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An Analysis of the Utility of Machine Learning in Predicting Outcomes of Cardiac
Resynchronization Therapy

A Thesis submitted in partial satisfaction of the requirements for the degree Master of Science

in

Bioengineering

by

Niaz Nafea

Committee in charge:

Professor Jeffrey Omens, Chair
Professor Pedro Cabrales, Co-Chair
Professor James Perry

2018

The Thesis of Niaz Nafea is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

Co-Chair

Chair

University of California San Diego

2018

EPIGRAPH

Knowledge is as wings to man's life, and a ladder for his ascent. Its acquisition is incumbent upon everyone.

Bahá'u'lláh

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LIST OF ABBREVIATIONS

AI: Artificial Intelligence
ANN: Artificial Neural Network
AV: Atrioventricular (node)
CoVW: Coefficient of Variation of Work
CRT: Cardiac Resynchronization Therapy
DI: Dyssynchrony Index
ECG: Electrocardiogram
EDV: End Diastolic Volume
EF: Ejection Fraction
ESV: End Systolic Volume
HF: Heart Failure
HFpEF: Heart Failure with preserved Ejection Fraction
HFrEF: Heart Failure with reduced Ejection Fraction
LA: Left Atrium
LBBB: Left Bundle Branch Block
LV: Left Ventricle
ML: Machine Learning
PCA: Principal Component Analysis
RA: Right Atrium
RAM: Random Access Memory
RV: Right Ventricle
SA: Sinoatrial (node)
SVM: Support Vector Machine
VCG: Vectorcardiogram

ABSTRACT OF THE THESIS

An Analysis of the Utility of Machine Learning in Predicting Outcomes of Cardiac Resynchronization Therapy

By

Niaz Nafea

Master of Science in Bioengineering

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Professor Jeffrey Omens, Chair

Professor Pedro Cables, Co-Chair

Cardiac dyssynchrony can lead to heart failure. Cardiac Resynchronization Therapy (CRT) is a procedure which restores synchrony to the heart, allowing the heart to function as intended. Previous research has shown that patient-specific computational modeling of

dyssynchrony and CRT can be useful in predicting the outcome of the clinical procedure. Machine learning may be another technique to predict outcomes of medical procedures, including CRT. The application of machine learning to CRT patient outcomes has not been thoroughly investigated, though it may be able to categorize dyssynchrony with similar accuracy as previous complex models, in less time. Patient models were analyzed to determine the efficacy of machine learning as a means to predict outcomes of CRT. Vectorcardiogram data for virtual patients was used to train and test the capabilities of machine learning for determining a dyssynchrony index output, the same output found with the patient-specific computational models. The accuracies of the machine learning outputs were compared to determine the optimal amount of input data needed. Patient physiological parameters were compared to the dyssynchrony index prediction. It was determined that when looking at the simulated patients for whom there was data, varying the amount of input data per patient had no effect. Increasing the number of patients increased the accuracy of the prediction, while most physiological parameters had no clear correlation to the accuracy of the prediction. Further tests with additional data can be carried out to look deeper into using machine learning to predict outcomes of CRT.

BACKGROUND

Cardiac Electrophysiology

The conduction system of the heart is based on the transmission of depolarizing waves throughout the heart. Sinus rhythm within the heart begins at the first depolarization of cardiac tissues which occurs in the sinoatrial node (SA node). The SA node is referred to as the heart's natural pacemaker because of its role in maintaining cardiac rhythm and beginning the depolarization which continues throughout the heart. After the SA node, the atrioventricular node (AV node) is depolarized. The depolarizing wave continues into the Bundle of His, the right and left bundle branches, and the Purkinje fibers (Medline).

Physiologically, these depolarizations have different intensities based on the fibers they are going through and the contractions and relaxations that occur as a result of the changing electrical potential (Theis). As the impulse travels from the SA node to the AV node, the atria contract, and as the impulse goes through the Purkinje fibers, the ventricular muscle is stimulated, causing the ventricles to contract (systole) as the atria relax. Ventricular relaxation (diastole) occurs afterwards (Federmann).

Dyssynchronous Heart Failure

Heart failure occurs when the heart is unable to supply the body with the amount of blood it needs. Mechanically, heart failure can be categorized based on the loss of ability of the left ventricle; systolic heart failure is the result of the left ventricle being unable to contract properly, and diastolic heart failure is the result of the left ventricle being unable to relax properly. Systolic

heart failure is also known as heart failure with reduced ejection fraction (HFrEF), and diastolic heart failure is also known as heart failure with preserved ejection fraction (HFpEF) (Lee, D).

One in every four deaths in the United States can be attributed to heart disease (CDC). This makes heart disease the leading cause of death in America for both men and women. It is important then to look at some of the causes of heart disease and heart failure in order to take preventative action.

Heart failure can be due to cardiomyopathy, coronary artery disease, valvular heart disease, high blood pressure, myocardial infarction, diabetes, obesity, sleep apnea, and other issues within the heart including cardiac dyssynchrony. Dyssynchrony is often caused by left bundle branch block (LBBB), and it can result in a widened QRS duration and dilated cardiomyopathy. Dyssynchrony in the heart is characterized by the out of tune pumping of the ventricles to each other, or the ventricles to the atria. It is caused by differences in time of electrical activation of the ventricles. Dyssynchrony within the heart is typically characterized by using QRS lengths and lack of cardiac efficiency, and is known to be a factor in heart failure (Verbeek). Not every dyssynchrony is the same, though, as some patients have normal QRS lengths while also having cardiac dyssynchrony.

Dyssynchrony Index

Dyssynchrony, occurring as a result of different regions of the heart contracting at different times, can be described using the dyssynchrony index (DI) (Miyazaki). The types of dyssynchrony seen with the LBBB consist of early activation of the interventricular septum, followed by late activation of the lateral and posterior left ventricle walls. This dyssynchrony results in loss of function of left ventricular systole (Bax). Measurement of the variance,

specifically the standard deviation, of the differences of times of activation, results in the value seen as the DI.

Cardiac Resynchronization Therapy

Cardiac Resynchronization Therapy (CRT) is a method used to restore electrical synchrony to the heart, thus allowing the heart to function mechanically as intended (Semigran). It is an invasive procedure and has been seen to increase long term survival.

CRT restores electrical synchrony by pacing both of the ventricles simultaneously. Leads for the left and right ventricles are placed in the endocardium or epicardium, connected to a subcutaneously implanted pacemaker. The pacemaker triggers the leads and allows the heart to pump in normal rhythm (Kass).

The Electrocardiogram

Electrocardiograms (ECGs) are readings which give an indication of the electrical impulses within the heart over a given time. ECGs are useful in determining electrophysiological properties of the heart (Davie). These properties are determined by measuring electrical potential from twelve different angles, and the ECG displays the potential throughout the entire sinus rhythm from each of these angles.

An electrocardiograph is a biomedical device which displays the electrical activity of the heart based on electrical impulses which occur during systole and diastole. The display is known as an electrocardiogram. Through the 19th century and beyond, physicians and clinicians began integrating technology into their practical methods. In 1877, a British physiologist published the first human electrocardiogram (AlGhatrif). This was done using a capillary electrometer (used to

measure current) and electrodes. This design continued to be improved into the late 1800's. A Dutch physiologist named Willem Einthoven coined the term "electrocardiogram" in 1893. Refining the capillary electrometer to catch smaller and smaller details, he more accurately saw (and named) the PQRST waves. In 1901, his string galvanometer, also known as Einthoven's galvometer, produced what was considered the first practical and reliable electrocardiogram (Serge). This string galvanometer worked differently from other machines in that it used metals, molten glass, and electromagnets, while the patient had his appendage placed in buckets of saline solution (Bowbrick). Einthoven was later awarded the Nobel Prize in Physiology or Medicine.

The original string galvanometer was very useful indeed, but not as practical as it could have been. Beyond requiring the placement of the hands and one foot into saline solutions, the machine itself was also hundreds of pounds. As it saw more use in clinical settings (the first ECG machine in the United States was in 1909), improvements were also made in order to make it more practical. The hardware of three-lead electrocardiographs continued improving. The three leads were placed at 60 degree angles in relation to each other, making a triangle on the chest known as Einthoven's Triangle. Although many initial uses of electrocardiographs were to study and spot arrhythmias, in 1910 myocardial infarction was determined to be a clinical entity (Cohen), and use of electrocardiograms to distinguish heart disease from other abdominal afflictions was on the rise. Certain patterns were becoming more obvious to those trained to read them. At the same time, portability was enhanced on ECG machines.

The trained eyes began to realize that certain myocardial infarctions were invisible on the ECGs, without any pattern or wave. Ground leads, also known as "exploring leads" were useful to track electrical changes in the heart compared to other places in the body. The six leads V1-V6 were born from this understanding, and were recommended in the West by 1938 (AlGhatrif).

Physicians and clinicians were also noticing that there was potential for other spots on the chest which would not be visible to the ECG of the day. Through tests, there were locations found for three other leads, in addition to the initial three and the six additional leads from 1938. Twelve lead ECGs were recommended in the West by 1954 (Edenbrandt). In this way the electrocardiogram evolved from being fairly limited to being a versatile test of cardiac electrical activity.

Since that time, many advances have been made in cardiology, especially with relation to the mechanical and electrical features of the heart. The first implantable pacemaker was implanted soon after, in 1958 (Plummer). Sudden death from ventricular fibrillation was noted in 1960 when premature beating occurred at the same time as the T wave, building off the studies of Einthoven (Smirk). Sudden heart death is also related to the arrhythmias initially studied (and still studied) by use of electrocardiographs. Throughout the coming decades, other diseases, symptoms, and maladies were discovered, observed, and researched through use of more accurate and sensitive electrocardiogram machines. The magnetocardiogram was detected and observed in 1963 (Baule). The idea of the magnetocardiogram is that it can detect the magnetic field of the heart, and through this, it can create an ECG without using physical electrodes attached to the body. There is a lot of potential use for a machine like this, however it would be susceptible to problems due to noise, and it has also proved to be expensive.

