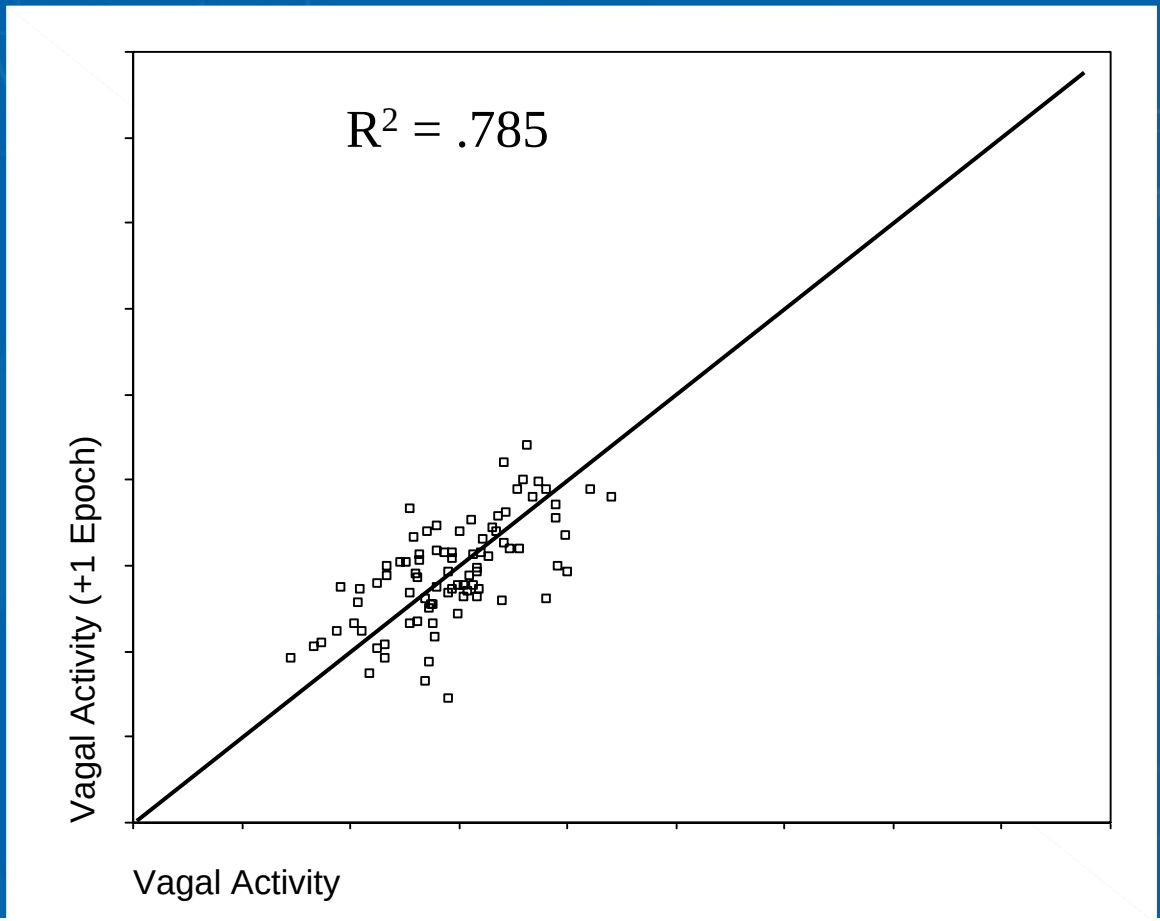
Poincaré Plot for Low Strain Subject at Work



