VIIP: Central Nervous System (CNS) Modeling

Jerry Vera\textsuperscript{1}, Lealem Mulugeta\textsuperscript{3}, Emily Nelson\textsuperscript{1}, Julia Raykin\textsuperscript{2}, Andrew Feola\textsuperscript{2}, Rudy Gleason\textsuperscript{2}, Brian Samuels\textsuperscript{4}, C. Ross Ethier\textsuperscript{2} and Jerry Myers\textsuperscript{1}

NASA Human Research Program Investigators Workshop
Galveston, TX
January 15, 2015

\textsuperscript{1}NASA Glenn Research Center, Cleveland, OH
\textsuperscript{2}Department of Biomedical Engineering, Georgia Institute of Technology/Emory University, Atlanta, GA
\textsuperscript{3}Universities Space Research Association, Houston, TX
\textsuperscript{4}Department of Ophthalmology, U. Alabama at Birmingham, Birmingham, AL
Multiscale model for VIIP research

- CNS model includes intra/extracranial cerebrospinal fluid (CSF) and cranial blood compartments
- For details on other modules, see companion works for IWS2015 by Ethier et al., Feola et al., Nelson et al., and Price et al.
Several lumped CNS models exist. Our starting point was a model that had been applied to microgravity (μg) (Stevens et al., 2005; Lakin et al., 2007):

- Time-dependent model composed of 6 fluid compartments (nodes)
  - 3 vascular:
    - Intracranial Arteries (1)
    - Capillaries (2)
    - Venous Sinous (3)
  - 2 cerebrospinal fluid
    - Ventricular CSF (4)
    - Extraventricular CSF (6)
  - 1 Brain node (5)
  - Boundary conditions at cranium and whole-body interaction provided by extracranial nodes
    - Central Arteries [A]
    - Central Veins [V]
    - Thoracic Space [Y]

\[ Q = \text{Flowrates between compartments (ml/min)} \]
\[ C = \text{Compartment compliance} \]

- Stevens et al. (2005)
### Governing Equations

Defining the pressures in the 6 compartments as dependent variables, the system is modeled in matrix form as a system of ordinary differential equations:

\[
C \begin{bmatrix} \frac{dP}{dt} \end{bmatrix} + ZP = S
\]

Note that G is explicitly included in the forcing terms in S.

<table>
<thead>
<tr>
<th>C</th>
<th>G</th>
<th>K</th>
<th>P</th>
<th>Q</th>
<th>S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compliance</td>
<td>Gravity</td>
<td>Filtration coefficient</td>
<td>Pressure</td>
<td>Flow rate</td>
<td>Source/forcing terms</td>
</tr>
</tbody>
</table>

- \( C_{ij} \): Matrix coefficients
- \( Z \): Fluidity \( \sim 1/resistance \)
- \( \theta \): Tilt angle
- \( \pi \): Osmotic pressure
- \( \sigma \): Reflection coefficient

\( C_{ij} \) entries:
- \( C_{15} + C_{34} \)
- \( C_{33} + C_{36} \)
- \( C_{45} \)
- \( -C_{15} \)
- \( -C_{36} \)
- \( -C_{33} \)
- \( -C_{25} \)
- \( -C_{25} \)
- \( -C_{35} \)
- \( -C_{45} \)
- \( -C_{45} \)
- \( -C_{15} \)
- \( -C_{25} \)
- \( -C_{35} \)
- \( -C_{35} \)
- \( -C_{44} \)
- \( -C_{45} \)

\( Z_{ij} \) entries:
- \( Z_{11} = P_1 \)
- \( Z_{12} + K_{25} \)
- \( -Z_{22} \)
- \( -K_{25} \)
- \( Z_{33} + Z_{43} \)
- \( Z_{43} \)
- \( Z_{55} + Z_{56} \)
- \( Z_{56} \)
- \( Z_{66} \)

\( S_{ij} \) entries:
- \( Q_{12} - Q_{24} - K_{25}(\pi_2 - \pi_4) \)
- \( Z_{33}(P_v - G_{33}sin\theta) \)
- \( K_{25} \)
- \(-K_{25}(\pi_2 - \pi_4) \)
- \( -C_{44}(dp/dt) + C_{45}(dq/dt) + Z_{45}(P_v) \)

Note that G is explicitly included in the forcing terms in S.
MATLAB Implementation

The boundary pressure in the Central Arteries [A] node is prescribed using an oscillating pressure function $P_A(t)$ simulating the carotid pulsatile pressure wave.

