

BMES WORKSHOP

Parameter estimation methods in physiological modeling

Correspondence Email: jerry.batzel@uni-graz.at

Course outline:

- **8:30 - 9:00:** Introduction to physiology and motivations
- **9:00 - 10:00:** Parameter estimation: an introduction (Hien Tran N.C.S.U)
- **10:00 - 10:15:** Break
- **10:15 - 11:45:** Further discussion of parameter estimation and sensitivity analysis (Franz Kappel, Univ. of Graz)
- **11:45 - 13:00:** Lunch break
- **13:00 - 14:30:** Neural network approach to model design and parameter estimation (Spiros Courellis, Univ. So. Calif.)
- **14:30 - 14:45:** Break
- **14:45 - 16:15:** Statistical methods for parameter estimation and inference (Ben Fitzpatrick, Loyola Marymount)
- **16:15 - 16:30:** Break
- **16:30 - 17:30:** Applications (Mette Olufsen, N.C.S.U.)

Cardio-Respiratory Control: Clinical Issues



Jerry J. Batzel

Institute for Mathematics and Scientific Computing
University of Graz

Email: jerry.batzel@uni-graz.at

Acknowledgements: This work was partially funded by FWF (Austria) project P18778-N13.

Talk outline: Exploring control interactions in the CVRS system



- Overview of cardiovascular-respiratory control system
- Definition of the control problem
- Examples of model equations
- Investigation of the control loops
- Aspects of model validation

Introduction I

- A number of clinical conditions are related to cardiovascular short-term control of blood pressure including:
 - Orthostatic intolerance and POTS;
 - Pressure stabilization during dialysis;
 - Pressure stabilization during hemorrhage.
- A great deal remains to be known about the interactions of the control mechanisms involved in pressure stabilization. For example:
 - It was noted in a recent issue of the New England Journal of Medicine that "The art of fluid administration and hemodynamic support is one of the most challenging aspects of treating critically ill patients. Considering that every year in the United States over 11 million units of red cells are transfused in more than 3 million patients, there is a surprising paucity of data to guide decisions on transfusion."

Introduction II

- Examples of clinical conditions and issues related to respiratory control include:
 - Ventilatory instability in the form of periodic breathing such as Cheyne-Stokes breathing;
 - Central and obstructive sleep apnea.
- A great deal remains to be known about the interactions of the control mechanisms involved in system adaptation and stabilization. For example:
 - There is a strong correlation between sleep apnea and hypertension;
 - Cheyne-Stokes respiration is often found in patients with congestive heart failure and this form of periodic breathing may exacerbate the deterioration of heart function.

General CVRS system physiology I

- The purpose of the cardiovascular system (CVS) is to transport CO_2 , and O_2 , nutrients, and hormones via blood flow to various tissues of the body.
- The purpose of the respiratory system (RS) is to exchange CO_2 produced by metabolism in the tissues for O_2 which is necessary for metabolism.
- These two systems are linked in a number of ways and influence each other.
- There are control systems which sense changes in these systems and respond in ways which stabilize the systems.

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 - Each CVS circuit is subdivided into arterial and venous volume components with the lungs or tissues acting as resistances.

General CVRS system physiology II

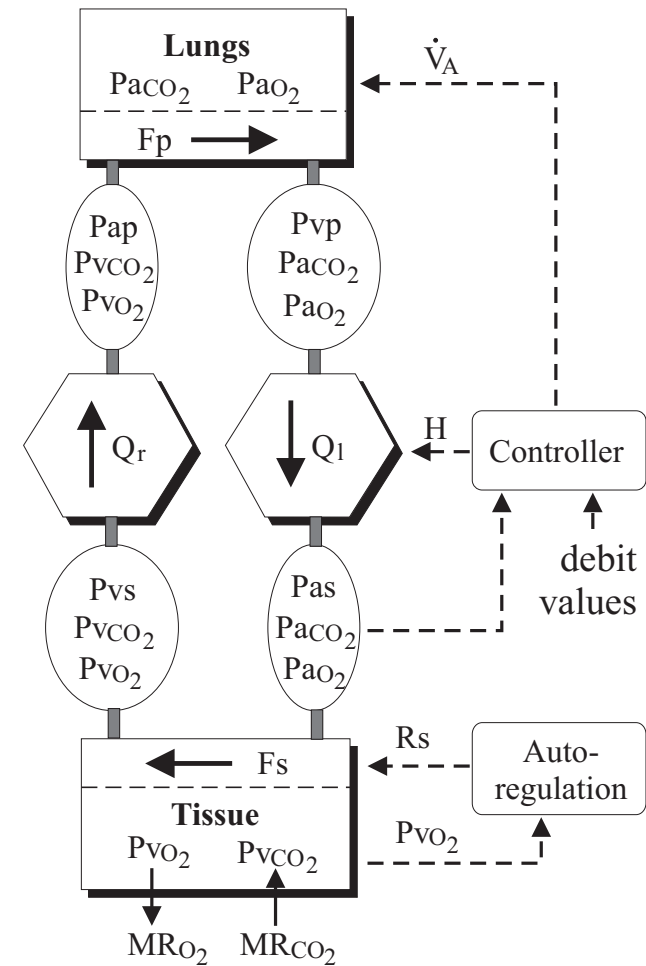
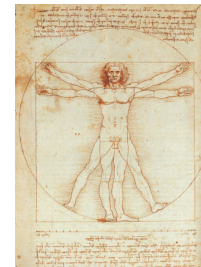
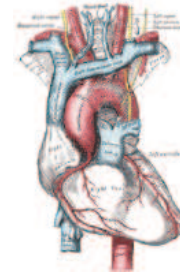
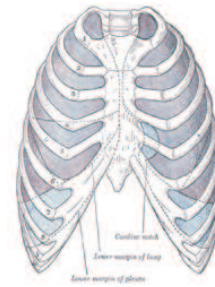
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- The cardiovascular-respiratory system can respond to a number of perturbations in the system via control mechanisms which monitor key elements.

