A Model for Determining a Patient-specific Oxyhemoglobin Dissociation Curve

Kyle M. Burk, Joseph A. Orr

Abstract*— <u>Introduction</u>: The oxyhemoglobin dissociation curve describes the relationship between the partial pressure of oxygen and the percent of hemoglobin saturated with oxygen. This relationship is a sigmoidal shaped curve. The oxyhemoglobin dissociation curve varies from patient to patient. If patient variability could be determined patient specific oxygen flow rates could be delivered. We have developed a model for characterizing patient specific variations in SpO2. Our model predicts saturation by generating a patient-specific oxyhemoglobin dissociation curve. The purpose of this study was to determine the effectiveness of our patient-specific model. <u>Methods:</u> We Probed SpO2 level at various oxygen inhalation amounts to provide input to our model. We linearized the relationship between SpO2 and EtO2 for each participant. We then fit a line to those linearized data points. We used model fit error techniques to show the ability of the model to fit volunteer and patient SpO2. Fit results were generated by using the fitted patient specific curve shift to estimate oxygen concentrations. Fit errors were used to assess the model's ability to fit SpO2 and to make an accurate patient specific oxyhemoglobin dissociation curve . <u>Results:</u> Thirty subjects participated in our volunteer study. The nominal average line is quite close to the standard curve. The cumulative density plot of the model fit error for the entire data set in our volunteer study and the average for each volunteer had greater accuracy than the standard fit. Sixty patients participated in our clinical trial. The nominal average line is quite different than the standard curve. The cumulative density plot of the model fit error for the entire data set in our clinical study and the average for each patient both had greater accuracy than the standard fit. <u>Discussion:</u> This study has shown that our model is able to fit patient saturation values with higher accuracy compared to using the standard oxyhemoglobin dissociation curve. We have also shown that the variability of the ODC from patient to patient is quite large, making predicting patient saturation quite difficult. We have developed and tested a model for fitting the oxyhemoglobin dissociation curve to patients. We have shown improved fit when compared to the standard oxyhemoglobin dissociation curve. This model could potentially be used to predict time to desaturation specific to a patient.

***Index Terms*—Oxyhemoglobin Dissociation, Model Fit Validation, Patient-specific Modeling**

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I. INTRODUCTION

The oxyhemoglobin dissociation curve (ODC) describes the relationship between the partial pressure of oxygen and the percent of hemoglobin saturated with oxygen [1]. This relationship is a sigmoidal shaped curve that typically reaches a plateau at a partial pressure of oxygen (P_{O_2}) of 70 mm Hg and then slowly approaches 100% saturation [2]. Below 70 mmHg the ODC has a sharp decline (Figure 1). The plateau of the ODC means for that portion of the curve large changes in P_{O_2} result in small changes in saturation while the sharp decline means that small changes in P_{O_2} result in drastic changes in saturation, which can be life threatening (Figure 2).

Monitored anesthesia care can result in drug-induced respiratory depression and subsequent desaturation [3]. For this reason, supplemental oxygen is often given to increase P_{O_2}. However, too much supplemental oxygen can delay the time until respiratory depression is noticed. Recognition that high levels of oxygen may impair detection of hypoventilation by pulse oximetry has led to the recommendation by some that oxygen should not be administered during monitored anesthesia care [4-6]. While this may be effective, low levels of oxygen can lead to frequent hypoxic episodes and decrease the alveolar oxygen reserve available at the time of a patient emergency.

Oxygen saturation is measured using pulse oximetry. Pulse oximeters determine oxygen saturation based on differences in light absorption in tissues and both venous and capillary blood [2].

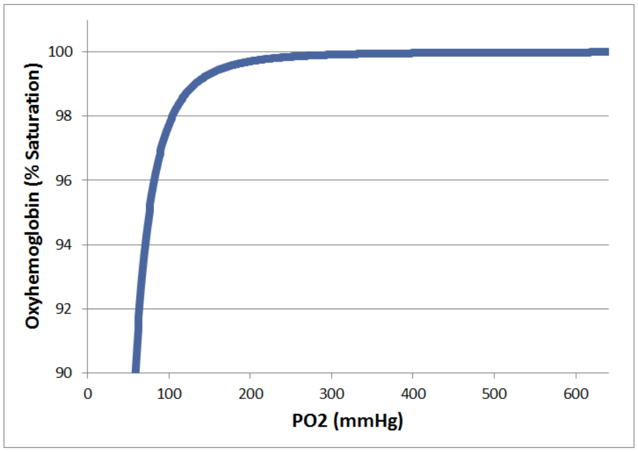

Figure 1: The oxyhemoglobin dissociation curve, a sigmoidal shaped curve which reaches a plateau and slowly approaches 100% saturation typically at a partial pressure of oxygen of 70 mmHg. Below 70 mmHg the ODC has a sharp decline.

