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Design, Implementation, and Evaluation of a Physiological Closed-loop Control Device for Medically-induced Coma

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Abstract

Concerns regarding reliability and safety, as well as uncertainties about what constitutes adequate performance evaluation, have impeded the clinical translation of PCLC devices. We describe an attempt to address these challenges through design, implementation, and evaluation of a PCLC device for delivering medically-induced coma, with the intention to eventually conduct a clinical trial. This device works by automatically adjusting the infusion rate of propofol – a general anesthetic – in response to an electroencephalogram (EEG) pattern called burst suppression. We also designed and implemented a computational patient model which interfaces with hardware and produces realistic EEG signals in response to propofol infusion. The computational patient model is used in hardware-in-the-loop studies to evaluate the behavior of our PCLC device under realistic perturbations. Finally, we have tested the performance of our PCLC device in rodents. Results from these studies suggest that closed-loop control of medically-induced coma in humans is feasible and robust. Consequently, our work produced a PCLC device and relevant pre-clinical evidence in support of a pilot clinical trial.

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I. Introduction

Physiological Closed-Loop Control (PCLC) devices are a group of emerging technologies, which use feedback from physiological sensor(s) to autonomously manipulate physiological variable(s) through delivery of therapies conventionally delivered by clinician(s)[1]. In recent years, researchers have made progress developing PCLC devices for mechanical ventilation, anesthetic delivery, and hemodynamic stability/fluid resuscitation applications. PCLC in these areas is expected to decrease drug dosage, increase consistency in drug dosing, facilitate patient recovery, increase patient safety, reduce healthcare costs, and decrease care-provider workload[2]–[5].

Despite these promises and potential benefits, there has been limited success in the translation of PCLC devices from bench to bedside. For example, although the idea of a closed-loop anesthetic delivery system was first proposed in the 1950s, no clinical trial has been performed in the United States to-date. A key challenge to bringing PCLC devices to a level required for a clinical trials in humans is risk management to ensure device reliability and safety. The United States Food and Drug Administration (FDA) classifies new hazards that might be introduced by PCLC devices into three categories, including *engineering* (e.g. algorithm robustness, hardware component availability, hardware-software integration issues), *clinical* (e.g. sensor validity and reliability, inter- and intra-patient physiological variability), and *usability/human factors* (e.g. loss of situational awareness, errors, and lapses in operation)[1]. The risks to patients as a result of these potential hazards need to be minimized in order for a PCLC device to be approved for testing in humans.

Another challenge closely related to risk management is the question of what constitutes adequate confirmation of device performance and safety. A number of pre-clinical evaluation methodologies have been proposed, including computer simulation (*in silico)*, hardware-in-the-loop (HIL) and animal studies[1]. *In silico* studies typically run faster than real-time. They enable rapid assessment of a PCLC device under a wide range of physiological conditions. *In silico* studies typically do not involve hardware and are therefore evaluations of the software performance only. HIL studies are real-time tests in which an operator uses a PCLC device on a computational patient model in lieu of a real patient. HIL studies retain the versatility of *in silico* studies, because the computational patient model can be used to create extreme conditions to stress-test the device in a controlled manner. In contrast to *in silico* studies, HIL studies evaluate both the software and hardware components of a PCLC device, and trade speed for realistic operating conditions. To the operator, the experience of using the PCLC device during a HIL experiment closely emulates the experience of using the device during a clinical trial. Therefore, usability of the device can also be assessed with HIL studies. Animal studies test the performance of a PCLC system in the presence of the full dynamics and uncertainties of real physiology. This differs from *in silico* and HIL studies, which rely on models that at best only capture a subset of the possible dynamics. However, due to differences between animals and humans (e.g. size, metabolism, and physiology etc.), the specific implementation of a PCLC device for animal studies may require different hardware and modifications to the software. Consequently, animal studies can be used to validate the device framework but can only partially validate the actual implementation of a PCLC device intended for human use.

Taking into account the above considerations, we designed, implemented, and evaluated a PCLC device for maintaining medically-induced coma, with the key design objective of enabling a clinical trial of the device in humans. We chose to work on medically-induced coma because there is a clear clinical need and an established PCLC framework.

