

Heart rate control and variability

Na (Lina) Li (CDS13')

EE @ SEAS

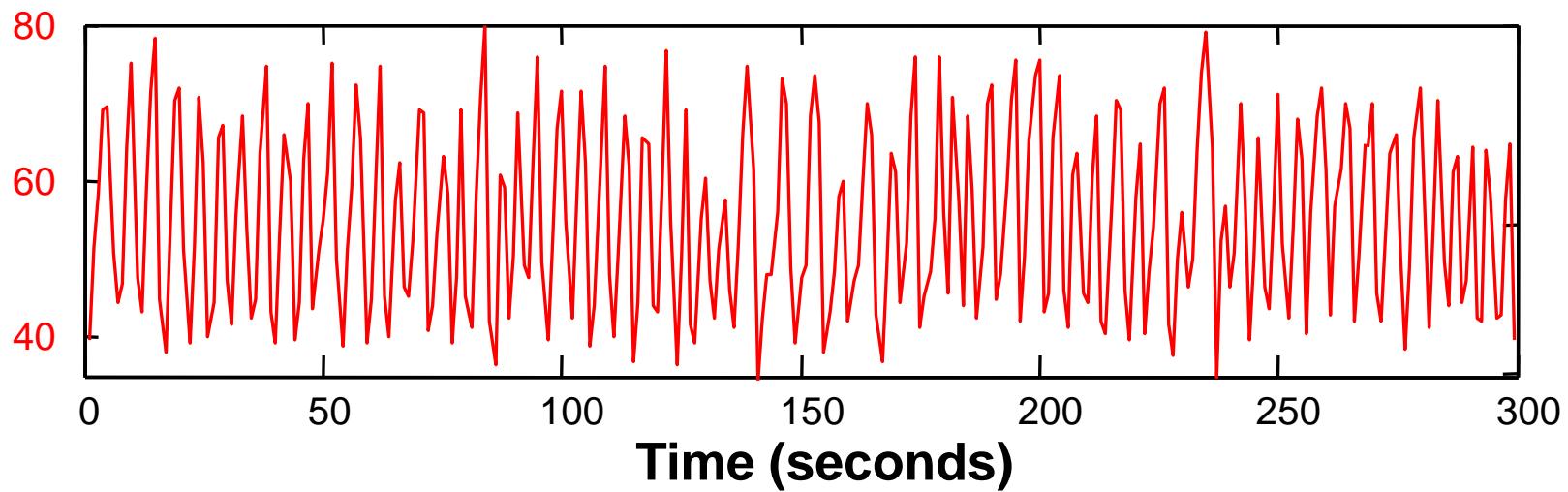
Harvard University

CDS @ 20

The persistent mystery

Young, fit, healthy \Rightarrow more extreme

Resting Heart Rate (bpm)



Noise?

Young, fit, healthy \Rightarrow more extreme

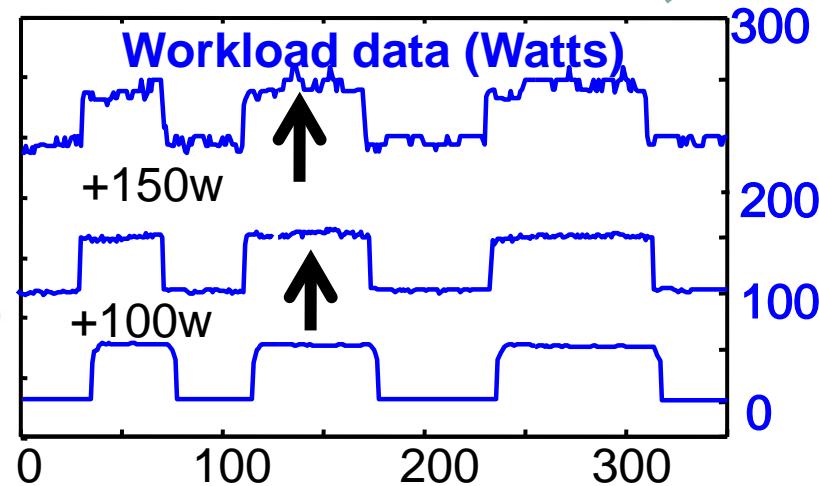


High mean, low variability



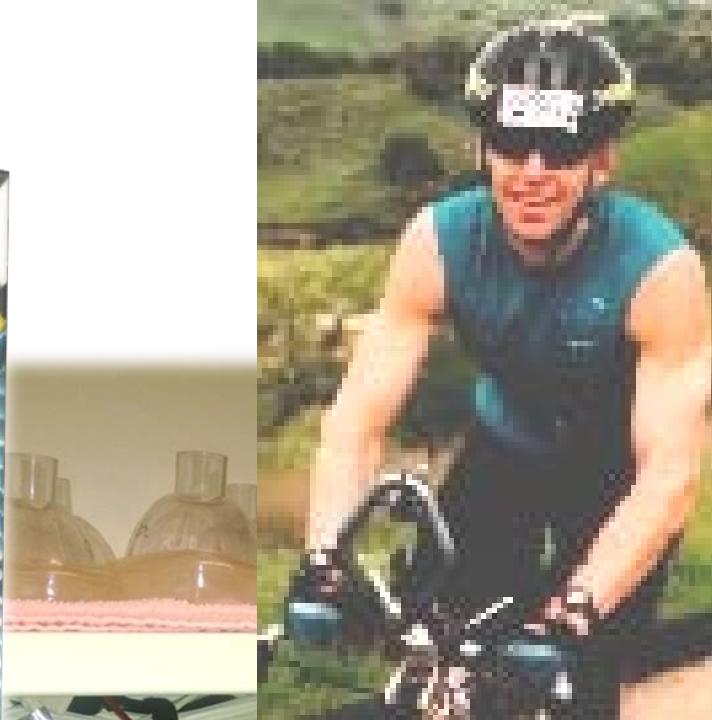
Time (seconds)

One subject
Three
experiments





Doyle's Physiology Lab



Thanks to

Theory/tools

- Jerry Cruz
- Simon Chien
- Somayeh Sojoudi
- Ben Recht
- John Doyle

Equipment

- Philips

Science Trans Med & PNAS
& Anonymous reviewers

Medical

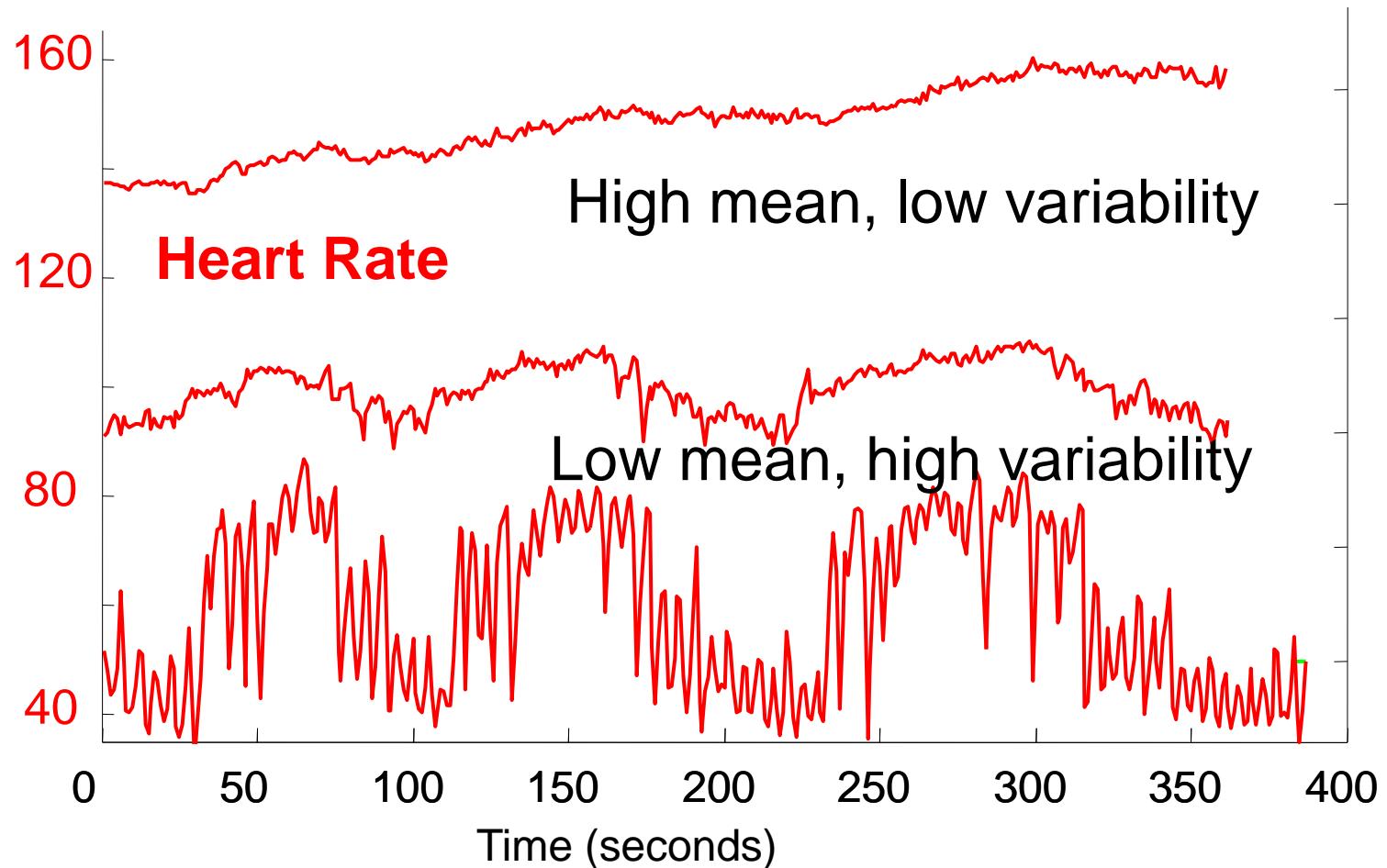
- Marie Csete MD PhD
- David Stone MD
- Dan Bahmiller MD
- SCAI and ICCAI

Subjects

- Caltech Faculty & Students

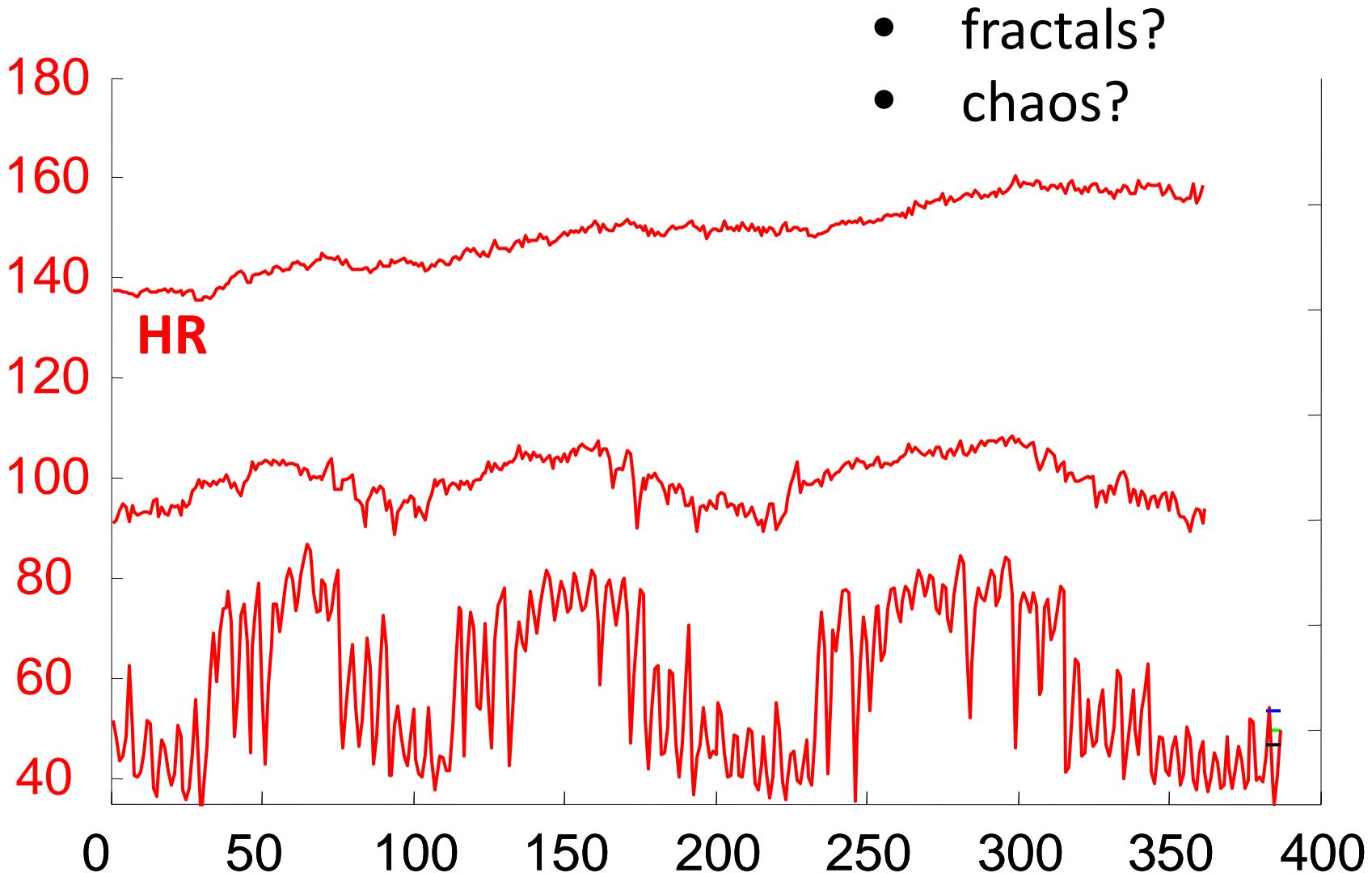
Funding

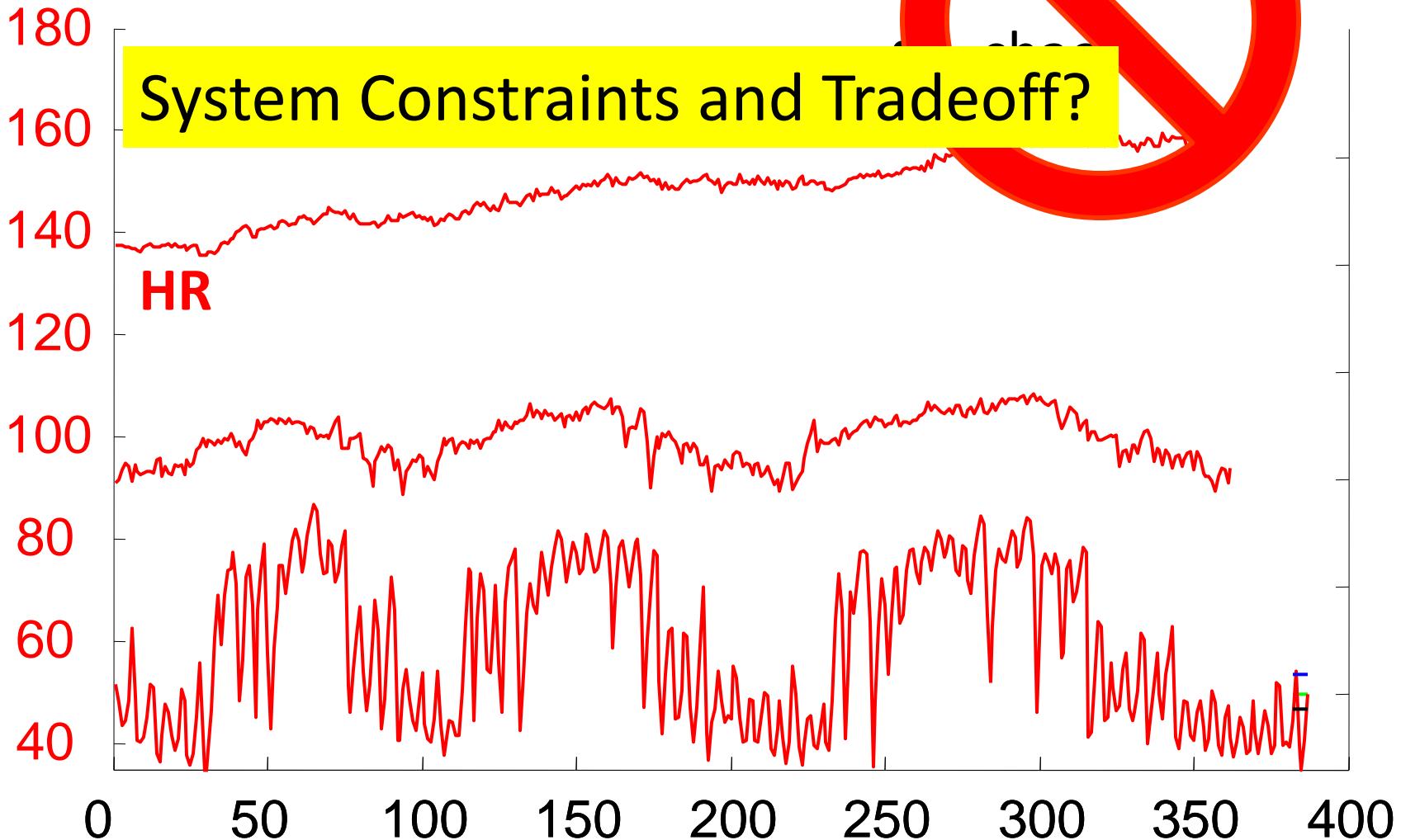
- NIH
- Army
- Pfizer
- Braun family
- AFOSR/NSF



Many diseases associated w/decrease HRV

- *Poon et al, Decrease of cardiac chaos in congestive heart failure*, Nature, 1997.
- *Carney et al, Depression, heart rate variability, and acute myocardial infarction*, Circulation, 2001.
- *Malpas et al, Heart-rate variability and cardiac autonomic function in diabetes*, Diabetes, 1990.
- *Pontet et al, Heart rate variability as early marker of multiple organ dysfunction syndrome in septic patients*, Journal of critical care, 2003.
- *Tateishi et al, Depressed heart rate variability is associated with high IL-6 blood level and decline in the blood pressure in septic patients*, Shock, 2007.
- *Roche et al, Depressed heart rate variability is associated with high IL-6 blood level and decline in the blood pressure in septic patients*, Circulation, 1999.
- *Kleiger et al, Decreased heart rate variability and its association with increased mortality after acute myocardial infarction*, Am Journal of Cardiology, 1987.
- *Liao et al, Age, race, and sex differences in autonomic cardiac function measured by spectral analysis of heart rate variability*, Am Journal of Cardiology, 1995.





Seeking mechanistic explanations

Homeostasis

controls

heart rate

ventilation

vasodilation

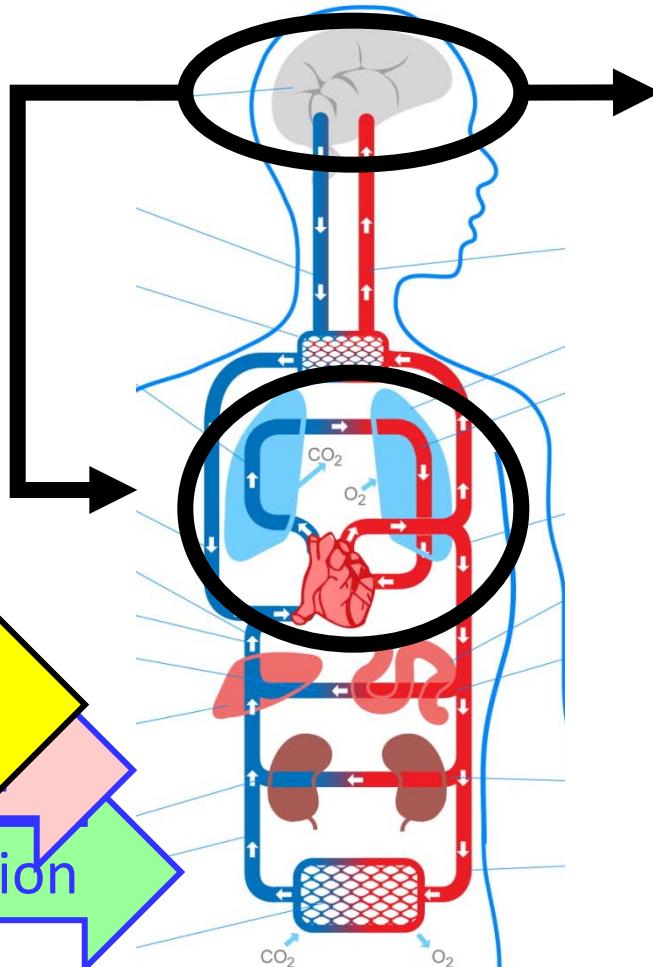
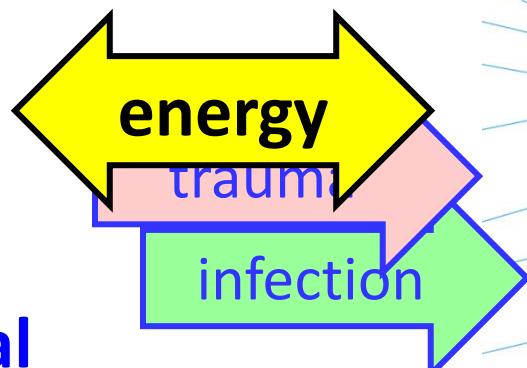
coagulation

inflammation

digestion

storage

...



errors

O₂

BP

pH

Glucose

Energy store

Blood volume

...

