Modeling the Dynamics of a Secondary Neurodegenerative Injury Following a Mild Traumatic Brain Injury

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***Abstract*- During a traumatic brain injury (TBI), there is an injection of GFAP from the brain into the bloodstream through a brain lesion that damages the blood-brain barrier (bbb). In the blood, a bio controller responds by upregulating IgG production into the bloodstream to remove the excess protein. We have modeled the reaction that takes place between the GFAP, IgG and their rate of consumption.**

***Clinical Relevance*- This research and model is relevant because it could lead to the analyzation of GFAP levels in the brain through methods as simple as a blood draw. This information can be used to predict the amount and severity of brain lesions as well as help understand the recovery process that the brain takes when having undergone TBI.**

I. Introduction

A. Traumatic Brain Injury (TBI)

Traumatic brain injury results from a violent blow or jolt to the head or body. An object that penetrates brain tissue, such as a bullet or shattered piece of skull can also cause traumatic brain injury. A traumatic brain injury (TBI) can be described by two major injuries: primary mechanical injury and secondary neurodegenerative injury.

B. GFAP and IgG

Following a primary injury, there is a disruption to the blood-brain barrier, which makes it more permeable, in turn leading to GFAP, a neural protein, being able to find its way into the bloodstream. Leakage of this brain protein triggers an immune response at the bloodstream for removal. This immune response consists of Immunoglobulin G (IgG) being released into the bloodstream and attaching to GFAP. Then IgG antibodies come and remove the IgG and GFAP combination.

C. Chronic Traumatic Encephalopathy (CTE)

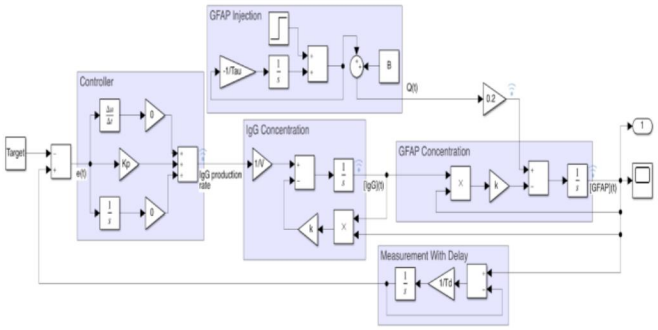
Chronic Traumatic Encephalopathy is a neurodegenerative disease that affects behavior, mood, and thinking. It is found in the brain of individuals with a history of repetitive brain trauma. It is still unclear how repetitive trauma, including quantity and severity of traumas and other factors that may contribute to changes in the brain, cause CTE.

II. Methods

A. Biosystem Model

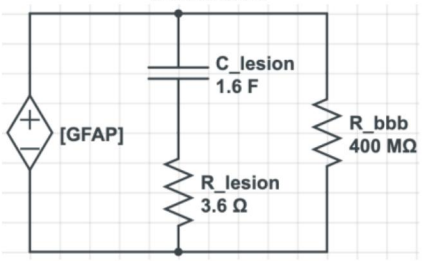
Figure 1 shows the full biosystem modeled in Simulink. The system includes the initial step function of GFAP in the brain, the flow of GFAP in the bloodstream over the blood-brain barrier as well as through the lesions caused by the TBI, the reaction between GFAP and IgG in the bloodstream, an IgG controller, and target GFAP concentration based on the steady state GFAP concentration found from an online data set [1]. A more detailed description of these parts can be found in their respective sections below.

FIGURE 1



Modeling Flow over the Blood-Brain Barrier and through TBI Lesions: Due to the physical damage to neural tissue caused from TBI, a step function models this biological response as an 'injection' of GFAP that represents the spike in GFAP concentration immediately after TBI. The flow has two components, the first being the natural permeability across the blood-brain barrier which is represented by the initial flow constant and the steady state after the flow has settled and the lesion has been healed. The second component is the flow through the lesion itself and the subsequent closing of said lesion. These two components have been combined and inspired by a similar electrical circuit as shown in Fig. 2. The top node represents the GFAP concentrations in the brain and the bottom node represents the rest of the body.

