Systems Level Model of Dietary Effects on Cognition via the Microbiome-Gut-Brain Axis*

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Abstract— Intercommunication of the microbiome-gut-brain axis occurs through various signaling pathways including the vagus nerve, immune system, endocrine/paracrine, and bacteria-derived metabolites. But how these pathways integrate to influence cognition remains undefined. In this paper, we create a systems level mathematical framework comprised of interconnected organ-level dynamical subsystems to increase conceptual understanding of how these subsystems contribute to cognitive performance. With this framework we propose that control of hippocampal long-term potentiation (hypothesized to correlate with cognitive performance) is influenced by inter-organ signaling with diet as the external control input. Specifically, diet can influence synaptic strength (LTP) homeostatic conditions necessary for learning. The proposed model provides new qualitative information about the functional relationship between diet and output cognitive performance. The results can give insight for optimization of cognitive performance via diet in experimental animal models.

I. INTRODUCTION

The gut is colonized with a complex community of bacteria (microbiota), which helps to shape the immune system, metabolic function and cognition in health and disease. Studies show that dysbiosis within the gut microbiome modulates peripheral and central nervous system function, leading to alterations in brain signalling and behavior [1], [2]. Therefore, research targeting the modulation of the gut microbiota as a novel therapy for maintaining brain health is gaining interest. Diet is one of the most critical modifiable factors regulating the gut microbiota and is shown to have a direct effect on the composition of the gut bacteria [3], [4]. Thus, increased understanding of the relationships between diet, changes in gut microbiota, activation of inter-organ pathways, and alterations in brain signalling (hypothesized to correlate with changes in cognition) is necessary for therapeutic intervention.

The bidirectional communication between the gut and the brain occurs through various pathways including the vagus nerve, the immune system, neuroendocrine pathways, and bacteria-derived metabolites. Systems level mathematical models can be used to elucidate significant organs necessary for the achievement of diet and microbial conditions for optimal cognition and help generate hypotheses and direct conceptual understanding. Models can also give insight into observed experimental trends and predict the outcomes of future experiments. Differential equation models and constraint-based stoichiometric models have been used to describe growth rates, relative abundances, and metabolic interactions of microbial communities at the macroscopic and microscopic level [5], [6]. Similar methods have been adapted to describe modulation of immune response via the gut microbiota [7]. Mathematical models of neurotransmitter modulated brain signalling within the hippocampus have been developed [8], [9]. However, to the best of our knowledge, few models exist describing the systems level effects of how intestinal microbes and immune interactions can regulate brain function while also considering vagal and vascular pathways.

To bridge this gap, we have combined microbial growth and competition, metabolic signaling, immune response and neural mathematical models in a unified physiological model to explore possible inter-organ pathways regulating brain signaling and cognitive performance. The proposed model provides new qualitative information about the functional relationship between diet and output cognitive performance. Furthermore, this work motivates the development of more comprehensive models of the dietary effects on cognition and encourage further investigations towards therapeutic intervention strategies.

II. SIGNALING INTERACTIONS BETWEEN ORGANS INFLUENCING THE MICROBIOME-GUT-BRAIN AXIS

We developed a prototype system of the signaling interactions between organ subsystems within the microbiome-gut-brain axis. This prototype system is an overview of generalized mechanisms observed in ongoing experiments conducted in mouse models by collaborators and can also be verified through past literature (see Figure 1).

Under a healthy low fat diet, the gut microbiota produces metabolites such as short chain fatty acids (SCFAs), bile acids, and neurochemicals (e.g., serotonin and GABA). Subsets of metabolites (such as SCFAs) can enter the bloodstream and cross the blood brain barrier. Other subsets of metabolites (such as neurochemicals) can stimulate afferent vagal nerve fibers in the gut and promote healy vagal nerve tone [10], [11]. These nutrient metabolites and vagal activity support neural activity of the hippocampus, specifically long-term potentiation (LTP) which underlies memory formation [12], [13].

