Model-Based Propofol Dosing to Improve Control of Patient EEG Dynamics

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***Abstract* – Propofol is a common anesthetic, which is being investigated as an antidepressant alternative to electroconvulsive therapy (ECT). Propofol can induce similar EEG effects to that of ECT, and has also demonstrated similar improvements in depression scores. However, propofol dosing is challenging because patients differ in their required drug doses. A model of the relationship between administered propofol and monitored EEG can be used to improve the accuracy and reliability of this treatment. Our objective is ultimately to automate processes in propofol's dose determination. A summary of patient-system modeling in anesthesia will be discussed, along with preliminary results from recent open-label trials.**

I. BACKGROUND

Depression impacts approximately 16.1 million US adults [1]. One third of these patients do not respond to conventional antidepressants [2]. Electroconvulsive therapy (ECT) can offer these patients effective relief [3], but its stigmatizing perception can deter many from receiving care. ECT's antidepressant effects have been attributed to the induced "burst suppression" [4] – an EEG state of alternating quiescence and bursts that can be induced by ECT. High concentrations of common anesthetics, such as isoflurane and propofol, can also induce burst suppression. Both anesthetics have also demonstrated antidepressant effects [4,5], along with other anesthetics such as nitrous oxide ("laughing gas") [6] and ketamine [7].

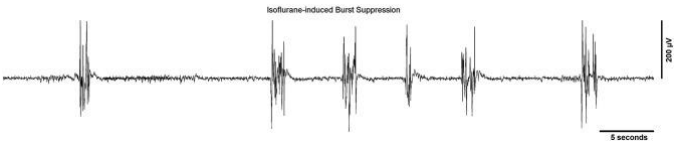

Figure 1. Burst suppression EEG state induced by isoflurane. EEG-based anesthetic depth monitors usually quantify burst suppression by the "ratio" between quiescence and bursts over a given epoch. (Kenny 2014) [8]

A recent open-label clinical trial at the University of Utah [5] investigated propofol's antidepressant effects, in which 6 of 10 subjects met the >50% criteria for improvement in their depression scores (HDRS-24), while 5 of those 6 met the criteria for remission (HDRS-24<10). Propofol demonstrated similar antidepressant effects to ECT [5] but without the side effects that can be associated with ECT, such as amnesia [9].

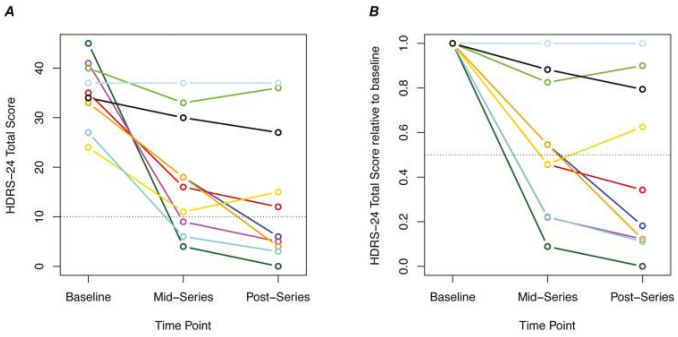

Figure 2. Change in depressive symptoms over a series of 10 treatments of propofol-induced burst suppression. (A) Overall changes in HDRS-24 scores, (B) HDRS-24 changes scaled to baseline score. (Mickey, Tadler 2018) [5]

If proven effective, propofol might become a viable therapeutic alternative for many patients with severe depression and limited treatment options. Propofol's neural and antidepressant effects are being further studied in a randomized controlled trial (see *ClinicalTrials.gov: NCT02935647*), along with revised dosing and administration strategies for propofol.

Propofol-induced burst suppression (PIBS) and deep anesthesia has already demonstrated utility in clinical practice. By reducing brain metabolism, it offers neuroprotection during aneurysm clippings [10], and can suppress seizure activity [11]. However, the relationship between propofol dose and induced EEG state is imprecise, with substantial pharmacokinetic and pharmacodynamic inter-individual variability [12]

Thus, accurate and reliable dosing of propofol to induce specific levels of burst suppression is challenging.