Medically-induced coma is a life-saving treatment for several important neurological conditions including severe intracranial hypertension, traumatic brain injury and refractory status epilepticus. Clinically, an adequate level of coma is indicated by a distinctive time-domain pattern called burst suppression on the electroencephalogram (EEG). As its name suggests, burst suppression consists of alternating periods of high (burst) and low (suppression) voltage brain activity. The amount of suppression increases with increasing amounts of anesthetic administered [6]. Usual practice targets a pattern of around one burst per 10 seconds of EEG [7]. This is equivalent to a burst suppression probability (BSP) of 0.8 ± 0.15 [8], [9].

Medically-induced coma is often administered over periods lasting days to months[9]. The current management paradigm requires intermittent manual adjustment of the infusion rates of general anesthetics based on a subjective interpretation of a brief observation of the EEG. This method is unlikely to be consistent and reliable at keeping the level of burst suppression within the target range over prolonged periods. PCLC is likely to be a better approach because it can provide continuous EEG monitoring, objective assessment of the level of burst suppression, and timely adjustments of the infusion rates of anesthetics. Prior work has demonstrated that closed-loop control of medically-induced coma is feasible. In particular, computer algorithms have been designed to process EEG in real time to quantify the burst suppression pattern as a series of BSP measurements, compare these estimated BSPs with a target BSP value specified by an operator, and compute the amount of propofol (a common general anesthetic used to induce medical coma) to be infused[10]–[14]. In the following, we report progress towards integrating these algorithms for closed-loop control of medically-induced coma into a complete end-to-end PCLC device that may be used in the clinical setting.

II. Design and Implementation

A PCLC device for closed-loop control of medically-induced coma has three major components including a computer, an infusion pump, and an EEG acquisition system. The computer executes real-time signal processing and control, and hosts a user-interface for operating the device. We follow recommendations from standards (e.g. IEC 60601-1 and ISO 14971) and relevant guidance documents when implementing our PCLC device to minimize risks associated with various engineering, clinical, and human factor hazards [15]–[18]. We also designed a “maximal common pathway” strategy to integrate the information of *in silico*, HIL and rodent studies to provide strong pre-clinical evidence of performance and safety. Here we briefly review algorithms used in our PCLC device, and then describe the methods developed for risk management and device evaluation.

A. Framework and Algorithms for Closed-loop Control of Medically-induced Coma

The algorithms used in our PCLC device are based on established frameworks for closed-loop control of medically-induced coma[10]–[13]. We use a threshold-based mechanism for EEG artifact reduction[19]. The artifact-reduced EEG is then band-pass filtered. A previously validated recursive algorithm is used to identify periods of suppression based on EEG variance in real-time[14]. Finally, an algorithm infers BSPs from the binary observations of bursts and suppressions, based on a state-space model of propofol pharmacokinetics and pharmacodynamics (PK-PD)[13]. For control, the inferred BSP is compared with a target BSP provided by the operator of the system. The difference between the inferred and target BSP is fed into a robust proportional-integral (PI) controller, which adjusts the infusion rate of propofol. The robust PI controller is tuned for individual patients to optimize performance and minimize sensitivity to disturbances[13]. Patient-specific parameters used for controller design and BSP inference are obtained from the Schnider model of propofol PK and a ramp-drop procedure designed to capture PD characteristics of individuals[13]. Specifically, the Schnider model produces customized PK parameters based on patients' mass, age, sex and height; and PD modeling uses an iterative least-squares algorithm to find the parameters of a sigmoidal PD curve that describes the BSPs as a function of the steady state propofol concentration in the brain[20].

B. Selection of an Infusion Pump

A major hurdle encountered when implementing our PCLC device is the lack of a commercially-available FDA-approved clinical infusion pump that supports closed-loop control. This is not surprising because there is currently no commercialized PCLC device in the United States, so pump manufacturers lack economic incentive and knowledge to build pumps for closed-loop applications. To overcome this limitation, we worked directly with pump manufacturers and created a customized pump communications interface for our device. Additionally, we also learned that most existing clinical-grade infusion pumps cannot respond reliably to instructions faster than ~0.2 Hz. Therefore, we slowed down the closed-loop frequency of the system from 1 Hz to 0.1 Hz and switched to a discrete-time paradigm for tuning the controller.

