COMPARISON OF 3D RESPONSE SURFACE MODELS: CAN BOUGIE TOLERANCE BE PREDICTED FROM ELECTRIC TETANY?

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Abstract- **Surgical surrogates are often used to determine if there is adequate sedation before starting a procedure. Adapting this process, it was hypothesized that subject response to electrical tetany could be used to predict subject tolerance to bougie placement. Twenty four volunteers were sedated with 15 random concentration pairs of remifentanil and propofol. At each pair, stimuli of electrical tetany and bougie placement were administered. Response surfaces were constructed from the data. Regression analysis was used to predict bougie response from tetany response. Future improvement of the model is needed. However, it is believed an accurate model for predicting patient response to esophageal instrumentation from their response to tetany can be developed.**

I. INTRODUCTION

Modern anesthesia uses a combination of drugs, often an opioid and hypnotic, to achieve the desired analgesia and sedation, respectively. The combined drugs can be treated as a new drug with properties of the constituents, but often modified due to interaction between the drugs. For example, remifentanil (hypnotic) and propofol (opioid), which were used in this study, are newly developed, rapid kinetic anesthetics. When combined, the kinetics are still rapid, but a synergistic interaction occurs, thus decreasing the dosing requirements needed to obtain a given effect compared to if each drug were used individually.

Due to the rapid kinetics and synergistic interaction, the combination of these drugs is becoming increasingly common. With the increasing trend in healthcare of moving towards outpatient care, an increasing number of non-anesthesia trained clinicians are administering anesthetics. These clinicians may not be familiar with how these new drugs interact and therefore may be overdosing their patients, placing them in risk of experiencing respiratory depression and airway obstruction, something the clinician may not have the equipment and training to recognize and respond to appropriately. In the operating room, surgical surrogates are often used to determine if there is adequate sedation before starting surgery.

The motivation for this study was to apply this approach to a common out-patient procedure: esophageal instrumentation. It was thought that response to electrical tetany, a common and readily available surrogate, could be used to predict subject tolerance to bougie placement. Doing so should lead to less discomfort during the procedure, reduced risk, and faster recovery time for the patient.

† The STANPUMP program, written by Steve Shafer, can be downloaded for free from http://anesthesia.stanford.edu/pkpd

II. METHODS

Following approval by the Human Institutional Review Board at the University of Utah Health Sciences Center (Salt Lake City, Utah), informed written consent was obtained from 24 male and female (non-pregnant/non-lactating) volunteers. All volunteers were American Society of Anesthesiology (ASA) class I or II, at least 18 years of age and within 25% of ideal body weight. Volunteers with a history of significant drug or alcohol abuse, adverse reaction to opioids or sedative hypnotics, or other medical condition determined to present unacceptable risk by the principle investigator, or member of vulnerable subject groups were not eligible.

Volunteers were required to fast for a period of 8 hours before the study. An intravenous catheter was placed for drug and fluid administration. An arterial catheter was placed for blood pressure monitoring and blood sampling. Bispectral index (BIS), pulse oximetry, ECG, expired CO_2 and abdomen and chest excursion were also monitored. Surface electrodes were placed on the left posterior tibial or ulnar nerve for application of electrical tetany. Before drugs were administered, subjects were treated with 0.2 mg of glycopyrrolate to prevent bradycardia, and 30 mL of sodium citrate.

Volunteers received fifteen escalating target controlled infusions of propofol and remifentanil over ranges of 0-4.2 μg/mL and 0-6.4 ng/mL respectively (Fig. 1) administered by a computer assisted infusion pump (Pump 22, Harvard Apparatus, Limited, Holliston, MA) controlled by STANPUMP† software. Target doses were randomly determined from a crisscross study design.[1]

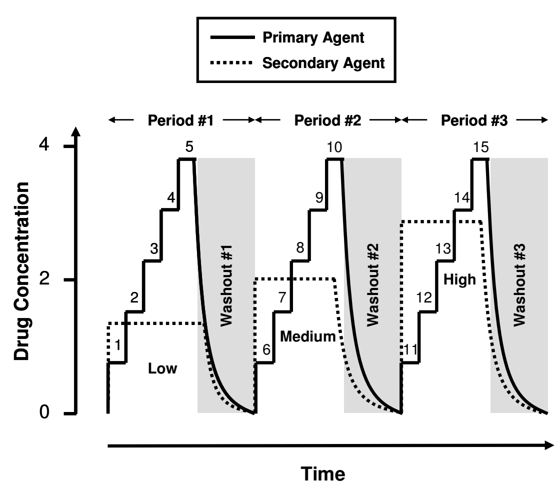


Figure 1. Each subject received 15 unique dosing combinations of remifentanil and propofol. The study was broken into three runs of five trials. One of the drugs was held constant while the other was increased.

