Measures of Entropy and Change Point Analysis as Predictors of Post-Surgical Adverse Outcomes*

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***Abstract*— A variety of adverse outcomes, such as kidney injury, death, cardiac injury, and respiratory failure affect a significant number of patients after surgery. Previous research has investigated possible predictors for these outcomes including features extracted from physiologic time series. This study builds upon this previous work by exploring entropy, long-term memory, and change point analysis as different and possibly predictive measures of volatility. To do this, we use both random forest models and the robust method of L_1 regularized logistic regression as modeling frameworks for the prediction. Predictive results from these models are evaluated using receiver operating characteristic (ROC) curves and their area under the curve (AUC) values. While the developed models did not show improvements in predictive accuracy, they did show that change point analysis and measures of entropy and long-term memory can be useful tools in predicting post-surgical adverse outcomes.**

I. INTRODUCTION

Anesthetized surgeries can have a variety of adverse outcomes, ranging from renal damage to death. Studies done by [1], [2] show that for different types of surgeries, the post-surgical death rate is between 1% and 3%. Studies [2] [3] have shown that factors, such as blood pressure, dosage of anesthesia, and surgery length are correlated with post-surgical adverse events. More recent studies [4] and [5] have increased the number and variety of predictor variables and have shown promise in terms of their predictive accuracy.

These more recent studies use perioperative data collected at the University of Virginia (UVA) Hospital on anesthetized patient surgeries since 2009. These data were combined with post-surgical adverse outcomes of patients. This combined data set was used to build mathematical models to predict death, kidney injury, cardiac injury, and respiratory failure [4]. The predictor variables for models were mostly raw or untransformed physiologic data about the patients. The one transformation performed was to several time series from which the researchers extracted statistics.

The work in [5] extended this previous study by examining volatility statistics for the time series as well as time series forecasts. These new predictors did improve forecast accuracy. However, the study [5] only looked at two adverse outcomes: death and kidney injury.

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To further extend these results, the study in this paper investigates information theoretic measures and change point analysis as well as a robust approach to logistic regression to predict death, kidney injury, cardiac injury, and respiratory failure. The information theoretic measures are used since they have been shown in other work to effectively capture volatility in time series [6], [7]. We are interested in determining if these measures can provide more effective representations of volatility than change point analysis. The robust approach to logistic regression will provide protection in the analysis from the inherent noise within the data streams for this important problem. Our goal in this work is to build predictive models that can improve diagnoses, reduce the rate of complications, and possibly provide the foundation for an advisory system to enhance post-surgical medical care.

The next section gives a summary of literature related to predicting post-surgical adverse outcomes and to relevant clinical applications that employ volatility measures from physiologic time series. Section III describes the predictor variables used in building the models and introduces the modeling and imputation techniques employed. Section IV contains results and Section V concludes the paper.

II. LITERATURE REVIEW

A. *Post-Surgical Adverse Outcomes*

Postoperative complications take a variety of forms. The research in this area has generated significant results for acute kidney injury (AKI), death, cardiac injury, and respiratory failure. This section provides brief summaries of this work and pointers to the literature.

AKI, which is associated with increased rates of morbidity and mortality, is a complication of great interest. Age, heart disease, and high-risk surgery have all been shown to have an association with the development of AKI in post-surgery patients [8]. In [9], researchers predicted onset of AKI following cardiac surgery using a collection of preoperative and postoperative variables with only two intraoperative predictors: hemorrhage and cardiopulmonary bypass time greater than 120 minutes. Weir, et al. added that perioperative blood pressure lability, or durations of blood pressure outside an acceptable range, can increase the risk of postoperative AKI as well as postoperative death within 30 days [10].

Postoperative death, another adverse outcome of interest, has been shown to have an association with age and poor lung and renal performance in patients undergoing repair of an abdominal aortic aneurysm [11]. In a study involving geriatric patients undergoing noncardiac surgery, numerous preoperative and intraoperative risk factors were examined for their usefulness in predicting post-surgical adverse outcomes [12]. This study reports that pre-existing conditions were not associated with postoperative outcomes. Additionally, the study in [12] concluded that the severity of preoperative comorbidities was more predictive than intraoperative factors, including durations of hypertension, hypotension, anesthesia; only the presence of invasive monitors and duration of tachycardia, or pulse$>$100 beats per minute, were predictive intraoperative factors of adverse outcomes. These results were confirmed in [13], which stated that preoperative comorbidities were more useful than intraoperative information in predicting adverse outcomes.

