

Individual Project - Interim Report

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1 Introduction

1.1 Schizophrenia, etiology and genes

Schizophrenia is a complex mental disorder that displays an array of symptoms. It is commonly perceived that schizophrenia is a hereditary disease that can be passed down within the family, but some individuals diagnosed with schizophrenia do not have a family member with the disorder [1]. Thus, it is postulated that the heritability of schizophrenia might not be as high as what is commonly believed [2].

Furthermore, there is a strong indication that environmental factors - such as tobacco smoke and viruses - and genetic factors have an influence on the development of psychiatric disorders in an individual [1, 3]. This results in a hypothesis that the epigenetics - “any process that alters gene activity without changing the DNA sequence” - of an individual might have a role to play in the development of schizophrenia (see Section 2.2) [4]. However, exactly how these two factors play a part is still unclear [5]. What we should also note about the current research on psychiatric disorders is that studies on such disorders do not receive as much attention as other illnesses such as cancer [6]. Thus, any insight generated from this project would be beneficial to helping us understand psychiatric disorders better.

Overall, this project aims to predict Schizophrenia cases on the basis of epigenetics and epivariations.

1.2 Using machine learning to predict Schizophrenia cases

Using data from a recent study on epigenetics and schizophrenia (see Section 2.3), the project aims to use machine learning to elucidate any statistical regularity in the data, in hope that any insight into the data can help geneticists and psychiatrists understand the etiology of schizophrenia - and indeed, other psychiatric disorders - better.

As a starting point, simple classifiers can be used on the data, to determine the classification accuracy of the data (see Section 2.5). Later on, we can explore more complex classifiers - by, for example, combining different methods - and techniques - like

performing numerical experiments on hyperparameters - which might produce better results.

Previous work on using machine learning on biological data (see Section 2.4) has always been plagued with the “Curse of dimensionality”, where the number of biological samples is far lesser than the number of features (or dimensions) of the data (the “ $p \gg n$ ” problem [7]). In our case, we have 847 samples (individuals) with 420374 features, resulting in about 2 gigabytes of data.

Here, we face a potential problem of a similar nature - the data has high dimensions, but not all the genes involved in the study would directly play a part in the classification of the disorder; some genes may only contribute a little to the outcome of the classification. In this case, we would need to perform feature/dimension reduction to only select features that have significant contribution to the classification outcome (see Section 2.6).

Moreover, linear classifiers may not be able to capture the complexity of the data, as it is hypothesised that subsets of genes - rather than single genes - contribute to the genesis of the disorder [3].

These potential problems make the project interesting, as we cannot simply use ordinary machine learning techniques to manipulate the data - we have to adapt our algorithms and classifiers to suit the complexity and context of the dataset and problem.

2 Background

2.1 Biological review

2.1.1 Molecular biology and definitions

This section outlines the necessary biology that will be relevant to the discussion in this project [8, 9, 10, 11].

- **DNA:** Deoxyribonucleic Acid, also known as DNA, is a molecule that contains all the hereditary material in all living things. It serves as the fundamental unit of heredity.
- **DNA bases:** The hereditary information stored in DNA molecules are made up of four bases - Adenine (A), Thymine (T), Cytosine (C) and Guanine (G). These bases pair up in a specific way: A with T and C with G. Along with other types of molecules, these pairs form a nucleotide. Nucleotides are then arranged in a double helix structure.
- **Genes:** A gene is the fundamental building block of heredity. Genes consist of DNA, and encode instructions to produce proteins. It is estimated that humans have about 20000 genes [12]. The instructions stored in genes are used to produce proteins through the process of transcription and translation (or, gene expression). This process is often called the “central dogma” of molecular biology.
- **Gene expression:** Gene expressions behave like a switch to determine when and what kind of proteins are produced by cells. All cells in a human being carry the same genome. Thus, gene expression allows cells to specialise into different functionalities (e.g. differentiate between a brain cell and a skin cell).
- **Epigenome:** The epigenome is a set of chemical compounds and modifications that can alter the genome, and thus alter DNA and the proteins that it produces. The epigenome can thus alter the “on/off” action in gene expression and control the production of proteins. The epigenome arises naturally, but can be affected by external factors (e.g. environmental factors, disease), which might explain why even though twins have the same genome, it often happens that one twin inherits a disease, while the other does not [13].
- **DNA methylation:** A common chemical modification is DNA methylation, where methyl groups ($-\text{CH}_3$) are attached to the bases of DNA at specific places. These methyl groups switch off the gene which they are attached to in the DNA, and thus no protein can be generated from that gene.

2.2 Relationship between epigenetics and disease

Studies that involve monozygotic twins (twins who share the same set of genomes) are useful to discover the effect of epigenetics on the phenotypes (observable, physical

characteristics) of these twins [14].

