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BRAIN-ON-A-CHIP: DESIGN AND MODELING

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Abstract. The aim of this paper is to lay the foundations of the basic science that will guide the design and making of an implantable neuro-glial-vascular unit optimized to perform certain fundamental processes that could facilitate monitoring and supporting the proper functionality of the brain. Such an engineered unit is called brain-on-a-chip. We first provide a possible structure of a brain-on-a-chip and then focus on the mathematical modeling of the coupled mechano-electrochemistry of a neuron and its membrane. We propose a constrained Lagrangian formulation that links the Hodgkin-Huxley model of the electronic membrane and the motion and diffusion processes of a triphasic porous medium that fills the inside of the neuron. The three phases of the triphasic medium are: solid, fluid and ionic. Lastly, a simplified Lagrangian formulation more suitable for practical applications is given whose corresponding Euler-Lagrange equations are obtained from the non-conservative form of Hamilton's principle.

Keywords. Neuronal Mechano-Electrochemistry, Triphasic Porous Media, Hamilton's Principle, Lagrangian Formulation, HodgkinHuxley Model.

1 Introduction

Imagine an engineered neuro-glial-vascular unit, *brain-on-a-chip*, that could perform some fundamental functions of a part of the brain. A brain-on-a-chip could provide much needed functional support during recovery after a stroke or serious traumatic injury, or could prevent seizures. Such a chip may be enhanced by adding specialized sensors to act as biomarkers and could send critical information about an imminent traumatic event to a receiver outside the body. In addition, a brain-on-a-chip might be optimized for targeted drug delivery to a brain's region affected by disease. A mathematical model that couples mechanical behavior and fundamental electro-chemical processes of such a neuro-glial-vascular unit could be used for instance to study mechanotrasduction mechanisms involved in traumatic brain injuries or in the growth and evolution of cerebral aneurysms. Therefore, the aim of this paper is to lay the foundations of the basic science that will guide the

mathematical modeling and design of the first prototype of a brain-on-a-chip.

We envision a brain-on-a-chip as a human-made neuronal-glial-vascular unit at the meso-scale level that links some basic mechano-electrochemical mechanisms of its constituents. At this stage we see this chip as an engineered, chemically driven, mechano-hydraulic system made of a generic neuron and its membrane, a glia cell, a blood vessel and interstitial fluid. While the electrochemistry of the individual components (neuron, glia cell, blood vessel) and their corresponding networks has been intensively studied by neuroscientists for many decades, only in recent years linkages among the electrochemical behavior of neurons, glial cells and cerebral vasculature have started to be reported [4, 15, 19]. However, these studies do not provide mechanical structures to these components and thus their mechanical behavior and mechanotransduction mechanisms are not accounted for. On the other hand, studies of the mechanical properties of individual neurons, glial cells and cerebral blood vessels can be found for instance in [2, 12, 16, 18, 22, 26]. To the best of our knowledge work on the mechanical interactions among these components has not been reported yet. In a couple of recent papers [6, 7], we proposed the first electromechanical model that couples Newton's law of motion of a linear viscoelastic Kelvin-Voigt solid-state neuron and the classical Hodgkin-Huxley equations of the neuron's membrane. The original model [6] uses a constrained Lagrangian formulation to incorporate relevant macroscopic (cell level) and microscopic (ionic level) mechanical and electrical information, and thus facilitates the study of neuronal mechanotransduction and the dynamics of neuronal stiffness due to the evolutions of the microstructural components of the neuronal membrane. A generalized model was given in [7] that provides the physical structure of a linear viscoelastic fluid for the ionic gates m, n, and h introduced by the Hodgkin-Huxley model[1]. In addition, fractional temporal derivatives of variable order are used to model the entangled temporal scales caused by the stochastic nature of the action potential and the inseparability of the multiple time scales involved in the neuronal electromechanical processes.

We begin this paper by presenting a possible mechanical structure of a brain-on-a-chip. Next we focus on a generalization of our previous work [7] that couples the modified Hodgkin-Huxley model proposed in [24] where the ionic gates m, n, and h are linear viscoelastic Maxwell fluidic elements and the model of a triphasic porous medium which is a more realistic representation of the inside of a neuron. The three phases of the triphasic structure are: 1) an intrinsically incompressible, porous-permeable, linearly elastic solid phase (cytoskeleton), 2) an intrinsically incompressible, interstitial fluid phase, and 3) an ionic phase with, for now, only two monovalent ion species: anion (Cl^-) and cation (Na^+). In addition, we assume that: 1)

[1]For instance, chemically-driven door closers give a possible visualization of the ionic gates that could lead to their material realization.

