Heart rate regulation: Modeling and parameter estimation

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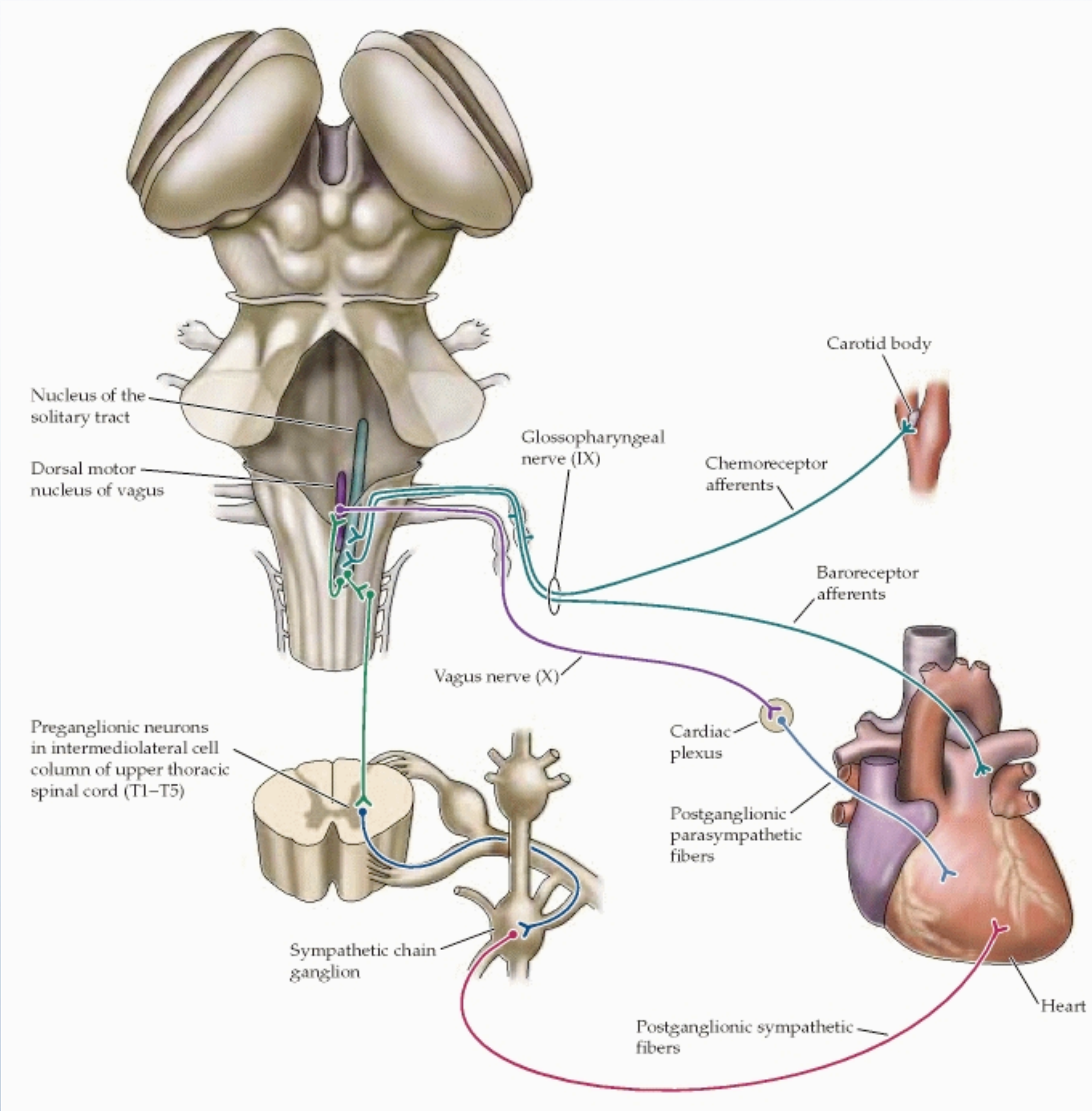
CV Regulation

- **Autonomic regulation**
  - Mechanical (barosensory) information about pressure in the arterial system
  - Chemical (chemosensory) information about the level of oxygen and carbon dioxide in the blood

  Parasympathetic and sympathetic activity relevant to CV control is determined by information supplied by these sensors.

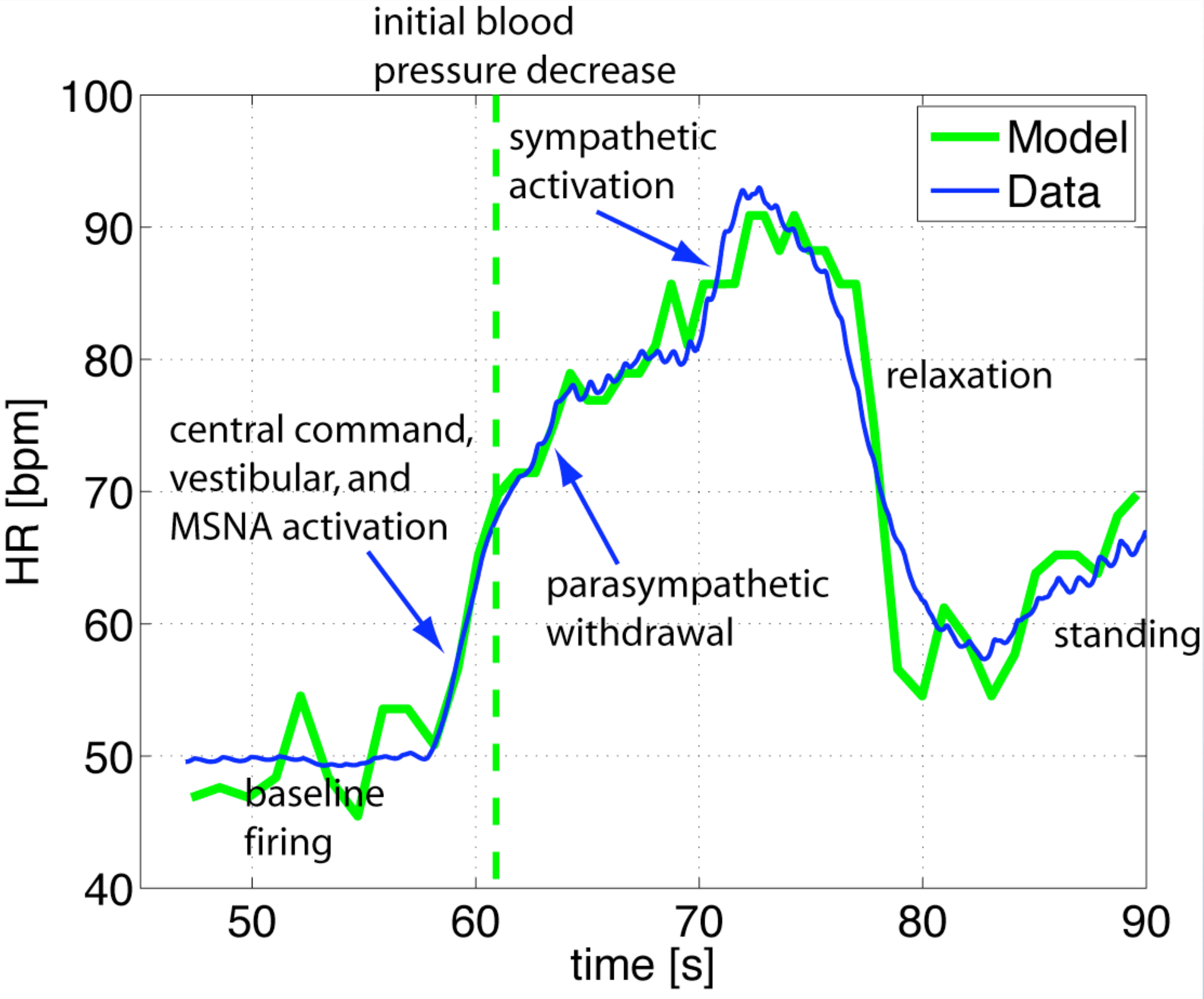
- **Autoregulation** is a process resulting from some internal adaptive mechanism that works to adjust the systems response to stimuli. Prominent in the kidney, the heart, and the brain to maintain perfusion.

- **Hormonal regulation** impact the vasculature in multiple ways: by regulating volume status, modifying smooth muscle contractility directly and through the NO pathway, and by altering cardiac output.

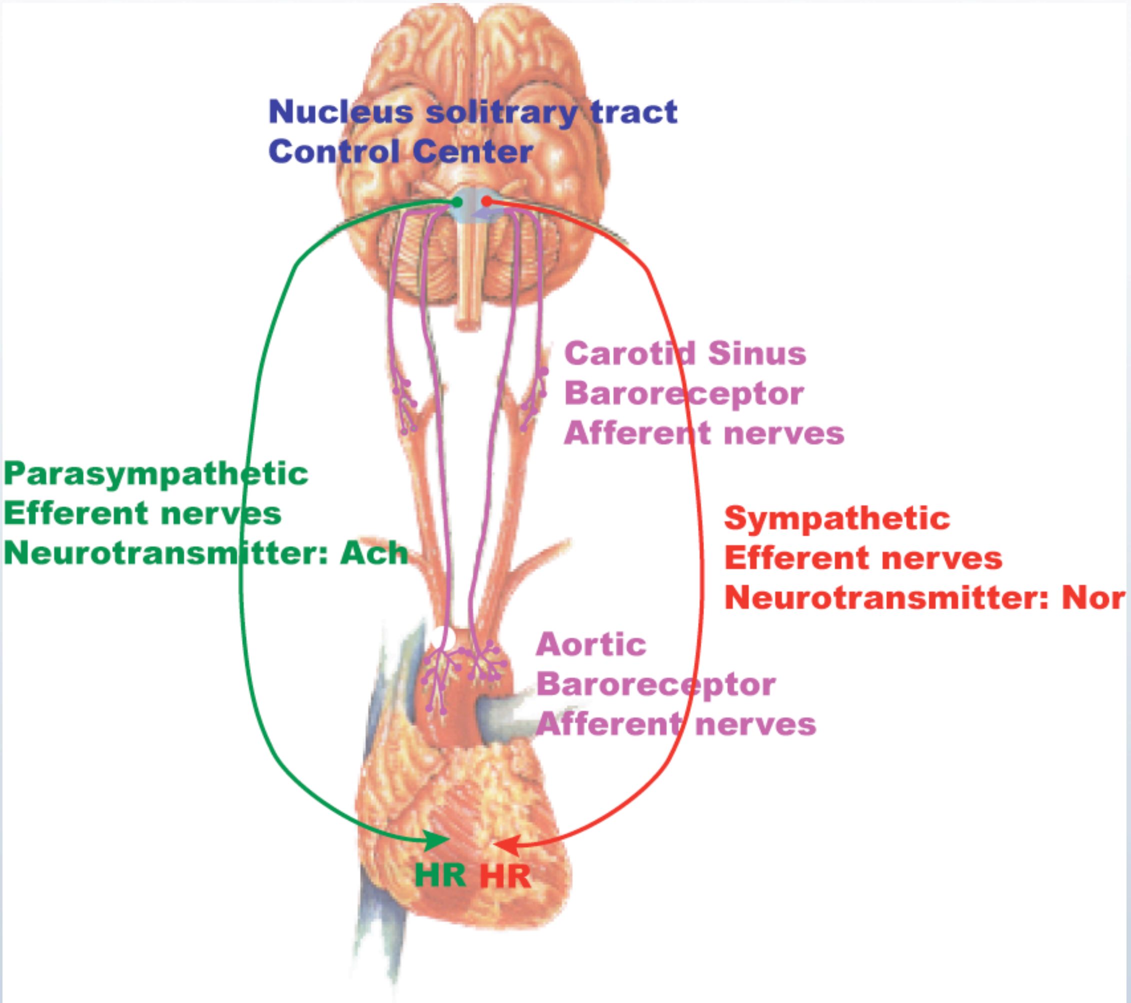


Carotid body
Nucleus of the solitary tract
Glossopharyngeal nerve (IX)
Chemoreceptor afferents
Dorsal motor nucleus of vagus
Baroreceptor afferents
Vagus nerve (X)
Preganglionic neurons in intermediolateral cell column of upper thoracic spinal cord (T1–T5)
Cardiac plexus
Postganglionic parasympathetic fibers
Sympathetic chain ganglion
Heart
Postganglionic sympathetic fibers

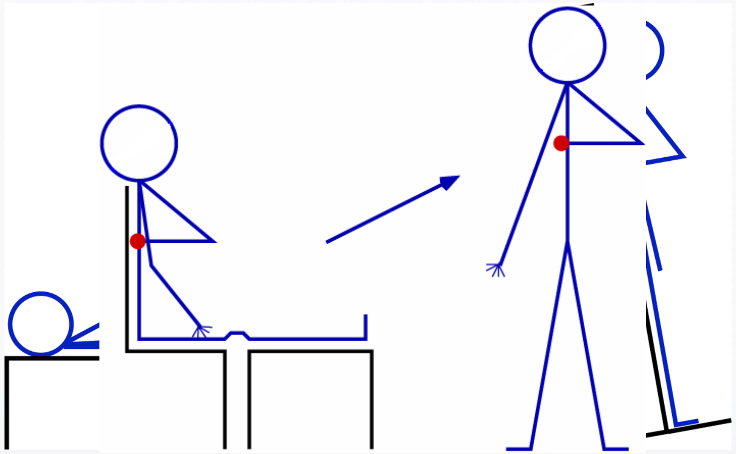
Heart rate regulation (sit-to-stand)