The characteristics of the ODC mean that at higher values PO_2 can drop for several minutes without any indication by pulse oximetry. Then as PO_2 continues to drop to lower values pulse oximetry drops abruptly.

The ODC varies from patient to patient depending on the values of different parameters (pH, T, PCO2, [DPG]) and these variations affect the position of the ODC but not the shape (Figure 3) [7]. The effect on position changes the PO_2 at which the ODC plateau transitions to the sharp curve. Thus patient-to-patient variability adds difficulty in determining at which PO_2 a patient's saturation will begin to decline rapidly.

Patient variability and limitations to pulse oximetry make measuring saturation using existing methods difficult. Maintaining sufficient levels of saturation is challenging because the response of a given individual to a particular oxygen flow rate is unpredictable. The accuracy of pulse oximetry, which ranges from ±2% to 4%, limits its utility as an indicator of alveolar oxygen concentration [8]. Because of this error combined with the nature of the ODC, high SpO_2 could indicate a wide range of PO_2, and give no indication as to how close to the steep portion of the curve a patient's saturation is (Figure 4).

If patient variability could be determined, and a patient specific ODC could be generated, the transition from plateau to sharp curve could be characterized and patient specific oxygen flow rates could be delivered and thus prevent saturation. Patient-specific model-based oxygen delivery could prevent hemoglobin desaturation while maintaining low enough oxygen levels for pulse oximetry to provide warning of respiratory depression. One possibility for determining patient variability is to create a model which can use a subset of saturation values to fit a patient specific ODC. We have developed such a model based on an oxygen delivery system we have developed and tested previously [9, 10].

We have developed a model for characterizing patient specific variations in SpO_2. We have identified patient specific variations by characterizing a patient specific ODC. Determining a patient specific curve relying solely on SpO_2

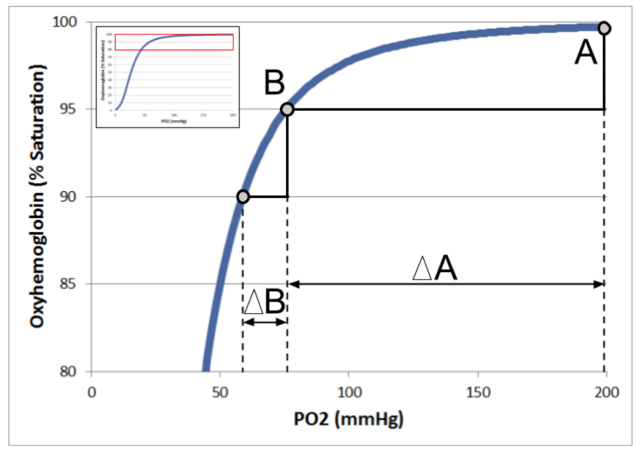

Figure 2: The plateau of the ODC means for that portion of the relationship large changes in Po_2 (ΔA) result in small changes in hemoglobin saturation while the sharp decline means that small changes in Po_2 (ΔB) result in drastic changes in hemoglobin saturation.

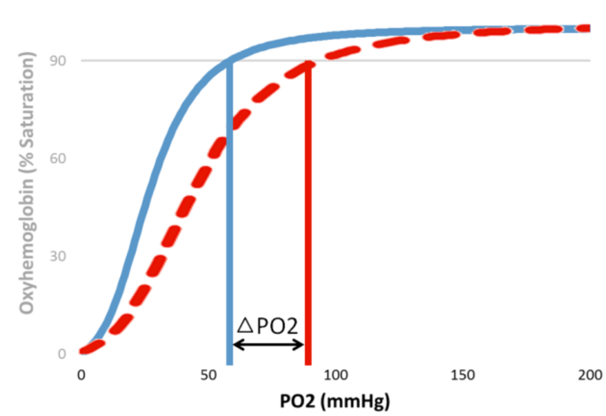

Figure 3: The ODC varies from patient to patient depending on the values of 4 parameters: concentration of the hydrogen ion (pH), temperature (T), partial pressure of carbon dioxide (PCO2), and concentration of 2,3-diphosphoglycerate ([DPG]). These variations affect the position of the ODC but not the shape. The effect on the position changes the location of the transition from the ODC plateau to the sharp curve.