the concentrations of K^+ inside and outside the neuron do not change much such that the potassium reversal potential is almost constant $E_K \approx -80\,mV$, and 2) 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 [23]. The solid and the ionic phases are electrically charged, the fluid phase is electrically neutral, and the neuron is near its rest state. As in our previous work, we will use a constrained Lagrangian formulation that adds together the energies from various physical fields and length scales. This approach has the advantage that can easily incorporate relevant mechano-electrochemical information of the other components of the brain-on-a-chip from various time and length scales which we intend to do in our further work. Two other noteworthy advantages of the Lagrangian formulation are as follows. The equations of motion are obtained from using one minimization principle (Hamilton's principle) which is independent of the system of coordinates. In addition, this variational formulation is the natural mathematical framework for the development of numerical solvers using finite element methods. We point out however that a Lagrangian formulation is not unique and it should probably not be seen as a fundamental method to obtain physical laws [9, 20]. Therefore, we consider our energy-based variational formulation to be phenomenological in nature, limited only to the mechanics and electro-chemistry that can be either directly observed or inferred from experiments. Lastly, we will give a simplified Lagrangian formulation that is more suitable for practical applications and the corresponding Euler-Lagrange equations will be obtained by applying the non-conservative form of Hamilton's principle.

2 Design of a Brain-on-a-Chip

In fig.1 we present a schematic of a brain-on-a-chip. The chip is made of the following components: a neuron and its membrane, a glia cell, a blood vessel and interstitial fluid. The glial cell and the inside of the neuron are modelled as triphasic porous media, while the ionic gates of the neuronal membrane (envisioned as chemically-driven door closers) are modelled as linear viscoelastic Maxwell fluids (fig.2). The triphasic porous medium has three phases: 1) an intrinsically incompressible, porous-permeable, charged elastic solid phase represented in figs.1 and 2 as a spring-mass system, 2) an intrinsically incompressible, interstitial fluid phase represented in figs.1 and 2 as a dashpot-mass system, and 3) an ionic phase.The electro-chemical dynamics of the neuron's membrane is described by the modified Hodgkin-Huxley model that contains transient sodium currents, delayed rectifier potassium currents, specific leak currents for sodium, potassium and chloride ions, and sodium/potassium pump current. The electric circuit corresponding to the Hodgkin-Huxley model is shown in fig.2. The interstitial fluid is modelled as an incompressible viscous Newtonian fluid filled with ions that travel in

and out from the other compartments of the brain-on-a-chip. The flow of the interstitial fluid is driven by the moving of the ions and the pulsations of the blood vessel. In fig.1, the interstitial fluid is represented by a dashpot-mass system. Lastly, the blood vessel is modelled as an elastic spring-mass system, while the blood is assumed to be an incompressible Newtonian fluid represented in fig.1 as a dashpot-mass system. If we presume that the blood is the supplier of interstitial fluid, ions and other proteins and molecules, then, at a later time, the blood will have to be modelled as a complex fluid mixture while the blood vessel will be assumed to be a semi-permeable biphasic medium.

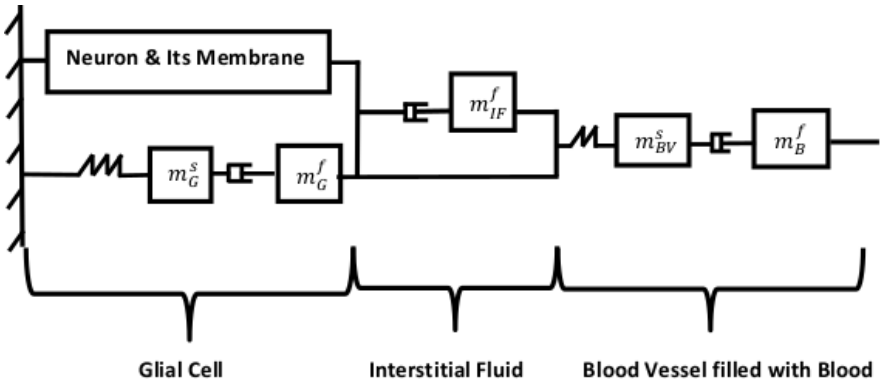

Figure 1: Schematic of a brain-on-a-chip. The box titled Neuron & Its Membrane is shown in fig.2. The solid phases are represented as spring-mass systems, while the fluid phases are drawn as dashpot-mass systems.

The coupled laws of mechanics and electro-chemistry of this chip can be obtained from a constrained Lagrangian formulation and the non-conservative form of Hamilton's principle. In order to make progress in this direction, we will focus first on a Lagrangian formulation for the neuron and its membrane. Once this formulation is established then the energetic contributions from the other components of the brain-on-a-chip will simply be added to the mechanical, electrical and chemical energies of the neuron and its membrane.

