Modeling Microgravity Induced Fluid Redistribution Autoregulatory and Hydrostatic Enhancements

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Numerical Approach to VIIP Physiology

A suite of integrated numerical models simulate physiology over a range of length scales

For studying VIIP, we use:

(1) Whole-body lumped parameter (LP) model:

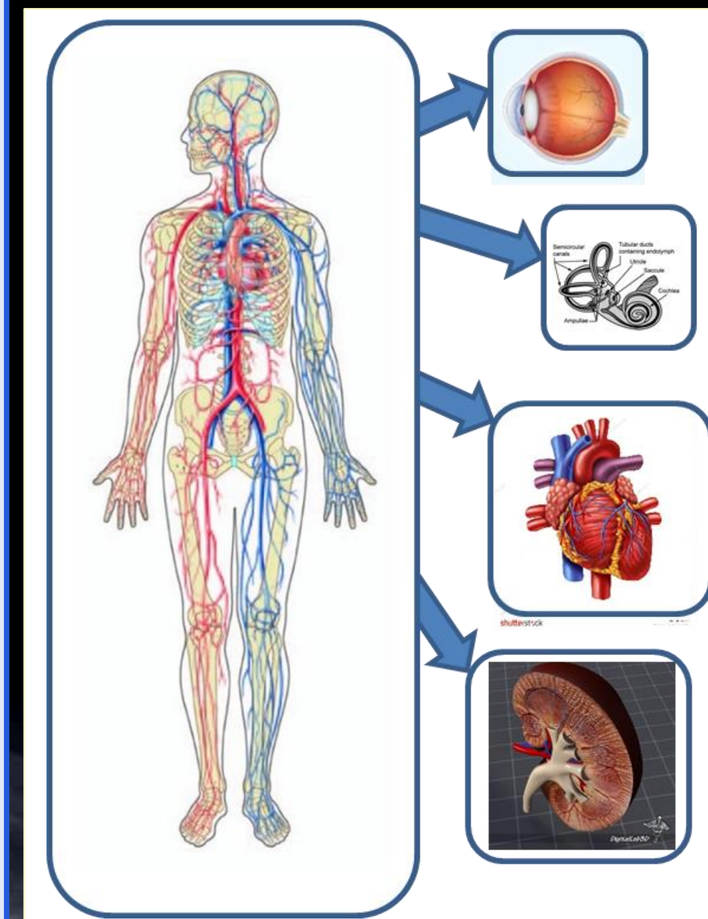
- Calculates fluid distribution and Intracranial Pressure (ICP) in response to altered gravity (g)

(2) LP eye model**:**

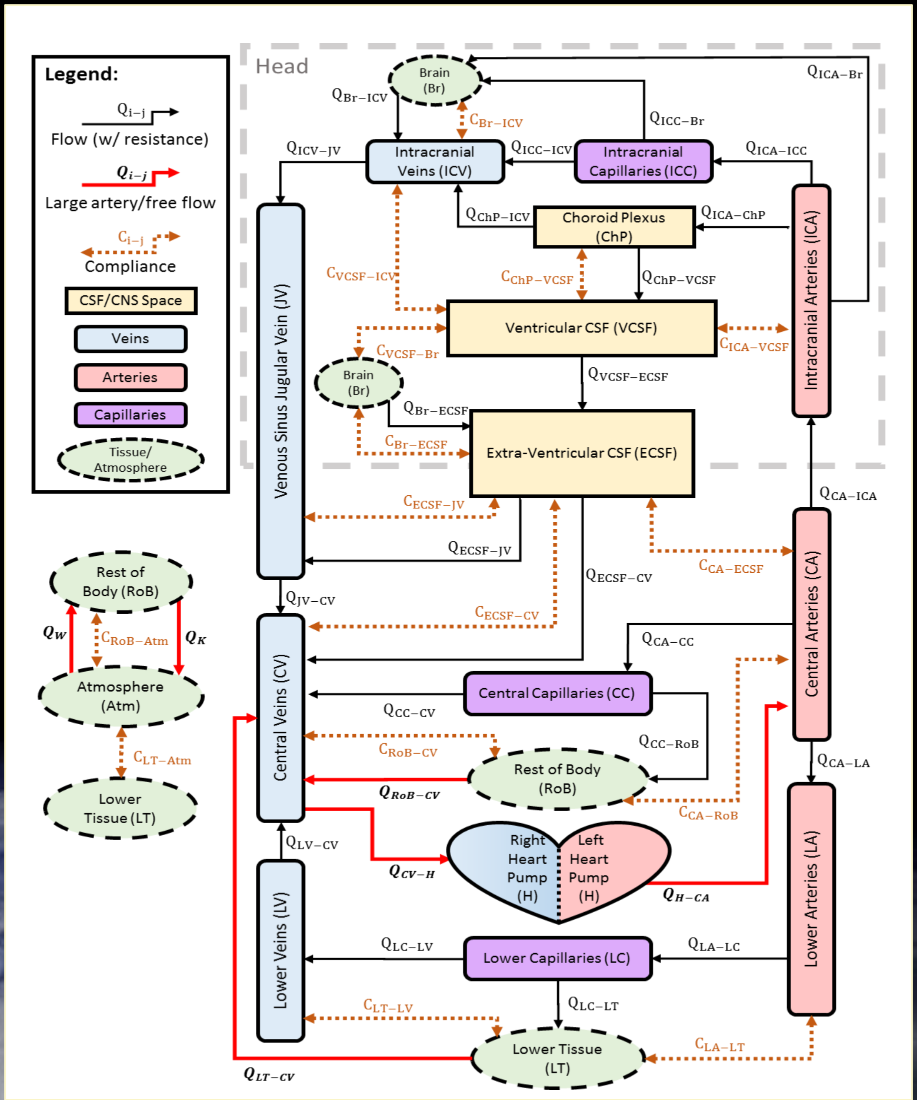
- Calculates Intraocular Pressure (IOP) and blood volume (V_b) in altered g

