The glymphatic system and Alzheimer's disease: possible connection?

Christina Rose Kyrtsos
Institute for Systems Research
University of Maryland
College Park, MD, US
ckyrtsos@hmc.psu.edu

John S. Baras
Institute for Systems Research
University of Maryland
College Park, MD, USA
baras@umd.edu

Abstract— **Alzheimer's disease (AD) is the most common cause of dementia in the elderly, accounting for 60-80% of all dementias. Symptoms of AD include memory loss (initially short term, later on long term as well), changes in mood and sun-downing. Magnetic resonance imaging (MRI) shows diffuse cortical atrophy and enlargement of the lateral ventricles due to neuronal cell loss. At the cellular level, neuroinflammation, activation of microglia, deposition of beta amyloid (Aβ) in the brain parenchyma and cerebral vasculature, and increases in the permeability of the blood-brain barrier (BBB) have all been observed as well. A newly developed theory purports that the glymphatic system of the brain may play a significant role in AD pathogenesis. This paper presents an initial mathematical model of the glymphatic system and studies how changes of transporter density and deposition of Aβ at the BBB changes clearance of Aβ. Changes in local neuronal cell density were also modeled. This represents one of the first attempts to computationally study the role of the glymphatic system in AD.**

Keywords-Alzheimer's disease, math model, glymphatic system, LRP1, Aβ clearance

I. INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia and affects nearly 1 in 6 people over the age of 65 years. The most common symptom associated with AD is the loss of short term memory (memory forming capability), followed by loss of long term memories important to the identity of the patient [7], [8]. Clinically, AD is diagnosed via post-mortem histology, and is identified from the presence of diffuse Aβ plaques throughout the cortices, which are particularly dense in the hippocampi and amygdala. Beta amyloid is generated in response to several known stimuli, including: trauma, inflammation, infection and synaptic remodeling [13], [14], [15]. Enhancements in the capability of imaging modalities have demonstrated that many AD brains have diffuse cortical atrophy that is more severe than that seen for normal aging, as well as enlargement of the lateral ventricles believed to be due to neuronal cell loss. Vascular dysfunction such as cerebral amyloid angiopathy (deposits of beta amyloid in the brain vasculature) and decreased cerebral blood flow have also been observed [11], [12].

Other features seen on histology include an increased number of neurofibrillary tangles (NFTs) and neuroinflammatory markers. Beta amyloid is known to activate microglia and induce the expression of pro-inflammatory cytokines, including interleukin-1 (IL-1) and tumor necrosis factor alpha (TNFα) [1]. This inflammation triggers further production of Aβ and creates a positive feedback loop if the inflammation is not controlled by IL-6 inhibition and Aβ is not cleared effectively. Such a local inflammatory environment is quite neurotoxic and can lead to synaptic dysfunction and neuronal cell death over time.

Recent experimental research has shown that this paravascular space, an area located between the cerebral vasculature and astrocytes, functions as a "lymphatic" system, clearing cerebral waste products via active (membrane transporters) and passive (transport to cervical lymph nodes) transport [5]. Experimental results demonstrated that the majority (approximately 50%) of fluid in the paravascular space was transported via this pathway to the cervical lymph nodes [5]. The remainder of solutes are either cleared by receptors along the venule or at the arachnoid granulations.

Conversely, cerebrospinal fluid (CSF) is believed to drain along cranial nerves, predominantly cranial nerve 1 via the cribiform plate [6]. CSF is mainly generated at the choroid plexus and travels through the ventricular system. Experiments have shown that significant changes in the choroid plexus occur in AD, aging and normal pressure hydrocephalus, and include: flattening and loss of the secretory epithelium; thickening of the basement membrane; cyst formation; lipid accumulation with fibrosis and calcification; hyalination; and especially important to AD pathogenesis, Aβ deposition in choroidal vessels [2]. The exact role of these changes is currently not well understood, but may contribute to abnormal clearance of Aβ from the brain which is studied in more detail in this paper.

This paper studies the role of the glymphatic system in clearance of Aβ from the brain. The generation of CSF and interstitial fluid (ISF), the effect of decreased densities of a key transport receptor, LRP-1 (low density lipoprotein-related receptor protein 1) and the effect of increased Aβ generation rate were studied. Section II will discuss more details on the model background information and it's basis in currently available experimental data, as well as describe derivations of key equations that were used in modeling. Section III will describe the results of the model, while section IV will delve into the discussion of these results and how they relate to current ideas on the pathophysiology of the biological processes occurring in AD. This represents one of the first mathematical models of the brain's glymphatic system and applies it to an important clinical scenario (AD).

