JOURNAL OF THE MECHANICAL BEHAVIOR OF BIOMEDICAL MATERIALS 61 (2016) 511–518

Available online at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/jmbbm

Research Paper

On the appropriateness of modelling brain parenchyma as a biphasic continuum

A.C.R. Tavner[a], T. Dutta Roy[a], K.W.W. Hor[a], M. Majimbi[b], G.R. Joldes[a], A. Wittek[a], S. Bunt[b], K. Miller[a,*]

[a]Intelligent Systems for Medicine Laboratory, School of Mechanical and Chemical Engineering, University of Western Australia, 35 Stirling Highway, Crawley 6009, WA, Australia
[b]School of Anatomy, Physiology and Human Biology, University of Western Australia, 35 Stirling Highway, Crawley 6009, WA, Australia

ARTICLE INFO

Article history:
Received 7 January 2016
Received in revised form
6 April 2016
Accepted 6 April 2016
Available online 13 April 2016

Keywords:
Brain
Mechanical properties
Biphasic continuum
Consolidation theory

ABSTRACT

Computational methods originally developed for analysis in engineering have been applied to the analysis of biological materials for many years. One particular application of these engineering tools is the brain, allowing researchers to predict the behaviour of brain tissue in various traumatic, surgical and medical scenarios. Typically two different approaches have been used to model deformation of brain tissue: single-phase models which treat the brain as a viscoelastic material, and biphasic models which treat the brain as a porous deformable medium through which liquid can move. In order to model the brain as a biphasic continuum, the hydraulic conductivity of the solid phase is required; there are many theoretical values for this conductivity in the literature, with variations of up to three orders of magnitude.

We carried out a series of simple experiments using lamb and sheep brain tissue to establish the rate at which cerebrospinal fluid moves through the brain parenchyma. Mindful of possible variations in hydraulic conductivity with tissue deformation, our intention was to carry out our experiments on brain tissue subjected to minimal deformation. This has enabled us to compare the rate of flow with values predicted by some of the theoretical values of hydraulic conductivity from the literature. Our results indicate that the hydraulic conductivity of the brain parenchyma is consistent with the lowest theoretical published values. These extremely low hydraulic conductivities lead to such low rates of CSF flow through the brain tissue that in effect the material behaves as a single-phase deformable solid.

*Corresponding author. Tel.: +61 8 6488 8545; fax: +61 8 6488 1024.
E-mail address: karol.miller@uwa.edu.au (K. Miller).

http://dx.doi.org/10.1016/j.jmbbm.2016.04.010
1751-6161/

1. Introduction

Computational biomechanics has been used extensively to investigate various mechanical phenomena affecting the brain, for example to model traumatic brain injury, neurosurgery, brain diseases (hydrocephalus, tumour growth) and drug delivery. Computational models require an appropriate mathematical framework for describing the mechanical behaviour of the brain parenchyma. The most widely-used models either treat the brain parenchyma as a single phase or a biphasic continuum. For example, biphasic theory (originally developed to model the behaviour of soils, and often termed soil consolidation theory) has been used to model the development of hydrocephalus (Kaczmarek et al., 1997; Momjian and Bichsel, 2008; Nagashima et al., 1987; Peña et al., 1999; Smillie et al., 2005; Taylor and Miller, 2004; Sobey and Wirth, 2006, Wirth and Sobey, 2006, 2009; Cheng and Bilston, 2010) and brain deformations during neurosurgery (Lunn et al., 2006; Miga et al., 1999, 2000; Paulsen et al., 1999; Platenik et al., 2002) as well as to understand phenomena such as convection enhanced drug delivery (Ding et al., 2010; Sampson, 2009; Vogelbaum et al., 2007; Sampson et al., 2007a, 2007b, 2007c; Song and Lonser, 2008; Jagannathan et al., 2008; Szerlip et al., 2007; Morrison et al., 2007; Lonser et al., 2007b, 2007a; Murad et al., 2007, 2002; Croteau et al., 2005; Degen et al., 2003; Sarntinoranont et al., 2003b, 2006, 2003a, 2003c; Raghavan, 2010; Linninger et al., 2008b, 2008a; Somayaji et al., 2008; Astary et al., 2010; Chen et al., 2008, 2007; Chen and Sarntinoranont, 2007). Single-phase continuum theory has been used to model brain injury (King, 2000; Yang and King, 2003; Zhang et al., 2001b, 2001a, 2002, 2004; Donnelly and Medige, 1997; Bilston et al., 2001; Brands et al., 2004; Hrapko et al., 2006, 2009; Nicolle et al., 2004; Ning et al., 2006; Shen et al., 2006; Takhounts et al., 2003), and more recently has been applied to the analysis of hydrocephalus (Dutta-Roy et al., 2008), modelling neurosurgery (Wittek et al., 2007) and surgical simulation (e.g. needle insertion) (Miller et al., 2010).

Franceschini et al. (2006) claim to have presented direct experimental evidence to support the hypothesis that brain tissue is well described by soil consolidation theory and hence is biphasic. Experimental work described by Cheng and Bilston, (2007) appears to support this conclusion.

The objective of the work presented here was to establish whether the response of brain parenchyma is consistent with the results produced by models using soil consolidation theory, which treat the parenchyma as a biphasic continuum (Biot, 1941; Bowen, 1976; Miller, 1998). We carried out simple experiments using samples of lamb and sheep brain tissue subjected to artificial cerebrospinal fluid (ACSF) at typical intracranial pressures to establish the rate at which ACSF moves through the brain parenchyma – an important parameter for setting up an accurate biphasic model. Other researchers working with similar types of tissue report significant reductions in permeability with compressive deformation (Heneghan and Riches, 2008). It was our intention to carry out our experiments on brain tissue subjected to minimal deformation.

