President's Plenary Symposium

Delineating the Impact of Weightlessness on Human Physiology Using Computational Models

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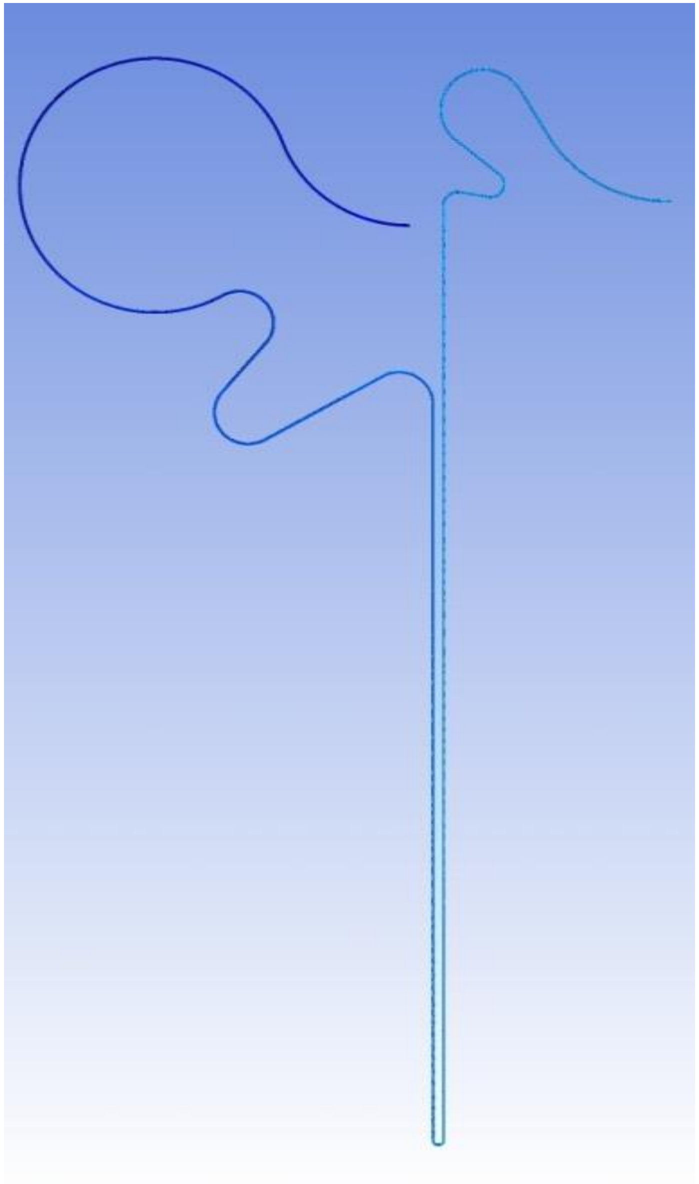
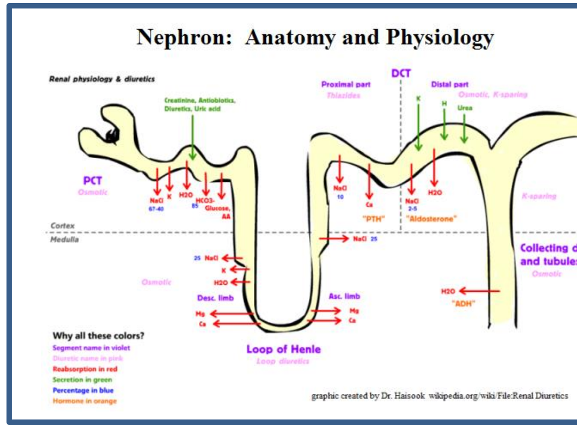
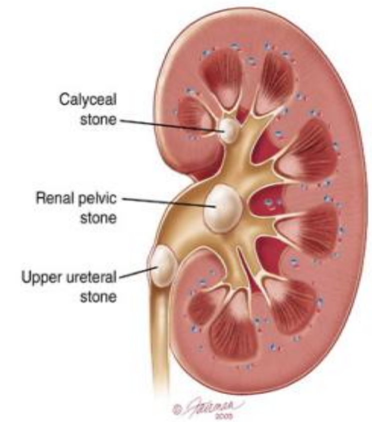
Outline

- PBE & CFD models for prediction of renal calculi development in microgravity .
- Fluid-Structural-Interaction (FSI) models to assess vestibular response.
- Multi-scale FE Heart model to investigate cardiac restructuring in weightlessness.
- Modeling overview
- Computational model to assess impact of AG.

System & Multiphase CFD Models for Renal Stone Development & Transport in 1G and Microgravity







RSFM was developed to address important NASA questions/needs:

- Evaluate the risk of developing a critical renal stone incident during long duration microgravity missions based *on available astronaut biochemical data*
- Assess efficacy of countermeasures such as
  - Increase Hydration
  - Potassium Citrate & Magnesium
- Perform "*what if*" parametric studies to understand and assess risk of developing renal stone upon entry into a 1g or a remote partial gravitational field such as Mars or Moon where relevant astronaut biochemical data is unavailable

Renal Stone Population Balance System Model: Nucleation, Growth & Agglomeration

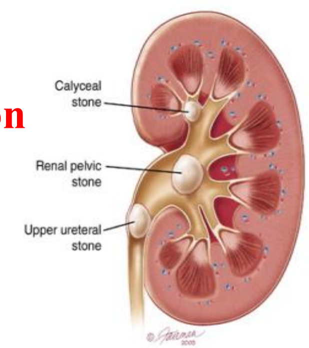
Population Balance Equation:

$$\frac{n(D)}{\tau} + \underbrace{G_D \frac{\partial n(D)}{\partial D}}_{\text{Growth}} = \underbrace{\int_0^{D/2} \beta n(D-D')n(D')dD'}_{\text{Agglomeration-Birth}} - \underbrace{n(D)\int_0^{\infty} \beta n(D')dD'}_{\text{Agglomeration-Death}}$$

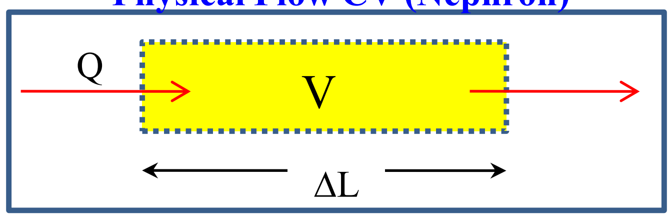
Nucleation BC:

$$n\,(D=0) = n^o = {B^o}/{G_D}$$

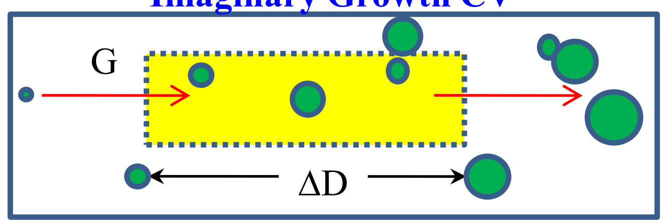
Kidney:
Mixed Suspension
Mixed Product
Removal
Crystallizer

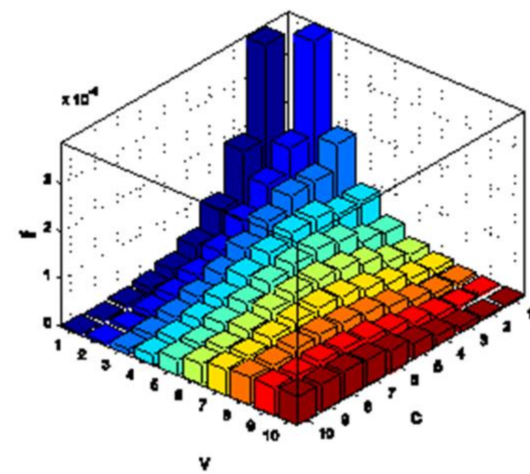


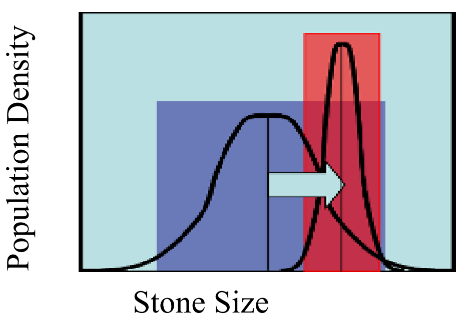
Physical Flow CV (Nephron)



Imaginary Growth CV







Relative Supersaturation:

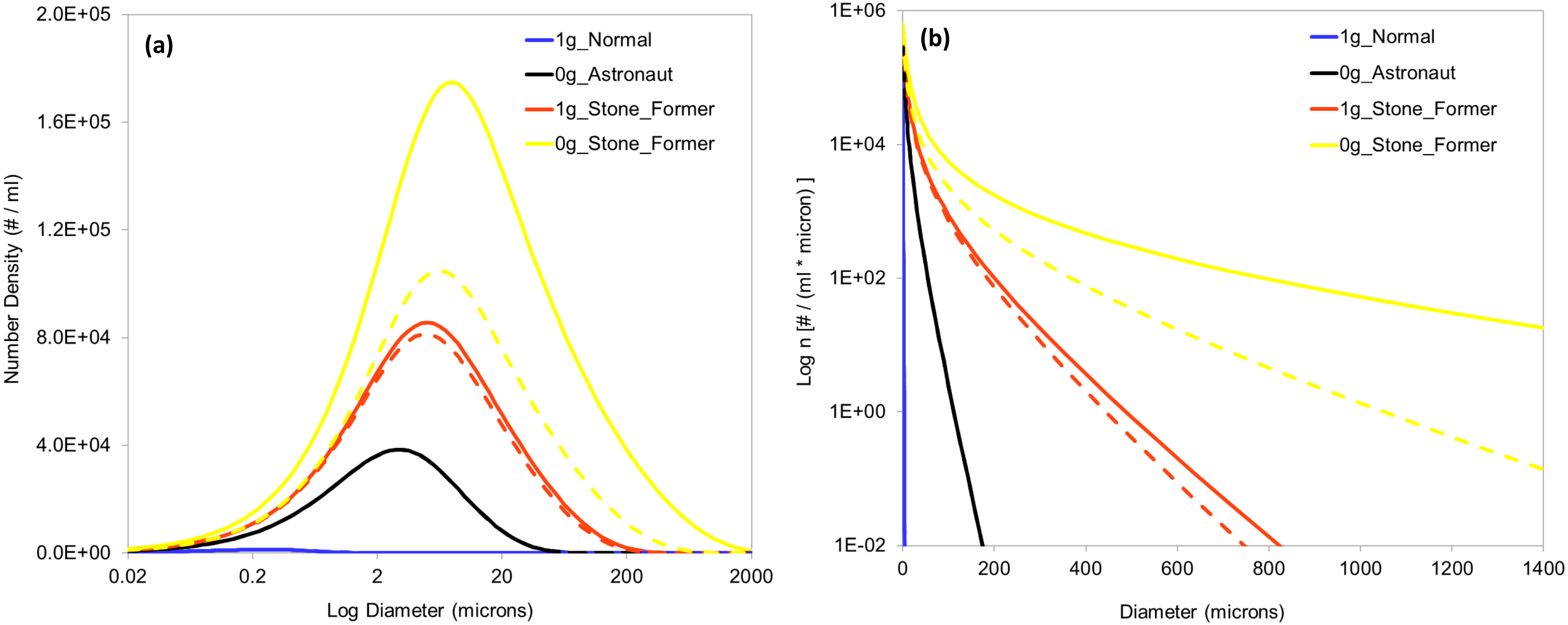
$$RS = \left[\frac{C_{ca,\infty}\, C_{ox,\infty}\, f_2^2}{K_{so}}\right]^{1/2} \quad (2)$$

