# VIIP: Central Nervous System (CNS) Modeling

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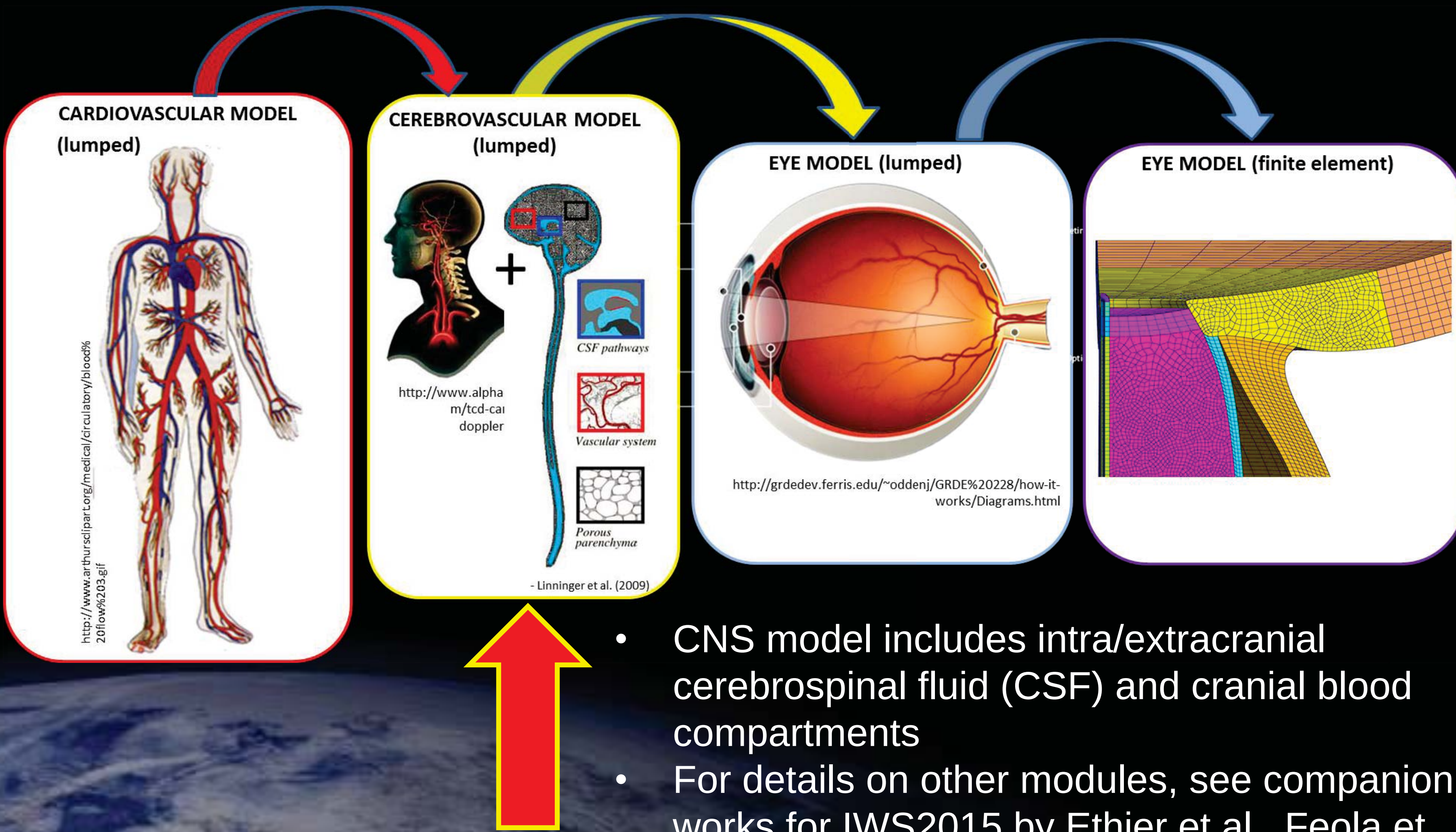
# Multiscale model for VIIP research