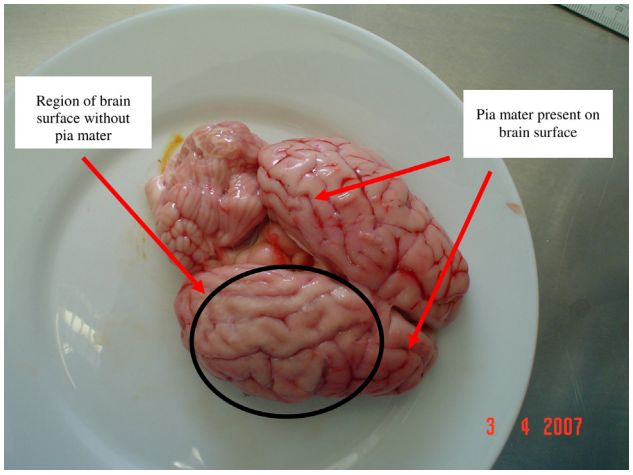

Fig. 1 – Brain surface after removal of the pia mater.

2. Experiments and results

2.1. *Specimen preparation*

Lamb brains were obtained as by-products of the commercial slaughter process, and sheep brains were obtained as a by-product of medical training procedures. The pia mater was carefully teased out from the Sulci features on the brain surface using two pairs of Dupont's Swiss Tweezers Number 7. Thereafter, the pia mater was gently removed from the brain surface (Fig. 1). An approximately cylindrical sample (diameter ~30mm and height ~20mm) was cut out of the region of the brain from which the pia mater was removed, using a sharp cylindrical punch and scalpel (Miller and Chinzei, 1997).

Artificial cerebrospinal fluid (ACSF) solution was prepared with the chemical composition 148 mM NaCl, 3 mM KCl, 1.4 mM $CaCl_2 \cdot 2H_20$, 801 mM $MgCl_2 \cdot 6H_20$, 800 mM $Na_2HPO_4 \cdot 7H_20$ and 225 mM NaH_2PO_4 dissolved in double distilled water.

2.2. *Experimental apparatus*

The experimental apparatus is shown in Fig. 2. It consists of a cylindrical die (1) of the same internal diameter as the punch used to remove specimens from the brain, and transparent plastic tube of length 85 cm (2). A taper was provided near the base of the cylindrical die, and a knife edge was machined on its base (Fig. 3a and b). To ensure sealing between the transparent plastic tube and cylindrical die, a groove to suit an O-ring was machined into the die (Fig. 3a and b). A wire mesh (mesh size: 2 mm) was attached to the bottom of the die.

2.3. *Biphasic theory predictions*

Soil consolidation theory (Biot, 1941; Bowen, 1976; Miller, 1998), such as that used in (Kaczmarek et al., 1997; Momjian and Bichsel, 2008; Nagashima et al., 1987; Peña et al., 1999; Smillie et al., 2005; Taylor and Miller, 2004; Sobey and Wirth, 2006, Wirth and Sobey, 2006, 2009; Cheng and Bilston, 2010) to model the development of hydrocephalus, and in (Lunn et al.,

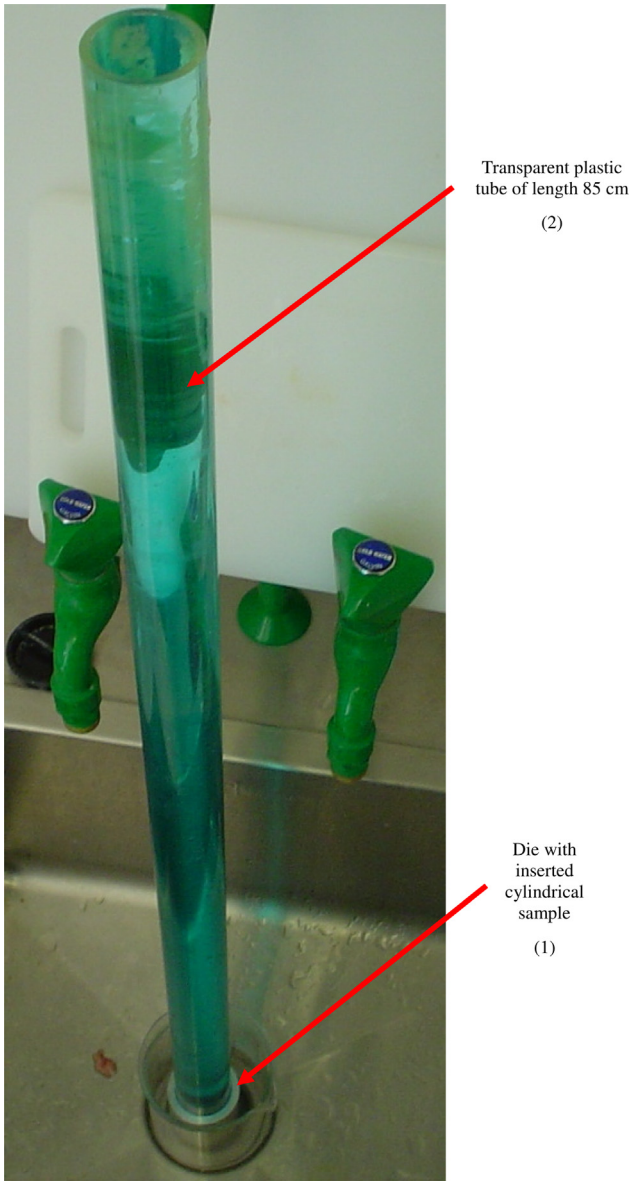

Fig. 2 – Assembled experimental setup with 85 cm ACSF column applying pressure on cylindrical brain sample inserted into the die.

