Numerical Modeling of Ocular Dysfunction in Space

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Background

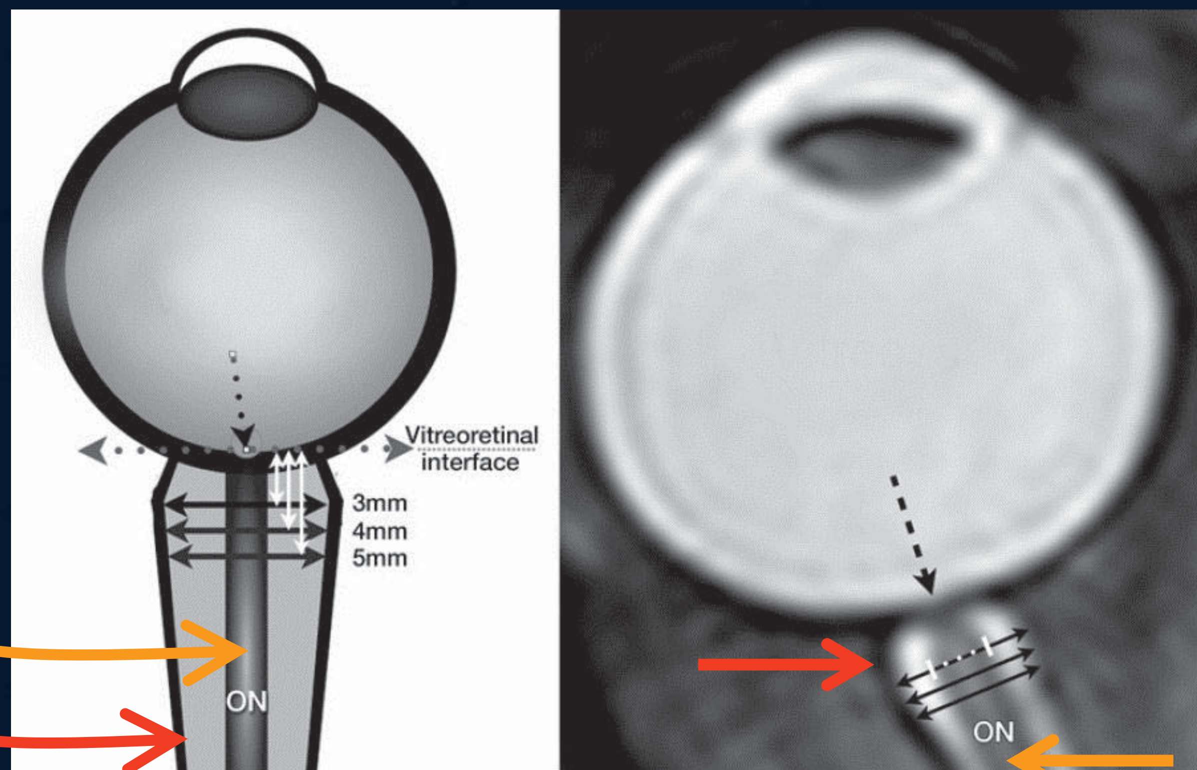
Astronauts in both short- and long-duration spaceflight have reported visual impairment in microgravity (29%[1] / 42.7% [2]) but relatively recently, severe cases of post-flight ocular pathology have been seen

- No definitive explanation as to why such ophthalmic changes might occur in microgravity (μg)
- The Digital Astronaut Project is seeking answers via integrated modeling

NORMAL EYE

Optic Nerve (ON)

Optic Nerve Sheath (ONS)



- Kramer et al. (2012)

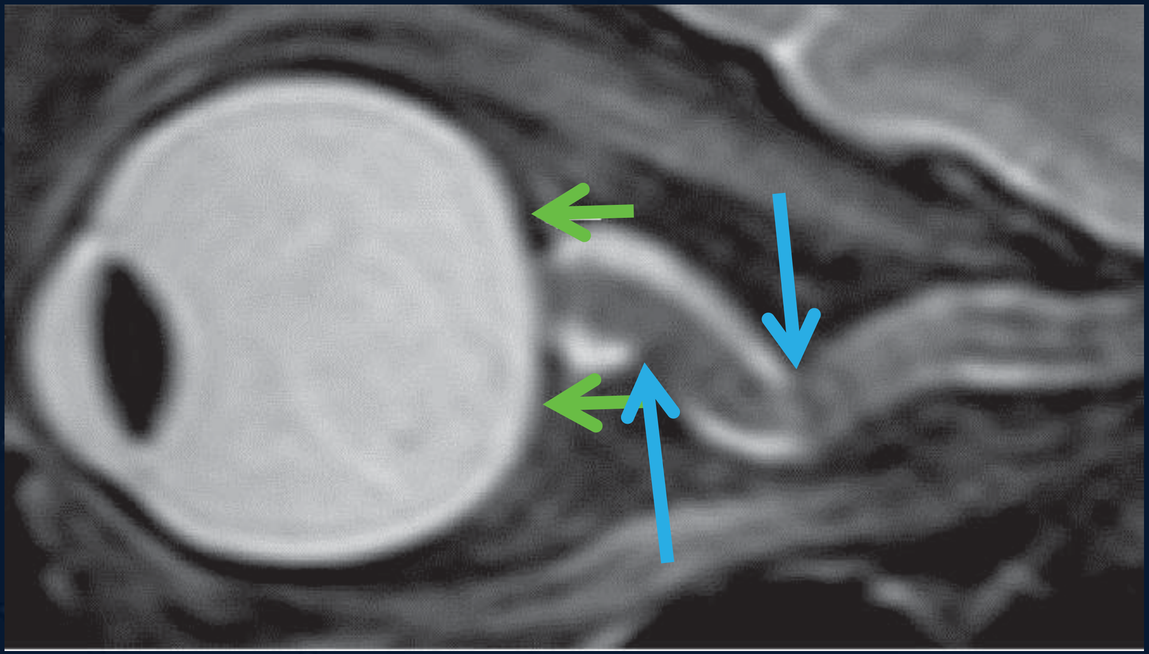
[1]Mader et al. (2011)

[2]Tarver and Otto (2012). Examinations are still in process

Post-flight ophthalmic pathophysiology

Some features of this pathophysiology resemble terrestrial Idiopathic Intracranial Hypertension, which is characterized by high Intracranial Pressure (ICP)

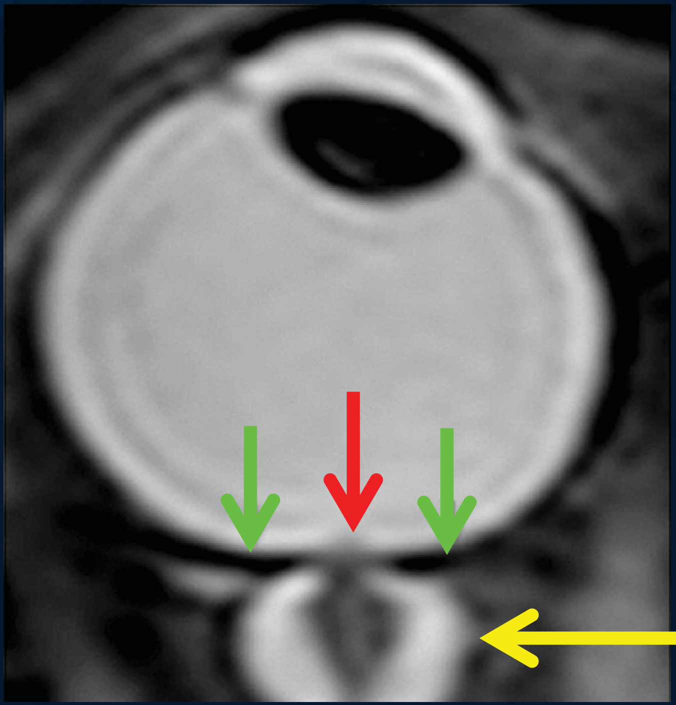
POST-FLIGHT IMAGE



- Kramer et al. (2012)

