Midterm Project

Robust Representation and Efficient Feature Selection Allows for Effective Clustering of SARS-CoV-2 Variants: Paper Reproduction dan Improvements

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The COVID-19 pandemic has led to an abundance of genomic data on the SARS-CoV-2 virus, presenting a unique opportunity for detailed analysis. This research benefits biologists, policymakers, and authorities in making informed decisions to control virus spread and prepares for future pandemics. Despite the challenge posed by the virus's diverse variants and mutations, this paper focuses on clustering spike protein sequences, crucial for understanding variant behavior. Utilizing a k-mers based approach, the original author of the paper create a fixed-length feature vector for spike sequences. The proposed feature selection method enables efficient clustering of spike sequences, demonstrating higher F_1 scores for clusters in both hard and soft clustering methods.

Keywords: COVID-19; SARS-CoV-2; Spike Protein Sequences; Clustering Analysis; Feature Selection; k-mers

I. INTRODUCTION

The SARS-CoV-2 virus, responsible for COVID-19, has a rapidly spreading genomic sequence worldwide. This genetic information is crucial for understanding outbreak dynamics, designing analyses, drugs, and vaccines, and monitoring changes in viral effectiveness over time. The virus's spike protein, particularly its S region, plays a key role in infection and exhibits significant genomic variation. To efficiently analyze this variation, the original author of the paper propose a focus on amino acid sequences encoded by the spike region using machine learning and clustering methods[1]. By converting these sequences into numeric vectors through k-mers, the original author of the paper aim to reduce data dimensionality and enhance analysis efficiency. The proposed approach integrates feature selection and clustering to gain insights into the virus's evolutionary dynamics, overcoming challenges posed by the vast number of available genomic sequences. The significance of the S protein makes it a potential target for therapeutic interventions and vaccine development. The methodology proposed ensures meaningful analytics, laying the foundation for effective strategies to combat the COVID-19 pandemic.

II. ALGORITHMS

In this section, the proposed algorithm is discussed in detail. The discussion start with the description of k-mers generation from the spike sequences. Then, the generation of feature vector representation from the k-mers information will be described. After that, discussion on different feature selection methods will be given in detail. Finally, the detail of the application of clustering approaches on the final feature vector represetation will be explained.

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A. k-mers Generation

Given a spike sequence, the first step is to compute all possible k-mers. The total number of k-mers that can be generated for a spike sequence are described as follows.

$$N - k + 1 \tag{1}$$

where N is the length of the spike sequence ($N = 1274$ for this paper dataset). The variable k is a user-defined parameter ($k = 3$ is chosen using standard validation set approach[2]).

B. Fixed-Length Feature Vector Generation

Since most of the Machine Learning (ML) models work with a fixed-length feature vector representation, the k-mers information is needed to be converted into the vectors. For this purpose, a feature vector Φ_k is generated for a given spike sequence a (i.e., $\Phi_k(a)$). Given an alphabet Σ (characters representing amino acids in the spike sequences), the length of $\Phi_k(a)$ will be equal to the number of possible k-mers of a. More formally,

$$\Phi_k(a) = |\Sigma|^k \tag{2}$$

Since there are 21 unique characters in Σ (namely $ACDEFGHIKLMNPQRSTVWXY$), the length of each frequency vector is $21^3 = 9261$.

C. Low Dimensional Representation

Since the dimensionality of data is high after getting the fixed length feature vector representation, different supervised and unsupervised methods is applied to obtain a low dimensional representation of data to avoid the problem of the *curse of dimensionality*[3,4]. Each of the methods for obtaining a low dimensional representation of data is discussed below:

1. Random Fourier Features

The first method that is used is an approximate kernel method called Random Fourier Features (RFF)[5]. It is an unsupervised approach, which maps the input data to a randomized low dimensional feature space (euclidean inner product space) to get an approximate representation of data in lower dimensions D from the original dimensions d. More formally:

$$z : \mathbb{R}^d \to \mathbb{R}^D \tag{3}$$

In this way, the inner product between a pair of transformed points is approximated. More formally:

$$f(x, y) = \langle \phi(x), \phi(y) \rangle \approx z(x)'z(y) \tag{4}$$

In Equation 4, z is low dimensional (unlike the lifting ϕ). Now, z acts as the approximate low dimensional embedding for the original data. Then, z can be used as an input for different ML tasks like clustering and classification.