2006; Miga et al., 1999, 2000; Paulsen et al., 1999; Platenik et al., 2002) to model brain deformation during neurosurgery, predicts that brain tissue subjected to ACSF at normal pressure gradients should allow the ACSF to percolate through the brain tissue. In our experiments, cylindrical brain samples subjected to pressure from a column of ACSF will not deform (due to incompressibility (Miller and Chinzei, 1997; Pamidi and Advani, 1978; Walsh and Schettini, 1984; Sahay et al., 1992; Mendis et al., 1995; Farshad et al., 1999; Miller, 2000) and confinement of the sample). In this simple case, soil consolidation theory reduces to Darcy's Law (Biot, 1941; Bowen, 1976; Miller, 1998), described by the following equations (ABAQUS/Standard, 2004):

$$q = -k\frac{\partial \phi}{\partial z} \tag{1a}$$

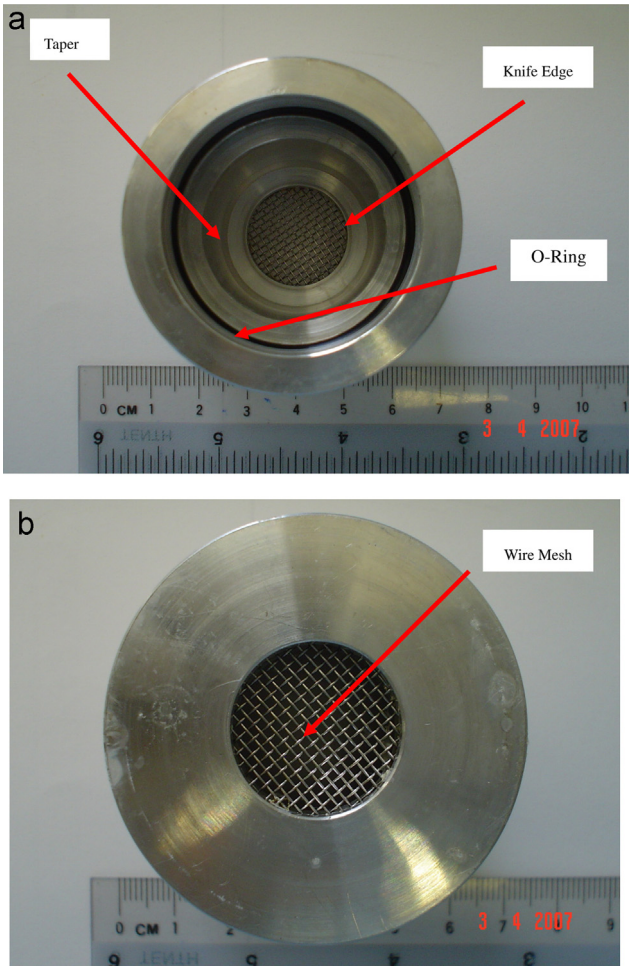

Fig. 3 – Top (a) and bottom (b) view of the cylindrical die.

Table 1 – Theoretical volume flowrate of CSF through the cylindrical brain parenchyma sample. The values of hydraulic conductivity (*k*) of the brain parenchyma were taken from the literature. To the best of the authors' knowledge none of these values was measured directly.

Hydraulic conductivity (m/sec)	ACSF flowrate (ml/h)
1.37×10^{-7} (Smillie et al., 2005)	3.8
1.59×10^{-7} (Kaczmarek et al., 1997)	4.4
2.42×10^{-10} (Franceschini et al., 2006)	0.007
8.11×10^{-8} (Cheng and Bilston, 2007)	2.2

$$\phi = z + \frac{u_\omega}{g\rho_\omega} \tag{1b}$$

where: q is the volumetric flowrate per unit area [m^3/m^2 sec], k is the hydraulic conductivity of the medium [m/sec], Φ is the piezometric head [m], u_ω is the pressure of wetting fluid [Pa], ρ_ω is the density of the wetting fluid [kg/m^3], z is the elevation above a datum [m] and g is the magnitude of the gravitational acceleration [m/sec^2] which acts in the reverse z direction. There are various values for the hydraulic conductivity (k) of the brain parenchyma used in the literature as summarised in Table 1. The brain samples used in our experiments were approximately cylindrical with a diameter ~30 mm and height ~20 mm. For a pressure equivalent to a

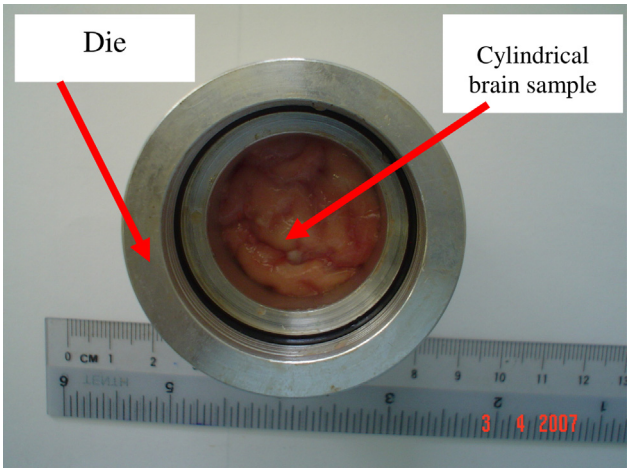

Fig. 4 – Cylindrical sample inserted into the die.