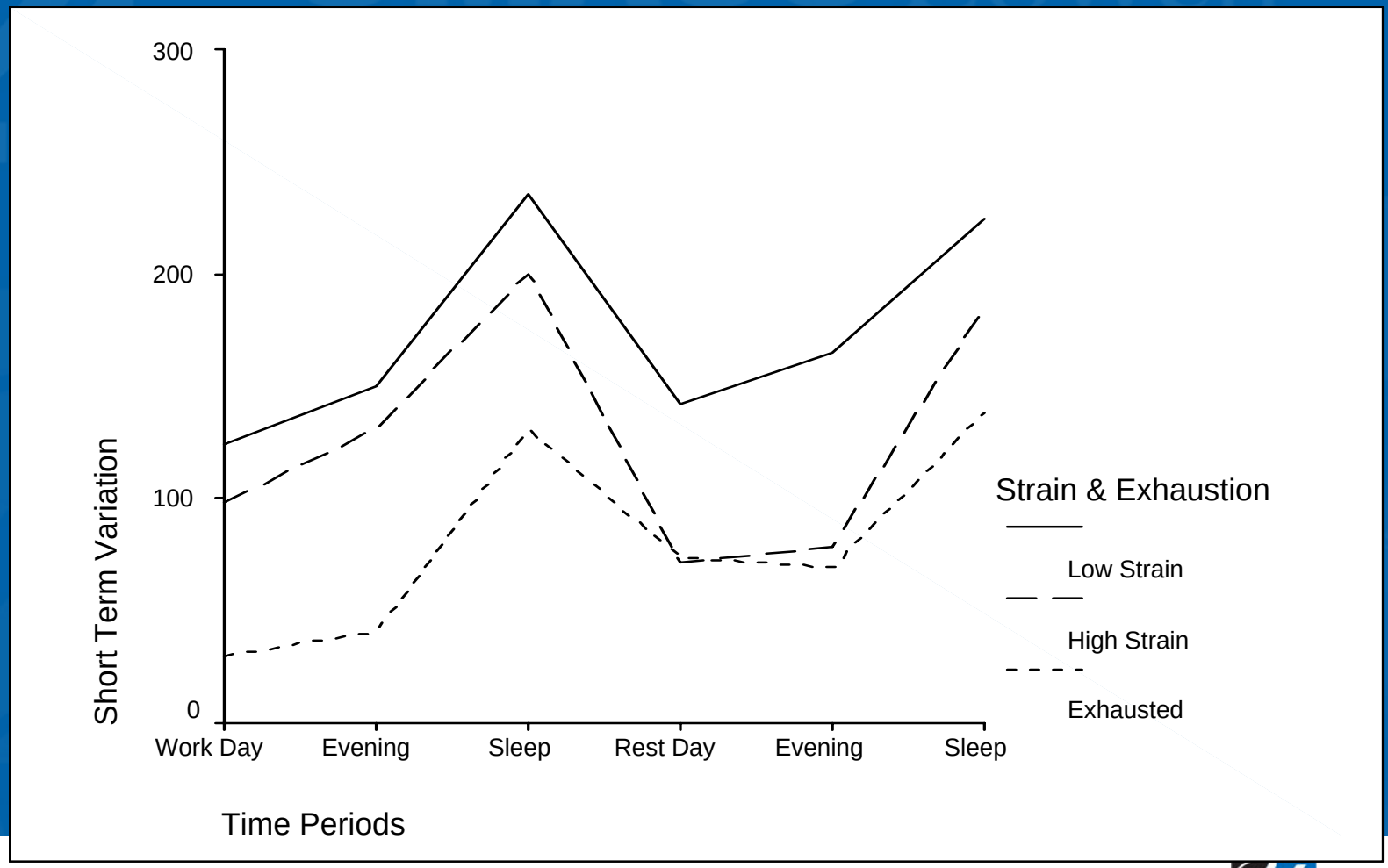
Poincaré Plot for High Strain Subject at Work



