Intro first draft

# An introduction into atrial fibrillation

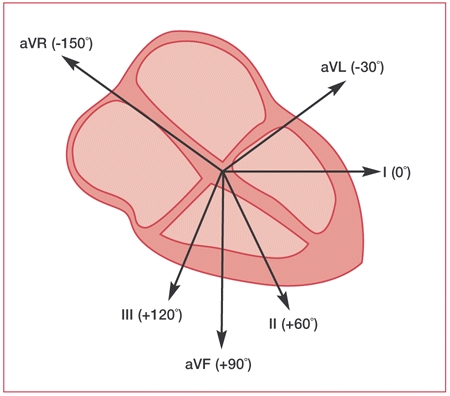
Atrial fibrillation is the one of the most common forms of cardiac arrhythmias leading to an increased risk of stroke event by 3 – 5 folds even when adjusting for external risk factors.(Wolf *et al.*, 1978). Based on statistics from 2017 , the prevalence of the disease is at 37,574 million and the incidence is now 31 percent higher than the incidence rate during 1997 at 403/millions inhabitants of incidence(Lippi, Sanchis-Gomar and Cervellin, 2021).There are different types of atrial fibrillation dependent on the amount of time a patient has been dealing with atrial fibrillation . Paroxysmal is categorized by a short term (under a week) return to normal sinus rhythm. Persistent atrial fibrillation, a focus point of this research, can last more than 7 day or more than a year in which it is then considered to be longstanding persistent AF. Lastly, permanent AF is usually considered when there seems to be no hope in the heart returning to normal sinus rhythm. The majority of the prevalence is made up of mostly people with permanent AF as seen in this European study which has found that persistent AF is prevalent in 25 percent of people while permanent AF occurs in 50 percent of people with AF (Zoni-Berisso *et al.*, 2014).The current gold standard for treating cases of atrial fibrillation that struggle to respond to antiarrhythmic drugs is Catheter ablation , this is especially successful with people with paroxysmal AF. The catheter ablation procedure requires installing a catheter into the heart through the groin to identify the driver(section) of the heart responsible and then ablating that is scarring a segment of tissue responsible for the atrial fibrillation. This has shown a great amount of success in preventing people from progressing to persistent atrial fibrillation, in which a systematic review has found that people that did not undertake the procedure had a between 10 – 20% change of progressing after 1 year follow-up while people who undertook the procedure had a 2.4 – 2.7 % change of progression over 5 years of follow up(Proietti *et al.*, 2015).These promising results are not reflected when it comes to catheter ablation procedures for people with persistent AF, with trials like the CAPLA trial only showing an effective treatment (no atrial arrythmia lasting for more than 30 seconds) for between 52.4 to 53.6 percent of patients among slightly differing catheter ablation methods and no change when paired with anti-arrhythmic drugs. It is reasonable to suggest that the majority prevalence of permanent AF is partially due to an inability to effectively treat patients with persistent AF which has driven research into finding more effective differing methods of treatment or looking at ways to better diagnose and suggest a pathway of current treatment earlier on in hopes of increasing the success rate of a procedure like catheter ablation. In this study I looked at deep learning-based approaches to see how clustering can help us derive phenogroups based on the characteristics of someone’s surface ECG reading relative to their intracardiac readings. I did this to see if we can put patients in groups and to see if those groups with similar ECGs may have had a similar treatment procedure (surgical or dug based) provided to them. Being able to establish groups based on ECG reading can help us decide the treatment that may be needed for future patients based on their ECG also.

# 2. A deeper understanding of atrial fibrillation

## 2.1. What is an ECG?

An electrocardiogram is a commonly used device in medicine which is normally used to give medical professionals an approximation of the heart’s electrical conductivity. Specific leads are placed on the skin hence the name surface ECG and these leads are placed to measure the electrical currents produced by the heart and conducted across the body.

