Influence of Population Variation of Physiological Parameters in Computational Models of Space Physiology

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Model Credibility

- Verification
- Validation
- Data Pedigree
- Results Uncertainty
- Results Robustness
- Input Pedigree
- Use History
- M&S Management

NASA Standard 7009a – Credibility of Models and Simulation
Results Robustness

**Sensitivity Analysis**: Assesses whether or not the result from an M&S changes in a meaningful way upon relatively slight variations in input parameters.

A Modeling and Simulation (M&S) result is:
- Robust if output is relatively stable with respect to changes in input parameters
- Sensitive if small perturbations of particular input parameters produce dramatic changes in results

“Sensitivity Analysis is the study of how variation in the output of a model can be apportioned, qualitatively or quantitatively, to different sources of variation (input) and how the given model depends upon the information fed into it.”

- Saltelli

Intent is to elucidate the sensitivity of the real-world system to potential changes in the variables and parameters of the system
Sensitivity Analysis Methodology

- Partial Rank Correlation Coefficient (PRCC) Analysis
  - Provides a measure of the linear relationships between input parameters and output parameters when all linear effects of other variables are removed after rank transformation.
  - Rank Transformation: non-linear monotonic relations to linear.
  - Used In Models of
    - Cell signaling pathways, infections disease progression, gene expression
Efficient Interrogation of Parameter Space
Latin Hypercube Sampling

Latin Hypercube Sampling (LHS)

- Sampling method without replacement
- Improved sampling of distribution “tails”
- Can achieve statistical convergence in fewer samples than standard Monte Carlo sampling by as much as 30%
- Is not affected by the number or size of the parameter space in achieving convergence efficiency

https://mathieu.fenniak.net/latin-hypercube-sampling/0
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

\[
[c] \frac{dp}{dt} + [z] \cdot [P] = [Q]
\]

- Compartments represented at 3 heights
  - cranial, upper, lower
- Baroreflex regulation of arterial pressure included
CVS Parameter Analysis

• 42 physiological parameters describe compartments
  – Supine steady-state parameters
  – For sensitivity analysis, each compartment utilizes mean supine pressures and flow rates with the physiological parameters to assess a:
    • Fixed distensibility or compliance per compliance interface
    • Fixed inter-compartment resistance per flow interface

• Estimates of Parameter ranges
  – Range set at +/-10% (uniform distribution)
  – Model trained at cardiac output of 5000 ml/min
  – Simulations performed are at 6900 ml/min in supine and standing configurations for ~2.5 Minutes of simulation time

• Note: Pressures in mmHg, flows in ml/min
Histograms of Select Pressures

- Supine: Small variations in pressure, uniformly distributed
- Standing: Larger variations in pressure, near normally distributed

- Represents 1000+ trials, with 100 discretizations of each LHS distribution
- Convergence is estimated as < 0.002 change in output standard distribution per 100 trials
PRCC Sensitivity Analysis Results For Output Pressures

- Supine position sensitive to initial Central Arterial Pressure
  - Venous pressure dominated by variations in initial flow
  - CSF space by initial compartment pressure.

- Standing position sees the same types of trends
Supine: Pressure in the Central Arteries plays a dominant role—Driving Pressure coupled with no regulation controls the majority of the model responses.

Standing: The initial distribution of blood flow in the central and lower compartments exhibits a strong influence on model performance. Also noted as influential:
- Central Artery Pressure
- Lower capillary pressure, used to determine the reference lower capillary resistance as the base state of the regulation of capillary resistance

Note: Not Regression coefficients. These are relative ranking of highest rank compartment pressures.
VIIP Modeling: Structured Approach

The suite of lumped parameter models should have the following capabilities:

- Bridge the gap between whole-body fluid shift in $\mu g$ and biomechanical response of ocular tissues
- Identify parameters that have the most effect on $IOP$ and $ICP$ in $\mu g$
- Provide a platform to explore the physiological envelope and find patterns of behavior
How can this be used in the integrated model of VIIP?

Platform provides a set of consistent data for exploring the physiological envelope and for finding patterns of behavior in altered g scenarios.
Peak Strains in the Optic Nerve


Dotted gray box indicates the normal physiological strain range under 1g conditions
Cumulative influence factor for all model inputs shows that:

- IOP and ICP are particularly influential
- ON and LC stiffnesses have large effect on ONH
- C1 – C4 represent the Mooney-Rivlin solid embedded with collagen fibers
Conclusions

• Sensitivity analysis of lumped CVS model identified parameters of strongest influence and population performance
  – As expected, most sensitive parameters change with model orientation
    • Central Artery Pressure, a corollary to MAP, is influential in both orientations
  – Arterial flow distribution appears to be the major influence in standing
    • Regulatory mechanisms likely damp some effects, although they exhibit sensitivities to calculated reference values of regulated parameters

• Extending uncertainty propagation techniques results in powerful method for examining the population parameter space
  – FEM-ONH study found that c. 47% of individuals would experience “extreme strains” in the optic nerve under assumed microgravity conditions
    • These strains may be sufficient to induce connective tissue remodeling
    • Note: This simulated population with extreme strains is comparable to the (presumably) 41% of astronauts suffering from VIIP syndrome
  – These CDFs also identified ICP, IOP, ON, and LC stiffness as influencing these extreme strains
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Results Robustness: Sensitivity Analysis

The characteristic that the result from an M&S does not change in a meaningful way to relatively slight variations in parameters.
- Robust if output is relatively stable with respect to changes in input parameters
- Sensitive parameters produce large changes in results from small perturbations

“Sensitivity Analysis is the study of how variation in the output of a model can be apportioned, qualitatively or quantitatively, to different sources of variation (input) and how the given model depends upon the information fed into it.”

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Intent is to elucidate the sensitivity of the real-world system to potential changes in the variables and parameters of the system
How can this be used in the integrated model for VIIP?
Optic Nerve

- Strains outside the predicted physiological range with elevated ICP

Cumulative Influence Factor

- Cumulative influence factor for all model inputs
- C1 - C4 represent the Mooney-Rivlin solid embedded with collagen fibers
- IOP and ICP particularly influential
- ON and LC stiffness have large effect on ONH