In cases found to date, changes to visual acuity began to emerge after ***3 weeks to 3 months*** in μg

POST-FLIGHT IMAGE

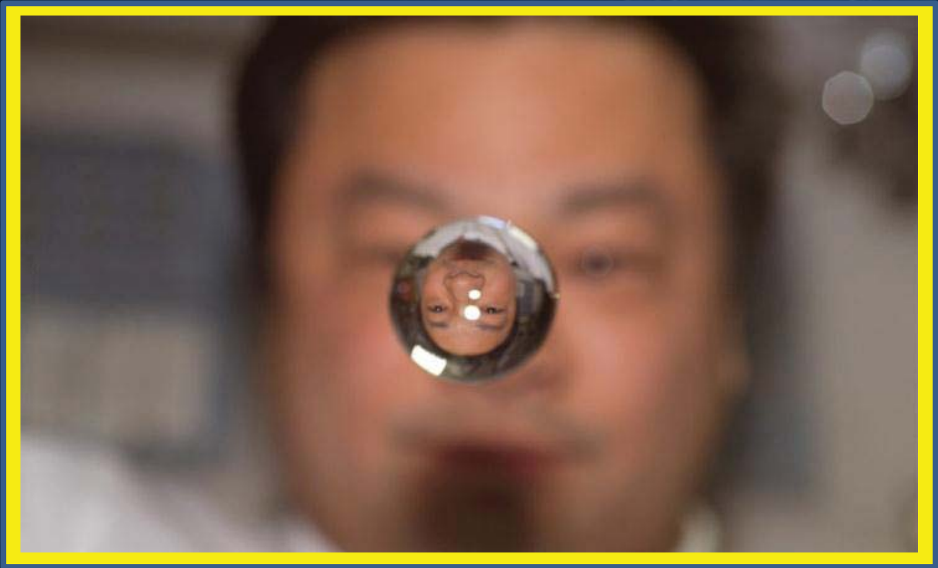


- Mader et al. (2011)

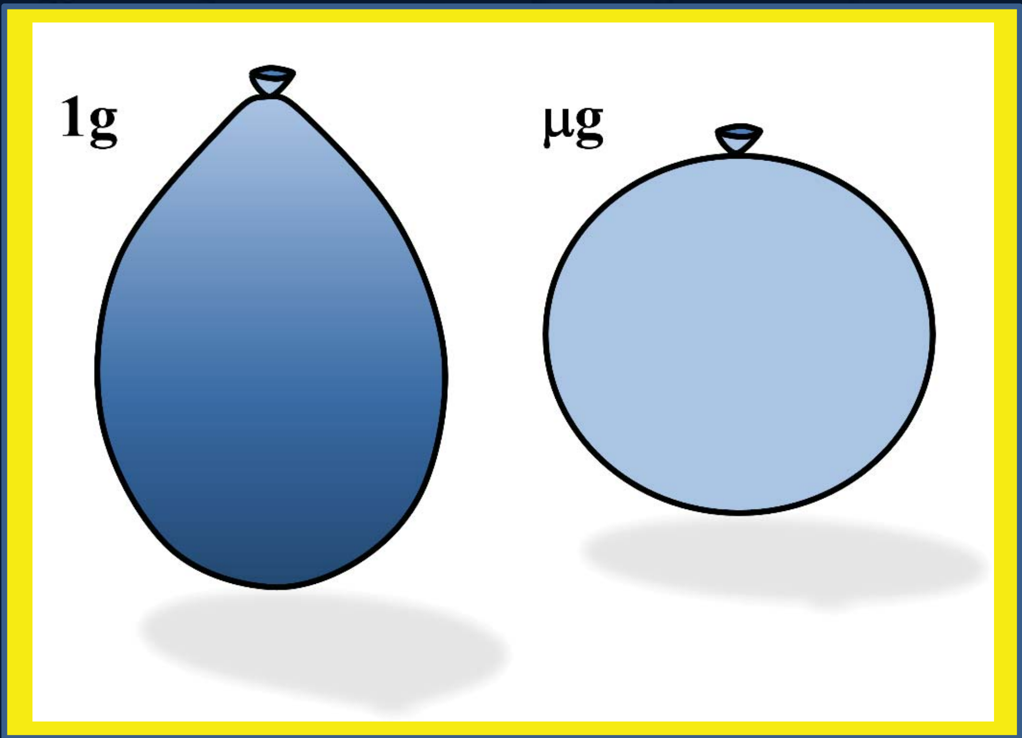
Astronauts exhibit:

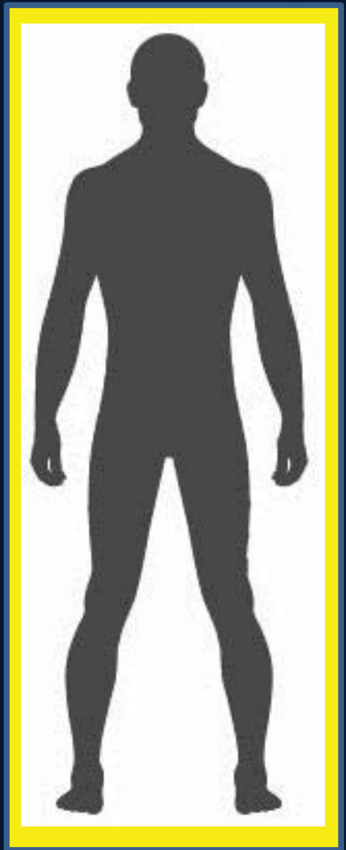
- **Optic disk edema**
- **ONS distension**
- **Globe flattening**
- Choroidal folds
- Increased CSF pressure
- Wool spots
- Decreased Intraocular Pressure (IOP) post-flight
- **ON kinking**

Fluid redistribution in space



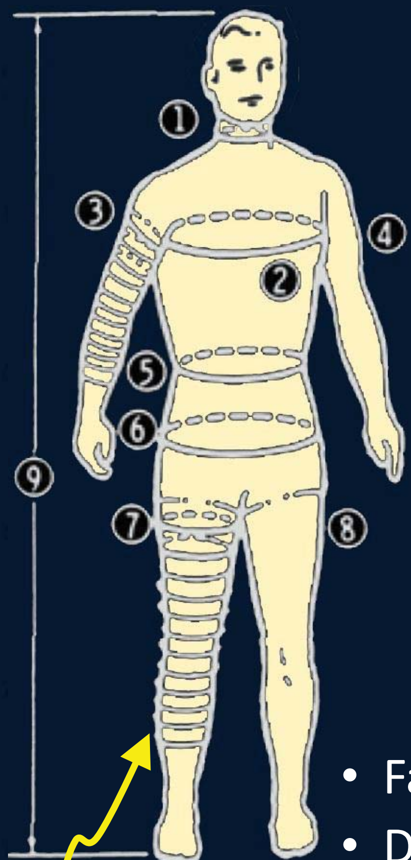
- The equilibrium shape for a blob of liquid water in μg is spherical (surface tension dominates in reduced gravity)
- When contained in a uniformly elastic sac, like a balloon, it is also spherical