3 Mechano-Electrochemical Model of a Neuron and Its Membrane

As in our previous work [6, 7], the neuron is modelled as an axi-symmetric circular cylindrical annulus whose inner core is filled with the intracellular space and the outer core is the cell's membrane (fig.2). The inner core has

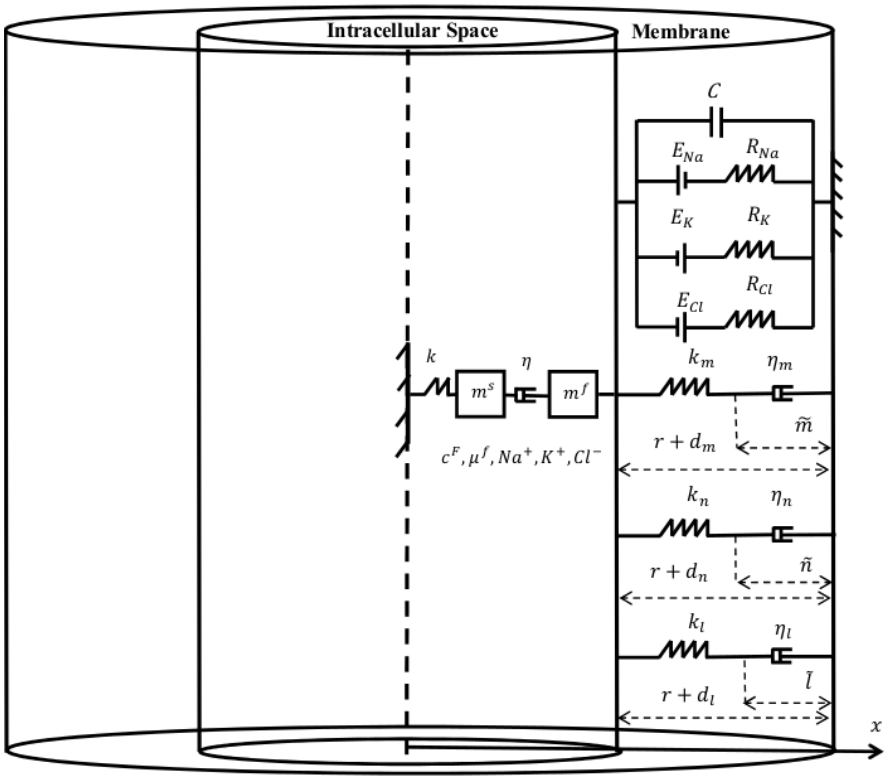

Figure 2: Schematic of a neuron and its menbrane. The neuron is assumed to be an axisymmetric homogeneous circular cylinder whose inner core is filled by the intracellular space, and the outer layer is the membrane. Because of the geometrical symmetry (dashpot line) and material homogeneity, it is enough to study half of the neuron whose properties are encapsulated into a spring-mass system representing the solid phase connected in series to a dashpot-mass msystem representing the fluid phase and both phases interact with a third, ionic phase. Neuronal membrane is represented as an electric circuit governed by the Hodgkin-Huxley model where the well-known ionic gates m, n, and h are modelled as linear viscoelastic Maxwell fluids connected in parallel. Here the spring constant of the solid phase is given by $k = \dfrac{EA}{r_0}$, where E is the Young's modulus, A is the cross-sectional area of the inner core of the cylinder of radius r_0. The viscosity of the fluid phase is denoted by η, and the damping coefficients of the Maxwell elements are η_m, η_n, and η_h. For now, we assume that the electric circuit and Maxwell elements representing the membrane are independent of each other.

radius r_0 and the radius of the outer core (membrane's thickness) is $r << r_0$. The deformation of the neuron is only along the radial direction and we denote by x the independent spatial variable. We assume that the center of the neuron is fixed ($x = 0$) while the interface $x = r_0$ between the intracellular space and the membrane is moving due to ionic transport across the membrane. Because the membrane's thickness is much smaller than the length of the intracellular space, the physical quantities describing the mechano-electrochemistry of the membrane are assumed to vary in time but not in space.

We model the intracellular space as a triphasic porous medium whose three phases are: 1) an intrinsically incompressible, porous-permeable, negatively charged, linearly elastic solid phase, 2) an intrinsically incompressible, electrically neutral, Newtonian fluid phase, and 3) an ionic phase with two monovalent ion species, Cl^- and Na^+. We further assume that: 1) the concentrations of K^+ inside and outside the neuron do not change much such that the potassium reversal potential is almost constant $E_K \approx -80\, mV$, and 2) there exist negatively charged groups on the solid phase, fixed charges, which are not as mobile as the ions flowing through the fluid phase. The porous medium is saturated with the volume fractions of the ions much smaller (diluted) than the solid and fluid volume fractions. In addition, there are no chemical reactions between components, and inertial terms, body forces and thermal eects are negligible. All the processes are adiabatic.

For the neuronal membrane we use the modified Hodgkin-Huxley equations given in [24] to model its macroscopic electrochemical dynamics of neuron's membrane. Hodkin-Huxley model introduces three ion gates, m, n, and h, that produce action potentials by controlling the ionic flow into and out the neuron. In [7] we proposed to use linear viscoelastic Maxwell fluids as physical structures for m, n, and h. The physical analogy for these ionic gates is a door closer. Given the empirical nature of the Hodgkin-Huxley model and the current lack of knowledge of neuronal mechanotransduction, we consider that the electric circuit and the Maxwell elements are independent of each other.

