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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 glial fibrillary acidic protein (GFAP) from the brain into the bloodstream through a lesion in the blood-brain barrier (BBB). In the blood, a bio controller responds by up-regulating Immunoglobulin G (IgG) production into the bloodstream to remove the excess protein. Here, we model the concentrations over time of GFAP and IgG in the bloodstream following a mild TBI. We apply these dynamics to repeated traumas that aggravate the recovery process, as well as increasing the severity of injury. Both show substantially elevated and prolonged GFAP levels. This research and model is clinically relevant in that 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 extent of brain lesions as well as help understand the recovery process that the brain takes when having undergone a TBI.**

I. Introduction

Traumatic brain injuries (TBIs) result from a violent blow or jolt to the head or body. This damages neurons and synapses and recovery can include treatments from rest to even surgery. To generate an effective treatment plan, it is essential to have an accurate diagnosis. Many current diagnostic techniques rely on self-report questionnaires which, for a variety of reasons, often fail to provide accurate results [1]. A diagnostic tool based on measurable quantities in the bloodstream can be of benefit to patients who suffer singular, random traumas, to even athletes of all levels, active members of the military, and others who often experience blows to the head.

A TBI can be separated into two distinct injuries. The primary injury is the mechanical injury that caused the TBI and the secondary injury follows after a disruption in the blood-brain barrier (BBB). A disruption of the epithelial tissue separating cerebrospinal fluid and blood allows for the exchange of brain and blood proteins, which then triggers an immune response in both the central nervous system and the bloodstream [2].

During the secondary injury, several brain proteins flow from the brain to the bloodstream. A potential TBI biomarker is glial fibrillary acidic protein (GFAP), a protein in charge of brain development [3]. These brain proteins have proved to be useful as potential bio-markers for the severity of TBIs due to its high variance across severities [4] - [5]. However, its concentration dynamics are highly variable in the first few hours post-TBI [6]. Leakage of GFAP triggers an immune response in the bloodstream for immediate removal. This immune response consists of the antibody Immunoglobulin G (IgG) being released into the bloodstream and attaching to GFAP, allowing phagocytic immune cells to bind to and remove the GFAP-IgG complex. To model the behavior, the approach was to consider the cellular dynamics of the adaptive immune response in the context of TBIs.

Chronic Traumatic Encephalopathy (CTE) is a neurodegenerative disease that affects behavior, mood, and thinking. It is often 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.

A biosensor sensitive to GFAP could be critical to understanding the connection between GFAP and the severity of a TBI for proper diagnosis. This calls for precise quantification of GFAP for TBI diagnostics, the subject of this paper.

II. Methods

A. Biosystem Model

Figure 1 shows a full Simulink model of relevant GFAP interactions in the body, with its three main components designated. The biosystem H(s) triggers a TBI and equates the subsequent GFAP and IgG concentrations in the bloodstream. The feedback mechanism G(s) describes the body's measurement of GFAP for comparison to a target concentration, including a natural delay for protein dissipation and cellular processes. The immune response to GFAP concentrations within the blood is modeled by a controller F(s) that injects IgG into the bloodstream. The equations governing the sensing of GFAP within the bloodstream and the production of IgG in response are:

$$\frac{dG_m}{dt} = \frac{1}{\tau_d}(G(t) - G_m(t)) \tag{1}$$

$$I(t) = K_p(G_m(t) - T) \tag{2}$$

where G_m is the measured GFAP concentration, I(t) is the IgG production rate, and T is the target GFAP concentration.

1) Modeling Flow over the BBB and through TBI Lesions: The physical damage to neural tissues caused by a TBI is relatively instantaneous, but the healing process occurs over a matter of days to weeks depending on the severity. Therefore, it is appropriate to model the GFAP flow through the BBB as a step function followed by decay to a steady state permeability. The negative feedback loop implements healing, and the constant block adds the healthy permeability.