(3) Finite element (FE) model of the optic nerve head (ONH) and retrobulbar subarachnoid space (rSAS):

- Calculates biomechanical tissue strains



Lumped Cardiovascular System Model: Modified Lakin et al: 16-compartment model



- Lumped Spatial (0-D) unsteady model
  - 16 Compartments
    - 11 blood, 3 CSF, 1 brain, 2 interstitial lymphatic

$$[c] * \left[\frac{dp}{dt}\right] + [z] * [P] = [Q]$$

- Compartments represented at 3 heights
  - cranial, upper, lower

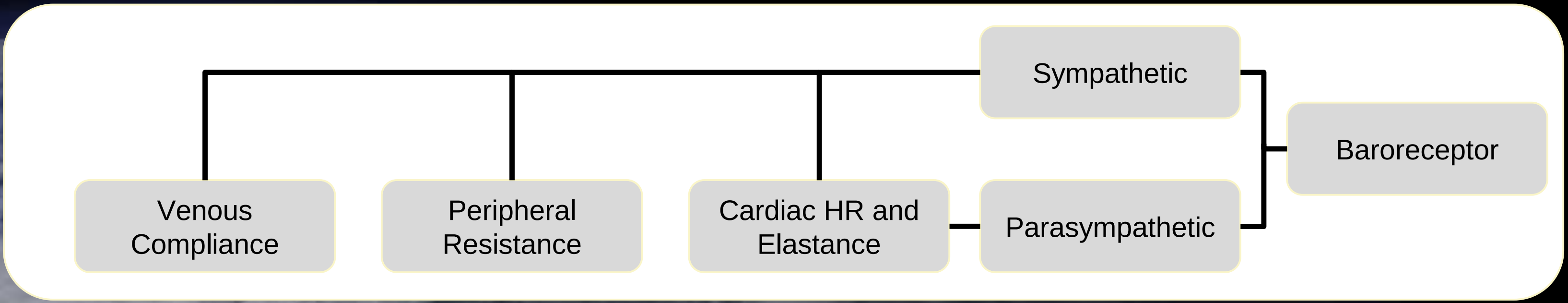
Regulatory Mechanisms

- Original Lakin Implementation
  - Lymphatic Autoregulation
  - Intracranial Autoregulation
  - *Sympathetic Nervous System (SNS)*
    - *Large vessel response*
    - *Arteriole response*
  - *Cardiac Output*
    - *Linear Function of aortic pressure changes*

- Testing illustrated several limitations
  - SNS functions
    - Unable to produce adequate responses
  - Cardiac output function
    - Could become unbounded

