Dynamic Intracranial Mass Transport with Uniform and Non-Uniform Osmolarity

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Abstract

We propose a dynamic computational model that predicts the effect of hydrostatic and osmotic pressure gradients on intracranial water shifts. The model includes distensible, distributed compartments that represent the cerebral vasculature, cerebrospinal fluid (CSF), and extracellular space (ECS). This tool is used to examine pathologies including cerebral edema and hydrocephalus. We assess the ability of the model to qualitatively reproduce the local effect of volume and pressure increases as a function of time and space during vasogenic and osmotic edema. The ability of the model to predict the effect of increasing blood tonicity on clearance of cerebral edema and decrease intracranial pressure is also determined.

1. Introduction

Intracranial water and species transport is the result of a complex and dynamic interactions between the cerebral vasculature, parenchyma, and CSF. Recent research has implicated the contribution of osmotic pressure to intracranial water flux\(^1\text{–}^\text{7}\), water cotransport with glucose across the blood brain barrier\(^8\text{,}^9\), and metabolic production of water due to glucose consumption by neurons and glia in the parenchyma\(^10\) as significant contributors to volume and pressure homeostasis in the brain.

1.1 Contribution of Osmotic Pressure to Intracranial Water Flux

Studies linking intracranial water flux with the osmolarity of the blood and ventricles\(^1\text{–}^6\) suggest that the normal balance of osmotic pressure in the plasma, ECS, and CSF plays a vital role in the water transport between these compartments. Ventriculocisternal perfusion (VCP) experiments show that alteration of the osmolarity of the lateral ventricles\(^1\text{–}^4\) or the plasma\(^2,^3,^6\) has a significant effect on CSF production. These experiments suggest that osmotic pressure gradients are a significant driving force in the transport of water\(^1\text{–}^6\) and solute\(^6\) between the blood, parenchyma, and the ventricles. These studies demonstrate both hydrostatic and osmotic pressure gradients (Starling forces) are fundamental aspects of water exchange in the CNS.
1.2 Previous Work

A steady state model that describes water transport phenomena governed by the interaction between osmotic pressure and glucose kinetics has been proposed. However, this steady state model did not dynamically simulate the physiological phenomena of distensible vasculature, ECS, and CSF, or simulate pulsatile blood flow. Due to these deficiencies the steady state model cannot simulate states associated with pathological accumulation of water in cerebral compartments including edema or hydrocephalus and cannot tract the effect of hydrostatic and osmotic pressure gradients on changes in volume or intracranial pressure (ICP) as a function of time.

1.3 Dynamic Intracranial Mass Transport Model with Uniform and Non-Uniform Osmolarity

The dynamic model described in the following section combines the interaction of hydrostatic and osmotic pressure on water flux between compartments in the brain, pulsatile blood flow, and distensible compartments to model the effect of cerebral edema on volume and pressure shifts as a function of time and space. Future work will include the non-linear relationship between dynamic species transport, osmotic pressure and water flux in order to create a more phenomenologically accurate model and to capture the water transport phenomena of water cotransport with glucose, and metabolic water production.

2. Methods

This work qualitatively assessed the ability of the proposed dynamic pressure and volume model with distensible compartments to replicate the physiology and pathophysiology of intracranial mass transport. The model uses a mass balance in the form of a first order ordinary differential equation for the intracranial compartments of the cerebral vasculature, parenchyma, and cerebrospinal fluid. The system is solved with an explicit 4th order Runge-Kutta method. Pulsatile flow is simulated with a boundary condition for pressure that changes with time to reproduce an experimentally measured pressure wave. Flow rates through the vasculature and CSF compartments are determined using the Hagen-Poiseuille equation while flow rate through the ECS is modeled as transport through a porous medium calculated by Darcy’s Law. Transmembrane transport between compartments is governed by Starling’s law which allows the model to include the contributions of osmotic pressure to intracranial water flux.