General CVRS physiology III

- The respiratory system can be viewed as consisting of two main compartments.
 - The lungs are the sites where CO_2 is eliminated and O_2 is absorbed into the blood.
 - The tissues are where metabolism occurs and where the opposite exchange occurs.
- The efficiency of the exchange in the lungs depends on the renewal of fresh air via breathing and this can be controlled by the ventilation rate.

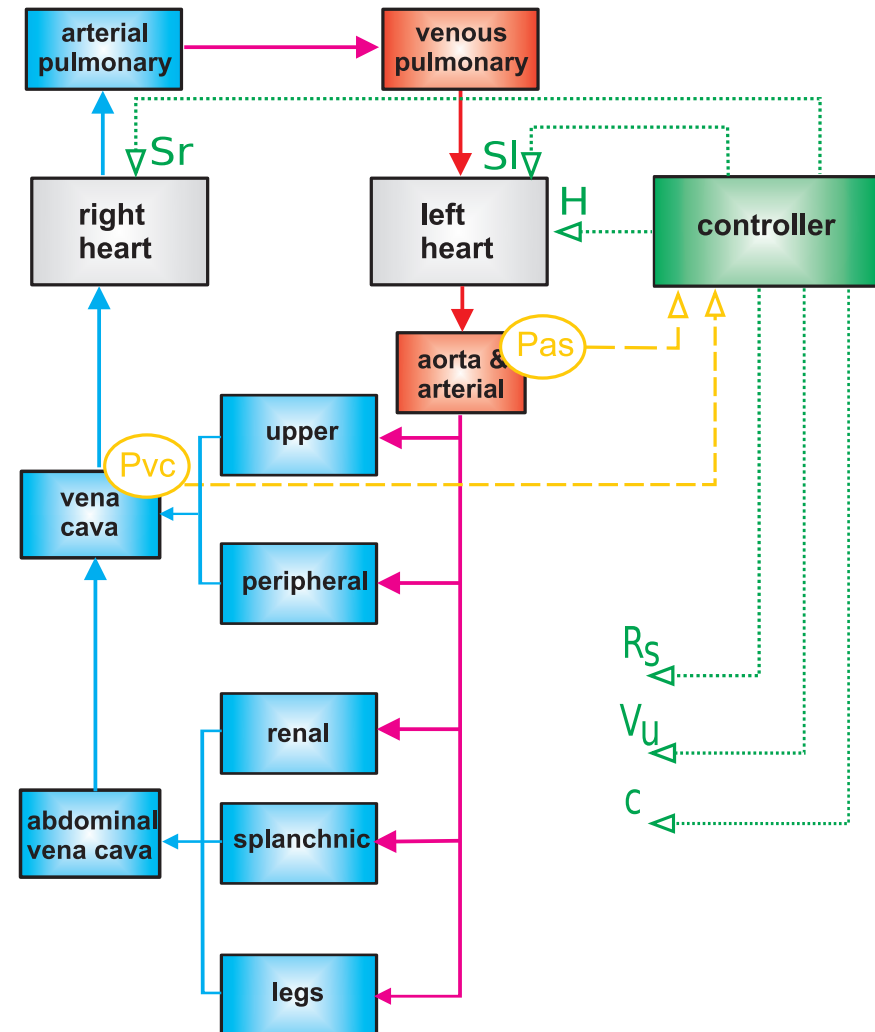
CVRS system block diagram I

- 4 cardiovascular compartments
 - Pulmonary arterial and venous volumes
 - Systemic arterial and venous volumes
- 2 respiratory compartments
 - lung compartment
 - tissue compartment