The coupling of the triphasic porous medium and Maxwell mechanical elements, and the Hodgkin-Huxley electric circuit is achieved by using a Lagrangian formulation and Hamilton's principle as follows. We denote by ρ^α, u^α the mass concentration and, respectively, displacement in the Lagrangian description of component α, $\alpha = s, f, +, -$, where s stands for the solid phase, f for the fluid phase, $+$ for Na^+, and $-$ for Cl^-. Let φ be the porosity, $c^\alpha,\ \alpha = +, -$ be the molar concentrations of the cation and anion, and $M_\alpha,\ \alpha = +, -$ be the molecular weights of the cation and anion. Then

[23]:

$$\begin{aligned}\rho^{\alpha} &= \varphi\, c^{\alpha} M_{\alpha},\ \alpha = +,-\\ \rho^{f} &= \varphi\, \rho_T^{f},\\ \rho^{s} &= (1-\varphi)\rho_T^{s},\end{aligned} \tag{1}$$

where ρ_T^s, ρ_T^f are the constant mass densities of the solid and respectively fluid phases which are incompressible in their unmixed states. Since the ionic species (sodium and cloride) are in this case dilute solutes, the van't Hoff law is used to express the electrochemical potentials of the ionic species as:

$$\begin{aligned}\tilde{\mu}^{+} &= RT\ln c^{+} + F\Psi\, c^{+},\\ \tilde{\mu}^{-} &= RT\ln c^{-} - F\Psi\, c^{-},\end{aligned} \tag{2}$$

where R is the universal gas constant, T is the absolute temperature, F is Faraday constant, and Ψ is the electric potential. For simplicity, in formulas (2) we made all the activity potential coefficients equal to 1. A simple calculation that combines the first law of thermodynamics, Gibbs-Duhem equation[2], and Hooke's law gives the following expression for the Gibbs free energy G of the triphasic porous medium:

$$\begin{aligned}\left(\rho^{s}+\rho^{f}\right) G =& RT\,\varphi(c^{+}\ln c^{+} + c^{-}\ln c^{-}) + F\Psi\,\varphi\,(c^{+}-c^{-})\\ &+\rho_T^{f}\,\varphi\,\frac{\mu^{f}}{M_f} + \rho_T^{s}\,(1-\varphi)\,EA\left(\frac{\partial u^{s}}{\partial x}\right)^{2},\end{aligned} \tag{3}$$

where μ_f is the chemical potential of the fluid phase, M_f is the molecular weight of the fluid phase, E is the Young's elastic modulus of the solid phase, and A is the constant cross-sectional area of the inside of the neuron (Fig.2).

Before moving forward, we belive that a clarification of the scientific language used in the literature is needed here. We noticed that some authors (see for instance [8]) used an equivalent expression for the Gibbs energy of complex ionic fluids which is given as the negative of the product between T and the so-called entropy of mixing whose expression is the same as that of the classical Boltzmann entropy[3]. The first three terms on the right-hand side of equation (3) were used in [8] without the porosity and thus they differ by a factor N_A, the Avogardo constant, from our terms in (3) and therefore the concentrations used in [8] have to be understood as number concentrations, rescaled molar concentrations by the same factor N_A. In addition, unlike other authors, we keep the chemical potential of the fluid phase as is since it is connected to the fluid pressure p by the following formula:

$$p = \mu^{f} + \Delta\,\pi, \tag{4}$$

[2]Gibbs-Duhem equation transforms the first law of thermodynamics into an exact 1-form that can be integrated [11].

[3]Interested readers may find an insighful presentation on entropy in [3].

where $\Delta\pi$ is the difference between the osmotic pressures inside and outside the neuron. This is a very important observation, since the classical approach used in fluid mechanics to introduce the pressure field of an incompressible fluid cannot be invoked when working with complex ionic fluids as some authors have done. This is because, in general, porous media are neither incompressible nor compressible[4], they can be either saturated or not. Thus the continuity equation of a porous medium is not a consequence of incompressibility but rather a saturation constraint. Our view and physical interpretation are in agreement for instance with [10, 21].

