Modeling Microgravity Induced Fluid Redistribution Autoregulatory and Hydrostatic Enhancements

J.G. Myers\textsuperscript{1}, C. Werner\textsuperscript{2}, E.S. Nelson\textsuperscript{1}, A. Feola\textsuperscript{3}, J. Raykin\textsuperscript{3}, B. Samuels\textsuperscript{4}, and C. R. Ethier\textsuperscript{3}

\textsuperscript{1}NASA Glenn Research Center, Cleveland, OH
\textsuperscript{2}Zin Technologies, Inc. Cleveland Ohio
\textsuperscript{3}Department of Biomedical Engineering, Georgia Institute of Technology/Emory University, Atlanta, GA;
\textsuperscript{4}Department of Ophthalmology, U. Alabama at Birmingham, Birmingham, AL.
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

\[
[c] \cdot \frac{dp}{dt} + [z] \cdot [P] = [Q]
\]

- 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

  - 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

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

- Linear combination of sympathetic and parasympathetic activities

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

\( \alpha_i, \beta_i \) - Weights for sympathetic and parasympathetic activities of each actuator

\( \gamma_i \) - Basel activation level of each actuator

\( i \) - Index range for set
\( \mathcal{E} = \{H, R_A, R_C, C_V\} \)

\( \tau_i \) - Characteristic Time Constant

\( H \) - Heart Rate

\( R_A, R_C \) - Flow Resistance

\( C_V \) - Venous Compliance

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

\[ n_p = \frac{1}{1 + \left( \frac{fa}{\mu} \right)^{-\nu}} \]

\[ n_s = \frac{1}{1 + \left( \frac{fa}{\mu} \right)^{\nu}} \]

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

\( \mu \) Baseline activation pressure mmHg

\( \nu \) 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 ($HR$)

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

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
<th>Value</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P_{RAZ}$</td>
<td>mmHg</td>
<td>-0.5</td>
<td>Intercept of cardiac pressure curve</td>
</tr>
<tr>
<td>$P_{RAN}$</td>
<td>mmHg</td>
<td>3</td>
<td>Slope of cardiac pressure curve</td>
</tr>
<tr>
<td>$CO_M$</td>
<td>ml/s</td>
<td>240</td>
<td>Reference Cardiac Output</td>
</tr>
<tr>
<td>$\overline{HR}$</td>
<td>bpm</td>
<td>72</td>
<td>Reference Heart Rate</td>
</tr>
<tr>
<td>$\Delta_{CO}$</td>
<td>--</td>
<td>0.7</td>
<td>Amplitude of sigmoid function</td>
</tr>
<tr>
<td>$K_{CO}$</td>
<td>s</td>
<td>0.5</td>
<td>Slope of sigmoid function</td>
</tr>
</tbody>
</table>
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 \( \tau = C_{RA}/Z_{RA} \)

\[
P_{RA} = P_{V,0} - \frac{CO_0}{Z_{RA}} + \left( P_{RA,0} - P_{V,0} + \frac{CO_0}{Z_{RA}} \right) e^{-\frac{t}{\tau}}
\]
Testing: Supine to Standing

- Heart Rate
- Ventricular CSF Pressure
- Cardiac Output
- Intracranial Artery to Capillary Flow

Cranial blood flow maintained
Validation: Head Up Tilt Simulations: Lim et al. 2013

Cardiac Output

Heart Rate

Central Artery Pressure

\[ \sin(\alpha) \]
Sensitivity of Whole-Body Model: Histograms of Select Pressures

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
Thanks to:
The NASA Human Research program for funding this work

Dr. Beth Lewandowski – Digital Astronaut Project Scientist

Dr. DeVon Griffin – Digital Astronaut Project Manager

Kelly Gilkey – Digital Astronaut Deputy Project Manager

Questions?
Parameter Definition

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

<table>
<thead>
<tr>
<th>Actuator ((i \in \mathcal{E}))</th>
<th>(\alpha_i / i^b)</th>
<th>(\beta_i / i^b)</th>
<th>(\gamma_i / i^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(H)</td>
<td>1.15</td>
<td>0.34</td>
<td>0.59</td>
</tr>
<tr>
<td>(E_{A,x}, x \in \mathcal{C})</td>
<td>0.40</td>
<td>0</td>
<td>0.80</td>
</tr>
<tr>
<td>(R_{a,y}, R_{c,y}, y \in \mathcal{W} \setminus \mathcal{W}_b)</td>
<td>0.80</td>
<td>0</td>
<td>0.60</td>
</tr>
<tr>
<td>(C_{v,z}, z \in \mathcal{V})</td>
<td>-0.20</td>
<td>0</td>
<td>1.10</td>
</tr>
</tbody>
</table>

Table III. Characteristic times \(\tau_i, i \in \mathcal{E}\), for the different actuators.

<table>
<thead>
<tr>
<th>Actuator ((i \in \mathcal{E}))</th>
<th>(\tau_i [s])</th>
</tr>
</thead>
<tbody>
<tr>
<td>(H)</td>
<td>4.0</td>
</tr>
<tr>
<td>(E_{A,x}, x \in \mathcal{C})</td>
<td>10.0</td>
</tr>
<tr>
<td>(R_{a,y}, R_{c,y}, y \in \mathcal{W} \setminus \mathcal{W}_b)</td>
<td>15.0</td>
</tr>
<tr>
<td>(C_{v,z}, z \in \mathcal{V})</td>
<td>30.0</td>
</tr>
</tbody>
</table>

\(\mu\) - Mean pressure at which the system remains at equilibrium
94.3 to 96 mm Hg

\(\nu\) - 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
  - $\mu$, $\nu$, $\tau$, $i_{b/i}$ 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 $\mu$, $i_{b/i}$ Threshold, and $i_b$ as a first approach