SNS Control - Modeling Baroreflex

- Blanco et al. Int. J. Numer. Meth. Biomed. Engng. 2012; 28:412–433
  - Ottesen and Larsen, SIAM 2004
  - Ursino, IEEE Trans Biomed V46, No 4, 1999
- Regulation occurs on
  - Heart Rate
  - Arteriole and Capillary resistances
  - Venous compliances
  - E – heart muscle elastance
- Assumptions
  - All baroreceptors locations behave the same
  - Afferent nerve fibers activation proportional to cyclic average BP
  - Activation based on previous cardiac cycle



Blanco et al Formulation

- Efferent response governed by 1st order ODE

$$\frac{dx_i}{dt} = \frac{1}{\tau_i}\left(-x_i + \sigma_i^b\right)$$

i - Index range for set

$\mathcal{E} = \{H, R_A, R_C, C_V\}$

τ_i - Characteristic Time Constant

H - Heart Rate

R_A, R_C - Flow Resistance

C_V - Venous Compliance

- Linear combination of sympathetic and parasympathetic activities

$$\sigma_i^b = \alpha_i n_s - \beta_i n_p + \gamma_i$$

α_i, β_i - Weights for sympathetic and parasympathetic activities of each actuator

γ_i - Basel activation level of each actuator

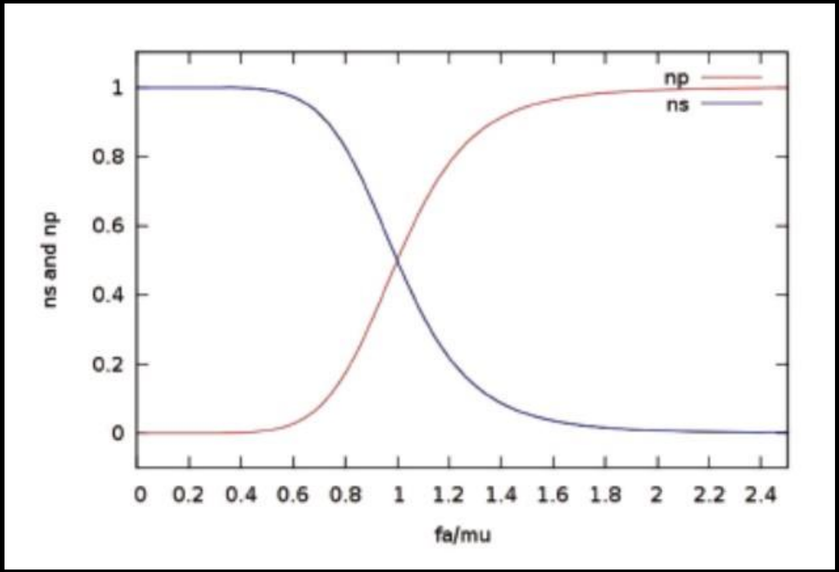
There is a closed form solution to the ODE assuming parameters are constant over the integration interval (one heart beat T = 1/HR)

$$x_{i,T} = \sigma_i^b + \left(x_{i,o} - \sigma_i^b\right)e^{\frac{-T}{\tau_i}}$$

Formulation cont

$$n_p = \frac{1}{1+\left(\frac{f_a}{\mu}\right)^{-\nu}}$$

$$n_s = \frac{1}{1+\left(\frac{f_a}{\mu}\right)^{\nu}}$$



$$f_a = \frac{\zeta}{T}\int_{-T}^{0} P_I dt = \frac{\zeta}{T} trapz(t, P_I) = \zeta * P_{I,avg}$$

μ **Baseline activation pressure mmHg**

ν **Slope Parameter**

Cardiac Output: Cavalcanti and Marco, 1999

- Hybrid model
  - Combination of correlated data and heart compartment model
- Heart: Continuous pump
  - Cardiac output a function of atrial pressure (P_{RA}) and heart rate (HR)

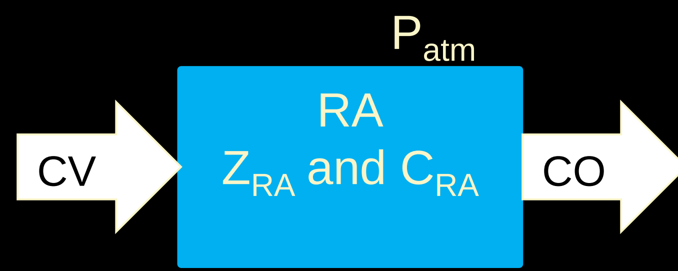
$$CO = CO_{sat}\left(1 - e^{\left(-\frac{P_{RA}-P_{RAZ}}{P_{RAN}}\right)}\right)$$

$$CO_{sat} = CO_M\left(1 + \Delta_{CO}\tanh\left(K_{co}\left(HR - \overline{HR}\right)\right)\right)$$

