

Survivability of ICU Patients with Severe Sepsis/Septic Shock

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1 Domain Background

1.1 Overview

Sepsis is a serious, life-threatening condition that is in part responsible for 6% of all deaths in the United States [1]. A septic condition is highly variable in nature. A patient may arrive at the ICU with sepsis or may be diagnosed during the stay. There is no diagnostic test to confirm or deny the existence of such a condition in a patient. It is diagnosed based on the clinical judgment of the physician. Regardless of the cause, the speed at which treatment is administered and the types of treatments are critical in stabilizing a patients blood pressure, body temperature, eliminate infection, and maintain stable cardiac output. Due to the variable and complex nature of the condition a machine learning solution may be able to aid in predicting the severity or survivability of the condition and the effectiveness of potential treatments.

A septic condition is caused by an overwhelming immune response to an infection. White blood cells release an array of chemicals to fight the infection which triggers systemic inflammation, vasodilation, increased permeability of vessels, and intracellular fluid build up. These “leaky vessels” deplete the body of coagulation factors. The increased fluid build-up and decreased blood pressure result in a lack of oxygenation of tissue, known as shock.

If sepsis is not treated quickly or with enough direct care, multiple organ dysfunction can occur which can result in kidney failure, liver failure, heart failure, acute respiratory distress, etc. The speed at which treatment is administered and types of treatments are directly correlated with the survivability of this severe condition. The speed of treatment has been found to be more important than the age of the patient [2]. Each hour of delay in antimicrobial administration over the initial 6 hours is associated with an average decrease in the survival rate of 7.6% [3].

Certain treatments may be highly effective, therefore it is important to pay special attention to several things: the type of infection and type of antibiotics used, the blood pressure and whether or not vasopressors were used, the correct amount of IV fluid provided to the patient. The correct type of antibiotic and appropriate administering of vasopressors can reduce the chance of organ failure and mortality greatly [4].

1.2 Problem

A predictive model would be highly useful for ICU staff and physicians. It would aid in prioritizing patients that are considered “high risk” and as a simple way to stratify patients in clinical research.

Upon patient admittance and initial blood and microbiology tests, patient survivability will be classified over a 30 day period. While survival rates are available long after 30 days, this is the most critical period for surviving a condition such as sepsis/septic shock.

The general strategy for solving this problem will mostly involve feature selection, dimensionality reduction, and data preprocessing. The MIMIC-III dataset has thousands of potential features. It will be key to understand the problem and features that help gauge the progress of sepsis as well as automating feature importance and feature correlation to reduce the dimensionality of the problem.

Test results and vitals from the first 24 hours in the ICU will be used for consideration. Several class features will be considered: gender, bacterial culture classification, antibiotic treatment, etc. Several continuous features will also be considered: blood urea nitrogen levels, age, blood PH, blood lactate levels, creatinine levels, blood pressure, etc.

Depending on the number of features being considered, dimensionality reduction through principal component analysis or linear discriminant analysis may be useful to shrink the feature space.

Several different machine learning models will be trained using available data and their results compared to discover an optimal solution. The four different models are adaptive boosting, extreme gradient boosting, support vector machines, and artificial neural networks.

Both of the boosted algorithms have the ability to handle variance in the data, handle missing values, and have the ability to reduce overfitting with little effort. Both Adaboost and XGBoost are known to be highly efficient and well-performing algorithms. While they perform slightly differently, they employ similar techniques that will be interesting to compare.

Support vector machines are great at handling somewhat small datasets and approximating non-linear functions. This is a go-to model on a dataset such as this and will be a great model to compare the results of the three other models.

Neural networks can form complex relationships between the features that other algorithms are incapable of forming but are therefore much more apt to overfitting. This model is another great comparison since it will likely form the most complex model.

1.3 Metrics

Originally the metric used to gauge the prediction quality was standard classification accuracy.

$$\text{accuracy} = \frac{\text{true positives} + \text{true negatives}}{\text{total datapoints}}$$

However, for a binary classification task with unbalanced data using the area under the receiver operating characteristic curve (AUROC) is a better indication of performance. This is especially the case when attempting to ensure low false negative rates.

The receiver operating characteristic curve represents the performance of a binary classifier as its discrimination threshold is varied. In other words, it shows the tradeoff between increasing/decreasing specificity vs sensitivity.

The area under the ROC curve represents the probability that a binary classifier will rank a randomly selected positive instance higher than a randomly chosen negative one. This can be written as:

$$A = \int_{\infty}^{-\infty} TPR(T)FPR'(T)dT$$

Since it is of higher importance to accurately classify positive instances (patient death), accuracy is of less importance and will be sacrificed for a higher area under the ROC curve. From hence forth, the area under the ROC curve will be denoted as the AUC.

2 Analysis

2.1 Data Exploration

For this study, the MIMIC-III dataset(<https://mimic.physionet.org/>) will be used. This dataset is freely accessible and suggested for use by Udacity. More than 40,000 individual patient entries will be utilized. 1184 patients were admitted with sepsis and thousands more diagnosed by the end of their stay. Most of the focus will be put on the patients admitted with sepsis since there is an associated time of admittance that will allow a standard time frame for feature consideration.

