Aging Impact on Brain Biomechanics with Applications to Hydrocephalus

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Brain Neuro-Mechanics Workshop

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MATHEMATICS

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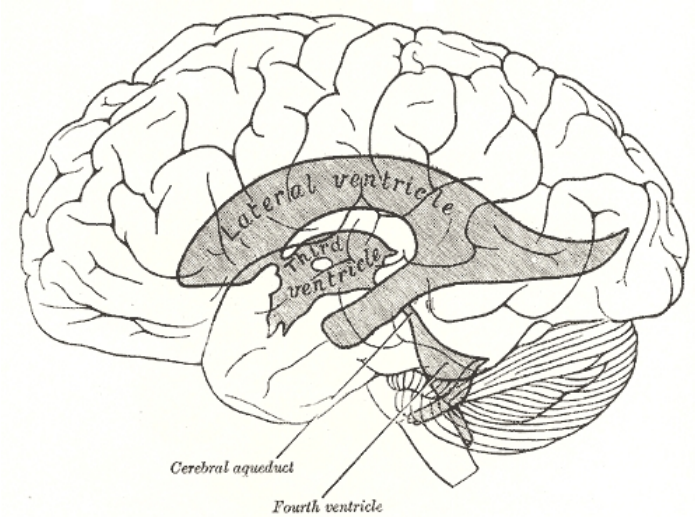
Outline

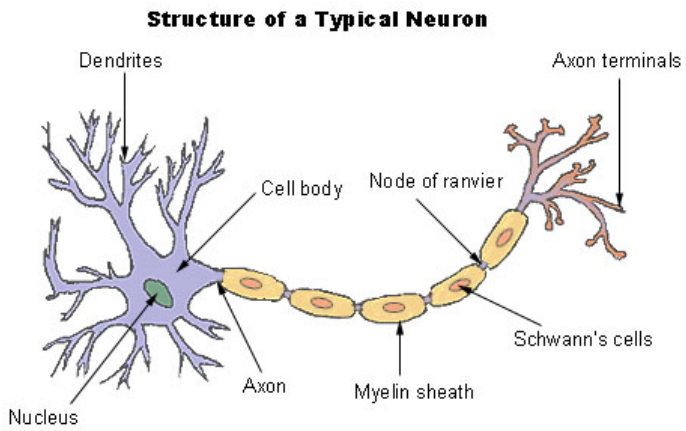
1. Brain Tissue Structure, Growth, and Aging
2. Age-Dependent Mechanical Parameters
3. Analysis of the Pulsation-Damage Hypothesis for both Infant and Adult Hydrocephalus
4. Results, Conclusions, and Future Work



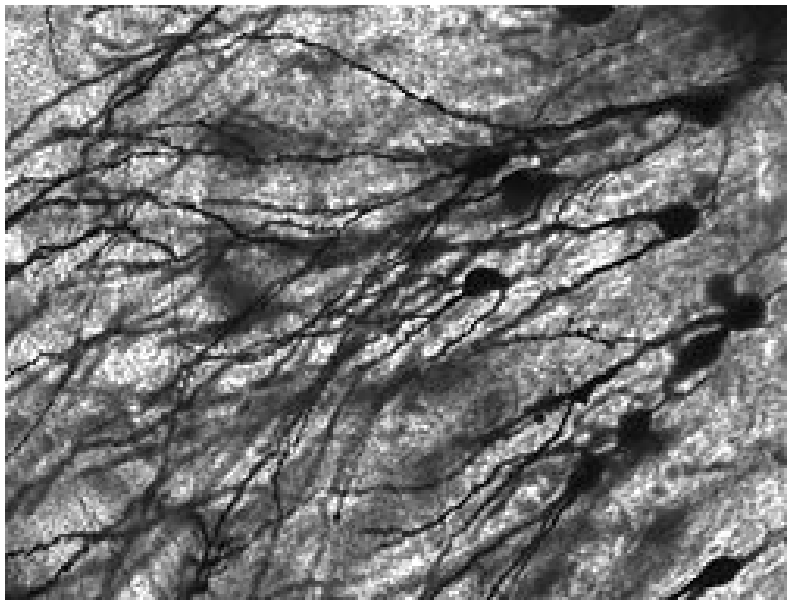
[wikipedia.org, 2008]

Brain Tissue Composition

- neurons
  - the human brain has 10 billion neurons
  - each neuron connects to a thousand neighboring neurons
  - one cell body, one axon, and one or more dendrites
- glial cells
  - provide physical and chemical support to neurons
- blood vessels
- extracellular matrix



[web-books.com, 2010]



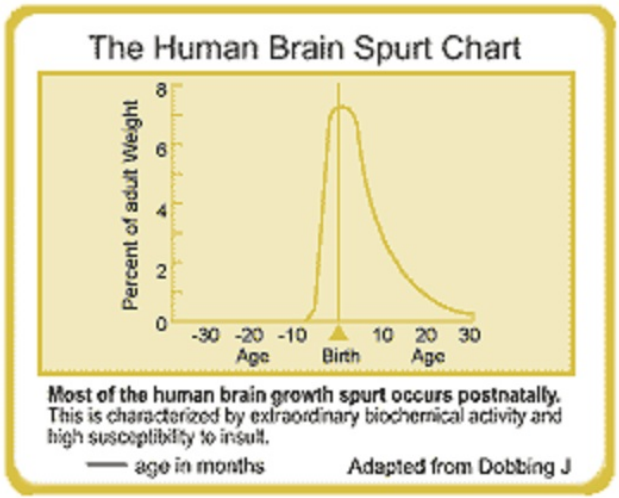
[wikipedia.org/wiki/Neuron]

Aging Effects: The Brain Growth Spurt

- period of extraordinary biochemical activity
  - starts four months after conception
  - ends around two years of age
- un-fused skull plates allow for rapid growth of the brain
- brain components synthesize from nutrients temporarily allowed to cross the blood-brain-barrier

During this time there is a significant

- increase in DNA-P content (measure of total cell number)
- increase in lipid content (due to myelination)
- decrease in water content



Aging Effects: Old-Age Degeneration

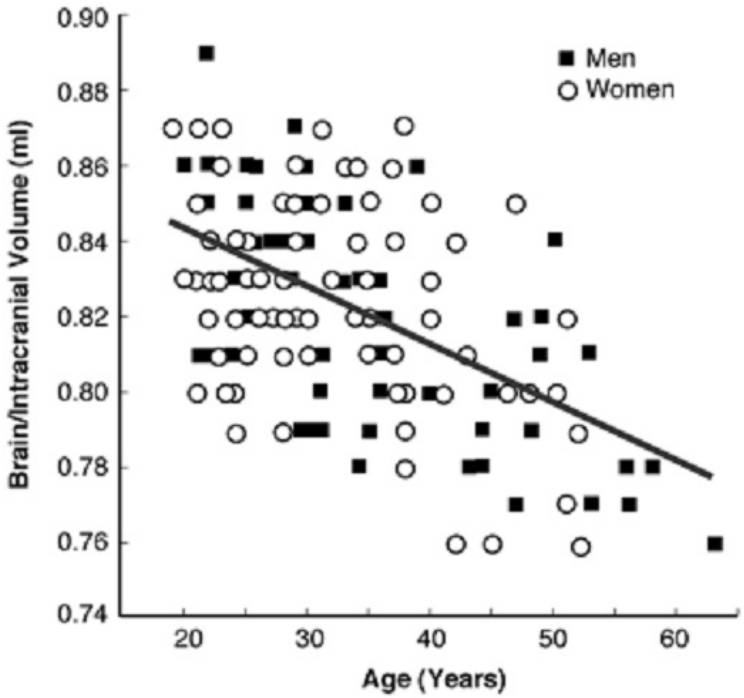
Normal aging effects include

- flattening and calcification of the choroid plexus epithelium
- thickening of epithelial basement membrane

which may reduce CSF production, ion transport, and fluid filtration

In Normal Pressure Hydrocephalus,

- resistance to CSF flow and ICP pulsations increase with age
- CSF production and cranial compliance decrease with age



[D.W. Hommer, 2001]

Brain Age is Important

- From the incredible growth and development that occurs at infancy to the degeneration that occurs with advancing age, the mechanical properties of human brain tissue must be age-dependent.
- Unfortunately, the infant brain is usually treated as a miniature adult brain.
- When mechanical parameters are required for infants, for example in determining head impact thresholds, they are usually inferred from the adult parameters.