We now return our attention to the Lagrangian formulation of our problem. We introduce the Lagrangian form of the neuron and its membrane as follows:

$$\begin{aligned}\mathcal{L} = \int_0^{r_0} [&\frac{1}{2}\rho_T^f \varphi \left(\frac{\partial u^f}{\partial t}\right)^2 + \frac{1}{2}\rho_T^s (1-\varphi)\left(\frac{\partial u^s}{\partial t}\right)^2 - \frac{1}{2}EA\left(\frac{\partial u^s}{\partial x}\right)^2 - \rho_T^f \varphi \frac{\mu^f}{M_f} \\ &-RT\varphi\left(c^+ \ln c^+ + c^- \ln c^-\right) - F\Psi\,\varphi\left(c^+ - c^-\right)]dx \\ &-\frac{1}{2C}q_C^2 - \frac{1}{2}k_m(r + d_m - \tilde{m})^2 - \frac{1}{2}k_n(r + d_n - \tilde{n})^2 - \frac{1}{2}k_h(r + d_h - \tilde{h})^2,\end{aligned} \tag{5}$$

where $r+d_m$, $r+d_n$, and $r+d_h$ are the relative displacements of the Maxwell elements representing the ionic gates m, n, and h introduced by the Hodgkin-Huxley model, $\tilde{m}$, $\tilde{n}$, and $\tilde{h}$ are the displacements of the dashpots in these Maxwell elements, and k_m, k_n, and k_h are the spring constants of the springs in the Maxwell elements (see fig.2). In addition, C is the macroscopic capacitance of membrane's lipid bilayer modelled as a capacitor of electric charge q_C, and let q_{Na}, q_K, and q_{Cl} be the electric charges of Na^+, K^+, and Cl^- channels, respectively. We notice that the integrand in equation (5) is the difference between the total macro-kinetic energy of the solid and fluid phases and the Gibbs free energy given by formula (3) of the triphasic porous medium inside the neuron, the first term outside the integral represents a macro-potential electric energy of the membrane, and the last three terms in equation (5) are micro-potential mechanical energies of the membrane.

The conservation law of electric charges gives the constraint:

$$q_C + q_{Na} + q_K + q_{Cl} = 0. \tag{6}$$

We take u^s, u^f, u^+, u^-, q_{Na}, q_K, q_{Cl}, $\tilde{m}$, $\tilde{n}$, and $\tilde{h}$ to be generalized coordinates and introduce corresponding independent variations δu^s, δu^f, δu^+, δu^-,

[4] In [5], de Boer showed a way to generalize the concept of macroscopic incompressibility to mixtures. This is a very involved mathematical process and therefore it is rarely used in modeling.

δq_{Na}, δq_K, δq_{Cl}, $\delta\tilde{m}$, $\delta\tilde{n}$, and $\delta\tilde{h}$ that vanish at some arbitrary times t_1 and t_2.

We define now the virtual work done by non-conservative forces as:

$$\begin{aligned}\delta\mathcal{W} = \int_0^{r_0} \Bigg\{ & \left[-\eta \left(\frac{\partial}{\partial t}\frac{\partial u^s}{\partial x} - \frac{\partial}{\partial t}\frac{\partial u^f}{\partial x}\right)\delta\left(\frac{\partial u^s}{\partial x}\right) + \eta \left(\frac{\partial}{\partial t}\frac{\partial u^s}{\partial x} - \frac{\partial}{\partial t}\frac{\partial u^f}{\partial x}\right)\delta\left(\frac{\partial u^f}{\partial x}\right)\right] \\ & + \left[-\varphi\, c^+ \left(\frac{\partial}{\partial t}\frac{\partial u^f}{\partial x} - \frac{\partial}{\partial t}\frac{\partial u^+}{\partial x}\right)\delta\left(\frac{\partial u^+}{\partial x}\right) + \varphi\, c^+ \left(\frac{\partial}{\partial t}\frac{\partial u^f}{\partial x} - \frac{\partial}{\partial t}\frac{\partial u^+}{\partial x}\right)\delta\left(\frac{\partial u^f}{\partial x}\right)\right] \\ & + \left[-\varphi\, c^- \left(\frac{\partial}{\partial t}\frac{\partial u^f}{\partial x} - \frac{\partial}{\partial t}\frac{\partial u^-}{\partial x}\right)\delta\left(\frac{\partial u^-}{\partial x}\right) + \varphi\, c^- \left(\frac{\partial}{\partial t}\frac{\partial u^f}{\partial x} - \frac{\partial}{\partial t}\frac{\partial u^-}{\partial x}\right)\delta\left(\frac{\partial u^f}{\partial x}\right)\right]\Bigg\}\, dx \\ & - \left[R_{Na}\left(\frac{dq_{Na}}{dt}\right)\delta q_{Na} + R_K\left(\frac{dq_K}{dt}\right)\delta q_K + R_{Cl}\left(\frac{dq_{Cl}}{dt}\right)\delta q_{Cl}\right] \\ & - \left[\eta_m\left(\frac{d\tilde{m}}{dt}\right)\delta\tilde{m} + \eta_n\left(\frac{d\tilde{n}}{dt}\right)\delta\tilde{n} + \eta_h\left(\frac{d\tilde{h}}{dt}\right)\delta\tilde{h}\right] \\ & + [-E_{Na}\delta q_{Na} - E_K\delta q_K - E_{Cl}\delta q_{Cl}] \end{aligned} \tag{7}$$

In formula (7) the terms inside the integral represent friction forces between two phases of the triphasic medium. As in [23], we neglected the friction forces between the solid and ionic phases. We denoted by η the viscosity of the fluid phase. The friction forces between the fluid and each ionic species can be further written as [8][5]:

$$\varphi\, c^\alpha \left(\frac{\partial}{\partial t}\frac{\partial^2 u^f}{\partial x^2} - \frac{\partial}{\partial t}\frac{\partial^2 u^\alpha}{\partial x^2}\right) = \frac{D^\alpha}{RT}\varphi\, c^\alpha \frac{\partial\tilde{\mu}^\alpha}{\partial x},\ \alpha = +, - \tag{8}$$

In equation (8) D^α is the diffusion coefficient of the ionic species α. We notice that the left-hand side of equation (8) resembles the friction term in the Navier-Stokes equations of a viscous Newtonian fluid.