Parameter	Unit	Value	Description
P_{RAZ}	mmHg	-0.5	Intercept of cardiac pressure curve
P_{RAN}	mmHg	3	Slope of cardiac pressure curve
CO_M	ml/s	240	Reference Cardiac Output
$\overline{HR}$	bpm	72	Reference Heart Rate
Δ_{CO}	--	0.7	Amplitude of sigmoid function
K_{CO}	s	0.5	Slope of sigmoid function

Cardiac Output Implementation

- CVS model formulation does not include atrial filling pressure
  - Requires we add an RA compartment
- Treated independently, can be implemented per closed form solution

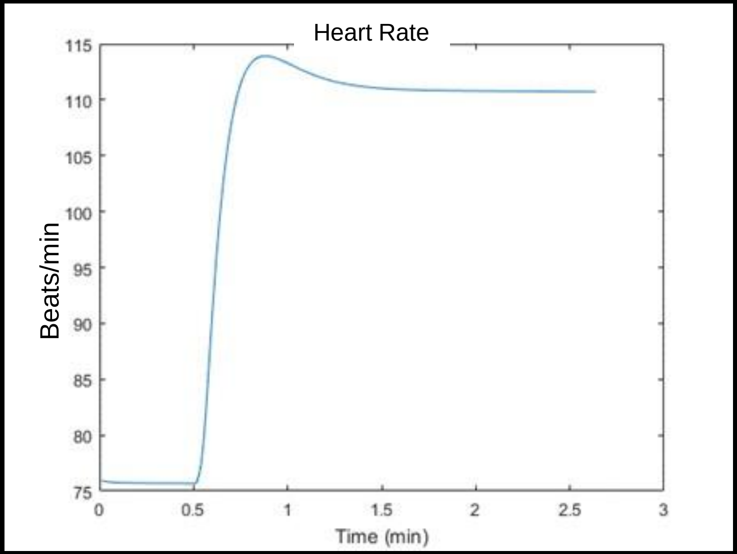


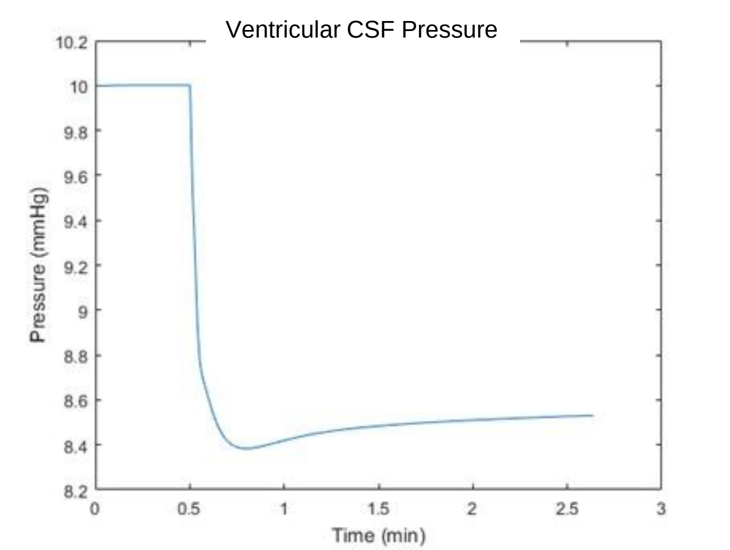
$$\frac{dV_{RA}}{dt} = Z_{RA}(P_V - P_{RA}) - CO$$