external disturbances

Homeostasis

controls

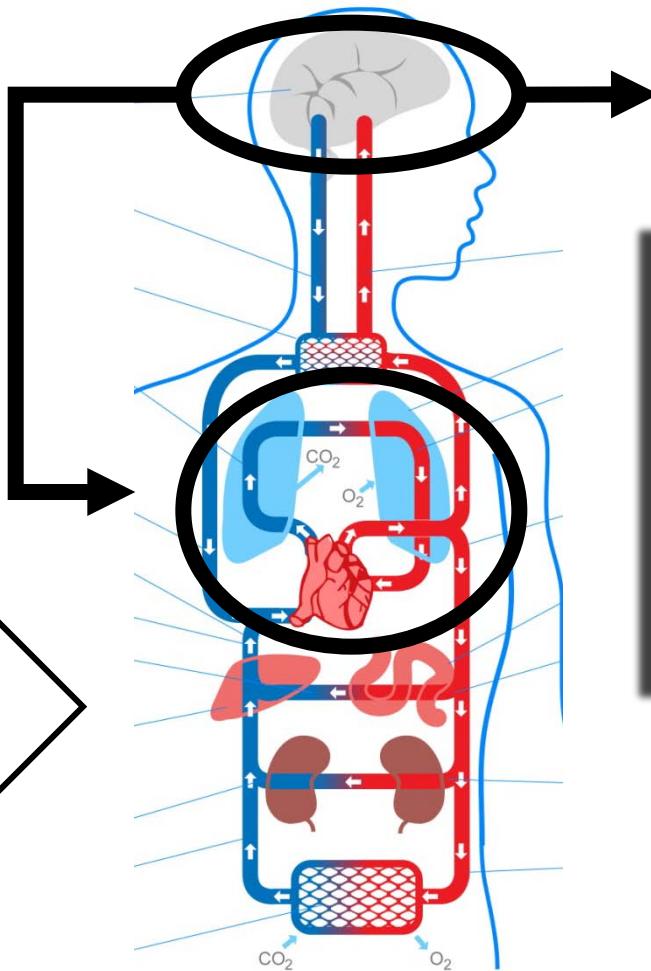
heart rate
ventilation

energy

errors

O₂
BP

Minimal
mechanistic
model
and experiment



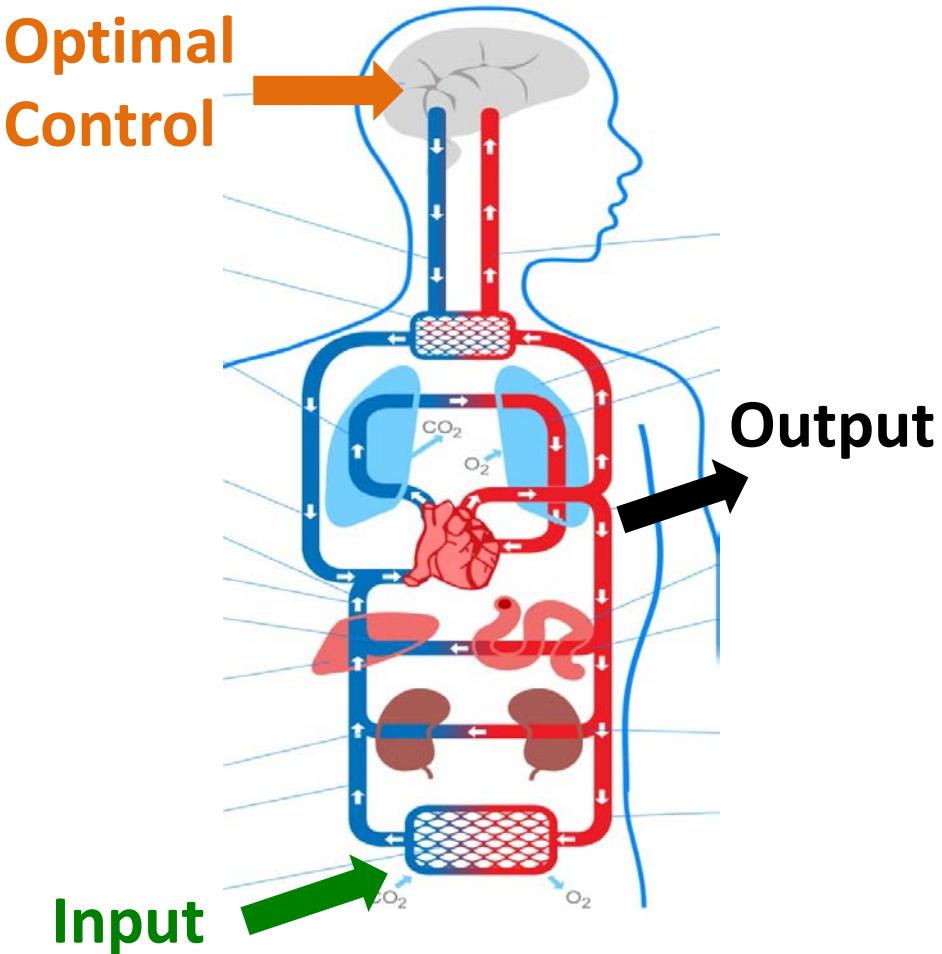
external
disturbances

System Identification Model

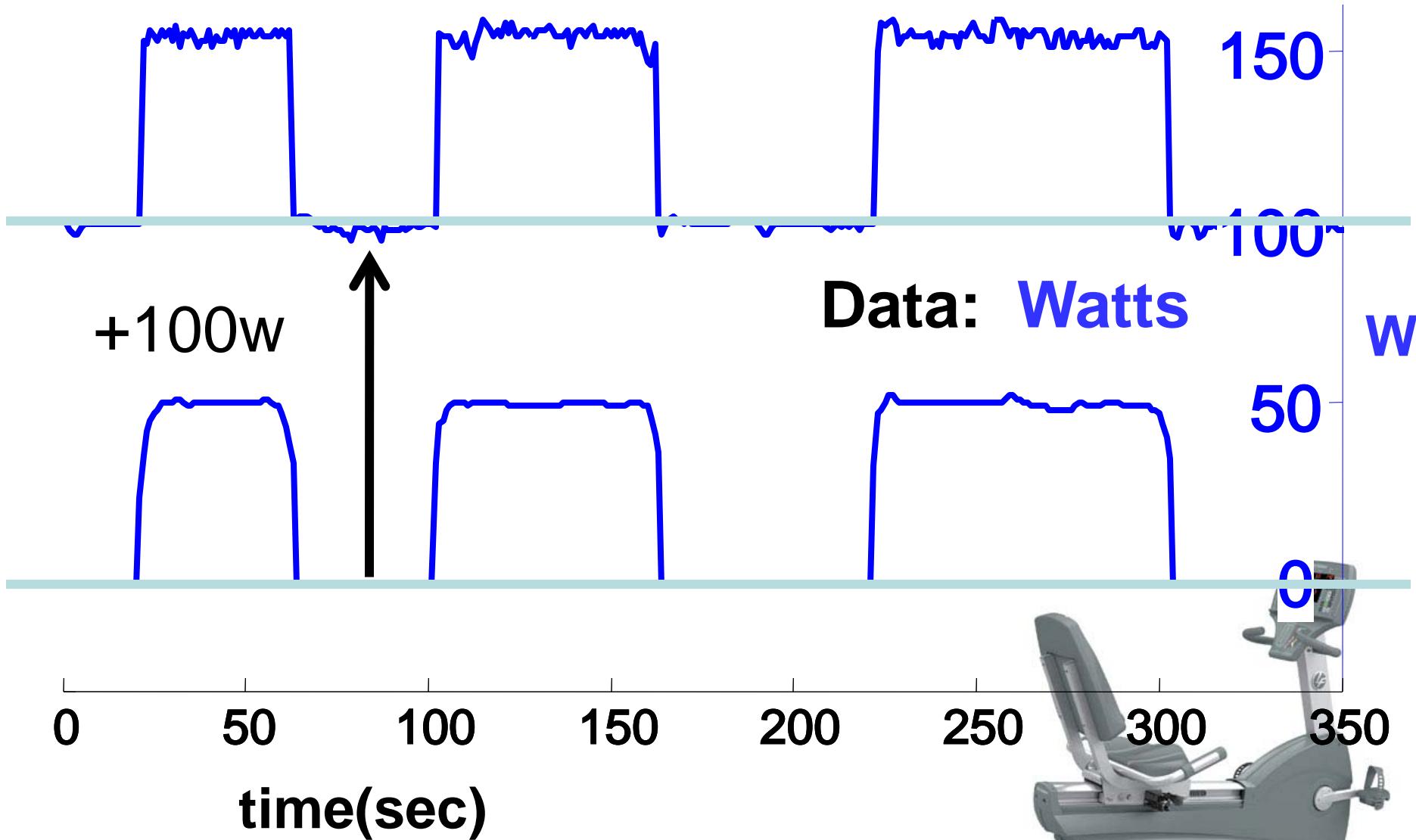
Output ← Black-box fitting ← Input

First Principle Model

Physiology + Optimal Control



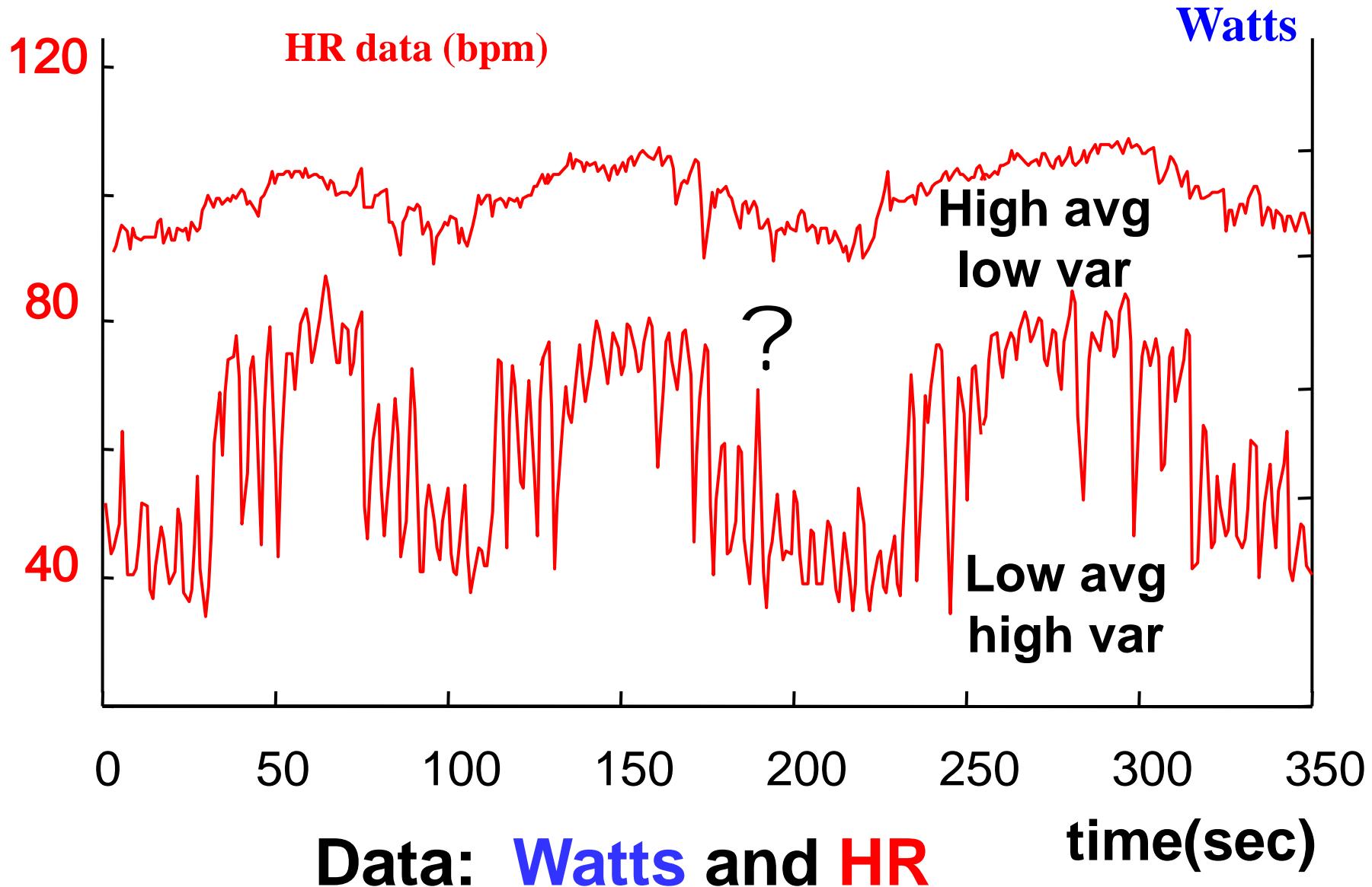
Two experiments



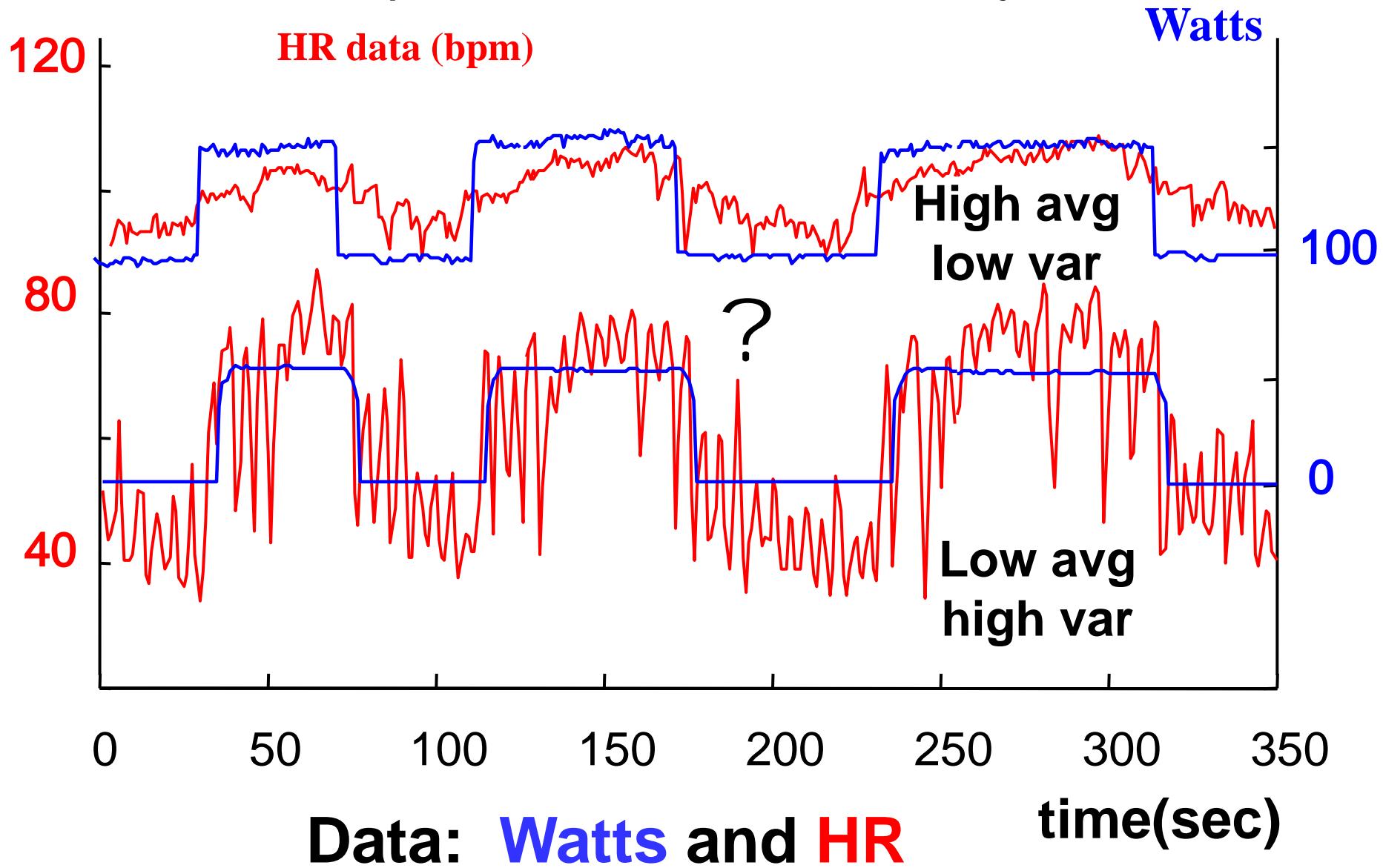
Input= “background+perturbation”



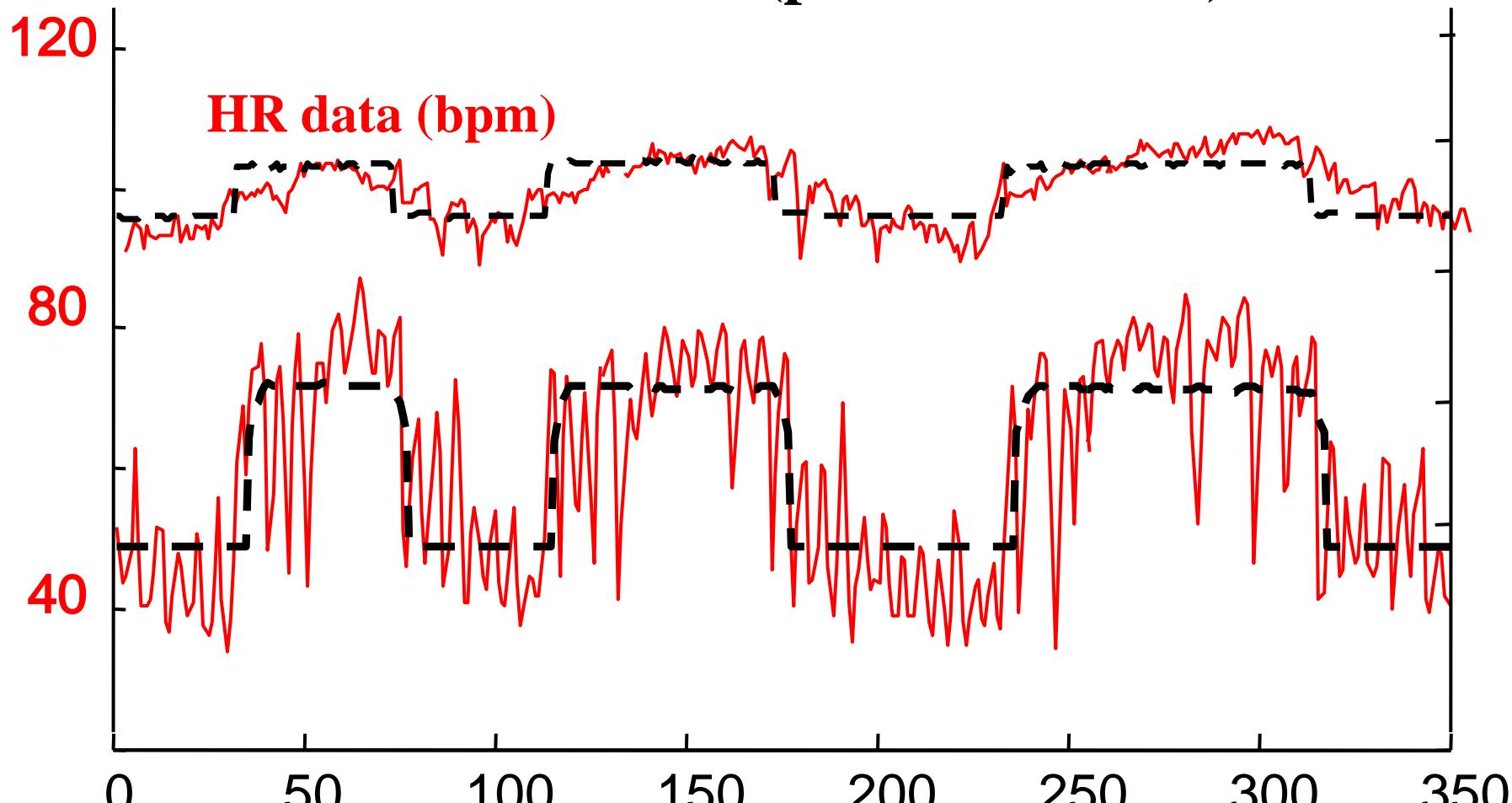
Two experiments with same subject #1



Two experiments with same subject #1

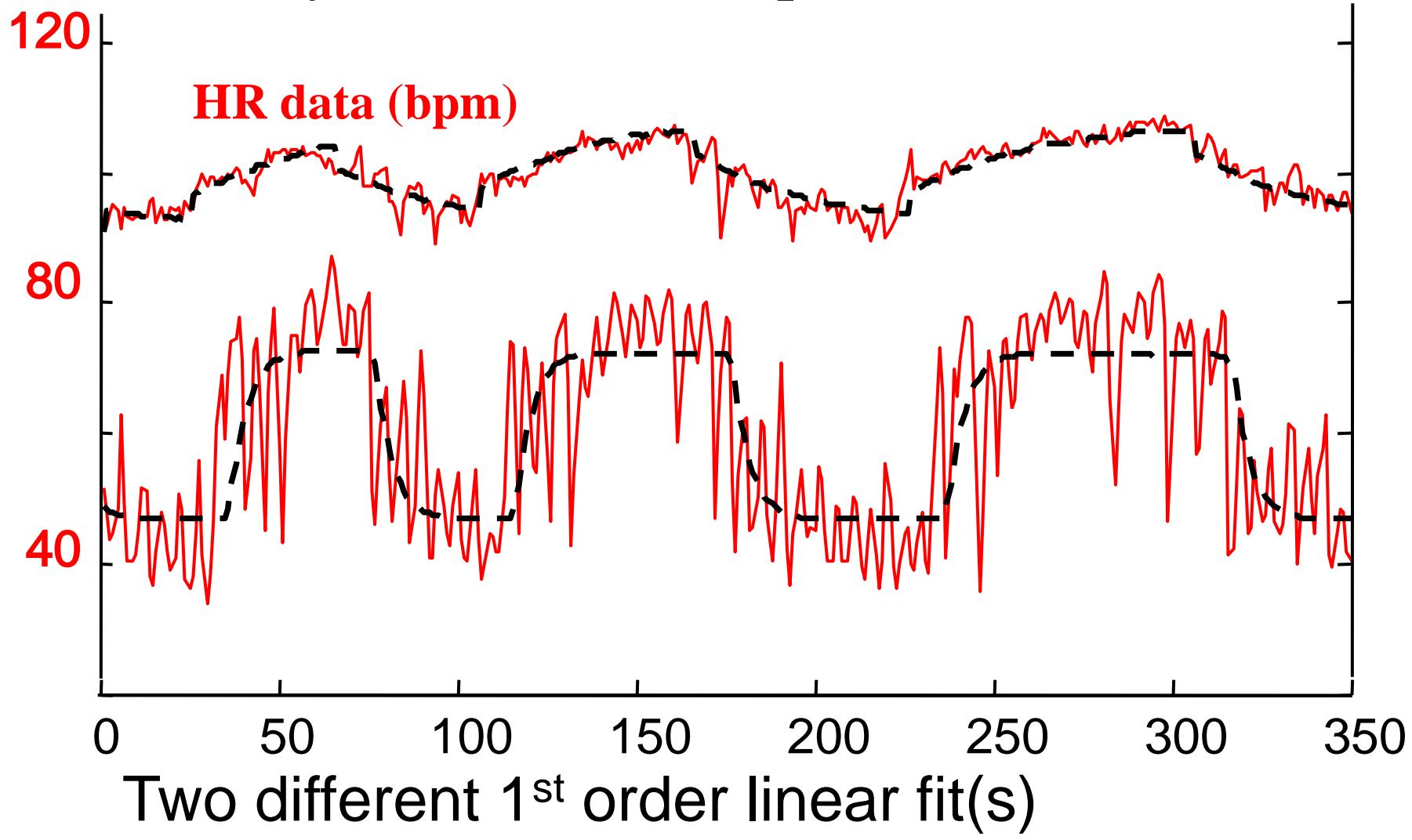


HR static nonlinear(piecewise linear) fit



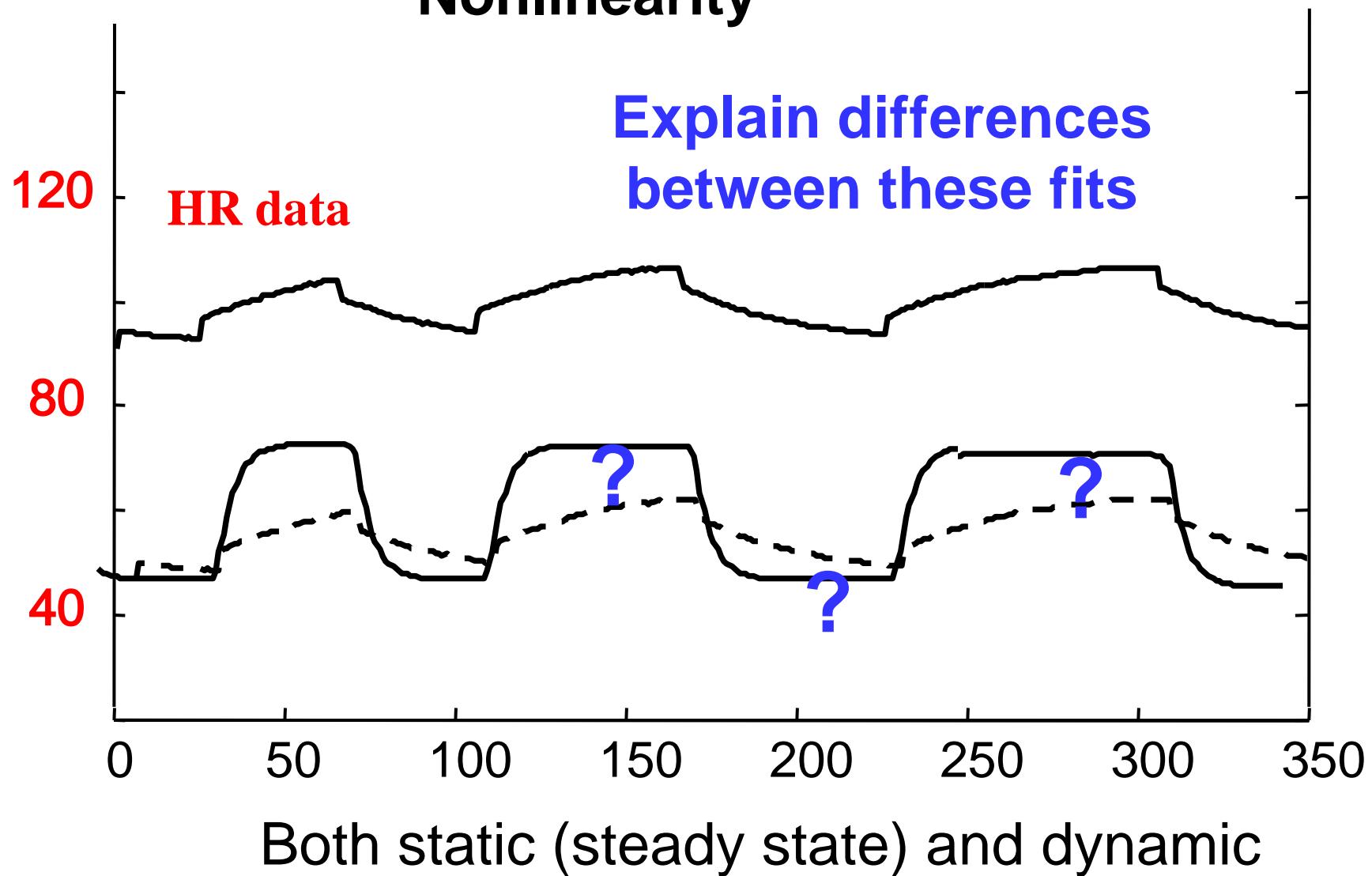
$$H = a_i W + b_i \quad \text{For each workout, } i=1,2,3$$

HR dynamic nonlinear (piecewise linear) fit

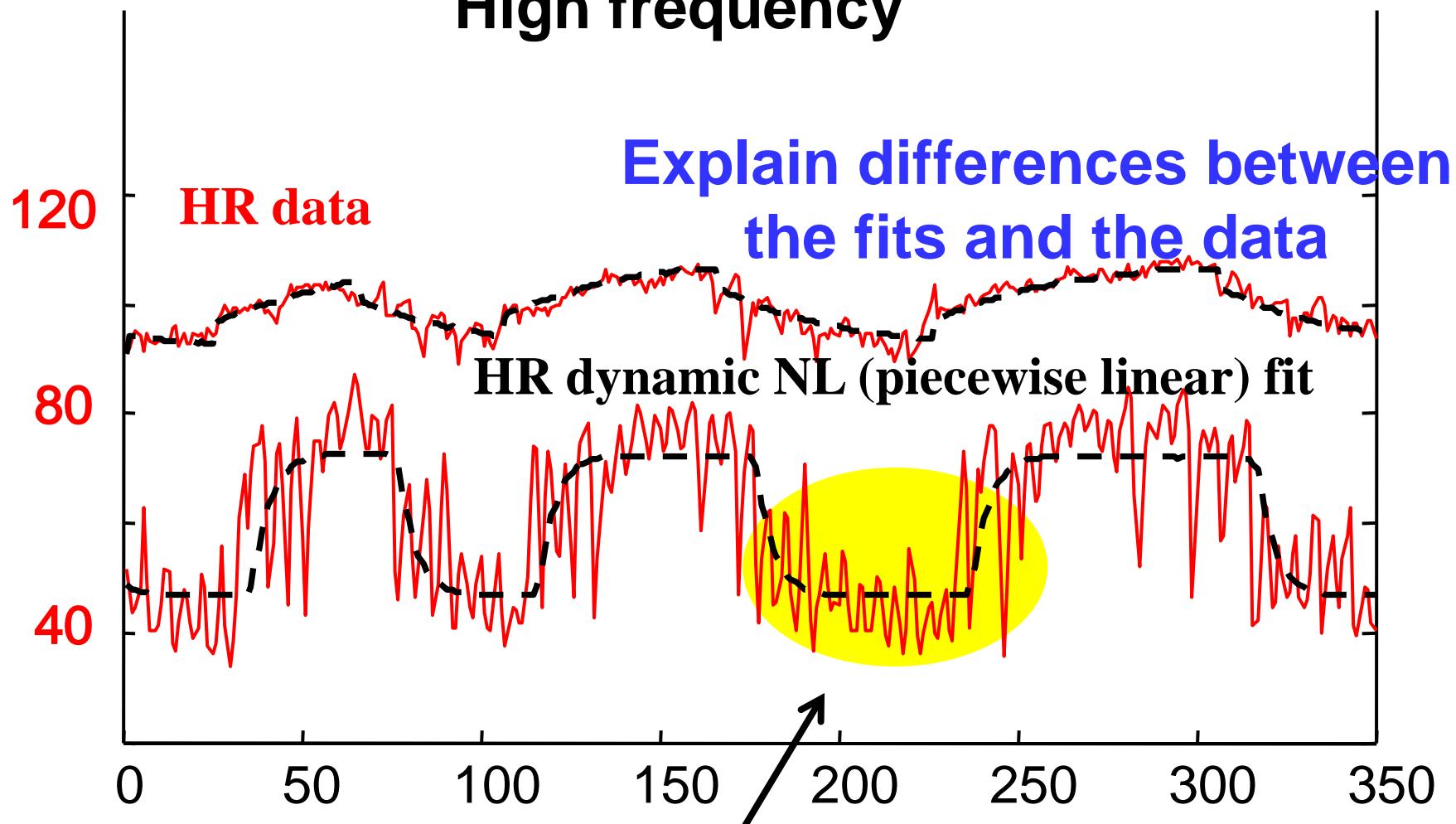


$$\Delta h(t) = h(t+1) - h(t) = a \cdot h(t) + b \cdot w(t) + c$$

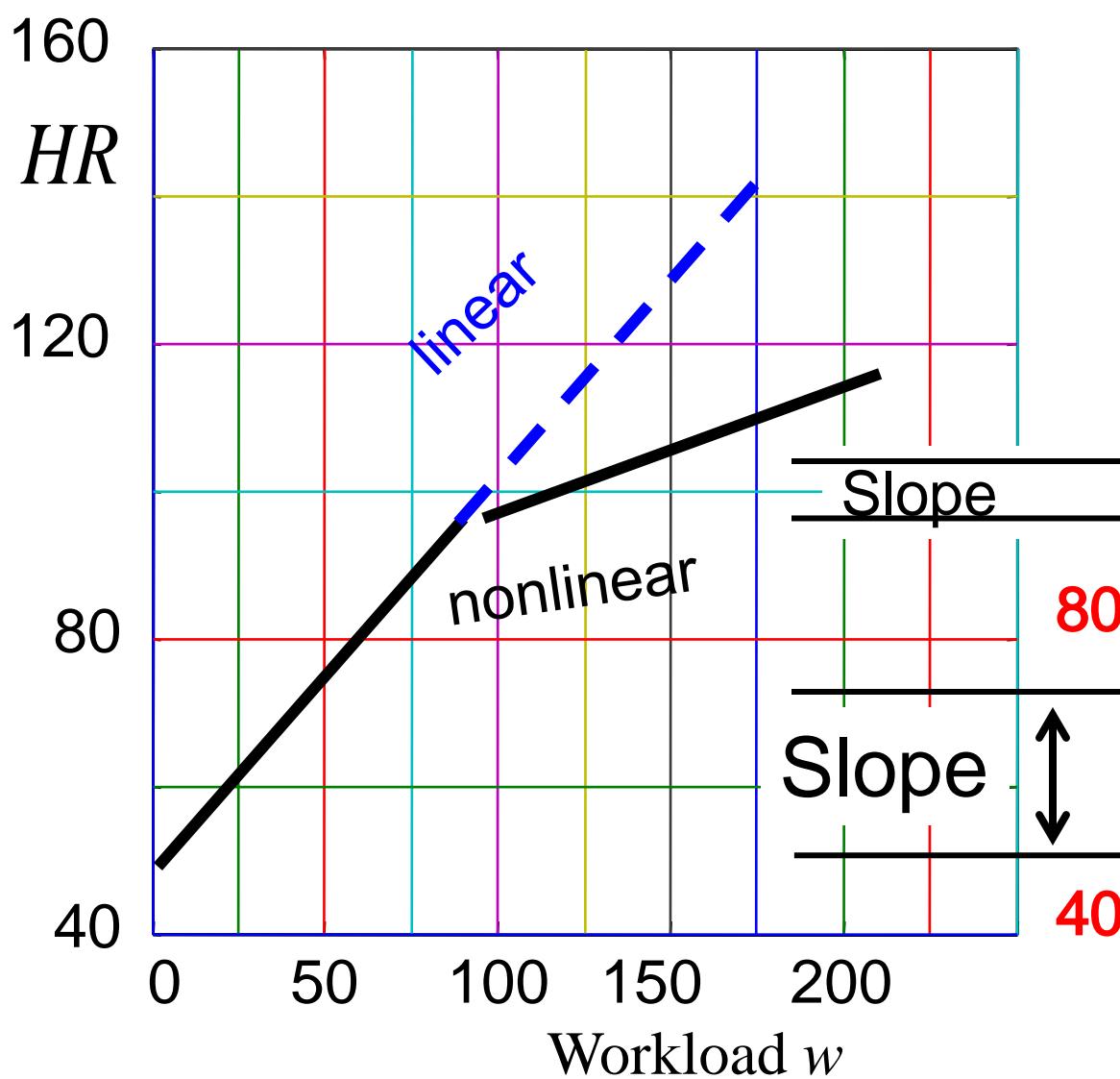
Nonlinearity



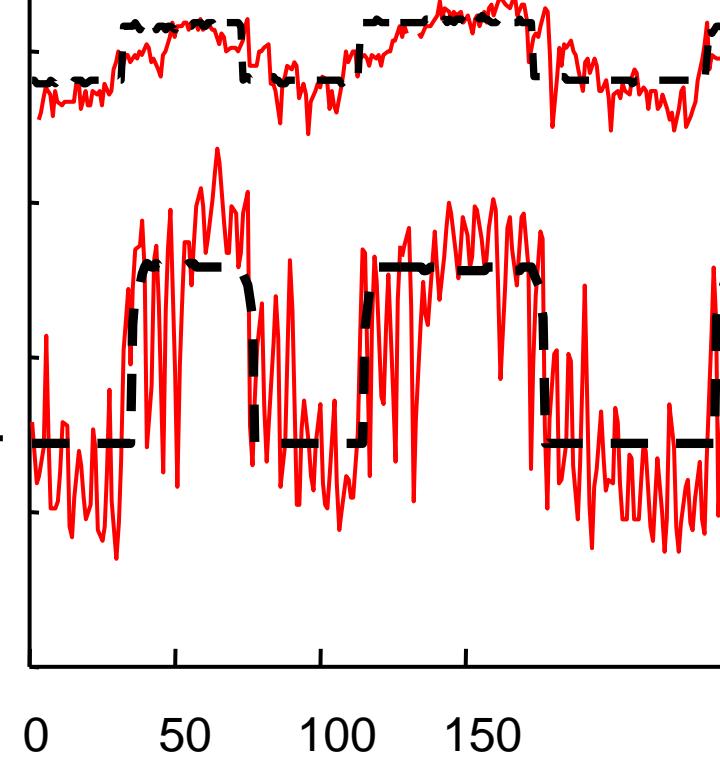
High frequency



Lower mean, higher variability (RSA)

