A Mean-field Model for Metabolic Homeostasis and Neuronal Bistability Induced via Anesthesia

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***Abstract*— Burst suppression is an inactivated brain state in which the electroencephalogram exhibits bistable dynamics consisting of alternating periods of activity and isoelectricity. It is most commonly associated with deep levels of general anesthesia. Recent experimental and modeling studies have suggested an important role for brain metabolic processes in governing the very slow time scales, i.e., duration of burst and suppressions. In these models, a reduction in metabolism leads to substrate depletion and consequent suppression of action potential firing. Such a mechanism accounts for the transition into burst suppression when metabolism is downregulated in an exogenous fashion. However, in many cases such as general anesthesia, metabolic downregulation occurs in part as a homeostatic consequence of reduced neuronal activity. Here, we develop a mean field model for neuronal actvity with metabolic homeostatic mechanisms. We show that with such mechanisms, a simple reduction in neuronal activity due, for example, to increased inhibition, will give rise to bistability due to a bifucration in the combined neuronal and metabolic dynamics. We then characterize the time scales of burst and suppression as a function of inactivation focusing on the key transitions to and from continuous activity and complete isoelectricity. The model reconciles a purely metabolic mechanism for burst suppression with one that includes important dynamical feedback from the neuronal activity itself.**

I. Introduction

In states of deep general anesthesia and patholigies such as coma, the brain, while signficianty inactivated, nevertheless exhibitis many nontrivial dynamical phenomena. A notable example is burst suppression, a pattern of the electroencephalogram (EEG) that is associated with deep general anesthesia (including medically-induced comas) and pathological states of coma following diffuse brain injury [1], [2], [3], [4], [5]. In burst suppression, the EEG alternates quasi-periodically between periods of high-voltage activity (bursts) and flatline (quescience) [5], [6].

The neuronal mechanisms of burst suppression were first investigated in a series of in vivo experinements in anesthetized animals [7]. This study reported that the onset of EEG burst suppression is associated with an overall membrane potential hyperpolarization in cortical neurons. It was suggested that ab increase in potassium (K^+) conductance is the reason for such hyperpolarization, and the subsequent enhanced inhibition may be responsible for the suppression epochs. More recent studies show that the BS is attributed to diminished inhibition by isoflurane [8], or cortical hyperexcitable state with subliminal stimuli as triggering events [9], [10].

Recent computational modes have gone further in suggesting the underlying mechanisms for burst suppression and why the state is seemingly common across multiple etiologies. In [11], the slow time scales associated with burst and suppression alternation were linked to cerebral metabolism. In this model, the termination of each burst is attributed to depletion of ATP, due to insufficient metabolic regeneration. Such a mechanism centers on the fact that the etioligies of burst suppression are generally associated with significant reductions in cerebral metabolic rate of oxygen. During suppression, the lack of action potential firing allows buildup of ATP until a critical threshold for spiking activitiy is reached and a burst can be initiated. The model made several hypothesis concerning the dynamical structure of activity within bursts that were subsequently observed in intracranial recordings of burst suppression [12]. In [13], a model for burst suppression was developed using a mean field computational framework. Here, the time scales of burst and suppression were attributed to physiolgic processes such as synaptic neurotransmitter depletion that could arise due to metabolic depression.

The models in [11] and [13] are similar insofar as they attribute the time scales of burst suppression to slower physiologic processes that modulate faster neuronal activity in a depletion-recovery cycle. Mathematically, this amounts to a dynamical system with separated time scales, which can be represented in the form:

$$\dot{x} = f_\alpha(x, y) \tag{1}$$

$$\dot{y} = \nu g_\beta(x, y), \tag{2}$$

where x are the fast 'neural' variables and y are the slower 'modulation' variables (see Figure X for schematic). The parameter set β, in particular, determines the rate of recovery which serves as a bifurcation parameter that, when decreased beyond a critical threshold, causes the system to transition from continuous activity in x to a bistable, burst suppress regimen. It is assumed in both [11] and [13] that β is downregulated *exogenously*, as a function of either increasing anesthetic dose or increasing pathology.

These models generate the key phenomenology of burst suppression: bistable dynamics in which the duration of suppression epochs grows as the parameter β becomes progressively further depressed. However, exogenous manipulation of β does not take into account homeostatic mechanisms of

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metabolic autoregulation. That is, with decreased neuronal activity comes decreased metabolic recovery – lower demand, lower supply – and vice versa. So while anesthetic drugs do decrease cerebral metabolism, this reduction is largely a consequence of drug-induced reduction in neuronal activity. So while a direct downregulation of β might be approriate when modeling *direct* perturbations of metabolic substrate, such as hypothermia or ischemia, in the case of general anesthesia an important piece of the mechanism remains missing. Conceptually, it may not be wholly appropriate to simply reduce β and leave the dynamics in $f_\alpha(x, y)$ in (1) intact, when, in reality, the primary drug effect is a change in those dynamics.