II. PK–PD MODELING

The amount of propofol interacting with the patient's brain is a time-sensitive function of how propofol accumulates and decays in the body. Thus, before relating drug input to EEG response, it is useful to determine the drug concentrations over the treatment duration. Unlike anesthesia based on inhaled anesthetics, the drug concentrations for intravenously delivered propofol cannot be monitored in real-time. Population-based models such as the Schnider pharmacokinetic model [13] can be used to estimate propofol concentrations, and take into account covariates such as age, BMI, and sex.

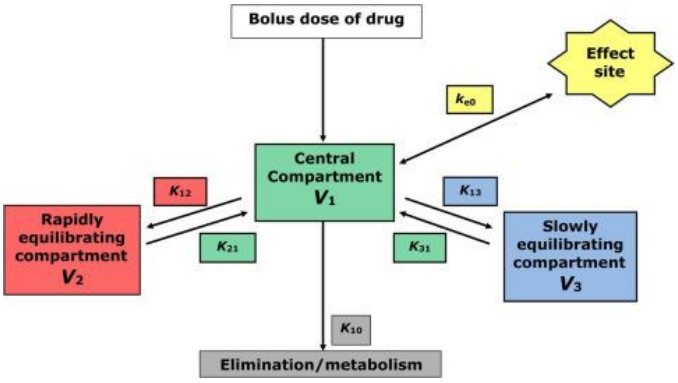

Figure 3. Three-compartment model illustrates the interactions between compartments and their associated rate constants. ke0 represents the rate constant for equilibration between plasma and effect-site concentrations. (Al-Rifai 2016) [14]

The Schnider model uses three compartments (central, rapid peripheral, slow peripheral) and a series of rate constants. These constants were derived from clinical data and govern the overall concentration at the effect-site compartment*:* a conceptual compartment that reflects the accumulation of propofol at the response site (presumably the brain). Euler's method was used to implement the associated differential equations [15].

The concentration domain is only an intermediate domain, which does not yield insight into how patients respond to the accumulated propofol. However, it does offer a much more convenient representation of the temporal implications of the propofol infusion course, which is critical to characterize the *pharmacodynamic* response to propofol.

III. OBJECTIVE

From the open-label trial, we directly observed challenges in formalizing, executing, and evaluating the PIBS protocol to treat severe depression. Clinicians had to "learn" and mentally "map" each patient's response, while relying on human intuition to dose propofol and target a burst suppression ratio (BSR) of 80% for 15 minutes. Variability was observed between patients and their successive treatments, highlighting the need for objective, quantitative and individualized guidance for dosing.

To improve the accuracy and reliability achieving BSR by PIBS, the utility of pharmacokinetic and pharmacodynamic (PK–PD) models will be applied and evaluated.

IV. METHODS

Following IRB approval and patient consent, 10 participants 33.6 ± 9.3 years old and BMI 29.3 ± 5.9 (mean ± standard deviation), received a series of 10 treatments of PIBS over the course of 3 weeks, similar to a typical treatment series of ECT. BSR was calculated over 1-minute epochs from a left frontal EEG obtained using the BIS VISTA Monitoring System (Aspect Medical Systems, Norwood, MA) and a 4-electrode sensor (BIS Quatro, Covidien, Dublin, Ireland). Additional monitoring included EKG, pulse oximetry, noninvasive blood pressure, respiratory rate, and end-tidal carbon dioxide.

For each treatment, an anesthesiologist administered an induction bolus of propofol (2,6-diisopropylphenol; Diprivan 1% injectable emulsion; Fresenius Kabi, Bad Homburg, Germany), along with a continuous infusion (Medfusion 3500 Syringe Pump, Smiths Medical, Minneapolis, MN) and additional bolus doses if needed. Following induction, subjects were intubated and ventilated to maintain an end-tidal CO2 of 35mmHg.

Propofol dosing was guided by real-time EEG measurements. Propofol induction doses ranged from 200–600 mg and continuous infusions ranged from 300–650 mcg/kg/min. Propofol was dosed to target a BSR of 80–100% for 15 minutes, similar to a previous protocol

studying the antidepressant effects of high-concentration isoflurane anesthesia [16].

Beyond clinical judgement and expertise no quantitative references or models were used in this "manual" approach of propofol dosing.

The recorded propofol infusion courses were analyzed by using Schnider pharmacokinetic model to estimate predicted effect-site concentrations over the course of each subject's treatment series.

