A Mean Field Model for Neural-Metabolic Homeostatic Coupling in Burst Suppression

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***Abstract*— Burst suppression is an inactivated brain state in which the electroencephalogram is characterized by intermittent periods of isoelectric quiescence. Recent modeling studies have suggested an important role for brain metabolic processes in governing the very slow time scales that underlie the duration of bursts 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 appearance of burst suppression when metabolism is directly downregulated. 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 activity with metabolic homeostatic mechanisms. We show that with such mechanisms, a simple reduction in neuronal activity due, for example, to increased neuronal inhibition, will give rise to bistability due to a bifurcation in the combined neuronal and metabolic dynamics. The model reconciles a purely metabolic mechanism for burst suppression with one that includes important dynamical feedback from the neuronal activity itself. The resulting fast-slow dynamical description forms a useful model for further development of novel methods for managing burst suppression clinically.**

I. Introduction

In states of deep general anesthesia and pathologies such as coma, the brain, while significantly inactivated, nevertheless exhibits complex dynamical phenomena. A notable example is burst suppression, an electroencephalogram (EEG) pattern associated with medically-induced coma following diffuse brain injury [1]–[5]. In burst suppression, the EEG alternates quasi-periodically between periods of high-voltage activity (bursts) and flatline (quiescence) [5], [6].

Significant effort has been directed at identifying the mechanisms of burst suppression at the cellular level [7] and, in particular, the role of various ion channels and membrane polarization in mediating the onset and offset of burst events [8]–[10]. Recent computational models have gone further in suggesting underlying biophysical mechanisms 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. Termination of each burst is attributed to depletion of ATP, the energetic substrate for action potential generation. During suppression, cessation of spiking allows recovery of ATP until a critical threshold is reached, and then another burst is initiated. In [12], a model for burst suppression was developed using a mean field computational framework. Here, the slow alternations of burst and suppression were attributed to physiologic processes such as synaptic neurotransmitter depletion that could also arise due to metabolic depression. The models in [11] and [12] are similar insofar as they attribute burst suppression to slower physiologic processes modulating the faster neuronal activity in a depletion-recovery cycle. Mathematically, this amounts to a dynamical system with separated time scales in form of:

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

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

where x is the 'neural' variable of the fast system (1) and y is the 'modulation' variable of the slower process (2) (e.g., ATP or neurotransmitter; see Figure 1 for schematic). The parameter ν governs the time scale of modulation, and α_m determines the rate of recovery. When α_m is lowered beyond a critical threshold, the fast system experiences transition from continuous activity in x to bistable dynamics (i.e. burst and suppression), in which the suppression epoch duration grows as α_m is progressively depressed, e.g., as metabolism is decreased. Here bistable dynamics describe the seeming phenomenology of burst and suppression. The fast system (1) may not necessarily have two stable states simultaneously.

In both [11] and [12], α_m is directly downregulated as a function of either increasing anesthetic dose or increasing pathology. This might be appropriate when modeling direct metabolic perturbations such as hypothermia or ischemia, but direct, exogenous manipulation of α_m does not take into account homeostatic mechanisms of metabolic autoregulation. That is, with decreased neuronal activity comes decreased cerebral metabolism – lower demand, lower supply – and

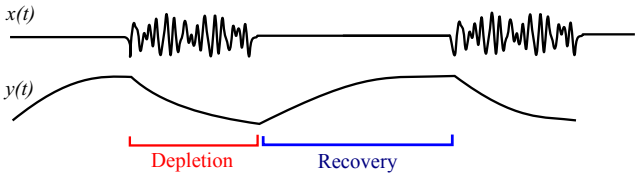

Fig. 1. **Conceptual Diagram of Fast-Slow Dynamics in Burst Suppression.** In burst suppression, neuronal activity ($x(t)$) exhibits bistable dynamics in which bursts of high voltage activity alternate with periods of suppression (see, e.g., [5], [11], [13]). Recent modeling efforts [11], [12] have attributed this phenomenon to a slower modulating physiologic variable ($y(t)$) that is depleted during bursts and recovers during suppressions, resulting in a fast-slow dynamical in the form (1) and (2).

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vice versa. For instance, while anesthetic drugs do decrease cerebral metabolism, this reduction is largely a consequence of a drug-induced reduction in neuronal activity. Thus, when modeling anesthesia-induced burst suppression, it may not be wholly appropriate to simply reduce α_m and leave the dynamics in $f_{\alpha_n}(x, y)$ in Eq. (1) intact, when, in reality, the primary drug effect is a change in those dynamics.