Baroreflex regulation

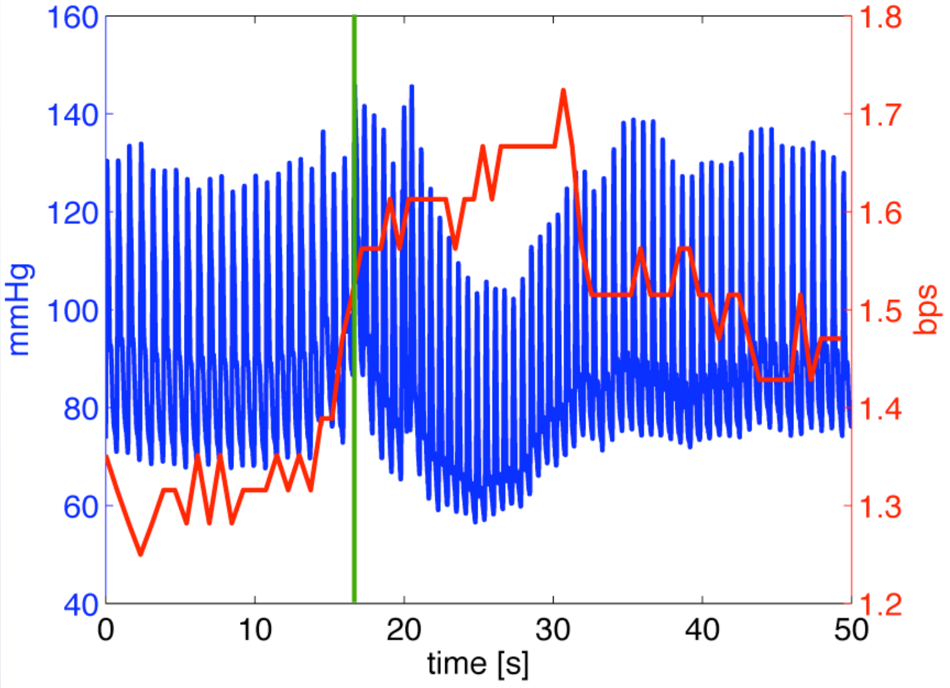


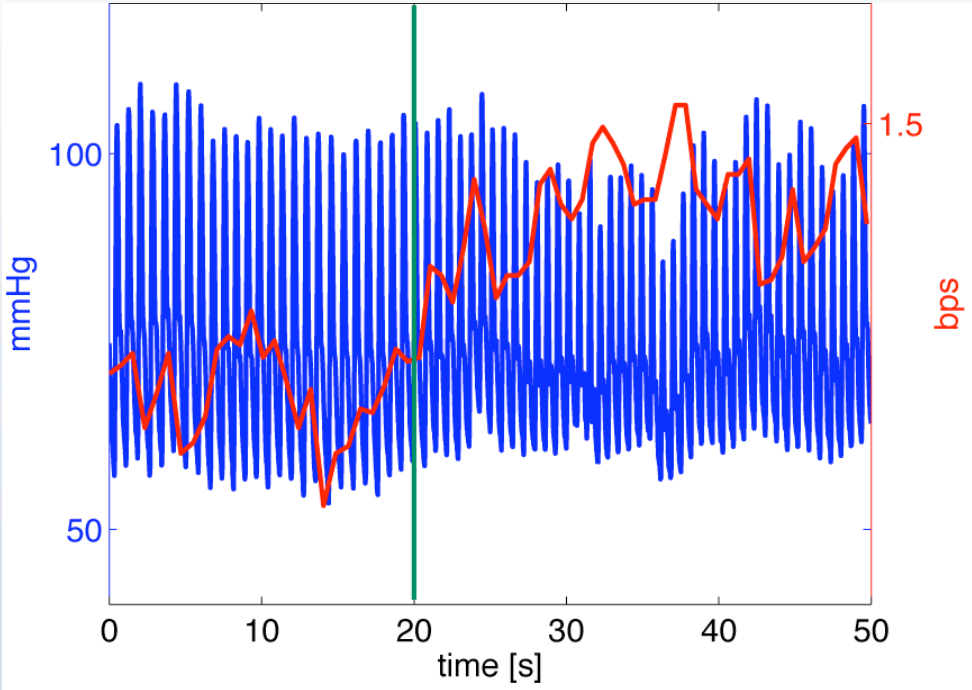
Head-up tilt & Sit-to-stand



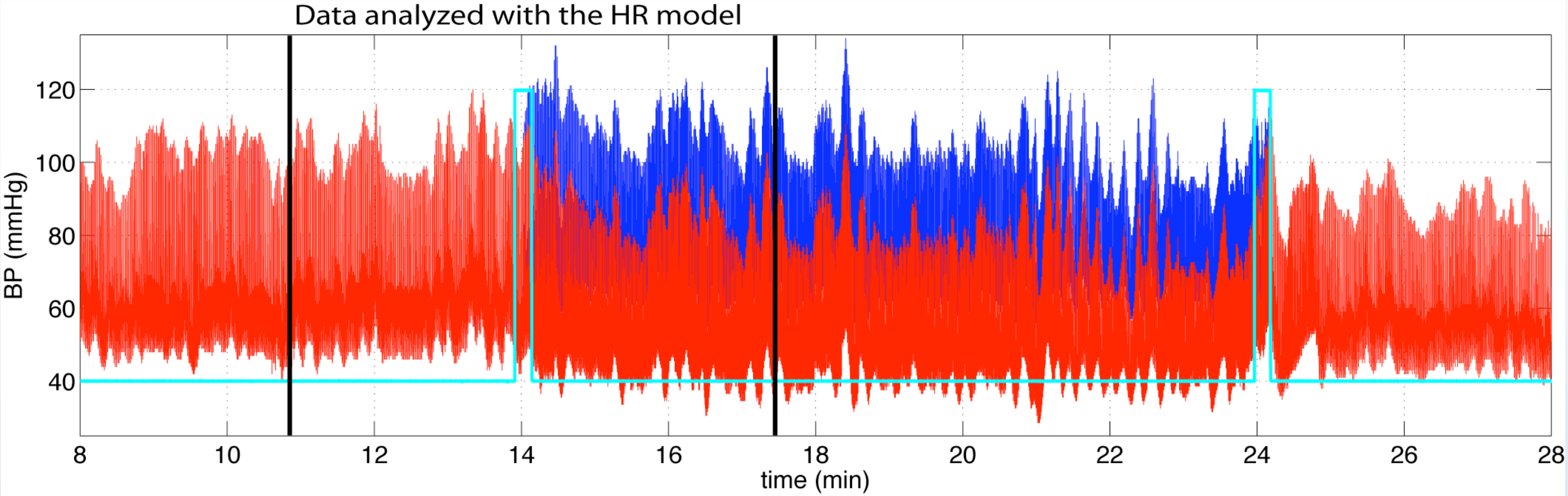
- During head-up tilt blood is pooled in the legs
- As a result, blood pressure in the upper body decreases while pressure in the legs increases
- To bring blood pressure back to homeostasis, heart rate (one of the controlled quantities) is increased

Blood pressure & Heart rate





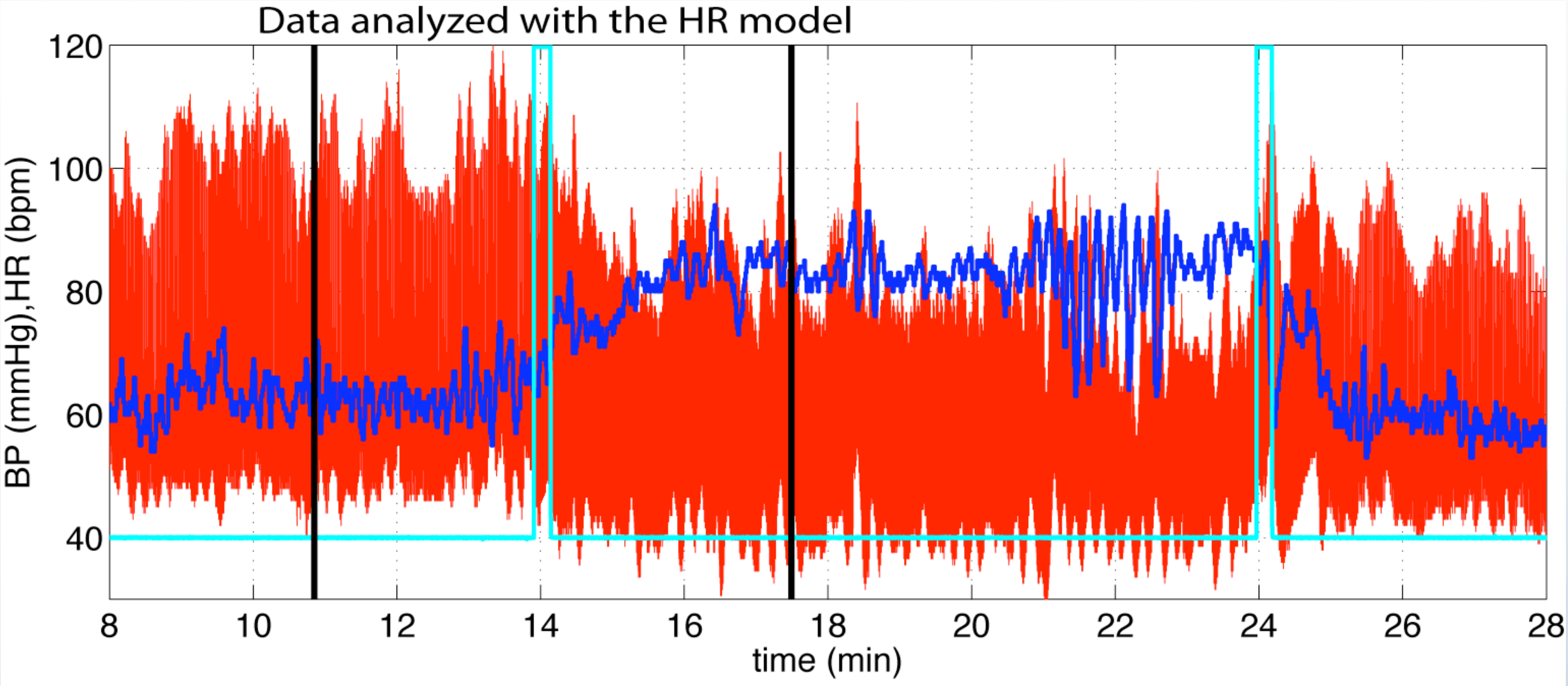
Head-up tilt BP-data



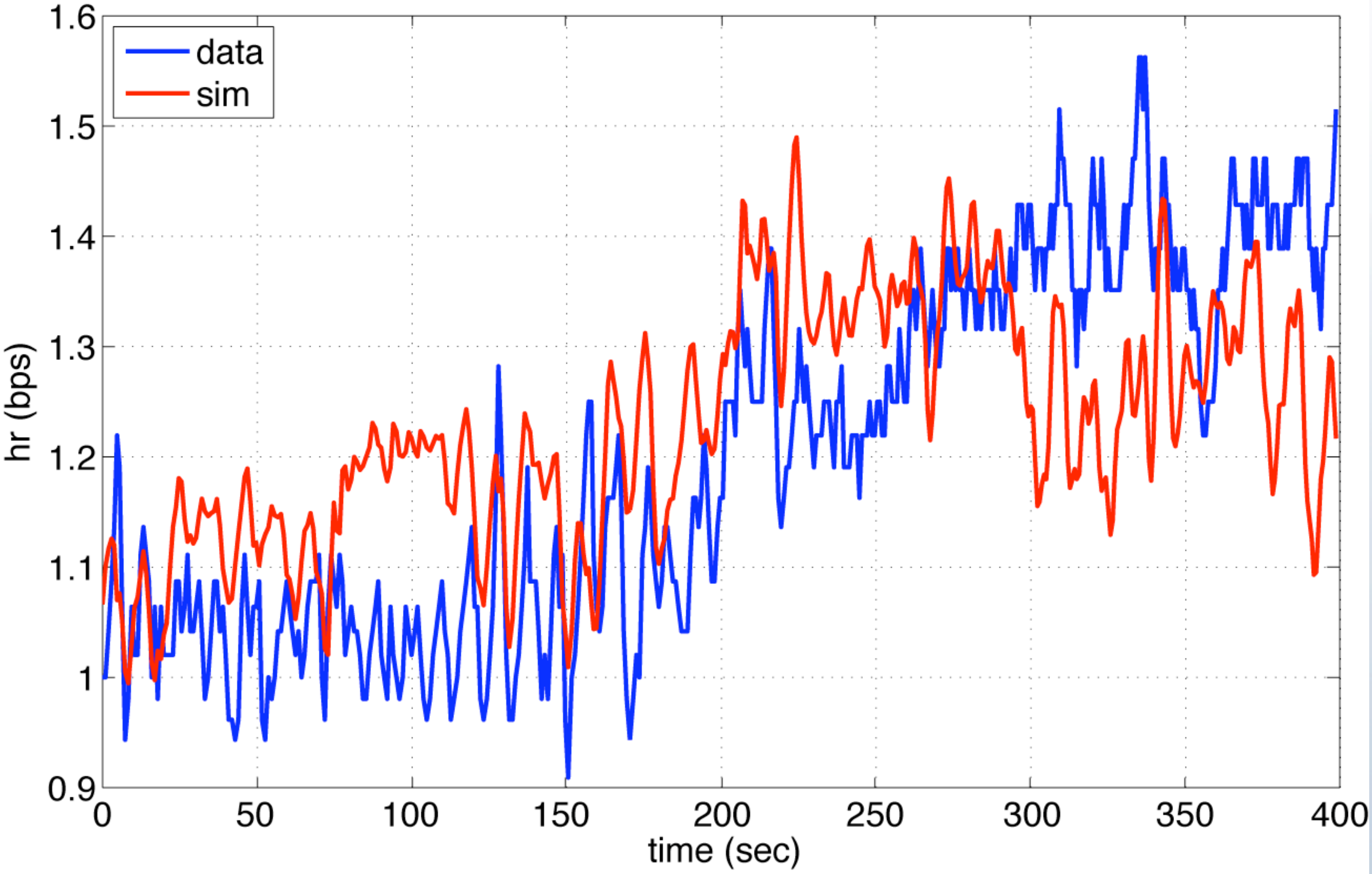
- Finger blood pressure (blue)
- Carotid sinus blood pressure (red)

$$p_{cs}(t) = \rho g h(t), \qquad h(t) = \begin{cases} 0 & t \le t_{st} \\ 60\dfrac{t - t_{st}}{t_{ed} - t_{st}} & t_{st} \le t \le t_{ed} \\ 60 & t > t_{ed} \end{cases}$$