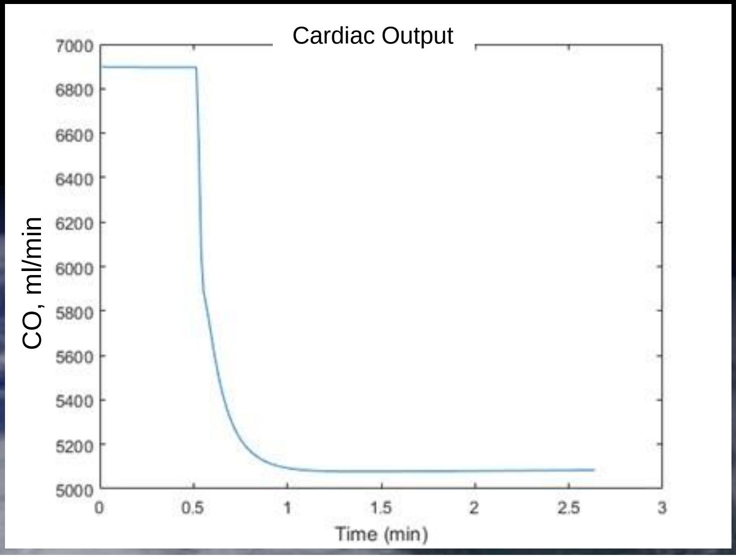
Assuming constant P_V and CO from the beginning of the T = 1/HR interval, denoted by 0; and assuming a characteristic time $\tau = C_{RA}/Z_{RA}$

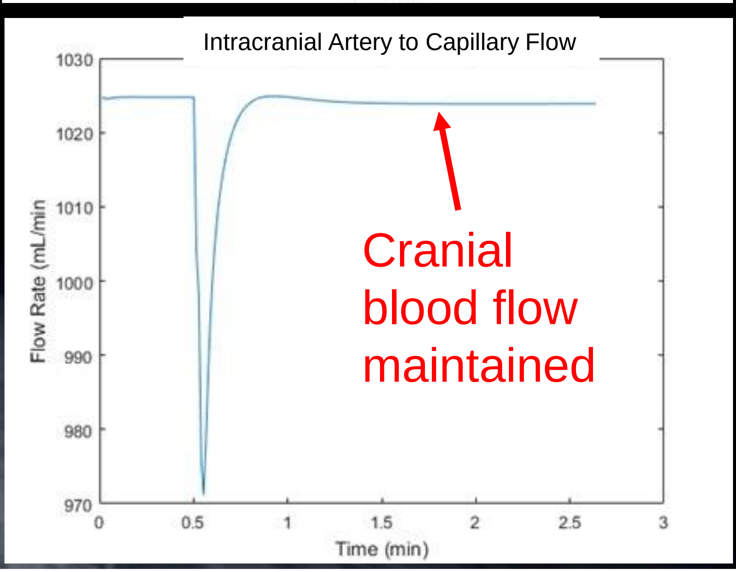
$$P_{RA} = P_{V,0} - \frac{CO_o}{Z_{RA}} + \left(P_{RA,0} - P_{V,0} + \frac{CO_0}{Z_{RA}}\right)e^{-\frac{T}{\tau}}$$