The network shown in Figure 1 consists of three main compartments; the vascular bed, the extracellular space, and the cerebrospinal fluid. The transport of water between these compartments occurs across a semipermeable membrane and is determined by hydrostatic and osmotic pressure. The proposed model contains the cerebrospinal fluid, the cerebral vascular system, and the parenchyma. The vascular
compartment includes arteries, arterioles, capillaries, venules, and veins. The parenchyma is composed of white and grey matter. The CSF system is composed of the lateral, 3rd and 4th, ventricles. Transmembrane water flux occur at the blood brain barrier between the blood and ECS, between the blood and ventricular CSF across the blood CSF barrier at the choroid plexus while the pia mater regulates the mass transport between the gray matter and the subarachnoid space.

The system shown in Figure 1 contains 96 nodes and 169 arcs. Each node has a pressure and a volume while each arc has a flux. The volume at each node is calculated with a mass balance shown in *Eq1* and the pressure is determined using the compliance equation shown in *Eq2*. The flux across each arc is given by Darcy’s law for flow through the ECS shown in *Eq4*, the Hagen-Poisuielle equation, *Eq3*, for transport through the CSF system and the vasculature and CSF, and Starling’s law, *Eq5*, for transport across membranes. The compliance, resistance to flow, initial pressure, and initial volume were the same for each compartment. This was done to save time by accelerating the convergence of the system.

**Figure 1**: The proposed model is composed of three main compartments; the cerebrospinal fluid, the vascular system, and the parenchyma. The cerebrospinal fluid system consists of the subarachnoid space and the lateral, 3rd and 4th, ventricles. The vascular compartment includes arteries, arterioles, capillaries, venules, and veins. The parenchyma is divided into white and grey matter. Water flux between the blood and cerebrospinal fluid occurs across the blood-CSF-barrier at the choroid plexus while flux between the blood and parenchyma occurs across the blood brain barrier. Transmembrane flux occurs across between the parenchyma and the CSF of the lateral ventricles across the ependyma. The pia mater regulates the exchange of water between the subarachnoid space and the parenchyma. Water is drained from the subarachnoid space into the veins through the arachnoid villi and the spine.
2.1 Conservation of Mass

The conservation of volume, $V$ for each node, $i$ is described by Eq 4 where the accumulation of volume is dependent on the difference between the flows in and the flows out of each node.

$$\frac{dV_i}{dt} = \nabla Q$$  \hspace{1cm} (1)

2.2 Compliance

The compliance of each compartment is given by Eq 5 where the change in volume, $V_i$, with respect to time at each node is related to the change in pressure, $P_i$, over time at each node by the compliance, $C$.

$$\frac{dV_i}{dt} = C \frac{dP_i}{dt}$$  \hspace{1cm} (2)

2.3 Vascular Resistance

The transport through the lumen of vessels is described by the Hagen-Poiseuille equation, Eq 1, where volumetric flow rate, $Q_{Blood}$, is dependent on the vessel radius, $r$, the vessel length, $L$, the hydraulic pressure drop across the vessel, $\Delta P$, and the dynamic fluid viscosity, $\mu$.

$$Q_{Blood} = \frac{\pi r^4 \Delta P}{8\mu L}$$  \hspace{1cm} (3)

2.4 Darcy’s Law

Water convection through the ECS is modeled using Darcy’s law, Eq 2, for transport through a porous medium where bulk flow, $Q_{ECS}$, is determined by the hydrostatic pressure gradient, $\Delta P$, cross sectional area of the interface between the capillaries and the ECS, $A_{Cap-ECS}$, the ECS permeability, $k$, for water and the hydraulic length of the porous media, $L$.

$$Q_{ECS} = \frac{kA_{Cap-ECS}}{\mu L} (\Delta P)$$  \hspace{1cm} (4)

2.5 Starling’s Law

The transmembrane transport of water, $J_{membrane}$, is modeled using Starling’s law, Eq 3, and is a result of the net driving force determined by hydrostatic pressure, $\Delta P$, osmotic pressure, $\Delta \pi$, the hydraulic permeability of the membrane to water, $L_p$, the surface area of the membrane, $S$, and the reflection coefficient of the osmolites, $\sigma$.

$$J_{membrane} = L_p S [ (\Delta P) - \sigma (\Delta \pi) ]$$  \hspace{1cm} (5)
2.6 ODE Solver