Once input into a Postgres database, there are 20 tables with patient information and 5 dictionary lookup tables. Much of the data is difficult to process due to lack of standardization across multiple source databases(CareVue and MetaVision). Most of the useful information with date-time information associated with it is available in the following tables:

1. **admissions:** Contains information related to a patient's admission. This information includes their hospital stay id, insurance type, date of admission, and suspected diagnosis/condition. An example is provided below. This snapshot of the table has not been manipulated in any way other than selecting patients admitted with sepsis.

row_id	subject_id	hadm_id	admittime	disctime	deathtime	admission_type	admission_location	discharge_location	insurance	language	religion	marital_status	ethnicity	edregtime	edsouttime	diagnosis	hospital_expire_flag	has_chartevents_data
0	458	357	122609	2198-11-01 22:36:00	2198-11-14 14:20:00	None	EMERGENCY ROOM ADMIT	REHAB/DISTINCT PART HOSP	Private	ENGL	NOT SPECIFIED	MARRIED	WHITE	2198-11-01 18:01:00	2198-11-01 23:06:00	SEPSIS	0	1
1	471	366	134462	2164-11-18 20:27:00	2164-11-22 15:18:00	None	EMERGENCY ROOM ADMIT	HOME HEALTH CARE	Medicare	ENGL	CATHOLIC	SINGLE	HISPANIC OR LATINO	2164-11-18 10:52:00	2164-11-18 21:31:00	SEPSIS	0	1
2	96	94	183686	2176-02-25 16:49:00	2176-02-29 17:45:00	None	EMERGENCY ROOM ADMIT	HOME HEALTH CARE	Medicare	CANT	NOT SPECIFIED	MARRIED	ASIAN	2176-02-25 10:35:00	2176-02-25 18:14:00	SEPSIS	0	1
3	20	21	111970	2135-01-30 20:50:00	2135-02-08 02:08:00	EMERGENCY	EMERGENCY ROOM ADMIT	DEAD/EXPIRED	Medicare	None	JEWISH	MARRIED	WHITE	2135-01-30 18:46:00	2135-01-30 22:05:00	SEPSIS	1	1

2. **patients:** Patient information such as date of birth, gender, hospital stay id, etc. An example is provided below. Again, this table has not been manipulated in any way other than selecting patients that were admitted with sepsis.

	subject_id	hadm_id	admittime	admission_type	insurance	ethnicity	death_period	gender	dob
0	357	122609	2198-11-01 22:36:00	EMERGENCY	Private	WHITE	0	M	2135-03-22
1	366	134462	2164-11-18 20:27:00	EMERGENCY	Medicare	HISPANIC OR LATINO	0	M	2112-05-22
2	94	183686	2176-02-25 16:49:00	EMERGENCY	Medicare	ASIAN	0	M	2101-09-20
3	21	111970	2135-01-30 20:50:00	EMERGENCY	Medicare	WHITE	1	M	2047-04-04

3. **labevents:** Patient lab events with date-time associated with the measurement. This includes information such as creatinine levels. This is a snapshot is an example of the layout of the database prior to any reading and pre-processing.

	row_id	subject_id	hadm_id	itemid	charttime	value	valuenum	valueuom	flag
0	430129	652	100262	50818	2142-04-28 04:15:00	47	47.00	mm Hg	abnormal
1	430130	652	100262	50820	2142-04-28 04:15:00	7.11	7.11	units	abnormal
2	430131	652	100262	50821	2142-04-28 04:15:00	116	116.00	mm Hg	abnormal

4. **microbiologyevents**: Patient microbiology tests with date-time associated. This includes tests for infections and resulting prescription. This snapshot below shows how the database is layed out prior to any pre-processing.

	row_id	subject_id	hadm_id	chartdate	charttime	spec_itemid	spec_type_desc	org_itemid	org_name	isolate_num	ab_itemid	ab_name	dilution_text	dilution_comparison	dilution_value	interpretation
0	8257	652	100262	2142-06-05	2142-06-05 17:12:00	70062.0	SPUTUM	80225.0	NON-FERMENTER, NOT PSEUDOMONAS AERUGINOSA	1	90013.0	TOBRAMYCIN	=>8	=>	8.0	R
1	8258	652	100262	2142-06-05	2142-06-05 17:12:00	70062.0	SPUTUM	80225.0	NON-FERMENTER, NOT PSEUDOMONAS AERUGINOSA	1	90028.0	CEFEPIME	16	=	16.0	R
2	8259	652	100262	2142-06-05	2142-06-05 17:12:00	70062.0	SPUTUM	80225.0	NON-FERMENTER, NOT PSEUDOMONAS AERUGINOSA	1	90018.0	CEFTRIAXONE	=>32	=>	32.0	R

Due to the size, variability, and nature of ICU care much of this data must be explored for feasibility in a machine learning model. A good example is blood pressure. While in the MetaVision database, it was standardized with mm/Hg, in the Carevue database that was not the case. It makes the data less useful since information is not standard across different patient entries.

Many features need to be calculated with missing values handled appropriately. As can be seen from the snapshot of labevents above, there are many readings, with potential duplicates and potential missing values. For example, some patients may never have creatinine tested for whatever reason, while some patients may have their creatinine tested multiple times in a day. Handling both of these instances will be important and critical to restructuring data properly. It is also necessary to standardize the scale of entries since all readings are using different units. Shifting all data to have zero mean is a good step to help prevent unexpected model behavior.

Observing the microbiology snapshot above, patients may have no infections or multiple. Handling these multi-class data entries will be tricky, but will essentially require multiple one-hot entry columns.

2.2 Exploratory Visualizations

The basic patient information housed within the **Admissions** table has some potentially useful information. Combining patient admission date with their dob we can calculate their age(except patients over 89 due to HIPAA regulations). The visualization of survivability with age can be observed in **figure 1**.

There is a somewhat noticeable trend in **figure 1** with regards to age and survivability of sepsis but it doesn't appear to be anything that an algorithm could rely on strongly. It is important to discover some other useful features.

It may be useful to look at the initial blood tests for feature correlation. Observing all of these blood tests that are correlated with sepsis, the following have enough datapoints: bicarbonate, INR, MCH, AST, alkaline phosphatase, PH, creatinine, platelet, PT, PTT, lymphocytes, RBCDW, calcium, neutrophils, glucose, hematocrit, hemoglobin, lactate, BUN, and age.

Looking at the feature correlation in **figure 2** gives a better understanding of how the features are correlated with one another as well as which features have a strong or negative correlation to the survivability of sepsis.

There appear to be a few values with very strong correlation such as PTT and INR. PTT, PT, and INR are all used to test for clotting factors in blood so this result is logical. This also means that these features could probably be compressed into fewer dimensions.