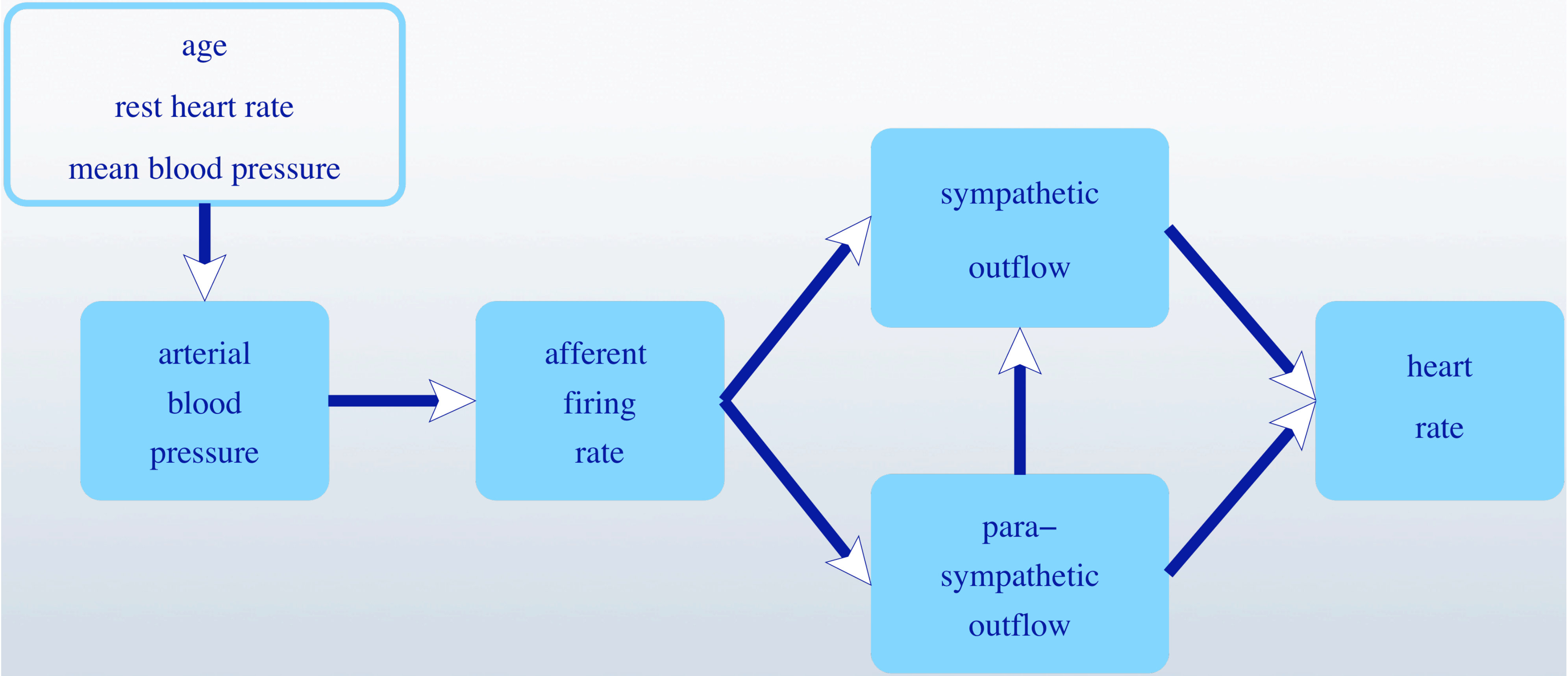
Head-up tilt HR-CBP data



Head-up tilt simulated HR data

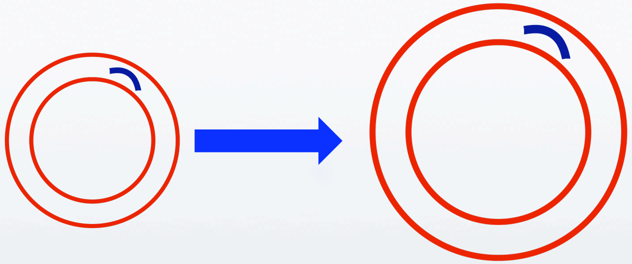


HR model


age
rest heart rate
mean blood pressure
arterial
blood
pressure
afferent
firing
rate
sympathetic
outflow
para–
sympathetic
outflow
heart
rate

Baroreceptors

- Stretch receptors sensing stretch of the arterial wall



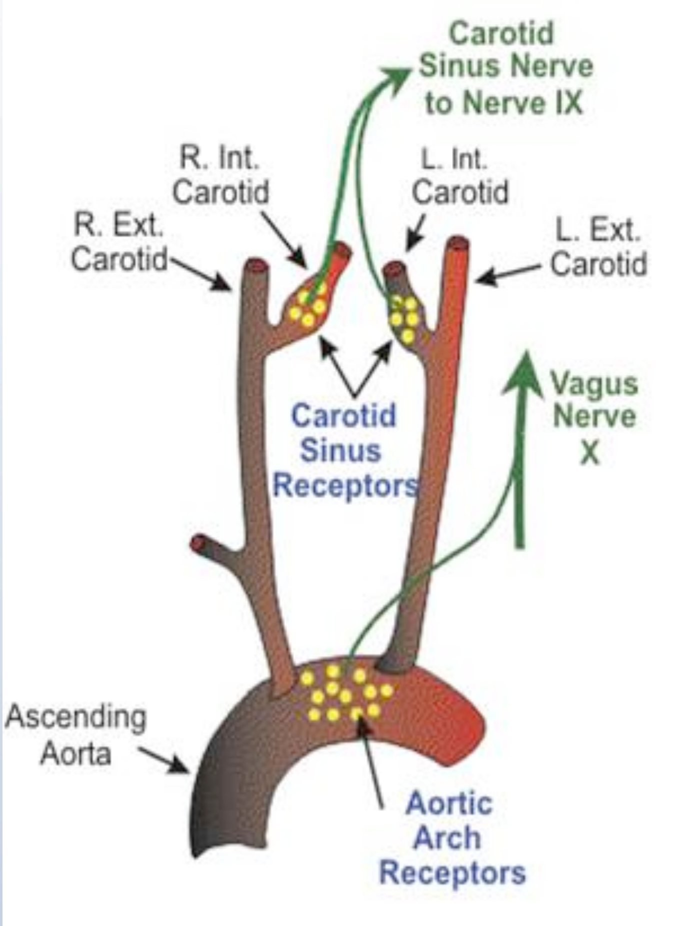
- Stretch proportional to circumference

$$c = 2\pi r$$

$$A = \pi r^2$$

- Blood pressure and area (elastic model)

$$p - p_0 = \frac{Eh}{r_0}\left(1 - \sqrt{\frac{A_0}{A}}\right)$$



Baroreceptors

- Blood pressure and area (viscoelastic models)

$$s(t) = K(0)s^{(e)}[p(t)] + \int_{-\infty}^{t} K(t-\gamma)\frac{\partial s^{(e)}[p(\gamma)]}{\partial \gamma} d\gamma, \qquad s(t) = 1 - \sqrt{\frac{A_0}{A(t)}}$$

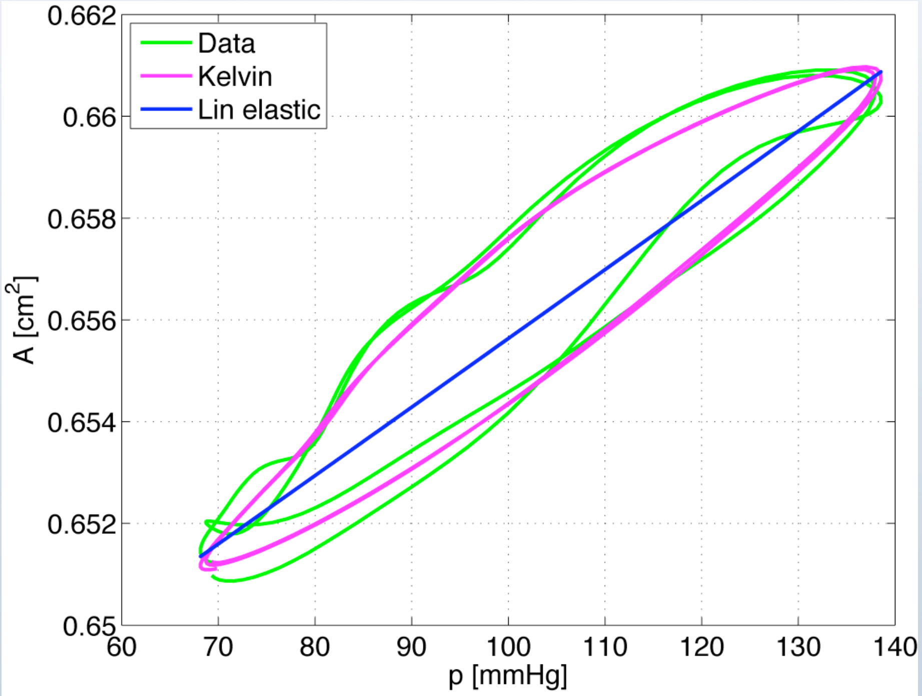
- Kelvin model

$$s^{(e)}[p(t)] = \frac{r_0}{Eh} p(t),$$

$$K(t) = 1 - A_1 e^{-t/b_1}$$

formulated as an ODE

$$s(t) + \tau_\sigma \frac{ds}{dt} = \frac{r_0}{Eh}\left(p + \tau_\varepsilon \frac{dp}{dt}\right)$$