In addition to death and AKI, numerous studies investigated postoperative cardiac injury. A study examining atrial fibrillation (AF) after coronary artery bypass surgery (CABG) found that systemic hypertension, male gender, pneumonia, and the need for mechanical ventilation were significant predictors of AF, which is a form of cardiac injury [14]. In a study of patients undergoing noncardiac surgery, researchers found that an early postoperative myocardial ischemia is associated with a 2.8-fold increase in the odds of suffering an adverse outcome and a 9.2-fold increase in the odds of having an ischemic event [15]. Additional studies focused on developing risk indices to predict post-surgical complications from cardiac and noncardiac surgery using a collection of preoperative and historical patient data; however, these either did not include intraoperative information [16] or did not find an association between an adverse outcome and intraoperative variables [17].

Researchers have also tried to identify risk factors for respiratory failure, another post-surgical outcome of interest. Canver and Chanda reported that cardiopulmonary bypass time (CPB), as well as several postoperative factors, increased risk of postrespiratory failure [18]. The study in [19] similarly developed a useful risk index to predict postoperative respiratory failure after major noncardiac surgery. Examining intraoperative factors, Fernandez-Perez et al. found that mechanical ventilation with large intraoperative tidal volume set (TVS) is associated with an increased risk of postpneumonectomy respiratory failure [20]. In another study, Fernandez-Perez et al. reported that TVS and fraction of inspired oxygen, or FiO_2, were not associated with acute lung injury, or ALI [21]. Additional research investigates the risk of ALI in specific circumstances [22], and how to prevent intraoperative lung injury during a cardiopulmonary bypass [23].

B. Volatility of Physiologic Time Series

Physiologic time series provide a major source of input variables for predicting quality in health care. Most of the work done in this area shows that the use of these time series for health applications requires the extraction of different features from those commonly used in economic and engineering applications. For example, low rates of variability or volatility turn out to be significant predictors of critical events as shown in Moorman et al. [24] monitored heart rate characteristics to reduce late-onset sepsis in low birth weight neonatal infants. Other studies have also examined patient physiologic data in an effort to predict the onset of infection or the occurrence of an adverse outcome, such as death. In [25] and [26], heart rate variability was studied in an effort to predict death in trauma patients. Politano et al. [7] studied heart rate, respiratory rate, and other physiologic characteristics to identify evolving respiratory failure in patients in a surgical/trauma intensive care unit (STICU). Each of these studies focused on measuring heart rate variability as a means of predicting or preventing the occurrence of a bad outcome.

Different approaches have been employed in health care studies to extract the different features for heart rate variability. In [25], the volatility in the heart rate was calculated by continuously computing the standard deviation of the heart rate over 5-minute intervals. Moorman et al. [27] used a heart rate characteristic (HRC) index that combines several volatility measures, including the sample entropy of a series, into its predictions. Politano et al. [7] discussed cross-correlation coefficients and summary statistics on heart rate and respiratory rate as they monitored the risk of intubation among STICU patients. Leite et al. [28] applied Fractionally Integrated Autoregressive Moving Average models with Generalized Autoregressive Conditional Heteroscedastic errors (ARFIMA-GARCH) in their differentiation between normal and abnormal subjects.

As noted in Section I this study develops statistical models to predict the post-surgical outcomes of death, kidney injury, cardiac injury, and heart injury using several measures of time series variability. Building on the work reported in this section, these models include measures of entropy, long-term memory, and change point analysis in multiple time series, as well as traditional measures of heart rate variability. Separate from previous research, we apply these predictors using both ensemble and robust techniques in an effort to understand the severity and frequency of adverse complications post-surgery, rather than for the real-time monitoring of patients in an intensive care unit.

III. MODELING AND IMPUTATION

To incorporate volatility measures for the prediction of adverse post-surgical outcomes, we used two modeling frameworks: L_1 regularized logistic regression and random forests. Basic logistic regression estimates parameters by maximizing the likelihood or the log likelihood, given by

$$L(\theta) = \Sigma \log P(y^i | x^i, w) \tag{1}$$

where y is the response vector, x is the vector of predictor variables, and w is the model's weight vector. Usually this objective is maximized by using iteratively reweighted least squares to minimize a squared error loss, or L_2 loss.

