A Mechanism for Ventricular Expansion in Communicating Hydrocephalus

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Abstract. This report investigates a new possible molecular mechanism for the pathogenesis of hydrocephalus. New research by Dr. Miles Johnston [4] has found that the injection of anti β_1 integrin antibodies into the ventricle of rats causes a drop in parenchymal pressure and causes the cerebral ventricles to enlarge which is characteristic of hydrocephalus. We investigate intramantle pressure gradients as a possible force to enlarge the ventricles and we propose a new poroelastic model incorporating the effect of the antibodies to determine if they are a possible mechanism for hydrocephalus.

1 Introduction

Hydrocephalus is a condition of the brain characterized by an accumulation of cerebrospinal fluid (CSF) in the brain and the resulting expansion of the cerebral ventricles and compression of the brain parenchyma. The four ventricles of the brain (two lateral, one third and one fourth ventricle) are located in the centre of the brain tissue and CSF flows from the lateral ventricles through the aqueducts to the third and fourth ventricles into the subarachnoid space. CSF also flows through the brain tissue into the subarachnoid space where it circulates with the spinal CSF and is absorbed by the arachnoid villi.

There are two classes of hydrocephalus: the first class, non-communicating hydrocephalus, occurs when there is an obstruction to the normal flow and circulation of CSF causing it to accumulate in the ventricles. Due to the obstruction (such as a tumour) a large

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pressure gradient exists between the ventricles and the subarachnoid space surrounding the brain parenchyma. This large pressure gradient is the cause of the ventricular expansion that occurs in this class of hydrocephalus.

Communicating hydrocephalus, the second class of hydrocephalus, occurs when there is no impediment to the normal flow of CSF from the ventricles, but when there is an imbalance between the production and absorption of CSF. Large pressure gradients cannot exists across the parenchyma in this class and so there is no obvious mechanism to explain the ventricular enlargement that occurs. This lack of a physical mechanism for ventricular expansion in communicating hydrocephalus was the focus of our study group.

1.1 Previous investigations. Linninger *et al.* [3] placed pressure sensors (transducers) in the ventricular CSF, the brain parenchyma, and the CSF of the subarachnoid space and showed that no significant difference was visible between the measured pressures before and after inducing kaolin hydrocephalus in dogs. However, it is possible that small, and perhaps transient, pressure differences do exist between the ventricular CSF and the brain parenchyma or subarachnoid space which were below the sensitivity of the transducers and which could provide a possible mechanism for ventricular enlargement.

In 2002, Peña *et al.* [5] numerically simulated hydrocephalus using a finite element method to solve Biot's equations of consolidation [1], now known as poroelasticity theory. They showed that a drop in parenchymal pressure coupled with a reduced elastic modulus produced the ventricular enlargement characteristic of hydrocephalus. In order to maintain a low pressure region inside the parenchyma, they assumed that CSF was absorbed by the parenchyma, which was represented mathematically by inserting sink terms into Biot's equations. No physical explanation of the reduced elasticity or of the absorption process was given.

Recent experiments by Wiig *et al.* [8] showed that the dissociation of $\alpha_1\beta_1$ integrins in the skin results in a significant reduction in the local interstitial fluid pressure. Nagra *et al.* [4] showed that this reduction in local pressure also occurs in brain parenchyma which suggests that β_1 integrin dissociation may provide a possible mechanism for the pathogenesis of hydrocephalus.

In Johnston's experiments [4], either antibodies to β_1 integrins or IgG/IgM isotype controls were injected into the lateral ventricle of adult rats. The ventricular or parenchymal pressures (measured 500-600 μm from the anterior horn of the lateral ventricle) were recorded with a servo-null micropipette (2 μm tip) before and after the antibodies or controls were injected in one group of rats. These measurements showed that following the injection of antibodies, the parenchymal pressure decreased relative to the pre-injection value. This drop in parenchymal pressure was not observed when controls were injected.

The remaining rats were sacrificed two weeks post injection and the brains were fixed with 10% formalin before coronal sections were obtained. The rats that received controls presented no ventricular enlargement but the rats that received anti β_1 integrin antibodies presented considerable ventricular enlargement.

Dr. Miles Johnston presented these results to the OCCAM-Fields-Mitacs workshop and proposed the following questions to our study group.

Question 1: Can one predict a ventricle size given a defined pressure gradient between the ventricles and the periventricular area?

Question 2: What is the smallest pressure gradient that would expand the ventricles?

These questions are difficult to answer accurately due to the dependence of tissue deformation on the material properties of brain parenchyma, which are difficult to determine experimentally and which vary in the reported literature. The second question is also difficult to answer since it is not quantitative in nature. Any applied pressure gradient would expand the ventricles by some amount, however small that expansion may be.

