INTERNATIONAL JOURNAL OF
NUMERICAL ANALYSIS AND MODELING, Series B
Volume 3, Number 1, Pages 82–93

A MECHANO-ELECTROCHEMICAL MODEL OF BRAIN NEURO-MECHANICS: APPLICATION TO NORMAL PRESSURE HYDROCEPHALUS

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Abstract. Normal pressure hydrocephalus (NPH) is a neurological condition that occurs in adults usually older than sixty years, characterized by an excessive accumulation of celebrospinal fluid in the brain ventricles in the absence of an elevated intracranial pressure. Although the first description of this disease has been given in 1965 by Hakim and Adams, the progress in improving the diagnosis and treatment outcome of NPH has been slow due mainly to the fact that the causes of NPH continue to remain unknown in most of the cases. The few existing biomechanical models of NPH existing in the literature are based on the bulk flow theory which requires an increased intracranial pressure and thus fail to properly explain the onset of NPH. The aim of the present paper is to formulate the first neuro-mechanical model that will couple the electro-chemical and mechanical properties of the brain. We assume that the brain tissue is a charged hydrated soft tissue made of a solid phase, an interstitial fluid phase and an ion phase with (for now) two monovalent ion species. Using our model, we will show that NPH could be caused by a change in the concentrations of Na^+ and Cl^- in the ventricular cerebrospinal fluid in the absence of an elevated intracranial pressure.

Key words. brain neuro-mechanics, triphasic model, normal pressure hydrocephalus, brain swelling

1. Introduction

Normal pressure hydrocephalus (NPH) is a serious neurological disorder characterized by gait disturbance, mental deterioration and urinary incontinence in patients with enlarged cerebral ventricles in the absence of increased intracranial pressure [1, 2]. NPH is predominantly found in adults over 60 years of age and is often missed or misdiagnosed because many conditions affecting older individuals can mimic the symptom profile of NPH, including Parkinson's disease, Alzheimer's disease, metabolic and psychiatric disorders, endocrine dysfunction, infections, trauma, vascular and neurodegenerative disorders [4]. In most of the cases, the cause of NPH is unknown.

Recent estimates of NPH incidence range from 50,000 to 375,000 people in the United States, with the higher figure more likely to be correct [3]. In 2002, the U.S. Census Bureau estimated that there were nearly 60 million people age 55 or older living in the United States. Average life expectancy was approximately 77 years in 2001, according to the National Center for Health Statistics, Centers for Disease Control and Prevention [5]. Since average life expectancy is expected to continue to increase, the number of diagnosed cases of NPH and the associated treatment costs will continue to grow, as well.

The efforts in treatment have been principally through the diversion of the ventricular cerebrospinal fluid (CSF) flow. Within limits, the dilation of the ventricles

Received by the editors August 29, 2011.
2000 *Mathematics Subject Classification.* 74D05, 74F10, 74F25, 92C10.

can be reversed by a surgical placement of a shunt in the brain to drain excess CSF into the abdomen where it can be absorbed. The extent of improvement after neurosurgical shunt procedures varies greatly: 45%-65% of patients respond positively [6, 7, 8], while morbidity is about 40%-50% [6, 8, 9]. Therefore, there is an urgent need for a proper selection of patients who may benefit by a shunt operation.

In order to design better diagnostic and treatment protocols for NPH, we need to develop realistic biomechanical models of the brain for the numerical simulation of NPH. The few existing models presented in the engineering literature on NPH are based on the hydrodynamics of CSF which tends to accumulate in the brain ventricular system during the development of NPH (in a healthy brain, the CSF circulates continuously between the ventricles, the site of CSF production, and the subarachnoid space, the site of CSF absorption) [10]-[20]. All these models are based on the bulk flow theory: the driving force of the CSF bulk flow is the CSF pressure at the production site being higher than the pressure at the absorption site. In this theory, the enlargement of the ventricles during the development of hydrocephalus is due to an increased intracranial pressure. However, NPH is incompatible with the bulk flow theory since in the case of NPH the ventricles dilate without an increase of the CSF pressure [21]. Recently, Levine [22] postulated that there exists an abnormal but very small gradient of static pressure across the cerebral mantle that should be sufficient to produce the ventricular dilatation of NPH. Although this is an attractive theory, it has very limited medical applicability since there are no instruments sensitive enough to measure such small abnormal gradients. Finally, none of the published biomechanical models of NPH incorporates any relevant clinical information about abnormal electro-chemical processes taking place during the development of NPH [23, 24].