FIGURE 2



These circuit components were designed to match the simulated flow of GFAP that best matched experimental data.

During steady state, the flow is equal to 1 $\frac{pmol}{hr}$, the capacitor is equivalent to an open circuit, and the [GFAP] gradient between the brain and body is 3.6 M [2-3]. Using Ohm's law, this produces a blood-brain barrier resistance to GFAP of the R_bbb in Fig. 2. Similarly, we solve for R_lesion using an instantaneous increase in [GFAP] in the brain to 310 $\frac{pmol}{hr}$, [4], representing the rapid bursting of astrocytes in the brain. The capacitor acts as a short due to the instantaneous voltage increase, so again, Ohm's law can be used to determine the equivalent of the parallel resistors and then R_lesion. The time constant of the above circuit is the Time Constant Equation (Eq. 1) which, when combined with the experimental time constant, was used to calculate C_lesion.

$$\tau_q = R_{Th} \cdot C = \left(\frac{R_{Lesion} \cdot R_{BBB}}{R_{Lesion} + R_{BBB}}\right) C_{Lesion} \quad (1)$$

$$Q(t) = Ae^{\frac{-t}{\tau_q}} u(t) + c \quad (2)$$

The voltage source is modeled as a variable voltage source to allow for the [GFAP] step and return to steady state. The parameter of interest in this circuit is the sum of the currents through the parallel resistor and resistor and capacitor branches which represents the GFAP flow into the bloodstream.

Regarding the healing property of the lesion, an estimation of platelet formation per volume was calculated using the flow of blood, average platelet count in the blood, and average size of mild TBI lesion. MATLAB code was used to determine the time constant for the circuit for mild, moderate and severe TBI; therefore, time values determine the capacitance in Fig. 2.

Modeling GFAP Concentration in the Bloodstream after lesion: A traumatic brain injury can be summarized by a series of two lesions. A primary injury is the mechanical injury that caused the TBI and the secondary injury follows after a disruption in the blood brain barrier. A disruption of the epithelial tissue separating the brain and blood allows for the interchange between brain and blood proteins, which then triggers an immune response in both the central nervous system and the bloodstream [5].

During the secondary injury, several brain proteins flow from the brain to the bloodstream. These brain proteins have proved to be useful as potential biomarkers for the severity of TBI due to its high variance across severities [6-7]. However, its concentration dynamics are highly variable in the first few hours post-TBI [1]. To model the behavior, the approach was to consider the cellular dynamics of the adaptive immune response in the context of TBI.

It has been shown that Immunoglobulin G is found in high concentration post-TBI up to 7-10 days after. Additionally, it has been shown that the levels of IgG in patients with subsequent TBI have higher levels of antibodies relative to patients without TBI history [7]. The proposed mechanism is then, the presence of IgG in the bloodstream activates B-cells which then go on to replicate to produce memory B-cells and plasma cells. The memory b-cells go on to explain the presence of higher GFAP antibodies in patients with TBI history. In an adaptive immune response, subsequent presence of antigens after initial exposure trigger faster responses by the creation of memory b-cells. On the other hand, upon production of plasma cells, IgG antibodies are mass produced and begin flowing in the bloodstream [8]. In addition to the removal of GFAP from the bloodstream, these antibodies have also been shown to remove injured neurons and other brain proteins [9]. When IgG antibodies bind to antigens within the bloodstream, they participate in phagocytosis for removal. The following biochemical reaction is assumed to occur within the bloodstream, and complex formation is assumed to be rate limiting.

$$[GFAP] + [IgG] \xrightarrow{k} [Complex] \quad (3)$$

where [GFAP] is introduced into the bloodstream in proportion to the blood flow and IgG by the adaptive immune system in response the presence of GFAP. Additionally, the antibody-antigen complex is removed via phagocytosis.