CVRS system block diagram II

- 10 cardiovascular compartments
 - Pulmonary arterial and venous volumes
 - Systemic upper and lower arterial and venous volumes, aorta, vena cavae
- Control responses
 - Change in heart rate H and contractility S
 - Change in systemic resistance R_s
 - Change in unstressed volume V_u and compliance C



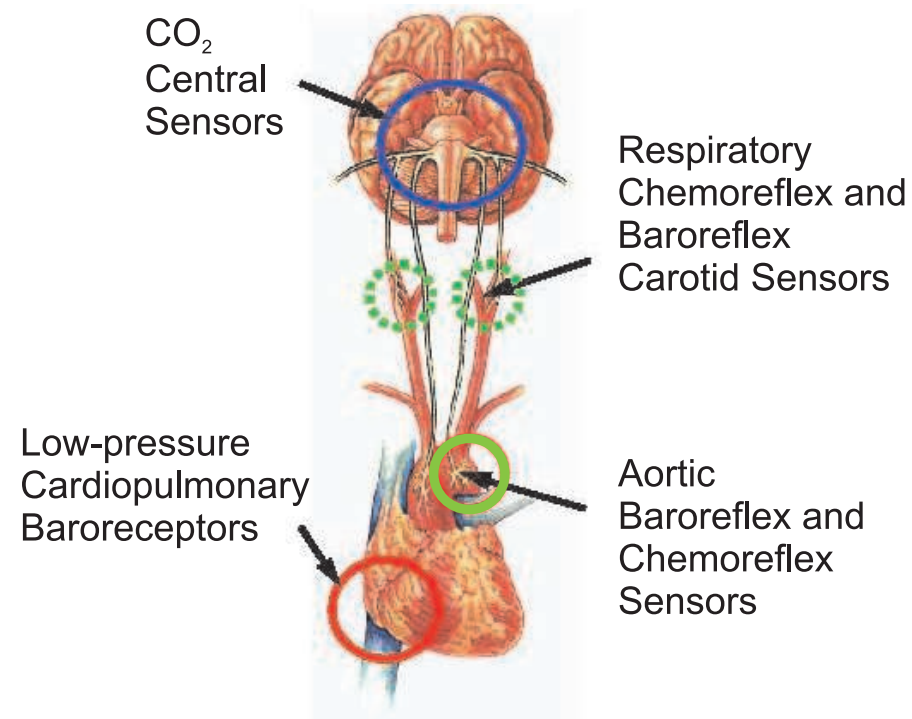
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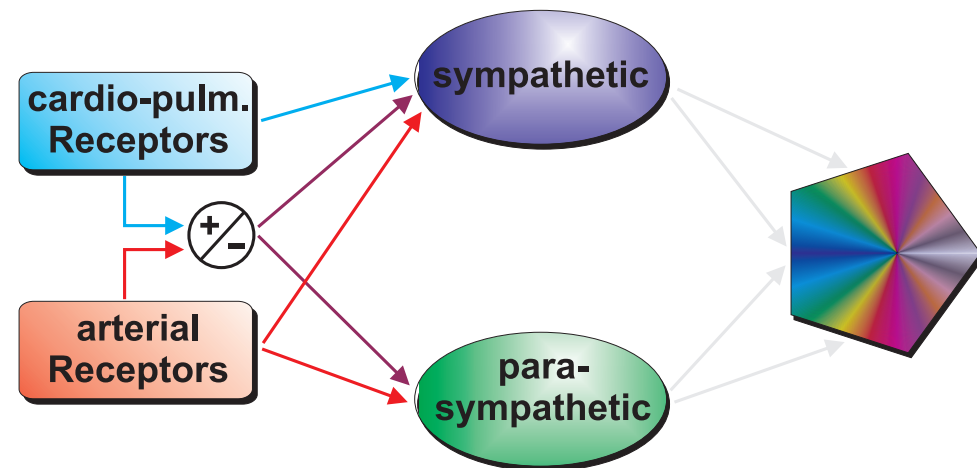
CVRS sensory systems

- Sensors for P_{a,CO_2} in brain
- Control processing center in medulla
- Sensors for P_{a,CO_2} and P_{a,O_2} in carotid bodies
- Sensors for P_{as} in aortic and carotid body region
- Sensors for P_{vs} in veno-atrial region, pulmonary artery



CVS control interactions

- Cardiopulmonary and arterial baroreflexes and chemosensors monitor status
- How this information is processed for appropriate response is under investigation
- The control processing center in the medulla generates responses via sympathetic and parasympathetic pathways



Control system quantities

Control action

- Heart frequency
- Heart muscle contractility
- Venous tone: capacitance and compliance
- Arterial resistance
- Ventilation rate
- Blood volume