20 cm column of CSF solution, the total volumetric flowrate of ACSF for different hydraulic conductivities through the cylindrical sample per hour was calculated (Eqs. 1a and 1b) and these values are summarised in Table 1.

In Eqs 1(a) and 1(b), the flowrate q is related to the seepage velocity (v_ω) by the saturation s and the porosity n (i.e. $q=s\,n\,v_\omega$). The unit of hydraulic conductivity of the medium (k) in our calculations is [m/sec]. Often in the literature hydraulic conductivity is used to relate the seepage velocity (v_ω) to the pressure gradient. In such cases, the unit of hydraulic conductivity of the medium (k) is [m^4/N sec].

2.4. *Experiment 1: experimental procedure*

Cylindrical brain samples were carefully inserted into the die (Fig. 4), ensuring that the sample did not deform during insertion. Because our samples were cut using a punch with the same internal diameter as the die, the strain induced by mounting within the die was negligibly small. The transparent plastic tube was then attached to the die and the assembly was stood in a beaker. ACSF solution was poured into the tube. Consequently, the brain sample in the die was subjected to hydrostatic pressure from a column of ACSF solution in the transparent plastic tube (Fig. 2). Because the pia mater had been removed from the brain surface, the brain parenchyma was directly exposed to the ACSF solution (Fig. 3a), while the ventricular surface of the brain parenchyma sample was retained within the die by the wire mesh at the bottom end (Fig. 3b). Under the ACSF solution pressure, the taper at the base and the knife edge in the cylindrical die, along with the slightly adhesive nature of the brain tissue itself, form a seal between the sample and the die. This effectively divided the die into two separate sections, one being above the brain tissue sample, the second being below it.

Three different heights of ACSF solution column were applied to the cylindrical brain samples held in the die and are summarised in Table 2. Each height of the ACSF solution column was applied for a period of 120 min. This time frame was chosen to prevent deterioration of the brain tissue sample, while still allowing enough time for the ACSF solution from the tube to move through the brain tissue. The O-ring seal between the die and the transparent plastic tube prevented any leakage of ACSF solution leakage at the tube-die connection.

Table 2 – Height of artificial CSF column applied on the brain sample.

Load case	Height of artificial CSF column (cm)	Comments (Milhorat, 1972)
Load case 1	10 cm or 981 Pa	Normal CSF pressure in ventricles
Load case 2	20 cm or 1962 Pa	CSF pressure in ventricles during Normal Pressure Hydrocephalus
Load case 3	85 cm or 8338.5 Pa	CSF pressure in ventricles during High Pressure Hydrocephalus

A first group of lamb brain samples (three samples from three different lamb brains) were tested at the different column heights for two hours each. A second group of sheep brain samples were tested at load case 2 (20 cm column height of ACSF) for longer periods of 4, 8, 16 and 20 h.

2.5. *Experiment 1: results*

In the first group of tests, for all three load cases (10 cm, 20 cm and 85 cm ACSF column heights), after 120 min we observed no leakage of ACSF solution into the beaker through the brain tissue. Also, no measurable change in the height of the ACSF solution column in the transparent plastic tube was observed. The same results were obtained using the sheep brains for varying and considerable longer time periods.

According to the theoretical predictions in Table 1 above, between 0.014 ml and 8.8 ml of ACSF should have passed through the brain tissue during the two-hour tests.

2.6. *Experiment 2: ACSF containing dye: procedure and results*

We carried out a second set of experiments using the same apparatus, modified to include a capillary tube above the ACSF column. This was added to allow us to detect the movement of a very small quantity of liquid into the brain tissue. Sheep brains were prepared in the same way as the first experiment described in 2.1 above. Brain samples were subjected to a column of ACSF as before, with the addition that the base of the test column was immersed in additional ACSF to keep the brain tissue hydrated, and a layer of filter paper was added to the grid at the base of the steel die to prevent extrusion of the brain tissue through the mesh. Toluidine Blue dye was added to the ACSF (170 mg/l) in the column above the brain tissue sample to assist with the observation of flow in the apparatus and into the brain tissue. The brain samples were left in the apparatus under 20 cm of ACSF for periods of up to 23 h, and were then removed, frozen, sectioned and mounted for observation under a microscope. Nine tests were carried out with samples from nine different sheep brains.

Following these tests, the un-dyed ACSF in the beaker below the test column showed no trace of the Toluidine Blue dye contained in the ACSF above the samples. The filter

papers from the base of each sample were also examined, and again there was no trace of the dye visible. Movement of the ACSF column in the capillary tube above the brain parenchyma sample indicated that ACSF was moving into the brain, at a rate of between 1.7 μl/h and 0.5 μl/h, however the extreme difficulty of measuring such small quantities calls into question the absolute accuracy of these numbers. However it is worth noting that the range of results here is appreciably smaller than the flowrates predicted using the smallest value of hydraulic conductivity from the literature (7 μl/h, see Table 1).

The sections of brain from these tests were observed under a microscope and the depth of penetration of the toluidine blue dye into the brain tissue was estimated. From these measurements (536 separate measurements across samples from 9 different brains) values for the seepage rate of ACSF into the brain tissue were estimated.

Values of the seepage rate into the brain across all nine samples ranged from 6 μm/h to 200 μm/h, with a mean of 60.8 μm/h with a standard deviation of 58.6 μm/h. Assuming a high level of saturation and a typical brain porosity value of 0.2 (Chen and Sarntinoranont, 2007) this would give an approximate flowrate of ACSF of 30 μl/h, treating the brain sample as a plain cylinder as with the calculations carried out for Table 1.

