Exploring Gene Causality Through Embedding Analysis

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Abstract

This report analyses the phenotype-gene embeddings produced by the GPT-3.5 to determine whether they are relevant to meaningful signals regarding gene causality, using PCA and clustering. The paper explains how to prepare the dataset for the experiment-together with methodology for using hash functions and random sampling to provide consistent input, and then analyze and visualize data. It is aimed at identifying patterns and associations between genes and the corresponding phenotypes with an eye to deducing some insights on genetic factors regulating the peculiarity of a particular trait.

1. Introduction

Phenotypes are observable characters or conditions which arise owing to genetic factors in an individual. It is crucial to find causal genes in genetics, medicine, and biology as it gives knowledge regarding the genetic basis behind those traits. Accurate identification means targeted treatments and diagnostics based on knowing the underlying genetic basis. Dimensionality reduction techniques like Principal Component Analysis (PCA) [6] and t-SNE [7] are widely used in genetic data analysis to reduce the complexity of high-dimensional data. These methods allow for the visualization of gene expression data and aid in identifying patterns that could be associated with phenotypic traits. For this task, OpenAI's model GPT-3.5 used the creation of embeddings of phenotypes and genes. Identify if there are hidden indicators of gene causality in these embeddings: apply techniques such as clustering, PCA, or vector analysis to visualize and further analyze relationships found between embeddings of phenotype and gene.Gene causality is crucial in understanding the genetic basis of diseases, and its exploration using machine learning techniques has been growing rapidly [3].

2. Model

2.1. Principal Component Analysis (PCA)

PCA is a widely used dimensionality reduction technique in bioinformatics [2].Its an orthogonal linear transformation technique, used in feature extraction and dimensionality reduction, which has been found to be widely applied because its aim is toward mapping the data from the high-dimensional space into the lower-dimensional space, to preserve all maximum variance from the original data, and to have minimum total squared error. That is the reason why this procedure is so desirable in terms of reducing space as well as time complexity such that it gives an especially favorable choice for differentiating signals coming from different sources. The method is theoretically quite straightforward, and it becomes easier to apply if the number of independent components is known in advance. The process of PCA includes the following:

- We now calculate the mean vector μ for the x_d dimensional space of the dataset and the $x \times x$ covariance matrix.
- Compute and write down in decreasing order the eigenvectors and eigenvalues.
- Output: Select the k largest eigenvectors.
- Construct a $k \times k$ matrix A whose columns are k eigenvectors.
- We pre-process this data using the formula:

$$x = A^t(x - \mu)$$

In this process, the remaining dimensions after selecting k eigenvectors are noise. Such a technique is prone to compress and analyze the data effectively, making it highly useful in many fields of data science and machine learning.

3. Proposed Methodology

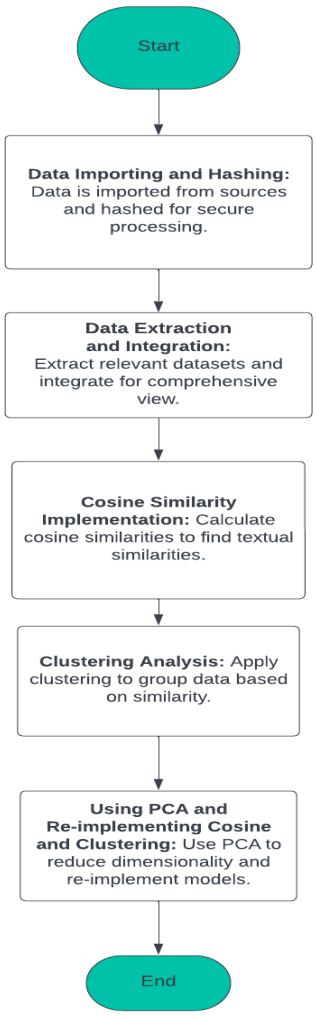

Figure 1. Workflow

3.1. Data Importing and Hashing

We begin the process of the project by importing the datasets we may need to analyze in the first step. This might include gene expression data or biological information held in CSV, TSV, or JSON format. We make use of libraries like Pandas in Python to load the data into a DataFrame, which offers better manipulation.

How to get ready for just one unique dataset to be analyzed:

- **Hashing the Participant's Name:**The participant's name was

hashed into a hash value in order to seed the random sampling. Consistent use was made of the participant's name in lowercase, without spaces; thereby, guaranteeing that the dataset sampled was unique per participant.
- **Random Sampling of Phenotypes:** Based on the hash as seed, 500 phenotypes were randomly sampled from the dataset given. This sample becomes the unique dataset for exploratory analysis.
- **Mapping Phenotypes to Genes:** For each phenotype, there are many genes. The task is to select the causal gene among them using the ground truth labels. For both phenotype embeddings, their causal and non-causal gene embeddings are prepared for further analysis.