Hypoxia and ketogenic diet promote anaerobic conditions and bile acids that enrich and expand bacterial species within
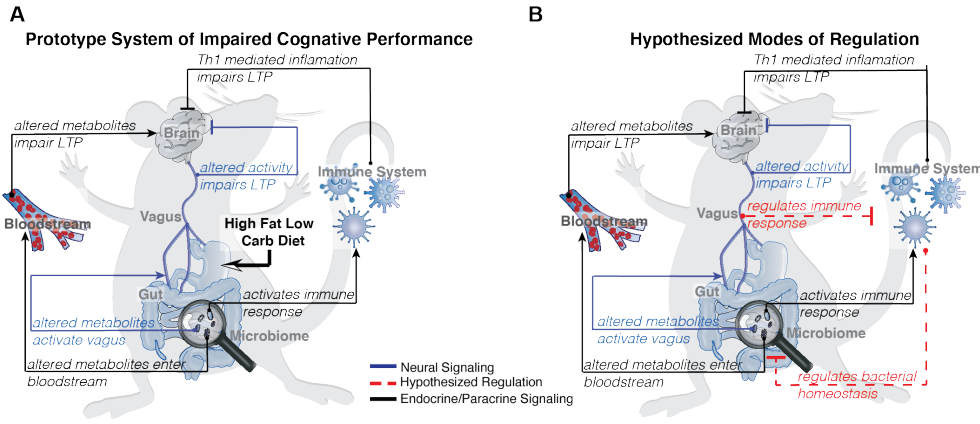
Fig. 1. Overview of prototype system and proposed regulation mechanisms conceived from generalized interactions of the Microbiome-Gut-Brain Axis. A. Factors for high fat, low carb diet-induced impaired cognitive performance. A high fat, low carb diet can initiate abberant gut microbial, vagal and immune responses that lead to impairment in hippocamal LTP which is associated with memory dysfunction. B. Hypothesized modes of regulation. High fat, low carb diet-induced microbial dysbiosis within the gut can activate immune response which can promote gut microbe homeostasis but also produce pro-inflammatory cytokines. Neurotransmitters released by the vagus nerve attenuate immune response thereby reducing inflammation.

the gut, such as *Bilophila wadsworthia*, which produce hydrogen sulfide (H_2S) and stimulate T-cell differentiation [10], [14]. Specifically, Th1 cells can be activated by *Bilophila wadsworthia* and produce pro-inflammatory cytokines leading to inflammation [15] and consequently impairment of hippocampal activity [16]. It is also believed that bile acids and H_2S can directly activate afferent vagal nerve fibers in the gut which can alter hippocampal LTP [13], [17]. Impaired hippocampal LTP affects memory [13] and therefore cognitive performance.

We also explored vagus and immune system regulation modes that could contribute to alleviation of an impaired cognitive state. These regulation mechanisms have been identified in literature although not yet corroborated by our collaborators (see Figure 1B). Specifically, immune cells stimulate production of antimicrobial proteins that prevent infection and promote homeostasis [18]. In order to decrease immune cell induced inflammation that can impair LTP, the vagus nerve releases neurotransmitter acetylcholine which can travel through the bloodstream and localize at sites of inflammation and suppress pro-inflammatory cytokines [16], [18].

III. MODELING OF INTERCONNECTED ORGAN-LEVEL DYNAMICAL SUBSYSTEMS INFLUENCING THE MICROBIOME-GUT-BRAIN AXIS

Figure 2 depicts the complete scheme of the unified gut microbial-immune-neural system model representing the flow of gut microbes, metabolites, immune cells and neural signals. Below, we describe each organ-level dynamical subsystem.

A. *Model of Gut Microbial Growth and Competition, Metabolite Production*

We constructed a model of bacterial growth and competition using Lotka-Volterra-type equations adapted from [7]. This model was selected for two main reasons: (i) it can implement simple qualitative interactions between bacterial

species (such as competition, cooperation and exploitation) and (ii) it has been used to successfully study the temporal dynamics of bacterial communities within the gut [5], [7]. The outputs of this model are the microbial population densities of the typical and aberrant species within the gut microbiome:

$$\frac{d}{dt}B_i = \left(K_i - \sum_{j=1}^{2} e_{ij}B_j - \gamma_i N + \psi_i D\right)r_i B_i \quad i = 1, 2. \quad (1)$$

Here, typical microbial species are represented by variable B_1 and aberrant species (e.g. *Bilophila wadsworthia*) are represented by variable B_2. The aberrant species expand when a ketogentic (high fat, low carb) diet is consumed. D is the input representing the ratio of fat to carb content within the consumed diet. Immune cells (represented by N) also have an effect on bacterial populations as previously discussed (see interaction between immuno-modulation and gut microbiota blocks in Figure 2). Parameters K_i and r_i represent bacterial carrying capacity and growth rate respectively. Parameter e_{ij} characterizes the effect of species j on the dynamics of species i, γ_i characterizes the effect of the immune cells on species i, and ψ_{ij} characterizes the effect of diet input on species i.