The aim of the present paper is to formulate the first neuro-mechanical model that will couple the electro-chemical and mechanical properties of the brain. We assume that the brain tissue is a charged hydrated soft tissue made of three phases: an intrinsically incompressible, porous-permeable, charged solid phase that includes the extracellular matrix and brain cells; an intrinsically incompressible, interstitial fluid phase that models the extracellular fluid; and an ion phase with, for now, only two monovalent ion species anion (-) and cation (+). In addition, there exist negatively charged groups on the solid phase called fixed charges since they are much less mobile than the freely mobile ions dissolved in the fluid phase. The existance of such fixed charges in the brain tissue has been proved experimentally by Erkin et al [33]. The solid phase and the ion phase are electrically charged, while the fluid phase and the tissue as a whole are electrically neutral. A schematic picture of the structure of the triphasic brain tissue is shown in Figure 1.

So far, the triphasic mechano-electrochemical theory has been applied successfully to model the mechanics of the articular cartilage [25]-[28]. In a series of conference papers [31, 32], we have shown some promissing preliminary results on NPH using the above mentioned triphasic model for the brain, and very recently a similar model has been used to analyze brain tissue swelling (cerebral oedema) due to traumatic brain injury or stroke [33].

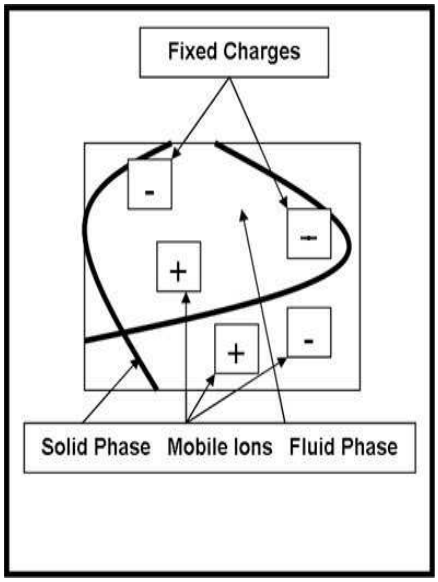

FIGURE 1. Structure of a charged hydrated soft tissue.

In this paper we extend our previous work [31, 32] and show that our neuro-mechanical model can predict the onset of NPH due to a change in ionic concentrations of the ventricular CSF in the absence of an elevated intracranial pressure. More precisely, we will show that an increase of the salt concentration in the ventricular CSF will produce a shrinkage of the brain tissue. The choice of the ions Na^+ and Cl^- is based on extensive experimental studies (see for instance [34, 35, 36]) on the linkage between the choroid plexus, an epithelial tissue that lies at the interface between the ventricular CSF and brain parenchyma, and CSF. Almost 80% of CSF is produced by the choroid plexus by active transport of Na^+ into CSF from blood, followed by water and anions. A very recent study by Fiocco et al [39] shows that older people above 67 years of age who lead sedentary lifestyles and consume a lot of sodium in their diet may be at risk not only for heart disease but also cognitive decline. Although there is no direct experimental or clinical evidence that an increase of salt in the ventricular CSF could cause NPH, the triphasic model has the advantage that the ion species can be changed as more information on the pathophysiology of NPH becomes available. In addition, the model could play an important role in understanding critical coupling relationships between brain mechanics and the electro-chemistry controlling brain functions and thus could predict brain's behavior in other clinical conditions such as traumatic injuries and neurological disorders.

The paper is organized as follows. In section 2 we present the mechano-electrochemical model we used to investigate brain neuro-mechanics. In section 3 we show

a computer simulation of NPH based on the proposed neuro-mechanical model. The paper ends with a section of discussion and further work.