The purpose of this paper is to: (i) introduce a computational model for burst suppression that includes homeostatic mechanisms in the interaction between neuronal and metabolic processes and; (ii) analyze this model to assess the extent to which manipulation of *only* neuronal dynamics can give rise to burst suppression-like bistability. To investigate this problem, we formulate a simple mean-field model in the form of Eq. (1) and (2), in which the slow system (2) corresponds to recovery of metabolic substrate. To this model we add a sigmoidal homeostatic coupling equation that specifies α_m as a function of x. It turns out that, in the model, bistable dynamics not only occur for direct (exogenous) reductions in metabolic recovery, but are also induced through a simple increase in cortical inhibition, consistent with the actions of many anesthetic drugs. Consequently, the model provides a more complete characterization of burst suppression as induced via general anesthesia.

The remainder of the paper is organized as follows. In Section II we introduce the model and specify parameters. In Section III we analyze the model, perform appropriate bifurcation analysis and demonstrate the important dynamics regimes. Conclusions and future work are formulated in Section IV, including a discussion of the implications of the model in the design of new schemes for clinical management of burst suppression.

II. Model

A. Mean field model of cortical activity

We formulate a model for the dynamical interaction between fast neuronal activity and slower, supportive metabolic activity. Since we are not investigating a particular cortical dynamical regime (e.g., type or frequency of oscillation) *per se*, we choose to model neuronal activity with a simple mean-field description based on the Wilson-Cowan model [14], [15]. This model characterizes the behavior of excitatory and inhibitory neuronal populations at the scale of the cortical macrocolumn. The equations that govern the system evolution are

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

$$\dot{i_j} = -i_j + (k_i - r_i e_j)\mathcal{F}[c_3 e_j - c_4 i_j + k_s \mathbf{e} + Q], \tag{4}$$

where e_j and i_j represent the overall activity in the excitatory and inhibitory populations. The constants P and Q determine the level of background excitation present in the system. Depending on these values, the system may exhibit either a stable equilibrium or periodic limit cycle behavior. Coupling between columns is dictated by the parameter k_s, and $\mathbf{e}$ denotes the vector of all afferent excitatory activity (noting a slight abuse of notation). 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.

Our investigation centers on the function $\phi(t)$, a gating process that supports neuronal activity as a function of metabolic substrate. It is a nonspecific variable and may correspond to actions of ATP-gated ion channels (e.g., [11]), excitatory synaptic conductance (e.g., [12]), or other modulating processes. When $\phi(t)$ is sufficiently large, the neuronal population will sustain oscillatory activity. When it is low, the system will produce a quiescent steady state, under the assumption that the background parameter P in Eq. (3) is also sufficiently low.

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 given by Eq. (3) and (4). Specifically,

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

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

where M denotes the metabolic substrate that supports the gating variable ϕ. To draw a parallel to the mechanism in [11], M would model extracellular 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

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

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

where the function $H_n(\cdot)$ denotes an n^{th} order Hill-form sigmoid and k_r, k_c are positive constants. Functions (8) and (9) describe neural-metabolic homeostatic mechanisms. Any change in excitatory activity results in a compensatory change in the rate of metabolic recovery, i.e., a supply-demand homeostatic loop. The constant term β serves as a baseline rate that models exogenous perturbations to metabolic recovery.

If Eq. (8) did not depend on e, then the rate of recovery would be totally decoupled from the underlying neuronal dynamics (in essence, corresponding to α_m in system (2)). In this case, any reduction in the basal parameter β could lead to a bistable regime. By modeling homeostatic dependence on e we can investigate the extent to which such bistability might occur through only a manipulation of the neuronal dynamics (3).

III. Results

We conducted simulations in a system of two Wilson-Cowan columns, connected via k_s in system (4), to demonstrate the behavior of the model for different parameter

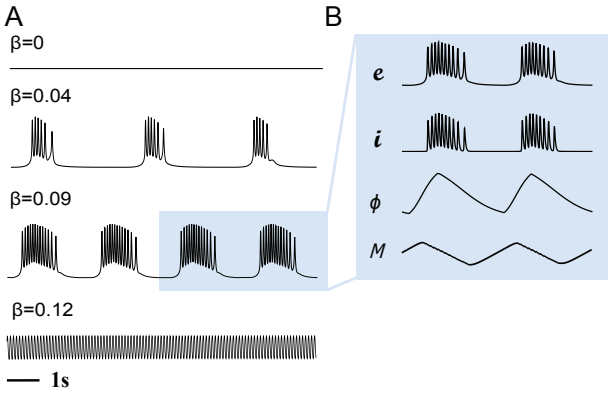

Fig. 2. **Bistable dynamics with direct downregulation of recovery rate.** As expected, decrease in the parameter β leads to a bifurcation from continuous oscillatory activity to burst suppression-like dynamics. $k_r = 1.8, k_c = 0.36$.

