A Computational Model for Prediction of Cardiac Arrest Outcome Using a Large Multi-Center Database

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Contributions:
As a group, we each contributed to and revised all sections of the paper. We also met multiple times a week to update each other on progress, and provide suggestions on how to tackle challenging problems and move forward in our individual tasks. Therefore, each member is knowledgeable and involved in all parts of the project, and made contributions to the proposal in numerous ways. However, the following describes each member's specific focus on the project, and the contributions to the initial proposal outline and presentation.
Tatiana Gelaf Romer - Drafted entire project background and significance section, and contributed to innovation section. Created innovative graphics and presented information for slides 4-6 in presentation. Currently, focusing on extracting GCS labels and time series data from nurse charting (taken manually).
Qingchu Jin - Drafted time-series data part of the aim 1 in proposal, and worked on and presented the aim 1 slides in presentation. Currently, conducting some time-series data preprocesses. This includes significant denoising and detecting potential clinically implausible data.
Han Kim - Focused on detailing the significance and innovation in proposal. Wrote the details of the project aims as well as the numerical and categorical data description, problems and approach in the pre-processing section. Put together and presented Aim 3 TTM slides. Currently looking at locating the subset of TTM patients by analyzing Temperature time series data. Also extracted and organized initial rhythm data. Currently looking at initial categorical encoding methods to convert initial diagnosis data into meaningful numerical data
Hieu Nguyen - Proposal: thoroughly described feature space and label space, wrote all supervised learning-related portions in the Approach section, drafted the timeline. Presentation: problem introduction slide, significance slide, backup appendix slides. Project: have been extracting and cleaning non-time-series data, such as patient demographics, physical exams, hospital information, lab tests, intubation/ventilation, etc.; also have been merging data, by creating a big data sheet that maps each cardiac arrest patient to their outcome (label) and their corresponding values for the static variables.
Sharmila Tamby - Drafted description of Aim 3 and explanation of unsupervised learning in proposal. Created informative diagrams on supervised learning techniques and Aim 2 for the presentation. Currently analyzing time series data to investigate clinically implausible data and calculate correlations.

Project Background

Problem: Cardiac arrest (CA) is a leading cause of death and poses a significant risk of long-term neurological impairment. Currently, clinicians have no reliable method of predicting neurological outcomes of CA patients soon after Intensive Care Unit (ICU) admission. This leads to mismanagement of resources, patient family expectations, and treatment options. ICU patient physiological data is continuously monitored from the moment of admission to the ICU. This data can be leveraged to provide clinicians with a probability of poor patient outcomes as well as a likelihood of positive response to treatment, informing the patient care plan within 48 hours of patient ICU admission. Specifically, Targeted Temperature Management (TTM) is a treatment that is commonly used on post-cardiac arrest patients. While this treatment has been shown to significantly improve both survival and neurological outcomes [1,2], there are also several potential complications that may arise from inducing hypothermia [3]. Currently, there is no way to tell if the patient will benefit from TTM before administering it.

Importance: Approximately 80% of patients resuscitated after cardiac arrest do not immediately regain consciousness. These patients may be in coma for hours, weeks, or in some instances remain in a persistent vegetative state [1]. As critical care resources grow increasingly scarce, physicians require a more consistent, quantitative method of deciding the best treatment regime for a specific patient. Knowing the future recovery probability of a patient will aid physicians in their decision making, providing an increasingly confident and accurate precision care for patients. In addition, providing accurate expectations of outcome for family members early on is undeniably of great value. Finally, it is clinically meaningful to be able to identify the specific subtype of patients that will respond favorably to TTM. This will optimize patient care so that TTM is administered only when it is likely the patient will benefit from it, and patients who are not likely to respond favorably are not put at risk to its complications.