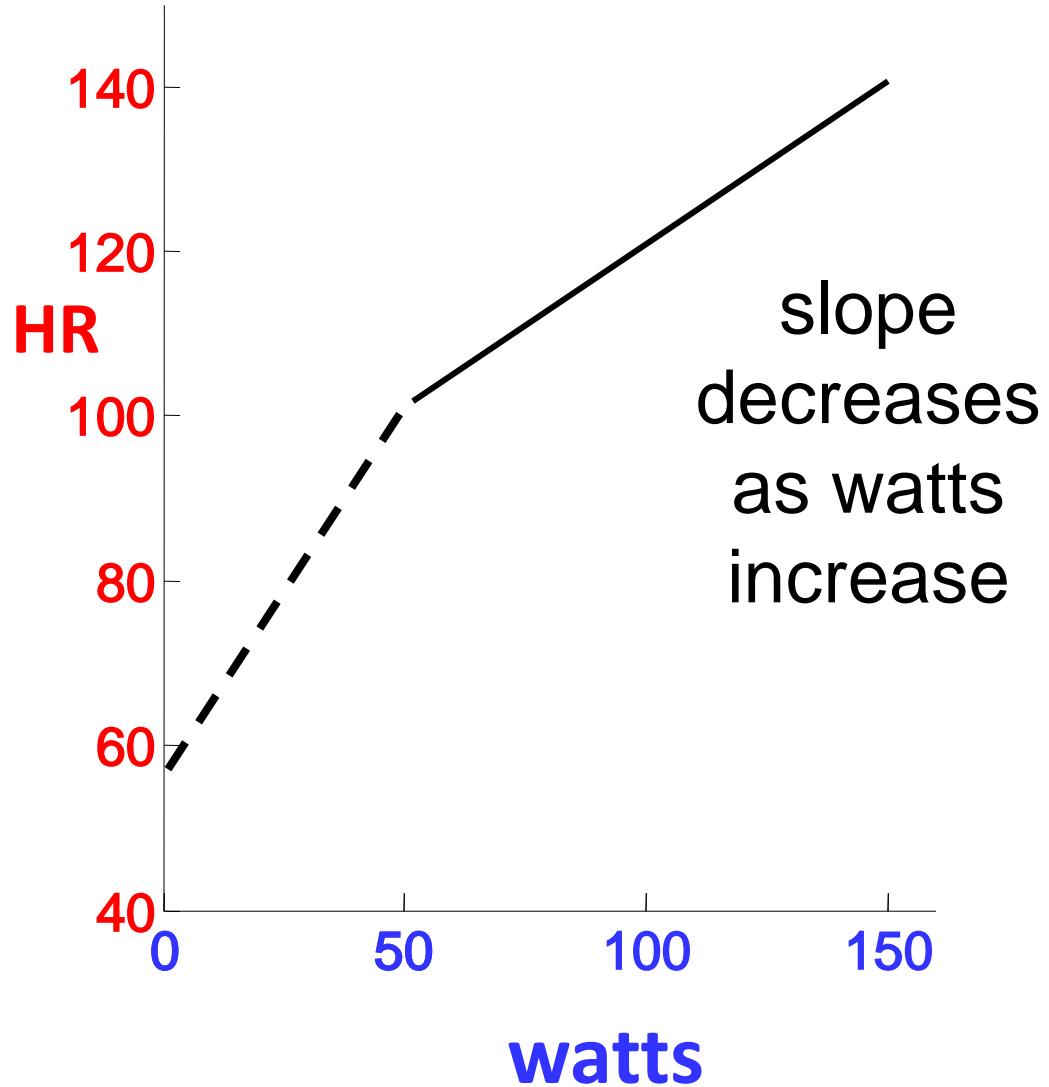


Static model:
HR vs W

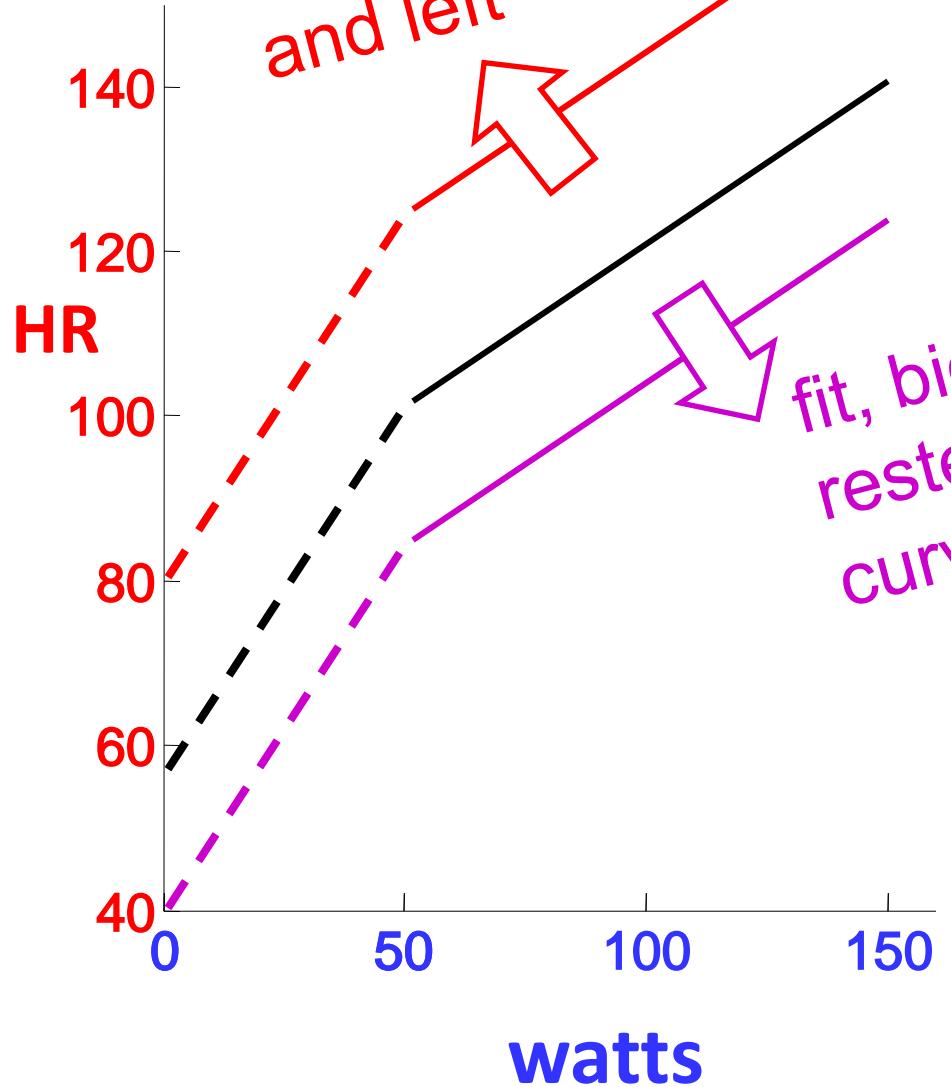


The simplest case of changing
HRV, mean ↑ and variability ↓

Standard picture



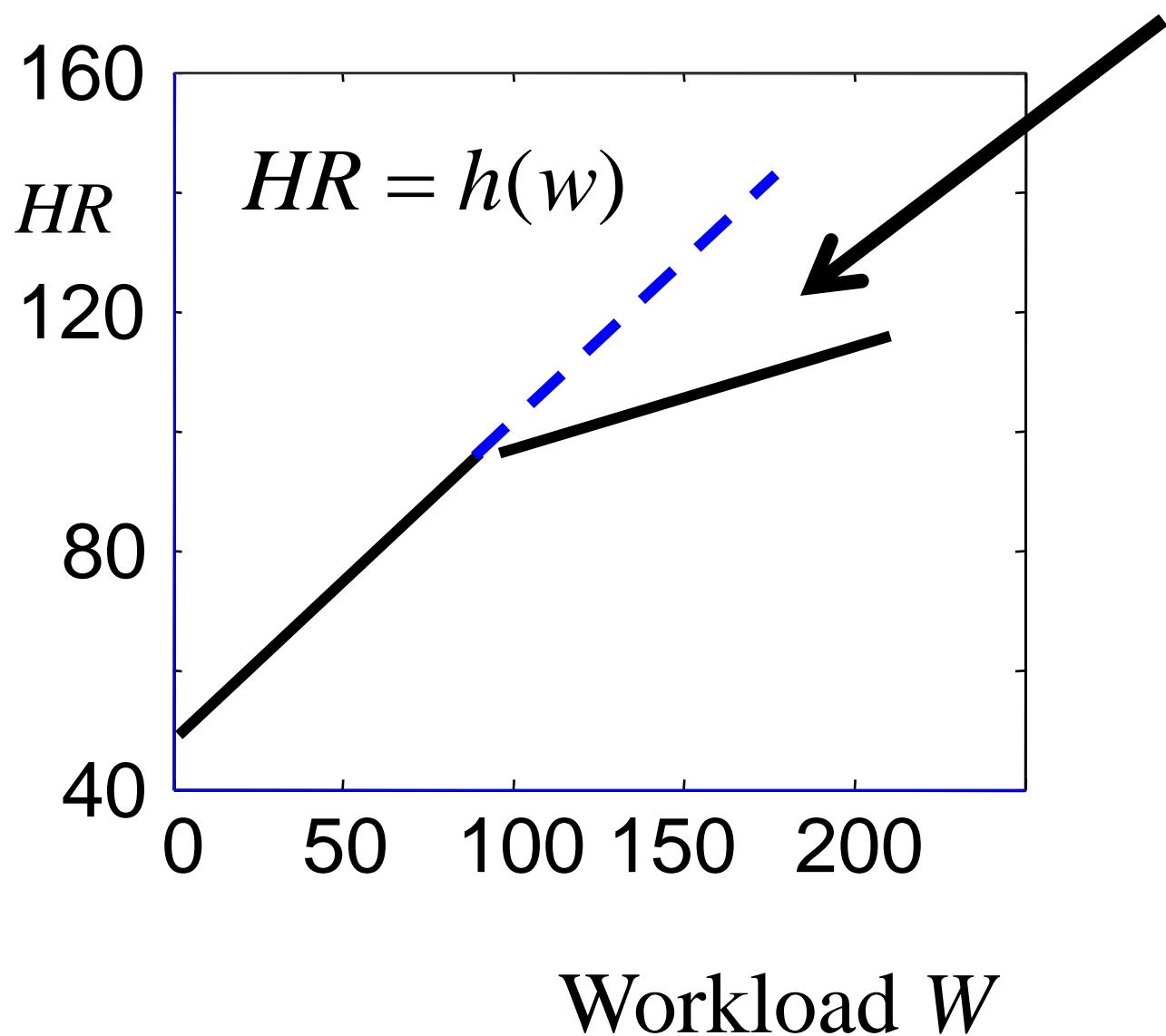
ill, weak, old, small,
etc moves curve up
and left



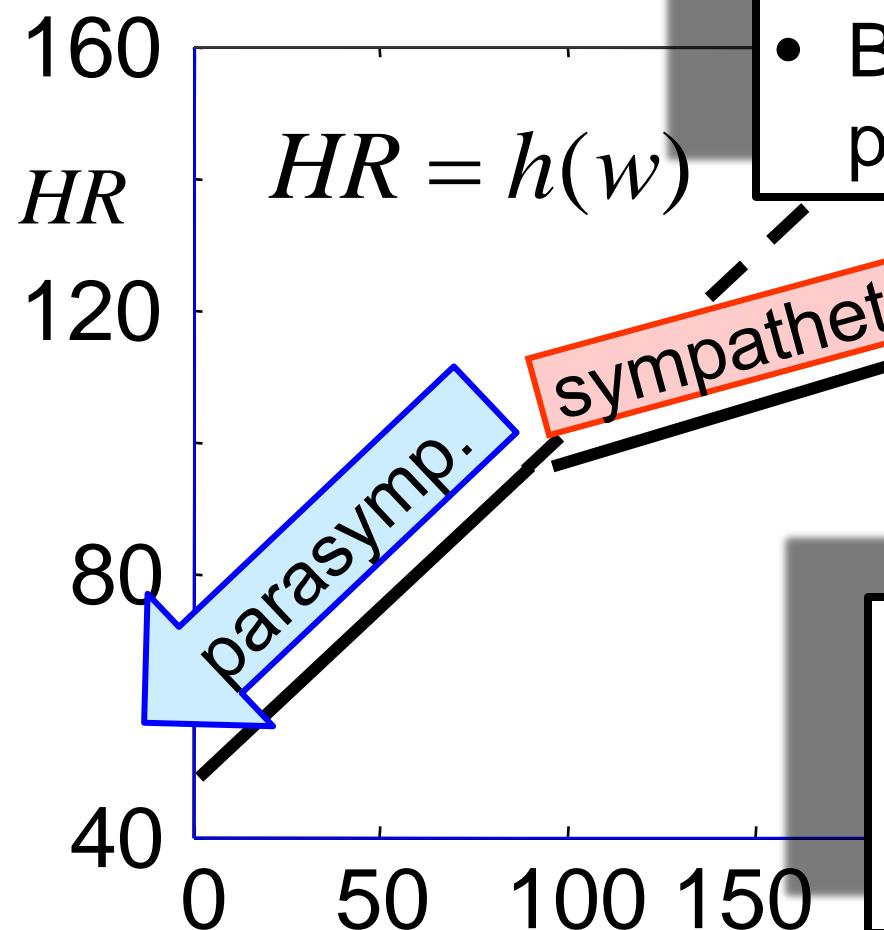
fit, big, young,
rested, etc... moves
curve down and right

slope still decreases
as watts increase

Nonlinearity in the *data*



Why?



- Proximal cause: Autonomic nervous system balance
- Between sympathetic and para-sympathetic

- Deeper why: evolution and physiology
- Accident or necessity?

Workload W

Homeostasis

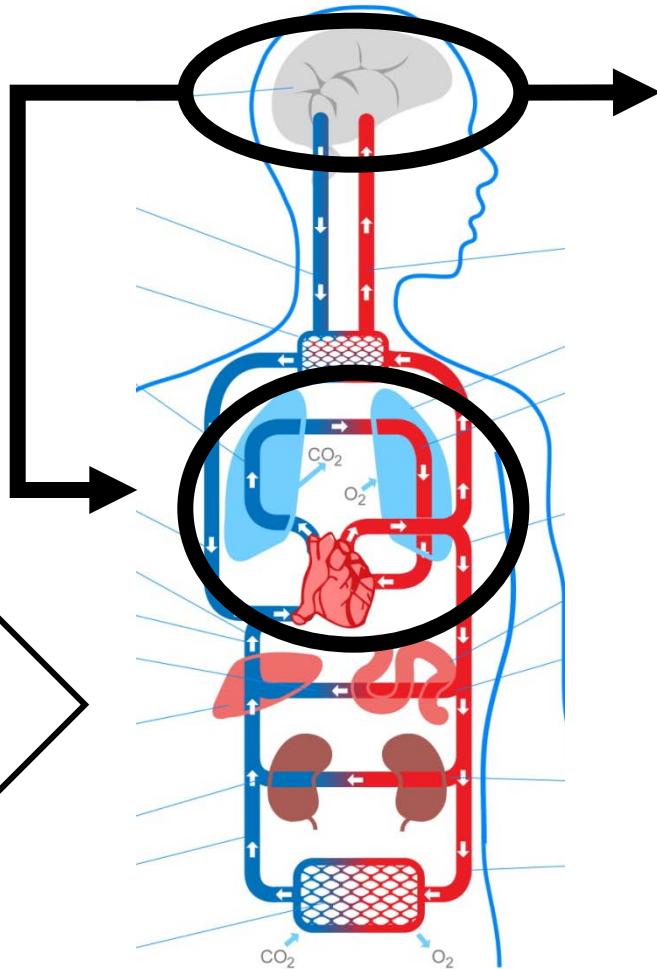
controls

heart rate
ventilation

energy

errors

O₂
BP

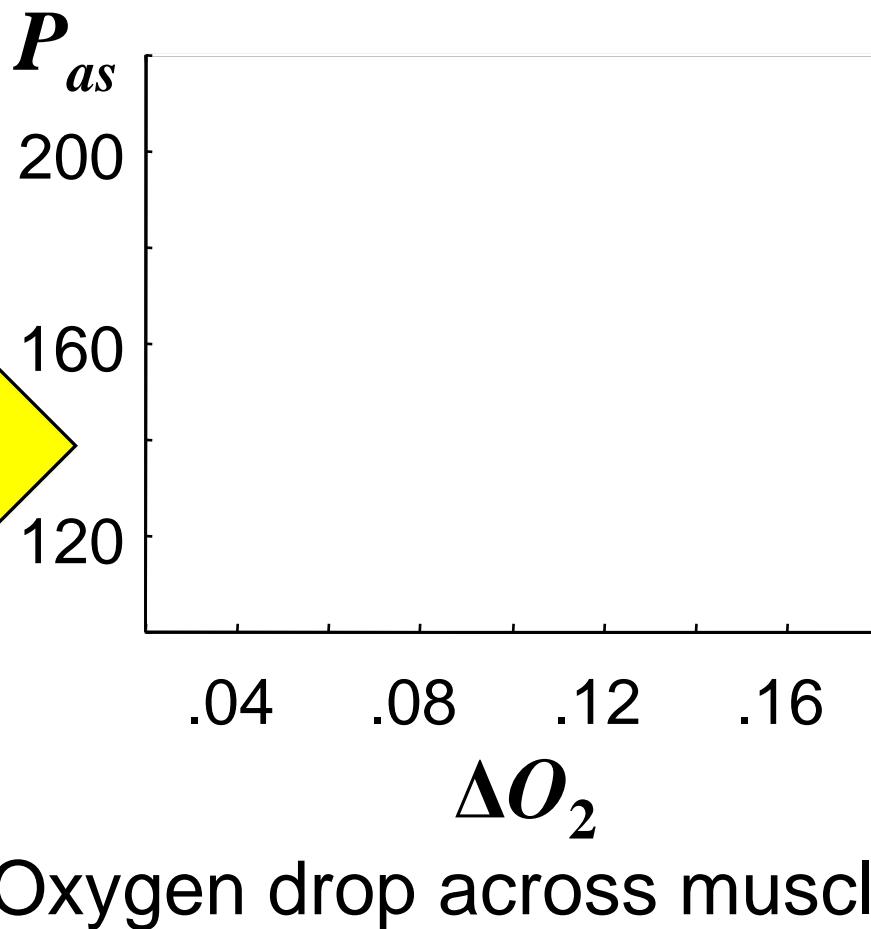
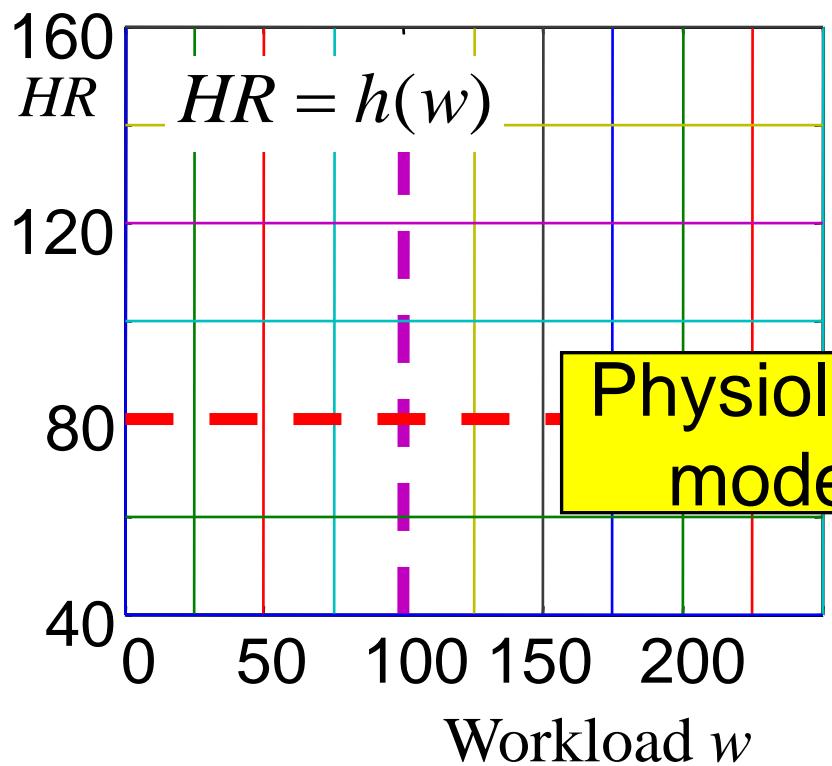


Minimal
mechanistic
model

external
disturbances

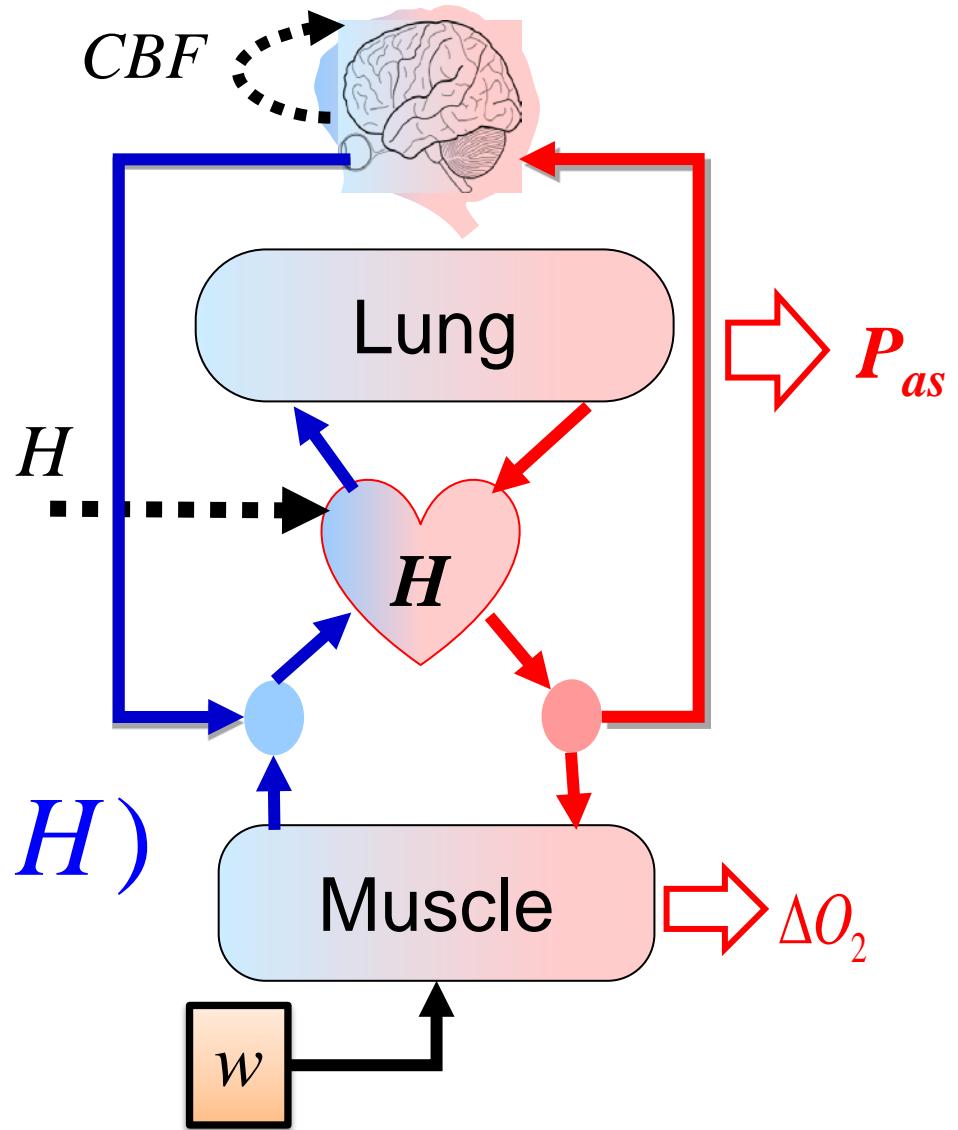
Physiological model

Mean Arterial Blood Pressure

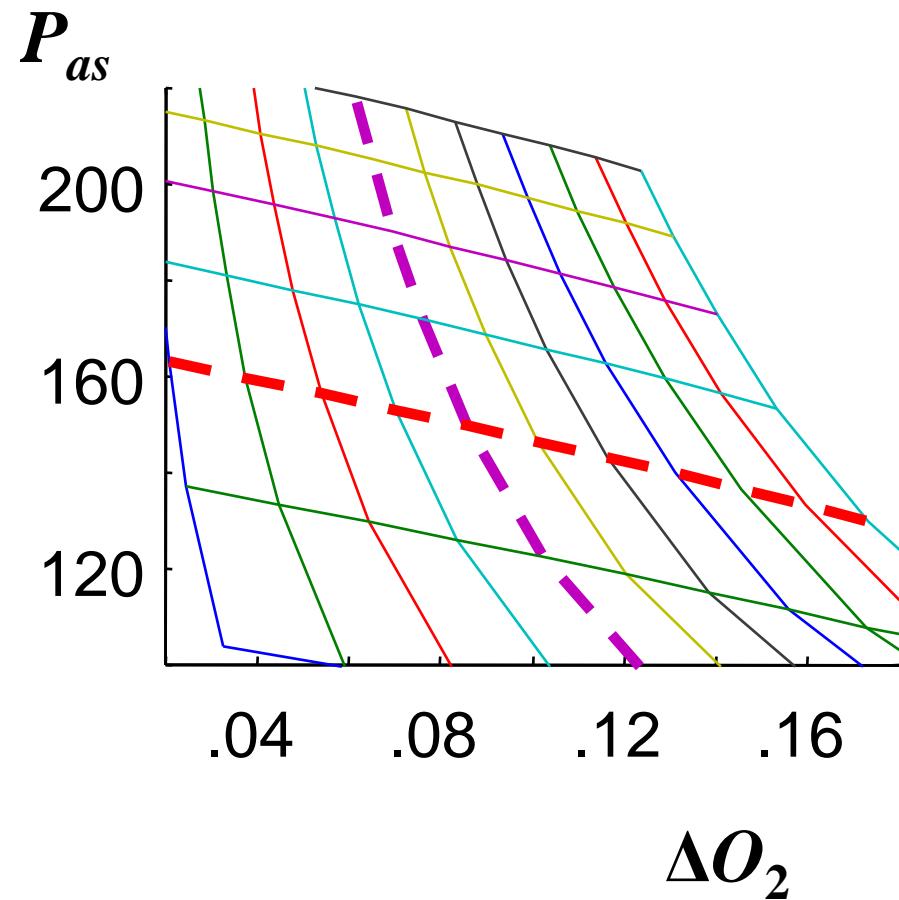
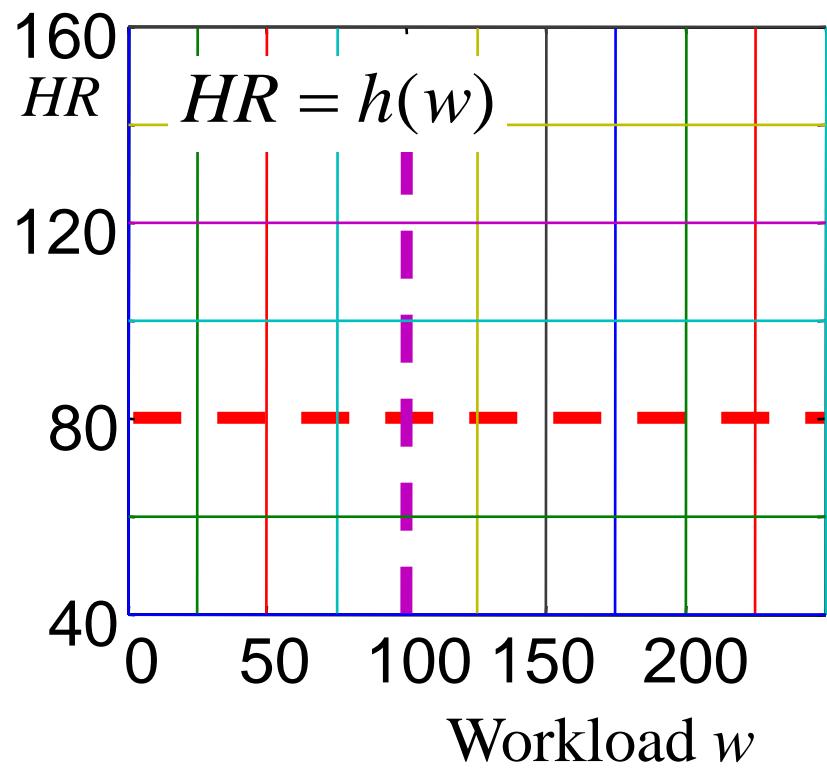


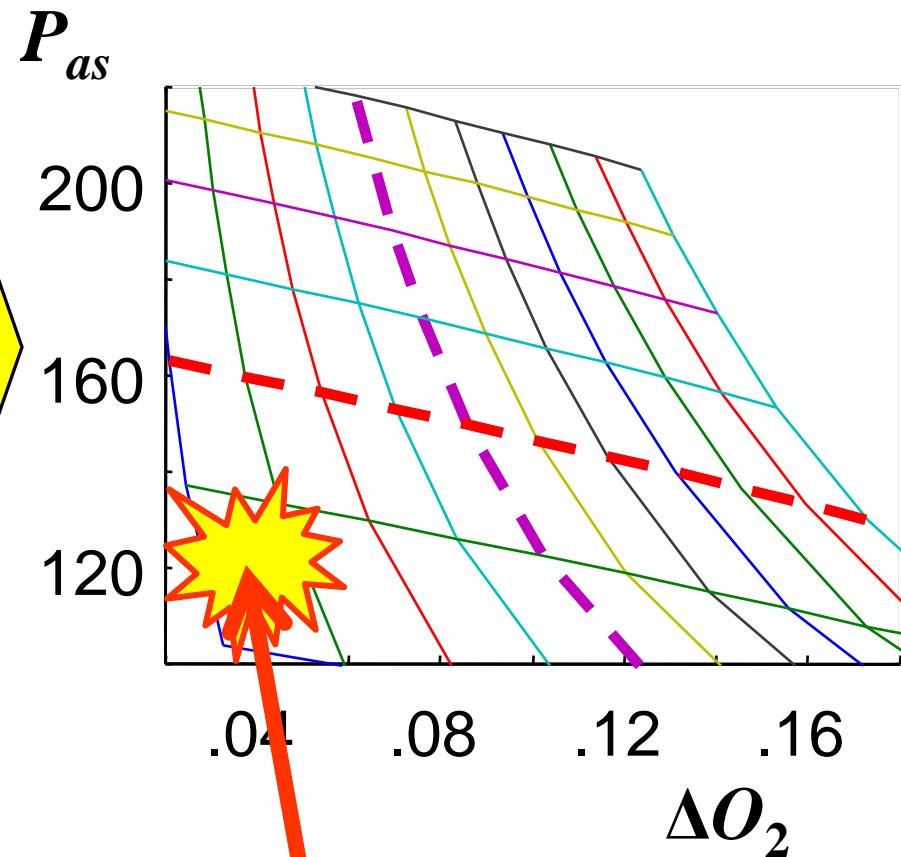
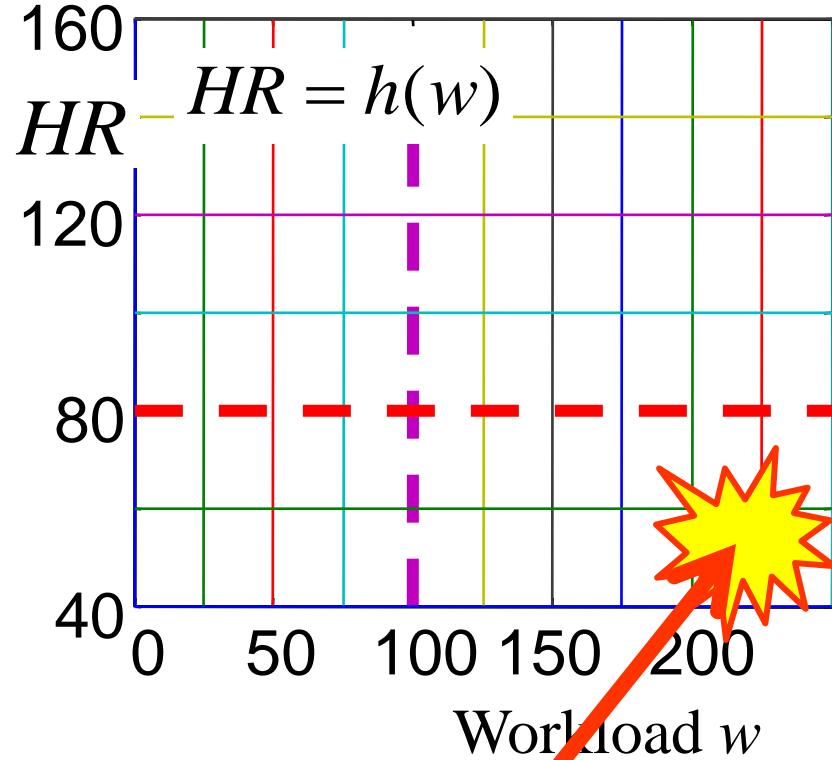
$$(BP, \Delta O_2) = F(w, H)$$