2. Least Absolute Shrinkage and Selection Operator (Lasso) Regression

Lasso regression is a supervised method that can be used for efficient feature selection. It is a type of regularized linear regression variants. It is a specific case of the penalized

least squares regression with an L_1 penalty function. By combining the good qualities of ridge regression[6,7] and subset selection, Lasso can improve both model interpretability and prediction accuracy[8]. Lasso regression tries to minimize the following objective function:

$$\min(\text{Sum of square residuals} + \alpha \times |\text{slope}|) \tag{5}$$

where $\alpha \times |\text{slope}|$ is the penalty term. In Lasso regression, the absolute value of the slope is chosen in the penalty term rather than the square (as in ridge regression[7]). This helps to reduce the slope of useless variables exactly equal to zero.

3. Boruta

The last feature selection method that is used is Boruta. It is a supervised method that is made all around the random forest (RF) classification algorithm. It works by creating shadow features so that the features do not compete among themselves but rather they compete with a randomized version of them[9]. It captures the non-linear relationships and interactions using the RF algorithm. It then extract the importance of each feature (corresponding to the class label) and only keep the features that are above a specific threshold of importance. The threshold is defined as the highest feature importance recorded among the shadow features.

D. Clustering Methods

In the original work, five different clustering methods (both hard and soft clustering approaches) namely k-means[10], k-modes[11], Fuzzy c-means[12,13], agglomerative hierarchical clustering, and Hierarchical density-based spatial clustering of applications with noise (HDBSCAN)[14,15] (note that is is a soft clustering approach). For the k-means and k-modes, default parameters are used. For the fuzzy c-means, the clustering criterion used to aggregate subsets is a generalized least-squares objective function. For agglomerative hierarchical clustering, a bottom-up approach is applied, which is acknowledged as the agglomerative method. Since the bottom-up procedure starts from anywhere in the central point of the hierarchy and the lower part of the hierarchy is developed by a less expensive method such as partitional clustering, it can reduce the computational cost[16].

HDBSCAN is not just density-based spatial clustering of applications with noise (DBSCAN) but switching it into a hierarchical clustering algorithm and then obtaining a flat clustering based in the solidity of clusters. HDBSCAN is robust to parameter choice and can discover clusters of differing densities (unlike DBSCAN)[15].

III. EXPERIMENTAL SETUP AND DATA PREPARATION

In this paper reproduction, the author utilizes only three clustering methods—k-means, k-modes, and Fuzzy c-means. HDBSCAN and agglomerative clustering are omitted due to their lack of parallelization, resulting in prolonged runtime execution, particularly for high-dimensional data such as genome sequences or fixed-length feature vector representations derived from raw data. For all clustering methods except k-means, the input data consists of low-dimensional representations obtained from processing the raw data. This approach is adopted to address the extended runtime execution associated with high-dimensional raw data input. The quality of the clustering algorithms is assessed using the F_1 score. The experiments are conducted on a Core i7 system with a MacOS operating system, 16GB of memory, and a 1.7GHz processor. The algorithm is implemented in Python, and the code is accessible at `https://github.com/erland-ramadhan/sars-cov2-variants-results-reproduction.git`.

TABLE I. Variant-wise F_1 (weighted) score for different clustering methods. (Reproduction work)

	F_1 Score (Weighted) for Different Variants				
Methods	Alpha	Beta	Delta	Gamma	Epsilon
K-Means	0.182	0.314	0.426	0.897	0.355
K-Means + Boruta	0.182	0.314	0.423	0.897	0.355
K-Means + Lasso	0.987	0.998	0.997	0.999	0.997
K-Means + RFF	0.917	0.0	0.0	0.659	0.320
K-Modes + Boruta	0.899	0.761	0.689	0.977	0.933
K-Modes + Lasso	0.994	0.970	0.997	0.999	0.995
K-Modes + RFF	0.178	0.0	0.0	0.981	0.320
Fuzzy + Boruta	0.186	0.316	0.414	0.897	0.356
Fuzzy + Lasso	0.976	0.998	0.985	0.997	0.972
Fuzzy + RFF	1.0	0.0	0.0	0.659	0.0