II. MODEL BACKGROUND

In this model, the glymphatic system of the brain has been studied with respect to the clearance of Aβ. The brain has been roughly divided into three overlapping compartments: the blood-brain barrier (BBB), the brain parenchyma and the paravascular space that runs between the two. The CSF fills the cerebral ventricles and empties into the dural venous sinuses at the arachnoid granulations. Flow progresses from the choroid plexus inferiorly before splitting and heading either anteriorly towards the frontal lobe, or inferiorly, transversing around the cerebellum and occipital lobes until both pathways converge and drain to the superior sagittal sinus. This is the location of the majority and largest of the arachnoid granulations, sites where the arachnoid delves into the dura and an exchange of CSF from the subarachnoid space to the venous blood occurs.

The CSF serves several roles, including: buoyancy for the brain; acid-base buffering; and delivery of electrolytes, signaling molecules and micronutrients to cells within the brain parenchyma [4]. In addition to these roles, the ISF also has the task of clearing solutes and waste products from the intraparenchymal space. At the cellular level, the abluminal Na+/K+ ATPase is responsible for generating both CSF and ISF; CSF is generated at a rate of about 350-400 μL/min, while ISF is generated at about 0.17 μL/min [3], [4]. CSF is predominantly generated at the choroid plexus by secretory epithelium, while ISF is generated at the BBB. Rate of production is a function of the following:

$$CSF\ Gen = f(\text{diuretics}, \text{digoxin}, \beta\ \text{blockers}, \text{longterm CSF}\ \mathbb{P}, \text{aging})$$

It is important to note that CSF generation rates do *not* change with acute changes in CSF pressure; however, ISF generation rates may vary with the blood pressure of the involved vasculature and can be modeled according to Starling's law:

$$J_v = L_p S(\Delta P - \sigma \Delta \pi) \tag{1}$$

where J_v is the net fluid flux, L_p is the hydraulic conductivity, S is the surface area through which fluid is being transferred across, ΔP is the hydrostatic pressure difference, σ is the osmotic reflection coefficient and $\Delta \pi$ is the oncotic pressure difference. The pressure differences (hydrostatic, oncotic) are taken across the BBB; that is, for ISF generation, the pressure gradient is the difference between the cerebral capillary and the interstitial space.

Once the ISF is generated, it flows with a predominantly convective nature as diffusion coefficients are so trivial compared to the fluid flow rate that they can be considered negligible. ISF generation at the BBB by astrocytes occurs at a constant rate k_5 (12 μL/hr) and is also dependent on the amount of CSF that is recycled into the interstitial space as described by the following equation:

$$\frac{dISF_a}{dt} = k_5 + k_2 CSF - d_1 ISF_a \tag{2}$$

where ISF_a is the amount of ISF produced by astrocytes, k_2 is the rate of CSF recycled into the ISF, and d_1 is the amount degraded at each time step. The total amount of ISF within the brain parenchyma (ISF) is modeled as the sum of that generated by astrocytes in addition to the amount produced by neurons:

$$\frac{dISF}{dt} = ISF_a + k_1 N - d_3 ISF_b \tag{3}$$

where k_1 is the rate of ISF generation by neurons and d_3 is the degradation rate of ISF within the brain parenchyma (ISF_b). Beta amyloid is generated by neurons (k_7) and cleared via LRP-1 at the BBB (k_3), at brain endothelial cells at the venule and at the dural venous sinuses as defined by the following:

$$\frac{dAB_b}{dt} = k_7 N + 0.001 AB_{csf} - AB_b \tag{4}$$

$$\frac{dAB_p}{dt} = 0.5 AB_b - k_3 AB_b LRP1 - AB_p \tag{5}$$

$$\frac{dAB_{csf}}{dt} = AB_p(1 - k_4 LRP_{csf}) \tag{6}$$

where AB_b is the amount of beta amyloid generated within the brain, AB_p is the total amount beta amyloid, ABCSF is the amount of beta amyloid in the CSF, and k_4 is the amount of Aβ transported to the CSF. LRP-1 levels at the venule and dural venous sinus were varied linearly to study the effect of decreased LRP-1 density on Aβ clearance from the brain. The system of equations was modeled using Matlab using a timestep of 1 day. The total time modeled was 5 years. For the simulations done here, the CSF concentration was held constant (blood pressure effect was not modeled here). The number of neurons was also modeled, dependent on the local concentration of Aβ such that neuron number decreased a specified percent if a level above a specified threshold ($>1 \times 10^{10}$) was reached. This threshold level was held constant for all simulations such that only very high levels of beta amyloid would lead to neuronal cell death. The model did not take into account neuronal cell injury (and subsequent death) that can occur at lower levels of Aβ that occur for prolonged periods of time.