Using MATLAB, the following outlines how Euler's method was applied to simplify the computations required in the Schnider model:

```
x1 = 0; %initial mass in central compartment
Cp = [0]; %initial plasma concentration
Ce = [0]; %initial effect-site concentration

step = 0.1 %minutes

for n = 1:length(t) %loop over desired duration of simulation
      dx1 = [x2*k21 + x3*k31 x1*(k10+k12+k13)]*step + B(n); %central
      dx2 = [x1*k12 - x2*k21]*step; %rapid peripheral
      dx3 = [x1*k13 - x3*k31]*step; %slow peripheral
      dCe = [keo*(Cp - Ce)]*step;  %effect-site

      nCp = x1/V1; %next Cp
      nCe = Ce + dCe; %next Ce

      Cp = [Cp nCp]; %updated Cp vector
      Ce = [Ce nCe]; %updated Ce vector
end
```

V. RESULTS

Figures 4 through 9 show an example of the pharmacokinetic and pharmacodynamic analysis and modeling of one of the subject's (ID: PROP03) ninth treatment from the open-label trial. Figure 5 offers further perspective into how PROP03 compared with other female subjects, as well as inter-treatment variability in propofol concentrations.

Pharmacokinetics

During the ninth treatment, PROP03 required 4 boluses of propofol to satisfy the treatment protocol's BSR range, as well as a continuous infusion of 600 mcg/kg/min.

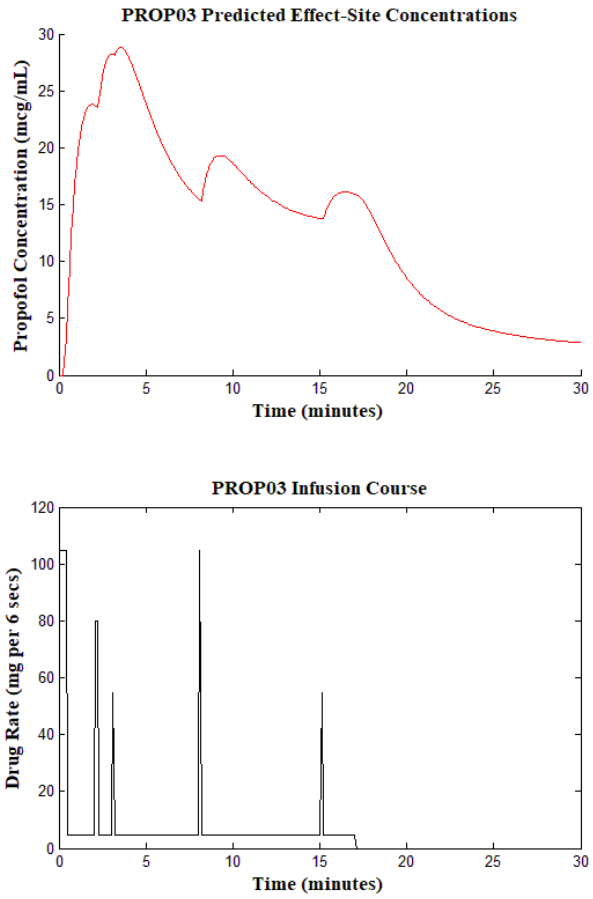

Figure 4. Pharmacokinetics of a subject's 9th treatment. TOP: the predicted effect-site concentrations determined by the Schnider model, derived from an infusion time course. BOTTOM: both bolus doses and a 600 mcg/kg/min propofol infusion can together be represented in time by their drug input rates over time. The concentration domain (red) accounts for the temporal aspect of drug dosing.

Beyond changes in concentration over each treatment domain, concentration differences between the treatments and between the patients were also analyzed. Given the rapid changes in concentration during induction, the 10-minutes prior to ending propofol administration were analyzed to more closely reflect steady state concentrations. Female subjects (n = 5) and each of their first nine treatments were examined because of a wider and more evenly distribution of BMI (30.0 ± 7.5kg m^{-2}) compared to male subjects (28.7 ± 4.7kg m^{-2}).