2.7. *Experiment 3: ACSF containing fluorescent nano-particles: procedure and results*

The experiments with toluidine blue dye were also repeated with a version of the ACSF containing 5 mg/l of PGMA polymer nano-particles (≈ 90 nm in diameter) with Rhodamine B attachments. For these experiments, sheep brains were prepared as before. The brain tissue samples were placed in the apparatus under 20 cm of ACSF for periods of up to 18 h. Once exposure to the ACSF column was complete, the brain samples were removed, frozen, sectioned and mounted for viewing under a microscope. The Rhodamine B attached to the nano-particles causes them to glow red when illuminated with green light, and therefore it was possible to see the depth of penetration of the particles into the brain samples. (Fig. 5). 420 individual measurements across 16 samples from 5 different brains were used to estimate the flowrate of ACSF into the brain parenchyma.

Values for the seepage rate in these experiments ranged from 6 μm/h to 84 μm/h with a mean of 31.4 μm/h and a Standard Deviation of 30.4 μm/h. Converting that to an absolute volume flowrate as before, gives a mean value of approximately 16 μl/h.

3. Discussion

As mentioned earlier, a number of researchers have used biphasic (soil consolidation) continuum theory to model the brain parenchyma (Kaczmarek et al., 1997; Momjian and Bichsel, 2008; Nagashima et al., 1987; Peña et al., 1999; Smillie et al., 2005; Taylor and Miller, 2004; Sobey and Wirth, 2006; Wirth and Sobey, 2006, 2009; Cheng and Bilston, 2010; Lunn et al., 2006; Miga et al., 1999, 2000; Paulsen et al., 1999; Platenik et al., 2002). According to biphasic theory, Darcy's Law (Eqs. 1a and 1b) models the flow of a wetting liquid through the porous solid phase. Simple calculations using Darcy's Law (Section 2.4 and Table 1), showed that in the experiments carried out here, with durations of up to 23 h, a noticeable and measurable amount of the ACSF solution should have passed into – or even through – the cylindrical brain sample. However, no ACSF solution passed through the brain tissue into the beaker below, and subsequent experiments using capillary tubes, dye, and nano-particles all show that the quantity of fluid passing into the brain tissue is very small indeed. Our experimental observations do not support the total volumetric flow of ACSF solution as predicted by Darcy's Law (Table 1) using theoretical hydraulic conductivities published in the literature, with the exception of the value used by Franceschini et al. (2006). This extremely low value of hydraulic conductivity, which gives values of seepage velocity closest to our experimentally measured values - effectively prevents any substantial flow through the solid matrix and therefore makes the biphasic model for all practical purposes equivalent to a single phase model at typical physiological pressure loads. In cases where compressive deformation of the brain tissue is occurring, it would be expected that the hydraulic conductivity would reduce even further (Heneghan and Riches, 2008). This suggests that the computational effort of running a biphasic model is unnecessary, and single phase viscoelastic models would be able to perform the same simulations of brain deformation more quickly and simply. It should be noted that our approximated

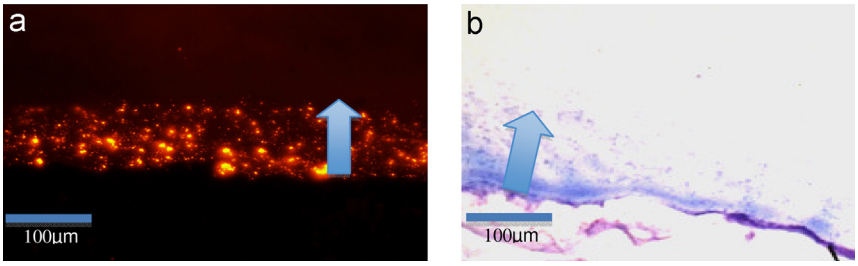

Fig. 5 – Showing (a) Nano-particles fluorescing under green light and (b) penetration of Toluidine Blue dye into brain tissue. The blue arrows indicate the direction in which measurements were taken to establish the depth of penetration of the ACSF into the brain tissue. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

surface area – treating the brain sample as a plain cylinder and ignoring the sulci on the upper surface – will have caused us to underestimate the theoretical flowrate of ACSF into the samples, and (combined with the assumptions made about the degree of saturation) to overestimate the experimental flowrate. This would be likely to bring our experimental results and the results predicted using Franceschini's (Franceschini et al., 2006) hydraulic conductivity closer together.

An obvious limitation of our work is that we have not attempted to establish the variation of hydraulic conductivity with changing deformation, and as mentioned earlier this was never the intention of our experiments. Because we would expect compressive deformation to reduce the hydraulic conductivity (Heneghan and Riches, 2008), which was already very low in strain-free tissue, it seems likely that another study using considerably more sophisticated apparatus and different measurement techniques would be required to establish this relationship.

A further limitation of our work is that the experiments were all carried out *in-vitro*, but hydraulic conductivity in the brain tissue decreases with increasing time *post mortem*. We attempted to minimise this possible effect by using artificial CSF for pressure loading, however we attribute the large standard deviations in our results to varying *post mortem* times at the point of testing. It should be noted that *post mortem* reduction of the hydraulic conductivity has not been considered by other experimenters either. In particular, work by Franceschini et al. (2006) and Cheng and Bilston (2007) still concludes that brain tissue *in-vitro* is biphasic. Furthermore, there are known to be differences in hydraulic conductivity measured in different species (Abbott, 2004).