C. System Integration and Graphical User Interface Design

Human factors and device usability are significant sources of potential hazards, so it is important to engineer a well-designed graphical user interface (GUI) to reduce the risks associated with device operation. Yet, creating a suitable GUI for our PCLC device is challenging. There is no existing design to refer to, there are no standards specifying the minimal feature requirements, and new requirements are expected to emerge due to the iterative nature of medical device development. To work with these constraints, we applied a user-centered design approach in which interactive models and paper prototypes were used to engage end-users in the design process from the beginning and to rapidly iterate. This approach allowed us to simultaneously clarify feature requirements and optimize the GUI design to meet these requirements.

We also followed the "ABCD" protocol during GUI development to ensure consistency and clarity. Under this protocol, each action performed on the PCLC device is 1) checked to

ensure **A**ppropriateness before execution, 2) executed to produce the desired **B**ehavior, 3) the effect of the action is then **C**ommunicated to the user, and finally 4) time-stamped **D**ata describing the action taken and results achieved are saved for retrospective analysis and troubleshooting. The algorithms (see Section IIA) and hardware communication protocols were also implemented using a modular architecture to facilitate future upgrades.

E. Ensuring System Robustness

To be ready for testing in human, a PCLC device needs to be robust to modelling errors, inter- and intra-patient variability in PK/PD, and sensor noise or signal drop-out. To achieve this we used a robust PI controller design methodology which has been shown to be stable despite sensor noise and load disturbances in our PCLC device[13], and measured the performance of the device in rodent and HIL studies to confirm its resilience to the perturbations.

There is no established protocol to experimentally evaluate the robustness of a PCLC device. We believe that the best pre-clinical evidence is achieved by integrating information across *in silico*, HIL and rodent studies because each of these have their own advantages and constraints. To do so, we designed our PCLC device to support two subject modes – human or rodent; and three operation modes – simulation, HIL or experimental mode – for each subject mode. In the back-end, we minimized alterations to the code when supporting different modes so that each mode matched the implementation for the human-experiment mode intended for clinical use as closely as possible. We call this the “maximal common pathway” strategy.

We also designed a computational patient model for the HIL studies. This model consists of a digital scale and a laptop computer running a simulation program. It interfaces with the EEG amplifier and infusion pump to produce simulated burst suppression signals in response to a propofol infusion. The signals are generated using a realistic pharmacokinetic-pharmacodynamic-observation (PK-PD-O) model with 8 adjustable parameters (see Figure 1A). During HIL, the digital scale continuously weighs the amount of drug output by the pump. Readings from the scale are fed into the PK-PD-O model and the burst suppression pattern generated is sent as an analog signal to the EEG amplifier over the audio port. We introduce drifts in the parameters of the (PK-PD-O) model to mimic physiologically meaningful scenarios such as changing volume of distribution, renal and hepatic clearances, and receptor level sensitivity to propofol. We also introduce EEG artifacts in a controlled manner using the computational patient model (see Figure 1B). With this model, we can use HIL studies to evaluate the performance of our PCLC device in real-world scenarios that might concern clinicians and regulators.

III. Results

We successfully developed a prototype of a PCLC device for closed-loop control of medically-induced coma that can be used for testing in rodents, HIL testing in a computational patient model, and potentially in human patients. The schematic in Figure 1C describes the full set-up. This system can perform the following major classes of functions: 1) interface with EEG amplifier to acquire and process data in real-time; 2) communicate

appropriate infusion rates to the infusion pump; 3) estimate patient-specific model parameters; 4) switch quickly between automated closed-loop control and manual infusion modes; 5) record details of the procedure performed; 6) manage and store data; 7) monitor patients in real-time; and 8) provide alarms and warnings when concerning events arise. The software of the PCLC device is implemented in the MATLAB/Simulink environment and communicates with hardware components using the RS-232 serial protocol.

We successfully used our PCLC device to maintain BSP within the target range of 0.8 ± 0.15 in 8 HIL and 6 rodent experiments. In each HIL experiment we introduced sinusoidal drifts with periods of 1, 5, 15, 30, and 60 minutes to one of the 8 parameters in the PK-PD-O model. Each parameter was perturbed up to 30% from its typical value. For the rodent studies we introduced a sinusoidal disturbance to the propofol infusion given to the animals since we cannot directly perturb the PK-PD parameters. The amplitude of the infusion disturbance was 20 mg/hr. This is approximately 30 – 50% of the median infusion rate required to keep the animals at a target BSP of 0.8 in the absence of disturbances. The periods of the infusion disturbances are 1, 5, 15, and 30 minutes. Our results indicate that the median percentage time spend above (PTa), within (PTi), and below (PTb) the target BSP range of 0.8 ± 0.15 in 8 HIL studies were 0%, 96.7%, and 3.3%. The median PTa, PTi, and PTb achieved in 6 rodents were 0%, 98.6% and 1.4%. These results are comparable to values reported in our previous studies[11], [12]. Examples of results from a rodent experiment and HIL test are shown in Figures 1D and 1E.

