Because most GI clinics do not have anesthesiologists available – placement of an ultrasound probe in the mid-gastrointestinal tract is not always possible (or advisable) in all patients. There is an increased risk of complications from these procedures in patients with a history of peptic ulcer disease, previous abdominal surgery, or recent procedures. Procedures performed in these settings increase patient morbidity and mortality.

Pharmacodynamic and pharmokinetic models have been considered in the development of a multiobjective optimization approach to patient-specific dosing schemes. These models include the effect of dosage, concentration, and time on the response of the patient. The models are used to predict the concentration-effect relationship from the onset to the maximal effect. Small changes in drug concentration lead to large changes in drug effect within this range. Similar changes made above or below this region only produce minimal change in effect. These models can simulate the ability to communicate with the patient (loss of responsiveness), respiratory drive (respiratory compromise) and loss of the ability to communicate with the patient (loss of responsiveness).

The optimization process will account for (i) the pharmacodynamic and pharmokinetic models, (ii) the cost of the procedure, (iii) the mechanical capabilities and limitations of the infusion pump delivery systems, (iv) the cost of the equipment, (v) the cost of the anesthesiologist's time, and (vi) the cost of the anesthesiologist's time. The optimization process will also account for (i) the cost of the equipment, (ii) the cost of the anesthesiologist's time, and (iii) the cost of the procedure. The cost function will be developed to combine the multiple cost functions into a single objective optimization problem. The optimization function will account for (i) the cost of the procedure, (ii) the cost of the equipment, (iii) the cost of the anesthesiologist's time, and (iv) the cost of the anesthesia.

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When two drugs are administered, their concentration-effect curves can be combined into a 3D response surface model. Response surface models consist of a set of parameters that estimate the extent of drug interaction (synergistic, antagonistic, or linear), the surface "slope", and the concentration of each drug alone that is required to achieve a 50% probability of maximal effect.

Response surface models provide a three dimensional visualization of combined drug effects (Fig 2) across various dosing schemes. Response surfaces may be a useful tool in identifying ideal concentration pairs that meet patient analgesic needs yet avoid adverse effects, thereby improving patient safety.

Control theory and drug delivery

Control systems often need to consider multiple conflicting objectives in the pursuit of a real world optimal solution. This can be expressed mathematically by the simultaneous minimization of a set of objective functions, \( \phi_k \) where \( k = 1, 2, \ldots, n \) and \( n \) is the number of objectives. (equation 1).

\[
\min \left( (d)\phi_{\cdot\cdot\cdot}(d)\phi(d)\psi \right)
\]

Generally, no single solution exists that optimally satisfies all objectives simultaneously. However, a set of equally efficient (Pareto-optimal) solutions does exist. A decision process is used to select a suitable compromise solution from this set. The methods used to solve control problems often include the use of multi-objective optimization algorithms. This can be achieved through mathematical modeling of the system of interest, followed by the simulation of various scenarios and the evaluation of the results.

For this study, the anesthetics are propofol and remifentanil. The variable vector for each the four objectives includes the amount of each drug that is delivered as a bolus and as an infusion. Time is the variable to be minimized in each objective.

Generally, no single solution exists that optimally satisfies all objectives simultaneously. However, a set of equally efficient (Pareto-optimal) solutions does exist. A decision process is used to select a suitable compromise solution from this set. The methods used to solve multi-objective optimization problems fall into three general classes:

1. a priori – an aggregating function is used to combine all objectives to a single value (scalarization) using weighting coefficients, priorities or goals prior to optimization
2. a posteriori – the Pareto-optimal set is presented to the decision maker before any preference is made
3. progressive articulation – an iterative process between the decision maker and the optimizer is used.

Figure 1. An example of a single-drug pharmacodynamic model. The curve shows the probability of no response to a given concentration of drug. The C50 isobol represents the concentration of drug that results in a 50% probability of a response.