Considering the vast amounts of new information and technology coming to light, the *Journal of Electrocardiology* was created in 1968. The purpose of the journal, as stated by the journal itself, is to present findings on the study of the relation of the heart to electricity, both applied to and by the heart (Zao). The writers stated that this journal was considered “long overdue” considering the amount of papers submitted to other journals. Cardiologists continued

discovering different uses for electrocardiographs, such as “rabbit ears” which could be used to distinguish ventricular ectopy from aberrations (Gozensky). Bioengineers later discovered, that by using a Laplacian map of anatomical electrical potentials, cardiac electric activity could be mapped (He).

There have been a handful of reasons for expanding study of electrocardiograms. Research has been done to allow ECGs to be non-invasive, cheaper, more precise, determine between different afflictions, allow for less noise, and to determine genetic differences in electrocardial properties. In general, these changes will allow for better readings of ECGs, yielding faster and more accurate differentiation of cardiac disturbances, ultimately resulting in a better understanding of electrocardiology. Different electrocardiographs have use in different settings, such as in surgeries, before surgeries, for ECG specific tests to determine the status of the heart, and even as a part of routine physical examinations. These electrocardiographs then may have differences amongst themselves, based on whether they need to be more portable, or whether they need to be as accurate as possible, or whether they need to be especially fast, or other such characteristics.

ECG Physiological Relevance

An ECG consists of waves in relation to a baseline. This baseline denotes the potential of the heart before depolarization and after repolarization. The first wave, the P wave, is a result of atrial depolarization, which occurs after the impulse passes through the SA node. The QRS complex follows, and it indicates ventricular depolarization, preceding ventricular contraction. The final wave is the T wave, which is a display of ventricular repolarization, preceding ventricular relaxation. The intervals between the waves are indicative of the time it takes for the

impulse to travel. For example, the interval between the P wave and the peak of the QRS complex, the R wave, is known as the PR interval. The PR interval indicates the amount of time taken between SA node depolarization and ventricular depolarization.

The Vectorcardiogram

Vectorcardiography (VCG) is a method of determining the magnitude and direction of electrical pulses within the heart. Three orthogonal leads are used in VCG in order to measure the direction of electrical current in three dimensions. Vectorcardiograms are useful to determine heart shape, to see electrical abnormalities occurring within the cardiac conduction system, and to determine the dyssynchrony index. They can be synthesized from electrocardiograms (Edenbrandt).

Machine Learning

Modern versions of computers and programming in general were pioneered around the 1800s by Charles Babbage, and expanded upon by Ada Lovelace. Babbage designed an Analytical Engine intended to carry out algorithms and math, with other potential purposes and functions (Swade). Over 100 years after his design, there was an implementation of his design into an actual machine. This is considered to be the first general purpose computing device, including logical loops, arithmetic calculations, and internal memory.

Late in the 19th century, the first analog computers were made for computation of single problems. In the early 1900s, analog computers began to rise in popularity, especially for time variant problems (Williams). This was in contrast with Turing machines, which are designed to be able to reproduce the same solution to the same problem. A Turing machine (named for Alan

Turing, a computer scientist) is a computing device which uses an infinite “tape” on which to solve certain problems (Hennie). It can be programmed to compute specific algorithms in a similar way as modern computers. In contrast, a modern computer can do more than just mathematical computations, without “infinite” memory; random access memory (RAM) takes the place of this.

After the era of analog computers, digital computers began to gain prominence. Digital computers use Boolean algebra to solve equations, often in binary or decimal (Muller). Electronic computers were built first in the late 1930s, with mass production beginning in the 1940s, but these computers were limited in the scope of their programming. A distinguishing feature of later computers of the 1940s is that they could be programmable, so these later computers are Turing-complete, meaning they can solve problems that any Turing machine can solve.

The programmability of computers was expanded upon in the 1950s, when initial machine learning was pioneered via the use of basic algorithms. In 1950, Alan Turing published *Computing Machinery and Intelligence*, a paper which is most widely known for its introduction of the ‘Turing test.’ The Turing test is designed to judge whether a machine is able to display intelligence equivalently to a human (Epstein). A typical Turing test would have a judge asking questions to two respondents, one machine and one human. If the judge cannot determine which participant is which, the machine has passed the Turing test. Around this time, artificial neural networks began to be created. Artificial neural networks are machines which are designed to work similarly to animal brains, specifically their natural neural networks (Hopefield). This works by the use of nodes and connections, which act as neurons and synapses, through which data is transmitted. For example, Stochastic Neural Analog Reinforcement Calculator (SNARC)

was created in 1951, which was essentially a simulation of a rat trying to find its way through a maze (Franklin).

Different machines pioneering artificial intelligence continued to be developed throughout the 1950s. In fact, in 1956, the Dartmouth Summer Research Project on Artificial Intelligence, also known as the Dartmouth Workshop, occurred. This event is often considered to be the seminal event for the field of AI. (Crevier) The Dartmouth Workshop lasted for over a month, with different professors, mathematicians, and scientists coming together to discuss topics related to artificial intelligence.

As the field of AI began to blossom, implementations of smart machines began focusing in many directions. For example, in 1966, a machine designed to respond to humans, aka a Chabot, was created. This Chabot, named ELIZA, was one of the first machines to pass the Turing Test (Bradesko). In 1970, the word “bioinformatics” was formed. Bioinformatics has come to include the computerization and study with machines of different kinds of biological data.

Historically, the field of AI has gone through some zeniths and nadirs of popularity; as hype increases, funding and public perception increase. However, with the hype come increased expectations, which often aren’t able to be met due to limitations in technological advances, so hype dies back down until the next wave of popularity. One such nadir of public acceptance of AI occurred around 1974, when the first “AI Winter” began (Hendler). At times like these, advances in technology of AI decrease due to a decrease in funding. In 1980, the International Conference on Machine Learning (ICML) was first held.

As artificial intelligence as a field continued to blossom, and machine learning began to grow into its own subfield, certain milestones began to be reached. For example, in 1985, the

term “computational neuroscience” was coined, indicating the advances in that field. The journal “Machine Learning” had its first volume in 1986. *Machine Learning* is a journal dedicated to recording advances in machine learning. In 2000, after a decade of deep learning rising in popularity, the *Journal of Machine Learning Research* was first published, with a similar aim as *Machine Learning*. Advances continue being made in a variety of fields. Commercial tasks, like facial recognition on Facebook, use deep learning, for example. Deep learning also has a variety of uses in the biomedical field, and as technology continues to advance, its uses in improving health will multiply.

Machine learning builds off of artificial intelligence in developing machines which can find patterns in data and use these patterns to predict or make decisions. Machines which use machine learning can be coded in various ways, using various algorithms. They can be grouped by similarities and in the ways they function. An example of a machine learning algorithm is an artificial neural network (ANN), which uses non-linear statistics to find patterns between inputs and outputs of data (Hopfield). Different machine learning devices can have inputs and outputs fed to them, and can use the data from these inputs and outputs to deliver outputs when new inputs are given. In supervised learning, the machine can be told when the output it has given is incorrect, so it can become more accurate. In unsupervised learning, the output of the data is unknown, so the machine cannot be corrected when it is wrong. A mixture of these is also possible, in semi-supervised learning.

Applications of machine learning to ECGs

The potential of machine learning for medical diagnoses has been seen for decades (Kononenko). Machine learning has been applied to ECGs in various ways. ECGs have been plugged into machine learning algorithms to predict cardiovascular disease (Jin).

Many different algorithms have also been made to use machine learning for arrhythmia analysis and classification (Guvenir, Kim, Soman). Many of these kinds of studies have made use of the MIT-BIH arrhythmia database, which has information from around fifty patients.

Analyzing and detecting arrhythmias is important since arrhythmias can be common, but can also lead to greater problems including cardiac arrest and stroke. This sort of arrhythmia analysis can also be paired with other forms of analysis including support vector machines and principal component analysis (Polat). Support vector machines are supervised learning algorithms which are often used for categorization. Other algorithms have been used for tachycardia classification, and ischemia classification (Li, Marsanova). Machine learning has also been used to analyze and improve the diagnosis of ischemia based on ECGs, helping to detect heart disease (Kukar). These sorts of studies can use data from anywhere between dozens to hundreds of patients.

Further applications of machine learning to ECGs include wearable devices meant to detect cardiovascular disease by continuous analysis of the ECGs (Oresko). Machine learning is also being used to classify the quality of ECGs themselves, which is important since clearer ECGs can lead to more accurate diagnoses (Li). Related, machine learning is also being used for general quality control of ECGs (Chen). Machine learning is also being used to detect shock rhythms generated from external defibrillators (Figuera).

Applications of machine learning to VCGs

Machine learning is being researched to improve general heart monitoring activity in conjunction with VCG data (Perumalla). Support vector machine models have been used for personal identification with the aid of VCGs (Lee). VGS have also been analyzed with machine learning models to detect myocardial infarction (Tripathy). The field for application of machine learning to VCGs is relatively new and still growing.

Previous Computational Model for CRT Patient Prediction

A previous model tested by Villongco was found to be able to determine patient specific left ventricular dyssynchrony (Villongco). The model has potential to predict reverse remodeling, which is a marker of lower mortality for patients with heart failure. The model applies different algorithms and math to the electrophysiological data of the patients in order to come to the dyssynchrony index, and to estimate the viability of cardiac resynchronization therapy for the tested patients. This model provides a stepping stone for the determination of dyssynchrony index from patient data, but the complexity of the model makes it more challenging to study many patients. It is possible that a machine learning algorithm could be used in a similar manner to predict the dyssynchrony, faster than the current available models.