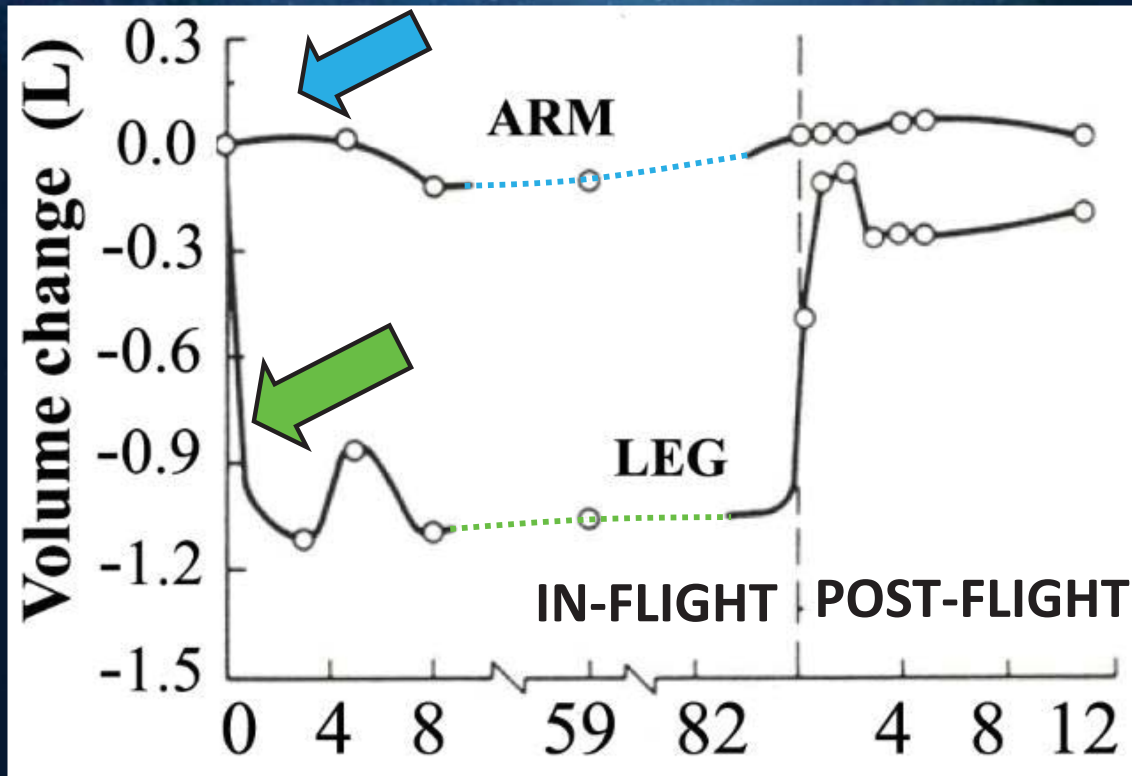




Now consider a human being…

Cephalic fluid shift



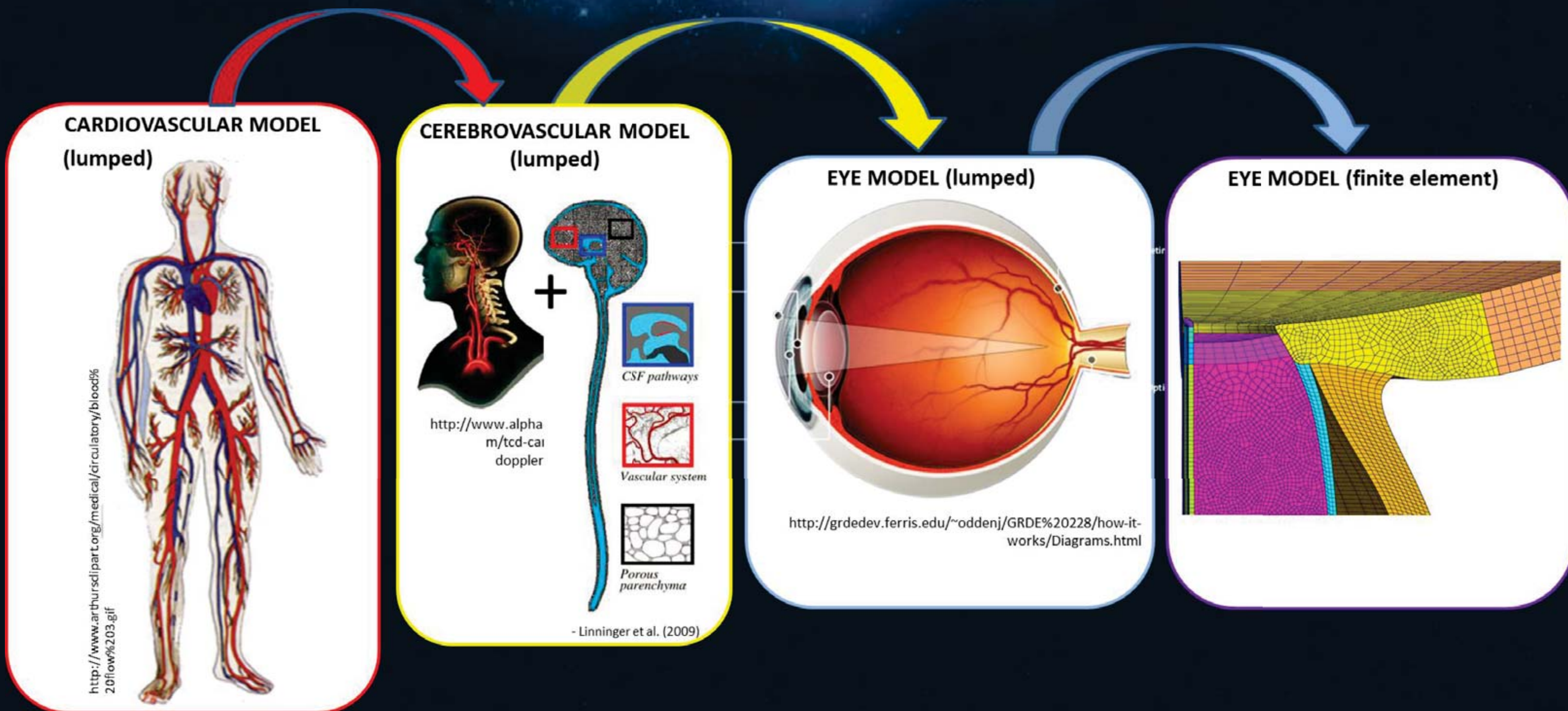


ΔV vs. time on Skylab 4 [1]

[1] Thornton et al. (1986) Skylab 4
[2] Kirsch et al. (1993)
[3] Herault et al. (2000) 6 mo on Mir
[4] Moore and Thornton (1987) Shuttle
[5] Kas'ian et al. (1980)
[6] Hoffler et al. (1975) Apollo

- Facial tissues swell[2]; jugular, temple and forehead veins are full & distended [1, 3]
- Dramatic changes to leg volume occur ***within the first 4-6h*** after entry to μg; leg volume ↓ by ~6-12% (~***1 L per leg***) within the first week (green arrow) [1,4,5] ; reaches a new homeostatic value within ~***1-2 weeks*** [1]
- Upper body expands, waistline ↓; Center of Mass shifts ↑; spine ↑ 4-6 cm [1]
- Smaller changes in arm volume (blue arrow) [1-2]
- Inference of fluid volume from circumferential measurements probably conflates with ***muscle atrophy*** (even seen in a 5-day Apollo flight [6])