Inhibition: Citrate, Pyrophosphare, Hydration

- ***Direct*** : K_B, K_D, β, τ
- ***Indirect*** : ***RS***

Prediction for 4 Subject Test Cases

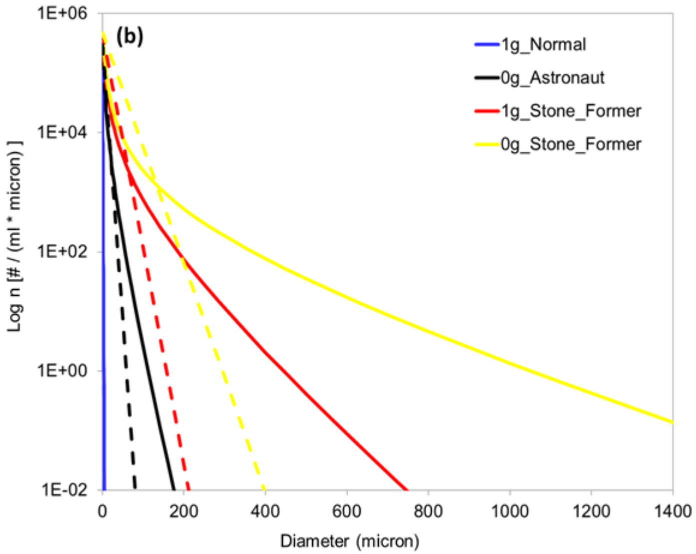
Kassemi & Thompson (JAP-Renal, 2015a)

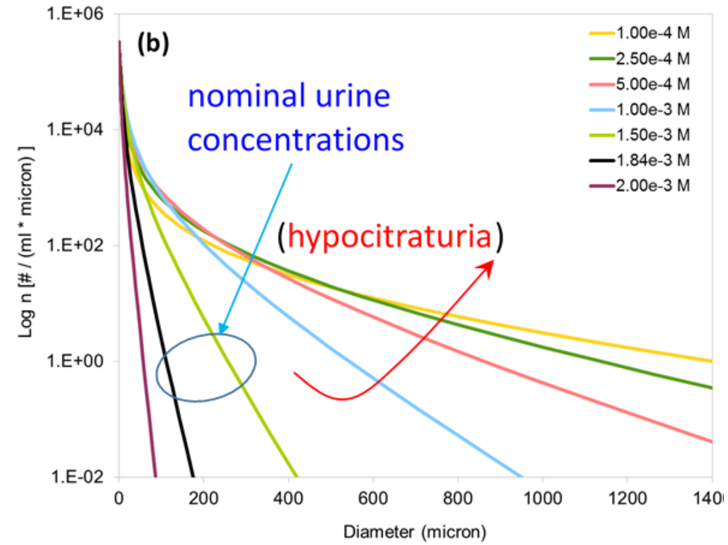


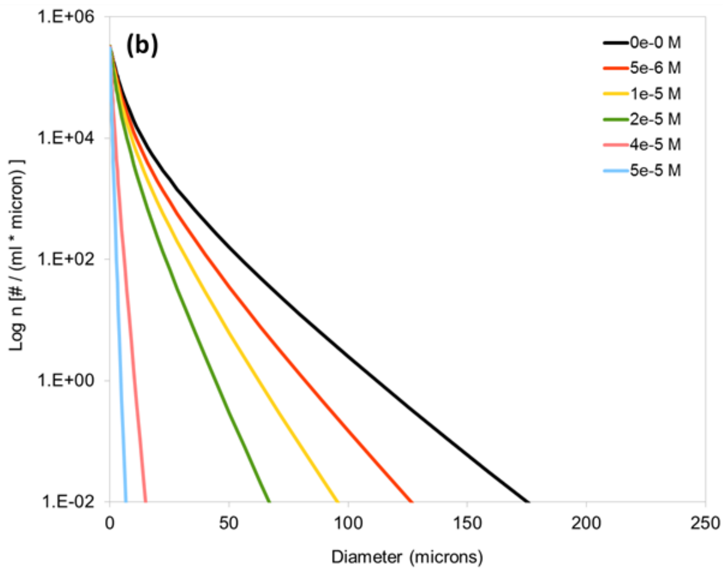
- **1G Normal:** 24 urine sample Mineral Metabolism Laboratory at University of Texas Southwestern Medical Center UTSW[34].
- **1G Recurrent Stone-former:** 24 Urine Sample (Robertson et al.[26], Laube et al.[13])
- **Microgravity Astronaut:** Average of 24-urine excretion rates obtained from 86 astronauts on the day of landing. (Whitson et al.[36])
- **Microgravity Stone Former:** *Hypothetical* worst case scenario constructed using the long duration 24-urine data R+2 (Whitson et al.[38].)

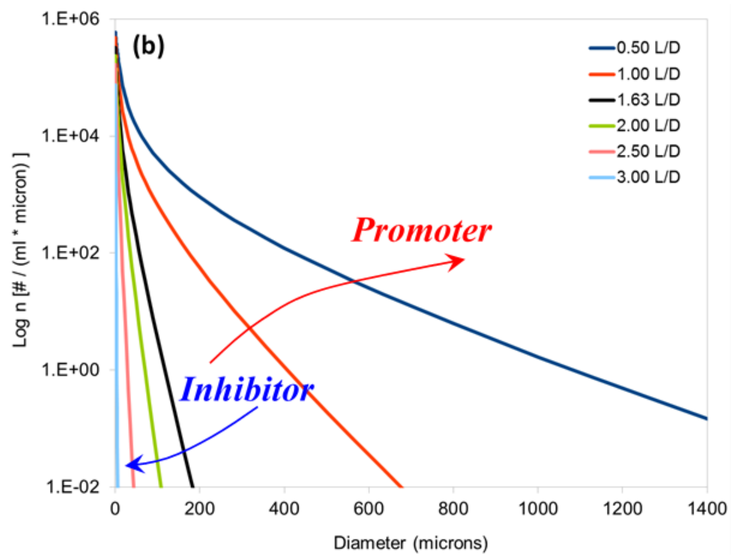
Effect of Dietary Countermeasures for **Microgravity Astronaut Subject**

Kassemi & Thompson (JAP-Renal, 2015b)

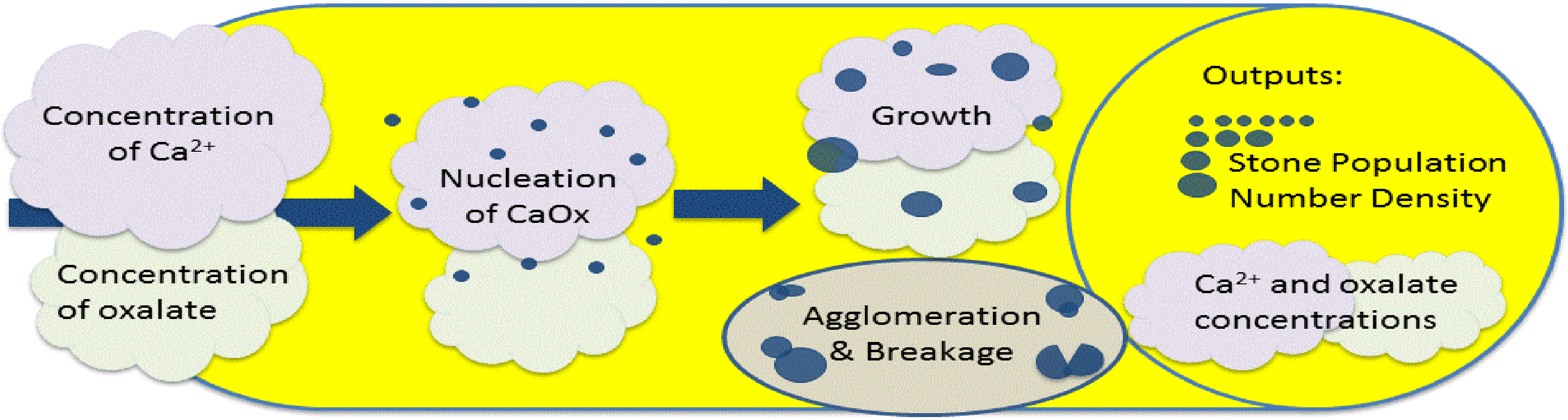








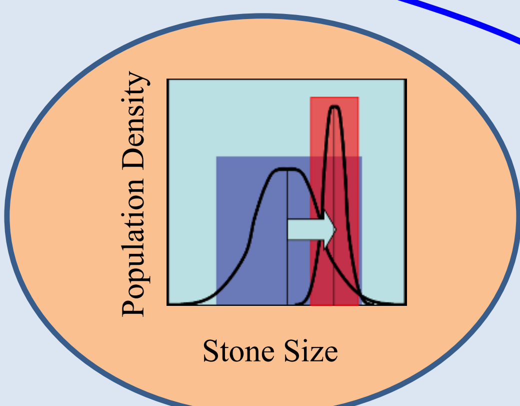
G Effect: Coupling Stone PBE to Urinary Flow & Ca and Ox Transport in the Nephron



Population Balance Equation Coupled to Urinary Flow & Species Transport

$$\frac{\partial}{\partial t}[n(V,t)] + \nabla\cdot[\vec{u}n(V,t)] + \underbrace{\nabla_v\cdot[G_v n(V,t)]}_{\text{Growth term}} = \underbrace{\frac{1}{2}\int_0^V a(V-V',V')n(V-V',t)n(V',t)dV'}_{\text{Birth due to Aggregation}} - \underbrace{\int_0^\infty a(V,V')n(V,t)n(V',t)dV'}_{\text{Death due to Aggregation}}$$

$$+ \underbrace{\int_{\Omega_v} \nu g(V')\beta(V \mid V')n(V',t)dV'}_{\text{Birth due to Breakage}} - \underbrace{g(V)n(V,t)}_{\text{Death due to Breakage}}$$