Machine Learning for CRT Outcome

A machine learning algorithm has been developed with the aim of predicting the dyssynchrony index quickly and effectively among potential cardiac resynchronization therapy patients. The algorithm takes VCG data as its input, processes and randomizes it. There are seven simulated patients from which data is taken. From an original set of eight patients, the first

patient (Patient 1) was removed due to lack of data. The data from each of the remaining seven patients (Patients 2-8) is tested against itself, and then against other data, in order to output a prediction of the dyssynchrony index. A related confidence level is calculated, which compares the machine learning DI prediction and the prediction from an algorithm like that used by Villongco.

There is an assumption that the algorithm DI prediction is correct, and the ML undergoes optimization to get a greater confidence level, and the algorithm is set to find a confidence level greater than 90%. The algorithm has not yet been analyzed to determine the accuracy of the machine learning given different inputs, and different amounts of inputs.

If proven to be effective in predicting DI, machine learning can be used to remove intermediate steps that are present in the current DI prediction model. This will be useful in reducing the amount of time and cost necessary to predict DI, and thus predict outcomes of cardiac resynchronization therapy.

Specific Aims

An aim of this project is to determine how varying input parameters of machine learning data will cause less error in the dyssynchrony index prediction outputs. A machine learning model that takes vectorcardiogram data to predict dyssynchrony indices will be used to determine the amount of patient data needed for optimal results. This includes the amount of data per patient, and the amount of patients used overall. The machine learning tool will be manipulated to alter the amount of data used for training per patient. Other parameters that will be considered are the order of data analysis and the specific patient being tested. These results

will be compared with non-machine learning computational model values to determine the efficacy of using machine learning as a means to predict patient outcomes of CRT.

Another aim of this project is to determine how heart geometry and physiological parameters are related to machine learning dyssynchrony index prediction. Factors in individual hearts can have different significances in the machine learning process, and possibly categorize the outputs of these prediction algorithms. Physiological parameters that will be tested include age and illness, as well as geometry of the heart. Comparing the results of the machine learning prediction values to the physiological parameters will help increase understanding of what causes the machine learning to be more or less effective in predicting patient outcomes.

If the machine learning algorithm is capable of predicting the same results as a more complex, patient-specific mathematical model, machine learning could replace the more complicated and time-consuming models. Machine learning could prove to be more effective and faster than computational models. This would provide a new way of understanding patient clinical VCG data, and applying it to cardiac resynchronization therapy outcome predictions. If the current process and algorithms with machine learning prove to be effective, they could also be applied to other aspects of cardiology, or other fields of medicine.

MATERIALS AND METHODS

Current machine learning tool for DI analysis

Beyond current machine learning tools currently used for DI analysis, searching was done online to determine if there were other viable general tools which could be specified for this sort of machine learning prediction. The overall conclusion from looking at various sources, including Google, Amazon, Github, Microsoft, and other machine learning software, was that it is currently better to stick to the present tools, and alternate tools may be considered in the future.

The current machine learning tool takes simulated VCG data derived from real patient data. Data is created for simulated patients based on real patient data. The data contains VCGs. The first part of the algorithm initializes Matlab, and then grabs the data and puts it into a form for Matlab to read more easily. It loads VCGs, dyssynchrony index, and conductivity. It discards where $DI=0$, so only the values where the DI is actually read remain (in theory). Since the patients are simulated, some of the data may be unrealistic. The input VCG data is randomized by the code, which is the most effective given a certain sample size.

The code trains the algorithm using patient data, first by initializing variables and matrices intended for use deeper in the experiment. The supervised learning portion of the algorithm then occurs, based on a certain kernel. During this portion, the training data is built up.

After the machine learning portion of the code is ran, validation occurs, with a Gramian (G) matrix which determines if a set of matrices is independent. It is independent if the G matrix is not equal to 0. This helps to establish a confidence level, which is used to tell the algorithm when to stop running.

Overall, the code takes VCG data, plugs parts of it into a machine learning code, and uses the data to predict the dyssynchrony index, which is presented at the output. Some data points are removed from the data. The removed data points give dyssynchrony indices of 0. These points are removed because they can be assumed to be errors, since all of the patients are assumed to have cardiac dyssynchrony resulting from left bundle branch block. The DI prediction can then be compared with a prediction from a computed algorithm, and the error between this prediction and the computed algorithm can be measured to determine the accuracy of the machine learning.

Application of Machine Learning Tool

An early aim of the experiment was to get outputs using different amounts of data and different data sets in order to determine whether there is significance in using different data.

Patient data is often randomized in machine learning applications to ensure that patient data being used does not correlate with the data around it. Patient data was randomized in different ways within the algorithm, and then trained without any randomization, to determine the effects of randomization on the outputs, given the patient subjects.

Different amounts of patient data can be used to train the patient data in order to determine the DI. With more patient data, the DI prediction error would supposedly go down, while with less patient data, the error would go up. However, running the code with more data takes more time. Another aim of the experiment was to determine whether the increase in accuracy is worth the increase in computation time, and if so, looking into using an alternate method of computation for the machine learning.

After altering the amounts of patient data put into the algorithm, different individual patients themselves were tested to determine the effect of patient number on dyssynchrony index

prediction error. It became apparent that patient number had less to do with error than the patients themselves being used. Different patients had different amounts of DI prediction error from machine learning predictions. One patient in particular had a higher error than the other patients, even when manipulating the amount of data used. Dimensionality reduction, especially through principal component analysis (PCA), is used to reduce random variables. In this case, it can be used for feature extraction to try to determine why a certain patient has higher error. Dimensionality reduction can also be done via non-negative matrix factorization and kernel principal component analysis. Kernels are used in machine learning for pattern analysis.

Looking into the discrepancy in patient dyssynchrony index prediction errors, physiological parameters were considered. Patient data was modeled in Blender, a three dimensional modeling software, and differences in heart geometry were observed and compared. Differences in VCG geometry were also visualized and compared using Blender, and physiological geometry was analyzed to determine if it had any apparent effect on the results.

RESULTS

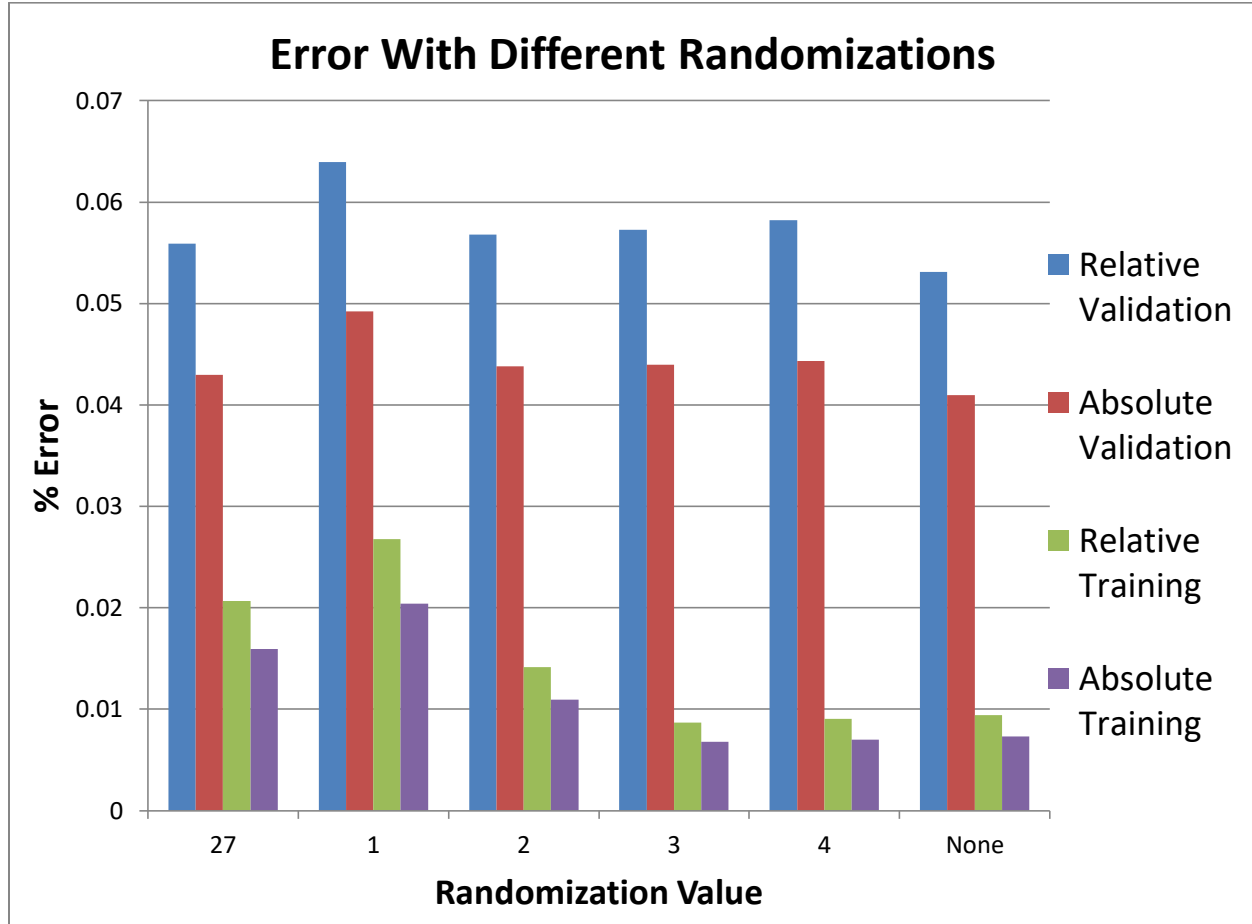


Figure 1: Data is re-ordered in machine learning projects to try to decrease correlations within data. In this project, changing the randomization did not affect the dyssynchrony index output by more than 1%. It is possible that this would not be the case with different amounts of data.