In addition, output metabolites M_1 and M_2 are produced by microbial species B_1 and B_2 respectively. To represent this interaction we adapted from the generalized form of the species-metabolite interaction model given in [19]:

$$\frac{d}{dt}M_i = \alpha_i \frac{B_i}{B_i + \kappa_i} - F(M_i) - \delta_i M_i \quad i = 1, 2. \quad (2)$$

Here, α_i and δ_i represent production rate of metabolite i by bacteria i and degradation of metabolite i respectively. Furthermore, we assume that production of metabolites saturates at higher and lower bacterial concentrations. $F(M_i)$ is a function describing metabolite transport kinetics to the brain which is explained in equation (6).
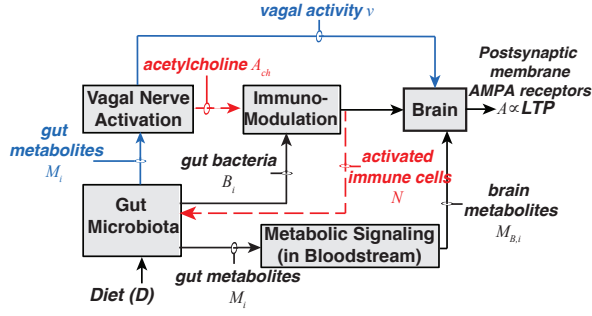
Fig. 2. Block diagram of modeling framework showing interconnection of organ-level dynamical subsystems. Hippocampal LTP (correlated with cognitive performance), is regulated via interorgan signaling with diet as the external control input.

B. Model of Immune Cell Activation Response

The dynamics of the immune cell population N is modeled with linear influx and exit terms and additive contributions from each bacterial species as developed in [7]:

$$\frac{d}{dt}N = \alpha_N - \delta_N N + \sum_{i=1}^{2} b_i B_i - \gamma_N A_{ch}. \quad (3)$$

Here, α_N and δ_N are the activation and deactivation rate of immune cells, respectively, and b_i is the effect of species i on immune cell influx. We incorporate the negative feedback effect of the vagus secreted neurotransmitter A_{ch} (see interactions between vagas nerve and immuno-modulation blocks in Figure 2) where γ_N characterizes the effect of A_{ch} on the immune cells.

C. Model of Vagus Nerve Activation and Neurotransmitter Secretion

There is evidence that the vagus nerve can differentiate between non-pathogenic and potentially pathogenic bacteria and can instigate an anti-inflammatory reflex via release of neurotransmitter acetylcholine that, through an interaction with immune cells, attenuates inflammation [11]. However, to our knowledge, there is limited previous literature regarding experimental data on the electrophysiology of these interactions.

Therefore, in this first proposal, we adapt a model from [20] where vagal nerve stimulus is represented as a train of squared pulses ($\nu(t) = 1$ during the pulse and $\nu(t) = 0$ otherwise), each of them with a duration (Δ_ν) that resembles that of the real physiological action potential. The frequency (f) of the train of pulses is decreased by decreased M_1, representing typical vagal tone and increased by increased M_2 representing aberrant vagal tone. Here we assume a sigmoidal function to represent this relationship:

$$f = \frac{\sigma_2 M_2}{\sigma_1 M_1 + \sigma_2 M_2 + 1}. \quad (4)$$

As shown in equation (4), higher concentration of gut metabolites derived from aberrant microbes (M_2) increase the stimulation frequency of the vagus nerve with effectiveness constant σ_2. Higher concentration of gut metabolites derived from typical microbes (M_1) attenuate stimulation

frequency of with effectiveness constant σ_1. Although the functional form of equation (4) is assumed the general trends can be corroborated data [13], [17].

The immuno-modulatory role of the vagus nerve is also adapted from [20] where neurotransmitter acetylcholine is released via stimulation of vagal fibers within the pancreas. Following their assumption that the kinetics of acetylcholine secretion do not change from one nerve terminal to another, we adapt the same sigmodial model structure to represent acetylcholine release as a function of vagal frequency:

$$A_{ch} = a_f \frac{\kappa_f f}{f + \kappa_f}. \quad (5)$$

This simplified neural model solely depends on the firing frequency of the stimulus, since the higher the frequency the higher the steady-state value for acetylcholine concentration (A_{ch}). Here a_f is a lumped parameter signifying the maximum effective concentration of acetylcholine. And κ_f represents the rate of renewal of synaptic vesicles containing acetylcholine.