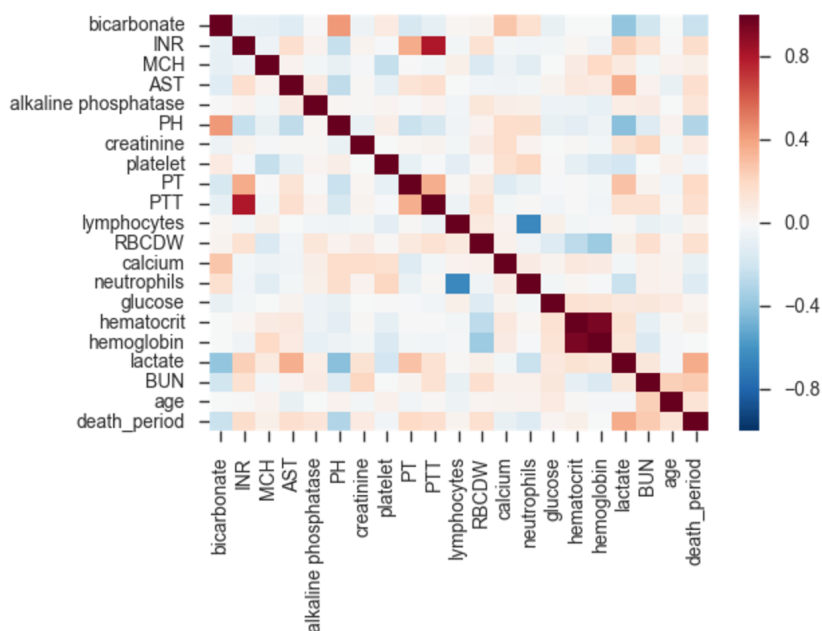


Figure 2: Patient Vitals Correlation

much more useful than age.

Finally, considering microbiology events. Every infection type is taken and the correlation considered. Though the assumption might be made that infection is strongly correlated with the survivability of sepsis, it is important to note that once a patient is septic, the infection type plays

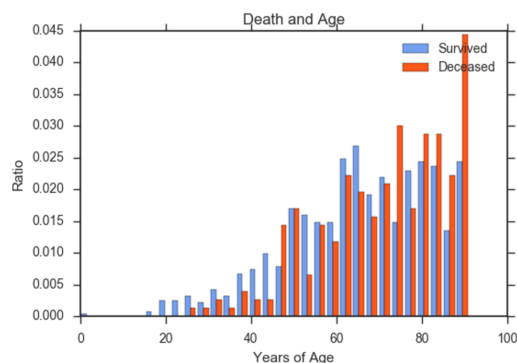


Figure 1: Age Breakdown

Within the 30 day period of mortality, none have a positive or negative correlation over ± 0.4 , however, there are some useful features to consider. Lactate is relatively strongly correlated with 0.38 with blood urea nitrogen(BUN), and PH not far behind. Lactate is an indication of shock since lactate is produced by cells that are not receiving enough oxygen. PH is a byproduct of the acidic lactate in the patient's blood hence the correlation. Blood urea nitrogen is an indication that the kidneys are failing to process the excess urea in the blood. This can indicate potential kidney damage or failure. All of these are

little role. Let us look at the number of infections and survivability in **figure 3**.

There appears to be very little correlation after further observation between survivability and number of infections. With the majority of patients not having an infection discovered within the first 24 hours. Due to this lack of information, the infection type is likely not useful.

These visualizations give some useful insights into the data. One insight is that nothing strongly indicates a patient survival. Therefore many independent features must be considered and trends found. Due to this observation about the data, a neural network, or an ensemble technique like adaptive boosting or extreme gradient boosting may prove useful.

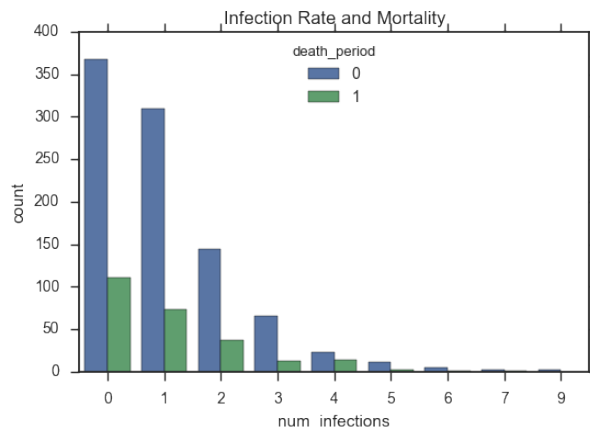


Figure 3: Infection Count and Mortality

2.3 Algorithms and Techniques

The area under the ROC curve of four different classifiers are to be compared. These classifiers are the following:

1. **Support Vector Machine:** Support vector machines are a flexible yet simple machine learning algorithm. When compared to a neural network, SVMs require much less grid-searching to optimize hyperparameters. SVMs can approximate complex non-linear functions with the “kernel trick”. This is useful considering the nature of this dataset. SVMs are also guaranteed to find the global optima, not local optima like some machine learning algorithms. Support vector machines like neural networks are a black box. It is hard to interpret the model once it has been created. SVMs can also suffer from too many training examples, bloating the time it takes to train. This potential issue will not be a problem with this relatively small dataset however.
2. **Adaptive Boosting:** Adaboost is another fantastic ensemble method. It is notorious for not overfitting data. It is quite flexible due to its ability to leverage any base estimator that works best in a certain situation. Adaboost itself has few parameters to tweak to optimize performance so it works relatively well right out of the box. Adaboost does have some weaknesses. It is typically not the best in class predictor. There usually are more accurate classifier options on the table. It is also sensitive to noisy data as well as outliers. This is similar to Random Forests. This is a great classifier but is unlikely to be the most accurate.
3. **Extreme Gradient Boosting** XGBoost is an optimized distributed gradient boosting library. Gradient boosting in general is thought of as a best in class predictor. It can approximate most nonlinear functions, and automatically handles missing values. This is a very powerful algorithm that is much less work to set up than a neural network.

Gradient boosting can overfit if run for too many iterations and can be sensitive to noisy data or outliers. This is an unfortunate downside but it is common in many algorithms. It will be important to preprocess the data to remove outliers.