Conclusion

For hydrocephalus, where the unfused skull makes the infant and adult cases differ so drastically in symptoms and treatment outcomes, age-appropriate mechanical parameters should be used.

Example: Rotational Acceleration Injury Threshold

- Due to the difficulty with acquiring human experimental data, mechanical properties are often inferred from animal experiments.
- When infant properties are needed they are determined from a brain-mass scaling relationship.

The relation for determining the rotational acceleration limit before injury is

$$\theta''_p = \theta''_m \left(\frac{M_m}{M_p} \right)^{\frac{2}{3}} \tag{1}$$

where p is the prototype (human infant or adult), m is the experimental model (usually a primate), θ is the angle of rotation, and M is the brain mass [Ommaya *et al.* 1967].

Example: Rotational Acceleration Injury Threshold

$$\theta''_p = \theta''_m \left(\frac{M_m}{M_p} \right)^{\frac{2}{3}}$$

This relation

- assumes that the prototype and model material parameters such as density and shear modulus are identical,
- assumes that the brain tissue is a linear elastic material,
- it does not consider the effects of the unfused sutures of the infant skull, and
- it predicts that infant brain can withstand larger rotational accelerations before injury onset than adult brains.

Age-Dependent Data

Recently, age-dependent data has been experimentally determined

in vitro Thibault and Margulies [1998] used excised infant and adult porcine cerebrum to determine the age-dependence of brain tissue (19 data points from 20 to 200 Hz).

in vivo Sack et al. [2009] used magnetic resonance elastography to determine the age-dependence of brain tissue on patients ranging from 18 to 88 years (4 data points from 25 to 62.5 Hz).

Frequency [Hz]	**20**	**25**	**30**	**37.5**	**40**	**50**	**60**	**62.5**
Infant [TM] G' [Pa]	758		674		747	800	842	
Adult [TM] G' [Pa]	1200		1053		1095	1200	1263	
Adult [S] G' [Pa]		1100		1310		1520		2010
Infant [TM] G'' [Pa]	210		300		330	430	460	
Adult [TM] G'' [Pa]	350		460		600	740	860	
Adult [S] G'' [Pa]		480		570		600		800

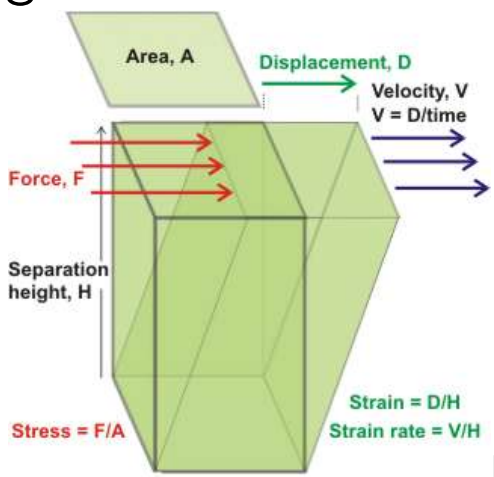
The Shear Complex Modulus

- describes the behaviour of a viscoelastic material under oscillatory shear strains

Under a strain $\epsilon(t) = \epsilon_0 e^{i\omega t}$, the long-time stress response of a viscoelastic material is $\sigma(t) = G^*(i\omega)\epsilon_0 e^{i\omega t}$, where G^* is the complex modulus. Separating real and imaginary parts gives

$$G^*(i\omega) = G'(\omega) + iG''(\omega) \tag{2}$$

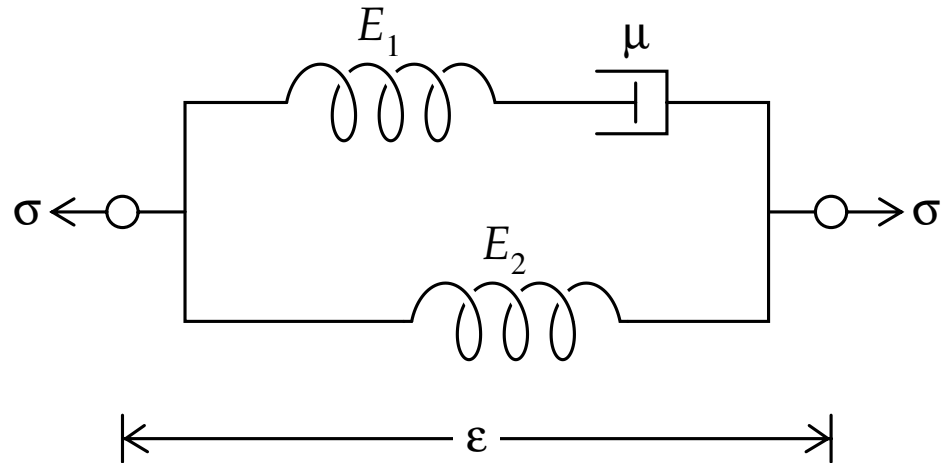
where G' is the storage modulus and G'' is the loss modulus.



[Chaplin, 2010]

The Fractional Zener Viscoelastic Model

- Davis et al. [2006] showed that the fractional Zener Viscoelastic model accurately describes the creep and relaxation behaviour of brain tissue.
- The mechanical analogue of the model is



- The strain rate ($\dot{\epsilon}$) is replaced by the fractional derivative of the strain ($D^{\alpha}\epsilon$), where α is the order of the derivative $0 \leq \alpha \leq 1$.

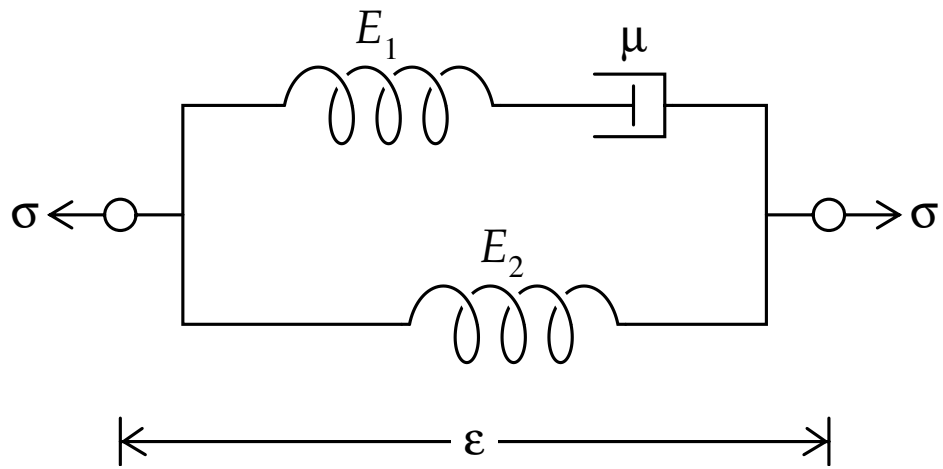
Fractional Zener Constitutive Equation

The relationship between stress and strain for a fractional Zener material is given by

$$\sigma + \tau^{\alpha} D^{\alpha} \sigma = E_{\infty} \epsilon + E_0 \tau^{\alpha} D^{\alpha} \epsilon, \tag{3}$$

where

- $\tau = \frac{\mu}{E_1}$ is the relaxation time,
- $E_0 = E_1 + E_2$ is the initial elastic modulus, and
- $E_\infty = E_2$ is the steady-state elastic modulus.