D. Model of Metabolic Signaling through the Bloodstream

Metabolite transport kinetics through the bloodstream and across the blood-brain barrier are modeled using Michaelis–Menten kinetics, which have been used successfully to study glucose and lactate transport kinetics into the human brain [21], [22]. The metabolite flux secreted from the gut into blood is described by:

$$F(M_i) = V \frac{M_i}{M_i + \beta}. \quad (6)$$

The dynamics of brain metabolites are given by:

$$\frac{d}{dt}M_{B,i} = F(M_i) - \delta_{B,i} M_{B,i} \quad i = 1, 2, \quad (7)$$

where V is the maximum transport rate that can be obtained and β is a threshold value for gut metabolites to be transported into the brain.

Assuming that the gut metabolites have passed swiftly through the blood brain barrier (i.e. $M_i \ll \beta$) we can simplify the equations (6) and (7) to the first order kinetic regime [22]:

$$F(M_i) = \frac{V}{\beta} M_i. \quad (8)$$

E. Model of Long-term Potentiation within the Hippocampus

It has been established that diet-induced microbial changes within the gut can lead to altered brain signaling and behavior [1], [2]. Futhermore, ongoing experiments with collaborators show that the composition of the gut microbiome due to diet and antibiotics can lead to changes in hippocampal long-term potentiation (LTP). LTP represents synaptic signal strength between adjacent neurons which can vary based on recent patterns of neural activity. Here we describe the process in simplified terms.

LTP is initialized when activation of AMPA receptors (ligand-gated ion channels) lead to depolarization of the

postsynaptic cell and release of the magnesium ion blocking the NMDA receptor. This allows calcium-glutamate molecule to enter the cell and activate protein kinases such as calcium/calmodulin-dependent protein kinase II (CaMKII) and protein kinase C (PKC). The activation of these two proteins allows for the two major mechanisms of LTP to proceed. The first is phosphorylation of existing AMPA receptors which increases their sensitivity. The second is increase of postsynaptic AMPA receptors due to kinase activity. Furthermore, sustained activation of the kinases (CaMKII and PKC) lead to postsynaptic changes including increase of AMPA receptors inserted in the postsynaptic membrane and increased dendritic area and spines which increase postsynaptic sensitivity. Presynaptic changes are based on retrograde signaling and include an increased binding and release of neurotransmitter vesicles from the presynaptic membrane and an increase in the total number of presynaptic neurotransmitter vesicles.

We use a simplified model adapted from [9] to describe the calcium dependent activation of intracellular kinases and phosphates (CaMKII and PKC) within the postsynaptic cell. CaMKII and PKC dynamics regulate insertion of AMPA receptor in the postsynaptic membrane. Within this model, we assume that long term potentiation is proportional to the amount of AMPA receptors in the postsynaptic membrane. The model is represented by three main equations.

(i) Calcium-glutamate (Ca) mediated CaMKII activation dynamics:

$$\frac{d}{dt}pK = k_1 \frac{K}{K + K_{m1}}pK - k_2 \frac{pK}{pK + K_{m2}}(P + P_0) + k_3 K_0 + k_4 \frac{Ca^4}{Ca^4 + K_m^4}K, \tag{9}$$

where K and pK are the unphosphorylated and phosphorylated forms of CaMKII respectively, k_1, k_2, k_3, k_4 are rate constants for each reaction, and K_{m1}, K_{m2}, and K_m are equilibrium constants. K_0 indicates the basal concentration of active kinase. The total amount of kinase is assumed to be conserved.

(ii) Calcium-glutamate (Ca) mediated PKC activation dynamics:

$$\frac{d}{dt}P = k_{11} \frac{pP}{pP + K_{m11}}P - k_{12} \frac{P}{P + K_{m12}}(K + K_0) + k_{13}P_0 + k_{14} \frac{Ca^3}{Ca^3 + K_m^3}pP, \tag{10}$$

where P and pP are the unphosphorylated and phosphorylated forms of PKC respectively. k_{11}, k_{12}, k_{13}, k_{14} are rate constants for each reaction. K_{m1} and K_{m2} are equilibrium constants. And P_0 indicates the basal concentration of phosphatase. The total AMPA receptor is assumed to be conserved. The total amount of phosphatase is assumed to be conserved.