4. **Neural Network:** Neural networks are an incredibly powerful machine learning algorithm. They can approximate any nonlinear function, they are highly customizable, and robust to outliers. With these features, it is possible to create a highly accurate predictor of the data that forms more complex feature relationships.

Neural networks, while powerful, have some pretty strong weaknesses. They are difficult to set up and difficult to tune because of the number of parameters. It is also necessary to decide on the architecture of the network yourself. It is not nearly as simple to set up as the previous examples. It is also quite easy to overfit data using neural networks. Without restraint, they have a strong affinity to fit to noise in the data. Due to the nature of this dataset, it will be an important task to keep this algorithm in reign to prevent overfitting.

These are relatively varied algorithms with much different predictive techniques. The comparison between the AUC will allow some insight into how the algorithms behave with moderately small datasets, natural noise, and outliers. It is a considerable task to preprocess the data properly in order to optimize the results.

2.4 Benchmark

There are few studies into the predictability of patient survival from severe sepsis. There are also many factors that are important in how the prediction is made. I will be focusing on the following research: “From vital signs to clinical outcomes for patients with sepsis: a machine learning basis for a clinical decision support system” by Eren Gultepe, et al.

“An accuracy of 0.73 and discriminability of 0.73 AUC for mortality prediction in patients with sepsis was achieved with only three features: median of lactate levels, mean arterial pressure, and median absolute deviation of the respiratory rate. ”[5]

While this study is mainly focused on predicting the survivability of sepsis through observing only 3 features: lactate levels, mean arterial pressure, and median absolute deviation of the respiratory rate, I do not access to all of these features in the MIMIC-III dataset. Therefore I will be considering more features in the hopes to outperform this benchmark’s AUC of 0.73.

In the analysis I am conducting, patients are admitted with suspected sepsis and all vitals and lab tests within 24 hours from admission are used in the classification task, similar to the benchmark. This is to standardize periods of importance across all patients observed.

3 Methodology

3.1 Data Preprocessing

Preprocessing the data is the most challenging and time-consuming step of this process. All preprocessing and visualizations were initially done in the Jupyter notebook titled **Septic Feature Probe.ipynb** and later all preprocessing is done again in the final model comparison analysis in the Jupyter notebook titled **Sepsis Model Comparison.ipynb** along with the helper python file **mimicpreprocess.py**. The following steps were taken to preprocess the data:

3.1.1 Acquire the Dataset

The MIMIC-III dataset is openly available and developed by the MIT Lab for Computational Physiology. It requires certification to handle de-identified medical information. The data is provided in CSV files, with each file representing a table in a database. The CSVs were then processed and imported into respective tables in a PostgreSQL database.

An exhaustive search of all potentially useful features was done by mapping and searching the database using the DBVisualizer application. Most features were not feasible for use due to lack of associated date-time information. Four tables were found to have all necessary information to link data to an individual patient, an individual patient's stay, and contained vital date-time information. These tables were related to:

1. **Admission Information:** This table included the patients ethnicity, language, insurance type, admission date, suspected diagnosis, and discharge information
2. **Patient Data:** This table is more of a "through table" with the patient's ID, date of birth, gender, and date of death (if applicable).
3. **Lab Test Results:** This table is extensive and contains all test results associated with each patient. Lab tests are identified with an ID (eg: 50912 represents results for blood creatinine tests), a numeric result, a unit, and a date-time. Several correlational studies were utilized to identify lab tests that provide insight into the stage of sepsis. Some of these included: Creatinine, blood ph, dissolved Co2, lactate levels etc. These features were acquired and explored further.
4. **Microbiology Results:** This table contains all microbiology lab results. It indicates the type of infection, the date-time for the test, and resulting treatment.

Multiple other tables were unusable for the most part due to lack of uniform data capturing between MetaVision and CareVue origin systems, and lack of date-time information.

With the data identified and obtainable, the next step was to import data into a usable format in python utilizing the SQLAlchemy python library.

3.1.2 Calculate Features

Most features must be calculated due to the nature of the database and of medical data in general. Missing values also need to be dealt with properly. The following was done to calculate the feature set:

1. For all potentially useful lab results the mean value was taken along with the maximum and minimum measurements as separate features over the first 24 hours.
2. Age was calculated from DOB and Admission date. For patients over 89 the median age of 93 was taken due to HIPAA constraints.
3. For each patient, infection types and infection count were taken as separate features. Each infection type was its own binary feature.
4. Prior hospital stays were calculated by looking at admission date and subject_id to see if the patient had been to the hospital since data collection began.

5. A binary death period value was calculated. This feature represented whether a patient expired within 30 days of hospital admission. Only deaths that are related to sepsis are of interest for this study. 30 days is a standard period to observe.

3.1.3 Handle Missing Values and Outliers

Many patients had missing vital measurements. If approximately 15% of the patients were missing values for a single feature, the feature was dropped. This was done to prevent any machine learning algorithm fitting to false or replaced values.

Patients that were missing approximately 30% of the selected lab results were dropped due to lack of information. These patients may have been admitted and discharged quickly or an error in recording could have occurred.

Medical information is irregular which resulted in most patients missing information from at least one feature. To handle this, the mean value from the entire feature set was taken and filled into this cell. There are many techniques to handle filling in missing information however, the mean value works well and is simple to implement.

Potential outliers were calculated and removed. First a step was calculated: $step = 1.5 * (Q3 - Q1)$. If the feature was less than the first quartile minus the step ($Q1 - step$) or greater than the third quartile plus the step ($Q3 + step$), it was considered a column outlier. If an entry had greater than 4 column outliers, it was removed.

3.1.4 Standardizing Features

Now the data is more or less usable but each column contains multi-categorical data or numerical data in different units.

Categorical data is converted into one-hot features where each category has its own column with 0 or 1. This task is made easy with Pandas' built in functionality of *pandas.get_dummies(df)*.