Fractional Zener Complex Modulus

We will use this model to fit the age-dependent experimental data, via the storage modulus

$$G'(\omega) = \frac{E_\infty + (E_0 + E_\infty)\tau^\alpha \omega^\alpha \cos\left(\frac{\alpha\pi}{2}\right) + E_0 \tau^{2\alpha}\omega^{2\alpha}}{1 + 2\tau^\alpha \omega^\alpha \cos\left(\frac{\alpha\pi}{2}\right) + \tau^{2\alpha}\omega^{2\alpha}}, \quad (4)$$

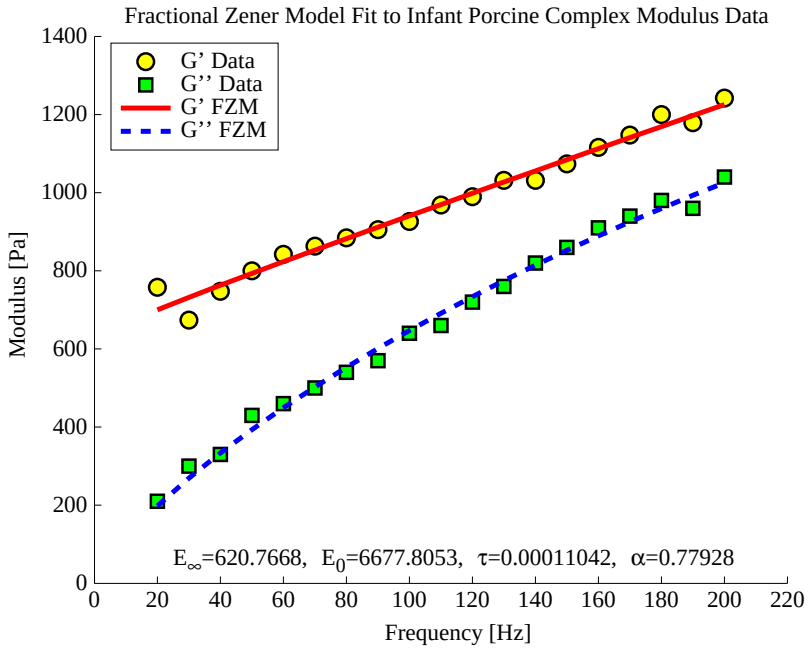
and the loss modulus

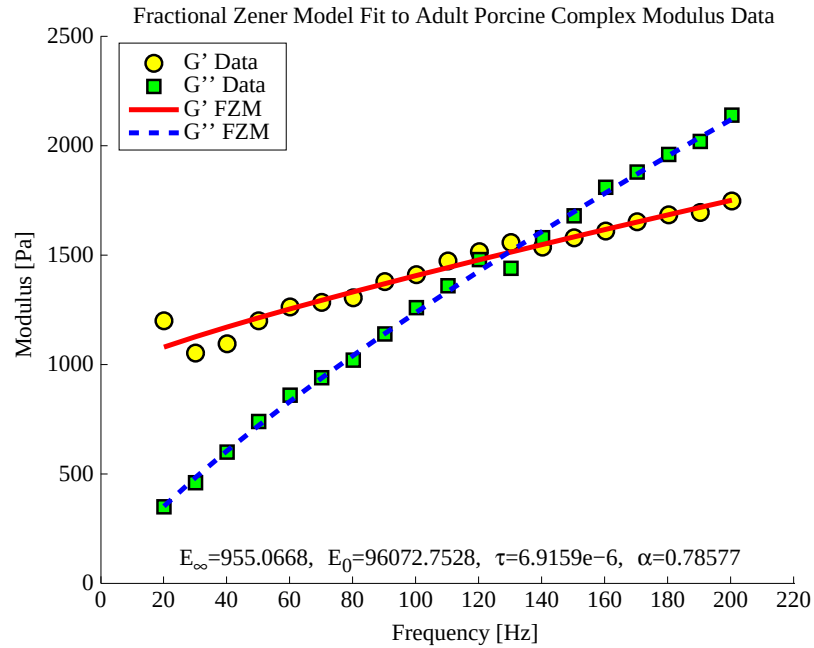
$$G''(\omega) = \frac{(E_0 - E_\infty)\tau^\alpha \omega^\alpha \sin\left(\frac{\alpha\pi}{2}\right)}{1 + 2\tau^\alpha \omega^\alpha \cos\left(\frac{\alpha\pi}{2}\right) + \tau^{2\alpha}\omega^{2\alpha}}. \quad (5)$$

These are nonlinear functions of the model parameters (E_0, E_∞, τ, and α). We use a nonlinear least squares algorithm `lsqcurvefit` in `MATLAB` to numerically fit the functions to the experimental data.

Parameter Determination Via Curve Fitting

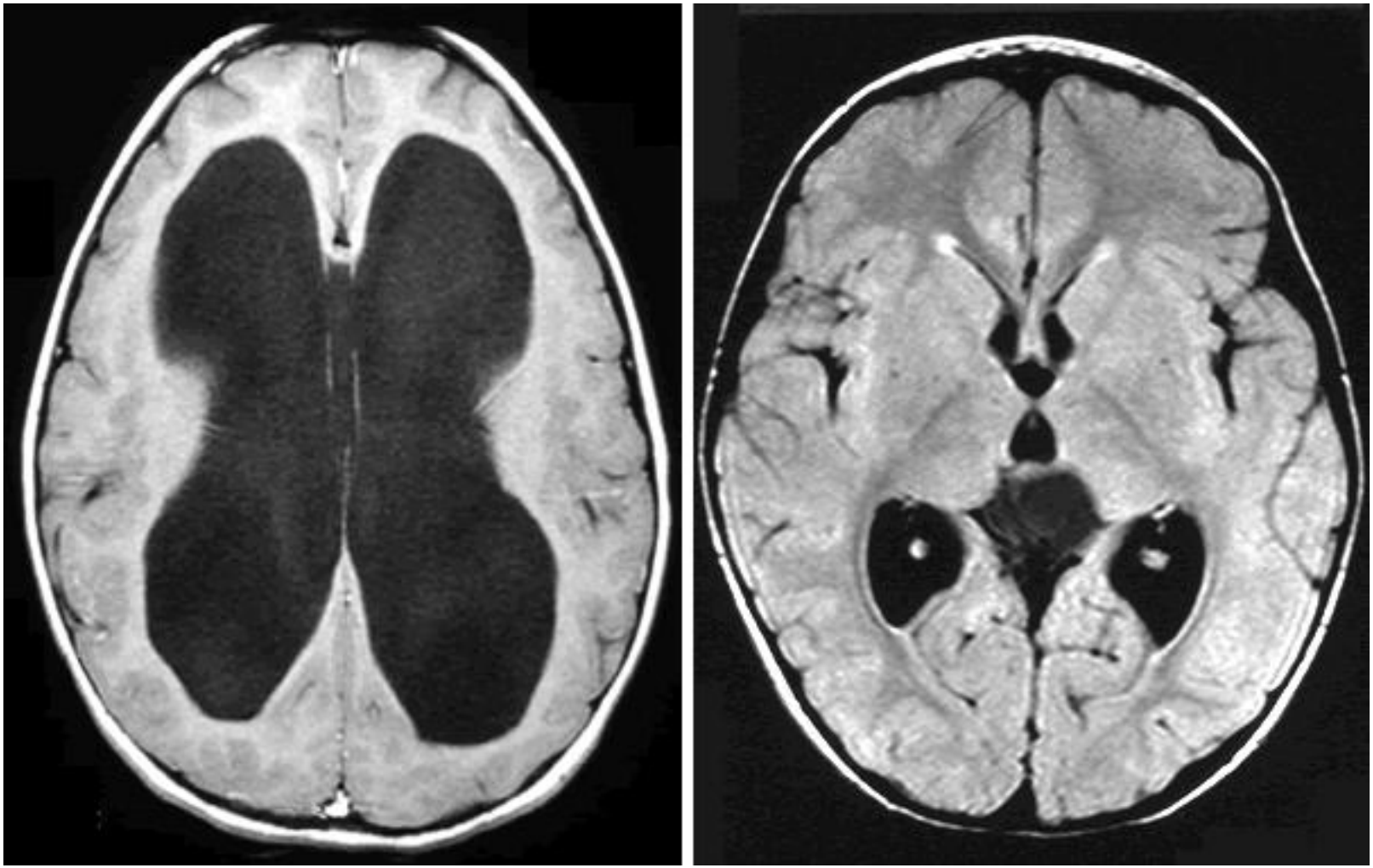
Infant and Adult porcine data from Thibault and Margulies [1998].