2. The Mechano-Electrochemical Model

In the mechano-electrochemical model the brain tissue is an electrically neutral ionised porous media with three phases: (1) an intrinsically incompressible, porous-permeable, charged solid phase made of the extracellular matrix and brain cells; (2) an intrinsically incompressible, electrically neutral, interstitial fluid phase that models the extracellular fluid; and (3) an ion phase with two monovalent species: negatively charged ions (anions) and positively charged constituents made of cations and nutrients dissolved within the fluid. We assume the existance of negatively charged groups on the solid phase, fixed charges, which are not as mobile as the ions flowing in the fluid phase. We further assume that the mixture is saturated with the volume fractions of the ions much smaller than the solid and fluid volume fractions, there are no chemical reactions between components, and inertial terms, body forces and thermal effects are negligible. Finally, based on the very slow evolution of NPH, the deformation process is quasi-static.

The constitutive equations of the triphasic tissue with infinitesimal deformations are [25, 28]:

$$\sigma = -pI + \lambda_s \mathrm{tr}(\epsilon) + 2\mu_s \epsilon \tag{1}$$

$$\mu^f = \mu_0^f + \left[p - RT\Phi(c^+ + c^-)\right]/\rho^f \tag{2}$$

$$\mu^a = \mu_0^a + (RT/M_a)\ln(\gamma_a c^a) + z_a F_c \psi / M_a,\ a = +, - \tag{3}$$

where equation (1) is Hooke's law for the linear elastic phase, and equations (2) and (3) are the constitutive equations for the fluid phase and the ion phase, respectively. We have denoted by p the fluid pressure, σ the stress tensor in the elastic solid, ϵ the strain tensor in the elastic solid, λ_s, μ_s the Lame coefficients which depend on solid volume fraction and ion molar concentrations c^a, $a = +, -$, R is the universal gas constant, T is the absolute temperature, μ^f is the chemical potential of the fluid phase with μ_0^f the reference chemical potential, Φ the osmotic coefficient, ρ^f the true mass density of the fluid, ψ the electric potential, γ_a the activity potential coefficients, μ^a the electro-chemical potential of the ion species a with μ_0^a its reference electro-chemical potential, z_a the valence of ion species a including sign, M_a the molar weight of the a ionic species, and F_c is Faraday constant.

As in [28], we denote by $c^k = c^+ + c^-$ and c^F the fixed charge density measured as equivalent moles per unit volume of water. The electroneutrality condition is:

$$z_+ c^+ + z_- c^- - c^F = 0 \text{ (the fixed charges are negatively charged)}$$

or, equivalently:

$$c^F = c^+ - c^-.$$

By combining the intrinisical incompressibility of the solid phase for infinitesimal strains, the saturation condition that relates the solidity ϕ^s (solid volume fraction) and the porosity of the tissue ϕ^f (fluid volume fraction): $\phi^s + \phi^f = 1$, and the definition of the fixed charge density, we obtain yet another expression for c^F that

shows its dependence on both initial porosity ϕ_0^f and dilatation $e = \mathrm{tr}(\epsilon)$:

$$c^F = \frac{c_0^F}{1 + \frac{e}{\phi_0^f}} \tag{4}$$

where c_0^F is the fixed charge density in the reference (assumed undeformed) configuration.

The governing equations are made of the equations of equilibrium and continuity of the mixture and the diffusion-convection equations of the ions, which combined with the electroneutrality condition become (for a detailed presentation see for example [28]):

$$\nabla \cdot (\lambda_s \, e \, I + 2\mu_s \, \epsilon) - \nabla \left(RT\epsilon^f + RT\Phi c^k \right) = 0 \tag{5}$$

$$\nabla \cdot \frac{\partial u^s}{\partial t} - RTk \, \nabla \cdot \left(\nabla \epsilon^f + \frac{c^+}{\epsilon^+} \nabla \epsilon^+ + \frac{c^-}{\epsilon^-} \nabla \epsilon^- \right) = 0 \tag{6}$$

$$\begin{aligned} &\nabla \cdot \left[-RTkc^F \nabla \epsilon^f - \left(\frac{\phi^f c^+ D^+}{\epsilon^+} + RTk \frac{(c^+)^2}{\epsilon^+} - RTk \frac{c^+ c^-}{\epsilon^+} \right) \nabla \epsilon^+ \right] \\ &+ \nabla \cdot \left[\left(\frac{\phi^f c^- D^-}{\epsilon^-} + RTk \frac{(c^-)^2}{\epsilon^-} - RTk \frac{c^+ c^-}{\epsilon^-} \right) \nabla \epsilon^- \right] = 0 \end{aligned} \tag{7}$$