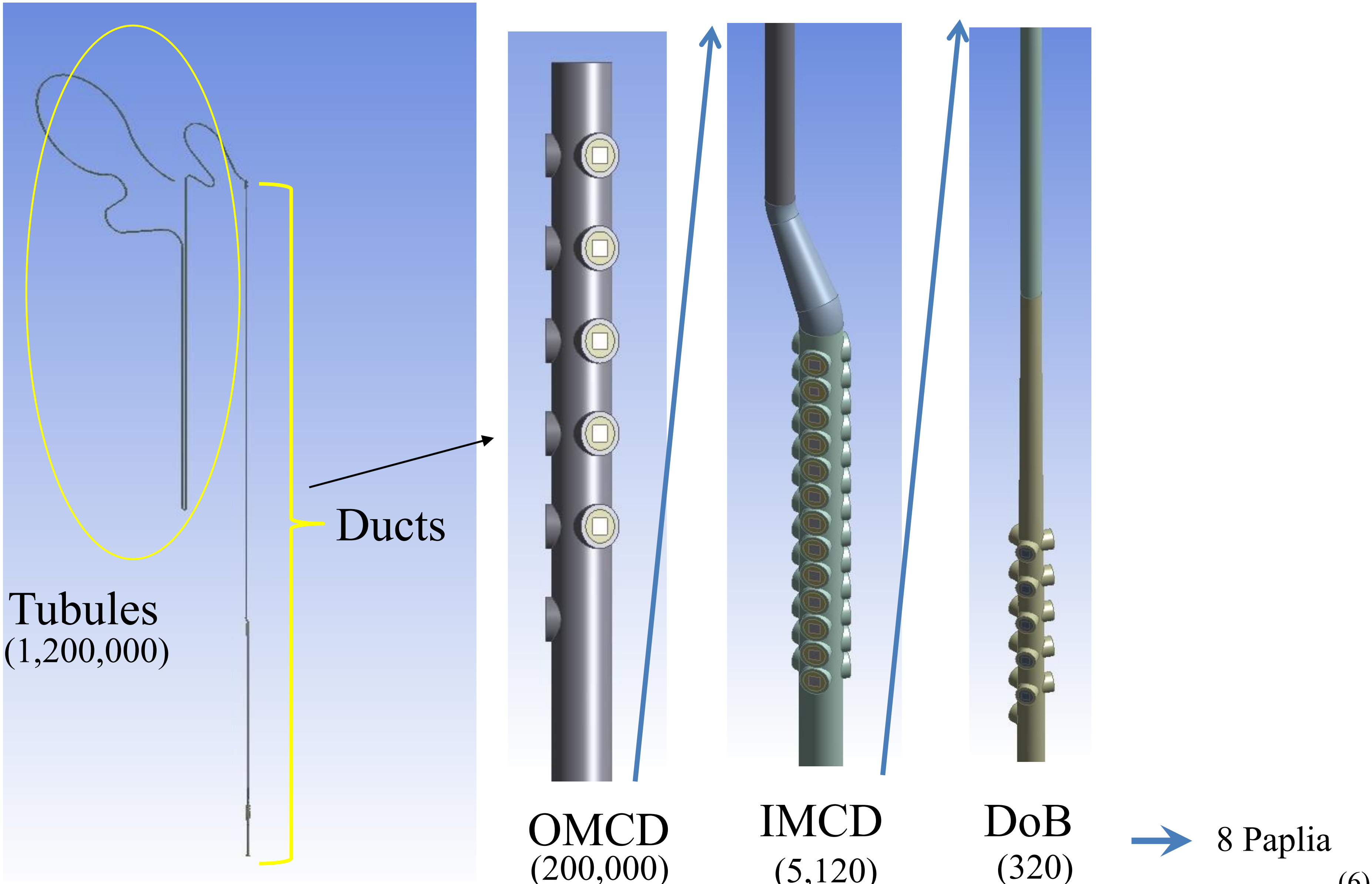


$$G_v = dV/dt$$

ANSYS/FLUENT CFD Code

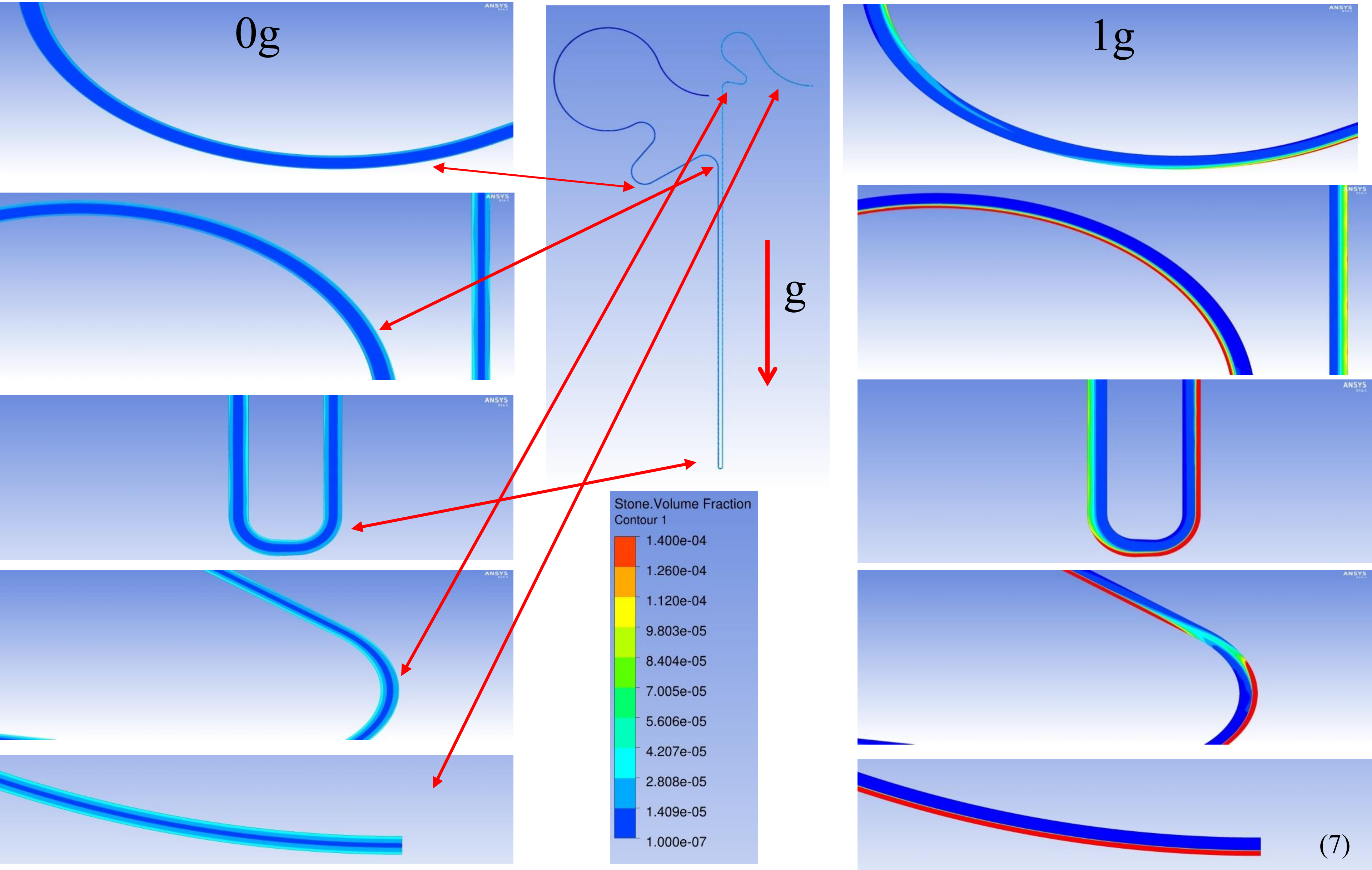
- Momentum Equation
- Species Transport Equation

Realistic 3D Nephron Geometry

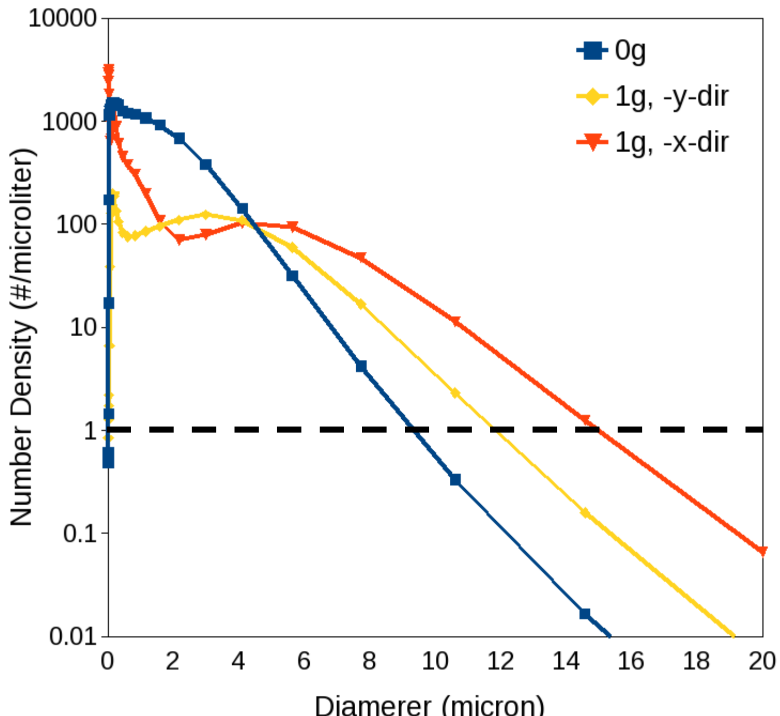


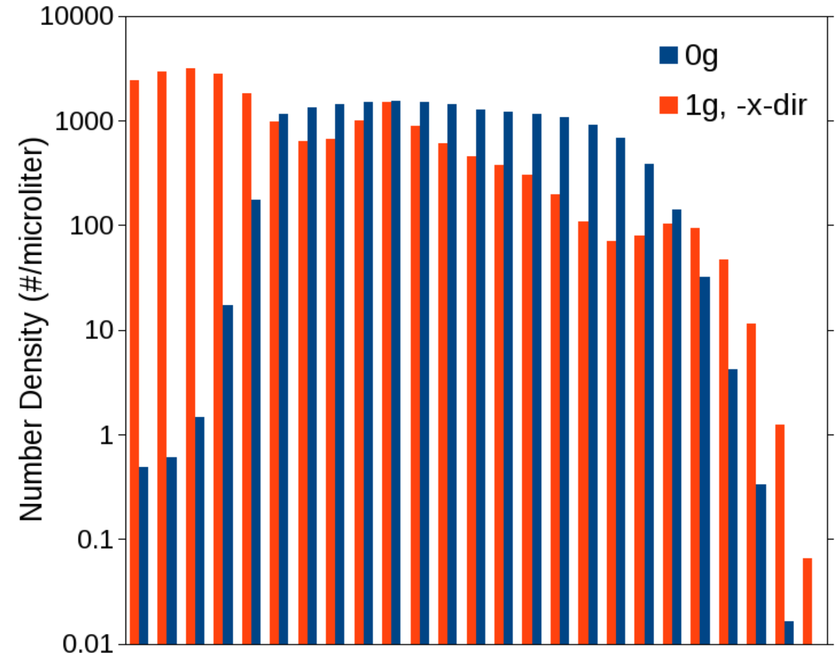
Effect of Gravity on Stone Transit through Nephron

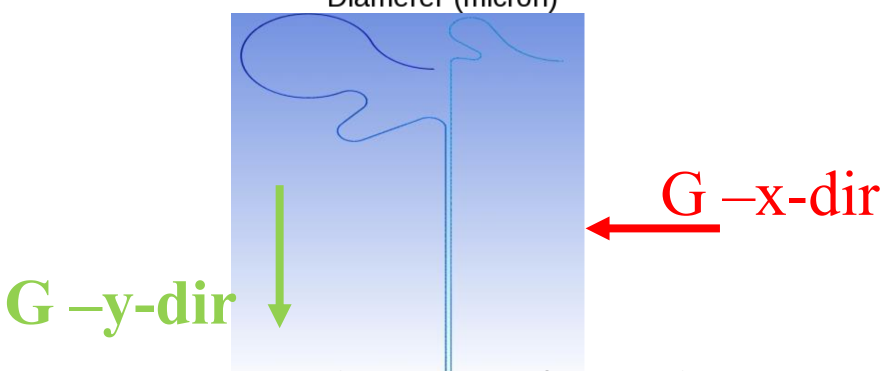
(Kassemi, Griffin & Iskovitz, ICES 2014)