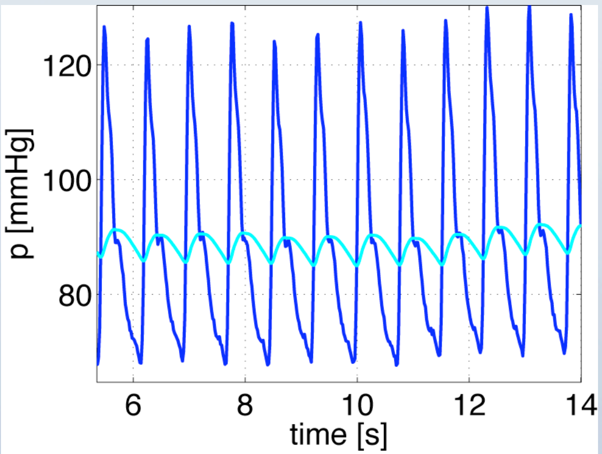


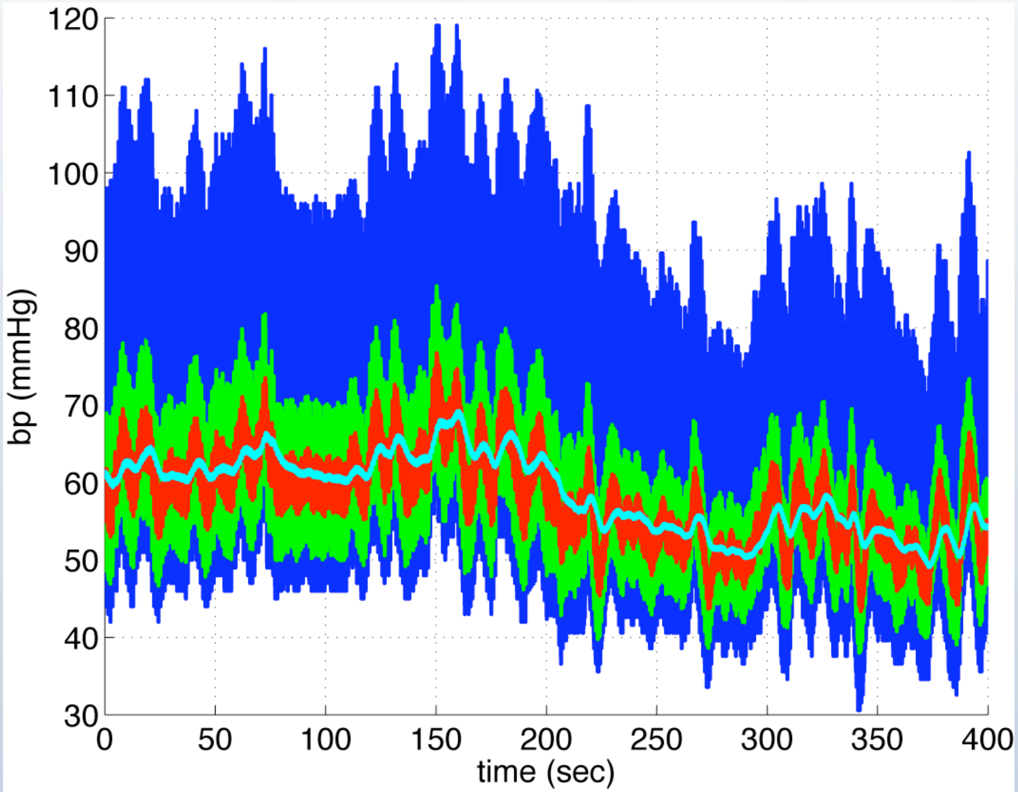
HR model

- Running average blood pressure

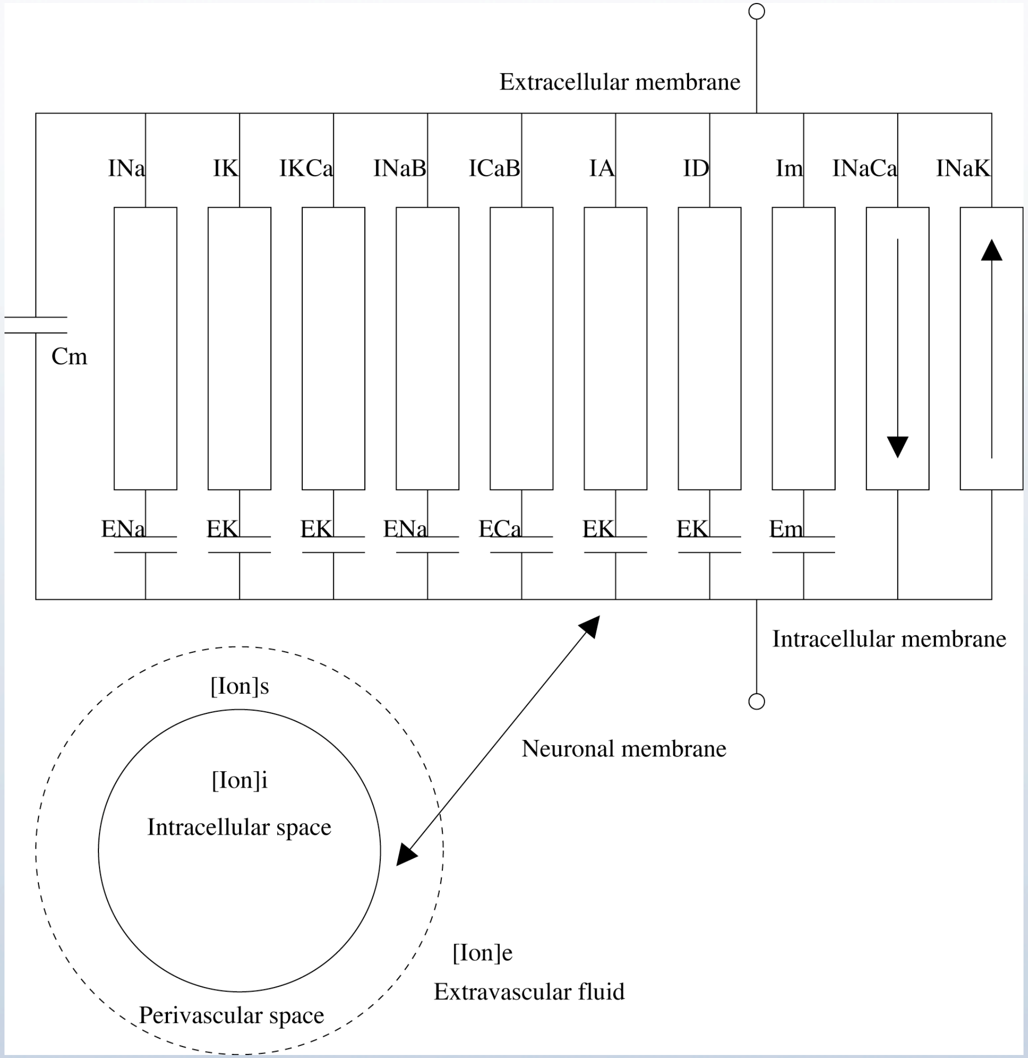
$$\overline{p}(t) = \alpha \int_{-\infty}^{t} p(s) e^{-\alpha(t-s)} \, ds$$

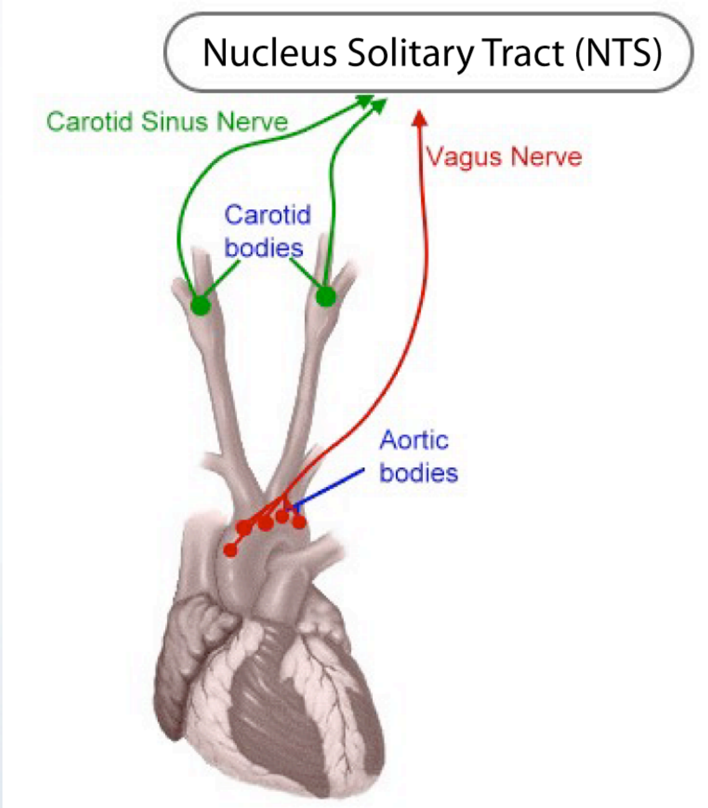
$$\frac{d\overline{p}}{dt} = \alpha(-\overline{p} + p)$$

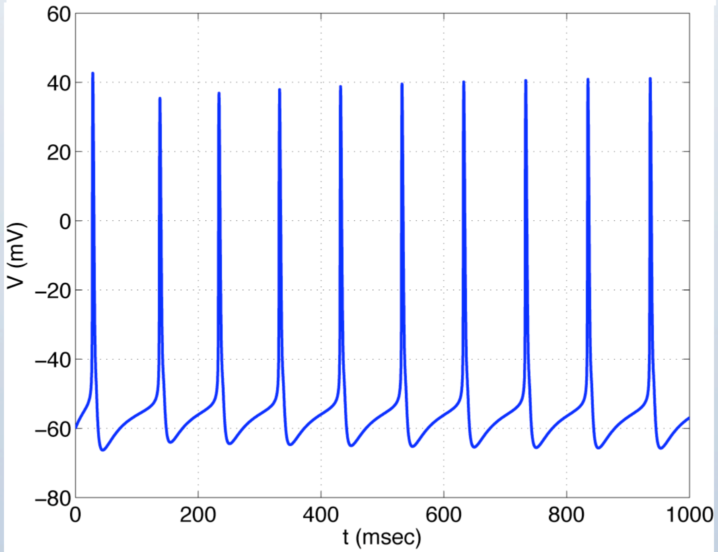




Afferent firing







Afferent firing

- Membrane voltage

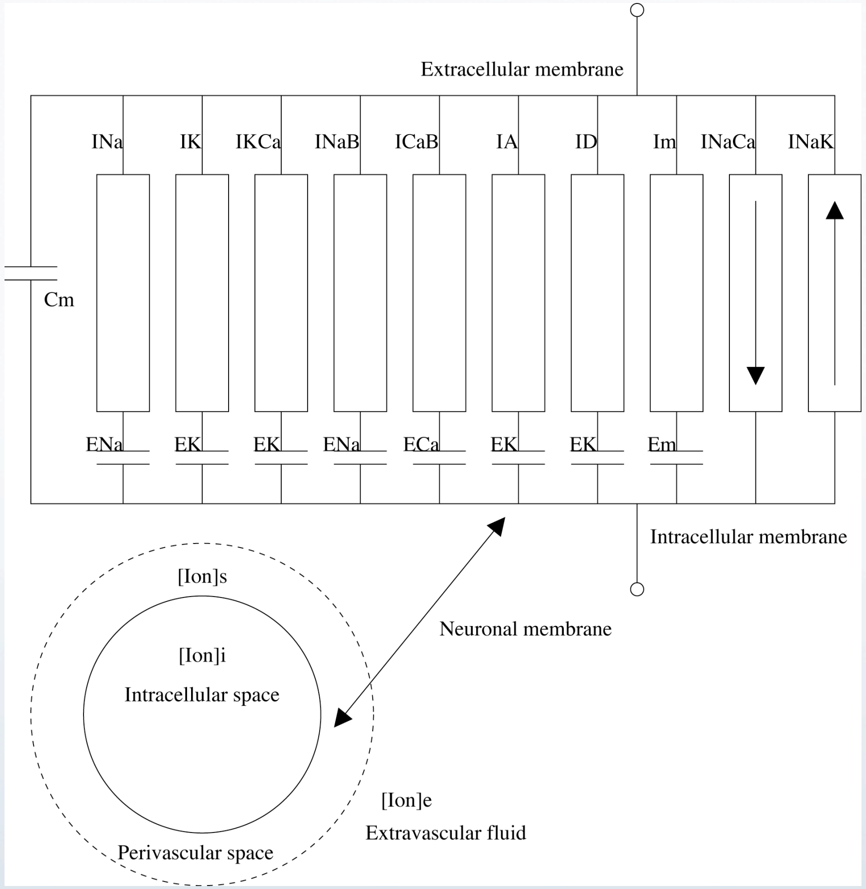
$$\frac{dV}{dt} = \frac{\sum I_{ion} - I_{stim}}{C_m}$$

- Ionic currents

$$I_{ion,i}(t,V) = \bar{g} m_{ion,i}^{x} h_{ion,i}^{y} (V - E_{ion,i})$$

$$\frac{dz}{dt} = \frac{z_\infty - z}{\tau_z}, \quad z_\infty(V) = \frac{1}{1 + \exp\left(\frac{V_{1/2} - V}{S_{1/2}}\right)}$$

$$\tau = A \exp\left[-B^2 \left(V - V_{peak}\right)^2\right] + C$$



Afferent firing

- Afferent firing rate

$$n(t) = f(V)$$

- Lumped model

$$n(t) = \sum_{i=1}^{2} n_i + N$$

$$\frac{dn_i}{dt} = k_i \overline{p} \frac{n(M-n)}{(M/2)^2} - \frac{n_i}{\tau}, \quad i = 1,2$$

Sympathetic and parasympathetic outflow

- Sympathetic and parasympathetic outflow

$$\gamma_{par} = \frac{n}{M}$$

$$\gamma_{sym} = \frac{1 - n(t - \tau_d)}{1 + \beta\gamma_{par}}$$

- Neurotransmitters acetylcholine and noradrenaline

$$\frac{dC_{ach}}{dt} = \frac{\gamma_{par} - C_{ach}}{\tau_{ach}}$$

$$\frac{dC_{nor}}{dt} = \frac{\gamma_{sym} - C_{nor}}{\tau_{nor}}$$

- Heart rate

$$h = h_0(1 + m_{nor}C_{nor} - m_{ach}C_{ach})$$

Initial values

- Running average pressure

$$\bar{p}(0) = \mathrm{mean}(P_R)$$

- Afferent firing rate

$$n_1(t) = n_2(t) = 0 \quad \Rightarrow \quad n = N, \quad -\tau_d \le t \le 0$$

- Sympathetic and parasympathetic outflow

$$f_{par}(0) = \frac{N}{M}, \quad f_{sym}(t) = \frac{1 - N/M}{1 + \beta N/M}, \quad -\tau_d \le t \le 0$$

- Concentrations

$$C_{ach}(0) = f_{par}(0), \quad C_{nor}(t) = f_{sym}(t), \quad -\tau_d \le t \le 0$$

- Heart rate

$$h(0) = H_R$$

Parameter values

- Heart rate (beats/min)
  - Max heart rate $h_M = 217 - 0.85 \cdot \text{age}$
  - Min heart rate $h_m = 30$
  - Rest heart rate $h_r = H_R$
- Acetylcholine impact on heart rate

  At $h = h_M$ then $n = M$ giving $f_{par} = 1$ and $f_{sym} = 0$ consequently

  $$h_M = h_0(1 - m_{ach}) \quad \text{and} \quad m_{ach} = \frac{h_M - h_0}{h_0}$$

- Noradrenaline impact on heart rate

  At $h = h_m$ then $n \approx 0$ giving $f_{par} = 0$ and $f_{sym} = 1$ consequently

  $$h_m = h_0(1 + m_{nor}) \quad \text{and} \quad m_{nor} = \frac{h_m - h_0}{h_0}$$

Parameter values

- Baseline firing rate N. At $t = 0$

$$h(0) = h_r = H_R = h_0 \left(1 + m_{nor} \frac{1 - N / M}{1 + \beta N / M} - m_{ach} \frac{N}{M} \right)$$

$$N = M \frac{-b + \sqrt{b^2 - 4ac}}{2a}$$

$$a = \beta m_{ach}$$

$$b = \beta (h_r - h_0) / h_0 + m_{nor} + m_{ach}$$

$$c = (h_r - h_0) / h_0 - m_{nor}$$

- Remaining parameters are estimated from literature values.

$$\{\alpha, k_1, k_2, \tau_1, \tau_2, \tau_{ach}, \tau_{nor}, \beta, h_0\}$$

HR model

- Differential equations

$$\frac{dx}{dt} = f(x(t), x(t-\tau_d), t; \theta),$$

$$x = \{\bar{p}, n_1, n_2, C_{ach}, C_{nor}\}$$

- Model output

$$y(t) = g(x(t;\theta), x(t-\tau_d;\theta), t;\theta), \quad y = \{h\}$$

- Output data

$$Y(t_i) = g(x(t_i;\theta), x(t_i-\tau_d;\theta), t_i;\theta) + \varepsilon_i$$

$$Y = \{H\}$$

$$E[\varepsilon_i] = 0,\ \operatorname{cov}(\varepsilon_i, \varepsilon_j) = 0 \text{ for } i \neq j,\ \operatorname{var}(\varepsilon_i) = \sigma^2 < \infty$$

HR model

- Model parameters

$$\theta = \left(\alpha, N, M, k_1, k_2, \tau_1, \tau_2, \tau_{nor}, \tau_{ach}, \beta, h_0, m_{nor}, m_{ach}, \tau_d\right)^T$$