In general, when predicting the patient outcomes, the patient data is randomized, as is the case with other machine learning projects, to reduce the number of correlations within the data being trained. The randomization occurs in the same way each time the data is used to predict the dyssynchrony index, depending on the “Randomization Value” used. The Randomization Value was changed multiple times, and removed altogether, to determine the effect of randomizing the data. It was determined that the randomization had a small effect on dyssynchrony index prediction. For validation, the change in error was less than 1% when comparing any two

randomization values, while for training, the change in error never exceeded 2%. Note that the relative error is the absolute error divided by the magnitude. Relative error is absolute error divided by the magnitude of the error. Training error is looking at the error based on the data trained by the algorithm, and validation error is the error based on the data which is not trained by the algorithm. All of the errors being examined are the errors between the machine learning dyssynchrony index prediction compared with the computational model.

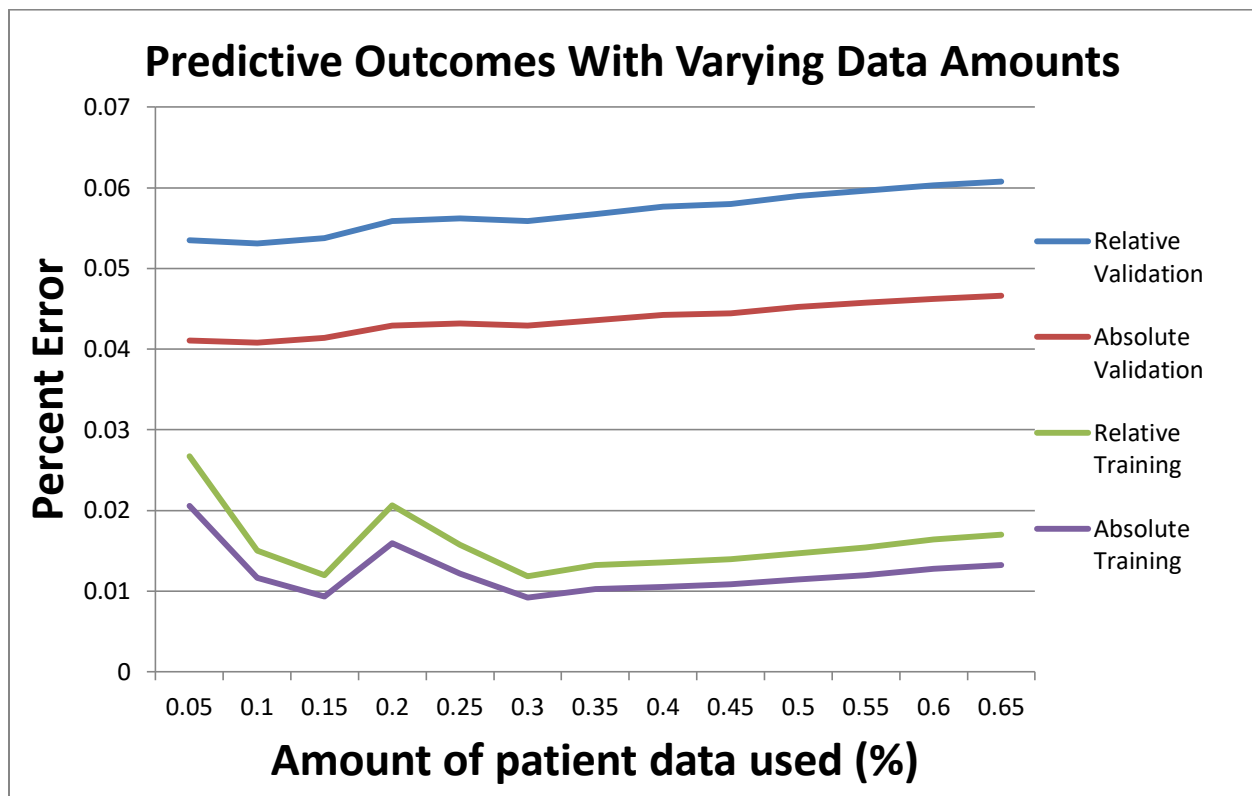


Figure 2: Error was very small throughout the experiment. Increasing the amount of data used often serves to decrease data, but in this case, after 30%, the error seemingly increased. This might be due to compounding of the small error.

Patient data was input to yield a prediction of CRT outcomes. Varying the amounts of patient data used to train the algorithm yielded low variance in DI prediction error. The training error, which is based on a comparison between the training data and the output prediction, was lower than the validation error, which is based on a comparison between the training data and

untrained data. This was expected. Absolute errors were lower than relative errors, and that was also expected. Notably, once at least 20% of the data was used for training, none of the errors changed by over one percent. In general, once at least 30% of the data used, using more data for training yielded slightly higher errors. Each amount of patient data used went through multiple trials, and the results were averaged.

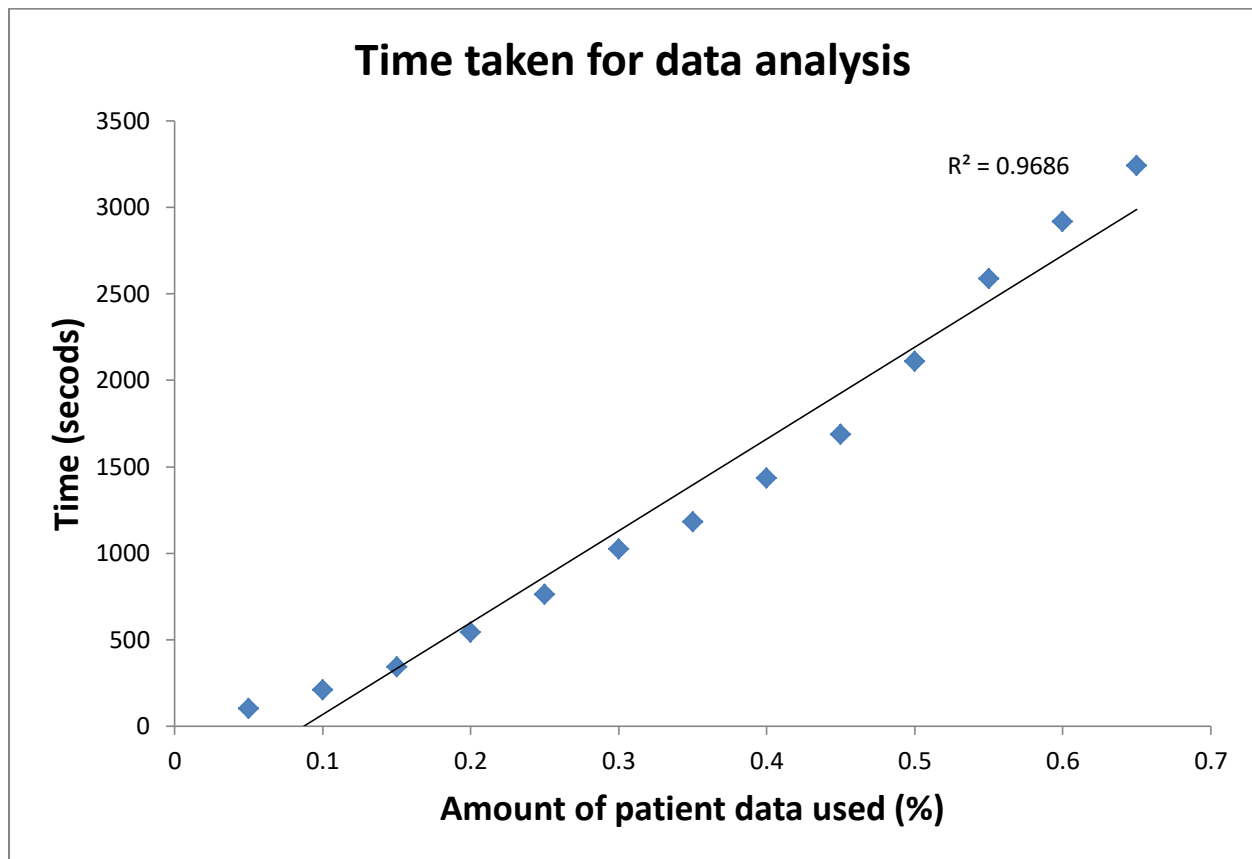


Figure 3: The linear relationship seen between the amount of data used and the time taken for the algorithm to run suggests that including a larger sample size will not cause the machine to run for an extreme amount of time. With this in mind, and given the strong correlation shown, adding more data should not be an issue as far as time is concerned.

Each trial was also timed, to see how the amount of patient data used in training would cause a change in the amount of time needed to take data analysis. As seen in Figure 3, the

results show that using more data for training increases the amount of time needed for a prediction to be output. The result was apparently linear with an R^2 value of 0.9686.

Testing was then conducted to determine whether the number of patients being tested at any given time had a bearing on the prediction. It was determined that certain patients caused the results to skew, which was even evident in groups of patients, as shown in Figure 3.

