VIIP: Central Nervous System (CNS) Modeling

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

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\(^1\)NASA Glenn Research Center, Cleveland, OH
\(^2\)Department of Biomedical Engineering, Georgia Institute of Technology/Emory University, Atlanta, GA
\(^3\)Universities Space Research Association, Houston, TX
\(^4\)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.
CNS Blood flow and pressure model

- 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 = Flowrates between compartments (ml/min)
C = 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:

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

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

<table>
<thead>
<tr>
<th>( C_{15} )</th>
<th>(-C_{15} )</th>
<th>( dP_1/dt )</th>
<th>( Z_{A1} )</th>
<th>( P_1 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( C_{25} )</td>
<td>(-C_{25} )</td>
<td>(-Z_{23} + K_{25} )</td>
<td>(-Z_{23} )</td>
<td>(-Z_{25} )</td>
</tr>
<tr>
<td>( C_{35} + C_{36} )</td>
<td>(-C_{53} )</td>
<td>(-Z_{25} + Z_{45} )</td>
<td>(-Z_{45} )</td>
<td>(-Z_{45} )</td>
</tr>
<tr>
<td>( C_{45} )</td>
<td>(-C_{45} )</td>
<td>(-Z_{45} )</td>
<td>(-Z_{45} )</td>
<td>(-Z_{45} )</td>
</tr>
<tr>
<td>(-C_{15} )</td>
<td>(-C_{25} )</td>
<td>(-C_{35} )</td>
<td>(-C_{36} )</td>
<td>(-C_{36} )</td>
</tr>
<tr>
<td>(-C_{15} )</td>
<td>(-C_{25} )</td>
<td>(-C_{35} )</td>
<td>(-C_{36} )</td>
<td>(-C_{36} )</td>
</tr>
</tbody>
</table>

\( C \) — compliance
\( G \) — gravity
\( K \) — filtration coefficient
\( P \) — pressure
\( Q \) — flow rate
\( S \) — source/forcing terms

\( Z \) — fluidity ~ 1/resistance
\( \theta \) — tilt angle
\( \pi \) — osmotic pressure
\( \sigma \) — reflection coefficient
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 4\textsuperscript{th} and 5\textsuperscript{th} order Runga-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>$\Delta(P_s-P_v)$ (mmHg)</th>
<th>$\Delta$ ICP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-10</td>
<td>3.1</td>
<td>3.86</td>
</tr>
<tr>
<td>-15</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conclusion: The current model agrees with prior experimental and numerical work.

Long-term HDT and Microgravity

Conclusion: Using their parameters, our predicted $\Delta IC$P is consistent with the prior model in $\mu g$ and long-duration HDT, but are their parameters correct?

<table>
<thead>
<tr>
<th>Condition</th>
<th>$\Delta IC$P (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model [1]</td>
<td>Our Model</td>
</tr>
<tr>
<td>Long-term HDT</td>
<td>4.9</td>
</tr>
<tr>
<td>$\mu g$</td>
<td>&lt;0</td>
</tr>
</tbody>
</table>

[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

<table>
<thead>
<tr>
<th></th>
<th>sigma</th>
<th>K</th>
<th>Simulated ICP (mmHg)</th>
<th>Target ICP (mmHg)</th>
<th>Error (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test0</td>
<td>1.000</td>
<td>0.066</td>
<td>13.78</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test1</td>
<td>0.583</td>
<td>0.052</td>
<td>15.15</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>Test2</td>
<td>0.665</td>
<td>0.105</td>
<td>17.18</td>
<td>17</td>
<td>1.06</td>
</tr>
<tr>
<td>Test3</td>
<td>1.081</td>
<td>0.064</td>
<td>13.23</td>
<td>13</td>
<td>1.77</td>
</tr>
<tr>
<td>Test4</td>
<td>0.438</td>
<td>0.113</td>
<td>19.14</td>
<td>19</td>
<td>0.74</td>
</tr>
</tbody>
</table>

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.