At the current timestep, a unique solution for the timestep-forward pressure at every node is calculated using the Matrix inverse.

Pressures are integrated through time using an adaptive-timestep 4th and 5th order Runge-Kutta solver.

After solutions are found, pressure equations are used to calculate flow rates.

Data for pressures and flow rate at current time is stored.

Timestep is advanced.
Verification Tests

- 20 independent verification tests that included variation in hydrostatic pressure
- 3 independent users of the code

**TEST**

- Short-term head down tilt (HDT)
- Long-term HDT
- Microgravity
- Blood-brain barrier influence

Verification tests also had a validation component

- Used Lakin and Stevens equation structure and parameters, but
- Developed independent implementation, arterial pressure that drives unsteady response and solution methodology
Short-term head down tilt

- Tests called for monitoring of changes in pressure differences pre- to post-tilt:

<table>
<thead>
<tr>
<th>Tilt angle (°)</th>
<th>Δ(P_s - P_v) (mmHg)</th>
<th>Δ ICP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-6</td>
<td>3.1</td>
<td>3.66</td>
</tr>
<tr>
<td>-10</td>
<td>3.1</td>
<td>3.86</td>
</tr>
<tr>
<td>-15</td>
<td>6.1</td>
<td>6.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


**Conclusion:** The current model agrees with prior experimental and numerical work.
Conclusion: Using their parameters, our predicted ΔICP is consistent with the prior model in μg and long-duration HDT, but are their parameters correct?

[1] Stevens et al. (2005)
Blood-brain barrier influence

- Later work by the Stevens/Lakin team hypothesized that the blood/brain barrier might weaken in μg.
- In Lakin et al. (2007), they performed a sensitivity study for a hypothetical change in the reflection and filtration coefficients.
- This *changed their findings* on ICP in μg.

**Conclusion**: Our model agrees with literature results to within 2% or better.

Revising prior findings, authors concluded that ICP could increase in μg. But how do we assess the credibility of this claim?
Preparing for μg simulations

• Before weighing in on the potential change in ICP in μg, we need to:
  • Re-assess parameters used by Lakin/Stevens based on the most current VIIP research
  • Quantify uncertainty in model parameters
  • Define a physiological envelope for parameters that will be relevant for the astronaut corps on orbit
  • Perform sensitivity studies over a much larger parameter space
  • Examine model predictions against independent studies in HDT, μg, and postural change, particularly for chronic conditions. We need our model to do a good job in predicting:
    • Volumes of intra/extracranial CSF compartments
    • Volumes of intracranial blood compartments
  • Only after these steps are taken can we make intelligent predictions about μg response
Sensitivity analysis

• We are analyzing this system by testing model sensitivity
  • Parameters include: compliances, resistances and filtration coefficients
  • Each described by statistical parameters
    • Mean and range of variation (variance)
    • Distribution of variation (density function)

• Methodology
  • Partial Rank Correlation Coefficient (PRCC) Analysis
    • Provides the linear relationships between two variables
      • one input parameter and one output parameter
    • All linear effects of other variables are removed after rank transformation
    • Rank Transformation: transforms nonlinear monotonic relations to linear
  • Latin Hypercube sampling
    • Efficient method to randomly characterize the sets of combined parameters
    • Many independent runs with randomly chosen parameter sets provide statistics on the system response
Conclusions

- A CNS lumped parameter model has been produced based on the model developed by Lakin and Stevens
  - Our solution methodology and computational platform is unique
- Our model has been tested and verified
  - ICP predictions agree with Lakin/Stevens in 20 cases of acute and chronic μg and HDT
- CNS model infrastructure is complete, but additional work is needed
  - Re-assess parameters used by Lakin/Stevens
  - Define flight and flight analog derived parameter ranges
  - Perform parameter sensitivity studies
  - Validate against the latest VIIP research
- In the future this model will be
  - integrated with lumped CVS and eye models
  - Used to establish spaceflight responses with fidelity sufficient to supply boundary conditions for more complex VIIP eye simulations.