Five minutes after the predicted effect site concentration reached the desired concentration, five assessments were made. Sedation was measured using the Observer's Assessment of Alertness/Sedation (OAA/S) score. A five minute CO_2 rebreathing challenge was then introduced, followed by a five minute recovery. Finally, responses to pressure algometry, electrical tetany and esophageal instrumentation were measured. Pressure algometry consisted of applying increasing pressure to the right shin using a 1 cm diameter piston up to a max of 50 psi or until the subject withdrew or signaled discomfort. Electrical tetany was gradually increased from 0 mA to a max of 50 mA or until the subject withdrew or signaled discomfort. For esophageal instrumentation, a 1.4 cm diameter blunt end bougie (215542, Teleflex Medical, RTP, NC) was used to mimic an endoscope or transesophageal echocardiography probe. Mid-esophageal insertion was attempted (approximately 40 cm), stopping if the subject signaled discomfort or gagged. For all stimuli, a response was also defined as a greater than 20% increase in heart rate or blood pressure from baseline.

Response surfaces were generated for tetany and bougie stimuli using the Logit construct (Eq. 1).[2] Response surfaces are essentially least-square fits to actual data using the chosen model's equation, but in three dimensions. The minimizing and building of the surfaces are accomplished in MATLAB (Math-Works, Inc., Natick, MA). This approach predicts the probability of patient response to a given stimulus (Emax) at any drug combination but, of course, is most accurate within the ranges tested.

$$Effect = \frac{1}{1+e^{(\beta_0-\beta_1 \cdot C_p-\beta_2 \cdot C_r-\beta_3 \cdot C_p \cdot C_r)}} \qquad (1)$$

There are an infinite number of drug combinations that would result in the same observed effect. This "equal-effect" line is known as an isobol curve, and is generally distinguished by the probability of no response it represents (Z-axis). For example, the C_{50} and C_{95} isobols are the lines showing all drug combinations where 50% and 95% of the population would not respond, respectively.

Response surface shape depends on the number of data points above and below Emax. Prediction of bougie tolerance from tetany response is greatly simplified if both response surfaces have similar shape. Therefore, a tetany Emax was chosen that yielded a response surface similar in shape to the bougie surface.

Once surfaces were built, a simple linear regression approach was used to relate predicted tetany response to predicted bougie response (i.e. the surfaces). However, it would be of greater clinical relevance to relate actual tetany response to actual bougie response. Therefore, various multiple regression models containing multiple predictors were also investigated using SPSS (SPSS, Inc., Chicago, Il). Additional predictors explored include drug concentrations, age, height, weight, gender, body surface area (BSA) and lean body mass (LBM).

(A)