Certain machine learning algorithms might behave poorly if individual features do not more or less look like standard normally distributed data. A feature that is naturally much higher could outweigh the naturally smaller values in the prediction. This is not always the case but it is a good technique to standardize all data to prevent such an error. This moves the mean to zero. The operation is easily done by fitting data to *sklearn.preprocessing.StandardScaler()*.

3.1.5 Feature Selection

There are many features that may be of little use when predicting the survivability of sepsis. The more irrelevant features that exist, the more data is required to ensure they do not fit to noise in those features. It is important to remove the features that are of little use.

Feature correlation was calculated and it was observed that the infection type was of little correlation to the survivability of sepsis. The existence of any infection was of little use in predicting survivability as well, therefore these features were dropped from the dataset.

With the remaining features, a random forest was trained and the resulting feature importances graphed in **figure 4**.

As can be seen in **figure 4**, gender, insurance type, and admission type are of little use when predicting survivability. For most algorithms, this data will be dropped. For the neural network, it may be included since more complex relationships could be developed between the features.

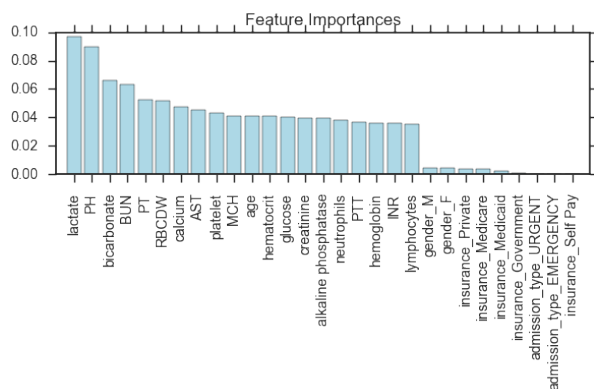


Figure 4: Feature Correlation Graph

The important features have been discovered and now machine learning models can be trained on this cleaned and standardized data.

3.2 Implementation

Four different machine learning algorithms were implemented and trained therefor four different processes were required to develop them. All work can be seen in the Jupyter notebook titled **Sepsis Model Comparison.ipynb** along with the helper python file **mimicpreprocess.py**. Prior to any models developed, the data must be loaded into a pandas dataframe and preprocessed as described in the previous section.

3.2.1 Support Vector Machine

Most of the ScikitLearn machine learning algorithms tend to be quite easy to set up and run, much more so than XGBoost or a Neural Network. SVMs should, in theory, work great with this dataset due to its size and complexity. The process is as follows:

1. **Define Model:** A model is defined with a random state in order to reproduce the results and the type of kernel, **rbf**.
2. **Define Parameters:** A parameter grid defines several important hyperparameters to test. They are as follows:
 - (a) **C:** The C hyperparameter controls the smoothness of the decision boundary by telling the SVM how much you want to avoid misclassification. Large C will cause the optimizer to find a smaller margin separating the hyperplane while small C will result in a larger margin separating the hyperplane at the expense of misclassifying points.
 - (b) **gamma:** gamma controls how many support vectors are used in placing said decision boundary. When gamma is very small, the model can be too constrained and is unable to capture the complexity of the data. However if gamma is too high, the model will fit to the noise of few support vectors.
3. **Grid Search:** Due to the size of the hyperparameter test set, GridSearchCV is used to iterate over every possible combination of parameters in the param_grid. Note that **stratified k-fold** cross validation is used with 10 folds total.

3.2.2 Adaptive Boosting

The AdaBoost model implementation is as follows:

1. **Define a Base Estimator:** The base estimator is what AdaBoost boosts. It is a very important selection. In order to make the algorithm generalizable and prevent overfitting, a decision stump (1d decision tree) is initially selected and defined as the base estimator.
2. **Define Model:** A model is defined with a random state in order to reproduce the results and the decision stump as the base estimator.
3. **Define Parameters:** The adaboost parameter grid is defined as follows:
 - (a) **n_estimators:** n_estimators controls the max number of estimators at which boosting is terminated. The more estimators, the more complex the model, so it is important to look for a reasonable number to prevent overfitting.
 - (b) **learning_rate:** The learning rate shrinks the contribution of each classifier. If the learning rate is too large, the optimal solution can be missed. If too small, too many iterations may be required. There is a tradeoff between the number of estimators and the learning rate.
4. **Random Search:** Due to the size of the hyperparameter test set, RandomSearchCV is used to iterate randomly over the possible combinations of parameters in the param_grid. Note that **stratified k-fold** cross validation is used with 10 folds total. Random search is used here instead of grid search since the number of hyperparameters that are tested is much larger and in practice works nearly as well with a reasonable number of iterations. In this case, 100 iterations were done.

While Adaboost may seem like a relatively complex algorithm, the most complex task is selecting a solid base estimator. There are few hyperparameters to tune and better performance comes from manipulating the data to work optimally with such an algorithm.

3.2.3 Extreme Gradient Boosting

Extreme gradient boosting is slightly more complex to implement than the previous models. The XGBoost python library will be used due to its performance and community support. The model implementation is as follows:

1. **Define Model:** A model is defined with the **objective = binary:logistic**. binary:logistic is for binary classification, it returns predicted probability not the class.
2. **Define Parameters:** There are more parameters to test in XGBoost than in the previous algorithms, they are as follows:
 - (a) **max_depth:** max_depth represents the maximum depth of a tree. Higher values will lead to a more complex model but also has the potential to fit to noise in the dataset. A typical value is between 3 and 10.
This value can have large ramifications since XGBoost makes splits up to the max_depth then starts pruning the tree backwards removing splits which provide no positive gain.
 - (b) **gamma:** gamma represents the minimum loss reduction required to further partition on a leaf node. The larger the value, the more conservative the algorithm.
It is important to note that the values of gamma can vary depending on the loss function and therefore should be tuned.