Prior Work/Challenges: There have been many attempts to understand which biomarkers are most predictive of neurological outcomes following cardiac arrest [4, 5]. These biomarkers generally rely on static features such as Glasgow Coma Scale (GCS) score at a set time after the cardiac arrest event, age, EEG activity, biochemical markers, or neuroimaging features [6]. However, none of these features have been proven to be reliable predictors of patient outcome. Certain independent predictive models have been developed: the APACHE score attempts to give a quantitative prediction of long-term neurological outcomes. However, it fails to incorporate physiological time-series data. Lack of access to robust clinical data, as well as the noisy and inconsistent nature of patient records, has likely hindered the use of large-scale patient data for the creation of a predictive model.

Opportunity: Despite the challenges, an overwhelming wealth of patient records from the ICU provides many great opportunities for innovation. Our team will use the eICU multicenter database, which consists of time-series, numerical, and categorical data for 240,000 ICU admissions spanning over 200 hospitals across the U.S.. Of these, approximately 5800 patients have suffered from a cardiac arrest event. Depending on the progress and success of this project, there are opportunities to gain access to the full database of over 2 million patients.

Approach: By leveraging the sheer volume of available patient records, we hope to denoise time-series data and interpolate missing values for all features. Subsequently, we plan to use statistical learning methods on selected features to classify predicted patient outcomes. Features are derived by using supervised and unsupervised learning on the available short-term physiological and static data. GCS at discharge, the best available surrogate of neurological outcome in the eICU database, will represent our label space.

Impact: It is estimated that continuing aggressive care for high-risk, comatose patients after day 3 of a coma results in a cost of $140,000 per quality-adjusted life-year (QUALY) [7]. In contrast, the cost for low-risk, comatose patients is $87,000 per QALY [7]. In helping the clinician better understand the risk of patient recovery, we may better inform their treatment plan, reducing the financial burden on patient families and insurance providers. In addition to this financial burden, family members of vegetative patients often suffer acute distress and anxiety, often culminating in psychological crises [8]. Many psychological disturbances are caused by the uncertainty of the afflicted patient's outcome, which may be mitigated by a predictive model.

Project Aims

Aim 1 (Data preprocessing and data exploration): Aim 1 will focus on preprocessing the numerical, categorical, and time series data in the eICU database to determine which features may serve as strong biomarkers in classification tasks of determining recovery probabilities in cardiac arrest (CA) patients. Once the feature space and label space are determined and preprocessed, unsupervised learning will be performed on randomly selected features to search for unknown features that may serve as biomarkers and identify clinically meaningful patient subtypes. While unsupervised clustering is being conducted, supervised learning will also be conducted to determine feature ranking and the optimal number of features to be utilized in our prediction algorithm.

Aim 2 (Prediction of favorable Cardiac Arrest recovery outcome): Aim 2 will focus on identifying the statistical method that will provide the most robust classification results based on the previously defined feature and label space. Using this method, a predictive algorithm will be created that yields a probability of favorable short-term neurological recovery using data limited to the first 48 hours of hospital admittance.

Aim 3 (Early prediction of favorable recovery outcome if TTM is administered): Aim 3 will focus on finding the subset of patients who have undergone TTM treatment. Data available within the first 6-8 hours of hospital admittance (the most effective time frame to administer TTM) will be used to determine features indicative of favorable TTM outcomes as an early warning to administer TTM to CA patients.

Significance

Cardiac arrest (CA) is a serious disorder affecting more than half a million people in the United States per year. In addition to being a leading cause of death, CA poses a significant risk of long-term disability due to the risk of hypoxic-ischemic encephalopathy (HIE), damage to the brain due to lack of oxygen, among survivors [9,10]. Over the past several decades, the rates of meaningful recovery from CA have steadily increased, partially due to more timely and effective treatments [11]. A particularly impactful advance is a treatment known as targeted temperature management (TTM) in which mild hypothermia is induced in the patient. This treatment may reduce the extent of neurological damage that occurs in HIE and has been associated with improved long-term neurological outcomes in CA patients [1-2,12]. By cooling the patient's body after resuscitation, reperfusion injury due to inflammation and free radical production is suppressed, thereby reducing cell death and injury to the brain and vital organs [2]. However, TTM is not beneficial for all patients, as inducing hypothermia, if not beneficial, is generally poorly tolerated by the patient. Several complications of TTM include are, but not limited to, shivering, risk of atrial and ventricular fibrillation, fever, gastrointestinal dysfunctions [3]. Our goal is to build a predictive model for neurological outcomes of CA patients based on the available ICU data. In addition, we hope to understand which CA patient features indicate a high probability of a positive response to TTM. In order to achieve these goals, we will be leveraging eICU data from over 5,800 CA arrest patients in the eICU database and examining different machine learning algorithms. Our results will have the potential to inform clinicians regarding prognostication and treatment selection to improve long-term survival and meaningful neurological recovery in CA patients.