$$\begin{aligned} \frac{\partial (\phi^f c^k)}{\partial t} = \; &- \; \nabla \cdot \left(\phi^f c^k \frac{\partial u^s}{\partial t} - RTkc^k \nabla \epsilon^f \right) \\ &+ \; \nabla \cdot \left[\left(\frac{\phi^f c^+ D^+}{\epsilon^+} + RTk \frac{(c^+)^2}{\epsilon^+} + RTk \frac{c^+ c^-}{\epsilon^+} \right) \nabla \epsilon^+ \right] \\ &+ \; \nabla \cdot \left[\left(\frac{\phi^f c^- D^-}{\epsilon^-} + RTk \frac{(c^-)^2}{\epsilon^-} + RTk \frac{c^+ c^-}{\epsilon^-} \right) \nabla \epsilon^- \right] \end{aligned} \tag{8}$$

where k is the hydraulic permeability, u^s is the infinitesimal displacement of the solid phase, and D^+, D^- are the diffusivity coefficients of the two ion species. We also denote by:

$$\epsilon^f = \frac{p}{RT} - \Phi c^k, \; \epsilon^a = \gamma_a c^a \exp\left(\frac{F_c \psi}{RT} \right), \; a = +, - \tag{9}$$

the so-called modified electrochemical potentials.

For the beginning we will neglect the electric field ($\psi = 0$). Since we assumed a linear strain-stress constitutive law for the mixture, it has been shown in [37] (the online supplementary materials of [37] contain the mathematical details) that a regular perturbation method can be employed to reduce the above system of coupled equations (5)-(8) to the following:

$$\begin{aligned} \frac{\partial e}{\partial t} &= A_1 \nabla^2 e - A_2 \nabla^2 \gamma \\ \frac{\partial \gamma}{\partial t} &= A_4 \nabla^2 \gamma - A_5 \nabla^2 e \end{aligned} \tag{10}$$

with

$$\gamma = \frac{RTc^k}{\lambda_s + 2\mu_s}$$

and

$$\begin{aligned}
A_1 &= D^b - \frac{D^b - D^a}{1 + \frac{D^f}{RTc_0^F \phi_0^f k}},\ A_2 = \frac{D^b D^d}{D^f} \frac{1}{1 + \frac{RTc_0^F \phi_0^f k}{D^f}} \\
A_3 &= D^b + \frac{RTc_0^F \phi_0^f k D^d}{D^f},\ A_4 = D^a - \frac{D^k}{D^b} A_2,\ A_5 = (A_3 - A_1)\frac{D^k}{D^b} \\
D^a &= \frac{D^+ + D^-}{2},\ D^d = \frac{D^+ - D^-}{2},\ D^b = (\lambda_s + 2\mu_s)k \\
D^k &= D^a + \frac{c_0^k}{c_0^F} D^d,\ D^f = D^d + \frac{c_0^k}{c_0^F} D^a
\end{aligned}$$

System (10) must be completed with Dirichlet and/or Neumann-type boundary conditions for the unknown e and γ. Once the dilatation e is known, c^F can be found from (4), and then the concentrations c^+, c^- follow from c^F and c^k (or γ).

3. Numerical Simulation of NPH

In this section we investigate the onset of NPH due to a change in the ionic concentrations of the ventricular CSF in the absence of an elevated intracranial pressure. For simplicity, we consider the linearized one-dimensional (1D) case described by the system of equations (10). Initially, a brain tissue sample made of white matter only is at equilibrium with the intraventricular CSF (external bathing solution) with concentration of monovalent ions. Since there is no existent clinical literature on what ions in the ventricular CSF might cause NPH, we assume for example that the two monovalent ions are Na^+ and Cl^-, because they have the largest concentrations in the ventricular CSF [29], and the mechanicsm of CSF formation involves the active transport of Na^+ into CSF from plasma among others [35]. In addition, an increase in salt intake in older adults has been recently linked to brain functions' decline [39]. We assume that the tissue of brain with NPH has length h and is confined by the rigid, impermeable skull which does not allow for lateral movement of the tissue (Figure 2).