Poincaré Plot for Exhausted Subject at Work



Short Term Variation as Determined by Poincaré Plot Residuals

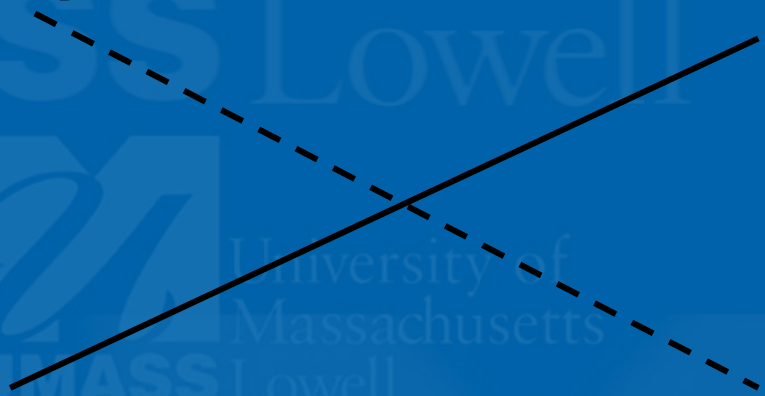


Berntson's Doctrine of Autonomic Space

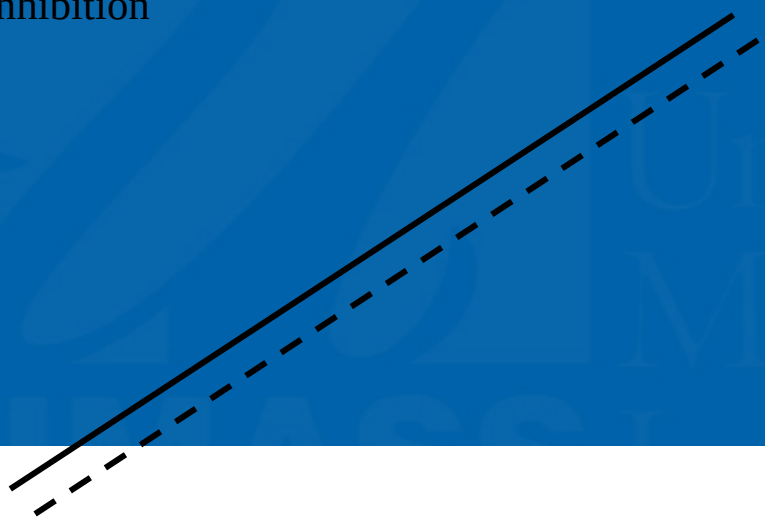
Sympathetic Activity

Parasympathetic Activity

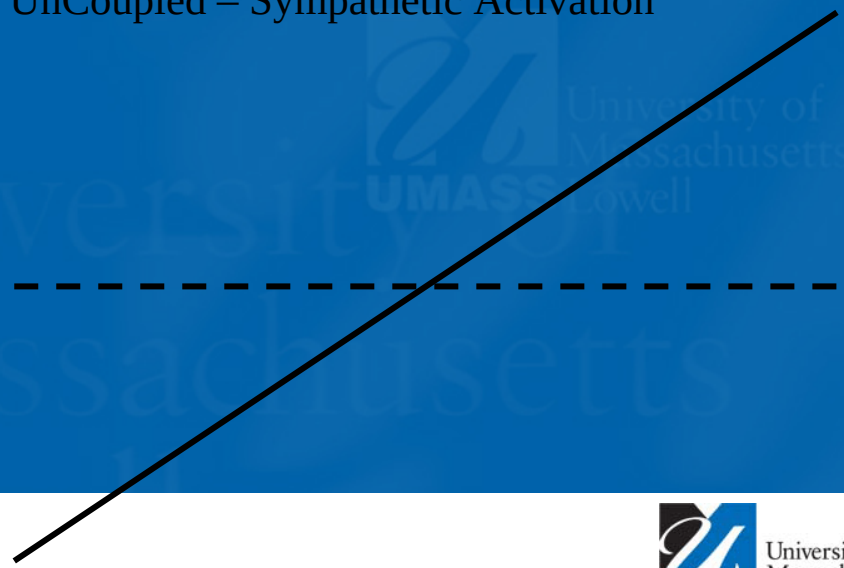
Reciprocal:

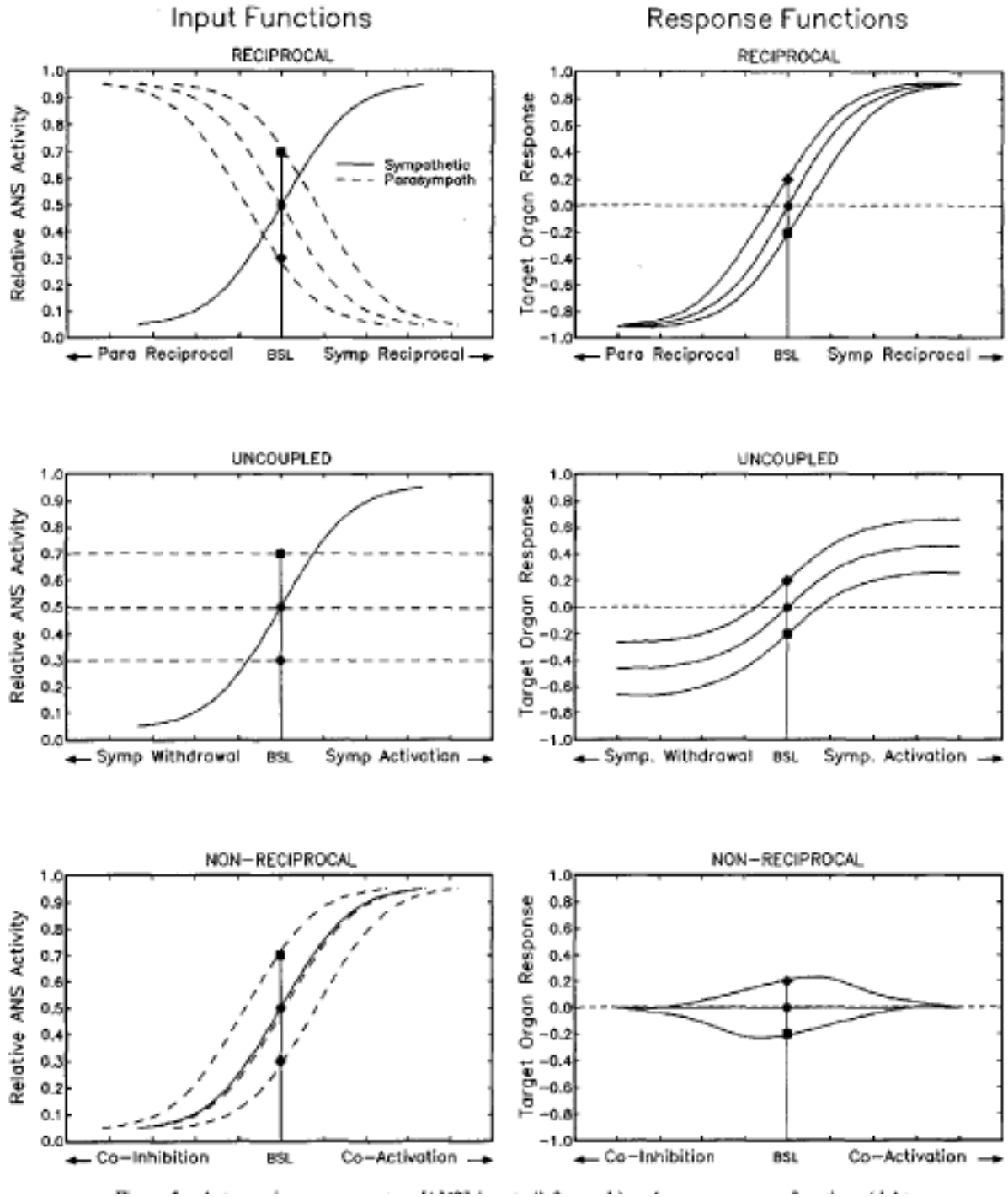


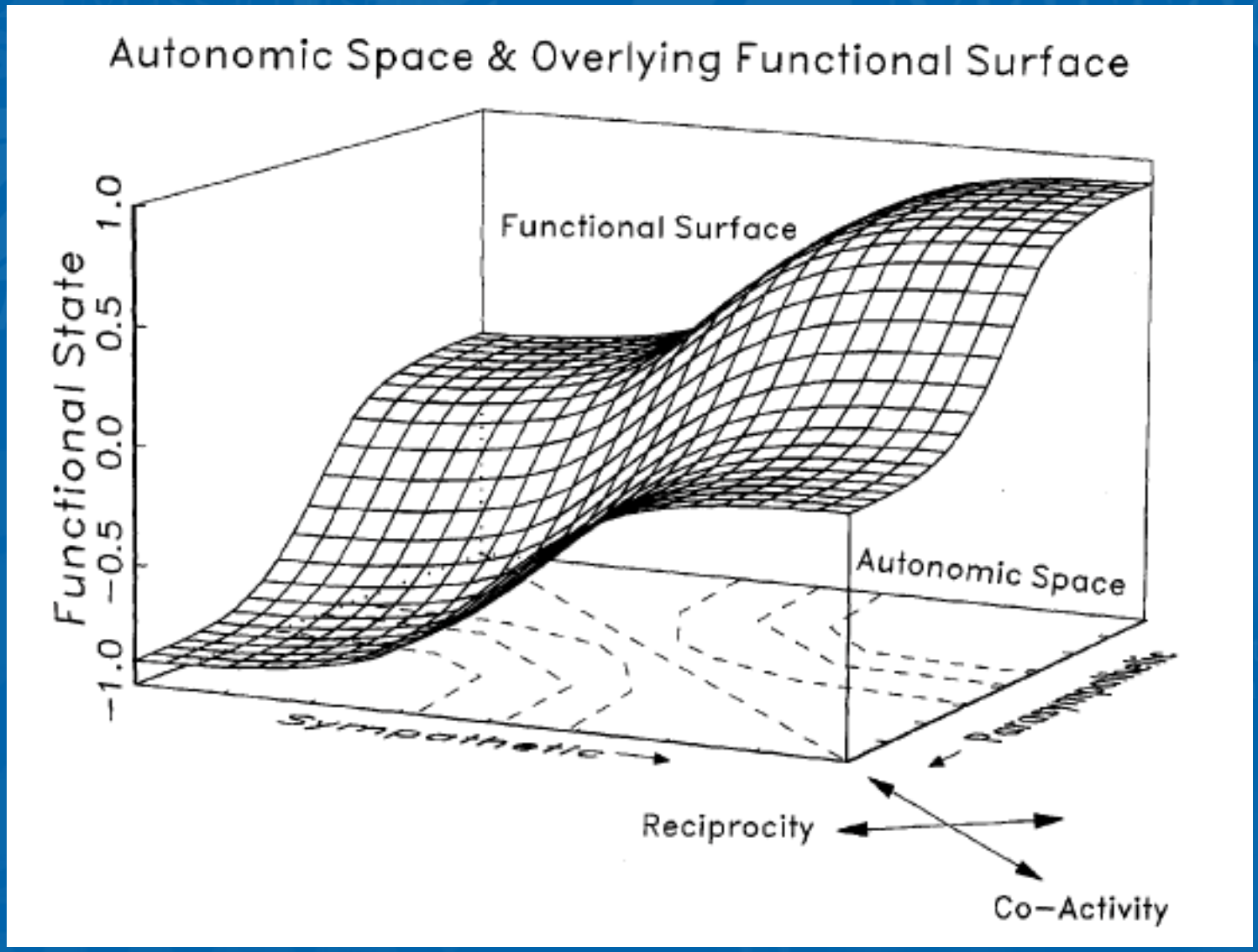
Non-Reciprocal: Co – Activation & Co – Inhibition