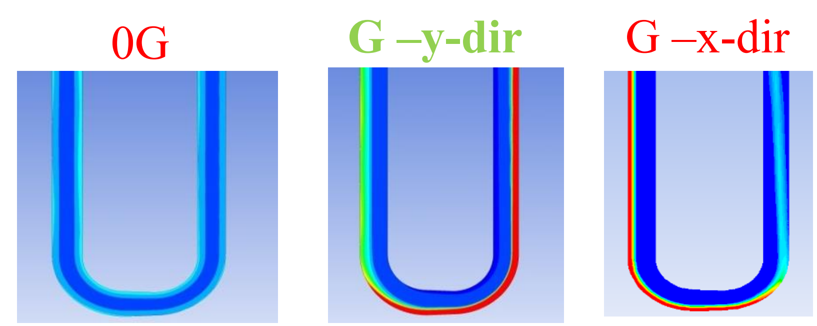


Effect of Gravity on Stone Size Distribution in 3D Nephron Simulations



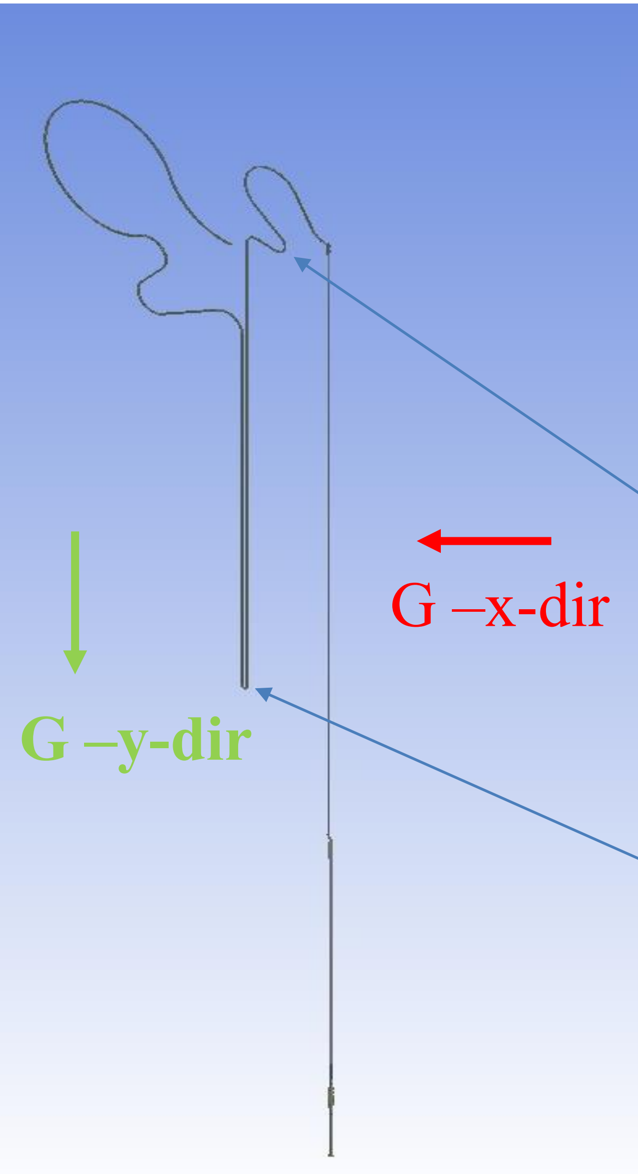




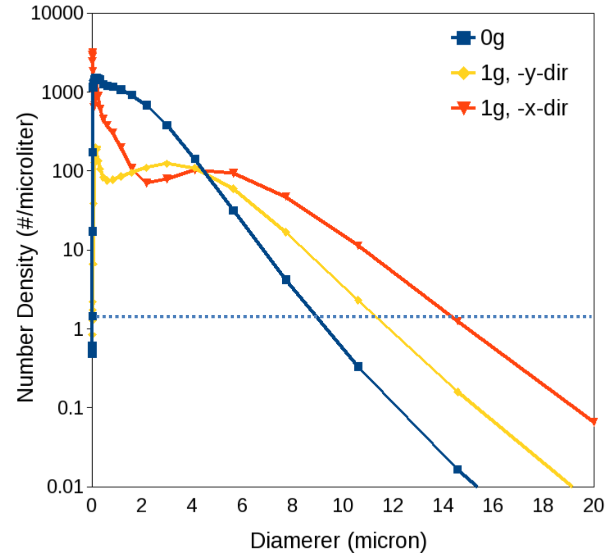


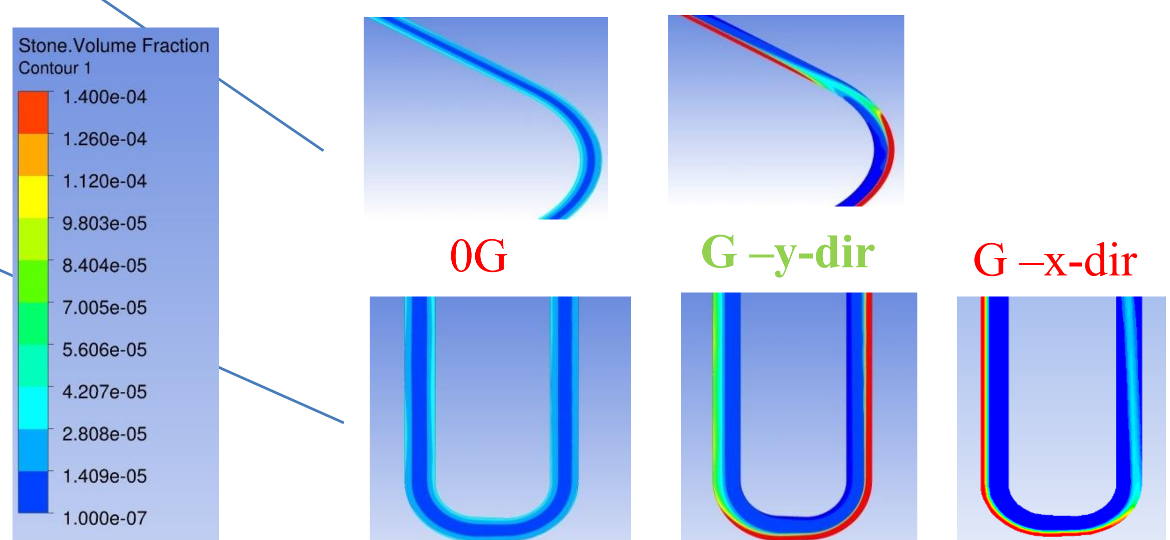
CFD results are confirmed by recent CT scans indicating CaOx Randal plaque formation: Cludin et al, 2012; Williams & McAteer, 2012 ; Kim et al, 2005.

Effect of Gravity & Flow on Stone Transport and Size Distributions in 3D CFD Nephron Simulations

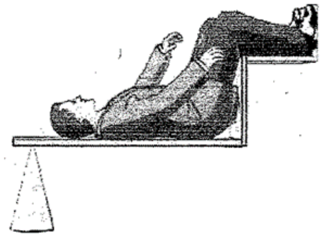


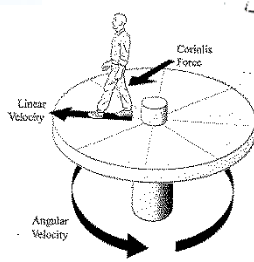
Preliminary 3D CFD results indicate preferential sedimentation of crystals in the vicinity of tubule/duct walls due to intricate coupling effect of flow and gravity resulting in increased propensity for nucleation and/or adherence on certain sections of the nephron tubule/duct wall and development towards critical stone condition in accordance to the Randall plaque hypotheses presented by Evan et al (2010).

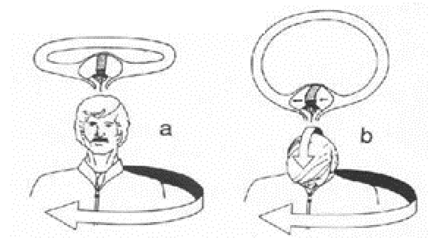




Fluid-Structural-Interactions in the Vestibular System

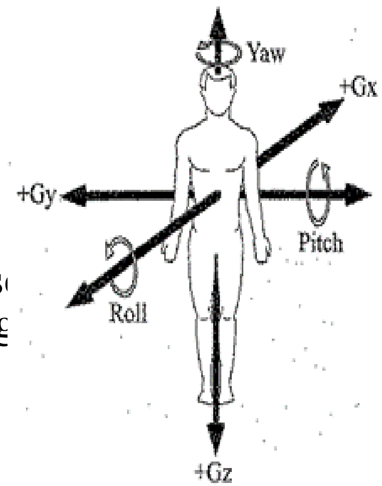






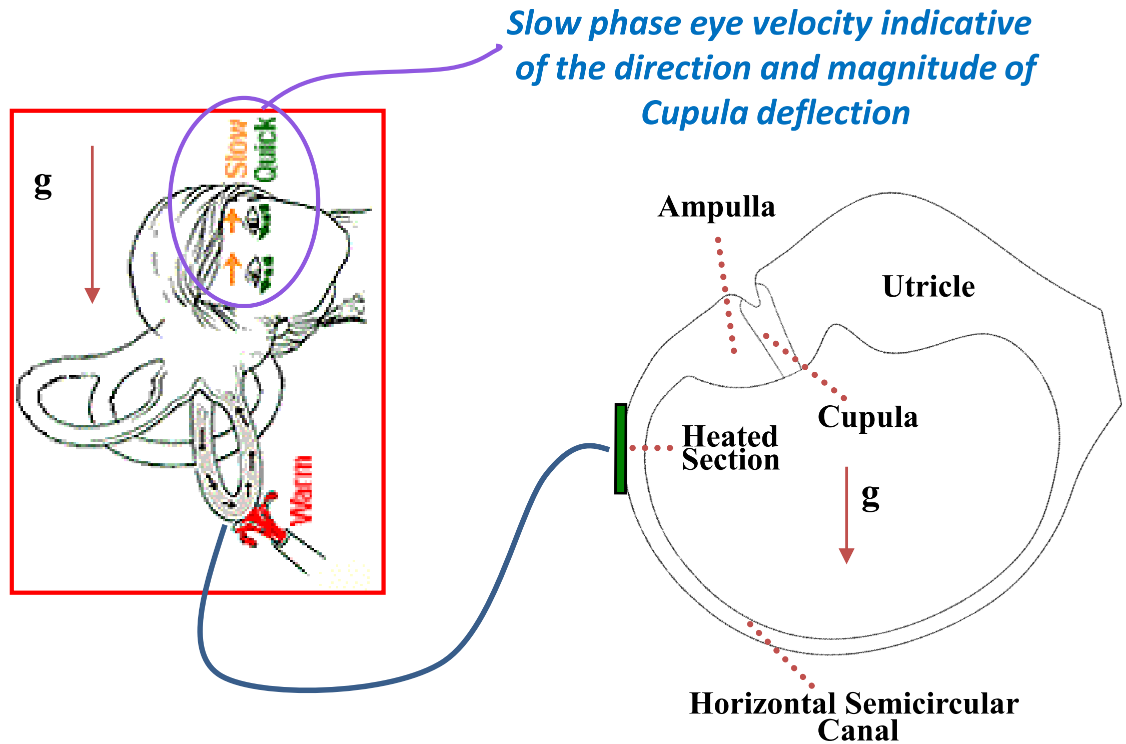
Caloric Stimulation Test

- Space Motion Sickness (SMS): Head movements result in conflicting signals from the Otolith Organs (OO) and the Semicircular Canals (SSC)
- Centrifuge Induced Sickness (CIS): Caused by transition between different gravity levels
- Coriolis Motion Sickness (CMS): caused by head movement/velocity out of the PoR
- Cross-Coupled Angular Acceleration Sickness: caus by head rotations around an axis other than centrifug axis of rotation
- End organ physics (cause) is partially masked by a neurological overhead (adaptation).
- Adaptation effects have to be isolated from end organ effects



Rotational Chair Test

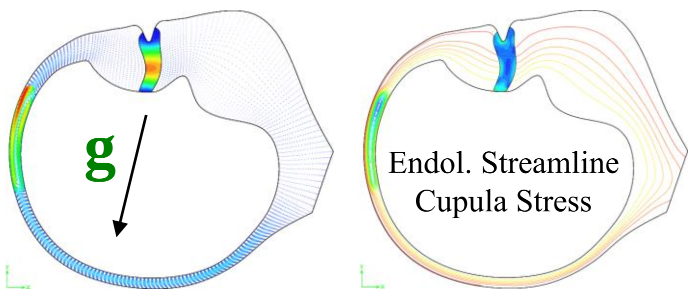
The Microgravity Caloric Irrigation Test (CIT)

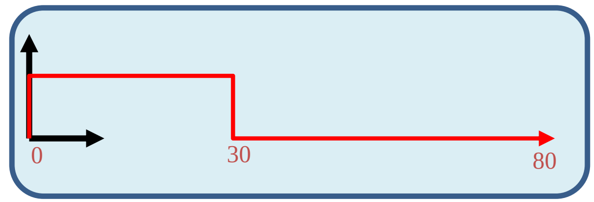


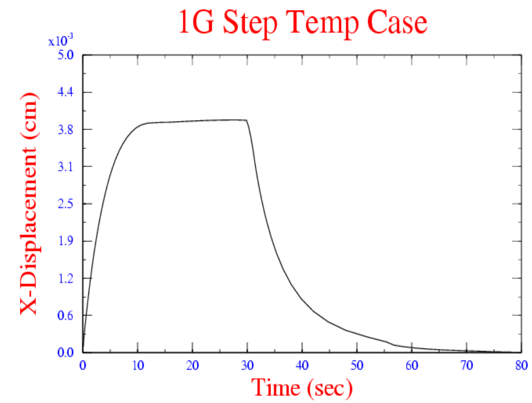
- Barany won the *1906 Noble prize* for his *natural convection* theory explaining CIT
- Skylab microgravity experiment negated Barany' s theory by recording *nystagmus in microgravity*
- Parabolic flight experiments have shown ***negative nystagmus attributed to adaptation or heating of the nerves.(Oostervald, 1985; Stahle, 1990)***