Testing : Supine to Standing

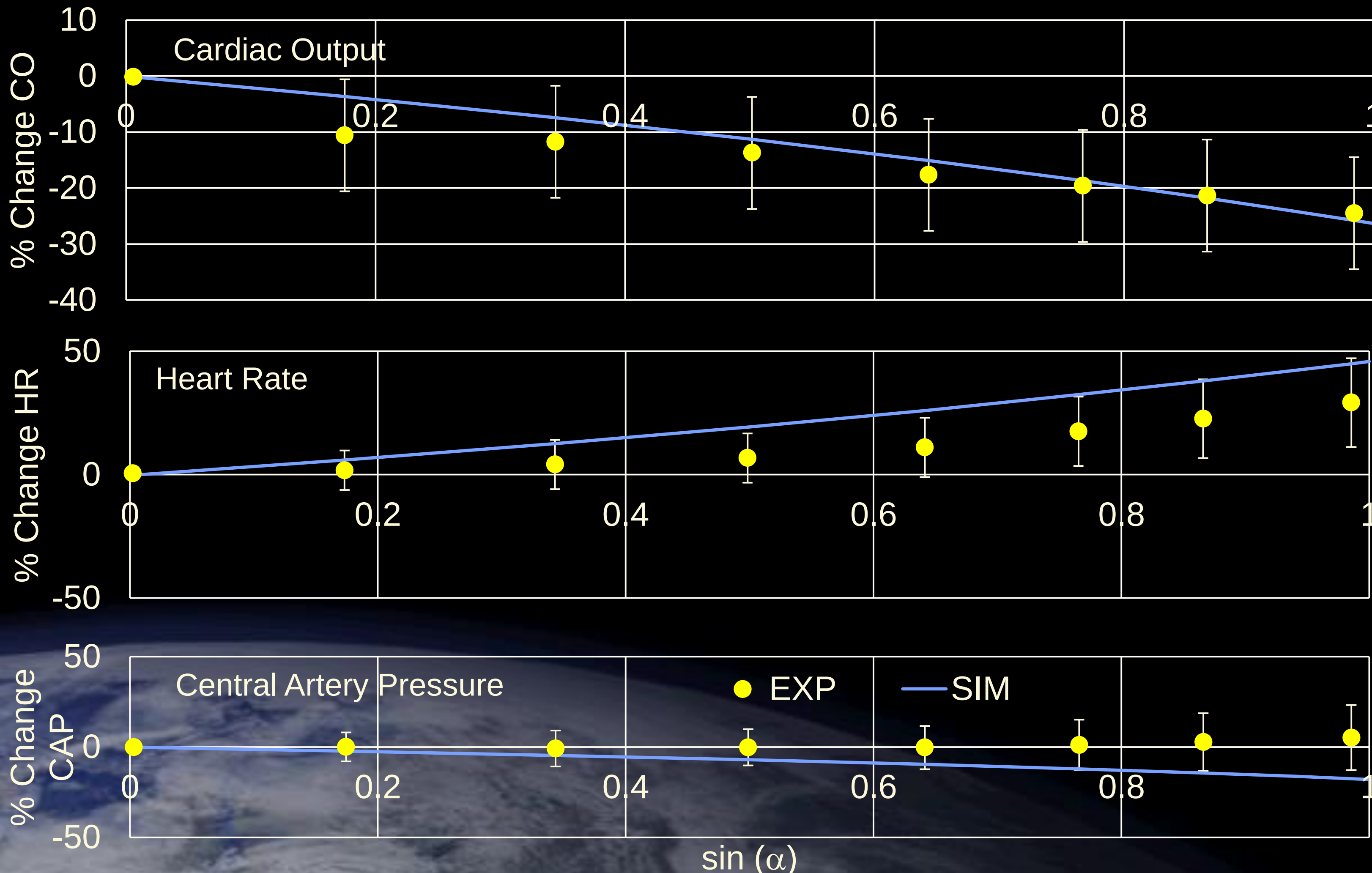






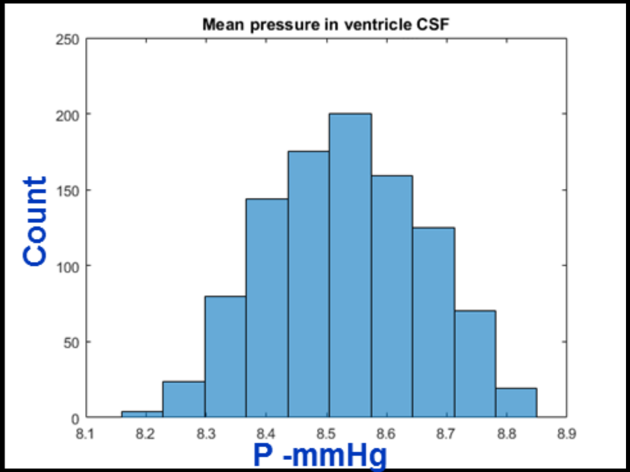


Validation: Head Up Tilt Simulations: Lim et al. 2013

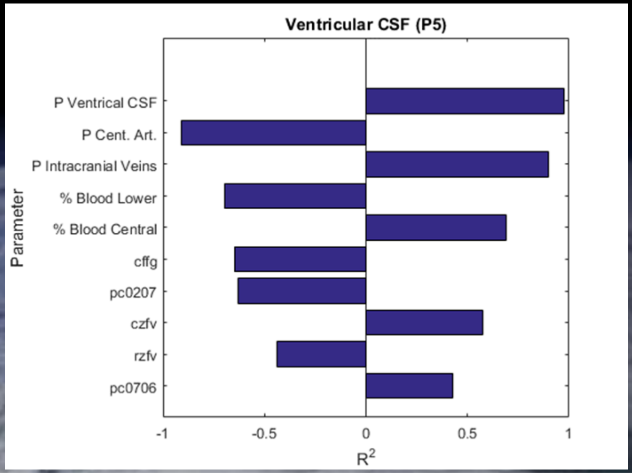


Sensitivity of Whole-Body Model: Histograms of Select Pressures

Ventricular CSF Pressure



Sensitivity



- Tested sensitivity of output (compartment pressures) to input (42 physiological parameters) – P, V, C, Z, etc.
- Standing posture, supine 30 sec, standing 3 minutes
- Varied each parameter by ±10%
- Histograms represent 1000+ trials, with 100 discretizations of each Latin hypercube distribution
- Convergence is estimated as < 0.002 change in output standard distribution per 100 trials
- There are similar histograms for each of the 16 compartments