Figure 5 illustrates our findings and suggests a correlation with required propofol concentrations to satisfy the target BSR range and BMI of the subject, given that the subjects are ordered by increasing BMI, as listed: PROP04 = 19.4 kg m^{-2}, PROP03 = 25.1 kg m^{-2}, PROP09 = 33.4 kg m^{-2}, PROP02 = 34.2 kg m^{-2}, PROP07 = 37.8 kg m^{-2}.

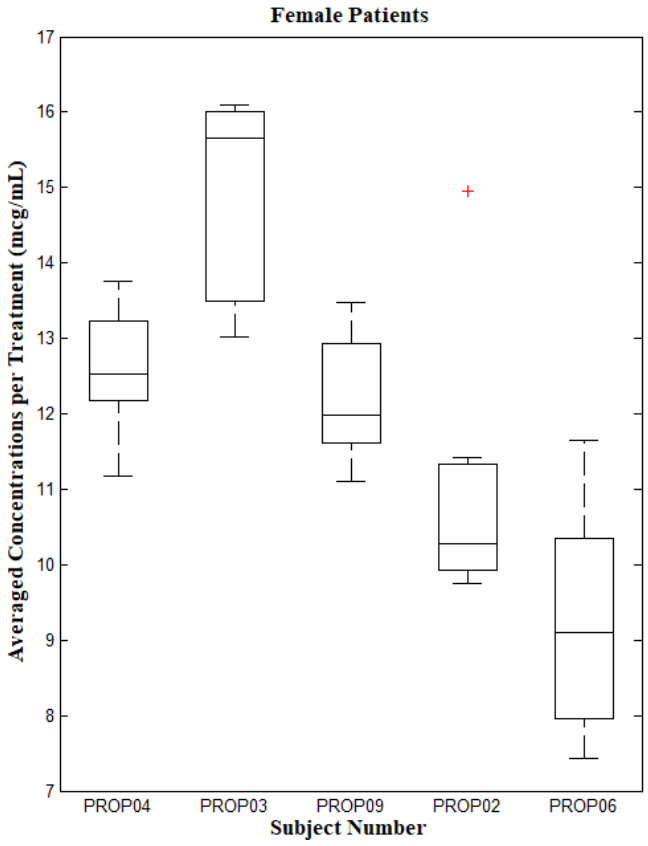

Figure 5. Female subjects (ranked from left to right by increasing weight) varied widely in their average propofol concentrations to satisfy the desired BSR range, according to the Schnider model. Average propofol concentrations were calculated over the 10 minutes before the propofol infusion was stopped. The boxplot highlights both inter-patient variability and inter-treatment variabilities in the concentration domain.

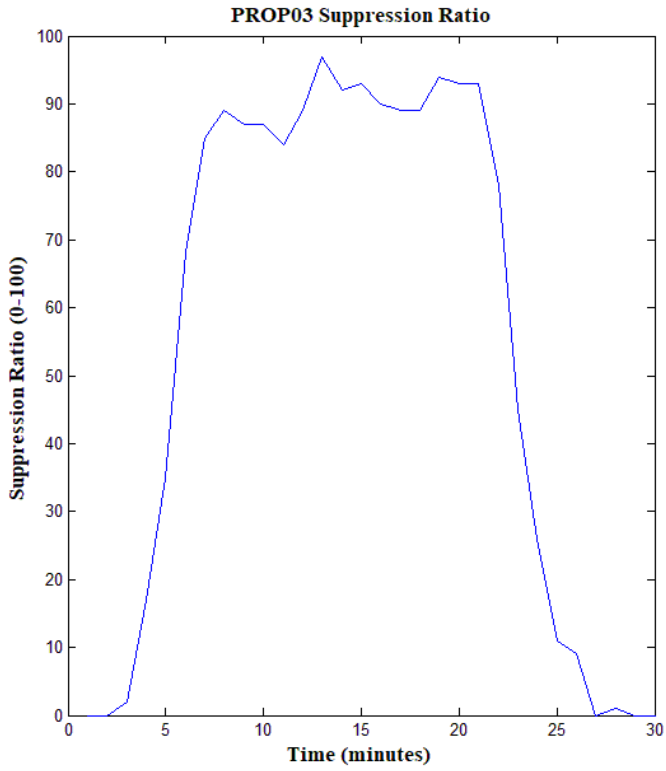

Figure 6. The corresponding monitored BSR output for PROP03's 9th treatment of propofol. Given experience from the previous 8 treatments to gauge the subject's response and sensitivity to propofol, the target BSR range (80-100% for 25 minutes) was well satisfied by the anesthesiologist.