The first two sets of parentheses outside the integral in formula (7) represent dissipative forces due to the resistors of resistances R_{Na}, R_K, and R_{Cl} in the Hodgkin-Huxley electric circuit and due to the linear dashpots in the Maxwell elements whose damping coefficients are η_m, η_n, and η_h. The last set of parentheses in the expression of $\delta\mathcal{W}$ contains the generalized forces E_{Na}, E_K, and E_{Cl} known as the reverse potentials of the Hodgkin-Huxley model. The choice of signs in formula (7) guarantees that $\delta\mathcal{W}$ is thermodynamically consistent.

The Euler-Lagrange equations are obtained from the non-conservative form of the Hamilton's principle [1]:

$$\int_{t_1}^{t_2} (\delta\mathcal{L} + \delta\mathcal{W})\, dt = 0. \tag{9}$$

[5]The authors of [23] use different expressions for these friction forces.

Lastly, the Kirchhoff's current law:

$$\frac{d}{dt}\left(CV + q_{Na} + q_K + q_l\right) = I, \tag{10}$$

is added to the system of differential equations. In equation (10) $V = q_C/C$ is the electric potential of the capacitor, and I is a known external current applied on the membrane.

In order to get the Euler-Lagrange equations, the Lagrangian variation $\delta\mathcal{L}$ must be calculated. The difficulty in calculating this variation comes from the fact that we do not acutally know all the relationships among the physical parameters and evolving fields. For instance, by invoking the conservation of mass of the solid phase in the reference configuration chosen to be the rest state of the neuron and using the intrinsic incompressibility of this phase, it can be shown that [23]:

$$\varphi = 1 - \frac{1 - \varphi_0}{1 + e} \tag{11}$$

where the dilatation is $e = \dfrac{\partial u^s}{\partial x}$. In [6, 7], we used the experimental obervations reported in [26, 14] regarding the stiffening of the neuron during an action potential to propose the following dynamics of the Young's modulus:

$$E(m, n, h) = E_0\left(1 + m^3(1 - h)n^4\right), \tag{12}$$

where E_0 is the Young's modulus of the neuron in the rest state, and $m = \frac{\tilde{m}}{r}$, $n = \frac{\tilde{n}}{r}$, $h = \frac{\tilde{h}}{r}$ are non-dimensional displacements which we identify with the variables representing the activations of the Na^+ and K^+ channels and,respectively, the inactivation of Na^+ channel. We could also assume that the membrane acts like a parallel-plate capacitor and introduce [6, 7]:

$$C = c_m\tilde{A} = \frac{\epsilon\tilde{A}}{r(1 + u/r)} \approx \frac{\epsilon\tilde{A}}{r}\left(1 - \frac{u}{r}\right), \tag{13}$$

where $\tilde{A}$ is the neuronal surface area, c_m is the specific membrane capacitance and ϵ is membrane's permittivity.

Not only that formulas (12) and (13) have not been confirmed experimentally but also there is very little known about the relationships among the other physical parameters and quantities of the proposed model. In addition, most of the physical parameters needed by the model have not been yet found experimentally. Given these limitations, we will not derive here the Euler-Lagrange equations for this variational formulation. Instead, we will propose a much simplified formulation which may not only be easier from a mathematical point of view but also more suitable for practical applications.

4 Simplified Model

If we assume that the neuron is near its rest state then the ionic concentrations are approximately equal to their equilibrium values. In this case the simplified biphasic swelling model proposed by [25] can be used instead of a triphasic model with similar results. Thus, in this section we assume that the inside of the neuron is a biphasic porous medium with only solid and fluid phases of constant masses m^s and respectively m^f, and with u^s and u^f the corresponding displacements from the reference configuration chosen to be the rest state of the neuron. In this case we also neglect the spatial variation and thus the Lagrangian form given by (5) reduces to:

$$\begin{aligned}\mathcal{L} =&\frac{1}{2}m^f\left(\frac{du^f}{dt}\right)^2+\frac{1}{2}m^s\left(\frac{du^s}{dt}\right)^2-\frac{1}{2}k\,(u^s)^2\\&-\frac{1}{2C}q_C^2-\frac{1}{2}k_m(r+d_m-\tilde{m})^2-\frac{1}{2}k_n(r+d_n-\tilde{n})^2-\frac{1}{2}k_h(r+d_h-\tilde{h})^2,\end{aligned} \tag{14}$$

