An Integrated Model of the Cardiovascular and Central Nervous Systems for Analysis of Microgravity Induced Fluid Redistribution

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A recognized side effect of prolonged microgravity (μg) exposure is visual impairment and intracranial pressure (VIIP) syndrome [1]. Though there is limited medical understanding of this phenomenon, it is hypothesized that cephalic shift of the cerebrospinal fluid (CSF) and blood in μg may be a contributor. Computational models can be used to provide insight into the origins of VIIP [1, 2]. In order to further investigate this phenomenon, NASA's Digital Astronaut Project (DAP), in collaboration with some of the world's leading experts in ocular biomechanics, is developing an integrated fluid physics-based computational model of the human body. The model is divided into the eye, the central nervous system (CNS), and the cardiovascular system (CVS). This poster summarizes our current progress on the development and testing of an integrated computational model of CVS and CNS based on the whole-body lumped-parameter (LP) model presented by Lakin *et al.* (2003) [3]. These models will provide unique capabilities to give insight in physiological changes that cannot be directly measured (e.g. changes in ICP), and to help answer questions related to the following research knowledge gaps:

VIIP1: We do not know the etiological mechanisms and contributing risk factors for ocular structural and functional changes seen in-flight and postflight.

CV7: How are fluids redistributed in flight?

VIIP13: We need to identify preventive and treatment countermeasures (CMs) to mitigate changes in ocular structure and function and intracranial pressure during spaceflight.

Methods

We reproduced the unsteady 16-compartment whole-body LP model presented by Lakin et al. [3] (Figure 1). The general structure of the model:

- Includes blood, cerebrospinal fluid (CSF), tissue, interstitial fluid, pulmonary circulation and organs
- Captures direct flow between compartments, as well as transfer of fluid between capillaries and tissue by filtration
- Includes compliant interactions between adjacent compartments
- Incorporates functions to allow the inclusion of the lymphatic system and the sympathetic nervous system (SNS) functions
- Includes a series of 13 differential equations to describe the pressure dynamics of the system in accordance with the laws of conservation:

$$\textit{flow in} - \textit{flow out} = \textit{rate of volume change} \qquad (1)$$

- Formulates the governing equations in a matrix form:

$$[\boldsymbol{C}] * \left[\frac{dp}{dt}\right] + [\boldsymbol{z}] * [\boldsymbol{P}] = [\boldsymbol{Q}] \qquad (2)$$

- Incorporates lymphatic, intracranial, and SNS through forcing and regulatory mechanisms

In addition, the following assumptions are applied:

- All fluids are assumed to be incompressible and isothermal
- Pressure-driven flows are laminar and governed by the hydrodynamic equation:

$$\boldsymbol{Q_{ij}} = \frac{\boldsymbol{P_i} - \boldsymbol{P_j}}{\boldsymbol{R_{ij}}} = \boldsymbol{Z_{ij}}\left(\boldsymbol{P_i} - \boldsymbol{P_j}\right) \qquad (3)$$

- Fluid filtration between the capillary and the interstitial spaces is governed by Starling-Landin equation

$$\boldsymbol{Filtration} = \boldsymbol{K_{ct}}\left((\boldsymbol{P_c} - \boldsymbol{P_t}) - \boldsymbol{\sigma_{ct}}(\boldsymbol{\pi_c} - \boldsymbol{\pi_t})\right) \qquad (4)$$

- Compliance between compartments depends on the change in pressure differences between compartments in the form of:

$$\frac{\boldsymbol{dV_{ij}}}{\boldsymbol{dt}} = \boldsymbol{C_{ij}}\frac{\boldsymbol{d(P_i - P_j)}}{\boldsymbol{dt}} \qquad (5)$$

- Revokes the Kellie-Monroe Doctrine in order to take into account the influence of extra-cranial physiology on ICP dynamics
- Hydrostatic pressure variation can be approximated through an *ad hoc* variation of resistances in the upper and lower portions of the body

Legend:

C_{ij} - compliance between the two compartments
K_{ct} - filtration coefficient
P_c - capillary pressure
P_i - spatially averaged pressure in compartment *i*
P_j - spatially averaged pressure in compartment *j*
P_t - interstitial fluid pressure
Q_{ij} - flow from compartment *i* to *j*
R_{ij} - lumped resistance
V_{ij} - deformation volume of the interface between adjacent compartments *i* and *j*
Z_{ij} - lumped fluidity ($1/R_{ij}$)
σ_{ct} - capillary membrane reflection coefficient,
π_c - blood plasma colloid osmotic pressure
π_t - interstitial fluid colloid osmotic pressure