The initial and boundary conditions are as follows:

$$\begin{aligned}
e(x,0) = 0,\ \gamma(x,0) &= \gamma_0 \\
e(0,t) = 0,\ \gamma(0,t) &= \gamma_0 \\
\sigma_{11}(h,t) = 0,\ \gamma(h,t) &= \gamma_0 + at
\end{aligned} \tag{11}$$

From Hooke's law and $\sigma_{11}(h,t) = 0$ we obtain the following expression for the CSF hydraulic pressure at the ventricular wall:

$$p = (\lambda_s + 2\mu_s)\, e \tag{12}$$

Donnan equilibrium theory provides the osmotic pressure gradient at the ventricular wall [38]:

$$\Delta\pi = \Phi_{in} RT \sqrt{\left(c^F\right)^2 + 4\left(c_{out}\right)^2} - 2\Phi_{out} RT c_{out} \tag{13}$$

where c_{out} is the salt concentration in the ventricles, and $\Phi_{in} = \Phi$, Φ_{out} are the osmotic coefficients in the brain tissue and, respectively, inside the ventricles.

If we replace now the expression of c^F from (4) into equation (13) and equate the hydrostatic and osmotic pressures given by (12) and respectively (13), we obtain a

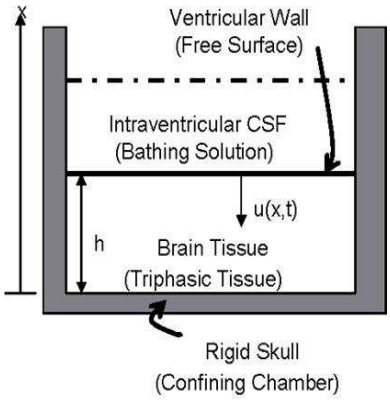

FIGURE 2. Schematic representation of the 1D brain.

nonlinear equation for e:

$$(14)\quad (\lambda_s + 2\mu_s)\, e - \Phi_{in} RT \sqrt{\left(\frac{c_0^F}{1+\frac{e}{\phi_0^f}}\right)^2 + 4\,(c_{out})^2} + 2\Phi_{out} RT c_{out} = 0$$

whose solution is a boundary condition for $e(h,t)$.

We assume that initially the concentration of salt in the intraventricular CSF c_{out} is 0.265 mol/l, a value in the normal range [29]. It increases linearly to 0.5 mol/l within 200 s and then remains constant (see Figure (3)).

We solved system (10) with initial and boundary conditions (11) and (14) using an unconditionally stable implicit numerical scheme with a central difference discretization of the spatial derivative.

In our simulations we used the following material parameters:

$$\begin{aligned} h &= 1\,mm,\ \lambda_s + 2\mu_s = 14\,kPa,\ T = 298\,K,\ R = 8.314\,J/(mol\,K), \\ \Phi_{in} &= \Phi = 0.75,\ \Phi_{out} = 1,\ \phi_0^f = 0.75,\ c_0^F = 0.5\,mol/l \\ D^+ &= 0.5\times 10^{-9}\,m^2/s,\ D^- = 0.8\times 10^{-9}\,m^2/s,\ k = 1.5\times 10^{-15}\,m^4/(N\,s) \\ \gamma_0 &= \frac{RT}{\lambda_s + 2\mu_s}\times 0.265,\ a = 0.0012 \end{aligned}$$

Most of these parameters are not known for the brain so we have taken them from [28]. In Figure 4 we show the variations in time of dilatation e and fixed charged density c^F at different depths and for different values of c_0^F. In Figure 5 we investigate the influence of the diffusion coefficient D^+ on the dilatation.

From Figure 4 we notice that the shrinkage of different layers of brain tissue decreases with increasing c_0^F, and there is even some initial swelling happening before shrinkage that corresponds to an initial decrease in c^F. These anomalous phenomena might be due to negative osmotic effects [27] and they will be the focus of a

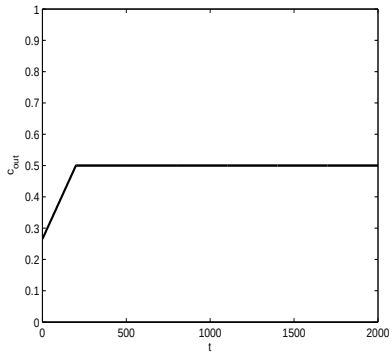

FIGURE 3. The profile of salt concentration prescribed inside the ventricles.

further analysis. As c_0^F increases, the fixed charge density increases in the brain tissue which we believe causes the tissue to become stiffer and thus to shrink less. In Figure 5 we see the influence of the diffusion coefficient D^+ on the dilatation of the brain. As D^+ increases, the layers of brain away from the ventricular wall shrink less. The focus of this paper was to show that the shrinkage of the brain tissue can be caused by the increase of salt concentration in the intraventricular CSF, and in our future work we plan to deepen our analysis of the model sensitivity to the material parameters.