III. RESULTS

An initial simulation was run to verify that the system was stable (Figure 1). The system of ODEs was simulated using Matlab and modeled over the course of a 5 year timespan. Results showed the absence of any perturbations and the simulation was stable over the time course and the range of rate constants used.

The highest concentration of Aβ is found within the brain, then within the dural venous sinuses and lastly in the CSF. Neuron number was constant over time and was dependent on the concentration of Aβ within the brain, as well as the nutrients from the ISF.
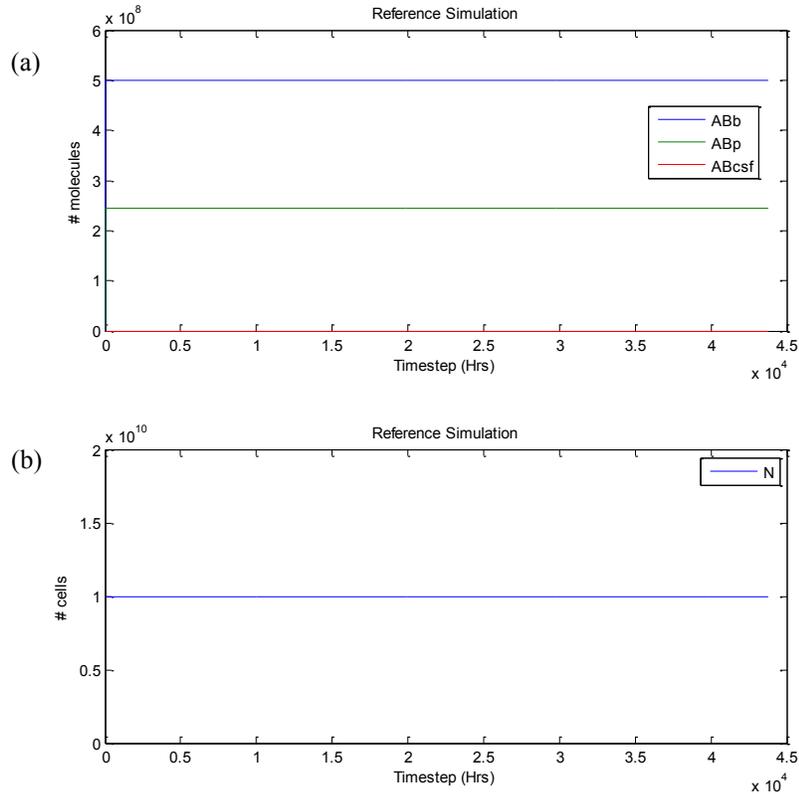
Figure 1: (a) Changes in Aβ levels in the brain, at the dural venous sinus and in the CSF. (b) Neuron number. There are no perturbations to the system.
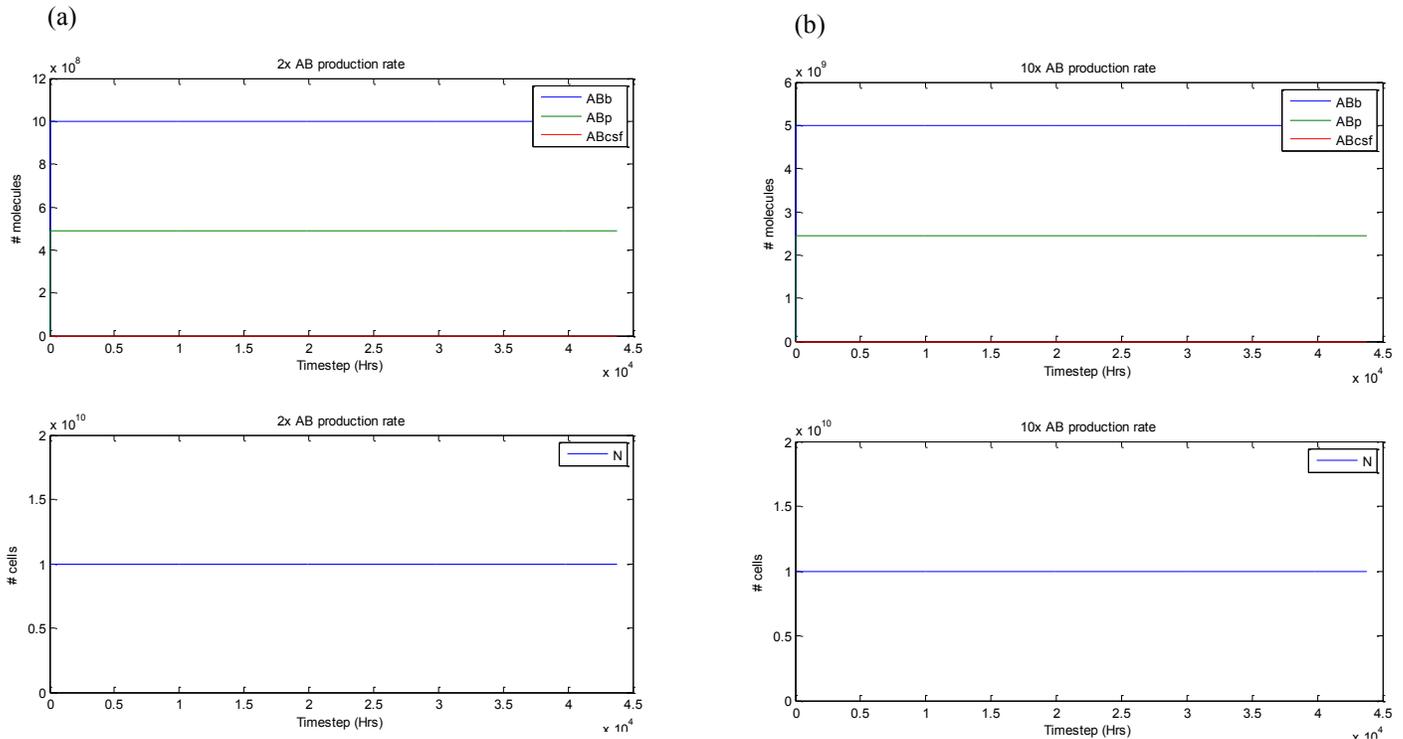