It could also be argued that the interstitial gap in the brain tissue is typically of the order of a few nanometres and as a result the capillary forces are high. High capillary forces might be expected to prevent the flow of ACSF through the brain parenchyma sample. It should be remembered that the biphasic models were developed to predict the behaviour of soils, and the interstitial gap in clay soils is of the order of a few angstroms (Mitchell, 1993) and no capillary effect is seen. Fluid passes through a clay soil, albeit at a very slow rate. Furthermore, soil consolidation theory is still used to understand and predict the deformation and effective stresses of clay soils due to fluid flow.

Our experimental results are inconsistent with many studies on convection-enhanced drug delivery (CED), which demonstrate that an infused agent can be delivered to volumes of the brain beyond that which would occur by diffusion alone. We do not wish to speculate how this is possible; however we do not believe that this mechanism can be adequately described by biphasic (soil consolidation) theory. Furthermore, the very low theoretical values of hydraulic conductivity already in use do not appear to provide adequate flowrates to explain CED. Work by Smith and Garcia (Smith and Garcia, 2011) on developing coupled biphasic – mass transport models using non-linear material properties along with non-linear variation of hydraulic conductivity with tissue deformation clearly demonstrates the complexity of studying CED in the brain and also illustrates the limitations of biphasic models in these applications. It should also be noted that the models of CED (or hydrocephalus and other complicated phenomena) have never been validated experimentally in a straightforward experiment such as the work we report here.

Furthermore, Abbott, (2004) presents a review for evidence of bulk flow of CSF through the brain parenchyma. The review showed that there are multiple mechanisms (pressure gradient, concentration gradient etc.) for bulk flow through the brain parenchyma, and pin-pointing the exact mechanism – or combination of mechanisms – is controversial. Moreover, it should be noted that flow rates of 0.15–0.29 μl min^{-1} $gbrain^{-1}$ for rats and 0.10–0.15 μl min^{-1} $gbrain^{-1}$ for rabbits were recorded. These rates could be regarded as bulk flow and be significant for some phenomenon associated with the brain (drug therapy, immune surveillance and inflammation, stem cell therapies etc.). But for phenomenon such as modelling of Normal Pressure Hydrocephalus (NPH), brain deformation during surgery etc. such extremely low flow rates are insignificant, and of course the deformation itself serves to reduce the hydraulic conductivity and hence the flow rates of CSF through the tissue. This further strengthens our argument that extremely low values of hydraulic conductivity (Table 1 and (Franceschini et al., 2006)), essentially prevent any substantial flow through the solid matrix and therefore make the biphasic model almost equivalent to single phase models at physiological pressure loads, with the computational advantages that brings. The large discrepancy in the theoretical hydraulic conductivities reported in the literature (covering three orders of magnitude) suggests that the use of biphasic (consolidation) theory for analyzing various phenomena in the brain may not be as solidly anchored in reality as one might hope.

4. Conclusions

Our experiments show that the rate at which ACSF flows through the brain parenchyma is very low, and our results broadly agree with the values that one might expect using the very lowest of the published theoretical values of hydraulic conductivity (Franceschini et al., 2006). These very low values of hydraulic conductivity appear to prevent any substantial flow though the brain tissue, therefore we believe that the modelling of brain deformation would be more efficiently performed using single-phase viscoelastic or hyperelastic models. If there is a need to model fluid flow within the brain parenchyma, for applications such as convection enhanced drug delivery or nutrient transfer, it is necessary to use more sophisticated models incorporating principles of mass transport phenomena (Smith and Garcia, 2011; Bird et al., 1960) coupled with mathematical formulations for the calculation of brain parenchyma deformation.

Acknowledgements

Financial support of the William and Marlene Schrader Trust in the form of the William and Marlene Schrader Post-Graduate Scholarship for the second author is gratefully acknowledged. This research has also been funded by Australian Research

Council (Grants nos. DP0343112, DP0664534) and National Institute of Health (Grant no. R03 CA126466-01A1). The authors gratefully acknowledge Mr Darryl Kirk, Mr Steve Parkinson, Ms Margaret Pollett and Mr Irving Aye for their assistance with the experimentation, Mr. Callum Ormonde for providing the nanoparticles, and Mr Nicholas Grainger from the Royal Perth Hospital for providing sheep brains.