* The standard practice for taking an egg involves using 10 cables/electrodes to in order to get a 12-lead surface A person with red hair and red hair with acupuncture needles

  Description automatically generatedECG.
* The leads labelled v1-v6 are placed on the chest and cover the areas closest to the heart seen in this figure, each v represents an electrode placed on the chest.
* The 4 other electrodes are all placed on the extremities and drive leads with the labels: I, II, III, aVR, aVL, and aVF . Three of which are placed on the distal limbs to measure a potential difference between limbs and the one electrode left acts as an ground electrode placed on the spare right ankle as to reduce background noise when recording the ECG **.** The limb leads I – III measure a potential difference between the limbs for example lead I measures the potential difference between the right and left arm , the augmented leads (aVR,aVL,aVF) are calculated by finding the potential difference of one of the three limbs to an estimate of zero potential. This creates a representation of the vertical plane of the heart as seen in the figure below.(Ashley and Niebauer, 2004)
* .
* 
* In this study we focus on four leads as the procedure in which data has been collected resulted in the 4 leads being more well aligned with the intracardiac reading as oppose to the full 12 leads, the four leads chosen where: I , aVF , V1,V6. Both I and V6 represent the lateral surface of the heart while V1 gives signals related to the right atrium and cavity of the left ventricle and aVF is related to the inferior surface of the heart(Meek and Morris, 2002). Being able to analyse the signals coming from these areas can help identify any abnormalities in the signal and therefore inform cardiologists of what area of the heart is being affected to aid in a diagnosis.

**What does an ECG look like and what does it mean?**

* **A diagram of a graph

  Description automatically generated**
* The figure above gives you a general idea of what and ECG should look like. The P wave acts to represent atrial depolarization which then can lead on to depolarization of the ventricles seen in the QRS segment. We expect and hope the QRS will be small to represent an efficient depolarization of the ventricles, however wider QRS may suggest less efficient depolarization due to dysfunction in the heart. Finally , a plateau is reached of the myocardial action potential and at this point the ventricles contract and pump blood around the body(‘ECG interpretation: Characteristics of the normal ECG (P-wave, QRS complex, ST segment, T-wave)’, no date).
* During Atrial fibrillation the action potential are fired at exceedingly fast rate from 400 to 600 beats per minute, the speed of this action potential means the threshold for the activation of the ventricles to fill up and contract is not always met therefore reducing ventricular activation subsequently presenting as a reduced amount of QRS waves relative to P waves. This presents itself in an ECG with a less than 1:1 ratio of p waves to QRS waves typically show up as an irregular amount of p waves followed by QRS dispersed irregularly through the reading. The figure below shows an example of the irregularity of the QRS waves seen by inconsistently placed peaks(*Atrial Fibrillation ECG Review*, no date).
* **A graph with a line drawn on it

  Description automatically generated**

## 2.2. What is pulmonary vein isolation ablation?

* Pulmonary vein isolation has become the current gold standard in medicine and as previously mentioned has shown high level of success with people with paroxysmal AF.
* Pulmonary veins are located on the left side of the heart they are responsible for taking in oxygen rich blood from the lungs into the heart, the entrance point for these veins into the heart are called Ostia.
* The majority of Humans normally will have 4 pulmonary veins and therefore 4 ostia but there are some scenarios where some people can have 5 pulmonary veins with a middle right pulmonary vein present there are also edge cases of hearts with 2,3 and 6 pulmonary veins (Klimek-Piotrowska *et al.*, 2016).
* Pulmonary vein has been linked to the pathogenesis of AF in multiple way, while not all the mechanism has been fully explored there are still some promising ideas of what causes AF. One proposed issue is re-entry into the Pulmonary veins, this has been linked to alteration in the electrophysiological properties of the muscle cells responsible for Pulmonary vein blood entry into the heart(Mahida *et al.*, 2015). More specifically the issue is seen in a shorter ERP, a refractory period of the action potential, this is responsible for coordinating the contractions within the heart which if effected in this way can lead to irregular contraction and therefore re-entry of blood into the veins(Nat℡, Bourne and Talajic, 1997).
* This makes pulmonary veins a an effective target as a common driver of AF , in pulmonary vein catheter ablation the veins and the areas around them become the target for ablation.
* This ablation procedure will involve creating a EAM(3d electro anatomical map) of the left atrium in which the pulmonary veins are connected to, then a single catheter is used to ablate around the pulmonary veins that are showing abnormal electrophysiological behaviour , this is referred to as point to point ablation. This gives surgeons time to identify other drivers in different chambers and location of the heart that may also be contribute to the Atrial fibrillation. (Reddy *et al.*, 2021).
* There are a multitude of factors that add complexity to the ablation procedure, the first is the time to create a map, the other is identifying what to ablate, both of these are related to each other. This is because there are a multitude of drivers of AF however we only have a simple classification process either paroxysmal, longstanding, or persistent AF which if failing to adequately capture the complete heterogeneity of the disease itself. This means when it comes to treatment whether it is deciding what drugs to use, or the details of the ablation procedure there will always be an exploratory stage to see what works and what doesn’t. We have seen this in ablation in which a secondary ablation is required due to the first ablation not resulting in freedom from AF which adds to the cost of treatment. It would be more effective if we had more specificity in diagnosing subcategories of AF, so that we can identify the most likely treatment pathway and rely less on an exploratory approach.