This paper centers on the question of whether the bifurcations and bistable dynamics survive when metabolic homeostasis is included. To investigate this problem, we formulate a mean-field neuronal model in the form (1)-(2), in which the slow system (2) corresponds to recovery of metabolic substrate, i.e., a generalization of cerebral metabolism. To this model we add a tertiary homeostatic coupling equation that specifies β as a function of x. We ask: if anesthetic drugs reduce neuronal activity, subsequently leading to reduced metabolic recovery, will the overall system dynamics still bifurcate, or will activity simply slowly 'taper off'? It turns out that, for a sigmoidal form of homestatic coupling, not ony do bistable dynamics still manifest for direct (exogenous) reductions in metaboic recovery, but they are induced through a simple increase in cortical inhibition, consistent with the actions of many anesthetic drugs. The model is also consistent with other aspects of burst suppression phenomenology, such a the ratio of burst duration to suppression duration, and refractory periods immediately following burst offset and the characteristic quasiperiodicity in burst and suppression durations.

The remainder of the paper is organized as followings. In Section X we introduce the model and specify parameters. In Section Y we analyze the model, perform appropriate bifurcation analysis and demonstrate the important dynamics regimes. The paper concludes with a Discussion in Section Z.

II. Model

The model consists of two interacting parts: the fast neuronal system is described through a simple, two-dimensional mean field model of the Wilson-Cowan type. The slower, metbaolic system is described with two state variables the describe nonspecific modulatory and recovery processes. The equations and modeling choices are fully described below.

A. Mean field model of cortical activity

Our objective here is to analyze the dynamical interaction between faster neuronal activity and the slower, supportive metabolic activity. In this sense, we are not investigating a particular cortical dynamical regime (e.g., type of oscillation, frequency) per se. Accordingly, we model neuronal activity with a simple mean-field description based on the popular Wilson-Cowan model [14], [15]. This model is used to characterize the behavior of excitatory and inhibitory neuronal populations at the scale of the cortical macrocolumn. The equation that govern the system evolution are

$$\dot{e_j} = -e_j + (k_e - r_e e_j)\mathcal{F}[c_1 e_j - c_2 i_j + P + \phi(t)] + W(t) \quad , \tag{3}$$

$$\dot{i_j} = -i_j + (k_e - r_i e_j)\mathcal{F}[c_3 e_j - c_4 i_j + Q] \quad . \tag{4}$$

where e_j and i_j represent the overall activity in the excitatory and inhibitory populations. The function $\mathcal{F}$ is a logistic sigmoid of the form

$$\mathcal{F}(x) = \frac{1}{1 + \exp[-a(x - \theta)]} - \frac{1}{1 + \exp(a\theta)} \quad . \tag{5}$$

where a, θ are free parameters. The constants P and $Q(e_j)$ determine the level of excitation present in the system. Depending on these values, the system may exhibit either a stable equilibrium or periodic limit cycle behavior. The noise term $W(t)$ models a weak activity from afferent populations.

Our investigation centers on the function $\phi(t)$, a gating function that supports neuronal activity as a function of metabolic substrate. It is a nonspecific variable and may correnspong to ATP-gated ion channels, excitatory synaptic conductance, or other modulating processes. When $\phi(t)$ is sufficiently large, the neuronal population will produce sustained oscillatory activity. When it is below a the bifurcation point in the parameter P in (3), the system will produce a quiescent steady state.

B. Metabolic model with homeostatic coupling

We now construct a model to describe the evolution of $\phi(t)$ as a function of the neuronal activity in (3)-(4). Specifically,

$$\dot{\phi} = -\mu\phi + \left(\frac{\nu \exp(\kappa M)}{1 + \exp(\kappa M)}\right) \tag{6}$$

$$\dot{M} = g_r(e) - g_c(e) \tag{7}$$

Here, the variable M is the metabolic substrate that supports/depletes the gating variable ϕ. To draw a parallel to the mechanism in [11], M would model extracelullar ATP (and the dynamics of the Sodium-ATP exchange during production of action potentials), while ϕ would correspond to the conductance of an ATP-gated potassium channel. The metabolic substrate is consumed and restored according to the functions $g_c(e)$ and $g_r(e)$, modeled as

$$g_r(e) = (k_r e^2 + \beta) \tag{8}$$

$$g_c(e) = \log(k_c H_4(\phi) H_2(e) + 1), \tag{9}$$

respectively. The function $H(\cdot)$ denotes a standard Hill-form sigmoid. Note, in particular the homeostatic mechanisms in both (8) and (9). Any change in excitatory activity results in a compensatory change in the rate metabolic recovery, i.e., a supply-demand homeostatic loop. The constant term β serves as a baseline rate to ensure that the rate of metabolic recovery can never be zero, noting that even in a resting excitatory state a certain amount of baseline energy is required in order to maintain the neuronal membrane integrity.

If (8) did not depend on e, then the rate of recovery would be totally decoupled from the underlying neuronal dynamics. In this case, any reduction in the basal parameter β could lead to a bifurcation into a bistable regime, which amounts to the mechanism in [13], [11]. By modeling homestatic dependence on e we can investigate the extent to which such a bifurcation might occur through only a manipulation in the neuronal dynamics in (3)-(4). Table * provides a summary of the various parameters and their values.

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