TABLE II. Variant-wise F_1 (weighted) score for different clustering methods. (Original work)

	F_1 Score (Weighted) for Different Variants				
Methods	Alpha	Beta	Delta	Gamma	Epsilon
K-Means	0.359	0.157	0.611	0.690	0.443
K-Means + Boruta	0.418	0.105	0.610	0.690	0.652
K-Means + Lasso	0.999	0.007	0.840	0.999	0.774
K-Means + RFF	1.0	0.0	0.288	1.0	1.0
K-Modes + Boruta	0.999	0.316	0.860	0.999	0.857
K-Modes + Lasso	0.999	0.173	0.917	0.998	0.076
K-Modes + RFF	1.0	0.0	0.0	0.613	1.0
Fuzzy + Boruta	0.357	0.154	0.613	0.690	0.443
Fuzzy + Lasso	0.999	0.314	0.647	0.999	0.816
Fuzzy + RFF	0.439	0.0	0.0	1.0	0.0

IV. RESULTS AND DISCUSSION

A. F_1 score

The clustering quality was assessed using the weighted F_1 score. As cluster labels were unavailable, each cluster was assigned a label based on the variant that had the majority of its sequences (e.g., assigning the label 'Alpha' to a cluster if most sequences belonged to the Alpha variant). Subsequently, the weighted F_1 score was calculated individually for each cluster using these assigned labels. The reproduction work presents the computed weighted F_1 scores for different methods in Table I, while the original work provides them in Table II. The results indicate that Lasso regression outperforms other feature selection methods in efficiently clustering all variants. In contrast to the original work, where pure clusters of certain variants were observed with RFF, the reproduction work only observed this phenomenon when using fuzzy c-means clustering. Therefore, k-means, k-modes, and fuzzy c-means exhibit better generalization across variants when employing Lasso regression as the feature selection method.

B. Runtime Comparison

After experimenting with various clustering methods and feature selection algorithms on spike sequences, it was noted that k-means, k-modes, and fuzzy c-means exhibit superior

TABLE III. Running time (in seconds) of different clustering methods and feature selection methods. The number of clusters is 5 (Alpha, Beta, Delta, Gamma, and Epsilon).

	Runtime for Different Feature Selection Methods			
Clustering Methods	No Feature Selection Method	Lasso	Boruta	RFF
K-means	153.211	2.029	2.353	2.802
K-modes	N/A	1485.150	1691.053	1501.018
Fuzzy c-means	N/A	66.509	89.783	198.234

performance when Lasso regression is employed as the feature selection method, as evident from the weighted F_1 score. Nevertheless, it is crucial to examine the runtime impact of these clustering approaches to assess the trade-off between F_1 score and runtime. To address this, the runtime for different clustering algorithms, both with and without feature selection methods, was calculated and is presented in Table III. The analysis reveals that k-modes is notably time-intensive, while k-means boasts the shortest execution time. This behavior underscores the efficacy of the k-means algorithm, not only in terms of F_1 score but also in terms of runtime efficiency.

V. CONCLUSION

A proposed feature vector representation and a range of feature selection methods were introduced to eliminate less significant features, enabling diverse clustering methods to effectively group SARS-CoV-2 spike protein sequences with high F_1 scores. The significance of runtime in clustering coronavirus spike sequences was emphasized, with the k-means algorithm emerging as capable of both achieving pure clustering across all variants and requiring the least runtime. Future work may involve expanding the dataset for analysis, exploring additional clustering methods, and applying deep learning to larger datasets for more nuanced insights. Another avenue is the exploration of alternative feature vector representations, such as those based on minimizers, which can be implemented without sequence alignment. This extension could facilitate the application of clustering techniques to study unaligned (even unassembled) sequencing reads of intra-host viral populations, providing insights into dynamics at this scale.

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