The simplified physiological model:



Intuition

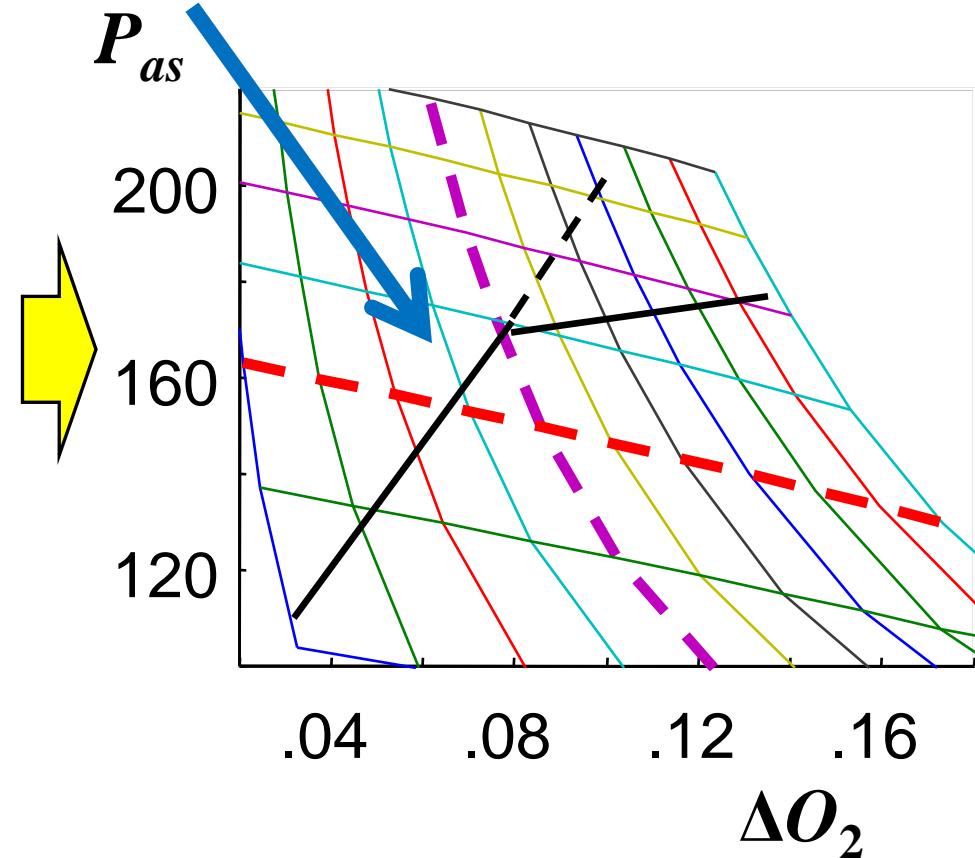
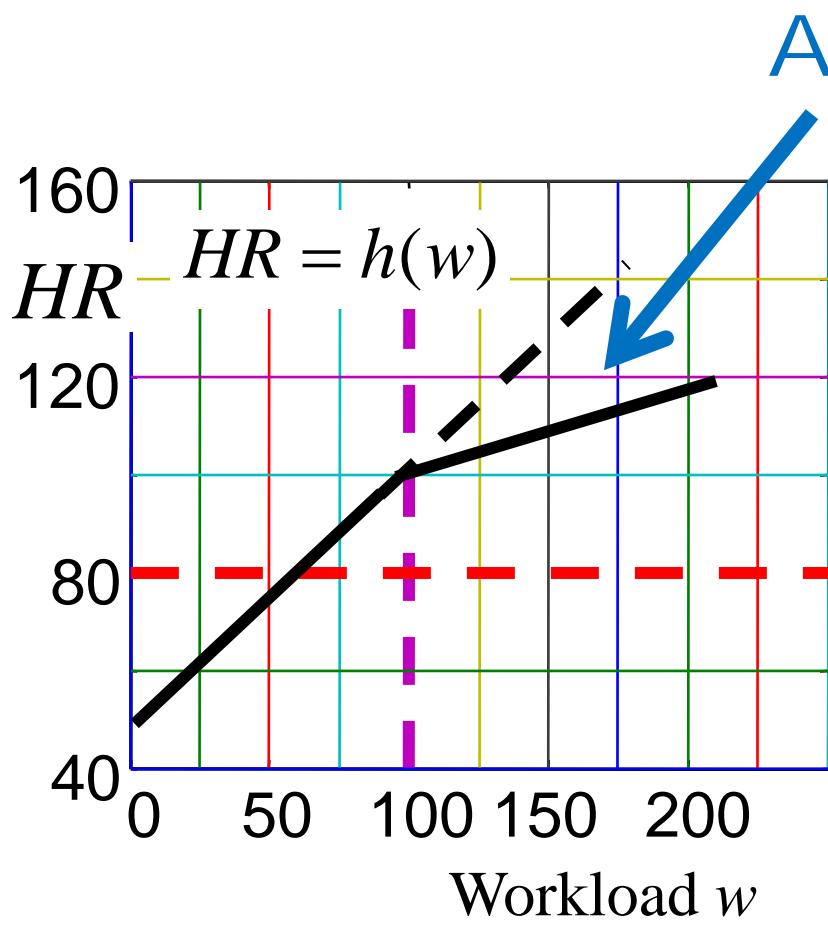




Oxygen drop across muscle

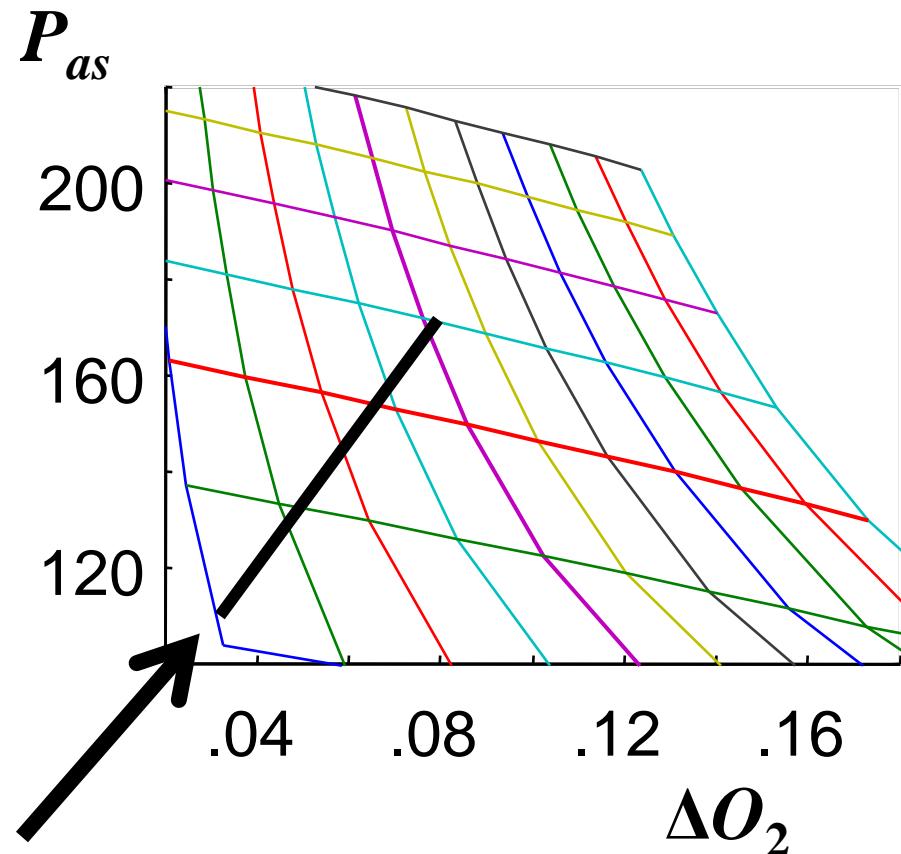
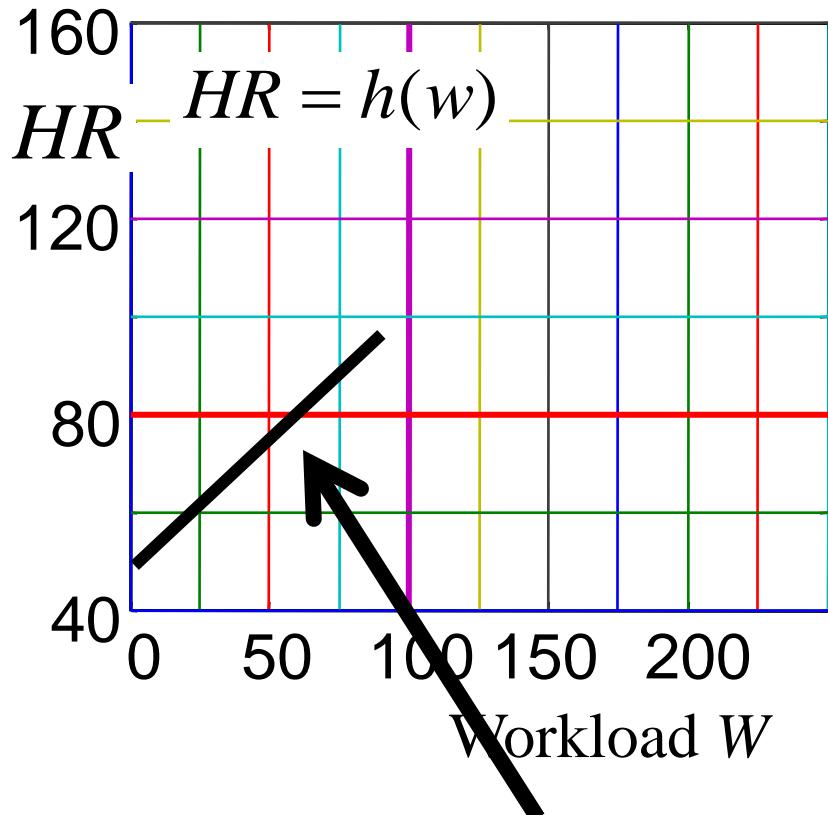


Why? Necessary?



Why?

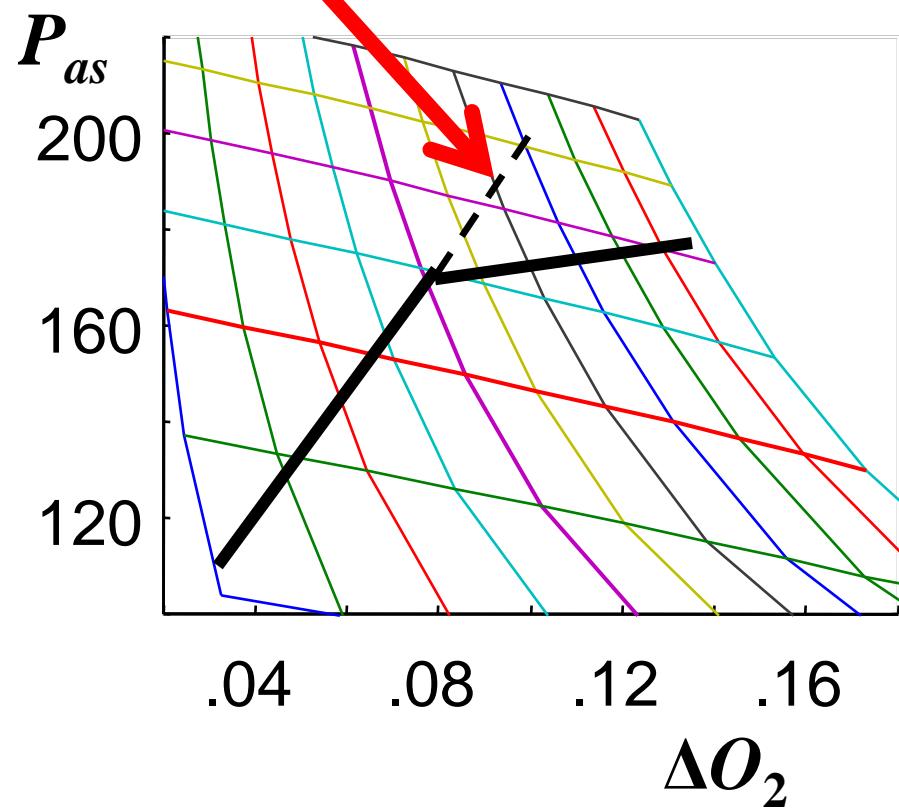
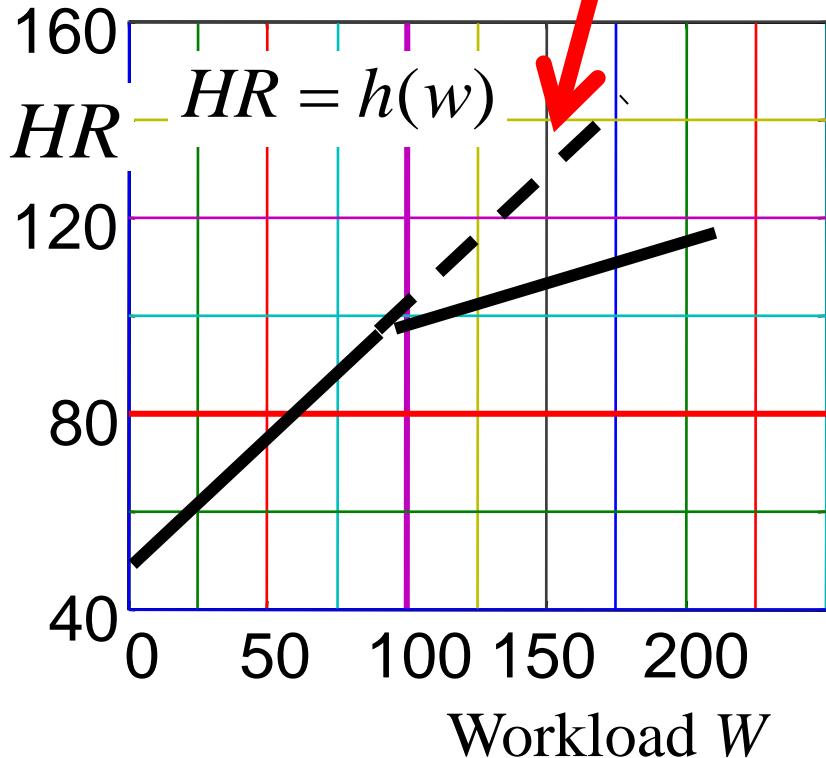
Intuition



- At low watts and HR,
- BP not an issue,
- so only metabolism matters.

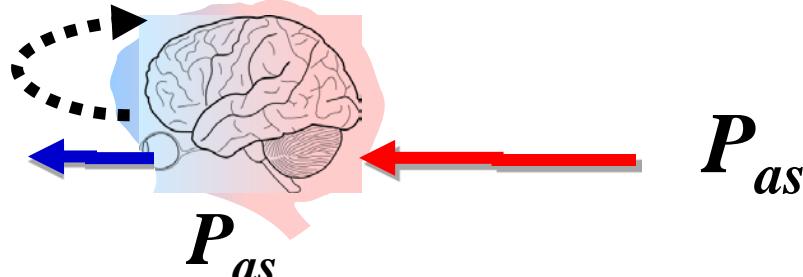
Why?

- At high watts and HR,
- high BP is an issue,



- At low watts and HR,
- BP not an issue,
- so only metabolism matters.

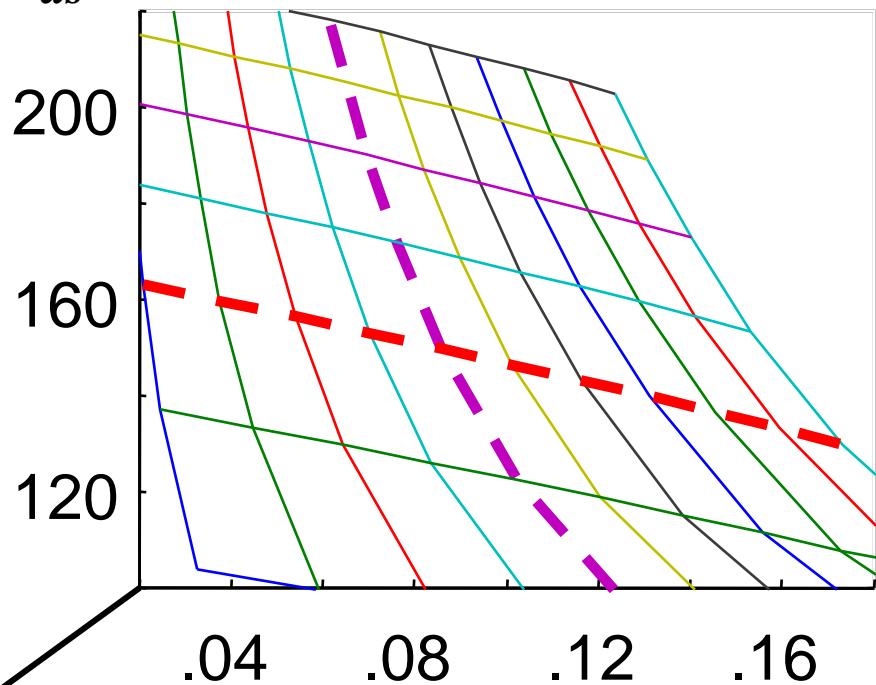
CBF



P_{as}

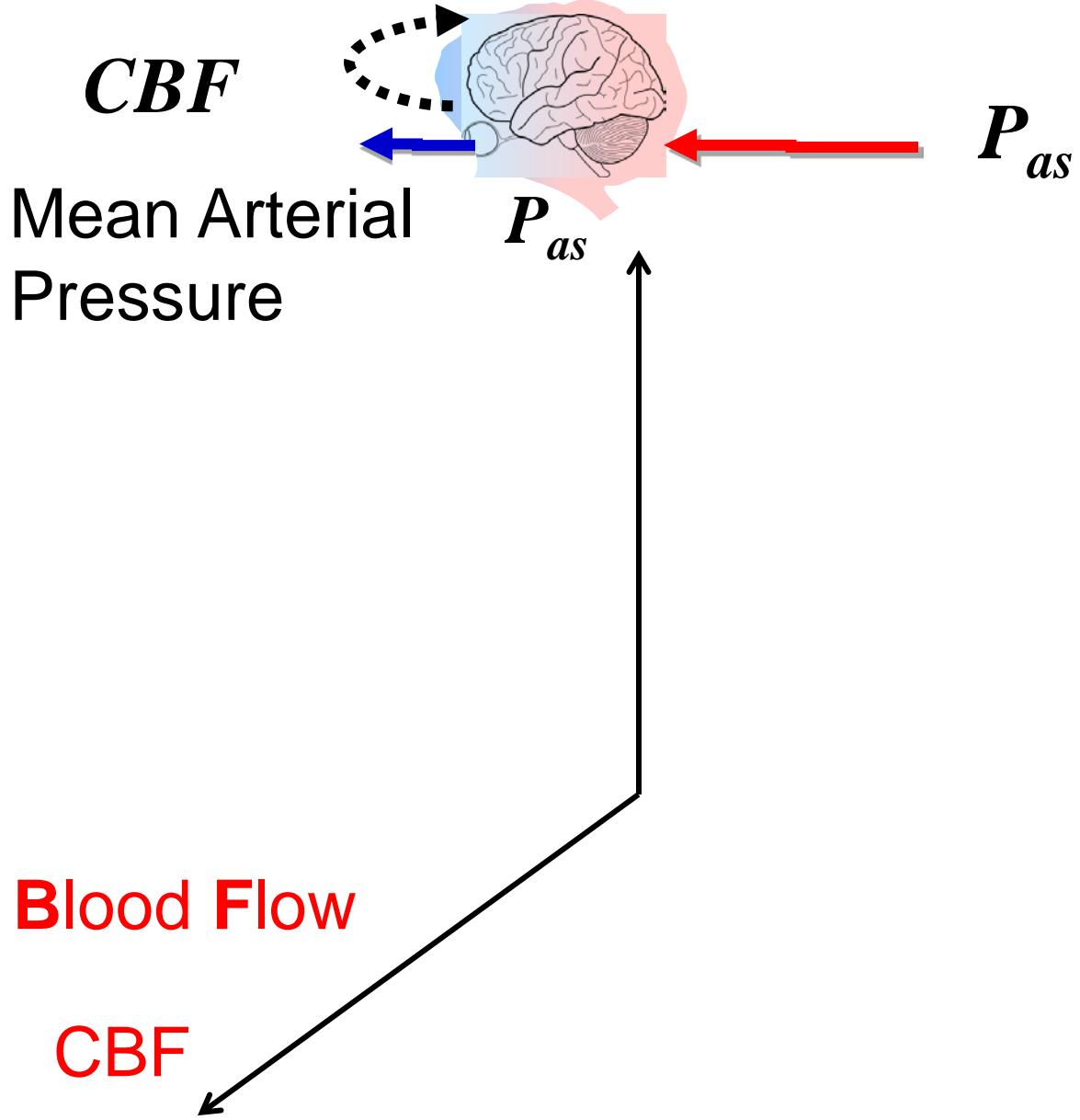
Cerebral Blood Flow

CBF



ΔO_2

Oxygen drop across muscle



Cerebral
Perfusion
Pressure

$\approx P_{as}$

(mm Hg)

CBF

P_{as}

200

150

50

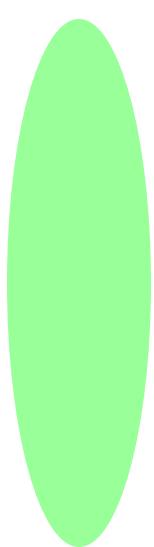
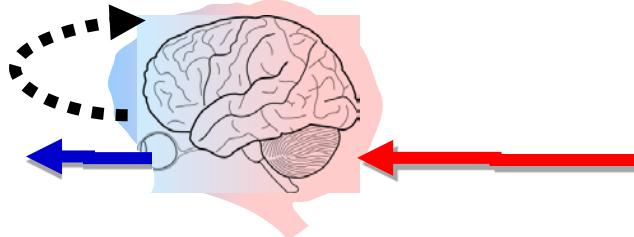
0

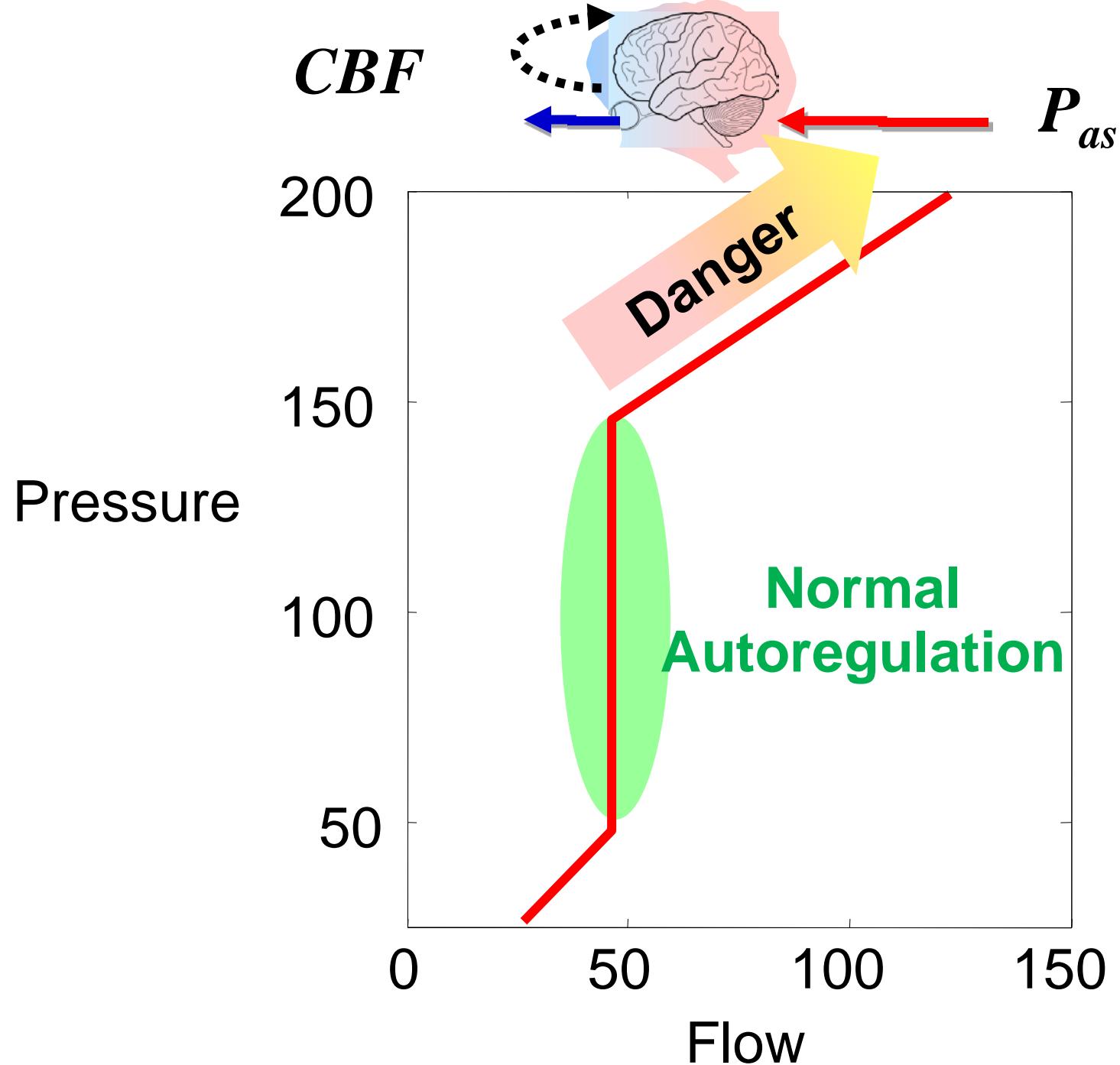
50

100

150

Cerebral Blood Flow (CBF) (ml/100g/min)