- Minimization problem

$$\tilde{\theta} = \arg\min_{\theta} J(\theta)$$

$$J(\theta) \approx \sigma^2 = R^T R = \frac{1}{K-q}\sum_{i=1}^{K}\left|y(t_i) - Y_i\right|^2,$$

$$R = \left(r_1, r_2, \ldots, r_K\right)^T,$$

$$r_i = \frac{y(t_i) - Y_i}{\sqrt{K-q}}$$

Sensitivities

- Classical sensitivity analysis

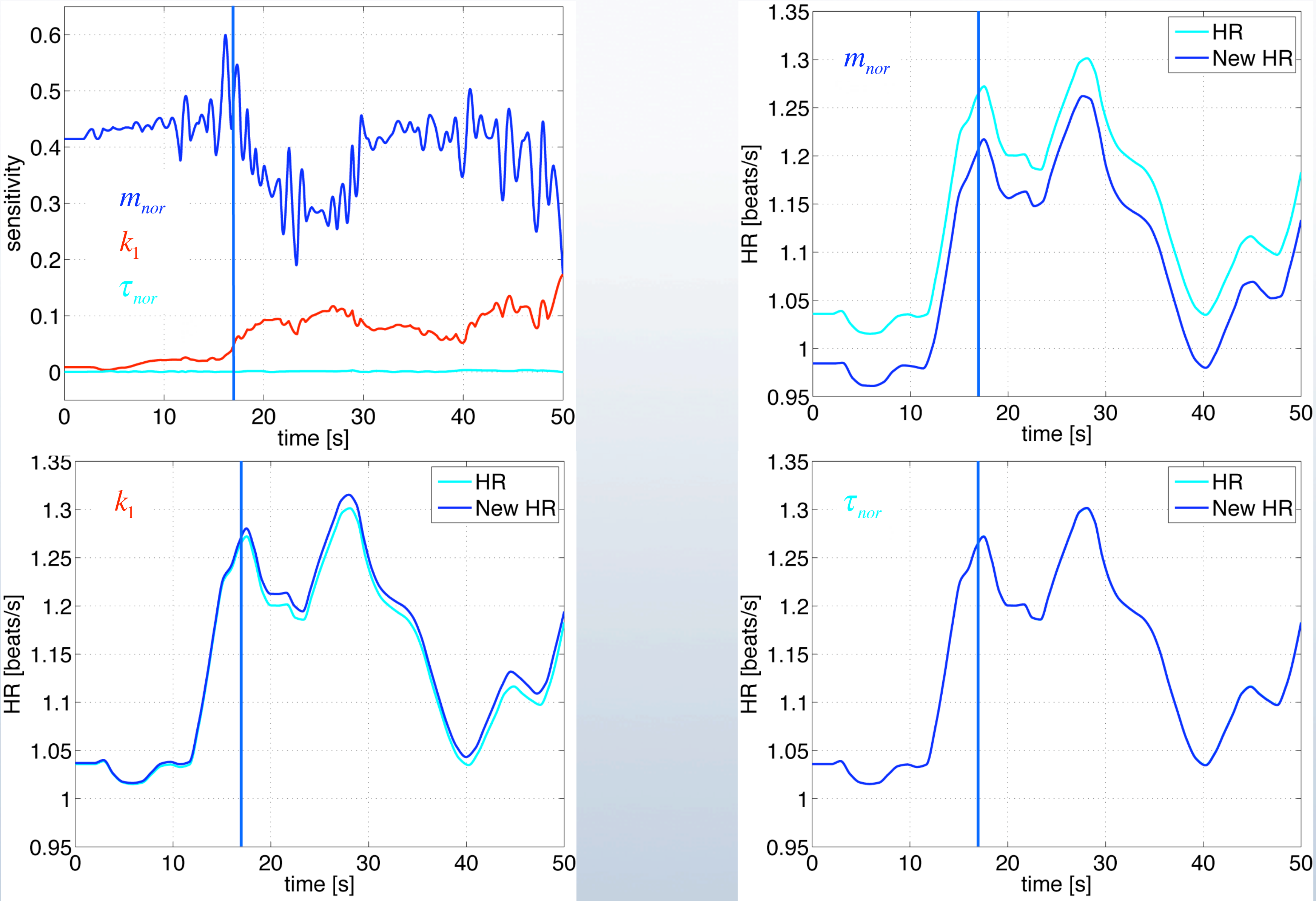
$$S = \frac{\partial y}{\partial \theta} = \frac{\partial y}{\partial x}\frac{\partial x}{\partial \theta} + \frac{\partial y}{\partial x'}\frac{\partial x'}{\partial \theta}, \quad x = x(t), \;\; x' = x(t - \tau_d)$$

$$S = \begin{bmatrix} \dfrac{\partial y(t_1)}{\partial \theta_1} & \cdots & \dfrac{\partial y(t_1)}{\partial \theta_q} \\ \vdots & \ddots & \vdots \\ \dfrac{\partial y(t_K)}{\partial \theta_1} & \cdots & \dfrac{\partial y(t_K)}{\partial \theta_q} \end{bmatrix}$$

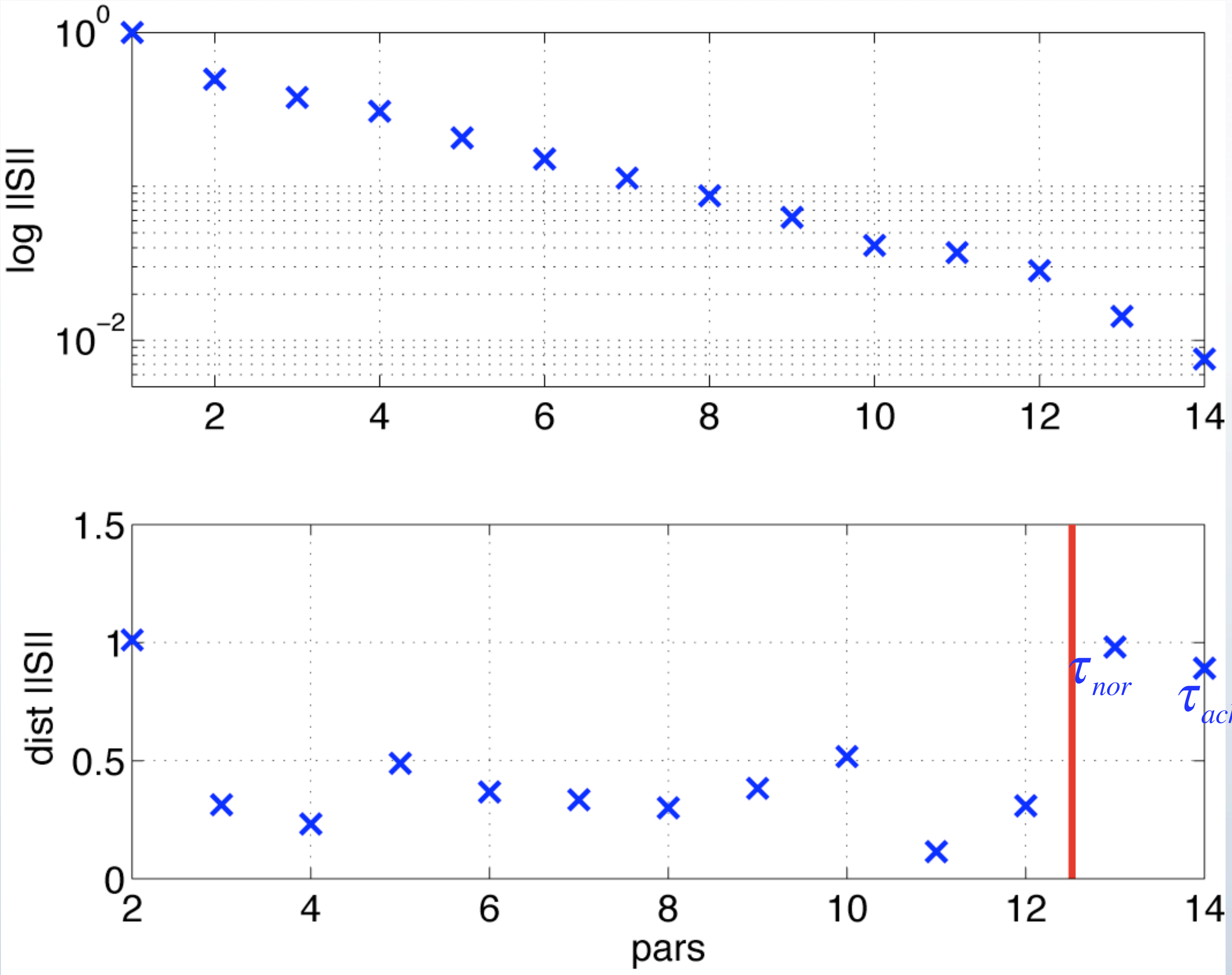
- Ranked sensitivities

$$\tilde{S}_i = \left\| S_{ij} \right\| = \left\{ \tilde{S}_{\theta_1}, \tilde{S}_{\theta_2}, \ldots, \tilde{S}_{\theta_q} \right\}$$

Sensitivities



Sensitivities



$$\theta = \left(\alpha, N, M, k_1, k_2, \tau_1, \tau_2, \beta, h_0, m_{nor}, m_{ach}, \tau_d\right)^T$$

Subset selection

- Structured correlation analysis
- Singular value decomposition and QR factorization

Structured correlation analysis

- Statistical model

$$Y(t_i) = g(x(t_i;\theta), x(t_i - \tau_d;\theta), t_i;\theta) + \varepsilon_i$$

$$Y = \{H\}$$

$$E[\varepsilon_i] = 0,\ \operatorname{cov}(\varepsilon_i, \varepsilon_j) = 0 \text{ for } i \neq j,\ \operatorname{var}(\varepsilon_i) = \sigma^2 < \infty$$

- Covariance matrix

$$C = \sigma^2 (S^T S)^{-1}$$

- Correlation matrix

$$c_{ij} = \frac{C_{ij}}{\sqrt{C_{ii} C_{jj}}}, \quad -1 \leq c_{ij} \leq 1, \quad c_{ii} = 1$$

Correlation analysis

	N	k_1	k_2	tau_1	tau_2	beta	h_0	m_{nor}	m_{ach}
N	1	-0.29	0.72	0.84	0.04	0.14	-0.52	-0.16	-0.80
k_1		1	0.12	-0.03	0.61	-0.33	-0.28	-0.27	-0.04
k_2			1	0.74	0.64	-0.13	**-0.91**	-0.43	**-0.97**
tau_1				1	0.14	0.13	-0.61	-0.14	-0.82
tau_2					1	-0.35	-0.73	-0.49	-0.54
beta						1	0.09	**0.91**	-0.02
h_0							1	0.26	**0.90**
m_{nor}								1	0.28
m_{ach}									1

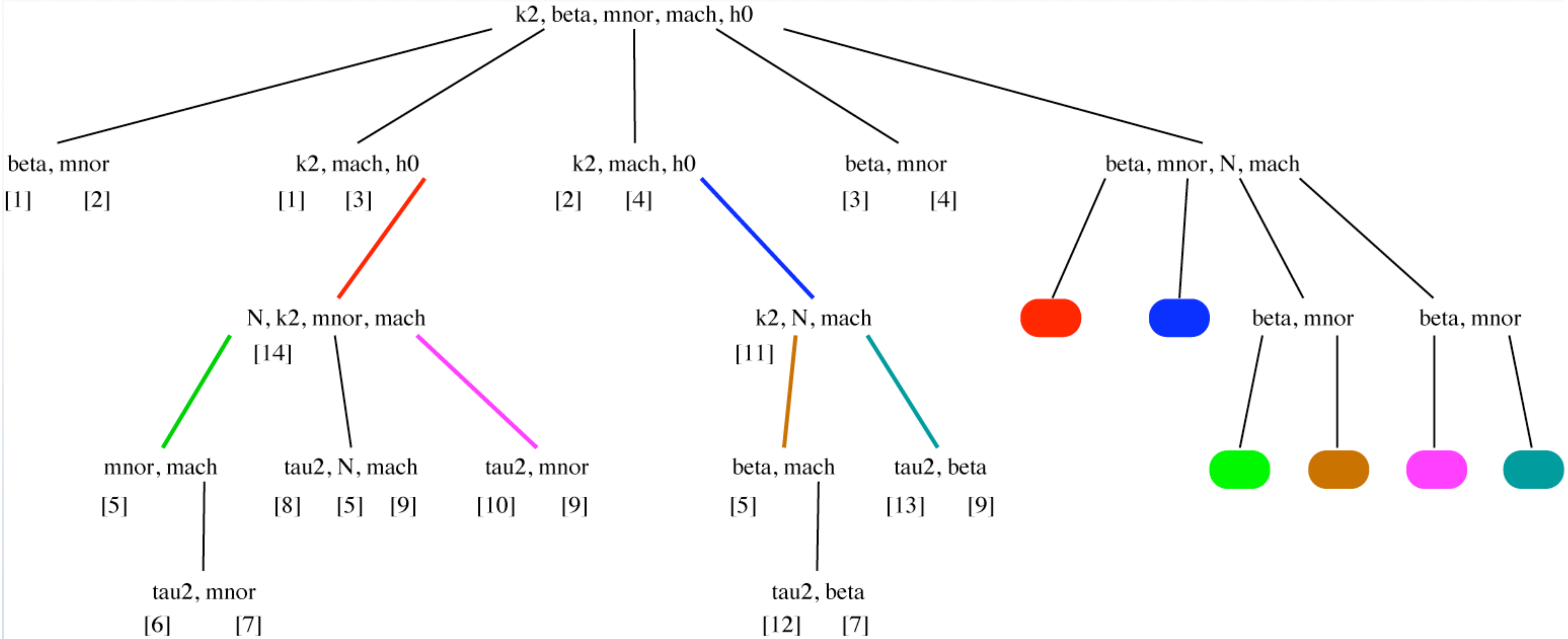
- Correlations: $k_2 \sim h_o \sim m_{ach}$, $m_{nor} \sim$ beta
- Sensitivity ranking: k_2, beta, m_{nor}, m_{ach}, h_o
- Fix at *a prori* value: k_2

Correlation analysis

	N	k_1	tau_1	tau_2	beta	h_0	m_{nor}	m_{ach}
N	1	-0.54	0.67	-0.79	0.34	0.46	0.24	-0.64
k_1		1	-0.18	0.71	-0.32	-0.42	-0.25	0.32
tau_1			1	-0.66	0.34	0.24	0.29	-0.62
tau_2					-0.35	-0.45	-0.31	0.47
beta					1	-0.07	**0.95**	-0.67
h_0						1	-0.33	0.19
m_{nor}							1	-0.66
m_{ach}								1