	Infant Porcine	Adult Porcine	Adult MRE
E_∞	621 Pa	955 Pa	829 Pa
E_0	6 678 Pa	96 073 Pa	2 842 Pa
τ	110 μs	6.92 μs	2 068 μs
α	0.779	0.786	0.8

A Normal Brain Versus a Hydrocephalic Brain



[neurosurgery.seattlechildrens.org, 2008]

CSF Pulsations and Hydrocephalus

There is an abundance of experimental evidence indicating that CSF pulsations may be involved in ventricular enlargement.

- Bering [1962] showed that a lateral ventricle with a choroid plexus dilates more than one without a choroid plexus.
- Wilson and Bertan [1967] showed that obstructing the leading artery to a lateral ventricle choroid plexus caused it to have a smaller CSF pulse amplitude and caused it to be smaller than the unaffected ventricle.
- Di Rocco [1984] showed that artificially increasing the CSF pulse amplitudes by pumping up a balloon caused that ventricle to dilate more than the other ventricle.

Pulsation-Damage Hypothesis for Hydrocephalus

Basic premise: CSF pulsations cause tissue damage that leads to ventricular enlargement.

- Choroid plexus generates pressure pulses with each influx of fresh arterial blood.
- Pulse transmitted to ventricle walls via the CSF.
- Pressurization cycle on walls causes
  1. brain tissue to cycle between compression and expansion,
  2. CSF to oscillate in and out of brain tissue.
- Oscillations may generate large shear strains and damage periventricular tissue.
- Damaged tissue allows fluid to penetrate further, propagating tissue damage, and leading to ventricular expansion.

Previous Work - A Poroelastic Modelling Approach

Stresses Induced by Fluid Flow

- Poroelastic model predicts a maximum fluid velocity in the periventricular tissue due to CSF pulsations (9.4 mm Hg peak-to-peak) to be 1 μm/s.
- Pipe flow model predicts the shear induced on the surrounding tissue by this flow to be 40 μPa.
- Dong and Lei [2000] found force required to rupture an adhesive bond to be 10^{-11} N.
- Assuming a cell diameter of 5 μm, this corresponds to a shear force of 60 000 μPa.

Conclusion: fluid flow in the tissue due to CSF pulsations is incapable of inducing damage in healthy tissue.

Current Modelling Goal

Goal Determine if the CSF pulsations are capable of causing sufficient stresses in the tissue to cause damage.

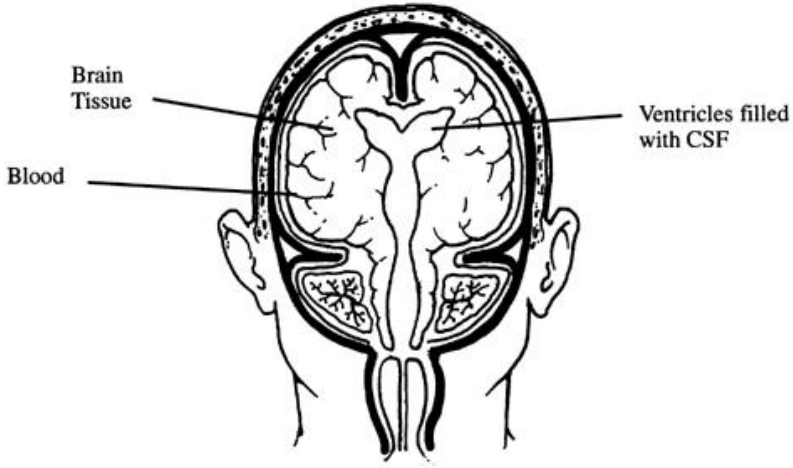
Modelling Approach: a viscoelastic material.

We will assume the brain tissue to be

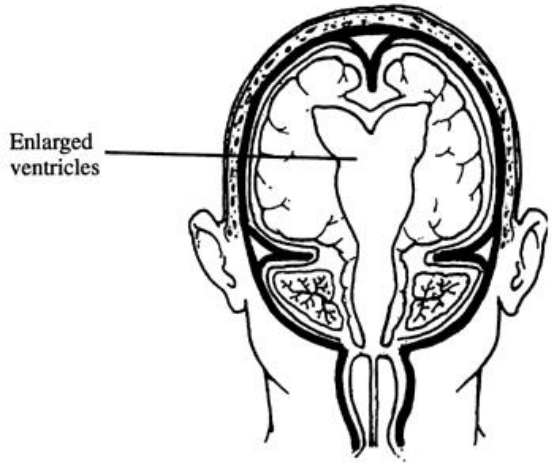
- homogeneous
- incompressible
- isotropic
- dilatational parts of stress/strain tensors behave like a linear elastic solid
- deviatoric parts of stress/strain tensors behave like a fractional Zener material

Model Set-Up

Normal Brain



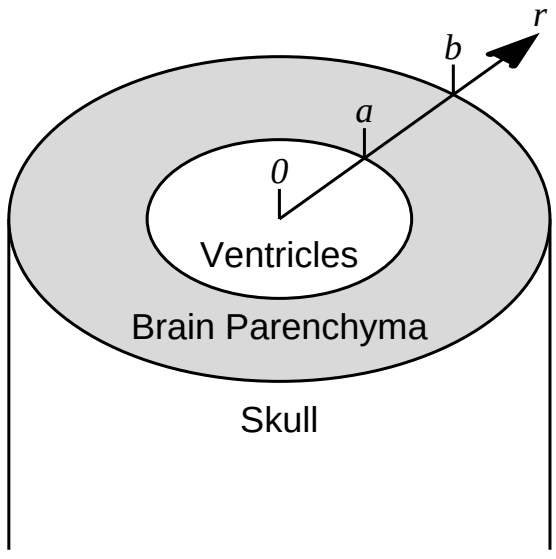
Hydrocephalic Brain



[uihealthcare.com, 2010]

- simplified cylindrical geometry
- assume planar strain
- solve the quasi-static equation of motion

$$\frac{\partial}{\partial r}\sigma_{rr} + \frac{1}{r}(\sigma_{rr} - \sigma_{\theta\theta}) = 0 \qquad (6)$$