Actuator saturation

$\approx P_{as}$

200

150

100

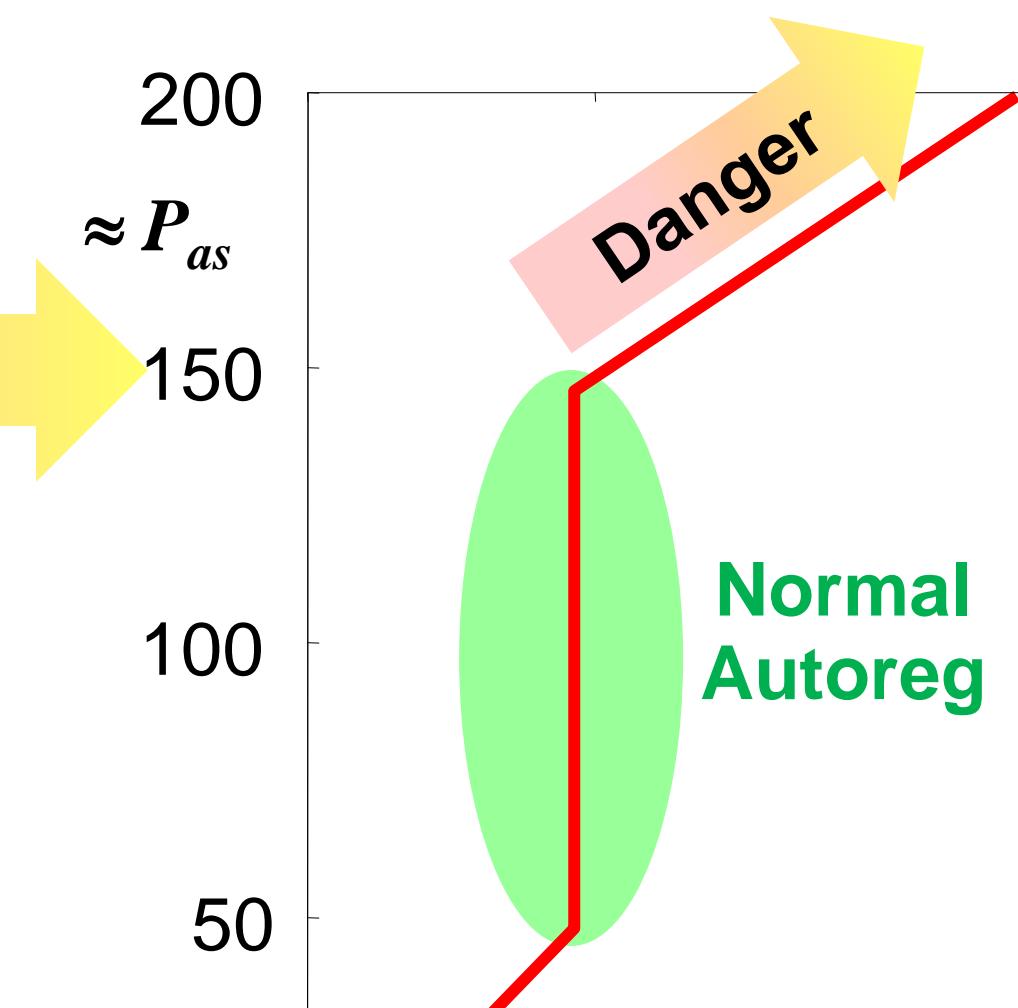
50

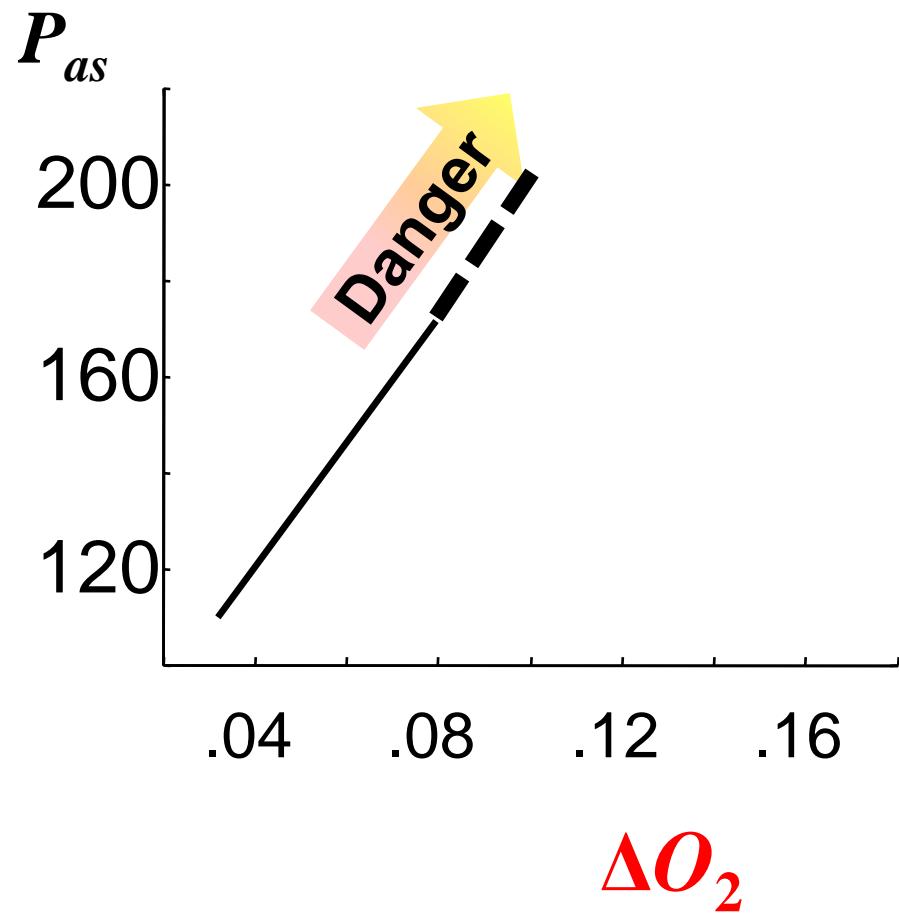
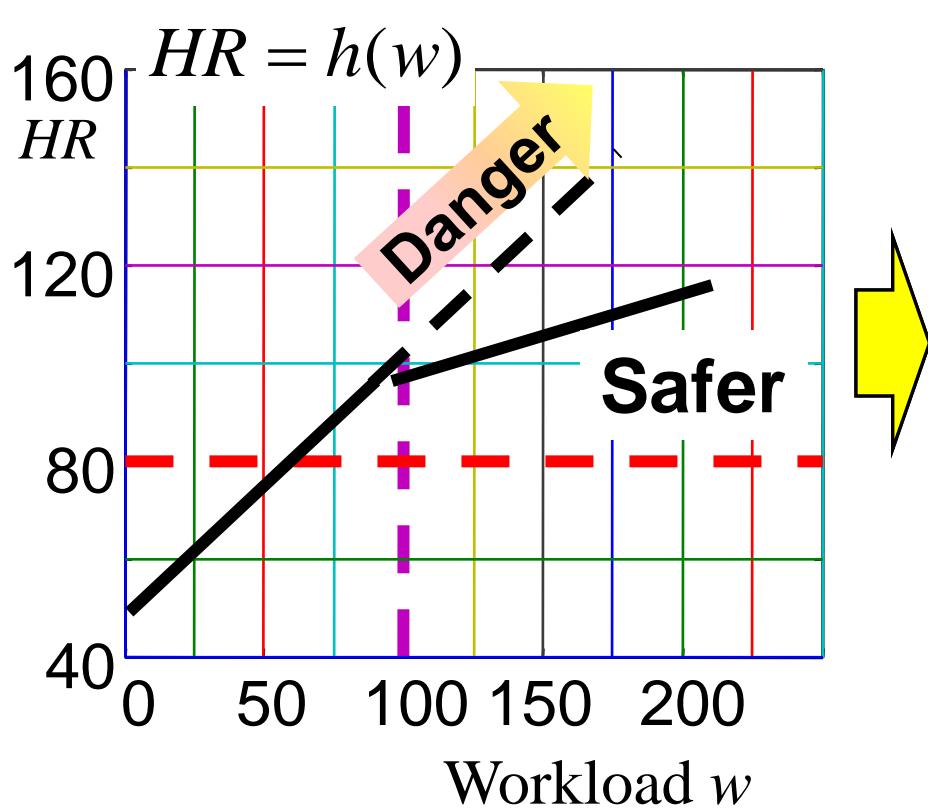
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Danger

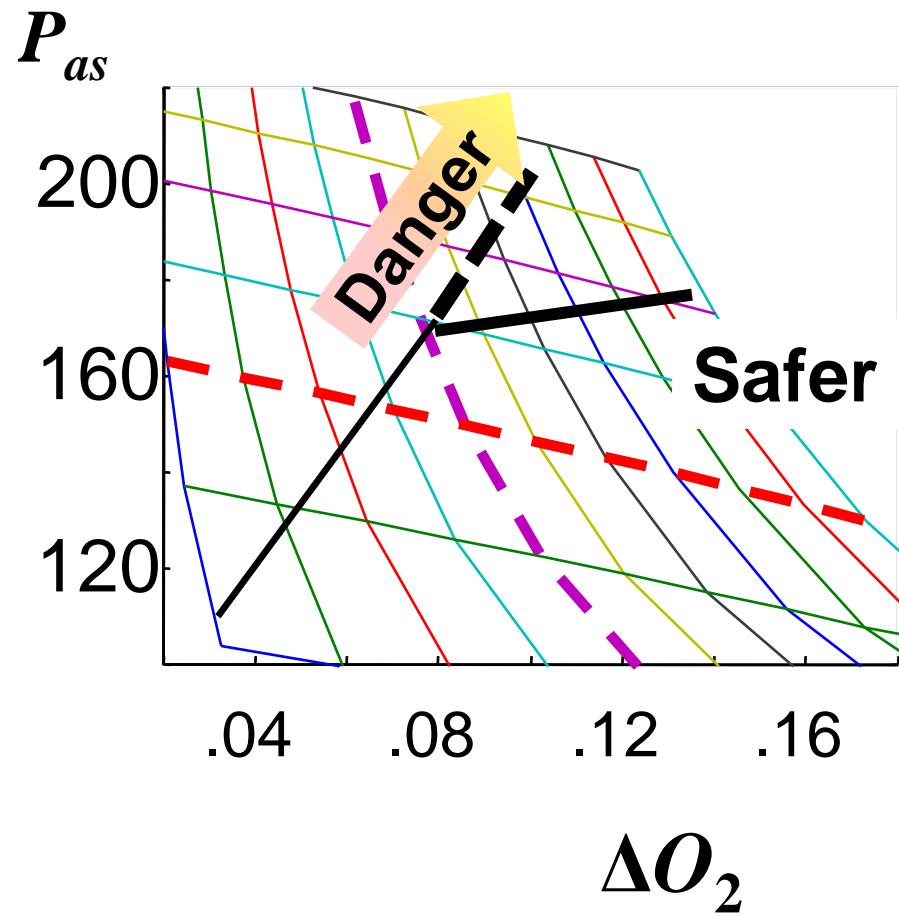
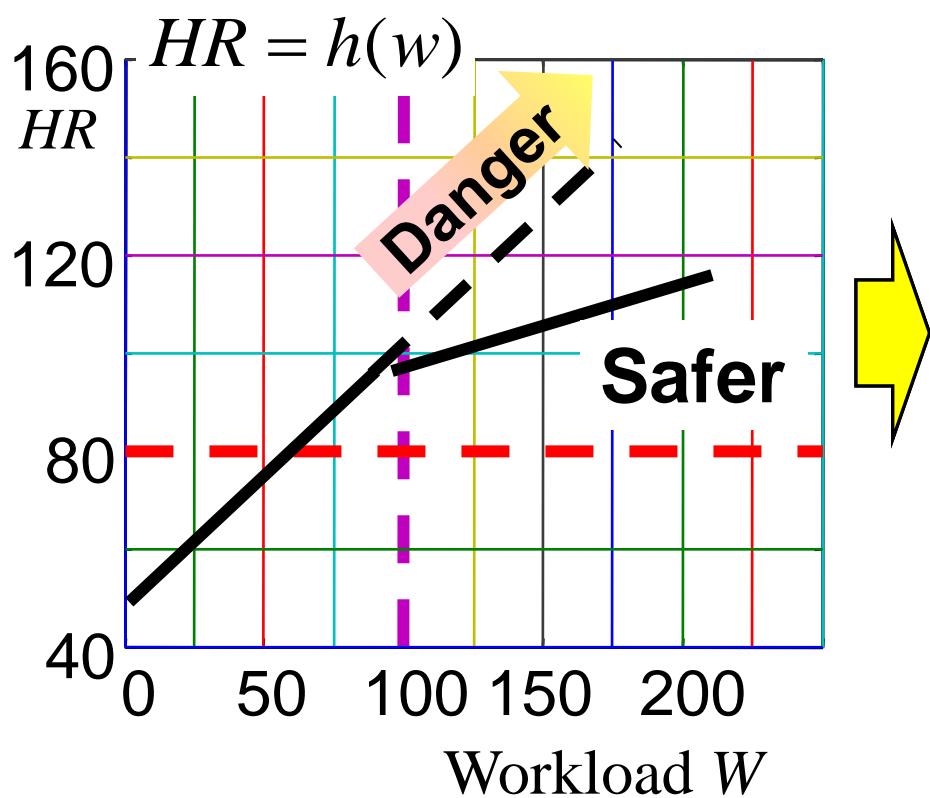
Normal
Autoreg

CBF

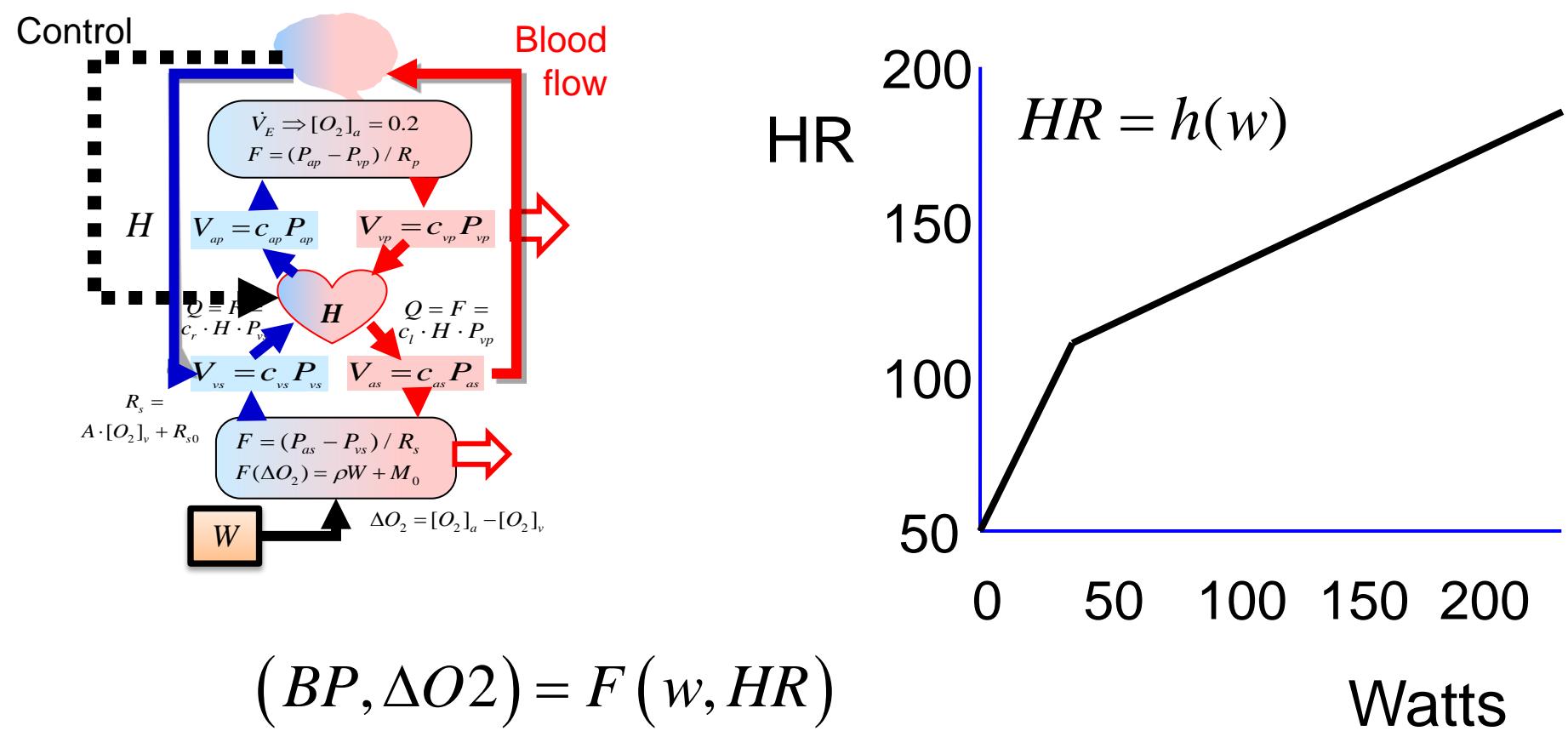




Oxygen drop
across muscle



Safer \Rightarrow worse ΔO_2
 \Rightarrow metabolic cost

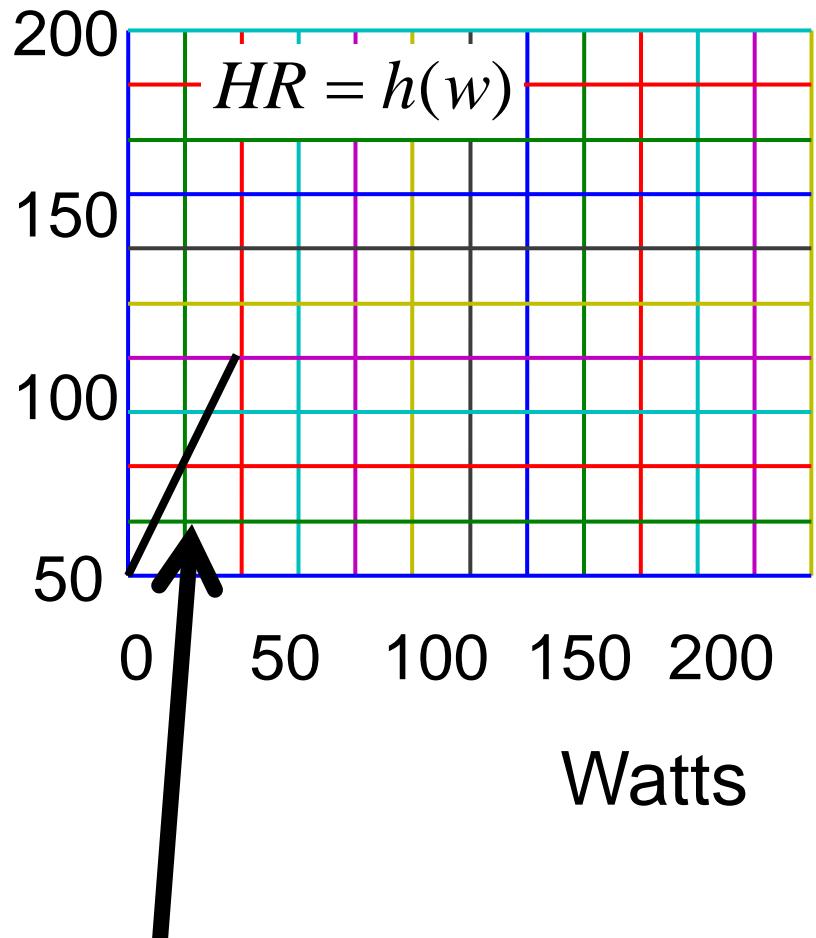
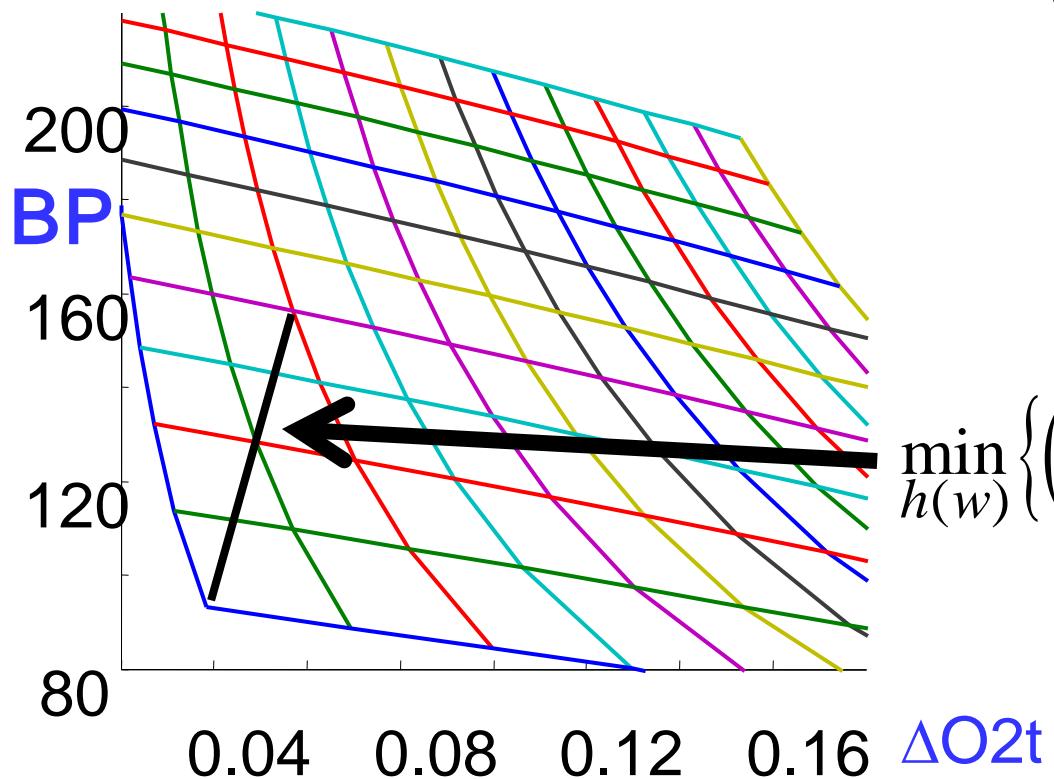


static optimization problem

$$\min_{h(w)} \left\{ \left(p(BP)^2 + q(\Delta O_2)^2 + r(HR)^2 \right) \right.$$

$$\left| HR = h(w) \quad (BP, \Delta O_2) = F(w, HR) \right\}$$

At low watts and HR, high BP is not an issue, so only metabolism matters.

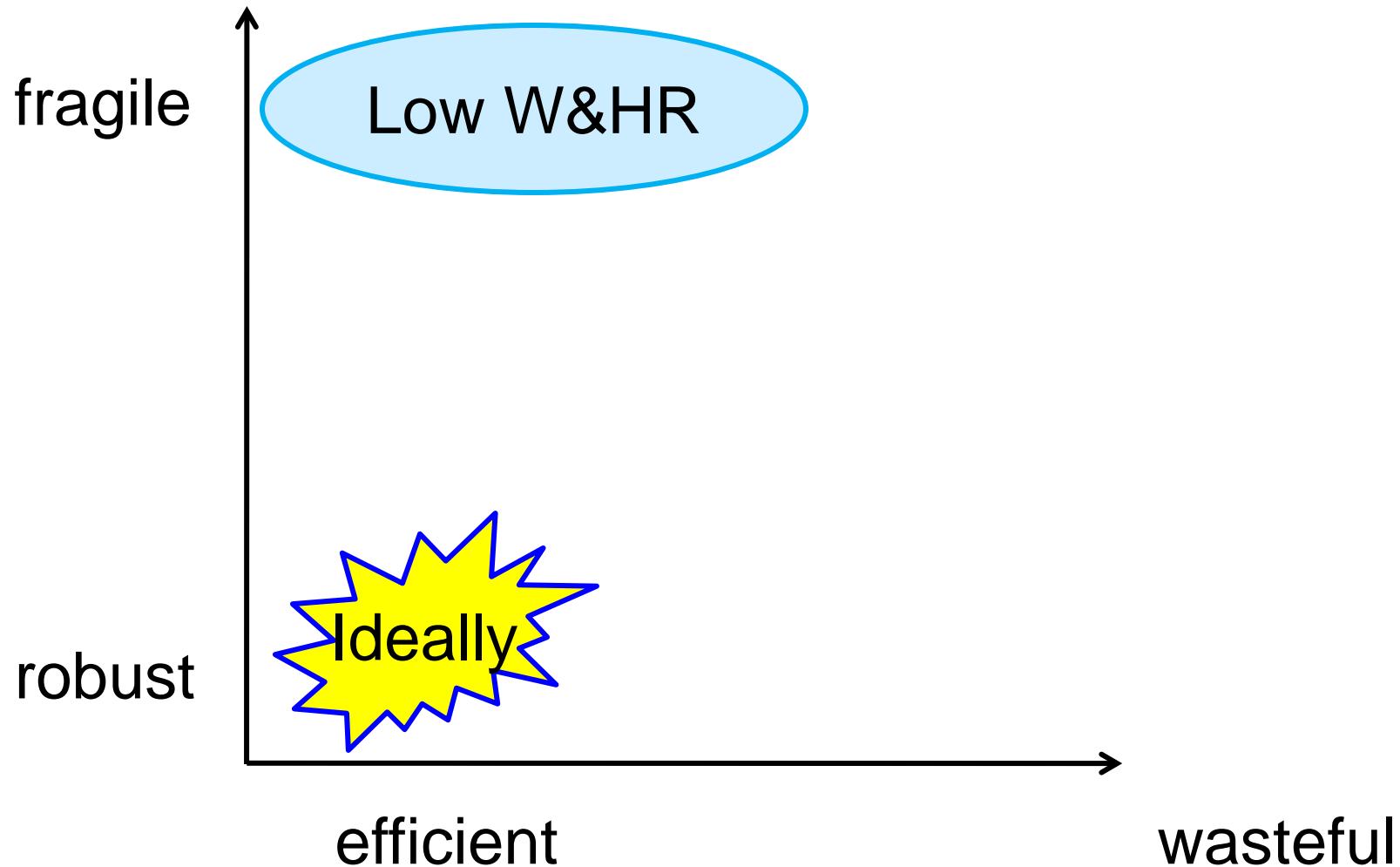


$$\min_{h(w)} \left\{ \left(p(BP)^2 + q(\Delta O_2)^2 + r(HR)^2 \right) \right\}$$

p, r : very small

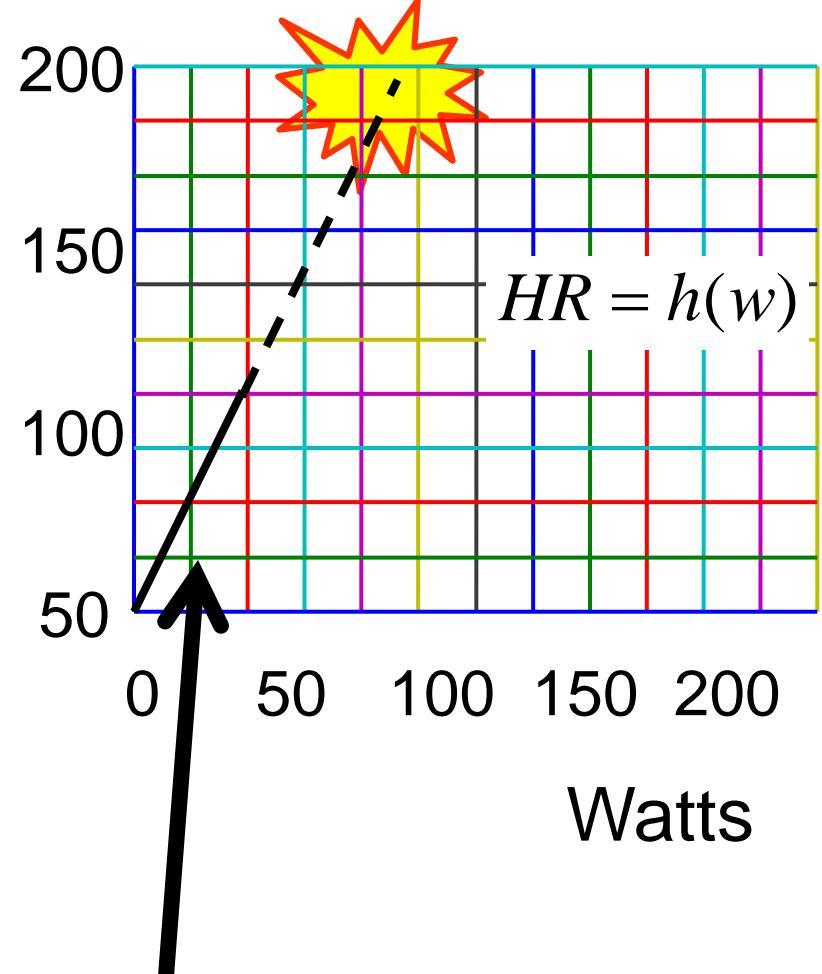
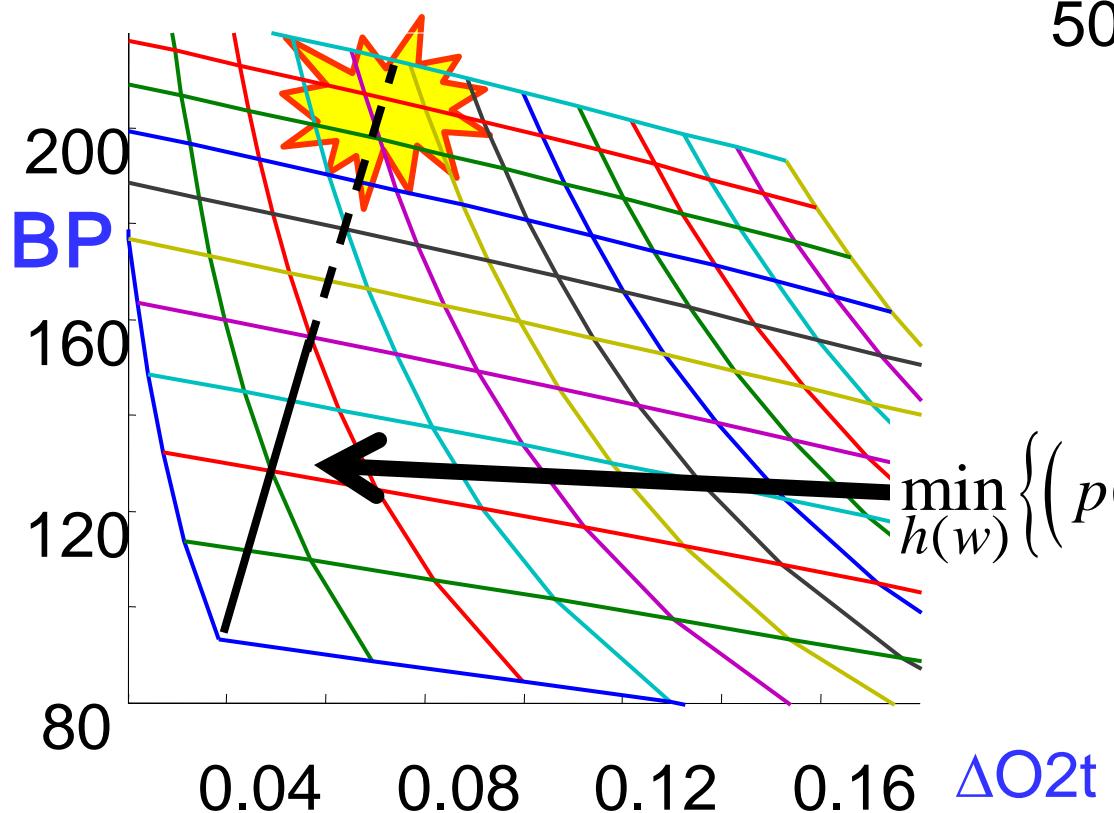
Architecture