while the virtual work (7) becomes:

$$\begin{aligned}\delta\mathcal{W} =&\left[-\eta\left(\frac{du^s}{dt}-\frac{du^f}{dt}\right)\delta u^s+\eta\left(\frac{du^s}{dt}-\frac{du^f}{dt}\right)\delta u^f\right]\\&-\left[R_{Na}\left(\frac{dq_{Na}}{dt}\right)\delta q_{Na}+R_K\left(\frac{dq_K}{dt}\right)\delta q_K+R_{Cl}\left(\frac{dq_{Cl}}{dt}\right)\delta q_{Cl}\right]\\&-\left[\eta_m\left(\frac{d\tilde{m}}{dt}\right)\delta\tilde{m}+\eta_n\left(\frac{d\tilde{n}}{dt}\right)\delta\tilde{n}+\eta_h\left(\frac{d\tilde{h}}{dt}\right)\delta\tilde{h}\right]\\&+[-E_{Na}\delta q_{Na}-E_K\delta q_K-E_{Cl}\delta q_{Cl}]+(p-\Delta\pi)\,A\,\delta u^f.\end{aligned} \tag{15}$$

Here k is the spring constant and η is the damping coefficient of the biphasic medium. The generalized coordinates are now u^s, u^f, q_{Na}, q_K, q_{Cl}, $\tilde{m}$, $\tilde{n}$, and $\tilde{h}$.

If we assume further that all the parameters are constant except $k = k(\tilde{m}, \tilde{n}, \tilde{h})$ that is assumed to be given by formula (12), then the variation of the Lagrangian given by (14) can be easily calculated from:

$$\begin{aligned}\delta\mathcal{L}=\lim_{\epsilon\to 0}\frac{d\mathcal{L}}{d\epsilon}(&q_{Na}+\epsilon\delta q_{Na},q_K+\epsilon\delta q_K,q_{Cl}+\epsilon\delta q_{Cl},u^s+\epsilon\delta u^s,u^f+\epsilon\delta u^f,\\&\tilde{m}+\epsilon\delta\tilde{m},\tilde{n}+\epsilon\tilde{n},\tilde{h}+\epsilon\tilde{h})\end{aligned} \tag{16}$$

By applying Hamilton's principle (9) we obtain the following Euler-Lagrange equations:

$$m^s \frac{d^2u^s}{dt^2} + \eta \left(\frac{du^s}{dt} - \frac{du^f}{dt} \right) + ku^s = 0 \tag{17}$$

$$m^f \frac{d^2u^f}{dt^2} - \eta \left(\frac{du^s}{dt} - \frac{du^f}{dt} \right) = (p - \Delta\pi)A \tag{18}$$

$$\frac{dm}{dt} = -\frac{k_m}{\eta_m} m + \frac{k_m}{\eta_m}(1 + d_m/r) - \frac{1}{2\eta_m} \frac{\partial k}{\partial m} (u^s)^2 \tag{19}$$

$$\frac{dn}{dt} = -\frac{k_n}{\eta_n} n + \frac{k_n}{\eta_n}(1 + d_n/r) - \frac{1}{2\eta_n} \frac{\partial k}{\partial n} (u^s)^2 \tag{20}$$

$$\frac{dh}{dt} = -\frac{k_h}{\eta_h} h + \frac{k_h}{\eta_h}(1 + d_h/r) - \frac{1}{2\eta_h} \frac{\partial k}{\partial h} (u^s)^2 \tag{21}$$

$$-R_{Na} \frac{dq_{Na}}{dt} + V - E_{Na} = 0 \tag{22}$$

$$-R_K \frac{dq_K}{dt} + V - E_K = 0 \tag{23}$$

$$-R_{Cl} \frac{dq_{Cl}}{dt} + V - E_{Cl} = 0 \tag{24}$$

The physical parameters required by equations (19)-(21) are not known so we will replace the right-hand sides of these equations by the expressions from the modified Hodgkin-Huxley model [24] and thus obtain the following system of equations:

$$\frac{dm}{dt} = \alpha_m(1 - m) - \beta_m m \tag{25}$$

$$\frac{dn}{dt} = \alpha_n(1 - n) - \beta_n n \tag{26}$$

$$\frac{dh}{dt} = \alpha_h(1 - h) - \beta_h h \tag{27}$$

$$\tag{28}$$

where:

$$\alpha_m = \frac{0.32(V + 54)}{1 - \exp(-0.25(V + 54))},\ \beta_m = \frac{0.28(V + 27)}{(\exp(0.2(V + 27)) - 1)}$$

$$\alpha_n = \frac{0.032(V + 52)}{1 - \exp(-0.2(V + 52))},\ \beta_n = \frac{1}{2}\exp(-(V + 57)/40)$$

$$\alpha_h = 0.128\exp(-(V + 50)/18),\ \beta_h = \frac{4}{1 + \exp(-0.2(V + 27))} \tag{29}$$