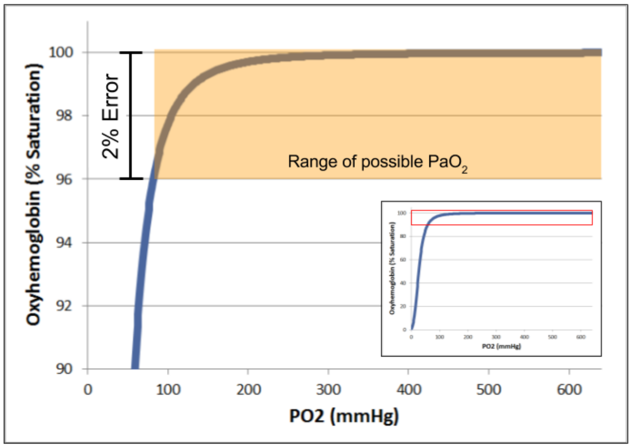

Figure 4: The accuracy of pulse oximetry, which ranges from ±2% to 4%, limits its utility as an indicator of alveolar oxygen concentration. Because of this error band combined with the nature of the ODC, high SpO_2 could indicate a wide range of PO_2, and give no indication as to how close to the steep portion of the curve a patient's saturation is.

could add value to pulse oximetry and provide a non-invasive way to determine a patient's curve.

Our model predicts saturation by generating a patient-specific oxyhemoglobin dissociation curve. The model automatically adapts to patient variability. Such a model could also help determine the minimum amount of oxygen necessary to maintain satisfactory oxygenation as considerable hyperoxia also has negative effects in some patients [11].

The purpose of this study was to determine the effectiveness of our patient-specific model. A model-based and patient specific approach to supplemental oxygen delivery could characterize patient variability and thus provide oxygen delivery specific to a patient's needs [12]. This approach would provide the ability to keep a patient saturated sufficient enough to provide time for intervention while still reducing fire hazard.

II. Methods

Study approval and risk determination came from the University of Utah Institutional Review Board. All volunteers and patients participated in this study with written informed consent.

A. Theory

The ODC is described using Hill's equation:

$$SHbO2 = \frac{\left(\frac{PO_2}{P50}\right)^n}{1+\left(\frac{PO_2}{P50}\right)^n}$$

Where P_{50} is the PO_2 at which 50% of hemoglobin are saturated and where n is 2.7 in normal human blood. The ODC can be linearized using natural logarithms as follows:

$$x = Ln[PO2];\ y = \ln\left[\frac{SHbO2}{1-SHbO2}\right]$$

We used this method to linearize the relationship between SpO_2 and EtO_2 for each participant.
For each participant, the values of expected P_AO_2, measured SpO_2, and measured expired oxygen concentration values were used to establish the framework for a specific ODC. To establish a specific ODC, we fit a line to linearized data points and transformed that linear fit back into a patient specific ODC.

B. Volunteer Study

During the study, our prototype system delivered oxygen flows between 0 and 10 L/min. Each flow rate and mode combination was delivered for two minutes. At the end of each two-minute period, oxygen flow was turned off and the expired oxygen was sampled for three breaths.

C. Clinical Study

Supplemental oxygen was given using a nasal cannula throughout the procedure. The protocol called to deliver varying flow rates from 0.4 L/min to 5 L/min. Each flow rate was delivered for 2 minutes. At the end of each two-minute period, oxygen flow was turned off and the expired gas was analyzed using for 3 breaths.

D. Model Validation

We used model fit error techniques to show the ability of the model to fit volunteer and patient SpO_2. Fit results were generated by using the fitted patient specific curve shift to estimate oxygen concentrations. Fit errors were used to assess the ability of the model to fit SpO_2.

To validate our model, we tested the ability of the volunteer developed model to fit data obtained in the volunteer study and clinical trial. Model fit values were compared with actual measurements for error analysis and absolute error was measured.