Pharmacodynamics

Pharmacodynamic modeling seeks to relate the estimated concentrations to the monitored effect, in our case: the BSR output reported by the BIS Monitor (one-minute averages), which is shown in Figure 6. Upon the initial bolus of propofol, BSR rapidly increases as brain activity becomes suppressed, and rapidly decreases as brain activity recovers and propofol is eliminated from the subject's body.

Figure 7 illustrates the relationship of a pharmacodynamic model of PROP03's ninth treatment.

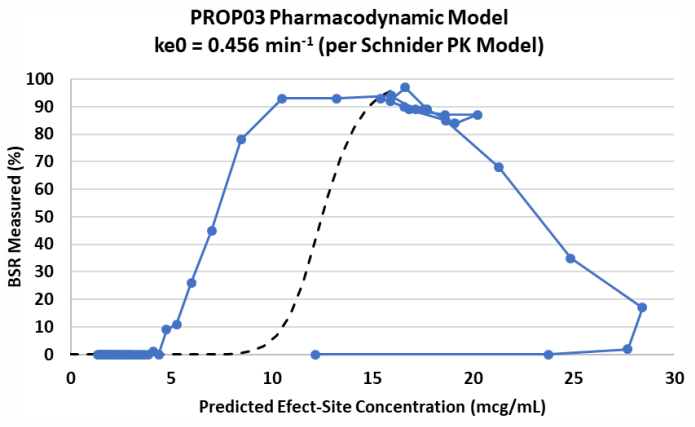

Figure 7. BSR outputs by the BIS Monitor are plotted against the estimated effect-site concentrations, derived from the infusion data. The data was fit according to a sigmoidal curve, with Hill and EC50 coefficients of 13 and 12.5 (mcg/mL). Over the duration of the treatment, the plot's general trend is to circulate counter-clockwise toward returning to lower concentrations, during emergence and recovery.

VI. DISCUSSION

As a retrospective analysis of data that was originally not collected with a pharmacokinetic/pharmacodynamic analysis in mind, the conclusiveness of the results is limited in a number of ways.

Time synchronization: Although updated drug inputs (see Figure 4) and EEG outputs (see Figure 5) have been gathered for all patients (n = 10) and all treatments (m = 99), synchronizing the clocks between the BIS monitor and clinical administration of propofol was *not* adequately conducted, *nor* was a major research priority. Assumptions were required to force-fit potential models of how BSR related to predicted effect-site concentrations.

Time resolution is another factor that required assumptions parameterizing the PK–PD models. The bolus and infusion data were recorded in minute intervals, while only the averaged BSR could be exported every minute. Assumptions had to be made about how long each bolus was administered for, and that they were administered at the beginning of each minute interval.

A common consequence that can occur from poor time synchronization and resolution is hysteresis: a phenomenon in which a clinical response (e.g. BSR) depends on its past trend of propofol concentration changes, yielding multiple effects associated with the same propofol concentration.

Notably, hysteresis can also result from a ke0 pharmacokinetic parameter that is not optimized for the individual patient. Once the time synchronization and time resolution has been eliminated as a source of the hysteresis loop, optimizing the ke0 constant, i.e., the estimated "time to peak effect" (see Figure 8) for its effect-site compartment, is a way to collapse a hysteresis loop (see Figure 9) and estimate the patient-individualized ke0 parameter.

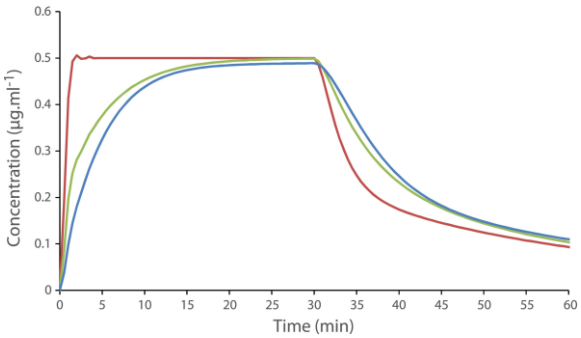

Figure 8. Plot of multiple predicted effect-site concentrations with different ke0s (Schnider in red, Sepúlveda in green, and Marsh original in blue). Altering the ke0 value of a pharmacokinetic model will alter the rates of accumulation and decay in the effect-site compartment. This directly relates to changes in the "time to peak effect" and alignment in the eventual pharmacodynamic model. (Sepulveda 2018) [17]