3.2. Data Extraction and Integration

This second stage of the project intends to get and integrate three types of crucial data: phenotypes, causal genes, and alternative genes. It is a cycle that yields a total dataset to analyze gene causality.

Important steps in this process are as follows:
- Fetching phenotype data descriptions
- Fetching causal genes associated with every phenotype
- Gathering information related to alternative genes associated with the same phenotypes
- Mapping all the three data types into a single dataset.

The merged dataset appears as an outcome, where for each phenotype entries about its causal and alternative genes are also present. This integration will become a good source for further analysis by leading to subsequent steps of dimension reduction and clustering techniques.

3.3. Cosine Similarity

We would then extract the phenotype, causal genes, and alternative genes into a unified dataset so that we may proceed to implement cosine similarity to quantify the relationships between the components. Cosine similarity has been used in gene-phenotype prediction with success in previous studies [1]. Cosine similarity is a method of calculating how similar two vectors are, independent of magnitude. It is defined as the cosine of the angle between two non-zero vectors, which gives a value between -1 and 1. Using cosine similarity between embeddings [5], we can assess the relationship between genes based on their vector representations. This technique is valuable in understanding gene function similarity and grouping genes with similar roles.

Mathematically, cosine similarity is calculated through the formula:

$$\text{Cosine Similarity} = \frac{A \cdot B}{||A||||B||}$$

where A and B are the vectors for which similarity is being measured, $A \cdot B$ represents the dot product of the vectors, and $||A||$ and $||B||$ are the magnitudes (or norms) of the respective vectors. This formula allows us to evaluate the cosine of the angle between two vectors, highlighting their similarity in orientation rather than magnitude.

3.3.1. Implementation:

For our project, we use cosine similarity in two scenarios as explained below:

1. **Causal Genes and Phenotypes:** Calculate cosine similarity between causal gene embeddings and phenotype embeddings. The higher the cosine similarity score, the more closely related are the causal gene and the phenotype.
2. **Alternative Genes and Phenotypes:** Their cosine similarity is calculated between alternative gene embeddings and alternative phenotype embeddings. Although these genes are still not classified as causal, a higher score may indicate important patterns or associations.

3.3.2. Steps Followed

The implementation of cosine similarity involves the following steps:

1. **Vector Preparation:**Prepare the embedding vectors for both causal and alternative genes and for phenotypes.
2. **Similarity Calculation:** Using appropriate computational libraries, calculate the cosine similarity of each causal gene-phenotype pair and alternative gene and phenotype.
3. **Analysis of Results:** Computed cosine similarity scores should be analyzed to better identify associated genes. Results are sorted in order of similarity score to emphasize the most powerful associations.

We can see how the use of cosine similarity helps deepen our understanding of gene and phenotype interaction and therefore will lead to further exploration and understanding of gene causality.

3.4. Clustering Analysis

We now present the clustering analysis after having calculated the similarity of the cosine between the causal genes and the phenotypes and between the alternative genes and the phenotypes. Clustering is an unsupervised learning technique used for groupings of similar data points with their characteristics so that it can find the pattern and the relationship between data sets.

3.4.1. Overview of Clustering

Clustering algorithms separate the dataset into clearly differentiated clusters in such a way that data points belonging to a cluster bear a high similarity to each other, while data points in two different clusters bear a dissimilarity. For this project, we operate the clustering algorithm separately on two sets of data, one to the causal genes and phenotypes and another to alternative genes and phenotypes.While K-means is useful, more advanced techniques like t-SNE or UMAP could be employed for better clustering visualization [4].

3.4.2. Implementation in Our Analysis

- **Causal Genes and Phenotypes:**
  - Get the dataset of cosine similarity scores between causal genes and phenotypes.
  - For this analysis, apply K-means clustering to further partition data into k clusters with respect to the similarity scores.
  - Determine the best value of k with the elbow method.
  - Assign each pair of causal gene-phenotype to its nearest centroid cluster.
- **Alternative Genes and Phenotypes:**
  - Use the same approach for the clustering analysis on the alternative genes and phenotypes dataset.
  - Calculate the scores of cosine similarities for all alternate genes and phenotypes.
  - Apply K-means clustering and determine the number of clusters to be taken by using the elbow method.

3.5. Using PCA and Re-implementing Cosine Similarity and Clustering

First, we used cosine similarity and clustering directly on the original high-dimensional data. But the resulting figures did not give out clear or meaningful patterns, so the next alternative was PCA, a technique for dimensionality reduction.

3.5.1. Why PCA is Necessary

PCA is particularly crucial when working with high-dimensional data where, often, many of the features may not significantly contribute to the variance or relationships. The embeddings have 3,072 dimensions, which makes clustering and measures of similarity less effective because of the "curse of dimensionality." In high-dimensional spaces:

- Data points can appear more similar than they are, leading to difficulty distinguishing meaningful relationships.
- Algorithms like clustering can become inefficient and less effective because distances between data points become less informative.