Squared error loss is notoriously sensitive to extreme cases. One way to reduce this sensitivity and get more robust parameter estimates is to minimize absolute error, known as L_1. In L_1, the objective function is

$$L(\theta) = \Sigma \log P(y^i | x^i, w) + \beta \|\theta\|_1 \tag{2}$$

[29]. Thus, L_1 regularization uses the sum of the absolute values of the weights as a penalty in the objective function, encouraging smaller, more robust models [30]. To create the regularized logistic regression models, we used the `LiblineaR` package in R [31].

[4] also used L_1 regularized logistic regression but with a subset of the predictors in this study. This subset consists of a combination of demographic factors, such as age, biological sex, race, and location of surgery. Dosages of the following four types of medicines are also included as predictors in the model: emergency medications, bronchodilators, local anesthetics, and cardiovasoactives which raise blood pressure. Finally, [4] used time series predictors from six data sources: blood pressure, fraction of inspired oxygen ($FiO_2\%$), blood oxygen saturation ($SpO_2\%$), tidal volume set (TVS), pulse rate, and temperature. These time series features included the means of the time series as well as descriptors of the autoregressive integrated moving average (ARIMA) model fit to the data. The study in this paper adds to this set of predictors new measures of volatility and variability from structural breaks, conditional volatility, long memory, and entropy, Hence, the results in this paper provide new understanding of the use of a robust modeling technique with these new time series features.

The second modeling framework used here is random forests. Random forests (RF) are groups or ensembles of tree-based classifiers. A tree classier is a model that segments the space of input predictors using boundaries defined by single predictor variables. The goal for a tree is to find subregions of the input space with small variation in the response variable. The root node in a tree represents the initial partitioning and leaf nodes output the predicted response. An ensemble approach, like RF, constructs many tree-based classifiers and then combines their results using voting or some measure of central tendency, such as averaging. To create diversity in the classifiers, random subsets of the predictors are allocated to each tree and the training data are bootstrapped. A complete description of RF can be found in [32].

Both [4] and [5] also used random forests, but as noted above, [4] used only a subset of the variables used here. Additionally, [5] did not include the range of outcomes considered here. So in this paper, we build upon the previous models by adding new predictors to summarize change point analysis and to measure entropy and long-term memory. We impute missing heart rate variability, entropy measures, and memory measures using a mean imputation [33] and all other missing predictor variables using the `missForest` package in R [34].

A. Structural Breaks, Conditional Volatilities, and Long Memory

Structural breaks, or events which denote a change in the structure of a time series, have been examined at length in recent econometric literature [35]. Additionally, structural breaks have been studied in literature on forecasting monthly hospital mortality data [36] and heart rate variability [28]. GARCH models are used to account for nonconstant variances in time series. Thus, structural breaks and GARCH models are often coupled together in time series analyses to examine data with time-dependent variances. An example pulse series with the structural breaks added to the graph is presented in Fig.1. Additionally, ARFIMA(0, d, 0) models, where $0 < d < 0.5$ indicates a slow, hyperbolic rate of decay in the autocorrelation function [37], can be coupled with GARCH models to quantify long-term memory in a time series [28].

In [5], we incorporated both GARCH models and the number of structural breaks in a series as measures of volatility. Previously, we fitted GARCH(1,1) models using the `fGarch` package in R [38], and computed the number of breakpoints using the breakpoints algorithm of the `strucchange` package in R [39], [40]. In this study, we fitted ARFIMA models to the pulse, temperature, blood pressure, and $SpO_2\%$ series using the `fracdiff` package in R [41]. From these models, we included d as a predictor in our models.

B. Approximate Entropy

Numerous studies have examined the use of approximate entropy in physiologic time series. Approximate entropy (ApEn) was developed as a measure of system complexity to distinguish between deterministic and highly stochastic systems [42]. Since it was introduced, it has been developed and studied in multiple applications, including in cardiovascular time series [43]. Sample entropy (SampEn), a variant on ApEn, was developed to correct for the bias inherent in ApEn's dependence on sufficient record length and its lack of relative consistency [44]. SampEn has been widely used in clinical applications to quantify the complexity in different series of heart rate variability [6], [7].