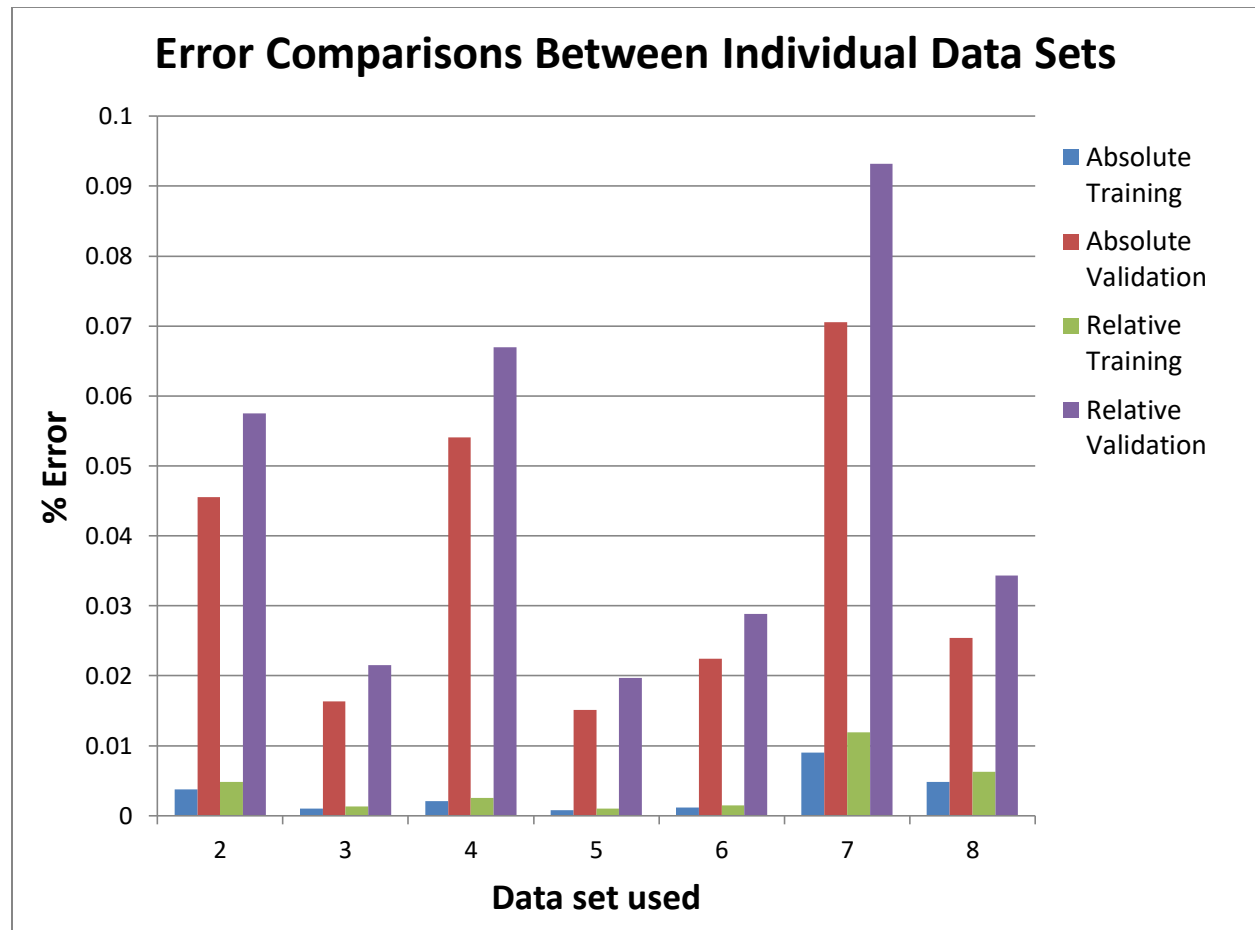


Figure 4: Patients can be placed into subgroups based on the amount of error they have. Here, patients 2, 4, and 7 seem to have almost twice the error of patients 3, 5, 6, and 8, meaning that their physiologies may be in such a manner that they can be divided into two groups. Especially of note is patient 7, with over 1% more error than any other patient. Patient 3, with low error, and patient 7, with high error, are observed further in following figures.

Individual data sets were ran multiple times to determine how well the algorithm was able to predict the dyssynchrony index given the VCG inputs, shown in Figure 4. Patient 7 was

found to have the most error in DI prediction, over twice that of many other patients when observing both training and validation error. This is highlighted in Figure 4, where patients 3, 5, and 6 are seen to have barely any training error, while Patient 7 has around 1% error simply from validation.



Figure 5: Patients placed with other patients in the same subgroup does not appear to affect error. It seems to be the case that patients with higher error, like patient 7, continue to affect the output with higher error. Error for couples is lower than error for individual data sets, in general.

When examining the data sets in groups of two, the disparity between datasets becomes more obvious. Dataset 3 is shown in Figure 5 in groupings with Patient 5, 2, and 7. When comparing the Relative Validation Error, for example, Patients 3 and 5 together had around a 2%

error, compared to around a 6% error when Patient 3 was put with Patient 7. Results when observing the differences between other patients were similar.

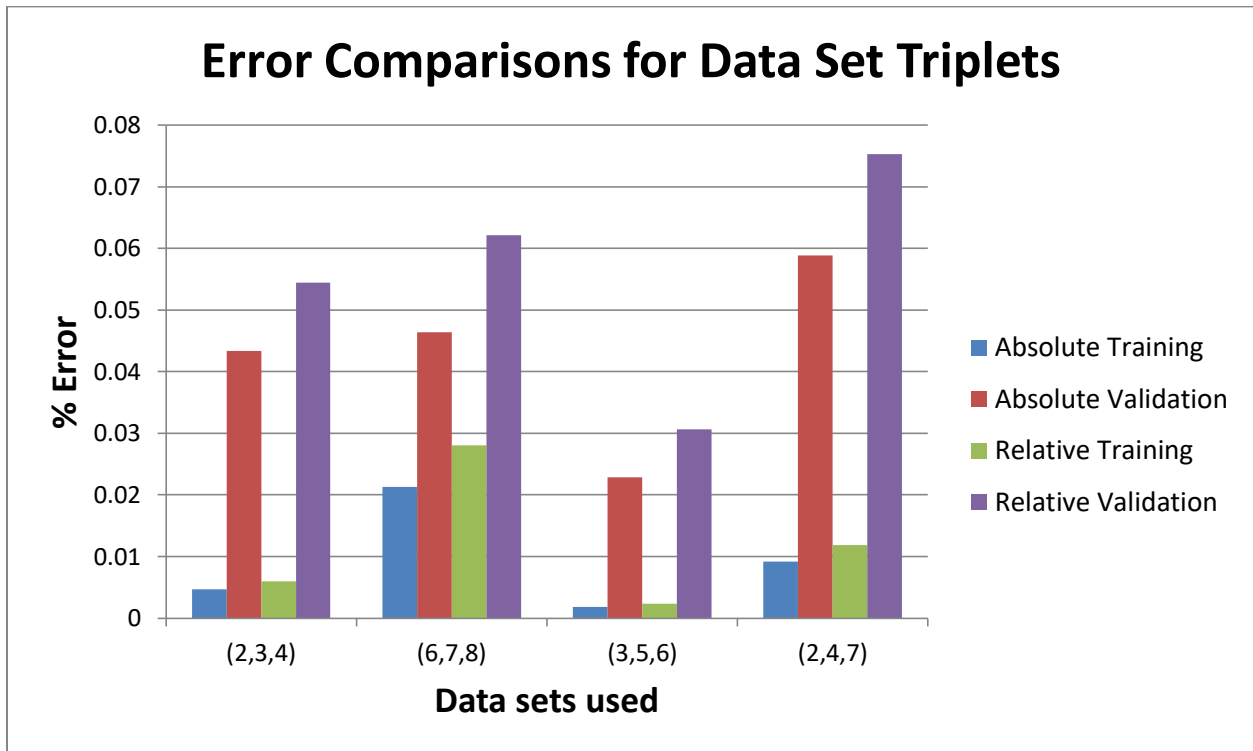


Figure 6: Combining subgroups such as 2, 4, and 7 appears to average out the output errors between these groups, rather than cause it to significantly decrease due to having the same type of error. Meanwhile, since patient 7 is no longer alone, the maximum error of any set is lower than when comparing individual patient sets. Patient 3 remains with fairly low error.

In each of these tests, shown in Figure 6, three different patients were used to train data for each other. With no other variations in how the amount of data changed, or how the data was used, it is evident that there is a change in error, even if one patient in a set of three is changed. For example, the relative validation error for the set of patients 2, 3, and 4 was around 5.5%, compared to around 7.5% when Patient 7 replaced Patient 3. These results were further highlighted when examining sets of two patients, and when highlighting individual patients.