A study that focuses on monozygotic twins and their susceptibility to disease found that the genes that make up an individual cannot fully explain how likely he/she would be diagnosed with a disease [15]. It is thus interesting to ascertain, using epigenetics data and machine learning, whether epigenetics has any influence on being diagnosed with psychiatric disorders, by detecting any statistical regularity in the data.

2.3 The data

This project makes use of data from a recent genetic-epigenetic analysis of schizophrenia, conducted in 2016 [16]. There are high-throughput methods that enable genomics researchers to perform epigenome-wide association studies (EWAS). In this study in particular, its researchers aimed to use these methods to identify positions in the genome that display DNA methylations associated with environmental exposure and disease. It turns out that there are significant differences in DNA methylation between individuals diagnosed with schizophrenia, and those who were not (controls).

In particular, we are interested in the data offered in “phase 2” of the study, where schizophrenia-associated differentially methylated positions (DMPs) - positions on the genome where there is a difference in patterns of DNA methylation between two sets of genomes - were tested among 847 individuals, 414 of whom were schizophrenia cases.

Throughout this project, we shall identify the data produced from this study as *the data*. At the time of writing, some work has already been done to the data. See section 3.1.

2.4 Cancer classification

There is a significant amount of literature on gene expression data and cancer classification. These works primarily aim to uncover biological or medical insights using biological data obtained from microarrays, which are tools to measure the gene expression of thousands of genes simultaneously [17]. For example, using neural networks, gene expression data can be used to distinguish between tumour types, which helps in solving cancer diagnosis problems [18, 19]. We can draw lessons from these studies to apply on this project.

What is similar about this project and previous work on cancer classification is that the data for both cases are plagued with high dimensionality (*Curse of dimensionality*). For example, in cancer studies, microarrays are used, with a large number of genes (features) but a small number of samples (observations) [19].

Furthermore, only a (small) subset of the features are relevant for the studies, as not all genes are relevant for determining the type of cancer a patient has. This is known as biological noise [20]. As such, a feature/dimensionality reduction on the data has to be performed to select only the relevant genes/features for the classification problem. In other words, the solution for our situation (and also for cancer classification) would

ideally be sparse, as we seek to identify the features that are most relevant to the classification.

However, what is fundamentally different about studies on psychiatric disorders and cancer, is that the latter is observable, such that we can know for sure that an individual has cancer using medical methods, such as conducting a blood test. However, it is not obvious that an individual has a psychiatric disorder, as its symptoms might not be straightforward.

For example, the manual “*Diagnostic and statistical manual of mental disorders*” discusses culture-related diagnostic issues of schizophrenia: “the assessment of disorganized speech may be made difficult by linguistic variation in narrative styles across cultures”. Furthermore, “ideas that appear to be delusional in one culture (e.g., witchcraft) may be commonly held in another” [21]. These highlight how diagnosing a psychiatric disorder like schizophrenia is not at all easy.

2.5 Review of machine learning classifiers

Eventually, we would need to select an ideal machine learning method to detect statistical regularity in our data. This section reviews machine learning classifiers that might be relevant for this project.

2.5.1 Decision Trees

In our context, the task is to classify the data according to whether a sample (individual) has a psychiatric disorder - in particular, schizophrenia - or not. In other words, the classification task is binary. An intuitive solution is to use decision trees; problems with discrete output values can be solved using decision trees [22].

A decision tree algorithm is capable of sorting the instances - in our context, samples with different features - down the tree until the algorithm reaches a leaf node, during which a classification is given to the node. At each level of the tree, the intermediate node is split according to some attribute. One variant of the decision tree algorithm is the ID3 algorithm [23]. The ID3 algorithm makes use of a statistical quantitative measure, the information gain, to determine the attribute to classify the samples with. Using definitions from [22], let S be the set of all the samples that we want to classify at a particular node. The samples can also be separated into two groups, those with a positive classification and those with a negative classification. Define the entropy of S as:

$$Entropy(S) \equiv -p_{(+)} \log_2 p_{(+)} - p_{(-)} \log_2 p_{(-)}$$

where $p_{(+)}$ and $p_{(-)}$ represents the proportion of samples with positive and negative classification respectively.

Then, the information gain with respect to the set S and an attribute (feature) A is

defined as:

$$Gain(S, A) \equiv Entropy(S) - \sum_{v \in Values(A)} \frac{|S_v|}{|S|} Entropy(S_v)$$

where $Values(A)$ is the set of all possible values of attribute A , and $|S_v|$ is the number of elements in the set S with value v for its attribute A .

We then classify the samples in the node according to the attribute with the highest information gain. Intuitively, we want to choose the attribute that can give the most distinct separation between the positive and negative classification (instead of choosing an attribute that, say, splits the samples into half according to their classification).