In this study, we used approximate entropy since the calculation of sample entropy required twice as many values to be imputed. We calculated approximate entropy for the pulse, blood pressure, $SpO_2\%$ and temperature time series of each patient and incorporated them as predictors in the models.

C. Change Point Analysis

Change point analysis, or the study of finding notable changes in a time-ordered process, has been studied in various domains, including financial markets, credit card fraud, and bioinformatics [45]. Specifically, Erdman and Emerson applied change point analysis in a study of segmentation in microarray data [46]. Wagner et al. conducted a change point analysis in medication use research as they study segmented regression analysis to estimate changes in processes and outcomes [47]. In the field of physiologic monitoring, Yang et al. constructed an adaptive scheme for change point detection to notify medical staff when respiratory variables exhibited a significant clinical change [48].

In this study, we employed change point analysis to study segmented portions of the physiologic data. Using the `changepoint` package in R, we divided the $SpO_2\%$ and pulse time series into segments of differing variance and differing mean [49]. From these segments, we included the maximum variance, maximum mean, and minimum mean as predictors to account for the variability and magnitude of patients' most extreme periods of surgery.

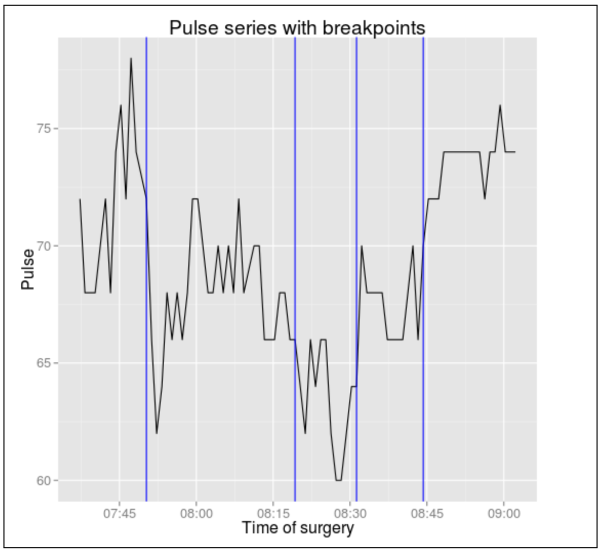

Fig. 1: Example pulse series with breakpoints

IV. RESULTS

We trained our predictive models on a random subset of $\frac{2}{3}$ of the data and tested it on the remaining $\frac{1}{3}$. We evaluated the models using ROC curves and their corresponding AUC values. For the RF models, significant predictors were chosen by examining the importance ratings using the gini criterion [32], but modified using a heuristic to correct feature importance bias in RF models [50]. For the L_1 models, the top nonzero coefficients are provided.

A. *Death*

The ROC curves for the death models are shown in Fig. 2 below. The inclusion of entropy measures, the fractional difference term, and change point analysis summary statistics did not improve AUC; the AUC of .861 for the RF model matches is on par with the AUC shown in [5].

The heuristic used to correct feature importance ratings in RF models, described in [50], normalizes the importances to a [0,1] scale. Table I below presents the predictors for the RF model rated at 0.99 or higher, and the top 12 predictors for the L_1 model in terms of coefficient absolute value.

As shown in Table I, the change point analysis measures of SpO_2% appeared consistently in both models. Specifically, numerous characteristics of the pulse and SpO_2% time series were rated as useful predictors in both of the models. Although we do not see improvement in the AUC of the models for predicting death, these ratings of predictors suggest that intraoperative pulse and blood oxygen saturation could be vital to understanding postoperative death.

To further investigate the relationship between the pulse and SpO_2% series, we created two-dimensional break plots to identify areas of high and low volatility where patients

