Deep Predictive Learning of Carotid Stenosis Severity

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Abstract

Carotid artery stenosis is the narrowing of carotid arteries, which supplies blood to the neck and head. In this work, we train a model to predict the severity of the stenosis blockage based on SRUC criteria variables and other patient information. We implement classic machine learning methods, decision trees and random forests, used in a previous experiment. In addition, we improve the accuracy through the use of the state-of-art Augmented Neural ODE deep learning method. Through systematic and theory-rooted analysis, we examine different parameters to achieve an accuracy of about 77%. These results show the strong potential in applying recently developing deep learning methods, while simultaneously suggesting that the current data provided by the SRUC criteria may be insufficient to predict stenosis severity at a high performance level.

1 Introduction

Carotid artery stenosis is the narrowing or constriction of carotid arteries, often due to atherosclerosis. While not as accurate as angiography, ultrasound imaging is popular due to its low costs and lack of radiation [21] [8]. Carotid duplex ultrasound is often performed as a screening test on patients who have no signs of carotid artery disease, with the intent to catch asymptomatic carotid artery stenosis at the earliest stage possible [5][1]. Here, we compare classical machine learning methods such as classification and and regression trees (CART) and random forest with more modern deep neural network methods on the prediction of angiography-measured carotid stenosis severity based on ultrasound-derived data, patient history, and patient demographics. Previously reported methods using decision trees and random forests resulted in a test accuracy ranging from 68-74%, depending on variables that the model trained on [18]. It is shown that the use of novel augmented neural ODEs improves the predictive ability of the carotid data set, compared to the traditional CART and random forest models.

2 Background

2.1 Carotid Artery Stenosis

There is a left and right common carotid artery (CCA) that runs along the neck, before branching into the internal carotid arteries (ICA) and external carotid arteries,
supplying the brain and face, respectively. The stenosis often occurs distally to the CCA bifurcation due to the local fluid dynamics in the region [11][17]. With the internal carotid artery (ICA) supplying the brain, the restriction of blood flow increases the risk of stroke and transient ischemic attack (TIA). A 2010 meta-analysis of 23,000 patients reported “severe” (> 70%) stenosis with a prevalence rate of 1.7% and 0.9% in men and women aged 80 or above, respectively [9]. The Asymptomatic Carotid Surgery Trial 1 (ACST-1) reported an annual stroke risk of 3% in patients with asymptomatic (> 60%) carotid stenosis [12]. The Asymptomatic Carotid Surgery Trial 2 (ACST-2) is currently ongoing [4]. Another study examining 216 patients with asymptomatic ICA stenosis of 60-99% over the span of five years put the annual risk of stroke at 3.2% [15].

Figure 1: Right common carotid artery splitting into the right internal carotid artery and right external carotid artery.

Carotid duplex ultrasound uses Doppler ultrasound to quantitatively assess blood flow velocities and conventional B-mode ultrasound imaging to visualize the artery and accompanying plaque. The severity of carotid artery stenosis is measured through percent blockage of the artery cross-sectional area at the site of plaque. Meanwhile, common blood flow measurements include the three variables used in the Society of Radiologists in Ultrasound Consensus (SRUC) criteria for carotid stenosis: ICA peak systolic velocity (ICA PSV), ICA end diastolic velocity (ICA EDV), and ICA/CCA PSV ratio. These three SRUC criteria variables are clearly not independent from each other, as these variables are all influenced by blood flow in the internal carotid artery. In our experiments, we will show that while these SRUC variables are valuable in the predictive models, it is suspected that a more comprehensive set of variables are necessary to create a more accurate model.

2.2 Augmented Neural ODEs (ANODEs)

Neural networks can approximate some unknown function that relates the inputs to outputs. In our case, the inputs are the patient data and ultrasound variables, and the output is the stenosis severity. A multilayer perceptron, the most basic form of a deep neural network, conveys information through hidden layers in a sequential order.
Residual neural networks (ResNets) are a variant of neural networks that utilize skip connections, in which the outputs from previous layers may skip up to several layers to feed directly into the next layer [13].

![ResNet diagram](image1)

Figure 2: On the left we see a regular block used in standard multilayer perceptrons, while on the right we see a residual block. The only difference between the residual block and the regular block is that the residual block allows the inputs $x$ to skip a hidden layer. Because of the residual block, ResNet can represent more functions than normal neural networks. Figure borrowed from [20].