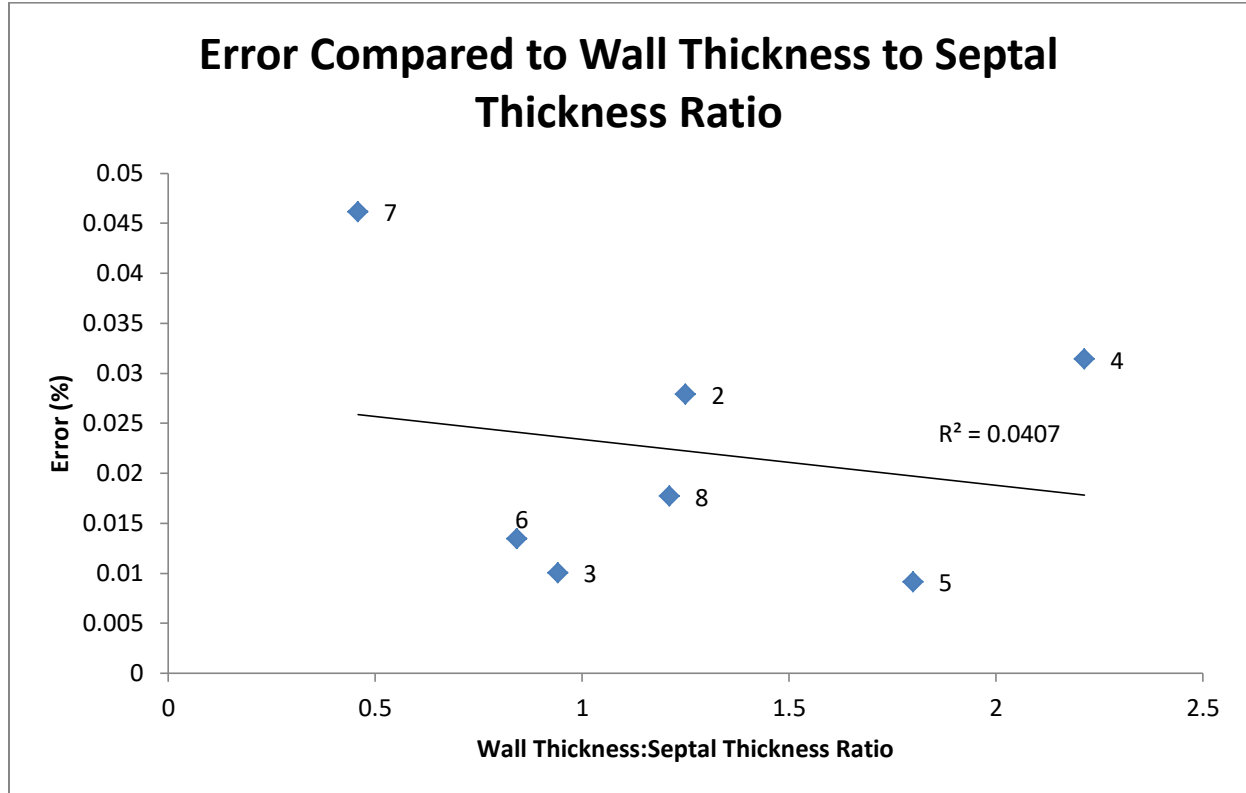


Figure 7: None of the geometric features which could be measured using 3D imaging software had any apparent effect on the overall dyssynchrony index output. Shown here, wall thickness to septal thickness had a very small R^2 value, suggesting that geometric features being analyzed had no bearing on the error.

Data from the patient hearts was observed using 3D modeling software, and specific measurements of heart geometry were measured, including diameter, wall thickness, and septal thickness. Related ratios, including wall thickness to septal thickness, shown in Figure 7, were also measured, and the results were plotted against the percent error which had been previously tested, with percent error averaged out. There was no correlation ultimately found between the error and the physiological measurements. For example, adding a linear trend line to the data in Figure 7 yielded an R^2 value of 0.04, and other potential trends including exponential and quadratic were similarly poor fits.

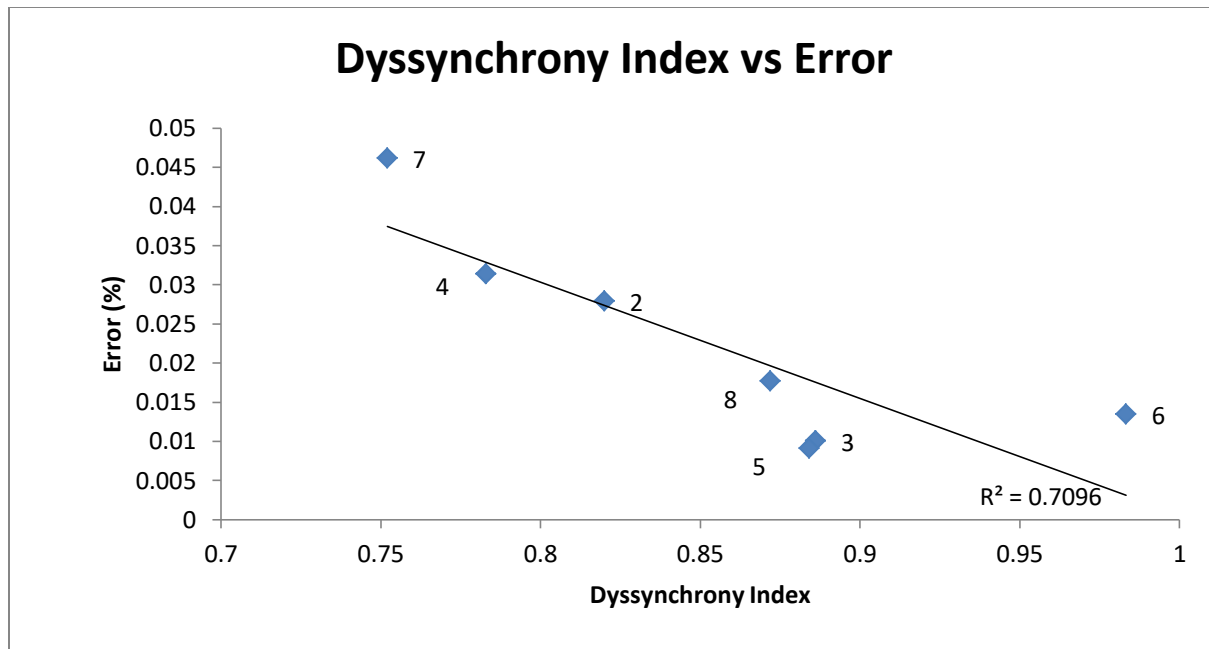


Figure 8: The model is used to examine vectorcardiograms to measure dyssynchrony, so more dyssynchrony would be more likely to be detected in the model. With that in mind, the result shown here that a higher DI correlates with a lower error, is sensible.

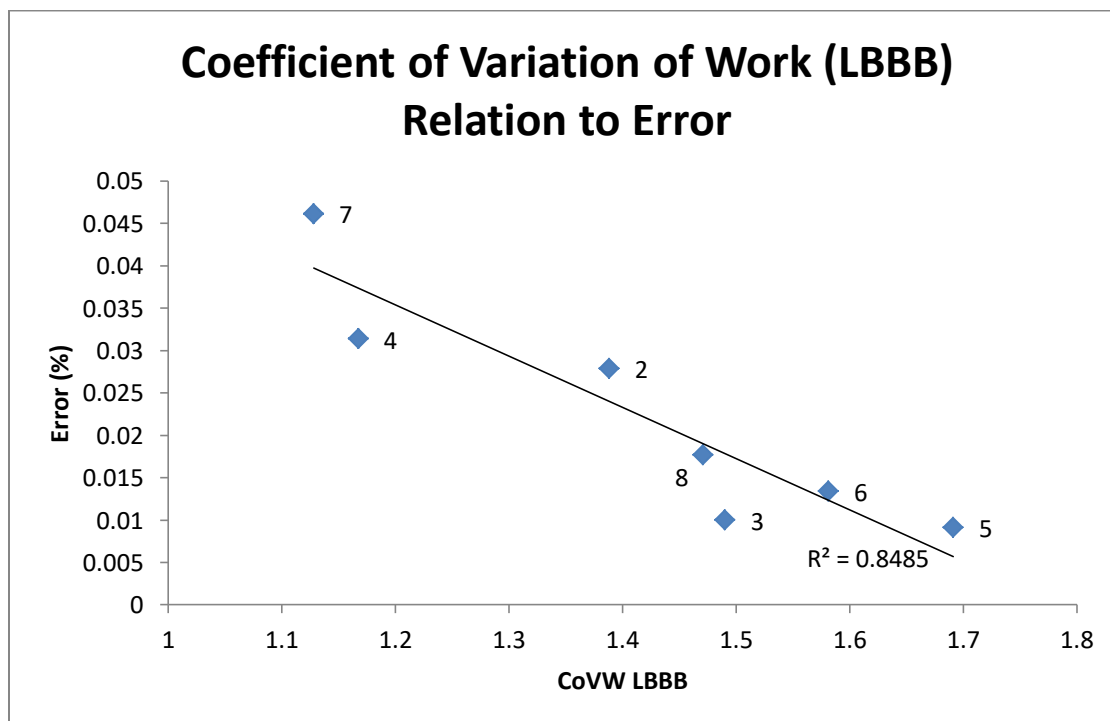


Figure 9: The coefficient of variation of work, which is a model of the variability, should be increasing as the dyssynchrony index increases, and so as the CoVW increases, there will be more dyssynchrony which the model will catch more easily. So here, it also makes sense that the error decreased as variance increased.

Other physiological features of the patients were compared to the prediction error from each patient. Some features, including left ventricular end diastolic volume, left ventricular end systolic volume, QRS length, and post left ventricular ejection fraction had no apparent bearing. Other features, including dyssynchrony index, and the Coefficient of Variation of Work (COVW) of the Left Bundle Branch Block were nearly proportional, with R^2 values of 0.710 and 0.849 respectively. Coefficient of Variation of Work is calculated by dividing the standard deviation by the mean, to determine the relationship of the variability of a process, in this case the Left Bundle Branch block. COVW is then essentially the variability of the work of hearts with LBBB. Synchronous hearts have lower variance.