Low watts and HR



Not sustainable

High BP >160 matters,
as does HR > 100

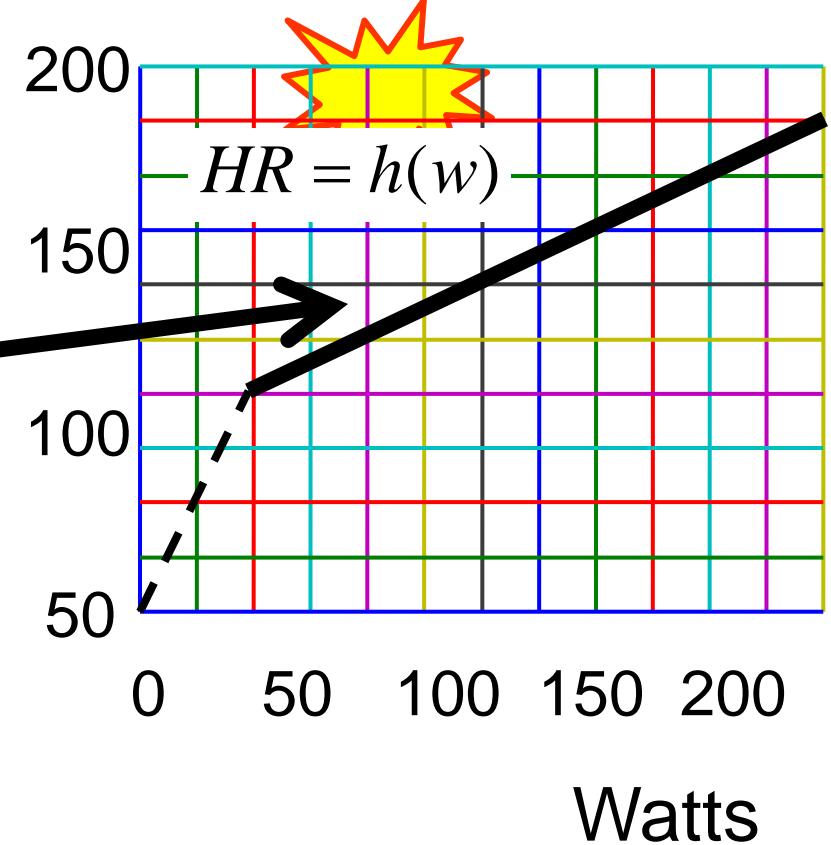
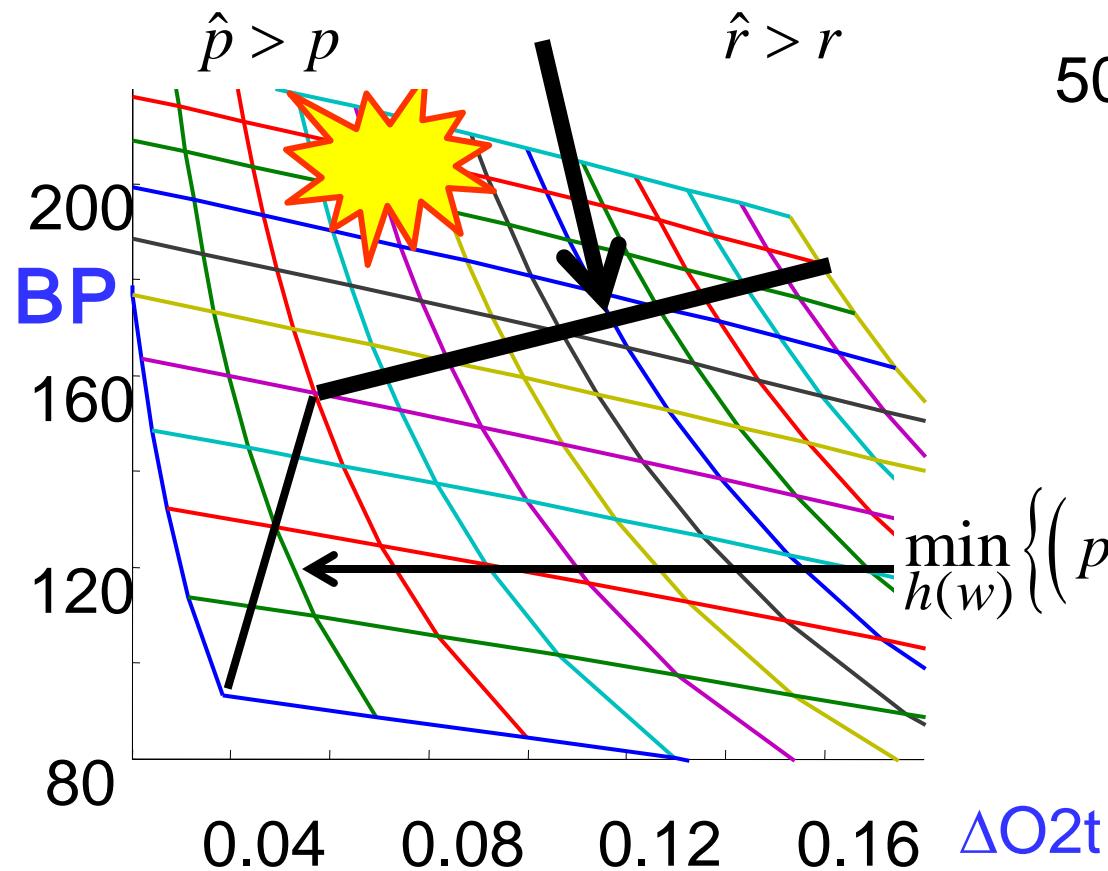


$$\min_{h(w)} \left\{ \left(p(BP)^2 + q(\Delta O2)^2 + r(HR)^2 \right) \right\}$$

$p, r:$ very small

So penalizing BP and HR more here

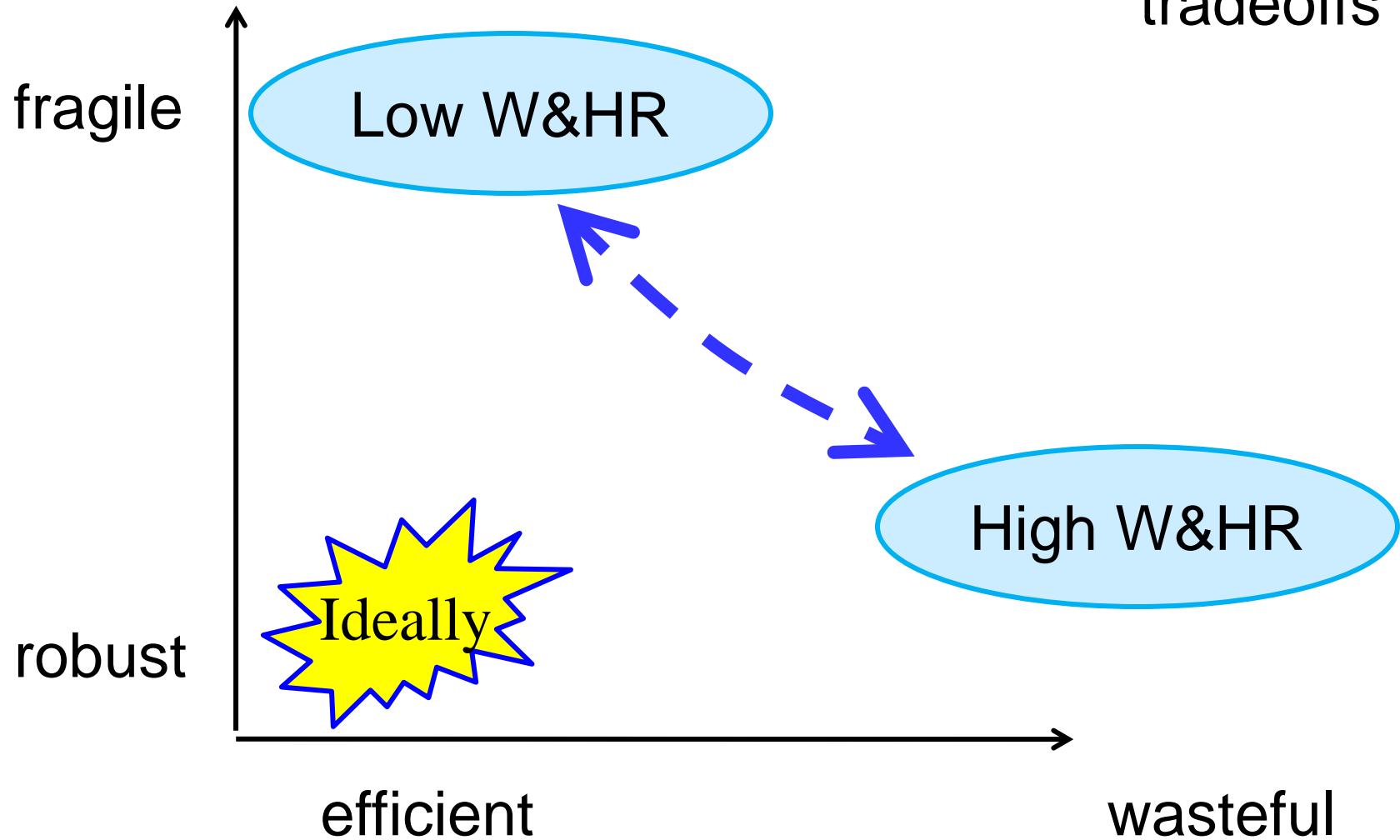
$$\min_{h(w)} \left\{ \hat{p} (BP)^2 + q (\Delta O2)^2 + \hat{r} (HR)^2 \right\}$$



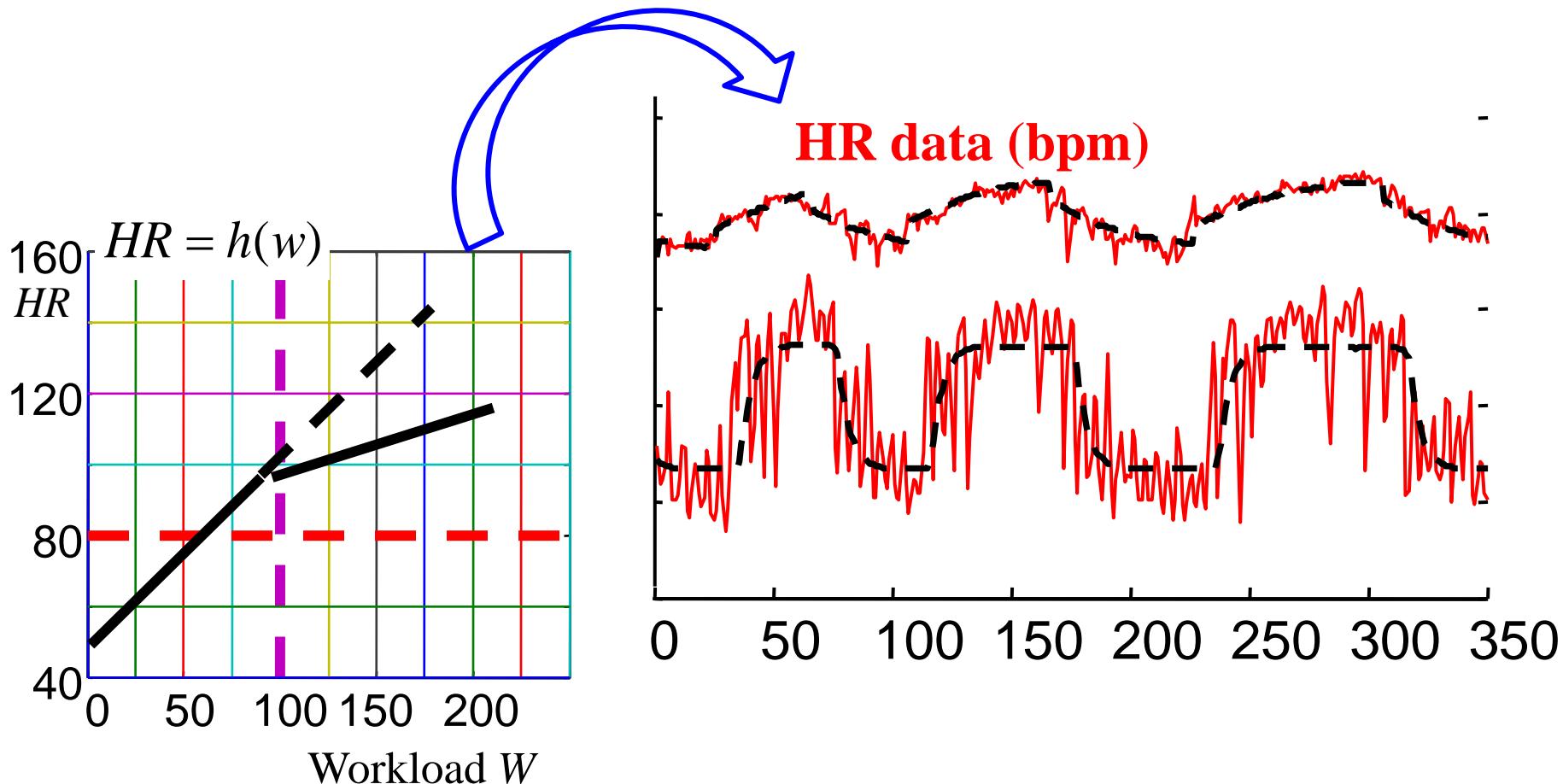
$p, r: \text{very small}$

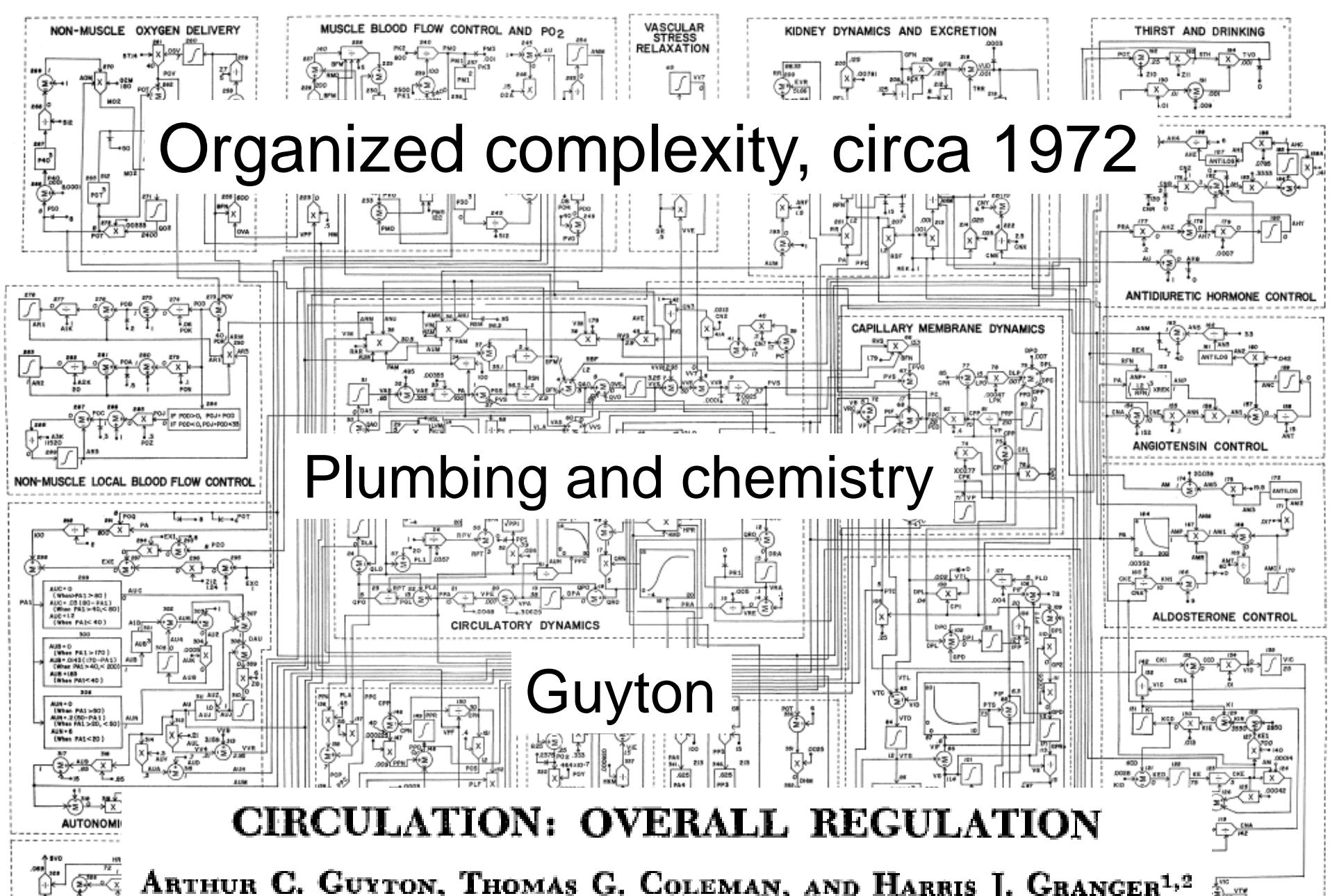
Laws & Architecture

Good architectures
allow for effective
tradeoffs



This idea can be used directly
with a *dynamic model*





ARTHUR C. GUYTON, THOMAS G. COLEMAN, AND HARRIS J. GRANGER^{1,2}

*The Department of Physiology and Biophysics, University of Mississippi
School of Medicine, Jackson, Mississippi*

This idea can be used directly with a dynamic model

Thousands of States???

11 States



9 States



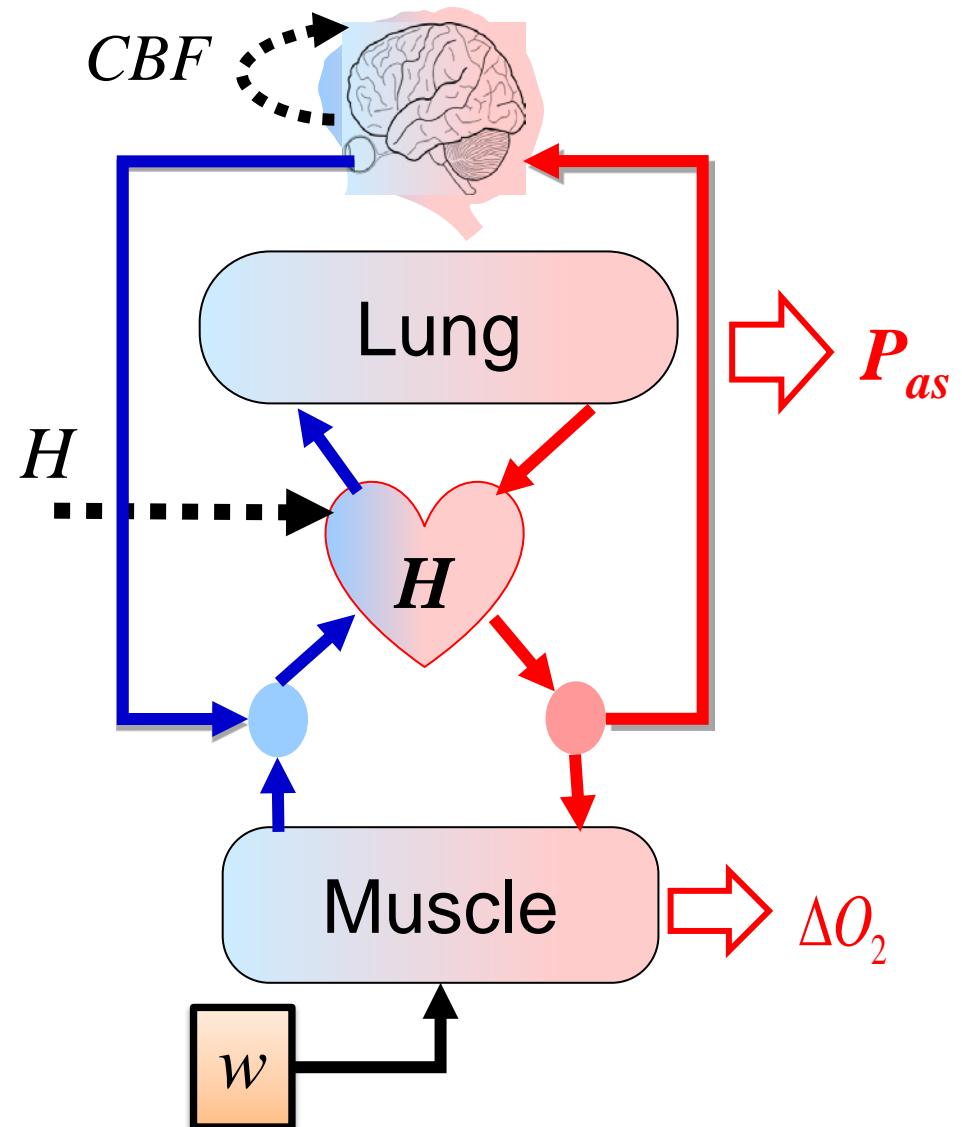
5 States



4 States



2 States



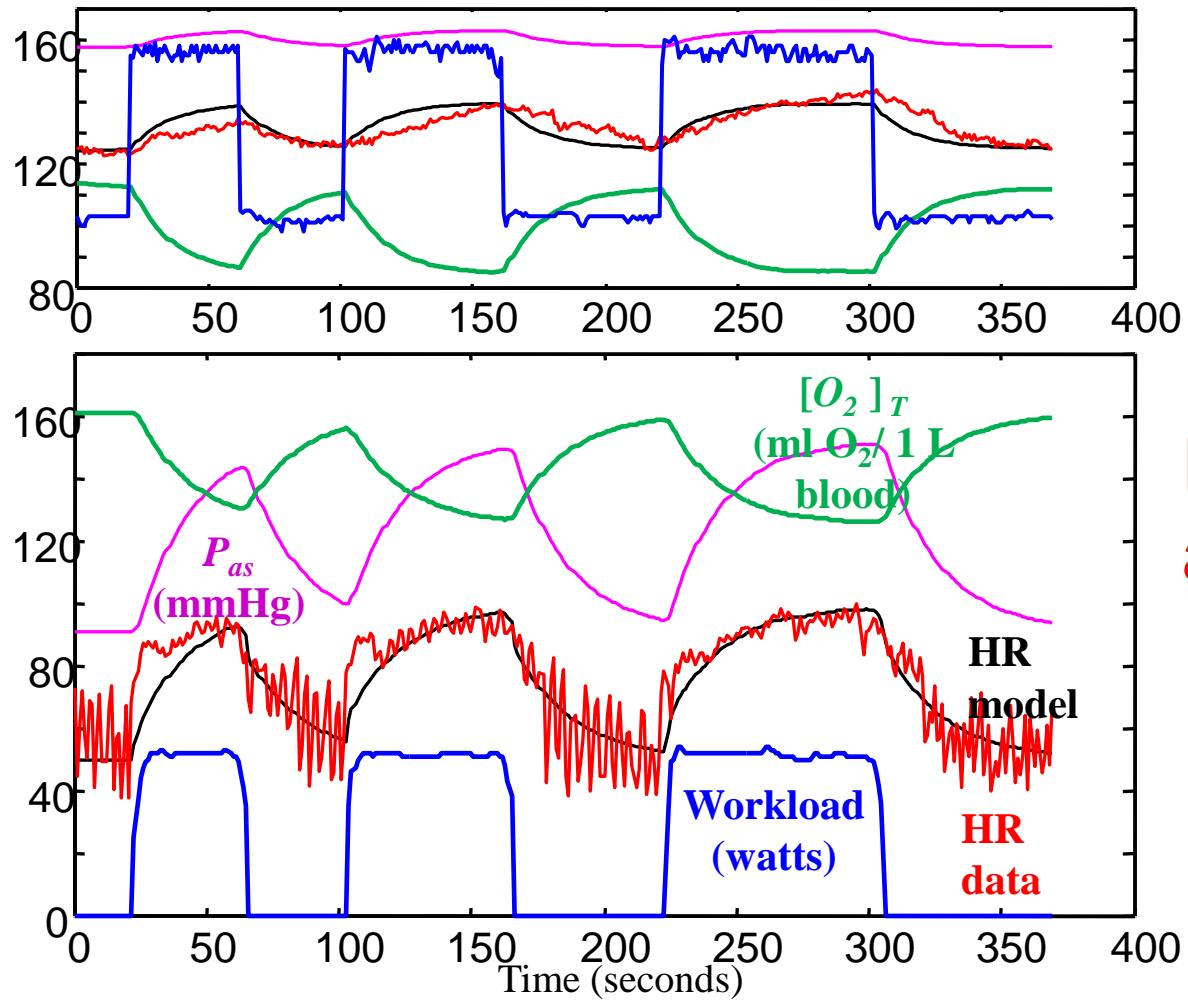
Dynamic optimal control

$$\min_{h(w)} \left\{ \left(p(BP)^2 + q(\Delta O2t)^2 + \hat{r}(HR)^2 \right) \right\}$$

$$p > 0 \quad \hat{r} > r$$

$$\boxed{\min_{H=u(\cdot)} \int \left(q_P^2 \left(P_{as} - P_{as}^* \right)^2 + q_{o_2}^2 \left(\Delta O_2 - \Delta O_2^* \right)^2 + q_H^2 \left(H - H^* \right)^2 \right) dt}$$

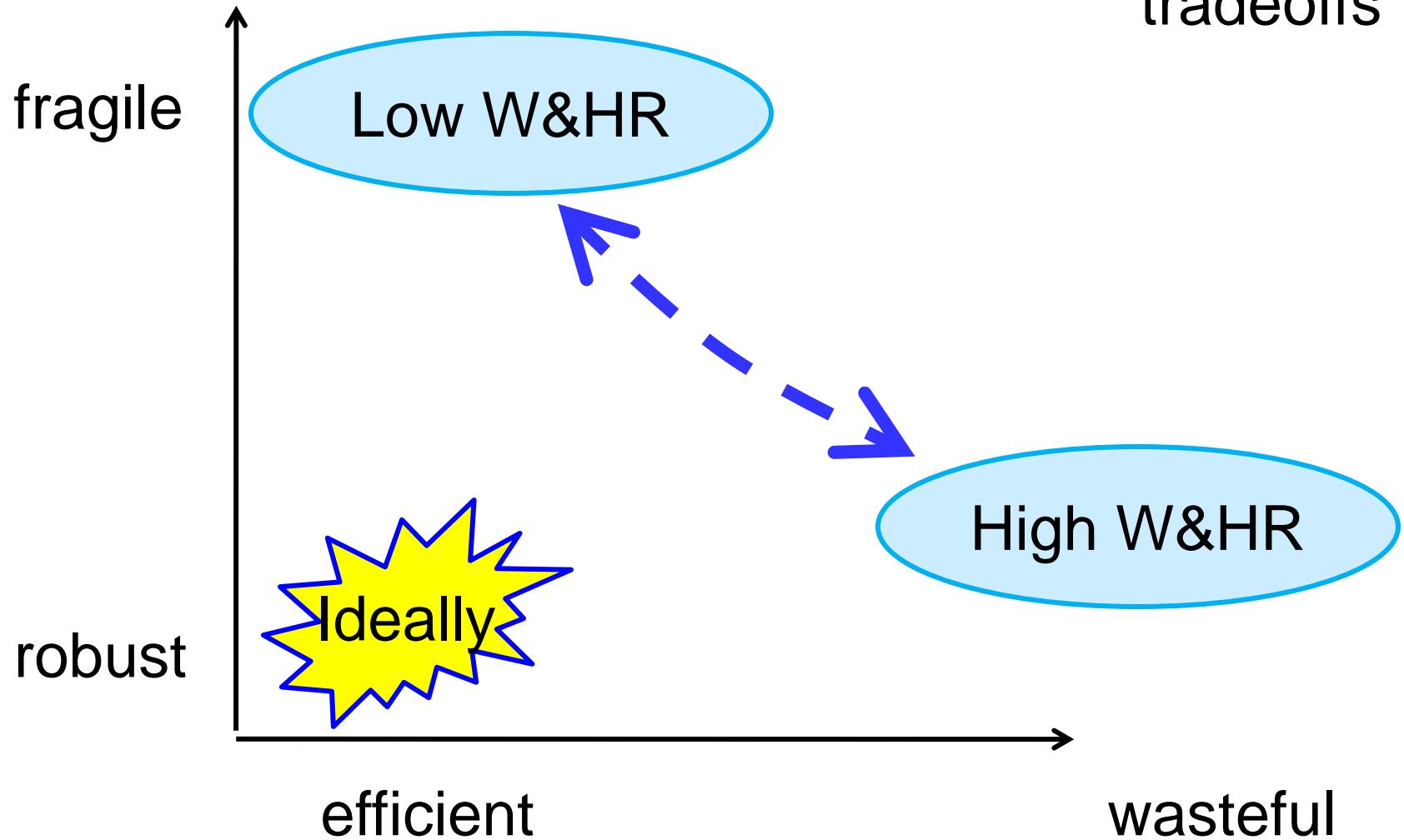
$$\min_{h(w)} \left\{ \left(q(\Delta O2)^2 + r(HR)^2 \right) \right\}$$

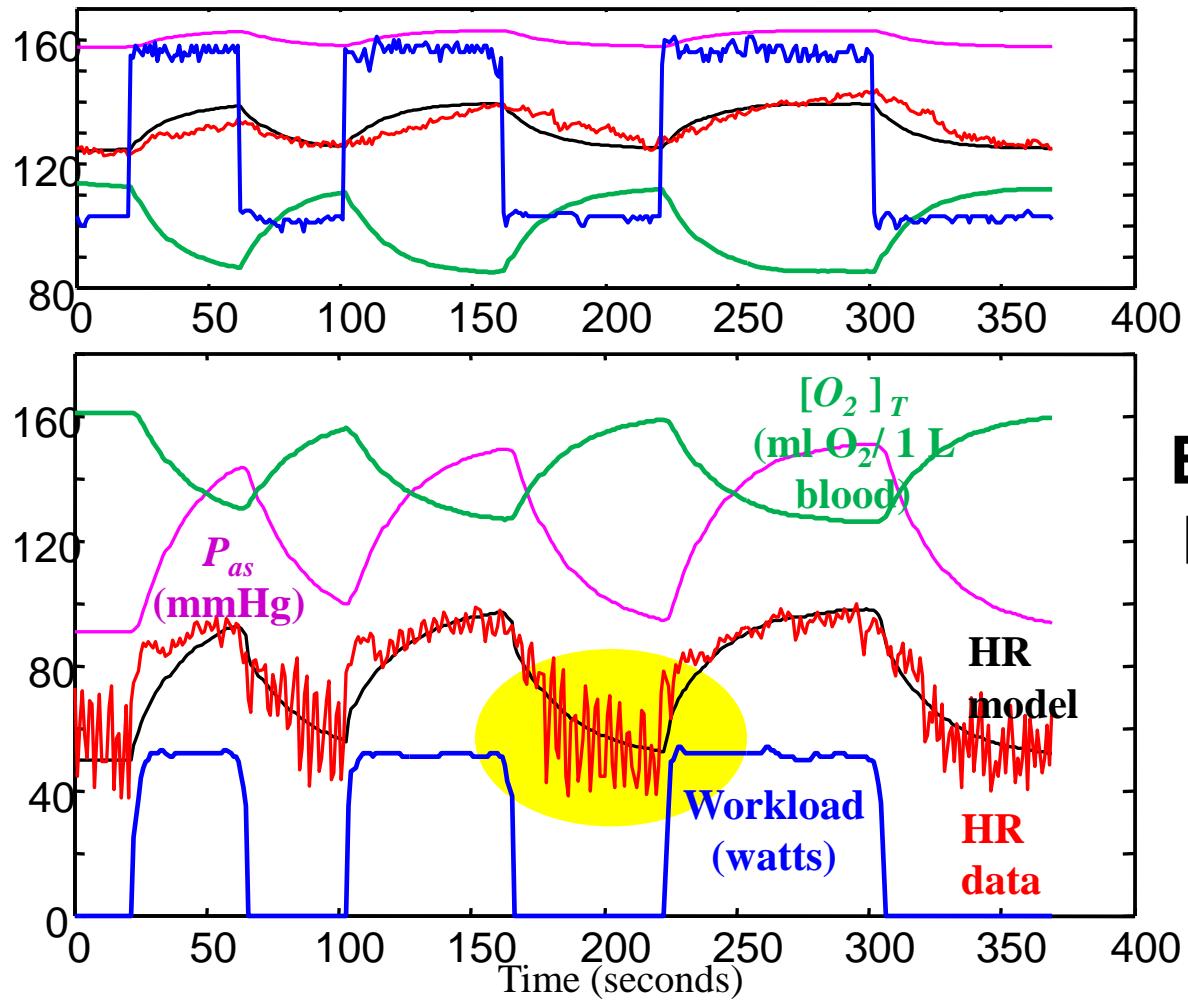


Penalize BP
and HR more

$$\min_{H=u(\cdot)} \int \left(q_P^2 \left(P_{as} - P_{as}^* \right)^2 + q_{o_2}^2 \left(\Delta O_2 - \Delta O_2^* \right)^2 + q_H^2 \left(H - H^* \right)^2 \right) dt$$

So far...