REFERENCES

ABAQUS/Standard, Version 6.5.4, 2004. Hibbit, Karlsson & Sorenson Inc.
Abbott, N.J., 2004. Neurochem. Int. 45, 545–552.
Astary, G.W., Kantorovich, S., Carney, P.R., Mareci, T.H., Sarntinoranont, M., 2010. J. Neurosci. Methods 187, 129–137.
Bilston, L.E., Liu, Z., Phan-Thien, N., 2001. Biorheology 38, 335–345.
Biot, M.A., 1941. J. Appl. Phys. 12, 1244–1258.
Bird, R.B., Stewart, W.E., Lightfoot, E.N., 1960. In: Transport Phenomena. Wiley, New York.
Bowen, R.M., 1976. Theory of mixtures. In: Eringen, A.C. (Ed.), Continuum Physics, 2. Academic Press, New York.
Brands, D.W.A., Peters, G.W.M., Bovendeerd, P.H.M., 2004. J. Biomech. 37, 127–134.
Chen, X., Sarntinoranont, M., 2007. Ann. Biomed. Eng. 35, 2145–2158.
Chen, X., Astary, G.W., Sepulveda, H., Mareci, T.H., Sarntinoranont, M., 2008. Magn. Reson. Imaging 26, 1433–1441.
Chen, X., Astary, G.W., Mareci, T.H., Sarntinoranont, M., 2007. Annual International Conference of the IEEE Engineering in Medicine and Biology – Proceedings, Art. no. 4352932 , pp. 2887–2890.
Cheng, S., Bilston, L.E., 2007. J. Biomech. 40, 117–124.
Cheng, S., Bilston, L.E., 2010. J. Biomech. Eng. – Trans. ASME 132.
Croteau, D., Walbridge, S., Morrison, P.F., Butman, J.A., Vortmeyer, A.O., Johnson, D., Oldfield, E.H., Lonser, R.R., 2005. J. Neurosurg. 102, 90–97.
Degen, J.W., Walbridge, S., Vortmeyer, A.O., Oldfield, E.H., Lonser, R.R., 2003. J. Neurosurg. 99, 893–898.
Ding, D., Kanaly, C.W., Brady, M.L., Mittermeyer, S., Raghavan, R., Sampson, J.H., 2010. Neuromethods 45, 291–318.
Donnelly, B.R., Medige, J., 1997. J. Biomech. Eng. – Trans. ASME 119, 423–432.
Dutta-Roy, T., Wittek, A., Miller, K., 2008. J. Biomech. 41, 2263–2271.
Farshad, M., Barbezat, M., Flueler, P., Schmidlin, F., Graber, P., Niederer, P., 1999. J. Biomech. 32, 417–425.
Franceschini, G., Bigoni, D., Regitnig, P., Holzapfel, A., 2006. J. Mech. Phys. Solids 54, 2592–2620.
Heneghan, P., Riches, P.E., 2008. J. Biomech. 41, 903–906.
Hrapko, M., van Dommelen, J.A.W., Peters, G.W.M., Wismans, J.S.H.M., 2006. Biorheology 43, 623–636.
Hrapko, M., van Dommelen, J.A.W., Petersa, G.W.M., Wismansb, J.S.H.M., 2009. Int. J. Crashworthiness 14, 245–257.
Jagannathan, J., Walbridge, S., Butman, J.A., Oldfield, E.H., Lonser, R.R., 2008. J. Neurosurg. 109, 547–552.
Kaczmarek, M., Subramaniam, R.P., Neff, S.R., 1997. Bull. Math. Biol. 59, 295–323.
King, A.I., 2000. Annu. Rev. Biomed. Eng., 55–81.
Linninger, A.A., Somayaji, M.R., Mekarski, M., Zhang, L., 2008. J. Theor. Biol. 250, 125–138.
Linninger, A.A., Somayaji, M.R., Zhang, L., Smitha Hariharan, M., Penn, R.D., 2008. IEEE Trans. Biomed. Eng. 55, 2303–2313.
Lonser, R.R., Walbridge, S., Garmestani, K., Butman, J.A., Walters, H.A., Vortmeyer, A.O., Morrison, P.F., Brechbiel, M.W., Oldfield, E.H., 2002. J. Neurosurg. 97, 905–913.
Lonser, R.R., Schiffman, R., Robison, R.A., Butman, J.A., Quezado, Z., Walker, M.L., Morrison, P.F., Walbridge, S., Murray, G.J., Park, D.M., Brady, R.O., Oldfield, E.H., 2007. Neurology 68.
Lonser, R.R., Warren, K.E., Butman, J.A., Quezado, Z., Robison, R.A., Walbridge, S., Schiffman, R., Merrill, M., Walker, M.L., Park, D.M., Croteau, D., Brady, R.O., Oldfield, E.H., 2007. J. Neurosurg. 107, 190–197.
Lunn, K.E., Paulsen, K.D., Liu, F., Kennedy, F.E., Hartov, A., Roberts, D.W., 2006. IEEE Trans. Biomed. Eng. 53, 1893–1900.
Mendis, K.K., Stalnaker, R.L., Advani, S.H., 1995a. J. Biomech. Eng. – Trans. ASME 117, 279–285.
Miga, M.I., Paulsen, K.D., Hoopes, P.J., Kennedy, F.E., Hartov, A., Roberts, D.W., 2000. IEEE Trans. Biomed. Eng. 47, 266–273.
Miga, M.I., Paulsen, K.D., Lemery, J.M., Eisner, S.D., Hartov, A., Kennedy, F.E., Roberts, D.W., 1999. IEEE Trans. Biomed. Eng. 45, 1199–1207.
Milhorat, T.H., 1972. Hydrocephalus and the Cerebrospinal Fluid. The Williams and Wilkins Company, Baltimore.
Miller, K., 1998. Comput. Methods Biomech. Biomed. Eng. 1, 216–263.
Miller, K., 2000. J. Biomech. 33, 367–373.
Miller, K., Chinzei, K., 1997. J. Biomech. 30, 1115–1121.
Miller, K., Wittek, A., Joldes, G., Horton, A., Dutta-Roy, T., Berger, J., 2010. Int. J. Numer. Methods Eng. 26, 117–138.
Mitchell, J.K., 1993. Fundamentals of Soil Behaviour. Wiley, New York.
Momjian, S., Bichsel, D., 2008. J. Neurosurg. 109, 100–107.
Morrison, P.F., Lonser, R.R., Oldfield, E.H., 2007. J. Neurosurg. 107, 74–83.
Murad, G.J.A., Walbridge, S., Morrison, P.F., Szerlip, N., Butman, J.A., Oldfield, E.H., Lonser, R.R., 2007. J. Neurosurg. 106, 351–356.
Nagashima, T., Tamaki, N., Matsumoto, S., Horwitz, B., Seguchi, Y., 1987. Neurosurgery 21, 898–903.
Nicolle, S., Lounis, M., Willinger, R., 2004. Stapp Car Crash J. 48, 239–258.
Ning, X., Zhu, Q., Lanir, Y., Margulies, S.S., 2006. J. Biomech. Eng. – Trans. ASME 128, 925–933.
Pamidi, M.R., Advani, S.H., 1978. Trans. ASME, J. Biomech. Eng. 100, 44–48.
Paulsen, K.D., Miga, M.I., Kennedy, F.E., Hoops, P.J., Hartov, A., Roberts, D.W., 1999. IEEE Trans. Biomed. Eng. 46, 213–225.
Peña, A., Bolton, M.D., Whitehouse, H., Pickard, J.D., 1999. Neurosurgery 45, 107–118.
Platenik, L.A., Miga, M.I., Roberts, D.W., Lunn, K.E., Kennedy, F.E., Hartov, A., Paulsen, K.D., 2002. IEEE Trans. Biomed. Eng. 49, 823–835.
Raghavan, R., 2010. Neuromethods 45, 85–135.
Sahay, K.B., Mehrotra, R., Sachdeva, U., Banerji, A.K., 1992. J. Biomech. 25, 319–326.
Sampson, J.H., 2009. Neurosurgery 65, 585–586.
Sampson, J.H., Raghavan, R., Provenzale, J.M., Croteau, D., Reardon, D.A., Coleman, R.E., Ponce, I.R., Pastan, I., Puri, R.K., Pedain, C., 2007. Am. J. Roentgenol. 188, 703–708.
Sampson, J.H., Brady, M.L., Petry, N.A., Croteau, D., Friedman, A.H., Friedman, H.S., Wong, T., Bigner, D.D., Pastan, I., Puri, R.K., Pedain, C., 2007. Neurosurgery 60 ONS-89-ONS-98.
Sampson, J.H., Raghavan, R., Brady, M.L., Provenzale, J.M., Herndon II, J.E., Croteau, D., Friedman, A.H., Reardon, D.A., Coleman, R.E., Wong, T., Bigner, D.D., Pastan, I., Rodríguez-Ponce, M.I., Tanner, P., Puri, R., Pedain, C., 2007. Neuro-Oncology 9, 343–353.
Sarntinoranont, M., Rooney, F., Ferrari, M., 2003. Interstitial stress and fluid pressure within a growing tumor. Ann. Biomed. Eng. 31, 327–335.
Sarntinoranont, M., Iadarola, M.J., Lonser, R.R., Morrison, P.F., 2003. Am. J. Physiol. – Regul. Integr. Comp. Physiol. 285, R243–R254.
Sarntinoranont, M., Banerjee, R.K., Lonser, R.R., Morrison, P.F., 2003. Ann. Biomed. Eng. 31, 448–461.