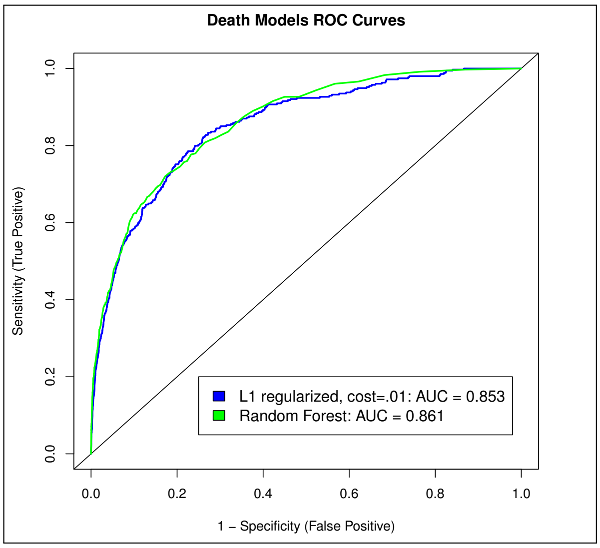

Fig. 2: Death ROC Curves

TABLE I: Significant Predictors for Death

Model	Variables
RF Model	FiO_2% MSE, 30-minute SpO_2 prediction, average TVS, BP below 60, cancer, max pulse variance, 60-minute SpO_2 prediction, SpO_2*BP interaction, FiO_2 AR lags, stroke, FiO_2 average, SpO_2 * temperature interaction, age*BP interaction, BP kurtosis, BP average, SpO_2 median volatility, max SpO_2 variance, temperature MSE, temperature mean volatility, temperature Freq, FiO_2 freq.
L_1 Model	Pulse avg, age*temp interaction, FiO_2% avg, patient age, HRV window below 1.0, Surgery location, heart disease, SpO_2 SD, cancer, average TVS, Surgery length, SpO_2 * BP interaction

are more likely to suffer a post-surgical adverse outcome. Fig. 3 presents the probability of suffering death assuming a patient has experienced the specified number of structural breaks in the pulse and SpO_2% time series. Fig. 4 presents the relative frequency of death segmented by the number of breaks in those series. As shown in Fig. 3, areas of low pulse volatility, characterized by the number of structural breaks, are associated with a higher probability of postoperative death; however, most incidents of postoperative death occur in areas of low SpO_2% volatility, as shown in Fig. 4.

B. *Kidney Injury*

The ROC curves for kidney injury are shown in Fig. 5 below. The inclusion of entropy measures, the fractional difference term, and change point analysis summary statistics did not improve AUC; the AUC of .856 is on par with the AUC shown in [5].

The heuristic used to correct feature importance ratings in RF models, described in [50], normalizes the importances to a [0,1] scale. Table II below presents the predictors for the RF model rated at 0.99 or higher, and the top 12 predictors for the L_1 model in terms of coefficient absolute value.