Boundary Conditions

Ventricle Wall Condition

For both the infant and adult cases, the inner boundary is subjected to the pressure of the CSF pulsations,

$$\sigma_{rr} = -p_i(t) \qquad \text{at } r = a. \tag{7}$$

Infant Skull Condition

The unfused sutures of the infant skull allow it to expand, so the outer boundary is stress-free

$$\sigma_{rr} = 0 \qquad \text{at } r = b. \tag{8}$$

Adult Skull Condition

The rigid adult skull restricts movement of the brain, so no displacements are allowed

$$u = 0 \qquad \text{at } r = b. \tag{9}$$

Solving for Displacement

Using the elastic-viscoelastic correspondence principle, the infant and adult displacements are

$$u_I(r,t) = \frac{a^2}{b^2-a^2}\left[\left(\frac{3r}{6K+E_0}+\frac{b^2}{E_0 r}\right)p_i(t) + \frac{b^2(E_0-E_\infty)}{E_0^2\tau^\alpha r}p_i(t) * \left(t^{\alpha-1}E_{\alpha,\alpha}\left(-\frac{E_\infty}{E_0}\left(\frac{t}{\tau}\right)^\alpha\right)\right) + \frac{3r(E_0-E_\infty)}{(6K+E_0)^2\tau^\alpha}p_i(t) * \left(t^{\alpha-1}E_{\alpha,\alpha}\left(-\frac{6K+E_\infty}{6K+E_0}\left(\frac{t}{\tau}\right)^\alpha\right)\right)\right]$$

$$u_A(r,t) = \left(\frac{b}{r}-\frac{r}{b}\right)\left[\frac{3a^2b}{(6K+E_0)a^2+3E_0b^2}p_i(t) + \frac{3a^2b(a^2+3b^2)(E_0-E_\infty)}{\left((6K+E_0)a^2+3E_0b^2\right)^2\tau^\alpha}p_i(t) * \left(t^{\alpha-1}E_{\alpha,\alpha}\left(-\hat{h}\left(\frac{t}{\tau}\right)^\alpha\right)\right)\right],$$

where $E_{\alpha,\alpha}(z)$ is the generalized Mittag-Leffler function and

$$\hat{h} = \frac{(6K+E_\infty)a^2+3E_\infty b^2}{(6K+E_0)a^2+3E_0b^2}$$

Model Parameter Values

- assume CSF pressure of the form $p_i(t) = p^* \cos(\omega t)$
- use the fractional Zener model parameters determined by Davis et al. [2006] from relaxation data [Galford and McElhaney, 1970]

$$E_\infty = 1\,612 \text{ Pa} \qquad \tau = 6.709 \text{ s}$$
$$E_0 = 7\,715 \text{ Pa} \qquad \alpha = 0.641$$

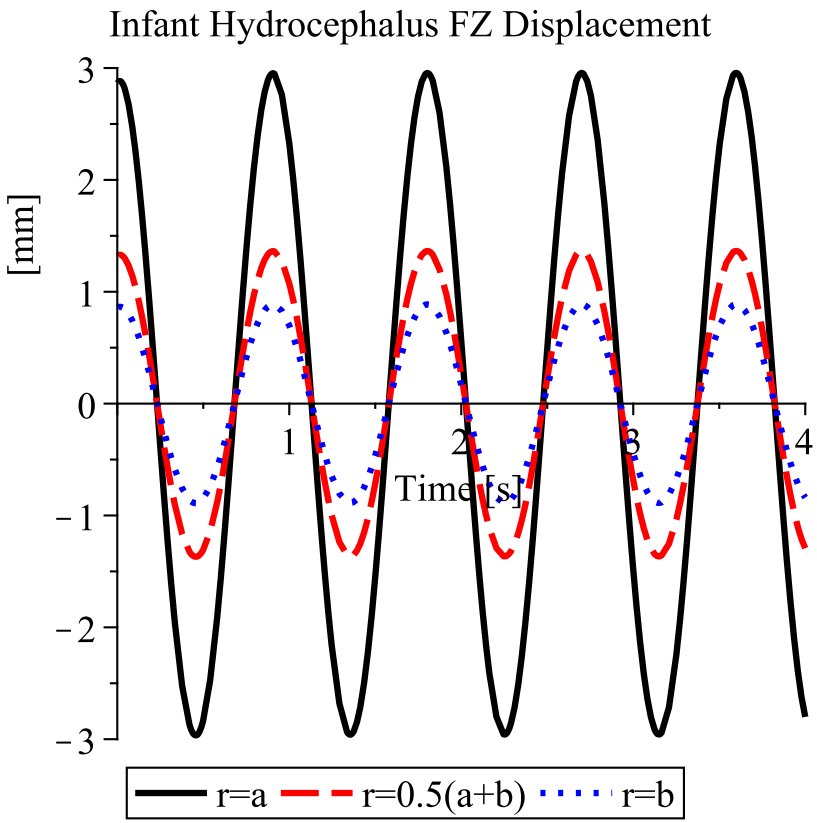
- also assume an adult head size for both infant and adult cases (to ease comparison)

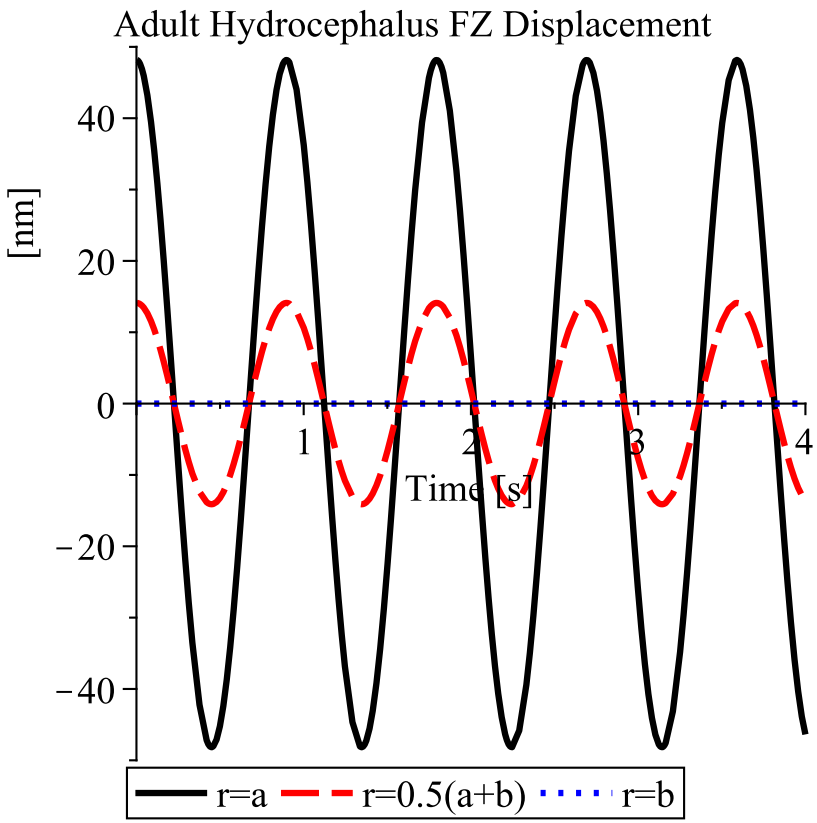
$$a = 0.03 \text{ m} \qquad b = 0.1\text{m}.$$

- other model parameters used are

$$K = 2.1 \text{ GPa} \qquad p^* = 667 \text{ Pa} \qquad \omega = 7 \text{ rad/s}$$