Simulation of 1G & Microgravity Caloric Test in Supine Position *(Kassemi & Oas , JVR 2005)*

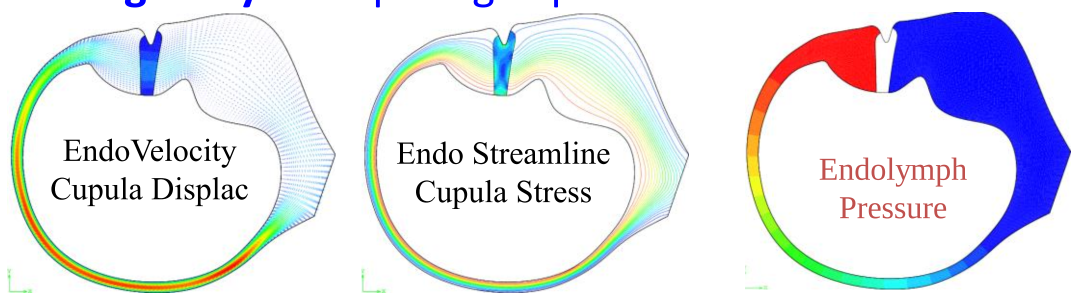
1G: Sustained Natural Convection

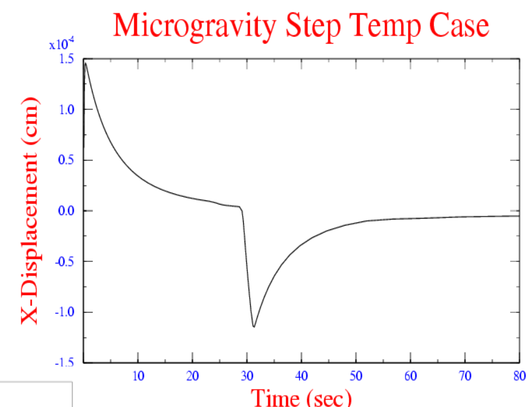




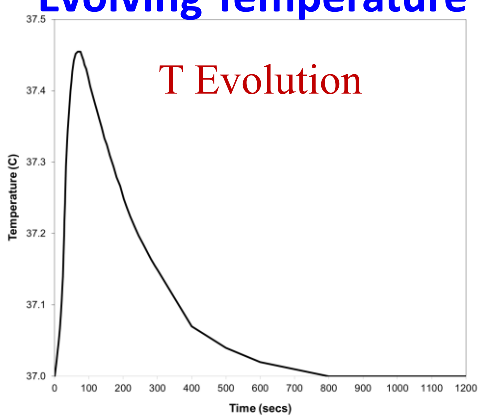


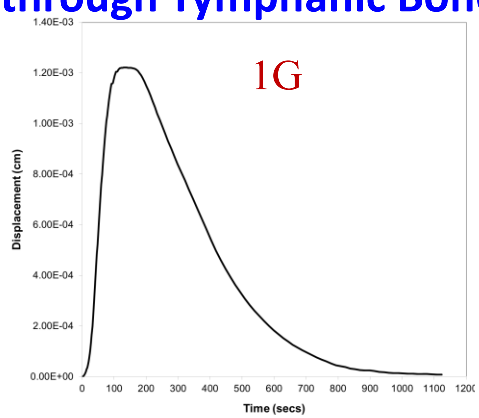
Microgravity: Dissipating Expansive Convection

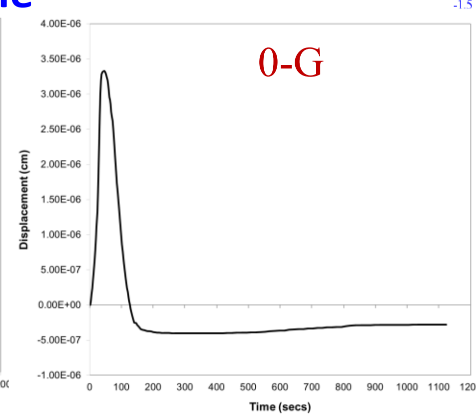




Evolving Temperature through Tymphanic Bone



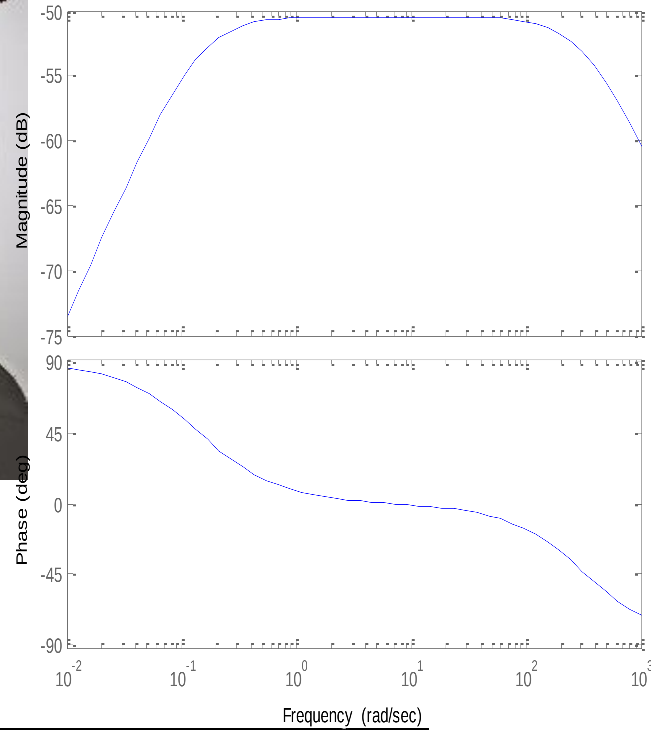


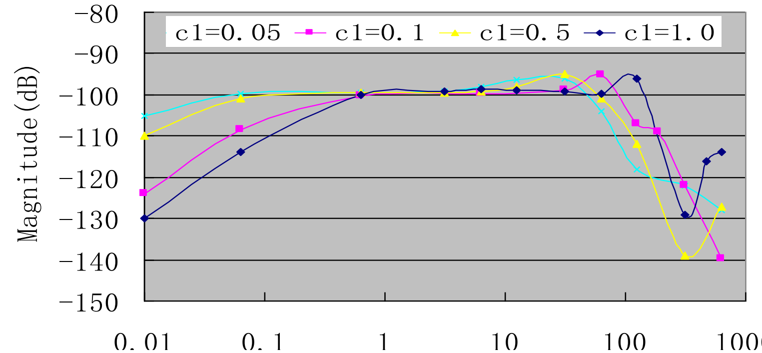


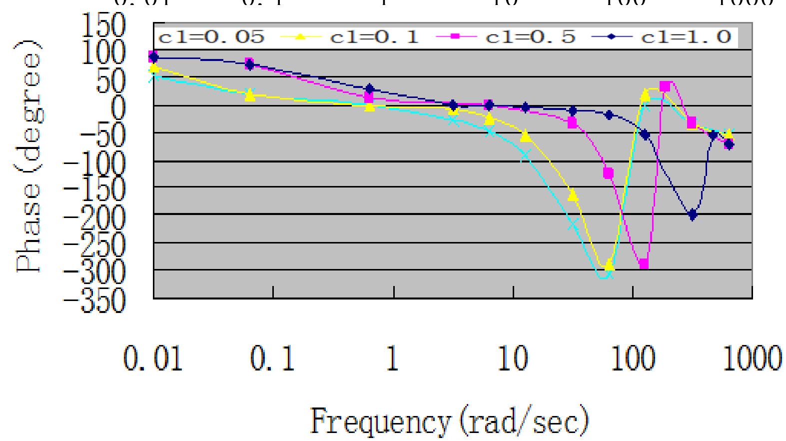
The dynamics of microgravity and 1g cupular displacements are entirely different in both magnitudes and trends. Microgravity case produces reverse nystagmus

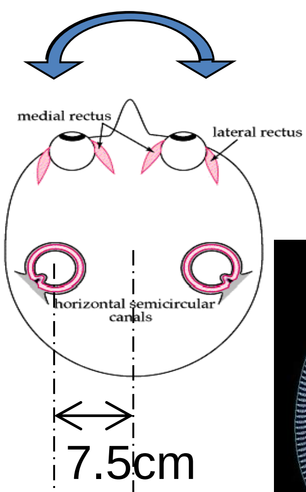
Rotational Chair Test (RCT) – Determining Angular Velocity Treshholds for Cupulae Displacements