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Key controlled quantities

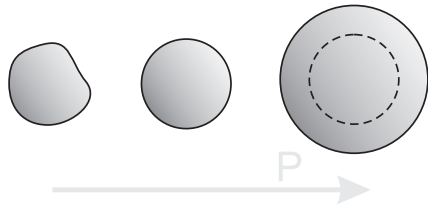
- Blood pressure
- Cardiac output
- Oxygen, carbon-dioxide, and pH

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Basic CVS model relationships

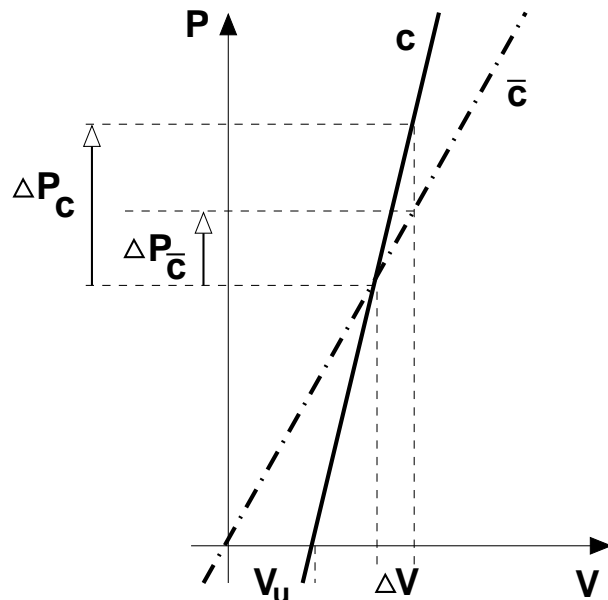


Vessels are **not rigid**. When the **trans-mural pressure is zero** they still contain the “**unstressed volume**” V_u .

$$V = c(P)P + V_u$$

Due to friction along the walls the vessels represent a **resistance for the blood flow**.

$$F = \frac{P_{in} - P_{out}}{R}$$



Pressure-Volume relation

Example ODEs for the CVS system

- For each compartment we have:

$$\frac{dV_{\text{comp}}}{dt} = F_{\text{in}} - F_{\text{out}},$$

- where F_{in} and F_{out} denote flow into and out of the compartment.

- Noting that total volume is the sum of stressed and unstressed volume we have:

$$\frac{dc}{dt}(P_{\text{comp}} - P_{\text{bias}}) + c\left(\frac{dP_{\text{comp}}}{dt} - \frac{dP_{\text{bias}}}{dt}\right) + \frac{dV_{\text{u}}}{dt} = F_{\text{in}} - F_{\text{out}}$$

representing a typical compartment equation, where “comp” stands for “as”, “per”, “up”, “ren”, “spl”, “leg”, “vc”, “avc”, “ap”, and “vp”.

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Reduction in Effective Blood Volume

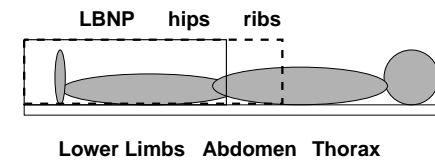
- Head Up Tilt (**HUT**), Lower Body Negative Pressure (**LBNP**), **orthostasis**, **hemorrhage**, and **dialysis** have the following in common:

There is a **reduced amount of blood available in the chest** for maintaining circulation.