Explain differences
between models &
data?

Homeostasis

controls

heart rate

ventilation

vasodilation

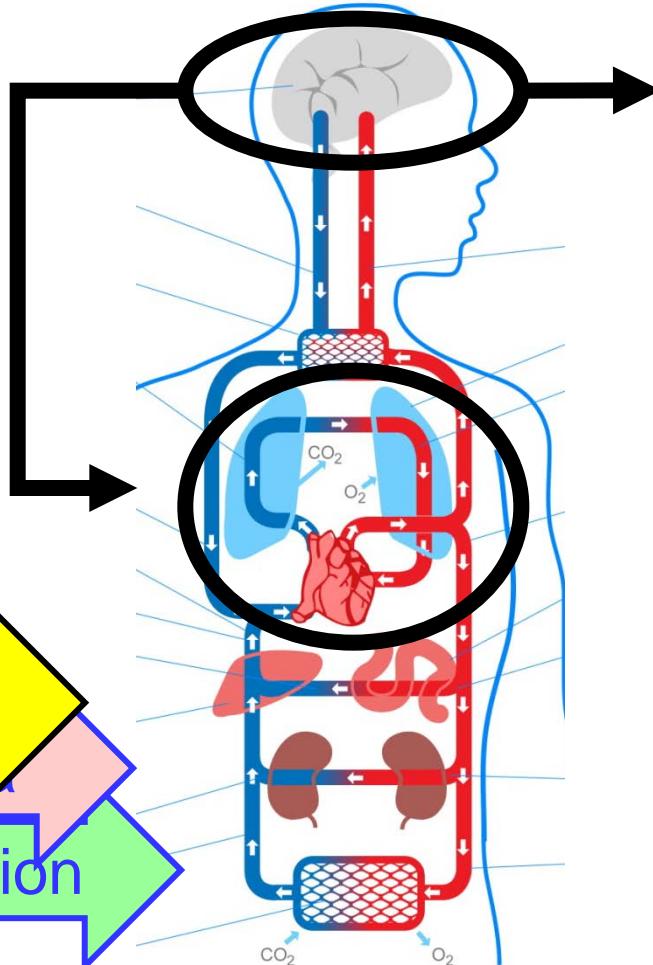
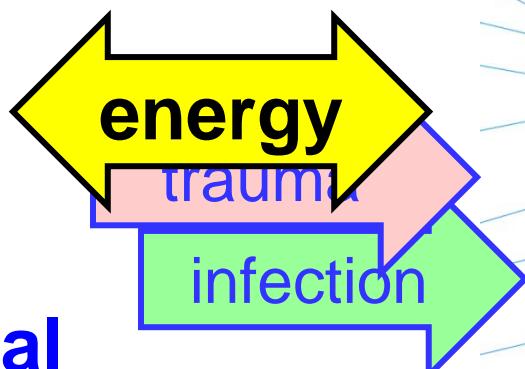
coagulation

inflammation

digestion

storage

...



errors

O₂

BP

pH

Glucose

Energy store

Blood volume

...

external
disturbances

Homeostasis

controls

heart rate

ventilation

vasodilation

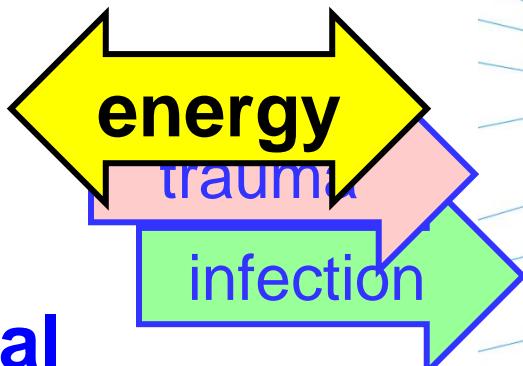
coagulation

inflammation

digestion

storage

...



external
disturbances

errors

O₂

BP

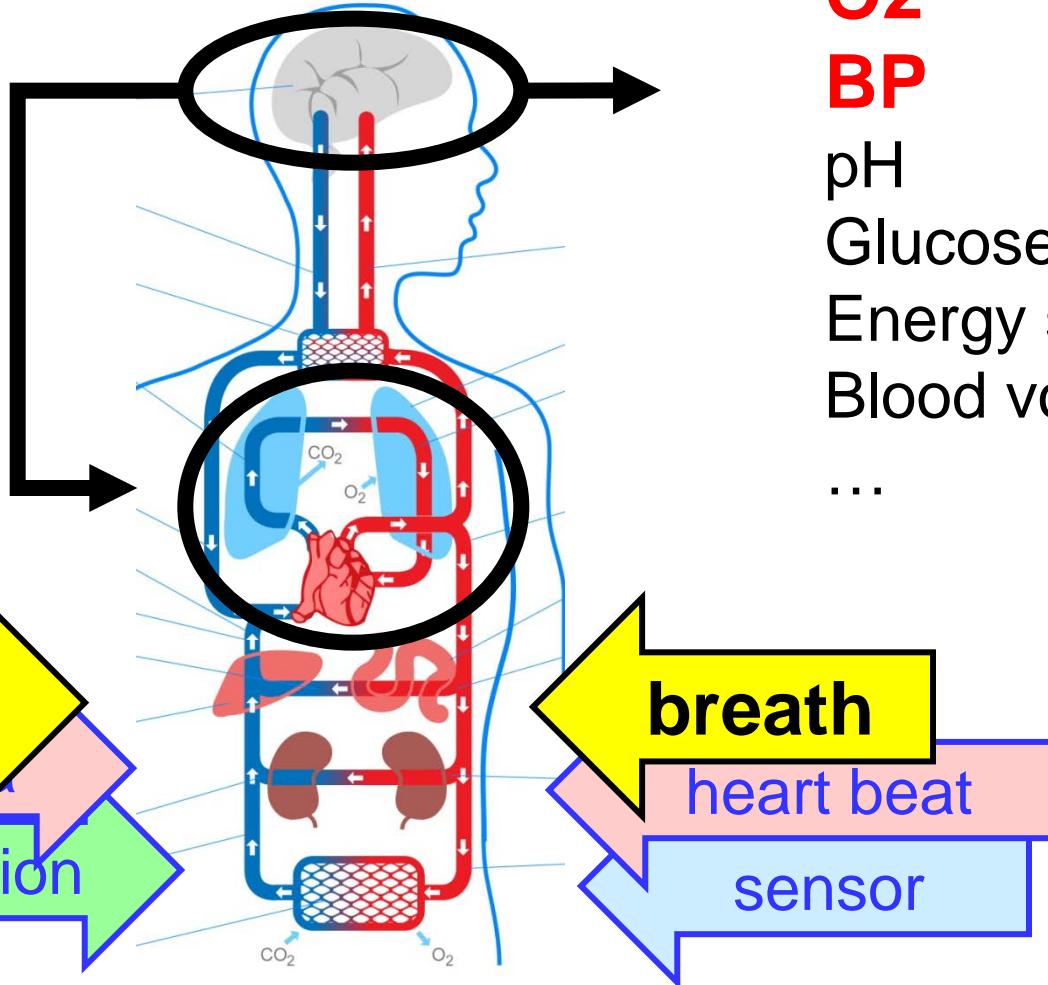
pH

Glucose

Energy store

Blood volume

...



internal noise

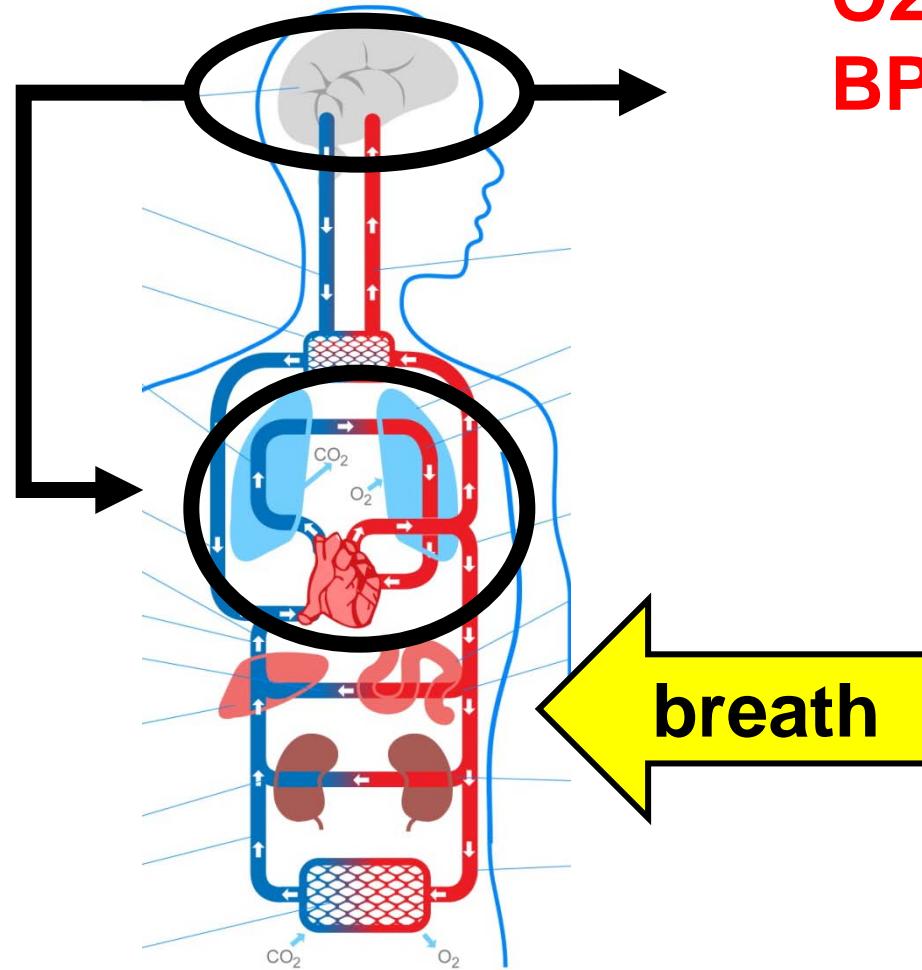
Homeostasis

controls

heart rate
ventilation

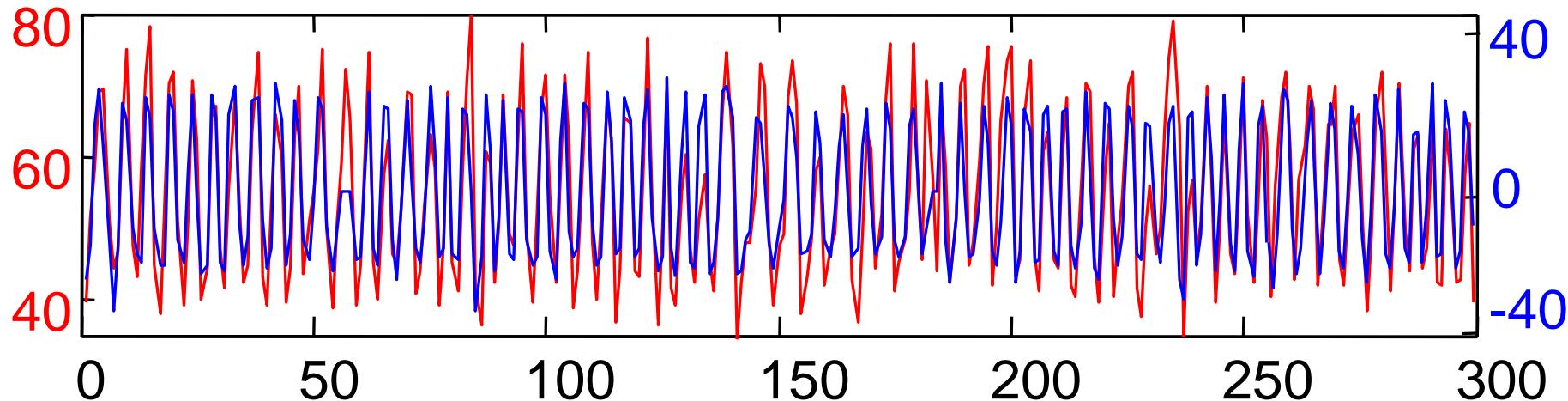
errors

O₂
BP

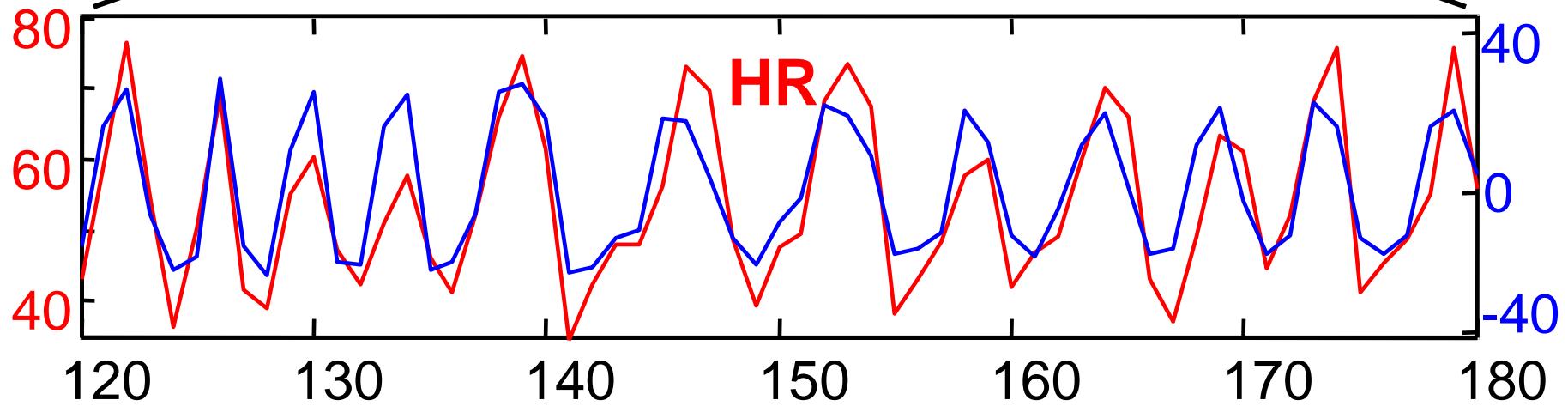


internal noise

raw data

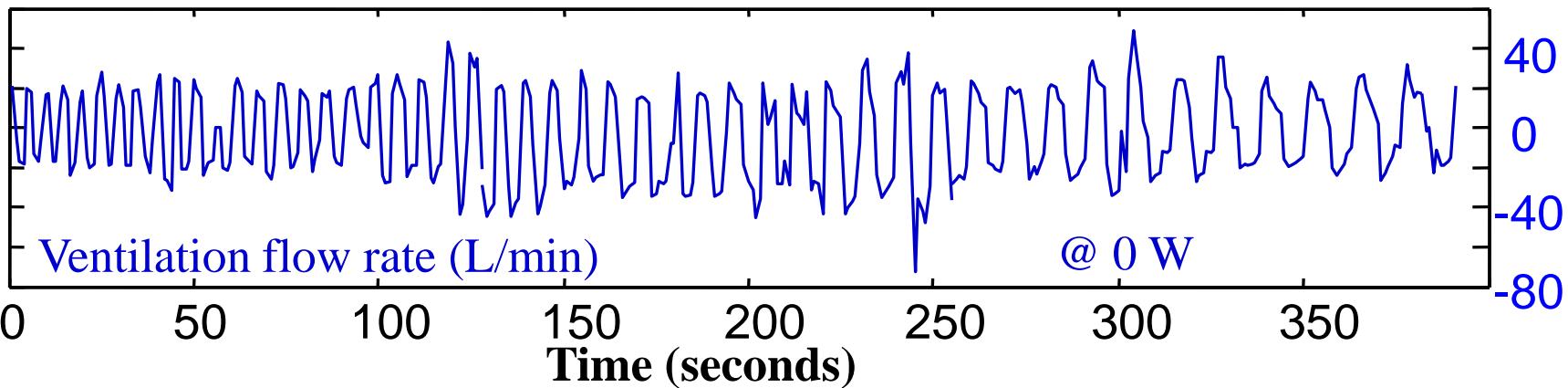
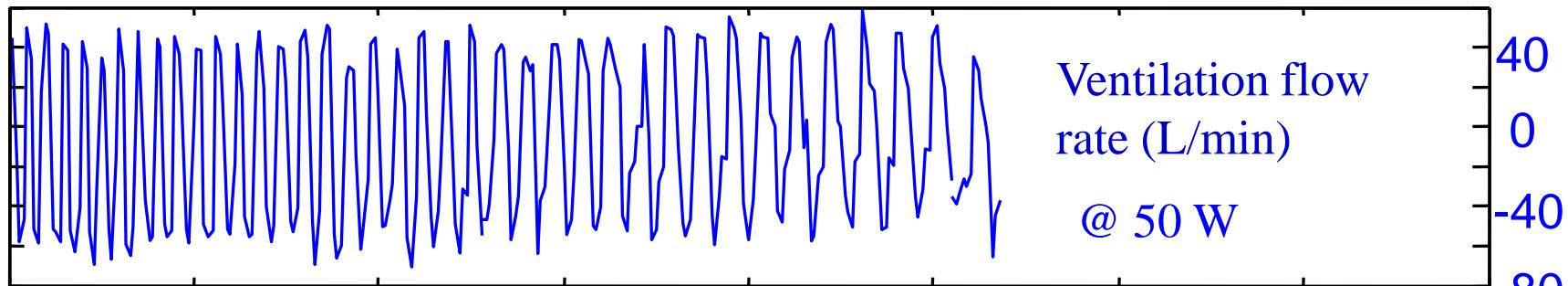
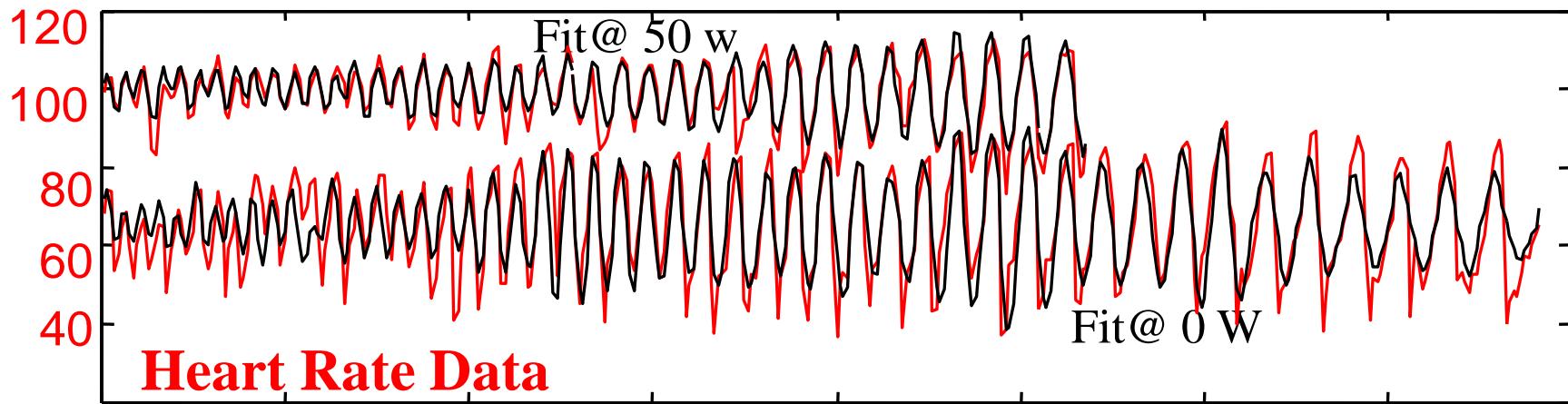


breath velocity at mouth



Respiratory Sinus Arrhythmia (RSA)

Second order piecewise linear dynamic model fitting



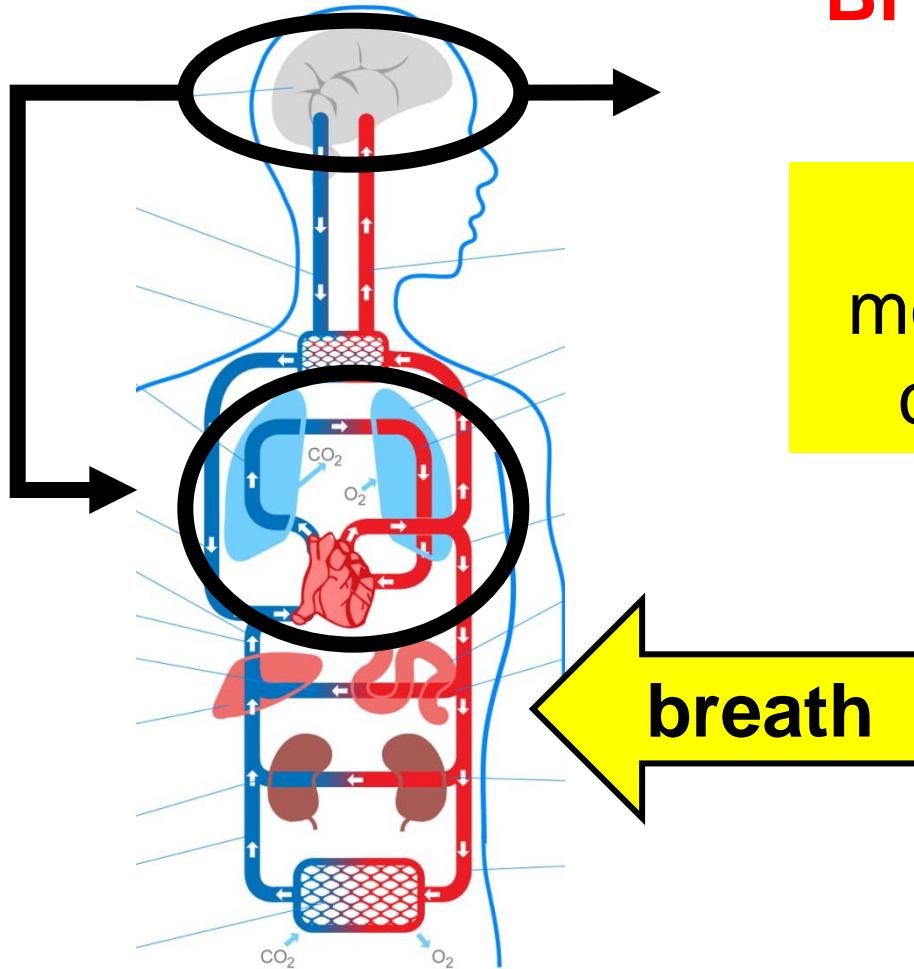
Homeostasis

controls
heart rate
ventilation

errors
BP

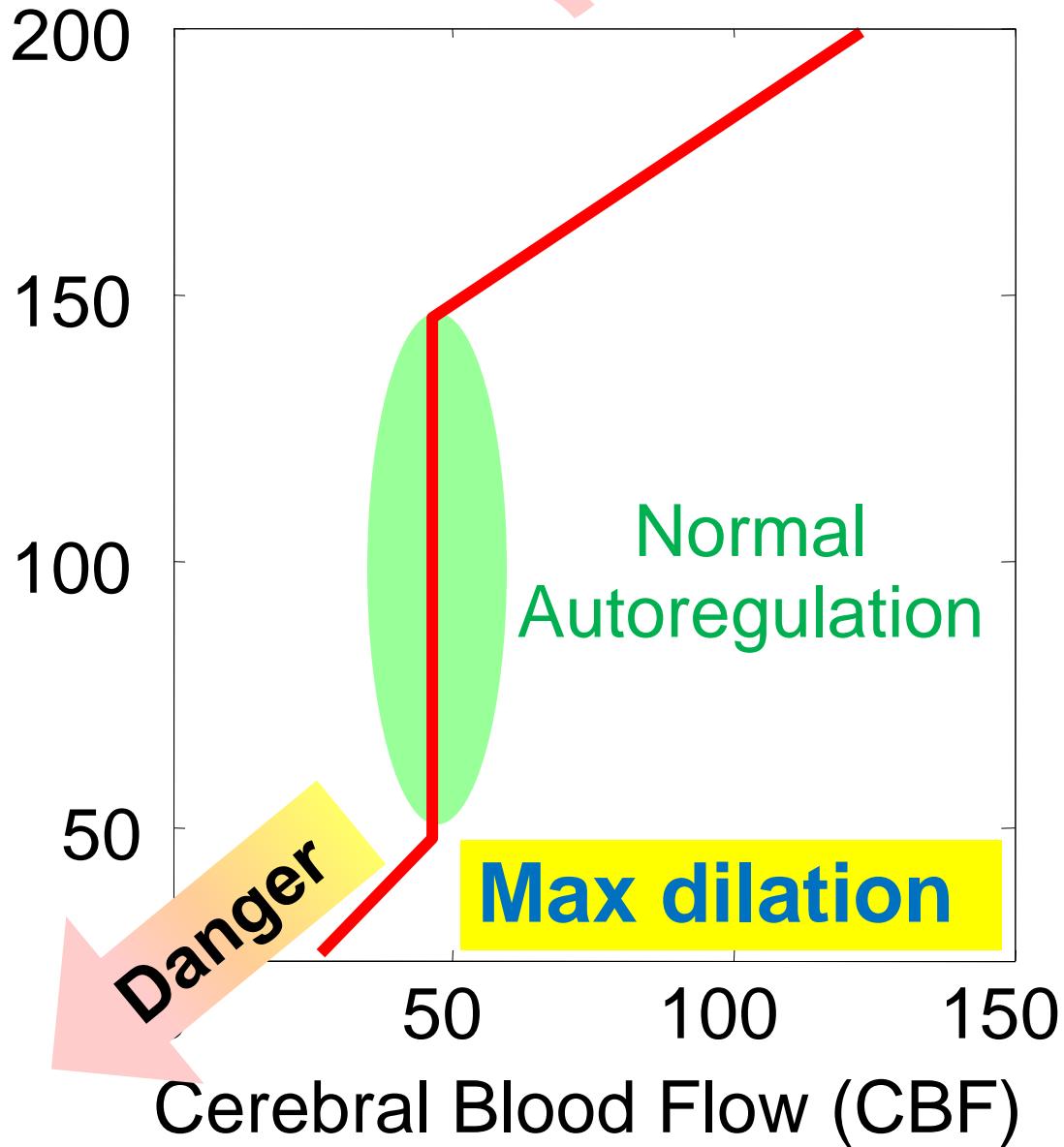
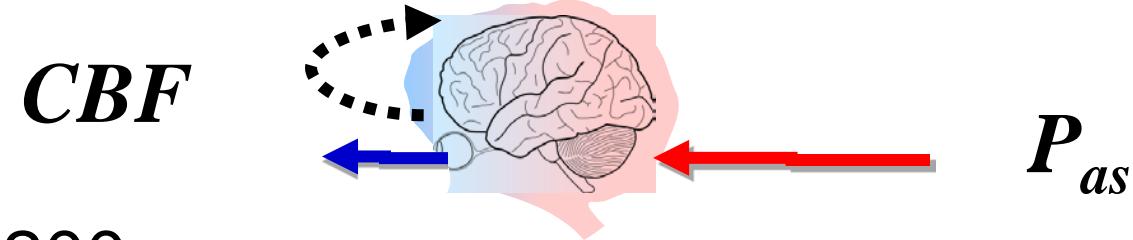
Need
mechanical
coupling