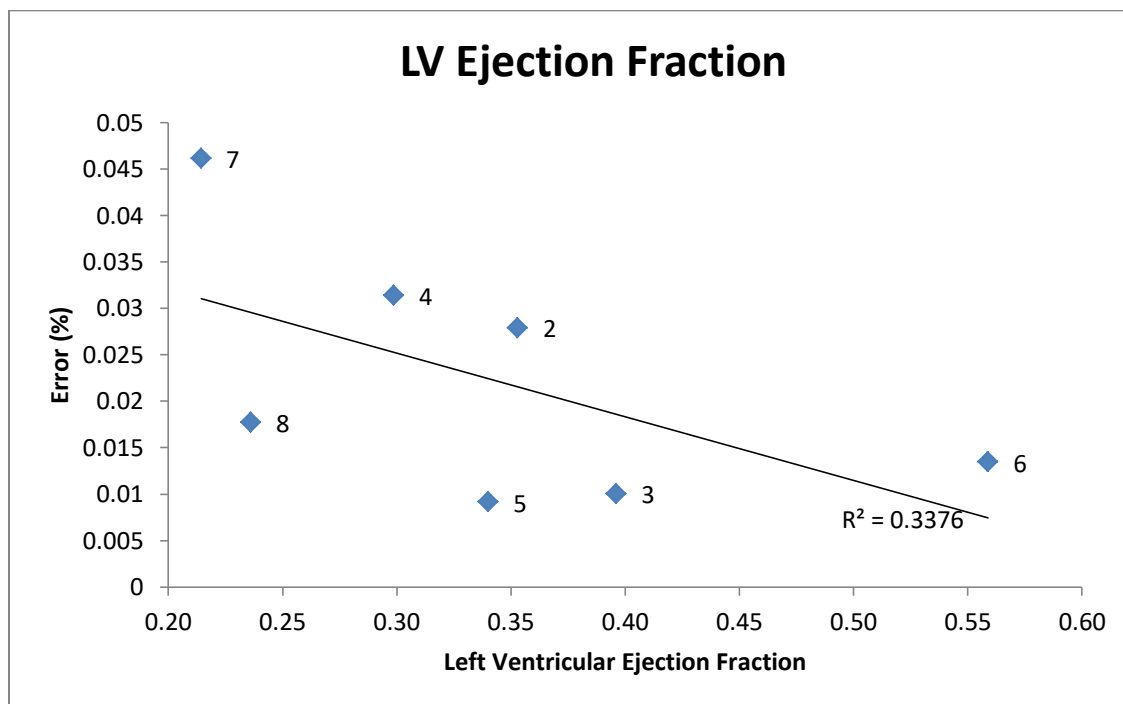


Figure 10: The error in general seemed to decrease as the ejection fraction increased. When considering subgroups, splitting the plot into the higher-error subgroup of patients 2, 4, and 7, compared to the lower error 8, 5, 6, and 3, would give more correlation when comparing subgroups.

When looking at ejection fraction, generally the error of the DI prediction seemed to go down as the ejection fraction increased. There was no distinct linear correlation between the two, however.

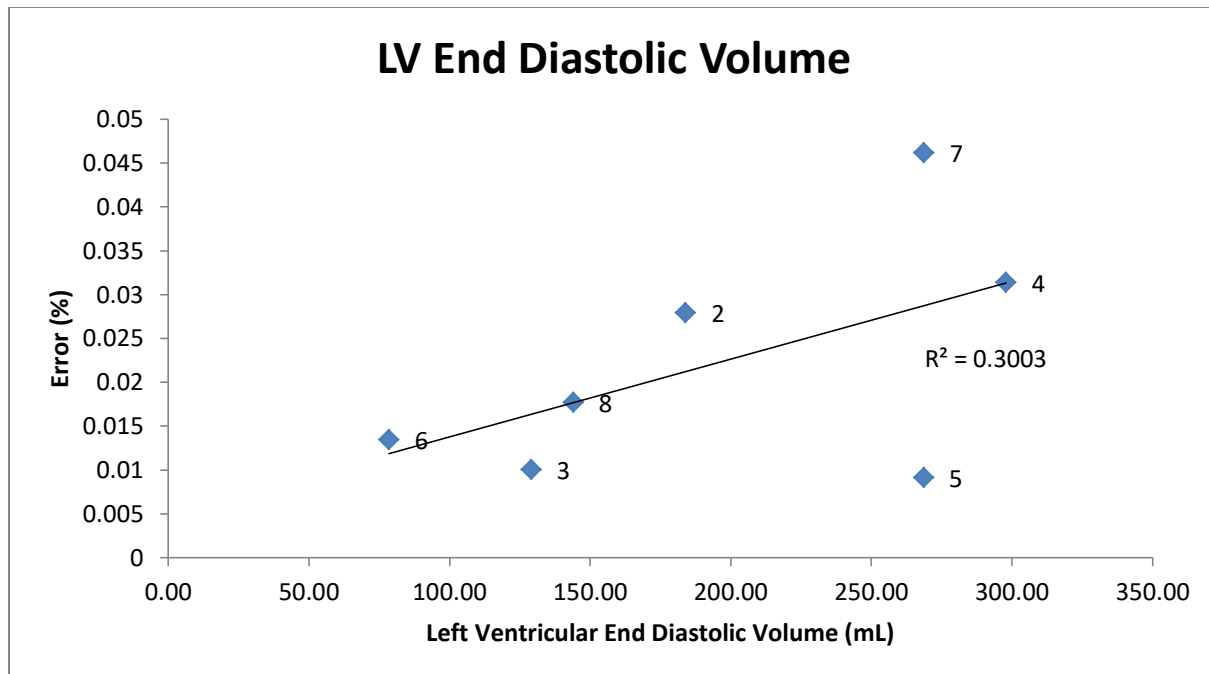


Figure 11: Error increased as the LVEDV increased. Considering the higher and lower error subgroups, the R^2 value might increase if 2, 4, and 7 were split from the other 4, for both sets of subgroups. However, this would cause a large decrease in the number of patients being examined by the graph.

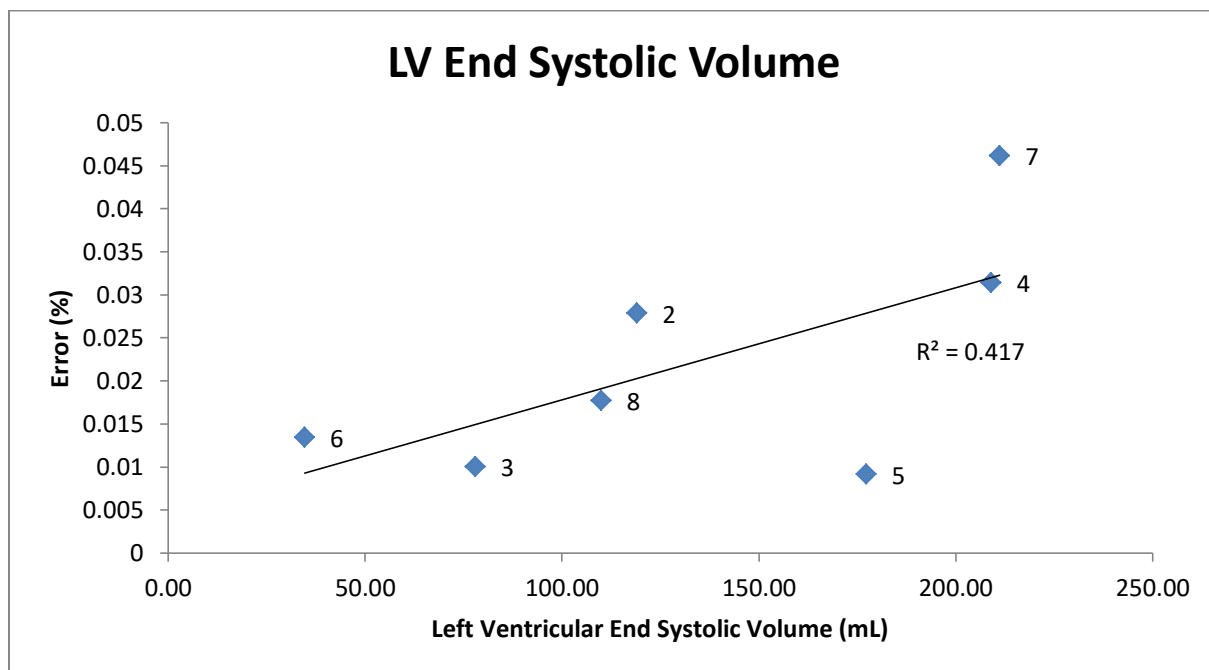


Figure 12: Error increased as the LVESV increased. Again, subgroups might give clearer trends, while also decreasing the number of samples being observed per trend line.

Left ventricular end systolic volume and end diastolic volume increasing both seemed to be associated with an increase in DI prediction error, but again no direct correlation was seen here, as shown in figures 11 and 12.

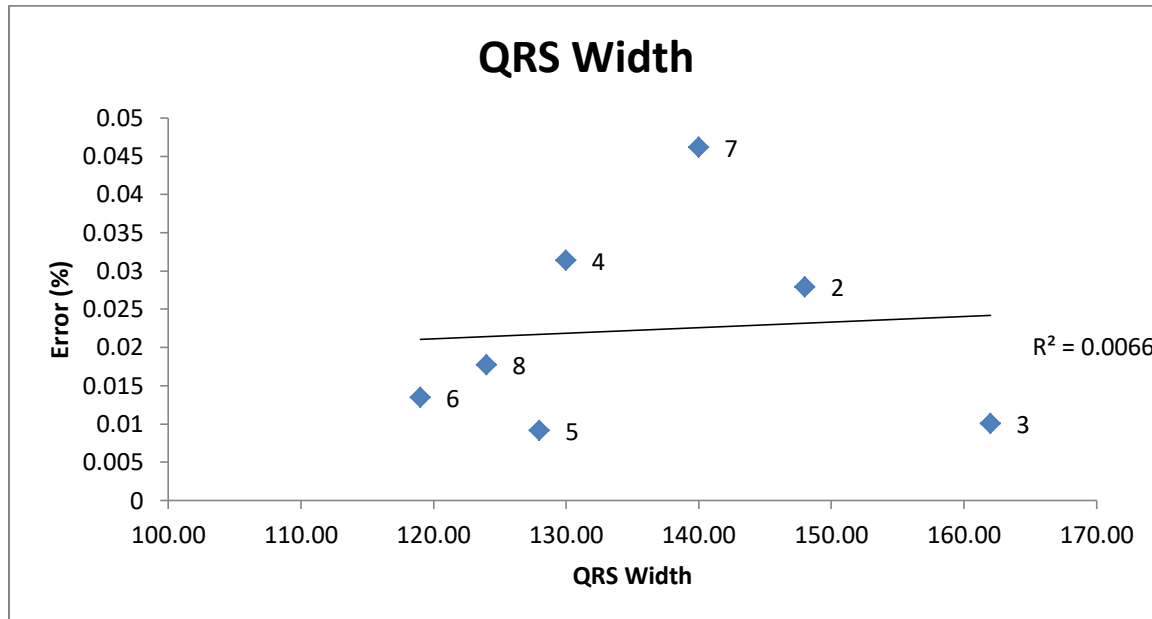


Figure 13: Many physiological factors had no correlation with the dyssynchrony index output. QRS Width had no effect on the accuracy of the model, suggesting it had no bearing on the variability of the data. Other parameters that also had no effect on the DI output were age and NYHA rating.