Chemical reactions occur at an order of milliseconds compared to the hour time-scales our model deals with [10]. For this reason, we can assume that the reaction reaches a state of equilibrium really fast and the dynamics of the system reduce to,

$$\frac{dC}{dt} = \alpha I(t) - kC(t)G(t) \quad (4)$$

$$\frac{dQ}{dt} = \alpha Q(t) - kC(t)G(t) \quad (5)$$

Where C(t) represents the IgG concentration as a function of time, G(t) represents the GFAP concentration as a function of time, I(t) represents the IgG production rate by the controller, and Q(t) represents the flow of GFAP into the blood.

B. Transfer Function

In order to study the dynamics of how our GFAP/IgG system works we had to linearize the system, in order to eliminate the nonlinearities caused by the second order reaction between IgG and GFAP. From this linearization we were able to obtain a transfer function that is in respect to two inputs, the GFAP flow from the brain and the IgG controller. We were able to obtain two separate transfer functions using superposition on this larger transfer function. These are the response to the GFAP injection coming from the brain and the IgG injection coming in from our controller input. We analyzed the transfer functions of each input component separately in order to gauge the dynamics of the system. With superposition, the overall response can be modeled by adding the two single input responses.

$$I(t) = K_p(G_m(t) - T) \quad (6)$$

$$\frac{dG_m}{dt} = \frac{1}{\tau_m}(G(t) - G_m(t)) \quad (7)$$

Modeling TBI Severity

TBI is usually classified from mild to severe depending on how much damage is sustained within the brain. We can model the GFAP response to different levels of TBI by changing the maximum GFAP leakage rate from the brain into the blood and by increasing the time constant for the decay of this leakage. A more severe TBI will cause more lesions that are larger in size, causing more brain proteins such as GFAP to leak into the bloodstream. The larger lesions will also take more time to heal, which is analogous to an increase in the decay time constant.

Linearization of GFAP-IgG Reaction

$$\frac{d\tilde{C}}{dt} = \alpha\tilde{I}(t) - k\bar{C}\tilde{G}(t) - k\bar{G}\tilde{C}(t) \quad (8)$$

$$\frac{d\tilde{G}}{dt} = \alpha\tilde{Q}(t) - k\bar{C}\tilde{G}(t) - k\bar{G}\tilde{C}(t) \quad (9)$$

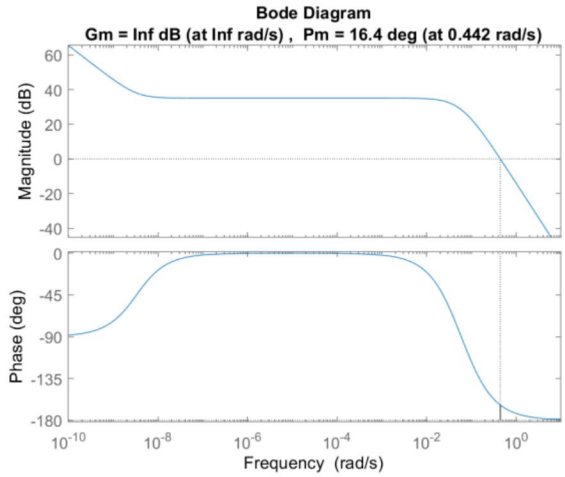
Overall Transfer Function via Superposition

$$\tilde{G}(s) = \frac{\alpha(s + k\bar{G})Q(s)}{s(s + k(\bar{C} + \bar{G}))} - \frac{k\bar{G}\alpha I(s)}{s(s + k(\bar{C} + \bar{G}))} \quad (10)$$

$H_1(s)$ *Derivation, Transfer Function of GFAP with blood-brain barrier*: Setting I(s) = 0 produces a transfer function of G(s) with respect to a single input, Q(s). This open loop transfer function describes the GFAP concentrations in the blood with respect to only the flow of GFAP from the brain.