It has been shown that ResNets effectively act as discretized ordinary differential equations (ODEs), where each residual block can be written as a forward step Euler discretization [13]. Neural ODE architecture [6] makes it continuous and more powerful. Its diagram is in Figure 3.

![Neural ODE diagram](image2)

Figure 3: Diagram of Neural ODE architecture. Its weights and biases in a Neural ODE are shared across the continuous hidden states, compared to ResNet. So it can represent even more functions [6].

The main advantage of parameterizing hidden states is that unlike ResNet where the weights and biases are time-dependent, the weights and biases in a Neural ODE are shared across the continuous hidden states. Consequently, Neural ODEs can perform with comparable accuracy with ResNet, while using significantly less parameters. Despite the advantages of Neural ODEs, there are several known types of functions that Neural ODEs are not able to train unless at great computational cost, if trainable at all.
In acknowledgement of these issues, augmented NODEs (ANODEs) were developed in 2019, where the data is lifted into a higher dimension by a multilayer perceptron before entering the NODE [11]. The central argument is that by first lifting the data that was initially hard to separate by the NODE, the augmented data is more separable and can be more effectively learned by the NODE.

3 Methods

3.1 Data Set

The data set contains SRUC criteria, patient demographics, and patient history variables from 257 patients. Patient demographic and patient history variables were excluded with there was not at least 20 samples in each class in a given variable. This resulted in 3 SRUC criteria variables and 23 patient demographic and patient history variables. The carotid artery stenosis severity is split into two classes, where a stenosis of 70 − 99% is a positive case (+1) and a stenosis of 50 − 69% is a negative case (-1).

3.2 Decision Trees and Random Forests

Machine learning methods for classification such as CART and Random Forest were trained to analyze a clinical carotid data set [18]. A decision tree is a flow-like chart in which data samples are separated sequentially based on the threshold of a particular variable. Meanwhile, random forests are a collection of decision trees in which the prediction of each individual tree is used to create a final overall prediction, reducing the bias of individual trees. Because our data set is slightly different from [18], we use the methods applied in the aforementioned study to serve as our own baseline reference. Two decision trees were generated under the following methods: (1) a decision tree that only the SRUC criteria variables and (2) a decision tree that uses patient demographic and patient history variables in addition to the SRUC criteria variables.

The decision tree splits were determined by measuring the weighted Gini index to maximize class discrimination. The decision tree depth was manually selected to reflect the same depth as the decision trees used previously [18]. The reported test accuracy is the average validation accuracy performed across five-fold cross validation. Then, the model was trained on the entire data set to generate the visualized decision trees. Next, we generated two random forest models through similar methods as in the past [18]. The first random forest model was trained on only the three SRUC criteria variables, while the second random forest model was trained on all available variables. The number of trees for both models were 100, while the maximum depth of each tree was 2 and 3 for the first and second model, respectively. As before, five-fold cross-validation was performed to provide the training and test accuracy.

3.3 Deep Learning Method

In our deep learning experiments, we use the three primary variables from the SRUC criteria, in addition to 23 other variables pertaining to patient demographics and patient history. Patient demographic and patient history variables were excluded if there
was not at least 20 samples in each class of a given variable. The data set contains information from 257 patients, in which 200 patient samples were used for the training set and 57 patient samples were used for the testing set.

Figure 4: General structure of our ANODE adapted to the carotid dataset. ANODE with activation layers have much more functional space than MLP, so it is much more powerful.

In our ANODE, we implement a smooth L1 loss function, which is a piece-wise combination of the L1 and L2 loss functions \[14\]. The reason for this distinction is because L1 loss has more steady gradients for large arguments, whereas L2 loss oscillates less for small arguments.

We implemented two augmented structures that use either exclusively the ReLU and sigmoid activation functions to map the data from its initial dimension of 26 to a higher dimension of 32 in all hidden layers preceding the NODE. The NODE then projects its output into a 32-dimension vector, whose output provides the prediction as shown in \[4\]. In the ANODEs, we set \( T = 1 \) with the initial time \( t = 0 \), the batch size to 64, and learning rate to \( 10^{-3} \). The model is trained for 100 epochs and evaluated with five-fold cross validation.