Figure 2: The generation rate of Aβ was increased to (a) 2x and (b) 10x   the normal rates. In both cases, neither simulation showed any change in the neuronal density. Only the levels of Aβ increased, demonstrating that having increased generation rate alone is not sufficient to lead to Aβ levels that are high enough to lead to neuronal cell loss.
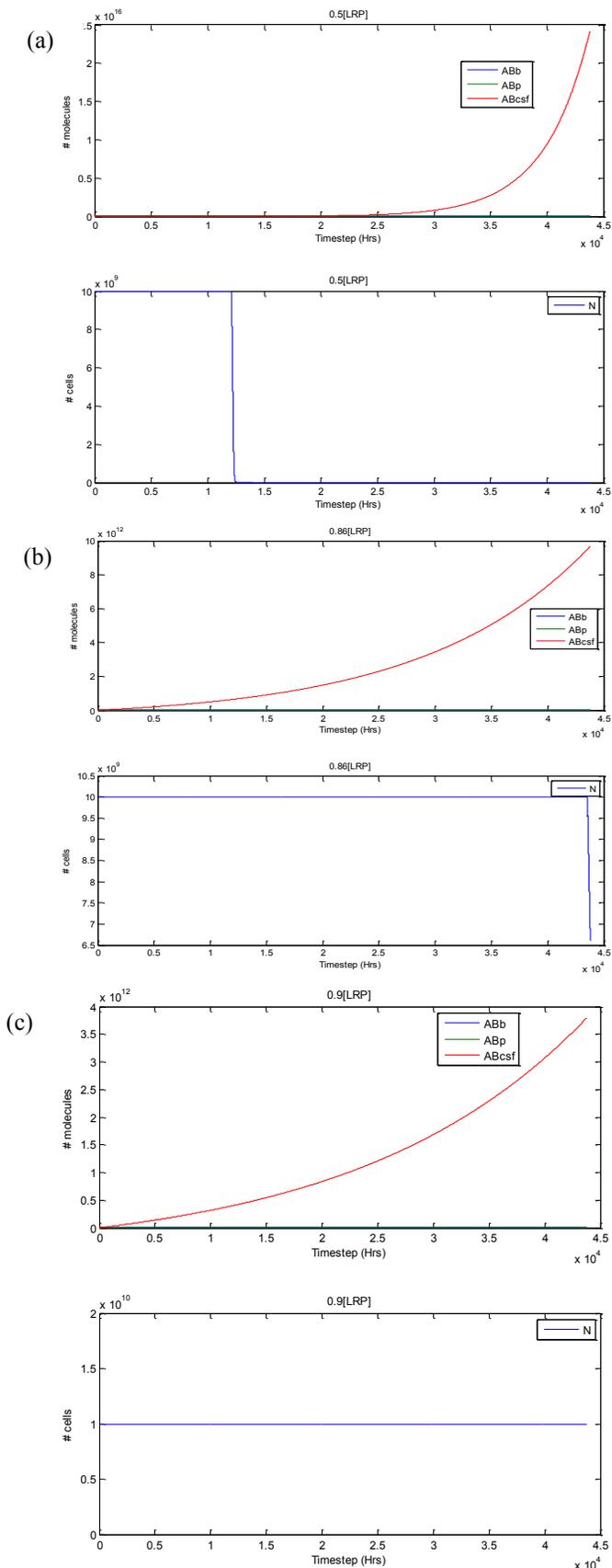
Figure 3: LRP1 levels at the venule and dural venous sinus were varied to study the effect of decreased expression LRP1 expression levels on the level of Aβ within the brain, CSF and paravascular spaces. (a) 50% normal LRP1 expression (b) 86% normal LRP1 expression; this is the transition point between a sustainable decrease in LRP1 and one that leads to neuron loss (c) 90% normal LRP1 expression.