Speculation

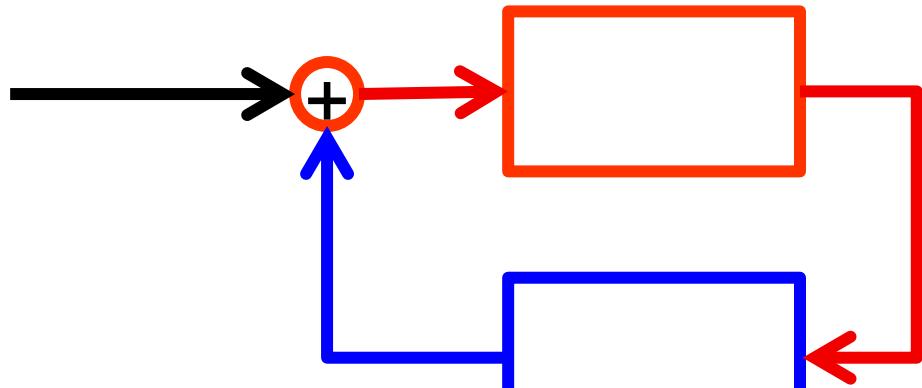


internal noise

Cerebral
Perfusion
Pressure
 $\approx P_{as}$



Universals



low variability outputs

+ *large* disturbances

⇒ *high* variability controls

- Independent of variability measure
- Universal in biology and technology
- Most important nonlinearity is **actuator saturation**

high variability

Health

low variability

Controls

pump

output

CBF medium

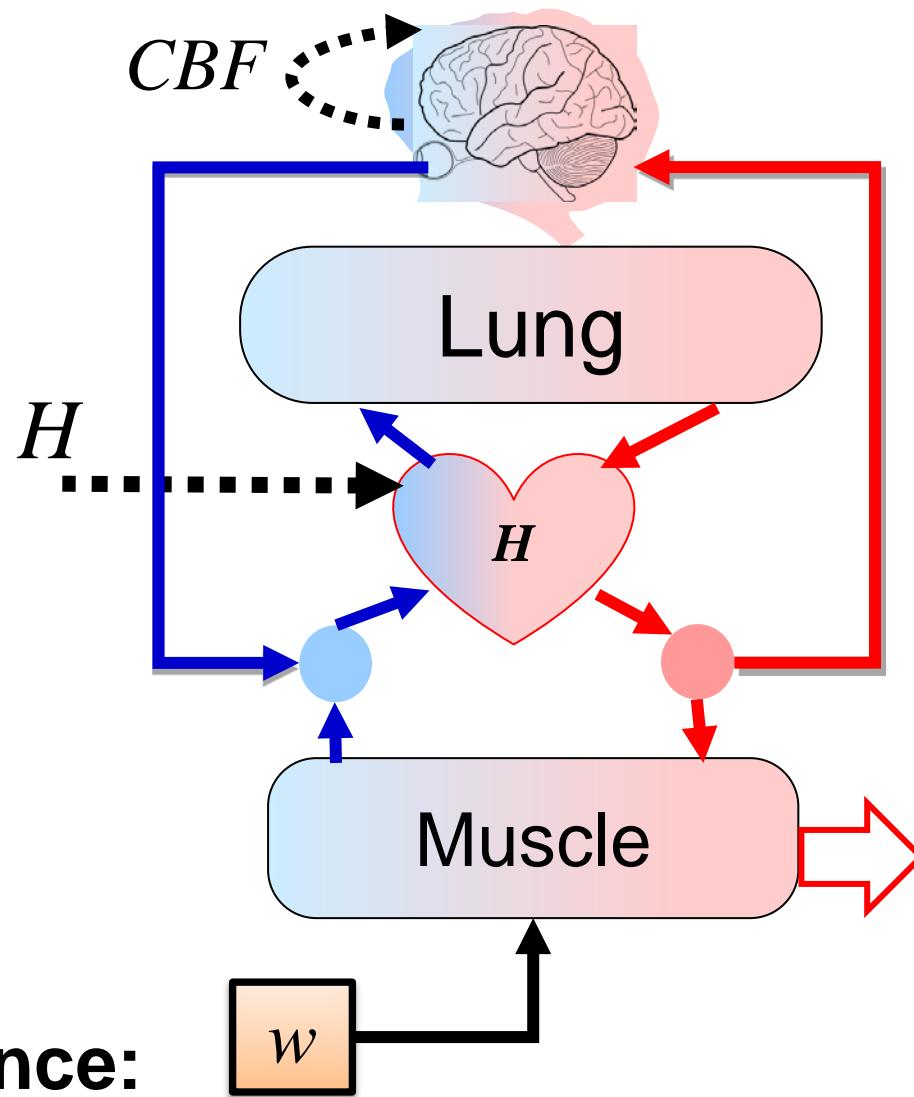
SaO_2 high

P_{as} medium

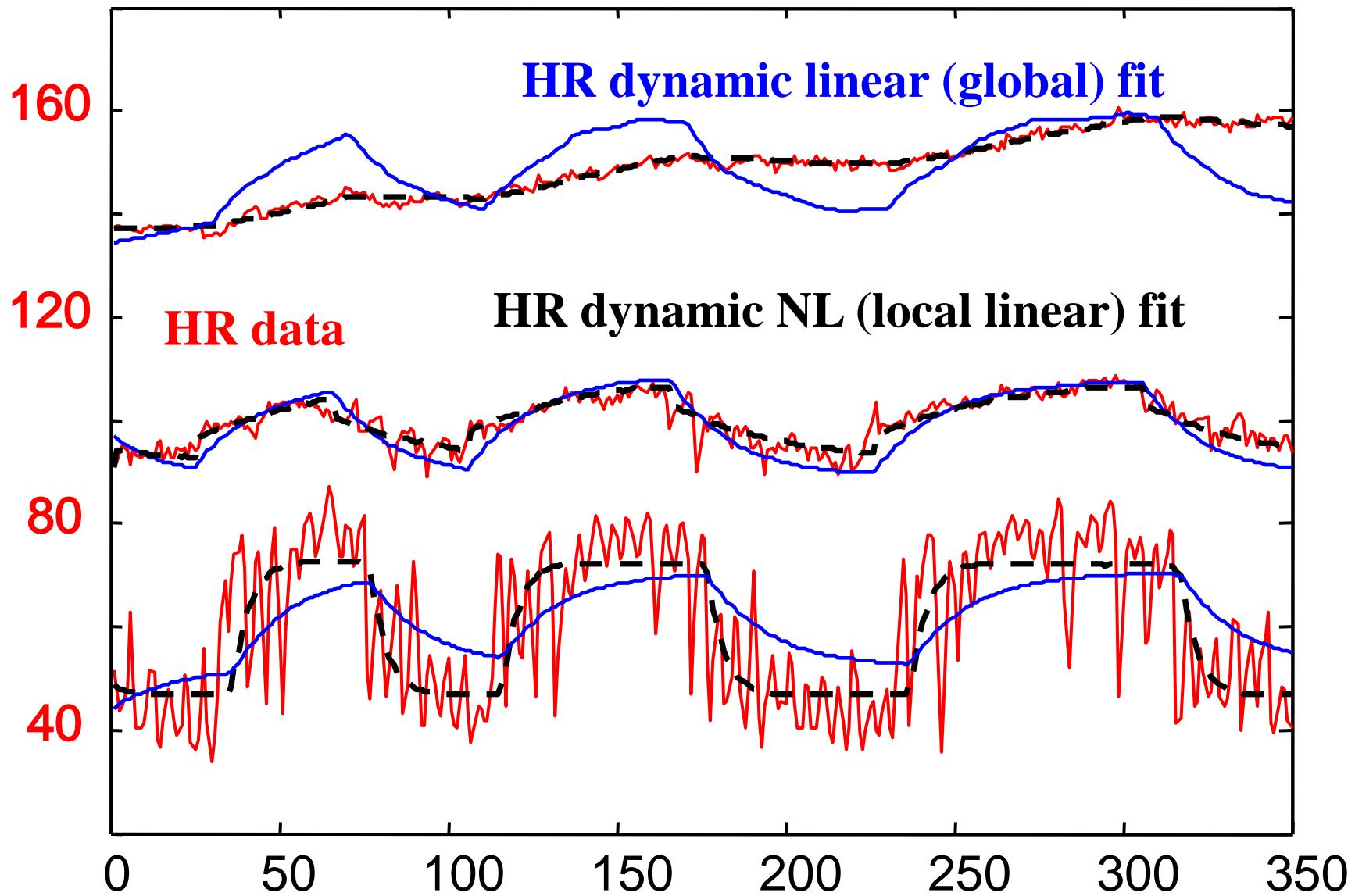
ΔO_2 low

Disturbance:

w

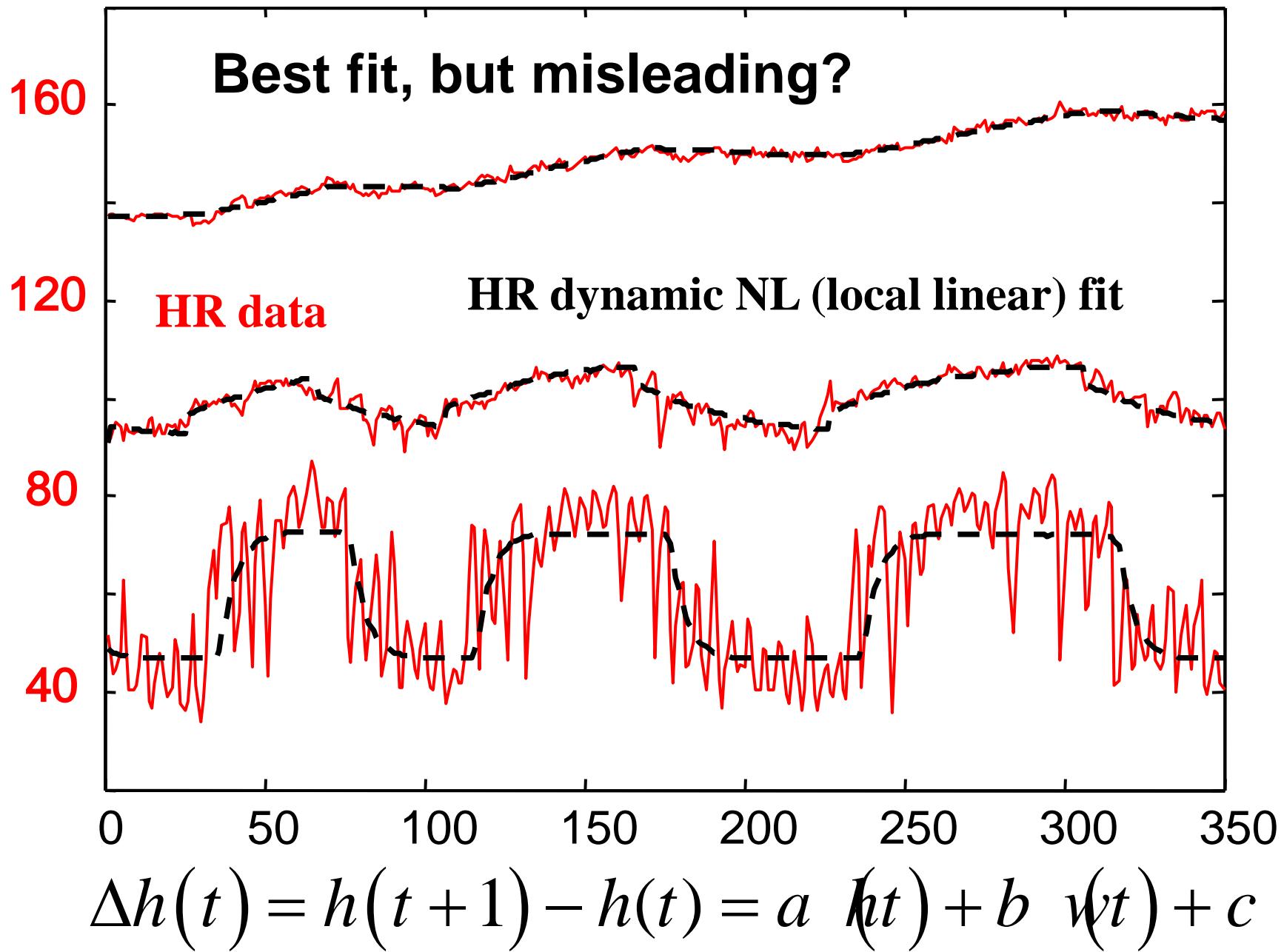


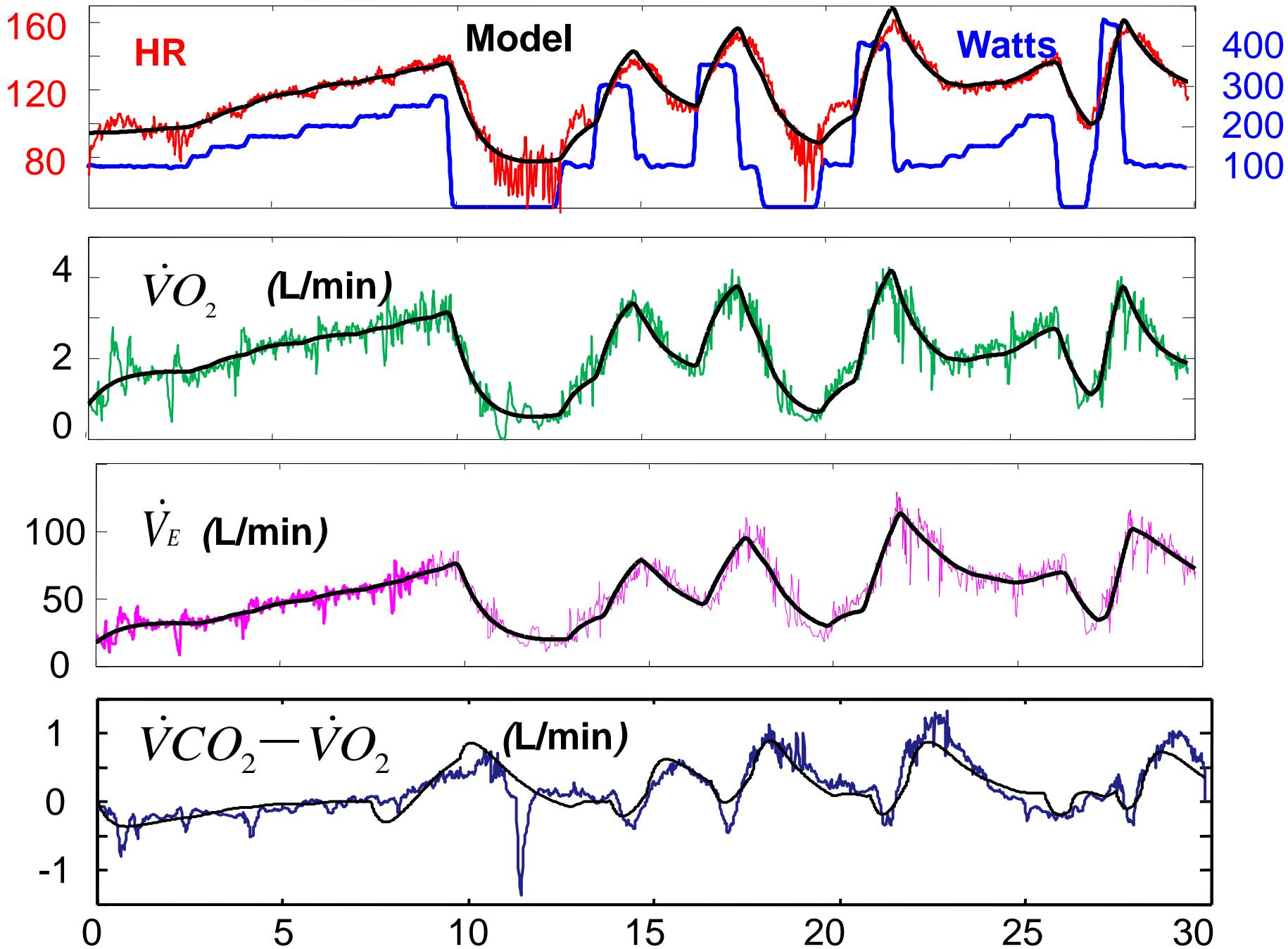
1st order linear model



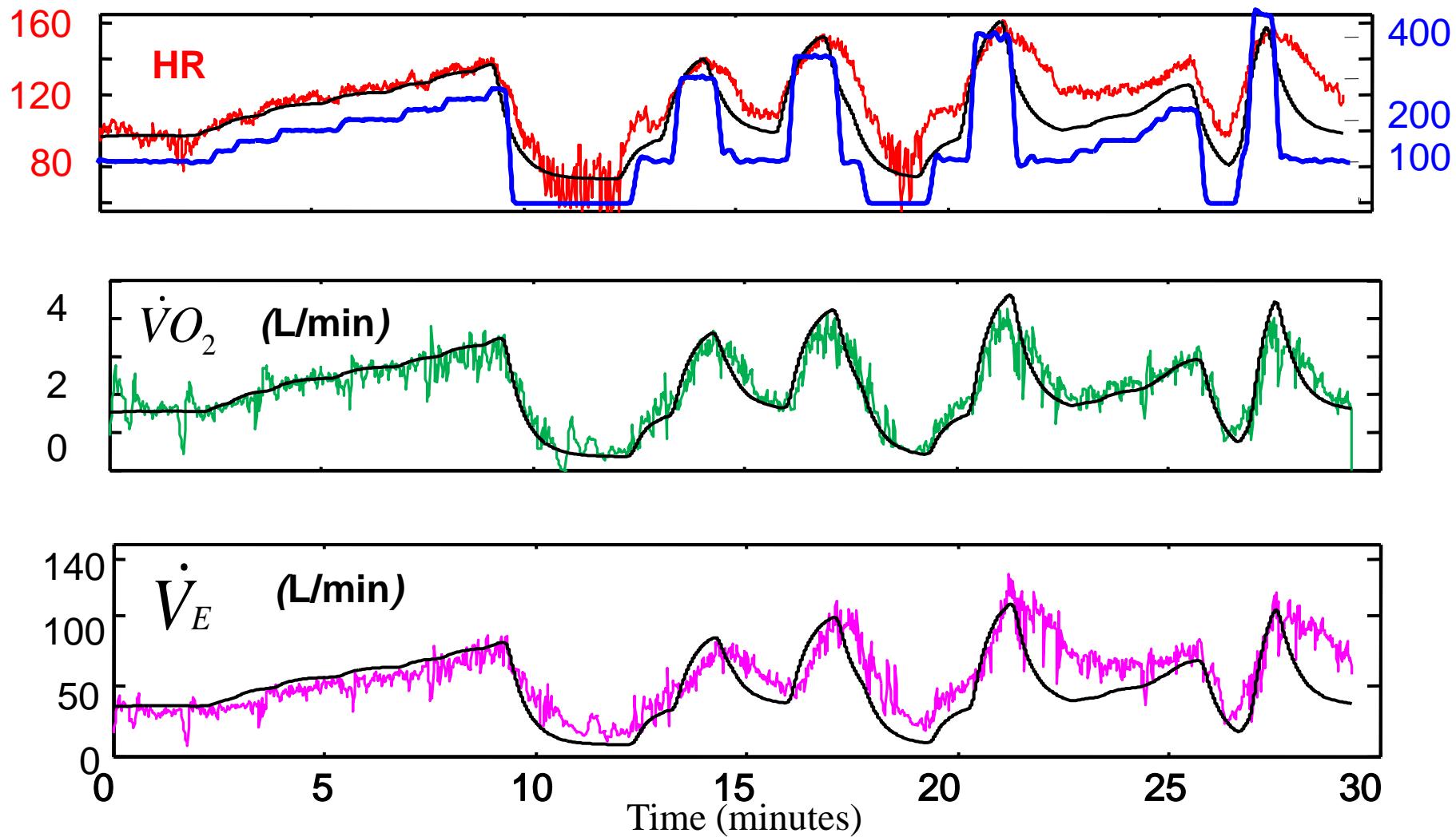
$$\Delta h(t) = h(t+1) - h(t) = a \ \mathbf{h}(t) + b \ \mathbf{w}(t) + c$$

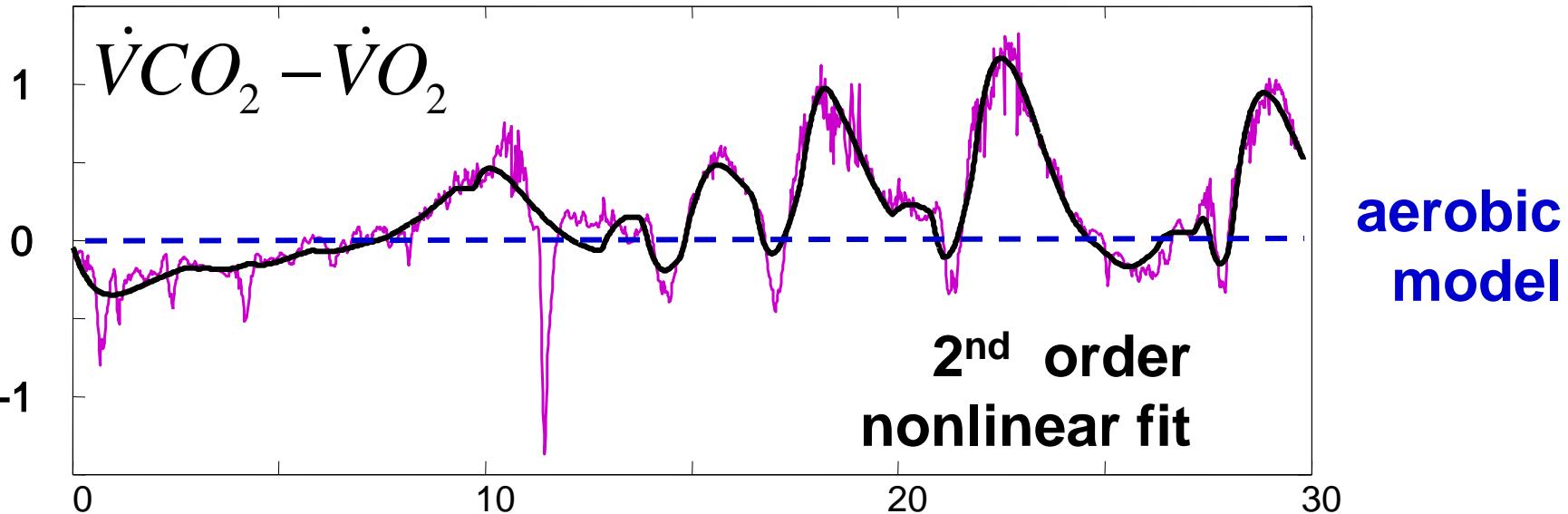
1st order linear model





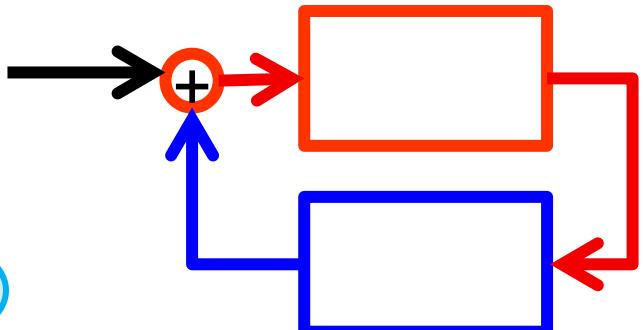
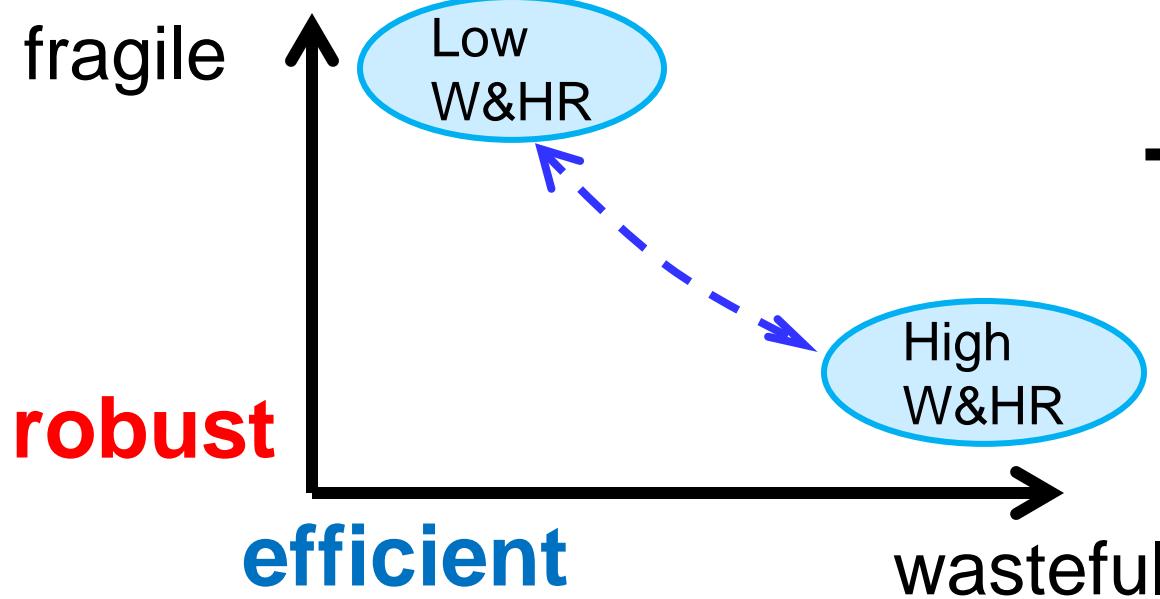
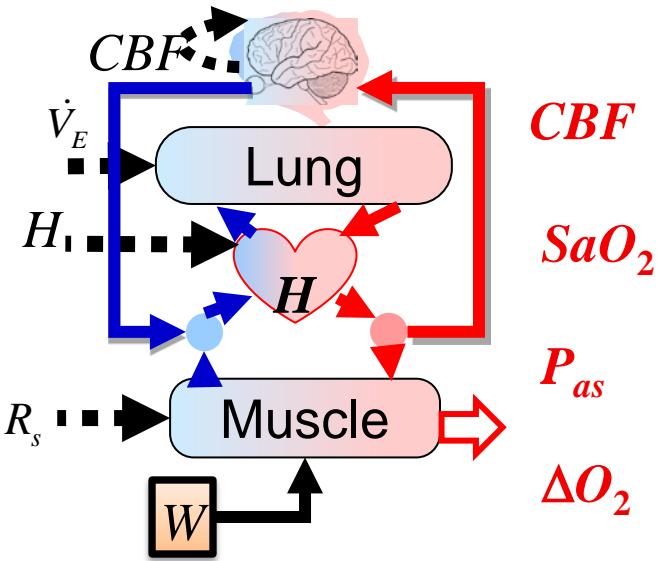
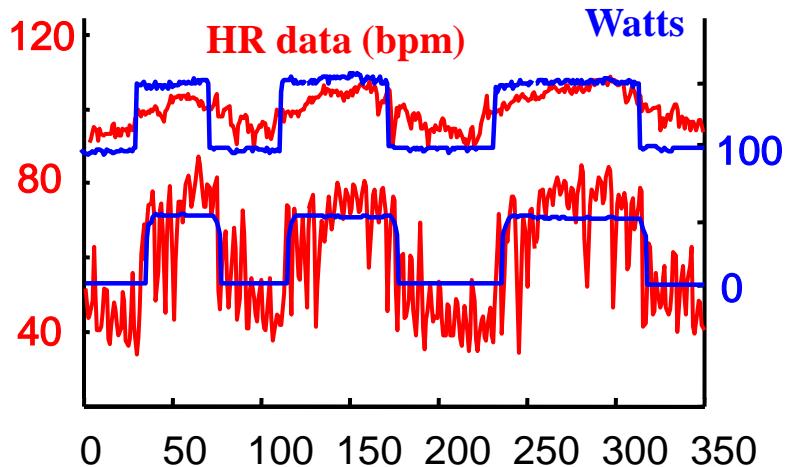
First principles *aerobic* model



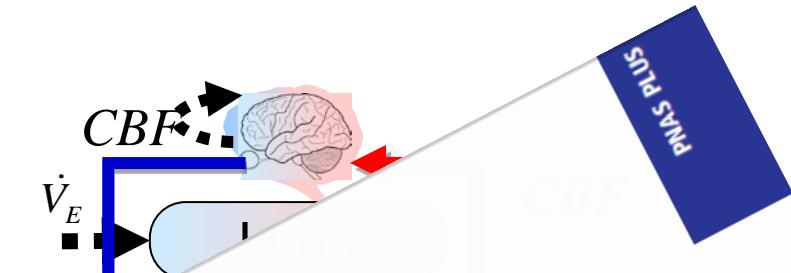
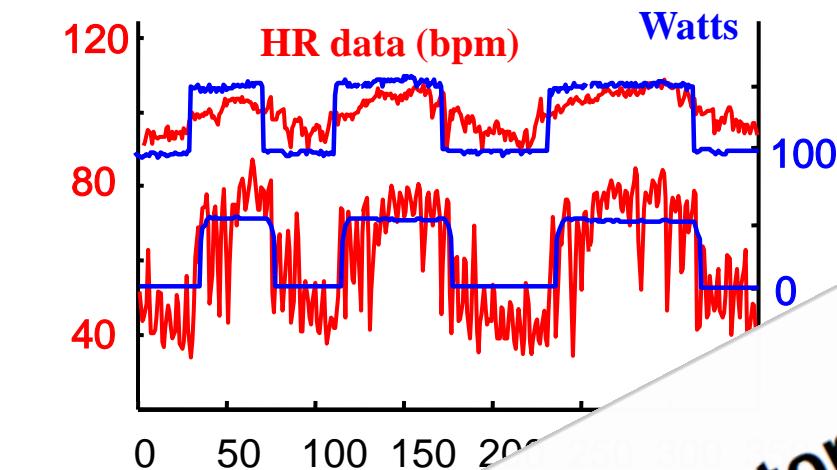


- Aerobic models can be way off at high watts
- Can still fit with simple “black box” models, but...
- Need nonlinear dynamics
- Mechanistic models? (Redox ☹️💀)
 - Need anaerobic mechanisms
 - Control of arterial pH is critical (and hard to model)

Summary



Summary



Robust efficiency and actuator saturation explain
healthy heart rate control and variability

Na Li^a, Jerry Cruz^b, Chenghao Simon Chien^{c,d}, Somayeh Sojoudi^e, Benjamin Recht^f, David Stone^g, Marie Csete^h,
Daniel Bahmiller^b, and John C. Doyle^{b,c,i,1}

fragile

efficient

wasteful

High
W&HR