Figure 2. A surface showing loss of responsiveness as a function of drug concentration. The solid line represents the C50 isobol, or the combination of drugs that would result in a 50% probability of a response.
METHODS

Clinical experience suggests that the depth of sedation and analgesia required to blunt the response to esophageal instrumentation through the oropharynx is significant and often leads to a loss of responsiveness. With the response surface models for esophageal instrumentation, moderately painful stimuli, respiratory compromise and loss of responsiveness, we will explore through simulation the ability of various dosing schemes to blunt the response to esophageal instrumentation and once instrumented, be quickly titrated to provide adequate analgesia and sedation for a moderately painful stimulus while minimizing loss of responsiveness. We hypothesized that dosing schemes exist to meet these clinical goals.

To model deep sedation, weights coefficients to be combined in the aggregate objective function (equation 3).

We will use a panel of experts (i.e. board certified anesthesiologists) to develop a set of consensus statements that will be used to prioritize the objectives using a modified Delphi technique. Weighting coefficients will be based on the relative importance of each objective to the provider. The response surface models will then be used to develop a set of objective functions that will be used to optimize the dosing regimen. This study will follow the "a priori" approach to converge on an optimal dosing scheme for a given patient demographic. Weighting coefficients will be used to adjust the influence of each objective in the aggregate objective function (equation 3).

\[
\sum_{k=1}^{n} \omega_k \phi_k \leq \eta
\]

In the first iteration, the objective function was selecting runs where the patient would not have tolerated esophageal instrumentation, evidenced by having negative times for criteria 1. Obviously, the procedure cannot occur if the probe is not inserted. Therefore, this target must be converted to a constraint – it absolutely must be reached.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>( \omega_k )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to 95% Esophageal Instrumentation</td>
<td>0.3</td>
</tr>
<tr>
<td>Time above 95% Esophageal Instrumentation</td>
<td>0.05</td>
</tr>
<tr>
<td>Time to 50% Respiratory Compromise</td>
<td>-1</td>
</tr>
<tr>
<td>Time above 50% Respiratory Compromise</td>
<td>0.1</td>
</tr>
<tr>
<td>Time above 95% 30 psi</td>
<td>0.05</td>
</tr>
<tr>
<td>Time above 95% Loss of Responsiveness</td>
<td>0.1</td>
</tr>
<tr>
<td>Time to 5% Sedation</td>
<td>0.1</td>
</tr>
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### Table 2

<table>
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<tr>
<th>Model</th>
<th>Remi C50</th>
<th>Prop C50</th>
<th>Alpha</th>
<th>n</th>
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<tr>
<td>Esophageal Instrumentation</td>
<td>27.8</td>
<td>4.0</td>
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<td>3.4</td>
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<tr>
<td>Loss of Responsiveness</td>
<td>33.1</td>
<td>2.2</td>
<td>3.6</td>
<td>5.0</td>
</tr>
<tr>
<td>Sedation</td>
<td>12.5</td>
<td>1.8</td>
<td>5.1</td>
<td>3.8</td>
</tr>
<tr>
<td>Respiratory Compromise</td>
<td>5.4</td>
<td>2.8</td>
<td>2.8</td>
<td>6.0</td>
</tr>
</tbody>
</table>

### Table 1

<table>
<thead>
<tr>
<th>Time to 95% Loss of Responsiveness</th>
<th>Time above 95% Loss of Responsiveness</th>
<th>Time to 50% Respiratory Compromise</th>
<th>Time above 50% Respiratory Compromise</th>
<th>Time above 95% 30 psi</th>
<th>Time above 95% Loss of Responsiveness</th>
<th>Time to 5% Sedation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
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<td>0.0</td>
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<td>0.0</td>
</tr>
</tbody>
</table>

(3)
Table 3. Constraints added to multiobjective optimization to ensure the
results will lead to successful procedures.

In the second iteration it was noticed that the new "top"
simulations were not keeping patients sufficiently
anesthetized after probe insertion for them to tolerate the
procedure. In other words, the patient would be able to
tolerate placement of the probe but drug levels would soon
drop, causing them to respond to the placed probe. This was
evident by having negative times for criteria 7 (see Table 2).
Correcting this required an additional constraint for wakeup
time. Constraints are listed in Table 3.

Following these modifications, the 6,615 simulated dosing
strategies were sorted by their aggregate objective function
criterion (score). The top five results are shown in Table 4 as
well as Figure 3.