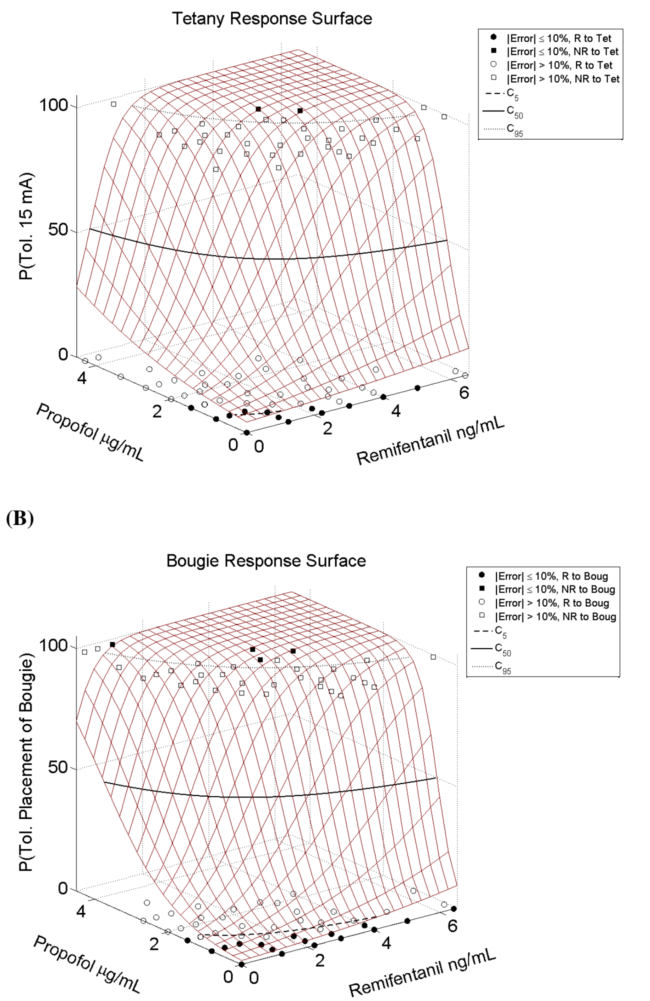


Figure 2. (A) Tetany response surface for Emax of 15 mA. All measurements greater than or equal to 15 mA without a 20% increase in heart rate or blood pressure from baseline are shown as 100, while all others are showed as 0.

(B) Bougie response surface. Bougie was considered tolerated if it was placed mid-esophageal (~40 cm) without subject discomfort, as indicated by the subject raising their hand, gag reflex, coughing, or greater than 20% increase in baseline heart rate or blood pressure.

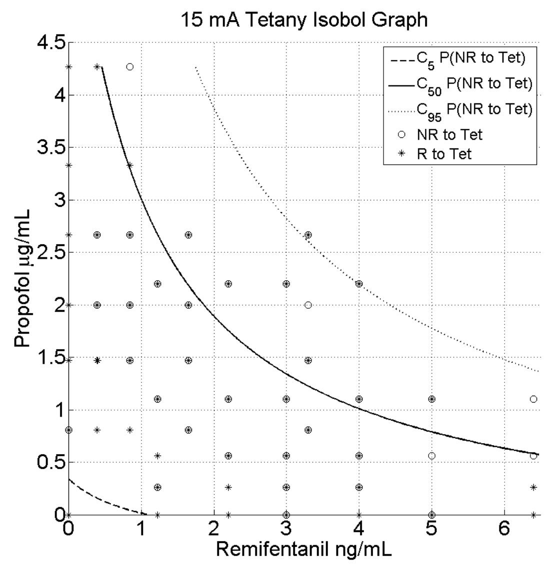
The interaction model was used to plot the remifentanil-propofol drug combinations necessary to result in a 5% (dashed line), 50% (solid line) and 95% (dotted line) probability of tolerating 15 mA. These are known as the C_5, C_{50} and C_{95} isobols. Circles and 'R' mark a response, squares and 'NR' indicate no response data points. Solid symbol = absolute error between the model predictions of no response and the observed responses less than or equal to 10%, Open symbol = absolute error between the model predictions of no response and the observed responses greater than 10%.

III. Results

Response surfaces were generated for tetany and bougie stimuli (Fig. 2). The tetany response surface is for an Emax of 15 mA, as it appeared to give a surface with a shape most similar to the bougie surface. In addition, C_5, C_{50} and C_{95} isobol graphs were also used to verify the similarity (Fig. 3). The selection was made based on visual inspection only.

Predicted responses for tetany and bougie were calculated using the Logit equation (Eq. 1), the respective optimized beta coefficients, and the actual propofol and remifentanil concentration pairs tested in the study. The data analysis add-in in Excel 2003 (Microsoft Corporation, Redmond, WA) was used to compute the linear regression, with predicted tetany response as the x-values and predicted bougie response as the y-values. The regression equation (Eq. 2) is plotted in Figure 4. The R^2 of the fit is 0.958 while the standard error is 5.8%. BR and TR are bougie and tetany response, respectively.