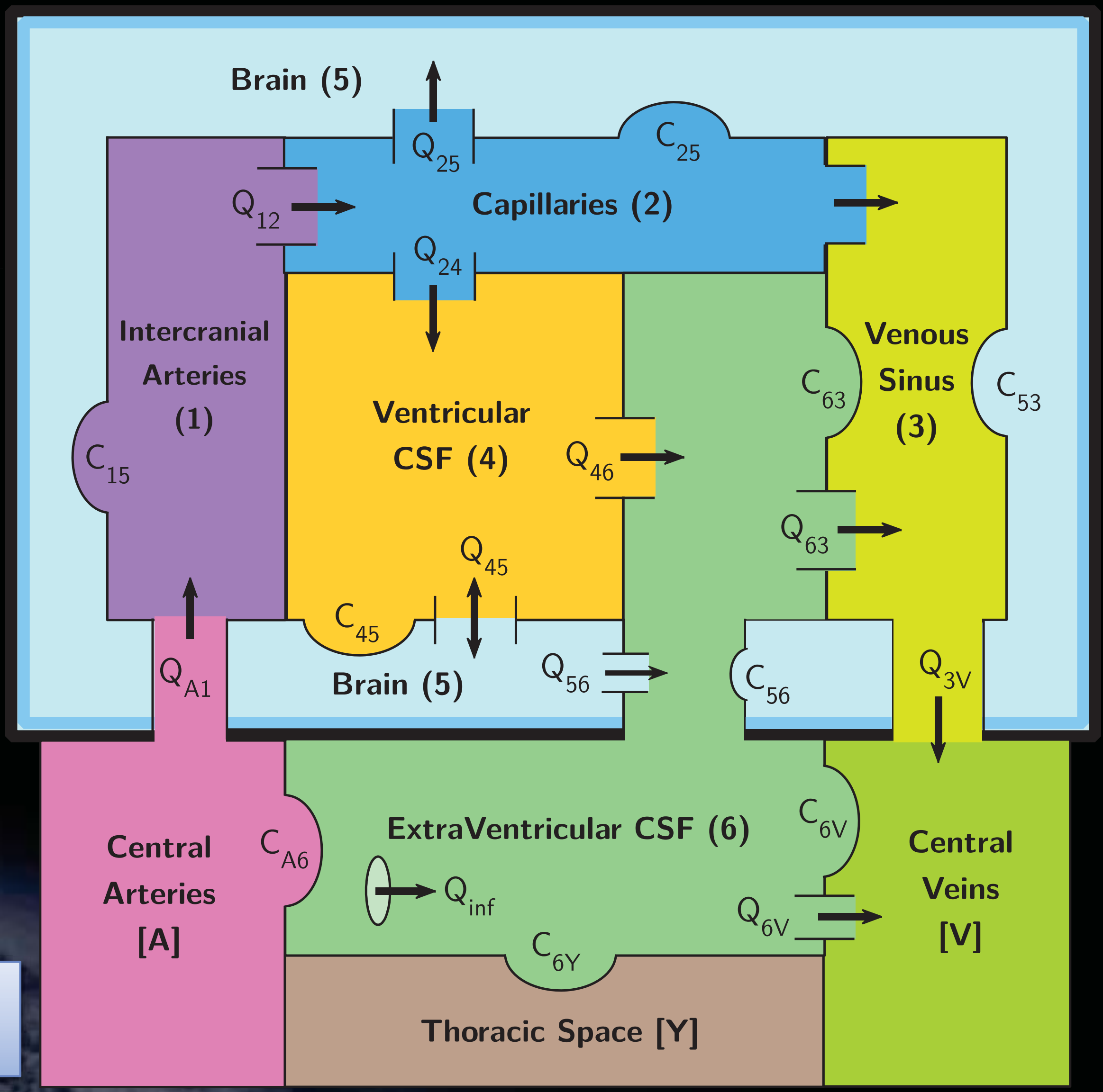



- CNS model includes intra/extracranial cerebrospinal fluid (CSF) and cranial blood compartments
- For details on other modules, see companion works for IWS2015 by Ethier et al., Feola et al., Nelson et al., and Price et al.