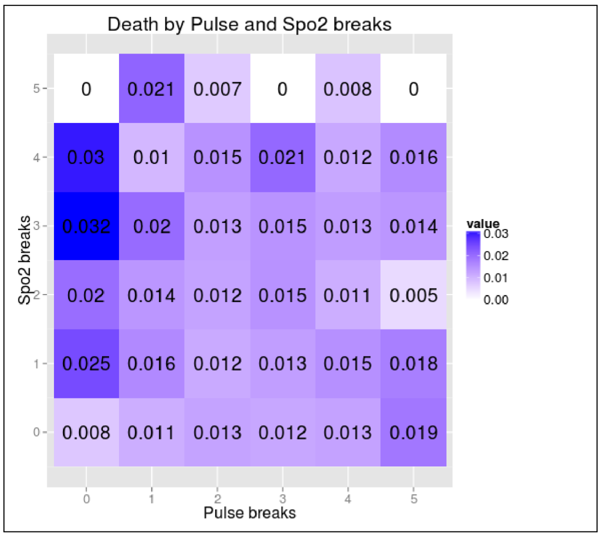

Fig. 3: Death risk map by pulse and $SpO_2\%$ breaks

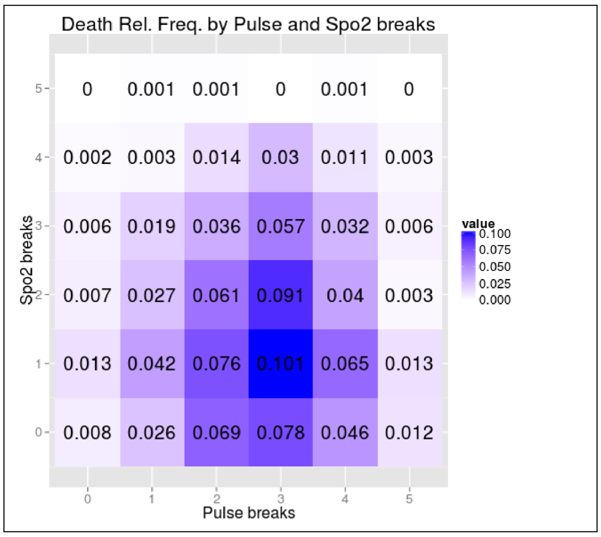

Fig. 4: Death relative frequency by pulse and $SpO_2\%$ breaks

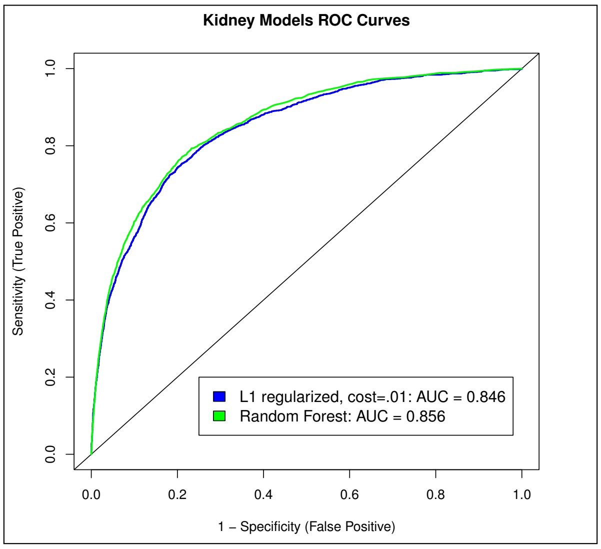

Fig. 5: Kidney Injury ROC curves

As shown in Table II, the change point analysis measures and the entropy measures appeared as important in the RF model. Specifically, the RF model focused on the pulse and $SpO_2\%$ series as important towards predicting kidney injury. The L_1 model, however, lists surgery location as well as a variety of different measures as significant predictors. Although we do not see improvement in the models for predicting death, these ratings of predictors suggest that intraoperative pulse and blood oxygen saturation, as well as surgery location, could help understand postoperative AKI.

TABLE II: Significant Predictors for Kidney Injury

Model	Variables
RF Model	Pulse start-end difference, TVS AR lags, max pulse variance, pulse AR lags, diabetes, max TVS mean, max $SpO_2\%$ volatility, $SpO_2\%$ Standard deviation, Surgery location, mean temperature volatility, Fractional BP term, mean pulse volatility
L_1 Model	Surgery location, age*temp interaction, SpO_2 * pulse interaction, male gender, TVS freq, average $FiO_2\%$, $SpO_2\%$ max variance, diabetes, HRV below 0.5, patient age, heart disease, average BP

C. Heart Injury

The ROC curves for heart injury are shown in Fig. 6 below. The inclusion of entropy measures, the fractional difference term, and change point analysis summary statistics did not improve AUC from the study in [4].

As described above, Table III below presents the top predictors for the RF model rated by corrected importance and the top 12 predictors for the L_1 model in terms of coefficient absolute value.

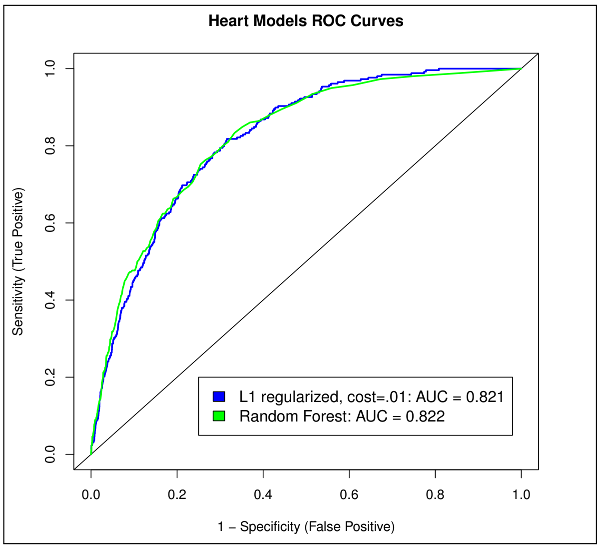

Fig. 6: Heart Injury ROC curves

As shown in Table III, the change point analysis measures and the entropy measures appeared as important in the RF model. In the RF model, $SpO_2\%$ and pulse change point analysis and pulse and temperature entropy were particularly important; in the L_1 model, SpO_2 maximum variance and the fractional difference term in the temperature series were useful. Although we do not see improvement in the models for predicting cardiac injury, these ratings of predictors suggest that variability in the series of TVS, pulse, temperature, and SpO_2% could add insight into predicting postoperative cardiac injury.