III. Results

Figure 5 shows representative data from a clinical trial patient. This data is an example of the ability of our model to adapt to the patient specific points. This model adaptation shows how, in this particular patient, oxygen saturation would begin to drop long before the standard ODC predicts. In this patient, oxygen saturation reaches 98% at an end-tidal oxygen value of approximately 50% as compared to the standard curves estimate of a regular end-tidal concentration obtained when breathing room air of 15%.

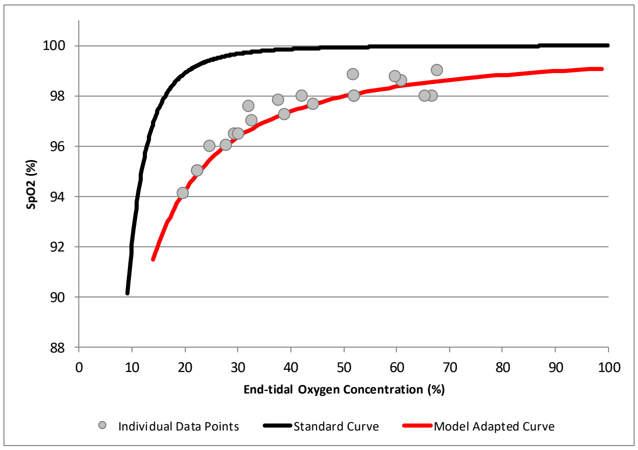

Figure 5: Representative data from a clinical trial patient. This data is an example of the ability of our model to adapt to the patient specific points. The model's adaptation shows how in this particular patient oxygen saturation would begin to drop long before the standard ODC would predict.

A. Volunteer Study

Thirty subjects (14 females/16 males; age: 34 ± 12 years, height: 172.4 ± 10.1 cm, weight: 75 ± 17.6 kg, mean ± SD) participated in this study. All participants enrolled finished the study.

For our volunteer study, the nominal average line is quite close to the standard curve (Figure 6). The standard deviation appears to be larger to the right compared to the left, this is most likely due to the nature of the curve where values approach 100% saturation asymptotically.

For both the whole data set and the average for each volunteer, the model adapted fit (red) showed great improvement over the standard curve fit (black). The cumulative density plot of the model fit error for the entire data set in our volunteer study and the average for each volunteer had greater accuracy than the standard fit. For the model adapted fit, 90% of data points had an error of less than 0.8% while for the standard fit 90% of data points had an error less than 2.0% (Figure 7). The largest average fit error when using our model adapted fit was 0.3% while the largest average standard curve fit was 2.4% (Figure 8).

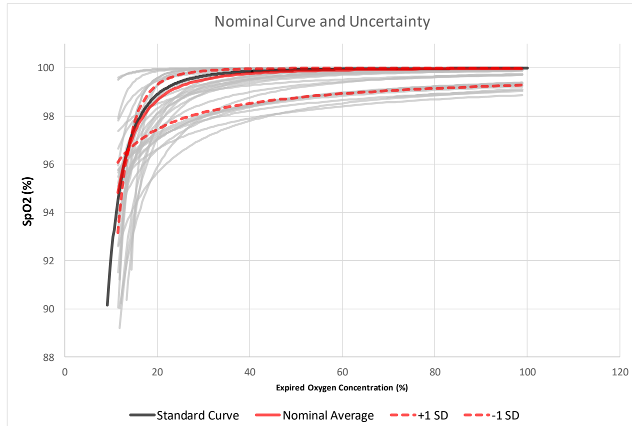

Figure 6: Nominal curve and uncertainty for our volunteer study with 30 healthy volunteers. The nominal average line (solid red) is quite close to the standard curve (solid black). Individual patient curves are shown in gray. The standard deviations shown show a good estimation of the variance in oxyhemoglobin dissociation curves between volunteers. The standard deviation appears to be larger to the right compared to the left, this is most likely due to the nature of the curve where values approach 100% saturation asymptotically.

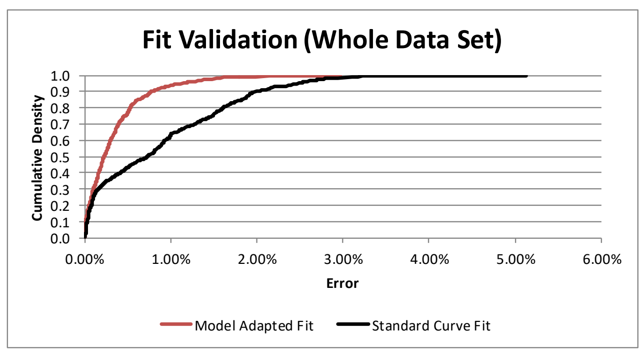

Figure 7: Cumulative density plot of the model fit error for the entire data set in our volunteer study. The model adapted fit (red) shows great improvement over the standard curve fit (black). This plot demonstrates the ability of our model to provide a more accurate estimate of healthy volunteer saturations when compared with the standard oxyhemoglobin dissociation curve. For the model adapted fit, 90% of data points had an error of less than 0.8% while for the standard fit 90% of data points had an error less than 2.0%.