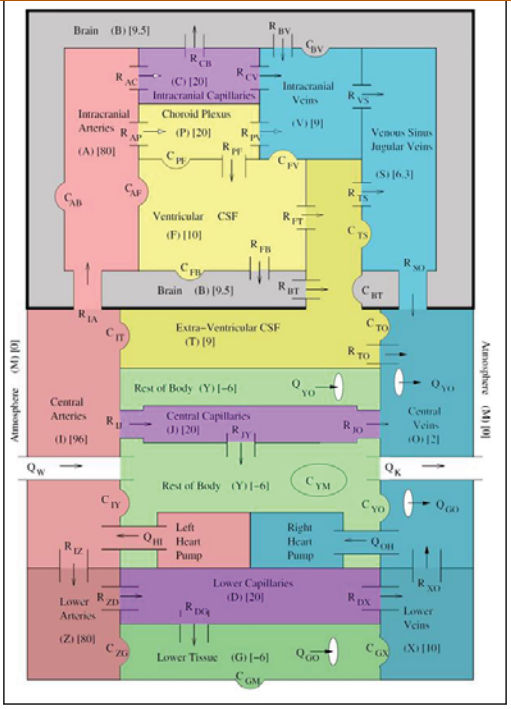

Figure 1: Diagram of the unsteady 16-compartment LP model presented by Lakin et al. (2003) [3] to simulate pressures, volumes, and flows within the CVS and CNS. C_{ij}, R_{ij}, and Q_{ij} represent compliance, resistance, and flow between compartments i and j, respectively. Numbers in brackets represent the spatially averaged mean pressure in mmHg for each compartment.

Verification and Validation

The initial verification test challenged the model in a time-dependent mode by specifying steady-state values that were offset by 10% from Lakin *et al.*'s [3] mean values to perturb the system. Since the system returned to the baseline mean values, our model successfully conserved all conservation parameters.

In addition, we performed two validation cases as outlined by Lakin *et al.* [3] to examine the dynamic behavior of the model for the situations of:

- Pulsatile heart flow, and
- Postural change

References

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The model successfully simulated a pulsatile cardiac cycle that was comparable to [3]. As can be seen in Figure 2, there are minor discrepancies in the period and amplitude of our prediction of heart outflow and Lakin *et al.*'s function, as digitized from the paper. However, when compared with literature values [4], our simulated systolic and diastolic pressures in the central and intracranial arteries were within physiological limits of 120/80 mmHg and 100/65, respectively, as presented in Figure 3. We therefore considered our model's response to be satisfactory.

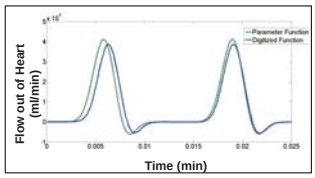

Figure 2: Plot of heart outflow against time for both the digitized function and the functional parameters obtained, as given in [3].

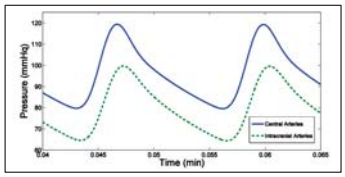

Figure 3: Simulation outputs for intracranial and central arterial pressure showing diastolic pressures within physiological limits of 120/80 mmHg and 100/65, respectively.

Head-down tilt simulations performed by Lakin *et al.* [3] predicted intracranial arterial flow of 100% and 94% of the mean when the SNS is activated and deactivated, respectively. Our implementation of their model predicted <1% change with the SNS activated, and almost no change when the SNS is deactivated (Figure 4). Model verification studies did not identify flaws in our implementation of this model. Consequently, we attempted to re-examine the original formulation as presented by Stevens and Lakin (2006) [5] but were unsuccessful in resolving the discrepancy. Since the acute regulatory model of Lakin *et al.* [3] still poses challenges to general implementation and potentially lacks capabilities critical for simulation of chronic μg exposure, we have abandoned their SNS model and will develop an independent strategy for regulation based on measured fluid redistribution due to long-duration μg [6].

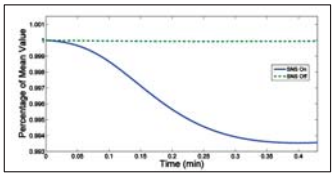

Figure 4: Plot of the percentage of mean flow from intracranial arteries to intracranial capillaries as a function of time. With SNS reflexes activated, the flow remains at approximately 99.99% of its mean value. In the absence of these reflexes, the curve tends to 99.34% of its prior value.

Forward Work

In order to leverage this model as a foundation for an integrated systems model to simulate the CNS and CVS for VIIP research, we will:

- Formally incorporate hydrostatic pressure variation into the matrix equation
- Modify system parameters such as tissue and flow properties, flowrates and pressures to reflect the most current VIIP research and to define a reasonable physiological envelope that encompasses the astronaut corps
- Analyze the model via sensitivity studies to identify most significant parameters
- Test the model against and train the model with independent studies in postural change, head-down tilt and μg to develop and validate regulatory functions that appropriately capture the observed fluid redistribution
- Ascertain trends and characteristic ranges of output variables for use by the CNS and eye models, including fluid redistribution and cranial blood flow in μg