Innovation

Current widely used patient outcome prediction models include the Acute Physiology and Chronic Health Evaluation (APACHE) and the Sequential Organ Failure Assessment (SOFA) score. Both APACHE and SOFA scores are used to determine the level of acuity and mortality risk of all patients admitted to the ICU. Unlike these two general mortality models, our predictive algorithm will be catered specifically to determine the likelihood of full neurological recovery from cardiac arrest. Unlike the APACHE and SOFA scores, which only incorporate a subset of static features, our model will utilize the previously untapped, highly valuable time series data from ICU bedsides, in addition to utilizing static features and previously unexamined features. We will focus on the first 48 hours of patient physiology after ICU admittance to rapidly determine the likelihood of full neurological recovery. By using this novel approach to create an early prediction algorithm, clinicians and other ICU personnel can be optimally dispatched to better assist those with poor recovery prediction, or to continue monitoring a patient in a coma with a favorable outcome prediction.

Approach

For each aim, we plan to implement supervised learning techniques with consistent feature and label spaces. The feature space will be determined through Aim 1. The label space and usage of supervised learning throughout the project are defined as follows:

Determining Label Space: For the supervised learning task, distinct classification labels are needed. When a CA patient enters the ICU, they have generally undergone resuscitation (AED or CPR) within 2 hours. Generally, the following describes the scenarios of a patient admitted to the ICU due to CA. In the best possible case, the patient revives and sustains no major neurological injury. The patient is then stabilized and monitored until discharge. More commonly, however, the patient sustains hypoxic-ischemic encephalopathy (HIE) and remains in a coma for hours to days. In this case, it is often uncertain whether the patient will die, become vegetative, suffer long-term neurological impairment, or regain consciousness and be able to return to their daily work without poor long-term outcomes. Currently, the most widely used indicators of patient outcome in clinical practice is the cerebral performance categories (CPC) scale. The CPC scale aligns well with the scenarios mentioned above, with a score of 1 and 2 indicating that the patient is able to work, 3 indicating impaired brain function, 4 indicating coma or vegetative state, and 5 indicating that the patient is brain dead [13]. Thus, the CPC score would be an ideal label. However, since CPC is not available in the eICU data, we determined that the most relevant available label variable is the Glasgow Coma Scale (GCS) score at time of discharge.

GCS consists of three subscores (verbal, motor, and eyes) which reflect the level of consciousness of a patient. Often, it is measured at different time points throughout the patient's stay in the ICU. If the time of discharge is greater than the timestamp of the last point of the GCS, we assume that the GCS at time of discharge equals the last recorded GCS. We will begin by using a binary label system: a perfect GCS score of 15 will indicate full recovery, and an imperfect GCS score of less than 15 will indicate some form of neurological impairment upon ICU discharge.

In addition to GCS, we also considered utilizing location of discharge as a label. However, we decided that this was not a reliable label space for various reasons. First, the distribution of discharge locations of patients with total GCS score greater than 10 is the same as those with GCS less than 10. Furthermore, it is difficult to determine whether a location is indicative of the actual state of the patient. For example, a patient discharged to a nursing facility may have suffered severe brain damage, but it is also possible that the patient had already been in a nursing facility prior to ICU admission and is simply returning to their daily life.