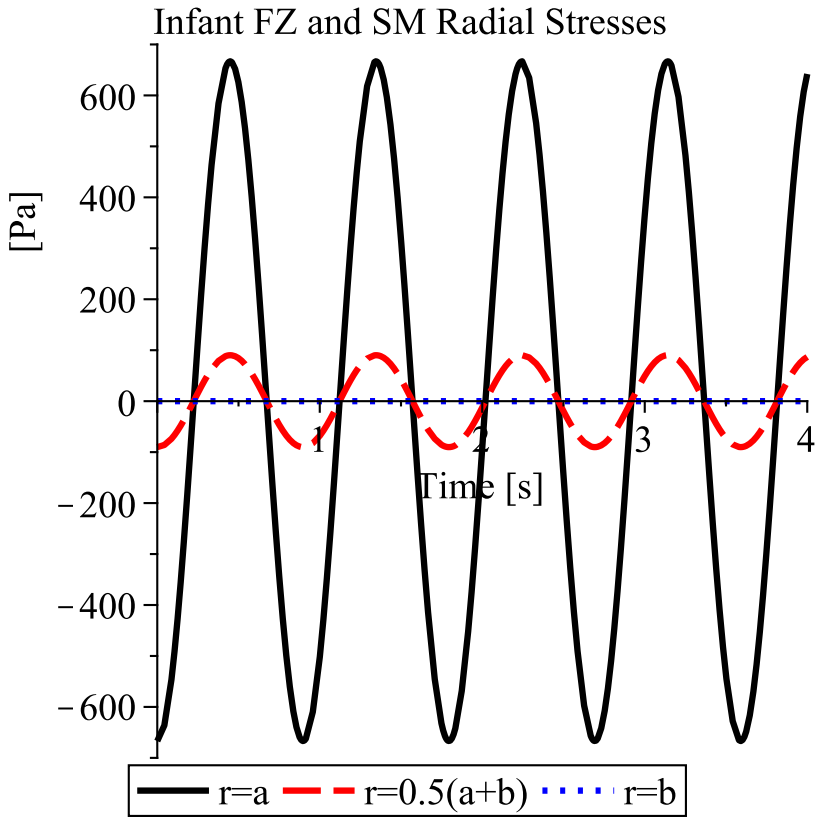
Displacements - Davis Model Parameters

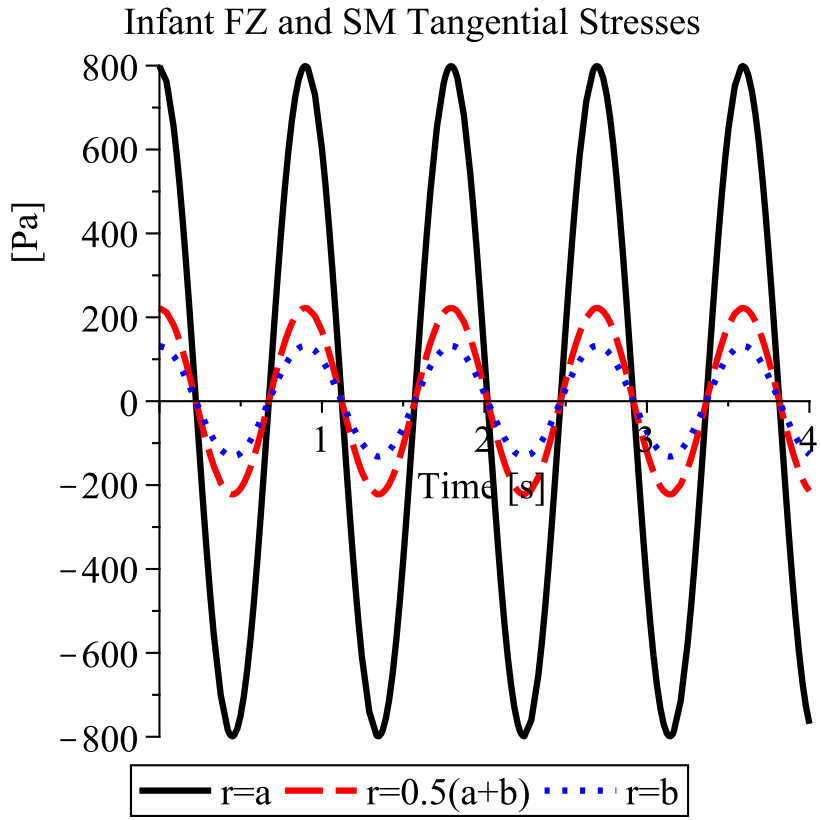




	Infant	Adult
ventricle maximum	3 mm	48 nm
cortical maximum	1 mm	0 nm

Tissue Stresses - Davis Model Parameters





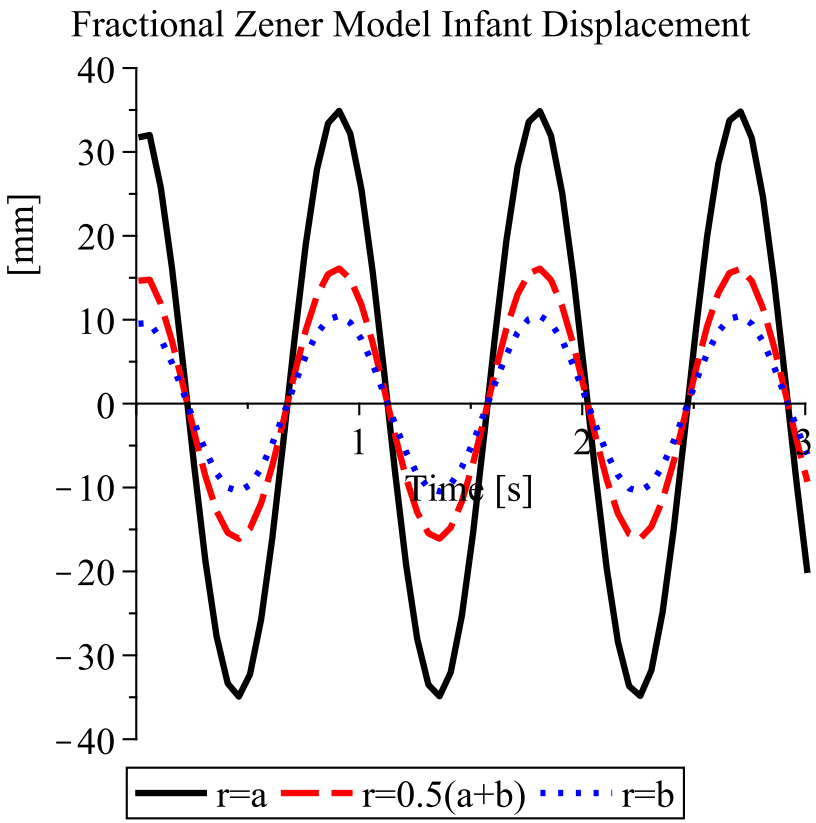
Infant tissue maximum stresses

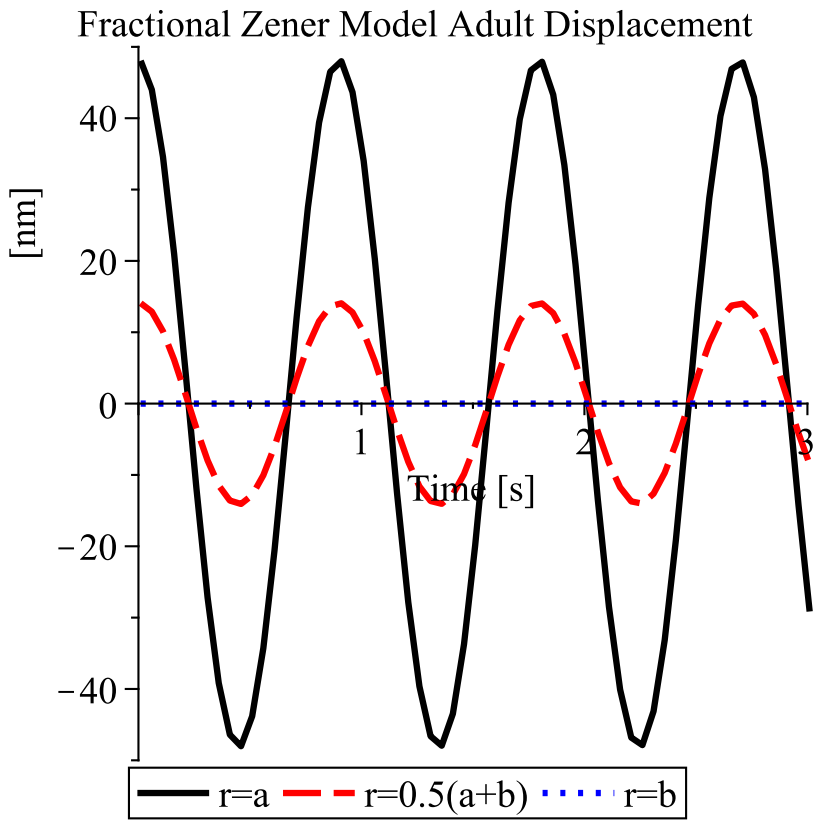
- radial 670 Pa
- tangential 800 Pa

Adult tissue maximum stresses

- radial 670 Pa
- tangential 670 Pa

Displacements - Age-Dependent Model Parameters





	Infant	Adult
ventricle maximum	35 mm	48 nm
cortical maximum	10 mm	0 nm

A New Infant Boundary Condition

Due to the unphysical displacement predicted by the age-appropriate model parameters, we need to modify the model.