- Correlations: m_{nor} ~ beta
- Sensitivity ranking: beta, m_{nor}
- Fix at *a prori* value: beta

Subsets via correlations



1: k2, beta

2: k2, mnor [tauA]

3: beta, mach

4: mnor, mach

5: beta, mnor, N, h0

6: tau2, beta, N, mach, h0 [mnor]

7: beta, mnor, N, mach, h0

8: tau2, beta, mnor, h0

9: beta, mnor, mach, h0

10: tau2, beta, mach, h0

11: k2, mnor, h0

12: tau2, mnor, N, mach, h0

13: tau2, mnor, mach, h0

14: k2, beta, h0 [mnor]

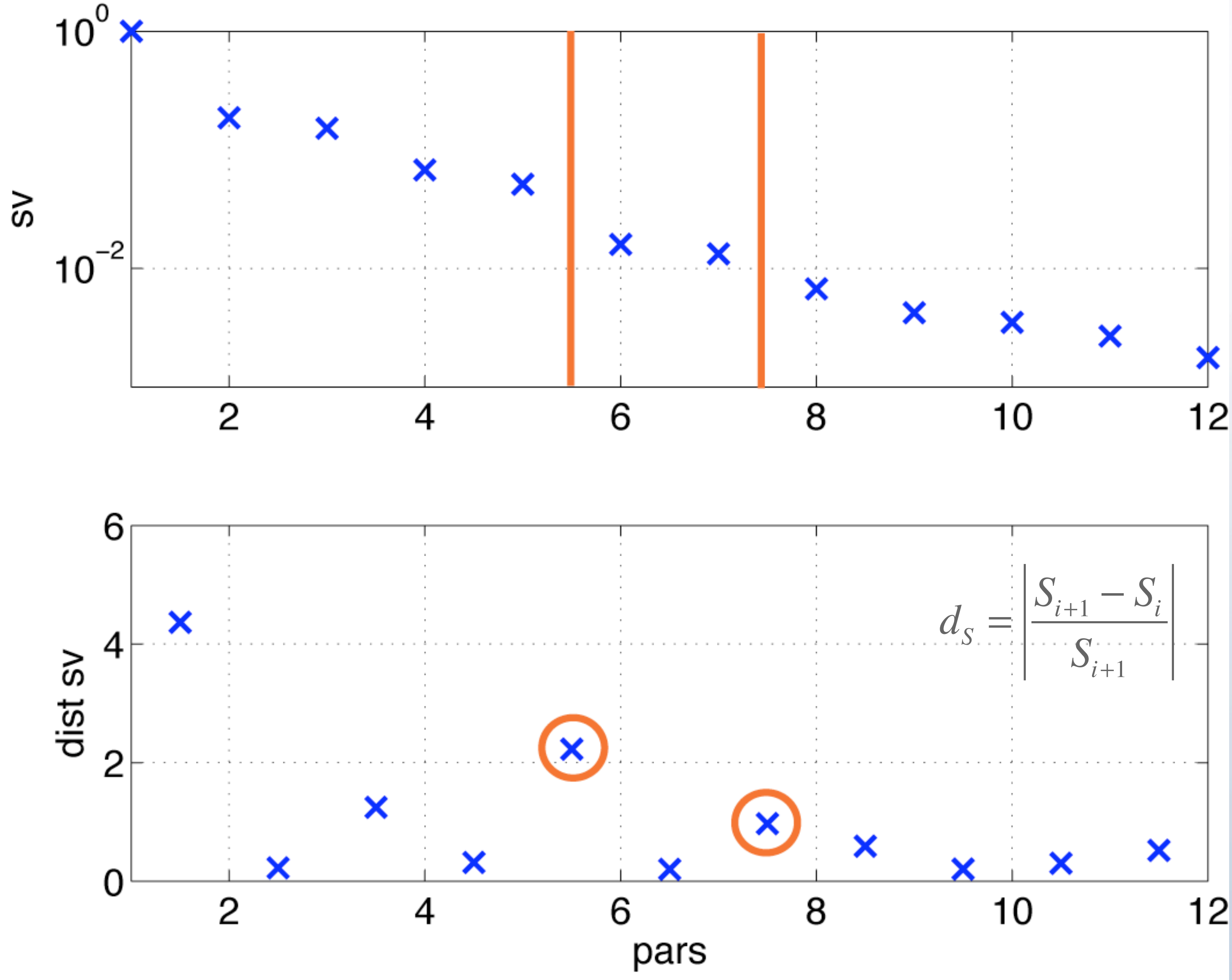
SVD - QR

- The goal of subset selection is to determine the largest set of uncorrelated parameters, that can be estimated given a set of data

- Subset selection via singular value decomposition of the sensitivity matrix $S = \partial h / \partial \theta$

- The numerical rank of the singular values used to estimate the number of parameters included in the subset
  - Analysis of error bounds: An integration tolerance of 10^{-8} implies that singular values (computed with finite differences) have an accuracy of 10^{-4}
    1. Singular values larger than 10^{-3} => All parameters included
    2. Singular values larger than 10^{-2} => 6 parameters
  - Study the relative distance between singular values

SVD - QR


10^0
10^{-2}
sv
2 4 6 8 10 12
6
4
2
0
dist sv
pars
$d_S = \left| \frac{S_{i+1} - S_i}{S_{i+1}} \right|$

SVD - QR

- Compute S and rewrite $S = U\Sigma V^T$, where the singular values $\mathrm{diag}(\Sigma)$ are sorted from the largest to smallest
- Determine the numerical rank ρ of S
- Partition the matrix of eigenvectors $V = \left[V_\rho \ V_{n-\rho}\right]$
- Determine a permutation matrix P by constructing a QR decomposition with column pivoting, i.e., determine P such that $V_\rho^T P = QR$
- Use P to reorder the parameter vector as $\hat{\theta}_0 = P^T \theta_0$
- Make the partition $\hat{\theta}_0 = \left[\hat{\theta}_{0,\rho} \ \hat{\theta}_{0,n-\rho}\right]$
- Fix $\hat{\theta}_{n-\rho}$ at the a priori estimates $\hat{\theta}_{0,n-\rho}$
- The subset of identifiable parameters contains $\hat{\theta}_\rho$

Parameter estimation

- For each subset of parameters, values were estimated using the Levenberg-Marquart method to solve the minimization problem

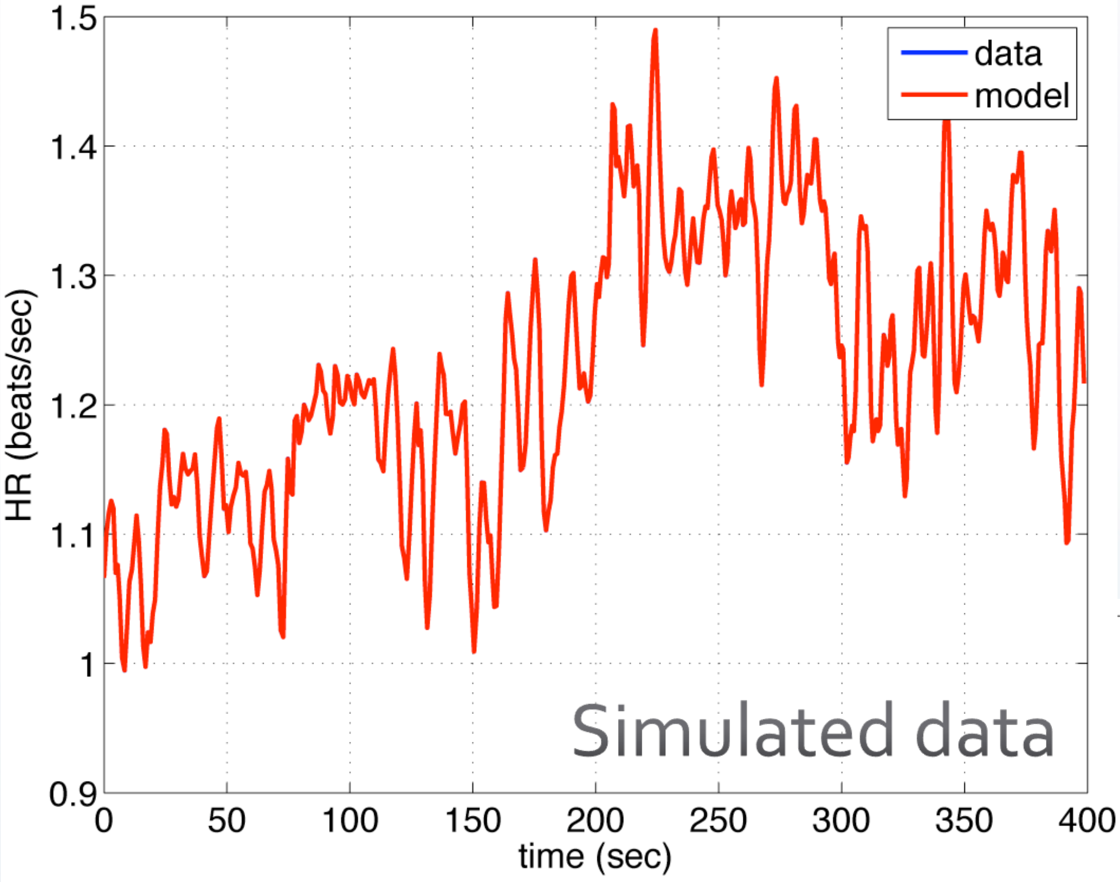
$$\tilde{\theta} = \arg\min_{\theta} J(\theta)$$

$$J(\theta) \approx \sigma^2 = R^T R = \frac{1}{K-q} \sum_{i=1}^{K} \left| y(t_i) - Y_i \right|^2,$$

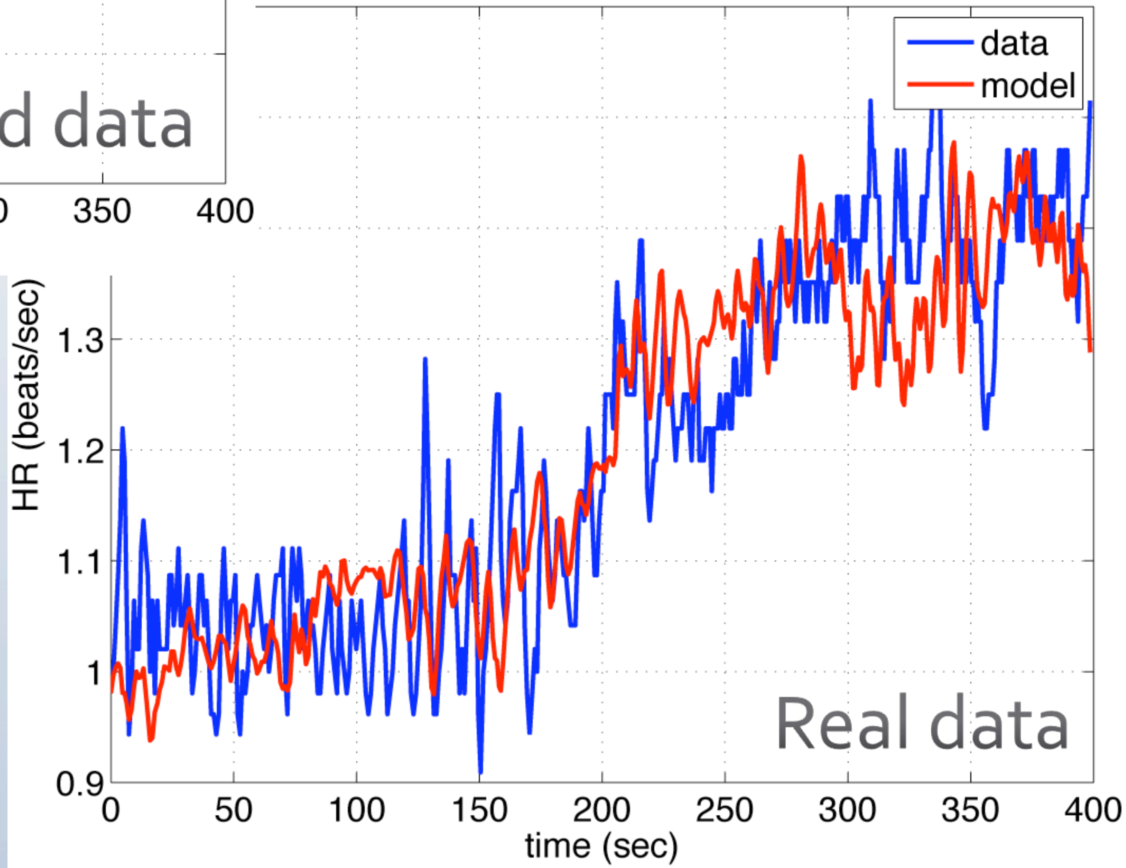
$$R = \left(r_1, r_2, \ldots, r_K \right)^T,$$

$$r_i = \frac{y(t_i) - Y_i}{\sqrt{K-q}}$$

Results



HR (beats/sec)
time (sec)
data
model
Simulated data



HR (beats/sec)
time (sec)
data
model
Real data

Akiake information criterion

- To compare results for each subset we used the Akiake information criterion, which for least squares problems can be formulated as