Usage of Supervised Learning: All data will be pre-processed and imputed in Aim 1. Supervised learning will then be used to perform feature ranking. The results from aim 1 will inform the feature space for various supervised learning techniques in Aim 2. Data will be split into a training set and a validation set. The training set will be used for model construction and model refinement, which entails choosing the best set of features and estimation of parameters. The validation set will be used to compare model performance, and evaluated by calculating the model's specificity, sensitivity, positive and negative predictive values, and overall accuracy.

Aim 1:

A. Preprocessing eICU database: The overall goal of preprocessing in this aim is to extract useful attributes and features that exist across every patient that can be use utilized as the feature space. Below we have divided the data into three main types: numerical, categorical, and time-series. Patientunitstayid, a unique patient identifier during hospital admittance, will be used to index each patient to their feature space. Before exploring the feature space, unique Cardiac Arrest patient were separated from the dataset.

1. Numerical Data: Numerical data consists of variables that are measured once or very intermittently during a patient's hospital stay. Some initial features that we have identified as important include: age, weight and height (which may be used to calculate BMI), Glasgow Coma Scale (GCS, which includes motor, eye, verbal, and total), blood pH, arterial blood gas (ABG), and a variety of sparse drug infusion records and lab results.

One method of replacing missing numerical data is to use the population mean. Another approach is to create an algorithm that will replace the missing value of one patient with the values of another patient based on the similarity of existing data values. Similarity can be determined via a similarity matrix, spatial distance correlation, or a comparison of feature histograms.

2. Categorical Data: We labeled any variables with character or binary values as categorical data. Several already identified categorical variables that may serve as important biomarkers include: gender, ethnicity, initial cardiac rhythm upon diagnosis, hospital admit source, discharge location, discharge status, intubation/ventilator use, pacemaker use, and medication. Additionally, using the many time offset values that exist per patient, we can identify the location of the cardiac arrest event.

The next step is assigning numerical values to replace character values for use in statistical and machine learning approaches. Unlike numerical data, once a categorical variable is assigned a numerical identifier, the numerical identifier may be interpreted incorrectly as a continuous numeric feature by a statistical or predictive algorithms. Thus, we plan to numerically represent categorical attributes by implementing commonly-used methods, such as One-hot encoding, dummy coding, effect coding, bin-counting, and feature hashing. To ensure correct categorical identifier assignment, we will implement and test at least 2 of the above methods to understand which method will provide the most significant results for a given learning method.

3. Time Series Data: Time-series data in the eICU database are recorded as a windowed median with a 5 minute frequency. The useful time-series data that may influence long-term neurological performance as identified by Drs. Stevens and Storm includes: heart rate (HR), systemic mean, systolic and diastolic blood pressure, respiratory rate (RR), temperature, O_2 saturation by pulse oximeter (SPO_2) and ST variability. Time-series data from the first 48 hours of the ICU stay are extracted because it contains most of the patient information that is valuable for predicting long-term neurological performance.

Time series data can be highly irregular, and the pre-processing step is needed to standardize and impute the data. Three problems that occur are clinically implausible data, missing data, and inconsistency between time-series data and EHR data. In general, we observe two categories of clinically implausible data: data with outliers and data with abnormally low variability.

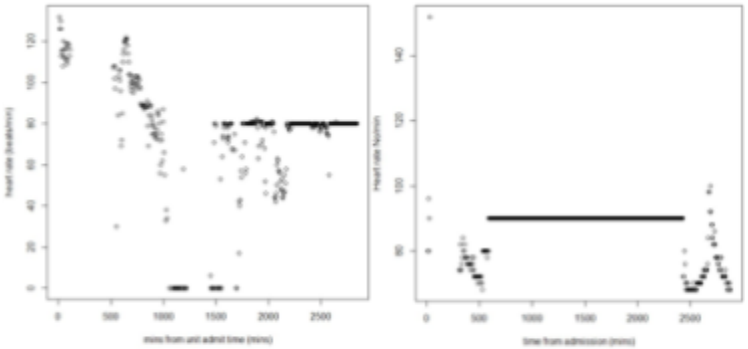

Fig 1. Data problem examples. The left figure shows a possible example of outlier and missing data. The right figure shows a possible example of data with abnormally low variability.