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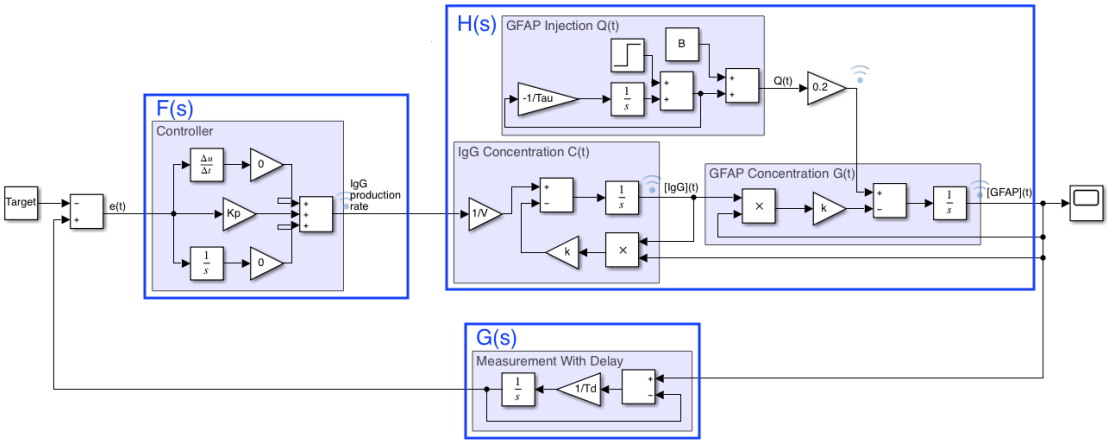

Fig. 1. Simulink block diagram of GFAP regulation within the bloodstream. The biosystem $H(s)$ includes input from the brain and immunoresponse mechanisms. The feedback $G(s)$ implements natural delay. The control $F(s)$ describes the IgG production.

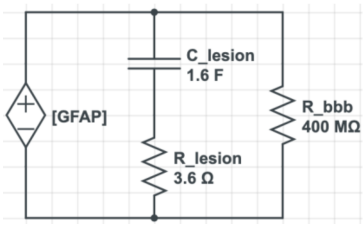

Fig. 2. Electrical circuit representation of BBB dynamics. The variable source represents the GFAP production by the brain. The middle branch represents the impedance of a TBI lesion. When a TBI occurs, the source instantly increases and the capacitor allows a current to flow through this branch. The natural pathway of GFAP is then a relatively constant current through the right branch.

Values necessary to this part of the system can be solved using a circuit analogy as shown in Figure 2. The top node represents the GFAP concentrations in the brain and the bottom node represents the rest of the body. The GFAP flow Q(t) is then the combined current between the middle and rightmost branches.

The values of these circuit components corresponding to a mild TBI can be solved using published steady state values along with well known circuit analysis concepts. During healthy steady state, the flow is equal to 1 pmol/hr and the [GFAP] gradient between the brain and bloodstream is 3.6 M [6]- [8]. Because this is in steady state, the capacitor acts as an open circuit and the R_{BBB} in Figure 2 is calculated. Similarly for R_{Lesion}, [GFAP] increases instantaneously in the brain, representing the rapid bursting of astrocytes in the brain. The capacitor is shorted due to the instantaneous voltage increase, so again, Ohm's law can be used to determine the equivalent of the parallel resistors, from which R_{Lesion} is found. Finally, the time constant of the above circuit is calculated as (3) which, when combined with the observed time constant, one fifth of the recovery time of TBI patients, was used to calculate C_{Lesion}.

The voltage source is modeled as a variable voltage source to allow for the instantaneous [GFAP] step. The parameter of interest in this circuit is the sum of the currents through the parallel resistor and resistor and capacitor branches, or the current upward through the source, which represents the GFAP flow into the bloodstream. (4) is generated to describe the flow of GFAP over time.

$$\tau_q = R_{Th}\ C = \left(\frac{R_{Lesion}\ R_{BBB}}{R_{Lesion} + R_{BBB}}\right) C_{Lesion} \tag{3}$$

$$Q(t) = Ae^{\frac{-t}{\tau_q}} u(t) + c \tag{4}$$

To apply this model to moderate and severe TBIs, new time constants were extrapolated from the mild case to increase healing time which is seen in [6]. The step function controlling the source is also increased to describe a larger lesion by area.