QRS width, seen in Figure 13, had no apparent correlation or connection with the error of the prediction of the machine learning model. Other physiological parameters, including New York Heart Association heart rating and patient age, did not have an effect on the dyssynchrony index.

CONCLUSION

Discussion

Current models used to determine the dyssynchrony index, and thus to predict outcomes of cardiac resynchronization therapy, are complicated and time consuming. Machine learning is a potential method to predict CRT outcomes more quickly, while still maintaining accuracy.

Varying the amount of training data per patient, when looking at seven or less patients, did not have an overall significant effect on the predicted outcomes. After around 30% of the data had been used as training data, adding further training data only marginally increased the error of the dyssynchrony index prediction of the machine learning tool. At 20% data usage for training, there was a notable bump in DI prediction error, which was higher than the prediction errors at 15% training data usage, and 25% training data usage. It is possible that these slight variations in prediction error were mostly due to random chance, and that looking at data from more patients could yield different results. However, considering the increase in machine learning runtime associated with an increase in amount of data used for training, simply increasing the amount of training data per patient does not appear to be the best way to increase the accuracy of the prediction of outcomes associated with CRT. It is also possible that error is intrinsic to the dataset, and increasing the amount of data used for training serves to compound the error, causing the gradual decrease in accuracy of prediction.

The computational time needed to test patient data increases proportionately to the amount of data being tested, so examining much more data could be beneficial with the addition of different patients being tested, assuming there are computational resources which could reliably examine the information quickly to provide the dyssynchrony index outcomes.

When examining the number of patients whose data are being trained using the algorithm, increasing the amount of patients seemed to correlate with lower DI prediction error. This highlights the need for more patients to have their data be input into the algorithm at the same time. However, it is also possible that the errors as a result of the DI predictions were being averaged. This is notable because certain patients had higher individual errors associated with them. These patients tended to skew the dyssynchrony index predictions and cause the errors to increase. Including more patient data would cause these patients to have a smaller effect on the overall error, and allow a better understanding of the accuracy of the machine learning model.

Alternately, splitting the patients into different subcategories may be a useful strategy. The DI predictions of the patients had varying amounts of error. This suggests that the patients can be split into two subgroups based on how accurate the machine learning algorithm was in determining the amount of dyssynchrony within their hearts. In the case of the seven patients being examined, patients 2, 4, and 7 might make up one subgroup with higher error, while patients 3, 5, 6, and 8 would make up the other. It is possible that the group with higher error skewed the overall readings, making the machine learning appear less effective, even for the patients for whom the machine learning had an average error of less than three percent, when considering the validation and the training errors.

Looking specifically at patients whose data skewed the results the most by showing the largest DI prediction error, the 3D geometry data did not provide any specific insight as to what the problem might be. Wall thickness, septal thickness, and radius size, both of the left ventricle and of the overall heart, did not appear to have a correlation to the accuracy of the predictions.

Physiological parameters including patient data of age, left ventricular end diastolic volume, left ventricular end systolic volume, QRS width, and post left ventricular ejection

fraction had no apparent correlation on the predictive accuracy, but dyssynchrony index, and the covariance of work of hearts with left bundle branch block did appear to have some correlation with the predictive capability of the algorithms. This suggests that patients with more variance in the electrical activation of their ventricles were measured more accurately by the machine learning, which is predicting the dyssynchrony, in the heart. Since the model is measuring dyssynchrony, it makes sense that the error would decrease as DI increases, and it also makes sense that the error decreases as COVW increases. These features can be examined in more detail in the future to determine if they have some effect on the dyssynchrony index predictions provided by the machine learning. It is possible that this is the case, and that patients with higher DI prediction error, including patient seven, simply have higher error because of a smaller magnitude of dyssynchrony.

Looking at features which did not correlate with the DI predictions of the algorithms, it makes sense that factors such as age and New York Heart Association class did not have a higher correlation, since those factors are not necessarily related to the dyssynchrony of cardiac electrical activation, and with a small sample size, any outlier can largely skew the data. A limitation of the simulated patients used in this dataset is their fairly narrow QRS widths. Observing a broader range of QRS widths may help to increase the understanding of their relevance to the DI prediction outputs.

Future aims

Overall, machine learning appears to be a promising alternative to current computational models, offering a faster and less complex method of analyzing the vectorcardiograms of multiple patients in order to predict the outcomes of cardiac resynchronization therapy.

The easiest way to build off current knowledge and understand the utility of machine learning in predicting CRT outcomes is to acquire more VCG datasets for analysis. Most of the data which was tested came from the seven complete data sets, meaning even a single outlier could potentially skew the data in a large way. This includes a physiological difference such as age or dyssynchrony index, or some other noise which may have come about through the creation of the synthetic patients.

More data from patients with different backgrounds could also be valuable. This includes patient data from people of different genders, since every patient was male, as well as illness information. This can be useful in splitting patients into subgroups, which can be analyzed separately to determine the efficacy of machine learning in predicting the dyssynchrony index of patients from varying backgrounds. If possible, it would also be preferable to get patient data from actual patients, rather than synthesizing simulated patient data as was done in the current study. Individual patients would offer data which can then be compared with the results of their CRT procedures, assuming they go through with them, and their data sets will be more complete in terms of the physiologic characteristics known about them. It is possible that there are other physiological characteristics unknown for the simulated patients which may cause a deviation in the dyssynchrony index prediction of the algorithm being used. It is also possible that the data from real patients, as opposed to the simulated patients, will respond to the machine learning

algorithm differently. With more patients being tested, the results will become clearer, and viewing in different subcategories and subgroups may be more apparent.

Related to the issues of actual vs. virtual patient data sets, faster computational systems may be able to run and examine the data faster through machine learning. Although the results here do not show a significant difference in predictive results after using more data for training, after a certain point, a dataset of hundreds of patients would certainly take hours, if not days, to compute. Different algorithms may also be developed in the future, and stronger computational systems may be able to more accurately predict CRT outcomes in less time. At the least, a more powerful system may be used to get a better understanding of the accuracy of the algorithm by running through the same data set hundreds of times, and averaging the overall DI prediction error. Additionally, this system could potentially run through hundreds of datasets of patients at a fast rate, allowing for patients, synthetic or real, to be examined quickly, if there is patient data that can be tested.

An alternative method to getting more patients is to divide up the current patients' VCG data sets, so each sub-patient accounts for around 100 VCGs instead of 600. This would result in a total number of 42 sub-patients, allowing for graphs which may show outliers in greater detail. Considering 42 sub-patients, there will be seven subgroups, each representing one of the original patients with the same physiological and geometric parameters. Each subgroup will consist of six sub-patients, and each sub-patient within the subgroup will have the same heart geometry and physiological characteristics, since they all come from the same simulated patients.

If this method is applied, it is important to consider the data which is used. Since the 600 VCGs per original patient were taken from different parts of the heart, dividing up the data into different sections of the heart could yield different results than randomizing the error, or using an

algorithm to ensure different parts of the heart are all covered within each of the six sub-patients within each of the original seven patients.

Physiological parameters may also be studied more deeply. Activation maps can be used to see which part of the heart is electrically stimulated at which time, for example. This can be used to determine which part of the heart was stimulated at which point in the data set, and the results can be compared with the DI predictions to determine if this had any effect. The QRS axis, showing the net depolarization direction, may be analyzed in a similar manner. Negative work can also be observed to determine if there is some correlation between that and the DI prediction.

While other machine learning algorithms can be developed, it is also possible that companies currently in the machine learning sphere, including Google, Amazon, Github, and Microsoft, may develop machine learning tools which can also be applied to this sort of problem. There are also various machine learning libraries online with different algorithms which can be potentially applied to this problem in the future. Machine learning tools from such organizations can be utilized to predict outcomes in a more sophisticated way, which may also yield more accurate results.

Deeper into the future, other forms of machine learning can be used to streamline the process of predicting dyssynchrony indices. These sorts of machine learning algorithms would be especially enhanced with the addition of extra data. A prime example of this is visual machine learning. Visual machine learning can be directly applied to electrocardiographs, and coupled with a tool to clean and standardize ECG images. In this way, the machine would simply view the ECG image as the input, instead of a numerical input of a VCG, which is currently being used. This ECG visualization could then be studied by the machine to predict the dyssynchrony

indices, likely by determining the VCG on its own, or by using other algorithms as the machine gets better at predicting VCG values.

Developing a tool like this could be useful for many applications. Beyond predicting CRT outcomes by going through VCGs to provide dyssynchrony indices, the tool could view the ECGs to provide QRS length in time, determine the peaks within the ECG, and even help cardiologists to diagnose patients with other electrophysiological afflictions of the heart.

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