UnCoupled – Sympathetic Activation




Input Functions
Response Functions
RECIPROCAL
Relative ANS Activity
Sympathetic
Parasympath
Para Reciprocal
BSL
Symp Reciprocal
Target Organ Response
UNCOUPLED
Symp Withdrawal
Symp Activation
Symp. Withdrawal
Symp. Activation
NON-RECIPROCAL
Co-Inhibition
Co-Activation



Bernston et al, 1991

Bernston's Doctrine of Autonomic Space

Subjects HR > Mean

Subjects HR < Mean

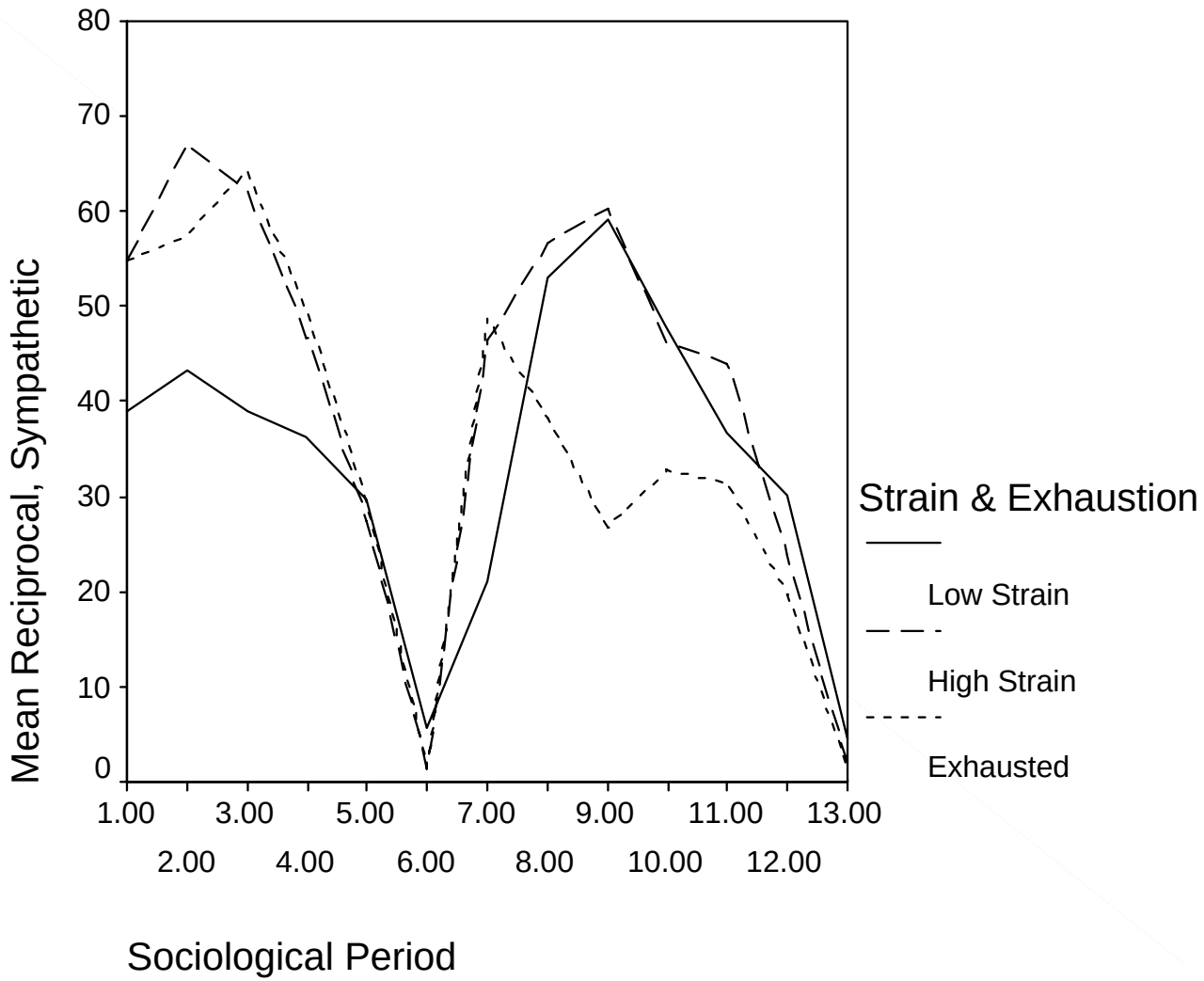
Autonomic Dominance	Coordination Pattern		
	Reciprocal	Unclassified	Other
Sympathetic	Symp-Recip	Symp-Uncl	Symp-Oth
Parasympathetic	Para-Recip	Para-Uncl	Para-Oth