TABLE III: Significant Predictors for Heart Injury

Model	Variables
RF Model	Patient age, pulse entropy, 30-minute TVS prediction, age*bp interaction, TVS AR lags, Pulse maximum variance, heart disease, Surgery location, SpO_2% * pulse interaction, SpO_2% * temp interaction, Pulse start-end difference, patient race, age*temp interaction, pulse MSE, max temp volatility, SpO_2% max variance, SpO_2% max volatility, FiO_2 MSE, SpO_2% start-end difference, BP Freq, temperature entropy, 30-minute pulse forecast
L_1 Model	Age*temp interaction, TVS Freq, SpO_2*pulse interaction, Surgery location, heart disease, BP MSE, average pulse, BP time below 55, SpO_2% max variance, SpO_2 MA lags, average TVS, Temp frac. diff.

Similar to the death model, we investigate the relationship between the pulse and SpO_2% series using two-dimensional break plots. Fig. 7 presents the probability of suffering cardiac injury assuming a patient has experienced the specified number of structural breaks in the pulse and SpO_2% time series. Fig. 8 presents the relative frequency of death segmented by the number of breaks in those series. As shown in Fig. 7, risk of postoperative heart injury increases marginally with additional breaks in pulse. Most incidents of postoperative heart injury occurs in areas of low SpO_2% volatility, as shown in Fig. 8.

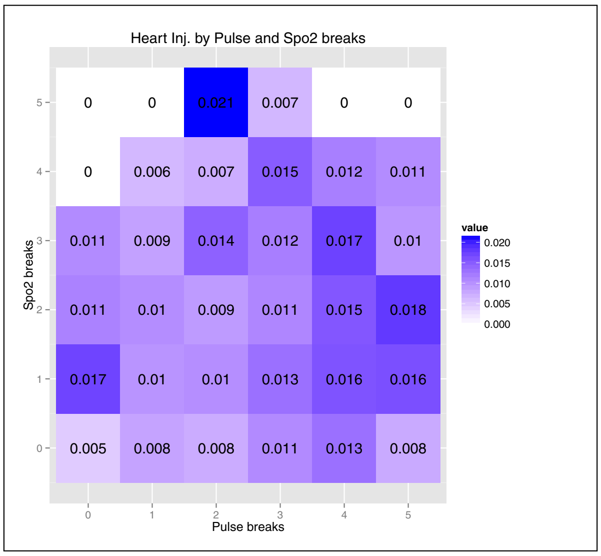

Fig. 7: Heart inj. risk map by pulse and SpO_2% breaks

D. Respiratory Failure

The ROC curves for respiratory failure are shown in Fig. 9. The inclusion of entropy measures, the fractional difference

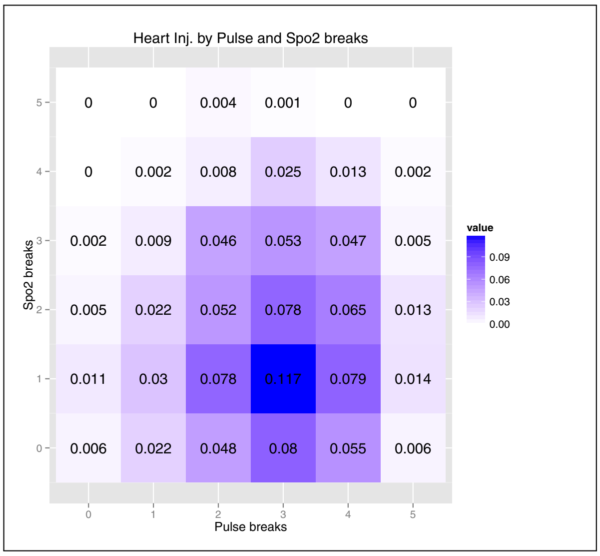

Fig. 8: Heart inj. relative frequency by pulse and SpO_2% breaks

term, and change point analysis summary statistics did not improve the AUC shown in [4].