Although the decision tree algorithm is said to be robust to errors [22] and the resulting decision tree can be easily interpreted by humans, it might be difficult to classify samples according to features that are highly correlated. This also happens to be a potential characteristic of our dataset, and we would expect some of the features to be correlated.

2.5.2 Random forest

The random forest method [24], a form of “ensemble learning”, is an extension of the decision tree algorithm described above, and it has been used in areas such as multi-class object detection in images [25]. Overall, a random forest algorithm can be outlined as such:

- Split the dataset into distinct subsets.
- Using each subset, train a decision tree using a relevant algorithm, such as the ID3, as outlined above.
- Suppose we have an unseen sample \mathbf{x} . Put the \mathbf{x} through each tree, and obtain the resulting classification for each tree.
- Based on a “majority vote” system, determine the final classification of \mathbf{x} ; that is, choose the classification that is the most popular among the decision trees.

Even though random forests have been shown to outperform decision trees [26], the limitations of decision trees as described above would still be inherent in the random forest method. Besides, Random Forest requires more parameters in general. For example, we would need to determine the number of trees to be trained, and the optimal number of trees to be trained is not obvious, as we would still need to perform numerical experiments to ascertain this optimal number.

Since the number of trees grow with the number of features that directly affect our classification (predictors) [27], and we do not know beforehand what these features are, we might potentially have to train a lot of trees. This might take up a lot of memory and time, and might also be computationally expensive.

So, overall, the decision tree and random forest methods might not be the best methods for our context, even though they are considered to be popular machine learning techniques [26].

2.5.3 Support vector machines

2.5.4 Lasso and Elastic net

In Section 1.2, we discussed how, in this project, not only are we seeking low classification errors, we also have to select features/variables in the data that are relevant in producing accurate predictions. An obvious, but naive, solution is to consider all the features in different combinations. But this solution is evidently computationally expensive, much less with data as large as the one we consider in this project.

One method to overcome this problem is by Lasso regression [28], which is a regularised least squares scheme that imposes an l_1 -norm penalty on an error function that it tries to minimise. More importantly, in the context of big data and especially this project, the Lasso is an appealing solution because it produces a sparse solution, by shrinking the coefficients of insignificant features to 0. However, Zou and Hastie [7] examined the limitations of the Lasso method, especially in the context of microarray data. In particular, Lasso has some limitations in variable selection, if a subset of features have high correlation with one another. This is precisely a characteristic of genes, as genes often interact with one another.

As a result, Zou and Hastie proposed the *elastic net*, which imposes a linear combination (weighted) of the l_1 -norm and the square of the l_2 -norm. This method performs feature selection, presents a sparse solution and takes into account variables with high correlation, where groups of correlated variables are not known in advance [29]. Furthermore, Zou and Hastie showed that the elastic net method outperforms Lasso. As such, elastic net might be used on our data set.

Besides, we can also utilise the elastic net library in `scikit-learn` implemented in Python. This allows us to experiment with elastic net easily, to see if it would be suitable for our dataset.

2.6 Feature selection and dimensionality reduction

As mentioned in section 1.2, the data suffers a *curse of dimensionality*, where the number of features exceeds the number of samples available. This usually causes *overfitting* on the classifier. This refers to the situation where the classifier can classify the training data perfectly, but performs poorly with unseen data.

Furthermore, there is a possibility that not all of the genes in our data set have a role to play in the classification of schizophrenia. As such, the feature selection method is necessary to select the significant features and eliminate the others. Besides, once we obtain only the relevant features, it would be less computationally expensive to train our classifier just on these features.

In 2010, a study was conducted to investigate the impact of feature selection methods (Kernel Principal Component Analysis (PCA), Greedy Kernel PCA and Generalised discriminant analysis) on real microarray gene expression data. It concluded that applying feature selection methods improved the performance of the SVM classifier

[30]. This strengthens our belief that the feature selection process would enable our classifier to perform better with our data set.

This study also explored these feature selection methods on various datasets. The number of genes/features available in these datasets ranges from 2000 to 12000, and the algorithm employed extracted 2, 4 and 10 features at a time.

2.7 Cross validation

3 Project plan

3.1 Work that has been done

3.1.1 Understanding the data

The first step that was done for this project was to find ways to understand the data. At the time of writing this report, the Python library `pandas` is used to manipulate the csv data set. `pandas` is a high-performance data analysis tool, which is suitable to be used on large datasets.

On a typical laptop, attempting to read the csv file row by row would result in a memory error in Python. The `pandas` library allows the file to be read chunk by chunk. This method then enables us to find out exactly how many rows and columns there are in the csv file. Moreover, we found that the rows represent the sites in the DNA that can be methylated (features), while the columns represent the samples (individuals).