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

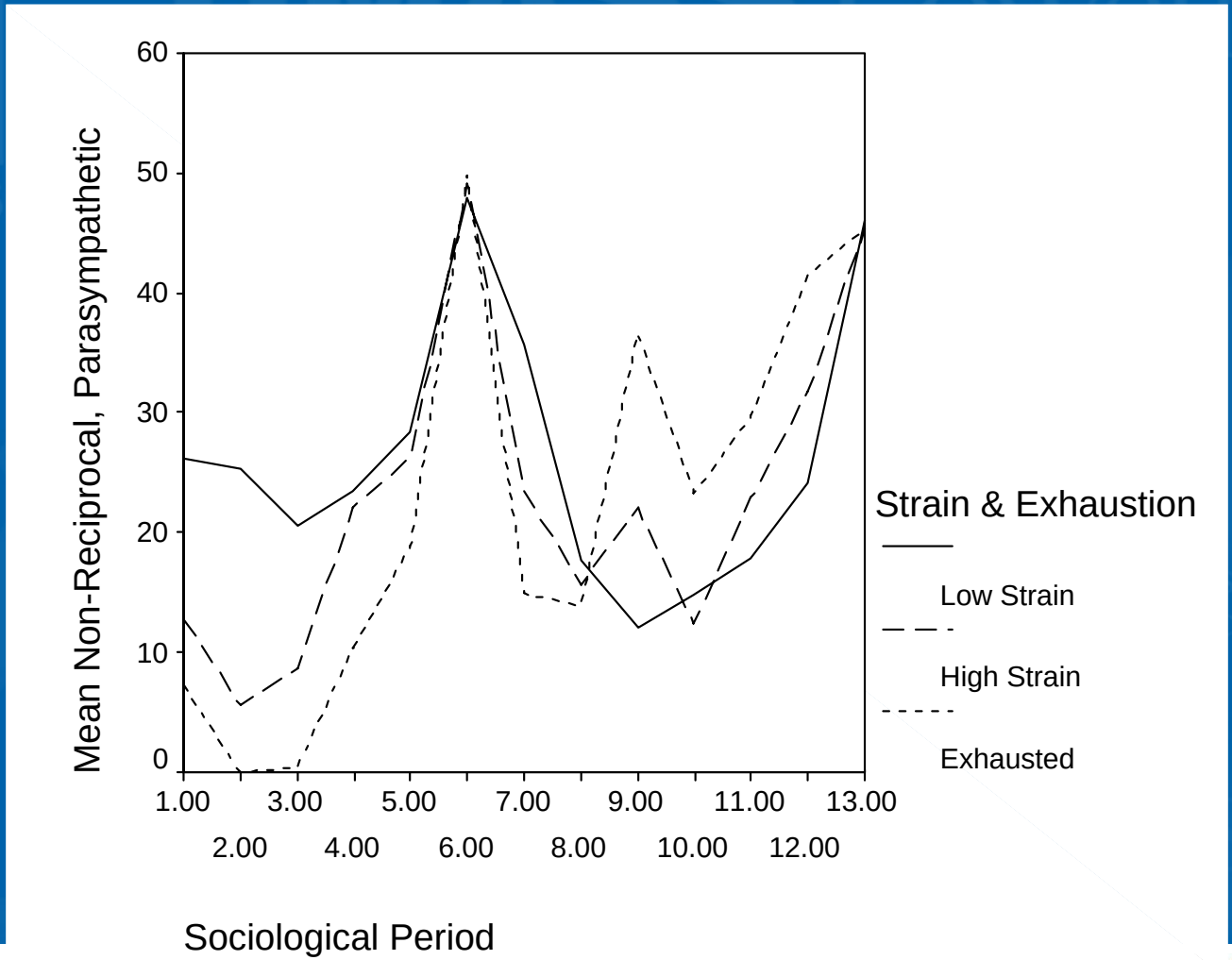
If: HFPnu and ResHR > .1 SD
If: HFPnu and ResHR < -.1 SD
If: HFPnu < .1 and > -.1 SD and ResHR > .25 or < -.25 SD
If: If: ResHR < .1 and > -.1 SD and HFPnu > .25 or < -.25 SD