3.4 Visualization of Augmented Data

We plot the lifted mapping of the three SRUC variables and use principal component analysis (PCA) to represent the high-dimensional, lifted features in a three-dimensional scatter plot. This allows for direct visualization of how the data points are distributed by class. As shown below, by lifting the SRUC variables into higher dimensions, the lifted features are better separated by class. We only show the first batch of the data set, containing 64 instances. The number of epochs was set to 100, with the data displayed at the completion of the last epoch.
3.5 Canonical Correlation Analysis

We use canonical-correlation analysis [3] on the SRUC criteria variables and carotid artery stenosis percentage. Canonical-correlation analysis is a method for establishing relationships or a mapping between two multivariate sets of variables of the same function or domain [7]. It could tell us whether the features have a strong correlation with label.

3.6 Bias and Variance Analysis in Model Selection

From [2], we know that Min Square Error (MSE) = Bias + Variance + Irreducible Error. Generally, big bias means underfitting, while high variance means overfitting. If we could make a good balance between bias and variance, we will find an optimal model.

For Neural Architecture Search, the simplest idea is to use one Neural Architecture Structure to search its best solution. We start with a simple MLP with only one layer, or a linear classifier. Then each time we add one layer, and of course, test this structure. We continue this until it is very deep (and becomes overfitting), then we choose the best number of layers which has the best validation error on our data set.

A more complicated idea is to use the binary search method. First, we have a simple model, $S$, as a lower starting point, for example, a linear classifier. For most cases, it would have high bias and underfit. Then, we have a complicated model, $C$, as a higher starting point, for example, a very deep neural network, which would have high variance and overfit. The general idea is shown in Algorithm 1.

\begin{algorithm}
\caption{NAS with Biase-Variance Trade-off using binary search}
\begin{algorithmic}[1]
\REQUIRE Simple model $S$, Complicated model $C$
\ENSURE A somewhat better model $B$
\STATE \textbf{repeat}
\STATE $M = \text{Find Binary Structure}(S, C)$
\STATE Train $M$ on given data set with validation
\STATE \textbf{if} $M$ overfits \textbf{then}
\STATE \hspace{1em} $C = M$
\STATE \textbf{else if} $M$ underfits \textbf{then}
\STATE \hspace{1em} $S = M$
\STATE \textbf{end if}
\STATE \textbf{until} $M$’s test accuracy is satisfactory, for example, several loops of $M$’s test accuracy almost converges, or their test accuracy does not vary much
\STATE \textbf{Output} a better model $B = M$
\end{algorithmic}
\end{algorithm}

As to the metric judging overfitting and underfitting, we could use generalization error, i.e., train accuracy - validation accuracy. If it exceeds some threshold, we assume it as overfitting. In our experiment, we set the threshold as 3%.
3.7 Energy-based learning and search of loss function

The core idea of energy-based learning [16] is that the final network is an energy function. For an input data, we find a label (classification) or prediction value (regression) that minimizes the energy. The loss function is controlling the adaptation of energy function, or measuring the quality of energy function. So the choice of loss function is the criterion to measure the energy function.

From the conclusion in the perspective of energy learning [16], log-likelihood loss function is better. It is due to the shape of energy function. Log-likelihood loss function is more concave and could converge more quickly. It is proved that generalized margin loss is also a relatively better loss function. The difference is that log-likelihood loss considers all possible labels, while margin loss only considers the correct and most offending incorrect answer. By setting a margin between correct answer and most offending incorrect answer, one can guarantee that the shape of energy function would not be too flat, which avoids a tie of different labels in the prediction. [19] also shows that entropy regularization can help find a better model with fast convergence.

For carotid data set, since we only have 2 classes, margin loss is enough. The search space enlarges because of the trade-off parameter between cross entropy loss and margin loss.

4 Results

4.1 Decision Trees and Random Forests

When training the decision tree on the three primary SRUC variables with the freedom to select any threshold, the training accuracy was $76.6526 \pm 0.9954\%$ and the testing accuracy was $73.1373 \pm 5.2375\%$. When training the decision tree on all available variables - ultrasound variables, patient demographics, and patient history - the training accuracy was $79.7656 \pm 0.9211\%$ and the testing accuracy was $72.3680 \pm 4.0209\%$. Meanwhile, the decision tree trained on all available data contains a slightly lower accuracy as a result of not predicting every single case to belong to the same class of 70-99% stenosis. In the random forest model trained only on the SRUC variables, the model had a training accuracy of $77.0438 \pm 0.8066$ and testing accuracy of $74.7134 \pm 2.7088$. In the random forest model trained on all available variables, the model had a training accuracy of $77.7239 \pm 0.6366$ and testing accuracy of $75.0974 \pm 0.9421$.