# 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:

$$\mathbf{C}\left[\frac{dP}{dt}\right] + \mathbf{ZP} = \mathbf{S}$$

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $C_{15}$ | | | | $-C_{15}$ | | $dP_1/dt$ | | $Z_{A1}$ | | | | | | $P_1$ | | $-Z_{A1}(P_A - G_{AI}\sin\theta) - Q_{12}$ |
| | $C_{25}$ | | | $-C_{25}$ | | $dP_2/dt$ | | | $Z_{23} + K_{25}$ | $-Z_{23}$ | | $-K_{25}$ | | $P_2$ | | $Q_{12} - Q_{24} - K_{25}\sigma_{25}(\pi_2 - \pi_5)$ |
| | | $C_{53} + C_{36}$ | | $-C_{53}$ | $-C_{36}$ | $dP_3/dt$ | + | | $-Z_{23}$ | $Z_{23} + Z_{63} + Z_{3V}$ | | | $-Z_{63}$ | $P_3$ | = | $Z_{3V}(P_V - G_{3V}\sin\theta)$ |
| | | | $C_{45}$ | $-C_{45}$ | | $dP_4/dt$ | | | | | $Z_{45} + Z_{46}$ | $-Z_{45}$ | $-Z_{46}$ | $P_4$ | | $Q_{24}$ |
| $-C_{15}$ | $-C_{25}$ | $-C_{53}$ | $-C_{45}$ | $C_{25} + C_{45} + C_{53} + C_{56} + C_{15}$ | $-C_{56}$ | $dP_5/dt$ | | | $-K_{25}$ | | $-Z_{45}$ | $K_{25} + Z_{45} + Z_{56}$ | $-Z_{56}$ | $P_5$ | | $-K_{25}\sigma_{25}(\pi_2 - \pi_5)$ |
| | | $-C_{36}$ | | $-C_{56}$ | $C_{56} + C_{36} + C_{6V} + C_{6Y} + C_{A6}$ | $dP_6/dt$ | | | | $-Z_{63}$ | $-Z_{46}$ | $-Z_{56}$ | $Z_{56} + Z_{63} + Z_{6V} + Z_{46}$ | $P_6$ | | $-C_{A6}(d_{PA}/dt) + C_{6Y}(d_{PY}/dt) + C_{6V}(d_{PV}/dt) + Z_{6V}(P_V)$ |

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

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

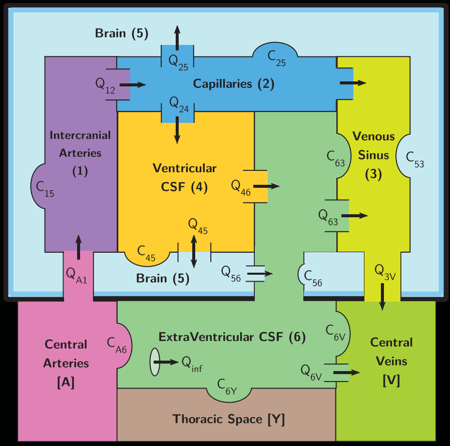
At the current timestep, a unique solution for the timestep-forward pressure at every node is calculated using the Matrix inverse

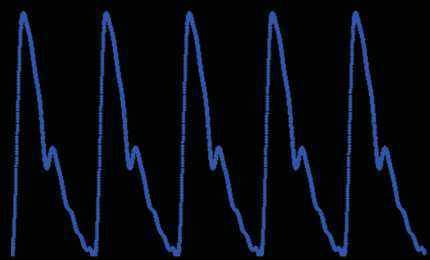
Pressures are integrated through time using an adaptive-timestep $4^{th}$ and $5^{th}$ order Runga-Kutta solver

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



$P_A(t)$

# 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 |

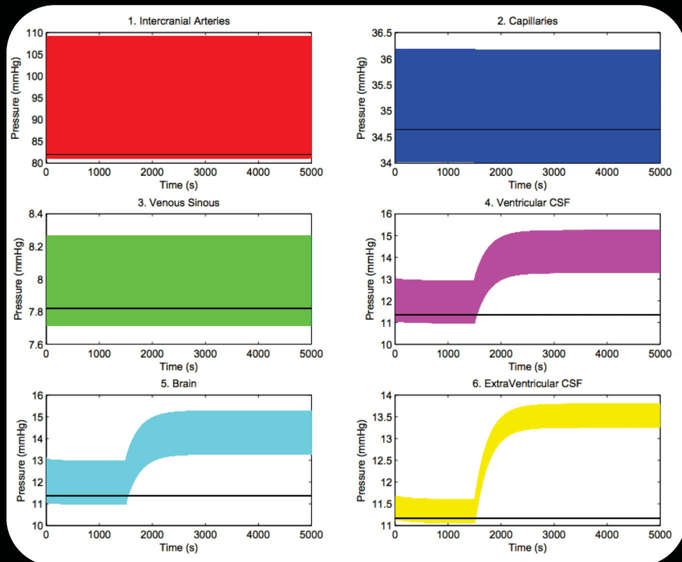
Verification tests also had a validation component