Bernston's Doctrine of Autonomic Space

Reciprocal Sympathetic Control

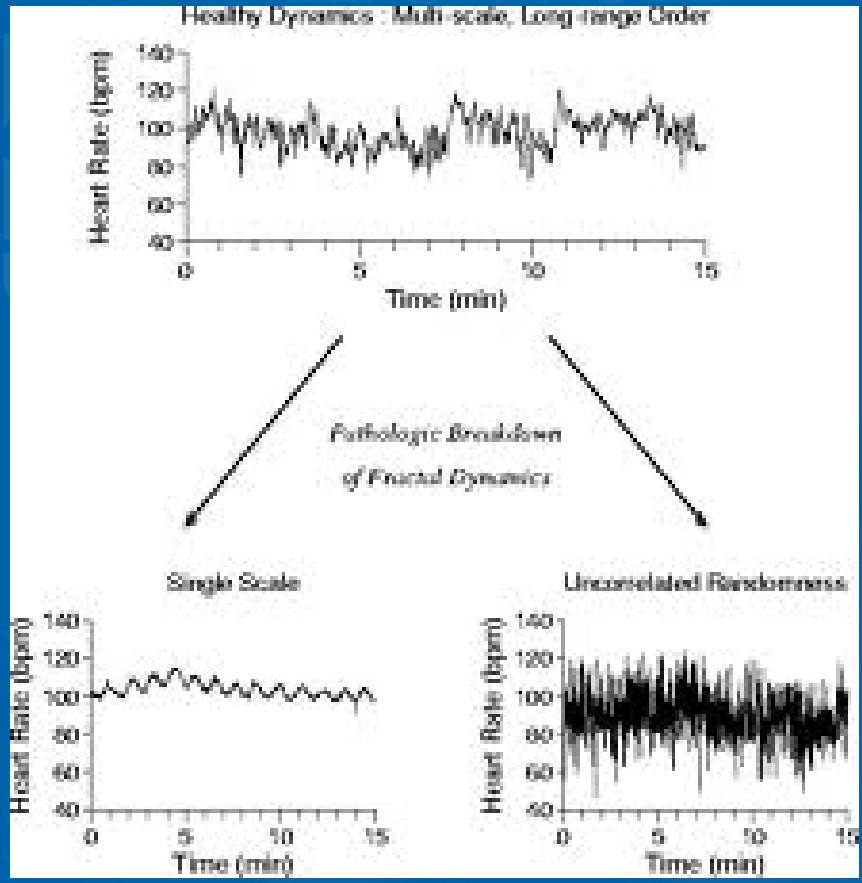


Bernston's Doctrine of Autonomic Space
Non Reciprocal Parasympathetic Control



Current Work: HR Dynamics

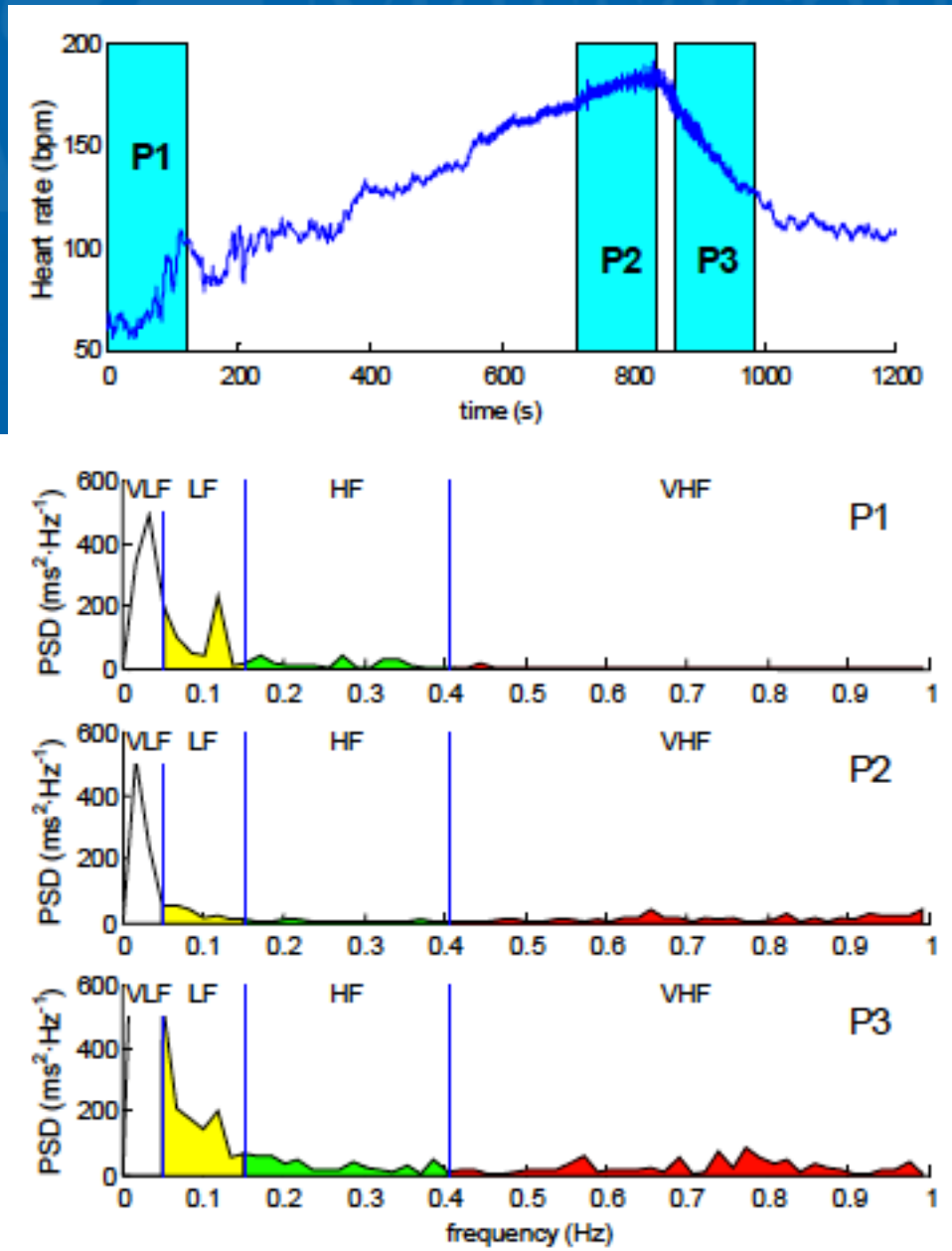
- Are there non-linear heart rate dynamics that identify “system” exhaustion and denote a pre clinical