We will apply PCA to reduce the number of dimensions in the data, keeping only the most important components. This will enhance the efficiency of the computations regarding the cosine similarity of patterns and the clustering.

3.5.2. Implementation of PCA

1. **Standardizing the Data:** Normalize the data so each contributing value can provide a similar contribution.
2. **Applying PCA:** We then apply PCA to the standardized data, using a Python library like `scikit-learn`. We choose the number of principal components based on the explained variance ratio. The goal is to retain enough components to capture a substantial amount of the variance (e.g., 95% of the total variance) while significantly reducing the dimensionality. This selection ensures that the most critical information is preserved, and noise or irrelevant dimensions are filtered out.
3. **Transforming the Data:** PCA transforms the original high-dimensional dataset into a new set of coordinates, where each axis corresponds to a principal component. This transformed dataset is now of much lower dimensionality but still retains the core structure and patterns present in the original data.

3.5.3. Reapplying Cosine Similarity and Clustering

After PCA, we re-calculate the cosine similarity between the reduced-dimensional vectors of causal genes and phenotypes, as well as alternative genes and phenotypes. By working with lower-dimensional vectors, cosine similarity becomes more informative because the vectors are now focused on the most relevant features.

Next, we perform clustering again using K-means. The reduced dimensionality enables the clustering algorithm to better differentiate between meaningful groups and noise. We determine the optimal number of clusters using methods like the elbow method, ensuring that the clustering results provide clearer patterns and groupings of genes and phenotypes.

3.5.4. Outcome

We first apply PCA to filter out the noise in our analysis and zoom in on the most meaningful patterns, and then apply cosine similarity followed by clustering. This gets us to more discernible clusters and meaningful similarity scores that enable clearer associations between genes and phenotypes.

3.6. Vector Analysis of Gene and Phenotype Embeddings

To perform vector analysis on the gene and phenotype embeddings, we can derive new vectors that represent the relationships between the causal gene embeddings, phenotype embeddings, and associated gene embeddings. This kind of analysis can provide insights into how closely the embeddings (which represent genes and phenotypes) relate to each other, and possibly reveal patterns in causality.

3.6.1. Difference Vectors

- We will create vectors that illustrate the difference between the causal gene embedding and the phenotype embedding, as well as between the associated gene embeddings and the phenotype embedding. This will help us understand the "distance" or difference in the embedding space, which may relate to causality.

3.6.2. Vector Operations

- **Magnitude (Norm)**: We will compute the magnitude (Euclidean norm) of the difference vectors to measure the distance.

$$\text{Magnitude} = \|\mathbf{v}\| = \sqrt{v_1^2 + v_2^2 + ... + v_n^2}$$

- **Direction**: We will use cosine similarity between vectors to explore the directional relationships between the gene and phenotype embeddings.

$$\text{Cosine Similarity} = \frac{\mathbf{u} \cdot \mathbf{v}}{\|\mathbf{u}\|\|\mathbf{v}\|}$$

3.6.3. Vector Comparison

We will compare the causal gene and associated gene embeddings with the phenotype to assess how closely they align.

4. Results and Discussion

The exploratory analysis revealed several insights:

- **Dimensionality Reduction:** PCA effectively reduced the complexity of the high-dimensional embeddings, enabling visual exploration. Visualizations indicated that embeddings of causal gene-phenotype pairs often form separable patterns in the reduced dimensions, although further refinement of techniques is necessary.
- **Clustering Performance:** The K-means clustering method provided initial evidence that causal and non-causal pairs form distinct groups. However, the effectiveness varied depending on the phenotype and gene categories, suggesting that additional feature engineering or alternative clustering methods may improve results.
- **Vector Manipulation:** Derived vectors offered new insights into causal relationships. Differences between embeddings (e.g., phenotype - gene) highlighted features correlating with causality, though the success was inconsistent across all data points.