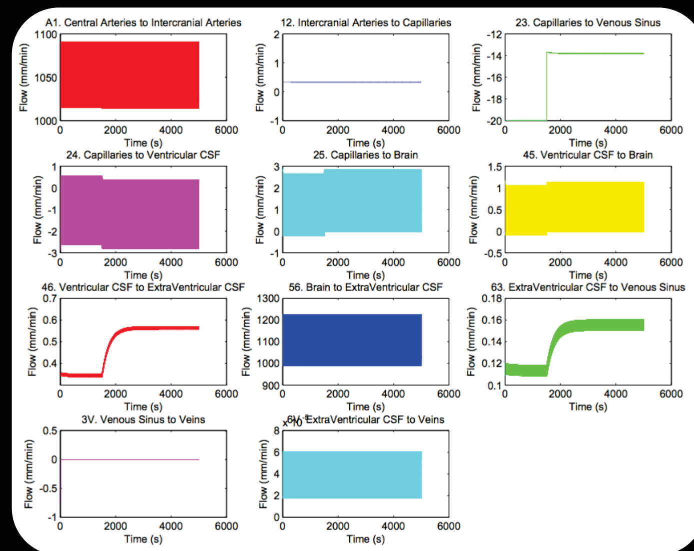
- Used Lakin and Stevens equation structure and parameters, but
- Developed independent implementation, arterial pressure that drives unsteady response and solution methodology

# Short-term head down tilt

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

PRESSURES




FLOWRATES

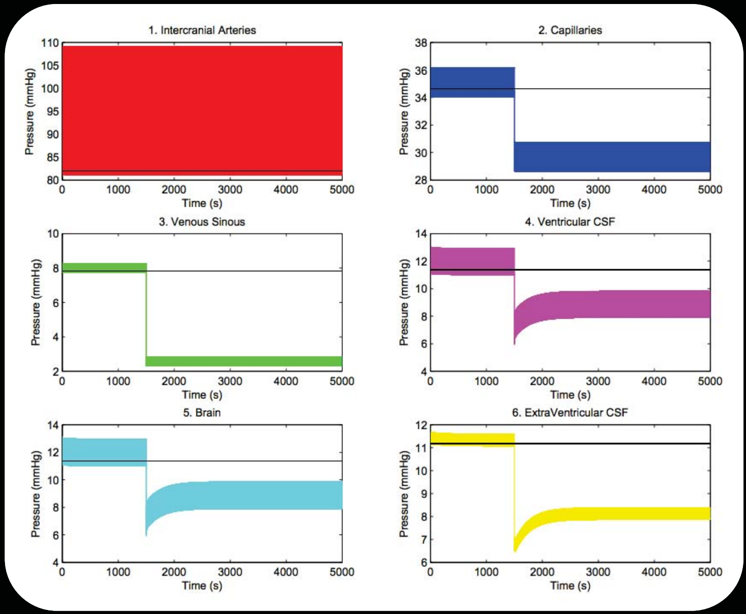
| Tilt angle (°) | Δ($P_s$-$P_v$) (mmHg) | | | Δ ICP (mmHg) | | |
|---|---|---|---|---|---|---|
| | Expt [1] | Model [2] | Our Model | Expt [3] | Model [2] | Our Model |
| -6 | | | | 3.3 | 2.10 to 3.70 | 2.20 |
| -10 | 3.1 | 3.86 | 3.66 | | | |
| -15 | | | | 6.1 | 5.18 to 7.78 | 5.46 |

