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

![Diagram of baroreflex model]

---

National Aeronautics and Space Administration
Glenn Research Center
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

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

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

- Characteristic Time Constant $\tau_i$

- Heart Rate $H$

- Flow Resistance $R_A, R_C$

- Venous Compliance $C_V$

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

- Basel activation level of each actuator $\gamma_i$

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

\[
x_{i,T} = \sigma_i^b + (x_{i,o} - \sigma_i^b) e^{-\frac{T}{\tau_i}}
\]
Formulation cont

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

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

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

- \( \mu \) 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 ($HR$)

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

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

<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>$HR$</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
  - % Change CO
  - % Change HR
  - Central Artery Pressure

Graphs showing the relationship between sin(α) and % change for Cardiac Output, Heart Rate, and Central Artery Pressure.
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
Questions?

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
Parameter Definition

\( \mu \) - 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.

<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>0.00</td>
<td>0.80</td>
</tr>
<tr>
<td>(R_{a,y}, R_{c,y}, y \in \mathcal{W}\setminus W_b)</td>
<td>0.80</td>
<td>0.00</td>
<td>0.60</td>
</tr>
<tr>
<td>(C_{v,z}, z \in \mathcal{V})</td>
<td>-0.20</td>
<td>0.00</td>
<td>1.10</td>
</tr>
</tbody>
</table>

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

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 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>
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
  - $\mu$, $\nu$, $\tau$, $(i_b/i)_\text{Threshold}$, $(i_b/i)_\text{Saturation}$, 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 $\mu$, $(i_b/i)_\text{Threshold}$, and $i_b$ as a first approach