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

Jason S. Fritz[1], Corina S. Drapaca[1]
[1] Pennsylvania State University, University Park, USA, jsf186@psu.edu, csd12@psu.edu

Abstract: *In recent years, the fields of brain biomechanics and neural engineering have started to play an increasingly important role to modern neuroscience. Although the object of study of these two research areas is the brain, the two fields have developed independently of each other, neglecting any possible linkage between the electric brain and the mechanical brain. The aim of the present paper is to formulate the first neuro-mechanical model of the brain 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 two monovalent ion species. To investigate the mechano-electrochemical coupling phenomena of the brain tissue, we study the onset of normal pressure hydrocephalus due to a change in the ionic concentrations of the ventricular cerebrospinal fluid in the absence of an elevated intracranial pressure.*
Keywords*: Brain Neuro-mechanics, NPH, Triphasic Model.*

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] (Figure 1). 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, and incontinence from urinary tract disorders [6]. In most of the cases, the cause of NPH is unknown.

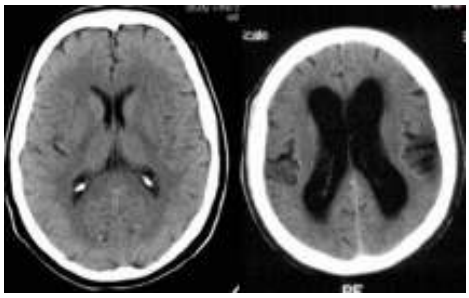

Figure 1: CT images of a normal brain (left, [3]) and a brain with NPH (right, [4]).

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 [5]. According to the U.S. Census Bureau, in 2002, 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 [7]. 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 CSF flow diversion. Within limits, the dilation of the ventricles 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 [8, 9, 10], while morbidity is about 40%-50% [8, 10, 11]. 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. Most of the models presented in the engineering literature on NPH are based on the hydrodynamics of cerebro-spinal fluid (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) [12-22]. 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 slightly in excess of 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 [23]. Recently, Levine [24] 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 [25, 26].

The aim of the present paper is to formulate ***the first neuro-mechanical model of the brain 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 two monovalent ion species. We will use the proposed model to study the onset of NPH due to a change in the ionic concentrations of the ventricular CSF in the absence of an elevated intracranial pressure.

2. THE TRIPHASIC MECHANO-ELECTROCHEMICAL MODEL

So far, the triphasic mechano-electrochemical theory has been applied to model the mechanics of the articular cartilage [27-30]. However the theory can be applied to any charged hydrated soft tissue made of an intrinsically incompressible, porous-permeable, charged solid phase; an intrinsically incompressible, interstitial fluid phase; and an ion phase with two monovalent ion species anion (-) and cation (+). Although the theory has been extended to include multiple species of ions [28], for simplicity we will consider the 1:1 electrolyte case first. In addition, there exist positively and 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 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 soft tissue is shown in Figure 2.

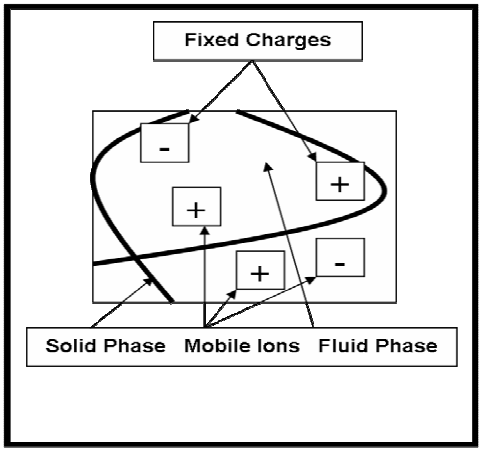

Figure 2: Structure of a charged hydrated soft tissue.

The constitutive equations of the thriphasic soft tissue with infinitesimal deformations are [27, 30]:

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

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

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

where equation (1) is Hooks law for the linear elastic phase, and equations (2), (3) are the constitutive equations for the fluid phase and the ion phase. 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 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. The governing equations are made of the equilibrium equation of the mixture, and the continuity equations of the mixture and of the ions, which combined with the electroneutrality condition become [30]:

$$\nabla \cdot (\lambda_s \mathrm{tr}(\varepsilon) I + 2\mu_s \varepsilon) - \nabla (RT\varepsilon^f + RT\Phi c^k) = 0 \tag{4}$$

$$\nabla \cdot v^s - \nabla \cdot \frac{RT}{\alpha}\left(\varphi^f \nabla \varepsilon^f + \frac{\varphi^f c^+}{\varepsilon^+}\nabla \varepsilon^+ + \frac{\varphi^f c^-}{\varepsilon^-}\nabla \varepsilon^- \right) = 0 \tag{5}$$