Definitions and approaches for handling clinically implausible data.

a) Outliers: In Figure 1 (left), two distinct intervals with a zero heart rate can be observed. We hypothesize that outliers are either an anomaly (due to a malfunctioning heart rate monitor) or are accurate (due to a patient experiencing a cardiac arrest and needing to be resuscitated). Zero-values that do not return to expected heart rate values may also suggest patient death. There are several possible methods for discriminating outliers that will have to be assessed for specificity and sensitivity. One method is to calculate the sliding window mean and variance for time series data. Within the window, any data point that falls outside of 3 standard deviations from the mean would be considered an outlier and excluded. Another method is to calculate the derivative of the time-series data. Outliers may have a larger derivative so that they are separable by thresholding the derivative. However, there are significant drawbacks to this method. For example, in Fig. 1 (left), for which we would like to identify all of the points with value zero, only the first few points in the anomalous interval will have a non-zero derivative. More information should be involved such as heart rate itself in order to improve its robustness. Moreover, correctly detected outliers may not necessarily indicate an error. Some outliers may relate to a cardiac event, drug infusion, or treatment. Hence, EHR information such as treatment and discharge location should be involved to reduce incorrectly detected errors. A final method of error detection is comparison of variability across different types of time-series data for a given patient. For example, if an outlier at a certain time point is detected in HR data, but all other data behave normally at this time point, we may assume that the anomalous HR data is erroneous.

b) Abnormally low variability: In Figure 1 (right), we observe an interval of approximately 2000 minutes with an unchanging heart rate (90 beats/mins), exemplifying abnormally low variability. Using EHR records of

pacemaker information (HR) or intubation (RR), we may determine if abnormally constant data within a given range (60-80 bpm for heart rate) is plausible. If patients have abnormally constant data but have not been noted to have pacemakers or be intubated, we may infer this is due to a technical error and exclude it.

Definition and possible approach for handling missing data.

The missing data problem can be observed in Fig 1. (left): at ~400 minutes, most of the heart rate data is missing for this patient. This problem may be mitigated for our project due to the fact that our label space describes neurologic performance at ICU discharge, a time-independent variable. As such, we may initially focus on extracting statistical parameters (mean, variance, average slope) of our data, in addition to analyzing potential critical predictive information in the moment-to-moment time points. If the missing data are just one or two points, it is reasonable to interpolate the data. However, if the missing data lasts for more than one hour, the data for a given patient may have to be discarded altogether.

Approaches for inconsistency between EHR data and time-series data.

In addition to the periodic time-series data, nurses may keep irregular records of various patient features such as temperature and blood pressure archived as EHR data. However, there may be severe inconsistencies between EHR data and time-series data for some patients. We plan to incorporate various, related patient data to comprehensively determine which record is more plausible. If it is still insufficient to identify the plausible data, data may have to be discarded altogether.

B. Supervised and Unsupervised Learning

The second part of this aim is to merge all preprocessed data for feature selection using supervised and unsupervised learning. We will start off by including most of the variables at time of admission (for non-time-varying variables, for example: demographics, GCS at admission time, etc.) or the first 48 hours (for time-varying physiological monitoring data). This could result in discovering important predictors that may have been overlooked by clinicians.

1. Unsupervised learning: After preprocessing the clinician-defined subset of features identified in section A, various unsupervised learning methods will be used to identify subgroups in the data. The goal of the unsupervised learning techniques is to identify if clusters that emerge from the data map on to different labels and learn if there are any other interrelationships between different elements in the data. This will reveal the underlying distribution of the preprocessed data, could help identify previously unknown biomarkers, and could inform our definition of the feature space . We will first use principal component analysis to help us identify variance and different sets of variables to pair together to feed into the supervised learning techniques. Next, we will try clustering algorithms, including k-means clustering and spectral clustering.