(iii) Activated CAM2KII and PP2A mediated AMPA receptor insertion dynamics:

$$\frac{d}{dt}A = k_{21}A_{int} - k_{22}A, \tag{11}$$

where A and A_{int} indicate the AMPA receptor on the synaptic membrane and the internalized AMPA receptor respectively. The total AMPA receptor is assumed to be conserved. Furthermore since the activities of kinase and phosphatase influence the insertion and the removal of AMPA receptor, k_{21} and k_{22} are assumed to be proportional to the concentration of active kinase and phosphatase respectively:

$$\begin{aligned} k_{21} &= c_1 pK + c_3, \\ k_{22} &= c_2 P + c_4, \end{aligned} \tag{12}$$

where c_1 and c_2 are proportional constants, and c_3 and c_4 are rate constants for the processes independent of kinase and phosphatase activities.

In order to incorporate this model within the larger modeling framework, we consider the dependency of calcium influx on the outputs from the vagal, immune and bloodstream submodels. There is evidence to show that vagal activity, immune cells and circulating metabolites can influence the influx of calcium within the postsynaptic neuron. Specifically, there is evidence that vagal nerve stimulation can lead to increased expression of synaptic proteins associated with LTP and decrease proteins associated with AMPA receptor endocytosis [23]. In addition, peripheral immune cells can penetrate the brain through the blood brain barrier and modulate synapse activity and neurotransmitters can circulate between neurons and glial cells within the brain [24]. Finally, metabolites (such as neurochemicals) can penatrate the blood brain barrier and affect calcium influx by activation of postsynaptic channels [25]. Therefore, although the functional form of equation 4 is assumed, the general trends can be corroborated with data.

Here, as a first proposal, we assume a sigmoidal function to describe the relationship between vagal activity, immune response, and circulating metabolites and calcium infux:

$$Ca = \begin{cases} \frac{\lambda_1 M_{B,1}}{\lambda_f f + \lambda_2 M_{B,2} + \lambda_1 M_{B,1} + \lambda_N N} & \text{if } t_s \leq t < t_s + \Delta_s \\ 0.1 & \text{otherwise.} \end{cases} \tag{13}$$

As shown in equation (13), at presynaptic firing time t_s the level of calcium within the postsynaptic cell changes from the baseline amount of $0.1\,\mu M$. This change in calcium is dependent on inputs from bloodstream, vagal and immune submodels. Specifically, higher concentration of circulating metabolites derived from aberrant microbes within the gut ($M_{B,2}$), increased immune response (N), and higher vagal frequencies (f) attenuate the influx of calcium (Ca) within the postsynaptic neuron with effectiveness constants λ_2, λ_N and λ_f respectively. Whereas, higher concentration of circulating metabolites derived from typical microbes within the gut ($M_{B,1}$) increase influx of calcium within the postsynaptic neuron with effectiveness constant λ_1.

IV. APPLICATION OF INTERCONNECTED MODELING FRAMEWORK TO STUDY THE EFFECT OF DIET ON BRAIN SIGNALING

A. Modulation of Long-Term Potentiation in Response to Dietary Changes via the Gut-Brain-Axis

Numerical simulations of the developed framework (Figure 3) show how dietary changes can affect the gut microbial environment leading to changes in gut metabolites which influence both brain metabolite concentration and vagal stimulation frequency initiating changes in LTP. In addition, gut microbial changes can initiate immune response which is further modulated by acetylcholine produced by the stimulated vagus nerve.

Specifically, a high fat/low carb diet ($D = 10$ introduced at day 2) causes expansion of aberrant gut microbes and associated metabolites while causing attenuation of typical gut microbes and associated metabolites. This leads to increase in immune response and vagal stimulus. A byproduct of the increase of vagal stimulation is acetylcholine which attenu-

ates immune cell activation. Increased aberrant metabolites, vagal stimulation frequency, and immune response cause significant decrease in calcium influx (Figure 3B). Excitatory postsynaptic potential (EPSP) of the postsynaptic neuron can be used to indicate LTP. We assume that EPSP is proportional to the amount of AMPA receptor (A) inserted within the postsynaptic neuron membrane. Between days 1 and 3 initiation of the bad diet causes a decrease in calcium influx and the EPSP can no longer be sustained above the baseline which indicates a removal of LTP.