$$\begin{aligned} &\nabla \cdot \left[-\frac{RT}{\alpha}\varphi^f c^F \nabla \varepsilon^f - \left(\frac{\varphi^f c^+ D^+}{\varepsilon^+} + \frac{RT}{\alpha}\frac{\varphi^f (c^+)^2}{\varepsilon^+} - \frac{RT}{\alpha}\frac{\varphi^f c^+ c^-}{\varepsilon^+} \right)\nabla \varepsilon^+ \right] \\ &+ \nabla \cdot \left[\left(\frac{\varphi^f c^- D^-}{\varepsilon^-} + \frac{RT}{\alpha}\frac{\varphi^f (c^-)^2}{\varepsilon^-} - \frac{RT}{\alpha}\frac{\varphi^f c^+ c^-}{\varepsilon^-} \right)\nabla \varepsilon^- \right] = 0 \end{aligned} \tag{6}$$

$$\begin{aligned} \frac{\partial \left(\varphi^f c^k \right)}{\partial t} &= -\nabla \cdot \left(\varphi^f c^k v^s - \frac{RT}{\alpha}\varphi^f c^k \nabla \varepsilon^f \right) + \nabla \cdot \left[\left(\frac{\varphi^f c^+ D^+}{\varepsilon^+} + \frac{RT}{\alpha}\frac{\varphi^f (c^+)^2}{\varepsilon^+} + \frac{RT}{\alpha}\frac{\varphi^f c^+ c^-}{\varepsilon^+} \right)\nabla \varepsilon^+ \right] \\ &+ \nabla \cdot \left[\left(\frac{\varphi^f c^- D^-}{\varepsilon^-} + \frac{RT}{\alpha}\frac{\varphi^f (c^-)^2}{\varepsilon^-} + \frac{RT}{\alpha}\frac{\varphi^f c^+ c^-}{\varepsilon^-} \right)\nabla \varepsilon^- \right] \end{aligned} \tag{7}$$

In equations (4)-(7) we denoted by $c^k = c^+ + c^-$, $\alpha = \varphi^f / k$ with k the hydraulic permeability and porosity $\varphi^f = \varphi_0^f + (1 - \varphi_0^f)\mathrm{tr}(\varepsilon)$, v^s the velocity of the solid phase, and D^+, D^- the diffusivity coefficients of the two ion species. The modified electrochemical potential functions are defined as:

$$\varepsilon^f = \frac{p}{RT} - \Phi c^k, \ \varepsilon^+ = \gamma_+ c^+ \exp\left(\frac{F_c \psi}{RT} \right), \ \varepsilon^- = \gamma_- c^- \exp\left(\frac{F_c \psi}{RT} \right) \tag{8}$$

In addition, the fixed charged density (FCD) is by definition $c^F = c^+ - c^-$.

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. Initially, a brain tissue sample made of white matter only is at equilibrium with the intraventricular CSF (external bathing solution) with concentration c_0^* 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^-, since they have the largest concentrations in the ventricular CSF [31]. 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 3).. The boundary conditions at the bottom of the specimen are that the solid displacement and all the electrochemical fluxes are zero, while the boundary conditions at the top are that the stress and the electrochemical potentials are continuous across this boundary. Initially, the ionic concentration in the ventricular CSF decreases from c_0^* to c_1^* linearly. If the total ionic concentration in the brain tissue is zero, then the brain tissue will swell. However, if we

assume that the brain tissue with NPH varies linearly from c_0^* at the top to zero at the bottom, then the brain tissue will shrink.

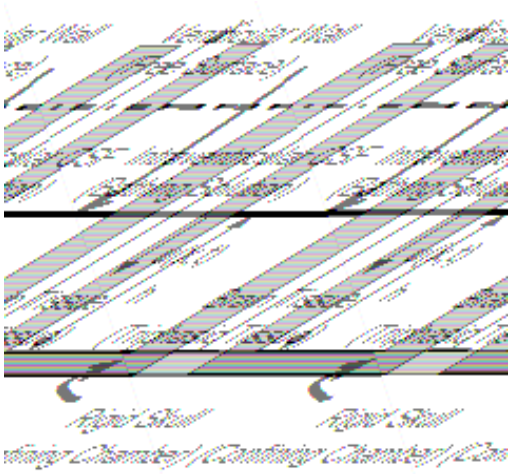

Figure 3: Schematic representation of the 1D brain.