Basel MAP (P Cent Art) and blood volume distributions are the models most sensitive parameters

Conclusions and Future Directions

- Successfully implemented regulation within the DAP-CVS model
  - Time averaged over cardiac cycle
  - Improved traceability and scalability of regulation parameters
    - Some calibration still necessary
- Future efforts to extend capabilities of each sub-model
  - Venous collapse functions using a new approach to Marchandise and Flaud (2010) Incorporate artificial gravity, LBNP and compression cuffs in WBM
  - Refine regulatory models for long-duration flight
- Complete integration of WBM, eye LPM and FEM
- Systematic verification and validation
  - Potentially follow the BioGears automated validation process

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Questions?

Parameter Definition

Table IV. Parameters for the efferent pathways normalized with respect to the corresponding baseline value.

Actuator ($i \in \mathcal{E}$)	α_i / i^b	β_i / i^b	γ_i / i^b
H	1.15	0.34	0.59
$E_{\mathrm{A,x}}, x \in \mathcal{C}$	0.40	0	0.80
$R_{\mathrm{a,y}}, R_{\mathrm{c,y}}, y \in \mathcal{W} \setminus \mathcal{W}_b$	0.80	0	0.60
$C_{\mathrm{v,z}}, z \in \mathcal{V}$	−0.20	0	1.10

Table III. Characteristic times τ_i, $i \in \mathcal{E}$, for the different actuators.

Actuator ($i \in \mathcal{E}$)	τ_i [s]
H	4.0
$E_{\mathrm{A,x}}, x \in \mathcal{C}$	10.0
$R_{\mathrm{a,y}}, R_{\mathrm{c,y}}, y \in \mathcal{W} \setminus \mathcal{W}_b$	15.0
$C_{\mathrm{v,z}}, z \in \mathcal{V}$	30.0

μ - Mean pressure at which the system remains at equilibrium

94.3 to 96 mm Hg

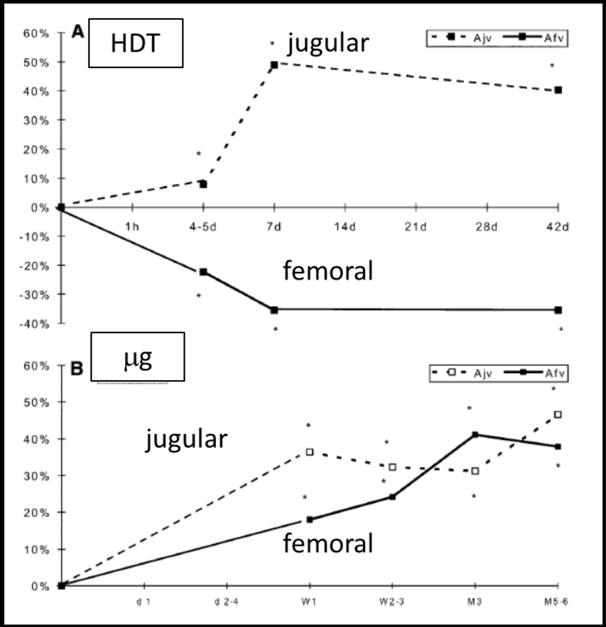
ν - Shape factor set at 7 based on Ottesen, 2004.

Formulation for Cardiac output

- Typically 3 options
  - Purely correlated function based on experimental responses
    - Lacks fidelity outside the experimental bases
  - Model the 4 chamber heart
    - Current state of the art
    - Excellent for in-beat calculations and assessment of heart / pulmonary interactions
    - Complex to implement and high numerical cost
  - Hybrid model
    - Uses a combination of correlated and heart component modeling

Initial Thoughts on Space Adaptation and Regulation

- Each regulated variable is premised on 6 parameters
  - μ, ν, τ, (i_b/i)_Threshold, (i_b/i)_Saturation, and i_b
- This set of parameters will “adapt” as homeostasis is reached during spaceflight
  - Hypothesis - The chronic response is represented as resting the acute response
  - Update μ, (i_b/i)_Threshold, and i_b as a first approach



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