3.1.2 Data preprocessing

Furthermore, in the National Center for Biotechnology Information (NCBI) database, a “series matrix” file explains what the data in the csv file represents. In particular, the columns (individuals) can be divided into the “control” (individuals with no schizophrenia) and the “cases” (individuals known to have schizophrenia). This is labelled by `disease_status=1` and `disease_status=2` respectively. This is helpful for classification, as we know beforehand what the label of each column (individual) is. This is necessary for supervised learning algorithms to be applied.

We also have to convert the data that can be read by our classifier. For example, we have to convert the csv file into matrices, and convert the classification (control or case) into a (binary) vector.

3.2 Performance of classifiers

Similar to previous work on cancer classification, we would need to employ different types of supervised learning algorithms on the dataset. Although several experiments have shown that support vector machines (SVMs) are superior compared to other methods [31], we should still consider other classifiers, such as decision trees and random forests, to ascertain their suitability on the data. We then need to determine the classification accuracy of each classifier, and select the best classifier for our data.

The classification accuracy of each classifier can be determined using methods such as k -fold or leave-one-out cross validation.

Furthermore, classifiers such as the SVM requires several parameters. We would then need to run numerical experiments to find out what the optimal values for these parameters are. These optimal values should give us the best classification accuracy.

Overall, this entire process of training the right classifier can be summarised in three steps:

- Training of the classifier using data
- Model selection: finding the best set of parameters for the classifier
- Classification error: accessing the performance of the classifier

3.3 Dimensionality reduction

As briefly mentioned in section 2.6, once we get the classifier working on the dataset to a satisfactory accuracy, we can then proceed to perform dimensionality reduction and feature selection on the data. This allows us to select only the most informative and relevant genes. It also helps to reduce the size and amount of data needed for the classifier.

3.4 Biological implications

Once the most optimal weights/parameters of the classifier are obtained, we can then see if we are able to select the most informative features. This has biological implications, as we can understand which part(s) of the genome has the most impact on the outcome of data (i.e. whether an individual has schizophrenia).

Next, after any insight found using our preferred classifier on the data set, we can extend our methodology to other datasets. In this way, we can investigate how well the classifier (together with the optimal parameters) generalises to other datasets.

3.5 Timeline and planning of project

The significant dates relevant for this project are stated in the table below.

Date	Significant event
27 Jan	Submission of interim report
17 Feb	Project review deadline
13 Mar	Spring term exam revision
20 Mar	Spring term exam
25 Mar	Start of Easter break Math summer exam revision
30 Apr	End of Easter break Math summer exam
15 May	Project health check-up
31 May	Latest date to start final report (3 weeks period to work on report)
21 Jun	Final report due

I would give myself the following dates to complete the following:

- *Before 17 February:* Complete experiments with classifiers, determine the best one (in terms of accuracy, computational cost etc.) (3 weeks).
- *Before 3 March:* Experiment with parameters of classifier(s); determine the most optimal set of parameters (2 weeks).
- *Before 13 March:* Experiment with feature reduction; we can see if it is possible to select the most informative features (1+ weeks).

The following are the fundamental components of this project. It is evident that there is plenty of time to complete this. In case any of the procedure takes a longer time than anticipated, there will be enough time to finish them. I would also need to consider the ongoing courseworks and deadlines within this period.

Besides, I would have 1 Math exam in Summer, whose date is not finalised yet, but it should occur in the month of May. This also means that I should be able to juggle between the exam and this project fairly well during the Easter break and in Summer.

Taking the above into consideration, if the above schedule works, I would then proceed with the extensions (see Section 3.6).

3.6 Possible extensions

First, more complex algorithms, such as the neural network, which requires more time to train due to the high dimensionality of the data, can be used. We can then, similarly, compare the classification accuracy of the neural network, and decide if we should adopt the classifier that was deemed the best, or the neural network. We also need to take into account the time that the network takes to be trained.

Second, we can create a toolbox or script that consists of an analysis pipeline for biomedical researchers to analyse similar epigenetic data. In other words, we can automate the process of manipulating the data and training the classification algorithm, such that future epigenetic data can be similarly analysed. We can then obtain biological and/or medical insight from the data much quicker.

Next, when conducting k -fold cross validation when selecting the most optimal set of parameters for our classifier, we would fix the value of k beforehand, typically 5, 10 or 20 [32]. However, we can go one step further to consider k as a hyperparameter, as suggested in [32]. We can then find the most optimal k by, say, using a grid search.

4 Evaluation plan

4.1 An investigation into the use of epigenetic data

Essentially, this project is about investigating whether the use of epigenetic data is relevant in helping us to identify individuals with psychiatric disorders. In other words, the project might conclude that epigenetic data is not able to help us to predict

individuals that potentially have schizophrenia. Nevertheless, this can also be seen as a beneficial development.

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