In contrast, a balanced fat/carb diet ($D = 1$ introduced at day 6) attenuates aberrant gut microbes and associated metabolites which allows for the expansion of typical gut microbes and associated metabolites. As a result, immune response and vagal stimulus frequency are attenuated and typical brain metabolites replace aberrant metabolites. This causes an increase in calcium influx and the EPSP can be sustained above the baseline reinstating LTP. Since LTP is associated with memory formation, these simulations hypothesize how a high fat, low carb diet may lead to decreased cognitive performance as indicated in preliminary data from collaborators.

B. Prediction of Hysteresis Associated with Dietary Effects on Long-Term Potentiation.

Further simulations of the developed framework revealed that under identical dietary input conditions, the EPSP can be in either an elevated (indicating LTP) or baseline (no LTP) state (Figure 4). As diet shifts from balanced ($D = 1$) to high fat, low carb ($D = 10$) conditions, EPSP lowers to baseline from an elevated (LTP) state at "tipping point" ($D \approx 7$). However, shifting in reverse from high fat, low carb diet back to a balanced diet the system gets "stuck" in the baseline state until a lower "tipping point" ($D \approx 5.5$) is reached. This suggests that it may take a more balanced diet to regain healthy cognition (elevated EPSP, LTP) after a high fat, low carb diet.
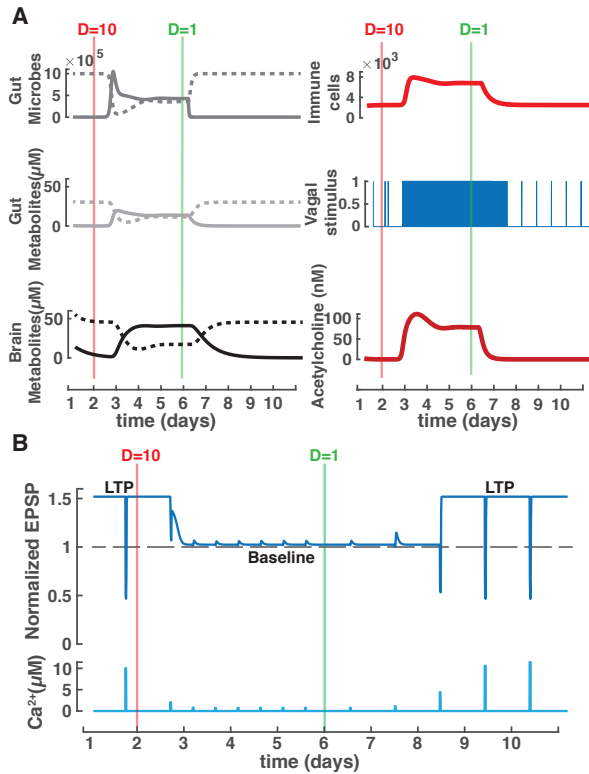

Fig. 3. Simulations of proposed modeling framework. A. With initiation of a high fat low carb diet at day 2 (D = 10), the altered gut microbiome triggers an increase of immune response and produces gut metabolites which circulate to the brain. As immune feedback regulates microbes within the gut, vagus derived acetylcholine regulate immune response. With the initiation of a balanced diet at day 6 (D = 1), gut bacterial homeostasis is restored causing a decrease in aberrant gut and brain metabolites and return of typical vagal tone. B. The inter-organ response upon initiation of a high fat, low carb diet (described in A.), results in a drop of calcium within the post synaptic neuron and consequently a return of EPSP to the baseline level. Initiation of a balanced diet results in a rise in calcium and consequently synaptic strength (LTP) from the previous baseline level as the gut bacterial homeostasis is restored.
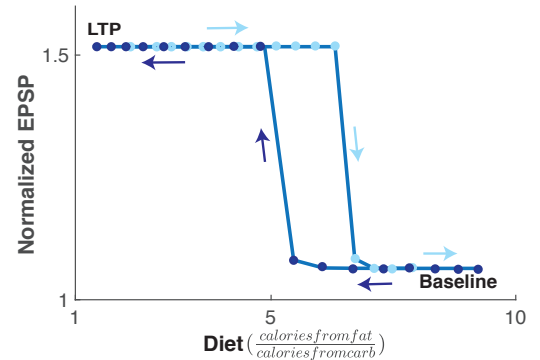

Fig. 4. As diet shifts from balanced ($D = 1$) to high fat, low carb ($D = 10$) conditions, EPSP lowers to baseline from an elevated (LTP) state at "tipping point" ($D \approx 7$) indicated by light blue points/arrows. However, shifting in reverse from high fat, low carb diet back to a balanced diet the system gets "stuck" in the baseline state until a lower "tipping point" ($D \approx 5.5$) is reached indicated by dark blue points/arrows.