This study addresses two objectives that aim to answer or extend the concepts of interest to Dr. Johnston.

Objective I: To determine the percentage of ventricular volume increase that occurs due to an intramantle pressure gradient of $400 - 500$ Pa and investigate the dependence of this increase on the pressure distribution through the brain parenchyma.

Objective II: To formulate a model to investigate the hypothesized macroscopic mechanical effects of anti β_1 integrin antibodies on brain parenchyma to determine if they are sufficient to induce hydrocephalus.

2 Intramantle Pressure Gradients - Objective I

To predict the ventricular volume increase given a prescribed pressure difference between the ventricles and the periventricular area (intramantle gradient), by defining a pressure distribution across the parenchyma, we use previous studies to define governing equations for our specific problem. In previous models of hydrocephalus [7, 2, 6] differential equations are used to describe the radial displacements of brain parenchyma in a simplified geometry, shown in Figure 1. In all three models, the brain is assumed to have a spherical or cylindrical geometry, and displacement and pressure distributions are assumed to be radially symmetric, allowing the differential equation to be solved in one-dimension.

These models are based on Biot's theory of consolidation [1] which describes the behaviour of porous elastic media under loads. The main limitation of Biot's theory is that it is based on linear elasticity, which is only applicable for small strains. To account for large strains, nonlinear elasticity should be used, however this is mathematically much more complicated.

The poroelastic model developed by Levine [2] is implemented to address the first objective in this study. MAPLE and MATLAB are used to solve the equations derived by Levine [2] describing parenchymal displacement in the spherical brain given a defined pressure distribution. The steady pressure profile was also determined according to Levine's theory [2].

2.1 Equations for displacement. Levine's equation for radial displacement is obtained from the quasi-static version of Biot's equations [1] assuming the displacement function u and pressure distribution P are radially symmetric. If we write $u(r)$ for the radial displacement at radius r, the following equation (given by Levine [2]) relates radial displacement and pressure:

$$\frac{\partial^2 u}{\partial r^2} + \frac{2}{r}\frac{\partial u}{\partial r} - \frac{2u}{r^2} = \frac{(1-2\nu)\alpha}{2G(1-\nu)}\frac{\partial P}{\partial r}, \tag{2.1}$$

where G is the shear modulus and ν is the Poisson's ratio of the saturated poroelastic solid. The parameter α, according to Biot [1], represents the ratio of the volume of fluid squeezed out to the volume change of the parenchyma if the parenchyma is compressed while allowing fluid to escape. In the following, the brain tissue is assumed to be incompressible. If the
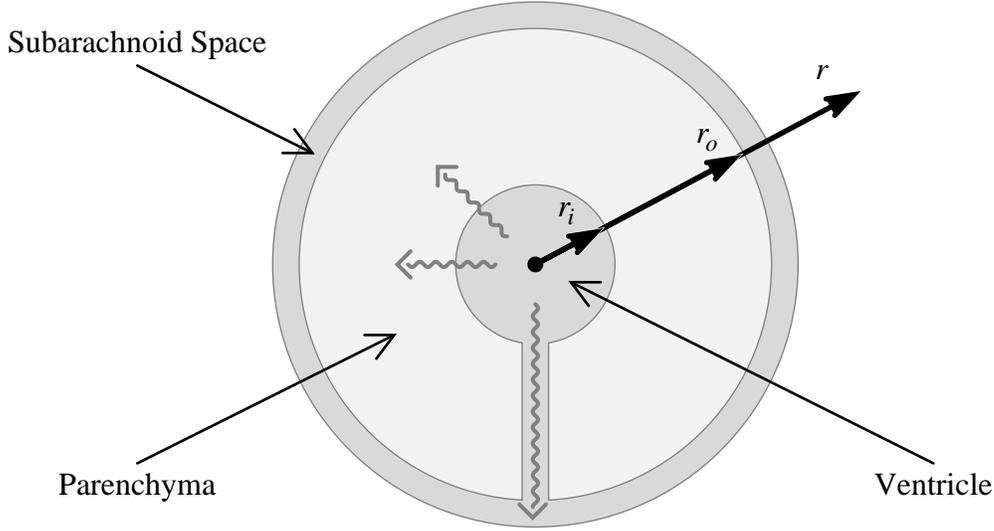
Figure 1: Schematic of the spherical brain. The brain is assumed to be a sphere, with a concentric spherical void in the middle representing the ventricles. CSF may either flow through the parenchyma or out through a channel representing the foramena and aqueduct. For our purposes, we consider the channel to be small enough that it does not affect the displacements near it. This allows for radially symmetric functions and reduces the number of dimensions in the problem.

parenchyma is compressed, the volume loss must be solely due to fluid loss or pore shrinkage. Thus, in the following, we assume that $\alpha = 1$.