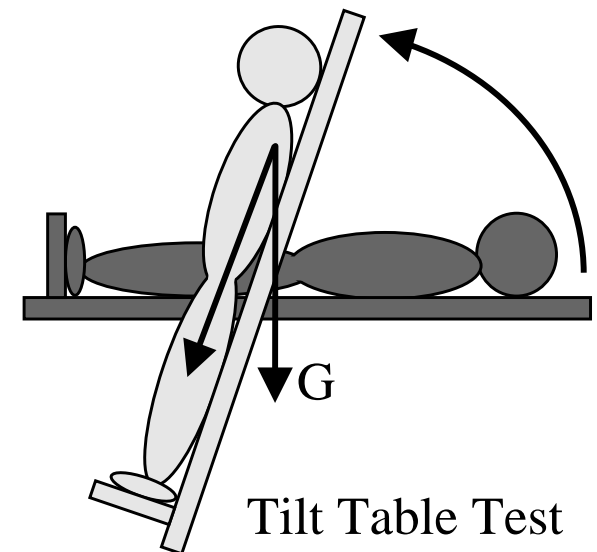
- Hydrostatic pressure for HUT

$$P_{\text{grav}} = c\rho gh \sin(\alpha)$$

- Lower cardiac output

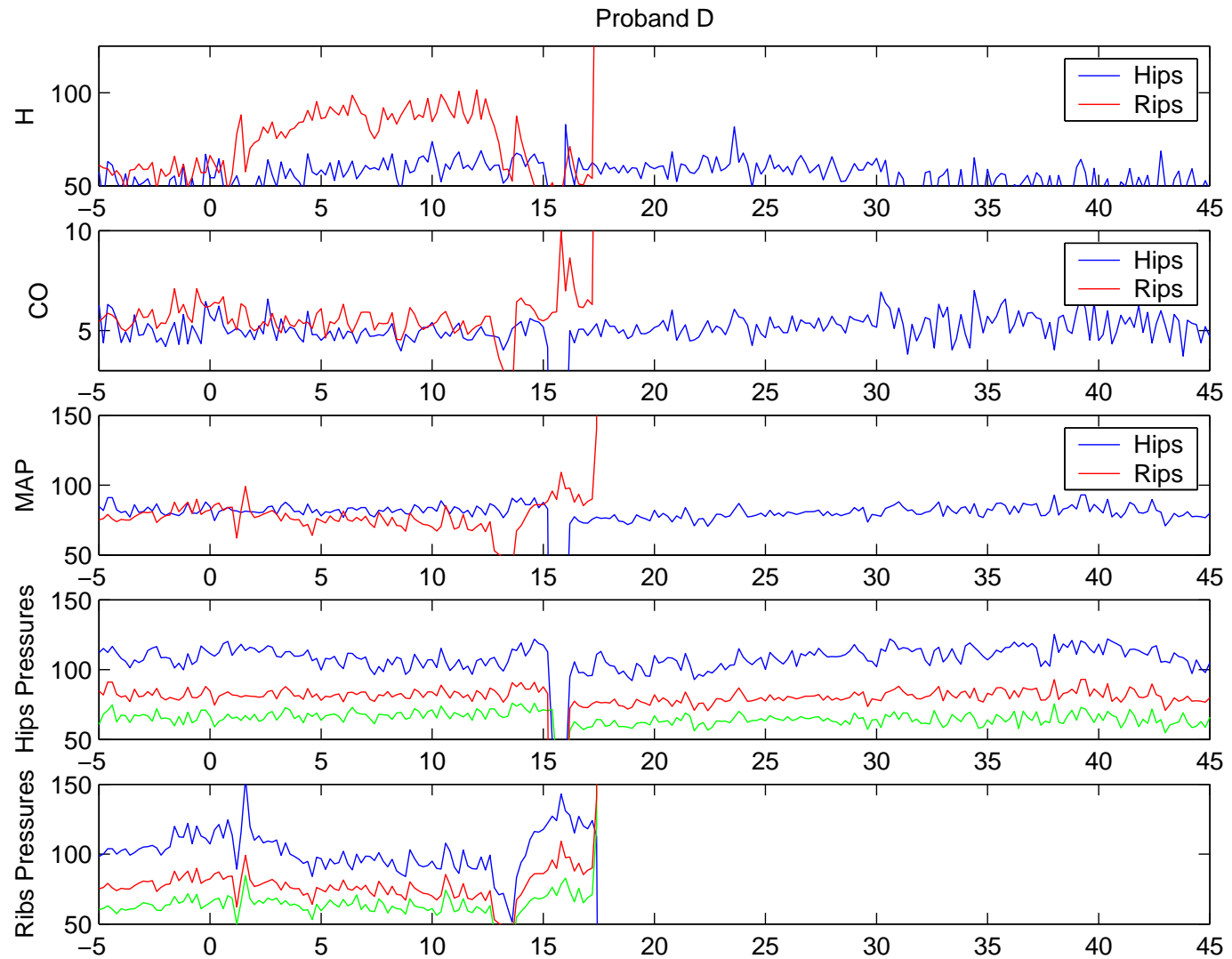


LBNP

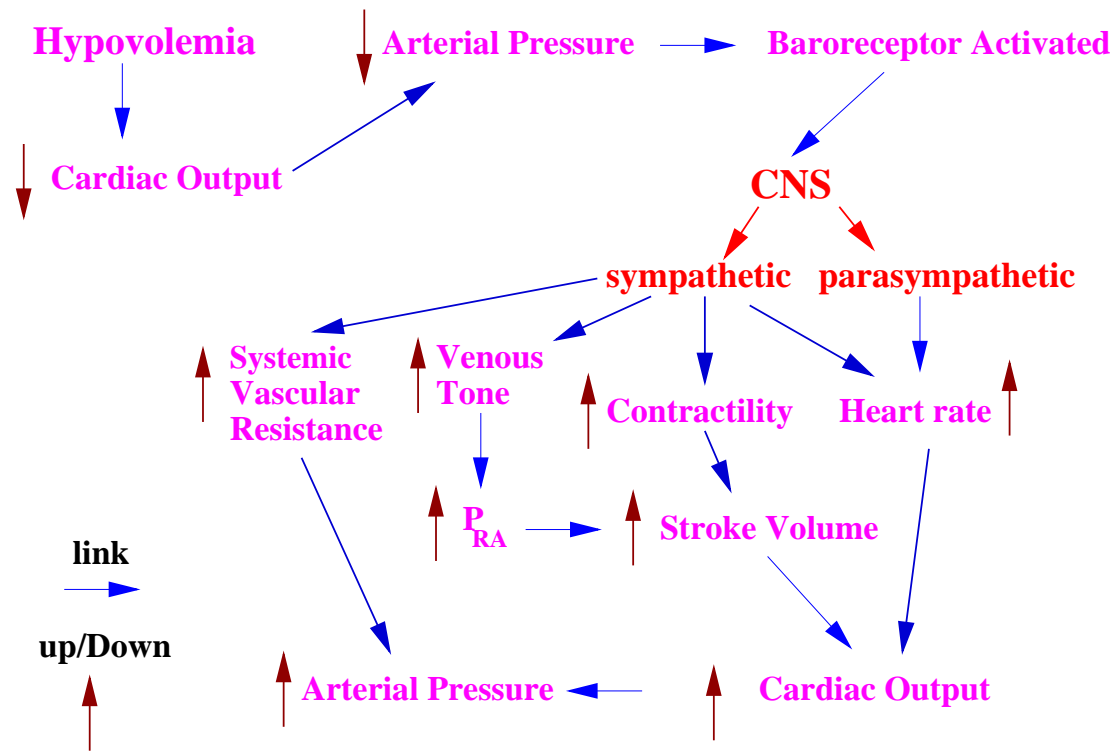


HUT

LBNP at hips and ribs - Data Example



Baroreflex Compensatory mechanisms



- Baroreflex firing falls due to reduced arterial pressure leading to increased vasoconstriction, increased H , and contractility which raises cardiac output and arterial pressure. Venoconstriction in splanchnic and skin tissue shifts blood to critical areas.

Control mechanisms II

The description of the control mechanism could take the form (e.g, Heldt et al. (2002), Ursino (2000), Cavalcanti (2006)):