Numerical approach

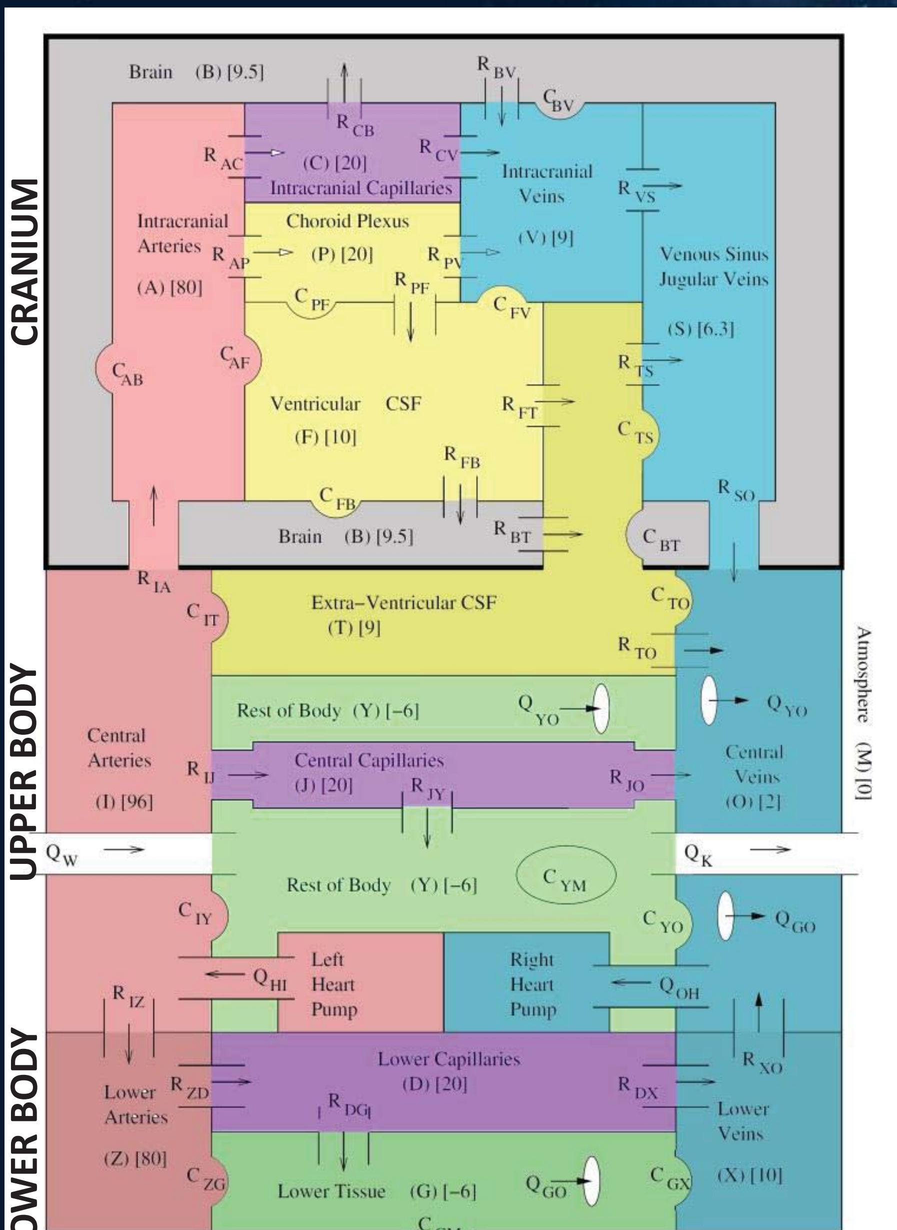


A sequence of stand-alone models at varying length scales and spatial fidelity:

- <u>Cardiovascular system (CVS)</u>: fluid shift, cranial blood flow
- <u>Central nervous system (CNS):</u> Intracranial Pressure (ICP), ocular blood flow
- <u>Eye model (lumped):</u> globe volume, Intraocular Pressure (IOP)
- <u>Eye model (finite element):</u> biomechanical stress/strain, tissue remodeling

Cardiovascular (CVS) model

16 COMPARTMENT MODEL

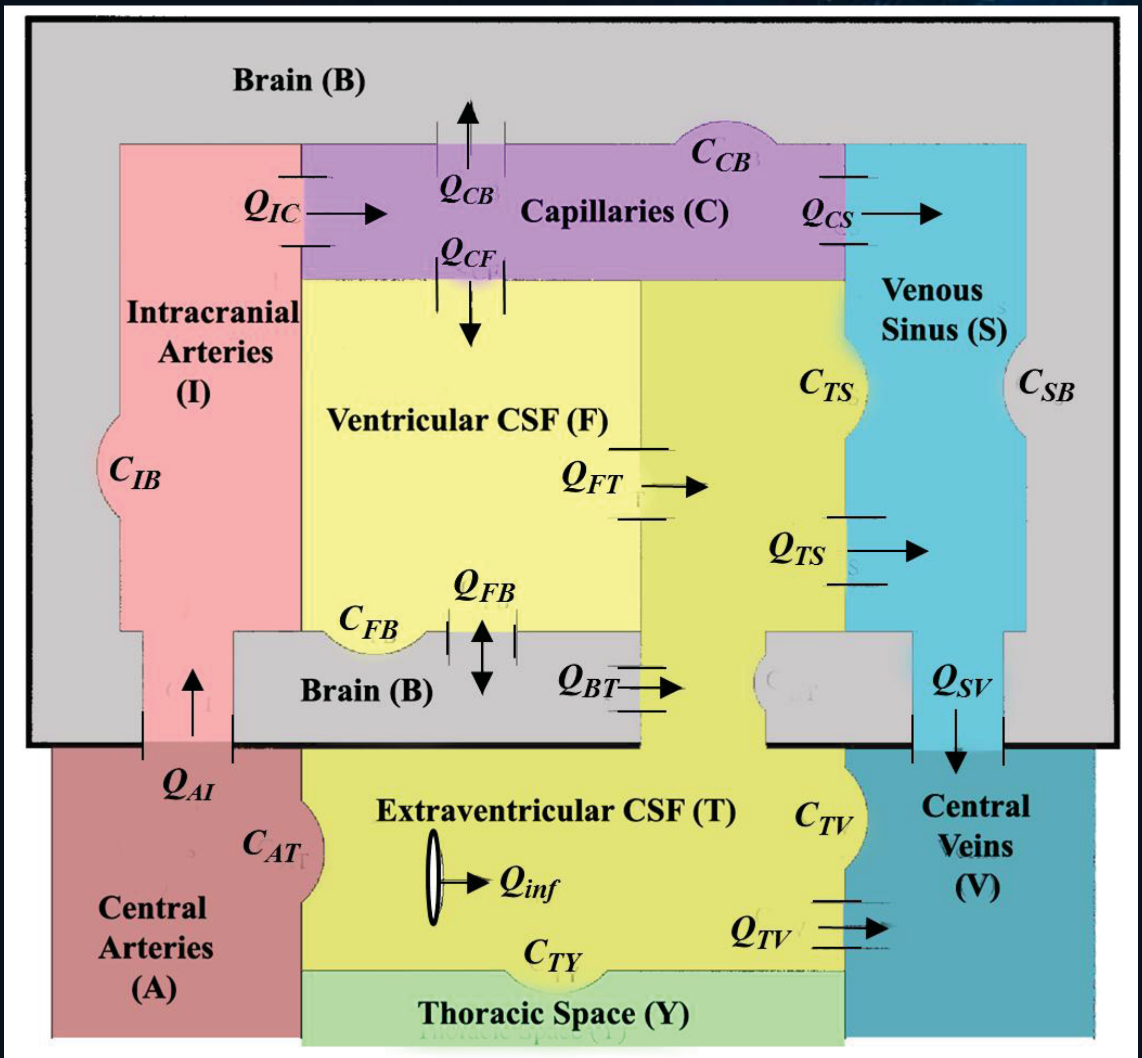


- Lakin et al. (2003)