- (c) **min_child_weight:** min_child_weight is the minimum sum of instance weight required in a child node. If a tree partition step results in a child weight less than the minimum, the building process will halt further partitioning.
The minimum child weight has high impacts on the model outcome and therefore must be heavily tuned.
 - (d) **n_estimators:** n_estimators represents the number of trees to be boosted by the XGBoost model. More trees can increase complexity and potential for overfitting so ensuring a reasonable value is tuned is important.
 - (e) **learning_rate:** The learning_rate or eta is the step size shrinkage used in update to prevents overfitting. After each boosting step the eta will shrink the feature weights to make the algorithm more conservative and reduce the likelihood of overfitting.
3. **Randomized Search:** Due to the size of the hyperparameter test set, RandomizedSearchCV is used to iterate over randomly the possible combinations of parameters in the param_grid. Note that **stratified k-fold** cross validation is used with 10 folds total.

It can be seen that many of the hyperparameters that are tuned have significant interaction and play between one another. XGBoost provides many "knobs" to increase and decrease model complexity while allowing granular selections to reduce the probability of overfitting. XGBoost is complex and quite powerful due to this flexibility.

3.2.4 Neural Network

An artificial neural network is the most complex machine learning algorithm that is used in this project. Much of its flexibility is due to the fact that the general architecture must be designed instead of simple hyperparameter tuning and data manipulation. To design a NN, the following steps were taken:

1. Define the basic network architecture
2. Define and test hyperparameters with dataset. These included:
 - (a) Number of neurons per layer.
 - (b) Activation function per layer.
 - (c) The kernel constraint per layer. Used to reduce the probability of overfitting.
 - (d) Dropout ratio per layer.
 - (e) Batch size.
 - (f) Number of epochs to observe results over.
3. Define the loss and accuracy function.
4. Create a custom callback to test the AUC score per-epoch since AUC is not a default metric in Keras.
5. Train the network and log per-epoch loss, accuracy, and AUC score.
6. Plot logged accuracy, loss, and AUC scores.

7. If accuracy, loss, and/or AUC are unacceptable return to the start, consider manipulating existing data by adding or removing features.

Figure 5 illustrates the general architecture of the neural network that was used on this dataset. The number of iterations through this graph is controlled by the batch size and the number of epochs. Smaller batch sizes require more iterations to see the entire dataset.

The acronyms and nodes on the graph are as follows:

1. **DL:** DL represents a densely connected layer. Each neuron is connected to all other neurons.
2. **DOL:** DOL represents a drop out layer. Drop out layers are used to reduce data memorization/overfitting by randomly removing a portion of the neurons which reduces fragility and over-reliance on individual neurons. Having a drop out layer is especially useful when the size of the dataset is relatively small.
3. **epoch:** An epoch is a single pass through the entire training set which is then followed by the testing set.
4. **loss:** A loss function is calculated using the desired and actual output of the network. The loss function will return an error value for each of the neurons in the output layer. Many different loss functions can be used but in this case, binary cross entropy is used.

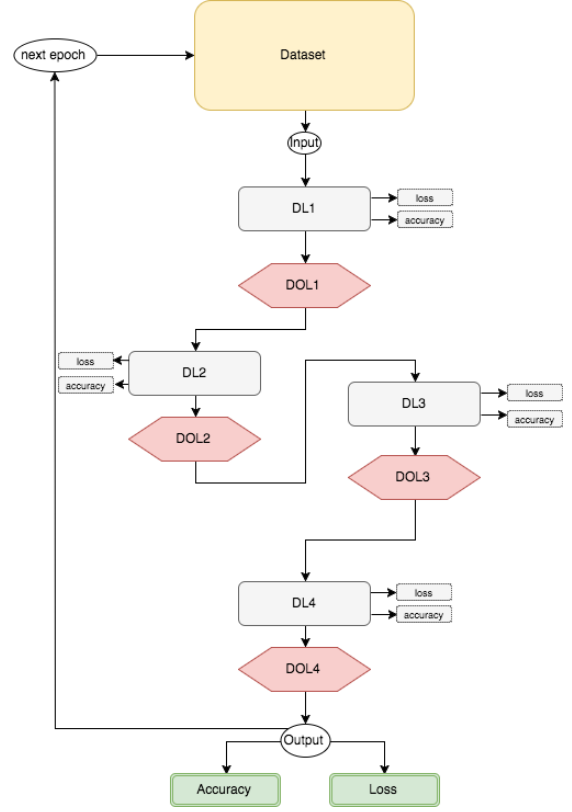


Figure 5: Keras Neural Network Flow

3.3 Refinement

As mentioned in the Benchmark section, an AUC score of 0.73 was achieved by Eren Gultepe, et al. The results from all of the machine learning algorithms will be compared to this result for refinement.

The initial pass of the data through each of the algorithms was the following:

3.3.1 SVM

The initial AUC score of the trained support vector machine was **0.735**. This is already higher than that of the benchmark which is a fantastic start.

At this point, the dataset contained the mean vital readings, as well as maximum and minimum readings, removing the maximum and minimum readings, was the first step to reduce dimensionality and potentially increase performance. After further testing, more features were trimmed to

improve performance. These trimmed features are: gender, prior, INR, lymphocytes, glucose, and hemoglobin. The next step was to grid search even more **gamma** and **C** values. After these optimizations, the performance of the SVM increased to **0.796** AUC.

3.3.2 Adaptive Boosting

The initial AUC of AdaBoost was **0.723**, slightly worse than the benchmark.

The same was done as with the SVM, where the max and min values were trimmed from the dataset along with the additional features removed for SVMs. The decision stump base estimator was also swapped out for the default estimator which is a standard decision tree. This resulted in an increase in AUC score to **0.768**.

3.3.3 Extreme Gradient Boosting

The initial AUC score of XGBoost was **0.743** slightly above the benchmark. This is quite a good result without manipulating the existing data or more hyperparameter tuning.

The max min and additional patient vital features appeared to be affecting XGBoost negatively, the same as Adaboost or SVM. No model performed better with PCA dimensionality reduction as well. The max and min values were dropped. The range of the hyperparameters being tested was widened and min_child_weight was added for testing instead of using the default value. These changes resulted in an increased AUC score to **0.790**.

3.3.4 Neural Network

The initial AUC score of the Keras Neural network using Tensor Flow was not impressive at **0.678**. The initial Neural network was much simpler than the final version discussed in detail in the previous section. The initial NN had no dropout layers, no kernel constraint parameter, had only 1 hidden layer and 10 neurons per layer.