$$\dot{\Delta}V_u = 5 \arctan\left(\frac{P_{vc} - P_{vc}(0)}{5}\right)$$

$$\dot{\Delta}R_s = -18 \arctan\left(\frac{P_{as} - P_{as}(0)}{18}\right)$$

$$\dot{H} = -18 \arctan\left(\frac{P_{as} - P_{as}(0)}{18}\right),$$

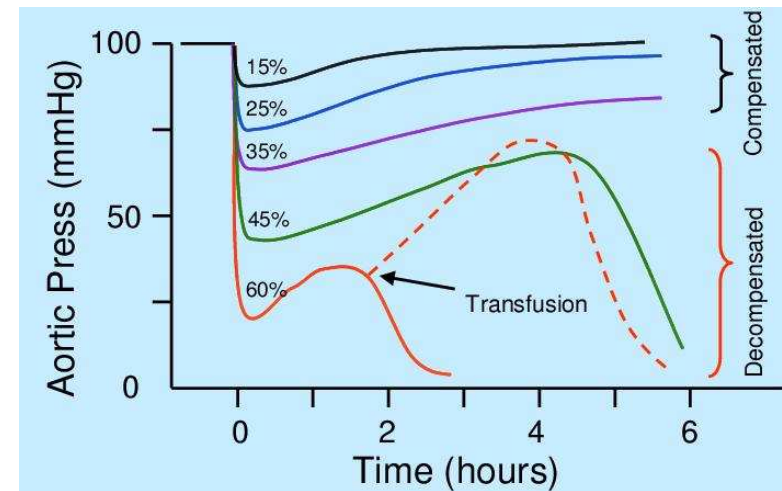
- Change in V_u is assumed to occur in the renal and splanchnic regions.
- Currently, contractility changes dependent on changes in H .
- There is a constraint on maximal resistance in a compartment.
- A model for fluid exchange between the vasculature and the interstitial fluid compartment should also be included.

Hemorrhage

- What are the short term responses?
- What is the origin of recovery?
- Why can a transfusion be insufficient at severe hemorrhage?