Boundary conditions at the inner and outer boundaries of the brain are defined for (2.1). At the inner boundary, located at $r = r_i$, equivalent normal forces must act on the fluid phase and the solid phase. Assuming zero rate of strain within the ventricle this translates, in the radial formulation of Levine[2], as:

$$(\alpha - 1)P(r_i) = \left[2G\frac{\partial u}{\partial r} + \frac{2G\nu}{1 - 2\nu}\left(\frac{\partial u}{\partial r} + 2\frac{u}{r}\right) \right]_{r=r_i}. \qquad (2.2)$$

At the outer boundary, $r = r_o$, there are two possible boundary conditions. One option is to impose the same condition on the forces at the outer boundary as at the inner boundary. This gives the boundary condition:

$$(\alpha - 1)P(r_o) = \left[2G\frac{\partial u}{\partial r} + \frac{2G\nu}{1 - 2\nu}\left(\frac{\partial u}{\partial r} + 2\frac{u}{r}\right) \right]_{r=r_o}. \qquad (2.3)$$

This condition describes hydrocephalus in infants where the unfused skull may deform to accommodate the enlarged brain.

Levine imposes the following condition describing adult hydrocephalus:

$$u(r_0) = 0, \qquad (2.4)$$

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[2]It is our opinion that Levine has a mistake at this stage. On the left hand side of the Equation (2.2) Levine would have $-P(r_i)$ according to equation (14) of [2], but this disagrees with both Equation (12) from [7] and Equation (4.3) from [6]. Levine seems to neglect the $-\alpha P$ term in the first of the equations (12) in [2]. Equation (2.2) is what we believe to be correct.

which enforces zero displacement at the outer boundary due to the rigid skull preventing radial expansion of the outer surface of the brain. This boundary condition, however, excludes contraction of the outer surface of the brain which means the brain behaves like it is welded to a perfectly rigid skull at the outer boundary.

If the model always predicts positive radial displacement then this is not a problem, since the boundary condition prevents expansion. However, in some cases the pressure distributions cause negative radial displacement near the outer boundary, indicating that the imposed boundary condition is preventing contraction of the outer surface of the brain.

The appropriate course may be to solve for the displacement using the boundary condition (2.3) and then, if $u(r_o) > 0$, apply a corrective radial traction at the outer boundary such that $u(r_o) = 0$. The magnitude of the corrective traction will correspond to the force exerted on the brain by the skull. The end result should be equal to that obtained by replacing (2.3) with (2.4).

2.2 Equations for pressure. The models in [7, 2, 6] all include a differential equation describing the pressure distribution in the brain. They are based on the static or quasi-static assumption that the volume fraction of the brain occupied by CSF at each point does not vary in time, and that the flow of fluid in the brain obeys Darcy's law. Levine [2] writes these equations as:

$$V_r(r) = -k'\frac{\partial P}{\partial r}, \tag{2.5}$$

$$V_{ab} = \hat{k}P, \tag{2.6}$$

$$\frac{\partial \zeta}{\partial t} = k'\left(\frac{\partial^2 P}{\partial r^2} + \frac{2}{r}\frac{\partial P}{\partial r}\right) - \hat{k}P. \tag{2.7}$$

Here, $V_r(r)$ is the radial flow of CSF, which corresponds to $\phi v(r)$, where ϕ is the volume fraction of CSF at a given point and $v(r)$ is the radial velocity of the fluid at the same point. Equation (2.5) is Darcy's law where k' is the hydraulic permeability of the parenchyma. Equation (2.6) is Starling's law which relates the volume of CSF absorbed per unit volume of the parenchyma per unit time (V_{ab}) to the pressure difference across the capillary wall. Here $\hat{k}$ is the absorbtion coefficient. This equation assumes that blood pressure and net colloid osmotic pressures sum to zero, leaving P as the driving force behind the transfer of fluid from the interstitium into the capillaries. Equation (2.7) gives an expression for the increment of fluid content, $\zeta = \zeta(r,t)$, in the parenchyma ($\zeta = \phi - \phi_0$, if ϕ_0 is the initial volume fraction of fluid in the parenchyma). The two factors affecting the volume fraction of fluid are the absorbtion of fluid by capillaries and the divergence of the fluid flow.