As described above, Table IV below presents the top predictors for the RF model rated by corrected importance and the top 12 predictors for the L_1 model in terms of coefficient absolute value.

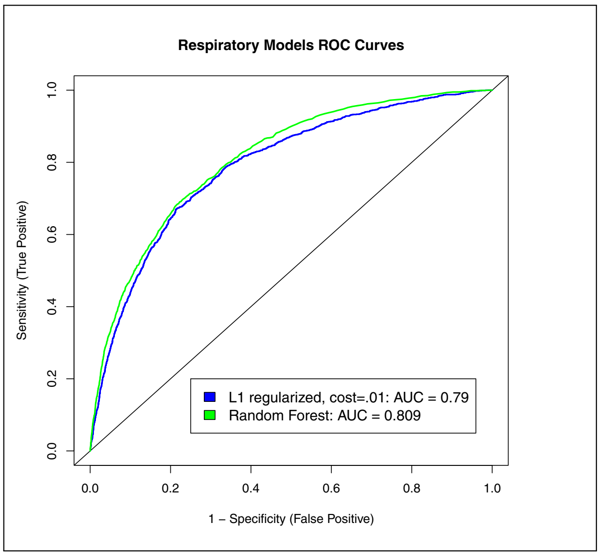

Fig. 9: Respiratory ROC curves

As shown in Table IV, the change point analysis measures appeared as important in the RF model. In the RF model, pulse change point analysis and numerous measures of blood pressure were particularly important; in the L_1 model, SpO_2 maximum variance and the fractional difference term in the blood pressure series were useful. Although we do not see improvement in the models for predicting respiratory failure, these ratings of predictors suggest that variability in the series of pulse, blood pressure, and SpO_2% could add insight into predicting postoperative respiratory injury.

TABLE IV: Significant Predictors for Respiratory Failure

Model	Variables
RF Model	TVS MA lags, pulse max variance, emergency medication dose, BP MA lags, previous stroke, TVS Freq, SpO_2*pulse interaction, cardiac vasoactive upper dose, mean pulse volatility, $SpO_2\%$ * BP interaction, 30-minute TVS forecast, Skewness of BP volatility $SpO_2\%$ max volatility, $FiO_2\%$ average, cardiac vasoactive upper dose, 30-minute BP forecast, BP kurtosis, BP kurtosis of volatility, BP mean volatility
L_1 Model	Average pulse, surgery length, average $FiO_2\%$, Age * temp interaction, Surgery location, heart disease, HRV below 1.0, Max $SpO_2\%$ variance, average temperature, local anesthetics dose, $SpO_2\%$ * bp interaction, BP fractional difference term

V. CONCLUSION

This paper described models to predict onset of post-surgical adverse outcomes using a variety of perioperative physiologic data. Building on results in [4] and [5], we add measures of entropy, long-term memory, and change point analysis to models that predict postoperative death, kidney injury, cardiac injury, and respiratory failure. Results suggest that these additional predictors did not improve the performance of these models, as measured by AUC; however, several of these predictors were important within the models themselves. For instance, maximum pulse variance and maximum $SpO_2\%$ variance, two predictors derived from change point analysis, repeatedly emerged as important portions of the analysis. Therefore, pulse and $SpO_2\%$ during surgery warrant additional research, as several derivatives of these time series appeared to be useful predictors with regards to every outcome.

We also graphically depicted the volatility in these series by segmenting the occurrence of adverse outcome by the number of breakpoints that occurred in the series. This representation of patient physiologic data could be particularly useful to anesthesiologists and medical staff, as it can inform them how the risks of adverse outcome change as patients' physiologic data exhibit different levels of volatility. This depiction also provides insight regarding the creation of variables which can improve the performance of predictive models.

Further research should investigate additional measures of low heart rate variability in predicting post-surgical adverse outcomes; for example, minimum variance within a change point may be crucial to understanding these events. Additionally, a holistic evaluation of the results indicates that certain time series may be more correlated to specific outcomes than others. For example, blood pressure predictors abounded in the respiratory model, suggesting that blood pressure may be an object of further consideration with regards to respiratory failure. Studying specific series with regards to specific outcomes may narrow the analysis, enhancing efforts to predict these adverse events.

Lastly, one might consider different modeling frameworks for this problem. Other supervised learning methods, such as support vector machines and neural networks, may prove useful for improving the AUC of the models.

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