Although there is no clinical or experimental evidence that NPH could be caused by an increase of salt concentration in the intraventricular CSF, the recent study by Fiocco et al [39] that links the increase of salt intake to cognitive decline in older adults is encouraging for the results presented in this paper. In addition, many other experimental studies on sodium transport in brain may support our hypothesis that a salt increase could play a role in NPH. Almost three decades ago, Johanson [35] established that choroid plexus transforms plasma into CSF by active transport of sodium into the ventricles, as well as water and ion movements. In 2010, Wang et al [36] showed that if the concentration of CSF Na^+ increases, then enhanced alpha- and beta- Epithelial Sodium Channel (ENaC) in the apical microvilli of the choroid plexus may facilitate sodium entry into the choroid plexus cells and thus into the intraventricular CSF. When the concentration of sodium in the hypothalamic tissue increases, higher alpha- and beta-ENaC immunoreactivities on the basal surface of the ependyma may reflect a mechanism to attenuate the increase in the sodium concentration in the brain tissue by transporting the sodium out of tissue into the CSF. However, a clear mechanism that links an increased salt concentration and brain's shrinkage has not been established yet. The difficulty appears to come from the fact that brain's volume is highly regulated to provide proper functionality. As a result, the shifts of Na^+, Cl^-, K^+ within the brain will produce a change in the osmotic pressure and movement of CSF from