In the quasi-static case, where $\frac{\partial \zeta}{\partial t} = 0$, we have

$$\frac{d^2 P}{dr^2} + \frac{2}{r}\frac{dP}{dr} - \frac{\hat{k}}{k'}P = 0. \tag{2.8}$$

The boundary conditions specified by Levine [2] are:

$$P(r_i) = P_v \qquad \text{and} \qquad P(r_o) = 0,$$

where P_v is the ventricular pressure. However, in communicating hydrocephalus the ventricular space and the subarachnoid space are connected via the cerebral aqueduct, so the boundary conditions should be closer to

$$P(r_i) = P(r_o) = P_v. \tag{2.9}$$

2.3 Radial displacement and ventricular expansion. It is probable that the absorbtion and permeability coefficients vary spatially and thus by choosing $\hat{k}$ and k' appropriately, one may obtain a pressure profile of any desired shape. For now, these coefficients are assumed to be constant and their ratio is defined as $k = k'/\hat{k}$. Equation (2.8) is solved subject to (2.9) to obtain pressure profiles for various values of the ratio k.

Figure 2 illustrates the dependence of this pressure distribution on the ratio k as well as the dependence of the parenchymal displacement (determined by (2.1) with boundary conditions (2.2) and (2.4)) on the pressure profile. When absorption is equal to permeability ($k = 1$), pressure drops only slightly mid-parenchyma which causes the negligible deformation seen in Figure 2b. When absorption dominates permeability ($k \ll 1$), significant drops in pressure occur mid-parenchyma and small negative displacements result near the outer surface of the brain.
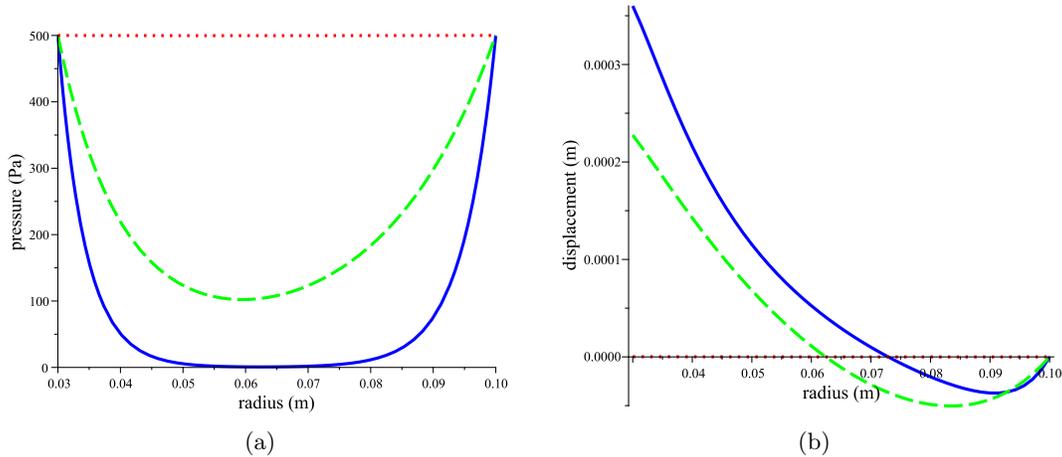

Figure 2:   (a) Pressure profiles obtained by solving (2.8) with (2.9) for various values of k, and (b) the corresponding displacements obtained by solving (2.1) with boundary conditions (2.2) and (2.4). The red dotted curves are for $k = 1$ and the blue solid and green dashed curves are for $k \ll 1$ ($G = 8$ kPa and $\nu = 0.35$).

If a small pressure gradient from the ventricles to the subarachnoid space was applied as well as the given pressure distribution through the parenchyma, the negative displacements near the outer boundary may be changed to positive displacements. A small pressure gradient, less than 1 mmHg, would be below the sensitivity of the transducers used by Linninger et al. [3], and thus would not have been observed in their measurements.