(A)



(B)

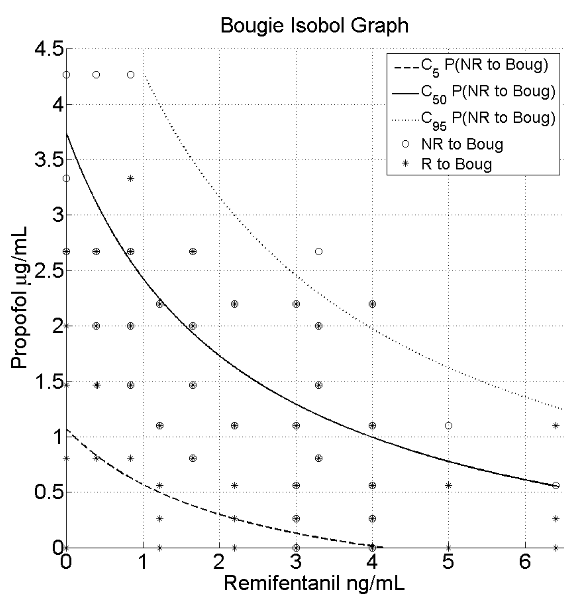


Figure 3. (A) Tetany isobol curves for Emax of 15 mA. (B) Bougie isobol curves surface. The interaction model was used to plot the remifentanil-propofol drug combinations necessary to result in a 5% (dashed line), 50% (solid line) and 95% (dotted line) probability of tolerating 15 mA. These are known as the C_5, C_{50} and C_{95} isobols. Stars indicate a subject response, circles indicate no response.

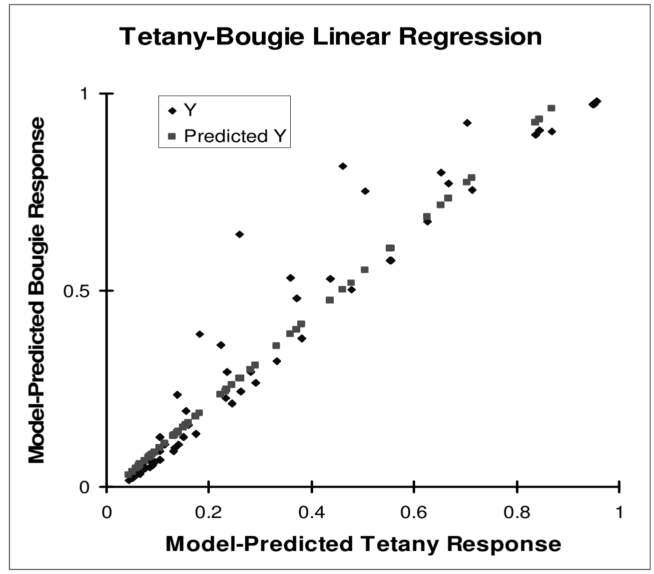


Figure 4. Result of linear regression. The equation was found to be $\hat{y} = 1.125*x - 0.018$, with an R^2 of 0.958. Logit-model tetany effect is plotted along the X-axis, and bougie effect along the Y-axis (shown as diamonds). Regression-predicted Y values are plotted as squares.

$$BR = 1.125 * TR - 0.018 \quad (2)$$

The linear regression shown in Figure 4 is a prediction using, as inputs, other predictions. It would be much more clinically relevant to use a patient's actual tetany response to predict actual bougie response. Therefore, eleven models were tested (Table 1), from which model 2 was selected as the best. The R^2 of this fit equation (Eq. 3) was 0.439. C_R and C_P are remifentanil and propofol concentrations, respectively.

$$BR = 0.4*TR + 0.08*C_R + 0.191*C_P - 0.222 \quad (3)$$

Table 1. Multiple regression models calculated in SPSS. Different predictors were used to find a correlation between actual tetany response and actual bougie response. Model 2 performed the best. Pred. 1 = Predictor 1, etc. Act. Tet is the actual tetany response (0 or 1). Cr is remifentanil concentration. Cp is propofol concentration. BSA is body surface area; LBM is Lean Body Mass (both calculated in STANPUMP)