4.2 Deep Learning with ANODEs

When using both the ReLU and sigmoid activation functions, the test accuracy obtained was approximately 77%, slightly better than decision tree method. The ReLU activation function showed significant overfitting, while the sigmoid activation function did not. The ReLU activation function results in a training error of nearly zero and a testing error of about 22%. The false negative rate in the test set is about 18%. Meanwhile, the sigmoid activation function provides better generalization, with both the training and testing error at about 23%. The false negative rate in the testing
Figure 5: Decision tree trained on SRUC variables only.

Figure 6: Decision tree trained on all available variables in the data set: SRUC variables, patient demographics, and patient history.

set for the sigmoid activation function is nearly zero. These results suggest that the sigmoid activation function is a better regularizer than the ReLU activation function.

The best separation achieved when the data is augmented to an additional 6 dimensions. When augmenting the data to an additional 4 dimensions, we see improved separation between the two classes. However, there is still significant overlap. Meanwhile, we see that augmenting the data to an additional 6 dimensions results in better separation. Lastly, augmenting the data to an additional 9 dimensions shows poor separation, suggesting that overfitting has occurred.

For the choice of activation function, ReLU has a tendency for better fitting. Prevalent views also regard ReLU as better activation function because it will tackle the gradient problem. However in this dataset, ReLU results in an overfitted neural network. Also when combined with batch norm, the sigmoid activation function performs better than ReLU.

Our work with Augmented Neural ODEs provides better performance than previous classical machine learning models. Although the current results are not satisfactory for diagnosis in clinical settings, it is shown that the use of more modern machine learning methods can provide modest improvements. In light of the complexity and robustness
of the Augmented Neural ODEs, these results suggest that the current SRUC criteria variables may be insufficient to accurately predict the severity of carotid artery stenosis. By incorporating more thorough ultrasound-derived data, it is likely that the ability to discriminate between different levels of carotid stenosis severity will significantly increase.

### 4.3 Canonical-Correlation Analysis

The correlation coefficient between the SRUC criteria and carotid stenosis percentage is 0.329. If we combine the SRUC criteria with the available 23 patient history and demographic variables, the correlation coefficient increases to 0.407. It is only weak linear correlation, which further proves that the features in carotid data set could not be a strong indicator for the stenosis artery severity.

### 4.4 Bias and Variance Analysis in Model Selection

For carotid data set, we first perform the idea of linear search for the depth of hidden layers. We automatically add a hidden layer to the model, one by one. Then we train on each model, getting the result of train error and test error. For model choice purpose, we want a balance of bias and variance. Bias means train error, variance means generalization error. When train acc $>$ test acc, bias + variance = test error; when train acc $<$ test acc, bias = train error, but variance cannot be smaller than 0. So we use train error to denote it. We would like to minimize bias + variance, in this analysis, we should maximize $\min\{\text{train acc, test acc}\}$. This is the criterion we choose.

Here is the experimental result we get for carotid data set. The best chosen model has 2 layers, where train accuracy = 75.5%, test accuracy = 77.2%. The best results are similar to that of Augmented Neural ODE Net.

Then we also try cross-validation method. We randomly divide the data set into training set and validation set, for several times. Then we use the gap between training
Figure 8: Transformation of data points when augmented with an additional: (A) 4 dimensions, (B) 6 dimensions, and (C) 9 dimensions prior to entering the NODE. Dark blue indicates a positive class with a stenosis of 70–99%, while light blue indicates a negative class with a stenosis of 50–69%. ReLU activation function used. It shows that the augmented layer cannot separate those two parties well, even with powerful Neural ODE Net.

accuracy and validation accuracy as the indicator of generalization error. In our setting, we use three-folder cross validation. Results are shown in Table 1.

Further, we consider both depth (in the step of 1) and number of neurons (in the step of 4). We try depth from 1 to 5, number of neurons from 8 to 32. Since carotid data set is small, we just search all those neural architecture spaces. The criterion for evaluating bias and variance is the same as previous sections. As a result, the
Figure 9: This picture shows the training process only using SRUC criterion. As is shown, both ReLU and Sigmoid activation function lead to a flat line, where the test error is about 25%. Because the amount of data are so limited, it can hardly find a connection to divide. And it has zero negative false and tends to predict as severe stenosis block.