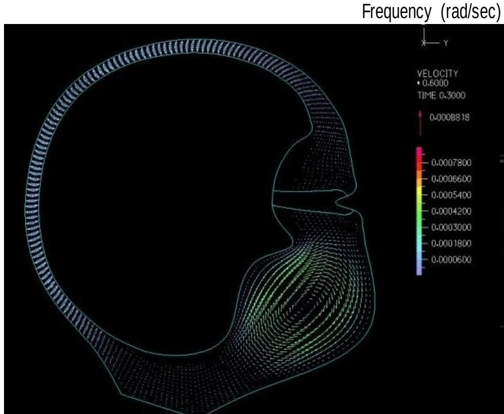
Pendulum Model Results



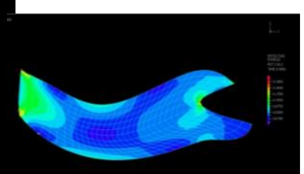


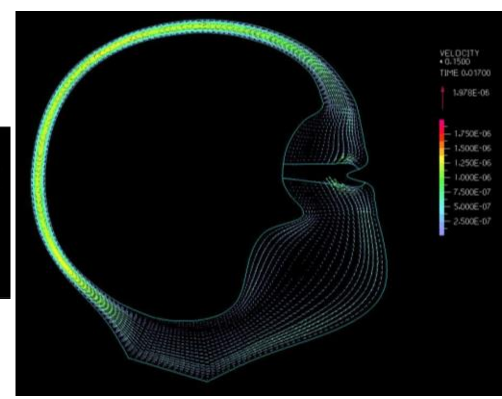




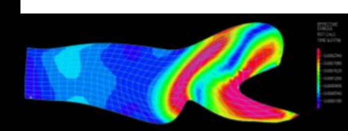


1 rad/s





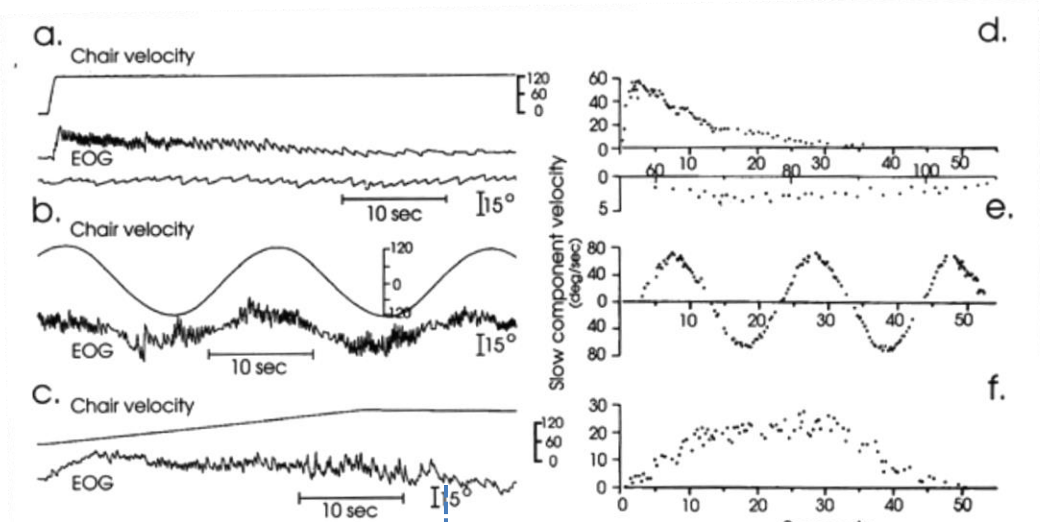
50 rad/s

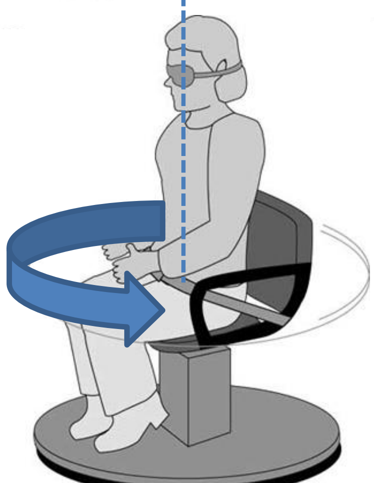


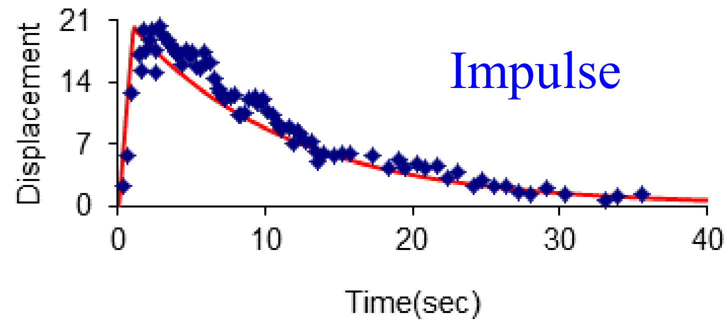
FSI Simulation Rotational Chair Test – Reverse Nystagmus

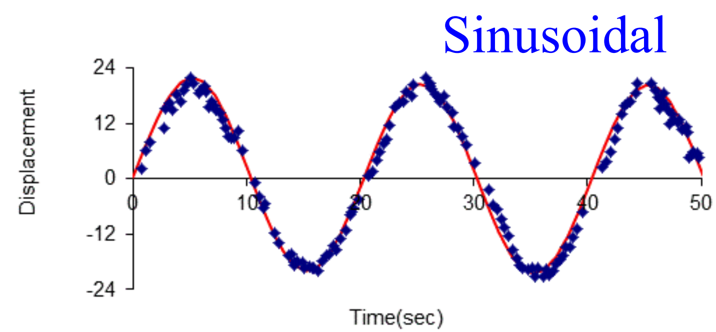
(Axis of rotation at the center of horizontal SCC)

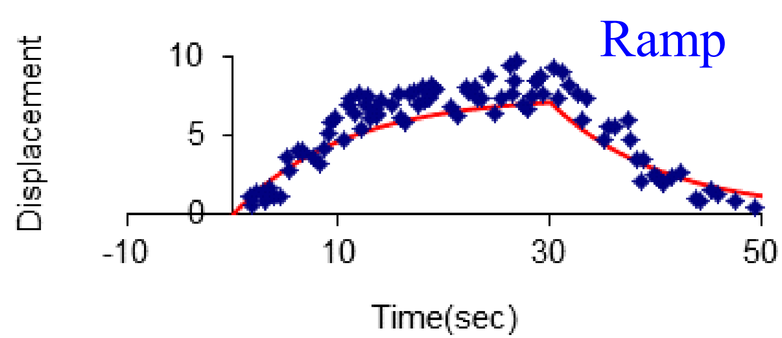
Baloh: *"Clinical Neurophysiology of Vestibular System"*



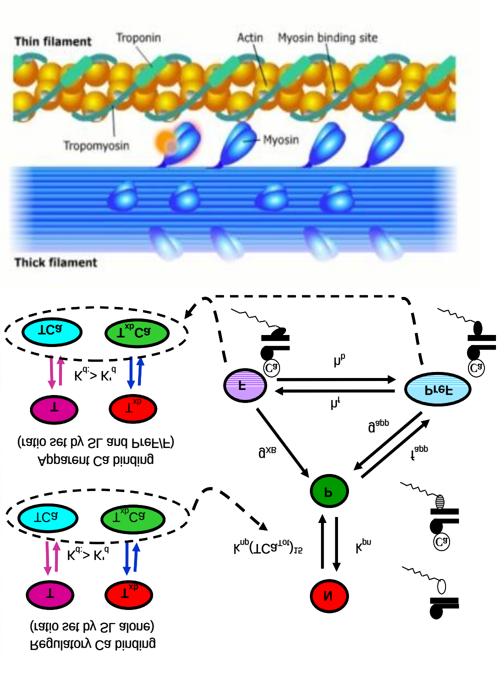


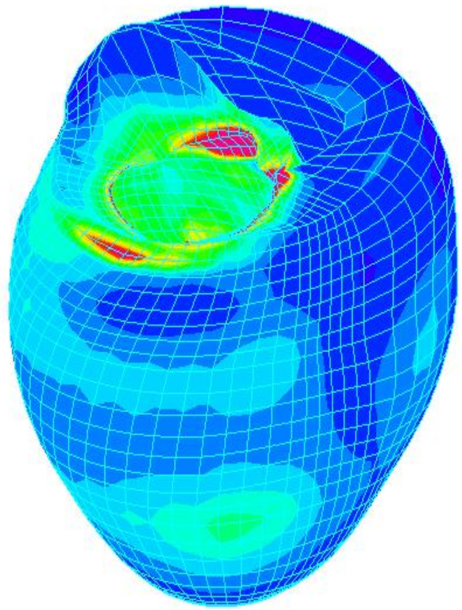


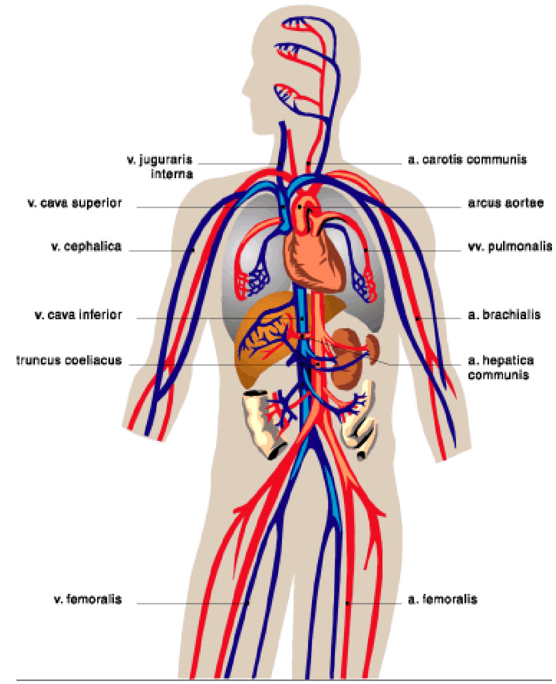




Multi-scale Cardiovascular Analysis







NASA's Space Cardiovascular Risks: ***Atrophy, Arrhythmia, Orthostatic Intolerance***

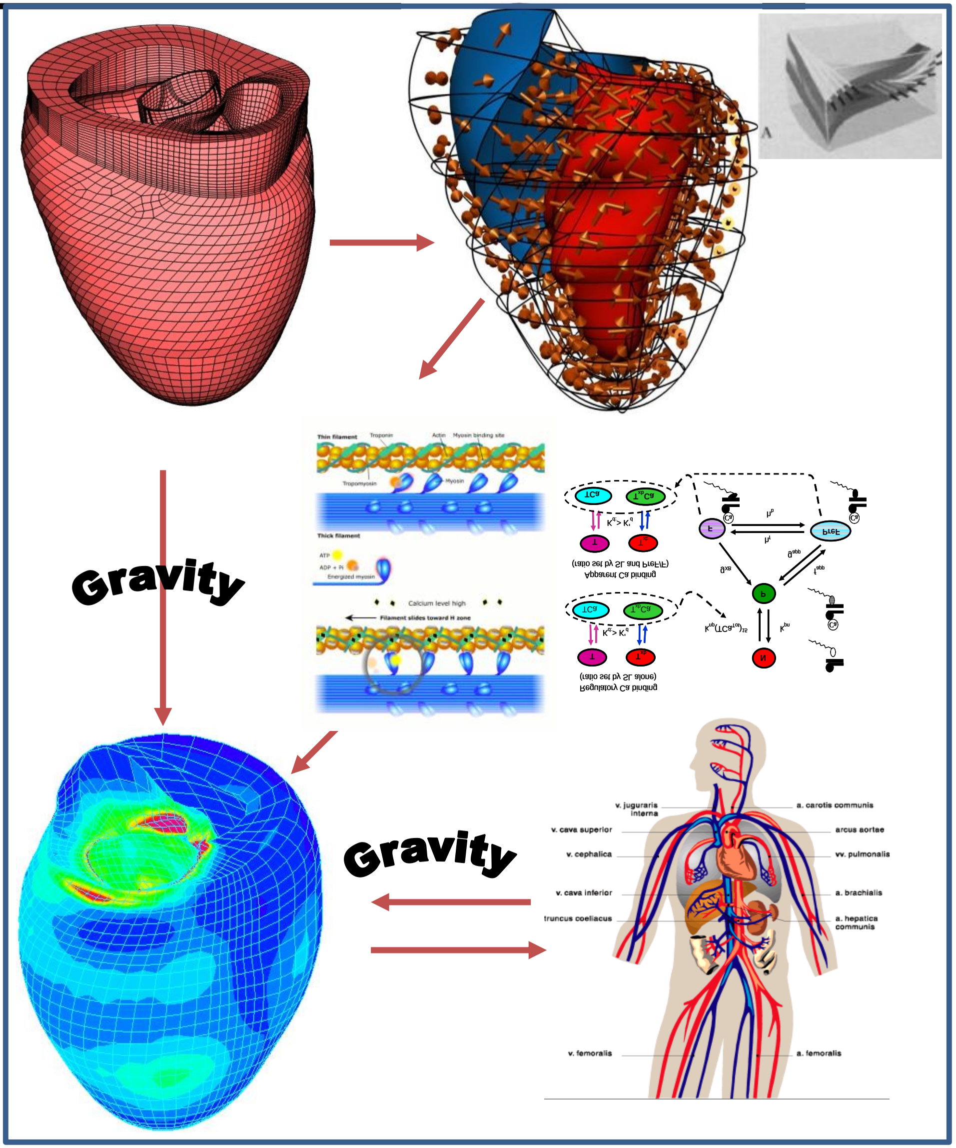
Gravity ➔ Blood Flow & *Shape* Change ➔ Spatial Distribution of *Stress* on the Muscle ➔ Spatial Distribution of *Strain* in the Tissue ➔ Spatial Nature of *Atrophy* & *Arrhythmia* ➔ Heart Performance/Failure

The Components of Multi-scale Heart Model

- ✓ Realistic 3D heart geometry
- ✓ Precise 3D fiber/sheet orientation
- ✓ Nonlinear orthotropic material model for passive behavior
- ✓ Cell level Cross-Bridging Calcium Kinetics models for active contraction
- ✓ An eight compartment lumped model of the cardiovascular system based on a earlier CCF version (Jim Thomas)
- ➢ Couple the lumped cardiovascular and Heart FSI/FE models
- ➢ Validate & Verify the integrated heart model at *local* and *global* levels
- ➢ Describe blood flow using continuum-based non-Newtonian Navier-Stokes analysis