In the final version, 3 hidden layers are present, dropout layers were added, a kernel constraint was added, additional data features were considered including gender, the number of nodes were iteratively increased and decreased per layer resulting in a much more robust model. This resulted in an increased AUC of **0.793** on the 26th epoch. This is also quite an impressive score compared to the benchmark and other models tested here.

It is important to note that this AUC was selected from the optimal section of hundreds of epochs. Due to the nature of neural networks, each running resulted in different AUC scores.

4 Results

4.1 Model Evaluation and Validation

During development stratified k-fold cross validation was used internally inside GridsearchCV and RandomizedSearchCV. The exception to this was the neural network that used a train(0.77) test(0.33) split. This was done due to the size of the dataset. With an already small dataset with even smaller batch sizes, irregular performance was seen. The batch size was increased and k-fold CV was not used for a standard train/test split.

Most of the discussion will be on the architecture of the NN but the following will show the final selected hyperparameters in all models that performed best among the attempted combinations.

4.1.1 Support Vector Machine

Initially when testing for accuracy, the support vector machine performed the poorest out of all the models. When testing for AUC, it performed the best by a small margin. This is an interesting result:

1. **C:** 1 - the default value for C is 1, this is a reasonable selection.
2. **gamma:** 0.01 - this value of gamma appears reasonable. It is a conservative value but not too constrained.

4.1.2 Adaptive Boosting

Adaboost performed the poorest out of all the models. The hyperparameter selection was reasonable after RandomizedSearchCV, they were:

1. **n_estimators:** 32 - This is a very conservative number of estimators but is logical consider the feature space and the size of the dataset. The default value is 50. If it was much higher, overfitting would be a likely concern.
2. **learning_rate:** 0.166 - This is also a conservative number for the learning rate considering the default value is 1. Both the number of estimators and learning rate were likely throttled to compensate for the relatively small feature set and data set while having a more complex base estimator than a decision stump.

4.1.3 Extreme Gradient Boosting

XGBoost hyperparameter selection is more complicated to analyze due to the complexity of the algorithm. The hyperparameter selection is as follows:

1. **n_estimators:** 47 - With a default of 100, a conservative value.
2. **gamma:** 5 - With a default of 1, this is also conservative. The larger the gamma, the more conservative the algorithm will be.
3. **learning_rate:** 0.1 - With a default of 0.3, this appears to be a conservative learning rate. This was likely selected due to reduce observed overfitting.
4. **max_depth:** 14 - With a default of 3, a max depth allows for some increased model complexity to compensate for the conservative number of estimators, gamma, and learning rate.
5. **min_child_weight:** 9 - with a default of 1, again a conservative value. A somewhat high minimum child weight is required otherwise partitioning is halted.

Observing the selected hyperparameters for XGBoost suggests that cross-validation was struggling to select parameters that increased model AUC while preventing overfitting. This can be seen through the conservative selection of hyperparameters.

4.1.4 Neural Network

The Neural network was the most complex system to set up and tune and required much more manual tweaking than the previous algorithms. The general architecture can be seen in **figure 5** in the previous section. The resulting architecture that was selected is as follows:

1. There are 5 densely connected layers of the neural network with 3 hidden layers. The number of neurons in each layer sequentially is as follows: **125, 50, 25, 10, 1**. A somewhat deep neural network with decreasing neuron count was selected in order to aid in finding more complex relationships between the features that other machine learning models may be incapable of learning.
2. Each densely connected layer, aside from the input and output layers, has a maximum-norm kernel constraint of 5 to fight data memorization. The kernel constraint value was selected through iterative testing.
3. Between each densely connected layer is a dropout layer with a dropout value of **0.5**, which results in 50% of randomly selected neurons being "dropped" or ignored during training. This helps fight complex co-adaptations among neurons, reduces the fragility of a highly specialized model, and reduces overfitting. 0.5 on all layers is somewhat high and was found to increase performance and delay overfitting significantly.
4. The only loss function that made sense for this specific NN application was **binary_crossentropy**.
5. Several different optimizers were tested but the most stable in this application was **rmsprop**. There is no evidence suggesting that it would perform better in this case rather than others however.
6. The selected metrics that are tested for are **accuracy**. However, a custom callback function logs the AUC between each epoch.
7. 500 epochs are run with a batch size of 128. With an approximate input size of 1200, around 4687 iterations are executed during the learning process.

To verify the robustness and ensure that data memorization is not occurring in the epochs chosen for the optimized model, the model accuracy, AUC and loss are stored. **Figure 6** shows these values graphed.

Comparing the model accuracy to the model loss graph is becomes apparent that data memorization gradually occurs as the testing accuracy climbs towards 100%. At around epoch 100, training accuracy has surpassed testing accuracy and steadily increases all 500 epochs. The model loss is a good indication of overfitting as well. We can see that the testing loss flattens around 50-100 and surpasses training loss at around epoch 100. It is important that the model cuts off training before 100 epochs to reduce overfitting and minimize loss.

The epochs with the highest accuracy and best AUC score are near epoch **26**. This is a sweet spot and indicates at this point the model has not begun to overfit so is generalizable but also highly accurate. While accuracy is not the metric explicitly being optimized and observed, it is still a good indication of performance as well as a sign of overfitting when comparing train/test accuracy divergence.

4.2 Justification

All of the tested models outperformed the benchmark by a significant margin. The support vector machine had an AUC of **0.796** which beats the benchmark by **12%**. The results are promising but it is important to note several limitations to the outcome of this model comparison study.

The dataset is small at around 1200 patient entries. To obtain a more reliable result, a dataset of several hundred thousand patients would be necessary. The nature of medical data is sparse, with high variability. The largest problem in dealing with this data was smoothing over irregularities, and swathes of missing and highly important features.

While the results are impressive for relying on around 20 features, there are many features that would have been highly useful and possibly more valuable if they could have been properly processed. Respiration rate is one feature that was unusable due to the state in which the two original sources saved the data. The benchmark study also used fewer features, however I was unable to obtain information regarding most of them in the MIMIC-III dataset.