The parameters used in our simulations are: h = 1mm, $\lambda_s + 2\mu_s$ = 51.35 kPa [32], $D^+ = 0.5\times10^{-9}\,\mathrm{m}^2/\mathrm{s}$, $D^- = 0.8\times10^{-9}\,\mathrm{m}^2/\mathrm{s}$, $\alpha = 0.7\times10^{15}\,\mathrm{Ns/m}^4$, T = 298 K, φ_0^f=0.75, Φ=1, c_0^F = 0.2 mEq/ml (most of these parameters are not known for the brain so we have taken them from [30]). The initial concentration of ions in the ventricular CSF has a normal value of c_0^*=0.265 mol/l [31]. It decreased linearly to the abnormal value of c_1^*=0.125 mol/l within 1500 s. The displacement of the ventricular wall is shown in Figure 4.

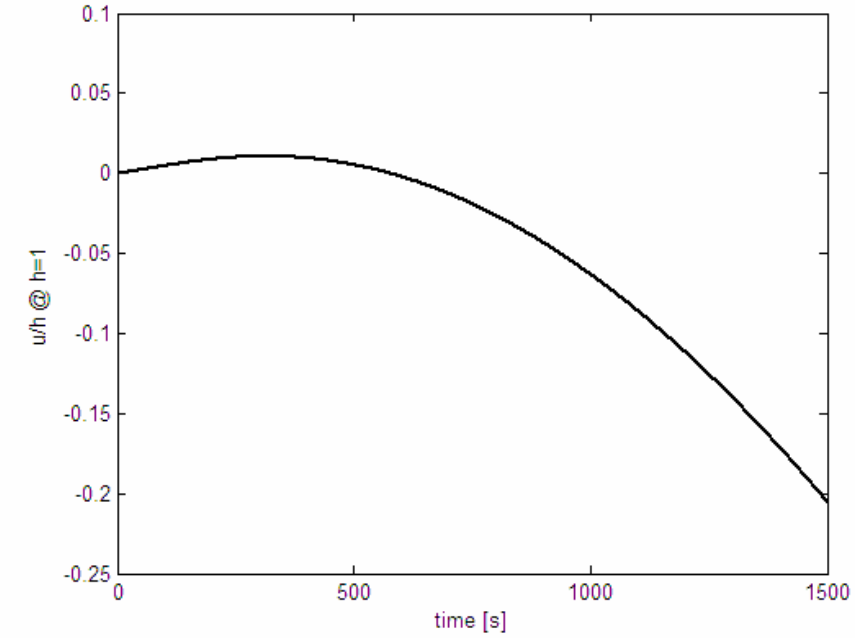

Figure 4: Ventricular wall displacement showing an initial swelling followed by shrinking.

In Figure 5 we show the influence of the initial fixed charged density c_0^F on the displacement of the ventricular wall, while in Figure 6 we show how this displacement varies with the initial porosity φ_0^f. We notice that as c_0^F increases the swelling and the displacement decrease, and as φ_0^f decreases the swelling and the displacement increase.

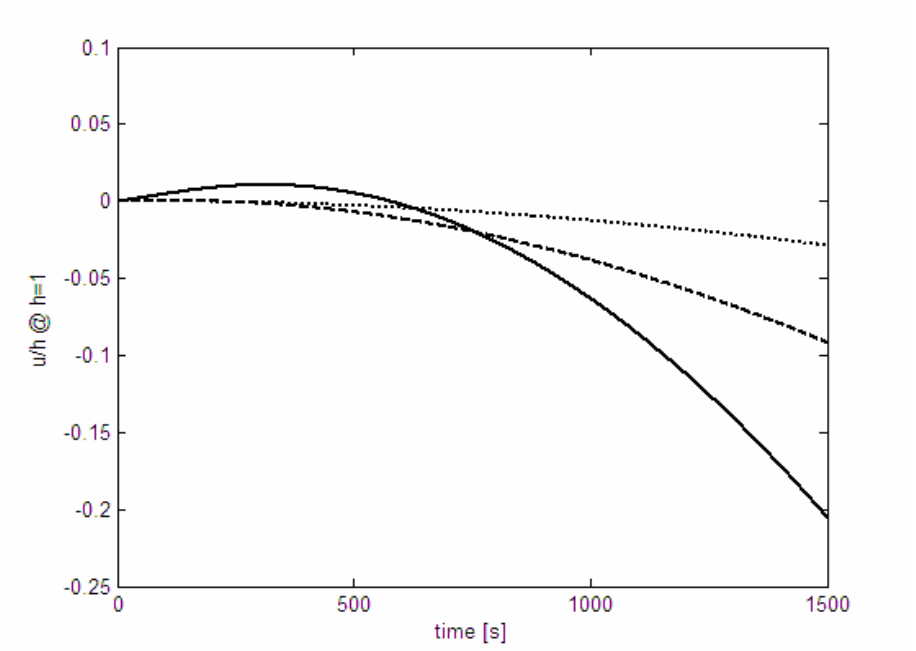

Figure 5: The ventricular wall displacement for c_0^F = 0.2 (straight line), 0.4 (dashed line) and 0.8 (dotted line).