$$H_1(s) = OL(s) = \frac{\alpha(s + k\bar{G})}{s(s + k(\bar{C} + \bar{G}))(s + \frac{1}{\tau_q})} \quad (11)$$

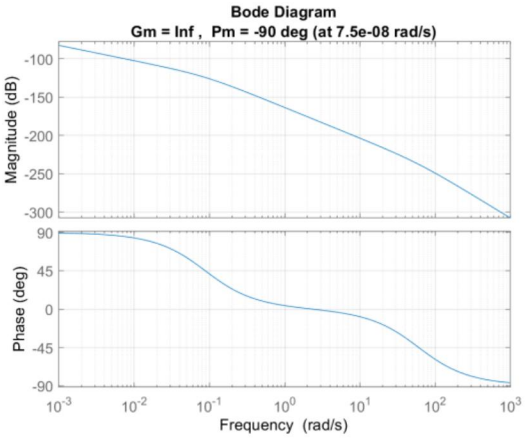
FIGURE 1



$H_2(s)$ *Derivation, Transfer Function of GFAP with IgG control*: Like above, setting Q(s) = 0 produces a transfer function of G(s) with respect to a single input, I(s). GFAP concentrations in the blood with respect to the IgG control response are given by the open loop transfer function.

$$H_2(s) = OL(s) = \frac{-K_p k\bar{G}\alpha}{s(s + k(\bar{C} + \bar{G})(\tau_m s + 1)} \quad (12)$$

FIGURE 2



C. Modeling TBI Severity

TBI is usually classified from mild to severe depending on how much damage is sustained within the brain. We can model the GFAP response to different levels of TBI by changing the maximum GFAP leakage rate from the brain into the blood and by increasing the time constant for the decay of this leakage. A more severe TBI will cause more lesions that are larger in size, causing more brain proteins such as GFAP to leak into the bloodstream. The larger lesions will also take more time to heal, which is analogous to an increase in the decay time constant.

D. Modeling Chronic Traumatic Encephalopathy (CTE)

To model CTE, it was assumed that the healing factor and magnitude of the consecutive TBI's was constant for each TBI and that the TBI's themselves were all mild. A sum of equivalent step function was added to the Simulink in Fig. 1 and were coded to occur one day after the previous mild TBI.

Table I. Equation Constant Values

Parameter	Mild/Moderate TBI Model Value
α	0.2 L^{-1}
k	1100 $Lmol^{-1}hr^{-1}$
K_p	10
$\bar{G}$	3 pM
$\bar{C}$	80 uM
τ_m	1/60 hr^{-1}
τ_q	1/25 hr^{-1}

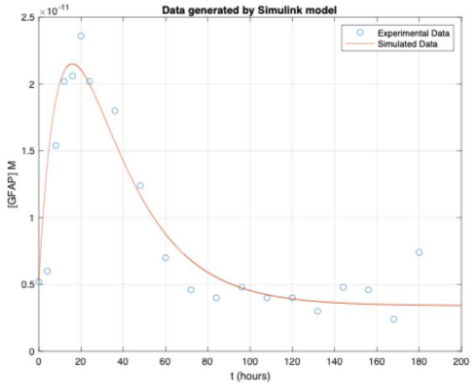
III. Results

A. Mild TBI (control)

A single mild TBI is a result indicative of a standard concussion. Figure 3 depicts the respective GFAP concentrations in the blood. The circled points are real data

from a study looking at blood serum concentrations following a mild TBI [1].