- The goal of the CVS model is to predict the modified homeostatic state in μg (fluid distributions, mean fluid flows, pressures)
- Some lumped CVS models exist, but none have the capabilities to properly simulate ***chronic*** μg. The CVS model must properly incorporate:
  - Hydrostatic forces
  - Adequate spatial resolution
  - Relevant regulatory functions
  - Astronaut-specific data
- Code is being verified/validated against Lakin et al. (2003) and others
- Revision includes:
  - physiological ranges relevant to astronauts (e.g., height, total blood volume, age)
  - μg and head-down tilt (HDT) data on plasma volume loss, spinal elongation, changes to osmotic pressure, etc.

Central Nervous System (CNS) model

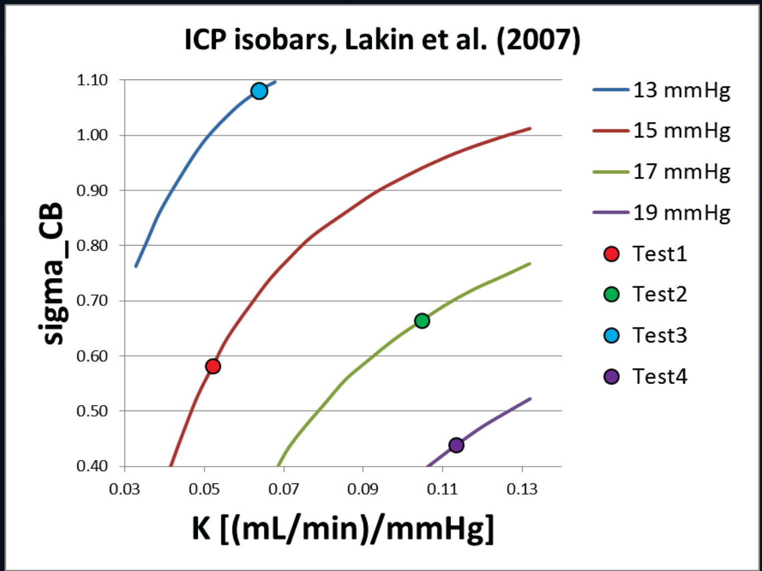
9 COMPARTMENT MODEL



- Stevens et al. (2005), Lakin et al. (2007)

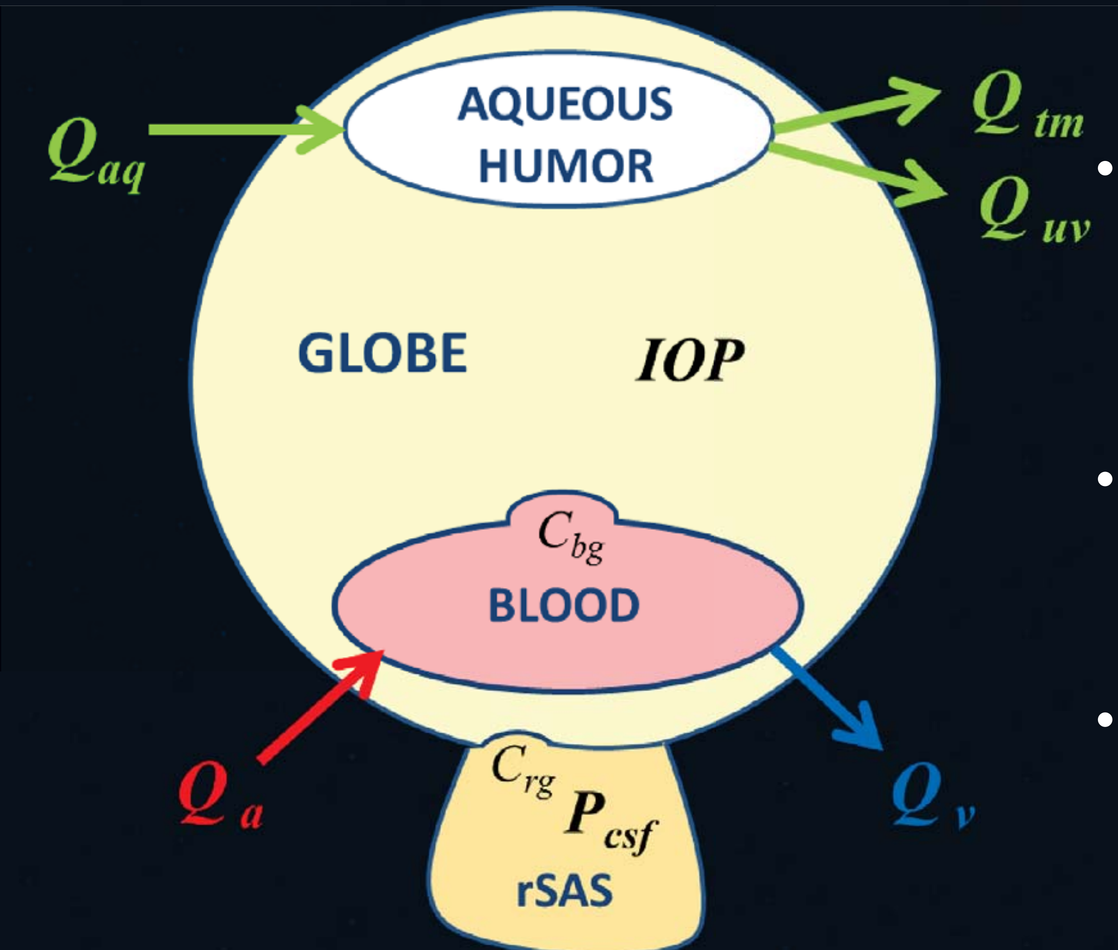
Verification test: Filtration properties at the blood/brain barrier

- Some lumped parameter CNS models exist; most use Monro-Kellie doctrine (rigid cranium)
- Initial implementation based on Stevens et al. (2005). Code is being validated
- Cranial blood flow provides the link between CVS and CNS models
- Revision to include better compliance models and μg/HDT data