Equations (22)-(24) are further substituted into Kirchhoff's law (10) and the relationships among each resistance and the corresponding conductances

of ionic and leak ionic currents given in [24] were used to get:

$$\begin{aligned} C\,\frac{dV}{dt} =& I - \left(G_{Na}m^3h + G_{NaL}\right)(V - E_{Na}) - \left(G_K n^4 + G_{KL}\right)(V - E_K) \\ & - G_{ClL}\,(V - E_{Cl})\,, \end{aligned} \tag{30}$$

where the constant parameters G_{Na}, G_K, G_{NaL}, G_{KL}, and G_{ClL} represent Na^+ voltage-gated maximal conductance, K^+ voltage-gated maximal conductance, Na^+ leak conductance, K^+ leak conductance, and Cl^- leak conductance, respectively. Nernst equations provide the following expressions for the reversal potentials [24]:

$$E_{Na} = 26.64 \ln\left(\frac{c_o^+}{c_i^+}\right),\ E_{Cl} = 26.64 \ln\left(\frac{c_i^-}{c_o^-}\right),\ E_K = 26.64 \ln\left(\frac{[K^+]_o}{[K^+]_i}\right), \tag{31}$$

where the subscripts i and o represent concentrations inside and outside the neuron, respectively, c^+ is the concentration of Na^+, c^- is the concentration of Cl^-, and $[K^+]$ is the concentration of K^+. We assumed that E_K is constant ($\approx -80\,mV$). If the outside concentrations of ions are known then $[K^+]_i$ can be found from the given value of E_K and (31), while the inner concentrations of sodium and cloride are obtained from the Donnan equilibrium [23, 25]:

$$\begin{aligned} c_i^+ + [K^+]_i =& \frac{c_F + \sqrt{c_F^2 + 4c_o^2}}{2}, \\ c_i^- =& \frac{-c_F + \sqrt{c_F^2 + 4c_o^2}}{2} \end{aligned} \tag{32}$$

where $c_o = c_o^+ + c_o^- + [K^+]_o$ and c_F is the fixed charged density (FCD). Then the difference in osmotic pressures inside and outside the neuron is:

$$\begin{aligned} \Delta\,\pi =& \phi_i RT\left([K^+]_i + c_i^+ + c_i^-\right) - \phi_o RT\left([K^+]_o + c_o^+ + c_o^-\right) \\ =& \phi_i RT\sqrt{c_F^2 + 4c_o^2} - 2\phi_o RT\,c_o. \end{aligned} \tag{33}$$

where ϕ_i and ϕ_o are known internal and external osmotic coefficients, respectively.

By combining the conservation of the mass density of FCD in a Lagrangian description and formula (11) the following expression is found:

$$c_F = c_{F_o}\frac{\varphi}{\varphi - 1 + J} \tag{34}$$

where c_{F_o} is the FCD in a reference configuration and the porosity φ is assumed to be constant in this case. In formula (34), J represents the ratio of neuronal volume after deformation over the initial neuronal volume which

could be find experimentally using for instance *in-vivo* optical imaging [13]. Lastly, values for k and η may be calculated from the parameters' estimates reported in [16, 26] where a linear viscoelastic Voigt model and experimental observations were used. This can be achieved by using the method given in [17] to build a mathematical mapping between the Voigt model of a neuron (which we used in [6, 7]) and the presented biphasic model.

5 Conclusions

In this paper we presented the design of an implantable neuro-glial-vascular unit that we called brain-on-a-chip which mimics some of the relevant structural and functional properties of a neuron, glial cell, and blood vessel. Such a chip could be optimized to perform certain desired processes that facilitate monitoring and supporting the proper functionality of the brain. We then focused on the modeling of the mechano-electrochemistry of a neuron and its membrane and introduced a constrained Lagrangian formulation that links the Hodgkin-Huxley model of the electronic membrane and the motion and diffusion processes of a triphasic porous medium that fills the inside of the neuron. Lastly, a simplified Lagrangian formulation that is more suitable for practical applications is given whose corresponding Euler-Lagrange equations are obtained from the non-conservative form of Hamilton's principle.

In our future work we intend to perform some computer simulations using the biphasic swelling model proposed here and compare the results with those from our previous work [6, 7]. In particular, we will use the simplified biphasic model to study whether a traumatic event such as jabbing causes a neuronal mechanotransduction similar to the one reported in [6, 7], namely: large sustained oscillations of neuronal volume and lack of action potentials. We also plan to extend our model by adding mechano-electrochemical contributions from the other components of the chip: glial cell and blood vessel. We intend to apply the extended model to study the growth and rupture of cerebral microaneurysms whose mathematical modeling has not been attempted yet. Lastly, we plan to investigate how a brain-on-a-chip interacts with the neuro-glial-vascular networks in the brain.

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