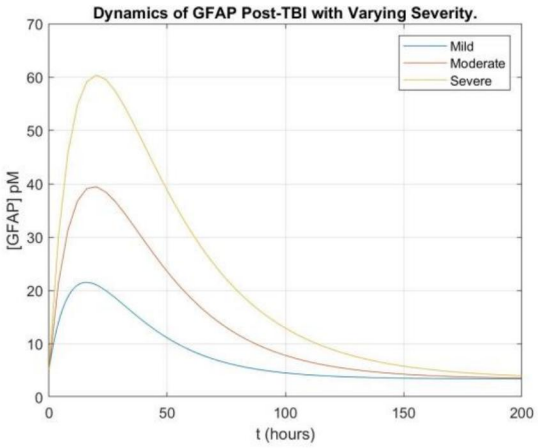
FIGURE 3



B. Moderate and Severe TBI

In the brain portion of our model, we can vary TBI severity by changing both the step function and the healing time constant. More severe TBI are modeled by increasing the referenced values. Figure 4 shows blood GFAP concentrations resulting from varying severities of TBI.

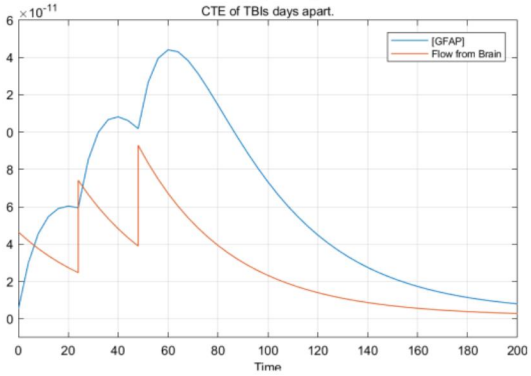
FIGURE 4



C. Consecutive mTBI (CTE)

In the equivalent circuit model of the brain flow system, successive TBIs would be modeled as additional changes to the voltage source. In the Simulink block diagram, successive TBIs would be structured as additional step functions into the addition block. The capacitor would behave appropriately to these additional steps in voltage, with the resulting current identical to Figure 5.

FIGURE 5



IV. Discussion

A. Mild, Moderate, and Severe TBI

The TBI severity index is based off of the Glasgow Coma Scale, ranking TBI from 3-15, with 15 being the most severe injury. Diagnosing TBI is primarily based on symptoms and, because of this, is somewhat subjective. Clinical data often contains relatively significant error bars, likely a result of differences in patient responses to identical severities. The chemical reaction between GFAP and IgG is an oversimplification of the actual immunoresponse. The immune system production was also simplified down to a proportional controller, where it is likely far more complex. Lastly, the healing factors for moderate and severe TBI were assumed based on the data found for mild TBI.

B. Consecutive mTBI (CTE)

Information on the causes and effects of CTE are relatively unknown. As a result, there are likely many aspects of successive TBIs that are missing from our model in patients with CTE. One contributing factor to CTE is likely the lack of complete healing after suffering multiple TBI. This could be implemented in our model by increasing the steady state flow following a TBI. Still, it is unclear how this incomplete healing contributes to the general degradation of the entire brain.

V. Conclusion

This system modeled GFAP in the brain, the flow of GFAP in the bloodstream over the blood-brain barrier, lesions caused by the TBI, the reaction between GFAP and IgG in the bloodstream, an IgG controller, and target GFAP concentration. In order to analyze the dynamics of this system it had to be linearized and from this linearization we were able to obtain 2 transfer functions pertaining to the GFAP and IGG injection inputs. From these two transfer functions we were able to model mild TBI, from this model we could see that GFAP in a mild TBI has a small peak soon after the TBI and then falls back to normal levels soon after. Once again using the transfer functions we obtained and our system we were able to model moderate and severe TBI by modifying our step function. Through modeling moderate and severe TBI we could conclude that as severity of TBI increased the higher amount of GFAP is found in the blood stream and a longer

time is needed to reach normal levels. Due to the lack of time course data of GFAP and IgG concentrations, it is difficult to validate the accuracy of our model, although it is clear that our model experiences several limitations. Further research should be done into the dynamics of GFAP and its immune response, so that better models can be built. These models can be used to better understand and diagnose the body's response to TBI.

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