To investigate the dependence of displacement on the shape of the pressure distribution through the parenchyma, two types of pressure profiles were constructed, inverted spike profiles and trough profiles. The constructed pressure profiles and their corresponding displacements according to (2.1) with (2.2) and (2.4) are shown in Figure 3. The pressure spikes cause the majority of the parenchyma to move inward while the ventricle walls move outward creating compression in the middle of the parenchyma. The trough profiles cause the majority of the parenchyma to move outward while a region near the outer boundary moves inward, again creating compression of the parenchyma.
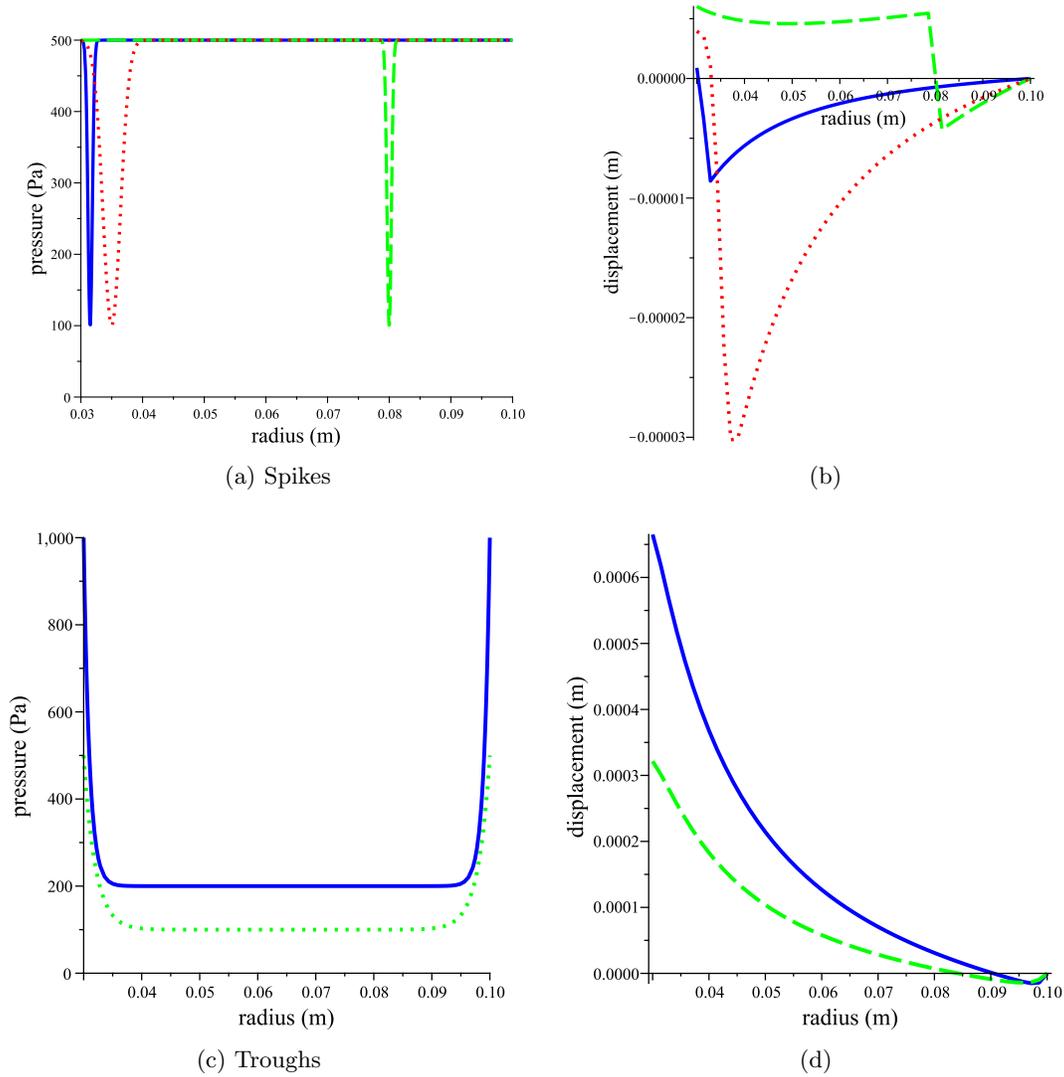
(a) Spikes

(b)

(c) Troughs

(d)

Figure 3: Hypothetical spike (a) and trough (c) pressure profiles and the corresponding displacements, (b) and (d) respectively, obtained from (2.1) with (2.2) and (2.4) ($G = 8$ kPa and $\nu = 0.35$).

Assuming a spherical ventricle, the percentage change in volume due to the trough pressure profiles from Figure 3c are given by the formula:

$$\text{Percentage Change} = 100\frac{\Delta V}{V} = 100\frac{(r + \mathrm{d}r)^3 - r^3}{r^3}.$$

Thus, at the ventricle wall, the percentage increase in volume due to a drop of 400 Pa is 3.2% and the percentage increase in volume due to a drop of 800 Pa is 6.7%, approximately double the increase caused by a 400 Pa drop. These percentages, however, depend on the values of G (8 kPa) and ν (0.35) used in the computation of displacement.

2.4 Discussion. The ventricular enlargements predicted by this model are small compared to the expansion seen in Johnston's animal experiments [4]. There are two possible explanations for this discrepancy. First, the material parameters of the animal brain parenchyma were not known and so rough estimates of the values were used. And second, the expansion seen in the animal experiments occurred over a time scale of two weeks. The displacements predicted by this model are equilibrium solutions, but the time scale on which this occurs is not known and may in fact be quite small depending on the material properties of the parenchyma. Thus, it is possible that large displacements may occur if these pressure distributions reoccur transiently and in response to each transient the parenchyma actively restructures its extracellular environment.

3 The Physical Mechanism - Objective II

To investigate the potential role of anti β_1 integrin antibodies in reducing the interstitial fluid pressure observed in the parenchyma, we hypothesize that the dissociation of the β_1 integrins creates a drop in local parenchymal pressure by changing the mechanical properties of the tissue, such as the elasticity, permeability, and absorption coefficients.