✓ Already Developed

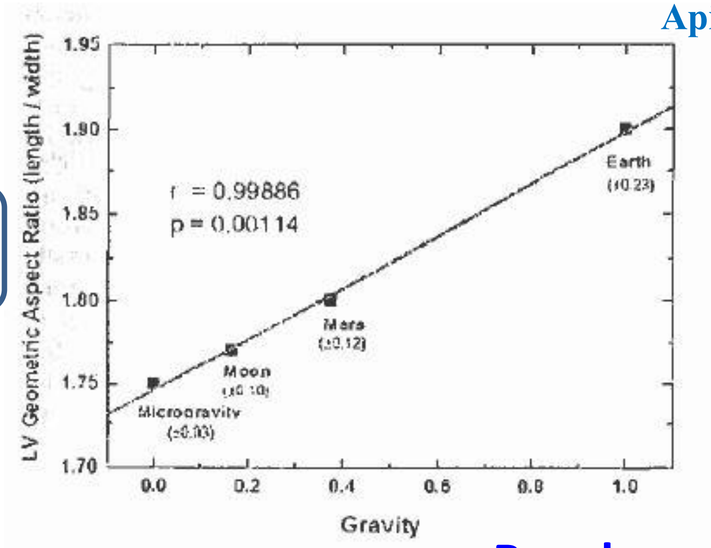
➢ Future Development



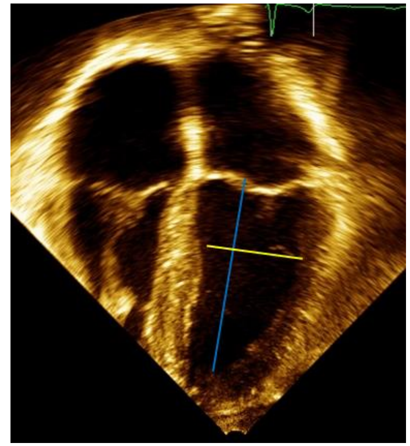
Change in Sphericity of the Heart in Reduced Gravity

Summers et al. (2011)

$$R_i = \frac{H}{W_i}$$

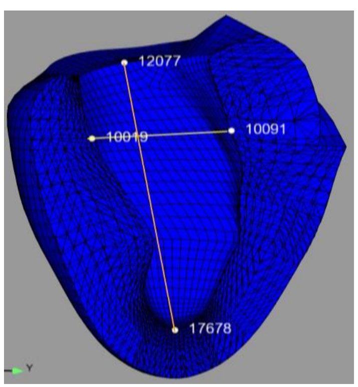


Apical 4-Chamber View of LV



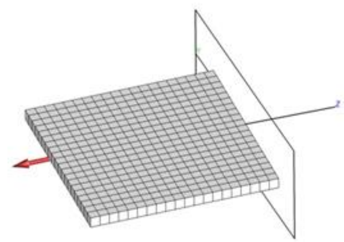
- End diastolic LV dimensions captured with echocardiography
- Six parabolic flights at each gravitational level:
  - Microgravity (20-25s)
  - Moon (30s)
  - Mars (40s)
- Subjects in upright positions
- Ventricular pressures predicted using QSP a physiological simulator

Benchmark Validation Experiments



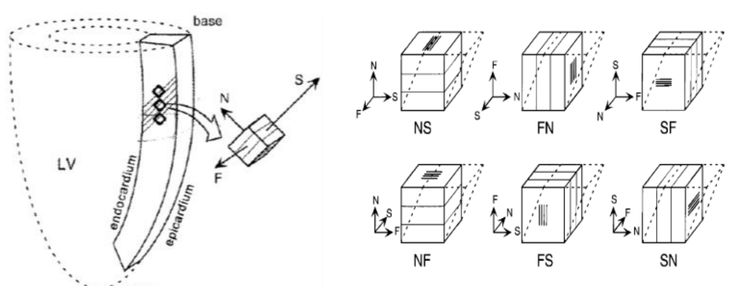
Uniaxial Test

(Demer et. al, 1983)



Shear Tests

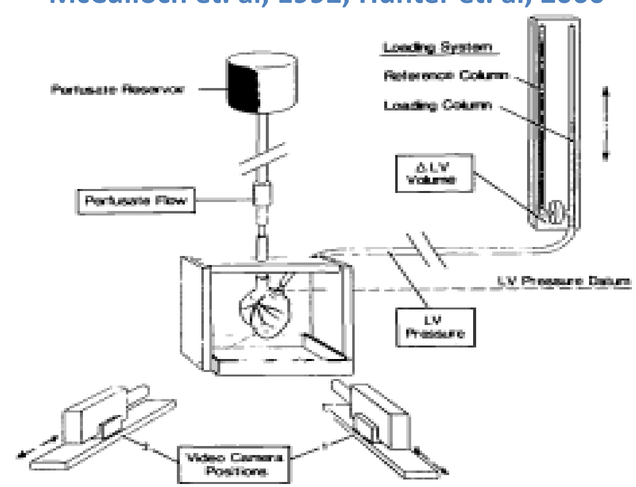
(Dokos et. al, 2002)



Intact Heart

Pressure vs. Volume

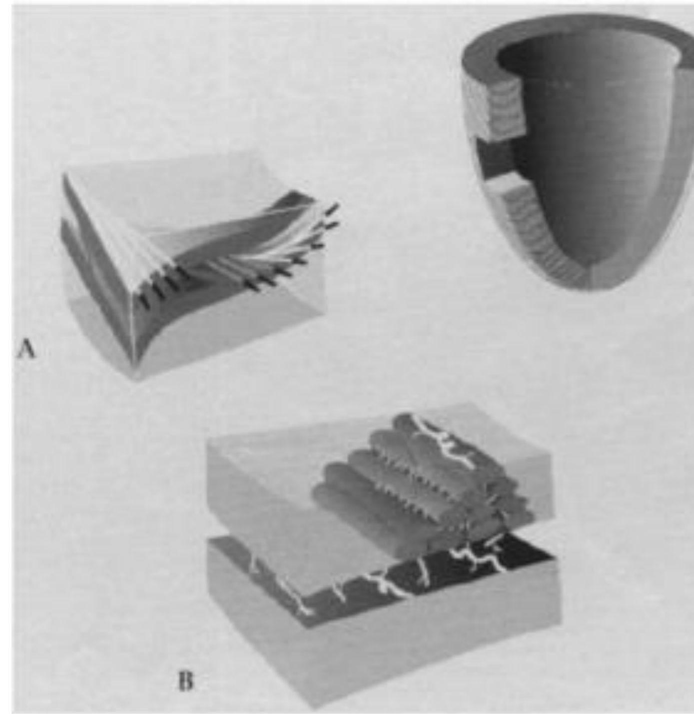
McCulloch et. al, 1992, Hunter et. al, 2000



Nonlinear Hyperelastic Cardiac Tissue Models

Transversely Isotropic Material Model

$$W(J_1, J_4, J_3) = \frac{c_1}{2c_2}\left[e^{c_2(J_1-3)^2} - 1\right] + \frac{k_1}{2k_2}\left[e^{k_2(J_4-1)^2} - 1\right] + \frac{1}{2}\kappa(J_3-1)^2$$



Orthotropic Material Model

$$W(J_1, J_f, J_s, J_{fs}, J_3) =$$

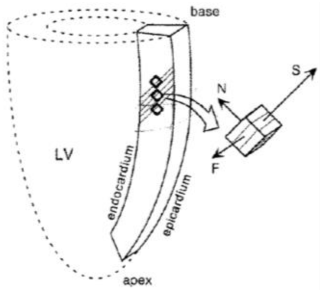
$$\frac{c_{m1}}{2c_{m2}}\left[e^{c_{m2}(J_1-3)} - 1\right] + \frac{k_{f1}}{2k_{f2}}\left[e^{k_{f2}(J_f-1)^2} - 1\right] + \frac{k_{s1}}{2k_{s2}}\left[e^{k_{s2}(Js-1)^2} - 1\right] + \frac{k_{fs1}}{2k_{fs2}}\left[e^{k_{fs2}(J_{fs})^2} - 1\right] + \frac{1}{2}\kappa(J_3-1)^2$$

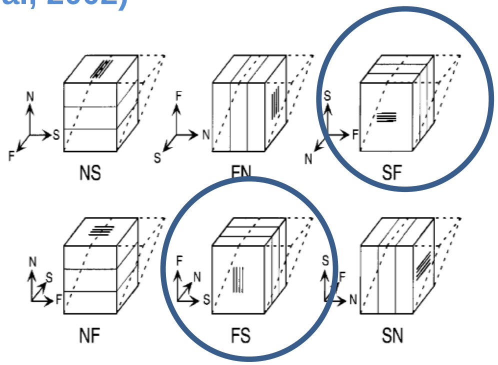
Validation of Transversely Isotropic Cardiac Tissue model

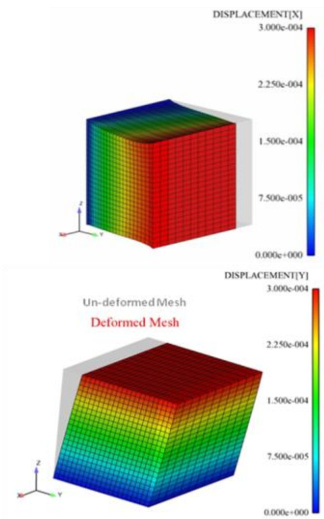
$$W(J_1, J_4, J_3) = \frac{c_1}{2c_2}\left[e^{c_2(J_1-3)^2} - 1\right] + \frac{k_1}{2k_2}\left[e^{k_2(J_4-1)^2} - 1\right] + \frac{1}{2}\kappa(J_3-1)^2$$

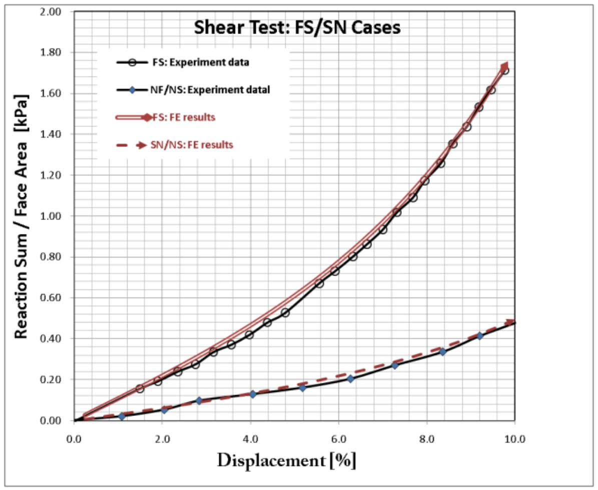
Shear Tests

(Dokos et. al, 2002)









Intact Heart

Pressure vs. Volume

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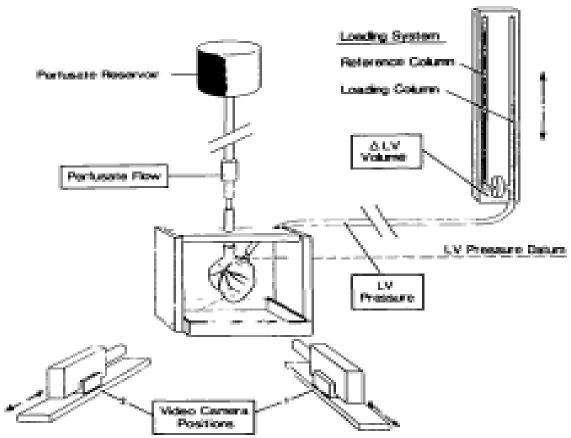
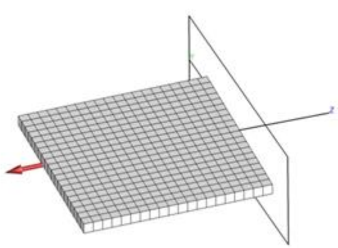
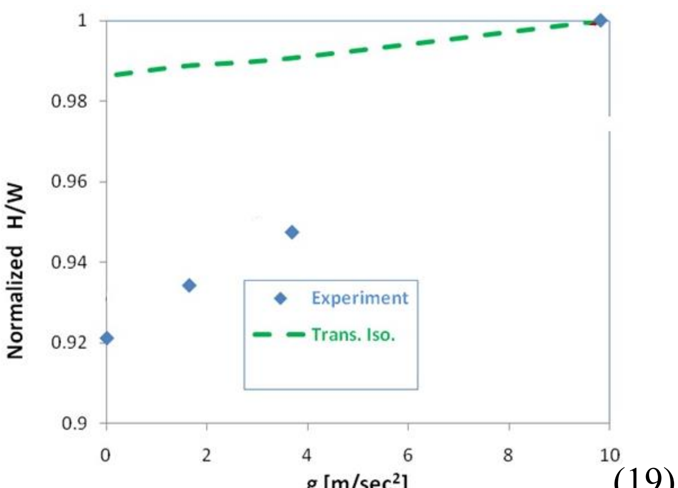