## 2.3. The idea behind AF phenotypes

* Researchers have made attempts to find different ways to create additional phenotypes for AF based on certain characteristics of patients, the main solution for this is clustering. This method involves using machine learning to interpret data from patients and cluster them based on similarities in that data. The clusters are then analysed using methods like univariate analysis to identify key characteristics that differentiate clusters of individuals from each other.
* When it comes to AF there has been some clustering to identify new AF phenotypes, one study has found 4 clusters which had been determined by CV risk factors and comorbidities. Cluster 1 had low rates of both however 2 and 3 where characterised by the high burden of CV risk factors and comorbidities with cluster 3 having a much higher number of comorbidities than cluster 2 and cluster 4 was defined by a high level of non-CV comorbidities which contained an older group of individuals seen in the cluster. From this cluster analysis we can determine that in a treatment situation that cluster 2 ,given its lower number of comorbidities but higher amount of risk factors would benefit from early treatment and change of lifestyle factors whereas cluster 4 who are already suffering from many comorbidities and where not responding to drug treatment which may need to go forth and look for ablation as a solution (Vitolo *et al.*, 2021).
* Another study identified clusters like the first study in which the first cluster contained young men with a low prevalence of CV comorbidities however this study identified 5 clusters as opposed to 4 with gender also being a deciding factor in addition to cardiovascular risk factors and comorbidities(Saito *et al.*, 2023).
* From looking at just two studies that share similarities and differences between their clusters we can see that AF is not a simple disease and can present itself in different ways among different patients and therefore requires differing tailored treatment for each type of patients. Clearly there is a need for a new phenotype of AF to be identified to provide a potential universal approach to treating AF with more specific approaches to treatment.
* However, it is worth noting that different regions seem to have different defining factors that differentiate themselves from each other (penultimate reference).

# 3. Deep learning and ECGs

## 3.1 What is deep learning.

* As researchers sometimes we are handed non-linear data with many complex relationships and patterns within it as nature can be unpredictable and a simple linear regression will not help achieve a suitable analysis based on the data being inputted.
* In light of this complex data, it has been essential to devise and leverage new ways to deal with it, this has come in the form of deep neural networks.
* These networks are comprised of an input layer that first deals with the data, a hidden layer which adds to the true depth within the model and is comprised of multiple neurons and multiple layers which serve the purpose of detecting and processing the complex patterns within the data and finally there is and output layer which provides a usable output like a prediction like if an ECG is normal or presenting atrial fibrillation.
* Of course, like humans these networks rarely get it right the first time and so usually these models are paired up with an optimizer function , these functions require a loss metric which can reflect the accuracy of a prediction like how many times a network identified the correct animal in a picture which allows the system to adjust the parameters of the network accordingly by adjusting the weights associated with the neurons in the hopes that these new weights can help the model reach a more accurate output(Alzubaidi *et al.*, 2021).
* More specifically this problem is referred to as the gradient problem which reflects how much the parameters must change (whether decreasing or increasing) to minimize the cost function (the loss function). Each neuron has a local gradient calculated by the chain rule which gives each neuron within ever layer a local gradient based on the partial derivatives of the outputs relative to its input. Finally to optimize the local gradients an algorithm often called gradient descent, adjusts the weights and biases of neurons which are initialized randomly but then are iteratively changed with the sole purpose of minimizing the cost function (Kostadinov, 2019).
* This algorithm also uses the learning rate, another pre-determined user defined number which decides how much influence the gradient has at each iteration, this number is normally kept small especially with large complex problems as to keep the model generalizable (can perform well on a new dataset) to a broad range of patterns across a large dataset(Wilson and Martinez, 2001).
* Each iteration which processes the whole data set and output an average loss value are referred to as epochs, the number of epochs can also be chosen. Method like early stopping will be used to make sure the model is optimized sufficiently. Usually, model users will have training data to train the model, a small segment of data as validation and a final section to really test the effectiveness of the model called the test dataset. In early stopping the model is trained on the training data but is stopped when the loss function of validation data stops improving over a certain number of epochs this will make sure that the model is trained on the data but is also generalizable on new data by preventing the model from overfitting to the training data set(Bai *et al.*, 2021).