More specifically, the antibodies bind to the β_1 integrins that protrude from cell membranes. Tissue cells are attached to the extracellular matrix (ECM) via integrins, and this forms the tight and rigid matrix structure of the tissue. When the integrins are blocked by the antibodies, the ability of cells to adhere to the ECM is reduced, increasing cell motility and decreasing the rigidity of the tissue structure, see Figure 4. We hypothesize that when cell adhesion decreases, the matrix relaxes slightly which creates a local drop in pressure and reduces the elasticity of the tissue.
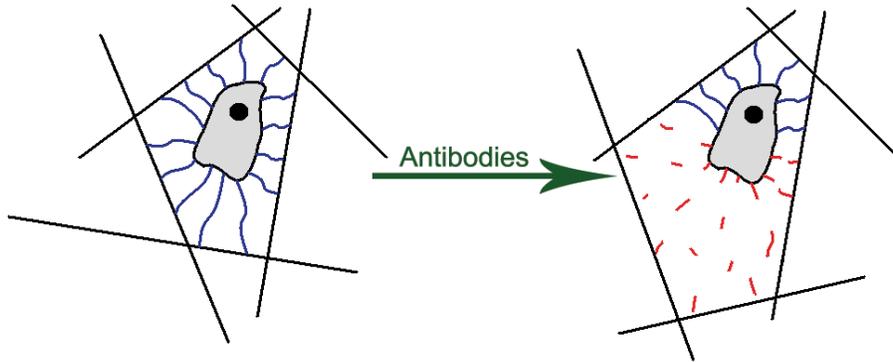

Figure 4: Schematic of the effect of antibodies on the extracellular matrix as cells lose their ability to bind to the matrix.

3.1 Deriving the model. To test this hypothesis, we develop a model on a macroscopic scale that considers the concentration of antibodies in the parenchyma and their overall effect on the tissue mechanics. To account for the flow of CSF (and thus antibodies) through the tissue the theory of linear poroelasticity based on Biot's theory of consolidation [1] is applied to the problem. In the model, material parameters that are assumed to be affected by the β_1 integrin antibodies, such as elasticity and permeability, have spatial and

temporal dependence determined by the antibody concentration history. The concentration of antibodies is governed by a convection-diffusion equation.

Let $\Omega \subset \mathbb{R}^3$ be the domain of the parenchyma, then on Ω conservation of momentum at steady-state, neglecting the inertia terms, gives,

$$\nabla \cdot \tau = 0. \tag{3.1}$$

Here, τ is the total stress tensor and is defined by

$$\tau_{ij} = \sigma_{ij} - p\delta_{ij}, \tag{3.2}$$

where σ is the effective stress tensor and p is the hydrostatic pressure. The effective stress is defined by

$$\sigma_{ij} = \lambda \mathrm{e}_{kk}\delta_{ij} + 2G\mathrm{e}_{ij}, \tag{3.3}$$

where $\lambda = \lambda(\mathbf{x},t)$ and $G = G(\mathbf{x},t)$ are the Lamé parameters of elasticity which depend on space and time due to the antibody concentration history through the parenchyma. The strain is assumed linear:

$$\mathrm{e}_{ij} = \frac{1}{2}\left(\nabla \vec{u} + \nabla \vec{u}^{\mathrm{T}}\right), \tag{3.4}$$

with $\vec{u}$ the displacement of the material and $(\cdot)^{\mathrm{T}}$ the transpose operator.

Combining (3.1)–(3.4) gives the following equation of motion:

$$\begin{aligned}
0 = &-\nabla p + (\lambda + G)\nabla(\nabla \cdot \vec{u}) + G\nabla^2 \vec{u} \\
&+ (\nabla \cdot \vec{u})\nabla\lambda + (\nabla \vec{u} + \nabla \vec{u}^T) \cdot \nabla G.
\end{aligned} \tag{3.5}$$

The first line in (3.5) is the standard equation of motion in linear poroelasticity and the second line arises due to the spatial variability of λ and G.

Darcy's law relates the velocity of the fluid through the porous material to the gradient of the pressure:

$$\phi\vec{W} = -k'\nabla p. \tag{3.6}$$

Here, ϕ is the porosity (or the fluid volume fraction which is equivalent in a saturated media), $\vec{W}$ is the filtration of the fluid (defined to be the velocity of the fluid relative to the solid phase), and $k' = k'(\mathbf{x},t)$ is the hydraulic permeability.

Remark 3.1 In order for CSF pressure to be equal in the ventricle and the subarachnoid space and to be lower inside the parenchyma, an absorption process must occur in the parenchyma to remove the fluid. One possible explanation is that the anti β_1 integrin antibodies degrade the blood brain barrier so that CSF is readily absorbed by the capillaries. This theory, however, is not complete since it only considers hydrostatic pressure gradients as the driving force for CSF into the capillaries.