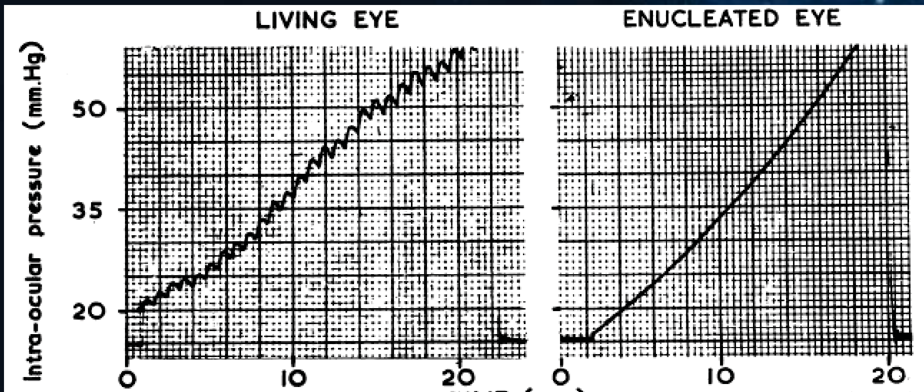
Eye model

4 COMPARTMENT MODEL

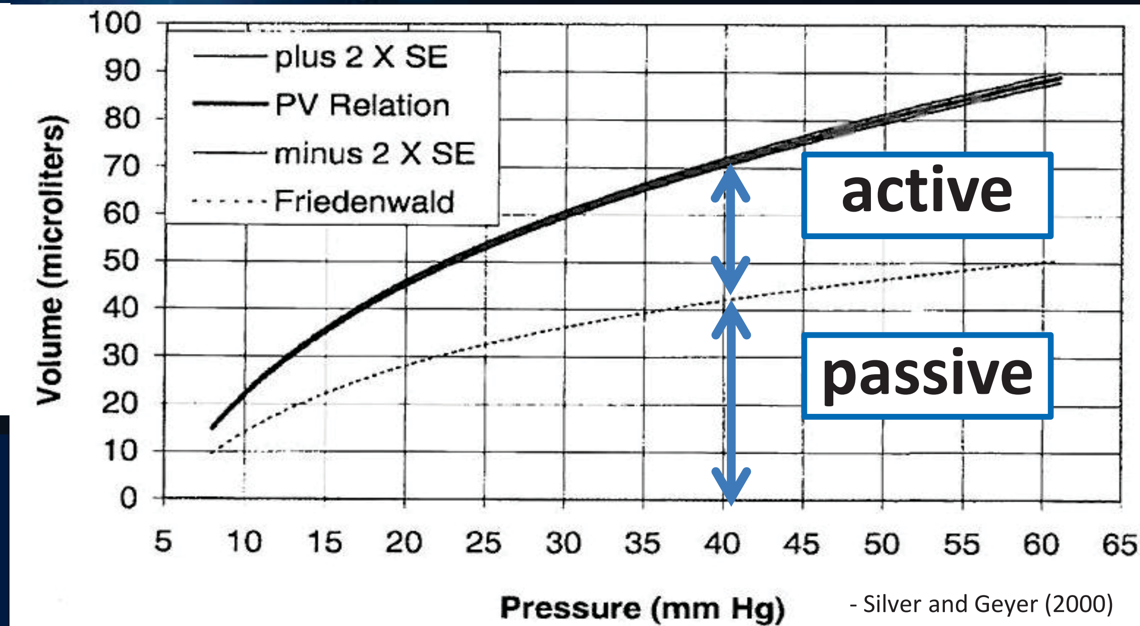


- Very few LP models of the eye exist; none incorporate the human choroid and retrobulbar subarachnoid space (rSAS)
- Almost all of the hydrodynamic data on ocular blood flow (volume, pressure, net flowrate) is qualitative, even in 1g
- Measured permeability of dura mater, the tissue surrounding the rSAS (previously assumed impermeable)
- Developed a means of estimating blood flow from choroidal thickness and pulsatility during a cardiac cycle
- Derived compliance models for the globe/rSAS and globe/blood compartment

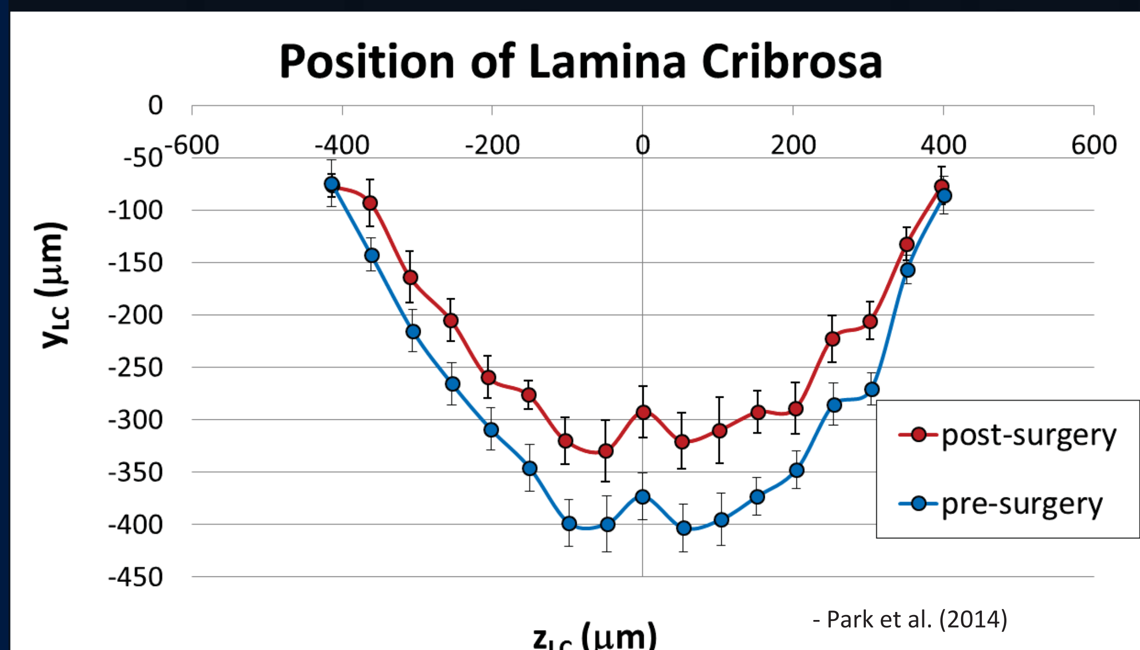
Compliance



- Eisenlohr et al. (1962)



- Silver and Geyer (2000)



- Park et al. (2014)

- Living eyes regulate blood flow in, e.g., saline injection tests
- Pressure/volume relations for the globe have been well-studied
- We attribute the net impact of ocular blood flow dynamics as the difference between P/V curves of living vs. enucleated eyes. Compliance = dV/dP
- Compliance of posterior globe tissue derived from surgical intervention which reduced IOP

Conclusions

- Established a suite of numerical models that could link the biomechanical effects of whole-body fluid shift to the stress/strain in tissues of the eye posterior
- Comprehensively explored literature to inform model development and credibility assessments at 1g and μg
- Used theoretical and experimental techniques to fill in the gaps for defining the choroid and retrobulbar space

Ongoing development

- Following NASA-STD-7009 standard for the development of credible, well-documented simulations with rigorous verification, validation and uncertainty analysis
- Coordinating with NASA's medical databases and current research to make smart choices on relevant physiological ranges and material properties
- Minimal quantitative data ➔ extensive sensitivity analysis