In summary, the application is useful in a very limited use case. It outperformed previous studies using similar methods. Due to the prioritization of ROC AUC, reducing false negatives was a priority at the expense of overall accuracy. For medical data, and for safety, AUC is more useful than accuracy.

5 Conclusion

5.1 Free Form Visualization

The most surprising and interesting result came from diving into a correlational breakdown of survivability and patient lab results. As seen in **figure 7**, several features had relatively strong positive or negative correlation to sepsis survival. Ignoring inter-feature correlations, most of these feature-survivability correlations are logical. Lactate, Blood Urea Nitrogen, PT, INR, and PTT have been thoroughly studied and documented in gauging the stage of a septic condition. Age and creatinine ranked relatively low in comparison as well as in feature importance ranked by a trained random forest. This fact was quite surprising.

This surprising discrepancy between previous studies and this dataset brings to question our collective understanding of sepsis and treatment. While treatment packages and standards are important in ensuring quality care, cases are vastly different with humans being incapable of discerning them typically. Machine learning algorithms may be capable of stratifying patients real time to provide optimal care on a per case basis. While these models are not suited for this real

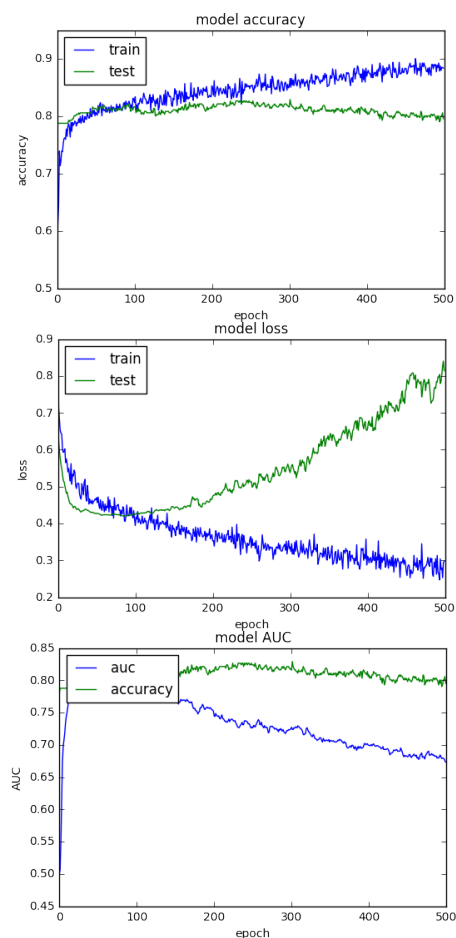


Figure 6: NN Accuracy, loss, and AUC by Epoch

time case, further studies and insights can be gained through its use in stratifying and analyzing patients in retrospect.

5.2 Reflection

The process used in developing this project can be summarized in the following steps:

1. Select a general topic to further study, in this case the medical field.
2. Select the most extensive and detailed dataset available and applicable to this project. In this case the MIMIC-III dataset.
3. Review and analyze features, categories, and issues with the dataset and select a relevant, interesting, and useful problem to analyze and break down.
4. After sepsis was selected due to the vast harm it does to humans and available data, look for studies and papers to better understand the condition and find a benchmark.
5. Visualize the dataset specifically looking for useful features in predicting the survivability of sepsis.
6. Pick 4 possible machine learning algorithms that are likely to work well with the available dataset and selected features.
7. Develop and train the respective classifiers with special attention on the architecture of the artificial neural network.
8. Tweak and optimize classifiers.
9. Select a classifier and weigh results.

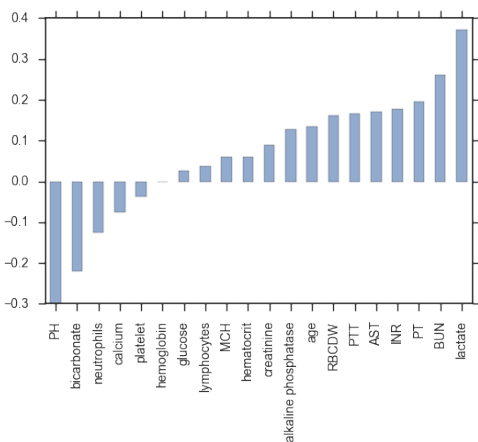


Figure 7: Sepsis Survival Feature Correlation

While developing the neural network was the most interesting and fun, the most difficult steps were **steps 3, 4, and 5**. The MIMIC-III dataset is vast and highly useful but there are some very distinct pitfalls. Much of the data does not include date-time information. The initial plan was to get hourly information from the time of diagnosis until release or death. The diagnosis table does not have date-time related information tied to them as they are used only for billing purposes. This same problem exists with procedures. It is impossible to see the outcome of procedures or do correlational studies when the procedure time is unknown. Due to these limitations, it was difficult to land on a project idea that was interesting, useful, and feasible.

Once a project was decided on, it was another challenge finding features that were also feasible to use. For example, respiration rate is one of the most important indicators of sepsis stage. Unfortunately, respiration rate

information is stored in a non-standardized way across the two origin databases. Due to this, too much information loss existed making the respiration rate unusable for this study.

In the end, enough information was present and accessible to make quality predictions even with a relatively small dataset. An important lesson was learned, however. Developing a machine learning algorithm is one of the smallest and easiest steps in most cases. Analyzing, preprocessing, and visualizing the data is much more work, much more complicated and equally as important.

5.3 Improvement

There are several improvements that could and should be made to this implementation. The first, and most important, is the size and origin of the dataset. While approximately 1200 patient samples is not trivial, it is not significant enough to compensate for the noise present in medical information. The other issue is related to the origin of the data. All data originated from the Beth Israel Deaconess Medical Center in Boston Massachusetts. This hospital has a high volume ICU which is good in producing useful medical data but it is geographically limiting. To obtain more generalizable results, more hospitals spanning the country would need to provide information for analysis as well.

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