A more complete explanation for parenchymal absorption is that the antibodies alter the osmotic pressure gradient that exists across capillary walls. By altering the osmotic gradient, CSF can be absorbed into the capillaries even when hydrostatic pressure gradients appear to be inconsistent with such absorption.

Applying conservation of mass to the fluid and solid phases gives

$$\phi_t + \nabla \cdot \left(\phi(\vec{W} + \vec{u}_t)\right) = -Q(\mathbf{x},t) \quad \text{and} \quad (1-\phi)_t + \nabla \cdot ((1-\phi)\vec{u}_t) = 0,$$

where $Q(\mathbf{x}, t)$ represents absorption of CSF by the capillaries (due to osmotic pressure gradients) and depends on space and time due to the antibody concentration. Adding these two equations gives

$$\nabla \cdot (\phi \vec{W} + \vec{u}_t) = -Q(\mathbf{x}, t).$$

Taking the divergence of Darcy's Law (3.6) and substituting into the above equation gives a second equation relating pressure to displacement:

$$\nabla k' \cdot \nabla p + k' \Delta p = \nabla \cdot \vec{u}_t + Q(\mathbf{x}, t). \tag{3.7}$$

Finally, the concentration of antibodies in the parenchyma is governed by the convection-diffusion equation:

$$c_t + \nabla \cdot (c(\vec{W} + \vec{u}_t)) = D\Delta c - \alpha c, \tag{3.8}$$

where D is the diffusion constant and α is an absorption constant. The initial condition $c(0) = 0$ is prescribed meaning that for all $\vec{x}$ the antibody concentration is zero at $t = 0$.

The remaining model parameters satisfy the following evolution equations and initial conditions:

$$k'_t = \nu c \qquad\qquad\qquad k'(0) = \frac{k}{\eta} \tag{3.9}$$

$$\lambda_t = -\gamma H(\lambda - \lambda_{crit})c \qquad\qquad \lambda(0) = \lambda_0 \tag{3.10}$$

$$G_t = -\mu H(G - G_{crit})c \qquad\qquad G(0) = G_0 \tag{3.11}$$

$$Q_t = \rho H(Q_{crit} - Q)c \qquad\qquad Q(0) = Q_0 \tag{3.12}$$

$$\phi_t = -\nabla \cdot \left(\phi(\vec{W} + \vec{u}_t) \right) - Q(\mathbf{x}, t) \qquad\qquad \phi(0) = \phi_0 \tag{3.13}$$

where ν, γ, μ, and ρ are positive constants, k is the initial permeability of the parenchyma, η is the viscosity of the CSF, $H(\cdot)$ is the Heaviside function, the subscript $crit$ denotes the critical value (maximum or minimum), and the subscript 0 denotes the initial value.

We assume the same spherical geometry as Figure 1, and thus prescribe boundary conditions at the ventricle boundary, $r = r_i$, and the subarachnoid space boundary, $r = r_o$. The pressure in the parenchyma should equal the pressure in the ventricle, p_i, at $r = r_i$ and it should equal the pressure in the subarachnoid space, p_o, at $r = r_o$, or:

$$p(r_i) = p_i \qquad\qquad \text{and} \qquad\qquad p(r_o) = p_o.$$

Note that for communicating hydrocephalus, p_i should approximately equal p_o.

The boundary condition for displacement arises due to the continuity of stress at each boundary. That is, the effective stress at each boundary is zero:

$$\sigma_{ij} n_j = 0 \quad \text{at } r = r_i \text{ and at } r = r_o.$$

Note that this case represents infant hydrocephalus where the cerebral plates have yet to fuse and so the skull may enlarge. For adult hydrocephalus, where the skull is rigid, the outer boundary condition should be changed to $u(r_o) = 0$.

Finally, the boundary conditions for the concentration of antibodies are:

$$c(r_i) = c_0 e^{-\theta t} \qquad\qquad \text{and} \qquad\qquad c(r_o) = 0.$$

The inner condition represents an exponentially decaying source of antibodies in the ventricle which approximates the bolus injection draining through the aqueduct. The outer condition represents absorption of the antibodies through the normal CSF absorption mechanisms (arachnoid villi or lymphatic drainage).

3.2 Sensitivity to permeability and absorption. Equations (3.5) and (3.7) are coupled equations for displacement and pressure. By assuming a quasi-static state, $\vec{u}_t = 0$, the equations are decoupled giving a single equation determining the pressure:

$$\nabla k' \cdot \nabla p + k' \Delta p = Q(\mathbf{x}, t). \tag{3.14}$$

The quasi-static state assumes the pressure distribution changes and the solid deforms in response to the pressure change. In reality, the deformation of the solid affects the pressure, but this simplifying assumption is made here to decouple the problem.