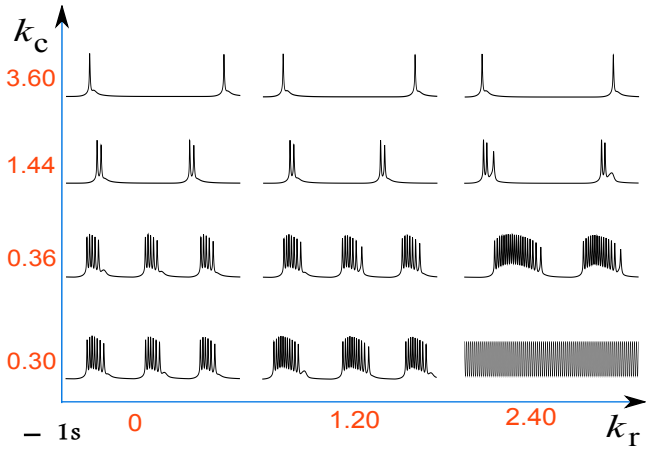

Fig. 3. **Burst and suppression duration dependance on** k_c, k_r when $\beta = 0.09$. An increase in k_c or decrease in k_r shortens the burst duration.

regimes. As in [15], the baseline parameters of the model (1) are

$$k_e = r_e = k_i = r_i = 1, k_s = 1.5$$
$$c_1 = 16, c_2 = 12, c_3 = 15, c_4 = 3, P = -4, Q = 0, \quad (10)$$
$$\theta_e = 4, \theta_i = 3.7, a_e = 1.3, a_i = 2$$

We consider the following parameterization for Eq. (6):

$$\mu = \nu = 0.008, \kappa = 50. \quad (11)$$

Since the model is dimensionless, the absolute values of these parameters do not have direct biophysical meaning and only the relative value is important. The remaining parameters will be varied to illustrate different dynamical regimes, below.

A. Direct manipulation of metabolic rate

We first establish the capacity of the model to produce burst-like activity via direct downregulation of the baseline metabolic rate β. This manipulation parallels direct modulation of recovery rate parameter in [11].

Figure 2 shows the system output for several choices of the basal recovery rate parameter β. Here, the parameter P is chosen such that, for sufficiently large β, the fast neuronal dynamics produce oscillatory activity. As anticipated, progressive reduction in β produces a dynamical bifurcation leading to intermittent periods of suppression during which the modulation process $\phi(t)$ is insufficient to sustain high amplitude activity. As $M(t)$ recovers, $\phi(t)$ again facilitates regeneration of a new oscillatory burst. Figure 3 illustrates the variation in burst and suppression duration for various values of the consumption and recovery rate parameters k_c, k_r, where we observe that any increase in k_c or decrease in k_r leads to shorter bursts and longer suppressions.

B. Decrease in neuronal activity leads to burst suppression-like activity

We now proceed to demonstrate and analyze a novel feature of the model (9) – the emergence of a bistable, burst-like regime achieved via downregulation of *only* the neuronal dynamics. In particular, we consider manipulation

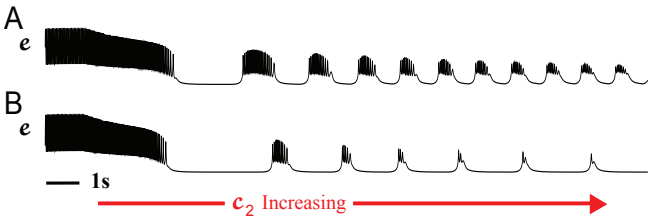

Fig. 4. **Increase in inhibitory coupling parameter** c_2 **leads to burst suppression-like dynamics.** (A) A simple increase in c_2 creates a bifurcation and bistability. The duration of suppressions is limited by the basal rate β. (B) If β is itself coupled to c_2, suppression epochs progressively increase. $k_r = 2.0, k_c = 0.3, \beta = 0.09$.

of the parameter c_2 in Eq. (3), i.e., the strength on inhibitory coupling within the cortical model. Such a manipulation may be thought of as a surrogate for the actions of certain common anesthetic drugs, such as propofol, that act by potentiating inhibitory synaptic currents [16], [17]. We note, however, that it is not this specific manipulation *per se*, but rather its consequent reduction in excitatory activity that is the key factor in the model behavior.