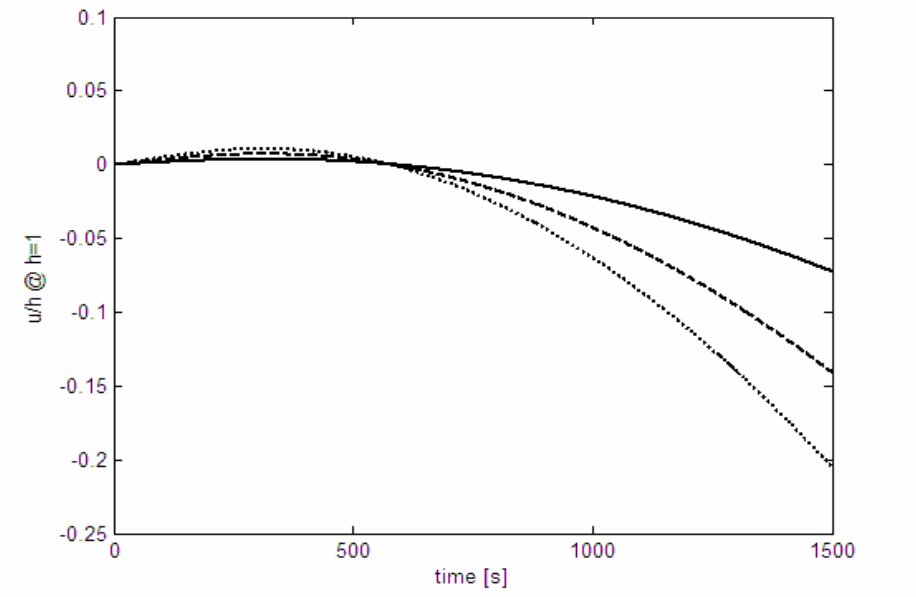

Figure 6: The ventricular wall displacement for φ_0^f = 0.25 (straight line) , 0.5 (dashed line) and 0.75 (dotted line).

4. CONCLUSION

In this paper we have proposed the first neuro-mechanical model of the brain that links the electro-chemical and mechanical properties of the brain. Using the thriphasic 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 a change in the ionic concentrations of 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.** In our future work we plan to study diffusion properties of ions in the brain and investigate other ions and proteins that might play a role in the development of NPH.