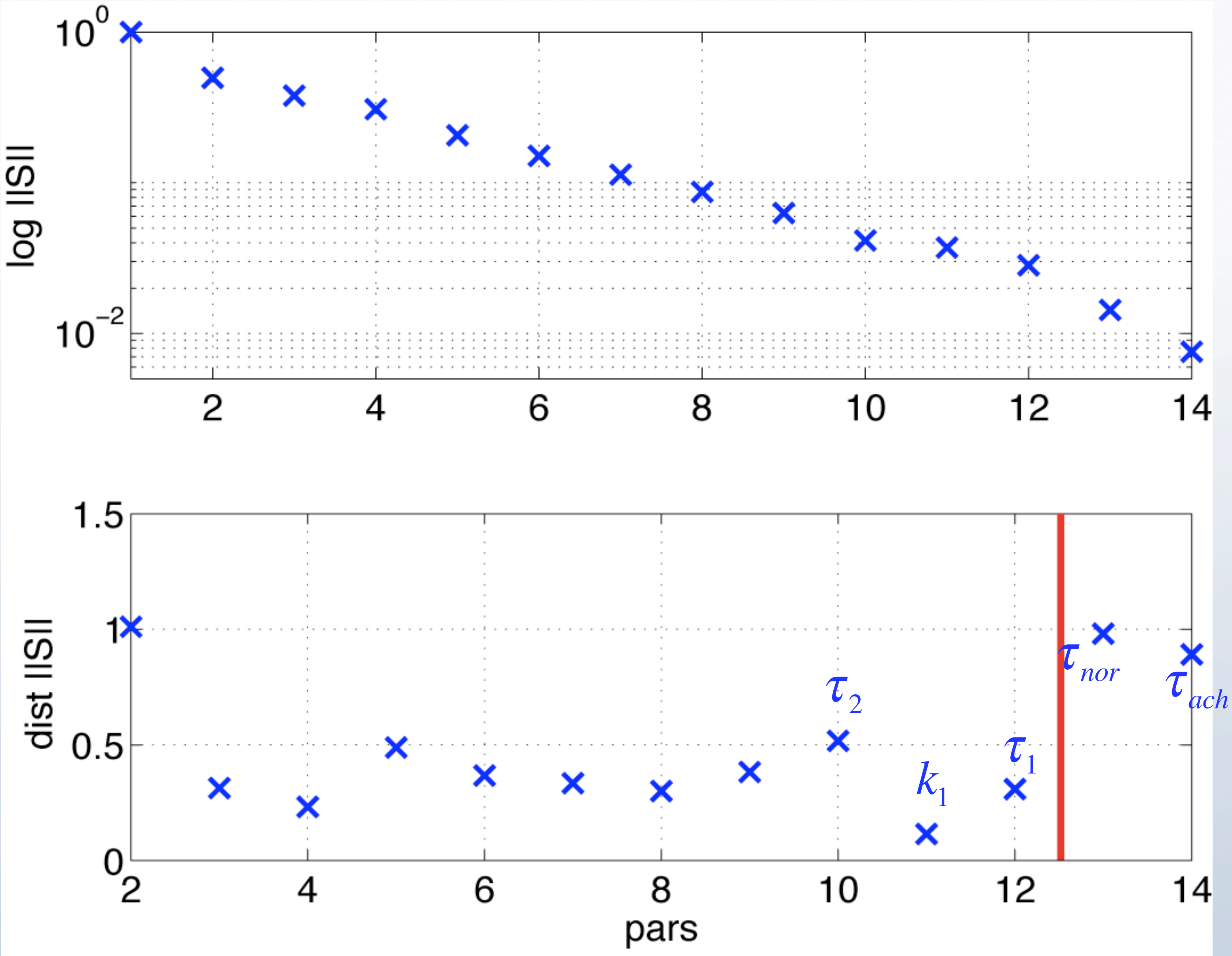
$$\mathrm{AIC} = K \log J + 2q$$

J is the least squares cost

K is the number of samples in the timeseries

q is the number of model parameters

Subsets	Grad	J	par	norm	cor	**AIC**	Rank
SVD-QR							
2 4 5 11 13	7.9e-5	7.1e-7	k2	6.68	5,11,13	-6.77	18
2 4 5 11 12 13	8.6e-5	8.0e-7	mnor	14. 7	5,13	-6.71	19
Correlation analysis							
2 4 6 7 11 12 13	**4.9e-5**	**1.5e-8**	**mnor**	**4.28**	**none**	**-8.61**	**5**
2 4 5 6 7 11 12	**2.0e-5**	**1.0e-8**	**k1**	**2.08**	**NA**	**-8.81**	**3**
2 4 6 7 11 12 13	**4.9e-5**	**1.5e-8**	**msym**	**4.28**	**NA**	**-8.61**	**5**
2 4 5 6 7 10 11	8.5e-5	3.0e-8	k1	3.03	NA	-8.29	7
2 4 6 7 10 11 13	7.8e-5	6.4e-6	k1	47.6	NA	-5.71	21
2 4 7 10 11 13	**3.5e-5**	**3.5e-9**	**k1**	**0.86**	**NA**	**-9.31**	**1**
2 4 6 7 10 13	**1.7e-5**	**9.7e-9**	**tau1**	**1.37**	**NA**	**-8.83**	**2**
2 4 6 7 12 13	5.4e-5	2.1e-7	mnor	30.1	NA	-7.35	14
2 4 6 7 13	**2.5e-5**	**1.6e-8**	**tau1**	**1.53**	**NA**	**-8.60**	**6**
2 4 5 6 12	4.4e-5	8.5e-8	k1	2.25	NA	-7.79	9
2 4 5 6 7	6.2e-5	8.6e-8	k1	1.84	NA	-7.79	10
2 4 5 6 13	6.1e-5	1.7e-e7	k1	2.89	NA	-7.45	11
2 4 5 6 10	7.0e-5	2.4e-e7	k1	2.31	NA	-7.30	15
4 5 6 7 13	9.9e-5	1.3e-6	k1	9.99	NA	-6.48	20
4 5 6 10	4.1e-5	8.0e-8	k1	1.55	NA	-7.82	8
4 5 6 7	4.5e-5	2.4e-7	k1	2.25	NA	-7.29	16
4 5 6 12	6.1e-5	2.9e-7	msym	11.99	NA	-7.21	17



10^0
10^{-2}
log ISI
2
4
6
8
10
12
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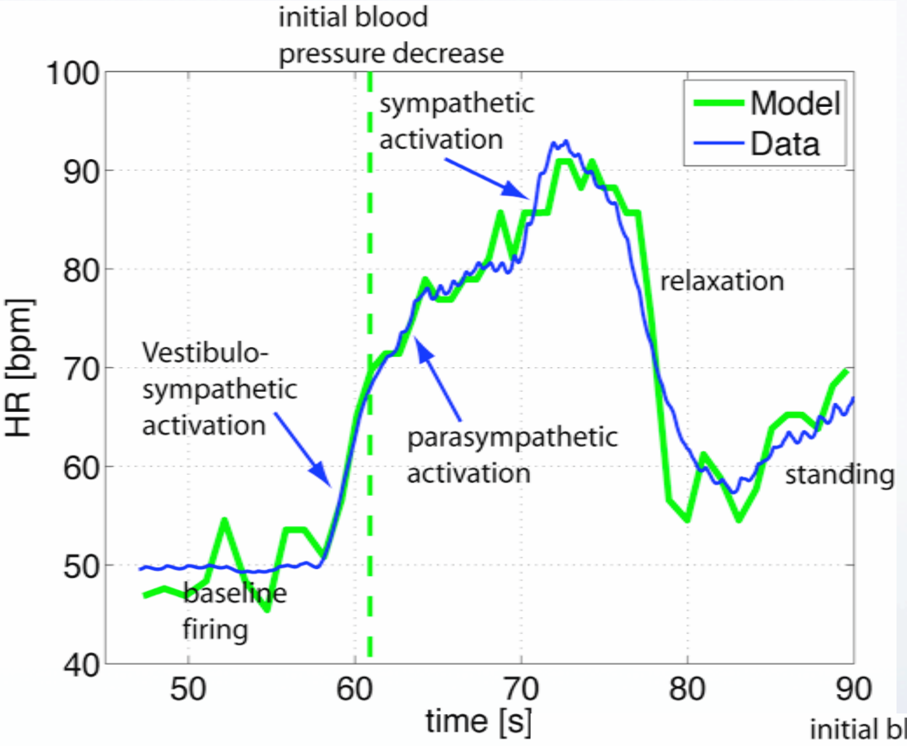
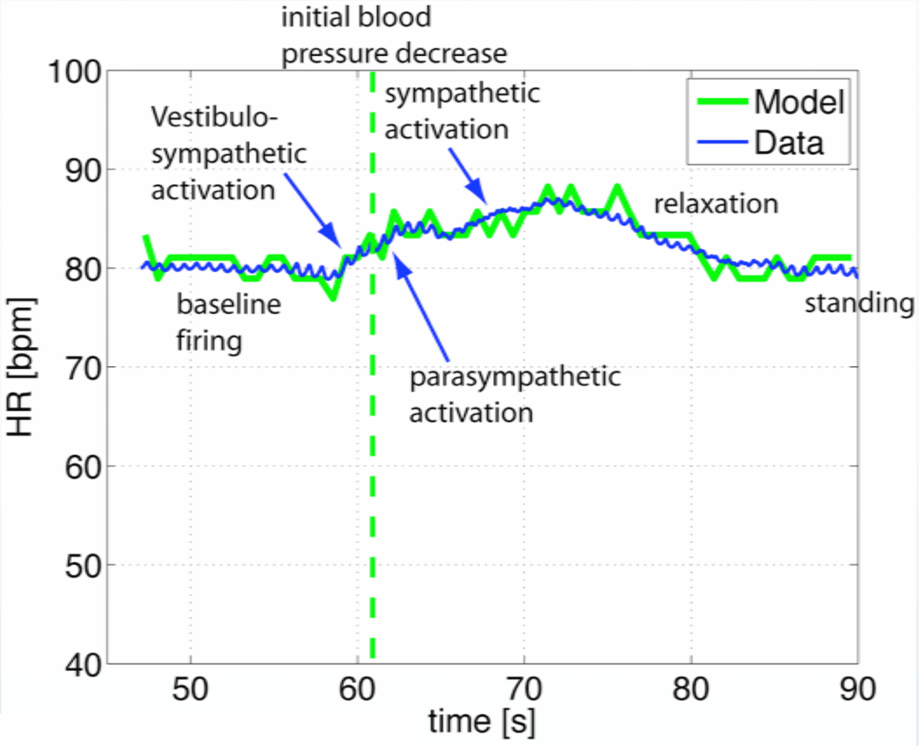
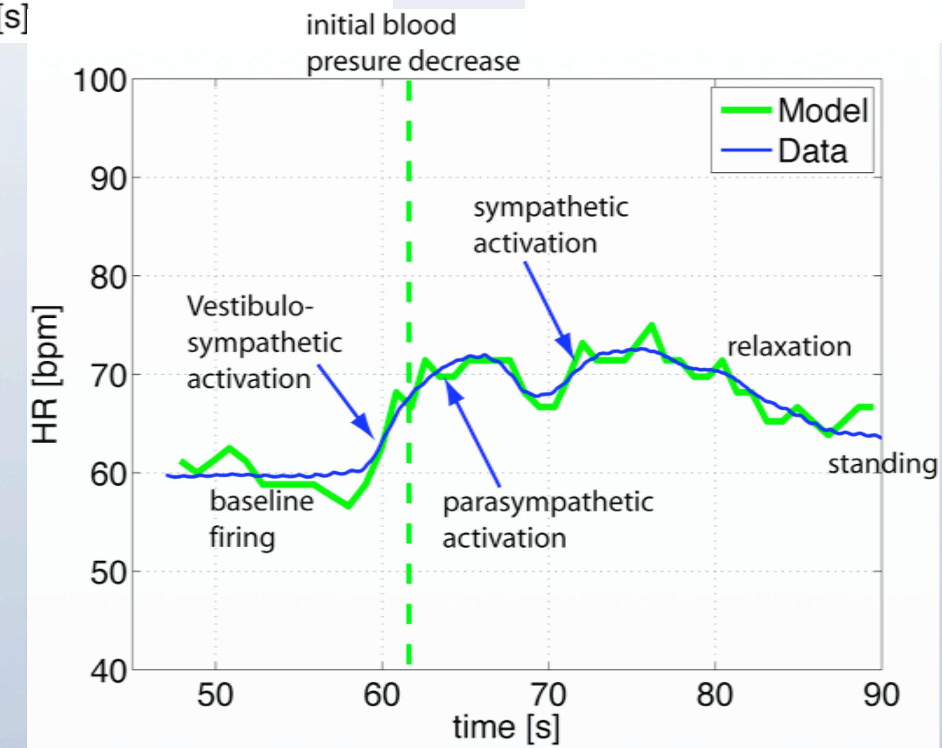
1.5
1
0.5
0
dist ISI
τ_2
k_1
τ_1
τ_{nor}
τ_{ach}
pars



Healthy young subject

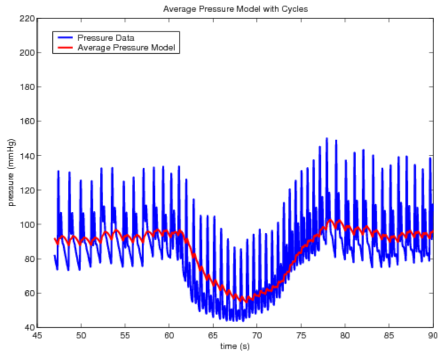


Hypertensive elderly subject

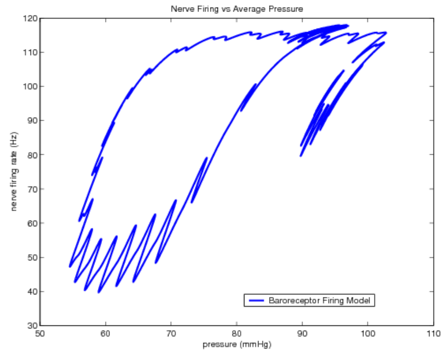


Healthy elderly subject

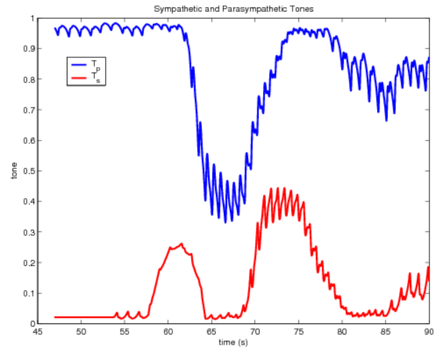
Healthy young subject



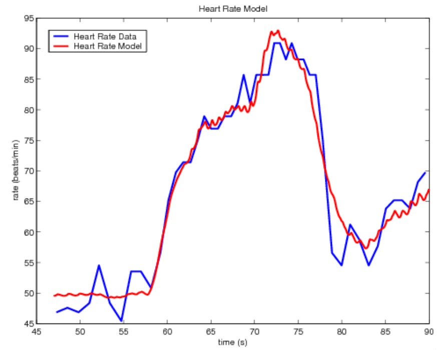
Pressure (blue, data) and mean pressure (red) vs. time