Equation 6 is a mass balance in terms of volume that is solved numerically with a 4th order Runge-Kutta method where \( \frac{dV}{dt} \), is a vector representing the change in volume of each compartment over time, \( G \) is a matrix containing the conductance of each arc in the network, \( V \) is a vector of volumes, and \( b \) is the target vector. This equation is obtained by inserting the constitutive flux, \( Eq1-Eq3 \), and compliance equations, \( Eq5 \), into the conservation of mass equation, \( Eq4 \), to obtain the matrix expression. A sample network with all equations and algebraic manipulations is provided in Appendix A.

\[
\begin{bmatrix}
\frac{dV}{dt}
\end{bmatrix} = \begin{bmatrix} G \end{bmatrix} \begin{bmatrix} V \end{bmatrix} + \begin{bmatrix} b \end{bmatrix}
\]

(6)

Several numerical solvers were considered to solve the characteristic first order ODE given in equation 6. Initially, Matlab solvers ode23 and ode15s were used to solve the system. Both solvers successfully produced results with ode 15s solving the system with fewer calculations, but the automatic step size control interfered with both result validation and debugging. The lack of control over the solvers resulted in a change to the 4th order Runge-Kutta solver in ode4 where equation 6 is solved for explicitly at each time step.

2.7 Simulation of the Creation and resolution of Cerebral Edema

The proposed dynamic model is capable of simulating the creation and resolution disease states characterized by pathological water accumulation in the ECS known as cerebral edema. Cerebral edema can be vasogenic, cytotoxic, or osmotic in origin and is most often a mixture of the three. This work qualitatively examines the effect of vasogenic and osmotic edema on pressure, volume, and flow rates.

2.7.1 Vasogenic Edema

Vasogenic edema occurs when the permeability of the blood brain barrier to water is increased which is most often the result of a rupture of cerebral capillaries. This phenomenon will be simulated by altering the hydraulic conductivity, \( L_p \), in Starling’s law, \( Eq3 \), for the cerebral capillaries.

2.7.2 Osmotic Edema

Osmotic Edema is caused by osmotic imbalances between the plasma and parenchyma. The osmotic pressure of a cerebral compartment is directly related to the concentration of osmotically active molecules in that compartment which are most often a combination of proteins and electrolytes. Because this
simulation doesn’t solve for the dynamic species concentration profile, the osmotic pressure of an ECS node will be increased in a step pattern simulate osmotic edema.

2.7.3 Osmotic Therapy

The primary treatment for resolution of cerebral edema is osmotic therapy which is the intravenous application of a hyperosmolar solution most often composed of mannitol or saline. It is most often applied after traumatic brain injury to reduce intracranial pressure and unwanted volume accumulation in the brain. This effect will be simulated by increasing the osmotic pressure at all blood nodes in order to mimic the effect of hypertonic plasma on water accumulation in the brain.

2.8 Input Pressure Signal

The input hydrostatic arterial blood pressure signal was obtained from MRI measurements of a normal patient and was approximated using a discrete Fourier series Eq. 7.

\[
P_{init}(t) = \left[ 1 + \sum_{k=1}^{8} a_k \cos(\omega t) + \sum_{k=1}^{8} b_k \sin(\omega t) \right], \quad \omega = 2k\pi, k = 1,2,\ldots,8
\]

3. Results

The data presented in this section includes a dynamic simulation with uniform osmolarity and without any insult to assess the ability of the system to simulate the dynamic pressure and volume of distensible compartments with pulsatile flow under normal conditions. The ability of the system to produce vasogenic edema by manually altering the hydraulic permeability of capillaries is determined. Manual manipulation of the osmotic pressure is used to examine the ability of the system to simulate the phenomena of osmotic edema and osmotic therapy.
3.1 Dynamic Pressure and Volume Simulation with uniform osmolarity: Non-Diseased State

The dynamic pressure results for the system with uniform osmolarity are shown in Figure 2 for the vasculature, cerebrospinal fluid, and ECS compartments. The results illustrate that pressure in the arteries is most affected by the pulsatile flow from the inlet pressure boundary given in Eq7 while the veins, capillaries, ECS, and CSF are less affected.