	Pred. 1	Pred. 2	Pred. 3	R^2	Std. Err
1	Act. Tet			0.328	0.367
2	Act. Tet	Cr	Cp	0.439	0.336
3	Act. Tet	Gender		0.331	0.366
4	Act. Tet	Weight		0.330	0.367
5	Act. Tet	Height		0.331	0.366
6	Act. Tet	Age		0.333	0.366
7	Act. Tet	BSA		0.331	0.366
8	Act. Tet	LBM		0.332	0.366
9	Act. Tet	LBM	Height	0.332	0.367
10	Act. Tet	LBM	Gender	0.332	0.367
11	Act. Tet	LBM	Age	0.335	0.366

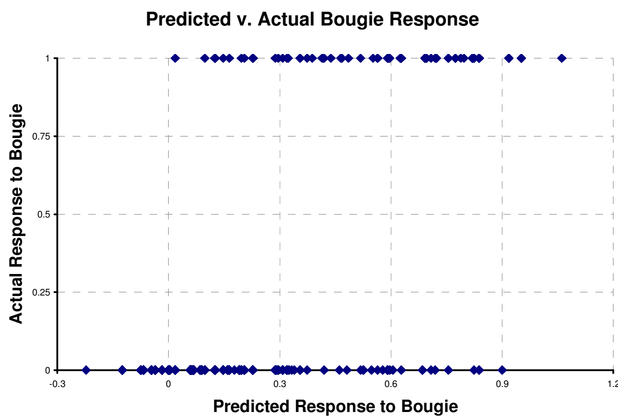


Figure 5. Multiple regression prediction of bougie response compared to actual bougie response. Actual response (Y-axis) is binary (0 or 1), while predicted response (X-axis) is continuous. The graph indicates poor predictive ability by the model. For example, for Y=0, there are many points predicted above 0.5. Similary, for Y=1, many points are predicted below 0.5.

Figure 5 shows actual bougie response plotted against predicted bougie response from equation 3. Actual bougie response is binary (0 or 1) while predicted response is continuous. Significant overlap of the predicted values is observed when the actual response is 0 compared to when it is 1. Also, because the predicted values are continuous, a determination must be made for when the predicted value indicates a response.

IV. DISCUSSION

It is possible to calculate Logit model predicted bougie response from Logit model predicted tetany response for this data set using the linear regression equation (Eq. 2). However, The Logit model itself has been calculated from all the data using a least-squares approach. Therefore, equation 2 really only predicts the average response; it works best on the "average" patient. However, there is huge variability between individuals. Knowing the average response is not useful when treating an individual. It is much more desirable to have a model that, with the appropriate inputs, can accurately predict an individual's response.

To this end, various models were run through SPSS' multiple regression tool. Covariates were selected that were thought to increase the predictive capability of the model. The selected covariates were metrics that were unique to each volunteer and therefore hopefully able to correlate to bougie response. Unfortunately, an accurate model was not able to be found. The plot of actual verse predicted response (Fig. 5) shows large errors in the predicted response. The current model is not acceptable for the intended use. Either other or more predictors need to be added to improve the model. All predictors in model 2 were significant ($p < .001$).

The models investigated did not include any interactions – a possible source of improvement. Additionally, the tetany response surface was built using an Emax of 15 mA. It may be helpful to use the percent increase from baseline instead of the raw mA value. This approach is also susceptible to errors introduced by approximation – the predicted response is continuous. None of the results actually equals 1, so a determination must be made to whether the predicted response is 'close enough'. One solution would be to develop rigid criteria for interpreting the result. Better would be to have an equation that has a binary output.

V. CONCLUSION

Similar response surfaces for esophageal instrumentation and tetany can be constructed by selecting an appropriate tetany Emax. Comparison of the response surfaces suggests tetany is the strong stimulus, meaning that Emax does not need to be particularly high for the surfaces to be similar.

Linear regression provides an accurate relation between the two response surfaces, but does not provide the needed individual accuracy. This is because both the surfaces and the linear regression use a least-squares approach, each time fitting to the average value.

Preliminary results from the multiple regression analysis suggests that, with additional work, an accurate model for predicting patient response to esophageal instrumentation from their response to tetany can be developed. Future work will focus on identifying possible covariates and interactions that were not considered in this study. Once an accurate model has been developed, validation studies will be conducted on other data sets, both volunteer and simulated, to further test and improve the model.

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