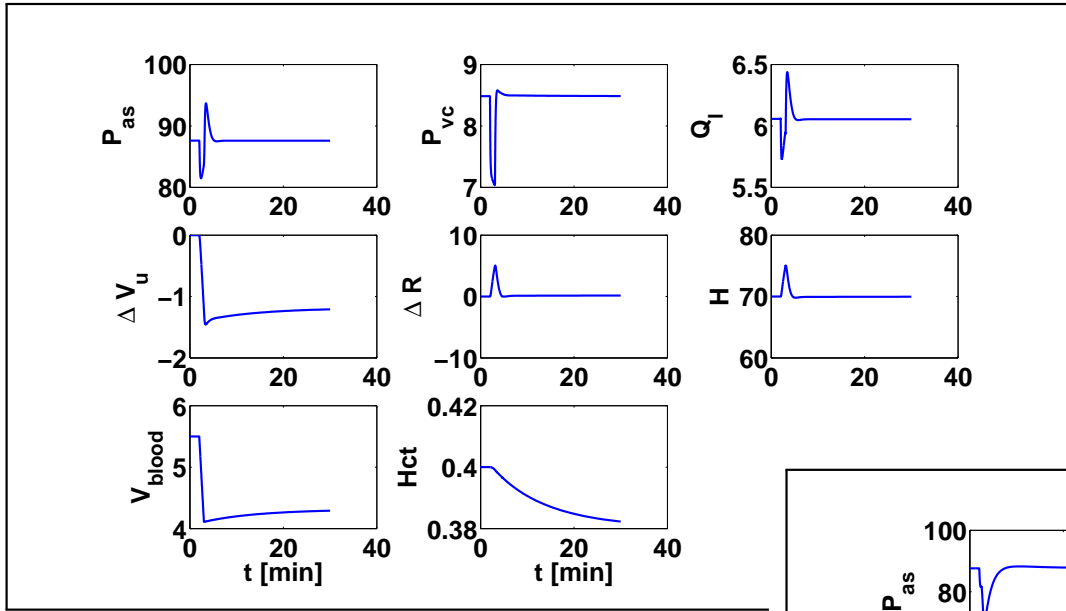
Different types of transfusions:

- Saline solution
- Plasma expander
- Whole blood

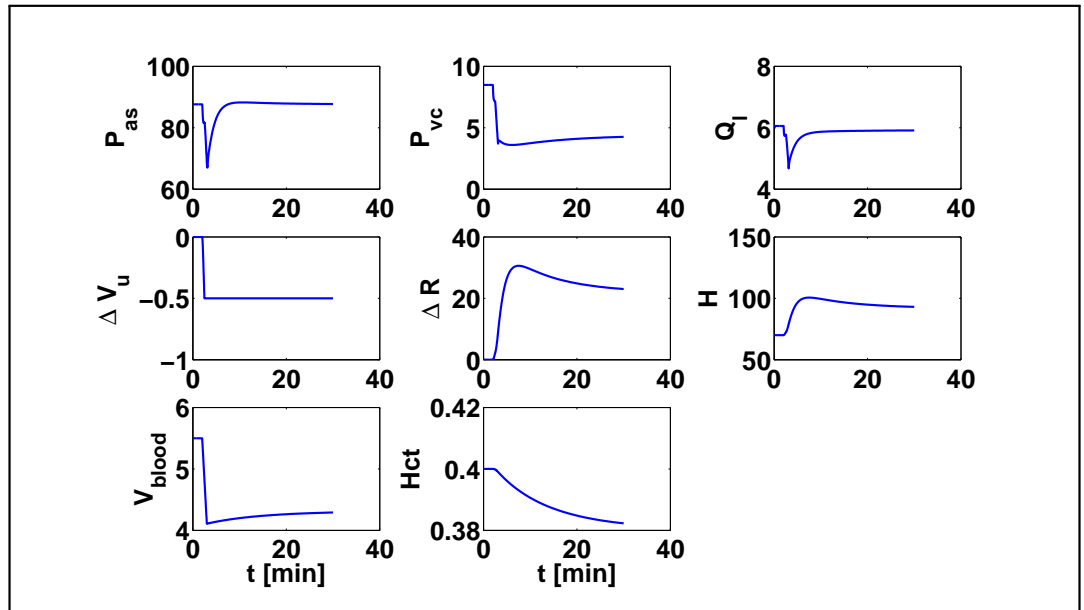


Blood pressure response to blood volume reduction (adapted from Guyton and Klaubundes).