An indication of the modelling attempt is obtained by solving (3.14) with prescribed hydraulic permeability and absorption as either constants or linear functions of r. The linear functions used are $k' = 0.05(1 - r)$ and $Q = 800(1 - r)$ and the constants used are $k' = 0.05(1 - 0.2)$ and $Q = 800(1 - 0.2)$ for $0.2 \leq r \leq 0.8$. These functions and values are not physical and were chosen for simplicity. Figure 5 shows these results.

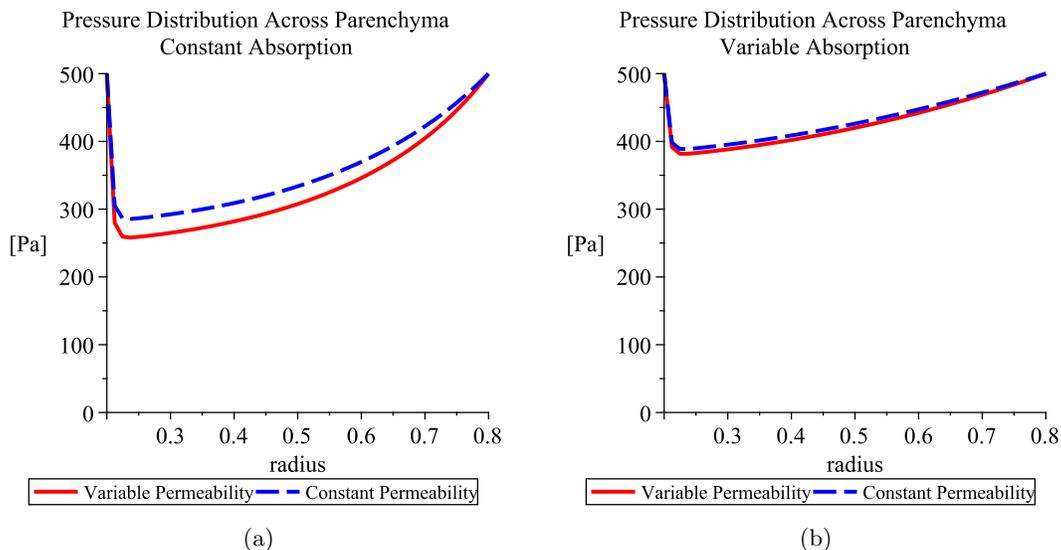|	Pressure Distribution Across Parenchyma Constant Absorption	Pressure Distribution Across Parenchyma Variable Absorption

(a)   (b)

Figure 5: Pressure distributions through the parenchyma assuming constant permeability or variable permeability for either constant absorption (a) or variable absorption (b).

As shown in the simulated pressures in Figure 5, variable permeability slightly lowers the minimum of the pressure curve and absorption strongly affects the shape of the pressure profile. This results from (3.14), since the only solution with $Q(\mathbf{x}, t) = 0$ is $p = p_i = p_o$. Thus, absorption in the parenchyma significantly affects the pressure distribution throughout the brain tissue but permeability does not, so hydraulic permeability, $k'(\mathbf{x}, t)$, may be assumed constant to further simplify the model.

4 Conclusions and Future Work

In working to complete the two objectives outlined in this report, we have identified the pressure distribution throughout the parenchyma and the material parameters of brain tissue as important factors. Future work addressing Objective I would investigate incorporating the compressibility of brain tissue ($\alpha < 1$) into the model and would perform

a sensitivity analysis on how the percentage volume change of the ventricles varies with respect to the model parameters (G and ν in the linear elasticity case as well as k' and $\hat{k}$).

Objective II presents a new model capable of simulating the effect of the antibodies on brain tissue. Future work would include solving the model presented in Section 3.1 and comparing the displacement results to those discussed in Objective I which were obtained from Levine's model [2]. A first approach would be to use the quasi-static state assumption to decouple the model equations for pressure and displacement and to assume constant permeability. A finite element scheme may be necessary to solve the fully coupled model. The large number of model parameters that must be determined from experimental data and the fact that the model is based on linear elasticity are the main limitations of the proposed model.

This preliminary investigation seems to indicate that our assumed mechanical alterations resulting from the injection of anti β_1 integrin antibodies provides the necessary environmental changes in the parenchyma for the pathogenesis of hydrocephalus. A drop in interparenchymal pressure combined with the required increase in CSF absorption by the parenchyma creates the necessary conditions for ventricular enlargement. Add to this, the possibility that antibodies may decrease the elasticity of brain tissue and even more favourable conditions for hydrocephalus are created.

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