B. GFAP and IgG Dynamics in the Bloodstream After Lesion

It has been shown that IgG is found in high concentrations up to 7-10 days post-TBI. Additionally, it has been shown that the levels of IgG in patients with a history of subsequent TBIs have higher levels of antibodies relative to patients without TBI history [5]. The proposed system 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 [9]. In addition to the removal of GFAP from the bloodstream, these antibodies have also been shown to remove injured neurons and other brain proteins [10]. When IgG antibodies bind to antigens within the bloodstream, they participate in phagocytosis for removal. The following irreversible biochemical reaction is assumed to occur within the bloodstream, and complex formation is assumed to be rate limiting.

$$[GFAP] + [IgG] \xrightarrow{k} [Complex] \tag{5}$$

Chemical reactions occur at an order of milliseconds compared to the hour time-scales the rest of the model deals with [11]. For this reason, we can assume that the reaction reaches a state of equilibrium rapidly and the dynamics of the system reduce to,

$$\frac{dC}{dt} = \alpha I(t) - kC(t)G(t) \tag{6}$$

$$\frac{dG}{dt} = \alpha Q(t) - kC(t)G(t) \tag{7}$$

where C(t) and G(t) represent the IgG and GFAP concentrations as a function of time respectively, k represents that reaction rate as GFAP is consumed, α represent the inverse of total blood volume, and Q(t) represents the flow of GFAP into the blood as in Figure 1.

C. Transfer Function

In order to further study the dynamics of how the GFAP/IgG system works, the system must be linearized 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 the 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.

The system equations (6)-(7) were linearized under the assumption of small signal perturbations ($\tilde{}$) relative to the concentrations around steady state points ($\bar{}$). This allowed us to assume linearity and analyze the system using Laplace transform techniques.

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

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

Combining (8)-(9) with the observed pathways in Figure 1 produces:

$$\tilde{G}(s) = \frac{k\bar{G}\alpha I(s)}{s\left(s + k(\bar{C} + \bar{G})\right)} \tag{10}$$

D. Open-loop Transfer Function $H(s)$ 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. The presence of the Laplace variable s in the denominator denotes an integrator that is the result of the large difference between $\bar{G}$ and $\bar{C}$, specifically because $0 < \bar{G} \ll \bar{C}$.

$$H(s) = OL(s) = \frac{K_p k\bar{G}\alpha}{s\left(s + k(\bar{C} + \bar{G})(\tau_m s + 1)\right)} \tag{11}$$

Table 1

Parameter	Mild/Moderate TBI Model Value
α	0.2 L^{-1}
k	1100 $Lmol^{-1}hr^{-1}$
K_p	10
T	1.4 pM
$\bar{G}$	3 pM
$\bar{C}$	80 uM
τ_m	1/60 hr^{-1}
τ_p	1/25 hr^{-1}

E. Modeling TBI Severity

Using the transfer function in (11), we validated the stability of the increased TBI severity models that are extrapolations of the mild case by observing negative poles. Moderate and severe TBI were modeled by increasing the peak leakage rate and the time constant of healing. The implemented parameter spaces are derived from educated guesses and trial and error because values for increased severity are not established in literature, or have a wide range of observed values. This derivation is appropriate for this model because values such as those used to calculate Figure 2 quantities have not been adequately observed for these cases.

F. Modeling (CTE)

To model CTE, it was assumed that the healing factor and magnitude of the consecutive TBIs was identical for each injury, the same values used in the mild case. A series of step functions were added to the Simulink in Fig. 1 and timed to occur one day after the previous mild TBI.

III. Results

Figure 3 depicts the GFAP concentrations in the blood following a mild TBI inducing trauma. The circled points are the average at the respective time interval of 325 patients who suffered mild TBI [6]. The closeness of the simulated solid line to the observed data serves to confirm the accuracy of the model.

Figure 4 shows blood GFAP concentrations resulting from varying the severity of TBIs. All parameters with the exception of GFAP spike magnitude and healing time constant were held constant.

In the analogous circuit model of the BBB flow, successive TBIs would be modeled as consecutive increases to the voltage source. The capacitor would behave appropriately to these additional steps in voltage, with the resulting total current identical to the orange line in Figure 5. The Simulink simulation shows this and the resulting bloodstream concentration.