A. Alteration of Aβ generation rates

Alteration of Aβ generation rates by two and ten times the basal rate demonstrated no change in neuron number. Only an increase in the level of Aβ proportionate to the increased generation rate was seen; however, these levels never crossed the threshold to lead to neuronal cell death (Figure 2).

B. Alteration of LRP-1 levels

LRP-1 levels were varied from 50-90% of normal levels to study whether decreased levels had a significant effect on the clearance of Aβ from the brain (Figure 3). By decreasing LRP-1 levels by just 10%, the amount of Aβ within the CSF started to increase exponentially but not to a level that caused neuronal cell death. At 86% of the normal density of LRP-1, there was a late occurring, catastrophic loss of neurons within the local region modeled as Aβ levels climbed above the threshold that lead to neuronal cell death. Decreasing the LRP-1 density further simply shifted the point at which neuronal loss occurred to earlier time points.

IV. DISCUSSION & CONCLUSION

In this paper, the role of the glymphatic system in the clearance of Aβ has been studied. Reference simulations showed that the basic model developed here was stable over a total time course equivalent to 5 years and for a range of rate constants. Altering the Aβ generation rate demonstrated that although Aβ levels increased in response to the elevated generation rate, levels never reached the threshold where neuronal cell death started to occur. This suggests that an increased Aβ generation rate alone is not sufficient enough to lead to the pathology seen in AD. This conclusion, however, is dependent on the threshold value set for where acute increases in Aβ lead to neuronal cell death. An alternative approach to this situation would be to study how chronic increases in Aβ at lower concentrations can have a negative effect on neuronal cell density.

Decreasing the density of LRP-1 receptors at the venule and dural venous sinuses did, however, have a significant effect on the neuronal cell number and Aβ level. A decrease of just 10% led to an exponential rise in Aβ over the duration of the simulation. This suggests that this clearance method is important in maintaining net balance of Aβ levels within the brain. When the LRP-1 density was further decreased to 86% of the normal levels, neuronal cell death occurred. Decreasing the density further to half of normal levels simply caused neuronal cell death to occur at an earlier time point. Interestingly, Aβ levels continued to rise after neuronal cell death as inflammation was rampant at this point and neurons died, releasing their Aβ into the interstitial fluid to be cleared. This is in accordance with the experimental literature which has shown that decreased

LRP-1 levels are common in AD and may be a significant contributing factor to the buildup of Aβ within the brain [9], [10]. The dramatic changes seen in neuronal cell number with this simulation suggest an important role for LRP-1 at the dural venous sinuses in maintaining normal Aβ levels within the brain, which has been demonstrated experimentally [9].