The VIIP Modeling Team

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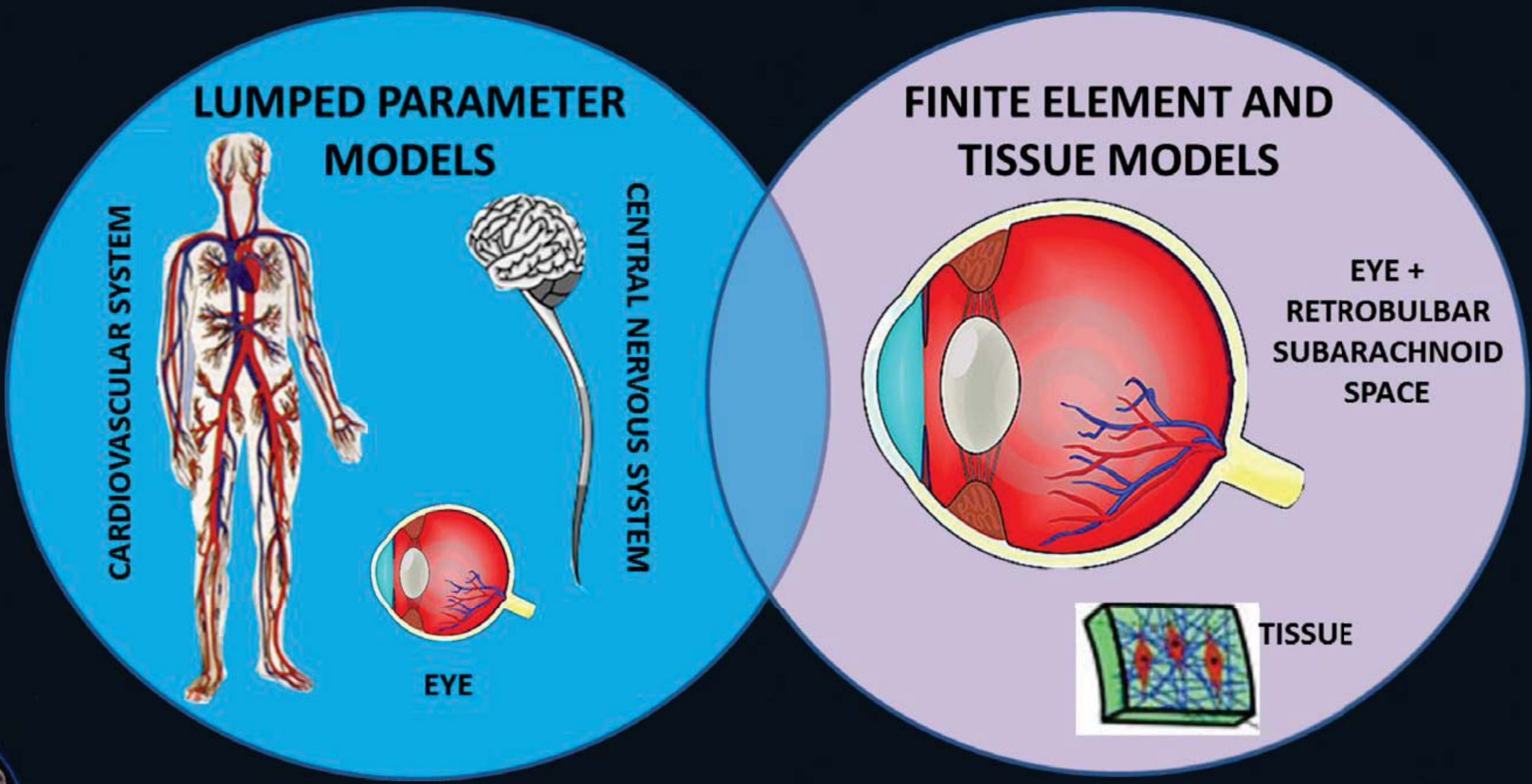
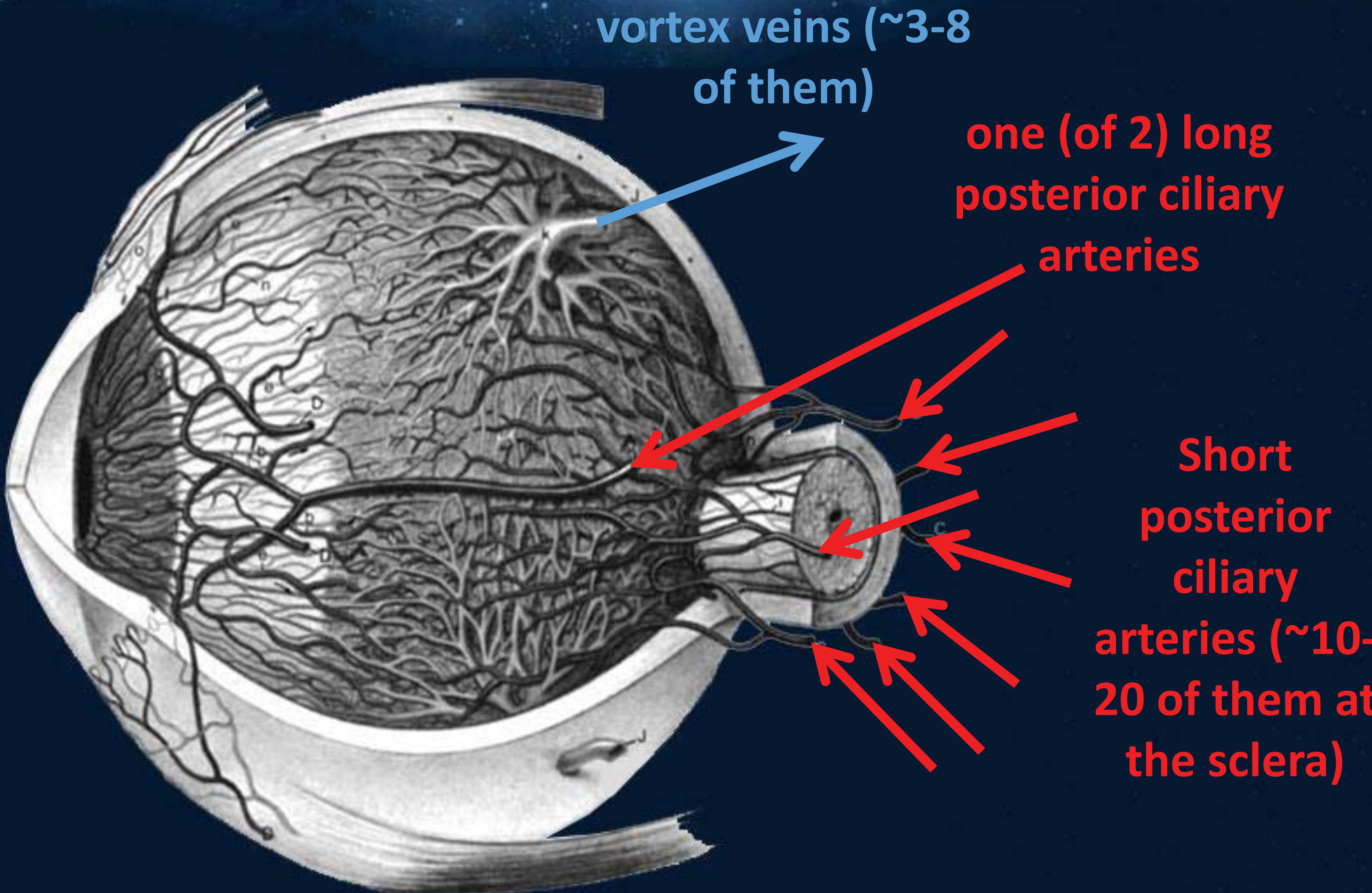


*Co-Investigators on NRA proposal "**Microgravity-driven Optic Nerve/Sheath Remodeling Simulator (MONSTR Sim)**"