Mixed Infant Skull Condition

The infant skull provides a fraction, δ, of the resistance to dilation provided by the adult skull

$$\sigma_{rr} = \delta \sigma^{A}_{rr} \qquad \text{at } r = b, \tag{10}$$

where, σ^{A}_{rr} is the radial stress at the cortical surface predicted by the adult BVP where zero-displacement is enforced.

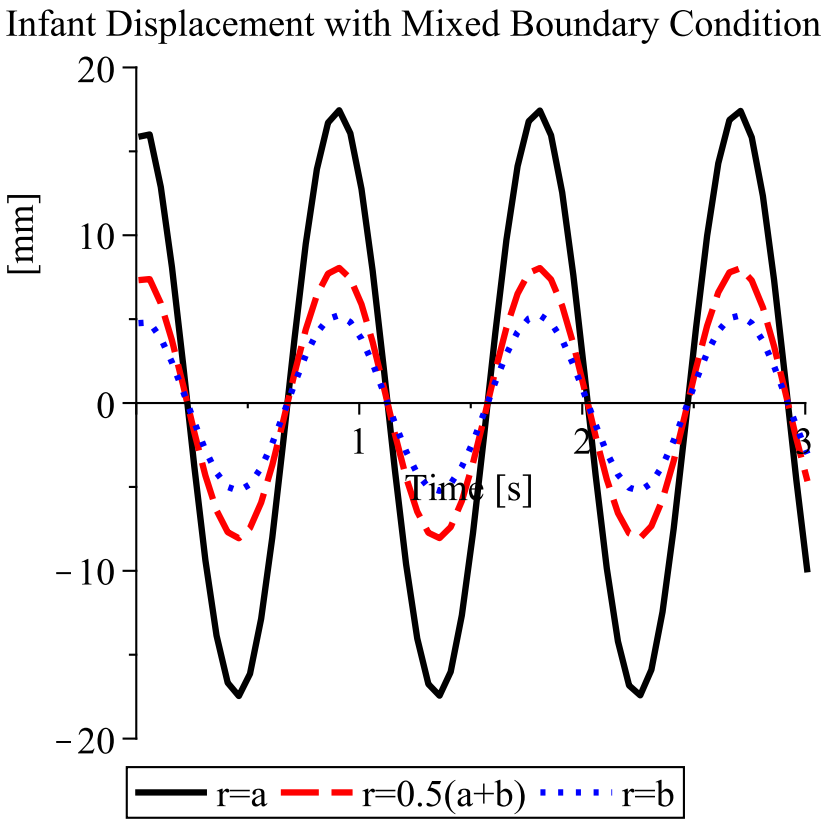
What Value for the Mixing Parameter δ?

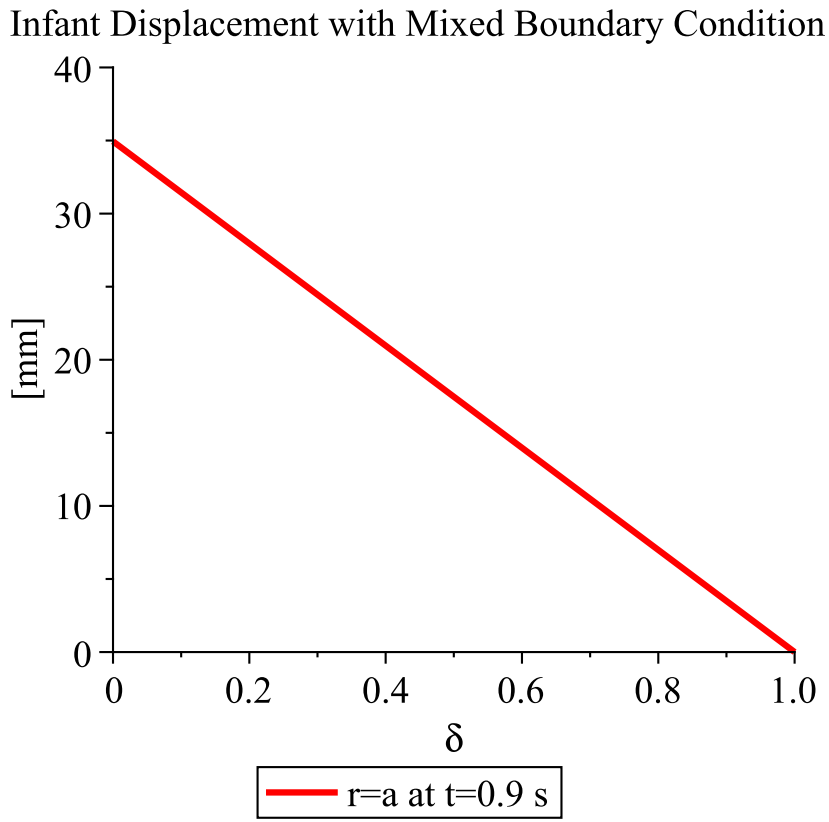
Skull deformation simulations from Margulies and Thibault [2000] indicate that

load	infant deformation	adult deformation	ratio
5000 N	10 mm	4 mm	0.4
1000 N	4 mm	2 mm	0.5

But, the force applied to the brain and skull by the CSF pulsations is much smaller than these loads!

Displacements





δ	**maximum ventricle displacement**
0	35 mm (unphysical infant BVP)
0.4	21 mm
0.5	17.5 mm
0.86	5 mm (physically reasonable)
1	48 nm (adult BVP)

Summary of Parameter Values

Parameter	Fractional Zener Model Parameter Values			
	Adult	**Adult**	**Adult**	**Infant**
	Relaxation	MRE	Porcine	Porcine
E_0	7 715 Pa	2 842 Pa	96 073 Pa	6 678 Pa
E_∞	1 612 Pa	829 Pa	955 Pa	621 Pa
τ	6.709 s	2068 μs	6.92 μs	110 μs
α	0.641	0.8	0.786	0.779
Viscosity	40 945 Pa·s	4.16 Pa·s	0.66 Pa·s	0.67 Pa·s
Shear Modulus	537 Pa	276 Pa	318 Pa	207 Pa

steady-state shear modulus: $G = \dfrac{E_\infty}{2(1+\nu)} \approx \dfrac{E_\infty}{3}$.

Taylor and Miller [2004] found $E \approx 584$ Pa.
Cheng and Bilston [2007] found $E \approx 350$ Pa.