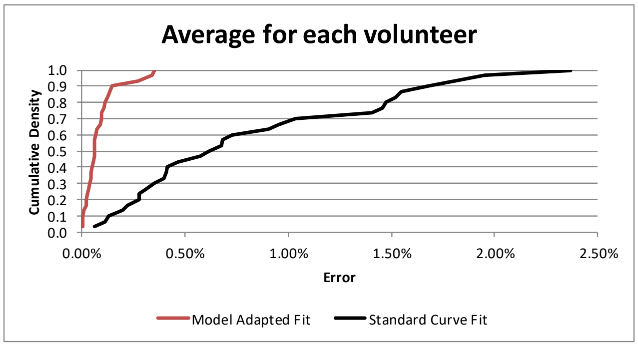

Figure 8: Cumulative density plot of the model fit error for our volunteer study using the average for each patient. The average model adapted fit (red) shows great improvement over the average standard curve fit (black). This plot demonstrates the ability of our model to provide a more accurate estimate of patient saturations when compared with the standard oxyhemoglobin dissociation curve. The largest average fit error when using our model adapted fit was 0.3% while the largest average standard curve fit was 2.4%.

B. *Clinical Study*

Sixty patients (32 females/28 males; age: 66.5 ± 12.7, height: 170.3 ± 12.2 cm, weight: 81.2 ± 19.3 kg, mean ± SD) participated in our trial and all patients completed the study. All patients met eligibility criteria and were recruited between 12/1/16 and 4/14/17.

For our clinical study, the nominal average line is quite different than the standard curve (Figure 9).

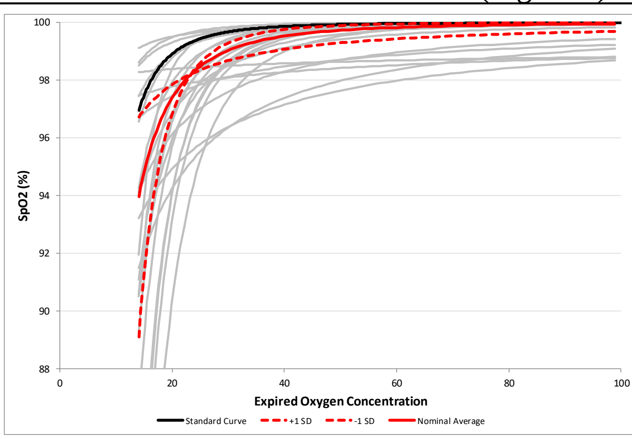

Figure 9: Nominal curve and uncertainty for our clinical study with 60 patients. The nominal average line (solid red) is quite different than the standard curve (solid black). The standard deviations shown show a good estimation of the variance in oxyhemoglobin dissociation curves between volunteers. This nominal curve is a good demonstration of the variability of the oxyhemoglobin dissociation curve from patient to patient and the difficulty of predicting patient saturation levels.

The standard deviations shown show a good estimation of the variance in oxyhemoglobin dissociation curves between volunteers. This nominal curve is a good demonstration of the variability of the oxyhemoglobin dissociation curve from patient to patient and the difficulty of predicting patient saturation levels.