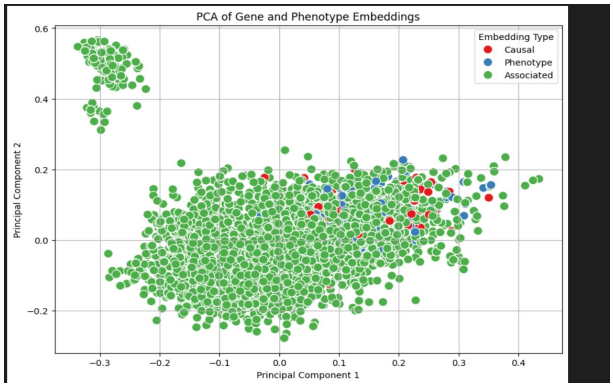

Figure 2. PCA Result

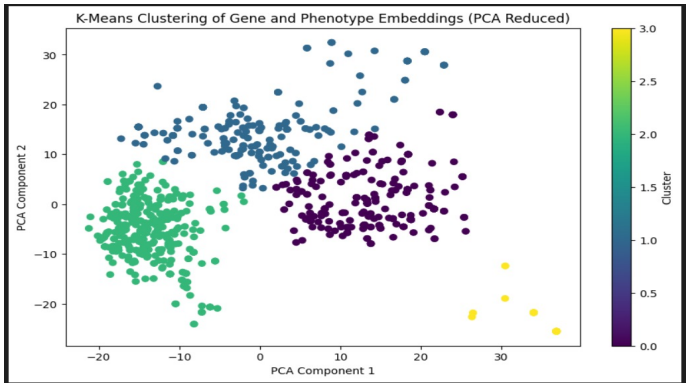

Figure 3. K-Means Clustering

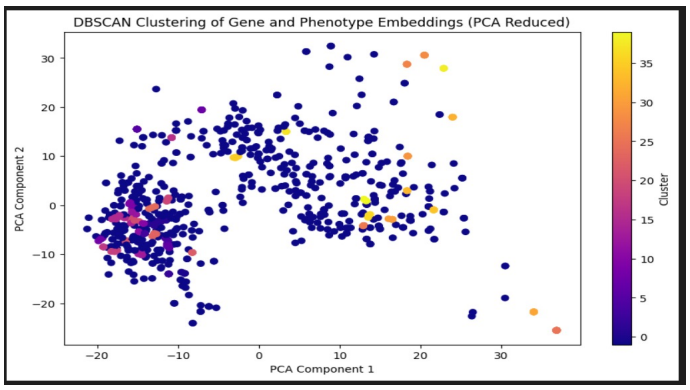

Figure 4. DBSCAN Clustering

5. Conclusion

In this project, we conducted an exploratory analysis to investigate the relationships between phenotype and gene embeddings with the goal of identifying gene causality. We mapped phenotypes to causal and non-causal genes, applied dimensionality reduction using PCA to facilitate visualization, and performed vector analysis by calculating cosine similarity between gene and phenotype embeddings. Additionally, unsupervised clustering methods such as K-Means and DBSCAN were employed to identify distinct patterns that could indicate causal relationships. The findings showed that causal genes exhibit higher similarity with their respective phenotypes compared to non-causal genes, and clustering revealed distinct groups that may suggest underlying causal patterns. This analysis provides a strong basis for further exploration into gene causality using embedding vectors, with potential applications in genomics and disease research.

6. Future Work

This project lays the foundation for the exploration of gene causality employing cutting-edge embedding techniques and unsupervised learning methods. Further development and improvement will, however, consist of the following:

- **Exploration of Alternative Embedding Models:** While GPT-3.5 embeddings correspond structurally, future work can explore other large language models such as GPT-4, or some specialized bioinformatics models like BioBERT. Hate speech models may aid in capturing succinct information about genes and phenotypes leading to better analysis and insight.
- **Integration of Additional Dimensionality Reduction Techniques:** : In addition to PCA, additional techniques can be used such as t-SNE or UMAP to visualize these high-dimensional embeddings. These high-dimensional visualization methods may provide alternative views that expose different and possibly more interesting patterns or clusters that are not apparent with PCA alone.Although PCA is commonly used, exploring alternative dimensionality reduction techniques like t-SNE [7] may provide improved visualization and interpretation of the data.
- **Incorporation of More Complex Clustering Algorithms:** For better clustering results, directed work could possibly consider moving beyond K-means to include clustering algorithms like hierarchical clustering, DBSCAN, or GMM. This may suit the purported biological complexity more adequately.
- **Application of Supervised Learning Models:** Given most of the project has relied on unsupervised techniques, incorporating some supervised learning methods may improve causal gene identification. Supervised learning could train other models to refine predictions using known causal genes as labels.
- **Expansion of the Dataset:** A very robust analysis could be performed by including considerably larger datasets emanating from other GWAS studies, pharmacogenetic databases or any large-scale population genomics repositories. Such a move will also enable validation of our model's performance and robustness on different gene and phenotype variations.
- **Biological Context:** Such biological annotations as gene ontologies, protein-protein interaction networks and pathway information could add other layers of context. These elements will help refine clustering outputs by increasing the biological relevance of the identified patterns.
- **Development of a User-Friendly Interface:** The necessary development of a user-friendly interface is very desirable for the analysis to reach a wider audience. Future work could go towards developing a web-based platform to allow users to input their own phenotype-gene datasets and start a more interactive visualization. Such a platform could facilitate working with genetic researchers and clinicians who might benefit from those insights.

With the pursuit of these directions, the project would grow into a more complete and definite tool to investigate gene-phenotype relationships, thus benefiting genetics research and personalized medicine.

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