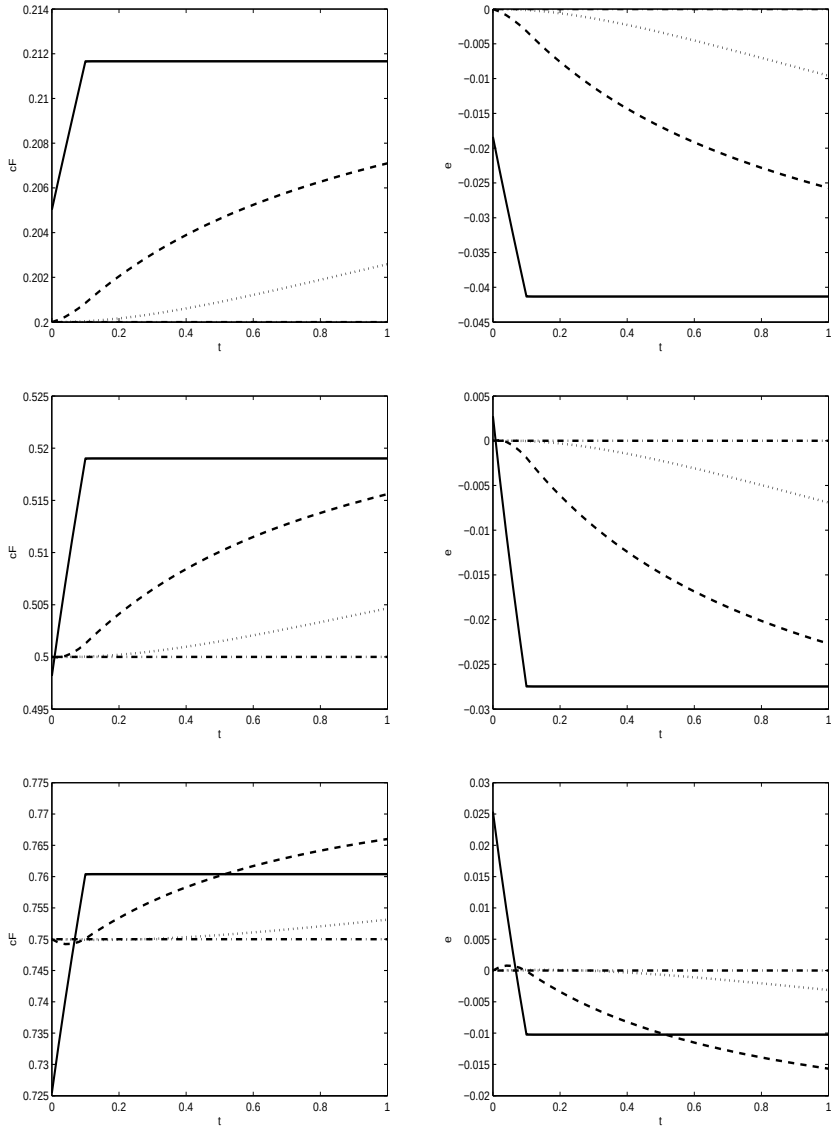

FIGURE 4. The profiles of c^F and e for different values of c_0^F: 0.2 mol/l (first row), 0.5 mol/l (second row), 0.75 mol/l (third row). The depths shown are: x=1mm (-), x=0.8mm(–), x=0.4mm(..), x=0mm (-.)

one region to another as expected, however, the brain does not shrink initially as an ideal osmometer to return to a normal volume afterwords, but rather it shrinks

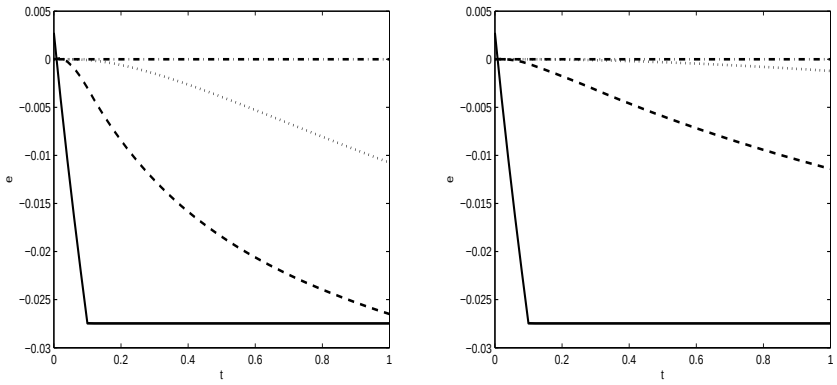

FIGURE 5. Dilation for different diffusion coefficient D^+: $D^+ = 0.35 \times 10^{-9} m^2/s$ (left) and $D^+ = 1.5 \times 10^{-9} m^2/s$ (right). The depths shown are: x=1mm (-), x=0.8mm(–), x=0.4mm(..), x=0mm (-.) Here $c_0^F = 0.5\, mol/l$.

slowly towards a new, reduced volume [40]. Many hormones synthesized and released within the central nervous system, such as vasopressin (AVP), atripeptin (ANP), angiotensin, and endogenous digoxin, and various brain cells are responsible for precise control of the brain and intracranial volumes. In [41, 43], it has been shown that the choroid plexus displays an increased number of receptors for ANP in hydrocephalic rats, while ANP concentrations in the CSF are elevated in patients with aneurysmal subarachnoid hemorrhage who develop raised intracranial pressure. On the other hand, AVP increased the glial cell volume by an average of 25% during 30 and 120 min exposure, whereas ANP decreased it by 29%, and the cell volume remained close to normal after co-administration of both AVP and ANP [42]. This might imply that in hydrocephalus the receptors for AVP are damaged, while those for ANP are elevated and these receptors might be either the cause for or the consequence of abnormal increases/decreases of ion concentrations in the brain. We intend to expand our model to account for the presence of such receptors and investigate through numerical simulations the onset of NPH.

4. Conclusion

In this paper we proposed the first neuro-mechanical model of the brain that links the electro-chemical and mechanical properties of the brain. Using the triphasic theory, we assumed that the brain is a charged hydrated soft tissue made of a solid phase, an interstitial fluid phase and an ion phase with two monovalent ion species. We have shown that the proposed model can predict the shrinkage of the brain tissue seen in NPH patients due to the increase of salt concentration in the ventricular CSF and in the absence of an elevated intracranial pressure. To the best of our knowledge this is the first time when such a result has been obtained

for studying NPH. We belive that our predictive neuro-mechanical model will open the possibility of treating NPH non-invasively, with drugs.

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