Uniaxial Test

(Demer et. al, 1983)



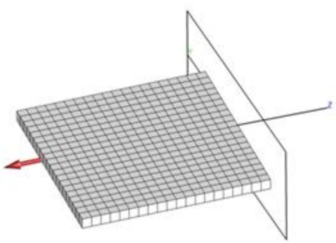


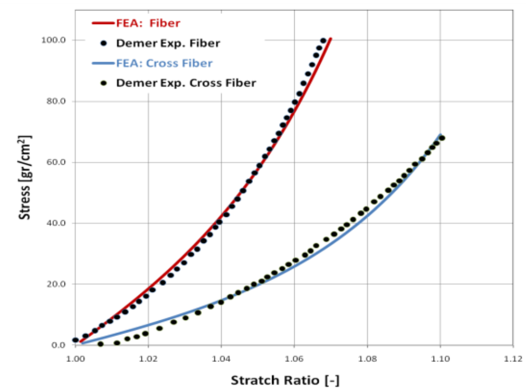
Local & *Global* Validation of Orthotropic Cardiac Tissue model

$$W(J_1, J_f, J_s, J_{fs}, J_3) =$$

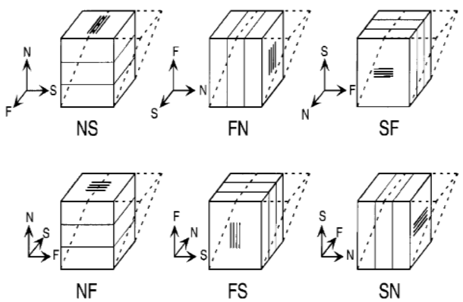
$$\frac{c_{m1}}{2c_{m2}}\left[e^{c_{m2}(J_1-3)}-1\right]+\frac{k_{f1}}{2k_{f2}}\left[e^{k_{f2}(J_f-1)^2}-1\right]+\frac{k_{s1}}{2k_{s2}}\left[e^{k_{s2}(Js-1)^2}-1\right]+\frac{k_{fs1}}{2k_{fs2}}\left[e^{k_{fs2}(J_{fs})^2}-1\right]+\frac{1}{2}\kappa(J_3-1)^2$$

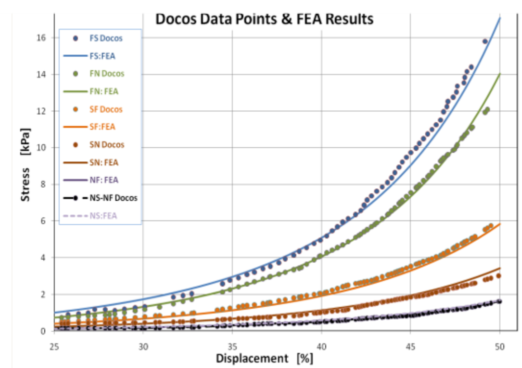
c_{m1} [kPa]	c_{m2} [-]	k_{f1} [kPa]	k_{f2} [-]	k_{s1} [kPa]	k_{s2} [-]	k_{fs1} [kPa]	k_{fs2} [-]
0.28	10.8	18.472	15.819	3.5	11	0.3	11



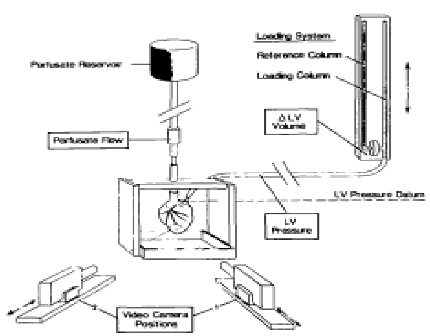


Uniaxial Test
(Demer et. al, 1983)

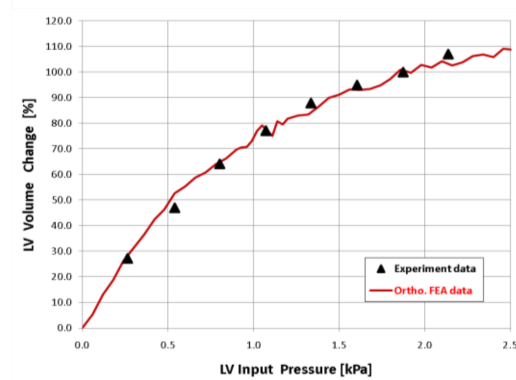




Shear Tests
(Dokos et. al, 2002)



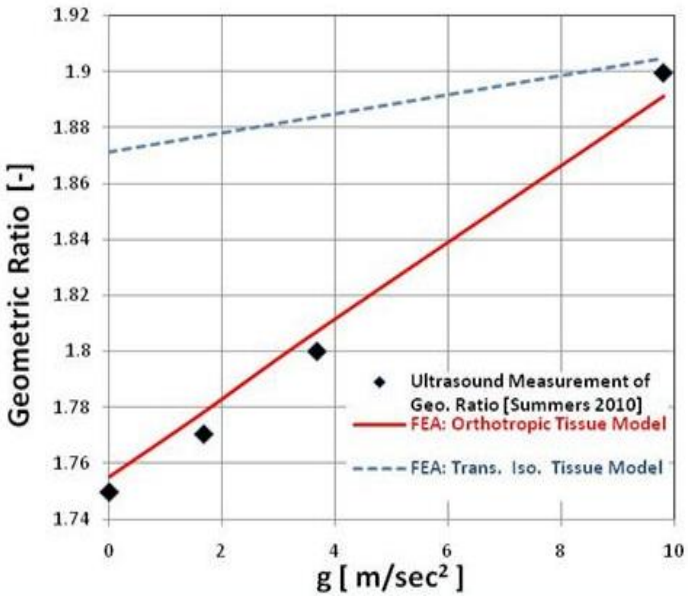
Intact Heart
Pressure vs. Volume
McCulloch et. al, 1992,
Hunter et. al, 2000

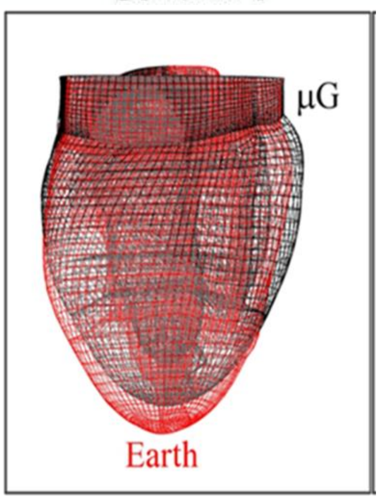


Prediction of Heart Sphericity & Stress in Reduced Gravity

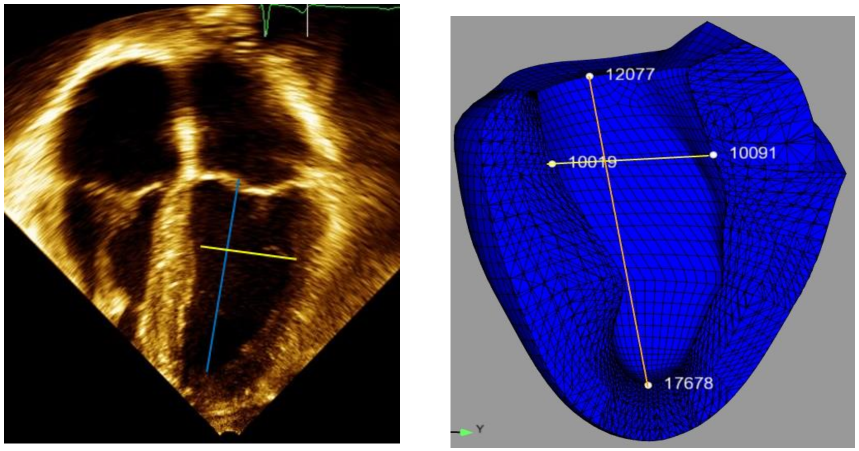
(Iskovitz & Kassemi, JBME 2013)

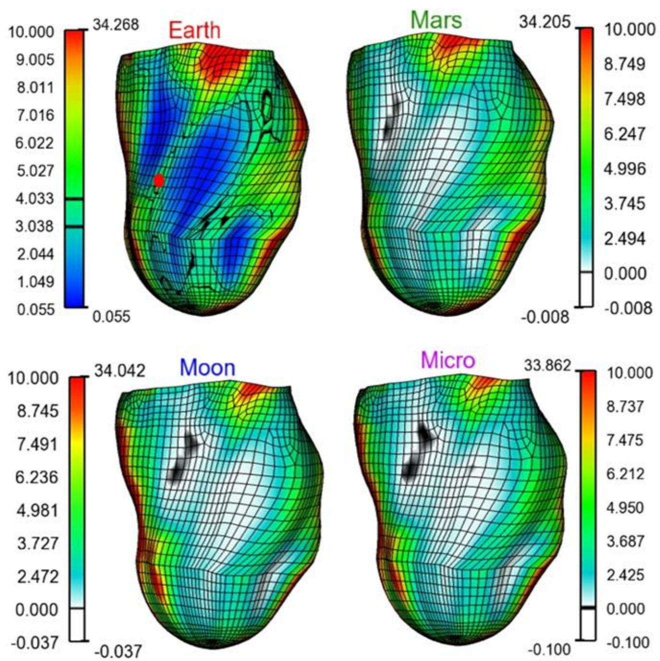
$$R_i = \frac{H}{W_i}$$





Ultrasound Images: Apical 4-Chamber View of LV





- May et al 2014: 9% sphericity increase in microgravity based on ISS astronaut data

Overview of Models

Renal Stone Growth & Transport in 1g and 0g: PBE & Multiphase Fluid Models

- Lumped PBE System Model: Effects of growth & agglomeration, assessment of different countermeasure
- 3D Spatial CFD-PBE Nephron Model: Effect of gravity on stone transport

Impact of weightlessness on cardiac structure: Multi-scale Computational Structural & Tissue Material Models

- Local Validation
- Global Validation
- Microgravity Prediction of cardiac shape change

Interactions between endolymph and cupula in the inner ear in 1g and 0g using Fluid-Structural Interaction Models ➔ Insight into the vestibular dynamics at the sensor level

- Delineating the response of the vestibular system by isolating the effects of the end organ physics (cause) from neurological overhead (adaptation)

Impact of Artificial Gravity: *Protective* or *Detrimental*?!!

Will daily AG treatment enhance the risk of renal stone formation:

Zwarf et al (JAP, 2008) - *Effect of 21 days bed rest with and without AG:*

- Calcium excretion remained relatively unchanged and subject to AG forces

How does the predominant gravitational field affect vestibular response to AG treatment on earth.

- Determine, at sensor-level, the difference/correspondence between vestibular responses to head movements that cause CMS in the AG environments in Space and on Earth to ensure protocols developed in 1g will be effective in microgravity and partial-g
- Bring clarity to the root-causes of CMS and CIS and how they can be countered by isolating the role played by end-organ physics (root-cause) from adaptation effects (response)

Will daily applications of AG result in cardiac shape change and/or remodeling:

- Both European and Japanese have plans to capture heart shape change during centrifuge operations. Computational models can capture the shape change but are also **the only means of predicting the associated changes in the cardiac stress field** during centrifuge operations that may be the instigator for cardiac remodeling
- Models can predict the effect of coriolis forces and gravity gradients on blood flow and blood vessel shape changes in 1G, microgravity, and partial gravity centrifuge operations.