For both the whole data set and the average for each patient, the model adapted fit (red) showed great improvement over the standard curve fit

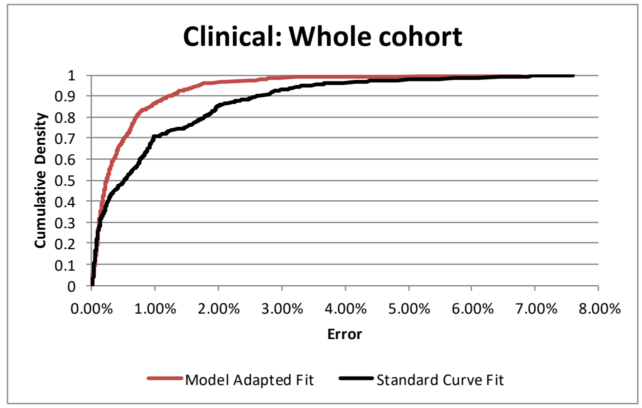

Figure 10: Cumulative density plot of the model fit error for the entire cohort in our clinical study. The model adapted fit (red) shows great improvement over the standard curve fit (black). This plot demonstrates the ability of our model to provide a more accurate estimate of patient saturations when compared with the standard oxyhemoglobin dissociation curve. For the model adapted fit, 90% of data points had an error of 1.3% or less while for the standard fit 90% of data points had an error of 2.6% or less.

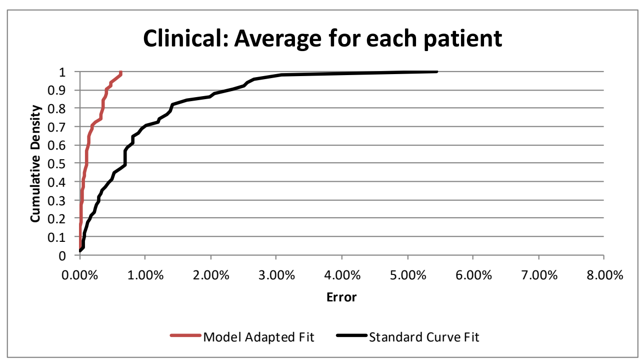

Figure 11: Cumulative density plot of the model fit error for our clinical study using the average for each patient. The average model adapted fit (red) shows great improvement over the average standard curve fit (black). This plot demonstrates the ability of our model to provide a more accurate estimate of patient saturations when compared with the standard oxyhemoglobin dissociation curve. The largest average fit error when using our model adapted fit was 0.6% while the average standard curve fit error approached 5.4%.

(black). The cumulative density plot of the model fit error for the entire data set in our clinical study and the average for each patient both had greater accuracy than the standard fit. For the model adapted fit, 90% of data points had an error of less than 1.3% while for the standard fit 90% of data points had an error less than 2.6% (Figure 10). The largest average fit error when using our model adapted fit was 0.6% while the largest average standard curve fit was 5.4% (Figure 11).

IV. Discussion

This study has shown that our model is able to fit patient saturation values with higher accuracy than when using the standard oxyhemoglobin dissociation curve. We have also shown that the variability of the ODC from patient to patient is quite large, making predicting patient saturation quite difficult.

Our results demonstrate the ability of our model to provide a more accurate estimate of healthy volunteer and patient saturations when compared with the standard oxyhemoglobin dissociation curve. These accurate estimates could help determine a patient's specific ODC and thus define where on the PO_2 scale the patient's SpO_2 would start to drop drastically.

We experienced large variations in the relationship between PO_2 and SpO_2 in both volunteers and patients. The larger variation in the relationship in patients could be attributed to the fact that the patients underwent sedation and experienced lower minute volume. The variation could also be attributed to the difference in age between the volunteers and patients. This variation can be quite difficult to predict and our model shows an initial step toward understanding and predicting these differences.

Although our model was able to fit patient data values within the range measured, we did experience unusual behavior beyond the ranges we tested. The model results would at times cross over from the right side of the standard ODC to the left side or vice versa. This behavior has not been experienced in clinical data and may be caused by a number of things including the ±2% error span of SpO_2 measurements and noise.

Future directions for this research include using a subset of patient data to create a model fit and subsequently using that model fit to predict remaining patient saturation values. This type of technique would make acquiring the patient-specific ODC less cumbersome as only a small amount of sample points would be needed to characterize the curve.

Once clinically validated, our model would increase the utility of pulse oximetry measurements when saturation is >98%. Future validation would include predicting patient saturation for a range of levels of supplemental O_2.

A future use for this model would be to combine the model with other existing models to simulate and predict O_2 saturation and time to apnea in patients with varying levels of respiratory drive. Predicting the course of SpO_2 for a given amount of time could help explore and experiment with simulations on different clinical scenarios that may not be safe to study in volunteers or patients.

In summary, we have developed and tested a model for fitting the oxyhemoglobin dissociation curve to patients. We have shown improved fit when compared to the standard ODC. This model could potentially be used to predict time to desaturation specific to a patient.

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