Sarntinoranont, M., Chen, X., Zhao, J., Mareci, T.H., 2006. Ann. Biomed. Eng. 34, 1304–1321.
Shen, F., Tay, T.E., Li, J.Z., Nigen, S., Lee, P.V.S., Chan, H.K., 2006. J. Biomech. Eng. – Trans. ASME 128, 797–801.
Smillie, A., Sobey, I., Molnar, Z., 2005. J. Fluid Mech. 539, 417–443.
Smith, J.H., Garcia, J.J., 2011. J. Biomech. 44, 524–531.
Sobey, I., Wirth, B., 2006. Math. Med. Biol. 23, 339–361.
Somayaji, M.R., Xenos, M., Zhang, L., Mekarski, M., Linninger, A. A., 2008. Comput. Chem. Eng. 32, 89–98.
Song, D.K., Lonser, R.R., 2008. J. Child Neurol. 23, 1231–1237.
Szerlip, N.J., Walbridge, S., Yang, L., Morrison, P.F., Degen, J.W., Jarrell, S.T., Kouri, J., Kerr, P.B., Kotin, R., Oldfield, E.H., Lonser, R.R., 2007. J. Neurosurg. 107, 560–567.
Takhounts, E.G., Crandall, J.R., Darvish, K.K., 2003. Stapp Car Crash J. 47, 107–134.
Taylor, Z., Miller, K., 2004. J. Biomech. 37, 1263–1269.
Vogelbaum, M.A., Sampson, J.H., Kunwar, S., Chang, S.M., Shaffrey, M., Asher, A.L., Lang, F.F., Croteau, D., Parker, K., Grahn, A. Y., Sherman, J.W., Husain, S.R., Puri, R.K., 2007. Neurosurgery 61, 1031–1037.
Walsh, E.K., Schettini, A., 1984. Am. J. Physiol. 247, R637–R700.
Wirth, B., Sobey, I., 2006. Math. Med. Biol. 23, 363–388.
Wirth, B., Sobey, I., 2009. Math. Med. Biol. 26, 25–61.
Wittek, A., Miller, K., Kikinis, R., Warfield, S.K., 2007. J. Biomech. 40, 919–929.
Yang, K.H., King, A.I., 2003. Int. J. Veh. Des. 32, 116–129.
Zhang, L., Yang, K.H., King, A.I., 2001. J. Neurotrauma 18, 21–30.
Zhang, L., Yang, K.H., King, A.I., 2004. J. Biomech. Eng. 126, 226–236.
Zhang, L., Bae, J., Hardy, N.W., Monson, K.L., Manley, G.T., Goldsmith, W., Yang, K.H., King, A.I., 2002. Stapp Car Crash J. 46, 145–163.
Zhang, L., Yang, K.H., Dwarampudi, R., Omori, K., Li, T., Chang, K., Hardy, W.N., Khalil, T.B., King, A.I., 2001. Stapp Car Crash J. 45, 369–394.