The mechanisms underlying this hysteresis are the result of the multi-stable dynamics within the calcium dependent activation of intracellular kinases and phosphates (equations (9) and (10)). Thus, we hypothesize that hysteresis region may be altered through interference with these interactions, potentially by altering the composition and amount of neurotransmitters contributing to the activation of ligand-gated ion channels. Other factors, like alteration of properties of the presynaptic neuron may also contribute to altering this region of hysteresis.

V. CONCLUSIONS

Within this work, we develop an early attempt at defining a physiological combined neural-immune-metabolic modeling framework to study dietary effects on cognition. The model considers effects of the immune system on the gut microbiome and effects of vagal feedback on immune system response. The results suggest how inter-organ mechanisms may interconnect to alter brain signaling. Furthermore, the model provides insight into the nonlinear functional relationship between diet and response by predicting hysteresis associated with dietary effects on synaptic strength (LTP). Future work includes consideration of additional feedback mechanisms between the brain and the gut. For example, a hypothalamic pituitary stress response in the brain can stimulate vagal efferents which alter intestinal permeability of the gut. Intestinal permeability may alter gut microbiota and subsequently metabolite production [26]. This model lays the foundation for the development of physiological models that can reproduce the complex mechanisms underlying the microbiome-gut-brain axis and have practical application for determining therapeutic diets for optimal cognitive performance.

APPENDIX

TABLE I
SUMMARY OF PARAMETER VALUES

Subsystem	Parameter	Value	Units
Gut Microbial Growth and Competition	K_1, K_2	$1, 1$	–
	e_{11}, e_{12}	$10^{-6}, 1.5 \cdot 10^{-6}$	cells^{-1}
	γ_1, γ_2	$0, 3 \cdot 10^{-4}$	cells^{-1}
	ψ_1, ψ_2	$0, 0.2$	–
	r_1, r_2	$1, 2$	day^{-1}
Metabolite Production	α_1, α_2	$10^2, 10^2$	μM/day
	κ_1, κ_2	$10^6, 10^6$	cells
	δ_1, δ_2	$0.1, 0.1$	day^{-1}
Immune Cell Activation	α_N	$5 \cdot 10^3$	cells/day
	δ_N	0.2	day^{-1}
	b_1, b_2	$0, 2 \cdot 10^{-3}$	day^{-1}
	γ_N	$3.3 \cdot 10^{-3}$	cells/μM day
Vagal Frequency	σ_1, σ_2	$1, 1$	μM^{-1}
Acetylcholine Release	$a_f \kappa_f$	$3 \cdot 10^5$	μM/day
	κ_f	$2 \cdot 10^3$	day^{-1}
Metabolite Transport	V/β	0.2	day^{-1}
	$\delta_{B,1}, \delta_{B,2}$	$0.2, 0.1$	day^{-1}
Hippocampal LTP	k_1, k_2, k_3, k_4 $k_{11}, k_{12}, k_{13}, k_{14}$ K_m K_{m1}, K_{m2} K_0, P_0 c_1, c_2, c_3, c_4	parameters taken from [9]	
	λ_1, λ_2	$10^{-2}, 10^{-2}$	μM^{-1}
	λ_f	1	day
	λ_N	0	cells^{-1}

The values of the parameters of each subsystem within the model are reported in Table I. Parameters within the gut microbial and metabolite production submodels were chosen based on [7] and [19] and such that major changes in microbial dynamics occurred within two to three days [27]. Parameters within the immune system submodel were estimated such that the parameters recapitulate the the response given in [7] within 1 order of magnitude. The parameters for the vagus nerve submodel were modified from [20] based on the variables used in the proposed submodel and recapitulate the responses reported in [20] . Metabolite transport kinetic parameters were estimated using [21], [22]. Finally, parameters within the model of hippocamplal LTP were taken directly from [9], with the exception of $\lambda_1, \lambda_2, \lambda_f, \lambda_N$ which were chosen such that the variable Calcium (Ca) was in the range given in [20].

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