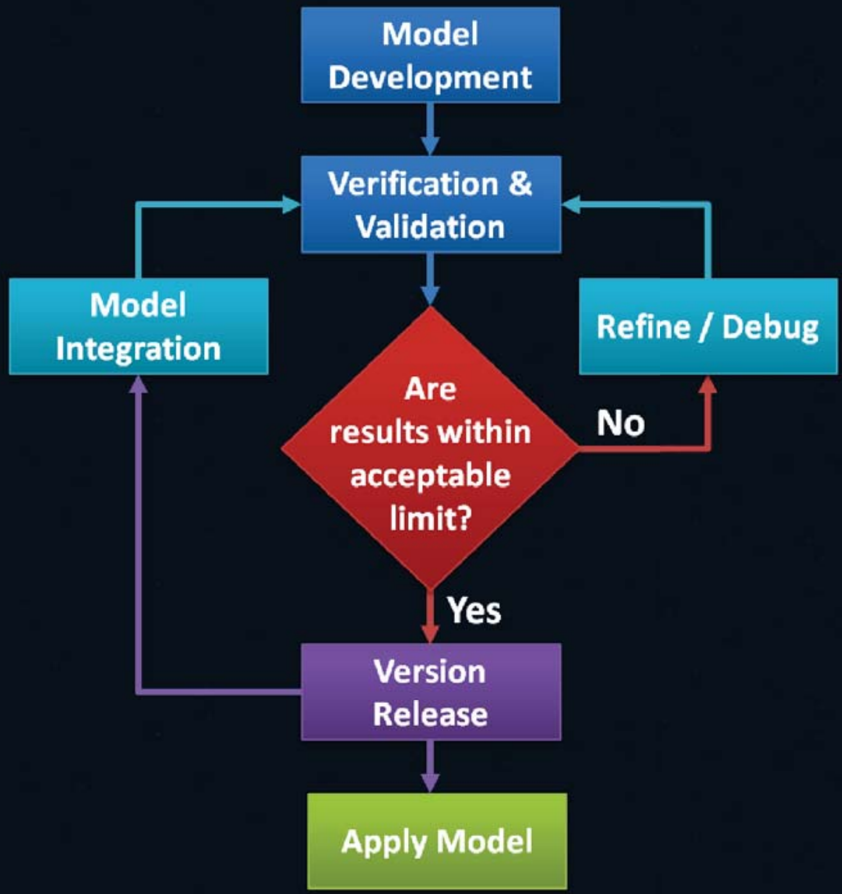
Backups

Choroidal blood flow



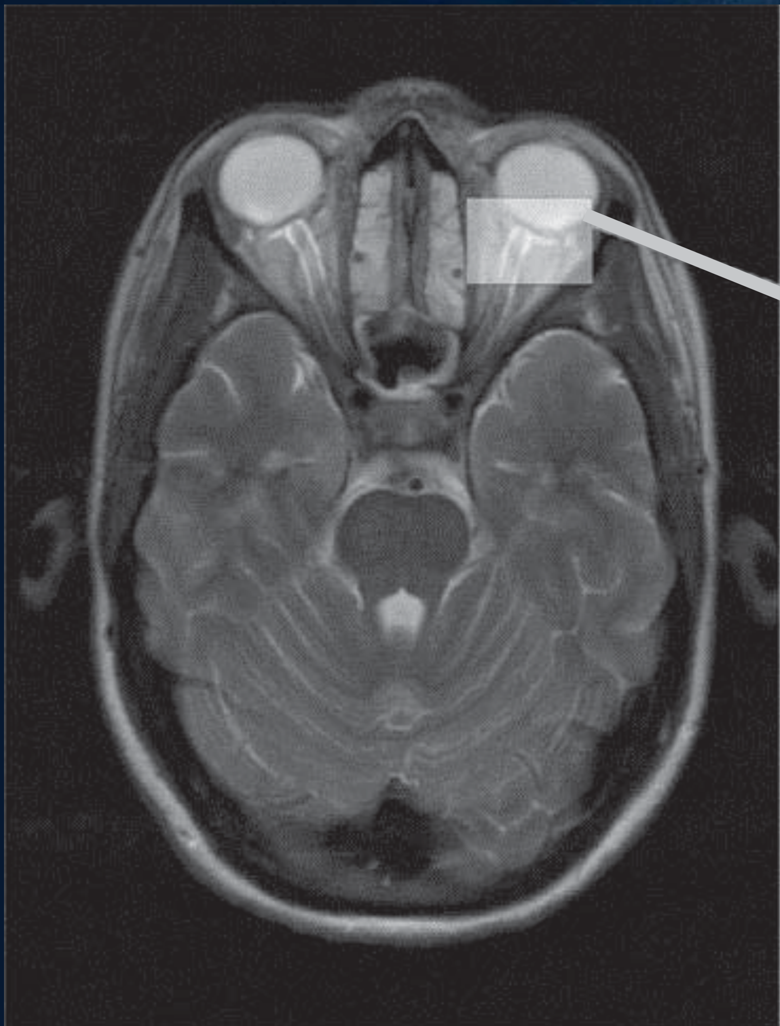
Verification and Validation

- All models and simulations (M&S) will be verified and validated in accordance to NASA-STD-7009
- Obtain data from LSAH/LSDA to develop and validate M&S
- Establish collaborative data sharing agreement with current and future NASA and NSBRI funded VIIP investigators
- Work closely with VIIP Project Scientist and subject matter experts for technical review of M&S

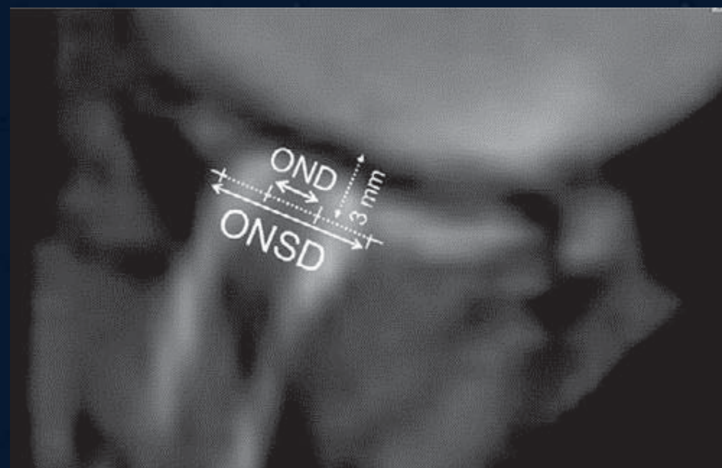


The optic nerve and its sheath

In clinical applications on earth, Optic Nerve Sheath Diameter (ONSD) has become a surrogate for Intracranial Pressure (ICP) in the diagnosis of Idiopathic Intracranial Hypertension (IIH)



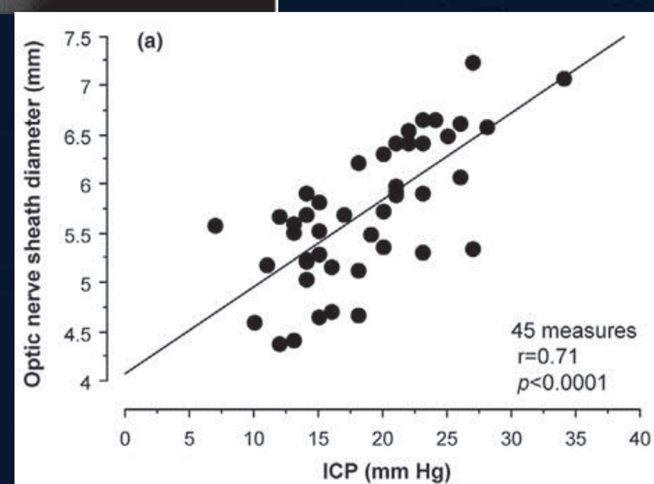
\- Geeraerts *et al*. (2008)



Zoomed to 300X

By convention, measurements are made 3mm behind globe

OND = Optic Nerve Diameter
ONSD = Optic Nerve Sheath Diameter



\- Geeraerts *et al*. (2008)

What we could do with the models?