REFERENCES

[1]. Adams RD, Fisher CM, Hakim S, Ojeman RG, Sweet WH. Symptomatic occult hydrocephalus with normal cerebrospinal-fluid pressure. A treatable syndrome. *N Engl J Med* 273:117–26, 1965.
[2]. Hakim S, Adams RD.The special clinical problem of symptomatic hydrocephalus with normal cerebrospinal fluid pressure. Observations on cerebrospinal fluid hydrodynamics. *J Neurol Sci* 2: 307–27, 1965.
[3]. Normal CT brain. See http://neurosun.googlepages.com/normalctbrainfindings
[4]. CT of NPH. See http://www.auntminnie.com
[5]. Brody, JE., A brain disorder easily missed, *The New York Times*, Health Section, May 25th, 2009.
[6]. Relkin N, Marmarou A, Klinge P, Bergsneider M, Black P. Diagnosing idiopathic normal pressure hydrocephalus. *Neurosurgery Online*, 57(Suppl.3):S4–S16, 2005.
[7]. Centers for disease control and prevention, national center for health statistics. See http://www.cdc.gov/nchs/releases/news/lifeex.htm
[8]. Katzman R. Normal pressure hydrocephalus. In: Wells CE (ed) Dementia, pp 69-92, 1977.
[9]. Greenberg JO, Shenkin HA, Adam R. Idiopathic normal pressure hydrocephalus-a report of 73 patients. *J Neurol Neurosurg Psychiatry* 40:336-341, 1977.
[10]. Black PMcL. Idiopathic normal-pressure hydrocephalus. *J Neurosurg* 52:371-377, 1980.
[11]. Lin S-M, Hung C-C (1979) Complications of cerebrospinal fluid shunts for hydrocephalus. *J Formosan Med Assoc* 78:258-266, 1979.
[12]. Cabanes J, Marti J, Orozco M, Beltran A. Bicompartmental analysis of cerebrospinal fluid circulation. Theory and clinical applications, *Journal of Neurosurgery* 59:311-21, 1983.
[13]. Czosnyka M, Czosnyka Z, Momjian S, Pickard JD. Cerebrospinal fluid dynamics, *Physiological Measurement* 25:R51-76, 2004.
[14]. Czosnyka Z, Czosnyka M, Owler B, Momjian S, Kasprowicz M, Schmidt EA. Smielewski P, Pickard JD. Clinical testing of CSF circulation in hydrocephalus, *Acta Neurochirurgica. Supplement* 95: 247-251, 2005.
[15]. Czosnyka Z, van den Boogaard F, Czosnyka M, Momjian S, Gelling L, Pickard JD. The relationship between CSF circulation and cerebrovascular pressure-reactivity in normal pressure hydrocephalus, *Acta Neurochirurgica. Supplement* 95:207-211, 2005.
[16]. Shulman K, Marmarou A. Analysis of intracranial pressure in hydrocephalus, *Developmental medicine and child neurology* Suppl 16:11-16, 1968.
[17]. Zarzhetskii IuV. Dynamics of the cerebrospinal fluid and elastic properties of the cerebrospinal system (a bolus technic) (in Russian), *Zhurnal Voprosy Ne¿rokhirurgiiimeni N. N. Burdenko*, vol. Jul-Aug:25-29, 1987.
[18]. Kosteljanetz M. Intracranial pressure: cerebrospinal fluid dynamics and pressure-volume relations, *Acta Neurologica Scandinavica. Supplementum* 111:1-23, 1987.
[19]. Razumovsky AY, Hanley DF. Intracranial pressure measurement/cranial vault mechanics: clinical and experimental observations, *Current Opinion in Neurology and Neurosurgery* 5:818-25, 1992.
[20]. Portnoy HD, Chopp M. Intracranial fluid dynamics. Interrelationship of CSF and vascular phenomena, *Pediatric Neurosurgery* 20:92-97, 1994.
[21]. Pena A, Harris NG, Bolton MD, Czosnyka M, Pickard JD. Communicating hydrocephalus: the biomechanics of progressive ventricular enlargement revisited, *Acta Neurochirurgica. Supplement* 81:59-63, 2002.
[22]. Baledent O, Gondry-Jouet C, Meyer ME, De Marco G, Le Gars D, Henry- Feugeas MC, Idy-Peretti I. Relationship between cerebrospinal fluid and blood dynamics in healthy volunteers and patients with communicating hydrocephalus, *Investigative Radiology* 39:45-55, 2004.
[23]. Greitz D. Radiological assessment of hydrocephalus: new theories and implications for therapy, *Neurosurg. Rev*. 27:145-165, 2004.
[24]. Levine DN. Intracranial pressure and ventricular expansion in hydrocephalus: have we been asking the wrong question? *J. Neurological Sciences* 269:1-11, 2008.
[25]. Wikkelso C, Blomstrand C. Cerebrospinal fluid proteins and cells in normal-pressure hydrocephalus, *J.Neurol*. 228:171-180, 1982.
[26]. Tarkowski E, Tullberg M, Fredman P, Wikkelso C. Normal pressure hydrocephalus triggers intrathecal production of TNF- α, *Neurobiology of Aging* 24:707-714, 2003.
[27]. Lai WM, Hou JS, Mow VC. A triphasic theory for the swelling and deformational behaviors of articular cartilage, *J. of Biomechanical Engineering* 113: 245-258, 1991.
[28]. Gu WY, Lai WM, Mow VC. A mixture theory for charged hydrated soft tissues containing multi-electrolytes: passive transport and swelling behaviors, *J. of Biomechanical Engineering* 20:169-180, 1998.
[29]. Gu WY, Lai WM, Mow VC. A triphasic analysis of negative osmotic flows through charged hydrated soft tissues, J.Biomechanics 30(1):71-78, 1997.
[30]. Sun DN, Gu WY, Lai WM, Mow VC. A mixed finite element formulation of triphasic mechano-electrochemical theory for charged, hydrated biological soft tissues, Int.J. Numer. Meth. Engng. 45:1375-1402, 1999.
[31]. Siegel A, Sapru HN. Essential neuroscience, Lippincott Williams & Wilkins, 2006.
[32]. Sarron JC, Blondeau C, Guillaume A, Osmont D. Indentification of linear viscoelastic constitutive models, *J.Biomech*. 33 :685-693, 2000.