3.2 Dynamic Pressure and Volume Simulation with Uniform Osmolarity: Vasogenic Edema

The ability of the system to reproduce the increase in water filtration across the blood brain barrier in vasogenic edema is illustrated in Figure 3. The increase in local flow rate of water across the blood brain barrier that occurs when the hydraulic permeability of the capillaries is increased is demonstrated in Figure 4 (Left). The increase in water extravasation from cerebral capillaries results a minimal increase of 0.2 mL in ECS volume shown in Figure 4 (Right).
**Figure 3:** Increase in flow rate due to an increase in transmembrane permeability across the cerebral capillaries representing a ruptured capillary (Left). Extracellular space (ECS) volume due to increasing capillary conductance (Right).

### 3.3 Dynamic Pressure and Volume Simulation with Non-uniform Osmolarity: Osmotic Edema

Figure 5 (middle right) demonstrates the spatial effect of an increase in the osmotic pressure at a single ECS node on ECS volume. The volume increase is greatest at the point with increased osmotic pressure while the effect decreases as the distance from the affected node increases.

### 3.4 Dynamic Pressure and Volume Simulation with Non-uniform Osmolarity: Osmotic Therapy

The ability of the system to reproduce osmotic therapy is shown in Figure 5 (bottom right) where the osmotic pressure of at all plasma nodes was increased by 20 mmHg to simulate plasma hypertonicity. The volume of the ECS is decreased in response to an increase in the osmotic pressure of the blood.
Figure 4: Dynamic volume changes of the extracellular space (ECS) during normal conditions (top right), osmotic edema (middle right), and osmotic therapy (bottom right). A local increase in the osmotic pressure at $E_1$ correlated with a significant increase in the volume of that node while the effect decreased as distance increased from $E_1$ to $E_5$. Simulation of osmotic therapy with a global increase in the plasma osmolarity at $P_1$ to $P_5$ decreased the volume of all ECS nodes.

**Discussion**

The results obtained from the simulations are at this point conceptual and are not validated. They are intended to assess the ability of the model to reproduce phenomena associated with dynamic pressure and volume in distensible cerebral compartments. The model was able to partially replicate the phenomena associated with vasogenic edema and was completely able to simulate osmotic edema and osmotic therapy.

The results suggest that the model was able to produce the increase in capillary filtration that occurs during vasogenic edema due to increased blood brain barrier permeability. The filtration rate out of cerebral capillaries was found to be directly related to the hydraulic permeability parameter of Starling’s law. However, an increase in capillary filtration alone will not result in an accumulation of volume in the ECS.
The results suggest that the model can replicate both the creation of edema and its clearance due to osmotic pressure gradients. A local increase in the osmotic pressure of a single ECS node increases the volume of both that node and adjacent nodes and the effect was found to decrease exponentially with the distance from the affected point. Simulation of osmotic therapy with a global increase in the osmotic pressure of the plasma corresponds to a global decrease in the volume of the ECS.

**Conclusion**

The results from several simulations suggest that the model can reproduce several important phenomena including vasogenic and osmotic edema as well as clinical interventions like osmotic therapy. While the results are scaled to compare with the physiological values for pressure and volume, the initial conditions, and flow resistances, and compliances have not been taken from the literature. The system is also sensitive to differences in these parameters, if the differences are too great, the system may not converge which may produce complications for future work. The model also cannot dynamically track the concentration of species and must rely on manual manipulation of osmotic pressure to simulate conditions of non-uniform osmolarity. The lack of dynamic species transport also prevents the model from simulating other water transport phenomena including metabolic water production and water cotransport across the blood brain barrier with glucose.

Future work would be to increase the physiological relevance of the model by using experimentally determined values for flow resistances, initial volume and pressure conditions, and compliances and adding dynamic species transport for both glucose and osmotically active particles such as albumin and sodium. The addition of species transport will significantly improve the physiological relevance of the model and couple the relationship between the concentration of osmolytes in each cerebral compartment to intracranial water flux and allow for the inclusion of secondary water transport phenomena.

**References**