Figure 10: Gradient changes for a parameter in each layer. It is augmented from 3 inputs to 6 dimensions using ReLU activation. As is indicated in the picture, the lifted mapping is working because the gradient is changing steadily. However it also shows the gradient vanishing, which means the variation of parameters become smaller as the layer goes down. For our example, however, the gradient still works, which indicates that the depth is proper. If we make the network deeper, then the gradient will vanish to almost 0.

program returns the best depth as 2, the best number of neurons as 16, where training accuracy is 0.77 and test accuracy is 0.772. Although we have searched for so large neural architecture space to balance bias and variance, the test accuracy still fails to improve any more. This could serve as another evidence that SRUC variables could not be a good indicator of carotid artery severity.
Table 1: Cross-validation results of model with different number of layers. All of these model can get only about 77% test accuracy.

| Number of Layers | Avg Train Acc | Avg Validation Acc |
|------------------|---------------|--------------------|
| 1                | 0.767         | 0.760              |
| 2                | 0.760         | 0.754              |
| 3                | 0.753         | 0.778              |
| 4                | 0.753         | 0.778              |
| 5                | 0.755         | 0.771              |

4.5 Search of loss function

We add the margin loss to the previous cross entropy loss. Besides the depth and number of neurons, we also search the trade-off parameter between cross entropy loss and margin loss. We try the trade-off parameter in \{0.05, 0.1, 0.2, 0.5\}. The best result is shown in Table 2.

Table 2: Neural architecture searching results of different trade-off parameter for the margin loss. The best test accuracy is just 78.9%, only a little bit better than 77%.

| Trade-off parameter | Best Train Acc | Best Test Acc |
|---------------------|----------------|---------------|
| 0.05                | 0.755          | 0.719         |
| 0.1                 | 0.765          | 0.789         |
| 0.2                 | 0.775          | 0.772         |
| 0.5                 | 0.765          | 0.789         |

As we can see, all results are still around 77% accuracy. It further proves that even with more powerful margin loss, we cannot get better results for carotid data set. From all these experimental results above, we can conclude that current features cannot be a good indicator to the carotid artery severity.

5 Discussion

Unsurprisingly, the random forest outperforms the decision tree, resulting in a testing accuracy of 75.1% when using SRUC variables in addition to the patient demographic and history variables. When only using the SRUC variables, the random forest testing accuracy drops to 74.7%. This suggests that the use of patient demographic and history variables may be beneficial in providing more predictive power. The impact of these variables may be more evident if the model is trained on a larger patient population.

Meanwhile, we see that implementing our final ANODE model results in a testing
error of about 77%, which is a modest improvement over the random forest models. It is believed that this improvement is due to the ANODEs ability to better separate data points through augmented dimensions and the NODEs general ability to capture complex relationships between the features. However, an accuracy of 77% is insufficient for use in assisted diagnostics. The general ability of ANODEs to capture complex relationships, in contrast to the relatively poor performance, suggests that the current SRUC criteria may be insufficient in satisfactorily determining the severity of carotid artery stenosis.

We use Canonical-Correlation Analysis to explore the possibility that the data set may not contain enough discriminatory information to accurately predict carotid artery stenosis. The weak correlation coefficient of 0.329 between the SRUC variables and carotid stenosis percentages indicates that the current SRUC criteria variables are lacking in discriminatory power to capture the severity of carotid artery stenosis. Even with the addition of patient history and demographics, the correlation coefficient is still weak at 0.407. Also, Neural Architecture Search tries to find an optimal structure of neural network for carotid data set, but none of those structures could exceed 77% test accuracy. These results support the possibility that the SRUC criteria is insufficient in determining carotid artery stenosis severity. To improve future variants of the ANODE, it is strongly believed that having more information ultrasound-derived information outside of the SRUC criteria will provide an significant increase in discriminatory power.

However, another possibility for relatively low performance of the machine learning models is that the current data set is lacking in size and class balance. Consequently, an important step forward would be increasing the sample size of the data set, in addition to increasing the number of ultrasound-derived variables.

6 Conclusion

This work aims to develop a model to predict the severity of stenosis blockage based on the SRUC criteria variables and other patient information. We implement the previously used classic machine learning methods to serve as a baseline reference [18]. We improve the accuracy through ANODEs to achieve a final accuracy of about 77%. Through our theoretical analyses with Canonical Correlation Analysis and experiments with different regularization methods and neural network architectures, we believe our model performs well when considering the constraints of the data set. We see that the deep learning method is able to capture more complex relationships to provide more predictive power. Despite the improved results, there is still a need for significantly larger data set with more patients and variables before using it for clinical applications.

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