physiological sign of “vital exhaustion” – or stress disequilibrium
- (Same collaborators)



Current Work: HR dynamics with exercise

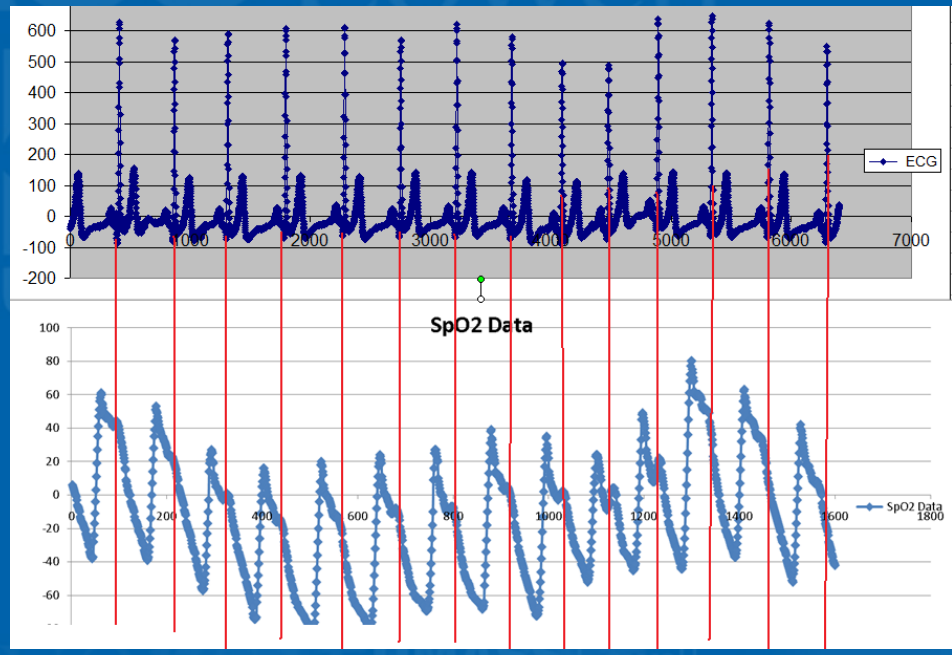
- Do changes in HR dynamics during exercise provide additional information about pre clinical status; or physiological response to demands?

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