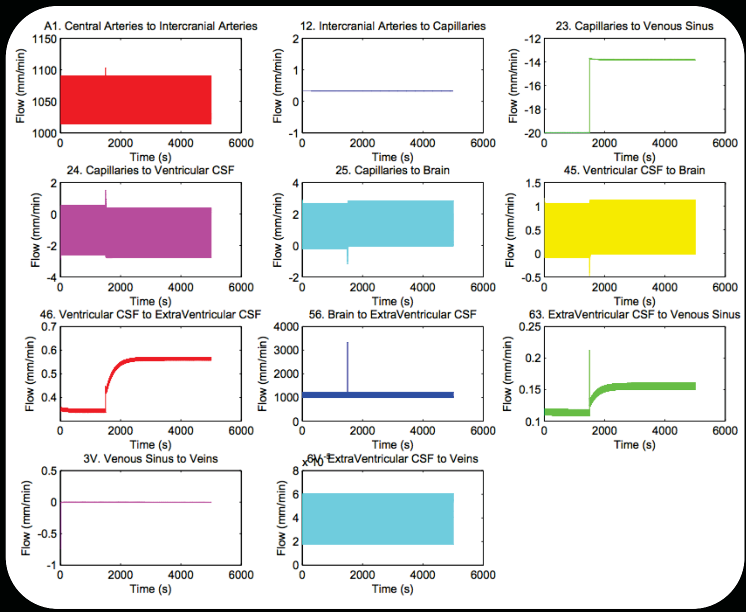
***Conclusion:*** *The current model agrees with prior experimental and numerical work.*


[1] Katkov and Chestukhin (1980)
[2] Stevens et al. (2005)
[3] Murthy et al. (1992)

# Long-term HDT and Microgravity

PRESSURES




FLOWRATES

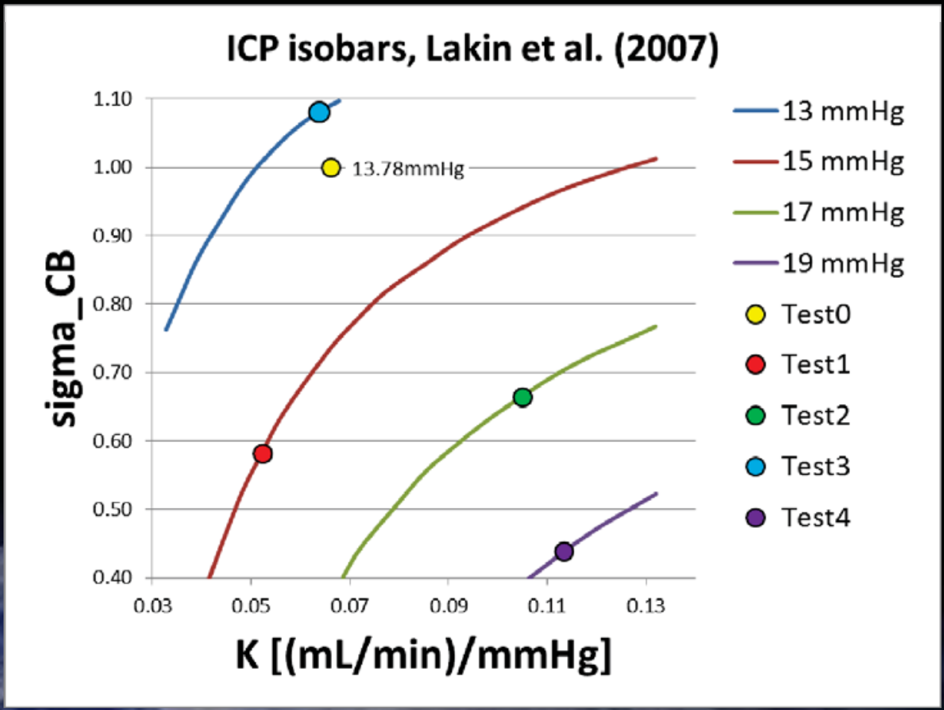
| Condition | Δ ICP (mmHg) | |
|---|---|---|
| | Model [1] | Our Model |
| Long-term HDT | 4.9 | 4.9 |
| μg | <0 | -3.1 |

***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




| | sigma | K | Simulated ICP (mmHg) | Target ICP (mmHg) | Error (%) |
|---|---|---|---|---|---|
| Test0 | 1.000 | 0.066 | 13.78 | | |
| Test1 | 0.583 | 0.052 | 15.15 | 15 | 1 |
| Test2 | 0.665 | 0.105 | 17.18 | 17 | 1.06 |
| Test3 | 1.081 | 0.064 | 13.23 | 13 | 1.77 |
| Test4 | 0.438 | 0.113 | 19.14 | 19 | 0.74 |

***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.