Table 4a. Dosing information for the top 5 simulations selected by the
aggregating objective function. (score).

Table 4b. Times (in minutes) used by the aggregating objective function
to determine a score for each simulation.

V. DISCUSSION
The peaks for the five selected doses look reasonable.
However, there might not be enough time above the
esophageal instrumentation isobole (EI) to ensure the
clinician has sufficient time to place the probe. This
constraint has sufficiently modified to place just those doses
that are above the 95% esophageal instrumentation isobole
for some minimum amount of time.

A second concern is that the maintenance infusion (the
infusion rate that remains once the bolus effect has worn off)
is still probably too low for someone to tolerate a placed probe. However, additional data collection
is necessary to determine what the minimum effect site
concentration must be for patients to not respond to a placed
probe. Once this isobole is built, an additional constraint can
be added to the aggregating objective function ensuring that
the selected doses do not fall below this target.

Another possible solution is to establish a minimum
infusion rate. As seen in Table 4a, the doses currently being
selected have a propofol infusion rate of 20 mcg/kg/min.
Adding a constraint requiring a minimum of, for example, 50
mcg/kg/min could yield the same result without requiring
additional data collection. It would still be necessary to
determine the minimum rate necessary to ensure patients do
not respond.

A preliminary look at this approach was taken. The results
for the top five simulations selected by the aggregating
objective function are shown in Table 5 and Figure 4.

In comparing Figures 3 and 4, it is interesting that this
time the aggregating objective function selected doses with
significantly lower remifentanil concentrations than
the propofol infusion rates. The times for criteria 6 and 7
are also higher than those listed in Table 4b. However,
the propofol infusion rates are significantly lower than those listed in Table 2.

Criteria Constraint
Time to 95% Esophageal Instrumentation >0
Time to 5% Sedation >1

Figure 3. Plot showing the isoboles for the optimization
targets as well as plots of the top 5 dosing simulations as
determined by the aggregating objective function. Markers represent whole minutes.

The bolus dose causes the peak while the infusion holds the subject at a
steady concentration. The duration of the procedure is shown above the isoboles. Text boxes show the score of the associated plots.
Table 5a. Dosing information for the top 5 simulations selected by the aggregating objective function (score) after a constraint has been added requiring a minimum propofol infusion rate of 50 mcg/kg/min. The bolus sizes are larger, as are the propofol infusion rates. However, the remifentanil infusion rates are significantly lower.

<table>
<thead>
<tr>
<th>Score</th>
<th>Bolus mg/kg</th>
<th>Infusion mcg/kg/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.19</td>
<td>1.2</td>
<td>50</td>
</tr>
<tr>
<td>4.21</td>
<td>1.47</td>
<td>50</td>
</tr>
<tr>
<td>4.36</td>
<td>1.6</td>
<td>50</td>
</tr>
<tr>
<td>4.37</td>
<td>1.33</td>
<td>60</td>
</tr>
<tr>
<td>4.39</td>
<td>1.2</td>
<td>50</td>
</tr>
</tbody>
</table>

Table 5b. Times (in minutes) used by the aggregating objective function to determine a score for each simulation. The times for criteria 6 and 7 are generally higher than those in Table 4b, a natural result of using higher infusion rates.

<table>
<thead>
<tr>
<th>Criteria # (from Table 2)</th>
<th>Score</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
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<tbody>
<tr>
<td></td>
<td>4.19</td>
<td>1.33</td>
<td>1.83</td>
<td>1.50</td>
<td>8.00</td>
<td>4.67</td>
<td>4.00</td>
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<td></td>
<td>4.21</td>
<td>1.50</td>
<td>1.50</td>
<td>2.00</td>
<td>7.67</td>
<td>4.33</td>
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<td>7.67</td>
<td>3.83</td>
<td>5.67</td>
<td>5.67</td>
</tr>
</tbody>
</table>

VI. CONCLUSION

These results show promise for the development of a multiobjective optimization approach to patient-specific selection of dosing schemes. Additional work is needed to determine applicable weighting coefficients and constraints.

ACKNOWLEDGEMENTS

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REFERENCES