Hemorrhage - Explicit Controls

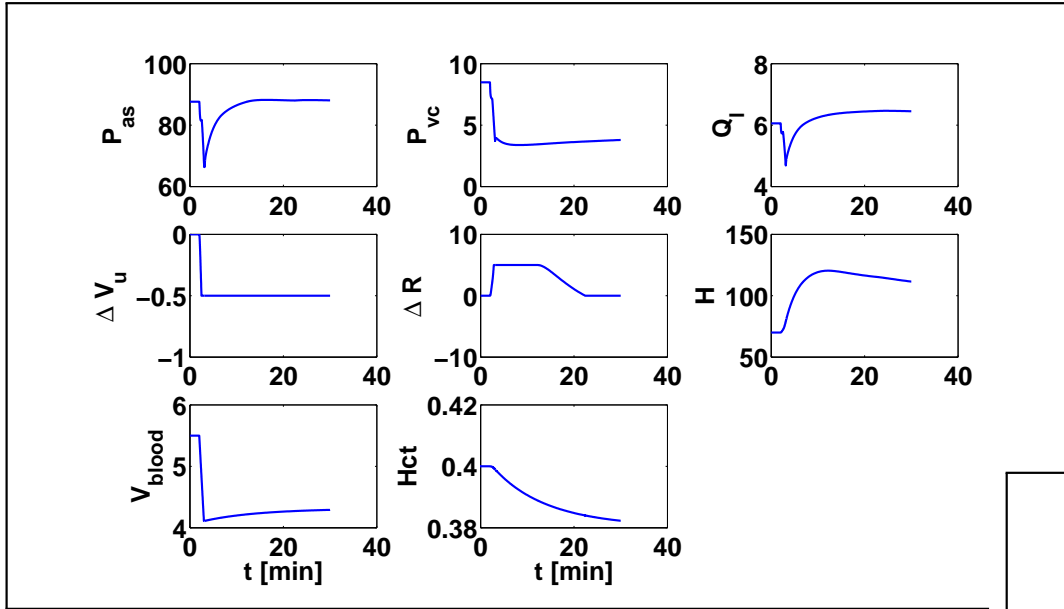


No limits

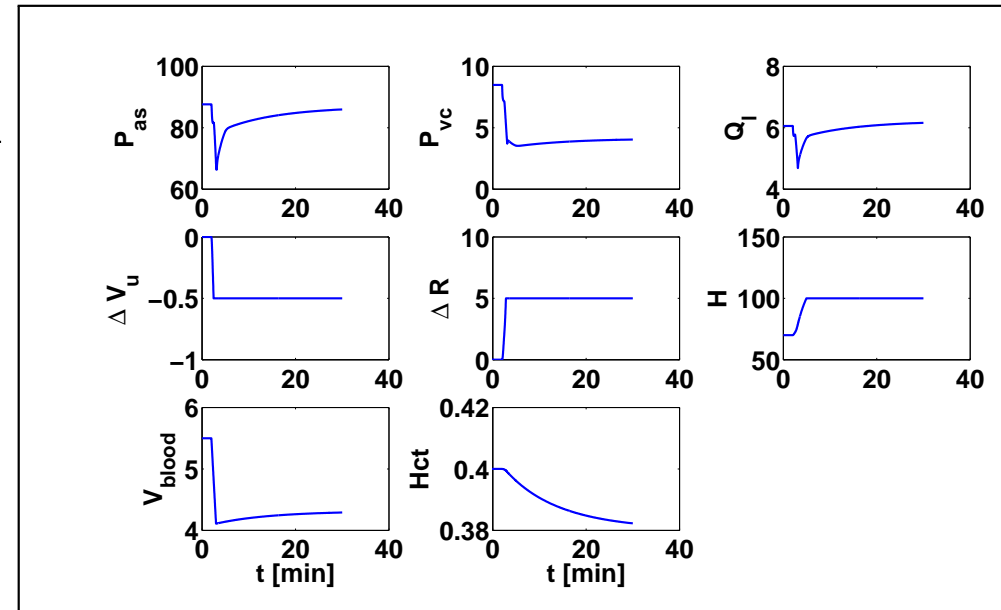


V_u limited

Hemorrhage - Explicit Controls



V_u and R_s limited



V_u and R_s and H limited

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Model adaptation to the clinical situation

- The key issue for adaptation of models to the clinical situation is the limitation on data due to:
 - Issues of time;
 - The restriction to noninvasive or minimally invasive collection of data;
 - Cost or risk considerations;
 - Inability to measure some parameters either because of technology or because they may be parameters of lumped systems.

Data sources

- Data for model development is available from:
 - Sequestration and replacement of blood volume during dialysis; This may impact primarily CVP;
 - Patients with clinical conditions that break some control loops such as orthostatic intolerance, POTS, autonomic inhibition due to diabetes and other conditions, and autonomic failure;
 - Data from HUT and low and high level LBNP;
 - Measurements of MSNA.
- Data for specific patient application is usually:
 - Collected from the Finapres or the Task Force Monitor;
 - Restricted to simple tests such as HUT etc.

Experimental design and data acquisition

Techniques which may aid in parameter estimation for individual patients include:

- Classical sensitivity analysis;
- *Generalized sensitivity functions* (GSF), which describe the sensitivity of parameter estimates with respect to measurements: GSF can provide insight into correlation between parameters and information on the which time frames of data are most useful for estimation of a parameter. This can aid in experimental design;
- Ordering of eigenvalues of the sensitivity matrix;
- New methods for estimation;
- A main goal is to understand the interaction of the various control mechanisms in the individual patient: how heart rate, compliance, unstressed volume and resistance controls interact under stress such as hemorrhage and the interaction of the cardiopulmonary and arterial baroreflexes in these controls.