2. Supervised learning: In this aim, supervised learning algorithms will be used to rank features, as well as to determine the optimal number of features for the prediction model that will be created in aim 2. Once the pre-process step is finished and the data has been imputed, variable frequency for each variable in the feature space will be counted, and all variables available in less than 40% of the CA population will be excluded from analysis. For feature selection, we will first use random forest. One challenging task is to minimize the number of features while maximizing the model's predictive power. Thus, nested random forest will be used to determine the ideal number of features. Random forest will be implemented n times, with n being the number of features. The feature space starts with the most important feature. For each iteration, the next most important feature is added to the feature space. Changes in AUROC will be monitored as a function of the number of features. Should random forest fail, we also plan to assess Multiclass logistic regression with AIC and Lasso regression.

Aim 2: Prediction of favorable CA recovery outcome

After the feature selection step is completed in aim 1, the selected features will be fed into several machine learning and conventional classifiers. These models will accurately classify patients into binary label space to signify neurological recovery. The framework is similar to the one described above for the feature selection task. We will implement commonly used and well-performing classifiers such as: GLM, K-nearest neighbors, random forest, boosting algorithms (AdaBoost, XGBoost, Gradient Boosting), support vector machine, and

recurrent neural networks (Gated Recurrent Unit, Long short-term memory). The model with the best performance (quantified by AUROC) on the validation set will be the final prediction model.

Aim 3: TTM patients

The third aim is to identify which patients are most likely to benefit from targeted body temperature management (TTM). First, we must identify the patients who underwent TTM. Although there is no explicit feature indicating TTM treatment, we have worked with Drs. Stevens, Suarez, and Storm to define TTM treatment as achieving a temperature of 32-36°C for at least 12 hours starting within 6-8 hours of admission to the ICU. As such, we will use temperature time series data to find this patient population. Subsequently, we will track other measures of the patient's recovery throughout the duration of the TTM treatment. Based off of the feature and label space explored in Aims 1 and 2, a model will be built to categorize different physiological features and how they relate to and react to a TTM treatment. Utilizing our results for the previous two aims, we hope to identify distinct physiological features in patients who respond favorably to TTM and use these features to build our model. Overall, the goal is to identify biomarkers that indicate TTM will improve patient outcomes, and build an efficient prediction model to find subsets of patients in whom we can predict a high likelihood of favorable outcome if they receive TTM.

Milestones & Timeline

Aim 1 Breakdown		Up to now	10/15/2018	11/1/2018	11/15/2018	12/1/2018	12/15/2018	1/1/2018
Part 1	**Numerical Data**							
1.1	Isolating data related to CA patients							
1.2	Dealing with Missing Data							
1.3	Organize into cohesive feature space							
Part 2	**Categorical Data**							
1.4	Isolating data related to CA patients							
1.5	Assigning numerical values to categorical data							
1.6	Dealing with missing data							
1.7	Organize into cohesive feature space							
Part 3	**Time series data**							
1.8	Classify data into abnormal vs. missing vs. inconsistent vs. reliable							
1.9	Abnormal data (outliers) preprocessing							
1.10	Abnormal data (strict constant data) preprocessing							
1.11	Investigate missing data problem							
1.12	Investigate inconsistencies between time series and EHR data							
1.13	Organize into cohesive feature space							

Research Aims		NOV	DEC	JAN	FEB	MAR	APR	MAY
AIM 2	**Prediction of CA recovery outcome**							
2.1	Train and refine models:							
	Logistic regression							
	Random forest							
	Boosting algorithms							
	SVM							
2.2	Validate models							
2.3	Try other models (like neural networks), if time allows							
AIM 3	**Prediction of favorable recovery outcome if TTM is administered**							
3.1	Identify patients who experience favorable TTM outcomes							
3.2	Train and refine models							
3.3	Validate models							

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