Firing rate vs. pressure (hysteresis loop is wide and closed)

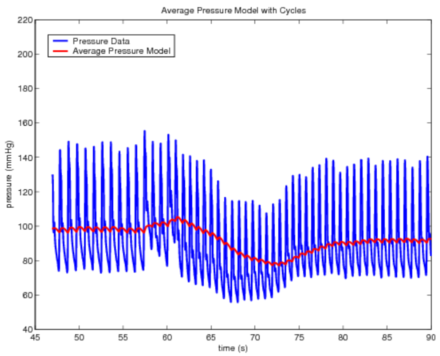


Parasympathetic (blue) and sympathetic (red) tones vs. Time:

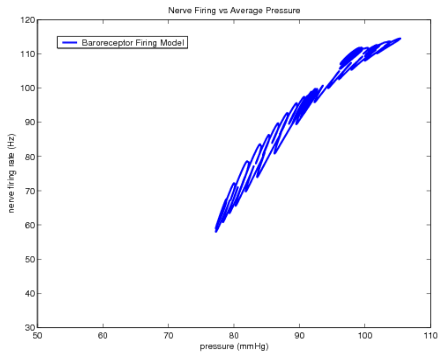


HR data (blue, data) and HR model (red) vs. time

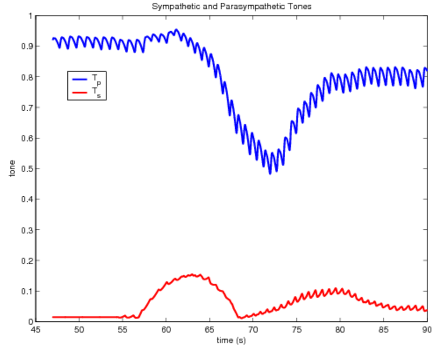
Healthy elderly subject



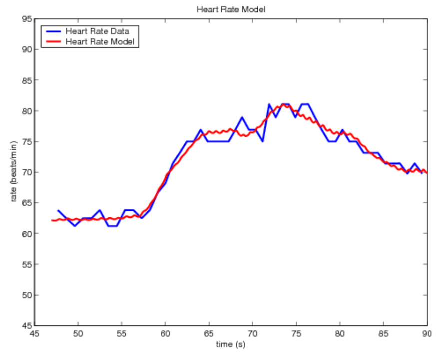
Reduced dynamics and lower resting state



Loop narrow with decreased slope; indicates reduced dynamics

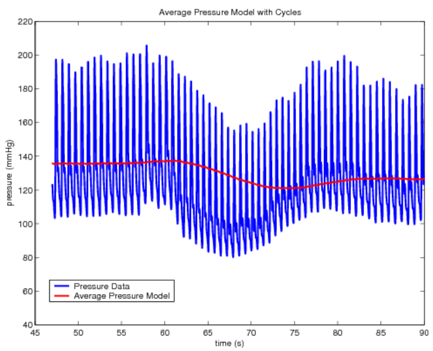


Diminished tone, in particularly sympathetic tone

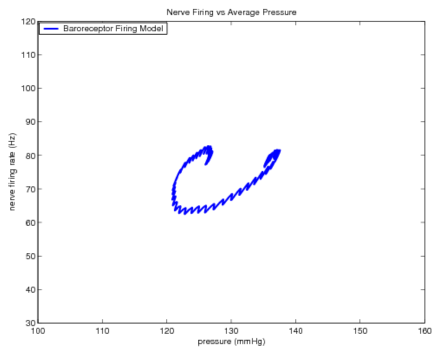


Reduced dynamics, higher resting state, slower regulation

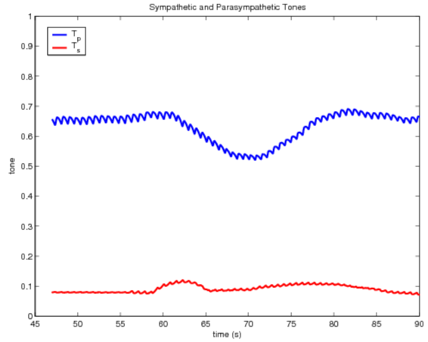
Hypertensive elderly subject



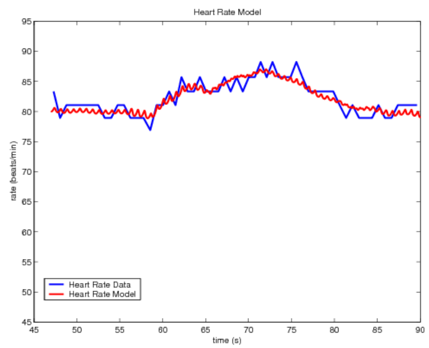
Reduced dynamics and longer regulation timescale



Reduced dynamics, not returning to steady state

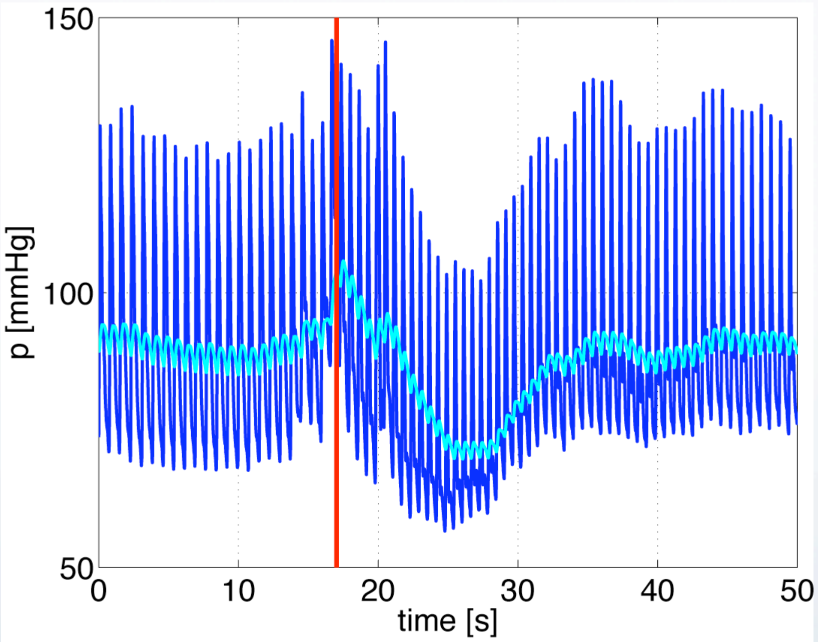


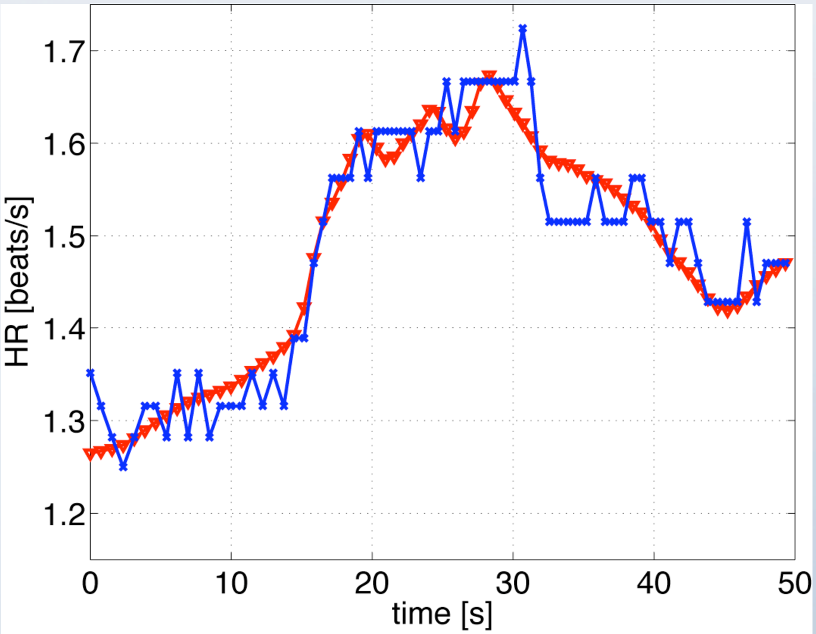
Significant sympathetic reduction



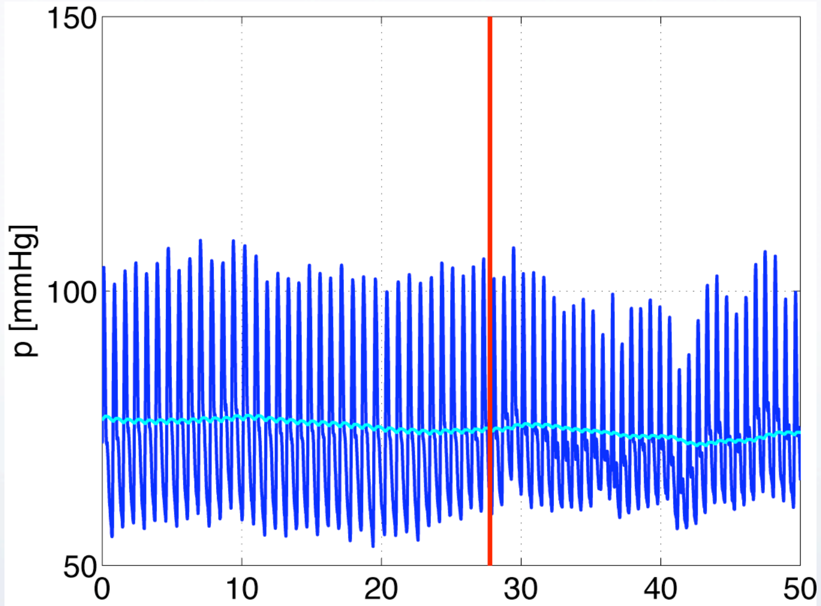
Reduced dynamics, higher rest state, slower regulation

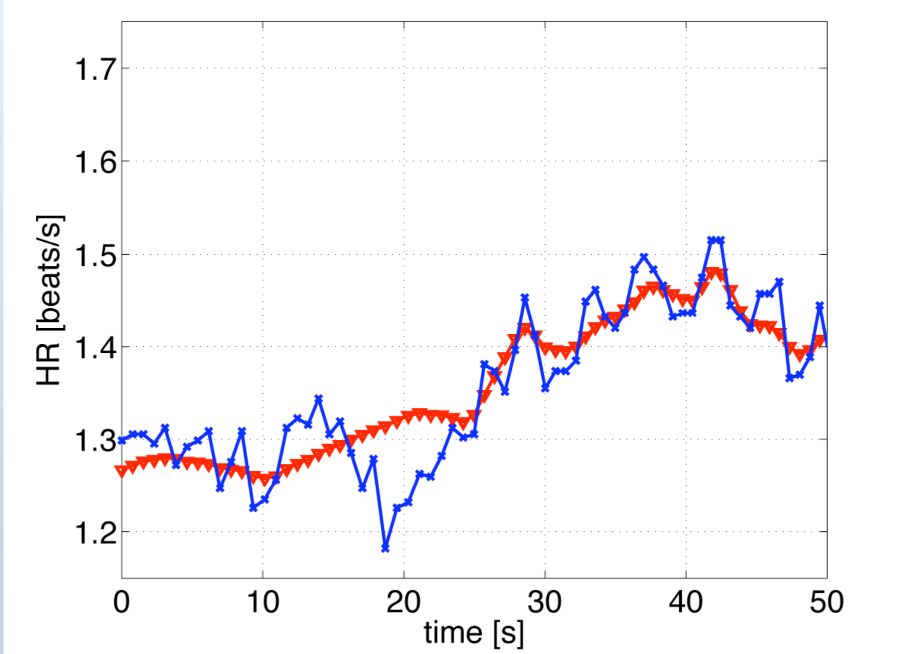
Sit-to-stand





Head-up-tilt





Discussion

- Estimation of all model parameters often leads to unreliable parameter estimates, in particular if the parameter set includes insensitive and correlated parameters
- Subset selection methods improves identifiability of parameters
- Numerous subset selection methods exists including Kalman filtering, principal component analysis, SVD-QR factorization and/or correlation analysis
- Physiological/biological considerations should be done as well to ensure estimation of parameters that have relevance for the user

Discussion

- Structured correlation analysis performs “better” than SVD-QR, the AIC values are lower
- The “winner” subset is more stable to pertubations in initial parameter values
- Note SVD-QR subsets still contain correlated parameters
- Note parameters with the largest error are always the least sensitive parameters left in the set

Discussion

- Correlation analysis is more time consuming to perform
- If analysis is performed with initial parameters far from the true parameters, the analysis should be repeated for a sweep of parameters using a Monte-Carlo type approach
- Methods could be combined using an iterative approach
- If the model is not correct, these methods do not perform well and parameter estimation methods do not converge even with a reduced parameter set

Acknowledgements

- Johnny Ottesen, Roskilde University, Denmark
- Jesper Mehlsen, Univ. Copenhagen, Frederiksberg Hospital, Denmark
- Hien Tran, Dept. of Mathematics, NCSU
- Vera Novak, Harvard Univ., Beth Israel Deaconess Medical Center, Boston
- Mikio Aoi, Biomathematics graduate student, NCSU
- April Alston, Applied mathematics graduate student, NCSU
- Anne, Dave, and Felix, REU students summer 2009
- NSF (USA) and Velux foundation (Denmark)