Summary of Model Predictions

	Maximum at Ventricle Wall				
	Infant	**Adult**	**Infant**	**Adult**	**Infant** (Mixed BC)
	Relaxation Values		Porcine Values		($\delta = 0.86$)
u	3 mm	48 nm	35 mm	48 nm	5 mm
σ_{rr}	670 Pa	670 Pa	670 Pa	670 Pa	482 Pa
$\sigma_{\theta\theta}$	800 Pa	670 Pa	800 Pa	670 Pa	688 Pa

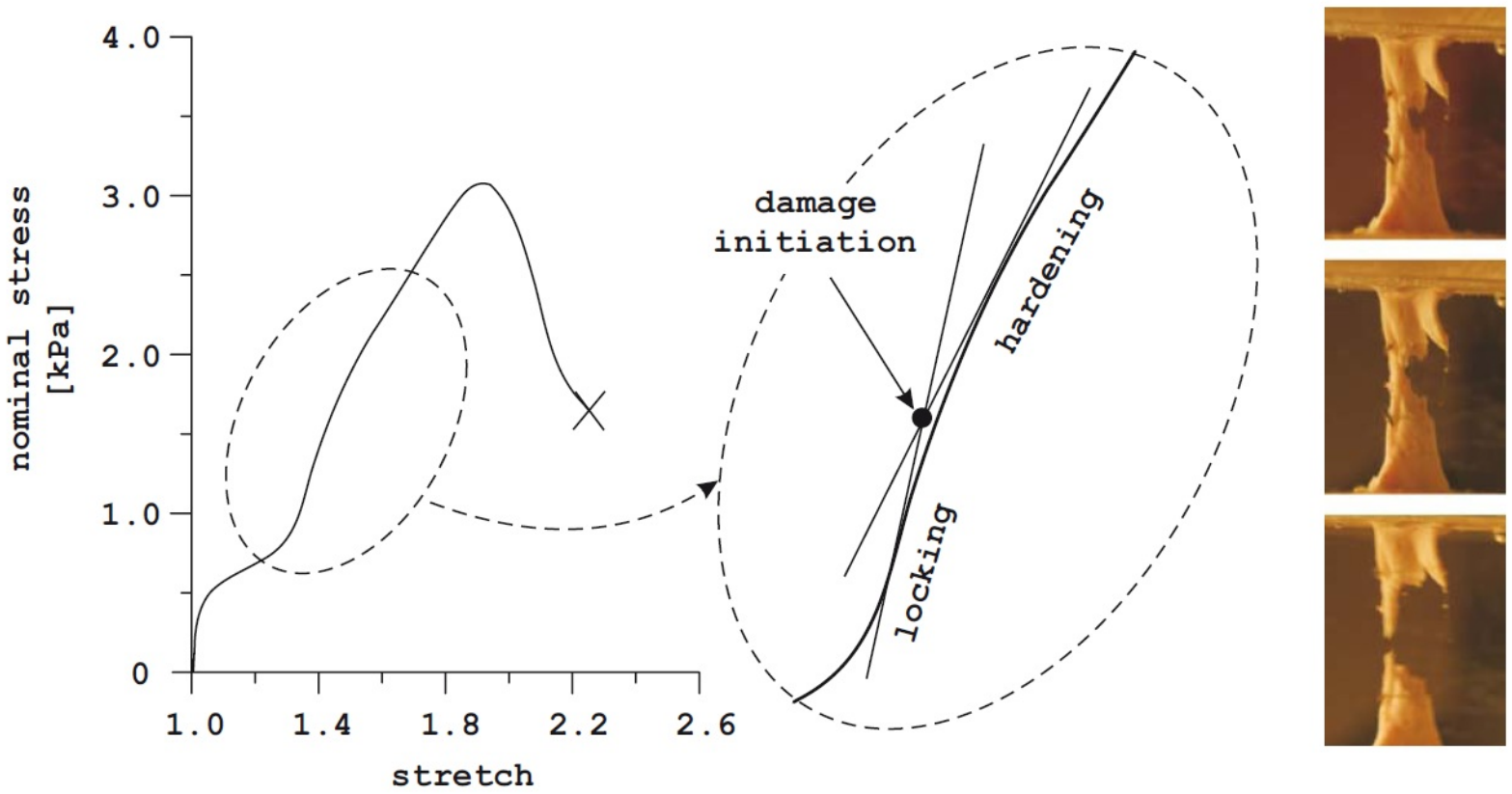
Measure of maximum shear stress:

$$\tau(r) = \frac{1}{2}\left(\sigma_{\theta\theta}(r) - \sigma_{rr}(r)\right) \tag{11}$$

decreases with r from ventricles to cortical surface, so maximum stress occurs at ventricle walls.

Damage Threshold for White Matter

- pulsation-damage hypothesis assumes tissue damage caused by large stresses / strains induced by CSF pulsations
- damage begins when *locking* section of a stress-strain curve transitions to *hardening* section



Comparison to Damage Threshold

- Franceschini et al [2006] found the damage threshold for white matter to be 2 710 Pa, their curve peaked at 3 430 Pa, and fracture occured at 2 520 Pa.
- The stresses predicted by our model are 25 to 30% of this damage threshold

	Maximum at Ventricle Wall				
	Infant	**Adult**	**Infant**	**Adult**	**Infant** (Mixed BC)
	Relaxation Values		Porcine Values		($\delta = 0.86$)
u	3 mm	48 nm	35 mm	48 nm	5 mm
σ_{rr}	670 Pa	670 Pa	670 Pa	670 Pa	482 Pa
$\sigma_{\theta\theta}$	800 Pa	670 Pa	800 Pa	670 Pa	688 Pa

Conclusion: CSF pulsations cannot be the cause of tissue damage

Steady-State Elastic Modulus

We found that for

- infants $E_\infty = 621$ Pa
- young adults $E_\infty = 955$ Pa
- Parameter sensitivity analysis shows E_∞ most significantly affects the model predictions in the range 500 to 10 000 Pa

Sack et al [2009] found both storage and loss moduli decrease with age in adults from 18 to 88 years.

Conjecture:

The steady-state elastic modulus of brain tissue (E_∞) increases from its value at infancy (621 Pa) to a maximum at early adulthood (955 Pa), and then if slowly decreases with age.

Implication:

reduced elastic modulus of infant and elderly brains may make these populations more susceptible to developing hydrocephalus

Conclusions - Age Dependence of Brain Tissue

- Brain growth spurt and age-induced degeneration make the mechanical properties of brain tissue age-dependent.
- Age-dependent mechanical properties should be used in mathematical models of age-dependent conditions such as hydrocephalus.
- Mathematical models may need to be improved to accept age-dependent model parameters.
  - stress-free BC replaced by percentage of adult skull stress

Conclusions - Hydrocephalus

CSF pulsations cause both fluid and solid movements, but

- fluid movement through tissue induces stresses that are too small to damage tissue
  - 40 μPa shear induced but 60 000 μPa required to rupture a single adhesive bond
- tissue movement induces stresses that are too small to damage tissue
  - 670 to 800 Pa stress induced by 2 710 Pa required to induce damage in white matter

CSF pulsations cannot be the primary cause of the tissue damage and ventricular enlargement observed in hydrocephalus.

The Pulsation-Damage Hypothesis needs to be revised.

Work for the Future - Correcting Limitations

To correct the limitations of this work, we should

- determine the effect of oscillatory shear flows of living cells
  - oscillatory shear flows can trigger cellular responses different from steady shear flows and this may increase the cells susceptibility to damage
- perform more extensive brain tissue mechanical testing to determine age-dependence of creep and relaxation behaviours
- perform age-dependence testing via MRE where the living tissue is contained in the cranial vault
  - more frequency values are required (> 4) for accurate data fitting of 3- or 4-parameter models
  - animal subject from infancy to old age should be used to test our conjecture on the age-dependence of the steady-state elastic modulus of brain tissue

Work for the Future - Modelling

- **Conjecture**: the steady-state elastic modulus of infant and aged brains is reduced, making it more susceptible to developing hydrocephalus.
- This may explain why hydrocephalus is most commonly found in the infant and elderly populations.
- Future work should investigate the micro-structure of brain tissue to determine what chemical and biological changes occur as the brain grows, develops, and ages, as well as the changes that occur due to disease.
  - polymer models (solid phase, fluid phase, ionic phase)
  - swelling/contracting gels – where hydration level and mechanical properties depend on ionic concentrations

Any Questions?

and

Thank You!

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