The mathematical model presented here is one of the first iterations that has been used to study the interaction between the glympahtic system and AD pathogenesis. The model has been developed to study how changes in key steps of clearance can affect the Aβ levels within the brain, and has focused here on the importance of LRP-1 in Aβ clearance. The model here is just a starting point and will be expanded to study the roles that alterations in clearance to the cervical lymph nodes play; how chronic hypertension and hypotension can play a role in decreased Aβ clearance; how Aβ deposition in the cerebral vasculature changes the ability of Aβ to be cleared as well as induces the breakdown of the BBB and subsequently causes a local inflammatory response; and how inflammation can change the clearance of Aβ. This work promises to be important in understanding how Aβ clearance mechanisms, especially how the glymphatic system, plays a significant role in the pathogenesis of AD and could be helpful in developing possible treatment modalities in the future.

REFERENCES

[1] R. O. Weller, D. Boche, and J.A.R. Nicoll. "Microvasculature changes and cerebral amyloid angiopathy in Alzheimer's disease and their potential impact on therapy." Acta neuropathologica, 118(1), Feb 2009, pp. 87-102.

[2] E. K. Agyare et al, " Traffic jam at the blood-brain barrier promotes greater accumulation of Alzheimer's disease amyloid β proteins in the cerebral vasculature," Mol Pharmaceutics, 10(5), Dec 2012, pp. 1557-1565.

[3] H. S. Sharma and J. Westman, " Blood-Spinal Cord and Brain barriers in Health and Disease," Elsevier Academic Press, 2004, pp. 92.

[4] G. D. Silverberg, M. Mayo, T. Saul, E. Rubenstein, and D. McGuire, "Alzheimer's disease, normal-pressure hydrocephalus, and senescent changes in CSF circulatory physiology: a hypothesis," Lancet Neurol, 2(8), 2003, pp. 506-511.

[5] Iliff et al, "A paravascular pathway facilitates CSF flow through brain parenchyma and the clearance of interstitial solutes, including beta amyloid," Sci. Transl. Med, 4(147), 2012, pp. 1299-1309.

[6] Battal et al, "Cerebrospinal fluid flow imaging using phase contrast MR technique," Br J Radiol, 84(1004), 2011, pp. 758–765.

[7] R. B. Maccioni, J. P. Munoz, and L. Barbeito, "The molecular bases of Alzheimer's disease and other neurodegenerative disorders." Arch Med Res 32(5), 2001, pp. 367-81.

[8] D. J. Selkoe, "Soluble oligomers of the amyloid beta-protein impair synaptic plasticity and behavior." Behav Brain Res 192(1), 2008, pp. 106-13.

[9] R. A. Fuentealba, Q. Liu, T. Kanekiyo, J. Zhang and G. Bu, "Low-density lipoprotein receptor-related protein 1 (LRP1) promotes anti-apoptotic signaling neurons by activating AKT survival pathway," J. Biol. Chem. 284, 2009, pp. 34045-34053.

[10] D. E. Kang et al, "Modulation of amyloid β-protein clearance ad Alzheimer's disease susceptibility by the LDL receptor-related protein pathway." J. Clin. Invest. 106, 2000, pp. 1159-1166.

[11] B. V. Zlokovic, "Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders." Nature Rev. Neurosci. 12, 2011, pp. 723-738.

[12] I.V. J. Murray, J.F. Proza, F. Sohrabji, J. M. Lawler, "Vascular and metabolic dysfunction in Alzheimer's disease: a review." Exp. Biol. Med 236(7), 2011, pp. 772-782.

[13] N. Marklund et al, "Monitoring of β-amyloid dynamics after human traumatic brain injury." J. Neurotrauma 31(1), 2014, pp. 42-55.

[14] J. W. Lee et al, "Neuro-inflammation induced by lipopolysaccharide causes cognitive impairment through enhancement of beta-amyloid generation." J. Neuroinflam. 5(37), 2008.

[15] M. S. Parihar and G. J. Brewer, "Amyloid beta as a modulator of synaptic plasticity." J. Alzheimers Dis. 22(3), 2010, pp. 741-763.

ACKNOWLEDGEMENT