Figure 4 shows the effect of increasing c_2 in the combined model, where the emergence of bistability is clearly seen. Conceptually, these dynamics can be understood as follows: when neuronal activity is sufficiently inhibited (i.e., the amplitude of e decreases), the rate function $g_r(\cdot)$ in (8) is (homeostatically) reduced. Consequently, the slow subsystem develops limit cycles in an analogous manner to those in Section III-A above. When the baseline rate β is held constant, the duration of the suppression is bounded (Figure 4A), since the contribution of the homeostatic coupling term in (8) is essentially zero during suppressions. If we include a dependence in β on overall activity via c_2, then, unsurprisingly, the length of suppressions will progressively increase (Figure 4B). While not presented here, such a dependence can be additionally modeled through a more detailed homeostatic mechanism where β itself is a function of more spatially widespread neuronal activity (see Future Work, below).

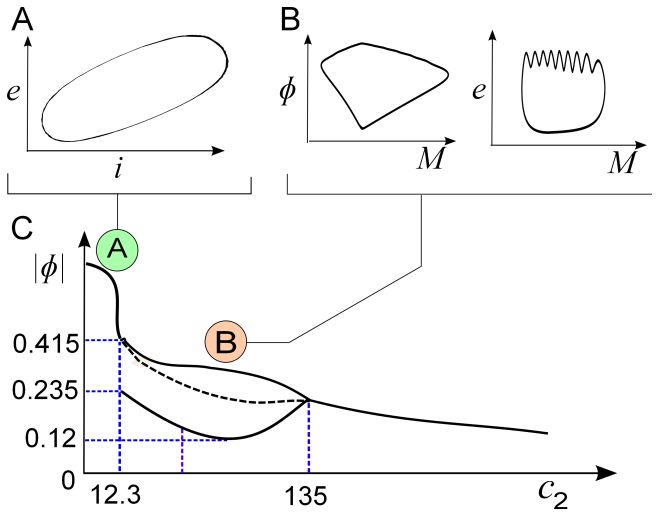

Fig. 5. **Bifurcation structure of model with respect to c_2.** (A) For low values of c_2, the model possesses a single equilibrium in which the slow subsystem lies at a fixed point. (B) Beyond a critical value, the slow subsystem manifests limit cycle oscillations (e.g., in the (ϕ, M) plane), leading to bursts of activity in e followed by relaxation (suppression). (C) Continuation diagram of the slow variable ϕ with respect to c_2 showing transition from the fixed point to limit cycles. A second bifurcation occurs at very large c_2.

C. Inhibition-induced bifurcation in slow subsystem

Figure 5 illustrates the basic bifurcation structure of the model with respect to the parameter c_2. We note, first, the presence of the single fixed point in the slow metabolic dynamics for low values of c_2. For the baseline parameterization we have chosen, this corresponds to sustained oscillations in the fast neuronal system. At the critical point around $c_2 = 12.3$ the system exhibits a bifurcation with rapid appearance of limit cycles in the slow system (Figure 5B,C). While this bifurcation appears to be of the Hopf-type (see also, Future Work), the amplitude increases virtually discontinuously, implying that regimes with short suppressions and long bursts are difficult to attain. A supercritical Hopf bifurcation occurs at $c_2 = 135$, creating a quiescent state for levels of inhibition above this value.

IV. Conclusions & Future Work

In this paper, we have introduced an extension of the popular Wilson-Cowan mean field model that includes dynamics for metabolic support and homeostasis. The key features of the model are the addition of two variables that represent metabolic substrate and neuronal modulation. The model provides a low-dimensional description of the interaction between neuronal activity and brain metabolism toward understanding phenomena such as burst suppression. In the model, burst suppression-like activity is achieved through downregulation of metabolism. This downregulation may arise either through direct, exogenous manipulation, or indirectly through neuronal inactivation. One feature that was not fully investigated here was the relative changes in burst and suppression lengths as a function of inactivation. To do so will likely require coupling the term β to neuronal activity over a larger, more diffuse spatial (or temporal) scale. In addition to this issue, several topics will be the study of future, more detailed work: (i) additional dynamical systems analysis, including characterization of all bifurcations; (ii) study of model robustness and sensitivity to the functional form of homeostatic coupling (8) and (9); and (iii) explicit inclusion of noise. Due to its tractability, the model here may also facilitate improved design of nonlinear controllers for closed-loop anesthesia delivery systems for clinical management of burst suppression in medically induced coma [18], [19].

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