Real-Time Measurement and Closed Loop Control of Burst Suppression for Management of Medical Coma

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***Abstract*— This talk will provide an overview of recent results on the design of a closed-loop anesthesia delivery (CLAD) system for controlling burst suppression for management of medical coma.**

I. Extended Abstract

Medical coma is a state of profound unconsciousness and brain inactivation induced to treat status epilepticus – unrelenting seizures – and to facilitate recovery following traumatic brain injuries [1], [2]. Typically, an anesthetic drug such as propofol is titrated to achieve a specific clinical target that indicates a coma-like state of large-scale brain inactivation. The standard approach is to monitor the patient's brain activity with the electroencephalogram (EEG) and use a specified level of burst suppression as an electrophysiological target. Burst suppression is an EEG pattern indicating a state of highly reduced electrical and metabolic activity in the brain defined by periods of high-voltage bursts that alternate with flatline periods termed suppressions [3]. Burst suppression can be controlled systematically, once the state is achieved, as the level of suppression can be increased or decreased by adjusting the infusion rate of the anesthetic.

In general, there are no established guidelines for specifying the level of burst suppression. A target level is agreed upon by the intensive care unit staff and control of the level is undertaken by continually monitoring the EEG and manually adjusting the drug infusion rate. A common goal of medical coma is to maintain a stable state of reduced brain activity and metabolism for 12 to 48 hours, a period significantly longer than any human operator can be expected to maintain tight control by visually monitoring the EEG and manually changing the infusion rate of the anesthetic. Defining a precise, quantitative target for the level of burst suppression and designing an automated system for maintaining that level would be a more prudent approach. Automation could be achieved by implementing a closed loop anesthesia delivery system.

The essential elements of a CLAD system are: a specific control or target criterion; a means of measuring or estimating the value of the criterion in real time from EEG recordings; and a controller that adjusts the instantaneous dosing of the anesthetic based on the difference between the current value of the criterion and its target value.

We present a CLAD system to automatically and precisely control the EEG state of burst suppression and efficiently maintain a medically-induced coma. Specifically, we constructed a CLAD system to control burst suppression reliably and accurately in real-time in both simulation [4] and in a rodent model using EEG and a computer-controlled infusion of propofol [5]. The CLAD system uses a two-compartment pharmacokinetics model to characterize the effect of propofol on the EEG. We introduce the burst suppression probability (BSP) algorithm [6], [7] to compute from the EEG in real time the instantaneous probability of the brain being in a state of suppression. We estimate the parameters of a pharmacokinetics model online and use them to define a proportional-integral (PI) controller. To assess performance of our CLAD system, we establish new statistical criteria to assess reliability and accuracy at individual target levels of burst suppression and a Bayesian statistical approach to assess reliability and accuracy across target levels and animals. We illustrate the application of our CLAD system by demonstrating precise control of burst suppression in individual rats. Finally, we discuss outstanding problems and forthcoming work related to translating the CLAD system for use in human patients.

*This work has been supported by NIH DP1-OD003646 (to ENB), DP2-OD006454 (to PLP) and K08-GM094394 (to KS). S.C. holds a Career Award at the Scientific Interface from the Burroughs-Wellcome Fund

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