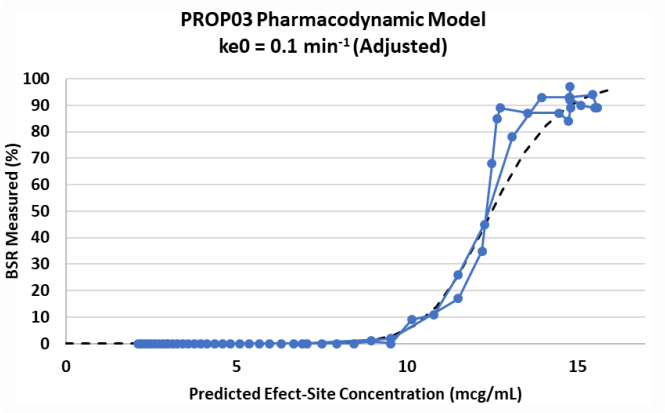

Figure 9. Upon adjusting the ke0 value from 0.456 min^{-1} (value determined by Schnider) to 0.1 min^{-1} (suggests longer time to peak effect), the plot's hysteresis loop visually collapses. Compare with Figure 6. This difference can offer much utility in future PK–PD of subjects.

Significance

Improving the accuracy and reproducibility of this propofol-based antidepressant therapy will directly reduce potential confounding variables impacting the clinical effect of propofol. As reported by Mickey, Tadler, et al. [5], subjects experienced a variety of degrees and durations of burst suppression. Subjects receiving *lower* degrees and duration of burst suppression within the 80-100% BSR range tended to demonstrate greater improvements in their depression scores [5]. Over the 10-treatment series, different clinicians administered the treatment, with presumably different approaches to dosing. Standardizing the control of patient EEG dynamics through individualized PK-PD models might reduce the impact of these factors.

Given the treatment's high propofol doses, safety is also an important concern. Individualized PK-PD modeling might help guide clinicians to identify the necessary doses and timing in a quantitative fashion. This also includes when and how to step down and taper the propofol infusion to achieve a desired time of PIBS.

Closed-loop control advances in anesthesiology can benefit space mission personnel through more independent and technological means of clinical care, where expertise may be limited. For example, without a formally trained anesthesiologist, an automated total intravenous anesthesia (TIVA) device can still help provide treatment options.

Follow-on Clinical Trial

The missing link to pharmacodynamically model subjects from the open-label trial was synchronized time. In a follow-up randomized controlled trial, we seek to align the BIS Monitor's clock with the room clock and align the drug input with the EEG outputs. Furthermore, we seek to successively build upon our pharmacodynamic models after each treatment to improve how we target BSR in the following treatment. The predicted concentrations associated with the desired BSR range will be pursued through updated dosing strategies.

Given quantitative guidance from our models, we hypothesize that 1) BSR accuracy will improve over successive treatments, and 2) the pharmacodynamics of each subject is constant over the treatment series. We can objectively evaluate the pharmacodynamics between the treatments by comparing their pharmacodynamic parameters. Moreover, we can further overcome hysteresis by developing a standard algorithm to collapse and minimize hysteresis loops.

The collection and processing of clinical data will not only be used to develop patient-models, but also help develop an automated controller to further compare those models with real-time EEG-BSR feedback, then objectively recommend changes in how propofol is administered to reduce error from the ideal BSR target. This controller will be evaluated by simulation, and potentially in the clinical setting.

More updates will be shared once the blinded study has concluded and proper due diligence has been conducted.

VII. FUTURE WORK

Extensive literature on PK–PD modeling exists and can be directly applied to a follow-up trial investigating propofol's neural and antidepressant effects. Adaptively modeling the patient-individualized relationship between drug input and BSR output may allow improved dosing to better target the desired EEG response. This would allow to augment the clinician's intuition by providing a model-based tool to individualize propofol dosing.

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