## 3.2 CNNs and autoencoders

What is a CNN?

* The benefit of deep neural network is that they can be modified to more specialised tasks. CNN are convolutional neural networks that contain convolutional layers within them. These layers can function more efficiently than normal dense layers as they are able to capture a spatial relationship in the data or in the case of of ECGs this is a temporal relationship.
* Usually, the convolutional layers are 2D and therefore are specialised for computer vision tasks like identifying what time of day a photo is taken in, in which a photo has two dimensions height and width. However, when we deal with ECGs, especially when they are digitally recorded, we then are dealing with a single dimension of a single value at each timepoint.
* Previously, if you had a 1d array, it was required to transform the data into two dimensions to be processed by 2D Convolutional layers however this created issues in requiring a large data set and the model dealing with overfitting and being less efficient overall. 1D convolutional networks serve a purpose of requiring no such preprocessing you can just put your raw 1d signal in and have features automatically extracted for the purpose of processes like classification. Instead of 2d matrices that are created by 2d CONV layers 1D Conv layers produce an output of 1d convolutional sequence that represent a weighted sum of two 1D arrays. Not dealing with 2d matrices allows us to have more efficient back propagation process and therefore have an efficient way of extracting and analysing features from a raw 1d signal like an ECG (Kiranyaz *et al.*, 2019).
* Using 1D CNNs has shown a lot of promise with detecting atrial fibrillation, there have been CNN models that have been tested on the MIT-BIH atrial fibrillation database and have achieved over 97% in sensitivity and specificity when classifying signals into normal, Atrial fibrillation , atrial flutter and AV junctional rhythm(Petmezas *et al.*, 2021).

What is an autoencoder?

* An autoencoder still utilizes the CNN architecture but in a different way. The model architecture consists of an encoder, a decoder and in the middle is a latent space. The encoder, aided by convolutional layers can act to dilute the input into lower dimensionality which makes up the latent space. Essentially it is a dimensionality reduction into a latent space, however with this method unlike principal component analysis (PCA) we can use non-linear transformation (due to using CNN architecture) to capture more complex and intricate relationships between the data as we reduce to a smaller set of dimensions. The decoder then works to reconstruct this signal and the loss function ( mean absolute error) is based on the models ability to reconstruct the signal as accurately as possible in which backpropagation is also used the adjust the networks parameter to provide the most accurate reconstructed signal that is possible(Bank, Koenigstein and Giryes, 2021).
* The promise of this model is that it can provide a more intricate set of features that can be clustered on or used for classification purposes in which researchers have regressed on these features to output classification based on the high-level features extracted from the autoencoder rather than the input itself. Researcher have shown promising success in classifying types arrhythmias, in which researcher have achieved 97% accuracy classifying 6 version of arrhythmia including : normal sinus beat, atrial fibrillation , ventricular bigeminy , pacing beat , atrial flutter , sinus brady cardia(Ramkumar *et al.*, 2022)

# 4.What is missing and what we can do about it?

* This will talk about why the intracardiac rhythm is used as the ground truth.
* Why and how sample entropy can represent the intracardiac rhythm.
* How clustering has only been done on CV risk factors, comorbidities and how we are clustering with a focus on the ablation procedure and some drug treatments.
* Basically, these paragraph is for gaps in the current knowledge and the aims of the study.