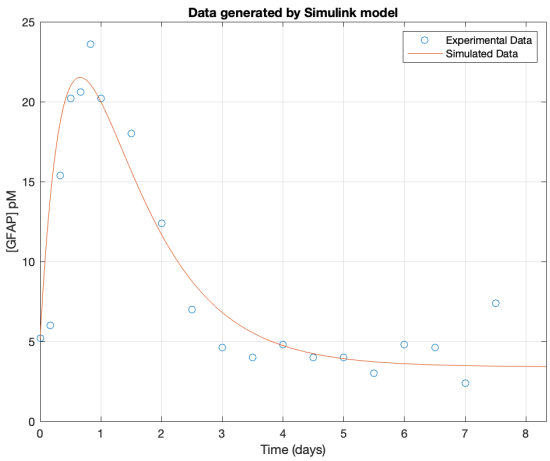

Fig. 3. MATLAB simulated GFAP concentration (orange line) overlaid on average serum samples (blue circles) from [6]. Data covers 200 and 180 hours respectively

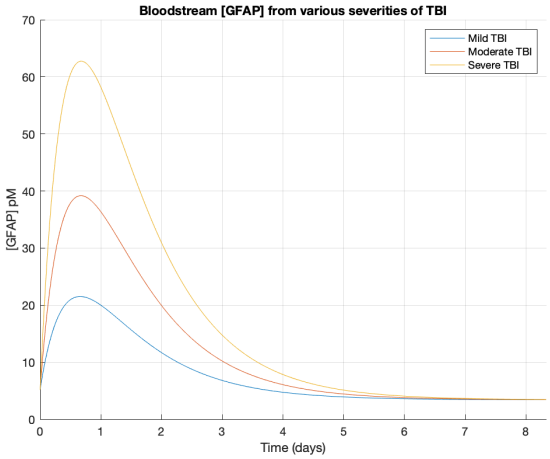

Fig. 4. MATLAB simulations of varying TBI severities covering 200 hours after the TBI. The magnitude of the moderate and severe TBIs are 2 and 3.33 times that of the mild case respectively.

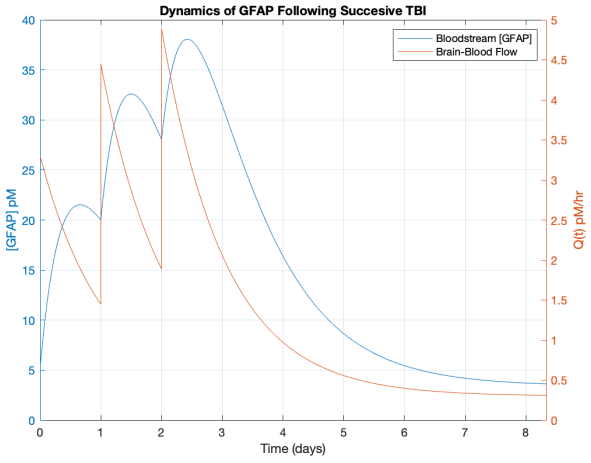

Fig. 5. GFAP flow from brain (orange) and bloodstream GFAP concentration (blue) due to successive TBIs, a likely contributor to CTE. Data includes 200 hours after first TBI.

IV. Conclusion

This system modeled the flow of GFAP in the brain through the BBB and its reaction with IgG in the bloodstream based on an IgG controller and target concentrations. In this model we see that bloodstream GFAP from a mild TBI peaks shortly after the primary TBI injury and then falls back to normal levels soon thereafter, matching the observed data. Extrapolating the dynamics of this system beyond the observed mild cases requires linearized. This linearization produced 2 transfer functions pertaining to the GFAP and IgG injection inputs independently, which are combined via superposition. Through modeling moderate and severe TBIs we could conclude that as the severity of a TBI increases, the higher amount of GFAP is found in the blood stream and a longer time is needed to return to steady state. This model contains inevitable limitations stemming from the lack of time course data of GFAP and IgG concentrations across severities and limited system boundaries. For example, more detailed immune system dynamics would tune both the healing rates and bloodstream reaction kinetics. Still, we have shown a novel approach to dynamically model the relationship between levels of GFAP and IgG components in the bloodstream with TBI severity. These models can provide a better understanding and more accurate diagnosis of the body's response to TBI for the overall improvement of treatment plans.

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