IV. Discussion and Conclusions

PCLC is a novel management paradigm for medically-induced coma. While many papers describing laboratory experiments for closed-loop control of medically-induced coma have been published, no clinical trial has been conducted in the United States to-date. A PCLC device for controlling medically-induced coma is classified as a significant risk device by the FDA due to its direct control over therapy delivery[15]. To gain regulatory approval for a clinical trial requires that the PCLC device is implemented with careful risk management strategies, and thoroughly evaluated to ensure safe and reliable performance.

We designed, implemented and evaluated a PCLC device for medically-induced coma with the intention to enable a clinical trial. Careful consideration during device development and implementation allowed us to minimize operational risks by design. Specifically, we emphasized the selection of hardware components, safety and human factor engineering, and “maximal common pathway” design to facilitate device evaluation. We have tested the performance of our PCLC device using HIL and animal studies. The results show that our PCLC device is able to automatically adjust the infusion rate of propofol to maintain BSP within the target range despite significant perturbations.

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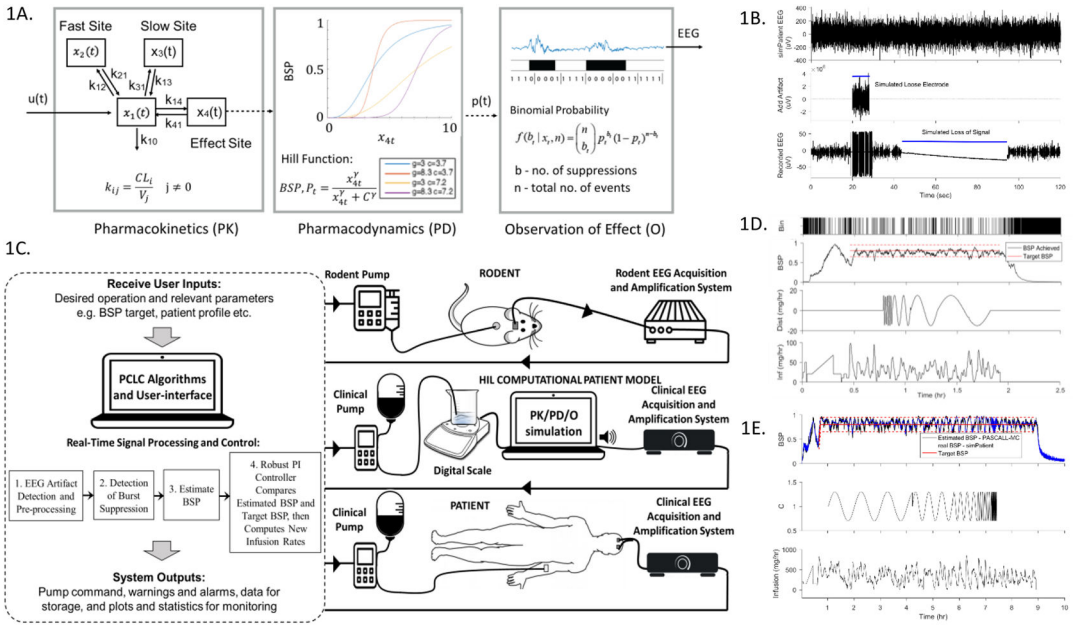

Figure 1.

A) The PK-PD-O model used to generated EEG signals in the computational patient model. The model has 8 adjustable parameters including 6 PK parameters (3 volumes of distributions V and 3 clearances CL) and 2 PD parameters (C and γ). B) Mimicking typical artifacts in EEG acquisition using the computational patient model. C) The PCLC device and experiment setup. D) Data from an experiment conducted in a rodent. Disturbance shown is applied to the infusion rate of propofol administered to the animal. E) Data from a HIL experiment performed using the computational patient model. Sinusoidal drift in the PD parameter C is applied to test the robustness of the PCLC device.